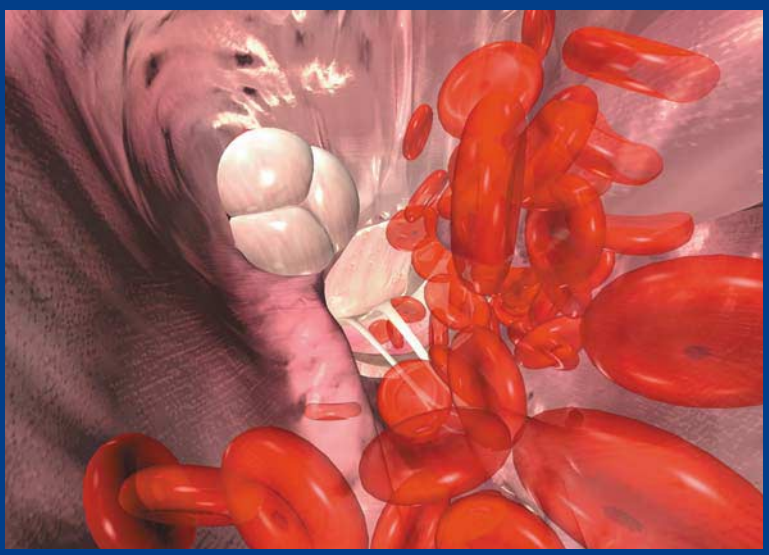
CONTEMPORARY CARDIOLOGY

Primary Angioplasty in Acute Myocardial Infarction

Edited by

James E. Tcheng, MD



HUMANA PRESS

Primary Angioplasty in Acute Myocardial Infarction

CONTEMPORARY CARDIOLOGY

CHRISTOPHER P. CANNON, MD
SERIES EDITOR

Primary Angioplasty in Acute Myocardial Infarction, edited by *James E. Tcheng, MD, 2002*
Cardiogenic Shock: *Diagnosis and Treatment,* edited by *David Hasdai, MD, Peter B. Berger, MD, Alexander Battler, MD, and David R. Holmes, Jr., MD, 2002*
Management of Cardiac Arrhythmias, edited by *Leonard I. Ganz, MD, 2002*
Diabetes and Cardiovascular Disease, edited by *Michael T. Johnstone and Aristidis Veves, MD, DSC, 2001*
Blood Pressure Monitoring in Cardiovascular Medicine and Therapeutics, edited by *William B. White, MD, 2001*
Vascular Disease and Injury: *Preclinical Research,* edited by *Daniel I. Simon, MD, and Campbell Rogers, MD 2001*
Preventive Cardiology: *Strategies for the Prevention and Treatment of Coronary Artery Disease,* edited by *JoAnne Micale Foody, MD, 2001*
Nitric Oxide and the Cardiovascular System, edited by *Joseph Loscalzo, MD, PhD and Joseph A. Vita, MD, 2000*
Annotated Atlas of Electrocardiography: *A Guide to Confident Interpretation,* by *Thomas M. Blake, MD, 1999*
Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease, edited by *A. Michael Lincoff, MD, and Eric J. Topol, MD, 1999*
Minimally Invasive Cardiac Surgery, edited by *Mehmet C. Oz, MD and Daniel J. Goldstein, MD, 1999*
Management of Acute Coronary Syndromes, edited by *Christopher P. Cannon, MD, 1999*

Primary Angioplasty in Acute Myocardial Infarction

Edited by

James E. Tcheng, MD

Duke Clinical Research Institute
and Division of Cardiology
Duke University Health System, Durham, NC

Humana Press
Totowa, New Jersey

© 2002 Humana Press Inc.
999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

www.humanapress.com

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341, E-mail: humana@humanapr.com; or visit our Website: http://humanapress.com

All rights reserved.

No part of this book may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, microfilming, recording, or otherwise without written permission from the Publisher.

All articles, comments, opinions, conclusions, or recommendations are those of the author(s), and do not necessarily reflect the views of the publisher.

Due diligence has been taken by the publishers, editors, and authors of this book to assure the accuracy of the information published and to describe generally accepted practices. The contributors herein have carefully checked to ensure that the drug selections and dosages set forth in this text are accurate and in accord with the standards accepted at the time of publication. Notwithstanding, as new research, changes in government regulations, and knowledge from clinical experience relating to drug therapy and drug reactions constantly occurs, the reader is advised to check the product information provided by the manufacturer of each drug for any change in dosages or for additional warnings and contraindications. This is of utmost importance when the recommended drug herein is a new or infrequently used drug. It is the responsibility of the treating physician to determine dosages and treatment strategies for individual patients. Further it is the responsibility of the health care provider to ascertain the Food and Drug Administration status of each drug or device used in their clinical practice. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences from the application of the information presented in this book and make no warranty, express or implied, with respect to the contents in this publication.

Cover illustration: Left chamber—Mitral and Aortic with Blood Cells. LifeART image copyright 2002 by Lippincott Williams & Wilkins. All rights reserved.
Cover design by Patricia F. Cleary.

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American National Standards Institute) Permanence of Paper for Printed Library Materials.

Photocopy Authorization Policy:
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Humana Press Inc., provided that the base fee of US $10.00 per copy, plus US $00.25 per page, is paid directly to the Copyright Clearance Center at 222 Rosewood Drive, Danvers, MA 01923. For those organizations that have been granted a photocopy license from the CCC, a separate system of payment has been arranged and is acceptable to Humana Press Inc. The fee code for users of the Transactional Reporting Service is: [0-89603-904-8/02 $10.00 + $00.25].

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

PREFACE

Over the past 50 years, care of the patient sustaining an acute myocardial infarction has undergone a stunning evolution. In the early days, there was little to offer the patient with an acute infarction except for weeks of absolute bedrest, and substantial morbidity and high rates of mortality were the norm. Just 15 years ago, thrombolytic therapies were being introduced as a pharmacologic approach to treat the acute event more aggressively and, fortunately, more successfully. About the same time, a few brave pioneers asked the question, why not perform emergency angioplasty as a primary reperfusion strategy? These individuals, despite being thought of as heretical by mainstream cardiology, nonetheless persevered, proving the benefit of "state of the art" balloon angioplasty compared to "state of the art" thrombolytic therapy in a series of landmark trials published in the *New England Journal of Medicine* in 1993. Since then, there has been no turning back, and today the technique has evolved to incorporate a multifaceted approach including the best of angioplasty technologies coupled with a rich and growing armamentarium of adjunctive medications, all designed to optimize both short- and long-term outcomes.

It is a pleasure to bring together in this volume the best available data about direct percutaneous coronary intervention (PCI) as primary treatment of acute myocardial infarction. The first three chapters provide critical background information about the lexicon and requirements personnel and institutions must understand and fulfill to have a safe and successful program. The next two chapters tell the early history of direct PCI, including a review of the inauspicious beginnings in plain old balloon angioplasty and how these beginnings led to current stent PCI strategies; a second chapter discusses the use of emergency PCI as a bailout procedure for failed thrombolysis. Chapters 6–9 survey the contemporary strategies that define direct PCI today, including the growing movement to institute direct PCI programs in hospitals that do not have full-time surgical backup; adjunctive therapies aimed at reducing reperfusion injury and maintaining TIMI grade 3 flow; the potent platelet inhibitors known as glycoprotein (GP) IIb/IIIa receptor inhibitors and their role in PCI; and the randomized clinical trial evaluations of stent implantation and GP IIb/IIIa inhibitors singularly and in combination. The final chapter fills in the economic justification for a medical procedure that could arguably be recommended to as many as half a million patients in the United States per year.

I am grateful to my colleagues, the authors of the chapters in this book, for their willingness to share their knowledge, their research, and their insights. In an age when any time spent away from research and practice is precious, it is a tribute to their dedication to the highest quality clinical care that they were

willing to spend so much time putting their thoughts down so that we could all benefit from them. I would also like to extend special notes of thanks to Joyce Sizemore and Penny Hodgson for their managerial and editorial contributions. Most importantly, I dedicate this book to my forever sweetheart, Mary Ann Powers, without whose patience, understanding, and love this project could not have been accomplished.

James E. Tcheng, *MD*

CONTENTS

CONTRIBUTORS

ABDULHAY ALBIRINI, MD, *Department of Cardiology, The Cleveland Clinic Foundation, Cleveland, OH*

SORIN J. BRENER, MD, *Department of Cardiology, The Cleveland Clinic Foundation, Cleveland, OH*

BRUCE R. BRODIE, MD, *LeBauer Cardiovascular Research Foundation and Moses Cone Heart & Vascular Center, Greensboro, NC*

WARREN J. CANTOR, MD, *Division of Cardiology, St Michael's Hospital, Toronto, Ontario, Canada*

DAVID A. COX, MD, *Mid Carolina Cardiology, Charlotte, NC*

STEPHEN G. ELLIS, MD, *Department of Cardiology, The Cleveland Clinic Foundation, Cleveland, OH*

CINDY L. GRINES, MD, *University of Michigan Medical Center, Ann Arbor, MI*

ALAN W. HELDMAN, MD, *Johns Hopkins University School of Medicine, Baltimore, MD*

RUSSELL J. IVANHOE, MD, *Winter Park, FL*

DAVID E. KANDZARI, MD, *Duke Clinical Research Institute, Durham, NC*

EDWARD KIM, MD, *Johns Hopkins University School of Medicine, Baltimore, MD*

NANCY SINCLAIR MCNAMARA, RN, BSN, *Division of Cardiology, Exeter Hospital, Exeter, NH*

DEBABRATA MUKHERJEE, MD, *Division of Cardiology, University of Michigan Health System, Ann Arbor, MI*

J. CONOR O'SHEA, MD, *Cardiology Division, Duke University Medical Center and Duke Clinical Research Institute, Durham, NC*

GREGG W. STONE, MD, *Cardiovascular Research Foundation, New York, NY*

JAMES E. TCHENG, MD, *Duke Clinical Research Institute, and Division of Cardiology, Duke University Health System, Durham, NC*

THOMAS P. WHARTON, JR., MD, *Division of Cardiology, Exeter Hospital, Exeter, NH, and Division of Cardiology, Portsmouth Regional Hospital, Portsmouth, NH*

1 Rationale and Lexicon of Primary Angioplasty

Warren J. Cantor, MD

Angiographic and pathologic studies have contributed greatly to our understanding of the pathogenesis of acute coronary syndromes. "Vulnerable" atherosclerotic plaques, characterized by thin fibrous caps, lipid-rich cores, and infiltration of leukocytes, undergo ulceration, fissure, or rupture *(1–3)*. Exposure of subendothelial collagen leads to adhesion and activation of platelets. The coagulation cascade is initiated by subendothelial tissue factor as well as vasoactive substances secreted by activated platelets. These processes result in platelet aggregation, thrombin generation, and fibrin deposition, ultimately leading to coronary thrombosis. In the case of ST-segment elevation acute myocardial infarction (AMI), the thrombosis is usually occlusive, resulting in transmural myocardial necrosis *(4)*. Reperfusion therapy, whether catheter-based or pharmacologic, is critically needed to restore antegrade flow to the infarct-related artery and thus arrest the propagating wave of necrosis *(5)*. To preserve myocardium and reduce morbidity and mortality, reperfusion must be rapid, complete, and sustained.

Traditionally, pharmacologic and catheter-based reperfusion therapies have been considered distinct and mutually exclusive strategies. Each strategy has its own advantages and shortcomings. Fibrinolytic therapy is widely available and can be given rapidly in emergency departments. Even with the most efficacious fibrinolytic agents, however, normal (thrombolysis in myocardial infarction [TIMI] grade 3) flow at 90 min is achieved in only 50%–60% of patients *(6–8)*. Intracranial hemorrhage occurs in approx 1% of patients treated with fibrinolytic therapy and is fatal in 60% of cases *(9)*.

In contrast, primary angioplasty results in TIMI grade 3 flow in >70% of patients and patency (TIMI 2 or 3 flow) in >90% of patients, without the hemorrhagic risks of fibrinolytic therapy *(10–12)*. However, angioplasty facilities

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

are not available at most hospitals. Even in hospitals equipped to perform angioplasty, the time required to deliver patients to the catheterization laboratory results in an average delay of 2 h from hospital arrival to the first balloon inflation *(13)*. Although the impact of time to reperfusion on clinical outcomes has not been as well characterized for primary angioplasty as for fibrinolytic therapy, primary angioplasty performed within 2 h of hospital arrival is associated with improved survival compared with angioplasty performed beyond 2 h *(13–15)*.

Angioplasty not only restores brisk anterograde flow but also treats the underlying stenosis. Almost 90% of patients with patent infarct-related arteries at 90 min after fibrinolytic therapy have a residual stenosis $\geqslant$50% at the culprit lesion *(16)*. Successful angioplasty of hemodynamically significant stenoses should therefore, at least in theory, reduce the risk of recurrent ischemia and reinfarction. A meta-analysis of trials comparing fibrinolytic therapy with primary angioplasty found lower rates of nonfatal reinfarction (2.9% vs 5.3%) and death plus nonfatal reinfarction (7.2% vs 11.9%) with primary angioplasty *(17)*. In the GUSTO-IIb study, the difference in reinfarction did not become apparent until after 5 d, lending further credence to the suggestion that the benefits of primary angioplasty extend beyond early restoration of TIMI grade 3 flow *(12)*. There was significantly less recurrent ischemia after primary angioplasty compared with tissue plasminogen activator (t-PA) (5.5% vs 9.0%; $p = 0.03$).

There are various contexts in which angioplasty can be performed in the setting of AMI (Table 1). Primary angioplasty (also referred to as direct angioplasty) refers to percutaneous coronary revascularization applied as the initial reperfusion strategy. Primary angioplasty has been compared with fibrinolytic therapy in 12 randomized trials *(10–12,18–26)* and two meta-analyses *(17,27)*. Angioplasty can also be used for patients who have already received fibrinolytic therapy. The latter category includes rescue angioplasty for patients who have failed to reperfuse *(28–32)*, and adjunctive angioplasty, in which all patients routinely undergo catheterization after thrombolysis with angioplasty performed whenever technically feasible, irrespective of the patency status of the culprit vessel. Adjunctive angioplasty has been studied at three time points: immediate (direct referral to the cardiac catheterization suite immediately after thrombolytic therapy), early (12–48 h after thrombolysis), and deferred (>48 h after thrombolysis) (Table 1).

Three large randomized trials of immediate and early adjunctive angioplasty were carried out in the 1980s and showed no benefit with angioplasty, with increased rates of bleeding complications and a trend toward increased mortality *(33–35)*. However, these trials were carried out prior to the widespread use of coronary stents and glycoprotein (GP) IIb/IIIa receptor antagonists. Patients with AMI treated with fibrinolytic therapy have increased levels of platelet activation and aggregation *(36–41)* and may be predisposed toward thrombotic complications during percutaneous coronary intervention. GP IIb/IIIa antago-

Table 1
Varieties of Percutaneous Coronary Intervention (PCI) Following AMI

	Thrombolytic therapy prior to PCI?	*Successful reperfusion after thrombolysis*	*Timing of PCI after thrombolysis*
Direct (primary, emergency)	No	N/A	N/A
Rescue (salvage)	Yes	No	1.5–12 h
Immediate (facilitated)	Yes	±	Immediate
Early	Yes	Yes	12–48 h
Deferred (elective)	Yes	Yes	> 48 h

N/A, not applicable.

nists appear to counteract this prothrombotic state *(36)*. Recently, the concept of facilitated angioplasty has been proposed, in which pharmacologic agents (fibrinolytics and GP IIb/IIIa antagonists) are administered, followed immediately by angioplasty *(42–46)*. The rationale behind this strategy is that reperfusion will occur in a higher proportion of patients prior to angioplasty, which may help preserve myocardium during the delay from presentation to the first balloon inflation. Early treatment with these medications may also improve the procedural success rates and subsequent clinical outcomes *(45)*. Facilitated angioplasty therefore combines the benefits of pharmacologic and catheter-based reperfusion strategies *(46)*.

Following successful angioplasty, long-term patency of the infarct vessel may be compromised by restenosis or reocclusion. Nakagawa and colleagues performed serial angiography on 137 patients after successful primary angioplasty at 3 wk, 4 mo, 1 yr, and 3 yr *(47)*. The cumulative restenosis rates (including reocclusion) were 20%, 43%, 47%, and 49%, respectively. By 3 wk, 16 patients (12%) had reocclusion of the infarct vessel, and only three patients developed reocclusion beyond 3 wk. The use of coronary stents and GP IIb/IIIa antagonists would be expected to help prevent restenosis and reocclusion. The Stent-PAMI randomized trial found that stenting reduced the incidence of restenosis and repeat target vessel revascularization at 6 mo from 34% to 20% ($p < 0.001$) *(48)*. Five smaller trials also documented lower rates of target vessel revascularization with stenting *(49–53)*. In the ADMIRAL study, patients undergoing primary angioplasty with stent implantation were randomized to receive abciximab or placebo. The patients treated with abciximab had higher rates of TIMI 3 flow at 24 h (86% vs 78%; $p < 0.05$) and lower rates of death, myocardial infarction, or urgent revascularization at 30 d (10% vs 11%; $p < 0.03$) *(54)*. Preliminary data from the CADILLAC trial indicate that stent implantation significantly reduces the need for target vessel revascularization at 6 mo and that abciximab significantly reduces the incidence of major adverse cardiac events (5.0% vs 7.1%;

$p = 0.04$) and stent thrombosis (0.0% vs 1.0%; $p = 0.03$) at 30 d *(55)*. In the STOPAMI trial, patients randomized to primary angioplasty with stenting and abciximab had improved myocardial salvage compared with thrombolytic therapy *(56)*. Ongoing trials will determine the role of facilitated angioplasty in the acute management of myocardial infarction.

REFERENCES

1. Falk E, Shah PK, Fuster V. Coronary plaque disruption. Circulation 1995;92:657–671.
2. Fuster V, Badimon L, Badimon JJ, et al. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:242–250.
3. Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina. Br Heart J 1985;53:363–373.
4. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897–902.
5. Reimer KA, Lowe JE, Rasmussen MM, et al. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977;56:786–794.
6. The GUSTO Investigators. An International Randomized Trial Comparing Four Thrombolytic Strategies For Acute Myocardial Infarction. N Engl J Med 1993;329:673–682.
7. Smalling RW, Bode C, Kalbfleisch J, et al. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. RAPID Investigators. Circulation 1995;91:2725–2732.
8. Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. Circulation 1996;94:891–898.
9. Gurwitz JH, Gore JM, Goldberg RJ, et al. Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. Ann Intern Med 1998;129: 597–604.
10. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993;328:673–679.
11. Zijlstra F, de Boer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328: 680–684.
12. The GUSTO IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–1628.
13. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–2947.
14. Berger PB, Ellis SG, Holmes DR Jr, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. Circulation 1999;100:14–20.
15. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312–1319.

16. Llevadot J, Giugliano RP, McCabe CH, et al. Degree of residual stenosis in the culprit coronary artery after thrombolytic administration (Thrombolysis in Myocardial Infarction [TIMI] Trials). Am J Cardiol 2000;85:1409–1413.
17. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–2098.
18. Gibbons RJ, Holmes DR, Reeder GS, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685–691.
19. Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1993;22:376–380.
20. Zijlstra F, Beukema WP, van't Hof AW, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908–912.
21. Ribichini F, Steffenino G, Dellavale A. Primary angioplasty versus thrombolysis in inferior acute myocardial infarction with anterior ST-segment depression: a single center randomized study. J Am Coll Cardiol 1996;27:221-A (abstract).
22. Grinfeld L, Berrocal D, Belardi J. Fibrinolytics vs. primary angioplasty in acute myocardial infarction (FAP): a randomized trial in a community hospital in Argentina. J Am Coll Cardiol 1996;27:222-A (abstract).
23. DeWood MA. Direct PTCA vs. intravenous t-PA in acute myocardial infarction: results from a prospective randomized trial. In: Proceedings from the Thrombolysis and Interventional Therapy in Acute Myocardial Infarction Symposium. George Washington University, Washington, DC, 1990, pp. 28–29.
24. Garcia E, Elízaga J, Soriano J, et al. Primary angioplasty versus thrombolysis with tPA in anterior myocardial infarction: results from a single center trial. J Am Coll Cardiol 1997;29(Suppl. A):389-A (abstract).
25. Le May MR, Labinaz M, Davies RF, et al. Stenting versus Thrombolysis in Acute Myocardial Infarction Trial (STAT). J Am Coll Cardiol 2001;37:985–991.
26. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000;343:385–391.
27. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and reinfarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. Circulation 1995;91:476–485.
28. Ellis SG, da Silva ER, Spaulding CM, et al. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. Am Heart J 2000;139:1046–1053.
29. Ross AM, Lundergan CF, Rohrbeck SC, et al. Rescue angioplasty after failed thrombolysis: technical and clinical outcomes in a large thrombolysis trial. J Am Coll Cardiol 1998;31:1511–1517.
30. Davies CH, Ormerod OJM. Failed coronary thrombolysis. Lancet 1998;351:1191–1196.
31. Ellis SG, Van De Werf F, Ribeiro-daSilva E, et al. Present status of rescue coronary angioplasty: current polarization of opinion and randomized trials. J Am Coll Cardiol 1992;19:681–686.
32. Ellis SG, da Silva ER, Heyndrickx G, et al. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994;90:2280–2284.
33. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction—results of the

Thrombolysis in Myocardial Infarction (TIMI) Phase II Trial. N Engl J Med 1989;320: 618–627.
34. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–588.
35. Simoons ML, Arnold AE, Betriu A, et al. Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty. Lancet 1988;1:197–203.
36. Coulter SA, Cannon CP, Ault KA, et al. High levels of platelet inhibition with abciximab despite heightened platelet activation and aggregation during thrombolysis for acute myocardial infarction: results from TIMI (Thrombolysis In Myocardial Infarction) 14. Circulation 2000;101:2690–2695.
37. Gurbel PA, Serebruany VL, Shustov AR, et al. Effects of reteplase and alteplase on platelet aggregation and major receptor expression during the first 24 hours of acute myocardial infarction treatment. GUSTO-III Investigators. Global Use of Strategies to Open Occluded Coronary Arteries. J Am Coll Cardiol 1998;31:1466–1473.
38. Ault KA, Cannon CP, Mitchell J, et al. Platelet activation in patients after an acute coronary syndrome: results from the TIMI-12 trial. Thrombolysis in Myocardial Infarction. J Am Coll Cardiol 1999;33:634–639.
39. Moser M, Nordt T, Peter K, et al. Platelet function during and after thrombolytic therapy for acute myocardial infarction with reteplase, alteplase, or streptokinase. Circulation 1999;100: 1858–1864.
40. Rasmanis G, Vesterqvist O, Green K, et al. Evidence of increased platelet activation after thrombolysis in patients with acute myocardial infarction. Br Heart J 1992;68:374–376.
41. Kerins DM, Roy L, FitzGerald GA, et al. Platelet and vascular function during coronary thrombolysis with tissue-type plasminogen activator. Circulation 1989;80:1718–1725.
42. Topol EJ, Ohman EM, Barnathan E, et al. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000;101:2788–2794.
43. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis—results of the Thrombolysis in Myocardial Infarction (TIMI) 14 Trial. Circulation 1999;99:2720–2732.
44. Ross AM, Coyne KS, Reiner JS, et al. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. Plasminogen-activator Angioplasty Compatibility Trial. J Am Coll Cardiol 1999;34:1954–1962.
45. Herrmann HC, Moliterno DJ, Ohman EM, et al. Facilitation of early percutaneous coronary intervention after reteplase with or without abciximab in acute myocardial infarction. Results from the SPEED (GUSTO-4 Pilot) trial. J Am Coll Cardiol 2000;36:1489–1496.
46. Gibson CM. A union in reperfusion: the concept of facilitated percutaneous coronary intervention. J Am Coll Cardiol 2000;36:1497–1499.
47. Nakagawa Y, Iwasaki Y, Kimura T, et al. Serial angiographic follow-up after successful direct angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:980–984.
48. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–1956.
49. Suryapranata H, van't Hof AW, Hoorntje JC, et al. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502–2505.
50. Antoniucci D, Santoro GM, Bolognese L, et al. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction: results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. J Am Coll Cardiol 1998;31:1234–1239.

51. Rodriguez A, Bernardi V, Fernandez M, et al. In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction (GRAMI trial). Gianturco-Roubin in Acute Myocardial Infarction. Am J Cardiol 1998;81:1286–1291.
52. Saito S, Hosokawa G, Tanaka S, et al. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. PASTA Trial Investigators. Cathet Cardiovasc Intervent 1999;48:262–268.
53. Maillard L, Hamon M, Khalife K, et al. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. STENTIM-2 Investigators. J Am Coll Cardiol 2000;35:1729–1736.
54. Alexander JH, Al-Khatib S, Cantor WJ, et al. Highlights from the American College of Cardiology 48th Annual Scientific Sessions: March 7 to 10, 1999: Session: Late-Breaking Trials. Am Heart J 1999;138:175–190.
55. Stone GW, Grines CL, Cox DA, et al. A prospective, randomized trial comparing primary balloon angioplasty with or without abciximab to primary stenting with or without abciximab in acute myocardial infarction—primary endpoint analysis from the CADILLAC trial. Circulation 2000;102 (Suppl. II):II-664 (abstract).
56. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. N Engl J Med 2000;343:385–391.

2 Operator and Site Requirements for Primary Angioplasty

J. Conor O'Shea, MD

CONTENTS

Direct recanalization of the infarct-related coronary artery by mechanical rather than chemical means simultaneously addresses both the occlusive thrombosis and the underlying stenosis, and is associated with a superior early patency rate of >90% *(1–3)*. Despite these inherent benefits, direct percutaneous transluminal coronary angioplasty (PTCA) remains a practical therapeutic option in the minority of facilities that have continuous access to a catheterization laboratory. Only 20% of hospitals in the United States have cardiac catheterization laboratories and even fewer have the capability of performing emergency PTCA *(4)*. Although transfer of the patient to a facility that can perform PTCA is possible, the consequent delay in achieving reperfusion may outweigh any added benefits.

As has been shown for stable and unstable angina, the results of primary angioplasty depend on the setting in which it is performed *(5)*, and therefore the results from various hospitals may differ considerably *(6)*. Establishing a proficient primary angioplasty program takes great institutional will and effort, and even centers with a large experience in coronary angioplasty will have a learning

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

curve for primary angioplasty *(7)*. It is axiomatic that centers undertaking primary PTCA must be properly equipped and staffed, their operators competent, and their cases selected appropriately. The purpose of this chapter is to describe in detail the site and operator requirements for primary PTCA and, where relevant, to review the American College of Cardiology/American Heart Association guidelines pertaining to this procedure.

GENERAL CONSIDERATIONS

In any catheterization setting, patient safety must be of paramount importance. Patients due to undergo the procedure should have received sound professional advice, and their procedure should be undertaken with the outcome and their safety being the central focus of attention for all those involved with their care. Audit of the quality of care delivered should be undertaken, and its implementation and subsequent refinement should be with the wholehearted involvement and cooperation of interventional cardiologists.

A center undertaking primary angioplasty must have a cardiac catheterization laboratory equipped with a physiological measurement system and full facilities for cardiopulmonary resuscitation, including capability for intra-aortic balloon pumping. Sedation is often given during procedures so transcutaneous or an equivalent method of monitoring arterial oxygen saturation must be available. High-quality radiographic imaging equipment (preferably digital) capable of imaging the coronary arteries from all directions, including caudal and cranial angulation, must be provided. Image manipulation including freeze frame, zoom, and playback should be immediately available. An adequate system should be in place for archiving and retrieving image data, with images being retained for at least 3 yr.

Because no level of exposure to ionizing radiation is considered safe, the cardinal principle of diagnostic imaging is to minimize X-ray exposure to the patient and staff. The National Council on Radiation Protection and Measurements has issued recommendations for the proper design and performance of cardiac radiological equipment (NCRP Report No. 49, 1976) and structural shielding systems (NCRP Report No. 102, 1989). An essential element of an effective radiation safety program is monitoring laboratory personnel's exposure to radiation.

The need for particular items of angioplasty hardware, such as balloons, guiding catheters, stents, and adjunctive pharmacology, often cannot be anticipated until a procedure is in progress; therefore, it is vital that an adequate range of equipment and drugs be kept available at all times. Advances in technology and hardware have been very rapid in the field of interventional cardiology, and the need to upgrade and extend the range of available equipment in light of these advances should be anticipated.

PRE-HOSPITAL PHASE

The greatest mortality reduction from acute myocardial infarction (AMI) can be achieved by very early treatment after the onset of symptoms *(8)*. Greater public awareness of the symptoms of AMI and speedy response and early recognition of AMI by general practitioners are of great importance in reducing time delays to treatment. Although the results of primary angioplasty therapy may be less time dependent than the results of thrombolysis, the adage that time is muscle during the first few hours of a myocardial infarction still holds true. Liem and colleagues have shown that an increase in the median time delay from presentation to balloon inflation from 60 to 103 min in patients with anterior infarctions resulted in a 24% larger enzymatic infarct size and a 4% lower left ventricular ejection fraction measured before hospital discharge *(9)*.

Confirmation of the diagnosis of AMI by 12-lead electrocardiography, and the speedy communication of this information to an on-call member of the primary angioplasty team, can trim more minutes off the time to balloon inflation by removing the need to visit the emergency and coronary care departments in the hospital. Furthermore, this allows the emergency medical staff transporting the patient to start the initial pharmacological therapy at the earliest possible stage. If a definitive diagnosis has not been made before hospital arrival, additional delays can be reduced by obtaining a limited history and physical and 12-lead EKG within 5–10 min in all patients with suspected myocardial infarction *(10)*.

STAFFING ISSUES

A flexible attitude shared by the catheterization staff and interventional cardiologists is a prerequisite for any center providing primary angioplasty. The staff must be prepared to change their program at a moment's notice. A backup laboratory (or laboratories) will facilitate this need for flexibility.

In their task force recommendations, the ACC/AHA define the performance standard for primary angioplasty as balloon inflation within 90 ($\pm$ 30) min of admission *(4,11)*. Although preferable, on-call laboratory staff does not have to be in-house. All centers should ensure that the intervention laboratory and its staff are fully operational within 60 min of being notified of need, and each member of the on-call team should be able to get to the hospital within 30 min. Adequate facilities and staff must be available to provide 24-h, 7-d a week service. At a minimum, the on-call team should consist of an appropriately trained and experienced interventional cardiologist and three nonphysician personnel. These can be a combination of specialized catheterization laboratory nurses and dedicated cardiovascular technicians.

The scrub technician/nurse is responsible for ensuring sterile preparation of the catheterization site and for maintaining a sterile field throughout the procedure. Another circulating technician/nurse is responsible for placing and main-

taining peripheral intravenous access, administering medications during the procedure, and monitoring the patient. A third technician/nurse is responsible for ensuring adequate documentation during the procedure, including verification of the patient's consent, recording of drugs given, duration of radiation exposure, and contrast volume used, and otherwise maintaining a detailed procedural log. While acknowledging that staffing levels will vary with local circumstances, The Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society suggests that an on-call coverage frequency of one out of three nights makes unreasonable and unsustainable demands on the participating staff and interventionists *(12)*. The ACC/AHA guidelines do not specify an appropriate on-call rotation.

During PTCA for AMI, the catheterization laboratory must function as a critical care unit. Primary PTCA is a difficult procedure that can have a number of potentially fatal complications. Reperfusion arrhythmias must be recognized and treated promptly. Timmis and co-workers have demonstrated a greater incidence of arrhythmias following direct PTCA than with thrombolytic therapy *(13)*. After restoration of flow in the right coronary artery, profound hypotension and bradycardia may develop due to the Bezold–Jarisch reflex, resulting in greater use of inotropic agents and intra-aortic balloon pumps and a need for cardiopulmonary resuscitation *(14,15)*. Recurrent ischemia (10%–15%) will occur more frequently than with elective procedures with one in 20 cases of recurrent ischemia resulting in emergency coronary artery bypass graft surgery (CABG) or death *(3)*. Complications such as anaphylaxis, ventricular tachycardia and fibrillation, pulmonary edema, and shock can occur without warning.

All catheterization laboratory staff must be attentive to patient comfort at all stages of the procedure. Close attention to the patient in the less intensive pre- and post-procedural stages can often reveal early warning signals of impending complications. These include restlessness and agitation indicating hypoxia, somnolence indicating hypoventilation, lower abdominal pain and distention suggesting retroperitoneal hemorrhage, and nausea, itching, hives, and rhinorrhea as precursors to anaphylaxis. In the event of an emergency all personnel must be able to handle any deterioration in patient status and be able to deliver basic life support. All members of the catheterization team—physicians, nurses, and technologists—should maintain a current course completion card in cardiopulmonary resuscitation. Certification in advanced cardiac life support is desirable.

PHARMACOLOGICAL REQUIREMENTS

Adequate pain relief and supplemental oxygen are essential. For sedation, a combination of opiates and benzodiazepines are used commonly. Intravenous drugs should be given slowly and the doses titrated according to a patient's clinical status. Naloxone and flumazenil must be available to reverse excess sedation. Aspirin should be given preferably in a dose of 325 mg, chewed or in

soluble form. Sublingual and intravenous nitroglycerin, as well as β-blockers, unless contraindicated, should be given to lower myocardial oxygen consumption and alleviate myocardial ischemia. A range of antiplatelet agents including thienopyridines and glycoprotein IIb/IIIa inhibitors and direct and indirect antithrombin agents should also be available at all times. The appropriate use of these agents is discussed in more detail in other chapters. Finally, a cardiopulmonary resuscitation cart must be available. It should be checked daily to ensure that it is adequately stocked.

OPERATOR ISSUES

The assessment of clinical proficiency in the catheterization laboratory is based on a composite of cognitive skills, procedural conduct, and clinical judgment. The assessment of professional competence clearly resides in the domain of the physicians themselves. Within the United States, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has recognized this principle by requiring that the granting of initial or continuing medical staff privileges in any hospital be based on assessments of individual applicants against professional criteria that are specified in medical bylaws. The origins of the current requirements for certification by the Subspeciality Board of Cardiovascular Disease can be traced back to the 17th Bethesda Conference on cardiology training cosponsored by the American College of Cardiology (ACC) and the American Heart Association (AHA) in November 1985 *(16)*. The Task Force on Training in Cardiac Catheterization that was established at the conference stipulated that a trainee should perform a minimum of 300 diagnostic cardiac catheterizations, including 200 as primary operator over a 12-mo period *(17)*. The trainee planning to perform coronary angioplasty is required to complete a fourth year of training. During this additional year, a minimum of 125 coronary angioplasty procedures must be performed, including 75 as primary operator. In 1996, the American Board of Medical Specialties approved a Certificate of Added Qualification in Interventional Cardiology. This certification was offered for the first time in November 1999 and will become the benchmark by which interventional cardiologists are judged and credentialed.

Other volume minimums are imposed on angioplasty facilities within the United States. The ACC/AHA Task Force on Clinical Privileges in Cardiology indicates that a significant volume of cases per institution is essential to ensure quality and safety *(18)*. To maintain these goals, an institution should perform at least 200 PTCA procedures annually. The Society for Cardiac Angiography and Interventions imposes the following requirements on institutions that offer formal training in coronary angioplasty *(19)*:

1. A minimum of two individuals highly skilled in coronary angioplasty is necessary.

2. A case volume in excess of 500 coronary angioplasty procedures per year is considered optimal.
3. An active cardiac surgery program is necessary and on-site surgical availability is mandatory.

It must be stressed, however, that these values all represent minimum, and not optimum, levels of experience. While experience is the *sine qua non* of proficiency, the myriad of techniques and technologies preclude rigid delineation of "the right way." There is one incontrovertible bottom line: patient outcomes. Many studies have documented an inverse relationship between the incidence of major complications of several procedures and the number of these procedures performed by individual practitioners or hospitals. Lower mortality rates have been associated with higher volumes of elective procedures in studies of PTCA *(5,20–22)*, coronary stenting *(23)*, and coronary artery bypass graft surgery *(24,25)*.

In a recently published study, Canto and co-workers examined in-hospital mortality rates among patients with myocardial infarction who were treated at hospitals with a range of experience with emergency reperfusion therapies; the study used June 1994 to March 1998 data from the National Registry of Myocardial Infarction (NRMI) *(26)*. A total of 257,602 patients with AMI were treated at 450 hospitals in the primary angioplasty group and a total of 277,156 patients with AMI were treated at 516 hospitals in the thrombolytic therapy group. Both sets of patients were subdivided into quartiles based on the number of primary PTCA or thrombolytic interventions performed at the hospital in which they were treated. A minimal volume of five patients per year was required for a hospital to be included in the analysis. The higher volume hospitals in both the angioplasty group and the thrombolytic therapy group were likely to administer those therapies sooner than the lower volume hospitals (170.4 vs 198.6 min [$p < 0.001$] and 63.6 vs 74.4 min [$p < 0.001$], respectively). The crude mortality rate during hospitalization was 7.7% among patients admitted to hospitals in the lowest volume quartile of the angioplasty group (volume of 5–11 primary angioplasty procedures annually) and 5.7% among those admitted to hospitals in the highest volume quartile (>33 primary angioplasty procedures annually, $p < 0.001$). These results support the recommendation of the ACC/AHA task force that primary PTCA should be used as an alternative to thrombolytic therapy *only if* performed in a timely fashion by individuals skilled in the procedure and supported by experienced personnel in high-volume centers.

SURGICAL BACKUP

The current national standard of accepted medical practice requires that an experienced cardiovascular surgical team be available within the same institution to perform emergency CABG should the need arise. Although the exact

arrangement will vary from one institution to another, the essential requirement is the capacity to provide surgery promptly when angioplasty fails.

It has been argued that the conditions in AMI present a special set of circumstances favoring a less rigid application of the need for surgical backup. Reperfusion of the infarct-related vessel as early as possible is clearly critical in AMI, and primary angioplasty provides additional survival benefits for certain high-risk patients, such as those in cardiogenic shock. The more widespread availability of primary angioplasty could provide improved care for patients with contraindications to thrombolytic therapy. At the same time, however, angioplasty performed in the early hours following an AMI is frequently difficult and requires even greater levels of skill and experience than routine angioplasty performed in stable patients. Limiting angioplasty in AMI to institutions with in-house surgical backup ensures that these procedures are performed in laboratories that have ongoing and regular experience with angioplasty. In fact, surgical backup has become a surrogate for experienced, well-equipped laboratories.

AUDIT AND PEER REVIEW

Audit of practice and outcome is an integral part of providing a primary angioplasty service and should not be regarded as an optional extra. If the audit process is to work, standards must be defined in all relevant areas that affect the quality of care. Performance must then be assessed against these standards, and conclusions drawn from these assessments must be used to implement appropriate changes. The auditing process should be continuous to allow individual operators or units as a whole to recognize early when problems are developing. This also allows ongoing evaluation of changes made to improve patient care.

The AHA/ACC Guidelines for Cardiac Catheterization Laboratories designate the catheterization laboratory director as the person responsible for establishing and monitoring internal quality control systems *(27)*. In the United States, the process of periodic external audit is the responsibility of the Joint Commission on Accreditation of Healthcare Organizations.

Specifically with respect to auditing of primary angioplasty, some additional points are important. In reviewing the interventional cardiologist's performance, the appropriateness of patient selection as well as the quality of the interventional procedure are equally important. In implementing the auditing process, it is essential to ensure that patients judged to be at high risk are not denied treatment because an adverse outcome might reflect badly on the operator's ratings. It would indeed be ironic if the audit process, intended to improve the treatment of patients, actually prevented appropriate care. Finally, if centers and operators are to be assessed and occasionally judged to be failing, such failings should be the result of their own shortcomings and not those of a system with wider inadequacies, for which others may more appropriately bear responsibility.

CONCLUSION

Primary angioplasty is an appropriate form of acute reperfusion therapy under the proper conditions. Requirements for a successful primary angioplasty program include procedure volumes sufficiently large for physicians to develop and maintain their skills. Centers with relatively low volumes of angioplasty procedures should take this factor into account in developing angioplasty programs and establish institutional mechanisms to ensure prompt reperfusion therapy in patients with AMI. Hospitals with low volumes of angioplasty procedures may be able to improve the outcomes of their patients and approach the results of high-volume centers if they improve the processes of care—for example, by reducing the interval between the patient's arrival at the hospital and the performance of angioplasty. All centers must be careful to develop clear-cut reperfusion protocols to minimize indecision in choosing between alternative treatments.

REFERENCES

1. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993;328:673–679.
2. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680–684.
3. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. N Engl J Med 1997;336:1621–1628.
4. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999; 34:890–911.
5. Kimmel SE, Berlin JA, Laskey WK. The relationship between coronary angioplasty procedure volume and major complications. JAMA 1995;274:1137–1142.
6. Christian TF, O'Keefe JH, DeWood MA, et al. Intercenter variability in outcome for patients treated with direct coronary angioplasty during acute myocardial infarction. Am Heart J 1998;135(2 Pt 1):310–317.
7. Caputo RP, Ho KK, Stoler RC, et al. Effect of continuous quality improvement analysis on the delivery of primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1997;79:1159–1164.
8. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771–775.
9. Liem AL, van 't Hof AW, Hoorntje JC, de Boer MJ, Suryapranata H, Zijlstra F. Influence of treatment delay on infarct size and clinical outcome in patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1998;32:629–633.
10. Acute myocardial infarction: pre-hospital and in-hospital management. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 1996;17:43–63.

11. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). Circulation 1999;100:1016–1130.
12. Coronary angioplasty: guidelines for good practice and training. Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society. Heart 2000;83:224–235.
13. Timmis G, Ramos R, Gangadharan V, et al. Determinants of reperfusion arrhythmias in a randomized trial of streptokinase versus angioplasty for acute myocardial infarction. Circulation 1985;72:III-219.
14. Topol EJ, Gacioch GM. Discordance in results of right coronary intervention. Circulation 1991;84:955.
15. Gacioch GM, Topol EJ. Sudden paradoxic clinical deterioration during angioplasty of the occluded right coronary artery in acute myocardial infarction. J Am Coll Cardiol 1989; 14:1202–1209.
16. 17th Bethesda Conference. Adult cardiology training. November 1–2, 1985. J Am Coll Cardiol 1986;7:1191–1218.
17. Conti CR, Faxon DP, Gruentzig A, Gunnar RM, Lesch M, Reeves TJ. 17th Bethesda conference: Adult cardiology training. Task Force III. Training in cardiac catheterization. J Am Coll Cardiol 1986;7:1205–1206.
18. Ryan TJ, Klocke FJ, Reynolds WA. Clinical competence in percutaneous transluminal coronary angioplasty. A statement for physicians from the ACP/ACC/AHA Task Force on Clinical Privileges in Cardiology. J Am Coll Cardiol 1990;15:1469–1474.
19. Cowley MJ, Faxon DP, Holmes DR, Jr. Guidelines for training, credentialing, and maintenance of competence for the performance of coronary angioplasty: a report from the Interventional Cardiology Committee and the Training Program Standards Committee of the Society for Cardiac Angiography and Interventions. Cathet Cardiovasc Diagn 1993;30:1–4.
20. Ritchie JL, Maynard C, Chapko MK, Every NR, Martin DC. Association between percutaneous transluminal coronary angioplasty volumes and outcomes in the Healthcare Cost and Utilization Project 1993–1994. Am J Cardiol 1999;83:493–497.
21. Hannan EL, Racz M, Ryan TJ, et al. Coronary angioplasty volume-outcome relationships for hospitals and cardiologists. JAMA 1997;277:892–898.
22. Jollis JG, Peterson ED, DeLong ER, et al. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. N Engl J Med 1994;331:1625–1629.
23. Kastrati A, Neumann FJ, Schomig A. Operator volume and outcome of patients undergoing coronary stent placement. J Am Coll Cardiol 1998;32:970–976.
24. Hannan EL, O'Donnell JF, Kilburn H, Jr, Bernard HR, Yazici A. Investigation of the relationship between volume and mortality for surgical procedures performed in New York State hospitals. JAMA 1989;262:503–510.
25. Peterson ED, DeLong ER, Jollis JG, Muhlbaier LH, Mark DB. The effects of New York's bypass surgery provider profiling on access to care and patient outcomes in the elderly. J Am Coll Cardiol 1998;32:993–999.
26. Canto JG, Every NR, Magid DJ, et al. The volume of primary angioplasty procedures and survival after acute myocardial infarction. N Engl J Med 2000;342:1573–1580.
27. Pepine CJ, Allen HD, Bashore TM, et al. ACC/AHA guidelines for cardiac catheterization and cardiac catheterization laboratories. American College of Cardiology/American Heart Association Ad Hoc Task Force on Cardiac Catheterization. Circulation 1991;84:2213–2247.

3 Primary Coronary Intervention for Acute Myocardial Infarction

Technical Approaches

David A. Cox, MD

CONTENTS

INTRODUCTION

For most operators, performing percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) presents a challenge that has the potential to greatly benefit patients at risk for significant mortality. Little doubt exists that primary as well as rescue PCI lower mortality and lessen morbidity compared to thrombolytic therapy *(1–4)*. In the past decade, according to the National

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

Registry for Myocardial Infarction (NRMI) database, the number of patients undergoing primary PCI for AMI has increased, and this has been accompanied by a concomitant increase in the use of rescue PCI for failed thrombolytic therapy *(5,6)*. Many interventionalists, however, find only limited opportunities to perform primary PCI for AMI in fellowship training and recognize that most of their skill in doing so comes from practical experience. The aim of this chapter is to provide some recommendations that will allow interventionalists to improve outcomes in patients with AMI and replicate in their clinical practices the improved mortality rates seen in recent clinical trials *(7–11)*.

EARLY TRIAGE IN THE EMERGENCY ROOM OR CARDIAC CARE UNIT

Success in performing PCI in AMI is a challenge quite different from that routinely encountered in performing elective procedures. Patients with AMI present in pain, have high catecholamine levels, and are often bordering on shock or deteriorating into congestive failure. Patients presenting in cardiogenic shock truly represent an emergency in which clinical stabilization and time-to-treatment critically affect outcome *(12,13)*.

Interventional cardiologists treating patients with AMI need to be skilled in critical care medicine. Properly assessing a critically ill patient can make a tangible difference if matters deteriorate later during an emergency PCI procedure. While the patient with an acute infarct needs to be taken to the catheterization laboratory with all due speed, the patient should always be briefly assessed regarding the onset of pain, presence of rales, murmurs suggesting a ventricular septal defect or papillary muscle dysfunction, and peripheral pulses for possible intra-aortic balloon pump (IABP) placement. Providing appropriate sedation, determining whether a true aspirin or clopidogrel allergy exists, and reviewing contraindications to platelet glycoprotein (GP) IIb/IIIa inhibitor therapy can all be done without delaying cardiac catheterization.

Hospitals performing PCI for AMI should have set protocols that rapidly triage patients with chest pain. Patients sustaining an AMI should be identified quickly and have medical therapy including aspirin, heparin, and β-blockers promptly initiated. Rapid transfer to the catheterization suite must be an immediate goal. Mobilization of catheterization personnel can be initiated as the interventionalist is called in or, if elective cases are ongoing, a catheterization suite must be opened urgently. Investigators in the Primary Angioplasty for Acute Myocardial Infarction with No Surgery On Site (PAMI-No SOS) trial demonstrated remarkably rapid door-to-balloon times, partly by abandoning intravenous nitroglycerin and heparin drips as sources of time delay *(14,15)*. Rather, a 50 U/kg bolus of heparin was given without a drip, with more heparin given in the laboratory after an activated clotting time (ACT) had been obtained

and once decisions had been made about the use of platelet GP IIb/IIIa inhibitors and the plan for revascularization.

Time does matter. Reducing time to treatment is particularly critical in decreasing mortality in the setting of cardiogenic shock, so these patients should be urgently mobilized to the catheterization suite, even if elective procedures are aborted or delayed. Patients in cardiogenic shock demand a level of urgency and immediate intervention that is too often lacking, even in major medical centers that treat trauma and gunshot wounds with appropriate haste.

In nonshock patients with AMI, time-to-treatment may be less critical, but inordinate delays should nonetheless not be tolerated no matter how seemingly stable a patient with a myocardial infarction appears *(16)*. In the Stent Primary Angioplasty in Myocardial Infarction (Stent PAMI) trial, time-to-treatment did not influence Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow rates or mortality: performing PCI 6–12 h into an AMI resulted in equivalent TIMI grade 3 flow and mortality rates compared with patients undergoing acute PCI fewer than 6 h into their event *(17)*. However, in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO)-IIb trial, time-to-treatment correlated with mortality in patients undergoing acute PCI *(18)*.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines previously suggested that institutions performing primary angioplasty strive for door-to-balloon times of 60–90 min. However, excellent results in nearly 3000 patients enrolled in the Stent PAMI and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trials were achieved with door-to-balloon times of 2 h in nonshock patients. Revised ACC/AHA guidelines now suggest a target door-to-balloon window of 60–120 min after presentation with an acute infarct *(19)*. Interventionalists should focus on their individual and institutional time-to-treatment and take corrective actions if door-to-balloon times are longer than 2 h.

Facilitating rapid transfer of a patient with an AMI to the catheterization laboratory during a busy day full of elective interventions can be difficult. In fact, lower volume catheterization laboratories often have quicker door-to-balloon times compared with higher-volume centers exactly for this reason. To improve door-to-balloon times, the catheterization laboratory coordinator should be charged with the responsibility of opening a catheterization suite even if elective cases are delayed or aborted. More than any other action, assignment of a coordinator to open a catheterization suite while the cardiologist rapidly assesses the patient will lead to improved door-to-balloon times.

ACUTE PCI: INITIAL CONCERNS IN THE CATHETERIZATION SUITE

On arrival, the patient with an AMI should again be rapidly assessed for hemodynamic compromise, the need for sedation, and rhythm disturbances. A fully

supplied cardiopulmonary resuscitation cart, temporary pacemaker with wires and cables, and an IABP should be readily available. "Fast" patches should always be placed for possible defibrillation. Respiratory status should be carefully evaluated for both the development of congestive heart failure and the effects of sedative drugs.

If there is a concern about respiratory compromise, a case can be made for early intubation before coronary intervention. The airway will then be protected against aspiration, and further sedation can be given without respiratory compromise. The patient who is uncooperative from respiratory distress during a critical moment of stent placement can be disastrous. Furthermore, as more patients with AMI receive platelet GP IIb/IIIa inhibitor therapy, the bleeding risk from traumatic emergency intubation needs to be carefully weighed against a more controlled elective approach before the intervention begins.

Both groins should be prepped in all patients in case intra-aortic balloon pump placement becomes urgently required. As door-to-balloon time is important, proceeding rapidly to diagnostic angiography is imperative. The initial pulse pressure is a critical early consideration: a blood pressure (BP) of 80/60 in an anterior myocardial infarction is an ominous sign, regardless of how stable the patient appears. Initial systolic blood pressure has been shown to be a powerful predictor of final ST-segment resolution and subsequent mortality *(20)*.

Routine IABP placement has not been shown to improve outcomes, even in high-risk patients *(21)*. However, Brodie and colleagues reported that early IABP placement before PCI may improve outcomes in selected patients *(22)*. Clearly, patients with hypotension unresponsive to fluids and in frank cardiogenic shock should undergo rapid IABP placement before intervention. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial, 86% of patients received IABP support *(13)*. The availability of flexible, low-profile 8 Fr IABP systems decreases many previous concerns about peripheral vascular insufficiency.

Right ventricular infarction should be clinically recognized and hypotension addressed with fluid resuscitation and vasoactive pressors. Rapid opening of a proximal right coronary artery (RCA) occlusion can result in remarkable improvement in mean BP but can also result in profound and sustained hypotension. If significant lesions coexist in the left coronary system, profound hypotension after successfully opening the proximal RCA can lead to shock from closure of a second stenosis in the left anterior descending or left circumflex distributions. Right ventricular infarction carries increased mortality risk; early hemodynamic improvement and urgent intervention are required *(23)*.

CORONARY ANGIOGRAPHY

Once these initial concerns have been assessed and addressed, diagnostic angiography should be accomplished quickly. If the infarct-related artery can be

determined by electrocardiographic criteria, angiography of the non–infarct-related artery should be performed first, followed by ventriculography. A guiding catheter can then be used to perform the initial angiograms of the infarct artery to further reduce the time to definitive therapy. Some operators delay the performance of left ventriculography until after the infarct vessel has been opened. However, early determination of the left ventricular end-diastolic pressure can help predict the development of pulmonary edema, and mechanical complications such as ventricular septal defect or a ruptured papillary muscle that should be surgically repaired will be identified. In the presence of surgical lesions, PCI is relatively contraindicated.

The choice of contrast agent remains controversial. The Stent PAMI and CADILLAC trials, as well as all previous PAMI trials, achieved excellent results using ionic contrast, and these investigators strongly believe the use of ionic contrast to be important *(24)*. However, the Contrast Media Utilization High Risk PTCA (COURT) trial presented data showing similar outcomes between ionic and non-ionic contrast in patients presenting with unstable angina and AMI *(25)*. Whether adjunctive platelet GP IIb/IIIa inhibition alleviates the concern about thrombogenicity with non-ionic contrast agents is undetermined.

