

Current Cardiovascular Therapy
Series Editor: Juan Carlos Kaski

Pablo Avanzas
Juan Carlos Kaski *Editors*

Pharmacological Treatment of Chronic Stable Angina Pectoris



Current Cardiovascular Therapy

Series editor

Juan Carlos Kaski
London, United Kingdom

For further volumes:
<http://www.springer.com/series/10472>

Cardiovascular pharmacotherapy is a fast-moving and complex discipline within cardiology in general. New studies, trials and indications are appearing on a regular basis. This series created with the support of the International Society of Cardiovascular Pharmacotherapy (ISCP) is designed to establish the baseline level of knowledge that a cardiovascular professional needs to know on a day-to-day basis. The information within is designed to allow readers to learn quickly and with certainty the mode of action, the possible adverse effects, and the management of patients prescribed these drugs. The emphasis is on current practice, but with an eye to the near-future direction of treatment. This series of titles will be presented as highly practical information, written in a quick-access, no-nonsense format. The emphasis will be on a just-the-facts clinical approach, heavy on tabular material, light on dense prose. The books in the series will provide both an in-depth view of the science and pharmacology behind these drugs and a practical guide to their usage, which is quite unique. Each volume is designed to be between 120 and 250 pages containing practical illustrations and designed to improve understanding and practical usage of cardiovascular drugs in specific clinical areas. The books will be priced to attract individuals and presented in a softback format. It will be expected to produce new editions quickly in response to the rapid speed of development of new CV pharmacologic agents.

Pablo Avanzas • Juan Carlos Kaski
Editors

Pharmacological Treatment of Chronic Stable Angina Pectoris



Springer

ISCP 
International Society of Cardiovascular Pharmacotherapy

Editors

Pablo Avanzas
Department of Cardiology
Hospital Universitario Central
de Asturias
Oviedo
Spain

Juan Carlos Kaski
Cardiovascular and Cell
Sciences Research Institute
St George's University
of London
London
UK

Current Cardiovascular Therapy

ISBN 978-3-319-17331-3

ISBN 978-3-319-17332-0 (eBook)

DOI 10.1007/978-3-319-17332-0

Library of Congress Control Number: 2015942523

Springer Cham Heidelberg New York Dordrecht London

© Springer International Publishing Switzerland 2015

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, express or implied, with respect to the material contained herein or for any errors or omissions that may have been made.

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer
Science+Business Media (www.springer.com)

Foreword

The pharmacological treatment of chronic stable angina is a major clinical challenge. Treatment of stable angina has two important goals: (1) to improve quality of life and (2) to improve “quantity” of life. The first aim is achieved by optimal symptom control and the second goal by implementation of optimal secondary prevention. Interestingly, despite the obvious importance of treating this condition, the information in this field is scattered and there is no convenient reference book that encompasses both aspects of the management of stable angina. Therefore, this excellent book is welcome and fills an important gap.

Pharmacological Treatment of Chronic Stable Angina Pectoris begins with a clear presentation of the pathophysiology of stable angina, highlighting its complexity, which goes beyond the presence of epicardial coronary artery stenoses. This is followed by an interesting overview and critical reappraisal of both European and North American Guidelines. The authors then describe the mechanisms of action and the clinical indications of traditional and of new antianginal drugs. An interesting chapter is dedicated to antianginal drugs still not available for clinical use, highlighting innovative therapeutic targets. The last chapter offers a balanced view of the ongoing harsh controversy on medical therapy versus revascularization in the management of stable angina pectoris. It shows how to interpret current evidence in order to offer each patient the most appropriate form of treatment.

This remarkable book edited by Pablo Avanzas and Juan Carlos Kaski is eminently readable, and guides the reader

through the complexities of the field. It will be highly appreciated by clinical cardiologists and will enhance the clinical care of patients affected by this important condition.

Rome, Italy

Filippo Crea, MD

Contents

1 Mechanisms of Angina Pectoris	1
Gaetano Antonio Lanza	
2 An Overview of Treatment and Guidelines: ESC/ACC-AHA/NICE	33
Jason M. Tarkin and Juan Carlos Kaski	
3 Beta-Blockers	57
Esteban López-de-Sá and José López-Sendón	
4 Calcium Channel Blockers	79
Peter Ong and Udo Sechtem	
5 Nitrates	87
Amelia Carro and Pablo Avanzas	
6 Nicorandil	115
Jason M. Tarkin and Juan Carlos Kaski	
7 Ivabradine	135
Alberto Dominguez-Rodriguez	
8 Trimetazidine	153
Alda Huqi, Giacinta Guarini, Doralisa Morrone, and Mario Marzilli	

9	Ranolazine	173
	Giuseppe M.C. Rosano, Cristiana Vitale, and Maurizio Volterrani	
10	New Antianginal Drugs Still Not Available for Clinical Use	189
	Juan Tamargo and Eva Delpón	
11	Medical Therapy Versus Revascularization in the Management of Stable Angina Pectoris ...	235
	Isaac Pascual, Pablo Avanzas, Raquel del Valle, and César Morís	
	Index	265

Contributors

Pablo Avanzas, MD, PhD, FESC Cardiac Catheterization Laboratories, Area del Corazón, Hospital Universitario Central de Asturias, Oviedo, Spain

Amelia Carro, MD, PhD Department of Cardiology, Hospital de Jove, Gijón, Spain

Eva Delpón Department of Pharmacology, School of Medicine, University Complutense, Madrid, Spain

Raquel del Valle, MD Cardiac Catheterization Laboratories, Area del Corazón, Hospital Universitario Central de Asturias, Oviedo, Spain

Alberto Dominguez-Rodriguez, MD, PhD, FESC Department of Cardiology, Hospital Universitario de Canarias, Tenerife, Spain

Giacinta Guarini Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, University of Pisa, Pisa (Pi), Italy

Alda Huqi Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, University of Pisa, Pisa (Pi), Italy

Juan Carlos Kaski, MD, DSc, FRCP, FESC, FACC, FAHA Cardiovascular and Cell Sciences Research Institute, St George's, University of London, London, UK

Gaetano Antonio Lanza, MD Department of Cardiovascular Sciences, Istituto di Cardiologia, Università Cattolica del Sacro Cuore, Rome, Italy

Esteban López-de-Sá Cardiology Department, Hospital Universitario La Paz, Madrid, Spain

José López-Sendón Cardiology Department, Hospital Universitario La Paz, Madrid, Spain

Mario Marzilli, MD Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, University of Pisa, Pisa (Pi), Italy

Doralisa Morrone Cardiovascular Medicine Division, Cardio-Thoracic and Vascular Department, University of Pisa, Pisa (Pi), Italy

César Morís, MD, PhD, FESC Cardiac Catheterization Laboratories, Area del Corazón, Hospital Universitario Central de Asturias, Oviedo, Spain

Peter Ong, MD Department of Cardiology, Robert-Bosch Krankenhaus, Stuttgart, Germany

Isaac Pascual, MD, PhD, FESC Cardiac Catheterization Laboratories, Area del Corazón, Hospital Universitario Central de Asturias, Oviedo, Spain

Giuseppe M.C. Rosano Cardiovascular and Cell Sciences Research Institute, St George's University of London, London, UK

Department of Cardiovascular Rehabilitation,
IRCCS San Raffaele, Rome, Italy

Udo Sechtem, MD Department of Cardiology, Robert-Bosch Krankenhaus, Stuttgart, Germany

Juan Tamargo Department of Pharmacology, School of Medicine, University Complutense, Madrid, Spain

Jason M. Tarkin, MBBS, MRCP Division of Cardiovascular Medicine, University of Cambridge, Cambridge, UK

London Deanery, London, UK

Cristiana Vitale Cardiovascular and Cell Sciences Research Institute, St George's University of London, London, UK

Department of Cardiovascular Rehabilitation, IRCCS San Raffaele, Rome, Italy

Maurizio Volterrani Cardiovascular and Cell Sciences Research Institute, St George's University of London, London, UK

Chapter 1

Mechanisms of Angina Pectoris

Gaetano Antonio Lanza

Introduction

Angina pectoris is the usual clinical manifestation of transient *myocardial ischemia*, which, in turn, is a condition of myocardial suffering occurring when coronary blood flow (CBF) is insufficient to meet oxygen requirements by myocardial cells necessary to carry out their contractile function.

Myocardial ischemia can result from two main general mechanisms: (1) failure of coronary circulation to adequately increase blood flow to myocardial cells to meet an increase in myocardial oxygen demand, usually due to the presence of obstructions in major coronary arteries, or even functional alterations in the coronary microcirculation (*secondary angina*), and (2) a reduction of CBF in rest conditions, usually caused by transient coronary vasoconstriction/spasm or thrombosis (*primary angina*). These different mechanisms, however, can variably combine to determine myocardial ischemia in different patients, as well as at different times in the same patient [1].

G.A. Lanza, MD

Department of Cardiovascular Sciences, Institute of Cardiology,
Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, Rome, Italy
e-mail: g.a.lanza@rm.unicatt.it

Angina and Silent Ischemia

While angina is the most frequent and typical manifestation of myocardial ischemia, it should be stressed that most ischemic episodes are not associated with angina or other symptoms, a conditions defined as *silent ischemia* [2]. It is indeed well-known that angina is often absent during myocardial ischemia induced by exercise stress test, and studies with electrocardiographic Holter monitoring have consistently shown that 70–80 % of myocardial ischemic episodes occurring during daily life are silent, independent of the mechanisms responsible for ischemia [3].

The reasons why myocardial ischemia causes angina in a minority of cases only has not fully been elucidated, but several mechanisms likely contribute to this phenomenon. A larger extent and severity of myocardial ischemia can be more frequently associated with angina, but the relation between the degree of myocardial ischemia and symptoms is poor; even in individual patients, indeed, angina may appear in presence of slight ischemia, whereas, at other times, severe signs of ischemia may occur without any symptom [4]. A peripheral and/or central modulation of cardiac pain signals is a likely major cause of the large variability of pain occurrence during myocardial ischemia, which can also be significantly influenced by psychological, emotional conditions (Fig. 1.1) [5].

