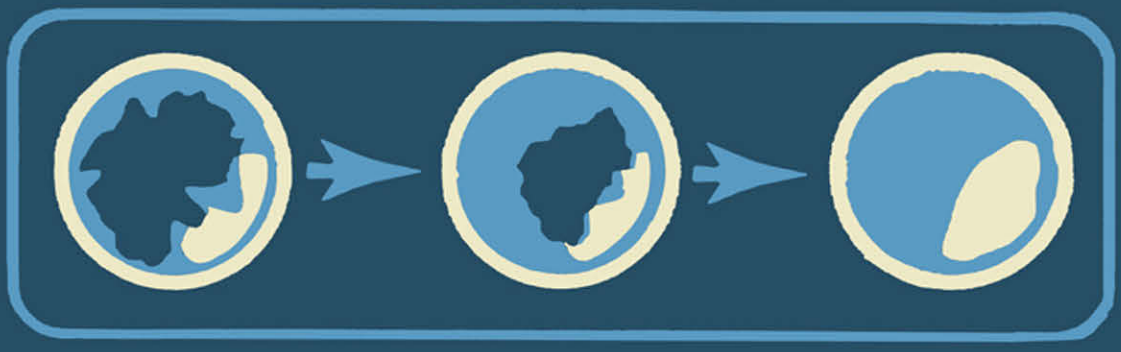
CONTEMPORARY CARDIOLOGY

Management of Acute Coronary Syndromes

Edited by

Christopher P. Cannon, MD



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Management of Acute Coronary Syndromes

CONTEMPORARY CARDIOLOGY

CHRISTOPHER P. CANNON
SERIES EDITOR

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Management of Acute Coronary Syndromes

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FOREWORD

Coronary artery disease, the great scourge of our times, may express itself in two major clinico-pathologic forns. The chronic form is caused by progressive atherosclerotic narrowing of the coronary arterial bed and usually presents as angina secondary to ischemia precipitated by increased myocardial oxygen demand, i.e., "demand ischemia." Treatment consists of pharmacologic agents and other measures to reduce oxygen demand, and when this approach is inadequate, surgical or catheter-based revascularization. The acute form, on the other hand, results from a sudden reduction in myocardial oxygen supply due, most commonly, to a thrombus on a fissured or eroded coronary atherosclerotic plaque that previously had not caused critical obstruction. This causes "supply ischemia," which may result in a variety of clinical syndromes, including unstable angina, non-Q-wave myocardial infarction, and Q-wave myocardial infarction These acute coronary syndromes are responsible for more than half a million deaths and a million hospitalizations each year in the United States. The incidence is similar in other developed nations and it is rising at an alarming rate in the developing portions of the world.

The management of patients with acute coronary syndromes represents one of the major challenges to contemporary cardiology. This field has been the subject of intensive investigation that has led to major advances in our understanding of the pathophysiology, as well as in the diagnosis and management of patients with these conditions.

Management of Acute Coronary Syndromes captures the many important developments in this rapidly moving area of cardiology. Dr. Cannon deserves thanks and congratulations for having organized a group of experienced clinicians and clinical investigators who present a comprehensive, up-to-date, and eminently readable picture of the field. This book is certain to aid cardiologists, internists, and emergency physicians in their management of patients with acute coronary syndromes.

Eugene Braunwald, *MD*

PREFACE

Over the past decade, there has been a revolution in our understanding of both the pathophysiology and the management of acute coronary syndromes (ACS). The conversion of a stable atherosclerotic lesion to a ruptured plaque with thrombosis has provided a unifying hypothesis for the etiology of acute coronary syndromes. From this, the concept of a "spectrum" of myocardial ischemia has provided a framework for understanding the pathogenesis, clinical features, treatment, and outcome of patients across the spectrum of myocardial ischemia.

Furthermore, a new paradigm for acute coronary syndromes has emerged with the results of the Thrombolysis in Myocardial Ischemia (TIMI) IIIB trial: While thrombolytic therapy has proven clearly beneficial in patients with ST segment elevation, no benefit has been observed in patients with unstable angina or non-ST elevation MI. Angiographic studies, including TIMI I and TIMI IIIA, have shown that this difference in outcome results from the initial status of the infarct-related artery, which usually demonstrates 100% coronary occlusion in ST elevation MI, in contrast to a patent, but stenotic coronary lesion in unstable angina and non-ST elevation MI. Thus, a classification of ST elevation MI vs non-ST segment elevation ACS provides the critical information regarding the pathophysiology and acute management of the patient.

Accordingly, *Management of Acute Coronary Syndromes* is the first book to approach the management of acute coronary syndromes based on this new paradigm. The initial sections are devoted to understanding the pathophysiology of ACS, as well as the diagnostic tools for assessing patients. There are then two separate sections, one for ST elevation MI and the other for non-ST elevation ACS, which discuss the state-of-the art management of these two groups of patients. I have felt privileged to have colleagues who are each world-renowned experts in their fields to provide concise, evidence-based recommendations on the optimal management of patients. The latest clinical trial data with numerous figures and tables are provided so that the reader will be able to have quickly available the key information that supports the recommended therapies. It is hoped that this compilation of the latest information will facilitate improvement in the management of patients with acute coronary syndromes.

On a personal level, my interest in acute coronary syndromes grew from many sources. First and foremost in guiding me has been my father, Paul Cannon, whose dedication to medicine and science has been a strong role model for me. His initial work in the measurement of coronary blood flow with radionuclide imaging two decades ago helped define the very basic pathophysiology of angina pectoris. He has also been one of my clinical teachers, as he has for many others at Columbia University College of Physicians and Surgeons over the past 30 years, teaching the students, housestaff, and fellows about the clinical presentation of angina to the acute management of myocardial infarction in the coronary care unit. The second major influence came from the writings of Fuster, Willerson, Braunwald, and others, on the emerging understanding of plaque rupture and coronary thrombosis in the pathophysiology of unstable angina. This new and rapidly emerging field sparked both my interest and enthusiasm to focus on acute coronary

syndromes where new treatments might be of benefit to patients. Next, beginning with my fellowship at the Brigham, it has been my privilege to work with Eugene Braunwald for nearly a decade in conducting the Thrombolysis in Myocardial Infarction (TIMI) trials. His expertise, insight, innovation, and judgment have been the greatest example any student of medicine could hope for. His support and teaching throughout has fueled my enthusiasm for design and participation in clinical trials and scientific research studies, with the goal of improving patient care. Finally, my numerous colleagues in the TIMI Group, notably Carolyn McCabe and Elliott Antman, and in the entire cardiology community have been a constant inspiration to delve deeper into trying to understand and improve the management of patients with acute coronary syndromes.

Christopher P. Cannon, *MD*

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I PATHOPHYSIOLOGY

1 The Spectrum of Myocardial Ischemia

The Paradigm of Acute Coronary Syndromes

Christopher P. Cannon, MD, and Eugene Braunwald, MD

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INTRODUCTION

Traditionally, ischemic heart disease has been divided into several separate syndromes: stable coronary artery disease, unstable angina *(1,2)*, non-Q-wave myocardial infarction (MI), and Q-wave MI. However, the recent understanding of the conversion of a stable atherosclerotic lesion to a plaque rupture with thrombosis has provided a unifying hypothesis for the etiology of acute coronary syndromes *(3–7)*. The concept of myocardial ischemia as a spectrum provides a framework for understanding the pathogenesis, clinical features, treatment, and outcome of patients (Fig. 1).

A new paradigm for acute coronary syndromes emerged with the results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB trial: whereas thrombolytic therapy is clearly beneficial in patients with ST-segment elevation *(8)*, no benefit was observed in patients without ST-segment elevation (i.e., patients with unstable angina or non-Q-wave MI) *(9)*. Thus, it was observed that reperfusion therapy is useful only for patients with acute coronary syndromes who have ST-segment elevation and is not indicated for patients

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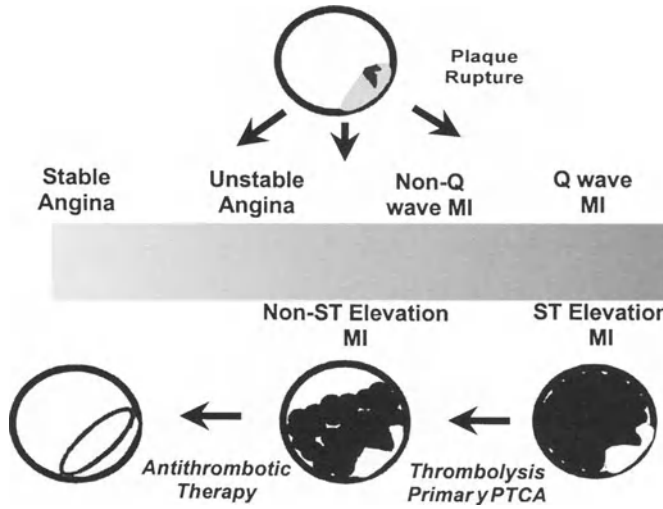


Fig. 1. The spectrum of myocardial ischemia. The various clinical syndromes of coronary artery disease can be viewed as a spectrum, ranging from patients with stable angina to those with acute Q-wave myocardial infarction (MI). Across the spectrum of the acute coronary syndromes, atherosclerotic plaque rupture leads to coronary artery thrombosis. In acute Q-wave MI, which usually presents with ST-segment elevation on the electrocardiogram, complete coronary occlusion is present. In those with unstable angina or non-Q-wave MI, a flow-limiting thrombus is usually present. In patients with stable angina, thrombus is rarely seen. The overall treatment objective is to move the patients back to a stable lesion. In acute ST-segment elevation MI, the objective over the first minutes to hours is to open the artery and achieve reperfusion. In patients with unstable angina and non-Q-wave MI, the goal is to stabilize or "passivate" the active thrombotic lesion over a period of hours to days. Then, over a period of months to years, the goal is to try to heal the lesion with risk factor reduction with treatment of hypercholesterolemia, hypertension, and diabetes, as well as smoking cessation, in an attempt to reduce the likelihood of subsequent rupture of the coronary plaques. Adapted with permission from ref. *123*.

without ST-segment elevation *(8–10)*. Angiographic studies have shown that this difference in outcome is owing to the initial status of the infarct-related artery, which usually exhibits 100% occlusion in ST-segment elevation MI *(11,12)*, in contrast to a patent, but stenotic coronary lesion in non-ST-segment elevation MI *(13,14)* (Fig. 1).

Thus, because of the advent of acute reperfusion therapy, the old distinction of Q-wave versus non-Q-wave MI (usually made days following MI) is no longer as useful for acute management. Instead, a classification of ST-segment elevation MI vs non-ST-segment elevation MI provides the critical information regarding the pathophysiology and acute management of the patient. Indeed, since non-ST-segment elevation MI patients share a pathophysiology similar to that of unstable angina patients, the pathophysiology and treatment is very similar.

Accordingly, in this book, separate sections are devoted to the management of these two broad types of patients with acute coronary syndromes, those with ST-segment elevation MI and those with non-ST-segment elevation. It should be noted that ST-segment elevation it is not a perfectly sensitive marker of acute occlusion *(15)*, and thus new technologies for proper identification and triage of patients with acute coronary syndromes are being evaluated extensively, as reviewed in Chapters 7 and 8.

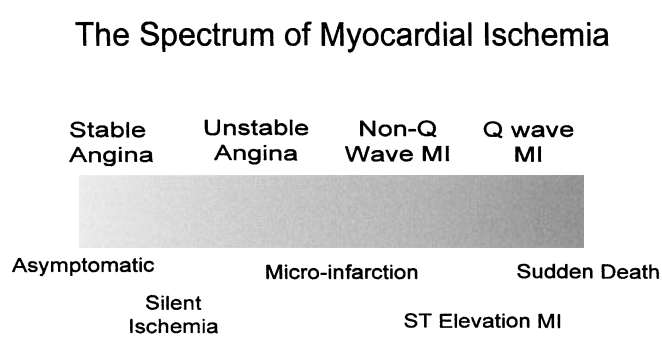


Fig. 2. The complete clinical spectrum of myocardial ischemic syndromes.

THE CLINICAL SPECTRUM OF ACUTE CORONARY SYNDROMES

It is useful to note that several other groups of patients fall within this spectrum of myocardial ischemia (Fig. 2). Among patients with stable coronary artery disease, many apparently stable patients have "active" lesions, which are prone to rupture over the subsequent months and years *(16)*. Although most patients remain clinically stable *(17)*, it is estimated that nearly all of these patients with "stable" coronary artery disease have subclinical plaque rupture events *(18,19)*.

Between patients with stable angina and those with unstable angina falls a high-risk group with clinically stable symptoms yet significant ambulatory ischemia, which can be detected by ambulatory Holter monitoring *(20,21)*. Similarly, between patients with unstable angina and those with non-Q-wave MI, is a group with what have been called *microinfarction (22)* or *infarctlet*; these patients have a very small but nondiagnostic elevation of cardiac creatine kinase, or no elevation in creatine kinase but elevation of other cardiac proteins such as troponin T *(23)* or troponin I *(24)*. Patients undergoing percutaneous coronary transluminal angioplasty (PTCA) can be considered part of the spectrum in that they have an intentionally disrupted plaque. Their clinical syndrome will be determined largely by the residual stenosis and characteristics of the lesion after PTCA: they usually have a stable clinical course when the stenosis is reduced to a minimum, but the course can be unstable if there is residual stenosis, especially with a coronary dissection and/or persistent thrombosis.

At the extreme right of the spectrum of ischemic heart disease (Fig. 2) are patients with sudden cardiac death. Many patients have an acute coronary occlusion as the etiology of the cardiac arrest. However, with aggressive emergency medical services that respond rapidly and treat with advanced }ù˙diac life support (ACLS) procedures, more patients are presenting with resuscitated "sudden cardiac death" *(25,26)*. Indeed, the National Heart Attack Alert Program (NHAAP) has as one of its major goals the improvement of emergency medical systems and early identification and treatment of acute MI patients as a means to reduce the overall mortality from myocardial infarction *(27–30)*. If more patients with cardiac arrest can be successfully resuscitated in the prehospital setting, they may become candidates for reperfusion and other therapies for acute coronary syndromes.

PLAQUE RUPTURE

Atherosclerosis is a silent process that usually begins 20–30 years before a patient's presentation with a clinical syndrome *(3,4)*. Hypercholesterolemia, hypertension, and other coronary risk factors damage the endothelium and initiate the atherosclerotic process *(3,4,31)*. When the endothelium is dysfunctional, macrophages bind to endothelial adhesion molecules and can infiltrate the endothelial cell. Low-density lipoprotein (LDL) molecules are able to penetrate into the vessel wall, and the macrophages digest the LDL, becoming foam cells, which thereby create a lipid-filled atherosclerotic plaque *(4,32)*. Oxidized LDL may also have a direct toxic effect on the endothelium and smooth muscle cells, which contributes to instability of the atherosclerotic plaque.

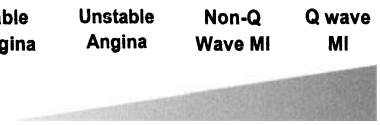
Multiple factors then contribute to plaque rupture, including endothelial dysfunction, plaque lipid content, degree of local inflamation *(33)*, coronary artery tone at the site of irregular plaques, local shear stress forces, platelet function *(34,35)*, and the status of the coagulation system (i.e., a potentially prothombotic state) *(36,37)*, all of which culminate in formation of platelet-rich thrombi at the site of the plaque rupture or erosion, and the resultant acute coronary syndrome *(5,38,39)*.

INFLAMMATION

Recent evidence has also pointed to a role for inflammation, which appears to play a key role in the development of atherosclerosis *(40)* and acute coronary syndromes *(41–44)*. Infectious agents, notably *Chlamydia pneumoniae,* appear to be one of the underlying causes of diffuse inflammation in the pathogenesis of coronary artery disease *(45–50)*. Evidence from histologic studies *(45–50)* and pilot treatment trials *(51,52)* suggests that *C. pneumoniae* may be an important *and potentially treatable* cause of acute coronary syndromes.

THROMBOSIS

The central role of coronary artery thrombosis in the pathogenesis of acute coronary syndromes is supported by a substantial body of evidence *(4,5,14,38,39,53–57)*. Six sets of observations contribute to this concept: (1) at autopsy, thrombi can usually be identified at the site of a ruptured plaque *(5,38)*; (2) coronary atherectemy specimens obtained in patients with acute MI or unstable angina demonstrate a high incidence of acute thrombotic lesions *(57)*; (3) coronary angioscopic observations indicate that thrombus is frequently present *(53,55,56)*; (4) coronary angiography has demonstrated ulceration or irregularities suggesting a ruptured plaque *(58,59)* and/or thrombus in many patients *(14,54)*; in the TIMI III-A trial, coronary angiograms in 306 patients with acute coronary syndromes revealed an apparent thrombus (globular intraluminal radiololucency) in 35% of all primary culprit lesions and a possible thrombus (adherent, flat intraluminal mass) in an additional 40% *(14)*; (5) evidence of ongoing thrombosis has been noted with elevation of several markers of platelet activity and fibrin formation *(3,6,60–66)*; and (6) improvement in the clinical outcome of patients with acute coronary syndromes using antithrombotic therapy with aspirin *(67–70)*, heparin *(69–73)*, low molecular weight heparin *(74–76)*, and platelet glycoprotein IIb/IIIa inhibitors *(77–79)*.



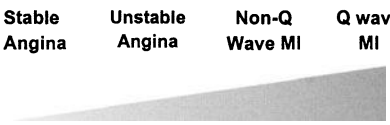
		Non-ST Elevation ACS	ST Elevation MI
CRP	13%	65%	76%
Chlamydia	25%	NR	90%
Increased FPA / TAT	0-5%	60-80%	80-90%
Activated Platelets	0-5%	70-80%	80-90%

Fig. 3. The pathophysiology of acute coronary syndromes (ACS). Atherosclerotic plaque rupture leads to coronary artery thrombosis, as indicated by angiographic evidence of thrombus, or biochemical markers of increased fibrinopeptide A (FPA), thrombin–antithrombin complexes (TAT), or activated platelets. In acute Q-wave MI, which usually presents with ST-segment elevation on the electrocardiogram, complete coronary occlusion is present. In those with unstable angina or non-Q-wave MI, a flow-limiting thrombus is usually present, but complete occlusion of the artery is uncommon. In patients with stable angina, thrombus is rarely seen. (NR, not reported.) Data from ref. *36,37,42,66,80,83*, and *124*.

THE "PATHOPHYSIOLOGIC SPECTRUM"

Across the spectrum of myocardial ischemia, markers of inflammation, thrombosis, and platelet activation increase in frequency in parallel with the clinical severity of the acute coronary syndrome (Fig. 3). Markers of inflammation, such as C-reactive protein, are found in 13% of patients with stable coronary artery disease vs 65% of patients with unstable angina and 76% of patients with acute MI *(42)*. Similarly, antibodies to *C. pneumoniae* are found in a higher percentage of patients with acute coronary syndromes *(80)*. Activated platelets and markers of ongoing thrombosis, such as fibrinopeptide A, are also found more often in patients with acute coronary syndromes *(35,37,66,81–84)*.

Coronary angiographic and angioscopic findings follow the same pattern across the spectrum of myocardial ischemia (Fig. 4). Angiographic studies have documented "white" thrombi, predominantly platelet-rich thrombi, in patients with unstable angina and non-ST-segment elevation MI, compared with "red" thrombi in patients with acute ST-segment elevation MI *(53,85,86)*. The latter was also noted in the landmark study by DeWood et al. *(11)*, in which coronary thrombi were aspirated with Fogarty catheters from patients with acute ST-segment elevation MI. Coronary angiography in patients with ST-segment elevation MI usually documents total occlusion of the infarct-related artery *(11,12)*. In patients with acute coronary syndromes without ST-segment elevation, "active lesions" are frequently observed, with irregular borders, associated intraluminal lucencies (which may represent thrombus), and ulcerated or eccentrically localized obstructions *(14,58,59)*. Such lesions are more likely to be associated with the pathologic features of plaque rupture, hemorrhage, and superimposed thrombus *(5,38)*. In addition, activated macrophages can frequently be identifed in the hinge point of the plaques, which may contribute to plaque rupture *(39)*. In patients with stable angina, "nonactive



		Non-ST Elevation ACS	ST Elevation MI
Angiographic Thrombus	0-1%	40-75%	>90%
Morphology	Smooth	Ulcerated	Occluded
Acute Coronary Occlusion	0-1%	10-25%	>90%
Angioscopy	No clot	"White clot"	"Red clot"

Fig. 4. Angiographic findings across the spectrum of acute coronary syndromes. Data from refs. *11–14,53,56,85,* and *125.*

lesions" (which are symmetric and concentric and have smooth borders) are usually observed *(14,58,59)*. The typical deformities are smooth, with an hourglass configuration and absence of intraluminal lucencies on coronary angiography. The presence of angiographic thrombus thus shows a gradient across the spectrum of acute coronary syndromes.

THE NEW PARADIGM OF CLINICAL SYNDROMES

The extent of local thrombosis at the site of coronary plaque rupture is largely responsible for the severity of the clinical syndrome (Fig. 1). If the thrombosis causes total occlusion of the coronary artery, persistent ischemic pain and ST-segment elevation develop, which usually evolve into a Q-wave MI *(11,12)*. In some patients, the amount of local thrombosis is extensive, but the obstruction is subtotal, resulting in a flow-limiting coronary stenosis and myocardial ischemia (e.g., unstable angina), sometimes associated with myocardial necrosis (e.g., non-Q-wave MI) *(13,14)*. Plaque rupture plays a major role even in patients with stable angina: large numbers of plaques are found to have undergone rupture and healing in the past *(5,16,57)*. Indeed, it is estimated that up to 99% of all plaque ruptures are clinically silent events *(18)*. This highlights the importance of continued antithrombotic therapy for all patients with coronary artery disease.

ST-Segment Elevation MI: The Open Artery Theory

The *open artery theory* explains the beneficial effects of thrombolytic therapy and catheter-based revascularization in acute ST-segment elevation MI: early achievement of an open infarct-related artery is associated with improved outcome *(87)*. If occlusion persists for more than 30 min, myocardial necrosis develops in the territory at risk (Fig. 5). If the area at risk is large and the artery remains occluded, left ventricular function is impaired. Thrombolytic therapy acts to interrupt this cascade of events *(88)*. By lysing the coronary thrombus, reperfusion of the infarct-related artery is achieved. This leads to a limitation of infarct size and decreases the extent of left ventricular dysfunction. The most important result of thrombolysis is improved survival *(89,90)*.

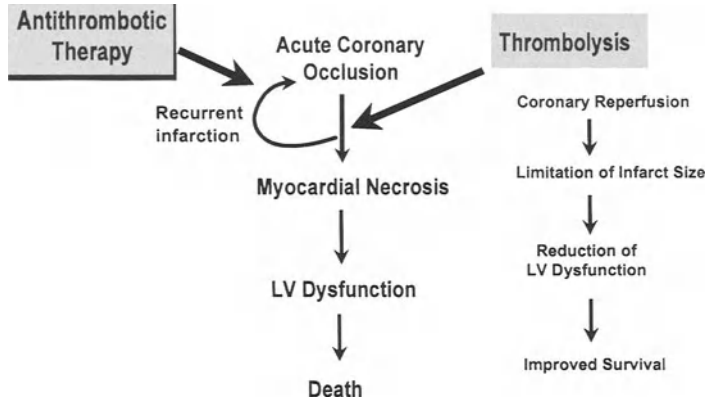


Fig. 5. The pathophysiology of acute ST-segment elevation myocardial infarction and the paradigm of thrombolytic therapy.

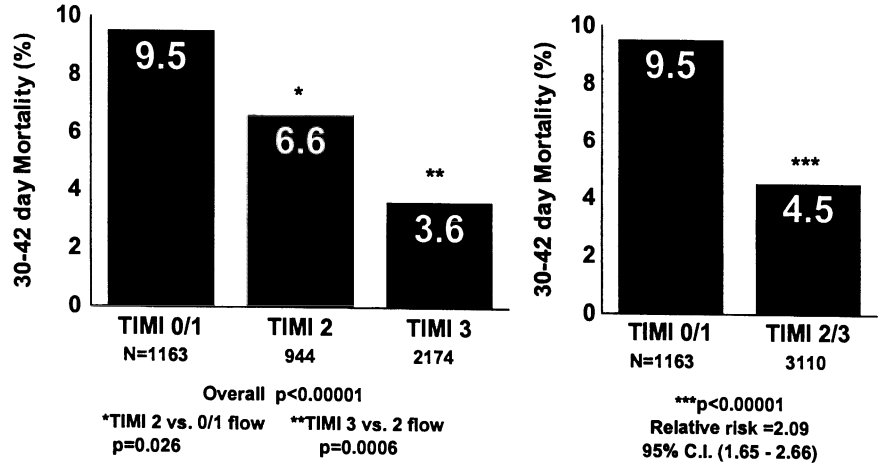


Fig. 6. The relationship between TIMI flow grade at 90 min following thrombolytic therapy and subsequent mortality. Reproduced with permission from ref. *94*.

First animal studies *(91)*, then the initial angiographic studies in patients using intracoronary streptokinase *(92,93)*, and then numerous other angiographic studies over the subsequent 15 yr have all lent strong support to this theory *(87,94)*. An overview of all the angiographic studies that used the TIMI flow grading system *(12)*, comprising over 4200 patients, found that patients who achieved complete and normal coronary perfusion, (TIMI grade 3 flow) at 90 min had the lowest mortality, 3.6%, compared with 9.5% with patients with TIMI grade 0 or 1 flow ($p < 0.00001$) (Fig. 6) *(94)*. Patients with slowed or delayed coronary flow in the infarct-related artery, compared with the uninvolved artery (TIMI grade 2 flow), had an intermediate mortality of 6.6% and a relative risk of mortality that was significantly better than an occluded artery *(94)*. These findings have also been confirmed in the GUSTO angiographic substudy, in which the mortality rates of patients with TIMI flow grades 2 and 3 were adjusted for differences in baseline characteristics *(95)*.

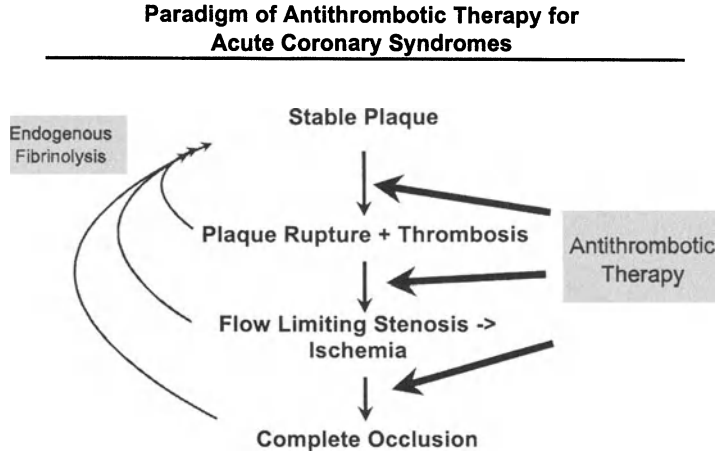


Fig. 7. The paradigm of antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: Antithrombotic therapy plays a major role in the treatment and prevention of acute coronary syndromes. If present at the time of plaque rupture (or administered acutely at the time of a clinical event) antithrombotic therapy can limit the development of thrombosis, or the degree of thrombosis and subsequent lesion stenosis, which causes clinical ischemia (e.g., unstable angina). Antithrombotic therapy could also prevent the local thrombosis from progressing to a complete occlusion (i.e., a myocardial infarction). Over a period of days to weeks, antithrombotic therapy acts to passivate the lesion and allow endogenous fibrinolysis to dissolve the acute thrombosis and restore the acute lesion to a stable plaque. Reproduced with permission from ref. *123.*

Non-ST-Segment Elevation

Among patients presenting without ST-segment elevation, the coronary artery is usually patent (i.e., TIMI grade 2 or 3 flow). In these patients, the principal approach is to use antithrombotic therapy, with the goal of preventing thrombus extension, enhancing endogenous fibrinolysis, and ultimately allowing healing (passivation) of the disrupted plaque. As shown in Fig. 7, if antithrombotic therapy is present at the time of plaque rupture, it can limit the degree of thrombosis and subsequent lesion stenosis. Another goal of antithrombotic therapy is to prevent the coronary thrombus from progressing to a complete occlusion. Over a period of days to weeks, antithrombotic therapy acts to passivate the lesion and allow endogenous fibrinolysis to dissolve the acute thrombosis and restore the acute lesion to a stable plaque.

MEDICAL TREATMENT

An overview of the medical treatment of acute coronary syndromes is shown in Fig. 8. As discussed in Chapters 12 and 16, aspirin has been shown in numerous studies to be beneficial across the entire spectrum of myocardial ischemia, from primary prevention of MI *(97,98)* to prevention of death or MI in all acute coronary syndromes *(67–70,90,99)*. Aspirin is also a highly effective agent for secondary prevention of events (see Chapter 24) *(100,101)*.

Heparin has also been shown to be beneficial in reducing death or MI in non-ST-segment elevation acute coronary syndromes *(69,71–73)*. Low molecular weight heparin also significantly reduces death or MI compared with aspirin alone *(74)*, and one agent, enoxaparin, has been shown to be superior to heparin in patients with non-ST-segment

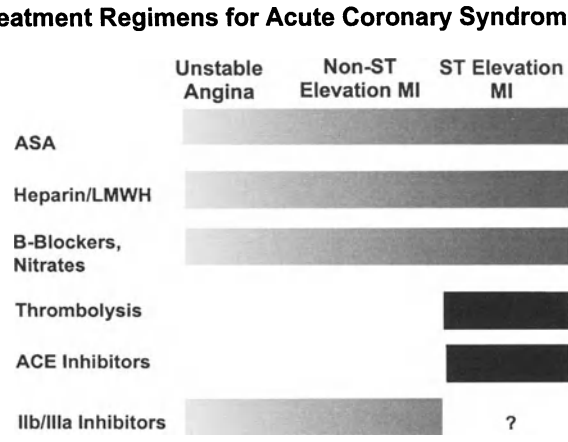


Fig. 8. Medical treatments across the spectrum of myocardial ischemia. Aspirin, heparin, β-blockers, and nitrates are all uniformly beneficial across the spectrum; thrombolytic therapy and angiotensin-converting enzyme (ACE) inhibitors are only beneficial in patients presenting with acute MI with ST-segment elevation (or new left bundle branch block). IIb/IIIa inhibitors are beneficial in non-ST-elevation ACS and are being tested with thrombolytic therapy in ST-elevation MI.

elevation acute coronary syndromes *(76)*. In ST-segment elevation MI, heparin improves infarct-related artery patency following tissue plasminogen activator *(102–104)*. The low molecular weight heparin enoxaparin has also recently been shown to reduce the incidence of death, MI, or recurrent ischemia following thrombolytic therapy *(105)*.

β-Blockers, nitrates, and calcium antagonists are useful in most patients with acute coronary syndromes *(10,106)*. Angiotensin-converting enzyme inhibitors have been shown to be beneficial in patients after MI *(107,108)* and more recently in acute ST-segment elevation MI in the GISSI-3, ISIS-4 , and Chinese trials *(109–111)*.

Inhibition of the platelet glycoprotein IIb/IIIa receptor has been shown to be beneficial in patients with non-ST-segment elevation acute coronary syndromes *(77–79)*. In ST-segment elevation MI, promising results with glycoprotein IIb/IIIa inhibitors have been observed with primary angioplasty *(112,113)*, and investigation is under way in the setting of thrombolysis *(114,115)*. Early and continued therapy with oral glycoprotein IIb/IIIa inhibitors is also being studied across the full spectrum of acute coronary syndromes *(116)*.

CLINICAL COURSE

The clinical course of all acute coronary syndromes can be complicated by recurrent unstable angina, the development or recurrence of myocardial infarction, or death (Fig. 9). For mortality, there appears to be a gradient in the risk across the spectrum: patients with acute Q-wave MI are at highest risk, those with non-Q-wave MI and unstable angina at intermediate risk *(24,117)*, and those with stable coronary artery disease at lowest risk *(17)*. The difference in outcome between patients who have non-Q-wave infarction compared with those who have unstable angina appears to be owing to the presence of myocardial necrosis in the former *(24)*.

Mortality following acute coronary syndromes is influenced by the patients' baseline characteristics, the severity of the initial and recurrent event(s), and the extent of coronary

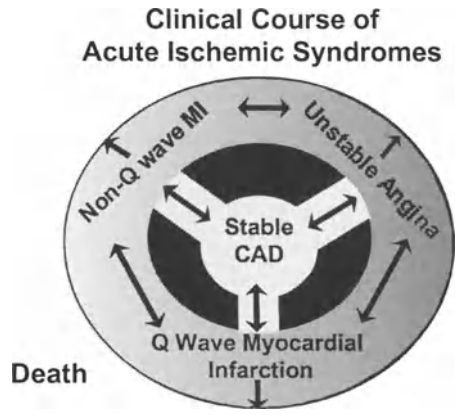


Fig. 9. The clinical course of acute coronary syndromes. Patients with any of the acute coronary syndromes have a significant risk of developing recurrent ischemic events. For example, a patient who presents with non-Q-wave MI could progress to develop postinfarction unstable angina or a Q-wave MI. A patient with a Q-wave MI could develop a recurrent infarction, and all syndromes carry a significant risk of mortality. The goal of therapy is to treat the ischemia and thrombosis and thereby return the patient to stable coronary artery disease. Reproduced with permission from ref. *123*.

artery disease and left ventricular dysfunction *(9,10,17,118)*. Following any of the acute coronary syndromes, patients remain at risk for recurrent events: approximately 15–25% develop recurrent ischemia or infarction by 1 y *(119,120)*. If such recurrent events occur, subsequent mortality is higher *(121,122)*. Thus, early identification and treatment to prevent recurrent ischemic complications is important and is described in detail in this book.

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2 Linking Biochemical, Pathologic, and Clinical Events in Acute Coronary Syndromes

Richard C. Becker, MD

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INTRODUCTION

Acute coronary syndromes represent the ultimate clinical expression of biochemical events and pathological processes occurring within atherosclerotic plaques. The sudden or rapidly progressive transition from a stable to an unstable clinical state implies increasing activity within the atheromatous core. Indeed, patients with unstable angina, non-ST-segment elevation myocardial infarction (MI), and ST-segment elevation MI are all at the metamorphosis stage of their disease. Much like physiologic hemostasis, pathologic thrombosis, representing the final common event that links acute coronary syndromes, represents a response to localized vascular injury and inflammation; however, unlike normal hemostasis, the cascade of events that follows is poorly regulated and responsible for compromised myocardial perfusion and at times cellular death.

VASCULAR ENDOTHELIUM

The vascular endothelium is intricately related to normal vessel responsiveness and thromboresistance. It is a multifunctional organ system composed of metabolically active and physiologically responsive component cells that meticulously regulate blood flow.

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Anatomic Considerations

Vascular endothelial cells form a single layer of simple squamous lining cells. The cells themselves are polygonal in shape, varying between 10 and 50 μm in diameter, and elongated in the long axis, orienting the cellular longitudinal dimension in the direction of blood flow. The endothelial cell has three surfaces: nonthrombogenic *(luminal),* adhesive *(subluminal),* and cohesive. The luminal surface is smooth and devoid of electron-dense connective tissue. Its luminal membrane or glycocalyx adds significantly to the vessels' thromboresistant properties, carrying a negative charge that repels similarly charged circulating blood cells. The subluminal (abluminal) surface adheres to connective tissue within the subendothelial zone. Small processes penetrate a series of internal layers to form myoendothelial junctions with subjacent smooth-muscle cells. The cohesive surface of the vascular endothelium joins adjacent cells to one another by cell junctions of two basic types, occluding *(tight)* and communicating *(gap).*

Thromboresistant Properties

As an active site of protein synthesis, endothelial cells synthesize, secrete, modify, and regulate connective tissue components, vasodilators, vasoconstrictors, anticoagulants, procoagulants, fibrinolytic proteins, and prostanoids. Possibly the most important function of the vascular endothelium is to prevent the initiation and development of nonphysiologic thrombi (i.e., thrombosis not required for hemostatic regulation).

Endothelial Cell Substances

Prostacyclin

Prostacyclin (PGI_2) is a potent vasodilating substance released locally in response to biochemical and mechanical mediators. PGI_2, by increasing intracellular cyclic adenosine monophosphate, also inhibits platelet aggregation. Furthermore, there is evidence that PGI_2 increases the rate of smooth muscle cell cholesterol ester metabolism, suppresses lipid metabolism within macrophages, and inhibits the release of growth factors, thus limiting proliferative responses to intravascular shear stress.

Nitric Oxide

Utilizing strips of arteries in organ baths (isolated system), Furchgott and Zawadski *(1)* discovered that acetylcholine-mediated vasodilation requires an intact vascular endothelium (i.e., it is endothelium dependent). Endothelium-derived relaxing factor, recently identified as nitric oxide, is an L-arginine derivative that relaxes smooth muscles by increasing intracellular cyclic guanosine monophosphate. It is released locally in response to a number of biochemical mediators, including thrombin, bradykinin, thromboxane A_2, histamine, adenine nucleotides, shear stress, and aggregating platelets. In addition to vasoactive properties, nitric oxide is also a potent inhibitor of platelet adhesion and aggregation. Moreover, nitric oxide and PGI_2 appear to have synergistic antiaggregatory properties (Fig. 1).

Plasminogen Activators

Vascular endothelial cells synthesize and release activators that are capable of converting plasminogen to the serine protease plasmin, an enzyme that proteolytically degrades fibrin (and fibrinogen). Tissue plasminogen activator (tPA) and urokinase-type plasminogen activator generate plasmin locally; therefore, fibrinolysis is limited to the

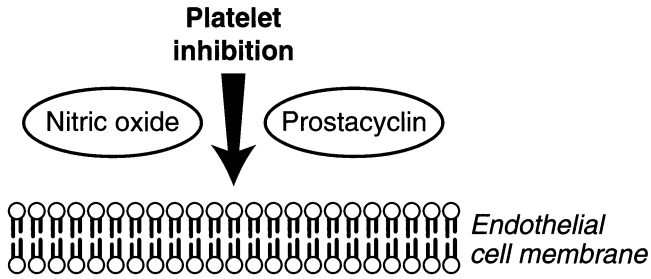


Fig. 1. The modulation of platelet aggregation is a vital component of normal vascular thromboresistance. Nitric oxide and prostacyclin (PGI_2) are particularly important.

immediate environment. Stimuli for the release of vascular plasminogen activators include epinephrine, thrombin, heparin, interleukin-1 (IL-1), venous occlusion, aggregating platelets, and desamino-8-D-arginine vasopressin. (Plasminogen activators and their role in atherosclerosis and thrombosis will be discussed in a section to follow).

Heparin-Like Species

In the past, mast cells were thought to be the only cells capable of synthesizing anticoagulant-active heparin. More recent investigations *(2)* have shown, however, that endothelial cells are in fact capable of synthesizing heparin-like molecules with anticoagulant properties. As a result, it is currently accepted that vascular thromboresistance is mediated, at least in part, through the interaction of heparin-like substances with antithrombin III and heparin cofactor II (both located on the endothelial surface), accelerating the neutralization of hemostatic (procoagulant) proteins.

Heparin cofactor II, a potent inhibitor of thrombin, is secreted by the liver into circulating blood, where it is present at a concentration of 1.0–2.0 μm/L. Unlike antithrombin III, heparin cofactor II is enhanced predominantly by dermatan sulfate; however, under high-shear stress heparan sulfate can stimulate its inhibiting action as well. In vivo, thrombin inhibition by heparin cofactor II appears to be mediated by the interaction of dermatan sulfate with the vessel wall, predominantly in the extracellular matrix *(3,4)*. At least four distinct subspecies have been identified in endothelial cells; two high molecular weight complexes, a heterodimeric form bound to fibronectin, and two small molecules referred to as decorin and biglycan *(5)*.

Antithrombin III

Antithrombin III (currently known as antithrombin) is a 58,000-Dalton plasma glycoprotein that circulates at a concentration of 2.3 mmol/L and is capable of neutralizing the coagulation proteins thrombin and factors IXa, Xa, XIa, and XIIa by covalent binding at their active sites. Clearly, antithrombin III is a major component of the vascular endothelium's thromboresistant properties.

Protein C and Protein S

Protein C is synthesized in the liver and secreted into plasma as a two-chain disulfide-bonded glycoprotein. It acts as an important anticoagulant (activated protein C [APC]) by preferentially destroying the activated forms of factor V and factor VIII (principally by cleaving their heavy chains). Protein S supports the anticoagulant function of APC by promoting its interaction with factors Va and VIIIa. Because protein S enhances APC-

mediated factor Va inactivation by only twofold, the existence of an APC-independent anticoagulant effect has been suggested *(6)*. Indeed, protein S is able to inhibit both the prothrombinase complex and the intrinsic tenase complex. Protein S can also interact directly with factor Va and factor VIIIa.

Both protein C and protein S are found on the vascular endothelial surface. Thrombomodulin, an integral membrane protein located on the luminal surface of most endothelial cells, forms a 1:1 complex with thrombin. In this complex, thrombin activates protein C (while at the same time thrombin is neutralized). Accordingly, thrombomodulin is able to inhibit thrombin-catalyzed fibrinogen clotting, factor V activation, and platelet activation.

Tissue Factor Pathway Inhibitor-1

Tissue factor pathway inhibitor (TFPI)-1, previously known as lipoprotein-associated coagulation inhibitor, is also located on the endothelial surface. It acts against the combined action of tissue thromboplastin (tissue factor) and factor VII in the presence of factor Xa. The proposed mechanism for inhibition of tissue factor-factor VIIa involves the formation of a quaternary complex with TFPI and factor X in a two-step reaction: factor Xa generated by tissue factor-factor VIIa binds reversibly with TFPI, and the binary complex formed binds, in a calcium-dependent manner, to membrane-bound tissue factor-factor VIIa *(7)*. In essence, TFPI prevents the extrinsic coagulation cascade from activating the prothrombinase complex; however, it has also been recognized that TFPI inhibits the intrinsic coagulation cascade, supporting the role of tissue factor on factor VIIIa and factor IX-mediated clotting *(8)*. The presence of factor IX also impairs TFPI-mediated inhibition of tissue factor VIIa.

In the presence of glycosaminoglycans, including heparin, heparan sulfate, and dextran sulfate, the inhibiting activity of TFPI is increased *(9)*.

Tissue Factor Pathway Inhibitor-2

A second human TFPI has recently been identified and characterized *(10)*. TFPI-2 is found within human umbilical vein endothelial cells, the liver, and the placenta and has been shown to inhibit tissue factor VIIa, kallikrein, factor XIa, and factor X activation by factor IXa *(11)*. It does not independently (in the absence of heparan) inactivate factor Xa or thrombin.

Annexin V

The annexins are an interesting family of nonglycosylated proteins that bind to negatively charged phospholipids, including phosphatidylserine and phosphatidylethanolamine *(12)*. One of the 13 recognized annexins, annexin V, is recognized as a potent endothelial surface anticoagulant based on its ability to displace phospholipid-dependent coagulation factors. It also reduces platelet adhesion (Fig. 2).

ATHEROSCLEROSIS

Perturbation of Endothelial Cell Function

Endothelial cell dysfunction can provoke a "downregulation" of normal thromboresistant properties. The most common disorder associated with impaired vascular thromboresistance is atherosclerosis.

Although frequently described as a focal process, coronary atherosclerosis is diffuse in nature, primarily involving the vessel intima (composed of the endothelium, the

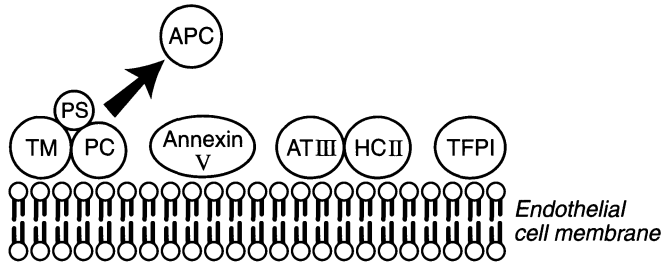


Fig. 2. The modulation of coagulation is a vital component of normal vascular thromboresistance. Protein C (PC) binds to surface thrombomodulin (TM) and, in the presence of protein S (PS), forms activated protein C (APC), which then neutralizes two coagulation proteins—factor V and factor VIII. Tissue factor pathway inhibitor (TFPI), antithrombin III (ATIII), heparin cofactor II (HCII), and annexin V are also important constituents of thromboresistance.

underlying basement membrane, and a layer of myointimal cells). A structurally and functionally normal coronary artery vasodilates in response to acetylcholine, physical exercise, or mechanical provocation. By contrast, an atherosclerotic coronary artery undergoes paradoxic vasoconstriction when exposed to acetylcholine, and a progressive decrease in cross-sectional luminal area follows rapid ventricular pacing. The failure to vasodilate prevents an increase in physiologic blood flow and, in addition, subjects the endothelial surface to excessive shear stress.

Recently it has become apparent that hypercholesterolemia in and of itself may adversely affect endothelial cell function (even before the development of atherosclerosis). Even though it is morphologically intact, the vascular endothelium in areas of intimal atherosclerosis fails to release nitric oxide *(13)*. Hypercholesterolemia has been shown to impair endothelium-dependent vascular relaxation in coronary resistance vessels—the vascular bed responsible for regulating myocardial perfusion *(14)*.

Vascular endothelial cells are strategically positioned to play an important role in the regulation of local vascular clotting processes. The cells are also ideally positioned to promote thrombosis following vascular injury. Damaged or "perturbed" endothelial cells, however, can lose their ability to maintain thromboresistance and can, in fact, promote pathologic thrombosis. Indeed, assembly of the complete coagulation pathway can take place on the endothelial surface of atherosclerotic vessels. Moreover, impaired local fibrinolytic activity can prevent clot dissolution.

Even the earliest stages of coronary atherosclerosis are associated with decreased endothelium-dependent dilation of the microvasculature, which may impair epicardial blood flow and increase cell-vessel wall, interactions *(15)*.

In addition to losing its thromboresistant capabilities, the dysfunctional vascular endothelium can become directly prothrombotic. Following vascular injury, endothelial cells amplify the coagulant response through the synthesis and expression of factors VIII, IX, and X *(16,17)*. Moreover, an abnormal endothelium can produce tissue factor, impair fibrinolytic activity, and decrease the effectiveness of the APC-mediated anticoagulant pathway (probably by impairing thrombomodulin-thrombin interactions on the endothelial surface) *(18)*.

Endothelial Response to Thrombotic Stimuli

Complete thromboresistance includes an appropriate response to thrombotic stimuli, preventing thrombus growth. Unfortunately, dysfunctional endothelial cells lose their

ability to synthesize and secrete proteins capable of inhibiting platelets and coagulation proteins. A prime example is the response to thrombin. Under normal circumstances thrombin stimulates platelet-mediated vasoconstriction (caused by thromboxane A_2 release), which is prevented by the simultaneous thrombin-induced release of prostacyclin and nitric oxide from endothelial cells. In atherosclerotic vessels, the response to thrombin is almost entirely vasoconstrictive (and thrombotic) *(19)*.

Macroscopic View

Coronary atherosclerosis, the most common underlying condition among patients with acute coronary syndromes, has been described macroscopically over the past century and a half by astute pathologists and clinicians ranging from Von Rokitansky and Virchow to Osler. The pathologic sequence of events includes an initiating step, defined as the fatty streak, followed by plaque maturation and transition, setting the stage for intravascular thrombosis. The progression of coronary atherosclerosis varies widely among individuals, as does the time course and influence of recognized risk factors (Fig. 3).

Microscopic View

Recent observations at the microscopic and cellular levels have contributed substantially to unraveling several of the mysteries that surround human atherosclerosis and have allowed a clearer view of the mechanisms leading to intravascular thrombosis. It is now evident that the atherosclerotic plaque and its cellular components represent an ideal substrate for thrombus formation; one is naturally led to the conclusion that coronary atherosclerosis represents the most common and widespread prothrombotic state.

Developmental Anatomy and Cellular Biology

In experimental animals focal sites of predilection for either spontaneous or dietary-induced atherosclerosis can be determined reliably prior to plaque development. These areas are delineated by their in vivo uptake of the protein-binding azo dye Evans blue. Salient features of these "lesion-prone areas" include increased endothelial permeability to an intimal accumulation of plasma proteins, including albumin, fibrinogen, and low-density lipoproteins (LDL). There is also increased endothelial cell turnover. Overall, the "prelesion" area within endothelial cells takes on a unique appearance, and the surface glycocalyx is two- to fivefold thinner than normal endothelial cells *(20)*.

Lesion-prone areas within blood vessel walls exhibit the property of blood monocyte recruitment, followed by accumulation of these cells in the subendothelial space, a process that is accelerated in the presence of hyperlipidemia. Based on the available information, it appears that at least two processes are pivotal in the initiation of atherosclerosis: (1) an enhanced focal endothelial transcytosis of plasma proteins, including LDL, which accumulate in the widened proteoglycan-rich subendothelial space; and (2) the preferential recruitment of blood monocytes to the intima, a process that is markedly augmented by even a short period of hyperlipidemia. Thus, the lesion-prone subendothelial space has two key participants in atherosclerosis, namely, the monocyte (macrophage) and LDL.

Monocyte recruitment in the intimal space of lesion-prone areas is thought to be mediated by an enhanced generation of chemoattractants of which monocyte chemoattractant protein-1 (MCP-1), a cationic peptide synthesized and secreted by both arterial smooth muscle cells and endothelial cells, is of particular importance. It is also recognized that the production of MCP-1 is stimulated by minimally modified (oxidized) LDL, whereas oxidized LDL itself is chemotactic *(21)*.

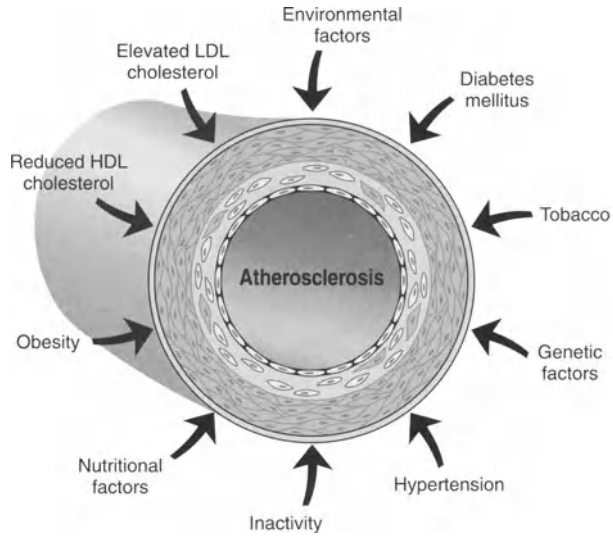


Fig. 3. Atherosclerosis is the end result of numerous risk factors, acting either alone or in combination. The overall impact of any given risk factor(s) is probably determined by genetic regulatory mechanisms.

Atherosclerotic Plaque Growth and Development

After monocytes (activated) attach to the morphologically intact but dysfunctional endothelium (receptive stage), there is a net directed migration of monocytes through the endothelium to the subendothelial space, where they undergo differentiation. The phenomenon of monocyte activation–differentiation plays an important role in atherosclerosis, particularly with regard to plaque remodeling and lesion progression. This complex process proceeds by means of at least two mechanisms: (1) the generation of reactive oxygen species (free radicals); and (2) the phenotypic modulation of expression of the scavenger receptor or family of receptors. The chemical modification of LDL results in its avid uptake by monocytes (now considered macrophages), and the subsequent transformation to foam cells follows. The specific receptor responsible for the uptake of modified LDL fails to downregulate; as a result, a substantial amount of intracellular LDL cholesterol accumulates. When the influx of LDL particles exceeds the capacity of the macrophage scavenger receptors to remove them from the intracellular space, oxidized LDL particles accumulate within the arterial intima (Fig. 4A). These particles are cytotoxic, causing both injury and death to endothelial cells, smooth muscle cells, and macrophages. The net result is disruption of the relatively fragile macrophage-derived foam cells, leading to release of their intracellular lipid into the extracellular compartment of the intima; this sequence of events gives rise to the origin of the pultaceous cholesteryl ester-rich core of the atherosclerotic plaque (Fig. 4B) *(22–25).*

Lipid Core

The release of copious foam cell lipids to the extracellular compartment induces a second cascade of inflammatory responses within the vascular intimal layer. In particular, granulomatous foci involving macrophages, lymphocytes, and multinucleate giant cells surround and invade the extracellular lipid.

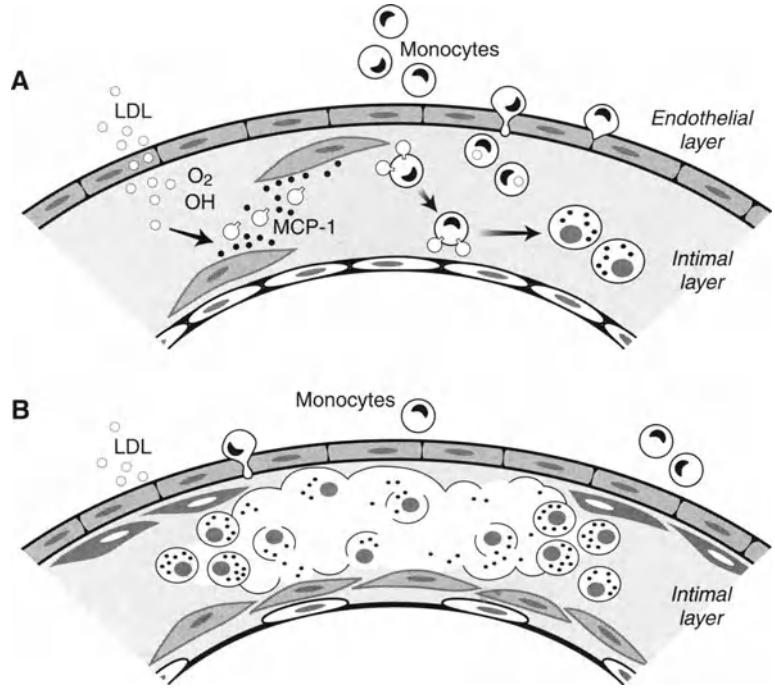


Fig. 4. (A) The Initial step in atherosclerosis involves monocyte and low-density lipoprotein (LDL) binding to an altered endothelial surface (receptive stage). Monocyte activation and chemical modulation (oxidation) of LDL (modified LDL) results in avid uptake and transformation to macrophages (foam cells). Transformed smooth muscle cells synthesize and secrete monocyte chemotactic proteins (MCP) that participate in monocyte recruitment and migration within the intimal layer. **(B)** The influx of modified LDL exceeds the capacity of macrophage surface receptors (impaired downregulation), allowing accumulation of potentially cytotoxic LDL particulars in the extracellular space. This step is central to the development of the necrotic (lipid) core.

Besides foam cell death, what other mechanisms can account for the formation of extracellular lipid deposits? New lines of evidence suggest that lipoproteins, particularly LDL, aggregate and then fuse with one another in the extracellular space to form microscopically evident lipid deposits *(26–32)*. Structures resembling lipoprotein aggregates have been visualized in human atherosclerosis by electron microscopy, and lipid aggregates containing apolipoprotein B (apo B) have also been isolated.

A number of proteins and peptides have been detected in relative abundance within or near the atherosclerotic core. Many of the proteins found in this region are relatively hydrophobic, including the apolipoproteins, C-reactive protein, and the 70- and 60-kDa heat shock proteins. A list of proteins and peptides detected by immunologic methods in the atherosclerotic lipid core is given in Table 1.

Cells that border and penetrate the atherosclerotic core not only participate in the deposition (or removal) of core lipids but can also be influenced by the accumulating lipids and proteins. Complement components have been found in relative abundance in the core, and both toxic and chemotactic responses may be generated via activation of complement. Antigenic markers of complement activation, including C3D and the terminal C5B-9 neoantigen, have been found in the atherosclerotic core, and terminal

Table 1
Proteins and Peptides Found
in the Lipid Core of Atherosclerotic Plaques

Myeloperoxidas	Heat shock protein 60
Hyaluronectin	Heat shock protein 70
Albumin	Fibrinogen
C-reactive protein	Tissue factor
Complement factor C3	Apolipoproteins
C56-9 neoantigen	Apo B
	Apo A
	Apo E

C5B-9 has been detected coincident with the cholesterol-rich vesicles in the subendothelium *(33–38)*.

Plaque Rupture

The clinical expression of atherosclerotic disease activity is determined by pathologic events leading to coronary thrombosis. In this regard, there are two key factors: (1) the propensity of plaques to rupture, and (2) the thrombogenicity of exposed plaque components.

The morphologic characteristics of plaques that determine their propensity to rupture have been determined from analysis of lesions exhibiting disruption. Observational studies conducted by pathologists using necropsy and atherectomy tissue samples have shown convincingly that plaques causing intraluminal thrombosis are rich in extracellular lipid and that the lipid core of these "vulnerable or rupture-prone" plaques occupies a large proportion of the overall plaque volume. The degree of cross-sectional stenosis involving the vessel lumen is typically <50% *(39)*. In addition to the predominant lipid core, vulnerable plaques are characterized by a thin fibrous cap and high macrophage density *(40)*. Whereas most individuals with atherosclerotic coronary artery disease exhibit a diversity of plaque types, most have a preponderance of one specific type (vulnerable or nonvulnerable) (Fig. 5). The genetic and acquired determinants of plaque type are subjects of intense investigation.

The lipid core of an advanced atherosclerotic plaque is bounded in its luminal aspect by a fibrous cap, at its edges by the shoulder region, and on its abluminal side by the plaque base. Because the lipid core contains a substantial amount of prothrombotic substrate (to be discussed in a subsequent section), the fibrous cap, separating the core from circulating blood components within the vessel's lumen, determines the overall stability of the plaque. In turn, the extracellular matrix of the fibrous cap, consisting of several proteinaceous macromolecules, including collagen (types I and III) and elastin secreted by transformed smooth muscle cells, determines its integrity.

The point should once again be made that core size and fibrous cap thickness are *not* related to absolute plaque size nor to the degree of luminal stenosis. The determinants of core size have not been fully elucidated, although death of lipid-filling macrophages by apoptosis (programmed cell death) is a possibility. Fibrous cap thickness appears to be related to macrophage and smooth muscle cell activity, particularly their production of metalloproteinases that degrade connective tissue.

Matrix metalloproteinases, part of a superfamily of enzymes that include collagenases, gelatinases, and elastases, require activation from proenzyme precursors to attain

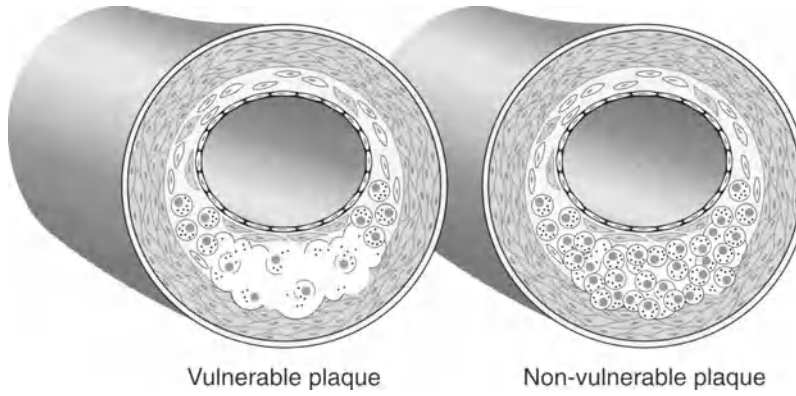


Fig. 5. Vulnerable plaques are typified by (1) a prominent lipid core; (2) a thin fibrous cap; and (3) high macrophage density located at the plaque shoulders. By contrast, nonvulnerable plaques contain few extracellular lipid particles and are fibrotic, making disruption a less common occurrence.

enzymatic activity. Under normal circumstances, tissue inhibitors hold these enzymes in check; however, exposure of smooth muscle cells to the cytokines IL-1 and tumor necrosis factor-α (TNF-α) causes induction of interstitial collagenase and stromelysin. Macrophages exposed to inflammatory cytokines also stimulate the production of matrix-degrading enzymes *(41–43)*.

Coronary atherectomy specimens from patients with acute coronary syndromes have been shown to contain a 92-kDa gelatinase that is produced predominantly by macrophages and smooth muscle cells *(44)*. Within atherosclerotic plaques, the highest stress regions have a twofold greater matrix metalloproteinase (MMP-1) expression than the lowest stress regions. Overexpression of MMP-1 in vulnerable plaques is associated with a substantial increase in circumferential stress. Degradation and weakening of the collagenous extracellular matrix at critical points of high shear stress may play an important role in the pathogenesis of plaque rupture.

Fibrous cap thickness can be maintained by smooth muscle cell-mediated collagen synthesis (local repair); however, interferon-γ (IFN-γ), an inflammatory cytokine found within atherosclerotic plaques, decreases the ability of smooth muscle cells to express the collagen gene. Because only T-lymphocytes can elaborate IFN-γ *(45,46)*, it has been suggested that chronic immune stimulation within atherosclerotic plaques leads to the production of IFN-γ from T-cells that subsequently inhibits collagen synthesis in vulnerable regions of the fibrous cap. IFN-γ can also contribute to apoptosis and, therefore, may be a key biochemical determinant of plaque vulnerability (Fig. 6).

The recent observation that mast cells may be involved with macrophage/foam cell development has raised questions concerning their potential involvement in plaque rupture. Human mast cells contain proteoglycans and proteolytic enzymes, including chymase and tryptase. In normal coronary arteries, mast cells amount to 0.1% of all nucleated cells; however, within the fibrous cap, lipid core, and shoulder regions of atheromatous lesions, there are 5-, 5-, and 10-fold increased densities, respectively *(47)*. Electron and light microscopic studies of mast cells in the plaque shoulder region have revealed evidence of degradation, a sign of activation that may contribute to matrix degradation and plaque rupture in acute coronary syndromes *(48)*.

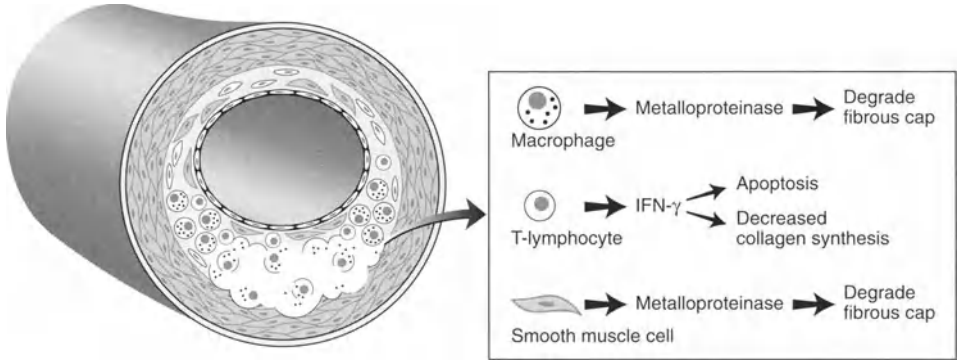


Fig. 6. Plaque vulnerability is determined by both structure and intrinsic activity. Macrophages and smooth muscle cells synthesize and secrete matrix metalloproteinases that can degrade the fibrous cap. Interferon-γ (IFN-γ), an inflammatory cytokine secreted by T-lymphocytes, participates in programmed cell death (apoptosis) and inhibits collagen synthesis, thereby weakening the plaque's supporting framework.

Models of Plaque Rupture

Shear stress. The coronary arterial intimal surface is constantly exposed to the dynamic influences of circulating blood that creates shear stress. Assuming a constant viscosity, shear stress is described by the following formula: $T = U\mathrm{d}v/\mathrm{d}r$, where U is viscosity, V is velocity, and r is the radius of the vessel. Within arterial segments containing laminar flow, shear stress (τ) = $4\,\mu Q/\mathrm{p}r^3$. Therefore, shear stress is directly proportional to flow (Q) and inversely proportional to the cube of the vessel's radius. In coronary atherosclerosis the lumen is reduced in size and there is increased flow velocity. The end result is increased shear stress.

Interestingly there is evidence *(49)* that atherosclerosis typically develops in low-flow/low-shear stress segments of the coronary arterial tree. Low-shear stress may also contribute, at least initially, to impaired vasoreactivity and thromboresistance by reducing the local stimulus to both prostaglandin and nitric oxide synthesis and release. It appears that unsteady (turbulent) flow is particularly detrimental to endothelial cell function *(50)*.

In contrast to plaque development, plaque disruption occurs most often in regions of high shear stress.

Wall stress. Plaque rupture occurs when the forces acting directly on the plaque exceed its tensile strength. Pressure generated within the arterial lumen exerts both radial and circumferential force, which must be countered by radial and circumferential wall tension. According to the law of Laplace, T (circumferential wall tension) = pr/h, where p is the intraluminal pressure, r is the vessel radius, and h is the wall thickness. Thus, atherosclerotic vessels with a thickened intima and small internal diameter maintain relatively low wall tension. This may explain why plaque rupture is more likely to occur in vessels with less severe stenosis.

Stress distribution. Computer models have been developed to study the relative stress distribution within atherosclerotic coronary arteries *(51,52)*. Overall, the circumferential stress is greatest at the intimal layer. In plaques that contain a large lipid pool, most of the stress is localized to the overlying fibrous cap. As the stiffness of the cap increases, the

maximal circumferential stress shifts from the center of the cap to the lateral edges or "shoulder" region.

The thickness of the fibrous cap is a major determinant of circumferential stress and the plaque's predisposition to rupture. In the presence of a constant luminal dimension, there is increasing stress with enlargement of the lipid core. With increasing fibrous cap thickness, even in the presence of decreasing luminal area, circumferential stress decreases. Another important feature is the lipid core itself, which, because of its semi-fluid nature, bears very little circumferential stress. Instead, stress is displaced to the fibrous cap.

Frequency of stress. Much like fatigue fractures occurring in metal, the frequency, extent, and localization of stress play important roles in plaque rupture. Atherosclerotic plaques, particularly fibrous caps overlying large lipid cores, become progressively more stiff with increasing stress and frequency of stress. Elevations in heart rate have been slow to increase stiffness and circumferential stress at the plaque's shoulder regions *(53)*.

Triggers for Plaque Rupture

Triggering events for plaque rupture are among the most contemplated and investigated areas in cardiovascular medicine. It has become clear, however, that triggers have less impact when they occur in the absence of a vulnerable plaque. This important feature allows for the development of several lines of prevention. Potential triggers include plasma catecholamine surges and increased sympathetic activity, blood pressure surges, exercise, emotional stress, changes in heart rate and myocardial contraction (angulation of coronary arteries), coronary vasospasm and hemodynamic forces *(54–62)*. This subject is discussed in another chapter.

Prevention of Plaque Rupture

Plaque rupture is the end result of a dynamic interplay between factors *intrinsic* to the plaque itself and *extrinsic* factors. The intrinsic factors primarily relate to rupture vulnerability; the extrinsic forces deliver the final blow. Each can be addressed when contemplating options for prevention.

Lipid-lowering strategies, antioxidants, anti-inflammatory agents, inhibitors of macrophages and their secreted proteins, and gene therapy can be used individually or concomitantly to change the plaque's composition, making it less *prone* to rupture. β-Adrenergic blockers *(63)* and possibly angiotensin-converting enzyme inhibitors *(64)* can reduce extrinsic forces capable of causing damage. The future in both basic and clinical research undoubtedly will devote considerable time, effort, and resources to these areas. Our laboratories' major interest lies in the links among atherosclerosis, inflammation and thrombosis.

Cellular Plaque Components: Thrombogenicity of Individual Constituents

Pathologic studies performed on patients who died suddenly or who recently experienced an episode of unstable angina or MI often reveal intraluminal thrombus anchored to a ruptured atherosclerotic plaque. Primarily based on the results of in vitro experiments and studies conducted in static systems, the thrombogenic capacity of atherosclerotic plaques has been attributed to collagen, fatty acids, and phospholipids. Fuster and colleagues *(65)* recently investigated dynamic thrombus formation using an ex vivo perfusion chamber and reported that the greatest stimulus was, in fact, the atheromatous core, yielding a sixfold greater degree of platelet deposition and thrombus production than

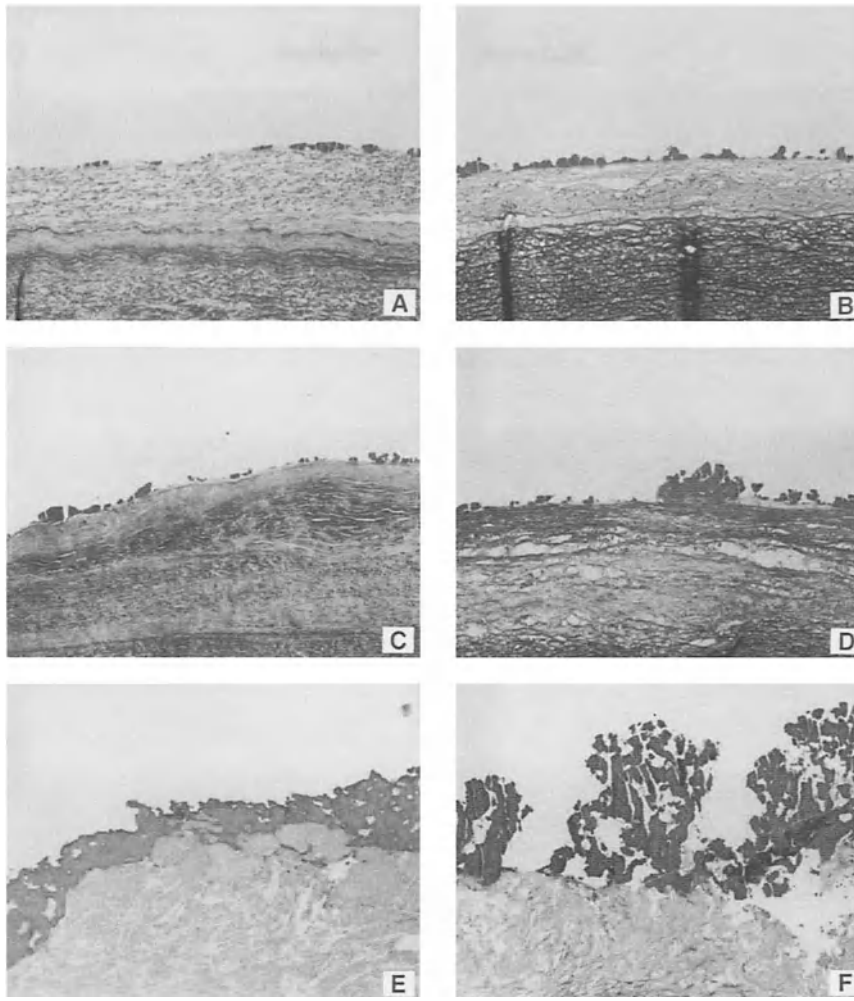


Fig. 7. Photomicrographs of varying tissue substrates found within the vessel wall and atheromatous plaque exposed to flowing blood. (**A**) Intima without lipid infiltration. (**B**) Foam cell-rich matrix. (**C**) Collagen-rich matrix. (**D**) Collagen-poor matrix without cholesterol crystals. (**E** and **F**) Collagen-poor matrix with abundant cholesterol crystals. Constituents within the core are the most thrombogenic (From ref. *65*, with permission.) (*see* color plate 1 appearing after p. 48)

other substrates, including foam cell-rich matrix, collagen-rich matrix, collagen-poor matrix without cholesterol crystals, and segments of normal intima (Fig. 7). Although research is ongoing, there is mounting evidence that tissue factor is the predominant thrombogenic mediator found within the atheromatous core. This substrate will be discussed in a section to follow.

VASCULAR THROMBOSIS

Under normal physiologic conditions, blood components do not interact with an intact vascular endothelium. The exposure of circulating blood to disrupted or dysfunctional surfaces initiates a series of complex yet orderly steps that give rise to the rapid deposition

of platelets, erythrocytes, leukocytes, and insoluble fibrin, producing a mechanical barrier to blood flow.

In most instances, thrombosis occurring in the arterial system is composed of platelets and fibrin in a tightly packed network (white thrombus). By contrast, venous thrombi consist of a tightly packed network of erythrocytes, leukocytes, and fibrin (red thrombus).

The process of vascular thrombosis, particularly in the arterial system, is dynamic, with clot formation and dissolution occurring almost simultaneously. The overall extent of thrombosis and ensuing circulatory compromise is therefore determined by the predominant force that "shifts" the delicate balance. If local stimuli exceed the vessel's own thromboresistant mechanisms, thrombosis will occur. If, on the other hand, the stimulus toward thrombosis is not particularly strong and the intrinsic defenses are intact, clot formation of clinical importance is unlikely. In some circumstances, systemic factors contribute to or magnify local prothrombotic factors, shifting the balance toward thrombosis. A prime example is cigarette smoking. A recent study *(66)* found that male smokers who died suddenly were as likely to have plaque erosion as they were to have vulnerable plaque rupture underlying coronary thrombi. This pivotal observation confirms prior suspicions that smokers are at risk for coronary arterial thrombosis even in the absence of marked plaque disruption.

Overall, the site, size, and composition of thrombi forming within the arterial circulatory system is determined by

1. alterations in blood flow;
2. thrombogenicity of cardiovascular surfaces;
3. concentration and reactivity of plasma cellular components; and
4. effectiveness of physiologic protective mechanisms.

Critical Steps

Platelet Deposition

Platelets attaching to nonendothelialized or disrupted surfaces undergo adherence by activation and distribution along the involved area and subsequent recruitment to form a rapidly enlarging platelet mass. Under physiologic conditions this represents the primary step in hemostasis. In pathologic thrombosis, however, platelet adherence initiates a process that can escalate to an extent that causes circulatory compromise.

The process of platelet deposition involves

1. platelet attachment to collagen or exposed surface adhesive proteins;
2. platelet activation and intracellular signaling;
3. the expression of platelet receptors for adhesive proteins;
4. platelet aggregation; and
5. platelet recruitment mediated by thrombin, thromboxane A_2, and adenosine diphosphate.

Activation of Coagulation Factors

Thrombin is rapidly generated in response to vascular injury. It also plays a central role in platelet recruitment and the formation of an insoluble fibrin network. The thrombotic process is localized, amplified, and modulated by a series of biochemical reactions driven by the reversible binding of circulating proteins (coagulation factors) to damaged vascular cells, elements of exposed subendothelial connective tissue (especially collagen), platelets (which also express receptor sites for coagulation factors), and macrophages.

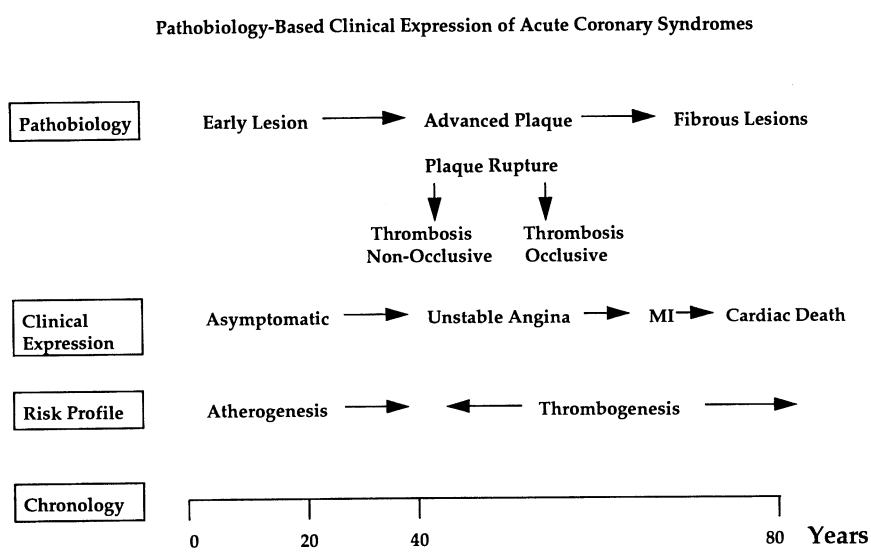


Fig. 8. Pathobiology-based clinical expression of acute coronary syndromes.

These events lead to an assembly of enzyme complexes that increases local concentrations of procoagulant material; in this way, a relatively minor initiating stimulus can be greatly amplified to yield a thrombus.

Fibrin Formation

The final phase in thrombus formation involves the generation of a stable fibrin network that provides the structural support for the circulating blood's cellular elements and the scaffolding for vascular remodeling. In this pivotal process, thrombin cleaves two small peptides, fibrinopeptide A and fibrinopeptide B, to form fibrin monomers, which in turn polymerize to form soluble fibrin strands. An orderly assembly, branching, and lateral association of fibrillar strands follows, terminating with factor XIII-mediated covalent crosslinking to form a mature fibrin network (mature thrombus).

Pathology of Thrombotic Events

There is evidence that the growth of atheromatous plaques occurs in a stepwise yet dynamic fashion in response to vascular injury. The clinical expression of a broad potential of pathobiologic events ranges from asymptomatic plaque growth to complete coronary arterial occlusion with a fatal outcome (Fig. 8).

James Herrick (1912) *(67)* is credited with describing the association between acute coronary thrombosis with MI, paving the way toward a greater understanding of acute coronary syndromes. Support for the *disrupted plaque theory* as a precipitant or nidus for luminal thrombosis can be traced to the work of Saphir et al. (1735) *(68)*, followed by the astute observations of Chapman (1965) *(69)*, Constantindines (1966) *(70)*, Bouch and Montgomery (1970) *(71)*, Ridolfi and Hutchins (1977) *(72)*, Falk (1983) *(73)*, and Davies and Thomas (1985) *(74)*. Additional support for the role of thrombosis-mediated processes in clinical events can be found in autopsy-based series that have revealed coronary microthrombi among patients with sudden cardiac death *(73,74)*.

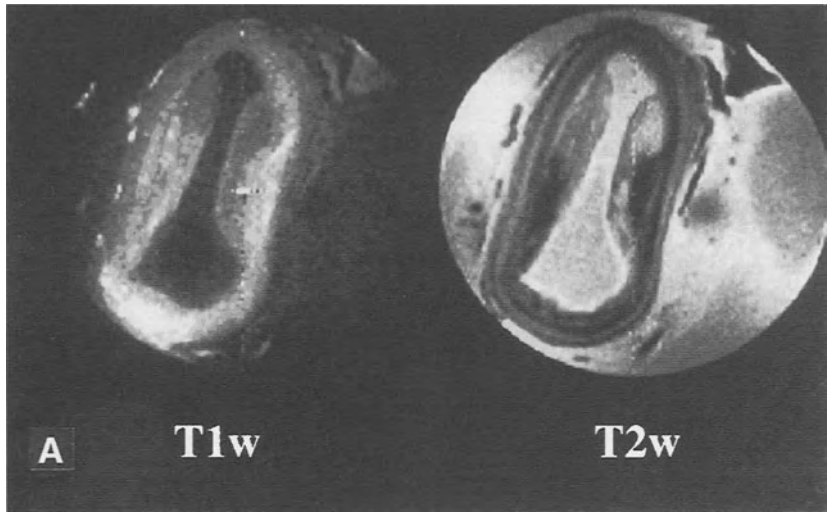


Fig. 9. (A) Nuclear magnetic resonance (NMR) images of a fatty plaque. The TZW image differentiates the lipid-rich region better. **(B)** Trichrome stain of fibrofatty plaque showing opposing plaques and circumferential intimal thickening. **(C)** Sudan black stain of atheromatous plaque. The lipid core (black) is covered by a collagenous cap. (From ref. *79*, with permission.)

Theory of Dynamic Plaque Disruption and Arterial Thrombosis

Despite early views, the evidence suggests that plaque disruption and coronary arterial thrombosis are *not* random events in atherosclerosis, rather the process is sudden and dynamic. In a series of 42 patients undergoing coronary angiography before and after MI, Little and colleagues (1988) *(39)* found that most had a stenosis of <50% of the infarct-related vessel *prior* to the event. Similar findings were reported by Taeymans et al. *(75)*. Computer-based modeling also supports the dynamic nature of coronary occlusion *(76)*. Comparing a rigid stenosis and a dynamic stenosis in which proximal vessel constriction and distal collapse were simulated, the latter model (with an added potential for vasoconstriction and passive collapse) required a much smaller thrombus burden for complete occlusion.

Atherosclerotic Plaque Imaging

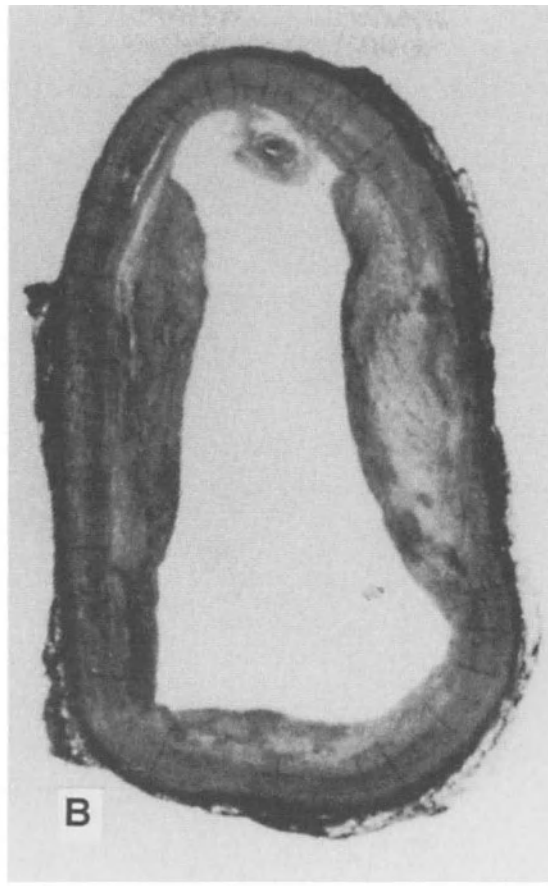
Intracoronary ultrasound has been used to assess plaque morphology and composition with the hope that it may also predict vulnerability to rupture *(77,78)*. Large sonolucent zones correlate with the lipid core, whereas echodense regions represent more fibrous material that is less likely to disrupt and precipitate intraluminal thrombosis.

Nuclear magnetic resonance (NMR) images without chemical-shift selection can characterize the components of human atherosclerotic coronary arteries *(79)*. In the atheromatous core, the water NMR signal predominates over that of lipid (lipid to water ratio, 0.11). The water relaxation constants (T_1 and T_2) differ for the lipid core, the fibrous cap, and the normal media (Fig. 9).

CLINICAL EXPRESSION OF PATHOBIOLOGICAL EVENTS

Acute Myocardial Infarction

Occurring in upwards of one million individuals yearly in the United States, ST-segment elevation (Q-wave) MI represents the most commonly observed arterial throm-



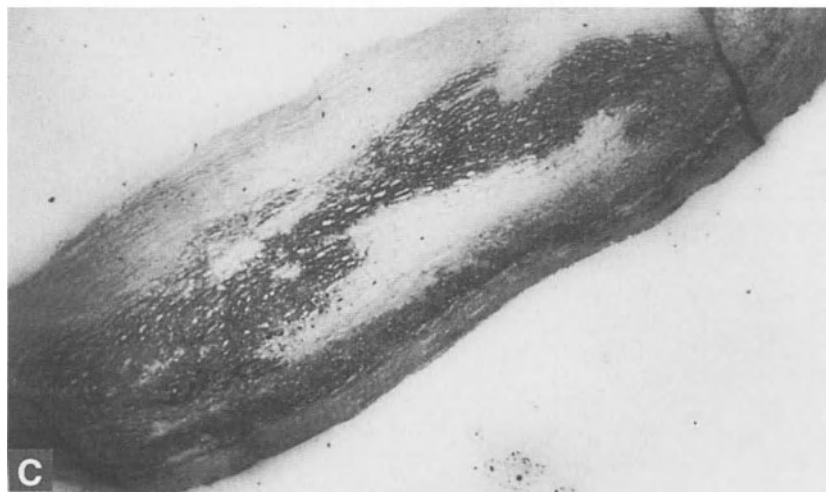


Fig. 9. (*continued*)

botic event in clinical practice. In the vast majority of cases, fissuring or rupture of an atherosclerotic plaque within a major epicardial coronary artery is followed by *occlusive* thrombosis, typically anchored to the damaged vascular surface and exposed plaque components.

It is of interest and of clinical importance that plaque rupture does not occur randomly throughout the coronary tree. Instead, there are "vulnerable" sites located in

1. the proximal portion of the left anterior descending coronary artery;
2. the right coronary artery near the origin of its marginal branch; and
3. the left circumflex coronary artery at the origin of the first obtuse marginal branch.

In general terms, the severity of vessel wall injury determines the extent of thrombosis. *Mild injury* (type I) is typically associated with the deposition of platelets in a single (nonocclusive) layer. *Moderate injury* (type II) provokes a loosely adherent platelet mass that can quickly be dispersed by normal blood flow. *Severe injury* (type III) leads to platelet adherence, activation, and stimulation of the coagulation cascade, producing an occlusive thrombus. Type III injury is present in most of patients with MI.

Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction

Angiographic, angioscopic, and pathologic studies have shown that atherosclerotic plaque rupture accompanied by varying degrees of intraluminal thrombosis is the primary pathologic event in unstable angina/non-ST segment elevation (non-Q wave) MI. Although considered an intermediate step in a continuum of advanced atherosclerosis and acute coronary syndromes, unstable angina and non-ST-segment elevation MI may, in fact, represent unique cardiac events. Mounting evidence suggests that chronic, recurrent plaque rupture of mild to moderate severity may be responsible. Thrombosis occurs with each episode but typically is not of adequate mass (clot burden) to compromise coronary arterial blood flow. Over time, however, plaque growth occurs, obstructing the coronary lumen. Thus, the obstructive lesion is a combination of mature plaque and layers of aged thrombus, consisting primarily of platelets in a tightly packed fibrin network.

In some patients, non-ST-segment elevation MI has clinical features reminiscent of ST-segment elevation MI, progressing suddenly because of plaque rupture and occlusive intracoronary thrombosis. Experience has shown that these patients frequently have multivessel coronary artery disease and therefore represent a high-risk group.

Most patients with unstable angina/non-ST-segment elevation MI have advanced underlying atherosclerotic coronary artery disease with nearly uniform distribution of single, double, and triple vessel involvement. The available evidence suggests that the clinical conversion from asymptomatic or stable angina to unstable angina is a direct result of pathologic changes within the atheromatous plaque, specifically plaque fissuring, disruption, and intraluminal thrombosis. Angiographic studies have revealed a high prevalence of eccentric, irregular, narrow-necked stenoses with overhanging edges (type II lesion) and reduced Thrombolysis in Myocardial Infarction (TIMI) flow *(80)*. By contrast, patients with stable angina most often exhibit concentric, symmetric stenoses or eccentric, broad-necked stenoses (type I lesion) (Fig. 10).

The presence of intracoronary thrombosis and the overall thrombus burden has varied greatly in studies of patients within unstable angina/non-ST-segment elevation MI. On average, thrombus has been reported in 40–50% of patients. The variability can be traced to differences in clinical presentation (accelerated angina, angina at rest, postinfarction

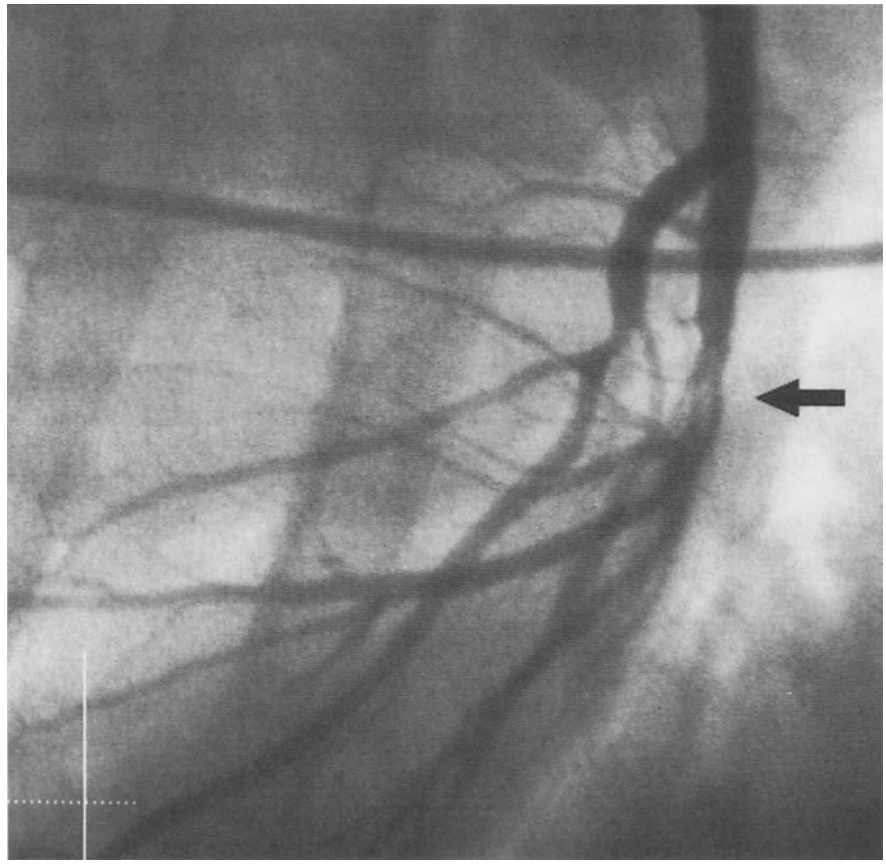


Fig. 10. Coronary angiogram in a patient with unstable angina revealing an intraluminal filling defect in the proximal aspect of the left anterior descending coronary artery.

angina), variability in electrocardiographic features (T-wave inversion, ST-segment shifts) the time frame of clinical assessment (early, late), and the method of imaging.

Coronary angioscopy has proved to be a useful tool in the evaluation of coronary arterial morphology. In a landmark study by Forrester and colleagues *(84)*, angioscopy was performed at the time of bypass grafting in 20 patients, 10 with unstable angina and 10 with advanced but clinically stable coronary artery disease. All patients with accelerated angina exhibited complex-appearing plaques (Fig. 11), and all patients with angina at rest had thrombus (Fig. 12). By contrast, patients with stable coronary disease had neither of these features. These observations, representing a pathobiology-clinical correlation "snapshot," suggest strongly that plaque morphology, in general, and intracoronary thrombosis, in particular, are major determinants of disease expression.

Pathologic Differences in Acute Coronary Syndromes

Although plaque disruption with thrombus formation has been associated with acute coronary syndromes, including unstable angina and MI, determinants of which particular entity within the spectrum of possibilities a patient will develop have not been fully elucidated. The challenge becomes greater when one considers that plaque disruption is

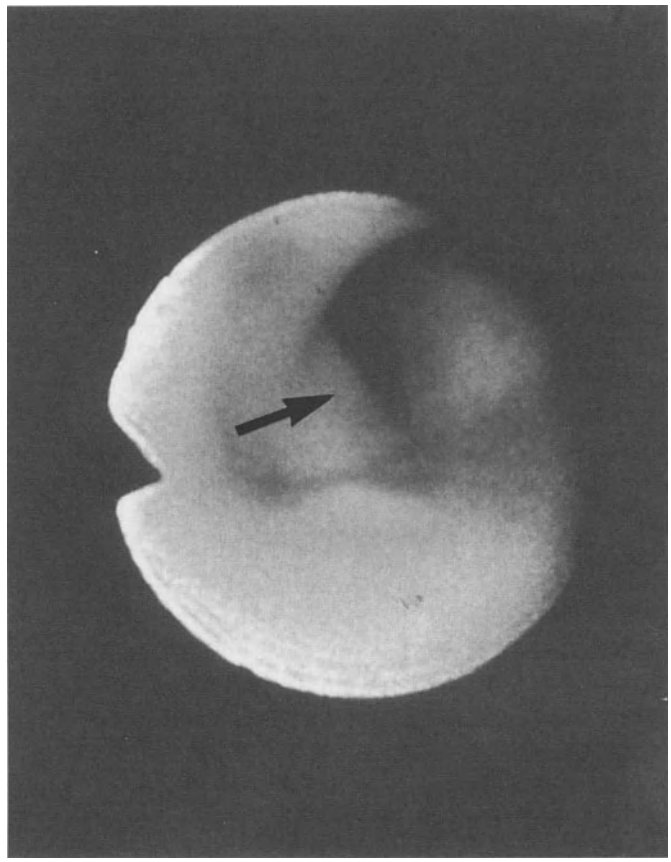


Fig. 11. Coronary angioscopy in a patient with accelerated angina. An eccentric plaque with disruption is evident (arrow). (From ref. *156*, with permission.) (*see* color plate 2 appearing after p. 48)

not an uncommon event, yet only certain individuals experience symptoms, as a clinical expression of mechanical and biochemical events, that are contained within the vast nature of acute coronary syndromes.

The available evidence suggests that although plaque rupture is a common theme in acute coronary syndromes, the degree and composition of the associated thrombus burden differs. Percutaneous angioscopy performed in patients with unstable angina frequently reveals gray-white nonocclusive thrombi; reddish occlusive thrombi are seen in patients with acute MI. These characteristics suggest that unstable angina is a platelet-mediated phenomenon and, by contrast, acute MI is predominantly fibrin-mediated. Autopsy-based studies have drawn similar conclusions. In a study of 14 patients with unstable angina and 32 patients with a fatal first MI, Kragel et al. *(85)* observed a predominance of platelets within nonocclusive thrombi in those with a diagnosis of unstable angina, whereas thrombi in patients with acute MI consisted almost entirely of fibrin and were occlusive. The investigators also found that the extent or depth of plaque rupture, approximated by the presence of hemorrhage, was less in patients with unstable angina when compared with those with acute MI (Table 2).

The question then remains: what are the determinants of disease progression (or suppression) and clinical expression in acute coronary syndromes? Our group has shown that

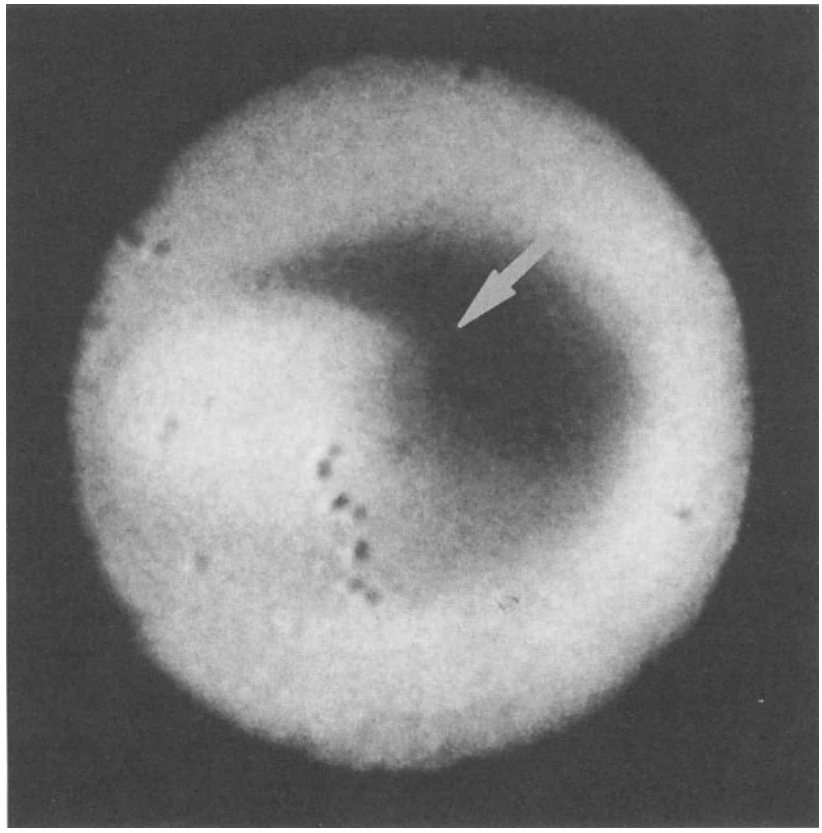


Fig. 12. Coronary angioscopy in a patient with angina at rest. Intraluminal thrombus (nonocclusive) is visualized (arrow). (From ref. *156*, with permission.) (*see* color plate 3 appearing after p. 48)

patients with unstable angina and non-ST-segment elevation MI exhibit varying degrees of platelet activation and thrombin generation, suggesting not only that the thrombotic stimulus may differ, but that regulation of thrombus growth may as well. A study of 543 apparently healthy men participating in the Physicians' Health Study *(86)* in whom MI (or ischemic stroke) occurred identified an elevated baseline C-reactive protein as being predictive (relative risk 2.9) of subsequent thrombotic events. Perhaps the extent or degree of inflammation (accompanied by endothelial cell dysfunction and prothrombotic biochemical mediators) is a prime determinant of atherosclerotic disease expression (Table 3).

MOLECULAR BIOLOGY, BIOCHEMISTRY, AND EMERGING CONCEPTS IN ARTERIAL THROMBOSIS

Tissue Factor

The initial hemostatic response to vessel wall injury, which is designed to prevent blood loss from the circulation, is generally regarded as a relatively short-term event preceding a more prolonged process of vascular repair. Shortly after tissue injury, including even superficial trauma to the endothelium, thrombin-like activity can be detected that persists for weeks thereafter *(87–89)*. The expression of tissue factor mRNA and

Table 2
Morphologic Characteristics
of Coronary Arteries in Patients with Acute Coronary Syndromes[a]

Clinical diagnosis	*No. of patients*	*Thrombus*	*Composition*	*Plaque rupture*	*Plaque hemorrhage*	*Multiluminal channels*
Unstable angina	14	4 (29)	Platelets, nonocclusive	5 (36)	3 (21)	14 (100)
Acute myocardial infarction	32	22 (69)	Fibrin, occlusive	33 (49)	27 (40)	60 (90)

[a]Data are numbers, with percent in parentheses.

Table 3
Theoretical Determinants of Clinical Expression and Cardiac Events in Coronary Atherosclerosis

Vascular endothelium	*Atherosclerotic plaque*	*Coronary artery*	*Systemic factors*
• Vasoreactivity	• Composition	• Degree of stenosis • Site and flow characteristics of stenosis	• Platelets • Activatability
• Thromboresistance	• Depth of rupture	• Extent of disease	• Coagulation factors • Prothrombotic state
• Regeneration capacity	• Inflammatory response	• Collateral circulation	• Neuroendocrine status • Sympathetic tone • Renin-angiotensin tone
• Prothrombotic potential	• Redox state • Diet • Gender	• Preconditioning	• Age
• Preconditioning	• Passivatibility • Platelets • Genetic regulation		• Preconditioning • Coagulation factors

antigen within atherosclerotic plaques has been characterized by *in situ* hybridization and immunohistochemistry *(90)*. In atherectomy specimens obtained from human carotid arteries, tissue factor mRNA and antigen can be detected in macrophages, mesenchymal intimal cells, and extracellular matrix *(91)*. Patients with unstable angina demonstrate high concentrations of tissue factor antigen and activity within coronary atherectomy specimens *(92)*, and it has been suggested that this potent procoagulant protein found within the lipid core may be released from macrophages during cell death or in the form of shed vesicles *(93)*.

Tissue factor serves as both a receptor and an essential cofactor for coagulation factors VII and VIIa. The biomolecular complex of tissue factor VIII/VIIa activates factors IX and X by limited proteolysis, leading to thrombin generation (Fig. 13).

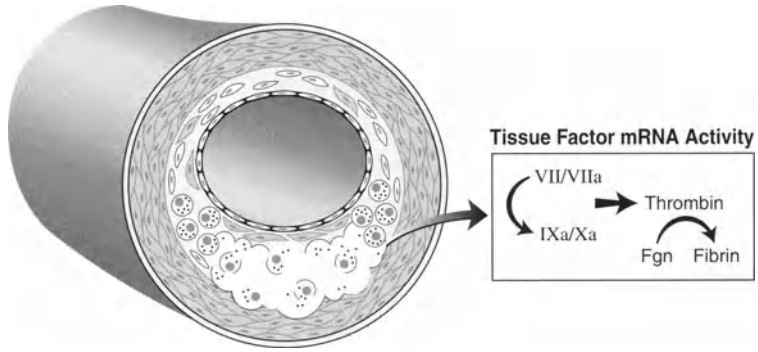


Fig. 13. Tissue factor is a receptor and an essential cofactor for intravascular coagulation, particularly after plaque disruption. In addition to activating factor X directly (extrinsic coagulation cascade) the TF-VII_a complex generates thrombin (and the conversion of fibrinogen [FgN] to fibrin) via the instrinsic coagulation cascade by factor IX activation (cascade crossover).

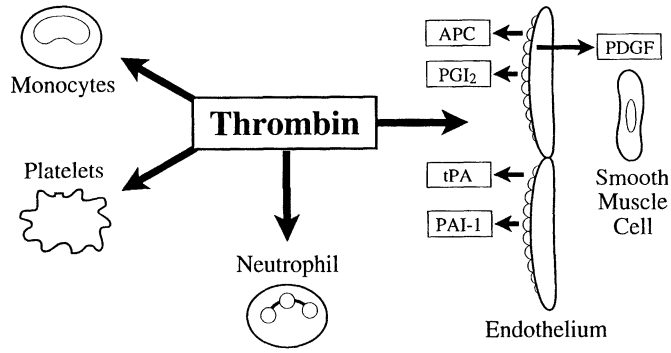


Fig. 14. In addition to serving as the pivotal enzyme for all coagulation processes, thrombin exhibits a broad range of direct cellular activating (and inhibiting) properties as well. Platelet, monocyte, and neutrophil activation may be particularly important in the maintenance of an inflammatory prothrombotic environment. Thrombin's effect on dysfunctional endothelial cells includes increased plasminogen activator inhibitor (PAI-1) secretion and decreased activated protein C (APC) secretion. Thrombin-mediated platelet-derived growth factor (PDGF) synthesis participates in smooth muscle cell migration and plaque growth. Prostacyclin (PGI_2) and tissue plasminogen activator (tPA) secretion are decreased as well. The latter may also be functionally defective (impaired fibrinolytic potential).

Thrombin and the Thrombin Receptor

Thrombin, a multifunctional serine protease generated at sites of vascular injury, is a potent platelet activator and possesses a variety of actions on inflammatory cells, the vascular endothelium, and smooth muscle cells. Arterial wall-associated thrombin activity is expressed following coronary angioplasty *(94)*, and thrombin bound to the subendothelial extracellular matrix is functionally active, localized, and protected from inactivation by circulating inhibitors *(95)*.

The multiple cell-activating functions of thrombin contribute to hemostatic, inflammatory, proliferative, and reparative responses of injured vessel walls (Fig. 14). In human atheroma, a functional thrombin receptor is expressed in regions rich in macrophages and

smooth muscle cells. Local thrombin generation in areas of dysfunctional endothelium and either fissured or ruptured atherosclerotic plaques activates surrounding cells, thereby contributing to plaque growth, inflammation, and thrombosis *(96)*.

Monocytes

As previously discussed, monocyte-endothelial interactions have been implicated in early atherosclerosis. Cultured endothelial cells exposed to monocytes release less nitric oxide, and the monocyte-derived cytokines, IL-1 and TNF-α, downregulate nitric oxide synthase *(97)*. Overall, the adhesion of monocytes to endothelial cells, as well as their secretory products, diminishes the steady-state levels of nitric oxide synthase, an event associated with an attenuated release of biologically active nitric oxide. The observed suppression is both monocyte concentration and time dependent *(98)*.

Nitric oxide is generated under basal conditions by vascular endothelial cells, and several lines of evidence suggest that the continuous tonic release of nitric oxide is important in maintaining normal vasoreactivity and thromboresistance by means of its potent vasodilating and platelet-inhibiting potential, respectively.

Tissue factor-based procoagulant activity has been demonstrated in vitro: monocytes exhibit a coagulant response to a variety of stimuli, including IL-1 and products of activated lymphocytes *(99)*. Macrophages derived from human atheromatous plaques also express procoagulant activity *(100,101)*. Activation of coagulation is an important component of the inflammatory response. After in vitro exposure to immune or nonimmune stimuli, monocytes express tissue factor on their surface *(102–105)*. Monocytes from patients with unstable angina express significant procoagulant activity; however, they must first bind to lymphocytes *(106)*. In addition, only activated lymphocytes can stimulate monocyte procoagulant activity.

The interaction between lymphocytes and monocytes (as well as other cells) is directly impacted by the expression of surface adhesion receptors that are increased among patients with acute coronary syndromes *(107)*. This important area warrants special consideration.

Cell Adhesion Molecules

In both physiologic and pathologic states cell surface receptors mediate the adhesion of cells (endothelial cells, monocytes, lymphocytes, neutrophils, smooth muscle cells, platelets) to one another and to structural components of the extracellular matrix. To date, six families of cell adhesion molecules have been described—integrins, selectins, immunoglobulins, adhesion molecules, proteoglycans, and mucins (Fig. 15).

Integrins comprise a superfamily of heterodimeric transmembrane proteins composed of noncovalently associated α– and β-subunits (Table 4). Thus far, 8 β-subunits and 12 α-subunits have been identified *(108–120)*. Integrins have been grouped according to their composition, which typically includes various combinations of α-subunits joined with a common β-subunit. Most integrins that bind matrix molecules recognize the tripeptide Arg-Gly-Asp (RGD) that can be found in fibrinogen, fibronectin, fibronectin, vitronectin, laminin, and type 1 collagen. Not all cellular interactions with matrix proteins are mediated by their RGD sequence.

Selectins are composed of a lectin domain, an epithelial growth factor domain, and complement regulatory-like molecules. P- and E-selectins bind to common sites of carbohydrates, and C-selectin binds to mucin-like endothelial cell glycoproteins. P-selectin (CD62, granule membrane protein, platelet activation-dependent granule external mem-

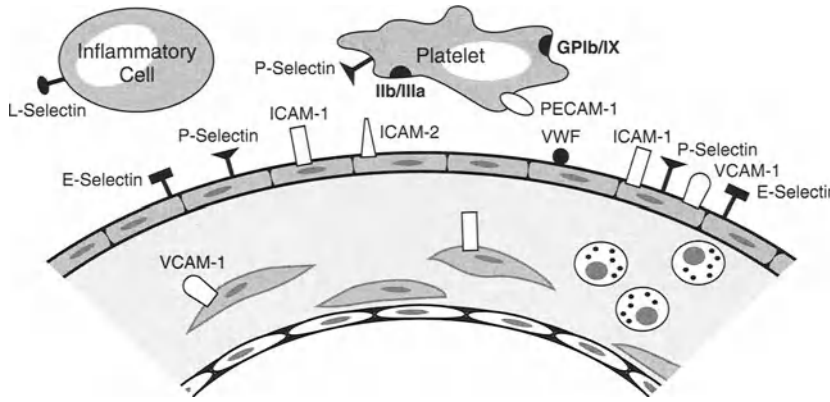


Fig. 15. The dysfunctional vascular endothelium and transformed intima and modified cellular components of the developing plaque are a virtual warehouse of inflammatory proteins and expressed receptors that mediate the adhesion of cells to one another and to structural components of the cell surface matrix. ICAM, (intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; PECAM, platelet endothelial cell adhesion molecule; vWF, von Willebrand factor; GP, glycoprotein.

Table 4
Major Integrins and Their Ligands

Integrin	*Ligands*
VLA integrins	
α, β_1 (VLA-1)	Laminin, collagen
α_2, β_1 (VLA-2)	Collagen, laminin
α_3, β_1 (VLA-3)	Fibronectin, laminin, collagen
α_4, β_1 (VLA-4)	Fibronectin, VCAM-1
α_5, β_1 (VLA-5)	Fibronectin
α_6, β_1 (VLA-6)	Laminin
Leukocyte integrins	
α_2, β_2	ICAM-1, ICAM-2
α_m, β_2	ICAM-1, fibrinogen, factor X
α_x, β_2	Fibrinogen
Cytoadhesions	
α_{IIb}/β_3	Fibrinogen, fibronectin, vitronectin
α_{Iv}, β_3	Vitronectin, fibrinogen, thrombospondin

ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule.

brane protein) can be found within platelet α-granules and endothelial cells (Weibel-Palade bodies). Because P-selectin binds to monocytes and neutrophils, it is felt to play an important role in platelet-leukocyte and endothelial cell-leukocyte interactions. The interaction of fibrinogen and P-selectin may have a particularly important role in regulating inflammatory and thrombotic responses (Table 5).

Table 5
Selectins: Cellular Distribution and Interactions

Cell	*Distribution binding*	*Site*
L-Selectin	All leukocytes	Endothelial cells
E-Selectin	Activated endothelial cells	Neutrophils, monocytes, T lymphocytes
P-Selectin	Platelets, endothelial cells (Weibel-Palade)	Neutrophils, monocytes, T lymphocytes

Table 6
Immunoglobulin Adhesion Molecules

Glycoprotein	*Distribution*
ICAM-1	Endothelial cells, fibroblasts, hematopoietic cells
ICAM-2	Endothelial cells, fibroblasts, hematopoietic cells
VCAM-1	Endothelial cells, smooth muscle cells
PECAM-1	Platelets, endothelial cells

ICAM, intracellular adhesion molecule; VCAM, vascular cell adhesion molecule; PECAM, platelet endothelial cell adhesion molecule.

Members of the *immunoglobulin* superfamily, including intercellular adhesion molecules (ICAM-1, ICAM-2) and vascular cell adhesion molecules (VCAM) play an important role in the transmigration of leukocytes. The cytokines TNF-α, IL-1, and IFN-γ stimulate the expression of ICAM on the vascular endothelial surface. Endothelial VCAM-1 supports the adhesion of lymphocytes, monocytes, eosinophils, and basophils. Platelet endothelial cell adhesion molecule (PECAM-1) exists on platelets, T-lymphocytes, and monocytes, suggesting that it contributes to leukocyte migration and thrombosis (Table 6).

Cadhesions represent a group of proteins whose major function is the maintenance of tight gap junctions and intercellular spacing within the vascular endothelium.

Proteoglycans constitute a large protein family with glycoaminoglycan side chains that mediate lymphocyte binding and epithelial cell binding to collagen, fibronectin, and thrombospondin. The glycoprotein Ib/IX complex is the most well-known cell adhesion molecule of the *mucin* family. It contains a thrombin-binding site and a von Willebrand factor binding site.

Cytokines and Inflammatory Responses

Histologic studies have shown that atherosclerotic plaques contain foci of monocytes, macrophages, and activated lymphocytes. The cytokine secretory capacity of monocytes expressing TNF, IL-1, IL-6, and IFN-γ is also increased. In a recent study *(121)*, the acute-phase reactants C-reactive protein and amyloid A protein were elevated in a majority of patients with unstable angina and identified those patients who were more likely to suffer an in-hospital ischemic/thrombotic event. The prognostic value of fibrinogen, an acute-phase protein directly involved with the cascade of events leading to thrombosis, has also been determined in patients with unstable angina and non-ST-segment elevation MI in whom elevations identify increased risk of spontaneous ischemia, MI,

and death *(122)*. Although fibrinogen may not reflect prothrombotic potential, it is a marker of atherosclerotic disease activity.

Patients with accelerated atherosclerosis and MI at a young age (<45 yr) frequently have detectable circulating immune complexes *(123)*. Similarly, patients with acute MI have increased plasma concentrations of IL-1, IL-6, IL-8, and TNF, and the intensity of the acute inflammatory response after infarction is associated with short-term mortality *(124)*. The inflammatory state also may determine the overall response to treatment *(125)*.

Plasminogen Activator Inhibitor-1

Plasminogen activator inhibitor (PAI)-1 is a globular glycoprotein with a molecular weight of 50,000 comprised of 379 amino acids in a single chain. The primary structure of PAI-1 designates it as a member of the superfamily of serine protease inhibitors (serpins), and it is structurally similar to other serpins, including angiotensinogen, antithrombin III, and α-2-antiplasmin. PAI-1 was first isolated by Van Mourik et al. *(126)* and has been cloned by several investigative groups *(127,128)*.

At least three distinct conformations of the intact PAI-1 molecule have been identified. In its latent form PAI-1 is not susceptible to cleavage by tPA nor does it form complexes with tPA. However, in its active form it is both susceptible to cleavage and does form complexes with the tPA molecule. The active form of PAI-1 is the inhibitory form of the molecule. In its conformation the reactive site of PAI-1 is readily accessible to cleavage by plasminogen activators; once this peptide bond is cleaved, a complex is formed between plasminogen activators and PAI-1. Thus, the active form of PAI has been appropriately termed a *suicide substrate*. It has a circulating half-life of approximately 60 min *(129)*.

Latent PAI-1 has been crystallized and its structure determined; it is inactive because part of its reactive centers is inaccessible to binding. Latent conformation of PAI appears to be a preferred state, and spontaneous reversions of latent PAI to an active state have not been described. However, if latent PAI is chemically denatured and allowed to refold, a fraction of the material will resume the active conformation *(130)*. It has been determined that most PAI-1 secreted into the blood is in the active state, although some of the PAI stored within platelets is inactive. The mechanisms responsible for activating latent PAI have not been fully described, but negatively charged phospholipids have been reported to activate the latent form of PAI in vitro *(131)*.

The primary source of PAI-1 in the circulation is thought to be the endothelium *(132)*; however, this is not the only synthetic site. Other sites of synthesis include the liver and vascular smooth muscle cells. Platelets store large quantities of PAI-1 that can be secreted following aggregation. Endothelial cells also have the capacity to secrete PAI-1 abluminally *(133–135)*. The relative abundance of vitronectin in the subendothelial matrix provides a mechanism for preserving PAI-1 activity. The PAI-1-vitronectin complex may represent the physiologically relevant form of the inhibitor in the extracellular matrix.

A wide array of compounds has been found to stimulate endothelial PAI-1 production. Inflammatory cytokines, including IL-1 and TNF can induce PAI-1 synthesis. Transforming growth factor-β, epidermal growth factor, and insulin can also stimulate PAI-1 production. Thrombin is a potent stimulus for PAI-1 in cultured endothelial cells *(136)*.

An excess of PAI-1 reduces the efficiency of the fibrolytic system, creating a permissive environment toward vascular thrombosis. There is compelling evidence that PAI-1 exists in excess quantities within human atherosclerotic vessels *(137)*. Elevated levels of

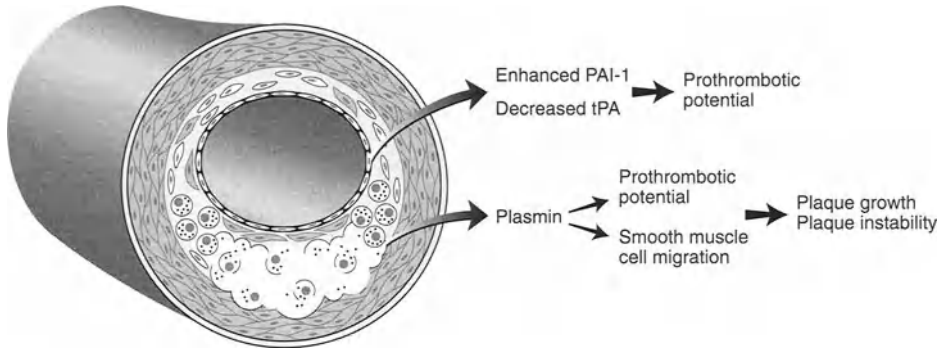


Fig. 16. Vascular plasminogen activators and their inhibitors play an important role in both plaque activity (predisposing to disruption) and thrombosis. TPA, tissue plasminogen activator; (PAI-1), plasminogen activator inhibitor.

PAI-1 are a risk factor for both venous and arterial thrombolic events. PAI-1 excess has been identified in young survivors of acute MI *(138)*. It has also found in excess among survivors of MI who subsequently experienced a second event (Fig. 16) *(139)*.

Plasma Fibrinolytic Factors

Lipoprotein (A) is composed of an LDL particle linked to a unique glycoprotein, apo A, which exhibits marked structural similarities to the plasma zymogen plasminogen. Experimental evidence suggests that increased levels of lipoprotein (A) impair fibrinolysis through binding to plasminogen receptors on fibrin, endothelial cells, mononuclear cells, and platelets.

Association of the Renin-Angiotensin System and Vascular Thromboresistance

Angiotensin II has been shown to promote the growth of vascular smooth muscle cells *(140,141)*, and it has been suggested that angiotensin-converting enzyme (ACE) inhibitors can reduce neointimal proliferation. Activity of the endogenous fibrinolytic system is regulated in large part by two proteins secreted by the vascular endothelium, tPA and its primary inhibitor PAI-1. Both endogenous tPA and PAI-1 have been implemented in the pathogenesis of thromboembolic disorders. Infusion of angiotensin II in low physiologic doses results in a rapid and significant increase in circulating levels of PAI-1 antigen *(142)*. Effects are apparent within 45 minutes of initiating the infusion; moreover, the effect of angiotensin II on PAI-1 production appears to be a simple dose-response relationship. Recent work suggests that angiotensin II preferentially induces the synthesis of PAI-1 I in both cultured endothelial cells and murine astrocytes *(143)*. In cultured endothelial cells, angiotensin II induces a dose-dependent increase in PAI-1 messenger RNA and in the concentrations of secreted PAI-1 in the media. Platelets express receptors for angiotensin II, and while angiotensin II is not a direct platelet agonist, it does sensitize platelets to the effects of other known agonists. As a result, angiotensin-treated platelets are more sensitive to the aggregating effects of epinephrine, adenosine diphosphate, and collagen. Recent work by Vaughn and colleagues *(144)* suggests that angiotensins, including angiotensin III and angiotensin IV (particularly the latter), has a direct effect on

endothelial cell and smooth muscle cell PAI-1. The results of a recently completed clinical trial suggest that ACE inhibitor therapy in survivors of anterior MI results in a marked depression of PAI-1 concentrations in plasma within 2 wk of treatment initiation *(144)*.

Plasma Coagulation Factors and Cardiac Events

Epidemiologic studies have examined factor VII and fibrinogen, two components of the natural hemostatic mechanism. In the Northwick Park Study *(145)*, factor VII coagulant activity was shown to correlate with cardiovascular mortality. Fibrinogen also correlated strongly, as did factor VIII, although less strongly than other hemostatic markers. The potential importance of factor VIII, however, is strengthened by the low incidence of atherosclerotic coronary artery disease in hemophiliacs. In the Atherosclerosis Risk Communities study, which included 15,800 individuals from four diverse areas in the United States *(146)*, baseline measurements of factor VIII and von Willebrand factor were performed to determine their relationship to the development of coronary atherosclerosis. In a univariate analysis, both factors were positively associated with plasma triglycerides and negatively associated with high-density lipoprotein cholesterol.

As in the Northwick Park, several large-scale epidemiologic studies have identified an association between both factor VIII activity and fibrinogen and the incidence of atherosclerotic coronary artery disease. In the Framingham Study *(147)*, fibrinogen and coronary disease were strongly correlated, and the association was stronger than was the association between cholesterol (and other standard risk factors) and coronary disease.

Involvement of the fibrinolytic system in the development of acute coronary syndromes has recently led investigative groups to explore several markers as predictors of thrombotic cardiovascular events. In a study of 213 consecutive patients with angina pectoris and angiographically confirmed coronary artery disease, tPA mass concentration was the only laboratory marker significantly associated with mortality at a mean follow-up of 7 yr *(148)*. As described previously, high circulating PAI-1 levels have also been shown to correlate with an increased risk of systemic thrombotic events.

Dietary Factors

A possible link among atherosclerosis, thrombotic events, and dietary factors has been explored in several epidemiologic studies. The first, referred to as the Seven Country Study *(149)*, observed a correlation between total calories consumed as saturated fats and the occurrence of coronary heart disease-related death.

The potential direct impact of dietary factors on cardiac events was investigated in the Lyon Diet Heart Study *(150)*. Patients with a prior myocardial infarction were given a diet previously shown in the Seven Country Study to be associated with a low cardiovascular mortality (the Cretan Mediterranean Diet, high in α-linolenic acid). Compared with a control group, dietary intervention patients had a lower incidence of MI and cardiac death during a 27-month follow-up period (risk ratio 0.27; $p = 0.001$).

Hypercholesterolemia, induced by a high dietary intake of saturated fatty acids and cholesterol, is associated with increased platelet coagulant activity, platelet aggregation, thromboxane A_2 production, and shorter platelet survival. Elevations in plasma cholesterol have also been associated with increases in prothrombin and coagulation factors VII and X *(151)*.

Of particular interest is the conversion of factor VII to its activated form (VIIa) among individuals with high triglyceride concentrations. Factor VII coagulant activity (VIIc) increases with rising plasma triglycerides and dietary fat intake. It has been proposed that the association between fat consumption and VIIc is related to increased concentrations of triglyceride-rich lipoprotein particles on the intrinsic coagulation pathway. The metabolism of triglyceride-rich lipoproteins may generate a negatively charged surface, which then activates the contact system of coagulation (factor XII, factor XI, prekallikrein, high molecular weight kininogen). Support for this hypothesis is derived from studies showing reduced prothrombin activation fragment 1.2 concentrations with triglyceride-reducing therapies *(152)*.

Regardless of the mechanism(s) involved, postprandial coagulant activity increases rapidly and may represent a common "trigger" for thrombotic coronary events. Our clinical research group is currently investigating the role of dietary factors in acute coronary syndromes.

Measurable Biochemical Markers of Thrombosis

In clinical practice, limited means exist to assess the physiologically relevant balance between in vivo anticoagulation and thrombosis. Ideally, if tests were readily available that reflected active intravascular thrombosis, clot dissolution, and thrombotic potential, treatment could be tailored more precisely. Conceptually, these markers could also be used to provide mechanistic and prognostic information.

Thrombin, a 308-amino acid serine protease, plays a central role in the natural history of ruptured atherosclerotic plaques. Thrombin, in essence, determines the extent of thrombus formation at sites of vascular injury. Thrombin activity can be assessed in plasma by measuring fibrinopeptide A (FPA) concentrations. Actually, FPA represents fibrin formation resulting from thrombin's activity on fibrinogen. Thrombin generation is represented by plasma concentrations of prothrombin activation fragment 1.2, thrombin-antithrombin III complexes, and APC (Fig. 17).

Nearly a decade ago, Eisenberg and colleagues *(153)* reported that thrombin activity was increased among patients with acute coronary thrombosis. Our group has shown that both thrombin activity and platelet activity (determined by the expression of surface proteins using flow cytometry) are increased in acute coronary syndromes and that heightened activity persists even after the acute clinical symptoms have resolved *(154)*. Plasma markers of thrombin activity and generation may provide useful information during the early assessment of patients with MI at rest in whom electrocardiographic changes are either absent or nondiagnostic. In this setting, elevations in FPA, thrombin-antithrombin III complexes, and prothrombin activation fragment 1.2 may identify patients with active coronary artery disease *(155)*. D-dimer, a breakdown product of fibrin, has shown promise as a diagnostic marker among patients with venous thromboembolic disease and is currently being evaluated in the setting of acute coronary syndromes. Rapid bedside tests are available that may be useful in the early management of these patients. The combined measurement of several biochemical markers that reflect decreased myocardial perfusion (troponin), inflammation (fibrinogen, C-reactive protein, amyloid A protein, leukocyte activation) and thrombosis (platelet activation, thrombin generation, fibrin formation, thrombin-mediated platelet activation) (Fig. 18) or combination markers (platelet-leukocyte aggregates, fibrinogen–P-selectin interaction) could potentially offer the greatest wealth of information on the pathobiology, prevention, and treatment of acute coronary syndromes.

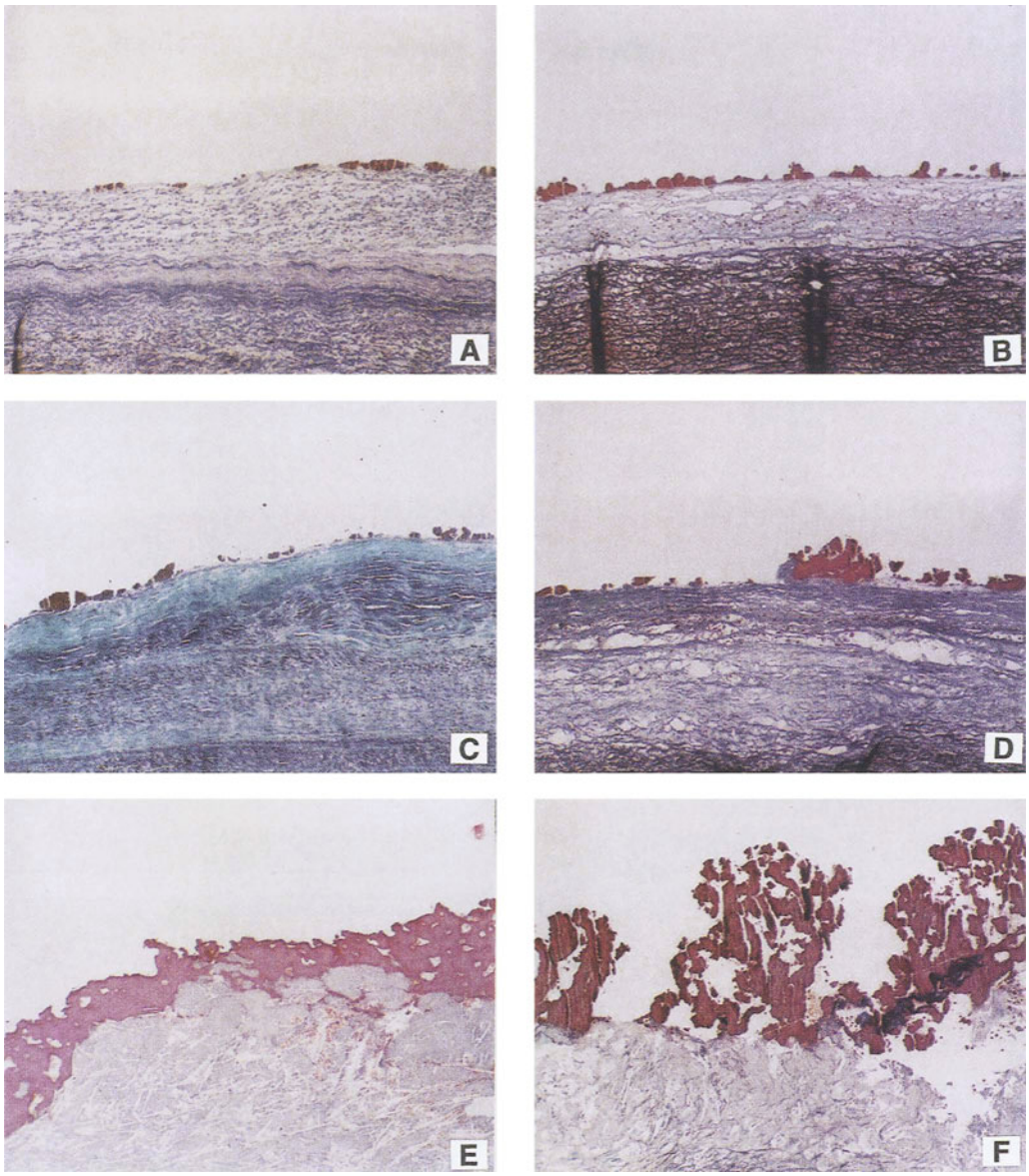


Plate 1, Fig. 7 (*see* discussion in Chapter 2, p. 31) Photomicrographs of varying tissue substrates found within the vessel wall and atheromatous plaque exposed to flowing blood. **(A)** Intima without lipid infiltration. **(B)** Foam cell-rich matrix. **(C)** Collagen-rich matrix. **(D)** Collagen-poor matrix without cholesterol crystals. (**E** and **F**) Collagen-poor matrix with abundant cholestrol crystals. Constituents within the core are the most thrombogenic (From ref. *65,* with permission.)

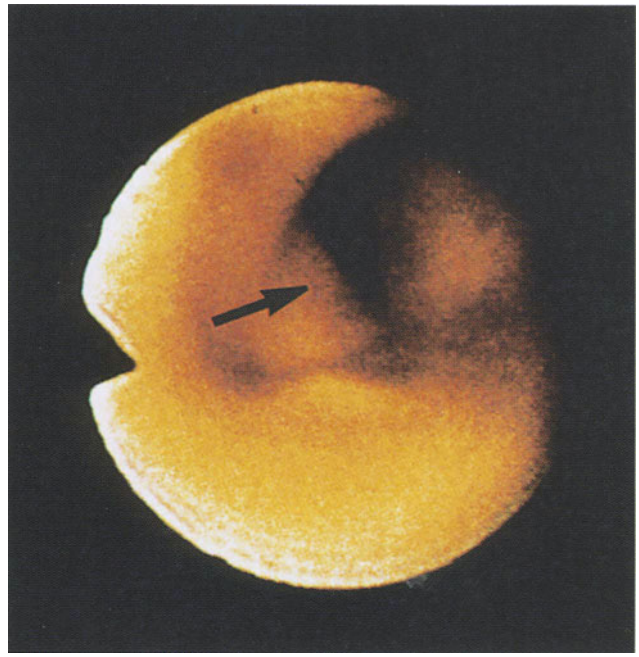


Plate 2, Fig. 11; (*see* discussion in Chapter 2, p. 38). Coronary angioscopy in a patient with accelerated angina. An eccentric plaque with disruption is evident (arrow). (From ref. *156,* with permission.)

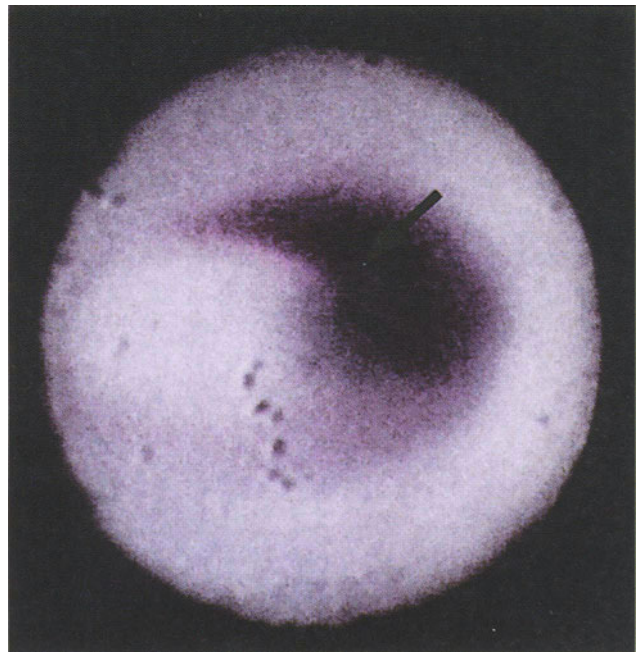


Plate 3, Fig. 12; (*see* discussion in Chapter 2, p. 39). Coronary angioscopy in a patient with angina at rest. Intraluminal thrombus (nonocclusive) is visualized (arrow). (From ref. *156,* with permission.)

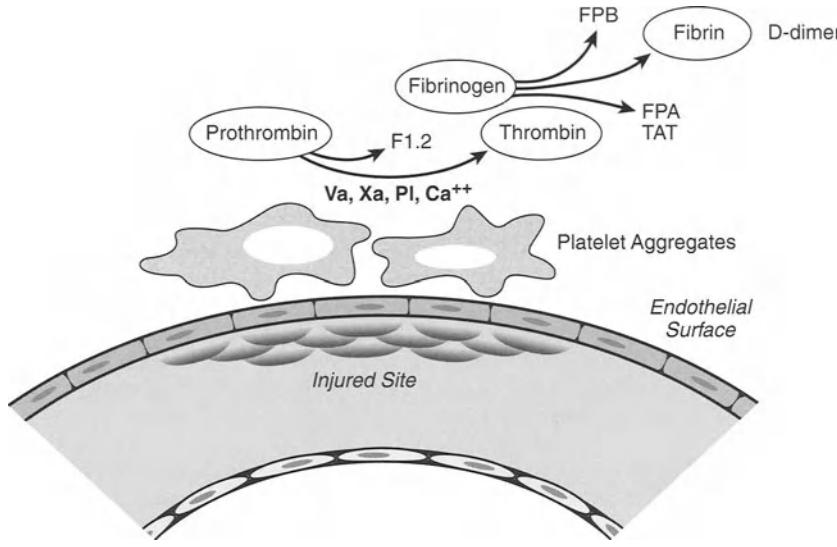


Fig. 17. The conversion of prothrombin to thrombin is mediated by the prothrombinase complex (coagulation factors Va and Xa, phospholipid, and calcium [Ca^{2+}]). This enzymatic reaction typically takes place on existing platelet aggregates; however, it can also occur on a dysfunctional endothelial surface. During the generation of thrombin, two small peptides, fibrinopeptide A (FPA) and fibrinopeptide B (FPB), are removed from the prothrombin molecule. Newly generated thrombin can either be complexed to antithrombin III (TAT) or participate in the conversion of fibrinogen to fibrin. D-dimer is a breakdown product of fibrin.

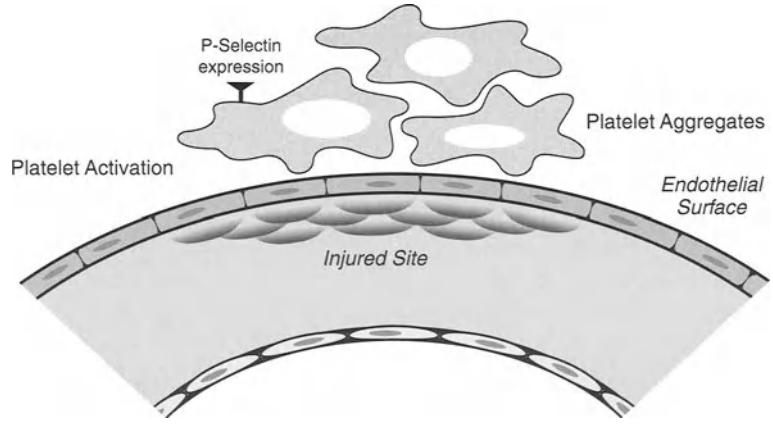


Fig. 18. Activated platelets undergo numerous structural and functional changes. Surface markers of activation, including P-selectin, can be measured using flow cytometry.

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3 Triggers of Acute Coronary Syndromes

Peter M. Sapin, MD, and James E. Muller, MD

CONTENTS

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INTRODUCTION

The likelihood that acute myocardial infarction (MI) is triggered by a specific event has been a subject of debate since the earliest description of this disorder, which incorporated the belief that specific physical or mental events precipitated the attack *(1)*. Controversy over the precipitating events continued for decades *(2–3)*, until 1960, when Master *(4)* published a retrospective study of over 2600 patients with acute MI *(4)*. This study was the largest to address MI triggers up to that time. Although no formal statistical analysis was applied, it was concluded from the data that the onset was unrelated to physical effort, time of day, day of the week, or the occupation of the patient. In the last 15 years, as knowledge of the pathologic processes underlying acute coronary syndromes has advanced, the possibility of the existence of specific triggers for the onset of acute MI and related syndromes has been reconsidered.

The current concept holds that acute coronary syndromes result from a breach in the surface of an atherosclerotic plaque, either by endothelial denudation of the fibrous cap overlying the plaque, or by frank rupture of the cap *(5–10)*. This event exposes collagen and the lipid material underlying the luminal surface of the plaque to blood. The interaction between the inner constituents of the plaque (and its cap) and blood, where platelets and clotting factor proteins are available for activation, initiates the formation of intracoronary thrombus. The competition between thrombosis and intrinsic fibrinolytic processes determines the natural history of the plaque rupture. One possible outcome is a voluminous thrombus little diminished by fibrinolysis, causing total coronary occlu-

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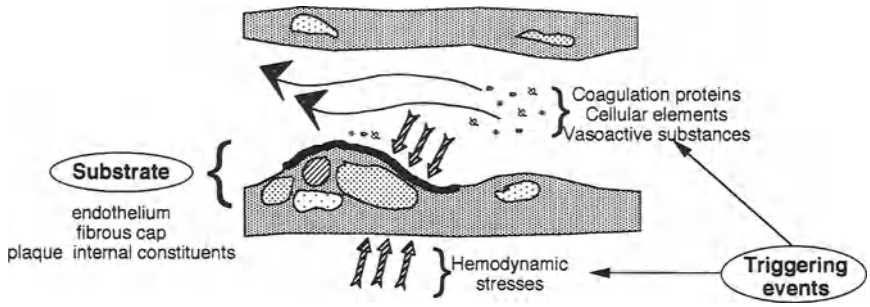


Fig. 1. Substrate, triggering events, and the physiologic processes linking the two. Atherosclerotic plaques with varying structural, cellular, and biochemical characteristics form the substrate for acute coronary events. The plaque is in contact with circulating cellular elements, coagulation proteins, and vasoactive substances produced locally in the endothelium and circulating systemically. The plaque also is acted on by physical forces related to systemic hemodynamics and coronary blood flow. Triggering events exert their effects by modifying local physiologic processes to promote plaque disruption and intracoronary thrombosis.

sion, extensive myocardial ischemia with electrocardiographic ST-segment elevation, and MI. A different clinical syndrome might be expected to result from a smaller thrombus mass, which is spontaneously lysed: transient symptoms, with or without ischemic electrocardiographic changes, and without MI. Another presentation of acute coronary artery disease is sudden cardiac death. There is evidence that acute changes in plaque morphology can be found in most cases *(11);* mechanisms including ischemia and reperfusion, hemodynamic factors, metabolic alterations, and autonomic influences are implicated *(12).*

The triggering of acute coronary syndromes requires two elements: a substrate and the triggering events or circumstances. The substrate is an atherosclerotic plaque with features predisposing to superficial erosion or rupture. The plaque exists in a microenvironment including the physical forces that stress or deform the plaque, coronary vasomotor tone and endothelial function, circulating catecholamines and other vasoactive substances, and the state of the intracoronary hemostatic environment. The activities and circumstances that may be recognized as triggering events for acute coronary syndromes produce their effects through alterations in the microenvironment that favor plaque erosion or rupture and intracoronary thrombus formation (Fig. 1).

THE VULNERABLE ATHEROSCLEROTIC PLAQUE

There is considerable heterogeneity in the structure of atherosclerotic plaques, and numerous investigations have attempted to identify special features of plaques that are involved in acute ischemic syndromes *(5–10).* In patients experiencing acute MI who have coincidentally undergone coronary arteriography at some point prior to the acute event, the site of coronary occlusion is often not the site of the most stenotic lesion in the coronary tree *(13,14).* It is now recognized that acute ischemic syndromes are often precipitated at atherosclerotic sites that are only minimally obstructive, suggesting that features other than plaque bulk contribute to the risk of a given plaque acting as the site of an acute coronary occlusion *(13,14).* Detailed anatomic studies of plaque structure at the site of rupture and thrombosis in patients who have died from acute MI have identified a variety of morphologic features that are more likely to be found in these plaques

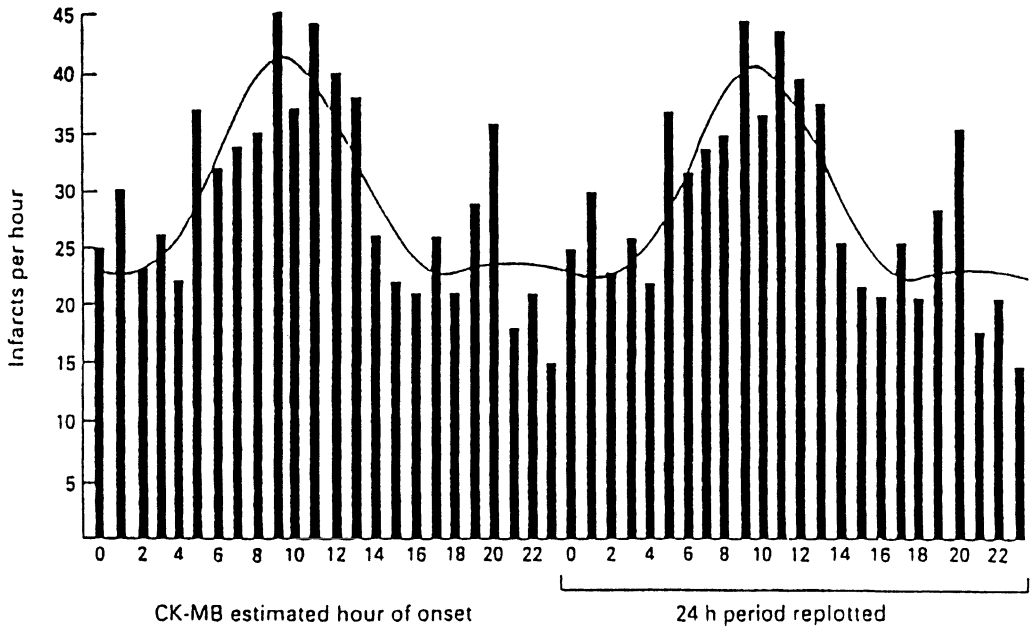


Fig. 2. Circadian variation in myocardial infarction onset. The number of infarctions per hour is plotted on the Y-axis, versus the time of onset on the X-axis (24-h clock), for 849 patients experiencing acute myocardial infarction. The hour of onset of infarction is determined from creatine phosphokinase MB fraction levels. There is a significant excess of infarctions between the hours of 6 AM and noon, with a small secondary peak at 7–8 PM. Reproduced with permission from ref. *15*.

compared with those at other, presumably more stable, sites *(5–10)*. These features include a relatively large lipid pool and a fibrous cap overlying the plaque that is relatively thin and more likely to contain an inflammatory cell infiltrate *(5–10)*. There is evidence that plaques with a thinner cap and a larger underlying lipid pool may be more susceptible to physical forces causing the cap to fissure, usually at the edge of the plaque, thus setting in motion the thrombogenic cascade leading to an occlusive clot *(5–10)*.

EVIDENCE FOR TRIGGERING

Periodicity in the Onset of Acute Cardiac Events

Morning Increase in Acute Cardiovascular Disease Onset

The concept of circadian variation in acute MI onset has been reexamined since the work of Master *(4)*. In 1985, Muller et al. *(15)* reported on the Multicenter Investigation of the Limitation of Infarct Size trial, involving 849 patients. Serial cardiac muscle enzyme levels were used to estimate the time of onset. These investigators identified a prominent morning increase, peaking from 9 AM to noon, with a smaller peak in the early evening. A nadir in the incidence of infarction onset was observed at night (Fig. 2). Similar findings were reported from the Intravenous Streptokinase in Acute Myocardial Infarction trial of 1741 patients, with infarction occurring 1.8 times more frequently between 6 AM and noon, compared with the other quarters of the day *(16)*. This pattern, with a predominance of infarctions beginning in the morning hours, and a relative paucity during what would be considered hours of sleep (midnight to 6 AM), has been confirmed

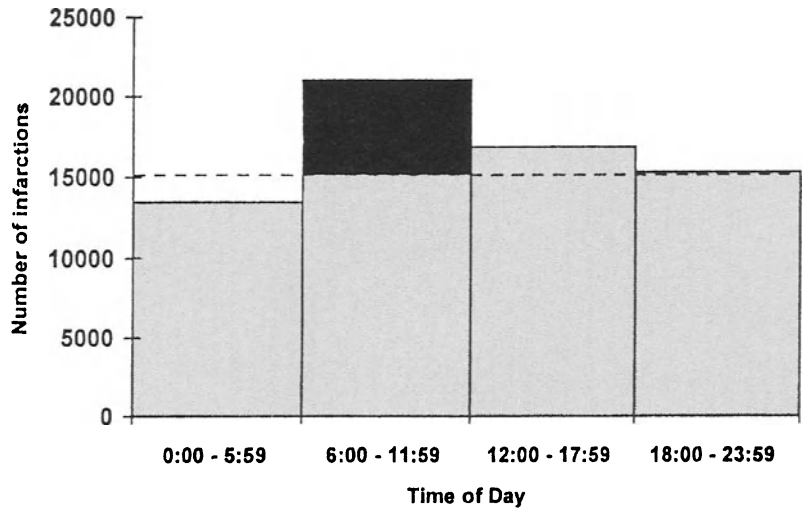


Fig. 3. Metaanalysis of time of onset of acute myocardial infarction in over 66,000 patients. In these studies the 24-h period is divided into 6-h segments, beginning at midnight. The dotted line shows the expected number of infarctions for each 6-h time period and the black shaded area the excess incidence of infarctions occurring during the 6 AM to noon segment. ■, excess incidence of morning infarctions; – –, expected number of infarctions. Reproduced with permission from ref. *27*.

in many other studies *(17–26)*. Some, but not all, investigators have also reported a second, smaller peak during the late afternoon or evening hours. A recently published metaanalysis of 30 studies including 66,635 patients found a relative risk of onset between 6 AM and noon of 1.38 (95% confidence interval [CI] 1.37–1.40) *(27)*. This study calculated that 27.7% of morning nonfatal infarctions and 8.8% (95% CI 8.5–9.0) of all nonfatal myocardial infarctions could be attributed to the excess morning risk of acute myocardial infarction (Fig. 3).

A similar pattern of circadian variation occurs in acute coronary and vascular events other than nonfatal MI. The onset of chest pain at rest in patients hospitalized with unstable angina pectoris also shows a statistically significant morning peak *(28–32)*. In the Thrombolysis in Myocardial Infarction (TIMI) III study of unstable angina and non-Q-wave myocardial infarction, 31.4% of 7730 patients entered into the registry had onset of pain between 6 AM and noon *(28)* (Fig. 4). One study of 1167 patients with non-Q-wave myocardial infarction failed to show a significant diurnal variation in time of onset of symptoms *(32)*. However, the larger TIMI III study demonstrated a significant morning excess of events in both the unstable angina and non-Q-wave MI subgroups *(28)*.

Ambulatory monitoring of patients with stable coronary artery disease and myocardial ischemia also demonstrates an increase in the number of episodes of transient myocardial ischemia occurring during the morning hours (between 6 AM and noon), again sometimes with a secondary peak in the late afternoon *(33–38)* (Fig. 5). One study of 150 patients found the relative risk for ischemic episodes during the morning hours to be 1.76 ($p < 0.01$) *(35)*. Another study of transient myocardial ischemia in the early posthospital phase of acute MI demonstrated a peak incidence of ischemic episodes in the early evening hours, rather than in the morning *(39)*. This suggests that circadian patterns may be altered transiently by an event such as acute MI.

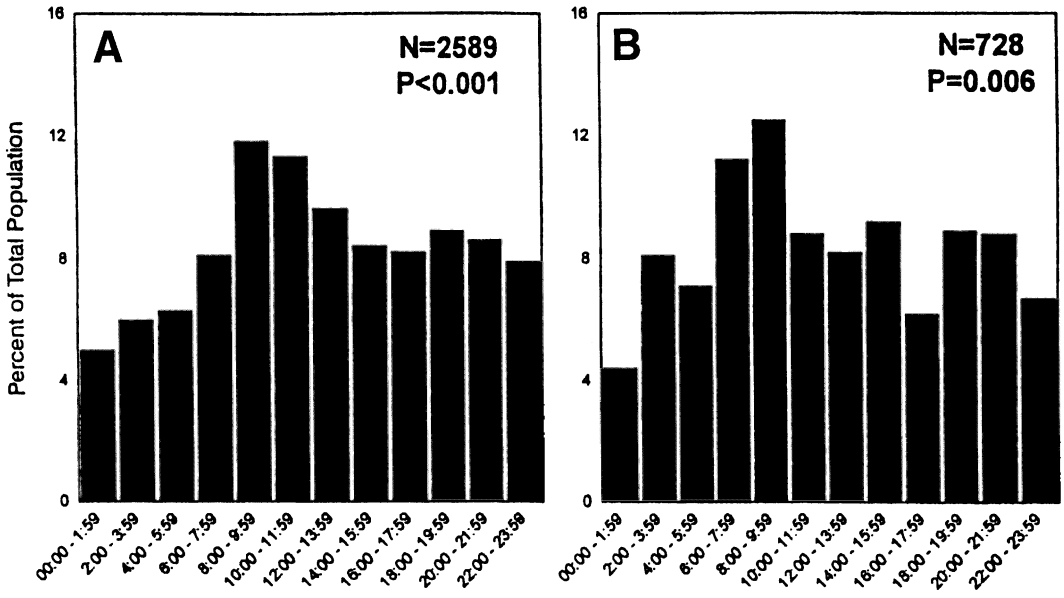


Fig. 4. TIMI III Registry. (**A**) unstable angina; (**B**) non-Q wave AMI. Circadian variation in the timing of the onset of unstable angina pectoris and non-Q-wave myocardial infarction, from the Thrombolysis in Myocardial Infarction III Registry. The percent of patients with onset of symptoms in each 2-h time period (X-axis) is shown. The *p* values are the result of the chi-square goodness-of-fit test for a uniform distribution, indicating a highly significant nonuniformity. Reproduced with permission from ref. *28*.

Ischemic stroke represents another vascular catastrophe with a pathogenesis similar to that of myocardial ischemic events. A significant variation in the time of onset of stroke symptoms, with a dominant peak in the 6 AM to noon time frame, has been demonstrated *(40,41)*. Even when accounting for stroke patients awakening with symptoms, when the time of onset may not be known, over 50% of strokes in one study *(40)* and 38% in another *(41)* were thought to have begun between 6 AM and noon.

The timing of sudden cardiac death also appears to have a similar circadian variation, as demonstrated in two Massachusetts studies *(42,43)*, in patients with advanced heart failure who died suddenly *(44)*, and in patients receiving antiarrhythmic agents during the Cardiac Arrhythmia Supression Trial (CAST) *(45)*. A metaanalysis also reviewed 19 published studies of time of onset of sudden cardiac death (5834 events) *(27)*. The relative risk of sudden cardiac death was 1.29 times greater (95% CI 1.26–1.32) in the morning compared with the rest of the day. The morning excess accounted for 22.5% of morning sudden deaths and 6.8% (95% CI 6.4–7.1) of all sudden deaths (Fig. 6). Ventricular tachycardia and ventricular fibrillation are the most frequent arrhythmias causing sudden cardiac death. Several studies of patients with automatic implantible cardioverter-defibrillators (AICDs) capable of documenting the time of arrhythmias *(46–49)*, as well as a study of the arrival time in the emergency room of patients with ventricular fibrillation *(50)*, demonstrated a morning peak and a nighttime nadir (Fig. 7).

The relationship between morning and MI has prompted consideration that the time of awakening, rather than the time of day per se, may better explain the variation. In one study of 224 patients, the relative risk of acute MI onset between 6 and 9 AM was 1.8 (95%

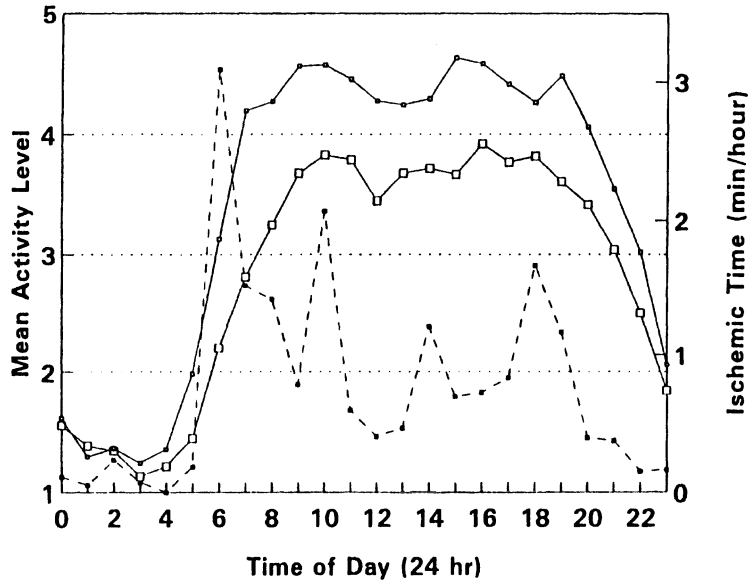


Fig. 5. Circadian variation in myocardial ischemic burden in patients undergoing 24-hourly ambulatory monitoring. –□–, physical; –□–, mental; –■–, ischemic time. The solid lines indicate the level of physical and mental activity (Y-axis on left) throughout the 24-h cycle (X-axis). These levels increase in the morning, remain elevated throughout the day, and decrease at night. The dotted line plots the total duration of myocardial ischemia per hour (Y-axis on right). There is a prominent morning peak in ischemic time, paralleling the rise in level of physical and mental activity. However, ischemic time decreases after the morning hours despite maintenance of high physical and mental activity levels, illustrating the independent effort of awakening on the total ischemic burden. Reproduced with permission from ref. *33*.

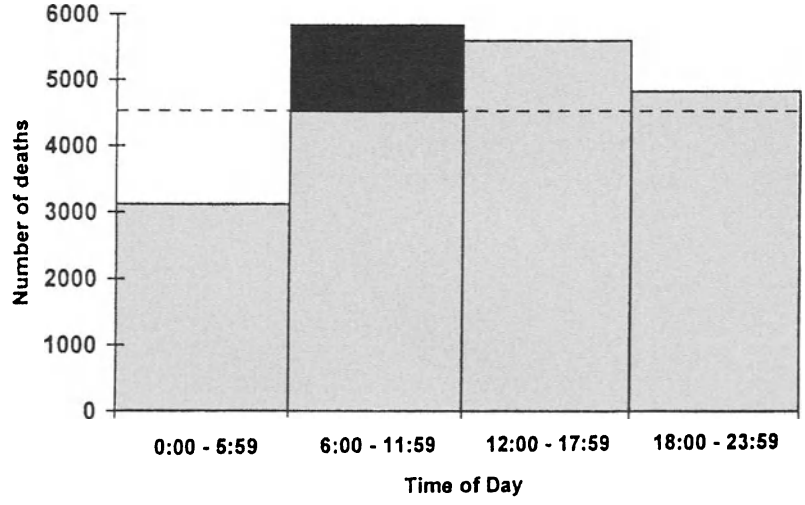


Fig. 6. Meta-analysis of time of sudden cardiac death in over 19,000 patients. In these studies the 24-h period is divided into 6-h segments, beginning at midnight. The dotted line shows the expected number of infarctions for each 6-h period and the black shaded area the excess incidence of sudden deaths occurring during the 6 AM to noon segment. ■, excess incidence of morning sudden cardiac deaths; – –, expected number of sudden cardiac deaths. Reproduced with permission from ref. *27*.

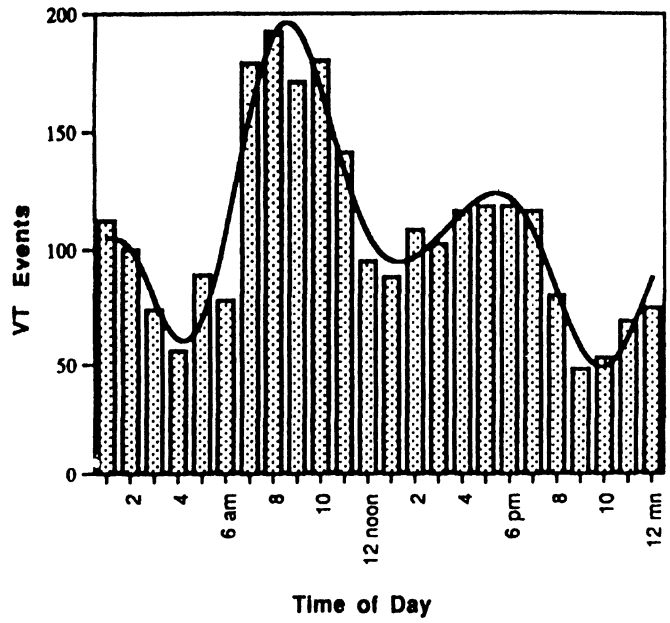


Fig. 7. Circadian variation in frequency of ventricular tachyarrhythmic events in 32 patients with automatic implantable defibrillators capable of recording the time of occurrence of arrhythmias. The Y-axis represents the number of events vs time of day. The predominance of events during the 6 AM to noon period is statistically significant by ANOVA (p = 0.007). The curve is a fourth-order harmonic regression curve, demonstrating a significant periodicity in the frequency of events over time ($R^2 = 0.91$, $p < 0.001$). Reproduced with permission from ref. *47*.

CI 1.3–2.4) *(51)*. After adjustment for individual wake times, the relative risk of infarction onset in the first 3 h after awakening increased to 2.4 (95% CI 1.8–3.1). Another study of 137 patients found that 23% reported onset of MI symptoms within 1 h of awakening *(52)*. In the CAST experience of 3309 patients with a history of MI, 24% experienced symptom onset within 4 h of awakening *(53)*. In patients with sudden cardiac death, a relative risk for the first 3 h after awakening was 2.6 (95% CI 1.6–4.2) compared with other times of the day *(54)*. Studies of ambulatory patients undergoing Holter monitoring to detect myocardial ischemic episodes found that ischemic time increased significantly for the 2 h after awakening *(33,37)*. This increase was observed even after correction for the greater level of physical and mental activity, which independently influenced ambulatory ischemia *(33)*. Although the lowest frequency of acute coronary syndrome onset has been found during the hours of sleep (generally midnight to 6 AM), one study found that in patients with stable coronary disease, arising at night was strongly associated with the occurrence of transient myocardial ischemia detectable by ambulatory monitoring *(55)*.

Other Patterns in the Timing of Acute Cardiac Events

In addition to diurnal variation, other temporal and environmental cycles have been shown to affect the timing of acute coronary events. Several studies have shown that MIs are more likely to occur on Monday *(17,56–58)*. One group reported that this pattern was present only in a working, as opposed to nonworking, population *(56)*, although this was not confirmed in another study *(25)*. An interesting observation was made concerning 148 sudden cardiac deaths over a 10-yr period on the Hawaiian Island of Kauai *(59)*. The

occurrence of sudden death in local residents demonstrated the typical 6 AM to noon peak, but sudden death in visitors coming from 2500 to 5400 miles distant (three to six time zones) showed a peak in the 6 PM to midnight time period, possibly reflecting altered sleep-wake cycles induced by jet lag.

A seasonal variation, with a peak in wintertime admissions for acute MI and a summertime trough, has also been reported *(19,25,57)*. One group studied the daily frequency of MI over a 10-yr period and found correlations to varying weather patterns from year to year; higher incidence correlated with lower temperature and higher humidity *(60)*. A study of vital statistics from five Minneapolis-St. Paul winters found no statistical relation between air temperature and cardiovascular mortality *(61)*. However, this study found that snowfall influenced mortality on the day of occurrence and for 2 d after. The combination of rain and snow was found to produce a dramatic increase in mortality from acute MI. Similar observations were made in Toronto, Ontario, Canada *(62)*. A study in patients with event-recording AICDs found that the frequency of ventricular tachyarrhythmias correlated with the temperature calculated to be "felt" by the individual. "Felt-temperatures" in the range considered to represent thermal stress were associated with higher frequencies of arrhythmia *(63)*.

Many of the studies examining the circadian variation of acute MI have performed analyses in subgroups of patients, with the goal of gaining insights into triggering mechanisms by identifying differences in circadian rhythms between groups with different characteristics. In most studies, age, sex, cigarette smoking, prior MI or angina pectoris have not affected circadian patterns. The findings for diabetic patients have been less consistent, with some studies showing attenuation of circadian variation in myocardial infarction onset in diabetics *(17,18,57,64)* and others showing preserved circadian variation *(15,22,65)*. One study found circadian variation to be present in treated diabetic subjects and abolished in untreated patients *(66)*.

Specific Activities as Potential Triggers

As discussed previously, morning and awakening appear to trigger acute coronary syndromes; other environmental changes, such as the transition from weekend to workweek and changes in weather cycles may also function as triggers. Many investigators have sought specific events identifiable by patients as triggers. Studies using interview techniques to determine the fraction of patients reporting a suspected "triggering activity" in the period immediately preceding the onset of symptoms found that 25–>50% of patients noted that moderate to heavy physical exertion, unusual emotional stress, lack of sleep, overeating, use of alcohol, noncardiac illness or surgery, or some other activity were ongoing at the time of (or in the 24 h preceding) infarction onset *(67–70)*. However, these data are limited by recall bias and by the difficulty in obtaining appropriate control data, i.e., the frequency with which the activity occurs without an acute event following.

New epidemiologic techniques have allowed a more sophisticated study of the relationship between specific patient activities and the onset of acute cardiac events. One such approach is the case-crossover method, which uses the patient as his or her own control to calculate the relative risk of a rare acute event such as an MI following an intermittently performed activity suspected of being a trigger *(71)*. This method reduces some of the bias inherent in this type of study. The case-crossover method has been used to study the role of physical exertion, anger, and sexual activity in triggering acute MI (Table 1).

Table 1
Relative Risk of Myocardial Infarction Following Triggering Events, Including the Effect of Exercise Frequency on Risk[a]

Trigger (ref.)	Duration of risk increase (h)[b]	Overall RR of triggering MI	RR of triggering MI (stratified by exercise frequency)[c]	
			<1/wk	3–4/wk
Exercise (73)	1 h	5.9 (4.6–7.7)	107 (67–171)	8.6 (3.6–20.5)
Sexual intercourse (78)	2 h	2.5 (1.7–3.7)	3.0 (2.0–4.5)	1.2 (0.4–3.7)
Anger (87)[d]	2 h	2.3 (1.7–3.2)	—	—
Morning (27)	—	1.38 (1.37–1.40)	—	—

[a]Data are relative risk (RR), with 95% confidence intervals in parentheses. MI, myocardial infarction. —, not reported.
[b]Duration, time period after trigger for which relative risk of infarction remained >1.0.
[c]Exercise frequency, sessions of ≥6 metabolic equivalents (METS) of effort (vigorous exertion with panting, overheating).
[d]Anger, very angry, furious, or enraged.

Physical Exertion

The role of physical exertion as a trigger of MI has been a subject of controversy, since most infarctions occur at rest or with mild activity. One study of 1194 German patients reported that 7.1% of infarct patients engaged in ≥6 metabolic equivalents (METS) of exertion at the onset of infarction vs 3.9% of a control group *(72)*. From case-crossover analysis, the relative risk of having engaged in this level of activity within 1 h of the onset of infarction was 2.1 (95% CI 1.1–3.6). This increased risk was modified by the frequency with which the patient engaged in physical exercise on a routine basis. Exercise >4 times/wk was associated with a relative risk of only 1.3 (95% CI 0.8–2.2), whereas exercise <4 times/wk imparted a relative risk of 6.9 (95% CI 4.1–12.2). Similar findings emerged from the Myocardial Infarction Onset Study of 1228 patients, which also used the case-crossover method *(73)*. Although only 4.4% of patients reported heavy physical exertion within 1 h of the onset of MI, the relative risk of infarction within 1 h of heavy exertion (≥6 METS) was 5.9 (95% CI 4.6–7.7). This risk increase persisted for 1 h after exercise (Fig. 8).These investigators also found that regular exercise lowered the risk of exertion-related infarction. The relative risks of infarction following exertion among individuals who exercised 0, 1–2, 3–4, and ≥5 times/wk were 107, 19.4, 8.6, and 2.4, respectively (Fig. 9)(Table 1). Known coronary artery disease, age, sex, and a variety of other clinical variables did not influence the increased relative risk of MI imparted by exercise, with the exception of diabetes mellitus, for which the relative risk was significantly higher (18.9 vs 5.4 for nondiabetics).

Similar results concerning the incidence of sudden cardiac death during exercise and the protective effect of regular exercise were reported by Siscovick et al *(74)*. In a group of men who spent less than 20 min/week engaged in vigorous exercise, the risk of sudden death during exercise was increased 56-fold, compared with a five-fold increase in risk seen in men exercising more than 20 min/d. The absolute risk of sudden death was very low (1 cardiac death/20,000 joggers/yr). In marathon runners, the sudden death incidence was lower still: among over 200,000 participants in separate marathon races, three such deaths occurred during or immediately after the race *(75)*.

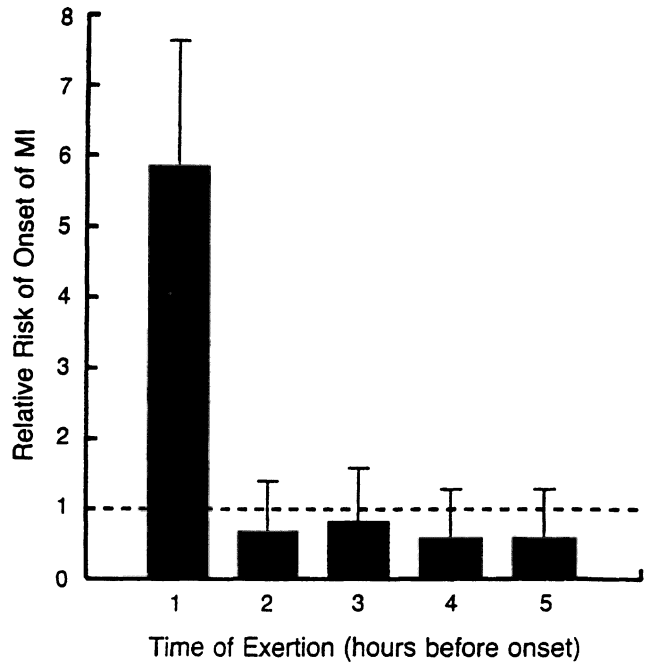


Fig. 8. Time of onset of myocardial infarction after an episode of heavy physical exertion (≥6 metabolic equivalents) in 1228 patients. The relative risk is increased nearly sixfold for the first hour after exertion and then decreases to approximately the baseline risk of 1.0 (dotted line). Whiskers indicate the 95% confidence limits. Reproduced with permission from ref. *73*. ©1993 Massachusetts Medical Society. All rights reserved.

Sexual Activity

Anecdotal reports have related sexual intercourse to the onset of MI *(76,77)*, but few systematic data have addressed this question. The Myocardial Infarction Onset Study interviewed 858 patients who were sexually active in the year prior to their MI: 9% reported sexual activity within 24 h, and 3% reported sexual activity within 2 h of the index acute MI *(78)*. From case-crossover analysis, the relative risk of MI following intercourse was 2.5 (95% CI 1.7–3.7). In contrast to the data for physical exertion (increased risk persisting for 1 h), the postcoital risk remained elevated for 2 h. There was no difference between patients with and without a history of angina pectoris; however, it was observed that regular exercise at +6 METs three or more times/wk decreased the relative risk to 1.2 (95% CI 0.4–3.7) (Table 1).

Mental Stress and Anger

Several studies have suggested that psychologically stressful life events such as the death of a spouse are potential triggers for MI and sudden death *(79,80)*. Other data have shown that periods of general calamity increase the frequency of MI. For example, during the 1991 Persian Gulf War, Iraqi missile attacks on Israel nearly doubled the relative frequency of cardiovascular deaths in that country on the day of attack *(81)* (Fig. 10). Immediately following severe earthquakes in Athens *(82)*, Hyogo, Japan *(83)*, and Los Angeles *(84)*, researchers documented an increase in cardiovascular mortality. In Los Angeles, 24 patients died of sudden cardiac death on the day of the quake, compared with

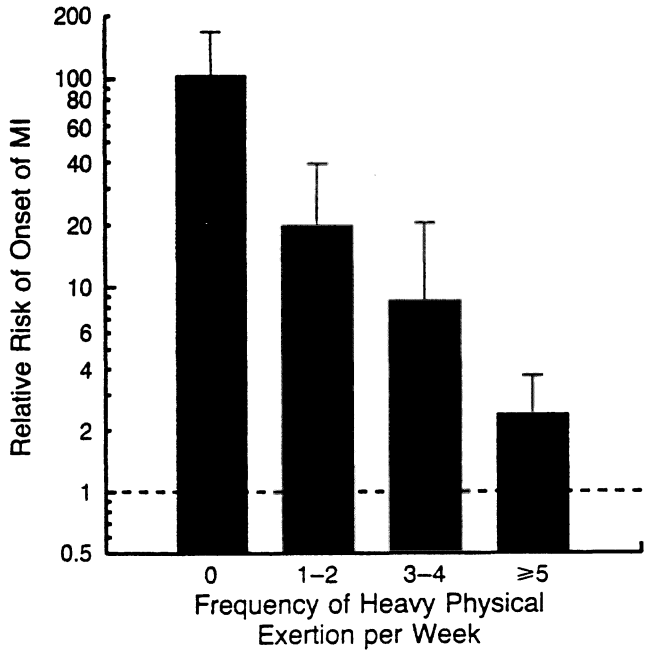


Fig. 9. Relation between risk of exertion-triggered myocardial infarction (MI) and weekly frequency of heavy exertion (≥6 METS). The relative risk of MI (Y-axis) following heavy exertion is approximately 100-fold in individuals who perform no heavy exertion during the week and falls to approximately 2.4-fold for individuals with five or more sessions of heavy exertion a week. Whiskers indicate the 95% confidence limits. The dotted line indicates the baseline risk. Reproduced with permission from ref. *73*. ©1993 Massachusetts Medical Society. All rights reserved.

an average of five such deaths a day the preceding week. Only 3 of the 24 deaths occurred in relation to unusual physical exertion *(84)*.

Events such as the death of a loved one, earthquake, and war occur rarely and thus are of lesser importance when considering daily activities that may function as triggers. A relation between acute cardiac events and more commonly experienced periods of high emotion such as anger has been suggested by work examining post-MI prognosis in relation to personality characteristics. For example, one study addressing the controversial subject of the "type A" personality found that increased first-year post-MI mortality correlated not with "global Type A" test scores, but with scores reflecting the subcomponents of anger expression, cynicism, and irritability *(85)*. A relation between mental stress and cardiac prognosis is suggested by another study of 126 patients, over half of whom demonstrated a mental stress-induced fall in left ventricular ejection fraction *(86)*. The relative risk of cardiac death, nonfatal MI, or coronary revascularization in that group was 2.4 times (95% CI 1.13–5.14) that of the patients who had no mental stress-induced change in left ventricular ejection fraction.

A more precise relation between anger and acute MI was elucidated by the Myocardial Infarction Onset Study, again using the case-crossover design *(87)*. The relative risk of onset of MI following an episode of anger was 2.3 (95% CI 1.7–3.2) and remained at this level for 2 h (Table 1). Further analysis of these data found that the relative risk increase was influenced by the socioeconomic status of the individual subject *(88)*. In patients

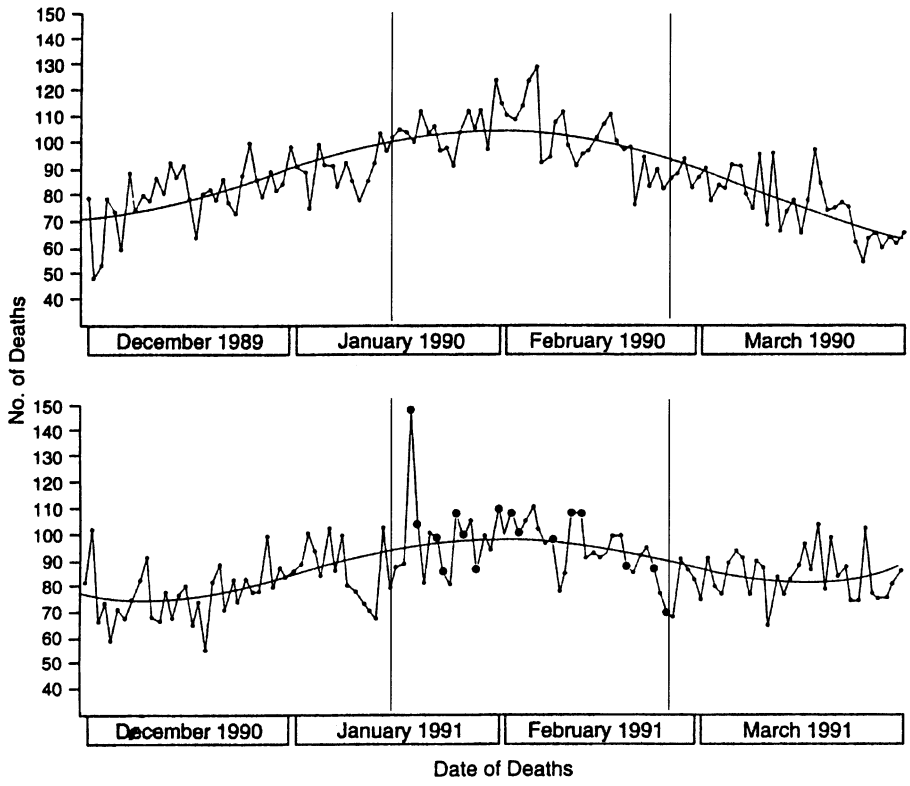


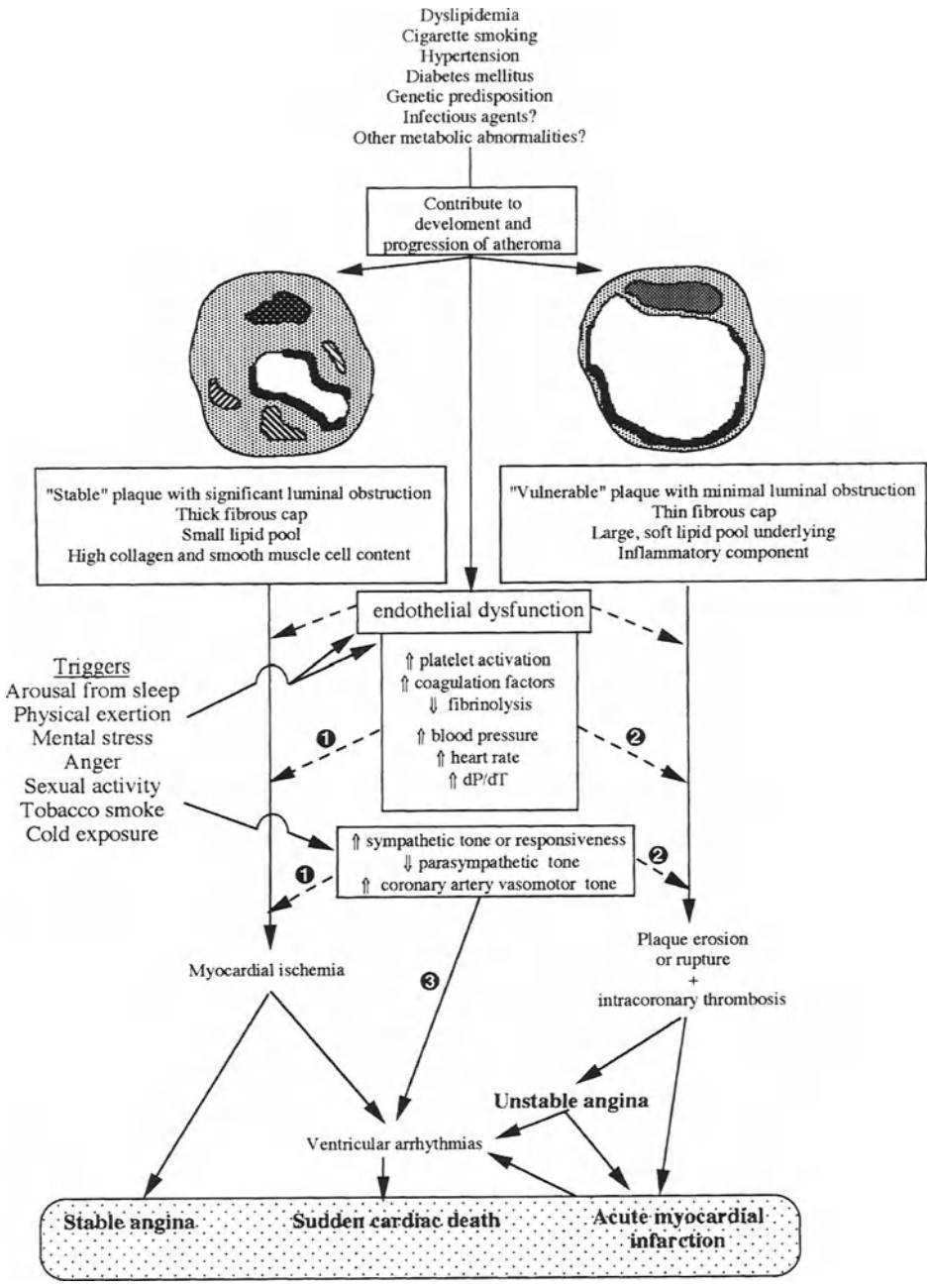
Fig. 10. The daily frequency of deaths in Israeli citizens >24 years of age during the Persian Gulf War (bottom plot) compared with the same period the year before (top plot). On January 18, 1991 (left vertical line), missiles launched from Iraq exploded in the Tel Aviv and Haifa areas. Daily warnings and attacks followed (larger filled points) until February 25 (right vertical line). The chi-square goodness-of-fit test demonstrated significant inhomogeneity for daily mortality during the 5-wk period, owing almost entirely to the excess of cardiovascular deaths during the 24-h period of January 18. Reproduced with permission from ref. *81.*

with less than a high school education, the risk increase was greater (relative risk 3.3), and it was least in patients with some college education (relative risk 1.6).