Rapid diagnostic angiography is an important cornerstone of any PCI program. However, attempts should be made to limit the volume of contrast administered, particularly in elderly patients and those with compromised left ventricular function. Some interventions involving primary PCI for AMI go smoothly and rapidly; others require significant time and contrast. Keeping the volume of contrast to a minimum may help reduce the incidence of contrast-induced renal failure, particularly in elderly patients.

WIRING THE LESION

Approximately one third of patients presenting with AMI will have an open infarct-related artery with TIMI grade 2 or 3 flow before intervention; these patients have better outcomes than those with TIMI 0–1 flow on the initial angiogram *(26)*. Final TIMI flow after PCI, however, remains a critical predictor of mortality both at 30 d and at 1 yr. Regardless of the initial TIMI flow, interventional cardiologists must strive to achieve TIMI 3 flow on the final angiogram when performing acute PCI. Final TIMI 3 flow results in improved mortality both in stent and balloon angioplasty patients when compared to TIMI 2 or 0–1 flow on the final angiogram *(27)*.

Successful PCI of an occluded infarct artery first requires successful wiring of the lesion. As opposed to the elective situation where the distal vessel can be visualized, the pathway to the distal lumen cannot typically be seen. Heightening the intellectual pressure on the cardiologist are such issues as dealing with a critically ill patient and knowing that failure to successfully open the lesion results in increased mortality. This environment can thus be a daunting challenge

for less experienced operators who may be striving to increase their AMI experience. Fortunately, most lesions are fairly soft and, with careful attention to detail, can be crossed with a guidewire.

Adequate guide catheter support is also key. Coaxial alignment of the guide catheter will facilitate the tactile sensation of crossing the lesion. Whether to use an over-the-wire balloon preloaded with a wire or to bare-wire the lesion is largely a matter of choice and experience. If difficulties are encountered with the bare-wire technique, particularly in tortuous vessels leading to limited control of the distal wire tip, an early switch to an over-the-wire balloon or a distal end-hole infusion catheter may aid crossing of the lesion. The most common reason for failure to cross with a guidewire is entry of the wire into a false channel. This typically occurs in a tortuous or distal vessel where wire tip control is not ideal. This can be compounded if the operator rushes to open the vessel, rather than carefully probing the occlusion and changing wires if necessary. Once a false lumen is entered, accessing the true lumen becomes quite difficult; the patient frequently is left with a closed vessel and TIMI 0–1 flow.

The choice of guidewire is a matter of personal preference. Some operators prefer to start with a floppy wire, while others begin with an intermediate-stiffness wire. While a standard wire may eventually be necessary to cross a stenosis, persistence with a series of more flexible wires may be safer, particularly for less experienced operators. Occasionally, a 0.016 wire will cross when a 0.014 wire will not. Avoiding a wire perforation at the lesion site or in the distal vessel, particularly if platelet GP IIb/IIIa inhibitors are given, is mandatory, and the decision to move to a stiffer wire should be cautiously entertained. Hydrophilic guidewires also increase the chances for distal vessel perforation.

Once the stenosis is successfully crossed, a firm working knowledge of coronary anatomy and the variants thereof is required. Inflating a 3.0-mm balloon over a wire lodged in a 2.0-mm branch vessel can be disastrous. If a question exists about the coronary anatomy distal to the lesion or about the location of the wire in the distal lumen, an over-the-wire balloon or end-hole infusion catheter should be advanced through the lesion, the wire withdrawn, and contrast gently injected to document that the distal true lumen has been properly accessed.

Often, crossing the lesion with the wire itself will reestablish partial flow. Particularly in right coronary artery infarcts and in left anterior descending infarcts with a narrow pulse pressure, transient arrhythmias or profound hypotension may occur and should be anticipated. Hypotension and arrhythmias should be promptly treated and allowed to resolve if possible before balloon or stent placement.

PERFORMING PRIMARY CORONARY INTERVENTION

With the wire appropriately placed into the distal true lumen, balloon angioplasty and/or stent placement can be performed. If the distal vessel is not

visualized and only TIMI 0–1 flow exists, most operators will proceed with balloon angioplasty to rapidly reestablish flow and define the distal anatomy. A definitive balloon inflation is not the goal here, as oversizing to the distal vessel should be avoided to prevent distal dissection. Marked generalized vasoconstriction usually accompanies AMI; administration of intracoronary nitroglycerin or nitroprusside after reestablishing flow often results in a marked increase in vessel size.

Once flow is reestablished, careful attention should be given to the ACT. Occasionally, in the emergency setting of the patient with an AMI, heparin doses are either misunderstood or not delivered. Intervention on a clot-laden vessel demands that appropriate anticoagulant and antiplatelet drugs be given to the patient. If the operator chooses to not give a platelet GP IIb/IIIa inhibitor, appropriate heparin doses should be given to achieve an ACT in the 300-s range. In patients receiving a GP IIb/IIIa inhibitor, heparin dosing should be adjusted downward to achieve an ACT in the 200–250-s range. An ACT higher than this in AMI patients receiving these potent inhibitors can lead to substantial bleeding complications, as will "bailout" GP IIb/IIIa inhibitor use when the ACT is already greater than 300 s.

Whether to proceed with further definitive balloon inflation or to place a stent once flow is reestablished is an ongoing debate. In Stent PAMI, patients assigned to the balloon angioplasty arm had a greater incidence of restenosis, target-vessel revascularization, and angina at 6 mo than patients randomized to stent implantation *(7)*. However, at 12 mo, patients randomized to stenting had an increased mortality compared to the balloon angioplasty patients, raising the issue of whether the bulky stent delivery system or the use of platelet GP IIb/IIIa antagonists in only 5.8% of patients contributed to worsened outcomes with stent implantation *(28)*.

In the CADILLAC trial, a study in which later generation, lower profile stents were used, stent patients with or without adjunctive abciximab had less restenosis than balloon angioplasty patients, with no differences in death or reinfarction between stent and balloon angioplasty patients. Stenting with abciximab had no long-term mortality or target-vessel revascularization benefits over stenting alone. Balloon angioplasty patients who received abciximab had less in-hospital ischemia than those not receiving abciximab, and abciximab significantly reduced subacute thrombosis in stent patients. Thus, contemporary low-profile stents do not result in increased mortality and adjunctive abciximab may provide early benefits.

Integrating these data together with the smaller Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-up (ADMIRAL) and Intracoronary Stenting and Antithrombotic Regimen (ISAR)-2 trials, most operators in clinical practice proceed with stent placement for patients with AMI. Balloon angioplasty with adjunctive abciximab

can also be justified, particularly in patients with tortuous anatomy in whom delivering even a newer generation stent may be a challenge requiring increased contrast load and greater ischemic time. Bailout treatment with platelet GP IIb/IIIa inhibitors should be avoided as the addition of abciximab when an ACT already exceeds 300 s increases the risk of major bleeding complications; the decision to use these drugs should be made before the intervention.

In patients with noncompliant, calcified vessels with ostial disease, a scenario frequently encountered in the elderly, attempts to force a stent into the coronary can induce dissection. Increased ischemia, sustained hypotension, and markedly larger contrast loads can all combine to result in poor outcomes in this subgroup. Both Stent PAMI and CADILLAC demonstrated excellent outcomes for balloon angioplasty patients with respect to death and reinfarction, with essentially equivalent acute results compared with stenting *(7,8)*. Thus, it may be acceptable to deal with restenosis at a later date under more elective conditions in selected patients who are elderly or have tortuous vessels.

If balloon angioplasty alone is chosen as the preferred technique, every attempt should be made to achieve an optimal result (absence of dissection, residual stenosis $<20\%$, TIMI 3 flow). Longer inflation times with appropriately sized balloons usually gives acceptable angiographic results. An optimal balloon angioplasty result in Stent PAMI was achieved in 50% of patients in the balloon arm; no differences were noted in death or reinfarction at 6 mo compared with stent patients *(7)*. However, even optimal balloon angioplasty patients had increased rates of restenosis and target vessel revascularization at 6 mo compared with stent patients *(29)*. Similarly, balloon angioplasty patients assigned to abciximab in the CADILLAC trial had increased rates of restenosis and target-vessel revascularization compared with stent patients but fewer major adverse cardiac events than the balloon without abciximab arm *(8)*.

With newer generation devices, stent placement in most acute infarct lesions is technically straightforward. The focus should be on treating the acutely ruptured plaque, not the entire infarct vessel. Unless a stenosis proximal or distal to the target lesion appears to be flow-limiting, the target lesion alone should be addressed.

Contemporary stent designs offer the advantage of deployment in the 12–16-atmosphere range with little risk of distal dissection from overhanging balloon edges. Thus, a quick predilatation to reestablish flow and allow lesion length to be assessed leads to rapid stent deployment, with post-dilatation reserved for less than optimal results.

Some enthusiasm for direct stenting in AMI exists, even in patients with occluded vessels where the distal anatomy cannot be assessed after wire placement. By protocol, stent patients in the Stent PAMI and CADILLAC trials underwent predilatation before device placement; on the other hand, direct stenting was permitted in the ISAR-2 and ADMIRAL trials. Particularly in

patients where the lesion length can be visualized, this approach might potentially reduce distal embolization and the no-reflow phenomenon by trapping more of the thrombotic debris during stent deployment. Direct stenting also results in lower volumes of contrast, an important consideration in elderly patients. Direct stenting, although technically feasible, remains to be rigorously evaluated in large clinical trials.

Whether balloon angioplasty or stent placement is chosen as the primary reperfusion technique, the goal remains the attainment of TIMI 3 flow. More than any other variable, final TIMI 3 flow after acute PCI predicts improved mortality, even when compared with patients with TIMI 2 flow. Of the nearly 3000 patients enrolled in Stent PAMI and CADILLAC, >90% of patients with AMI achieved TIMI 3 flow. These results were not limited to a select group of "expert interventionalists." In Stent PAMI, 42 of the 62 enrolling sites had no previous PAMI trial experience. When compared with sites that had previous PAMI trial experience, no differences were noted with respect to death, procedural success, or achievement of TIMI 3 flow *(30)*.

Recently, a newer concept has been reported focusing on the microcirculation as manifested by myocardial blush scores *(31)*. While TIMI 3 flow predicts mortality, final TIMI flow rates focus only on epicardial blood flow. Myocardial blush scores attempt to quantify improvements in microvascular reperfusion and can further risk stratify even in patients with TIMI 3 epicardial coronary blood flow. In 163 patients undergoing PCI within 24 h of an AMI, patients with TIMI 3 flow after acute intervention but only a grade 0–1 myocardial blush score had increased early and late mortality compared with those with both TIMI 3 flow and grade 3 blush scores *(32)*.

Early ST resolution is another important marker of improvement in microvascular reperfusion *(33)*. Patients with successful acute PCI who do not have >50% resolution of their initial EKG have markedly increased 1-yr mortality *(20)*. Thus, interventionalists who until recently accepted an "open and flowing" artery should pay increased attention to final TIMI 3 flow, myocardial blush score, and ST-segment resolution. A final TIMI 2 flow with poor blush scores and persistent ST elevation after intervention results in worse short- and long-term outcomes.

IABP COUNTERPULSATION, PERCUTANEOUS CARDIOPULMONARY BYPASS, AND LEFT VENTRICULAR ASSIST DEVICES

Although the PAMI investigators found little support for routine IABP placement even in high-risk patients, Brodie reported that early balloon pump support before PCI begins improves outcomes in selected patients *(22)*. Recent findings underscore the importance of initial blood pressure as a predictor of myocardial

blush score and ST-segment resolution *(20)*. Early use of balloon pump support has been made easier with the advent of low-profile 8 Fr systems. Particularly in anterior infarctions of the left anterior descending artery, which carry the highest immediate and long-term mortality, borderline hypotension is best treated with balloon pump support before the intervention.

In patients with cardiogenic shock, IABP counterpulsation should be promptly instituted before any intervention. While percutaneous cardiopulmonary bypass is an option in selected labs, most interventionalists are unlikely to have a perfusionist available 24 h per day. In most cases, balloon pump support should provide enough hemodynamic improvement to complete the intervention.

If significant hemodynamic improvement has not occurred after acute intervention with balloon pump support, some consideration should be given to using a left ventricular assist device. Most cardiac surgeons are willing to implant these devices in appropriate patients, given the forbidding mortality rates associated with emergency coronary bypass surgery for cardiogenic shock. In the revascularization arm of the SHOCK trial, 3.6% of patients received a left ventricular assist device with 86% undergoing IABP placement *(13)*. In young, viable patients who have a successful PCI but remain in shock with minimal improvement despite balloon pump support, 24–96 h of left ventricular assist device support can be lifesaving. In laboratories facile with percutaneous cardiopulmonary bypass, this modality can be used rather than an initial balloon pump with left ventricular assist device approach, but most catheterization suites are not prepared to deliver cardiopulmonary bypass support in a timely fashion. Importantly, definitive intervention should not be delayed while awaiting the arrival of a perfusionist.

MULTILESION PCI DURING PRIMARY ANGIOPLASTY

For most interventional cardiologists performing emergency primary PCI during AMI, addressing the infarct lesion already presents a substantial challenge. Patients with multivessel disease without shock are best left to recover from the initial platelet activation and hemodynamic insult once the infarct-related artery is successfully treated. Still, given the availability of platelet GP IIb/IIIa inhibitor therapy and the ease and confidence that stent placement brings to the treatment of most lesions, some operators have made a case for complete revascularization of all significant stenoses during acute intervention.

Multilesion PCI in addition to primary PCI of an infarct vessel has not been systematically studied. The superb results noted by the PAMI-No SOS investigators were achieved with intervention on the infarct-related artery only, as were the results reported in Stent PAMI and CADILLAC where multivessel intervention was prohibited by protocol. Common sense and clinical judgment should prevail, as subjecting an already compromised patient with an infarct to contin-

ued contrast exposure and ischemia may not be ideal. Even the simplest lesion can have an unpredictable outcome; a new territory of wall motion dysfunction is obviously not a desirable outcome in a patient already sustaining an AMI.

In patients in shock who manifest decreased left ventricular dysfunction in non–infarct-related arteries (or in whom the infarct involves two different epicardial arteries with reduced TIMI flow in both), a case can be made for rapid revascularization of both vessels with balloon pump support. In patients with cardiogenic shock who have multivessel disease but normal left ventricular function in segments fed by a non–infarct-related artery, little is to be gained by intervening upon non–infarct-related vessels; potentially disastrous results may result if complications arise related to treatment of the non-infarct vessel.

ARRHYTHMIC COMPLICATIONS

For most interventionalists, a working knowledge of cardiac arrhythmias rapidly becomes second nature when performing primary angioplasty. Appropriate treatment of bradyarrhythmias with atropine or temporary pacing is obvious. Particularly in infarction secondary to occlusion of a dominant right coronary artery (or dominant left circumflex), maintenance of atrioventricular synchrony by either the judicious use of atropine or atrial or atrioventricular sequential pacing can usually resolve hypotension. In this situation, a "stable" infarct patient will suddenly become hypotensive, develop increasing chest pain, and exhibit atrioventricular block or ventricular dysrhythmias with initial reperfusion with the guidewire passage or balloon dilation.

Ventricular arrhythmias are common and defibrillation pads should routinely be placed on infarct patients. Hemodynamic compromise resulting from an untoward delay in defibrillation can turn a relatively stable situation into full-blown shock. Attention to early recognition and prompt defibrillation of ventricular tachycardia and ventricular fibrillation cannot be overemphasized, particularly in catheterization laboratories just initiating a primary angioplasty program.

Recognizing and differentiating accelerated idioventricular rhythms, true ventricular tachycardia, and atrial fibrillation with aberrancy can be a challenge. Whenever hemodynamic compromise occurs, rapid countershock should be done to improve coronary and systemic perfusion pressures. Ventricular tachycardia can occur suddenly in a stable infarct patient simply with wire passage, initial balloon inflation, or during left ventriculography and should always be anticipated. Treatment with intravenous amiodarone, β-blockers, or lidocaine should be instituted rapidly. Given the likelihood of automaticity as the cause of ventricular tachycardia, amiodarone should either be used as a first-line drug or rapidly started if lidocaine is ineffective.

MECHANICAL COMPLICATIONS OF INFARCTION AND CARDIAC CATHETERIZATION

Recognizing mechanical complications can be difficult. Mechanical complications such as ventricular septal defect or papillary muscle rupture should be rapidly diagnosed with either left ventriculography or a prompt transthoracic or transesophageal echocardiogram. These complications should be suspected when a patient appears sicker than the coronary anatomy would predict. Rapid diagnosis is necessary as the treatment is often surgical.

An acquired ventricular septal defect should be vigorously searched for, particularly in elderly patients. A cranial left anterior oblique ventriculogram is critical. Often, the clinical presentation of AMI is confusing, as some patients have precedent infarcts 24–48 h before presentation, develop a ventricular septal defect, and then present to the emergency room. A loud holosystolic murmur should raise suspicion but can be missed relatively easily. Because the treatment of ventricular septal defect is surgical rather than interventional, a case can be made for proceeding with left ventriculography before coronary intervention to rule out this complication.

Papillary muscle dysfunction with chordal rupture is most easily diagnosed by echocardiography; again the treatment is surgical repair rather than coronary intervention. Papillary muscle dysfunction without chordal rupture is best managed by completing the coronary intervention and medically treating mitral regurgitation with afterload reduction. Often, marked and rapid resolution of ischemic mitral regurgitation will occur after coronary flow is reestablished. Particularly with large circumflex infarcts or infarcts involving the distal right coronary artery, a high suspicion for ischemic mitral regurgitation should be maintained. These patients can rapidly develop severe pulmonary edema with the added insult of contrast injections.

Pericardial tamponade is unlikely to exist in patients presenting within 12 h after the onset of infarction, but a hemorrhagic pericardial effusion can occur after heparin anticoagulation in patients who present late. Thrombolytic therapy also is associated with the possibility of hemorrhagic pericardial effusion and this concern should be considered whenever dealing with a hypotensive patient after rescue PCI. A quick echocardiogram and pericardiocentesis can be lifesaving.

Careful attention to distal placement of the guidewire is critical and care should be given to keeping the wire in the main arterial channel. Distal wire perforation, particularly in the setting of treatment with platelet GP IIb/IIIa inhibitor therapy, may not always be apparent on the final angiogram where the focus is on the infarct lesion. For this reason, pericardial tamponade should be ruled out in any patient with an infarct who is hypotensive 2–6 h after an intervention.

Hypotension early after PCI should also raise the question of retroperitoneal hemorrhage. Meticulous arterial access is even more important in primary angioplasty during acute myocardial infarction, and decreased arterial pulses from hypotension secondary to an acute infarction increase the potential for back wall puncture. Whether to use a groin closure device in infarct patients is a matter of choice, but careful attention to groin bleeding is critical in the first 12 h after intervention. In an already compromised patient, increasing the workload upon a damaged ventricle because of groin bleeding and hypotension is not an optimal situation and should be promptly treated. The diagnosis can be made in minutes with ultrafast computed tomography without giving further contrast.

THROMBOTIC COMPLICATIONS AT THE INFARCT TREATMENT SITE

Once flow has been reestablished, abrupt vessel closure occurs only rarely. Contemporary techniques of primary angioplasty and stenting carry little risk of vessel closure—the best treatment for clot is improved blood flow. All patients should receive aspirin before the acute intervention, appropriate activated clotting times should be achieved during the intervention, and strong consideration should be given to using platelet GP IIb/IIIa inhibitors.

The risk of subacute thrombosis is low. In Stent PAMI, where abciximab was used in only 5% of patients, rates of subacute thrombosis in the balloon angioplasty and the stent arms were 0.9% and 1%, respectively. In CADILLAC, all 524 stent patients randomized to abciximab were completely free of subacute thrombosis at 1 mo, compared with 5/512 or 1% of stent patients randomized to heparin only ($p = 0.03$).

Combining balloon and stent patients in this trial, subacute thrombosis was significantly reduced with abciximab (1.4% vs 0.3%, $p < 0.001$). While no differences in reinfarction were noted, there is a clear advantage to using abciximab to avoid subacute thrombosis in patients with an infarction.

Distal embolization occurs frequently with attaining reperfusion, and probably occurs to some extent in all patients. Large macroemboli in the distal coronary bed are easily managed with a low-pressure balloon inflation with an appropriately sized device. This approach does not seem to entail a higher restenosis risk at the site of distal embolization and is often required to achieve TIMI 3 flow and higher myocardial blush scores. Sometimes, even the stent delivery balloon can rapidly resolve a distal embolus if it is pushed uninflated to the distal clot after stent deployment.

No-reflow represents more of a challenge, as the microscopic capillary beds are the culprit and are not amenable to further mechanical interventions. Minimizing manipulation of the infarct vessel may help avoid no-reflow, as well as using the same "light touch" techniques seen with saphenous vein graft stenting.

In Stent PAMI, where high-pressure post-dilatation of the stent was required, degradation of final flow to TIMI 0–1 or 2 occurred in only 2.7% of 343 patients who had TIMI 3 flow before stent placement *(34)*.

Successfully treating no-reflow entails rapid recognition and action *(35)*. In general, little is to be gained by using intracoronary nitroglycerin, as this agent has no effect on the distal capillary bed. Treatment with intracoronary calcium channel blockers, adenosine, or nitroprusside with drug delivered directly to the distal epicardial artery beyond the target lesion with an end-hole infusion catheter or through the lumen of an over-the-wire balloon will often immediately resolve the problem. Large doses should be given as long as blood pressure is maintained. Careful maintenance of adequate blood pressure with fluids and/or pressors should be anticipated when using these agents. No-reflow is unlikely to resolve if sustained hypotension is induced by its treatment. In refractory cases of no-reflow and in any case where a large coronary bed has less than TIMI 3 flow, placement of an IABP should be considered.

Managing no-reflow is a critical hurdle for interventionalists performing PCI for acute infarction. Clinical studies likely underreport the incidence of transient no-reflow. Sustained no-reflow may have an important influence on clinical course and long-term mortality, as these patients are less likely to have TIMI 3 flow or normal blush scores. Elevation of ST-segments immediately after the intervention likely reflects impaired microvascular perfusion and, particularly when resolution does not occur on serial electrocardiograms, these patients have a higher mortality.

The continuous electrocardiographic monitoring system used in the cardiac catheterization suite is an underutilized tool. If acute ST elevation on the catheterization laboratory monitor resolves and then recurs after stent deployment or subsequent balloon inflations, further manipulation of the infarct vessel should be done with caution if at all, particularly if transient no-reflow occurred. Managing restenosis electively can be safely performed later, while worsening a no-reflow situation or creating sustained and dramatic ST elevation by further intervention may result in poorer clinical outcomes.

ALTERNATIVE DEVICES

Recent clinical trials of PCI in AMI demonstrate 30-d mortality rates with both angioplasty and stenting of 3%–4% with TIMI 3 flow obtained in >90% of patients and little risk of stroke. Stent PAMI demonstrated a low ischemic target-vessel revascularization rate at 6 mo in the stent arm of 7.7%. With aggressive post-dilatation strategies and treatment of longer lesions, the CADILLAC trial reported 6-mo ischemic target-vessel revascularization rates of only 6.2% in stent patients.

However, significant subsets exist where improved outcomes have not been noted. Infarction of the proximal left anterior descending represents one such subset. In Stent PAMI, patients with infarction involving this vessel had a 6-mo mortality of 8.2%, vs 2.2 % for all others *(36,37)*. Elderly patients, women, and patients with cardiogenic shock also have worse outcomes when undergoing acute PCI.

Because TIMI 3 flow and blush scores have such an important influence on outcomes, some patients may benefit from adjunctive devices that remove thrombus before intervention or provide distal protection to the capillary bed. The POSSIS AngioJet can remove clot in patients with AMI, but is limited by the bulky size of the device and the lack of any data showing improved outcomes *(38)*. The EndiCOR X-SIZER is a novel thrombectomy device that is presently undergoing clinical trials. Improvement in myocardial blush scores has been seen in patients with TIMI 3 flow after stenting for AMI compared with historical controls *(39)*. Randomized AMI trials in both Europe and the United States are anticipated.

The PercuSurge Guardwire uses a distal occlusion balloon to trap embolic debris, which can then be aspirated. The system has been shown to decrease the incidence of no-reflow during elective intervention in saphenous vein grafts. Particularly in vessels that are already occluded, this device may prove useful in removing embolic debris and lessening the occurrence of no-reflow in AMI patients. A randomized clinical txrial using this device in AMI patients will begin shortly.

Finally, filter devices offer the potential for capturing embolic debris while allowing blood flow to the distal coronary bed. Most distal protection devices are currently limited by a large profile and difficulties with delivery. Defining the subsets of patients with AMI who may benefit from thrombectomy or distal protection devices will be an important task.

CONCLUSION

Clinical trials reported in the last 3 yr have defined the benefits of stenting for primary PCI and clarified the role of platelet GP IIb/IIIa blockade, particularly with abciximab. Unanswered questions remain about the role of small molecule GP IIb/IIIa inhibitors in primary PCI; "upstream" combination therapy before primary PCI; defining the role of IABP placement in improving outcomes in the setting of a final TIMI 2 flow or TIMI 3 flow with low myocardial blush scores; avoiding and treating no-reflow; clarifying the role of thrombectomy and distal protection devices; and improving myocardial salvage. All of these issues demand the best technical expertise of the interventional cardiologist performing PCI for AMI. Improvement in patient outcomes begins with the technical skills needed to attain final TIMI 3 flow, ST-segment resolution, and optimal myocardial blush scores in patients sustaining an AMI.

REFERENCES

1. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–679.
2. Zijlstra F, de Boer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328: 680–684.
3. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. N Engl J Med 2000;343:385–391.
4. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–2098.
5. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2, and 3. J Am Coll Cardiol 2000;36:2056–2063.
6. Ross AM, Lundergan CF, Rohrbeck SC, et al. Rescue angioplasty after failed thrombolysis: technical and clinical outcomes in a large thrombolysis trial. J Am Coll Cardiol 1998;31:1511–1517.
7. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:949–956.
8. Stone GW, Grines CL, Cox DA, et al. A prospective, randomized trial comparing balloon angioplasty with or without abciximab to primary stenting with or without abciximab in acute myocardial infarction—primary endpoint analysis from the CADILLAC trial. Circulation 2000;102(Suppl II):II-664 (abstract).
9. Montalescot G, Barragon P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–1903.
10. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa blockade on recovery of coronary flow and left ventricular function after placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.
11. Suryapranata H, van't Hof AW, Hoorntje JC, et al. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502–2505.
12. Brodie BR, Stuckey TD, Muncy DB, et al. Importance of time to reperfusion in patients with acute myocardial infarction with and without cardiogenic shock treated with primary angioplasty. Circulation 2000;102 (Suppl II):II-386 (abstract).
13. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999;342:625–634.
14. Wharton TP, McNamara NS, Fedele FA, et al. Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. J Am Coll Cardiol 1999;33:1257–1265.
15. Wharton TP, Johnston JD, Turco MA, et al. Primary angioplasty for acute myocardial infarction with no surgery on site: outcomes, core angiographic analysis, and six-month follow-up in the 500 patient prospective PAMI-No S.O.S Registry. J Am Coll Cardiol 1999;33:352–3A.
16. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–2947.
17. Brodie BR, Stone GW, Morice MC, et al. Importance of time to reperfusion on outcomes after primary PTCA for acute myocardial infarction: results from Stent PAMI. J Am Coll Cardiol 1999;33:353A (abstract).

18. Berger PB, Ellis SG, Holmes DR et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcomes in patients with acute myocardial infarction: results from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) Trial. Circulation 1999;100:14–23.
19. Smith SC, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary interventions. J Am Coll Cardiol 2001;37:2238ii.
20. Claeys MJ, Bosmans J, Veenstra L, et al. Determinants and prognostic implications of persistent ST-segment elevation after primary angioplasty for acute myocardial infarction. Circulation 1999;99:1972–1977.
21. Stone GW, Marsalese D, Brodie BR, et al. A prospective, randomized evaluation of prophylactic intraaortic balloon counterpulsation in high risk patients with acute myocardial infarction treated with primary angioplasty. J Am Coll Cardiol 1997;29:1459–1467.
22. Brodie BR, Stuckey TD, Hansen C, et al. Intra-aortic balloon counterpulsation before primary percutaneous transluminal coronary angioplasty reduces catheterization laboratory events in high-risk patients with acute myocardial infarction. Am J Cardiol 1999; 84:18–23.
23. Mehta SR, Eikelboom JW, Natarajan MK, et al. Impact of right ventricular involvement on mortality and morbidity in patients with inferior myocardial infarction. J Am Coll Cardiol 2001;37:37–43.
24. Grines CL, Stone GW, O'Neill WW. Establishing a program and performance of primary PTCA-the PAMI way. J Invas Cardiol 1997;9:44B–52B.
25. Davidson CJ, Laskey WK, Hermiller JB, et al. Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. Circulation 2000;101:2172–2177.
26. Stone GW, Cox DA, Garcia E, et al. TIMI-3 flow prior to mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction. Circulation 2001;104, 636–641.
27. Lefevre T, Morice MC,Garcia E, et al. Predictive factors of suboptimal flow after primary percutaneous transluminal angioplasty in acute myocardial infarction: results from the Stent PAMI randomized study. Circulation 1998;98 (Suppl I):I-151 (abstract).
28. Grines CL, Cox DA, Stone GW, et al. Stent PAMI: 12 month results and predictors of mortality. J Am Coll Cardiol 2000;35:402A (abstract).
29. Cox DA, Stone GW, Niess GS, et al. Does "stent-like" primary PTCA in acute myocardial infarction confer long-term freedom from restenosis similar to primary stenting? Analysis from the PAMI Stent Randomized Trial. J Am Coll Cardiol 1999;33:382A (abstract).
30. Cox DA, Stone GW, Brodie BR, et al. Stent PAMI: are excellent outcomes achieved only by experienced sites? J Am Coll Cardiol 2000;35:363A (abstract).
31. van't Hof AW, Liem A, Suryapranata H, et al. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Circulation 1998;97:2302–2306.
32. Stone GW, Peterson MA, Lansky AJ, et al. Impact of normalized myocardial perfusion in high risk patients with TIMI-3 flow after angioplasty in acute myocardial infarction. J Am Coll Cardiol 2002;39:591–597.
33. van't Hof AW, Liem A, de Boer MJ, et al. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997;350:615–619.
34. Stone GW, Garcia E, Maranon G, et al. Does stent implantation in acute myocardial infarction degrade TIMI flow and result in early higher mortality than PTCA? The PAMI Stent randomized trial. Circulation 1998;98 (Suppl I):I-151 (abstract).
35. Assali AR, Sdringola S, Ghani M, et al. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no-reflow" phenomenon. Catheter Cardiovasc Interv 2000;51:27–31.
36. Cox DA, Stone GW, Grines CL, et al. Do proximal LAD lesions in acute myocardial infarction benefit from stenting? The PAMI Stent Randomized Trial. J Am Coll Cardiol 1999;33:353A (abstract).

37. Garcia E, Elizaga J, Perez-Castellano N, et al. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. J Am Coll Cardiol 1999;33:605–611.
38. Ramee SR, Baim DS, Popma JJ, et al. A randomized, prospective, multi-center study comparing intracoronary urokinase to rheolytic thrombectomy with the POSSIS Angiojet catheter for intracoronary thrombus: final results of the VeGAS 2 trial. Circulation 1998;98(Suppl I): I-86 (abstract).
39. Cox DA, Stuckey TD, Low RI, et al. Adjunctive thrombectomy combined with stenting for AMI: the EndiCOR X-SIZER AMI Registry. J Am Coll Cardiol 2001;37:306A (abstract).

4 Primary Angioplasty (POBA) vs Thrombolysis

The Early 1990s Experience

Bruce R. Brodie, MD

CONTENTS

The reperfusion era for acute myocardial infarction (AMI) began when Rentrop and colleagues demonstrated in 1979 that an acutely occluded coronary artery could be successfully recanalized with the combination of *mechanical intervention* with a guidewire and *pharmacologic intervention* with the infusion of intracoronary streptokinase *(1)*. Multiple clinical trials subsequently demonstrated the effectiveness and survival benefit of intravenous streptokinase, and thrombolytic therapy became the standard of care as reperfusion therapy for AMI in the late 1980s and 1990s *(2–4)*. During the same time period, Hartzler and others demonstrated that mechanical reperfusion with primary angioplasty was also a highly effective strategy *(5–7)*. While it was clear that primary angioplasty had certain advantages over thrombolytic therapy in achieving greater patency rates and avoiding the life-threatening complication of intracranial hemorrhage, primary angioplasty did not become a competitive reperfusion strategy until the early 1990s with the publication of the Primary Angioplasty in Myocardial Infarction (PAMI) and Zwolle trials *(8,9)*. The 1990s have produced a number of randomized trials that provide meaningful comparisons between primary

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

angioplasty (performed in the pre-stent era with plain old balloon angioplasty [POBA]) and first- and second-generation thrombolytic therapy (streptokinase, tissue plasminogen activator [t-PA], and accelerated t-PA).

COMPARISON OF CLINICAL OUTCOMES IN RANDOMIZED TRIALS

The Early Randomized Trials

The first randomized trial comparing primary angioplasty with thrombolytic therapy was published by O'Neill and colleagues in 1986 *(10)*. These investigators randomized 56 patients with AMI to intracoronary streptokinase vs primary angioplasty and found that primary angioplasty was more effective in reducing residual stenosis and resulted in better preservation of left ventricular function.

In 1993, Grines and colleagues and Zijlstra and colleagues published the results of the PAMI and Zwolle trials, which were the first randomized trials large enough to evaluate clinical outcomes *(8,9)*. The PAMI trial randomized 395 patients with AMI to primary angioplasty or t-PA (nonaccelerated dosing) and found a significant reduction in the combined endpoint of death and reinfarction (5.1% vs 12.0%, $p = 0.02$) and a significant reduction in intracranial hemorrhage (0% vs 2.0%, $p = 0.05$) for the primary angioplasty arm compared with t-PA *(8)*. The Zwolle group randomized 142 patients with AMI to primary angioplasty or intravenous streptokinase and found that primary angioplasty was associated with a lower mortality (0% vs 5.6%, $p = 0.13$) and less reinfarction (0% vs 12.5%, $p = 0.003$) *(9)*.

The largest randomized trial comparing these two reperfusion strategies was the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO) IIb trial, which randomized 1138 patients with AMI to primary angioplasty vs accelerated t-PA *(11)*. The GUSTO investigators found that primary angioplasty was associated with a lower incidence of the primary endpoint of death, reinfarction, or disabling stroke at 30 d (9.6% vs 13.7%, $p = 0.03$) and a lower incidence of intracranial hemorrhage (0% vs 1.4%, $p = 0.008$). Although the results of GUSTO IIb were significant in favor of primary angioplasty, they were not as impressive as the results of the PAMI and Zwolle trials. This did not appear to be related to better outcomes in the thrombolytic arm of the GUSTO IIb trial with the use of accelerated t-PA compared with the less effective lytic strategies of nonaccelerated t-PA and streptokinase used in the PAMI and Zwolle trials. Rather, the difference appeared to be due to poorer outcomes in the percutaneous transluminal coronary angioplasty (PTCA) arm of GUSTO IIb compared with the PTCA arms of the PAMI and Zwolle trials *(12)*. In patients randomized to PTCA in GUSTO IIb, PTCA was actually performed in only 81% of patients and Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow was achieved in only 73% of these patients *(11)*. In contrast, in the PAMI

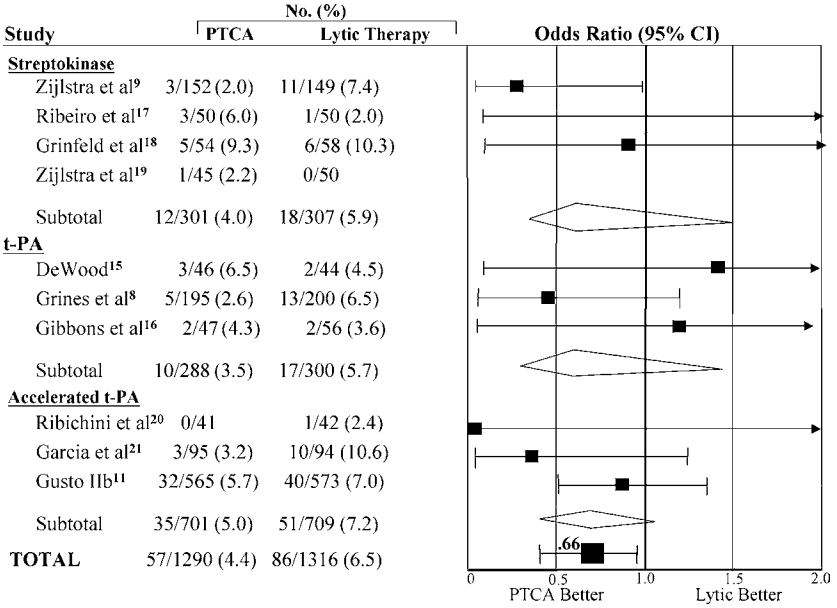


Fig. 1. Summary of mortality outcomes from 10 randomized trials comparing primary angioplasty with intravenous thrombolytic therapy. (Adapted from Weaver et al. *[14]* with permission.)

and Zwolle trials, PTCA was performed in 90%–93% of patients with TIMI 3 flow achieved in >90% of patients *(13)*.

Meta-Analysis of Randomized Trials

In 1997, Weaver and colleagues *(14)* published a meta-analysis of these *(8,9,11)* and other smaller randomized trials *(15–21)* that included a total of 2606 patients where intravenous thrombolytic therapy was compared to primary angioplasty (Fig. 1). In this meta-analysis, primary angioplasty was associated with a lower in-hospital mortality rate, a lower incidence of nonfatal reinfarction, and a lower incidence of death or nonfatal reinfarction (Fig. 2). Primary angioplasty was also associated with a significantly lower incidence of stroke (0.7% vs 2.0%, $p = 0.007$) and hemorrhagic stroke (0.01% vs 1.1%, $p = 0.0005$). The survival benefit of primary angioplasty compared to thrombolytic therapy reported in this meta-analysis was substantial (21 lives saved per 1000 patients treated) and compared favorably to the survival benefit of thrombolytic therapy compared with placebo from nine randomized trials reported by the Fibrinolytic Therapy Trialists' (FTT) Collaborative Group (19 lives saved per 1000 patients treated) (Fig. 3) *(4)*.

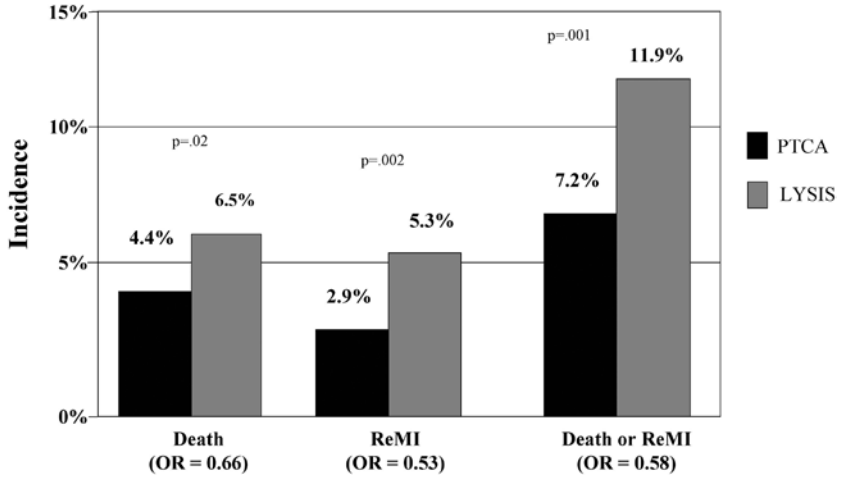


Fig. 2. Comparisons of the incidence of death, reinfarction (reMI) and death or reinfarction from ten randomized trials comparing primary angioplasty with intravenous thrombolytic therapy.

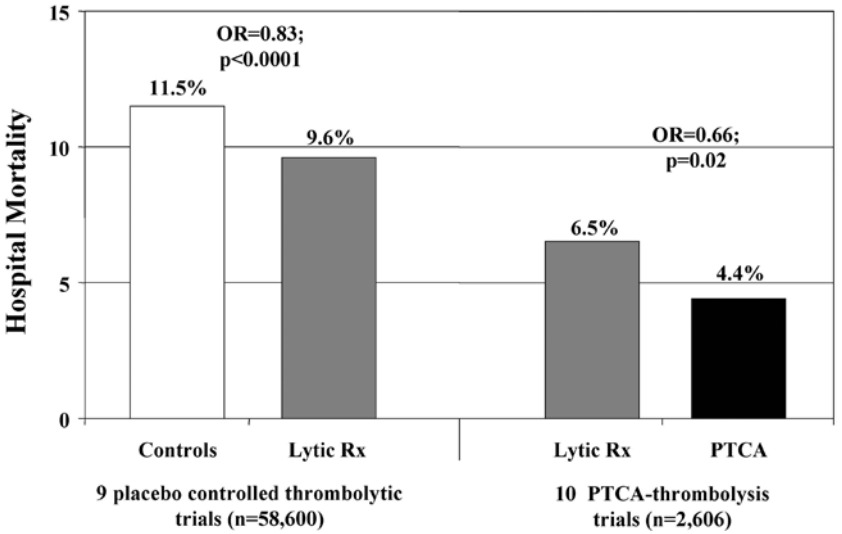


Fig. 3. Comparisons of hospital mortality in patients with AMI treated with thrombolytic therapy (Lytic Rx) vs placebo from nine randomized trials *(4)*, and with primary angioplasty (PTCA) vs thrombolytic therapy from 10 randomized trials. (Adapted from Weaver et al. *[14]* with permission.)

Table 1
Mortality in High- and Low-Risk Patients with AMI Treated with Primary PTCA vs Lytic Therapy in Randomized Trials

Study		*PTCA (%)*	*Lytic (%)*	p *Value*
PAMI-1				
Not low risk	($n = 206$) *(8)*	2.0	10.4	.01
Low risk	($n = 189$)	3.1	2.2	NS
Age > 65 yr	($n = 150$) *(22)*	5.7	15.0	.07
Age < 65 yr	($n = 245$)	0.8	0.8	NS
Anterior MI	($n = 138$) *(24)*	1.4	11.9	.01
Non-anterior MI	($n = 257$)	3.2	3.8	NS
Women	($n = 107$) *(26)*	4.0	14.0	.07
Men	($n = 288$)	2.1	3.5	NS
GUSTO IIb				
Age > 70 yr	($n = 314$) *(23)*	11.0	20.7	.02
Age < 70 yr	($n = 824$)	3.6	3.5	NS
Anterior MI	($n = 473$) *(25)*	6.8	6.8	NS
Garcia et al.				
Anterior MI	($n = 220$) *(21)*	2.8	10.8	.02

PAMI, primary angioplasty in myocardial infarction; GUSTO, global use of strategies to open occluded arteries; MI, myocardial infarction.

Outcomes in High-Risk Patients

Patients sustaining an AMI who are at highest risk for mortality include patients with cardiogenic shock, elderly patients, patients with anterior wall myocardial infarction, and women. Data from randomized trials indicate that the greatest mortality benefit with primary angioplasty is seen in these high-risk patients (Table 1). The PAMI-1 investigators found a significant mortality benefit with primary angioplasty compared with t-PA in the non–low-risk patients (patients older than 70 yr, with an anterior infarction or with heart rate >100), but no difference in mortality in low-risk patients *(8)*. Likewise, elderly patients showed a substantial mortality benefit with primary angioplasty compared with t-PA in both the PAMI-1 trial and the GUSTO IIb trial while younger patients showed no mortality difference *(22,23)*.

The PAMI-1 investigators found a substantial mortality benefit with primary angioplasty vs thrombolytic therapy in patients with anterior wall myocardial infarction but no mortality benefit in non–anterior-wall myocardial infarction *(24)*. Garcia and colleagues also found mortality benefit with primary angioplasty in patients with anterior wall myocardial infarction, but the GUSTO IIb trial did

not *(21,25)*. The lack of benefit in GUSTO IIb may be related to the trial's lower rate of achieving TIMI 3 flow *(11)*.

Women are also at high risk for mortality with AMI, partly related to the presence of a greater number of risk factors at baseline. In the PAMI-1 trial, mortality in women was lower with primary angioplasty than with t-PA (Table 1) *(26)*.

Patients with cardiogenic shock are the highest risk subgroup of patients with AMI and appear to receive the greatest benefit from primary angioplasty. Unfortunately, thrombolytic therapy is not very effective in patients with cardiogenic shock. In the GISSI-1 trial, there was no difference in mortality in patients with cardiogenic shock treated with intravenous streptokinase vs placebo (70% in each), and the International Study Group found that mortality was high with both streptokinase and t-PA (65% and 78%, respectively) *(2,27)*. In contrast, pooled data from 19 observational studies with primary angioplasty for cardiogenic shock showed an overall mortality of 44% *(28)*. Recently the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial, which randomized patients with cardiogenic shock to emergency revascularization vs medical stabilization, found lower 6-mo mortality with emergency revascularization (50% vs 63%, $p = 0.03$) *(29)*. Survival benefit was especially pronounced in patients randomized within 6 h of symptom onset and in patients under the age of 75 yr. These data and previous observational data strongly support the use of primary angioplasty to provide survival benefit in patients with AMI complicated by cardiogenic shock, especially in young patients who present early after symptom onset.

Outcomes in Low-Risk Patients

While the survival benefit with primary angioplasty vs thrombolytic therapy is limited to high-risk patients, low-risk patients benefit from a reduction in the incidence of reinfarction and recurrent ischemia. In randomized comparisons, the PAMI-1 trial found a lower incidence of recurrent ischemia (9.7% vs 27.8%, $p = 0.0002$) and the Zwolle group found a lower incidence of reinfarction (0% vs 16%, $p < 0.01$) in patients with non–anterior-wall myocardial infarction treated with primary angioplasty *(19,24)*. Similarly, Ribichini and colleagues, in a randomized comparison of primary angioplasty vs thrombolytic therapy in patients with inferior infarction, found a lower incidence of reinfarction (1.8% vs 9.1%, $p = 0.10$) and recurrent ischemia (1.8% vs 20.0%, $p = 0.002$), higher infarct artery patency (100% vs 71%, $p = 0.0001$), and better left ventricular ejection fraction (55.2% vs 48.2%, $p = 0.001$) at hospital discharge in patients treated with primary angioplasty *(20)*. Thus, although low-risk patients have no survival benefit with primary angioplasty, they do benefit by having less reinfarction, less recurrent

Table 2
Relationship between TIMI Flow and 30-d Mortality after Reperfusion Therapy for AMI

	30-d Mortality	
TIMI flow	*GUSTO-1* (30) *(Lytic Therapy)*	*PAMI-1 and PAMI-2* (13) *(Primary PTCA)*
TIMI 0–1	8.9%	17.2%
TIMI 2	7.4%	7.6%
TIMI 3	4.4%	2.1%

ischemia, and higher infarct artery patency rates without the risk of intracranial hemorrhage.

THE IMPORTANCE OF TIMI FLOW

The importance of achieving timely restoration of normal blood flow in the infarct artery in patients with AMI was convincingly demonstrated in the GUSTO trial *(30)*. Patients with normal (TIMI 3) antegrade flow in the infarct artery at 90 min after treatment had the best left ventricular function at follow-up catheterization and the lowest 30-d mortality (Table 2). Patients with slow (TIMI 2) flow had a left ventricular ejection fraction and 30-d mortality that was significantly worse than patients with TIMI 3 flow and similar to patients with no flow (TIMI 0–1).

A similar relationship between TIMI flow and mortality has been found with primary angioplasty (Table 2) *(13)*. These data indicate that only restoration of TIMI 3 flow is associated with optimal outcomes and that only TIMI 3 flow should be regarded as "true patency." A comparison of the rates of TIMI 3 flow with various thrombolytic strategies from the GUSTO trial *(30)* and the TIMI-14 trial *(31)*, and with primary angioplasty from the PAMI-1 and PAMI-2 trials *(13)* is shown in Fig. 4. The ability of primary angioplasty to achieve significantly higher TIMI 3 flow rates than thrombolytic therapy probably explains most of the mortality advantage seen with primary angioplasty. Indeed, there appears to be a tight inverse relationship between short-term mortality and the ability to achieve TIMI 3 flow with various thrombolytic regimens and with primary angioplasty (Fig. 5). Newer thrombolytic strategies combining low-dose thrombolytics with platelet glycoprotein (GP) IIb/IIIa inhibitors have shown improved TIMI 3 flow rates, but these rates are still well below the TIMI flow rates achieved with primary angioplasty *(31)*. These strategies have recently been tested in the GUSTO V trial, which showed less reinfarction but no mortality benefit compared with full-dose thrombolytic therapy *(32)*.

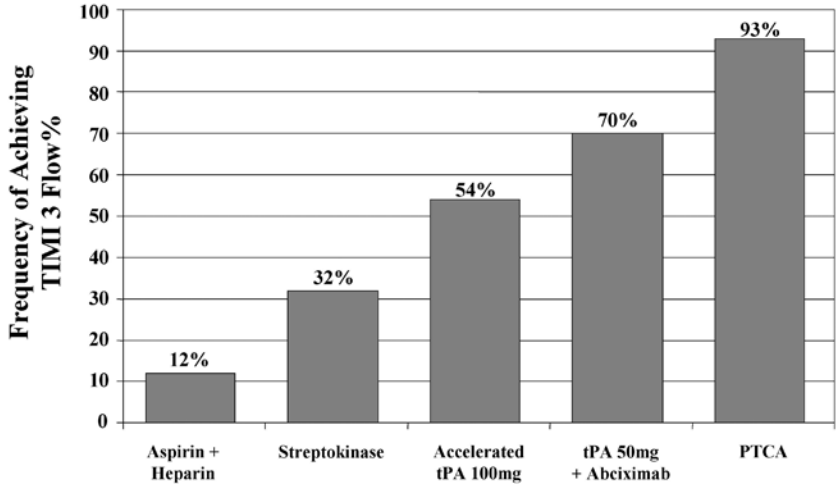


Fig. 4. Frequency of achieving TIMI 3 flow in the infarct artery acutely with aspirin and heparin *(45)*, streptokinase *(30)*, accelerated t-PA *(30)*, low-dose t-PA plus abciximab *(31)*, and primary angioplasty *(13)*.

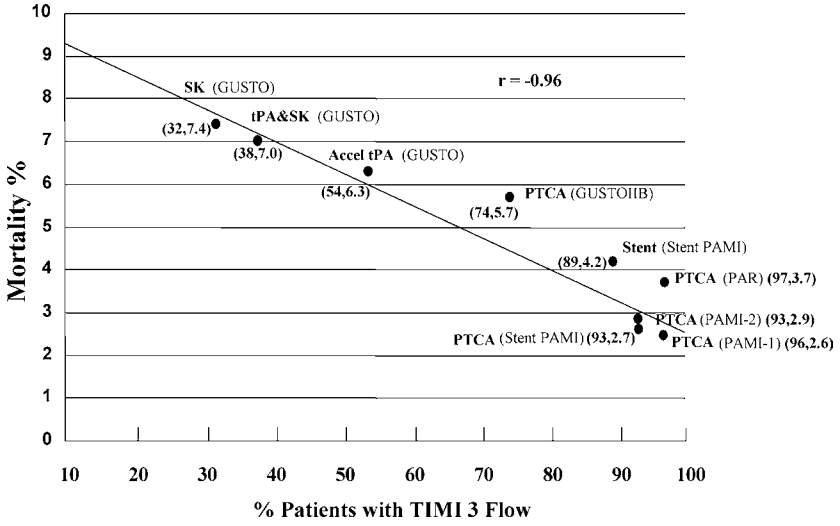


Fig. 5. Relationship between early mortality and frequency of achieving TIMI 3 flow acutely in the infarct artery with several thrombolytic strategies from the GUSTO trial *(30)* and several primary angioplasties (PTCA) trials *(11,13,30,46,51)*.

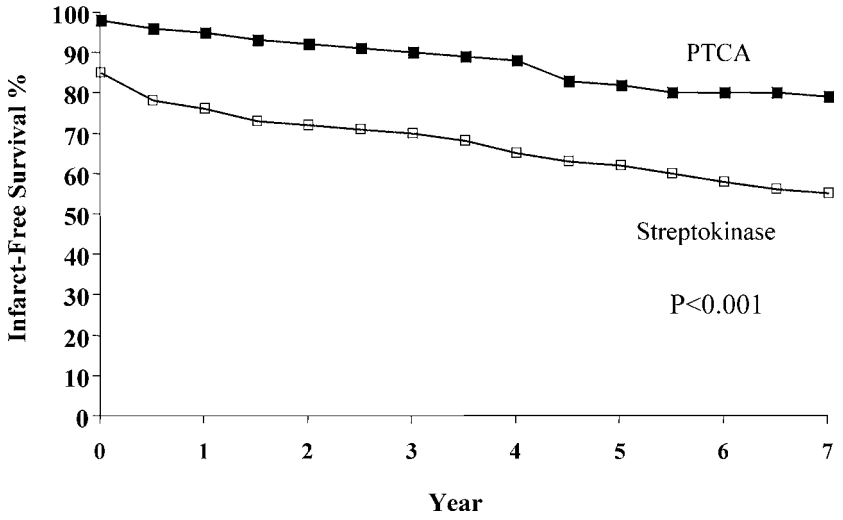


Fig. 6. Kaplan–Meier curves for survival free of reinfarction comparing patients with AMI treated with primary angioplasty vs streptokinase. (Adapted from Zijlstra et al. *[34]* with permission.)