Patients with predominant or exclusive silent myocardial ischemia, on the other hand, have some evidence of a defective processing of painful stimuli [6, 7]. Compared to patients with predominantly painful ischemia, they have been shown to have a higher threshold and tolerance for pain stimuli [6]. An increased release of endogenous opioids in the central nervous system has also been proposed as a possible mechanism, but assessment of plasma endorphins has given controversial results [8, 9].

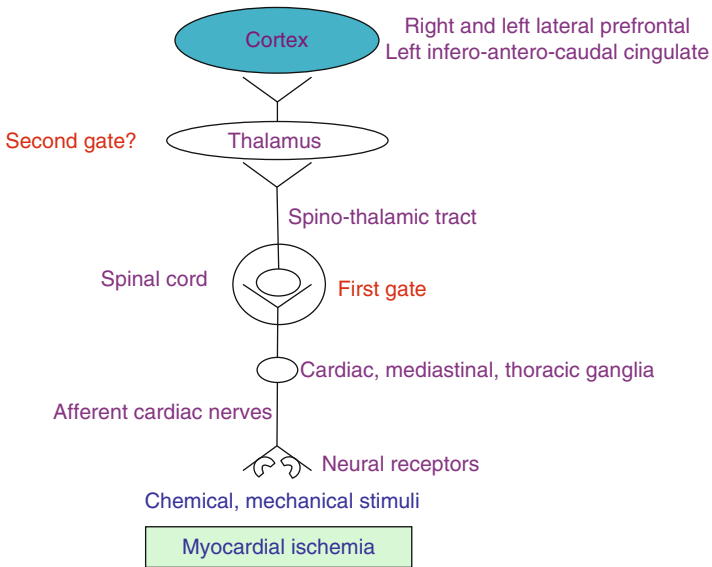


FIGURE 1.1 Scheme of cardiac pain pathway. Pain originated from the heart is transmitted to a second neuron in the dorsal horn of the spinal cord, which carries out the signal to a third neuron in the thalamus, from where the signal is transmitted to cortical pain centres. The pain signal is modulated at various levels by intermediate neurons (gates) (Modified from Ref. [2])

Obstructive Coronary Atherosclerosis

Pathophysiology of Coronary Stenosis

The presence of stenosis caused by atherosclerotic plaques in epicardial conductive coronary vessels is the most frequent substrate for myocardial ischemia and angina.

In normal individuals, any increase in myocardial oxygen demand can only be met by a proportional increase of

CBF. This is possible because coronary resistance in resting conditions is quite elevated, due to a high basal tone of small coronary arteries; the increase in myocardial oxygen demand induces dilatation of these vessels, thus reducing coronary resistance and increasing blood flow (*metabolic CBF regulation*). Of note, in normal conditions large epicardial conductive vessels do not offer an appreciable resistance (and therefore obstacle) to flow, which can increase up to five folds during elevated myocardial oxygen demand, as during maximal exercise.

When present, a significant coronary stenosis, instead, offers a resistance to blood flow able to cause a decrease of the driving pressure distal to the stenosis. As perfusion pressure is a major determinant of blood flow, the pressure drop distal to a stenosis tends to reduce blood flow in the supplied myocardial territory. In basal conditions this does not have any significant effect on myocardial perfusion because the pressure drop is compensated by a parallel reduction of distal coronary resistance, determined by dilatation of arteriolar vessels.¹ This compensatory vasodilatation, however, also results in a reduction of *coronary flow reserve* (CFR) i.e., the magnitude of maximal increase of CBF, as compared to basal. The level of cardiac work at which it is not possible to further proportionally increase CBF to fully meet the increased metabolic requirements, thus resulting in myocardial ischemia (and angina), is defined *ischemic* (and *angina*) *threshold*.

Experimental studies [10] have shown that coronary stenosis usually starts to limit flow only when its lumen diameter is reduced at least by 50 %, while lower degrees of stenosis do not usually offer significant obstacle to blood flow at rest. Beyond this critical reduction of vessel lumen, however, any further increase of the stenosis causes a considerable reduction of the distal driving perfusion pressure, which, according to

¹ Blood flow (F) can be calculated as $F = P/R$, where P is the driving pressure and R is resistance.

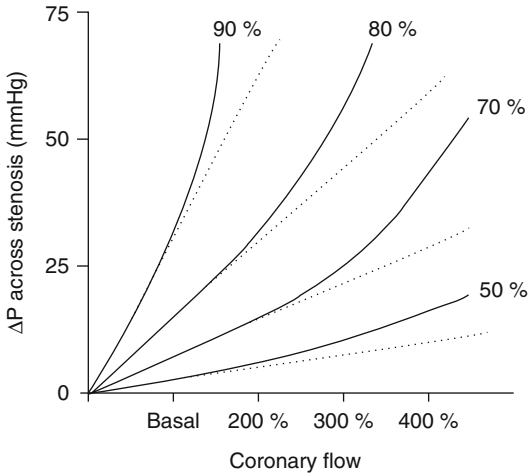


FIGURE 1.2 Relation between coronary blood flow and pressure gradient across a coronary stenosis. Post-stenotic pressure decreases progressively with the increase of stenosis severity and, for a given stenosis, it decreases markedly with increasing flow. The relation becomes curvilinear because of energy losses caused by blood flow turbulence across the stenosis (*solid lines*) (Modified from Ref. [10])

Poiseuille law,² is inversely proportional to the fourth power of the minimum radius of the vessel lumen. Thus, increasing reductions in vessel diameter cause an exponential increase of trans-stenotic pressure gradient and a progressive reduction of maximal CBF, and therefore of CFR (Fig. 1.2). Of note, a reduction of 85–90 % of coronary artery diameter was required to cause myocardial ischemia at rest in dog. The relationship between the severity of coronary stenosis at angiography and the impairment of CFR has been confirmed in patients [11].

² According to Poiseuille law, blood flow (Q) can be calculated as:

$$Q = \frac{\pi r^4 (p_1 - p_2)}{8 \eta l}$$

where, r=vessel radius; p_1 =pressure in the proximal segment of the vessel; p_2 =pressure in the proximal segment of the vessel;; η =blood viscosity; l=segment length.

Myocardial ischemia consequent to an increase of myocardial oxygen demand, related to the presence of a coronary stenosis, typically involves subendocardial layers. The latter, indeed, present a lower flow reserve, and are therefore more vulnerable to ischemia compared to subepicardial layers. Subendocardial cells are indeed subject to the effect of diastolic intraventricular pressure, which increases their stretching and, therefore, according to Starling law, their systolic stress and contractility; as a result, oxygen consumption of subendocardial cells is slightly higher at rest, compared to that of subepicardial cells. Accordingly, blood flow in subendocardial layers is, in basal conditions, 15–20 % higher than that in subepicardial layers, which results in a lower flow reserve.

Moreover, subendocardial layers have greater susceptibility to ischemia also because subendocardial flow during diastole can be directly contrasted by the effects of intraventricular pressure and extravascular forces (Fig. 1.3) [10, 12], which exert scarce effect on subepicardial strata. Again, in normal heart, this disadvantageous condition does not have relevant effect on subendocardial flow, even in conditions of maximal oxygen demand, as during strenuous exercise. In presence of a flow-limiting coronary stenosis, instead, shortening of diastole (due to tachycardia) and a further increase of extravascular force (due to an increase of end diastolic left ventricular pressure that can result from ischemia), combined with the reduced driving pressure distal to the stenosis, can become crucial in favouring subendocardial ischemia during increased myocardial work and oxygen requirements.

In clinical practice the hemodynamic relevance of a coronary stenosis is assessed by coronary angiography, either visually or using quantitative measurements. However, the assessment of a coronary stenosis on the base of its angiographic severity only has several limitations: (1) coronary angiography is often inadequate to evaluate the tri-dimensional structure of a stenosis; (2) other factors may have relevance in determining the clinical effects of a stenosis, including the diameter of the original vessel, the length and the concentric or eccentric profile of the stenosis, as well as the presence of

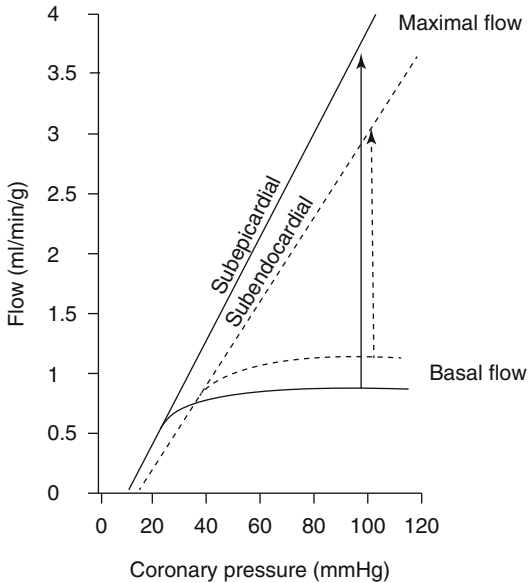


FIGURE 1.3 Basal flow, maximal flow and coronary flow reserve (CFR, arrows) in subendocardial (dotted lines) and subepicardial (continuous lines) layers of the left ventricle in relation to the driving pressure. CFR is lower in subendocardial layers, where resting blood flow is higher due to a higher basal oxygen consumption and maximal blood flow is lower due to extravascular resistance (Modified from Ref. [12])

other stenoses in series; (3) the hemodynamic effects of the stenosis are scarcely correlated with its angiographic severity; the driving post-stenotic pressure, indeed, also depends on other factors, including basal arterial pressure, collateral vessel development, dynamic modulation of the stenosis and of distal microcirculation, and extravascular resistance.