LINKING TRIGGERS AND ACUTE CORONARY EVENTS

Circadian Changes in Physiologic Variables

Daily activities and experiences that act as triggers of acute coronary syndromes must act through the perturbation of the physiologic milieu in which a vulnerable atherosclerotic plaque exists (Fig. 11). Circadian variation in hemodynamic variables has been studied to explain the circadian variation of acute cardiac events. The morning hours are associated with increased arterial blood pressure and increased heart rate, both of which are reduced during sleep *(89,90).* This hemodynamic surge appears to be related to assumption of the upright posture *(91).* Most studies have shown that episodes of ambulatory ischemia are related to an increase in rate-pressure product *(91)* and that ambulatory myocardial ischemia is more frequent and more prolonged in the morning *(33–38).* Angina patients and normal subjects have a significantly greater blood pressure and heart rate response during an exercise test in the morning compared with the response during



❶ Contribute to both increased myocardial oxygen demand and decreased supply

❷ May subject plaque to excessive physical stresses and augment hemostatic consequences of plaque rupture

❸ May trigger arrhythmia in patients with abnormal cellular electrophysiology, in the absence of ischemia

Fig. 11. Potential interactions among atherogenic risk factors, plaque evolution, and the means by which external triggers produce various acute coronary syndromes.

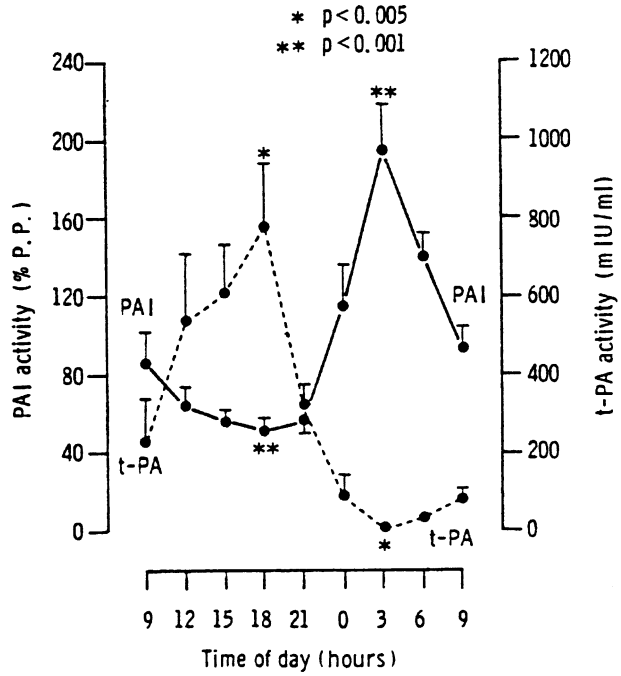


Fig. 12. Circadian variation in physiologic processes mediating the triggering of acute coronary events. The level of plasminogen activator inhibitor (higher levels favor thrombosis) in six healthy volunteers undergoing sampling every 3 h (including during sleep from midnight to 8 AM) is shown by the dotted line. The level of tissue-type plasminogen activator (higher levels favor fibrinolysis) is shown by the solid line. Whiskers indicate standard error of the mean. Asterisks indicate significant difference between peak and nadir values. The balance of factors favors thrombosis in the morning and fibrinolysis in the evening. Reproduced with permission from ref. *103.*

an afternoon exercise test *(92).* In another study the rate-pressure product at which ischemia was induced was lower in the morning, in parallel with an increase in postischemic forearm vascular resistance *(93).* This finding suggests that coronary vascular resistance may be increased in the morning, in addition to the morning increase in myocardial oxygen demand.

A number of hemostatic variables follow a circadian rhythm paralleling that of cardiac events *(94).* The morning hours are associated with an increase in platelet aggregability, which occurs with the assumption of the upright posture *(95–97).* Plasma viscosity *(98),* fibrinogen levels *(99),* and white blood cell aggregation *(100)* increase in the morning, changes favoring thrombosis. The morning hours bring a decrease in resting tissue-type plasminogen activator (tPA) levels *(101–103)* and an increase in tPA inhibitor, plasminogen activator inhibitor-1 *(101–104),* which reduces the activity of the intrinsic fibrinolytic system (Fig. 12). Recent studies of other markers of coagulability and fibrinolysis have further strengthened the appreciation of the morning hours as a period of relative hypercoagulability *(105).*

The activity of the autonomic nervous system has been studied to elucidate circadian patterns. Plasma norepinephrine falls to a nadir at night and increases in the morning in association with awakening and resumption of upright activity *(106,107).* Forearm vascular resistance has been shown to increase in the morning in normal subjects, a change attenuated by phentolamine but not nitroprusside, suggesting that the increase in vaso-

motor tone in the morning is mediated through α-adrenergic activity *(108)*. A morning withdrawal of vagal tone and an increase in sympathetic tone has been suggested by spectral analysis of heart rate variability *(109–114)*. Autonomic nervous system dysfunction in diabetic patients with coronary artery disease was shown to be associated with a blunted circadian pattern of myocardial ischemia *(115)*.

Circadian variation has been shown for electrophysiologic variables such as the length of the refractory period *(116)* and the QT interval *(117)*. Increased QT interval dispersion (difference between the longest and shortest QT interval in a given patient) has been considered to represent inhomogeneous ventricular repolarization and is thought to be a risk factor for malignant ventricular arrhythmias *(118,119)*. Variations in QT-interval dispersion throughout the day support the concept of the morning hours as a period of heightened sympathetic tone and suggest that autonomic imbalance, with increased sympathetic nervous system output or sensitivity, may be a risk factor for malignant ventricular arrhythmias and sudden cardiac death *(118,119)*.

Effects of Physical Exertion and Mental Stress

Various forms of physical exertion have been shown to be triggers of acute MI, and investigators have found marked changes in hemodynamic variables associated with exertion. Both dynamic and static forms of exercise increase blood pressure, heart rate, and plasma catecholamines *(120,121)*. Similar changes are seen with mental stress and cold exposure *(120,121)*. Exercise and mental stress have been demonstrated to increase platelet activity, but they also appear to increase fibrinolytic activity, and it is not clear whether the balance in these situations would favor thrombosis or thrombolysis *(120)*. The potential effect of mental stress on hemodynamic and hemostatic variables is illustrated by a study of individuals who experienced a major earthquake in Japan, but escaped physical injury *(83)*. The investigators compared a variety of measures of hemodynamic and hemostatic status 7–14 d after the quake with samples that were coincidentally obtained during the 60 d before the quake. There were significant increases in systolic and diastolic blood pressure, hematocrit, fibrinogen level, von Willebrand factor level (which reflects endothelial cell dysfunction), D-dimer (which reflects the formation and degradation of fibrin—its elevation is an indicator of activation of the hemostatic system), and two fibrinolytic factors. All values decreased to prequake levels after 4–6 mo (Fig. 13).

THERAPEUTIC CONSIDERATIONS

β-*Adrenergic Blocking Drugs*

Given the pivotal role of the sympathetic nervous system as a mediator of the triggering process, close attention has been paid to the effects of β-adrenergic blocking agents on the onset of acute coronary syndromes. Several studies of circadian variation in time of onset of acute MI reported that the morning excess of events was attenuated in patients taking β-blockers compared with patients not taking these agents at the time of the acute event *(15,16,18,26,57,122)* (Fig. 14). β-Blocking agents have also been shown to reduce the morning increase in frequency of ventricular tachyarrhythmias in patients with AICDs *(123)* and to attenuate the morning increase in sudden cardiac deaths in post-MI patients *(124)*. Studies of unstable angina and non-Q-wave MI have not demonstrated this beneficial effect of β-blockade on the circadian variation of these events *(28,32)*. However, this finding is still consistent with a beneficial effect of β-blockers on triggering mechanisms, in that it may represent a β-blocker therapy-related shift in morning events from

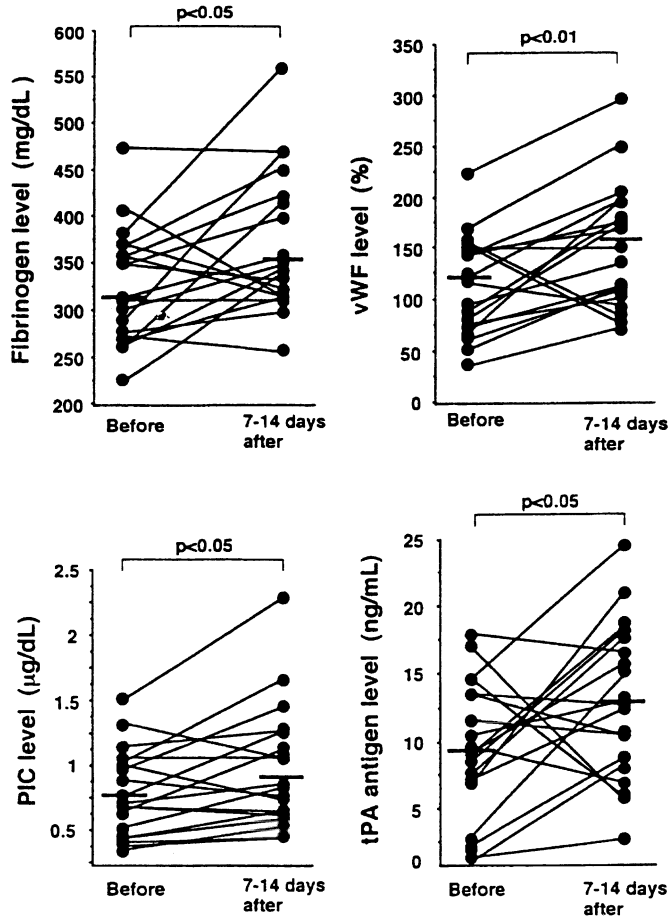


Fig. 13. In 42 elderly patients who experienced "high stress" but no physical injury during a major earthquake in Japan, levels of coagulation and fibrinolysis-related proteins increased significantly following the quake. Blood samples from within the 60 d preceding the quake were available for analysis (X-axis, "before"), and were matched with samples 7–14 d after the quake. In addition to fibrinogen levels, results are reported for plasmin–α_2–plasmin inhibitor complex (PIC; a fibrinolytic factor), von Willebrand factor (vWF; an endothelial cell-derived factor), and tissue-type plasminogen activator (tPA antigen; also a fibrinolytic factor). Levels had returned to baseline 6 mo later. Reproduced with permission from ref. *83*.

acute MI to less serious acute ischemic syndromes *(28)*. Several randomized prospective studies of β-blocker therapy in patients with ambulatory ischemia have also shown a beneficial effect of these drugs on the frequency of acute ischemic events *(125,126)*.

Calcium Channel Blocking Agents and Nitrates

The ability of other antiischemic drugs such as calcium channel blocking agents and nitrates to blunt potential triggering mechanisms is less clear. Two large studies of the circadian variation in time of onset of acute MI identified a subset of patients taking calcium channel blockers and found a persistent morning increase in infarctions in these patients *(18,26)* (Fig. 14). On the other hand, some smaller trials reported the absence of a morning increase in infarction *(122)* and sudden cardiac death *(127)* in patients taking

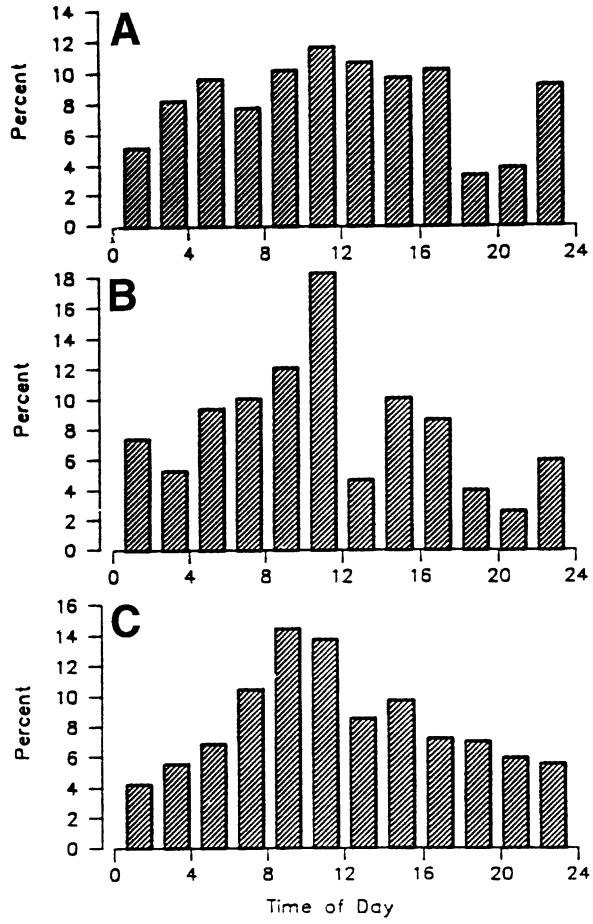


Fig. 14. The effect of β-blockade on the morning increase in infarctions. The morning increase in infarctions seen in the Intravenous Streptokinase in Acute Myocardial Infarction (ISAM) trial (**C**) was preserved in patients taking calcium channel blocking agents (**B**) but was attenuated in patients taking β-blocking drugs (**A**). Reproduced with permission from ref. *16.*

calcium channel blocking agents. Two subset analyses from trials reporting nitrate usage described no beneficial effect of this agent on the circadian variation of MI onset *(26,122).* However, one study found that the lack of use of nitrates or calcium channel blockers in the 24 h prior to the onset of infarction was associated with a higher frequency of infarction during physical exertion *(26).*

Antithrombotic Agents

The effect of aspirin on the circadian pattern of MI is also uncertain. In the TIMI II and the second International Study of Infarct Survival patient populations, a history of aspirin use or nonuse at the time of infarction did not affect the morning increase in infarction incidence *(18,26).* By contrast, the Physician's Health Study followed 22,071 healthy middle-aged men randomized to aspirin or placebo over five yr *(128).* The aspirin group had a 44.8% reduction in the incidence of nonfatal infarction, with an additional 25.2% reduction between 4 AM and 10 AM (Fig. 15). One other study of consecutive MI admissions reported a beneficial effect of aspirin similar to that in the Physician's Health Study

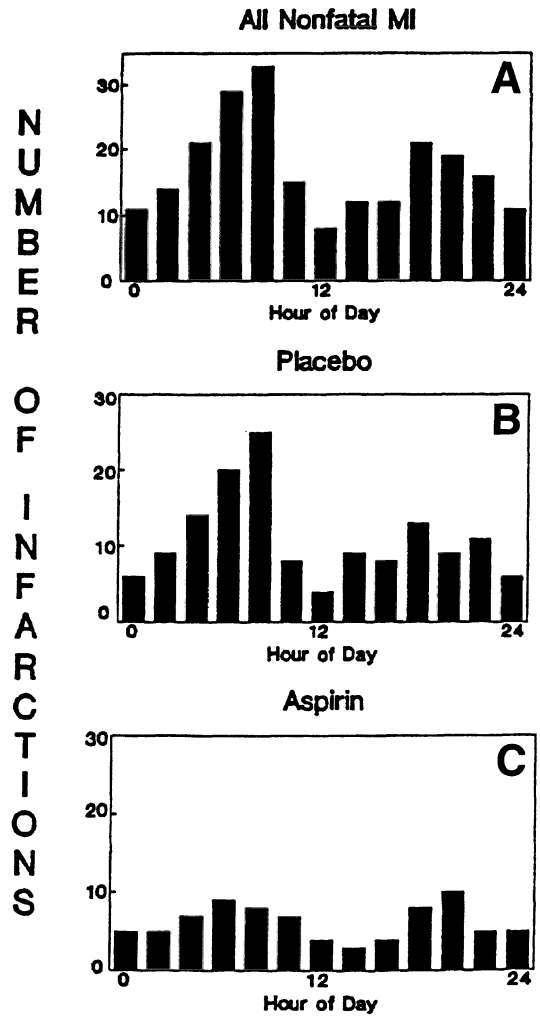


Fig. 15. In the Physician's Health Study of the effect of aspirin on cardiovascular disease, the significant ($p < 0.001$) morning increase among 211 nonfatal myocardial infarctions (top) was preserved in patients randomized to placebo ($p < 0.001$) (middle) and attenuated ($p = 0.16$) in patients randomized to aspirin 325 mg every other day (bottom). Reproduced with permission from ref. *128.*

(57). The Myocardial Infarction Onset Study also found that regular users of aspirin had a reduction in the relative risk of MI induced by episodes of anger *(87).*

The efficacy of thrombolytic agents also appears to have a circadian variation *(129–131).* In one study of 692 patients undergoing coronary arteriography 90 min after receiving intravenous tPA, complete patency was observed in 42% of patients given the drug between noon and midnight, compared with 29% of patients given the drug between midnight and noon ($p < 0.001$) *(129).* Two smaller studies demonstrated similar effects *(130,131).*

Treatment of Myocardial Ischemia and Triggering

Episodes of myocardial ischemia may presage the onset of acute coronary events and may trigger malignant ventricular arrhythmias. Studies of β-blocking agents *(35,132–133),*

calcium channel blocking agents *(134,135)* and their combination *(132,135)* have shown that both agents alone or in combination can reduce the total number of ischemic episodes in a 24-h period, and that β-blocking drugs are particularly effective at attenuating the well-documented morning increase in ischemia *(35,132,133)*. The effect of β-blockers may be mediated by the reduction in heart rate, as heart rate increases precede most episodes of ambulatory ischemia *(91,132,133)*. Long-acting calcium channel blocking agents may not have the same effect on the circadian variation of ischemic episodes *(35,134)*. Calcium channel blocking agents such as nifedipine appear to prevent ischemic episodes that are unrelated to heart rate increases, suggesting that their effect may be mediated by increasing myocardial oxygen supply rather than by decreasing myocardial oxygen demand *(133)*. One randomized crossover study comparing atenolol, amlodipine, and placebo found that atenolol was more effective at suppressing episodes of ambulatory ischemia, whereas amlodipine was more effective at suppressing exercise-induced ischemia *(136)*.

β-Blocking agents have been shown to blunt the heart rate and blood pressure increases that occur in association with mental stress, and with handgrip *(137)*, but do not appear to affect indices of hemostatic function *(137,138)*. This further supports the role of β-blockade as primarily a modifier of the hemodynamic factors thought to play a role in the triggering of acute coronary events.

The link between ischemia suppression and cardiac prognosis is supported by at least two randomized studies. The Atenolol Silent Ischemia Study randomized 306 patients to atenolol or placebo *(125)*. The group treated with the β-blocker had significantly fewer episodes of ischemia on ambulatory monitoring, and after 1 yr of follow-up had significantly fewer cardiac events (relative risk 0.44 [95% CI 0.26–0.75]). The Total Ischemic Burden Bisoprolol Study followed 520 patients for 1 yr, with a similar result: patients randomly assigned to the β-blocking agent bisoprolol had significantly fewer cardiac events *(126)*.

OTHER IMPLICATIONS FOR PATIENT MANAGEMENT

A number of practical clinical considerations emerge from the current state of knowledge of the triggering of acute cardiovascular events. One of these is information given to patients concerning the role of activities as precipitants of past or future acute events. Four specific triggers—awakening, heavy physical exertion, sexual activity and anger—have been linked by epidemiologic studies to the onset of acute MI. Data concerning triggering of acute cardiac disease onset is of value when a physician is involved in a legal debate over the role of a given event in precipitating acute cardiovascular disease.

It is important to specify the difference between the absolute and relative risk of cardiac events in relation to specific triggers when advising patients concerning activities. The baseline risk of MI in a sedentary but otherwise healthy middle-aged man is estimated at 1%/y, or an hourly risk (8760 h/yr) of slightly greater than 1/1 million *(139,140)*. As an example, consider this individual engaging in sexual activity, which triples the risk of MI onset during the 2 postcoital hours *(78)*. Twice-weekly sexual activity would be predicted to increase the annual mortality from 1% to only 1.06%. These statistics should be reassuring to individuals concerned about the possibility of intercourse-induced MI. On the other hand, heavy physical exertion in a sedentary patient increases relative risk of MI 100-fold *(73)*. For a hypothetical postinfarction patient with an annual MI risk of 4%, 1 h of active singles tennis once a week as his or her sole form of exercise increases the annual MI risk from 4% to 6% *(73)*.

Regular physical exercise has beneficial effects on a variety of health-related parameters, including cardiovascular disease and mortality *(141–143)*. These benefits include reducing the increased risk of acute MI immediately after heavy exertion and intercourse. Healthy individuals at risk for coronary artery disease, as well as patients with known cardiovascular disease, should be encouraged to begin and maintain a program of regular exercise after appropriate medical screening *(143)*. Given the well-documented morning increase in the risk of MI and sudden cardiac death, a prudent recommendation concerning the timing of exercise sessions might be that patients with a higher baseline risk of events who are sedentary and beginning a regular exercise program perform exercise at times other than in the morning. After the patient has become conditioned to a schedule of regular moderate to heavy exercise, and the relative risk of an exercise-related event decreases, morning exercise times can be included.

β-Blocking drugs are ideal agents for modulating the surges in sympathetic nervous system activity that appear to be associated with myocardial ischemia and acute cardiac events. This class of drugs should be the first choice for the treatment of patients with coronary artery disease and myocardial ischemia, and for post-myocardial infarction patients. The ability of β-blockers to blunt the morning increase in infarctions suggests that these agents may be beneficial in some patients without clinically manifest coronary disease, and thus β-blocker therapy could reasonably be considered as the first-line agent for treatment of hypertension in patients who are considered to be at high risk for the presence of underlying atherosclerotic coronary artery disease. There are no data concerning the effect of β-blocker therapy on prognosis in patients with atherosclerotic coronary artery disease, no prior infarction, and no demonstrable ischemia. The role of calcium channel blocking drugs in the management of patients with coronary disease is controversial *(144,145)*. The data on the ability of calcium channel blockers, as monotherapy, to blunt the morning increase in infarctions and ambulatory ischemic episodes are conflicting, although these drugs reduce the total burden of ambulatory ischemic episodes. Given the early morning increase in cardiac events, it is preferable to select drug formulations with long half-lives, to provide a pharmacologic effect over the entire 24-h period *(146,147)*.

The evidence of a morning procoagulant state, and the possible reduction in morning cardiac event rate with aspirin gives further support to the recommendation for indefinite use of this drug for patients with proven or suspected coronary atherosclerosis. The demonstration of morning resistance to thrombolysis could conceivably influence clinical decision making concerning management of patients presenting with acute MI at different times of the day. Although there are as yet no data to support a change in current thrombolytic drug dosing strategies, some authors have suggested a possible need for varying drug dosages for patients presenting at different times of the day *(148,149)*.

The data tying states of high emotional and mental stress to myocardial ischemia and acute cardiac events also have potential implications regarding therapy. Individuals with coronary artery disease who suffer frequent periods of emotional stress or outbursts of anger might be considered for pharmacotherapy or counseling in an attempt to reduce the frequency and severity of these experiences. However, studies to date have not clearly shown that such therapy reduces the incidence of acute cardiac events *(150)*. In addition, heightened preparations by emergency service personnel for dealing with victims of acute cardiac disease can be considered during periods of general calamity such as natural disasters.

In addition to therapy mitigating potential triggers of acute cardiovascular events, the clinician must address the factors contributing to the development of the atheromatous lesions that will eventually develop into vulnerable plaques. This includes control of hypertension and diabetes mellitus, treatment of dyslipidemia, and cessation of cigarette smoking. Cigarette smoking poses a particular threat, as it promotes development of the atherosclerotic substrate and in addition may facilitate triggering mechanisms involving the sympathetic nervous system and hemostatic factors *(120)*. Recent evidence supports the aggressive use of lipid-lowering therapy to reduce the incidence of cardiac events in patients with *(151)* and without *(152)* documented coronary artery disease.

FUTURE DIRECTIONS

The development of the concept of the vulnerable atherosclerotic plaque has spurred investigation into the biologic differences between stable and vulnerable plaques, and the means by which therapeutic agents may convert a plaque from a vulnerable plaque to a stable lesion resistant to forces triggering plaque rupture *(153)*. Aggressive lipid-lowering therapy might exert its beneficial effects on acute event rates by altering the size and composition of the lipid pool, thereby altering the physical characteristic of the plaque *(153)*. Recent investigations into the beneficial effects of lipid-lowering therapy on coronary artery endothelial function suggest that endothelial function plays a critical role in the development of cellular and biochemical features characteristic of vulnerable plaques, and in determining the rheologic and hemostatic milieu in which a plaque exists when it is exposed to triggering stimuli *(154,155)*. An exciting new area of investigation is related to the possible role of infectious agents in atherogenesis *(156,157)*. Future therapy to reverse the alterations in plaque biology favoring vulnerability may include antimicrobial agents.

In addition to improving understanding of plaque biology, clinically applicable methods will need to be developed to detect vulnerable plaques in patients. Contrast arteriography, currently the most widely used technique to visualize the coronary arteries, shows the degree to which plaques obstruct the arterial lumen and can determine gross features of plaque such as large ulcerations *(14)*. Arteriography has a limited ability to identify obstructive plaques that are likely to produce acute coronary syndromes and cannot identify the minimal, nonobstructive lesions that are often the culprits in acute syndromes *(14)*. Intravascular ultrasound, a clinically available imaging modality, has greatly improved the ability to visualize the structure of the coronary artery, albeit with limited resolution *(158)*. Emerging new technologies, such as optical coherence tomography *(158,159)* magnetic resonance imaging of the coronary arteries *(160)*, thermal detection techniques *(161)*, and near-infrared spectroscopy *(162,163)* may provide a superior means of imaging vulnerable plaques. Near-infrared spectroscopy has the potential to image both the architecture and the biochemical composition of atherosclerotic material. When vulnerable plaques are identified, future therapeutic options may include lesion-specific approaches such as gene transfer techniques *(164)* or local irradiation *(165)*, in addition to systemic pharmacotherapy.

Current data suggest that the well-characterized triggers of infarction (awakening, heavy exertion, anger, and sexual activity) account for 15–20% of all infarctions *(166)* (Fig. 16). It is likely that further epidemiologic studies will identify additional triggers, particularly the less well-studied issues related to mental stress and to the onset of events

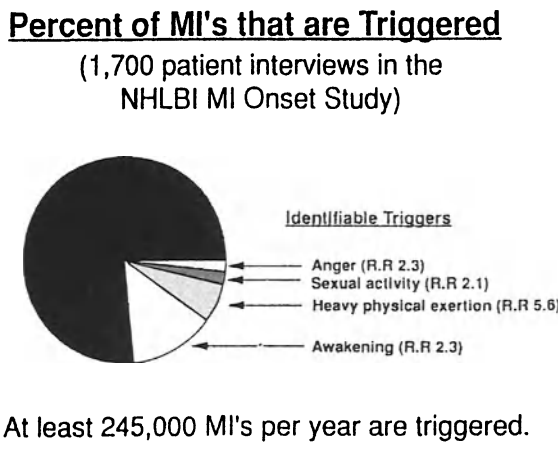


Fig. 16. Percent of myocardial infarctions that are triggered. Reproduced with permission from ref. *166*.

occurring during sleep. It is not possible to free human beings from the circumstances that appear to trigger the onset of acute cardiovascular disease. The goals of future research will be to elucidate further the mechanisms connecting human circumstances to plaque rupture and intracoronary thrombosis and to develop therapy to weaken or sever these links.

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4 Insights into the Pathophysiology of Acute Coronary Syndromes Using the TIMI Flow Grade and TIMI Frame Counting Methods

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INTRODUCTION

For over a decade now, the Thrombolysis in Myocardial Infarction (TIMI) flow grade classification scheme has been successfully used to assess coronary blood flow in acute coronary syndromes *(1)*. Although this scheme has been a valuable tool for comparing the efficacy of reperfusion strategies and identifying patients at higher risk of adverse outcomes in acute coronary syndromes, it has limitations *(2,3)*. To overcome them, the TIMI Angiographic Core Laboratory developed a new index of coronary blood flow called the TIMI Frame Count *(2)*. In contrast to the TIMI flow grades, which are subjective categoric variables, the TIMI frame count is an objective continuous variable *(2)*. The

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goal of this chapter is to review these two methods and to discuss the insights into the pathophysiology of acute coronary syndromes provided by these indexes of coronary blood flow.

THE TIMI FLOW GRADE CLASSIFICATION SCHEME

The original definition of the TIMI flow grades from the TIMI 1 study in 1986 *(1)* are as follows:

Grade 0: No perfusion. No antegrade flow beyond the point of occlusion.

Grade 1: Penetration without perfusion. Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.

Grade 2: Partial perfusion. Contrast material passes across the obstruction and opacifies the coronary distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its flow into or clearance from comparable areas not perfused by the previously occluded vessel.

Grade 3: Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Recently, several groups have begun to define TIMI grade 3 flow as opacification of the coronary artery within three cardiac cycles *(4,5)*. As the definition above shows, this is not how TIMI grade 3 flow was originally defined *(1)*. This substantial departure from the original definition will result in much higher rates of TIMI grade 3 flow. In most patients with TIMI grade 3 flow in thrombolytic trials (TIMI 4, 10A, and 10B) *(6–8)*, it requires just under 1 s (26.8 ± 9.1 frames or 0.9 s; $n = 693$) or one cardiac cycle to traverse the length of the artery. Obviously, increasing the time for dye to go down the artery by a factor of 3 (i.e., from one to three cardiac cycles) that is permissible to qualify for TIMI grade 3 flow greatly increases the rate of TIMI grade 3 flow. Preliminary data from the TIMI Angiographic Core Laboratory suggests that the three-cardiac cycle definition of TIMI grade 3 flow results in an approximately 15% increase over the original definition of TIMI grade 3 flow.

It is possible that TIMI grade 1 flow may sometimes be classified as TIMI grade 2 flow. In the TIMI Angiographic Core Laboratory, we follow the original definition in classifying TIMI grade 2 flow: the dye must reach the apex of the heart during the duration of filming. It is our experience that TIMI grade 1 flow comes in two varieties: one in which the dye barely penetrates the lesion and the other in which dye penetrates the lesion fairly well but the dye moves down the artery so slowly that the operator stops filming before it reaches the apex. We interpret the original definition of TIMI grade 1 flow very literally, and if the dye is not filmed as it reaches the apex, we classify this as TIMI grade 1 flow. It is unclear whether other angiographic core laboratories would classify dye that may reach the apex but is not filmed reaching the apex as TIMI grade 2 flow. If they do classify flow in this fashion, then this may account for the higher rates of mortality that have been reported by other angiographic core laboratories for TIMI grade 2 flow.

Limitations

One limitation of the TIMI flow grade classification scheme is a high rate of interobserver variability in the assessment of TIMI flow grades. The rate of agreement between an angiographic core laboratory and clinical centers is best when determining if a culprit artery is either open or closed (κ value = 0.84 ± 0.05, which indicates good agreement) *(2)*. By contrast, the rate of agreement is only moderate when assessing TIMI grade 3 flow (κ value = 0.55 ± 0.05) and is actually poor in the assessment of TIMI grade 2 flow (κ value = 0.38 ± 0.05) *(2)*. Even between experienced angiographic core laboratories, there can be a frequent lack of concordance. In a recent study, the rate of agreement between two core laboratories in the assessment of TIMI grades 2 and 3 flows was only 83%, and three experienced angiographic core laboratories achieved complete agreement in only 71% of the cases *(3)*.

For many years it has been assumed that there are distinct categories of coronary blood flow. However, we have shown that coronary blood flow is unimodally distributed as a continuous variable *(2)*. It has also been assumed that the flow in the nonculprit artery (the flow used as the gold standard for assessing TIMI grade flow in the infarct-related artery) is truly "normal". As is discussed below, this assumption is not well justified. Finally, as newer reperfusion strategies achieve a higher rate of TIMI grade 3 flow, this categoric method may have limited statistical power and sensitivity in distinguishing the efficacy of different reperfusion strategies as a range of velocities may be associated with TIMI grade 3 flow *(2)*.

THE TIMI FRAME COUNT

To overcome the limitations associated with the TIMI flow grade classification scheme, we have recently described a more objective and precise method of estimating coronary blood flow, the TIMI frame count, in which the number of cineframes required for dye to reach standardized distal landmarks are counted *(2)*. In the first frame used for TIMI frame counting, a column of dye touches both borders of the coronary artery and moves forward (Fig. 1). In the last frame, dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery (Fig. 1). These standard distal landmarks are as follows: in the right coronary artery the first branch of the posterolateral artery; in the circumflex system the most distal branch of the obtuse marginal branch, which includes the culprit lesion in the dye path; and in the left anterior descending artery (LAD) the distal bifurcation, which is also known as the "moustache," "pitchfork," or "whale's tail" (Fig. 1). These frame counts are corrected for the longer length of the LAD by dividing by 1.7 to arrive at the Corrected TIMI Frame Count (CTFC) *(2)*.

In contrast to the conventional TIMI flow grade classification scheme, the CTFC is quantitative rather than qualitative, objective rather than subjective, a continuous rather than a categoric variable, and reproducible *(2)*. Indeed, with respect to variability, the mean absolute value of the difference between two consecutive hand injections of the infarct-related artery was only 4.7 ± 3.9 frames ($n = 85$) *(2)*. Other groups, such as Ellis et al *(9)*, have shown even better measures of reproducibility. These authors examined angiograms on two different occasions separated in time by 6 mo; they found correlations of 0.97 in their readings over time and 0.99 between three different observers *(9)*. There was a 0.7–2.0 frame difference between observers *(9)*.

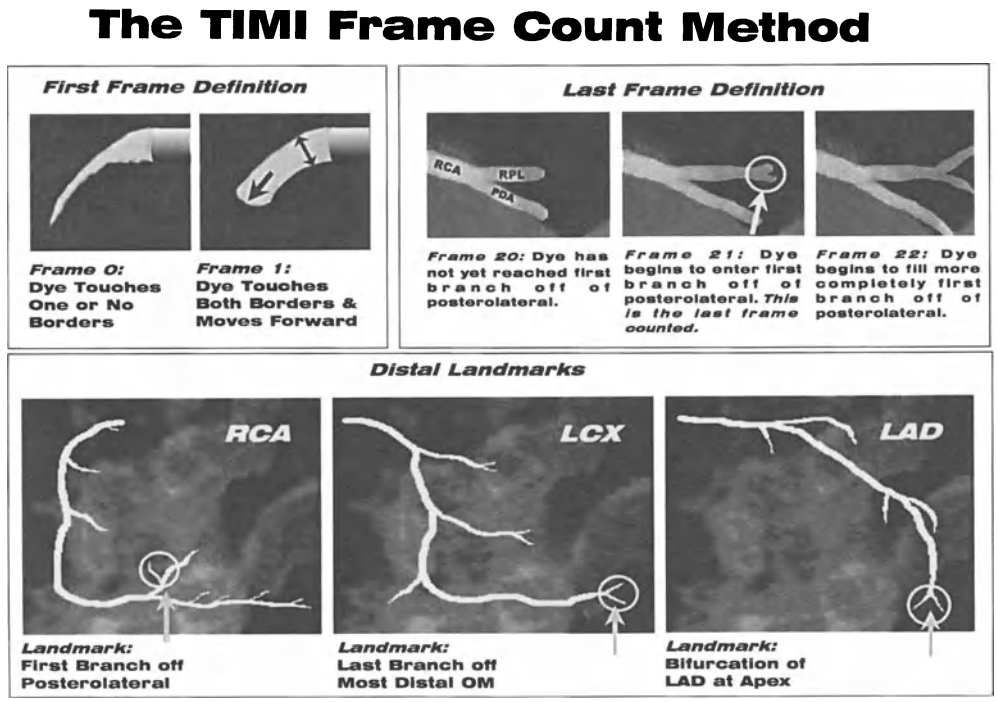

Fig. 1. The TIMI Frame Counting method. In the first frame (upper left), a column of nearly or fully concentrated dye touches both borders of the coronary artery and moves forward. In the last frame (upper right), dye begins to enter (but does not necessarily fill) a standard distal landmark in the artery. These standard distal landmarks are as follows: the first branch of the posterolateral artery in the right coronary artery (lower left); in the circumflex system the most distal branch of the obtuse marginal branch, which includes the culprit lesion in the dye path (lower middle); and in the left anterior descending artery the distal bifurcation, which is also known as the "moustache," "pitchfork," or "whale's tail" (lower right).

Normal flow in normal arteries in the absence of acute myocardial infarction (MI) has been found to be 21.0 ± 3.1 frames (n = 78) *(2)*, with the 95% confidence interval for normal flow extending from >14 frames to <28 frames. Despite differences in length of the coronary arteries, force of injections, diameter of the arteries, heart rates, cardiac output, and catheter engagement, we have found that the standard deviation among 78 arteries with normal flow was only 3.1 frames, a coefficient of variation of approximately 14% *(2)*. We have recently studied the impact of the force of injection and shown that the CTFCs following power injections performed at the 10th and 90th percentiles of human injection rates differ from each other by only two frames *(10,11)*.

Using the CTFC, coronary blood flow appears to be unimodally distributed as a continuous variable *(2)* (Figs. 2 and 3). Thus, any division of flow into normal and abnormal categories is arbitrary. Although we do not use the CTFC to determine the TIMI flow grades, in a retrospective analysis the TIMI Angiographic Core Laboratory tended to classify flow as TIMI grade 2 flow if the CTFC was >40 (approximately 1.3 s) *(2)*. In the TIMI 4, 10A, and 10B trials *(6–8)*, the 90-min CTFC in culprit arteries is unimodally distributed with a mean CTFC of 35.6 ± 20.8 frames (n = 960) at 90 min after thrombolysis (Figs. 2 and 3). Approximately one-fourth of patients achieved normal flow with a

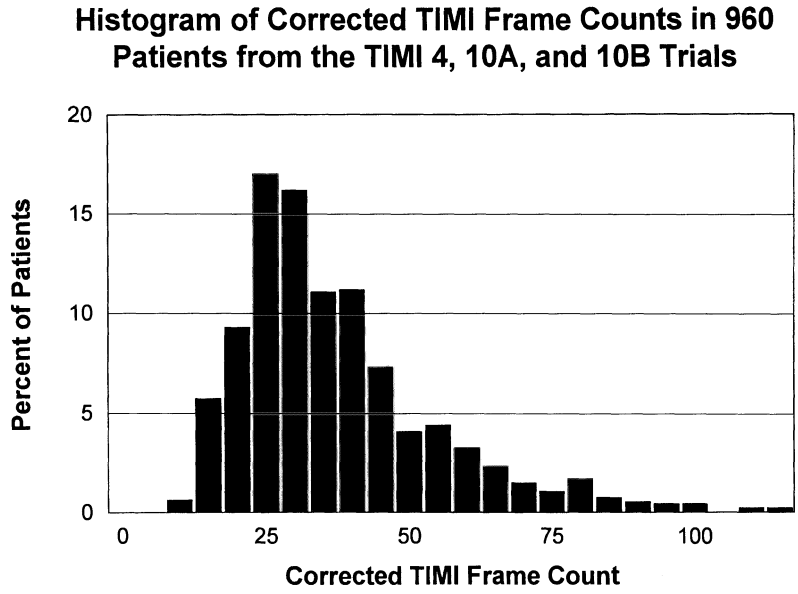

Fig. 2. Histogram displaying the percent of patients with a given Corrected TIMI Frame Count (CTFC; grouped by bins of five frames) following thrombolysis in the TIMI 4, TIMI 10A, and TIMI 10B trials. Note that very few patients have a CTFC > 100.

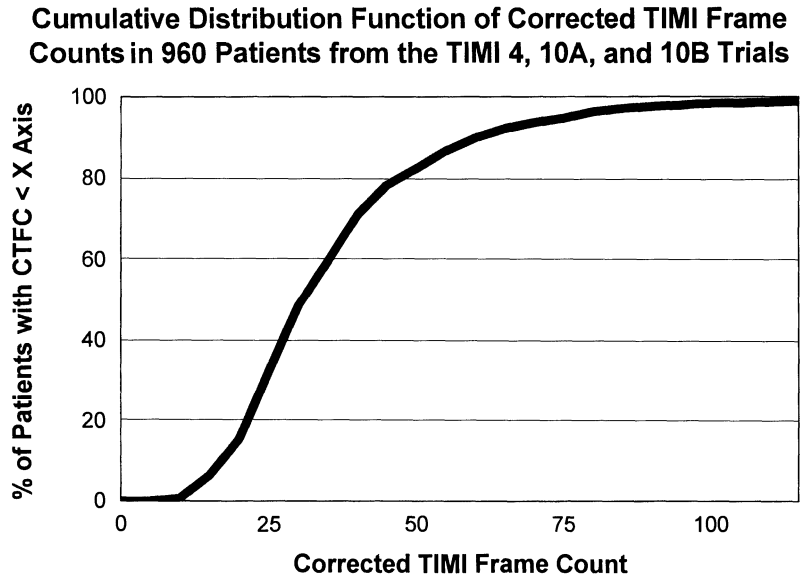

Fig. 3. Cumulative distribution function of Corrected TIMI Frame Counts (CTFCs) in 960 patients from the TIMI 4, 10A, and 10B studies. Any CTFC can be chosen on the X-axis as a definition of thrombolytic success. The corresponding value on the Y-axis displays the percent of patients that satisfy that definition of success. Only approximately one-fourth of patients have normal flow (i.e., a CTFC < 28) following thrombolysis.

CTFC < 28 frames, (i.e., within the 95% confidence interval for flow in patients without acute MI) (Fig. 3).

NONCULPRIT FLOW AS A FLAWED GOLD STANDARD

Traditionally, it has always been assumed that the basal flow in nonculprit arteries in the setting of acute MI following thrombolysis is "normal." However, using the CTFC, basal flow in the uninvolved artery is in fact *not normal (2)*. In the setting of acute MI, the mean CTFC at 90 min following thrombolysis among the nonculprit arteries (30.5 ± 15.0; n = 1049) *(6–8)* was 45% higher than minimally diseased arteries with normal flow in the absence of acute MI (21.0 ± 3.1; $p < 0$ .001) but returned to that of normal arteries by 18–36 h following thrombolysis (21.3 ± 7.1; n = 76; p = NS) *(2)*.

This problem is further complicated by the fact that nonculprit arteries may not all be slowed to the same degree, depending upon their location. We have shown that flow in nonculprit LAD arteries was disproportionately slowed by 36% when compared with that in uninvolved circumflex arteries, which confounds the classification of conventional TIMI flow grades *(2)*. While our original study showed that the CTFC in LAD culprits is on the whole *higher* (reflecting slower flow) than that in other locations at 90 min following successful thrombolysis, the CTFC *for TIMI grade 3* flow was actually 32% *lower* for LAD culprits when compared with the circumflex artery (25.7 vs 34.0 frames) *(2)*. This paradox was explained by the fact that TIMI grade 3 flow in culprit LAD arteries was gauged against faster flow in nonculprit circumflex arteries (22.5 frames), and consequently few LAD culprits (26.2%) achieved a rapid enough velocity to be classified as achieving TIMI grade 3 flow. By contrast, flow in circumflex culprits was graded against the 36% slower flow in nonculprit LADs (30.5 frames), and therefore most circumflex arteries (92%) were classified as achieving TIMI grade 3 flow *(2)*. Thus, the conventional notion that flow in uninvolved arteries is "normal" may be erroneous and may lead to the misclassification of TIMI flow grades. In the right coronary artery, no other "normal" artery is even present for comparison. The complexity of visual flow grade assessment is further compounded by the fact that international cinefilms are filmed at wide, subtle varieties of speeds (12.5, 15, 25, 30, 50, 60 frames/s).

In addition to these reductions in basal nonculprit flow, Uren et al. *(12)* have shown in positron emission tomography scanning experiments that the coronary vasodilatory response (the ratio of myocardial blood flow after the administration of dipyridamole to the basal myocardial blood flow) in angiographically normal nonculprit arteries remains reduced at 1 wk following acute MI compared with control patients without acute MI (1.53 ± 0.36 vs 3.17 ± 0.72; p = 0.009). Similarly, in a study by Marjorie et al *(13)* in isolated perfused rat hearts, basal coronary blood flow in acute MI hearts was completely normalized within one week, whereas maximal coronary blood flow was not normalized until 5 wk after acute MI. Thus, acute MI impairs both basal and maximal flow in nonculprit territories. In addition, Wyatt et al. *(14)* and Corday et al. *(15)* have shed some light on the pathophysiology of delayed flow in remote areas of the heart by demonstrating that focal necrosis (microinfarcts) and regional lactate derangements occur in the nonoccluded (remote) posterior segments of the left and right ventricles after occlusion of the proximal LAD in closed chest dogs.

We have reported that the predictors of delayed flow in the nonculprit artery include slower flow in the culprit artery, a longer length of culprit vessel distal to the stenosis (i.e., a bigger infarct), a tighter stenosis in the nonculprit artery, and pulsatile flow in the culprit

artery *(16)*. The observation relating pulsatile culprit flow to delayed nonculprit flow sheds light on the potential mechanism of global flow delays. Doppler velocity wire studies have shown that a pulsatile pattern of flow with systolic flow reversal is observed in the setting of the no-reflow phenomenon and that this flow pattern reflects heightened downstream microvascular resistance.

We have recently reported that flow improves in the nonculprit artery as flow improves in the culprit artery in the setting of acute MI *(17)*. The CTFC in nonculprit arteries improved by 8% between 60 and 90 min following thrombolysis (34.9 to 32.1 frames; $p < 0.0005$) *(17)*. When flow improved in the associated culprit artery between 60 and 90 min, nonculprit artery flow improved by 13% (36.0 to 31.1 frames, a change of 4.7 frames, $p < 0.0005$) *(17)*. By contrast, when flow did not improve in the associated culprit artery, there was no significant improvement in the nonculprit artery flow (33.8 vs 33.3 frames, p = NS) *(17)*. Similarly, in the setting of percutaneous transluminal coronary angioplasty (PTCA) for unstable angina syndromes, we have shown that PTCA of the culprit lesion was associated with a 3-frame improvement in the nonculprit artery after the intervention *(18)*. Again, if abnormal flow was present in the nonculprit artery at baseline (i.e., CTFC > 28), then the improvements in nonculprit flow were more dramatic (10 frames) *(18)*. It could be speculated that the delayed flow in nonculprit arteries may be the result of more extensive necrosis in shared microvasculature, or a result of vasoconstriction mediated through either a local neurohumoral or paracrine mechanism. Further studies are needed, however, to determine the cause of delayed flow in the nonculprit arteries.

It has recently become apparent that epicardial flow does not necessarily imply tissue level or microvascular perfusion *(19,20)*. In myocardial contrast echocardiography (MCE) studies by Ito et al. *(19,20)*, the culprit artery was patent after angioplasty or thrombolysis within 24 h of symptom onset in 126 patients with anterior MI. However, despite epicardial patency, one-fourth of patients had a lack of tissue level perfusion and the no-reflow phenomenon; these patients had a higher rate of adverse outcomes (sustained arrhythmias, pericardial effusion, cardiac tamponade, congestive heart failure or death) and a lower rate of improvement in global (5% vs 11%) as well as regional left ventricular, (LV) contractile function (SD/chord) (–0.4 vs –0.9) *(19,20)*.

Several mechanisms have been postulated in the development of the no-reflow phenomenon following acute MI: a loss of microvasculature integrity and profound spasm of microvasculature caused by the release of potent vasoconstrictors from activated platelets (e.g., serotonin), or neutrophil infiltration and platelet fibrin clots in the microvasculature *(21–27)*. Adjunctive therapies such as superoxide dismutase, catalase, adenosine, verapamil, papaverine, ketanserine (a serotonin inhibitor), and other new therapies targeted at the microvasculature may warrant further investigations *(28–30)*.

Unlike the epicardial artery, the microvasculature responds poorly to nitroglycerine due to impaired synthesis of endothelium-derived relaxing factor (EDRF) *(24)*. Calcium channel blockers act directly on vascular smooth muscle rather than EDRF and may be of benefit in minimizing microvascular spasm. Indeed, in a prospective trial by Taniyama et al. *(31)*, MCE has been used after primary angioplasty to demonstrate that the low reflow ratio (ratio of no-flow zone plus low-reflow zone to the risk area) decreased by 45% after the administration of 0.5 mg of intracoronary verapamil (from 0.39 ± 0.23 to 0.29 ± 0.17; $p < 0.05$) *(31)*. The improvement in the regional wall motion score index from baseline to follow-up study at 24 d was higher in the verapamil-treated group than in the control group (0.7 ± 0.8 vs 0.2 ± 1.3; $p < 0.05$) *(31)*. A major question has been whether

microvascular spasm is an epiphenomenon in acute MI and whether improving microvascular spasm will lead to improved clinical outcomes. This small preliminary study suggests that intracoronary verapamil can attenuate microvascular spasm and that it can in turn augment basal tissue level perfusion. It provides a critical link in relating these improvements in tissue perfusion to improved wall motion in patients with acute MI *(31)*.

RELATIVE CONTRIBUTION OF THE EPICARDIAL STENOSIS AND MICROVASCULAR RESISTANCE TO FLOW DELAYS

Although the no-reflow phenomenon exists in many patients with acute MI, the magnitude of its contribution to flow delays following thrombolysis is unclear and may be relatively small. For instance, verapamil administration in the previous study reduced the CTFC by only 9 frames (from 50 ± 15 to 41 ± 14; $n = 40$; $p < 0.01$) *(31)*. The relief of the residual stenosis by conventional PTCA and the scaffolding provided by intracoronary stent placement present unique opportunities to examine the potential role of both the residual stenosis and intraluminal obstruction to flow delays following thrombolysis *(32,33)*. Unlike conventional PTCA, intracoronary stenting relieves any residual intraluminal obstruction caused by dissection planes that may cause baffling and nonlaminar flow. Any persistent delay in flow following adjunctive stenting is unlikely to be due to the residual stenosis or intraluminal obstruction and probably represents the contribution of downstream microvasculature resistance. Both rescue and adjunctive PTCA of the residual stenosis at 90–120 min largely normalized discrepancies in pre-PTCA frame counts between the TIMI flow grades *(32,33)*. Adjunctive and rescue angioplasty also restored flow in culprit vessels that was nearly identical to that of nonculprit arteries in the setting of acute MI (28.6 vs 30.5 frames; p = NS) *(32,33)*. These observations should not, however, be misinterpreted as demonstrating that PTCA completely restores "normal" flow. It is important to note that post-PTCA CTFCs and nonculprit CTFCs of 30 are both in actuality *abnormally* slowed, and they are nearly 45% slower ($p < 0.001$) than the CTFC of 21 previously reported in patients without acute MI and normal flow *(2)*. Despite a 13% residual diameter stenosis and the relief of intraluminal obstruction that would be anticipated following stent placement, flow was persistently delayed to 26 frames, and likewise 34% of stented vessels had abnormal flow with a CTFC ≥ 28 (the 95th percentile of the upper limit of normal) *(32,33)*. This persistent delay is unlikely to be due to either the residual stenosis or intraluminal obstruction and probably represents the contribution of downstream microvascular resistance. To summarize the magnitude of flow delays attributable to microvascular resistance, nonculprit and culprit artery flow following relief of the stenosis by PTCA/stenting is delayed by approximately 5 to 10 frames; likewise, treatment of heightened microvascular resistance with verapamil improves flow by approximately 9 frames.

We have reported the multivariable determinants of coronary blood flow at 90 min following thrombolysis; a map of the multiple colinearities we observed is shown in Fig. 4 *(34)*. Obviously the residual percent stenosis plays a critical role, with the average 70% stenosis increasing the CTFC by approximately 17 frames *(34)*. The presence of residual thrombus adds approximately 4 frames *(34)*. Thus, superior revascularization strategies will reduce the residual stenosis and eliminate thrombus. There were also some unanticipated contributors to delayed flow such as the timing of reperfusion, i.e., those patients who were patent at 60 min had 15 frames faster flow than those patients who achieved flow between 60 and 90 min. LAD infarcts had slower flow by 8 frames than infarcts in

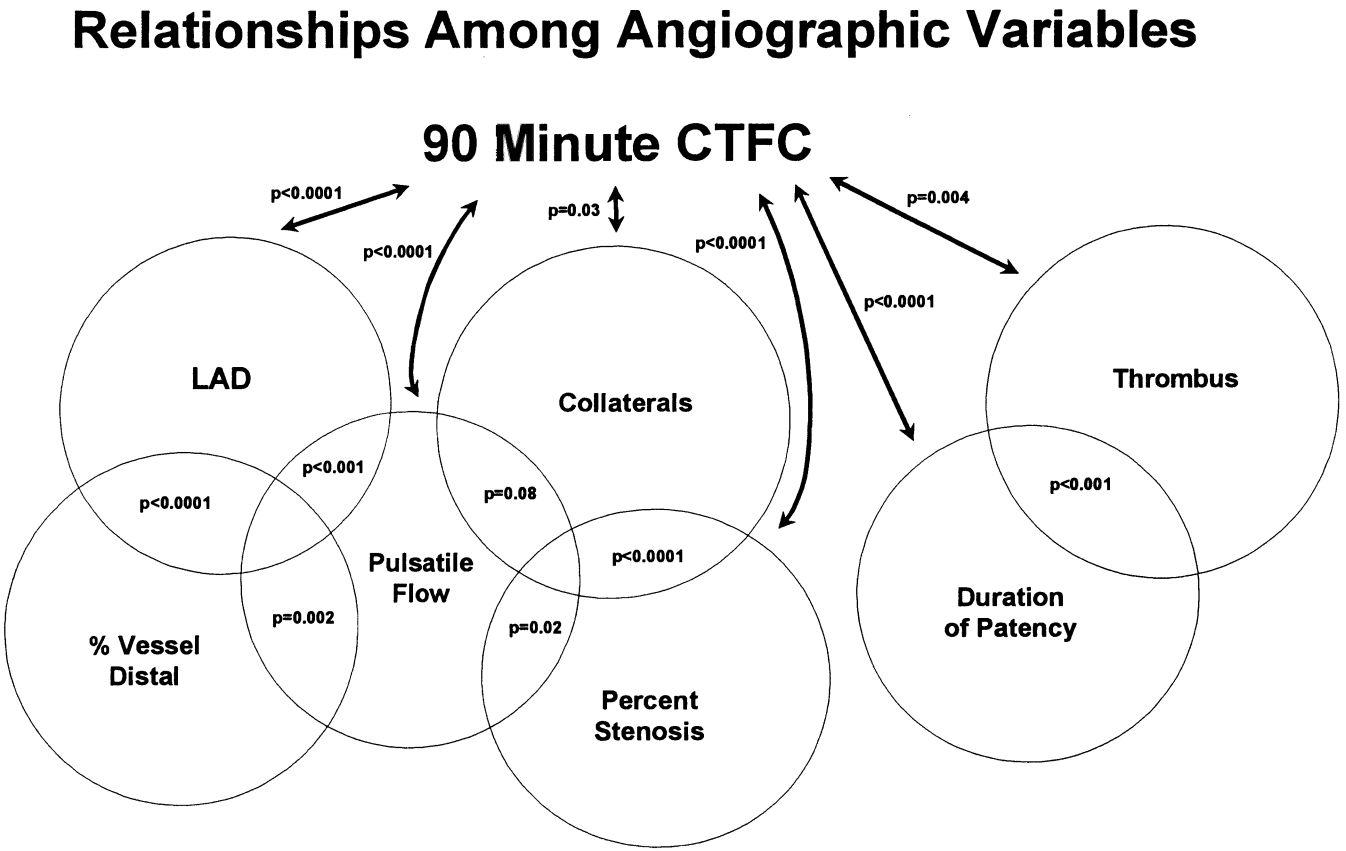

Fig. 4. Multiple, often related, variables determine flow at 90 min. For instance, left anterior descending artery (LAD) location, percent of the vessel distal to the stenosis, and presence of a pulsatile flow pattern were all related, as was the 90-min Corrected TIMI Frame Count (CTFC). In particular, there was a greater percent of the culprit vessel distal to the stenosis in patients with a LAD lesion (76.6 ± 11.1% [n = 252] vs 61.4 ± 22.9% [n = 422]; $p < 0.0001$); LAD lesions predominated in patients with pulsatile flow (61.1% LAD [n = 66/108] vs 38.9% non-LAD [n = 42/108]; $p < 0.001$); and finally patients with a pulsatile flow pattern also had a greater percent of the vessel distal to the stenosis (72.9± 16.2% [n = 97] vs 65.8 ± 21.3% [n = 548]; $p = 0.002$). Patients with pulsatile flow had less severe percent stenoses (68.6± 18.8% [n = 106] vs 73.0 ± 18.9% [n = 733]; $p = 0.02$), and pulsatile lesions tended to be collateralized less frequently (pulsatile lesions collateralized in 9.5% [n = 10/105]; nonpulsatile lesions collateralized in 16% [n = 116/723]; $p = 0.08$). Patients who were patent for less than 30 min also had a higher incidence of thrombus (50.0% [n = 24/48) vs 21.4% [n = 119/555]; $p < 0.001$).

other locations. It could be speculated that left system infarcts have slower flow because they have lesions that are located more proximally, they subtend the thicker LV wall, and there is higher wall stress in the left than in the right ventricle *(34)*.

RANGE OF VELOCITIES CONSTITUTING TIMI GRADE 3 FLOW

As newer reperfusion strategies are reported to achieve a higher incidence of TIMI grade 3 flow, a categoric scale may fail to distinguish their efficacies because there is a *range* of dye velocities that constitute TIMI grade 3 flow *(2,35–37)*. Even if two reperfusion strategies result in the same proportion of TIMI grade 3 flow, the TIMI grade 3 flow of one strategy may be faster than the TIMI grade 3 flow of another strategy, and there may be a difference in the dye velocity between the two strategies when analyzed as a *continuous* variable using the CTFC. This range of velocities that constitutes TIMI grade 3 flow can be demonstrated by the following example *(36)*. We have developed a new method of measuring absolute velocity called the PTCA guidewire velocity *(36)*. After PTCA, the guidewire tip is placed at the coronary landmark and a Kelly clamp is placed on the guidewire, where it exits the Y-adapter. The guidewire tip is then withdrawn to the catheter tip, and a second Kelly clamp is placed on the wire where it exits the Y-adapter. The distance between the two Kelly clamps outside the body is the distance between the catheter tip and the anatomic landmark inside the body. Velocity (cm/s) may be calculated as this distance (cm) ÷ TFC (frames) × film frame speed (frames/s). Flow (cc/s) may be calculated by multiplying this velocity (cm/s) and the mean cross-sectional lumen area (cm^2) along the length of the artery to the TIMI landmark *(36)*. In 30 patients, velocity increased from 13.9 ± 8.5 cm/s pre-PTCA to 22.8 ± 9.3 cm/s post-PTCA ($p < 0.001$). Despite TIMI grade 3 flow both before and after PTCA in 18 patients, velocity actually increased 38% from 17.0 ± 5.4 cm/s to 23.5 ± 9.0 cm/s ($p = 0.01$). For all 30 patients, flow doubled from 0.6 ± 0.4 mL/s pre-PTCA to 1.2 ± 0.6 mL/s post-PTCA ($p < 0.001$). In the 18 patients with TIMI grade 3 flow both before and after PTCA, flow increased 86% from 0.7 ± 0.3 cc/s to 1.3 ± 0.6 cc/s ($p = 0.001$) *(36)*. These data illustrate the wide range of velocities associated with TIMI grade 3 flow and the possibility that TIMI grade 3 flow can be improved on and made faster. A range of velocities that constitutes different TIMI flow grades has also been described using the Doppler velocity wires *(38–40)*. We have also planimetered the length of arteries from the angiogram and combined this with the frame count to calculate what is called the QCA velocity; we have shown that the QCA velocity proximal and distal to the lesion is almost identical to that reported using Doppler velocity wires *(41,42)*.

CORONARY BLOOD FLOW IN THE ASSESSMENT OF THROMBOLYTIC AGENTS

A variety of thrombolytic agents have been developed over the past two decades with the hope of improving coronary blood flow and hence mortality in acute MI. Initial efforts to restore antegrade flow to occluded vessels began with the administration of intracoronary thrombolytic agents in the late 1970s and the early 1980s *(43–46)*. These recanalization trials and the intracoronary route of thrombolytic administration were logistically demanding, and they were soon replaced by trials involving the simpler and the more rapid intravenous route of thrombolytic administration in 90-min patency trials in the mid-1980s *(46,47)*. The original open artery hypothesis, namely, that early and full

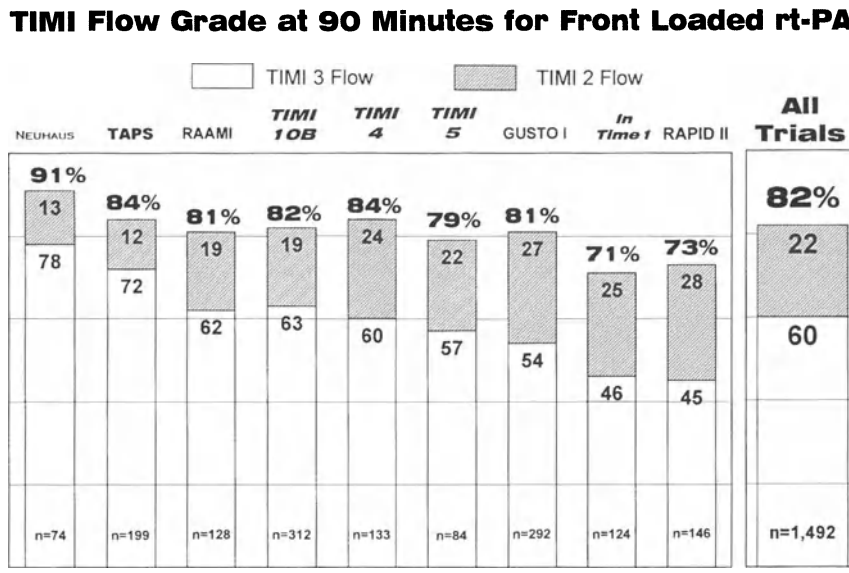

Fig. 5. Interobserver variability in assessment of TIMI grade 3 flow for a single drug (tissue-type plasminogen activator [tPA]). The rate of TIMI grade 3 flow following front-loaded tPA administration extends from a high value of 71% to a low value of 45%. Overall, the rate of TIMI grade 3 flow is 60%, the same as that reported over the years by the TIMI Angiographic Core Laboratory.

reperfusion would lead to improved clinical outcomes, was subsequently confirmed by large-scale megatrials with angiographic substudies that linked improved 90-min patency profiles of front-loaded recombinant tissue-type plasminogen activator (rtPA) to improved LV function and in turn to improved mortality *(48,49)*.

The interobserver variability inherent in the TIMI flow grade classification scheme is reflected in the wide range of rates of TIMI grade 3 flow reported for a single drug, front-loaded tPA. A pooled analysis involving 1492 patients from all large angiographic thrombolytic trials of front-loaded tPA to date reveals a 90-min patency rate of 82% (60% rate of TIMI 3 flow and 22% rate of TIMI 2 flow) *(49–56)* (Fig. 5). As shown in Fig. 5, the rates of TIMI grade 3 flow vary tremendously, from a high of 71% in the initial report of Neuhaus et al. *(49)* to a low of 45% in the RAPID 2 trial *(56)*. The overall rate of TIMI grade 3 flow in the TIMI Angiographic Core Laboratory over the years has been 60%, which is the same as the rate reported across all trials to date. Thus, the TIMI Angiographic Core Laboratory reflects the central tendency of how TIMI grade 3 flow is read in a variety of angiographic core laboratories from around the world.

In an effort to improve on this 60% rate of TIMI grade 3 flow, variants of tPA have been developed such as r-PA *(56)* (a nonglycosylated deletion mutant of wild-type tPA), novel plasminogen activator (NPA) and TNK-tpa (a genetically engineered mutant of tPA) *(53)*. The RAPID-2 trial was a small angiographic patency study that demonstrated a higher 90-min rate of TIMI grade 3 flow for r-PA compared with tPA (60 vs 45%, $p = 0.01$). It should be noted that this 45% rate of TIMI grade 3 flow for front-loaded tPA was significantly lower than the rates reported in many of the trials in Fig. 5. Consistent with the 60% rate of TIMI grade 3 flow observed for r-PA, the results of the GUSTO III trial demonstrated no significant difference in mortality at 30 d (7.47% for rPA vs 7.24% for tPA; $p = 0.54$) or the combined end point of death/disabling stroke (7.89% for r-PA

vs 7.91% for tPA; $p = 0.97$) (56). Both TNK-tpa and NPA have also achieved approximately 60% rates of TIMI grade 3 flow at the doses studied *(53)*.

ADJUNCTIVE MECHANICAL INTERVENTION TO IMPROVE FLOW FURTHER

As the previous section indicates, stand-alone thrombolytic therapy faces a formidable challenge in increasing the rate of TIMI grade 3 flow beyond 60%. Although there are clear angiographic benefits to rescue (opening a closed artery) and adjunctive PTCA (further dilating an open artery with TIMI grade 2 or 3 flow), as discussed above, the clinical benefits are less clear. Previously the routine use of immediate adjunctive conventional angioplasty to supplement the results of thrombolysis has not been shown to be any more efficacious than a conservative approach of deferred angioplasty *(58–60)*. PTCA/stenting in the subgroup of patients with suboptimal TIMI 2 flow has not been fully assessed. Preliminary results from the TIMI study group have shown that in the 38 patients in which TIMI grade 2 flow was dilated, TIMI grade 3 flow was restored in 34 (89.5%), and the mean postintervention CTFC was 30.8 ± 26.8 frames *(61)*. The 30-d risk of death or recurrent MI was 11.2% in patients who were medically managed for TIMI grade 2 flow (12/107) and was 10.0% in those patients who were treated with PTCA/stenting for TIMI grade 2 flow (4/40; p = NS) *(61)*. Thus PTCA/stenting may not offer a major advantage in clinical outcomes over medical management. Larger randomized trials are obviously needed to ascertain the clinical benefit (if any) of mechanical intervention over medical management for TIMI grade 2 flow following thrombolysis.

If thrombolytic therapy is not effective in opening the infarct related artery, a rescue or salvage PTCA may be performed. Experience with rescue angioplasty sheds important light on the relative importance of coronary blood flow and the timing with which that flow is achieved. In the TIMI 4 trial, although successful rescue angioplasty for an occluded artery at 90 min resulted in a much higher rate of TIMI 3 flow than successful thrombolysis (86.5 vs. 64.8%; $p = 0.002$), this higher rate of grade 3 flow was achieved later, at over 120 min after thrombolysis; this time delay may explain in part the higher rate of mortality (9.6%) for this strategy than successful thrombolysis (3.3%; Fig. 6) *(62)*.

Direct or primary angioplasty in acute MI has been demonstrated to achieve high rates of patency and TIMI grade 3 flow in several small angiographic trials *(63–71)*. In the initial study in this area, the Primary Angioplasty in Myocardial Infarction (PAMI) investigators reported a success rate of 97.1% for primary angioplasty *(63)*. There was a trend for patients treated with primary angioplasty to have a lower mortality rate than patients treated with thrombolysis alone (2.6 vs 6.5% respectively; $p = 0.06$) in this trial; however, other randomized trials of primary angioplasty at the time, each involving <100 patients/treatment arm, revealed no significant difference in mortality between the two strategies *(64–66)*.

These early comparisons of primary angioplasty with thrombolysis, however, were limited by the use of either older dosing regimens of tPA or streptokinase rather than utilizing the more efficacious regimen of front-loaded tPA. Fortunately, the most recent randomized trial in this field (the GUSTO IIB trial) overcomes many of these limitations in its comparison of direct angioplasty to front-loaded tPA in a large series of 1138 patients *(67)*. The composite end point of the trial (death, reinfarction, or stroke) was lower in the primary angioplasty group than in the front-loaded tPA group (9.6 vs 13.7%; $p = 0.03$), and there was a trend for the 30-d mortality rate to also be slightly lower (5.7

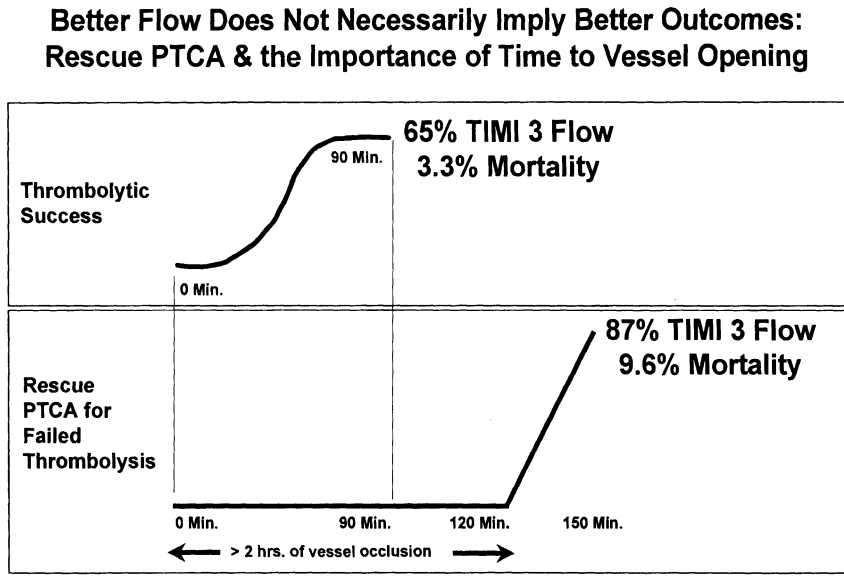

Fig. 6. Data from the TIMI 4 rescue PTCA experience, showing that TIMI grade 3 flow is not always associated with improved outcomes if it is achieved too late. In the TIMI 4 trial, although successful rescue angioplasty for an occluded artery at 90 min resulted in a much higher rate of TIMI 3 flow than successful thrombolysis (86.5 vs 64.8%; $p = 0.002$), this higher rate of grade 3 flow was achieved later, at over 120 min after thrombolysis; this time delay may partly explain the higher rate of mortality (9.6%) for this strategy than successful thrombolysis (3.3%).

vs 7.0%; p = NS) with this strategy *(67)*. In contrast to the 90–99% success rate previously reported by primary angioplasty operators and the 84% rate reported in the GUSTO IIb trial, only 73% of patients achieved TIMI grade 3 flow following angioplasty in this trial when the TIMI flow grades were evaluated by an independent angiographic core laboratory. Although this core laboratory rate of TIMI grade 3 flow is lower than the rate assessed by the primary PTCA operators themselves, this 73% rate of TIMI grade 3 flow following primary PTCA still compares favorably with the 60% rate reported for all trials of front-loaded tPA to date. It is also notable that the survival curves did not diverge early (i.e., within 24 h), but rather they began to diverge at 1–2 wk in this trial, indicating that the occurrence of reinfarction, rather than early flow, may be the driving force in the mortality differential between the strategies.

Although individual trials, including the relatively large GUSTO IIb trial, were unable to show significant difference in mortality between the two strategies, metaanalysis of all 10 randomized trials of primary angioplasty to date involving 2066 patients (large enough to detect clinically relevant differences) reveals lower rates of mortality at 30 d (4.4 vs 6.5%; $p = 0.02$), death/reinfarction (7.2 vs 11.9%; $p < 0.001$), and stroke (0.7 vs 2.0%; $p = 0.007$) when primary angioplasty is compared with thrombolysis *(69)*.

Primary angioplasty may restore a high rate of TIMI 3 flow, but stenting may further improve upon lumen dimensions and may relieve intraluminal obstruction due to dissection planes and thrombus. In a pooled analysis of 20 nonrandomized trials of primary stenting within 24 h of acute MI involving 1357 patients, the incidence of mortality was 2.4%, the incidence of stent thrombosis was 1.5%, and the incidence of emergency bypass surgery was 1.3% *(72)*. Even if stenting was the ideal treatment modality for acute

MI, it is unclear how many patients would have vessels ideally suited in size for stent placement. In a pooled analysis of quantitative angiographic data from the TIMI 4, 10A, and 10B trials, only 69% of patients had a proximal reference segment diameter (PRSD) > 2.75 mm, and only 56% of patients had a PRSD of >3.0 mm *(72)*. Given these restraints regarding the adequacy of vessel size, randomized trials of intracoronary stenting may facilitate the enrollment of patients with right coronary artery lesions, and this may result in favorable clinical outcomes in these trials. Thus, adequate reporting of the outcomes in smaller vessels and the number of patients excluded on the basis of reference segment diameter are needed to evaluate further the generalizability of the primary stenting technique.

As stated previously, the rate of agreement between an angiographic core laboratory and clinical centers is only moderate in assessing TIMI grade 3 flow, and it is poor in the assessment of TIMI grade 2 flow *(2)*. Indeed, whereas the PAMI investigators have reported a 96% rate of TIMI grade 3 flow following stent placement in acute MI *(5)*, the TIMI study group has reported a much lower 83% rate of TIMI grade 3 flow following adjunctive stent placement after thrombolysis *(33)*. As discussed previously, the 3-cardiac cycle definition used by the PAMI group may increase the rates of TIMI grade 3 flow by 15%. As suggested by Drs. Topol, Ellis, and Califf, the disparity in the rate of TIMI grade 3 flow following primary angioplasty in the PAMI and GUSTO trials may be overstated, and a more objective method of assessing coronary blood flow such as the TIMI frame count may be the preferred method in the assessment of TIMI grade 3 flow in these interventional trials *(68)*. As discussed previously, the TIMI frame count method indicates that stenting does not restore a CTFC of 21 to infarct arteries, highlighting the fact that downstream microvascular resistance remains elevated despite relief of the epicardial stenosis.

When comparing thrombolytic and interventional strategies, it must be kept in mind that a successful revascularization strategy is one that opens arteries both fully and quickly. Figure 7 shows the relationship between vessel patency and the time after a patient comes to the emergency room. The advantage of a thrombolytic regimen is speed, and the advantage of an interventional strategy is a higher rate of full reperfusion. The data for thrombolytic agents are taken from Kawai et al. *(73)*; they performed cardiac catheterization at 15, 30, 45, 60, 75, and 90 min after the administration of a thrombolytic agent that is a variant of tPA. By 15 min after thrombolytic administration, 37% of culprit arteries were patent, and by 45 min after thrombolytic administration 74% were patent *(73)*. This 74% rate of patency is 90% of the treatment effect that is achieved by 90 min (84% patency). If the patient undergoes primary PTCA with a door to balloon time of 120 min (shown by the light gray line), the GUSTO IIb trial has shown that there will be a 25% spontaneous rate of vessel opening. As shown by the blocked area in the figure, there will be a significant amount of time during which the patency rates for a thrombolytic will exceed that of primary angioplasty. This is what we have termed the early PTCA *flow debt*. At 120 min, however, the patency for PTCA will exceed that of thrombolysis. If the primary PTCA is performed more quickly, with a door to balloon time of 75 min, as shown by the dark gray line, then by 75 min the patency rate for the interventional strategy will exceed that for lysis. We would term this the *late flow debt* for thrombolysis. Despite the superior patency of the interventional strategy at 75 min, it appears that thrombolytics may open a substantial number of vessels more quickly prior to the performance of the intervention. Thus, whereas interventional strategies may achieve a higher rate of patency, it appears that thrombolytics have the advantage of opening arteries very quickly in a

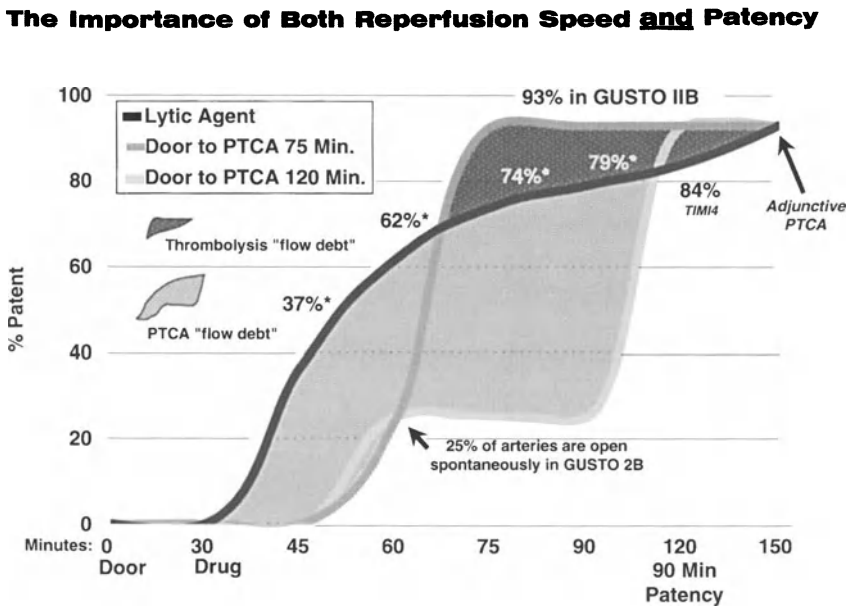

Fig. 7. Combined data pertaining to both speed and patency for a variety of strategies. If a patient enters the door at time 0, 30 min later he or she will be given a thrombolytic, (signified by "drug"). According to data of Kawai et al. *(73)* (dark black line), 15 min after lytic administration (45 min after presentation) there will be a 37% patency rate, at 30 min after lytic administration a patency rate of 62%, at 45 min a patency rate of 74%, and at 90 min a patency rate of 84%. Thus, speed of reperfusion is the advantage of a thrombolytic agent. If the patient undergoes primary percutaneous transluminal coronary angioplasty (PTCA) with a door to balloon time of 120 min (light gray line), the GUSTO IIb trial has shown that there will be a 25% spontaneous rate of vessel opening; however, as shown by the blocked area, there will be a significant amount of time during which the patency rates for a thrombolytic will exceed that of primary angioplasty. We have termed this phenomenon the early PTCA *flow debt.* At 120 min, however, the patency for PTCA will exceed that of thrombolysis. If the primary PTCA is performed more quickly, with a door to balloon time of 75 min (dark gray line), then by 75 min the patency rate for the interventional strategy will exceed that for lysis. We term this the *late flow debt* for thrombolysis. Despite the superior patency of the interventional strategy at 75 min it appears that thrombolytics may open a substantial number of vessels more quickly prior to the performance of the intervention.

substantial number of patients. Thus, the challenge for interventional strategies is to achieve even earlier opening than is currently the case, and the challenge for thrombolytic agents is still to achieve higher rates of patency.

RELATIONSHIP OF CORONARY BLOOD FLOW TO CLINICAL OUTCOMES

Several thrombolytic trials have demonstrated an important relationship between the different TIMI flow grades at 90 min after thrombolysis and clinical outcomes *(49, 74–77)*. The GUSTO angiographic substudy involving 1431 patients provided important insight into the mechanism linking TIMI grade 3 flow with reduced mortality *(49)*. Although the rate of TIMI grade 2 flow did not differ significantly among the thrombolytic regimens (25% with the streptokinase [SK] and subcutaneous heparin regimen, 28% with the SK and intravenous heparin regimen, 27% with the tPA and intravenous

heparin regimen, 35% with the tPA and SK combination regimen; p = NS), the rate of TIMI grade 3 flow was highest for the tPA with intravenous heparin regimen (54% compared with 29% for SK with subcutaneous heparin regimen, 32% for the SK with intravenous heparin regimen, and 38% for the tPA and SK combination regimen) *(49)*. The mortality rate of 7.4% for patients with TIMI grade 2 flow approximated that of TIMI grades 0 or 1 flow (mortality 8.9%) *(49)*. By contrast, TIMI grade 3 flow was associated with nearly half this mortality (4.4%) *(49)*. This trial also linked improved TIMI flow grades with improved LV ejection fractions *(49)*. Thus, it appears that the survival benefit of front-loaded tPA (6.3% mortality compared with 1% higher mortality with the other regimens in GUSTO) was due at least in part to the improved coronary blood flow (both higher patency and TIMI grade 3 flow rates) in the infarct-related artery with this regimen *(49)*.

The results of GUSTO 1 raise important questions as to the potential mortality benefits that could be accrued by improved flow at 90 min following thrombolysis. An increase in the rate of TIMI grade 3 flow by 22% (from 32% with SK and intravenous heparin to 54% with front-loaded tPA) reduced the mortality by 1% (from 7.4% with SK and intravenous heparin to 6.3% with front-loaded tPA) in this trial *(49)*. If there is a linear relationship, to improve mortality by yet another 1%, the rate of TIMI grade 3 flow in the infarct-related artery would need to improve by another 20% from the current mean value of 60% in all thrombolytic trials to approximately 80%. The achievement of 80% rates of TIMI grade 3 flow appears to be a formidable challenge given the previous observation that there was only a 73% rate of TIMI grade 3 flow following primary angioplasty in GUSTO IIB *(67)*.

To evaluate further the relationship between TIMI flow grades at 90 min after thrombolysis and clinical outcome, a pooled analysis of all angiographic thrombolytic trials performed to date involving 5498 patients is presented in Fig. 8. The 30–42-d mortality rate was lowest (3.7%) in patients with TIMI 3 flow at 90 min following thrombolysis, which was significantly lower than that in patients with TIMI grade 2 flow (6.1%; $p < 0.0001$) or TIMI grades 0/1 flow (9.3%; $p < 0.0001$) flow (Fig. 8). The mortality rate difference between patients with TIMI grades 2 and 0/1 flows was also significant ($p = 0.003$) (Fig. 8). Only with the larger sample size of this pooled data does the distinction between TIMI grades 0/1 and 2 flows become apparent.

This pooled data analysis reconfirms the superiority of achieving complete reperfusion (i.e., TIMI grade 3 flow) after thrombolysis. Although TIMI grade 2 flow (partial perfusion) is not equivalent to TIMI grade 3 flow, it nevertheless confers a significant survival advantage compared with TIMI grade 0/1 flow and therefore should not be regarded as a failure of reperfusion, but rather as intermediate in benefit between TIMI grade 0/1 and 3 flows.

The assessment of the clinical significance of TIMI grade 2 flow has, however, been confounded by the tremendous interobserver variability in the visual assessment of coronary blood flow *(2)*. In addition, TIMI grade 2 flow encompasses a wide spectrum of flows from markedly delayed to near normal flows *(2)*. Finally, the analysis of the relationship between TIMI grade 2 flow to clinical outcomes is confounded by the observation that most of the TIMI grade 2 flow is observed in LAD arteries (63%); most of the TIMI grade 3 flow has been observed in right coronary arteries (approximately 75%). This statistical colinearity in infarct artery location and coronary blood flow could explain, at least in part, the significant differences in clinical outcomes *(2)*.

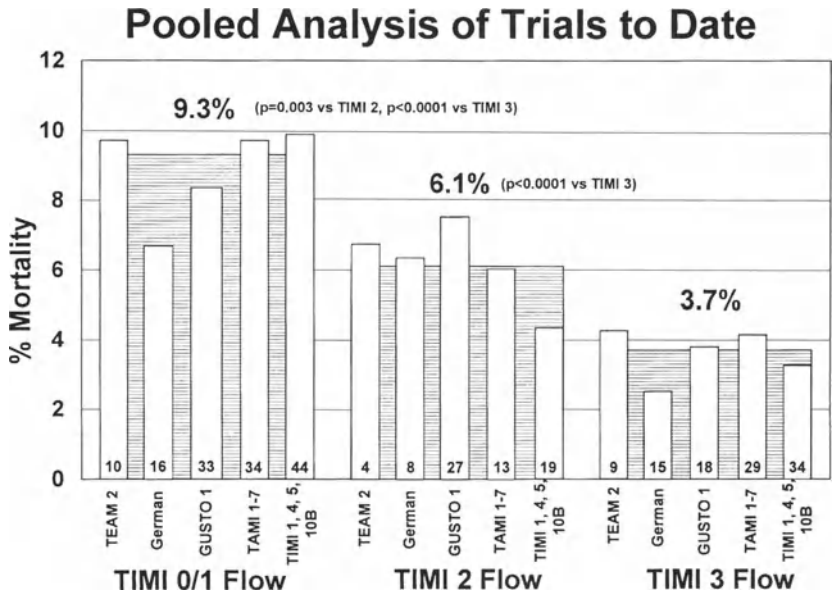

Fig. 8. A pooled analysis of all angiographic thrombolytic trials performed to date involving 5498 patients. The 30–42-d mortality rate was lowest (3.7%) in patients with TIMI grade 3 flow at 90 min following thrombolysis, which was significantly lower than that in patients with either TIMI grade 2 flow (6.1%; $p < 0.0001$) or TIMI grade 0/1 flow (9.3%, $p < 0.0001$).

The more objective CTFC is also related to clinical outcomes *(78–83)*. In the TIMI 4, 10A, and 10B trials, the flow in the infarct-related artery in survivors was significantly faster than in patients who died (CTFCs of 49.2 ± 32.2 [$n = 1184$] vs 69.0 ± 35.4 [$n = 52$], respectively; $p = 0.0004$) *(78)*. In this dataset, mortality increases by 1% for every 14-frame rise in CTFC ($p = 0.003$) *(78)*. Thus the CTFC at 90 min following thrombolysis would be required to increase from its current value of 35 frames to approximately 21 frames (normal flow) to improve mortality by 1% *(78)*. This is a formidable challenge given that flow in nonculprit arteries at 90 min is approximately 30 frames and that culprit CTFCs following adjunctive PTCA are also approximately 30 frames.

None of the patients in the TIMI studies who have had a CTFC < 14 (hyperemic or TIMI grade 4 flow) have died *(78)*. Likewise, in the RESTORE trial (tirofiban + heparin vs heparin alone in patients undergoing angioplasty for acute ischemic syndromes), the postangioplasty culprit flow in survivors was significantly faster than in those patients who died (CTFCs 20.4 ± 16.7 [$n = 1073$] vs 33.4 ± 27.1 [$n = 10$], respectively; $p = 0.017$) *(80)*. Again, none of the 376 patients with a CTFC < 14 following angioplasty died in this trial, underscoring the fact that within the subgroup of patients with "normal flow" there may be further subgroups with even better flow *(80)*. The CTFC in this trials was also related to a lower rate of restenosis, even when correction was made for postprocedure diameters *(81)*. Thus, not only is bigger better, but faster is also better *(81)*.

We have also shown that slower flow distal and not proximal to the lesion is related to adverse outcomes following thrombolysis *(79)*, that higher CTFCs are also related to increased myoglobin release *(82)*, and that other more refined measures of coronary blood flow, such as the QCA velocity, are also related to clinical outcomes *(83)*.

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II DIAGNOSIS

5 Identifying Acute Cardiac Ischemia in the Emergency Department

J. Hector Pope, MD and Harry P. Selker, MD

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IDENTIFYING ACUTE CARDIAC ISCHEMIA IN WOMEN AND MEN
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INTRODUCTION

Accurate identification of acute cardiac ischemia (ACI) in the emergency department (ED) remains a task that challenges the skill of the most seasoned clinician, even though angina pectoris was described in great detail more than 200 years ago by Heberden *(1)* and the presentation of acute myocardial infarction (AMI) was first reported 85 years ago by Herrick *(2)*. Each year in the United States, over 6 million patients with chest pain or Imminent Myocardial Infarction Rotterdam (IMIR) Study *(3)* inclusion symptoms present to EDs *(4)*, and approximately 25% of these will have ACI. Physicians have the task of identifying, treating, and hospitalizing (in the appropriate unit) the approximately one-third of these patients who have true ACI *(5)* (i.e., either AMI or unstable angina pectoris [UAP]), to avoid filling hospital telemetry, stepdown units, and coronary care units with the large majority of patients who do not have ACI.

For many years, the diagnosis of ACI was of more prognostic than therapeutic importance. Over the past three decades, physicians' diagnostic and triage decisions for patients with suspected cardiac ischemia have reflected two tendencies. First, as the number of acute interventions for treating dysrhythmias and preventing or limiting the size of AMI has grown, clinicians have tended to admit all patients with even a low suspicion of acute

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Table 1
Key Methodologic Issues for Applicability of Study Results

Representative patient sample.
Representative prevalence of ischemic heart disease.
Broad patient inclusion criteria, not just chest pain.
Study setting includes a range of settings.
Diagnostic end point includes unstable angina as well as acute infarction.
Completeness of follow-up.
Follow-up data appropriate and significant.
Validation of findings in generalizable clinical trials.

ischemia. As a result, clinicians have generally admitted nearly all (92–98%) patients presenting with AMI *(3–8)*, as well as nearly 90% of those presenting with ACI (i.e., including those with AMI as well as those with UAP) *(5,6,9)*. The conscious strategy of maintaining a high diagnostic sensitivity, i.e., that any error be toward overdiagnosis, has the intended effect: among patients with AMI who seek attention in EDs, the diagnosis is generally missed in <5% *(8–16)*. High diagnostic sensitivity has been achieved at the cost of admitting many patients who do not have ACI (low diagnostic specificity). Only 18–42% (typically about 30%) of the 1.5 million patients admitted annually to coronary care units (CCUs) *(10)* actually experience AMI *(6,11–15)*, and only 50–60% have ACI *(5,6,9,11)*.

Our understanding of coronary syndromes has evolved: unstable angina (i.e., rest angina, new-onset angina, or increasing angina) and AMI are now well appreciated as part of a continuum of ACI that is the focus of the diagnosing emergency clinician. For ED triage, the overarching diagnosis of ACI better identifies patients for CCU or stepdown unit admission than does the diagnosis of AMI alone. This is both because of the difficulty in differentiating unstable angina from infarction and because CCU/stepdown unit admission is intended to reverse ischemia and prevent frank infarction. In fact, for patients with acute cardiac ischemia and prolonged chest pain, but without infarction, the medium- and long-term mortality may be as poor or worse than mortality in those who actually have AMI *(16)*.

For clinical reasons, to promote the optimal use of a limited resource, and to reduce unnecessary expenditure, research has focused on improving physicians' diagnostic and triage accuracy. There remains a need for improved methods of diagnosis that can reduce unnecessary hospitalization for patients incorrectly presumed to have acute ischemia without increasing the number of patients with acute ischemia who are sent home inappropriately *(17,18)*.

This chapter reviews the roles of the clinical history, physical examination, and electrocardiogram (ECG) in diagnosis and triage of patients with suspected ACI, by first considering some of the methodologic pitfalls inherent in this type of research.

METHODOLOGIC ISSUES

Consideration of the specific methods used in studies of patients with ACI is vital when critically reviewing studies of the diagnosis and triage of ED patients with suspected ACI (Table 1). Central to any study is whether the patient sample studied is *representative* of ED patients seen in actual practice. Also, the positive predictive value (i.e., the proportion

of patients that actually have ACI among all those with a positive test or attribute) of a symptom, sign, or test result depends on the *prevalence* of ischemic heart disease in the study population *(19)*. Thus, the proportion of patients with false-positive results will be higher (and positive predictive value lower) in a population with a low prevalence of ischemia (all ED patients) compared with a population with a high prevalence (CCU patients). Even studies carried out in EDs may not be comparable when ACI prevalence is significantly different. *Inclusion criteria* can limit studies of ED patients if, for example, only patients with chest pain are studied *(20–22)* compared with the use of broad entry criteria including multiple symptoms that could be anginal equivalents, such as any chest discomfort, epigastric pain, arm pain, shortness of breath, dizziness, or palpitations *(23)*. *Study setting* (e.g., urban vs rural, or teaching vs community hospital) can also affect the applicability of any findings to various practice settings.

Aside from the study sample, other methodologic issues warrant attention, including the appropriateness of the measured *diagnostic end point*. Some past ED studies have focused on identifying or predicting only AMI, but identifying UAP is also important for monitoring and early therapy, especially when it is considered that on the order of 9% of patients admitted with new-onset or UAP progress to infarction *(24,25)*. *Completeness of follow-up* must be considered. Studies with substantial numbers of patients lost to follow-up may have ascertainment bias, especially when the participation rate among eligible patients is not high. Also important is the type of follow-up data collected; for example, the occurrence of AMI will be underestimated if follow-up evaluation does not include cardiac enzyme determination results.

Finally, *validation of the findings* of clinical studies is critical, especially for prediction rules and diagnostic aids: findings may be center or data dependent. The ideal validation study is a prospective trial of a finding's or prediction rule's effects on patient care in diverse settings *(26)*.

CLINICAL PRESENTATION

Chest Discomfort

It is sometimes difficult to distinguish cardiac from noncardiac chest discomfort, even though chest pain is the hallmark of ACI. Taking the time to elicit the exact *character of the sensation* (i.e., without prompting the patient) and any *pattern of radiation* (if present) is most helpful. Typically, the chest discomfort of acute ischemia has a deep visceral character, preventing the patient from localizing the discomfort to a specific region of the chest. It is often described as a pressure-like heavy weight on the chest, a tightness, a constriction about the throat, and/or an aching sensation, not affected by respiration, position, or movement, that comes on gradually, reaches its maximum intensity over a period of 2–3 min, and lasts for minutes or longer rather than seconds. In our study of 10,689 ED patients with suspected ACI *(27)* (Tables 2–6, and see Tables 9–11), we found that the 76% of patients presenting with the complaint of chest pain or discomfort (including arm, jaw, or equivalent discomfort) had a 29% incidence of ACI at final diagnosis (10% AMI, 19% UAP); in 69% of patients, chest pain or discomfort was the chief complaint, and this group had a 31% incidence of ACI (10% AMI, 21% UAP); in 21% of patients, it was the only complaint, and this group had a 32% incidence of ACI (9% AMI, 23% UAP). Furthermore, the same study showed that chest pain or discomfort, as a chief complaint or presenting symptom, was more frequently associated with a final diagnosis of ACI (88% ACI vs 62% non-ACI; 92% ACI vs 71% non-ACI, respectively;

Table 2
Clinical Presentation
Features of ED Patients (N = 10,689)

Clinical feature	*All (%)*
Mean age (yr) (SD)	59 (16)
Gender (% female)	48
Ethnic group	
White	62
Black	32
Hispanic	5
Other	1
Chief complaint (%)	
Chest pain	69
Presenting symptoms (%)	
Chest pain	76
Shortness of breath	56
Abdominal pain	14
Nausea	28
Vomiting	10
Dizziness	28
Fainting	6
Past medical history (%)	
Diabetes	21
Myocardial infarction	26
Angina pectoris	37
Diagnosis (%)	
Confirmed angina pectoris	15
Confirmed acute infararction	8
Other	77
Mortality (%)	
30-day mortality	2.5

Data from ref. *27.*

$p = 0.001$). Sharp, stabbing, or positional pain is less likely to represent ischemia *(28)* but does not exclude it: Lee et al *(29)* found that among ED patients with *sharp or stabbing pain*, 22% had acute ischemia (5% AMI, 17% UAP). Among those with *partially pleuritic pain*, 13% had acute ischemia (6% AMI, 7% UAP), and among the group with *fully pleuritic pain,* none were shown to have acute ischemia. Notably, 7% of the patients whose pain was *fully reproduced by palpation* nonetheless had acute ischemia (5% AMI, 2% UAP), and 24% of patients with pain *partially reproduced with palpation* had ischemia (6% AMI, 18% UAP).

Combinations of variables improved discrimination in these patients *(21)*. In patients with sharp or stabbing pain that was also pleuritic, positional, or reproducible by palpation, 3% had UAP and none had AMI. Furthermore, if these same patients had no history of ischemic heart disease, none had acute ischemia. The "partially" and "fully" groups were subjective and small in number.

Table 3
Final Diagnosis for Patients by Chief Complaint and Presenting Symptom[a]

		Final diagnosis ACI (%)			*Final diagnosis not ACI*				
	No.[b]	*AMI*	*UAP*	*Total ACI*	*Non-ACI cardiac*	*GI*	*MS*	*Other*	*Total Non-ACI*
Chief complaints									
Chest pain	7335	10	21	31	33	10	16	11	69
Shortness of breath	1682	6	5	11	53	3	2	31	89
Abdominal pain	47	2	2	4	19	60	2	15	96
Nausea/vomiting	47	11	4	15	23	26	0	36	85
Dizziness/fainting	584	2	2	4	33	5	1	58	96
Presenting symptoms									
Chest pain	8127	10	19	29	34	9	15	13	71
Shortness of breath	5843	8	16	24	41	7	10	18	76
Abdominal pain	1333	6	9	15	29	29	8	18	85
Nausea	2850	10	16	26	32	15	9	18	74
Vomiting	1003	13	10	23	28	19	7	22	77
Dizziness	2599	5	11	16	37	10	10	28	84
Fainting	571	4	2	6	38	3	4	49	94

[a]Abbreviations: ACI, acute cardiac ischemia; AMI, acute myocardial infarction; UAP, unstable angina pectoris; GI, gastrointestinal; MS, musculoskeletal.
[b]Total number of patients with chief complaint or presenting symptom.
Data from ref. *27*.

Exact location of chest pain is not significantly different in patients with or without AMI *(30)*, but chest pain that *radiates to the arms or neck* does increase the likelihood *(31–33)*. In the study by Sawe *(30)*, that looked at admitted patients with AMI, 71% had pain radiation to arms and/or necks; pain radiated in 39% of patients admitted without AMI. Consistent with the classical description, 33% of patients who proved to have infarction had radiation to both arms, 29% to the left arm only, and 2% to the right arm only *(30)*.

Some investigators feel that a significant number of patients with cardiac ischemia can present with abdominal pain as their chief complaint *(20,21)*. However, in our series of ED patients *(27)*, we found that 14% of study subjects had this complaint; this group had a 15% incidence of ACI at final diagnosis (6% AMI, 9% UAP), but <1% complained of abdominal pain as their chief or only complaint and had a 4% incidence of ACI (2% AMI, 2% UAP). In the same study, abdominal pain as a chief complaint or presenting symptom was associated with a higher incidence of a non-ACI final diagnosis (0.6% non-ACI vs 0.1% ACI; 16% non-ACI vs 9% ACI, respectively; $p = 0.001–0.002$). Esophageal reflux and motility disorders are common masqueraders of ACI. In a study of all patients discharged from a CCU with undetermined causes of chest pain, over half had esophageal dysfunction *(34)*. When these patients' presenting complaints were compared with those of patients without ACI, those with esophageal disorders were more likely to complain of a lump in their throat, acid taste, overfullness after eating, a hacking cough, and chest pain that caused awakening at night; they were less likely to report effort-related chest pain, a history of nitroglycerin use, or reliable chest pain relief with its use.

Table 4
Comparison of Patients With and Without a Final Diagnosis of ACI: Clinical Features, Chief Complaints, Presenting Symptoms, and Past Medical History[a]

		Final diagnosis ACI			*Final Diagnosis not ACI*					*Total ACI vs total non-ACI*
	Total no.	*AMI (894)*	*UAP (1645)*	*Total ACI (2539)*	*Non-ACI cardiac (3916)*	*GI (962)*	*MS (1268)*	*Other (2004)*	*Total non-ACI (8150)*	p *value*[b]
Clinical features										
Mean age (SD)	(10,689)	65 (13)	65 (13)	65 (13)	58 (17)	56 (15)	49 (14)	58 (16)	57 (16)	0.001[c]
Gender (% Female)	(10,689)	36	47	43	48	52	52	52	50	0.001
Ethnic group (%)										0.001
White	(10,661)	76	75	75	60	55	45	62	58	
Black		20	21	21	34	38	46	33	36	
Hispanic		3	3	3	5	5	8	5	6	
Other		2	1	1	1	2	1	1	1	
Chief complaints (%)										
Chest pain	(10,689)	82	92	88	62	73	93	40	62	0.001
Shortness of breath	(10,684)	12	5	7	23	5	2	26	18	0.001
Abdominal pain	(10,686)	0.1	0.1	0.1	0.2	2.9	0.1	0.3	0.6	0.002
Nausea/vomiting	(10,685)	0.6	0.1	0.3	0.3	1.2	0	0.8	0.5	0.15
Dizziness/fainting	(10,682)	2	1	1	5	3	0	17	7	0.001
Presenting symptoms (%)										
Chest pain	(10,689)	88	95	92	70	79	96	52	71	0.001
Shortness of breath	(10,493)	56	57	56	62	43	45	55	56	0.5
Abdominal pain	(9,422)	11	8	9	11	43	10	13	16	0.001
Nausea	(10,152)	34	29	30	25	44	22	28	27	0.003
Vomiting	(9,913)	16	7	10	8	21	6	12	10	0.8
Dizziness	(9,222)	17	20	19	29	29	23	40	31	0.001
Fainting	(8,920)	3	1	2	7	2	2	16	8	0.001
Past medical history (%)										
Diabetes	(10,281)	30	32	31	20	18	12	18	18	0.001
History of MI	(10,396)	37	50	45	25	16	12	18	20	0.001
History of angina	(10,328)	43	73	63	33	28	23	24	29	0.001

[a]Abbreviations: see footnote to Table 3.
[b]p values from chi-square test comparing total ACI vs total non-ACI unless noted otherwise.
[c]p value from Student's *t*-test.
Data from ref. *27*.

Table 5
Comparison of Patients With and Without a Final Diagnosis of ACI: by Physical Findings[a]

		Final diagnosis ACI			*Final Diagnosis not ACI*					*Total ACI vs total non-ACI*
	Total no.	*AMI (894)*	*UAP (1645)*	*Total ACI (2539)*	*Non-ACI cardiac (3916)*	*GI (962)*	*MS (1268)*	*Other (2004)*	*Total non-ACI (8150)*	p *value*[b]
Physical findings										
Pulse										
Median atrial rate	(7,164)	78	75	76	80	75	74	80	78	0.001[c]
Blood pressure										
Systolic (SBP)										
Median 1st	(10,675)	144	148	147	144	141	138	140	141	0.001[c]
Median highest	(10,676)	154	154	154	150	148	140	148	149	0.001[c]
Median lowest	(10,675)	111	125	120	123	128	127	125	124	0.001[c]
Diastolic										
Median 1st	(10,596)	84	80	82	82	82	80	80	81	0.5[c]
Median from highest SBP	(10,619)	88	83	84	84	84	82	84	84	0.7[c]
Median from lowest SBP	(10,557)	69	72	70	73	77	77	74	74	0.001[c]
Pulse pressures										
Initial	(10,596)	60	64	62	60	59	54	58	58	0.001[c]
Highest	(10,619)	68	70	70	65	61	58	63	63	0.001[c]
Lowest	(10,556)	44	51	50	49	50	50	50	50	0.001[c]
Rales (%)	(10,387)									0.001
None		71	78	76	73	93	95	82	81	
Basilar		19	17	18	18	6	4	14	3	
<Basilar		8	4	6	8	1	1	4	5	
Entire lung		2	0	1	1	0	0	1	1	
S3 gallop (%)	(8,769)	5	2	3	5	1	1	1	3	0.3

[a]Abbreviations: see footnote to Table 3.
[b]p values from chi-square test comparing total ACI vs total non-ACI unless noted otherwise.
[c]p value from Wilcoxon rank-sum test.
Data from ref. *27*.

Table 6
Summary Statistics for Blood Pressure Stratified by Killip Classes (1–3) vs Killip Class 4

	Final diagnosis AMI		
	Killip classes 1–3 (n = 860)	*Killip class 4 (n = 34)*	p *value*[a]
Systolic blood pressure (SBP)			
Median 1st	145	120	0.001
Median highest	155	137	0.001
Median lowest	111.5	90.5	0.001
Diastolic blood pressure			
Median 1st	84	69	0.002
Median from highest SBP	88	80	0.12
Median from lowest SBP	70	60	0.11

[a]p value from Wilcoxon rank-sum test.
Data from ref. *27*.

ANGINAL PAIN EQUIVALENTS

Dyspnea, present in about one-third of patients with infarction in some series *(21,31,35)*, is the most important anginal equivalent. We found in our multicenter ED trial *(27)* that 16% of patients with suspected ACI presented with a chief complaint of shortness of breath and had an 11% incidence of ACI at final diagnosis (6% AMI, 5% UAP); in 8%, this was the only complaint, with a 10% incidence of ACI (5% AMI, 5% UAP). However, a final diagnosis of ACI was not more frequent in patients with a presenting symptom of shortness of breath (56% ACI vs 56% non-ACI; $p = 0.5$); as a chief complaint, shortness of breath was more commonly associated with a final diagnosis of non-ACI (18% non-ACI vs 7% ACI; $p = 0.001$), possibly reflecting a high prevalence of patients with lung disease in the study population. Yet, because 4–14% of AMI patients *(20,21,23)* and 5% of unstable angina patients present only with sudden difficulty breathing *(27)*, ACI should be considered as a cause of unexplained shortness of breath.

Both diaphoresis and vomiting, when associated with chest pain, increase the likelihood of infarction *(14,26,31)*. *Diaphoresis* occurs in 20–50% of AMI patients *(32,36)*. One study showed that the presence of nausea without vomiting did not discriminate, but *vomiting* was significantly more frequent in patients who "ruled in" *(31)*. Our study *(27)* found nausea in 28% of patients with suspected ACI: patients with nausea as a presenting symptom had a 26% incidence of ACI at final diagnosis (10% AMI, 16% UAP); patients with nausea or vomiting as chief complaint (2%) had a 15% incidence of ACI (11% AMI, 4% UAP); and <1% of patients had nausea or vomiting as their only symptom. The same study found vomiting present in 10% of patients: patients with vomiting as a presenting symptom had a 23% incidence of ACI (13% AMI, 10% UAP); patients with vomiting as the chief or only complaint had <1% incidence. Furthermore, we showed that a chief complaint of nausea or vomiting was more frequently associated with a final diagnosis of non-ACI (0.5% non-ACI vs 0.3% ACI; $p = 0.15$), yet a presenting complaint of nausea was more commonly associated with a final diagnosis of ACI (30% ACI vs 27% non-ACI; $p = 0.004$); a presenting complaint of vomiting did not show this association (10% ACI vs 10% non-ACI; $p = 0.7$). In a CCU study, 43% of patients with Q-wave

infarction but only 4% of patients with non-Q-wave infarctions or prolonged angina had vomiting *(37)*.

So-called *soft clinical features*, such as fatigue, weakness, malaise, dizziness, and "clouding of the mind" are surprisingly frequent, occurring in 11–40% of patients with AMI *(26,30,31,35)*. Prodromal symptoms (those occurring in the preceding days or weeks) are also frequent: 40% report unusual fatigue or weakness, 20–39% dyspnea, 14–20% "emotional changes," 20% change in appearance (i.e., "looked pale"), and 8–10% "dizziness" *(21,35)*. In our series *(27)*, we found that 28% of patients with suspected ACI presented to the ED with dizziness and had a 16% incidence of ACI (5% AMI, 11% UAP); in 5% of study patients dizziness was their primary complaint, with a 4% incidence of ACI (2% AMI, 2% UAP) and in 1% of patients it was their only symptom (2% AMI, 0% UAP). In the same study, dizziness or fainting as a chief complaint were more commonly associated with a final diagnosis of non-ACI (7% non-ACI vs 1% ACI; $p = 0.001$); similarly, dizziness or fainting as presenting symptoms were more frequently associated with final diagnoses of non-ACI (31% non-ACI vs 19% ACI; 8% non-ACI vs 2% ACI; respectively; $p = 0.001$). ECG evaluation is very helpful in low-prevalence patients with these vague complaints.

ATYPICAL PRESENTATIONS

Few studies address what proportion of ED patients with ACI present with atypical symptoms, a group for whom the diagnostic/triage decision is often most problematic. Among hospitalized patients with AMI, 13–26% had no chest pain or had chief complaints other than chest pain (i.e., dyspnea, extreme fatigue, abdominal discomfort, nausea, or syncope) *(20,21)*. In our ED study of 10,689 patients *(27)* presenting with a wide range of clinical symptoms, we found that 31% of patients with suspected ACI presented without chest pain, with a 26% incidence of ACI at final diagnosis (18% infarction, 8% unstable angina), and had chief complaints other than chest pain (i.e., shortness of breath, abdominal pain, nausea, vomiting, dizziness, or fainting).

Among ED patients, no single atypical symptom is of overwhelming diagnostic importance, although combinations of symptoms can identify high-risk patients who should be admitted regardless of ECG findings. In our series, we ranked atypical presenting symptoms in decreasing order of association with ACI at final diagnosis as follows: nausea (26%), shortness of breath (24%), vomiting (23%), dizziness (16%), abdominal pain (15%), and fainting (65%) *(27)*.

Data from community-based epidemiologic studies *(22,38–40)* suggest that 25–30% of all Q-wave infarctions go clinically unrecognized: half were truly silent, and half were associated with atypical symptoms in retrospect *(22,38)*. Because Q waves often resolve (in the Framingham Study, 10% of patients discharged after anterior infarction and 25% of those discharged after inferior infarction lost their Q waves within 2 yr), the true incidence was underestimated *(41)*.

The rate of erroneous discharge from the ED of patients with AMI may be a marker for atypical cases but such studies are limited by inclusion criteria, small numbers, and lack of complete follow-up. Rates of 2% *(42)*, 4% *(8)*, and as high as 8% *(7)* have been reported. In our ED series *(27)*, patients with suspected ACI reported rates of erroneous discharge of 4%. Significantly, the early mortality for these "missed" AMIs may be as high as 26–33% *(7,8)*.

PAST MEDICAL HISTORY

In addition to the presenting clinical features, the presence of a coronary artery disease risk factor has traditionally been considered diagnostically helpful in the ED setting. Not surprisingly, in our ED series *(27)*, an association was shown between patients having a past history of diabetes mellitus (31% ACI vs 18% non-ACI; $p = 0.001$), myocardial infarction (45% ACI vs 20% non-ACI; $p = 0.001$), or angina pectoris (63% ACI vs 29% non-ACI; $p = 0.001$) and a final diagnosis of ACI; however these findings require careful interpretation. From the Framingham Study, it is well known that the risk of developing ischemic heart disease are increased over decades by male gender, advancing age, a smoking habit, hypertension, hypercholesterolemia, glucose intolerance, ECG abnormalities, a type A personality, a sedentary life style, and a family history of early coronary artery disease *(21,43,44)*. Clinicians customarily assess these factors when providing preventive care, because they predict the incidence of future coronary disease. However, coronary risk factors were established to provide an estimate of risk *over years*. Thus, the Framingham Study showed that hypertension increases the risk of ischemic heart disease twofold over 4 yr *(22)* but only a very small portion of this risk applies to the few hours of the ED patient's acute illness. A patient's report of coronary risk factors is also subject to biases and inaccuracies. This history is presumably less reliable than the methods used to assign risk in longitudinal studies.

Indeed, in a multicenter study, Jayes et al. (45) found that most of the classical coronary risk factors have little predictive value for ACI when used in the ED setting. Except for diabetes and a positive family history in men, no coronary risk factor significantly increased the likelihood that a patient had acute ischemia. Diabetes and family history each confer only about a twofold relative risk for acute ischemia in men, whereas chest discomfort, ST-segment abnormalities, and T-wave abnormalities confer relative risks of about 12-, 9-, and 5-fold, respectively. Because these results run counter to the prevailing clinical wisdom, it is possible that physicians who give risk factor history great weight may inappropriately diagnose/triage ED patients, an issue that deserves further attention and investigation.

Finally, a past history of medication use for coronary disease increases the likelihood that the current chest pain is ACI. Not surprisingly, in the Boston City Hospital and the multicenter predictive instrument trials, a history of nitroglycerin use was found to be one of the most powerful predictors of ACI *(5)*. Nonetheless, nitrates can cause dramatic relief of chest pain from esophageal spasms *(46)* and thus the details of the history must be noted carefully.

PHYSICAL EXAMINATION

The physical examination is generally not very helpful in diagnosing ACI when compared with the value of historical data and ECG findings, except when it points to an alternate process. On the other hand, clinicians must not be lulled into a sense of security by chest pain that is partially or fully reproduced by palpation, because 11% may have infarction or unstable angina *(23)*.

Table 5 shows a comparison of patients with and without a final diagnosis of ACI by physical findings from our series *(27)*. We found the pulse rate to be lower in patients with a final diagnosis of ACI vs those with a final diagnosis of non-ACI ($p = 0.02$), but this difference was not considered clinically significant.

Pulse rate observation in isolation appeared to be generally not helpful in ACI identification. First, the patient's pulse rate could be slowed by the presence of β-blockers as part of a prior treatment regime or by coincident vagal stimulation from ACI (i.e., reflex bradycardia and vasodepressor effects associated with inferoposterior wall ACI) or therapeutic procedures in the ED (i.e., phlebotomy, intravenous access). Second, the patient's pulse may be increased by adrenergic excess from just having to come to the ED and everything that accompanies such a visit, in addition to the adrenergic excess (i.e., tachycardia and increased peripheral vascular resistance) associated with possible on-going ACI.

In our series of ED patients *(27)*, median first and highest systolic blood pressures (SBPs) were higher in patients with a final diagnosis of ACI. This suggested to us that the adrenergic excess associated with ACI might be greater than that associated with non-ACI diagnoses. However, to use this hypothesis as a predictive factor, clinicians must have some idea of their patient's baseline blood pressure, which is not the case in most ED evaluations. Thus, the usefulness of this observation may be limited.

In the same series *(27)*, in addition to the effect of adrenergic release during acute ischemia, the higher initial and highest pulse pressures found in patients with a final diagnosis of ACI may also reflect the lower compliance of the ischemic left ventricle. Of relevance to those who are candidates for thrombolytic therapy, excess pulse blood pressure (the extent to which a patient's pulse pressure exceeded 40 mm Hg for patients with SBP of >120 mmHg) places these patients at increased risk of thrombolysis-related intracranial hemorrhage *(26)*.

We discovered that median first, median highest, and median lowest SBPs of patients with AMI, who subsequently were classified as Killip class 4 (cardiogenic shock), were above the threshold of this classification (SBP ≤90 mmHg) for these three blood pressure observations. This suggests that the adrenergic excess associated with ACI may be greater than that associated with non-ACI diagnoses. More importantly, although the number of such patients in this analysis was relatively small, it did suggest that patients with ACI can present with apparently "normal" blood pressures and can go on to develop cardiogenic shock.

Abnormal vital signs and certain combinations of these have been shown to be critically important observations in clinical outcome prediction. The reported probability of infarction decreases with a normal respiratory rate *(31)* and increases with diaphoresis *(14)*, but other signs mainly help identify high-risk patients with infarction *(47)*. In the predictive instrument for AMI mortality proposed by Selker et al. *(48)*, blood pressure, pulse, and their interaction figured prominently in three of the six clinical variables used to develop the prediction instrument.

In our series *(27)*, rales, of any degree, but not S3 gallops, were more frequently seen in patients with a final diagnosis of ACI. This finding is not surprising, as several clinical syndromes of pump failure can complicate ACI. Our failure to find an association between an S3 gallop rhythm and ACI at final diagnosis is surprising, but it may have to do with a failure to document this finding consistently in the medical record on the part of the ED physicians at study sites.

ELECTROCARDIOGRAM

A complete summary of evidence related to the diagnostic utility of the ECG was recently published *(17)*, and this background will not be repeated here.

Table 7
Limitations of Electrocardiography

Single brief sample
Lack of perfect detection
Baseline patterns
Interpretation
Clinical context
Imperfect sensitivity and specificity

The ECG provides essential information when the diagnosis is not obvious by symptoms alone *(49)*, despite one study noting that the results of the ECG infrequently changed triage decision based on initial clinical impressions *(50)*. The generally dominant weights given to ECG variables in mathematical models for predicting ACI substantiate this impression *(5,6,9,14,15)*. Moreover, the initial ECG is increasingly important in intrahospital triage because of its value in predicting complications of AMI *(51–53)*.

There are fundamental limitations in the standard ECG (Table 7). First, it is a *single brief sample* of the whole picture of the changing supply and demand characteristics of unstable ischemic syndromes. If a patient with UAP is temporarily pain free when the ECG is obtained, the resulting tracing may poorly represent the patient's ischemic myocardium.

Second, 12-lead electrocardiography is limited by its *lack of perfect detection (54)*. Small areas of ischemia or infarction may not be detected; conventional leads do not examine satisfactorily the right ventricle *(55)* or posterior basal or laterals walls well (i.e., AMIs in the distribution of the circumflex artery) *(56,57)*.

Third, some *ECG baseline patterns* make interpretation difficult or impossible including prior Q waves, early repolarization, left ventricular hypertrophy, bundle branch block, and dysrhythmias *(58)*. Lee et al. *(8)* demonstrated that when the current ECG shows ischemic findings, availability of a prior comparison ECG improved triage.

Fourth, ECG wave forms are frequently *difficult to interpret* causing disagreement among readers, so-called missed ischemia. In a study of AMI patients sent home, ECGs tended to show ischemia or infarction not known to be old, with 23% of the missed diagnoses owing to misread ECGs *(7)*. Jayes et al. *(59)* compared ED physician readings of ECGs with formal interpretations by expert electrocardiographers and calculated sensitivities of 0.59 and 0.64 and specificities of 0.86 and 0.83 for ST-segment and T-wave changes, respectively. Both McCarthy et al. *(16)* and a review of litigation in missed AMI cases *(60)* emphasized this factor of incorrect ECG interpretation. Correct ECG interpretation by ED physicians is doubly important today because of the need to use thrombolytic agents appropriately in AMI.

Fifth, the implications of the ECG findings must be *interpreted in their clinical context*, a process done intuitively by clinicians and formally stated in Bayesian analysis. When symptoms alone strongly suggest ischemia, a normal or minimally abnormal ECG will not substantially decrease the probability of ischemia. Conversely, when the presentation is inconsistent with acute ischemia, an abnormal ECG, unless diagnostic changes are present, will only modestly increase the likelihood of ischemia. Bayes' rule tells us that the ECG will have the greatest impact when symptoms are equivocal *(61)*. This is illustrated by Table 8, which shows the probability of acute ischemia for combinations

Table 8
The Original ACI Predictive Instrument's Probabilities of Acute Ischemia for ED Patients

	ECG Abnormalities (%)					
Question: *Chest pain or pressure or left arm pain?*	*ST0 T0*	*ST— T0*	*ST0 ↑↑↓*	*STT ↑↓ T0*	*ST— ↑↑↓*	*ST ↑↓ T ↑↓*
Answer: Yes, chief complaint.						
History						
No heart attack *and* no NTG use	19	35	42	54	62	70
Either heart attack *or* NTG use *(not both)*	27	46	53	64	73	85
Both heart attack *and* NTG use	37	58	65	75	80	90
Answer: Yes, but not chief complaint.						
History						
No heart attack *and* no NTG use	10	21	26	36	45	64
Either heart attack *or* NTG use *(not both)*	16	29	36	48	56	74
Both heart attack *and* NTG use	22	40	47	59	67	82
Answer: No.						
History						
No heart attack *and* no NTG use	4	9	12	17	23	39
Either heart attack *or* NTG use *(not both)*	6	14	17	25	32	51
Both heart attack *and* NTG use	10	20	25	35	43	62

Key to ECG abnormalities (must be in two loads, excluding aVR); ST—, ST-segment "straightening; "ST ↑↓, ST segment elevated at least 1 mm or depressed at least 1 mm; T↑↓, T wave "hyperacute" (>50% of R wave) or inverted at least 1 mm; ST0/T0, above-specified changes absent.

Directions: To determine a given patient's probability of acute ischemia, start by answering the questions at the top of the chart about the presence of chest pain and whether or not it is the chief complaint. This will lead to one of the three large boxes of probability values. Under the History heading are questions regarding history of heart attack or nitroglycerine (NTG) use. Choose the row that corresponds to the patient's report of none, one, or both of these historical features. Then to find the specific probability value, move across the appropriate row to the column corresponding to the ECG ST-segment and T-wave changes for the given patient. For example, for a patient with a chief complaint of chest pain, no history of heart attack or nitroglycerine use, and 1 mm or ST-segment depression and T-wave inversion, the probability of true ACI would be 78%. (Reproduced from McCarthy BD, Wong JB, Selker HP: Detecting acute cardiac ischemia in the emergency department: A review of the literature. *J Gen Intern Med* 5:365–373. Reprinted with permission of Blackwell Science, Incorporated.

Note: Specific definitions of clinical features (questions) for original ACI predictive instrument are modified for use in this chart.

of history and ECG findings among 2,801 emergency patients *(62)*; this formed the basis for the Acute Ischemic Heart Disease Predictive Instrument *(5)*.

Finally, the ECG suffers from *imperfect sensitivity and specificity* for ACI. When interpreted according to liberal criteria for myocardial infarction (i.e., ECGs that show any of the following as positive for AMI: nonspecific ST-segment or T-wave changes abnormal but not diagnostic of ischemia; ischemia, strain, or infarction, but changes known to be old; ischemia or strain not known to be old; and probable AMI) , the ECG operates with relatively high (but not perfect) sensitivity (99%) for AMI, at the cost of

low specificity (23%; positive predictive value 21%; negative predictive value 99%). Conversely, when interpreted according to stringent criteria for AMI (only ECGs that show probable AMI), sensitivity (61%) drops and specificity equals 95% (positive predictive value 73%; negative predictive value, 92%) *(17)*.

Despite its usefulness, the ECG is insufficiently sensitive to make the diagnosis of ACI consistently. The ECG should not be relied on to make the diagnosis but rather should be included with history and physical examination characteristics to identify patients who appear to have a high risk for ACI (i.e., a supplement to, rather than a substitute for, physician judgment). In "rule out AMI" patients, a negative ECG carries an improved short-term prognosis *(51,63–66)*. Providing the interpreter with old tracings would intuitively seem to be of value because baseline abnormalities make current evaluation difficult, yet, Rubenstein and Greenfield *(67)*, in a study of 236 patients presenting to EDs with the complaint of chest pain, found that only a small proportion might have benefited from having a previous baseline ECG available (5% might have avoided unnecessary admission). Furthermore, there was no patient for whom a baseline ECG would have aided in avoiding an inappropriate discharge. ECG sampling should be periodic, not just static. The pitfalls of not ordering ECGs in younger, atypical patients and of misinterpretation should be anticipated. Finally, clinicians should not be reluctant to obtain a second opinion, by fax transmission if necessary, for difficult tracings (Table 9).

ST-Segment and T-Wave Abnormalities

ST-segment and T-wave abnormalities are the *sine qua non* of ECG diagnosis of ACI. Numerous studies *(54,66,68)* have found that 65–85% of CCU patients with ST-segment elevation alone will have had an infarction. Other investigators found that if both Q waves and ST-segment elevation were present, 82–94% actually sustained AMI *(54)*. However, it must be remembered that ST-segment elevation can occur in the absence of ischemia (i.e., "early repolarization" variant, pericarditis, left ventricular hypertrophy, and previous infarction even in the absence of a ventricular aneurysm) *(69)*. Conversely, we have shown in our series *(27)* that a large percentage of patients with ACI (20% AMI, 37% UAP) can present with initial normal ECGs.

In our study of ED patients with suspected ACI *(27)* (Table 10), we found that ST-segment elevation of either 1–2 or 2+ mm was more frequently associated with a final diagnosis of ACI (9% ACI vs 7% non-ACI; 5% ACI vs 1% non-ACI, respectively; $p = 0.001$). A full 30% of patients with ST-segment elevation of 1 mm or greater had a final diagnosis of AMI.

ST-segment depression usually indicates "subendocardial ischemia." If these changes are new, persistent, and marked, the likelihood of AMI increases. About 50–67% of admitted patients with new or presumed new isolated ST-segment depression have infarctions *(54,68)*; even more patients have probable ischemia. We found that all degrees of ST-segment depression (0.5, 1, 1–2, and 2+ mm) were more commonly associated with a final diagnosis of ACI (12% ACI vs 7% non-ACI; 8% ACI vs 3% non-ACI; 2% ACI vs 0% non-ACI, respectively; $p = 0.001$). A full 19% of patients with ST-segment depression of at least 0.5 mm or greater had a final diagnosis of AMI. It should also be remembered that ST-segment depression may occur in nonischemic settings, including patients who are hyperventilating, those taking digitalis, those with hypokalemia, and those with left ventricular strain (without voltage criteria) *(69)*.

Inverted T-waves may reflect acute ischemia: one study showed that isolated T-wave inversion occurred in 10% of CCU admissions, of whom 22% had AMI *(70)*. T-wave

Table 9
Comparison of Patients With and Without Electrocardiographic (ECG) Data

Clinical Feature (no.)	*With ECG data (%) (n = 8545)*	*Without EGC data (%) (n = 2144)*	p *value*
Mean age (yr) (SD) (10,689)	58.6 (16.1)	58.9 (16.0)	0.4
Gender (% female) (10,689)	49	47	0.12
Ethnic group (10,661)			0.001
White	62	61	
Black	33	31	
Hispanic	4	7	
Other	1	1	
Presenting Symptoms			
Chest pain (10,689)	76	77	0.2
Shortness of breath (10,493)	56	55	0.8
Past medical history			
Diabetes (10,281)	21	21	0.7
Myocardial infarction (10,396)	26	25	0.5
Angina pectoris (10,328)	36	39	0.010
Diagnosis (10,689)			0.013
Confirmed angina pectoris	15	15	
Confirmed acute infarction	8	10	
Other	77	75	
Mortality (10,116)			
30-d mortality	2.4	2.8	

Data from ref. *27*.

changes may reflect prior myocardial damage or left ventricular strain *(69)*. Our study *(27)* found that certain T-wave patterns (inverted 1–5 mm, inverted 5+ mm, or elevated) were more frequently associated with a final diagnosis of ACI (32% ACI vs 17% non-ACI; 1% ACI vs 0% non-ACI; 4% ACI vs 1% non-ACI, respectively; $p = 0.001$). Flattened T-waves did not have the same association with an ACI final diagnosis (18% ACI vs 20% non-ACI; $p = 0.001$). Furthermore, 39% of patients with inverted T-waves of at least 1 mm or greater had a final diagnosis of AMI.

Q-Waves

Q-waves are diagnostic of myocardial infarction, but what is the age of the Q-wave? In the MILIS study of admitted CCU patients, isolated new or presumed new inferior or anterior Q-waves were associated with acute infarction in 51% and 77% of patients, respectively *(54)*. Other findings of the MILIS study should be kept in mind: 12% of

Table 10
Comparison of Patients With and Without a Final Diagnosis of ACI by Electrocardiographic Findings[a]

Findings	Total no.	Final diagnosis ACI			Final diagnosis not ACI (%)					Total ACI vs total non-ACI p value[b]
		AMI (894)	UAP (1645)	Total ACI (2539)	Non-ACI cardiac (3916)	GI (962)	MS (1268)	Other (2004)	Total non-ACI (8150)	
ST-segment	(8,545)									0.001
Normal		42	74	63	78	85	88	83	81	
Elevated 1–2 mm		16	6	9	8	8	8	6	7	
Elevated 2+ mm		14	1	5	1	0	1	1	1	
Depressed 0.5–1 mm		14	12	12	9	5	3	8	7	
Depressed 1–2 mm		10	6	8	4	1	1	2	3	
Depressed 2+ mm		5	1	2	1	0	0	0	0	
T-waves	(8,545)									0.001
Normal		38	48	44	57	66	73	61	61	
Flat		14	20	18	20	21	17	20	20	
Inverted 1–5 mm		37	30	32	21	13	9	17	17	
Inverted 5+ mm		2	1	1	0	0	0	0	0	
Elevated		10	1	4	1	1	1	1	1	
Q-waves	(8,545)	29	23	25	13	8	6	11	11	0.001
Normal ST/ T, no Q	(8,545)	20	37	31	46	55	63	50	51	0.001

[a]Abbreviations: see footnote to Table 3.
[b]*p* values from chi-square test comparing total ACI vs total non-ACI, unless noted otherwise.
Data from ref. *27*.

healthy young men have inferior Q-waves; *(69–71)* pathologic Q-waves can be from a previously unrecognized infarction and can mask new same-territory ischemia; Q-waves alone do not identify ACI and are rarely the sole manifestation of AMI (6% in the MILIS study); and, finally, infarction can occur in the absence of Q-waves *(72,73)*. In our ED study *(27)*, we showed that Q-waves were more commonly associated with a final diagnosis of ACI (25% ACI vs 11% non-ACI; $p = 0.001$) and that 29% of patients with Q-waves present on their ECGs had a final diagnosis of AMI.

"Nondiagnostic" ECG Patterns

"Non–diagnostic" ST-segment and T-wave abnormalities may be defined as follows: (not having ≥1 mm (0.1 mV) ST-segment elevation or depression in two contiguous leads, not having new T-wave inversion in two contiguous leads, absence of significant Q-waves (>1 mm deep and 0.3 s duration) in two contiguous leads, not having second- or third-degree heart block, and not having a new conduction abnormality (bundle branch block, etc.). These are the most difficult to interpret and can result in overdiagnosis (no comparison ECG available) and underdiagnosis (baseline abnormality obscuration of ischemia) *(74)*. Lee et al. *(29)* found that emergency patients with chest pain and nondiagnostic ECG abnormalities had a low risk of AMI but a significant risk of ACI.

Normal ECG

Among ED patients with normal ECGs (i.e., lacking Q-waves, primary ST-segment and T-wave changes, and criteria for nondiagnostic changes), 1% *(29)* to 6% *(74)* have been found to have AMI. Among admitted patients with normal ECGs, 6–21% had AMI *(11,70,73,74,75)*. Of patients discharged home with a normal ECG, only 1% had acute infarction *(74)*. Patients with a normal ECG and a suggestive clinical presentation still have a significant risk of ACI, especially if the ECG was obtained when the patient was pain free. On the other hand, a truly normal ECG in a patient unlikely to have acute ischemia provides strong evidence against ACI *(29)*.

In our series, patients with normal ST/T waves and no Q-waves more commonly had a final diagnosis of non-ACI, yet 20% of these patients had AMI and 37% had UAP at final diagnosis.

IDENTIFYING ACUTE CARDIAC ISCHEMIA IN WOMEN AND MEN

Knowing whether gender influences the likelihood that a given ED patient is having ACI, and whether any specific presenting clinical features are differentially associated with ACI in women compared with men, can aid clinicians in the accurate diagnosis of ACI. The incidence of AMI in the general population has been shown to be higher in men than women *(80–83)*, but until recently it has not been clear whether this gender difference holds among symptomatic patients who come to the ED.

Several studies have looked at gender differences in the presentation of patients with AMI *(84–88)*. In a retrospective analysis of patients with confirmed AMI, women had higher rates of atypical presentations such as abdominal pain, paroxysmal dyspnea, or congestive heart failure (CHF) *(38,80,89–91)*. In a group of ED patients with typical presentations such as chest pain, the prevalence of AMI was lower in women *(29,92)*. However, in another study of ED patients with chest pain, when adjustments were made for other presenting clinical features (specifically ECG), the gender difference was no longer significant *(87)*. From these results it is difficult to assess whether the gender-

Table 11
Final Diagnosis (%) for ACI-TIPI Trial Control Subjects by ED Triage Disposition (N = 5951)[a]

Triage disposition	*AMI (n = 496) Control*	*UAP (n = 898) Control*	*Non-ACI (n = 4557) Control*
Home	3	8	41
Ward	1	2	6
Telemetry	31	61	43
CCU	66	29	10

[a]Abbreviations: (ACI-TIPI), acute cardiac ischemia-time-sensitive predictive instrument; ED, emergency department; AMI, acute myocardial infarction; UAP, unstable angina pectoris; CCU, coronary care unit.

specific differences in AMI prevalence among symptomatic ED patients were the result of gender-specific biology or limitations in a particular study's patient selection.

Zucker et al. *(93)*, in a study of 10,525 patients ≥30 yr old who presented to the ED with chest pain or other symptoms suggestive of ACI, found that AMI was almost twice as common in men as in women (10% vs 6%). Among women with ST-segment elevation or signs of CHF, however, AMI likelihood was similar to that in men with these characteristics. This finding suggests that the presence of CHF should be given substantial weight in assessing the likelihood of AMI in women presenting to the ED with symptoms suggestive of ACI.

CLINICAL OUTCOMES

Each year in the United States, over 6 million patients with chest pain or other symptoms suggesting ACI (i.e., IMIR Study inclusion symptoms) *(20)* present to EDs *(3)*. These patients can have various clinical outcomes ranging from discharge home to hospital admission after thrombolytic therapy. Table 11 shows the final diagnosis for Acute Cardiac Ischemia-Time Insensitive Predictive Instrument (ACI-TIPI) Trial control subjects by ED triage disposition. These data were employed to develop a flowchart (Fig.1) to represent the diagnoses and triage dispositions of ED patients presenting with chest pain or other symptoms suggestive of ACI.

The flowchart demonstrates that *of all such patients*, only 23% of patients (hospital range 12–34%) had ACI at final diagnosis, of whom 94% were hospitalized and 6% sent home. Conversely, 77% did not have ACI at final diagnosis, of whom 59% were hospitalized and 41% were sent home. In the ACI group of patients, 36% of patients had AMI and 64% had UAP. This represented, respectively, 8% and 15% of the overall group. In the AMI group, 97% were hospitalized and 3% sent home; in the UAP group, 92% were hospitalized and 8% sent home. Of those with AMI, 27% received thrombolytic therapy, representing 2% of the overall group.

Our work with Pozen et al. *(5)* from 1979–81, at the same hospitals as the present report, demonstrated a 7% ED discharge rate for patients with a final diagnosis of ACI; McCarthy et al. *(16)* found that 2% of these subjects had AMI at final diagnosis. In the mid 1980s, Lee et al. *(8)* reported a 4% AMI discharge rate. Our study found a 6% discharge rate for ACI and a 3% AMI discharge rate, demonstrating stability of these figures over the decade. The proportions of AMI and UPA in our present study (36%

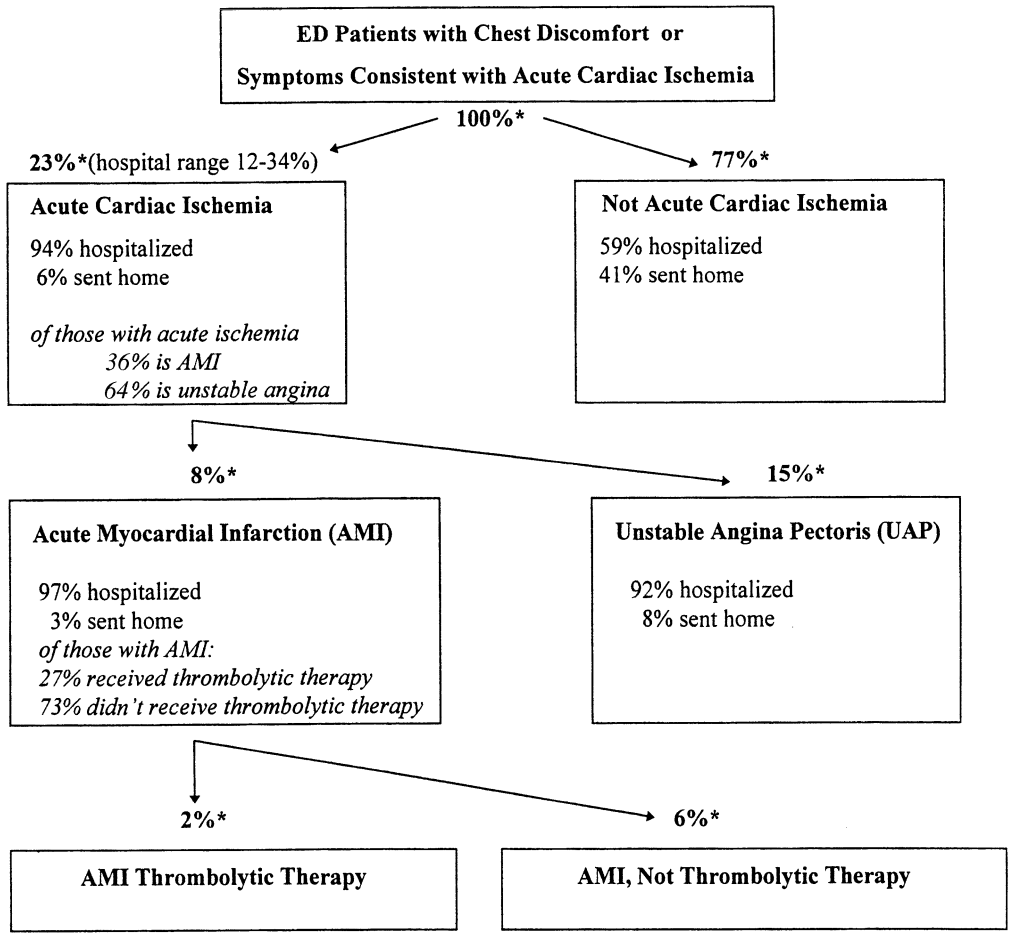

Fig. 1. Flowchart illustrating diagnoses and triage dispositions of patients presenting to the emergency department (ED) with chest pain or other symptoms suggesting acute cardiac ischemia (AMI). *, percent of total ED patients in the control group with chest pain or symptoms consistent with ACI.

AMI, 64% UAP) were essentially identical to those from our work with Pozen et al. *(5)* in 1979–81 (35% AMI, 65% UAP).

CONCLUSIONS

Our better understanding of coronary syndromes allows us to appreciate UAP and AMI as part of a continuum of ACI. ACI is a life-threatening condition whose identification can have major economic and therapeutic importance as far as treating dysrhythmias and preventing or limiting myocardial infarction size. Its identification continues to challenge the skill of even experienced clinicians. Physicians continue (appropriately) to admit the overwhelming majority of patients (93%) with ACI; in the process, they admit many patients without acute ischemia (59%) *(27)*, still overestimating the likelihood of ischemia in low-risk patients because of a magnified concern for this diagnosis for both prognostic and therapeutic reasons.

Studies of admitting practices from a decade ago yielded useful clinical information but showed that neither clinical symptoms nor the ECG could reliably distinguish most

patients with ACI from those with other conditions. Our work in this area suggests that certain clinical features from the history, physical examination, and ECG can greatly assist with the identification of ED patients with ACI. We think that our refinement of the understanding of the clinical presentation of the coronary syndromes based on this large dataset and our acknowledgment of the limitations inherent in the ECG may improve decision making for this group of patients. In the future, other diagnostic technologies to support the clinical features reported here need further evaluation, as recently reported by the National Institutes of Health National Heart Attack Alert Program *(17)*. In the mean time, several computer-based decision aids for identification of ACI, including those described by Pozen et al. *(5)*, Goldman et al. *(15)*, and Selker et al. *(47)*, can be applied in the ED as a supplement to the clinician's judgement.

Our clinical outcome data provide a useful point of reference for clinicians regarding the diagnosis and triage dispositions of ED patients presenting with chest pain or other symptoms suggestive of ACI. In general, *of all such patients*, only 23% will have ACI. Of those with ACI, 36% will have AMI and 64% will have UAP. This represents, respectively, 8% and 15% of this overall group. Of those with AMI, 27% will receive thrombolytic therapy, representing 2% of the overall group.

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6 Early Identification and Treatment of Patients with Acute Coronary Syndromes

Costas T. Lambrew, MD

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INTRODUCTION

Mortality from acute myocardial infarction (AMI) has been dramatically reduced through successful myocardial reperfusion strategies with thrombolytics or primary percutaneous transluminal coronary angioplasty. The 6.3% mortality in the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO) I Trial is approximately half the mortality for patients with AMI reported in the immediate prethrombolytic era *(1)*. Reduced mortality is directly related to early reperfusion of the infarct-related artery and myocardial salvage; clear evidence from both the original animal work and extensive clinical trials with all agents supports this time-dependent relationship *(2)*. The time-benefit curve is very steep, with maximum benefit accruing to those patients who are reperfused within the first 1–2 h after symptomatic occlusion. Analysis of clinical trials provides evidence that equates 1 hour of delay in reperfusion to an increase in absolute mortality by approximately 1%, or 10 lives per thousand; this is a linear relationship in the first 4–6 h following symptom onset *(2,3)* (Fig. 1). Therefore, it is imperative that time be considered as much of an adjunct to the treatment of patients

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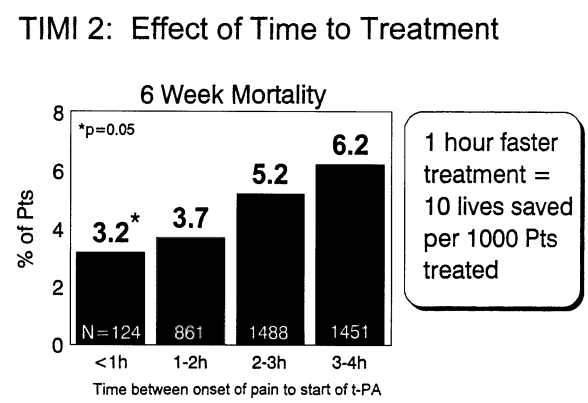


Fig. 1. Relationship between time to treatment and mortality in the TIMI 2 trial (Adapted with permission from ref. *2*).

with AMI, as proposed by Cannon, as drugs that have been shown to have efficacy in reducing mortality *(4)*.

NATIONAL HEART ATTACK ALERT PROGRAM

In 1991, a conference was convened by the National Heart, Lung, and Blood Institute (NHLBI) to discuss issues in the treatment of patients with AMI, given the availability of a new standard of care, specifically early reperfusion of jeopardized myocardium. Delay in early identification and treatment was identified as a major problem; such delay was assigned to three phases. Patient-mediated delay was noted to be the most significant component of total delay, ranging from 2.5–6 h in reported studies. Delays related to Emergency Medical Services response and transportation of the patient to the hospital were also noted, but very disturbing was delay in the early identification and treatment of patients suitable for reperfusion therapy after arrival in the emergency department. This hospital delay was found to be in the range of 90 min in several well-conducted clinical trials. It also became evident that the magnitude of delay in the emergency department was not appreciated by most physicians until times from patient arrival to treatment were actually recorded *(5)*.

Therefore, the NHLBI developed the National Heart Attack Alert Program (NHAAP) with the goal of promoting early identification and treatment of patients with AMI and reducing the incidence of sudden cardiac death in the community. It became clear that patient-mediated delay was not well understood. Furthermore, there was no evidence from previous trials that a community intervention was in place that would consistently enable patients to recognize that symptoms were related to an acute ischemic cardiac event and cause them to seek earlier help. The NHAAP Coordinating Committee felt it imperative, therefore, to address first the issue of delay in that environment that the health professional community controlled most effectively, the emergency department.

A working group examined the emergency department process related to the care of these patients and concluded that patients presenting with symptoms consistent with AMI, with ST-segment elevation on the initial electrocardiogram (ECG) and who had no contraindications to reperfusion therapy, could be effectively identified and treated within 30 min after emergency department arrival *(6)*. The working group also concluded that to examine process and track improvement through a continuous quality improvement

effort, time from emergency department arrival to initiation of reperfusion therapy would have to be recorded for each patient, for the purpose of tracking reductions in delay over time related to changes in the process of identification and treatment.

THE FOUR Ds

Four critical time points in the care of these patients were identified and called the *four D's* (Fig. 2). *Door* is the time of arrival and registration of the patient in the emergency department. *Data* refers to the time that the first ECG showing ST-segment elevation is recorded, since this ECG finding is clearly the trigger for consideration of reperfusion therapy. *Decision* is the time when the decision to proceed with reperfusion therapy is made (the drug is ordered). *Drug* is the time when the thrombolytic infusion is actually begun. The elapsed time between the patient's emergency department arrival and initiation of thrombolytic drug is then referred to as door to drug time. In the case of patients receiving balloon angioplasty, the interval is referred to as the door to balloon time.

CONTINUOUS QUALITY IMPROVEMENT

It is further recommended that a multidisciplinary team examine door to drug times in a continuing manner to identify opportunities for reducing delay and improving the process of care. It is clear from reported experience in the quality improvement process that once decreases in door to drug or door to balloon times occur, the team must continue to record and consider these times and the process of patient care to prevent recurrence of delays. Included in this quality improvement process is data recording to determine what percent of patients who qualify for reperfusion therapy actually receive it and how often drugs that have been found to have efficacy in improving outcomes are used. The quality improvement process should then explain variances and exceptions and attempt to improve care by feedback of these data to health professional staff responsible for the care of these patients (Fig. 3).

Mechanisms for gathering data as defined above may be developed through a hospital database. On a national level, there are currently over 1,500 hospitals participating in the National Registry for Myocardial Infarction (NMRI). Data are recorded by a hospital-based Registry Coordinator on a two-page case report form and submitted for entry and analysis to a Central Data Coordinating Center. Feedback of hospital-specific data is received by each participating institution on a quarterly basis, with a comparison benchmark for all variables consisting of aggregated national or regional figures, thereby affording each institution the opportunity to monitor change from quarter to quarter and year to year, and to measure effectiveness of changes in process over time and in relationship to regional and national experience. The Joint Commission on Accreditation of Health Care Organizations has also supported this line of analysis and quality improvement as a model for its accredited hospitals.

REDUCING DELAYS IN PATIENT TREATMENT

The greatest delay in initiating reperfusion therapy for patients with ST-elevation AMI is patient-mediated delay. The median delay between symptom onset and hospital arrival ranges between 2 and 6.4 h. In the Grupo Italiano per lo Studio della Streptochinasi nell'Infarto Myocardio (GISSI)-I trial, 10.9% of patients were treated with intravenous streptokinase within the first hour after onset of symptoms *(7)*. In both the Thrombolysis

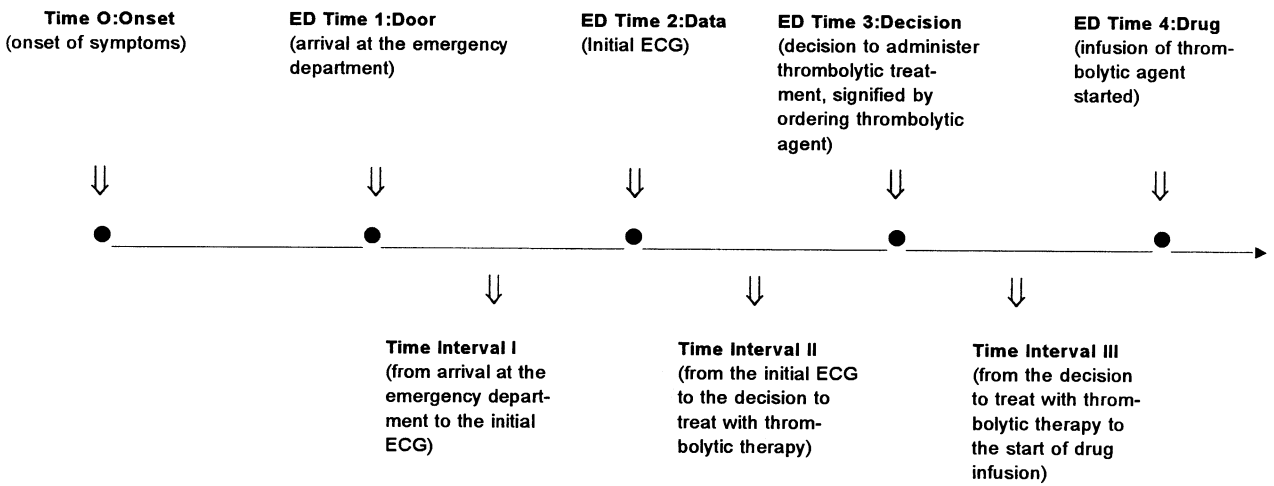


Fig. 2. Process timepoints and intervals through which the AMI patient passes until treatment in the emergency department.

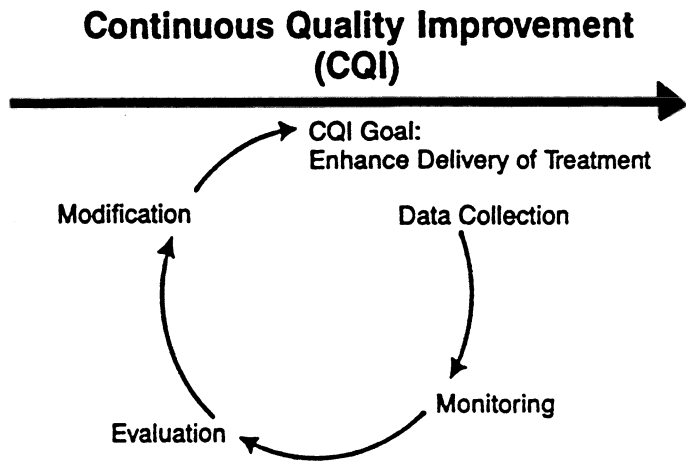


Fig. 3. Process for using data feedback to improve quality of care.

in Myocardial Infarction (TIMI)-2 and GUSTO I trials, only 3% of patients were treated within the first hour *(1,8)*. Delay occurs not only in recognizing symptoms and attributing them to a potential acute ischemic cardiac event, but also in calling for help. Community interventions thus far attempted have not consistently increased symptom recognition and reduced delay in calling for help in the community at large. The NHLBI is currently completing a trial to develop community interventions that would cause persons at risk to recognize symptoms as cardiac in origin more consistently and to act on them earlier.

HIGH-RISK PATIENTS

However, until that time, the NHAAP has targeted a high-risk group of patients for education by the medical community *(9)*. Nearly 11 million patients in the United States have either known coronary, peripheral vascular, or cerebral vascular disease. These patients account for about 50% of all myocardial infarction admissions each year and are five to seven times more at risk of developing myocardial infarction than the population at large. Therefore, it is recommended that these patients receive specific instructions from their caregivers on recognition of symptoms, including an understanding that symptoms of a recurrent myocardial infarction may not be the same as those of a previous event. They are also to be instructed on what to do in terms of taking nitrates or taking an aspirin and are urged to call 911. It is recommended that these recommendations be shared not only with the patient but also with family, and *written down* as reinforcement to the patient, family members, and others who may be around when symptoms occur (Fig. 4). It should be noted that late arrival is frequently cited as a reason for not offering thrombolytic therapy to appropriate patients. It is also of note that those who do not receive reperfusion therapy frequently do not receive other adjunctive therapy that has proved to be efficacious in reducing morbidity and mortality in such patients *(10)*.

PREHOSPITAL ELECTROCARDIOGRAM

Over 50% of patients with AMI arrive at hospital by way of a private automobile or other conveyance *(11)*. Those arriving by ambulance undergo triage and assessment earlier than those arriving by private automobile. Furthermore, it is clear that those

Patient Advisory Form

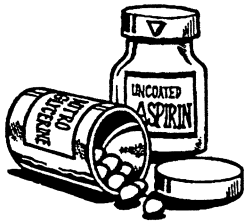
Patient's Name: _____

Physicians now have treatments that can stop heart attacks and lessen damage to the heart. To make sure you can benefit from these treatments, you need to act promptly if you begin to experience symptoms that might signal a heart attack.

What To Do If You Think You Are Having a Heart Attack

1. This is what you may feel:

- ☐ Chest pain or discomfort
- ☐ Left arm pain
- ☐ Pain radiating to your neck or jaw
- ☐ Shortness of breath
- ☐ Sweating
- ☐ Upset stomach
- ☐ Discomfort in the area between your breastbone and navel
- ☐ A sense of dread
- ☐ Other: _____



2. Medication instructions:

- ☐ Chew one 325 mg. tablet of uncoated (nonenteric) aspirin
- ☐ Place one tablet of nitroglycerin under your tongue as soon as you feel discomfort. Take a second tablet if the discomfort does not go away in 5 minutes. Take a third tablet after 5 more minutes if the discomfort does not go away.
- ☐ Other: _____

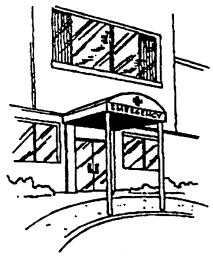
3. If the symptoms stop, call your physician at: _____

4. If symptoms continue for more than 15 minutes, call the emergency medical services phone number below. (Often this is 9-1-1, but you should check to make sure.)

At home, the emergency phone number is: _____

At work, the emergency phone number is: _____

At _____ , the emergency phone number is: _____



5. Know the location of the nearest 24-hour emergency department.

At home, the closest emergency department is: _____

At work, the closest emergency department is: _____

At _____ , the closest emergency department is: _____

Signed: _____ M.D./ R.N.

Place this form next to the phone, near your other emergency numbers!

Fig. 4. Patient advisory form.

patients arriving by ambulance have the initial ECG recorded earlier than those who arrive by automobile and that median door to drug time is significantly shorter in the ambulance patients. Recording of a prehospital ECG reduces door to drug time even more significantly *(12)*. Because the finding of ST-segment elevation on the 12-lead ECG is the trigger that results in consideration of reperfusion therapy, prehospital ECGs are being performed in several Emergency Medical Services systems throughout the country, with a significant impact on reducing door to drug time *(13)*.

EMERGENCY DEPARTMENT CRITICAL PATHWAY

Once the patient arrives in the emergency department, the initial encounter with the nurse or registration representative should be focused on clinical symptoms and not on the collection of demographic information *(6)*. If a patient complains of chest pain, then triage to a high category with an ECG done within 5 min and physician assessment within 10 min should be expected. Placing an ECG machine in the emergency department will reduce door to data time. Acquisition of the 12-lead ECG should be possible within 5 minutes, 24 hours a day, 7 days a week. If this cannot be accomplished effectively using technical staff, then emergency department personnel including nurses or physicians should be trained to perform a high-quality 12-lead electrocardiogram.

FACTORS INFLUENCING DOOR TO DRUG TIME

The nurse should have authority to order the 12-lead ECG, rather than waiting for a physician assessment and order. Once the ECG is available, it should be delivered to the physician for interpretation rather than placed on the chart or at the nurse's desk. Fax consultation for the purpose of interpreting the ECG significantly reduces data to decision time and therefore median door to drug time *(14)*. Contacting the primary care physician delayed the decision to give a thrombolytic drug by 18 min (median) in one study. Bedside consultation by the cardiologist in the same study delayed median door to drug time by 21 min *(14)* (Table 1).

It is imperative that the process of assessing patients with chest pain, acquiring the 12-lead ECG, and making decisions to initiate reperfusion therapy be seamless and consistent. Protocols for assessment and initiation of thrombolytic therapy have consistently and dramatically reduced door to drug times. The experience from three different institutions was that prior to initiation of the protocol, door to drug times were between 69 and 76 min (mean) and were reduced to between 21 and 29 minutes following protocol development and implementation *(4,15,16)*. Furthermore, for patients with clear-cut clinical symptoms of AMI and unequivocal evidence of ST elevation on the ECG with no question of contraindications, the responsibility to order and initiate thrombolytic therapy should be delegated by protocol to the emergency department physician *(6)*. Waiting for the cardiologist has been found to result in significant delays. Given the clear-cut relationship between delay and mortality, a 30-min delay will result in 5 lives lost per thousand and a 1-hour delay in 10 lives lost per thousand *(2,3)*. Preparation of the drug in the emergency department as opposed to the pharmacy can result in substantial decrease in door to drug time, with a difference in one study being 61.5 as opposed to 84.6 min (mean) *(14)*. Furthermore, waiting to initiate drug infusion in the cardiac intensive care unit results in the greatest delay, 75 min, compared with 50 min when the infusion is begun in the emergency department *(14,17)*.

Table 1
Emergency Department Protocol Components that Decrease Door to Drug Time[a]

Door
Radio or cellular phone communications with EMS that facilitate triage
Prehospital 12-lead ECG
Initial focus on clinical symptoms rather than demographic information by registration representative
"Fast track" evaluation of any patient with nontraumatic chest pain (10 min)
Data
Prehospital 12-lead ECG
Standing order for 12-lead ECG on any patient with chest pain, initiated by nurse
ECG machine in ED
ECG available within 5 minutes
Delivery of ECG to physician on completion
Computer-enhanced ECG interpretation
Decision
Interdepartmental protocols specifying inclusion, exclusion criteria, drugs to be administered, and process of administration
Delegation of authority to initiate thrombolytic therapy to patients with ST-elevation MI, no contraindications to emergency physician
Immediate consultation with cardiologist by phone/fax, digital transfer of information regarding indications, contraindications, ECG interpretation
Drug
Initiate thrombolytic drug in ED rather than cardiac unit
Store and prepare drug in the ED
Effectively inform patient of problem, plan, risks within 2–3 min
Initiate drug at receiving hospital rather than after transport to tertiary center
Document administration of other adjunctive and conjunctive therapies by checklist, and record times
Record Door, Data, Decision, Drug times on *all* patients and review times with multidisciplinary team on *regular* basis

[a]Abbreviations: EMS, Emergency Medical Services; ECG, electrocardiogram; ED, emergency department; MI, myocardial infarction.

Extensive written informed consent is not appropriate for a patient with severe chest pain who is suffering an AMI. The patient may be appropriately informed verbally of benefit and risk within 1–2 min by the physician because reperfusion therapy, like many other therapies in medical emergencies, is now the standard of care. There is no evidence that patients who qualify for thrombolytic therapy should be transferred to a tertiary care hospital or center for initiation of drug, because the delay related to transfer will invariably increase mortality. Rural hospitals and community hospitals in urban settings must be capable of treating patients with AMI with thrombolytic drugs according to the same standards for early diagnosis and treatment as the cardiology centers. Telephone and fax consultation with cardiologists in other hospitals may be appropriate to facilitate care in difficult cases.

It is very clear that reductions in delay can only occur if times are recorded consistently on every patient and if door to drug time trends are monitored by quarterly analysis of these data. Significant reductions in door to drug times may drift back to unacceptable

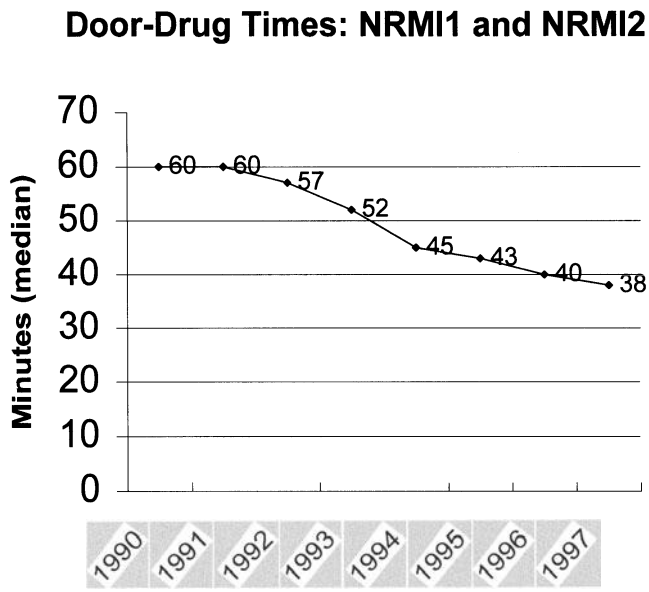


Fig. 5. Changes in door-drug time in the NRMI national population of patients.

levels should a multidisciplinary quality improvement team not meet on a regular basis to review times to diagnosis and treatment for the purpose of improving process. Feedback of these times to participating physicians, nurses, and technologists is critical in improving performance and outcomes. In the NMRI, median door to drug time has fallen from 60 min in 1990, when the Registry was initiated, to 38 min in 1997 (C. Lambrew, personal communitation) (Fig. 5). This is a result of continuing surveillance and feedback of these data to the team involved in caring for these patients.

It is also evident that a strategy of primary angioplasty for AMI may not be effective when applied in real world practice. In one study from NRMI 2, door to dilation time was >2 h in 53% of the patients and indeed, >3 h in 29% of patients. These delays resulted in significant increases in mortality. A multivariate analysis demonstrated a 15% increase in mortality per hour of delay *(18)*. If this strategy is to be effective, then door to balloon times of <60 min are optimal. If patients arrive at a hospital without angioplasty capability, there can be no justification on the basis of studies of effectiveness in the community for the delay incurred in reperfusion by the transfer of such patients to angioplasty-capable hospitals. These patients, if they cannot be dilated within 60 min, should be treated with thrombolytics at the receiving hospital.

CONCLUSIONS

In summary, delays in early identification and treatment of AMI patients with reperfusion therapy result in significant loss of myocardium and significant, quantifiable increase in mortality. Whereas patient-mediated delays have yet to be resolved, delays in the emergency department have been effectively addressed by a continuous quality improvement (CQI) program that includes gathering of data on door to drug time, frequency with which all patients (as well as subgroups of patients) are treated with reperfusion therapy, frequency with which drugs are used, and outcomes. A 30-min door

to drug time, as recommended by the NHAAP, can be achieved safely and effectively through a CQI program that continuously scrutinizes process in relationship to time. Protocols that designate process as well as responsibility for implementation will facilitate early identification and treatment of patients with ST-segment elevation AMI. Elements of hospital process that are driven by hospital policy and "turf" issues without benefit to the patient significantly delay reperfusion therapy and result in worse outcomes. A seamless, patient-oriented protocol will promote a team approach to the care of these patients, which will result in the best outcomes.

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7 Serum Markers for Diagnosis and Risk Stratification in Acute Coronary Syndromes

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INTRODUCTION

Both economic and clinical pressures increasingly necessitate accurate diagnosis and risk stratification of patients presenting to Emergency Departments (EDs) with suspected or actual acute coronary syndromes. Of the more than 6 million patients who present to EDs in the United States each year for evaluation of chest pain or anginal-equivalent symptoms, only about 15% are identified as having an acute myocardial infarction (MI). Conversely, the conventional evaluation, which includes a history, physical examination, screening electrocardiogram (ECG), and creatine kinase (CK)-MB assays, may miss up to 25% of acute MIs at presentation. When unstable angina and nonacute coronary artery disease presentations are accounted for, 40% of patients with chest pain do not have an underlying coronary etiology for their symptoms. The challenge is to identify both this group and the group at higher risk as early as possible, to promote rapid treatment of those who may benefit from specific medical or interventional approaches and to avoid costly hospitalization and testing in those at low risk.

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This chapter discusses the evaluation and management of patients with suspected acute coronary syndromes and the use of serum cardiac markers of myocardial necrosis for diagnosis and risk stratification in all chest pain populations. The focus is placed on the use of cardiac markers in conjunction with the Chest Pain Unit concept for efficient evaluation and triage of patients with chest pain.

INITIAL EVALUATION OF CHEST PAIN IN THE EMERGENCY DEPARTMENT

Perhaps the greatest diagnostic and triaging challenge for the ED physician lies in the evaluation of patients presenting with chest pain. The tools immediately available, which are limited in their sensitivity and specificity for acute coronary ischemia, include the initial history, the physical examination, and the 12-lead ECG.

History and Physical Examination

In the setting of chest pain, the physician's impression of the symptoms as definitely, probably, probably not, or not angina, along with key historical features of prior MI, sex of the patient, age, and number of risk factors (diabetes, smoking, hypercholesterolemia, and hypertension), help to establish the likelihood of coronary artery disease *(1)*.

Chest pain or pressure or epigastric burning discomfort, often with radiation to the neck, arms, shoulders, or jaw, is the most common description of ischemic pain *(2–5)*. Dyspnea, diaphoresis, nausea, and vomiting may accompany these symptoms or, in less typical presentations, may occur as the sole manifestation of ischemia *(4,6)*. Less often, ischemic pain may be described as sharp or pleuritic *(4,5)*. Older patients and diabetics are more likely to have atypical clinical presentations of ischemia; this warrants increased attention to evaluation of their symptoms *(7)*.

The physical examination is nonspecific for establishing the diagnosis of acute coronary ischemia, but the presence of an S4 or S3 gallop, rales, or hypotension, or the development of transient or worsening mitral regurgitation during symptoms, are important in risk stratification and can support this diagnosis or one of underlying coronary disease *(1,4,8–10)*. If chest pain is reproduced with palpation or movement, it should not lead to a false sense of security: the etiology may still be cardiac. In one study by Tierney et al. *(4)*, 15% of patients with acute MI complained of tenderness on chest wall palpation, and Lee and colleagues *(5)* found that to be completely certain that chest wall pain is not due to acute coronary ischemia, the pain must be described as sharp or stabbing and be completely reproduced by palpation *(5)*.

The 12-Lead Electrocardiogram

The 12-lead ECG is usually the earliest available objective test for the presence or absence of cardiac ischemia and can provide important diagnostic and prognostic information in patients with chest pain. In the presence of ST-segment elevation on the 12-lead ECG, the diagnosis of acute MI is confirmed in >90% of cases by serial CK-MB testing *(11,12)*. Unfortunately, only about 10% of all acute MIs present with ST-segment elevation on the initial ECG; most are confirmed only in retrospect, by serial tracings showing the development of new Q-waves or by serial CK-MB testing *(11,13,14)*. The initial 12-lead ECG is further limited in that it provides only a static image of what is usually a dynamic ischemic process and that it has limited ability to evaluate for ischemia in the posterior basal and lateral walls. Despite the lack of diagnostic sensitivity of the initial

Table 1
Likelihood of Significant Coronary Artery Disease
in Patients with Symptoms Suggesting Unstable Angina[a]

High likelihood (0.85–0.99)
Any of the following features:
History of prior MI or sudden death or other known history of CAD
Definite angina: men ≥60 or women ≥70 yr of age
Transient hemodynamic or ECG changes during pain
Variant angina (pain with reversible ST-segment elevation)
ST-segment elevation or depression ≥1 mm
Marked symmetrical T-wave inversion ≥1mm in multiple precordial leads
Intermediate likelihood (0.15–0.84)
Absence of high likelihood features and any of the following:
Definite angina: males <60 or females <70 yr of age
Probable angina: men ≥60 or women ≥70 yr of age
Chest pain probably not angina and two or three risk factors other than diabetes[b]
Extracardiac vascular disease
ST depression 0.05–1 mm
T-wave inversion ≥1 mm in leads with dominant R-waves
Low likelihood (0.01–0.14)
Absence of high or intermediate likelihood features but may have:
Chest pain classified as probably not angina
One risk factor other than diabetes
T-wave flattening or inversion <1 mm in leads with dominant R-waves
Normal ECG

[a]Abbreviations: MI, myocardial infarction; CAD, coronary artery disease; ECG, electrocardiogram.

[b]Coronary artery disease risk factors include diabetes, smoking, hypertension, and elevated cholesterol.

ECG for acute MI, it can support the overall clinical impression of underlying coronary artery disease (for example, the presence of Q-waves) and can provide prognostic information. Dynamic ST-segment elevation or depression and T-wave changes predict a higher short-term risk of death or MI, and can be used along with the clinical evaluation to risk-stratify patients presenting with chest pain into high-, moderate-, and low-risk categories for initial triage *(1,15–19)* (Tables 1 and 2).

Analysis of presenting ECGs from patients in the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIa) trial showed that the presenting ECG category (ST-segment elevation, ST-segment depression, T-wave inversion/normal, or confounding ECG factors) was an important predictor of short-term mortality in a logistic regression model *(20)*. The highest risk group included patients with ECG confounders that obscured interpretation of the ST-segment (left bundle branch block, paced rhythm, or left ventricular hypertrophy), who had a 30-d mortality of 11.6%, followed by ST-segment depression (8.0%), ST-segment elevation (7.4%), and, finally, the very low-risk T-wave inversion/normal group, with a 30-d mortality of only 1.2%. The relationship of the baseline ECG findings with mortality and nonfatal cardiac events in the GUSTO-IIa population is shown in Table 3. A similar gradation of risk by initial ECG characteristics occurred in studies of chest pain patients by Brush and colleagues

Table 2
Short-Term Risk of Death or Nonfatal
Myocardial Infarction in Patients with Unstable Angina[a]

High risk
At least one of the following features must be present:
Prolonged ongoing (>20 min) rest pain
Pulmonary edema, most likely related to ischemia
Angina at rest with dynamic ST changes ≥1 mm
Angina with new or worsening MR murmur
Angina with S3 or new/worsening rales
Angina with hypotension
Intermediate risk
No high-risk feature but must have any of the following features:
Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of CAD
Rest angina (>20 min or relieved with rest or sublingual nitroglycerin)
Nocturnal angina
Angina with dynamic T-wave changes
New-onset CCSC III or IV angina in the past 2 wk with moderate or high likelihood of CAD
Pathologic Q-waves or resting ST depression ≤1 mm in multiple lead groups (anterior, inferior, lateral)
Age >65 yr
Low risk
No high- or intermediate-risk features but may have any of the following features:
Increased angina frequency, frequency, severity, or duration
Angina provoked at a lower threshold
New-onset angina with onset 2 wk to 2 mo prior to presentation
Normal or unchanged ECG

[a]Abbreviations: MR, mitral regurgitation; CAD, coronary artery disease; CCSC, Canadian Cardiovascular Society Class.

(21) and Villanueva et al. *(8)*. In 12,124 acute coronary syndrome patients enrolled in the GUSTO-IIb trial, Savonitto and colleagues *(22)* showed that, as for 30-d events, the baseline ECG correlated with mortality at 6 mo. In their analysis, patients with T-wave inversion had the lowest mortality (3.4%), followed by ST-segment elevation (6.8%), ST-segment depression (8.9%), and combination ST-segment elevation and depression (9.1%) *(22)*.

In summary, using the conventional tools of the history, physical examination, and initial ECG evaluation, the sensitivities of ED physicians for admitting acute MI and unstable angina patients are 92–98% and 90%, respectively *(23–27)*. Specificity is low, however, as only about 30–40% of admitted patients are ultimately found to have an acute coronary syndrome as the etiology for their symptoms *(28,29)*. In the Thrombolysis in Myocardial Infarction (TIMI) IIIb study of conservative vs early interventional care in patients meeting clinical and ECG criteria for unstable angina, 19% of patients were found to have no significant coronary artery disease at cardiac catheterization *(30)* (Fig. 1).

Conversely, 2–10% of patients sent home from the ED after initial evaluation of their symptoms will actually have had an unrecognized acute MI *(25,31–33)*; up to 25% of these are due to misinterpretation of the initial 12-lead ECG *(25,32)*. Approximately 25%

Table 3
Characteristics and Outcomes by Admission Electrocardiographic Category[a]

	ST elevation (n = *435*)	*ST depression* (n = *88*)	*T-wave depression, normal* (n = *163*)	*Electrocardiographic counfounders*[b] (n = *69*)	p *value*
Baseline characteristics					
Duration of chest pain (h)	3.0 (1.7, 4.7)	2.9 (1.5, 5.6)	2.1 (0.8, 4.5)	2.6 (1.0, 4.0)	0.093
Creatine kinase-MB >7 ng/mL	143 (32.9)	30 (34.1)	44 (27.0)	28 (40.6)	0.218
Troponin T >0.1 ng/mL	138 (31.7)	43 (48.9)	49 (30.1)	39 (56.5)	<0.0001
30-d outcomes[c]					
Death	32 (7.4)	7 (8.0)	2 (1.2)	8 (11.6)	0.010
Myocardial infarction	366 (84.1)	50 (56.8)	83 (50.9)	46 (66.7)	<0.0001
Bypass surgery	63 (14.5)	23 (26.1)	32 (19.6)	7 (10.1)	0.016
Angioplasty	142 (32.6)	20 (22.7)	53 (32.5)	21 (30.4)	0.319
Composite outcome[d]	393 (90.3)	67 (76.1)	114 (69.9)	51 (73.9)	<0.0001

[a]Values are medians (25th, 75th percentiles) or frequencies (percentages).
[b]Bundle branch block, ventricular hypertrophy, idioventricular or paced rhythms.
[c]Multiple outcomes are possible.
[d]Occurrence of death, myocardial infarction, or revascularization by 30 d.
Adapted with permission from ref. *20*.

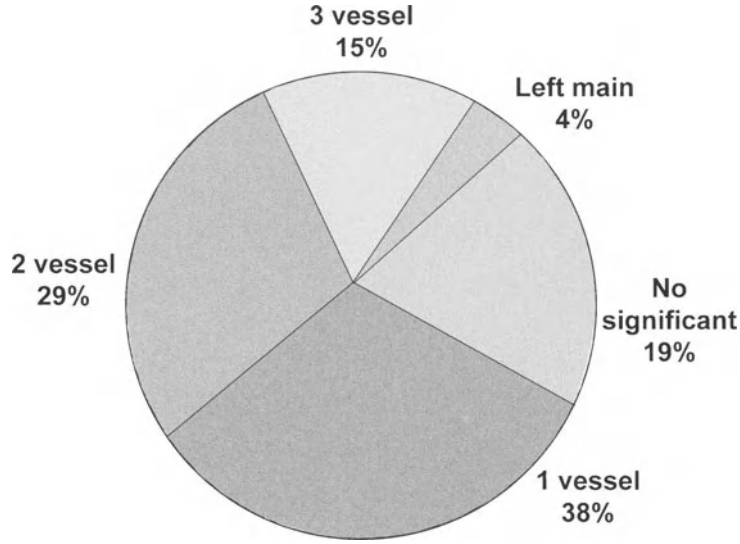

Fig. 1. Extent of coronary artery disease in 720 patients with unstable angina or non-Q-wave infarction who underwent angiography in TIMI-IIIB. Adapted with permission from ref. *30*.

of patients sent home from the ED with an unrecognized MI may die *(25,31,32)*. This figure, coupled with the recognition that the leading cause of malpractice litigation against ED physicians (about 20% of awards) is related to misdiagnosis of acute MI in this minority of patients *(34)*, creates understandable pressure for ED physicians to admit a large proportion of the chest pain patients they see. This practice pattern leads to significant drains on limited in-hospital resources, including beds and nursing staff, and results in an estimated $600 million in hospital costs annually for patients without a coronary etiology for their symptoms *(35)*.

STRATEGIES TO IMPROVE DIAGNOSTIC ACCURACY OF INITIAL CHEST PAIN EVALUATION

To improve the diagnostic accuracy of the ED physician for acute coronary syndromes, many evaluation strategies and diagnostic adjuncts to the traditional history, physical examination, and baseline ECG have been developed. The use of diagnostic decision aids (algorithms, predictive instruments, and neural networks) that incorporate and synthesize the information gleaned from the presenting history, physical examination, and the initial ECG are discussed in more detail in Chapters 5 and 8. Serial ECGs or continuous 12-lead ECG monitoring for ST-segment shifts, as well as both acute echocardiographic and sestamibi nuclear imaging, offer promise in facilitating diagnosis and triage in the ED setting. U wever, they remain limited by availability of services and technical expertise in many facilities. Research addressing the diagnostic ability and cost of such strategies will be needed before widespread use can be promoted.

Serial ECG Analysis and Continuous ST-Segment Trend Monitoring

Because the process of ischemia is a dynamic one, the initial 12-lead ECG, which captures only a static image of the process at one time point, may miss patients with significant underlying ischemic disease. The use of serial ECG tracings over 3–4 h

or with a change in symptoms is one method for diagnosing the cause of the symptoms and detecting early ischemia that might prompt intervention, including thrombolytic therapy, in a patient who was initially not a candidate. However, detection of changes in serial ECGs that warrant intervention is infrequent; in addition, an overall strategy of serial ECGs has been shown to have a lower sensitivity and specificity than serial CK-MB testing over the same interval *(36)*.

Some ischemic changes may be silent, technical and logistic limitations may prevent acquisition of 12-lead ECGs that are truly diagnostic of the ongoing process, and serial ECGs even at 3–4 h intervals may even miss diagnostic changes. The use of continuous 12-lead ECG monitoring for ST-segment trends attempts to circumvent these problems. Patients are hooked to an instrument that samples a 12-lead ECG in the usual configuration every 20 s and repeatedly compares it with the previously acquired tracing for changes in the ST-segment (elevation or depression) of $\geq$0.1 mV. At this point, an alarm sounds, and a 12-lead ECG is printed for review. If there are no alarm ECGs, serial 12-lead ECGs are saved approximately every 20 min and can be used for later review. This method creates a dynamic record of the patient's course; diagnostic changes are picked up that would otherwise have been missed by static 12-lead ECG evaluation.