LATE CLINICAL OUTCOMES

A comparison of late clinical outcomes of patients with acute myocardial infarction treated with primary angioplasty vs thrombolytic therapy has been provided by the PAMI and Zwolle investigators *(33,34)*. The PAMI investigators found that the initial benefit of primary angioplasty in reducing death and reinfarction was maintained after 2 yr with event-free survival curves that remained nearly parallel after hospital discharge *(33)*. Primary angioplasty was also associated with lower hospital readmission rates (59% vs 69%, $p = 0.035$) and lower rates of target vessel revascularization with either angioplasty or bypass surgery (33% vs 54%, $p = 0.001$) compared with t-PA. More recently, the Zwolle group found that the early mortality and reinfarction benefit with primary angioplasty was enhanced over time with infarct-free survival curves that diverged over 5-yr follow-up (Fig. 6) *(34)*.

LATE ANGIOGRAPHIC OUTCOMES

Infarct Artery Reocclusion

Reocclusion of the infarct artery at follow-up angiography occurs frequently after thrombolytic therapy when adjunctive percutaneous coronary intervention is not employed. The Anti-thrombotics in the Prevention of Re-occlusion in Coronary Thrombolysis (APRICOT) study performed follow-up angiography at

Table 3
Infarct Artery Restenosis and Reocclusion Rates at 3–12 mo after Reperfusion Therapy for AMI

		Time to follow-up angiography	*Restenosis rate*[a]	*Reocclusion rate*
Primary angioplasty				
O'Neill et al. *(7)*	($n = 63$)	6 mo	38%	13%
Primary Angioplasty Registry *(36)*	($n = 203$)	6 mo	46%	13%
Nakagawa et al. *(37)*	($n = 137$)	12 mo	47%	14%
Zwolle Trial *(34)*	($n = 136$)	3 mo	24%	5%
Thrombolytic therapy				
APRICOT Trial *(34)*	($n = 248$)	3 mo	83%[b]	28%
White et al. *(35)*	($n = 215$)	12 mo	—	25%

[a]Restenosis rate includes patients with reocclusion.
[b]Residual stenosis at 3 mo angiography after thrombolytic therapy, like primary angioplasty, was defined as >50% luminal diameter narrowing.

3 mo in patients with AMI treated with intravenous streptokinase who had a patent infarct artery at catheterization at 24–48 h and found a late reocclusion rate of 28% *(35)*. Similarly, White and colleagues found that 25% of patients with an initially patent infarct artery after thrombolytic therapy at 4 wk had an occluded artery at 1 yr *(36)*. In contrast, reocclusion rates at 6-mo follow-up angiography after primary angioplasty have ranged from 5% to 14% (Table 3) *(7,35,37,38)*. In a randomized comparison of primary angioplasty with streptokinase from the Zwolle group, reocclusion rates were significantly lower with primary angioplasty (9% vs 32%, $p = 0.001$) *(9)*. These lower rates of reocclusion with primary angioplasty are likely related to the reduction in residual stenosis, as residual stenosis after thrombolytic therapy is highly correlated with late reocclusion *(36)*.

Infarct artery patency is important for recovery of left ventricular function *(37)* and may be important for late survival *(39,40)*. Several observational studies with thrombolytic therapy and primary angioplasty have found that both left ventricular function and infarct artery patency are strong independent predictors of late cardiac survival *(39,40)*. This suggests that the late angiographic outcomes after primary angioplasty may translate into better long-term clinical outcomes. This finding may explain the divergence of the mortality curves between primary angioplasty and thrombolytic therapy in the long-term Zwolle follow-up.

Infarct Artery Restenosis

The restenosis rate at 6-mo follow-up angiography after primary angioplasty is similar to that after elective angioplasty and occurs in 24%–47% of patients

(7,35,37,38). While this remains a significant clinical and economic problem with primary angioplasty, only about one half of patients with restenosis require repeat target vessel revascularization, and restenosis does not interfere with recovery of left ventricular function as long as the infarct artery remains patent. In comparison with primary angioplasty, the frequency of significant residual stenoses (>50% diameter narrowing) at 3-mo follow-up angiography after thrombolytic therapy is quite high (Table 3) *(35)*.

Preservation of Left Ventricular Function

The relative benefit of primary angioplasty vs thrombolytic therapy in preserving left ventricular function is not clear. The Zwolle trial found that the left ventricular ejection fraction measured by radionuclide angiography in 138 survivors prior to hospital discharge was greater with primary angioplasty than with intravenous streptokinase (51% vs 45%, $p = 0.004$) *(9)*. In contrast, the PAMI trial found no difference in left ventricular ejection fraction measured at 6 wk with radionuclide ventriculography after primary PTCA vs t-PA (53% vs 53%, $p =$ NS) *(8)*. Likewise the Mayo Clinic trial found no difference in myocardial salvage measured by acute and predischarge myocardial perfusion imaging with technetium sestamibi between primary angioplasty and t-PA (13% vs 15%, $p = 0.64$) *(16)*. With higher reperfusion rates, less residual stenosis, and lower reocclusion rates, one might expect better recovery of left ventricular function with primary angioplasty than with thrombolytic therapy. However, when reperfusion is established later than 2 h, myocardial salvage is very modest with either reperfusion strategy *(41–44)*. Because only 5%–10% of patients present early enough to establish reperfusion at <2 h, overall myocardial salvage in a large group of patients is modest with both strategies *(44,45)*.

PRIMARY ANGIOPLASTY AS A REPERFUSION STRATEGY

Primary angioplasty differs from thrombolytic therapy in that primary angioplasty is a strategy with several treatment options, and not all patients selected for this strategy undergo primary angioplasty. Following emergency cardiac catheterization, approx 10% of patients are triaged either to medical treatment or are treated with coronary bypass surgery as the primary reperfusion treatment (primary CABG) *(46)*. Patients may be selected for primary CABG when there is severe left main disease or severe three-vessel coronary artery disease with preserved (TIMI 3) flow in the infarct artery. These patients may undergo emergency or deferred CABG and constitute a little fewer than one half of patients not treated with percutaneous coronary intervention. The remaining patients not treated with percutaneous coronary intervention are treated medically. These include patients with no myocardial infarction (mistaken diagnosis), patients with no significant stenosis in the infarct artery (resolution of spasm or

thrombus), those in whom it is not possible to identify the infarct artery, and occasionally patients with unsuitable anatomy or a very small infarct artery.

Bypass surgery may be performed on an emergency basis after failed angioplasty, urgently for reinfarction or recurrent ischemia, and electively for definitive treatment of left main or severe multivessel disease. Even before the availability of stents, emergency bypass surgery for failed angioplasty was rare (about 0.4%) and the need for urgent bypass surgery for reinfarction or recurrent ischemia that could not be managed with repeat percutaneous coronary intervention was infrequent (1%–2%) *(46,47)*. Elective bypass surgery for treatment of residual coronary artery disease after initial successful primary angioplasty has been used in about 4%–5% of patients. Altogether, bypass surgery has been performed in about 10% of patients with the primary angioplasty approach in the pre-stent era *(46,47)*. Considering the severity of illness of these patients, surgical mortality has been very acceptable (6.4% with emergency or urgent bypass surgery and 2.0% with elective bypass surgery in the PAMI-2 trial) *(47)*.

The primary angioplasty strategy of performing diagnostic cardiac catheterization before deciding the most appropriate treatment has potential advantages over thrombolytic therapy. Patients who have no myocardial infarction can be identified and can avoid the hemorrhagic risk of thrombolytic therapy. Selected high-risk patients with left main and severe three-vessel coronary artery disease can be triaged to early surgery, and low-risk patients can be identified and targeted for early discharge.

CONCLUSIONS AND RECOMMENDATIONS

The data from observational studies and randomized trials in the pre-stent era have provided meaningful comparisons of outcomes and safety between primary angioplasty (performed in an era preceding stents and platelet GP IIb/IIIa inhibitors) and first and second generation thrombolytic therapy (streptokinase, t-PA, and accelerated t-PA). These data indicate a clear advantage of primary angioplasty over thrombolytic therapy in institutions where primary angioplasty can be performed by experienced operators. Primary angioplasty achieves higher patency rates with less residual stenosis and less frequent reocclusion of the infarct artery. Mortality is lower in high-risk patients and primary angioplasty results in less reinfarction and less recurrent ischemia in all patients. Primary angioplasty also avoids the dreaded complication of intracranial hemorrhage. The results of these trials serve as a valuable reference for future investigation but are not the final answer in evaluating these two reperfusion strategies. Both strategies are in a state of rapid evolution. The use of stents and GP IIb/IIIa platelet inhibitors is significantly improving outcomes with mechanical intervention *(48–50)*, and the combined use of thrombolytics and GP IIb/IIIa platelet inhibitors has enhanced reperfusion rates with pharmacologic intervention *(31)*.

The combined use of low-dose thrombolytics with GP IIb/IIIa platelet inhibitors followed by emergency percutaneous coronary intervention ("facilitated PCI") holds promise to improve outcomes further. In the end, mechanical and pharmacologic reperfusion may merge once again to optimize outcomes in patients with acute myocardial infarction.

REFERENCES

1. Rentrop KP, Blanke H, Karsch KR, et al. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. Clin Cardiol 1979;2:354–363.
2. Gruppo Italiano per lo Studio Della Streptochinasi nell' Infarcto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–402.
3. ISIS-2 (Second International Study Of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction; ISIS-2. Lancet 1988;2:349–360.
4. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Lancet 1994;343: 311–322.
5. Hartzler GO, Rutherford BD, McConahay DR, et al. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. Am Heart J 1983;106:965–973.
6. Brodie BR, Weintraub RA, Stuckey TD, et al. Outcomes of direct coronary angioplasty for acute myocardial infarction in candidates and non-candidates for thrombolytic therapy. Am J Cardiol 1991;67:7–12.
7. O'Neill WW, Weintraub R, Grines CL, et al. A prospective, placebo-controlled, randomized trial of intravenous streptokinase and angioplasty vs. lone angioplasty therapy of acute myocardial infarction. Circulation 1992;86:1710–1717.
8. Grines CL, Brown KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–679.
9. Zijlstra F, Jan de Boer M, Hoorntje JCA, Reiffers S, Reiber JHC, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680–684.
10. O'Neill W, Timmis GC, Bourdillon PD, et al. A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty for acute myocardial infarction. N Engl J Med 1986;314:812–818.
11. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–1628.
12. Stone GW, Grines CL, O'Neill WW. Primary coronary angioplasty versus thrombolysis. N Engl J Med 1997;337:1168–1169 (letter).
13. Stone GW, O'Neill WW, Jones B, Grines CL. The central unifying concept of TIMI-3 flow after primary PTCA in thrombolytic therapy in acute myocardial infarction. Circulation 1996;94(Suppl I):I-515 (abstract).
14. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–2098.

15. DeWood MA. Direct PTCA versus intravenous tPA in acute myocardial infarction: Results from a prospective randomized trial. In: Proceedings from the Thrombolysis and Interventional Therapy in Acute Myocardial Infarction Symposium VI. George Washington University, Washington, DC, 1990; pp. 28–29.
16. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685–691.
17. Ribeiro EE, Silva LA, Carneiro R, et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. J Am Coll Cardiol 1993;22:376–380.
18. Grinfield L, Berrocal D, Belardi J, et al. Fibrinolytics versus primary angioplasty in acute myocardial infarction (FAP). J Am Coll Cardiol 1996;27(Suppl):A-222 (abstract).
19. Zijlstra F, Beukema WP, Van't Hof AWJ, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908–912.
20. Ribichini F, Steffenino G, Dellavalle A, et al. Comparison of thrombolytic therapy and primary coronary angioplasty with liberal stenting for inferior myocardial infarction with precordial ST-segment depression: immediate and long term results of a randomized study. J Am Coll Cardiol 1998;32:1687–1694.
21. Garcia E, Elizaga J, Perez-Castellano N, et al. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. J Am Coll Cardiol 1999;33:605–611.
22. Stone ZW, Grines GL, Browne KS, et al. Predictors of in-hospital and six month outcomes after acute myocardial infarction in the reperfusion era: the Primary Angioplasty in Myocardial Infarction (PAMI) Trial. J Am Coll Cardiol 1995;25:370–377.
23. Holmes DR Jr, White HD, Pieper KS, Ellis SG, Califf RM, Topol EJ. The effect of age on outcome with primary angioplasty versus thrombolysis. J Am Coll Cardiol 1999;33:412–419.
24. Stone ZW, Grines CL, Browne KF, et al. Influence of acute myocardial infarction location on in-hospital and late outcomes after primary percutaneous transluminal coronary angioplasty versus tissue plasminogen activator therapy. Am J Cardiol 1996;78:19–25.
25. Vassanelli C, Ellis SG, Phillips HR, Betriu A, Van de Werf FJJ, Stebbins A. No greater benefit with PTCA in patients with anterior infarction—updated 30-day results of the GUSTO IIb substudy. Circulation 1996;94(Suppl I):I-329 (abstract).
26. Stone GW, Grines CL, Browne KF, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 1995;75:987–992.
27. The International Study Group. In-hospital mortality and clinical course of 2,891 patients with suspected acute myocardial infarction randomized between Alteplase and streptokinase with and without heparin. Lancet 1990;336:71–75.
28. Moscucci M, Bates ER. Treatment of acute myocardial infarction: cardiogenic shock. Cardiol Clin 1995;13:391–406.
29. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. N Engl J Med 1999; 341:625–634.
30. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase or both on coronary artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–1622.
31. Antman EM, Giugliano RP, Gibson M, et al. Abciximab facilitates the rate and extent of thrombolysis: Results of the Thrombolysis In Myocardial Infarction (TIMI) 14 Trial. Circulation 1999;99:2720–2732.
32. Topol EJ, Califf RM, Van de Werf F, et al. Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO randomised trial. Lancet 2001;357:1905–1914.

33. Nunn CM, O'Neill WW, Rothbaum D, et al. Long-term outcome after primary angioplasty: report from the Primary Angioplasty in Myocardial Infarction (PAMI-1) Trial. J Am Coll Cardiol 1999;33:640–646.
34. Zijlstra F, Hoorntje JCA, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413–1419.
35. Veen G, de Boer MJ, Zijlstra F, Verheugt FWA. Improvement in three-month angiographic outcomes suggested after primary angioplasty for acute myocardial infarction (Zwolle trial) compared with successful thrombolysis (APRICOT trial). Am J Cardiol 1999;84:763–767.
36. White HD, French JK, Hamer AW, et al. Frequent re-occlusion of patent infarct-related arteries between four weeks and one year: effects of antiplatelet therapy. J Am Coll Cardiol 1995;25:218–223.
37. Brodie BR, Grines CL, Ivanhoe R, et al. Six month clinical and angiographic follow-up after direct angioplasty for acute myocardial infarction: final results from the primary angioplasty registry. Circulation 1994;25:155–162.
38. Nakagawa Y, Iwasaki Y, Kimura T, et al. Serial angiographic follow-up after successful direct angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:980–984.
39. White HB, Cross DB, Elliott JM, Norris RM, Yee TW. Long-term prognostic importance of patency of the infarct related coronary artery after thrombolytic therapy for acute myocardial infarction. Circulation 1994;89:61–67.
40. Brodie BR, Stuckey TD, Kissling G, Hansen CJ, Weintraub RA, Kelly TA. Importance of infarct-related artery patency for recovery of left ventricular function and late survival after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1996;28:319–325.
41. O'Keefe JH, Grines CL, DeWood MA, Bateman TM, Christian TF, Gibbons RJ. Factors influencing myocardial salvage with primary angioplasty. J Nucl Cardiol 1995;2:35–41.
42. Milavetz JJ, Giebel DW, Christian TF, Schwartz RS, Holmes DR Jr, Gibbons RJ. Time to therapy and salvage in myocardial infarction. J Am Coll Cardiol 1998;31:1246–1251.
43. Weaver WD, Cerqueira M, Hallstrom AP, et al. Prehospital—initiated vs. hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Intervention Trial. JAMA 1993;270:1211–1216.
44. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312–1319.
45. Berger PB, Ellis SG, Holmes DR Jr, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb Trial). Circulation 1999;100:14–20.
46. O'Neill WW, Brodie BR, Ivanhoe R, et al. Primary coronary angioplasty for acute myocardial infarction (The Primary Angioplasty Registry). Am J Cardiol 1994;73:627–634.
47. Stone GW, Brodie BR, Griffin JJ, et al. Role of cardiac surgery in the hospital phase management of patients treated with primary angioplasty for acute myocardial infarction. Am J Cardiol 2000;85:1292–1296.
48. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–1956.
49. Brener SJ, Barr LA, Burchenal JEB, et al. Randomized placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998;98:734–741.
50. Neumann FJ, Kastrati A, Dirschinger J, Pache J, Mehilli J, Schomig A. Use of platelet glycoprotein IIb/IIIa blockade in acute myocardial infarction treated with intracoronary stenting: Thirty-day clinical results of a randomized study. J Am Coll Cardiol 1999;33(Suppl A):339A (abstract).
51. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–1956.

5 Rescue Percutaneous Coronary Intervention for Failed Thrombolysis

Debabrata Mukherjee, MD
and Stephen G. Ellis, MD

CONTENTS

Rescue or salvage percutaneous coronary intervention (PCI) entails mechanical reopening of an infarct-related artery (IRA) after unsuccessful fibrinolytic therapy. Although rescue PCI is commonly performed, data describing clinical outcomes are sparse.

Early restoration of patency of the infarct-related artery is a universally accepted goal in the treatment of acute myocardial infarction (AMI). Either fibrinolysis or primary PCI is currently used to achieve this goal, but at present and in the foreseeable future fibrinolysis is and will be the most widely used first-line approach. Even with the most successful fibrinolytic regimen evaluated to date, however, the patency rate (defined as Thrombolysis in Myocardial Infarction [TIMI] grade 2 or 3 flow) at 90 min after the onset of fibrinolysis has been 81%. The rate of normal flow (defined as TIMI grade 3 flow) was only 54% in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) angiographic substudy *(1)*. The 30-d mortality rate was 4.4% for patients with normal coronary flow at 90 min, as

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

opposed to 8.9% for those with occluded arteries at 90 min, regardless of the subsequent therapeutic strategy ($p = 0.009$). Normal flow at 90 min also predicted higher ejection fraction and lower end-systolic volume than impaired flow.

Several studies have shown a clinical benefit to not only restoring patency but also normalizing flow (TIMI grade 3 as opposed to TIMI grade 2 flow). In the GUSTO angiographic substudy, ejection fraction was significantly better and there were fewer wall motion abnormalities both acutely and at 5–7 d after infarction in patients who achieved TIMI grade 3 reperfusion after fibrinolysis, compared with patients with TIMI 2 flow. There also was a beneficial trend in the 30-d mortality rate (4.4% vs 7.4%, $p = 0.08$). This trend is in line with data reported in earlier multicenter and meta-analysis studies, including a series of trials from Germany documenting a 2.7% in-hospital mortality rate for TIMI 3 reperfusion, 6.6% with TIMI 2, and 7.1% for persistent occlusion *(2)*.

Ultimately, however, restoration of adequate myocardial blood flow rather than epicardial coronary blood flow is the goal of reperfusion therapy; experimental and clinical observations caution against proposing too simplistic an equation of restored TIMI 3 coronary flow equaling myocardial salvage *(3)*. The situation in which oxygenated blood does not reach the myocardium because of microvascular damage despite sufficient epicardial coronary flow has been described as the *no-reflow phenomenon (4,5)*. In the presence of the no-reflow phenomenon, despite angiographically successful rescue percutaneous transluminal coronary angioplasty (PTCA), the clinical benefit is likely to be minimal. Unfortunately, the no-reflow phenomenon cannot be predicted, although it is more frequent after interventions in saphenous vein grafts than in native vessels. Possible causes of no reflow include tissue edema, platelet microembolization from the intervention, neutrophil microvessel plugging, and microvascular spasm. Although no reflow is by definition difficult to ascertain by angiography alone, in the future, intracoronary or even intravenous echocardiographic contrast application may allow detection of a lack of myocardial perfusion in spite of restoration of epicardial coronary blood flow, possibly prompting more aggressive medical adjunctive treatment *(6–8)*. The no-reflow phenomenon is clinically relevant; Ito and colleagues *(7)* found the incidence of heart failure to be higher in patients who had reduced myocardial reperfusion or no-reflow. Sakuma and co-workers *(9)* demonstrated a relative risk of 10.7 for major cardiac events (death, myocardial infarction, heart failure, and hospital readmission) in patients with impaired myocardial perfusion after AMI when measured by contrast echocardiography.

Most patients are candidates for additional therapy to recanalize the occluded vessel and optimize coronary flow. The most attractive therapeutic option in these patients is mechanical reopening of the occluded artery by PTCA, an approach that has been termed rescue PTCA. This approach should be distinguished from primary or direct PTCA for AMI, in which antecedent fibrinolytic

therapy is not administered. Although intuitively appealing, many questions regarding rescue PTCA remain to be settled. This is largely because of (1) the impossibility of accurately diagnosing IRA patency without angiography and (2) the dilemma of withholding PTCA in a control group once angiography has been performed *(10)*.

TECHNICAL CONSIDERATIONS

No specific strategy or armamentarium has been proposed that would fundamentally distinguish rescue PTCA from other types of emergency PTCA, such as primary PTCA for myocardial infarction. Usually, only the infarct-causing lesion is treated and "complete revascularization" is not attempted during the acute intervention. Recently, stents and the platelet glycoprotein (GP) receptor blockers have broadened the therapeutic options and are used increasingly in the acute setting. This is particularly appealing in view of the extremely high rate of adverse events, including death, after failed conventional rescue PTCA. Preliminary data from the randomized use of stents and abciximab in primary angioplasty for myocardial infarction showed a solid advantage in terms of adverse events in patients receiving these new adjunctive treatments *(11,12)*. These results should encourage the use of stents and GP IIb/IIIa blockade (particularly with abciximab) in rescue PTCA as well. Not surprisingly, because of the fibrinolytic and anticoagulant pretreatment, bleeding at the site of catheter insertion is more frequent than in elective angioplasty.

KEY CLINICAL FACTORS SUPPORTING THE RESCUE ANGIOPLASTY APPROACH

The diagnosis of the success or failure of fibrinolysis to achieve reperfusion by noninvasive means is notoriously difficult. Table 1 enumerates some clinically relevant criteria for failed fibrinolysis. Resolution of ST-segment elevation within 3 h from the start of fibrinolysis has been shown to correlate with 35-d mortality. In the International Joint Efficacy Comparison of Thrombolytics (INJECT) study of 1398 patients, complete (≥70%), partial (30%–70%), and lack of (<30%) resolution of ST-segment elevation was associated with 2.5%, 4.3%, and 17.5% rates of 35-d mortality, respectively ($p < 0.0001$) *(13)*. However, other reports have been less optimistic regarding the diagnostic accuracy of ST-segment monitoring. In a GUSTO substudy *(14)*, the significantly higher fibrinolytic potency of the accelerated tissue plasminogen activator regimen did not translate into earlier resolution of ST-segment elevation compared with other fibrinolytic regimens, casting doubt on the usefulness of this parameter. No other reliable markers of reperfusion have been thoroughly validated, although early (60 min after reperfusion) release of cardiac troponin T subunits has been reported to indicate reperfusion *(15)*, and continuous ST-segment monitoring may pro-

Table 1
Criteria for Failed Fibrinolysis

Persistent ST-elevation 75–90 min after fibrinolysis
Persistent or recurrent angina 75–90 min after fibrinolysis
Persistence or development of hypotension, tachycardia, decreased urine output after fibrinolysis (other causes such as mechanical complications may also contribute to hemodynamic instability)
Myocardial perfusion defect by contrast echocardiography

vide important help in the future. Newer techniques are currently being evaluated including myocardial contrast echocardiography, the Doppler flow wire, magnetic resonance imaging, and nuclear scintigraphy. These techniques can define not only the presence of myocardial perfusion but also the degree of perfusion. Thus the clinical nonangiographic assessment of the success of fibrinolytic therapy remains one of the most difficult decisions a cardiologist has to make in the treatment of myocardial infarction, and at present it is entirely based on symptoms and ST elevation dynamics.

Early and complete resolution of ST elevation is specific for epicardial patency and restoration of myocardial flow *(16)*, but absence of ST resolution is fairly insensitive. However, even angiography does not clearly indicate the success or failure of fibrinolysis. Given the outcome benefit from achieving full normalization of coronary flow (TIMI 3) as opposed to only TIMI 2 patency, TIMI 2 flow after fibrinolysis might be viewed as the equivalent of ongoing ischemia despite medical treatment. PCI may therefore be indicated to improve TIMI flow and thus favorably influence outcomes. In spite of its theoretical soundness, proof of benefit from this strategy is lacking. It is clear, however, that current advances in interventional practice (in particular, stents and abciximab) might tip the balance toward a more aggressive stance regarding this question.

Another critical issue is the time window during which to perform rescue PTCA. Both the beginning and end of this window pose clinical dilemmas. On the one hand, patency rates and TIMI 3 flow rates after fibrinolysis increase over 24 h *(1)*; on the other hand, there is ample evidence that patients fare better the earlier brisk flow is restored. Also, the substantial "door-to balloon" time necessary to prepare for PTCA has to be taken into account. Thus, if rescue PTCA is an option, the decision should ideally be made within 90 min from the beginning of fibrinolysis.

At the other end of the time window, although a limit of 6–8 h after the onset of chest pain has traditionally been observed for reperfusion therapy, late recanalization of the vessel may benefit the patient independent of the acute salvage of ischemic myocardium. This extension of the "open artery theory" has been supported by clinical studies showing benefit of reperfusion therapy well into

the 8–24-h time frame and possibly later *(17)*. The exact mechanism of this benefit is not clear, but the beneficial influence of the open artery on the healing process, the preservation of ventricular shape by the tethering effect of open large epicardial vessels, and the prevention of malignant arrhythmias appear to play a role.

The experience from the large reperfusion trials suggests that the benefit of reperfusion therapy in terms of mortality is commensurate to the initial risk, that is, patients with large infarcts benefit the most. In fact, it appears that timely reperfusion therapy allows patients to survive previously uniformly fatal, extensive infarctions *(18)*. Thus, it may be inferred that the same proportionality of potential benefit to initial risk holds for rescue PTCA; rescue of a large myocardial perfusion territory at risk implies a higher clinical benefit in terms of survival and post-infarct left ventricular function than a small one. An additional proposed benefit of rescue PTCA beyond the salvage of ischemic myocardium is that it provides "definitive" treatment of the underlying lesion, as opposed to deferred invasive diagnosis and therapy, and should reduce or eliminate recurrent ischemia.

PROCEDURAL SUCCESS AND CLINICAL OUTCOME

Randomized Clinical Trials

Patients with failed fibrinolysis are difficult to randomize into clinical trials, as it has become the standard of care for these individuals to undergo rescue PCI whenever possible. Four small randomized trials of rescue PCI vs conservative treatment in failed fibrinolysis have critically analyzed whether or not rescue PCI is beneficial (Table 2) *(19)*. The first included only 28 patients; 16 were randomly assigned to rescue PTCA, which was successful in 13 patients and unsuccessful in three patients, one of whom died *(20)*. Twelve patients were randomly assigned to conservative treatment, among whom four died. The difference was not statistically significant. The second randomized trial was a larger, multicenter trial that enrolled 151 patients with anterior myocardial infarction, fibrinolysis, and an angiographically occluded vessel within 8 h of chest pain *(21)*. Patients in cardiogenic shock or with left main stenosis were excluded. A procedural success rate of 92% in the PTCA group was associated with a 30-d mortality rate of 5%, whereas the conservatively managed group had a mortality rate of 10% (p = NS). There was a trend toward less severe heart failure in the PTCA group. Exercise ejection fraction at 30 d, but not baseline ejection fraction, was significantly higher in the PTCA group (45% vs 40%, $p = 0.05$).

Preliminary results of two small "rescue" trials were reported recently *(22,23)*. Both trials were performed as a part of a three-way randomization with primary PCI as one of the treatment arms. Both trials reported modest trends in the reduction of 30-d composite endpoint rates favoring rescue PCI.

Table 2
Randomized Trials of Rescue Angioplasty

	Belenkie (20) (n = *28)*		*RESCUE* (21) (n = *151)*		*PRAGUE* (23) (n = *40)*		*Vermeer* (22) (n = *149)*	
	PTCA (n = *16)*	*Medical* (n = *12)*	*PTCA* (n = *78)*	*Medical* (n = *73)*	*PTCA* (n = *20)*	*Medical* (n = *20)*	*PTCA* (n = *75)*	*Medical* (n = *74)*
30-d mortality (%)	6.3	33.3	5.1	9.6	20	18	9.4	6.7
30-d MI (%)	—	—	—	—	0	9	5.4	12.0
30 d CHF III-IV (%)	—	—	1.3	7.0	15	27	—	—
6-mo revascularization (%)	—	—	16.6	23.3	—	—	27.0	33.0
30-d composite of death, MI, CHF (%)	6.3	33.3	6.4	16.6	20	45	14.8	18.7

PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; CHF III–IV, congestive heart failure class III–IV.
Adapted with permission of the publisher from Ellis et al. *(19)*.

The PRAGUE trial *(23)* reported a 20% event rate (death, reinfarction, heart failure, or urgent revascularization) in the rescue group vs a 45% event rate in the conservatively treated group ($p = 0.09$). Vermeer et al. *(22)* reported in-hospital death or reinfarction rates of 5% vs 12% ($p = 0.15$) favoring rescue PCI.

Thus, the only studies to provide a direct comparison between PTCA and conservative treatment in the face of failed fibrinolysis did not conclusively prove a clear-cut benefit of the more aggressive strategy by showing a significant difference in outcome in a single study. However, these studies have shown a consistent trend toward benefit in the group randomized to rescue PCI. An analysis of all the patients in these four randomized studies revealed a mortality of 8.4% with rescue angioplasty and 11.1% with medical treatment ($p = 0.38$). Using a composite endpoint of death, reinfarction, congestive heart failure, however, the event rate was 11.1% with rescue angioplasty and 21% with medical treatment ($p = 0.009$). Taken in aggregate, these data thus support the referral of patients for urgent angiography and revascularization where possible if they have sustained a moderate or large AMI, demonstrate persistent electrocardiographic changes or hemodynamic instability, and appear not to have achieved adequate reperfusion by 75–120 min after fibrinolytic therapy.

Finally, *post hoc* analyses of data from other clinical trials have provided insight into the potential value of rescue angioplasty in the setting of partial early reperfusion (TIMI 2 flow). In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI)-1 *(24)* study, performed during 1985–1986, PCI was successful in 79% of patients. There was no apparent benefit in preventing infarct artery occlusion, heart failure, or mortality, although there was a suggestion, particularly when PCI was performed within 5 h of chest pain onset, that left ventricular ejection fraction was improved. In the TIMI 9B study *(25)*, 328 patients with TIMI 2 flow after treatment with either tissue plasminogen activator (t-PA) or streptokinase were treated at the discretion of the investigator and clinical outcomes were measured at 60 d. One hundred and ten patients were treated medically and 218 patients were revascularized while in-hospital. Baseline clinical and hemodynamic characteristics in the two groups were similar. Of the 218 patients who underwent revascularization, 19% had bypass surgery and 81% underwent PCI. Outcomes were better in the revascularized group (rehospitalization 14% vs 28%, $p = 0.003$; angina at latest follow-up 18% vs 29%, $p = 0.017$; reinfarction 4% vs 9%, $p = 0.05$). There was a trend favoring revascularization in 60-d mortality (0.5% vs 2.8%, $p = 0.12$).

Observational Studies and Retrospective Subgroup Analyses

In a large observational study from one center, 244 patients with AMI underwent angiography 90 min after the onset of fibrinolytic therapy *(26)*. TIMI 2 or 3 flow was demonstrated in the infarct artery of 69% of these patients. In 59 of the remaining 75 patients, rescue PTCA was attempted and was successful

in 93%. In-hospital mortality was 3.9% in the whole group treated by fibrinolysis and 3.4% in those treated by rescue PTCA.

Retrospective subgroup analyses of the large fibrinolytic trials affords some further insight into the subject, although these trials were not designed to test the value of rescue PTCA. When comparing rescue PTCA performed at the operator's discretion in the TIMI trials with a previously studied patient group in whom the protocol did not provide for rescue PTCA, neither mortality nor post-infarct ejection fraction differed significantly *(27,28)*. Of note, failed rescue PTCA was associated with a dismal 33% mortality rate at 21 d after the infarct, much higher than mortality in patients with a patent vessel after fibrinolysis (3%), with successful PTCA (10%), or with an occluded vessel and no rescue PTCA attempted (11%). However, patients who failed rescue PCI were usually already *in extremis* prior to the procedure with a very high incidence of preprocedure cardiogenic shock *(29)*.

In the TAMI 5 study, 575 patients who were randomly allocated to 90-min angiography with possible subsequent rescue PTCA or to deferred angiography were compared *(30)*. Rescue PTCA was performed in 52 cases. Early angiography with possible subsequent rescue PTCA had no effect on predischarge ejection fraction or in-hospital mortality, although regional wall motion in the infarct zone was significantly improved by the early catheterization strategy. The patients in this group also had a trend toward fewer adverse events (combined endpoint of death, stroke, reinfarction, heart failure, and recurrent ischemia). In a further analysis of a subset of patients with data on ejection fraction after 6 wk *(31)*, the beneficial effect of early catheterization on infarct zone wall motion vanished at 6 wk, and ejection fractions were the same.

In an analysis of a larger database of combined data from the TAMI trials, the authors compared the outcomes of 607 patients with successful fibrinolysis (under several fibrinolytic protocols) with 169 patients with successful rescue PTCA after failed fibrinolysis. They found comparable in-hospital mortality rates (4.6% vs 5.9%, respectively) but a much higher rate of subsequent reocclusion of the infarct vessel after rescue angioplasty *(32,33)*. Failed rescue PTCA carried an ominous prognosis with a mortality rate of 39.1%. The disproportionately high mortality (and adverse event rate) in patients with failed rescue PTCA is consistent in the literature and has been explained by patient selection and the added risk from untoward contrast effects, vessel injury, tachycardic and bradycardic arrhythmias, and bleeding resulting from the procedure.

ADVANCES IN THERAPY

Several trials such as the ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) *(12)* and Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-

up (ADMIRAL) *(34)* evaluated GP IIb/IIIa inhibition in the setting of primary PCI for AMI; GP IIb/IIIa inhibition as an adjunct to rescue PCI with failed thrombolysis was studied in the GUSTO III rescue PTCA registry *(35)*. These trials showed a significant benefit with adjunctive use of GP IIb/IIIa antagonists. In the Global Use of Strategies To Open Occluded Coronary Arteries (GUSTO-III) trial of reteplase versus alteplase for acute infarction (n = 15,059), 392 patients underwent angioplasty a median of 3.5 h after failed thrombolysis. The authors compared 30-d mortality and in-hospital outcomes between patients who received abciximab (n = 83) and those who did not (n = 309). The 30-d mortality rate tended to be lower with abciximab (3.6% vs 9.7%, p = 0.076), more so after adjustment for baseline differences (p = 0.042). The use of abciximab for rescue angioplasty after clinically failed thrombolysis resulted in trends toward lower 30-d mortality *(35)*. Use of stents in the setting of rescue PCI has also shown significant benefit *(36)*. Bleeding risk with full-dose fibrinolytics and GP IIb/IIIa inhibitors in the setting of rescue PCI was of concern. Also, the addition of GP IIb/IIIa antagonists to fibrinolytics alone without PCI may significantly increase the TIMI 3 flow in IRAs *(37,38)*.

CONCLUSIONS

A substantial proportion of patients with AMI do not achieve reperfusion despite fibrinolytic therapy. In these patients, rescue PTCA appears to be beneficial in terms of clinical outcomes, although clear-cut superiority has not been unequivocally proven. This is at least in part because of the difficulties in enrolling these patients into a prospective study design. However, early mechanical intervention for patients with failed thrombolysis and moderate to large infarction appears to be beneficial. In particular, the effect of contemporary aggressive adjunctive medical therapy (platelet GP IIb/IIIa integrin blockade) and of stenting may be reasonably expected to augment the benefit of rescue PTCA. This would appear to extend to those patients with TIMI 2 flow in the infarct vessel at angiography, Thus, clinical wisdom indicates that angiography and rescue PTCA should be strongly considered if fibrinolysis is clinically thought to have failed, in a time window up to 12 h (and possibly longer) after onset of infarction, and in particular if the electrocardiogram or hemodynamics indicate that the infarct is large.

REFERENCES

1. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–1622.
2. Vogt A, von Essen R, Tebbe U, Feuerer W, Appel KF, Neuhaus KL. Impact of early perfusion status of the infarct-related artery on short-term mortality after thrombolysis for acute myocardial infarction: retrospective analysis of four German multicenter studies. J Am Coll Cardiol 1993;21:1391–1395.

3. Lincoff AM, Topol EJ. Illusion of reperfusion. Does anyone achieve optimal reperfusion during acute myocardial infarction? Circulation 1993;88:1361–1374.
4. Kaplan BM, Benzuly KH, Kinn JW, et al. Treatment of no-reflow in degenerated saphenous vein graft interventions: comparison of intracoronary verapamil and nitroglycerin. Cathet Cardiovasc Diagn 1996;39:113–118.
5. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of "no-reflow" after percutaneous coronary intervention. Circulation 1994;89:2514–2518.
6. Kaul S, Senior R, Dittrich H, Raval U, Khattar R, Lahiri A. Detection of coronary artery disease with myocardial contrast echocardiography: comparison with 99mTc-sestamibi single-photon emission computed tomography. Circulation 1997;96:785–792.
7. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the "no reflow" phenomenon. A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996;93:223–228.
8. Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–1705.
9. Sakuma T, Hayashi Y, Sumii K, Imazu M, Yamakido M. Prediction of short- and intermediate-term prognoses of patients with acute myocardial infarction using myocardial contrast echocardiography one day after recanalization. J Am Coll Cardiol 1998;32:890–897.
10. Ellis SG, Van de Werf F, Ribeiro-daSilva E, Topol EJ. Present status of rescue coronary angioplasty: current polarization of opinion and randomized trials. J Am Coll Cardiol 1992;19:681–686.
11. Steinhubl SR, Topol EJ. Stenting for acute myocardial infarction. Lancet 1997;350: 532–533.
12. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT) Investigators. Circulation 1998;98:734–741.
13. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol 1995;26:1657–1664.
14. Langer A, Krucoff MW, Klootwijk P, et al. Noninvasive assessment of speed and stability of infarct-related artery reperfusion: results of the GUSTO ST segment monitoring study. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995;25:1552–1557.
15. Abe S, Arima S, Yamashita T, et al. Early assessment of reperfusion therapy using cardiac troponin T. J Am Coll Cardiol 1994;23:1382–1389.
16. de Lemos J, Antman E, Gibson M, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST elevation myocardial infarction: A TIMI 14 analysis. Circulation 1999;100(Suppl I):I-649.
17. Late Assessment of Thrombolytic Efficacy (LATE) study with alteplase 6- 24 hours after onset of acute myocardial infarction. Lancet 1993;342:759–766.
18. McCallister BD Jr, Christian TF, Gersh BJ, Gibbons RJ. Prognosis of myocardial infarctions involving more than 40% of the left ventricle after acute reperfusion therapy. Circulation 1993;88:1470–1475.
19. Ellis SG, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley JD. Review of immediate angioplasty after fibrinolytic therapy for acute myocardial infarction: insights from the RESCUE I, RESCUE II, and other contemporary clinical experiences. Am Heart J 2000;139:1046–1053.

20. Belenkie I, Traboulsi M, Hall CA, et al. Rescue angioplasty during myocardial infarction has a beneficial effect on mortality: a tenable hypothesis. Can J Cardiol 1992;8:357–362.
21. Ellis SG, da Silva ER, Heyndrickx G, et al. Randomized comparison of rescue angioplasty with conservative management of patients with early failure of thrombolysis for acute anterior myocardial infarction. Circulation 1994;90:2280–2284.
22. Vermeer F, Ophuis AJ, Berg EJ, et al. Prospective randomised comparison between thrombolysis, rescue PTCA, and primary PTCA in patients with extensive myocardial infarction admitted to a hospital without PTCA facilities: a safety and feasibility study. Heart 1999; 82:426–431.
23. Widimsky P, Groch L, Zelizko M, Aschermann M, Bednar F, Suryapranata H. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. Eur Heart J 2000 May; 21(10):823–831.
24. Ellis SG, Lincoff AM, George BS, et al. Randomized evaluation of coronary angioplasty for early TIMI 2 flow after thrombolytic therapy for the treatment of acute myocardial infarction: a new look at an old study. The Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Study Group. Cor Artery Dis 1994;5:611–615.
25. McKendall G, Antman E, Braunwald E, McDonald M, Williams D, for the TIMI 9B Investigators. What is the clinical impact and outcome of revascularization of TIMI 2 flow following acute myocardial infarction? J Am Coll Cardiol 1997;29:389A (abstract).
26. Juliard JM, Himbert D, Golmard JL, et al. Can we provide reperfusion therapy to all unselected patients admitted with acute myocardial infarction? J Am Coll Cardiol 1997;30:157–164.
27. McKendall GR, Forman S, Sopko G, Braunwald E, Williams DO. Value of rescue percutaneous transluminal coronary angioplasty following unsuccessful thrombolytic therapy in patients with acute myocardial infarction. Thrombolysis in Myocardial Infarction Investigators. Am J Cardiol 1995;76:1108–1111.
28. Gibson CM, Cannon CP, Greene RM, et al. Rescue angioplasty in the thrombolysis in myocardial infarction (TIMI) 4 trial. Am J Cardiol 1997;80:21–26.
29. Ross AM, Lundergan CF, Rohrbeck SC, et al. Rescue angioplasty after failed thrombolysis: technical and clinical outcomes in a large thrombolysis trial. GUSTO-1 Angiographic Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1998;31:1511–1517.
30. Califf RM, Topol EJ, Stack RS, et al. Evaluation of combination thrombolytic therapy and timing of cardiac catheterization in acute myocardial infarction. Results of thrombolysis and angioplasty in myocardial infarction—phase 5 randomized trial. TAMI Study Group. Circulation 1991;83:1543–1556.
31. Ward SR, Sutton JM, Pieper KS, Schwaiger M, Califf RM, Topol EJ. Effects of thrombolytic regimen, early catheterization, and predischarge angiographic variables on six-week left ventricular function. The TAMI Investigators. Thrombolysis and Angioplasty in Acute Myocardial Infarction. Am J Cardiol 1997;79:539–544.
32. Muller DW, Topol EJ. Thrombolytic therapy: adjuvant mechanical intervention for acute myocardial infarction. Am J Cardiol 1992;69:60A–70A.
33. Abbottsmith CW, Topol EJ, George BS, et al. Fate of patients with acute myocardial infarction with patency of the infarct-related vessel achieved with successful thrombolysis versus rescue angioplasty. J Am Coll Cardiol 1990;16:770–778.
34. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.
35. Miller JM, Smalling R, Ohman EM, et al. Effectiveness of early coronary angioplasty and abciximab for failed thrombolysis (reteplase or alteplase) during acute myocardial infarction

(results from the GUSTO-III trial). Global Use of Strategies To Open occluded coronary arteries. Am J Cardiol 1999;84:779–784.
36. Moreno R, Garcia E, Abeytua M, et al. Coronary stenting during rescue angioplasty after failed thrombolysis. Catheter Cardiovasc Interv 1999;47:1–5.
37. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. Circulation 1999;99:2720–2732.
38. Califf RM. Glycoprotein IIb/IIIa blockade and thrombolytics: early lessons from the SPEED and GUSTO IV trials. Am Heart J 1999;138:S12–15.

6 Primary Angioplasty in Community Hospitals without On-Site Cardiac Surgery

Thomas P. Wharton, Jr., MD
and Nancy Sinclair McNamara, RN, BSN

Contents

THE SUPERIORITY OF PRIMARY ANGIOPLASTY

It is now firmly established that primary angioplasty is superior to fibrinolytic therapy for the treatment of acute myocardial infarction (AMI) in lytic-eligible patients *(1–3)* when the procedure is performed at qualified centers. Compared with fibrinolytic therapy, primary angioplasty has been demonstrated to reduce rates of death, stroke, recurrent ischemia, and reinfarction *(1)*. In the current era

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

of newer generation stents and glycoprotein (GP) IIb/IIIa platelet inhibitors, the advantage of primary angioplasty over fibrinolytic therapy is even more clear. One recent randomized trial of 140 patients showed that the combined incidence of death, reinfarction, and stroke at 6 mo was almost three times greater in patients treated with fibrinolytics than with coronary stenting and abciximab (8.5% vs 23.2%, $p = 0.02$; relative risk, 0.34; 95% confidence interval, 0.13–0.88) *(2)*. Recently pooled "real world" outcomes of 9906 patients with AMI in two current German registries demonstrated that primary angioplasty was independently associated with lower hospital mortality compared with fibrinolytic therapy in all subgroups, whether high or low risk: 6.4% vs 11.3%, respectively (odds ratio [OR] 0.54, 95% confidence interval [CI] 0.43–0.67) *(3)*. Other reports indicate that patients with low-risk AMI treated with primary angioplasty have very low rates of in-hospital mortality (<1%) *(4,5)*, fewer reinfarctions, and decreased hospital costs as a result of safe early discharge (3–4 d) and avoidance of both intensive care and in-hospital exercise testing *(4)*. The benefits of primary angioplasty over fibrinolytic therapy have been shown to be sustained over 5 yr *(6)*. Moreover, early knowledge of the coronary anatomy gained from the initial angiogram enables greater diagnostic precision and more informed therapeutic decisions and enhances risk stratification *(4)*.

Patients Ineligible for Fibrinolytic Therapy

Primary angioplasty is potentially applicable to a much broader spectrum of patients with AMI than is fibrinolytic therapy. Only one in three patients with AMI is eligible to receive fibrinolytics, and only one in four is actually treated *(7)*. Fibrinolytic therapy is not appropriate for patients without ST elevation (another high-risk group), patients who present late, patients with an increased risk of bleeding, patients in cardiogenic shock, and those with prior bypass surgery *(8)*. Furthermore, fibrinolytic therapy fails in a significant percentage of patients *(9)*.

Groups in whom fibrinolytic therapy is inappropriate may have better outcomes with primary angioplasty. In one large registry in Germany, the Maximal Individual Therapy in Acute Myocardial Infarction Study Group (MITRA), there was an 11-fold reduction in mortality in patients ineligible for fibrinolytics due to bleeding risk who were treated with primary angioplasty compared with conservative therapy (Table 1) *(10)*. In this same registry, there was a twofold reduction in mortality associated with primary angioplasty compared with fibrinolytics in patients who are normally excluded from randomized trials: those with nondiagnostic ECG findings, left bundle branch block, late presentation (>12 h), or pre-hospital delay *(11)*. There was a similar reduction in the combined endpoints of death, reinfarction, stroke, advanced heart failure, and post-infarction angina for primary angioplasty in this population (Table 1).

In the Myocardial Infarction Triage and Intervention (MITI) Registry, patients with non-ST elevation AMI and thus not appropriate candidates for fibrinolytic

Table 1
Outcomes of Primary Angioplasty in Patients Inappropriate or Ineligible for Fibrinolytic Therapy (MITRA Registry) *(10,11)*

Patients with high bleeding risk *(19)* ($n = 335$)

	Primary angioplasty	*Conservative care*	p *Value*	*Odds ratio*
Mortality	2.2%	24.7%	0.001	0.46

Patients considered ineligible for randomized studies[a] *(11)* ($n = 737$)

	Primary angioplasty	*Fibrinolytic therapy*	*Odds ratio*	*95% CI*
Mortality	8.2%	16.4%	0.46	0.25–0.84
Combined endpoint[b]	24.1%	42.3%	0.43	0.29–0.64

[a]Non-diagnostic ECG, left bundle branch block, late presentation >12 h or unknown prehospital delay.
[b]Death, reinfarction, stroke, advanced heart failure, or post-infarction angina.

therapy had improved mortality rates when treated at hospitals that favored an early invasive vs a conservative treatment strategy *(12)*. The 30-d mortality rate was 5.5% at hospitals with an invasive strategy vs 9.5% at hospitals with a conservative strategy ($p = 0.026$); the 4-yr mortality was 20% vs 37%, respectively ($p < 0.001$).

A recent report of outcomes of 7864 Medicare patients demonstrated that fibrinolytic therapy in patients >75 yr old, especially in women, conferred a survival disadvantage compared with no reperfusion therapy *(13)*. This population represents almost one third of patients with AMI *(14)*. Nevertheless, fibrinolytic therapy in this age group is supported as a Class IIa indication by the 1999 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Treatment of AMI *(36)*. The editorial that accompanied this study *(14)* noted that "a recent observational study of a cohort that overlaps with the population studied by Thiemann et al. has shown a marked reduction in 30-day mortality for primary angioplasty relative to fibrinolytic therapy in the elderly. However, primary angioplasty is not available at the hospitals where most elderly patients present with AMI" *(14,15)*.

THE NEED FOR MORE WIDESPREAD APPLICATION OF PRIMARY ANGIOPLASTY

Fibrinolytic therapy is not applicable to a large proportion of patients with AMI. These patients are at higher risk of death than those eligible to receive fibrinolytics *(16–18)*. Furthermore, fibrinolytic therapy fails to produce brisk

Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow *(19)* in at least 30%–40% of patients, placing them at higher risk. These groups of high-risk patients need a reperfusion alternative to "morphine and bed rest."

There is thus a need to implement programs at a greater number of hospitals to provide primary angioplasty for this majority of fibrinolytic-ineligible patients. This is certainly feasible at hospitals that already have catheterization laboratories and experienced interventionalists. Patients with high-risk AMI should benefit through lowered rates of death, stroke, and reinfarction *(1,20)*; low-risk patients should benefit through decreased lengths of stay, lowered reinfarction rates, and decreased hospital costs, while sustaining negligible risks of death or stroke *(4,5)*.

In addition, the number of patients with heart disease is increasing with the aging of the "baby boomers" *(21)*, increasing further the need for primary angioplasty. In addition, angioplasty becomes applicable to more types of patients, and this need should grow faster than the need for bypass surgery. Uncoupling angioplasty from bypass surgery therefore will enable increased access to angioplasty for the growing number of patients who will need it in the future, while at the same time reducing the pressure to build new low-volume surgical programs to support these angioplasty programs.

Primary Angioplasty as First-Line Therapy for AMI

Hospitals that establish primary angioplasty programs should perform the procedure as routine first-line care for all patients presenting with AMI. This should maximize institutional and operator volumes, streamline care paths, improve door-to-balloon times, and optimize outcomes. A higher institutional volume of primary angioplasty (but not necessarily elective angioplasty *[22]*) correlates with improved mortality rates. In the Second National Registry of Myocardial Infarction (NRMI-2), the odds-adjusted mortality of patients with AMI who received primary angioplasty was 33% lower at institutions that performed more than 36 primary angioplasty procedures per year than at institutions that performed fewer than 12 per year *(23,24)*. Furthermore, the most recent guidelines from the United Kingdom recommend that hospitals that provide angioplasty for acute coronary syndromes provide 24-h coverage 7 d a week *(25)*.

Cardiogenic Shock

Offering primary angioplasty at the point of initial presentation is especially important for patients with cardiogenic shock. In the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial, revascularization in <6 h conferred the best survival advantage of all descriptors examined *(26)*. Ideally, patients presenting with AMI and cardiogenic shock should be treated with emergency insertion of an intra-aortic balloon pump (IABP) and immediate mechanical revascularization at the point of first contact

(27–33). In this scenario, the on-site availability of coronary bypass surgery is largely moot, as these patients are already critically ill *(34,35)*. Immediate intervention with IABP support at initial presentation may improve the effectiveness of the initial treatment of cardiogenic shock in salvaging viable myocardium and preserving other organ systems; it can also avoid the delays and risks that are associated with the inter-hospital transfer of unsupported patients in shock. Furthermore, if shock develops a median of 6.2 h after onset of infarction, as seen in the SHOCK trial, emergency revascularization in <6 h might prevent the onset of shock. The 1999 updated ACC/AHA guidelines for management of AMI *(36)* now include cardiogenic shock as a Class I indication for primary percutaneous transluminal coronary angioplasty (PTCA), although the guidelines are not completely specific about the requirement for on-site cardiac surgery in this circumstance.