A method now considered more reliable to assess the hemodynamic significance of a coronary stenosis is the measure of *fractional flow reserve* (FFR) [13]. FFR is calculated as the ratio between the mean pressures distal and proximal to the stenosis during maximal vasodilatation, usually induced

by intracoronary administration of adenosine. An FFR <0.80 is believed to identify a flow-limiting stenosis, able to cause myocardial ischemia during increased myocardial oxygen consumption. However, the results of this method can also be influenced by several factors, including collateral circulation, basal microvascular state, as well as preload and afterload at the time of assessment, and clinical trials failed to demonstrate a significant usefulness of FFR measurement for improving major clinical events by coronary revascularization [14]. Accordingly, at present, the consequences of a stenosis in the clinical setting seem to be more adequately evaluated by assessing the presence, degree and extension of myocardial ischemia in the correspondent myocardial territory by appropriate imaging stress tests.

Finally, the hemodynamic significance of a stenosis can also be assessed by obtaining a measure of CFR, expressed as the ratio between CBF velocity during maximal coronary vasodilatation induced by a vasodilator drug (usually adenosine) and CBF velocity at baseline, as assessed by intracoronary Doppler recording. CFR >2.5 as measured by this method is usually believed to be normal [15]. Measurements of CBF velocity, however, are also subject to variations and significantly depend on the state of coronary microcirculation and basal CBF as well.

Factors Influencing Epicardial Stenosis

Dynamic Changes

In only a minor number of cases coronary stenoses are *fixed*, i.e., do not show any variation at their site of vessel lumen able to significantly influence blood flow. These stenoses are usually associated with a quite stable and predictable pattern of myocardial ischemia and angina. Nevertheless, coronary stenoses often present at their site vasomotor changes that are able to significantly modify their severity, and therefore CFR and angina threshold, thus resulting in a variable and much less predictable angina pattern. The tendency to

dynamic changes of a stenosis can be assessed by evaluating the vasomotor response to intracoronary administrations of vasodilator or vasoconstrictive substances [16].

Collateral Circulation

When a stenosis, or even a chronic coronary occlusion, causes a reduction of blood flow, myocardial perfusion can still be guaranteed by the development of coronary collateral vessels, which connect a normal vascular territory to that supplied by the obstructed vessel. Collateral blood flow, indeed, increases post-stenotic pressure in the supplied territory, and therefore improves CBF and CFR.

Collateral vessels mainly develop from pre-existing inter-coronary arterial anastomoses, which are stimulated to grow by the pressure gradient that develops between their origin from the normally supplied vessels and their termination at the site of vessels supplied by the stenotic vessel [17]. These preexisting anastomoses progressively transform into mature small vessels, with a final diameter of 20–200 μm , through a complex process that involves their initial widening and remodelling, subsequent proliferation of endothelial cells and smooth muscle cells, with development of a smooth muscle coat. Collateral vessels may also develop as new vessels, but this mechanism does not seem to contribute significantly to collateral circulation in man. Collateral circulation can be assessed by coronary angiography and shows significant variations among patients, the reasons for which remain poorly known (Fig. 1.4) [18].

As specified above, collateral blood circulation may contribute significantly to the variability of ischemic and angina threshold in individual patients; blood flow in collateral vessels may indeed undergo significant variations in different conditions, due to influences by neural, humoral and autacoid stimuli. Furthermore, collateral circulation may have protective effects in several conditions; it can be associated with scarce or no ischemia during coronary occlusion caused by thrombosis or spasm, a minor extension of myocardial infarct

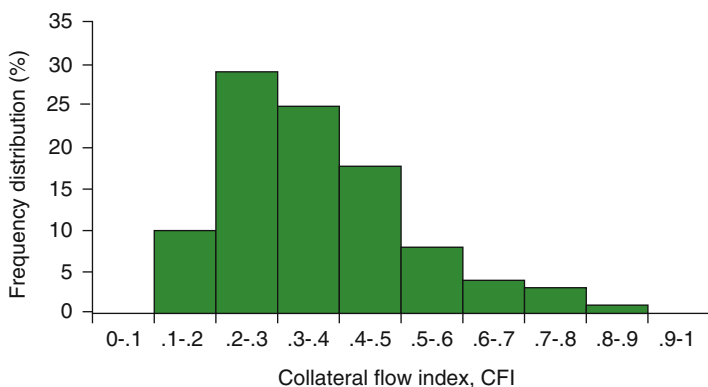


FIGURE 1.4 Distribution of collateral flow index in patients with total occlusion of a coronary artery vessel; a large variability of collateral blood flow is observed (Modified from Ref. [18])

following persistent thrombotic occlusion, and a better functional recovery after coronary by-pass surgery in patients with left ventricular dysfunction [19].

Coronary Steal

Coronary steal is a particular mechanism of myocardial ischemia and angina occurring when blood flow to a myocardial region supplied by a severely stenotic vessel becomes insufficient because of a diversion of a significant quote of blood flow towards another myocardial region, following maximal arteriolar dilation occurring in the latter. Coronary steal typically occurs in subendocardial layers as a result of microvascular dilatation in the subepicardial circulation supplied by the same stenotic vessel. The reduction of coronary resistance in the subepicardium, indeed, favours blood flow towards these areas, which, together with the consequent reduction of the driving perfusion pressure, will compromise blood flow to the subendocardium, which, as discussed above, present a reduced vasodilator reserve (*transmural or vertical steal*) (Fig. 1.5) [20].

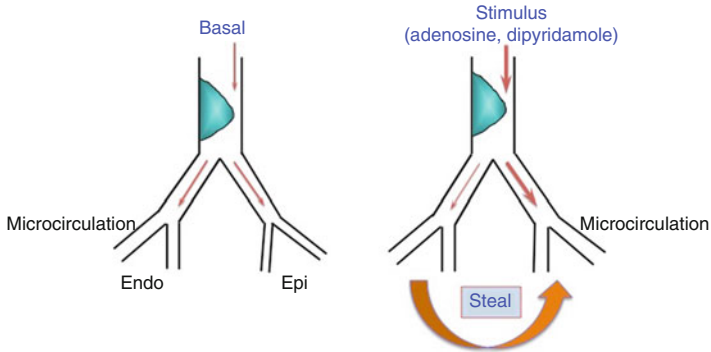


FIGURE 1.5 Myocardial ischemia caused by transmurular coronary flow steal. In presence of a stenosis, subendocardial flow (*Endo*) at baseline is guaranteed by a higher degree of microvascular dilatation, as compared to subepicardial layers (*Epi*). During vasodilator stimuli, subepicardial vessels are maximally dilated causing a steal of blood from subendocardial vessels

Coronary steal can also occur in myocardial areas which depend on collateral circulation to maintain a valid blood flow; maximal dilatation in the territory of the supplying normal (or even mildly stenotic) coronary vessel will indeed result in a parallel reduction of blood flow in the collateral vessels, thus causing myocardial ischemia in the supplied territory (*intercoronary or lateral steal*) [21].

Typically, coronary steal can be induced by arteriolar dilatory drugs (e.g., adenosine, dipyridamole), an effect utilized in pharmacological stress tests for diagnosis of coronary artery disease [22]. Some other drugs, as xanthines, on the other side, can contrast the induction of coronary steal. Xanthines prevent arteriolar dilatation in the territory responsible for the steal by antagonizing the effects of adenosine (the main mediator of arteriolar dilatation during myocardial ischemia) and by inducing α -mediated vasoconstriction through inhibition of norepinephrine re-uptake by sympathetic nerve endings [23].

Coronary Artery Spasm and Vasoconstriction

The term *coronary artery spasm* (CAS) specifically indicates a sudden, intense, occlusive or subocclusive constriction of an epicardial coronary artery, which determines a dramatic primary reduction of CBF, usually resulting in transmural myocardial ischemia. CAS should be taken distinct from abnormally increased vasoconstriction, which can be defined as an enhanced, but not occlusive/subocclusive, response, as compared to a normal response, to low-medium doses of constrictor stimuli.

Recurrent CAS typically results in the clinical syndrome of Prinzmetal's variant angina [24], which is characterized by angina attacks occurring at rest and associated with ST segment elevation on the electrocardiogram (ECG) (Fig. 1.6). The vasospastic mechanism of variant angina was clearly demonstrated by coronary angiographic studies performed during spontaneous angina attacks [25]. CAS, however, can also be a major or contributing mechanism, in some cases, of a clinical presentation of acute coronary syndrome. Enhanced vasoconstriction, on the other side, may contribute to cause subendocardial ischemia at rest or favour exercise-induced angina when severe or occurring at the site of sub-critical stenoses.

CAS can occur at the site of a stenosis (either minor or severe) or in angiographically normal coronary arteries. Furthermore, CAS can be localized to a segment of an epicardial artery (*focal spasm*) (Fig. 1.7), involve two or more segments of the same artery (*multifocal spasm*) or different epicardial arteries (*multivessel spasm*), or may also involve diffusely one or multiple coronary branches (*diffuse spasm*) [26].

CAS usually lasts a few minutes, but in some cases it can be prolonged and cause myocardial injury. Furthermore, CAS can cause local mechanical damage of the endothelium and vessel wall, thus favouring coronary thrombosis and acute myocardial infarction [26]. Importantly, transmural ischemia caused by CAS can be complicated by malignant ventricular arrhythmias [27].