In retrospective studies of the use of continuous ST-segment trend monitoring in the ED setting, the sensitivity and positive predictive value were low in overall low-prevalence chest pain ED populations *(37,38)*. The use of the technology is limited by patient comfort (patients cannot be ambulatory during the time of monitoring), and baseline artifact related to patient movement can make interpretation inaccurate. In addition, the financial expense of such a monitoring system may be prohibitive. Although the potential for this technology is clear, the National Heart Attack Alert Program Working Group has recommended further prospective studies of its benefit and cost effectiveness before widespread use in the general ED chest pain population *(39)*. The ongoing Prognostic Accuracy of Cardiac Troponin Studies and Holter ST Monitoring (PACTS) trial was designed to answer these questions. This 1000-patient multicenter study will evaluate the prognostic utility and cost effectiveness of ST-segment trend monitoring alone and in combination with cardiac troponin I (TnI) measurement in patients who present with non-ST-segment elevation acute coronary syndromes.

Imaging in the Emergency Department

Acute Echocardiographic Imaging

In the setting of acute coronary ischemia, insufficient blood flow to the myocardium results in abnormalities of both wall motion and normal systolic wall thickening. Echocardiographic imaging can detect these abnormalities but cannot distinguish ischemia from acute infarction. However, in patients with chest pain without clear ischemia on ECG and atypical or low-risk clinical features, echocardiographic imaging may help to clarify the diagnosis. In general, the greatest value has been shown in young male patients without prior cardiac history. Small studies in highly selected populations of patients without known coronary artery disease or prior infarction have shown sensitivities of 86–92% and specificities of 53–90% depending on the timing of the echocardiogram with chest pain symptoms and whether acute MI or acute coronary ischemia was the end point *(39)*. In a larger study of unselected chest pain patients, Sabia and colleagues *(40)* reported that 94% of studies were technically adequate, with a sensitivity of 93% and a specificity of 57% for acute MI.

When considering the use of echocardiographic imaging for diagnosis of MI in ED chest pain patients, keep in mind that obtaining good images of all segments of the myocardium is critical for the accuracy of this means of evaluation. In addition, assessing wall motion abnormalities owing to ischemia in patients with prior infarction or left bundle branch block or after bypass surgery is challenging due to baseline abnormalities of wall motion. Specialized equipment and highly trained individuals capable of performing and interpreting the studies are necessary on-site (24 h/d). The use of telemedicine interpretation of ED echocardiograms, as described by Trippi and colleagues *(41),* could obviate the need to have a cardiologist available on-site for interpretation.

Although early work offers promise, it is not clear that echocardiography adds to the diagnostic accuracy of simpler and more routine ECG and cardiac marker evaluation. At least one small study in the ED setting has shown no advantage from the addition of echocardiographic imaging in the evaluation of chest pain patients *(42).* Further studies in this group will be needed to assess echocardiography's effect on clinical outcomes, as well as its cost effectiveness.

Nuclear Imaging

The National Heart Attack Alert Program Working Group has recently published a summary and analysis of the published literature on the use of nuclear perfusion imaging in the ED for the evaluation of chest pain patients *(39; see* also Chapter 8*).* In general, the reported sensitivities and specificities of Tc99 sestamibi imaging for predicting acute MI in these studies were >90% and in the 80–90% range, respectively. Positive and negative predictive values in these studies were also high. In addition, their review of the literature suggests that negative sestamibi imaging in the ED identifies a population at low risk for both short- and long-term cardiac events.

As with echocardiographic imaging, the widespread use of nuclear imaging for evaluation of chest pain patients in the ED is limited by the need for 24-h availability of personnel trained in the use of radioisotopes and nuclear imaging techniques, as well as someone to interpret the results in real time. Furthermore, the cost effectiveness of using nuclear imaging alone or in conjunction with other diagnostic aids such as serial ECGs or ST-segment trend monitoring or cardiac marker analysis has yet to be demonstrated. However, in a study that compared the use of Tc99 sestamibi imaging with troponin I analysis for detection of acute MI or the need for revascularization in 424 ED patients with chest pain, Kontos and colleagues *(43)* concluded that the two tests provided complementary information. Tc99 sestamibi imaging identified more patients for revascularization than TnI, but the sensitivity for detecting MI in the low-risk population was similar for both strategies. TnI was more specific for the diagnosis of MI than the nuclear imaging strategy, however.

Markers of Myocardial Necrosis

The use of cardiac markers in the ED setting is now commonplace and provides additional valuable information to that from the initial ECG, history, and physical examination. For most available markers, the quantitative assay time is 20 min or less, and the overall turnaround time is within an hour or two of ordering the test. The development of bedside qualitative assays for various markers or panels of markers promises not only to shorten the overall time to test result, but also to place the testing and result reporting in the hands of the caregivers, a feature that should aid in rapid decision making in the ED. The use of individual bedside testing assays for cardiac TnI (cTnI) and TnT (cTnT) has

Table 4
Characteristics of Various Biochemical Markers of Myocardial Necrosis[a]

	Myoglobin	*Total CK*	*CK-MB (mass)*	*MB2/MB1*	*cTnT*	*cTnI*
Molecular weight (kDa)	17.8	85	85	NA	33	23.5
Cardiac-specific	No	No	++	++	+++	+++
Affected by renal function	Yes	No	Yes	No	Yes	Yes
Initial detection (h)	1–3	4–8	3–4	3–4	4–6	4–6
Duration of elevation	18–4 h	12–24 h	24–36 h	Unknown	10–14 d	7–10 d
Laboratory assay time (min)[b]	8–20	10–20	8–30	25	45[c]	8–25
Bedside assay	Yes	Yes	Yes	No	Yes	Yes

[a]Abbreviations: CK, creatine kinase; cTnT, cardiac troponin T; cTnI, cardiac troponin I; ++, very specific; +++, extremely specific.

[b]The times listed represent on-instrument duration only and do not take into account sample transport or specimen handling. Specimen handling routinely includes accessioning, labeling, centrifugation, and aliquoting, which typically requires about 15 min.

[c]12-min assay currently in final phase of Food and Drug Administration approval process.

Adapted with permission from ref. *48a*.

been studied in several large trials studying both chest pain evaluation in the ED and acute ST-segment elevation MI *(44–46)*. In a study of 609 chest pain patients, van Lente and colleagues *(44)* directly compared bedside qualitative cTnT testing (cutpoint 0.2 ng/mL) with in-laboratory quantitative testing using the same cutpoint; they found that the methods were comparable in identifying patients at increased risk for cardiac events.

The likelihood of a positive cardiac marker result drawn in the ED in a patient with true myocardial necrosis depends on the release and clearance properties of the marker, the time since symptom onset, and the sensitivity of the marker assay. Whereas a positive marker result identifies a patient at higher risk who should be admitted to a closely monitored setting (if not a cardiac care unit) *(47)*, a negative result should not be the sole determinant of whether a patient is released from the ED. This is especially important if other high-risk features supporting the diagnosis of unstable angina or possible acute MI have been identified. Almost 50% of patients with an ultimate diagnosis of acute MI will be missed by a single screening CK-MB test obtained on presentation to the ED, and the combination of the initial ECG and CK-MB will miss about 25% of patients with acute MI *(48)*. Research is ongoing to determine the best marker or combination of markers to evaluate chest pain in the emergency setting. The markers of myocardial necrosis that are currently available to the ED physician are discussed in the following section; their properties are summarized in Table 4 and Fig. 2 *(48a)*.

The Ideal Marker

An ideal marker of cardiac injury should be cardiac specific and should have zero blood concentration in the absence of myocardial injury. It should become elevated in the serum soon after the onset of an episode of chest pain to allow the detection of high-risk patients as early as possible, and should remain elevated for many hours to allow detection in patients who delay in seeking evaluation. Persistent elevation of a marker for several days could aid in diagnosis and risk stratification of patients with periodic symptoms or those presenting to the ED well after the episode that prompted evaluation. The

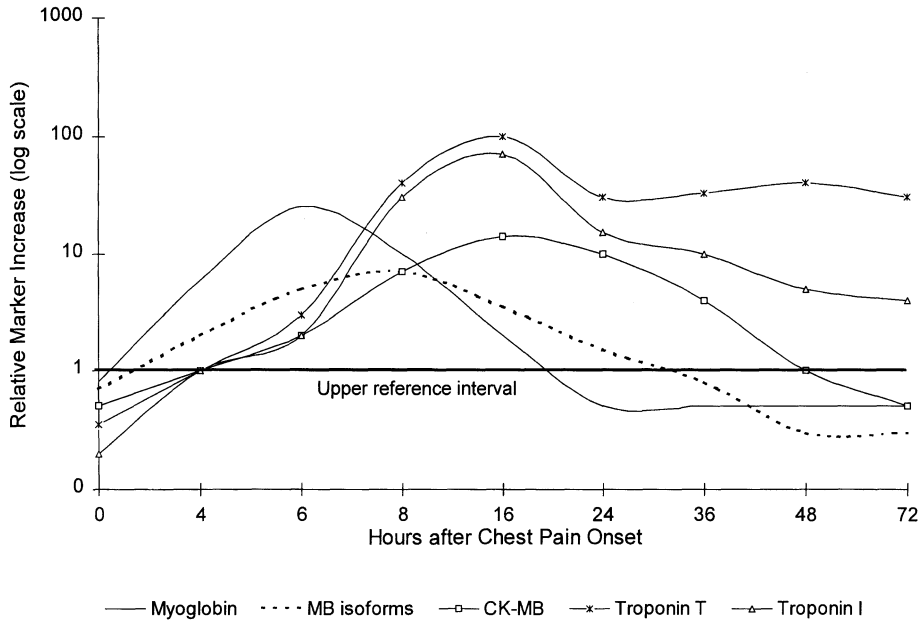

Fig. 2. Relative marker release over time. Adapted with permission from ref. *48a.*

ideal cardiac marker assay would be inexpensive, have rapid in-laboratory and reporting turnaround times, or be available at the bedside, where ordering, testing, and results feedback would be in the hands of the caregivers.

The most commonly used markers of myocardial necrosis include myoglobin, CK, the cardiac-specific isoenzyme of CK (CK-MB), CK-MB subforms (MB1 and MB2), and cTnI and cTnT. Although none of these individual markers meets all characteristics of the ideal marker, a combination of the individual assays into a panel of tests could cover all needs efficiently. Because of the superiority of these markers (alone or in combination), lactate dehydrogenase has largely fallen out of use as a marker of myocardial necrosis. The in-laboratory assay times for all of these markers are within 15–20 min, and bedside assays are available for most.

Although the use of cardiac markers (including bedside assays) in chest pain patients has been shown to be of prognostic importance, and Downie and colleagues *(49)* have shown that in the CCU setting bedside assessment of myocardial necrosis was feasible and allowed for more rapid management decisions, the question remains whether point-of-care testing can measurably shorten ED evaluation time. In their study of point-of-care testing of routine chemistries in the ED, Parvin and colleagues *(50)* found no significant difference in ED length of stay through physician use of bedside point-of-care testing, even after adjusting for differences in presenting conditions. Further study of the effect of point-of-care testing of cardiac markers on ED length of stay, rapidity of treatment decisions, and, ultimately, outcome versus standard testing will be needed.

Myoglobin

Myoglobin is a 17.8-kDa heme protein common to all striated muscle and thus is not cardiac specific. Owing to its small size, it may be detected in the serum within 1–3 h after the onset of ischemic symptoms. Despite a lack of specificity, myoglobin has high diagnostic sensitivity; thus, a negative myoglobin during this time frame has excellent nega-

tive predictive value *(51,52)*. Because of rapid renal clearance, myoglobin remains elevated above the reference range for only 12–18 h. This makes it less useful as a diagnostic marker in later presentations of acute coronary syndromes. Because it is eliminated renally, it may be elevated (in the absence of cardiac muscle injury) in patients with chronic renal insufficiency; it also may be falsely elevated in patients with skeletal muscle trauma or even after strenuous exercise. These factors limit the use of myoglobin alone as a diagnostic marker for patients with suspected acute MI.

Creatine Kinase

CK is an 85-kDa enzyme found in all striated muscle cells, where it catalyzes the phosphorylation of creatine to creatine phosphate. There are three isoenzymes of CK, each composed of two subunits (M and B): CK-MM, the predominant form in striated muscle (cardiac and skeletal); CK-MB, most common in the heart; and CK-BB, most common in the brain but also found in the gut and kidney. Sensitivity for acute MI is >90% by 6 h, and total CK may be detectable in the serum as early as 4 h after the onset of symptoms. Because assays for total CK detect all three isoenzymes, however, total CK is not cardiac specific.

The reference range for total CK assays depends on the patient's age, sex, and race, and levels of total CK may be falsely elevated in many pathologic and other conditions *(13,53)*. Therefore, it is a relatively nonspecific marker that alone has limited utility for the diagnosis of myocardial injury.

Creatine Kinase-MB

Although CK-MM is the predominant isoenzyme of CK in both cardiac and skeletal muscle, CK-MB is relatively cardiac specific, with only small amounts (up to 5%) detected by immunoassay in skeletal muscle. However, CK-MB may be produced in increased amounts in skeletal muscle after trauma or in inflammatory conditions. Because the CK-MB isoform is found predominantly in cardiac muscle, it is more specific for the diagnosis of myocardial injury and therefore provides a distinct advantage over total CK. It becomes elevated within 3–4 h after the onset of ischemic myocardial injury and returns to baseline within 24–36 h. Therefore, although it provides a nearly ideal timing profile for a marker of major myocardial necrosis, it remains limited in its ability to detect small amounts of myocardial damage (infarctlets) that may be prognostically important but obscured by background release from normal turnover of skeletal muscle cells.

CK-MB Subforms. In the bloodstream, CK-MB exists predominantly in equilibrium between two forms, the tissue form (MB2) and the circulating, seroconverted form (MB1). As cardiac muscle cells die, the MB2 subform is released and converted to MB1in the serum by carboxypeptidase cleavage of the N-terminal lysine on the M subunit. During an acute MI, large amounts of MB2 are released, increasing the ratio of MB2 to MB1 as well as the absolute amount of circulating MB2. Puleo and colleagues *(33)* have shown that an absolute level of MB2 >1 U/L and an MB2/MB1 ratio of $\geq$1.5 are highly sensitive markers of myocardial necrosis. Using the CK-MB subform assay, myocardial necrosis can be detected as early as 3 hours after the onset of ischemic symptoms. The use of the MB subform assay has the same limitations in specificity as does CK-MB, but it has excellent sensitivity and negative predictive value in patients presenting with chest pain.

The Troponins

The troponins (T, I, and C) are a group of three distinct proteins that are part of the contractile apparatus of all striated muscle. Troponin T (33 kDa) provides the structural

component that links the troponin complex with tropomyosin to the actin filament. Troponin I (23.5 kDa) is the regulatory subunit involved in the contraction/relaxation process, and troponin C (18 kDa) is a calcium-binding subunit. Troponin I and troponin T each exist in three isoforms—skeletal (slow- and fast-twitch) and cardiac—that are readily identified as distinct amino acid sequences recognized by immunoassay techniques. This provides the basis for the cardiac specificity of TnI and TnT assays for the diagnosis of myocardial injury. As yet, no tissue-specific isoforms of TnC have been identified.

cTnI is not expressed in skeletal muscle, even during fetal development. However, there is coexpression of the cardiac and skeletal muscle isoforms of TnT in fetal muscle of both types *(54)*. In normal adults, TnT isoforms are not coexpressed, but in stressed human hearts, there may be re-expression of the skeletal isoform *(55)*. Reexpression of the cardiac isoform has occurred in animal models of skeletal muscle injury *(56)* and has been detected on biopsy of regenerating skeletal muscle in humans *(57)*. It is unknown if these findings represent a clinical or diagnostic disadvantage for cTnT.

Unlike myoglobin, total CK, and CK-MB, which exist solely in the soluble state in the cytosol of muscle cells, only about 6% of cTnT and 2–3% of cTnI exist in soluble form in the cytosol of the cardiac muscle cell. The remainder is structurally bound in the contractile apparatus. Because of early release of the cytosolic pool, cTnI and cTnT are detectable about 3–4 h after the onset of myocardial injury. Somewhat earlier release of cTnT compared with cTnI after myocardial necrosis has been documented *(58–60)*. No studies have directly compared the timing of the rise of cTnT vs cTnI in myocardial injury, but it has been shown that cTnT rises earlier than CK-MB mass in these patients *(61)*. Conversely, studies with one assay show that cTnI rises later than, or at the earliest concurrently with, CK-MB mass in myocardial injury patients *(54,59)*. As suggested by Christenson and colleagues *(62)* in their comparison of cTnI vs cTnT in acute coronary syndrome patients, these differences may have important implications for use of the troponins for diagnosis in the ED chest pain population and for determining prognosis in acute coronary syndrome patients.

After myocardial necrosis, cTnI remains elevated for 7–10 d and cTnT for up to 14 d, probably reflecting sustained release of the structurally bound components. Because of the sustained elevation of the troponins, detection of recurrent events is more difficult. However, the troponin assays do offer the advantage that remote events may be detected in patients who present several hours to days after symptoms occur.

Like CK-MB, and to a variable extent (greater with cTnT than with cTnI), these markers may be "falsely" elevated in patients with end-stage renal disease, particularly those on hemodialysis *(63–74)*. This elevation may be related to the risk of coronary artery disease *(75,76)*, but extensive outcomes correlation is not available. Pending further study, the interpretation of the results of troponin testing in chest pain patients with end-stage renal disease must be done with caution.

CARDIAC MARKERS IN PATIENTS WITH HIGH-RISK FEATURES ON INITIAL EVALUATION

ST-Segment Elevation Acute Myocardial Infarction

Although the diagnosis of acute MI is later confirmed by serial CK-MB testing in >90% of patients presenting to the ED with chest pain and ST-segment elevation on the

initial ECG *(11,12)*, cardiac marker testing can provide useful information about the size of the MI as well as short- and long-term risk stratification.

In both the prethrombolytic and thrombolytic eras, studies have shown a correlation between infarct size and residual left ventricular function and serum CK or CK-MB concentrations *(77–80)*. These findings have also been linked to differences in both death and nonfatal outcomes, as shown by Christenson and colleagues *(81)* in an analysis of 145 patients who received accelerated alteplase. They showed that the area under the CK-MB release curve was inversely correlated with both ejection fraction ($r = 0.21, p = 0.04$) and infarct-zone left ventricular function ($r = 0.21$, $p = 0.04$). In addition, there was a trend ($r = 0.12$, $p = 0.16$) toward higher rates of congestive heart failure and death in patients with larger CK-MB areas.

Plasma α-hydroxybutyrate dehydrogenase is not a standard marker of myocardial necrosis, but in a substudy of the Global Utilization of Streptokinase and TPA (alteplase) for Occluded Coronary Arteries (GUSTO-I) trial, Baardman and colleagues *(82)* showed that infarct size so measured correlated with infarct-artery TIMI flow grade at 90-min angiography. They also showed that smaller infarcts were correlated with accelerated alteplase or combined alteplase-streptokinase treatment *(82)*. These findings provide mechanistic support for the correlation between TIMI grade 3 flow at 90-min angiography and improved survival seen in the GUSTO-I angiographic substudy *(83)* and the higher overall survival of alteplase-treated patients in the GUSTO-I trial *(84)*.

The use of cTnT for risk stratification in patients presenting with ST-segment elevation acute MI has been studied by several groups. In the GUSTO-IIa TnT substudy, a single cTnT measure at baseline provided significant information for predicting short-term mortality, even when the baseline ECG showed ST-segment elevation *(20)*. In this group, patients who were cTnT positive (1 ng/mL) at baseline had a 30-d mortality of 13%, compared with 4.7% in those who were cTnT negative on presentation. Similarly, in a 3-yr follow-up study of patients with acute ST-segment elevation MI, Stubbs and colleagues *(85)* showed that patients who were cTnT positive (≥0.2 ng/mL) had a significantly higher mortality rate (32%) than patients who were cTnT negative (13%).

Most recently, in a substudy of the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO-III) trial, Ohman and colleagues *(46)* evaluated the use of a qualitative bedside rapid assay for cTnT at presentation for risk stratification of patients with ST-segment elevation MI. Overall, 8.9% of patients were cTnT positive at baseline. In general, patients who were positive at baseline had longer symptom duration, were slightly older, were more likely to have diabetes, prior angina, and Killip class >II, and more often had anterior MI. Both in-hospital and 30-d mortality (14.4 and 15.6%, respectively) were higher in the cTnT-positive patients than in the cTnT-negative patients (5.5% and 6.3%, respectively). In addition, the rates of nonfatal in-hospital events, including congestive heart failure and cardiogenic shock, were higher in TnT-positive patients. When the results of the baseline cTnT test were added to an established mortality model developed by Lee and colleagues *(86)*, the TnT result contributed significantly ($\chi^2 = 22, p = 0.001$) although slightly less than the clinical predictors of Killip class, heart rate, age, and infarct location *(87)*.

These results suggest that cTnT can be used to identify at presentation a subgroup of patients with ST-segment elevation acute MI who are at higher risk for both in-hospital complications as well as short- and long-term mortality. The challenge will be to identify

medical or interventional treatments that can be applied early in this subgroup of patients to mitigate their risk.

Non-ST-Segment Elevation Acute Coronary Syndromes

The history, physical examination, and baseline ECG can all be used to risk-stratify patients with non-ST-segment elevation acute coronary syndromes. Woodlief and colleagues *(88)* developed a regression model in 1384 patients in the GUSTO-IIa trial that identified age, Killip class, systolic blood pressure, and previous hypertension as significant predictors of 30-d mortality. In 393 patients with unstable angina, Calvin and colleagues *(89)* found previous infarction, lack of β-blocker or calcium channel blocker therapy, ST-segment depression on the presenting ECG, and diabetes to be predictors of death or acute MI.

As described previously, in the absence of ST-segment elevation on the initial ECG, the diagnosis of acute MI versus unstable angina is largely made in retrospect on the basis of serial CK-MB testing. However, because even small infarcts as measured by CK-MB sampling confer worse outcomes, and the best outcomes in these patients are likely to be obtained when specific treatments are started early, it is clearly important to identify these groups as soon as possible. The use of the sensitive, specific cardiac markers discussed previously may aid in diagnosis, risk stratification, and management of this diverse group of patients as well. Specifically, TnT and TnI have now been studied extensively as indicators of prognosis in patients with non-ST-segment elevation acute coronary syndromes.

In an enzyme substudy of the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, cTnT was measured at baseline in 976 patients who presented within 12 h of symptom onset *(90)*. At 5 mo, there was a correlation between the combined rate of death or MI and the level of TnT measured in the serum at baseline; cTnT <0.06 ng/mL, 4.3%; 0.06–0.18 ng/mL, 10.5%; >18 ng/mL, 16.1%. cTnT level, age, hypertension, number of antianginal drugs, and ECG changes were identified in multivariable analysis as the most important independent predictors of risk in this population of unstable angina patients.

The GUSTO-IIa TnT substudy evaluated the use of a single baseline measure of cTnT compared with the baseline ECG and CK-MB as a risk marker in 855 patients across the spectrum of acute coronary syndromes *(20)*. Of the 755 patients who had all three studies at baseline, 36% were cTnT positive and 32% had elevated CK-MB. As in the FRISC analysis, the probability of short-term mortality correlated with the serum concentration of cTnT at baseline; when the result of the cTnT test was considered as a dichotomous variable, 30-d mortality was 11.8% in the cTnT-positive patients compared with 3.9% in cTnT-negative patients. This relationship of TnT status to outcome held across all ECG categories (ST-segment elevation, ST-segment depression, T-wave inversion/normal, and confounding factors), and the incidence of in-hospital complications was also higher in the cTnT-positive patients. When the results of the baseline ECG, cTnT, and CK-MB were evaluated in an unadjusted mortality model, baseline cTnT had the largest χ^2 value, followed by the ECG and the CK-MB. However, when the mortality model was adjusted for the presence of the other two variables (which were forced in first), the ECG was the strongest predictor of 30-d mortality ($\chi^2 = 11.5, p = 0.009$), followed by the baseline cTnT result ($\chi^2 = 9.2, p = 0.027$). In the adjusted model, the baseline CK-MB added no significant information after the ECG and cTnT results were considered.

TnI has also been evaluated as a risk marker in acute coronary syndrome patients. In a retrospective analysis of serum from 1404 acute coronary syndrome patients enrolled

in the TIMI-III trial, cTnI was positive in 41% of patients *(91)*. The risk of mortality increased with increasing levels of cTnI; when troponin I status (positive >0.04 ng/mL) was analyzed as a dichotomous variable, mortality was significantly higher in positive than in negative patients (3.7 vs 1.0%). In a multivariable mortality model, ST-segment depression ($p < 0.001$), age >65 yr ($p = 0.026$), and baseline cTnI status ($p = 0.03$) were independent predictors of mortality.

Christenson and colleagues *(92)* have shown that obtaining serial measures of TnT adds significantly to the result of the baseline measure in determining the risk of both in-hospital and 30-d events in the same GUSTO-IIa TnT substudy population. The results of both baseline and serial cTnT testing remained predictive of events in the GUSTO-IIa TnT substudy cohort at 1 yr (mortality 14.2% in baseline cTnT-positive patients vs 5.8% in negative patients; 9.6 vs 5.6% for any positive) *(93)*. Similarly, Stubbs and colleagues *(94)* showed a significant relationship between baseline cTnT measures and death, combined death/MI, and revascularization at a median follow-up of 3 yr. However, when the event rates between 30 d and 1 yr were evaluated, there was no significant difference in mortality over this period for either the baseline or any positive result on serial testing. Based on these results, the increased risk identified by TnT testing in acute coronary syndrome patients appears to be for events that occur early, suggesting that the next step is to identify treatment strategies that can favorably alter this risk when applied early.

Analyses of troponin testing in populations of unstable angina patients enrolled in several large clinical trials suggest that troponin measurement shortly after presentation may be useful to define subgroups of patients who would benefit most from early medical or percutaneous intervention strategies. Such use of troponin testing may improve clinical outcome as well as facilitating cost-effective use of expensive medical and interventional therapies.

The FRISC study of a low molecular weight heparin treatment strategy suggested that troponin-positive subgroups achieved greater benefit from treatment than troponin-negative patients. In the FRISC study, TnT-positive (≥0.1 ng/mL) patients had greater reduction in the 40-d incidence of death or MI (14.2 vs 7.4%) with long-term administration of dalteparin than did those who were TnT negative (<0.1 ng/mL), in whom there was no difference with or without treatment *(95)*. A similar analysis in 1265 unstable angina patients receiving percutaneous intervention who were randomized to treatment with abciximab or placebo in the CAPTURE trial suggested that TnT analysis might be used to identify a subgroup of patients who would realize the most benefit from abciximab treatment *(96)*. This evaluation showed that in 640 TnT-positive patients, the incidence of MI was 4.1% in the placebo group vs 0.9% in the abciximab-treated group. Among 444 TnT-negative patients, the incidences of MI in treated vs control patients were 0.6 vs 0.9%.

Comparisons of TnT with TnI as risk markers have been attempted. However, the lack of standardized assays and use of different cutoff values for the same assay in different studies make the results difficult to interpret. Luscher and colleagues *(97)* compared cTnT with cTnI by the Sanofi assay in 491 patients with unstable angina and found them to identify similar groups of patients at high risk for 30-d death or MI.

Using the Dade Stratus II cTnI assay at a cutpoint of 1.5 ng/mL in comparison with cTnT in the GUSTO-IIa TnT substudy cohort, both markers, when measured at baseline, predicted 30-d mortality, but cTnT provided the most prognostic information. In a mortality model with the ECG and the other marker forced in first, only cTnT still provided additional prognostic information *(62)*. Furthermore, the area under the receiver-operator

characteristic curve, which is independent of the cutpoint used for an assay, was larger for cTnT compared with cTnI (0.68 vs 0.64).

Serial bedside tests for cTnT and cTnI at baseline and 4 h were evaluated by Hamm and colleagues *(45)* with similar performance (sensitivity and negative predictive value) by both markers. In a logistic regression model, both markers were strong predictors of 30-d death or MI and remained so even after ST-segment depression on the initial ECG was forced into the model first *(45)*. The individual chi-square for cTnI in this model was larger, however.

The results of these studies suggest that the prognostic information demonstrated in individual studies of cTnT or cTnI should not be generalized to other assays or testing conditions. Differences in analytic characteristics and measurement precision for the different cTnI assays may translate into important differences in their ability to risk-stratify the acute coronary syndrome patient. Differences in the characteristics of the marker proteins themselves, including the timing and magnitude of release after both myocardial necrosis and injury, may also translate into the differences in prognostic ability seen in individual studies performed under different testing circumstances and in different patient populations. Further study with standardized techniques under well-defined clinical circumstances will be needed to characterize the importance of these differences.

THE ROLE OF CHEST PAIN UNITS IN PATIENT EVALUATION

Because symptoms, the physical examination, and the initial ECG and cardiac marker evaluations are often inconclusive, Chest Pain Units have been devised as one strategy to optimize diagnosis and management in low- to moderate-risk chest pain patients while maintaining reasonable costs of care and avoiding the inherent medicolegal problems of patients who are sent home with undetected MIs.

In general, Chest Pain Units use protocol-driven strategies for observation and "rule-out" of myocardial infarction in low- to moderate-risk patients—those without clear ischemic changes on the initial ECG, with negative initial cardiac marker assessment, and without high-risk clinical features. These centers provide for faster and earlier detection of and therapeutic intervention for acute MI missed by initial evaluation, or the development of an unstable clinical course, than routine admission might allow. Most provide for continuous observation either in or adjacent to the ED with serial sampling of cardiac markers (usually CK-MB, MB subforms, or troponins) every 3–4 h and serial ECG or continuous ST-segment monitoring over a period of 9–12 h. Cardiac evaluation and later risk stratification with exercise stress testing are often included before release in patients who have been "ruled out."

In one of the earliest studies of rule-out strategies, Lee and colleagues *(98)* showed that in the absence of recurrent chest pain and with negative CK-MB enzymes, a 12-h period was sufficient to exclude the diagnosis of acute MI in 99.5% of low-risk patients. Similarly, Gibler and colleagues *(28,29)* showed that serial sampling of CK-MB over a period of 9 h was sufficient to eliminate the diagnosis of MI in nearly 100% of patients. In study of a 12-h, short-stay observation strategy, Gaspoz et al. *(99)* showed that if serial CK-MBs were negative in a patient with no recurrent chest pain or ECG changes, the risk of later MI or death was <1%. In a randomized trial of 9 h of rule-out observation in the Chest Pain Unit vs conventional care, Gomez and colleagues *(100)* showed no significant difference in outcome between the management strategies.

Table 5
Length of Stay and Financial Implications of Chest Pain Unit Rule-Out Protocols[a]

Study	*Reduction in length of stay (d)*	*Cost reduction[b] [$ (%)]*
Gaspoz et al. *(101)*		
CCU	4.0	7,274 (76)
Step-down	2.0	2,104 (52)
Wards	3.0	2,785 (63)
Gomez et al. *(100)*	0.5	981 (47)
Mikhail et al. *(103)*	ND	1470 (62)
DUMC Chest Pain Program *(102)*	2.3	1765 (47)

[a]DUMC, Duke University Medical Center; ND, no data recorded; CCU, coronary care unit.
[b]For hospital stay except Gaspoz, which reflects total costs through 6 mo.
Adapted with permission from ref. *(102)*.

At many sites, the use of Chest Pain Centers or Chest Pain Units has eased the pressure on the ED physician to commit high-cost cardiac care unit resources or release the patient. Several groups have shown the safety of this approach, as well as significant reductions in costs and charges with such short-stay observation strategies (Table 5). In their randomized study, Gomez and colleagues *(100)* showed a 40% reduction in charges for Chest Pain Unit observation vs conventional care. Gaspoz and colleagues *(101)* showed reductions in hospital-care costs of $7,274 and $2,785 for the comparison of a protocol-driven, short-stay strategy vs a CCU- or floor-based strategy, respectively. In our own experience at Duke University Medical Center, the use of a Chest Pain Unit compared with conventional admission and rule-out has resulted in a 2.3-d shorter length of stay and a 47% reduction in hospital costs *(102)*. In their chest pain rule-out program, Mikhail and colleagues *(103)* found that hospital costs fell from an average of $2,364 before institution of the program to $894 using their protocol. They also demonstrated the cost effectiveness of routine stress testing in patients who had been ruled out for MI. The cost of identifying one patient with coronary artery disease after a negative rule-out was $3,125; for identifying one patient with disease that warranted bypass surgery or angioplasty, the cost was $10,714. The projected cost per year of life saved was < $2,000.

Cardiac Markers in the Chest Pain Unit

Newer markers, such as the cardiac troponins and CK-MB subforms, could further enhance the process of care in the low- to moderate-risk undifferentiated chest pain population. With markers that are more sensitive, cardiac-specific, and (in some cases) detected earlier than CK-MB, the standard observation time for definitive rule-out of MI could be reduced from 9–12 h to 6–8 h. An ongoing prospective trial is comparing the sensitivity, specificity, and positive and negative predictive values of multiple markers at various times across the spectrum of patients presenting to EDs with chest pain, and also plans to address the prognostic value of the marker results *(104)*.

The duration of symptoms before presentation varies widely from patient to patient. In the ED or Chest Pain Unit, then, for the earliest and most sensitive and specific diagnosis of myocardial necrosis, the use of a panel of markers that includes myoglobin or MB subforms as a very early marker, CK-MB mass (4–6 h), and TnT or -I (4–8+ h) could be ideal (Fig. 3). In a study of 190 ED patients with chest pain, Levitt and colleagues

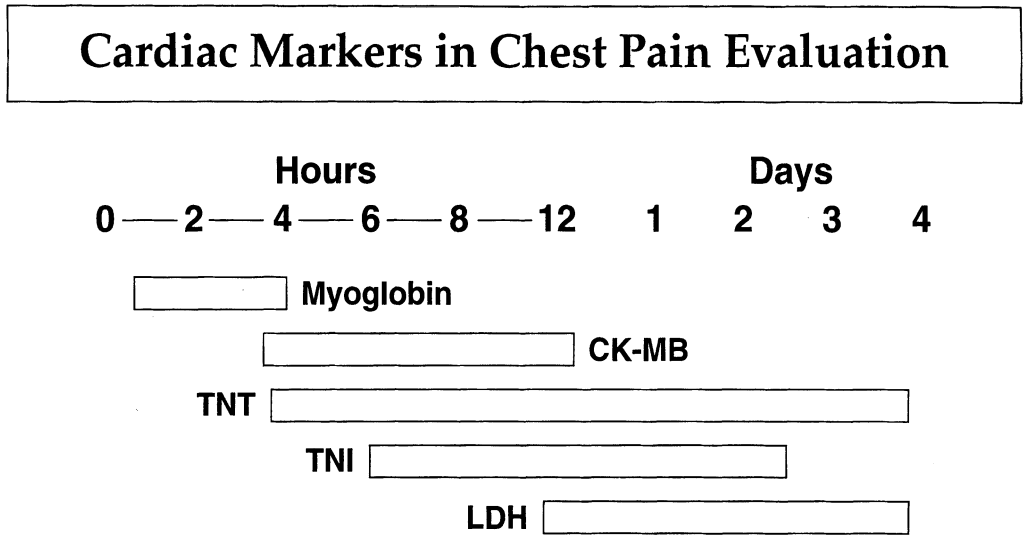

Fig. 3. Overlapping time frames of markers.

Table 6
Predictive Capabilities of Serum Enzymes in the Emergency Department[a]

Serum marker value	*Sensitivity*	*Specificity*	*Positive predictive value*	*Negative predictive value*
Myoglobin	90.59 (69.6–98.8)	88.4 (83.6–93.2)	48.59 (27.9–61.9)	98.79 (95.4–99.8)
CK-MB	81.0 (58.1–94.5)	99.4 (96.8–100)	94.4 (72.7–99.9)	97.7 (94.2–99.4)
Combination	100 (83.2–100.0)	91.2 (85.9–95.0)	58.3 (39.3–73.7)	100 (97.6–100.0)

[a]Presented as percent (95% confidence intervals). A positive serum myoglobin test is defined as a level 88.7 ng/mL or higher, and a positive serum creatin kinase (CK)-MB as 11.9 ng/mL or higher, either at the time of ED presentation or 3 h later. The combination test is defined as positive if either of the above two tests is positive. Adapted with permission from ref. *42*.

(42) evaluated the use of CK-MB alone, myoglobin alone, or a combination of myoglobin and CK-MB at baseline and 3 h for diagnosis of acute MI in the ED. Positivity was noted if the marker was positive at either time point; myoglobin was more sensitive than CK-MB but less specific, and the combination of both markers was most sensitive and specific. The sensitivity, specificity, and positive and negative predictive values are shown in Table 6. In a similar study of 101 ED patients with chest pain, Kontos et al. *(105)* showed that when patients with diagnostic ECGs were excluded, the sensitivity and specificity of a combination of myoglobin and CK-MB mass results at baseline were 80% and 84%, respectively, for the diagnosis of acute MI and were superior to those for either marker alone *(105)*. The combination of the markers' results on serial sampling at 0 and 4 h had both sensitivity and specificity of 100%, suggesting that a combination of markers could identify or exclude the diagnosis of acute MI as early as 4 h after ED presentation.

The Biochemical Markers of Acute Coronary Syndromes Study Group evaluated the use of serial testing of CK-MB, myoglobin, and cTnT alone or in combination and at different discriminatory levels to confirm or exclude the diagnosis of acute MI within 6 h of presentation in 142 patients with chest pain and nondiagnostic ECGs *(52)*. They

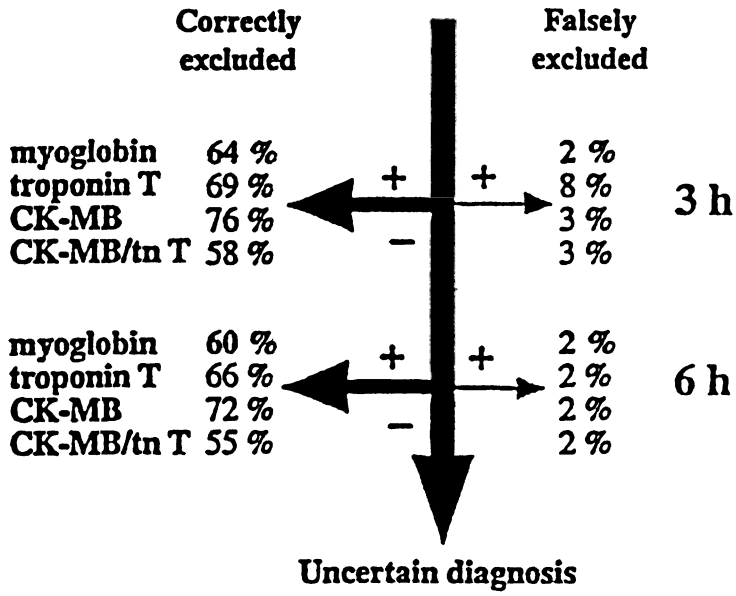

Fig. 4. Percentage of correctly and falsely excluded acute myocardial infarction in all patients (59 with and 83 without infarction) 3 and 6 h after admission. Reproduced with permission from ref. *52*.

concluded that no markers alone or in combination could safely exclude the diagnosis of acute MI with certainty on admission, but that by monitoring a combination of myoglobin, CK-MB, and cTnT, MI could be excluded in up to 72% by 6 h with a low rate of patients falsely excluded (Fig. 4). For the diagnosis of MI, no single marker regardless of the discriminatory level used combined high sensitivity and specificity, but the combination of myoglobin and CK-MB or myoglobin and cTnT on serial testing had sensitivities of 92% and 82%, respectively, at 2 h and 98% for both combinations at 6 h. Specificities of the combinations were 98% and 94%, respectively, at 2 h, and 93% and 82%, respectively, at 6 h.

Small studies have investigated the potential of some of the newer cardiac markers in diagnosis and risk stratification in the low- to moderate-risk Chest Pain Unit population. Puleo and colleagues *(33)* showed that the use of CK-MB subforms in the evaluation of chest pain patients had excellent negative predictive value to rule out MI. Trahey and colleagues *(106)* reported that serial sampling of CK-MB subforms over a 6-h period followed by diagnostic exercise testing was sufficient to rule out the diagnosis of MI in their Chest Pain Unit patients and to stratify patients with a negative stress test into a low-risk group with only a 1.3% risk of later MI or recurrent ischemia.

TnT testing also shows promise for risk stratification in the low- to moderate-risk Chest Pain Unit population. In a meta-analysis of published reports of cTnT testing in chest pain patients without documented MI, Wu and Lane *(107)* calculated an odds ratio for prediction of the need for coronary revascularization of 4.4 (95% confidence interval 3.0–6.5) in cTnT-positive patients. A similar metaanalysis revealed an odds ratio for death or infarction of 4.3 (95% confidence interval 2.8–6.8) in cTnT-positive patients (Fig. 5). In an analysis of 439 consecutive patients assigned to observation in the Duke University Chest Pain Unit, 10% of patients were cTnT-positive on serial testing over 8 hours *(108)*. A positive cTnT result identified a group at higher risk for significant (>75% stenosis) underlying coronary artery disease (90%) and multivessel disease (63%) than

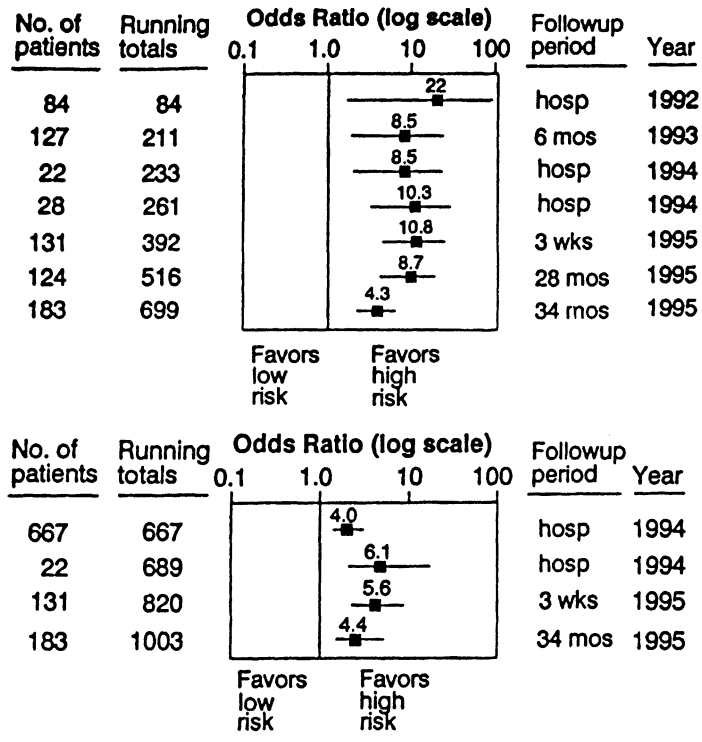

Fig. 5. Cumulative odds ratios for use of cTnT in patients without infarction for an outcome of infarction of cardiac death (top) or for an outcome of coronary artery revascularization (bottom). Squares indicate the actual values; lines indicate the 95% confidence intervals. Reproduced with permission from ref. *105.*

those found in the cTnT-negative group (31% and 26%, respectively). Furthermore, serial testing of TnT over an 8-h period (compared with CK-MB analysis over 12 h) detected the only patients who were CK-MB positive. No patient who was cTnT negative 8 h later had positive CK-MB, but there were 24 patients who were cTnT positive and CK-MB negative. At short-term follow-up (mean 21 d), there were no deaths in either group. Further work on correlation of TnT status and outcome in this group is ongoing.

Hamm and colleagues *(45)* recently reported the use of serial bedside testing for cTnT and cTnI baseline and 4 h after presentation in the ED with acute chest pain. In their outcome study of 773 consecutive patients presenting within 12 h of onset of symptoms and without ST-segment elevation on initial ECG, the use of qualitative, monoclonal antibody-based bedside assays for cTnT and cTnI identified by 4 h after presentation 94 and 100%, respectively, of patients later determined to have MI by follow-up CK and CK-MB testing. Among unstable angina patients, 22% were positive by TnT and 36% by TnI bedside testing. Importantly, the 30-d risks of death or nonfatal MI in patients negative for TnT or TnI were only 1.1and 0.3%, respectively. These results may be further enhanced by development of a cTnT device having a lower cutoff (0.08 vs 0.2 ng/mL) and greater cardiac specificity.

As these studies suggest, the use of highly specific cardiac markers or panels of markers and new testing strategies can identify early a subset of patients (of those who present without high-risk features) who might benefit from earlier intervention. The challenge for future research in this area will be to identify which medical or interventional

strategies can modify the future risk these patients face. Furthermore, because these markers also identify a low-risk population earlier than conventional testing might allow, the potential exists for further reductions in length of stay and expensive diagnostic testing, thus amplifying the cost savings possible through the use of Chest Pain Units.

CONCLUSIONS

For evaluation of the thousands of patients with acute, nontraumatic chest pain who present to Emergency Departments each year, serum markers of myocardial injury (alone or in combination) will continue to play an increasingly important role, not only in diagnosis and triage decisions but also in identifying patients who are at increased risk for adverse outcomes in both the short and long term. In both regards, their utility extends across the spectrum of low-, moderate-, and high-risk patients as defined by the initial clinical assessment. As an adjunct to the basic history, physical examination, and baseline ECG, the use of cardiac markers, particularly the troponins, can provide crucial information for initial and later risk stratification. The use of serial measurements of cardiac markers not only increases their sensitivity and negative predictive value for acute infarction but also, in the case of the troponins, adds to prognostic ability. With the identification of patients who are negative on serial testing, particularly those with low-risk features, length of hospital stay for evaluation can be reduced and in-hospital resources better allocated, with substantially decreased costs. However, perhaps the most important feature of the cardiac markers in risk assessment of chest pain patients is that in patients with positive marker studies, most of the risk for adverse events is incurred early. Thus, the challenge for the future investigations will be to define the management and treatment strategies (medical and interventional) that, when applied early in marker-positive patients, will reduce their likelihood of adverse events.

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8 Technologies to Diagnose Acute Ischemia

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INTRODUCTION

As the most common cause of death in this country, acute myocardial infarction (AMI) has deservedly been the subject of substantial efforts of clinicians, scientists, governmental and other agencies, and the public in efforts to reduce its devastating impact. Although significant progress continues to be made, The National Heart, Lung, and Blood Institute of the National Institutes of Health recognized the need for a concerted and coordinated effort to reduce mortality and morbidity in this country from AMI and in 1991 initiated the National Heart Attack Alert Program (NHAAP).

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Detecting AMI and unstable angina (UAP) in the emergency department (ED) is a challenging task, and the consequences of a missed diagnosis can be detrimental to both patients and physicians. The high prevalence of disease, the common, atypical presentations, and the poor sensitivity or specificity of the clinical examination have led to the use of many technologies to assist in establishing an accurate diagnosis. Recognizing this central and growing role of diagnostic technologies for AMI and for acute cardiac ischemia (ACI) in general (including both unstable angina pectoris and AMI) in emergency settings, which represent patients' entry points into the health care system, in 1994, the NHAAP Working Group on Evaluation of Technologies for Identifying Acute Cardiac Ischemia in the Emergency Department was formed to assess the utility of diagnostic technologies for ACI/AMI in the ED. This chapter summarizes the Working Group's assessment of the diagnostic performance and impact on care of those technologies *(1,2)* and updates its base of scientific evidence. The technologies reviewed address the diagnosis of ACI (i.e., both AMI and UAP), as this is the condition that must be identified in the treatment of patients with AMI and potential AMI. The review included technologies directed at the *diagnosis* of ACI in the ED; methods primarily directed at prognostic or risk stratification of such patients were not included.

WORKING GROUP METHODS

To accomplish this review, a formal process of review and evaluation of the scientific literature related to these technologies was undertaken based on Medline and related electronic literature searches and supplemented by the panelists' (see list of acknowledgments) understanding of the literature and ongoing research. Relevant English literature on each technology was reviewed, summarized, and analyzed. For each technology, studies were formally evaluated and then rated. The *quality of evidence* provided by the relevant studies was rated as A, B, C, or NK, as follows: A, prospective controlled clinical trials of high quality (e.g., large multicenter trials with concurrent controls); B, substantial clinical studies; C, limited studies or evidence (e.g., case series, small clinical studies); or NK, not known (e.g., expert opinion or case reports only).

Based on these reviews, each technology, for its primary purpose, was rated in terms of its diagnostic performance for identifying ACI/AMI in actual use and its demonstrated clinical impact. *Diagnostic performance* indicates the accuracy of the technology and is measured by sensitivity, specificity, or receiver-operating characteristic curve, for ACI. *Clinical impact* indicates its demonstrated impact on diagnosis, triage, treatment, or outcome (e.g., mortality) when used by clinicians in actual practice. Performance in each of these two dimensions was rated as: +++, very accurate/large clinical impact; ++, moderately accurate/medium impact; +, modestly accurate/small impact; NK, not known; or NE, not effective.

In assigning these ratings, each technology was evaluated on the basis of its performance of its *primary* diagnostic purpose of general ED detection (G), early detection (E), and detection in specific subgroup (S). These designations are noted in Table 16.

The Working Group's conclusions and ratings for each diagnostic technology reviewed are given below. The ratings of the Working Group reflect its estimation of the accuracy or impact of the test in actual practice in the ED. These assessments incorporate the quality of the literature, the magnitude or effect size of the reported findings, and considerations of generalizability and feasibility.

Table 1
Standard Electrocardiogram[a]

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
A	++	Standard of care	Standard of care

[a]For abbreviations and gradings in Tables 1–15, see footnotes to Table 16.

STANDARD ELECTROCARDIOGRAM

The primary purpose of the standard electrocardiogram (ECG) is to detect ACI in broad, symptomatic ED populations. However, there are several fundamental limitations to the standard ECG. First, it is a single brief sample from a highly varied domain. Because unstable ischemic syndromes have rapidly changing demand and supply characteristics, a single ECG may not adequately represent the entire picture *(3)*. If a patient with unstable angina is (temporarily) pain-free at the time the ECG is obtained, the resulting normal tracing will poorly represent the patient's ischemic myocardium. A tracing taken minutes later may have a very different appearance. Second, 12-lead electrocardiography is limited because of its lack of perfect detection in areas of the myocardium it samples. Small areas of ischemia or infarction may not be detected. Additionally, the conventional leads do not directly examine the right ventricle *(4)* or the posterior basal or lateral walls very well. AMIs in the distribution of the circumflex artery are likely to have a nondiagnostic ECG *(5,6)*. Third, some ECG baseline patterns make the ECG tracing difficult or impossible to interpret. These findings include early repolarization, left ventricular hypertrophy, bundle-branch block, and arrhythmias *(7)*. Also, prior Q-waves can mask zones of reinfarction, although the presence of any significant abnormality in a patient with chest pain or other related symptoms should generally be considered "positive."

Fourth, the waveforms of ECGs are often difficult to interpret, and thus there is much disagreement among readers. Such nonagreement frequently includes cases of "missed ischemia." This has been studied by Lee and colleagues *(8)* in their review of patients with AMI who were sent home. The ECGs of such discharged patients tended to show ischemia or infarction not known to be old; 23% of missed diagnoses were due to misread ECGs. These patients were younger, were less likely to have prior infarct or angina, and had more atypical symptoms.

In spite of these shortcomings, the standard ECG functions as an integral component of the evaluation of patients with acute chest pain and should continue to be incorporated in strategies that incorporate other clinical characteristics such as historical and physical examination parameters. The ECG is not a perfectly sensitive test, and it should always be considered a supplement to, rather than a substitute for, physician judgment. The Working Group recommends that the ECG continue to be considered the standard of care in the evaluation of chest pain in the ED patient. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 1.

PREHOSPITAL ELECTROCARDIOGRAM

The primary test purpose for the prehospital ECG is the early detection of AMI with acute ST-segment elevation. Additional important issues are whether the prehospital ECG reduces the time to an appropriate intervention for ST-segment elevation AMI detected in the prehospital setting and whether the intervention yields clinical benefit. A 12-lead prehospital ECG is obtained at the scene or in the ambulance, and a preliminary ECG interpretation is printed out in the ambulance. The ECG is then sent to the hospital via cellular telephone through a modem, which takes approximately 20 s. Error-free data transmission is ensured by an interactive method of data transfer *(9)*. The following patients are eligible for prehospital ECGs: cooperative adult patients with a complaint of chest pain or other symptoms of heart attack, with systolic blood pressure >90, and without malignant dysrhythmias (ventricular tachycardia or fibrillation, or second/third-degree atrioventricular block) *(10)*.

A prospective evaluation demonstrated that 91.4% of prehospital chest pain patients met these eligibility criteria *(11)*. From 3–5% of prehospital patients with complaints of chest pain may be identified as candidates for thrombolytic therapy, which comprises one-half or more of all patients receiving thrombolytic therapy *(10,12,13)*. Multiple studies have shown the feasibility of performing prehospital 12-lead ECGs *(9–21)*. Diagnostic quality ECGs can be acquired and successfully transmitted in approximately 70% of prehospital chest pain patients eligible for 12-lead ECGs *(11)*. ECG acquisition increases the time spent at the scene of an emergency an average of 3.9 min over control *(11)*. Additionally, there is no difference between the information collected in the prehospital setting and that received by cellular transmission at the base station *(9)*.

Effect on Hospital-Based Time to Treatment

Several studies have demonstrated significant reductions in hospital-based time to treatment with thrombolytic therapy for AMI patients identified prior to patient arrival with prehospital 12-lead ECG *(16,17,19,22)*.

Kereiakes et al *(16)* demonstrated that the median hospital delay to treatment was 64 min for patients transported by private automobile, 55 min for patients transported by local ambulance, 50 min for patients transported by the emergency medical services (EMS) system with a prehospital ECG obtained but not transmitted to the receiving hospital, and 30 min for patients transported by the EMS system who had a 12-lead ECG transmitted from the field. Specialized EMS system transport alone did not facilitate in-hospital initiation of thrombolytic therapy; a significant reduction in hospital time delay to treatment was observed only in patients transported by the EMS who had cellular transmission of a prehospital 12-lead ECG from the field. Karagounis et al *(17)* demonstrated a statistically significant 20-min time reduction in hospital-based treatment with thrombolytic therapy in AMI patients identified by prehospital 12-lead ECG.

Prehospital Thrombolysis

The Myocardial Infarction Triage and Intervention (MITI) trial randomized 360 prehospital AMI patients to receive either prehospital or hospital-based thrombolytic therapy *(23)*. Using prehospital 12-lead ECGs and a paramedic contraindication checklist, the MITI trial demonstrated that 353 (98%) of the 360 patients enrolled had subsequent evidence of AMI. Two percent of patients had nondiagnostic abnormalities on the

Table 2
Prehospital Electrocardiogram

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
A	++	B	+

initial ECG. Prehospital identification of patients eligible for thrombolysis by paramedics reduced the hospital treatment time from 60 min (for patients not in the study) to 20 min (for study patients allocated to begin treatment in the hospital). Because this was not a comparable group by definition, it is only suggestive of the potential benefit of a protocol-driven prehospital thrombolytic program.

The MITI trial also showed that administration of thrombolytics occurred 33 min earlier in the prehospital group than in the hospital group, although the investigators found no significant differences overall in mortality, ejection fraction, or infarct size between the prehospital group and the hospital treatment group. Although there was no improvement in outcome associated with initiating treatment before hospital arrival, treatment within 70 min of symptom onset was associated with a statistically significant lowered mortality rate of 1.2% *(23)*.

A number of other studies outside the United States have demonstrated that it is possible to identify thrombolytic candidates accurately in the prehospital setting *(20,21,24–34)*. The Grampion Region Early Anistreplase Trial *(30)* conducted in northern Scotland demonstrated a median time difference of 130 min between prehospital and hospital-based treatment with thrombolytic therapy. This trial demonstrated a statistically significant 52% relative reduction in 1-yr mortality. Furthermore, significantly fewer Q-wave (smaller) myocardial infarctions were seen in patients treated with prehospital thrombolytic therapy compared with patients treated in the hospital *(30)*.

In summary, *prehospital identification* of thrombolytic candidates through the use of prehospital 12-lead electrocardiography has been shown in almost every study to reduce hospital-based time to treatment significantly. This time savings is perceived as beneficial but has not, by itself, demonstrated a reduction in mortality. *Prehospital treatment* with thrombolytic therapy may result in a significant mortality reduction if the time savings is in the area of 1 h or more. Parallel controlled randomized prospective studies are required to analyze further the cost-benefit issues, additional uses, and ultimate role of prehospital 12-lead electrocardiography.

The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are given in Table 2.

CONTINUOUS 12-LEAD ELECTROCARDIOGRAM

A typical instrument for continuous ST-segment monitoring is microprocessor controlled and fully programmable *(35)*. It can continuously acquire a new 12-lead ECG every 20 s and analyzes the ST segments. The initial ECG is defined as the pretrigger ECG. If ST-segment elevation or depression occurs 0.2 mV in a single lead or 0.1 mV in

two leads compared with the pretrigger ECG, the device enters a potential alarm state. If four sequential ECGs have met the threshold criteria, then an alarm sounds, and a 12-lead ECG is printed for physician review. This ECG then becomes the new pretrigger ECG for future ST-segment comparisons. Typically, a 12-lead ECG is saved every 20 min as well as any alarm ECGs. One can also print two-dimensional graphs of ST-segment trends (magnitude vs time) for the 12 individual leads or the average ST-segment magnitudes for the four regional groupings: anterior (V_1–V_3), inferior (II, III, AVF), low lateral (V_4–V_6), and high lateral (I, AVL).

The practice of monitoring dysrhythmias in suspected cardiac patients became the standard of care when electrical and chemical defibrillation demonstrated the potential to terminate dysrhythmias. Similarly, with the advent of specific proven modalities to treat both AMI (with thrombolytics or angioplasty) and myocardial ischemia (with anticoagulants, vasodilators, circulation support devices, and angioplasty), there are sound reasons to evaluate and test the continuous 12-lead ECG.

There are two questions that continuous ECG could address: first, it could aid in the early detection of potential candidates for thrombolysis or angioplasty while they are undergoing monitoring in the ED. This may occur in patients with suspected AMI whose initial ECG is nonspecific but whose second ECG has at least 0.1 mV of ST-segment elevation in two contiguous leads. Second, in subgroups of ED patients, it could improve the diagnosis of ACI by detecting ST-segment changes that confirm the diagnosis of unstable angina or non-Q-wave AMI. Because approximately 50% of the patients with chest pain and AMI present to the ED without ST-segment elevation, and nearly 20% of these patients develop in-hospital ECG evidence of transmural infarction, continuous serial ECGs with ST-segment trend monitoring may identify the patient population most likely to benefit from rapid interventions following detection of ECG criteria diagnostic for AMI *(36)*.

In a retrospective study, Gibler et al. *(37)* used ECG/ST-segment trend monitoring to monitor 1010 patients in a chest pain evaluation and treatment program located in the ED. Of 52 patients with cardiac disease, 11 had evidence of ischemia or evolving AMI by ST-segment trend monitoring. As this population had a low prevalence of acute ischemic coronary syndrome, it is hypothesized that such a monitoring device may actually demonstrate a higher utility in a population with greater disease prevalence. In an earlier trial, Gibler et al. *(36)* evaluated 86 patients with chest discomfort admitted to a heart ED program. Eighteen (20.9%) patients had cardiac diagnoses on discharge from the hospital after in-hospital evaluations for ACI. Serial 12-lead ECGs with ST-segment trend monitoring detected 7 of 18 patients (39%) with a final cardiac diagnosis consistent with ACI. Ten patients had ST-segment trend monitoring with positive results, but hospitalization revealed a noncardiac cause of their chest discomfort. Thus, the positive predictive value was <50%, meaning that there were more false positives than true positives.

There have been no large randomized prospective ED or coronary care unit (CCU) studies evaluating this technology. Cost-benefit analysis of this technology has not been accomplished. Although ED ST-segment monitoring holds the potential to detect silent myocardial ischemia and infarction, reduce missed ischemic diagnoses, and provide the earliest evidence for coronary occlusion in patients presenting with preinfarction angina, larger prospective studies are required to make this assessment. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 3.

Table 3
Continuous 12-Lead Electrocardiogram

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
NK	NK	NK	NK

NONSTANDARD ECG LEADS

The standard 12-lead ECG is a less than perfect predictor of AMI. The sensitivity of ST-segment elevation for AMI is approximately 50% *(38)*, and up to 30% of AMI patients have nonspecific or normal ECGs.

One of the explanations offered for these limitations is that the 12-lead ECG poorly detects posterior wall *(39)* and right ventricular infarction (RVI) *(4)*. These areas of the myocardium are not directly interrogated by standard leads but are assessed by posterior leads V_7, V_8, and V_9 and right-sided leads V_{4R}, V_{5R}, and V_{6R} *(40)*.

Posterior AMI is one of the most commonly missed ECG findings, and this may be explained by the lack of direct ECG examination *(41)*. In their study, Seyal and Swiryn *(42)* found that 6% (13 of 250) of infarctions are isolated to the posterior basal surface of the left ventricle.

Posterior and right-sided leads are acquired using the same ECG as standard leads. For right-sided leads, the lead placement is just the reverse of standard left-sided leads (i.e., midclavicular line, fifth intercostal space for V_{4R}, anterior axillary line for V_{5R}, and midaxillary line for V_{6R}). Posterior leads continue in the same horizontal plane as the precordial leads (i.e., fifth intercostal space, but continue on to the posterior axillary line for V_7, midscapular line for V_8, and paraspinal for V_9) *(40)*.

A plethora of articles assess the diagnostic value of V_{4R} and other right-sided leads to detect RVI *(4,43–47)*. There is a consensus that within this context, right-sided leads detect RVI with a sensitivity of 80–90% and a specificity of 80%. Most recently, Zehender and colleagues *(43)* showed that right ventricular leads are independent predictors of in-hospital and long-term prognosis in inferior wall AMI.

Posterior wall AMI usually occurs in the setting of inferior AMI but is seen as an isolated phenomenon about 5% of the time. Posterior leads occasionally have been reported to assist in the diagnosis of AMI. However, detecting "true" posterior wall AMI from the numerous noninfarct cases is difficult, partly because it is an uncommon finding.

Although the literature has documented that the standard 12-lead ECG is insensitive for detecting posterior AMI, there have been only occasional reports comparing standard 12-lead with posterior-lead findings.

In a multicenter study of the diagnostic accuracy of an ECG that contained 3 right ventricular and 3 posterior leads against the standard 12 lead, 533 patients were enrolled *(40)*. Sensitivity for the diagnosis of AMI was improved with the "18-lead ECG," by 8.5%, but specificity decreased by 6.5%. This was largely due to high false-positive rates for isolated ST-segment elevation in the right ventricular leads. Posterior leads had better specificity, comparable to the 12-lead ECG. Logistic regression analysis found that right ventricular leads had independently contributed to the diagnosis of AMI; posterior leads just missed standard levels of significance ($p = 0.055$), indicating a small level of impact.

Table 4
Nonstandard Electrocardiogram Leads

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy*	*Quality of evidence*	*Impact*
C	+	NK	NK

In summary, sampling right ventricular leads is clinically practical, uses the universally available 12-lead ECG, and appears to increase the sensitivity and specificity for detection of RVI (a strong, independent predictor of major complications and in-hospital mortality in patients with inferior AMI). Such leads have the potential to improve severity classification of AMIs, help refine the process of risk-benefit assessment for emergency interventions, possibly provide an indication for thrombolytic treatment, and avoid nitrate-induced hypotension in patients with RVI. Sampling posterior leads has improved the sensitivity of the ECG for posterior AMI, but the effect size is small. Right ventricular leads do not contribute to the diagnosis of AMI generally, but only to the diagnosis of RVI. The results of the Working Group's final ratings of the quality of evidence evaluating these technologies and of their ED diagnostic performance and clinical impact are shown in Table 4.

ECG EXERCISE STRESS TEST

After ruling out an AMI or an unstable angina, a graded exercise test *(48)* prior to discharge from the ED may assist in the diagnosis of coronary artery disease (CAD) and result in more appropriate referral *(49–54)*. In a study of patients evaluated in a Chest Pain Center located in the ED, 791 of 1010 patients underwent graded ECG exercise stress testing after 9 h of nondiagnostic serial ECG/ST-segment trend monitoring; 0-, 3-, 6-, and 9-h creatine kinase isoenzyme-cardiac muscle subunit (CK-MB) testing; and resting echocardiography *(37)*. None of the patients undergoing ECG exercise stress testing suffered an adverse event while being tested. Of these 791 patients, 782 (98.9%) had a negative or nondiagnostic ECG stress test, and the positive predictive value was 44% (4/9) for CAD. Thirty-d follow-up revealed a 0.1% AMI rate and 0.5% all-cause mortality rate. Prior studies by Kerns et al. *(51)* and Tsakonis et al. *(52)* were pilot efforts to show the feasibility or potential favorable economic impact of such studies. When the risk of coronary artery disease is low to moderate, the expedited ECG stress test may offer the benefit of an expedited workup and may reduce hospital admissions for chest pain *(53–54)*. However, ECG exercise stress testing in the ED cannot be routinely recommended; expedited stress testing in appropriately selected patients is acceptable. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 5.

ORIGINAL ACI PREDICTIVE INSTRUMENT

The original ACI predictive instrument was developed by Pozen et al. *(55,56)* and uses readily available clinical and ECG data to provide physicians with patients' probabilities of ACI. In a multicenter study, the predictive instrument was developed on the basis of data on the 2801 study subjection in the six participating hospitals' EDs from March 1979

Table 5
Electrocardiogram Exercise Stress Test

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
C	+	C	NK-NE

Table 6
Original Acute Cardiac Ischemia Predictive Instrument

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
A	+++	A	+++

through February 1980 *(55)*. Beginning with 59 clinical features available to ED physicians, including clinical presentation, history, physical findings, ECG, sociodemographic characteristics, and coronary disease risk factors, an equation was developed that used only seven variables and that was applicable to all six hospitals. This mathematically based instrument provides an estimate of a patient's likelihood to have true ACI expressed as a value between 0% and 100%. In controlled prospective trials of its use, first at Boston City Hospital, and then in the Multicenter Predictive Instrument Trial, it reduced false positive CCU admission by 30% without an increase in false-negative discharges to home *(55,56)*. Although appropriate for general clinical use, it has not been widely adopted in EDs, possibly owing to the need for a hand-held calculator to compute the probability of ACI. In the near future, the original ACI predictive instrument will probably be superseded by the ACI-time-insensitive predictive instrument (TIPI), which is discussed below. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 6.

ACUTE CARDIAC ISCHEMIA TIME-INSENSITIVE PREDICTIVE INSTRUMENT

The ACI-TIPI represents the next generation of ACI predictive models developed by Selker and colleagues *(57,58)*. The ACI-TIPI, like the original ACI predictive instrument *(55,56)*, provides the ED physician with the 0–100% probability that a given patient truly has ACI, to supplement the ED triage decision. The variables used for the ACI-TIPI are:

1. age,
2. gender,
3. the presence or absence of chest pain or pressure or left arm pain,
4. whether chest pain or pressure is the patient's most important presenting symptom,
5. the presence or absence of ECG Q-waves,
6. the presence and degree of ECG ST-segment elevation or depression, and
7. the presence and degree of ECG T-wave elevation or inversion.

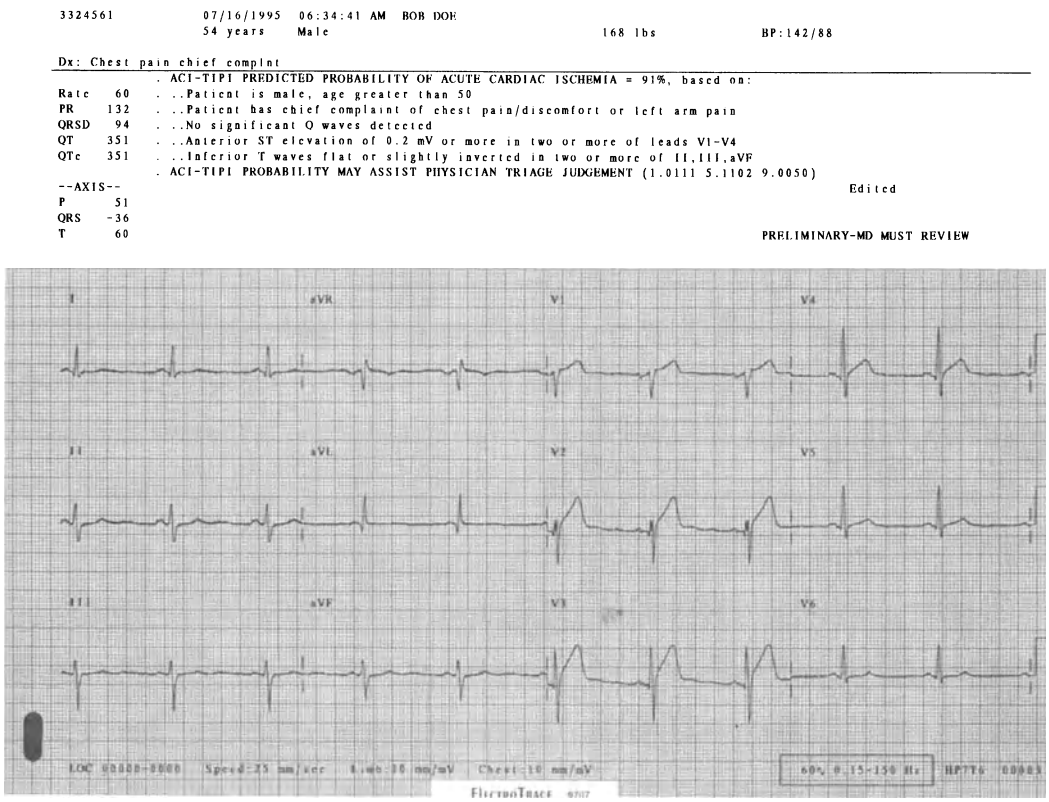

Fig. 1. Acute cardiac ischemia time-insensitive predictive instrument.

Its diagnostic performance has been tested in large studies that included ED *(57,59)* and EMS *(60)* patients and has been demonstrated to be diagnostically equivalent to the earlier version *(57)*, except for a slightly higher sensitivity for AMI. Thus it should be comparable to the original ACI predictive instrument *(57)*, with two advantages for clinical use. First, its incorporation into the conventional computerized ECG allows direct measurement of details of the ECG waveform without the need for physician interpretation, with automatic printing of the ACI probability on the ECG header (Fig. 1). Second, its time insensitivity makes it valid for retrospective review and assessment of care as well as for real-time ED clinical care.

Two published early trials have shown an impact on the speed and accuracy of ED triage *(59,61)*. Although published only in abstract form, data on clinical impact on ED triage decision making in a 10,689-patient multicenter controlled clinical trial showed that the diagnostic performance of the ACI-TIPI ECG (by itself and by ACI-TIPI risk groups) was very good *(62,63)* and that its use improved patient ED triage *(64)*. In terms of its actual impact on ED care, for patients *without* ACI in hospitals with low telemetry capacities, use of ACI-TIPI decreased CCU admissions by 16% and increased ED discharges to home by 7% ($p = 0.09$). Moreover, for patients seen by residents without supervising attending physicians, ACI-TIPI reduced CCU admissions by 31%, reduced telemetry admissions by 19%, and increased discharges to home by 18% ($p = 0.005$).

For patients with stable angina pectoris, in hospitals with *low* telemetry bed capacities, ED use of ACI-TIPI reduced CCU admission by 50%, increased telemetry admissions by

Table 7
Acute Cardiac Ischemia–Time-Insensitive Predictive Instrument

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
A	+++	C[a]	+[a]

[a]Abstract and pending reports are not included in the ratings.

25%, and increased ED discharges to home by 10% ($p = 0.04$). At hospitals with *high* telemetry capacities, ACI-TIPI reduced telemetry admissions by 14% and increased ED discharges to home by 101% ($p = 0.03$; to the level of discharge seen in hospitals with lower telemetry unit capacities). Across all hospitals, ACI-TIPI reduced CCU admission by 26% and increased ED discharges to home by 48% ($p = 0.04$). Finally, for patients with AMI or unstable angina pectoris, at both the low- and high-capacity hospitals, and with both supervised and unsupervised residents, ED use of ACI-TIPI did not change the appropriate admission of 96% of patients to either CCU or telemetry beds.

However, because results of abstracts were not considered in arriving at the Working Group's ratings, as of this writing the quality of evidence warrants a C rating and the clinical impact A + until rerating once the trial's results are fully published. The overall results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 7.

GOLDMAN CHEST PAIN PROTOCOL

The Goldman chest pain protocol is a computer-derived decision aid developed to assist physicians in using routinely collected clinical and test data in the ED; it is meant to help identify likely AMI patients who therefore require triage to the CCU. A statistical technique of recursive partitioning was used to divide the subjects into subgroups by ED data elements (history, physical examination, and ECG); higher or lower AMI proportions were then noted (Fig. 2) *(65,66)*.

The protocol was developed using prospectively collected data on patients presenting to the ED with acute chest pain *(66)*. AMI was used as the outcome on which to base triage to the CCU, given that the risk of emergency complications early in admission is 17% compared with 0.5% in patients without AMI. Recursive partitioning was used to develop a decision tree with the probability of ruling in for an AMI as the outcome of each branch. The protocol was prospectively validated in a population of 4770 patients who presented with chest pain *(65)*. Follow-up of the 2232 patients who were discharged from the ED was performed by either physical examination, follow-up measurement of CK, or telephone to determine whether an AMI had occurred after discharge from the ED. Diagnostic performance for AMI compared with that of physicians for the same patients is shown in Table 8.

These data show that the sensitivity of the protocol for predicting AMI with triage to the CCU is the same as that of physicians, but that the specificity is higher. It was projected that 11.5% of patients without AMI would have been triaged elsewhere had the protocol been used.

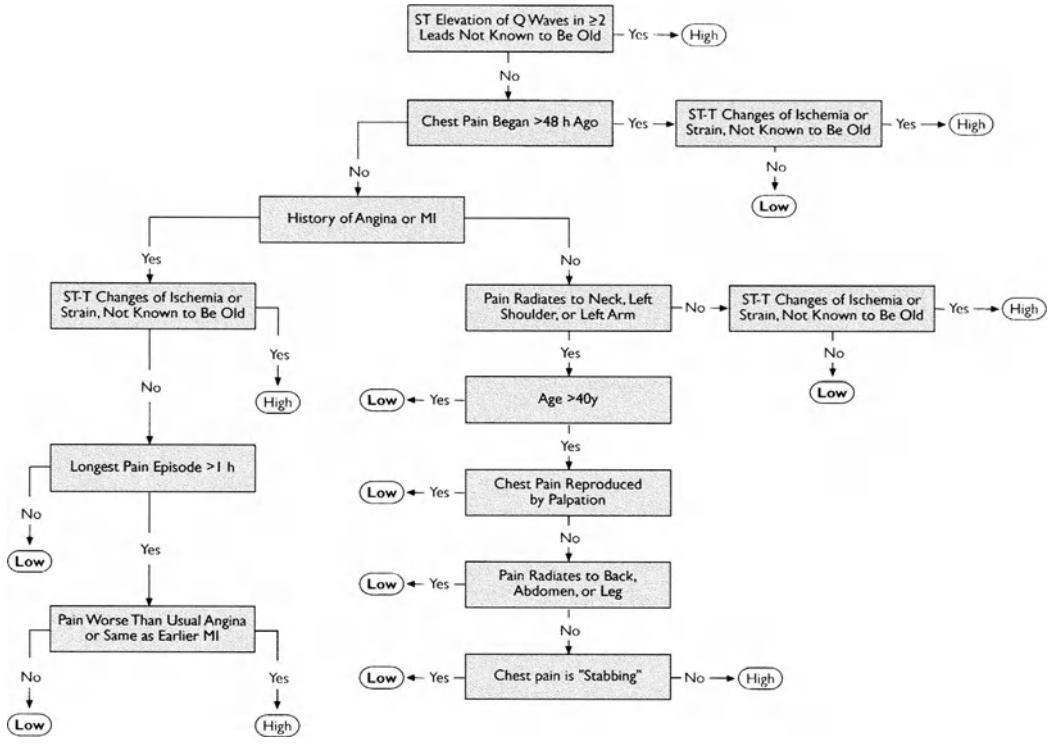

Fig. 2. Goldman chest pain protocol divides patients into high and low risks of acute myocardial infarction on the basis of a recursive partitioning model. It uses routinely collected and interpreted history, physical examination, and electrocardiographic data. Reproduced with permission from ref. *53*.

A prospective trial used a time series study design to determine the impact of the protocol on the triage and outcomes of patients presenting to the ED at the Brigham and Women's Hospital in Boston *(67)*. The time series design used six 14-wk cycles, consisting of a 5-wk control and/or intervention period separated by 2-wk washout cycles. Risk estimates and triage recommendations were provided to physicians in a nonobtrusive fashion. Rates of admissions during intervention and control periods were unchanged in the hospital (52% and 51%, respectively) and in the CCU (10% each). Also, there were no significant differences in hospital length of stay or average total costs *(67)*. The Goldman computer-based chest pain protocol was developed using a sound methodology. The fact that it was validated in a large population that included two university and four community hospitals, with at least two of the hospitals having racially diverse populations, supports its potential utility in a diverse patient population. As the protocol currently stands, its greatest potential benefit would probably be in improving physician specificity for AMI and avoidance of triage to the CCU with attendant cost savings. However, this impact has not been demonstrated in a controlled clinical trial of its use. Also, given that UAP is important with regard to clinical and cost implications, the fact that non-AMI ACI is not addressed by the Goldman protocol is a significant limitation. The protocol cannot be applied to all ED patients who have symptoms consistent with ACI. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown Table 9.

Table 8
Goldman Chest Pain Protocol: Comparison with Physician Diagnoses

	Physicians (%)	*Protocol (%)*	p *value*
Sensitivity[a]	88	88	NS
Specificity[b]	71	74	<0.00001
Positive predictive value[c]	29	32	0.10
Overall accuracy	73	76	<0.00001

[a]Percentage of patients with acute myocardial infarction (AMI) admitted to the coronary care unit (CCU).
[b]Percentage of patients without AMI not admitted to CCU.
[c]Percentage of patients with AMI among the total admitted to CCU.

Table 9
Goldman Chest Pain Protocol

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
A	For AMI: +++ For UAP: NE	B	NK-NE

OTHER COMPUTER-BASED DECISION AIDS

Other computer-based decision aids, including neural networks, provide examples of a variety of ways to identify patients for CCU admission and to predict myocardial infarction *(68–73)*; they are reviewed in the full Working Group report *(1)*. Published models have some limitations, especially in that they often predict AMI rather than ACI and have not yet been demonstrated to be safe and effective in actual use. Although each has some promise, including very encouraging performance in preliminary studies, at this point none can be considered ready for clinical use. The results of the Working Group's final ratings of the quality of evidence evaluating these technologies and of their ED diagnostic performance and clinical impact are shown in Table 10.

CREATINE KINASE

CK and CK-MB measurements are traditionally obtained early in the ED course of a patient admitted to the hospital for suspected AMI or ACI *(74–77)*. The utility of the assay in the ED as a one-time test is limited because levels do not significantly increase until 4–6 h after the onset of AMI *(74)*. Mass measurements of CK-MB *(76,77)*, compared with the older activity analysis, have significantly early improved sensitivity. Improved sensitivity may also be achieved by CK-MB subforms, and these may be more useful in making the diagnosis of AMI in the ED for patients who present early after the onset of symptoms *(78–80)*. This is also achieved by repeated measurements of CK-MB in the ED or the hospital *(81–83)*. However, and importantly, CK and CK-MB do not identify patients with UAP, who comprise about half of the patients with ACI.

Despite improvements in the diagnostic performance and practicality of CK and CK-MB assays, no controlled clinical impact trial has shown that these tests assist in decisions to send patients home or delineate the appropriate level of care when patients

Table 10
Other Computer-Based Decision Aids

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
B	+	NK	NK

Table 11
Creatine Kinase

	ED diagnostic performance		*ED clinical impact*	
	Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
Single test	A	For AMI: + For UAP: NE	NK	NK
Multiple tests over time	A	For AMI: +++ For UAP: NE	NK	NK

with suspected ACI are admitted, either as one-time or serial tests. A prospective intervention study, with follow-up of all (including nonadmitted) patients, of the effect of serial CK and CK-MB on patient outcomes is needed before a strategy incorporating CK-MB into medical decision making can be fully evaluated or recommended. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 11.

OTHER BIOCHEMICAL TESTS

Myoglobin, an early marker of AMI *(84,85)*, and cTnT and -I, which are specific for myocyte damage and are late markers *(86–88)*, hold promise to improve the identification of patients with AMI and minor myocardial injury. However, the use of new biochemical markers in the ED as a routine measure to improve either the initial triage or therapy of patients with AMI is currently unproved, although recent studies suggest that the cardiac troponins add additional predictive value to CK-MB measurements *(89–91)*. The value of these studies needs further bolstering by additional data from carefully controlled studies. Ultimately, serum protein testing may include a panel of multiple markers providing a spectrum of information regarding the time of AMI onset. An early sensitive marker such as myoglobin, when combined with CK-MB and TnT (elevated in the presence of AMI), could provide the clinician with critical information necessary to make decisions in the emergency setting.

The results of the Working Group's final ratings of the quality of evidence evaluating these technologies and of their ED diagnostic performance and clinical impact are shown in Table 12.

ECHOCARDIOGRAM

Resting echocardiography has appeal as a technique to detect ACI and is systematically reviewed in the Working Group's report *(1)*. When the myocardium becomes

Table 12
Other Biochemical Tests

	ED diagnostic performance		*ED clinical impact*	
	Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
Triponin T and troponin I	B	For AMI: ++ For UAP: NE	NK	NK
Myoglobin	B	For AMI: + For UAP: NE	NK	NK

ischemic, there is a nearly immediate alteration in wall motion, and the wall becomes hypokinetic or dyskinetic *(92)*. Peels et al. *(93)* studied 43 patients with nondiagnostic ECGs in the ED. Patients without prior AMI, with known CAD, or who had had procedures were excluded from the study, as were patients whose echo window was technically inadequate. Imaging was done prior to relief of chest pain, or as soon as possible. Sensitivity for ACI was 88% (22 of 25) with a specificity of 78% (14 of 18). Sensitivity for AMI was 92% (12 of 13) with a specificity of 53% (16 of 30). Although the results of these study are somewhat encouraging, aside from the very small size of the study, the fraction of ED patients to which its results are applicable is questionable, namely, only those without technical limitation or precluding history who are having ongoing chest pain. Sabia et al. *(94)* also evaluated regional wall motion abnormalities prospectively in the ED in 185 patients during 202 ED visits for chest pain or shortness of breath. Of 60 patients without regional or global dysfunction, 2 (4%) had AMI. Of the 87 patients with regional wall motion with or without global changes, 31% experienced AMIs. Although triage results were projected to reduce hospital stay, triage with echocardiography was not actually tested.

Although echocardiography in the ED has shown initial promise, it is labor intensive and inaccurate for distinguishing new from old ischemia. Its primary role is as an adjunctive test if readily available during active chest pain; there are insufficient data demonstrating that it can triage patients effectively in large clinical settings.

In the ED setting, when looking for ACI, it still has a false-negative rate that precludes discharging all patients with a negative echocardiogram. For the purpose of ruling in or ruling out AMI, echocardiography cannot be done accurately by ED personnel. Considerable expertise is needed for data acquisition and interpretation *(95,96)*. When this is readily available, echocardiography might improve the accuracy of diagnosis and might thereby lead to a reduction in unnecessary admissions and costs. Beyond the diagnosis of ACI, for those with AMI, additional potentially useful clinical information about complications and hemodynamic status (ejection fraction, pulmonary artery pressure) would also become known, possibly leading to improvements in management and prognosis. Study results that suggest that alternative diagnoses needing acute care would also be potentially beneficial. Overall, the available investigations to date suggest that even in a *selected* ED population, echocardiography may be reasonably specific but not clearly sufficiently sensitive for either ACI or AMI for this tool to be recommended for ED use. Its role for the overall ED population is even less clear, and it cannot be recommended without much more information about the appropriate patients, its diagnostic performance in the usual ED setting, and its safety and effectiveness in this setting when tested in a controlled interventional clinical trial. The results of the Working Group's final

Table 13
Echocardiogram

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
B	+	NK	NK

Table 14
Thallium Scanning

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
C	NK-NE	NK	NK-NE

ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 13.

THALLIUM SCANNING

The use of radionuclide imaging for the diagnosis of ACI/AMI in the ED should be restricted to specialized and limited situations in which the clinical triad of history, ECG changes, and enzymatic/laboratory measurements is not available or is unreliable. Such imaging may be helpful, for example, in patients with equivocal chest pain histories and nondiagnostic ECG findings. Thallium-201 is an excellent perfusion tracer, but the available data indicate that a resting thallium scan has relatively poor diagnostic accuracy in the setting of AMI or UAP, with a low specificity *(97–99)*. There are also difficulties with isotope availability and tracer redistribution (necessitating imaging within 15–20 min after injection) *(100)*. This is impractical in the ED setting. Hence thallium-201 does not appear to be an ideal agent for use in the ED management of patients with chest pain. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 14.

SESTAMIBI AND OTHER TECHNETIUM-99M PERFUSION AGENTS

Technetium-99m sestamibi (^{99m}Tc sestamibi) is an excellent perfusion tracer *(100–103)*, with advantageous physical characteristics compared with thallium-201 *(101,103)*. Its availability, excellent imaging properties, and stable tracer distribution with time make it a practical agent for ED use. There is minimal redistribution after its initial coronary flow-related distribution in the myocardium *(100,101)*; thus images made up to 1–4 h after injection will still reflect myocardial blood flow as it was at the time of injection *(104)*. Although large-scale trials are lacking, the available data (in relatively small numbers of patients) indicate that ^{99m}Tc sestamibi is a promising agent for use in the ED evaluation of selected patients with chest pain.

Smaller trials have shown high sensitivity and good specificity *(104,105)*. Its use to date in a small number of centers with considerable expertise has been promising *(106)*.

Table 15
Sestamibi and Other Technetium-99m Perfusion Agents

ED diagnostic performance		*ED clinical impact*	
Quality of evidence	*Accuracy (max = +++)*	*Quality of evidence*	*Impact*
C	+++	NK	NK

It is uncertain whether the technique will have good generalized applicability, particularly as a screening test in lower risk ED patients without ongoing chest pain or when used by less experienced interpreters. Until more evidence is available, it cannot be recommended at this stage for general use. The results of the Working Group's final ratings of the quality of evidence evaluating this technology and of its ED diagnostic performance and clinical impact are shown in Table 15.

CONCLUSIONS AND RECOMMENDATIONS

Summary of Clinical Recommendations Based on Demonstrated Diagnostic Performance and Clinical Impact

Recommendations regarding the use of a technology should be based on both ED diagnostic performance and clinical impact data obtained in high-quality or substantial studies. Of the various test technologies evaluated in the sections, however, only five met this highly desirable standard of evaluation. A summary is provided in Table 16.

The *prehospital ECG* was found to have good (++) diagnostic performance based on evidence from high-quality prospective studies (A). However, this technology was judged to have a small clinical impact (+) based on substantial clinical studies (B). It was the impression of the Working Group, based on these results, that although this technology has promise, it will probably be realized in areas with long EMS transport times. Thus, until more evidence is obtained, its general use cannot be recommended.

The original ACI predictive instrument was found to be excellent for diagnostic performance (+++) and substantial clinical impact (+++) in a high-quality prospective multicenter trial (A) for both forms of ACI (UAP and AMI). Its accuracy and demonstrated improvement in ED triage make it possible to recommend it for general use in the ED evaluation and triage of patients with symptoms suggestive of ACI. Its main drawback has been that its use requires a programmed calculator or chart, which has been an obstacle to its widespread use. This may be overcome by its successor, the ACI-TIPI, which is incorporated into and reported as part of the header printout on a standard 12-lead ECG.

The third technology is the *Goldman chest pain protocol*. An important caveat, however, is that this protocol was designed only for AMI detection and not the more general detection of ACI in the form of UAP. Its diagnostic performance for AMI has been demonstrated to be excellent (+++) in multicenter high-quality studies (B). However, in a high-quality prospective study (B), it has not had a demonstrable impact on clinical care (NK-NE), and thus, at this point, its general use cannot be recommended.

The fourth diagnostic technology is the *ACI-TIPI*, although the largest clinical trial of impact is available only in abstract form. It has comparable diagnostic performance (+++) to the original ACI predictive instrument based on multicenter prospective studies

Table 16
Summary Ratings of Diagnostic Technologies
for Acute Cardiac Ischemia (ACI) for Emergency Department (ED) Use[a,b]

		ED diagnostic Performance[c,d]		*Demonstrated ED clinical impact*	
Technology	*Primary diagnostic use*	*Quality of evidence*	*Accuracy (max = +++)*	*Quality of evidence*	*Impact (max = ++)*
Standard electrocardiogram (ECG)	G	A	++	Standard of Care	Standard of Care
Original ACI predictive instrument	G	A	+++	A	+++
ACI-TIPI (time-insensitive predictive instrument)	G	A	+++	C[e]	+[e]
Prehospital ECG	E	A	++	B	+
Goldman chest pain protocol	G	A	For AMI: +++ For UAP: NE	B	NK-NE
Creatine kinase, multiple tests over time	S	A	For AMI: +++ For UAP: NE	NK	NK
Sestamibi	S	C	+++	NK	NK
Creatine kinase, single test	S	A	For AMI: + For UAP: NE	NK	NK
ECG exercise stress test	S	C	+	C	NK-NE
Echocardiogram	S	B	+	NK	NK
Other computer-based decision aids	G	B	+	NK	NK
Troponin-T and troponin-I	S	B	For AMI: ++ For UAP: NE	NK	NK
Myoglobin	S	B	For AMI: + For UAP: NE	NK	NK
Nonstandard ECG leads	S	C	+	NK	NK
Thallium scanning	S	C	NK-NE	NK	NK-NE
Continuous 12-lead ECG	S	NK	NK	NK	NK

[a]Abbreviations: AMI, acute myocardial infarction; UAP, unstable angina pectoris; G, general detection of acute myocardial infarction (ACI); E, early detection; S,detection in subgroup.

[b]The technologies are listed in order of the Working Group's ratings of diagnostic accuracy and demonstrated clinical impact, and alphabetically among equivalent ratings, with the exception of standard ECG, which is considered to be a standard of care.

[c]Diagnostic Rating: A, high-quality clinical studies; B, substantial clinical studies; C, limited studies; NK, not known; NE, not effective.

[d]Clinical impact rating: +++, very accurate/large clinical impact; ++, moderately accurate/medium impact; +, modestly accurate/small impact; NK, not known; NE, not effective.

[e]Abstract and pending reports are not included in the ratings.

(A), and the ECG-based ACI-TIPI has ease of use. Based on published clinical trials but not including the results of a large prospective trial published to date only in abstract form, its quality of evidence is a C and clinical impact rating a +. More definitive recommendations regarding its general use await the full publication of the results of the multicenter trial.

The final diagnostic technology, the *ECG exercise stress test*, a different extension of the standard ECG, has also been evaluated to some extent in the ED. Its diagnostic performance for CAD in this setting has been only modest. Given this finding, and because its actual impact on triage has received only limited testing, its routine ED use cannot be recommended.

Summary of Clinical Recommendations Based on Demonstrated Diagnostic Performance but Without Data on Clinical Impact

All but one of the technologies reviewed had some published evidence of diagnostic performance, and nine had no studies of actual impact on clinical care (i.e., all clinical impact grade NK based on evidence grade NK). The Working Group strongly advises that, with the exception of the standard 12-lead ECG (see immediately below), diagnostic performance alone is an insufficient basis for recommendation for general use. This is from the long experience of numerous examples of technologies that have excellent or good diagnostic performance but negligible or even negative clinical impact when tested under conditions of actual use.

The *standard 12-lead ECG* has been shown in many studies to have very good, although not perfect, diagnostic performance in the ED. However, despite its key role in the diagnosis of ACI in the ED, it has not been demonstrated to have an impact on care in the ED setting other than its central role in other technologies such as the ACI predictive instruments described above. In fact, given that the ECG is part of standard ED evaluation, in the view of the Working Group, a trial to demonstrate its impact would be neither necessary nor ethical. Indeed, the 12-lead ECG should be part of the initial evaluation of any ED or EMS patient with symptoms suggestive of ACI.

Although they have not yet been demonstrated to actually improve clinical care in the ED, *blood biochemical tests of myocardial necrosis, particularly CK,* including a variety of assay types and protocols, have undergone prospective testing of their diagnostic performance for the detection of AMI. Available data suggest that the use of a *single CK-MB* test yields performance insufficient for use in ED triage but that the use of *multiple CK-MB* tests over several or more hours has very good diagnostic performance for AMI. Although less complete, the data for *troponin* also suggest that performance of a single test is not satisfactory. The use of multiple tests over time may improve diagnostic performance. The one other biochemical test that has undergone considerable testing is that for *myoglobin*, but its exact role as an early marker of AMI has not yet been defined. Finally, neither myoglobin nor CK detect UAP, which raises the possibility of missing this form of ACI if triage depends on such tests. This is one of the reasons that, in the absence of prospective trials of the impact of this technology on ED triage (level of admission or discharge), these tests cannot yet be recommended for general ED triage use at this time, although they are very useful for observation units or in-hospital care.

Echocardiography, well studied in other settings, has undergone several studies in the ED that have generally shown modest diagnostic performance for initial ED evaluation. Given this finding, and because its actual impact on ED care has not been evaluated, this technology cannot be recommended for general ED use at this time.

Radionuclide imaging, although generally used in non-ED settings, has undergone some study of diagnostic performance in the ED. *Thallium scanning* is less appropriate for ED use than sestamibi, has not been well evaluated in ED use, and cannot be recommended. *Sestamibi and other ^{99m}Tc perfusion agents* have been studied in the ED setting, and although the overall diagnostic performance of sestamibi has been promising, it has

not been sufficiently tested to recommend its general ED use. Whether sestamibi will be found to be more helpful when evaluated for special subgroups and when tested for its actual impact on care remains to be seen. At this point, its general ED use cannot be recommended.

As an extension of the standard ECG, *nonstandard ECG leads* have undergone some limited testing in the ED for detecting ACI; another prospective trial was just completed. The quality (C) of published data at the time of the Working Group's ratings provides evidence of only minor diagnostic utility. In addition, its impact on care has not been tested, and thus nonstandard ECG leads cannot yet be recommended for general use.

Although reported in several case studies in EDs or suggested in a preliminary way in discussions of work done in other settings such as the CCU, *continuous ECG* has not been tested for performance in general ED use or for impact on ED care, and it cannot be recommended for general use at this time.

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III ST-Segment Elevation Myocardial Infarction

9

Thrombolytic Therapy for Acute Myocardial Infarction With ST-Segment Elevation

Jeffrey L. Anderson, MD, and Sanjeev Trehan, MD

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INTRODUCTION

Heart disease continues to be the leading cause of mortality in the United States, responsible for almost 750,000 deaths a year (one-third of total deaths) *(1)*. Two-thirds of these deaths are attributable to coronary heart disease, and half of coronary heart deaths are directly related to acute myocardial infarction (AMI), which causes a quarter of a

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million deaths a year. Despite the substantial remaining health challenge presented by coronary heart disease and AMI, substantial progress has been made over the past 30 years. Coronary heart disease mortality declined 58% from 1963 to 1994, and mortality from AMI has been declining more rapidly than mortality from the more chronic forms of coronary heart disease *(1)*. AMI mortality is also generally decreasing elsewhere in the Western world, with some exceptions *(2)*. Improvements in primary prevention, therapy, and secondary prevention are believed to have contributed approximately one-third each to this decline *(3)*. Progress has resulted from improved understanding of AMI pathophysiology (a result of extensive basic and clinical research efforts), as well as pathophysiology-based therapies, of which the primary goal in ST-segment elevation MI is rapid reperfusion, most frequently achieved with thrombolytic therapy *(4)*.

It has now been over 85 years since Herrick in the United States *(5)* and Obrastzow and Straschesko in the Soviet Union *(6)* described the clinical syndrome of acute coronary occlusion. Coronary thrombosis as a precipitating event was postulated. However, it was not until 1980 that coronary thrombosis as the mechanism of abrupt coronary occlusion was demonstrated and accepted. In a precedent-setting study, DeWood and colleagues *(7)* performed coronary angiography in the early hours of AMI and found coronary occlusion to be present in 87% of patients studied within 4 h of symptom onset. The nature of the occlusion was shown to be thrombotic at emergency coronary bypass surgery. Renewed interest in coronary thrombosis and thrombolysis resulted and continues to the present.

A basis for early reperfusion therapy was laid by the late 1970s in classical studies by Reimer, Jennings, and colleagues *(8,9)*. In a canine model of coronary occlusion and reperfusion, they found that myocardial cell death began within about 15 min of occlusion and proceeded rapidly in a wave front from endocardium to epicardium. Significant myocardial salvage could be achieved by releasing the occlusion within a narrow time frame (<3–6 h), the degree of salvage being inversely proportional to the duration of ischemia and occurring in a reverse wave front, from epicardium inwards. The extent of necrosis could also be modified by changing metabolic demands and varying collateral blood supply.

A progressive understanding of the underlying pathophysiologic events leading to coronary thrombosis has also been forthcoming over the past two decades. Pathologic, angiographic, and angioscopic observations have allowed formulation of the concept that erosion, fissuring, or rupture of a vulnerable atherosclerotic plaque is the initiating mechanism of coronary occlusion, resulting in coronary spasm, intraplaque hemorrhage, and occlusive luminal thrombosis *(10–14)*. Additional studies have suggested that plaque erosion or rupture most frequently occurs in lipid-laden plaques with the endothelial cap weakened by internal metalloproteinase activity derived primarily from macrophages *(15,16)*. When the plaque ruptures, elements in the bloodstream are exposed to plaque matrix elements, including collagen and the intensely thrombogenic lipid core with its associated macrophage-derived tissue factor *(16a)* (Fig. 1). The result is stimulation of platelet adhesion, activation, and aggregation; secretion of vasoconstrictive and thrombogenic mediators; thrombin generation; and fibrin formation, causing vasospasm and the formation of a platelet- and fibrin-rich thrombus. The result is reduction (non-ST elevation) or interruption (ST elevation) of coronary blood flow, with rapid onset of myocardial cell dysfunction and death. These and other observations set the stage conceptually and scientifically for the evaluation of reperfusion therapies in clinical AMI.

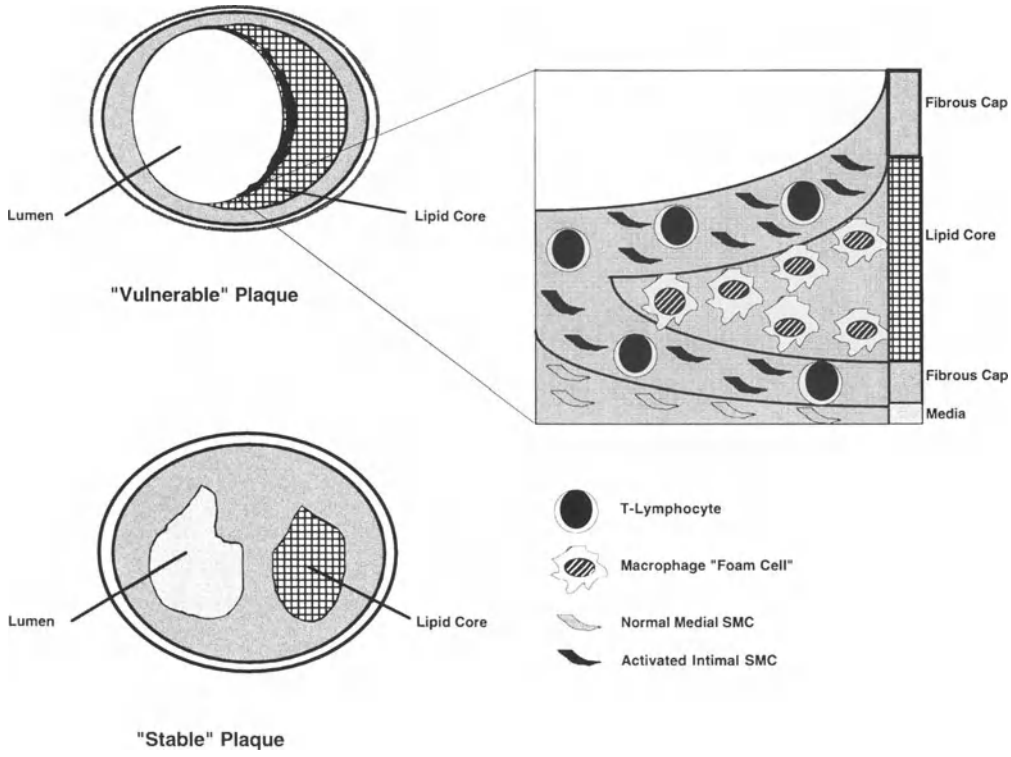

Fig. 1. Schematic diagram showing comparison of the characteristics of "vulnerable" and "stable" plaques. Vulnerable plaques often have well-preserved lumen because plaques grow outward initially. The vulnerable plaque typically has a substantial lipid core and a thin fibrous cap separating the thrombogenic materials such as macrophage-derived tissue factor from the blood. At the sites of lesion disruption, smooth muscle cells (SMCs) are often activated, as detected by their expression of HLA-DR. By contrast, stable plaque has a relatively thick fibrous cap protecting the often smaller lipid core from contact with the blood. Clinical data suggest that stable plaques often show greater luminal narrowing detectable by angiography than do vulnerable plaques. Adapted with permission from ref. *16a.*

DISCOVERY AND EARLY CLINICAL APPLICATION

Early Work

In 1933, Tillet and Garner *(17)* reported the discovery of a streptococcal fibrinolysin. They observed the ability of filtrates of streptococcal cultures to lyse human clots. Streptokinase (SK) was subsequently characterized, as reviewed by Sherry *(18,19)*. SK was first successfully applied clinically for the liquefaction of a pleural clot, as reported in 1949 *(20)*. Use of SK in AMI began in 1954, with the first series reported in 1958 *(21)*. This experience suggested that intravenous SK infusions could be given safely and that treatment begun within 14 h of symptom onset could lead to a more favorable hospital course than later treatment (at 20–72 h), which resulted in outcomes similar to those of no treatment.

At least 17 studies of iv SK in AMI were reported over the following two decades, but acceptance was limited by poor understanding of AMI pathophysiology and the role of

SK, or by study designs, or by delay of treatment *(22–25)*. The largest and most promising of these early studies was the European Cooperative Study Group report in 1979 *(22)*. Among 315 AMI patients, 6-mo mortality was substantially lower in those receiving a 24-h infusion of SK than placebo (15.6 vs 30.6%, $p < 0.01$). Bleeding was observed more frequently with SK, but was mostly minor. Despite the difficulties of these early studies, an overview of the results of the eight major trials of iv SK of acceptable, randomized design suggested a significant (20%) reduction in mortality among a total of 3275 patients *(26)* and set the stage for further development.

Intracoronary Thrombolysis

Despite the promise of these early studies, the mechanism of potential benefit did not focus on the coronary thrombus until angiographic demonstration of the thrombotic nature of coronary occlusion was established in 1976–1981 *(7,27–29)*. These observations led to feasibility studies of clinical thrombolysis with intracoronary (ic) SK under angiographic monitoring *(27–31)*. A high rate of coronary occlusion (>80%) was confirmed during the early hours of AMI, and the ability of SK to achieve early reperfusion with a success rate of approx 75% was demonstrated *(31)*. Application was generally safe, and clinical outcomes appeared to be favorable. Based on these promising results, randomized studies of intracoronary (ic) thrombolysis were undertaken.

Anderson et al. *(32)* first demonstrated the beneficial potential of ic SK in the setting of AMI based on a randomized study-design in 1983. They enrolled 50 patients with AMI within a mean of 2.7 h of symptom onset and randomized them to receive either standard coronary care (without thrombolysis) or immediate catheterization with ic SK, begun an average of 4 h after symptom onset. In the intervention group, perfusion was achieved in 79% after a mean of 30 min of SK infusion. The intervention strategy was associated with statistically significant relief of ischemic discomfort (quantified by morphine requirement), prevention of heart failure (Killip class), and improvement in functional recovery by hospital discharge (as measured by radionuclide left ventricular ejection fraction). Cardiac markers (creatine kinase [CK], CK-MB, lactate dehydrogenase [LDH], LDH-1) peaked earlier, ST-segment elevations resolved more rapidly, and Q-wave development was more limited in the SK group, compared with the standard therapy group. Also, echocardiographic wall motion abnormality score was reduced in the intervention group, and convalescent thallium perfusion studies showed a smaller defect size (reduced infarct size) with the early reperfusion strategy. A smaller ($n = 40$) concurrently published randomized study treated patients later (at >6 h after symptom onset) and demonstrated relief of ischemic pain, but found no improvement in global or regional myocardial function *(33)*.

Randomized studies of intermediate size followed and suggested the potential for mortality benefit. In the Western Washington Trial, Kennedy et al. *(34)* randomized 250 patients with AMI to ic SK or standard (nonthrombolytic) therapy (iv nitroglycerin). Early reperfusion was documented in 69% of SK-treated patients vs 12% ($p < 0.01$) of controls at a mean of about 6.5 h after symptom onset. Ischemic pain was relieved in the SK group, although improvement in global and regional ejection fraction could not be shown. However, 30-d mortality was 3.7% in SK vs 11.2% in control patients ($p < 0.02$). After 1 yr in this Western Washington randomized trial, mortality continued to be lower in the thrombolysis group (8.2 vs 14.7%), although the difference was no longer significant ($p = 0.1$) *(35)*. However, within the SK group, mortality was only 2.5% among those

achieving early reperfusion, compared with 16.7% in those with partial or no reperfusion ($p < 0.01$), which was similar to mortality in the untreated group. This observation provided the first suggestion that benefits of thrombolytic therapy were directly related to the achievement of early reperfusion.

Additional evidence for a survival benefit of ic SK came from a Dutch study of 533 patients *(36)*. The study design was complicated by the initial use of iv streptokinase in the last 117 patients, followed by angiography and additional ic SK in those remaining occluded at the time of early angiography. This evolving thrombolytic strategy was associated with reduced mortality at both 1 mo (5.9 vs 11.7%, $p < 0.03$) and 1 yr (8.6 vs 15.9%, $p < 0.001$). However, the highly positive results in these initial IC SK trials were counterbalanced by variable results in other studies *(37)*.

Intracoronary urokinase was also tested in AMI and, along with SK, was approved for ic infusion to achieve recanalization in coronary artery thrombosis *(31,38,39)*. Perfusion rates similar to those reported for SK were achieved (range, 62–94%) over a wide range of infusion rates (2000–24,000 U/min) *(31)*. In a randomized comparison of ic urokinase (UK) and ic SK, the two drugs were found to produce comparable rates of recanalization *(38)*, although urokinase was associated with smaller reductions in circulating fibrinogin and a lower incidence of bleeding and allergic complications in a total average dose of 500,000 IU.

In a metaanalysis of nine randomized trials of ic SK involving approximately 1000 patients, Yusuf et al. *(37)* found an 18% overall mortality reduction, but the confidence intervals were wide (44% reduction, 19% increase) and the difference not significant. The variability in results, the logistic difficulties, and time delays inherent to ic SK administration (believed to be the cause of suboptimal outcomes) stimulated the reevaluation of iv SK as a more practical, universally applicable approach to thrombolytic therapy.

Intravenous Thrombolysis

Schröder et al. *(40)*. tested a strategy of short-term (1 h), high-dose (0.5–1.5 million [M]U) infusions of SK given to patients at an early time (within 12 h) of symptom onset. In an initial clinical trial, a baseline angiographic study was followed by a 500,000-U SK infusion. After 1 h, occluded coronary arteries from 11 of 21 patients (52%) had opened, and total patency rate (adding those with initial subtotal occlusions) was 62%. In a subsequent study, 93 patients were treated with 1.5 MU over 1 h. Early angiography was not performed, but an 84% late patency rate (in the fourth week) was shown. Serum CK-MB concentrations peaked early (within 10–12 h after therapy), consistent with the pattern seen with angiographically demonstrated recanalization, and myocardial salvage was suggested by improved motion in the infarct zone. A successful racanalization pattern was more frequent in patients treated within 3 h than with later administration. The safety profile of iv SK in these doses, including bleeding rates, was acceptable. Several small to intermediate-sized, randomized trials of iv vs ic SK followed these feasibility studies *(31,41–44)*. These trials generally supported "equivalence" between the two routes of administration, with little difference in coronary patency at 24 h and no significant difference in clinical outcome by route of SK administration. The potential utility of iv SK in the modern era of investigation was further supported by a larger randomized trial (Intravenous Streptokinase in Acute Myocardial Infarction, n = 1741 patients), which observed an 11% mortality reduction, from 7.1% to 6.3% *(45)*; this favorable trend did not, however, achieve statistical significance.

In parallel with studies demonstrating the feasibility of coronary recanalization with ic or iv thrombolytic therapy, other studies investigated its effects on ventricular function. An overview of results suggested the potential for initial improvement (myocardial salvage) with therapy begun early (within 3–4 h), but inconsistent or negative results for later therapy *(31)*, consistent with predictions from animal models (8,9). In 12 studies, SK was begun within 4 h of symptom onset; an increase in infarct-zone ventricular function was observed in each study, and an increase in global function (ejection fraction) was noted in nine *(31,46)*. By contrast, in six studies, therapy was begun more than 4 h after symptom onset; regional wall motion improved in only one and global ejection fraction in none *(31,46)*.

Although functional improvement could be shown to be feasible in patients with later therapy (after >4 h) *(31,47)*, it was variable and appeared to be based on the presence of collateral or residual antegrade blood flow or other factors modifying the rate of necrosis *(48)*. By contrast, consistent improvement in function was observed when reperfusion interventions occurred within 2 h *(48–50)*. Given variability in functional response to reperfusion and the perception that other mechanisms (such as remodeling) might be relevant to patient outcomes in additional to myocardial salvage, the focus shifted to large mortality trials for the assessment of thrombolytic benefits.

APPROVED THROMBOLYTIC AGENTS

General Mechanisms of Action

All of the so-called thrombolytic (more specifically, fibrinolytic) agents are either direct or indirect activators of plasminogen, a circulating fibrinolytic proenzyme *(19)*. Plasminogen is converted by plasminogen activators or activator complexes to plasmin, the active fibrinolytic enzyme form, by cleavage of the arginine 560-valine 561 bond. Plasmin has relatively broad proteolytic properties, degrading fibrin, fibrinogen, prothrombin, and factors V and VII. Plasminogen activator-induced fibrinolysis may then act to disrupt forming thrombus and lead to reperfusion.

Specific Drugs and Drug-Specific Properties

Five thrombolytic agents have been approved and marketed for use in the United States, four of them for iv application. They differ in several properties, including structure, fibrin specificity, speed and duration of action, and antigenicity, as summarized in Fig. 2 *(50a)* and Table 1.

Streptokinase

The first fibrinolytic agent to be discovered and applied clinically, SK is a 415-amino acid protein of bacterial origin that shares homology with several serine proteinases *(32,33,51,52)*, and is the prototype of an indirect-acting agent. As with other thrombolytics, SK induces fibrinolysis by activating the body's intrinsic fibrinolytic system (plasminogen/plasmin). On administration, SK rapidly combines with circulating plasminogen in an equimolar (1:1) ratio to form a SK-plasminogen activator complex (Fig. 2). A catalytic site on the plasminogen in the activator complex is activated, leading to conversion of free circulating plasminogen in the region of the activator complex to plasmin. Similarly, the SK-plasminogen complex itself is autocatalytically cleaved to form SK-plasmin, but this form of the complex retains its activator activity. The in vivo half-life of the SK-plasminogen/plasmin activator complex is approximately 23 min.

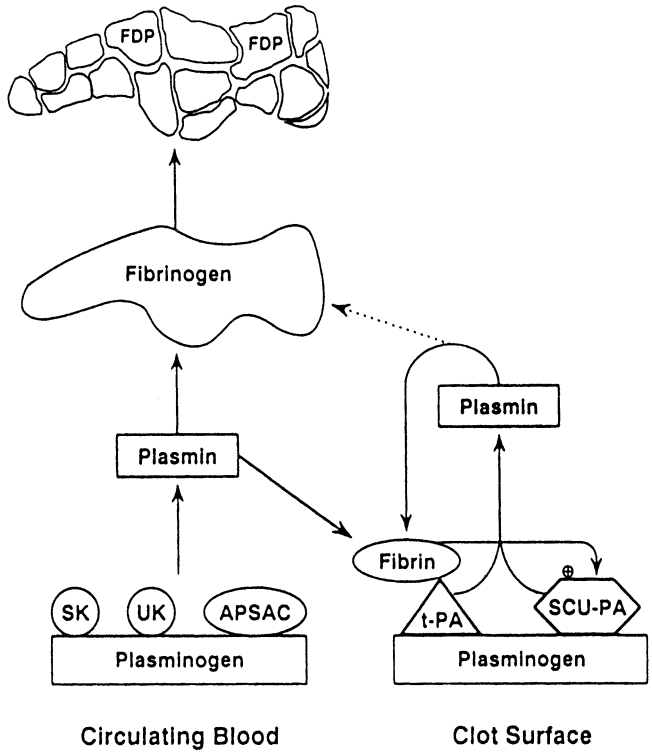

Fig. 2. Schematic representation of the action of fibrinolytic enzymes. Streptokinase (SK), urokinase (UK), and anisoylated plasminogen streptokinase activator complex (APSAC) work extensively on circulating plasminogen, whereas tissue-type plasminogen activator, (tPA) and single-chain urokinase-type plasminogen activator (scu-PA) are relatively selective for plasminogen within clot. Reproduced with permission from ref. *50a.*

SK is antigenic and has little fibrin specificity, so that substantial systemic lytic effect occurs in clinically applied doses. The generation of circulating fibrinogen degradation products (FDPs) (which exert antiplatelet and antithrombotic effects) and the depletion of circulating fibrinogen and α_1-antiplasmin, along with other clotting factors, provide long-acting (up to 1–2 d) antithrombotic actions that far exceed the time-course of fibrinolytic effects. This may explain why the addition of iv heparin to SK and aspirin increases bleeding risk but has provided little additional benefit in clinical trials (*see* below).

Urokinase

A native protein responsible for part of the proteolytic activity in human urine was first reported in 1861 and was shown to have specificity for fibrin *(53)*. It was later established that renal parenchymal cells are the production site for UK. Currently used formulations are obtained from human kidney cells grown in culture and are primarily of the low molecular weight form (33,000 Daltons), whereas that purified from human urine is of higher molecular weight (55,000 Daltons). However, the therapeutic efficacy of the two molecular species in clinical applications is very similar. UK, unlike SK, is a direct-acting proteolytic agent (trypsin-type serine proteinase). UK contains 410 amino acid residues in two polypeptide chains connected by a disulfide bridge. UK activity is not found in the circulation under normal conditions. When present, UK directly converts plasminogen to plasmin through enzymatic cleavage at the L-arginine 560-valine 561 site (the identical

Table 1
Comparison of US FDA-Approved Thrombolytic Agents[a]

Parameter	*SK*	*APSAC*	*tPA (alteplase)*	*r-PA (reteplase)*
Dose	1.5 MU in 30–60 min	30 mg in 5 min	100 mg in 90 min[b]	10 U + 10 U, 30 min apart
Circulating half-life (min)	~20	~100	~6	~18
Antigenic	Yes	Yes	No	No
Allergic reactions	Yes	Yes	No	No
Systemic fibrinogen depletion	Severe	Severe	Mild	Moderate
Intracerebral hemorrhage (%)	~0.4	~0.6	~0.7	~0.8
Patency (TIMI 2/3) rate, 90 min (%)[c]	~51	~70	~84	~83
Lives saved/100 treated	~3[d]	~3	~4[e]	~4
Cost per dose (approx U.S. dollars)	290	1700	2200	2200

[a]Abbreviations: US FDA, United States Food and Drug Administration; SK, streptokinase; APSAC, anisoylated plasminogen streptokinase activator complex; tPA, tissue plasminogen activator; r-PA, reteplase.

[b]Accelerated tPA given as follows: 15-mg bolus, then 0.75 mg/kg over 30 min (maximum, 50 mg), then 0.5 mg/kg over 60 min (maximum, 35 mg).

[c]Based on data from refs. *65* and *98*.

[d]Patients with ST elevation or bundle branch block, treated in <6 h.

[e]Based on the finding from the GUSTO trial that tPA saves 1 more additional life/100 treated than does SK. Adapted with permission from ref. *120*.

site of attack of SK); no additional cofactors are required. A single bolus of UK is cleared from the circulation with a half-life of 14–16 min by degradation to inert metabolytes in the liver. UK is nonantigenic.

For AMI, UK has been approved only for ic use, dosing with 6000 IU (4-mL solution) a minute for periods up to 2 h or until lysis of the coronary arterial thrombus is observed. Heparin therapy, iv, is recommended concurrently with UK. UK has also been tested by the iv route in doses of 2–3 MU (generally administered as a bolus plus a short-term infusion regimen). However, iv UK is less well studied than iv SK or tissue-type plasminogen activator (tPA), and its mortality benefits have been less well established *(54)*. Hence, tPA is generally used when a nonantigenic agent with less systemic-fibrinolytic activity than SK is desired. Currently, UK is most frequently used clincally in catheter-directed infusions to remove thrombus and restore patency in appropriately selected cases of venous, arterial, and graft thromboses, and intravenously for massive pulmonary embolism *(55)*.

Anistreplase

Anistreplase (anisoylated plasminogen streptokinase activator complex [APSAC]) was the first custom-designed, biochemically modified fibrinolytic agent to be developed *(56,57)*. It was designed to allow rapid delivery (2–5 min injection), rapid onset, more prolonged duration of action, and improved plasma stability and fibrin binding, compared with SK. However in doses used clinically, it retains the antigenic and nonspecific systemic lytic effects of SK. Anistreplase is synthesized by complexing SK with lys-plasminogen and reversibly acylating the complex by reacting it with the anisoyl group of a special acylating agent, producing a molecule of131,000-Dalton molecular weight. Placed in aqueous solution or plasma, anistreplase deacylates by a simple ester hydrolysis, rate-limiting process that follows first-order kinetics. Anistreplase's fibrinolytic activity has a half-life of approximately 105 min in plasma. The commonly used clinical dosage of 30 U of anistreplase corresponds to approximately 1.1 MU of SK.

Tissue-Type Plasminogen Activator (Alteplase)

tPA is the primary physiologic (intrinsic) plasminogen activator in the circulation *(58)*. A two-subunit form can be generated by limited proteolytic cleavage; both single and two-chain forms activate plasminogen with approximately similar catalytic efficacy and biologic potency *(59)*. tPA demonstrates partial fibrin selectivity, in comparison with SK, in that tPA generates greater plasmin and fibrinolytic activity locally, in the neighborhood of thrombus, than systemically. The result is relatively less plasminemia, fibrinogenolysis, and general (systemic) proteolysis than SK. tPA is subject to inhibition by a circulating plasminogen activator inhibitor (PAI-1), and its activity is rapidly cleared from the circulation with a half-life of <5 min *(60)*. tPA is nonantigenic and, unlike SK, may be reutilized without concern about interference with activity by neutralizing antibodies.

Reteplase (Recombinant Plasminogen Activator)

Reteplase (recombinant plasminogen activator [r-PA]) is the first clinically available mutant (modified) form of native plasminogen activator *(61–63)*. Reteplase is a deletion mutant of alteplase in which the finger, epidermal growth factor, and kringle-1 domains have been deleted. As a result of structural and biosynthetic modifications, r-PA, compared with tPA, is nonglycosylated, smaller, and less fibrin specific (with lower fibrin affinity and more readily reversible binding), but has an extended half-life (13–18 min-

utes). The slower clearance allows reteplase to be given in a double-bolus regimen (two boluses separated by 30 min) compared with a 90-min infusion (for tPA). Following the demonstration of a favorable (at least "equivalent") effect on clinical events in AMI compared with SK *(61)*, reteplase received market approval in the United States in 1997. An apparent advantage in establishment of early patency compared with tPA in a relatively small study *(62)* was not associated with a superior mortality outcome in a large (15,000-patient), randomized AMI trial, Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO) III *(63)*.

CORONARY RECANALIZATION AND PATENCY PROFILES

Based on theoretic considerations and clinical observations, it is believed that the establishment and maintenance of coronary perfusion is the major mechanism of thrombolytic benefit in AMI ("open artery hypothesis"). Given the difficulty in performing adequately sized mortality trials, angiographic studies have first been undertaken during development of thrombolytic regimens. These have assessed the recanalization (reperfusion) and patency profiles of the infarct-related coronary artery in response to thrombolytic therapy.

Recanalization (Reperfusion) vs Patency

The earliest series of studies assessed coronary patency at baseline and, for those initially showing total coronary occlusion, the ability of thrombolytic regimens to recanalize ("reperfuse") through the site of obstruction on subsequent angiography (generally at 60–90 min). Larger and more recent studies have omitted the baseline angiogram in favor of rapid administration of iv therapy and have compared coronary *patency* between regimens at 60–90 min and later. Because spontaneous (re)perfusion (grade 2 or 3 flow) has occurred in approximately 15–20% of patients studied angiographically in the early (<4–6) h of AMI, coronary patency rates are generally higher than recanalization rates *(64,65)*. Although recanalization rates may be a better indicator of pharmacologic activity, patency rates may correlate better with patient outcome, are easier to obtain, and form the basis of the present discussion.

Overview of Thrombolysis-Associated Patency Rates

A pooled analysis of 58 studies (N = 14,124 angiographic observations) allows an overall profile of patency rates of commonly used reperfusion regimens to be generated (Fig. 3) *(65)*. In the absence of thrombolytic therapy, spontaneous perfusion was observed early after ST-elevation AMI in only 15% and 21% of patients at 60 and 90 min after study entry, respectively. No further increases were observed in spontaneous patency rates within the first day, but subsequent follow-up demonstrated gradually increasing patency rates (to about 60% by 3 wk) associated with spontaneous- or aspirin- or heparin-facilitated intrinsic thrombolysis. In contrast, all thrombolytic regimens improved early patency rates, although the speed of thrombolysis was found to vary. SK (generally, 1.5 MU/1 h) achieved the lowest patency rates at 60 and 90 min (48 and 51%, respectively). Intermediate and roughly similar rates of patency at 60 and 90 min were achieved by anistreplase and 3-h tPA infusions (about 60 and 70%, respectively). Accelerated (90-min) tPA bolus/infusion regimens achieved the highest patency rates (74 and 84% at 60 and 90 minutes, respectively).

In contrast to the differing *early* patency profiles observed among various regimens, patency rates at 3–24 h and beyond have been found to be generally similar, averaging

Therapy	Baseline	60 min	90 min	2-3 hr	24 h	3-21d
None	20%(16-24)	15%(6-24)	21%(11-31)	24%(14-35)	21%(9-32)	61%(57-64)
SK	*	48%(41-56)	51%(48-55)	70%(65-75)	86%(82-89)	73%(70-78)
APSAC	*	61%(55-67)	70%(66-74)	74%(68-80)	80%(77-83)	85%(81-89)
tPA	*	74%(70-77)	84%(82-87)	*	86%(82-90)	89%(85-94)
rPA	*	80%(69-88)	84%(77-89)	*	*	92%(83-99)

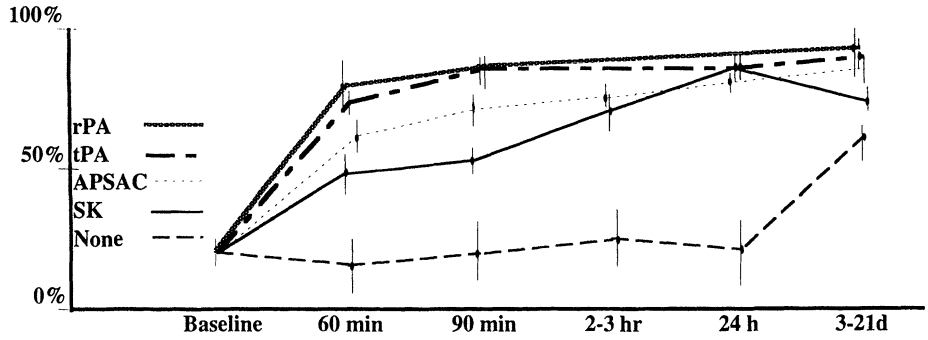

Fig. 3. Pooled angiographic patency rates with 95% confidence intervals over time after no thrombolytic agent, streptokinase (SK), accelerated dose tPA, APSAC, and reteplase (r-PA). Based on data from refs. *62,65*, and *66*.

80–85% *(65)*. Reocclusion rates have generally been higher after fibrin-specific therapy (as with tPA) than after non-fibrin-specific (systemically active) agents (13 vs 8%, $p = 0.002$), especially in the absence of optimal, concurrent iv heparin after fibrin-specific therapies.

The validity of these composite patency rates, generated from many studies of varying design and size, was confirmed by the single large GUSTO angiographic substudy *(66)*. This substudy, embedded within the much larger (41,021 patients) GUSTO mortality trial *(67)*, also enabled clear demonstration of the importance of early (90-min) TIMI grade 3 (complete perfusion) compared with TIMI grade 2 (incomplete perfusion) or lower grade (TIMI 0,1) perfusion as an accurate predictor of mortality outcomes among AMI therapies. Specifically, the GUSTO Angiographic Study ($N = 2431$ patients) demonstrated a 90-min patency rate (TIMI grades 2/3) of 81% for accelerated-dose tPA and heparin, compared with the 54% for SK and sc heparin ($p < 0.001$ vs tPA) and 60% for SK with intravenous heparin ($p < 0.001$ vs tPA). At 180 min, patency rates were the same in the four treatment groups and remained constant over 7 d of observation (range of patency rates, 72–86%). Reocclusion rates in the study were similar among regimens (about 6% over follow-up); the better relative performance of tPA than in previous experience may have been owing to a more aggressive iv heparin regimen.

Patency/Mortality Correlations

The achievement of early complete (Thrombolysis in Myocardial Infarction [TIMI] grade 3) perfusion, recognized recently to be a more optimal predictor of a favorable result, was specifically evaluated in GUSTO I *(67)*. Rates of complete (grade 3) perfusion at 90 min were 54% with accelerated tPA, 29% with SK plus sc heparin, and 32% with SK plus IV heparin ($p < 0.001$ for comparison of SK groups with tPA). Differences in measures of left ventricular function and mortality paralleled differences in rates of

patency at 90 min but not thereafter: ventricular function was best in those with normal flow (grade 3) irrespective of treatment; likewise, mortality at 30 d was lowest among those with normal (TIMI 3) flow at 90 min (4.4%), highest (8.9%) among those with absent flow ($p = 0.009$), and intermediate in those with partial (TIMI 2) flow (7.4%). In a formal predictive model, based on patency differences alone, the correlation between predicted and observed mortality rates was 0.97, providing strong evidence for the importance of early and complete infarct artery patency in determining mortality outcomes *(68)*.

MAJOR MORTALITY STUDIES OF INTRAVENOUS THROMBOLYSIS VS NONTHROMBOLYTIC THERAPY

During the late 1980s, a few key placebo or nonthrombolytic controlled studies were performed that firmly established the basis for a survival benefit of iv thrombolysis *(69–71)*. These studies are summarized in Fig. 4 *(71a)* and discussed below.

Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Myocardio (GISSI) Study

The Italian GISSI study was the first adequately powered and designed mortality study in the "modern era" of thrombolysis to establish a survival benefit for intravenous fibrinolytic therapy *(72)*. GISSI enrolled 11,806 patients with presumed AMI within 12 h of symptom onset who had ST-segment deviation (elevation or depression) on electrocardiogram (ECG) and assigned them to receive 1.5 MU of IV SK over 1 h or standard therapy alone. Treatment was unblinded. The primary end point was 21-d mortality, which could be assessed in 11,712 patients. Aspirin was not routinely given, and heparin use was left to the physician's discretion. Most patients (about 90%) showed ST elevation, and 94% were confirmed to have suffered AMI by discharge. Coronary angiography and coronary interventions were rarely used. Overall, a relative mortality risk reduction of 19% was observed ($p = 0.0002$). Survival benefit was time dependent: relative risk reduction was not significant for treatment begun after 6 h but averaged 26% for therapy begun within 3 h ($p = 0.0005$) and, in an exploratory analysis, 51% ($p < 0.0001$) in a subgroup treated within 1 h of symptom onset. Other subgroup analyses specifically demonstrated benefit in patients with anterior infarction (relative risk [RR] = 0.75), with no previous MI (RR = 0.75), with Killip class I or II (RR = 0.80), and with age <65 yr (RR = 0.72). A trend also favored treatment in more elderly patients. Thus, GISSI, published in 1986, suggested that iv SK was safe and conferred a significant early survival benefit in AMI, at least among patients presenting within 6 h of symptom onset who generally had ST-segment elevation electrocardiographically. Moreover, mortality benefits appeared to be maintained in the long term *(73)*.

Second International Study of Infarct Survival (ISIS-2)

ISIS-2, an even more ambitious test of iv thrombolysis, followed in 1988 *(74)* and confirmed and extended the observations of GISSI. ISIS-2 used a 2 by 2 factorial design to assess the effects of iv SK (1.5 MU over 1 h), aspirin (162 mg/d on admission and daily for 1 mo), both, or neither (placebo) in 17,187 patients entering 417 hospitals worldwide with suspected AMI within 24 h of symptom onset. The primary end point was vascular death at 5 wk. In the double placebo group, the mortality rate was 13.2%. The odds of dying were reduced by 25% using SK alone (standard deviation [SD] 4) ($p < 0.0001$), but

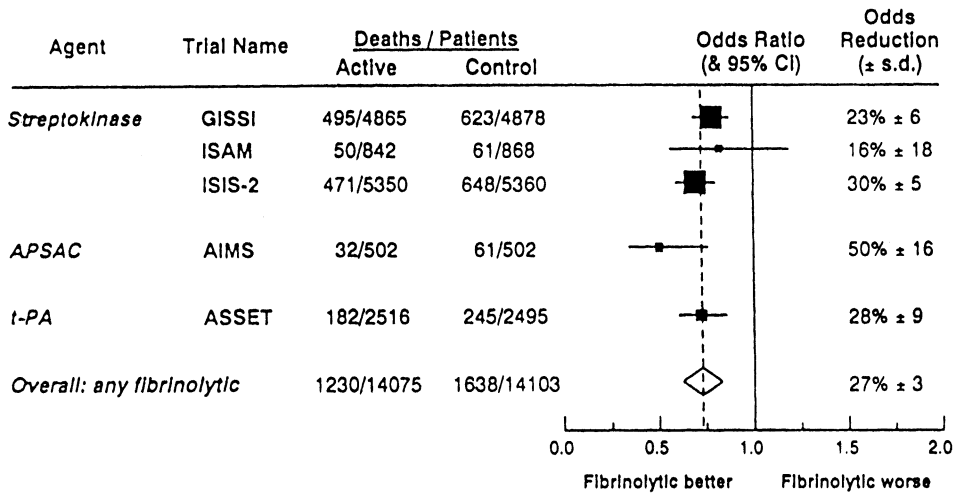

Fig. 4. Reduction in odds of early death among patients treated within 6 h; overview of the five largest randomized control trials of thrombolytic therapy vs placebo. Reproduced with permission from ref. *71a.*

were also reduced by aspirin alone (23% odds reduction, SD 4). Additive benefit was observed with the combination of SK and aspirin (42% [SD 5] odds reduction; $p < 0.00001$). When SK and aspirin were given early (within 4 h of symptom onset), a 53% (SD 8) odds reduction in mortality was achieved. Benefits were time dependent, although less so than in GISSI (odds reduction declined to 32% for h 5–12 with combination therapy).

Subgroup analyses specifically demonstrated lower mortality rates with thrombolytic therapy in the same subgroups shown to benefit in GISSI and, in addition, in those presenting with bundle branch block, with inferior infarction, and at all ages (including those >70 yr). A notable exception to SK's benefit was the group presenting with ST-segment depression.

A small excess (0.1%) of confirmed cerebral hemorrhage was observed with SK, as were larger excesses in hypotension and presumed allergic reactions, as well as minor bleeds. Overall, however, therapy was regarded as safe, and iv SK was believed to be "established" as appropriate therapy in a broad group of patients with AMI. Importantly, ISIS-2 also established antiplatelet therapy with aspirin, given on admission and daily thereafter, as a routine part of AMI management.

APSAC Intervention Mortality Study (AIMS)

Contemporary with ISIS-2 (1988), AIMS established a substantial survival benefit of iv anistreplase (APSAC) in a multicenter trial from the United Kingdom *(75,76)*. Patients were entered who presented within 6 h of onset of AMI symptoms, who were under age 70, and who showed ST elevation on admission ECG. The randomized, double-blind design compared anistreplase, 30 U injection, with placebo. The primary end points were 30-d and 1-yr mortality. Aspirin was not routinely used, but iv heparin was begun 6 h after anistreplase. Patients were subsequently transferred to warfarin anticoagulation, which was given for at least 3 mo. AIMS was stopped by the safety monitoring board before recruitment of the entire 2000-patient planned cohort because of a substantial survival benefit in favor of thrombolytic therapy. In the final analysis of all 1258 patients

studied, 30-d mortality was reduced from 12.1% in the placebo group to 6.4% in the anistreplase group (odds reduction 51%, 95% confidence interval [CI] 26–67%, $p = 0.0006$) *(76)*. After 1 yr, mortality reductions persisted (17.8% with placebo, 11.1% with anistreplase, odds reduction 43%, 93% CI 21–59%, $p = 0.0007$) *(76)*. Hence, the absolute differential mortality benefit at 30 d (about 6%) for anistreplase, followed by heparin and warfarin, was maintained (or increased slightly) to 1 yr of follow-up.

None of the subgroups included in the study failed to benefit. The need for adjunctive iv heparin when aspirin is added to anistreplase therapy was not addressed in AIMS (performed before the aspirin results from ISIS-2 were known). However, the first Duke University Clinical Cardiology Study, of intermediate size, found no obvious differences in clinical end points other than a higher rate of bleeding in AMI patients treated with anistreplase and randomly assigned to receive iv heparin compared with no heparin, together with aspirin *(77)*. Hence, current recommendations for heparin with APSAC follow those for its parent drug SK *(4)*, derived from a larger experience, including GUSTO-1 *(67)*, which demonstrated no advantage of concomitant iv over SC heparin with SK.

Anglo-Scandinavian Study of Early Thrombolysis (ASSET)

Concurrent (1988) with the ISIS-2 and AIMS studies with SK or its congener anistreplase, ASSET provided evidence for the first time of a survival benefit in AMI with the recombinant form of native tissue-type plasminogen activator (rtPA) *(78)*. ASSET enrolled 5013 patients with suspected AMI (ECG confirmation not required) within 5 hours of symptom onset and randomized them to double-blind therapy with rtPA, 100 mg over 3 h, together with iv heparin 5000 U, then 1000 U/h for 1 d, or placebo plus heparin. Aspirin was not routinely given. The primary end points were 1-mo and 6-mo mortality. Thirty-day mortality was significantly lower in the tPA than the placebo group (7.2 vs 9.8%, RR reduction 26%, 95% CI 11–39%, $p = 0.0011$). Bleeding complication rates were higher with tPA (1.4 vs 0.4% for major hemorrhage), but total stroke rates were similar (1.1 vs 1.0%).

Late Assessment of Thrombolytic Efficacy (LATE) Study

Earlier studies had conclusively demonstrated the benefit of iv thrombolytic therapy begun within 6 h of onset of symptoms. The LATE study aimed to assess the more controversial question of treatment effects in a randomized double-blind comparison of iv alteplase (100 mg over 3 h) with matching placebo in patients with symptoms of 6–24 h duration and ECG criteria consistent with AMI *(79)*. A total of 5711 patients were entered and randomized to tPA or placebo plus oral aspirin. Heparin, iv, for 48 hours was recommended. The primary end point, 35-d mortality, was reduced by 14.1% (95% CI 0–28%). In the prespecified analysis of the patient group given treatment within 12 h of symptom onset, a significant mortality reduction by tPA was observed (8.9% vs 12.0%, RR reduction 26%, 95% CI 6–45%, $p = 0.023$). The results of LATE suggested that the time window for thrombolysis (with alteplase) should be extended to at least 12 h from symptom onset in patients with AMI. An overview of "late" studies with SK also supported a survival benefit up to 12 h *(80,81)*.

Fibrinolytic Therapy Trialists' (FTT) Collaborative Group Report

By about 1990, the benefits of iv thrombolytic therapy in appropriate AMI patients was regarded as established, ending the era of placebo (or nonthrombolytic therapy)-

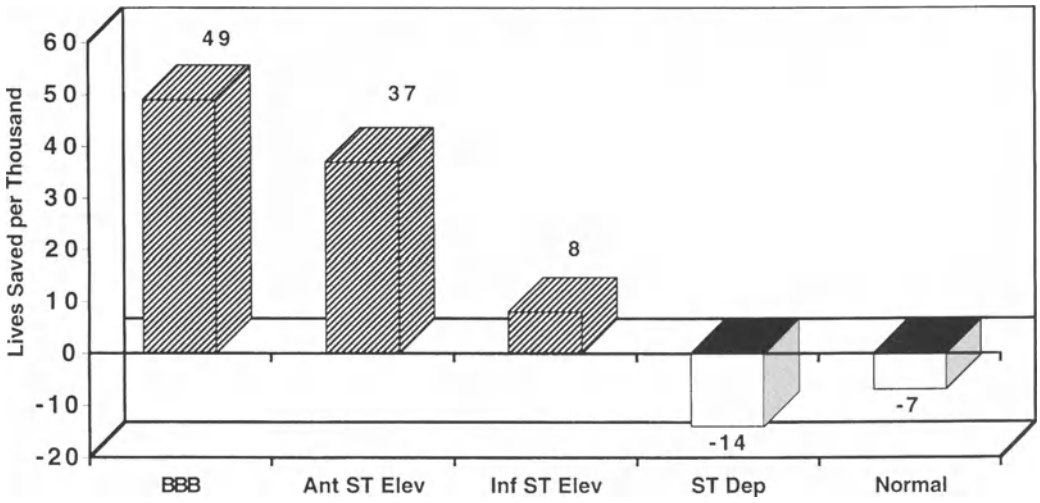

Fig. 5. Effect of thrombolytic therapy on mortality (lives saved/1000 treated) in various patient subgroups classified according to their admission ECG. Patients presenting with bundle branch block and anterior segment elevations derived most benefit from thrombolytic therapy. Patients with inferior ST-segment elevation derived much less benefit, whereas those with ST-segment depression or with normal or nonspecific ECG did not benefit. Based on data from the FTT Collaborative Group *(81)*.

controlled trials *(81,82)*. To maximize information gained from this important era of controlled clinical trials, the FTT collaborative group pooled data from the nine major controlled thrombolytic trials that had randomized 1000 or more patients with suspected AMI *(81)*. The FTT database included 58,600 patients. Overall, an 18% reduction in 5-wk mortality (from 11.5 to 9.6%) was observed with fibrinolytic therapy, a highly significant result ($p < 0.0001$). Most patients (approx 45,000) presented with ST elevation or bundle branch block (BBB) on ECG, and benefit was found to be concentrated in these groups: within the group with BBB on admission ECG, 49 lives were saved per 1000 treated; within the ST-segment elevation group, greater benefit was observed in those with anterior (37 saved per 1000) than with inferior ST elevation only (8 saved per 1000), and combined or other site ST-elevation showed intermediate benefit (27 saved per 1000). No mortality benefit was observed in patients presenting with normal ECGs or ST depression; indeed, they showed a slight adverse trend (7 and 14 more deaths per 1000 treatments, respectively) (Fig. 5).

The mortality reductions seen in the ST-elevation and BBB groups showed time dependence: absolute benefits declined from about 40 lives saved per 1000 for treatment within the first hour, to 20–30 for h 2–12, to 7 for h 13–24 (an insignificant trend). When other studies that evaluated very early therapy (i.e., emergency ward or paramedic-based) are also included, even greater benefits are observed. Boersma et al. *(83)* reappraised very early therapy based on a database of 50,246 patients derived from all randomized trials of 100 or more patients published between 1983 and 1993. Overall, a nonlinear relation of treatment delay to benefit was seen (Fig. 6). These results more clearly demonstrate a time dependency of benefit, particularly when large numbers of patients are treated within the first 1 or 2 "golden hours."

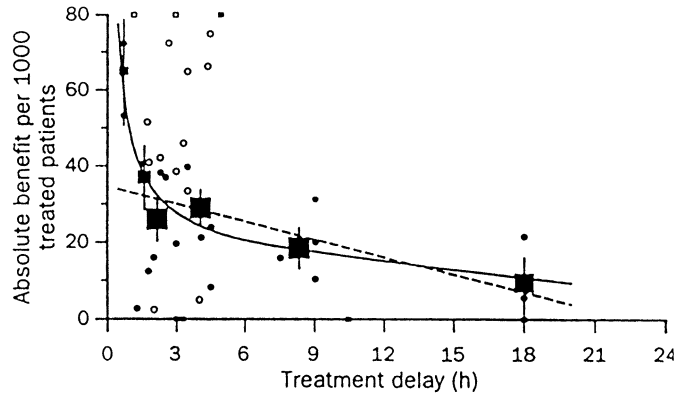

Fig. 6. Absolute 35-d mortality reduction vs treatment delay. Small closed dots, information from trials included in the FTT analysis; open dots, information from additional trials; small squares, data beyond scale of XY cross—the linear (34.7–1.6 ×) and nonlinear (19.4–0.6 × + 29.3 x – 1) regression lines are fitted within these data and weighted by the inverse of the variance of the absolute benefit for each data point; black squares, average effects in six time to treatment groups (area of squares inversely proportional to the variance of absolute benefits). Reproduced with permission from ref. *83*.

The FTT collaborative group analysis provides important information on therapy for patients over age 75, for whom relatively few data are available in single randomized trials. For patients over age 75, proportionate mortality reductions were less (the trend to benefit was not significant), although the absolute mortality reduction was still preserved.

Mortality reductions were little influenced by systolic blood pressure or heart rate except at their extremes. Hypotension (systolic blood pressure < 100 mmHg) was associated with greater AMI risk overall but also greater absolute mortality reductions with therapy (60 lives saved per 1000 treated; $p < 0.001$) (Fig. 7). Benefits of thrombolytic therapy were also confirmed by FTT for other high-risk groups, including those with prior MI (absolute reduction 15 lives per 1000) and diabetes (absolute reduction 37 lives per 1000) (Fig. 7).

PIVOTAL COMPARATIVE TRIALS OF THROMBOLYTIC REGIMENS

Of the many comparative trials, GISSI 2/International, ISIS-3, GUSTO-1, and GUSTO-3 (among the largest and most important), are summarized in Table 2 *(83a)*.

GISSI-2/International Study Group Trial

The GISSI-2/International Study was the first adequately powered mortality study to compare streptokinase with tPA and also to explore the effect of sc heparin *(84,85)*. Patients with suspected AMI of <6 h duration (12,490 from the Italian GISSI-2 centers and 8,401 from the balance of the International Study centers; total 20,891) were randomly allocated to alteplase (100 mg given over 3 h) or SK (1.5 MU over 30–60 minutes), given in an open-label (unblinded) fashion. In a factorial fashion, patients were also randomly allocated to receive either sc heparin (12,500 U twice daily, beginning 12 h after the start of thrombolytic therapy) or no heparin. Aspirin (325 mg/d) was given as

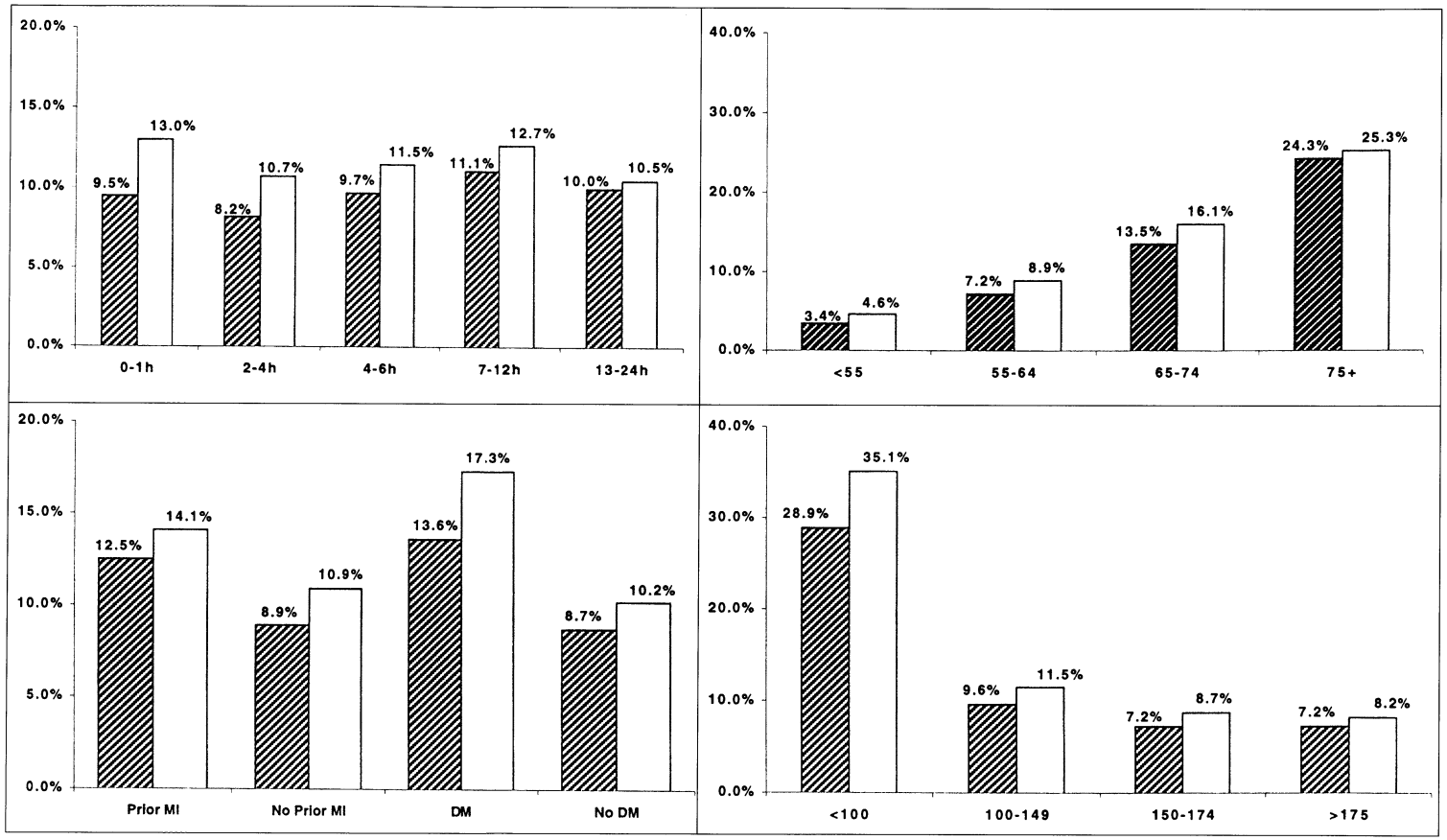

Fig. 7. Effect of thrombolytic therapy on mortality in various patient subsets classified according to time to presentation (top left), age (yr) at presentation (top right), prior history of myocardial infarction or diabetes mellitus (bottom left), systolic blood pressure (mmHg) at presentation (bottom right). The thatched bars represent fibrinolytic treated patients; open bars represent nonfibrinolytic treated patients. Based on data from the FTT Collaborative Group *(81)*.

Table 2
Clinical End Points in Comparative Thrombolytic Trials[a]

	GISSI-2/International (85)		*ISIS-3 (86)*			*GUSTO-1 (94)*			*GUSTO-III (99)*	
End points	*SK (10,396)[c]*	*tPA (10,372)*	*SK (13,607)*	*tPA (13,569)*	*APSAC (13,599)*	*SK (20,173)*	*tPA+[b] (10,344)*	*SK + tPA (10,328)*	*tPA (4,921)*	*r-PA (10,138)*
Death (%)	8.5	8.9	10.6	10.3	10.5	7.3	6.3*	7.0	7.2	7.5
Reinfarction (%)	3.0	2.6	3.5	2.9*	3.6	3.7	4.0	4.0	4.2	4.2
Any stroke (%)	0.9	1.3*	1.0	1.4*	1.3	1.3	1.6	1.7	1.79	1.64
Hemorrhagic stroke (%)	0.3	0.4	0.2	0.7*	0.6	0.5	0.7*	0.9	0.87	0.91
Non-CNS bleeds (%)	0.9	0.6*	4.5	5.2*	5.4	6.0	5.4*	6.1	6.8	6.9

[a]Abbreviations: SK, streptokinase; tPA, tissue-type plasminogen activator; APSAC, anistreplase; r-PA, reteplase; CNS, central nervous system.
[b]Accelerated-dose.
[c]Number of patients.
*Statistical comparisons are only listed for SK vs tPA; $p < 0.05$.
Adapted with permission from ref. *83a.*

standard therapy in all treatment groups. Early β-blockade was encouraged (iv atenolol was administered in 23%).

The primary efficacy end point, in-hospital mortality, occurred in 8.5% of SK and 8.9% of tPA patients (RR 1.05, 95% CI 0.96–1.16, p = NS) *(84)*. In the heparin comparison, in-hospital mortality rate was 8.5% for the sc heparin and 8.9% for the no heparin group (RR 0.95, 95% CI 0.86–1.04, p = NS). Definite hemorrhagic stroke was reported in 0.3% in the SK and 0.4% in the tPA group. A small excess of major bleeds was seen with subcutaneous heparin (1.0% vs 0.5%), but heparin did not affect the incidence of stroke or reinfarction. A combined in-hospital end point of death or severe left ventricular function, measured in the GISSI-2 cohort *(85)*, also did not differ by thrombolytic (SK 22.5%, tPA 23.1%).

Third International Study of Infarct Survival (ISIS-3)

ISIS-3 was the second adequately powered mortality comparison between SK and tPA (given as duteplase) and between sc heparin and no heparin *(86)*. The thrombolytic anistreplase also was evaluated. A total of 41,299 patients from 914 hospitals worldwide with a diagnosis of suspected AMI were entered within 24 h of the onset of symptoms (median 4 h) and randomly allocated to SK (1.5 MU infusion over 1 h), tPA (duteplase, 0.6 MU/kg infused over 4 h), or anistreplase (APSAC, 30 U over 3 min). Aspirin (162 mg) was given on admission and daily. Half the patients were allocated to subcutaneous heparin (12,500 IU), starting at 4 h and given twice daily for 7 d, and the other half to no heparin, in a second randomization. Study drug was administered in an open-label (unblinded) fashion.

The primary end point, mortality at 35 d, occurred in a similar percentage of the three treatment regimens (SK 10.6%, APSAC 10.5%, tPA 10.3%). Six-mo survival also showed no differences among thrombolytic regimens (SK 14.0%, APSAC 13.7%, tPA 14.1% mortality).

The addition of sc heparin reduced mortality modestly during the first week (7.4 vs 7.9%, p = 0.06), but the difference diminished by 35 d (10.3 vs 10.6%, p = NS), and 6-mo mortality was almost equivalent (0.1% difference) in the two heparin groups. Combining the heparin results of ISIS-3 and GISSI-2 strengthened the conclusion that a modest benefit occurred during the 1-week treatment period (avoidance of 5 deaths per 1000 patients treated; $p < 0.01$) with loss of significant benefit by later follow-up (5 wk, 6 mo). tPA was associated with fewer reports of allergy or hypotension but a higher rate of cerebral hemorrhage than the other regimens.

Unresolved Issues with GISSI-2 and ISIS-3

The failure to show a survival advantage of tPA over SK was surprising, given tPA's more rapid reperfusion profile. In attempting to explain this paradox, several possibilities have been raised *(87,88)*, including the following:

1. Inadequate heparin dosing: heparin was given subcutaneously, to only one-half of the patients, and after a delay of 4–12 h. Concurrently with GISSI-2 and ISIS-3, several angiographic trials demonstrated higher patency rates with short-acting tPA when iv heparin was added to aspirin therapy *(89–91)*. These early patency rates with tPA plus iv heparin were substantially superior to those reported for SK *(64,65,67)*. Subcutaneous heparin (12,500 U twice daily) achieves a mean activated partial thromboplastin time (aPTT) of only 35 s at 24–36 h, believed to be suboptimal for adjunctive therapy with

tPA *(92,93)*. Thus, the short-acting, relatively fibrin-specific tPA may have been specifically disadvantaged by a suboptimal heparin regimen.
2. tPA was not front-loaded. Several angiographic trials have shown higher patency rates with an accelerated (90-minute) regimen than with standard (3–4-hour) infusion regimens *(65)*. Whether the use of duteplase in ISIS-3, instead of alteplase, substantially affected the comparison is uncertain but appears improbable *(86)*.
3. Generally, treatment was begun relatively late, particularly in ISIS-3 (mean times to therapy >4 h), whereas the potential for a differential benefit of a rapidly acting thrombolytic may occur primarily early (<4 h) after symptom onset when the potential for myocardial salvage is greatest.
4. ST-segment elevation was not required, but predicts thrombolytic benefit (patients without ECG change or with ST depression showed no benefit in ISIS-2 or the FTT studies) *(81)*.

These concerns led to the planning and performance of a further mortality comparison, the Global Utilization of Streptokinase and tPA for Occluded coronary arteries (GUSTO) *(94)*.

Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO)

GUSTO tested the hypothesis that more aggressive thrombolytic strategies would produce earlier and more sustained reperfusion and would result in improved survival. Importantly, tPA (alteplase) was given as an accelerated regimen, known to improve early patency rates, and with immediately administered iv heparin, shown to be associated with high rates of retained patency after tPA. A combination of somewhat lower individual doses of SK and tPA was also tested. These test regimens were compared with a standard regimen of SK given with either sc or iv heparin. Also, patients were enrolled early (within 6 h, mean 2.7) after the onset of symptoms and were required to show ST elevation on entry ECG. GUSTO enrolled 41,021 patients in 1081 hospitals from 15 countries and randomly assigned them to (1) iv SK 1.5 MU/1 h with sc heparin 12,500 U sc q12h starting 4 h after SK; (2) 1.5 MU SK with iv heparin, 5000 U bolus, then 1000 U/h, titrated to achieve an aPTT between 60 and 85 s; (3) An accelerated tPA regimen (15-mg bolus, 0.75 mg/kg to 50 mg over 30 min, then 0.5 mg/kg to 35 mg over 60 min, for a maximum of 100 mg over 90 min) and iv heparin as above; or (4) a combination of tPA 1 mg/kg and SK 1 MU, given concurrently over 60 min, with iv heparin. The primary end point was death from any cause at 30 d.

Mortality was modestly but significantly lowered with accelerated tPA plus iv heparin (6.3%), representing a 14% risk reduction ($p = 0.001$), compared with combined SK strategies (mortality 7.3%). SK outcomes did not differ by heparin regimen (7.2% with sc heparin, 7.4% with iv heparin). The combined strategy (tPA plus SK) gave an intermediate outcome. The risk of hemorrhagic stroke was modestly higher with tPA (0.7%) than with SK (0.5%). However, even after combining death with nonfatal disabling stroke, the tPA regimen continued to be favored (event rate 6.9, vs 7.8% with SK; $p = 0.006$).

In an angiographic substudy embedded within GUSTO ($n = 2431$ patients), the patency rate (TIMI grades 2 + 3) of the infarct-related artery at 90 min was found to vary inversely with mortality rates in the overall study, being highest in the tPA plus heparin group (81%), intermediate in the combined tPA and SK group (73%), and lowest in the SK groups with either iv heparin (60%) or sc heparin (53%) *(67)*. Differences were accounted for by differences in complete (TIMI grade 3) reperfusion (respective rates 54%, 38%, 32%, 29%). After 90 min, angiographic patency rates tended to equalize among therapeu-

tic strategies and were not predictive of mortality outcomes. A formal predictive model was developed for mortality assuming that thrombolytic therapy achieved its survival benefit only through increasing coronary artery patency at 90 min and not through other mechanisms *(68)*. Using this model, a close match between predicted and observed 30-d mortality rates was found for the four treatment limbs, with a correlation coefficient (r) of 0.97, strongly supporting the concept that an important mechanism for improved survival of thrombolytic therapy is the early achievement of complete perfusion.

Retrospectively comparing the results of GUSTO with a GUSTO-like subgroup of patients in ISIS-3 suggests that the differences in mortality effects of tPA and SK in the two trials are probably accounted for by several factors, including:

1. a greater early patency rate of front-loaded tPA vs SK (compared with standard tPA vs SK);
2. better maintenance of the initial patency advantage of tPA by iv heparin;
3. treatment at an earlier time, when greater differential myocardial salvage was possible; and,
4. better selection of thrombolysis-amenable patients (i.e., those presenting with ST elevation) *(87)*.

OTHER COMPARATIVE STUDIES OF tPA WITH ANISTREPLASE

tPA-Eminase AMI Study (TEAM-3)

The third Thrombolysis trial of Eminase in AMI (TEAM-3) was designed as a controlled, multicenter study of intermediate size comparing the two second-generation thrombolytic agents anistreplase and tPA (alteplase), given in a standard (3-h) infusion *(95)*. The primary end points were left ventricular ejection fraction at discharge and 30 d; secondary end points included coronary patency at 1 d and clinical event rate. A total of 325 AMI patients with symptoms of <4 h duration and ECG ST-segment elevation were enrolled and randomly assigned to double-blind, double-dummy therapy with anistreplase, 30 U/2–5 min, or tPA, given over 3 h. Heparin was given with both therapies (5000-U bolus, then 1000 U/h), beginning 2 h after the start of therapy (i.e., before the end of the tPA infusion), and continued for 48 h. Aspirin was given to all patients (160 mg on entry, then 160–325 mg qd). Coronary patency rate was high after both anistreplase (89%) and tPA (86%; $p = 0.37$) after 1 d (90-min patency rates were not measured). Also, clinical event rates were generally comparable in the two groups and within the frequency range expected, although bleeding occurred more frequently after anistreplase. However, the primary end point, left ventricular ejection fraction, was higher after tPA than APSAC therapy, both at discharge (54 vs 51%; $p = 0.038$), and at 1 mo (54 vs 50%; $p = 0.002$). It was speculated that earlier or more complete patency might explain the advantage observed of tPA for left ventricular function.

tPA-APSAC Patency Study (TAPS)

A German angiographic study of intermediate size compared *accelerated* tPA (Neuhaus regimen) with APSAC in 421 AMI patients *(96)*. Both groups received aspirin and iv heparin. Early patency rates were greater with tPA than APSAC (73 vs 60% at 60 min; $p = 0.05$; 84% vs 70% at 90 min; $p = 0.0007$). These differences were owing to differences in complete (TIMI grade 3) perfusion (tPA 72%, APSAC 54% at 90 min). By contrast, reocclusion within 1–2 d occurred more frequently after tPA (10 vs 3%), and later patency rates, at 1 d and discharge, did not differ between the regimens. Bleeding was more frequent with APSAC, which was given with early and aggressive iv heparin dosing. Mortality rates were lower with tPA, although the study was not powered for survival comparisons.

Thrombolysis in Myocardial Infarction (TIMI)-4 trial

The TIMI-4 study, of intermediate size, compared APSAC, front-loaded tPA, or combination thrombolytic therapy *(97)*. Study entry required onset of pain within 6 h in association with ST-segment elevation or new left BBB. A total of 382 eligible patients were randomly allocated to receive double-blind therapy with front-loaded tPA (up to 100 mg/90 min), APSAC (30 U/2–5 min), or a combination of tPA (up to 50 mg) and APSAC (20 U). All patients received aspirin (325 mg on entry and daily) and immediate iv heparin (5000 U, then 1000 U/h), later titrated to an aPTT of 1.5–2 times control. The primary end point was a composite of events defining an "unsatisfactory outcome," including mortality, heart failure, low ejection fraction, reocclusion or TIMI grade <2 at 90 min or 1 d, and major hemorrhage during hospitalization, or severe anaphylaxis during hospitalization.

TIMI-4 found that the patency rate of the infarct-related artery was higher in tPA- than APSAC-treated patients both at 60 min (78 vs 60%; $p = 0.02$), and at 90 min (84 vs 73%, $p = 0.02$). Complete perfusion (TIMI grade 3 flow) was also more frequent at 90 min (60% vs 45%, $p < 0.01$). Patency rates with combination therapy paralleled those of APSAC alone. For the primary end point, "unsatisfactory outcome," rates were 41% with tPA, 49% for APSAC ($p = 0.19$ vs tPA), and 54% for combination therapy ($p = 0.06$). Although the study was not powered as a survival comparison, mortality rates at 6 wk differed, being lowest after tPA. Bleeding was more frequent in the APSAC-containing regimens, which were given with immediately-initiated iv heparin. The findings of TIMI-4 and those of the GUSTO angiographic study *(67)* are mutually supportive of the early open-artery hypothesis of benefit and establish that early patency is better achieved with an accelerated dose of tPA and iv heparin than with SK or APSAC.

MAJOR COMPARATIVE TRIALS WITH RETEPLASE

r-PA, a nonglycosylated deletion mutant of wild-type tPA, shows less fibrin specificity but greater plasma persistence, allowing administration of a double-bolus regimen with a favorable patency profile.

International Joint Efficacy Comparison of Thrombolytics Trial (INJECT)

In INJECT, 6010 patients with AMI were randomly assigned in double-blind fashion to reteplase (two 10-MU boluses given 30 min apart) or SK (1.5 MU/1 h) *(61)*. The primary end point was survival at 5 wk. At the 35-d end point, mortality was 9.0% for r-PA and 9.5% for SK, a nonsignificant absolute change of –0.5% (95% CI –1.98% to +0.96%). Based on the premise that a new thrombolytic agent should achieve a mortality rate no worse than 1% *more* than a standard regimen (i.e., SK) with 95% confidence. r-PA was FDA approved in 1996.

Reteplase Vs Alteplase Patency Investigation During Acute Myocardial Infarction (RAPID 2)

A subsequent comparison was made between reteplase and its parent drug, tPA, in an angiographic patency study of intermediate size *(62,98)*. RAPID 2 enrolled 324 patients with AMI and randomized them to therapy with r-PA (10 MU in two boluses, 30 min apart) or accelerated-dose tPA (up to 100 mg/90 min). At the primary, 90-min end point, infarct-related artery patency was 83% with r-PA vs 73% with tPA ($p = 0.03$), and respective TIMI grade 3 rates were 60% vs 45% ($p = 0.01$). However, very early patency

rates (of 30 min) tended to favor tPA. On the basis of this favorable patency study, a mortality comparison, GUSTO-3, was undertaken.

Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-III

The aim of GUSTO-III, an international, multicenter, randomized comparison of reteplase with alteplase for AMI, was to test whether reteplase would significantly reduce mortality compared with accelerated alteplase in AMI patients presenting within 6 h of symptom onset with ST-segment elevation *(63,99)*. To test this hypothesis, 15,059 patients were enrolled in 807 hospitals in 15 countries and randomly allocated to receive reteplase (two 10-MU boluses 30 min apart) or alteplase (given as a 90-min infusion). Both therapies were given with aspirin (160 mg, then 160–325 mg qd) and immediate iv heparin (5000 U, then 800–1000 U/h, adjusted later to a target aPTT of 50–70 s). The study was designed to have at least 85% power to detect a 20% relative mortality reduction with reteplase, apparently based on a projection from patency differences at 90 min in RAPID-2. However, mortality rates at 30 d did not differ: 7.50% for reteplase compared with 7.28% for alteplase ($p = 0.64$, ratio 1.03, 95% CI 0.91–1.18). The incidence of hemorrhagic stroke was similar for reteplase and alteplase (0.93% vs 0.85%). Other outcomes also were similar.

GUSTO-III demonstrates that reteplase is not superior in its survival benefits to tPA. Indeed, also considering its direct comparisons with SK (INJECT) suggests that it may be viewed as either approximately "equivalent" to accelerated tPA or, in another view, as slightly less effective and "intermediate" between SK and accelerated tPA. GUSTO-III emphasizes the hazards of allowing relatively small studies (of a few hundred patients or less) using surrogate outcomes (patency rates) to project mortality outcomes in comparing thrombolytic regimens. Earlier, a double-bolus regimen of tPA (50 mg + 50 mg administered 30 min apart) was also reported to yield an improved patency outcome compared with the accelerated tPA infusion regimen *(100)*, but a later study failed to show superiority and, in fact was discontinued owing to increased bleeding *(101)*. A review of RAPID-2 suggests that a relatively lower than expected patency rate with accelerated tPA (compared with GUSTO) rather than a higher than expected patency rate with reteplase may have been the anomaly. Alternatively, 90-min patency may not be an adequate surrogate for the overall early patency profile of a thrombolytic drug (e.g., the patency rate with tPA may have been higher at 30 min or less). Thus, accelerated tPA with iv heparin remains the current "standard" in terms of thrombolysis survival-benefit.

BLEEDING RISKS AND OTHER ADVERSE POTENTIALS OF THROMBOLYTIC THERAPY

Bleeding

Bleeding is the major risk associated with thrombolytic therapy. Fortunately, bleeding is usually managable with conservative measures, only occasionally requires transfusion, and most frequently (70% of cases) occurs at sites of vascular puncture. A caveat is that with studies involving invasive vascular procedures, the risk of major bleeding is increased several fold, with transfusion requirements often in excess of 15%. In ISIS-3 *(86)*, which did not require angiography, noncerebral bleeding was reported in 4.5% of patients after SK, 5.4% after APSAC, and 5.2% after tPA; hemorrhage required transfusion or was otherwise defined as "major" in only 0.9%, 1.0%, and 0.8% of patients, respectively. In the FTT overview experience of about 60,000 patients *(81)*, a major

bleeding event occurred in 1.1% after fibrinolytic therapy (most frequently with SK) compared with 0.4% after control, a small but significant difference ($p < 0.00001$).

Life-threatening internal hemorrhage may occur after thrombolytic therapy, of which intracranial hemorrhage (ICH) is the most important. The fatality rate with ICH is approximately 60% (range 44–75%) *(81,102–105)*, and disability is common among survivors. The risk of ICH in clinical trials averages about 0.5% but varies with patient characteristics, particularly advancing age, as well as the specific dose and type of the thrombolytic agent and the antithrombotic therapies given *(102–108)*. In recent trials, the rate of ICH appears to be increasing, perhaps because of the increasing age and comorbidity of patients selected for therapy as well as more aggressive thrombolytic/antithrombotic regimens. Fortunately, because of the preventive effect of thrombolytics and antithrombotics on thrombotic and embolic stroke, the rate of total stroke may be only slightly increased with thrombolytic therapy. Placebo or nonthrombolytic therapy controlled studies often did not ascertain the cause of stroke, but found nonfatal stroke rates of 0.67% with fibrinolytic therapy compared with 0.46% without ($p < 0.001$), a difference of approximately 2 of 1000 patients treated. The FTT metaanalysis suggested that for every 1000 patients treated with fibrinolytic agents, therapy will cause seven major noncerebral hemorrhages and two nonfatal, noncerebral hemorrhages while preventing 18 deaths by 35 d *(81)*.

In studies comparing various thrombolytic regimens, ISIS-3 reported rates of ICH of 0.2% for SK, 0.55% for APSAC and 0.66% for tPA (duteplase) regimens *(81)*. Respective total stroke rates were 1.04, 1.26, and 1.39% (slightly but significantly greater with tPA than SK). In the subsequent GUSTO study *(94)*, rates of ICH were 0.54% with SK plus iv heparin and 0.72% with accelerated tPA (alteplase) plus iv heparin. Respective total stroke rates were 1.40 and 1.55%. In a still more recent comparison of reteplase and alteplase, hemorrhagic stroke rates were 0.93 and 0.87%, respectively, and total stroke rates 1.68 and 1.81 (differences not significant) *(99)*.

Although only modest differences in ICH and hemorrhagic rates were observed in GUSTO comparing SK with sc heparin vs SK with iv heparin (0.49 vs 0.54%) *(94)*, unacceptable increases in ICH and other bleeding have been observed with aggressive adjuvant antithrombotic regimens given together with thrombolytics. Indeed, the GUSTO-IIA, TIMI-9A, and r-Hirudin for Improvement of Thrombolysis (HIT)-III trials *(109–111)* were stopped prematurely and reconfigured because of excessive rates of hemorrhage, including ICH. In the subsequent trials, (e.g., GUSTO-IIB, TIMI-9B), hemorrhage rates decreased to an expected and acceptable range *(112,113)*.

In an effort to build a predictive model for ICH, Simoons et al. *(107)* collected information from five clinical study sources providing information on 150 patients with documented ICH after thrombolytic therapy. These were compared with 294 matched controls. A multivariate analysis identified four independent predictors of ICH: age > 65 yr (OR 2.2, CI 1.4–3.5), weight < 70 kg (OR 2.1, CI 1.3–3.2), hypertension on admission (OR 2.0, CI 1.2–3.2), and use of tPA (alteplase; compared primarily with SK) (OR 1.6, CI 1.0–2.5). Assuming an overall incidence of ICH of 0.75%, the model predicted incidences of ICH of 0.26, 0.96, 1.32, and 2.17% for those with no, one, two, or three risk factors, respectively. For patients over 75 yr, the risk was predicted to be 1.5% with no other risk factors, climbing to 3.3% with the other two risk factors. Comparing the expected benefit of thrombolytic therapy with these predicted risks may allow the physician to individualize the selection of therapy, which might include a less aggressive thrombolytic or antithrombotic regimen or primary percutaneous transluminal coronary angioplasty (PTCA) in those at very high risk for ICH.

Allergy, Hypotension, and Fever

SK and anistreplase are antigenic and potentially allergenic, although serious anaphylaxis and bronchoconstriction are rare (incidence <0.2–0.5%) *(74,75,81,86,94,114,115)*. In ISIS-2, any allergic reaction was observed with 4.4% receiving SK compared with 0.9% receiving placebo, an absolute excess of 3.5% *(74)*. In the comparative study ISIS-3 *(86)*, any allergic-type reaction was reported after SK in 3.6%, APSAC in 5.1%, and tPA (duteplase) in 0.8% ($p < 0.00001$, SK vs tPA). Most of these reactions were minor; only 0.3% (SK), 0.5% (APSAC), and 0.1% (tPA) required treatment. In GUSTO, severe or "anaphylactic" reactions recurred in 0.6% and 0.2% of SK and tPA patients, respectively *(94)*. Angioneurotic and periorbital edema have been reported rarely after SK or APSAC. Other rare reactions have included hypersensitivity vasculitis, purpuric rashes, serum sickness, or renal failure due to interstitial nephritis *(52,75,115–117)*; these rare reactions appear to be more frequent after repeated administration.

Fever, with or without other associated manifestations of allergic or immune response, has been reported in 5–30% of patients given SK and 5–10% given APSAC. Fever has been reported to respond to acetaminophen.

Hypotension, usually readily managed, occasionally occurs after SK and APSAC. These drugs generate bradykinin, a potent vasodilator. In ISIS-2, "significant" hypotension and/or bradycardia was reported in 10.0% after SK and 2.0% after placebo infusion, an excess of about 8% with SK *(74)*. In the ISIS-3 comparative study, hypotension was reported in 11.8% receiving SK, and, similarly, 12.5% receiving APSAC, but a lower percentage (7.1%) receiving tPA *(86)*; only half of hypotensive episodes required treatment. In GUSTO, rates of reported hypotension were more comparable between SK (13%) and tPA (10%) *(94)*.

Other Associated Adverse Effects

The effect of thrombolytic reperfusion on the incidence of arrhythmias was an early concern. It is now realized that although transient changes in rhythm may occur at the time of reperfusion, overall during hospitalization, the incidence of serious ventricular arrhythmias does not increase, and late ventricular fibrillation is reduced.

Reperfusion therapy has been associated with a small increase in reinfarction (absolute excess over control patients of about 1–2%). This is believed to be primarily accounted for by recurrent occlusive events in the infarct-related artery with infarction of previously salvaged myocardium. Differences in reinfarction rates among thrombolytic agents may be accounted for by either differences in initial salvage rates associated with differences in effective early recanalization and/or a greater tendency to reocclusion with one vs another regimen (e.g., after tPA vs SK).

INDICATIONS FOR THROMBOLYTIC THERAPY IN AMI

Recently revised guidelines for the use of thrombolytic therapy in AMI have been published by the American College of Chest Physicians *(118)*, the European Society of Cardiology *(119)*, and the American College of Cardiology/American Heart Association (ACC/AHA) (report of the Task Force on Practice Guidelines, Committee on Management of AMI) *(4)*. Importantly, these guidelines are primarily "evidence based," deriving from the wealth of clinical trial information forthcoming over the past decade, rather than primarily from expert opinion. Recommendations from the most recent and detailed guidelines (ACC/AHA) are presented in Table 3 *(4)*. A class I indication is given for

Table 3
Guidelines for Management of Acute Myocardial Infarction

Study	*Prerequisites for considering thrombolytic therapy*	*Choice/time of thrombolytic agent*	*Adjuvant therapy*
ACC/AHA 1996	Class I: available evidence for efficacy and benefit 1. ST elevation, time to therapy <12 h, and age <75 yr 2. BBB with history suggestive of MI Class IIa: weight of evidence favors use/efficacy and benefit 1. ST elevation, age >75 yr Class IIb: usefulness/efficacy is less well established 1. ST elevation, time to therapy 12–24 h 2. SBP >180 mmHg, or DBP >110 mmHg with high-risk MI Class III: no benefit or evidence for harm 1. ST elevation, time to therapy >24 h, pain resolved 2. ST-segment depression	No specific recommendations In patients with large area of infarction, early after symptom onset, and at low risk for ICH, may consider the use of tPA In smaller infarcts with smaller potential of survival benefit and if a greater risk of ICH exists, SK may be the choice "Door to needle" time <30 min	Aspirin 160–325 mg/d β-Blockers unless contraindicated or CHF ACE inhibitors for anterior MI, CHF, or EF <40% (alternatively; all patients, reassess need for continued therapy at 6 wk) Heparin iv with t-PA and non-ST-elevation MI Heparin sc if SK or APSAC unless at high risk for thromboembolism, then V heparin is preferred
ACCP 1995	A. Certainty of diagnosis of AMI 1. At least 0.5 h of chest pain and 2. ST elevation or complete BBB B. Timing post-MI onset 1. Presenting within 6 h and 2. Perhaps from 7 to 12 h 3. Not recommended beyond 12 h C. Patient subgroups 1. Anterior or inferior infarction 2. First or subsequent MI 3. All age groups including those >75 yr	1. *t-PA* should be considered if patient meets all the criteria: Age <75 yr, anterior or bad prognosis inferior infarction, <6 h from onset, or has history of prior K or APSAC 2. All other patients without characteristics in (1) may be treated with *SK or APSAC or t-PA* 3. Patients treated within 7–12 h may be given SK or APSAC or t-PA; SK is the least expensive.	Aspirin 160–325 mg/d β-Blockers Heparin iv with SK, APSAC only if high risk for systemic or venous thromboembolism Heparin sc 7500 U bid for low risk with SK or APSAC ACE inhibitors for large infarction, reduced EF, hypertension, or CHF

(*continued*)

Table 3 *(Continued)*
Guidelines for Management of Acute Myocardial Infarction

Study	*Prerequisites for considering thrombolytic therapy*	*Choice/time of thrombolytic agent*	*Adjuvant therapy*
ESC 1996	All patients, unless there are contra-indications: 1. With clinical history and ST elevation or BBB within 12 h of symptom onset 2. Thrombolytics should not be given in patients with normal ECG, T-wave changes or ST depression, or infarction of >12 h unless there is evidence of ongoing ischemia	No specific recommendations. Choice based on individual assessment of risk, availability, and cost-benefit. "Call to needle" time 90 min "Door to needle" time 20 min	Aspirin 75 mg/d or higher β-Blockers in patients without contra-indications and those considered not low risk ACE inhibitors in all patients, with reevaluation at 4–6 wk Heparin iv with t-PA No recommendation with SK, APSAC, or urokinase

[a]Abbreviations: ACC/AHA, American College of Cardiologists/American Heart Association; ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; AMI, acute myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; BBB, bundle branch block; ECG, electrocardiogram; ICH, intracranial hemorrhage; t-PA, tissue-type plasminogen activator; SK, streptokinase; APSAC, anisoylated plasminogen streptokinase activator complex; CHF, congestive heart failure; ACE, angiotensin-converting enzyme; EF, ejection fraction.