THE POTENTIAL FOR MORE WIDESPREAD APPLICATION OF PRIMARY ANGIOPLASTY

Only 39% of hospitals in the National Registry of Myocardial Infarction provide cardiac surgery *(37)*. Most patients with AMI present to community hospitals that do not provide this service *(38)*, yet well over 800 of these hospitals have diagnostic cardiac catheterization laboratories *(39)*. It is not unusual for these diagnostic laboratories to be staffed by experienced interventionalists who also routinely perform interventions at surgical centers. Such laboratories have the potential to establish effective primary angioplasty programs if they can provide experienced personnel, optimal interventional and imaging equipment, and formal arrangements for expeditious transfer to a surgical center. Many investigators have convincingly demonstrated that such hospitals can establish safe and effective primary angioplasty programs with excellent outcomes that are not compromised by the lack of on-site cardiac surgery *(35,40–51)*.

REGULATORY LIMITATIONS OF PRIMARY ANGIOPLASTY

State Regulations

Despite the growing body of evidence that supports the safety and feasibility of primary angioplasty at hospitals without on-site cardiac surgery, many states have regulations that prohibit the performance of all angioplasty at all hospitals that do not have cardiac surgery programs. These strict statutes were, for the most part, established in the 1980s, when the risk of elective angioplasty causing a surgical emergency (abrupt vessel closure) was around 5%. These statutes were written before the advent of primary angioplasty for totally occluded arteries in patients with AMI, and well before the advent of stents and GP IIb/IIIa platelet inhibitors, which have decreased the risk of abrupt vessel closure and improved outcomes substantially *(52–59)*.

Interventionalists are thus often prohibited by statute from administering potentially life-saving therapy solely because open-heart surgery backup is not physically on site. Yet open-heart surgery may not be a consideration in some critically ill patients with AMI. It is difficult to identify any other circumstances in the medical profession in which a qualified physician is prevented by statute from doing what is necessary in an emergency to save the life of a critically ill patient when other therapies fail or would be futile. Cardiologists are mounting efforts in several states to change such regulations.

ACC/AHA Guidelines

The 1996 ACC/AHA guidelines for management of AMI *(60)* did not take the statutory position maintained by some states. These guidelines advised that "primary PTCA should be performed in centers with cardiac surgical capability or in those institutions with a proven plan for rapid access to cardiac surgery in a nearby facility. The guidelines stated that operators must have interventional volumes of >75 cases per year and hospitals must have interventional volumes of >200 cases per year.

The newly revised ACC/AHA guidelines for percutaneous coronary intervention *(61)* now recommend primary angioplasty at hospitals without on-site cardiac surgical backup with a "Class IIb" indication (usefulness/efficacy less well established by evidence/opinion), provided that at least 36 primary angioplasty procedures per year are performed at such hospitals, that the interventionalist performs at least 75 procedures per year, that procedures are performed within 90 ± 30 min of arrival, and that there is a proven plan for rapid access to a cardiac surgical center. These guidelines also include tables listing further operator, institutional, and patient selection criteria for the performance of angioplasty and emergency coronary bypass surgery at such hospitals, as originally proposed by the authors of this chapter *(35)* (Tables 2 and 3).

New Guidelines from Abroad

The British Cardiac Society and British Cardiovascular Intervention Society together recently issued new guidelines for coronary angioplasty in the United Kingdom *(25)*. These guidelines now allow both emergency and elective angioplasty to be performed at hospitals without on-site cardiac surgery, provided that they otherwise meet standards of care and have systems in place to enable patients to be on cardiopulmonary bypass within 90 min of calling the cardiac surgeon. Regulations in the Netherlands and in Australia have been modified to allow angioplasty programs at hospitals without cardiac surgery. Recently the Cardiac Care Network of Ontario, Canada, recommended to the Ontario Ministry of Health that pilot programs be set up in Ontario to perform coronary angioplasty at hospitals without on-site surgical backup *(62)*.

Table 2
Criteria for the Performance of Primary Angioplasty at Hospitals without On-Site Cardiac Surgery

1. The operators must be experienced interventionalists who regularly perform elective intervention at a surgical center (≥75 cases/yr). The institution must perform a minimum of 36 primary PCI procedures per year.
2. The nursing and technical catheterization laboratory staff must be experienced in handling acutely ill patients and comfortable with interventional equipment. They must have acquired experience in dedicated interventional laboratories at a surgical center. They participate in a 24-h, 365-d call schedule.
3. The catheterization laboratory itself must be well equipped, with optimal imaging systems, resuscitative equipment, intra-aortic balloon pump (IABP) support, and must be well stocked with a broad array of interventional equipment.
4. The cardiac care unit nurses must be adept in hemodynamic monitoring and IABP management.
5. The hospital administration must fully support the program and enable the fulfillment of the above institutional requirements.
6. There must be formalized written protocols in place for immediate (within 1 h) and efficient transfer of patients to the nearest cardiac surgical facility which are reviewed/tested on a regular (quarterly) basis.
7. Primary intervention must be performed routinely as the treatment of choice around the clock for a large proportion of patients with AMI, to ensure streamlined care paths and increased case volumes.
8. Case selection for the performance of primary angioplasty must be rigorous. Criteria for the types of lesions appropriate for primary angioplasty and for selection for transfer for emergent aortocoronary bypass surgery are shown in Table 3.
9. There must be an ongoing program of outcomes analysis and formalized periodic case review.
10. Institutions should participate in a 3- to 6-mo period of implementation during which time development of a formalized primary PCI program is instituted that includes establishing standards, training staff, detailed logistic development, and creation of a quality assessment and error management system.

AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; PCI, percutaneous coronary intervention.

Adapted with permission from Wharton TP Jr, McNamara NS, Fedele FA, Jacobs MI, Gladstone AR, Funk EJ. Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. J Am Coll Cardiol 1999;33:1257–1265.

RATIONALE FOR PRIMARY ANGIOPLASTY AT HOSPITALS WITHOUT ON-SITE CARDIAC SURGERY

The superiority of primary angioplasty over fibrinolytic therapy for patients with AMI, and the need for the more widespread availability of this procedure, demand that the requirement for on-site cardiac surgical support be readdressed. There are many theoretical reasons why this surgical requirement is no longer essential.

Table 3
Patient Selection for Angioplasty and Emergency Aortocoronary Bypass at Hospitals without On-Site Cardiac Surgery

Avoid intervention in hemodynamically stable patients with:
- Significant (≥60%) stenosis of an unprotected left main (LM) coronary artery upstream from an acute occlusion in the left coronary system that might be disrupted by the angioplasty catheter
- Extremely long or angulated infarct-related lesions with TIMI grade 3 flow
- Infarct-related lesions with TIMI grade 3 flow in stable patients with three-vessel disease *(83,84)*
- Infarct-related lesions of small or secondary vessels
- Lesions in other than the infarct artery

Transfer for emergency aortocoronary bypass surgery patients with:
- High-grade residual left main or multivessel coronary disease and clinical or hemodynamic instability
  – After angioplasty of occluded vessels
  – Preferably with intraaortic balloon pump support

Reproduced with permission from Wharton TP Jr, McNamara NS, Fedele FA, Jacobs MI, Gladstone AR, Funk EJ. Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. J Am Coll Cardiol 1999;33: 1257–1265.

First, the strategy of primary angioplasty is not the same as that of elective angioplasty. In elective angioplasty, the need for emergency surgery stems from the risk of causing abrupt *closure* of an *open* vessel. Primary angioplasty in acute myocardial infarction is used to *open closed* vessels, and should succeed in achieving TIMI grade 3 flow in well over 90% of patients.

Second, the need for emergency surgery as a result of mishap in the catheterization laboratory is very rare today in light of the major technological and pharmacological advances related to percutaneous coronary intervention. The advent of newer generation stents and glycoprotein IIb/IIIa platelet inhibitors has lowered the risk of abrupt vessel (re)closure from 2% to 5%, as reported in the 1980s, to approx 0.4% *(52,53,63–65)*. In an analysis of the Primary Angioplasty in Myocardial Infarction (PAMI) trials, emergency surgery for failed primary angioplasty was required in only 0.4% of patients *(64)*. The authors of this study concluded: "In concert with the declining incidence of emergent CABG with the use of stents, these data suggest that skilled physicians and personnel may safely perform primary angioplasty at select hospitals without operative facilities (allowing patients to benefit from enhanced survival free from reinfarction and stroke with primary angioplasty compared with fibrinolytic therapy) as long as steps are in place to facilitate surgical revascularization expeditiously by transfer to a nearby tertiary center when necessary."

Third, the current practice of surgical "standby" for interventional procedures at surgical hospitals has relaxed considerably. Instead of having an operating room open and available, with surgeon and staff in waiting (which is costly and wasteful for a procedure that will be needed for only 0.4% of coronary interventions), the operating rooms at busy surgical centers are in use most of the time. Thus the patient who suffers the rare cath lab accident "in house" may face a waiting time of 1–3 h for an operating room to become available *(63,66–68)*. This delay might not be any longer for a patient who is transferred from an outlying hospital, with the operating room and team being readied while the patient is en route, if appropriate protocols and transfer agreements are in place.

In one study from Ireland, the delay to revascularization after PTCA complication was 270 min, and the delay was the same whether the angioplasty complication occurred at the facility without surgery or the facility where the surgery was performed *(67)*. In this study, the length of the delay was dependent primarily on when the next operating room became available. The authors stated, "The absence of immediate surgical help did not influence the outcome in any patient." Another similar study from the UK concluded: "Delays in operating on stable patients in centers which operate a 'next available theatre' backup policy may not differ from some units performing angioplasty with offsite cover for angioplasty complications" *(68)*.

Advantages of Smaller Hospitals

Smaller community hospitals have certain advantages over larger inner city institutions for performing primary angioplasty, which may enable them to perform primary PTCA faster than larger centers *(69)*. The catheterization laboratory can be made available more readily, unlike in larger and busier centers. Members of the cath team usually live close by, with decreased travel times that can minimize the time-to-procedure in off-hours cases. In addition, the line of communication from the emergency department physician to the interventional cardiologist may be more direct than at a teaching center.

Reperfusion Alternatives for High-Risk or Fibrinolytic-Ineligible Patients at Hospitals without On-Site Coronary Intervention

It is often recommended that, instead of setting up a primary angioplasty program, community hospitals (even those with cath labs) transfer patients with AMI who are at high risk or with fibrinolytic contraindications to nearby surgical centers. One recent European study, Primary Angioplasty in Patients Transferred from General Community Hospitals to Specialized PTCA Units With or Without Emergency Thrombolysis (PRAGUE), compared fibrinolytic therapy with or without immediate transfer for angioplasty vs immediate transfer without

fibrinolytic therapy in 300 patients *(70)*. In this small but provocative study, the combined occurrence of death, reinfarction, and stroke at 30 d was significantly less frequent in patients transferred for angioplasty without fibrinolytic therapy. In the United States, however, the routine emergency transfer of patients early in the throes of an acute myocardial infarction from a community hospital emergency department (ED) to a tertiary center is not generally considered to be safe or effective, and it is not commonly practiced, even for high-risk fibrinolytic-ineligible patients.

Although immediate transfer of patients with AMI for angioplasty may yield more favorable outcomes than fibrinolytic therapy with or without transfer, immediate angioplasty at the point of first contact obviates the risk and delay of transfer. In the NRMI-2 registry, patients transferred for angioplasty underwent the procedure a mean of 2.3 h later than patients receiving angioplasty at the point of first presentation. Transferred patients had a significantly higher mortality rate (7.7% vs 5.0%, $p = 0.0001$) *(71)*. A 15- to 45-min travel time to a hospital with surgical backup can easily translate into a delay of 2 h or more, considering the time that is required to call the receiving hospital and enlist the cooperation of the interventional cardiologists, to call the ambulance and transfer team, to transport the patient (sometimes through heavy traffic or in the middle of a snowstorm), and to move the patient from the receiving ED into the cath lab *(72)*. A further complicating factor is that many cath labs at tertiary centers do not themselves offer primary angioplasty as first-line therapy for patients with AMI, and thus may be less than willing to routinely accept such critically ill patients in transfer.

Offering primary angioplasty at the point of first contact can provide the most rapid reperfusion alternative for the two-thirds of patients with AMI who are not eligible for fibrinolytics and for the high proportion who fail to reperfuse with fibrinolytic therapy.

Heart Attack Intervention Centers

The establishment of "Heart Attack Intervention Centers" with 24-h, 365-d emergency interventional capability, to which all patients with suspected AMI would be triaged by ambulance for primary angioplasty (analogous to trauma centers), is a clear potential solution *(73)*. The Prehospital Infarction Angioplasty Triage (PHIAT) trial in Europe demonstrated very favorable results in 213 patients with large AMI as identified by prehospital electrocardiogram who underwent triage directly to a waiting angioplasty center *(74)*. Routine pre-hospital triage of AMI patients within a reasonable distance would, however, require a major change in practice standards in the United States. Furthermore, if universal triage of all such patients were limited to current interventional centers, this could quickly flood the capability of the existing tertiary hospitals—even if all of them provided primary angioplasty as first-line treatment. In addition, many patients

with AMI do not arrive in the ER by ambulance. (Of our last 565 primary PCI patients at Exeter Hospital, NH, 235 [42%] arrived by automobile.)

EVIDENCE SUPPORTING PRIMARY ANGIOPLASTY AT HOSPITALS WITHOUT ON-SITE CARDIAC SURGERY

As a larger proportion of patients with AMI are not candidates for fibrinolytic therapy, and as most do not present to hospitals with cardiac surgery *(38)*, it is imperative to study how to provide primary angioplasty safely and effectively to more of them in broader geographical locations.

Elective angioplasty at hospitals without on-site surgical backup is quite common in Europe, with outcomes that equal those of surgical hospitals *(63,67,75–83)*. A large registry of more than 50,000 patients undergoing elective stenting in France recently reported no differences in the outcomes of centers with and without cardiac surgery, with fewer than 0.4% of patients requiring emergency surgery: 0.44% of patients at surgical hospitals and 0.25% of patients at nonsurgical hospitals were sent for emergency bypass *(63)*. Two-thirds of the hospitals in this registry did not have on-site surgical facilities. The mortality rate at the surgical hospitals was 0.7%; at nonsurgical hospitals it was 0.4%.

Seven other registries of elective angioplasty without on-site surgery, from Canada, the United Kingdom, Germany, and Italy, reported outcomes of more than 70,000 patients undergoing nonemergency angioplasty at hospitals without in-house surgery *(67,75–83)*. The overall mortality, pooling data from all of these series, was 0.48%. Thus outside of the United States, the world's literature reports outstanding outcomes in 120,000 patients receiving elective PTCA in hospitals without bypass surgery.

Many investigators have convincingly demonstrated that primary angioplasty can be performed safely and effectively at hospitals without on-site cardiac surgery *(35,40–51)*. Most of the procedures reported by these investigators were performed before stents and IIb/IIIa platelet inhibitors were commonly used in patients with AMI. These agents further improve the safety and efficacy of coronary intervention *(52–59)*.

MITI Registry

Weaver and co-workers compared the outcomes of 470 patients with AMI treated with primary angioplasty in hospitals without on-site cardiac surgery with those of 592 patients with AMI in hospitals with surgical backup, using data from the MITI Registry *(41)*. The median times-to-treatment (77 min vs 80 min), procedural success rates (88% vs 88%), in-hospital mortality (7% vs 7%), and 1-yr mortality (11% vs 11%) were not different for the two types of hospitals. Bypass surgery was performed within 24 h of admission on 2.6% of patients from hospitals without on-site surgery.

Norfolk, Virginia, Registry

Brush and co-workers performed primary angioplasty on 85 of 102 patients (83%) with AMI or refractory unstable angina at a hospital in the United States without cardiac surgery *(45)*. TIMI 2 or 3 flow was obtained in 85%. The overall in-hospital mortality was 8.8%, with a mortality rate of 32% for patients in shock and 4.2% for patients not in shock. Urgent bypass surgery was performed in 9.8% because of critical anatomy, with none for an angioplasty mishap.

Christchurch, New Zealand, Registry

Smyth and co-workers performed primary angioplasty on 71 patients with AMI at a hospital in New Zealand that was 220 miles from the nearest cardiac surgery center *(47)*. The mean time from decision to balloon was 72 min. TIMI 3 flow was obtained in 89%. The overall in-hospital mortality rate was 9.8%, with mortality of 60% for patients in shock and 1.7% for patients not in shock. Two patients (2.8%) were transferred for urgent bypass surgery: one whose AMI was caused by dissection of the left anterior descending artery at elective angiography and one for three-vessel disease after emergency recanalization of the right coronary with residual dissection.

Exeter and Portsmouth, New Hampshire, Registry

In the authors' experience at two community hospitals without cardiac surgery, three experienced operators performed 506 consecutive immediate coronary angiograms with primary angioplasty when appropriate in patients with AMI, using the criteria shown in Tables 2 and 3 *(35)*. This is the largest single-group experience of primary angioplasty in hospitals without on-site cardiac surgery reported to date.

The study population included patients with >30 min of ischemic pain not controlled by conventional medications (aspirin, nitroglycerin, β-blockers, and heparin, but not fibrinolytic agents) and/or an ECG demonstrating ≥2.0 mV of ST-segment elevation in two or more contiguous leads. There was no time cutoff if the clinical impression suggested ongoing myocardial necrosis (ongoing chest pain and ST deviation with some preservation of R waves in two or more infarct leads).

In this series, more than two-thirds of the patients had clinical high-risk predictors (Killip Class 3 or 4, age ≥75 yr, anterior AMI, out-of-hospital ventricular fibrillation) and/or angiographic high-risk predictors (left main or three-vessel disease or ejection fraction <45%). Sixty-one percent were considered fibrinolytic-ineligible. The median time from emergency department presentation to first angiogram was 94 min. Intervention was performed in 66% of patients; the angioplasty success rate was 94.3% (TIMI grade 3 flow and ≤50% residual stenosis). Most of the procedures were performed before stents became commonly used in AMI; stents and IIb/IIIa platelet inhibitors were used in only 3%

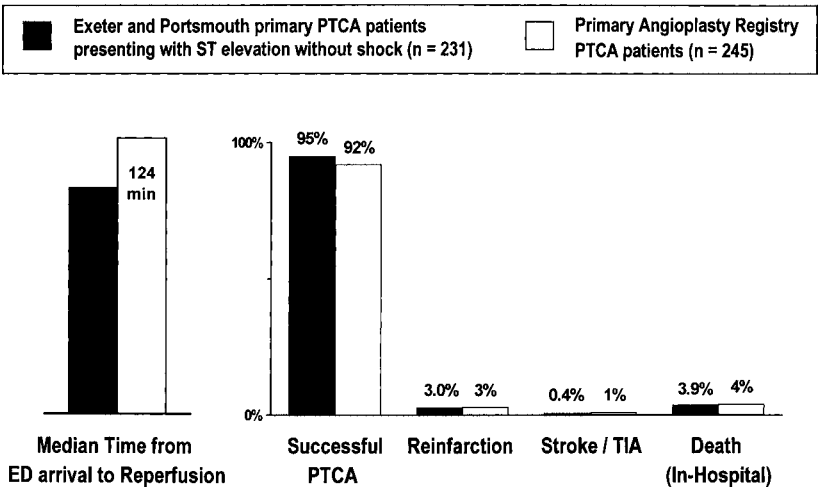


Fig. 1. Comparison of the outcomes of primary angioplasty without on-site surgery in the 231 patients in the Exeter and Portsmouth series who had acute myocardial infarction with ST-segment elevation but without cardiogenic shock *(35)* to a similar population of 245 patients undergoing primary percutaneous transluminal coronary angioplasty (PTCA) in the Primary Angioplasty Registry *(83)*, which required ST-segment elevation and excluded patients with shock. The median times from emergency department (ED) arrival to reperfusion and the rates of PTCA success, reinfarction, stroke, or transient ischemic attack (TIA), and in-hospital mortality were similar in the two groups. Filled columns: Exeter and Portsmouth primary angioplasty patients presenting with presenting with ST elevation without shock (n = 231). Open columns: Primary Angioplasty Registry patients (n = 245). (Reprinted from ref. *35* with permission of the publisher.)

of procedures. In this pre-stent era, angioplasty was deferred until after transfer to a surgical center for patients who had TIMI grade 3 flow on first angiogram and were stable and pain free.

The overall in-hospital mortality rate was 5.3%. In 56 patients who presented with cardiogenic shock the mortality rate was 23.2%, and in patients without shock it was 3.0%. Stroke occurred in two patients, and there was no intracerebral bleeding. Outcomes for patients who presented at night or on weekends were similar to those who presented during working hours, despite a somewhat longer "door-to-balloon" time due to the callback status of the cath team *(84)*. No patient died or needed emergency aortocoronary bypass surgery because of new myocardial jeopardy caused by a complication of the cardiac catheterization or angioplasty procedure. The low mortality rate in patients having primary angioplasty was sustained 6 mo after discharge.

The rates of successful angioplasty, reinfarction, stroke, and death in this series compare favorably to the outcomes of large, high-volume surgical centers reported in the literature (Fig. 1) *(4,5,20,85–87)*. Moreover, the initial angiogram

provided early knowledge of coronary anatomy; this enabled informed therapeutic decisions, including early selection of highest risk patients for aortocoronary bypass surgery and early recognition of a subgroup of patients who had patent vessels after aspirin and heparin and thus could be managed more conservatively.

The Primary Angioplasty for Myocardial Infarction No Surgery On Site (PAMI—No SOS!) Study

The PAMI—No SOS! study represents the first prospective multicenter registry of primary angioplasty at nonsurgical hospitals. In this registry, experienced interventional cardiologists at 19 community hospitals without cardiac surgery prospectively enrolled 500 patients with high-risk AMI without shock. Six-month follow-up results were recently reported, including core laboratory cine analysis, in 492 of the 500 patients *(48)*. Angioplasty was performed in 88%. The outcomes of this registry, which are still being analyzed, demonstrated outstanding times to reperfusion, rates of angioplasty success and TIMI grade 3 flow (assessed by core laboratory), and in-hospital and 6-mo combined endpoints of mortality, stroke, and reinfarction. The outcomes in patients presenting off-hours were similar to those presenting during regular hours *(88)*. Emergency cardiac surgery related to catheterization laboratory mishap was needed in one patient in whom a vein graft was perforated by deployment of a stent. The graft was recanalized, and the patient was transferred for uneventful surgical correction after pericardiocentesis in the cath lab. The in-hospital death rate in the 492 high-risk patients was 2.7%. The outcomes of this exclusively high-risk population were as favorable as the outcomes of similar high-risk patient groups in other PAMI trials at tertiary care centers *(89)*.

Cuneo, Italy, Registry

Ribichini and co-workers performed primary angioplasty on a 24-h basis in 92% of 310 patients with AMI at a hospital in Italy without cardiac surgery *(49)*. Of these, 19.4% had failed to reperfuse with antecedent fibrinolytic therapy. The mean door-to-balloon time was 56 ± 17 min. TIMI-3 flow was obtained in 90%. The overall in-hospital mortality rate was 8.5%; for patients in shock it was 32% and 4.9% for patients not in shock. Urgent bypass surgery was performed in 2.8% because of critical coronary anatomy; no patient needed surgery for procedure-related complications. Reinfarction occurred in 4.9% and stroke in 0.7%.

Overall Mortality and Incidence of Complications Requiring Emergency Surgery

In the combined experience of these six registries, which included a total of 1679 primary angioplasty procedures, the overall mortality was 6.1%. In five of the registries (excluding MITI), which include 1208 primary angioplasty proce-

dures, the overall mortality was 6.4%. Mortality in the 1102 of these patients who did not have cardiogenic shock was 3.7%. Only 2 patients out of the 1209 patients about whom data are available (0.17%) required emergency bypass surgery because of new myocardial jeopardy caused by the angioplasty procedure. Most recently, the Cardiovascular Patient Outcomes Research Trial (C-PORT) randomized patients with AMI to primary angioplasty vs fibrinolytic therapy at hospitals without on-site cardiac surgery *(51)*. This 453-patient trial, the second largest of all prospective randomized trials to date of primary angioplasty vs fibrinolytic therapy demonstrated a 42% reduction in the combined rate of death, reinfarction, and stroke at 6 mo for angioplasty ($p = 0.04$) at nonsurgical hospitals performing more than one procedure per month, with no significant difference at lower volume centers. Patient groups that particularly benefited in this trial were women, those with diabetes mellitus, and the elderly. No patient in this trial required emergency surgery for an angioplasty mishap. The investigators concluded that the need for in-house cardiac surgery backup is not supported by the results of the C-PORT study.

These registries at hospitals without on-site cardiac surgery demonstrate that primary angioplasty can be provided safely and effectively in a high-risk population, with outcomes similar to those reported from high-volume surgical centers *(4,5,20,85–87)*.

ARGUMENTS AGAINST THE PERFORMANCE OF PRIMARY ANGIOPLASTY AT HOSPITALS WITHOUT ON-SITE CARDIAC SURGERY

With the emerging recognition that the on-site availability of cardiac surgery in case of cath lab mishap is no longer essential to the establishment of a safe and effective primary angioplasty program, other arguments are being made to support continued restriction of emergency intervention to large tertiary surgical centers. Summarized below are the major arguments being advanced (italics), with responses (plain text).

The requirement for on-site cardiac surgery should be maintained as a surrogate for experienced interventionalists, an experienced catheterization team, and a well-equipped laboratory with state-of-the-art digital imaging equipment.

Clearly, guidelines should be rewritten to specifically define these latter standards; use of a surrogate does not preclude the better approach of an actual standard. Guidelines should not continue to demand on-site cardiac surgery merely because it is a "surrogate" for more pertinent standards, such as those shown in Tables 2 and 3.

The outstanding outcomes reported by the PAMI and other randomized studies represent the work of elite groups of highly experienced and highly skilled

interventionalists. Their superb results may not be able to be reproduced by the average hospital or operator.

The results of the PAMI and other high-volume tertiary centers have been reproduced in large numbers at many hospitals without on-site cardiac surgery, including the 19 PAMI-No SOS! community hospitals *(35,40–51)*.

The Second National Registry of Myocardial Infarction (NRMI-2) (90) *and the MITI Registry* (91) *indicate that "real world" community experience does not reproduce the results of the randomized trials, such that mortality is similar between patients receiving thrombolytic therapy and primary angioplasty. Thus there is little impetus to establish new primary angioplasty programs.*

Observational results from national registries are flawed in that they can never be fully risk-adjusted: low-risk patients who are doing well clinically may be more likely to receive fibrinolytic therapy; higher-risk patients or those experiencing clinical deterioration or bleeding risks may be more likely to be referred for intervention. The NRMI-1 registry, in particular, may have included very few hospitals that use primary angioplasty rather than fibrinolytic therapy as routine first-line therapy for acute myocardial infarction.

Counter to the findings of the NRMI-2 and MITI registries is a recent analysis of pooled data on 9906 patients from two registries, MITRA and the Myocardial Infarction Registry (MIR), which reflect current clinical practice in Germany *(3)*. This analysis demonstrated that primary angioplasty in fibrinolytic-eligible patients was independently associated with lower hospital mortality compared with fibrinolytic therapy: 6.4% vs 11.3%, respectively (OR 0.54, 95% CI 0.43–0.67).

Data from the NRMI-2 registry (37) *indicate that patients with AMI admitted to hospitals without cath labs do just as well as those admitted to tertiary centers with interventional programs.*

In this report, only 31% of patients with AMI were treated with primary angioplasty even at larger tertiary centers. The value of this report is to point out the current low use of primary angioplasty even in centers capable of offering it. No conclusions can be drawn from this study about the relative value of interventional vs fibrinolytic therapy. It would be interesting to examine the outcomes of the subset of hospitals that provide primary angioplasty exclusively as first-line treatment of choice for acute myocardial infarction, as NRMI data also indicate that hospitals performing more than 36 *primary* angioplasty procedures per year have lower mortality rates than hospitals that perform fewer procedures *(23,24)*. In addition, the MITI registry found that patients with non-ST elevation AMI have improved mortality rates when treated at hospitals that favored an early invasive treatment strategy vs a conservative treatment strategy *(12)*.

Newer advances in pharmacotherapy with combination reduced-dose fibrinolytic and platelet GP IIb/IIIa blockade may result in reperfusion rates similar to those of primary angioplasty, rendering the whole question of extending the availability of primary angioplasty obsolete.

It is debatable whether newer pharmacology is likely to render primary angioplasty "obsolete." Two-thirds of patients with AMI are not candidates for fibrinolytic therapy, either because they have bleeding risks or shock, present late, or do not have diagnostic electrocardiograms; these patients are generally at higher risk than fibrinolytic-eligible patients, and they need a reperfusion alternative *(16–18)*. The citation of a 70% reperfusion rate at 60 min for patients treated with combination fibrinolytic and platelet GP IIb/IIIa inhibitor therapy—a reperfusion rate still inferior to angioplasty—is based on very small numbers of patients in two pilot studies *(92,93)* and thus is not yet thoroughly "evidence based."

This 70% reperfusion rate may represent a "ceiling" no matter how effective the fibrinolytic agent. A recent report, using aspiration thrombectomy in patients with AMI, found no thrombosis in 30% of these patients, a percentage that is strikingly similar to the rates of failed reperfusion reported in fibrinolytic studies *(94)*. Many acute coronary occlusions may not be due to thrombosis but rather to intramural plaque hemorrhage, spontaneous intimal dissections, or occlusion due to plaque rupture, with associated severe spasm *(94,95)*. Thus the quest for better fibrinolytic and antiplatelet recipes may be doomed to failure. The authors of this provocative study concluded, "Intracoronary thrombus contributes little to the pathogenesis of the average AMI, and therefore mechanical approaches may. . . maximize reperfusion therapies. . ." *(94)*.

Fibrinolytic therapy can be administered with less time delay than primary angioplasty, so community hospitals should concentrate their efforts on decreasing "door-to-needle" times, rather than setting up primary angioplasty programs.

The outcomes of primary angioplasty are better than those of fibrinolytic therapy *(1)* and are not nearly so time dependent *(23,95–99)*. If the average "door-to-needle" time is as long as 45 min *(9)* and the average "needle-to-reperfusion" time is 60–90 min *(100)*, then the average time-to-reperfusion for those fibrinolytic-treated patients who do achieve TIMI grade 3 flow *(9)* is very similar to the time-delay for on-site primary angioplasty. In fact, normal basal coronary flow rates may be reestablished faster with primary angioplasty than with fibrinolytics in coronary arteries that are successfully reperfused *(101)*. The decreased effect of door-to-treatment times on primary angioplasty outcomes, however, is no reason not to strive to achieve rapid reperfusion: in the NRMI-2 registry, a door-to-balloon time of >2 h was associated with a 41%–62% increase in mortality compared with shorter time intervals *(23)*.

The needed expansion of the availability of primary angioplasty to more patients with AMI should be accomplished by instituting programs of pre-hospital ambulance triage and facilitated emergency transfer of such patients to tertiary centers rather than by opening more primary angioplasty programs at hospitals without cardiac surgery.

Pre-hospital ambulance triage *(74)* and facilitated emergency transfer *(70)* of patients with AMI for primary angioplasty, especially those at higher risk, are necessary but not sufficient *(73)* to extend the availability of optimal therapy for AMI to patients who present to hospitals without onsite cardiac surgery, who compose the majority of patients with AMI *(38)*. Universal triage of all such patients to current interventional centers would require major policy changes and could quickly flood the capability of the existing tertiary hospitals—even if all of them provided primary angioplasty as first-line treatment. In addition, the question is moot in regions that are geographically distant from tertiary centers.

Thus the practice of pre-hospital ambulance triage to angioplasty centers and the establishment of more angioplasty centers at nonsurgical hospitals are *mutually interdependent* solutions to the problem of improving the delivery of primary angioplasty: more receiving angioplasty centers are needed in broader geographical locations to handle the increasing loads; the transfer of more patients to such centers will increase their procedural volumes and thus improve outcomes.

Some reports demonstrate less favorable outcomes for elective angioplasty performed at lower volume hospitals. Community hospitals without surgical programs are less likely to perform large volumes of interventional procedures.

Reports of less favorable outcomes of coronary intervention at lower volume hospitals should not be a reason to limit primary angioplasty to higher volume hospitals for multiple reasons.

1. The reported differences in mortality for elective angioplasty between the lowest and highest volume hospitals are very small. A recent ACC clinical competence statement on coronary intervention included reviews of 11 papers that related institutional interventional volume to outcomes *(102)*. Only 3 of the 11 found any relationship between institutional volume and mortality in hospitals performing more than 25–50 cases per year in the early 1990s; these differences in absolute mortality were 0.2%–0.8% *(103–105)*. Five of the 11 studies examined data on patients with AMI; none of these five found any volume-related mortality differences in hospitals performing more than 40–50 cases per year *(90,106–109)*.
2. Many lower volume hospitals perform a disproportionately larger percentage of interventions on patients with high-risk diagnoses such as acute myocardial infarction. Many of the above reports do not use risk-adjusted data, and thus may

have "disregarded robust risk factors that explain most of the variation in outcome attributed to hospital volume" *(110)*.

3. All else being equal, patients with AMI might have a very slight advantage if they were to present to higher volume instead of lower volume hospitals—if each practiced primary angioplasty routinely. But all else is not equal. Patients with AMI cannot make this choice, but must be managed starting where they present. Thus the outcomes of primary angioplasty at lower volume hospitals must be compared not to outcomes at higher volume hospitals but rather to the risk of not offering any reperfusion therapy at all to the majority of patients who are lytic-ineligible, or to the risk and delay of transfer of such patients to a willing tertiary referral center for primary angioplasty. The differences in mortality among these alternatives may be far greater than the ≤0.8% volume-related mortality difference cited above *(10,11,71)*. In the NRMI-2 registry, patients transferred for angioplasty had a significantly higher mortality rate than patients receiving angioplasty at the point of first presentation (7.7% vs 5.0%, $p = 0.0001$) *(71)*. There is as yet no "evidence-based" reason to conclude that either of these two alternatives is superior to early primary angioplasty on site. Unfortunately, randomized studies of inter-hospital transfer of patients with AMI have met with only limited success in enrolling patients *(72)*.
4. Outcomes data on low-volume hospitals may disproportionately reflect the outcomes of low-volume operators. Outcomes of experienced operators at low-volume institutions have not been examined. It is reasonable to require that primary angioplasty be performed at such hospitals only by experienced higher volume operators who also regularly perform elective angioplasty.
5. Primary angioplasty is different from elective angioplasty and requires simultaneous intensive medical care of the acutely ill AMI patient. Relatively more patients with AMI present to community hospitals than to tertiary centers. Thus the nursing and technical staff at smaller hospitals may already have thorough experience in the medical care of such patients.
6. Furthermore, smaller hospitals with only one catheterization team and few operators may gain more experience in performing primary angioplasty—on a per operator and per team basis—than larger surgical centers with many more teams and operators. Most of the nonsurgical hospitals in the PAMI-No SOS! study performed an average of 85 primary angioplasty procedures per year (data on file—Wharton), with only one cath lab and team. A hospital with several cath labs must perform correspondingly more primary angioplasty procedures for each team to gain the same experience. Many high-volume hospitals and operators perform little if any primary angioplasty, having full schedules that do not easily permit interruptions. Recall that AMI mortality improves if hospitals perform more than 36 *primary* angioplasty procedures per year *(23,24)*.
7. Available evidence from the many reported series cited above indicates that qualified but necessarily low-volume hospitals without cardiac surgery can achieve outcomes of primary angioplasty that are similar to those of high-volume surgical centers *(35,40–51)*.

8. In the ACC clinical competence statement, Hirshfield and colleagues noted that the studies of outcomes vs procedural volumes cited therein were done before the era of stents and platelet GP IIb/IIIa inhibitors, and observed, "It is likely that the availability of these treatments has reduced the expected frequency of death and emergency CABG. . . . Consequently, these data may not accurately reflect current practice. . ." *(102)*.
9. In a recent report of outcomes of 6635 patients undergoing angioplasty at hospitals in Canada, there was no significant difference in adjusted rates of repeat revascularization, recurrent MI, or death at 6 mo between hospitals doing less than 200 procedures per year and those doing more than 400 procedures per year *(111)*. Another recent report of outcomes of 353,488 patients undergoing angioplasty at hospitals in California from 1984 to 1996 *(112)* found that the improvements that low-volume hospitals have achieved were substantial and were comparable in size to the relative outcomes advantage of high-volume hospitals. In fact, the mortality of patients in the period 1993–1996 was 1.7% in hospitals performing <200 angioplasties/yr, 1.7% for 200–400 angioplasties/yr, and 1.3% for >400/yr. This difference in mortality of only 0.4% was not even risk adjusted. Furthermore, the new guidelines from the United Kingdom do not recommend a minimum institutional volume cutoff, but rather recommend close scrutiny of hospitals performing fewer than 200 procedures per year to ensure that their standards and outcomes are in accordance with good practice *(25)*.
10. The insight of Paul Teirstein on this subject is also relevant to this discussion: "The dramatically low event rate [with stents and newer antiplatelet regimens] begs the question: Is elective coronary stenting now so predictable that outcomes are no longer operator dependent?" *(113)*. Teirstein adds, "Recent data support the use of a direct mechanical approach to acute infarction. However, widespread acceptance of this technique will require increased patient access to adequate physician and institutional expertise. . . . Therefore, to achieve overall public health benefits, credentialing for these urgent procedures may necessarily be different from elective procedures" *(113)*.

CONCLUSIONS

Primary angioplasty can be performed at hospitals without on-site cardiac surgery consistently, rapidly, at all hours, with outstanding outcomes and very low complication rates. These excellent outcomes can be achieved by establishing rigorous standards for operators, staffing, equipment, and case selection, and by maintaining ongoing review and analysis of outcomes. Although primary angioplasty neither can nor should be done at every community hospital with a cardiac catheterization facility, the lack of cardiac surgery backup, *per se*, need not limit the safety or efficacy of this valuable modality in the treatment of a larger and more inclusive group of patients with acute myocardial infarction.

For reasons of safety, efficacy, and the need for broader applicability, primary angioplasty is the treatment of choice for patients with acute myocardial infarc-

tion at selected well qualified hospitals that do not provide cardiac surgery. Such hospitals should establish rigorous standards for the performance of this procedure, such as those listed in Tables 2 and 3, with intensive and ongoing case analysis, outcomes monitoring, and quality improvement.

Following the lead of our colleagues in the United Kingdom *(25)*, and based on the large published experience from many nonsurgical hospitals, guidelines and regulations in the United States are being updated to better support primary angioplasty programs at nonsurgical hospitals. It would be desirable for cardiologists in such community hospitals to play more of a role in this process of establishing new guidelines for treatment of AMI. Physicians must work with legislative bodies to change overly restrictive and outdated statutes. It is now not only possible, but in fact imperative, to offer this potentially lifesaving therapy to more patients with acute myocardial infarction in more hospitals in broader geographical locations. The current rules that demand the availability of effective emergency revascularization in the event of iatrogenic coronary occlusion should be expanded to include patients with coronary occlusion of "the much more common spontaneous variety" *(114)*.

REFERENCES

1. Weaver WD, Simes J, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous fibrinolytic therapy for acute myocardial infarction. JAMA 1997;278:2093–2098.
2. Schömig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. N Engl J Med 2000;343:385–391.
3. Zahn R, Schiele R, Schneider S, et al. Primary angioplasty versus intravenous thrombolysis in acute myocardial infarction: can we define subgroups of patients benefiting most from primary angioplasty? Results from the pooled data of the Maximal Individual Therapy In Acute Myocardial Infarction Registry and the Myocardial Infarction Registry. J Am Coll Cardiol 2001;37:1827–1835.
4. Grines CL, Marsalese DL, Brodie B, et al. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. PAMI-II Investigators. Primary Angioplasty in Myocardial Infarction. J Am Coll Cardiol 1998; 31:967–972.
5. Zijlstra F, Beukema WP, van't Hof AW, et al. Randomized comparison of primary coronary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908–912.
6. Zijlstra F, Hoorntje JC, de Boer MJ, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999;341:1413–1419.
7. Barron HV, Bowlby LJ, Breen T, et al. Use of reperfusion therapy for acute myocardial infarction in the United States: data from the National Registry of Myocardial Infarction 2. Circulation 1998;97:1150–1156
8. Grines CL, Booth DC, Nissen SE, et al. Mechanism of acute myocardial infarction in patients with prior coronary artery bypass grafting and therapeutic implications. Am J Cardiol 1990;65:1292–1296.

9. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–1622.
10. Zahn R, Schuster S, Schielel R, et al. Comparison of primary angioplasty with conservative therapy in patients with acute myocardial infarction and contraindications for thrombolytic therapy. Maximal Individual Therapy in Acute Myocardial Infarction (MITRA) Study Group. Catheter Cardiovasc Interv 1999;46:127–133.
11. Zahn R, Schiele R, Schneider S, et al. Primary dilatation versus thrombolysis in patients with acute myocardial infarct, not included in randomized studies. Results of the MITRA Study: Maximal Individual Optimized Therapy for Acute Myocardial Infarct. Z Kardiol 1999; 88:418–425.
12. Scull GS, Martin JS, Weaver WD, Every NR, for the MITI Investigators. Early angiography versus conservative treatment in patients with non-ST elevation acute myocardial infarction. J Am Coll Cardiol 2000;35:895–902.
13. Thiemann DR, Coresh J, Schulman SP, et al. Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 2000;101:2239–2246.
14. Ayanian JZ, Braunwald E. Thrombolytic therapy for patients with myocardial infarction who are older than 75 years. Circulation 2000;101:2224–2226.
15. Berger AK, Schulman KA, Gersh BJ, et al. Primary coronary angioplasty vs thrombolysis for the management of acute myocardial infarction in elderly patients. JAMA 1999;282:341–348.
16. Rogers WJ, Bowlby LJ, Chandra NC, et al. Treatment of myocardial infarction in the United States (1990 to 1993). Observations from the National Registry of Myocardial Infarction. Circulation 1994;90:2103–2114.
17. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311–322.
18. The TIMI Study Group. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. Circulation 1994;89:1545–1556.
19. The TIMI study group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–936.
20. Garcia E, Elizaga J, Perez-Castellano N, et al. Primary angioplasty versus systemic thrombolysis in anterior myocardial infarction. J Am Coll Cardiol 1999;33:605–611.
21. Foot DK, Lewis RP, Pearson TA, Beller GA. Demographics and cardiology, 1950–2050. J Am Coll Cardiol 2000;35:66B–80B.
22. Every NR, Maynard C, Schulman K, Ritchie JL. The association between institutional primary angioplasty procedure volume and outcome in elderly Americans. J Invas Cardiol 2000;12:303–308.
23. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patient undergoing angioplasty for acute myocardial infarction. JAMA 2000;283:2941–2947.
24. Canto JG, Every NR, Magid DJ, et al. The volume of primary angioplasty procedures and survival after acute myocardial infarction. N Engl J Med 2000;342:1573–1580.
25. Joint Working Group on Coronary Angioplasty of the British Cardiac Society and British Cardiovascular Intervention Society. Coronary angioplasty: guidelines for good practice and training. Heart 2000;83:224–235.
26. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should we emergently revascularize occluded coronaries for cardiogenic shock. N Engl J Med 1999;341:625–634.

27. Holmes DR Jr, Topol EJ, Berger PB, et al. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries. J Am Coll Cardiol 1995;26:668–674.
28. Antoniucci D, Valenti R, Santoro GM, et al. Systematic direct angioplasty and stent-supported direct angioplasty therapy for cardiogenic shock complicating acute myocardial infarction: in-hospital and long-term survival. J Am Coll Cardiol 1998;31: 294–300.
29. Bengtson J, Kaplan J, Pieper K, et al. Prognosis in cardiogenic shock after myocardial infarction in the interventional era. J Am Coll Cardiol 1992;20:1482–1488.
30. Stomel RJ, Basak M, Bates ER. Treatment strategies for acute myocardial infarction complicated by cardiogenic shock in a community hospital. Chest 1994;105:997–1002.
31. Kovack PJ, Stomel RJ, Ohman EM, et al. Thrombolysis plus aortic counterpulsation: improved survival in patients who present to community hospitals with cardiogenic shock. J Am Coll Cardiol 1997;29:1454–1458.
32. Berger PB, Topol EJ, Califf RM, et al. Impact of an aggressive invasive catheterization and revascularization strategy on mortality in patients with cardiogenic shock in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial. An observational study. Circulation 1997;96:122–127.
33. Hernandez F, Hernandez P, Tascon JC, et al. Emergency revascularization and hybrid approaches in cardiogenic shock. Eur Heart J 1999;20(Suppl):169 (abstract).
34. Wharton TP Jr, McNamara NS, Lew D, et al. Cardiogenic shock at community hospitals with no surgery on site: outcomes after primary angioplasty in 101 patients in a multicenter registry. Circulation 1998;98(Suppl I):I-307-8 (abstract).
35. Wharton TP Jr, McNamara NS, Fedele FA, et al. Primary angioplasty for the treatment of acute myocardial infarction: experience at two community hospitals without cardiac surgery. J Am Coll Cardiol 1999;33:1257–1265.
36. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1999;34: 890–911.
37. Rogers WJ, Canto JG, Barron HV, et al. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. Investigators in the National Registry of Myocardial Infarction. J Am Coll Cardiol 2000;35:371–379.
38. Mehta RH, Stalhandske EJ, McCargar PA, et al. Elderly patients at highest risk with acute myocardial infarction are more frequently transferred from community hospitals to tertiary centers: reality or myth? Am Heart J 1999;138:688–695.
39. The Society for Cardiac Angiography and Interventions. Directory of cardiac catheterization laboratories in the United States, 4th edit. Raleigh, NC; 1996.
40. Vogel J. Angioplasty in the patient with an evolving myocardial infarction: with and without surgical backup. Clin Cardiol 1992;15:880–882.
41. Weaver WD, Litwin PE, Martin JS. Use of direct angioplasty for treatment of patients with acute myocardial infarction in hospitals with and without on-site cardiac surgery. Circulation 1993;88:2067–2075.
42. Iannone LA, Anderson SM, Phillips SJ. Coronary angioplasty for acute myocardial infarction in a hospital without cardiac surgery. Texas Heart Inst J 1993;20:99–104.
43. Ayres M. Coronary angioplasty for acute myocardial infarction in hospitals without cardiac surgery. J Invas Cardiol 1995;7(SupplF):40F–48F.
44. Weaver WD, Parsons L, Every N. Primary coronary angioplasty in hospitals with and without surgery backup. J Invas Cardiol 1995;7(SupplF):34F–39F.

45. Brush JE, Thompson S, Ciuffo AA, et al. Retrospective comparison of a strategy of primary coronary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction in a community hospital without cardiac surgery. J Invas Cardiol 1996;8:91–98.
46. Weaver WD for the MITI Project Investigators. PTCA in centers without surgical backup—outcome, logistics, and technical aspects. J Invas Cardiol 1997;9(SupplB):20B–23B.
47. Smyth DW, Richards AM, Elliott JM. Direct angioplasty for myocardial infarction: one-year experience in a center with surgical backup 220 miles away. J Invas Cardiol 1997;9:324–332.
48. Wharton TP Jr, Johnston JD, Turco MA, et al. Primary angioplasty for acute myocardial infarction with no surgery on site: outcomes, core angiographic analysis, and six-month follow-up in the 500-patient prospective PAMI—No S.O.S. Registry. J Am Coll Cardiol 1999;33:352A–353A (abstract).
49. Ribichini F. Experiences with primary angioplasty without on site-cardiac surgery. Semin Intervent Cardiol 1999;4:47–53.
50. Ribichini F, Steffenino G, Dellavalle A, et al. Primary angioplasty without surgical back-up at all. Results of a five years experience in a community hospital in Europe. J Am Coll Cardiol 2000;35:364A (abstract).
51. Aversano T, et al. Atlantic cardiovascular patient outcomes research team trial of primary percutaneous coronary intervention vs thrombolysis in acute MI (C-PORT PCI). Oral presentation during the 73rd Annual Scientific Sessions of the American Heart Association, 2000 Nov 12–15; New Orleans, LA. Available from URL: http://www.scientificsessions.org/archive/abstract/clinicaltrialsresults@CPORT-PCI.pdf
52. Stone GW, Brodie BR, Griffin JJ, et al. Prospective, multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30-day results of the PAMI stent pilot trial. Primary Angioplasty in Myocardial Infarction Stent Pilot Trial Investigators. J Am Coll Cardiol 1998;31:23–30.
53. Antoniucci D, Santoro GM, Bolognese L, et al. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction. Results of the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. J Am Coll Cardiol 1998;31:1234–1239.
54. Suryapranata H, van't Hof AW, Hoorntje JCA, et al. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502–2505.
55. Brener SJ, Barr LA, Burchenal J, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. The RAPPORT trial. Circulation 1998;98:734–741.
56. Topol EJ, Mark DB, Lincoff AM, et al. Outcomes at 1 year and economic implications of platelet glycoprotein IIb/IIIa blockade in patients undergoing coronary stenting: results from a multicentre randomised trial. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. Lancet 1999;354:2019–2024.
57. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–1956.
58. Katz S, Green SJ, Kaplan BM, et al. Nonrandomized comparison between stent deployment and percutaneous transluminal coronary angioplasty in acute myocardial infarction. Am Heart J 2000;139:44–51.
59. Kleiman NS, Lincoff AM, Flaker GC, et al. Early percutaneous coronary intervention, platelet inhibition, and clinical outcomes in patients with acute coronary syndromes. Circulation 2000;101:751–757.
60. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996;28:1328–1419.

61. Smith SC Jr, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention: executive summary and recommendations: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 2001;37:2215–2238.
62. Expert Panel on Invasive Cardiology in Ontario, Cardiac Care Network of Ontario: final report and recommendations. Submitted to the Ontario Ministry of Healthy and Long-Term Care, June 2001. Available from URL: http://www.ccn.on.ca.
63. Loubeyre C, Morice MC, Berzin B, et al. Emergency coronary artery bypass surgery following coronary angioplasty and stenting: results of a French multicenter registry. Cathet Cardiovasc Intervent 1999;48:441–448.
64. Stone GW, Brodie B, Griffin J, et al. Role of cardiac surgery in the hospital phase management of patients treated with primary angioplasty for acute myocardial infarction. Am J Cardiol 2000;85:1292–1296.
65. Shubrooks SJ Jr, Nesto RW, Leeman D, et al. Urgent coronary bypass surgery for failed percutaneous coronary intervention in the stent era: is backup still necessary? Am Heart J 2001;142:190–196.
66. Haraphongse M, Kunjara Na-Ayudhaya R, Burton J, et al. Clinical efficacy of emergency bypass surgery for failed coronary angioplasty. Can J Cardiol 1990;6:186–190.
67. Richardson SG, Morton P, Murtagh JG, et al. Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty: experience of complications in a hospital without on site facilities for cardiac surgery. Br Med J 1990;300:355–358.
68. Carey JA, Davies SW, Balcon R, et al. Emergency surgical revascularization for coronary angioplasty complications. Br Heart J 1994;72:428–435.
69. Simpson DE, Boura JA, Grines LL, Grines CL. Predictors of delay from ER to cath with primary PTCA for acute MI. J Am Coll Cardiol 2000;35:3520A (abstract).
70. Widimsky P, Groch L, Zelizko M, et al. Multicentre randomized trial comparing transport to primary angioplasty vs immediate thrombolysis vs combined strategy for patients with acute myocardial infarction presenting to a community hospital without a catheterization laboratory. The PRAGUE study. Eur Heart J 2000;10:823–831.
71. Tiefenbrunn AJ, Chandra NC, Every NR, et al. High mortality in patients with myocardial infarction transferred for primary angioplasty: a report from the National Registry of Myocardial Infarction-2. Circulation 1997;96(Suppl I):I–531 (abstract).
72. Grines CL, Balestrini C, Westerhausen DR Jr, et al. A randomized trial of thrombolysis vs transfer for primary PTCA in high risk AMI patients: results of the AIR PAMI trial. J Am Coll Cardiol 2000;35:376A (abstract).
73. Wharton TP Jr, McNamara NS. Management of acute coronary syndromes in the community hospital without cardiac surgery: how can access to interventional therapy be improved? Am J Cardiovasc Drugs 2001;1:375–385.
74. Ernst N, de Boer MJ, van't Hof AW, et al. Prehospital infarction angioplasty triage (PHIAT): results from the Zwolle myocardial infarction study group. J Am Coll Cardiol 2001;37:339A (abstract).
75. Reifart W, Schwarz F, Preusler W, Stoerger H, Hofmann M. Results of PTCA in more than 5,000 patients without surgical standby in the same center. J Am Coll Cardiol 1992;19:229A (abstract).
76. Meier B, Urban P, Dorsaz PA, Favre J. Surgical standby for coronary balloon angioplasty. JAMA 1992;268:741–745.
77. Klinke WP, Hui W. Percutaneous transluminal coronary angioplasty without on-site surgical facilities. Am J Cardiol 1992;770:1520–1525.
78. Ribichini F, Uslenghi E, Picco L, et al. Elective coronary angioplasty in total absence of heart surgery. G Ital Cardiol 1994;24:949–956.