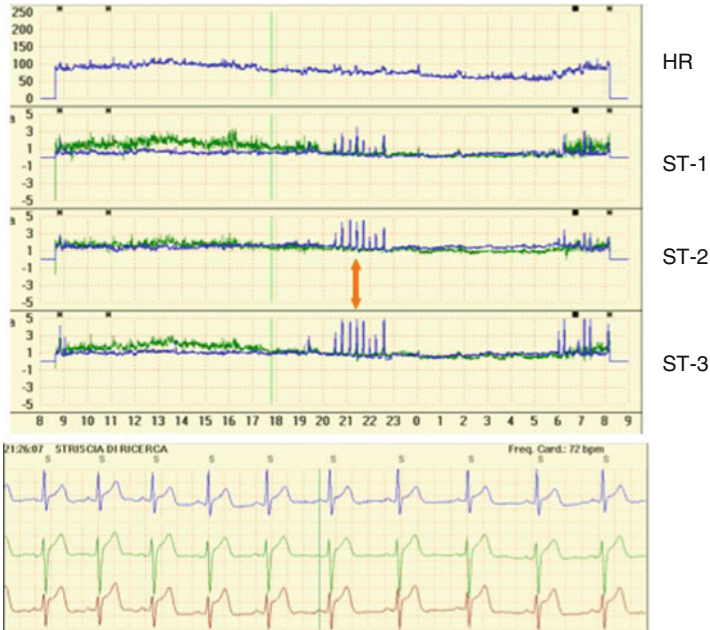


FIGURE 1.6 Twenty-four-hour Holter ECG recording in a patient with variant angina. *Top panel:* The four graphs represent the 24-h trends of heart rate (HR) and ST-segment (ST) level (*blue lines*) and slope (*green lines*) of 3 ECG leads (CM5-CM3-modified aVF), respectively. Several short episodes of ST-segment elevation can be seen between 20:00 and 23:00 and between 6:00 and the end of the recording. *Bottom panel:* ECG strip taken at the time indicated by the arrow, with the patient reporting chest pain in the diary; typical ST-segment elevation can be observed in all three ECG leads

Although its causes and mechanisms are still poorly known, CAS results, anyway, from the interaction of two components (Fig. 1.8): (1) an abnormality of a coronary artery which makes it hyper-reactive to vasoconstrictor stimuli, and (2) a vasoconstrictor stimulus able to trigger the spasm of the hyper-reactive coronary segment [28].

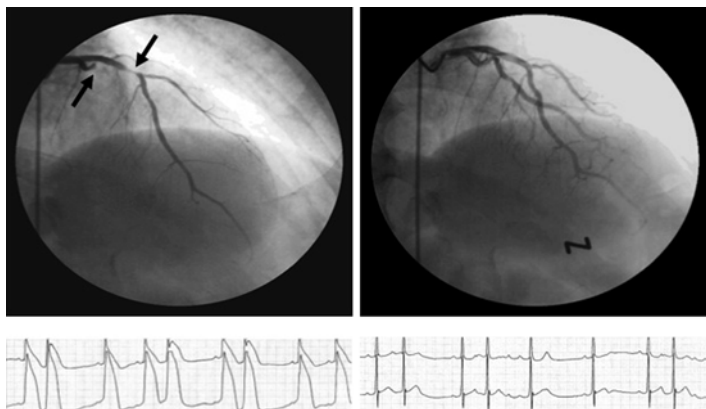


FIGURE 1.7 Occlusive spasm of the left circumflex coronary artery and subocclusive spasm of the left anterior descending coronary artery (*arrows*) during coronary angiography (*left, top*), associated with dramatic ST segment elevation at monitoring ECG leads (*left, bottom*). Complete resolution of spasm (*right, top*) and ST segment elevation (*right, bottom*) after intravenous nitrate administration (Modified from Ref. [28])

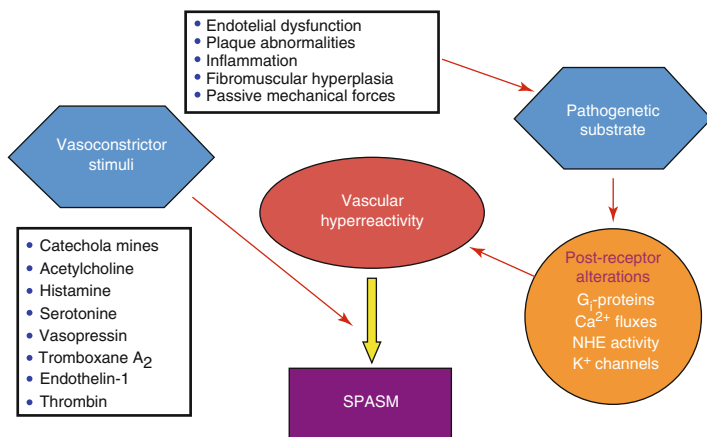


FIGURE 1.8 Pathophysiologic mechanisms of coronary artery spasm. See text for details (Modified from Ref. [28])

Several factors suggest that CAS substrate requires a hyper-reactivity of vascular smooth muscle cells (SMCs): (1) vasoconstrictor stimuli that induce CAS in the involved coronary segments are unable to induce spasm in other coronary segments of the same patients as well as in patients with other forms of angina [29, 30]; (2) CAS can usually be elicited by various stimuli that act through different receptors and cellular pathways [31], which also suggests a post-receptorial, intracellular alteration of SMC hyper-reactivity; (3) coronary SMC hyper-reactivity to constrictor stimuli, resulting in spasm, can be induced in experimental models [32].

Experimental and clinical data suggest that an increased activity of Rho-kinase, an intracellular enzyme which increases myosin light chains sensitization to intracellular Ca^{++} , can be involved in the SMC hyperreactivity responsible for CAS [33, 34]. Rho-kinase was indeed found increased in patients with vasospastic angina [34] and its inhibitor fasudil prevented acetylcholine-induced CAS in these patients [35]. Other cellular pathways, however, have been suggested to be potentially involved in CAS, including protein kinase C activation, lack of SUR-2, a component of the ATP-dependent K^+ channel, and increased membrane $\text{Na}^+\text{-H}^+$ exchanger [28].

Some studies have suggested that a significant endothelial dysfunction might also contribute to CAS, as the consequent impairment of vasodilation favours the response to vasoconstrictor stimuli [36]. Of note, several drugs able to cause spasm through direct stimulation of vascular smooth muscle cells (i.e., acetylcholine, serotonin, histamine) in normal vessels cause endothelium-mediated vasodilation. Thus, in presence of endothelial dysfunction, their release in the vessel wall can lead to vasoconstriction or CAS. Furthermore, endothelial activation might also facilitate CAS due to endothelial release of vasoconstrictor substances, mainly endothelin-1 [37].

Other mechanisms have been proposed for susceptibility to CAS of coronary arteries, including passive mechanical collapse in presence of an eccentric stenosis, medial fibromuscular hyperplasia, adventitial release of vasoconstrictor substances from neural termination or inflammatory cells [38] and

magnesium deficiency, but their role is likely limited to specific cases; in some patients an excessive consumption of alcohol or use of some drugs (e.g., cocaine, amphetamines, marijuana, 5-fluorouracil, capecitabine, sumatriptan, etc....) can result in susceptibility to CAS [28]. Among traditional cardiovascular risk factors, instead, only smoking has been found to show a significant association with CAS occurrence [39].

Finally, other factors shown to be potentially able to cause spasmogenic vascular changes include acute inflammation [38, 40], increased oxidative stress [41] and genetic factors, which have mainly concerned genes encoding for NO synthase [42] or adrenergic receptors [43].

As previously observed, a large number of stimuli can usually trigger spasm when acting at the site of a hyper-reactive coronary artery, although they are in most cases not promptly identifiable. They include a raise of either sympathetic or parasympathetic tone. In clinical practice sympathetic outflow seems responsible for CAS when the latter is induced by exercise or cold pressor test [44, 45], as well as substances (e.g., cocaine, amphetamines) known to increase sympathetic drive and/or sensitization to catecholamines of vascular smooth muscle cells [46].

Acetylcholine, the neurotransmitter of parasympathetic fibres, on the other side, is known to induce CAS in patients with vasospastic angina through stimulation of muscarinic receptors on smooth muscle cells [47]. In patients with vasospastic angina, attacks often occur during the night, suggesting a role for vagal activity [26]; ischemic episodes occurring at night, however, might be related to a transient surge of sympathetic, rather than parasympathetic, activation [48].

Vasoconstrictor substances, able to trigger spasm, can be released by activated platelets, endothelium or inflammatory cells. Finally, hyperventilation, by inducing alkalosis, is a well-known stimulus for CAS and can be a possible under-recognized trigger of spasm in at least some patients with vasospastic angina [49].

Coronary Microvascular Dysfunction

Experimental studies clearly showed that myocardial ischemia can be induced by abnormalities in the coronary microcirculation. The intracoronary infusion of the vasoconstrictor endothelin-1 or fLMP in dog and rabbit, respectively, was indeed able to induce myocardial ischemia in the absence of any changes in large coronary vessels, thus suggesting constriction of small coronary arteries [50, 51].

In the past few decades a large number of studies has provided evidence that abnormalities of resistance coronary arteries (i.e., arterioles and/or prearterioles) can also be responsible for myocardial ischemia and angina symptoms in patients.

Angina caused by coronary microvascular alterations is defined as *microvascular angina* (MVA) [52]. In contrast with angina caused by obstructive coronary macrovascular disease or CAS, MVA cannot be directly diagnosed by coronary angiography; resistance coronary vessels, indeed, cannot be imaged by angiography, as their dimensions are below radiologic resolution (about 500 μm). Thus, in clinical practice, the diagnosis of MVA, in patients with typical angina symptoms and evidence of myocardial ischemia (usually, ST-segment changes at the ECG and/or scintigraphic perfusion defects), is based on the absence of obstructive coronary plaques and dynamic changes (i.e., vasoconstriction or spasm) of epicardial arteries [53].

In most cases MVA occurs as a unique cardiac issue, i.e., in the absence of any other apparent cardiac or systemic disease, thus suggesting a selective abnormality of small coronary artery vessels, a condition defined *primary MVA*. In several cases, instead, MVA occurs in the setting of specific cardiac or systemic diseases, and might therefore result from specific mechanisms/alterations of coronary microcirculation related to the underlying disease, a condition defined *secondary MVA* [53]. A classification of coronary microvascular dysfunction (CMVD), based on the clinical ground in which it occurs, is shown in Table 1.1 [54].