Adapted from guidelines of the ACC/AHA *(4)*, ACCP, 1995 *(118)*, and European Society of Cardiology, 1996 *(119)*.

therapy of conditions for which there is a strong evidence base and general agreement of utility. A class IIa indication is given when evidence is less compelling but generally in favor of therapeutic efficacy (generally recommended). A class IIb indication is given when usefulness/efficacy of a therapy is less well established. Finally, a class III means that evidence or general agreement suggests that treatment is not effective and in some cases may be harmful. The ACC/AHA guidelines strongly recommend thrombolytic therapy (class I indication) for patients with ST elevation or BBB obscuring ST-segment analysis, a history suggesting AMI, and symptoms beginning within 12 h and age <75 yr. Thrombolytic therapy is also generally recommended (class IIa) for the same presentations (ST elevation, BBB) for patients aged >75 yr in the absence of contraindications. Thrombolysis is not indicated (Class III indication) for those with ST-segment depression only or for ST elevation but with time to therapy more than 24 h and ischemic pain resolved. Therapy is considered possibly effective (class IIb indication, evidence and opinion divided) for ST elevation and time to therapy 12–24 h in selected patients (i.e., ongoing ischemic pain), or for high-risk AMI but in the presence of a relative contraindication, such as hypertension (blood pressure >180/110 mmHg).

One caveat is that the presentation of ST depression in leads V_1–V_3 may occasionally be the equivalent of "reciprocal ST elevation," a finding with left circumflex coronary occlusion. These patients have generally been excluded from thrombolytic trials. However, some physicians believe that thrombolytic therapy should be extended to this subgroup, by analogy with other ST elevation (transmural ischemia/injury) groups. Small numbers of AMI patients without ST-segment change ("normal" or nonspecific ECG pattern) have been included in thrombolysis trials but have not benefited.

SELECTION OF A THROMBOLYTIC REGIMEN AND ADJUNCTIVE THERAPIES

A number of algorithms for selecting the approach to reperfusion (i.e., a specific thrombolytic regimen or primary PTCA) in individual patients have been proposed based on outcomes of comparative trials *(4,118,120–123)*. All these await prospective testing and validation. Aspirin is universally recommended as an adjunctive therapy in all these regimens. Heparin, iv, is recommended with tPA, whereas its use with nonselective thrombolytics (SK, APSAC) is more controversial *(4,84–86,118,119,124,125)*, being recommended for iv use only after 4–6 h and only in those at high risk for thromboembolism (atrial fibrillation, severe left ventricular dysfunction, mural thrombus, recurrent coronary ischemia, etc).

Thrombolytic Agent and Dosing Regimen

In current practice in the United States, the most frequent choices for thrombolytic regimens include SK, the accelerated (90–min) tPA regimen (now always preferred over the previous "standard" 3-h regimen, because of greater efficacy and similar safety), and reteplase (recently approved). In reviewing GUSTO and other recent studies, the ACC/AHA guidelines *(4)* comment that the benefit-cost ratio of tPA is greatest "in patients presenting early after symptom onset with a large area of injury (e.g., anterior AMI) and at low risk of ICH. In groups with a smaller potential for survival benefit and a greater risk for ICH, SK appears to be the agent of choice, particularly in view of the cost." The ACCP guidelines *(118)* recommend accelerated-dose tPA with iv heparin and aspirin as a first-choice regimen for high-risk MI patients who also have the potential for a large

therapeutic benefit, i.e., anterior AMI, BBB-related AMI, or poor-prognosis inferior AMI (i.e., those with right ventricular ischemia/infarction, or with anterior reciprocal ST depression, or with lateral and/or posterior extension, all high risk markers), time <6 h from symptom onset, and age <75 yr (older patients have greater mortality risk, but also have greater bleeding risk and derive less proportionate and absolute benefit from therapy). ACCP recognizes flexibility in their selection, however, indicating that some physicians/health care systems may wish to select tPA only when all criteria are met, and others when one or two are met. In patients not meeting criteria for tPA, any of the approved thrombolytic regimens may be justified, with SK preferred when ICH risk is great or when cost is an important consideration and tPA preferred when even a modest incremental benefit in mortality is valued or is associated with important morbidity reductions (as in younger, active patients). tPA (or r-PA) is also indicated in those with a history of prior SK or APSAC exposure (for at least 2 yr, preferably indefinitely, in those with prior SK or APSAC exposure, because of the possibility of neutralizing antibodies to SK, which develop within a few days and may persist for several years.

The recent guidelines predate the approval of reteplase, which appears to provide similar (or slightly smaller) mortality reductions than accelerated tPA, with similar cost and bleeding risk but greater convenience (double bolus). For those who view the GUSTO-III results as indicating "equivalence," reteplase might be considered when alteplase would otherwise be used, especially when convenience is an important issue. For others, the greater experience with alteplase and a (weak) trend toward better survival (2 additional lives saved per 1000 patients treated) argues for continued use of alteplase in high-risk patients. The only subgroup analysis in GUSTO-III *(99)* to show a potentially significant difference between tPA and r-PA outcomes was in patients treated more than 4 h after symptom onset, who had a significantly lower mortality rate with alteplase (tPA) therapy. Perhaps alteplase should be preferentially used in this subgroup pending further information. Primary PTCA is also recognized as a preferred reperfusion strategy by the guidelines, but with specific stipulations, as summarized later.

Adjunctive Antiplatelet and Antithrombotic Therapies

Aspirin is strongly recommended (class I indication) in the current guidelines on admission in all patients (unless contraindicated) in an initial dose of 160–325 mg, preferably chewed, and then continued in the same dose once daily indefinitely (an enteric coated form is popular) *(4,118)*. For aspirin-allergic patients, ticlopidine may be considered, but probably should be stopped after 1 mo because of the risk of associated neutropenia. Clopidogrel, a congener of ticlopidine not associated with neutropenia, may be an attractive option in the future *(126)*.

More potent initial antiplatelet therapy can now be envisioned with antagonists of the common final pathway for platelet aggregation, the platelet membrane fibrinogen receptor, glycoprotein IIb/IIIa. Abciximab, a monoclonal chimeric antibody fragment directed against this receptor, has been approved and marketed for adjunctive therapy with angioplasty (PTCA) in patients at high risk (including that associated with AMI and unstable angina) *(127)* and is currently undergoing testing as conjunctive therapy with lower doses of tPA or SK (TIMI 14 study). Also being tested are new, orally effective antagonists of the platelet membrane glycoprotein IIb/IIIa fibrinogen receptor *(128–130)*.

Two new intravenous effective glycoprotein IIb/IIIa antagonists, tirofiban and eptifibatide, have recently been approved to reduce cardiovascular events when used for acute therapy of unstable angina or non ST-elevation AMI *(130a,130b)*.

Current guidelines recommend iv heparin as standard therapy with tPA *(4,118)*, beginning during the tPA infusion and continued for 48 h, with a target aPTT (measured at >12 h) of 50–75 s (1.5–2 times control) *(4,93)*. This is achieved with a bolus of 70 U/kg (about 5000 U/kg person), and then 15 U/kg/h (about 800–1000 U/h). Heparin dosing is titrated using aPTT levels measured beginning 6 h after starting heparin and after dose changes. Dose adjustments may be made using a published nomogram *(4)*.

In contrast to use with tPA, iv heparin is not routinely recommended with SK or APSAC, agents that cause long, systemic antithrombotic effects, and should generally not be given within 6 h of starting these agents. However, iv heparin is viewed as probably effective (class IIa indication) in those at high risk for coronary thrombosis or systemic thromboembolism (e.g., those with current ischemic discomfort, large anterior MI, atrial fibrillation, prior embolus, or a known left ventricular thrombus) *(4,118)*.

For other patients receiving thrombolytics, subcutaneous heparin (7500–12,500 U twice daily until ambulatory) may be possibly effective (class IIb indication). Newer antithrombins may replace heparin as an adjunct to thrombolytic therapy in the future: these include direct antithrombins (e.g., hirudin) *(113,131)*, and fractionated (low molecular weight) heparins *(132,133)*, both of which are more easily and reliably dosed and have been tested in unstable angina/non-ST elevation AMI and with PTCA. However, these new antithrombin strategies have not yet been demonstrated to be clearly superior to heparin in ST-elevation AMI. In subgroup analysis of the GUSTO-IIb study *(113)*, however, 30-d death/reinfarction was lower when hirudin was used as an adjunct to SK, a finding that needs to be prospectively validated. The new antithrombins will be dealt with more extensively in other chapters.

THROMBOLYSIS VERSUS PRIMARY CORONARY ANGIOPLASTY

Primary coronary angioplasty (PTCA) is dealt with extensively in another chapter. Only a brief overview of information relating to the comparison of these two strategies of reperfusion is given here. An overview of seven early randomized trials (in 1154 total patients) suggested a superior outcome for primary PTCA (performed without prior thrombolytic therapy) when compared with thrombolytic therapy (primarily SK or standard dose-regimen tPA; mortality odds ratio 0.56, 95% CI 0.33–0.94) *(134)*. Primary PTCA also compared favorably with thrombolytic therapy for the combined end point of death or nonfatal MI.

However, these studies raised questions about study design issues and generalizability of the procedure. Indeed, a broad (but nonrandomized) registry experience in the United States National Registry for Myocardial Infarction-2 (NRMI-2) reported better outcome in a sample of approx 9000 AMI patients given thrombolysis than early PTCA, even when shock patients were excluded (4.1 vs 5.6% mortality) *(135)*. A single-center, well-controlled registry (Seattle-based MITI Registry) found a virtually identical outcome with either reperfusion strategy both in-hospital (6% mortality rate) and at 1 yr among approx 3600 AMI patients *(136)*.

Recently, the comparability of these two strategies has been retested in a larger, broader based randomized experience using a more contemporary thrombolytic regimen (accelerated-dose tPA with IV heparin) *(137)*. This GUSTO-IIb angioplasty substudy involved 1138 patients from 57 hospitals presenting within 12 h of AMI onset. The 30-d mortality end point occurred in 5.7% in the PTCA group and 7.0% in the tPA group

($p = 0.37$). A composite end point (including death, reinfarction, or disabling stroke) occurred significantly more frequently after tPA (13.6%) than PTCA (9.6%). The authors concluded that PTCA is an excellent alternative method of myocardial perfusion although, in most situations, thrombolytic therapy should also be regarded as an excellent strategy.

Explaining the "PTCA Paradox"

As noted above, primary PTCA performed better than *(134)*, worse than *(135)*, or similar or potentially somewhat better than thrombolytic therapy *(136,137)*. An explanatory model for this "paradox" has been proposed *(138)*. Earlier trials were disadvantaged by suboptimal thrombolytic regimens. Also, centers selected for trials may perform PTCA more quickly and effectively than in general practice. Indeed, delays in "door to balloon time" appear to average approximately 2 h (compared with the goal of <60 min), whereas delays to thrombolysis have been consistently decreasing (currently, about 40 min). Recent reports *(139–141)* confirm the operator dependence of PTCA, with increasing rates of death and emergency bypass surgery being observed in low-volume centers (<200–300 PTCA cases/yr) and/or when performed by low-volume operators (<75/yr). Thus, the preferred reperfusion strategy depends on the specific center/system: In centers without PTCA capability, with low volumes, or without surgical backup, thrombolysis is preferred. In high-volume centers with a dedicated, efficient primary PTCA program, PTCA is an excellent (if not preferred) alternative.

Current Use of Thrombolytic Therapy and Primary PTCA

The largest registry of reperfusion strategies in the United States is the NRMI, which tracks AMI therapy in 1470 hospitals. In a recent report, over a 2-yr period between June 1994 and July 1996, NRMI-2 registered 330,928 patients with AMI (H.V. Barron, personal communication). Of these, 37% received reperfusion therapy. Reperfusion therapy consisted of thrombolytics in 82% of patients and primary PTCA or (occasionally) immediate bypass surgery in 18%. How frequently is reperfusion therapy given to patients regarded as "ideal candidates" by current guidelines? In NRMI-2, only 31% of AMI patients presented with characteristics ideal for thrombolysis (note, however, that the NRMI definition of ideal used a time of <6 h rather than <12 h, as currently recommended). Of these, 72% received therapy, a good but not perfect record. Thus, additional effort must be made, particularly among patients presenting within 6–12 h, the elderly, and those with relative but not absolute contraindications but with a high-risk AMI. Finally, not only the receipt of thrombolytic therapy but also the speed of therapy deserves emphasis. (Currently, door-to-needle time averages at least 40 min, whereas the guidelines suggest that a goal of <30 min is reasonable and desirable). In summary, progress has been made in providing widespread, efficient availability of thrombolytic therapy to appropriate patients, but more efforts are needed.

INCORPORATING THROMBOLYTIC THERAPY INTO A RAPID TRIAGE AND TREATMENT ALGORITHM

Effective use of thrombolytic therapy (and other reperfusion strategies) requires its incorporation into an efficiently managed, emergency ward-based system *(142)* that is tailored to each specific hospital's capabilities and strategic preferences (i.e., toward

primary PTCA or thrombolytic therapy). The importance of developing and implementing such a strategy consistently and efficiently cannot be overemphasized. Outcomes appear to be determined more importantly by the care with which a strategy is developed and implemented than whether thrombolytic therapy or primary PTCA forms the preferred approach to reperfusion. Only a small percentage of patients presenting with chest pain will be candidates for thrombolytic therapy (approximately 5–10%) . However, the importance of rapidly identifying, triaging, and treating these patients cannot be overemphasized. Patients with chest pain are rapidly screened with a targeted history, physical examination, and electrocardiogram, within 10 min of arrival. They are then provisionally assigned to one of five chest pain pathways (definite ST elevation AMI, unstable angina/non-ST elevation MI, probable unstable angina, possible unstable angina, or noncardiac chest pain). In group I further screening for thrombolytic contraindications and therapy is rapidly performed. A summary of chest pain management in our algorithm is shown in Fig. 8.

INVESTIGATIONAL THROMBOLYTIC AGENTS AND ANTICIPATED FUTURE DEVELOPMENTS

Investigational thrombolytic agents are dealt with in detail in a subsequent chapter. Only a brief summary of new thrombolytic regimens currently being investigated is provided here. TNK-plasminogen activator (TNK-PA) is a mutant of native tPA that has been modified at three sites, conferring a longer half-life (allowing for single-bolus administration), increased fibrin specificity (unlike reteplase), and increased resistance to PAI-1 *(143)*. Lanoteplase (n-PA) is a less fibrin-specific tPA deletion mutant with a prolonged half-life now undergoing phase II and phase III studies *(144)*. Staphylokinase is a thrombolytic derived from the bacterium *Staphylococcus aureus* and produced by recombinant DNA technology *(145,146)*. It has shown excellent early reperfusion potential and a high degree of fibrin specificity, distinguishing it from SK. Like SK, however, it is antigenic. Pro-urokinase (glycosylated single chain-plasminogen activator [scu-PA]) derives from another native plasminogen activator, is highly specific, and has shown promise in angiographic trials *(147)*. Saruplase, a recombinant nonglycosylated scu-PA, has undergone more extensive clinical testing, is superior to SK in achieving early reperfusion, and has a comparable safety profile to alteplase *(148)*. Angiographic patency profiles are shown in Fig. 9 *(98,144,146,148,149)*.

Another approach to improving the reperfusion profile of thrombolytic therapy is to focus on improving adjunctive therapy. Both current and newer agents appear to have a "ceiling" of total (grade 2 + 3) and complete (grade 3) patency rates of about 85 and 60%, respectively, at 90 min. Breaking the "thrombolytic ceiling" requires a more aggressive attack, which may be able to be obtained using the new antiplatelet GP IIb/IIIa inhibitors, discussed more extensively in other chapters *(150)*. The ability of GP IIb/IIIa inhibition to facilitate "intrinsic fibrinolysis" has already been demonstrated in animal studies and small patient series *(151,152)*; it is now being tested in larger clinical trials. In the TIMI-14a study, for example, abciximab is being tested in combination with lower doses of tPA and SK and compared for its reperfusion and clinical effects with abciximab alone and with accelerated-dose tPA alone. It is hoped that these initiatives will lead to additional advances in the clinical application of thrombolytic therapy. However, care must be taken and progress must be incremental. Thrombolytic therapy is a double-edged sword that

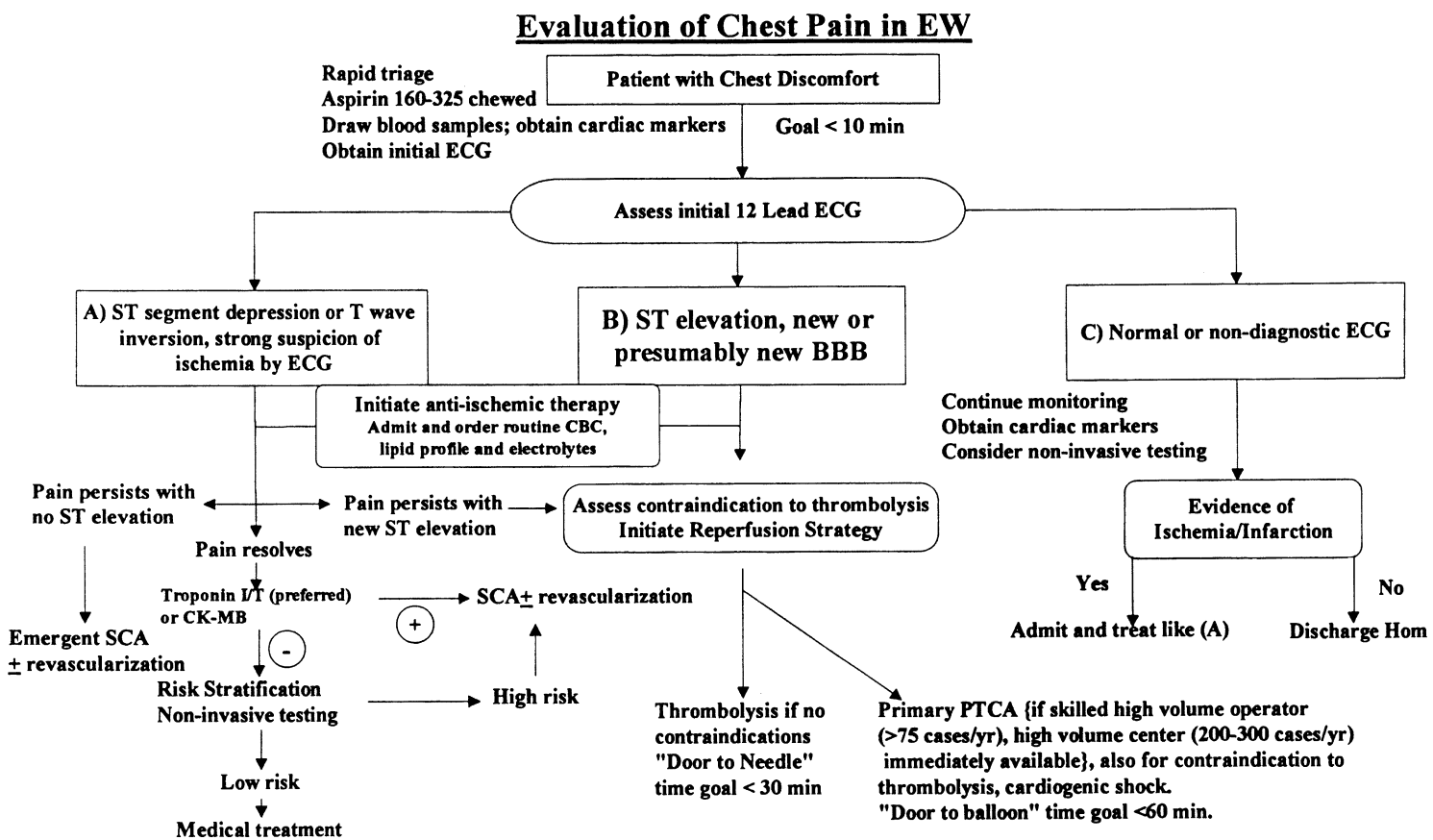

Fig. 8. Management algorithm for patient with chest pain presenting to the Emergency Department.

	TIMI-3(%)		TIMI-2/3(%)		
	Drug	tPA	Drug	tPA	P value
Reteplase	59.9	45.2	83.4	73.3	<0.05
Staphylokinase	74	58	82	77	NS
TNK-tPA	66	63	88	82	NS
Lanoteplase	57.1	46.4	83	71.4	<0.05
SCUPA	*	*	82	81.5	NS

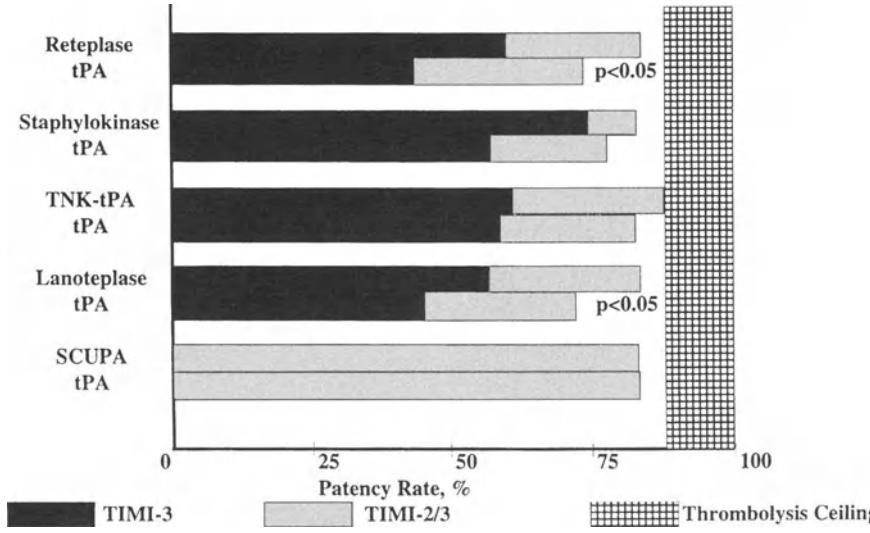

Fig. 9. Angiographic patency rates (TIMI-2/3 and TIMI-3) for the newer thrombolytic agents and comparison with the control group in individual trials utilizing accelerated dose tPA. Based on data from the RAPID 2 *(98)*, STAR *(146)*, TIMI 10B *(149)*, In-TIME *(144)*, and SESAM *(148)* trials.

may result in substantial clinical benefit but also has the potential for unacceptable bleeding risks. Thus, the course must be carefully planned and results carefully documented.

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10 New Thrombolytic Agents

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INTRODUCTION

In over 90% of cases, a thrombotic occlusion of a coronary artery is the cause of an acute myocardial infarction (AMI) *(1)*. Thrombolytic therapy has been shown to reduce short- and long-term mortality of AMI patients *(2)*. As a result of several large placebo-controlled trials, thrombolysis has become a routine treatment in patients presenting within 6–12 h after symptom onset and with ST elevations or bundle branch block on electrocardiogram (ECG). The aim of the thrombolytic therapy is to achieve an early (within 30–90 min), complete (TIMI grade 3 flow), and sustained restoration of blood flow in the infarct-related artery. This "optimal reperfusion" is associated with a remarkably low in-hospital mortality of 3–4% *(3,4)*. The more rapid and complete the restoration of flow, the better the clinical outcome (Fig. 1). However, even with the most effective thrombolytic regimens available, rapid and complete perfusion can be achieved in only 50–60% of the patients *(5,6)*. Besides the initial failure of reperfusion, reocclusion after primarily successful thrombolysis (occuring in up to 15%) and bleeding complications (especially intracranial bleeding, observed in 0.5–1.0%) are the current problems of thrombolytic therapy. The ideal thrombolytic agent should be highly effective (high early and complete reperfusion rate), safe (low rate of hemorrhagic complications, e.g., intracranial bleeding), easy to administer (single-bolus application), and cheap. The most

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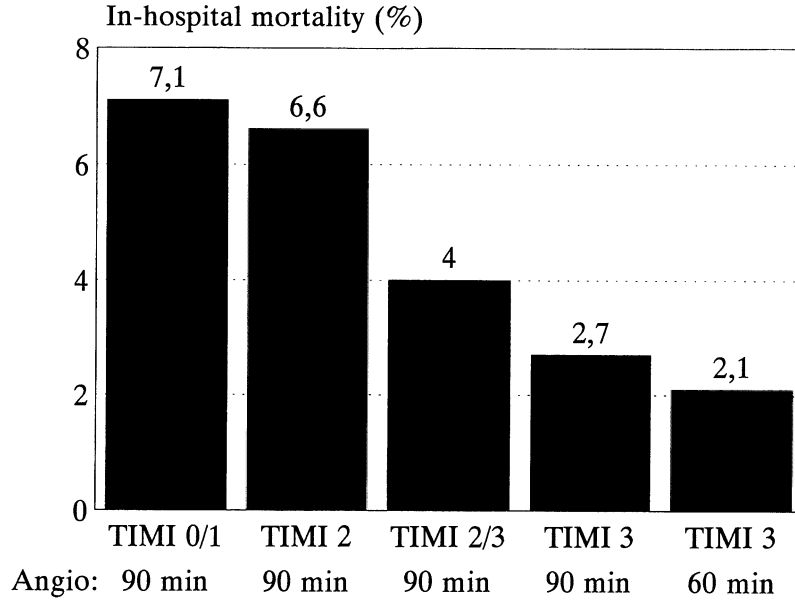

Fig. 1. Early patency of the infarct-related artery and in-hospital mortality in patients after thrombolysis for AMI. Results of a meta-analysis of four German multicenter trials. Adapted with permission from ref. *3*.

widely used agent worldwide, streptokinase, has limited efficacy with regard to early patency, has major side effects (including hypotension), and must be infused over at least 30 min *(7)*. Recombinant tissue-type plasminogen activator (tPA; alteplase) achieves higher rates of early patency but necessitates a rather complicated dose regimen to achieve optimal efficacy *(4,8)*. Therefore the search for new thrombolytic regimens is still ongoing *(9–11)*.

There are several approaches to improve thrombolytic therapy: shortening of time to thrombolysis by reducing patient decision delay, transportation delay, and door-to-needle time; new dose regimens of approved thrombolytic agents; combination therapy of different thrombolytics; development of new plasminogen activators; and optimization of conjunctive therapies with thrombin inhibitors and antiplatelet agents.

This chapter focuses on the development of new thrombolytic agents and reviews the status of those currently under clinical investigation (Table 1). Other developments in the experimental stage are discussed briefly.

SARUPLASE

Characteristics

Single-chain urokinase-type plasminogen activator (scu-PA, prourokinase) is a naturally occurring human protein first isolated from natural sources and then produced through recombinant technology in *Escherichia coli (12)*. It consists of a peptide chain of 411 amino acids, representing a molecular mass of 46 kDa, and it is not glycosylated. Saruplase is the native zymogenic precursor of urokinase and is readily activated by plasmin to the two-chain form of urokinase. This conversion may, however, play a less important role in in vivo thrombolysis, due to preferential fibrin-associated activation of

Table 1
Properties of New Plasminogen Activators Under Clinical Investigation

	scu-PA	*r-PA*	*n-PA*	*TNK-tPA*	*Staphylokinase*
Generic name	Saruplase	Reteplase	Lanoteplase	?	?
Molecular weight (Daltons)	47,000	39,000	53,600	70,000	16,500
Half-life (min)	8–10	11–15	26–32	11–20	6–7
Fibrin specificity	(+)	+	+	+	++
Antigenicity	–	–	–	–	++
Bolus application	?	double	single	single	?
Recommended dose	20 mg B, 60 mg/1 h	2 × 10 MU	120 KU/kg	30–40 mg	?
90-min TIMI 3 (%)	55	60	55–60	60	50–65
Phase III Study	COMPASS	INJECT GUSTO III	(InTIME-II)	(ASSENT-2)	–

plasminogen by saruplase *(13)*. The functional properties of scu-PA and its two-chain derivates, the urokinases, differ in several aspects. In contrast to urokinase, scu-PA is not rapidly inactivated by plasma inhibitors but persists in blood as a proenzyme, which is activated, e.g., by plasmin initiating a positive feedback cycle. Scu-PA is able to act specifically at fibrin, although it is not fixed to fibrin like tPA. The most reasonable explanation is that scu-PAs has differential efficiencies on the different types of plasminogen in plasma and at the fibrin clot. It is almost inactive against the plasminogen found in plasma but rapidly activates fibrin-bound plasminogen *(14)*.

Experimental Studies

In an in vitro model of human clots saruplase and urokinase were equally effective in inducing a dose-dependent clot lysis, whereas the fibrinogen breakdown was less pronounced after saruplase *(15)*. Additionally, in several animal models saruplase exerted equipotent fibrinolytic activity and better fibrin specificity compared with urokinase *(13,15)*.

Phase I Studies

In humans, saruplase is rapidly cleared from the blood following disappearance kinetics that can be described by two exponential terms with a distribution half-life of 8–10 min and a terminal half-life of 90–100 min *(16)*. These findings suggest the need for continuous intravenous infusion to achieve and maintain steady-state plasma levels required for thrombolytic efficay. There was a dose-dependent systemic fibrinolytic activation in humans, which was related to the quantity of saruplase converted to urokinase.

Phase II Studies

Only two small angiographic dose level studies were performed in patients with a first AMI. The first study with 17 patients showed no difference in the 60-min reperfusion rate after 40 mg (6 of 8) or 70 mg (7 of 9) saruplase *(17)*. In the second trial, a patent infarct vessel after 90 min was observed in 4 of 12 and 10 of 12 after 40 and 80 mg (20 mg bolus + 60 mg/1 h) saruplase, respectively. The median time to first reperfusion was 80 min with 40 mg and 50 min with 80 mg saruplase *(18)*. The greatest changes in plasminogen,

Table 2
Comparison of Early and 24–36-h Patency of the Infarct-Related Artery and Reocclusion Rates After Thrombolysis with Saruplase[a] and Streptokinase[b] in the PRIMI Trial

	Streptokinase (%) (n = 203)	*Saruplase (%) (n = 203)*	p *value*
60-min TIMI 2/3	48.0	71.8	0,001
90-min TIMI 2/3	63.9	71.2	n.s.
24–36-h TIMI 2/3	88.4	84.7	n.s.
Reocclusion 90 min–24 h	4.4	5	n.s.

[a]Bolus 20 mg and infusion 60 mg/1 h.
[b]1.5 Mio IU/1 h.
Data from ref. *29*.

α_2-antiplasmin, fibrinogen, and fibrinogen-degradation products were observed in the 80-mg group at 2 h after start of saruplase. As a result of these studies, the dose of 80 mg was chosen for the following trials.

The conjunctive use of heparin starting with a bolus of 5,000 IU preceeding the 80-mg dose of saruplase has been shown to be beneficial in a double-blind study in 118 patients. Coronary patency assesssed 6–12 h after the saruplase therapy was 78.6% in the heparin group and 56.5% in the placebo group ($p = 0.01$). There was no increase in bleeding events in the heparin-bolus group *(19)*.

In an angiographic study (PRIMI) with 401 patients, saruplase was more effective than streptokinase with regard to early and sustained patency (Table 2). Bleeding complications were less common in the saruplase group (14.6 vs 25.1%, $p = 0.01$); in-hospital reinfarction rates (7.1 vs 5.9%) and mortality (2.5 vs. 4.9%; p = NS) were comparable in both groups *(20)*.

In another angiographic trial saruplase compared with urokinase (1.5 Mio IU bolus + 1.5 Mio IU over 1 h) showed similar 24 –72 h patency rates (75.4 vs 74.2%) and bleeding events (10.7% in both groups) *(21)*.

In a pilot study in 52 patients the conventional alteplase regimen (100 mg over 3 h) induced significantly less systemic activation of the fibrinolytic system than saruplase. By contrast, minor and major bleeding complications tended to be more frequent in the alteplase group *(22)*. Subsequently a larger angiographic comparison of saruplase and alteplase was performed in 473 patients with AMI < 6 h (SESAM study). The 60- and 90-min Thrombolysis in Myocardial Infarction (TIMI) 2/3 patency rates were 74.6 and 79.9% in the saruplase group and 68.9 and 81.4% in the alteplase group *(23)*. Reocclusions between 90 min and 24 and 48 h occurred in 6.7 and 10.3% after saruplase and alteplase, respectively ($p = 0.2$). Severe bleeding episodes, mostly related to the invasive procedure, were observed in 21% in the two treatment groups, with two patients (0.8%) having a hemorrhagic stroke in both groups. In this study the efficacy and safety profiles of saruplase and the conventional alteplase regimen were quite similar. To investigate the possibility of giving saruplase as single or double bolus, a double-blind study was performed in 192 patients. The dose regimens tested were a single bolus of either 60 or 80 mg, a double bolus of 2×40 mg 30 min apart, and the conventional 20-mg bolus and 60-mg infusion regimen. The preliminary results showed comparable early and sustained patency rates and bleeding complications in the 80-mg single bolus and the conventional 20-mg bolus and 60-mg infusion rate (personal communication). Although there appears

Table 3
Mortality and Bleeding Complications in the COMPASS Study Comparing Thrombolysis with Saruplase[a] and Streptokinase[b]

	Saruplase[c] *(n = 1542)*	*Streptokinase*[c] *(n = 1547)*	p *value*
30-d mortality	88 (5.7)	104 (6.7)	0,2
Hemorrhagic stroke	11 (0.7)	4 (0.3)	NS
Death or disabling stroke	90 (5.8)	107 (6.9)	NS

[a]Bolus 20 mg and infusion 60 mg/1 h.
[b]1.5 Mio IU/1 h.
[c]Data are numbers, with percent in parentheses.
Data from ref. *25.*

to be no additional benefit when saruplase is given as a bolus, the use of bolus therapy has practical advantages, and the 80-mg single bolus was chosen for further development.

Phase III Studies

An open label study in 1698 patients was performed to assess the practical applicability and safety of saruplase in the daily routine *(24)*. The in-hospital mortality was 5.4% (92 of 1698). Major bleeding complications were seen in 1.17%, including hemorrhagic strokes in 0.47%. Allergic reactions were reported in 10 patients. However, in none of 455 patients examined were antibodies detected against saruplase or *E. coli* protein.

In the Comparison Trial of Saruplase and Streptokinase (COMPASS) trial, saruplase given as a bolus of 20 mg followed by an infusion of 60 mg over 1 h was compared with streptokinase (1.5 Mio IU over 1 h) in 3089 patients with AMI < 6 h. The results showed a nonsignificant trend favoring saruplase with regard to 30-d mortality (Table 3) *(25)*. The rate of bleeding complications was similar in the treatment groups.

Currently, a prospective, multicenter double-blind study (Bolus versus Infusion in Rescuplase Development [BIRD]) comparing the safety and efficacy of saruplase given as an 80-mg bolus or as in the conventional regimen (20-mg bolus and 1 hour infusion of 60 mg) is under way.

RETEPLASE

Characteristics

Reteplase (r-PA) is produced by expression in *E. coli* cells using genetic engineering. It is a deletion mutant of wild-type tPA; as for many proteins expressed in prokaryotic cells, the fully functional, nonglycosylated protein becomes available after an in vitro refolding process *(26)*. Sodium dodecyl sulfate-polyacrylamide electrophoresis and amino acid analysis revealed the single-chain form of reteplase, which can be cleaved by plasmin to a two-chain form. Reteplase consists of the protease domain, which is responsible for the enzymatic activity, and the kringle 2 domain for the fibrin-directed properties; it is not glycosylated. It has a longer half-life due to the lack of glycosylation and the removal of domains. The apparent molecular weight is 40 kDa, and the specific activity is 500 kU/mg. In vitro, reteplase has a low affinity for fibrin but is fibrin selective in vivo.

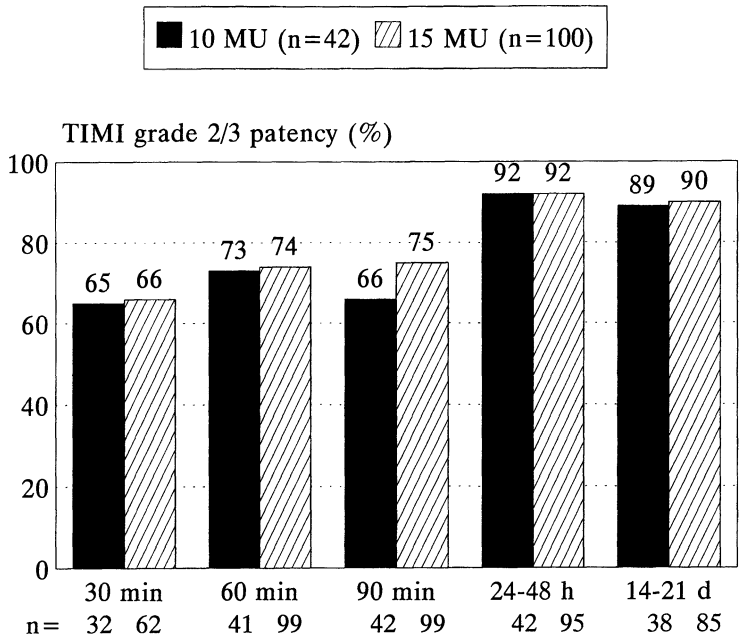

Fig. 2. Conventional (TIMI grade 2/3) patency rates of the infarct-related artery at different time points after bolus administration of 10 MU or 15 MU reteplase in the GRECO study. Adapted with permission from ref. *31*.

Experimental Studies

The fibrinolytic properties of reteplase were documented in human clot systems in vitro *(27)*. The intended prolonged half-life of reteplase compared with alteplase was demonstrated in rats, dogs, and nonhuman primates *(28)*. In a canine model of coronary artery thrombosis, reperfusion was achieved most rapidly with reteplase (18 min), compared with alteplase (35 min), anistreplase (57 min), streptokinase (67 min), and urokinase (84 min); reocclusion rates were similar *(29)*.

Phase I Studies

In a randomized, single-blind, placebo-controlled crossover study, pharmacokinetic and hemostatic properties of 6 MU reteplase were investigated in seven healthy volunteers. Reteplase was well tolerated, with no bleeding episodes, no blood pressure decrease, and no allergic reactions. The half-life was 11.2 min. in plasma. There was no evidence of antibody formation in a 6-mo period after injection *(30)*.

Phase II Studies

The first phase II trial with reteplase was designed as an open sequential dose-finding study. Patients with AMI <6 h received aspirin, 5000 IU heparin, and a bolus of either 10 or 15 MU reteplase. After inclusion of 42 patients, the dose of 10 MU was found to have reached the lower preset limit of efficacy (90-min TIMI 2/3 patency of 70%). According to the study protocol, the bolus was increased to 15 MU, and the preset number of 100 patients were treated without approaching the lower limit of efficacy. The patency data for the angiograms at the different time points are shown in Fig. 2. Very early reocclusion,

Table 4
Clinical Results of the INJECT Trial:
No Significant Differences Between Treatment with
10 + 10 MU Reteplase and 1.5 Mio IU/1 h Streptokinase[a]

	Reteplase[a] *(n = 2991)*	*Streptokinase*[a] *(n = 2994)*
35-d mortality	270 (9.0)	285 (9.5)
Reinfarction	149 (5.0)	162 (5.4)
Hemorrhagic stroke	23 (0.8)	11 (0.4)
Significant bleeding	138 (4.6)	141 (4.7)
Transfusions	21 (0.7)	30 (1.0)

[a]Data are numbers, with percent in parentheses.
Data from ref. *33*.

defined as TIMI 0/1 at 90 min in vessels that had been patent at 30 or 60 min, occurred in 17 and 13% in the 10- and 15-MU groups, respectively. Serious bleeding was seen in four patients in the entire study, including one nonfatal cerebral hemorrhage in the 15-MU group. It was concluded that reteplase can be given as a single bolus with an early patency comparable to that of standard thrombolytic treatment, without an increase in bleeding complications *(31)*.

A double-bolus injection was thought to avoid fluctuations in the patency of the infarct vessel by prolongation of high reteplase plasma concentration. Therefore subsequently an open, noncontrolled study with a double bolus (10 + 5 MU 30 min apart) was initiated. The timing of the sequence of boluses to be administered was defined from the data of a pharmacokinetic study. Conventional TIMI 2/3 patency in 50 evaluable patients was 72, 78, and 94% after 60 min, 90 min, and 24–48 h, respectively. Five patients with an open vessel at 30 or 60 min showed an occluded infarct-related artery on the 90-min angiogram. These data indicate that the problem of incomplete lysis was not resolved by the double bolus of 10 + 5 MU *(32)*.

Subsequently a randomized study, Reteplase versus Alteplase Patency Investigation During Acute Myocardial Infection (RAPID-1), enrolling 606 patients compared three reteplase regimens (15 MU bolus, 10 + 5 MU double bolus, and 10 + 10 MU double bolus) and the conventional regimen of alteplase (100 mg over 3 h). The 10 + 10 MU reteplase regimen led to the highest early complete patency rate (TIMI grade 3) of about 62% after 90 min (Table 4). The clinical events are summarized in Table 4: no excessive bleeding complications were seen with the 10 + 10 MU reteplase regimen. The 10 + 10 MU double bolus seemed superior to the other reteplase regimens and was therefore chosen for the subsequent angiographic and clinical trials *(33)*.

The RAPID-2 study was an open, randomized trial enrolling 320 patients to compare the front-loaded regimen (100 mg/90 min) with the 10 + 10 MU reteplase double bolus. The angiographic complete patency (TIMI grade 3) of the infarct vessel after 30 min was higher in the alteplase group, and after 60 and 90 min significantly higher in the reteplase group (Fig. 3). The 35-d mortality was 4.1% in the reteplase and 8.2% in the alteplase group (p = NS). Hemorrhagic strokes were observed in five patients (two [1.2%] in the reteplase and three [1.8%] in the alteplase group). There was no difference in the rate of

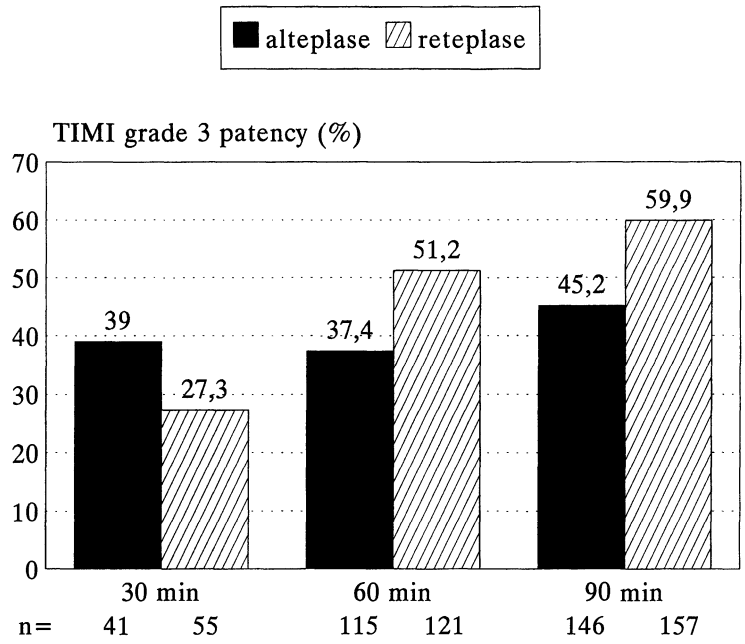

Fig. 3. Comparison of the early complete (TIMI grade 3) patency rates after front-loaded alteplase (100 mg/90 min) or double bolus (10 + 10 MU) reteplase in the RAPID-II trial. Adapted with permission from ref. *34*.

major bleeding *(34)*. These patency data favoring the reteplase 10 + 10 MU double bolus over the front-loaded alteplase regimen formed the bias for the subsequent large mortality trial, Global Use of Strategies To Open Coronary Arteries (GUSTO) III.

Phase III Studies

The objective of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial was to compare the efficacy and safety of reteplase (given as double bolus 2 × 10 MU 30 min apart) with streptokinase (1.5 Mio IU over 1 h) in patients with AMI < 12 h. The study was double blind and randomized, with 35-day mortality as the primary end point; it was designed to show equivalence between the two agents. Adjunctive therapy with aspirin and heparin was mandatory. There was no significant difference in mortality, stroke rate, and major bleeding after 35 d (Table 5). The in-hospital clinical profile was similar for both treatment groups, although the cumulative incidence of cardiogenic shock, heart failure, and allergic reactions was significantly lower in the reteplase group. In the subgroup of patients with a previous AMI ($n = 772$), reteplase led to a lower mortality than streptokinase (11.3 vs 17.3%). This trial gives a probability of 0.95 (one-sided) that the true mortality associated with reteplase use is either better than that associated with streptokinase or at most 0.71% worse. Thus, reteplase seems to be as least as effective and as safe as streptokinase *(35)*.

In the GUSTO III study, 15,063 patients with AMI < 6 h were randomized in a 2:1 fashion to receive a double bolus of 2 × 10 MU reteplase or front-loaded alteplase. The trial tested the hypothesis that bolus reteplase therapy could significantly reduce mortality (by a relative 18%) at 30 d compared with alteplase. The results revealed no significant difference between the two treatment regimens with respect to mortality or bleeding

Table 5
Angiographic and Clinical Results After
Thrombolysis with Three Different Reteplase Regimens
and the Standard Alteplase Regimen (100 mg/3 h) in the RAPID-I Trial

	rtPA 100 mg/3 h	*r-PA 15 MU*	*r-PA 10 + 5 MU*	*r-PA 10 + 10 MU*
No. of patients	154	146	152	154
60-min TIMI 3	32.7	38.5	42.3	51.0
90-min TIMI 3	49.0	40.9	45.7	62.7
90-min TIMI 2/3	77.2	62.8	66.7	85.2
Intracranial hemorrhage	2.6	0.7	0	0
Transfusions	9.2	5.4	6.5	12.0
Reinfarctions	3.9	4.7	3.9	3.3
Reocclusions	7.0	7.0	11.2	2.6
30-d mortality	3.9	4.0	7.2	2.0

[a]Data are percents.
Data from ref. *35*.

complications (Fig. 4) *(36)*. Mortality in patients with anterior infarcts (9.3% vs 10.1%) and in patients > 75 yr (20.2 vs 21.4%) were lower in the alteplase group. The 95% confidence interval leaves the possibility that the 30-d mortality after alteplase is 1.1% lower or at most 0.7% higher than after reteplase. Therefore the 10 + 10 MU reteplase regimen is not superior to the front-loaded alteplase regimen; the opposite was suggested from the angiographic data of the RAPID-II trial.

LANOTEPLASE

Characteristics

Lanoteplase (novel-plasminogen activator [n-PA]) is a designer mutant of wild-type tPA produced by recombinant DNA technology *(37)*; it lacks the fibronectin finger-like and epidermal growth factor domains, leading to a prolonged half-life in vivo. An Asn→Gln change was also made at one site (Asn-117) to prevent this glycosylation site from being occupied. This change was made on the basis of the previous findings that nonglycosylated wild-type tPA binds better to fibrin than wild-type tPA *(38)*. The purified protein is primarily a single-chain molecule with an intact plasmin cleavage site. The molecular weight is 53 kDa.

Experimental Studies

Fibrinolytic activity produced in in vitro human clots by clinically relevant concentrations of alteplase and lanoteplase was similar. Binding to fibrin clots in vitro was reduced when compared with alteplase.

In vivo lanoteplase showed a 6.4 fold higher thrombolytic potency than alteplase in a rabbit jugular vein thrombolysis model *(37)*. When lanoteplase and alteplase bolus injections were given in a canine model of coronary artery thrombosis, lanoteplase induced faster and more frequent recanalization (100 vs 40%) than alteplase.

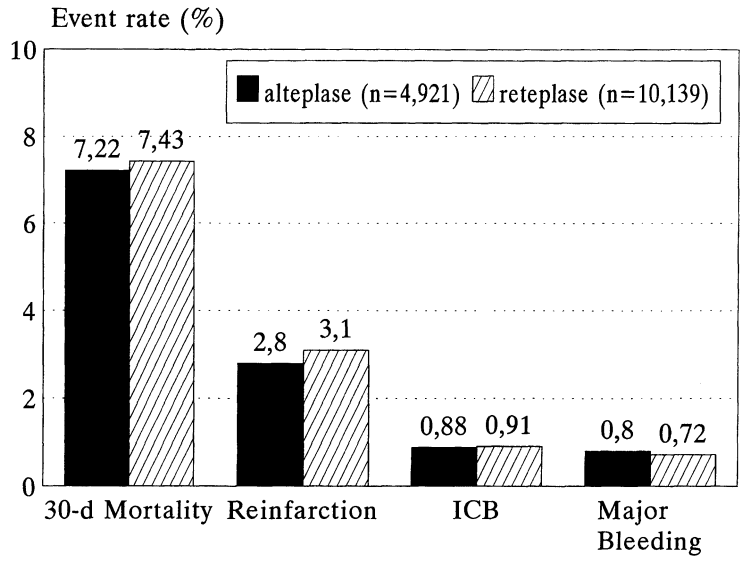

Fig. 4. Clinical events after 30 d in the GUSTO-III trial comparing the front-loaded alteplase with the double bolus (10+10 MU) reteplase regimen in patients with AMI. Adapted with permission from ref. *36*.

Phase I Studies

Six single doses between 0.05 and 2.0 mg lanoteplase were administered to 24 healthy volunteers over 3 min. There was no significant decrease in fibrinogen or plasminogen concentrations. The plasma elimination half-life was 26–32 min *(39)*.

Phase II Studies

In an early dose-finding study 137 subjects with angiographically demonstrated acute coronary occlusion were given 50, 100, or 150 KU/kg lanoteplase. No clear dose response with respect to 60-min patency (TIMI 2/3 71.8, 65.3, and 75.6%) was seen. The overall bleeding rate was 0% (50 KU/kg), 13.2% (100 KU/ kg), and 31.5% (150 KU/kg), respectively. The only cerebral hemorrhage occurred in the 150 KU/Kg group *(40)*.

The second study was conducted in 181 patients, again with angiographic demonstration of an occluded infarct vessel. The 60-min TIMI 2/3 and TIMI 3 patency rates after 25 KU/kg (62.5 and 42.9%), 50 KU/ kg (74.1 and 43.1%), and 75 KU/kg (75.4 and 47.4%) were not significantly different. The mean time to recanalization was 22–29 min. Bleeding was similar in the three groups *(41)*. Again, no dose response was evident with respect to 60-min patency.

In a double-blind study 75 kU/kg lanoteplase were compared with a bolus and 1-h infusion regimen of alteplase in 201 patients with AMI < 6 h. Angiographic evaluation revealed a 60-min TIMI 2/3 patencies of 74.5 and 66.7%, with a complete TIMI grade 3 perfusion of 45.7 and 49.5% after lanoteplase and alteplase, respectively. No difference was observed in the rate of bleeding complications *(42)*.

The Intravenous n-Pa for Treating Infarcting Myocardium Early (InTIME-I) study enrolled 602 patients with AMI < 6 h and compared four doses of lanoteplase and front-loaded alteplase using a double-blind, double-dummy design. At 60 min, lanoteplase achieved complete reperfusion (TIMI grade 3) in a dose-related manner ($p > 0.001$)

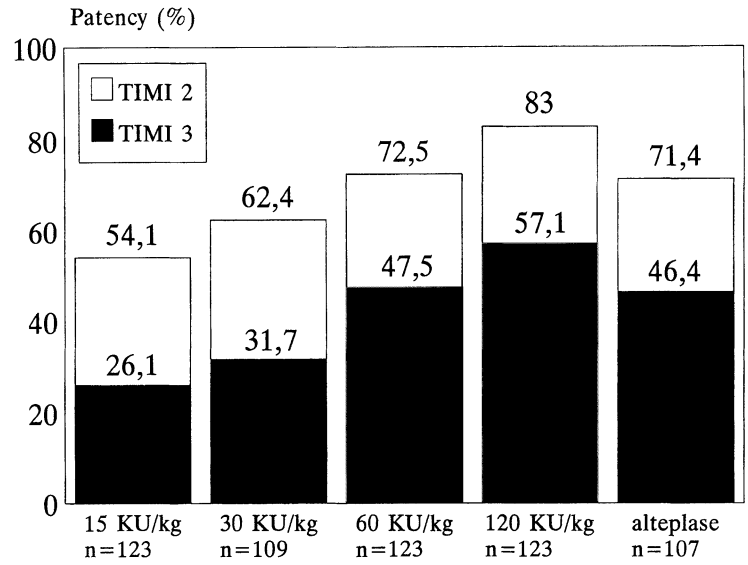

Fig. 5. Ninety-min patency rates after different bolus regimens of lanoteplase and front-loaded alteplase. Results of InTIME-I. Adapted with permission from ref. *43*.

ranging from 23.6% after 15 KU/kg, 29.5% after 30 KU/kg, 44.0% after 60 KU/kg to 47.1% after 120 KU/kg. In comparison, TIMI 3 flow was seen in 37.4% after alteplase. The 90-min patency rates are shown in Fig. 5. There was only one hemorrhagic stroke, which occurred after alteplase. Major bleeding was observed in 1.5% of all patients receiving lanoteplase, 1.7% receving the highest dose of 120 KU/kg, and 4.8% of the patients receiving alteplase (Fig. 6). Reinfarctions occurred in 1.1 and 7.3% of patients after lanoteplase and alteplase, respectively. Mortality ranged between 0.9% in the 30-KU/kg lanoteplase group and 6.5% in the alteplase group, without any statistically significant differences.

According to these results the bolus administration of 120 KU/kg lanoteplase appears to be at least as effective as front-loaded alteplase in reestablishing early and complete coronary perfusion and has an acceptable safety profile *(43)*.

Phase III Studies

InTIME-II, an international, randomized, double-blind study, is planned with the objective of demonstrating that a weight-adjusted single bolus of lanoteplase (120 KU/kg) is as safe and effective as the front-loaded regimen of alteplase. The projected number of patients is 15,000, which will be randomized in a 2:1 ratio.

TNK-tPA

Characteristics

Using tPA as the parent compound, a large number of variants have been developed; one with particularly promising attributes is TNK-tPA *(44)*. It is similar to wild-type tPA but has amino acid substitutions at three sites: a threonine (T) is replaced by an asparagine, which adds a glycosylation site to position 103; an asparagine (N) is replaced by glutamine, thereby removing glycosylation from site 117; and four amino acids are

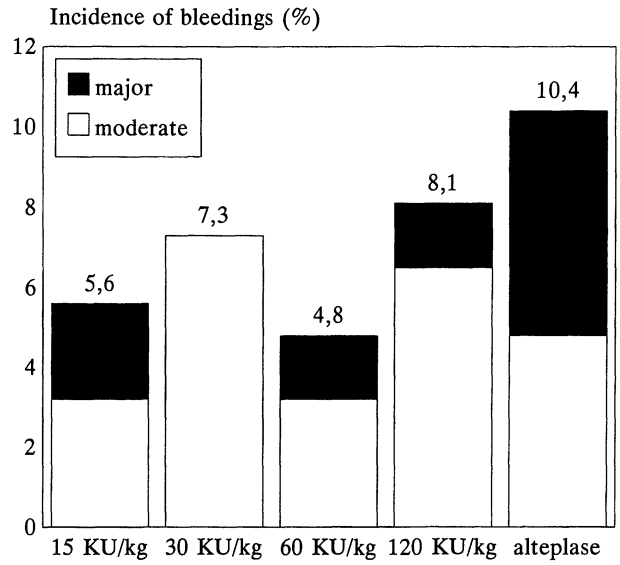

Fig. 6. Incidence of bleeding complications after treatment with different doses of lanoteplase and the front-loaded altelase regimen (100 mg/90 min). The only cerebral hemorrhage was observed in the alteplase group. Adapted with permission from ref. *43*.

Table 6
Alterations in the Structure of tPA that Result in TNK-tPA[a]

Designation	*Substitution*	*Description*
T	T103N	Adds glycosylation site Decreases plasma clearance
N	N117Q	Removes glycosylation site Decreases plasma clearance Increases fibrin binding
K	KHRR (296–299) AAAA	Increases fibrin specificity Increases resistance to PAI-1

[a]Abbreviations: T, threonin; N, asparagine; Q, glutamin; K, lysine; H, histidine; R, arginine; A, alanine; PAI-1, plasminogen activator inhibitor-1.

replaced by four alanines at the third site (Table 6). Together, these substitutions led to a prolonged half-life of the molecule, increased fibrin specificity, and increased resistance to inhibition by plasminogen activator inhibitor-1 (PAI-1) compared with wild-type tPA *(45)*. The molecular weight is 70 kDa.

Experimental Studies

In in vitro models of thrombolysis, TNK-tPA was noted to be 8–13-fold more potent at clot lysis than tPA on a per-milligram weight basis *(44)*. In a rabbit carotid occlusion model, the average time to reperfusion was 11 ± 2 min for TNK-tPA compared with 23 ± 7 min for tPA (p = 0.02) *(44)*. In several other animal models of acute arterial occlusion, a bolus of TNK-tPA was found to produce more rapid reperfusion and a greater degree of clot lysis compared with a front-loaded alteplase regimen *(46,47)*. Addition-

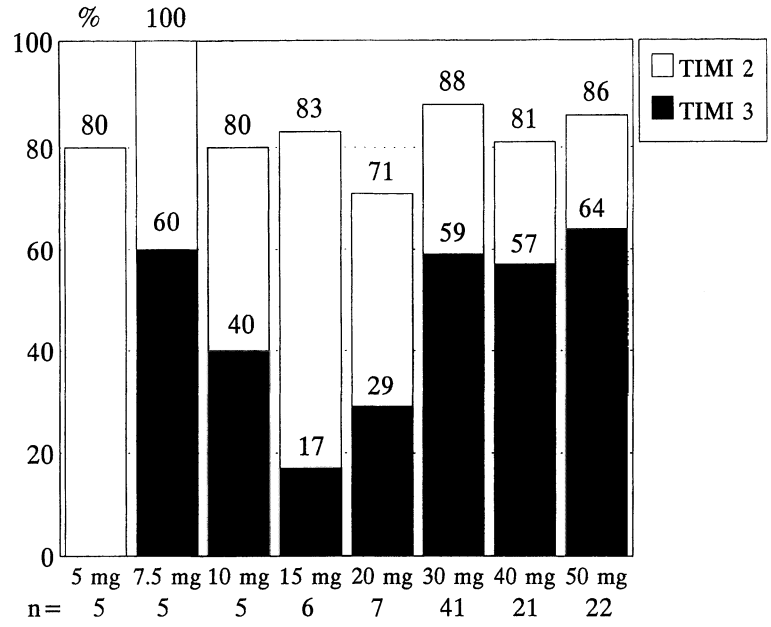

Fig. 7. Patency rates of the infarct vessel 90 min after bolus administration of 8 ascending doses of TNK-tPA in the TIMI-10A trial. Adapted with permission from ref. *48*.

ally, the duration of reperfusion was substantially prolonged, and no increase in bleeding complications was observed *(44)*.

Phase I Studies

TIMI-10A was a dose-ranging trial with several goals, including evaluation of the preliminary safety profile of TNK-tPA, assessment of efficacy with respect to early angiographic patency of the infarct-related artery, and assessment of the effects on coagulation parameters *(48)*. One hundred thirteen patients with AMI < 12 h were enrolled and treated with a single bolus of TNK-tPA of either 5, 7.5, 10, 15, 20, 30, 40, or 50 mg. The plasma half-life of elimination ranged from 11.5 to 20.6 min. The time-course of TNK-tPA plasma concentrations after a single bolus of 30 or 50 mg was very similar to that of patients treated with the front-loaded alteplase regimen from the tPA-APSAC Patency Study (TAPS) trial *(49)*. There was a dose-dependent increase in the consumption of α_2-antiplasmin (up to 25%), indicating a dose-dependent increase in the level of systemic plasmin generation. However, there was on average only a 3% reduction in fibrinogen and a 13% reduction in plasminogen even at the 50-mg dose. In comparsion, alteplase leads to a 50% decrease in fibrinogen and a 60% reduction in plasminogen. Thus TNK-tPA appears to be substantially more fibrin specific than alteplase. The angiographic results are shown in Fig. 7, revealing a TIMI grade 3 patency of about 60% and a TIMI grade 2/3 patency of about 85% in the 30–50-mg dose groups, which appeared to be higher compared with the patency rates in the lower dose groups ($p = 0.032$). Most of the patients in the 30- and 50-mg group with successful reperfusion at 90 min already had an open artery after 60 min (Fig. 8), which indicates a fast reperfusion by TNK-tPA. The hemorrhagic events were equally distributed across the doses; in total 7 (6.2%) patients had serious bleeding, mostly related to the vascular access site. There were no strokes or intracranial hemorrhages.

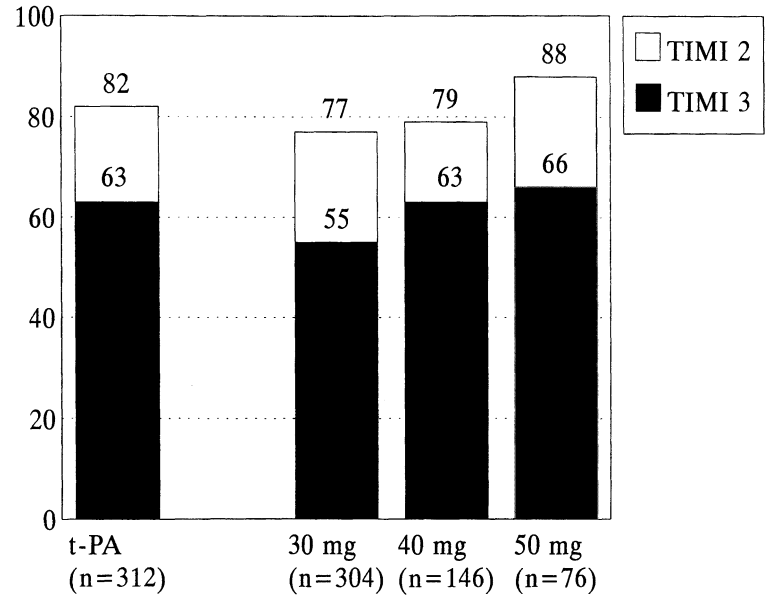

Fig. 8. Patency rates at 90 min after start of therapy with front-loaded rtPA (100 mg/90 min) or 30–50 mg TNK-tPA. Results of the TIMI 10B trial. Adapted with permission from ref. *49a.*

Phase II Studies

For the phase II dose-ranging investigations, two trials were conducted to evaluate two important aspects of TNK-tPA: its efficacy, as measured by the rate of TIMI grade 3 flow at 90 min in the TIMI 10B study, and its safety, as measured by the rate of intracranial hemorrhage in a larger clinical trial, Assessment of the Safety of a New Thrombolytic (ASSENT-I).

In TIMI 10B, 886 patients were randomized to the front-loaded rtPA or to a single bolus of 30 or 50 mg TNK-tPA over 5–10 s. The 50 mg regimen was discontinued after 76 patients because of increased bleeding and was replaced with a 40-mg dose. The results are shown in Fig. 8 and revealed a comparable TIMI 3 rate of 63% with rtPA and 40 mg TNK-tPA, whereas the administration of 30 mg TNK-tPA resulted in a lower TIMI 3 patency rate of 55%. The clinical results are shown in Table 7 *(49a).*

In ASSENT-I 3325 patients received either 30, 40, or 50-mg TNK-tPA. Whereas in TIMI 10B, there was an increased rate of intracerebral bleedings in the 50-mg group (3.8%), there was no intracranial bleeding in the 69 patients receiving 50 mg in the ASSENT-I study. However, this dose regimen was stopped prematurely. The incidence of intracerebral bleedings was below 1% with 30 and 40 mg TNK-tPA (Table 8). This rate is considered to be low, because 15% of the patients were older than 74 yr.

Phase III Studies

The primary objective of the planned phase III ASSENT-II trial is to demonstrate therapeutic equivalence in 30-d mortality between a weight-adjusted dose of TNK-tPA and the front-loaded infusion of 100 mg alteplase. The study is being conducted as an international, 1:1 randomized, double-blind, parallel group study in 18,000 patients with AMI < 12 h and started in September 1997.

Table 7
Incidence of Death and Intracerebral Hemorrhage
After Thrombolysis With rtPA or 30–50 mg TNK-tPA

	rt-PA (n = *319*)	*30 mg TNK* (n = *311*)	*40 mg TNK* (n = *153*)	*50 mg TNK* (n = *76*)
Death	18 (5.6%)	11 (3.5%)	11 (7.2%)	3 (3.8%)
Intracerebral hemorrhage	6 (1.9%)	3 (1.0%)	3 (2.0%)	3 (3.8%)

Table 8
Clinical Results of the ASSENT-I Trial

	30 mg TNK-tPA (n = *1711*)	*40 mg TNK-tPA* (n = *1463*)
Death	6.6%	6.1%
Reinfarction	7.3%	5.1%
Cardiogenic Shock	3.7%	3.5%
Stroke	1.11%	1.51%
Intracerebral hemorrhage	0.94%	0.76%

STAPHYLOKINASE

Characteristics

Although the fibrinolytic properties of staphylokinase have been well known for more than four decades *(50)*, its thrombolytic potential and fibrin specificity were demonstrated only recently *(51)*. Staphylokinase is a bacterial protein from *Staphylococcus aureus* strains and builds a 1.1 inactive stoichiometric complex with plasminogen that is activated by plasminogen activators. The most important difference compared with streptokinase is that the staphylokinase-plasminogen complex is quickly neutralized by α_2-antiplasmin if no fibrin is present, thus providing staphylokinase with a fibrin-specific activity. Staphylokinase is actually a family of at least four plasminogen activators, all with a molecular weight of about 16 kDa. One of these plasminogen activators, STAR-C, which is produced by recombinant techniques in *E. coli*, is under clinical investigation *(52,53)*. Recombinant staphylokinase consists of 136 amino acids in a single polypeptide chain. Staphylokinase, being of nonhuman origin, carries the potential of immunogenicity, and antibody formation has been observed in all patients treated *(54, 55)*. In an effort to reduce the antigenicity of staphylokinase, immunodominant domains of the molecule were identified and eliminated by site-directed mutagenesis, yielding combination mutants with relatively maintained specific activities that were not recognized by antibodies elicited in patients treated with staphylokinase *(56)*. One of these mutants, KER staphylokinase, has been administered to patients with peripheral arterial occlusion. Currently, a study to compare the antigenicity of the wild-type staphylokinase and the KER mutant in patients with AMI is under way.

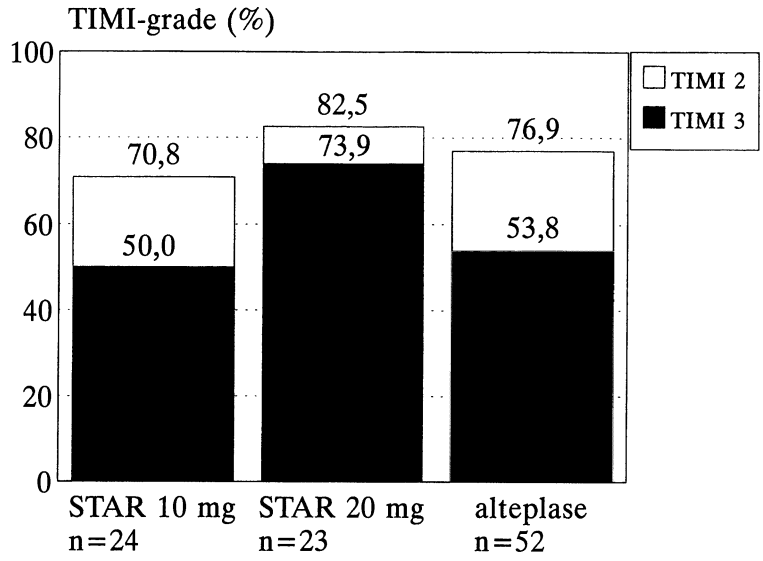

Fig. 9. Comparison of the 90-min patency rates after thrombolysis with 10 or 20 mg STAR and front-loaded alteplase (100 mg/90 min). Adapted with permission from ref. *60.*

Experimental Studies

In vitro experiments demonstrated that staphylokinase is a potent plasminogen activator that compares favorably with streptokinase in terms of fibrinolytic efficacy, fibrin selectivity, and potency toward platelet-rich clots. In several animal models these properties could be confirmed, and staphylokinase was more effective than streptokinase in dissolving platelet-rich clots in baboons *(53,57,58).*

Phase I Studies

In a pharmacologic phase I trial in five patients with AMI treated with an infusion of 10 mg STAR over 30 min, a plasma half-life of 6.3 min was found. Plasma levels of fibrinogen and α-$_2$-antiplasmin were unchanged, indicating a high fibrin specificity. Neutralizing antibodies could not be detected at baseline and within 1 wk after STAR administration but were consistently observed after 14–35 d. These induced antibodies did not crossreact with streptokinase. There was no allergic reaction. Coronary recanalization within 40 min was angiographically documented in four of five patients treated with 10 mg STAR over 30 min *(59).*

Phase II Studies

In a randomized trial, two doses of STAR (10 or 20 mg over 30 min) were compared with front-loaded alteplase in 100 patients. After 25 patients had been treated with 10 mg STAR, it became obvious that the initial 10-mg dose resulted in unexpectedly low patency rates (50% TIMI grade 3 after 90 min). The dose was increased thus to 20 mg. The rates of bleeding complications did not differ between the treatment arms. Systemic fibrinogen degradation, α-$_2$ antiplasmin consumption, and plasminogen activation were nearly absent in the STAR group but were substantial in the alteplase group. Antibodies to STAR and STAR neutralizing activity were low at baseline and increased substantially in almost all STAR-treated patients. The angiographic results are shown in Fig. 9. In this

study STAR compared favorably with alteplase in achieving early coronary artery recanalization in patients with AMI at dosages that preserve circulating fibrinogen (60).

A multicenter study comparing a 2 × 15-mg STAR double bolus with the front-loaded rtPA regimen was stopped after an interim analysis of the results of 100 patients. Preliminary results revealed an identical TIMI 2/3 patency after 90 min (42 of 50 [84%]) in the two treatment arms *(61)*.

Phase III Studies

A phase III trial has not been conducted or planned with recombinant staphylokinase.

OTHER AGENTS

A number of agents are under experimental investigation; clinical investigations are expected for some in the near future.

Vampire Bat Plasminogen Activator

Plasminogen activator of the vampire bat is a naturally occurring thrombolytic agent. The family of the BATPAs comprises four structural distinct proteins, of which DSPA-α_1 exerts the most favorable thrombolytic properties. It is produced by recombinant technology in mammalian cells. In experimental models, DSPA-α_1 showed a higher fibrin specificity and a comparable thrombolytic potency when compared with tPA. The dominant half-life was 2.8 h in a clinical phase I study, which warrants single bolus administration in therapeutic use for most thrombolytic indications. Being of a nonhuman nature, this substance has a potential for immunogenicity, and antibody formation was observed in animal models *(62)*.

Chimeric Plasminogen Activators

Many attempts have been made to engineer the physiologic plasminogen activators including chimeras of tPA and scu-PA. However, whether the fibrin binding domain or the catalytic domain were altered, none of these derived substances demonstrated convincing efficacious properties *(63)*. The increased thrombolytic potency of these chimeras appeared to be mainly owing to a reduced plasma clearance. Bolus administration of one of these chimeras, $K_1K_2P_u$, was investigated in six patients with AMI; four had an occluded infarct vessel after 30 min *(64)*. No further trials were undertaken with these molecules.

Antibody-Directed Agents

Antibody targeting for the treatment of thrombi entails the engineering of a bifunctional molecule containing both a highly specific antibody-combining site for concentrating the molecule at the desired target (the thrombus) and an effector site with thrombolytic properties. With the aim of selecting the most potent combination of antibody and effector agent for recombinant production, model molecules were created by chemically crosslinking urokinase, tPA, and scu-PA to antifibrin and antiplatelet antibodies or their Fab fragment *(65–68)*. These molecules have been shown to have a several times (up to 20) greater thrombolytic potency than their parent plasminogen activators. However, they are potentially antigenic, they are costly, and none of them has yet been used in patients.

EVALUATION OF NEW REPERFUSION STRATEGIES IN CLINICAL TRIALS

The evaluation of new reperfusion strategies in clinical trials involves two essential steps: definition of the optimal dose and duration of treatment for the new drug or regimen by appropriate dose-finding studies (phase II) and assessment of clinical value by large phase III trials.

Phase II

For most thrombolytic drugs and adjunctive antithrombotics, systemic dose ranging has not been done. Nevertheless, many tens of thousands patients have been enrolled in phase III trials. Dose-escalating studies have been performed only recently, e.g., for reteplase and lanoteplase *(31,33,43)*. The conventional parallel group design is adequate for testing an optimal or near optimal dosage of a new drug vs a standard, but dose finding may be achieved more efficiently by a sequential design *(31)*. In contrast to the parallel group design, there is no generally accepted sequential statistical design. Sequential testing is thought to reduce the number of patients who are treated with inappropriate doses, thus leaving more patients for near optimal dose groups, which then are compared head to head with the standard. A serious limitation for dose ranging in thrombolysis is use of the end point angiographic patency, which is invasive, expensive, and available in a rather limited number of institutions. Early and complete resolution of ST-segment elevation measured from a standard 12-lead ECG 3 h after treatment onset has been shown to correlate as least as closely to in-hospital mortality as 90-min patency *(69,70)*. In spite of its limitations as an indicator of reperfusion in the individual patient, ST-segment resolution 90 and 180 min after treatment onset should be a useful surrogate for patency in reperfusion trials and should allow a more systematic dose ranging before large phase III trials.

Phase III

Since the ISIS era began, it is indisputable that the only firm basis for establishing a new therapeutic strategy in common diseases such as myocardial infarction is often megatrials. On the other hand, it is equally indisputable that the number of megatrials that can be conducted even in world-wide networks is limited. The combined end point conception, which was designed to increase the statistical power of smaller clinical trials *(71)*, has not gained wide acceptance, since consensus regarding the relative weight of the components is lacking.

In recent studies of thrombolytics, i.e., the COMPASS *(25)* and INJECT *(35)* trials, the level of sample sizes has been reduced by introducing the hypothesis of equivalence instead of superiority in comparing study drug and standard treatment. The rationale for such a design is acceptance of equivalency for approval by the authorities, which is an obvious prerequisite for drug development and hence sponsoring by the pharmaceutical industry. An unresolved problem in phase III trials is the definition of stopping rules for early termination, which may be considered because of lack of benefit or untoward risks *(72)*.

CONCLUSIONS

The ideal thrombolytic agent should be effective (high early and complete recanalization rate of the infarct-related artery), safe (low rate of bleeding complications, especially

intracranial hemorrhages), easy to administer (single bolus), and cheap. The available thrombolytic regimens have a limited efficacy with regard to early complete patency and must be given as infusions over 60–90 min. Several strategies are available for the development of new thrombolytic agents, and two such techniques are in the clinical investigation stage:

(1) the production of naturally occurring plasminogen activators with recombinant techniques (scu-PA, staphylokinase, BatPA, etc.); and
(2) the design of mutants and variants of plasminogen activators with altered properties (reteplase, lanoteplase, TNK-tPA, KER-staphylokinase, and so forth).

Saruplase is the native precursor of urokinase and, in contrast to urokinase, is able to act specifically at fibrin. With respect to early patency, the current recommended dose of saruplase (20-mg bolus and 60-mg infusion over 1 h) is equally effective as urokinase and the standard alteplase regimen. The COMPASS trial in >3000 patients showed a nonsignificant trend favoring saruplase over streptokinase with regard to 30-d mortality (5.7 vs 6.7%).

Of a variety of designer drugs (mutants and variants of tPA with altered fibrin affinity, half-life, fibrin specificity, and resistance to PAI-1), reteplase, lanoteplase, and TNK-tPA are under clinical investigation. Reteplase is a deletion mutant of tPA with a prolonged half-life. In the phase II trials, a double-bolus regimen (10 + 10 MU) has been shown to be the most effective reteplase regimen and to be at least as effective as the front-loaded alteplase regimen in achieving early and complete patency. In INJECT, an "equivalence" trial, the patients treated with the 10 + 10 MU double bolus showed a slightly lower mortality (9.0 vs 9.5%) and an excess of hemorrhagic strokes (0.77 vs 0.37%) when compared with streptokinase. In the subsequent GUSTO III study, reteplase was not superior to the front-loaded alteplase regimen with respect to 30-d mortality (7.4 vs 7.2%) and bleeding complications.

Lanoteplase has a greater fibrin affinity and a longer half-life compared with tPA. In phase II trials, lanoteplase given as a single bolus of 120 KU/kg has been shown to achieve early complete patency rates of about 60%, without an excess in bleeding complications when compared with alteplase. The unique feature of TNK-tPA is its higher resistance to PAI-1 compared with tPA. It has a prolonged half-life, and preliminary results of single-bolus administration of different doses suggest that 30–50 mg TNK-tPA is as effective as the front-loaded alteplase regimen. Two large phase III trials comparing the front-loaded alteplase regimen with 120 KU/kg lanoteplase (InTIME II) and 40 mg TNK-tPA (ASSENT-II) are underway and will define the clinical value of these new compounds.

Recombinant staphylokinase (STAR) is highly fibrin specific but is antigenic. So far there is limited clinical experience with STAR, suggesting that 20 mg STAR given over 30 min is equally effective in achieving early patency as the front-loaded alteplase regimen. Molecules with altered immundomains (KER-STAR) are currently being tested in clinical trials.

A still unresolved problem is evaluation of the optimal dose for a new thrombolytic agent in phase II studies. Whereas a sequential design seems superior to the conventional parallel group approach (reducing the number of patients treated with an inappropriate dose), there is no generally accepted design for sequential statistical testing. The current gold standard for efficacy, early angiographic patency, has some major limitations (cost,

invasiveness, etc.). Therefore measurement of early resolution ST-segment elevation should be considered as a surrogate end point.

It seems that thrombolysis is limited by a sealing of the early infarct vessel patency. Further enhancements of the speed and completeness of reperfusion will be unavoidably accompanied by an increased risk of bleeding complications. Therefore it seems doubtful whether the "designer drugs" will exhibit a significant clinical improvement compared with the currently available naturally occurring plasminogen activators. The major advantage of these agents is ease of administration (single bolus), which might further reduce time to treatment.

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11 Primary Angioplasty

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INTRODUCTION

Acute myocardial infarction (AMI) affects 1.5 million people in the United States alone every year. Of those patients who seek (and reach) medical attention, approximately 25–50% present with typical ST-segment elevation on their initial electrocardiogram (ECG), within 12 h of symptom onset, and are candidates for pharmacologic or mechanical revascularization. Rapid and effective reperfusion can be achieved with fibrinolytic therapy or primary (direct) angioplasty, as demonstrated in numerous randomized trials and registries. A voluminous body of literature is devoted to the comparative analysis of the two strategies, in an effort to select the optimal therapy for patients with AMI.

FIBRINOLYTIC THERAPY VS MECHANICAL REPERFUSION

The use of fibrinolytic therapy, the most widely applied reperfusion therapy, has been investigated extensively in almost 200,000 patients enrolled in randomized clinical trials *(1–4)*. It is logistically ideal for widespread use at almost any medical facility. A few key concepts, corroborated by angiographic evaluation and substantial clinical follow-up, have emerged from this vast experience.

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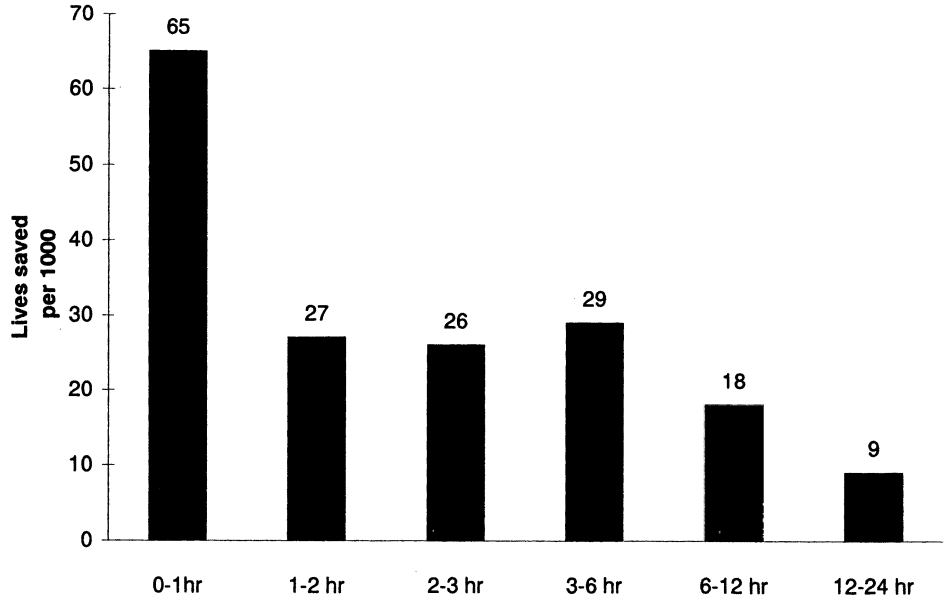

Fig. 1. Effectiveness of fibrinolytic therapy: relation to time to administration. Adapted with permission from ref. *6*.

Acute thrombotic coronary occlusion results in a front of ischemia, leading eventually to tissue necrosis *(5)*. The resulting injury depends on the duration of the insult, the rapidity and completeness of reperfusion, the presence and extent of collateral circulation, and destruction of microvasculature. Boersma et al. *(6)*, in a systematic evaluation of fibrinolytic therapy, have shown that its use within the first hour of symptom onset saves 65 lives/1000 patients treated, compared with only 29 when the therapy is given ≥3 hours from infarct onset *(6)* (Fig. 1). Similar data from the Grupo Italiano per lo Studio della Streptochinasi nell'Infarto myocardio (GISSI)-I trial *(7)* and studies of prehospital thrombolytic administration *(8,9)* have focused our attention on the need for very early therapy for AMI. Regrettably, the same studies showed that only a small fraction (3–5%) of patients present within this "golden hour." This impressive relationship between time to treatment and outcome includes the inherent delay of fibrinolytic agent action, which adds 30–60 min to the period of ischemia. By contrast, mechanical reperfusion with balloon angioplasty restores flow almost simultaneously with its successful application.

Besides early administration of therapy, complete reperfusion, or Thrombolysis in Myocardial Infarction classification (TIMI) 3 flow in the infarct artery at 90 min is also an extremely potent predictor of improved outcome. The primacy of rapid and sustained infarct artery patency was highlighted in the angiographic substudy of the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO) I trial *(10)*. Compared with lesser degrees of reperfusion, TIMI 3 flow was associated with a markedly improved survival at 30 d (Fig. 2). Simes et al. *(11)* showed that the differences in the rate of TIMI 3 flow at 90 min among the four fibrinolytic regimens tested in GUSTO I explained almost entirely the differences in mortality among the four groups. Retrospective analyses of other fibrinolytic trials have confirmed this observation *(12,13)*. Furthermore, even when brisk antegrade flow is initially achieved with lytic therapy, substantial attrition of the benefit occurs because of intermittent patency (25%), reocclusion (13%),

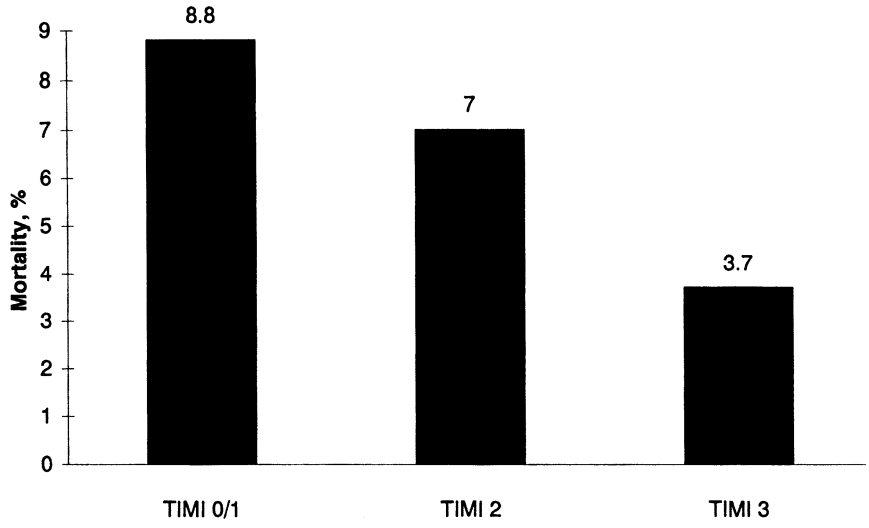

Fig. 2. Thirty-d mortality and 90-min infarct-artery TIMI flow. Adapted with permission from ref. *13*.

and impaired microvasculature, or "no-reflow" (23%) *(14)*. The concept of the "illusion of reperfusion" *(15)* reflects our overestimation of the actual rate of complete reperfusion induced by lytic therapy, which probably occurs in only one-fourth of those treated.

Since, compared with optimal fibrinolytic therapy, primary angioplasty is capable of achieving TIMI 3 flow in 15–35% more patients *(10,16,17)*, it is reasonable to expect that this difference in patency rates will translate into clinical benefit. As a mechanistic confirmation of the improved outcome with better patency, the relation between completeness of flow restoration with percutaneous transluminal coronary angioplasty (PTCA) and myocardial salvage was examined by Laster et al. *(18)* in 180 patients enrolled in the Mayo Clinic Registry of Primary Angioplasty. TIMI 3 flow was achieved in 163 (91%) patients, TIMI 2 in 13 (7%), and TIMI 0/1 in 4 (2%) of the group. Postangioplasty TIMI flow grade was significantly associated with infarct size and degree of myocardial salvage.

The seminal contribution by DeWood et al. *(19)* highlighted the importance of arterial thrombus in the initiation and propagation of the events leading to myocardial necrosis. In most cases, thrombus dissolution produced by the lytic agents leaves behind a significant coronary stenosis, which serves as a substrate for recurrent ischemic events. Thus, a large proportion of patients have revascularization procedures before hospital discharge, or within the first few months after an AMI. This varies with physician preference, availability, and prevailing clinical practice. For example, among the 21,772 patients enrolled in the United States in the GUSTO I trial, 71 and 58% underwent coronary angiography and revascularization, respectively, prior to hospital discharge *(20)*. Successful primary angioplasty virtually eliminates residual high-grade stenoses in the infarct artery, at least until restenosis occurs.

The hazard of intracranial hemorrhage, especially in elderly patients with uncontrolled hypertension, constitutes another important challenge in the treatment of AMI with fibrinolytic therapy *(21–23)*. The incidence of hemorrhagic stroke has been less with mechanical, compared with pharmacologic reperfusion.

PRIMARY ANGIOPLASTY: OBSERVATIONAL SERIES

Many series reported the results of primary angioplasty in various settings of clinical practice. Most are small in size (<100 patients) and include patients selected for this procedure because of contraindications to lytics, or institutional preference *(24–27)*. In these series, comparison with outcome of patients treated with fibrinolytic agents is either not possible, based on historical controls, or is confounded by critical selection biases.

O'Keefe et al. *(28)* reported from the Mid America Heart Institute, which pioneered the procedure in the United States, on the outcome of 1000 consecutive patients treated with primary angioplasty. The mean time from symptom onset to reperfusion was 5.4 ± 4.0 h, and 7.9% of the patients were in cardiogenic shock. Infarct artery patency (not specifically categorized as TIMI 2 or 3 flow) was 94% overall, with lower rates observed for venous bypass grafts (86%). The in-hospital mortality was 7.8% overall, and 44% in those presenting with cardiogenic shock. The global ejection fraction increased from 50% before angioplasty to 57% before discharge. Major bleeding and strokes occurred in 2.8% and 0.5%, respectively. Reocclusion was documented in 13% by angiography in selected patients before hospital discharge.

Rothbaum et al. *(24)* reported on 151 patients who underwent primary angioplasty with a success rate of 87%. In-hospital mortality was 5% and 37% for successful and failed PTCA, respectively. Most of the deaths occurred in patients with cardiogenic shock. Angiographic follow-up, performed in 70% of eligible patients at 6 mo, demonstrated restenosis in 31%. The mortality at an average follow-up of 1.7 yr was 2.2%.

The Primary Angioplasty Registry (PAR) included 271 patients treated within 12 h of symptom onset at six centers with considerable expertise in primary angioplasty *(29)*. Patients with contraindications to lytic therapy or with cardiogenic shock were excluded from the registry. The procedural success rate (TIMI 3 flow with <50% residual stenosis), assessed by an independent angiographic laboratory, was 92%. The rates of death (4%), reinfarction (3%), and stroke (1%) were very favorable. Only 2% of those discharged from the hospital died during the 6-mo follow-up, and an additional 3% experienced a nonfatal myocardial infarction *(30)*. Repeat angioplasty was performed in 16% and bypass surgery was necessary in 4%. Systematic, protocol-driven repeat angiography was performed in 76% of the patients eligible for it. Almost half the patients (45%) demonstrated angiographic restenosis, including 13% total occlusion.

The Myocardial Infarction Triage and Intervention (MITI) program in the Seattle area collated a large cohort of consecutive patients with AMI treated with primary angioplasty (1050) or fibrinolytic therapy (2095) at 19 hospitals, between 1988 and 1994 *(31)*. Despite nonrandomized treatment allocation, the two groups were well matched with respect to age, gender, incidence of anterior infarction, and presence of high-risk characteristics *(17)* (Table 1). As expected, the time to treatment in the PTCA group exceeded that in the lytic group by almost a full hour. The in-hospital mortality was similar in the two groups, 5.5 and 5.6%, respectively. Before hospital discharge, 74 and 32% of lytic treated patients underwent angiography and angioplasty, respectively. The initial hospitalization was significantly longer and less costly in the lysis group. The mortality at 1 and 3 yr was similar in the two groups (Fig. 3),whereas the use of repeat angiography and angioplasty remained higher in the angioplasty group at both intervals (Fig. 4). The initial choice between lysis and angioplasty was not independently associated with improved survival at 3 yr.

Rogers et al. *(32)* gathered data from the Alabama Registry of Myocardial Ischemia on 1,170 AMI patients, of whom 10% and 19% were treated with primary angioplasty and

Table 1
The Myocardial Infarction Triage and Intervention (MITI) Registry[a]

Characteristic	*Lytic therapy (n = 2095)*	*Primary angioplasty (n = 1050)*
Age (yr)	60 ± 12	60 ± 12
Female gender (%)	24	23
Prior infarct (%)	13	15
Prior bypass surgery (%)	6	8
Prior stroke (%)	4	7
Prior GI tract bleeding (%)*	1	3
HR >100 bpm (%)	10	12
SBP < 100 mmHg (%)	10	12
Current anterior MI (%)	37	34
High risk (%)[b]	55	57
Time to therapy (hr)*	1.0 ± 1.0	1.7 ± 1.2

[a]GI, gastrointestinal; MI, myocardial infarction; HR, heart rate; SBP, systolic blood pressure.
[b]Based on data from ref. *17.*
*from presentation, $p < 0.01$ (p = NS for all other findings).
Adapted from ref. *31.*

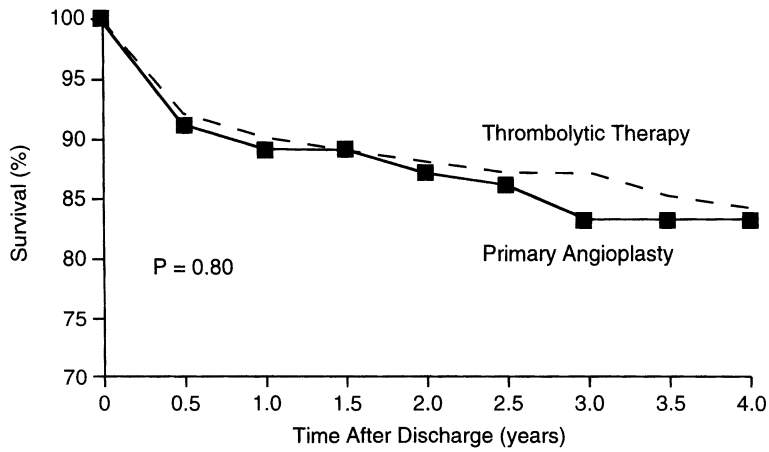

Fig. 3. Survival up to 4 yr in the angioplasty and lytic patients in the MITI registry. Reproduced with permission from ref. *31.*

lytics, respectively, within 6 h of symptom onset. The average time to treatment was 252 and 184 min, respectively. In the lysis group, 90 and 49% had angiography and angioplasty, respectively, before hospital discharge. The in-hospital mortality was similar in the two groups. At 1 yr, 85 and 88%, respectively, were free of death and reinfarction.

The German Multicenter Registry (ALKK) accumulated data on 758 patients treated with primary angioplasty in 1994–1995 *(33).* Time to treatment was almost 6 h from symptom onset, and 17% were in cardiogenic shock. Complete reperfusion (TIMI 3 flow) was achieved in 90%. The overall in-hospital mortality was 11.5 (3.5, and 50% in those without, and with, cardiogenic shock, respectively). From the same registry, Zahn et al.

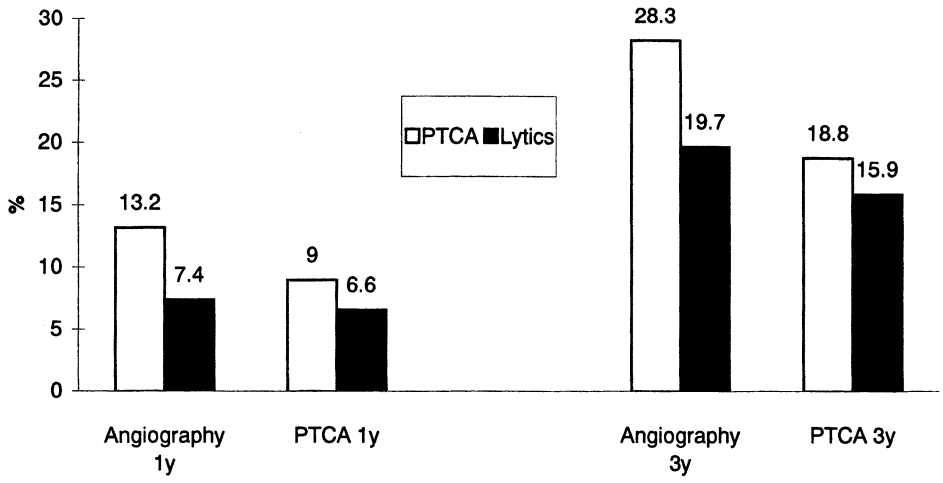

Fig. 4. One- and 3-yr repeat invasive procedures in the angioplasty (white bars) and lytic (black bars) patients in the MITI registry. Adapted with permission from ref. *31*.

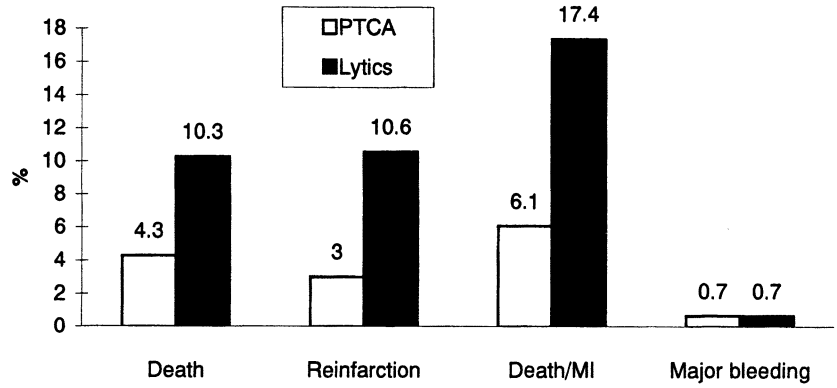

Fig. 5. In-hospital events in angioplasty (white bars) and lytic (black bars): matched patients from the German Registry of Acute Myocardial Infarction. Adapted with permission from ref. *34*.

(34) reported a comparative analysis of 156 and 437 patients treated with primary angioplasty and lytics, respectively, matched by age, gender, infarct location, systolic blood pressure, and delay to treatment. Contraindications to thrombolysis were significantly more common in the angioplasty group. In-hospital death, as well as death and reinfarction were significantly less common in the angioplasty group, compared with lytic-treated patients (Fig. 5). The improvement in outcome was apparent by the end of the first 48 h after treatment. The clinical benefit observed in the angioplasty group was strengthened by a low incidence of major bleeding (0.7%) and cerebral hemorrhage (0%).

Nakagawa et al. *(35)* studied survivors of AMI treated with primary angioplasty from the angiographic standpoint. The cumulative rates of restenosis and reocclusion at 3 wk, 4 mo, and 1 yr were 8.8 and 12%, 29 and 14%, and 33 and 14%, respectively. Thus, restenosis was very prevalent in this cohort, whereas reocclusion was less frequent and tended to occur early in the follow-up period (Fig. 6).

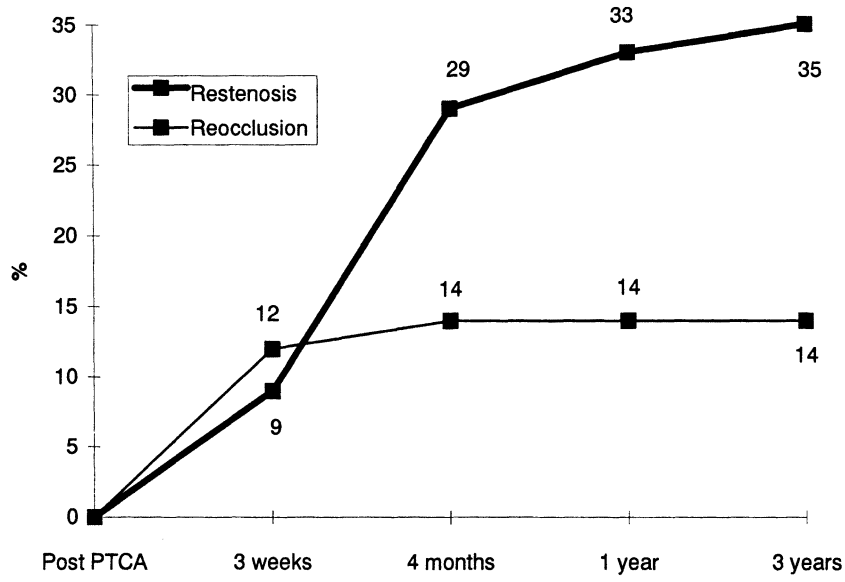

Fig. 6. Incidence of angiographic restenosis and reocclusion in primary angioplasty patients. Reproduced with permission from ref. *35*.

Table 2
Criteria for Low-Risk
Classification in the PAMI II Study[a]

Age < 70 yr
EF > 45%
One- or two-vessel disease
Native culprit artery
Successful PTCA
No (recurrence of) ventricular arrhythmia

[a]Abbreviations: PTCA, percutaneous transluminal coronary angioplasty; EF, ejection fraction.
Adapted with permission from ref. *36*.

The Primary Angioplasty in Myocardial Infarction (PAMI-II) investigators studied two other aspects of mechanical reperfusion for AMI *(36)*. They tested the hypotheses that early angiography helps to stratify the risk of in-hospital death in patients with AMI, and that intraaortic counterpulsation (IABP) may improve the patency of the infarct-related artery after primary angioplasty in patients at high-risk for recurrent ischemia. Within 12 h of symptom onset of acute ST-elevation myocardial infarction, 1099 patients were identified, including fibrinolytic therapy ineligible patients. Of the 908 patients entered in the study, emergency angiography identified 437 and 471 patients at high and low risk, respectively, for in-hospital death. The criteria for assignment to low-risk status are shown in Table 2, and the study protocol is detailed in Fig. 7. The in-hospital event rates are shown in Fig. 8. Importantly, there were no deaths or reinfarctions in the week following discharge in low-risk patients randomized to early discharge without functional testing. Early angiography and angioplasty indeed identified a low-risk group of

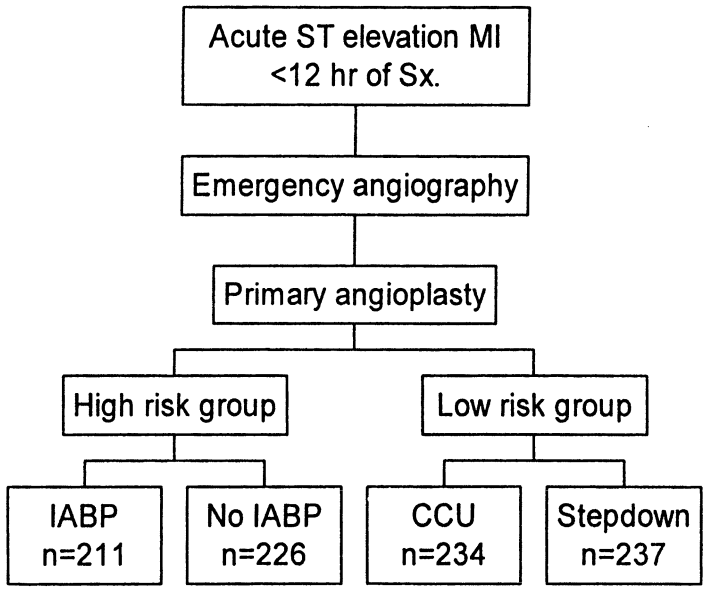

Fig. 7. PAMI-II study design. Primary endpoint: composite of death, reinfarction, reocclusion of infarct artery, stroke, new-onset heart failure, or sustained hypotension by hospital discharge. Adapted with permission from ref. *36*.

patients with a mortality comparable to that of elective angioplasty patients. IABP did not confer a significant advantage in death, reinfarction, or reocclusion in the high-risk patients. Nevertheless, IABP was associated with a significantly lower need for repeat angiography and repeat PTCA of the infarct-artery in these patients.

RANDOMIZED STUDIES OF PRIMARY ANGIOPLASTY VS FIBRINOLYTIC THERAPY

Table 3 details the important characteristics of the 10 randomized studies (approx 2600 patients) *(16,17,37–44)* comparing primary angioplasty with various regimens of intravenous fibrinolytic therapy, according to time of publication. All patients were candidates for both interventions and received at least 100 mg of aspirin and an antithrombin agent for at least 2 d after the intervention. Consistently, the first balloon inflation occurred later (17–59 min) than the initiation of lytic therapy. The principal end points were assessed at hospital discharge, or 30 d. Some of the studies provided additional follow-up up to 2 yr.

Although all these studies examined the relative benefit of the two strategies in similar clinical scenarios, the study size and the rigor of angiographic and clinical end-point assessment varied greatly.

The recently published GUSTO-IIb substudy *(16)* was the largest and most contemporaneous of these trials, accounting for 40% of all randomized patients. Patients presenting within 12 h after the onset of an AMI without contraindications for either fibrinolytic therapy or primary angioplasty were randomly allocated to one of the two strategies, after receiving chewable aspirin and a thrombin inhibitor. Seventy-five percent of the patients were male, and 90% were in Killip class I. The lytic and angioplasty patients had similar intervals from symptom onset to presentation (1.8 and 1.9 h, respectively), but the time

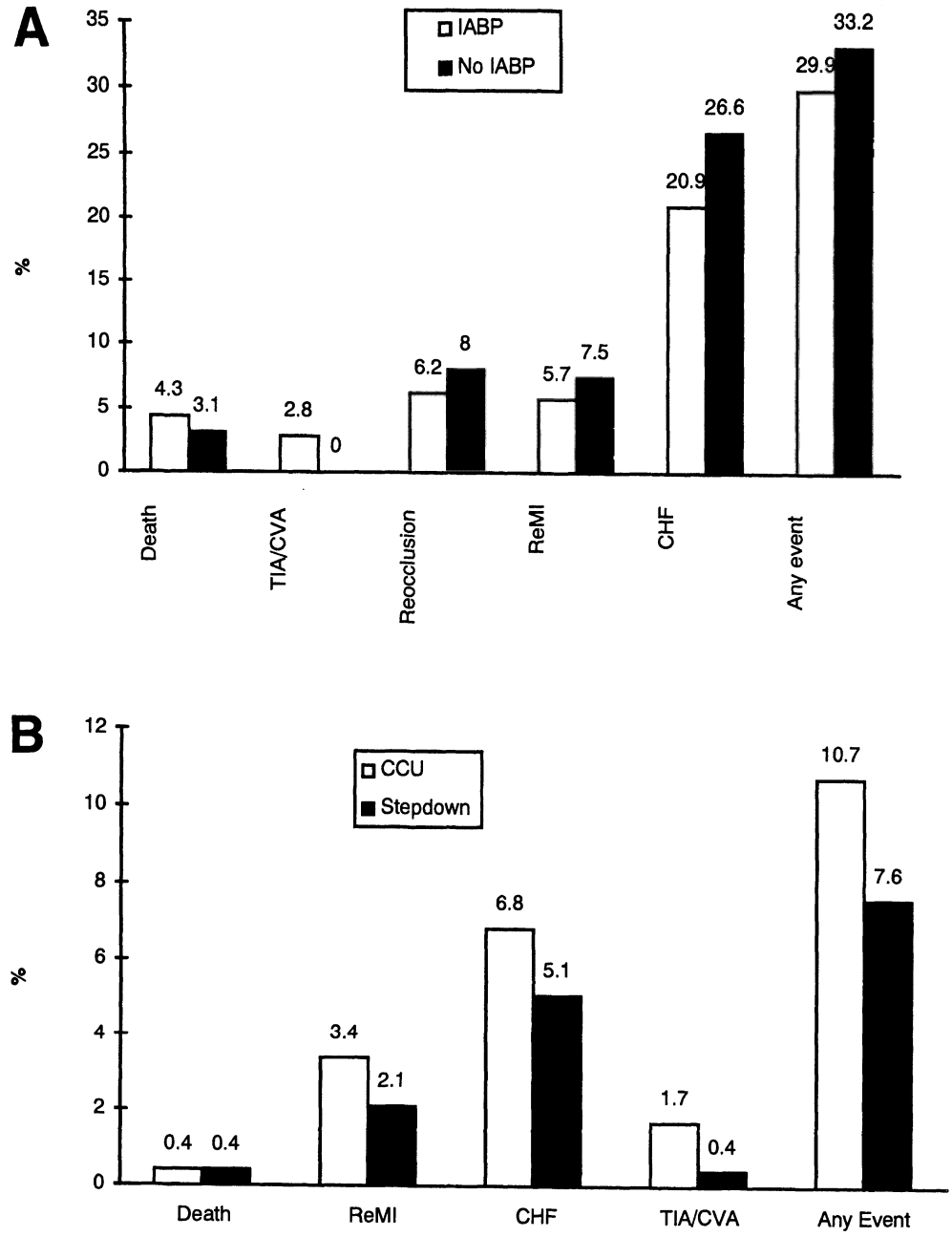

Fig. 8. (A) In-hospital event rates for high-risk patients treated with IABP (white bars) or no IABP (black bars) in the PAMI II study. Adapted with permission from ref. *36*. **(B)** In-hospital event rates for low-risk patients randomized to intensive care (white bars) or stepdown (black bars) care in the PAMI II study.

to treatment was 50 min longer in the angioplasty group. The primary end-point of 30-d death, reinfarction, or nonfatal stroke was significantly reduced by primary angioplasty, compared with lytic therapy (Fig. 9). This benefit was less impressive than that suggested by previous smaller studies (see below). The difference can be attributed to the rigorous, independent adjudication of angiographic and clinical end points in

Table 3
Randomized Studies of Primary Angioplasty vs Fibrinolytic Therapy[a]

Author (ref)	Lytic		Duration of symptoms (h)	First end-point time (d)	PTCA		Lytics	
	Agent	Time (h)			No. of patients	Time to (min)	No. of patients	Time to (min)
De Wood *(37)*	tPA	4	N/A	30	46	126	44	84
Grines et al. *(17)*	tPA	3	<12	Discharge	195	60	200	32
Zijlstra et al. *(38)*	SK	1	<6	Discharge	152	62	142	30
Gibbons et al. *(40)*	tPA	4	<12	Discharge	47	45	56	20
Ribeiro et al. *(39)*	SK	1	<6	Discharge	50	238	50	179
Zijlstra et al. *(44)*	SK	1	<6	30	45	68	50	30
Ribichini et al. *(43)*	tPA	1.5	<6	Discharge	41	40	42	33
Grinfeld et al. *(42)*	SK	1	<12	30	54	63	58	18
GUSTO IIb *(16)*	tPA	1.5	<12	30	565	114	573	72
Garcia et al. *(41)*	tPA	1.5	5	30	95	84	94	69

[a]Abbreviations: tPA, tissue-type plasminogen activator; SK, streptokinase; PTCA, percutaneous transluminal coronary angioplasty.

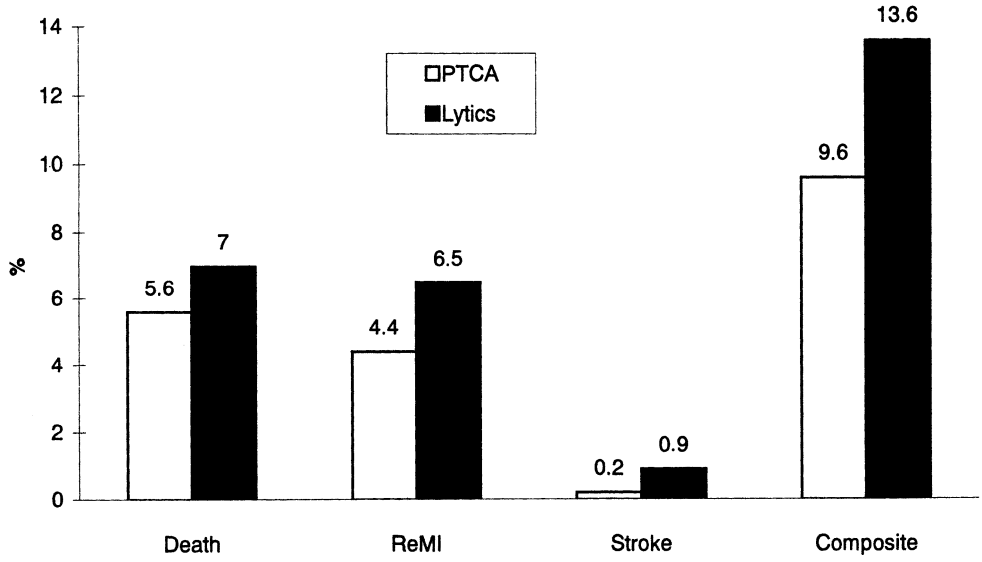

Fig. 9. Thirty-d event rates in the GUSTO IIb primary angioplasty (white bars) and lytic (black bars) patients: GUSTO IIb angioplasty substudy.

GUSTO-IIb, the larger size of this study, the use of a more potent fibrinolytic regimen, and perhaps the inclusion of centers more representative of the current practice of primary angioplasty, in terms of procedural success and ability to restore flow within 60–90 min from presentation. Interestingly, the difference in the outcome became evident only 5–7 d after randomization, suggesting that the advantage of angioplasty was due to reduction in recurrent ischemic events, rather than in immediate mortality. These findings were divergent from the earlier studies, in which the advantage of primary angioplasty manifested in the first 48 h.

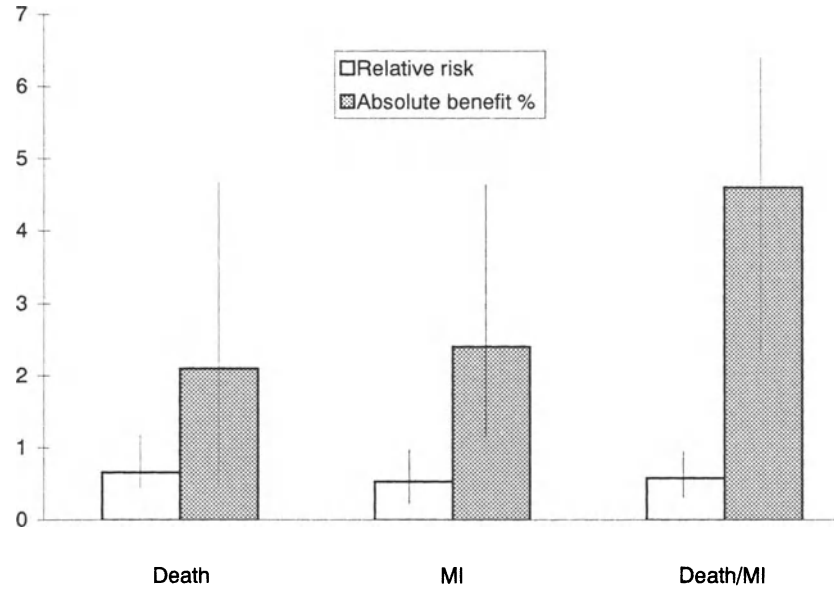

Fig. 10. Relative (white bars) and absolute (gray bars) risk reduction of death, reinfarction and death plus reinfarction in 10 randomized trials of primary angioplasty vs lytic therapy. Adapted with permission from ref. *45*.

As expected, on-site evaluation of the quality of postprocedure flow overestimated the actual rate of TIMI 3 flow determined by the core laboratory by 12% (85 vs 73%, respectively). The GUSTO-I angiographic substudy observations were confirmed in this angioplasty trial with respect to the correlation between completeness of reperfusion and 30-d mortality, and the lack of benefit afforded by "partial" or TIMI 2 flow. Patients with TIMI 3 flow had a 1.6% mortality rate, compared with 19.9, 14.3, and 21.4% for TIMI 2, 1, and 0, respectively.

According to the overview by Weaver et al. *(45)*, compared with fibrinolytic therapy, primary angioplasty reduces the relative risk of death by 34%, death plus nonfatal reinfarction by 42%, and nonfatal reinfarction by 47%, by hospital discharge, or 30 d. Among the various small trials, there were no differences in outcome among the lytic agents and regimens used. The absolute reductions for the above-mentioned end points were 2.1, 4.6, and 2.4%, respectively (Fig. 10). Except for GUSTO-IIb, the studies were insufficiently powered to show a statistically significant difference in mortality, or death and reinfarction, respectively, as demonstrated in Fig. 11.

Importantly, compared with lytic therapy, the rate of stroke was reduced by 65% with primary angioplasty, and the incidence of hemorrhagic stroke was even more drastically affected (93% relative reduction). The difference in stroke was particularly striking in the trials using tissue-type plasminogen activator (tPA) (0.6% for PTCA vs 2.1% for tPA) and less impressive in those using streptokinase (1.0% for PTCA vs 1.6% for streptokinase). Major bleeding episodes (other than intracranial) associated with blood product transfusions were as common in the angioplasty patients (8.8%) as in the lytic group (8.4%).

It should be noted, however, that the rate of hemorrhagic stroke in rigorous, large-scale thrombolytic trials has been consistently much less than in the small PTCA comparative trials. The reason(s) for this discrepancy is not known.

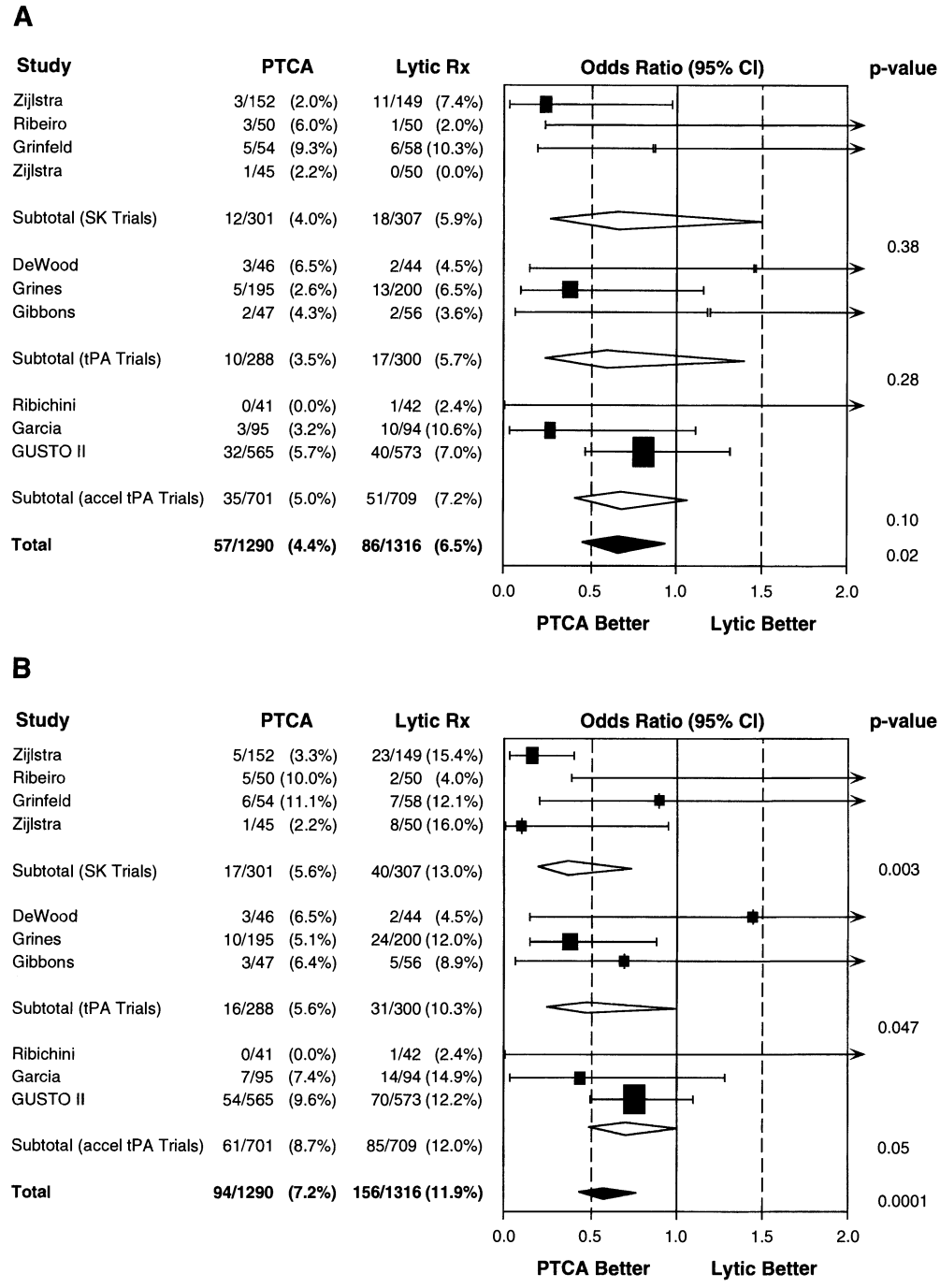

Fig. 11. Relative risk reduction in death **(A)** and death plus reinfarction **(B)** in individual randomized trials of primary angioplasty vs lytic therapy. Reproduced with permission from ref. *45*.

Despite convincing short-term benefit afforded by primary angioplasty, there appears to be an attrition of this advantage in the first year following the index infarction. In the GUSTO-IIb angiographic substudy *(16)*, the composite end point of death, reinfarction, or disabling stroke occurred in 13.3 and 15.7% of the angioplasty and lytic patients, respectively, at 6 mo, a statistically insignificant 11% relative risk reduction. In the

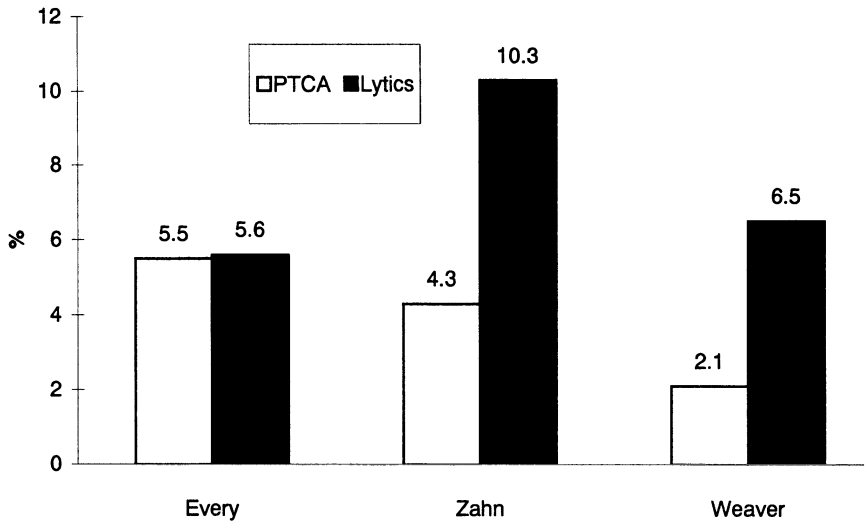

Fig. 12. Overview of in-hospital mortality in comparative randomized and observational studies of primary angioplasty (white bars) and lytic therapy (black bars). Data from refs. *31*, *34*, and *45*.

PAMI-I trial *(46)*, treatment with angioplasty, compared with tPA, significantly reduced the incidence of death or reinfarction from 17 to 8.2% at 6 mo after randomization. By 2 yr, percutaneous or surgical revascularization had been performed significantly more frequently in the lytic group. Nonfatal reinfarction also tended to occur more commonly in the lytic patients *(47)*. In the Zwolle trial, the rate of recurrent ischemic events at 3 months was 8% in the angioplasty group. At 1 yr, survival was 94 and 90% in the PTCA and streptokinase groups, respectively, and cumulative revascularization rate was 17 and 23%, respectively.

Understanding the Discrepancies Between Controlled and Observational Studies

It is obvious from the data presented above that, compared with fibrinolytic therapy, the benefit of primary angioplasty in controlled, randomized trials exceeds that observed in registries and observational series. In the latter, the mortality in angioplasty patients equals or exceeds that of lytic patients, even after excluding patients in cardiogenic shock. Pooled data from the National Registry of Myocardial Infarction (NRMI) and the MITI registries, compared with the 10 randomized studies analyzed by Weaver et al. *(45)*, are shown in Fig. 12.

Anderson et al. *(48)* examined the major determinants of short-term survival in AMI patients treated with angioplasty or lytic therapy and developed a theoretical model to explain the differences in outcome. Based on their analysis, and assuming that the benefits of reperfusion are independent of the way it is achieved, time to, and completeness of reperfusion, rates of stroke and reinfarction, and operator experience can accurately explain the discrepant results of randomized trials and registries. They predicted that in an optimal practice environment, in which an accelerated tPA regimen can be administered within 25 min of presentation, the expected mortality is 6.3% at 30 d, similar to the GUSTO-I results. If expert primary angioplasty can be performed within 75 min of presentation, the expected mortality would be 5.8%, a much smaller benefit than that observed in randomized trials. Because the delay in performing primary angioplasty in

"the real world" is much greater (2–2.5 h in NRMI-2), even assuming very high TIMI 3 patency rates, the resulting increment in mortality attributed to this delay is approximately 1.4%, which eliminates much of the advantage of primary angioplasty, when performed earlier. Cannon et al. *(49)* analyzed the influence of door to balloon time on mortality in the NRMI-2 patients. Among 3648 patients, first balloon inflation was delayed by more than 2 h in 53%, and in 29% by more than 3 h. In the subset presenting within 6 h of symptom onset (2924 patients), a delay of >2 h was associated with an in-hospital mortality of 9.1%, compared with 6.9% for those treated within 1 h of presentation. As expected, for those presenting later than 6 h from symptom onset, the delay in mechanical reperfusion did not correlate with mortality.

Furthermore, the rate of TIMI 3 flow after angioplasty may vary from 73% in GUSTO-IIb to over 90% in PAMI-I. Some of these differences can be explained by operator experience and variability in determination of flow grade among angiographic laboratories. There are insufficient data on the actual proportion of salvaged myocardium, particularly with primary angioplasty, to be able to provide a mechanistic explanation for the differences in outcome. Thus, most of the "discrepancy" in results is actually consistent with the circumstances in which they are obtained.

TARGETED SUBGROUPS

Whereas primary angioplasty is an alternative to lytic therapy in most reperfusion candidates, certain subgroups of patients are particularly suited for immediate angiography and primary angioplasty, in view of the poor outcome or the hazard associated with lytic therapy.

Absolute and Relative Contraindications for Lytic Therapy

In a pooled analysis of eight trials of fibrinolytic therapy, enrolling more than 50,000 patients, only one-third of those screened (range 9–51%) were eventually enrolled. Few patients have absolute contraindications to lytic therapy, such as recent bleeding episodes, major surgery, or previous stroke with residual neurologic deficits. The common reasons for exclusion were more relative contraindications, such as presentation >6 h from symptom onset (13–37%), advanced age with its inherent increased risk of intracranial hemorrhage (2–31%), and lack of "classical" electrocardiographic findings (11–62%) *(50,51)*. Although the Worcester Heart Attack Study Group reported a 175% increase in the use of lytics in AMI between 1986 and 1993, still only 25.5% of those screened received the therapy *(52)*. Subjects younger than 55 yr were 4.5 times more likely to receive it than patients older than 75 yr. Because it is well established that ineligibility for thrombolytic therapy is associated with a four- to eightfold increase in 30-d mortality *(53)*, such patients should be considered for mechanical reperfusion.

Cardiogenic Shock

Cardiogenic shock is the result of substantial loss of myocardial function (>40% of left ventricular mass) in 80%, or the development of mechanical complications in 20% of those in whom it occurs *(54,55)*. Historically, cardiogenic shock was associated with an exceedingly poor prognosis, with mortality averaging 70% *(55–57)*. Temporizing measures, such as intraaortic counterpulsation and inotropic support do not affect survival in the absence of reperfusion. Overall, fibrinolytic agents have not favorably affected

the survival in these patients, probably because of poor delivery of the drug to the infarct site. Patients with cardiogenic shock were infrequently enrolled in fibrinolytic trials. In GISSI-I *(7)* 146 and 134 patients with cardiogenic shock (Killip class 4) were randomized to streptokinase and placebo, respectively. The mortality at 21 d was 70% in both groups. By contrast, two other placebo-controlled studies documented a modest mortality reduction in patients assigned to fibrinolysis, compared with placebo *(58,59)*. In the GISSI-II International Study *(60)* the in-hospital mortality of patients with cardiogenic shock assigned to tPA (80 patients, 100 mg over 3 h), or streptokinase (93 patients) was 78 and 65% ($p = 0.04$), respectively. In GUSTO-I, 315 patients presented in cardiogenic shock and were evenly distributed among the four lytic regimens *(61)*. Patients assigned to streptokinase-based regimens tended to have a lower mortality than those assigned to tPA (51 vs 57%, respectively). In selected patients who underwent rescue angioplasty, the survival was improved (43%), compared with those who did not undergo revascularization (77%). Obviously, patients who did not undergo emergency angiography and revascularization were more likely to be critically ill than those referred for intervention.

Mechanical reperfusion for patients with cardiogenic shock has been studied mostly in observational trials. Among 539 patients in 16 studies (7–81 patients each) *(62)*, the average mortality was 50%. When reperfusion was successful, the fatality rate was only 35%, whereas failure to restore flow was associated with a mortality of 84%. None of these studies had an adequate control or an alternative therapy arm. An international registry *(55)* prospectively followed 251 patients with cardiogenic shock (8% owing to mechanical complications). Among those selected on clinical grounds for emergency angiography and revascularization, the mortality was 51%, compared with 85% in those treated conservatively.

Thus, because of the generally unsatisfactory results of fibrinolytic therapy and the potential for improved outcome with mechanical reperfusion, this subset of patients represents an important target for primary angioplasty.

Prior Bypass Surgery

Prior bypass surgery patients tend to have a less favorable result with lytic therapy, especially when saphenous vein grafts are the culprit conduit. Preliminary analysis of the GUSTO-I patients revealed a higher mortality rate in patients with than without prior bypass surgery treated with lytics at 30 d (10.7 vs 6.7%, respectively). Although not proved in clinical randomized trials, mechanical revascularization, when available promptly, may improve outcome in this subgroup.

Diagnostic Uncertainty: Early Triage Angiography

Some patients present with atypical symptoms or signs, which preclude immediate administration of fibrinolytic therapy, because of the uncertainty that a myocardial infarction is evolving. Emergency angiography, with subsequent primary angioplasty on identification of a culprit artery, may afford an immediate diagnosis and therapy and may eliminate the risk of exposing the patient to an unneeded and potentially dangerous therapy. McCullough et al. *(63)* reported on a randomized study of early triage angiography vs conservative therapy in 197 patients ineligible for lytic therapy. Revascularization was performed in 52 and 35% of the two groups, respectively. The early angiography group had a significantly lower rate of recurrent ischemia (14 vs 33%) and markedly reduced hospital stay.

Availability of On-Site Facilities

Approximately 20% of U.S. hospitals are equipped with the facilities and personnel necessary to provide primary angioplasty 24 h/d. Patients having onset of AMI in such an institution, or being able to reach it rapidly, are obvious candidates for mechanical revascularization. More controversial is the transfer of candidates for either pharmacologic, or mechanical therapy from an institution not geared to primary angioplasty to one able to offer this service. Rigorous data concerning this issue are currently being gathered in studies randomizing patients to airborne transfer to another institution for PTCA vs lytic therapy administered locally, followed by transfer if reperfusion fails. For patients who present with cardiogenic shock, or with absolute contraindications to fibrinolytic therapy, consideration for such a transfer is vital.

Traditionally, primary PTCA was performed only in institutions with surgical backup. Such an approach is supported by the frequent incidence of multivessel disease discovered during acute angiography, as well as the need to salvage patients with unsuccessful PTCA. Recent advances in equipment and techniques, especially coronary stents, have minimized the incidence of unsuccessful angioplasty and led to a more aggressive approach, favoring immediate intervention over the risk of transferring an unstable patient. This strategy requires additional study.

TECHNICAL ASPECTS

The patient with an evolving myocardial infarction should be brought to the catheterization suite as soon as the decision to perform emergency angiography has been reached. Aspirin (at least 325 mg) and 5000 U of heparin should be administered, while obtaining at least two intravenous access lines. Larger doses of heparin may be detrimental if potent platelet inhibitors are to be administered later during the procedure. Intravenous nitroglycerin and morphine are helpful in controlling symptoms, if hemodynamic status permits. Both groins should be prepared for access, in case intraaortic counterpulsation or percutaneous bypass are needed. Eight French arterial and venous sheaths should be placed with meticulous care to prevent access site hematoma. Regular contrast agents can be used, unless severe left ventricular dysfunction or pulmonary edema exist. Nonionic preparations have been associated with enhanced platelet aggregability *(64)*. A left ventriculogram, preceded by measurement of left ventricular end-diastolic pressure, is very helpful in assessing degree of dysfunction before reperfusion and unsuspected mechanical complications. It is contraindicated in the presence of cardiogenic shock or severe respiratory distress. The suspected noninfarct artery should be visualized first to assess extent of coronary disease and presence of collateral flow. Finally, the suspected infarct-related artery should be engaged with a guiding catheter, in anticipation of primary angioplasty. If anatomy is suitable, additional heparin is administered to obtain an activated clotting time >300 s. The size of the occluded artery can be estimated from its proximal portion. Usually a soft tip wire is sufficient to cross the thrombus-laden lesion. Rarely, a stiffer wire or additional support with a balloon are needed for crossing. Intubation of branches is helpful in ensuring intraluminal guidewire advancement. If doubt persists, the balloon can be advanced distally, and a small amount of contrast can be injected via the wire port to assess the distal vessel. Next, the balloon (frequently undersized) is placed across the total obstruction and inflated at low pressure for brief periods to restore flow. Balloon deflation may result in "reperfusion arrhythmia," especially with inferior infarcts. Defibrillation may be necessary, and the equipment should be readily

available. Rarely, the only way to interrupt the electrical storm is to reinflate the balloon and administer antiarrhythmic therapy. After antegrade flow is restored, the vessel size can be better evaluated and appropriate adjustments in balloon size made. It is important to administer intracoronary nitroglycerin and assess the completeness of flow restoration. If TIMI 3 flow is not present, additional dilation, stent implantation (discussed later), or placement of an IABP may be indicated. The lack of TIMI 3 flow may be attributed to a significant residual epicardial stenosis, a dissection that is difficult to appreciate, or dysfunction of the small distal vasculature from microembolization, edema, or permanent ischemic damage. Frequently these adverse factors coexist. Persistent attempts to correct the epicardial vessel problem and large doses of nitroglycerin and adenosine may ultimately improve flow.

According to the patient's hemodynamic status, an additional ventriculogram may be obtained to assess improvement in previously dysfunctional segments. A pulmonary artery catheter may be placed to facilitate hemodynamic management in patients with complicated procedures. Transvenous temporary pacemakers are rarely needed for treatment of persistent bradycardia or high-degree atrioventricular block. Intravenous heparin should be continued for 24–48 h, preferably after sheath removal. If the angioplasty result is less than optimal, many operators prefer to continue the heparin infusion without interruption for sheath removal for at least 24 h. Standard adjunctive pharmacology, coronary risk factor modification, and rehabilitative care for post-MI patients are subsequently provided.

If the culprit vessel is a venous bypass graft, local infusion of a fibrinolytic agent may be beneficial, although the risk of distal embolization is high. Platelet activation caused by the lytic agent can further exacerbate the thrombotic tendency. The transluminal extraction catheter has been utilized *(65)* to facilitate thrombus extraction. One hundred patients were prospectively studied, after experiencing lytic failure (40%), postinfarct angina (28%), or cardiogenic shock (11%). A large thrombus was observed in 66% of the patients. The culprit vessel was an occluded saphenous vein bypass in 29%. Recanalization of the infarct artery was achieved in 94%. In-hospital death occurred in 5%. At 6 mo, target vessel revascularization was necessary in 38%, and a disappointing angiographic restenosis rate of 68% was noted. These results tempered the use of this device in the setting of AMI. Its use may be rejuvenated by the combination of platelet GPIIb/IIIa receptor blockade and stenting following thrombus extraction. More recently, a new suction device (Angiojet) has been introduced and is currently in clinical trials.

In 5–10% of patients *(17)*, emergency angiography reveals either a patent infarct artery without severe stenosis, or severe and diffuse coronary disease (including left main coronary stenosis) that is better suited for surgical revascularization. For the latter case, primary angioplasty may still be indicated, if feasible, to prevent myocardial damage and enable the performance of semielective coronary bypass surgery and use of arterial conduits.

ADVANCES: DEVICES AND PHARMACOLOGY

Although the immediate results of primary angioplasty are highly satisfactory, the rate of restenosis and recurrent clinical events is still disappointing. Preservation of the initial angiographic result, in conjunction with aggressive coronary risk factor modification, is the ultimate goal of postangioplasty care.

Elective coronary stent implantation has become extremely popular in the last 2–3 yr because this device has been shown to reduce angiographic restenosis and the need for

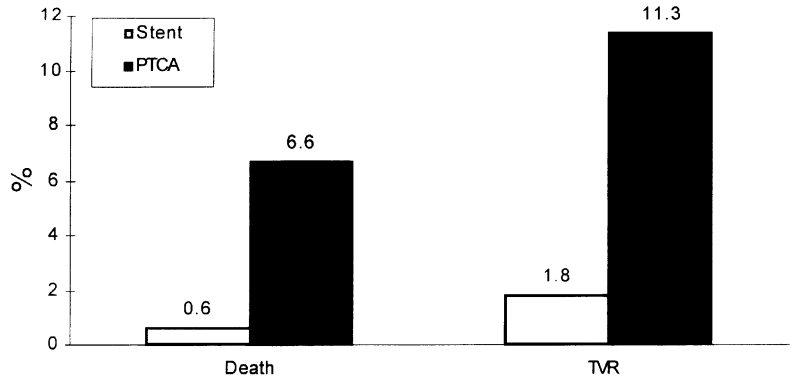

Fig. 13. Overview of in-hospital mortality and urgent target vessel revascularization (TVR) in 312 patients treated with stents (white bars) or balloon angioplasty (black bars) during primary angioplasty.

repeat target vessel revascularization *(66,67)*. The placement of such a device in the highly thrombogenic milieu of a recently ruptured arterial plaque was initially considered unsafe. Recently, better stent deployment techniques and optimized anticoagulation regimens have led to revised scrutiny of this notion. Four controlled studies randomly allocated patients treated with primary mechanical revascularization for AMI to either balloon angioplasty or primary stenting *(68–71)*. Altogether, 312 patients were enrolled in these small series. An overview of the in-hospital death and urgent revascularization rates is provided in Fig. 13. In the randomized comparison of primary stenting with heparin-coated Palmaz-Schatz stent vs primary PTCA (Stent-PAMI trial), 900 patients were enrolled at 62 centers within 12 h of symptom onset. Although the residual stenosis in the infarct artery was improved by stenting (12 vs 24%), there was no significant difference in death ($p = 0.15$), or reinfarction ($p = 0.29$) at 30 d. Urgent repeat revascularization was significantly reduced ($p = 0.006$) *(71a)*. Angiographic and clinical follow-up at 6–12 mo appears promising. Moreover, it appears that, at least initially, planned stenting is superior to both bailout stenting, or stenting following suboptimal angioplasty. In the Stenting in Acute Myocardial Infarction (STAMI) trial *(72)*, the death rate was 3.3% for planned stenting, compared with 6.5 and 9.7% for provisional and bailout stenting, respectively. The other major complications, including need for bypass surgery, were significantly reduced in the planned stenting group. After primary stenting of 55 patients, the same investigators reported a reinfarction rate of 3.8% and target vessel revascularization in 12% at 6 mo follow-up. The PAMI investigators recently completed a pilot study *(73)*, designed to test the efficacy and safety of stenting in primary angioplasty patients with adequate anatomy, among 201 patients treated within 12 h of symptom onset. In 75% of patients, stenting was deemed anatomically feasible and was successful in all but three patients (98%). The main reason for ineligibility for stenting was infarct vessel size <2.5 mm. Death (0.7%), reinfarction (1.4%), and repeat intervention (1.4%) were distinctly uncommon among the stented patients. There were no instances of out-of-hospital stent thrombosis.

Advances in adjunctive pharmacology have also influenced the management of primary angioplasty patients. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study *(74)*, among 2,099 patients referred for high-risk angioplasty, 64 were evolving an AMI. As shown in Fig. 14, the patients treated with bolus and

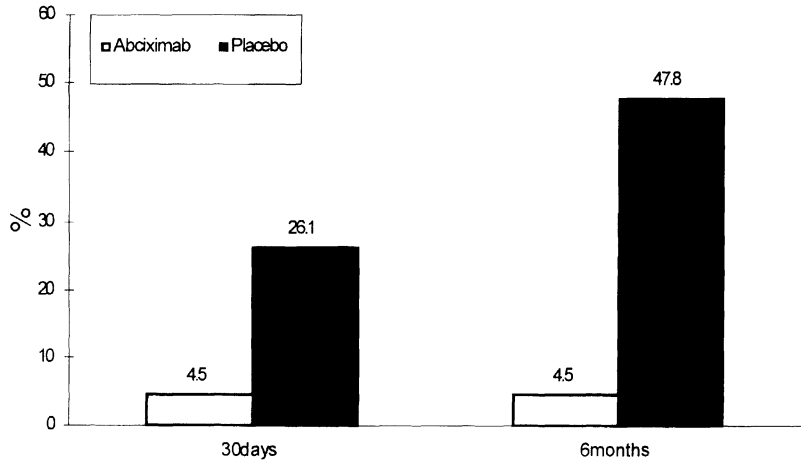

Fig. 14. Thirty-d and 6-mo outcome (death, MI, or revascularization) in primary angioplasty patients receiving bolus and infusion of abciximab (white bars) or placebo (black bars) in the EPIC trial. Adapted with permission from ref. *74*.

infusion of the potent platelet glycoprotein receptor IIb/IIIa abciximab had a dramatic reduction in the composite end point of death, reinfarction, and need for repeat revascularization both at 30 d, and 6 mo. This important observation led to the ReoPro in Acute Myocardial Infarction Primary PTCA Organization and Randomized Trial (RAPPORT) study. Within 12 h of the onset of 483 patients were treated with primary angioplasty and were randomly allocated to bolus and 12-h weight-adjusted infusion of abciximab or matching placebo. Abciximab significantly reduced the incidence of death, reinfarction, and urgent revascularization (9.9 vs 3.3%, $p = 0.003$ at 7 d; 11.2 vs 5.8%, $p = 0.03$ at 30 d) *(74a)*.

Furthermore, new strategies of "facilitated" angioplasty are currently under investigation in various trials. Combination of low-dose fibrinolytic therapy (25–50% of usual dose) with potent platelet glycoprotein receptor blockade (abciximab or Integrilin) may provide initial patency and facilitate immediate angioplasty, without the adverse effects of full-dose lytics, especially the enhanced platelet aggregability. If it is proved beneficial, this approach may further expedite the care of patients with AMI.

ECONOMIC ASPECTS

The expense incurred in treating patients with primary angioplasty is composed of the cost of maintaining a 24-h availability for this procedure and the cost of the equipment and resources consumed during the actual procedure. Lieu et al. *(75)* determined that the additional cost of the procedure is only $1597 if the hospital already has 24-h coverage for acute coronary interventions. By contrast, if night call for the support personnel were a new expense, the cost would increase to at least $3206 for each procedure (assuming 200 patients/yr). A hospital planning to build a new catheterization suite to provide primary angioplasty services would spend $3866–14,339 for the same volume per case.

From the PAMI-I study, Stone et al. *(76)* reported the cost analysis of 90% of the patients enrolled in the study. Total hospital charges (including professional fees) were similar in the PTCA and tPA groups. At a mean follow-up of 2.1 yr, there were no significant differences in late events, such as death, reinfarction, revascularization, or

recurrence of unstable angina, suggesting similar late resource consumption. Similar results were obtained from the Dutch primary angioplasty study *(77)*. In the Mayo Clinic randomized trial of primary angioplasty and lytic therapy, the in-hospital costs were similar in the two groups, but the late costs were increased in the lytic group, because of increased need for angiography and revascularization *(40)*.

In the PAMI-II study, analysis of cost in a small subset of low-risk patients revealed marked savings in those allocated to early discharge, compared with standard care following primary angioplasty.

The GUSTO-IIb Investigators reported the cost analysis in a subset of patients enrolled in the primary angioplasty study (374 of 1138) *(78)*. The costs were remarkably similar for angioplasty and tPA patients both in-hospital and at 6 mo.

By contrast, the large observational series from the MITI registry *(31)* suggested that both the in-hospital cost and subsequent resource utilization over 3 yr were higher in the angioplasty compared with the lytic group.

LIMITATIONS

To make percutaneous mechanical revascularization strategy preferable to fibrinolytic therapy in most patients with an evolving myocardial infarction, the following limitations and obstacles have to be overcome:

1. Need for dedicated expert personnel 24 hours a day.
2. A longer delay to reperfusion in most instances, especially during off-hours.
3. A high rate of restenosis and need for repeat target vessel revascularization.
4. Intensive resource utilization, especially with the more widespread use of coronary stents and potent platelet inhibitors.

These limitations have to be weighed against the potential for more complete reperfusion, avoidance of recurrent ischemic events, faster hospital discharge, and better rehabilitation afforded by primary PTCA. These constraints obviously do not apply to patients who are not candidates for lytic therapy.

CURRENT GUIDELINES

Ryan et al. *(79)* have recently updated the comprehensive recommendations for the management of AMI. Under these guidelines, primary angioplasty is strongly advised (class I) as an alternative to fibrinolytic therapy, "only if performed in a *timely* fashion by individuals skilled in the procedure (>75 PTCA cases/yr) and supported by personnel in high-volume centers (>200 PTCA cases/yr)." Less enthusiastic support is offered for its use in patients at risk of bleeding, or those in cardiogenic shock, or those who do not qualify for lytic therapy for a reason other than bleeding risk. The authors further stress the need to restore flow within 90 min of diagnosis and have consistent high rates of success (i.e., TIMI 3 flow in at least 90% of patients, emergency coronary artery bypass grafting in <5%, and overall mortality <12%).

CONCLUSIONS

Restoration of brisk antegrade flow in the infarct-related artery is the principal goal in the initial phase of management of AMI. Consequently, the choice of therapy needs

to be tailored to the patient's presenting signs and symptoms, institutional capabilities, timing of presentation, existing comorbid conditions, and patient and physician preference.

The following statements and recommendations, assume "ideal" circumstances and need to be adjusted to the local conditions. There are insufficient data to weigh the benefit of surgical backup (in all institutions performing primary angioplasty) against the delay created sometimes by trying to secure it.

1. Primary angioplasty is the preferred reperfusion strategy in patients who present to an experienced facility, in which the procedure can be performed (i.e., TIMI 3 flow achieved) within 60 and no later than 90 min of presentation.
2. Primary angioplasty is the preferred strategy in patients with cardiogenic shock presenting to an institution with the appropriate facilities. Elsewhere, a trial of lytic therapy may be warranted, while transfer to a catheterization laboratory for possible rescue angioplasty is arranged.
3. Primary angioplasty should be strongly considered in patients with previous bypass surgery or large infarctions (anterolateral, or extensive inferoposterior involvement), especially with hemodynamic compromise. This is predicated on the ability to perform emergency angiography and angioplasty within 60–90 min of presentation.
4. Primary angioplasty should be strongly considered in all patients with ST-elevation AMI and absolute contraindications to lytic therapy (bleeding hazard), even if its performance may mandate rapid hospital transfer with appropriate medical supervision.
5. Emergency angiography and angioplasty (when appropriate) should be undertaken in patients with non-ST-elevation infarctions or long presentation delay (>12 h), or in cases of atypical presentations and diagnostic uncertainty.

Future developments in the field of interventional cardiology are likely to broaden these indications. Sophisticated combination pharmacotherapy, consisting of lytics and platelet inhibitors, may become the "facilitating" regimen before mechanical revascularization, performed soon after their administration. Such a paradigm would ensure rapid and complete revascularization, while minimizing myocardial loss and hospital stay, reducing short-term recurrent ischemic events, and accelerating recovery.

Until these improvements materialize, fibrinolytic therapy remains the mainstay of therapy for most patients with AMI, who are candidates for reperfusion therapy.

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12 Antiplatelet and Antithrombotic Therapy

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INTRODUCTION

The contemporary pharmacologic treatment of acute myocardial infarction (AMI) includes reperfusion via a thrombolytic agent as well as adjunctive therapy with aspirin and heparin *(1)*. Despite the advances made, current management is limited by the fact that infarct-related artery patency is achieved in only 60–80% of patients at 90 min and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow is achieved in only 30–55% of patients *(2)*. Moreover, even after successful thrombolysis, reocclusion occurs in 5–10% of patients and is associated with increased morbidity and mortality *(2,3)*.

The rationale behind adjunctive therapy with aspirin and heparin is to inhibit activation of platelets and the coagulation cascade, both of which play a fundamental role in the pathogenesis of AMI *(4,5)*. However, there are several important limitations to current antiplatelet and antithrombotic agents. Aspirin is only a weak inhibitor of platelet activation, allowing platelet activation to occur by cyclooxygenase-independent pathways *(6)*. Persistent platelet activation leads to platelet aggregation, creating platelet-rich coronary thrombi, which are relatively resistant to thrombolysis *(7)*, and to further stimulation of the clotting cascade by providing a catalytic surface for coagulation factor interactions *(8)*.

Heparin has several major limitations as an ideal anticoagulant. First, although heparin is able to inactivate fluid-phase thrombin, it is unable to inactivate fibrin monomer-bound *(9)* or clot-bound *(10)* thrombin. Second, heparin is inactivated by platelet factor 4 and heparinases, both of which are released by activated platelets *(11)*. Third, heparin is a heterogeneous mixture with highly variable pharmacokinetics *(12)*. Fourth, heparin requires the presence of antithrombin III *(12)*.

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Along with these theoretical limitations of our current adjunctive therapy, there is evidence that a hypercoagulable state exists during acute coronary syndromes that may persist as far as 6 mo out *(13)*. Furthermore, thrombolysis may even potentiate this hypercoagulable state. Thrombolytic therapy has been shown to cause platelet activation *(14,15)*, increased thrombin generation *(16–18)*, and increased thrombin activity *(19,20)*, which heparin may not be able to suppress adequately *(17,21–23)*. The mechanisms underlying this hypercoagulable state and its potentiation by thrombolysis are incompletely understood, but they may involve clot digestion, leading to thrombin liberation *(24)*, reexposure of prothrombotic lesions, or direct effects on the coagulation cascade *(25)*.

Thus, research efforts have focused on developing new antiplatelet and antithrombotic agents that are capable of overcoming the above limitations and achieving higher rates of infarct-related artery patency and lower rates of reocclusion, thereby enabling us to reduce the morbidity and mortality still associated with AMI.

PLATELET INHIBITION

Platelet Activation and Aggregation

Platelets play a key role in initiating coronary artery thrombosis *(4–6)*. Damage to the vessel wall exposes the subendothelial matrix and allows platelet adhesion through glycoprotein (GP) Ib binding to von Willebrand factor (vWF), GP Ia binding to collagen, and other adhesion molecule interactions *(26)*. Platelets can then be activated by a variety of agonists including thrombin, adenosine diphosphate (ADP), collagen, and thromboxane A_2 (TXA_2) (Fig. 1). There are three main signal transduction pathways: activation of *phospholipase C* (PLC) (e.g., by thrombin, collagen, and TXA_2) leads to an increase in intraplatelet calcium concentration and subsequent phosphorylation and activation of downstream signal transducers; activation of *phospholipase* A_2 (PLA_2) (e.g., by ADP) leads to an increase in arachidonic acid levels with subsequent conversion to TXA_2; and inhibition of *adenylate cyclase* (e.g., by epinephrine) leads to a decrease in cyclic adenosine monophosphate (cAMP), which normally antagonizes the activity of PLC *(26–29)*. Importantly, platelet activation can occur through both TXA_2-dependent and TXA_2-independent pathways. Regardless of the pathway, platelet activation results in changes in morphology *(26)*, degranulation, induction of procoagulant activity *(8)*, and activation of the GP IIb/IIIa receptor *(27)*. The final step, platelet aggregation, occurs when fibrinogen molecules bind to the activated GP IIb/IIIa receptor and connect platelets to one another *(30)*. Thus, platelet inhibition can occur by interfering with any one of these steps (Fig. 1 and Table 1) *(31–33)*.

Cyclooxygenase Inhibitors

Aspirin

Pharmacology. Aspirin irreversibly inhibits cyclooxygenase (CO) by acetylating a serine residue at position 529 of the CO polypeptide *(34,35)*. CO converts arachidonic acid into the eicosanoid prostaglandin G_2 (PGG_2), which is the precursor of PGH_2. PGH_2 is converted into either prostacyclin (PGI_2) by prostacyclin synthase or TXA_2 by thromboxane synthase. Which of the two eicosanoids is synthesized depends on whether prostacyclin synthase or thromboxane synthase predominates; the former predominates in endothelial cells and the latter in platelets *(36)*. Because platelets lack the biosynthetic machinery to synthesize new proteins, aspirin inhibits thromboxane synthesis for the life

span of the platelet (approximately 10 d). Conversely, vascular endothelial cells can generate new CO and therefore the duration of aspirin's inhibitory effect on prostacyclin synthesis may be shorter *(37)*. Clinically, this translates into aspirin acting as an antiplatelet and antithrombotic agent.

However, as thromboxane acts only on one of the platelet activation pathways, aspirin is unable to inhibit platelet activation by mediators such as thrombin that can utilize TXA_2-independent pathways. Interestingly, some preliminary evidence shows that aspirin may have an antithrombotic effect unrelated to inhibition of CO *(38,39)*.

Plasma levels of aspirin are detectable 20–30 min after administration of a single crushed or chewed dose, and platelet inhibition is achieved after approximately 60 min *(40)*. Although the current recommendations *(41,42)* call for 162–325 mg of aspirin orally daily in AMI, it appears that 100 mg of aspirin is probably sufficient to inhibit the synthesis of thromboxane almost completely in individuals both with and without atherosclerotic disease *(43,44)*. Studies with low-dose aspirin have failed to demonstrate consistently a dose at which selective inhibition of thromboxane and not prostacyclin synthesis occurs. There is evidence, however, that 75 mg of a controlled-release aspirin formulation inhibits platelet thromboxane synthesis without affecting systemic vascular endothelial cell prostacyclin production *(45)*. This may be owing to inhibition of CO in prehepatic platelets in the portal circulation, with hepatic removal of aspirin preventing systemic levels from being achieved.

Clinical data. A meta-analysis of all clinical trials involving aspirin in the treatment of AMI demonstrates that antiplatelet therapy confers statistically significant reductions in nonfatal reinfarction, nonfatal stroke, vascular death, and overall mortality *(46)*. The definitive study in this area is the Second International Study of Infarct Survival (ISIS-2) in which 17,187 patients who presented within 24 h of the onset of symptoms consistent with AMI and who had no history of stroke or gastrointestinal hemorrhage were randomized in a 2 by 2 factorial design to receive streptokinase (SK) 1.5 MU iv over 60 min, enteric-coated aspirin 162.5 mg po qd, both, or neither *(47)*. At 5 wk, treatment with aspirin reduced vascular mortality by 23% (from 11.8 to 9.4%) (Fig. 2) and nonfatal reinfarction by 49% (from 2.0 to 1.0%). Treatment with aspirin was not associated with any significant increase in cerebrovascular bleeding or bleeding requiring transfusion. Follow-up of the patients in ISIS-2 has shown that these benefits from short-term antiplatelet therapy with aspirin have persisted for several years *(48)*.

Aspirin's effects on vascular death were similar whether or not patients received fibrinolytic therapy or heparin and whether or not they were treated within 4 hours or between 4 and 24 h after the onset of symptoms *(1)*. In fact, the reductions in vascular mortality seen with SK and aspirin were additive (vascular mortality 13.2% with neither, 10.7% with aspirin, 10.4% with SK, and 8.0% with both). Moreover, aspirin produced an even greater reduction in the in-hospital reinfarction rate in the group that received fibrinolytic therapy (from 3.8 to 1.8%) than in the group that did not (from 2.9 to 1.9%). It has been shown that fibrinolytic therapy can activate platelets *(14,15)* and it appears that antiplatelet therapy with aspirin may abolish this effect and prevent potential thrombolysis-induced platelet aggregation, coronary artery reocclusion, and reinfarction.

Flurbiprofen

Pharmacology. Flurbiprofen is a nonsteroidal antiinflammatory drug (NSAID) that is a propionic acid derivative *(49)*. Unlike aspirin, flurbiprofen is a reversible inhibitor of cyclooxygenase *(50)* (Fig. 1).

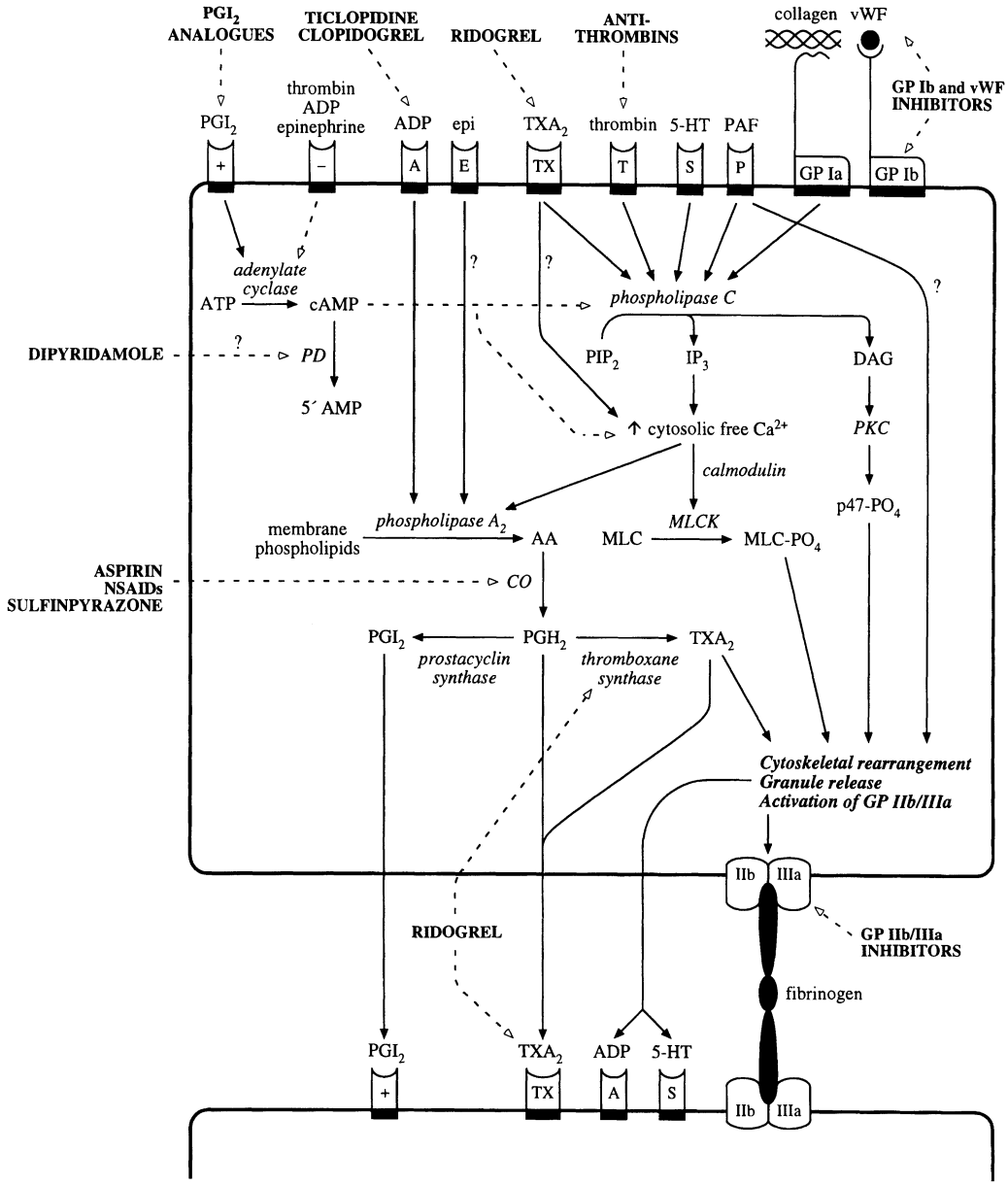

Fig. 1. A greatly simplified schematic depicting platelet adhesion, activation, and aggregation and the sites of action of antiplatelet agents. Platelet adhesion is mediate primarily by collagen binding to glycoprotein (GP) Ia and von Willebrand factor (vWF) binding to GP Ib. Platelet activation is extremely complex and only incompletely understood. Three major pathways have been identified. One pathway involves stimulation of phospholipase C (PLC) by agonists such as thomboxane (TXA_2), thrombin, serotonin (5-HT), platelet-activating factor (PAF), and collagen. PLC converts phosphatidylinositol 4,5-bisphosphate (PIP_2) to inositol 1,4,5-triphosphate (IP_3) and diacyl glycerol (DAG). Increased levels of IP3 cause translocation of calcium from intracellular storage sites to the cytosol, which, with the help of calmodulin, leads to the activation of a variety of enzymes including myosin light chain kinase (MLCK). The other product of PLC activity is DAG, which activates protein kinase C (PKC). These two kinases, MLCK and PKC, phosphorylate, respectively, myosin light chain (MLC) and a 47-kDa protein (p47), ultimately leading to platelet activation. Another pathway involves stimulation of phospholipase A (PLA) by agonists such as

Clinical data. The utility of flurbiprofen in AMI was examined in the Flurbiprofen French Trial *(51)*. To be eligible, patients needed to have been admitted to a coronary care unit within 6 h of the onset of an AMI, have received reperfusion therapy with either thrombolysis or primary angioplasty, and have achieved TIMI grade 2 or 3 as determined by a coronary angiogram within 24 h. Enrolled patients were then randomized to receive flurbiprofen 50 mg po bid or placebo starting within 48 h of admission. Patients receiving aspirin or ticlopidine were excluded. At 6 mo, flurbiprofen did not produce a statistically significant difference in the primary end points of mortality (0.8% with flurbiprofen vs 1.3% with placebo) or reocclusion of the infarct-related artery (14% with flurbiprofen vs 15% with placebo). However, flurbiprofen did produce a 71% reduction in reinfarction (from 10.5 to 3%) and a 51% reduction in secondary intervention (i.e., percutaneous transluminal coronary angioplasty [PTCA] or coronary artery bypass grafting [CABG]) (from 33.3 to 16.7%). There was an increase in the incidence of hemorrhage (14.5% with flurbiprofen vs 7.9% with placebo), but most of these events were minor. The applicability of these data to all patients presenting with AMI is limited, as the above trial was conducted in a highly select group of patients who had angiographic confirmation of successful restoration of flow to the infarct-related artery. Moreover, the control group did not receive aspirin, which is now standard therapy for this patient population.

ADP Antagonists

Ticlopidine

Pharmacology. Ticlopidine is a thienopyridine derivative that inhibits the binding of ADP to its receptor (Fig. 1) *(52)*. Ticlopidine can also indirectly inhibit the activity of several other platelet agonists such as arachidonic acid, collagen, thrombin, epinephrine, and serotonin. This is thought to occur because the aggregation response to these agonists is augmented by the initial release of ADP from activated platelets. At high concentrations of these agonists, platelet aggregation is ADP independent, and therefore ticlopidine has no significant effect. Unlike aspirin, ticlopidine can inhibit platelet aggregation in response to vascular shear stress *(53)*. Observations that ticlopidine can block GP IIb/IIIa-mediated platelet aggregation *(54)* probably reflect a downstream effect of ADP inhibition rather than a direct effect. Ticlopidine's full antiplatelet effects require 3–5 d of oral administration and persist for 4–8 d after drug discontinuation, consistent with an in vivo metabolite causing irreversible platelet inhibition *(55)*.

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adenosine diphosphate (ADP) and epinephrine (epi). PLA liberates arachidonic acid (AA) from membrane phospholipids. AA is then converted by cyclooxygenase (CO) to prostaglandin H_2 (PGH_2), which can then be converted either into TXA_2 by thromboxane synthase (TxS) or into prostacyclin (PGI_2) by prostacyclin synthase. TXA_2 is a platelet activator and a vasoconstrictor. A third pathway involves adenylate cyclase, which, when inhibited by thrombin, ADP, or epinephrine, leads to decreased levels of cyclic adenosine monophosphate (cAMP) and consequent derepression of the phospholipase C pathway described above. The end result of activation of any of these three pathways is to induce platelet activation specifically by bringing about cytoskeletal rearrangement, granule release, and the activation of GP IIb/IIIa. Platelet aggregation then occurs through fibrinogen binding to GP IIb/IIIa receptors on different platelets. The sites of action of platelet inhibitors are shown using open arrowheads and dashed lines. (+), receptors that lead to activation of adenylate cyclase; (–), receptors that lead to inhibition of adenylate cyclase; A, ADP receptor; E, epinephrine receptor; TX, TXA_2 receptor; T, thrombin receptor; S, 5-HT receptor; P, PAF receptor; ATP, adenosine triphosphate; 5′AMP, 5′adenosine monophosphate; PD, phosphodiesterase.

Table 1
Antiplatelet Agents

- Platelet adhesion inhibitors
  - Glycoprotein Ib inhibitors
  - von Willebrand factor inhibitors
- Platelet activation inhibitors
  - Cyclooxygenase inhibitors
    - Aspirin
    - Nonsteroidal antiinflammatory drugs
    - Sulfinpyrazone
  - Adenosine diphosphate antagonists (i.e., thienopyridine derivatives)
    - Ticlopidine
    - Clopidogrel
  - Thromboxane inhibitors (i.e., synthase inhibitor and receptor antagonist)
    - Ridogrel
  - Prostacyclin and analogs
  - Thrombin inhibitors
  - Serotonin receptor antagonists
  - Dipyridamole
- Platelet aggregation inhibitors
  - Glycoprotein IIb/IIIa inhibitors
    - Disintegrins
    - Monoclonal antibodies (e.g., abciximab)
    - Synthetic peptide compounds (e.g., eptifibatide)
    - Nonpeptide mimetics (e.g., lamifiban, tirofiban, xemlofiban, orbofiban)

Gastrointestinal upset, nausea, vomiting, and diarrhea occur in approximately 10% of patients; many of these side effects can be eliminated by having the patient take ticlopidine with food. Skin rashes occur in approximately 2% of patients. The most serious adverse effect is neutropenia, which has been reported to occur in 1% of patients *(56,57)*.

Clinical data. There are very little data on ticlopidine for acute coronary syndromes. In the Studio della Ticlopidina nell'Angina Instabile (STAI) trial, 652 patients with unstable angina who did not present with AMI and who had not had a myocardial infarction in the past 6 wk were treated with conventional therapy (β-blockers, calcium channel blockers, and nitrates) and randomized to receive ticlopidine 250 mg po bid or placebo *(58)*. Treatment with ticlopidine resulted in a 46.3% reduction in the combined endpoint of vascular death and nonfatal myocardial infarction (from 13.6 to 7.3%) at 6 mo. However, this trial took place before aspirin had become an integral part of the treatment of unstable angina or AMI. In another study, patients presenting within 24 hours of AMI and treated with heparin, nitrates, and β-blockers were given either ticlopidine or aspirin *(59)*. The percent of patients who achieved initial rapid relief of anginal pain and the number of patients who had a recurrence of angina during the first 48 h were similar in both antiplatelet treatment groups. Thus, there is no evidence yet that ticlopidine offers any advantage over aspirin in acute coronary syndromes.

Ticlopidine has become the standard of care after intracoronary stent deployment, including after primary angioplasty and stenting for AMI. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial compared antiplatelet therapy using ticlopidine 250 mg po bid for 4 wk and aspirin 100 mg po bid to anticoagulant therapy using iv heparin for 5–10 d, phenprocoumon for 4 wk (target international normalized ratio [INR]

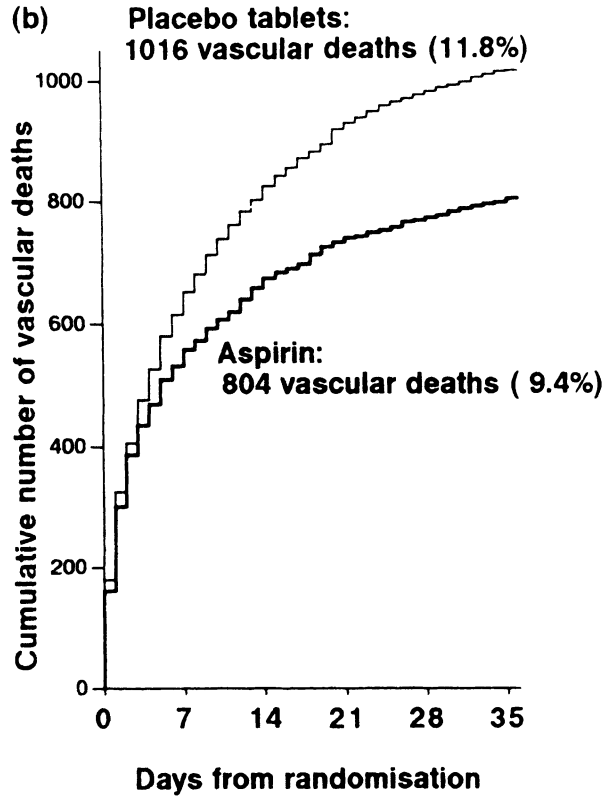

Fig. 2. Cumulative vascular mortality in d 0–35 in the ISIS-2 trial for all patients allocated aspirin vs all patients allocated placebo tablets. Reproduced with permission from ref. *47*.

3.5–4.5), and aspirin 100 mg po bid for all patients undergoing intracoronary stenting *(60)*. Compared with anticoagulant therapy, antiplatelet therapy resulted in an 86% reduction in stent occlusion, an 82% reduction in reinfarction, a 78% reduction in reintervention, and elimination of severe hemorrhagic complications. In a subgroup analysis of 123 patients with stent placement for AMI *(61)*, antiplatelet therapy resulted in a significant 84% reduction (from 21 to 3.3%) in clinical events defined as cardiac events (cardiac death, reinfarction, reintervention) plus noncardiac events (noncardiac death, stroke, severe hemorrhage). Specifically, with antiplatelet therapy there was a trend toward fewer cardiac deaths (84% reduction, from 9.7 to 1.6%), and there was a significant reduction in severe hemorrhagic complications (from 12.9 to 0%). Antiplatelet therapy also resulted in a significant elimination of stent occlusion (from 9.7 to 0%).

Whether aspirin plus ticlopidine is superior to aspirin alone is under investigation. In one small study, treatment with aspirin plus ticlopidine vs aspirin alone resulted in a lower percentage both of platelets with activated fibrinogen receptors and of P-selectin-positive platelets *(62)*. In another study, 226 patients, after undergoing successful intravascular ultrasound-guided stent implantation, were randomized to ticlopidine 250 mg po bid for 4 wk and aspirin 325 mg po qd for 5 d vs aspirin 325 mg po qd *(63)*. At 1 mo, combined antiplatelet therapy resulted in fewer stent thromboses (0.8 vs 2.9%), fewer myocardial infarctions (0.8 vs 3.9%), and no deaths (0 vs 2.9%). The relatively small size of the trial and the small number of events made the study underpowered to detect a statistically

significant difference between the treatment arms. The Stent Anticoagulation Regimen Study (STARS) examined three regimens (aspirin alone, aspirin plus ticlopidine, and aspirin plus coumadin) in patients undergoing elective intracoronary stent deployment *(64)*. Preliminary data show that the incidence of adverse events (death, emergency CABG, myocardial infarction, or subacute closure) was significantly lower with aspirin plus ticlopidine (0.6%) compared with aspirin alone (3.6%) or aspirin plus coumadin (2.4%). Whether this benefit extends to patients undergoing primary angioplasty for AMI has yet to be seen.

Clopidogrel

Pharmacology. Clopidogrel is a thienopyridine derivative related to ticlopidine. It selectively and irreversibly inhibits ADP from binding to its receptors on platelets, thereby preventing ADP-dependent activation of GP IIb/IIIa receptors *(65,66)* (Fig. 1). Clopidogrel's major adverse effects include rash and diarrhea. Unlike ticlopidine, clopidogrel has not been associated with an excess of neutropenia.

Clinical data. Clopidogrel has been studied in one major clinical trial to date: Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) *(67)*. In this trial, 19,185 patients who had either a recent ischemic stroke, a myocardial infarction in the past 35 d, or symptoms of atherosclerotic peripheral arterial disease were randomized to clopidogrel 75 mg po qd or aspirin 325 mg po qd. Treatment with clopidogrel resulted in a statistically significant 8.7% reduction in the combined primary end points of ischemic stroke, myocardial infarction, or vascular death (from 5.83 to 5.32%). However, in the group of patients whose qualifying event was a myocardial infarction, there was no significant difference in the occurrence of nonfatal or fatal myocardial infarctions or of the combined end points of ischemic stroke, myocardial infarction, or vascular death. Whether the dose of clopidogrel used in the trial achieved maximal antiplatelet effect is unclear. In an additional analysis in which all patients with a history of myocardial infarction (not just those whose qualifying event was a myocardial infarction) were examined, treatment with clopidogrel resulted in a 7.4% reduction in the combined end points of ischemic stroke, myocardial infarction, or vascular death. Subgroup analysis of patients presenting with AMI is not available. Thus, the role of clopidogrel in AMI remains undefined.

Thromboxane Inhibitors

Thromboxane Synthase Inhibitors

Theoretically, inhibition of thromboxane synthase (TxS) should be superior to inhibition of CO because inhibition of the latter also results in decreased synthesis of prostacyclin, a platelet activation inhibitor that acts by increasing platelet cAMP levels (Fig. 1). By contrast, inhibition of TxS decreases production of TXA_2 while leaving prostacyclin production unimpaired. There may even be increased prostacyclin production as accumulating prostaglandin endoperoxides (PGENDs) such as PGH_2 are reoriented down the prostacyclin pathway. Nonetheless, several animal studies have failed to show a significant effect of TxS inhibitors on preventing thrombosis or enhancing thrombolysis *(68–70)*.

Thromboxane/Prostaglandin Endoperoxide Receptor Antagonists

One of the reasons why TxS inhibitors may be less efficacious than anticipated is that it appears that PGENDs, the substrates upon which TxS acts and the precursors to TXA_2, can

activate platelets both directly by binding to the TXA_2 receptor and indirectly by blunting the increase in cAMP production triggered by prostacyclin. Therefore, TXA_2/PGEND receptor antagonists have been developed and tested *(71–74)*. However, as competitive antagonists, these agents can be displaced from their receptors, making them less effective when TXA_2 levels are highest. Also, as with aspirin and other CO inhibitors, platelets can still be activated via TXA_2-independent pathways.

Ridogrel

Pharmacology. Ridogrel is a thromboxane synthase inhibitor as well as a competitive TXA_2/PGEND receptor blocker *(75,76)*. This dual activity allows ridogrel to inhibit platelet activation several ways (Fig. 1) and potentially overcome the limitations of the above-mentioned other members of this class.

Clinical data. There has been one randomized controlled trial of ridogrel in AMI. In the Ridogrel versus Aspirin Patency Trial (RAPT), 907 patients presenting within 6 h of an AMI were treated with SK 1.5 MU and randomized to receive either ridogrel 300 mg iv bolus followed by 300 mg po bid or aspirin 250 mg iv bolus followed by 160 mg po qd *(77)*. There was no difference in the primary end point of infarct-related artery patency rates at predischarge angiography (72.2% with ridogrel and 75.5% with aspirin). There was also no difference in clinical markers of reperfusion at 2 h such as decreases in anginal pain, ST-segment elevation, or creatine phosphokinase (CPK) levels (54% with ridogrel and 51% with aspirin). Similarly, mortality was similar in both groups (6.4% with ridogrel and 7.1% with aspirin). In a *post hoc* analysis, treatment with ridogrel did result in a 32% reduction (from 19 to 13%) in new ischemic events including ischemic stroke, angina, and reinfarction. There was a trend toward more bleeding in the ridogrel group (10 vs 7.1%). Thus, ridogrel has yet to be shown to confer any mortality benefit over aspirin, and its ability to decrease new ischemic events will need to be confirmed in a trial that prospectively defines that as an end point.

Glycoprotein IIb/IIIa Inhibitors

Pharmacology

The GP IIb/IIIa receptor is a member of the integrin superfamily of heterodimeric adhesion molecules that is found on platelets *(30)*. It is the primary receptor for platelet aggregation through binding to fibrinogen. GP IIb/IIIa contains two domains responsible for the binding of adhesive proteins *(77a)* (Fig. 3). One domain is on the GP IIIa subunit, and its ligand is the peptide sequence RGD. The other domain is on the GP IIb subunit, and its ligand is the dodecapeptide HHLGGAKQAGDV. The dodecapeptide is found only in fibrinogen and is located on the γ-chain. Conversely, the RGD sequence is found in many peptides including fibrinogen (where it is located on the α-chain), fibronectin, vitronectin, vWF, and thrombospondin. GP IIb/IIIa is unable to bind fibrinogen unless the platelet is first activated by an agonist, which then induces a conformational change in GP IIb/IIIa, revealing the binding domain and rendering the molecule a competent fibrinogen binder. Platelet aggregation occurs when two activated platelets bind to the same fibrinogen molecule (each to one end), thereby forming a fibrinogen bridge between the two platelets.