79. Reifart N, Preusler W, Schwarz F, et al. A large center experience of coronary angioplasty without on-site surgical standby. In: Topol EJ, Serruys PW, eds. Current Review of Interventional Cardiology, 2nd edit. Current Medicine, Philadelphia; 1995, pp. 296–303.
80. Dellavalle A, Steffenino G, Ribichini F, et al. Elective coronary angioplasty with and without surgical standby: clinical and angiography for the selection of patients. Coron Arter Dis 1995;6:513–520.
81. Shaw TRD, Starkey IR, Essop AR, et al. Emergency coronary bypass surgery after vessel occlusion at angioplasty in centres without on-site facilities for cardiac surgery. Br Heart J 1989;61:438 (abstract).
82. Baduini G, Belli KR, de Benedicdtis M, et al. Coronary angioplasty in an Italian hospital without on-site cardiac surgery: the results and outlook [in Italian]. G Ital Cardiol 1994; 24:1529–1536.
83. Vogt A, Bonzel T, Harmjanz D. PTCA registry of German community hospitals. Eur Heart J 1997;18:1110–1114.
84. McNamara NS, Hiett D, Allen B, et al. Can community hospitals provide effective primary PTCA coverage at all hours? J Am Coll Cardiol 1997;29:91A (abstract).
85. O'Neill WW, Brodie BR, Ivanhoe R, et al. Primary coronary angioplasty for acute myocardial infarction (The Primary Angioplasty Registry). Am J Cardiol 1994;73:627–634.
86. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993;328:673–679.
87. Zijlstra F, Jan de Beer M, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328:680–684.
88. McNamara NS, Wharton TP Jr, Johnston J, et al. Can hospitals with no surgery on site provide effective infarct intervention at all hours? The PAMI-No SOS experience. Circulation 1998;98(Suppl I):I-306-I-307 (abstract).
89. Johnston J, O'Neill W, Slota P, et al. Primary PTCA at community hospitals without surgical backup is performed as effectively and with less delay compared to tertiary care centers. Circulation 1998;98 (Suppl I):I-770 (abstract).
90. Tiefenbrunn AJ, Chandra NC, French WJ, et al. Clinical experience with primary percutaneous transluminal coronary angioplasty compared with alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: a report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 1998;31:1240–1245.
91. Every NR, Parsons LS, Hlatky M, Martin JS, Weaver WD. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. N Engl J Med 1996;335:1253–1260.
92. Strategies for Patency Enhancement in the Emergency Department (SPEED) Group. Trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000;101:2788–2794.
93. Antman EM, Giugliano RP, Gibson M, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. Circulation 1999;99:2720–2732.
94. Murakami T, Mizuno S, Takahashi Y. Intracoronary aspiration thrombectomy for acute myocardial infarction. Am J Cardiol 1998;82:839–844.
95. O'Neill WW. Coronary thrombosis during acute myocardial infarction. Roberts was right! Am J Cardiol 1998;82:896–897.

96. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998;32:1312–1319.
97. Zahn R, Schiele R, Hauptmann KE, et al. Longer pre-hospital delays are associated with increasing mortality in patients with acute myocardial infarction treated with intravenous thrombolysis but not in patients treated with primary angioplasty. Circulation 1999; 100(Suppl I):I-358-I-359 (abstract).
98. Zahn R, Schneider S, Schiele R, et al. Primary angioplasty in acute myocardial infarction: is there an influence of time from onset of symptoms to start of treatment on in-hospital delay and clinical course? Eur Heart J 1999;20(Suppl):400 (abstract).
99. Weaver WD. Relation of time to treatment on relative effects of primary coronary angioplasty vs. thrombolytic therapy. J Am Coll Cardiol 2000;35:376A (abstract).
100. Kennedy JW, Stadius ML. Combined thrombolytic and platelet glycoprotein IIb/IIIa inhibitor therapy for acute myocardial infarction: will pharmacological therapy ever equal primary angioplasty? Circulation 1999;99:2714–2716.
101. Vrachatis A, Alpert M, Nikas D, et al. Primary angioplasty re-establishes basal coronary artery flow faster than thrombolysis after acute Q-wave myocardial infarction. Circulation 1999;100(Suppl I):I-358 (abstract).
102. Hirshfield JW Jr, Ellis SG, Faxon DP, et al. Recommendations for the assessment and maintenance of proficiency in coronary interventional procedures: statement of the American College of Cardiology. J Am Coll Cardiol 1998;31:722–743.
103. Jollis JG, Peterson ED, DeLong ER, et al. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. N Engl J Med 1994;331:1625–1629.
104. Jollis JG, Peterson ED, Nelson CL, et al. Relationship between physician and hospital coronary angioplasty volume and outcome in elderly patients. Circulation 1997;95:2485–2491.
105. Hannan EL, Racz M, Ryan TJ, et al. Coronary angioplasty volume-outcome relationships for hospitals and cardiologists. JAMA 1997;277:892–898.
106. Ritchie JL, Phillips KA, Luft HS. Coronary angioplasty: statewide experience in California. Circulation 1993;88:2735–2743.
107. GUSTO (IIb) Angioplasty Substudy Group. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes: a clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;3365:1621–1628.
108. O'Neill WW, Griffin JJ, Stone G, et al. Operator and institutional volume do not affect the procedural outcome of primary angioplasty therapy. J Am Coll Cardiol 1996;27 (Suppl A):13A (abstract).
109. Zahn R, Vogt A, Neuhaus KL, et al. Angioplasty in acute myocardial infarction in clinical practice: results in 4625 patients from the ALKK Angioplasty Registry. J Am Coll Cardiol 1997;29 (Suppl A):15A (abstract).
110. Huff ED. Volume of coronary angioplasty procedures and mortality rates. N Engl J Med 1995;332:1304.
111. Doucet M, Eisenberg MJ, Joseph L, Pilote L. The effect of hospital volume on long-term outcome after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 2000;35:12A (abstract).
112. Ho V. Evolution of the volume-outcome relation for hospitals performing coronary angioplasty. Circulation 2000;101:1806–1811.
113. Teirstein PS. Credentialing for coronary interventions: practice makes perfect. Circulation 1997;95:2467–2470.
114. Smith D, Dean J. Transferring patients for primary angioplasty. Heart 1997;78:323–324.

7 Drug Strategies for Angioplasty in Acute Myocardial Infarction

Edward Kim, MD and Alan W. Heldman, MD

CONTENTS

INTRODUCTION

While the timely restoration of infarct-artery patency is central to the optimal treatment of the patient with an acute myocardial infarction (AMI), the ultimate goal of early reperfusion therapy is to reestablish normal myocardial metabolism. Although epicardial coronary atherosclerosis and thrombosis initiate most acute ischemic events, complete treatment of these conditions requires both rapid and effective epicardial coronary reperfusion and attention to preserving microvascular integrity. The closely related phenomena of microvascular obstruction and reperfusion injury underlie the often-observed paradox of a patent epicardial infarct artery yet poor distal runoff, whether manifest as slow or no reflow, reduced myocardial perfusion, or continuing or worsening ischemic injury after reperfusion.

Kloner et al. described reperfusion injury in the heart in a dog model *(1)*. Reperfusion after temporary ligation of the circumflex coronary artery resulted in a slow washout of dye, which Kloner termed "no reflow." Reports of "no reflow"

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

in humans emerged in angiographic studies of thrombolytic therapy for AMI, in the setting of percutaneous coronary intervention (PCI) of lesions with thrombus, and with the use of new angioplasty devices, particularly rotational ablation. Whether these two phenomena, experimental and procedural, share the same name for valid reasons is debatable. Nonetheless, many of the mechanisms and therapeutic implications are shared.

Angiographically apparent microvascular obstruction and reperfusion injury portend worsened clinical outcomes in AMI. A recent meta-analysis of five thrombolytic trials confirmed the tight association between death and the failure to achieve brisk epicardial coronary flow, with diminished 30-d survival in patients having Thrombolysis in Myocardial Infarction (TIMI) 0 and 1 vs TIMI 2 vs TIMI 3 flow at 90 min *(2)*. In this meta-analysis, the 30-d mortality rate was 8.8% for TIMI grade 0/1, 7.0% for grade 2, and 3.7% for grade 3. TIMI grade 3 flow was associated with improved outcome measures including extent of enzyme release, infarct size, and left ventricular dysfunction, while grade 2 flow was often not much better than that of an occluded infarct artery.

Even among patients with TIMI 3 epicardial flow, the TIMI myocardial perfusion (TMP) grade can further predict clinical outcomes. With this angiographic assessment of tissue-level flow, TMP grade 0 has no ground-glass myocardial blush, TMP grade 1 has myocardial blush that does not clear ("no reflow"), TMP grade 2 blush clears slowly, and TMP grade 3 blush largely clears within three cardiac cycles of the washout phase. In the TIMI 10b angiographic study, among patients with TIMI grade 3 epicardial flow after thrombolysis, TMP grade 0 or 1 was associated with a 5.0% mortality rate at 30 d, TMP grade 2 with 2.9% mortality, and TMP grade 3 with 0.7% mortality *(3)*.

Despite early restoration of epicardial coronary patency, microvascular damage can occur during both the acute ischemic event and reperfusion. Indeed the process of reperfusion is not at all benign; placebo-controlled thrombolytic trials demonstrated an excess mortality hazard *(4)* in the thrombolytic arms during the first 24 h, not only from intracranial or other hemorrhage, but also as reperfusion injury-precipitated pump failure, arrhythmias *(5)*, or myocardial rupture.

During the past decade, primary PCI has evolved as the optimal reperfusion therapy for acute ST-elevation myocardial infarction, particularly those presenting to high-volume centers with experienced operators. However, just as for thrombolysis, the benefits of primary percutaneous transluminal coronary angioplasty (PTCA) are attenuated by reperfusion injury. Delays in performing the mechanical revascularization procedure translate into substantially worse outcomes *(6)*. Implementation of systems providing for rapid treatment, and use of modern angioplasty equipment, stents, and adjunctive drug therapies (principally the platelet glycoprotein [GP] IIb/IIIa inhibitors) have resulted in further improved outcomes. Accurate assessment of myocardial perfusion grade might

provide a more accurate measure of microvascular integrity and further discriminate the important predictors of outcome after primary PCI.

Clearly, treatments directed at maintaining microvascular integrity during reperfusion therapy, whether thrombolysis or PCI, are critical to the optimal management of acute occlusive coronary syndromes. This remains a fruitful area for investigation; despite the growing body of evidence clarifying the basic mechanisms involved in reperfusion injury and microvascular obstruction, few proven therapies are available.

REPERFUSION INJURY

The benefits of establishing early infarct-artery patency are reduced by reperfusion injury. Reperfusion injury results from a cascade of cellular events culminating in obstruction or collapse of the myocardial microvasculature *(7)*. The generation of toxic oxygen-derived free radicals, the release of proteolytic enzymes and inflammatory mediators including complement, microvascular spasm, and microvascular plugging from fibrin, platelets, and neutrophils result in both endothelial dysfunction and myocyte damage. In turn, endothelial dysfunction causes increased vascular permeability and tissue edema, reduced coronary vasodilator reserve, and increased coronary vascular resistance. Neutrophils are activated by oxygen free radicals and by cytokines. The expression of surface adhesion molecules facilitates the process of neutrophil attachment to and transmigration across the endothelium where direct myocardial toxicity can result. Direct myocardial effects include impaired contractility, loss of membrane integrity, arrhythmogenesis, and myocyte necrosis and apoptosis.

Based on the cellular mechanisms of reperfusion injury, rational therapeutic interventions may be designed. Both nitric oxide and adenosine are promising strategies for preventing reperfusion injury; these agents affect neutrophil-mediated phenomena, reduce vascular resistance, and modulate the myocyte response to ischemia. Beyond their direct cellular toxicity, oxygen free radicals also modulate gene expression, including genes determining the apoptotic program for cell death *(8)*, suggesting a role for antioxidant drug therapies.

To the coronary angiographer, "no reflow" with a static column of contrast represents a very high degree of damage, while a diminished degree of myocardial perfusion blush reflects a more minor degree of microvascular impairment. Contrast agents for other imaging methods—echocardiography and magnetic resonance imaging (MRI)—are even more sensitive at revealing microvascular obstruction, and the combined use of these angiographic and noninvasive techniques has been valuable for understanding the course of infarction. Myocardial contrast echocardiography (MCE) and contrast-enhanced MRI are sensitive techniques allowing the detection of mild levels of capillary injury, reflecting slower contrast penetration through obstructed capillaries *(9)*. Abnormal microvascular

flow post-infarction assessed by MCE, MRI, and/or angiography correlates with fibrous scar formation, ventricular remodeling *(10)*, LV dilation, congestive heart failure, reinfarction, target vessel revascularization, and death *(11)*. Imaging studies suggest that the territory affected by microvascular obstruction may continue to enlarge for many hours after reperfusion *(12)*, evidence for an active process of reperfusion injury.

ISCHEMIC PRECONDITIONING

"Preconditioning" with brief periods of ischemia protects the myocardium from subsequent ischemic injury, with an early phase of protection elicited within minutes *(13)* and a delayed phase *(14)* appearing hours later. In cellular and tissue preparations, as well as in clinical conditions, brief periods of hypoxia and ischemia confer protection against subsequent ischemia and reperfusion injury. Harnessing this phenomenon as a therapy for emergency coronary revascularization procedures would be a breakthrough, particularly if the protective effect could be achieved after the initiation of ischemia. Other initiators of a similar effect include adenosine receptors, α_1-adrenergic receptors, opioid receptors, protein kinase C agonists, and reactive oxygen species *(15)*. These triggers phosphorylate and open ATP-sensitive potassium (K^+_{ATP}) channels in myocardial mitochondria, which seem to mediate the protective effect and may further influence the redox state and redox-sensitive cellular processes *(16)*. Both nitric oxide *(17)* and adenosine *(18,19)* enhance the opening of mitochondrial K^+_{ATP} channels, a recent finding that brings together the concepts of microvascular dilatation and ischemic preconditioning.

ADMINISTRATION OF SPECIFIC THERAPIES

As interventional techniques moved into the era of new devices, operators (reluctantly) gained more experience with the complication of no reflow in PCI of degenerated vein grafts and in rotational atherectomy. In these cases, angiographic and clinical complications are often the result of distal embolization of atherothrombotic material into the distal coronary bed, and are not necessarily the same as the no reflow seen following infarct reperfusion *(20)*. Angiographic flow complications are very serious; in the experience of the William Beaumont Hospital (1988–1993), PCI procedure-related no reflow was associated with a 10-fold increase in death or myocardial infarction *(21)*. Intracoronary drugs and drug combination "cocktails" for preventing these events were adopted based on local experience validated by published case series (Table 1). Despite two decades of experience, however, only intracoronary nitroglycerin is universally used, and no single strategy of intracoronary drug treatment has yet achieved the broad acceptance seen with the use of systemic platelet GP IIb/IIIa inhibitors.

Table 1
Intracoronary Drugs

Agent	*Dose*	*Delivery*	*Effects*	
Nitroglycerin	50–200 μg	Injected through guiding catheter	Epicardial coronary dilation	
Adenosine *(81)*	18–24 μg	"High velocity boluses" with a 3-mL syringe injected through guiding catheter	Reversed no-reflow caused by vein graft stenting	Dose repeated 10–40 times
Adenosine high dose	4 mg	Through inflated balloon's wire lumen, before reperfusion	Increased TIMI 3 flow, improved LV function and clinical endpoints	
Papaverine	10 mg	Via guide catheter	Improved flow velocity after PCI-related no-reflow	No effect on blood pressure at this dose
Nitroprusside	50–1000 (mean 200) μg injections	Via guide catheter or angioplasty balloon		
Verapamil	100–500 μg	IC	Maximal effect on coronary resistance at 1.0 mg into left coronary artery *(82)*	100 μg IC did not affect BP, but 1.0 mg did reduce BP *(83)*
Diltiazem	1 mg	IC	Heart block	
Nicardipine	200 μg	IC	More potent and prolonged effect on coronary flow velocity than Diltiazem (1 mg) or Verapamil (200 μg)	
Urokinase	250,000–1,000,000 U	IC infusion	Increased complications, acute closure	
Urokinase	300–500 U	Local delivery	No benefit	
Abciximab	10 mg	IC bolus	Case reports	

While frequently used in this way, most drugs are not approved nor recommended by manufacturers or regulatory agencies for intracoronary use. Medical literature, local experience, and individual catheterization laboratory standards should be considered. Literature citations include those noted in this chapter. IC, intracoronary.

Although no reflow is not specific to PCI reperfusion therapy for AMI, the incidence is certainly significant in this setting. For example, Piana et al. *(22)* reported an incidence of no reflow (defined as less than TIMI 3 flow) of 2% in almost 2000 PCIs performed at the Beth Israel Hospital between 1991 and 1993. In this series, PCI for AMI was associated with a sevenfold higher incidence of "no reflow" (11.5% vs 1.5%).

When performing primary, salvage, facilitated, or delayed PCI for AMI, the operator must make rational choices among a large number of therapeutic options. The ultimate goal is to provide solutions for all of the various forms of ischemic injury, including angiographic no reflow due to macroembolization and vasoconstriction as well as the (sometimes) more subtle derangements of metabolic no reflow and the "pure" no reflow of reperfusion injury. The discussion that follows is offered as a starting point, with a review of the scientific bases for and against these approaches. Note that many of these are "off-label" (not approved by the US Food and Drug Administration) and may or may not reflect "standard care" in a given community.

To maximize the benefits of reperfusion therapy in AMI, treatments should preserve microvascular integrity and reduce reperfusion injury. Therapies that have been examined are directed at relieving microvascular spasm, neutralizing free radical damage or changing the redox state, repleting electrolytes, preventing calcium overload, and inhibiting neutrophil adhesion, platelet aggregation, and coagulation. Specific agents are discussed in the following paragraphs including vasodilators and other drugs given via the intracoronary route. Anticoagulant and antiplatelet aggregation drugs are covered in detail in other chapters and are not discussed here except as they relate to reperfusion injury.

Endothelium-Independent Vasodilators

Relaxation of coronary vascular tone during PCI has several purposes. By reducing epicardial vessel spasm, the sizing of interventional devices may be optimized. More intriguing is the potential for limiting microvascular occlusion by dilating resistance arterioles and increasing the velocity and pressure gradient of perfusion through the capillary circulation. A number of vasospastic factors including serotonin are expressed from aggregating platelets. The combination of microvascular spasm and clumping of platelets, neutrophils, and fibrin is a vicious cycle that is difficult to interrupt. As with most situations in medicine, it would seem preferable to prevent rather than attempt to reverse this process.

Nitroglycerin

Nitroglycerin has been given via the intracoronary route for treatment of AMI since the first direct PCI procedures in AMI *(23)*. Sytemic Nitrates dilate venous and systemic conductance vessels, reduce cardiac wall tension, and improve the balance between perfusion and oxygen demand. At higher doses, including the

doses typically given via the intracoronary route, nitroglycerin dilates epicardial coronary arteries and to some extent arteriolar resistance vessels, making it useful for the angiographic measurement of vessel size during PCI. While generally well tolerated, the value of nitroglycerin for the treatment of serious microvascular complications is limited, and trials have suggested that other drugs may be more effective.

Administration of nitroglycerin or another nitrate is routine in most labs. It loses activity in contact with polyvinylchloride plastic; specially designated syringes and containers should therefore be used. Hypotension may result, particularly when filling pressures are low; this generally responds to volume resuscitation.

Adenosine

Adenosine is an endogenously produced molecule; its release in the myocardium is increased during ischemia as a result of the breakdown of ATP. Adenosine has a variety of effects at crucial signaling points. It is a potent short-acting vasodilator, giving it an autoregulatory effect in the case of ischemia *(24)*. Multiple lines of evidence suggest an important role of endogenous adenosine in the myocardial protection associated with ischemic preconditioning. In animal models, intracoronary adenosine infusion mimics the benefits of ischemic preconditioning at maintaining coronary perfusion despite stenosis and thrombosis *(25)*. Similar findings have been reported for patients undergoing PCI after pretreatment with intracoronary adenosine or intracoronary dipyridamole (which may increase production of adenosine) *(26)*. A direct protective effect against reperfusion injury on cardiac myocytes has also been proposed, including in patients undergoing cardiac surgery *(27)*.

Adenosine prolongs conduction through the atrioventricular node. Administration of adenosine, whether intravenous or intracoronary, can produce heart block and profound bradycardia. This effect is short lived; in fact, some patients who are able to cooperate during the intervention can be taught to "auto-CPR" by repetitive forced deep coughing for a short period when an intrinsic heart rhythm is absent *(28)*. Heart block ascribed to increased endogenous adenosine activity (as in rotational ablation) has been antagonized with theophylline. Given the important protective properties of adenosine in coronary ischemic events, however, inhibiting the effects of adenosine with theophylline *(29)* raises at least some theoretical concerns for interventional use.

Marzilli et al. *(30)* studied the effects of adjunctive intracoronary adenosine in mitigating reperfusion injury during primary angioplasty for AMI. In this study, 54 patients presenting within 3 h of symptom onset were randomized to receive intracoronary adenosine vs placebo infusion. Baseline demographics between groups were similar. Patients with TIMI 3 flow on the initial angiogram or a history of bronchospasm were excluded. On the initial inflation of an over-

the-wire balloon across the obstruction in the infarct artery, the guidewire was withdrawn and a high dose of intracoronary adenosine (4 mg) was slowly infused through the central lumen of the balloon catheter over 1 min. The treatment procedure, including initial balloon inflation and infusion of adenosine, was completed in <2 min in all cases, and the balloon was deflated, allowing reperfusion into the now-dilated distal bed. Interestingly, there were no episodes of bradyarrhythmias or AV block. At the end of the procedure, all 27 patients in the adenosine-treated group achieved TIMI 3 flow, whereas only 19 of 27 patients exhibited TIMI 3 flow in the placebo group. There was a trend toward decreased CK release and there was a significant decrease in the cumulative clinical endpoint (recurrent ischemia, nonfatal myocardial infarction, heart failure, and cardiac death) in the adenosine-treated group. Improvement in left ventricular function 1 wk post-infarct was significantly greater in the adenosine-treated group.

Assali et al. *(31)* retrospectively studied the outcomes of 79 patients undergoing PCI for AMI at Hermann Hospital from 1997 to 1999. In this study, 51 patients received boluses of intracoronary adenosine (24 μg) both before and after balloon inflations. The incidence of angiographic "no reflow" was 5.9% vs 28.6% in the adenosine-treated vs no-treatment group, $p = 0.014$. Final TIMI flow grades, however, were similar between groups.

The results of the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) *(32)* further support a role for adjunctive adenosine in attenuating reperfusion injury. The trial evaluated the administration of intravenous adenosine during thrombolytic therapy for AMI. In the AMISTAD trial, 236 patients undergoing thrombolysis for AMI were randomized to adjunctive intravenous adenosine vs placebo. Intravenous adenosine was infused up to 70 μg/kg/min for 3 h. The majority of patients received a 6-h lidocaine infusion since an animal study suggested that adenosine exerted a beneficial effect on reperfusion injury only when administered with lidocaine. The primary endpoint was infarct size as determined by technetium-99m (Tc-99m) sestamibi SPECT imaging. There was a 33% relative reduction in infarct size ($p = 0.03$) and a trend toward a reduced composite of clinical endpoints (death, reinfarction, shock, congestive heart failure, and stroke). In patients with anterior infarction, there was a 67% relative reduction in infarct size, while no difference was found in other infarct locations.

Fischell and colleagues showed the potential of adenosine to reverse no-reflow phenomenon precipitated by angioplasty of coronary bypass vein grafts *(33)*. They administered high-velocity bolus injections through the guiding catheter, using small (3-mL) syringes to generate high-pressure jets of drug. Repeated injections of 18–24 μg of adenosine reversed no-reflow in 10 of 11 cases. This dose of adenosine contrasted markedly with the high dose (3 mg) used in Marzilli's AMI study.

Papaverine

In an observational study, Ishihara and colleagues *(34)* evaluated whether intracoronary papaverine could effectively treat angiographic "no reflow" (defined as TIMI 1 or 2 flow despite a <50% residual stenosis). Nine patients who developed "no reflow" despite adequate epicardial artery patency after primary angioplasty for a first AMI served as the study population. Intracoronary papaverine (10 mg) was administered through the guiding catheter as a bolus injection. Coronary flow was assessed by the mean number of cine frames required for contrast medium to pass two selected landmarks. By this measure, flow significantly improved after papaverine injection.

Nitroprusside

Nitric oxide (NO) is the principal "endothelium-derived relaxing factor" *(35)* and may have other cellular effects including inhibition of platelet aggregation and modulation of ischemic preconditioning. Nitroprusside is an NO donor drug that has a greater effect on the microvasculature than do nitroglycerin or other nitrates.

Hillegass et al. *(36)* analyzed 19 patients with no or slow flow following PCI who were treated with nitroprusside (50–200 µg per injection, up to 1000 µg total) through either the guiding catheter or the angioplasty balloon. Fourteen of 19 patients responded with a significant increase in coronary flow velocity, without hypotension or other complications.

Calcium Channel Blockers

In many laboratories, this class of drugs is used frequently as adjunctive therapy. Although they are classified as vasodilators, other effects including direct myocardial actions are also possible.

Verapamil

Taniyama et al. *(37)* reported that intracoronary verapamil after primary PCI attenuated microvascular dysfunction and led to improved outcomes compared with primary PCI alone. In this study, 40 patients were randomized to receive 0.5 mg of intracoronary verapamil or placebo over 1 min through the guiding catheter after patency in the infarct artery was restored. There were no adverse hemodynamic outcomes due to drug infusion. Microvascular function was assessed by myocardial contrast echocardiography (MCE) after infusion of sonicated ioxaglate, and a "no-reflow ratio" was calculated as the size of the no-reflow zone over the area at risk. Despite the establishment of TIMI 3 flow in 70% of verapamil-treated patients (no difference from controls) immediately after PCI, MCE still revealed no or low reflow in 14 of 20 patients before verapamil. After verapamil treatment, the low reflow ratio decreased from 0.39 to 0.29. Left ventricular function improved more in the verapamil group vs

placebo group as assessed by a wall motion score index and left ventricular end-diastolic and end-systolic volume indices.

Verapamil (100–500 μg) was compared to nitroglycerin (100–300 μg) for intragraft infusion in the treatment of reduced flow during interventions on degenerated saphenous vein grafts. Verapamil restored TIMI 3 flow in 88% of cases, while nitroglycerin was ineffective *(38)*. Extrapolation to the AMI setting should be done only with caution, as the predominant mechanism of these vein graft complications is embolization of friable material *(39)*.

Diltiazem

In an animal model, Herzog and colleagues *(40)* showed attenuated reperfusion injury and decreased infarct size with intracoronary diltiazem. Occlusion of the left anterior descending arteries for 50 min in 14 Yorkshire swine was followed by a 3-h period of reperfusion. Eight animals were treated with intracoronary diltiazem (2.5 mg) at the onset of reperfusion while six were given a placebo saline infusion. Infarct size was significantly reduced in the diltiazem-treated vs placebo group (0.13 ± 0.06 vs 0.42 ± 0.04 g/kg; $p = 0.01$). The authors hypothesized that intracoronary diltiazem may be a valuable adjunct in patients undergoing coronary bypass surgery, PCI, or thrombolysis for AMI.

We are aware of no reports of diltiazem therapy for treating or preventing reperfusion injury specifically during primary PCI in humans. In a large series of patients undergoing direct coronary atherectomy (DCA), Jalinous and colleagues demonstrated that intracoronary diltiazem (2–6 mg) given prior to DCA resulted in a significant decrease in non-Q-wave myocardial infarctions compared with historical controls (2.7 vs 6.8%; $p < 0.04$) *(41)*.

Nicardipine

In a small sample of patients treated serially with intracoronary diltiazem, verapamil, and nicardipine, the greatest increase in and the longest-lasting effect on coronary blood flow velocity (measured by Doppler flow wire) was seen with nicardipine *(42)*. In our laboratory nicardipine is the calcium channel blocker most frequently used for intracoronary administration.

Anticoagulants, Platelet Inhibitors, and Thrombolytics

Proper management of anticlotting drugs around the time of infarct angioplasty is critical to obtaining good outcomes. These agents are discussed next as related to issues concerning reperfusion injury.

Heparin

The Heparin in Early Patency (HEAP) trial *(43)* evaluated whether high-dose heparin prior to primary PCI improved rates of pre- and post-procedure TIMI flow. The treatment group ($n = 299$) received a heparin bolus of 300 IU/kg intravenously (IV), while the control group ($n = 285$) received either a fixed

5000 IU heparin bolus ($n = 73$) or no heparin ($n = 212$). Heparin was administered in the emergency room of the angioplasty facility or at the referring institution prior to transportation. Median ischemic times (time from symptom onset to balloon inflation) were similar between groups (195 vs 210 min for the high- vs low-dose group, respectively). Initial pre-angioplasty grades of TIMI flow were similar between groups, as were grades of immediate post-procedure TIMI flow. Left ventricular ejection fraction and enzymatically determined infarct size were likewise similar between groups. The authors concluded that early high-dose heparin was of no benefit.

Thrombolytic Drugs for Primary PCI

No trials have evaluated the systematic use of thrombolytic therapy (either intravenous or intracoronary) during primary PCI. Several case reports have been published suggesting that residual thrombus may be effectively treated with local injections of intracoronary tissue plasminogen activator (t-PA), urokinase, or streptokinase. The Thrombolysis and Angioplasty in Unstable Angina (TAUSA) *(44)* trial evaluated the prophylactic use of intracoronary urokinase in patients undergoing PCI for rest angina in a randomized, double-blind, placebo-controlled study. The urokinase-treated group experienced a significant increase in acute closures (10.2 vs 4.3%; $p < 0.02$) and a higher incidence of adverse in-hospital clinical endpoints including ischemia, reinfarction, or emergency bypass surgery (12.9 vs 6.3%; $p < 0.02$). The worsened outcomes in the urokinase-treated group were hypothesized to be due to hemorrhagic dissection, lack of intimal sealing, or platelet-activating effects of urokinase. Whether these issues would remain relevant in the era of platelet GP IIb/IIIa inhibitors and stents remains to be determined, but the routine use of thrombolytic drugs in conjunction with primary PCI is not warranted.

Inhibitors of Platelet Aggregation

Several studies have suggested that the inhibition of platelet aggregation with platelet GP IIb/IIIa receptor antagonists during or prior to catheter-based reperfusion therapy for AMI improves microvascular flow. Neumann and colleagues randomized 200 patients undergoing stenting for AMI to abciximab ($n = 102$) or placebo ($n = 98$). Primary endpoints included differences in peak coronary flow velocities and wall motion index scores immediately post-procedure and at 14 d. Peak flows improved significantly at 14 d in the abciximab-treated group compared with those receiving placebo (18.1 cm/s vs 10.4 cm/s; $p = 0.024$). Likewise, abciximab-treated patients exhibited a significantly greater improvement in their wall motion index scores. Left ventricular ejection fraction at follow-up was 62% vs 56% ($p = 0.003$) for the abciximab-treated versus the placebo group *(45)*.

Giri and colleagues *(46)* examined 650 consecutive patients who were treated with primary PCI for AMI (presenting within 12 h of symptom onset) between

August 1995 and December 1998. Patients were divided into one of four groups based on treatment received: (1) PTCA; (2) stent; (3) PTCA plus abciximab; and (4) stent plus abciximab. Rates of TIMI 3 flow immediately post-procedure were 82%, 90%, 93%, and 97% ($p = 0.0001$) for the four groups, respectively. Rates of persistent no-reflow were 14%, 9%, 4%, and 2% ($p = 0.0001$), respectively. Significant reductions in the composite endpoint of death, recurrent myocardial infarction, and target vessel revascularization at 30 d were observed among groups in a graded fashion (24.5%, 19.5%, 16.5%, and 6.1%, respectively; $p = 0.0001$).

The Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-Up (ADMIRAL) trial suggested that the early administration of abciximab before angiography and PCI for AMI improves infarct artery flow. Rates of TIMI 3 flow before the procedure (16.8% vs 5.4%; $p = 0.01$), immediately afterward (95.1% vs 86.7%; $p = 0.04$), and 6 mo afterward (94.3% vs 82.8%; $p = 0.04$) were higher for the abciximab-treated than for the placebo group, respectively. Clinical endpoints of death, reinfarction, or urgent target vessel revascularization were reduced at 30 d (6.0% vs 14.6%; $p = 0.01$) and at 6 mo (7.4% vs 15.9%; $p = 0.02$). A substudy showed that abciximab reduced platelet aggregate size in this setting *(47)*.

The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial *(48)* demonstrated that administration of eptifibatide reduced complications of stenting, primarily by reducing procedural myocardial infarctions. In a substudy of that trial, Gibson and colleagues measured coronary flow reserve and angiographic myocardial perfusion and found both were significantly increased with eptifibatide *(49)*. Coronary flow reserve was calculated as the ratio of coronary flow velocity (by an angiographic technique, the corrected TIMI frame count) after microvascular vasodilation with adenosine, over the velocity before adenosine. The rate of increase of myocardial contrast blush (myocardial perfusion) was calculated using digital subtraction angiography. Both measurements reflect function of the microvasculature; improvement with platelet inhibition may reflect reduced microvascular plugging.

Nonplatelet effects of abciximab have been speculated to have significance for microvascular protection by inhibiting neutrophil activation. While use of small molecule IIb/IIIa inhibitors has not been fully studied in primary PCI, we might hypothesize from early experience using IIb/IIIa inhibitors in combination with reduced dose thrombolytic drugs. In several studies, TIMI 3 flow resulted more frequently with the combination than with thrombolytic therapy alone. For example, adding eptifibatide to thrombolytic therapy with t-PA increased TIMI grade 3 flow (66% vs 39% for t-PA alone; $p = 0.006$) with a shorter time to ST-segment recovery (65 min vs 116 min; $p = 0.05$) *(50)*. Dose-finding studies continue in this rapidly evolving field, and no clear standard has emerged.

Several case reports advocate the use of ad hoc intracoronary abciximab *(51)* for persistent thrombus during primary PTCA. The mounting data supporting the

routine administration of platelet GP IIb/IIIa inhibitors for primary PCI diminishes the relevance of these observations.

RheothRX (Poloxamer 188)

RheothRX is a surfactant with hemorheological and antithrombotic properties. This surfactant associates with the cell membranes of erythrocytes, neutrophils, and endothelial cells, as well as circulating macromolecules, sterically hindering adhesive interactions between these components. This association has been hypothesized to reduce red blood cell aggregation and blood viscosity and improve microcirculatory flow. Multiple clinical trials have tested the efficacy of RheothRX in preventing reperfusion injury, with conflicting results.

O'Keefe and colleagues *(52)* randomized 150 patients undergoing primary PTCA to receive RheothRX vs placebo. Drug was initiated prior to PTCA-induced reperfusion at 300 mg/kg/min over 1 h followed by a 30 mg/kg/min infusion over 47 h. Primary endpoints included infarct size and myocardial salvage as determined by Tc-99m SPECT imaging, and left ventricular ejection fraction at 5–7 d as measured by radionuclide angiography. No differences in the primary endpoints were observed between groups.

In a companion study, Schaer and co-workers observed a beneficial effect for adjunctive RheothRX therapy in patients undergoing thrombolysis for AMI *(53)*. This randomized, double-blind, placebo-controlled, multicenter trial included 114 patients. Those treated with RheothRX (48-h infusion initiated immediately after the start of the thrombolytic therapy) exhibited a 38% reduction in infarct size compared with placebo (16 vs 26%; $p = 0.031$) and a 13% relative improvement in left ventricular function at 5 –7 d (52 vs 46%; $p = 0.02$).

In a randomized, placebo-controlled trial of 2948 patients undergoing thrombolysis for AMI, the Collaborative Organization for RheothRx Evaluation (CORE) investigators concluded that adjunctive RheothRX provided no clinical benefit and may in fact be detrimental *(54)*. No differences were observed between RheothRX-treated and placebo groups with respect to mortality, reinfarction, and cardiogenic shock. RheothRX treatment was, however, associated with adverse effects on left ventricular ejection fraction 5–7 d post-infarct, along with increased rates of heart failure and renal dysfunction.

ATP-Sensitive Potassium Channel Openers

Nicorandil

Nicorandil is an adenosine triphosphate (ATP)-sensitive potassium channel opener having the properties of a nitrate and a nicotinamide; it is hypothesized to act as a vasodilator, inhibitor of calcium influx, and/or neutrophil modulator *(55)*. Ito randomized 81 patients with a first anterior AMI (within 12 h of symptom onset) to receive nicorandil vs placebo. Prior to angioplasty, nicorandil was administered as a 4-mg IV bolus followed by a 6-mg/h infusion for 24 h and then

an oral dose of 15 mg/d for 1 mo. Baseline characteristics were similar between groups. In-hospital complications were significantly reduced in the nicorandil-treated group vs controls (VT or VF, 5 vs 20%; $p = 0.048$; tamponade, 0 vs 4%; $p = 0.043$; CHF, 15 vs 37%; $p = 0.027$; in-hospital death, 0 vs 10%; $p = 0.043$). MCE with sonicated ioxaglate revealed that the incidence of echocardiographic no reflow was significantly reduced in the nicorandil-treated vs control group (6 of 40 vs 14 of 41; $p < 0.001$) *(56)*.

Diazoxide

Diazoxide is an antihypertensive drug and is also used to suppress hypoglycemia associated with hyperinsulinemic states. In models, diazoxide protects from ischemic injury, preventing cellular damage and apoptosis *(57)*. It is a K^+_{ATP} opener, which causes increased production of reactive oxygen species in cardiac muscle. This change in cellular redox state may serve a signaling function itself, altering protein biochemistry and cell processes. In fact, antioxidants block ischemic preconditioning, including that induced by diazoxide *(58)*.

Catheterization Technique: Considerations for Drug Therapy

Over-the-wire balloon systems are useful for angioplasty of infarct vessels and total occlusions, allowing the injection of contrast through the central channel to confirm the intraluminal position. By the same route, drugs can be administered to the distal coronary bed, even prior to reperfusion. Attention to technique makes this a safe and useful maneuver. Balloon catheter position beyond the area of trouble should be secure before temporarily removing the guidewire. Using a 3–5-cc syringe, aspirate from the central lumen until blood is seen. Injection of air into the closed distal bed is to be avoided with at least the same degree of caution given to angiographic or guiding catheters. Support, infusion, or probing catheters can also be used for drug delivery in this way, as can the AngioJet rheolytic thrombectomy system. The volume of dead space in a 0.014-inch compatible coronary balloon's central lumen is <1 mL, but this may be significant and will be infused when the wire is reinserted.

Infusion of drugs through the guiding catheter might be hypothesized to be less effective when coronary flow is already severely impaired. Fischell's findings noted above using an *ex vivo* model for the delivery of adenosine suggest that if this technique is used, a smaller syringe (which allows higher developed pressure and velocity of drug delivery) may facilitate reaching the distal bed.

When injecting drugs with negative chronotropic (slowing) effects, pacing should be available. Judgment is required to decide the extent of preparation for potential bradycardia or asystole. The range of options includes having transvenous pacing equipment at hand, placing electrodes for transcutaneous

pacing, gaining venous access, inserting a temporary pacing wire, or teaching the patient how to cough to perform auto-CPR. This last may be a particularly appropriate standby measure for adenosine with its short duration of action.

Finally, as the number and complexity of drugs being used in the catheterization lab increases, care should be taken that agents are clearly labeled to avoid medication administration errors.

AGENTS FOR DIRECT MYOCARDIAL PROTECTION

Cariporide

The sodium–hydrogen exchanger type 1 (NHE-1) has been implicated in the pathogenesis of myocyte necrosis during ischemia-reperfusion. Rapid activation of NHE-1 during ischemia-reperfusion results in a drop in intracellular pH and an influx of calcium. This may lead to contractile dysfunction, ventricular arrhythmias, and myocyte necrosis. Numerous animal studies have demonstrated that NHE-1 inhibitors such as cariporide preserve myocyte viability and limit infarct size during ischemia-reperfusion.

The Guard During Ischemia Against Necrosis (GUARDIAN) trial assessed whether cariporide reduced the frequency of death or myocardial infarction in 11,733 patients with unstable angina or non-ST-elevation myocardial infarction, or those undergoing high-risk PCI or coronary artery bypass graft surgery (CABG) *(59)*. Doses of 20, 80, and 120 mg of cariporide were given intravenously every 8 h for 2–7 d. No benefit was observed overall for cariporide treatment compared with placebo; in the subset of CABG patients, treatment with the highest dose was associated with fewer myocardial infarctions, suggesting that the drug be evaluated in the setting of reperfusion. Animal studies assigning the protective effect of cariporide to ischemia, rather than reperfusion, following infarction *(60)* make these results no clearer.

In contrast (and in a very different set of conditions), Rupprecht and co-workers demonstrated a cardioprotective effect for cariporide in patients undergoing primary or direct PCI for acute anterior myocardial infarction *(61)*. In this study, 100 patients presenting within 6 h of symptom onset of an anterior AMI were randomized to receive a 40-mg IV bolus of cariporide ($n = 49$) vs placebo ($n = 51$) prior to reperfusion. Only patients with TIMI 1–0 flow in the left anterior descending artery were included in the study. The ejection fraction over a 3-wk period remained unchanged in the placebo group at 40 ± 2% vs 40 ± 3%, whereas an increase from 44 ± 2% to 50 ± 2% was observed with cariporide treatment ($p < 0.045$). The area-under-the-curve (AUC) for CK-MB was significantly reduced in the cariporide-treated vs placebo group; however, peak total CK and the AUC for total CK were similar for both groups. Clinical outcomes at 3 wk including death, heart failure, acute reocclusion, and emergency CABG were similar although the number of events was small.

Trimetazidine

Trimetazidine is an antianginal agent used outside the United States; its mechanism of action remains incompletely understood, although it seems to alter myocardial metabolism, shifting away from fatty acid oxidation and toward glucose oxidation *(62)*. Steg and colleagues randomized 94 patients undergoing primary angioplasty for AMI (within 6 h of symptom onset) to receive trimetazidine vs placebo. Baseline and procedural characteristics were similar between groups. A 40-mg IV bolus of trimetazidine was administered prior to PCI followed by a 60-mg/d IV infusion. Although the trimetazidine group experienced a more rapid resolution of ST-segment elevations, clinical outcomes including left ventricular function and infarct size (determined by myoglobin mass) were similar to controls *(63)*.

Modulators of Free-Radical Injury

Recombinant Human Superoxide Dismutase (h-SOD)

Flaherty et al. studied whether treatment with h-SOD prior to primary PCI reduces free-radical mediated reperfusion injury and improves clinical outcomes *(64)*. In this study, 120 patients were randomized to receive h-SOD ($n = 61$) as a 10-mg/kg IV bolus followed by a 60-min IV infusion at 0.2 mg/kg/min vs placebo ($n = 59$) immediately prior to PCI. Primary clinical endpoints were similar between h-SOD-treated and placebo groups (rates of death or in-hospital urgent revascularization were 29.5% vs 35.6%, respectively; p = NS). Improvement in left ventricular function was no different between groups.

Fluosol

Fluosol, a perfluorochemical emulsion, offers a potential means to improve oxygenation of the heart during periods of ischemia-reperfusion. Interestingly, Fluosol contains 2.7% RheothRX. In a small pilot trial of nine patients presenting within 4 h of symptom onset of an anterior AMI, Forman and co-workers found that intracoronary Fluosol delivered immediately after primary PTCA (40 mL/min over 30 min) resulted in a significant reduction in infarct size and in greater improvement in regional left ventricular function *(65)*. Only patients with TIMI 0 or 1 flow were included in this study.

The TAMI-9 investigators found no benefit for adjunctive Fluosol therapy in a randomized, open-labeled trial of 430 patients undergoing thrombolysis for AMI. Fluosol infusion was initiated at 15 mL/kg IV over 1 h immediately after the start of t-PA therapy. Primary endpoints included infarct size and changes in left ventricular function *(66)*.

Other Strategies

A number of adjunctive therapies for either thrombolysis or primary PCI for AMI are currently being evaluated in randomized clinical trials. Magnesium is

much studied yet its value remains unclear; in a trial of intravenous magnesium with primary PCI, no benefit was found *(67)*. Glucose–insulin–potassium infusion tended to reduce adverse outcomes in a myocardial infarction trial, with significant improvement compared with placebo in the subgroup undergoing revascularization *(68)*. A number of agents have promising preclinical animal data and undoubtedly there will be continued attention to the possibility of cardioprotection during infarction.

CONTRAST AGENTS

Although often not thought of as a drug, radiographic contrast has effects beyond the primary purpose of facilitating coronary imaging. Contrast media are vasodilators *(69)*. Nonionic contrast can initiate platelet degranulation *(70)*. In animal models, contrast has protective effects suggesting the induction of ischemic preconditioning *(71)*. It is controversial whether the selection from among the current generation of contrast media can impact clinical outcomes in the setting of PCI, but there are certainly reasons to wonder. Older contrast media such as diatrizoate (Renograffin, Hypaque) have a high osmolality of approx 2000 mosM/kg. These high-osmolar agents are associated with increased rates of hemodynamic and electrophysiologic perturbations as well as clinical complications compared with the low- and isosmolar agents. Modern contrast media can be categorized as nonionic vs ionic, and low-osmolar (600 mosM/kg) vs isosmolar (290 mosM/kg).

From the TIMI 14 trial of t-PA or reteplase (r-PA) vs low-dose lytic + abciximab, a recent analysis related the angiographic, electrocardiographic, and clinical outcomes to the (nonrandomized) selection of ionic or non-ionic contrast for the 90-min angiogram and PCI. While there was no effect of contrast on the rate of TIMI 3 epicardial flow, ionic contrast was associated with a longer duration of ischemia, suggesting microvascular obstruction as a possible mechanism *(72)*.

Patients ($n = 856$) undergoing high-risk PCI in the COURT trial, a multicenter prospective double-blind study, received the isosmolar nonionic dimer iodixanol (Visipaque) vs the low-osmolar ionic agent ioxaglate (Hexabrix) *(73)*. Baseline characteristics, index presentations, extent of coronary disease, stent implantation (~30%), adjunctive device use, abciximab use, and ACT levels were similar between groups. Approximately half of the patients presented with unstable angina, one-third with AMI, and the remainder with post-infarction angina. The composite in-hospital primary endpoint (abrupt closure, emergency repeat catheterization, stroke, peri-procedural CK $>$ three times control, emergency coronary bypass surgery, and cardiac death) occurred less frequently in those receiving iodixanol compared with those receiving ioxaglate (5.4% vs 9.5%, respectively; $p = 0.027$). There was a trend toward fewer total clinical events at 30 d in patients randomized to iodixanol (9.1% vs 13.2% for ioxaglate; $p = 0.07$).

Interestingly, the use of abciximab eliminated the difference between the two contrast agents.

In the Visipaque in Percutaneous Transluminal Coronary Angioplasty (VIP) study, 1411 patients received either iodixanol or ioxaglate during PCI. Exclusion criteria included AMI, unprotected left main stenosis, left ventricular ejection fraction $< 35\%$, and preintervention use of abciximab. Baseline demographics and use of heparin, abciximab (~40%), and stents were similar between groups. The primary endpoint, a composite of death, stroke, myocardial infarction, coronary artery bypass grafting, and re-PCI after 2 d, occurred in 4.3% of the total population, with no statistically significant difference between groups (iodixanol, 4.7%; ioxaglate, 3.9%; $p = 0.45$).

Given the increased use of platelet GP IIb/IIIa antagonists and higher rates of stenting, the role of contrast agents deserves further investigation.

LOCAL DRUG DELIVERY TO THE ARTERIAL WALL

AMI is initiated by the interaction of local phenomena in the vascular wall with systemic factors. As such, it is intriguing to speculate on the possibility that drug therapy delivered locally to the site of the atherosclerotic/thrombotic event might offer additional benefits beyond the systemic drug therapies that are currently being employed. A variety of catheters have been developed for the purpose of applying drugs to a local segment of the coronary artery. While these have been useful for vascular experimentation and clinical studies of local abciximab administration *(74)*, they have not been adopted into clinical practice. In pig coronaries the infusion itself (of saline) induced a neointimal restenotic response *(75)*.

Urokinase (300–500 U) loaded onto a hydrogel-coated balloon or a control balloon was used for PCI in patients with acute coronary syndromes. There was no effect on the acute results, but more patients receiving urokinase had ischemic events in follow-up. These results may be attributable to persistent elevation of fibrinopeptide A in the urokinase group but not in the control group *(76)*.

Despite a number of such negative studies, local drug delivery may ultimately succeed as an important tool, having the potential to achieve high concentrations of therapeutic agents at the site of arterial disease while avoiding systemic toxicities. Stents provide a platform for drug delivery, being implanted into direct and permanent contact with the diseased artery, and have the potential to carry significant quantities of therapeutic compounds, either with or without polymeric vehicle coatings. Heparin-coated stents have been associated with excellent clinical results including AMI trials *(77,78)*. Randomized comparisons of heparin-coated and uncoated stents, however, are lacking.

Early clinical data suggest that local delivery of paclitaxel *(79)* or rapamycin *(80)* in drug-eluting stents may limit restenosis due to neointimal hyperplasia. As we gain further understanding of the mechanisms of plaque instability, deliv-

ery of plaque-modulating drugs via stents may also be used to interrupt or prevent the phenomena that predispose to myocardial infarction.

CONCLUSIONS

A major limitation of reperfusion therapy is the consequent impairment of the microvasculature. Defining treatments directed at preserving the microcirculation during reperfusion therapy is therefore an active area of investigation. The outlook appears optimistic since basic mechanisms are being clarified and the tools necessary to study microvascular integrity (such as MCE and MRI in addition to the angiographically derived TMPG) have been validated. A number of small studies have revealed promising candidates; however, definitive data from large-scale trials are currently lacking. Several large-scale trials are currently underway to evaluate promising therapies.

At present, optimum management of patients with AMI undergoing percutaneous revascularization must be guided by judgment, with careful attention to good technique, anticoagulation, and inhibition of platelet aggregation. For now, prevention and treatment of microvascular and reperfusion complications can begin with consideration of the vasodilator drugs nitroglycerin, adenosine, calcium channel blockers, and nitroprusside.

REFERENCES

1. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–1508.
2. Anderson JL, Karagounis LA, Califf RM. Metaanalysis of five reported studies on the relation of early coronary patency grades with mortality and outcomes after acute myocardial infarction. Am J Cardiol 1996;78:1–8.
3. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125–130.
4. Ohman EM, Topol EJ, Califf RM, et al. An analysis of the cause of early mortality after administration of thrombolytic therapy. Coron Artery Dis 1993;4:957.
5. Boissel JP, Castaigne A, Mercier C, Lion L, Leizorovicz A. Ventricular fibrillation following administration of thrombolytic treatment. Eur Heart J 1996;17:213–221.
6. Berger PB, Ellis SG, Holmes DR Jr, Granger CB, Criger DA, Betriu A, et al. Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction. Results from the Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO-IIb) Trial Circulation 1999;100:14–20.
7. Forman MB, Puett DW, Virmani R. Endothelial and myocardial injury during ischemia and reperfusion: pathogenesis and therapeutic implications. J Am Coll Cardiol 1989;13:450–459.
8. Vanden Hoek TL, Shao Z, Li C, Zak R, Schumacker PT, Becker LB. Reperfusion injury on cardiac myocytes after simulated ischemia. Am J Physiol 1996;270(4 Pt 2):H1334–1341.
9. Wu KC, Kim RJ, Bluemke DA, Rochitte CE, Zerhouni EA, Becker LC, Lima JA. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. J Am Coll Cardiol 1998;32:1756–1764.

10. Destro G, Marino P, Barbieri E, Zorzi A, Brighetti G, Maines M, et al. Postinfarctional remodeling: increased dye intensity in the myocardial risk area after angioplasty of infarct-related coronary artery is associated with reduction of ventricular volumes. J Am Coll Cardiol 2001;37:1239–1245.
11. Morishima I, Sone T, Okumura K, Tsuboi II, Kondo J, Mukawa H, et al. Angiopathic no-reflow phenomenon as a predictor of adverse long-term outcme in patients treated with percutaneous transluminal coronary angioplaaasty for first acute myocardial infarctions. J Am Col Cardiol 2000; 36(4): 1202–1209.
12. Rochitte CE, Lima JA, Bluemke DA, Reeder SB, McVeigh ER, Furuta T, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation 1998;98:1006–1014.
13. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124–1136.
14. Kuzuya T, Hoshida S, Yamashita N, Fuji H, Oe H, Hori M, et al. Delayed effects of sublethal ischemia on the acquisition of tolerance to ischemia. Circ Res 1993;72:1293–1299.
15. Bolli R. The late phase of preconditioning. Circ Res 2000;87:972–983.
16. Forbes RA, Steenbergen C, Murphy E. Diazoxide-induced cardioprotection requires signaling through a redox-sensitive mechanism. Circ Res 2001;88:802–809.
17. Sasaki N, Sato T, Ohler A, O'Rourke B, Marban E. Activation of mitochondrial ATP-dependent potassium channels by nitric oxide. Circulation 2000;101:439–445.
18. Sato T, Sasaki N, O'Rourke B, Marban E. Adenosine primes the opening of mitochondrial ATP-sensitive potassium channels: a key step in ischemic preconditioning? Circulation 2000;102:800–805.
19. Miura T, Liu Y, Kita H, Ogawa T, Shimamoto K. Roles of mitochondrial ATP-sensitive K channels and PKC in anti-infarct tolerance afforded by adenosine A1 receptor activation. J Am Coll Cardiol 2000;35:238–245.
20. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. Eur Heart J 2001;22:729–739.
21. Abbo KM, Dooris M, Glazier S, O'Neill WW, Byrd D, Grines CL, Safian RD. Features and outcome of no-reflow after percutaneous coronary intervention. Am J Cardiol 1995;75: 778–782.
22. Piana RN, Paik GY, Moscucci M, Cohen DJ, Gibson CM, Kugelmass AD, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. Circulation 1994;89:2514–2518.
23. Rentrop KP, Blanke H, Karsch KR, Wiegand V, Kostering H, Oster H, Leitz K. Acute myocardial infarction: intracoronary application of nitroglycerin and streptokinase. Clin Cardiol 1979;2:354–363.
24. Linden J. Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. Annu Rev Pharmacol Toxicol 2001;41:775–787.
25. Hata K, Whittaker P, Kloner RA, Przyklenk K. Brief antecedent ischemia attenuates platelet-mediated thrombosis in damaged and stenotic canine coronary arteries: role of adenosine. Circulation 1998;97:692–702.
26. Heidland UE, Heintzen MP, Schwartzkopff B, Strauer BE. Preconditioning during percutaneous transluminal coronary angioplasty by endogenous and exogenous adenosine. Am Heart J 2000;140:813–820.
27. Wasir H, Bhan A, Choudhary SK, Sharma R, Chauhan S, Venugopal P. Pretreatment of human myocardium with adenosine. Eur J Cardiothorac Surg 2001;19:41–46.
28. Miller B, Lesnefsky E, Heyborne T, Schmidt B, Freeman K, Breckinridge S, et al. Cough-cardiopulmonary resuscitation in the cardiac catheterization laboratory: hemodynamics during an episode of prolonged hypotensive ventricular tachycardia. Cathet Cardiovasc Diagn 1989;18:168–171.