TABLE 1.1 Classification of coronary microvascular dysfunction according to the clinical setting in which it occurs

1. Coronary microvascular dysfunction in the absence of obstructive CAD and myocardial diseases
2. Coronary microvascular dysfunction in the presence of myocardial diseases
3. Coronary microvascular dysfunction in the presence of obstructive CAD
4. Coronary microvascular dysfunction caused by coronary recanalization (iatrogenic)

From Ref. [54]

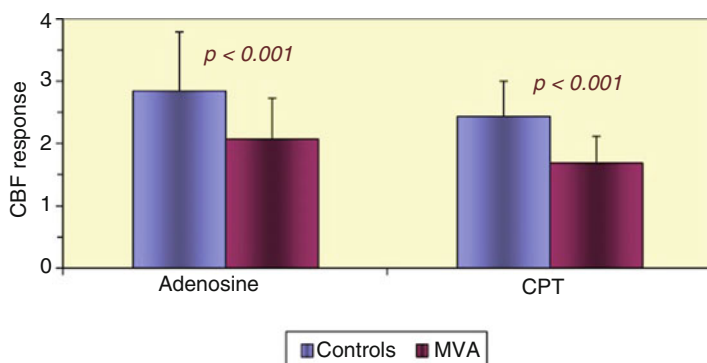


FIGURE 1.9 Reduced coronary blood flow response to an endothelium-independent (adenosine) and an endothelium-dependent (CPT) stimulus, as assessed by transthoracic Doppler echocardiography of the left anterior descending coronary artery, in 71 patients with MVA, as compared with 20 healthy controls (Modified from Ref. [56])

Furthermore, MVA (either primary or secondary) most frequently occurs as a stable angina pattern, mainly related to efforts (*stable MVA*). In several cases, however, it can present as an acute typical chest pain, usually at rest, which suggests a non ST-segment elevation acute coronary syndrome (*unstable MVA*) [53] (Fig. 1.9).

While, as seen above, MVA in clinical practice is usually diagnosed after excluding other possible (cardiac and non cardiac)

causes of chest pain, it would be more desirable to achieve a documented diagnosis by obtaining objective evidence of CMVD. An impairment of coronary microvascular dilatation, which can predispose to MVA related to increased oxygen requests (e.g., exercise-induced, stable MVA) can be identified by assessing CBF response to vasodilator stimuli. This can be performed invasively, during coronary angiography, mainly using intracoronary Doppler recording. This method, however, can be complex and time-consuming, and may present unjustified adjunctive risks [55].

Coronary microvascular dilator function, however, can now be assessed by some valuable noninvasive methods, as cardiac magnetic resonance and positron emission tomography. Although reliable, however, these methods may not be widely available and are quite expensive. The use of *transthoracic echocardiographic Doppler recording* (TTE-DR) of CBF has been proposed as the first-line method for CMVD detection due to its large availability and low cost; it requires, however, particular expertise and in most cases allows valuable assessment of CBF in the LAD artery only. *Contrast stress echocardiography* might obviate to these pitfalls, but experience in this field has hitherto been limited [55].

A full assessment of coronary microvascular dilator function should concern both endothelium-dependent and endothelium-independent vasodilator mechanisms. Endothelium-independent vasodilation is usually assessed by administration of direct vasodilator agents (mainly adenosine or dipyridamole); CMVD is diagnosed when the ratio between diastolic CBF velocity at peak vasodilation and CBF velocity at rest is <2.0 , with a ratio between 2.0 and 2.5 being considered as a borderline response [56].

Stimuli used to assess endothelium-mediated coronary microvascular dilatation mainly include intracoronary administration of acetylcholine [57], and, also in non invasive studies, cold pressor test (CPT) [56]. Caution, nevertheless, should be applied in interpreting CBF impairment in response to these stimuli as certainly related to impaired endothelium-dependent dilation, as they are not exclusively endothelium-mediated dilators, but may also have direct constrictor effects on microcirculation, in particular in dysfunctional vessels [58].

Finally, abnormal coronary microvascular constrictor response should also be investigated in the suspect of MVA, in particular, in patients with rest chest pain, which has to necessarily be done during coronary angiography. Increasing doses of acetylcholine [57] are usually administered to this scope, but ergonovine, mental stress and hyperventilation might also be applied [52, 59]. Obviously, CMVD responsible for MVA can result from a variable combination of the abnormalities described above. Documentation of myocardial ischemia in patients with angina and no evidence of epicardial abnormalities would also provide evidence for the diagnosis of MVA. As stated above, myocardial ischemia in these patients is usually suggested by stress-induced ST-segment changes and/or perfusion defects. On the other hand, some more specific markers of ischemia, as stress-induced left ventricular contractile alterations and myocardial release of ischemic metabolites, can be more difficult to demonstrate when ischemia is caused by CMVD as compared to that caused by obstructive epicardial stenosis [60, 61]. In the latter case, indeed, myocardial perfusion during increase of myocardial work is homogeneously impaired in the myocardial layers perfused by the stenosed artery (Fig. 1.10, *upper panel*), thus resulting in detectable impairment of contractile function and increased lactate production. In MVA patients, instead, CMVD can patchily involve microvessels [62] (Fig. 1.10, *bottom panel*) thus creating small ischemic areas only, which makes difficult the detection of both LV dysfunction and lactate release, in spite of ECG abnormalities and myocardial perfusion defects. Detection of common signs of myocardial ischemia would be possible only when severe CMVD is uniformly present in sufficiently large myocardial regions.

In the past 30 years CMVD has particularly been assessed in patients with primary stable MVA (usually previously classified as cardiac syndrome X), who mainly have angina episodes related to efforts [53]. In these patients CMVD has been shown to be heterogeneous, variably resulting from impaired coronary microvascular dilation (endothelium-dependent

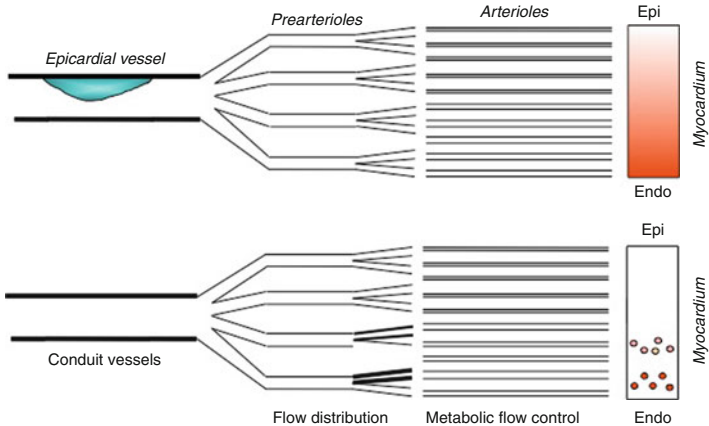


FIGURE 1.10 Differences in myocardial ischemia caused by a coronary artery stenosis (*upper panel*) or by coronary microvascular abnormalities (*bottom panel*). In case of an epicardial stenosis, ischaemia during increased myocardial oxygen demand diffusely involves the myocardial (usually subendocardial) territory supplied by the vessel (*red area*), which results in impairment of regional contractile function. In case of microvascular abnormalities ischaemia is likely localized only in small myocardial areas, patchily diffused in the myocardial wall (*small circles*); this does not usually result in detectable impairment of contractile function due to the presence of normal contractile myocardial cells in the same territory (Modified from Ref. [53])

and/or endothelium-independent), but also enhanced coronary microvascular constriction [53]. In particular, abnormal microvascular constrictor response to adrenergic stimulation (as during exercise) [63] and increased release of endothelin-1 from dysfunctional activated endothelium [64] have been suggested. It is worth noting that structural abnormalities of small coronary arteries have also been described in some patients (e.g., smooth muscle hypertrophy, intimal thickening) as involved in determining CMVD [65].

The causes of CMVD in stable MVA seem also heterogeneous and different in individual patients. Common

cardiovascular risk factors (e.g., hypertension, hyperlipidemia, diabetes, smoking) likely contribute to CMVD in at least a proportion of patients [56, 66]. Other abnormalities described in these patients that can variably contribute to CMVD include increased cardiac adrenergic activity [67] increased insulin resistance [68], estrogen deficiency in women [69] and subclinical inflammation [70].

In recent years there has been growing evidence that CMVD can also be responsible for a clinical picture of *acute/unstable MVA* [53]. Again, a coronary microvascular origin of symptoms can be suspected among patients presenting with a typical clinical picture of acute coronary syndrome (mainly rest angina chest pain) when coronary angiography unexpectedly shows normal or near-normal coronary arteries.

The possibility of a coronary microvascular origin of symptoms can be taken into account, in particular, in patients presenting with a non ST elevation acute coronary syndrome (NSTEMI-ACS), 5–12 % of whom are found to have non significant coronary atherosclerosis [71]. The mechanism of chest pain in these patients, however, are certainly heterogeneous, and may include transient thrombosis, epicardial spasm and myocarditis [71]. Thus, again, diagnosis of unstable MVA would require documentation of CMVD in the absence of other causes of chest pain.

In this case, the usual mechanism that can be responsible for MVA is coronary microvascular constriction. The detection of SCF at angiography can be a clue to microvascular constriction in some patients [72] (Fig. 1.11), while an abnormal CBF response to constrictor stimuli (as cold pressor and acetylcholine), in absence of epicardial vessel changes, can also be documented during coronary angiography with Doppler recording, as described above [73].