GP IIb/IIIa inhibitors are theoretically particularly attractive as antiplatelet agents since, unlike CO and TxS inhibitors or ADP and TXA_2/PGEND receptor antagonists, they can block the final step in platelet aggregation triggered by all endogenous platelet activators. There are several types of GP IIb/IIIa inhibitors *(33)*. *Disintegrins* are natural

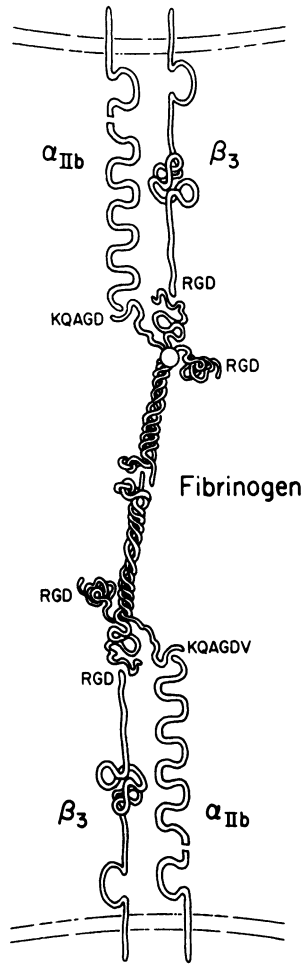

Fig. 3. Glycoprotein IIb/IIIa structure. The IIIa (β3) subunit contains a domain whose ligand is the peptide sequence RGD, which is found in each α-chain of fibrinogen. The IIb ($\alpha_{II\beta}$) subunit contains a domain whose ligand is the dodecapeptide HHLGGAKQAGDV, which is found in the γ-chain of fibrinogen. Reproduced with permission from ref. *77a*.

peptides derived from snake venom that contain either an RGD-based or KGD-based sequence and that compete with fibrinogen for binding to GP IIb/IIIa (and other members of the integrin family). However, their antigenicity and their tendency to induce thrombocytopenia limit their clinical utility. In 1985, a mouse *monoclonal antibody* against GP IIb/IIIa (known as 7E3) was generated *(78)*; subsequent clinical trials have used abciximab (ReoPro), which is a Fab fragment of a chimeric human-mouse genetic reconstruction of 7E3 (abbreviated c7E3 Fab). Abciximab binds irreversibly to GP IIb/IIIa and possess both high affinity and high specificity. Based on the disintegrins, researchers have developed *synthetic peptide compounds*, including the cyclic KGD peptide analog eptifibatide (Integrilin), and *nonpeptide mimetics*, including lamifiban, tirofiban, xemlofiban, and orbofiban, that can block fibrinogen from binding to GP IIb/IIIa.

There are several important differences in the pharmacokinetics and pharmacodynamics of the two most extensively tested compounds *(79)*. Abciximab has a much stronger affinity than eptifibatide does for GP IIb/IIIa. Thus, after a bolus of abciximab, only small

amounts are needed by continuous infusion to achieve platelet inhibition and after discontinuation of the infusion platelet function returns gradually. By contrast, eptifibatide has a short half-life, effective platelet inhibition occurs only with a continuous infusion, and platelet function returns abruptly after discontinuation of the infusion. Abciximab is relatively nonspecific and binds to other integrins, including the vitronectin receptor (GP $\alpha_V\beta_3$) which is found on endothelial cells. By contrast, eptifibatide is extremely specific for GP IIb/IIIa.

In addition to the expected side effect of excess bleeding, abciximab has also been associated with profound thrombocytopenia in 0.5–1.0% of cases *(80)* and the development of anti-mouse antibodies in 6–52% of cases *(81,82)*, the clinical significance of the latter has yet to be fully explored.

Clinical Data

Abciximab. Abciximab has been extensively studied in patients undergoing angioplasty, including patients receiving primary angioplasty for AMI. In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial, 2099 patients who were undergoing high-risk angioplasty for AMI or early postinfarction angina, or who had high-risk lesions, were randomized to one of three groups: abciximab bolus (0.25 mg/kg) 10 min before the procedure followed by abciximab infusion (10 μg/min) for 12 h, abciximab bolus (0.25 mg/kg) 10 min before the procedure followed by placebo infusion for 12 h, or placebo bolus 10 min before the procedure followed by placebo infusion for 12 h *(83)*. All patients also received aspirin 325 mg po before angioplasty and then qd and fixed dose iv heparin for 12 h. Treatment with both the bolus and the infusion of abciximab resulted in a 35% reduction (from 12.8 to 8.3%) in the primary end point of death, nonfatal myocardial infarction, unplanned revascularization, or insertion of an intraaortic balloon pump at 30 d. Treatment with abciximab bolus alone did not result in a significant decrease in the rate of the primary end point. The major bleeding complication rate was 14% in the abciximab bolus and infusion group vs 7% in the placebo group. The benefit seen with treatment with abciximab was maintained at 3 yr *(84)*. The EPIC investigators speculate that these observations may be owing to abciximab's ability to bind not only $\alpha_{IIb}\beta_3$ integrin (the GP IIb/IIIa receptor) but also $\alpha_V\beta_3$ integrin (the vitronectin receptor). Binding to the latter may result in inhibition of thrombin generation *(85)*, inhibition of smooth muscle migration *(86,87)*, and modulation of smooth muscle cell apoptosis *(88)*, all of which could decrease thrombosis and restenosis *(87,89)*.

Sixty-four patients who underwent primary or rescue angioplasty for AMI in the EPIC trial were analyzed in the EPIC-AMI substudy *(90)*. There was a striking 83% reduction (from 26.1 to 4.5%) in the rate of the primary end point of death, nonfatal myocardial infarction, or unplanned revascularization at 30 d. At 6 mo, the difference was even more impressive, with a 91% reduction (from 47.8 to 4.5%) in the rate of the primary end point (Fig. 4). Most of this benefit was owing to a decreased need for repeat revascularization. As with the EPIC trial, major bleeding was increased with abciximab (24 vs 13%).

Subsequent trials involving abciximab in patients undergoing elective or urgent angioplasty have attempted to address the issue of excessive bleeding. In the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study *(91)*, slightly lower doses of heparin and greater attention to vascular access sites led to a lower rate of major bleeding (3.8%) than in the EPIC trial, but still greater than in the control group (1.9%). In the Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP

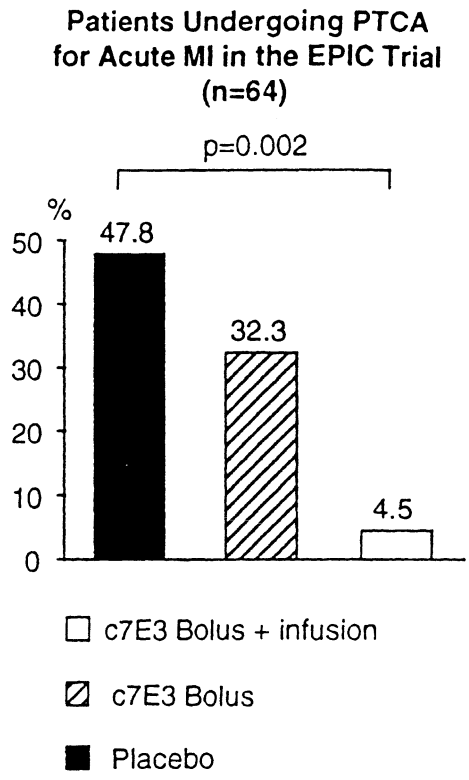

Fig. 4. Six-mo composite event rates in the EPIC-AMI trial. Bar graph showing the rates of the primary composite end point of death, nonfatal myocardial infarction, or unplanned revascularization in patients randomized to placebo (solid bars), abciximab bolus (hatched bars), or abciximab bolus and infusion (open bars). Reproduced with permission from ref. *90*.

IIb/IIIa Blockade (EPILOG) trial *(81)*, in addition to being randomized to abciximab or placebo, patients were also randomized to standard or weight-adjusted iv heparin, and in both groups the heparin was discontinued after the intervention rather than the 12-h infusion used in the EPIC trial. Furthermore, the abciximab infusion was also weight based and given at the rate of 0.125 μg/kg/h (maximum, 10 μg/min). Although there was no significant difference among the two heparin groups in the risk of major bleeding, there was a significant reduction in the risk of minor bleeding with weight-based heparin (4.0 vs 7.4%). The benefits of abciximab seen in this study (56% reduction in death, myocardial infarction, or urgent revascularization at 30 days) were seen equally in both the standard and the weight-based heparin groups. This finding suggests that the use of a weight-based heparin regimen and early removal of vascular sheaths in patients receiving abciximab might result in a lower bleeding complication rate while still achieving reductions in mortality and recurrent ischemia.

The powerful effect of GP IIb/IIIa inhibitors on preventing coronary thrombosis prompted the evaluation of abciximab as adjunctive therapy initiated *before* primary angioplasty for AMI. In one recent study *(92)*, patients with AMI were brought to the cardiac catheterization laboratory and, after confirmation of TIMI grade 0 or 1 flow in the culprit artery, given abciximab (a 0.25-mg/kg iv bolus, followed by an infusion at 0.125 μg/kg/h). At 10 min, 85% of the patients experienced improved flow in the infarct-related artery by at least one TIMI grade, and 54% of the patients achieved TIMI grade

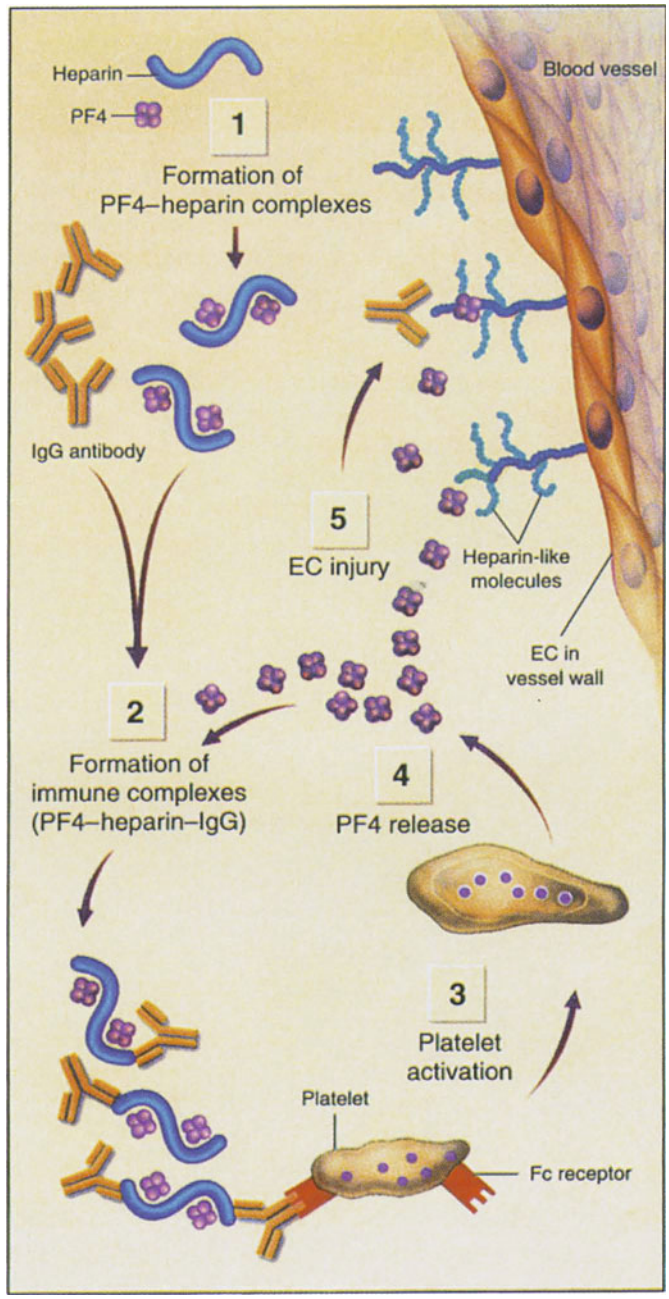

Plate 4, Fig. 11; (*see* discussion in Chapter 12, p. 313). Heparin-induced thrombocytopenia. Heparin interacts with platelet factor 4 (PF4) that is released in small quantities from circulating platelets to form PF4-heparin complexes (1). Specific IgG antibodies react with these conjugates to form immune complexes (2) that bind to Fc receptors on circulating platelets. Fc-mediated platelet activation (3) releases PF4 from α-granules in platelets (4). Newly released PF4 binds to additional heparin, and the antibody forms more immune complexes, establishing a cycle of platelet activation. PF4 can also bind to heparin-like molecules on the surface of endothelial cells (EC) to provide targets for antibody binding, potentially leading to immune-mediated EC injury(5) and thrombosis. Reproduced with permission from ref. *137a*.

2 or 3 flow in the infarct-related artery. In the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study *(93,94)*, patients with AMI were given abciximab on admission and then brought to the catheterization laboratory as soon as possible. The preliminary data show that the infarct-related artery was occluded in only 60% of patients, compared with a 73–90% occlusion rate in historical controls *(95,96)*. Presumably, by inhibiting further platelet aggregation, abciximab is allowing the endogenous lytic system to restore patency. There is, however, preliminary evidence suggesting additional potential mechanisms of action including increased elaboration of urokinase plasminogen activator, diminished synthesis of plasminogen activator inhibitor-1 *(97)*, and reduced tissue factor-mediated thrombin generation *(85)*. In the ReoPro in Acute Myocardial Infarction and Primary PTCA Organization and Randomized Trial (RAPPORT) study, 483 patients were randomized to abciximab or placebo before primary angioplasty for AMI *(98)*. Treatment with abciximab was associated with a statistically nonsignificant 44% reduction in death, myocardial infarction, and urgent revascularization at 30 d; the 6-mo follow-up data are being analyzed.

Abciximab has also been studied in AMI for which thrombolysis rather than primary angioplasty was utilized to achieve reperfusion. In animal models, the combination of abciximab and tissue-type plasminogen activator (tPA) was more effective than tPA alone both in achieving reperfusion and in preventing reocclusion *(99–101)*. In humans, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 pilot study examined the safety and utility of abciximab given after thrombolysis for AMI *(82)*. Patients who presented within 6 h of the onset of chest pain and who had ST-segment elevation were treated with accelerated tPA and aspirin and were randomized to receive a bolus of abciximab at 15, 6, or 3 h after the beginning of the tPA infusion and at doses ranging from 0.1 to 0.25 mg/kg. GP IIb/IIIa receptor blockade and in vitro platelet aggregation both showed a clear dose-response curve. The peak effect on platelet aggregation occurred 2 h after the infusion; aggregation returned to 50% of baseline at 6 h and nearly completely to baseline at 24 h. There was no significant difference in the bleeding or thrombocytopenia rates. Although not designed to detect differences in clinical cardiac events (e.g., angina, myocardial infarction, urgent revascularization, or death) this combined end point was seen in 13% in the pooled abciximab group vs 20% of the control group. Moreover, the combined end point was seen in none of the patients receiving abciximab at 3 h and in only 9.5% of the patients receiving abciximab at a dose of 0.20 or 0.25 mg/kg. Angiography, obtained at the discretion of the clinician, demonstrated TIMI grade 2 or 3 flow in 92% of the abciximab group vs 56% in the control group.

Currently under way is a phase II angiographic trial (TIMI 14) evaluating 90-min TIMI grade 3 flow in patients presenting with AMI randomized to tPA, abciximab infusion with reduced doses of tPA, abciximab infusion with reduced doses of SK, and abciximab infusion alone. Preliminary data demonstrate a slightly higher percentage of patients with TIMI grade 3 flow in the infarct-related artery in the group that received abciximab with reduced doses of tPA *(102)*.

Eptifibatide. As with abciximab, eptifibatide has to date been tested more extensively in the setting of coronary interventions and unstable angina than in AMI. Eptifibatide has been shown to reduce the rate of myocardial infarction, repeat revascularization, or death at 30 days in patients undergoing elective, urgent, or emergency coronary intervention in the Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT) *(103)* and IMPACT-II *(104)* trials, although there is evidence of increased restenosis at 6 mo. Eptifibatide has also been shown to decrease mortality and reinfarction

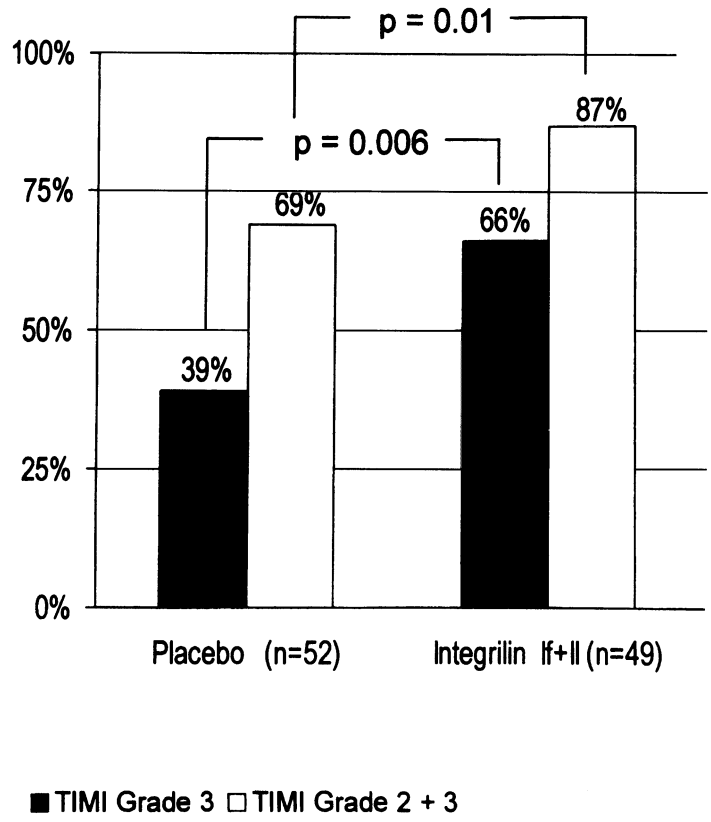

Fig. 5. Angiographic end points in the IMPACT-AMI trial. Bar graph showing TIMI grade 3 flow rates (solid bars) and patency rates (TIMI grade 2 or 3 flow, open bars) at 90 min (as assessed by the angiographic core laboratory) in patients randomized to placebo compared with the combination of patients who either received eptifibatide at the highest dose in the dose-ranging phase or who were randomized to eptifibatide in the randomized phase. Reproduced with permission from ref. *106*.

in patients with non-ST-segment elevation acute coronary syndromes in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial *(105)*.

There have been two angiographic trials examining the role of eptifibatide in AMI. IMPACT-AMI was a dual phase, dose-ranging and randomized, placebo-controlled trial examining the effect of eptifibatide in 180 patients receiving tPA, aspirin, and iv heparin for AMI *(106)*. The patients receiving the highest dose of eptifibatide in the dose-ranging study were combined with the patients in the eptifibatide limb in the double-blind study and compared with all the patients who received placebo in both studies. Using this approach, treatment with eptifibatide was associated with a higher percentage of patients achieving TIMI grade 3 flow (66 vs 39%), a higher percentage of patients achieving patency (87 vs 69%), earlier resolution of ST-segment elevation (65 vs 116 min), similar rate of death or myocardial infarction (7.8 vs 7.3%) (Fig. 5). In contrast to the results seen with abciximab in EPIC-AMI, there was no excess of severe bleeding (4% with eptifibatide vs 5% with placebo).

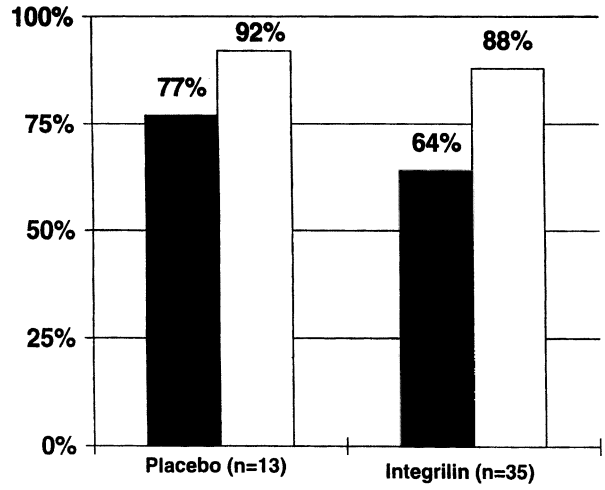

Fig. 6. Angiographic end points only in the randomized phase of the IMPACT-AMI trial. Bar graph showing TIMI grade 3 flow rates (solid bars) and patency rates (TIMI grade 2 or 3 flow, open bars) at 90 min (as assessed by the angiographic core laboratory) in patients randomized to either placebo or eptifibatide. Reproduced with permission from ref. *107.*

However, the statistical validity of combining patients from an open, dose-ranging study with a double-blind study is questionable, as pointed out in an accompanying editorial *(107)*. In fact, an analysis of the data only from the double-blind study leads to the exact opposite conclusions. Eptifibatide was associated with a lower percentage of patients achieving TIMI grade 3 flow (64 vs 77%) and a higher rate of death or myocardial infarction (11 vs 0 percent) (Fig. 6). There are several potential explanations for eptifibatide's lack of efficacy compared with abciximab. The double-blind study was underpowered to detect a significant difference between the two treatment arms. Moreover, the correct dose of eptifibatide has yet to be firmly established. Studies with abciximab have demonstrated that inhibition of platelet aggregation by at least 80% corresponds to therapeutic efficacy. In the IMPACT-AMI trial, there was no clear dose-response curve, and the degree of inhibition of platelet aggregation may have been overestimated because of collection techniques. There are also important mechanistic difference between abciximab and eptifibatide, as discussed above. Abciximab is an irreversible inhibitor of GP IIb/IIIa and may block other integrins such as vitronectin, which is found on endothelial cells. By contrast, eptifibatide is a reversible inhibitor with a shorter half-life, which may contribute to a rebound effect at the end of the bolus, and it is specific only for GP IIb/IIIa.

In another trial, patients with AMI were given SK and either eptifibatide or placebo *(108)*. Treatment with eptifibatide was associated with a higher likelihood of achieving TIMI grade 3 flow in the infarct-related artery at 90 min (50 vs 32%), but at the expense of increased bleeding complications. A reevaluation of the optimal dosing regimen is under way.

Other GP IIb/IIIa inhibitors. Other GP IIb/IIIa inhibitors are now just starting to be tested in acute coronary syndromes. Both lamifiban and tirofiban have been examined in unstable angina with promising results *(109,110)*, and we await data on their efficacy in AMI.

Other Antiplatelet Agents

Sulfinpyrazone

Sulfinpyrazone is a uricosuric agent structurally related to phenylbutazone. It is a competitive inhibitor of cyclooxygenase, but it may inhibit platelets through other mechanisms as well. Although in one study it reduced the rate of reinfarction in patients after myocardial infarction *(111)*, no consistent data support the utility of sulfinpyrazone in acute coronary syndromes.

Dipyridamole

Dipyridamole inhibits platelets through an unknown mechanism: it may act as a phosphodiesterase inhibitor, thereby increasing concentrations of cAMP and maintaining the platelet in its resting state, it may stimulate prostacyclin synthesis, or it may inhibit cellular uptake and metabolism of adenosine *(112)*. Clinically, dipyridamole is a weak antiplatelet agent with no established role in acute coronary syndromes *(113)*.

Prostacyclin and Analogs

Prostacyclin acts both as an antiplatelet agent and as a vasodilator. Its antiplatelet effects are mediated through stimulation of adenylate cyclase. This causes an increase in levels of cAMP, thereby stimulating cAMP-dependent protein kinases, decreasing cytoplasmic calcium levels, and maintaining the platelet in its resting state *(114)*. Receptor downregulation and unacceptable vasodilation leading to hypotension have limited the clinical efficacy of current prostacyclin preparations as antiplatelet agents *(115)*.

Thrombin Inhibitors

As thrombin is the most potent endogenous platelet activator *(116–118)*, antithrombins should exert an antiplatelet effect. This has been established in experimental models *(119,120)*, and these agents are discussed in detail below.

Serotonin Receptor Antagonists

A combination of TXA_2 prostaglandin receptor antagonist and a serotonin antagonist have been used in an animal thrombosis model *(121)*, but no clinical data are available.

Glycoprotein Ib and vWF Inhibitors

Analogous to the development of GP IIb/IIIa inhibitors to block platelet aggregation, GP Ib and vWF inhibitors are being developed to block platelet adhesion *(32,122,123)*. No clinical data are available at this time. However, there is concern that these inhibitors would significantly interfere with normal hemostasis and produce unacceptable bleeding complications, as seen clinically in GP Ib deficiency (Bernard-Soulier syndrome) and von Willebrand's disease homozygotes.

Summary

- Platelets play a pivotal role in acute coronary syndromes, and platelet activation is a complex process with multiple pathways leading to the final common pathway of platelet aggregation.
- Aspirin, a CO inhibitor and a relatively weak platelet antagonist, is the standard of care for antiplatelet therapy in acute coronary syndromes and has been shown to reduce the rates of death and nonfatal reinfarction significantly.
- NSAIDs such as flurbiprofen have not been shown to be efficacious.

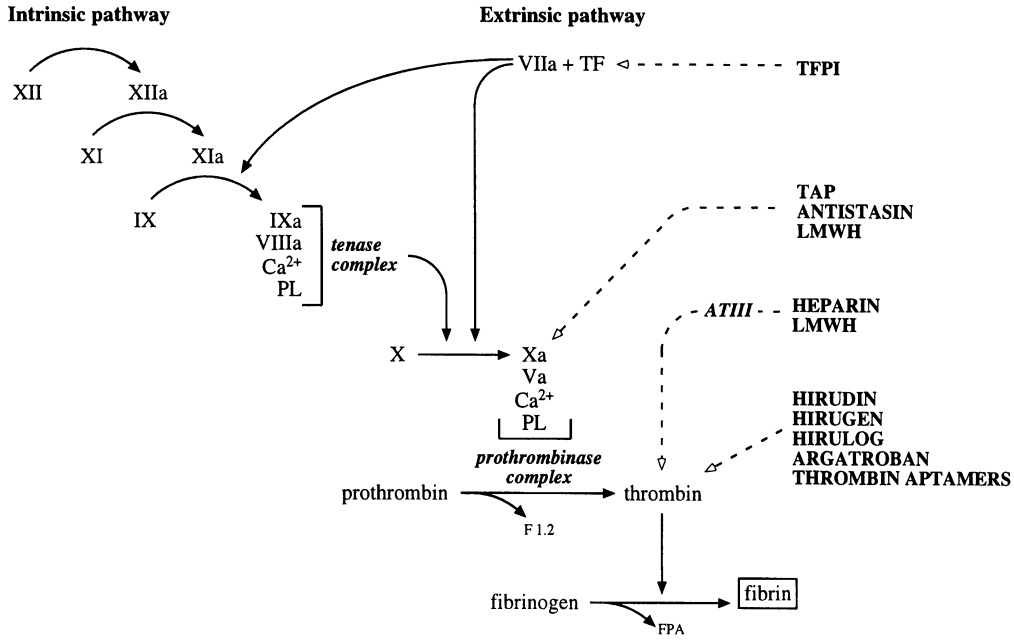

Fig. 7. The intrinsic and extrinsic pathways of coagulation cascade and the sites of action of antithrombin agents (open arrowheads and dashed lines). TF, tissue factor; TFPI, tissue factor pathway inhibitor; TAP, tick anticoagulant peptide; LMWH, low-molecular-weight heparin; F1.2, prothrombin fragment 1.2; FPA, fibrinopeptide A.

- Ticlopidine, an ADP antagonist, may, when combined with aspirin, be beneficial in patients undergoing intracoronary stent deployment, but no data are available examining the utility of ticlopidine in acute coronary syndromes.
- Clopidogrel, another ADP antagonist, may be marginally superior to aspirin in patients with recent ischemic syndromes, but its efficacy in patients presenting with AMI has yet to be addressed.
- Ridogrel, an antiplatelet agent that functions both as a TxS inhibitor and as a TXA_2/PGEND receptor antagonist, may be more efficacious in reducing the number of new ischemic events, but has not been shown to confer any mortality benefit over aspirin.
- Most promising are the GP IIb/IIIa inhibitors. These agents have shown a clear benefit in the setting of angioplasty and a particularly striking benefit in patients undergoing primary angioplasty for AMI. Studies are now under way to assess their potential benefit in conjunction with or as an alternative to thrombolytic therapy.
- Other agents under development include platelet adhesion antagonists such as GP Ib and vWF inhibitors.

THROMBIN INHIBITION

Thrombin

Thrombin is a glycosylated serine protease that plays a fundamental role in thrombosis *(124)*. Thrombin is generated from prothrombin by the prothrombinase complex, which includes factors Xa, Va, calcium, and phospholipids (Fig. 7). Its main action is to transform fibrinogen into fibrin. Thrombin is also the most potent endogenous platelet activator *(116–118)*. The *active catalytic site* lies within a relatively narrow canyon

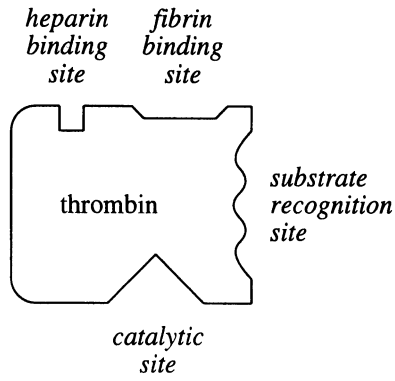

Fig. 8. Simplified depiction of thrombin and several of its key binding sites.

Table 2
Antithrombotic Agents

Indirect thrombin inhibitors
Heparin
Low molecular weight heparin
Direct thrombin inhibitors
Hirudin
Hirugen
Hirulog
Argatroban
Thrombin aptamers
Thrombin generation inhibitors
Factor Xa inhibitors
Tick anticogulant peptide
Antistasin
Low molecular weight heparin
Tissue factor pathway inhibitor

on the molecule's surface (Fig. 8) *(125)*. Adjacent to this site is the *substrate recognition site*, also known as the anion-binding exosite, to which fibrinogen binds *(125)*. In addition, there is a separate *fibrin-binding site (10)*. Finally, there are several other well-characterized binding sites including an apolar binding site *(126)*, which is involved in both substrate binding as well as platelet attachment via GP Ib, a *heparin-binding site*, and the primary platelet attachment site, which is an anion-binding exosite similar to the substrate recognition site and which binds to platelets using a tethered-ligand motif *(117)*. Thrombin inhibition can be achieved either by binding to one of these critical sites or by inhibiting thrombin generation (Fig. 7 and Table 2) *(32,124,127,128)*.

Heparin

Pharmacology

Heparin is a glycosaminoglycan that contains a unique pentasaccharide sequence with high binding affinity for antithrombin III (ATIII) *(12,129)*. When bound to heparin, ATIII undergoes a conformational change that results in an acceleration of its ability to

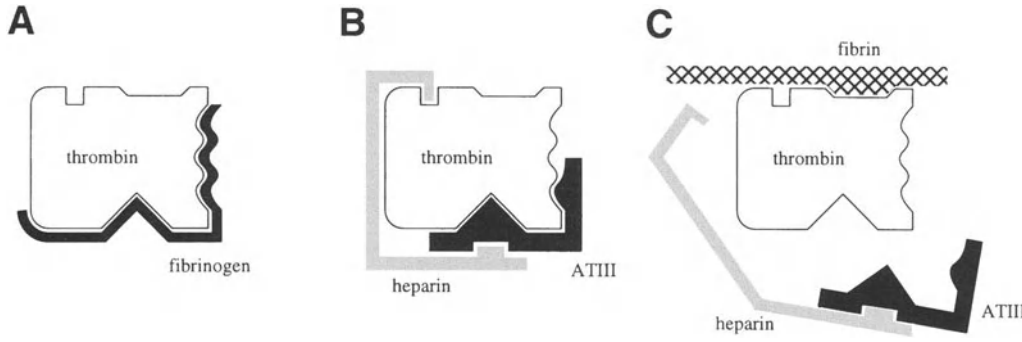

Fig. 9. Interaction between thrombin and heparin. **(A)** Thrombin binding to its natural substrate fibrinogen. **(B)** Inactivation of thrombin by antithrombin III (ATIII) and heparin. **(C)** Fibrin-bound thrombin is enzymatically active but resistant to inactivation by ATIII and heparin.

inactivate both thrombin and factor Xa by acting as a "suicide substrate" (Fig. 9). Heparin also increases the rate of the thrombin-ATIII reaction by greater than 1000-fold by acting as a catalytic template to which both the inhibitor and the protease bind, thereby forming a ternary complex. Of note, ternary complex formation is not required for factor Xa inactivation. Once thrombin binds to ATIII, heparin is released from the complex. There is also some evidence that part of heparin's anticoagulant effect is due to its ability both to stimulate the release and to enhance the activity of tissue factor pathway inhibitor *(130–132)*. Heparin molecules that contain fewer than 18 saccharide units (i.e., low molecular weight heparins) are unable to bind thrombin and ATIII simultaneously and are therefore unable to form ternary complexes to accelerate thrombin inhibition (see below). Heparin is largely ineffective against fibrin monomer-bound *(9)* or clot-bound *(10)* thrombin (Figs. 9 and 10) and against factor Xa bound in the prothrombinase complex.

Heparin is a heterogeneous mixture of glycosaminoglycans of varying molecular sizes *(133)*. This translates into heterogeneous anticoagulant activity for three reasons. First, only approximately 30% of heparin molecules actually contain the specific pentasaccharide sequence mentioned above that is required for ATIII binding *(129)*. Second, the anticoagulant profile of heparin in terms of the ratio of thrombin to factor Xa inhibition is influenced by the chain length *(134)*. Third, the clearance of heparin is proportional to its molecular size *(135)*.

Heparin can be administered either by continuous iv infusion or by intermittent subcutaneous injections with comparable efficacy, although there is a 1–2-h delay in achieving an anticoagulant effect via the subcutaneous route. The half-life of heparin varies depending on the dose given but is approximately 60–90 min.

Heparin-induced thrombocytopenia (HIT) is a well-documented complication of heparin administration *(136)*. HIT type I occurs in approximately 10% of patients receiving heparin and is manifested by mild thrombocytopenia occurring within 48 h of the initiation of therapy. The platelet count rarely falls below 100,000/mm^3 and returns to normal within 5 d even if heparin therapy is continued. The mechanism is thought to be direct heparin-mediated platelet aggregation. Patients with HIT type I do not go on to have thrombotic complications. By contrast, HIT type II is marked by more severe thrombocytopenia and a greatly increased risk of thrombosis. This syndrome occurs in 1–5% of patients receiving heparin, approximately one-third of whom will go on to develop thrombosis. The platelet count usually starts to decrease after 5–12 d of therapy

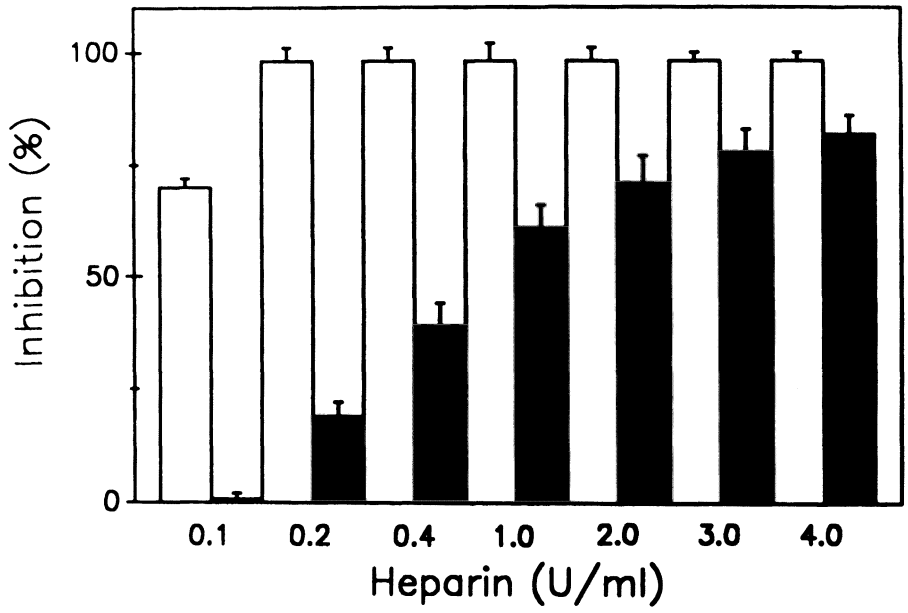

Fig. 10. Comparison of the inhibitory effects of heparin against fluid-phase (open bars) and clot-bound (solid bars) thrombin activity. Thrombin or fibrin clots were incubated with citrated plasma in the presence or absence of heparin. Fibrinopeptide A (FPA) levels were then measured by radioimmunoassay, and the percent inhibition of FPA generation was calculated for each inhibitor concentration. Heparin concentrations of 0.2–0.4 U/mL span the therapeutic range for this agent. Reproduced with permission from ref. *10*.

(and potentially earlier if the patient has been exposed to heparin before) and usually falls by more than 50% or drops to <100,000/mm^3. If heparin is discontinued, the platelet count usually returns to normal in 4–10 d. The pathogenesis of this syndrome is believed to be antibodies forming against heparin-platelet factor 4 complexes *(137,137a)* (Fig. 11). These immune complexes can then bind to Fc receptors on platelets and trigger platelet activation, thereby releasing more platelet factor 4. Platelet factor 4 can bind to heparin-like molecules on the surface of endothelial cells, providing a target for the aforementioned antibodies and leading to endothelial cell injury and thrombosis.

Several investigators have reported a "rebound effect" after the cessation of heparin therapy in patients with acute coronary syndromes. In one trial that randomized patients with unstable angina to heparin, aspirin, both, or neither, there was a nearly threefold higher incidence of disease reactivation (i.e., recurrent unstable angina or myocardial infarction) in patients who had received heparin than in the other groups (13 vs 5%) *(138)*. Most of these recurrences were severe enough to require urgent intervention. Other investigators have noted that after the cessation of heparin in patients with acute coronary syndromes there is a transient increase in prothrombin fragment 1.2 and fibrinopeptide A levels, suggesting that both thrombin generation and activity were increased *(139)*. Similar observations have been made after the discontinuation of heparin in patients undergoing coronary angioplasty *(140)*. The mechanism underlying this rebound phenomenon is unclear, but it may be owing to an accumulation of prothrombotic factors during heparin therapy that then create a hypercoagulable state after the cessation of heparin.

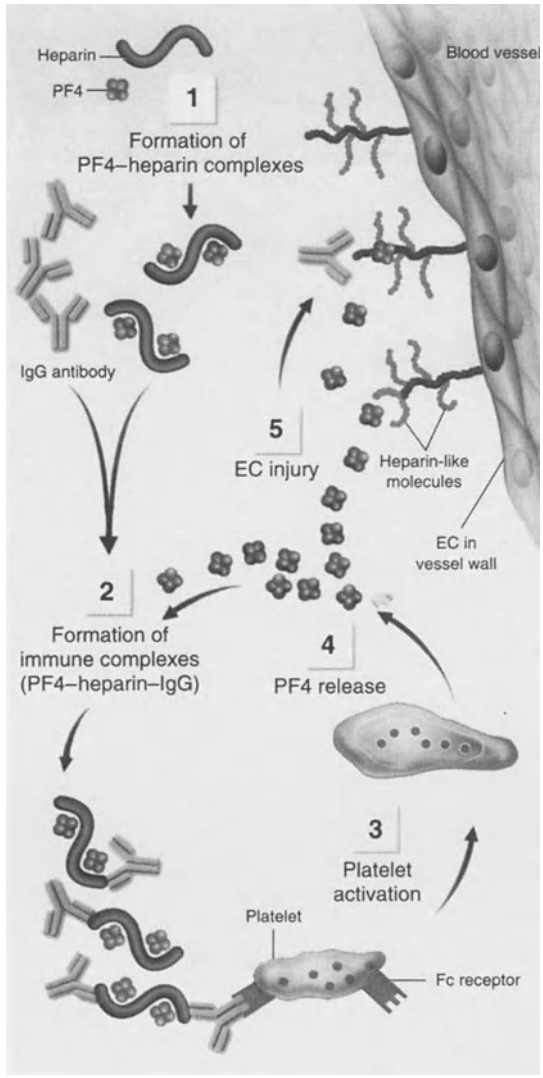

Fig. 11. Heparin-induced thrombocytopenia. Heparin interacts with platelet factor 4 (PF4) that is released in small quantities from circulating platelets to form PF4-heparin complexes (1). Specific IgG antibodies react with these conjugates to form immune complexes (2) that bind to Fc receptors on circulating platelets. Fc-mediated platelet activation (3) releases PF4 from α-granules in platelets (4). Newly released PF4 binds to additional heparin, and the antibody forms more immune complexes, establishing a cycle of platelet activation. PF4 can also bind to heparin-like molecules on the surface of endothelial cells (EC) to provide targets for antibody binding, potentially leading to immune-mediated EC injury (5) and thrombosis. Reproduced with permission from ref. *137a*. (*see* color plate 4 appearing after p. 304)

Clinical Data

Trials with no routine aspirin. Twenty-one trials enrolling a total of approximately 5000 patients have examined the effects of heparin in AMI in the preaspirin era (i.e., pre-ISIS-2). Most of these trials were also in the prethrombolysis era, as only 14% of the patients in these trials received thrombolytic therapy. A meta-analysis *(141)* revealed that treatment with heparin resulted in a statistically significant 25% reduction in mortality

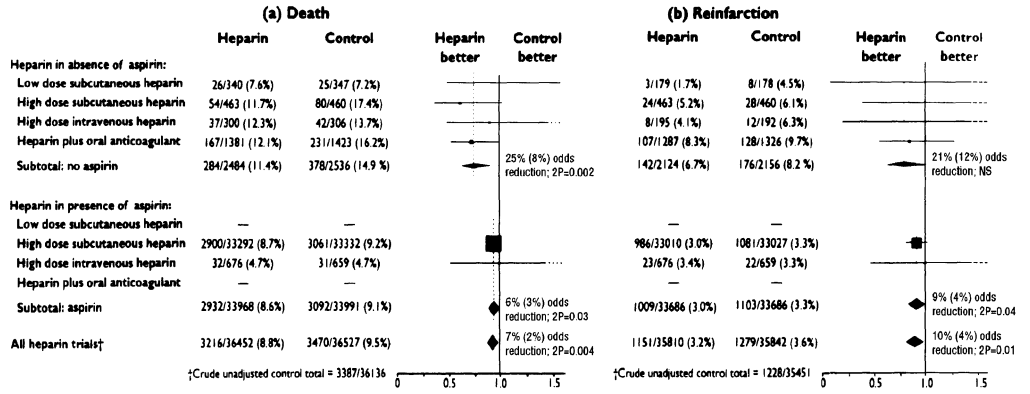

Fig. 12. Meta-analysis of the effects of heparin in the absence and presence of aspirin in patients with suspected acute myocardial infarction. Reproduced with permission from ref. *141*.

Table 3
Randomized Trials of Heparin in Patients
Receiving Thrombolysis for Acute Myocardial Infarction[a]

Trial (ref.)	*Year*	*Aspirin*	*Heparin*	*Thrombolytic*	*Patients*
SCATI *(142)*	1989	–	sc	± SK	711
Bleich et al. *(143)*	1990	–	iv	tPA	95
ISIS-2 pilot *(144)*	1987	±	iv	± SK	619
HART *(151)*	1990	±	iv	tPA	205
GISSI-2 *(145)*	1990	+	sc	SK	20,891
ISIS-3 *(146)*	1992	+	sc	SK	45,856
DUCCS-I *(150)*	1994	+	iv	APSAC	250
OSIRIS *(149)*	1992	+	iv	SK	128
ECSG-6 *(148)*	1992	+	iv	tPA	652

[a]Abbreviations: SK, streptokinase; tPA, tissue-type plasminogen activator; APSAC, anisoylated plasminogen streptokinase activator complex.

(from 14.9 to 11.4%) and a statistically nonsignificant 18% reduction in reinfarction (from 8.2 to 6.7%) (Fig. 12). Conversely, treatment with heparin was also associated with a near doubling of the major bleeding rate (1.9 vs 0.9%). Two trials *(142,143)* (Table 3) have examined the role of heparin in patients receiving a thrombolytic but not aspirin. Treatment with heparin was associated with a higher infarct-related artery patency rate *(143)* and a lower mortality rate *(142)*. However, the applicability of these data is limited now that treatment with aspirin has become standard of care.

Trials with routine aspirin. Six trials *(144–150)* (Table 3) enrolling approximately 68,000 patients have examined the effects of heparin in AMI in patients who routinely received aspirin as part of the treatment protocol. Ninety-three percent of the patients in these trials received thrombolytic therapy. A meta-analysis *(141)* revealed that treatment with heparin resulted in a marginally statistically significant in-hospital 6% reduction in mortality (from 9.1 to 8.6%) and a 9% reduction in reinfarction (from 3.3 to 3.0%) (Fig. 12). Again, treatment with heparin was also associated with an increased major bleeding rate (1.0 vs 0.7%).

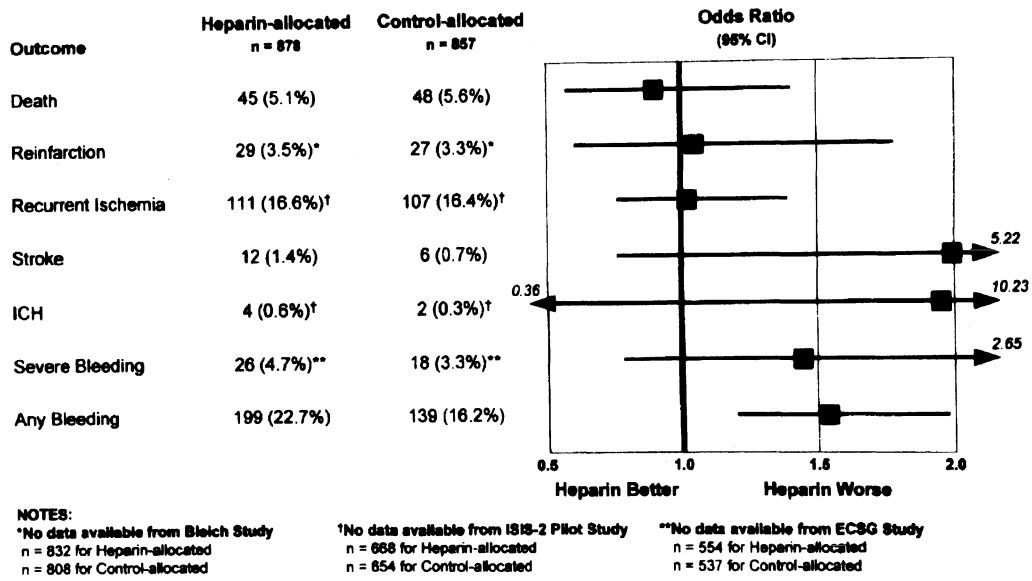

Fig. 13. Meta-analysis of the effects of intravenous heparin in patients with suspected acute myocardial infarction. Reproduced with permission from ref. *152*.

Most of the data come from the Second Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico (GISSI-2) trial *(145,146)* and the Third International Study of Infarct Survival (ISIS-3) trial *(147)*. During the actual period of heparin treatment in these trials there was a 7% reduction in mortality (from 7.3 to 6.8%), but at 35 days, the difference in mortality was no longer statistically significant (2% reduction, from 10.2 to 10.0%). There is, however, concern that these two megatrials may have underestimated the beneficial effects of heparin because of the way in which the heparin was administered. In GISSI-2 the heparin was started 12 h after the initiation of fibrinolytic therapy and in ISIS-3 it was started 4 h after the initiation of fibrinolytic therapy. Moreover, in both trials, the heparin was administered subcutaneously, which further delayed the achievement of an anticoagulated state.

Trials with intravenous heparin. Given the fact that patients enrolled in GISSI-2 and ISIS-3 accounted for >95% of the patients included in the above meta-analysis and that there are concerns regarding the efficacy of the heparin regimens in those two megatrials, it is reasonable to undertake a separate inspection of trials that have used intravenous heparin. Six randomized, controlled trials *(143,144,148–151)* (Table 3) have directly examined the effect of iv heparin in patients receiving thrombolytic therapy for AMI. A meta-analysis of these trials *(152)* revealed a statistically nonsignificant 9% reduction in mortality (from 5.6 to 5.1%) (Fig. 13). There was no significant difference in the rates of reinfarction or recurrent ischemia. There was, however, a statistically nonsignificant 42% increase in the rate of severe bleeding with double the rates of stroke and intracranial hemorrhage.

The above trials, however, are a heterogeneous group. None of the patients in the study by Bleich and colleagues *(143)*, half of the patients in the ISIS-2 pilot study *(144)*, and only those patients who did not receive heparin in the Heparin-Aspirin Reperfusion Trial (HART) *(151)* received aspirin, whereas all the patients in the European Cooperative Study Group (ECSG)-6 *(148)*, Optimization Study of Infarct Reperfusion Investigated

Table 4
Angiographic Studies Randomizing Intravenous Heparin (Hep) in Patients Receiving Thrombolysis for Acute Myocardial Infarction

				TIMI grade 2 or 3 (%)		*TIMI grade 3 (%)*	
Trial (ref.)	*Year*	*Aspirin*	*Patients*	*– Hep*	*+ Hep*	*– Hep*	*+ Hep*
Bleich et al. *(143)*	1990	–	95	43	71	38	52
HART *(151)*	1990	±	205	52	82	31	56
ECSG-6 *(148)*	1992	+	652	75	83	66	76

by ST-Monitoring (OSIRIS) *(149)*, and Duke University Clinical Cardiology Study (DUCCS)-1 *(150)* received aspirin. An analysis of the subgroup of patients in these six trials who were given aspirin revealed that heparin had no effect on mortality. By contrast, in patients who were not given aspirin, treatment with heparin was associated with a statistically nonsignificant 28% reduction in mortality, similar to the effect seen in the meta-analysis of trials in the preaspirin and prethrombolytic era.

When SK is used as the thrombolytic agent, the data from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial *(153)* demonstrated that treatment with iv heparin conferred no mortality benefit over high-dose sc heparin. There was, in fact, a statistically significant increase in the reinfarction rate (4.2 vs 3.5%). Since iv heparin is not superior to sc heparin (from GUSTO), and sc heparin is not superior to placebo (from GISSI-2 and ISIS-3), indirect data show that iv heparin offers no advantage in patients receiving thrombolysis with SK for AMI.

By contrast, when tPA is used as the thrombolytic agent, iv heparin is a standard part of adjunctive therapy *(42)*. There are two indirect lines of evidence that support this practice. First, if one analyzes the patients receiving tPA in GISSI-2, ISIS-3, and GUSTO-I, the mortality rates are 9.8% for tPA alone, 9.6% for tPA plus sc heparin, and 6.3% for tPA plus iv heparin. However, the mortality rates in general were lower in GUSTO-I than in GISSI-2 or ISIS-3 for comparable groups, raising doubts about the validity of indirect comparisons between different subsets in these studies. Second, several small trials *(143,148,151)* have shown improved infarct-related artery patency (defined as TIMI grade 2 or 3 flow) when iv heparin is added to thrombolysis with tPA (Table 4). More importantly, these trials have also demonstrated that a higher percentage of patients achieve TIMI grade 3 flow with the addition of iv heparin to thrombolysis with tPA. These trials were themselves too small to show a significant difference in mortality or reinfarction. However, extrapolating from the GUSTO-I data *(2)* showing that TIMI grade 3 flow at 90 min is associated with lower mortality and better left ventricular function at 30 d, one can argue that the addition of iv heparin to thrombolysis with tPA may improve patient outcome.

Trials with more intensive intravenous heparin regimens. In GUSTO-I, 50% of patients failed to achieve therapeutic anticoagulation. Therefore, a more intensive iv heparin regimen (increasing the upper limit of the target activated partial thromboplastin time [aPTT] to 90 s and increasing the initial infusion of heparin to 1300 U/h for patients weighing 80 kg or more) was initially used in TIMI-9A *(154)*, GUSTO-IIa

Table 5
Bleeding Complications with Heparin vs Hirudin

	ICH (%)		*Major bleeds (%)*	
Trial (ref.)	*Heparin*	*Hirudin*	*Heparin*	*Hirudin*
TIMI-9A *(154)*	1.9	1.7	10.1	13.9
GUSTO-IIa *(155)*	0.7	1.3	n/a	n/a
Thrombolytic therapy	1.5	2.2		
No thrombolytic therapy	0	0.5		
HIT-III *(156)*	0	3.4	1.9	3.4
Total	0.9	1.6	7.7	10.8

(155), and r-Hirudin for Improvement of Thrombolysis (HIT)-III *(156)*. This resulted in 20% more heparin being administered in GUSTO-IIa than in GUSTO-I. All three trials were stopped prematurely because of an increased rate of intracerebral hemorrhage (ICH) and other major bleeding events (Table 5). Whereas the rate of ICH was 0.7% in GUSTO-I, it was 1.9% in the heparin arm of TIMI-9A and 1.5% in the heparin arm of GUSTO-IIa (for the subset of patients receiving thrombolytic therapy for AMI); there were no ICHs in the heparin arm of HIT-III, but there was a 3.4% rate in the hirudin arm, prompting the termination of that trial. The mean aPTT of patients with ICH was 100 s in TIMI-9A and 110 s in GUSTO-IIa, compared with a mean aPTT of 85 s (both trials) for patients without ICH. An analysis of the aPTTs from patients enrolled in the GUSTO-I trial revealed that a lower mortality was associated with aPTT at 12 h between 50 and 70 s; aPTTs higher than this were associated with an increased rate of moderate to severe bleeding, ICH, and, interestingly, reinfarction *(157)*.

In summary, in patients ineligible for thrombolytic therapy, heparin is of proven benefit in patients unable to take aspirin and is of no proven benefit in those taking aspirin. For patients receiving thrombolytic therapy with SK, there is convincing data that heparin, either subcutaneous or intravenous, offers no benefit. For patients receiving tPA, heparin continues to be used based on angiographic data showing higher infarct-related artery patency, but clinical trials demonstrating decreased mortality or reinfarction are lacking. If heparin is to be used, it should be adjusted to achieve an aPTT between 50 and 70 s.

Direct Thrombin Inhibitors

Hirudin

Pharmacology. Hirudin is a naturally occurring anticoagulant derived from the saliva of the medicinal leech (*Hirudo medicinalis*) that has subsequently been produced via recombinant DNA technology *(158)*. It is a 65-amino acid protein with a molecular weight of 7000 Daltons that contains two domains: the N-terminal domain binds to and inhibits the active catalytic site of thrombin *(159)* and the C-terminal tail binds to the substrate recognition site of thrombin *(160)* (Fig. 14). The apolar binding site of thrombin may also be involved in the interaction *(126)*. Unlike heparin, hirudin is a direct thrombin inhibitor and therefore does not require the presence of ATIII to neutralize thrombin. Hirudin is uniquely specific for thrombin *(161)*, should not crossreact with the antibodies responsible for HIT, and is not inactivated by platelet factor 4 or heparinases. Hirudin is an extremely potent antithrombin and can inactivate both fluid-phase and clot-bound

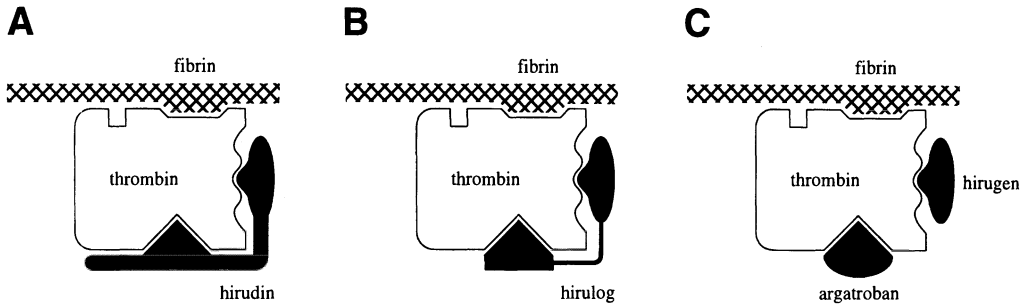

Fig. 14. Interaction between thrombin and direct thrombin inhibitors. Hirudin (**A**) and hirulog (**B**) bind to both the catalytic and substrate recognition sites. Hirugen (**C**) binds only to the substrate recognition site and argatroban (**C**) binds only to the catalytic site. All of the direct thrombin inhibitors can inactivate clot-bound thrombin, and none of them require the presence of antithrombin III (ATIII).

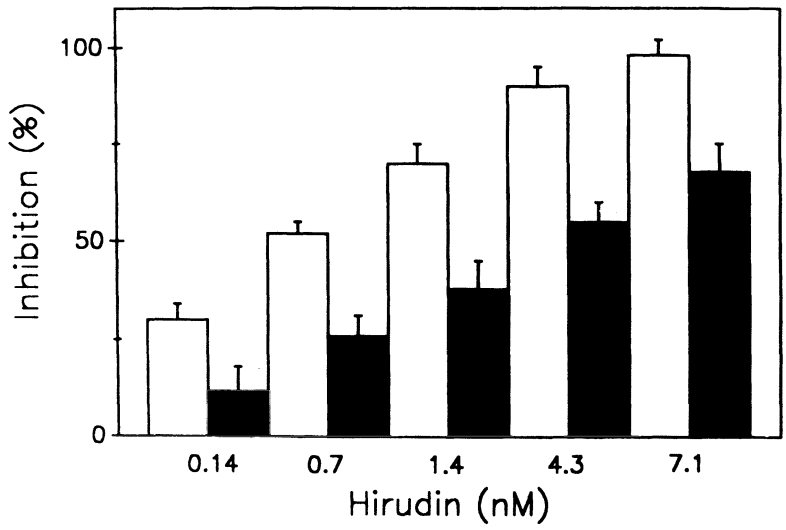

Fig. 15. Comparison of the inhibitory effects of hirudin against fluid-phase (open bars) and clot-bound (solid bars) thrombin activity. Thrombin or fibrin clots were incubated with citrated plasma in the presence or absence of hirudin. Fibrinopeptide A (FPA) levels were then measured by radioimmunoassay, and the percent inhibition of FPA generation was calculated for each inhibitor concentration. Reproduced with permission from ref. *10*.

thrombin, although it is less effective against the latter, requiring approximately 10-fold higher doses to achieve comparable degrees of thrombin inhibition (Fig. 15) *(10,162)*.

Clinical data. After demonstrating promising results in two pilot studies when given as adjunctive antithrombin therapy with tPA (TIMI-5) *(163)* and SK (TIMI-6) *(164)*, hirudin was compared with heparin in three phase III trials [TIMI-9A *(154)*, GUSTO-IIa *(155)*, and HIT-III *(156)*]. In both TIMI-9A and GUSTO-IIa, hirudin was given as a 0.6-mg/kg intravenous bolus followed by an infusion at 0.2 mg/kg/h; in HIT-III a different recombinant hirudin was used and at a slightly lower dose (0.4-mg/kg intravenous bolus followed by an infusion at 0.15 mg/kg/h). As stated above, these trials were stopped prematurely because of an unexpectedly high rate of ICH. Combining the data from the

three trials, treatment with hirudin was associated with a higher rate of ICH (1.6 vs 0.9%) and a higher rate of major bleeding (10.8 vs 7.7%) (Table 5). However, these differences failed to reach statistical significance in any individual trial, and no formal meta-analysis has been completed. Based on these data, the TIMI, GUSTO, and HIT investigators altered their anticoagulation protocols, with a reduction in the hirudin and heparin doses in TIMI-9B and GUSTO-IIb and changes from tPA to SK and from iv to sc hirudin and heparin in HIT-4.

In TIMI-9B *(165)*, 3002 patients with AMI were treated with aspirin and either tPA or SK (at the discretion of the treating physician) and were randomized within 12 h of symptoms to receive anticoagulation for 96 h with either hirudin 0.1-mg/kg iv bolus followed by an infusion at 0.1 mg/kg/h or heparin 5000-U iv bolus followed by an infusion at 1000 U/h. Both anticoagulants were adjusted to achieve an aPTT of 55–85 seconds. At 24 h there was a slightly higher rate of death or nonfatal myocardial infarction with hirudin (2.8 vs 2.3%). At 30 d, treatment with hirudin was associated with a 21% higher incidence of death (6.1 vs 5.1%), a 19% reduction in the rate of myocardial infarction (3.6 vs 4.4%), and a 9% higher incidence of the combined end point of death, recurrent myocardial infarction, congestive heart failure, or shock (12.9 vs 11.9%). None of these differences achieved statistical significance. There was also no significant difference in the rates of ICH or other major bleeding events.

In GUSTO-IIb *(166)*, 12,142 patients with acute coronary syndromes were randomized to receive anticoagulation for 72 h with either hirudin or heparin, each dosed according to the same protocol used in TIMI-9B. Of the 12,142 patients, 4131 presented with ST-segment elevation, and 74% of those patients received thrombolytic therapy with either tPA or SK (again, at the discretion of the treating physician). At 24 h, treatment with hirudin (for both ST elevation and non-ST-elevation patients) was associated with a statistically significant 39% reduction in the combined end point of death or myocardial infarction (from 2.1 to 1.3%). At 30 d, for the patients with ST-segment elevation, there was only a 6% reduction in mortality (from 6.2 to 5.9%), an 18% reduction in myocardial infarction (from 6.0 to 5.0%), and a 14% reduction in the primary combined end point of death or myocardial infarction (from 11.3 to 9.9%). None of these differences achieved statistical significance. For patients with ST-segment elevation, there was no significant difference in the rates of ICH or of severe or moderate bleeding (although for all patients, treatment with hirudin was associated with a 14% higher rate of major bleeding).

In HIT-4 *(167)*, 1208 patients with AMI were treated with SK and randomized to hirudin 0.2-mg/kg iv bolus followed by 0.5 mg/kg sc bid for 5–7 d or a bolus of placebo followed by heparin 12,500 U sc bid. Early data from an angiographic substudy revealed a trend toward higher rates of TIMI grade 3 flow at 90 min with hirudin than with heparin (41 vs 34%), but this did not reach statistical significance. Moreover, 30-d mortality and reinfarction rates were equivalent, with a 6.8% mortality and a 4.4% reinfarction rate in the hirudin group compared with a 6.4% mortality and a 4.9% reinfarction rate in the heparin group.

Thus, despite promising angiographic data, three large randomized controlled trials have failed to show any statistically significant benefit of hirudin over heparin in terms of mortality or reinfarction, (although in the largest trial, GUSTO-IIb, there was a trend showing an approximate 18% reduction in reinfarction). There are several possible reasons for the lack of a significant demonstrable benefit with hirudin in these trials *(168)*.

First, the trials may have been underpowered given the relatively low event rates. Calculations by the TIMI-9B investigators, however, show that the likelihood that a 25%

relative superiority of hirudin over heparin failed to be detected in TIMI-9B is less than 1 in 1000 and that the likelihood that even a 10% relative superiority failed to be detected is 1 in 20. Second, hirudin may have been dosed inadequately. However, in GUSTO-IIa, despite a higher dose of hirudin that was associated with an unacceptably high rate of ICH, the rate of death or myocardial infarction was 11.7% in the hirudin group. Third, the duration of antithrombin therapy may have been inadequate. There is, however, no indication that treatment for 96 h (in TIMI-9B) was clearly superior to treatment for 72 h (in GUSTO-IIb).

Fourth, the effects of direct thrombin inhibitors such as hirudin may not be durable. In GUSTO-IIb, all of hirudin's beneficial effect on reducing the rate of death or reinfarction was evident at 24 h; subsequent to this the event-rate curves neither converged nor diverged. (This pattern, however, was not seen in TIMI-9B in which hirudin was associated with mixed results in terms of the rate of death or reinfarction at 24 h.) This potential lack of a durable effect also been noted in other trials using thrombin inhibitors *(169–171)*. The mechanistic implication of this observation is that thrombin inhibitors may not be able to "passivate" the arterial surface to prevent the generation of platelet thrombi after the treatment is discontinued.

Fifth, although hirudin may be a more potent inhibitor of thrombin activity, it may be a less potent inhibitor of thrombin generation. Prothrombin fragment 1.2 (F1.2) levels are used as a marker of thrombin generation, and fibrinopeptide A (FPA) levels are used as a marker of thrombin activity. Data show that heparin causes a greater reduction in F1.2 levels than hirudin does, whereas hirudin causes a greater reduction in FPA levels than heparin does *(172,173)*, implying that heparin may possess a greater ability to decrease thrombin generation (potentially through its enhancement of ATIII's inhibition of factor Xa), and hirudin may possess a greater ability to decrease thrombin activity.

Hirugen

Hirugen is a synthetic derivative of hirudin that contains the terminal 12 residues of the C-terminal end of hirudin and has a molecular weight of 524 Daltons *(174)*. The molecule was designed to block the substrate recognition site of thrombin while leaving the catalytic site free to interact with and be inhibited by ATIII (Fig. 14) *(175)*. In vivo, however, hirugen has been found to be a relatively weak antithrombotic and has not gone on to extensive testing in clinical trials *(176)*.

Hirulog

Pharmacology. Hirulog is a 20-amino acid synthetic peptide with a molecular weight of 873 Daltons that contains the [D]Phe-Pro-Arg-Pro sequence of the amino terminus of hirudin connected by a polyglycyl link to a 12-amino acid sequence from the carboxy terminus of hirudin *(124,177)*. The former sequence binds to and blocks the catalytic site, and the latter sequence binds to and blocks the substrate recognition site (Fig. 14). Hirulog has been shown to be equally active against both fluid-phase and clot-bound thrombin *(10)*, and it is not inhibited by platelet factor 4. Interestingly, there is evidence that hirulog is slowly cleaved by thrombin at the Arg-Pro bond, effectively transforming hirulog into hirugen *(177)*.

Clinical data. After promising data was seen in a pilot angiographic study *(178)*, Théroux and colleagues *(179)* at the Montreal Heart Institute randomized 68 patients presenting with AMI and treated with aspirin and SK to iv heparin, low-dose hirulog (0.5 mg/kg/h for 12 h followed by 0.1 mg/kg/h for 4–6 d), and high-dose hirulog (1.0 mg/kg/h for 12 h

followed by a placebo infusion). The primary end point of TIMI grade 3 flow at 90 min was achieved in 31% of patients who received heparin, 85% of patients who received low-dose hirulog, and 61% of patients who received high-dose hirulog (all differences statistically significant). At follow-up angiography at 4–6 d, TIMI grade 3 flow was seen in 83, 96, and 81% of patients, respectively. There were fewer serious bleeding events in the hirulog groups than in the heparin group. The study size was too small to detect significant differences in mortality. The group that received high-dose hirulog followed by the placebo infusion had more clinical events and a higher reocclusion rate than the other two groups. This finding suggests that antithrombin therapy with direct thrombin inhibitors may need to continue for at least several days.

The Hirulog Early Reperfusion/Occlusion (HERO) trial randomized 412 patients presenting with AMI and treated with aspirin and SK to iv heparin, low-dose hirulog (0.125-mg/kg iv bolus, followed by an infusion at 0.25 mg/kg/h for 12 h, followed by an infusion at 0.125 mg/kg/h for < 60 h), and high-dose hirulog (0.25-mg/kg iv bolus followed by an infusion at 0.5 mg/kg/h for 12 h, followed by an infusion at 0.25 mg/kg/h for < 60 h) *(180)*. Again, the primary end point was achievement of TIMI grade 3 flow at 90–120 min. There was a statistically significant higher percentage of patients achieving TIMI grade 3 flow with high-dose hirulog (48%) and low-dose hirulog (46%) than with heparin (35%). However, at 2–3 d, repeat angiography revealed similar percentages of patients achieving TIMI grade 3 flow (77% with high-dose hirudin, 79% with low-dose hirudin, and 70% with heparin). Although there was a decreased need for rescue angioplasty and a decreased incidence of death, cardiogenic shock, and recurrent infarctions in the hirulog groups (12.5% with high-dose hirudin and 14% with low-dose hirudin compared with 17.9% with heparin), this difference did not reach statistical significance. Major bleeding was significantly less in the low-dose hirulog group (14%) than in the high-dose hirulog (19%) or heparin (27%) groups. A phase III trial including 17,000 patients is now under way to compare hirulog with heparin as an adjunct to SK in patients with AMI.

Argatroban

Pharmacology. Argatroban is an arginine derivative tripeptide synthetic compound with a molecular weight of 527 Daltons that is structurally similar to fibrinopeptide A *(124,181–183)*. Argatroban contains a sequence corresponding to the cleavage sequence in fibrinogen and inhibits thrombin by acting as a competitive antagonist, binding to the apolar binding site and blocking the catalytic site (Fig. 14). Like hirudin, argatroban does not require the presence of ATIII to neutralize thrombin and it is not inhibited by platelet factor 4 or heparinases. Argatroban is equally effective against fluid-phase and clot-bound thrombin (Fig. 16) *(162)*. This is in contrast both to heparin, which is largely ineffective against clot-bound thrombin, and to hirudin, which demonstrates reduced activity against clot-bound thrombin *(10,162,184)*. This may be related to argatroban's relatively small size (Table 6), which may allow it to penetrate better into the interstices of a fibrin clot and thus inhibit fibrin-bound thrombin more effectively. In animal models, argatroban has been shown to be superior to heparin in preventing platelet-rich thrombosis, enhancing thrombolysis, and preventing reocclusion *(185–187)*. As with heparin, there is some evidence that there may be a rebound coagulation phenomenon after discontinuation of argatroban *(188)*.

Clinical data. In the Myocardial Infarction with Novastan and tPA (MINT) trial *(189)*, 120 patients with AMI received tPA and aspirin and were randomized to receive iv

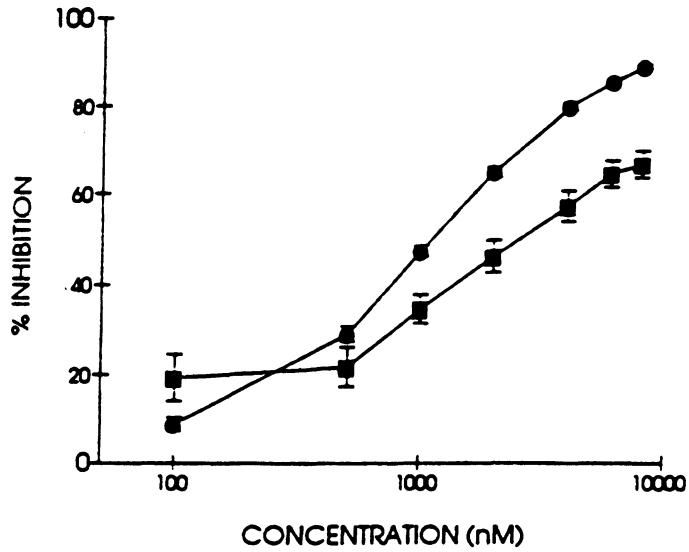

Fig. 16. Comparison of the inhibitory effects of argatroban against fluid phase (circles) and clot-bound (squares) thrombin activity. Thrombin or fibrin clots were incubated with the chromogenic synthetic substrate S2238 in the presence or absence of argatroban. *p*-nitro-aniline (*p*-NA) release was then assayed, and the percent inhibition of *p*-NA release was calculated for each inhibitor concentration. Reproduced with permission from ref. *162*.

Table 6
Molecular Weights of Antithrombins

Antithrombin	*Molecular weight (Daltons)*
Heparin	Average 15,000
Hirudin	7000
Hirugen	524
Hirulog	873
Argatroban	527

heparin (70-U/kg iv bolus followed by an infusion at 15 U/kg/h), low-dose argatroban (100-μg/kg iv bolus followed by an infusion at 1.0 μg/kg/min), or high-dose argatroban (100-μg/kg iv bolus followed by an infusion at 3.0 μg/kg/min). Treatment with argatroban was associated with a higher rate of achieving TIMI grade 3 flow at 90 min (59.5% in the high-dose argatroban group and 55.9% in the low-dose argatroban group compared with 41.9% in the heparin group) and a lower corrected TIMI frame count (cTFC) at 90 min (28.0 in the high-dose argatroban group and 30.2 in the low-dose argatroban group compared with 39.3 in the heparin group). In patients who received treatment between 3 and 6 h after the onset of symptoms, the superiority of argatroban was even more striking, with the cTFC significantly lower in the high-dose argatroban group compared with the heparin group (cTFC 26.3 in the high-dose argatroban group, 32.8 in the low-dose argatroban group, and 49.2 in the heparin group). The rates of major bleeding were approximately 70% lower with argatroban compared with heparin (2.6% with low-dose argatroban and 2.1% with high-dose argatroban vs 7.5% with heparin). Larger, phase III trials using argatroban are being planned.

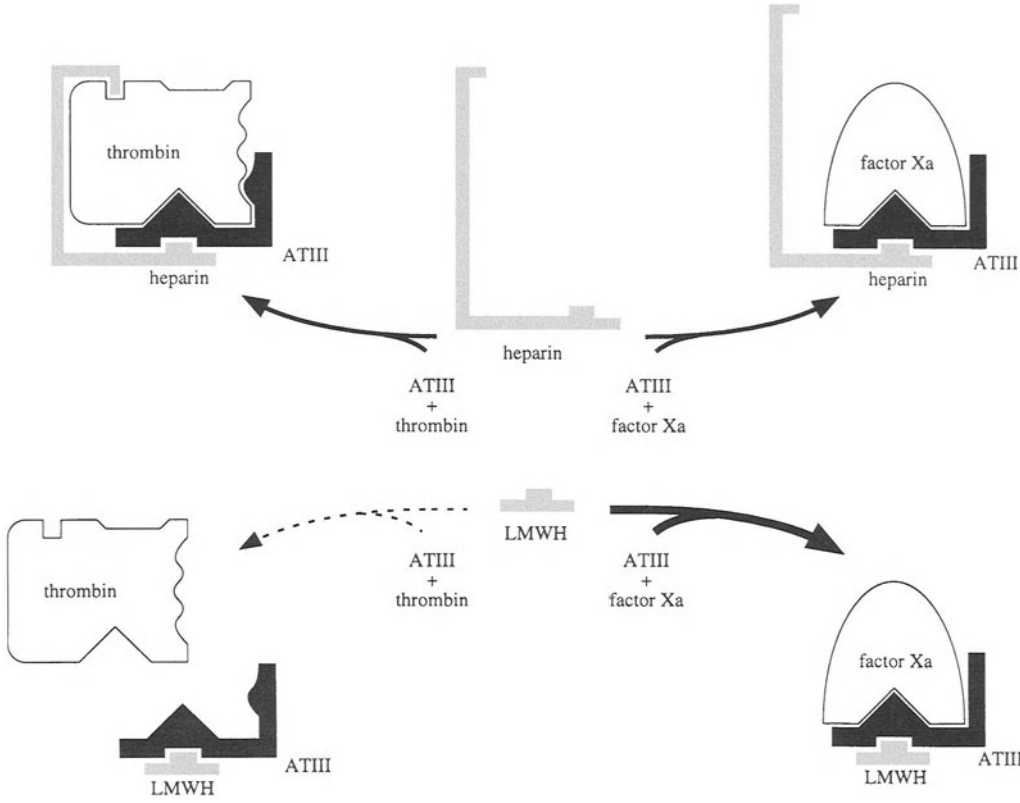

Fig. 17. Mechanism of action of heparin versus low molecular weight heparin (LMWH). Unfractionated heparin (UFH) induces a conformational change in antithrombin III (ATIII), allowing the latter to inhibit thrombin and factor Xa more readily. In the case of thrombin inhibition, UFH also acts as a catalytic template, forming a ternary complex with thrombin and ATIII and accelerating their interaction by >1000-fold. By contrast, LMWH does not contain a sufficient number of polysaccharide residues to act as a catalytic template for ATIII and thrombin but still can induce the conformational change in ATIII and therefore is primarily a factor Xa inhibitor.

Low-Molecular-Weight Heparin

Pharmacology

Low molecular weight heparins (LMWHs) are fragments of standard unfractionated heparin (UFH) produced by controlled depolymerization to yield chains with mean molecular weights of 4000–6000 Daltons *(190,191)*. As with UFH, the anticoagulant activity of LMWH is due to the unique pentasaccharide sequence that binds to ATIII, thereby inducing a conformational change that makes the reactive site more accessible to both factor Xa and thrombin. However, unlike UFH, only a small percentage of LMWH contains the sufficient number of polysaccharide residues to be able to act as a catalytic template by binding ATIII and thrombin simultaneously. Thus, LMWH exerts its anticoagulant effect primarily by inhibition of thrombin generation that is achieved by inactivating factor Xa (Fig. 17) *(192)*. Like UFH, LMWH cannot inactivate clot-bound thrombin *(193)* nor can it inactivate factor Xa once it is part of the prothrombinase complex. LMWHs are resistant to inactivation by platelet factor 4 *(194)*, are less bound by acute-phase reactants and vascular endothelial cells, thereby resulting in a more pre-

dictable anticoagulation effect *(135,190)*, and are far less likely to trigger HIT *(195)* (although in a patient with HIT and antiplatelet antibodies LMWH may crossreact).

Clinical Data

In several large trials, LMWH has been shown to be equivalent and perhaps even superior to intravenous UFH in unstable angina and non-Q-wave myocardial infarction *(171,196,197)*. However, relatively few data exist on the role of LMWH in AMI. In patients with AMI who were treated with SK, aspirin, and iv UFH for 5 d, there was a decreased rate of reinfarction in patients who received LMWH for an additional 25 d compared with placebo *(198)*. In animal models of AMI, LMWH has been shown to be superior to UFH in maintaining patency rates after thrombolysis *(199,200)*. In 100 patients with AMI who received SK and who were randomized to LMWH or intravenous UFH, there was no significant difference in the levels of serum markers for thrombin activity (FPA, thrombin-ATIII complexes) or factor Xa activity (prothrombin fragment 1+2) *(201)*. A recent trial comparing LMWH with intravenous UFH in 300 patients with AMI who received thrombolytic therapy with tPA, SK or anistreptelase demonstrated a statistically significant 30% reduction in the number of acute cardiac events at 3 months (from 36.4 to 25.5%) *(202)*. Larger trials will need to be conducted to confirm these initial reports suggesting the superiority of LMWH to UFH.

Other Antithrombotics

Fibrin-Targeted Hirudin

Fibrin-targeted hirudin consists of hirudin covalently linked to the Fab′ fragment of an antifibrin monoclonal antibody *(203)*. In response to the excessive bleeding seen in the initial trials with hirudin, fibrin-targeted hirudin was created to allow local thrombin inhibition to be achieved while minimizing systemic side effects. Early experimental data in animals indicate that fibrin-targeted hirudin is 10-fold more potent than hirudin *(204)*, but it has yet to be demonstrated that fibrin-targeted hirudin causes fewer bleeding complications.

Thrombin Aptamers

Thrombin aptamers are single-stranded DNA oligonucleotides that inhibit the activity of thrombin *(205)*. They bind the fibrinogen recognition site *(206)* and retain their activity against clot-bound thrombin *(207)*. In animal models of thrombosis, they have been shown to be potent antithrombotics with a rapid onset of action and a short half-life *(207,208)*.

Tick Anticoagulant Peptide

Tick anticoagulant peptide (TAP) was originally derived from the soft tick (*Ornithodorus moubata*) and is now produced via recombinant DNA technology *(209–211)*. TAP can inhibit factor Xa both in its free form and as part of the prothrombinase complex. In animal models, TAP proved superior to heparin *(212)* and hirudin *(213,214)* in accelerating thrombolysis and preventing acute reocclusion.

Antistasin

Antistasin is a 119-amino acid protein isolated from the salivary gland of the Mexican leech *H. officinalis (124,215)*. It too is a specific factor Xa inhibitor *(216)*. Although superior to heparin in enhancing thrombolysis and preventing reocclusion in an animal thrombosis model *(217)*, its immunogenicity may ultimately limit its clinical utility *(32)*.

Tissue Factor Pathway Inhibitor

Tissue factor pathway inhibitor (TFPI), also known as lipoprotein-associated coagulation inhibitor, has been examined as a means to block one of the pathways leading to factor Xa generation. TFPI is a 276-amino acid protein containing three Kunitz-type inhibitor domains *(218–220)*. TFPI can bind and inhibit factor Xa, and the Xa-TFPI complex can inhibit the VIIa-tissue factor complex, which generates factor Xa *(221,222)*. In animal studies, TFPI prevented reocclusion after thrombolysis *(223–225)*, although not effectively as TAP *(226)*.

Thrombin Generation vs Thrombin Activity

The pattern of reocclusion seen in experiments with thrombin generation inhibitors confirms previous observations that both active thrombin generation and preformed thrombin play a role in reocclusion. Inhibition of prothrombinase prevents further thrombin generation but leaves preformed, clot-bound thrombin to trigger reocclusion once it is exposed during ongoing thrombolysis. Conversely, thrombin inhibition may effectively prevent preformed thrombin from triggered thrombosis, but such therapy must continue until prothrombinase activity has been neutralized by endogenous anticoagulant systems or new thrombin generation will lead to thrombosis. Therefore, inhibition of both thrombin and prothrombinase may allow rapid achievement of thrombolysis and prevention of reocclusion using the shortest duration of therapy with the lowest systemic effects.

Summary

- Thrombin is a complex molecule that plays a key role in both the coagulation cascade and platelet activation. Multiple agents have been developed in an attempt to block its role in coronary thrombosis.
- In patients not receiving aspirin, heparin has been shown to reduce mortality and nonfatal reinfarctions.
- In patients receiving aspirin and undergoing thrombolysis, neither sc nor iv heparin is of benefit when SK is used, but iv heparin remains the standard of care when tPA is used, based primarily on extrapolations from angiographic data. Attempts to use more intensive iv heparin regimens have resulted in unacceptably high rates of bleeding.
- Despite several theoretical advantages, direct thrombin inhibitors have yet to be shown to be superior to heparin, but the optimal dose and duration of therapy with these new agents remain unresolved issues. Hirudin has been shown to be no better than heparin in three large mortality trials. Hirulog and argatroban have been shown to confer short-term angiographic benefits (as has hirudin) and are being investigated in larger mortality trials.
- LMWH, primarily a factor Xa antagonist and hence a thrombin generation inhibitor, has shown promise in a small trial and also awaits further testing in larger mortality trials.
- Additional promising new agents include specific thrombin generation inhibitors such as TAP and TFPI.

CONCLUSIONS

The current standard for adjunctive therapy with thrombolysis is still aspirin and heparin. Both these medications came into use more than 50 years ago when our understanding of the molecular biology underlying acute coronary syndromes was nonexist-

ent. As we have deciphered the mechanisms underlying platelet activation and aggregation and thrombin generation and activity, we now stand at the threshold of a new era in which exquisitely tailored pharmacotherapy can be used to inhibit the pathways leading to coronary artery thrombosis.

Platelet physiology has now been sufficiently dissected to allow us to target and inhibit specifically platelet adhesion, activation, and aggregation. Although aspirin remains a vital component of AMI therapy, GP IIb/IIIa inhibitors are now emerging as powerful new adjunctive agents with potential long-lasting benefits. Similarly, we now have at our disposal inhibitors both of thrombin generation and of thrombin activity, and we are able to attack both fluid-phase and clot-bound thrombin. The right direct thrombin inhibitor at an optimal dose and duration, and perhaps in conjunction with other antithrombotics acting at different parts of the coagulation cascade, may yet emerge as the new standard of care for acute ST-segment elevation myocardial infarction.

As we continue to refine our knowledge, the next step will be to design appropriate combinations of agents. Variations of "quadruple therapy" in which acute ST-segment elevation myocardial infarction is treated with a thrombolytic, aspirin, a GP IIb/IIIa inhibitor, and a direct thrombin inhibitor are already being tested. In TIMI-14A, patients are receiving low-dose thrombolytic, aspirin, abciximab, and heparin. In animal studies, a combination of tPA, eptifibatide, and hirudin has been used and has demonstrated improved reperfusion and decreased reocclusion compared with tPA and either eptifibatide or hirudin *(227)*. Ultimately, adjunctive therapy for acute ST-segment elevation myocardial infarction may specifically target each of the major factors contributing to reocclusion and therefore may include a thrombolytic, a platelet activator inhibitor such as aspirin, a platelet aggregation inhibitor such as a GP IIb/IIIa inhibitor, a direct thrombin inhibitor such as hirulog or argatroban, and a thrombin generation inhibitor such as TAP or TFPI.

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13 β-Adrenergic Blockers, Calcium Channel Blockers, and Nitrates

Peter H. Stone, MD

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INTRODUCTION

During the past two decades the pathophysiologic mechanisms considered responsible for the acute coronary syndromes (Q-wave myocardial infarction [MI], non-Q-wave MI, and unstable angina) have been evolving dramatically. In the mid-to-late 1970s, episodic coronary vasospasm was thought to be responsible for the development of unstable angina and acute (A)MI *(1,2)*. In the mid-to-late 1980s and mid-1990s, plaque rupture and subsequent thrombus formation were considered paramount *(3,4)*, and coronary vasoconstriction was considered quite inconsequential. The different acute coronary syndromes were perceived simply to represent different points on a single continuum of plaque rupture and thrombus formation: the continuum ranged from a ruptured plaque with little or no thrombus (often asymptomatic), to a ruptured plaque with moderate thrombus leading to only partial coronary occlusion (unstable angina and MI associated with ST-segment depression), to a ruptured plaque with extensive thrombus and complete occlusion of the artery (MI associated with ST-segment elevation). In the mid-to-late 1990s, however, it has been appreciated that this two-component pathophysiologic model of the acute coronary syndromes may be simplistic and inadequate for some patients. Recent evidence from atherectomy samples, for example, indicate that a substantial number of patients with unstable angina , and perhaps those with non-Q-wave MI as well, may be manifesting disease due to a rapid cellular proliferation of the atherosclerotic plaque itself, with little contribution from either major thrombus formation or vasoconstriction *(5,6)*. These three mechanisms (ruptured plaque, thrombus formation, and

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rapid cellular proliferation) may also be closely interrelated in a given patient, with a substantial contribution from each.

As the understanding of culprit mechanisms has evolved, the targets of therapeutic intervention have likewise evolved. Because the predominant pathophysiology of the acute coronary syndromes relates to an abrupt cessation of coronary blood flow and myocardial oxygen supply, therapeutic strategies have focused on restoration of coronary blood flow: therapies to limit thrombus formation and enhance thrombus dissolution (thrombolytic therapy, thrombin inhibitors, and platelet inhibitors) and therapies to "debulk" the luminal obstruction mechanically (percutaneous transluminal coronary angioplasty, stent, atherectomy, laser, and so on). A critical foundation in the therapeutic approach to patients with the acute coronary syndromes remains, however, the reduction in myocardial oxygen demand since this approach may limit the amount of infarction for a given amount of ischemia, and it may also widen the window of time within which other therapeutic interventions may be effective. The purpose of this chapter is to focus on the role of the conventional antiischemic therapies, i.e., β-adrenergic blockers, calcium channel blockers, and nitrates, in the management of the acute coronary syndromes. Although an effort is made to review the experience with these agents separately for patients who present with ST-segment elevation compared with those who present with ST-segment depression or unstable angina, this distinction often cannot be made from many of the clinical trials conducted before the thrombolytic era. Entry criteria for most of the older studies included persistent ST-segment elevation *or* depression ≥1.0 mm, whereas many of the newer studies include only those with persistent ST-segment elevation if thrombolytic therapy was administered.

β-ADRENERGIC BLOCKING AGENTS

Mechanisms of Action

β-blockers function as competitive antagonists to the beta-adrenergic receptors on cell membranes. Selective β-1 antagonists act at receptor sites found primarily in the myocardium, inhibiting catecholamine-mediated increases in cardiac contractility and nodal conduction rates. β-2 receptors are found mainly in vascular and bronchial smooth muscle; inhibition at these receptor sites can lead to vasoconstriction and bronchospasm. These β-blockers exert their beneficial effect in the acute coronary syndromes by preventing catecholamine-mediated β-1 activation, leading to decreased contractility and heart rate, thereby improving the oxygen supply/demand balance. These drugs also exert an antiarrhythmic effect, as evidenced by an increase in the threshold for ventricular fibrillation in animals and a reduction in complex ventricular arrhythmias in humans *(7–9)*. Finally, β-blockers may prevent plaque rupture by reducing the mechanical stresses imposed on the plaque *(10)*.

Use in ST-Segment Elevation Myocardial Infarction

The β-blockers were among the first therapeutic interventions designed to limit the size of an AMI. In most of these studies, all patients with AMI were included together regardless of the direction of the ST-segment deviation on admission. Norris and colleagues in New Zealand *(11,12)* demonstrated in 1978 that early administration of β-blockers decreased the size of AMI measured enzymatically (as a function of creatine kinase enzyme release) or by reduction of ST-segment elevation. Some of the early studies of β-blockers to reduce infarct size *(13)* were limited by the lack of appreciation

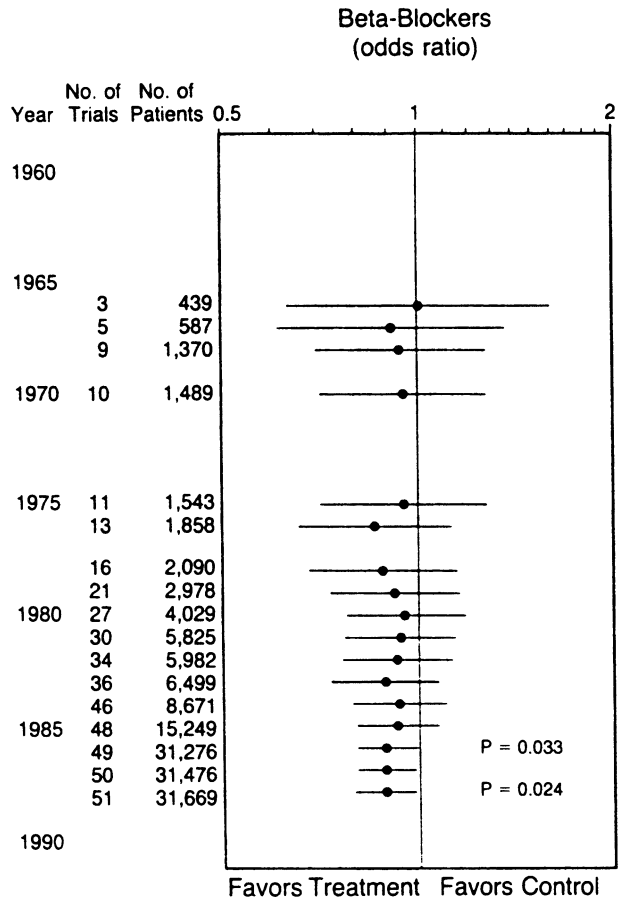

Fig. 1. Results of 51 randomized clinical trials of the effects of oral or iv followed by oral β-blockers for the treatment of AMI (odds ratios and 95% confidence intervals for effect of treatment on mortality). Reproduced with permission from ref. *59*.

that the window of time within which myocardium may be salvaged was in the range of 6–12 h. In the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study, for example, β-blockers were administered up to 24 h after onset of chest pain *(13)*.

More recent studies using a more appropriate design to administer the β-blocker within an appropriate time window have definitively demonstrated a benefit associated with β-blocker therapy (Fig. 1) *(14,15)*. In the largest trial, the First International Study of Infarct Survival (ISIS-1) *(16)*, over 16,000 patients with suspected MI were treated with immediate iv atenolol, 5–10 mg, within 12 h of the onset of symptoms followed by 100 mg daily. The mortality difference between those receiving atenolol and the controls was evident by the end of day 1; the 7-d mortality was reduced from 4.3 to 3.7% ($p < 0.02$). Metaanalyses from 27 randomized trials, totaling about 27,000 patients, indicate that early iv (followed by oral) β-blockers reduced mortality by 13% in the first week (95% confidence interval [CI] -2 to -25; $p < 0.02$) *(14,17)*. The mortality reduction was greatest in the first 2 d (about 25%), supporting the value of early initiation of β-blockade *(17)*. Early treatment also reduced nonfatal reinfarction by about 19% (95% CI -5 to -33; $p < 0.01$) and nonfatal cardiac arrest by about 16% (95% CI -2 to -30; $p < 0.02$). Composite end points of death, nonfatal reinfarction, and nonfatal arrest were reduced by 16%

($p < 0.001$) *(17)*. Data from the ISIS-1 trial suggest that the reduction in mortality is largely due to prevention of cardiac rupture and ventricular fibrillation *(16)*. Detailed analyses of the results based on various subgroups (initial heart rate, risk category, presence or absence of ventricular arrhythmia, and so on) indicated a benefit in all groups.

When β-blockers are used in conjunction with thrombolytic therapy, they provide incremental benefit, particularly if they can be administered early after the onset of infarct symptoms. In the Thrombolysis in Myocardial Infarction (TIMI)-II trial *(18)*, patients with persisting ST-segment elevation who were randomized to receive early metoprolol (15 mg iv, followed by oral metoprolol 50 mg bid for 1 d and then 100 mg bid thereafter) in addition to iv alteplase experienced a 49% lower incidence of subsequent nonfatal reinfarction ($p = 0.02$) and a 27% lower incidence of recurrent ischemia ($p = 0.005$) compared with those patients randomized to receive metoprolol only orally beginning 6 d after the acute event. Those patients who were treated within 2 h of symptom onset had the greatest reduction of the composite end point of death or reinfarction compared with those treated with only late oral metoprolol.

A number of studies have classified the mechanism of death as *sudden* or *nonsudden*, based on the duration of time from the onset of symptoms to actual death. Sudden death is variably defined as "instantaneous" to "within 2 h of symptoms" and is presumably due to arrhythmias or cardiac rupture; nonsudden deaths are those occurring later after the onset of symptoms, presumably owing to nonarrhythmic causes such as reinfarction, and may include a few noncardiac deaths. Tabulation of the results from the available studies indicates a highly significant reduction of approximately 30% in the incidence of sudden death and a nonsignificant reduction of only about 12% in the incidence of nonsudden death (Fig. 2) *(14)*. The fact that β-blockers were particularly effective in reducing both sudden death and mortality among patients with complex ventricular ectopy at baseline *(19)* suggests that β-blockers exert their beneficial effect primarily by reducing the frequency and severity of arrhythmias *(20)*.

It is striking that the long-term mortality benefits of the β-blockers following an index MI (i.e., secondary prevention) extend to most members of this class of agents *(14)*. There does not seem to be a significant difference between agents with or without cardioselectivity (Fig. 3). However, the presence of intrinsic sympathomimetic activity reduced the benefit to nonsignificance (odds ratio 0.90; 95% CI 0.77–1.05) (Fig. 3) *(14)*. Reduction in heart rate appears to be a critical feature associated with the protective effect of β-blockers. Indeed, there is a significant relationship between the magnitude of heart rate reduction observed on the active agent and the magnitude of reduction in mortality (Fig. 4A) *(21)*.

Many of the large-scale clinical trials have also reported the effects of long-term β-blocker use on nonfatal reinfarction. Results from pooled analyses indicate that β-blocker use is associated with an odds ratio of 0.74 (95% CI 0.66–0.83; $p < 0.001$). As observed for mortality, there is also a significant relationship between the magnitude of reduction in heart rate and the reduction in nonfatal recurrent MI ($r = 0.54$; $p < 0.05$) (Fig. 4B) *(21)*. This observed benefit of reducing nonfatal reinfarction is in addition to the benefit on mortality.

The magnitude of benefit from long-term use of a β-blocker is also dependent on the patient's risk of mortality associated with their index MI (Table 1). Post hoc analyses of data from the Beta Blocker Heart Attack Trial (BHAT) *(22)* indicate that those MI patients without electrical or mechanical complications experienced only a 6% relative benefit from the use of propranolol. MI patients with electrical complications experienced a 52% relative benefit, those with mechanical complications experienced a 38%

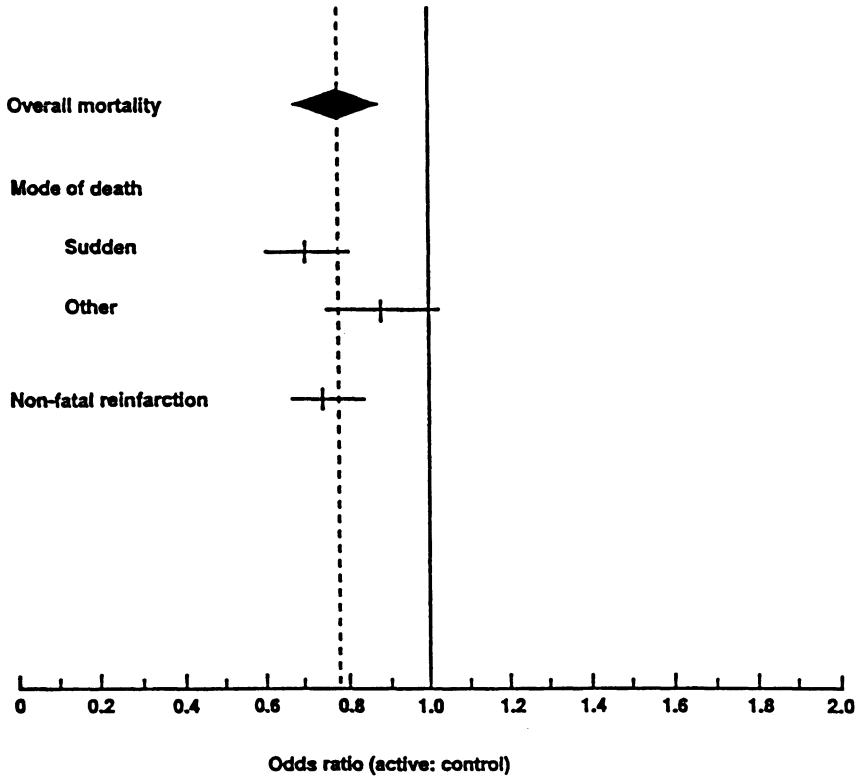

Fig. 2. Sudden death, other death, and nonfatal reinfarction in long-term β-blocker trials that reported these end points separately (odds ratios [active/control], together with approximate 95% confidence ranges). See original article for citation of specific trials. Reproduced with permission from ref. *14*.

relative benefit, and those with both mechanical and electrical complications experienced a 25% relative benefit. Considering the low cost of routine β-blocker use and its substantial benefit, such therapy has a relatively favorable cost-effectiveness ratio: an estimated cost of therapy per year of life saved would be $13,000 in low-risk patients, $3600 in medium-risk patients, and $2400 in high-risk patients *(23)*.

The benefits from routine β-blocker use seem to persist as long as the active agent is continued *(24–26)*. It is therefore most appropriate after MI to maintain β-blocker therapy indefinitely in patients who can tolerate it *(27)*.

The benefits of a β-blocker in long-term secondary prevention appear to extend to most patient subgroups. The Beta-Blocker Pooling Project *(28)* combined the results of nine large trials and found that although high-risk patients were most likely to benefit from β-blocker therapy, lower risk patients also benefited, even though the absolute and relative benefits were small. The experience using β-blockers in the elderly is limited, but available data indicate that the benefit may even be greater in patients older than 50–60 than in younger patients. Benefit appeared to be similar in both men and women.

The side effects from prolonged β-blocker use have generally been minor and are similar to those seen with placebo *(29)*. In studies that report it, the incidence of heart failure is slightly but significantly higher in patients receiving β-blocker (5.9%) than in patients receiving placebo (5.4%) (pooled odds ratio 1.16; 95% CI 1.01–1.34) *(14)*.

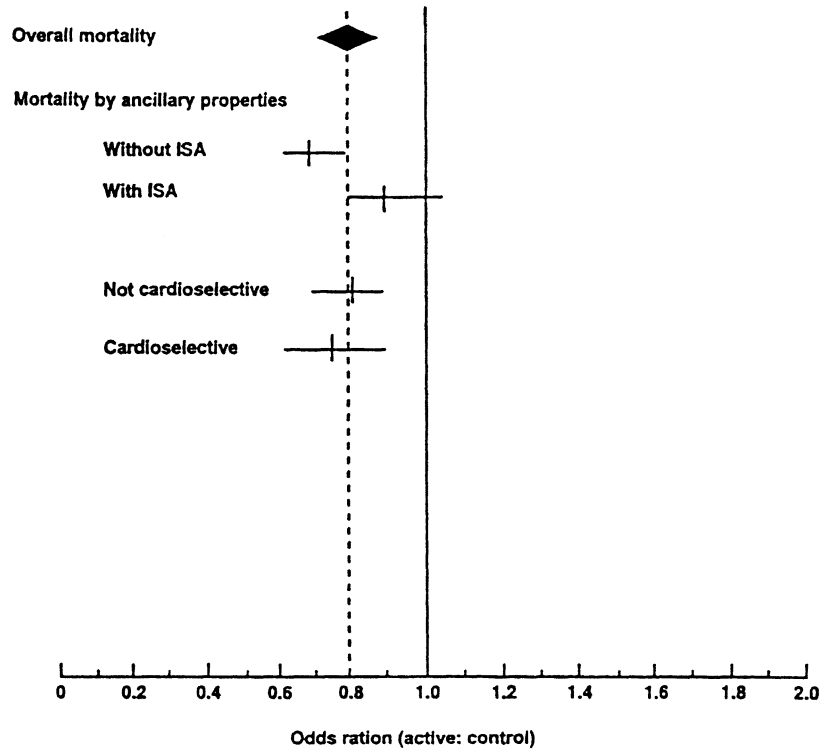

Fig. 3. Mortality in long-term β-blocker trials, by ancillary properties of agent tested (odds ratios [active/control], together with approximate 95% confidence intervals). See original article for citation of specific trials. Reproduced with permission from ref. *14*.

However, even patients with a history of mild or moderate congestive heart failure actually experienced greater benefit from β-blockade than did patients without that condition *(20)*.

Use in Patients with Unstable Angina and ST-Segment Depression Myocardial Infarction

Many of the studies evaluating the efficacy of β-blockers for AMI were conducted before the era of thrombolytic therapy and patients were included with either ST-segment elevation or depression on their presenting electrocardiogram (ECG). Since treatment was administered as early as possible after the onset of symptoms, criteria were not available to identify who would evolve a Q-wave MI, a non-Q-wave MI, or even unstable angina. Most of the experience previously discussed, therefore, concerning patients with "ST-segment elevation MI" actually represents a heterogeneous mix of "acute coronary syndromes" and is applicable to patients with non-Q-wave MI and those with unstable angina as well.

Only one placebo-controlled trial *(30)* specifically examined the effectiveness of β-blockers in unstable angina. In this study, patients not on prior β-blocking therapy were randomized to receive metoprolol, nifedipine, or both. Patients already on β-blockers were randomized to either nifedipine or placebo. The use of β-blockers alone was associated with a 25% reduction in recurrent ischemia or MI at 48 h. This reduction was not

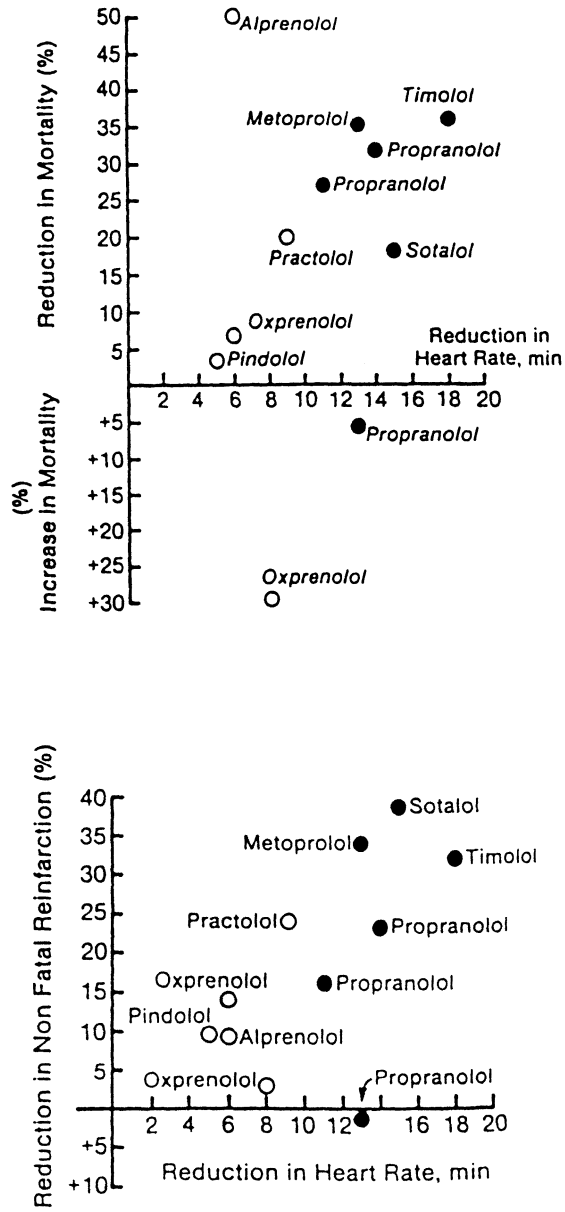

Fig. 4. **(A)** Relation between reduction in heart rate (difference between treatment groups) and percentage of reduction in mortality in large, prospective, double-blind trials with β-blockers. Open circles, β-blockers with intrinsic sympathomimetic activity: $r = 0.6$: $p < 0.05$. See original article for citation of specific trials. Reproduced with permission from ref. *21*. **(B)** Relation between reduction in heart rate and percentage of reduction in recurrent nonfatal infarctions in large, prospective, double-blind trials with β-blockers. Open circles, β-blockers with intrinsic sympathomimetic activity; $r = 0.59$; $p < 0.05$. See original article for citation of specific trials. Reproduced with permission from ref. *21*.

statistically significant. However, the addition of nifedipine to existing β-blockade was associated with a 20% reduction in short-term cardiac end points.

Other trials of β-blocker use in unstable angina have been small and uncontrolled *(31–33)*. A metaanalysis of these trials *(34)* showed a 13% reduction in progression

Table 1
All-Cause Mortality by Risk and Treatment Groups: Beta Blocker Heart Attack Trial[a]

	Placebo group		*Propranolol group*				
Risk group	*No. of patients*	*Mortality rate (%)*	*No. of patients*	*Mortality rate (%)*	*Absolute efficacy (100)*	*Relative efficacy (%)*	*Adjusted relative efficacy (%)*
No electrical or mechanical complications	1079	6.6	1047	6.2	0.4	6	–4
Electrical complications only	423	10.9	443	5.2	5.7	–52	–57
Mechanical complications only	202	16.8	201	10.4	6.4	–38	–43
Both electrical and mechanical complications	217	17.1	225	12.9	4.2	–25	–30

[a]Average length of follow-up was 25 mo. Data adjusted for 13 variables predictive of mortality.
Reproduced with permission from ref. *20*.

Table 2
Recommendations for the Use of β-Blocker Therapy Administered Early During Acute Myocardial Infarction

Conditions for which there is evidence that treatment is beneficial, useful and effective
Patients without a contraindication to β-adrenoceptor blocker therapy who can be treated within 12 h of onset of infarction, irrespective of administration of concomitant thrombolytic therapy
Patients with continuing or recurrent ischemic pain
Patients with tachyarrhythmias, such as atrial fibrillation with a rapid ventricular response
Conditions for which evidence is less well established
Non-Q-wave myocardial infarction
Conditions for which evidence suggests treatment is not useful and may be harmful
Patients with moderate or severe left ventricular failure or other contraindications to β-adrenoceptor blocker therapy

Data from ref. *15*.

Table 3
Recommendations for Long-Term Administration of β-Blockers (i.e. Secondary Prevention)

Conditions for which therapy is beneficial, useful, and effective
All but low-risk patients without a clear contraindication to β-adrenoceptor blocker therapy; treatment should begin within a few days of the event (if not initiated acutely) and continue indefinitely
Conditions for which beneficial effects are less well established but weight of evidence favors their use
Low-risk patients without a clear contraindication to β-adrenoceptor blocker therapy
Conditions for which evidence suggests treatment is not useful and may be harmful
Patients with a contraindication to β-adrenoceptor blocker therapy

Data from ref. *15*.

from unstable angina to MI, but no significant reduction in mortality. However, a number of randomized trials have shown a clear mortality benefit from β-blockers in other coronary syndromes, including acute MI, stable angina, and postinfarction angina, as discussed above.

Thus, β-blockers remain a cornerstone of the acute treatment of MI. Treatment is generally initiated intravenously, especially if it can be administered within 12 h of symptom onset, followed by continuation using oral formulations. The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with AMI are noted in Tables 2 and 3 *(15)*. β-Blockers are consistently useful for secondary prevention following MI *(27)* and should be maintained indefinitely.

CALCIUM CHANNEL BLOCKING AGENTS

Mechanisms of Action

Calcium channel blocking agents inhibit the entry of calcium into vascular smooth muscle cells and myocardial cells during the action potential, which triggers the contractile process. This calcium entry blockade leads to direct effects of vasodilation, nega-

tive inotropy, negative chronotropy (decreased heart rate), and negative dromotropy (decreased arteriovenous [AV]-nodal conduction) *(35)*. The systemic vasodilation leads to reflex sympathetic activation, which, in turn, promotes an increase in AV-nodal conductions.

The net clinical effects of the calcium channel blockers will be a composite of their direct effects and their reflex-mediated indirect effects. The two major categories of calcium channel blockers, the dihydropyridines (including nifedipine, amlodipine, nicardipine) and the nondihydropyridines (including diltiazem and verapamil) differ fundamentally: the dihydropyridines have greater vascular selectivity, leading to more peripheral vasodilation, and the potential for increased reflex sympathetic activation, whereas the nondihydropyridines have greater myocardial selectivity with a greater negative inotropic, chronotropic, and dromotropic effect. Both types of calcium channel blockers prevent coronary vasoconstriction and lower blood pressure. Thus, the principal antiischemic effects of the calcium blockers are to reduce myocardial oxygen demand by lowering blood pressure (dihydropyridines and nondihydropyridines) and lowering contractility and heart rate (nondihydropyridines only), as well as preventing coronary vasoconstriction if it is present. It should be noted that if reflex sympathetic activation predominates, as may be observed with use of immediate-release dihydropyridines, then the increase in contractility and heart rate may lead to an exacerbation of oxygen supply/demand imbalance.

The calcium channel blockers may also exert a fundamental cardioprotective effect of limiting calcium influx during ischemia, thereby limiting the amount of necrosis that ensues from a given ischemic result *(35)*.

Use of Calcium Channel Blockers in Patients with Myocardial Infarction

Dihydropyridine Calcium Blockers (Nifedipine and Nicardipine)

Early studies investigated the use of calcium channel blockers, particularly the dihydropyridines, for the early treatment of MI, but they were not found to be useful (Fig. 5) *(36)*. Patients were generally included regardless of the direction of ST-segment deviation on presentation. The dihydropyridines were studied in particular because they could be safely combined with β-adrenergic blockers without the concern for excessive reduction in myocardial contractility or bradycardia. The available formulation of dihydropyridines in this early era consisted of short-acting nifedipine, and this agent was found to be actually detrimental when used without a β-blocker to blunt the reflex sympathetic activity *(37–41)*. When combined with a β-blocker, nifedipine was significantly beneficial in reducing symptomatic manifestations of AMI *(37)*. Many of the studies *(17,26,36,42)* may not be methodologically comparable because the doses tested varied, and both the underlying disease manifestation and the timing from onset of the acute ischemic manifestation to initiation of the study drug may have been different.

Nevertheless, nifedipine has been uniformly unsuccessful in reducing either mortality or the rate of reinfarction (Fig. 5). A recent update of a pooled analysis *(42)* of stable coronary patients in a coronary regression trial with either nifedipine *(43)* or nicardipine *(44)* showed a trend toward an increase in mortality (7.4 vs 6.5%; odds ratio 1.16; 95% CI 0.99–1.35; $p = 0.07$) and a nonsignificant increase in reinfarction (3.5 vs 3.1%; odds ratio 1.19; 95% CI 0.92–1.53) (Table 4).

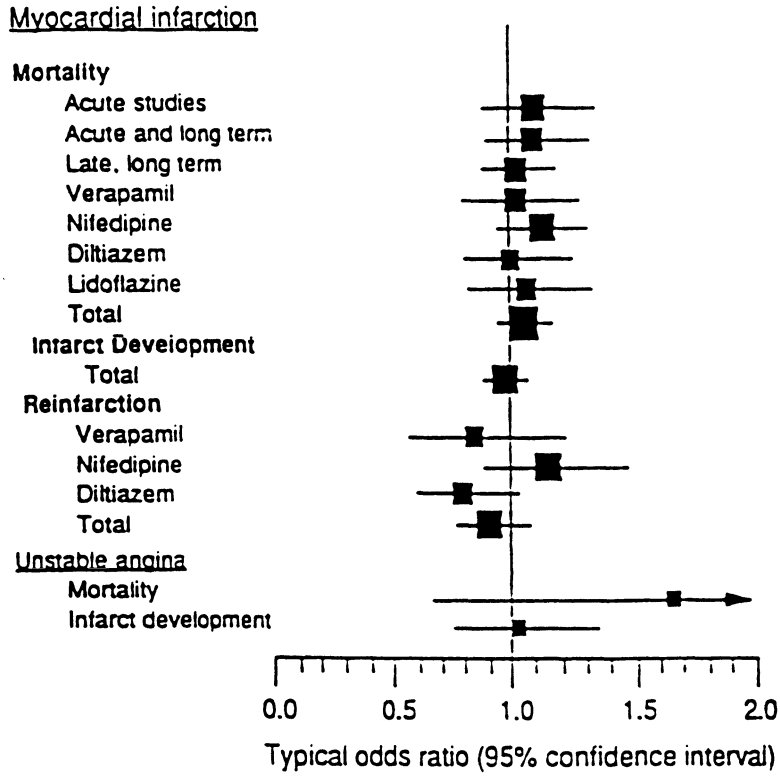

Fig. 5. Typical odds of death, infarct development, and reinfarction by disease, type of trials, and drug. Areas of squares are proportional to numbers of patients. *Bars*, 95% confidence intervals. *Portions to left* of vertical line (corresponding to odds ratio <1) indicate risk with treatment; *portions to right* of vertical line indicate increased risk with treatment. Upper 95% confidence limit for effect on mortality in unstable angina = 6.2. Note that treatment does not seem to reduce risk of any event. See original article for citation of specific trials. Reproduced with permission from ref. *36.*

Table 4
Secondary Prevention Trials of Calcium Channel Blocking Agents[a]

Event and agent	*Active*	*Control*	*Odds ratio (CI)*
Mortality			
Dihydropyridine	379/5137	335/5135	1.16 (0.99–1.35)
Verapamil	244/2644	266/2649	0.91 (0.76–1.10)
Diltiazem	180/1574	181/1577	0.99 (0.80–1.24)
Reinfarction			
Dihydropyridine	138/3838	119/3871	1.19 (0.92–1.53)
Verapamil	138/2606	171/2624	0.80 (0.63–1.01)
Diltiazem	113/1557	142/1560	0.79 (0.61–1.02)

[a]Data are number of events/number of subjects.

Calcium blockers to treat pathophysiologic disturbances associated with AMI remain extremely useful, such as treating hypertension with a dihydropyridine in combination with a β-blocker. A short-acting dihydropyridine like nifedipine may be extremely helpful in that setting because it can be selective to reduce blood pressure, it can be effective

quickly, and it can be titrated to the desired effect rapidly. Treatment of supraventricular tachycardias with a nondihydropyridine (diltiazem and verapamil) may also be useful, especially if treatment with a β-blocker is contraindicated.

Verapamil and Diltiazem

The calcium channel blockers verapamil and diltiazem can be considered together because their net pharmacologic effect is that of slowing the heart rate and, in some instances, reducing myocardial contractility *(35)*, thereby reducing myocardial oxygen demand. These studies are closer to more conventional secondary prevention design, since patients in these studies were treated with the active agent after their index MI was stabilized. A recent pooled analysis by Yusuf and colleagues *(42)* indicated that verapamil and diltiazem had no effect on mortality following AMI but that they exerted a significant effect on reducing the rate of reinfarction (6.0 vs 7.5%; odds ratio 0.79; 95% CI 0.67–0.94; $p < 0.01$) (Table 4). The effect seems similar for both agents.

Although the overall results of trials with verapamil showed no mortality benefits, subgroup analysis showed that immediate-release verapamil initiated several days after AMI in patients who were not candidates for a β-blocking agent may be useful in reducing the incidence of the composite end point of reinfarction and death, provided left ventricular function is well preserved with no clinical evidence of heart failure. In a placebo-controlled trial of almost 1800 patients, verapamil 360 mg/d started in the second week after AMI and continued for a mean of 16 mo had no effect on mortality compared with the control group, but reduced major event rates (death or reinfarction) from 21.6% in the control group to 18.0% in the active treatment group ($p = 0.03$) *(45)*. In patients without heart failure in the coronary care unit, however, verapamil significantly reduced both mortality (from 11.8% in the control group to 7.7% in the active treatment group; $p = 0.02$) and major events (from 19.7% in the control group to 14.6% in the active treatment group; $p = 0.01$), but there was no effect on either end point among patients who experienced congestive heart failure (CHF) in the coronary care unit *(45)*. Verapamil is detrimental to patients with heart failure or bradyarrhythmias during the first 24–48 h after AMI *(15,46,47)*.

Data from the Multicenter Diltiazem Postinfarction Trial (MDPIT) and the Diltiazem Reinfarction Study (DRS) *(48,49)* suggest that patients with non-Q-wave MI or those with Q-wave infarction, preserved left ventricular (LV) function, and no evidence of heart failure may also benefit from treatment with immediate-release diltiazem. In the DRS 576 patients with non-Q-wave MI were treated with either diltiazem (90 mg every 6 h) or placebo initiated 24–72 h after the onset of MI and continued for 14 days *(49)*. There was no difference in mortality, but diltiazem reduced the rate of reinfarction from 9.3% in the control group to 5.2% ($p < 0.03$) and the rate of refractory postinfarction angina from 6.9% in the control group to 3.5% ($p = 0.03$). In the MDPIT 2466 patients with a Q-wave or non-Q-wave MI were treated with either diltiazem (240 mg/d) or placebo 3–15 d after the MI onset and followed for a mean of 25 mo. There was no difference in mortality in the two treatment groups *(48)*. A significant bidirectional interaction was observed, however, between diltiazem and the presence of pulmonary congestion during the index MI (Fig. 6). In the 1909 patients without pulmonary congestion, diltiazem was associated with a significant *reduction* in cardiac events at 1 year from 11% in the control group to 8%, whereas in the 490 patients with pulmonary congestion diltiazem *increased* the cardiac event rate from 18% in the control group to 26%. A similar pattern was observed with respect to the ejection fraction, which was dichoto-

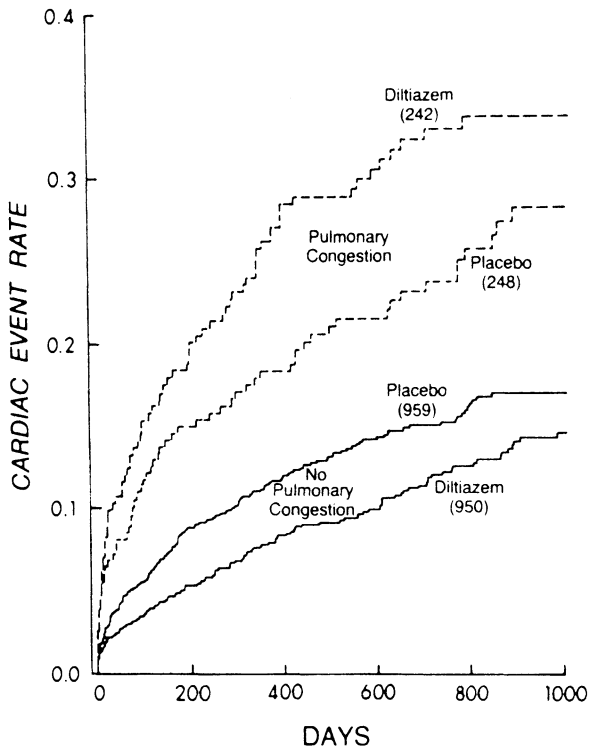

Fig. 6. Diltiazem-treated patients with pulmonary congestion had a higher rate of cardiac events than patients receiving placebo; diltiazem-treated patients without pulmonary congestion had a lower rate of cardiac events than patients receiving placebo. The values in parentheses are numbers of patients.

mized at 40% *(48)*. The results of MDPIT may be confounded by the fact that 53% and 55% of placebo- and diltiazem-treated patients, respectively, received concomitant β-blocker therapy. Also, both the MDPIT and DRS projects were conducted in an era when the use of aspirin was not as prevalent as it is today, raising further uncertainty about the relevance of their findings for contemporary management of AMI *(15)*. Of particular clinical importance is the detrimental mortality effect of diltiazem in patients with LV dysfunction.

It should be emphasized that there have not been studies comparing the efficacy of verapamil or diltiazem with that of a β-blocker. β-Blockers more consistently reduce both mortality and reinfarction and should be recommended for those patients who can tolerate such medication. Verapamil or diltiazem may be a reasonable alternative for those patients who cannot tolerate a β-blocker, but who can tolerate one of the calcium blockers, for example, patients with severe chronic obstructive pulmonary disease or asthma. It should be noted, however, that many patients who cannot tolerate a β-blocker because of concern of excessive bradycardia or CHF may experience similar complications from diltiazem or verapamil.

Use of Calcium Blockers in Patients with Unstable Angina

Several small randomized trials have examined the use of nifedipine and diltiazem in unstable angina. A metaanalysis of these trials *(36)* showed no reduction in MI or death

rates in patients given calcium antagonists (110 of 561 patients [20%] treated with calcium antagonists developed MI, compared with 104 of 548 [19%] in the control group; death rates were 2.4 and 1.6% for the calcium antagonist and control groups, respectively) (Fig. 5). The largest trial, the Holland University Nifedipine/Metoprolol Trial (HINT) *(30)* described above, was discontinued prematurely because of a trend toward more nonfatal MIs in patients receiving nifedipine alone. When combined with a β-blocking agent, however, patients receiving nifedipine had a decreased rate of MI and death comparedwith placebo.

Several studies, however, have shown symptomatic benefit from calcium antagonists *(49–51)*. Thus, evidence for calcium channel blockers in unstable angina does not suggest any beneficial effect on mortality or progression of myocardial infarction, but does support their use for relief of refractory symptoms. Because of randomized trials showing an increased risk of death in patients treated with calcium channel blockers in the setting of AMI, particularly in patients with LV dysfunction *(48)*, calcium antagonists should be used only in patients with refractory symptoms despite the use of nitrates and β-blockers.

Calcium blocking agents have also been used successfully to reduce symptoms and possibly decrease morbidity in patients with vasospastic (also known as Prinzmental's or variant) angina *(52–55)*. Although patients with either Prinzmetal's variant angina or unstable angina may present with rest angina, patients with Prinzmetal's angina are characterized by preservation of exercise capacity without angina. By contrast, patients with unstable angina, who usually have severe epicardial coronary plaques that reduce blood flow, typically have very limiting exertional angina, as well as rest angina. In several small controlled and uncontrolled trials, a significant reduction in angina frequency was reported with the use of calcium antagonists *(52–54)*. There are no data to suggest superior efficacy of any one agent in particular. In one very small trial of patients with refractory angina, the combination of diltiazem and nifedipine was more effective than either agent alone *(54)*, although intolerable side effects precluded the use of both drugs in several of these patients. Because vasospastic angina is due to transient coronary arterial spasm rather than plaque rupture and thrombus, there is no role for antithrombotic or antiplatelet agents. Medical therapy, with an emphasis on nitrates and calcium antagonists titrated to symptom relief, is the mainstay of treatment. However, because most patients with vasospastic angina have some degree of underlying epicardial coronary artery disease, they may occasionally present with AMI due to plaque rupture. These patients should be managed according to standard practice.

The most recent ACC/AHA guidelines concerning use of the calcium channel blockers are shown in Table 5 *(15)*.

NITRATES

Mechanisms of Action

Nitroglycerin remains central to the treatment of coronary artery disease. The clinical effects of nitrates are mediated through several distinct mechanisms, including the following:

1. Dilation of large coronary arteries and arterioles with redistribution to blood flow from epicardial to endocardial regions. Nitroglycerin provides an exogenous source of nitric acid in vascular endothelium, facilitating coronary vasodilation even when damaged endothelium is unable to generate endogenous nitric oxide production due to coronary artery disease. It is important to emphasize that these coronary vasomotor effects may either increase or decrease collateral flow.

Table 5
Recommendations for the Use of Calcium Blocker Therapy for the Acute Coronary Syndromes[a]

Conditions for which there is evidence that treatment is beneficial, useful and effective
Verapamil or diltiazem may be given to patients in whom β-adrenoceptor blockers are ineffective or contraindicated (i.e., bronchospastic disease) for relief of ongoing ischemia or control of a rapid ventricular response with atrial fibrillation after AMI in the absence of CHF, LV dysfunction, or arteriovenous block

Conditions for which beneficial effects are less well established
In non-ST-elevation infarction, diltiazem may be given to patients without LV dysfunction, pulmonary congestion, or CHF; it may be added to standard therapy after the first 24 h and continued for 1 yr

Conditions for which evidence suggests treatment is not useful and may be harmful
Nifedipine (shortacting) is generally contraindicated in routine treatment of AMI because of its negative inotropic effects and the reflex sympathetic activation, tachycardia, and hypotension associated with its use
Diltiazem and verapamil are contraindicated in patients with AMI and associated LV dysfunction or CHF

[a]Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; LV, left ventricular. Data from ref. *15*.

2. Peripheral venodilation leads to an increase in venous capacitance and a substantial decrease in preload, thus reducing MVO2. Nitrates are consequently of particular value in treating patients with LV dysfunction and CHF.
3. Peripheral arterial dilation, typically of a modest degree, may decrease afterload.

In addition, nitrates have been shown to relieve dynamic coronary constriction, including that induced by exercise. Nitrates may also have an inhibitory effect on platelet aggregation in patients with unstable angina *(56)*, although the clinical significance of this finding is unclear.

Use of Nitrates in Patients with ST-Segment Elevation Myocardial Infarction

Early studies demonstrated that nitrates may be of value to reduce infarct size and improve regional myocardial function when administered early in the course of AMI (Fig. 7) *(57–59)*. Judgutt et al. *(58)*, for example, found that iv nitroglycerin administered to patients with AMI preserved LV function, particularly in patients with an anterior MI, and led to improved survival. A metaanalysis of these earlier studies prior to the acute reperfusion era indicated that nitrates reduced the odds of death after AMI by 35% (95% CI 28–49; $p < 0.001$) *(60)*. However, it should also be noted that use of nitroprusside was actually found in early studies to exacerbate MI by causing a coronary steal phenomenon. Routine use of nitroprusside to limit infarct size has led to conflicting results *(61–63)*, and its use cannot be recommended.

The use of nitrate therapy was investigated in the context of routine use of thrombolytic therapy and aspirin with short-term mortality as the primary end point in two recently completed large trials *(15)*. The GISSI-3 trial *(64)* randomly assigned 19,394 patients to a 24-h infusion of nitroglycerin (beginning within 24 h of onset of pain), followed by topical nitroglycerin (10 mg daily) for 6 wk (with patch removed at bedtime, allowing a

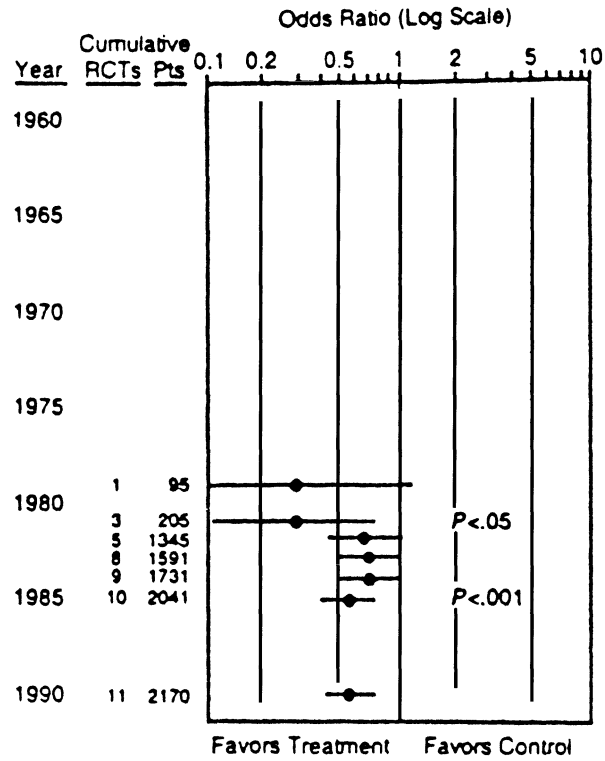

Fig. 7. Cumulative metaanalyses of the use of intravenous nitroglycerin for AMI. Reproduced with permission from ref. *59*.

10-h nitrate-free interval to avoid tolerance), or control. Approximately 50% of patients in the control group received nitrates on the first day or two at the discretion of their physician. There was an insignificant reduction in mortality at 6 wk in the group randomly assigned to nitrate therapy alone, compared with the control group (6.52 vs 6.92%, respectively). GISSI-3 evaluated lisinopril in a similar fashion; 6-wk mortality was reduced slightly. At both 6-wk and 6-mo follow-up, the combined use of lisinopril and nitrates led to a greater reduction in mortality when compared with the group that received no nitrate therapy or lisinopril alone. The other large trial *(65)*, compared 28-d treatment of controlled-release oral isosorbide mononitrate with placebo control (as well as intravenous magnesium sulfate vs control and the angiotensin-converting enzyme inhibitor captopril vs placebo control) in a 2 by 2 by 2 factorial design of 58,050 patients with supsected MI. Nitrate therapy in ISIS-4 was associated with a small, nonsignificant reduction in 35-d mortality compared with the control group (7.34 vs 7.54%) in the overall comparison. All subgroups examined, including those not receiving short-term nonstudy iv or oral nitrates at entry, failed to demonstrate a significant mortality benefit with nitrate use. In both GISSI-3 and ISIS-4, the power to detect potential beneficial effects of routine nitrate therapy was reduced by the extensive early use (>50%) of nontrial nitrate in the control subjects. When data from all randomized control trials of nitrate use in the management of AMI are combined, there is a small relative reduction in mortality (5.5%) that is statistically significant ($p = 0.03$) *(15)*.

A review of evidence from all pertinent randomized clinical trials does not support routine use of long-term nitrate therapy in patients with uncomplicated AMI *(15)*. How-

Table 6
Recommendations for the Use of Nitrate Preparations for Acute Coronary Syndromes[a]

Intravenous nitroglycerin may be useful for the first 24–48 h in patients with AMI and recurrent ischemia, CHF, or management of hypertension
It should be continued orally or topically in patients with CHF and large transmural MI
Routine use of long-term nitrate therapy is not recommended in patients with uncomplicated AMI

[a]Abbreviations: MI, myocardial infarction; CHF, congestive heart failure.
Data from ref. *15*.

ever, it is reasonable to use iv nitroglycerin for the first 24–48 h in patients with AMI and recurrent ischemia, CHF, or management of hypertension. It should be continued orally or topically in patients with CHF and large transmural MIs as well. Intravenous administration is recommended in the early stage of AMI because its onset of action, ease of titration, and opportunity for prompt termination in the event of side effects (Table 6).

These agents remain of major value in the treatment of recurrent angina or hypertension associated with AMI.

Use of Nitrates in Patients with Unstable Angina

Despite a clear benefit when applied in patients with chronic coronary artery disease or ischemic left heart failure, there are no data from randomized placebo-controlled trials that demonstrate an effect of nitrates with respect to symptom relief or reduction in morbid events in patients with unstable angina.

In patients receiving continuous nitrates, tachyphylaxis may be seen as early as 24–48 h after initiation. This problem can be managed by increasing the dose as needed until symptom relief is achieved. Once a patient has been pain free for 24 h, it is advisable to switch to a topical or oral form of nitrate therapy, with a nitrate-free interval of 6–8 h/d.

CONCLUSIONS

β-Adrenergic blockers are effective in reducing cardiac events in the acute coronary syndromes by lowering heart rate and contractility (i.e., myocardial oxygen demand).

1. When administered early without thrombolytic therapy, they reduce mortality by about 15% in the first week, with the greatest reduction in the first 2 d; they reduce nonfatal reinfarction by about 20%.
2. When administered with thrombolytic therapy for patients with MI associated with ST-segment elevation, β-blockers reduce nonfatal reinfarction and recurrent ischemia.
3. Beta-Blockers are most effective improving outcome in patients whose AMI is complicated by electrical or hemodynamic disturbances.
4. The benefit of β-blockers in secondary prevention supports indefinite use of these agents following AMI.

Calcium channel blockers reduce myocardial oxygen demand by lowering blood pressure dihydropyridines and nondihydropyridines) and lowering contractility and heart rate (nondihydropyridines), as well as preventing coronary vasoconstriction, if it is present.

1. Dihydropyridines should not be used without concomitant treatment with a β-blocker because reflex-mediated increases in sympathetic activation may exacerbate the myocardial supply/demand balance.
2. Nondihydropyridines (verapamil or diltiazem) may be given to patients in whom β-blockers are ineffective or contraindicated in the absence of CHF, LV dysfunction, or AV block.

Intravenous nitroglycerin may be useful for the first 24–48 h in patients with AMI and recurrent ischemia, CHF, or management of hypertension.

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14 Angiotensin-Converting Enzyme Inhibitors in Acute Coronary Syndromes

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INTRODUCTION

A century ago, Tigerstedt and Bergman *(1)* infused extracts of rabbit kidney into experimental animals and noted a hypertensive response. The chemical effector in the extracts would later be named renin. Years later, in another landmark study, Goldblatt et al. *(2)* produced systemic hypertension in dogs by clipping their renal artery, further supporting the hypothesis that the kidneys played a central role in blood pressure regulation. It was not, however, until the 1950s that the bloodborne complement of enzymes and substrates comprising the renin-angiotensin system would be elucidated. We now understand that renal juxtaglomerular cells secrete renin in response to intravascular volume depletion, decreased serum sodium concentration, and adrenergic stimulation. In the bloodstream, renin proteolytically cleaves the prohormone angiotensinogen, produced and secreted by the liver, into the decapeptide angiotensin I. Angiotensin I, in turn,

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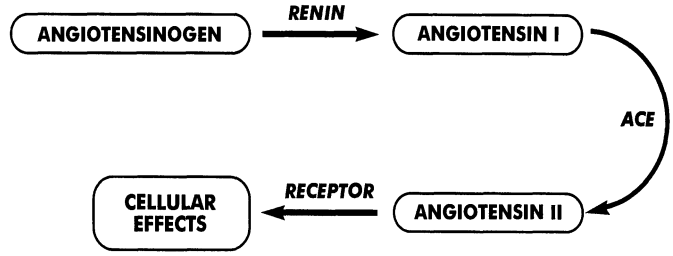


Fig. 1. Schematic of the components of the renin-angiotensin system. As indicated in the text, Angiotensinogen is the major substrate for renin, which generates angiotensin I. This molecule, in turn, is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II then binds to its receptor, which mediates its many different cellular effects. Data from ref. *98*.

is cleaved into the octapeptide angiotensin II by angiotensin-converting enzyme (ACE), a ubiquitous enzyme present on the surface of endothelial cells. The many important effects of the renin-angiotensin system discussed in this chapter may be attributed to the action of angiotensin II on its receptors in multiple organs (Fig. 1).

Extensive investigation of the renin-angiotensin system over the last 25 years has altered the traditional restrictive view of its role in only regulating blood pressure and volume status. We now know that an activated renin-angiotensin system is a maladaptive response to many disease states. As such, it is associated with an increased risk of initial and subsequent myocardial infarction, myocardial hypertrophy, development and progression of congestive heart failure, ventricular remodeling following myocardial infarction, and risk of ventricular arrhythmias. These observations are therefore the basis for the beneficial effects of blockade of the renin-angiotensin system. This chapter focuses on the actions and clinical effects of ACE inhibition in acute ischemic syndromes.

The Renin-Angiotensin System During Acute Ischemic Syndromes

Clinical Significance

A considerable body of evidence exists supporting the link between myocardial infarction and activation of the renin-angiotensin system. The time-course of neurohumoral rise and subsequent decline and the degree of neurohumoral activation are functions of the patient's clinical condition and hemodynamic compensation. In patients whose myocardial infarction is complicated by congestive heart failure, cardiogenic shock, or arrhythmias, activation of the renin-angiotensin system can be detected within 6 h of symptom onset *(3)*. In others, elevation of renin and angiotensin II does not occur until after d 1, with peak levels on d 3 *(3)*. The highest levels of renin and angiotensin II are seen in patients who develop heart failure or cardiogenic shock *(3)* and in those treated with diuretics *(4)*. By d 10, renin and angiotensin II levels return to normal except in patients treated with diuretics, in whom renin levels may remain elevated for a longer period *(3)*. However, even in patients who are hemodynamically compensated but who have sustained an extensive infarction, generally higher levels of renin and angiotensin II may be detected. For example, Vaughan et al. *(4)* studied patients 11–30 d after a first anterior wall acute myocardial infarction (AMI), who were not taking diuretics and who did not have overt congestive heart failure at the time of neurohumoral sampling. These investigators found mild but significant increases in angiotensin II and renin in those individuals with the most severe left ventricular dysfunction defined anatomically by the

presence of left ventricular aneurysm or with an extensive abnormally contracting segment; as well as in patients with a history of pulmonary congestion early after infarction.

Intuitively, it would appear that activation of the neuroendocrine system with its attendant vasoconstriction and tachycardia has some value in supporting hemodynamic stability during the periinfarct phase. However, except for extreme conditions such as cardiogenic shock or circulatory collapse, neurohormonal activation has detrimental clinical effects on cardiovascular function during the acute and convalescent phases of myocardial infarction.

Published studies of Cohn et al. *(5–7),* and Packer et al. *(8)* clearly show that higher levels of catecholamines and renin are associated with increased mortality in heart failure patients. The prognostic importance of neurohormonal activation in patients following myocardial infarction is less obvious, but has finally become apparent. Rouleau et al. *(9)* measured neurohormones in 534 patients an average of 12 d after infarction. Multivariate analyses, which included clinical characteristics as well as ejection fraction, showed that plasma renin activity (relative risk 1.6) and atrial natriuretic peptide (relative risk 2.2) independently predicted postinfarct cardiovascular mortality. A broader end point of cardiovascular mortality, or congestive heart failure, or recurrent infarction was predicted by plasma renin activity, aldosterone, atrial natriuretic peptide, and arginine vasopressin. These careful analyses strongly suggest that an activated neurohormonal system is not merely an epiphenomenon of left ventricular dysfunction, but is directly maladaptive and detrimental to cardiovascular survival. The clinical implications of these analyses of Rouleau et al. *(9)* are bolstered by the results of therapeutic trials using ACE inhibitors. Similarly, the improvement in survival seen in patients treated with β-blockers during both acute and chronic phases following myocardial infarction argues in favor of at least some direct detrimental effects of unabated elevations of neurohormones. Thus, at present, neurohumoral activation should be considered a cause of poor postinfarct prognosis.

Myocardial Hypertrophy and its Prognostic Implications

Left ventricular remodeling following myocardial infarction, the process by which the infarcted ventricle changes in size and shape, provides a plausible link between neurohumoral activation and postinfarct prognosis. Elevated blood pressure, a hemodynamic stress, leads to the development of cardiac muscle hypertrophy *(10).* Indeed, systolic wall stress has been identified as important in regulating the growth of the heart in vivo *(11–13.)* Myocardial hypertrophy has been associated with poorer cardiac prognosis, myocardial ischemia, and congestive heart failure *(14).* Left ventricular remodeling, a change in the size and shape of the heart in response to hemodynamic and other stresses of infarction, involves selective regional hypertrophy of the noninfarcted segments *(15).* There is ample experimental evidence that angiotensin II plays a role in both mechanical stress-induced and stress-independent myocyte hypertrophy. For example, Yamazaki et al. *(16)* stretched cardiac myocytes on deformable silicone dishes. This mechanical stress rapidly increased the activity of mitogen-activated protein kinases (MAPKs) and activators. Saralasin, an angiotensin II antagonist peptide, and CV-11974, a specific antagonist to type 1 angiotensin II receptors, both partially inhibited the stretch-induced activities of these enzymes.

However, the application of this concept to the bedside is less than simple. Patients do not present with degrees of hypertrophy or remodeling in exact proportion to the calculated hemodynamic stress *(17,18).* Nonhemodynamic mechanisms may therefore be at

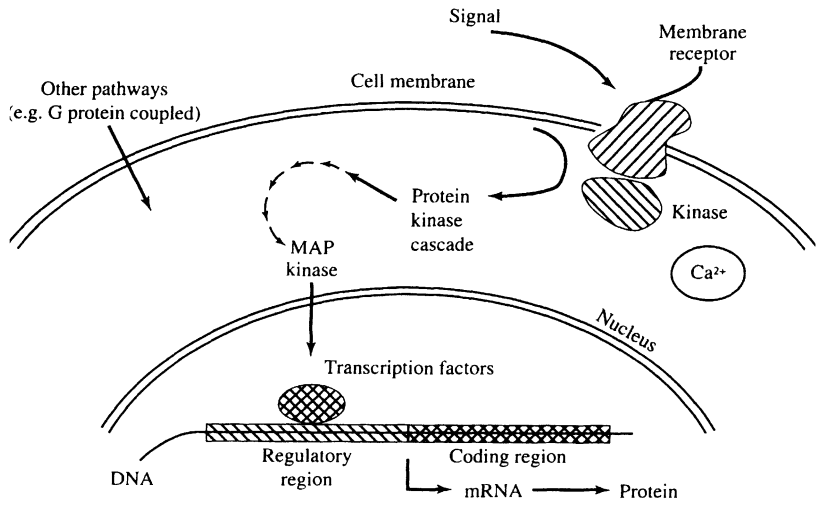


Fig. 2. Signal transduction pathways of myocytes for hypertrophic external stimuli. A specific membrane-associated receptor binds the extracellular ligand, which stimulates receptor-associated intracellular kinase activity that induces phosphorylation of a specific substrate. This activates a cascade of protein kinases and ultimately mitogen-activated protein (MAP) kinase, which in its phosphorylated form translocates into the nucleus, where it activates transcription factors via phosphorylation. In turn, the transcription factors bind to specific DNA motifs in the regulatory domains (promoters) of cardiac genes and transactivate gene transcription by interference with the basic transcription system of the cell. Data from ref. *99*.

play in determining the extent of left ventricular hypertrophy. Schunkert et al. *(19)* assessed the effects on new protein synthesis in isolated rat hearts of angiotensin II infusion. Angiotensin II infusion stimulated protein synthesis in this model, and the signal transduction pathway appeared to involve the type 1 angiotensin II receptor and protein kinase C. It appears there are significant similarities in the signal transduction pathways induced by both mechanical stimulation of myocytes and by angiotensin II. Both stimuli employ activation of protein kinase C which in turn leads to phosphorylation and activation of MAPKs. These translocate into the cell nucleus and activate nuclear transcription factors modulating the hypertrophic response (Fig. 2). Further evidence in support of the role of angiotensin II as a cardiac growth factor has been developed by showing that angiotensin II causes an increase in protein synthesis without changing the rate of DNA synthesis in cultured myocytes (hypertrophy). Similarly, in cultured cardiac fibroblasts, angiotensin II induces an increase in protein synthesis, DNA synthesis, and cell number (mitoses), independent of hemodynamic or neurohumoral effects *(20)*. These effects are modulated by the angiotensin II type I receptor subtype and can be inhibited by subtype I angiotensin II receptor antagonists *(20)*. Blockade of the renin-angiotensin system with ACE inhibitors has been shown to regress left ventricular hypertrophy *(21)*. However, the clinical significance in terms of any mortality benefits to be gained from regression of hypertrophy is presently unknown.

Thus, the process of postinfarct left ventricular remodeling has been tied to hypertrophy by morphologic *(22,23)* and experimental studies, and to angiotensin II by the studies noted above and by many others. The positive clinical results of the early use of ACE inhibitors to prevent remodeling is a logical bedside correlate of these experimental findings.

INTERACTION OF THE RENIN-ANGIOTENSIN SYSTEM WITH THE FIBRINOLYTIC SYSTEM

Clinical Implications During Acute Ischemic Events

Another important, recently proposed role of the renin-angiotensin system in ischemic heart disease centers on its effects on the plasma fibrinolytic system, which is based on the balance between plasminogen activator inhibitor-1 (PAI-1) and tissue-type plasminogen activator (tPA). tPA is released from endothelial cells and is present in small amounts in plasma where it catalyzes the conversion of plasminogen to plasmin. Plasmin proteolytically degrades fibrin, hence its antithrombotic activity. PAI-1, also secreted mainly from endothelial cells, is a major inhibitor of tPA, thereby slowing degradation of the fibrin clot and promoting hemostasis. Both have short plasma half-lives, on the order of 5 min, and their relative concentrations play an integral role in modulation of both thrombosis and fibrinolysis. PAI is elevated in a variety of prothrombotic or ischemic states, such as in young survivors of myocardial infarction *(24)*. Angiotensin II stimulates endothelial cells in culture to release plasminogen activator inhibitor *(25,26)*, an observation confirmed in vivo, in normal volunteers *(27)*. Furthermore, bradykinin, a vasoactive peptide that is degraded by ACE, induces dose-dependent increases in circulating plasminogen activator levels *(28)*.

Vaughan et al. *(29)* studied plasma fibrinolytic balance in patients following anterior myocardial infarction participating in the Healing and Early Afterload Reducing Therapy (HEART) study and treated with ramipril or placebo. At d 14 after the infarct, plasminogen activator inhibitor levels were 44% lower in the ramipril-treated group ($p = 0.004$) than in placebo patients. Furthermore, the ratio of circulating PAI to tPA was higher than at baseline in those patients *not* treated with ACE inhibition (Fig. 3). These observations form the basis of a new paradigm for the treatment of acute ischemic syndromes, namely, that protection against intravascular thrombosis depends on the balance between prothrombotic influences such as PAI, and fibrinolytic influences such as tPA *(30)*, and that ACE inhibition through nonhemodynamic humoral mechanisms may move this balance toward fibrinolysis and prevention of thrombotic events (Fig. 4).

Additional tentative evidence for the involvement of the renin-angiotensin system in ischemic events has also come from studies of the ACE gene in humans. An initial report by Cambien et al. *(31)* suggested a link between polymorphism of the ACE gene with increased risk of myocardial infarction. This ACE gene polymorphism consists of an insertion (I) or deletion (D) of a 287-bp sequence of DNA. Individuals containing the D/D genotype exhibit plasma ACE levels twice that of individuals containing the I/I genotype *(31)*. The D/D genotype also is more prevalent in middle-aged men with a prior history of myocardial infarction when compared with age-matched controls *(31)*. Moreover, an increased incidence of the ACE D/D genotype has been identified in children of patients with a history of myocardial infarction compared with controls *(32)*. An additional host of disease states have been associated with the D/D genotype. These include left ventricular hypertrophy *(33)*, hypertrophic cardiomyopathy *(34)*, restenosis after coronary angioplasty *(35)*, and progressive ventricular dilation following anterior myocardial infarction *(36)*. Pinto et al. *(36)* have investigated the link between on-going left ventricular dilation and the presence of the D/D genotype. Subjects enrolled in the Captopril and Thrombolysis Study (CATS) *(37)* underwent quantitative echocardiography immediately following therapy with streptokinase. After 1 year of follow-up, both end-systolic and end-diastolic volumes, as well as plasma norepinephrine levels,

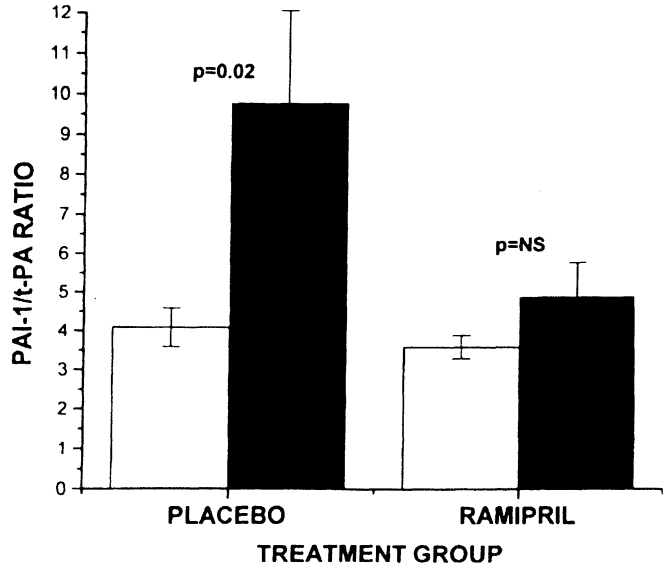


Fig. 3. Comparison of plasminogen activator inhibitor-1/tissue-type plasminogen activator (PAI-1/tPA) ratios at baseline (open bars) vs d 14 (shaded bars) in the placebo group and combined ramipril-treated subjects. Values are mean + SEM. At presentation, both tPA and PAI-1 levels were elevated in all groups. By d 14, while the molar ratio of PAI-1/tPA more than doubled in placebo-treated subjects, the ratio remained stable in ramipril-treated subjects. Therefore, ramipril appears to shift fibrinolytic balance toward lysis in patients after myocardial infarction, possibly accounting for the beneficial effects seen in patients treated with angiotensin-converting enzyme (ACE) inhibitors. Data from ref. *29*.

were greater in the D/D genotype group. Furthermore, these effects were attenuated in patients with the D/D genotype group by therapy with captopril. The degree of increase in volume indexes, both systolic and diastolic, were found to be proportional to the number of deletion alleles.

The finding that the presence of the D-allele may identify individuals at increased risk of cardiovascular disease may provide yet another link toward the treatment of ischemic syndromes with ACE inhibition. However, this link does remain controversial, and its existence is not unanimously accepted. For example, some follow-up studies examining the association between heart disease and the presence of the D/D genotype have failed to produce positive results *(38,39)*. Furthermore, the association between the ACE gene deletion polymorphism and risk of heart disease has been challenged based on the use of small study groups and the use of variable selection criteria *(40)*. In a large, prospectively followed population of male physicians enrolled in the Physician's Health Study *(41,42)*, Lindpaintner et al. *(39)* found no association between the presence of the ACE gene D-allele and an increased risk of ischemic heart disease or myocardial infarction. Explanations advanced in attempts to reconcile the conflicting and variable experimental results hinge on the influences that multiple environmental factors may have on the expression of a particular disease process and variations of genetic backgrounds among differing populations being studied *(39,40)*. Still another possibility is that the genetic mutation responsible for the D- and I-alleles is not of direct pathogenetic significance, but rather serves as a marker for a putative disease-relevant mutation existing in linkage disequilibrium elsewhere in the ACE gene complex *(39,40)*.

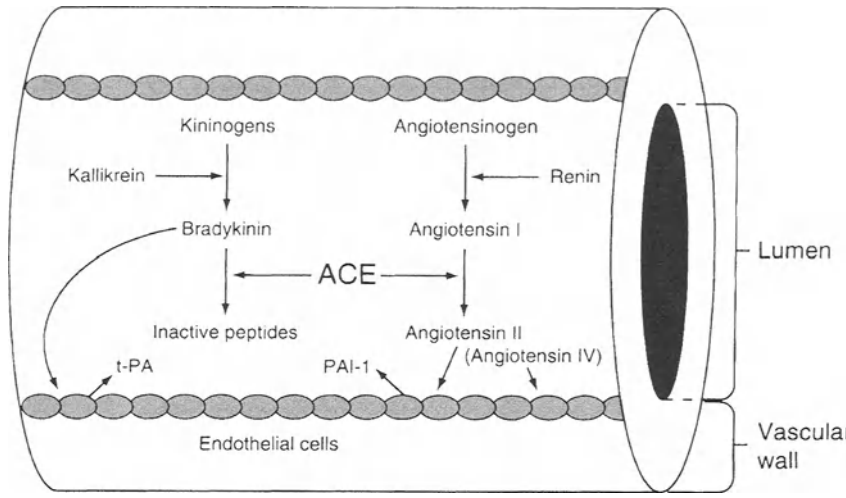


Fig. 4. Angiotensin-converting enzyme (ACE) plays a crucial dual role in the fibrinolytic balance between plasminogen activator inhibitor (PAI-1) and tissue-type plasminogen activator (tPA). Conversion of angiotensin I to angiotensin II leads to increased expression of PAI-1; degradation of bradykinin inhibits the production of tPA. Inhibition of ACE enhances bradykinin-mediated release of tPA from the endothelium while decreasing angiotensin II-mediated release of PAI-1. The net effect is a shift in the fibrinolytic balance toward lysis, an advantageous condition during acute ischemic syndromes. Data from ref. *100*.

VASCULAR ENDOTHELIAL FUNCTION AND ACE INHIBITION

Endothelial cells line the entire inner surface of the vasculature providing a smooth interface between circulating blood and the vessel wall as well as mediating crucial metabolic functions. An appreciation for the role of the endothelium as an organ system with autocrine, paracrine, and even endocrine functions regulating vascular tone, regional blood flow, and intimal proliferation has played a central role in the evolving concept of early atherosclerosis, as well as that of stable and unstable ischemic syndromes.

In 1980, Furchgott and Zawadski *(43)* were able to show that the presence of an intact endothelium is required in order for acetylcholine to elicit vasorelaxation in isolated rabbit aortas. This phenomenon would ultimately be termed endothelium-dependent vasorelaxation and considered to be mediated via endothelium-derived relaxation factor (EDRF), secreted from endothelial cells. EDRF has subsequently been identified as a nitric oxide (NO) molecule complexed with a sulfhydryl moiety *(44,45)*. NO is a potent vasodilator produced by the enzymatic action of constitutive nitric oxide synthase on the amino acid L-arginine *(45)*. At least two other vasodilators, prostacyclin *(46,47)* and endothelium-derived hyperpolarizing factor (EDHF) *(48,49)*, have been identified and their vasoregulatory roles in humans described.

The predominant tone of a vascular bed is the sum of simultaneously acting vasodilator and vasoconstrictor influences. In normally functioning endothelial cells, a basal rate of production of NO is maintained by the action of the constitutive enzyme NO synthase *(50)*. This basal production, which requires a normal endothelium, maintains a net vascular relaxation. However, various vasoactive substances (i.e., bradykinin, serotonin, adenosine diphosphate, and substance P), as well as the effect of blood's shearing force on the endothelium, can upregulate NO synthase activity, increasing production and secre-

tion of NO *(51–53)*. Conversely, treatment with the NO synthase inhibitor *N*-G-monomethyl-L-arginine abolishes the basal release of NO, resulting in vasoconstriction *(54)*.

A number of physiologic stressors have been used to assess endothelial function in coronaries and peripheral arteries of patients and normal volunteers. The initial demonstration of human endothelial dysfunction in vivo was in a report by Ludmer et al. *(55)*, who produced paradoxic vasoconstriction in atherosclerotic human coronaries on infusion of acetylcholine. These studies were followed by others demonstrating that coronary endothelial function was closely paralleled by the endothelial function of muscular arteries such as the brachial artery. Moreover, other simple physiologic stressors, such as postischemic brachial hyperemia, could be used to grade the function of vascular endothelium in vivo noninvasively. On a clinical level, investigations of endothelial function have led to the conclusions, however tentative, that most atherosclerotic risk factors lead to endothelial dysfunction *(56,57)*. Furthermore, clinical interventions that reduce cardiovascular risk, such as cholesterol reduction, cessation of smoking, and estrogen replacement, all appear to improve endothelial function.

The renin-angiotensin system influences endothelial function, and there is evidence that ACE inhibition may improve endothelial function through multiple potential mechanisms. Mancini and coworkers *(58)* reported on a series of 129 patients with documented coronary atherosclerosis. Patients were randomly assigned to receive quinapril or placebo for 6 mo. Coronary endothelial function was assessed with intracoronary infusions of acetylcholine. Quinapril-treated patients had an improvement in endothelial function, and placebo-treated patients showed no change. The authors postulated that, among other causes, decreased degeneration of NO and bradykinin-mediated NO release may play a part. Thus, improvement in endothelial function is an additional potential mechanism to explain the evident benefits of inhibition of the ACE in patients with coronary disease (Fig. 5).

ARRHYTHMOGENESIS

As discussed above, activation of the renin-angiotensin system along with other neurohormones occurs during the acute and convalescent phases of myocardial infarction. The renin-angiotensin system may play an important role in arrhythmogenesis, mediated by direct and indirect effects of angiotensin II *(59–61)*. At least five mechanisms are recognized through which angiotensin II may promote cardiac arrhythmias during myocardial infarction, including the following:

1. Angiotensin II mediates increases in cardiac filling pressures thereby abnormally increasing wall stress *(62)*.
2. Angiotensin II directly produces coronary vasoconstriction and decreases coronary blood flow.
3. Angiotensin II enhances sympathetic tone and the effects of circulating catecholamines *(63)*.
4. Angiotensin II has direct electrophysiologic effects on cardiac myocytes *(64)*.
5. Angiotensin II stimulates the adrenal glands to produce aldosterone, promoting renal salt and water retention and potassium excretion leading to potential electrolyte disturbances such as hypokalemia *(65)*.

There is ample experimental, and some clinical evidence of an antiarrhythmic effect of ACE inhibition. For example, captopril administered before the start of or at the end of experimentally induced ischemia in isolated rat myocardium reduces reperfusion-induced ventricular fibrillation and decreases purine outflow and peak creatinine phos-

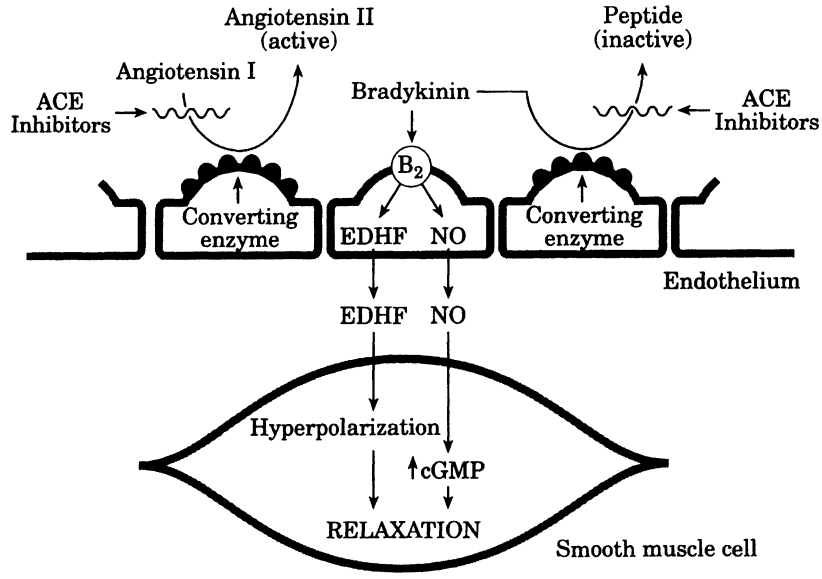


Fig. 5. Local vascular effects of angiotensin-converting enzyme (ACE) inhibitors in the blood vessel wall. ACE inhibitors can enhance vascular smooth muscle cell relaxation both by inhibiting the formation of angiotensin II, a potent direct vasoconstrictor, and by inhibiting degradation of bradykinin, Bradykinin enhances the expression of endothelium-derived hyperpolarizing factor (EDHF) and nitric oxide (NO), potent vasodilators. Data from ref. *101*.

phokinase levels during reperfusion *(66)*. Similarly, in the closed chest pig model, captopril (continued beyond the acute phase of experimentally produced ischemia) decreases the inducability of ventricular arrhythmia by programmed electrical stimulation performed 2 wk after myocardial infarction *(67)*. Such evidence suggests the possibility that postinfarct ACE inhibition may reduce the incidence of sudden, presumably arrhythmic death.

CLINICAL EVIDENCE OF ACE INHIBITOR BENEFIT

Left Ventricular Remodeling Following Acute Myocardial Infarction

The clinical association of cardiomegaly , congestive heart failure, and decreased survival has been extensively documented *(68)*. Over half a century ago, early research was being conducted on the relationship between the development of cardiomegaly following myocardial infarction and its impact on life expectancy . For example, Waris et al. *(69)* presented data on 125 patients who had sustained their first myocardial infarction. Patients exhibiting cardiac enlargement on chest radiography demonstrated a significantly increased 5-yr mortality. A high proportion of the survivors with an enlarged heart developed New York Heart Association class III angina or congestive heart failure during follow-up. More recently, White et al. *(70)*, and St. John Sutton et al. *(71)* have demonstrated that left ventricular volumes following AMI predict clinical outcome. Thus, the early clinical impression regarding the paramount importance of cardiac enlargement following myocardial infarction was correct and provided the impetus for defining the mechanisms responsible for the topographic alterations observed, as well as therapeutic maneuvers that would limit them.

Infarct Expansion: Mechanism of Early Remodeling

Immediately after myocardial infarction, rapidly occurring and complex alterations in the histology of the infarcted segment lead to the morphologic and geometric change termed infarct expansion. Morphologically, infarct expansion is thinning and lengthening of the infarcted segment. Histologic analyses show that infarct expansion may begin within hours to days following acute infarction, prior to the period when phagocytic cells begin debriding the area of necrotic tissue *(72,73)*. Therefore, wall thinning, an essential part of infarct expansion, is not due to removal of necrotic tissues by phagocytic cells, but rather to slippage and rearrangement of necrotic myocytes, leading to a decrease in the number of cells across the left ventricular wall.

Multiple factors are known to determine the degree to which infarct expansion occurs. Large infarcts involving the anteroapical walls *(74)*, elevated intracardiac pressures *(75)*, and impaired infarct healing *(76)* all increase expansion. Infarct expansion is an important but transient mechanism for left ventricular dilation and distortion. As scar tissue forms in infarcted areas, its tensile strength increases, affording stability, and making it better able to resist deforming forces. By 3 wk after infarction, infarct expansion has largely halted.

Infarct expansion and the resulting alterations in left ventricular size and geometry are important physiologic triggers for the late phase of left ventricular remodeling. The law of Laplace relates wall tension to the pressure and shape of the fluid-filled chamber being examined. Wall tension is directly proportional to pressure and inversely proportional to curvature. Thus, at any intracavitary pressure examined, wall tension is lowest for a normally shaped, highly curved left ventricular apex. This physiologic principle is precisely why the left ventricular wall is thinnest at the apex. Furthermore, as apical curvature becomes even greater in systole, wall tension in the normal apex tends to fall, offsetting the systolic rise in wall tension caused by the increase in systolic pressure *(77)*.

These favorable physiologic conditions may be adversely affected by infarct expansion. In an expanded apex, the normal, sharp curvature of the apex is blunted. Thus, wall tension is higher. Furthermore, and most importantly, the periinfarct regions are tethered to the akinetic segments. During systole, these periinfarct regions develop a concave-outward curvature, or anticlastic curve, which has the effect of severely increasing wall tension *(74)*.

The degree of systolic dysfunction resulting after myocardial infarction is a key determinant of early and chronic alterations in ventricular topography. With small insults involving <20% of the left ventricular muscle *(78)*, ejection fraction and stroke volume remain normal due to compensatory hyperfunctioning of remaining viable tissues. However, with larger impairments of left ventricular function, the ability of remaining viable muscle to compensate is overcome, ejection fraction falls, and left ventricular dilation must occur to maintain stroke volume.

Thus, the morphologic and physiologic forces that lead to progressive left ventricular remodeling in the chronic phase of the infarct are based on the degree of systolic dysfunction, as well as the extent of geometric ventricular derangement. These proposed mechanisms focus on increases in ventricular wall stress as the physiologic trigger for hypertrophy of the noninfarcted myocardium. In this scheme, a decreased ejection fraction following transmural myocardial infarction results in elevation of end-systolic volume with an attendant increase in end-systolic wall stress. If the infarct has sufficiently compromised systolic function, alterations in local geometry, particularly in the

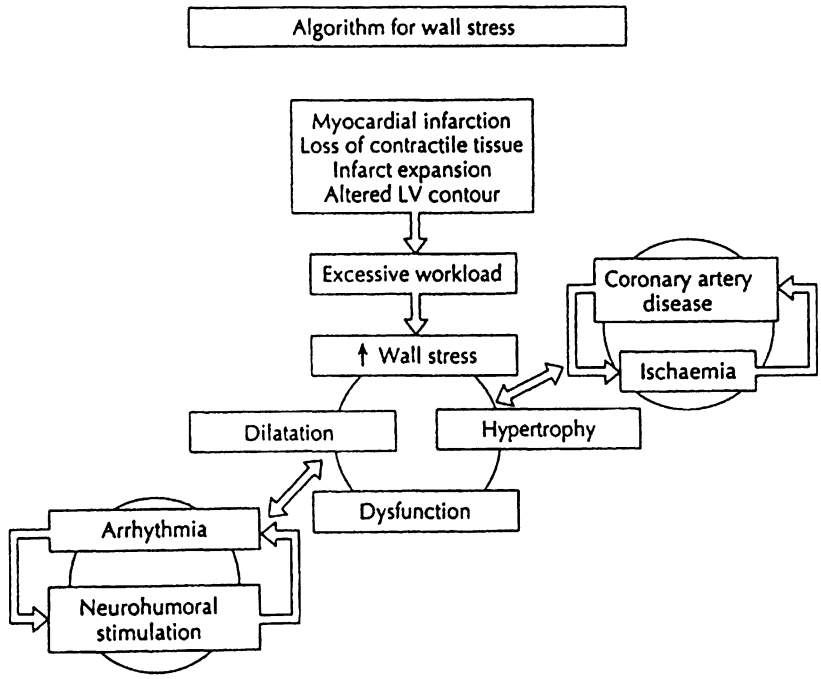


Fig. 6. Conceptual scheme whereby the loss of contractile tissue leads to an excessive workload on the remaining myocardium, promoting the central positive feedback loop of dilation, further augmenting wall stress and leading to more progressive dysfunction. Data from ref. *102*.

periinfarct regions, may lead to the development of small periinfarct segments with an anticlastic curve. These abnormalities in volume and stress all are markedly exaggerated by infarct expansion, if it occurs. Thus, the chronic phase after infarction may be characterized by regional hypertrophy of the noninfarcted segment, as well as progressive left ventricular dilation and dysfunction. A vicious circle is set into action whereby dilation is the catalyst for increased wall stress. Mass to volume ratio cannot be normalized, and further dilation ensues (Fig. 6).

Strategies Proved to Limit Remodeling

In the early phase after infarction, which encompasses the first several days, there is evidence from clinical trials that improvement in loading conditions, either with iv nitroglycerin *(79)* or with ACE inhibitors, may reduce infarct expansion. However, the data with intravenous nitroglycerin remain controversial, and the acute impact of early ACE inhibition on left ventricular volumes appears small. By contrast, long-term ACE inhibition has demonstrated remarkable success in postinfarct patients, particularly in those with left ventricular dysfunction.

The original work on this important subject was performed on rats with experimental infarctions. Captopril significantly decreased ventricular dilation and prolonged survival *(80)*. The experimental work was rapidly followed by two clinical studies first demonstrating that the process of left ventricular remodeling could be attenuated in humans by treatment with ACE inhibition *(81,82)*. In the study published by Pfeffer et al. *(81)*, patients with a first anterior infarction and an ejection fraction of 45% or less were treated with captopril or placebo. Patients who demonstrated the most severe left ventricular

Table 1
Angiotensin-Converting Enzyme Inhibitor
Acute Myocardial Infarction: Selective Clinical Trials[a]

Study[b]	*No.*	*Duration (d)*	*Placebo (%)*	*RR (%)*	*Lives/1000*
SAVE	2231	42	25	19	42
AIRE	2006	15	23	27	57
SMILE	1556	1	8	(22)	18
		12	14	33	41
TRACE	1749	24	42	22	76

[a]Abbreviations: AIRE, Acute Infarction Ramipril Efficacy study; SAVE, Survival and Ventricular Enlargement trial; SMILE, Survival of Myocardial Infarction Long-Term Evaluation trial; TRACE, Trandolapril Cardiac Evaluation trial; RR, risk reduction.

[b]These trials of postinfarct ACE inhibitors studied only high-risk patients: patients with asymptomatic left ventricular dysfunction (SAVE), patients with manifested symptoms of heart failure in the early myocardial infarction period (AIRE), patients with anterior wall myocardial infarction and not receiving thrombolytic therapy (SMILE), and patients with acute myocardial infarction exhibiting wall motion abnormalities (TRACE). Each of these studies have clearly shown a mortality benefit with the use of ACE inhibitors. Data from ref. *102*

Table 2
Angiotensin-Converting Enzyme Inhibitor Acute
Myocardial Infarction: Broad Inclusion Clinical Trials[a]

Study	*No.*	*Duration (d)*	*Placebo mortality (%)*	*RR (%)*	*Lives/1000*
CONSENSUS II	6090	5.0	9.4	Null	—
GISSI-3	19394	1.5	7.1	12.0	8
ISIS-4	58043	1.0	7.6	7.0	5
Chinese	13634	1.0	9.6	9.1	5

[a]Abbreviations: CONSENSUS-II, Cooperative New Scandinavian Enalapril Survival Study; GISSI-3, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-4, Fourth International Study of Infarct Survival; RR, risk reduction.

[b]These studies tested the use of ACE inhibitors in a much broader population of patients with acute myocardial infarction not screened for any particular functional or clinical markers of high risk. In all these studies, patients were randomly assigned to receive ACE inhibitors or placebo within 24 h after presentation, except the Chinese study (36 h). Except for the CONSENSUS II, all showed a definite survival benefit with ACE inhibitor therapy. Data from ref. *102*.

dilation in the placebo group were those with an occluded infarct artery and a large infarct. Captopril completely attenuated remodeling in this high-risk subgroup. These studies have been reproduced with other ACE inhibitors and other patient subsets with remarkable consistency in their ability to save lives (Tables 1 and 2). Nevertheless, the clinical significance of small (15-mL) differences in left ventricular volumes needed to be assessed in large randomized trials.

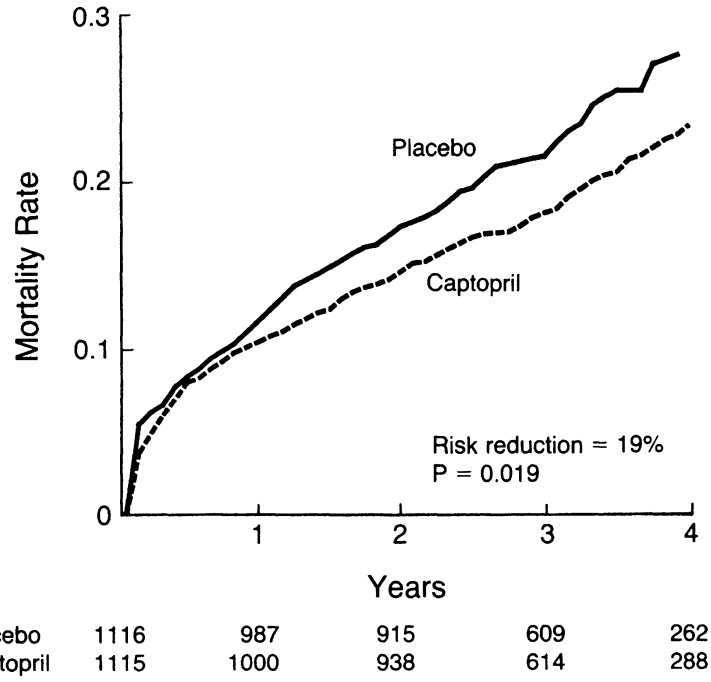


Fig. 7. Cumulative mortality from all causes in the study groups. The number of patients at risk at the beginning of each year is shown at the bottom. Therapy with captopril (within 3–16 d after myocardial infarction) significantly reduced mortality from all causes compared with the placebo group. The reduction in risk was 19% (95% CI 3–32; $p = 0.019$). Data from ref. *83*.

CLINICAL TRIALS OF ACE INHIBITORS AFTER INFARCTION

SAVE, AIRE, TRACE, and SMILE

The Survival and Ventricular Enlargement Study (SAVE) *(83)* was the first large, randomized, double-blind, placebo-controlled study to evaluate the effects of an ACE inhibitor (captopril) on clinical outcome in patients with recent AMI. Patients were selected who had ejection fractions of ≤40% (average 31%) and no overt congestive heart failure or severe on-going ischemia. Patients were started on the study drug 3–16 d after infarction and were followed for 2 –5 yr. The SAVE study demonstrated a 19% relative risk reduction in all-cause mortality (Fig. 7) and relative risk reductions of 21% for cardiovascular mortality, 37% for development of severe congestive heart failure, and 22% for heart failure requiring hospitalization. Thus, SAVE established the role of ACE inhibition in the treatment of patients after myocardial infarction.

Subsequent to the SAVE study, other trials have been published that expand the clinical utility of ACE inhibition following myocardial infarction.

The Acute Infarction Ramipril Efficacy (AIRE) study *(84)* differed from SAVE in that it selected for study the important subgroup of patients with early pulmonary congestion after infarction (Killip class >1) and assigned them to ramipril vs placebo. Follow-up was continued for an average of 15 mo. There was a 27% relative reduction in the risk of mortality from all causes (from 23% in placebo patients to 17% in treated patients (Fig. 8). Furthermore, there was a relative risk reduction of 19% in the first occurrence of a prespecified combined end point of death, severe heart failure, myocardial infarction, or stroke.

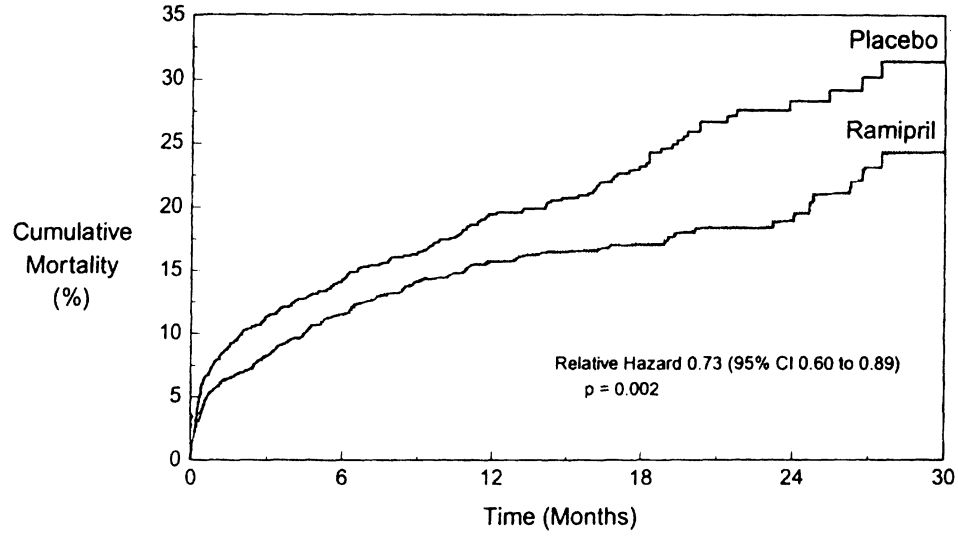
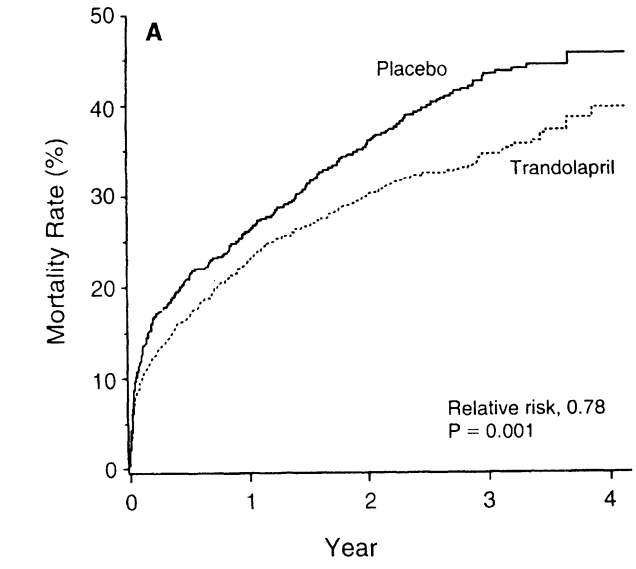


Fig. 8. Mortality curves from the AIRE study illustrating the primary end point of all-cause mortality analyzed by intention to treat. Separation of the curves occurred early, and they continued to diverge throughout the study. There was a 27% overall reduction in risk of death (95% CI 11–40; $p = 0.002$) in the ramipril group. Data from ref. *84*.