29. Claeys MJ, Vrints CJ, Bosmans JM, Conraads VM, Snoeck JP. Aminophylline inhibits adaptation to ischaemia during angioplasty. Role of adenosine in ischaemic preconditioning. Eur Heart J 1996;17:539–544.
30. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. Circulation. 2000;101:2154–2159.
31. Assali AR, Sdringola S, Ghani M, Denkats AE, Yepes A, Hanna GP, et al. Intracoronary adenosine administered during percutaneous intervention in acute myocardial infarction and reduction in the incidence of "no reflow" phenomenon. Catheter Cardiovasc Interv 2000;51:27–31.
32. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, et al. Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. J Am Coll Cardiol 1999;34:1711–1720.
33. Fischell TA, Carter AJ, Foster MT, Hempsall K, DeVries J, Kim DH, Kloostra A. Reversal of "no reflow" during vein graft stenting using high velocity boluses of intracoronary adenosine. Cathet Cardiovasc Diagn 1998;45:360–365.
34. Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, Sakai K. Attenuation of the no-reflow phenomenon after coronary angioplasty for acute myocardial infarction with intracoronary papaverine. Am Heart J 1996;132:959–963.
35. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 1987;327:524–526.
36. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. J Am Coll Cardiol 2001;37:1335–1343.
37. Taniyama Y, Ito H, Iwakura K, Masuyama T, Hori M, Takiuchi S, et al. Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. J Am Coll Cardiol 1997;30:1193–1199.
38. Kaplan BM, Benzuly KH, Kinn JW, Bowers TR, Tilli FV, Grines CL, et al. Treatment of no-reflow in degenerated saphenous vein graft interventions: comparison of intracoronary verapamil and nitroglycerin. Cathet Cardiovasc Diagn 1996;39:113–118.
39. Webb JG, Carere RG, Virmani R, Baim D, Teirstein PS, Whitlow P, et al. Retrieval and analysis of particulate debris after saphenous vein graft intervention. J Am Coll Cardiol 1999;34:468–475.
40. Herzog WR, Vogel RA, Schlossberg ML, Edenbaum LR, Scott HJ, Serebruany VL. Short-term low dose intracoronary diltiazem administered at the onset of reperfusion reduces myocardial infarct size. Int J Cardiol 1997;59:21–27.
41. Jalinous F, Mooney JA, Mooney MR. Pretreatment with intracoronary diltiazem reduces non-Q-wave myocardial infarction following directional atherectomy. J Invas Cardiol 1997; 9:270–273.
42. Fugit MD, Rubal BJ, Donovan DJ. Effects of intracoronary nicardipine, diltiazem and verapamil on coronary blood flow. J Invasive Cardiol 2000;12:80–85.
43. Liem A, Zijlstra F, Ottervanger JP, Hoorntje JC, Suryapranata H, de Boer MJ, Verheugt FW. High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the Heparin in Early Patency (HEAP) randomized trial. J Am Coll Cardiol 2000;35: 600–604.
44. Ambrose JA, Almeida OD, Sharma SK, Torre SR, Marmur JD, Israel DH, et al. Adjunctive thrombolytic therapy during angioplasty for ischemic rest angina. Results of the TAUSA Trial. TAUSA Investigators. Thrombolysis and Angioplasty in Unstable Angina trial. Circulation 1994;90:69–77.
45. Neumann FJ, Blasini R, Schmitt C, Alt E, Dirschinger J, Gawaz M, Kastrati A, Schomig A. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.

46. Giri S, Mitchel JF, Hirst JA, McKay RG, Azar RR, Mennett R, et al. Synergy between intracoronary stenting and abciximab in improving angiographic and clinical outcomes of primary angioplasty in acute myocardial infarction. Am J Cardiol 2000;86:269–274.
47. Collet JP, Montalescot G, Lesty C, Mishal Z, Soria J, Choussat R, et al. Effects of abciximab on the architecture of platelet-rich clots in patients with acute myocardial infarction undergoing primary coronary intervention. Circulation 2001;103:2328–2331.
48. The ESPRIT investigators. Novel dosing regimen of eptifibatide in planned coronary stent implantation (ESPRIT): a randomised, placebo-controlled trial. Lancet 2000;356:2037–2044.
49. Gibson CM, Cohen DJ, Cohen EA, Lui HK, Murphy SA, Marble SJ, et al. Effect of eptifibatide on coronary flow reserve following coronary stent implantation (an ESPRIT substudy). Enhanced suppression of the platelet IIb/IIIa receptor with integrilin therapy. Am J Cardiol 2001;87:1293–1295.
50. Ohman EM, Kleiman NS, Gacioch G, Worley SJ, Navetta FI, Talley JD, et al. Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled, dose-ranging trial. IMPACT-AMI Investigators. Circulation 1997;95:846–854.
51. Bartorelli AL, Trabattoni D, Galli S, Grancini L, Cozzi S, Ravagnani P. Successful dissolution of occlusive coronary thrombus with local administration of abciximab during PTCA Catheter Cardiovasc Interv 1999;48:211–213.
52. O'Keefe JH, Grines CL, DeWood MA, Schaer GL, Browne K, Magorien RD, et al. Poloxamer-188 as an adjunct to primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:747–750.
53. Schaer GL, Spaccavento LJ, Browne KF, Krueger KA, Krichbaum D, Phelan JM, et al. Beneficial effects of RheothRx injection in patients receiving thrombolytic therapy for acute myocardial infarction. Results of a randomized, double-blind, placebo-controlled trial. Circulation 1996;94:298–307.
54. CORE investigators. Effects of RheothRx on mortality, morbidity, left ventricular function, and infarct size in patients with acute myocardial infarction. Circulation 1997;96:192–201.
55. Taira N. Similarity and dissimilarity in the mode and mechanism of action between nicorandil and classical nitrates: an overview. J Cardiovasc Pharmacol 1987;10(Suppl 8):S1–9.
56. Ito H, Taniyama Y, Iwakura K, Nishikawa N, Masuyama T, Kuzuya T, et al. Intravenous nicorandil can preserve microvascular integrity and myocardial viability in patients with reperfused anterior wall myocardial infarction. J Am Coll Cardiol 1999;33:654–660.
57. Akao M, Ohler A, O'Rourke B, Marban E. Mitochondrial ATP-sensitive potassium channels inhibit apoptosis induced by oxidative stress in cardiac cells. Circ Res 2001;88:1267–1275.
58. Forbes RA, Steenbergen C, Murphy E. Diazoxide-induced cardioprotection requires signaling through a redox-sensitive mechanism. Circ Res 2001;88:802–809.
59. Theroux P, Chaitman BR, Danchin N, Erhardt L, Meinertz T, Schroeder JS, et al. Inhibition of the sodium-hydrogen exchanger with cariporide to prevent myocardial infarction in high-risk ischemic situations. Main results of the GUARDIAN trial. Guard during ischemia against necrosis (GUARDIAN) Investigators. Circulation 2000;102:3032–3038.
60. Klein HH, Pich S, Bohle RM, Lindert-Heimberg S, Nebendahl K. Na(+)/H(+) exchange inhibitor cariporide attenuates cell injury predominantly during ischemia and not at onset of reperfusion in porcine hearts with low residual blood flow. Circulation 2000;102:1977–1982.
61. Rupprecht HJ, vom Dahl J, Terres W, Seyfarth KM, Richardt G, Schultheibeta HP, et al. Cardioprotective effects of the Na(+)/H(+) exchange inhibitor cariporide in patients with acute anterior myocardial infarction undergoing direct PTCA. Circulation 2000;101:2902–2908.
62. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res 2000;86:580–588.

63. Steg PG, Grollier G, Gallay P, Morice M, Karrillon GJ, Benamer H, et al. A randomized double-blind trial of intravenous trimetazidine as adjunctive therapy to primary angioplasty for acute myocardial infarction. Int J Cardiol 2001;77:263–273.
64. Flaherty JT, Pitt B, Gruber JW, Heuser RR, Rothbaum DA, Burwell LR, et al. Recombinant human superoxide dismutase (h-SOD) fails to improve recovery of ventricular function in patients undergoing coronary angioplasty for acute myocardial infarction. Circulation 1994;89:1982–1991.
65. Forman MB, Perry JM, Wilson BH, Verani MS, Kaplan PR, Shawl FA, Friesinger GC. Demonstration of myocardial reperfusion injury in humans: results of a pilot study utilizing acute coronary angioplasty with perfluorochemical in anterior myocardial infarction. J Am Coll Cardiol 1991;18:911–918.
66. Wall TC, Califf RM, Blankenship J, Talley JD, Tannenbaum M, Schwaiger M, et al. Intravenous Fluosol in the treatment of acute myocardial infarction. Results of the Thrombolysis and Angioplasty in Myocardial Infarction 9 Trial. TAMI 9 Research Group. Circulation 1994;90:114–120.
67. Santoro GM, Antoniucci D, Bolognese L, Valenti R, Buonamici P, Trapani M, et al. A randomized study of intravenous magnesium in acute myocardial infarction treated with direct coronary angioplasty. Am Heart J 2000;140:891–897.
68. Diaz R, Paolasso EA, Piegas LS, Tajer CD, Moreno MG, Corvalan R, et al. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group. Circulation 1998;98:2227–2234.
69. Limbruno U, Petronio AS, Amoroso G, Baglini R, Paterni G, Merelli A, et al. The impact of coronary artery disease on the coronary vasomotor response to nonionic contrast media. Circulation 2000;101:491–497.
70. Chronos NA, Goodall AH, Wilson DJ, Sigwart U, Buller NP. Profound platelet degranulation is an important side effect of some types of contrast media used in interventional cardiology. Circulation 1993;88(5 Pt 1):2035–2044.
71. Falck G, Bruvold M, Schjott J, Jynge P. Protective effects of repetitive injections of radiographic contrast media on the subsequent tolerance to ischemia in the isolated rat heart. Cardiovasc Intervent Radiol 2000;23:466–471.
72. Gibson CM, Kirtane AJ, Murphy SA, Marble SJ, de Lemos JA, Antman EM, Braunwald E. Impact of contrast agent type (ionic versus nonionic) used for coronary angiography on angiographic, electrocardiographic, and clinical outcomes following thrombolytic administration in acute myocardial infarction. Catheter Cardiovasc Interv 2001;53:6–11.
73. Davidson CJ, Laskey WK, Hermiller JB, Harrison JK, Matthai W Jr, Vlietstra RE, et al. Randomized trial of contrast media utilization in high-risk PTCA: the COURT trial. Circulation 2000;101:2172–2177.
74. Bailey SR, O'Leary E, Chilton R. Angioscopic evaluation of site-specific administration of ReoPro. Cathet Cardiovasc Diagn 1997;42:181–184.
75. Kim WH, Hong MK, Kornowski R, Tio FO, Leon MB. Saline infusion via local drug delivery catheters is associated with increased neointimal hyperplasia in a porcine coronary in-stent restenosis model. Coron Artery Dis 1999;10:629–632.
76. Wilensky RL, Pyles JM, Fineberg N. Increased thrombin activity correlates with increased ischemic event rate after percutaneous transluminal coronary angioplasty: lack of efficacy of locally delivered urokinase. Am Heart J 1999;138(2 Pt 1):319–325.
77. Shin EK, Son JW, Sohn MS, Jin DK, Park GS, Koh KK, et al. Efficacy of heparin-coated stent in early setting of acute myocardial infarction. Catheter Cardiovasc Interv 2001;52:306–312.
78. Grines CL, Cox DA, Stone GW, Garcia E, Mattos LA, Giambartolomei A, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1999;341:1949–1956.

79. Heldman AW, Cheng L, Jenkins GM, Heller PF, Kim DW, Ware M Jr, et al. Paclitaxel stent coating inhibits neointimal hyperplasia at 4 weeks in a porcine model of coronary restenosis. Circulation 2001;103:2289–2295.
80. Sousa JE, Costa MA, Abizaid A, et al. Lack of neotintimal proliferation after implantation of sirolimus-coated stents in human coronary arteries. Circulation 2001;103:192–195.
81. Fischell TA, Foster MT 3rd. Adenosine for reversal of "no reflow." Catheter Cardiovasc Interv 1999;46:508.
82. Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, et al. Effects of various doses of intracoronary verapamil on coronary resistance vessels in humans. Jpn Circ J 1997;61:755–761.
83. Oldenburg O, Eggebrecht H, Herrmann J, Naber CK, Haude M, Erbel R, Baumgart D. Dose-dependent effects of intracoronary verapamil on systemic and coronary hemodynamics. Cardiovasc Drugs Ther 2000;14:651–655.

8 Platelet Glycoprotein IIb/IIIa Receptor Blockade in Primary Angioplasty

Abdulhay Albirini, MD
and Sorin J. Brener, MD

CONTENTS

RATIONALE FOR USING PLATELET RECEPTOR BLOCKERS IN ACUTE MYOCARDIAL INFARCTION

Platelet Activity in Acute Myocardial Infarction—Thrombus Composition

Acute coronary syndromes, including acute myocardial infarction (AMI), have a common underlying pathophysiologic mechanism initiated by atherosclerotic plaque disruption and followed by platelet aggregation and thrombus formation. Exposure of thrombogenic plaque components, including collagen, fibronectin, and von Willebrand factor, to circulating platelets, together with local high shear stress, lead to platelet adhesion, activation, and aggregation. In turn, platelet aggregation facilitates thrombin generation and conversion of fibrinogen to fibrin. Thrombin further stimulates platelet activation and aggregation, leading to a vicious cycle. Ultimately, a thrombus composed of platelets

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

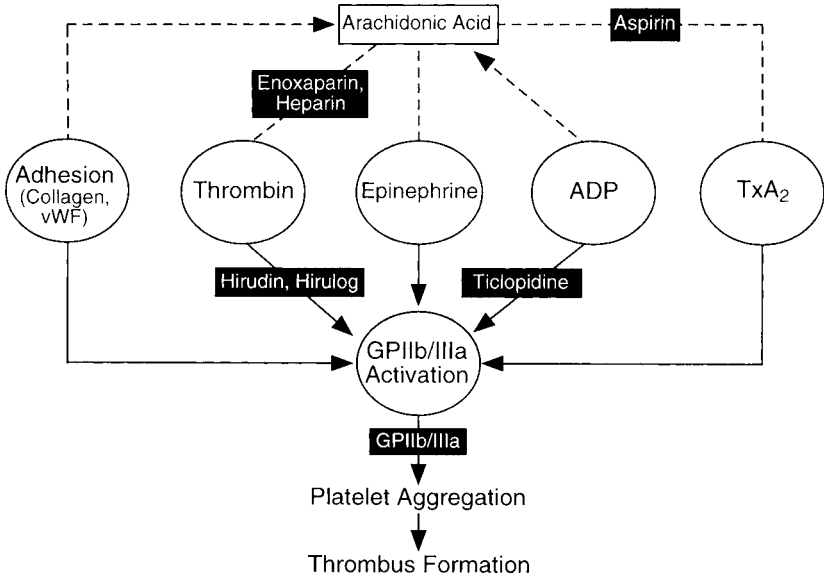


Fig. 1. Pathways of platelet activation and inhibition by various therapies. (Reprinted with permission from Greenbaum AB, Harrington RA, Ohman EM. The use of glycoprotein IIb/IIIa inhibition in acute myocardial infarction. In Lincoff AM and Topol EJ (eds): Platelet Glycoprotein IIb/IIIa Inhibitors in Cardiovascular Disease. Humana Press, Totowa, NJ, 1999, p. 230.)

and fibrin causes complete occlusion of the coronary artery and results in AMI *(1)*.

Whereas platelet activation occurs via several pathways (Fig. 1) *(2)*, aggregation is funneled through one final common pathway: the binding of fibrinogen to the glycoprotein (GP) IIb/IIIa receptor on the platelet surface *(3)*. The GP IIb/IIIa receptor in the resting platelet has a configuration permitting slow ligand binding, but platelet activation induces a conformational change in this complex, facilitating the binding of fibrinogen and inducing platelet aggregation and thrombosis *(4)*.

Evidence of platelet hyperactivity abounds in patients with AMI. Elevated plasma concentrations of platelet-derived substances such as platelet factor 4, thromboxane B_2, and β-thromboglobulin have been well described *(5–7)*. Increased numbers of circulating aggregated platelets have also been found in patients with AMI *(8)*. Thus platelets play a major role in the thrombotic response to plaque rupture, are integrally involved in the development of AMI, and would be a prime target for inhibition as an approach to improving outcomes.

Treatment with aspirin, the main platelet antagonist used in AMI, results in a significant reduction in mortality *(9)* and reduces the risk of early reinfarction

and recurrent ischemia *(10)*. Aspirin is a weak antiplatelet agent *(11)*, however, inhibiting only the thromboxane A_2-mediated pathway of platelet activation. Platelet activation continues to occur through thromboxane A_2-independent pathways, leading to platelet aggregation and thrombin formation *(12)*.

Rapid and durable reperfusion of the occluded coronary artery is the aim of treatment in patients with AMI. Fibrinolytic therapy *(13)* and primary angioplasty *(14)* are the two main treatment modalities used to achieve reperfusion; this chapter focuses on the latter.

Primary Angioplasty and Platelet Activation

Although a successful strategy, primary angioplasty is still complicated by ischemic events including death, reinfarction, and urgent revascularization procedures in as many as 25% of patients by 6 mo *(15)*. The additional plaque disruption superimposed on the initial rupture and the interaction of the atherosclerotic plaque contents, exposed endothelium, platelets, and coagulation factors lead to thrombosis and compromise arterial patency in 10%–20% of patients.

Intravascular ultrasound (IVUS) performed after angiographically successful primary angioplasty can detect predictors of abrupt vessel closure such as the presence of residual disrupted plaque and intraluminal thrombus *(16)*. Platelets may adhere more avidly to the preexisting coronary thrombus or disrupted vessel surface *(17,18)*. Reocclusion may be difficult to treat in the presence of a large thrombus burden, and repeat angioplasty may be complicated further by abrupt closure if thrombus persists. Effective blockade of platelet aggregation may substantially reduce this risk and eliminate the consequences of plaque-thrombus embolization.

Thus in AMI, in an environment of platelet hyperactivity, percutaneous interventions add insult to the injury and induce more platelet activation *(18)*. It is intuitive that more powerful platelet inhibition is needed in the setting of primary angioplasty for AMI. The GP IIb/IIIa receptor blockers, a very potent class of platelet inhibitors, are among the latest advances in therapy for AMI and have shown promise as an adjunct to primary angioplasty.

Experimental Evidence—The Concept of Dethrombosis

In early experimental studies, GP IIb/IIIa inhibitors resulted in less platelet aggregation and vessel closure than aspirin alone during percutaneous coronary intervention. Bates et al. *(19)* randomized 24 dogs to one of three intravenous treatment groups: saline placebo, 325 mg aspirin, or 0.8 mg/kg 7E3 (a monoclonal antibody directed against the platelet GP IIb/IIIa receptor), prior to arterial injury induced by balloon angioplasty and external clamps. Platelet aggregation was decreased in the groups given aspirin or 7E3, and the 7E3 antibody was superior to aspirin in maintaining hyperemic coronary blood flow after release of the external stenosis. In the placebo group, arterial occlusion developed in five

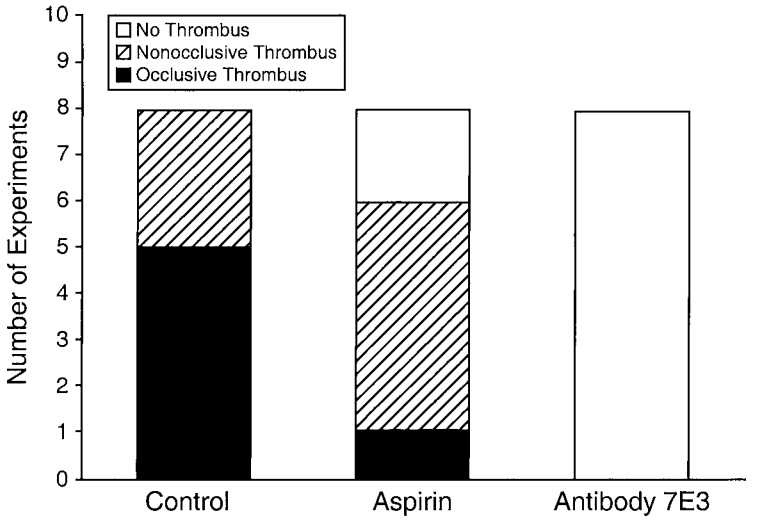


Fig. 2. Occlusive and nonocclusive thrombus formation after balloon arterial injury. (Adapted with permission from ref. *19*.)

dogs, and nonocclusive thrombus was seen in the other three. In the aspirin group, arterial occlusion developed in one dog, and nonocclusive thrombus was seen in five dogs. Neither arterial occlusion nor thrombus formation was seen in the group treated with 7E3 (Fig. 2). This study suggested the possibility of improving outcomes after balloon angioplasty for AMI using stronger antiplatelet therapy with GP IIb/IIIa inhibition.

Gold et al. *(20)* studied 14 dogs after left anterior descending coronary artery thrombosis was induced by endothelial trauma and thrombin instillation in the presence of distal stenosis. Twenty minutes after induction of coronary thrombosis, the animals were divided into three groups: five were treated with heparin alone; four received heparin and aspirin; and five were treated with heparin, aspirin, and intravenous 7E3. Four of the five animals treated with heparin, aspirin, and 7E3 showed stable and sustained reflow at 50 ± 9 min. No other animals showed even transient reflow ($p < 0.05$). Figure 3 is a scanning electron micrograph of the thrombosed segment of a canine left anterior descending artery from group 3 obtained 1 h after 7E3-induced reflow; channels are seen through a large, segmented residual thrombus. This study demonstrated the ability of 7E3 to restore coronary flow in the absence of exogenous plasminogen activator. In addition, once flow had begun through the thrombus, reocclusion did not reoccur.

In another study, Gold et al. *(21)* induced coronary thrombosis in the left anterior descending coronary artery in 39 dogs by intimal damage and thrombin

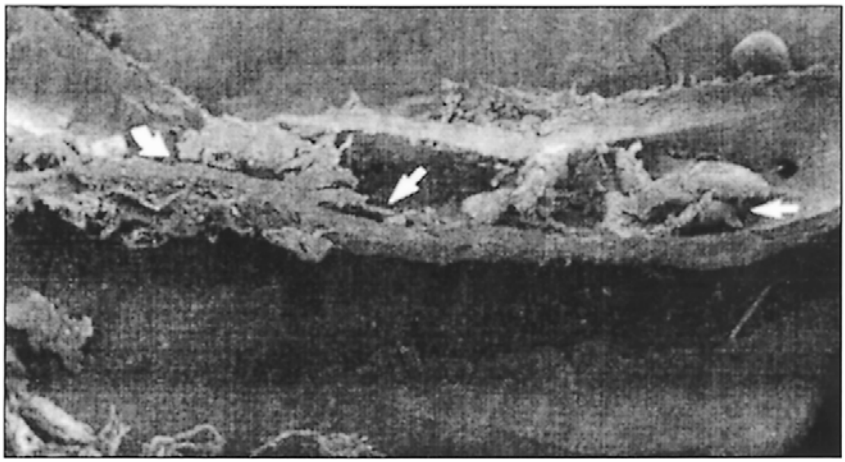


Fig. 3. Scanning electron micrograph at low magnification of the thrombosed segment of the left anterior descending coronary artery in a dog treated with 7E3, heparin, and aspirin. Reflow was from right to left. The lumen contains large residual thrombi, penetrated by small channels (*arrows*). The external stenosis is shown at the curved arrow. (Reprinted with permission from ref. *20*.)

Table 1
Infusion Protocols and Coronary Artery Reperfusion and Reocclusion with rt-PA and 7E3 in a Canine Model of Thrombosis and Thrombolysis

				Reperfusion		*Reocclusion*	
Group	*7E3 (mg/kg)*	*rt-PA (mg/kg)*	*N*	*n/N*	*min*	*n/N*	*min*
I	0.8	—	6	2/6	19 ± 37	0/2	—
II	—	0.45	7	5/7	33 ± 15	5/5	11 ± 11
III-A	0.8	0.45	6	6/6	6 ± 3	0/6	—
III-B	0.6	0.45	5	5/5	8 ± 5	1/5	4
III-C	0.4	0.45	4	3/4	9 ± 9	3/3	7 ± 1
III-D	0.2	0.45	3	3/3	35 ± 23	3/3	3 ± 1
III-E	0.1	0.45	4	3/4	34 ± 18	3/3	3 ± 2
IV	0.6	0.225	4	3/4	12 ± 8	1/3	19
Total			39				

Adapted with permission from ref. *21*.

injection, then randomized the dogs to four groups (Table 1): 7E3 alone at 0.8 mg/kg (group I), recombinant tissue-type plasminogen activator (rt-PA) alone as 0.45 mg/kg boluses (group II), combinations of variable doses of 7E3 and 0.45 mg/kg boluses of rt-PA (group III), and a combination of 0.6 mg/kg 7E3

and 0.225 mg/kg boluses of rt-PA (group IV). Injection of a single bolus of 0.8 mg/kg of 7E3 (group I) was followed by reperfusion in two of six (33%) dogs after 19 and 37 min, and no reocclusion occurred during an observation period of 100 min. Five of the seven (71%) dogs given rt-PA alone (group II) achieved reperfusion at an average of more than 30 min. All five reperfused dogs rapidly showed evidence of reocclusion and intermittent patency. When 0.8 mg/kg 7E3 was given 10 min before a single bolus injection of 0.45 mg/kg rt-PA (group III-A), reperfusion occurred in all animals and was achieved significantly more rapidly than with rt-PA alone; reocclusion did not occur in any of these animals. Similar results were obtained with 0.6 mg/kg 7E3 in combination with a single bolus of 0.45 mg/kg rt-PA (group III-B), although one of the five (20%) dogs showed a single brief period of reocclusion followed by stable reperfusion. Further dose reductions of 7E3 to 0.4 mg/kg and below (groups III-C, III-D, and III-E) resulted in a progressive prolongation of the time to reperfusion, and reocclusion was consistently observed. When 0.6 mg/kg 7E3 was combined with bolus injections of 0.225 mg/kg rt-PA (group IV), rapid and persistent reperfusion was not consistently obtained. This study showed that the combination of 0.8 mg/kg 7E3 and a single bolus injection of 0.45 mg/kg rt-PA was more effective than 7E3 or rt-PA alone. Fibrinolysis occurred more rapidly and reocclusion was prevented. The 7E3 dose–response data indicate that prevention of reocclusion requires profound (~80%) inhibition of platelet aggregation, as achieved by a dose of 0.8 mg/kg 7E3. The combination of 0.6 mg/kg 7E3 with 0.225 mg/kg rt-PA was only partially effective, indicating that facilitation of lysis occurs within a narrow concentration range of these agents.

The No-Reflow Phenomenon

The no-reflow phenomenon is a reduction in epicardial coronary artery blood flow without overt mechanical obstruction. It was first described in animal studies after release of prolonged coronary artery occlusion causing sustained ischemia and was attributed to an ischemic, time-dependent injury to the microvasculature *(22)*. More recently, the no-reflow phenomenon has been observed after a relatively brief ischemic period in the setting of percutaneous coronary intervention *(23–25)*. It has been reported to occur in 12%–48% of cases of primary angioplasty for AMI *(23,26)*. The no-reflow phenomenon has consistently been demonstrated to be a negative prognostic indicator. Patients with no-reflow have larger infarctions, an increased incidence of cardiac rupture and congestive heart failure, and higher mortality rates *(27,28)*.

Several structural and functional alterations at the microcirculatory level have been proposed as mechanisms for the no-reflow phenomenon. Animal and postmortem histologic studies have documented varying degrees of small vessel vasospasm, neutrophil plugging, myocyte contracture, interstitial edema, and hemorrhage. No-reflow may represent a type of reperfusion injury as the free

radicals released locally during reperfusion of ischemic tissue and activation of infiltrating neutrophils are thought to play an important role in vascular injury and loss of capillary autoregulation.

Platelets have also been consistently implicated as contributors to the genesis of no reflow *(29,30)*. Obstructive platelet aggregates within myocardial capillaries and platelet degranulation have been experimentally and clinically observed in reperfused ischemic tissue. The substances released from platelet granules contain multiple vasoactive and chemotactic mediators that exacerbate tissue ischemia and increase neutrophil infiltration. Because of the potential role of platelets in inducing the no-reflow state, the GP IIb/IIIa inhibitors may be of benefit in preventing and treating this phenomenon *(31)*.

One of the important observations in primary angioplasty for AMI has been that stenting is associated with a lower rate of final TIMI flow grade 3 than percutaneous transluminal coronary angioplasty (PTCA) *(32,33)*. This is presumably due to distal embolization of plaque-platelet material during the high-pressure inflation associated with stent deployment. The addition of abciximab increases the rate of TIMI 3 flow after stenting in AMI *(33)*. Considering the common occurrence of no-reflow after percutaneous intervention in AMI and the role platelets play in this phenomenon, GP IIb/IIIa inhibition may be of significant benefit in this setting.

OBSERVATIONAL DATA

The EPIC Trial

The Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial was the first landmark study to evaluate GP IIb/IIIa inhibitors during percutaneous coronary intervention (PCI). It was designed to assess the efficacy of the GP IIb/IIIa inhibitor c7E3 (abciximab) in preventing ischemic complications in the high-risk PCI setting. Patients were randomized to receive either an abciximab bolus, an abciximab bolus plus 12-h infusion, or placebo before PCI.

Of the 2099 patients enrolled in the trial, 64 underwent PCI for AMI; 42 patients were treated with primary PTCA and 22 patients had rescue PTCA after failed fibrinolysis. For the entire cohort of 64 patients, there were no major differences among the three groups in angiographic or procedural characteristics. Outcomes in the direct and rescue PTCA groups were similar and are therefore pooled for the following analyses.

At 30 d, patients who received the bolus and infusion of abciximab had the composite endpoint of death, reinfarction, emergency coronary artery bypass surgery (CABG), or repeat emergency angioplasty reduced by 83% (26.1% vs 4.5%). This suggested an even greater efficacy of abciximab in AMI than in the other patients in the EPIC trial, for whom the reduction in these endpoints was 35% (12.8% vs 8.3%) *(29,34)*.

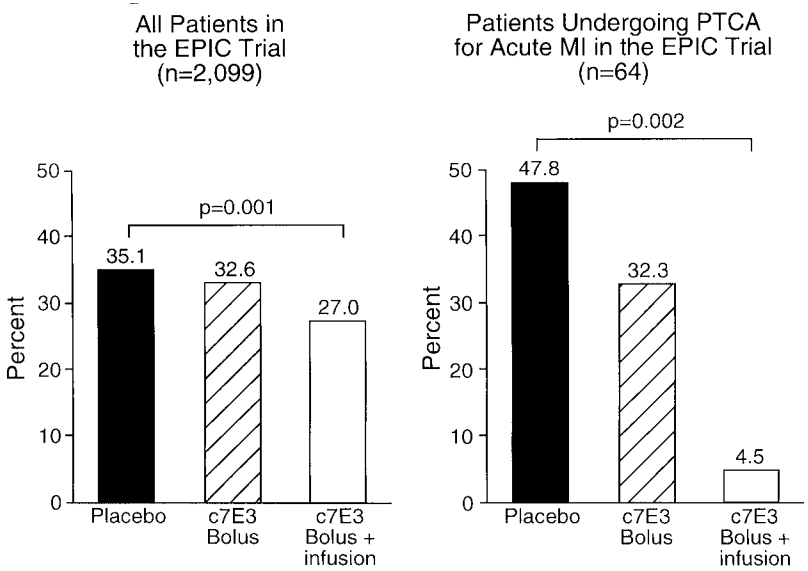


Fig. 4. Comparison of 6-mo composite event rates of death, reinfarction, and emergency revascularization between patients undergoing PTCA for AMI in the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) Trial and the overall EPIC trial patient population. (Adapted with permission from ref. *34*.)

At 6-mo follow-up for the cohort of patients who underwent PCI for AMI, abciximab bolus plus infusion was associated with a 91% reduction in the composite endpoint of death, myocardial infarction, or repeat percutaneous or surgical revascularization when compared with placebo (47.8% vs 4.5%, $p = 0.002$), while the reduction in this composite endpoint was 23% in the total patient population (35.1% vs 27%, $p = 0.001$) (Fig. 4). There was a clear dose response with abciximab in the reduction of reinfarction (17.4%, 5.6%, and 0%, $p = 0.05$ for placebo, bolus, and bolus plus infusion, respectively), and in the incidence of repeat revascularization (34.8%, 11.6%, and 0%, $p = 0.003$, respectively) *(34)*. The magnitude of benefit from abciximab bolus and infusion in AMI is even more compelling when one considers that patients undergoing PTCA for AMI were at higher risk for recurrent ischemic events; this was evident from the higher incidence of clinical restenosis in the placebo arm of the AMI patients than in the placebo arm of the overall trial.

Major bleeding events were more frequent in patients who received abciximab. The only hemorrhagic stroke and all three major spontaneous hemorrhages occurred in abciximab patients. Furthermore, 9 of the 13 major bleeding episodes (including the case of intracranial hemorrhage) occurred in rescue PTCA patients, all of whom had received thrombolytic therapy within the previous 12 h.

IMPACT-II and RESTORE Trials

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) and the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trials evaluated, respectively, the use of eptifibatide and tirofiban, two specific non-antibody inhibitors of the GP IIb/IIIa receptor, in patients undergoing PCI *(35,36)*. In IMPACT-II, 126 of 4010 patients (3%) underwent primary or rescue angioplasty for AMI; in RESTORE, 139 of 2141 (6.4%) underwent primary PTCA for AMI. The use of these two GP IIb/IIIa inhibitors was associated with a trend toward a reduction at 30 d in the primary endpoint of death, myocardial infarction, coronary artery bypass surgery, percutaneous revascularization, or coronary stent implantation for abrupt closure. Prospectively specified subgroup analyses of patients undergoing percutaneous revascularization for AMI revealed trends similar to those of the entire cohorts of both trials with respect to reductions in ischemic events. There was no increase in the risk of major bleeding.

The Mayo Clinic Registry

Data retrospectively analyzed from the Mayo Clinic PTCA registry also suggested improvements in short- and intermediate-term outcomes with abciximab in primary PTCA. Of 292 patients treated with primary PTCA for AMI, 52 received abciximab (0.25 mg/kg bolus followed by 10 μg/min infusion over 12 h) and 240 did not. All patients received standard antiischemic therapy. Abciximab use was associated with a trend toward a decreased in-hospital incidence of death, reinfarction, and CABG (5.8% in the abciximab vs 13.8% in the no-abciximab group, $p = 0.17$) and a significantly reduced incidence of both death (5.8% vs 17.1%, $p < 0.05$) and the composite of death, reinfarction, or the need for CABG at 1 yr (5.8 vs 28.8%, $p < 0.05$) *(37)*.

In summary, these observational data suggested a significant benefit from GP IIb/IIIa receptor inhibition in primary angioplasty for AMI and provided the impetus for the design and conduct of randomized trials of abciximab in primary PTCA.

RANDOMIZED TRIALS

The RAPPORT Trial

The Reopro in Acute myocardial infarction and Primary PTCA Organization and Randomized Trial (RAPPORT) was the first prospective, randomized study to evaluate GP IIb/IIIa blockade during primary angioplasty for AMI, testing the hypothesis that GP IIb/IIIa inhibition would reduce both acute events (death, reinfarction, and urgent revascularization) and ischemic complications. Four hundred eighty-three patients who presented within 12 h of AMI onset and were referred for primary angioplasty were randomized to receive abciximab

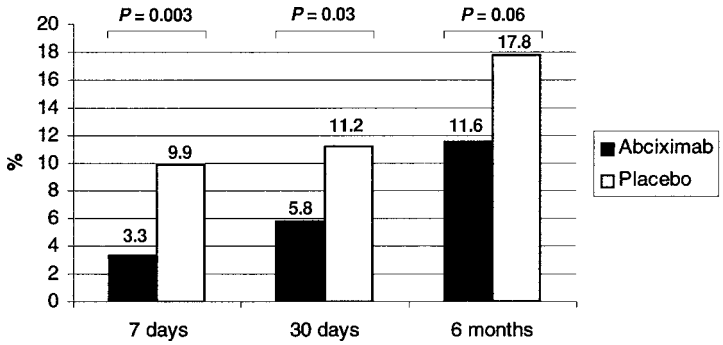


Fig. 5. Incidence of death, reinfarction, or urgent TVR at 7 d, 30 d, and 6 mo in the RAPPORT trial. (Adapted with permission from ref. *38*.)

(241 patients) or placebo (242 patients) before revascularization *(38)*. Only balloon angioplasty and directional atherectomy were permitted. Stent implantation was allowed only for bailout purposes. The activated clotting time was maintained at >300 s during the procedure and early sheath removal was strongly encouraged. The primary efficacy endpoint was the composite of death, reinfarction, and target vessel revascularization (TVR) within 6 mo. The acute phase endpoints were the composite of death, reinfarction, or urgent TVR at 7 and 30 d. Safety was assessed as the incidence of major bleeding (intracerebral hemorrhage or a >5 g% adjusted decline in hemoglobin). On an intention-to-treat basis, abciximab administration prior to angioplasty was associated with a significant reduction in ischemic events at 7 and 30 d (9.9% vs 3.3%, $p = 0.003$ and 11.2% vs 5.8%, $p = 0.03$, respectively). The incidence of death, reinfarction, or urgent TVR at 6 mo was also significantly reduced (17.8% vs 11.6%, $p = 0.048$) (Fig. 5). The 6-mo composite endpoint of death, reinfarction, and any target lesion revascularization was not statistically different (Fig. 6). Abciximab administration prior to PTCA was associated with a 33% reduction in the need for bailout stenting (17.4% vs 11.6%, $p = 0.057$).

Analysis of the data by actual treatment received (study drug and PTCA) revealed an even more pronounced benefit with 73% (2.8% vs 10.5%) and 62% (4.6% vs 12.0%) reductions in the 7-d and 30-d composite endpoints, respectively. There was a 49% reduction in the 6-mo incidence of death, reinfarction, or urgent target vessel revascularization (10.6% vs 19.9%, $p = 0.004$) (Table 2).

Abciximab-treated patients in RAPPORT had a higher incidence of major bleeding (16.6% vs 9.5%, $p = 0.02$) and blood product transfusion (13.7% vs 7.9%, $p = 0.04$) than patients in the placebo arm. Most of the excess major bleeding was confined to the access site. There were no intracranial hemorrhages

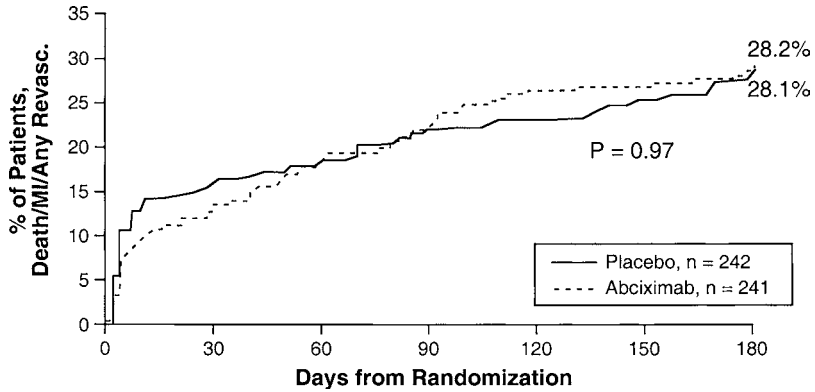


Fig. 6. Probability of death, reinfarction, or any TVR within 6 mo in placebo (*solid line*) and abciximab (*dashed line*) groups in the RAPPORT trial. (Reprinted with permission from ref. *38*.)

Table 2
Outcome in the Treatment Groups
by Actual Treatment Analysis in the RAPPORT Trial

Event	*Placebo, %*	*Abciximab, %*	*OR (95% CI)*	p *value*
7 d				
Death/Re-MI	4.7	1.4	0.28 (0.08–1.06)	0.047
Urgent TVR	6.3	1.4	0.21 (0.06–0.75)	0.008
Death/Re-MI/uTVR	10.5	2.8	0.24 (0.10–0.62)	0.001
30 d				
Death/Re-MI	5.8	3.2	0.54 (0.21–1.43)	0.20
Urgent TVR	7.9	1.8	0.22 (0.07–0.67)	0.004
Death/Re-MI/uTVR	12.0	4.6	0.35 (0.16–0.76)	0.005
6 mo				
Death/Re-MI	12.0	6.9	0.54 (0.27–1.07)	0.07
Urgent TVR	10.5	3.7	0.33 (0.14–0.76)	0.006
Death/Re-MI/uTVR	19.9	10.6	0.45 (0.26–0.80)	0.004

Adapted with permission from ref. *38*.

in either group. Abciximab resulted in a 27-s prolongation of the median activated clotting time (ACT) compared to placebo (364 vs 337 s, respectively). This prolongation in ACT and the generally high intensity of anticoagulation contributed to the increased bleeding observed in RAPPORT with abciximab, which can be reduced by using less heparin when GP IIb/IIIa inhibitors are used.

Table 3
Doppler Flow Velocity Measurements and Ejection Fraction in the Munich Trial

	Abciximab (n = *80*)	*Usual care* (n = *72*)	p
Immediately after stent placement			
Basal flow velocity, cm/s	23.9 ± 9.3	23.7 ± 11.8	0.89
Peak flow velocity, cm/s	40.8 ± 14.8	40.5 ± 18.7	0.91
Flow velocity reserve	1.79 ± 0.49	1.80 ± 0.53	0.93
Global ejection fraction	55.7 ± 12.4	53.5 ± 13.5	0.30
At 14-d follow-up			
Basal flow velocity, cm/s	27.4 ± 11.6	24.5 ± 8.9	0.085
Peak flow velocity, cm/s	58.9 ± 21.2	50.9 ± 16.9	0.012
Flow velocity reserve	2.29 ± 0.65	2.19 ± 0.67	0.36
Global ejection fraction	62.2 ± 13.2	55.9 ± 12.6	0.003

Adapted with permission from ref. *39*.

The Munich Experience

In a prospective randomized trial, Neumann et al. *(39)* assigned patients undergoing stenting within 48 h of AMI symptom onset to receive either standard dose heparin or abciximab plus low-dose heparin. Immediately after the procedure, coronary flow velocities in the stented segment were measured with the Doppler FloWire, basal and peak coronary flow velocity after intracoronary papaverine were determined, and left ventriculography was performed. Fourteen days after the intervention, coronary and left ventricular angiography and flow velocity measurements were repeated.

The study enrolled 200 consecutive patients; 98 were assigned to usual care and 102 to abciximab. At the initial study, both treatment groups had similar basal and peak flow velocities in the recanalized coronary artery. Within 14 d, peak flow velocities increased significantly in both treatment groups and basal flow velocity increased significantly in the abciximab group. The increase in peak flow velocity in patients assigned to abciximab was significantly larger than that in the control group. In both treatment groups coronary flow reserve in the infarct-related artery increased significantly. Improvement of regional left ventricular function within the first 2 wk, as assessed by wall motion index or number of chords with hypokinesis, was significantly greater in patients assigned to abciximab (Table 3). A significant correlation was found between changes in peak flow velocity and changes in wall motion index, and a similar trend was observed for the relation of changes in peak flow velocity to changes in left ventricular ejection fraction. At the 30-d follow-up, death, myocardial infarction, or target lesion reintervention had occurred significantly less fre-

quently in patients in the abciximab group than in the control group (2% vs 9%, $p = 0.031$).

This study presented evidence that abciximab has important effects beyond the maintenance of epicardial vessel patency after stent placement in AMI, suggesting that periinterventional administration of abciximab improves the recovery of coronary microcirculation function and of regional wall motion. This effect could not be attributed to differences in angiographic parameters, hemodynamic characteristics, or epicardial artery patency. Instead, the larger increase in peak flow velocity after administration of abciximab compared to usual care is more likely explained by the prevention of embolization of platelet aggregates to the microvasculature, as well as the attenuation of capillary dysfunction following such an event *(40,41)*. Blockade of the vitronectin receptor and other integrins, such as MAC-1, might also be responsible. Through the MAC-1 receptor, abciximab may attenuate the interaction of leukocytes with the reperfused microvasculature *(42)*, effects known to generate procoagulant and cytotoxic inflammatory responses *(43,44)*.

The GRAPE Trial

In the Glycoprotein Receptor Antagonist Patency Evaluation (GRAPE) pilot study *(45)*, 60 patients less than 6 h from onset of AMI and eligible for primary angioplasty were treated in the emergency room with 160 mg of oral aspirin and 5000 IU of heparin. All patients were then treated with a bolus of abciximab 0.25 mg/kg and a 12-h infusion of 10 μg/min followed by coronary angiography. The endpoint of the study was patency of the infarct-related artery at first contrast injection *(46)*. In 36 patients (60%), Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1 was seen at first contrast injection. TIMI flow grade 3 was seen in 11 patients (18%), and TIMI flow grade 2 or 3 was seen in 24 patients (40%). There was no difference in the incidence of TIMI flow grade 2 or 3 between patients who received abciximab within 2.5 h of the onset of symptoms ($n = 30$) or thereafter ($n = 30$) (Fig. 7). There was also no difference in the rate of TIMI flow grade 2 or 3 between patients who underwent angioplasty within 45 min after initiation of the abciximab administration and those who underwent angioplasty thereafter. None of the 60 patients in the trial died or suffered a stroke or major hemorrhage requiring blood transfusion.

This study demonstrated the positive effect of abciximab bolus given in the emergency room on early infarct-related artery patency. In patients treated early, the TIMI flow grade was 2 or 3 in 40% at 45 min; more typically, no more than 25% of patients are expected to have TIMI grade 2 or 3 flow after 90 min with standard heparin and aspirin treatment *(46–48)*.

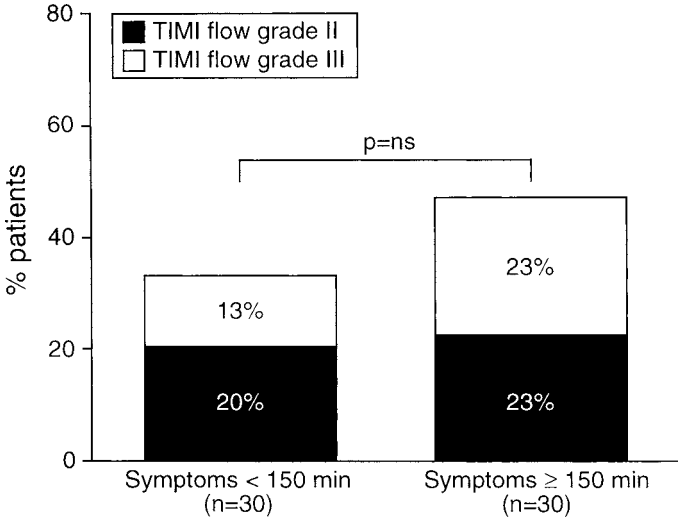


Fig. 7. Relation between the interval from symptom onset to abciximab bolus and the patency of the infarct-related artery at angiography. (Adapted with permission from ref. *45*.)

The ADMIRAL Trial

The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial was a placebo-controlled study to evaluate abciximab as an adjunct to primary PTCA and stenting in patients with AMI. In this multicenter trial, 300 patients presenting with AMI were referred for emergency coronary angiography and percutaneous revascularization. They were randomly assigned to receive either abciximab (0.25 mg/kg bolus and 0.125 μg/kg/min infusion) or placebo before intervention. All patients received heparin, aspirin, and ticlopidine. The abciximab patients had a significantly higher rate of TIMI 3 flow before PTCA (21% vs 10.3%), as well as at 24 h after intervention (92% vs 82.5%), compared with the placebo group. Pre-hospital administration of abciximab was associated with a higher rate of TIMI 3 flow at first coronary angiography (32% vs 12%) and at 24 h after PTCA (100% vs 86%) than administration in the hospital. The primary combined endpoint of death, reinfarction, and urgent TVR at 30 d was significantly reduced from 14.7% in the placebo group to 7.3% in the abciximab group (Fig. 8). Moreover, abciximab improved each of the individual components; there was a 50% lower mortality, 35% lower incidence of myocardial infarction, and 80% lower rate of TVR. Abciximab use was associated with a similar rate of major bleeding as placebo (4% vs 2.6%, respectively) but an increased incidence of minor bleeding (6.7% vs 1.3%, respectively, $p = 0.02$) *(49)*. At 6-mo follow-

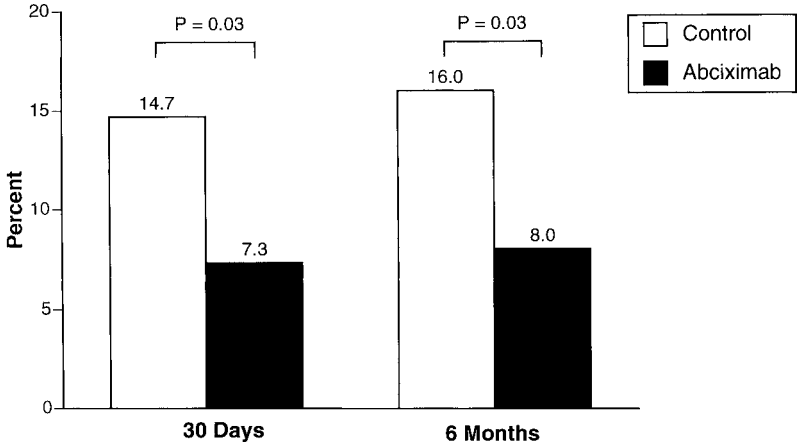


Fig. 8. Incidence of death, reinfarction, or urgent TVR at 30 d and 6 mo in the ADMIRAL trial. (Reprinted with permission from ref. *49*.)

up, the incidence of death, reinfarction, or urgent TVR was significantly reduced from 16% to 8% with abciximab treatment (Fig. 8). In diabetic patients, the incidence of death, reinfarction, and any revascularization was also significantly reduced from 34.7% to 23.3% ($p = 0.03$).

The ADMIRAL trial provides further evidence that abciximab can improve TIMI flow grade and decrease the incidence of death, myocardial infarction, and urgent TVR. In addition, the composite endpoint of death, reinfarction, and any TVR was reduced in diabetic patients, a group at particular risk for restenosis.

The CADILLAC Trial

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complication (CADILLAC) trial, the effects of balloon angioplasty (with or without abciximab) or stenting (with or without abciximab) were compared. Two thousand and eighty-one patients with AMI met the clinical and angiographic criteria for enrollment. These patients were randomized to one of four arms: PTCA with abciximab, PTCA without abciximab, stenting with abciximab, or stenting without abciximab. The primary endpoint of the study was the 6-mo composite of death, myocardial infarction, stroke, or ischemic TVR. Patients were treated with aspirin, ticlopidine, heparin, and intravenous β-blockers in the emergency room. Following percutaneous intervention, patients were treated with aspirin, ticlopidine (if stenting was performed), and heparin for 60 h if abciximab was not used. Among patients treated with stents, the incidence of death (2.8% vs 3.8%) or the primary endpoint at 6 mo (10.9% vs 10.8%) did not differ significantly in the placebo and abciximab groups,

respectively. Nevertheless, at 30 d, patients treated with abciximab had a lower rate of ischemic events compared with the placebo cohort, 5.0% vs 7.1%, $p = 0.04$ *(50)*. More complete details of this trial are provided in Chapter 9.