In some patients diffuse intense constriction or spasm of small coronary arteries may result in MVA caused by severe transmural myocardial ischemia, as indicated by ST-segment elevation [74]. Furthermore, takotsubo disease (stress related cardiomyopathy or apical ballooning syndrome) might also

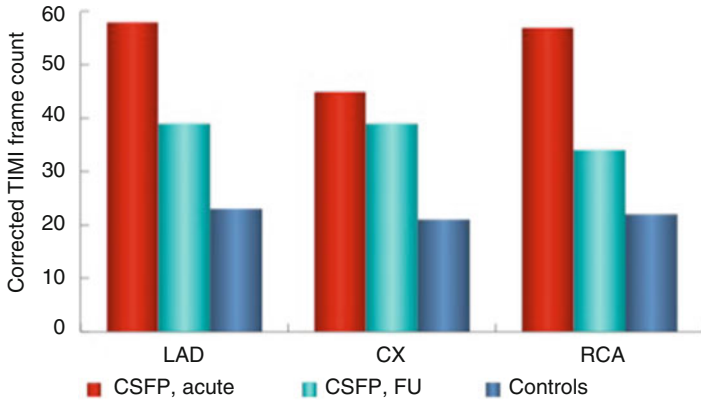


FIGURE 1.11 Corrected TIMI frame count (cTFC) in the 3 major coronary vessels in patients presenting with unstable angina but showing angiographically normal coronary arteries, as assessed in the acute phase (*red bars*), and at follow-up (*cyan bars*); data in controls are also shown. Prolonged cTFC was present on admission, indicating coronary slow flow, compatible with microvascular constriction; cTFC improved at follow-up, but remained higher than in controls. *CSFP* coronary slow flow patients, *CX* left circumflex coronary artery, *FU* follow-up, *LAD* left anterior descending coronary artery, *RCA* right coronary artery (Modified from Ref. [73])

be caused by severe coronary microvascular constriction. In these patients the usual strict relation with acute intense emotional or physical stresses suggests a heightened adrenergic stimulation [75], which can trigger intense coronary microvascular constriction/spasm. Reduced CBF response to adenosine in the acute phase of the disease has been found, which improves in parallel with clinical improvement [76]. Interestingly, tako-tsubo disease is largely prevalent in post-menopausal women and has a good prognosis, findings that are both in agreement with the epidemiology of the other clinical presentations of CMVD [53].

Thrombosis

Acute coronary thrombosis constitutes the main pathophysiologic mechanism of myocardial ischemia responsible for the clinical picture of acute coronary syndromes. Coronary thrombi usually occur at the site of complicated atherosclerotic plaque, which can variably present rupture, ulceration, erosion, and intra-plaque haemorrhage. Blood contact with the damaged vessel results in the activation of pro-aggregant and pro-coagulant processes, which eventually lead to intra-coronary clot formation [77].

Of note, acute thrombosis, resulting in ACS, may occur at the level of flow-limiting stenosis, but also at the level of non significant, or even minimal, stenosis, as a result of abnormal endothelial function and vessel wall damage [78]. Furthermore, it is worth noting that in about 30 % of cases coronary thrombi form at the site of apparently uncomplicated plaques, and occasionally also in vessels without any apparent stenosis or wall injury [77, 79]. In these cases, thrombus formation is probably favoured by microscopic lesions and/or functional alterations of the endothelium, induced by a series of stimuli (mechanical, anoxic, chemical, immunologic, infectious), which can considerably impair the anti-thrombotic and vasodilator functions of the endothelium, which can become a structure able to produce powerful vasoconstrictor and pro-thrombotic substances as well as receptors able to activate platelets and inflammatory cells [80]. In recent years, in particular, evidence has been accumulated that inflammatory reactions are a relevant component in the pathogenesis of acute coronary syndromes, favouring plaque complications and causing local stimulation of both thrombosis and vasoconstriction [77, 80]. Of note, as observed above, thrombosis can also locally complicate a coronary spasm [81], facilitating prolonged vessel occlusion and myocardial infarction.

Independently of the mechanisms, the clinical picture resulting from thrombus formation depends on its volume and evolution. A sub-occlusive thrombus will mainly reduce CBF in subendocardial layers, and therefore cause

subendocardial ischemia and angina at rest or, if the reduction of the lumen vessel is not critical, for low-level efforts; an occlusive thrombus, on the other hand, will totally impede CBF and therefore result in transmural myocardial ischemia. Persistence of thrombus (and subocclusion/occlusion) will result in myocardial necrosis (non ST-segment elevation and ST-segment elevation, respectively).

A spontaneous resolution of the thrombus in a few minutes (up to about 20 min), instead, will allow rapid CBF restoration and therefore transient myocardial ischemia only, resulting in the clinical picture of unstable angina.

It is worth noting that a spontaneously lysed thrombus may resolve only partially and remain adhered to the vessel wall; this part will organize and increase the degree of the previous coronary plaque, thus increasing stenosis and reducing ischemic and angina threshold. A lysed thrombus might also result in peripheral coronary microembolism of thrombus debris, with induction of small, possibly microscopic, areas of ischemia or necrosis, according to the destiny of the embolic material. The final destiny of thrombus is the result of a complex interaction between pro-thrombotic and anti-thrombotic factors, which also involves haemodynamic, vaso-motor and coagulative/fibrinolytic factors.

References

1. Maseri A. Ischemic heart disease. New York: Churchill Livingstone; 1995.
2. Cohn P, Fox KM. Silent myocardial ischemia. *Circulation*. 2003;108:1263–77.
3. Schang SJ, Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. *Am J Cardiol*. 1977;39:396–402.
4. Hirzel HO, Leutsyler R, Krayenbuehl HP. Silent myocardial ischemia: hemodynamic changes during dynamic exercise in patients with proved coronary artery disease despite absence of angina pectoris. *J Am Coll Cardiol*. 1985;6:275–84.
5. Crea F, Camici PG, De Caterina R, Lanza GA. Chronic ischaemic heart disease. In: Serruys P, Camm J, Lüscher TJ, editors.

- The ESC textbook of cardiovascular medicine. Oxford: Blackwell Pub./European Society of Cardiology; 2009. p. 597–664.
6. Droste C, Roskamm H. Experimental pain measurement in patients with asymptomatic myocardial ischemia. *J Am Coll Cardiol.* 1983;1:940–5.
 7. Rosen SD, Paulesu E, Nihoyannopoulos P, et al. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. *Ann Intern Med.* 1996;124:939–49.
 8. Falcone C, Guasti L, Ochan M, Codega S, Tortorici M, Angoli L, Bergamaschi R, Montemartini C. Beta-endorphins during coronary angioplasty in patients with silent or symptomatic myocardial ischemia. *J Am Coll Cardiol.* 1993;15(22): 1614–20.
 9. Oldroyd KG, Harvey K, Gray CE, Beastall GH, Cobbe SM. Beta endorphin release in patients after spontaneous and provoked acute myocardial ischaemia. *Br Heart J.* 1992;67:230–5.
 10. Klocke FJ. Measurements of coronary blood flow and degree of stenosis: current clinical implications and continuing uncertainties. *J Am Coll Cardiol.* 1983;1:31–41.
 11. Di Carli M, Czernin J, Hoh CK, et al. Relation among stenosis severity, myocardial blood flow, and flow reserve in patients with coronary artery disease. *Circulation.* 1995;91:1944–51.
 12. Canty Jr JM. Coronary pressure-function and steady-state pressure-flow relations during autoregulation in the unanesthetized dog. *Circ Res.* 1988;63:821–36.
 13. De Bruyne B, Banohuin T, Melin J, et al. Coronary flow reserve calculated from pressure measurements in humans. *Circulation.* 1994;89:1013–22.
 14. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, Jagic N, Möbius-Winkler S, Rioufol G, Witt N, Kala P, MacCarthy P, Engström T, Oldroyd KG, Mavromatis K, Manoharan G, Verlee P, Frobert O, Curzen N, Johnson JB, Jüni P, Fearon WF, FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med.* 2012;367:991–1001.
 15. Bach RG, Kern MJ. Practical coronary physiology. Clinical application of the Doppler flow velocity guide wire. *Cardiol Clin.* 1997;15:77–99.
 16. Tousoulis D, Crake T, Kaski JC, et al. Enhanced vasomotor responses of complex coronary stenoses to acetylcholine in stable angina pectoris. *Am J Cardiol.* 1995;75:725–8.

17. Chilian WM, Mass HJ, Williams SE, Layne SM, Smith EE, Scheel KW. Microvascular occlusions promote coronary collateral growth. *Am J Physiol.* 1990;258:H1103–11.
18. Teunissen PFA, Horrevoets AJG, van Royen N. The coronary collateral circulation: genetic and environmental determinants in experimental models and humans. *J Mol Cell Cardiol.* 2011;52:897–904.
19. Kozman H, Cook JR, Wiseman AH, et al. Presence of angiographic coronary collaterals predicts myocardial recovery after coronary bypass surgery in patients with severe left ventricular dysfunction. *Circulation.* 1998;98(19 Suppl):II57–61.
20. Ball RM, Bache RJ. Distribution of myocardial blood flow in the exercising dog with restricted coronary artery inflow. *Circ Res.* 1976;38:60–6.
21. Holmvang G, Fry S, Skopicki HA, Abraham SA, et al. Relation between coronary “steal” and contractile function at rest in collateral-dependent myocardium of humans with ischemic heart disease. *Circulation.* 1999;99:2510–6.
22. Hansen CL, Williams E. Severe transmural myocardial ischemia after dipyridamole administration implicating coronary steal. *Clin Cardiol.* 1998;21:293–6.
23. Crea F, Pupita G, Galassi AR, et al. Effect of theophylline on exercise-induced myocardial ischaemia. *Lancet.* 1989;1:683–6.
24. Prinzmetal M, Kenamer R, Merliss R, Wada T, Bor N. Angina pectoris. I. The variant form of angina pectoris. *Am J Med.* 1959;27:375–88.
25. Maseri A, Mimmo R, Chierchia S, Marchesi C, Pesola A, L’Abbate A. Coronary spasm as a cause of acute myocardial ischemia in man. *Chest.* 1975;68:625–33.
26. Lanza GA, Sestito A, Sgueglia GA, Infusino F, Manolfi M, Crea F, Maseri A. Current clinical features, diagnostic assessment and prognostic determinants of patients with variant angina. *Int J Cardiol.* 2007;118:41–7.
27. Myerburg RJ, Kessler KM, Mallon SM, Cox MM, de Marchena E, Interian Jr A, Castellanos A. Life-threatening ventricular arrhythmias in patients with silent myocardial ischemia due to coronary-artery spasm. *N Engl J Med.* 1992;326:1451–5.
28. Lanza GA, Careri G, Crea F. Mechanisms of coronary artery spasm. *Circulation.* 2011;124:1774–82.
29. Kaski JC, Tousoulis D, Gavrielides S, McFadden E, Galassi AR, Crea F, Maseri A. Comparison of epicardial coronary artery tone and reactivity in Prinzmetal’s variant angina and chronic stable angina pectoris. *J Am Coll Cardiol.* 1991;17:1058–62.

30. Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FA, Delforge MR, Carre AG, Asseman P, Berzin B, Libersa C, Laurent JM. Frequency of provoked coronary arterial spasm in 1089 consecutive patients undergoing coronary angiography. *Circulation*. 1982;65:1299–306.
31. Kaski JC, Maseri A, Vejar M, Crea F, Hackett D. Spontaneous coronary artery spasm in variant angina results from a local hyperreactivity to a generalized constrictor stimulus. *J Am Coll Cardiol*. 1989;14:1456.
32. Shimokawa H, Ito A, Fukumoto Y, Kadokami T, Nakaike R, Sakata M, Takayanagi T, Egashira K, Takeshita A. Chronic treatment with interleukin-1 β induces coronary intimal lesions and vasospastic responses in pigs in vivo: the role of platelet-derived growth factor. *J Clin Invest*. 1996;97:769–76.
33. Kandabashi T, Shimokawa H, Miyata K, Kunihiro I, Kawano Y, Fukata Y, Higo T, Egashira K, Takahashi S, Kaibuchi K, Takeshita A. Inhibition of myosin phosphatase by upregulated Rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1beta. *Circulation*. 2000;101:1319–23.
34. Kikuchi Y, Yasuda S, Aizawa K, Tsuburaya R, Ito Y, Takeda M, Nakayama M, Ito K, Takahashi J, Shimokawa H. Enhanced Rho-kinase activity in circulating neutrophils of patients with vasospastic angina: a possible biomarker for diagnosis and disease activity assessment. *J Am Coll Cardiol*. 2011;58:1231–7.
35. Masumoto A, Mohri M, Shimokawa H, Urakami L, Usui M, Takeshita A. Suppression of coronary artery spasm by the Rho-kinase inhibitor fasudil in patients with vasospastic angina. *Circulation*. 2002;105:1545–7.
36. Vanhoutte PM, Shimokawa H. Endothelium-derived relaxing factor and coronary vasospasm. *Circulation*. 1989;80:1–9.
37. Toyooka T, Aizawa T, Suzuki N, Hirata Y, Miyauchi T, Shin WS, Yanagisawa M, Masaki T, Sugimoto T. Increased plasma level of endothelin-1 and CAS induction in patients with vasospastic angina pectoris. *Circulation*. 1991;83:476–83.
38. Forman MB, Oates JA, Robertson D, Robertson RM, Roberts 2nd LJ, Virmani R. Increased adventitial mast cells in a patient with coronary artery spasm. *N Engl J Med*. 1985;313:1138–41.
39. Sugiishi M, Takatsu F. Cigarette smoking is a major risk factor for CAS. *Circulation*. 1993;87:76–9.
40. Katayama N, Nakao K, Horiuchi K, Kasanuki H, Honda T. Disease activities and serum C-reactive protein levels in patients with vasospastic angina pectoris. *J Cardiol*. 2005;46:63–70.

41. Miwa K, Miyagi Y, Igawa A, Nakagawa K, Inoue H. Vitamin E deficiency in variant angina. *Circulation*. 1996;94:14–8.
42. Kaneda H, Taguchi J, Kuwada Y, Hangaishi M, Aizawa T, Yamakado M, Ogasawara K, Aizawa T, Ohno M. Coronary artery spasm and the polymorphisms of the endothelial nitric oxide synthase gene. *Circ J*. 2006;70:409–13.
43. Park JS, Zhang SY, Jo SH, Seo JB, Li L, Park KW, Oh BH, Park YB, Kim HS. Common adrenergic receptor polymorphisms as novel risk factors for vasospastic angina. *Am Heart J*. 2006;151:864–9.
44. Specchia G, De Servi S, Falcone C, Bramucci E, Angoli L, Mussini A, Marinoni GP, Montemartini C, Bobba P. Coronary arterial spasm as a cause of exercise-induced ST-segment elevation in patients with variant angina. *Circulation*. 1979;59:948–54.
45. Raizner AE, Chahine RA, Ishimori T, Verani MS, Zacca N, Jamal N, Miller RR, Luchi RJ. Provocation of coronary artery spasm by the cold pressor test. Hemodynamic, arteriographic and quantitative angiographic observations. *Circulation*. 1980;62:925–32.
46. El Menyar AA. Drug-induced myocardial infarction secondary to coronary artery spasm in teenagers and young adults. *J Postgrad Med*. 2006;52:51–6.
47. Yasue H, Horio Y, Nakamura N, Fujii H, Imoto N, Sonoda R, Kugiyama K, Obata K, Morikami Y, Kimura T. Induction of coronary artery spasm by acetylcholine in patients with variant angina: possible role of the parasympathetic nervous system in the pathogenesis of coronary artery spasm. *Circulation*. 1986;74:955–63.
48. Lanza GA, Pedrotti P, Pasceri V, Lucente M, Crea F, Maseri A. Autonomic changes associated with spontaneous CAS in patients with variant angina. *J Am Coll Cardiol*. 1996;28:1249–56.
49. Magarian GJ, Mazur DJ. The Hyperventilation challenge test. *Chest*. 1991;99:199–204.
50. Ohta H, Suzuki J, Akima T, Kawai N, Hanada K, Nishikibe M. Hemodynamic effect of endothelin antagonists in dogs with myocardial infarction. *J Cardiovasc Pharmacol*. 1998;31:S255–7.
51. Gillespie MN, Booth DC, Friedman BJ, Cunningham MR, Jay M, DeMaria AN. fMLP provokes coronary vasoconstriction and myocardial ischemia in rabbits. *Am J Physiol*. 1988;254:H481–6.
52. Cannon RO, Epstein SE. “Microvascular angina” as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol*. 1988;61:1338–43.

53. Lanza GA, Crea F. Primary coronary microvascular dysfunction: clinical presentation, pathophysiology, and management. *Circulation*. 2010;121:2317–25.
54. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;356:830–40.
55. Lanza GA, Camici PG, Galiuto L, Niccoli G, Pizzi C, Di Monaco A, Sestito A, Novo S, Piscione F, Tritto I, Ambrosio G, Bugiardini R, Crea F, Marzilli M. Gruppo di Studio di Fisiopatologia Coronarica e Microcircolazione, Società Italiana di Cardiologia. Methods to investigate coronary microvascular function in clinical practice. *J Cardiovasc Med (Hagerstown)*. 2013;14:1–18.
56. Sestito A, Lanza GA, Di Monaco A, Lamendola P, Careri G, Tarzia P, Pinnacchio G, Battipaglia I, Crea F. Relation between cardiovascular risk factors and coronary microvascular dysfunction in cardiac syndrome X. *J Cardiovasc Med (Hagerstown)*. 2011;12:322–7.
57. Chauhan A, Mullins PA, Taylor M, Petch MC, Schofield PM. Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms. *Eur Heart J*. 1997;18:60–8.
58. Motz W, Vogt M, Rabenau O, Scheler S, Luckhoff A, Strauer BE. Evidence of endothelial dysfunction in coronary resistance vessels in patients with angina pectoris and normal coronary angiograms. *Am J Cardiol*. 1991;68:996–1003.
59. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Effect of hyperventilation and mental stress on coronary blood flow in syndrome X. *Br Heart J*. 1993;69:516–24.
60. Nihoyannopoulos P, Kaski JC, Crake T, Maseri A. Absence of myocardial dysfunction during stress in patients with syndrome X. *J Am Coll Cardiol*. 1991;18:1463–70.
61. Camici PG, Marraccini P, Lorenzoni R, Buzzigoli G, Pecori N, Perissinotto A, Ferrannini E, L'Abbate A, Marzilli M. Coronary hemodynamics and myocardial metabolism in patients with syndrome X: response to pacing stress. *J Am Coll Cardiol*. 1991;17:1461–70.
62. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol*. 1991;17:499–506.
63. Bortone AS, Hess OM, Eberli FR, Nonogi H, Marolf AP, Grimm J, Krayenbuehl HP. Abnormal coronary vasomotion during exercise in patients with normal coronary arteries and reduced coronary flow reserve. *Circulation*. 1989;79:516–27.
64. Lanza GA, Lüscher TF, Pasceri V, Shaw SG, Buffon A, Montenero AS, Crea F, Maseri A. Effects of atrial pacing on arterial and