These studies selected patients based on clear-cut evidence of left ventricular dysfunction. SAVE required a radionuclide ventriculogram prior to enrollment, and AIRE required clinical evidence of pulmonary congestion. However, at the present time the most frequent assessment of ventricular function following infarction is with echocardiography. This technique was used to select patients participating in the Trandolapril Cardiac Evaluation (TRACE) study *(85)*. Patients were screened within 2–6 d with echocardiography. A wall motion index was calculated based on the nine-segment wall motion assessment described by Heger et al. *(86)* and calculated to select patients with ejection fractions of ≤35%. The screening process suggested that approximately 39% of all myocardial infarction patients will have an early ejection fraction of ≤35%. As in the other studies, those patients treated with the ACE inhibitor had improved survival (Fig. 9A) and a lower incidence of heart failure (Fig. 9B). Another high-risk patient subgroup was studied in the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study *(87)*. These investigators enrolled patients with anterior wall infarctions who *had not* received thrombolytic therapy. Patients receiving the ACE inhibitor zofenopril had an improved outcome. Thus, for the above studies, maintaining therapy for 2–4 y will lead to saving between 30 and 70 lives per 1000 patients treated (Table 1).

As discussed above, additional analyses have suggested that ACE inhibition may well prevent sudden as well as nonsudden death. For example, both SAVE and TRACE reported the incidence of sudden and nonsudden death. In SAVE there was a relative risk reduction of 16% in sudden deaths, while in TRACE there was a similar relative risk reduction of sudden deaths of 21.3%. Thus, in spite of the difficulties inherent in classification of mortality, these clinical studies suggest that ACE inhibition may reduce sudden as well as heart failure deaths.



No. at Risk					
Trandolapril	876	677	613	319	20
Placebo	873	647	562	280	22

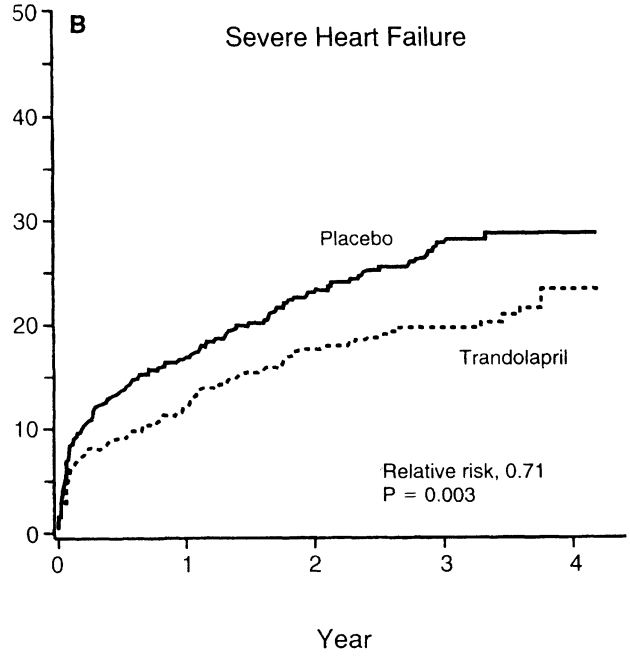


Fig. 9. (A) Cumulative mortality from all causes among patients receiving trandolapril or placebo. Mortality curves diverged early, with estimated mortality at 1 month of 8.8% in the trandolapril group and 11.2% in the placebo group. The relative risk of death from any cause in the trandolapril group, compared with the placebo group, was 0.78 (95% CI 0.67–0.91; $p = 0.001$). Data from ref. *85*. **(B)** Progression to severe heart failure occurred more often and developed earlier in the placebo group compared with the trandolapril group (relative risk, 0.71; 95% CI 0.56–0.89; $p = 0.001$). Data from ref. *85*.

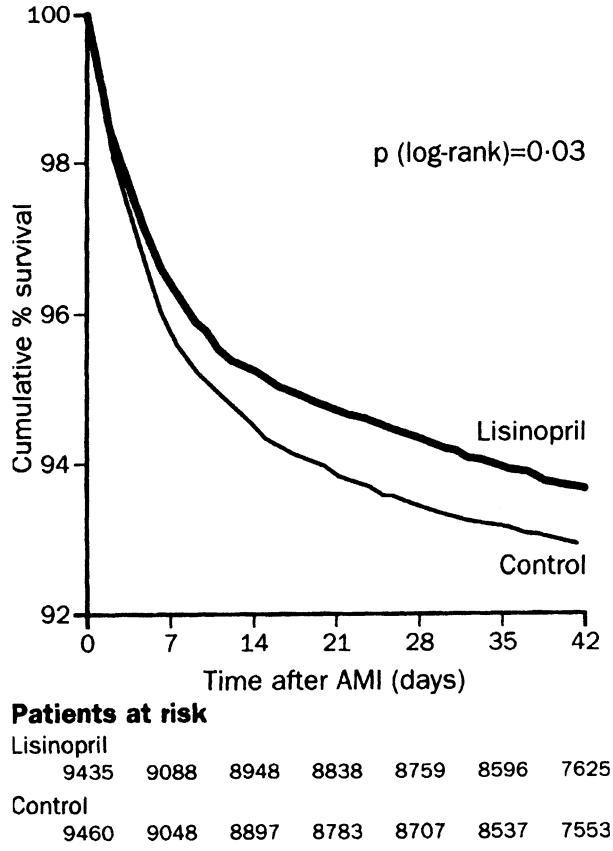


Fig. 10. Six-wk survival curves for lisinopril-treated patients and controls. The curves separated early (day 0–1) and continued to diverge throughout the next 6 wk, supporting the argument for the early institution of therapy with angiotensin-converting enzyme (ACE) inhibitors in selected patients. Patients allocated lisinopril had an 11% lower risk of death than the controls (6.3 vs 7.1%). Data from ref. *88*.

GISSI and ISIS

Although each of the above studies addresses a different patient population or utilizes a different screening process, there is an important methodologic feature in common. They were all designed to select a high-risk patient group to study and therefore did not address most postinfarct patients. Furthermore, any screening test also imposes time constraints, and therefore therapy may have to be delayed. This implied alternative strategy of early global utilization of ACE inhibitors in all patients with infarction has been tested in two megatrials.

The third Gruppo Italiano della Sopravvivenza nell'Infarto Miocardico (GISSI) study *(88)* enrolled 19,394 patients to determine whether administration of the long-acting ACE inhibitor lisinopril for 6 wk after infarction would improve survival. This study had a factorial design that also tested postinfarct nitrate therapy. A small (relative risk reduction of 11%, absolute risk reduction of 0.8%) but significant reduction ($p = 0.03$) in mortality was observed at 42 d after infarction only with lisinopril therapy (Fig. 10). Similarly, the larger fourth International Studies of Infarct Survival (ISIS) study enrolled

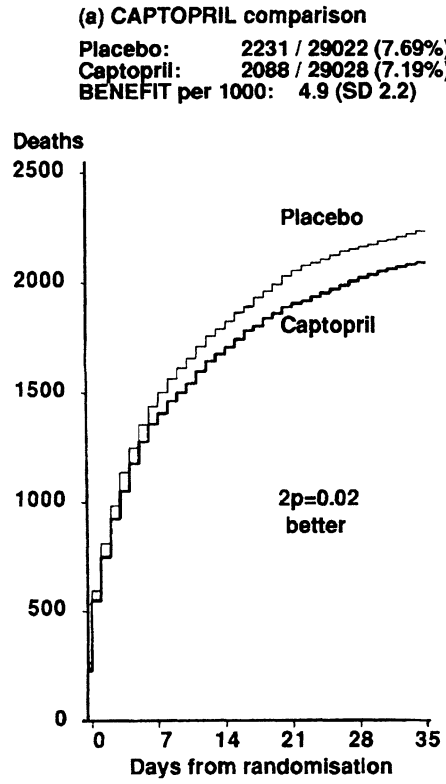


Fig. 11. Effects on mortality during the first 5 wk; there were 7.19% deaths in the captopril group compared with 7.69% deaths in the placebo group. Relative reduction in mortality for captopril-treated patients was 7%; absolute risk reduction was 0.5% (95% CI 13–1: $p = 0.02$). Data from ref. *89*.

58,050 patients within 1 d of infarction to test the effect of 1 mo of captopril therapy, magnesium, or nitrates in a factorial design *(89)*. There was a significant ($p = 0.02$) benefit of captopril therapy with a relative reduction in mortality risk for captopril-treated patients of 7% at 5 wk and an absolute reduction in risk of 0.5% (Fig. 11). Some benefit of early treatment seemed to persist for at least 1 yr.

These studies have particular clinical relevance because they address the patient during the very acute phase of the infarct, prior to the time when any screening tests or evaluations for left ventricular function could be done. However, their strength in generalizability and ease of application has to be critically evaluated in the context of an important potential weakness. In effect, *the therapeutic benefit of ACE inhibition is diluted, leading to an average of 5 lives saved per 1000 patients treated per year.*

Given the seemingly marginal therapeutic effectiveness of early, unselective ACE inhibition in patients with acute infarction, other analyses of the time-course of benefit become particularly relevant. In the ISIS-4 and GISSI-3 studies, encompassing 77,444 patients, 219 lives were saved by 4–6 wk of ACE inhibition. Latini and coworkers *(90)* analyzed the time-course of the total survival difference between active therapy and control. In both studies, patients were treated within 24 h of presentation. By the end of the first day of therapy, there were already 65 fewer deaths in the treatment arm than in

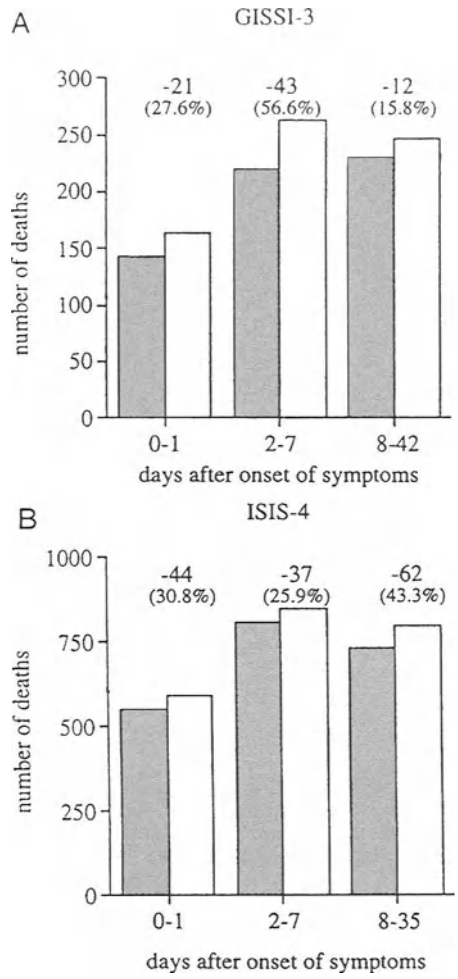


Fig. 12. Bar graphs showing that in GISSI-3 and ISIS-4 angiotensin-converting enzyme (ACE) inhibitors saved lives during the very early phases. **(A)** In the GISSI-3 lisinopril-allocated patients (crosshatched bar), there were 76 fewer deaths than in the control-allocated group (open bar): 21 fewer for d 0–1, 43 fewer for d 2–7, and 12 fewer for the following days of treatment. **(B)** In the ISIS-4 captopril-allocated patients (crosshatched bar), there were 143 fewer deaths than in the control-allocated group (open bar): 44 fewer for d 0–1, 37 fewer for d 2–7, and 62 fewer for the following days of treatment. Absolute reductions and percent contribution to total benefit are shown. Data from ref. *90*.

the control group, so that 29.7% of the total difference between groups was already present at the end of d 1. By the end of d 7, the difference between groups had increased to 145 lives, or 66.2% of the total number of lives destined to be saved. The sum total benefit of the remaining weeks of therapy accounted for a minority (33.8%) of lives saved (Fig. 12). These analyses have relevance with regard to the clinical choice of early vs late therapy and to the choice of targeted therapy for patients with left ventricular dysfunction vs unselected therapy for all patients with myocardial infarction. Additionally, one must also consider whether attenuation of left ventricular remodeling may account for early survival benefit, or whether there is convincing clinical evidence that the paradigm for an antiischemic mechanism discussed above is supported by clinical evidence.

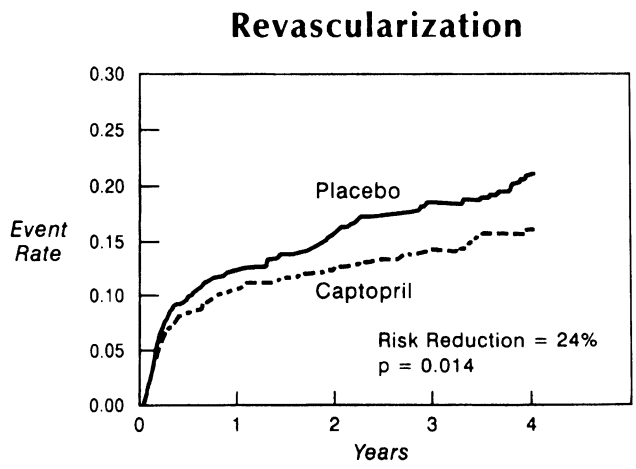


Fig. 13. Life table of cumulative need for revascularization (by either percutaneous transluminal coronary angioplasty or coronary artery bypass surgery) after randomization. For this combined analysis, the time to first event was used. Data from ref. *91*.

PREVENTION OF ISCHEMIC EVENTS

Pertinent to the hypotheses of Vaughan and coworkers *(4)* described above, the association of activation of the renin-angiotensin system with greater risk of acute ischemic events is not without clinical significance. Specifically, if inhibition of the renin-angiotensin system prevents myocardial infarction and other ischemia through alterations in the fibrinolytic system, then the surprising early benefit of ACE inhibition observed in GISSI-3 and ISIS-4 could be more easily explained.

Although the primary end point of SAVE focused on the assessment of survival and prevention of deterioration of left ventricular function, recurrent myocardial infarction was a prospectively defined and carefully sought end point. The captopril-treated group demonstrated a 25% relative reduction in the risk of recurrent myocardial infarction. A more careful analysis for predictors of myocardial infarction by Rutherford et al. *(91)* clearly demonstrated that left ventricular ejection fraction was not a predictor of recurrent myocardial infarction. Captopril therapy was associated with similarly decreased risk of reinfarction for SAVE patients with ejection fractions above and below the median. Furthermore, captopril therapy also decreased the incidence of angioplasty or bypass surgery (relative reduction in risk 24%; $p = 0.014$) compared with placebo (Fig. 13). A preliminary study by Lamas et al. *(92)* expanded on these findings and demonstrated that the principal predictor of recurrent infarction was the number of vessels diseased and not revascularized. Captopril therapy reduced the incidence of recurrent infarction in patients with single, as well as multivessel disease. Another large study also reported a reduction in ischemic events. The Studies of Left Ventricular Dysfunction (SOLVD) enrolled 6797 patients in two separate placebo-controlled studies of enalapril in left ventricular dysfunction—a treatment *(93)* and a prevention trial *(94)*. All patients had an ejection fraction of ≤35%. Patients in the prevention arm had asymptomatic left ventricular dysfunction, and patients in the treatment arm had clinically established heart failure. Although this was a study of patients with chronic left ventricular dysfunction of any etiology, 79% of patients were thought to have an ischemic cardiomyopathy. However, none of the patients in either trial had unstable angina at the time of enrollment, nor had

they suffered an AMI in the month before enrollment. There was a relative reduction in the risk of myocardial infarction by 23%, and a relative reduction in the risk of unstable angina by 20% in the enalapril-treated group.

These findings support the hypothesis that an important part of the early and late benefit of ACE inhibition relates to the prevention of ischemic events, and not only to hemodynamic and cardiac architectural benefits. Indeed, perhaps the surprising degree of early benefit has more to do with prevention of early recurrent myocardial ischemia than with other mechanisms.

Cautionary Notes

Although the accumulating data appear to support strongly the concept that ACE inhibition may prevent myocardial infarction, it is important to analyze the limitations of the data and discuss how far and to what other patient populations these findings can be extrapolated. The most significant limitation stems from the uniformity of the patient populations studied. Specifically, the clinical event data on infarct presentation are mainly derived from studies in which patients had either sizable myocardial infarctions, or had hemodynamic embarrassment following infarction. Thus, it may be assumed that in a sizable proportion of patients, the renin-angiotensin system may have been activated. Thus, in the absence of controlled data to the contrary, these results cannot be extrapolated to patients with small infarctions or with coronary disease without left ventricular dysfunction, in whom there is no reason to expect an activated renin-angiotensin system.

At the present time, the cocktail for treating patients with AMI includes intravenous β-blockade, thrombolysis or primary angioplasty, occasional nitrates, and aspirin. β-Adrenoceptor blocking agents, streptokinase, and nitrates may all lead to an undesirable lowering of blood pressure. Therefore, another cautionary note to be addressed is the potential for harming some patients through the hypotension that may occasionally accompany ACE inhibition.

Several years ago, results from the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II) *(95)* contributed to physicians' reluctance to administer ACE inhibitors during the acute phase of myocardial infarction. CONSENSUS II had intended to study 9000 patients to determine whether early administration (within 24 h) of iv enalapril followed by oral enalapril chronically would reduce mortality during a 6-mo follow-up period. Mortality at 6 months did not significantly differ between groups (9.4% in the placebo group and 10% in the enalapril group, $p = 0.26$). However, the study was terminated prematurely after about 6000 patients were enrolled due to concerns of adverse effects from early hypotension. This side effect, defined as a systolic blood pressure <90 mmHg or diastolic blood pressure <50 mmHg, was observed more commonly in the treatment group than in the placebo group. Furthermore, patients with hypotension had a poorer clinical outcome than patients without hypotension. These findings have led to the recommendation against the use of iv ACE inhibition in acute infarction, particularly when accompanied by thrombolytic therapy with streptokinase, which may itself lead to hypotension via similar enzymatic pathways.

RECOMMENDED USE OF ACE INHIBITORS FOLLOWING MYOCARDIAL INFARCTION

Patient Selection for Early Therapy

Based on the current data reviewed above and personal clinical experience, ACE inhibition should be started early, within 24 h, in *all patients* who are sustaining an AMI

and have a systolic blood pressure >100 mmHg. Any ACE inhibitor may be used, since the effect of these drugs is very clearly a class effect. However, a valuable clinical point is to use a small dose of a short-acting agent such as captopril (6.25 mg) initially, especially in unstable patients or in patients with systolic blood pressure <110 mmHg.

Patient Selection for Chronic Therapy

Selecting patients for chronic therapy has to balance the results of the long-term trials (which selected patients with left ventricular dysfunction) with the results of the short-term trials (with broad entry criteria that did not select patients based on ventricular function). Moreover, there are no objective data at present that would support the long-term use of ACE inhibitors for patients with normal left ventricular function. Thus, a composite clinical strategy has evolved for treatment of the postinfarct patient.

As stated above, unless strongly contraindicated, *all* patients start therapy within a day or two of myocardial infarction. Patients who have had pulmonary congestion during the infarct would have qualified for the AIRE study. Thus, they do not need an assessment of ventricular function prior to being committed to long-term ACE inhibition. All other postinfarct patients should have a noninvasive assessment of ventricular function within 6 wk after the acute event prior to being committed to long-term therapy. In patients with objective evidence of left ventricular dysfunction resulting in an ejection fraction of ≤45%, therapy is continued for at least 5 yr, which is the duration of the longest postinfarct trial. However, this duration of therapy may be extended to a lifetime of treatment based on the results of the SOLVD trials. By contrast, when the postinfarct noninvasive assessment demonstrates preserved left ventricular function, we recommend stopping therapy 4–6 wk after myocardial infarction. We await with interest the results of large clinical trials now in progress that may broaden the use of this class of drugs to patients with coronary disease and good left ventricular function.

Alternately, Pfeffer *(96)* recommends a more flexible "loose-fit" approach, whereby early treatment is initiated in high-risk patients who have or appear to have left ventricular dysfunction prior to objective assessment of cardiac function. Such a strategy would avoid unnecessary delay with lost opportunity to save early lives while minimizing risks of untoward events in low-risk patients who are least likely to benefit from treatment.

NEW FRONTIERS

At the present time, most of the beneficial effects of ACE inhibition depend on reduction in angiotensin II levels or activity, although the potential benefit of elevations in bradykinin on venodilation and on the fibrinolytic system should not be discounted. Recently, two new classes of agents have been developed and brought into clinical trials that may prove to have important hemodynamic or antiischemic effects possibly equaling or surpassing those of traditional ACE inhibition. Angiotensin II antagonists such as losartan, valsartan, and ibesartan offer selective blockade of the type 1 angiotensin II receptor. This receptor is thought primarily to mediate the vasoconstrictive and proliferative effects of angiotensin II. Given the recent appreciation that there are non-ACE pathways for the formation of angiotensin II, direct receptor blockade promises an even more complete reduction of angiotensin II-mediated effects.

Another exciting new pharmacotherapy involves the development of cell surface metalloprotease inhibitors. These agents promise a host of potentially beneficial hemo-

dynamic effects that include inhibition of ACE, inhibition of endopeptidase, and increases in levels of natriuretic peptides. Although a successful study of losartan in heart failure patients has been published *(97)*, insufficient clinical data are available to encourage or discourage the use of these agents in patients with ischemic syndromes, including those with myocardial infarction.

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15 Risk Stratification: Exercise Testing, Imaging, and Cardiac Catheterization

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CONTENTS

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INTRODUCTION

Each year, approximately 1.5 million patients in the United States suffer an acute myocardial infarction (AMI) and 500,000 patients die *(1)*. Reperfusion therapy, increased use of adjunctive medication such as aspirin, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and hypocholesterolemic treatment coupled with better risk stratification to identify those most likely to benefit from early coronary revascularization has led to significant improved long-term prognosis after myocardial infarction (MI).

Effective risk stratification after AMI encompasses several phases: emergency triage within the initial hours of symptom onset, the intermediate hospital phase, and the prehospital discharge or early (<3 wk) posthospital discharge phase. The risk estimates for mortality provided in this chapter are based on physiologic information provided by a detailed clinical history, judicious use of certain noninvasive tests, anatomic information provided by coronary angiography in selected patients, and prognostic importance of various treatment options that may favorably impact long-term survival. Although the focus of this chapter is a review of risk stratification procedures for mortality in the early postinfarction phase, additional end points such as reinfarction, unstable angina, readmission for heart failure, or serious cardiac arrhythmias are also discussed.

From: *Contemporary Cardiology: Management of Acute Coronary Syndromes*
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Risk Factor	Patients with risk factor (%)	Deaths in 6 wk (%)
Age ≥ 70 yr	11.5	11.2
Previous infarction	13.7	7.9
Anterior infarction	51.5	5.6
Atrial fibrillation	2.0	10.6
Rales in more than 1/3 lung field	3.2	12.4
Hypotension & sinus tachycardia	4.8	10.1
Female gender	17.7	7.1
Diabetes mellitus	13.0	8.5

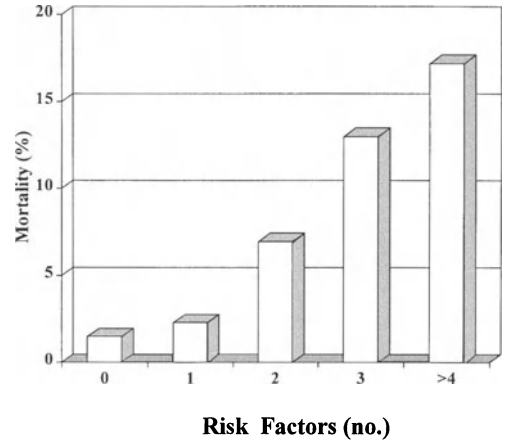

Fig. 1. Clinical variables at the time of hospital admission predictive of 6-wk mortality rates in the Thrombolysis and Myocardial Infarction Trial (TIMI II). Reproduced with permission from ref. *2*.

EARLY CLINICAL RISK STRATIFICATION

The use of clinical variables alone at the time of hospital admission to estimate risk was examined in the Thrombolysis in Myocardial Infarction (TIMI) II trial of 3339 patients <76 yr treated within 4 h of symptom onset with recombinant tissue-type plasminogen activator (rt-PA), aspirin, and heparin. Eight variables were found to be associated with an increased 6-wk mortality risk (Fig. 1). The mortality rate was only 1.5% in the absence of any of the risk factors listed in Fig. 1 compared with 13% in patients with two risk factors, patients with three risk factors and 17% in patients with four or more risk factors *(2)*.

Age

Age is a major risk factor for increased mortality in patients after AMI treated with thrombolytic therapy. In-hospital mortality rates were 28% in patients >85 yr in the community-based National Registry of Myocardial Infarction *(5)*, 21% after 30 d in patients >65 yr in the Cooperative Cardiovascular Project, 11.2% in patients ≥70 yr in the TIMI II trial after 42 d, and 17.2% in patients >70 yr after 30 d in the Global Use of Strategies To Open Occluded Arteries in Acute Coronary Syndromes (GUSTO)-1 trial *(2–4,7)*.

By contrast, in-hospital mortality rates were only 3, 3.8, and 1.1% in patients <55 yr, <50 yr, and <45 yr enrolled in the Myocardial Infarction Registry, TIMI II trial, and GUSTO-1 trials, respectively *(5–8)*. Older patients are prone to an increased reinfarction rate and readmission for cardiac events *(4)*. Multivessel coronary disease, important comorbid conditions, and aging myocardium with concomitant decreased myocardial reserve explains some of the increased mortality risk compared with younger individuals.

Gender

Women tend to be older than men at the time of first infarction and have a greater prevalence of associated comorbidity *(9,10)*. The 35-d mortality rate for women compared with men was 12.5 vs 8.2% in the Fibrinolytic Therapy Trialists Group *(8)*. In this report, 44% of patients >75 yr were women. Kober et al. *(11)* reported a 1-yr mortality

rate of 28% for women and 21% for men in a consecutive series of 6676 patients with AMI; the increased mortality risk in women occurred relatively early (<30 d).

Diabetes

Diabetes mellitus increases the relative risk of in-hospital mortality by at least 1.5–2 compared with nondiabetic patients *(12)*. Diabetic women in particular have a relatively poor prognosis, in part related to an increased incidence of congestive heart failure, reinfarction, and recurrent ischemic events *(12–15)*. Late mortality is significantly increased in diabetic compared with nondiabetic patients *(16)*.

Race

The 1-year mortality rate in TIMI II was similar in White, African-American, and Hispanic patients although the presence of atherosclerotic risk factors was greater in African-American and Hispanics *(17)*. Similar findings were reported in GUSTO-1 *(7)* and in the Charleston Heart Study *(18)*.

Prior Myocardial Infarction

The relative mortality risk of patients with a previous MI is approximately 1.5 times greater than in patients with a first infarction regardless of whether or not the patient is treated with thrombolytic therapy *(7,8)*. The mortality gradient is greatest in patients with major left ventricular dysfunction prior to the reinfarction event. In TIMI II, a prior vs no prior history of MI was associated with 7.9 vs 4.3% mortality rate after 42 d *(2)*. Multivessel coronary disease was present in 60 vs 28% of patients with prior vs no prior infarction.

Prior Revascularization

In GUSTO-1, the 30-d mortality rate was 10.7% in 41,021 patients who had prior coronary bypass grafting vs 6.7% in those without prior cardiac surgery. The mortality rates were 5.6 vs 7.0% in patients who had prior vs no prior coronary angioplasty *(7)*.

Physical Examination

Hypotension, systolic pressure <100 mmHg, sinus tachycardia (ventricular rate >100 beats/min), a third heart sound, jugular venous distension, and pulmonary rales may indicate significant left ventricular dysfunction and are markers of increased mortality *(20,21)*. The physical examination is important in the early recognition of catastrophic mechanical complications such as ventricular septal defect, mitral valve dysfunction, or myocardial rupture.

Cardiogenic Shock

Cardiogenic shock occurs in approximately 7% of patients in the acute infarct setting and is associated with a mortality rate >70% *(22,23)*. Retrospective analyses of thrombolytic trials do not show a significant mortality reduction in patients presenting with cardiogenic shock *(8,24,25)*. In an overview of 386 patients who were treated with coronary angioplasty for cardiogenic shock, Bates and Topol *(24)* reported an overall reperfusion rate of 73% and in-hospital mortality rate of 44%. Emergency coronary bypass grafting in this setting has an associated mortality rate of approximately 40% *(24)*. The approximate 60% survival rate after coronary revascularization is better than the

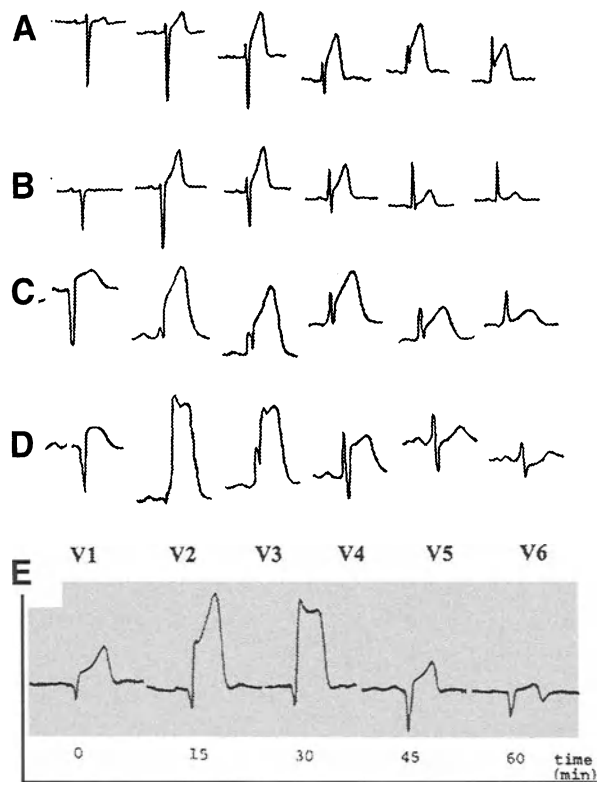

Fig. 2. Prognostic information from ECG patterns. Examples A and B are from patients without distortion of terminal position of the QRS complex. Examples C and D are from patients with terminal QRS distortion (emergence of J point at >50% of R-wave in leads with qR configuration or disappearance of S-wave in leads with Rs configuration). Reproduced with permission from ref. *26*. Tracing E is from a patient with anterior infarction with additional ST elevation 15 min after initiation of thrombolysis with final resolution suggestive of favorable clinical outcome. Reproduced with permission from ref. *35*.

expected 70% mortality rate. However, until adequate randomized trials are completed, these finding must be interpreted cautiously as they are uncontrolled with significant imbalance in baseline characteristics. The ongoing SHOCK trial, which randomizes patients with cardiogenic shock <36 h post-MI to acute coronary revascularization (<6 h after randomization) or conventional medical therapy may provide important information on the role of emergency coronary revascularization as a routine procedure in patients with cardiogenic shock.

Noninvasive Testing: The 12-Lead ECG

Electrocardiographic (ECG) findings associated with increased mortality risk include (1) anterior ST elevation, (2) distortion of the terminal portion of the QRS complex (Fig. 2), (3) left bundle branch block, (4) advanced atrioventricular block, and (5) atrial fibrillation *(1,7,8,17,26)*. In GUSTO-1, the 30-d mortality rate was 9.9 vs 5.0% in patients with anterior vs inferior ST-segment elevation. The relative risk of death, reinfarction, or

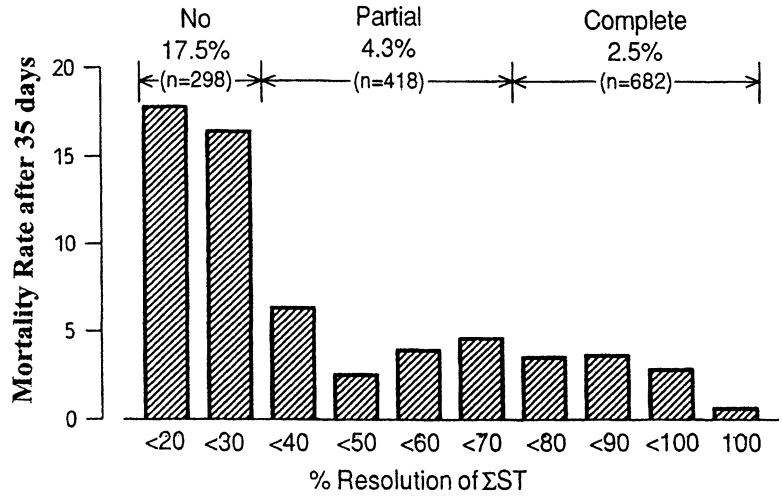

Fig. 3. Thirty-five-d mortality rates by percent sum (Σ) of ST segment resolution within 3 h after start of thrombolysis. Reproduced with permission from ref. *34*.

congestive heart failure was fourfold greater in patients with inferior infarction if ST-segment depression was also noted in the anterior lead group, particularly leads V_4–V_6 or if evidence of right ventricular involvement was present *(27–31)*. In GUSTO-1, the 30-d mortality rates were 18.7, 17, 14, and 17% for patients with left bundle branch block, right bundle branch block, left anterior fascicular block, and left posterior fascicular block compared with 6% in patients with a normal conduction pattern *(32)*.

Early resolution of ST-segment elevation (within hours of thrombolysis) is associated with a more favorable prognosis than in patients with persistent ST-segment elevation. Additional ST-segment elevation over and above the initial elevation seen in the first hour of thrombolysis with ultimate resolution is also associated with favorable clinical outcome *(33)* (Fig. 2E). The 30- and 180-d mortality rates of patients who had >50% resolution of ST-segment elevation within 4 h of treatment were 3.5 and 5.7% compared with 5.7 and 7.4% in patients without these findings in the Gruppo Italiano per lo Studio della Sopravvienza nell'Infarto Miocardico (GISSI)-2 *(34)*. The International Joint Efficacy Comparison of Thrombolytics (INJECT) study, which compared the effects of reteplase or streptokinase in 6010 patients reported a 35-d mortality rate of 2.5% in patients with complete resolution of ST-segment elevation compared with 17.5% in patients without ST-segment resolution *(35)* (Fig. 3).

Left ventricular function can be estimated from the resting ECG at the time of hospital discharge. Silver et al. *(36)* reported a positive predictive value of 98% to estimate left ventricular ejection fraction >40% in patients with new non-anterior Q-wave infarction, no previous history of Q-wave MI, or congestive heart failure. The findings were validated in 10,756 patients enrolled in GUSTO-1 *(37)*.

Early Coronary Angiography

In the acute infarct setting, coronary angiography is usually performed because of hemodynamic instability, persistent chest pain, or evidence of continued infarct artery occlusion, and thrombolytic ineligibility *(38–42)*. Clinical trials comparing PTCA

with thrombolytic therapy or PTCA in the setting of failed thrombolysis or ineligibility for thrombolytic drugs is discussed in Chapters 9 and 11.

INTERMEDIATE HOSPITAL PHASE

In the intermediate phase of hospitalization (>24 h before discharge), low-risk patients who might be candidates for early hospital discharge should be identified *(43,44)*. In TIMI II, absence of significant risk factors at the time of emergency room presentation was associated with a 6-wk mortality rate of only 1.5% *(1)*. In the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) trials, Mark et al. *(45)* reported on 708 patients who underwent early coronary angiography and identified 30% of patients at low risk who were discharged on d 4 after the index event. In GISSI-2, 53% of patients were able to perform an exercise test and had an ejection fraction >40%; the 6-mo mortality rate after hospital discharge was <1% *(46)*. In GUSTO, absence of ischemic cardiac complications and need for coronary revascularization or cardioversion was reported in 57.3% of enrolled patients; the 30-d mortality rate was 1% and the 1-yr mortality rate 3.6% *(47)*. Low-risk patients subsets account for as many as half of all recent postinfarct survivors and may not require extended hospitalization or expensive diagnostic procedures. Active cholesterol lowering therapy as per the National Cholesterol Education Project guidelines, motivation to stop smoking, and identification of social isolation and depression are all part of the postinfarct rehabilitative strategy.

Recurrent ischemic cardiac pain, reinfarction, and congestive heart failure significantly increase mortality risk during the intermediate hospital phase. In TIMI II, reinfarction significantly increased mortality rates after 3 yr of follow-up *(48)*. In the TAMI trials, the in-hospital mortality rate was 21% for reinfarction, 11% for recurrent ischemia, and 4% when neither complication occurred. Congestive heart failure symptoms occurred in 50% of patients who developed reinfarction, 31% of patients who developed recurrent ischemia, and 17% of patients when neither ischemic complication occurred *(49)*. Recurrent in-hospital ischemic cardiac events after infarction are a class I indication for cardiac catheterization according to American College of Cardiology/American Heart Association (ACC/AHA) guidelines *(42)*.

PREDISCHARGE RISK STRATIFICATION

The use of noninvasive testing in the prethrombolytic era for risk stratification after AMI has been extensively reviewed *(50–52)*. The predictive value of noninvasive testing for cardiac events is somewhat less in patients who received thrombolysis or direct coronary angioplasty; the patients tend to be younger and have better preserved left ventricular function, and less extensive multivessel coronary disease *(53)* (Fig. 4). A substantial number of patients who undergo early coronary angiography have high-risk anatomy and are subsequently revascularized. This results in a relative lower risk patient population at the time of hospital discharge with a subsequent anticipated lower number of cardiac events to be investigated by noninvasive testing. The 1-yr mortality rates in patients who survive to hospital discharge range from 2 to 3.3% in the TIMI II and the Should We Intervene Following Thrombolysis? (SWIFT) trials respectively *(54–56)*. Thus, according to bayesian theory, noninvasive testing would need to be extremely precise to separate the 98 patients who survive from the 2–3 patients who will die in the year following AMI.

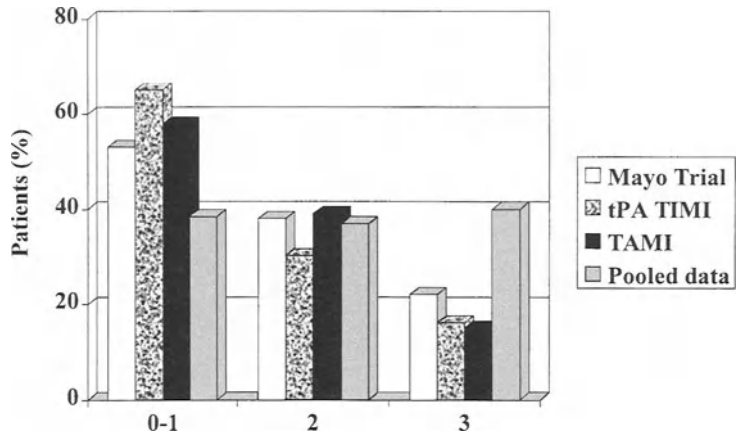

Fig. 4. Comparison of angiographic findings in reperfusion trials with the pooled data from studies done in the prethrombolytic era. Reproduced with permission from ref. *53*.

Noninvasive Testing

Left Ventricular Function Assessment

Early detection of clinical or radiologic evidence of congestive heart failure and predischarge left ventricular function assessment are among the most important and accurate predictors of subsequent cardiac events after AMI. The 1-yr cardiac mortality of patients with acute pulmonary edema approaches 25–30% *(57,58)*. In the acute postinfarct phase, pulmonary edema may represent permanent damage from the infarct and myocardial stunning as a result of the ischemic insult. The finding of clinical evidence of pulmonary congestion as a prognostic indicator is independent of ejection fraction measurements at the time of hospital discharge *(59)*. Increased left ventricular volume, extensive left ventricular wall motion abnormalities, and severe depressed left ventricular ejection fraction identify patients at significantly increased mortality risk in the 1–5 yr follow-up after AMI (Fig. 5 and Table 1) *(59–67)*.

Exercise Electrocardiography

The use of exercise ECG provides an estimate of functional capacity after infarction to prepare patients for cardiac rehabilitation and occupational work evaluation and also provides information regarding adequacy of medical therapy or coronary revascularization therapy and on subsequent cardiac event rates.

In TIMI II, 1-yr mortality was 7.7% in patients unable to perform an exercise test at the time of hospital discharge vs 1.8% in patients who were able to perform the test *(68)*. Similar results were reported by the GISSI-2 investigators *(69)*. Exercise-induced ST-segment depression ≥1 mm increased the relative mortality risk in patients assigned to the invasive strategy in TIMI II *(68)*.

Approximately 25% of patients who receive thrombolysis for AMI have an abnormal exercise test at the time of hospital discharge *(68–74)* (Table 2). The frequency of ischemic responses is increased with symptom-limited as opposed to target heart rate or workload-limited tests *(75,76)*. The positive predictive value of exercise-induced ST-segment

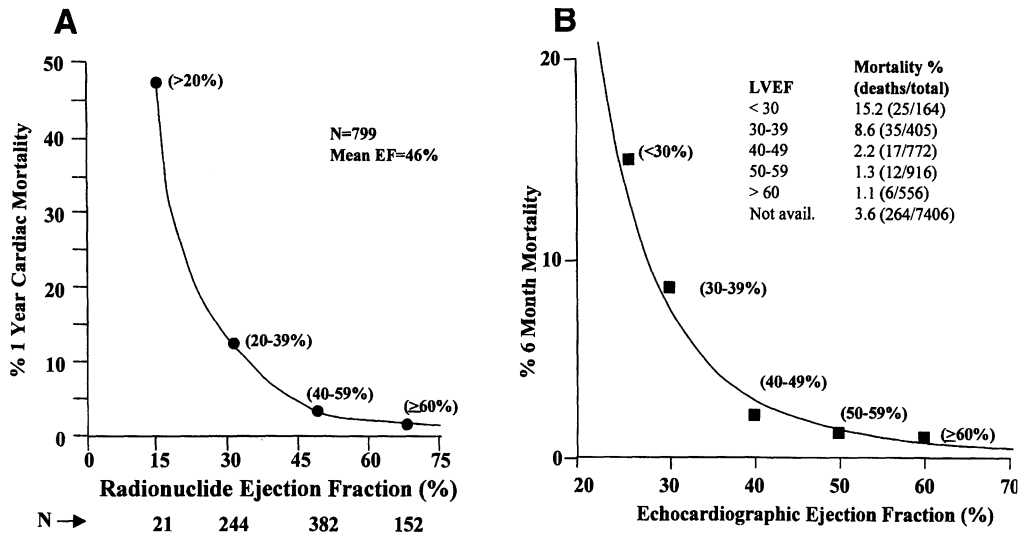

Fig. 5. Effect of left ventricular function on survival following MI. **(A)** Prethrombolytic era; the curvilinear relationship between radionuclide ejection fraction (EF) and 1-yr cardiac mortality showing a sharp increase in mortality with EF <40%. **(B)** Thrombolytic era: although not strictly comparable to A, the same curvilinear relationship between echocardiographic ejection fraction and 6-mo mortality rates suggest that the use of thrombolytic therapy shifts the mortality curve to the left. Reproduced with permission from ref. *58*.

Table 1
Noninvasive Tests, Echocardiography, and Prognostic Value of Resting Wall Motion Abnormalities in Patients with Acute Myocardial Infarction[a]

Study[b]	*Year*	*No. of patients*	*Sensitivity (%)*	*Specificity (%)*	*PPA (%)*	*NPV (%)*	*End points*
Gibson et al. (*60*)	1982	68	79	61	34	92	Cardiogenic shock
Horowitz et al. (*61*)	1982	43	85	17	69	93	Death, serious arrhythmias, pump failure
Nishimura et al. (*62*)	1984	61	80	90	89	82	Death, serious arrhythmias, pump failure
Jaarsma et al. (*63*)	1988	77	88	57	35	95	Severe heart failure
Saabia et al. (*64*)	1991	30	100	12	46	100	Shock, arrhythmias, angina

[a]Abbreviations: PPA, positive predictive accuracy; NPV, negative predictive value.
[b]Thrombolysis was not used in these studies.

Table 2
Selected Exercise Treadmill Studies Done in the Thrombolytic Era and Relationship to Prognosis

Studies	*No. of patients*	*Year*	*Type of test*	*Duration of follow-up (mo)*	*% Abnormal test*	*Prognostic information*	*Strongest predictor of cardiac events*
Piccalo et al. (*73*)	157	1992	Symptom Ltd. (12 ± 2 d)	6	33	No variables predictive of mortality	ST depression with angina predicted more postinfarct angina
Chaitman et al. (*68*) TIMI II	2502	1993	Submaximal (14 d)	12	13	Mortality for positive test 2.4%; for negative test 1.8%; 7.7% for patients unable to exercise	Predictor of mortality: inability to exercise
Stevenson et al. (*70*)	256	1993	Symptom Ltd. (7–21 d)	6–12	49	Low PPV for new cardiac events (17%) (D, RI, UA, R)	Inability to reach workload of <7 METS
Arnold et al. (*71*)	981[b]	1993	Symptom Ltd. (predischarge)	12	24	2.2 relative risk of mortality for patients unable to exercise	Systolic BP rise <30 mmHg
Villela et al. (*69*) GISSI	6296	1995	Symptom Ltd. (28 d)	6	26	Mortality for positive test 1.7%; for negative test 0.9%; 7.1% for patients unable to exercise	Predictors for mortality: Systolic BP rise <28 mmHg (RR 1.85) Symptomatic ischemia (RR 2.54) Submaximal positive (RR 2.28) Low work capacity (<100 W) (RR 2.05)
Toft et al. (*72*)	178	1995	Symptom Ltd. (predischarge)	26–50	40	Low PPV for new cardiac events (19%) (D, RI)	ST segment depression >1 mm and ΔST/ΔHR index
Khattur et al. (*74*)	114	1997	Symptom Ltd. (5–8 d)	18	31	Ejection fraction <40%; (PPA 69%) Exercise time <6 METS, PPA 58% for D, RI, UA, CHF, VA	Exercise time <6 METS

[a]Abbreviations: D, death; RI, reinfarction; UA, unstable angina; CHF, congestive heart failure; VA, ventricular arrhythmia; PPA, positive predictive accuracy; R, revascularization; METS, metabolic equivalents; BP, blood pressure.
[b]490/981 received thrombolytics.

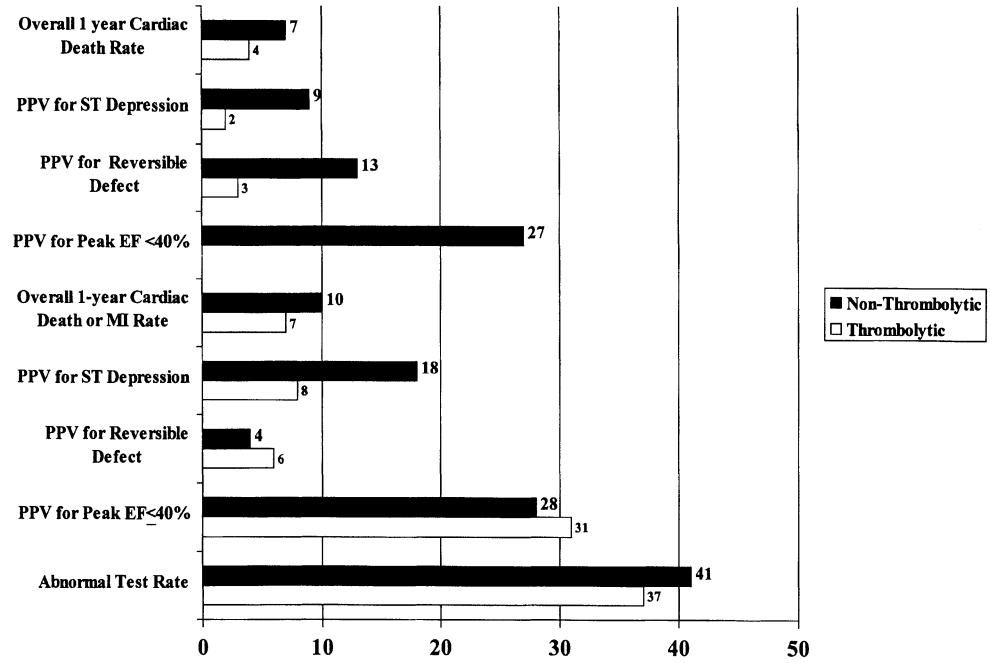

Fig. 6. Meta-analysis of noninvasive tests in thrombolytic and nonthrombolytic treated patients. The positive predictive accuracy for cardiac death, reinfarction rate and rates of abnormal tests are lower in thrombolytic patients. Reproduced with permission from ref. *77*.

depression ≥1 mm was 8% in patients who received thrombolysis vs 18% who did not for the end point of recurrent MI or death in a recent metaanalysis of 54 studies *(77)* (Fig. 6).

A normal exercise ECG at the time of discharge is associated with a 1-yr mortality rate of <1% with >90% predictive accuracy. Additional noninvasive testing with more expensive modalities in this low-risk patient subset is unlikely to be warranted since coronary revascularization is unlikely to reduce overall cardiac mortality at 1 yr below 1%. However, no data is presently available that tests this strategy against 5-yr outcome data. A practical approach to the use of exercise testing in the postinfarct setting adapted from recent ACC/AHA guidelines is illustrated in Fig. 7 *(42,67)*.

Myocardial Perfusion Imaging

Myocardial perfusion scintigraphy localizes ischemia to a specific myocardial territory and distinguishes periinfarction ischemia from ischemia at a remote distance from the infarct site. The test is particularly useful in patients who cannot exercise or who have noninterpretable rest ECGs (Fig. 7). The incremental prognostic value using myocardial perfusion scintigraphy to that obtained by exercise ECG alone has not been extensively studied in patients who receive thrombolysis or direct primary coronary angioplasty. In a series of 210 patients who received thrombolytic therapy and were followed for 21 mo, Miller et al. *(79)* reported a 2-yr survival rate free of cardiac events of 86 vs 80% in patients with high- vs low-risk scans. Table 3 illustrates exercise myocardial perfusion studies of patients who received thrombolysis or direct coronary angioplasty and their relationship to prognosis *(80–86)*.

In patients who cannot perform exercise, dipyridamole or adenosine myocardial perfusion imaging can be useful for risk stratification *(87,88)*. Mahmarion et al. *(83)* studied the value of quantitative adenosine thallium 201 myocardial scintigraphy 2–5 d after

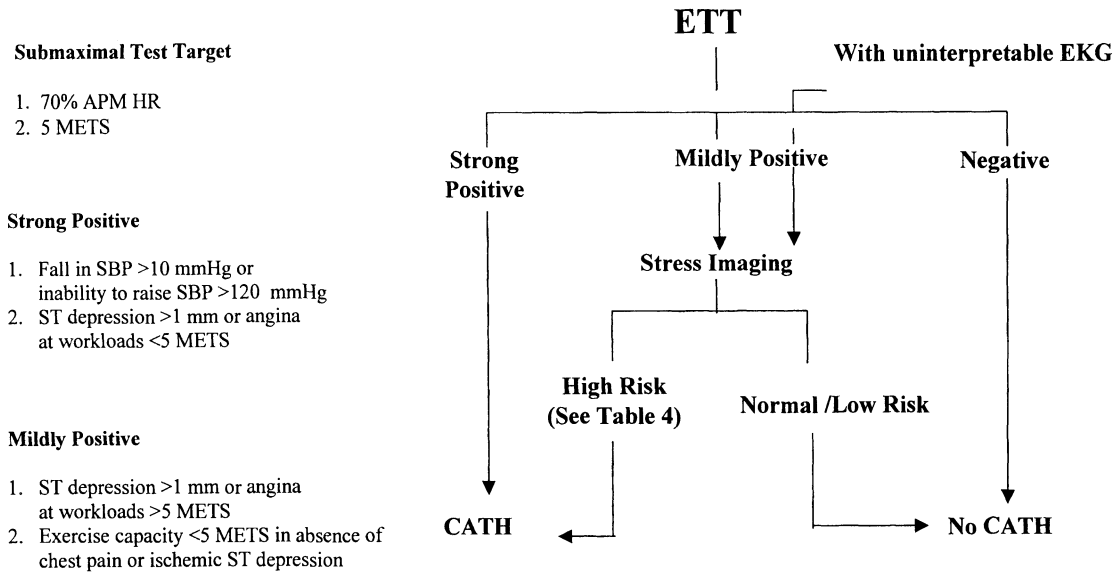

Fig. 7. Use of noninvasive testing with exercise (ETT) to risk stratify lower risk survivors after myocardial infarction. Submaximal, rather than symptom-limited, testing should be done if exercise is scheduled early (3–5 d) after the index event. APM HR, age-predicted maximum heart rate. METS, metabolic equivalents. Reproduced with permission from ref. *58*.

acute myocardial infarction. Multivariate analysis of the 146 patients, 36% of whom received thrombolytic therapy, revealed that a combination of ejection fraction and extent of myocardial ischemia provided the optimal model for risk stratification. When the extent of myocardial ischemia was <10% and ejection fraction >40%, 1-yr survival free of reinfarction was 94%. In this report, mortality was best predicted by total infarct size. Miller et al. *(89)* showed that infarct size <12% of the left ventricle measured by ^{99m}Tc sestamibi SPECT was associated with no mortality in 274 patients over a 2-yr follow-up (Fig. 8). Characteristics of a high-risk nuclear study include

1. reversible defect >10% left ventricle (LV),
2. perfusion defect >20% LV,
3. increased lung uptake of thallium 201.

Exercise or Dobutamine Echocardiography

There are few data reporting the prognostic value of exercise echocardiography after infarction in patients who received thrombolysis or direct PTCA. In three small patient series (<100 patients), exercise echocardiography was associated with a greater sensitivity and specificity for cardiac events than exercise ECG alone *(90–92)*.

Smart et al. *(93)* reported sensitivity, specificity, and safety of dobutamine-atropine stress echocardiography 5 ± 2 d after MI in a 232-patient series. Wall motion abnormalities remote from the infarct zone were associated with 97% specificity and 68% sensitivity for multivessel coronary disease. The most sensitive and specific findings for residual infarct-related stenoses were an ischemic response (decrease in wall thickness in more than two contiguous segments at peak dose without improvement at low dose) and a biphasic response (improved wall thickening in more than two contiguous segments from rest to low dose but decreased wall thickening from low to peak dose). Carlos

Table 3
Prognostic Value of Stress Nuclear Imaging Studies in Patients Undergoing Thrombolysis

Study	*No. of patients*	*Type of stress*	*Time after MI (d)*	*Follow-up (mo)*	*%ST depression/% reversible defects*	*Cardiac events (%)*	*Multivirate predictors of cardiac events*
Tilkemeier et al. (*80*)	64/171	Low-level exercise thallium	10 ± 4	12	15/42	D, RI, R (7)	LV enlargement
Hendel et al. (*81*)	71	Dipyridamole thallium	10 ± 2	24	NR	D + MI (14)	No clinical or scintigraphic variable
Bowling et al. (*82*)	84	Exercise thallium	Predischarge	6	NR	D, MI, UA (13)	Postdischarge angina
Miller et al. (*79*)	210	Symptom-limited exercise thallium	9 ± 6	24	15/56	D (3)	Rate pressure product
Mahmarian et al. (*83*)	146 (36%) received thrombolysis	Adenosine thallium	5 ± 3	16	NR	D, RI, VA/CHF (33)	Absolute extent ofischemia; EF; total perfusion defect size best predicted death
Basu et al. (*84*)	100	Symptom-limited exercise	42	21	39/68	D, RI, UA, CHF (37)	Cardiac events in 89% of patients
Travin et al. (*85*)	134/54[b]	Symptom-limited exercise Tc sestamibi	7	15	23/70	D, MI, UA (13)	Event rate 38% in patients with >3 reversible sestamibi defects
Dakik et al. (*86*)	71	Symptom-limited exercise thallium	13	24	15/38	D, RMI, VA/CHF (37)	EF reversible; perfusion defect size >20%

[a]Abbreviations: D, death; RI, reinfarction; UA, unstable angina; CHF, congestive heart failure; VA, ventricular arrhythmia; PPA, positive predictive accuracy; R, revascularization; NR, not reported; MI, myocardial infarction; LV, left ventricular; EF, ejection fraction.

[b]Number of patients with imaging studies/number of patients in study.

[c]All patients received primary PTCA

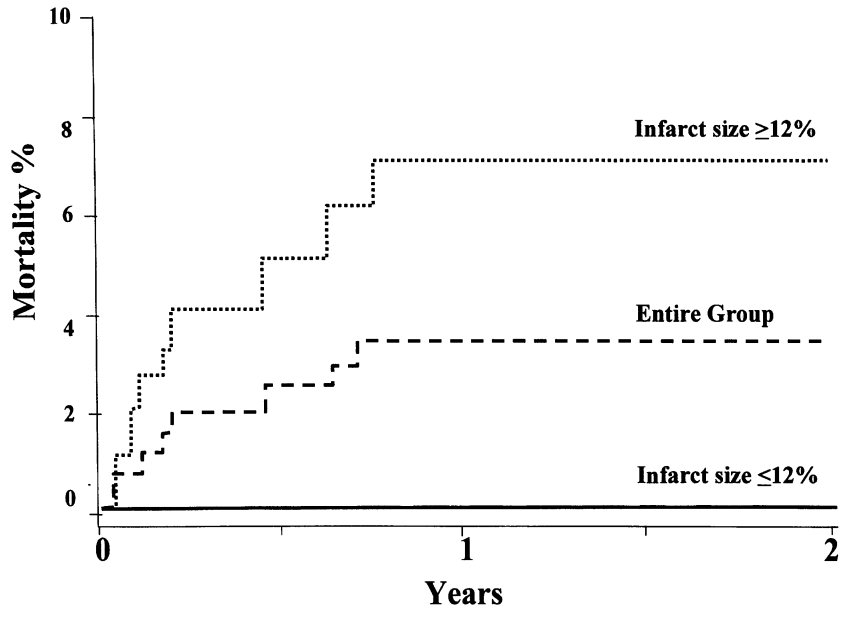

Fig. 8. Influence of infarct size measured by ^{99m}Tc sestamibi on mortality during 2-yr follow-up. Two-yr mortality was 7% for 137 patients with infarct size >12% and 0% for 137 with infarct size <12%. Reproduced with permission from ref. *89*.

et al. *(94)* used dobutamine stress echocardiography for risk stratification after acute MI in 214 patients, 121 of whom received thrombolytic drugs. A lower basal wall motion score index (1.55 vs 1.88), higher number of infarcted segments (4.1 vs 1.9) and lower number of dobutamine-responsive segments (1.2 vs 2.9) were associated with an adverse prognosis. Absence of viability was associated with the worst prognosis ($p < 0.0001$) in multivariate analysis. In Carlos et al.'s *(94)* report, dobutamine echocardiography was a better predictor of cardiac events than coronary angiography (Fig. 9). The prognostic information provided by stress echocardiography after AMI is reviewed in Table 4 *(90–92,94–98)*. Indications for nuclear/echo stress testing adapted from recent ACC/AHA guidelines are reviewed in Table 5 *(42,67,79,99)*.

Evaluation for Electrical Instability

The risk of sudden cardiac death in survivors of MI with normal ejection fraction is low, whereas patients with an ejection fraction <35–40% have a 10% risk of sudden cardiac death over 3.5 yr, 6–8% in the first year and 2–4% a yr thereafter *(101)*. In GISSI-2, the prevalence of frequent ventricular ectopy (>10 PVC/h) was 20% in 8676 patients, not significantly different from the frequencies reported in the prethrombolytic era *(102)*. The predictive accuracy for cardiac events is lower in the postthrombolytic patient (Table 6) *(102–106)*.

In GUSTO, Singh et al. *(107)* reported lower heart rate variability (HRV) 24 h after AMI in patients with anterior vs nonanterior MI (SDANN 53 ± 21 vs 63 ± 24 ms; $p < 0.005$), increased HRV with TIMI II flow (LF 5.3 ± 1.0 vs 4.8 ± 1.2 ms^2; $p < 0.01$), and lower HRV in those who died at 1 yr compared with survivors.

Low-amplitude (<25 V) late potentials along with increased filtered QRS duration (>120 ms) is suggestive evidence of slowed and fragmented conduction. Absence of these findings in the postinfarct setting is associated with a 96–99% negative predictive

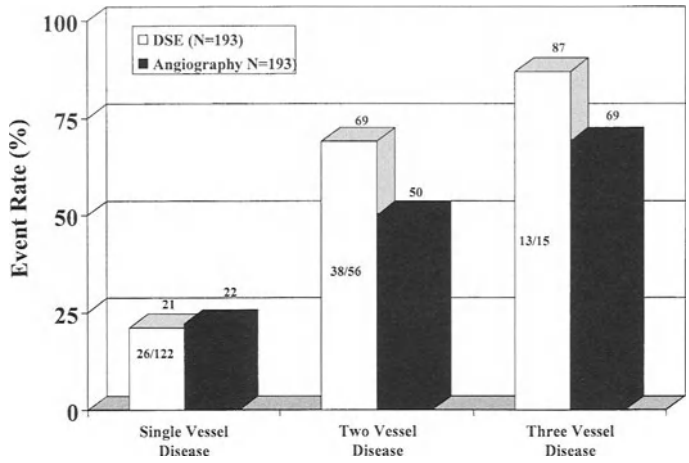

Fig. 9. Comparison of cardiac events (death, reinfarction, unstable angina, congestive heart failure, ventricular arrhythmias) according to extent of coronary artery disease detected by dobutamine echocardiography and coronary angiography. Reproduced with permission from ref. *97*.

Table 4
Prognostic Value of Stress Echocardiography in Patients After Myocardial Infarction[a]

					Cardiac Events		
Study	*Year*	*Test*	*No. of patients*	*Follow-up (mo)*	*Ischemic*	*Non-ischemic*	*Comments*
Ryan et al. (*90*)	1987	EX	40	6–10	94	17	MI, D, UA, R
Applegate et al. (*91*)	1987	EX	67	11	50	13	D, MI, R
Iliceto et al. (*95*)	1990	Pacing	83	14 ± 5	65	8	D, MI, UA, R
Bolognese et al. (*96*)	1992	DIP	217	24	16	5	D, MI, UA
Camerici et al. (*97*)	1993	DIP	190	14 ± 10	52	17	D, MI, UA, R
Picano et al. (*98*)	1993	DIP	1080	16	5.4	2.8	MI
Quintanta et al. (*92*)	1995	EX	70	36	27	9	D, MI, R
Carlos et al. (*94*)	1997	DOB	214	16 ± 6	44	28	D, MI, CHF, UA

[a]Abbreviations: D, death; RI, reinfarction; UA, unstable angina; CHF, congestive heart failure; VA, ventricular arrhythmia; R, revascularization; EX, exercise; DOB, dobutamine; DIP, dipyridamole.

value for sustained ventricular tachycardia or sudden cardiac death after 1 yr *(106,108–111)*. The combined use of ambulatory ECG variables, signal-averaged ECG, and HRV leads to a greater positive predictive accuracy for cardiac events *(108–110)*.

Programmed electrical stimulation inducing monomorphic ventricular tachycardia with cycle length >230 ms performed 2–4 wk after MI in patients with ejection fraction <35% is a good predictor of spontaneous sustained ventricular tachycardia *(112,113)*. Pedretti et al. *(114)* reported a sensitivity of 81% and specificity of 97% for inducibility of ventricular tachycardia to predict future arrhythmia in patients after MI who had two or more of the following: ejection fraction <40%, late potentials, or high-grade ectopy. Zoni-Berisso et al. *(113)*, using up to two extra stimuli for induction of monomorphic ventricular tachycardia, found inducibility to have a sensitivity, specificity, and positive predictive accuracy of 55, 99, and 67% for an arrhythmic event. Patients were selected

Table 5
Indications for Nuclear/Echo Stress Testing Based on ACC/AHA Guidelines

1. Uninterpretable electrocardiogram
2. Mild abnormality on exercise treadmill test (ETT)
3. Unable to exercise
4. Myocardial infarction not treated with acute reperfusion
5. Myocardial viability assessment

Data from refs. *42, 67, 79,* and *99.*

Table 6
Prevalence of Frequent PVCs (>10/h), Risk of SCD, Sensitivity, Specificity, and PPA of Frequent PVCs to Predict SCD and Sustained Ventricular Arrhythmias[a]

Study	*Year*	*No. of patients*	*Prevalence (%)*	*SCD (%)*	*Sensitivity (%)*	*Specificity (%)*	*PPA (%)*
Moss et al. (*103*)	1979	940	23	5.9	42	78	11
Bigger et al. (*104*)	1984	819	15	6.6	55	72	12
Mukharji et al. (*105*)	1984	533	15	4.6	67	47	8
Maggioni et al. (*102*)[b]	1993	8626	20	0.9	42	80	3
McClements et al. (*106*)[b]	1993	301	26	4.3	38	74	6

[a]Abbreviations: SCD, sudden cardiac death; PPA, positive predictive accuracy; PVCs, premature ventricular couplets.
[b]After thrombolysis.

if they had either ejection fraction <40%, late potentials, or complex ventricular arrhythmias. Lack of inducibility in this high-risk population carries a better prognosis. The Multicenter Automatic Defribillator Implantation Trial showed that in a select group of patients enrolled 4 wk to 2 yr after MI (with ejection fraction <35%, an episode of nonsustained ventricular tachycardia, and nonsuppressible ventricular tachyarrhythmia during electrophysiologic study) randomization to automatic implantable cardioverter-defibrillator was associated with significantly improved survival rates compared with conventional therapy *(115).* The Multicenter Unsustained Tachycardia Trial (MUSTT) trial is testing the hypothesis that treatment guided by electrophysiologic testing will decrease the incidence of sudden cardiac death in high-risk coronary artery disease patients, many of whom have had prior MI. The use of noninvasive predictors of sudden cardiac death to select candidates for electrophysiologic studies to identify the highest risk patient for sudden cardiac death after AMI is shown in Fig. 10.

Coronary Angiography

Ellis et al. *(116)* randomized 87 patients treated with thrombolysis who had a negative noninvasive risk stratification workup to medical therapy or coronary angioplasty (4–14 d). After 12-mo follow-up, survival free of MI was 97.8% in patients who did not receive PTCA compared with 90.5% in patients who did ($p = 0.07$). Mark et al. *(117)* compared the use of angiography, angioplasty, and survival rates of patients enrolled in GUSTO-1 from the United States and Canada. The rate of coronary angiography was 72 vs 25%, coronary

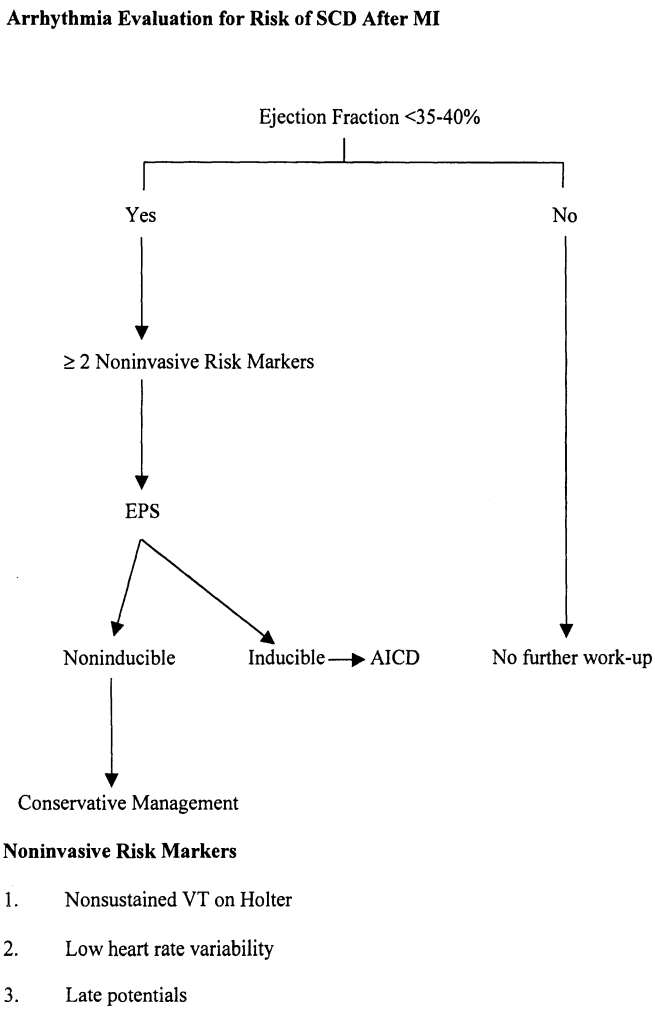

Fig. 10. Use of noninvasive electrophysiologic markers to identify high-risk patients for electrophysiologic studies and evaluation for risk of sudden cardiac death after myocardial infarction.

angioplasty 29 vs 11%, and 1-yr survival rate 90.7 vs 90.3% in the United States and Canada, respectively. In the Survival and Ventricular Enlargement (SAVE) trial 31% compared with 12% of American vs Canadian patients underwent coronary revascularization. The 1-yr mortality rates, however, were virtually identical (11%) *(118)*. Results were similar in 240,989 patients surveyed in 1073 U.S. hospitals from 1990 to 1993 *(119)*. The indications for cardiac catheterization after MI adapted from ACC/AHA guidelines are illustrated in Table 7.

CONCLUSIONS

Using mostly data from the thrombolytic era, a logical sequence of clinical and noninvasive test procedures has been given to risk-stratify postinfarct survivors into high and lower risk populations. The highest risk patients should be considered for early coronary angiography and revascularization therapy if clinically indicated, and the lowest risk patients could be managed medically. However, all risk stratification algorithms

Table 7
Indications for Coronary Angiography After MI[a]

Indication	*Class*[b]
1. Postinfarction angina	I
2. Before definitive therapy of mechanical complications of MI (acute MR, VSD, pseudoaneurysm)	I
3. Patients with hemodynamic instability	I
4. Objective evidence of ischemia on stress testing	I
5. Noninvasive evidence of LV dysfunction (EF <40%)	IIa
6. Survivors of MI who had clinical heart failure, but subsequently demonstrated normal EF	IIa
7. Unsuccessful thrombolytic therapy	IIa
8. Malignant ventricular arrhythmias 48–72 h after acute MI	IIa

[a]Abbreviations: MI, myocardial infarction; MR, mitral regurgitation; VSD, ventricular septal defect; LV, left ventricular; EF, ejection fraction.

[b]Class I, evidence that the given procedure is beneficial, useful, and effective; class IIa, weight of evidence in favor of usefulness.

Adapted from the ACC/AHA 1996 Guidelines (*42*).

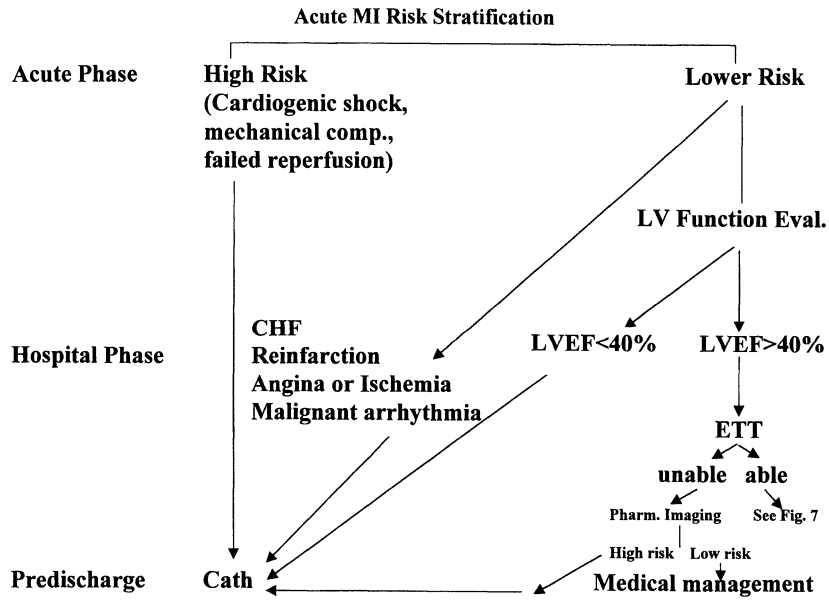

Fig. 11. Overall strategy to risk stratify postinfarct survivors and identify optimal candidates for cardiac catheterization or continue medical management.

that are developed based on noninvasive testing will continue to evolve as ongoing clinical outcome studies and consensus statements are tested. Presently, the strategy given in Fig. 11 can be used to assess cardiac risk after AMI in the postthrombolytic/direct angioplasty era.

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IV Non-ST-Segment Elevation Myocardial Ischemia

16 Antithrombotic Therapy in Unstable Angina and Non-Q-Wave Myocardial Infarction

Marc Cohen, MD, and Reginald Blaber, MD

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INTRODUCTION

Unstable angina is a broad term representing a wide spectrum of ischemic coronary syndromes, ranging from progressive or accelerating angina to the high-risk subset of patients with rest angina and reversible electrocardiographic (ECG) changes. The underlying precipitant is the ruptured or fissured coronary plaque, which elicits a complex interaction between the coagulation cascade and platelets to form a thrombus. The majority of these disruptions and resulting thrombi cause only insignificant obstruction to coronary blood flow. However, a large thrombus can cause a significant impediment to coronary flow, resulting in ischemia. This thrombus may resolve spontaneously, with restoration of blood flow, or may propagate to cause further ischemia. Often this process can lead to complete occlusion of the vessel, precipitating a myocardial infarction (MI) *(1–10)*. Unstable angina and non-Q-wave myocardial infarction (NQMI) represent two different points within the continuum of coronary thrombosis.

Since 1980, when DeWood et al. *(11)* proved that MI was the result of in vivo thrombus formation, great resources have been expended to understand and curtail coronary thrombosis. A number of antiplatelet and antithrombotic regimens have been investigated that include indirect thrombin inhibitors (heparin), direct thrombin inhibitors (hirudin and hirulog), and low molecular weight heparin in coronary syndromes. The core of the problem lies within the ruptured plaque itself. Cellular and lipid elements such as tissue factor, surface-bound von Willebrand factor, and types I and III collagen are exposed,

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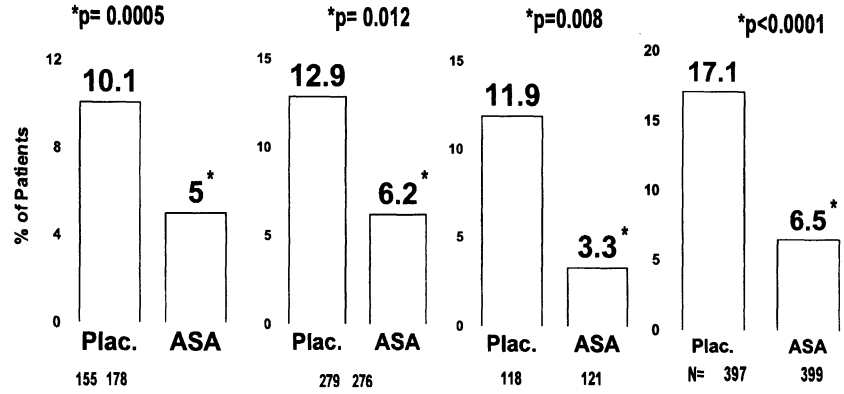

Fig. 1. Effect of ASA in non-ST elevation MI and unstable angina: incidence of death or subsequent MI. Plac, placebo; ASA, aspirin. Adapted with permission from refs *12–14* and *20*.

activating the intrinsic and extrinsic coagulation cascades. These pathways lead to the activation of thrombin, which, among a number of activities, cleaves fibrinogen to fibrin, activates factor XIII to stabilize the fibrin clot, and activates factors V and VIII in a positive feedback loop to accelerate thrombin's own generation. Simultaneously, thrombin as well as collagen, adenosine diphosphate (ADP), von Willebrand factor, thromboxane A_2, and local shear forces activate platelets. There is then an exocytosis of the platelets' α and dense granules, releasing ADP and thromboxane A_2, which, in turn, feeds back to accelerate local platelet activation. Activated platelets then expose IIb/IIIa receptors, which allow platelets to bind fibrin to form a thrombus *(1–6)*.

A number of randomized clinical trials have established the beneficial role of antiplatelet agents such as aspirin in unstable angina and NQMI *(12–15)* (*see* Fig. 1). Several antithrombotic regimens have been investigated as well, including the indirect thrombin inhibitor heparin, direct thrombin inhibitors, and low molecular weight heparin. To date, despite antiplatelet and antithrombotic therapy, approximately 7–12% of patients with unstable angina go on to suffer an MI *(16)* within 14 d. The 1-yr mortality of patients with unstable angina is 5–14%, with half of the deaths occurring within the first 4 wk *(16)*. Thus, there remains great interest in improving the efficacy of the current antiplatelet and antithrombotic therapy. This chapter summarizes the data generated in investigation of aspirin and new antithrombotic therapies.

ASPIRIN

Aspirin, a cyclooxygenase and hydroperoxidase inhibitor, blocks the synthesis of thromboxane A_2 and prostaglandin I_2. Those pathways that cause platelet aggregation involving thromboxane A_2 are hindered in the presence of aspirin *(17,18)*. The International Study of Infarct Survival (ISIS)-2 *(19)* was the first study to show that aspirin, when given at 162.5 mg daily, decreased mortality after MI by 21% ($p < 0.001$). These benefits persisted out to several years. Additionally, the risk of reinfarction and stroke were halved at 1 mo.

In unstable angina, aspirin has been shown to improve early and late outcomes unequivocally. Four randomized, placebo-controlled trials *(12–14,20)* have shown that aspirin reduces the incidence of myocardial infarction and death from cardiac causes by

50–70% in patients with unstable angina despite significant differences in the cohorts studied, time to initiation of therapy, and duration of follow-up. The Veterans administration (VA) study *(12)* randomized 1266 men in a double-blinded fashion within 48 h after admission to aspirin 324 mg daily vs placebo. As in the other three studies, previous aspirin users were excluded. Aspirin decreased the incidence of fatal and nonfatal MI from 10.1 to 5.0% ($p = 0.0005$). Even though the aspirin was stopped at 12 wk, the mortality rate remained 43% lower at 1 yr (9.5 vs 5.5%).

The Canadian Multicenter Trial *(13)* randomized 555 men and women in a factorial design trial to aspirin 325 mg qid, sulfinpyrazone 200 mg qid, both, or neither. Drug therapy was initiated within 8 d of admission and continued for a mean of 18 mo. Intention to treat analysis yielded a 14.7% incidence of cardiac death and nonfatal MI vs 10.5% with aspirin, a 30% risk reduction ($p = 0.07$). Secondary events of unstable angina requiring rehospitalization and coronary artery bypass graft surgery were not affected by the use of aspirin.

Theroux et al. *(20)* compared aspirin, heparin, and combination therapy in 479 patients with unstable angina. His group found a significant reduction in cardiac death and MI: 11.9% in the placebo group, 3.3% in the aspirin group ($p = 0.01$), and 1.6% in the aspirin and heparin group. Furthermore, the Research Group on Instability in Coronary Artery Disease in Southeast Sweden (RISC) *(14)* randomized 945 men with unstable angina or NQMI within 72 h of admission to placebo or low-dose aspirin. They found that the rates of death and MI were reduced by 57% ($p = 0.033$) at 5 d, with the magnitude of the risk reduction increasing at 30 and 90 d. One-year follow-up of these patients continued to show a nearly 50% reduction ($p < 0.0001$) in death and MI in aspirin-treated patients compared with placebo.

Therefore, despite varying doses of aspirin, time to initiation of therapy, and duration of therapy in these studies, a consistent and substantial reduction in the relative risk of adverse cardiac events was seen. Pooling data from over 2000 patients *(12–14,20)*, the occurrence of infarction or death was reduced from 11.8% (control) to 6.9% (aspirin).

Interestingly, all these studies excluded those on aspirin at presentation. Up to 40% of those presenting with unstable angina and NQMI were taking aspirin and therefore represented "aspirin failures." Thus, the question arose: "is aspirin resistance a consequence of the inhibition of prostaglandin I_2 synthesis, a potent platelet aggregation inhibitor and vasodilator?" Cohen and the Antithrombotic Therapy in Acute Coronary Syndromes Research (ATACS) *(21)* studied the efficacy of controlled-release aspirin, which acetylates platelet cyclooxygenase in the enterohepatic circulation, preserving endothelium-derived prostaglandin I_2 synthesis. They found no outcome advantage of prostacyclin-sparing aspirin over conventional aspirin.

HEPARIN

Of the available antithrombotic regimens for acute coronary syndromes, unfractionated heparin is the oldest, the most widely available, and the current standard by which new antithrombotic agents are judged *(22)*. Heparin was first identified in 1916. In 1939, investigators found that its anticoagulant properties required the presence of a cofactor that was later named antithrombin III (ATIII) *(23)*. Heparin binds to the lysine site of ATIII and produces a conformational change at the arginine reactive center, converting ATIII from a slow to a rapid inhibitor of thrombin (factor IIa). Heparin then dissociates from the complex to be reutilized *(22,23)*.

Commercial preparations of unfractionated heparin are heterogeneous, with compounds ranging in molecular weight from 3,000 to 30,000 Daltons. One-third of these molecules with the essential pentasaccharide sequence bind ATIII and are responsible for most of heparin's anticoagulant effect. The remaining two-thirds have little anticoagulant effect at therapeutic doses *(23)*.

The heparin–ATIII complex inactivates factors IIa (thrombin), Xa, XIIa, XIa, and IXa. Thrombin is 10 times more sensitive to the heparin – ATIII complex than is factor Xa *(23)*. However, the inactivation of thrombin requires that both ATIII and long-chain heparin bind to thrombin. The inactivation of factor Xa can be accomplished with short or long chains of heparin. Heparin moieties <5,400 Daltons are unable to bind thrombin and ATIII simultaneously, but can bind factor Xa if it contains the correct pentasaccaride. As such, unfractionated heparin exerts most of its anticoagulant properties through thrombin inactivation. Unfortunately, the anticoagulant effect of heparin is modified by platelets, fibrin, vascular surfaces, and plasma proteins. Platelet-bound factor Xa is inaccessible to unfractionated heparin. Thrombin, when bound to fibrin, is also protected from inactivation by the heparin–ATIII complex. Finally, heparin binds to, and is inactivated by, a number of plasma proteins including vitronectin, and other acute-phase reactant proteins *(23)*. Therefore, despite its compelling anticoagulant properties the use of heparin in the platelet-rich arterial thrombus may be somewhat limited.

From 1962 to 1973, six randomized trials encompassing 3800 patients with acute coronary syndromes were conducted involving heparin, as well as warfarin and phenindione, either alone or in combination *(24)*. Pooling of the data from these trials showed a 22% reduction in total mortality ($p < 0.002$). Another overview of 5700 patients treated with heparin alone demonstrated a 16% reduction in mortality as well *(25)*.

The first randomized, placebo-controlled trial of heparin in 1981 by Telford and Wilson *(26)* showed a significant reduction (vs placebo) in the incidence of MI (15 vs 3%) after 7 d of intravenous heparin. Theroux et al. *(20)* performed a placebo-controlled randomized trial evaluating aspirin alone, vs heparin alone, vs a combination of the two in 479 patients with acute unstable angina. The incidence of refractory angina decreased by 63% in the heparin group and 53% in the combination group, but there was no change in the aspirin alone group. The incidence of MI was reduced in the group receiving aspirin (3%, $p = 0.01$), heparin (0.8%; $p = 0.001$), and combination therapy (1.6%, $p = 0.003$) vs placebo (12%). Compared with aspirin, heparin was associated with a relative risk of 0.47 for refractory angina ($p = 0.006$), 0.25 for MI ($p = 0.52$), and 0.52 for any event ($p = 0.10$). The combination of aspirin and heparin was only slightly superior to aspirin alone and worse than heparin alone. Thus, there was a trend toward the superiority of heparin over aspirin in unstable angina. Because of the efficacy of both drugs in unstable angina, the study was underpowered to show a benefit of combination therapy.

Theroux et al. *(27)* then continued this study, altering the design to evaluate aspirin alone vs heparin alone, deleting the placebo and combination therapy arms. MI during the study period occurred in 0.8% in the heparin group vs 3.7% in the aspirin group ($p = 0.035$). An extended factorial analysis of the 479 patients in the first trial and 245 patients in the second trial was performed. Four of 362 patients on heparin therapy experienced a fatal or nonfatal MI compared with 23 of 362 patients without heparin (odds ratio 0.16; $p < 0.005$). Eleven of 366 patients who received aspirin suffered an event, compared with 16 of 358 patients without aspirin (odds ratio 0.66; p = NS). Bleeding complications were seen in 4 aspirin-treated patients vs 15 heparin-treated patients ($p = 0.008$). The degree of risk reduction with heparin compared with aspirin exceeded 75%.

The RISC Group *(14)* in the interim had published data showing that aspirin (75 mg daily), not heparin (delivered in intermittent boluses) decreased the risk for MI in patients with unstable angina. The results of this study should be qualified by the fact that heparin was delivered by intermittent boluses, and the average dose of heparin was only 15,000 U/d. There was no adjustment of the activated partial thromboplastin time (aPTT), making it likely that many patients had subtherapeutic anticoagulation. Additionally, patients were randomized up to 72 h after the last episode of chest pain, with an average time to randomization of 33 h. This resulted in the selection of a less acute cohort with less unstable coronary syndromes.

In another study of patients with refractory unstable angina *(28)*, heparin was administered by continuous infusion; a significant decrease was seen in the number of anginal attacks (71–77%), silent ischemia episodes (84–94%), and total duration of ischemia (81–86%) compared with baseline ($p < 0.001$). Neither aspirin alone nor alteplase significantly reduced these end points.

In a more recent study *(29)*, the same authors randomized patients with unstable angina to sc heparin, iv heparin, or aspirin. The study design called for all patients to receive aspirin for 3 d prior to taking the study drug. Patients begun on heparin were taken off aspirin on d 4. After 72 h of the study drug, aspirin alone was found to have no effect on the number of anginal attacks, total ischemic episodes, or the duration of ischemia. Heparin, however, significantly lowered all three end points, whether given subcutaneously or intravenously. Analysis would suggest that those receiving heparin actually also benefited from the residual effects of 3 d of aspirin. Similar to observations by Theroux et al. *(30)*, a rebound of clinical symptoms was observed after heparin discontinuation. This study also showed a trend suggesting that continuation of heparin therapy (12,500 U sc daily) for at least 4 wk may be useful in patients with unstable angina. A similar trend was not observed in the aspirin group.

The ATACS Trial *(31)* randomized 214 nonprior aspirin users with unstable angina to aspirin (162.5 mg daily) alone, vs aspirin plus heparin (aPTT adjusted) for 5 d followed by 12 wk of coumadin. Of the 214 patients, 147 had unstable angina, 46 had a NQMI, and 16 had a Q-wave MI. At 14 d, 27% of patients in the aspirin-alone group reached a primary end point of recurrent angina, or MI, or death, vs 10% in the combination therapy group ($p = 0.004$) (*see* Fig. 2). In the subset with unstable angina, a primary end point was attained in 29% of the aspirin group vs 21% of the heparin group. Major bleeding was observed in 2.9% of the combination group, but none was reported in those taking aspirin alone. By the end of 12 wk of therapy, 25% of those solely on aspirin experienced a primary end point compared with 13% assigned to the aspirin and heparin group ($p = 0.06$). Pooling data from the ATACS, RISC, and Theroux studies produced an estimated relative risk of 0.44 for infarction or death at 5 d among patients treated with combination antithrombotic and antiplatelet therapy compared with aspirin alone *(31)* (*see* Fig. 3).

Holdright et al. *(33)*, using Holter ECG detection of ischemia, published results discordant with those above in a single-blind study of 285 patients with unstable angina randomized to aspirin (150 mg daily) or aspirin plus intravenous aPTT-adjusted heparin. ST-segment monitoring was performed for the first 48 h of therapy. No significant difference between the two groups was noted for episodes of ischemia, total duration of ischemia, or secondary end points of MI or death.

Finally, in a metaanalysis *(16)* of six trials involving 1353 patients with unstable angina and NQMI that included the previously described trials, the incidence of MI or death during combination heparin/aspirin therapy was shown to be 7.9 vs 10.4% in those

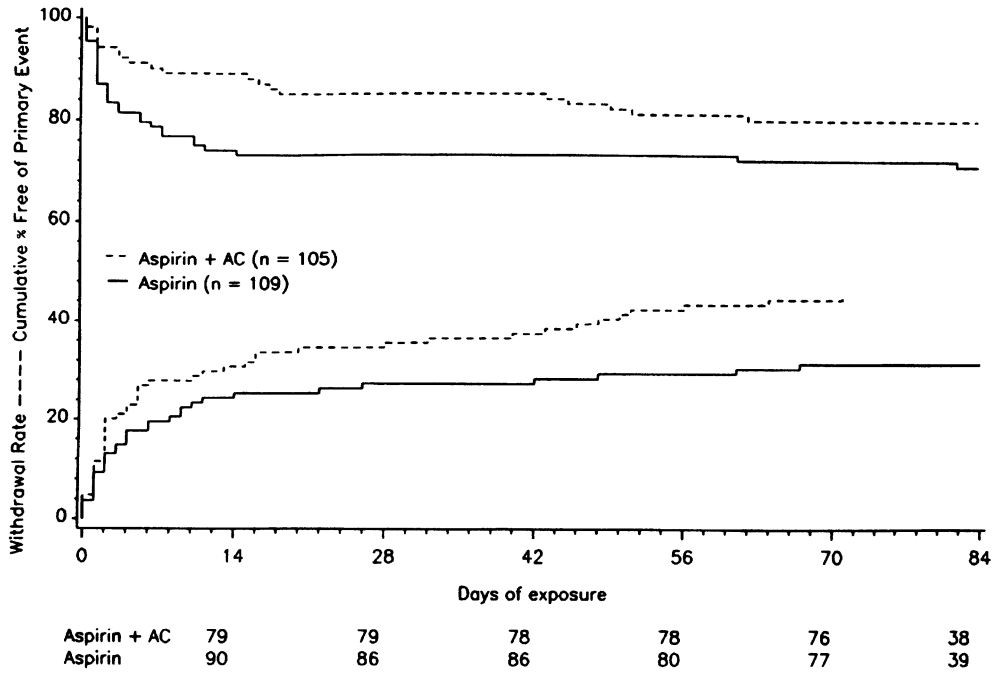

Fig. 2. Cumulative percent of patients free of any primary end points. Also depicted in the bottom half of the panel is the withdrawal rate from trial therapy. AC, anticoagulant. Adapted with permission from ref. *31*.

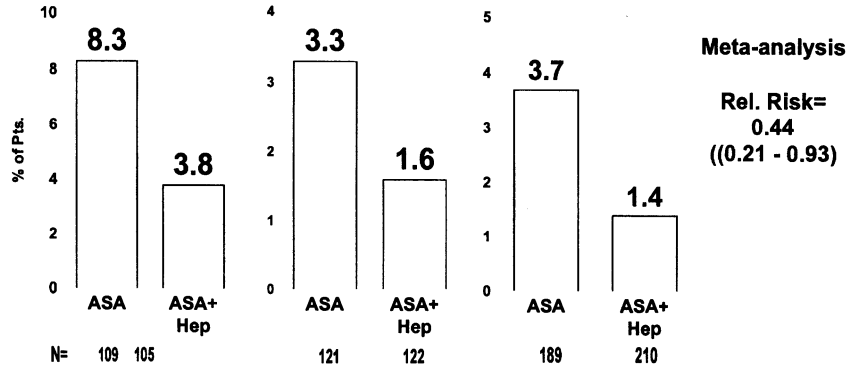

Fig. 3. Pooled analysis of relative risk of combination therapy vs aspirin alone on incidence of death or MI during first 5 d. Adapted with permission from refs. *14, 20,* and *31*.

on aspirin alone at 2 wk. This represents a risk reduction of 0.67 (p = 0.057). Risk of recurrent ischemic pain was 17.3 vs 22.6% (p = 0.08), respectively. Major bleeding occurred in 0.4 and 1.5% (p = NS), respectively. Heparin had no effect on the rate of revascularization.

Thus, although the data show that heparin is superior to aspirin alone in therapy of patients with unstable angina, the superiority of aspirin plus heparin over aspirin alone is not as strongly supported. Certainly there is at least a strong trend evidenced by the data to support this notion *(14,27,31)*. Additionally, it is also clear that aspirin, when used in conjunction with heparin, reduces the incidence of rebound ischemic episodes that appear

to cluster around 9.5 h after termination of the heparin infusion *(30)*. As unstable angina represents a heterogeneous collection of ischemic pathology with varying degrees of risk for infarction and death, the potential benefit of heparin across these different groups probably differs. However, even when most would advocate the use of heparin, there is considerable disagreement as to the optimal duration of therapy.

DIRECT THROMBIN INHIBITORS

Unlike heparin, direct thrombin inhibitors such as hirudin, and hirulog do not require a cofactor to inhibit thrombin *(33,34)*. The class prototype, hirudin, is a 65-amino acid polypeptide derived from the medicinal leech *(Hirudo medicinalis)* that binds selectively to thrombin in a 1:1 fashion at two sites. The 72-amino acid carboxy terminus binds to the fibrinogen recognition site of thrombin. The amino terminus binds to thrombin's catalytic site. This binding is not covalent, but the dissociation rate is so slow that hirudin is essentially an irreversible inhibitor of thrombin. Importantly, it can bind and inactivate both free and bound thrombin. Additionally, platelet factor 4 (PF4), vitronectin, or other plasma proteins do not inactivate it. Finally, direct thrombin inhibitors have a more predictable and stable anticoagulant response *(33–35)*.

The antithrombotic effects of hirudin have been demonstrated in animal models. Most notably in the pig model of deep arterial injury *(36)*, hirudin was a more effective inhibitor of both platelet deposition and thrombus formation than heparin at the site of arterial injury. Furthermore, hirudin completely eliminated macroscopic thrombus formation at an aPTT at least twice normal *(36)*.

Given the mechanistic advantages of hirudin, one might expect hirudin to result in better outcomes in acute coronary syndromes. In fact, in a small safety and efficacy trial of 20 patients with unstable angina *(37)*, hirulog (a synthetic analog of hirudin) was found to be more favorable than heparin controls treated for 5 d using a composite end point of death, MI, intractable angina, intracoronary thrombus, and bleeding. The Thrombolysis in Myocardial Infarction (TIMI) 5 *(38)* study investigated the efficacy of hirudin vs heparin as an antithrombotic adjunct in acute MI patients receiving thrombolytic therapy and aspirin. The primary end point was TIMI grade 3 flow at 90 min and 18–36 h. At 90 min, 62% of the hirudin group and 49% of the heparin group exhibited TIMI grade 3 flow ($p = 0.07$). At 18–36 h of therapy, the infarct-related artery patency was significantly higher in the hirudin group (98 vs 89%; $p = 0.01$). Although the trial was not designed to investigate clinical end points primarily, a composite end point of death, reinfarction, congestive heart failure, and cardiogenic shock favored the hirudin group (9.3 vs 19%; $p = 0.03$). The rate of major spontaneous or instrumented hemorrhage was 23% for heparin and 6.8% for hirudin.

In another angiographic study, Topol et al. *(39)* randomized 116 patients with unstable angina and baseline angiograms showing a $\geq$60% stenosis of a culprit coronary artery or saphenous vein graft to one of two doses of heparin or one of four doses of hirudin. After 72–120 h of study drug therapy, repeat coronary angiography showed that patients receiving hirudin had significantly better improvement of caliber diameter and minimal cross-sectional area, reflecting thrombus dissolution or prevention of thrombus propagation. Additionally, hirudin exhibited a more consistent and stable elevation of the aPTT. Although not designed for clinical end points, there was a trend toward an improved composite end point of death, MI, and recurrent angina with hirudin (14 vs 24%; $p = 0.14$).

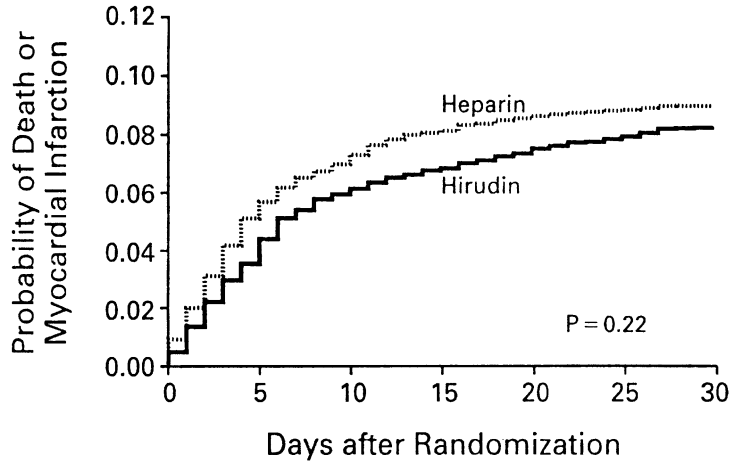

Fig. 4. Kaplan-Meier estimate of the probability of death or myocardial or reinfarction in patients. p value was determined by the Cochran-Mantel-Haenszel test. Adapted with permission from ref. *41*.

These data suggest that resolution of a coronary thrombus as judged by various measures of lesion severity might be associated with clinical benefit in patients with unstable angina and NQMI.

The TIMI 7 investigators *(40)* randomized in double-blinded fashion patients with unstable angina to four different doses of hirulog. All patients received an aspirin daily. The primary end point was a composite of death, nonfatal MI, rapid clinical deterioration, or recurrent angina at rest by 72 h. Although there was no difference among the four groups of ascending hirulog dosing, the secondary end point of death or nonfatal MI was 10% in the lowest dose group vs 3.2% in the three combined higher dose groups at hospital discharge and persisting out to 6 mo. The authors reasoned that the lowest dose could be used as a control group and concluded that this direct thrombin inhibitor was effective in preventing adverse outcomes when used in addition to aspirin.

The Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO)-IIb *(41)* examined 12,142 patients with chest pain associated with ST-segment elevation or depression, or T-wave inversion. They were put into two groups, according to the presence or absence of ST-segment elevation. Those with ST-segment elevation received tissue-type plasminogen activator, aspirin, and hirudin or heparin. Those without ST-segment elevation were given aspirin and hirudin or heparin. As a whole, the risk of death or MI at 24 h was lower in the hirudin group (1.3 vs 2.1%; p = 0.001). However, at 30 d, the degree of separation between the hirudin and heparin groups was not as significant with respect to this end point (9.8 vs 8.9%; p = 0.06) (*see* Fig. 4). Additionally, when the group with unstable angina and NQMI was examined separately, there was no difference between hirudin and heparin therapy. There was also no difference in serious or life-threatening hemorrhage, although hirudin was associated with a higher incidence of moderate bleeding (8.8 vs 7.7%). Similarly, the TIMI 9B study group *(42)* evaluated the efficacy of hirudin vs heparin therapy in patients with acute MI receiving thrombolytic therapy and aspirin. They found no difference in "unsatisfactory outcomes" such as death, recurrent nonfatal MI, or development of new congestive heart failure or cardiogenic shock.

In summary, direct thrombin inhibitors have thus far failed to live up to their initial billing. One can theorize that although thrombin is an important antagonist of platelet activation, it represents only one pathway of platelet activation among nearly 100.

LOW MOLECULAR WEIGHT HEPARIN

To date, combination antithrombotic therapy with iv heparin and aspirin remains the current standard of care for hospitalized patients with unstable angina and NQMI *(16,31)*. Unfortunately, a significant failure rate still exists. This is probably secondary to the unpredictable anticoagulant response to standard unfractionated heparin, as well as neutralization by serum proteins and activated platelets *(43)*.

The last decade has seen the introduction of low molecular weight heparin (LMWH). Standard unfractionated heparin is a heterogeneous mixture of sulfated polysaccharides with an average molecular weight of 12,000–15,000 Daltons and a range from 5,000–30,000 Daltons. LMWH is comprised of molecules averaging 4,000–6,500 Daltons, depending on the preparation *(43–46)*. Importantly, heparin molecules <5,400 Daltons lack the ability to bind thrombin and ATIII simultaneously. Therefore, its predominant effect is the inactivation of factor Xa rather than factor IIa. As such, the anti-factor Xa to antithrombin ratio of LMWH ranges from 1.5 to 3.9, depending on the preparation *(43,44)*.

LMWH has several clear advantages over standard heparin. First, its effective half-life is approximately 4 h, which allows bid dosing. Because it does not bind to plasma proteins such as PF4 and von Willebrand factor, it cannot be neutralized, and its anticoagulant response is much less erratic than that of heparin. Therefore, laboratory monitoring is not required. Furthermore, LMWH remains active in a platelet-rich environment, as it can bind platelet-bound factor Xa. Unlike heparin, it does not increase vascular permeability and inhibit platelet function *(43,44)*. In animal models, LMWH has produced significantly less bleeding than heparin at similar levels of antithrombotic activity *(47)*. Finally, heparin-induced thrombocytopenia occurs much less frequently with LMWH *(43)*.

LMWH was first found to be superior to unfractionated heparin in the prophylaxis of deep venous thrombosis *(48–53)*. In fact, several blinded randomized trials have demonstrated that LMWH is as good as, if not better than, unfractionated heparin in the treatment of deep venous thrombosis *(54–59)*.

In arterial diseases, Edmonson et al. *(60)* observed better peripheral artery bypass graft patency with LMWH than standard aspirin plus dipyridamole. Kay et al. *(61)* compared LMWH (nadroparin) with placebo in patients with ischemic stroke and found a favubable dose-dependent effect of twice-daily LMWH given for 10 d with respect to dependency at 6 mo without a significant increase in rates of hemorrhagic transformation of the infarct ($p = 0.005$).

Given these studies, there was great enthusiasm to utilize LMWH in acute ischemic syndromes such as unstable angina. Gurfinkel et al. *(62)* studied patients with unstable angina ($n = 219$) randomized to aspirin alone, aspirin plus aPTT-adjusted heparin, and aspirin plus LMWH nadroparin (214 units international choay [UIC]/kg anti-factor Xa) twice daily sc for 5–7 d after presentation. The combination of aspirin plus LMWH was superior to the aspirin-only group with respect to recurrent angina ($p = 0.03$), nonfatal MI ($p = 0.01$), and urgent revascularization ($p = 0.01$). This combination was also superior to aspirin and heparin with respect to recurrent angina ($p = 0.002$) and myocardial ischemia

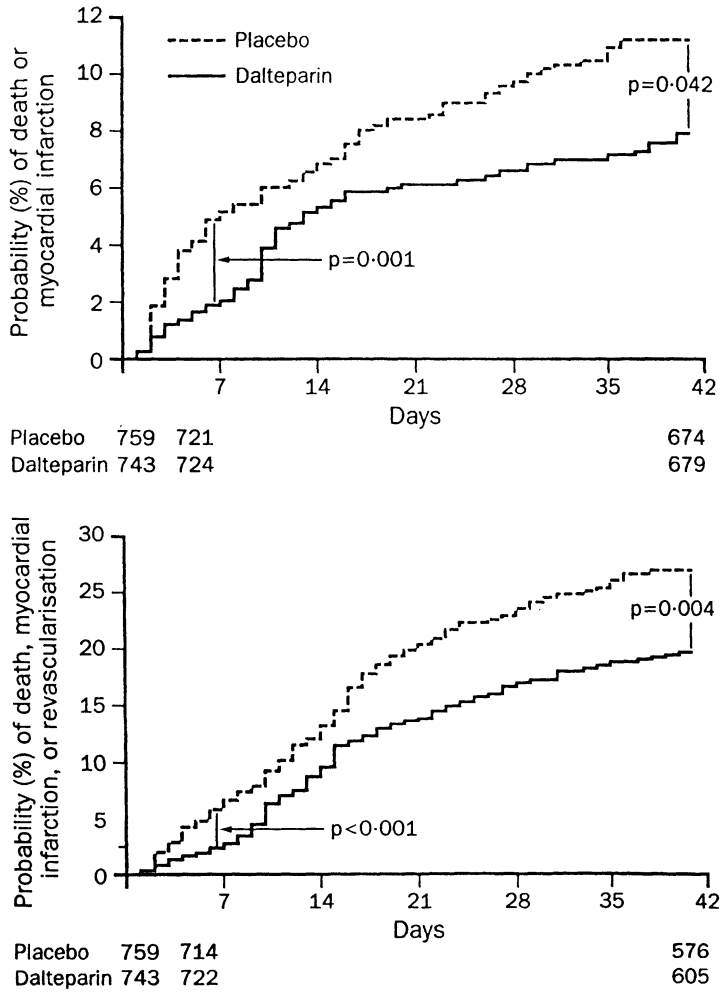

Fig. 5. Cardiac events in dalteparin and placebo groups during the first 40 d. Patients censored at last follow-up visit. Four silent MIs between d 6 and 45 (3 dalteparin, 1 placebo) excluded because time of infarction was unknown. Adapted with permission from ref. *63*.

($p = 0.04$). Additionally, patients receiving LMWH were less likely to suffer hemorrhagic complications than those receiving intravenous heparin ($p = 0.01$).

The Fragmin During Instability in Coronary Artery Disease (FRISC) study *(63)* examined the efficacy of LMWH ($n = 1506$) in patients with unstable angina or NQMI. It was a double-blinded, randomized, parallel group, multicenter trial comparing aspirin alone (75 mg daily) with aspirin plus dalteparin (120 IU/kg twice daily) for 5–7 d, followed by dalteparin (7,500 IU sc daily) for the next 35–45 d. The primary end point of death and new MI was decreased by 48% (an absolute decrease of 3%) in the first 6 d by dalteparin. The rates of urgent revascularization also decreased significantly. At 40 d, the benefit of LMWH persisted, but subgroup analysis showed this only to extend to nonsmokers (*see* Fig. 5). There was evidence of a rebound in ischemic events when the dose was changed from bid to qd.

Thus, the FRISC study showed that aspirin plus LMWH was better than aspirin plus placebo. The Fragmin in Unstable Coronary Artery Disease (FRIC) study *(64)* compared aspirin plus LMWH with aspirin plus aPTT-adjusted intravenous heparin. Patients with

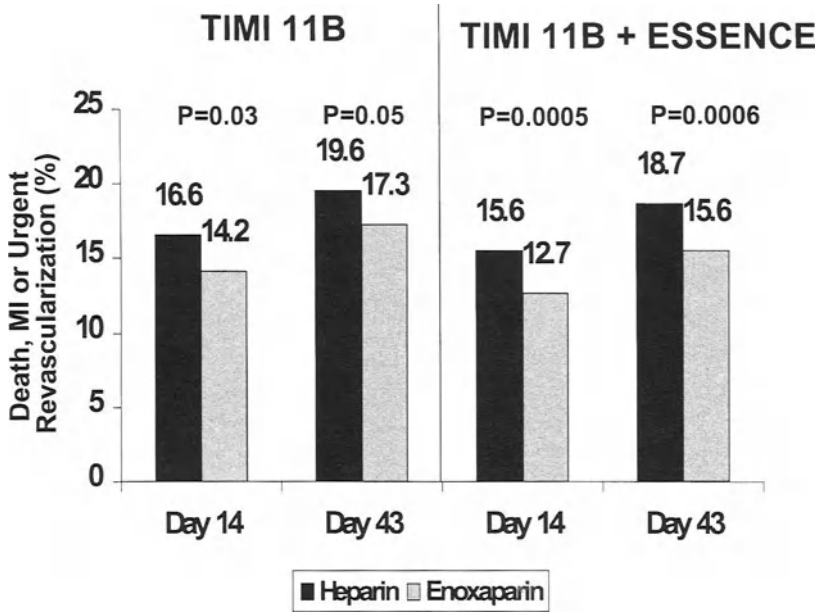

Fig. 6. TIMI 11B and Essence trials comparing of the rates of death, MI, or urgent revascularization with intravenous, unfractionated heparin vs enoxaparin over a 43-d period in patients treated for unstable angina and non-ST elevation MI. Adapted with permission from ref. *67*.

unstable angina or NQMI ($n = 1482$) were assigned randomly in an open label fashion to receive either twice-daily sc dalteparin (120 IU/kg) or aPTT-adjusted iv heparin, in addition to aspirin. In the second phase, patients in both groups were randomized to receive one daily injection of dalteparin (7,500 IU) or placebo in a double-blinded fashion. The composite end point of death, MI, or recurrent angina was 9.3% in the dalteparin group and 7.6% in the standard heparin group. The combined end point of death and MI for the two groups was 3.9 vs 3.6%, respectively. In the prolonged treatment phase, there was no difference in composite end point of death, MI, or recurrent angina (12.3% in both groups). The authors speculated that although dalteparin did not provide prolonged benefit at this dose, it might with twice daily treatment.

The Enoxaparin versus Unfractionated Heparin for Unstable Angina and Non-Q-Wave Myocardial Infarction (ESSENCE) trial *(65)* studied 3171 patients with rest unstable angina and NQMI randomly assigned to sc enoxaparin (1 mg/kg) twice daily, or continuous aPTT-adjusted iv standard heparin for 2–8 d in a double-blinded, placebo-controlled fashion. After 14 d of therapy, the risk of death, MI, or recurrent angina was significantly lower in patients assigned to enoxaparin compared with heparin (16.6 vs 19.8%; $p = 0.019$). This difference remained significant at 30 d (19.8 vs 23.3%; $p = 0.016$) The secondary end point of death or MI was reached at 14 d in 4.9% of the enoxaparin group vs 6.1% of the unfractionated heparin group ($p = 0.13$) and at 30 d by 6.2% of the enoxaparin group vs 7.7% of the unfractionated heparin group ($p = 0.08$). Furthermore, at 30 d the need for coronary revascularization was significantly lower in patients assigned to enoxaparin (27.1 vs 32.2%; $p = 0.001$) (*see* Fig. 6). With regard to major hemorrhagic complications, there was no difference between the two groups.

Thus, the ESSENCE study is the first to show a significant benefit over standard unfractionated heparin that is sustained over 30 d. These results are contrary to those of

the FRIC study. This may be a result of a number of factors. One major difference is the choice of LMWH preparation. Enoxaparin has an anti-factor Xa/anti-factor IIa activity ratio of 3:1 compared with 2:1 for dalteparin. This difference and the open label nature of the FRIC study (in-hospital phase) make it difficult to compare these two studies head to head.

The TIMI 11A investigators *(66)* showed that enoxaparin 1.0 mg/kg twice daily is the optimal dose, as the risk of major hemorrhage was almost threefold less than in those taking 1.25 mg/kg twice daily. Importantly, there was no difference in the composite end point of death, MI, or recurrent ischemia at the two doses.

TIMI 11B trial studied high-risk patients with unstable angina and non-ST elevation MI. They were required to have ST deviation or positive cardiac serum markers (CK-MB or troponin) to be enrolled. TIMI 11B compared intravenous unfractionated heparin with enoxaparin (1.0 mg/kg subcutaneously twice daily in-hospital and a fixed dose bid as an outpatient) for a total of 43 d. Preliminary results presented at the European Society of Cardiology showed that the rate of death, MI, or severe recurrent ischemia requiring urgent revascularization through d 14 occurred in 16.6% of patients treated with heparin vs 14.2% of patients treated with enoxaparin ($p = 0.03$), a 15% relative risk reduction (Fig. 6) *(67)*. The rate of the primary endpoint to 43 d was 19.6% for unfractionated heparin vs 17.3% for enoxaparin ($p = 0.049$). Parallel reductions in death and MI were also observed. A meta-analysis of the TIMI 11B and ESSENCE trials showed that at 43 d, enoxaparin reduced the rate of death, MI, or urgent revascularization from 18.7% to 15.6%, $p = 0.0006$. Death or MI at 43 d was reduced from 8.6% to 7.1% ($p = 0.02$). Thus, enoxaparin has been shown in two large randomized trials to be superior to unfractionated heparin for the treatment of unstable and non-ST elevation MI.

SUMMARY

Although great strides in the understanding of coronary thrombosis have been made in the last two decades, our current standard of care for the treatment of non-Q-wave ischemic syndromes remains aspirin and heparin. Even with this combination therapy, approximately 12% of patients with unstable angina go on to suffer an MI within 14 d *(16)*. Direct thrombin inhibitors have not been shown to improve outcomes in patients with unstable angina and NQMI.

Certain LMWH preparations do appear to improve outcomes. Ample opportunity remains to decrease adverse outcomes even further. Perhaps this can be accomplished by further investigation using different LMWH preparations. These advances, coupled with new antiplatelet therapies, will probably result in even greater reductions in adverse clinical outcomes in acute ischemic non-Q-wave coronary syndromes.

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17 Novel Antiplatelet and Antithrombotic Agents in the Treatment of Non-ST-Segment Elevation Coronary Ischemia

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INTRODUCTION

The relationship between coronary artery disease and intravascular thrombosis has intrigued cardiologists for almost a century. In the early 1960s, Friedman and Van den Bovenkamp described the pathology of arterial thrombus as consisting of a platelet-rich core and a fibrin-rich tail *(1)*. However, the significance of arterial thrombus was debated over the next 15 years until De Wood et al. *(2)*, in 1980, reported occlusive coronary thrombosis in 87% of patients presenting within 6 h of acute transmural myocardial infarction, initiating the era of thrombolysis and coronary revascularization in the treatment of acute transmural myocardial infarction.

However, in patients with non-ST-segment elevation acute coronary syndromes of unstable angina pectoris and non-Q-wave myocardial infarction (NQMI), *occlusive* coronary thrombosis is an uncommon finding, seen in only 9% of patients studied early in the

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presentation *(3)*. These syndromes of "nontransmural" coronary ischemia share many of their pathophysiologic and clinical characteristics, and are frequently indistinguishable on presentation. The distinction between unstable angina and NQMI is usually made retrospectively based on examination of enzymatic markers of myocardial necrosis. Treatment within the first 24 h of presentation is therefore identical. Additionally, new and more sensitive markers indicate that small amounts of myocardial necrosis are present in many patients with unstable angina in whom conventional markers of myocardial infarction remain negative *(4–7)*. Patients with non-ST-segment elevation acute coronary syndromes respond poorly to thrombolytic therapy *(8)*, but results with antiplatelet and antithrombotic therapies have been encouraging *(9–15)*. Therefore in the last decade, a series of such novel antithrombotic and antiplatelet agents has been developed, and our understanding of the role of older agents has expanded as well *(16)*.

PATHOPHYSIOLOGIC CORRELATES OF ACUTE ISCHEMIC SYNDROMES

Rupture or erosion of an atherosclerotic plaque with subsequent platelet aggregation and coronary artery thrombosis is the central pathophysiologic event across the entire spectrum of acute coronary syndromes. It provides a stimulus for the conversion of physiologic hemostatic mechanisms into pathologic processes resulting in partial or complete obstruction of the coronary arterial lumen. Infiltration of the plaque by activated mast cells and macrophages rich in matrix metalloprotinease enzymes plays an important role in weakening the fibrous cap *(17–19)*. The central core of the atheromatous plaque consists of a lipid pool surrounded by a cellular fibrous cap. The presence of a soft lipid core, especially when liquefied, imparts further structural instability to the plaque. Plaque rupture occurs primarily at the shoulder of the plaque, where mechanical stress is highest *(20)*. The resulting discontinuity in the fibrous cap leads to exposure of the lipid core to flowing blood *(17)* and the development of thrombosis on the luminal surface of the plaque. The loss of endothelium and exposure of subendothelial collagen and the atheromatous lipid core *(21)*, coupled with a high degree of tissue factor (TF) expression by activated macrophages *(22,23)* and turbulent flow around a swollen plaque, are potent stimuli for platelet deposition and thrombus formation.

Whether plaque rupture results in complete or partial arterial occlusion depends on a number of factors including the depth of arterial injury, the degree of luminal occlusion by the underlying plaque material, the degree of associated intraplaque hemorrhage, the status of the systemic coagulation system, and the local rheology. The clinical presentation depends on the severity of the coronary obstruction, acuity of onset, ability to recruit collaterals, ventricular function, and, to a lesser extent, myocardial oxygen requirements *(24,25)*. In patients with non-ST-segment elevation acute coronary syndromes, mural thrombosis leads to a reduction in coronary blood flow with or without superimposed transient episodes of thrombotic vessel occlusion. A nonocclusive mural thrombus within a stenosis, typical of these syndromes, is usually platelet-rich and resists thrombolysis *(26)*. Distal embolization of these platelet-rich thrombi may contribute to the episodes of rest pain. Loss of normal endothelial function, abnormal response of the vessel wall to vasodilatory substances, and local release of thromboxane A_2 (TXA_2) *(27)* and serotonin lead to vasoconstriction *(28)* and add to the ischemia. Cyclic coronary flow variations have been observed in experimental models of vascular stenosis and injury and in patients

with acute coronary syndromes; such variations are hypothesized to represent intermittent vasoconstriction and transient platelet-induced coronary occlusions *(29,30)*.

Acute angiographic studies have demonstrated that about 80% of patients with unstable angina pectoris or NQMI have a severely stenosed but patent coronary artery *(25,31–38)*. The culprit vessels commonly contain irregular, complex, or eccentric lesions, which often have Ambrose type II morphology in the form of a convex intraluminal obstruction with a narrow base or neck due to overhanging edges *(39,40)*. Lesion borders are irregular or scalloped, ulcerated, and hazy. Angiographic evidence for lesion-associated thrombus in patients with unstable angina pectoris and NQMI has been extremely variable, being reported in 1–85% of cases in different studies *(32,34,41–43)*. The definition of thrombus used in different studies and the duration of time from the onset of symptoms to the time of angiography explain the variability of angiographic studies. Angiography is specific but insensitive for detection of thrombus. The intramural or extraluminal location of associated thrombus makes angiographic detection difficult. Angioscopic studies have shown intracoronary thrombi in 50–70% of patients presenting with acute coronary syndromes of unstable angina pectoris or NQMI *(44)*.

It is apparent from the above discussion that intracoronary thrombus plays an integral part in the pathophysiology of acute coronary syndromes. This arterial thrombus is generated and regulated by the complex interactions between platelets and the soluble coagulation cascade. It is not surprising, therefore, that much effort has been invested in studying the role of antiplatelet and antithrombotic/antithrombin agents in the therapy of these syndromes.

PLATELET PATHOPHYSIOLOGY IN ARTERIAL THROMBOSIS

Platelets, the tiny non-nucleated fragments of precursor megakaryocytes, play a central role in the drama of hemostasis and coagulation. When a pathologic stimulus evokes a hemostatic response, platelet activation leads to a cascade of events involving platelets, adhesive ligands, and coagulant proteins that generate a platelet-rich thrombus (Fig. 1).

Platelet Adhesion

Platelet deposition occurs almost instantaneously after arterial injury, primarily by adherence to subendothelial collagen *(45)* and fibrinogen *(46,47)*. When exposed to a nonendothelial surface, platelets undergo morphologic change into spiny spheres with long fine filopodia. These activated platelets adhere to the exposed surface and flatten to form a platelet monolayer. This process of adhesion is mediated by von Willebrand factor (vWF), a multimeric glycosylated protein secreted by subendothelial cells. vWF is attached to subendothelial collagen and binds the platelet surface glycoprotein (GP)Ib, a constitutively expressed integrin *(48)*. vWF binding with the GPIb/IX complex is especially important under conditions of high shear stress and results in platelets covering the exposed subendothelium *(49–52)* (Table 1). This process is unaffected by either heparin or aspirin *(49)*.

Platelet Aggregation

The presence of agonists, like adenosine diphosphate (ADP), epinephrine, platelet activating factor (PAF), TXA_2, arachidonic acid, collagen, and thrombin, induces platelet activation and binding in a polyvalent fashion called *aggregation*. Platelet aggregation

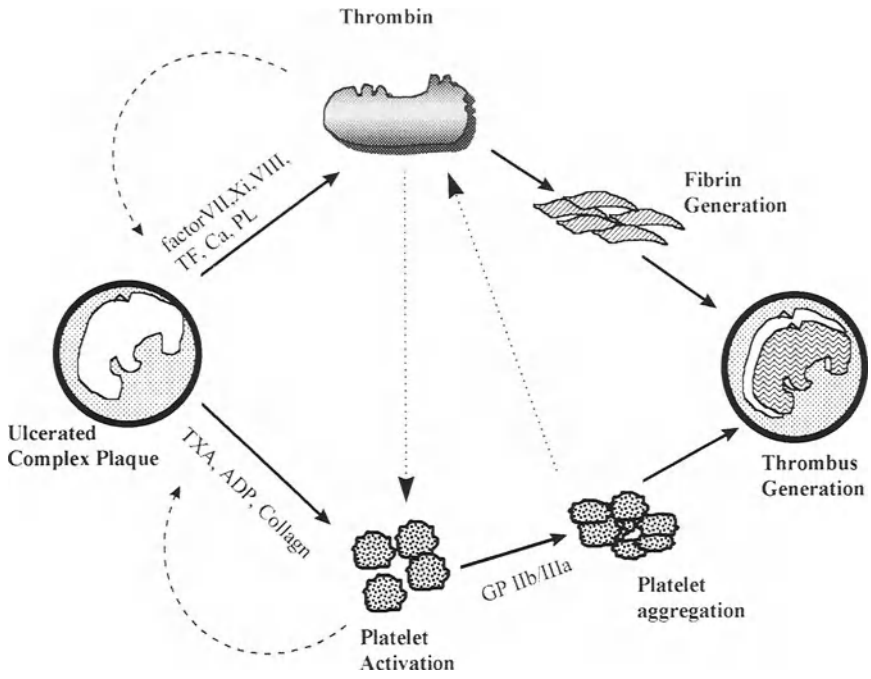

Fig. 1. Platelet and coagulation cascade activation by ulcerated plaque and interactions between platelets and thrombin leading to arterial thrombus formation. TF, tissue factor; PL, phospholipid; TXA_2, thromboxane A_2; GP, glycoprotein.

Table 1
Platelet Membrane Adhesion Molecules[a]

Glycoprotein receptor	*Activity*	*Ligand*	*Recognition motif*
GPIIb/IIIa ($\alpha_{IIb}\beta_3$)	Activation dependent	Fb, Fn, Vn, vWF, TSP, fibrin	RGD
Vitronectin receptor ($\alpha_v\beta_3$)	Constitutive	Fb, Fn, Vn, vWF, TSP	RGD
GPIa/IIa ($\alpha_2\beta_1$)	Constitutive	Collagen	DGEA
GPIc/IIa ($\alpha_5\beta_1$)	Constitutive	Fibronectin	RGD
GPIc/IIa ($\alpha_6\beta_1$)	Constitutive	Laminin	Fragment E8
GMP-140 (P-selectin)	Constitutive	L-selectin	CD-15
GPIIa (PECAM-1)	Constitutive	—	—
GPIV (IIIb)	Constitutive	TSP, collagen	?

[a] Abbreviations; Fb, fibrinogen; Fn, fibronectin; TSP, thrombospondin; vWF, von Willebrand factor; Vn, vitronectin.

is primarily mediated by an activation-dependent receptor complex, GPIIb/IIIa (integrin $\alpha_{IIb}\beta_3$), a member of the integrin family of cell adhesion molecules *(50,53–55)*. The α or IIb subunit is composed of two polypeptide chains linked by a disulfide bond. The large chain is of 125,000 Daltons and the small chain, which possesses a transmembrane domain, is of 22,000 Daltons. The β or IIIa subunit is a single polypeptide chain of 105,000 Daltons with two arginine-glycine-aspartate (RGD) binding domains *(56)*. These

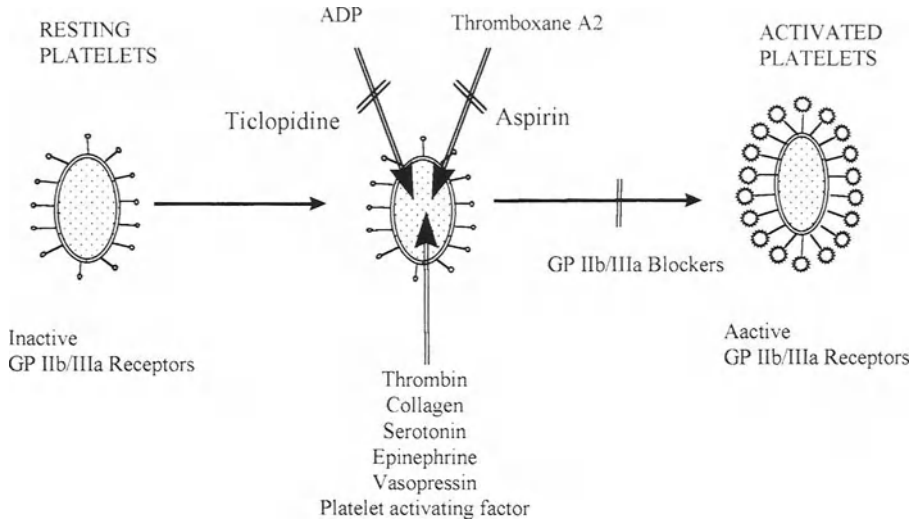

Fig. 2. Activation of resting platelets by a variety of agonists and the change in GPIIb/IIIa receptor complex upon activation. The mechanism of action for aspirin, ticlopidine, and GPIIb/IIIa antagonists.

domains recognize and bind RGD sequences in ligand molecules. The entire IIb/IIIa complex is present as a Ca^{2+}/-dependent, noncovalently associated heterodimer on the platelet surface. Resting platelets express about 70,000–80,000 molecules of GPIIb/IIIa on their surface, which are in dynamic equilibrium with a pool of additional GPIIb/IIIa molecules stored in the α-granules *(57,58)*. In the resting state, these receptors do not bind circulating ligands *(59)*. Activation by platelet agonist stimuli leads to conformational reconfiguration of the GPIIb/IIIa complex, exposing the ligand binding sites. Epinephrine, PAF, ADP, TXA_2, collagen, and thrombin act through several transmembrane helix receptors coupled to G proteins leading to stimulus–response-coupled activation of GPIIb/IIIa receptors *(60)*. Thrombin activates platelets by at least two separate transmembrane receptors and is by far the most potent biologically active agonist *(61–64)*. Thrombin stimulation causes both increased surface expression and activation of GPIIb/IIIa molecules (Fig. 2)

Once activated, the GPIIb/IIIa receptor binds RGD-containing ligands including fibrinogen, vitreonectin, fibronectin, and vWF. Soluble fibrinogen is the highest affinity ligand to bind the GPIIb/IIIa receptor complex and is essential for platelet aggregation induced by such agonists such as ADP and thrombin. Fibrinogen contains two RGD sequences located on each of two α-chains and another GPIIb/IIIa recognition domain near the carboxyl terminus of each of the two γ-chains. Binding of fibrinogen to the GPIIb/IIIa receptor leads to unmasking of further binding sites or *neoepitopes*, called ligand-induced binding sites. vWF is believed to be the principal ligand mediating shear-induced aggregation *(49,51,52,65)*.

Platelet Secretion

Although they are incapable of protein synthesis, platelets contain potent ingredients prepackaged in various granules. The aggregated platelets undergo the release reaction, secreting the contents of α-granules and dense bodies (Table 2). These platelets form the

Table 2
Platelet Contents[a]

Platelet particle	*Contents*
α-granule	Coagulation factor V, platelet factor IV, vWF, Fibrinogen, PDGF, GMP-140, β-thromboglobulin, fibronectin, thrombospondin, GPIIb/IIIa, α1-antitrypsin, α2-macroglobulin
Dense body	Ca^{2+}, Mg^{2+}, ATP, ADP, serotonin
Lysozome	Lysozyme

[a]Abbreviations: VWF, von Willebrand factor; PDGF, platelet-derived growth factor.

initial hemostatic plug and play a pivotal role in the activation of soluble coagulation cascade. Aggregated platelets provide the phospholipid surface on which the prothrombinase complex is formed. This complex contains activated factors Va and Xa and amplifies the generation of thrombin by as much as 10^5. Inhibition of platelet aggregation in vitro can reduce the formation of thrombin by as much as 50% *(66)*.

ANTIPLATELET AGENTS

Thromboxane Inhibitors

Aspirin

First synthesized and marketed in the 18th century, aspirin was not recognized as an antiplatelet agent until the 1970s. The antiplatelet action of aspirin is due to irreversible acetylation of the serine 529 residue, causing permanent inhibition of enzyme cyclooxygenase *(67)*. This action prevents the conversion of arachidonic acid to prostaglandin G_2, blocking the synthesis of prostacyclin in the endothelial cells and platelets production of TXA_2. Although a number of other roles for aspirin have since been proposed, including acetylation of other proteins such as thrombin and fibrinogen, and 12-hydroxyeicosanotetraenoic acid antagonism *(68)*, it has recently been shown that point mutations in the cyclooxygenase gene render platelets impervious to the antiaggregatory effect of aspirin *(69)*.

The benefits of aspirin in unstable angina pectoris have been established by four major well-controlled clinical trials (Table 3). In the Veterans Administration Cooperative study *(13)*, 1266 men were randomized to 324 mg of aspirin or placebo. At 3 mo, the combined risk of death or nonfatal myocardial infarction was reduced by 51% (10.1 vs 5%). This benefit was maintained at 12 mo by risk reduction of 43% for the combined end point, even though the study drugs were stopped at 3 mo after enrollment. In the Canadian Multicenter Trial *(12)*, 555 patients with unstable angina pectoris were randomized to receive aspirin, sulfinpyrazone, both, or placebo. At 2 yr of follow-up (mean 18 mo), the risk reduction for the combined end point of cardiac death and nonfatal myocardial infarction, by intention to treat analysis, was 30%. An efficacy analysis for cardiac death alone showed a dramatic reduction of 70%. The Montreal Heart Institute study *(14)* included 479 patients with unstable angina pectoris randomized to receive aspirin, heparin, both, or neither. Patients treated with aspirin had a risk reduction of 71% for in-hospital myocardial infarction. In the RISC study *(15)*, 796 patients with unstable angina or NQMI were randomized to aspirin, intermittent bolus

Table 3
Major Trials of Aspirin, Heparin, and Ticlopidine in Syndromes of Non-ST-Segment Coronary Ischemia[a]

Trial	No. of patients	Drugs studied	Follow-up	Death and Nonfatal MI (%)	P value	Risk Reduction (%)
VA Cooperative Study *(13)*	1338	ASA 325 mg/d	3 mo	5 vs 10.1	0.0005	51
Canadian Multicenter Trial *(12)*	555	ASA 1300 mg/d	24 mo	8.6 vs 17	0.008	51
Montreal Heart Institute *(14)*	479	ASA 650 mg/d	6 d	3.3 vs 12	0.01	72
		Heparin, aPTT	6 d	1.2 vs 7	<0.05	85
RISC study *(15)*	652	ASA 75 mg/d	30 d	4.3 vs 13.4	0.0001	68
		Heparin 14–20,000 U	30 d	3.4 vs 4.9	NS	30
Italian Study *(70)*	652	Ticlopidine 500 mg/d	6 mo	7.6 vs 13.6	0.009	53
Montreal Heart Institute *(14)*	484	ASA vs heparin	5.3 d	3.7 vs 0.8	0.035	88
Telford and Wilson *(157)*	214	Heparin 30–40,000 U	7 d	3 vs 15	<0.05	80

[a]Abbreviations: MI, myocardial infarction; aPTT, activated partial thromboplastin time; ASA, aspirin.

heparin, both, or placebo. Risk reduction in the aspirin group was 57% at 5 d, 69% at 30 d, and 61% at 3 mo. The largest study of aspirin therapy in acute coronary syndromes is the International Study of Infarct Survival (ISIS)-2 investigation *(70)*. In this study of 17,187 patients with suspected infarction, patients presenting within 24 h of chest pain were randomized to receive streptokinase 1.5 million U, or 162.5 mg of aspirin, or both, or neither. Forty-three percent of patients enrolled in the trial did not have ST-segment elevation but rather had ST-segment depression (8%), T-wave inversion (7%), conduction abnormality (6%), Q-waves (16%), or normal electrocardiogram ECG (2%) at presentation. In ISIS-2, 8587 patients were randomized to receive aspirin, and 8600 patients received placebo. Overall, patients receiving aspirin had a 23% reduction in vascular mortality at 5 weeks (9.4% in aspirin group vs 11.8% in placebo), and this benefit was present in both ST-segment elevation and non-ST-segment elevation groups of patients.

The dose required to achieve optimal clinical response remains controversial. The dose–response effect of aspirin on platelet aggregation and TXA_2 production is log-linear, but reaches a plateau at approximately 80 mg *(71)*. Lower doses can inhibit platelet aggregation without blocking the vascular production of vasodilating and antiaggregatory prostaglandins *(72,73)*. However, increased clinical efficacy of a lower dose has never been demonstrated in any study. In chronic studies, doses as low as 30 mg have been shown to be as effective as 283 mg for the secondary prevention of acute myocardial infarction, and the benefit is comparable to that seen with doses as high as 1200 mg/day. However, during the acute phase, there are few data concerning the rapidity of onset of aspirin and the minimum dose needed to produce a clinically meaningful effect in patients with acute coronary syndromes. Thus, at the current time, prudent practice would dictate administering an initial dose at least equal to the 162 mg used in ISIS-2.

Limitations and adverse effects of aspirin therapy. The incidence of side effects seen with (low-dose) aspirin therapy is relatively low and can easily be monitored. The major toxicity of aspirin therapy is gastrointestinal bleeding. Its incidence is dose dependent and has ranged from 0.9% over 1 yr in patients receiving 75 mg to 4.7% over 3 yr in patients receiving 1200 mg daily *(74)*. In a small number of patients, particularly those with adult-onset asthma, aspirin can cause bronchospasm and angioedema.

Although aspirin is a potent inhibitor of platelet aggregation induced by arachidonic acid, it is a very weak inhibitor of platelet aggregation induced by a number of other agonists including ADP and thrombin. Aspirin does not prevent α-granule release in response to platelet agonists and does not inhibit epinephrine-induced aggregation *(75)*. Although aspirin blocks cyclic flow variations in a canine model of coronary stenosis and endothelial injury, this inhibition can be overcome by the addition of epinephrine *(76)*.

Other Thromboxane A_2 Antagonists

Other inhibitors of TXA_2 including synthesis inhibitors and receptor antagonists have been studied in attempts to improve on the benefit of aspirin. Selective TXA_2 inhibitors and/or TXA_2 receptor antagonists have the advantage of sparing the antiaggregatory and vasodilatory prostaglandin synthesis. However, lack of clinical superiority over aspirin and incidence of side effects have limited their clinical development. Clinical trials of other drugs acting at other points in the thromboxane pathway have also been generally disappointing. Ridogrel is an inhibitor of TXA_2 production (through blockade of thromboxane synthase) and an antagonist of the TXA_2 receptor. In the Ridogrel versus Aspirin Patency Trial (RAPT) trial, 907 patients with acute myocardial infarction treated with streptokinase were randomized to receive aspirin or Ridogrel as an adjunct *(77)*. Ridogrel did not produce more profound inhibition of TXA_2 production than aspirin even though it had considerably less suppressive effect on prostacyclin production. There was no benefit in noninvasive signs of early reperfusion, nor on arterial patency assessed angiographically at 7–14 d.

Vapiprost and Ifetroban both have TXA_2 receptor blocking activity and in animal models are at least as effective as aspirin in blocking cyclical flow variation *(78)*. Picotamide, is another agent with combined thromboxane synthase inhibitor and TXA_2 receptor antagonist properties. It has been shown to decrease platelet deposition in injured, ex vivo, vessel segments. Triflusal is a salicylate-derived antiaggretory agent that irreversibly inhibits platelet cyclooxygenase activity and also inhibits platelet phosphodiesterase *(79,80)*. In a multicenter, double-blind, placebo-controlled study of 281 patients with unstable angina, triflusal reduced the incidence of myocardial infarction compared with placebo (4.2 vs 12.3%, $p = 0.013$), but the small number of deaths and the absence of aspirin treatment in the placebo group hampered statistical analysis of mortality rates *(81)*.

Prostacyclin Analogs

Prostacyclin is the most potent endogenous inhibitor of platelet aggregation *(82)*. Prostacyclin and related exogenous compounds like Iloprost, Cicaprost, and Taprostene, elevate platelet cyclic adenosine monophosphate (cAMP) content via receptor-dependent stimulation of adenyl cyclase. Increased cAMP levels lead to Ca^{2+} uptake into intracellular storage sites, resulting in lower cytoplasmic Ca^{2+} levels. Lower cytoplasmic Ca^{2+} levels maintain platelets in their resting discoid state and inhibit all platelet responses to various agonists *(83–85)*.

All prostacyclin analogs have low selectivity for platelet receptors. Platelet receptors for prostaglandins also become downregulated under various conditions, and receptor desensitization may result in a rebound increase in platelet reactivity. Intravenous prostacyclin analogs undergo extensive first-pass catabolism in the pulmonary circulation. Unfortunately, prostacyclin and its more stable analogs have an unacceptable level of side effects, particularly vasodilation, hypotension, skin rashes, and gastrointestinal upset *(83,85)*.

Thienopyridines

Ticlopidine and Clopidogrel

Ticlopidine and clopidogrel belong to a unique class of antiplatelet agents that interfere with ADP-mediated platelet activation, lower circulating fibrinogen levels, and also partially block GPIIb/IIIa receptor binding to fibrinogen and vWF *(86–91)*. Functional interference of GPIIb/IIIa receptor by these agents probably occurs through inhibition of signal transduction rather than structural alteration of the receptor. These drugs also inhibit shear-induced platelet aggregation more effectively than aspirin *(88,92)*. The antiplatelet effect can be detected by aggregometry after 3 d of therapy, peaks at 5–7 d, and persists for up to 10 d after withdrawal of therapy *(90,93)*. Ticlopidine and its stable metabolites fail to inhibit platelets in platelet-rich plasma when added in vitro. However, platelets from ticlopidine-treated patients, when resuspended in normal plasma, show inhibition to the proaggregatory action of ADP. Although the exact mechanism of action of ticlopidine and clopidogrel remains unknown, they may act on platelets during megakaryocytopoesis and subsequent platelet production in bone marrow. These actions are most likely mediated by a short-lived active metabolite of the parent drug. Regardless of its mechanism, the action of ticlopidine is relatively mild. In platelet aggregation studies, ticlopidine inhibits aggregation induced by low-dose ADP, by approximately 50% or less from its baseline values *(94)*.

Ticlopidine and clopidogrel prevent cyclic flow variations in experimentally stenosed animal coronary arteries *(95)*. In animal models, clopidogrel is superior to aspirin for maintaining arterial patency after thrombolytic therapy *(96)*. Ticlopidine has been shown to reduce the incidence of stroke in several studies. In the Canadian American Ticlopidine Study (CATS) trial *(97)* of stroke prevention, ticlopidine reduced the risk of composite end point of stroke, myocardial infarction or vascular death by 30.2%. In a randomized multicenter Italian trial of patients with unstable angina, ticlopidine 250 mg twice daily, led to a risk reduction of 46.3% (13.6 vs 7.3%) in the combined end point of vascular death and myocardial infarction. However, this trial did not incorporate aspirin therapy in either the placebo or the treatment group. Clopidogrel was studied in a large trial Clopidrogel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) *(98)* for secondary prevention of complications of atherosclerotic disease following stroke, myocardial infarction, or symptomatic peripheral vascular disease in 19,185 patients. After 1.9 yr of follow-up, the combined end point of ischemic stroke, myocardial infarction, or vascular death was 5.32% in the clopidogrel group vs 5.83% in the aspirin group ($p = 0.043$, risk reduction 8.7%). However, there are no data supporting its use in the acute stages of ischemic coronary syndromes at the present time, and its use is limited by relatively slow onset of action.

Limitations and adverse effects of ticlopidine and clopidogrel. The most frequent side effect of ticlopidine is diarrhea, occurring in 20% of patients. Skin rash, commonly

morbilliform or urticarial, is seen in 11.5%. The most severe adverse reaction to ticlopidine is transient neutropenia, which occurs in approximately 2.3% of patients and is severe in nearly 1% *(99)*. This reaction generally occurs between 3 wk and 6 mo of initiation of therapy and is usually reversible on discontinuation of ticlopidine. A complete blood count should be performed every 2 wk during the first 6 mo of therapy. Given its high cost, and the occurrence of hematologic adverse effects, ticlopidine should be prescribed in place of aspirin as treatment for unstable angina only in patients who are unable to tolerate aspirin. Clopidogrel is better tolerated than ticlopidine, but its place in the therapy of unstable angina pectoris needs to be established.

Glycoprotein IIb/IIIa Antagonists

Recognition of the role of the GPIIb/IIIa receptor in platelet aggregation and the RGD sequence to which IIb/IIIa receptor binds has led to the design of a variety of RGD-containing and RGD-mimetic inhibitors. These include murine or chimeric antibodies *(100)*, synthetic peptides, and synthetic peptidomimetics. Antibodies are costly to produce and have a high degree of affinity for the receptor. The RGD peptides are derived from snake venom proteins called disintegrins including echistatin, kistrin, trigramin, bitistatin, barbourin, and applagin *(101–104)*. These peptides are modified by structural changes and amino acid substitutions, resulting in compounds with higher specificity for GPIIb/IIIa. The RGD peptides have short plasma half-lives and can only be administered intravenously. The peptidomimetics are nonpeptide molecules capable of blocking the GPIIb/IIIa receptor. These agents share the ability to block the RGD binding site of GPIIb/IIIa through steric interactions, without actually containing the RGD sequence. They are less costly to produce and offer the hope of being bioavailable after oral ingestion.

Abciximab

Abciximab (ReoPro) is the chimeric Fab fragment of a monoclonal antibody, with a human constant chain and murine variable chain *(100,105–107)*. It binds avidly to the β (IIIa) subunit of the *activated* GPIIb/IIIa receptor. Owing to its affinity for the β-subunit, abciximab also binds other β_3 integrins, most notably the vitreonectin ($\alpha_v\beta_3$) receptor, although the significance of this interaction is unknown. In animal models of arterial injury and stenosis, abciximab causes profound inhibition of platelet aggregation, reduces cyclic flow variations, prevents thrombotic occlusion *(108–110)*, shortens the time to reperfusion *(111,112)*, and prevents reocclusion after experimental thrombolysis *(55,112–114)*. When administered intravenously, the plasma half-life is brief (5–10 min), as the molecule is rapidly bound to platelet receptors. The biologic half-life is 6–12 h after a single bolus dose *(115,116)*. Receptor blockade following abciximab dosage is dose dependent *(117–119)*. Following a dose of 0.25 mg/kg, 80–90% of the surface receptors are blocked, and aggregation in response to 20 μM ADP is inhibited by 80% *(54,115)*. After 6–8 h, receptor blockade decreases, and aggregation returns to approximately 50% of its baseline value. When abciximab is given as a bolus followed by a continuous infusion of 0.1 mg/min, this degree of receptor blockade is maintained for the duration of infusion; following the cessation of the infusion, receptor blockade decays at approximately the same rate as is seen following bolus administration alone. One week following administration of a bolus, as many as 50% of receptors are blocked *(115,120)*, and some abciximab binding is probably present for several weeks thereafter. Platelet aggregability

returns to normal more rapidly than does receptor occupancy, suggesting that there may be a threshold number of receptors occupied in order for aggregation to be inhibited.

The European Cooperative Study Group *(121)* studied 60 patients with dynamic ST-segment changes and refractory unstable angina who were randomized to receive abciximab or placebo 18–24 h prior to angioplasty. The combined end point of death, myocardial infarction, or urgent revascularization occurred in 23% of the placebo-treated group compared with 3% in the abciximab group.

In the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study *(122)*, a large randomized trial of 2099 patients undergoing high-risk coronary angioplasty, a bolus of abciximab followed by a 12-h infusion led to a reduction in the combined end points of death, myocardial infarction, or urgent revascularization from 12.8% to 8.3% (Table 4). A subgroup analysis of 534 patients with unstable angina, NQMI, or evolving myocardial infarction showed that patients receiving bolus and infusion of abciximab had a reduction in composite end point of 36.9% (14.8 vs 3.9%) at 30 d and 40.7% (36.9 vs 21.9%) at 6 mo *(123)*. The difference persisted and at 3 yr, there was a statistically significant reduction in mortality. In another trial, Evaluation in PTCA to Improve Long-Term Outcome with Abciximab GP IIb/IIIa (EPILOG) *(124)*, 2792 patients of all risk categories, undergoing percutaneous transluminal coronary angioplasty (PTCA) were randomized to receive abciximab with standard-dose heparin (100 U/kg bolus, activated clotting time [ACT] >300 ms), abciximab with low-dose heparin (70 U/kg bolus, no ACT adjustment), or placebo with standard dose heparin. The results from the EPILOG study show a similar magnitude of benefit in both heparin dose groups and regardless of the procedural risk level. Almost 50% of patients enrolled in the EPILOG trial had unstable angina as their admitting diagnosis and at 30 d, the combined end point occurred in 11.7% of placebo-treated patients vs 5.2% and 5.4% in the two abciximab-treated groups. More important, perhaps, the incidence of bleeding complications with low-dose heparin and abciximab was lower than the standard dose heparin group and was similar to that in the placebo group.

A third trial of abciximab, e7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) *(125)* is the most intriguing. Patients with refractory unstable angina underwent angiography and were subsequently randomized to receive 18–24 h of either placebo or abciximab prior to planned angioplasty (n = 1266). Following angioplasty, the abciximab infusion was continued for one more hour. Originally planned to include 1500 patients, this study was terminated after the enrollment of approximately 1266 patients because of overwhelming evidence of efficacy. The composite end point of death, myocardial infarction, or urgent revascularization at 30 d occurred in 71 of 630 (11.3%) patients receiving abciximab compared with 101 of 635 (15.9%) in patients receiving placebo (relative risk 0.64). Examination of the timing of events indicates that the benefit of abciximab therapy began prior to the angioplasty. The rate of myocardial infarction prior to the planned angioplasty was reduced from 2.1% in the placebo group to 0.6% in patients randomized to abciximab therapy ($p = 0.029$). This finding suggests a beneficial role of GPIIb/IIIa blockade in patients with unstable angina, independent of its beneficial effects in prevention of angioplasty-related complications. The benefit in CAPTURE at 6 mo was considerably less than that seen in either the EPIC or EPILOG trials. Since these study designs differed in that patients in CAPTURE received abciximab for only 1 h after PTCA compared with 12 h in EPIC and EPILOG, these findings suggest that the infusion of abciximab for 12 h after PTCA may be critically important in producing a benefit that is sustained over the long term.

Table 4
Major Clinical Trials of Intravenous Platelet GPIIb/IIIa Blocking Agents[a]

Drug	*Study*	*Indications*	*No.*	*End point*	*Follow-up*	*Drug (%)*	*Placebo (%)*
Abciximab	EPIC	PTCA (high risk)	2,099	D, MI, UR	30 d	8.3[b]	12.8
(antibody)	EPILOG	PTCA	2,792	D, MI, UR	30 d	5.2[c]	11.7
	CAPTURE	PTCA (R. angina)	1,265	D, MI, UR	30 d	15.9	11.3
	TAMI 8	MI (tPA)		D, MI			
	PRIDE	MI (tPA, placebo)	N/A	D, MI	N/A	N/A	N/A
Integrilin	IMPACT-AMI	MI (tPA)	170	TIMI-3 flow		66	39
(peptide)	PURSUIT	USA	10,948	D, MI	96 h	7.6	9.1
					30 d	14.2	15.7
	IMPACT-II	PTCA	4,010	D, MI, UR	30 d	9.2[d]	11.4
Tirofiban	PRISM	USA	3,231	D, MI, RI	48 h	3.8	5.9
(peptidomimetic)	PRISM-PLUS	USA	1,570	D, MI, RI	7 d	12.9	17.9
	RESTORE	PTCA (USA or MI)	2141	D, MI, RI	48 h	5.4	8.7
					30 d	10.3	12.2
Lamifiban	Canadian study	USA	440			2.5	8.1
(Peptidomimetic)	PARAGON	USA	2,282	D, MI	30 d	21.6[c]	21.9
	PARADIGM	MI (tPA or SK)	353				
Xemilofiban	Oral pilot	PTCA					
(peptidomimetic)	TIMI12						

[a]Abbreviations: R. angina, refractory angina; D, death; MI, myocardial infarction; UR, urgent revascularization; RI, recurrent ischemia; PTCA, percutaneous transluminal coronary angioplasty; USA, unstable angina; TPA, tissue-type plasminogen activator; SK, streptokinase.

[b]Bolus plus infusion group.

[c]Drug with low-dose heparin group.

[d]135 μg/Kg bolus; 0.5 μg/Kg/min infusion.

Eptifibatide (Integrilin)

Eptifibatide (Integrilin) is a cyclic heptapeptide derived from the venom of the Southeastern pigmy rattlesnake *Sistruris m. barbouri*. The molecular structures of a peptide derivative of this venom was modified by substitution of lysine for arginine (thus a KGD sequence), enhancing its specificity for the GPIIb/IIIa, whereas cyclization of the amino acid sequence enhanced the antiaggregatory potency of the compound *(101,102)*. Eptifibatide is therefore highly specific for GPIIb/IIIa and has a half-life of 1.5–2 h *(126)*. In a pilot study of eptifibatide in patients with unstable angina pectoris, 227 patients were randomized to receive either placebo or low-dose or high-dose eptifibatide *(127)*. The study was not designed to detect clinical end points, but ECG ischemia was suppressed in a dose-dependent fashion. Eptifibatide has also been studied in patients receiving thrombolytic drugs for acute myocardial infarction and in patients undergoing coronary angioplasty. In the Integrilin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT)-II trial, 4010 patients undergoing angioplasty were randomized to receive either placebo or eptifibatide 135 μg/kg bolus followed by 0.75 μg/kg/min infusion for 24 h or eptifibatide 135 μg/kg bolus followed by 0.50 μg/kg/min infusion for 24 h after the procedure *(128)*. The composite end point of death, myocardial infarction, or urgent revascularization was reduced by 35% at 24 h, although most of this benefit was lost at 30 d. The doses of eptifibatide were selected based on data suggesting that the "low-dose" group should have had 60% inhibition of platelet aggregation and the high-dose group 80% inhibition, at the end of infusion *(126)*. This degree of inhibition may be critical because dosing studies with abciximab showed that the dose resulting in clinically significant benefit in the EPIC trial achieved 80% inhibition of ADP-induced platelet aggregation *(120)*. Current evidence suggests that assays of platelet aggregation used to determine the doses of eptifibatide, overestimated the true eptifibatide-induced platelet inhibition. Blood samples collected in disodium citrate caused Ca^{2+} chelation leading to a hypocalcemic medium, which artificially enhances binding of eptifibatide to the GPIIb/IIIa receptors, thus overestimating the potency of a given dose *(129)*. Data from such assays may have led to the selection of a dose lower than those that would achieve an optimal balance between efficacy and safety. Bleeding complications in the IMPACT-II trial were the same in all three groups, further raising the possibility of underdosing relative to the desired efficacy.

Subsequently higher doses of eptifibatide (180 μg/kg bolus, 2 μg/kg/min) were studied in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial of patients with acute coronary syndrome without ST-segment elevation. In 10,948 patients, the rate of death or myocardial infarction was reduced from 9.1 to 7.6% at 96 h, 11.6 to 10.1% at 7 d, and 15.7 to 14.2% at 30 d ($p = 0.011$, 0.016, and 0.043, respectively) *(130)*. Although at 30 d, the *relative* reduction in events decreased from 17 to 10%, the *absolute* reduction in the number of events was maintained at 15/1000 patients treated. This occurred at the price of an increase in the rate of transfusion from 9.3 to 11.8%.

Tirofiban

Tirofiban (Aggrastat) is a peptidomimetic agent with the geometric, stereotactic, and charge characteristics of the RGD sequence. It thus acts as a competitive GPIIb/IIIa receptor antagonist *(131,132)*. In the first major clinical study of tirofiban, RESTORE, 2141 patients undergoing angioplasty for unstable angina or acute myocardial infarction were randomized to a receive tirofiban or placebo *(133)*. Tirofiban was administered as

a 10-μg/kg bolus over 3 min followed by 0.15-μg/kg/min infusion for 36 h. At 48 h, there was a 38% relative reduction in the composite clinical end point (8.7 vs 5.4%; $p = 0.022$), but at 30 d, approximately half of this benefit was lost (12.2 vs 10.3%; $p = 0.16$). Bleeding complications were not significantly different between the groups. Data from two recent trials in patients with unstable angina and NQMI are now available. In the Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial, 3232 patients with unstable angina or NQMI were randomized to receive either tirofiban for a 48-h infusion *or* intravenous heparin for 48 h *(134)*. Tirofiban was given as a bolus of 0.6 mg/kg/min over 30 min followed by a 0.15-mg/kg/min infusion. The composite end point of death, new myocardial infarction, or refractory ischemia at 48 h occurred in 3.8% of patients on tirofiban vs 5.9% on heparin (odds ratio 0.637; $p = 0.007$). At 30 d, the composite end point was not different between the groups (12.8 vs 13.9%), although mortality at 30 d was 2.3 vs 3.6% with 39% risk reduction in favor of tirofiban. In a related trial, PRISM-PLUS, 1570 patients with unstable angina or NQMI with documented ECG changes and/or elevated creative kinase were studied *(134a)*. All patients received aspirin and, in contrast to PRISM, all patients also received intravenous heparin and were randomized to receive either placebo or tirofiban. Mandatory angiography was performed after 48 h and, if indicated, angioplasty was performed. Tirofiban was given as a bolus of 0.4 mg/kg/min over 30 min followed by a 0.1-mg/kg/min infusion for 48–96 h. Early in the trial, a tirofiban-only arm (no heparin, tirofiban 0.6-mg/kg/min over 30 min loading dose followed by 0.15-mg/kg/min tirofiban infusion) was discontinued based on observed high mortality (6%) in that arm. The composite clinical end point at 7 d was 17.9% in the tirofiban plus heparin group vs 12.9% in heparin-only group, with risk reduction of 34%. The secondary end point of death or myocardial infarction was reduced from 8.3 to 4.9% by tirofiban, a 44% risk reduction. At 30 d, the combined end point was reduced by 23% and death or myocardial infarction by 31%. The PRISM study demonstrated the feasibility of using a GPIIb/IIIa blocking agent without concomitant use of heparin, albeit in a relatively lower risk group of patients. However, most of the benefit was in the refractory ischemia component, and there was considerable loss of efficacy at 30-d follow-up. Interestingly, when longer duration of tirofiban infusion was used in the PRISM-PLUS study, there was a much smaller attenuation of the benefit at 30 d. Differences in the patient populations, longer duration of the infusion in PRISM PLUS, the role of compulsory angiography coupled with angioplasty *during* the GPIIb/IIIa inhibitor infusion, or a key role for adjunctive heparin therapy may also be important parts of the explanation.

Lamifiban

Lamifiban is another peptidomimetic agent that causes steric blockade of the GPIIb/IIIa receptor and produces dose-dependent inhibition of ADP-induced platelet aggregation *(135)*. In the Canadian Lamifiban Study of patients with unstable angina, it led to reductions in recurrent ischemia at doses that inhibit ADP-induced platelet aggregation by >70% accompanied by minimal increases in the risk of hemorrhage. In this study, 365 patients with unstable angina were randomized to one of the four doses of lamifiban infusion or placebo *(136)*. Aspirin was administered to all patients, but only 28% patients received heparin. At 30-d, death or myocardial infarction occurred in 8.1% patients on placebo and 2.5% of patients on the two high doses. In the subsequent trial Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON), 2245 patients with non-ST-segment elevation acute

coronary syndromes, patients were randomized in a 3 × 20 factorial design to receive up to 72 h of therapy with either a low dose of lamifiban (300-mg/kg bolus and 1-mg/kg/min infusion), or a high dose of lamifiban (750-mg/kg bolus and 5-mg/kg/min infusion), with or without heparin *(137)*. At the end of 30 d, lamifiban was not associated with a reduction in death, myocardial infarction, or recurrent ischemia at either dose, and the rate of major bleeding doubled in the group receiving high-dose lamifiban and heparin. By 6 mo, however, there was some benefit, with the lowest rate of death and myocardial infarction in patients receiving low-dose lamifiban with heparin (12.7%), an intermediate rate in patients receiving low-dose lamifiban alone (14.8%), and identical rates in patients receiving high-dose lamifiban, with or without heparin (18.1%).

Oral GPIIb/IIIa Antagonists

Several trials of peptide and peptidomimetic antagonists of GPIIb/IIIa in patients with acute coronary syndromes and patients undergoing percutaneous revascularization demonstrate that clinical events continue to occur after completion of drug therapy. Such ongoing events have lead to attrition of the benefit initially obtained in trials like RESTORE, PURSUIT, and PRISM. Prolonged inhibition of platelet aggregation may prevent events after completion of intravenous therapy and may prevent short- to medium-term loss of benefit. Because intravenous peptide and peptidomimetic agents have relatively short half-lives, prolonged inhibition of platelet aggregation requires orally active GPIIb/IIIa antagonists. However, the degree of chronic platelet inhibition required and the optimum duration of chronic therapy are as yet undetermined. A large number of nonpeptide GPIIb/IIIa antagonists with high oral bioavailability are in various stages of development *(135,138–140)*.

Xemilofiban is a prodrug of a peptidomimetic RGDF molecule that inhibits ADP- and collagen-induced platelet aggregation in a dose-dependent fashion. In a pilot study of patients undergoing percutaneous transluminal coronary angioplasty, xemilofiban was administered as a high oral loading dose followed by a lower maintenance and was associated with an unacceptably high rate of severe and life-threatening bleeding *(141)*. In the subsequent studies, a loading dose was eliminated, and the first maintenance dose was administered after angioplasty sheaths had been removed. This regimen proved to have a safety profile equivalent to that seen with placebo *(142)*.

In the ORBIT-2 study, 549 patients undergoing PTCA were randomized to placebo or xemilofiban at 15 mg or 20 mg (unpublished data). Xemilofiban was administered three times daily for 2 wk after PTCA followed by twice daily for another 2 wk. In this study, 29% of the patients received abciximab during the procedure. These patients were randomized to receive either placebo or the lower of the two doses of xemilofiban. Patients randomized to low doses of xemilofiban after receiving abciximab demonstrated that platelet aggregation in response to xemilofiban was inhibited to a considerably greater extent than was seen in patients who did not receive abciximab *(143)*. After 1 wk, platelet aggregation responses were commensurate with those seen in patients who had not received abciximab.

In the Thrombolysis in Myocardial Infarction (TIMI) 12 study, patients with acute coronary syndromes were assigned to receive 1 mo of treatment with either sibrafiban, a long-acting oral inhibitor of GPIIb/IIIa, or aspirin *(143a)*. This study did not combine the oral GPIIb/IIIa inhibitor with aspirin and thus may have led to selection of a relatively more potent dose of sibrafiban. The study was done as a dose-ranging trial and served to approximate the degree of "nuisance" bleeding likely to occur at each level of platelet

inhibition. At a dose at which ADP-induced aggregation was inhibited by 80%, minor bleeding occurred in 12% of patients, and the study drug was discontinued in 10% of patients; a slightly higher dose that led to 90% inhibition of platelet aggregation was associated with minor bleeding in 21% of patients and drug discontinuation in 18%. There were no major bleeding events at the highest dose. It therefore appears that in the absence of aspirin, the upper limit of GPIIb/IIIa inhibition that will be tolerable over the long term in an outpatient setting is approximately 70% inhibition.

COAGULATION CASCADE AND THROMBIN PATHOPHYSIOLOGY IN ACUTE CORONARY SYNDROMES

Thrombin plays an integral role in the pathophysiology of acute coronary syndromes and, in concert with the platelets, is of pivotal importance in thrombus generation and propagation. Several studies have shown increased levels of biologic markers of thrombin generation and activity in patients with acute coronary syndromes *(144–146)*. Following plaque fissuring or rupture, in concert with platelet activation, a self-amplifying activation of the coagulation cascade occurs and culminates in thrombin generation. TF, a coenzyme found on the surface of injured endothelial cells, activated macrophages, fibroblasts, and smooth muscle cells, comes in contact with, and activates, factor VII. Preferentially assembled on the surface of activated platelets, the TF/VIIa complex, in the presence of factor V and Ca^{2+}, activates factor X to Xa. Activated factor Xa forms a quaternary complex with factor Va (prothrombinase complex) on the platelet surface, which catalyzes thrombin generation with an efficiency approximately 10^5 fold greater than free factor Xa *(147)*. This prothrombinase complex cleaves prothrombin to enzymatically active thrombin and F1.2 fragment, the latter being a marker of thrombin generation. Thrombin causes feedback activation of factor V to factor Va, as well as activation of intrinsic pathway factors VIII and XI, and activates platelets, thus initiating a positive feedback amplification loop. The intrinsic pathway is activated by factor XIa, which cleaves factor IX to IXa. Factor IXa, in the presence of factor VIIIa, platelets, and Ca^{2+} activates factor X to Xa, thus generating further prothrombinase complex. (Figs. 3 and 4).

In animal models, thrombin generation can be detected within seconds of vascular injury. Thrombin generation peaks approximately 5 hours after vascular injury at 50 fmol/min/cm^2 followed by a slow decline over the next 24 h to 10 fmol/min/cm^2, at which level it stays for 10 d or longer *(148)*. Thrombin's proteolytic action results in the production of fibrin monomer and the fibrinopeptides A and B (FPA and FPB). Arginyl–glycine bonds are cleaved to release 16-amino acid (FPA) from the NH_2 segment terminal of the α-chain and 14-amino acid FPB from the NH_2 segment terminal of the β-chain *(149,150)*. Under physiologic conditions, the generation of FPA and FPB is almost completely owing to thrombin action, and FPA levels can be used to monitor thrombin activity in vivo or in vitro *(144,151)*. Thrombin binds to the newly laid fibrin mesh, and this clot-bound thrombin is protected from the neutralizing action of heparin–antithrombin III (ATIII) complexes *(152)*. The substrate recognition site of clot-bound thrombin is occupied, although the catalytic site remains active and capable of fibrinogen proteolysis as well as platelet activation (Fig. 5).

Several physiologic mechanisms limit thrombin generation and prevent widespread intravascular thrombosis. Thrombomodulin is an endothelial cell membrane-bound glycoprotein that binds thrombin and enables it to activate protein C. Activated protein C

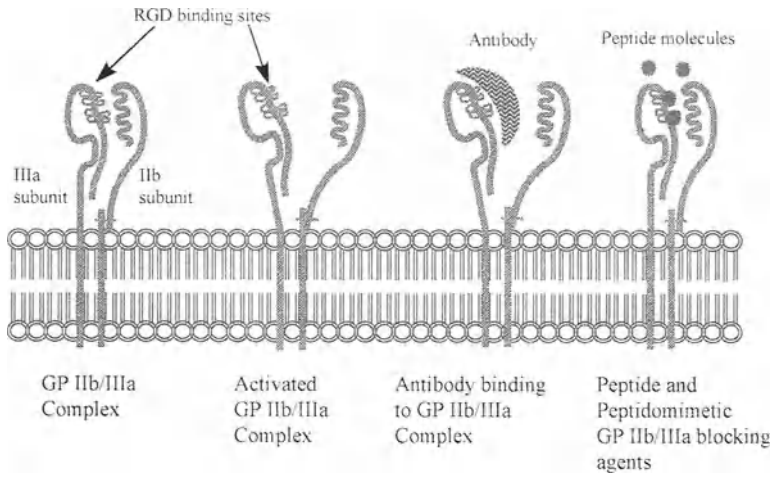

Fig. 3. Resting GPIIb/IIIa receptor complex on the surface of inactive platelets and exposure of RGD binding sites upon activation. Abciximab binds the IIIa subunit of activated receptor complex, and peptide and peptidomimetic molecules act as competitive antagonists binding both activated and inactive receptor complexes.

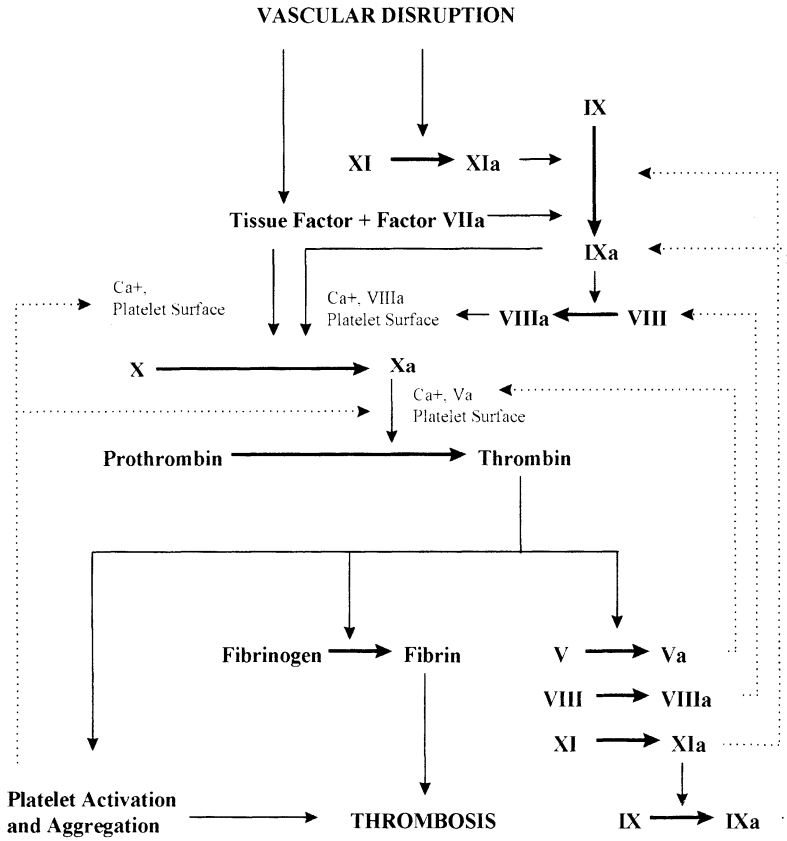

Fig. 4. Coagulation cascade and feedback amplification of thrombin generation by both intrinsic and extrinsic pathways.

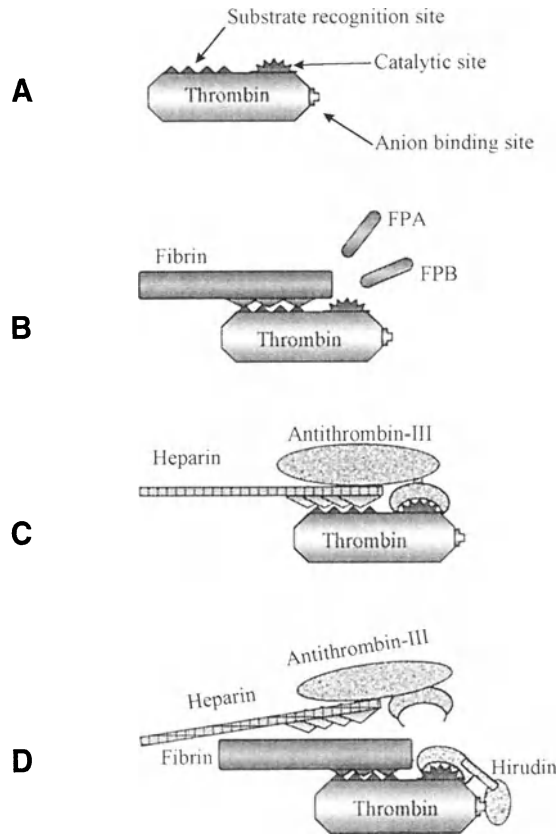

Fig. 5. Thrombin molecule and its interactions with fibrinogen, heparin, antithrombin- III (ATIII), and hirudin. FPA, fibrinopeptide A; FPB, fibrinopeptide B. **(A)** Thrombin molecule. **(B)** Proteolytic cleavage of fibrinogen to fibrin, FPA and FPB. **(C)** Heparin-ATIII complex neutralizes the actions of thrombin. **(D)** Heparin-ATIII complex is unable to neutralize clot-bound thrombin, whereas hirudin is able to inhibit clot-bound thrombin.

with cofactor S inactivates factors Va and VIIIa, thus inhibiting the intrinsic pathway of thrombin generation *(153)*. Tissue factor pathway inhibitor (TFPI) is a lipoprotein-associated coagulation inhibitor that avidly binds factor Xa. The TFPI–Xa complex is adsorbed onto the platelet membrane, where it binds and inhibits the TF–VII–PL complex, thus quenching the extrinsic pathway of thrombin generation *(154)*. ATIII, a serine protease inhibitor, is the principal physiologic antagonist of both thrombin and factor Xa. Endothelial cell surface glycoaminoglycans like heparan sulfate, as well as exogenous heparin, bind ATIII, inducing a conformational change in the molecule that increases its serine protease inhibitory activity by about 2,000 times *(155,156)*.

These physiologic mechanisms are, however, overwhelmed in the disease state. The high degree of TF expression, exposure of highly thrombogenic materials, and excessive platelet activation accompanying plaque rupture overcome the physiologic inhibitors and result in inappropriate and excessive thrombin activity, fibrinogen cleavage, and thrombus formation.

ANTITHROMBIN AGENTS

Heparins

Unfractionated Heparin

Heparin has been used as an anticoagulant for decades. Pharmaceutical heparin is derived from bovine and/or porcine sources and consists of an unfractionated mixture of glycosaminoglycans with molecular weights from 5,000 to >30,000 Daltons. Heparin binds ATIII through a high-affinity pentasaccharide sequence and induces allosteric modification in the reactive arginine site of the ATIII molecule, enhancing its interaction with thrombin and other serine proteases. The heparin–ATIII complex attaches to the thrombin molecule, forming thrombin–ATIII complexes (TATs); as heparin disassociates from the complex, TATs are cleared from circulation by the reticuloendothelial cells.

A randomized trial by Telford and Wilson *(157),* published in 1981, suggested that heparin infusions might prevent patients with unstable angina from progressing to myocardial infarction. Although there were methodologic problems with this trial, subsequent trials performed in Montreal and Scandinavia indicated that the combination of aspirin and heparin reduced the rate of myocardial infarction by approximately 50% during the first few days or weeks after presentation *(9,14,158).* Data from Montreal showed that in 479 patients, the incidence of progression to myocardial infarction was 3% in the aspirin group, 0.8% in the heparin group, and 1.8% in the heparin plus aspirin group *(14).* Another follow-up study in 484 patients demonstrated that heparin was superior to aspirin in prevention of fatal or nonfatal myocardial infarction (0.8 vs 3.7%) *(9).* Because of these findings, heparin has become part of the standard armamentarium of treatment for patients presenting with unstable coronary syndromes.

It is important to recognize that not all studies have provided convincing evidence of heparin's benefit. In the RISC study, most of the benefit in patients receiving both aspirin and heparin was derived from treatment with aspirin *(15).* Another study by Holdright et al. *(158)* found no difference in the rates of death or myocardial infarction between aspirin-treated and heparin-treated patients. In a study by Gurfinkel et al. *(159),* the incidence of combined end point was not significantly different in patients treated with aspirin vs patients treated with aspirin and heparin (59 vs 63%).

Heparin withdrawal. Heparin withdrawal in patients with acute coronary syndromes has been associated with a rebound increase in angina and infarction *(160,161).* This syndrome peaks at 4–8 hours after heparin discontinuation and may be prevented at least partially with aspirin. The mechanism of this effect is not known; prolonged heparin administration has been variably reported to decrease circulating ATIII levels; reductions in circulating activated protein C have also been reported. There are data to suggest that thrombin generation and activity increase when heparin is stopped suddenly *(160).* Therefore, it seems logical that after prolonged heparin therapy, heparin should not be abruptly stopped but rather weaned over 12–24-h, or a subcutaneous injection of heparin before termination of infusion may provide a gradual tapering of serum levels.

Heparin dosing and monitoring. Despite heparin's availability for more than 70 years, there is still little agreement about the optimal dose. Heparin binds to circulating plasma proteins, macrophages, and endothelial cells with variable affinity *(162),* and because its clearance is variable, the response of a given patient to any given dose of heparin is largely unpredictable. Currently, most patients with unstable angina or myocardial infarction are treated with a "standard" heparin dose consisting of a 5000-U bolus

and infusion beginning at 1000 U/h tailored by frequently monitored activated partial thromboplastin time (aPTT) results. The major determinant of aPTT response to a fixed dose of heparin is body weight. Raschke and colleagues *(163)* randomized patients with venous thrombosis to either a "weight-based" regimen (80-U/kg bolus and 18-U/kg/h infusion) or "standard dose" heparin. Patients treated with the weight-based regimen achieved a therapeutic aPTT more rapidly (86 vs 32% at 6 h) than did the "standard" dose group, and there were no increases in bleeding complications. The TIMI 4 investigators found that hospitals that elected to use weight-based nomograms had markedly smaller proportions of patients with either supratherapeutic or subtherapeutic aPTT at 24 or 48 h, and subsequently required fewer adjustments of the heparin infusion rate *(164)*. More recently, in the PARAGON trial, patients with unstable angina were given heparin in a blinded fashion using a computerized nomogram. The range of aPTTs measured following titration was extremely narrow, indicating that weight-based nomograms are more likely to provide precise adjustment of aPTT than physician-directed determinations. Analysis of data from the TIMI III and Global Use of Strategies To Open Occluded Arteries (GUSTO) II trials reveals that among patients with unstable angina or NQMI, the relationship between mortality and aPTT seems to follow a J-shaped curve. Patients with lowest rates of myocardial infarction appear to have aPTT values of 55–65 s *(165,166)*, thus emphasizing the need for precise adjustments of the aPTT.

Low Molecular Weight Heparins

Commercial heparin consists of a mixture of variable weight and length of glycosaminoglycans. This mixture can be fractionated or depolymerized by a variety of techniques, so that the final product predominantly contains heparins of molecular weight of <8,000 Daltons *(167)*. Compared with unfractionated heparin, low molecular weight heparins (LMWHs) have longer half-lives, bind less avidly to plasma proteins *(168)* and cellular receptors, and produce more efficient increases in circulating levels of TFPI *(169–172)*. LMWHs potentiate ATIII activity, but are relatively less efficient in binding thrombin and thus lead to a higher ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity *(173)*. The anti-factor Xa activity is particularly important, as it can prevent thrombin generation and interrupt feedback amplification of thrombin production. The thrombin binding activity of heparin resides primarily in the higher weight glycosaminoglycan chains; therefore the anti-factor Xa/anti-factor IIa ratio of various LMWHs varies according to the molecular sizes of the subfractions they contain. The lesser antithrombin effects of LMWHs leads to less prolongation of the aPTT than unfractionated heparin, thus eliminating the need for aPTT monitoring for therapeutic use. The LMWHs have a longer half-life and predictable bioavailability after subcutaneous administration *(174)*.