PRACTICAL RECOMMENDATIONS

Heparin Dosing

A low-dose, weight-adjusted heparin regimen, given as an initial bolus of 70 U/kg (maximum 7000 U), adjusted to achieve and maintain an ACT greater than 200 s, is recommended when abciximab therapy is planned *(51)*. Abciximab has been frequently used as a rescue treatment, albeit without clearly demonstrated benefit *(52)*. In this situation, heparin is typically given initially in a higher dose to achieve an ACT $>$ 300 s. When abciximab is added during the procedure, higher than desired levels of ACT may be reached; the addition of abciximab elevates the ACT by approx 30–40 s . This excessive anticoagulation leads to prolongation of sheath dwell time and a doubling of major bleeding events *(53)*. An initial heparin dose aimed at maintaining an ACT in the 250–300-s range should be a good strategy if abciximab therapy is not intended and would allow administration of abciximab on a rescue basis, thus avoiding very high levels of anticoagulation. If the ACT is already very high ($>$350 s) before bailout abciximab administration, a small dose of protamine (5–10 mg) may lower it sufficiently to prevent major bleeding complications *(54)*. There are no data to suggest that heparin after a successful intervention adds benefit beyond administration of abciximab. Heparin dosing with eptifibatide and tirofiban treatment has not been thoroughly investigated, but the small molecules tend to increase the ACT to a lesser degree than abciximab.

Vasodilator Therapy

There are recent data indicating that the use of some vasodilators such as verapamil and adenosine can attenuate microvascular dysfunction and reverse the no-reflow state after percutaneous coronary interventions. Taniyama et al. *(55)* documented that intracoronary verapamil given after PTCA for AMI augmented myocardial blood flow as demonstrated by myocardial contrast echocardiography, and improved TIMI flow grade by angiography. Fischell et al. *(56)* demonstrated the ability of adenosine to reverse slow-flow complicating stenting of diseased vein grafts. Although the data are limited, it is also the authors' experience that the use of such vasodilators reverses and may prevent many instances of this phenomenon.

Sheath Removal

Vascular access sheaths should be removed as soon as possible post-procedure, during abciximab infusion, once the activated partial thromboplastin time

is less than 50 s or the activated clotting time is less than 175 s. In two large randomized trials of planned abciximab use, this strategy has been shown to be safe *(51,57)*. After sheath removal, pressure should be applied for at least 30 min followed by bed rest for 6–8 h. Recently, femoral artery closure devices have been used with increased frequency and appear to be promising. The advantage of early ambulation and a decrease in the hospital stay *(58)* is less critical in patients with AMI. However, these devices may lessen patients' discomfort *(59)* and lessen the burden for the medical staff.

SUMMARY AND RECOMMENDATIONS

The available data on the use of GP IIb/IIIa inhibition in primary angioplasty for AMI provide robust evidence that this strategy is beneficial in this high-risk group of patients. When treatment is given to patients presenting with AMI in the emergency room, it increases the infarct-related artery patency by the time coronary angiography and PTCA are performed. Although these agents do not lyse fibrin, they assist the endogenous fibrinolytic system in dissolving the thrombus, can produce dethrombosis, and, by inhibiting platelet aggregation, diminish further accumulation of thrombus and prevent reocclusion. GP IIb/IIIa inhibition yields marked and consistent benefits in the prevention of major ischemic events. This benefit is particularly pronounced with respect to reinfarction and need for urgent revascularization. The reduction in urgent revascularization is especially important in patients undergoing primary angioplasty as it is a surrogate endpoint for reinfarction. The Munich trial presented evidence that this treatment has positive effects on the microvasculature, which translates into an increase in flow velocity in the infarct-related artery and improvement in left ventricular function. These effects are probably related to the prevention of platelet embolization and adhesion to the injured endothelium. These same mechanisms may also explain the increase in TIMI flow grade 3 and the beneficial effects on the no-reflow phenomenon with GP IIb/IIIa blockade.

From the data presented, it appears that all patients undergoing primary PTCA deserve GP IIb/IIIa inhibitor therapy unless a specific contraindication exists. Abciximab was the drug used in most of these trials. Eptifibatide and tirofiban use was limited to the IMPACT-II and RESTORE trials, and until more data become available, abciximab should be considered the drug of choice in this setting. GP IIb/IIIa blockers are relatively expensive and financial concerns have been raised about using them routinely in primary angioplasty. Abciximab costs approx $1400 per patient (bolus plus 12-h infusion). Eptifibatide and tirofiban cost approx $400 per day, although the optimal duration of therapy for these drugs is not exactly known. It is important to recognize, however, that the reduction in ischemic complications by the use of GP IIb/IIIa blockers may actually translate into cost savings. In an economic assessment of GP IIb/IIIa use for the

prevention of ischemic complications in high-risk coronary angioplasty in the EPIC trial, Mark et al. *(60)* demonstrated that abciximab use resulted in a cost savings of $622 per patient during initial hospitalization from reduced acute ischemic events, and $1270 during the 6-mo follow-up by reducing repeat hospitalization and revascularization. In that trial, however, the initial hospitalization savings were offset by a rise of $521 in costs from an increase in bleeding episodes. Thus, considering these savings and the ability to reduce bleeding episodes by using low-dose heparin, the net cost of using these drugs may become much lower than their actual prices, and in fact their use might even be cost saving.

REFERENCES

1. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. N Engl J Med 1992;326:310–318.
2. Stein B, Fuster V, Israel DH, et al. Platelet inhibitor agents in cardiovascular disease: an update. J Am Coll Cardiol 1989;14:813–836.
3. Coller BS. Antiplatelet agents in the prevention and therapy of thrombosis. Annu Rev Med 1992;43:171–180.
4. Shattil SJ, Hoxie JA, Cunningham M. Changes in the platelet membrane glycoprotein IIb/IIIa complex during platelet activation. J Biol Chem 1985;260:11,107–11,114.
5. Pumphrey CW, Dawes J. Plasma beta-thromboglobulin as a measure of platelet activity. Effect of risk factors and findings in ischemic heart disease and after acute myocardial infarction. Am J Cardiol 1982;50:1258–1261.
6. Hughes A, Daunt S, Vass G, Wickes J. In vivo platelet activation following myocardial infarction and acute coronary ischemia. Thromb Haemost 1982;48:133–135.
7. Fitzgerald DJ, Catella F, Roy L, Fitzgerald GA. Marked platelet activation in vivo after intravenous streptokinase in patients with acute myocardial infarction. Circulation 1988; 77:142–150.
8. Fuchs J, Weinberger I, Rotenberg Z, Joshua H, Almozlino A, Agmon J. Circulating aggregated platelets in coronary artery disease. Am J Cardiol 1987;60:534–537.
9. ISIS-2(Second International Study of Infarct Survival) Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–360.
10. Roux S, Christeller S, Ludin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis. A meta-analysis. J Am Coll Cardiol 1992;19:671–677.
11. Antiplatelet Trialists' Collaboration. Collaborative overview of randomized trials of antiplatelet therapy, I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 1994;308:81–106.
12. Weitz JI, Califf RM, Ginsberg JS, Hirsh J, Theroux P. New antithrombotics. Chest 1995; 108:471s–485s.
13. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–682.
14. Grines CL, Browne KF, Marco J, et al. for the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–679.
15. Brodie BR, Grines CL, Ivanhoe R, et al. Six-month clinical and angiographic follow-up after direct angioplasty for acute myocardial infarction: final results from the primary angioplasty registry. Circulation 1994;90:156–162.

16. Iwabuchi M, Haruta S, Taguchi A, et al. Intravascular ultrasound findings after successful primary angioplasty for acute myocardial infarction: predictors of abrupt occlusion. J Am Coll Cardiol 1997;30:1437–1444.
17. Weinberger I, Fuchs J, Davidson E, Rotenberg Z. Circulating aggregated platelets, number of platelets per aggregate, and platelet size during acute myocardial infarction. Am J Cardiol 1992;70:981–983.
18. Gasperetti CM, Gonias SL, Gimple LW, Powers ER. Platelet activation during coronary angioplasty in humans. Circulation 1993;88:2728–2734.
19. Bates ER, McGillem MJ, Mickelson JK, Pitt B, Mancini GB. A monoclonal antibody against the platelet glycoprotein IIb/IIIa receptor complex prevents platelet aggregation and thrombosis in a canine model of coronary angioplasty. Circulation 1991;84:2463–2469.
20. Gold HK, Garabedian HD, Dinsmore RE, et al. Restoration of coronary flow in myocardial infarction by intravenous chimeric 7E3 antibody without exogenous plasminogen activators: Observations in animals and humans. Circulation 1997;95:1755–1759.
21. Gold HK, Coller BS, Yasuda T, et al. Rapid and sustained coronary artery recanalization with combined bolus injection of recombinant tissue-type plasminogen activator and monoclonal antiplatelet Gp IIb/IIIa antibody in a canine preparation. Circulation 1988;77:670–677.
22. Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–1508.
23. Piana RN, Piak GY, Moscucci M, Cohen DJ, Gibson CM. Incidence and treatment of "no-reflow" after percutaneous coronary intervention. Circulation 1994;89:2514–2518.
24. Kitazume H, Iwama T, Kubo I, Ageishi Y, Suzuki A. No-reflow phenomenon during percutaneous transluminal coronary angioplasty. Am Heart J 1998;116:211–215.
25. Feld H, Lichstien E, Schachter J, Shani J. Early and late angiographic findings of the "no-reflow" phenomenon following direct angioplasty as the primary treatment for acute myocardial infarction. Am Heart J 1992;123:782–784.
26. Marzilli M, Gliozheni E, Marraccini P, Fedele S. Primary coronary angioplasty in acute myocardial infarction: clinical correlates of the "no-reflow" phenomenon. Int J Cardiol 1998;65(Suppl 1):S23–28.
27. Komamura K, Kitakaze M, Nishida K, et al. Progressive decrease in coronary vein flow during reperfusion in acute myocardial infarction: clinical documentation of the no-reflow phenomenon after successful thrombolysis. J Am Coll Cardiol 1994;24:370–377.
28. Seydoux C, Goy J, Graham D. Platelet and neutrophil imaging techniques in the investigation of the response to thrombolytic therapy and the no-reflow phenomenon. Am Heart J 1993;125:1142–1147.
29. EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956–961.
30. Mehta JL, Nichols WW, Mehta P. Neutrophils as potential participants in acute myocardial ischemia: relevance to reperfusion. J Am Coll Cardiol 1988;11:1309–1316.
31. Rawitscher D, Levin TN, Cohen I, Feldman T. Rapid reversal of no-reflow using abciximab after coronary device intervention. Cathet Cardiovasc Diagn 1997;42:187–190.
32. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. Stent Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1999;341:1949–1956.
33. Stone GW. The CADILLAC trial. Presented at the 72nd Scientific Sessions of the American Heart Association, November 10, 1999, Atlanta, GA.
34. Lefkovits J, Ivanhoe RJ, Califf RM, et al. Effects of platelet glycoprotein IIb/IIIa receptor blockade by a chimeric monoclonal antibody (abciximab) on acute and six-month outcomes after percutaneous transluminal coronary angioplasty for acute myocardial infarction. Am J Cardiol 1996;77:1045–1051.

35. The IMPACT II Investigators. Randomized placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Lancet 1997;349:1422–1428.
36. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997;96:1445–1453.
37. Grantham JA, Hasdai D, Kopecky SL, Holmes DR. Platelet glycoprotein IIb/IIIa receptor inhibition during PTCA for acute MI. J Am Coll Cardiol 1998;31:231A (abstract).
38. Brener SJ, Barr LA, Burchenal JEB, et al. for the RAPPORT Investigators. A randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998;98:734–741.
39. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.
40. Coller BS. GP IIb/IIIa antagonists: pathophysiologic and therapeutic insights from studies of c7E3 fab. Thromb Haemost 1997;78:730–735.
41. Gawaz M, Neumann FJ, Dickfeld T, et al. Vitronectin receptor ($\alpha v\beta 3$) mediates platelet adhesion to the luminal aspect of endothelial cells: implications for reperfusion in acute myocardial infarction. Circulation 1997;96:1809–1818.
42. Simon DI, Xu H, Ortlepp S, Rogers C, Rao NK. 7E3 monoclonal antibody directed against the platelet glycoprotein IIb/IIIa cross-reacts with the leukocyte integrin Mac-1 and blocks adhesion to fibrinogen and ICAM-1. Arterioscler Thromb Vasc Biol 1997;17:528–535.
43. Fan ST, Edginton TS. Integrin regulation of leukocyte inflammatory functions: CD11b/CD18 enhancement of tumor necrosis factor-alpha responses of monocytes. J Immunol 1993;150: 2972–2980.
44. Murphy JF, Bordet JC, Wyler B, et al. The vitronectin receptor ($\alpha v\beta 3$) is implicated, in cooperation with P-selectin and platelet-activating factor, in the adhesion of monocytes to activated endothelial cells. Biochem J 1994;304:537–542.
45. Van den Merkhof LFM, Zijlstra F, Olsson H, et al. Abciximab in the treatment of acute myocardial infarction eligible for primary percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1999;33:1528–1532.
46. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in myocardial infarction (TIMI) trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987;76:142–154.
47. Zijlstra F, De Boer MJ, Hoorntje JCA, et al. A comparison of immediate angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328: 680–684.
48. GUSTO-IIb Angioplasty Substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–1628.
49. Montalescot G, Barragan P, Wittenberg O, Ecollan P, Elhadad S, Villain P, et al. for the ADMIRAL Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–1903.
50. Stone G, for the CADILLAC Investigators. The CADILLAC Study. Circulation 2000; 102(Suppl II):II-64 (abstract).
51. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–1696.
52. Muhlestein JB, Karagounis LA, Treehan S, Anderson JL. "Rescue" utilization of abciximab for the dissolution of coronary thrombus developing as a complication of coronary angioplasty. J Am Coll Cardiol 1997;30:1729–1734.

53. Brener SJ, Ellis SG, DeLuca S, Topol EJ. Abciximab in coronary angioplasty—comparison of planned and rescue administration. J Invest Cardiol 1997;9:50C.
54. Kereiakes DJ, Broderick TM, Whang DD, et al. Partial reversal of heparin anticoagulation by intravenous protamine in abciximab-treated patients undergoing percutaneous intervention. Am J Cardiol 1997;82:633–634.
55. Taniyama Y, Ito H, Iwakura K, et al. Beneficial effect of intracoronary verapamil on microvascular and myocardial salvage in patients with acute myocardial infarction. J Am Coll Cardiol 1997;30:1193–1199.
56. Fischell TA, Carter AJ, Foster MT, et al. Reversal of "no-reflow" during vein graft stenting using high velocity boluses of intracoronary adenosine. Cathet Cardiovasc Diagn 1998;45: 360–365.
57. The EPISTENT Investigators. Randomized placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. Lancet 1998;352:87–92.
58. Krause PB, Klein LW. Utility of a percutaneous collagen hemostasis device: to plug or not to plug? J Am Coll Cardiol 1993;22:1280–1282.
59. Silber S. Rapid hemostasis of arterial puncture sites with collagen in patients undergoing diagnostic and interventional cardiac catheterization. Clin Cardiol 1997;20:981–992.
60. Mark DB, Talley JD, Topol EJ, et al., for the EPIC Investigators. Economic assessment of platelet glycoprotein IIb/IIIa inhibition for prevention of ischemic complications of high-risk coronary angioplasty. Circulation 1996;94:629–635.

9

Integrating Coronary Stents and Glycoprotein IIb/IIIa Inhibitors into a Mechanical Reperfusion Strategy

The CADILLAC and ADMIRAL Trials

Gregg W. Stone, MD, David E. Kandzari, MD, and Cindy L. Grines, MD

CONTENTS

INTRODUCTION

The pathogenesis of acute myocardial infarction (AMI) is characterized by atherosclerotic plaque rupture, platelet activation and aggregation, and resultant thrombus formation *(1,2)*. Whether the thrombotic mass becomes occlusive, subocclusive, or nonobstructive (in concert with other variables such as collateral flow, baseline left ventricular function, amount of myocardium at risk, diabetes, etc.) will determine whether the clinical presentation is one of severe chest

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

pain with ST-segment elevation, unstable angina, mild angina, or absent symptoms. Restoring effective myocardial perfusion and metabolism is fundamental to limiting infarct size and enhancing survival. Reperfusion therapy for AMI may be achieved by either the systemic administration of fibrinolytic therapy or primary (formerly called direct) percutaneous transluminal coronary angioplasty (PTCA). Despite its widespread availability and proven efficacy *(3)*, fibrinolytic therapy is limited by the failure to achieve normal antegrade Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in 40% or more of patients; early and late reocclusion of the infarct vessel in approx 10% and 30% of patients, respectively; and iatrogenic hemorrhagic risks, including intracranial bleeding, in approx 1% of patients *(4–8)*. Alternatively, the timely performance of primary PTCA offers the advantages of anatomic definition, higher rates of patency and TIMI 3 flow, and virtually eliminates the risk of intracranial hemorrhage *(9)*, although the majority of hospitals in the United States do not have the invasive facilities for emergency cardiac catheterization and intervention *(10)*. Nonetheless, more than 10 randomized trials comparing fibrinolytic therapy to primary PTCA (mostly balloon angioplasty) have clearly demonstrated a clinically meaningful and statistically significant reduction in death, recurrent myocardial infarction, hemorrhagic stroke, and all stroke in patients treated with primary PTCA in a variety of clinical settings; these results have established mechanical reperfusion therapy as the treatment of choice for patients presenting at appropriately equipped facilities and in a timely fashion *(9,11–14)*.

In the past decade, advances in interventional drugs and devices have significantly improved outcomes for patients undergoing elective percutaneous coronary intervention (PCI). Stenting has decreased the incidence of abrupt vessel closure to $<0.5\%$ and has reduced the need for repeat revascularization from angiographic restenosis by 30%–50% *(15–17)*. In addition, numerous randomized trials have demonstrated that glycoprotein (GP) IIb/IIIa inhibition during elective PCI reduces the composite 30-d and 6-mo incidence of death, nonfatal myocardial infarction, or need for target vessel revascularization (TVR) *(18,19)*. The synergy between PCI and GP IIb/IIIa blockade is especially prominent in patients with acute coronary syndromes without ST-segment elevation *(20–23)*. Until recently, however, few studies have examined the role of stenting and GP IIb/IIIa inhibition in the contemporary management of patients with AMI.

In the last 2 yr, several randomized trials have provided important insight into the effects of coronary stenting and GP IIb/IIIa inhibition in primary angioplasty. The results of these studies have been surprising, in some respects counterintuitive, and have resulted in a paradigm shift in our understanding of the underlying pathophysiology of AMI. Importantly, these studies have revealed novel mechanisms of the interaction between the thrombotic, ruptured plaque, and reperfusion therapies that have and will result in new approaches to further

improve the prognosis of patients with AMI. In this chapter we review these studies, focusing on the two largest trials of stenting and IIb/IIIa inhibitors, the CADILLAC and ADMIRAL trials *(24,25)*, and interpret these findings in the context of the contemporary management of AMI.

RATIONALE FOR CORONARY STENTING AND GP IIB/IIIA INHIBITION IN AMI

Stent Implantation in Acute Myocardial Infarction

Prospective, randomized clinical trials have demonstrated the superiority of primary balloon angioplasty over fibrinolytic therapy for reperfusion in AMI *(9,11–14)*. Nonetheless, primary PTCA is still limited by the development of recurrent ischemia in 10%–15% of patients *(9,11–13,26)*, and rarely abrupt vessel closure that may result in reinfarction and death *(26)*. Infarct artery reocclusion (either clinically silent or apparent) following primary PTCA occurs in 5%–10% of patients prior to hospital discharge and in as many as 15% of patients at 6 mo *(9,27,28)*. Furthermore, following initially successful balloon dilatation, angiographic restenosis occurs in 25%–50% of patients at 6 mo *(29–32)*. As a result, approx 20% of survivors require repeat percutaneous or surgical revascularization within the first 6 mo following primary angioplasty *(9,11,12,31)*. These adverse events result in significant morbidity and mortality, as well as prolonging the initial hospital stay and increasing costs *(26)*.

The rationale to consider stenting in the thrombotic milieu of AMI derived from improving results and greater understanding of stenting in patients with stable coronary artery disease. Early trials investigating elective coronary stenting of *de novo* lesions demonstrated significant reductions in restenosis and the need for late TVR compared with PTCA alone *(15,16)*. Stenting in patients with AMI, however, was avoided because of concerns about stent thrombosis, which occurred in 3%–6% of patients in these early trials despite intense anticoagulation. However, technique evolution including high-pressure implantation, in concert with antiplatelet regimens including aspirin and a thienopyridine, have reduced the risk of stent thrombosis after elective stenting to $<2\%$ and further lowered restenosis rates compared with PTCA alone *(17,33–35)*. The confidence to carefully explore stenting in thrombotic lesions thus developed.

The expectation that stent implantation in AMI may further improve results "beyond the balloon" is supported by a sound conceptual basis. In the 2nd Primary Angioplasty in Myocardial Infarction (PAMI-2) trial, the incidence of recurrent ischemia after balloon angioplasty in 1100 patients was doubled among patients with either a post-angioplasty residual stenosis of $>30\%$ (present in 14% of patients) or dissection (present in 20% of patients) *(36)*. The salutary

benefits of stents in sealing intimal dissection planes and typically eliminating the residual stenosis after PTCA was thus postulated to reduce the occurrence of early adverse events such as recurrent ischemia, reinfarction, and infarct artery occlusion compared with balloon angioplasty alone *(37)*. Moreover, because the residual stenosis after elective intervention is a critical determinant of restenosis *(38–41)*, the larger lumens achieved after stenting compared with PTCA was expected to significantly improve survival free from late clinical or angiographic restenosis *(42)*.

Pilot studies demonstrating favorable procedural success and short-term and late clinical outcomes in AMI supported the rationale for coronary stenting. In the PAMI Stent Pilot, the feasibility, safety, and long-term results of stenting were prospectively evaluated in 312 consecutive patients with AMI at nine international centers *(37,42)*. Stenting with the Palmaz–Schatz sheathed stent was considered possible in 240 patients (77%) and was successful in 236 patients. Primary stenting was associated with low rates of early mortality (0.8%) and reinfarction (2%) *(37)*. The 6-mo angiographic restenosis rate was 27.5%, including infarct artery reocclusion in 6.4% of vessels, both better than historical controls *(42)*.

The PAMI Stent Pilot and other favorable single-center experiences formed the basis for randomized trials comparing primary PTCA vs stenting in eligible lesions. Small to moderate-sized randomized studies demonstrated reduced rates of recurrent ischemia, restenosis, and clinical TVR with stenting, although these trials were underpowered to examine death or reinfarction *(28,43–48)*. Differences among the trials in patient selection, stent type, anticoagulation regimens, and methodology also made firm conclusions difficult. Moreover, the crossover rates from balloon angioplasty to stenting in these studies varied greatly, ranging from 0% to 36%.

Coincident with these trials, the PAMI Stent Trial was performed, in which 1458 patients presenting within 12 h of AMI were enrolled *(49)*. The anatomy was considered appropriate for stenting in 900 patients (63%), who were randomized to receive either the Palmaz–Schatz heparin-coated stent ($n = 452$) or PTCA ($N = 448$). Bailout stenting with a non-heparin-coated stent was performed in 15% of the PTCA patients because of unacceptable results. The primary composite 6-mo endpoint of death, myocardial infarction, disabling stroke, or ischemia-driven TVR was significantly lower in the stent group (12.6% vs 20.1%, $p < 0.01$), as was the 6-mo binary restenosis rate (20.3% vs 33.5%, $p < 0.001$). Surprisingly, however, there was a strong trend for increased early and late mortality with stenting compared with PTCA (5.4% vs 3.0%, $p = 0.054$) *(50)*. The higher mortality in the stented patients correlated with the unexpected finding of a reduced rate of post-procedural TIMI grade 3 flow with stenting compared with PTCA (89.5% vs 92.7% by core lab analysis, $p = 0.046$) *(49)*.

The phenomenon of reduced TIMI grade 3 flow after primary stenting has now been confirmed by others, and is felt to represent distal capillary block resulting from thromboembolism after stent implantation (with or without neurohumoral release mediated vasospasm) *(51–53)*. Although distal thromboemboli can occur spontaneously in AMI after thrombolytic therapy or following balloon dilatation, empirically it appears that the excellent scaffolding property of stents results in the maximal likelihood for thrombus extrusion, separation, and embolization. As a result of this phenomenon, stenting in AMI following Stent PAMI could be recommended only for suboptimal balloon angioplasty results. Whether improved stent design or potent pharmacotherapeutic agents could mitigate stent-induced distal embolization was unknown.

GP IIb/IIIa Inhibition in Acute Myocardial Infarction

In addition to plaque rupture-induced platelet activation and thrombus formation *(54)*, endothelial denudation and medial dissection caused by balloon angioplasty exposes the underlying cellular basement membrane and collagen matrix, which may contribute to thrombosis and reocclusion following primary PTCA *(26)*. Even in the era of stent implantation, rates of acute and subacute thrombosis in AMI have ranged from 0.5% to 8.6% *(43–47,49)*, emphasizing the need for more intensive antithrombotic therapy.

The discovery of the platelet GP IIb/IIIa receptor as the "final common pathway" of platelet aggregation has resulted in numerous studies evaluating inhibition of this surface-expressed integrin to further improve the safety of interventional cardiology procedures *(55)*. A compelling body of evidence has been generated from large-scale multicenter randomized trials supporting the use of parenteral GP IIb/IIIa inhibitors in patients with acute coronary syndromes and in those undergoing percutaneous intervention *(18–23,56–62)*. These studies have clearly demonstrated that the administration of intravenous GP IIb/IIIa inhibitors prior to interventional procedures with balloon angioplasty, atherectomy, and stents reduces peri-procedural myonecrosis and myocardial infarction, as well as urgent TVR within 30 d after balloon angioplasty. Whether survival is improved with GP IIb/IIIa inhibitor use during elective intervention remains a topic of great debate *(63)*. Given the underlying presence of abundant platelet-rich thrombus in almost all patients with AMI, it is intuitive that these agents might be of the greatest benefit in this syndrome. In this regard, it is noteworthy that only approx 5% of patients undergoing PTCA or stenting in Stent PAMI received GP IIb/IIIa inhibitors *(49)*, providing hope that the tendency for stent-induced thromboemboli might be mitigated by more potent antiplatelet regimens.

Abciximab (ReoPro™, Centocor, Malvern, PA) has been the GP IIb/IIIa receptor blocker most widely tested in patients with AMI undergoing mechanical

reperfusion therapy. In the multicenter ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT), 483 patients undergoing primary balloon angioplasty were randomized to intravenous abciximab prior to intervention vs matching placebo *(64)*. Abciximab use reduced the 30-d composite incidence of death, myocardial infarction, or urgent TVR by 62% (5.8% vs 11.1%, $p = 0.04$). However, the 6-mo composite endpoint of death, myocardial infarction, or any TVR occurred in 28% of patients in both groups, independent of randomization assignment *(64)*.

Abciximab as an adjunct to coronary stenting might be expected to be of even greater benefit than during balloon angioplasty, given the greater tendency to distal embolization with stent implantation. Indeed, in the single-center open-label randomized Stent vs Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOP-AMI) trial, the combination of stenting plus abciximab was shown to enhance myocardial salvage and markedly improve event-free survival at 30 d and 1 yr compared with accelerated tissue plasminogen activator (t-PA) *(65)*. The same group explored the benefits of adding abciximab to acute infarct stenting in the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) Trial *(66)*. In that study, 200 patients within 48 h of onset of AMI in whom a primary or rescue stent strategy was planned were randomized to a bolus plus 12-h infusion abciximab regimen vs control. Patients treated with abciximab had a lower composite rate of in-hospital death, reinfarction, or urgent TVR than patients in the control group (9.2% vs 2.0%, $p < 0.05$). Routine follow-up catheterization was completed at 14 d in 141 patients. Regional wall motion, global left ventricular function, and peak coronary blood flow velocity by Doppler were greater in abciximab-treated patients, consistent with improved distal microcirculatory function, presumably owing to reduced distal thromboemboli and/or capillary plugging. No significant differences in clinical events or angiographic restenosis were present at 6 mo *(67)*.

Taken collectively, these studies suggest that abciximab as an adjunct to primary PTCA and stenting may improve 30-d outcomes and possibly enhance short-term recovery of left ventricular function. These trials were underpowered, however, to state with certainty whether stenting plus abciximab results in equivalent or greater survival than PTCA alone (with or without abciximab), or whether the early improvement in left ventricular function with abciximab after stenting would be sustained. Adequate power was also lacking to examine whether abciximab truly confers any late benefits as an adjunct to primary PTCA or stenting. Larger, multicenter trials would also be required to evaluate the safety of abciximab in this patient population, as well as determine whether the results could be generalized to multiple centers and operators. To examine these and related issues, two multicenter studies, the ADMIRAL and CADILLAC trials, were performed.

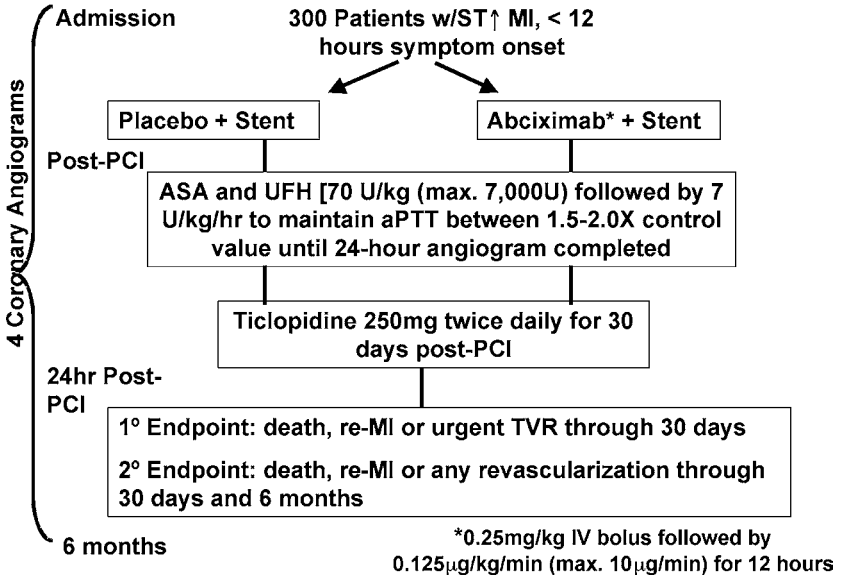


Fig. 1. ADMIRAL trial design.

THE ABCIXIMAB BEFORE DIRECT ANGIOPLASTY AND STENTING IN MYOCARDIAL INFARCTION REGARDING ACUTE AND LONG-TERM FOLLOW-UP (ADMIRAL) TRIAL

Study Overview

The ADMIRAL trial was a multicenter, double-blind, placebo-controlled prospective study in which 300 patients presenting to 26 centers in France with acute ST-segment elevation MI were randomized to treatment with abciximab vs placebo, followed by primary PTCA with stenting if appropriate (Fig. 1) *(24)*. The entry criteria were nonrestrictive; patients >18 yr of age and presenting within 12 h of symptom onset were eligible for enrollment. Abciximab was administered as a 0.25 mg/kg intravenous bolus followed by a 12-h infusion of 0.125 μg/kg/min; it was initiated either prior to or after reaching the cardiac catheterization laboratory. All patients received ticlopidine (250 mg twice daily, without a loading dose) for 30 d post-stenting, and aspirin indefinitely.

Study Hypothesis and Endpoints

The principal hypothesis of the ADMIRAL trial was that treatment with abciximab followed by stenting would be superior to stenting alone for acute myocardial infarction. The primary endpoint was the composite occurrence of death, reinfarction, or urgent TVR by 30 d. The key secondary endpoint was the

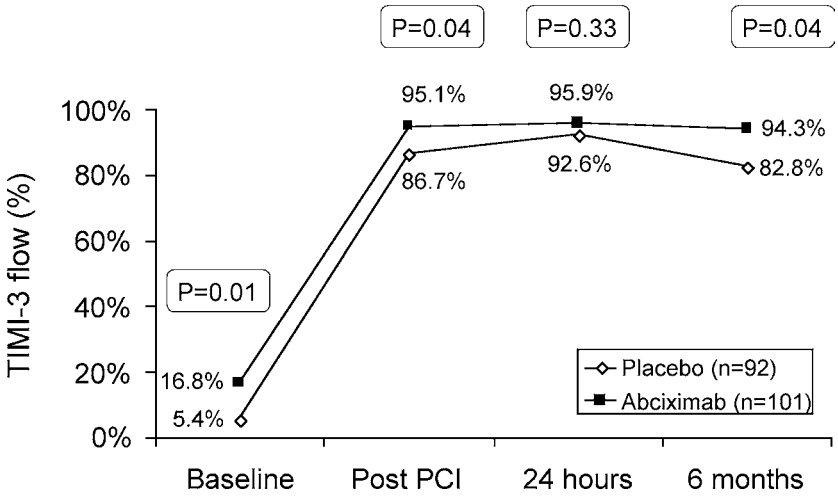


Fig. 2. TIMI 3 flow rates at four time points in the ADMIRAL trial.

composite of death, reinfarction, or any revascularization (percutaneous intervention or bypass surgery) at 30 d and 6 mo. Other secondary endpoints included death or reinfarction at 30 d and at 6 mo; death, reinfarction, or urgent TVR at 6 mo; TIMI flow grade before, immediately after, 24 h after, and 6 mo after revascularization; and left ventricular ejection fraction within 24 h and at 6 mo after percutaneous revascularization.

Results

Of the 300 randomized patients, 149 were assigned to abciximab and 151 to placebo. The baseline clinical and angiographic characteristics were similar between these two groups. The proportion of vessels <2.5 mm, however, was greater in abciximab-treated patients (18.3% vs 5.9%, $p = 0.006$). Of note, approx 17% of patients had diabetes mellitus, approx 11% of patients had prior myocardial infarction, and 1% presented in heart failure, although cardiogenic shock was present in approx 8% of patients within 24 h of randomization. The infarct vessel was the left anterior descending artery in approx 46% of patients.

Approximately 26% of patients were enrolled and received abciximab or placebo during ambulance transport or in the emergency room. As a result, a significantly greater proportion of abciximab-treated patients had a patent infarct vessel (TIMI grade 2 or 3 flow) at baseline than those receiving placebo (25.8% vs 10.8%, $p = 0.006$). TIMI grade 3 flow was also present more frequently prior to angioplasty in the abciximab-treated patients (Fig. 2). PTCA was performed in 92% of patients randomized to abciximab vs 95% randomized to placebo

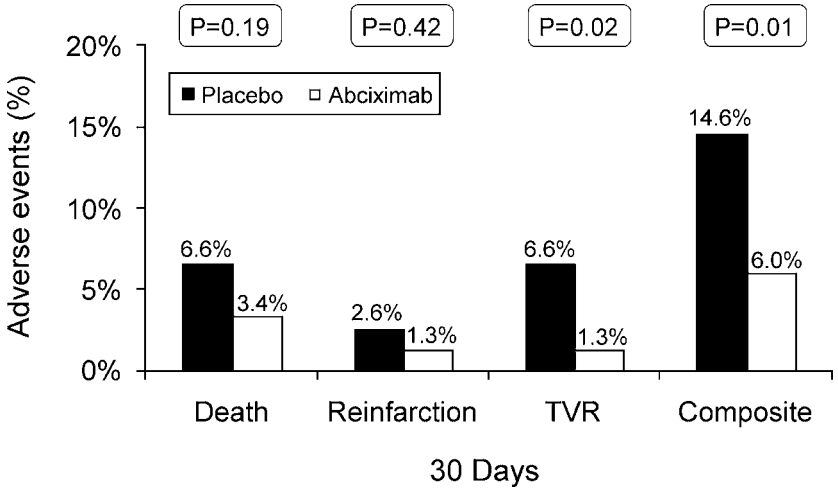


Fig. 3. Primary composite endpoint events at 30 d in ADMIRAL.

(p = NS). Stenting was performed in 92% of patients undergoing PTCA, most commonly with the balloon-expandable, slotted tube Saint-Côme stent (Saint-Côme-Chirurgie, Marseilles, France), although alternative stents were used in 34% of patients.

TIMI grade 3 flow was present more commonly in abciximab-treated patients immediately following revascularization, at 24 h, and at 6 mo (Fig. 2). Abciximab therapy was also associated with greater procedural success, lower rates of angiographic reocclusion of the infarct artery (2.9% vs 12.1%, $p = 0.04$), and strikingly higher 6-mo patency rate in vessels <2.5 mm in diameter (TIMI 2–3 flow, 100% vs 60.0%, $p = 0.02$) than was placebo. Significantly improved left ventricular function was also present at 24 h and at 6 mo among patients randomized to abciximab rather than placebo (mean left ventricular ejection fraction at 24 h, 57.0 ± 10.4% vs 53.9 ± 10.4%, $p < 0.005$; at 6 mo, 61.1 ± 10.6% vs 57.0 ± 11.1%, $p = 0.05$).

As seen in Figs. 3 and 4, treatment with abciximab significantly reduced the composite incidence of death, reinfarction, or urgent TVR at 30 d (6.0% vs 14.6%, $p = 0.01$) and at 6 mo (7.4% vs 15.9%, $p = 0.02$). Most of the benefit was present in the first week after randomization. As in prior studies, favorable clinical outcomes were strongly related to the achievement of post-procedural TIMI grade 3 flow (Fig. 5).

Although consistent reductions were seen in each individual component of the composite endpoint, only urgent TVR was statistically significantly reduced at 30 d and 6 mo (Figs. 3 and 4). At 6 mo, TVR for any indication (i.e., both urgent and elective) was performed in 11.4% of patients in the abciximab group and in

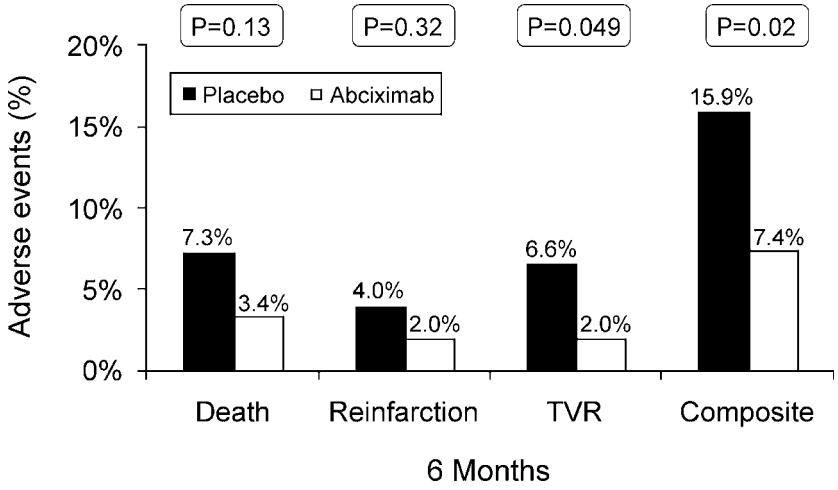


Fig. 4. Primary composite endpoint events at 6 mo in ADMIRAL.

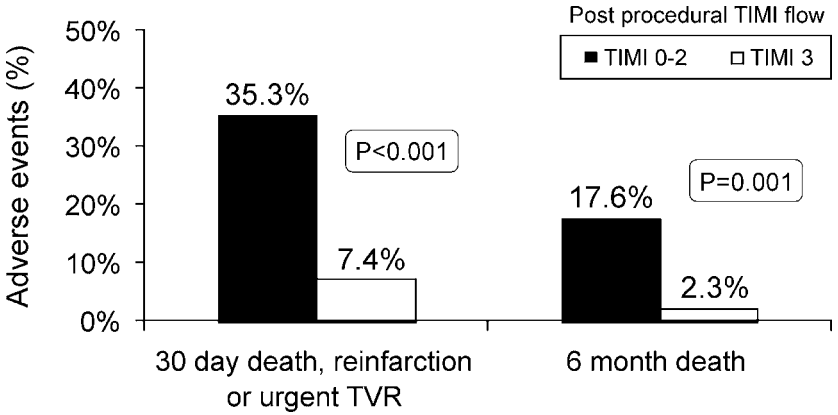


Fig. 5. Relationship between post-procedural TIMI grade 3 flow and 30-d composite adverse events, and 6-mo mortality in the ADMIRAL trial. The relationship effect between TIMI 3 flow and mortality was significantly affected by abciximab ($p = 0.03$).

23.8% of patients receiving placebo ($p = 0.005$). Elective revascularization was required in only 9.4% of abciximab-assigned patients vs 17.2% of placebo-assigned patients ($p = 0.046$), consistent with a reduction in restenosis (although angiographic restenosis rates have not been reported).

In a further analysis, the 30-d and 6-mo composite endpoint of death, reinfarction, or urgent TVR was reduced to a similar degree in most subgroups, except women, in whom no sustained benefit of abciximab was found.

The 6-mo composite endpoint was also favorably impacted by abciximab only in vessels >2.5 mm in diameter, that is, those that were stented (by protocol, vessels ≤2.5 mm in diameter were treated by balloon angioplasty only). Of note, abciximab therapy in diabetic patients was associated with significant reductions in TVR (13.8% with abciximab vs 37.5% with placebo, $p = 0.046$) and mortality (0.0% with abciximab vs 16.7% with placebo, $p = 0.02$) at 6 mo, although these were not prespecified secondary endpoints.

While the incidence of major bleeding did not significantly differ between treatment groups, minor bleeding was significantly increased with abciximab compared to placebo (12.1% vs 3.3%, $p = 0.004$), largely due to groin hematomas (6.0% vs 0.7%, $p = 0.009$). Abciximab also more frequently resulted in thrombocytopenia (platelet count $<100{,}000/mm^3$ 4.7% vs 1.3%, $p = 0.08$), although severe thrombocytopenia (platelet count $<50{,}000/mm^3$) occurred in 1.3% of patients in both groups.

The ADMIRAL Trial—Conclusions and Clinical Implications

Thus, the results of the ADMIRAL trial strongly support the use of GP IIb/IIIa receptor inhibition with abciximab prior to acute infarct intervention, especially with stenting. Abciximab use resulted in better patency and TIMI grade 3 flow rates in the infarct vessel, greater recovery of left ventricular function at 24 h and 6 mo, and reduced 30-d and 6-mo rates of urgent and elective TVR, consistent with less recurrent ischemia and restenosis. Although the trial was underpowered to detect differences in the individual endpoints of mortality and reinfarction, favorable trends were also present for these outcomes.

THE CONTROLLED ABCIXIMAB AND DEVICE INVESTIGATION TO LOWER LATE ANGIOPLASTY COMPLICATIONS (CADILLAC) TRIAL

Study Overview

The CADILLAC trial *(25)* was an international multicenter, prospective trial in which 2082 patients at 76 sites in 9 countries were randomized to one of four open-label reperfusion therapies in a 2×2 factorial design: (1) primary PTCA, (2) primary PTCA plus abciximab, (3) primary stent implantation, or (4) primary stent implantation plus abciximab (Fig. 6). Clinical entry criteria included symptoms of AMI within 12 h of onset and either ≥1 mm ST-segment elevation in two contiguous leads or a high-grade stenosis by angiography with associated regional wall motion abnormality. The major clinical exclusion criterion was the presence of cardiogenic shock on admission. All consented patients received aspirin, ticlopidine, and heparin. Clinically eligible patients were consented and emer-

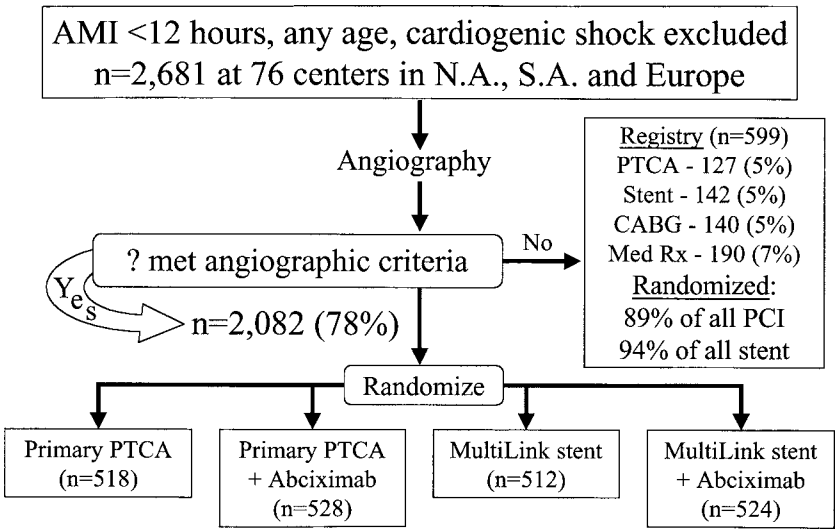


Fig. 6. CADILLAC trial design and patient enrollment.

gency coronary arteriography was performed, after which angiographic eligibility for stent implantation was determined. Major angiographic exclusion criteria included saphenous vein graft infarct artery, vessel size <2.5 mm, lesion length >64 mm, likelihood for urgent bypass surgery during the index admission, and contraindications to standard therapies for primary PTCA.

Angiographically eligible patients were randomized to one of four arms as described in the preceding paragraph. The activated clotting time was closely monitored and adjusted by nomogram to >350 s in patients not receiving abciximab, and to 200–300 s in abciximab-treated patients. Patients randomized to stent implantation received the MultiLink or MultiLink Duet stent (Guidant Corp., Santa Clara, CA), available in diameters from 2.5 mm to 4.5 mm, and in lengths from 8 mm to 38 mm. Abciximab was administered as a 0.25 mg/kg intravenous bolus followed by a 0.125 μg/kg/min infusion for 12 h. Patients randomized to PTCA were allowed to cross over and receive stents for unacceptable results. Similarly, patients in the no abciximab arms were allowed to receive "bailout" abciximab for refractory slow or no reflow, or persistent peri-stent thrombus.

Patients randomized to the abciximab arms were scheduled for discharge 2–3 d after presentation if clinically stable. Patients not receiving abciximab were discharged at the discretion of the treating physician. Aspirin was continued indefinitely in all patients. Ticlopidine was administered for 4 wk in stented patients; ticlopidine use was optional in patients undergoing balloon angioplasty alone.

Study Hypothesis and Endpoints

Two primary hypotheses were prespecified in CADILLAC: (1) Stenting without abciximab would be superior to PTCA without abciximab, and (2) stenting without abciximab would not be inferior to PTCA plus abciximab. A major secondary hypothesis was that patients undergoing primary angioplasty or stenting with abciximab followed by early hospital discharge would have equivalent or superior 30-d outcomes compared with patients undergoing percutaneous intervention without abciximab.

The primary study endpoint was the occurrence of major adverse cardiac events (MACE) at 6 mo, defined as the composite incidence of death, reinfarction, adjudicated ischemia-driven TVR, and nonfatal disabling stroke. Prespecified secondary clinical endpoints to be examined included 30-d and 12-mo MACE rates; the individual components of the MACE endpoint at 30 d, 6 mo, and 12 mo; and hemorrhagic and hematologic complications. Angiographic outcomes included TIMI flow rates, standard quantitative measures, and the occurrence of dissection, new thrombus formation, distal thromboemboli, side branch occlusion, or no-reflow. Other endpoints included cost-effectiveness, hospital length of stay, and angiographic restenosis and myocardial recovery from baseline to follow-up angiography at 7 mo. Multiple clinical and angiographic subgroups were prespecified for examination.

Results

A total of 2681 patients with AMI were consented, of whom 2082 (78%) met the angiographic criteria for stent implantation and were randomized. Among the 599 nonrandomized patients, 31% were managed medically, 24% underwent bypass surgery, and 45% underwent percutaneous intervention, of whom 142 received stents. Thus, 89% of all patients undergoing primary PTCA, and 94% of those receiving or eligible for stent implantation were randomized. No significant differences were present in baseline clinical or angiographic characteristics between the patients randomized to PTCA alone ($n = 518$), PTCA plus abciximab ($n = 528$), stenting alone with the MultiLink stent ($n = 512$), or MultiLink stenting plus abciximab ($n = 524$). Approximately 14% of patients had prior myocardial infarction, 17% were diabetic, and 10% presented with Killip class ≥II heart failure. The infarct vessel was the left anterior descending artery in 37% of patients.

Stent implantation was performed in 98% of patients assigned to stenting, while approx 16% of patients assigned to PTCA received stents for suboptimal balloon angioplasty results. Bailout abciximab was administered in <10% of patients not assigned to abciximab. TIMI grade 3 flow was achieved in 94.5%–96.9% of patients and did not significantly vary with randomization arm. Compared with PTCA *with or without* abciximab, stenting *with or without* abciximab

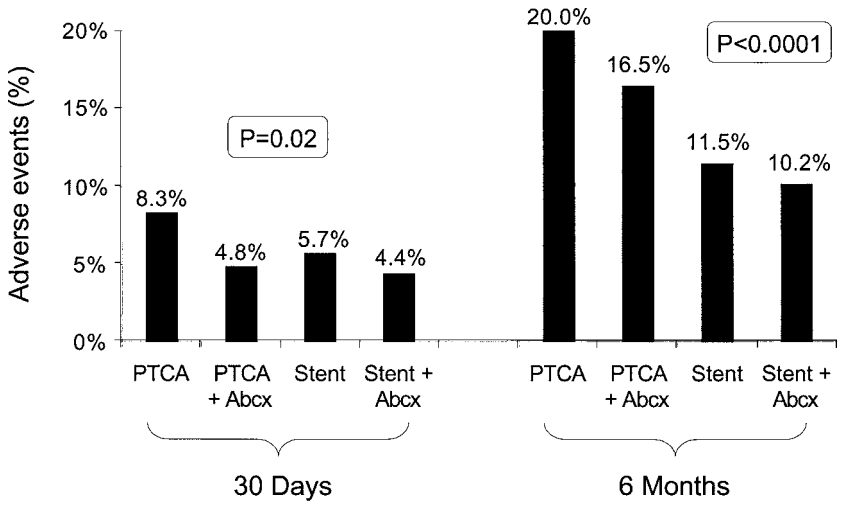


Fig. 7. The 30-d and 6-mo rates of the composite endpoint in the CADILLAC Trial.

resulted in a significantly lower post-procedural residual diameter stenosis and larger minimal luminal diameter.

The 30-d and 6-mo composite endpoints are shown in Fig. 7. Event-free survival at 30 d was the worst with the PTCA-only strategy, and similar with the other three approaches. There were no differences at 30 d in the rates of death, reinfarction, or disabling stroke among the four treatment strategies. A gradient was present in the occurrence of ischemia necessitating TVR within 30 d, ranging from 5.6% after PTCA only to 1.6% with stenting plus abciximab. Abciximab also reduced the 30-d incidence of subacute thrombosis, which occurred in 1.9% of patients assigned to PTCA only, 0.8% with PTCA plus abciximab, 1.0% with stenting only, and 0% with stenting plus abciximab (p for trend = 0.01) (Fig. 8). The early discharge strategy in abciximab-treated patients was therefore safe, although only approx one-half day was saved with this approach (median duration of hospitalization 75 h in abciximab-assigned patients vs 84 h in those not assigned to abciximab, $p < 0.001$). Formal cost-effectiveness analysis is pending.

By 6 mo, a clear pattern had emerged; event-free survival was greatest in patients assigned to routine stenting (with or without abciximab), intermediate in patients assigned to PTCA plus abciximab, and lowest in those assigned to PTCA only (Fig. 7). There were no significant differences in the rates of death, reinfarction, or disabling stroke among the four groups; the differences in the composite endpoint were driven entirely by reduced rates of ischemic TVR after routine stent implantation (Fig. 9). The magnitude of the benefit of stenting was similar in all prespecified subgroups. In contrast, analysis of the 6-mo primary composite endpoint comparing all patients assigned to abciximab vs no

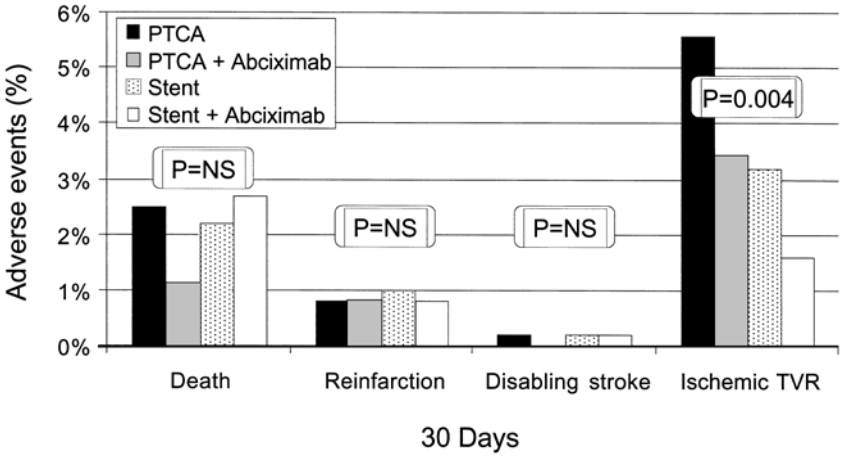


Fig. 8. The 30-d component adverse event rates in the CADILLAC Trial.