A number of LMWH fractions have been developed commercially and differ in molecular weight, bioavailability, and anti-factor Xa activity (Table 5). The broadest experience with these agents has been in the prophylaxis of deep venous thrombosis. A meta-analysis of trials comparing LMWHs with unfractionated heparins revealed a 53% reduction in the rate of thromboembolic complications and a 68% reduction in the rate of major bleeding complications *(175)*. Several studies have been reported in patients with unstable angina. In these studies, the doses of LMWH have been higher than that used for prophylaxis of deep venous thrombosis. Gurfinkel et al. *(159)* studied 219 patients presenting within 24 h of an episode of unstable angina. Patients were randomized to receive either aspirin alone, aspirin in combination with intravenous unfractionated heparin, or aspirin in combination with nadroparin, a LMWH. The composite end point

Table 5
Low Molecular Weight Heparins in Syndromes of Acute Coronary Ischemia

Name	*Weight (Daltons)*	*Anti-factors Xa/II activity*	*Study*	*No.*	*Comments*
Dalteparin	5000	2:1	FRISC	1506	Better than heparin
			FRISC	N/A	Ongoing trial
			FRIC	1482	Same as heparin
Enoxaparin	4500	3:1	TIMI-11A	630	Dose-finding study
			ESSENCE	3171	Better than heparin
Nadroparin	4500	3.2:1	Gurfinkel et al.	219	Better than heparin
Danaparoid	6500	28:1	N/A	N/A	Approved for DVT prophylaxis
Tinzaparin	4500	2:1	N/A	N/A	N/A
Ardeparin	6000	2:1	N/A	N/A	N/A

DVT, deep venous thrombosis.

of death, acute myocardial infarction, recurrent angina, urgent revascularization, or major bleeding occurred in 59% of patients receiving aspirin alone, 63% of patients receiving aspirin and unfractionated heparin, and 22% of patients receiving aspirin and LMWH. In the Fragmin during Instability in Coronary Artery Disease (FRISC) study, 1506 patients with unstable angina or NQMI were randomized to receive either aspirin and placebo or aspirin and subcutaneous dalteparin (Fragmin), 120 IU/kg twice daily for 6 d followed by 7500 IU daily for the next 35–45 d *(176)*. The composite end point of death or new myocardial infarction was reduced significantly at 6 d (1.8 vs 4.8%; risk ratio 0.37). These differences diminished over the ensuing 5 mo, possibly as a result of reactivation of the disease process when the dalteparin dose was reduced. The next phase of this study (FRISC-2) is currently in progress and involves continuing a full dose of dalteparin for a prolonged period following hospital discharge. The FRISC study did not incorporate unfractionated heparin in the control group and therefore does not establish superiority of dalteparin over unfractionated heparin. In a second study, FRIC, dalteparin was compared with unfractionated heparin in 1,482 patients with unstable angina and was shown to be as effective as standard heparin in preventing recurrent ischemic events *(177)*. The TIMI 11-A investigators studied two doses of enoxaparin (1 mg/kg and 1.25 mg/kg) in a pilot study *(178)*. The incidence of death, myocardial infarction, or recurrent ischemia at 14 d was 5.6% and 5.2% in the two dose groups, which compares favorably with historical controls. In the ESSENCE trial, 3171 patients with non-ST-segment elevation acute coronary syndromes were randomized to receive either intravenous unfractionated heparin or 1 mg/kg enoxaparin administered subcutaneously, twice daily *(179)*. Median duration of therapy was 2.6 d. At 14 d, the composite end point of death, myocardial infarction (or recurrent myocardial infarction), or recurrent ischemia occurred in 16.6% of patients randomized to receive enoxaparin vs 19.8% of patients receiving unfractionated heparin (odds ratio 0.80; $p = 0.019$). Most of the difference between the groups was driven by the differences in the rates of recurrent ischemia, and this benefit was maintained at 30 d. There was also a trend in favor of enoxaparin in reduction of death or nonfatal myocardial infarction at 14 d (4.9 vs 6.1%; $p = 0.13$), and at 30 d (6.2 vs 7.7%; $p = 0.08$).

Limitations of heparin as an anticoagulant. The efficacy of heparin as an antithrombin is limited owing to several reasons. Thrombin bound to the subendothelial matrix or

fibrin monomers is largely protected from heparin-mediated inhibition *(152)*. The heparin–ATIII complex is relatively ineffective against clot-bound thrombin, and its efficacy is approximately 1 in 20 compared with that against fluid-phase thrombin. Several plasma proteins such as vitronectin, fibronectin, and histidine-rich glycoprotein *(162,168)*, as well as platelet factor 4, bind and neutralize heparin *(180,181)*. The unpredictable anticoagulant response to unfractionated heparin necessitates frequent laboratory monitoring of its effect.

Direct Thrombin Inhibitors

Given the inherent drawbacks of heparin and the LMWHs, the search for newer, more potent agents that can overcome these limitations has led to extensive research into direct thrombin inhibitors. All these agents act independently of ATIII and are unaffected by heparin-inactivating proteins. All are able to inactivate clot-bound thrombin, the smaller molecules more so. All have been shown in animal models to potentiate the activity of thrombolytic drugs, to prevent reocclusion, and to inhibit platelet and fibrin deposition on arterial grafts or injured arterial surfaces.

Hirudin

Hirudin is the principal anticoagulant found in the saliva of the medicinal leech, *Hirudo medicinalis* and is the most potent and specific naturally occurring inhibitor of thrombin *(182)*. This 65-amino acid protein is stabilized by three disulfide bridges and forms a highly stable, reversible complex with thrombin, eliminating all its proteolytic activities *(183,184)*. Hirudin binds three sites on the thrombin molecule including the anion-binding exosite, the active catalytic site, and the apolar binding site. Hirudin is now produced as a recombinant desulfato hirudin (r-hirudin), which lacks the sulfate group on tyrosine 63 and has a dissociation constant approximately 10-fold higher than that for naturally occurring hirudin *(185–187)*. Hirudin requires parenteral administration and is excreted in the active form by the kidney *(188)*. Pharmacokinetic studies in volunteers revealed a half-life of 40–60 min when the drug was given intravenously, although in older patients with coronary artery disease, the half-life may be as long as 2–3 h *(186,189)*. Hirudin prolongs the aPTT and thrombin time in dose-dependent fashions, but in clinically applicable doses, it has no effect on the bleeding time *(190,191)*. Hirudin activity is highly specific for thrombin and it has better activity against clot-bound thrombin then does heparin *(192)*.

Pilot studies in patients with unstable angina pectoris or myocardial infarction suggested that hirudin was safe, led to therapeutic degrees of anticoagulation, and had low rates of adverse outcomes *(191,193,194)*. Topol et al. *(190)* reported the results of a randomized pilot trial comparing 2 doses of intravenous heparin with four escalating doses of hirudin in 166 patients with unstable angina who had angiographic findings suggestive of intracoronary thrombus. The doses of r-hirudin studied ranged from an 0.1-mg/kg bolus with a 0.1-mg/kg/h infusion to an 0.9-mg/kg bolus with an 0.3-mg/kg/h infusion. Hirudin demonstrated better improvement of the angiographic caliber of the culprit vessel and more consistent and stable elevation of aPTT. However, bleeding occurred in patients treated at the highest dose, and the angiographic effect appeared to reach a plateau at 0.6-mg/kg bolus with 0.3-mg/kg/h infusion.

GUSTO II is the largest trial of hirudin. Patients with acute coronary syndromes were randomized to receive antithrombin therapy with either intravenous heparin or hirudin. In GUSTO II, hirudin was initially administered as a 0.6-mg/kg bolus and 0.2-mg/kg/h

infusion. The trial was halted after enrollment of 2564 patients because of excessive intracranial bleeding *(195)*. The overall incidence of hemorrhagic stroke was 1.3% in the hirudin group and 0.7% in the heparin group. The incidence was highest in the patients receiving thrombolytics (1.8 vs 0.3%), particularly those randomized to streptokinase (2.7% in the heparin group and 3.2% in the hirudin group). In patients not treated with thrombolytic therapy (unstable angina and NQMI patients), the incidence of hemorrhagic stroke was 0% with heparin and 0.55% with hirudin. Similar results from two other randomized trials of hirudin as an adjunct to thrombolysis, TIMI 9 and HIT, prompted a decrease in the dose of hirudin to a 0.1-mg/kg bolus and 0.1-mg/kg/h infusion, given for 72 h. In all, 12,142 patients with acute coronary syndromes were enrolled in the GUSTO IIb trial (4131 patients with, 8011 patients without ST-segment elevation) and were randomized to 72–120 h of infusion of hirudin or heparin *(196)*. The overall composite end point of death or myocardial infarction at 30 d was 8.9% in the hirudin group and 9.8% in the heparin group ($p = 0.058$). In the patients without ST-segment elevation, the end point occurred in 8.3% of patients receiving hirudin and 9.1% of those receiving heparin ($p = 0.22$). Similarly, disappointing results emerged from the TIMI 9b trial of hirudin as an adjunct to thrombolysis in patients with acute myocardial infarction. Owing to the concern that the dose studied in GUSTO IIb may have been too low, the Canadian Organization to Assess Strategies for Ischemic Syndromes (OASIS) group performed a pilot study in patients with non-ST-segment elevation myocardial ischemia. Patients (n = 909) were randomized to receive a 72-h infusion of either heparin, low-dose hirudin (0.2-mg/kg bolus followed by 0.1-mg/kg/h infusion), or medium-dose hirudin (0.4-mg/kg bolus followed by 0.15-mg/kg/h infusion) *(197)*. The composite end point of death, myocardial infarction (or reinfarction), or refractory angina occurred in 3% and 4.4% of patients treated with medium and low doses of hirudin, respectively, compared with 6.5% of patients receiving heparin (heparin vs medium-dose hirudin, $p = 0.047$). The OASIS trial is an ongoing, randomized, double-blind, placebo-controlled trial involving a 2 by 2 factorial design comparing heparin versus hirudin and warfarin versus placebo in 8000–10,000 patients with unstable angina or NQMI.

Hirulog

Hirulog is a 20-amino acid synthetic analog of hirudin that binds the catalytic site and the anion binding exosite on thrombin molecules. The carboxy terminus of hirulog binds and inhibits the anion binding exosite and is separated by a "spacer" consisting of four glycine residues from a Phe-Pro-Arg group at its amino terminus, which inactivates active catalytic site of thrombin. It has a half-life of approx 36 min after intravenous dosing and is cleared predominantly via hepatic metabolism. It also prolongs the aPTT and thrombin time without affecting the bleeding time. Hirulog can inhibit clot-bound thrombin more effectively than hirudin owing to its smaller size, although both are superior to heparin in this aspect *(198–200)*.

A few trials of hirulog in unstable angina have been completed. The largest was TIMI 7, a dose-ranging study involving 410 patients and four escalating doses of hirulog *(201)*. Patients were randomized to receive infusions of either 0.02, 0.25, 0.5, or 1.0 mg/kg/h for 72 h. Hirulog produced dose-dependent elevations in the aPTT ranging from 38.1 s in the lowest dose group to 87.1 s in the highest dose group. The aPTT remained within a narrow window in nearly all patients. Major hemorrhage occurred in 0.5% of patients. No differences were noted in the primary composite end point of death, myocardial infarction, rapid clinical deterioration, or recurrent ischemia. However, the combined rate of death

or nonfatal myocardial infarction was reduced in patients assigned to the three highest dose groups. In another study, hirulog was used as anticoagulant instead of heparin in 291 patients undergoing PTCA in a dose-ranging study and appeared safe and effective *(193)*. Recently, Bittl et al. *(202)* reported the use of hirulog in patients with unstable angina undergoing angioplasty. Patients (n = 4098) were randomized to a 24 h infusion of heparin or hirudin. Bleeding complications were significantly less frequent in hirulog-treated patients. The overall composite end point of death, myocardial infarction, or abrupt vessel closure was not significantly different between the two groups (11.4 vs 12.2% for heparin). However, in the subgroup with post-infarction angina, the composite end point was reduced in the hirulog patients (9.1 vs 14.2%; p = 0.04). Hirulog is now being studied in a larger trial, Hirulog Early Reperfusion/Reocclusion (HEROZ), as an adjunct to thrombolysis and in the CACHET trial as an anticoagulant during angioplasty.

Argatroban, Efegatran, and Hirugen

Argatroban is a synthetic arginine derivative that blocks the active catalytic site of thrombin *(203)*. Argatroban, like hirudin and hirulog, has demonstrated excellent safety in phase I trials along with dose-dependent prolongation of the aPTT *(204)*. It has a half-life of 25 min after intravenous dosing and does not appear to prolong the bleeding time. In a small study involving 43 patients with unstable angina, there was a dose-dependent increase in aPTT and decreased thrombin activity with escalating argatroban infusion doses, given over a period of 4 h. However, thrombin generation continued as evidenced by stable plasma concentrations of thrombin–ATIII complexes during the infusion.

Efegatran is a tripeptide agent in the same class as argatroban and also blocks the active catalytic site of thrombin *(204)*. No benefit of efegatran was seen in the ESCALATE study when used as an adjunct to thrombolytics. Hirugen is a 12-amino acid synthetic derivative of the carboxy-terminal of hirudin that binds only the anion binding exosite, but clinical testing has been limited due to its inability to decrease platelet-rich arterial thrombus formation *(204)*.

Limitations of Direct Acting Antithrombin Agents

The trials with direct thrombin inhibitors have made several points apparent. First, it is now clear that more aggressive thrombin inhibition is not necessarily beneficial, regardless of the thrombin inhibitor used, especially in conjunction with thrombolysis. The disappointing lack of therapeutic efficacy can be attributed to a narrow therapeutic window and the difficulty in finding appropriate dosage in different patient groups. Furthermore, all the direct antithrombins are potent inhibitors of thrombin activity, but, unlike the heparin–ATIII complex, they lack activity against factor Xa and therefore do not prevent thrombin generation. On the other hand, the precise control afforded over the aPTT and ACT may be beneficial, especially in patients receiving a GPIIb-IIIa antagonist concomitantly.

Unabated thrombin generation is evidenced by continued presence of TAT complexes and may therefore negate any benefit once the direct antithrombin drug is discontinued. The direct-acting antithrombins lack the synergy that heparin has with TFPI *(172)* and, unlike heparin, do not increase TFPI levels. Heparin binding to the exposed subendothelium ensures local heparin levels at the site of vascular disruption, and the negatively charged heparin contributes to restore the negative charges on the endothelial surfaces. Direct-acting antithrombins lack these beneficial properties.

FACTOR Xa INHIBITORS

A variety of new strategies are directed toward preventing the *de novo* generation of thrombin. At least two different but interdependent mechanisms activate the soluble coagulation cascade, the intrinsic and the extrinsic pathways. Both pathways serve the ultimate purpose of activating factor X to factor Xa.

Antistasin and Tick Anticoagulant Peptide

Recognition of structural similarities among the serine proteases has led to the search for specific inhibitors of factor Xa. Specific inhibitors of factor Xa have been discovered in the saliva of many hematophagous species. Antistasin is a 119-amino acid peptide derived from the saliva of the Mexican leech and has been produced in a recombinant system *(205–207)*. It can inhibit TF-induced FPA generation in a dose-dependent fashion, but has no direct effect on thrombin activity *(207,208)*. The tick anticoagulant peptide (TAP) is a 60-amino acid protein originally purified from salivary extracts of the soft tick, *Orithodoriso moubata*, and currently elaborated using recombinant technology. Like recombinant antistasin, it is a potent inhibitor of factor Xa and has no known inhibitory activity against any of the other serine proteases *(209,210)*. The abilities of both antistasin and recombinant TAP to inhibit arterial or venous thrombosis and platelet deposition have been shown in a wide variety of experimental preparations although they have not been subjected to clinical trials.

TISSUE FACTOR PATHWAY INHIBITOR

The tissue factor pathway is the primary pathway in the early stages of thrombin generation *(211)*. TFPI inactivates this pathway by binding factor Xa, forming a TFPI–Xa complex, which then reversibly binds TF–VIIa complex on the cell membrane and forms a stable quaternary complex *(212,213)*. Heparin and ATIII interact at several points in the extrinsic pathway *(214)*. Heparin binds TFPI, enhancing the TFPI-mediated inactivation of factor Xa, and directly augments TFPI–Xa interaction with the TF–VIIa complex. The heparin–ATIII complex causes the TF–VIIa complex to dissociate from cell membranes and prevents it from reattaching to these surfaces. There is also evidence that LMWHs cause the release of massive amounts of TFPI from endothelial cells.

A variety of experiments have suggested a potential therapeutic role for TFPI in the treatment of arterial thrombotic disease.

rTFPI

Incubation of recombinant rTFPI with factors Xa and VIIa can inhibit thrombus formation on extracellular matrix. In a rabbit model of venous thrombosis, rTFPI reduced thrombus formation in a dose-dependent fashion. rTFPI has also been shown to reduce arterial thrombosis in human aortic segments placed in a baboon shunt model. rTFPI after thrombolysis prevents reocclusion and markedly inhibits cyclic flow variations in vessels with experimental electrothermal injury *(215,216)*.

THERAPEUTIC IMPLICATIONS

Despite the salutary effects of conventional antithrombotic therapy with aspirin and/or heparin in patients with non-ST-segment elevation acute coronary syndromes,

death or reinfarction rates at 30 d remain a sobering 9–16% *(134,179)*. Twenty to 30% of patients also develop recurrent ischemia, often requiring rehospitalization and revascularization within the first month after presentation *(8,134)*. Several studies have documented the futility of thrombolytic therapy in this patient population *(8)*. Angiographically guided revascularization therapy does not appear to be of advantage over conservative therapy *(8,134)*. With more than 850,000 annual admissions to acute care hospitals, it becomes imperative to improve on the efficacy of present antiplatelet and antithrombotic therapies for non-ST-segment elevation coronary ischemic syndromes.

Antiplatelet Therapy

Aspirin remains the cornerstone of antiplatelet therapy for patients with non-ST-segment elevation acute coronary syndromes. It should be administered, as early as possible, in all patients, unless there is a history of *severe* intolerance. At least 162.5 mg should be administered, preferably of a rapidly absorbable, nonenteric coated formulation. There are no data to allow direct comparison of ticlopidine or clopidogrel with aspirin therapy in the acute setting. The relatively higher cost, the higher incidence of side effects with ticlopidine, and (most important) the slow onset of action make them unlikely candidates for the acute therapy of non-ST-segment elevation coronary syndromes. Their use as first line treatment should only be considered in the rare patient who is intolerant to aspirin therapy.

GPIIb/IIIa blocking agents represent a truly exciting development in antiplatelet therapy. Three of these agents have proved to be clinically useful in addition to aspirin and heparin therapy. The most widely studied drug, abciximab, has already established a role in preventing acute ischemic complications of angioplasty, and eptifibatide and tirofiban have been shown to be useful in the therapy of acute coronary syndromes. Certainly, in patients with acute coronary ischemic syndromes undergoing percutaneous revascularization, abciximab use should be considered whenever possible. However, abciximab use in patients with non-ST-segment elevation ischemia in the absence of a planned percutaneous revascularization procedure has not yet been studied in a randomized clinical trial.

The data from PRISM, PRISM-PLUS, and PURSUIT studies make a very strong argument for the use of these agents in patients with non-ST-segment elevation acute coronary syndromes. This becomes particularly convincing in light of the fact that in these studies, there was no significant difference in major bleeding events between the treatment and placebo groups although in PRISM-PLUS, a trend in favor of placebo (1.8 vs 1.2%) was noted. Taken in aggregate, the findings suggest that the benefit from GPIIb/IIIa inhibition in patients with acute coronary syndromes may be a class effect.

A critical issue regarding GPIIb/IIIa antagonists in patients with acute coronary syndromes is the role of concomitant heparin therapy. Theoretic evidence suggests that some degree of thrombin inhibition may be needed even in the presence of a GPIIb/IIIa antagonist. In patients treated with a GPIIb/IIIa antagonist, platelet aggregation can still be evoked in response to stimulation with a strong agonist, thrombin receptor-activating peptide *(217)*. Data from clinical studies performed in the era preceding GPIIb/IIIa antagonists supported but did not establish the effectiveness of heparin in patients with unstable angina. Clinical data from the recent clinical trials supporting the use of heparin with GPIIb/IIIa antagonists are even less direct.

The most interesting data are from PARAGON, a factorial study of lamifiban and heparin (see above). Although there were no intergroup differences at 30 d, the combination of low-dose lamifiban with heparin had a dramatically lower rate of death or myocardial infarction than the other groups (heparin alone, low- or high-dose lamifiban alone, or high-dose lamifiban with heparin) at 6 months, and a lower mortality at 1 yr. Although this study would provide direct evidence supporting the use of both classes of agents, it was not adequately powered to establish differences between the two groups.

Data from PRISM and PRISM-PLUS also provide some insight into the issue. In PRISM, tirofiban was compared with heparin whereas in PRISM-PLUS, tirofiban was combined with heparin. Early exclusion of a tirofiban-alone arm from the latter study precluded a meaningful direct comparison. Although there were comparable effects of tirofiban in both studies at the time the primary end point was ascertained, the treatment effect suffered considerable erosion shortly after the study drug was terminated (48 h) in PRISM, but remained present for 6 mo in PRISM-PLUS despite the infusion of the drug for only 72–96 h. The third, and least direct, source of evidence is the PURSUIT study of eptifibatide. Although heparin was used at the discretion of treating physicians in this trial, and comparisons are therefore indirect at best, both the lowest rates of death or myocardial infarction and the greatest treatment effects attributable to the GPIIb/IIIa antagonist were observed in geographic regions where heparin use was highest.

Thus, the bulk of clinical evidence provides indirect but consistent support for the notion that GPIIb/IIIa antagonists will need to be combined with heparin. The experience with abciximab in the EPIC, EPILOG, and CAPTURE trials has clearly indicated that the hemorrhagic potential increases when abciximab is combined with otherwise safe doses of heparin *(122,124,125)*. Findings with lamifiban suggest that other GPIIb/IIIa antagonists are likely to exhibit similar interactions. In the absence of direct evidence, it therefore seems reasonable that heparin doses should be reduced in patients who are also receiving GPIIb/IIIa antagonists, although the optimal level of anticoagulation is not known. Current observational data suggest that an aPTT exceeding 60–65 s should be avoided. The recent emergence of LMWHs as equivalent and possibly superior therapies to heparin alone raises the question of their use in combination with GPIIb/IIIa antagonists, although this area has thus far been unexplored.

Chronic use of oral GPIIb/IIIa antagonists is another exciting development that has just began to be explored. The risks of out of hospital GPIIb/IIIa blockade and the potential for bleeding complications and drug interactions are complex issues that need to be resolved, but hold promise.

Antithrombin Therapy

Heparin remains the mainstay of present day antithrombin therapy. Despite the limitations of unfractionated heparin, it has the most extensive clinical use of all the antithrombins. The most important issue with heparin therapy is how it is used. This becomes even more critical when heparin is used concomitantly with other potent antiplatelet agents like GPIIb/IIIa antagonists. Weight-based nomograms should be used to avoid wide fluctuations in the degree of anticoagulation. After several days of heparin therapy, abrupt discontinuation of infusion should be avoided, and it seems most reasonable to wean heparin infusions over 12–24 h.

Although there is accumulating evidence that LMWHs are at least as effective as unfractionated heparin in the therapy of acute coronary syndromes, their superiority in

efficacy or safety is not yet firmly established. The LMWHs are more costly, but the cost of monitoring aPTTs with standard heparin needs to be incorporated to make any meaningful cost comparisons. The subcutaneous route of injection offers the possibility of outpatient therapy in many patients, although the efficacy and safety of such an approach needs to be studied.

The safety and efficacy profile of direct-acting antithrombins (hirudin and hirulog) has so far not been established for clinical use in acute coronary syndromes. The narrow therapeutic window makes the dosing a critical issue. Intermediate doses of hirudin are being investigated in the OASIS trial, and newer agents including hirulog offer some hope of improving the safety and efficacy of this class of drugs. At the present time, the use of these agents can only be considered in patients with heparin-induced thrombocytopenia or severe hypersensitivity to porcine and/or bovine products.

Role of Revascularization

A final issue that has yet to be resolved is the role of revascularization in the context of these newer agents. Data from studies performed prior to the availability of these newer agents fail to establish any firm benefit from revascularization. In the TIMI III-B study, 1473 patients were randomized to angiographically guided revascularization or conservative therapy. There was no benefit of the early invasive strategy. In the VANQWISH study, 920 patients with NQMI were randomized to either early invasive strategy with myocardial revascularization or conservative strategy with a predischarge thallium stress test. There were 21 deaths in the invasive arm compared with 6 in the conservative arm, a significant difference. Additionally, the OASIS registry shows no difference in outcome in patients with acute coronary syndromes from countries with high revascularization rates compared with those with low revascularization rates.

However, the ability of GPIIb/IIIa antagonists to prevent ischemic complications of PTCA suggests that they may improve on the role of percutaneous revascularization in acute coronary syndromes. The extremely robust and durable results of GPIIb/IIIa antagonists *(218)* in patients with acute coronary syndromes has the potential to make acute revascularization a more definitive therapy in such patients.

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18 Thrombolytics and Invasive vs Conservative Strategies

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INTRODUCTION

The coronary syndromes of unstable angina pectoris and non-Q-wave myocardial infarction (NQMI) represent a pathophysiologic continuum all the way from brief myocardial ischemia to partial, nontransmural myocardial necrosis. The clinical presentation of these two syndromes is identical, typically consisting of intermittent episodes of chest pain lasting from only a few minutes to hours, and occurring either at rest or with minimal exertion. Patients with unstable angina, by definitygn, sustain only myocardial ischemia, whereas patients with NQMI, by definition, sustain at least some myocardial necrosis as evidenced by the leakage of creatine phosphokinase-MB, troponin T, and troponin I, but without the development of Q-waves on the electrocardiogram. Thus, NQMI can be viewed as a manifestation of more prolonged or severe unstable angina. Clinically the two syndromes are similar with respect to cardiovascular mortality and morbidity. They may be thought of as warning signs of impending or threatening myocardial infarction (MI). Older natural history studies *(1–3)* have shown that the development of unstable angina is associated within a year with a 10%–20% incidence of death and a 20%–40% incidence of nonfatal MI. In addition, in more recent studies, 60% of patients hospitalized with unstable angina typically have required revascularization with either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) within 1 yr.

The pathophysiologic mechanisms underlying unstable angina and NQMI involve fissuring and rupturing of coronary atherosclerotic plaque with associated acute throm-

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bus formation and coronary spasm. *In situ* thrombus formation occurs in response to the exposure of circulating blood elements to thrombogenic subendothelial elements like tissue factor, von Willebrand factor, collagen, and fibronectin. The local accumulation of vasoactive substances such as thromboxane A_2, serotonin, thrombin, and platelet-activating factor promotes coronary vasoconstriction, further contributing to myocardial ischemia. Angioscopy studies have demonstrated intracoronary thrombus or complex plaques in 90%–100% of patients presenting with unstable angina *(4,5)*. Angiography studies, on the other hand, are limited by a low sensitivity for detecting intracoronary thrombus and have revealed its presence in only about 30%–40% of patients *(6,7)*.

Importantly though, several studies have shown that the presence of angiographically detected intracoronary thrombus is associated with increased adverse cardiac events *(8)* and with increased cardiac morbidity if patients undergo angioplasty *(9,10,11)*. The demonstration of improved clinical outcome with the administration of aspirin and heparin in these syndromes has provided indirect evidence that coronary thrombosis plays a central role in the clinical evolution of unstable angina *(12,13)*. Because of the high incidence and detrimental role of intracoronary thrombus, much attention has been focused on the potential use of thrombolytic agents, given either as primary treatment or as adjunctive therapy with angioplasty, to reduce cardiac mortality and morbidity in patients with unstable angina and NQMI.

THROMBOLYTIC AGENTS

During the late 1980s and early 1990s, numerous small randomized trials were reported comparing the effects of thrombolytic agents with placebo when added to conventional therapy in patients with unstable angina (Table 1). Most of these trials, which randomized between 25 and 100 patients each, demonstrated a reduction in the incidence of recurrent ischemic attacks, nonfatal MI, and improved angiographic outcomes with a variety of thrombolytic agents including tissue-type plasminogen activator (tPA) streptokinase, and urokinase (UK). The findings were not consistent, however, and several of the trials reported no angiographic improvement or net clinical benefit to thrombolytic therapy. Because of their small size and the conflicting results, no definitive conclusions could be reached about the efficacy of thrombolytic therapy in unstable angina.

The Thrombolysis in Myocardial Infarction III (TIMI III) trial was designed to define clearly the role of thrombolytic therapy in a large group of patients with unstable angina and NQMI. A total of 1473 patients presenting within 24 h of ischemic chest discomfort at rest, consistent with unstable angina or NQMI, were randomly assigned to therapy with placebo or tPA (0.8 mg/kg up to a maximum of 80 mg infused over 90 min, with one-third given as an initial bolus). All patients received a continuous infusion of heparin, along with aspirin, β-blockers, calcium channel antagonists, and nitrates.

As one part of TIMI III, the TIMI IIIA *(14)* substudy reported the results of a group of 306 patients who underwent angiographic analysis at the time of randomization and again after 18–48 h. The prospectively defined study end point in TIMI IIIA was measurable improvement in the caliber of the culprit lesion of ≥10% reduction, or improvement by at least two TIMI flow grades, between the baseline and 18–48 h arteriograms. Arteriographically apparent thrombus was seen in 35% of patients at the baseline angiogram, with an additional 40% of patients having filling defects classified as possible thrombus. The prevalence rates of apparent thrombus in patients with unstable angina and NQMI were 29 and 47%, respectively. Treatment with tPA did not improve the

Table 1
Results of Small Randomized Trials
Using Thrombolytic Agents in Patients with Unstable Angina[a]

Study	*No. of patients*	*Thrombolytic agent*	*Results*
Serneri et al. *(36)*	97	tPA	tPA mildly reduced angina within 24 h only
Ardissino et al. *(37)*	24	tPA	tPA reduced the incidence of recurrent ischemia
Chaudhary et al. *(38)*	50	tPA	tPA reduced recurrent ischemia and need for revascularization
Gold et al. *(39)*	24	tPA	tPA improved intracoronary thrombus and reduced severity of angina
Romeo et al. *(40)*	67	tPA	tPA reduced recurrent ischemia and acute MI
Topol et al. *(41)*	40	tPA	tPA reduced the need for PTCA
Williams et al. *(42)*	67	tPA	Mild improvement in coronary stenosis
Freeman et al. *(43)*	70	tPA	tPA reduced intracoronary thrombi but had no effect on clinical events
van den Brand et al. *(44)*	36	tPA	No effect on coronary stenosis or clinical course
Saran et al. *(45)*	48	SK	SK reduced recurrent ischemia, acute MI, and mortality at 6 months
Chatterjee et al. *(46)*	100	SK	SK reduced recurrent ischemia, acute MI, and need for revascularization
White et al. *(47)*	112	SK	No effect on ischemia or MI
Schreiber et al. *(48)*	25	UK	UK reduced early progression of ischemia and MI
Sansa et al. *(49)*	43	UK	No improvement in angiographic outcome

[a]Abbreviations: tPA, tissue-type plasminogen activator; SK, streptokinase; UK, urokinase; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty.

angiographic end point in the entire population. However, in the subgroups of patients with arteriographically apparent thrombus, and in those with NQMI, treatment with tPA did significantly improve the angiographic end point.

In the larger component of TIMI III, the TIMI IIIB substudy reported the clinical outcomes of patients treated with tPA or placebo at 6 wk *(15)* and then at 1-year follow-up *(16)*. The incidence of death or MI at 6 wk among all patients was *higher* with tPA treatment compared with placebo (8.8% tPA vs 6.2% placebo; $p = 0.05$), however by 1 yr, there were no significant differences observed in this combined end point (12.4% tPA vs 10.6% placebo; $p = 0.24$) (Fig. 1). Subgroup analysis of patients with true unstable angina without infarction demonstrated a significant excess of death or MI at 6 wk with tPA treatment (9.1% tPA vs 5.0% placebo; $p = 0.01$). Among the subgroup of patients with NQMI, the incidence of death or MI was not different between tPA and placebo at either 6 wk or 1 yr. Thus, the TIMI III trial convincingly demonstrated that iv thrombolytic therapy produced no benefit and may even have had a detrimental effect when given in conjunction with other standard therapies to patients with unstable angina or NQMI.

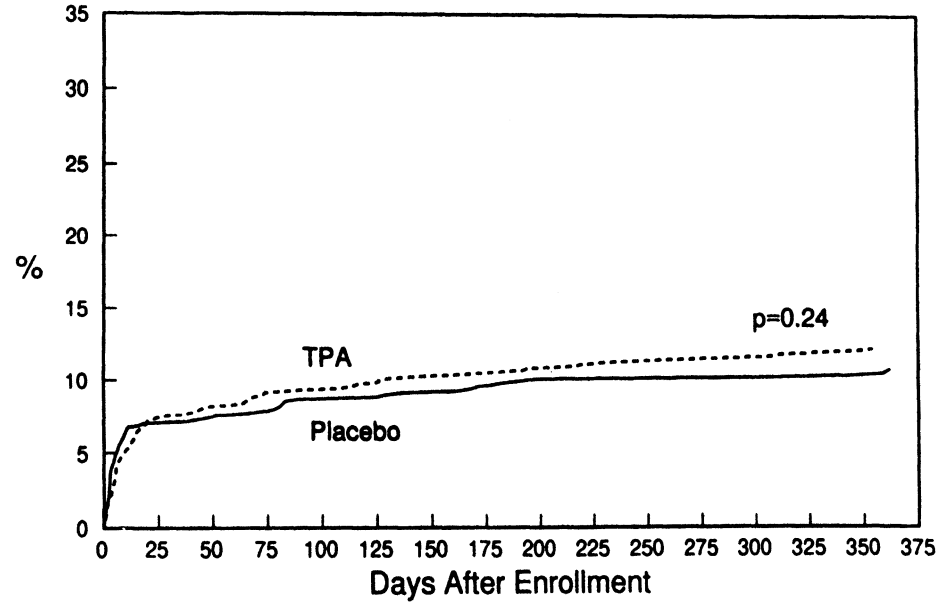

Fig. 1. Cumulative rates of death or myocardial infarction in patients with unstable angina or non-Q-wave myocardial infarction treated with tissue-type plasminogen activator (tPA) or placebo at 1 yr. Reproduced with permission from ref. *16*.

Conjunctive Use with Angioplasty

The use of PTCA in patients with unstable angina has been associated with increased complications, particularly acute closure presumably due to thrombosis at the angioplasty site *(17,18)*. The role of intracoronary thrombolytics given as prophylactic adjunctive therapy prior to PTCA to reduce the intracoronary thrombus burden, and potentially to decrease acute complications, was examined in the Thrombolytics and Angioplasty in Unstable Angina trial (TAUSA) *(19,20)*. This study randomized 469 patients with angina at rest to receive intracoronary UK (250,000–500,000 U given as a slow bolus) or placebo, prior to angioplasty. The goal was to determine the effect on thrombus, as well as the incidence of acute closure and clinical end points. All patients received aspirin and iv heparin. Treatment with urokinase significantly *increased* the incidence of acute closure (10.2% UK vs 4.3% placebo; $p < 0.02$) with no significant effect on thrombus after angioplasty. Furthermore, the administration of urokinase significantly increased the combined clinical end point of recurrent ischemia, infarction, or emergency CABG (12.9% UK vs 6.3% placebo; $p < 0.002$) (Table 2).

Despite the central role and apparent high incidence of intracoronary thrombus in the pathogenesis of unstable angina and NQMI, thrombolytic agents do not appear to be useful. Thrombolytic agents, either given in conjunction with other antianginal medications or used adjunctively with PTCA, have produced no net clinical benefits, and may even be detrimental, as evidenced in TAUSA and TIMI IIIB.

It is unclear why thrombolytic agents are not beneficial in patients with unstable angina or NQMI but are clearly beneficial in prolonging life and reducing infarct size in patients with acute Q-wave MI. Despite similar pathophysiologic mechanisms involving plaque rupture, with similar high incidences of intracoronary thrombus in both of these acute coronary syndromes, there must clearly be biologic differences that explain the

Table 2
Clinical End Points in the TAUSA Trial Demonstrating Worse Clinical Outcome with the Use of Intracoronary Urokinase in Conjunction with Angioplasty in Patients with Unstable Angina[a]

End point	*Urokinase [No. (%)]*	*Placebo [No. (%)]*	p *value*
Recurrent ischemia	23 (9.9)	8 (3.4)	0.005
(Re)infarction	6 (2.6)	5 (2.1)	NS
CABG	12 (5.2)	5 (2.1)	0.09
Recurrent ischemia, MI, or CABG	30 (12.9)	15 (6.3)	0.018

[a]CABG, coronary artery bypass grafting; MI, myocardial infarction.

opposite responses to fibrinolytic agents. It is well established that the administration of fibrinolytic agents results in a transient procoagulant state. It is possible that the procoagulant and platelet-activating effect of thrombolytic agents may act to promote thrombus propagation at the site of plaque rupture, leading to worsened obstruction and spasm in patients with unstable angina or NQMI. There may be differences in the characteristics of the thrombus found in patients with various acute coronary syndromes. The thrombus associated with unstable angina may be poorly organized or may be predominantly a platelet-rich aggregate that contains little fibrin and would therefore be relatively resistant to fibrinolytic agents *(5)*. By contrast, patients with acute Q-wave MI have been shown to have more mature erythrocyte-rich thrombi containing abundant fibrin, which are more susceptible to lysis by thrombolytic agents *(21,22)*. There are probably other differences between the coronary plaque in unstable angina and that causing acute MI that are as yet poorly understood. Further elucidation of the thrombotic milieu leading to unstable angina ought to allow for the development of novel therapeutic agents targeted to specific mechanisms.

EARLY INVASIVE VS EARLY CONSERVATIVE STRATEGIES

After patients with unstable angina and NQMI have been stabilized with aspirin, heparin, and other antianginal medications, a decision must be made regarding risk stratification. It is important to detect accurately patients with more advanced coronary artery disease who would probably benefit from early revascularization. One approach would be to perform predischarge stress perfusion testing in all patients, followed by cardiac catheterization and revascularization only in those patients with significant reversible perfusion defects. This strategy has the advantage of being more noninvasive and may reduce costs when compared with a more invasive approach of performing angiography routinely. The major limitation of this strategy lies in the limited sensitivity and specificity of perfusion imaging: 85–90% sensitivity and 70–80% specificity *(23)*. This indicates that 10–15% of patients with significant coronary artery disease will not be detected, and 20–30% of patients without significant disease will have abnormal perfusion tests, leading to unnecessary cardiac angiography.

An alternative strategy would be to perform coronary angiography in all patients with unstable angina or NQMI, with revascularization by PTCA or CABG whenever appropriate. One advantage of this approach would be the ability to employ appropriate management strategies earlier. A component of this advantage would be the high sensitivity

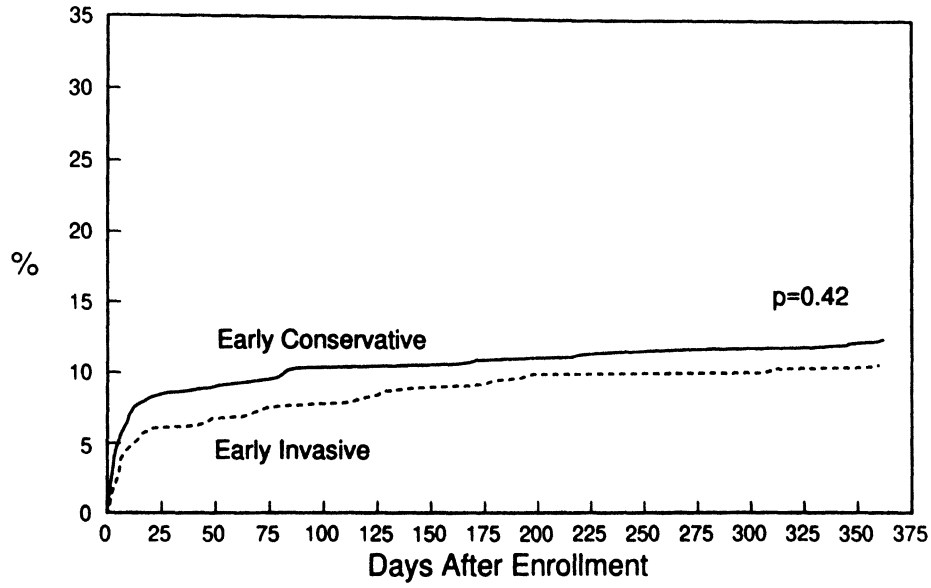

Fig. 2. Cumulative rates of death or myocardial infarction among patients with unstable angina treated with an early invasive or an early conservative strategy at 1-yr follow-up. Reproduced with permission from ref. *16*.

(approaching 100%) for detecting significant coronary lesions that would benefit from early revascularization, along with the reassurance that could be given to other patients who do not have critical coronary disease. On the other hand, routine angiography in all patients will certainly lead to "excess information" by overestimating the clinical importance of marginally stenotic vessels (60–70% diameter stenosis), which may lead to the excessive use of angioplasty.

The TIMI IIIB trial, in addition to randomizing patients either to tPA or placebo, also randomized patients in a 2 by 2 factorial design either to an early invasive or an early conservative strategy. The early invasive strategy was defined as coronary arteriography performed at 18–48 h followed by revascularization with PTCA or CABG, if appropriate, as soon as possible. The early conservative strategy was defined as coronary arteriography performed during the first 6 wk only if there was evidence of failure of initial medical therapy to prevent recurrent ischemia. After 6 wk, patient management was at the discretion of the treating physician.

By 1 yr, the performance of coronary arteriography was 100% in the early invasive strategy compared with 73% in the early conservative strategy. Coronary angioplasty was performed significantly more often by a year in the early invasive strategy compared with the early conservative strategy, although the absolute difference was small (39% invasive vs 32% conservative; $p < 0.001$). CABG was performed in 30% of patients in both groups by 1 yr. There were no significant differences in a combined end point of death or MI between patients randomized to the early invasive or early conservative strategies (10.8% invasive vs 12.2% conservative; $p = 0.42$) (Fig. 2). The early invasive strategy reduced the incidence of repeat hospitalizations at one year (26% invasive vs 33% conservative; $p < 0.05$) and significantly reduced the use of antianginal medications at 6 wk. Thus, the early invasive strategy resulted in slightly more coronary angioplasty procedures but was associated with fewer repeat hospitalizations and use of antianginal

medications. Both strategies resulted in similar incidences of death or MI and equivalence in the need for CABG. The TIMI IIIB results demonstrate that either management strategy (early invasive or early conservative) is appropriate and results in similar incidences of major cardiac events.

The fact that >60% of patients in the early conservative arm of TIMI IIIB underwent some form of revascularization by 1 yr indicates the substantial recurrence of ischemic events in this population. Early coronary arteriography after 18–48 h has the advantage of providing a definitive anatomic diagnosis, leading to an appropriate management strategy. Patients who should benefit from early revascularization, those with left main or triple vessel disease or impaired left ventricular function, are easily identified with early coronary arteriography, and revascularization can be performed in a timely manner. On the other hand, those patients without significant coronary disease can be counseled on risk factor modification, placed on appropriate medical management, and reassured of their good prognosis.

Subgroups Benefiting from Early Angiography

Subgroups of patients at high risk of developing adverse cardiac events should undergo early cardiac catheterization. These include patients with impaired left ventricular function, evidence of prior MI suggesting multivessel disease, ischemic chest pain refractory to maximal medical therapy, significant ST-segment depression on resting electrocardiogram (ECG), and large reversible perfusion defects on stress testing. Patients with unstable angina who have mildly elevated troponin T and I with normal levels of creatine phosphokinase-MB also appear to have increased risk of future events. All these patients have much higher rates of mortality and nonfatal MI than patients with low clinical risks and as such warrant an early aggressive approach.

Furthermore, there will be a group of patients who, by choice, desire early coronary arteriography to define the extent of coronary artery disease and obtain definitive treatment. The psychological impact of coronary artery disease, particularly the uncertainty and fear of not knowing the risk of future cardiac events, can be very troublesome in particular patients and can often lead to undue emotional stress. In these patients, the slightest sensation of chest discomfort results in increased anxiety and numerous visits to the physician or emergency room. Self-imposed limitations of activity, including changing their working environment to a more sedentary position and an unwillingness to perform regular activities in their home environment, can result in increased emotional stress and impaired self-esteem, the so-called cardiac cripple. For these types of patients, early angiography with appropriate revascularization would often provide the best treatment option to provide reassurance and allow for prompt resumption of their normal activities of life.

Cost Analysis

A cost analysis of TIMI IIIB has been reported *(24)*, comparing early invasive with early conservative strategies, including estimates of hospital and physician charges for the initial emergency room visit to follow-up at 6 wk. The cost per 100 patients in the early invasive strategy was estimated to be $235,367 compared with $218,409 in the early conservative strategy. This suggests a 7.2% cost savings in the early conservative arm. This analysis, however, did not take into account additional visits to doctors' offices or emergency rooms for recurrent chest pain that did not result in hospital admissions. These probably occurred more often in the early conservative arm. The economic impact of days

lost at work owing to rehospitalizations and emergency room visits would also probably increase the costs in the early conservative arm. Furthermore, between 6 wk and 1 yr of follow-up, significantly more patients in the early conservative arm underwent revascularization (6% early invasive vs 19% early conservative; $p < 0.001$) such that at 1-yr follow-up, the costs of the two management strategies would probably be equivalent.

VANQWISH Trial

The recent VANQWISH Trial (Veterans Administration Non-Q-Wave Infarction Strategies in-Hospital), compared invasive and conservative strategies in patients with non-Q-wave MI. A total of 920 patients 1–3 d after MB-CK confirmed non-Q-wave infarction to either an invasive ($n = 462$) or a conservative ($n = 458$) strategy. There was no significant difference in the primary end point of death or non-fatal MI during a 12–44-mo follow-up (average 23 mo): 26.9% in the invasive arm vs. 29.9% in the conservative arm ($p = 0.35$) *(24a)*. However, there were significantly more deaths in patients assigned to the invasive compared to the conservative strategy at hospital discharge (4.5 vs 1.3%, $p = 0.007$), which was sustained at 1 yr. Of the 21 in-hospital deaths in the invasive group, 11 followed coronary bypass surgery, indicating a 13.4% peri-operative mortality. Although this explains a great deal of the early hazard of the early invasive group in this relatively high-risk population of patients with non-Q-wave MI, similarly high peri-operative mortality rates have been recently reported from a large database in Canada. In a study of 5517 patients at all hospitals in Ontario, overall peri-operative mortality was 3.14%, but for patients with recent MI, peri-operative mortality was 12.6% *(24b)*. Of note, there were no deaths attributed to coronary angioplasty in the invasive strategy of VANQWISH. These data from VANQWISH indicate that non-Q-wave MI patients, such as those enrolled in the trial, did not benefit from a routine, early invasive management strategy, and may even be harmed. The investigators concluded that a conservative, "ischemia-guided" strategy is most appropriate in this population.

Thus, balancing TIMI IIIB and VANQWISH, one must individualize the approach for the patient population and the success rates of the coronary interventions—both angioplasty and bypass surgery. In a broad group of patients with unstable angina and non-ST elevation MI, in which angioplasty can be carried out in the majority of patients with low complication rates, an invasive strategy may be considered appropriate and more expeditious than an early conservative strategy. In patients with more severe infarction, and higher frequency of multivessel disease requiring bypass surgery, and/or at hospitals where intervention complication rates are higher a more conservative approach may be most appropriate. Given the importance of this issue, trials are currently ongoing to re-examine the relative benefits of invasive vs conservative strategies in this patient population in the current era of IIb/IIIa inhibition and coronary stenting.

REVASCULARIZATION VS MEDICAL THERAPY STRATEGIES

Fundamental to the decision to treat patients with myocardial revascularization, either early or late in the course of unstable angina, lies the presumption that revascularization is beneficial in reducing cardiac end points such as mortality, nonfatal MI, and the incidence of angina. The effect of CABG in patients with unstable angina has been evaluated in a Veterans Administration (VA) Cooperative Study *(25,26)*, which randomized 468 men with unstable angina to treatment with early CABG or medical therapy. CABG was performed a median of 5 d after randomization. Medical therapy was left to

the discretion of the treating physician. The mean age of the patients was 56 yr, with incidences of one-, two-, and three-vessel coronary artery disease of 18, 35, and 47%, respectively. At the 5-yr follow-up, no significant difference in mortality was observed among all patients; however, the subgroup of patients with triple-vessel disease had significantly reduced mortality with CABG (11% surgical vs 24% medical; $p < 0.02$). By 8 yr of follow-up, an additional subgroup of patients with refractory rest angina and impaired left ventricular function had derived significantly lower mortality from CABG (13% surgical vs 46% medical; $p = 0.04$) (Fig. 3). There were no significant differences in the incidence of nonfatal MI among any subgroup throughout the 8-yr follow-up. There were substantial crossover rates from medical to surgical therapy at 1 and 5 yr: 25 and 43%, respectively. This argues for the high incidence of failure of medical therapy in patients with unstable angina. Thus, the VA CABG trial has demonstrated a survival advantage of early CABG at least in patients with three-vessel disease and those with refractory angina and impaired left ventricular function.

There is a paucity of data from randomized clinical trials comparing PTCA with medical therapy for a reduction in major cardiac end points. In fact, no large randomized clinical trial to date, with the power to determine differences in hard cardiac end points, has compared PTCA with medical therapy in patients with either stable or unstable angina. PTCA has been shown to reduce the incidence of recurrent angina and to increase exercise duration compared with medical therapy in two randomized trials of patients with stable angina and single-vessel disease, the Angioplasty Compared to Medicine (ACME) *(27)* trial and the Medicine Angioplasty Surgery Study (MASS) *(28)*. No conclusions could be drawn with respect to mortality or the incidence of nonfatal MI, due to the small size of these trials, which enrolled approximately 200 patients each.

Numerous randomized clinical trials have compared PTCA with CABG in patients with stable and unstable angina with multivessel coronary artery disease *(29–34)*. The overall prevalence of unstable angina in these trials was 48%. These trials, including a metaanalysis *(35)* of all 3371 patients enrolled, have demonstrated that the incidence of death or MI is similar among patients treated with PTCA or CABG regardless of the number of diseased coronary vessels or ejection fraction. Therefore, since PTCA and CABG appear to be equally effective techniques for myocardial revascularization, it can be presumed that PTCA should be beneficial in a similar group of patients with unstable angina that might benefit from surgical revascularization.

CONCLUSIONS

The syndromes of unstable angina and NQMI result in significant morbidity and mortality. The high incidence of recurrent ischemic events typically mandates substantial rates of revascularization. Atherosclerotic plaque rupture with thrombus formation and coronary spasm forms the pathophysiologic basis for these syndromes. Thrombolytic agents, administered either as primary treatment or given as adjunctive therapy to angioplasty, have produced no net clinical benefit in these patients despite the high incidence of intracoronary thrombus detected. Thrombolytic therapy may actually be harmful. Initial management of these patients can be accomplished either with routine early coronary arteriography and revascularization or, alternatively, with a more conservative approach of risk stratifying patients with stress testing. Patients suspected on clinical grounds to have a high risk of developing adverse cardiac events should undergo early cardiac catheterization. Early coronary arteriography offers the advantage of clearly

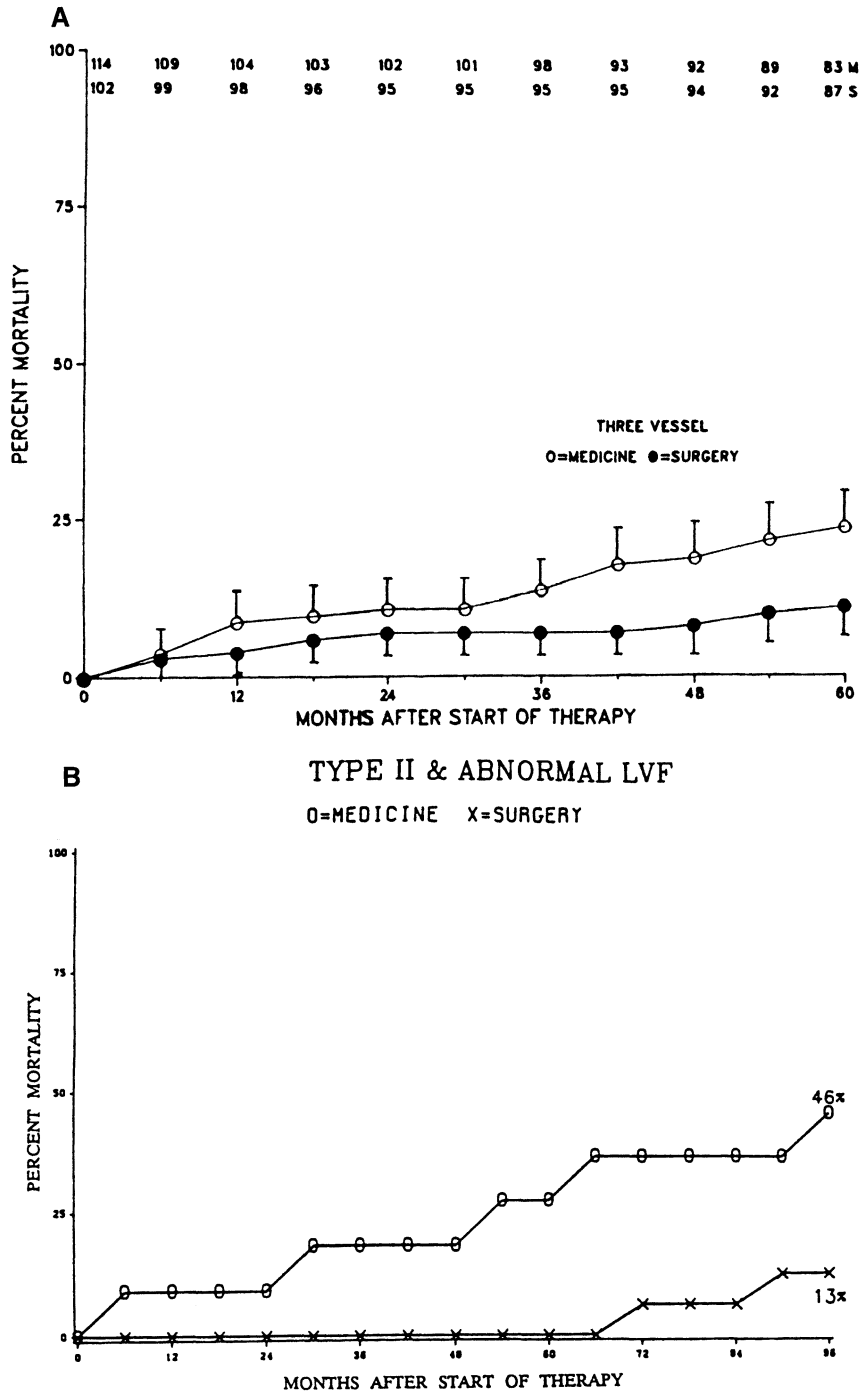

Fig. 3. Cumulative mortality of early coronary artery bypass grafting compared with medical therapy in patients with unstable angina with triple vessel disease **(A)** and with refractory rest angina and impaired left ventricular function **(B)**. Reproduced with permission from refs. *25*(**A**) and *26*(**B**).

defining high-risk patients with left main or triple-vessel disease and those with impaired left ventricular function, such that revascularization can be performed in a timely manner. The costs of invasive or conservative management strategies are probably similar. Regardless of the initial management approach, approximately 60% of these patients will eventually require revascularization within 1 yr owing to the high incidence of recurrent ischemic events.

Despite appropriate revascularization and medical therapy, the incidence rates of death and nonfatal MI were 4.3 and 8.8%, respectively, in the TIMI III trial. Although these numbers are much improved over the 1-yr natural history figures for unstable angina of 10–20% mortality and 20–30% nonfatal MI, there is still opportunity for improvement in outcomes. The use of newer interventional procedures such as coronary stents, novel antithrombotic drugs such as the direct thrombin inhibitors, new antiplatelet agents such as the glycoprotein IIb/IIIa receptor antagonists, and aggressive lipid-lowering medications may reduce the mortality and morbidity from unstable angina and NQMI to even lower, more acceptable figures.

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19 New Device Strategies in the Management of Acute Coronary Syndromes

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INTRODUCTION

Conventional percutaneous transluminal coronary angioplasty (PTCA) has been used to treat patients with coronary artery disease for over a decade now, but it is limited by a 5% rate of death or acute myocardial infarction (MI), a 2–3% rate of coronary artery bypass graft (CABG) surgery, and a 30–50% risk of restenosis *(1–4)*. These limitations are partly due to coronary artery dissection with the attendant risk of acute vessel closure, as well as the late restenotic response to injury following the uncontrolled plaque disruption and vessel stretching associated with balloon dilation.

As a result, a great deal of attention has focused on new device strategies that produce more predictable acute results and degrees of trauma. These include plaque removal (atherectomy) and mechanical support (stenting) devices, the use of which leads to larger residual lumen diameters and decreased rates of restenosis. In addition to these new devices, administration of new pharmaceuticals such as glycoprotein (GP) IIb/IIIa inhibitors may further reduce risk of acute complications in patients undergoing high-risk

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coronary interventions *(5–9)*. This chapter reviews the results of recent trials of new device strategies in the treatment of acute coronary syndromes.

GENERAL MECHANISMS OF ACTION OF NEW DEVICES

The mechanism by which percutaneous devices enlarge obstructed coronary arteries can be classified using two basic categories: *dilating devices* and *tissue removal devices*. Dilating devices displace the obstructing plaque or thrombus radially to create an expanded arterial lumen diameter. These devices generally use balloon dilation to provide the force for radial displacement; examples include conventional angioplasty balloons, heated balloons, cutting balloons, and balloon-expandable stents. Atherectomy devices work by removing the obstructing plaque or thrombus, thus expanding the arterial lumen diameter by "debulking" the lesion. Although the predominant mechanism of action with these devices is debulking the lesion, they also dilate the lesion via "Dottering" (i.e., lumen dilation that accompanies the insertion of a rigid body). Atherectomy devices may be further divided into *ablative lasers*, which remove plaque via tissue vaporization, and the *mechanical atherectomy* devices. Directional atherectomy and transluminal extraction catheters are examples of such devices that collect plaque in an isolated chamber that can be removed from the body. Rotational atherectomy, on the other hand, ablates plaque into debris <10 μm in diameter that ultimately passes through the coronary microcirculation and is then cleared by the reticuloendothelial system.

CONVENTIONAL ANGIOPLASTY

Although balloon catheters are used as adjunctive devices in most interventional therapies, they are used alone in conventional PTCA. The technical design of conventional PTCA equipment has evolved considerably in the last few years. Improvements include more supportive and flexible guiding catheters, more trackable and flexible guidewires, and improved crossing profiles of balloon catheters. These technical improvements have led to a procedural success rate of 92% and periprocedural mortality and emergency CABG rate of <1% *(10)*.

Most luminal improvement following conventional PTCA results from plaque *redistribution* and overstretching of the vessel. This frequently results in elastic recoil following balloon deflation, often leaving behind a stretched vessel with some residual stenosis *(11)*. Recent studies have shown that a larger postprocedural lumen diameter is associated with less restenosis, that is, a larger lumen at 6-mo follow-up. This observation has come to be known as "bigger is better" *(12)*. However, this benefit in late outcomes must be carefully weighed against the acute risk of coronary dissection and abrupt closure if oversized balloons are used *(13)*. By reducing and even eliminating elastic recoil, new device strategies such as stenting and directional atherectomy can provide lower postprocedural residual stenoses (0–10%), which are associated with a lower rate of restenosis. Fortunately, achieving a larger lumen diameter with new device strategies does not carry the same risk of dissection and abrupt closure as conventional PTCA.

LASER ANGIOPLASTY

Excimer laser coronary angioplasty (ELCA) utilizes light emission from optical fibers at the catheter tip to vaporize obstructing atherosclerotic tissue. This technique is used to treat complex lesions (i.e., diffuse, ostial, and vein graft lesions) not suited for conven-

tional PTCA. The New Approaches to Coronary Intervention (NACI) registry of 1000 lesions in 887 patients reported a high procedural success rate (84%) and low rates of death (1.2%), Q-wave MI (0.7%), and CABG surgery (4.5%) with ELCA *(14)*. However, in the Excimer Laser Rotablator and Balloon Angioplasty for the treatment of Complex Lesions (ERBAC) trial, a randomized trial comparing ELCA with conventional PTCA, there was an increased risk for target vessel revascularization in the ELCA group (46 vs 35% for PTCA; $p = 0.004$) *(15)*.

Failure to achieve large residual lumen diameters without adjunctive PTCA is a significant limitation of ELCA. Dissection is the major complication associated with this procedure, although it usually does not result in acute vessel closure and has been reduced by the use of saline solution flush techniques during the procedure *(16)*. The special training required in laser safety for operators and cardiac catheterization laboratory personnel also limits its use.

ATHERECTOMY

To overcome some of the limitations previously described for conventional PTCA, coronary atherectomy was developed as a method of excising or ablating atherosclerotic tissue by using directional, rotational, and extractional devices.

Directional Atherectomy

Directional coronary atherectomy (DCA) enlarges the stenotic coronary lumen by cutting and extracting the atherosclerotic tissue, and via the "Dottering" effect. Whereas initial single-center experiences reported that DCA was a highly effective interventional therapy *(17)*, subsequent randomized controlled trials of DCA versus conventional PTCA—the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT-I) *(18)*, the Canadian Coronary Atherectomy Trial (CCAT) *(20)* in native coronary lesions, and CAVEAT-II *(19)* in saphenous vein graft lesions—did not show a significant reduction in angiographic restenosis rates for DCA, although there was a trend favoring DCA over conventional PTCA in the CAVEAT-I trial (50 vs 57%; $p = 0.06$) (Table 1). The 1-yr follow-up in CAVEAT-I showed a higher mortality rate in patients treated with DCA than in patients treated with conventional PTCA (2.2 vs 0.6%; $p = 0.035$), however, these results are confounded by noncardiac deaths *(21)*. Because routine balloon postdilation was discouraged in these trials, the postprocedural residual stenosis was >25%, a value similar to that of conventional PTCA. Indeed, a multivariate analysis of CAVEAT-1 angiographic data showed the postprocedural lumen diameter to be the most significant determinant of angiographic restenosis, regardless of the device used *(22)*. The high rate of restenosis associated with DCA in these trials was attributed to the 25% residual stenoses that were not treated with routine postdilation following DCA. Thus, the goal of more recent trials has been to perform "optimal" atherectomy, in which case the postprocedure lumen diameter is made as large as possible and the residual stenosis minimized. Two recent atherectomy trials—the Balloon versus Optimal Atherectomy Trial (BOAT) and the Optimal Atherectomy Restenosis Study (OARS)—tested DCA followed by adjunctive low-pressure balloon dilation *(23–24)*. High procedural success rates 97–98% and low rates of major in-hospital complications (death, Q-wave MI, CABG surgery) (2.1–3.5%) were achieved in DCA patients with adjunctive PTCA *(23–24)*. In addition, final diameter stenosis was reduced to <10% in both trials after adjunctive PTCA. The BOAT study also confirmed a 21% relative reduction in the 6-mo angiographic

Table 1
Results from Randomized Trials Comparing PTCA with DCA[a]

	CAVEAT-I (18)		*CCAT (20)*		*CAVEAT-II (19)*	
	PTCA (n = 500)	*DCA (n = 512)*	*PTCA (n = 136)*	*DCA (n = 138)*	*PTCA (n = 156)*	*DCA (n = 149)*
Procedural success (%)	76	82*	88	94†	79	89*
Residual diameter percent stenosis (%)	36	29	33	25**	38	32**
Abrupt closure (%)	3	7	5.1	4.3	2.6	4.7
Death, Q-MI, CABG (%)[b]	4.4	5	4.4	2.1	5.7	4.7
Angiographic Restenosis (%)[c]	57	50†	43	46	46	51
Repeat revascularization* (%)	37.2	36.5	26.4	28.3	26	19

[a]Abbreviations: PTCA, percutaneous transluminal coronary angioplasty; DCA, directional coronary atherectomy; Q-MI, Q-wave myocardial infarction; CABG, coronary artery bypass grafting.
[b]In-hospital events.
[c]Follow-up at 6 mo.
*$p < 0.05$ vs PTCA.
†$p = 0.06$ vs PTCA.
**$p < 0.01$ vs PTCA.

restenosis rate for DCA with adjunctive PTCA over PTCA alone (31.4 vs 39.8%; $p = 0.01$), thereby confirming that "bigger is better" *(23)*. Because an increased postprocedural lumen diameter is such a significant correlate of reduced restenosis rates, conventional PTCA has become a common adjunct to successful but suboptimal (>10% residual stenosis) DCA procedures when the risk of additional atherectomy cuts seem to be substantial.

DCA provides a unique opportunity essentially to "biopsy" the lesion. This has demonstrated that the risk of restenosis following DCA may be influenced by other factors, such as prior cytomegalovirus infection *(25)*. DCA is well suited for the treatment of proximal accessible lesions with large lumen diameters, and it may be used in the treatment of ostial and bifurcation lesions.

Rotational Atherectomy

Rotational atherectomy utilizes a diamond-studded burr spinning at approximately 180,000 rpm to ablate atherosclerotic tissue in coronary arteries. This technique operates under the principle of differential cutting, whereby the less compliant diseased calcified tissue is preferentially abraded in preference to the more compliant nondiseased vascular tissue. The abrasive nature of lesion debulking leads to distal embolization of plaque microparticles, which are approximately 10 μm in size (i.e., smaller than a red blood cell) and generally pass through microcirculation. Occasionally, when they are liberated to the distal microvasculature in large concentrations, they can, however, cause myocardial ischemia or even infarction.

Rotational atherectomy can be an effective technique in those lesions with angiographic characteristics predictive of low success rates following conventional PTCA. These include eccentric lesions, calcified lesions, angulated lesions, ostial lesions, and possibly total occlusions. Intravascular ultrasound (IVUS) studies of rotational atherectomy have shown that improvement in lumen diameter is primarily owing to selective removal of

calcified plaque, with minimal stretching of the vessel *(26)*. Owing to the small diameter of available burrs, however, low-pressure adjunctive balloon PTCA is required in most rotational atherectomy cases *(27)*.

In the ERBAC trial, rotational atherectomy was compared with conventional PTCA in complex lesions. Rotational atherectomy had a higher procedural success rate (91 vs 80%; $p < 0.001$), a lower residual percent diameter stenosis (31 vs 36%; $p < 0.05$), a similar restenosis rate (62 vs 54%; p = NS), and a higher repeat revascularization rate at 6 mo (46 vs 35%; $p = 0.04$) compared with conventional PTCA *(15)*. A report from a 709-patient multicenter rotational atherectomy registry showed a high rate of procedural success (95%), and low rates of death (0.8%), Q-wave MI (0.9%), non-Q-wave MI (3.8%), and emergency CABG surgery (1.7%) *(28)*. There was a somewhat lower 6-mo angiographic restenosis rate (38%) in 527 patients available for repeat angiography in this registry compared with that reported in the ERBAC study *(28)*.

A pooled analysis of 5250 patients undergoing rotational atherectomy shows a 93.7% (4920 of 5250) rate of procedural success, a 0.6% (32 of 5035) mortality rate, a 1.6% (83 of 5035) rate of CABG surgery, a 1.4% (72 of 5035) rate of Q-wave MI, and a 6.8% (276 of 4033) rate of non-Q-wave MI *(15,27–36)* (Table 2). The rate of restenosis was 42% (697 of 1657) at follow-up, a rate similar to that of conventional PTCA. Although observational data suggest clinical benefits from rotational atherectomy in certain lesion subsets, no multicenter randomized trials have demonstrated its superiority over conventional PTCA. Presently, three large multicenter randomized trials—the Study to Determine Rotablator System and Transluminal Angioplasty Strategy (STRATUS), the Dilation versus Ablation Revascularization Trial (DART), and the Coronary Angioplasty versus Rotablator Atherectomy Trial (CARAT)—are comparing rotational atherectomy with conventional PTCA in a randomized fashion.

Transluminal Extraction Catheter

Transluminal extraction catheter (TEC) atherectomy enlarges the arterial lumen by cutting, aspirating, and removing thrombus, plaque, and other obstructing debris. In contrast to the discrete tissue fragments retrieved by DCA, TEC results in a slurry of blood and debris. The difficulty associated with treating highly thrombotic native coronary or saphenous vein graft lesions, distal thromboembolism, and the no-reflow phenomenon with conventional PTCA prompted the development of the TEC device and the rheolytic thrombectomy catheter.

The NACI registry has reported on the largest cohort of patients treated with this device. These results show a low device success rate (48%) but an acceptable procedural success rate with adjunctive PTCA (87%) *(37)*. As a result of the small size ($\leq$ 2.5 mm) of the TEC cutters and a limited ability to aspirate, this procedure is associated with inadequate lumen enlargement when used as a stand-alone device *(37)*.

CORONARY STENTING

Coronary stents are fenestrated stainless steel tubes expanded by balloon dilation to scaffold disrupted atherosclerotic tissue within the culprit vessel, maintain the expanded lumen diameter by supporting stretched diseased segments, and minimize contact between blood and thrombogenic subintimal tissue. Stent implantation reduces elastic recoil and medial dissection, both of which contribute to the high rates of abrupt closure and restenosis associated with conventional PTCA *(2–4)*.

Table 2
Pooled Data from Studies of Rotational Atherectomy[a]

Study	*No. of patients*	*Procedural success (%)*	*Mortality (%)*	*CABG (%)*	*Q-wave MI (%)*	*Non-Q-wave MI (%)*	*Restenosis (% patients)*
Dietz et al., 1991 *(29)*	106	73	0.0	1.9	0.0	4.7	42
Barrione et al., 1993 *(30)*	166	95	1.8	0.0	0.6	8.4	—
Gilmore et al., 1993 *(31)*	143	92	0.9	2.8	0.9	2.8	—
Guerin et al., 1993 *(32)*	67	93	0.0	1.6	1.6	6.6	—
Stertzer et al., 1993 *(33)*	346	94	0.0	1.0	2.6	—	37
Ellis et al., 1994 *(27)*	400	90	0.3	0.9	2.2	5.7	—
Safian et al., 1994 *(34)*	116	95	1.0	1.9	4.8	2.9	51
Vandormael et al., 1994 *(15)*	215	91	—	—	—	—	62
Warth et al., 1994 *(28)*	874	95	0.8	1.7	0.9	3.8	38
MacIsaac et al., 1995 *(35)*	2161	95	0.8	2.0	0.7	8.8	—
Stertzer et al., 1995 *(36)*	656	96	0.5	1.4	3.4	—	—
Total experience	5250	93.7 (4920/5250)	0.6 (32/5035)	1.6 (83/5035)	1.4 (72/5035)	6.8 (276/4033)	42 (697/1657)

[a]For abbreviations, see footnote to Table 1.
Procedural success is defined as a residual stenosis <50% with no incidence of death, Q-wave MI, or emergency CABG.
All complications (mortality, CABG surgery, Q-wave MI, non-Q-wave MI) are in-hospital.

Stents differ in composition (metallic or nonmetallic), thickness, architectural design (slotted tube vs coiled wire), and mode of implantation (self-expanding or balloon expandable). To date, almost all stents have been made from either stainless steel or tantalum. Ideally, a stent should consist of nonthrombogenic material, and it should have sufficient flexibility for passage through tortuous vessels, great radial strength, minimal metal surface area, and sufficient radiopacity for fluoroscopic visualization. Although it has been difficult to develop a single stent with all these properties, stenting procedures continue to grow in number, partly owing to the impressive early and late angiographic results achieved to date.

Coronary stent implantation was originally assessed in the treatment of focal *de novo* lesions of large native coronary arteries *(2–3)*, but recent randomized trial data suggest that it may also be superior to conventional PTCA in the treatment of proximal left anterior descending artery lesions *(38)*, focal saphenous vein graft lesions *(39)*, chronic total occlusions *(40–41)*, restenotic lesions *(42)*, and revascularization of patients with acute vessel closure following conventional PTCA *(47–51)*. In addition, observational data suggest benefits of stent deployment in aortoostial lesions *(52)*, left main lesions *(53)*, bifurcation lesions *(54)*, residual stenoses, and mild dissections following conventional PTCA.

Bail-Out Stenting

Maintaining the patency of severely injured vessels by means of mechanical scaffolding was one of the first roles envisioned for intracoronary stenting. Although techniques such as prolonged balloon inflations *(43)*, directional atherectomy *(44)*, and intracoronary thrombolytic infusion *(45)* were effective at times, MI and/or death were not infrequent sequelae of acute vessel closure prior to the introduction of coronary stenting. Indeed, the 1985/86 National Heart, Lung, and Blood Institute (NHLBI) registry showed that following acute vessel closure, 5% of patients died in hospital, 32% were sent for CABG surgery, and 42% sustained MI *(46)*. Several small randomized trials have shown stenting to be an effective bail-out technique in cases of post-PTCA acute vessel closure, which can be caused by coronary dissection, spasm, or thrombus *(47–49)*. A pooled analysis of bail-out stenting in 1033 patients (25% presenting with acute vessel closure) reported a procedural success rate of 85.6%, a mortality rate of 2.4%, an emergency CABG rate of 8.2%, an acute MI rate of 6.9%, and a stent thrombosis rate of 8.5% *(47–51)* (Table 3). Given the apparent benefits from prior historical NHLBI data, a randomized trial testing the efficacy of bail-out stenting seems highly unlikely.

Subacute Thrombosis after Coronary Stenting

A major limitation of coronary stenting in early trials was the risk of subacute thrombosis, which occasionally led to MI or death *(2,3,55,56)*. Because subacute thrombosis generally occurs late, at 2–14 d after intervention, it is more serious than abrupt closure immediately following conventional PTCA, which generally occurs while the patient is still in the cardiac catheterization laboratory. Initial efforts involving intensive anticoagulation regimens of aspirin, dipyridamole, dextran, and heparin during stent deployment and warfarin post procedure, failed to prevent subacute thrombosis and caused concurrent bleeding complications.

IVUS studies have shown that subacute thrombosis appears to arise primarily at sites of poorly supported plaque. Despite the angiographic appearance of complete stent expansion, it was observed that many stents were inadequately deployed by traditional

Table 3
Results of Large-Series Bail-Out Stenting Studies

	Schomig (Palmaz-Schatz Stent) (47)	*Palmaz-Schatz NACI Registry (48)*	*Gianturco-Roubin Multicenter (49)*	*Wiktor European Stent Study (50)*	*Total experience*
No. of patients	339	107	518	69	1,033
Indication of acute closure (%)	15	19	32	30	25
Angiographic success (%)	96.5	99	92.9	92.6	94.7
Procedural success (%)[a]	87.2	78	87.3	76.6	85.6
Death (%)[b]	1.8	4.9	2.2	2.9	2.4
MI (%)[b]	5.6	17.6	5.5	NR	6.9
CABG (%)[b]	9.1‡	3.9	7.3	14.5[d]	8.2
Stent thrombosis (%)[b]	7.0	NR	8.7	15.6	8.5
Repeat PTCA (%)[c]	16.1	6.5	8.5	21.0	12.4
Restenosis Rate (%)[c]	30	—	39	27	35

[a]Procedural success was defined as angiographic success (stent deployed and <50% residual stenosis) with no in-hospital death, myocardial infarction (MI), or coronary artery bypass grafting (CABG) surgery. Procedural success is recorded as the percentage of patients with angiographic success, since not all studies reported the procedural outcome of patients without angiographic success.

[b]All early adverse events were assessed in-hospital except for the Schomig study, which assessed early adverse event within 4 wk. NR, not reported.

[c]Six-mo follow-up data.

[d]In 26 patients (8% with successful stent deployment) from the Schomig study, and 5 patients (7.8%) from the Wiktor European Stent study, stenting was performed prior to early nonemergency CABG surgery due to uncertainty regarding subacute thrombosis risk and the extent of myocardium at risk.

Adapted with permission from ref. *51*.

balloon inflation pressures (6–8 atmospheres) and had poor apposition to the arterial wall *(57)*. However, repeat balloon inflations using higher pressures (16–20 atm) were observed to result in larger lumen diameters with complete apposition of the stent struts, thereby reducing subacute thrombosis even in patients not receiving anticoagulation therapy *(58)*. Although IVUS imaging was initially used regularly to assess adequacy of stent expansion, subsequent reports have suggested that it is not routinely needed if high-pressure balloon inflations are used *(59)*.

A variety of antithrombotic regimens including aspirin, ticlopidine, or sc heparin are being evaluated in an effort to reduce further the rates of subacute thrombosis following stent implantation. In a study by Walter et al. *(60)*, patients treated with antiplatelet therapy (aspirin plus ticlopidine) had a lower rate of adverse outcomes (death, acute MI, CABG surgery, or repeat PTCA) than patients treated with anticoagulation therapy (aspirin plus coumadin) (3.3 vs 21%; $p = 0.05$). Patients treated with antiplatelet therapy also had a lower rate of stent thrombosis at 30 d (0 vs 9.7%; $p = 0.03$) and at 6 mo (1.6 vs 14.5%; $p = 0.02$) than those treated with anticoagulation therapy. Similarly, the Stent Anticoagulation Regimen Study (STARS), a randomized trial evaluating elective Palmaz-Schatz stenting in patients treated with aspirin, aspirin and coumadin, or aspirin and ticlopidine, showed 2.9, 2.4, and 0.6 rates of stent thrombosis, respectively, at 30 d ($p < 0.05$) *(61)*. Thus, inhibition of platelet activation may be a more effective way of limiting subacute thrombosis than inhibition of the coagulation cascade. In recent trials evaluating aspirin therapy without additional antithrombotic agents—the WEST-II trial

and the Multicenter Ultrasound Stenting in Coronaries (MUSIC) trial—low rates of stent thrombosis were achieved (1.2 and 1.3%, respectively) *(62)*.

As a result of adjunctive high pressure balloon inflations and antiplatelet therapy, the rate of subacute thrombosis is now <2%. A pooled analysis of 8176 patients from 33 studies evaluating coronary stenting using aspirin and ticlopidine in the absence of acute MI shows a 1.5% rate of subacute thrombosis, a 0.8% mortality rate, a 1.1% rate of MI, and a 0.5% rate of emergency CABG surgery *(58–61,63–90)* (Table 4). Newer stent designs, such as heparin-coated stents *(91)*, may further reduce rates of subacute thrombosis as a result of coating the thrombogenic metallic surface with antithrombotic agents or biologic conduits like veins or biodegradable materials (i.e., either endogenous materials like fibrin, or exogenous materials like a polymer). Urgent PTCA is currently the preferred method of treating subacute thrombosis, particularly if a technical problem is discovered on review of the initial deployment (inadequate coverage of dissection, inadequate expansion, outflow obstruction, etc.), and CABG surgery is usually performed in refractory cases. The use of newer antiplatelet agents (e.g., either iv or oral glycoprotein (GP) IIb/IIIa inhibitors) may be an effective adjunctive treatment to prevent subacute thrombosis, but this approach has yet to be tested in a randomized study.

Coronary Stenting and Restenosis

New insights into the pathophysiology of restenosis have emerged concurrently with developments in coronary stenting. Some early animal studies suggested that intimal proliferation after arterial injury is the predominant cause of restenosis. As a result, several clinical trials tested the effect of various antiproliferative agents on coronary restenosis. These trials, however, showed no significant beneficial effect in preventing restenosis *(92)*.

The results of several recent studies have challenged the theory that intimal proliferation is the sole or predominant mechanism of restenosis following conventional PTCA. For instance, molecular studies using immunohistochemical labeling of proliferating cell nuclear antigens in human atherectomy specimens revealed minimal evidence of cellular proliferation in both primary as well as restenotic lesions following conventional PTCA *(93)*. In addition, serial IVUS imaging studies have shown intimal proliferation to be a minor contributor (30%) to late diameter loss and have demonstrated that shrinkage of the dilated segment (measured as a reduction in the cross-sectional area of the vessel subtended by the external elastic lamina) is a major contributor to lumen loss following conventional PTCA *(94)*. With respect to coronary stenting, serial IVUS studies have demonstrated that neointimal proliferation through the stent struts accounts for almost all the late diameter loss, with almost no evidence of vessel shrinkage or stent collapse *(95)*. Two large randomized trials comparing stenting (using Palmaz-Schatz stents) with conventional PTCA for the treatment of focal *de novo* native vessel lesions—the Belgium Netherlands Stent Study (Benestent-I) *(2)* and the Stent Restenosis Study (STRESS-I) *(3)*—revealed larger acute lumen diameters and a 25–30% relative reduction in the rate of restenosis after stenting compared with conventional PTCA (Table 5). Thus, coronary stenting is associated with reduced restenosis rates because it maintains expanded lumen diameters and prevents pathologic remodeling.

Although current stenting techniques have reduced restenosis, they have not eliminated it. Recently, much attention has been focused on stent designs with better scaffolding properties that may be able to minimize intimal injury and prevent subsequent restenosis. The rate of restenosis at 6 months using aspirin (without ticlopidine) with the ACS multilink stent (WEST-II trial) was lower (10%) than that found when using the

Table 4
Pooled Analysis of Stenting using Aspirin and Ticlopidine in the Absence of Acute MI[a]

Study	*No. of patients*	*Stent*	*Subacute thrombosis (%)[b]*	*Mortality (%)[b]*	*MI (%)[b]*	*CABG (%)[b]*
Jordan et al., 1994 *(63)*	132	PSS	0	—	—	—
Wong et al., 1994 *(64)*	28	PSS	0	0	0	0
Colombo et al., 1994 *(65)*	50	Wiktor	2.2	—	—	—
Elias et al., 1994 *(66)*	79	Wiktor	1.3	0	0	0
Hall et al., 1994 *(67)*	44	GRS	0	—	—	—
Aubry et al., 1994 *(68)*	643	All	2.5	3.7	3.7	1.3
Morice et al., 1995 *(69)*	1250	All	1.7	0.7	0.6	0.4
Morice et al., 1995 *(70)*	397	All	1.5	1	0.3	1
Morice et al., 1995 *(71)*	246	All	1.2	0.4	0	0.8
La Blanche et al., 1995 *(72)*	98	All	0	2	4	3
Barragan et al., 1995 *(59)*	208	PSS, GRS	0.5	1	1	0.5
Colombo et al., 1995 *(58)*	60	GRS	0	1	—	4
Wong et al., 1995 *(73)*	33	PSS	0	0	0	0
Fajadet et al., 1995 *(74)*	119	PSS	0	0.8	—	—
Blassini et al., 1995 *(75)*	60	PSS	0	0	0	0
Reifart et al., 1995 *(76)*	98	GRS	—	1	0	1
Hall et al., 1995 *(77)*	68	GRS	3	1.5	—	—
Hasse et al., 1995 *(78)*	46	PSS	0	0	0	0
Goods et al., 1995 *(79)*	152	GRS	0.7	0	0	0.7
Belli et al., 1995 *(80)*	88	—	0	0	0	0
Morice et al., 1995 *(81)*	1156	All	1.6	0.3	2.7	0.3
Caravalho et al., 1995 *(82)*	87	GRS	1.1	0	0	0
Hall et al., 1996 *(83)*	123	All	0.8	0	0.8	0
Lefevre et al., 1996 *(84)*	245	All	2	3	1.6	0
Morice et al., 1996 *(85)*	260	PSS	1.2	—	1.9	0.4
Goods et al., 1996 *(86)*	296	GRS	0.7	0.3	—	0.7
Marco et al., 1996 *(87)*	18	GRS—II	0	0	0	0
Elias et al., 1996 *(88)*	240	Wiktor	3.6	1.2	—	1.2
Elias et al., 1996 *(88)*	182	Wiktor	1	1	—	0
Walter et al., 1996 *(89)*	257	PSS	0.8	0.4	0.8	0
Leon et al., 1996 *(61)*	244	PSS	0.6	—	—	—
Moussa et al., 1997 *(90)*	1042	All	1.9	—	—	—
Nakamura et al., 1997 *(59)*	127	All	3.1	—	3.1	0.8
Total experience	8176	—	1.5% (n = 121)	0.8% (n = 63)	1.1% (n = 86)	0.5% (n = 38)

[a]Abbreviations: GRS, Gianturco-Roubin stent; PSS, Palmaz-Schatz stent; see Table 1 footnote.
[b]All event rates (mortality, MI, CABG) are in-hospital.

Palmaz-Schatz stent (MUSIC) (13%), despite the inclusion of smaller vessels and a greater number of patients with unstable angina in the WEST-II trial *(62)*. Another recent report on 55 patients by Teirstein et al. *(96)* suggests that stents emitting radiation may be more effective in reducing angiographic restenosis (17 vs 54% for conventional stenting; $p = 0.01$) by reducing intimal hyperplasia. The optimal dose and type of radiation is a critical issue that remains to be determined.

Primary Stenting in Acute Myocardial Infarction

Several current reperfusion trials are focusing on the use of intracoronary stenting in acute MI. By reducing residual stenoses, relieving intraluminal obstruction, and sealing

Table 5
Multicenter Randomized Trials Comparing Conventional PTCA with Stenting[a]

	STRESS[b]		*Benestent*[c]	
Results	*PTCA (n = 202)*	*Stent*[d] *(n = 205)*	*PTCA (n = 257)*	*Stent*[d] *(n = 259)*
Procedural success (%)[e]	90	96	91	93
Residual stenosis (%)	35	19	33	22
Mortality (%)	1.5	0	0	0
Q-wave MI (%)	3.0	2.9	0.8	1.9
Non-Q-wave MI (%)	2.0	1.5	2.3	1.5
CABG (%)	4	2	3.9	3.1
Repeat PTCA (%)[f]	22	14	27	18
Angiographic restenosis (%)	42	31	32	22

[a]Abbreviations: PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; CABG, coronary artery bypass grafting.

[b]Patients presented with stable or unstable angina and native coronary lesions ≥3.0 mm in diameter.

[c]Patients presented with stable angina and native coronary lesions ≥3.0 mm in diameter.

[d]All patients receiving stent implantation (Palmaz-Schatz) were treated with warfarin.

[e]Procedural success was defined as a residual stenosis <50% with no death, MI, or emergency CABG while in hospital.

[f]Repeat PTCA was performed in patients with >50% angiographic stenosis presenting at least 4 mo after treatment.

[*]$p < 0.005$.

dissection planes created by PTCA, primary stenting may provide additional short- and long-term benefits in acute MI. Despite concerns of stent thrombosis in the setting of acute MI, initial experiences with primary stenting have revealed favorable results thus far. A pooled analysis of 1357 patients from 20 nonrandomized studies of primary stenting shows a mortality rate of 2.4%, a reinfarction rate of 1.1%, an emergency CABG rate of 1.3%, and a stent thrombosis rate of 1.5% (using ticlopidine) of patients *(97)*. In the recent Primary Angioplasty in Myocardial Infarction (PAMI) Stent Pilot trial involving 240 patients undergoing primary stenting, high rates of procedural success (98%) and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow (96%) and low rates of in-hospital mortality (0.8%), reinfarction (1.7%), recurrent ischemia (3.8%), rethrombosis (1.7%), and repeat revascularization (1.3%) were reported *(98)*. However, TIMI grade 3 flow was defined as vessel opacification within three cardiac cycles, which is a significant departure from the definition used by the TIMI study group *(99)*.

Limitations

The preprocedural arterial lumen size remains a major issue in stenting procedures. A metaanalysis of the Benestent-I and STRESS-I/II trials showed that arteries <2.6 mm and >3.4 mm in diameter (the smallest and largest quintiles treated) did not have better restenosis rates than arteries treated with conventional PTCA *(100)*. A pooled analysis of quantitative angiographic data from the TIMI 4 and 10 trials shows that 69% of patients presenting with acute MI had a proximal reference segment diameter (PRSD) > 2.75 mm, and 56% had a PRSD > 3.0 mm *(97)*. Despite recent advances in stenting techniques, the fact that smaller vessels may derive reduced benefits from coronary stenting owing to

greater risks of subacute thrombosis and intimal hyperplasia remains a significant challenge in coronary stenting.

Another challenge associated with stenting involves the treatment of in-stent restenosis. Although balloon angioplasty is the most common method of treating in-stent restenosis and is associated with a >90% procedural success rate, it has been observed to have a high rate of restenosis (54%) *(101)*. This is perhaps because balloon angioplasty of in-stent restenosis works by compressing and extruding the intimal tissue rather than by expanding the stent.

Although the stenting of highly thrombotic lesions is generally avoided, in a recent trial stents were placed in 86 thrombus-containing lesions in patients with acute coronary syndromes. Even so, there was a low rate of subacute thrombosis (1%) and restenosis (33%) *(102)*. In addition to the risk of subacute thrombosis, other potential limitations of stenting include side branch occlusion, stent embolization, inadequate access to more distal disease and significant side branches after stent implantation, the occasional inability to deliver a stent to the target lesion, and the potential for the wire to become entrapped in stents while recrossing. The impact of stenting on subsequent bypass procedures is unknown.

Many new stent designs currently under investigation include welded tubular stents, integrated flexible-coil stents, interlocking coil-strut stents, self-expanding stents, and radiation-emitting stents. Although it is unlikely that any single design will be suitable for all patients, diversity in composition and structure are likely to offer the interventionalist a wide variety of options in the future.

NEW PHARMACOTHERAPEUTIC THERAPIES DURING INTERVENTIONAL PROCEDURES

Combined aspirin and heparin is the most frequently used antithrombotic therapy during coronary angioplasty to achieve and maintain activated clotting times (ACTs) >350 s. Because thrombin is generated during PTCA and potentially activates platelets, direct thrombin inhibitors (hirudin and hirulog) were developed as agents that could potentially inhibit platelet activation.

Despite these theoretical benefits, several multicenter trials have been unable to demonstrate that hirudin is a superior antithrombotic agent compared with heparin *(103–108)*. Although hirudin has a greater potential to reduce thrombin activity by inhibiting both fluid-phase and clot-bound thrombin, heparin has a greater potential to inhibit earlier steps in the coagulation cascade. The net result may be an equal decrement in thrombus deposition within the culprit vessel. Although not significantly more efficacious than heparin, direct thrombin inhibitors may be safer than heparin.

Whereas multiple pathways exist for platelet activation, a single receptor (the glyGP IIb/IIIa receptor) on the platelet surface mediates the final common pathway of platelet aggregation. By preventing the platelet GP IIb/IIIa receptor from binding fibrinogen to crosslink platelets, GP IIb/IIIa inhibitors seem quite promising as adjunctive antiplatelet agents during coronary interventions.

One particular GP IIbI/IIa inhibitor, the monoclonal antibody c7E3 (abciximab or Reopro), was evaluated in the Evaluation of Abciximab for the Prevention of Ischemic Complications (EPIC) trial, a randomized controlled trial of 2099 patients undergoing high-risk PTCA or directional atherectomy. The results showed a 35% reduction in clinical events (freedom from death, nonfatal MI, and urgent intervention) at 30 d for patients treated with an abciximab bolus and a 12-h infusion (8.3% events) vs placebo

(12.8% events) ($p < 0.01$) *(5)*. The reduction of clinical events in the abciximab bolus and infusion group remained evident at 6 mo (23%; $p = 0.001$) and at 3 yr (13%; $p = 0.009$) *(6)*. These long-term results favoring abciximab were largely driven by a reduced need for repeat revascularization, and not by death or reinfarction. Although it has been claimed that the drug reduced the incidence of "clinical restenosis," the true rate of angiographic restenosis in patients treated with abciximab was not determined in this trial. Major bleeding complications were twice as frequent in the abciximab bolus and infusion group (14%) than in the placebo group (7%; $p = 0.001$) *(5)*. The risk of excessive bleeding with abciximab tended to be greater in patients with higher ACT levels, lower body weights, and higher doses of heparin *(5)*.

Given this bleeding risk, lower doses of weight-adjusted heparin were used in the Evaluation in PTCA to Improve Long-term Outcome with Abciximab GP IIb/IIIa Receptor Blockade (EPILOG). This randomized prospective multicenter placebo-controlled trial of 2792 patients undergoing elective PTCA evaluated lower doses of weight-adjusted heparin. The results again revealed favorable outcomes with abciximab, with no significant increase in bleeding complications *(7)*. At 30 d, abciximab again significantly reduced the incidence of the composite end point (acute MI, urgent revascularization, or death; 5.2% in the abciximab and low-dose heparin group vs 11.7% in the placebo and standard-dose heparin group; $p < 0.0001$), but this did not come at the expense of excess bleeding (2.0 vs 3.1% for placebo; p = NS) *(7)*.

In addition to monoclonal antibody inhibitors, some synthetic agents like eptifibatide (Integrilin) and tirofiban (MK-383, Aggrastat), appear to be promising GP IIb/IIIa inhibitors of platelet aggregation. In the Integrilin to Manage Platelet Aggregation to prevent Coronary Thrombosis (IMPACT-II) trial of 4010 patients undergoing PTCA, the 30-d clinical event rate (death, acute MI, or repeat PTCA) tended to be lower in patients treated with a low-dose bolus and infusion of Integrilin than in the placebo group (9.2 vs 11.4%; $p = 0.06$), with no significant increase in bleeding complications *(8)*. The benefits were especially evident in patients undergoing elective procedures. In patients treated with high-dose bolus and infusion Integrilin, there was no significant reduction in the 30-d clinical event rate.

In the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) of 2139 patients, there was a 38% relative reduction (5.4 vs 8.7% in the placebo group; $p = 0.005$) of the composite end point (death, acute MI, repeat revascularization, or stent placement) at 2 d, and a 27% relative reduction at 7 d ($p = 0.02$) in patients treated with tirofiban, with no significant increase in bleeding complications *(9)*. At 30 d and 6 mo, the 3% difference in absolute event rates was unchanged, and the reduction in the event rates tended to be significant *(9)*. When the end point was constructed to be consistent with that in other trials (i.e., urgent revascularization rather than repeat revascularization), a significant difference in event rates was maintained (8.0 vs 10.5% for placebo; $p = 0.05$) *(9)*. The RESTORE study is the only angiographic substudy to evaluate the risk of restenosis following GP IIb/IIa inhibition, and there was no significant difference in the rate of restenosis between treated and control patients *(109)*.

A pooled analysis of 11,040 patients in trials of GP IIb/IIIa inhibitors during interventional procedures shows lower 30-d (7.8 vs 11.4%; $p < 0.001$) and 6-mo (26.2 vs 29.6%; $p = 0.001$) event rates, but a higher rate of bleeding complications (5.9 vs 4.3%; $p = 0.001$) for GP IIb/IIIA inhibitors when compared with placebo *(5–9,109)* (Table 6). Several orally bioavailable synthetic inhibitors of GP IIb/IIIa have been developed and are being tested in clinical trials.

Table 6
Trials of GP IIb/IIIa Inhibitors During Interventional Procedures[a]

Trial	No. of patients	30-day composite end point[b]			30-day major bleeding			6-month composite end point[c]		
		Drug (%)	Placebo (%)	p value	Drug (%)	Placebo (%)	p value	Drug (%)	Placebo (%)	p value
EPIC[d]	2099	8.3	12.8	0.008	14.0	6.6	0.001	27.0	35.1	0.001
EPILOG[e]	2792	5.2	11.7	<0.001	2.0	3.1	0.19	22.8	25.8	0.07
IMPACT-II[f]	4010	9.2	11.4	0.06	4.8	5.1	NS	30.1	31.5	NS
RESTORE[g]	2139	10.3	12.2	0.16	5.3	3.7	0.09	24.1	27.1	0.11
Total experience	11,040	8.4 (341/4063)	11.9 (479/4033)	<0.001	5.9 (240/4063)	4.3 (175/4033)	0.001	26.2 (1057/4029)	29.6 (1183/3999)	0.001

[a]Abbreviations: GP, glycoprotein; PTCA, percutaneous transluminal coronary angioplasty; DCA, directional coronary atherectomy; MI, myocardial infarction.
[b]Death, MI, or urgent revascularization.
[c]Death, MI, or repeat revascularization.
[d]c7E3 bolus and infusion vs placebo in high-risk PTCA/DCA.
[e]c7E3 with low-dose heparin vs placebo in elective PTCA/DCA.
[f]Integrelin (low-dose bolus and infusion) in elective and high-risk PTCA/DCA except elective stents (randomized group).
[g]Tirofiban bolus and infusion vs placebo in high-risk PTCA/DCA.

FUTURE DIRECTIONS

The remarkable development of new devices for coronary revascularization over the last decade has led to considerable expansion in the number of patients treatable using interventional procedures and also to improvements in short and long-term outcomes. Indications and methods of use for the current devices will continue to be refined, with randomized trials playing a major role. Newer technologies directed at plaque removal or modification with minimal arterial injury and site-specific drug delivery systems that could inhibit thrombosis and restenosis are likely to be developed. In addition, adjunctive technologies like IVUS and angioscopy will be refined to allow more precise guidance of interventional devices, as well as optimal plaque ablation and remodeling while limiting arterial injury. Finally, an increased understanding of vascular biology, thrombosis, and restenosis will lead to pharmacologic therapies designed to ameliorate adverse thrombotic, proliferative, and remodeling responses.

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V Special Aspects of Acute Coronary Syndromes

20 Women and Acute Coronary Syndromes

Alice K. Jacobs, MD

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INTRODUCTION

Cardiovascular disease remains the leading cause of death in women in the United States and claims the lives of approximately 500,000 women annually *(1)*. In addition, despite an overall reduction in the death rate due to cardiovascular disease in this country, the rate of decline is less for women than for men, and, due to an aging population, the absolute number of deaths due to cardiovascular disease has actually increased in women *(2)*. During the past several years, with the focus on women's health in general and heart disease in women in particular, there is an increased awareness of the problem. Thus the management of women with coronary heart disease has come under close scrutiny, and gender differences in the presentation, evaluation, access to care, management, and acute and long-term outcome of patients with acute coronary syndromes has been under active investigation.

Therefore, the goal of this chapter is to review briefly the epidemiology, risk factors, clinical presentation, and evaluation of women with coronary heart disease, discuss the general considerations of gender differences in patients with acute ischemic syndromes undergoing coronary revascularization in terms of baseline clinical and angiographic characteristics and acute and long-term outcome, and focus on specific considerations of gender differences in patients treated with thrombolytic therapy, particularly in patients with ST-segment and non-ST-segment elevation myocardial infarction.

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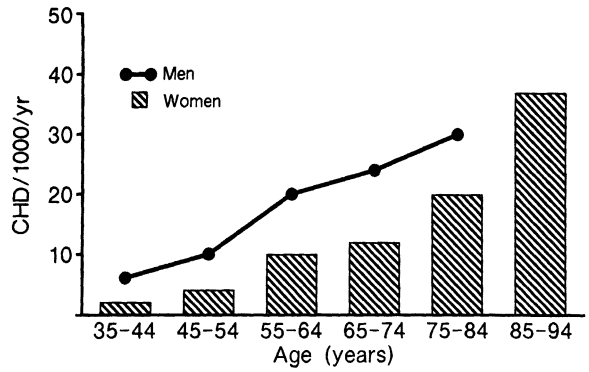

Fig. 1. Relationship between annual rate of coronary heart disease and age in women and men in the Framingham Heart Study. CHD, coronary heart disease. Reproduced with permission from ref. *3*.

EPIDEMIOLOGY

As in men, the incidence of coronary heart disease increases with age in women (Fig. 1), although the clinical presentation of the disease lags 10 years behind that in men *(3)*. Coronary heart disease has been the leading cause of morbidity and mortality in women since the early 1900s, accounting for the death of 52% of women in the United States compared with 46% of men. Despite the female advantage in age-specific risk of death owing to coronary heart disease, the greater survival to advanced age in women produces equal numbers of death in women and men *(2)*. Moreover, although the incidence of myocardial infarction is higher in men than in women at any age (Fig. 2), the risk of death and reinfarction following a nonfatal myocardial infarction is higher in women than in men *(4)*.

RISK FACTORS

The traditional and well-studied risk factors for coronary heart disease in men, namely, hypertension, diabetes mellitus, hypercholesterolemia, cigarette smoking, a family history of premature coronary disease, and obesity appear to be operative in women as well. However, in the presence of any of the risk factors, the incidence of coronary heart disease is higher in men than in women *(3)*. For example, although the incidence of coronary heart disease is higher among men than among women with systolic hypertension, the relative risk of coronary heart disease (in comparison with a gender-matched population without hypertension) is the same in women and men. Furthermore, women have a higher incidence of hypertensive heart disease than men *(5)*. Women with diabetes mellitus have twice the risk of myocardial infarction as nondiabetic women and the same risk of a myocardial infarction as a nondiabetic male of the same age *(3)*.

It is noteworthy that cigarette smoking remains the leading cause of preventable coronary heart disease in women and that over 50% of myocardial infarctions occurring among middle-aged women are attributable to smoking *(2)*. The magnitude of excess risk is similar in women and men and is related to the number of cigarettes smoked. Moreover, the risk of coronary heart disease declines toward normal within 3–5 yr following smoking cessation. Although the prevalence of current smoking is similar in women and men with acute coronary syndromes undergoing revascularization, the prevalence of former smoking is higher in men and is in concert with reports documenting a slower decline in

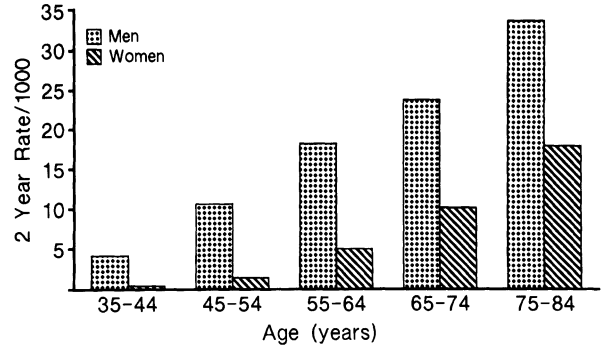

Fig. 2. Relationship between age and incidence of myocardial infarction in women and men in the Framingham Heart Study. Adapted with permission from ref. *4*.

smoking cessation rates in women *(6)*. These unfavorable smoking patterns in women, particularly among young women, have widespread implications.

CLINICAL PRESENTATION

Whereas almost two-thirds of men with coronary heart disease present with myocardial infarction or sudden death as the initial manifestation of disease, over 50% of women may have angina pectoris as their first symptom *(7)*, yet establishing the diagnosis of ischemic heart disease in women remains problematic. This is owing in part to the relatively high prevalence of chest pain among women who do not have significant coronary artery disease.

To address this issue, several studies have evaluated the predictive value of chest pain, based on angiographic assessment of coronary anatomy; a poor correlation between chest pain symptoms and angiographic evidence of disease has been reported *(8)*. At best, a clinical history of angina correlated with angiographic disease only one-half of the time in women. Even when unstable symptoms were present, the correlation was no better than 59%. The best correlation occurred in women thought not to have angina by history in whom coronary artery disease was absent 95% of the time. Some added predictive value occurred when women were stratified by risk factors. For example, significant coronary artery disease was found in 55% of women with two or more risk factors, but only 7% of women with fewer than two risk factors *(9)*.

The diagnostic value of chest pain in women was also evaluated in the Coronary Artery Surgery Study (CASS) *(10)*. In this study, definite angina, probable angina, probably not angina, and definitely not angina were carefully defined. Over 20,000 patients, of whom 4000 were women, were prospectively enrolled in this study, and all underwent coronary angiography to define coronary disease prevalence. Significant coronary disease, defined as at least 70% coronary artery stenosis, was found in 72% of the women with definite angina and 36% of the women with probable angina. The other two categories, probably not angina and definitely not angina, were combined under a category of nonspecific chest pain, and 6% of the women so classified had significant coronary artery disease. In men, a similar classification resulted in significantly different prevalence rates of 93%, 66%, and 14%, respectively.

Therefore, chest pain in women is neither sensitive nor specific in predicting the presence of underlying coronary artery disease. The highest sensitivity is found in women

presenting with symptoms of typical angina pectoris, whereas the highest specificity is found in women presenting with nonspecific symptoms of chest pain.

The magnitude and frequency of anginal chest pain as well as nonspecific chest pain in the absence of clinically significant coronary artery disease is of practical importance but remains largely unexplained. Recent studies of the control of coronary blood flow suggest that endothelial vasomotor dysfunction of epicardial and resistance coronary arteries may contribute to myocardial ischemia even in the presence of angiographically smooth or only mildly stenotic coronary arteries by contributing to pathologic coronary constriction or failure to dilate appropriately under conditions of increased demand *(11)*. Reduction of circulating estrogen following menopause is associated with profound impairment of endothelial vasodilator function *(12)*. For these reasons, vasomotor dysfunction probably plays a more important role in the production of ischemia in women than in men, and reliance on simple angiography may be inadequate. The relationship of these abnormalities to clinical outcomes remains undefined.

NONINVASIVE EVALUATION

In general, noninvasive evaluation of coronary artery disease in women is less accurate than in men, due primarily to a lower prevalence of disease and of multivessel disease in women. The most widely employed and best studied test modality is the exercise treadmill test *(13)*, and it is predictably problematic in women due to a lower prevalence of coronary artery disease in premenopausal women, a higher prevalence of mitral valve prolapse and hyperventilation-induced ST-segment depression, a higher incidence of hypertensive heart disease, and limited ability to exercise to an adequate heart rate response. Myocardial perfusion imaging with thallium has improved sensitivity, but breast tissue attenuation of radioactivity may result in false-positive results in women *(14)*. Exercise echocardiography appears promising in women and is more specific than exercise electrocardiography *(15)*. In addition, the presence of a new echocardiographic wall motion abnormality following dobutamine administration has been found to be a highly specific manifestation of ischemia, even in women *(16)*. Furthermore, three-dimensional imaging with magnetic resonance or positron emission tomography as well as electronic beam computed tomography are under active investigation in women *(17)*.

GENDER DIFFERENCES IN REFERRAL PATTERNS

It has been suggested that women are referred for coronary angiography (and subsequent revascularization) less often or later in the course of their disease than men. The reason for these apparent gender-related differences in patient management are unclear, but a true gender bias (presumably on the part of physicians) has been implicated. In a prospective postinfarction trial, women underwent cardiac catheterization only half as often as men, despite controlling of variables of comorbid disease, severity of angina prior to myocardial infarction, and advanced age *(18)*. In another report, women in Massachusetts and Maryland were significantly less likely than men to undergo coronary angiography or revascularization procedures when admitted to a hospital with a diagnosis of myocardial infarction, unstable angina, chronic ischemic heart disease, or chest pain *(19)*. Even when objective evidence of ischemic heart disease was based on nuclear exercise testing and findings were similar in women and men, follow-up coronary angiography was recommended less often in women *(20)*. More recently, several studies have corroborated these findings, reporting that women with both acute myocardial

infarction and unstable angina were less likely to undergo coronary angiography and revascularization than men *(21–25)*. Whether the difference in the use of angiography and revascularization for women and men represents appropriate use of procedures in women and or inappropriate use in men (or the contrary) is unclear. In addition, whether these perceived gender differences in the use of invasive testing are based on the limited predictive value of noninvasive diagnostic studies in women or the uncertainty surrounding the chest pain syndrome is unknown. Most of these studies were retrospective reviews, the diagnosis was based on hospital discharge diagnosis codes, and much of the gender differences in management were accounted for by advanced age in women. Furthermore, it is unclear whether the decisions were made for women or by women and were based on complex sociocultural factors.

GENERAL CONSIDERATIONS

Although the epidemiology of coronary heart disease and coronary risk factor profile is similar in women and men, when patients present with acute coronary syndromes (or stable angina) in need of revascularization, there are numerous and remarkably consistent gender differences in baseline characteristics and acute and long-term outcome. As expected, women are older than men and have a higher risk profile and undergo coronary revascularization at increased risk for an adverse outcome *(26)*. However, although patients undergoing revascularization with coronary angioplasty and coronary bypass surgery more recently are older with more advanced comorbid disease and complex coronary anatomy, the outcome of women continues to improve *(27)*.

Gender Differences in Patients Undergoing Coronary Revascularization

Baseline Clinical and Angiographic Characteristics

Gender differences in patients with coronary heart disease undergoing surgical (Table 1) *(28–33)* or percutaneous (Table 2) (34–40) revascularization or treatment with thrombolytic therapy *(41)* and primary coronary angioplasty *(42)* have been extremely consistent in virtually all published reports. Women are older (with more women older than 65 yr) and have a higher prevelance of hypertension, diabetes mellitis, and hypercholesterolemia than men. Fewer women have had prior myocardial infarction, and the prevalance of left ventricular dysfunction is lower in women than in men. In addition, women have a higher incidence of comorbid disease, and fewer women are judged to be candidates for surgical revascularization in comparison with men.

Large-scale studies of patients undergoing revascularization have also consistently shown that women have a significantly higher incidence of congestive heart failure than men *(43)*. This is contrary to what one would predict since women have an overall higher left ventricular ejection fraction, which probably reflects a history of fewer previous myocardial infarctions. This "gender paradox" has been explained by the finding of a steep left ventricular pressure–volume relationship in women in comparison with men and diastolic dysfunction, perhaps on the basis of hypertension and diabetes *(44)*. Whether this diastolic function is related to ischemia in women is unclear, especially since there is a significantly lower incidence of triple vessel coronary disease in women in comparison with men.

Despite the possibility of gender-related differences in referral patterns for the use of diagnostic cardiac catheterization, when women present for coronary angiography, they

Table 1
Gender Differences in Baseline Clinical Characteristics in Patients Undergoing Coronary Bypass Surgery[a]

Authors	Patients Sex	Patients No.	Mean age (years)	Hypertension (%)	Diabetes mellitus (%)	CHF (%)	Unstable angina (%)	Reduced LVEF (%)
Tyras	W	241	53.9	36.5	19.3	-	89.7[b]	22.3
et al. *(31)*	M	1300	52.0**	33.3	15.7	-	78.8**	31.3**
Douglas	W	492	57.6	48.0	19.0	-	62.0	31.0
et al. *(32)*	M	2663	54.2**	34. 0**	10.0**	-	65.0*	40.0*
Fisher	W	1153	57.8	-	-	9.5	51.4	14.0
et al. *(51)*	M	6258	54.4	-	-	5.0**	39.1**	23.1**
Loop	W	2445	57.0	14.6	10.1	-	59.6	40.3
et al. *(33)*	M	18,079	54.0**	13.7	6.6**	-	44.8**	47.4**
Kahn	W	482	68.2	63.0	26.0	41.7	76.1	-
et al. *(30)*	M	1815	64.0**	49.0**	20.0**	33.1**	69.8*	-
Hannan	W	3169	66.4	57.8	27.8	-	19.5	47.7
et al. *(48)*	M	9279	62.7**	46.6**	17.3**	-	13.4**	53.0**
Rahimtoola	W	1979	64.0	58.0	22.0	-	34.0	45.0
et al. *(59)*	M	6927	61.0**	41.0*	12.0**	-	30.0**	52.0**

[a]Abbreviations: CHF, congestive heart failure; LVEF, left ventricular ejection fraction; M, men; W, women.
[b]Class III or IV angina.
* $p < 0.05$.
** $p < 0.005$ men vs women.
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Table 2
Gender Differences in Baseline Clinical Characteristics in Patients Undergoing Coronary Angioplasty[a]

Authors	Patients Sex	Patients No.	Mean age (years)	Hypertension (%)	Diabetes mellitus (%)	Hyper cholesterolemia (%)	Prior MI (%)	CHF (%)	Unstable angina (%)
Cowley	W	705	56.3	44.9			22.4		48.2
et al. *(34)*	M	2374	52.6*	32.3[b]			25.7		37.0*
McEnierly	W	969	61.0	56.0	6.4	20.0	32.0		65.0
et al. *(35)*	M	2727	57.0	39.0**	3.5+	19.0	34.0		61.0**
Bell	W	1106	66.0	58.0	18.8	40.5	53.4	9.0	74.5
et al. *(37)*	M	2965	61.0**	40.9**	11.7*	28.5**	55.8	5.0**	68.4**
Kelsey	W	546	61.0	57.8	20.2	39.9	31.5	8.6	60.4
et al. *(36)*	M	1590	56.5*	41.7**	11.0**	32.3*	36.8	4.2**	49.9**
Weintraub	W	2667	61.0	54.0	19.0		31.0	4.1	70.0[b]
et al. *(104)*	M	7619	56.0**	39.0**	11.0**		35.0**	1.9**	57.0**
Kahn	W	2033	64.0		23.0				53.0[b]
et al. *(38)*	M	7142	59.0		12.0**				36.0**
Malenka	W	3982	64.7	60.5	30.3	59.9	28.5		51.6
et al. *(39)*	M	8250	59.4*	47.3*	17.2*	54.9*	32.0*		42.7*

[a]Abbreviations: CHF, congestive heart failure; M, male; MI, myocardial infarction; W, women.
[b]Class III or IV angina.
* $p < 0.01$.
** $p < 0.001$ men vs women.

have no more, and in many instances less, angiographic evidence for coronary artery disease than their male counterparts *(36,43)*. This is unexpected on the basis of age and risk factor profile in women. These findings support the concept that the traditional risk factors are less potent in women than in men. Whether this is due to a protective effect of estrogen in women is unclear. However, when reviewing the magnitude of the gender difference in coronary heart disease mortality across the life span, it is apparent that there is an exponential increase in mortality with an increase in age that is similar for both women and men and that there is no detectable alteration in this relationship for women around the age of menopuase *(3)*.

It is also noteworthy that on presentation for revascularization, women have a higher level of functional disability in terms of anginal chest pain, despite a similiar (or lesser) extent of disease. Specifically, women have evidence of more severe angina (Canadian Cardiovascular Society class III or IV) and unstable angina than men *(29,36,39)*. This was most clearly demonstrated in the CASS registry, in which the severity of angina among women was stratified according to the number of vessels diseased. Independent of the extent of the disease, women had more severe angina than men *(43)*. This phenomenon has traditionally been attributed to the documented gender difference in the timing of referral for angiography. However, this is an unlikely explanation because when eventually studied, women have no more extensive epicardial coronary artery disease than men. It is more likely that the higher incidence of unstable angina is based on gender differences in the pathophysiology or pathobiology of the ruptured plaque *(45,46)*.

In studies reporting detailed angiographic characteristics, coronary lesion morphology and the distribution of lesions appearsto be similiar in women and men, although women tend to have more ostial lesions and calcified lesions than men *(36)*. As expected, coronary artery diameter is smaller in women in comparison with men (29,47).

Acute Outcome

Despite improvements in myocardial protection and advances in surgical techniques, gender differences in in-hospital mortality following coronary artery bypass surgery have persisted and have been notably consistent during the past 20 yr (Table 3). Specifically, in-hospital mortality is approximately $2^1/_2$-fold higher in women in comparison with men and is only partially explained by older age and a higher risk profile in women *(28–33,48)*. Although earlier studies suggested that women received fewer saphenous vein grafts and less complete revascularization *(31,32)*, more recently, the extent of revascularization has been similar in women and men *(49)*. However, women do receive fewer internal mammary artery conduits *(30)*, which is unexplained by clinical status, presence of diabetes mellitus, or degree of left anterior descending artery disease *(50)*. In fact, absence of internal mammary artery grafting has been shown to be associated with increased risk of death from heart failure in women *(29)*.

The excess mortality in women has been attributed to more urgent or emergency procedures due to unstable symptoms, greater technical difficulty in operating in women, and differences in diagnosis and treatment of coronary artery disease *(29)*. In addition, smaller coronary vessel diameter has been implicated, and several studies have reported that when body surface area (a surrogate for vessel size) is considered, female gender is no longer an independent predictor of in-hospital mortality *(29,51,52)*. Congestive heart failure has been shown to be independently associated with mortality *(49)*, particularly in women, and excess mortality in women has been attributed to death from heart failure and to a lesser extent from hemorrhage *(29)*.

Table 3
Gender Differences in Operative Mortality
in Patients Undergoing Coronary Artery Bypass Surgery

Author	Patients		Years	Operative mortality (%)	p value
	Sex	No.			
Tyras et al. *(31)*	W	241	1970–1977	3.7	NS
	M	1300		2.4	
Douglas et al. *(32)*	W	492	1973–1979	2.2	<0.05
	M	2663		1.0	
Loop et al. *(33)*	W	2245	1967–1980	2.9	<0.001
	M	18,079		1.3	
Fisher et al. *(51)*	W	1153	1975–1980	4.5	<0.0001
	M	6258		1.9	
Khan et al. *(30)*	W	482	1982–1987	4.6	0.036
	M	1815		2.6	
Hannan et al. *(48)*	W	3169	1989	5.4	<0.001
	M	9279		3.1	
O'Connor et al. *(29)*	W	819	1987-1989	7.1	<0.001
	M	2236		3.3	
Rahimtoola et al. *(59)*	W	1979	1974–1991	2.7	0.02
	M	6927		1.9	
Weintraub et al. *(28)*	W	2648	1974–1991	3.8	<0.0001
	M	10,720		1.6	

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It is noteworthy that in a recent reports of patients undergoing coronary bypass surgery at single centers, in-hospital mortality was similar in women and men *(53,54)*. In addition, in the Bypass Angioplasty Revascularization Investigation (BARI), a randomized clinical trial in which rigorous inclusion and exclusion criteria resulted in a homogeneous population in which gender differences could be evaluated without as much concern for confounding, in-hospital mortality was also similar in women and men undergoing coronary bypass surgery *(49)*.

Although early reports of patients undergoing coronary angioplasty revealed a lower procedural success in women *(34)*, more recent reports have noted similar angiographic outcome and incidence of myocardial infarction and emergency coronary bypass surgery in women and men (Table 4) *(36,49)*. However, in-hospital mortality is significantly higher in women, and an independent effect of gender on acute mortality following coronary angioplasty persists after adjustment for the baseline differences in clinical and angiographic characteristics *(36,39)*. The reason for the increase in mortality is unclear, but small vessel size and hypertensive heart disease in women have been implicated. Although a few studies have noted that gender is not an independent predictor of mortality when body surface area is accounted for *(37)*, the impact of body size on outcome is less consistent than in patients undergoing coronary bypass surgery. It has been postulated, however, that the volume shifts and periods of transient ischemia during coronary angioplasty are less well tolerated by the hypertrophied ventricle in women *(55)*, and congestive heart failure has been shown to be an independent predictor of mortality in both women and men undergoing coronary angioplasty *(36,39,49)*.

Table 4
Gender Differences in Acute Outcome Following Coronary Angioplasty[a]

Authors	Patients		Angiographic success (%)	Death (%)	Nonfatal MI (%)	Emergency CABG (%)
	Sex	No.				
Cowley et al. *(34)*	W	705	60.3	1.8	5.7	6.5
	M	2374	66.2**	0.7**	5.5	6.6
McEniery et al. *(35)*	W	969	93.0	0.3		3.8
	M	2727	93.5	0.1		3.2
Bell et al. *(37)*	W	1106	85.0	4.2		
	M	2965	86.0	2.7***		
Kelsey et al. *(36)*	W	546	84.1	2.6	4.6	4.8
	M	1590	86.5	0.3***	4.3	3.3
Weintraub et al. *(104)*	W	2667	88.0	0.8	2.0	6.1
	M	7619	88.0	0.2***	1.5	5.6
Kahn et al. *(38)*	W	2033	95.0	1.4	1.7	1.6
	M	7142	95.0	0.8**	1.4	1.6
Malenka et al. *(39)*	W	3982	90.5	1.6	2.7	2.6
	M	8250	90.4	0.7**	2.2	2.0*

[a]Abbreviations: CABG, coronary artery bypass surgery; M, men; MI, myocardial infarction; W, women.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.005$ men vs women.
Reproduced with permission from ref. *26*.

It is encouraging that recent reports have noted an improved outcome in women following angioplasty, even though women (like men) are older, with more complex disease than women treated previously (Fig. 3). In fact, in the 1993–1994 National Heart, Lung, and Blood Institute (NHLBI) percutaneous transluminal coronary angioplasty (PTCA) registry (reopened to women only), procedural success was higher (Fig. 4) and major complications lower (Fig. 5) in comparison with women treated in the 1985–1986 registry *(27)*. In addition, in a recent report of patients undergoing balloon angioplasty in BARI, in-hospital mortality, myocardial infarction, and emergency coronary bypass surgery was similar in women and men although women had a higher incidence of periprocedure congestive heart failure and pulmonary edema *(49)*.

It is important to note that early reports of women undergoing coronary intervention with new devices, including coronary stents, note a similar outcome in comparison with men *(56,57)*, although in-hospital complications (coronary dissection, vascular repair, hypotension, transfusion) occur more frequently in women than in men treated with both balloon angioplasty and new devices *(36,58)*. Whether or not intracoronary stents will have a particularly favorable outcome in women is under active investigation.

Long-Term Outcome

Several studies have noted an increase in anginal symptoms following coronary bypass surgery in women in comparison with men *(32,33,59)*; whether this is due to less complete initial revascularization, fewer repeat revascularization procedures, or a higher incidence of symptoms for a similar extent of disease in women is unclear. However, following hospitalization for coronary bypass surgery, long-term mortality and event-

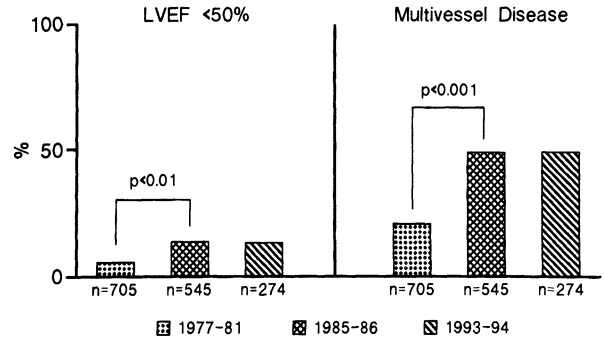

Fig. 3. Prevalence of left ventricular dysfunction and multivessel disease in women undergoing coronary angioplasty in the 1977–1981, 1985–1986, and 1993–1994 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registries. LVEF, left ventricular ejection fraction.

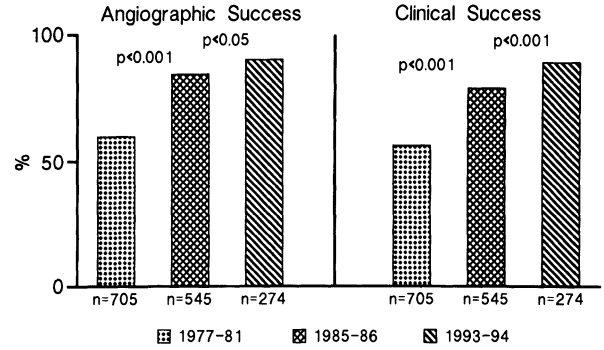

Fig. 4. Comparison of angiographic success and clinical success in women undergoing coronary angioplasty in the 1977–1981, 1985–1986, and 1993–1994 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registries. Angiographic success, all lesions dilated ≥20%; clinical success, all lesions dilated ≥20% without in-hospital death, myocardial infarction, or emergency coronary bypass surgery.

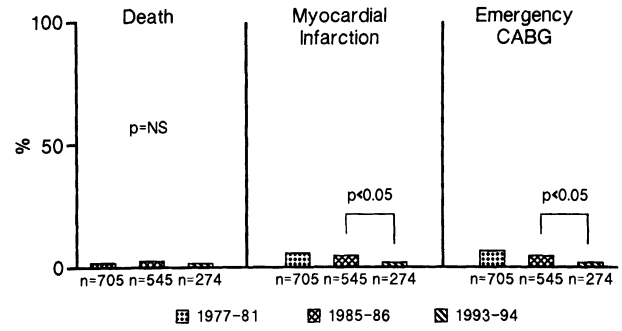

Fig. 5. Comparison of major complications in women undergoing coronary angioplasty in the 1977–1981, 1985–1986. and 1993–1994 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registries. CABG, coronary artery bypass graft surgery. Reproduced with permission from ref. *27*.

Table 5
Gender Differences in Long-Term Outcome Following Coronary Artery Bypass Surgery

Authors	Patients		Years	Months	Survival (%)
	Sex	No.			
Tyras et al. *(31)*	W	241	1970–1977		88.3
	M	1,300		60	93.5
Douglas et al. *(32)*	W	492	1973–1979		92.0
	M	2,663		42	92.0
Loop et al. *(33)*	W	1,153	1967–1980		90.6
	M	6,258		60	93.0
Eaker et al. *(60)*	W	1,097	1975–1980		91.3
	M	6,100		72	92.1
Rahimtoola	W	1,979	1974–1991		37.0
et al. *(59)*	M	6,927		108	42.0

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Table 6
Gender Differences in Long-Term Outcome Following Coronary Angioplasty[a]

Authors	Patients		Death (%)	MI (%)	Repeat PTCA (%)	CABG (%)	Symptomatic improvement (%)	Mean follow-up
	Sex	No.						
Cowley	W	305	0.3	4.0	9.9	10.9	89.8	18 mo
et al. *(34)*	M	109	2.2*	4.0	17.5*	14.3	91.7	
Philippides	W	361	10.6	19.7	16.8	25.4	20.2	7 yr
et al. *(61)*	M	1226	8.7	17.0	22.9*	27.8	20.1	
McEniery	W	876		2.9	4.9	7.0	89.0	20 mo
et al. *(35)*	M	2550		2.0	5.3	6.8	94.0**	
Kelsey	W	546	10.8	11.9	24.0	15.8	70.8	4 yr
et al. *(36)*	M	1590	6.6**	12.3	26.5	18.3	64.4	
Weintraub	W	2667	12.0					7 yr
et al. *(104)*	M	7619	8.0**					

[a]Abbreviations: CABG, coronary artery bypass surgery; M, men; MI, myocardial infarction; W, women.
* $p < 0.05$.
** $p < 0.001$ men vs women.
Reproduced with permission from ref. *26*.

free survival are similar in women and men (Table 5) *(33,60)*. In fact, after adjusting for advanced age and a higher risk profile in women, female gender has been shown to be an independent predictor of improved survival *(49)*.

Reports of gender differences in long-term outcome in patients treated with percutaneous coronary intervention are less consistent and are limited to patients treated with balloon angioplasty *(36,61–63)*. Women tend to be more symptomatic following the procedure *(35,36)* but have a similar incidence of repeat revascularization, nonfatal reinfarction, and death in comparison with men (Table 6). In the 1985–1986 NHLBI PTCA registry, women had a significantly higher cumulative mortality at 4 yr, but after adjustment for baseline differences, female gender was not an independent risk factor for

late mortality *(36)*. In BARI, unadjusted survival at 5 yr was similar in women and men following coronary angioplasty and, therefore, female gender was a predictor of improved survival (following coronary bypass surgery and coronary angioplasty) after accounting for a higher baseline risk profile *(49)*.

SPECIFIC CONSIDERATIONS

Unstable Angina

A few studies have specifically addressed gender differences in treatment of patients with unstable angina. In one report, 941 women and 2073 men underwent coronary angioplasty with a similiar success rate as well as in-hospital mortality rate (4.1 and 3.2%, respectively) and emergency coronary bypass surgery rate. Fewer women than men had a Q-wave myocardial infarction. During a mean of 4 yr of follow-up, overall survival and survival free of Q-wave myocardial infarction were similiar. Women were less likely than men to undergo coronary bypass surgery and the occurrence of severe angina was higher in women than in men *(64)*.

In another report on patients with unstable angina or non-Q-wave myocardial infarction, women were less likely than men to receive intensive antiischemic therapy and less likely to undergo coronary angiography (relative risk 0.71; 95% confidence interval [CI], 0.65, 0.78; $p = 0.001$). Women had less severe and extensive coronary disease and were less likely to undergo revascularization, yet had a similar risk of an adverse cardiac event by 6 wk *(65)*.

To test the hypothesis that in patients with acute coronary syndromes, control of platelet activity may require stronger antagonists in women in comparison with men, a retrospective review of patients with unstable angina treated with Integrelin was undertaken. Platelet aggreation and Holter-detected ischemic episodes were significantly reduced in women treated with the glycoprotein IIb/IIIa inhibitor Integrelin compared with aspirin. By contrast, both platelet aggregation and ischemic episodes were effectively treated with aspirin in men. It was concluded that platelets from women require stronger and more specific inhibition to limit activity and that platelets may play a more important role in women with acute coronary syndromes than in men *(66)*.

Myocardial Infarction

Prognosis

Numerous studies have documented a worse prognosis following acute myocardial infarction among women than among men, both prior to and following the advent of thrombolytic therapy *(67–68)*. In the Framingham Study cohort, the initial fatality rate was 44% in women and 27% in men. In addition, during the first 5 yr following the initial myocardial infarction, women had an average annual rate of reinfarction of 9.6% in comparison with 2.9% in men *(4)*. In the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study, in-hospital mortality was 13% in women vs 7% in men, and cumulative mortality at 48 mo was 36% in women vs 21% in men *(69)*. In addition, women had a worse prognosis following myocardial infarction than men, even after adjustment for advanced age (Fig. 6).

Other studies from the 1980s in patients with acute myocardial infarction have corroborated these findings, noting that in-hospital mortality was higher and 1-year age-adjusted mortality rates in women in comparison with men and female gender were

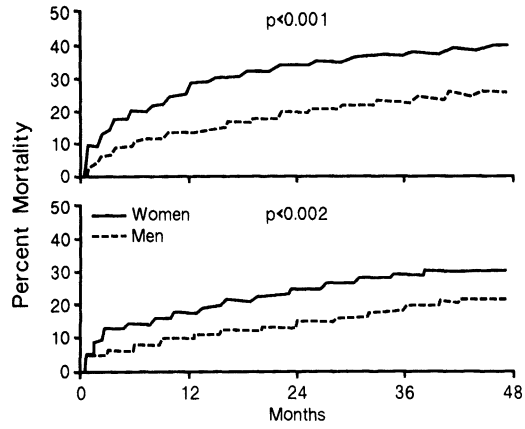

Fig. 6. Mortality following myocardial infarction in women and men in the Multicenter Investigation of the Limitation of Infarct Size (MILIS) study. Top unadjusted mortality; bottom adjusted mortality. Reproduced with permission from ref. *69*.

independently and significantly associated with increased mortality *(70–71)*. Although age did not fully account for these findings, diabetic women were at particularly high risk following myocardial infarction *(72,73)*. However, it has been suggested that gender differences in survival following myocardial infarction may be owing, in part, to methodology rather than biology, noting that several studies evaluating selected populations (randomized trials such as MILIS) could not account for patients who died prior to hospital admission nor the impact of differences in therapeutic interventions on mortality among women and men *(74)*. Furthermore, a recent review of 27 studies in patients with acute myocardial infarction that compared gender differences in acute and 1-month mortality revealed that in all but one study, unadjusted death rates were higher among women than among men. In all but 2 of 11 studies that reported age-adjusted analyses, the relative risk of death in women in comparison with men was reduced. In all six studies that were further adjusted for additional variables, the relative risk of death was further reduced in women in comparison with men but was still greater than 1.0 *(75)*. It was concluded that most, though not all, of the excess risk noted in women was due to older age and the presence of more unfavorable clinical characteristics *(76)*. However, many of these studies included only small numbers of patients, and a metaanalysis was not performed due to differences in study design. In addition, no distinction was made between patients treated with or without thrombolytic therapy.

Review of the large-scale placebo-controlled trials of thrombolysis in acute myocardial infarction revealed that intravenous thrombolytic therapy significantly reduced mortality rates in both women and men (Fig. 7). However, mortality rates were higher among women than among men in both the placebo and thrombolysis groups, and in the majority of studies, there was a relatively lower reduction in mortality rates in women than in men *(41)*. Furthermore, in the Fibrinolytic Therapy Trials Study metaanalysis, women were shown to have a 60% greater mortality than men 35 d after presentation to the hospital with acute myocardial infarction *(77)*. In the Fourth International Study of Infarct Survival (ISIS 4), an increase in short- and long-term mortality in women was suggested *(78)*. Similarly, in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO-1) trial, 30-day mortality of women was twice that of men *(79)*.

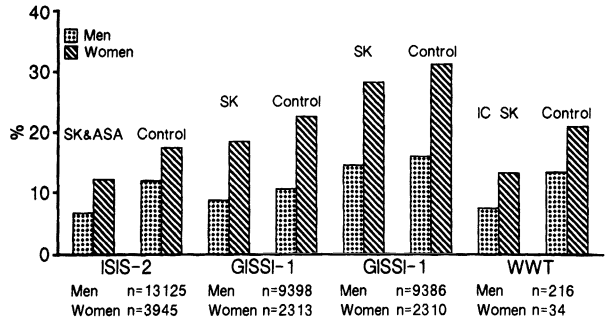

Fig. 7. Mortality in women and men with acute myocardial infarction treated with thrombolytic therapy. ASA, aspirin; GISSI, Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Micardico; IC, intracoronary; ISIS, International Study of Infarct Survival; SK, streptokinase; WWT, Wester Washington Trial. Adapted with permission from ref. *41*.

Several potential explanations of the observed gender differences in outcome following treatment with thrombolytic therapy exist. One hypothesis attributes the lower reduction in mortality among women to be due to their older age. However, data from the Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Myocardico (GISSI-2) *(41)* and the Thrombolysis in Myocardial Infarction (TIMI-II) trial *(68)* revealed that for every decade (even less than 40 yr), women had higher mortality rates than men. Another hypothesis is that women have more complications following thrombolytic therapy than men, in part owing to advanced age. Support for this hypothesis is based on data from TIMI-II in which 5.9% of women vs 3.8% of men had a major hemorrhagic event, and 22% of women vs 10.8% of men had a major or minor hemorrhagic event *(68)*. These differences were thought to be due to the relatively smaller body size in women and highlighted the potential impact of weight- or age-adjusted dosing regimens. Data from GISSI-2 corroborated these findings, noting an excess of hemorrhagic stroke in women (0.6%) in comparison with men (0.3%) and an odds ratio of 1.72 after adjusting for baseline differences in age, risk factors, and body mass index *(80)*. In addition, in the International Tissue Plasminogen Activator/Streptokinase Mortality Study, women had similar morbidity and mortality to men but a higher incidence of hemorrhagic stroke *(81)*.

Finally, gender differences in mortality in the postthrombolytic era may reflect differences in utilization and outcome of revascularization in women in comparison with men *(82–88)*. In the Myocardial Infarction Triage and Intervention (MITI) registry, women had twice the in-hospital mortality of men and were half as likely to undergo acute catheterization, coronary angioplasty, thrombolysis, or coronary bypass surgery, suggesting that the gender gap in mortality is associated with a lower likelihood of women being treated with acute interventions *(89)*. Similarly, in the Atherosclerosis Risk in Communities (ARIC) study, women hospitalized for a myocardial infarction were less likely to receive thrombolytic therapy or undergo coronary angioplasty and coronary bypass surgery, even after adjustment for multiple clinical and demographic variables *(90)*.

It is important to note that although the relative reduction in mortality following thrombolytic therapy is lower in women than in men, the absolute reductions appear similar. Therefore, the relative decrease in benefit in women may be attributed to higher underlying mortality rates rather than to reduced efficacy of thrombolytic therapy.

Gender Differences in Treatment and Response to Thrombolytic Therapy

Early studies have revealed the absence of a difference in the pharmacokinetics of tissue-type plasminogen activator in women and men with acute myocardial infarction *(91)*. Moreover, 90-min coronary artery patency rates, reocclusion rates, and left ventricular function have been reported to be similar in women and men, although women have more recurrent ischemia *(92)*. In addition, women tend to present later following onset of symptoms and experience a delay in the initiation of thrombolytic therapy with comparison with men *(93,94)*. Although women may be less likely to receive thrombolytic therapy than men, perhaps due to advanced age, similar factors are associated with the decision to use this therapy in both sexes. However, one study has suggested that only 55% of eligible women compared with 78% of eligible men receive tissue plasminogen activator, although the mean age was the same for women and men who were not treated *(95)*.

Treatment of young women with thrombolytic therapy may be particularly problematic. Although studies have suggested that there may be an increase in the risk of moderate bleeding in menstruating patients treated with thrombolytic therapy, the GUSTO-I experience supports the concept that the life-saving benefit of thrombolytic therapy for acute myocardial infarction should not be withheld because of active menstruation *(96,97)*.

Gender Issues Related to Medical Treatment

The role of pharmacologic therapy in the treatment of patients with acute myocardial infarction has been well studied, although data on gender differences in response to treatment are limited. In general, results of trials performed predominantly in men (due to the lower prevalence of disease in women and upper age restrictions for entry into trials) have been extrapolated to women, and treatment recommendations are consistent for women and men. It should be noted, however, that women with a high baseline risk profile may have the most to gain from risk reduction therapy.

Although few studies addressed the efficacy of primary prevention in women, a metaanalysis of randomized trials of aspirin therapy revealed a 25% reduction in the risk of subsequent cardiovascular events in both women and men with vascular disease *(98)*. In addition, six trials in which women with coronary heart disease and hyperlipidemia were included suggested a >50% reduction in coronary heart disease mortality among women treated with lipid-lowering therapy *(99)*.

Cardiogenic Shock

Multiple nonrandomized trials in patients with acute myocardial infarction complicated by cardiogenic shock have suggested a survival benefit in patients treated with primary coronary angioplasty in comparison with conservative therapy, although treated patients represent a highly selected and lower risk population *(100)*. In an analysis of gender differences and outcome in patients entered into the Should We Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial registry in which 40% of patients were women, there was no difference in the incidence of revascularization between women and men. Women had a higher incidence of severe valvular heart disease and acute ventricular septal defect. However, in-hospital mortality was similarly high (67.9% vs 63.7%) in women and men, respectively, and adjusted analysis did not reveal gender to be independently associated with mortality *(101)*.

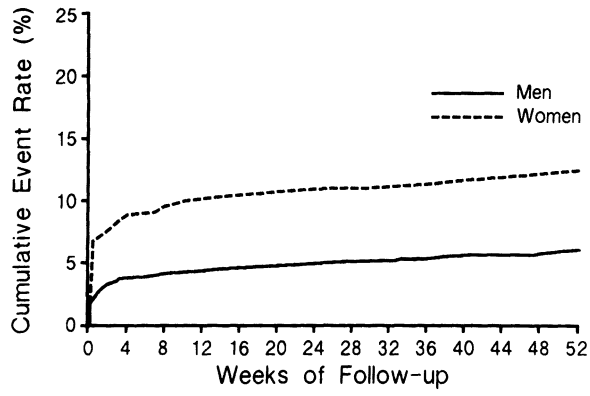

Fig. 8. One-yr mortality following acute myocardial infarction in women and men in the Thrombolysis in Myocardial Infarction (TIMI) trial. Reproduced with permission from ref. *68*.

ST-Segment Elevation Myocardial Infarction

Thrombolytic Therapy

Gender differences in outcomes of patients treated with thrombolytic therapy specifically for ST-segment elevation myocardial infarction are limited, although the majority of patients in the large-scale, placebo-controlled trials had ST-segment elevation *(77)*. Most notably, the TIMI-II investigators evaluated the difference in morbidity and mortality between women and men treated with recombinant tissue plasminogen activator for acute myocardial infarction and the relation of these differences to baseline clinical characteristics. In this study, the 6-wk mortality was 9% in women in comparison with 4% in men (Fig. 8), and the adjusted relative risk of death was 1.54 ($p = 0.01$). Death or reinfarction occured in 15.9% of women and 9.5% of men with an adjusted relative risk of 1.33 ($p = 0.02$). Among patients assigned to the conservative strategy of "watchful waiting" following thrombolytic treatment, mortality at 6 wk was 7.5% in women and 3.8% in men ($p = 0.01$), and death or reinfarction occurred in 14.2% of women and 8.9% of men ($p = 0.01$) *(68)*. It was concluded that among patients with ST-segment elevation myocardial infarction eligible for thrombolytic therapy, women had higher morbidity and mortality than men and that age and a history of diabetes mellitus accounted for much, although not all, of the difference.

Among patients treated with thrombolytic therapy for ST-segment elevation myocardial infarction in the Primary Angioplasty Myocardial Infarction (PAMI) trial *(42)*, in-hospital mortality was nearly fivefold higher in women than in men (14.0 vs 3.5%, respectively; $p = 0.006$). Intracranial hemorrhage after tissue plasminogen activator treatment was also more common in women (5.3%) than in men (0.7%; $p = 0.037$).

Primary Coronary Angioplasty

In the cohort of patients treated with primary PTCA in PAMI *(42)*, women and men had similiar in-hospital mortality (4.0 vs 2.1%, respectively; $p = 0.46$), and no intracranial bleeding occured in women or in men. Furthermore, a univariate trend was noted for reduced in-hospital mortality in women treated with primary PTCA rather than tissue plasminogen activator (4.0 vs 14%; $p = 0.07$), and multiple logistic regression analysis revealed treatment with primary PTCA in addition to younger age to be independently predictive of in-hospital survival in women. In men, in-hospital mortality was similar

with both primary PTCA and tissue plasminogen activator therapy, and only advanced age independently correlated with death. It was concluded that women treated with thromoblytic therapy are at increased risk for death and intracranial hemorrhage in comparison with men and that primary PTCA decreases these risk and results in an improved survival in women.

These findings were corroborated in a larger study of patients undergoing primary PTCA that noted a similar acute success rate and overall mortality of 7% in women and 9% in men at a mean follow-up of 86 wk. However, in this study, treatment limited to patients with acute ST-segment elevation myocardial infarction was presumed but not specified *(102)*.

Non-ST-Segment Elevation Myocardial Infarction

Although most studies of patients undergoing coronary revascularization (as noted above), excluded patients with acute myocardial infarction and noted a higher incidence of unstable angina in women in comparison with men, few studies have specifically addressed gender differences in outcome of patients treated with non-ST-segment elevation myocardial infarction. Notably, women and men enrolled in the TIMI-IIIB trial of unstable angina and non-Q-wave myocardial infarction were evaluated to determine gender differences in characteristics and outcome. As expected, for both acute coronary syndromes, women were older and had a higher prevalance of diabetes mellitis and hypertension. Mortality at 42 d was similar in women (7.4%) and in men (7.5%). Coronary angiography revealed less severe coronary artery disease in women, and rates of cardiac catheterization, coronary angioplasty, or coronary bypass surgery were similar for women and men in both the conservative and invasive strategies. Mortality associated with revascularization was also similiar among women and men *(103)*.

CONCLUSIONS

In patients with coronary artery disease, numerous and consistent gender differences in presentation, evaluation, treatment strategies, and outcome of treatment with thrombolytic therapy, percutaneous coronary intervention, and coronary bypass surgery have been well documented. In general, women with acute coronary syndromes are older, with more risk factors and comorbid disease than men and undergo treatment with higher risk for an adverse outcome. Most, but not all, of the gender differences in acute and long-term outcome can be attributed to the older age and higher risk profile in women. However, recent studies suggest that the outcome in women treated with coronary angioplasty and coronary bypass surgery is improving and, in particular, primary PTCA may be an effective strategy in women.

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21 Myocardial Infarction in the Younger Patient

Jorge Plutzky, MD

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INTRODUCTION

In discussing premature myocardial infarction (MI), it is important to begin with a simple fact: coronary atherosclerosis is quite common in younger patients *(1,2)*. It is the clinical manifestations of coronary artery disease (CAD)—MI and angina pectoris—that may be less frequently encountered *(3)*. The underlying disease process appears to be present in many, if not most, Americans by the age of 30 *(4)*. Autopsy studies on casualties of both war and motor vehicle accidents reveal early signs of atherosclerosis in up to 70% of individuals 30 yr old or younger, with significant flow-limiting stenoses in 10% *(5)*.

In this context, premature CAD—MI and angina pectoris—is worthy of attention for several reasons. First, the number of patients experiencing MI at an age of 45 yr or younger is not insignificant: approximately 125,000 patients a year, or 5% of all MIs in the United States *(6)*. Second, there are unique etiologies to consider more closely in evaluating these patients *(7)*. Third, we may be able to learn a great deal about the CAD process itself by studying its manifestations in younger patients, and insights may be gained regarding novel risk factors and biologic variables that may be applicable to all patients. In fact, the younger MI patient may afford the possibility of observing CAD without other confounding variables and comorbid conditions. Finally, manangement of younger survivors of MI may present a particular challenge to the physician given the potential number of years in which to attempt risk reduction and efforts to prevent anginal and/or congestive heart failure (CHF). This chapter reviews unique pathologic

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and clinical features regarding premature CAD and then explores additional risk factors that clinicians may want to consider evaluating when treating the younger patient who has suffered an MI. Study of these issues is limited both by the lack of consolidated data in this population and by differences in definitions as to what constitutes a young patient. In general, we will define this group of patients as individuals 45 yr of age or younger, although we consider data from studies that set somewhat different standards for "premature" CAD.

ETIOLOGIC CONSIDERATIONS

In discussing the possible etiogies for MI in the younger patient, we can begin by distinguishing between nonatherosclerotic and atherosclerotic mechanisms *(7)*. Although it is tempting to consider more unusual reasons for the acute infarct in the young patient, statistically the process is more often due to typical atherosclerosis stemming from traditional risk factors *(8)*. Nevertheless, it is also true that the nonatherosclerotic and more unusual risk factors are found disproportionately more often among younger MI patients *(9)*. This may be owing in part to selection bias; physicians may be more inclined to look for unusual etiologies in the younger patient.

NONATHEROSCLEROTIC MECHANISMS OF ACUTE MI

Any process that blocks coronary artery blood flow will lead to acute ischemia and ultimately infarction *(10)*. In addition, focal areas of myocardial damage can occur independently of a change in the vascular supply to that area. An extensive list of nonatherosclerotic causes have been reported in studies and case reports in the medical literature (summarized in Table 1). Although all these causes have been reported to cause MI, not all have been reported per se in the younger patient. A select few are discussed here with the reader directed to other sources and reviews for more details.

Coronary artery spasm (CAS), also known as variant or Prinzmetal's angina, can account for MI in the absence of obvious atherosclerosis *(11)*. First described in 1959, CAS is defined by an abrupt decrease in the diameter of an epicardial artery owing to vasoconstriction. The classical description is of symptoms that occur at rest, unrelated to exertion *(7)*. Subsequent studies have shown electrocardiographic (ECG) abnormalities consistent with acute injury, as well as responsiveness to nitroglycerin. Prolonged vasospasm can lead to frank infarction. There is a suggestion of coincident atherosclerosis contributing to the tendency for spasm as well as worsening what is otherwise an excellent prognosis (89–97% 5-yr survival). CAS is important to consider in the younger MI patient given the frequency of normal-appearing arteriograms at the time of catheterization in young MI victims *(12)*. CAS is one potential explanation for an "evanescent" cessation in coronary blood flow. In the catheterization laboratory, CAS can be elicited through the administration of various intracoronary pharmacologic agents (acetylcholine, methacholine, epinephrine, histamine) or application of certain techniques (cold pressor test, hyperventilation). The discontinuation of Ergonovine by its manufacturer, the prior standard provocative agent, may be reflective of the declining attention this syndrome is receiving. Management of CAS may include nitrates and/or calcium channel blockers, as well as a tendency to stay away from β-blockers out of concern for unopposed α-stimulation.

Interestingly, CAS has been one of the mechanisms invoked as an explanation for the association between MI and cocaine abuse, another cause of nonatherosclerotic MI, seen

Table 1
Nonatherosclerotic Causes of MI

Aortic disease
Aortic stenosis
Aortic insufficiency
Aortic dissection extending to cornary arteries
Toxicity
Carbon monoxide poisoning
Cocaine
Hematological abnormalities
Polycythemia vera
Thrombocytosis
Disseminated intravascular coagulation
Trauma
Myocardial contusion
Coronary artery laceration
Coronary artery abnormalities
Coronary artery dissection
Coronary artery spasm (Prinzmetal's Angina)
Coronary anomalies
Anomalous coronaries
AV fistula
Aneurysm
Emboli to the coronary artery
Myocardial processes
Focal myocarditis
Metabolic or intimal proliferative diseases
Inherited metabolic syndromes/Mucopolysaccharidose
Fabry disease
Amyloidosis
Juvenile initimal sclerosis
Intimal hyperplasia (contraceptive steroids or post-partum state)
Cerebrotendinous Xanthomathomatosis
Pseudoxanthoma elasticum
sitosterolemia
Werner's syndrome
Miscellaneous
Progeria
Idiopathic MI with normal coronary arteriogram

disproportionately in the young *(13)*. As a hyperadrenergic stimulus, cocaine can precipitate coronary artery spasm while also increasing myocardial oxygen demand through increased blood pressure and heart rate. Patients may present many hours after the cocaine use, perhaps owing to the effects of active metabolites such as benzoyiergonovine *(14)*. Other mechanisms suggested as contributing to myocardial ischemia in the setting of cocaine include evidence for its atherogenic properties, changes in platelet aggregation, and endocarditis with embolic infarcts from intravenous abuse. One-third of cocaine users can be shown to have underlying CAD. A routine toxicology screen for cocaine use is warranted in young patients presenting with acute MI or chest pain in the absence of

Table 2
Frequency of Lipoprotein Abnormalities
in Men with Premature Coronary Heart Disease

	Controls (*n* = 901)	*Cases* (*n* =321)	
		Not Adjusted	*Adjusted**
HDL-c < 10th%	10%	46%	36%
Apo A-I < 10th%	10%	37%	36%
Apo B > 90th%	10%	24%	36%
Triglycerides > 90th%	10%	26%	26%
LDL-c > 90th%	10%	12%	22%
Lipoprotein (a) > 90th%	10%	16%	16%

* Significantly different than controls ($p < 0.01$).

HDL-c, High-density lipoprotein cholestrol; LDL-c, low-density lipoprotein cholesterol.

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other known major predisposing factors. Coronary angiography is normal in one-third of cocaine-related infarcts, with most of the remaining angiograms demonstrating some degree of thrombus *(15)*.

In addition to infectious endocarditis, a variety of conditions can lead to coronary emboli, another nonatherosclerotic cause of MI in the young *(10)*. The frequency of patent foramen ovale in the general population also allows for the possibility of venous thrombi, resulting in arterial circulation occlusions. Arterial thrombi can also occur, for example, with infective endocarditis, atrial thrombi, or myxoma. In general, such occurrences in the coronary circulation appear to be rare. More common are coronary artery anomalies, which can lead to ischemia, infarction, and/or sudden cardiac death owing to compression by surrounding structures *(16)*. For example, origin of the left coronary artery from the right or noncoronary aortic sinus of Valsalva can be associated with sudden cardiac death, particularly when the artery runs between aortic and pulmonary artery roots.

ATHEROSCLEROTIC MECHANISMS OF ACUTE MI

Although it is important to consider nonatherosclerotic etiologies for acute MI, most of them will be owing to traditional risk factors leading to typical atherosclerosis. Genest and colleagues *(17)* evaluated these issues in patients younger than 60 yr of age who underwent admission to the cardiac intensive care unit for MI. As shown in Table 2, *(17a)*, most of these patients demonstrate known risk factors for CAD. This is also supported by other data showing that an increasing number of traditional risk factors in a young patient predicts more extensive CAD *(3)*. The most common of these risk factors are smoking *(18)*, dyslipidemia *(19)*, and a family history of CAD *(20)*. Hypertension and diabetes are less correlated with MI in the young patient, perhaps reflecting the long-term toll these processes take on the vasculature.

Why one patient with multiple but common risk factors experiences an MI at an earlier age than another patient may be because of the particular severity of a given known risk factor, the combination of multiple known risk factors, an underlying genotype that has

amplified the pathologic response, or a combination of the above. In addition, young patients with atherosclerosis may place higher demands on the myocardium owing to increased exertion. A world class athlete who has an MI receives extensive attention *(21)*.

In considering traditional risk factors, cigarette smoking must be placed at the very top of list. Several studies have estimated that between 60 and 90% of young patients experiencing an MI are smokers *(6,22,23)*. The Pathologic Determinants of Atherosclerosis in the Young (PDAY) study has found a correlation between raised atherosclerotic lesions in the right coronary artery and abdominal aorta of young men, (15–34 yr of age) who died of violent causes and their thiocynate levels (a marker of cigarette smoke) *(24,25)*. Thrombolysis in Myocardial Infarction studies have also suggested that cigarette smoking is associated with infarction at a younger age and is more often associated with thrombosis of a less critical lesion, thus implicating plaque rupture *(26)*. More recent work has suggested the importance of counseling high-risk patients to avoid passive smoke inhalation. Certainly not all smokers develop *premature* clinical atherosclerosis, thus suggesting a "two-hit" process in premature CAD, with some patients being more susceptible to its toxic vascular effects. Regardless, cigarette smoking remains a obvious target for the physician who hopes to subtract a powerful risk factor. This is particularly attractive given that we are (at least currently) helpless in trying to modify certain risk factors like genotype.

Another reason why one patient may develop CAD sooner than another is the presence of either undefined, or not yet confirmed, risk factors. Although statistically most premature CAD does result from traditional risk factors, emerging risk factors have also been disproportionately associated with the younger patient *(17,27)*. As mentioned earlier, this may stem from increased attention to these other risk factors in the younger MI patient. In fact, these emerging risk factors may not be solely associated with premature CAD but may be relevant to CAD in general. Clinicians should consider screening for these risk factors in any patient who suffers an MI in the absence of other obvious risk factors.

It has been suggested that the patient who has an MI before the age of 45 yr has an approximately 50% chance of having some form of an inherited genetic disorder *(20,28)*. The possibilities are considerable and reflect much of our new insight into vascular biology. A detailed review of these disorders is beyond the scope of this chapter, although their broad nature can be considered.

Lipoprotein a

One study of acute MI in 102 young men revealed significant lipoprotein a (LpA) excess among male premature CAD patients (Table 2) *(17,29)*. Other studies have suggested a similar correlation between LpA and CAD *(30,31)*, although no such correlation was noted in the Physicians' Health Study *(32)*. LpA is a particularly intriguing molecule because basic science work has suggested a plausible mechanism to support its association with CAD *(33)*. LpA consists of a low-density lipoprotein (LDL)-like apolipoprotein B particle linked to an apolipoprotein a (apo a) moiety *(34)*. LpA is known to be deposited directly in the arterial wall, where it may incite pathologic reactions contributing to atherosclerosis. In addition, the apo a moiety bears considerable homology to plasminogen, thus creating a "decoy" for plasminogen activator, resulting in a competitive inhibition of fibroinolysis, and possibly a hypercoaguable state. LpA thus represents a potential intersection between lipoproteins and the coagulation system. LpA may be of particular importance in explaining the striking increased incidence of premature atherosclerosis among young Asian Indians, in spite of typical vegetarian diets *(35,36)*. Treat-

ment of LpA excess is difficult. No significant LpA lowering is achieved with most medications that lower LDL although there have been reports of lowering with niacin *(37)*.

High-Density Lipoprotein

Most clinicians who care for MI patients will eventually encounter one young patient, usually a male, with premature CAD, whose sole lipid abnormality is a significantly low high-density lipoprotein (HDL) level *(38)*. Often such patients will have low LDL levels, suggesting that LDL is not the major culprit lipoprotein. Most likely such patients have hypoalphalipoproteinemia, an inherited lipid disorder *(39)*. The inverse relationship between HDL levels and CAD has been well established. What is less clear is the ease with which we can significantly change someone's HDL levels, or if such a change in HDL levels will alter their clinical course *(40)*. A major limitation has been in part owing to the lack of medications that can change HDL levels significantly. Diet and exercise, in particular raising the body mass index, can raise HDL levels. Niacin is probably the most effective drug for raising HDL levels, perhaps as much as 10–15% in the patients who can tolerate its side effects *(41)*. Niacin in fact can be administered successfully if carefully managed by the physician. Manufacturers of new preparations of niacin given once in the evening report fewer side effects, although clinical experience continues to emerge. Although modest alcohol intake can raise HDL levels, many physicians feel uncomfortable endorsing such a practice. In patients with low HDL who are β-blockers, one should consider using one with intrinsic sympathomimetic activity (ISA), given evidence that those with ISA tend not to lower HDL as much. The indications to continue with a more standard β-blocker with proven efficacy in post-MI survival requires clinical judgment on a case by case basis *(41)*.

One should also be alert to the potential for improving HDL levels by lowering triglyceride levels through changes in diet (especially the high-carbohydrate diet so often taken by those on low-fat regimens), exercise, and exclusion of secondary factors (diabetes, nephrotic syndrome, thyroid disorders) contributing to triglyceride levels *(42,43)*. More recent studies, some of which have been reported only in abstracts (AFCAPS), raise the question of treating isolated low HDL by lowering the LDL level further. Some studies with fibrates have suggested that their benefit may be owing to an HDL effect *(44,45)*. More data is anxiously awaited, as is a therapeutic agent that might raise HDL levels. One cannot ignore evidence suggesting that MIs, regardless of age, are almost unheard of inpatients with hyperalphalipoproteinemia, a protective genetic mutation in which HDL levels are often above 100 mg/dL *(46)*. One can easily imagine the appeal of a pharmacologic agent that might be able to induce such levels.

Interestingly, familial hypercholesterolemia, a disease that we associate the most clearly with a predisposition to premature CAD, represented only 3% of the premature infarct population in the ICY study previously cited. This percentage would be expected to change depending on location, due to the known association of familial hypercholesterolemia with certain ethnic groups, e.g., French Canadians.

In addition to inherited lipid disorders, we are continuing to learn more about the interactive nature of modest levels of dyslipidemia. Recent work has suggested that the combination of elevated LDL, lower HDL, and elevated triglycerides may be particularly atherogenic. The exact reasons for this remain unclear but may involve small dense LDL, low HDL, an effect of triglycerides themselves, or underlying insulin resistance, all of which have been implicated in association with this deadly triad (high LDL, low HDL, high triglycerides). Interestingly, some studies such as post hoc analysis of the Helsinki

Table 3
Nontraditional/Emerging Risk Factors for Atherosclerosis/Premature Vascular Disease

LpA
Homocysteine levels
Insulin levels
Fibrinogen levels
DHEA-s
LDL particle size (small, dense, LDL, Pattern B)
Oxidized LDL levels
Decreases HDL2 subfractions

Heart Study and more recently the Prospective Study suggest that the elevated triglyceride level confers increased risk even among patients with the same LDL/HDL ratio *(47)*.

Also of note is the frequency with which no known familial lipid disorder is found in genetic studies of young MI survivors *(17)*. This must be a reflection of how much we have yet to learn about the variables that contribute to atherosclerosis, in particular those that extend beyond lipids and lipoproteins. Table 3 lists many of the nontraditional risk factors (and an associated reference) currently under intensive investigation both at the bench and in clinical trials.

Homocysteine

Homocysteine is one such example of an emerging risk factor that may play a role in premature atherosclerosis *(48,49)*. The suggestion that homocysteine might be atherogenic stemmed from the recognition that congenital homozygous hyperhomocysteinemia, a disease fatal in early childhood, included premature vascular disease as part of its phenotype *(50)*. Subsequent studies have implied that elevated homocysteine levels, as part of the genetic makeup or in a heterozygous form of homocysteinuria, contribute to more common forms of CAD and vascular disease *(51)*. A basis for this interaction has been suggested by in vitro studies demonstrating damage to endothelial cells, perhaps through oxidation, as well as stimulation of smooth muscle cell proliferation, inhibition of endothelial cell nitric oxide production, and increased endothelial cell production of thrombomodulin *(52)*. In vivo primate studies suggest that vascular lesions can be induced by infusion of homocysteine. The incidence of homocysteinuria, an autosomal recessive disorder, has been estimated at 1:200,000; heterozygosity is placed at 1:100 *(53)*.

Several epidemiologic studies have supported an association of hyperhomocysteinemia with MI and peripheral and central vascular disease, with a suggestion of a "concentration-dependent" effect, even within normal ranges. In the Physicians' Health Study, the highest homocysteine levels (upper 5%) of men 40–84 yr of age were associated with a 3.1 relative risk of increase in MI compared with those who had the lowest levels of homocysteine. An association between homocysteine and vascular disease in other beds (for example, carotid disease) has also been reported *(54)*.

The relationship between homocysteine and CAD in the younger MI patient has not been fully explored. In attempting to establish the relationship between homocysteine and vascular disease, most studies have set age cutoffs around 50 yr of age. Nevertheless, a Framingham Heart Study study suggested that homocysteine was an independent risk factor in 170 men (mean age 50 yr) with CAD *(48)*. By contrast, other studies have failed

to demonstrate a clear association between homocysteine levels and premature CAD. Kang and colleagues *(55)* could not demonstrate a difference in homocysteine levels between patients with CAD who were younger than 40 yr of age and case controls *(55)*. There was a significant difference in homocysteine between case and control groups among older patients. The use and study of homocysteine in clinical practice has been limited by the different methods of checking homocysteine levels (random level vs methione loading), the existing overlap between normal and abnormal levels of homocysteine, and the ease of treatment with oral folate, leading some clinicians simply to have their patients take folate supplementation empirically.

Fibrinogen

Fibrinogen represents yet another nontraditional risk factor now being evaluated extensively for a role in atherosclerosis in general, as well as (to a more limited extent) in premature CAD *(20,56)*. Multiple studies have suggested a relationship between fibrinogen levels and CAD/MI *(56)*. This association is biologically reasonable given the presumed effects of increased fibrinogen levels on coagulation and blood viscosity. Framingham data (1315 patients) suggest that fibrinogen levels increase with age, with the incidence of CAD being significantly greater when baseline levels of fibrinogen exceeded 3.1 g/L. Five of the published fibrinogen studies have included patients younger than 45 yr of age, with the answer regarding its contribution to premature CAD remaining elusive *(57)*. Hamsten et al. *(58)* reported on the largest group, although in a retrospective case-controled study. In this setting, elevated fibrinogen was among the best markers of ischemic heart disease in the 148 patients younger than 45 yr of age. Perhaps fibrinogen as a risk factor has received less attention due to our inability to modify its levels. Thus far, only alcohol use and estrogen therapy in women have been suggested to decrease its levels.

Other nontraditional risk factors and biologic variables for both vascular disease and premature vascular disease exist, among them dehydroepiandrosterone sulfate (DHEA-s), iron, and insulin levels.

CLINICAL FEATURES AND PATTERNS OF CAD

The younger patient with MI typically has a less extensive pattern of disease, with fewer lesions and stenoses that tend to be less severe *(6)*. Negus and colleagues *(54)* found that most angiograms in post-MI patients younger than 40 yr of age revealed stenoses in a single vessel, usually the left anterior descending artery *(59)*. Similar results were reported by Wolfe and Vacek *(60)* in catheterizations in 35 patients younger than 35 yr of age from the US Air Force: high rates of single-vessel left anterior descending artery disease, with more frequent total occlusions compared with a group of 100 patients over 55 yrs. It is also not unusual to find no evidence for significant flow-limiting lesions on cardiac catheterization of the younger MI survivor. In the Coronary Artery Surgery Study (CASS) database, 504 young adults with MI underwent angiograms; 16% of men and 21% of women had normal coronary arteries *(61)*. Some of the possible etiologies for MI in these patients were considered previously. In addition, particularly in this age group, one has to keep in mind that the early stages of atherosclerosis move in an abluminal direction, preserving the lumen despite the presence of significant atherosclerosis within the vessel wall. Such "young" lesions may well be more prone to rupture, thus explaining recent evidence that most MIs occur in lesions with stenoses of $\leq$70% *(62,63)*. Cardiac catheterization in fact only reveals the nature of the lumen, thus potentially limiting its

value in resolving premature atherosclerosis issues. Intravascular ultrasound and ultrafast computed tomography scanning, looking for calcium in the vessel as a marker for CAD, have been suggested as alternatives in these settings.

Beyond the anatomic distribution of the CAD, the younger patient is more likely to experience an infarct as opposed to angina pectoris. This is also suggestive of plaque rupture as a primary mechanism for infarction in these patients as opposed to increasing degrees of stenoses, with supply ultimately outstripped by demand. Pathologic studies support such notions, even if only studies with small numbers have been done so far *(64)*. Dollar and coworkers *(65)* analyzed the atherosclerotic plaques in the coronaries of 8 women who had MIs before the age of 40 yr and compared them with those in 37 adults over 45 yr. These young women tended to have more foam cells and less dense fibrous tissue, both markers of more unstable plaques. Corrado et al. *(66)* also found similar results in 200 consecutive Italian patients younger than 35 yr who died suddenly: one-fourth had acute thrombosis superimposed on a lipid-rich core.

Only the CASS study has addressed left ventricular function in young patients with MI *(61)*. There was no significant difference in overall left ventricular function compared with older patients with MI. This may correlate with observations that younger patients tend to have less extensive multivessel CAD. Perhaps these younger patients had less time to develop collateral circulation. Interestingly, despite this lack of difference, the younger patients tended to have less symptoms of CHF.

CONCLUSION

The presence of atherosclerosis and its consequences (such as MI) in a younger population highlights the need for risk reduction efforts in a primary care, primary prevention setting. Beyond primary prevention in the adult, issues of screening and treatment in pediatric populations are raised *(67–69)*. It is a struggle (with significant failure rates) to ensure that high-risk adults are screened and treated for established risk factors. Studies suggest that most events in the younger population are greatly influenced by remediable risk factors like cigarette smoking, hypertension, and common forms of dyslipidemia for which we have efficacious interventions *(70)*. The issues surrounding these younger patients with atherosclerosis offer support for the National Cholesterol Education Panel's recommendation that all Americans over the age of 21 undergo total cholesterol and HDL screening at least once, with further testing based on overall risk and the results of the screening tests. Although a contrarian view has argued against this approach out of concern for inducing unnecessary treatment too early in a patient's life, such caution ignores the significant risk this common disease poses to so many Americans, including many younger than 40. For many patients who have a first MI that is fatal, there will be no opportunity to benefit from the many cardiovascular interventions and therapies we now have available. For others, the loss of ventricular function will leave them incapacitated to various extents and will move the focus away from angina/CAD to one of managing CHF/transplantation. Beyond the usual calculations regarding numbers of events and cost-benefit analysis, it is difficult to estimate the toll and impact on an individual's psyche, productivity, or family, or to society in general. The loss seems all the greater if an MI might have been prevented. These issues are perhaps even more dramatic when the patient has not even reached midlife. The ability to identify risk factors (either established or newly emerging), define risk, and intervene remains among the few options we have against a complex, variable, and recurrent disease.

Careful study of MI in the younger patient will yield further insight into the atherosclerotic process, with implications both for this population and for other patients with vascular disease. For now, a common-sense approach to these patients would include consideration of screening and treating nontraditional risk factors when MI occurs in the absence of other established significant risk factors, particularly when there is a clear family history for premature CAD. Similarly, older patients with CAD without obvious risk factors should also be considered for screening for these other emerging risk factors. Physicians must not pass up the opportunity to mitigate those established risk factors for which we have proven interventions, especially in the younger patient who may be facing the challenge of surviving 30–40 more years, to equal the life expectancy of peers. For now, physicians are left to their own clinical judgment regarding young MI patients in terms of several issues. Should one use empiric folate treatment for homocysteine levels? What is an appropriate goal for LDL? Is the young post-MI patient with a baseline LDL <100mg/dL missing out on a benefit from statin therapy? Hopefully study of this population will offer us some answers to these questions, if not insight into the basic biologic mechanisms at work in atherosclerosis

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22 Aggressive Management of Cardiogenic Shock

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INTRODUCTION

The shift in the treatment paradigm of myocardial infarction from supportive measures to an emphasis on reperfusion-based myocardial salvage has resulted in an impressive survival improvement. Despite these advances, the Worcester Heart Attack Study identified an increase in fatality rates of cardiogenic shock patients during the dynamic period of this therapeutic development (Fig. 1) *(1)*. The mortality rates of cardiogenic shock reported from representative trials conducted over the past two decades are depicted in Figure 2 *(2–4)*.

This review discusses the modern concepts and controversies regarding the management of cardiogenic shock occurring as a result of myocardial damage in the setting of acute myocardial infarction (AMI).

DEFINITION AND RECOGNITION

Circulatory shock describes a state of tissue hypoperfusion. In the setting of an acute ischemic event (usually MI) the "shock" state may arise from cardiogenic or noncardiogenic mechanisms. Noncardiogenic causes occurring in the setting of MI include adverse

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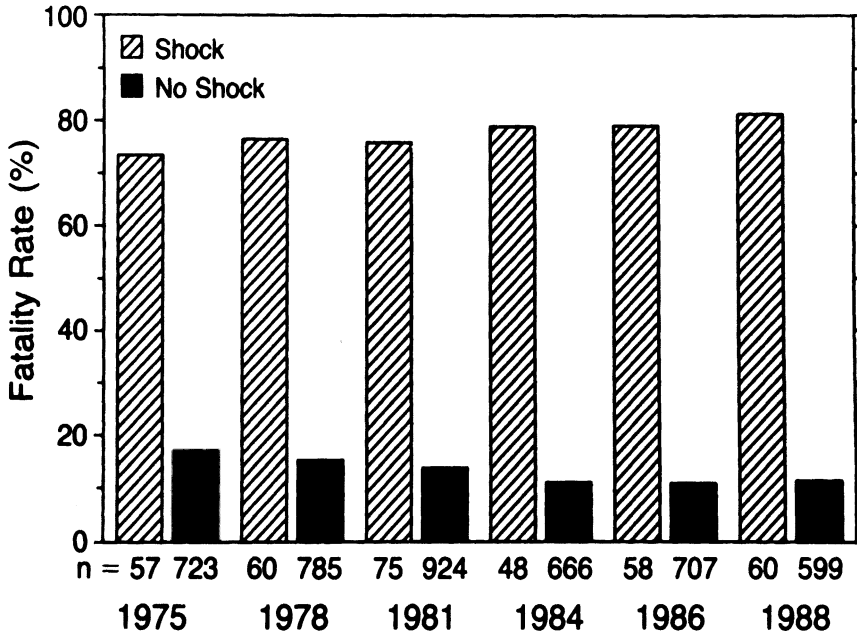

Fig. 1. Hospital case fatality rates for patients with and without cardiogenic shock admitted with myocardial infarction to 16 Worcester, MA area hospitals 1975–1988. Reproduced with permission from ref. *1*.

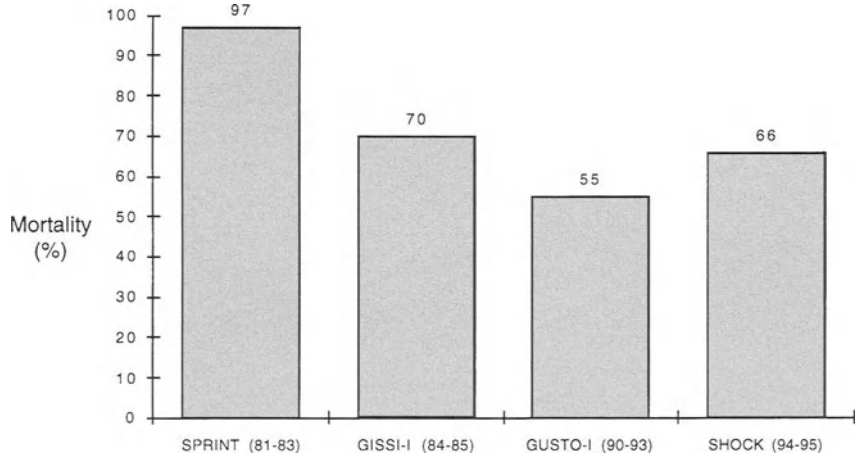

Fig. 2. Hospital mortality rates of patients with cardiogenic shock from recent trials.

effects of pharmacologic agents such as nitrates, angiotensin-converting enzyme inhibitors, and other vasodilator drugs. Hypotension may also arise during infusion of the thrombolytic agents streptokinase or anisoylated plasminogen streptokinase activator complex (APSAC). Hemorrhagic shock may occur secondary to gastrointestinal or occult retroperitoneal bleeding, as most patients receive anticoagulant and/or thrombolytic agents. Massive pulmonary emboli can result in circulatory shock. A tension pneumothorax may result from mechanical ventilation or may occur after cardiac arrest.

Hypovolemia should always be considered as a result of diaphoresis, vomiting, and overdiuresis. Sepsis can result in a shock state in patients with other comorbid illnesses.

Cardiogenic etiologies of shock may occur in the setting of myocardial infarction independent of myocardial damage. Tachyarrhythmias such as ventricular tachycardia and rapid atrial fibrillation require prompt correction in the setting of hypotension. Hypotension may not only arise from direct effects of thrombolytic agents but may also result from hemopericardium with tamponade without identifiable rupture *(5)*. Ascending aortic dissection can lead to the complex of pericardial tamponade and MI. Associated cardiac conditions such as significant aortic stenosis may contribute importantly to the development of shock. Excessive vagal tone can result in hypotension in the early phase of infarction commonly in association with bradycardia, although isolated hypotension can occur from this accentuated cardiac reflex *(6)*.

Direct myocardial damage may lead to a heterogeneous group of derangements resulting in circulatory shock. Pump failure from extensive left ventricular damage is the primary cause of cardiogenic shock. Mechanical defects as a direct result of myocardial injury occur less commonly and include papillary muscle dysfunction/rupture, ventricular septal defect, and free wall myocardial rupture with tamponade. Right ventricular infarction with an accompanying left ventricular infarction may also lead to shock.

Clinical recognition of circulatory shock includes identifying manifestations of a low cardiac output such cyanosis, cool extremities, altered mental status, and oliguria in the setting of hypotension. These findings, along with concomitant pulmonary edema, establish relatively confirmatory evidence for cardiogenic shock. However, hemodynamic monitoring allows diagnostic confirmation and can guide management decisions. The hemodynamic manifestations of cardiogenic shock include a systolic blood pressure <90 mmHg (or >30 mmHg below basal levels), an elevated pulmonary capillary wedge pressure >15 mmHg, and a reduced cardiac index <2.2 L/min/m^2.

EPIDEMIOLOGY

Examination of several investigations elucidates the circumstances of cardiogenic shock. The incidence of cardiogenic shock was reported in 1954 to occur in 19.7% of 816 patients admitted with AMI *(7)*. Killip and Kimball *(8)* described shock in 19% of 250 patients seen in a single cardiac care unit over a 2-yr period. A more modern profile of this complication can be appreciated by examining the Multicenter Investigation of the Limitation of Infarct Size (MILIS) and Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) trials conducted in 1981–1983, which tested the acute effects of propranolol and nifedipine, respectively, on patients with AMI *(9,10)*. The overall incidence of cardiogenic shock in the SPRINT registry was 6.4% and was noted in 6.5% of patients meeting MILIS inclusion criteria. The Worcester Heart Attack Study determined the incidence of cardiogenic shock in six 1-yr periods from 1975 to 1988 in 4762 patients hospitalized with MI. The incidence (average 7.5%) actually increased during the study to 9.1% in 1988 *(1)*. A single center experience (1611 patients, 1987–1988) reported in the era of reperfusion therapy identified cardiogenic shock in 12.4% *(11)*.

Several trials of thrombolytic therapy have reported this complication. Shock was identified in 7.2% of 41,021 patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial and in 7.0% of 40,775 patients enrolled in the Third International Study of Infarct Survival (ISIS-3)

(4,12). A recent report from the National Registry of Myocardial Infarction (NRMI) of 350,755 patients recorded a 3.5% incidence of cardiogenic shock *(13)*.

Mechanical complications of infarction account for cardiogenic shock in a minority of patients. The recent SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) registry identified a mechanical etiology (ventricular septal rupture or severe mitral regurgitation) in 14% of 444 patients *(14)*. The incidence of ventricular septal rupture was 5.1%, and significant mitral regurgitation was 10.3% in the 60 patients reported by the MILIS study group *(9)*. Free wall rupture has been reported to be responsible for approximately 10% of deaths in AMI *(15)*.

The onset of shock in the temporal course of infarction has varied considerably depending on study conditions. In the MILIS trial of 2931 patients screened, 4.5% presented with cardiogenic shock *(9)*. Of patients randomized in this study 7.1% developed cardiogenic shock. In the SPRINT trial 2.6% (24% of shock patients in the registry) of 3465 patients admitted in Killip class I went on to develop cardiogenic shock. Shock developed an average of 4 ± 4 days (median 2 d) after admission *(10)*. The contemporary international SHOCK registry reported a median time from MI onset to shock of 8 h (2).

By comparison, cardiogenic shock occurred after admission (most within 48 hours) in 89% of 2972 patients in the GUSTO-I trial *(4)*. However, early shock may be underestimated in thrombolytic trials. Several reasons have been cited for exclusion of patients with cardiogenic shock from these trials. Besides elimination of patients from these investigations because of trial or thrombolytic exclusions, difficulties with informed consent in critically ill patients or physician bias regarding management strategy also influence trial entry *(16)*. Nevertheless, a significant proportion of patients develop shock after hospital admission (even in patients presenting without hemodynamic compromise), emphasizing the value of identifying predictive features and exploring preventive approaches.

THE PATHOPHYSIOLOGY OF CARDIOGENIC SHOCK FROM MYOCARDIAL INFARCTION

A comprehensive understanding of the pathophysiologic characteristics and events of cardiogenic shock must be attained to impact the discouraging outcome of patients with this entity. The assiduous hemodynamic decline involves several interactive processes.

Early (initial 60 min) in the course of infarction autonomic disturbances have a predominant influence on a patient's hemodynamic status. As reported by Webb et al. *(6)*, sympathetic overactivity (tachycardia and hypertension) occurred in 36% of patients (monitored within 30–60 min of infarction onset). However, the majority (55%) exhibited bradyarrhythmias and/or hypotension. This is a manifestation of the Bezold-Jarish reflex *(17)*, which is commonly expressed during acute inferior–posterior infarction (77%). Webb and colleagues also noted vagal effects in 32% of anterior infarctions. The likely mechanism of this response involves a mechanical stimulus of vagal afferents, probably from systolic bulging of ischemic myocardium, which results in vasodilation and bradycardia with additional inhibition of the arterial baroreflex *(6,17,18)*.

An intravascular volume deficit has been recognized in up to 20% of patients with cardiogenic shock *(19)*. This would be characterized as a Killip or hemodynamic class III state. Relative hypovolemia is most commonly encountered in the setting of right ventricular infarction. It has been shown that left ventricular performance is optimal during infarction with a pulmonary capillary wedge pressure of 14–18 mmHg *(20)*.

Although volume infusion can restore class I status to some patients initially categorized in class III, the majority do not appreciably improve, reflecting evidence of primary cardiac compromise *(21)*.

The early development of cardiogenic shock in the course of infarction most commonly results from the loss of a large amount of myocardium. Autopsy studies have demonstrated that cardiogenic shock typically occurs after damage to ≥35–40% of the left ventricular muscle *(22–24)*. This may result from occlusion at a perilous site within a single coronary artery supplying a large region of myocardium or from cumulative damage after previous infarction. The elimination of the collateral function of an infarct-related artery could significantly enhance the destructive effect of a single vessel occlusion.

Later in the course, extension of infarct damage may occur as a result of multiple mechanisms. Infarct extension or reinfarction by enzyme elevation was reported in 23.3% of patients developing cardiogenic shock by the MILIS study group compared with 7.4% of patients without shock ($p < 0.0001$) *(9)*. In the GUSTO-I trial reinfarction occurred in 11% of patients with shock compared with 3% without shock ($p < 0.001$) *(4)*. Reinfarction most commonly results from reocclusion, and this event has been shown to increase the risk of shock *(25)*. Thrombus propagation or embolization might also result in reinfarction. Passive collapse and vasoconstriction at a second site within the coronary circulation could also result in ischemia or a second acute infarction *(26)*.

Extension of infarction into the border zone in a subepicardial or lateral direction has been documented pathologically in most patients with cardiogenic shock in some series *(22,23)*. Factors that could adversely extend infarction into the border zone include impaired collateral flow, increased myocardial oxygen consumption by sympathetic activation or inotropic agents, changes in the balance of arterial driving pressure (aortic pressure – left ventricular diastolic pressure) from hypotension or congestive failure, and the possibility of reperfusion injury.

The phenomenon of reperfusion injury remains controversial *(27–29)*. Investigation in experimental models has demonstrated pathologic evidence for progression to irreversible injury of viable myocardium in reperfused infarct zones and reduction of infarct size with agents that modify reperfusion injury. However, data are lacking to corroborate the importance of this phenomenon in a clinical situation. In fact, the GUSTO-I trial demonstration that rapid achievement of Thrombolysis in Myocardial Infarction (TIMI) grade III flow by thrombolysis results in the lowest mortality would suggest that reperfusion injury is unlikely to have an important effect on outcome *(30)*.

The pathologic picture of cardiogenic shock is characterized by progressive myocardial necrosis with an irregular extension of infarction not only into the border zone but with focal regions of necrosis throughout both the left and right ventricles *(22,23)*. This latter form of extension is a reflection of the hemodynamic state, as it can be seen with other etiologies of circulatory shock.

Hypotension leads to ongoing myocardial injury. This progressive myocardial necrosis is confirmed by observation of a persistent elevation of creatine kinase (CK)-MB *(31)*. Left ventricular function is further impaired by the inefficiency of infarct zone expansion leading to increased wall stress *(32)*. This progressive cardiac dysfunction leads to a vicious cycle of hypotension, declining coronary perfusion, and deteriorating left ventricular function, culminating in an irreversible shock state.

As stated earlier in this section, typically shock occurs when ≥35–40% of the left ventricular muscle is involved. No threshold level of damage exists for defining patients with cardiogenic shock. A series of 16 patients with final infarct sizes of >40% of the left

ventricle quantitated by technetium 99m sestamibi tomography reported a 94% survival with development of cardiogenic shock in only one patient *(33)*.

The variable neurohumoral response to left ventricular dysfunction has often been implicated to explain the discrepancies in the clinical manifestations of similar size infarctions. However, the function of myocardium remote from the infarct region plays a pivotal role in hemodynamic response and has been recognized to be of considerable prognostic importance *(34)*. Normally the noninfarct segments become hyperkinetic. An absence of hyperkinesis or asynergy of noninfarcted regions identify patients at high risk for early mortality *(35)*. Diffuse hypokinesis has been recognized as a distinguishing feature for the development of cardiogenic shock in patients with similar size infarctions by echocardiography *(36)*.

The corollary of abnormal remote myocardial function is multivessel coronary artery disease. In two autopsy series of patients dying from cardiogenic shock, two- or three-vessel disease (>75% obstruction) was identified in all patients *(36,37)*. The left anterior descending artery is predominantly involved. Angiographic studies have reported left main and/or multivessel disease in 60–90% of patients with cardiogenic shock *(36,38–42)*.

A canine model of myocardial infarction simulating the presence of single or multivessel disease illustrates the devastating effect of additional coronary obstructive disease remote from the infarct artery. Beyersdorf et al. *(43)* demonstrated that although animals with isolated left anterior descending occlusion exhibited a 100% 6-hour survival of the acute infarction, those with a coexistent 50% left circumflex stenosis suffered a 57% mortality from cardiogenic shock or intractable ventricular fibrillation.

Shock can also result from distinct cardiac structural damage with a less extensive left ventricular infarction. Right ventricular infarction can be detected in 40–50% of patients with left ventricular inferior infarction. A deficit of right ventricular pump function from proximal occlusion of the right coronary artery leads to a decline in left ventricular preload as the principle mechanism of the shock state seen in approximately 10% of patients with right ventricular infarction. The right ventricle dilates and the pericardium further constrains left ventricular filling, resulting in hemodynamic parameters similar to pericardial constriction (diastolic equalization and right ventricular dip/plateau pressure configuration). Abnormal interventricular septal function shifts toward the left ventricle in diastole, contributing to the low-output state *(44)*.

Rupture of the ventricular free wall, interventricular septum, and papillary muscle represents the major mechanical complications of myocardial infarction. These complications result from necrosis of critical cardiac structures and share a similar pathophysiologic substrate. They have been commonly associated with a first MI *(45–49)*. The infarction is usually small to moderate in size *(24,45)* in patients with free wall or papillary muscle rupture. Most studies have reported less extensive coronary artery disease in patients with these complications compared with other patients with infarction *(45,47,48,50)*. It has been proposed that patients with more severe coronary artery disease and left ventricular dysfunction cannot generate sufficient contractile stress to produce cardiac rupture. Infarct expansion has been demonstrated to be a harbinger of myocardial rupture *(51)*.

Considerable controversy remains over the possible accentuation of cardiac rupture by thrombolytic therapy *(52)*. Honan et al. *(53)*, reporting a metaanalysis of clinical trials, suggested that although early thrombolysis decreases the risk of cardiac rupture, late therapy may enhance this potential complication *(53)*. However, Late Assessment of Thrombolytic Efficacy (LATE) trial results did not show an increased risk of rupture in

patients treated >12 h from onset; thrombolysis did accelerate the time to rupture *(54)*. In a report from the NRMI participants, data suggested that thrombolysis accelerated myocardial rupture typically within 24–48 h *(13)*. Significantly, it has been shown that patients with cardiac rupture almost uniformly exhibit ineffective perfusion of the infarct artery *(55)*.

Rupture of the free wall of the left ventricle can occur with left and less commonly right ventricular infarction *(15,24)*. Rupture usually results from a transmural infarction *(24)*. Free wall rupture is often a sudden catastrophic event culminating in electromechanical dissociation and death. However, a subacute presentation (about 20%) manifested as hypotension and right heart failure has been recognized, perhaps representing an initial small hemopericardial accumulation *(56,57)*. Patients may exhibit a transient episode of hypotension and bradycardia portending death in minutes to days.

An acute ventricular septal defect arises more commonly with transmural infarction of the anterior than inferior wall *(58)*. A simple direct perforation or complex serpentine tracts may communicate between the two ventricles. The hemodynamic derangement is usually more substantial, with inferior infarction reflecting associated right ventricular involvement and ineffective compensation for the shunt volume *(59)*.

The complexity of the mitral valve apparatus and the subendocardial location of the papillary muscle blood supply explain the occurrence of papillary muscle dysfunction during infarction. Cardiogenic shock commonly occurs in patients with partial or complete rupture of one of the papillary muscles *(45,60)*. The posteromedial papillary muscle is more frequently involved because of the single-vessel blood supply from the posterior descending branch of the right or left circumflex coronary artery. The anterolateral muscle has a dual blood supply from the left anterior descending and left circumflex arteries *(61)*.

PREDICTIVE INDICATORS OF CARDIOGENIC SHOCK

Recognition of the predictive indicators of cardiogenic shock may allow implementation of strategies that could impact on the disappointing survival of these patients (Table 1). Although many patients present to the hospital in shock, most develop this syndrome after admission. The GUSTO trial demonstrated the nearly identical mortality of patients who presented with or developed shock (57% vs 56%) during hospitalization *(4)*.

Historical characteristics have been defined that are predictive of cardiogenic shock. Patients who develop shock are typically older *(1,4,9,10,62)*. A relative preponderance of women has been identified compared with the overall population of patients hospitalized with myocardial infarction *(1,10,62)*. A previous infarction enhances the risk of cardiogenic shock, as documented in several trials *(1,4,9)*. Patients with shock in the SPRINT trial were more likely to have a history of angina, stroke, or peripheral vascular disease *(10)*.

A diagnosis of diabetes mellitus increased the likelihood of cardiogenic shock in the GUSTO-I and MILIS trials *(4,9)*. However, the presence of diabetes mellitus did not increase risk in the SPRINT trial; an admission glucose of >180 mg% was predictive of shock, particularly in nondiabetics *(10)*. An enhanced activation of stress-related compensatory mechanisms (release of catecholamines, cortisol, etc.) in patients destined for shock may explain this finding *(63)*. Elevation of blood lactate levels have also preceded the manifestations of cardiogenic shock *(64)*.

Table 1
Predictive Indicators of Cardiogenic Shock

Historical features
Age >65 yr
Female gender
Previous infarction
Diabetes mellitus
History of angina, stroke or peripheral vascular disease
Physical examination
Sinus tachycardia
Clinical hemodynamic class III–IV
Agitation, abnormal mental status
Clinical events
Reinfarction
Hypotension
Laboratory findings
Hyperglycemia (>180 mg%)
Increased blood lactate
CK-MB >160 IU/L
Peak LDH >4× normal
Cardiac testing
LVEF < 0.35
Remote asynergy
Wall motion index
Coronary artery jeopardy score

[a]Abbreviations: CK, creatine kinase; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction.

Considering the pathophysiology of cardiogenic shock, the clinician may embrace certain clues from examination of the patient to lower the threshold for the diagnosis of shock *potential.* Certainly evaluation of every hypotensive event should lead to consideration of a cardiogenic etiology. Sinus tachycardia has been recognized as a significant risk factor for early death *(65).* Abnormal mental status, agitation, and cool extremities should lead to further clarification of the hemodynamic status *(21,66).* The survival of patients with MI has been categorized by clinical and hemodynamic subsets. Patients may be stratified in class IV (hypoperfusion and pulmonary congestion) without blood pressure criteria for a diagnosis of cardiogenic shock. Moreover, patients in class III (isolated hypoperfusion) often do not respond to volume expansion and are probably in an early phase of cardiogenic shock *(21).*

Events occurring during the course of infarction should alert the clinician to the potential for hemodynamic deterioration. The principle predictive event for cardiogenic shock is represented by recurrent infarction. Infarct extension or reinfarction was detected in a significantly greater proportion of patients with than without shock in both the MILIS (23.3 vs 7.4%; $p < 0.001$) and GUSTO-I trials (11 vs. 3%; $p < 0.001$) *(4,9).*

Some studies have identified significant elevation of cardiac enzyme levels (CK-MB > 160 IU/L, lactate dehydrogenase >4× normal) reflecting infarct size as risk factors for cardiogenic shock *(9,10).* However, enzyme determinations may be confounded by

timing, the early peak of reperfusion, and reinfarction. Determination of acute global left ventricular function by contrast ventriculography, radionuclide angiography, and echocardiography has been demonstrated to have predictive value for mortality and complications such as cardiogenic shock *(34,67–69)*. An ejection fraction of <0.35 was an independent predictive variable for cardiogenic shock occurring after admission in the MILIS trial *(9)*. The presence of remote asynergy and/or the absence of regional hyperkinesia has important prognostic implications regarding mortality and cardiogenic shock *(35)*. Quantitation of regional function by echocardiography has been utilized as a predictive instrument for cardiogenic shock. Gibson et al. *(70)* showed that calculation of a wall motion index in Killip class I or II patients was highly predictive of later hemodynamic deterioration. A discriminate equation was developed from their data (1.44 [Killip class] + 2.11 [wall motion index]) with a result of ≥6.04 predicting 78% of patients with cardiogenic shock.

Multivessel disease is a common component of cardiogenic shock. Knowledge of coronary anatomy from previous or acute coronary angiography may allow foresight into the potential for the development of shock. In theory, utilization of a coronary artery jeopardy score could predict hemodynamic deterioration as utilized for prediction of cardiogenic shock in patients undergoing elective angioplasty *(71)*.

Multivariate analysis utilizing logistic regression of patients in the SPRINT registry and the MILIS trial identified several predictive variables that allowed assignment of a probability for the development of cardiogenic shock with additive accumulation of each variable. The MILIS study determined that the variables of age >65 yr, admission left ventricular ejection fraction < 0.35, CK-MB >160 IU/L, diabetes mellitus, and previous infarction gave a probability of developing cardiogenic shock of 18% with three variables and 54% with five *(9)*. In a similar fashion, the SPRINT registry determined that age, female gender, history of angina, stroke, or peripheral vascular disease, and admission glucose >180 mg% gave a probability of shock of 20% for four risk factors and 35% for all six *(10)*. Future investigation may allow additional predictive models to be developed allowing implementation of early aggressive treatment or preventative strategies.

CLINICAL ASSESSMENT

A decline in blood pressure should prompt a search for correlative findings to confirm a diagnosis of circulatory shock. This includes assessment of vital signs, peripheral perfusion, mentation, and urine output. A consideration of noncardiogenic causes of shock should be entertained and appropriate diagnostic testing should be performed directly.

Physical examination should be directed toward assessment of volume status with attention to pulse volume, jugular veins, and perfusion. Cardiac examination must focus on a search for signs of tamponade, aortic dissection, or pulmonary embolus. Auscultation of a murmur should lead to consideration of severe mitral regurgitation or a ventricular septal defect. Occasionally the murmur from these defects may be unimpressive or absent *(72)*.

A portable chest X-ray will support the diagnosis of pulmonary edema, tamponade, emboli, or dissection. Laboratory studies should include determinations of hemoglobin, platelets, electrolytes, glucose, and lactate.

Electrocardiography (ECG) will aid in the assessment of acute hemodynamic deterioration. Most patients with cardiogenic shock will demonstrate ECG findings of an acute transmural infarction with ST-segment elevation or a new left bundle branch block. The

infarction is most commonly in an anterior distribution (50–80% in recent series) *(2,4,9,11)*. A non-Q-wave/subendocardial infarction is present in 14–36% of recent series without a significant difference in mortality compared to patients with ST-segment elevation/left bundle branch block *(2,9,11)*. Cardiogenic shock occurred in 2.6% of non-ST-segment elevation patients in the GUSTO-IIB trial *(73)*. Compared with shock patients with ST-segment elevation, these patients exhibited more adverse baseline clinical characteristics with a similar incidence of 30-d reinfarction and death. Electrocardiography (ECG) is also a necessary component in the evaluation of patients developing shock after admission in view of the common association of reinfarction *(4,9)*.

Echocardiography is a vital tool in the evaluation of patients with cardiogenic shock. The technique allows rapid quantitation of global ventricular function and assessment of regional wall motion *(70, 74)*. Mechanical complications can be accurately diagnosed in an expedient manner *(75)*. Two-dimensional and Doppler echocardiographic studies can identify the site of ventricular septal rupture and allow shunt quantification *(76)*. Echocardiography is essential for the diagnosis of free wall rupture and associated cardiac tamponade *(57)*. Papillary muscle rupture can also be detected *(77,78)*. Transesophageal echocardiography may be necessary in patients on mechanical ventilators and can more accurately quantitate mitral regurgitation *(79)*.

Hemodynamic monitoring is usually required to manage patients with cardiogenic shock. Right heart catheterization with a Swan-Ganz catheter can confirm the hemodynamic diagnosis and greatly aid in monitoring the effectiveness of therapy *(66,80)*. This technique is usually combined with arterial pressure monitoring, especially when vasoactive pharmacologic agents are being administered. By sampling oxygen saturations, a ventricular septal defect can be detected, and severe mitral regurgitation may be suggested by detection of giant V-waves in the wedge position. The characteristic hemodynamic findings of right ventricular infarction include a disproportionate elevation of right heart filling pressure with a normal or only mildly elevated left heart filling pressure (right atrial/pulmonary capillary wedge; RA/PCW > 0.80) *(81)*. Tamponade can be established with the presence of a pericardial effusion and differentiated from the "constrictive" physiology of a right ventricular infarction *(44)*. The multifaceted benefits of hemodynamic monitoring warrant its application in these critically ill patients despite the risks involved.

THERAPEUTIC MEASURES

General Measures

While the patient is being evaluated it is essential to begin therapeutic measures to reverse circulatory shock. A trial of volume expansion is warranted unless the patient exhibits clear signs of pulmonary edema. Oxygenation should be assessed, and hypoxia must be rapidly corrected by supplemental oxygen and mechanical ventilation if necessary to reduce myocardial oxygen demand. Prompt treatment of arrhythmias (including direct current (DC) cardioversion and temporary pacing) may lead to considerable hemodynamic improvement *(82)*.

Pharmacologic Treatment

In Griffith and colleagues' *(7)* original 1954 description of a large series of patients with cardiogenic shock, the use of sympathomimetic agonists provided encouraging evidence for effective medical therapy. There is little evidence that vasopressor therapy

improves the survival of these patients yet it remains a critical component for early stabilization and ongoing hemodynamic support *(83)*. The principal pharmacologic agents utilized are compared in Table 2.

These agents increase cardiac contractility and enhance cardiac performance but often at the expense of an elevated myocardial oxygen demand. The sympathomimetic drugs have a similar rapid onset (<5 min) and peak effect (15 min), with a half-life of 1.5–2.5 min *(84)*. Proarrhythmic actions are the most serious side effect. The pharmacodynamics of these drugs must be considered, including the logarithmic increase in concentration necessary to produce linear increases in effect, the development of tolerance owing to receptor desensitization and the complex interaction of individual agents on the adrenergic receptor subtypes *(85)*. The balance of inotropic, chronotropic, and vasoactive effects of each drug are optimally applied, using accurate information regarding the patient's hemodynamic status.

Dopamine is usually the initial drug utilized in treating patients with cardiogenic shock. It is effective in increasing arterial pressure and raising cardiac output, providing a necessary initial step in the patient with significant hypotension. The effectiveness of dopamine diminishes after 24 h not only from receptor downregulation but also from depletion of norepinephrine stores *(86)*. Dobutamine's β-effects increase cardiac output, and reduce vascular resistance and pulmonary capillary wedge pressure but without alteration in arterial pressure *(87)*. Norepinephrine is usually reserved for patients with very severe hypotension or those who fail to respond to other inotropic agents. It can effectively improve coronary perfusion by increasing arterial pressure *(88)*. Epinephrine is a potent inotropic agent, but its use may be limited by tachycardia and ventricular arrhythmias *(85)*. The phosphodiesterase inhibitors amrinone and milrinone have positive inotropic and significant vasodilator actions, producing a rise in cardiac output, a fall in left ventricular filling pressure with minimal effect on myocardial oxygen demand. However, there is a risk of significant hypotension with these agents, and they possess a long half-life *(89)*.

By combining agents, therapy may achieve the advantages of modest inotropic doses while minimizing the risk of side effects. Dopamine and dobutamine have often been utilized together to optimize the benefits of each drug. Both drugs infused at a rate of 7.5 μ/kg/min have been shown to achieve a more ideal hemodynamic state than higher doses of either drug alone in patients with cardiogenic shock *(90)*. Other drugs can also be utilized in combination such as norepinephrine and low-dose dopamine to maintain arterial pressure and renal perfusion. The addition of a phosphodiesterase inhibitor may further improve cardiac output in patients on sympathomimetic drugs. Vasodilators such as nitroprusside may be used cautiously in patients with an adequate arterial pressure but a low cardiac output. Diuretics are utilized in an ongoing fashion to optimize left ventricular filling pressures. A vigilant attention to the patient's status is critical to avoid wide variations in hemodynamic parameters that may lead to excessive drug doses, proarhythmia, and catastrophic deterioration.

Innovative pharmacologic advances may be proved effective in the future. The incremental benefits of limiting reperfusion injury may prove substantial in cardiogenic shock. Several methods have been examined to impede oxygen free radical damage utilizing oxygen radical scavengers, adenosine, and neutrophil inhibitors (antibodies to adhesion receptors or selectin blockade) *(28,29,91,92)*.

Myocardial metabolism is not only altered within the infarct zone but also in remote regions with or without ongoing ischemia *(43,93)*. "Substrate" infusions of glutamate/

Table 2
Inotropic Agents

Agent	*Mechanism/ receptor action*	*Dose*	*Cardiovascular effects*					*Comments*
			HR	*BP*	*CO*	*SVR*	*PCW*	
Dopamine	DA 2–5 μg/kg/min β_1, NE release @ 5–10 μg/kg/min α >10 μg/kg/min	2–30 μg/kg/min	↑	↑	↑	0–↑	↑	50% of action secondary to NE release; stimulation of dopamine receptors leads to increased renal and splanchnic blood flow
Dobutamine	β_1, β_2	2–30 μg/kg/min	+	0	↑	↓–0	↓–0	Racemic mixture of (+) and (-) isomers; renal perfusion is increased by elevated cardiac output
Norepinephrine	α, β_1	0.5–80 μg/min	↓–0	↑	↓–0	↑	0–↑	Potent vasoconstrictor
Epinephrine	α, β_1, β_2	0.005–0.5 μg/kg/min	↑	↑	↑	↓	↑	Potent renal vasoconstrictor; epinephrine induced hypokalemia may accentuate potential for arrhythmias
Amrinone	Phosphodiesterase inhibitor; increases cAMP-enhancing contractility and vasodilation	0.75 mg/kg then 5–10 μg/kg/min	0–↑	0–↓	↑	↓	↓	Half-life: 2–6 h thrombocytopenia: 2–4%
Milrinone	Same as amrinone	50 mg/kg then 0.25–1.0 μg/kg/min	0–↑	0–↓	↑	↓	↓	Half-life: 0.5–2 h Thrombocytopenia rare

CO, cardiac output; SVR, systemic vascular resistance; PCW, pulmonary capillary wedge pressure; DA, dopamine; HR, heart rate; BP, blood pressure; NE, norepinephrine; cAMP, cyclic adenosine monophosphate.

aspartate, glucose–insulin–potassium, coenzyme Q_{10}, and 2-mercapto-propionyl-glycine have restored remote myocardial function in an experimental model of cardiogenic shock *(94)*. A survival of 78% was reported for 27 patients receiving high doses of intravenous L-carnitine *(95)*. Although previous studies of glucose–insulin–potassium in myocardial infarction did not show a benefit, there is renewed interest in applying these citric acid cycle-repleting techniques to patients with cardiogenic shock *(96)*. Ongoing clinical investigation will examine the benefits of these approaches.

Mechanical Support of the Circulation

Intraaortic Balloon Counterpulsation

Intraaortic balloon counterpulsation has been used to treat patients with cardiogenic shock for the past 25 years. Experimental augmentation of coronary diastolic flow was described by Kantrowitz and Kantrowitz in 1953 *(97)*. The application of this principle was reported by Claus and colleagues *(98)* utilizing a device that cycled blood in the aorta. The gas-driven balloon displacement pump introduced clinically by Kantrowitz et al. *(99)* in 1968 has persisted as an essential adjunct in the therapy of patients with cardiogenic shock.

By inflating the balloon catheter during diastole, coronary perfusion pressure increases, and the collapse of the balloon with the onset of systole results in a decline in left ventricular afterload. Hemodynamic effects in cardiogenic shock include a reduction in systolic aortic pressure and a rise in diastolic aortic pressure, with no change in mean aortic pressure *(100)*. Cardiac output improves and heart rate decreases. The reduction in afterload is beneficial to patients with mechanical complications (mitral regurgitation and ventricular septal defect) *(101)*. Overall, there is a decline in myocardial oxygen demand with a reduction in diastolic left ventricular pressure and volume *(102,103)*. Coronary sinus lactate levels are decreased with counterpulsation, indicating a beneficial effect on myocardial energetics *(100,104)*.

Counterpulsation increases coronary driving pressure, with a resultant rise in coronary blood flow *(102,104)*. Although there is controversy regarding the efficacy of this technique to increase flow beyond a coronary obstruction, variations in experimental preparations or clinical conditions along with differences in coronary flow measurements may account for these discrepancies *(102,105,106)*. In theory, regional perfusion may be enhanced to remote myocardium through a subcritical compliant stenosis or via collateral circulation *(26,102,107)*. Counterpulsation alone has not been shown to decrease infarct size in acute infarction *(108)* but theoretically may minimize the "piecemeal" extension of necrosis induced by the shock state.

The use of the intraaortic balloon pump will result in hemodynamic stabilization of >75% of patients with medically refractory cardiogenic shock *(100,109,110)*. Early studies noted a persistent high mortality rate of patients treated with shock. For example, a cooperative trial of 87 patients reported a 77% hospital mortality in 1969 *(100)*. Other investigation also suggested little survival benefit despite the marked clinical improvement *(111)*. In most studies counterpulsation was often applied many hours after shock had developed and nearly always after a failure of intense vasopressor support. More recent observational investigation suggest an independent survival benefit with early prolonged counterpulsation *(109,112)*. Examination of patients with cardiogenic shock in both the SHOCK registry *(2)* and the GUSTO trial *(4)* reveals the association of enhanced survival with intraaortic balloon counterpulsation. However, in both studies,

patients who underwent counterpulsation were younger and had a higher likelihood of undergoing catheterization or revascularization procedures.

The intraaortic balloon pump improves the safety of cardiac catheterization during cardiogenic shock. It remains an important adjunct for the application of both transluminal and surgical revascularization. The combination of counterpulsation and emergency coronary bypass surgery has been utilized in the treatment of cardiogenic shock for over 25 years with success enhanced by early revascularization *(110,113–116)*. Retrospective investigation of patients undergoing angioplasty in acute infarction with or without thrombolysis demonstrated a reduction in infarct artery reocclusion as reported by Ishihara et al. *(117)* (2 vs 18%; $p = 0.03$; $n = 114$) and Ohman et al. *(118)* from the TAMI study group (0 vs 13%). Two randomized trials have been conducted to determine the efficacy of counterpulsation in preventing reocclusion after acute infarct artery angioplasty. Ohman et al. *(119)* reported a reduction in reocclusion (8 vs 21%; $p < 0.03$) and recurrent ischemia (4 vs 21%; $p < 0.001$) in a trial of 182 patients undergoing primary or rescue angioplasty. By contrast, the recently reported Second Primary Angioplasty in Myocardial Infarction (PAMI-II) trial did not demonstrate a similar preventative effect on reocclusion *(120)*.

Early institution of counterpulsation will maximize the benefits of its use in cardiogenic shock *(109,114)*. Percutaneous insertion has become standard. Major complications (10–20%) are primarily related to limb ischemia requiring surgery. Other major complications include thromboembolism, aortic dissection, sepsis, limb loss, significant hemorrhage, cholesterol embolization, and stroke *(121)*. Death may occur as a result of balloon pump insertion (<1%). Female gender, diabetes, and peripheral vascular disease are significant predictors of complications *(122,123)*. Improved insertion technique and heparin anticoagulation can minimize the risk of complications. The TAMI study group noted an increased risk of hemorrhagic complications with combined thrombolytic therapy and intraaortic balloon counterpulsation *(118)*. Other investigators did not find a significant increase in complications with thrombolysis *(124,125)*. Although initial data suggested a reduction in complications by smaller catheter size and sheathless insertion, a recent prospective investigation did not demonstrate a benefit for these advances *(123)*.

Other Mechanical Support Devices

Although adequate circulation can be restored in many patients by intraaortic balloon counterpulsation, approximately 25% will fail to improve, and a stable cardiac rhythm is necessary for continued effectiveness *(100)*. Several innovative techniques have been introduced recently to extend hemodynamic support to even the most critically ill patients. These methods have been utilized to allow time for recovery of ischemic border zone myocardium, favorable remodeling processes *(126)*, and an opportunity for corrective procedures such as revascularization or transplantation.

The ideal mechanical support device should maintain an adequate cardiac output, improve coronary perfusion, and decrease myocardial oxygen consumption while allowing rapid, uncomplicated, safe implementation *(127)*. Although no device fulfills all these criteria, several have effectively supported critically ill patients.

Peripheral cardiopulmonary bypass has been used to support patients in cardiogenic shock *(121,128,129)*. The components of the percutaneous cardiopulmonary bypass support (PCPS) device include a centrifugal nonocclusive pump, hollow-fiber membrane oxygenator, and a heat exchanger. Femoral arterial and venous access is obtained via 18–20-French cannulas. The PCPS device can achieve flow rates of up to 6 L/min. PCPS has

been utilized primarily to support patients undergoing elective high-risk angioplasty. In these patients bypass support results in a reduction of left ventricular afterload and left ventricular systolic volume with no change in mean arterial pressure (summation of a fall in systolic and rise in diastolic pressure). However, there is deterioration of regional myocardial function in areas supplied by stenotic vessels *(130)*. Complications of PCPS are principally related to hemorrhage at the access sites. Other limitations include difficult application with significant peripheral vascular disease, a time restriction of about 8 hours, and inadequate ventricular unloading with severe ischemia.

Emergency PCPS has been applied to patients with cardiogenic shock. Shawl and colleagues *(129)* reported institution of bypass within 30–180 min of shock onset (4.4 h from infarct onset) in eight patients. All patients achieved hemodynamic stability with a rise in mean arterial pressure. All seven patients who underwent angioplasty survived at a mean follow-up of 8.2 mo.

The Hemopump support device consists of a continuous flow pump based on an Archimedes screw principle, contained within a 14- or 21-French catheter. The pump rotates at 27,600–45,000 rpm, propelling blood from a vent within the left ventricle to the aorta. The larger device allows flow rates up to 3.5 L/min, whereas the smaller percutaneously inserted 14-French device is limited to rates of 1.7–2.2 L/min *(121,131)*. The Hemopump has been shown to effect significant ventricular unloading while improving regional function to ischemic and reperfused myocardium *(132,133)*. The device can be utilized for several days. Its use is also limited by peripheral vascular disease and is contraindicated with significant aortic vascular or aortic valve disease. Complications are primarily related to thrombocytopenia requiring platelet transfusion (7%), thromboembolism (9.6%), and ventricular arrhythmias (27%) *(121)*.

The Hemopump significantly improves the hemodynamic status of patients with cardiogenic shock *(131,134)*. In a series of 11 patients, there was a significant rise in mean arterial pressure and a fall in left ventricular end-diastolic pressure. Only 4 of the 11 patients survived despite performance of revascularization procedures in 10 of 11 patients *(134)*.

A variety of other ventricular assist devices have been utilized to support patients in cardiogenic shock. These devices provide sufficient hemodynamic support and can unload the left ventricle, potentially reducing infarct size *(135–137)*. Long-term support can be provided, but a thoracotomy is usually required. Recently a method was introduced that results in left atrial to axillary artery bypass by cannulating the left atrium via a transeptal catheter *(127)*. A percutaneous application of this technique has also been reported *(138)*.

Although these devices provide a considerable increment in circulatory support compared with the intraaortic balloon pump, survival (<20%) remains disappointing with mechanical support alone *(135,136)*. Revascularization procedures or cardiac transplantation must be considered in addition to enhance survival.

Reperfusion and Survival

The myocardial salvage and survival benefits of achieving a patent infarct artery have established the importance of reperfusion therapy for MI *(3,139,140)*. A critical link was established between early attainment of complete (TIMI grade 3 flow) infarct artery patency and survival by the GUSTO-I angiographic substudy *(141)*. Intuitively, one would predict a similar salutary connection between early patency and survival in cardiogenic shock. In a series of 200 patients with cardiogenic shock, the mortality rate in

Table 3
Cardiogenic Shock and Thrombolytic Agents

Trial	No.	Mortality (%)	Treatment
GISSI	280	69.9	Streptokinase
International Study Group	322	65	Streptokinase
		78	tPA
GUSTO	2972	51	Streptokinase
		57	tPA

patients with patent infarct arteries was 33 vs 75% with closed arteries *(11)*. The strong association of infarct artery patency and outcome highlights a meaningful achievable target in the progress toward improving the survival of cardiogenic shock.

Thrombolysis

The remarkable reduction in AMI mortality by pharmacologic thrombolysis led to hopeful speculation that these agents would have the potential to impact on the survival of the subgroup with cardiogenic shock favorably. It appears that thrombolysis does reduce the incidence of cardiogenic shock. In the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) *(140)*, the incidence was reduced from 5.1 to 3.8% ($p < 0.05$) with tissue-type plasminogen activator (tPA). Shock (onset >24 h after admission) was also decreased with treatment in the APSAC multicenter trial from 9.5 to 3.2% ($p = 0.03$) *(142)*.

Despite investigation of thrombolytic therapy for MI involving thousands of patients, its utility in established cardiogenic shock remains uncertain. An analysis of 94 thrombolytic trials involving 81,005 patients with MI noted that 22% included patients with cardiogenic shock. Only three trials performed subgroup analysis on this complication and one trial reported data comparing thrombolysis with a control group *(16)*.

The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) trial reported data regarding the effect of intravenous streptokinase on patients with defined cardiogenic shock, and no benefit on hospital survival was identified with treatment ($n = 280$; mortality: streptokinase 69.9%, untreated 70.1%; p = NS) *(3)*. However, both the APSAC Intervention Mortality Study (AIMS) *(143)* and the International Study of Infarct Survival (ISIS)-2 (streptokinase) *(139)* trials reported a survival benefit for treatment with these agents in patients with hypotension, with 33 and 23% reductions in mortality, respectively. Likewise, the Fibrinolytic Therapy Trialists analysis noted that the absolute benefits of thrombolysis are largest in patients with evidence of hemodynamic impairment identified by hypotension, defined by a systolic blood pressure <100 mmHg (60 lives saved/1000 patients treated) or the combination of hypotension and tachycardia (heart rate > 100 beats/min; 73 lives saved/1000 patients) *(144)*. Nevertheless, the mortality of cardiogenic shock patients treated with thrombolytic agents remains high (Table 3).

The equivocal or marginal benefit apparent in these trials may reflect the diminished efficacy of thrombolysis in cardiogenic shock. A reperfusion rate of 44% was reported for 44 cardiogenic shock patients receiving intracoronary streptokinase in the Society for Cardiac Angiography's registry compared with an overall reperfusion rate of 71% *(145)*. Bengston et al. *(11)* reported similar results with a patent infarct artery found in 48% (33

of 69) of patients receiving intravenous thrombolysis. The effectiveness of thrombolysis is determined by complex mechanical, hemodynamic, and metabolic factors. For example, acidosis can impair the transformation of plasminogen to plasmin, decreasing the efficacy of thrombolytic agents in circulatory shock *(146)*.

The reduction of coronary perfusion pressure occurring with cardiogenic shock interferes with the delivery of plasminogen and plasminogen activators to the thrombus *(147)*. Experimental data with magnetic resonance imaging have demonstrated enhanced lysis with pressure-induced permeation of whole blood thrombi *(148)*. Both norepinephrine infusion and intraaortic balloon counterpulsation has been shown to augment coronary thrombolysis in intact animal models *(149–151)*. This principle of pressure-dependent thrombolysis has been extended to the clinical setting. Garber et al. *(152)* reported successful thrombolysis (tPA) in cardiogenic shock patients who responded to dopamine or norepinephrine with a rise in mean arterial pressure (from 64 to 102 mmHg, in six of eight patients treated). A small retrospective community hospital series has demonstrated an improved survival of patients who underwent combined thrombolysis and counterpulsation compared with either treatment alone (n = 36; combined 40%, intraortic balloon counterpulsation 10%, thrombolysis 6%, p = 0.04), all without angioplasty or surgery *(153)*. This combined strategy may play an important role in hospitals without revascularization facilities by stabilizing patients and facilitating their transfer to tertiary centers *(154)*.

Differences have been noted in the relative efficacy of thrombolytic agents in cardiogenic shock. Patients receiving accelerated tPA were less likely to develop cardiogenic shock in the GUSTO-I trial (5.5%) compared with those treated with streptokinase (6.9%; $p < 0.001$) *(4)*. However, there was a trend for a lower 30-d mortality in those who developed shock and were treated with streptokinase and subcutaneous heparin compared with tPA (51 vs 57%; $p = 0.061$). An agent-specific difference was also noted by the International Study Group with a reported mortality of 64.9% with streptokinase and 78.1% with tPA ($p = 0.04$) *(155)*. This advantage may reflect the prolonged systemic fibrinolytic state with decreased viscosity produced by streptokinase.

The exclusion criteria and selection bias present in most trials of thrombolytic therapy have led to an incomplete understanding of its role in treating patients with cardiogenic shock. Patients who experience successful reperfusion of the infarct artery with thrombolysis attain a survival benefit similar to that achieved with other reperfusion modalities. The mortality rates of patients with successful reperfusion by thrombolysis in the Society for Cardiac Angiography's registry *(145)* (n = 44) and the series reported by Bengston et al. *(145)* (n = 33) were 42% and 30%, respectively. Although the reperfusion efficiency of thrombolysis appears to be insufficient without pressure augmentation, this therapy must still be utilized when other reperfusion modalities are not immediately available. Future investigation will be necessary to clarify further the role of thrombolytic therapy in the management of patients with cardiogenic shock.

Coronary Angioplasty

The temporally parallel development of intracoronary thrombolytic therapy and coronary angioplasty within the catheterization laboratory led to their combined application in patients with MI. The hazards of immediate angioplasty in patent coronary arteries after thrombolytic therapy tempered the use of angioplasty in acute infarction. However, the increasing success in patients ineligible for thrombolysis led to confidence in its application as the primary method of reperfusion. Primary angioplasty has been shown

to achieve superior patency (TIMI grade 3 flow) in patients with AMI *(156)*. Evidence has suggested a particular benefit for patients with higher risk characteristics (age >70, anterior location, heart rate >100 beats/min) *(157)*. The recently published GUSTO IIb trial randomized 1138 patients to primary angioplasty or accelerated tPA therapy. Although there was not a significant difference in the incidence of death, reinfarction, or disabling stroke, the composite of these end points demonstrated an advantage for primary angioplasty (9.6 vs 13.7%; $p = 0.033$) *(158)*. A clear benefit in higher risk patients was not observed in this trial. However, analogous to thrombolytic investigation, higher risk patients (especially those with cardiogenic shock) are excluded or underrepresented in trials comparing primary angioplasty with thrombolysis.

A review of nonrepetitive patient series (Table 4) *(2,11,38,39,41,42,159–167)* examining angioplasty as the principal reperfusion modality in cardiogenic shock demonstrates considerable improvement in the hemodynamic parameters of patients undergoing successful angioplasty, with a reduction in left ventricular filling pressure and a rise in cardiac output *(164,167–171)*. A significant increase in left ventricular ejection fraction has also been reported after angioplasty *(170)*.

Reperfusion efficacy in cardiogenic shock is decreased compared with the >90% success rate reported for the overall patient population undergoing primary angioplasty, *(172)*. However, it is superior to the rates reported with thrombolytic therapy.

Examination of these series suggests that survival is enhanced by angioplasty. It should be noted that these studies are nonrandomized and retrospective, with largely undefined entry criteria. Concomitant thrombolytic therapy has often been administered. The patients in reported series tend to be younger, with fewer comorbidities. Considerable selection bias may be operative. Patients who are more critically ill may be excluded or die prior to arrival in the catheterization laboratory, selecting a group with a more favorable chance of survival. These concerns are illustrated by the profile of patients who underwent revascularization in the SHOCK registry. Patients selected for catheterization were younger, with a lower incidence of non-Q-wave infarction. The mortality rate of 55 patients undergoing angioplasty was 55%. However, 43 patients underwent catheterization without revascularization (primarily because of diffuse coronary artery disease) with a similar mortality of 58% *(2)*. A comparable favorable outcome was noted for patients who underwent catheterization only in the GUSTO-I trial *(4)*. More intense use of nonreperfusion therapy such as intraaortic balloon pumping has been reported in patients undergoing catheterization *(2)* and angioplasty *(42)*. A report by Himbert et al. *(162)* may reflect the effects of mechanical reperfusion on a group more representative of the cardiogenic shock population. An overall mortality of 78% was reported in a consecutive series of 25 patients treated with revascularization. The mortality of patients undergoing a successful primary angioplasty in this unselected group was 81% (13/16).

Notwithstanding the lack of a controlled randomized investigation of angioplasty in cardiogenic shock, it is apparent that patients who are successfully reperfused commonly exhibit improved survival compared with patients who remain with a closed infarct artery. This coincides with the documented importance of patency and infarct survival. Most reports have included patients undergoing relatively early reperfusion therapy, and Moosvi et al. *(42)* reported a distinct survival advantage for patients undergoing revascularization within 24 h of the onset of shock (77 vs 10%; $p = 0.0006$). By contrast, Lee and colleagues *(171)* did not demonstrate a temporal relation to outcome at a mean reperfusion time of 20 ± 32 h. Late reperfusion may palliate the shock process of ongoing myocardial necrosis and has been demonstrated to reduce infarct expansion *(173,174)*.

Table 4
Angioplasty and Cardiogenic Shock[a]

Series	No.	Age (yr)	Thrombolysis (%)	Reperfusion (%)	Time (h)	Mortality (%) Hospital/ 30-day	Mortality (%) Successful RP	Mortality (%) Unsuccessful RP	Mortality (%) Long term	MVD (%)	Year
O'Neill et al. *(165)*	27	—	41	88	17[b]	30	25	67	—	—	Pre-85
Lee et al. *(41)*	69	58	29	71	4.7[c]	45	31	80	45 (24 mo)	60	82–85
Shani et al. *(168)*	9	59	0	67	2.3[b]	33	—	—	38 (10 mo)	—	Pre-86
Heuser et al. *(161)*	10	—	0	60	—	40	17	75	—	—	Pre-86
Laramie et al. *(163)*	39	64	0	86	3.9[b]	41	—	—	32 (24 mo)	87	81–87
Hibbard et al. *(39)*	45	63	29	62	6[b]	44	29	71	56 (27 mo)	58	82–89
Yamamoto et al. *(167)*	26	67	23	62	3.5[b]	62	44	90	69 (12 mo)	53	85–90
Moosvi et al. *(42)*	38	63	25	76	33[c]	44	38	78	—	66	85–90
Gacioch et al. *(160)*	48	59	46	73	24[c]	55	39	93	64 (12 mo)	—	85–90
Eltchaninoff et al. *(38)*	33	65	21	76	23[b]	36	24	75	48 (12 mo)	67	86–90
Bengston et al. *(11)*	50	66	36	85	2.8[c]	43	38	71	—	—	87–88
Morrison et al. *(164)*	17	—	0	71	—	53	25	100	—	65	88–94
Himbert et al. *(162)*	21	67	14	86	4.5[b]	70	72	66	84 (17 mo)	68	98–93
Emmerich et al. *(159)*	16	53	0	100	2.9[b]	19	19	—	19 (14 mo)	69	90–94
Hochman et al. *(2)*	55	62	51	69	<24[c]	55	—	—	—	—	92–93

[a] Abbreviations: RP, reperfusion; MVD, multivessel disease.
[b] MI symptoms—angioplasty.
[c] Shock—angioplasty.

In the GUSTO-I trial, most patients developed shock after admission, and those who underwent angioplasty had a significantly lower 30-d mortality (32 vs 61%; $p = 0.028$). Patients with shock on arrival also exhibited a reduction in mortality with angioplasty (43 vs 61%; $p < 0.001$) *(4)*. In addition, this analysis demonstrates the benefits of angioplasty for cardiogenic shock in patients who have received thrombolytic therapy.

The important role of multivessel disease in the pathogenesis of cardiogenic shock has been emphasized. It is difficult to decipher the effects of angioplasty in patients with cardiogenic shock and multivessel disease. A lower reperfusion success rate and a higher mortality in shock patients undergoing angioplasty have been noted in some series. Gacioch et al. *(160)* reported a lower success rate (89 vs 59%; $p = 0.03$) and 30-d survival (56 vs 38%; $p = 0.04$) in patients undergoing angioplasty with multivessel compared with single-vessel disease. Lee et al. *(171)* described an 83% mortality rate of patients with multivessel disease and successful angioplasty. By contrast, multivessel disease was not a disadvantage to angioplasty outcome in other reports *(39,159,167)*. These differences may reflect the divergent spectrum of multivessel disease present in these series. Nonetheless, multivessel disease may mitigate the benefits of angioplasty, as the noninfarct zone function exerts a substantial influence on cardiogenic shock prognosis. Although multivessel angioplasty in the setting of cardiogenic shock has been reported in a few patients *(38,129,169,170)*, operators usually confine transluminal revascularization to the infarct artery in this setting. There is justifiable concern regarding the risk of further hemodynamic compromise with angioplasty of noninfarct vessels. Shawl et al. *(129)* have successfully extended angioplasty to achieve more complete revascularization by utilizing percutaneous cardiopulmonary bypass. Further investigation will be necessary to determine the feasibility and value of multivessel angioplasty in cardiogenic shock.

Little information is available regarding the role of other transluminal revascularization devices in cardiogenic shock. Directional and extraction atherectomy have been used to treat few shock patients *(175,176)*. There is an expanding practice of coronary stent implantation for revascularization of acute infarction *(177)*. Recently, in a selected series, 15 patients underwent stent implantation in the infarct artery during cardiogenic shock, with a reported mortality of 27% *(178)*. Other preliminary data have suggested that coronary stenting has an advantage over balloon angioplasty and may facilitate the application of multivessel transluminal revascularization for shock in the future *(179)*.

Additional adjunctive therapies may augment the application of angioplasty in cardiogenic shock. The use of platelet glycoprotein IIb/IIIa receptor blockade with agents such as abciximab has been shown to decrease ischemic events in patients undergoing primary or rescue infarct angioplasty *(180)*. It has been utilized as an adjunct to stent implantation in cardiogenic shock *(181)*.

Although no firm justification for angioplasty of patients in cardiogenic shock exists, this technique offers promise for attenuating the distressing outcome of this syndrome. Fortunately, both the SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK) and SMASH (Swiss Multicenter evaluation of early Angioplasty for SHock) trials will provide valuable information regarding the effects of angioplasty in cardiogenic shock.

Coronary Artery Bypass Surgery

The introduction of the intraaortic balloon pump brought considerable immediate hemodynamic improvement to patients in cardiogenic shock. However, the challenge of

Table 5
Coronary Artery Bypass Grafting

Series	No.	Age (yr)	Time (h)	Infarctectomy (%)	Hospital/ Mortality (%)	Year
Johnson et al. *(116)*	5	58	2.5–12[a]	40	40	62–74
Mundth et al. *(196)*	22	51	>24	40	40	58–72
Keon et al. *(192)*	21	—	7.8[b]	0	67	70–74
Mills et al. *(195)*	10	50	<24–48[a]	0	0	71–74
Miller et al. *(194)*	10	55	36–144[b]	40	40	Pre-74
O'Rourke et al. *(182)*	6	54	74[a]	0	67	71–72
Cascade et al. *(186)*	7	57	4–24[b]	71	29	71–74
Bardet et al. *(110)*	4	54	24–40[b]	50	50	72–74
Ehrich et al. *(188)*	3	51	>24[b]	0	67	72–74
Willerson et al. *(113)*	3	46	>48[b]	100	67	Pre-75
DeWood et al. *(114)*	19	52	—	5	42	73–78
Nunley et al. *(197)*	14	58	—	0	14	74–81
Subramanian et al. *(200)*	20	55	—	0	45	76–78
Hines et al. *(191)*	7	—	276[b]	0	14	76–80
Phillips et al. *(198)*	34	51	8[a]	0	24	75–82
Connolly et al. *(187)*	14	66	230[a]	0	28	82–84
Laks et al. *(193)*	50	—	103[a]	8	30	81–86
Guyton et al. *(190)*	9	63	6.7[a]	0	22	83–86
Sergeant et al. *(199)*	89	61	2.8[a]	0	21	71–92
Allen et al. *(201)*	66	59	6.2[a]	0	9	86–91
Donatelli et al. *(189)*	8	65	2.2[b]	0	50	94–95

[a]MI symptoms—surgery.
[b]Shock—surgery.

balloon pump-dependent patients and the realization of limited survival benefits led to early use of cardiac surgery. Patients were commonly operated on >24–48 h after the onset of shock, but mortality rates of <60% were encouraging *(40,182,183)*. Infarctectomy or aneurysmectomy (sometimes performed without revascularization) was often combined with bypass grafting. The benefits of myocardial resection have not been proved, and this is now rarely performed *(184,185)*.

The reports (Table 5) of patients undergoing coronary artery bypass surgery for cardiogenic shock share many of the same drawbacks as those noted with angioplasty series *(110,113,114,116,182,186–201)*. Primarily, selection bias interferes with analysis of the effectiveness of bypass surgery in treating cardiogenic shock.

Dewood and colleagues *(114)* emphasized the importance of early revascularization in achieving successful results of bypass surgery. In their series patients operated on within 16 h of infarction onset had a significantly lower mortality than those operated on later (25 vs 71%; $p < 0.03$). If revascularization is delayed and there is evidence of multiorgan failure, mortality rates are high *(184,193)*. Patients undergoing bypass surgery for cardiogenic shock may have a relatively high rate of postoperative complications *(190)*.

The results of coronary bypass surgery in cardiogenic shock have improved over the past two decades. Although better patient selection may play a role, the necessity of early

and complete revascularization has been recognized. Advances in surgical practice have evolved that have led to impressive results in some series. There has been considerable progress in techniques of myocardial protection utilizing blood-based cardioplegia solutions, sometimes substrate enriched (amino acids, oxygen, glucose) and implemented through novel methods of administration (continuous, retrograde). These techniques continue to evolve. The strategy of revascularization may depend on the timing of surgery, proceeding with the infarct artery in early evolving infarction and revascularizing critical "remote" vessels initially when surgery occurs later in the course. Controversy remains regarding the choice of conduits (mammary artery or vein grafts), with some utilizing double-grafting techniques to the left anterior descending artery *(93,202)*.

Perhaps the most compelling results have been reported by Allen et al. *(201)* in a multicenter study reporting a 9% mortality for 66 patients in cardiogenic shock undergoing controlled surgical reperfusion including vented cardiopulmonary bypass and warm, amino acid-enriched blood cardioplegia. Although the investigators emphasize the benefits of prolonged controlled surgical reperfusion in minimizing reperfusion injury *(93,201)*, the surgical advantage of allowing early complete revascularization of remote ischemic myocardium is probably the predominant influence explaining these results.

Of 2972 patients with cardiogenic shock in the GUSTO-I trial, 11.4% underwent coronary bypass surgery with an average 30-d mortality of 29% *(4)*. The SHOCK registry reported a 19% mortality in 19 patients who underwent bypass surgery for shock (29% <24 h) *(2)*. In reviewing the breadth of recent studies involving reperfusion therapy of cardiogenic shock in MI, coronary bypass surgery has shown the most favorable overall results. However, concern remains regarding the frequent lack of details, the nonrandomized nature of these studies, and the selection process occurring before the patient reaches the operating room. The experimental and clinical importance of multivessel disease in the pathophysiology of cardiogenic shock has been established *(36,37,43)*. For now, emergency coronary bypass surgery remains an effective method of revascularization for patients with cardiogenic shock in the presence of left main or the common circumstance of multivessel coronary artery disease. Future investigation such as the ongoing SHOCK trial will clarify its role.

Cardiac transplantation is another alternative surgical therapy that has been successfully applied for salvage of patients with cardiogenic shock. Chamagnac et al. *(203)* reported a 70% survival at 30 mo for 15 patients who underwent transplantation at an average of 15 ± 14 d after the onset of infarction. A left ventricular assist device was used prior to transplantation in six patients.

Right Ventricular Infarction

The initial management of patients with shock from right ventricular infarction involves administration of volume to augment right ventricular function and maintain adequate left ventricular preload. Venous dilation with drugs such as nitroglycerin must be avoided. Inotropic agents such as dobutamine or dopamine may be necessary. Maintenance of right atrial contraction is important and may require arteriovenous sequential pacing or cardioversion of arrhythmias. Intraaortic balloon counterpulsation should be employed with persistent hypotension, especially in the presence of multivessel coronary artery disease. Right ventricular assist devices or pulmonary artery counterpulsation have also been utilized *(44)*.

Reperfusion therapy has been shown to reduce the right atrial pressure and the RA/PCW ratio in patients with right ventricular infarction undergoing angioplasty of the right coronary artery within 24 hours of hospital admission *(204)*.

Therapy of Mechanical Complications

The onset of shock in patients suffering the major mechanical complications of MI portends a poor outcome (mortality rate of 77% for patients with severe mitral regurgitation or ventricular septal defect in the recent SHOCK registry) *(14)*. Early recognition and prompt corrective maneuvers are necessary to improve survival.

Previous data suggested a lower operative mortality when surgery was delayed for patients with acute severe mitral regurgitation or ventricular septal rupture. However, a deadly selection process occurs, with a substantial proportion of patients unable to survive until a late operation. This process is especially evident in patients who are in cardiogenic shock, with nearly 100% mortality without surgery *(50,205,206)*. Intraaortic balloon counterpulsation may stabilize the hemodynamic derangement *(101)* but the potential for sudden decompensation remains *(205,206)*. Although overall mortality with surgical treatment remains high *(14)* excellent survival statistics have been reported by the early operative approach of some series reports *(72,207)*. A few patients in cardiogenic shock with acute severe mitral regurgitation secondary to papillary muscle dysfunction have been successfully treated with emergency coronary angioplasty *(208,209)*. This approach requires careful differentiation of ischemic dysfunction from rupture via echocardiography. The current standard of care dictates urgent completion of diagnostic studies and transfer for operative correction of these defects.

Free wall rupture of the left or right ventricle is commonly a fatal event. Patients identified by electromechanical dissociation requiring ongoing cardiopulmonary resuscitation have rarely survived, although a few successful surgical cases have been reported *(185)*. Surgical results in subacute rupture are more favorable (50% survival) *(57)*. Hemodynamic improvement may occur through the maneuvers of volume administration, inotropic agents, and pericardiocentesis, allowing stabilization for transfer to the operating room *(210)*. Recently medical management of selected patients with left ventricular free wall rupture has been reported by Figueras and colleagues *(211)*. Fifteen patients with continuing electromechanical dissociation underwent suture of the rupture site, with only two survivors. Of 19 patients who recovered from electromechanical dissociation or hypotension through the use of pericardiocentesis (15 patients), intravenous volume, and dobutamine, 15 survived with subsequent bed rest and β-blocker administration. Thus survival is possible through cautious medical management in some patients who recover from initial tamponade.

The Modern Strategic Approach

The management of patients with cardiogenic shock mandates a rapid decision process and efficient delivery of care (Fig. 3). Assessment of the predictive indicators of shock should accentuate the goal of myocardial salvage in patients at risk. Salvage angioplasty and early intervention in treating recurrent ischemia may curtail myocardial injury, thereby decreasing the possibility of left ventricular power failure. Early meticulous management of hypotension or heart failure may prevent progression.

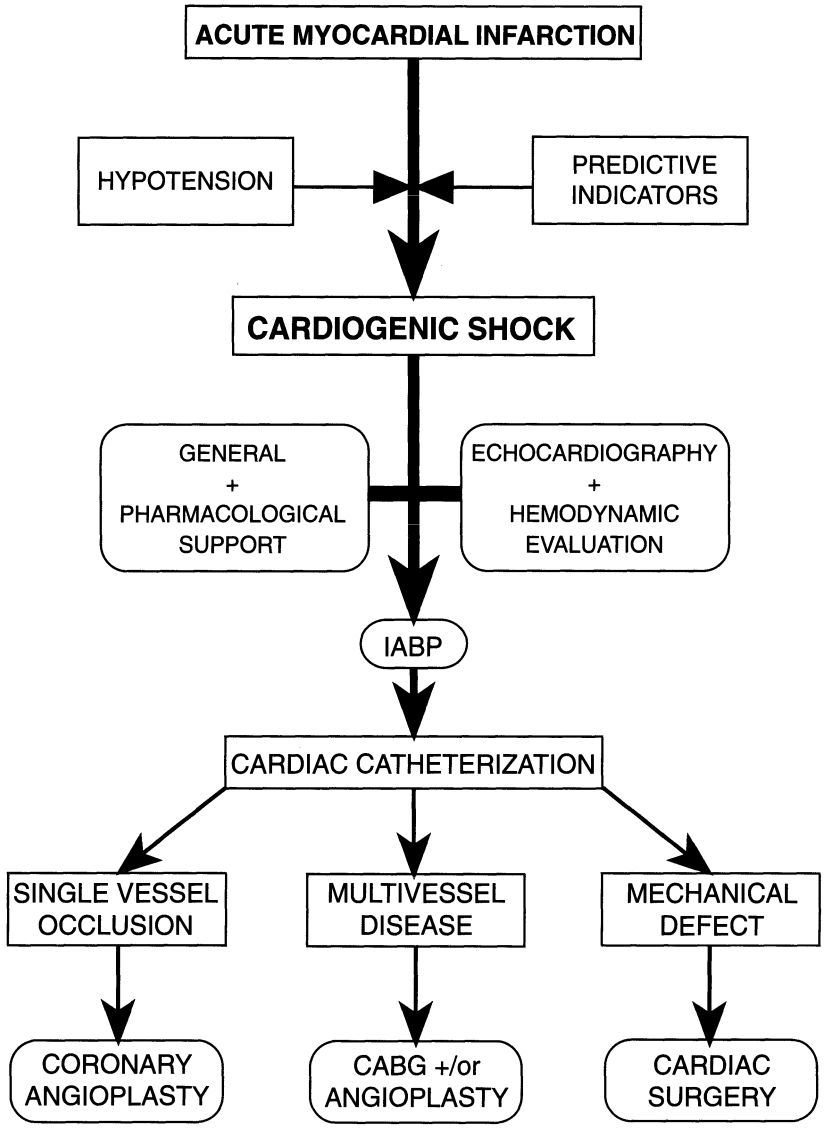

Fig. 3. Modern strategy of cardiogenic shock.

In patients with established shock, diagnostic evaluation and supportive therapy should proceed as parallel processes. Hemodynamic evaluation, echocardiography, and vasopressor therapy should be enacted promptly. Assessment of comorbidities and other factors may direct the intensity of care (see below). The current balance of available data suggests a significant survival advantage for patients undergoing revascularization procedures. The benefits of early application of these procedures has been emphasized *(42,114)*. The GUSTO-I experience and success of rescue angioplasty supports the use of thrombolytic therapy in patients who present with shock to hospitals without revascularization facilities. Institution of counterpulsation if possible and transfer to a revascularization center should follow. Most patients will require counterpulsation prior to coronary angiography. Single-vessel obstruction can usually be approached with coro-

nary angioplasty. Correlation of coronary anatomy and regional left ventricular function may aid decisions regarding revascularization of patients with multivessel disease.

CONTEMPORARY DECISIONS IN CARDIOGENIC SHOCK

The persistently high mortality of patients with cardiogenic shock invites controversy over the intensity of care. Aggressive revascularization and support of patients with cardiogenic shock shows considerable promise, but the modern outcome-directed distribution of health-care resources requires justification for these approaches. Societal opinion, advanced care directives, and outcome-linked reimbursement influence the direction of therapeutic intensity. Although selection criteria and other bias may have affected the observations, the reduced mortality of shock patients treated in the United States compared with other countries participating in the GUSTO-I trial has been attributed to more extensive use of invasive diagnostic and therapeutic modalities *(212)*. Even in the United States, aggressive therapeutic modalities may be underutilized. In 1891 patients with cardiogenic shock, intraaortic balloon counterpulsation was used in 35%, angioplasty in 26%, and bypass surgery in 16%. Patients in the SHOCK registry who did not undergo catheterization had a significantly higher mortality (85 vs 51%; $p < 0.0001$), were older (70 vs 64 y), and had a higher likelihood of non-Q-wave infarction (23 vs 7%) *(2)*. The more rapid demise of patients who do not receive these procedures partially explains the lack of intervention, but the international differences mentioned above demand analysis of the decision processes employed by physicians caring for patients with cardiogenic shock.

Refinement in the application of resources may be possible through further characterization of prognostic indices. Advanced age has been associated with a poor outcome of patients undergoing revascularization in cardiogenic shock *(39,162,166,167,184,185,190)*. Quigley et al. *(213)* reported a 94% mortality for the "left main shock syndrome" (acute anterior infarction, severe left main stenosis, and cardiogenic shock) and suggested that conservative therapy may be indicated in this subset. Certainly futile efforts are undesired, but ultimately the determination of the benefits of aggressive intervention can only be ascertained through controlled randomized investigation.

CONCLUSIONS

Cardiogenic shock is the primary cause of hospital death after MI. Several conditions must be distinguished from left ventricular power failure as the etiology of hypotension accompanying MI. Multivessel coronary artery disease effects abnormal function of regions remote from the infarct segment and plays a major role in the pathophysiology of cardiogenic shock.

Aggressive management of cardiogenic shock includes concomitant diagnostic and therapeutic measures. Identification of predictive indicators may allow early preventative actions. Although not of proven survival benefit, pharmacologic and mechanical supportive maneuvers are necessary adjuncts. In patients with ventricular septal defect or papillary muscle rupture, early operative correction is necessary to affect the poor overall outcome of these mechanical defects.

The survival benefit of early infarct artery reperfusion in acute MI appears to extend to the subset with cardiogenic shock. Angioplasty and coronary artery bypass surgery appear to be superior to thrombolytic therapy in effecting infarct artery patency in this hemodynamic subset.

Despite increased understanding and therapeutic promise, cardiogenic shock remains an ominous diagnosis. The revascularization strategy for cardiogenic shock will continue to evolve through trials to be completed in the near future. The role of metabolic myocardial support, mitigation of reperfusion injury, and newer circulatory support devices must also be clarified.

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23 Cholesterol Lowering

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INTRODUCTION

The evidence that cholesterol has the central role in the atherosclerotic process is derived from all disciplines of medical research, ranging from molecular biology to randomized clinical trials. The epidemiologic proof is particularly strong and consistent. Coronary heart disease (CHD) is rare in populations with low serum cholesterol levels *(1,2)*. In comparisons of countries with varying incidence of CHD, there is a strong positive correlation between serum cholesterol levels and the risk of coronary heart disease events *(3)*. In countries experiencing an increase in mortality from CHD, a preceding substantial rise in serum cholesterol levels was observed *(4)*. In Finland, where the mortality from CHD has been the highest in the world, the recent decline in mortality has been preceded by a decline in population serum cholesterol levels *(5)*. In epidemiologic studies within Western societies serum cholesterol is a strong risk factor for CHD *(6,7)*. A raised level of low-density lipoprotein (LDL) constitutes the main cause of coronary atherosclerosis *(8)*, in particular small, dense LDL *(9)*. In addition, there is strong evidence that low levels of serum high-density lipoprotein (HDL) cholesterol and

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high levels of serum triglycerides are independent risk factors of CHD *(7,10,11)*. The combination of borderline high-risk LDL cholesterol, raised triglycerides, small LDL particles, and low HDL cholesterol has been labeled as atherogenic lipoprotein phenotype *(12)* or atherogenic dyslipidemia *(13)*, being a typical feature of the metabolic syndrome. The other components of this syndrome are central obesity, hypertension, insulin resistance, and a procoagulant state. Increasing evidence is identifying another apolipoprotein B-containing particle, intermediate-density lipoprotein (IDL), as atherogenic *(14–17)*. The predictive information of serum triglyceride levels may reflect high levels of very-low-density lipoprotein (VLDL) and IDL as triglyceride-rich lipoprotein particles.

Metaanalysis of epidemiologic studies on the link between serum cholesterol and the risk of CHD shows that a sustained increase of population cholesterol by 10% will double the risk *(18)*. Because CHD is almost entirely absent in societies with very low serum cholesterol levels, even though smoking and hypertension are prevalent, elevated serum cholesterol seems to be a prerequisite for development of coronary atherosclerosis. On the other hand, risk factors like smoking and hypertension are not a prerequisite for atherosclerosis in individuals with genetically elevated serum LDL cholesterol. Such risk factors can, however, strongly enhance the rate of transport of LDL through the arterial wall *(19)* and can increase its atherogenic modifications *(20–23)*.

In patients with established CHD, serum cholesterol has not been among the strongest predictors of subsequent risk, because the myocardial damage from atherosclerosis and thrombosis have dominated *(24)*. Still, serum cholesterol stands out as a significant risk factor in patients surviving acute myocardial infarction *(25)*.

ANTIATHEROSCLEROTIC MECHANISMS OF CHOLESTEROL LOWERING

The complexity of the pathogenesis of atherosclerosis makes it difficult to understand what parts of the process are most influenced by cholesterol lowering. Atherosclerosis results from an interaction between blood and the vessel wall. Components of importance are of a genetic, immunologic, inflammatory, particle kinetic, cell kinetic, proliferative, synthetic, degenerative, cytotoxic, and mechanical nature, like blood pressure and flow pattern *(21,26)*. The diseased vessel wall tends to activate the coagulation system and platelets to form thrombi that may further enhance the process of atherosclerosis. Plasma lipoproteins seem to be involved in the spectrum of the process, e.g., LDL seems to have a direct, receptor-independent augmentative effect on platelet reactivity *(27)*. Much emphasis has been placed on the formation of foam cells and the resulting core of lipids that is found in many atherosclerotic plaques *(28)*. Oxidized LDL particles have been believed to be pivotal for this process *(20,29)*. The idea that marked reduction in serum LDL concentration would lead to a net flux of lipids out of the plaque core, which would make the plaque shrink and "stabilize," has been an attractive one, but it probably represents an oversimplification *(26)*. Studies in primates have demonstrated that such shrinkage may take place *(30)*. With the recent knowledge of the role of plaque inflammation, an overripened lipid-loaded plaque does not seem to be a prerequisite for thrombus formation. In many cases of death from CHD and unstable coronary syndromes, plaque morphology does not include a lipid core, but signs of cell proliferation are present, as well as endothelial damage and inflammatory components *(31,33)*.

CHOLESTEROL AND DIET

Cholesterol levels are strongly related to consumption of saturated fatty acids in the diet *(34,35)*; high consumption of animal fat, in particular from milk *(36)*, seems to explain much of the excess mortality from CHD in Western countries. Whereas energy from fat is 35–45% in countries with a high prevalence of CHD, a rate of 15% and lower is typical in populations in which CHD is rare *(37)*; the difference is largely due to saturated fatty acids. Diets rich in monounsaturated fatty acids such as olive oil and polyunsaturated fatty acids such as those found in plant seed oil tend to reduce serum LDL cholesterol and increase HDL cholesterol *(38)*. Such diets seem not to be atherogenic even when fat consumption constitutes 40% of energy, as exemplified by diets typical for Crete and other Mediterranean societies (38).

EFFECT OF DIETARY INTERVENTION

Substituting fish for red meat had no effect on CHD in three epidemiologic studies but seemed protective against CHD in six epidemiologic and two case-control studies *(39)*, and in one randomized controlled trial in patients surviving myocardial infarction, the Diet and Reinfarction Trial (DART) *(40)*. In the Chicago Western Electric Study, 430 deaths from CHD over 30 yr of follow-up were analyzed *(39)*. In men consuming ≥35 g fish/d, the relative risk of death from CHD was 0.62 (95% confidence interval 0.40–0.94) compared with nonconsumers; also a significant ($p = 0.04$) graded relation between the relative risks and strata of fish consumption was seen. The protective components in fish have not yet been clearly defined; the n-3 long-chain polyunsaturated fatty acids may be effective, or it may simply be that less atherogenic nutrients are substituted for saturated fat.

Apart from DART, there have been few randomized clinical trials on dietary intervention following acute coronary syndromes, and all have been small. The first to show encouraging results was the study by Leren in *(41)* 412 hypercholesterolemic men with a first myocardial infarction who were randomized to usual diet or advice to substitute vegetable oil for animal fats and avoid dietary cholesterol. In the first 5 yr of follow-up, serum total cholesterol was reduced by 14% relative to the control group, from a mean baseline level of nearly 300 mg/dL. After 11 yr of follow-up, a significant 44% relative risk reduction in fatal myocardial infarction was found ($p = 0.004$) in the diet group, but total CHD mortality was not statistically significantly different between the groups (diet 79 cases; control 94; $p = 0.097$).

The Lyon Heart Study randomized 605 patients younger than 70 yr old with a first myocardial infarction to receive no dietary advice or to receive advice from a cardiologist and dietitian to adopt a Mediterranean-type diet: more bread, root and green vegetables, more fish, no day without fruit, less meat, and substitution of a margarine consisting of 48% oleic acid and enriched with linoleic and α-linolenic acid for butter *(42)*. Interestingly, the advice did not result in any significant differences between the two groups in serum lipids and lipoprotein levels. Nevertheless, a significant ($p < 0.001$) reduction in the primary end points cardiac death and nonfatal acute myocardial infarction was observed after a follow-up period of up to 5 yr, (mean 27 mo) (Fig. 1). Unfortunately, the study was small, comprising only 41 primary end-point events and has been criticized for premature termination and insufficient statistical power. When only fatal

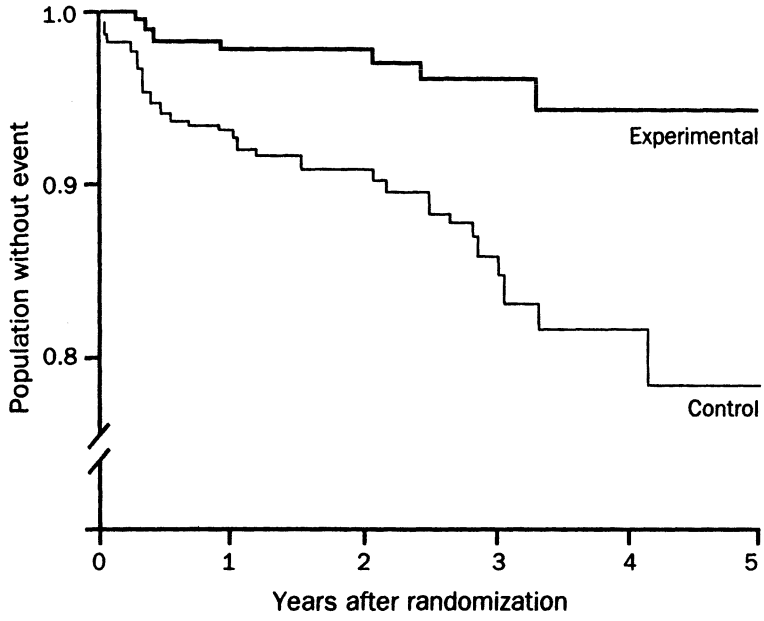

Fig. 1. Survival curves for combined cardiac death and nonfatal acute myocardial infarction in the Lyon Heart Study, comparing a Mediterranean-type diet with a conventional French diet. Reproduced with permission from ref. *42*.

events are analyzed, the upper 95% confidence interval for the risk ratio is a less impressive 0.98 *(43)*.

CURRENT DIET GUIDELINES: DO THEY WORK?

There is no general consensus on the most appropriate dietary advice for adults at high risk or with established CHD. The Expert Panel of the National Cholesterol Education Program issued guidelines consisting of a two-step approach, focusing on reduction of saturated fat and cholesterol content *(44)*: step I, 8–10% of calories from saturated fat and ≤30% of calories from total fat, and <300 mg of cholesterol a day; and for step II, <7% saturated fat and <200 mg of cholesterol/d. It is recommended that CHD patients should begin immediately on the step II diet. The guidelines of the European Atherosclerosis Society are essentially identical to the step I diet *(45)*. However, few randomized controlled clinical trials have been carried out to establish the clinical benefit of these guidelines, in particular in middle-aged CHD patients. Since the consumption of dietary fat has decreased in Western populations during the last decades, the strategy of a step I and II diet following a CHD event may produce relatively less clinical benefit than was possible before. In the Oslo Study in 1232 healthy males with cholesterol levels of 290–380 mg/dL, a step I-type diet was tested in a randomized fashion; however, the participants were also given advice to give up smoking *(46)*. It is therefore not clear what part of the observed 47% reduction of CHD events ($p = 0.028$) was caused by the dietary advice, which produced 13% reduction in total cholesterol, but the authors estimated the effect of cholesterol reduction to account for 60% of the effect. The diet and

smoking intervention group also achieved 20% lower triglyceride levels and 19% higher HDL cholesterol levels than the control group.

In a dietary trial in U.S. patients with LDL cholesterol of 160–200 mg/dL, the step II diet produced only 5% reduction in total and LDL cholesterol *(47)*. In this trial HDL cholesterol was reduced 5% with the step II diet. More recently the Dietary Alternatives Study showed that diets restricting fat intake to 22–25% of energy offered little further advantage than diets with 26–28%, in particular in men with combined hyperlipidemia (both high triglycerides and LDL cholesterol) *(48)*. In the latter group, reducing fat intake from 34% to 25% of energy reduced LDL cholesterol by only 4.4%. Similarly, diets of 15% and 20% fat offered no LDL cholesterol advantage over a diet with 30% fat *(49)*. Greater nonpharmacologic reductions in LDL cholesterol seem to require more extreme life style changes. Ornish and colleagues *(50)* achieved a 37% reduction of LDL cholesterol in a small group of CHD patients through a diet of <10% fat combined with daily meditation, considerable weight loss, and exercise. Only a small minority of patients is today willing and able to undergo such a turnabout of life.

The response of LDL cholesterol to a low-fat diet is dependent on hereditary factors. Individuals with the atherogenic lipoprotein phenotype with small dense LDL particles respond with reduction in apolipoprotein B and hence LDL, whereas those with a predominance of larger LDL particles respond with only a modest reduction in LDL cholesterol and apolipoprotein B *(51)*. In hypercholesterolemic patients without elevation of triglycerides, a low-fat diet will tend to raise triglycerides *(48)*.

DIETARY FAT: QUALITY OR QUANTITY?

The replacement of saturated and trans-saturated fats by unhydrogenated monounsaturated and polyunsaturated fats may be as effective as a drastic reduction in overall fat intake in reducing CHD. In the Nurses' Health Study, a prospective epidemiologic investigation of over 80,000 women, it was calculated that replacement of 5% of energy from saturated or trans-unsaturated fat with mono- or polyunsaturated fat would reduce the risk of CHD by 32–53% *(52)*. A meta-analysis of studies comparing butter, hard high-trans margarines, and soft low-trans margarines concluded that substituting low-trans margarines for the other two resulted in a favorable reduction of 0.2 in the total/HDL cholesterol ratio *(53)*. Recently, use of a margarine enriched with the plant sterol sitostanol ester has been shown to reduce LDL cholesterol by 14%, probably by inhibiting the absorption of dietary cholesterol *(54)*.

FIBER

Another dietary component that may have a favorable impact on serum lipids is fiber, especially from cereals, vegetables, and fruit, possibly from decreased absorption of fatty acids and biliary cholesterol *(55)*. Such diets may also substantially lower blood pressure *(56)*. In the Health Professionals Follow-Up Study of over 51,000 men followed prospectively since 1986, the relative risk of CHD was 0.59 (95% confidence interval 0.46–0.76) among men in the highest quintile of total dietary fiber intake, compared with men in the lowest quintile *(57)*. However, one randomized trial of men with CHD failed to demonstrate a benefit of increased fiber intake with regard to reinfarction rate, possibly because the follow-up period was too short, only 2 yr *(40)*. Consumption of 25–75 g/d of soy protein, rather than animal protein, has been shown to reduce LDL cholesterol by 13% in a large metaanalysis *(58)*.

ALCOHOL

Several epidemiologic investigations have now found that regular moderate consumption of alcohol is associated with an increase in HDL cholesterol and a decreased mortality from CHD. In a study of 490,000 men and women, the rates of death from cardiovascular diseases were 30–40% lower among those reporting at least one drink daily than among abstainers *(59)*. However, the drinking pattern may be important, as binge drinking of beer was associated with a sixfold increased risk of fatal myocardial infarction, in comparison with men drinking less than three bottles a session *(60)*. In other investigations, the lowest mortality from CHD was seen in individuals drinking 2–3 U/d *(61)*. Another study found that the lower mortality was associated with wine drinking only and not beer or spirits *(62)*. Small amounts of alcohol taken regularly instead of taking the same amount 1 or 2 d/wk seem to result in greater benefit *(63)*. Alcohol increases the HDL cholesterol subclasses that are protective of CHD and slightly reduces the level of LDL cholesterol; red wine with meals reduces the propensity of LDL to undergo peroxidation *(64)*. Alcohol also has theoretically favorable effects on platelets and the coagulation–fibrinolytic system *(65)*. To date, however, no prospective randomized study has evaluated the feasibility and clinical and social consequences of advising abstainers and people who rarely taste alcohol to take up regular drinking to reduce the risk of CHD. Therefore, the knowledge of effects of alcohol on CHD should be applied more to reassure moderate drinkers that their habits are not harmful.

DRUGS TO REDUCE CHOLESTEROL

Statins

A wide range of drugs affecting lipid metabolism has become available. They vary greatly in their mechanism of action and their potency in reducing LDL cholesterol and increasing HDL cholesterol. During the last decade, the hydroxy-methylglutaryl-CoA-reductase inhibitors, or statins, have become the most widely prescribed class of drugs because of their very low rate of side effects and greater effectiveness in reducing LDL cholesterol than other classes of drugs. Because they are the only class of drugs proved to reduce all-cause mortality, physicians without expert insight into lipid metabolism and pharmacology of the other classes of drugs are perfectly safe in using statins as the only lipid-lowering therapy.

Statins inhibit the rate-limiting step of mevalonate synthesis in the production of cholesterol, mainly in the liver. The number of LDL receptors on the liver cell membrane is therefore upregulated to increase import of cholesterol from the blood to meet demand in the liver. As a consequence, the number of LDL particles in plasma is reduced. Ability to reduce LDL cholesterol concentrations, using the currently highest recommended dosages, ranges from 30 to 60% on average according to the following rank order: fluvastatin, cerivastatin, pravastatin, lovastatin, simvastatin, and atorvastatin. Statins usually do not increase HDL cholesterol levels >10%, even at high dosages, but doubling of any dose typically produces another 6% decrease in LDL cholesterol. Usually triglycerides are reduced by 10%, but at higher dosages and in patients with hypertriglyceridemia, 30–45% reduction can be seen.

Statins have been found to induce a large number of direct, possibly beneficial effects on components in plasma and cells involved in the atherosclerotic and thrombotic process. These include inhibition of smooth muscle cell proliferation and migration *(66,67)*, inhibition of endogenous cholesterol synthesis in macrophages *(68)*, regulation of natural

killer cell function *(69)*, and decreased platelet aggregation *(70)*, as well as numerous others. The clinical importance of these ancillary effects, beyond reduction of LDL cholesterol, remains to be demonstrated.

Fibrates

Fibrates decrease the synthesis and increase the catabolism of VLDL particles, rich in triglycerides, and typically decrease serum triglycerides by 30–40% or even more in hypertriglyceridemia. Apparently LDL clearance is also increased, causing LDL cholesterol reductions of up to 10–15% with clofibrate, gemfibrozil, and bezafibrate. Fenofibrate and ciprofibrate may reduce LDL cholesterol by 20–35% at maximum dosages. HDL cholesterol is increased 10–15% with gemfibrozil and up to 20% with bezafibrate, fenofibrate, and ciprofibrate. Adverse events are mostly gastrointestinal in nature and include increased incidence of gallstones. A metaanalysis of clinical trials with fibrates indicated increased mortality from all causes when the cholesterol-lowering effect was modest *(71)*.

Other Drugs

Niacin

Niacin reduces the synthesis of VLDL and thus reduces plasma triglyceride levels by about 30%. The reduction in LDL cholesterol is modest, typically 10%, but occasional patients tolerating higher dosages may experience a 20% reduction. An increase in HDL cholesterol of 10–15% is also obtained. The main advantages of niacin are first that it is relatively inexpensive and second that it reduces the plasma concentration of lipoprotein (a), a potentially atherogenic particle, by up to 30%. The disadvantages are that niacin has several side effects; the more serious adverse reactions include deterioration of diabetes and gout and hepatotoxicity.

Resins

Resins bind to bile acids in the intestine, and the complex is not reabsorbed but excreted. This causes the liver to increase the synthesis of bile acids, and the subsequent increased demand for cholesterol induces the same effect as inhibition of cholesterol synthesis: an increase in the number of LDL receptors on the cell surface. This results in a reduction in plasma LDL cholesterol of up to 20% when cholestyramin or colestipol is used at dosages of 20–24 g daily. Adverse effects of a gastrointestinal nature are frequent with high dosages. The resins offer no advantage over the statins, either in price or potency, and are used today mostly in combination with statins in patients with severe hypercholesterolemia. One disadvantage of resins is that triglyceride levels are sometimes increased, especially in hypertryglyceridemia. HDL cholesterol may increase by up to 10%.

Fish Oils

Fish oils with concentrated omega-3 fatty acids decrease the production of VLDL; thus triglyceride levels decrease by up to 30% in hypertriglyceridemic patients. The exact role of fish oils in prevention of CHD has not been established in randomized clinical trials.

Hormone Replacement Therapy

Hormone replacement therapy with estrogen or the combination of estrogen and a progestin is widely used in the United States even though no randomized study has

established a clinical benefit of such therapy in CHD. Estrogen typically produces a 10–15% reduction in LDL cholesterol and 25% increase in HDL cholesterol. In combination with progestin, the effect on HDL cholesterol is attenuated to an approximately 10% rise. The effect on triglycerides is variable, and sometimes an increase is observed.

CHOLESTEROL LOWERING: THE ANGIOGRAPHIC EVIDENCE

Since 1984, the objective of a large number of clinical trials has been to investigate coronary vessel lumen morphology by angiography and the changes induced by long-term cholesterol lowering *(50,72–89)*. In most of these trials angiographic evidence of retardation of progression of atherosclerosis and prevention of new lesions were demonstrated with cholesterol lowering, almost regardless of what methods were used. However, even though these are often referred to as "regression" trials, signs of plaque shrinkage were much less convincing, and at best the lumen diameter increased by a few percentage points or by a few hundred millimeters. Angiographic determination of the extent of atherosclerosis has inherent methodologic problems, as compensatory remodeling of the vessel takes place over time *(90)* and plaques vulnerable to rupture and thrombosis are often invisible *(91)*. It is often not possible to determine the difference between plaques and thrombi from an angiogram. The latter commonly undergo lysis or growth, and finally, local changes in vascular tone may be mistaken for atherosclerotic changes. Despite these pitfalls, the groups randomized to cholesterol lowering on average experienced regression in about one-fourth of lesions. A metaanalysis of 12 of these trials found that the relative risk of progression was 0.66 (95% confidence interval 0.59–0.73), and that of regression was 2.03 (95% confidence interval 1.64–2.52) with cholesterol lowering *(92)*.

In addition, trials have demonstrated retardation of intimal thickening of carotid arteries with cholesterol lowering using B-mode ultrasound *(93–95)*.

ACUTE EFFECTS OF CHOLESTEROL LOWERING

In the angiographic "regression" studies, treatment duration was typically 2–4 yr before any morphologic changes could be observed. In the Multicentre Anti-Atheroma Study (MAAS) trial, no significant difference between the two treatment groups was observed at the first angiography performed after 2 yr. Only after 4 yr of therapy did the difference become evident *(85)*.

A number of investigations have shown that other physiologic responses to cholesterol therapy can be observed much earlier. Gould and coworkers *(96)* found improvement in myocardial perfusion abnormalities after only 90 d of intensive cholesterol lowering, using dipyridamole and positron emission tomography imaging. The pathologic vasoconstrictory response of atherosclerotic coronary arteries to infusion of acetylcholine was blunted after 6 mo of cholesterol lowering with lovastatin in one study *(97)* (Fig. 2), and after 12 mo with lovastatin with a combination of cholestyramine or probucol in another *(98)*. It was later shown that cholesterol lowering produced more rapid improvements in endothelial function. One-month therapy with simvastatin induced significant increases in the vasodilator response to acetylcholine in the forearm vasculature in hypercholesterolemic subjects, as measured by strain-gauge plethysmography *(99)*. Even a single LDL apheresis was shown to improve endothelium-dependent vasodilation immediately, as measured by plethysmography in hypercholesterolemic individuals *(100)*. In this study, the 2-h apheresis procedure reduced LDL cholesterol by 76% and

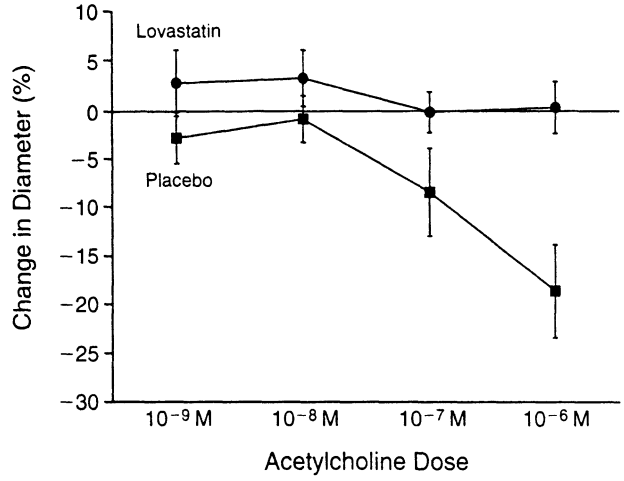

Fig. 2. Change in lumen diameter of coronary arteries with increasing doses of acetylcholine infusion after 6 mo of therapy with lovastatin or placebo. Reproduced with permission from ref. *97*.

oxidized LDL by 67%. The underlying mechanism for this rapid response may be that oxidized LDL decreases the synthesis of endothelial nitric oxide and inactivates it by transfer of free radicals *(101)*. In vitro studies shows that oxidization may induce marked changes in the composition of LDL and its fatty acids, but interference with arterial relaxation appears to be mainly linked to cholesterol oxides *(102)*.

The abnormal vascular response is not only seen in patients with marked hypercholesterolemia. Even healthy individuals with LDL cholesterol levels well within the range considered "normal" (>25th and <75th percentile in the United States [mean 119 mg/dL]) had blunted responses to infusion of the endothelium-dependent vasodilator metacholine chloride, compared with those with low levels (<25th percentile [mean 87 mg/dL]) *(103)*.

The experimentally induced rapid changes in vascular response with cholesterol lowering have been quite profound and consistent. However, translation of these findings into clinically important changes of symptoms and events has not yet been clearly demonstrated. Andrews and colleagues *(104)* provided proof that the acute effects may be of benefit to a subset of patients with myocardial ischemia. Using lovastatin in combination with diet for 4–6 mo to reduce LDL cholesterol, ST-segment depression by 48 h of ambulatory electrocardiographic (ECG) monitoring resolved in significantly more patients (65%) than in patients on diet alone (10%) ($p < 0.001$) (Fig. 3). Symptomatic effects or clinical events were not studied. Large-scale clinical trials of severely symptomatic patients or in the immediate follow-up period of unstable coronary syndromes will be needed to demonstrate such potential clinical effects; these have not yet been carried out.

CLINICAL END-POINT TRIALS OF CHOLESTEROL-LOWERING DRUGS

Until 1994, over 25 randomized clinical trials of long-term cholesterol-lowering drug therapy had reported mortality data *(18)*. The most important of these trials, involving patients with previous myocardial infarction as well as healthy, hypercholesterolemic

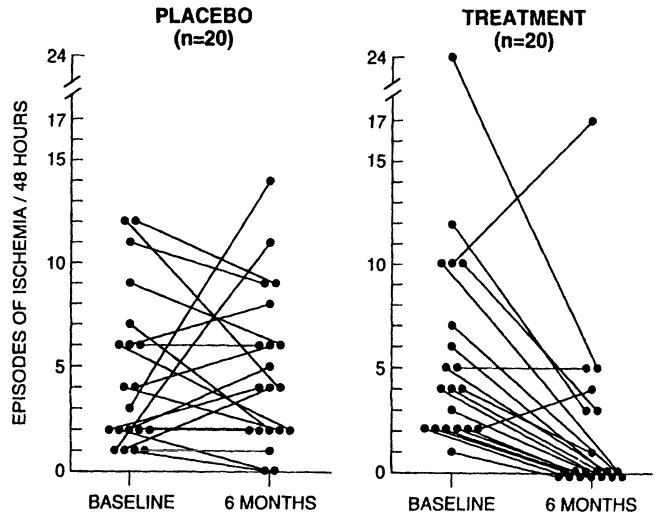

Fig. 3. Patient-by-patient effect of cholesterol lowering over 6 mo on the number of episodes of ischemic ST-segment depression in patients with coronary disease. Two of 20 in the placebo group vs 13 of 20 in the treatment group show resolution of ischemia. Reproduced with permission from ref. *104.*

individuals, had used clofibrate, niacin, colestipol, cholestyramine, and gemfibrozil *(105–110).* One trial used surgical therapy with ileal bypass rather than drugs or diet as experimental interventions *(78).* However, no single trial had been able to demonstrate convincingly that all-cause mortality would be reduced with such therapies, even in high-risk populations such as patients with myocardial infarction. The focus on insignificant findings from these trials, suggesting increased risk of cancer, suicide, and violent deaths as well as other hazards from cholesterol lowering created mistrust in the majority of physicians. Consequently, even if new powerful cholesterol-lowering drugs became available, they were rarely used by most of physicians, not even in hypercholesterolemic patients with acute coronary syndromes. Since 1994, clinical practice has started to change as new, large-scale controlled trials using simvastatin, pravastatin, and lovastatin have demonstrated great clinical benefit with the long-term use of such drugs.

When considering trials of cholesterol-lowering therapy, the distinction between so-called primary and secondary prevention is artificial and should be avoided. None of the primary prevention trials were really primary in preventing atherosclerosis, as they have been randomizing middle-aged or elderly individuals and observing the rate of CHD events over a few years. At the time of randomization, it can be assumed that all patients developing a CHD event already had extensive coronary atherosclerotic lesions. Therefore, the primary and secondary preventive trials are only different with regard to the absolute risk of the study population.

The Statin Trials

The first study to demonstrate improved survival was the Scandinavian Simvastatin Survival Study *(111).* This study randomized 4444 men and women aged 35–70 yr to long-term therapy with simvastatin or placebo in a double-blind fashion. Only patients with a fasting total cholesterol level of 5.5–8.0 mmol/L (212–309 mg/dL) and triglyceride level <2.5 mmol/L (221 mg/dL) 2 mo after receiving dietary advice equivalent to the

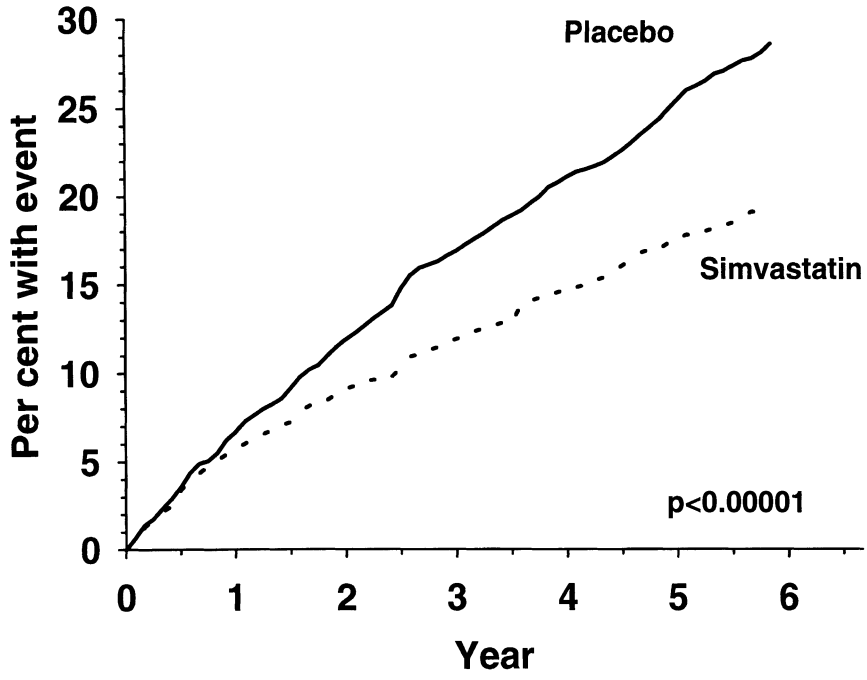

Fig. 4. Kaplan-Meier curves of the incidence of major coronary events: fatal CHD or nonfatal myocardial infarction in 4S.

step I diet of the NCEP guidelines *(44)* and the European Atherosclerosis Society guidelines *(45)* were included. The simvastatin dose was 20 mg daily and was titrated to 40 mg after 12 or 24 wk if serum total cholesterol exceeded 5.2 mmol/L (200 mg/dL), which was necessary in 37% of patients. This therapy led to a mean reduction in LDL cholesterol over the whole course of the study of 35% and 10% in triglycerides, whereas HDL cholesterol increased by 8%. During the median follow-up of 5.4 yr (range of those surviving 4.9–6.3), 256 patients (11.5%) died in the placebo group, against 182 (8.2%) in the simvastatin group, a relative risk reduction of 30% ($p = 0.0003$). CHD mortality was reduced 42% relative to placebo, and fatal and nonfatal infarction and coronary deaths were reduced by 34% (Fig. 4). In addition, coronary revascularization procedures (bypass surgery or angioplasty) were reduced by 37%. The difference between placebo and simvastatin groups with regard to coronary events was small in the first year of therapy and reached clinical significance after approximately 14 mo from randomization.

Three large studies with pravastatin were published in the next 3 yr. The first was the West of Scotland Coronary Prevention Study (WOS) in 6595 men with LDL cholesterol in the range of 4.0–6.0 mmol/L (155 to 232 mg/dL) using pravastatin 40 mg daily or placebo over a period of 5 yr *(112)*. Pravastatin lowered LDL cholesterol by 26%, leading to a relative risk reduction of 33% in the risk of coronary deaths, which resulted in a 22% reduction in all-cause mortality ($p = 0.39$ when adjusted for baseline variables). Nonfatal myocardial infarction or death from CHD was reduced 31% ($p > 0.001$), and the need for coronary revascularisation was reduced 37% ($p = 0.009$).

The Cholesterol and Recurrent Events (CARE) study randomized 4159 men and women with previous myocardial infarction and LDL cholesterol levels of 3.0–4.5 mg/dL (115–174 mg/dL) to placebo or pravastatin 40 mg daily for 5 yr *(113)*. In this study, pravastatin

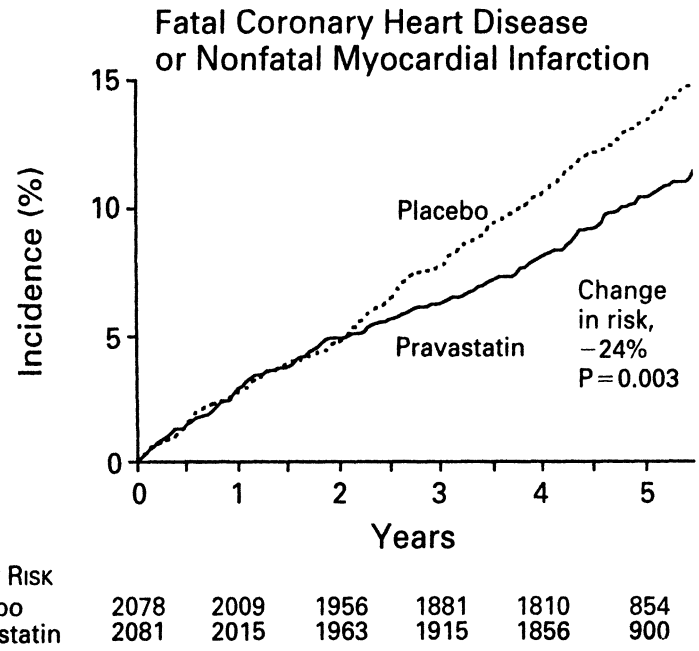

Fig. 5. Kaplan-Meier curves of the incidence of fatal CHD or nonfatal myocardial infarction, from the CARE study. Reproduced with permission from ref. *113*.

lowered LDL cholesterol by 28% relative to placebo, which was associated with a risk reduction of major coronary events of 24% (Fig. 5). Coronary bypass surgery and angioplasty was done in 26% fewer cases in the pravastatin group. The rates of death from CHD were low, and the 20% reduction in the pravastatin group did not reach statistical significance. Although similar in size, the 4S and CARE studies differed in the risk of the study population (Table 1), not only because the CARE patients had lower cholesterol levels, but probably more because 54% of the patients had undergone a recent coronary bypass surgery or angioplasty. In 4S such patients were excluded, unless they had experienced a new infarction or recurrent angina following the procedure (8% of the patients).

The largest study with pravastatin was the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, which included 9014 men and women with previous acute coronary syndromes *(114)*. The placebo-controlled double-blind study was stopped prematurely after 5 years because of significant results in favor of pravastatin 40 mg daily. The study population had baseline total cholesterol levels in the range of 4.0–7.0 mmol/L (155–270 mg/dL), triglyceride levels <5 mmol/L (445 mg/dL), and a median LDL cholesterol of 3.88 mmol/L (150 mg/dL). Preliminary results presented at the 70th Scientific Session of the American Heart Association in November 1997 included a highly significant 24% reduction in CHD mortality and a 23% reduction in all-cause mortality as well as similar percent reductions in coronary revascularization procedures and major CHD events.

At the same meeting, in November 1997, the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) were presented. This study included 6605 men and women without clinical evidence of cardiovascular disease and total cholesterol in the range 4.7–6.8 mmol/L (180–264 mg/dL), HDL cholesterol <1.3 mmol/L (50 mg/dL), and triglycerides <4.5 mmol/L (400 mg/dL) *(115)*. This study used

Table 1
Mortality and Morbidity in the Scandinavian Simvastatin Survival Study (4S) and in the Cholesterol and Recurrent Events (CARE) Study[a]

	4S *[No (%) of patients]*		*CARE* *[No (%) of patients]*	
Event	*Placebo* *(n = 2223)*	*Simvastatin* *(n = 2221)*	*Placebo* *(n = 2078)*	*Pravastatin* *(n = 2081)*
Coronary deaths	189 (8.5)	111 (5.0)	119 (5.7)	96 (4.6)
Other cardiovascular deaths	18	25	11	16
Death from cancer	35	33	45	49
Suicide, violence, trauma	7	6	4	8
Other deaths	7	7	15	11
Unclassified cause of death			2	0
All deaths	256 (11.5)	182 (8.2)	196 (9.4)	180 (8.6)
Nonfatal MI (definite)	270 (12.1)	164 (7.4)	173 (8.3)	135 (6.5)
Nonfatal MI (definite/probable)	418 (18.8)	279 (12.6)		
Death from CHD or nonfatal MI[b]	622 (28.0)	431 (19.4)	274 (13.2)	212 (10.2)
CABG or PTCA	383 (17.2)	252 (11.3)	391 (18.8)	294 (14.1)

[a]Abbreviations: MI, myocardial infarction; CHD, coronary heart disease; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

[b]Numbers for 4S include definite and probable MI as well as silent MI, diagnosed by annual electrocardiogram.

lovastatin 20–40 mg daily with the goal of lowering LDL cholesterol to <2.9 mmol/L (110 mg/dL), and a 27% reduction relative to placebo was achieved at yr 1. The primary end point of major coronary events, which included unstable angina pectoris, was reduced 36% ($p < 0.001$) with lovastatin, but the study was not powered to show reductions in coronary or total mortality.

The previous concern of increase in the risk of noncardiovascular mortality was not confirmed in the statin studies. Furthermore, in the studies with most events there was a significant 20–30% reduction in the risk of cerebrovascular disease. The safety of long-term therapy with statins seems reassuring. Apart from a minimal risk of myopathy, no other serious adverse experiences have been seen in the long-term trials. The slight elevation of liver enzymes observed in a small proportion of patients has not been associated with increased incidence of clinical signs of liver disease *(116)*.

Another important finding from the statin trials is the consistency of benefit observed across all major subgroups of patients that have been analyzed. This included patients at the highest risk of major CHD events, like the elderly and patients with multiple risk factors, including smoking, hypertension, and diabetes. In 4S the diabetic subpopulation had a 55% reduction in the risk of major coronary events ($p = 0.002$), and since the diabetic sugroup have a 2.5-fold higher risk (almost half of the diabetic patients in the placebo group suffered a major event), the absolute risk reduction is formidable *(117)*.

In 4S, significant reductions in major CHD events were seen regardless of the baseline LDL cholesterol level, which ranged from 3.0 to 6.8 mmol/L (115–262 mg/dL) *(118)*. In the CARE study, similar benefits were observed at baseline LDL cholesterol levels down

Table 2
Major Randomized Clinical Trials of Cholesterol Lowering[a]

		Reduction (%)		Risk reduction (%)	
Study	*Therapy*	*Total cholesterol*	*LDL cholesterol*	*Coronary mortality*	*Major coronary events*
CDP *(105)*	Clofibrate	7	?	13	9
WHO *(107)*	Clofibrate	9	?	11	20
CDP *(105)*	Niacin	10	?	2	13
LRC *(109)*	Cholestyramine	13	20	30	15
LIPID[b]	Pravastatin	20	24	24	23
WOS *(112)*	Pravastatin	20	26	33	31
CARE *(113)*	Pravastatin	20	28	20	24
POSCH *(78)*	Ilial bypass	23	38	37	35
4S *(111)*	Simvastatin	26	36	42	34

[a]Showing reduction in total and low-density lipoprotein (LDL) cholesterol with therapy relative to the control group, as well as relative risk reduction in coronary mortality and major coronary events.
[b]Preliminary data.

to 125 mg/dL but not in the subgroup with LDL cholesterol of 115–125 mg/dL *(113)*. However, in this subgroup there may have been too few end points to detect a benefit, as the 95% confidence interval ranged from 23% reduction to 38% increase in the relative risk. It is possible that the attributable risk of LDL cholesterol is smaller in patients who develop CHD with low levels. Other factors may promote cholesterol uptake by the arterial intima and subsequent atherosclerosis. Therefore, to minimize risk in such patients, greater reductions in the level of LDL cholesterol than the 28% achieved with pravastatin may be necessary. Table 2 shows the reduction in total and LDL cholesterol achieved in the largest trials and the resulting reduction in clinical end point. There is a clear trend that the more cholesterol is reduced, the greater is the reduction in events.

In 4S and WOS, the time until significant differences appeared between the placebo and treated groups in CHD events was approximately 14–18 mo, although a numerically small difference was present from mo 1 in 4S and mo 6 in WOS. This early difference precedes the morphologic effects observed in the angiographic regression studies and may be linked to the early changes in endothelial function discussed above.

Cost Effectiveness of Statins

Statins are regarded as relatively expensive drugs, in comparison with, e.g., antihypertensive therapy. However, health-economic calculations of data from the end point 4S trial speaks in favor of wide application of this therapy in high-risk populations such as those with acute coronary syndromes. In a cost-minimization analysis based on prospectively collected data in 4S, the daily cost of simvastatin averaged U.S. $2.30 when U.S. costs were applied to the data. This cost was offset by 88% in the United States because of reduction in the use of health care resources, especially hospitalization for acute CHD and coronary revascularization procedures, making the effective cost of therapy only U.S. $0.28/d *(119)*. Cost-minimization analyses only quantify the direct economic impact of therapy and do not convert clinical benefits into financial terms (cost-benefit analysis) or into life-years saved (cost-effectiveness analysis).

In a cost-effectiveness analysis of the 4S data, using base costs in Sweden, the cost per life year saved was on average SEK 56,400 (approximately U.S. $7,700) *(120)*. The cost-effectiveness ratio is thus comparable to that of percutaneous angioplasty for severe or moderate angina and much more favorable than coronary artery bypass grafting in patients with three-vessel disease or treatment of mild hypertension *(121)*.

In a sensitivity analysis limited to direct cost, the cost per life-year gained ranged from U.S.$3,800 for a 70-yr-old man with CHD and total cholesterol 8.0 mmol/L (309 mg/dL) to U.S.$27,400 in a 35-yr-old woman with 5.5 mmol/L (212 mg/dL) of total cholesterol *(122)*. When health-care costs in gained years are included in the analysis, the cost per life year saved is U.S.$10,400 in men and U.S.$16,800 in women. When both direct and indirect costs (such as increased labor production because of improved disease-free survival) are included in the analyses, reduction in the health care costs exceeded the cost of intervention in both men and women aged 35 yr. In patients aged 59 yr, cost per life-year saved ranged from U.S.$1,200 to U.S.$8,600 according to sex and baseline total cholesterol level.

TREATMENT RECOMMENDATIONS

In 1995 the American Heart Association convened a panel that arrived at a consensus on strategies to reduce risk in patients with coronary and other vascular disease *(123)*. The Consensus Panel statement was endorsed by the American College of Cardiology. The recommendations on lipid management have the primary goal of reaching an LDL cholesterol level of <100 mg/dL (2.6 mmol/L) and the secondary goal of an HDL cholesterol >35 mg/dL (0.9 mmol/L) and triglyceride level of <200 mg/dL (2.3 mmol/L) (Table 3). These goals are slightly more ambitious than those of the European Atherosclerosis Society, which recommends an LDL cholesterol level of <3 mmol/L (115 mg/dL); however, cholesterol levels in European CHD patients are generally higher than in the United States.

The 1995 guidelines are likely to undergo modifications in the future as more evidence from clinical trials becomes available. Presently, the AHA guidelines are supported by reanalysis of 4S data and results of other more recent trials. In 4S the relationship of LDL cholesterol levels achieved with simvastatin and the subsequent risk of major CHD events was almost linear down to levels well below 100 mg/dL *(124)*. In the Post Coronary Artery Bypass Graft Trial the strategy to reduce LDL cholesterol to <85 mg/dL (2.2 mmol/L) was more beneficial in preventing death or angiographic deterioration of atherosclerosis than a strategy to obtain levels of 130–140 mg/dL (3.4–3.6 mmol/L). Metaanalyses of clinical trials show that the more cholesterol is lowered, the greater the reduction in CHD events *(71)*. Recent trials of statins used in higher dosages show that some of them reduce elevated triglyceride levels as efficiently as fibrates and niacin, and therefore it is likely that statins will dominate the field of risk prevention, even in hypertriglyceridemic patients *(125,126)*.

In all clinical trials published to date, a trial of dietary intervention of several months preceded the randomization to control or lipid-lowering intervention. All trials were carried out in patients in stable condition with their most recent event having occurred several months previously. Nevertheless, the American Heart Association Task Force on Risk Reduction has recommended that drug treatment should not be delayed in patients hospitalized with an acute CHD event and with LDL cholesterol >130 mg/dL (3.4 mmol/L), but should be started at the time of discharge *(127)*. In patients with LDL cholesterol in the range of 100–129 mg/dL, a trial of maximal dietary therapy alone can

Table 3
American Heart Association (AHA) Guide to Lipid Management to Reduce Risk for Patients with Coronary and other Vascular Disease[a]

Goal	*Action*		
Lipid management	Start AHA step II diet in all patients: ≤30% fat, <7% saturated fat, <200 mg cholesterol		
Primary goal LDL < 100 mg/dL	Assess fasting lipid profile. In post-MI patients, lipid profile may take 4–6 wk to stabilize. Add drug therapy according to the following guide:		
Secondary goal HDL > 35 mg/dL TG < 200 mg/dL			
LDL < 100 mg/dL	*LDL 100–130 mg/dL*	*LDL > 130 mg/dL*	*HDL < 35 mg/dL*
No drug therapy	Consider adding drug therapy to diet, as follows:	Add drug therapy to diet, as follows:	Emphasize weight management and physical activity Advise smoking cessation If needed to achieve LDL goals, consider niacin, statin, fibrate
	↓ Suggested drug therapy	↓	
TG < 200 mg/dL	*TG 200–400 mg/dL*	*TG > 400 mg/dL*	
Statin Resin Niacin	Statin Niacin	Consider combined drug therapy (niacin, fibrate, statin)	
If LDL goal not achieved, consider combination therapy			

[a]Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; MI, myocardial infarction.

be tried for 6 wk. It should be noted that this requires active follow-up by the discharging clinician or referral to a physician with knowledge of lipid management. Cholesterol lowering is now established beyond reasonable doubt as a fundamental part of risk reduction in patients with established CHD. Future challenges are not only to implement treatment and reach goals but also to prevent discontinuation of therapy, which presently occurs in 15–46% of patients after 1 yr *(128)*. Cost reduction of statins as well as substitution of statins for niacin and fibrates will undoubtedly contribute to such improvement.

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24 Secondary Prevention of Myocardial Infarction

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INTRODUCTION

The patient who survives a first myocardial infarction (MI) now faces an approximately 80% chance of some cardiovascular event within the next 5 years *(1)*, having doubled their chances of dying from such an event *(2)*. Thus informing patients that they have had a heart attack is not unlike telling them they have cancer. Surprisingly, the reaction of many patients to these pronouncements appears to be quite different, perhaps because of antiquated notions, propagated at times by physicians, that cardiac therapy (bypass surgery, angioplasty) can "fix" the problem. Perhaps these responses arise from knowledge of the many therapeutic interventions available to cardiologists and their patients. In reality, modern medicine is better at "curing" cancer than eradicating atherosclerosis. Physicians today may be more sanguine about the complex nature of atherosclerosis, a nature that makes it a recurrent problem for most patients. We are left with using every tool available in an attempt to modify the natural history, whittling away at those ominous percentages that an MI survivor faces. Fortunately, the number of interventions (medical and otherwise) for secondary prevention continues to grow. Similarly, our understanding of atherogenesis and MI is also deepening, creating hope for the developments of new, and perhaps more effective, therapies, for example, gene therapy, plaque stabilizers, and radial artery bypass.

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Table 1
Risk Factor (RF) Intervention Categories
for Cardiovascular Disease (CVD): 27th Bethesda Conference[a]

Category I: RFs for which interventions have been proved to lower CVD risk
Cigarette smoking
LDL cholesterol
High fat/cholesterol diet
Left ventricular hypertrophy
Thrombogenic factors
Category II: RFs for which interventions are likely to lower CVD risk
Diabetes mellitus
Physical inactivity
HDL
Triglycerides/small dense LDL
Obesity
Postmenopausal status in women
Category III: RFs associated with increased risk that if modified might lower CVD risk
Psychosocial factors
Lipoprotein a
Homocysteine
Oxidative stress
No alcohol consumption
Category IV: RFs associated with CVD risk but cannot be modified
Age
Male gender
Family history of early onset CVD

[a]Abbreviations: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

The need to use all interventions available for modifying risk factors and ameliorating the natural history of coronary artery disease (CAD) in the MI survivor is supported by epidemiologic and clinical trial data *(3,4)*. There is no higher risk group for cardiac events and death than the patients who have survived a heart attack *(5)*. Post-MI mortality rates are the greatest in the first year but continue to be about 5%/yr for men and 7%/yr for women *(1,2)*. The simple presence of angina after MI doubles the risk of subsequent coronary heart disease mortality *(6)*. Issues regarding the secondary prevention of MI have been discussed throughout this book, as well as in recent thorough discussions in the literature *(3,7–9)*. The aim here is not an exhaustive review of the literature on secondary prevention but rather a compendium of the interventions to consider in the post-MI patient. The 27th Bethesda Conference, sponsored by the American College of Cardiology, carefully reviewed risk factors for atherosclerosis, organizing them into four categories: I) intervention proved to lower cardiovascular disease (CVD) risk; II) likely to lower CVD risk; III) associated with increased risk that if modified might lower risk; and IV) associated with CVD risk, but cannot be modified (Table 1) *(10)*. Before discussing some of these therapies, it is important to face some issues of definition that arise when discussing the secondary prevention of MI.

Approximately 1.5 million first MIs will occur this year in the United States *(2)*. Although the survivors of these events are now technically candidates for "secondary prevention," there is little doubt that in most cases, in the days, weeks, months, and even years prior to that first MI, these patients already had CAD. Given that fully one-third of those first 1.5 million MIs will prove fatal, the need to intervene in high-risk patients, even in the absence of anginal symptoms, becomes even more apparent. As such, there has been a trend away from using terms such as primary and secondary prevention based simply on documentation of an MI. Instead, one can view patients as being on a spectrum of risk, independent of a qualifying myocardial event. In this way, one would consider that in patients without a history of MI but with angina or with a history of coronary bypass surgery both groups need aggressive secondary prevention. Using this same approach, one should apply focused preventive measures to any patient with evidence of atherosclerosis in any vascular bed. A similar argument can be made for the patient with diabetes mellitus *(11,12)*. The presence of this comorbidity makes significant CAD so likely that some have argued for a "secondary prevention" approach to the management of all diabetic patients. Along with this notion of a spectrum of risk, one must keep in mind those interventions specifically directed toward the infarcted myocardium (for example, β-blockers), as opposed to those that merely reduce risk in general (for example, lipid lowering). As used here, the term secondary prevention refers in general to those patients at high risk for cardiac events and likely to benefit from application of these measures.

CHOLESTEROL/LDL LOWERING

Part of the experience of our medical generation has to be the proving of the cholesterol hypothesis, which did not occur conclusively until 1994 with the publication of the Scandinavian Simvastatin Survival Study (4S) *(13)*. Although prior studies had shown decreased cardiac events with lipid lowering, no trial had demonstrated a mortality benefit by decreasing cholesterol or low-density lipoprotein (LDL) levels in patients with a prior history of MI. Given the side effects that often came with the older generation of lipid-lowering therapies, many physicians were hesitant to use these agents. The 4S investigators studied these issues directly in this large randomized placebo-controlled study designed to investigate a primary end point of mortality benefit using simvastatin versus placebo. Patients had an average cholesterol level of 260 mg/dL, and 80% were men. There was a 30% reduction in overall mortality with a statistical significance of $p = 0.0003$. Subgroup analysis showed benefit across the board in women, smokers, hypertensives, and the elderly *(14)*. The benefit in diabetics was particularly striking, with a risk reduction of 55% ($p = 0.018$) *(15)*. Also noteworthy was the significant reduction in need for angioplasty or coronary artery bypass grafting (CABG) (37% risk reduction; $p < 0.00001$). Beyond the clear-cut clinical benefit for patients, economic analysis revealed significant cost savings in the treated vs untreated groups. Similar results have been reported in the largest statin trial to date, Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID), using pravastatin in patients with CAD *(16)*.

Subsequent studies have confirmed and extended these findings to other CAD populations with lower risk. The Cholesterol and Recurrent Events (CARE) study, published in 1996, revealed that similar results could be seen in patients who had survived a prior MI but had more "average" cholesterol levels (average cholesterol 209 mg/dL) *(17)*. Of particular relevance to cardiologists, once again the need for CABG or angioplasty was decreased, by 26% ($p = 0.005$).

The issue of LDL lowering underscores several points raised earlier. The first is the relatively arbitrary distinction between what is truly secondary prevention versus primary prevention, and the need for intervention in high-risk patients who have not yet experienced a first MI. The West of Scotland Coronary Outcome Prevention demonstrated a decrease in cardiac events in patients with high cholesterol and no prior MI *(18)*. The recommendation by the American Diabetes Association that all diabetic patients begin lipid-lowering interventions if their LDL is >130 mg/dL, independent of other risk factors, reflects this notion of cardiovascular risk as a continuous spectrum rather than discrete categories. The statin trials also underscore the importance of modifying risk related to atherosclerosis in any vascular bed; both 4S, as part of post hoc analysis, and CARE, as a primary end point, show decreased stroke rates with lipid lowering using a statin *(19)*.

A separate and important issue for secondary prevention is raised by subgroup analysis of the CARE data. If one segregates patients with LDL <125 mg/dL, no apparent benefit is seen with LDL-lowering therapy *(17)*. Is there a "floor" to the LDL level beyond which further lowering no longer accrues benefit to the patient? The answer is not clear but continues to be studied carefully. The CARE investigators have found via post hoc analysis that the absolute or percentage reduction in LDL had little relationship to subsequent coronary events in their study population, CAD patients who had average cholesterol levels *(20)*. Similarly, the WOSCOPS investigators found that treatment benefit was not related to a patient's baseline LDL and that there was no further benefit beyond an LDL lowering of 24%. By contrast, the 4S investigators have reported in their patients (CAD patients with elevated cholesterol levels) that benefit was related to the magnitude of LDL lowering. Several caveats might make physicians cautious about not treating post-MI patients with LDL levels <125 mg/dL with lipid-lowering therapy. First, all these studies are post hoc analyses, designed to generate hypotheses and possibly further studies. One might also expect that it would take a longer period of exposure to a lower LDL level prior to seeing the benefit of treatment. Approximately 60% of both placebo- and drug-treated CARE patients had undergone some form of revascularization by CABG or angioplasty, which may have afforded some additional protection against events in the short term *(17)*. Grundy *(8)* in his editorial accompanying these reports summarizes these issues cogently and points out the probable diminishing return as one lowers LDL further and further. Given these points (the tolerability of the agents, the risk of recurrent events in the MI survivor, and many years of evidence demonstrating the association between LDL and CAD), many have advocated, as does Dr. Grundy, continuing to treat (within limits of rational clinical judgment) to a target LDL goal of about 100 mg/dL, at least until a clearer answer is available *(21)*. Studies are being initiated to address this "low versus lower" issue. This controversy has been heightened by evidence from vascular biology laboratories regarding potential LDL-independent benefits of statin therapy *(22,23)*.

What is perhaps more important is ensuring that all post-MI patients undergo screening and, when appropriate, treatment for dyslipidemia. It is important to remember that whereas the acute phase of an MI may change lipid levels, these effects will only *lower* LDL levels. Thus, one *can* check the post-MI LDL level; if it returns to >100–125 mg/dL, one can begin LDL therapy with the safe assumption that the baseline LDL level was only higher. If the LDL returns to <100 mg/dL in the acute setting, it then becomes incumbent on the physician to recheck levels about 2 mo later to see if treatment is warranted.

HYPERTENSION

Most studies involving hypertension after MI have suggested that persistently elevated blood pressure leads to higher reinfarction and mortality rates *(24,25)*. Many pharmacologic interventions made in CAD patients have an effect on blood pressure, for example, the use of β-blockers or angiotensin-converting enzyme (ACE) inhibitors *(26)*. It is less clear that the mortality and event rate benefits of these agents are due simply to their effects on lowering blood pressure.

ASPIRIN

Unless contraindicated, essentially every post-MI patient should be taking aspirin. Benefits have been demonstrated in acute MI in the Second International Study of Infarct Survival (ISIS-II) trial, in which acute use of aspirin was almost as effective as thrombolytic therapy in changing short-term mortality (23%) *(27)*. Benefit has also been shown for unstable angina in three studies, with doses ranging from 75–1300 mg/d. There appears to be no further benefit beyond 324 mg/d *(28)*. Finally, a decrease in recurrent cardiac events has been seen in established CAD *(29)*. The Anti-Platelet Trialists metaanalysis consisted of a pooling of 11 studies covering almost 20,000 patients with CAD. A 25% risk reduction in cardiac events was seen *(30)*.

β-BLOCKERS

β-blockers appear to minimize the risk of recurrent cardiac events through effects on several mechanisms that might be contributing to myocardial ischemia: decreased oxygen consumption, decreased blood pressure, and decreased ventricular arrhythmia *(31,32)*. Older trials before thrombolytics demonstrated the mortality benefit of β-blockers, with decreased incidence of sudden death (14% short-term mortality risk reduction suggested by metaanalysis). The use of β-blockers is countered by their adverse effects on the lipid profile, primarily in lowering high-density lipoprotein (HDL) *(33,34)*. Some studies have suggested an adverse effect on lesion progression. β-Blockers with intrinsic sympathomimetic activity (ISA) do not decrease HDL levels, although their cardioprotective effects have also not been demonstrated in clinical trials. There may be some question of how long it is necessary to have CAD patients on β-blockers after MI, but their short-term benefit in appropriate patients makes it difficult not to use them as standard care after infarction.

ACE INHIBITORS

ACE inhibitors have been shown to have a mortality benefit after MI *(26,35)*. The benefits also include improved ventricular function, decreased symptoms and admission for CHF, fewer cardiovascular events in patients with left ventricular dysfunction, and, in the diabetic, a noncardiac benefit of less progression of nephropathy. In the SAVE trial, there was a 19% decrease in mortality among patients on ACE-I. Currently the general recommendation is for initiation of such therapy within 1–2 d after MI *(36)*.

HORMONE REPLACEMENT THERAPY

Estrogen has been reported to have significant vascular system benefits, with the assumption being that estrogen may explain the approximately 10-yr lag phase in CAD

events among women compared with men *(37)*. Thus, hormone replacement therapy (HRT) has received much scrutiny and study in both the literature and the media regarding its potential risks and benefits *(38)*. Although large clinical trials are still under way, most cardiovascular studies suggest a benefit for postmenopausal women on HRT *(39)*. The Nurses Health Study (NHS) demonstrated a 44% reduction in cardiovascular risk through HRT use *(40)*. A metaanalysis also reports a 40–50% decrease in cardiovascular events *(41)*. The controversy regarding HRT has been most focused on the question of increased risk of breast cancer *(42,43)*. In the NHS, the relative risk was 1.0 for current users and 1.3 for past users. The risk of CAD in women so far outweighs the risk of breast cancer that many have suggested that female patients are being done a disservice by not having HRT more aggressively recommended to them. Nevertheless, it remains a charged issue for many women, requiring discussion between patient and physician. In the patient with CAD, HRT is likely to offer some cardio-protective benefit. The lipid profile benefits from estrogen are somewhat offset by the concomitant use of progesterone, although not to an extent that outweighs the overall benefit. In the patient who has had a total hysterectomy, estrogen should be used alone.

EXERCISE AND REHABILITATION

Many physiologic benefits relevant to the cardiovascular system can be seen in response to exercise whether within or independent of a rehabilitation program. A 22-trial metaanalysis (4600 patients) suggested that post-MI rehabilitation programs led to decreases in total mortality (20%), cardiovascular mortality (22%), and recurrent infarction (25%) *(44)*.

CONCLUSIONS

A comprehensive approach to the prevention of MI in high-risk patients must be tailored to the individual. (A list of these approaches was developed by the National Institute of Health Consensus Conference.) Given our inability to offer a "cure" for atherosclerosis, every effort must be expended to modify its course and minimize its effects on the myocardium. Of course, such therapies only work when physicians implements them appropriately and then do their best to ensure continued compliance *(45)*. Most studies to date suggest a very poor performance on the part of physicians in using proven secondary prevention therapies. For example, best estimates suggest that only about 30% of patients who have MIs will undergo appropriate screening and treatment for LDL. Much work has been done to establish the benefit of these interventions in altering the course of the high-risk patient. We can expect more to come. It remains part of our challenge to ensure that these therapies are put into practice.

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25 Cost-Effectiveness Analysis and the Treatment of Acute Coronary Syndromes

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INTRODUCTION

The emergence of novel mechanical and pharmacologic interventions for the treatment of cardiovascular disease prompts questions about their value. The development of these approaches provides greater opportunity for patients to survive cardiac events. The adoption of these strategies has traditionally depended on their efficacy and safety. However, the rapid development of efficacious therapies and the dissemination of medical innovations also present strong challenges to a health care system that is increasingly constrained by finite resources. Currently, an estimated 7 million Americans suffer from coronary heart disease and incur $88 billion in health care expenditures yearly *(1)*. As the availability of new interventions exceeds our ability to afford them, how should we select which interventions to use as standard practice? Which interventions should be available in the office or at the hospital? How should the resources of the managed care organization be allocated? Are the health benefits worth the health care resources that are consumed?

These questions are difficult to answer and commonly cannot be resolved easily. Cost-effectiveness analysis is a formal, quantitative method that has evolved to compare alternative strategies by explicitly examining their costs and benefits. Although these analyses cannot dictate which programs should be implemented, they can demonstrate the relative economic attractiveness of programs in producing a health benefit. This chapter briefly reviews the important methodologic features of cost-effectiveness analy-

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sis and then examines the high-quality studies that have evaluated interventions for the treatment of acute coronary syndromes.

COST-EFFECTIVENESS ANALYSIS

The objective of medical cost-effectiveness analyses is to compare clinical and economic outcomes of interventions designed to improve health. The first step of a cost-effectiveness analysis is to define clearly the alternative interventions that are being compared. New therapies should be compared with the current best clinical strategies. The primary analysis should be performed from the societal perspective and should consider all health effects and changes in resource use. The time horizon should be appropriate to capture all the relevant health effects and costs of the alternative clinical strategies. The major components of cost-effectiveness analyses, including resource use, health effects, discounting, indication for a formal analysis, cost-effectiveness ratio, sensitivity analysis, and application to decision, are discussed in more detail in the following sections.

Resource Use

Health resource use in these analyses is expressed as costs. Costs should reflect the incremental resources consumed. The costs of a program are not equivalent to what is charged for the program or intervention. Costs represent the monetary value of the resources consumed in providing the service. Charges, or what is asked for a product or service, may not be closely related to the value of the resources consumed in providing the product or service *(2)*.

There are several layers of costs to consider. The cost of the intervention itself may represent only a small proportion of the total incremental costs. There may also be costs associated with adverse events related to the intervention. In addition, the patient may incur costs relating to illness that would not have occurred if the patient had not received the intervention. Indirect costs, such as lost work days, may also be included in the calculation of costs.

Effectiveness

Health effects are commonly conveyed as lives saved or years of life saved (YLS). In some cases, surrogate outcomes are used, such as a coronary event avoided or a millimeter of mercury lowered. These measures may be employed when more comprehensive outcome data are unavailable, but they are less desirable since they preclude comparison with other types of medical interventions.

The focus on lives saved, however, neglects the impact of morbidity on those lives. Using this measure, an intervention that produces nonfatal but important adverse events may appear to have the same effectiveness as an intervention that is equally effective in saving lives but does not cause any adverse effects. To incorporate this information, the concept of quality-adjusted life years (QALYs) has been developed. This measure combines life years gain with a factor that takes into account the quality of the life relative to "perfect health."

Discounting

Future costs and benefits are not valued as much as current costs and benefits. Consequently, in cost-effectiveness analyses, costs and health outcomes are discounted to the

present value. It is currently recommended that a discount rate of 3% be used; most older studies have employed a rate of 5%.

Indications for a Formal Analysis

Once the incremental costs and benefits are specified, there is a need to determine whether a formal analysis is necessary. The results at this stage can produce unequivocal findings. For example, if the new strategy is less costly and more effective than the alternative strategy (which may be no treatment), then the new approach is considered "strongly dominant." Conversely, if the new therapy is more expensive and less effective, then the alternative approach is considered "strongly dominant." In these cases, the favored strategy is clear, and further economic analysis is unnecessary. The implementation of these favored strategies has the potential to save money and improve health. Although these interventions are relatively rare, they are economically extremely attractive and should be very highly recommended.

In other cases, one strategy may be "weakly dominant," which occurs when one strategy is favored by only cost or effectiveness—but not both. For example, a strategy would be considered "weakly dominant" if it was more effective than the alternative strategy but had the same cost. Even though these comparisons do not provide as clear a result when one strategy is "strongly dominant," there is a clear favored strategy that is economically attractive and should be highly recommended.

Finally, there are the cases in which cost-effectiveness analysis has its most value. In these comparisons, neither strategy is obviously dominant. One strategy commonly provides more effectiveness at an increased cost. For this situation, it is useful to calculate the incremental cost-effectiveness ratio.

The Cost-Effectiveness Ratio

The cost-effectiveness ratio is calculated by dividing the net change in health resource use of one program compared with another by the net change in health effects of one program over another.

Cost-effectiveness ratios can only be interpreted in comparison with other analyses. Whereas lower cost-effectiveness ratios are more economically attractive than higher ratios, there is no accepted external standard that anoints those interventions below a certain level as cost effective. After a thorough review of the literature, Laupacis and colleagues *(3)* found that interventions with a cost-effectiveness ratio < $20,000/QALY were almost always accepted and considered appropriate; those between $20,000/QALY and $100,000/QALY were commonly provided, but there were questions about appropriateness; and those >$100,000/QALY were routinely considered inappropriate.

Sensitivity Analyses

Most cost-effectiveness analyses depend on many assumptions. Many of these assumptions represent "best estimates" because there are no large studies of the subject. Since these assumptions may not be accurate, it is important for the analysis to be repeated with varying estimates. The investigators need to determine whether the results of the analysis would change substantially if the assumptions were changed to a reasonable extent.

Application to Decisions

Finally, even though these results may be informative, they are not comprehensive. The interpretation of the results of cost-effectiveness analysis can only be made relative

Table 1
Summary of Cost Per Year Saved or Quality-Adjusted Years of Life Saved (YLS) in Selected Interventions for Cardiovascular Disease

Intervention	*Reference*	*Incremental cost-effectiveness ratio*
β-Blockers after myocardial infarction for high-risk 55-yr-old man	*(4)*	2400/YLS (1987 dollars)
Streptokinase for 80-yr-old patient with suspected myocardial infarction	*(5)*	21,200/YLS (1992 dollars)
Tissue-type plasminogen activator instead of streptokinase for myocardial infarction	*(6)*	32,678/YLS (1994 dollars)
Smoking cessation program after myocardial infarction	*(7)*	220/YLS (1993 dollars)
Simvastatin to lower cholesterol levels in 70-yr-old patient with coronary heart disease and initial cholesterol of 309 mg/dL	*(8)*	3800/YLS (1997 dollars)
Simvastatin to lower cholesterol levels in 35-yr-old woman with coronary heart disease and cholesterol of 213 mg/dL	*(8)*	27,400/YLS (1997 dollars)

to external criteria that determine what is considered economically attractive. They can provide an economic perspective and provide information about which strategies are economically attractive, but this analysis does not include the range of domains that may influence the decision by society, an organization, or an individual to accept a new treatment as standard practice. The results should not be considered proscriptive. The analyses are intended to assist decisions, not dictate them.

COST-EFFECTIVENESS STUDIES OF TREATMENTS FOR ACUTE CORONARY SYNDROMES

The following section reviews the high-quality cost-effectiveness analyses that have focused on treatments for acute coronary syndromes. These analyses were conducted from a societal perspective, report (when appropriate) incremental cost-effectiveness ratios in US dollars per YLS or QALYs, and discount future costs and health effects. For perspective, in Table 1, we show cost-effectiveness ratios of selected interventions in cardiovascular disease *(4–8)*.

Acute Reperfusion Therapy

The efficacy of thrombolytic therapy for the treatment of suspected acute myocardial infarction was definitively established in 1986 by the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) trial *(9)*. Subsequently, other trials confirmed their result. An overview of the 58,600 patients enrolled in the nine randomized trials with more than 1,000 subjects found that thrombolytic therapy produced an 1KE reduction in mortality *(10)*. These trials indicated that, on average, 56 patients needed to be treated to avoid one death.

As the clinical value of thrombolysis for suspected acute myocardial infarction was established, several economic questions emerged regarding its value compared with other treatments. How much does it cost for the benefit of thrombolytic therapy compared with not using thrombolytic therapy? How do different agents compare? How do different techniques of achieving coronary recanalization compare?

Comparison with No Reperfusion Therapy

Several studies have evaluated the cost effectiveness of thrombolytic therapy compared with no reperfusion therapy. Since the two largest and earliest trials of thrombolytic therapy used streptokinase, an inexpensive agent that was first isolated in 1941, the early economic evaluations focused on this agent.

For example, Krumholz and colleagues *(5)* examined the use of streptokinase for the treatment of elderly patients with suspected acute myocardial infarction, a group for which there is less enthusiasm about using thrombolytic therapy. Based on data from GISSI -1 *(9)* and ISIS-2 *(11)*, the relative benefit of thrombolytic therapy was estimated to be lower in elderly patients than what was reported for the overall study sample. Also, the risk of hemorrhage from thrombolytic therapy, including hemorrhagic stroke, was estimated to be higher than was reported in the overall trial results. The absolute risk of an acute myocardial infarction was also estimated to be much higher compared with younger patients. In the decision analysis, the smaller relative reduction from the therapy was offset by the higher absolute risk of the infarction—and the benefit overshadowed any increase in the risk of hemorrhage. After considering the costs of the treatment, complications, and long-term health care of survivors, the authors estimated that the cost-effectiveness ratio of streptokinase compared with conventional medical therapy was $21,200/YLS for an 80-yr old patient. Economically attractive estimates were also calculated for younger patients. In the sensitivity analysis, the use of thrombolytic therapy was favored over a broad range of assumptions about the risks and benefits. Several other investigators have also calculated favorable cost-effectiveness ratios for thrombolytic therapy *(12–14)*.

Comparison of Thrombolytic Agents

Once the value of thrombolytic therapy was widely accepted, attention turned toward the identification of the best agent. Streptokinase was used in the early trials with great success, but small studies suggested that a second-generation agent, tissue-type plasminogen activator (tPA), could open coronary arteries faster and possibly produce a superior clinical outcome. The issue engendered much discussion, since the genetically engineered tPA is much more costly than streptokinase.

The controversy stimulated the development of several large randomized trials. The first two large trials failed to demonstrate a significant mortality difference between the two agents *(15,16)*. Because the less expensive agent was equally effective, streptokinase was considered "weakly dominant." Consequently, there was no need for further economic analyses.

The controversy would have ended except that concerns persisted that tPA was superior in the proper dose and in conjunction with intravenous heparin. Consequently, a third trial, the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO), was developed; this trial administered tPA in an accelerated regimen with intravenous heparin. GUSTO demonstrated that this regimen of tPA led to significantly

greater recanalization at 90 min than streptokinase *(17)* and, on average, saved one life for every 100 patients treated.

The publication of GUSTO led to discussions about whether the benefit of tPA was large enough to justify its cost. In anticipation of this issue, the GUSTO trial investigators planned an economic substudy *(6)*. In a subgroup of their subjects, the investigators collected detailed information about resource consumption. They found that patients who received tPA and streptokinase were similar in their use of resources in the year after admission for the acute myocardial infarction. Both treatment groups had a mean length of stay of 8 d, including an average of 3.5 d in the intensive care unit. The treatment groups had a similar rate of bypass surgery (13%) and angioplasty (31%) during the initial hospitalization. Overall, the 1-yr health costs, excluding the difference in the cost of the thrombolytic agent, were $24,990 per patient treated with tPA and $24,575 per patient treated with streptokinase. The major difference in the cost of the therapies was the cost of the drugs: $2,750 for tPA and $320 for streptokinase. The total incremental cost was calculated to be $2,845. The primary analysis assumed no increase in costs for the tPA group after the first year. This incremental cost is similar to that estimated by Kalish and colleagues *(18)* by modeling the costs.

The effectiveness of tPA over streptokinase was expressed as the years of life saved. This number was calculated by taking the number of lives saved and multiplying it by an estimate of the patients' life expectancy. The addition in life expectancy per patient treated with tPA was 0.14 yr.

Based on these estimates, and including a discount rate of 5%, the authors concluded that the cost-effectiveness ratio of using tPA instead of streptokinase was $32,678/YLS. The investigators also showed that the cost-effectiveness ratio varied considerably among eight groups based on the infarction site and the age of the patient. In general, the younger and lower risk patients had higher (less favorable) cost-effectiveness ratios. For example, $203,071/YLS was the cost-effectiveness ratio for tPA in a patient aged 40 yr or younger with an inferior infarction compared with $13,410/YLS for a person aged 75 yr or older with an anterior infarction.

Currently, several new thrombolytic agents are under development. Since the efficacy of these agents over tPA has not been established, the need for detailed economic analyses has not yet emerged.

Comparison with Mechanical Approaches to Reperfusion

The success of reperfusion therapy depends on its ability to achieve early and complete recanalization of the occluded coronary artery *(17)*. Recently, in medical centers that perform percutaneous coronary revascularization, mechanical approaches to reperfusion have been employed with increasing frequency. The clinical or economic advantage of primary angioplasty remains controversial *(19–21)*. Several early studies demonstrated a substantial advantage of primary angioplasty over thrombolytic therapy *(22–24)*. Economic analyses based on the early studies have suggested that primary angioplasty reduces mortality without substantially increasing cost *(25)*. In this case, primary angioplasty would be considered the "weakly dominant" strategy. More recent clinical studies, however, have provided less impressive results associated with the use of primary angioplasty *(26,27)*. For primary angioplasty, the effectiveness may depend on the site. In some sites with skilled operators who have substantial experience, primary angioplasty may be favored. In other sites, the advantage may be lost or thrombolytic therapy may be favored.

Moreover, in some sites primary angioplasty would only be possible after the construction of the appropriate facilities and the recruitment of an interventional team. Thus, the average result may not be relevant to all settings.

Interventional cardiology is a moving target, as new approaches to mechanical revascularization continue to evolve. For example, stenting for percutaneous coronary revascularization is growing in popularity. Stents were initially considered to be contraindicated in acute myocardial infarction because of concerns that they would incite thrombus formation. These concerns were recently allayed in small randomized trials revealing that patients with an acute myocardial infarction who underwent stenting had a much lower mortality *(28,29)*. Although stenting is more expensive than balloon angioplasty, there are no economic studies evaluating its value for the treatment of acute myocardial infarction compared with primary balloon angioplasty or conventional thrombolytic therapy. As evidence of the efficacy of stents and other mechanical approaches accumulates, there will be a need to examine their economic impact compared with balloon angioplasty and thrombolytic therapy.

Antithrombotic Agents

Aspirin provides important benefits for patients presenting with acute coronary syndromes. As a result of the marked benefit and the minimal cost of the therapy, no formal economic analysis of aspirin for the treatment of acute coronary syndromes has been published in the mainstream journals. The ISIS-2 trial showed that the use of aspirin avoided 25 deaths for every 1,000 patients with suspected acute myocardial infarction *(11)*. In addition, the 1 mo of aspirin therapy in ISIS-2 was associated with halving the risk of stroke or reinfarction. Aspirin avoided about 10 reinfarctions and three strokes for every 1,000 patients treated. Because the avoidance of complications would probably translate into cost savings, aspirin should be considered a "strongly dominant" therapy.

Heparin has also not been formally evaluated in an economic analysis. Moreover, it has not been shown to provide a strong benefit for acute myocardial infarction in the aspirin era *(30)*. Although aspirin plus heparin is the standard of care for patients hospitalized with unstable angina, a meta-analysis of the unstable angina studies found a borderline significant result in favor of heparin *(31)*. There is no evidence that heparin reduces cost.

New agents are emerging with increasing frequency. For example, low molecular weight heparin is emerging as an effective therapy for unstable angina *(32)*. The greater cost and benefit of these new treatments make them ideal subjects for economic analyses.

Treatment of high-risk patients undergoing coronary revascularization with a monoclonal antibody fragment against the platelet receptor glycoprotein IIb/IIIa reduces the long-term risk of death, myocardial infarction, or coronary revascularization *(33)*. An economic analysis of this treatment in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial demonstrated a mean savings per patient at 6 mo of $1,270, exclusive of the drug cost *(34)*. At the time of the study, the cost of the bolus and infusion of the drug regimen was $1,407. As a result, the incremental cost of using the new therapy was calculated to be relatively small. The improvement in quality of life was not measured, but the avoidance of the ischemic events would be expected to produce some benefit for the patients. In unpublished data from the RESTORE trial *(35)*, another study of a platelet receptor glycoprotein IIb/IIIa blocker for patients undergoing high-risk angioplasty, the new treatment was cost saving at 30 d. These studies did not directly

examine the use of these agents in patients with acute ischemic syndromes, but other studies are showing promise in this area *(36)*. Future studies (with economic substudies), such as the Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Therapy (TACTICS)–Thrombolysis in Myocardial Infarction (TIMI) 18 trial will address this issue.

Other Pharmacologic Agents

Several other pharmacologic agents, such as β-blockers *(37)* and angiotensin-converting enzyme inhibitors *(38)*, have been shown to improve outcomes in the treatment of acute coronary syndromes. However, these acute treatment strategies have not received rigorous evaluation of their cost-effectiveness in the medical literature.

CONCLUSIONS

Cost-effectiveness analysis is a method to inform decisions about the incremental value of one strategy compared with another. While these analyses cannot designate clinical strategies as "cost effective," they can identify strategies that are "economically attractive." These analyses can also illuminate the relative value of various strategies and assist in decisions about resource allocation.

Economic analyses have been applied to several clinical strategies for the acute treatment of coronary syndromes. These interventions are commonly well suited to these analyses because they produce an incremental benefit compared with current therapies at an increased cost.

These economic analyses have indicated that thrombolytic therapy compared with conventional medical therapy for suspected acute myocardial infarction has a cost-effectiveness ratio of <$30,000/YLS. Compared with streptokinase, tPA has a cost-effectiveness ratio of approximately $30,000/YLS, although there was marked variation by subgroup, with the most favorable ratios for the highest risk patients. Compared with thrombolytic therapy, primary angioplasty appears to be a weakly dominant strategy, but the value of the strategy may depend heavily on the site. Other strategies have received much less economic scrutiny. As new strategies evolve that confer greater benefit with increased cost, it is likely that economic analyses will be important in describing their value compared with conventional strategies.

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26 Critical Pathways for Acute Coronary Syndromes

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INTRODUCTION

Critical pathways are standardized protocols for the management of specific disorders that attempt to optimize and streamline patient care. Numerous other names have been developed for such programs, including "clinical pathways" (so as not to suggest to patients that they are in "critical" condition), or simply "protocols," such as the acute myocardial infarction (MI) protocols used in emergency departments to reduce time to treatment with thrombolysis *(1,2)*. The broader term *Disease Management* is currently used to denote that these pathways extend beyond the hospital phase of treatment and to optimize medical management of diseases over the long term.

Use of critical pathways is currently growing rapidly primarily as a means of reducing length of hospital stay. However, several other components can be added to critical pathways, with the overall goal of improving patient care. Indeed, physicians involved in developing critical pathways focus on these positive aspects of pathways as a means of utilizing them to advance medical care. These other goals involve improving the use of medications and treatments and increasing participation in research protocols (Table 1). In addition, limitation of unnecessary tests can reduce costs, allowing resources to be allocated to other treatments that have been shown to be beneficial. With involvement of physicians in developing these pathways, those responsible for patients can thus control

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Table 1
Goals of Critical Pathways

1.	Increase use of recommended medical therapies (e.g., aspirin for all acute coronary syndromes, reperfusion therapy for ST-elevation MI).
2.	Decrease use of unnecessary tests.
3.	Decrease hospital length of stay.
4.	Increase participation in clinical research protocols.
5.	Improve patient care *and* decrease costs.

how the patients are managed. It should be noted that data are only beginning to emerge regarding the success of various critical pathways. Indeed, we should continue to analyze such pathways and should monitor performance to ensure that they meet the overall goal of reducing costs while improving (or at least maintaining) quality of patient care.

NEED AND RATIONALE

Underutilization of Recommended Medications

A major problem in the management of acute coronary syndromes is that a large proportion of patients does not receive recommended medical therapies. For example, aspirin has been shown in numerous studies to be beneficial across the entire spectrum of myocardial ischemia, from primary prevention of MI *(3,4)* to prevention of death or MI in unstable angina and acute MI *(5–10)* to secondary prevention events (see Chapter 25) *(11,12)*.

However, in the first National Registry of Myocardial Infarction (NRMI), involving 240,989 patients, among MI patients receiving thrombolytic therapy, only 87% received aspirin; among those not receiving thrombolysis, only 63% received aspirin *(13)*. Similarly, in the Cooperative Cardiovascular Project, among patients fully eligible to receive aspirin (i.e., no contraindications to aspirin such as bleeding ulcer), only 80% of patients received aspirin *(14)*. In the GUARANTEE registry of unstable angina patients, conducted in 1996, 82% of patients received aspirin *(15)*. Thus, despite the overwhelming benefits of aspirin (arguably the best studied and most beneficial medication in cardiovascular medicine) *(12)*, significant proportions of patients do not receive it. The American Heart Association (AHA) recently published a scientific statement strongly urging physicians to increase the use of aspirin in appropriate patients *(16)*. Thus, a major focus for physicians, hospitals, and health care systems is to increase the use of aspirin, as well as other important medications.

Numerous other medications have been shown to be beneficial in acute coronary syndromes. Both heparin and low molecular weight heparin have also been shown to be beneficial in reducing death or MI in non-ST-elevation acute coronary syndromes *(7,17–21)*. In ST-elevation MI, heparin improves infarct-related artery patency following tissue plasminogen activator *(22–24)*, and the low molecular weight heparin enoxaparin has recently been shown to reduce the incidence of death, MI, or recurrent ischemia following thrombolytic therapy *(25)*.

β-Blockers, nitrates, and calcium antagonists are useful in patients with acute coronary syndromes (without contraindications) *(26,27)*. Angiotensin-converting enzyme (ACE) inhibitors have been shown to be beneficial in *post*-MI patients with either documented left ventricular dysfunction *(28)* or congestive heart failure *(29)* and more recently in

acute MI in the third Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI-3), International Study of Infarct Survival (ISIS-4), and Chinese trials *(30–32)* although in the ISIS-4 study, no benefit was observed in patients without ST elevation.

Unfortunately, not all these medications are being utilized. In the ninth Thrombolysis in Myocardial Infarction (TIMI 9) Registry, 91% of patients received heparin, and β-blockers were given to 61%. In patients who developed congestive heart failure or had documented left ventricular dysfunction after MI, only 39% were treated with ACE inhibitors at hospital discharge. Although these numbers are better than those observed in the NRMI *(13)*, opportunity for improvement remains.

The other most notable example of underutilization of medications is thrombolysis. It appeared that only 25–30% of patients with acute MI receive thrombolysis. However, thrombolytic therapy is only beneficial in patients with ST-elevation MI *(33–35)*. Accordingly, we conducted the TIMI 9 Registry, which looked at all patients who presented to 20 hospitals in the United States and Canada with ST elevation or new left bundle branch block. Overall, we observed that 69% either received thrombolysis (60%) or underwent primary angioplasty (9%) *(36)*. Of those who presented to the hospital within 12 h of the onset of pain, 75% received reperfusion therapy. Thus, of the 31% of the total group who did not receive reperfusion therapy, delay in presentation explained one-third, another third had contraindications to thrombolysis, and for the final third, there were no clear reasons identified why thrombolysis was not given. Thus, despite a reasonable percentage of patients receiving reperfusion therapy for ST-elevation MI, opportunities for improvement exist, with the ultimate goal of extending the benefits of reperfusion therapy to all patients with ST-elevation MI.

Overutilization of Cardiac Procedures

Another area for potential improvement is in the use of cardiac procedures following admission for acute MI and unstable angina. In acute MI, numerous studies have found wide differences in the use of cardiac procedures but no difference in mortality *(37–43)*. Such observations have been made comparing hospitals that had on-site cardiac catheterization facilities vs those without *(37–39)* when comparing patients in Canada vs the United States; many fewer procedures are performed in Canada, but overall mortality for patients in the United States and Canada is similar *(40–43)*. These data suggest that unnecessary procedures may be performed in some patients.

To study this important question, the TIMI investigators carried out two trials, TIMI IIB in patients with ST-elevation MI treated with thrombolytic therapy *(44)* and TIMI IIIB in patients with unstable angina and non-ST-elevation MI *(33)* (additional trials are ongoing, e.g., TACTICS-TIMI 18 in patients with unstable angina and non-ST-elevation MI).

TIMI IIB

In TIMI IIB, 3,339 patients with ST-elevation MI were treated with tissue plasminogen activator (tPA), aspirin, and heparin and were randomized to either an invasive strategy consisting of cardiac catheterization 18–48 h later followed by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) if the anatomy was suitable, or to a conservative strategy in which catheterization and PTCA were performed only for recurrent spontaneous ischemia or a positive exercise test *(44–46)*.

Death or recurrent MI through 42 d occurred in 10.9% of patients in the invasively treated group compared with 9.7% of the conservatively treated group (p = NS) *(44)*. Similarly, no difference between the two strategies was observed through 1-yr *(45)* or 3-yr follow-up (21.0% death or reinfarction for the invasive strategy vs 20.0% for the conservative strategy; p = NS) *(46)*. By contrast, the rate of revascularization in the two groups was vastly different: 72.3% of patients in the invasive strategy group underwent PTCA or CABG by 1 yr, compared with only 35.5% in the conservative strategy group.

Approximately 750,000 patients with acute MI are admitted to acute care hospitals in the United States annually. Estimating that one-half have an ST-segment elevation MI, the potential cost savings of following a conservative strategy are astounding: using a rough estimate of $2,000 for a diagnostic catheterization and $4,000 for a PTCA procedure *(47)*, this would translate into an annual savings of $1 billion. Even when performing a sensitivity analysis and reducing the cost of the procedures by one-half, the savings of following a conservative strategy still amounts to $500,000,000 annually in the United States. Thus, since both strategies lead to similar long-term outcome, this trial established the "watchful waiting" approach as the preferred strategy for the management of patients treated with thrombolytic therapy for acute MI.

The findings from TIMI IIB, with the added support of the findings from the Should We Intervene Following Thombolysis (SWIFT) trial *(48)* and other studies *(37–43)*, lend strong support to the notion that coronary angiography can be reserved for patients who demonstrate recurrent ischemia after thrombolysis for ST-elevation MI. In the current era of cost containment, close scrutiny of the indications for cardiac catheterization, with stricter adherence to its need in patients with true recurrent ischemia after MI, may allow reductions in the use of cardiac procedures (and thus costs), without any loss of clinical benefit.

Reducing Other Cardiac Testing

Other areas of potential overutilization of testing also exist, e.g., laboratory tests and echocardiography. For example, echocardiography is widely used to assess post-MI left ventricular function, the most powerful determinant of subsequent prognosis *(49–51)*. The American College of Cardiology (ACC)/AHA Acute MI Guidelines recommend that left ventricular function be assessed in all patients *(26)*. However, a recent study, now validated by three other groups, has shown that several clinical features (nonanterior MIs, no Q-waves or total creatine kinase (CK) <1000 IU, and no evidence of congestive heart failure) can predict normal left ventricular function with 97% specificity *(52–54)*. Thus, for patients with small non-ST-elevation MIs, assessment of left ventricular function via echocardiograpy or ventriculography may not be necessary, a strategy which could have potential implications for more cost-effective care.

REDUCING HOSPITAL (AND INTENSIVE CARE UNIT) LENGTH OF STAY

Reduction in hospital length of stay has been the driving force behind the creation of critical pathways. As noted in the initial pathways for cardiac surgical patients, early discharge was the main outcome variable *(55)*. In acute coronary syndromes, length of stay was very long just 5 yr ago. In patients with unstable angina and non-Q-wave MI enrolled in the TIMI IIIB trial, the average length of stay was over 9 d. In the parallel TIMI 3 Registry of patients *not* entered into the trial, length of stay was also 9 d. Among patients

treated with thrombolysis for ST elevation MI, similar observations have been made. In Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-I), the median length of stay was 9 d *(56)*. In a follow-up analysis that divided patients into those with an uncomplicated course (no recurrent ischemia, congestive heart failure, or any other complication) vs any one of these complications, the median length of stay *for both groups* was 9 d. In the TIMI 9 Registry conducted in 1995, for uncomplicated patients with ST-elevation MI, the median length of stay was 8 d *(36,57)*. Thus it appears that length of stay historically has been long in patients with acute coronary syndromes, and opportunities exist to reduce it safely, especially in low-risk patients.

Identification of Low-Risk Patients

With the benefit of aggressive reperfusion therapy in acute MI, it has been possible to identify patients who are at low risk of subsequent mortality or morbidity *(58)*. In the TIMI II trial, a group of patients were prespecified as "low risk" if they had the following characteristics: age <70 yr, no prior MI, inferior or lateral MI, normal sinus rhythm, and Killip class 1 at admission *(44)*. This classification was subsequently validated *(59)*. Similar observations have been made in the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) trials *(60)*, and more recently in the GUSTO-I trial *(56)*.

Strategy of Early Discharge Following Thrombolysis

Identification of low-risk patients has led to the possibility of early hospital discharge for such uncomplicated patients *(56,60)*. A pilot trial of such a strategy in 80 patients suggested that hospital stay and costs could be significantly reduced without an increase in complications *(61)*. It should be noted, however, that in this trial, all patients who received reperfusion therapy also underwent immediate coronary angiography, the information from which was used in the triage of the patients. Such a strategy is not applicable to standard practice *(61)*. Thus the strategy of early hospital discharge looks very promising and feasible, but more information is needed to establish it in clinical practice.

Early Discharge Following Primary PTCA

Early hospital discharge for low-risk patients after *primary angioplasty* has recently been reported *(62)*. The Primary Angioplasty in Myocardial Infarction (PAMI)-2 trial divided patients into low- and high-risk groups based on clinical and angiographic features *(62)*. The 471 low-risk patients were randomized to a strategy of early discharge or to conventional hospital discharge. Clinical outcomes at 6 mo were similar in both groups: mortality 0.8 vs 0.4% for early discharge vs standard care ($p = 1.0$), unstable angina 10.1 vs 12.0% (p = NS), recurrent MI 0.8 vs 0.4% (p = NS), or the combination of death, unstable angina, MI, congestive heart failure or stroke 15.2 vs 17.5% $p = 0.49$) *(62)*. On the other hand, hospital length of stay was 3 d shorter (4.2 d vs 7.1 d; $p = 0.0001$), and hospital costs were lower ($9,658 ± $5,287 vs. $11,604 ± $6,125; $p = 0.002$) *(62)*. Thus the strategy of acute catheterization and primary PTCA allowed identification of low-risk patients and showed that early discharge was safe and resulted in substantial reduction in hospital length of stay and costs.

Overutilization of Intensive Care

Overutilizûíion of the intensive care and coronary care units (CCU) is another area in which critical pathways may reduce costs. A decade ago, admission to the CCU was

Table 2
Steps in Developing and Implementing a Critical Pathway

1.	Identify problems in patient care.
2.	Identify the task force that develops guidelines for medical care.
3.	Distribute draft critical pathway to all departments involved.
4.	Implement the pathway.
5.	Collect and monitor data on critical pathway performance.
6.	Modify the pathway as needed to improve performance further.

standard for all unstable angina and MI (and frequently "rule out MI" patients *(63,64)*. Even recently, in the multicenter GUARANTEE Registry conducted in the United States in 1996, 40% of patients with unstable angina and non-ST-elevation MI were admitted to the CCU *(15)*. Given that in the current era, CCU admission is generally recommended for higher risk patients, i.e., those with ST-elevation MI and/or hemodynamic compromise or other complications, these current data suggest that opportunities may exist for reducing the number of patients cared for in intensive care units.

METHODS OF DEVELOPMENT

The process of developing a critical pathway involves first defining the problem (Table 2). Thus, the specific problems in the care of patients with specific diagnoses need to be identified in general (as noted above), as well as specific issues at the individual institution. For example, the use of blood tests might be higher than necessary when left to the individual house staff or physicians (e.g., multiple cholesterol measurements during a single hospital stay).

The next step is to establish a task force or committee to create (or adapt) a critical pathway that would include guidelines for patients with the specific diagnoses. The third step is to distribute the draft critical pathway(s) to all health care professionals and services who care for patients with those diagnoses, to ensure adequate input from all parties involved. For example, for an unstable angina pathway, one should include staff from the cardiology, emergency medicine, cardiac surgery, nursing departments, the noninvasive testing laboratory, the cardiac rehabilitation group, social service department, the case management group, and the dietary service. Comments from these parties are then included in the final pathway.

Implementation of the pathway can begin with "pilot" testing and then routine use. The next step is to collect and monitor data regarding performance of the pathway. This could include the number of patients for whom the pathway was used, use of recommended therapy, and hospital length of stay. The final step is to interpret the initial data and modify the pathway as needed. These latter three steps collectively comprise the *continuous quality improvement* that must be ongoing during the implementation of any pathway. In addition, as new therapies become available, the data should be reviewed to determine which should be added or modified as part of optimal patient management.

METHODS OF IMPLEMENTATION

Several potential methods of implementation exist, beginning with voluntary participation. Although this appears to be inefficient, it is frequently all that can be accom-

Table 3
Cardiac Checklist for Unstable Angina
and Non-ST-Elevation Myocardial Infarction[a]

Medications	
1. Aspirin	❑
2. Heparin/low molecular weight heparin	❑
3. gp IIb/IIIa inhibition	❑
4. β-Blockers	❑
5. Nitrates	❑
6. Heart-rate-lowering Ca^{2+} blocker (if no CHF or low EF)	❑
7. ACE inhibitors if low EF/CHF	❑
Interventions	
8. Catheterization/revascularization for recurrent ischemia or in high-risk patients	❑
Secondary prevention	
9. Cholesterol: check + Rx as needed	❑
10. Treat other risk factors (smoking)	❑

[a]Abbreviations: CHF, congestive heart failure; EF, ejection fraction; ACE, angiotensin-converting enzyme.

plished with limited resources at individual hospitals. The pathway could be sent to physicians and nurses with presentation at staff and house staff meetings. Another method is to send physicians and nurses reminders via electronic mail messages triggered by the admission diagnosis, or else monthly reminders. Another approach is to employ independent screening of all admissions, with copies of the pathway placed in the chart. Use of the pathway would be expected to be low with such a voluntary approach. On the other hand, if a pathway is implemented in a proportion of patients, it may become the standard of care at a particular hospital, and it may not be necessary to involve additional personnel to "implement" a particular pathway.

Another approach that some hospitals have used is to have a designated case manager evaluate each patient and ensure that all steps in the pathway are carried out. Such an approach would be expected to improve the use of the pathway. However, this obviously requires additional resources from the hospital or health care system. The approach used by individual hospitals for specific diagnoses needs to be individualized.

The pathways reviewed in the literature to date, as well as several examples are available on the National Heart Attack Alert Program (NHAAP) web page (http://www.nhlbi.nih.gov/nhlbi/othcomp/opec/nhaap/nhaapage.htm), and are provided to facilitate use and reduce the time and effort needed for hospitals to implement critical pathways. The ultimate goal is to improve the care of patients and to make such care more cost effective.

Cardiac Checklist

A very simplified version of a critical pathway is use of a *cardiac checklist.* Checklists exist for many purposes including admission tests and procedures, and thus this format can be extended to medical treatments. It is a simple means to ensure that each patient receives all the recommended therapies. Table 3 shows a proposed cardiac checklist for

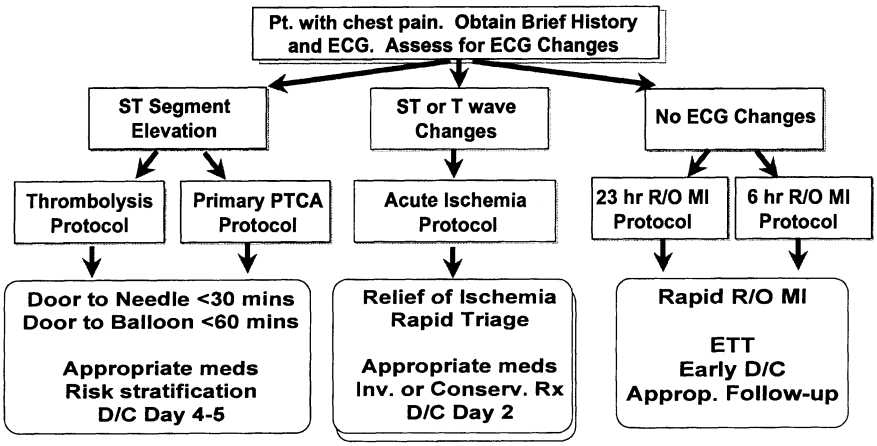

Fig. 1. Critical pathways for acute coronary syndromes at Brigham and Women's Hospital.

the patient with unstable angina/non-ST-elevation MI that includes aspirin, heparin or low molecular weight heparin, a glycoprotein (gp) IIb/IIIa inhibitor, β-blockers, heart-rate-lowering calcium antagonists (if needed and in the absence of congestive heart failure or left ventricular dysfunction), cholesterol lowering, and other risk factor modifications.

This checklist could be used in two ways: physicians could keep a copy on a small index card in their pocket and could run down the list when writing admission orders for patients, or it could be used in developing standard orders for an MI patient, either printed order sheets or computerized orders, from which the physician can choose when admitting a patient to the hospital. Such a system has worked well in ensuring extremely high compliance with evidence-based recommendations at Brigham and Women's Hospital (Cannon, unpublished data). In the era of "scorecard medicine" *(65,66),* many outside observers such as health maintenance organizations or insurers tally up use of recommended medications as quality of care measures; use of a cardiac checklist should allow physicians (and patients) to "win" the game and improve the quality of care for patients.

Critical Pathways and Triage

At many institutions, critical pathways for acute MI and unstable angina have been adopted with the goals of quickly identifying patients with acute coronary syndromes, rapidly treating with appropriate medications (e.g., anti-ischemic and antithrombotic medications), and triaging the patient to the appropriate level of care *(1,67–70).*

BRIGHAM AND WOMEN'S HOSPITAL ACUTE CORONARY SYNDROME PATHWAYS

An overview of our critical pathways for acute coronary syndromes is shown in Fig. 1. There are five pathways for the different types of syndromes: two for acute ST-elevation MI patients (one for thrombolysis and one for primary angioplasty) (Fig. 2), one for unstable angina and non-ST-elevation MI (Fig. 3), and two for patients with chest pain of unclear etiology (one 6-hr emergency department-based "rule out MI" pathway and one 23-hr short stay unit-based pathway) (Fig. 4).

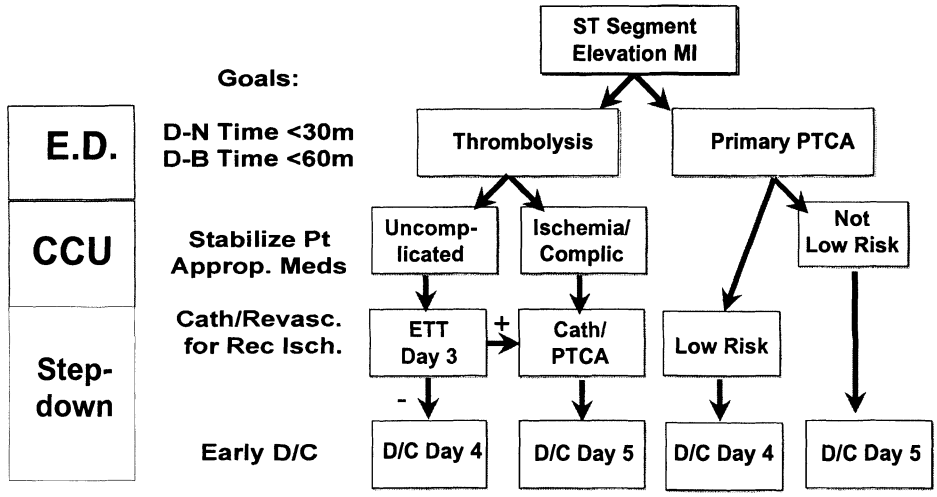

Fig. 2. Thrombolysis and primary angioplasty for acute ST-elevation MI critical pathways.

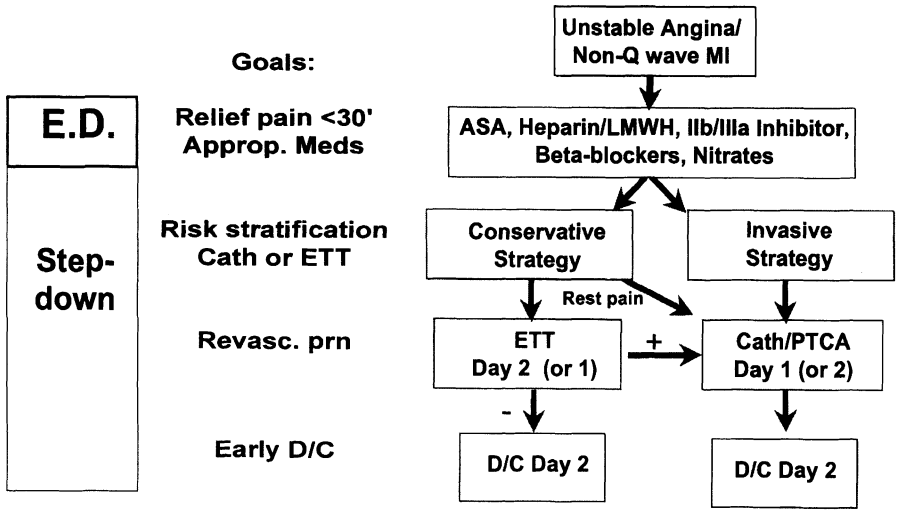

Fig. 3. Unstable angina/non-ST-elevation MI critical pathway.

ST-Elevation Myocardial Infarction

The critical pathway for all acute coronary syndromes begins immediately with the triage nurse who brings patients with chest pain into an "acute" room of the emergency department. A brief history is obtained and electrocardiogram performed. If ST-segment elevation is present, the patient is immediately evaluated for thrombolysis or primary angioplasty (Fig. 2). The treating physician decides which form of reperfusion therapy to use; however, the key guideline (based on the importance of time to reperfusion with either strategy) *(1,71,72)* is to triage patients according to the strategy that will achieve patency of the infarct-related artery most rapidly. Thus, during the day primary angioplasty is the preferred strategy, whereas on nights and weekends thrombolysis is

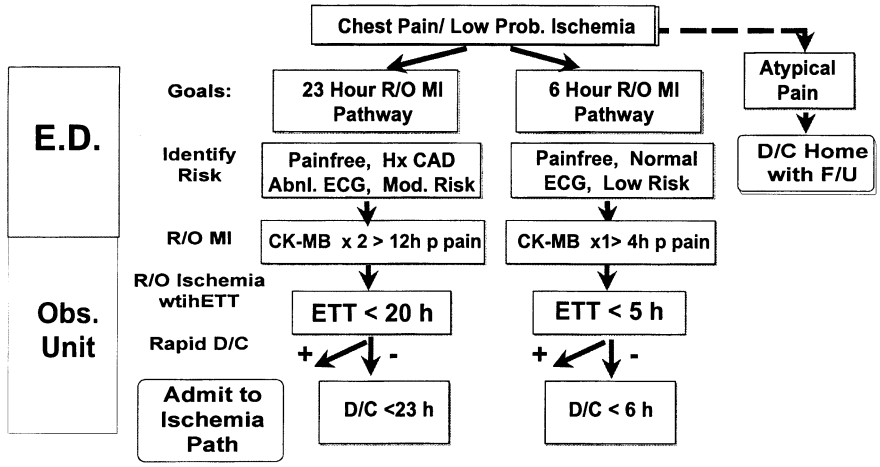

Fig. 4. "Rule-out MI" critical pathways.

preferred, in recognition of the time frequently necessary to mobilize the catheterization laboratory team.

After initial diagnosis, if the patient is eligible, thrombolytic therapy is administered in the emergency department with a goal of starting drug in <30 minutes from arrival *(1)*. The second goal of the pathway (begun in the emergency department but continued in the CCU) is to treat the patient with all other appropriate medications, such as aspirin, intravenous heparin, and anti-ischemic and cholesterol lowering medications. The third goal is to ensure that patients are considered for ongoing clinical research trials.

For the thrombolysis pathway, patient are treated in the emergency department and admitted to the CCU. Low-risk patients are transferred out of the CCU after 24 hr; others are transferred when their condition allows. Risk stratification is the next goal of the pathway. Rescue angioplasty is performed only if patients have evidence of ongoing symptoms and ST-segment elevation. Research is ongoing to identify other electrocardiographic (ECG) *(73,74)* and serum marker criteria *(75,76)* to assist in this decision. Otherwise, patients are treated according to the TIMI IIB conservative strategy, with cardiac catheterization performed only if patients have rest ischemia or evidence of ischemia on a stress test, the latter being performed on hospital d 4 or 5 for low-risk and higher risk patients, respectively. Echocardiography is recommended for most patients, except those with small inferior MIs without complications, in whom normal left ventricular function can be inferred using a clinical prediction rule *(52)*.

For the primary angioplasty pathway, the low-risk patients are admitted to the stepdown unit in accordance with the PAMI-II trial *(62)*. Primary stenting is common *(77)*, as is the use of GP IIb/IIIa inhibition *(78)*. No additional stress testing is performed except if patients have evidence of significant other coronary stenoses other than the infarct-related artery. Discharge is targeted for hospital day 4 or 5 depending on the extent of infarction.

Unstable Angina and Non-ST-Elevation Myocardial Infarction

The pathway for unstable angina and non-ST-elevation MI at Brigham and Women's Hospital emphasizes the following factors: (1) early relief of ischemic pain, which has

been found to be a determinant of development of myocardial infarction *(79);* (2) administration of antithrombotic and antiischemic therapy; (3) reminders of eligibility criteria for ongoing clinical research trials (e.g., trials of new gp IIb/IIIa inhibitors or treatment strategy trials); (4) a detailed list of suggested blood tests in an effort to reduce unnecessary tests; (5) choice of either an early conservative strategy or an early invasive strategy, as used in TIMI IIIB *(67).*

Inclusion criteria for the pathway are essentially patients with true unstable angina. This is defined as ischemic pain occurring either at rest or minimal exertion and with an accelerating pattern (i.e., Braunwald class 1–3 unstable angina) *(80).* Corroborative information that supports the clinical history is helpful in establishing the diagnosis and identifying higher risk patients *(27)*: prior history of MI or documented coronary disease by catheterization, or ST- or T-wave changes with the presenting syndrome. ST deviation of ≥0.5 mm is used since it appears to have prognostic significance equal to ≥1 mm ST depression *(79).* Since only a third of patients presenting unstable angina have ECG changes *(80),* the admission diagnosis relies mainly on the history.

The treatment involves aspirin, heparin and more recently consideration of enoxaparin *(21)* and gp IIb/IIIa inhibition *(81,82–83),* β-blockers, nitrates, and calcium antagonists if needed, as well as cholesterol-lowering medications as guided by prior history or by the admission cholesterol (or low-density lipoprotein) level.

Tests on Admissions

The pathway recommends three CK-MB determinations to diagnosis non Q-wave MI. In addition a troponin I level at entry is measured, as was done in TIMI IIIB. This is very useful in risk stratifying patients, as it provides information beyond that available from CK-MB *(84).* Trials are currently ongoing (TACTICS-TIMI 18) to determine whether the treatment strategy should be different based on the troponin value *(85).* Additional blood work and ECGs are limited in the pathway (to avoid multiple chemistry panels on the same admission). Assessment of left ventricular function with an ECG is recommended only if there are symptoms of congestive heart failure, or for moderate to large-sized non-Q-wave MIs (by CK and CK-MB determination).

Treatment Strategy

Patients are managed by either an early invasive or an early conservative strategy. Since TIMI IIIB showed equivalent outcomes through 1 yr, the choice of which strategy is left to the discretion of the treating physicians, although the early invasive strategy is the more commonly practiced.

The early invasive strategy involves cardiac catheterization within 18 hr of admission (either the same day or the following morning). Angioplasty (with or without stenting and gp IIb/IIIa inhibition—used at the discretion of the interventionalist) is carried out immediately. If the patient is referred for CABG, a call is placed to the on-call surgeon and scheduling is arranged as soon as possible. Patients then follow the CABG pathway, which targets a length of stay of 5 d for uncomplicated patients.

The early conservative strategy involves aggressive medical management and clinical monitoring. If the patient has recurrent ischemic pain, ECGs are performed and if either the pain is strongly suggestive of ischemia or the ECG changes are present, the patient is referred for catheterization that day. In the absence of recurrent ischemia, an exercise test is performed on the morning of d 2. If it is negative, the patient is discharged home; if it documents ischemia, then the patient has a catherization that same day. It should also

be noted that because unstable angina is so heterogeneous in its clinical presentation, the exercise testing is sometimes performed on hospital d 1 in low-risk patients, i.e., after approximately 24 h of optional medical management.

The overall goal for length of stay with the pathways is 2 d. This includes patients who have angioplasty in the early invasive strategy. If patients fail the early conservative strategy and have an angioplasty on d 2, then their target length of stay will be 3 d. Initial experience with this pathway has shown a reduction in hospital length of stay from a median of 5 d prior to the pathway to 2 d, as well as an improvement in the use of appropriate medications (Cannon, unpublished data). As institutions gain experience with implementation of critical pathways, their impact on coronary care will be assessed more clearly. Such pathways offer a means of improving care while attempting to control costs.

Secondary Prevention and Follow-Up

Because follow-up is critical in the overall management of all acute coronary syndromes, the primary care physician receives a phone call, a fax summary or the hospital discharge instructions, a letter from the cardiologist, and the hospital discharge summary. (The latter three are also sent to other physicians caring for the patient.) This also provides the opportunity for us as cardiologists to justify long-term management with key medications such as aspirin, β-blockers, and cholesterol-lowering medications *(86,87)*.

"Rule-Out MI Pathways"

For the large population of patients without ECG changes, risk stratification is used: patients with clearly atypical pain not suggestive of ischemia are discharged home with follow-up to their primary physicians. The remaining patients with pain possibly suggestive of ischemia are observed in the emergency department. If stable, these patients undergo early exercise testing to determine the presence and extent of ischemia *(68)*. If positive, the patients are admitted for further evaluation and treatment. If negative, they are discharged home (within 6 hours of emergency department arrival) with follow-up assigned to their physicians *(68)*.

We also established a "23-hr rule-out MI" pathway for patients who have chest pain but who are not clearly low-risk patients (e.g., patients with a prior history of coronary artery disease and new chest pain). In this pathway, patients receive aspirin and β-blockers, have serial CK-MB and admission troponin-I measurements taken, and undergo exercise testing between 12 and 20 hr after presentation. The use of such an approach has reduced the rate of hospital admission for chest pain at our institution, as well as others *(88)*.

CONCLUSIONS

The use of critical pathways is currently growing rapidly. They offer great potential for both reducing hospital length of stay and costs and improving patient care. Standardized approaches with simple checklists to ensure that appropriate medications are being given will be a significant improvement in the care of patients. Improving the administrative links between different departments to make these pathways work may also benefit patient care. After development of pathways, we must monitor their performance to ensure that they meet the overall goal of reducing costs while improving the quality of patient care. It is our belief that this goal can be achieved.

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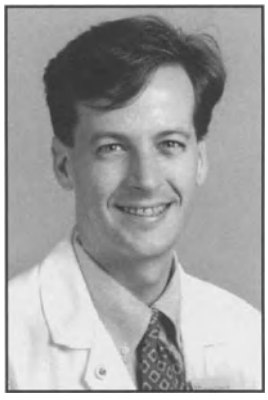
About the Editor



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