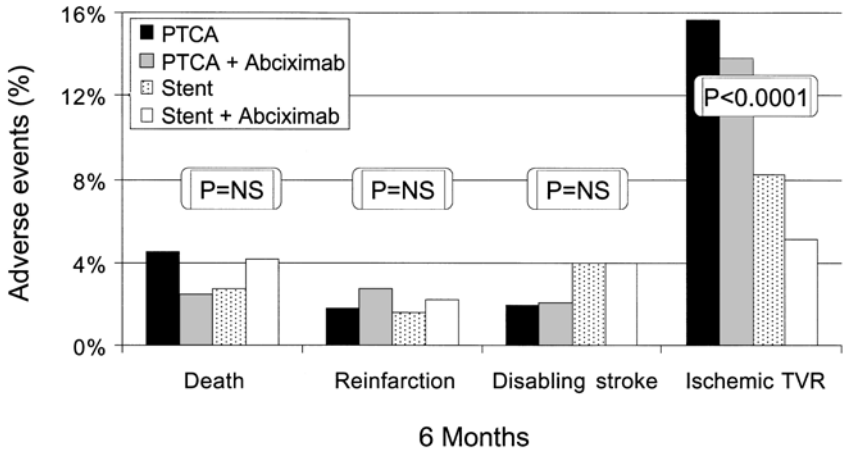


Fig. 9. The 6-mo component adverse event rates in the CADILLAC Trial.

abciximab did not identify major subgroups benefiting by routine abciximab treatment, except possibly patients with well-preserved left ventricular function or a right coronary artery infarct vessel (Table 1).

Abciximab therapy was safe, with no increase noted in moderate or major bleeding. By treatment-received analysis, however, patients administered abciximab were more likely to develop thrombocytopenia (platelet count $<100{,}000$ mm^3 4.2% vs 1.9%, $p = 0.002$; platelet count $<50{,}000$ mm^3 1.2% vs 0.1%, $p < 0.001$) and require blood product transfusions (5.3% vs 3.4%, $p = 0.03$).

Follow-up protocol angiography was completed in 656 (73%) of 900 prespecified eligible patients at 7 mo. As seen in Table 2, restenosis and infarct

Table 1
Pooled Analysis of the 6-mo Composite Primary Endpoint in Patients Randomized to Abciximab vs No Abciximab (Regardless of Device Assignment), Stratified by Prespecified Clinical Subgroups in the CADILLAC Trial

	Abciximab	*No abciximab*	*Odds ratio [95% confidence interval]*
n	1053	1029	
Age			
<65 yr	11.5%	14.2%	0.79 [0.57, 1.09]
≥65 yr	14.8%	16.2%	0.90 [0.61, 1.34]
Gender			
Male	11.2%	11.9%	0.93 [0.68, 1.28]
Female	17.2%	22.6%	0.71 [0.47, 1.08]
Diabetes			
Yes	17.4%	16.7%	1.05 [0.60, 1.85]
No	11.7%	14.5%	0.78 [0.59, 1.03]
Prior MI			
Yes	9.8%	12.9%	0.74 [0.35, 1.54]
No	13.2%	15.2%	0.85 [0.65, 1.11]
Killip class			
I	11.9%	14.2%	0.81 [0.62, 1.06]
II/III	20.7%	20.2%	1.03 [0.54, 1.97]
LVEF			
<50%	16.6%	17.6%	0.93 [0.66, 1.30]
≥50%	8.7%	12.4%	0.67 [0.45, 1.00]
Infarct vessel			
RCA	9.2%	14.9%	0.58 [0.39, 0.86]
LAD	20.3%	17.3%	1.22 [0.85, 1.76]
LCX	7.7%	9.3%	0.81 [0.39, 1.70]

LVEF, left ventricular ejection fraction; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

Table 2
Restenosis and Reocclusion of the Infarct-Related Artery in the CADILLAC Trial

	PTCA	*PTCA + abciximab*	*Stent*	*Stent + abciximab*	p *Value*
Restenosis[a]	36.5%	44.8%	23.7%	20.8%	<0.001
DS >70%	18.9%	18.4%	9.2%	6.4%	<0.001
Reocclusion	12.1%	10.4%	6.5%	5.2%	0.086

[a]Follow-up diameter stenosis (DS) >50%.

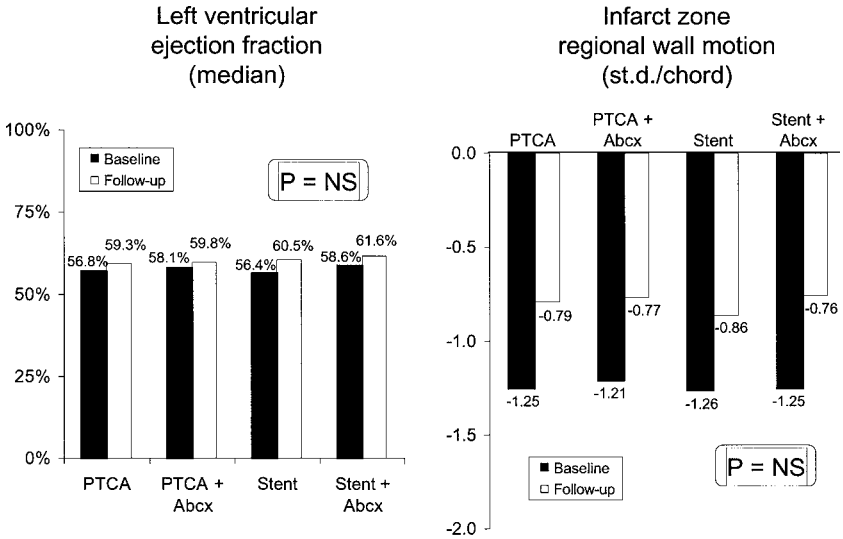


Fig. 10. Myocardial function at baseline (index procedure) and during the protocol 7-mo follow-up angiogram in the four randomized groups in the CADILLAC Trial. (*Left*) Global left ventricular ejection fraction. (*Right*) Infarct zone regional wall motion.

artery reocclusion were markedly reduced in patients randomized to stenting vs PTCA, independent of abciximab. Pooling the abciximab and no abciximab patients, binary restenosis was reduced from 40.8% after PTCA to 22.2% after stenting ($p < 0.001$), and infarct artery reocclusion was reduced from 11.3% to 5.7%, respectively ($p = 0.01$). As shown in Fig. 10, myocardial salvage was similar with all four reperfusion strategies.

The CADILLAC Trial—Conclusions and Clinical Implications

The CADILLAC trial, representing the largest randomized trial to date investigating mechanical reperfusion strategies in evolving AMI, demonstrated that routine MultiLink stent implantation improves event-free survival and angiographic outcomes compared with PTCA with stenting reserved for suboptimal results. The clinical benefits of stenting were consistent across all clinical subsets, independent of abciximab use, and attributable primarily to a reduction in early and late infarct artery restenosis and reocclusion. The comparative results in the "PTCA only" arm vs the "stent only" arm were particularly reassuring, as stenting in this large trial did not negatively affect post-procedural TIMI grade 3 flow or survival rates, in contrast to Stent PAMI *(49)*. Thus, with modern stent design and optimal use of contemporary pharmacologic regimens, stent implantation can now be recommended without reservation for all anatomically eligible patients with AMI undergoing a primary mechanical reperfusion strategy.

Abciximab use in the CADILLAC trial resulted in reduced rates of recurrent ischemia necessitating repeat TVR within 30 d (especially in PTCA patients), reduced subacute thrombosis rates (in both PTCA and stent patients), and facilitated early discharge. However, no significant benefits of abciximab persisted to 6 mo, in patients randomized to PTCA or to stenting, although some of the early reduction in ischemic TVR in PTCA patients treated with abciximab was (non-significantly) preserved. There was no evidence, however, that abciximab reduces death, reinfarction, or restenosis in patients with AMI undergoing primary PTCA or stenting. The principal clinical implication from CADILLAC, therefore, is that for patients presenting at centers experienced in the interventional management of AMI, stent implantation (with or without abciximab) should be considered the default (routine) reperfusion strategy. The decision to use abciximab should be individualized; the benefits of a more stable early clinical course must be weighed against the excess costs and the moderately increased risks of thrombocytopenia and blood product transfusion. Of note, however, no conclusions may be drawn from the CADILLAC trial regarding optimal treatment strategies for cardiogenic shock, vein graft occlusion, or other high-risk clinical and anatomic conditions that were excluded from enrollment.

The results of CADILLAC are therefore concordant with the earlier RAPPORT trial *(64)* in patients undergoing primary PTCA; abciximab as an adjunct to balloon angioplasty with bailout stenting results in improved 30-d outcomes, primarily due to reduced rates of recurrent ischemia necessitating urgent TVR. These findings are consistent with the results of EPIC, EPILOG, RESTORE, and other trials of elective balloon angioplasty *(58,59,61)* in which GP IIb/IIIa inhibitors, by "passivating" the inherently unstable, freshly dissected plaque, affords clinical stability until neointimal formation and reendothelialization occurs. Abciximab as an adjunct to primary PTCA did not, however, improve restoration of TIMI-3 flow in either RAPPORT or CADILLAC, nor was any evidence for enhanced myocardial salvage evident. Moreover, by 6 mo after primary PTCA, restenosis dominated the clinical picture, and thus the event-free survival rates in patients treated with and without abciximab converged or equalized, consistent with the paucity of evidence that abciximab (or any other GP IIb/IIIa inhibitor) reduces angiographic restenosis *(62,67,68)*.

Considering only the patients undergoing stent implantation randomized to routine abciximab administration vs control, the results in CADILLAC were similar to most findings from the ISAR-2 trial; abciximab as an adjunct to stenting tended to improve 30-d clinical outcomes, but by 6 mo the clinical event rates converged, with most of the early benefits of reduced ischemic TVR surrendered to late restenosis *(66,67)*. In both ISAR-2 and CADILLAC, angiographic restenosis rates were similar among stented patients randomized to abciximab vs control *(67)*. One important difference remains between the two studies, however; in ISAR-2, left ventricular function at 14 d was significantly enhanced in

stented patients treated with abciximab *(66)*, whereas in the larger CADILLAC trial, no difference in myocardial recovery with abciximab was found at 6 mo. These data are consistent with the possibility that abciximab, by decreasing distal embolization and/or capillary plugging, might enhance the speed, but not the ultimate extent of left ventricular recovery. Alternatively, the disparity in myocardial recovery noted between the two studies might be due to differences in patient selection (ISAR-2 included lytic failures, some patients with shock, and patients stented out to 48 h), or differences in methodology.

Thus, the results of CADILLAC, Stent-PAMI, RAPPORT, and ISAR-2 are reasonably consistent given evolving stent design, pharmacotherapy, operator technique and experience, and differences in trial design and methodology. Markedly different conclusions may be drawn, however, regarding the utility of abciximab in patients undergoing primary stenting when the disparate results of CADILLAC and ADMIRAL are reviewed (Table 3). Fortunately, new data from ADMIRAL has recently been presented affording reconciliation between these two studies.

RECONCILING ADMIRAL AND CADILLAC

ADMIRAL and CADILLAC differed significantly in patient selection and methodology. As shown in Table 4, CADILLAC enrolled a greater percentage of women (notable for the fact that abciximab in ADMIRAL was of benefit only in men), while a greater proportion of infarcts in ADMIRAL involved the left anterior descending artery. Given differing definitions and data reporting, it is difficult to compare the baseline left ventricular function and presence of heart failure or shock on admission between the two trials. Specifically, cardiogenic shock, which was excluded in CADILLAC, was present *within 24 h after randomization* in 8% of patients in ADMIRAL; unknown is how many patients in ADMIRAL presented in shock prior to randomization. The relative benefit of abciximab in ADMIRAL, however, was similar in patients with and without cardiogenic shock. Furthermore, heart failure was reported to be present in only 1% of patients on admission in ADMIRAL, as compared with 11% in CADILLAC.

The stents used in the two trials were also different; in CADILLAC, the Guidant MultiLink or MultiLink Duet (a stent design similar to that in use today) was exclusively used, whereas in ADMIRAL, the most commonly used stent was the Saint-Côme, which is similar in configuration and handling to the Palmaz–Schatz stent. Moreover, as randomization occurred in CADILLAC only after the angiographic anatomy was visualized and judged suitable for stenting, intervention was performed in all patients, whereas in ADMIRAL, in which randomization and drug administration were initiated *before* angiography, not all patients were eligible for stenting (primarily because of vessel diameter <2.5 mm), or even underwent intervention. The impact of this observation on the study results is unclear. In addition, in contrast to CADILLAC, the lack of an option to "crossover"

Table 3
Impact of Abciximab on 30-d and 6-mo Outcomes in the CADILLAC Trial (Stent Arms) and the ADMIRAL Trial

	CADILLAC			*ADMIRAL*		
	Abciximab	*No abciximab*	p *Value*	*Abciximab*	*No abciximab*	p *Value*
n	524	512	—	149	151	—
TIMI-3 flow achieved	96.9%	94.5%	NS	95.1%	86.7%	0.04
30-d events						
Death	2.7%	2.2%	NS	3.4%	6.6%	NS
Reinfarction	0.8%	1.0%	NS	1.3%	2.6%	NS
Urgent/ischemic TVR[a]	1.6%	3.2%	NS	1.3%	6.6%	0.02
Disabling stroke	0.2%	0.2%	NS	—	—	—
Composite	4.4%	5.7%	NS	6.0%	14.6%	0.01
6-mo events						
Death	4.2%	3.0%	NS	3.4%	7.3%	NS
Reinfarction	2.2%	1.6%	NS	2.0%	4.0%	NS
Urgent/ischemic TVR[a]	5.2%	8.3%	NS	2.0%	6.6%	0.049
Disabling stroke	0.4%	0.4%	NS	—	—	—
Composite	10.2%	11.5%	NS	7.4%	15.9%	0.02
Elective TVR[b]	3.6%	4.2%	NS	9.4%	17.2%	0.046
Any TVR	5.7%	8.9%	0.09	11.4%	23.8%	0.005
LVEF (%) (mean)						
Baseline[c]	58.6%	56.4%	NS	57.0%	53.9%	<0.05
6 mo[d]	61.6%	60.5%	NS	61.1%	57.0%	0.05

[a]Ischemia driven TVR in the CADILLAC; urgent TVR in the ADMIRAL Trial.
[b]Nonischemic TVR in the CADILLAC; elective TVR in the ADMIRAL Trial.
[c]During the index procedure in CADILLAC; at 24 h in ADMIRAL.
[d]6 mo in ADMIRAL; 7 mo in CADILLAC.

Table 4
Comparison of Baseline Features and Procedural Data in the CADILLAC and ADMIRAL Trials

	CADILLAC	*ADMIRAL*
n enrolled	2681	300
n randomized	2082	300
n countries	9	1
n institutions	76	26
Baseline characteristics		
Age (mean)	~60 yr	~61 yr
Gender (female)	27%	19%
Diabetes	17%	17%
Prior MI	14%	11%
Heart failure on admission	11% (Killip class ≥2)	1% (Not specified)
Cardiogenic shock within 24 h after randomization	Not reported	8%
Time from symptom onset to ER arrival (median)	1.8 h	Not reported
Time from ER arrival to PTCA (median)	1.5 h	Not reported
Infarct artery = left anterior descending	37%	46%
Infarct artery = saphenous vein graft	0%	1.4%
Procedural data		
Abciximab initiated in cath lab	99%	74%[a]
Study drug blinded	No—open label	Yes—placebo controlled
Crossover from control to abciximab	5%	0%
PTCA performed in randomized patients	99%	93.5%
Stenting performed in randomized patients (stent arms in CADILLAC)	98%	86.5% (92% of dilated patients)
Stent type	100% MultiLink and MultiLink Duet	66% Saint-Côme, 34% Multiple others

[a]In the cath lab or in the intensive care unit on way to cath lab.

and administer abciximab to control patients with TIMI 0–2 flow in ADMIRAL may have contributed to the relatively low post-procedural TIMI 3 flow rate of 86.5%.

Another major difference between ADMIRAL and CADILLAC was the rate of infarct artery reocclusion. In CADILLAC, the incidence of reocclusion of the infarct vessel in patients assigned to stenting was 5.8% at 7 mo and was independent of abciximab use. In contrast, in ADMIRAL, infarct artery reocclusion at 6 mo was noted in 12.0% of patients randomized to stenting plus placebo, compared with 2.8% for the stenting plus abciximab group ($p < 0.05$). Whether the high reocclusion rate in patients not treated with abciximab in ADMIRAL can

be attributed either to the specific stent used or to the fact that approx 15% of patients in this study were treated with PTCA or medical therapy rather than stenting is unknown. Regardless, this high reocclusion rate likely contributed to excess reinfarction and reduced left ventricular function in patients not treated with abciximab in ADMIRAL.

Finally, perhaps the most important distinction between the two studies relates to the timing of study drug administration. In CADILLAC, abciximab was administered within minutes prior to angioplasty. In contrast, in ADMIRAL, abciximab (or placebo) was started *in all patients before the arterial sheath was placed*, well before PTCA was performed. The mean time from study drug to angiography in ADMIRAL was 36 min, corresponding to abciximab administration approx 1 h before angioplasty. Furthermore, patients in ADMIRAL were randomized in either the cardiac catheterization laboratory or the intensive care unit (on the way to the cath lab)—the "late" group, representing 74% of patients, or earlier in the emergency room (15%), or much earlier in the ambulance (11%)—collectively the "early" group, representing 26% of patients. The length of time from chest pain onset to study drug administration was shorter for patients receiving the drug in the ambulance (178 $\pm$ 94 min) vs the emergency room (266 $\pm$ 139 min, $p = 0.02$) or the cath lab/intensive care unit settings (238 $\pm$ 142 min, $p = 0.002$). Additional data from ADMIRAL regarding these subgroups were recently reported which has illustrated the major impact that variations in timing of GP IIb/IIIa administration may have [Gilles Montalescot, Transcatheter Cardiovascular Therapeutics (TCT) 2001, Washington DC].

As previously discussed, TIMI 3 flow rates in ADMIRAL were greater at baseline in patients randomized to abciximab than to control. Of note, baseline TIMI-3 flow was present in 31.7% of patients randomized and treated with abciximab very early (in the ambulance), compared with 12.7% of patients in whom abciximab was initiated later in the other three settings ($p < 0.001$). In contrast, initial TIMI-3 flow was present in 17.6% of patients receiving placebo in the ambulance vs 6.8% of patients elsewhere (p = NS). These data are consistent with other studies demonstrating a 25%–35% TIMI-3 reperfusion rate with abciximab when given 60–90 min before angiography *(69,70)*.

Consistent with this finding, the improvement in left ventricular ejection fraction noted in the abciximab-treated patients at 24 h in ADMIRAL was primarily confined to those patients treated very early, during transport in the ambulance (Fig. 11). Moreover, the statistically significant improvements in 30-d and 6-mo event-free survival with abciximab in ADMIRAL were also confined to the patients treated very early (Fig. 12).

Thus, the results of the CADILLAC and ADMIRAL trials are quite concordant after all. When abciximab is started shortly before stenting, only weak, nonsignificant trends are present for benefit at 30 d and 6 mo compared with control (Fig. 13), and left ventricular function is not significantly enhanced,

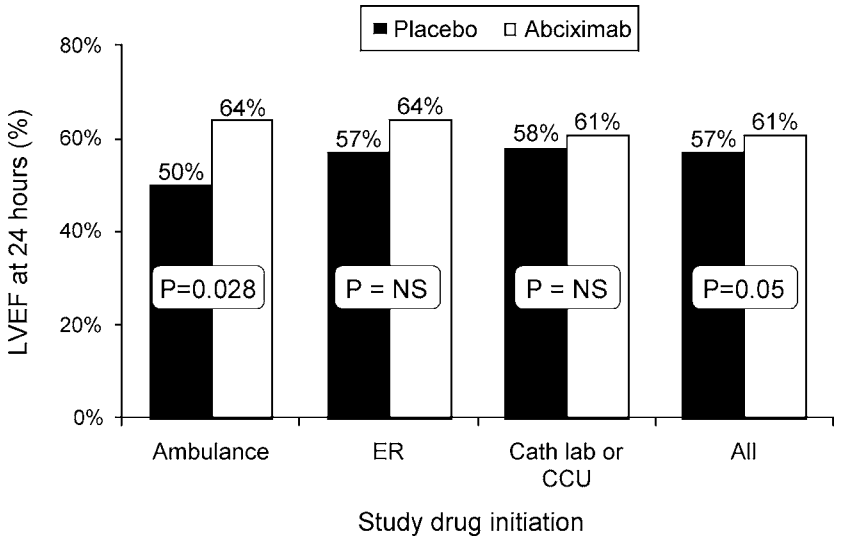


Fig. 11. Left ventricular ejection fraction at 24 h in patients randomized to placebo vs abciximab in the ADMIRAL trial, stratified by site of randomization and study drug initiation. ER, emergency room; CCU, coronary care unit.

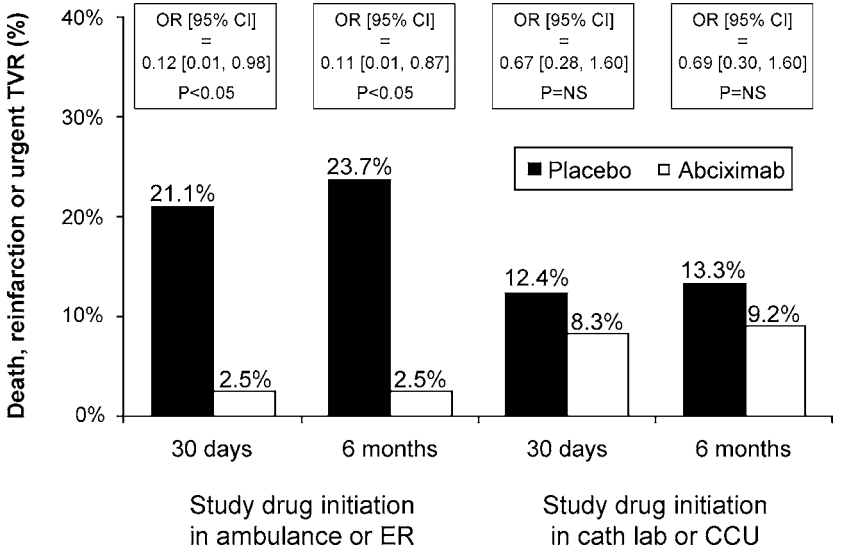


Fig. 12. Incidence of the primary composite endpoint in ADMIRAL (death, reinfarction, or urgent TVR), at 30 d and 6 mo, stratified by site of initial randomization and study drug administration. Abbreviations as in Fig. 11.

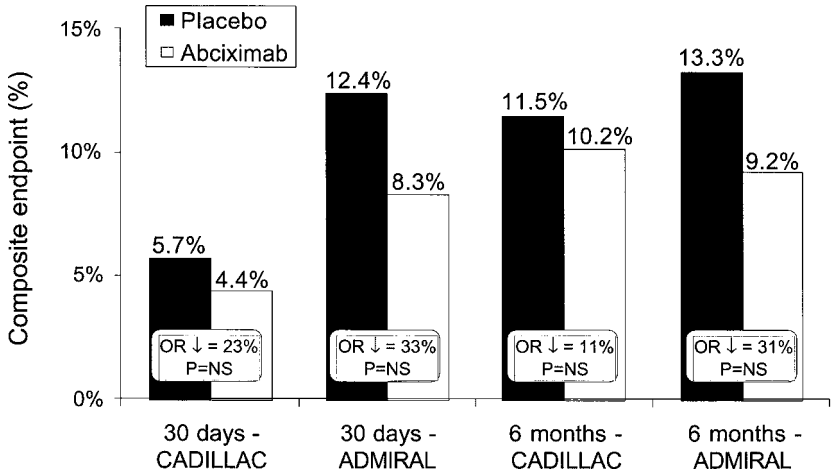


Fig. 13. The 30-d and 6-mo rates of the primary composite endpoint in CADILLAC (considering only the patients randomized to stenting vs stenting + abciximab), and ADMIRAL (considering only the patients with drug started in the cath lab or coronary care unit). The primary endpoint for CADILLAC = death, reinfarction, disabling stroke, or ischemic TVR. The primary endpoint for ADMIRAL = death, reinfarction, or urgent TVR.

either at 24 h or 6 mo. The apparently greater risk reduction in clinical events (though still nonsignificant) in the "late" patients randomized to abciximab vs placebo in ADMIRAL compared with all stent patients in CADILLAC may be due to differences in patient selection; chance; the stent used; the lack of abciximab crossover in ADMIRAL; differing endpoint definitions; or the fact that abciximab, even in the "late" group, was still started earlier in ADMIRAL than in CADILLAC.

In striking contrast, however, profound effects of early abciximab administration were observed in stented patients in ADMIRAL, with marked improvements in left ventricular function and early and late event-free survival, mediated at least in part through earlier attainment of TIMI 3 flow pre-intervention. These data are consistent with (1) a previous report from 2507 patients in the PAMI trials, in which early and late mortality were strikingly reduced in patients with spontaneously occurring pre-procedural TIMI 3 flow, independent of the final TIMI flow *(71)*; (2) the randomized Primary Angioplasty Compatibility Trial (PACT), in which early reperfusion with reduced dose t-PA resulted in greater early recovery of left ventricular function *(72)*; and (3) the meta-analysis demonstrating that mortality is decreased when thrombolytic therapy is initiated prehospital as compared to the emergency room *(73)*. Although some of the marked benefit in the early treated group in ADMIRAL may be due to chance, having

resulted in an inexplicably high rate of adverse events in the placebo-treated patients, these data support ongoing trials of pharmacologically mediated reperfusion prior to definitive mechanical revascularization ("facilitated PCI").

Furthermore, the safety of abciximab use in AMI was confirmed in both trials. Major bleeding and intracranial hemorrhage were not significantly increased by abciximab use in either study. Mild hemorrhage and thrombocytopenia were increased with abciximab in both trials, however, resulting in a modest increase in blood product transfusions.

CONCLUSIONS

A great deal has been learned about mechanical reperfusion therapy over the last decade which has directly resulted in improved survival and quality of life for patients with AMI. The superiority of percutaneous intervention over thrombolytic therapy has been established and is now widely accepted. With advances in interventional devices (stents), improved operator experience and technique, and greater recognition of the importance of optimal adjunct pharmacology, outcomes of primary angioplasty in AMI continue to improve. Compared with balloon angioplasty alone, stenting plus GP IIb/IIIa inhibitors has been shown to enhance the early safety profile of mechanical intervention, increase long-term patency of the infarct vessel, and reduce restenosis, with an acceptable risk and cost profile. The promise for even greater improvements in outcomes of patients with AMI may be anticipated from new approaches under investigation, including facilitated PCI, innovative applications of devices such as distal embolic protection and thrombectomy to further enhance microcirculatory function after reperfusion, novel devices to reduce reperfusion injury (e.g., with supersaturated oxygen delivery or myocardial cooling), and multiple new pharmacologic adjuncts to enhance patency, epicardial and myocardial blood flow, and myocardial metabolism after mechanical reperfusion therapy.

REFERENCES

1. DeWood MA, Spores J, Notske R, et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. N Engl J Med 1980;303:897–902.
2. Davies MJ, Thomas AC. Plaque fissuring-the cause of acute myocardial infarction, sudden ischemic death, and crescendo angina. Br Heart J 1985;53:363–373.
3. The Fibrinolytic Therapy Trialists (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311–322.
4. Herrmann HC. Triple therapy for acute myocardial infarction: combining fibrinolysis, platelet IIb/IIIa inhibition, and percutaneous coronary intervention. Am J Cardiol 2000;85:10C–16C.
5. The GUSTO Investigators. An international randomized trial comparing four thrombolytic regimens consisting of tissue plasminogen activator, streptokinase, or both for acute myocardial infarction. N Engl J Med 1993;329:673–682.

6. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–1622.
7. Meijer A, Verheugt FWA, Werter CPJP, et al. Aspirin versus coumadin in the prevention of reocclusion and recurrent ischemia after successful thrombolysis: a prospective placebo-controlled angiographic study. Circulation 1993;87:1524–1530.
8. Berkowitz SD, Granger CB, Pieper KS, et al, for the GUSTO Investigators. Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. Circulation 1997;95:2508–2516.
9. Grines CL, Brown KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–679.
10. Lange RA, Hillis LD. Immediate angioplasty for acute myocardial infarction. N Engl J Med 1993;328:726–728.
11. Gibbons RJ, Holmes DR, Reeder GS, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unite in Catheterization Laboratory groups. N Engl J Med 1993;328:685–691.
12. Zijlstra F, de Boer MJ, Hoorntje JC, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Engl J Med 1993;328: 680–684.
13. The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO-IIb) Angioplasty Substudy Investigators. A clinical trial comparing coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. N Engl J Med 1997;336:1621–1628.
14. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093–2098.
15. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489–495.
16. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994;331:496–501.
17. Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stents with balloon angioplasty in selected patients with coronary artery disease (Benestent II). Lancet. 1998 Aug 29;352(9129):673–681.
18. Adgey JAA. Overview of the results of clinical trials with glycoprotein IIb/IIIa inhibitors. Am Heart J 1998;135(Suppl):S43–S55.
19. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. Circulation 1998;98:2829–2835.
20. The Capture Investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the Capture study. Lancet 1997;349:1429–1435.
21. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. N Engl J Med 1998;338:1488–1497.
22. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. N Engl J Med 1998;339:436–443.

23. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001 Jun 21;344(25):1879–1887.
24. Montalescot G, Barragan P, Wittenberg O, et al. for the ADMIRAL Investigators. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895–1903.
25. Stone GW, Grines CL, Cox DA, et al. A prospective, randomized trial comparing primary balloon angioplasty with or without abciximab to primary stenting with or without abciximab in acute myocardial infarction—primary endpoint analysis from the CADILLAC Trial. Circulation 2000;18(Suppl 2):II-664.
26. Stone GW, Grines CL, Browne KF, et al. Implications of recurrent ischemia after reperfusion therapy in acute myocardial infarction: a comparison of thrombolytic therapy and primary coronary angioplasty. J Am Coll Cardiol 1995;26:66–72.
27. O'Neill WW, Brodie BR, Ivanhoe R, et al. Primary coronary angioplasty for acute myocardial infarction (The Primary Angioplasty Registry). Am J Cardiol 1994;73:627–634.
28. Fry JA, Grines CL. Does primary stenting in acute myocardial infarction increase mortality? ACC Curr J Rev 2001;10:68–71.
29. Nakae I, Fujita M, Fudo T, et al. Relation between preexistent coronary collateral circulation and the incidence of restenoses after successful primary coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1996;27:1688–1692.
30. O'Keefe JH, Rutherford BD, McConahay DR, et al. Early and late results of coronary angioplasty without antecedent thrombolytic therapy for acute myocardial infarction. Am J Cardiol 1989;64:1221–1230.
31. Brodie BR, Grines CL, Ivanhoe R, et al. Six-month clinical and angiographic follow-up after direct angioplasty for acute myocardial infarction. Circulation 1994;90:156–162.
32. Nakagawa Y, Iwasaki Y, Kimura T, et al. Serial angiographic follow-up after successful direct angioplasty for acute myocardial infarction. Am J Cardiol 1996;78:980–984.
33. Colombo A, Hall P, Nakamura S, et al. Angiographic follow-up and restenosis results after Palmaz–Schatz intracoronary stenting without anticoagulation. Circulation 1994;90:I-124.
34. Leon MB, Baim DS, Gordon P, et al. Clinical and angiographic results from the Stent Anticoagulation Regina Study (STARS). Circulation 1996;95:I-685.
35. Carrozza JP, Kuntz RE, Levine MJ, et al. Angiographic and clinical outcome of intracoronary stenting: immediate and long-term results form a large single center experience. J Am Coll Cardiol 1992;20:328–337.
36. Grines CL, Brodie BR, Griffin JJ, et al. Which primary PTCA patients may benefit from new technologies? Circulation 1995;92(Suppl I):I-146.
37. Stone GW, Brodie BR, Griffin JJ, et al. A prospective, multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30 day results of the PAMI Stent Pilot Trial. J Am Coll Cardiol 1998;31:23–30.
38. Nakamura S, Colombo A, Gaglione A, et al. Intracoronary ultrasound observations during stent implantation. Circulation 1994 May;89(5):2026–2034.
39. Schiele F. Intravascular ultrasound guidance for stent implantation. Circulation 2001 May 29;103(21):E110–120.
40. Morino Y, Honda Y, Okura H, et al. An optimal diagnostic threshold for minimal stent area to predict target lesion revascularization following stent implantation in native coronary lesions. Am J Cardiol 2001 Aug 1;88(3):301–303.
41. Kuntz RE, Gibson CM, Nobuyoshi M, Baim DS. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993 Jan;21(1):15–25.
42. Stone GW, Brodie BR, Griffin JJ, et al. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction: The PAMI Stent Pilot Trial. Circulation 1999;99:1548–1554.

43. Antoniucci D, Santoro GM, Bolognese L, et al. A clinical trial comparing primary stenting of the infarct-related artery with optimal primary angioplasty for acute myocardial infarction. Results from the Florence Randomized Elective Stenting in Acute Coronary Occlusions (FRESCO) trial. J Am Coll Cardiol 1998;31:1234–1239.
44. Suryapranata H, van't Hof A, Hoorntje J, et al. Randomized comparison of coronary stenting with balloon angioplasty in selected patients with acute myocardial infarction. Circulation 1998;97:2502–2505.
45. The GRAMI Investigators. In-hospital and late results of coronary stents versus conventional balloon angioplasty in acute myocardial infarction (GRAMI trial). Am J Cardiol 1998;81: 1286–1291.
46. The PASTA trial Investigators. Primary stent implantation is superior to balloon angioplasty in acute myocardial infarction: final results of the primary angioplasty versus stent implantation in acute myocardial infarction (PASTA) trial. Cathet Cardiovasc Intervent 1999;48: 262–268.
47. The STENTIM-2 Investigators. A comparison of systematic stenting and conventional balloon angioplasty during primary percutaneous transluminal coronary angioplasty for acute myocardial infarction. J Am Coll Cardiol 2000;35:1729–1736.
48. Stone GW. Stenting in acute myocardial infarction: observational studies and randomized trials—1998. J Inv Cardiol 1998;10:16A–26A.
49. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. N Engl J Med 1999;341:1949–1956.
50. Grines CL, Cox DA, Stone GW, et al. Stent PAMI: 12 month results and predictors of mortality. J Am Coll Cardiol 2000;35(Suppl A):402A.
51. Wakatsuki T, Nakamura M, Tsunoda T, et al. Coronary flow velocity immediately after primary coronary stenting as a predictor of ventricular wall motion recovery in acute myocardial infarction. J Am Coll Cardiol 2000;35:1835–1841.
52. Belli G, Pezzano A, De Biase AM, et al. Adjunctive thrombus aspiration and mechanical protection from distal embolization in primary percutaneous intervention for acute myocardial infarction. Cathet Cardiovasc Interv 2000;50:362–370.
53. Erbel R, Heusch G. Coronary microembolization—its role in acute coronary syndromes and interventions. Herz 1999;24:558–575.
54. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndrome. N Engl J Med 1992;326:242–250, 310–318.
55. Coller BS, Scudder LE, Beer J, et al. Monoclonal antibodies to platelet glycoprotein IIb/IIIa as antithrombotic agents. Ann NY Acad Sci 1991, 614:193–213.
56. Lincoff AM, Califf RM, Topol EJ. Platelet glycoprotein IIb/IIIa receptor blockade in coronary artery disease. J Am Coll Cardiol 2000;35:1103–1115.
57. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein IIb/IIIa blockade. Lancet 1998;352:87–92.
58. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. N Engl J Med 1994;330:956–961.
59. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low dose heparin during percutaneous coronary revascularization. N Engl J Med 1997; 336:1689–1696.
60. O'Shea JC, Hafley GE, Greenberg S, et al. Platelet glycoprotein IIb/IIIa integrin blockade with eptifibatide in coronary stent intervention: the ESPRIT trial: a randomized controlled trial. JAMA 2001 May 16;285(19):2468–2473.
61. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. Circulation 1997;96:1445–1453.

62. Gibson CM, Goel M, Cohen DJ, et al. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. J Am Coll Cardiol 1998 Jul;32(1):28–34.
63. Anderson KM, Califf RM, Stone GW, et al. Long-term mortality benefit with abciximab in patients undergoing percutaneous coronary intervention. J Am Coll Cardiol 2001;37(8):2059–2065.
64. Brener SJ, Barr LA, Burchenal JE, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998;98:734–741.
65. Schomig A, Kastrati A, Dirschinger J, et al. Coronary stenting plus platelet glycoprotein IIb/IIIa blockade compared with tissue plasminogen activator in acute myocardial infarction. Stent versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction Study Investigators. N Engl J Med 2000 Aug 10;343(6):385–391.
66. Neumann FJ, Blasini R, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade on recovery of coronary flow and left ventricular function after the placement of coronary-artery stents in acute myocardial infarction. Circulation 1998;98:2695–2701.
67. Neumann FJ, Kastrati A, Schmitt C, et al. Effect of glycoprotein IIb/IIIa receptor blockade with abciximab on clinical and angiographic restenosis rate after the placement of coronary stents following acute myocardial infarction. J Am Coll Cardiol 2000;35:915–921.
68. The ERASER Investigators. Acute platelet inhibition with abciximab does not reduce in-stent restenosis. Circulation 1999;100:799–806.
69. Antman EM, Giugliano RP, Gibson CM, et al. Abciximab facilitates the rate and extent of thrombolysis: results of the Thrombolysis in Myocardial Infarction (TIMI) 14 trial. Circulation 1999;99:2729–2732.
70. Strategies for Patency Enhancement in the Emergency Department (SPEED) Investigators. A trial of abciximab with and without low-dose reteplase for acute myocardial infarction. Circulation 2000;101:2788–2794.
71. Stone GW, Cox D, Garcia E, et al. Normal flow (TIMI-3) before mechanical reperfusion therapy is an independent determinant of survival in acute myocardial infarction: analysis from the primary angioplasty in myocardial infarction trials. Circulation 2001;104:636–641.
72. Ross AM, Coyne KS, Reiner JS, et al. A randomized trial comparing primary angioplasty with a strategy of short-acting thrombolysis and immediate planned rescue angioplasty in acute myocardial infarction: the PACT trial. J Am Coll Cardiol 1999;34:1954–1962.
73. Morrison LJ, Verbeek PR, McDonald AC, et al. Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. JAMA 2000 May 24–31;283(20):2686–2692.

10 Health Economics of Primary Percutaneous Transluminal Coronary Angioplasty

Russell J. Ivanhoe, MD

CONTENTS

INTRODUCTION

There has been significant change in the manner in which the limited resources of health care are distributed. The era wherein physicians diagnosed and treated illness without much thought about cost or the economic consequences of their medical decisions has evaporated under the heat of managed care and DRG-based measurements. While most physicians bristle at the thought of oversight of their medical decisions, they have come to accept the fact that every decision they make has some economic impact. In consequence, more attention and effort are being placed on analyzing the economic impact of new therapies or new applications of established therapies.

An understanding of economic analysis, including its strengths and pitfalls, is germane to the implementation of new approaches to treating illnesses. By taking a prominent place in the decision-making process of physicians delivering care, however, economic analysis has created an ethical burden. The additional costs

From: *Contemporary Cardiology: Primary Angioplasty in Acute Myocardial Infarction*
Edited by: J. E. Tcheng © Humana Press Inc., Totowa, NJ

of a new treatment, despite proven effectiveness, may at the least delay, and at the worst preclude, its use. The decision *to not* offer a particular treatment because of cost, a decision typically made by nontreating hospital or health-plan administrators, thwarts the treating physician from assuming the role of fiduciary for the patient's health. The treating physician thus faces an economic conflict of interest.

An evaluation of the economic impact of a new treatment cannot be taken out of context. Such an analysis must be considered in light of the clinical benefit and it must account for the responsibility physicians assume as trustees of their patients' health. This chapter discusses the basic tools of health economics and their application to clinical studies. It then evaluates the existing economic data regarding primary percutaneous transluminal coronary angioplasty (PTCA) during acute myocardial infarction and related topics.

COST

The analysis of cost is sometimes mistakenly substituted for a more in-depth analysis of the economics of a medical intervention, such as cost-effectiveness or cost–benefit ratio. Cost is a fundamental economic concept that assigns a monetary value to a product or treatment in order to compare disparate resources or, in the case of health care, the consumption of health care resources by different treatments. Cost must be distinguished from charges and payments. Economists discuss cost in the context of opportunity cost. If limited resources were applied to a particular item, another item would not be funded. In other words, what is the lost opportunity?

It is very difficult to determine exact costs, particularly hospital costs. Therefore a specific methodology has been developed for estimating hospital costs in a cost analysis *(1)*. The UB92 is a widely used billing form employed by all hospitals that treat Medicare patients. The charges on the UB92 are tallied and a Medicare conversion ratio is then applied to arrive at a best estimate of cost. Several factors must be considered in the cost analysis that may not appear on the UB92. For instance, physician professional charges, particularly when several visits occur, are not necessarily accounted for in the cost analysis. Productivity costs are those costs to society related to morbidity and time out of work. It is difficult to account for such costs or, for that matter, to assign a definite value to them. For this reason, productivity costs are rarely incorporated into any analysis of the cost of medical interventions. That does not diminish the importance of productivity costs, however, especially if a certain treatment decreases the length of the hospital stay and shortens the out-of-hospital recovery period, allowing the patient to return to productivity. If two or more treatments are compared and are equal in effectiveness but one is less costly than the other, or if the costs are equal but one treatment clearly prevails in effectiveness, then no further analysis, beyond comparing cost, is necessary.

Table 1
The Relationship between Levels of Evidence and Grades of Recommendations

Level of evidence		*Grade of recommendation*
Level 1	Large randomized trials with clear-cut results (and low risk of error)	Grade A
Level 2	Small randomized trials with uncertain results (and moderate to high risk of error)	Grade B
Level 3	Nonrandomized, contemporaneous controls	Grade B
Level 4	Nonrandomized, historical controls	Grade C
Level 5	No controls, case series only	Grade C

Adapted from Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1992;102:305S–311S.

COST-EFFECTIVENESS ANALYSIS (CEA)

There are many instances when two treatments are compared and one of the two treatments is established as superior in both effectiveness and cost. In that case there is no reason to undertake further economic analysis. Furthermore, if two treatments are compared and found to be equally effective but one costs less than the other, a strong case can be made for abandoning the more costly procedure. In reality, physicians and administrators are often faced with deciding on the adoption of new therapies that have proven benefit over an established therapy but at a greater cost. It is in the latter case that health economists apply the tool of cost-effectiveness analysis (CEA).

Cost-effectiveness analysis is used when two or more treatments are compared and one is found to prevail but at a higher cost. Cost-effectiveness analysis can be simply described by the following relationship:

$$\frac{\Delta\text{Cost}}{\Delta\text{Effectiveness}}$$

Effectiveness is typically measured by assessing cumulative life years saved (LYS) or by various quality measures such as quality-adjusted life years (QALY). The measurement of effectiveness usually is derived from randomized trials. In fact, the quality of the clinical trial is the foundation for the quality of the CEA (Table 1). However, clinical trials may have restricted entry criteria or short time horizons. In such cases data may be supplemented with data derived from epidemiological studies *(2)*. A full discussion can be found in Gold *(3)* and Califf *(4)*.

For a new treatment to be considered cost-effective it must be shown to be an improvement over the current best practice and it must meet generally accepted parameters for cost effectiveness. It is generally accepted that a procedure that

Table 2
Cost-Effectiveness Benchmarks ($/LYS)

Treatment	*Cost*
CABG for left main disease	$7000
Cervical cancer screening	$12,000
Neonatal ICU	$12,000
Renal transplant	$19,000
t-PA vs Streptokinase for AMI	$32,000
Hemodialysis	$35,000
Heart transplant	$54,000
Cholesterol treatment (first-degree prevention)	$154,000

Table 3
Cost-Effectiveness Safety Devices ($/Life Saved)

Safety sensors—escalators	$1,600,000
Automobile airbags	$1,700,000
Automobile seat belts	$150,000
Automatic parachute activation devices	$125,000

Based on data from Smedinghoff G: Is the Metro too safe? Washington Post, Aug. 7, 1999, p. A19.

has a cost-effectiveness ratio of less than or equal to $35,000/life year saved is a cost-effective procedure or treatment (Table 2). It can be shown that this is an arbitrary cutoff. *The Washington Post* has published a CEA for various safety procedures that are mandated by law (Table 3). What actually constitutes a fair value in assessing the cost-effectiveness of a medical procedure is complex and beyond the scope of this chapter.

ECONOMICS OF PRIMARY PTCA

The Primary Angioplasty Registry enrolled 270 patients with acute myocardial infarction (AMI) at six private tertiary care medical centers. An economic analysis of the PAR study describes detailed medical resource use patterns and associated medical costs with primary angioplasty *(4)*. Economic outcomes were assessed in terms of both medical costs and medical resource consumption using hospital and physician billing records. Charges were converted to costs using cost/charge ratios. The total baseline hospital cost for the primary reperfusion strategy averaged $13,113 (1995 dollar value). Physician fees added another $5694 to the overall cost of the episode of care. The independent predictors of higher cost were older age, anterior myocardial infarction, higher initial Killip class, and greater number of diseased vessels. The need for coronary artery

bypass graft (CABG) surgery substantially raised the cost over that of coronary angioplasty alone. Other myocardial infarction complications that contributed to an increase in cost included recurrent ischemia and new or worsened congestive heart failure. Overall, a 10-yr difference in age was associated with a 5% increase in adjusted hospital costs, whereas recurrent ischemia was associated a 53% average increase. The need for CABG after angioplasty was associated with a 142% increase in cost.

Economics of Primary PTCA vs Thrombolysis

The Primary Angioplasty in Myocardial Infarction (PAMI) trial was a large-scale multicenter randomized trial of tissue plasminogen activator (t-PA) vs PTCA for AMI *(5)*. In this study, compared with thrombolytic therapy using t-PA, primary PTCA resulted in reduced rates of in-hospital mortality, reinfarction, recurrent ischemia, and stroke. Hospital length of stay was significantly reduced. An analysis of the cost of intervening in each arm revealed that, despite the initial costs of cardiac catheterization in all patients with the invasive strategy, total mean hospital costs were $3436 lower per patient with PTCA than with t-PA *(6)*. Professional fees were higher with the angioplasty arm. Thus in the end there was no significant difference in cost between the two arms of the study. In this randomized study, the invasive arm had significantly improved outcomes over the thrombolytic arm at no increase in cost.

The second PAMI study evaluated the hypothesis that primary PTCA with early (3-d) discharge from the hospital is safe and cost-effective in low-risk patients *(7)*. Patients who were randomized to accelerated care were discharged 3 d earlier than those randomized to the conventional treatment arm; hospital costs were reduced by $1946 in the early discharge arm. Outcomes at 6 mo were equivalent in both groups.

The GUSTO-IIb study randomized 1138 patients to either primary PTCA or front-loaded t-PA. The Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow rate in the angioplasty arm was either 73% or 85% depending on whether the angiogram was reviewed at the angiographic core lab or the hospital, respectively. The immediate results showed a significant benefit for primary PTCA. At 6-mo follow-up, however, there was no significant difference between treatment arms for the combined endpoint. No economic analysis was deemed necessary because of a failure to show benefit in the primary angioplasty arm (Daniel B. Mark, MD, personal communication).

Most studies have shown primary PTCA to be more effective at a cost that is equivalent to or lower than fibrinolytic therapy for AMI. In fact, the success of primary PTCA and whether or not it should be used as the first approach to treating AMI may depend on operator experience and local success rates.

Lieu et al. created a decision analytic model to compare three approaches to treating acute myocardial infarction: primary angioplasty, intravenous throm-

bolysis, or no intervention *(8)*. Outcomes were derived from published randomized studies and meta-analyses. The parameter of QALY was used as the outcome measure. For a hypothetical cohort of 10,000 patients with an AMI, primary angioplasty improved outcomes by 741 undiscounted QALYs relative to thrombolysis (514 discounted QALYs). When a hospital met efficacy assumptions and a volume of >200 cases/yr, there was a substantial cost-effectiveness benefit for primary PTCA. This benefit was lost when the hypothetical hospital was inexperienced or redundant in the community. The authors concluded that consideration should be given to regionalization of primary angioplasty services.

ECONOMICS OF GLYCOPROTEIN IIB/IIIA INHIBITION IN PRIMARY PTCA

The success of primary PTCA as a treatment for AMI is operator dependent. In experienced centers, where the system is primed to move a patient swiftly through the emergency room to the catheterization suite, there is every reason to expect success rates in excess of 97% in concert with a shortened hospital stay and lower initial costs. The use of intracoronary stenting with and without glycoprotein (GP) IIb/IIIa integrin blocking drugs can be expected to further reduce complications, although at an added cost. The economic evaluation of this enhanced therapy is eagerly awaited.

CONCLUSIONS

The aggregate data suggest improved outcomes with direct angioplasty for AMI at a cost equal to or lower than that of thrombolytic therapy. This therapy thus uniquely qualifies as an approach where better outcomes are achieved at the same or lower cost, diminishing the impetus for justification of direct angioplasty on a cost-effectiveness basis. The resource constraints (of more widespread availability of emergency catheterization facilities) notwithstanding, a discussion of whether the data support regionalization of services for primary PTCA in the setting of AMI is beyond the scope of this chapter. Well-designed clinical trials that include an economic analysis should help cardiologists sort through the issues of how best to treat AMI in the era of stents, platelet GP IIb/IIIa inhibition, direct thrombin inhibitors, and more expeditious use of thrombolytic therapy.

REFERENCES

1. Weintraub WS, Culler S, Boccuzzi SJ, et al. Economic impact of GPIIB/IIIA blockade after high-risk angioplasty: results of the RESTORE trial. Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. J Am Coll Cardiol 1999;34:106–116.
2. Kupersmith J. Cost-effectiveness analysis. In: Cost Effectiveness in Health and Medicine, Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. Oxford University Press, New York, 1996.

3. Califf RM, ed. Economics and cost-effectiveness in evaluating the value of cardiovascular therapies. Am Heart J 1999;137:S35–S144.
4. Mark DB, O'Neill WW, Brodie B, et al. Baseline and 6-month costs of primary angioplasty therapy for acute myocardial infarction: results from the Primary Angioplasty Registry. J Am Coll Cardiol 1995;26:688–695.
5. Grines CL, Browne KF, Marco J, et al. A comparison of primary angioplasty with thrombolytic therapy for myocardial infarction. N Engl J Med 1993;328:673–679.
6. Stone GW, Grines CL, Rothbaum D, et al. Analysis of the relative costs and effectiveness of primary angioplasty versus tissue-type plasminogen activator: the Primary Angioplasty in Myocardial Infarction (PAMI) Trial. J Am Coll Cardiol 1997;29:901–907.
7. Grines CL, Marsalese DL, Brodie B, et al. Safety and cost-effectiveness of early discharge after primary angioplasty in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1998:31:967–972.
8. Lieu TA, Gurley RJ, Lundstrom RJ, et al. Projected cost-effectiveness of primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1997;30:1741–1750.

INDEX

C

Contemporary Cardiology™

Christopher P. Cannon, MD, *Series Editor*

Primary Angioplasty in Acute Myocardial Infarction

Edited by

James E. Tcheng, MD

Duke Clinical Research Institute and Division of Cardiology
Duke University Health System, Durham, NC

The emergency treatment of acute myocardial infarction (AMI)—one of the leading causes of death throughout the world—with immediate cardiac catheterization and percutaneous coronary intervention, or primary angioplasty, is now considered the optimal approach to this deadly disorder. In *Primary Angioplasty in Acute Myocardial Infarction,* leading investigators and experienced clinicians collect and summarize the world's literature and augment this with practical wisdom concerning this critically important form of care. Technical, professional, and administrative aspects are reviewed in clear detail. Among the topics covered are the technique and technology of direct angioplasty, patient selection, regulatory issues, performance metrics, clinical trials and outcomes, adjunctive pharmacology, economics, and implications for the health care system. The practicing cardiologist will appreciate the many useful how-to tips and pointers; the cardiology fellow will value the a-to-z approach that addresses all critical issues; and the administrator will learn the details of creating, maintaining, evaluating, and justifying a successful program.

Comprehensive and highly practical, *Primary Angioplasty in Acute Myocardial Infarction* summarizes for today's cardiologists, internists, family practitioners, and emergency room physicians all the accumulated knowledge and experience needed to ensure that primary angioplasty becomes the standard of care for acute myocardial infarctions.

Features

- Complete coverage of all aspects of using the primary angioplasty approach to treating acute myocardial infarction
- Numerous practical tricks, tips, and recommendations useful in daily practice
- Emphasis on state-of-the-art developments and techniques
- Essential information for anyone caring for a cardiac patient

Contents

ISBN 0-89603-904-8

9 0 0 0 0

9 780896 039049

Contemporary Cardiology™
Primary Angioplasty in Acute Myocardial Infarction
ISBN: 0-89603-904-8
humanapress.com