- coronary sinus endothelin-1 levels in syndrome X. *Am J Cardiol.* 1999;84:1187–91.
65. Opher D, Zebe H, Weihe E, Mall G, Durr C, Gravert B, Mehmel HC, Schwarz F, Kubler W. Reduced coronary dilator capacity and ultrastructural changes of the myocardium in patients with angina pectoris but normal coronary arteriograms. *Circulation.* 1981;63:817–25.
 66. Wessel TR, Arant CB, McGorray SP, Sharaf BL, Reis SE, Kerensky RA, von Mering GO, Smith KM, Handberg EM, Mankad S, Olson MB, Johnson BD, Merz CN, Sopko G, Pepine CJ, NHLBI Women's Ischemia Syndrome Evaluation (WISE). Coronary microvascular reactivity is only partially predicted by atherosclerosis risk factors or coronary artery disease in women evaluated for suspected ischemia: results from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). *Clin Cardiol.* 2007;30:69–74.
 67. Lanza GA, Giordano AG, Pristipino C, Calcagni ML, Meduri G, Trani C, Franceschini R, Crea F, Troncone L, Maseri A. Abnormal cardiac adrenergic nerve function in patients with syndrome X detected by [¹²³I]meta-iodo-benzylguanidine myocardial scintigraphy. *Circulation.* 1997;96:821–6.
 68. Bøtker HE, Møller N, Ovesen P, Mengel A, Schmitz O, Orskov H, Bagger JP. Insulin resistance in microvascular angina (syndrome X). *Lancet.* 1993;342:136–40.
 69. Kaski JC. Cardiac syndrome X in women: the role of oestrogen deficiency. *Heart.* 2006;92 Suppl 3:5–9.
 70. Koren W, Koldanov R, Peleg E, Rabinowitz B, Rosenthal T. Enhanced red cell sodium/hydrogen exchange in microvascular angina. *Eur Heart J.* 1997;18:1296–9.
 71. Lanza GA, Sestito A, Cammarota G, Grillo RL, Vecile E, Cianci R, Speziale D, Dobrina A, Maseri A, Crea F. Assessment of systemic inflammation and infective pathogen burden in patients with cardiac syndrome X. *Am J Cardiol.* 2004;94:40–4.
 72. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon—a new coronary microvascular disorder. *Cardiology.* 2002;97:197–202.
 73. Beltrame JF, Limaye SB, Wuttke RD, Horowitz JD. Coronary hemodynamic and metabolic studies of the coronary slow flow phenomenon. *Am Heart J.* 2003;146:84–90.
 74. Mohri M, Shimokawa H, Hirakawa Y, Masumoto A, Takeshita A. Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. *J Am Coll Cardiol.* 2003;41:15–9.

75. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. *Circulation*. 2008;118:397–409.
76. Kume T, Akasaka T, Kawamoto T, Watanabe N, Yoshitani H, Akiyama M, Koyama Y, Neishi Y, Tsukiji M, Yoshida K. Relationship between coronary flow reserve and recovery of regional left ventricular dysfunction in patients with tako-tsubo-like transient left ventricular dysfunction. *J Cardiol*. 2004;43:123–9.
77. Libby P. Mechanisms of acute coronary syndromes. *N Engl J Med*. 2013;369:883–4.
78. Ambrose JA, Winters SL, Arora RR, Eng A, Riccio A, Gorlin R, Fuster V. Angiographic evolution of coronary artery morphology in unstable angina. *J Am Coll Cardiol*. 1986;7:472–8.
79. Reynolds HR, Srichai MB, Iqbal SN, Slater JN, Mancini GB, Feit F, Pena-Sing I, Axel L, Attubato MJ, Yatskar L, Kalhorn RT, Wood DA, Lobach IV, Hochman JS. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation*. 2011;124:1414–25.
80. Liuzzo G, Crea F. Pathogenesis of acute coronary syndromes. *J Am Coll Cardiol*. 2013;61:1–11.
81. Robertson RM, Robertson D, Friesinger GC, et al. Platelet aggregates in peripheral and coronary-sinus blood in patients with spontaneous coronary-artery spasm. *Lancet*. 1980;2:829–31.

Chapter 2

An Overview of Treatment and Guidelines: ESC/ACC-AHA/NICE

Jason M. Tarkin and Juan Carlos Kaski

Introduction to Stable Angina Treatment

Treatment of stable angina aims not only to relieve symptoms, but also to reduce the total ischaemic burden and improve long-term prognosis through secondary preventative measures that halt progression of atherosclerosis and its clinical sequelae. The treatment of stable angina should ideally be tailored to individual patient needs, taking into consideration the nature and severity of symptoms, risk factors, functional and anatomical significance of established coronary artery disease, co-morbidities and patient preference.

J.M. Tarkin, MBBS, MRCP

Division of Cardiovascular Medicine, University of Cambridge,
Cambridge, UK

London Deanery, London, UK

J.C. Kaski, MD, DSc, FRCP, FESC, FACC, FAHA (✉)

Cardiovascular and Cell Sciences Research Institute,

St George's, University of London, London, UK

e-mail: jkaski@sgul.ac.uk

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_2,

© Springer International Publishing Switzerland 2015

For each patient, the success of any angina treatment (whether pharmacological, invasive or surgical) will rely on an understanding of the culprit pathogenic mechanisms underlying their symptoms, and balanced assessment of potential and perceived risks, side-effects and likelihood of adherence.

The pharmacological agents used in stable angina fall broadly into two categories: anti-atherosclerosis and anti-angina therapies. Drugs to treat atherosclerosis, mainly anti-platelets and statins, are used in tandem with lifestyle modification and aggressive risk factor control. Anti-angina agents serve predominately for symptomatic benefit, although some may have an additional prognostic role. Several newer drugs for stable angina are more specifically targeted, with fewer side-effects, and can potentially improve efficacy of medical therapy.

This chapter will first discuss the diagnosis of angina and its symptoms in order to introduce an individualized, mechanism-based approach to treatment. It will then focus mainly to provide an overview of the pharmacological agents used to treat stable angina, including recommendations from the major clinical practice guidelines [1–3]. More detailed discussion of individual anti-angina drugs is provided in subsequent chapters.

Symptomatic/Mechanistic Approach to Angina Management

When a patient presents with chest pain, details of the nature and pattern of symptoms elicited from the clinical history are key to establishing the diagnosis and to guide treatment. Often the prevailing underlying mechanism (see Chap. 1) determines the pattern of clinical presentation; knowledge of this may allow selection of a more precise, and effective, management strategy.

Symptoms of Stable Angina

Chronic stable angina is defined by its symptoms (unchanged for at least 3 months): typical cardiac chest pain, brought on by a predictable and reproducible level of exertion (or emotional stress), and relieved following a brief period of rest or short-acting nitrates. Angina is often described as ‘tight/ constricting’ pain, felt in the centre or left side of the anterior chest, with characteristic radiation to the neck, jaw and along the ulnar distribution of the adjacent arm.

There is, of course, the caveat that not all patients report typical symptoms, and *silent* ischaemia can occur in diabetic and elderly patients due to impaired autonomic function. Exertional dyspnoea, fatigue and dizziness may represent *angina equivalents* in this group. Those with new-onset, severe or prolonged chest pain, which is not relieved by nitrates and occurs at rest, or with increased frequency, by definition do not have angina that is *chronic* or *stable*; and thus warrant further investigation for more acute pathology.

Effort-Induced Angina

The typical *crescendo-decrescendo* pattern of chest pain experienced by patients with stable angina results from transient myocardial ischaemia most often ascribed to a chronic epicardial artery obstruction due to long-standing atherosclerosis. Indeed, effort-induced angina is the most common manifestation of atherosclerotic coronary artery disease, present in about half of patients, and due to flow-limiting epicardial artery stenosis usually $\geq 70\%$ diameter reduction [2]. In effort-induced stable angina, the symptom threshold is predictable, and can be graded according to the *Canadian Cardiovascular Society* functional classification system for stable angina [4]. On the whole, the management of stable angina is targeted primarily to treat obstructive, effort-induced symptoms and

underlying atherosclerosis, although it is helpful to remember that other contributory factors may influence the overall response to therapy.

Microvascular, Vasospastic and Mixed Angina

The typicality of presenting symptoms, along with a patient's cardiovascular risk profile, will direct further clinical investigations including diagnostic coronary angiography. However, notably up to 62 % of patients without previous cardiac disease who undergo elective diagnostic angiography do not have obstructive coronary artery disease [5]. Many of these patients will have significant cardiac risk factors and recurrent symptoms. Even without angiographically determined coronary artery disease, this group nonetheless has increased risk of major adverse cardiac events and higher all cause mortality [6]. In this context, symptoms due to endothelial dysfunction and microvascular disease may represent early manifestations of atherosclerotic coronary artery disease [1].

The pattern of symptoms can be particularly helpful to differentiate between various mechanisms causing chest pain in patients with angina who lack obstructive coronary atherosclerosis, and for those with persistent symptoms despite conventional therapy. Typical cardiac symptoms and demonstrable ischaemia on stress testing, in the absence of significant epicardial artery stenosis, suggests cardiac syndrome X; which encompasses several pathogenic mechanisms involving the coronary microcirculation [7]. On the other hand, primary vasospastic angina (e.g. Prinzmetal's variant angina) produces characteristic cardiac pain, relieved by nitrates, which is not typically related to exertion. These findings have specific implications for treatment (see section "[Special considerations and refractory angina](#)").

In the ACOVA (Abnormal Coronary VAsomotion in patients with stable angina and unobstructed coronary arteries)

study, approximately two-thirds of patients with angina and angiographically normal coronary arteries tested positive for epicardial or microvascular spasm on acetylcholine testing [8]. Coronary spasm also often occurs in patients with established atherosclerosis, which results in variable threshold effort-angina and occasionally angina at rest (mixed angina) [9]. Testing for coronary spasm is not routine practice in most centres, and thus coronary spasm may affect a much larger proportion of the angina population than previously anticipated.

Other factors, which may add to the symptomatology of stable angina, include structural heart abnormalities (e.g. left ventricular hypertrophy and aortic stenosis) and systemic conditions (e.g. anaemia and hyperthyroidism). While most patients with stable angina have effort-induced symptoms due to obstructive coronary atherosclerosis, other mechanisms contribute to varying degrees and diagnostic clues are often revealed by the clinical history, which may influence choice of treatment.

Overview of Guidelines (ESC/ACC-AHA/NICE)

The major clinical practice guidelines for stable angina provided by the European Society of Cardiology (ESC), American College of Cardiology-American Heart Association (ACC-AHA), and the National Institute for health and Clinical Excellence (NICE) in the UK have been updated in recent years (Fig. 2.1). Among other topics, these include recommendations on: (a) treatment of atherosclerosis and event prevention, (b) treatment of ischaemia and symptoms, and (c) special considerations and refractory angina. These areas will be further discussed here, within the framework of the treatment guidelines. Specific points where guidelines differ will be highlighted.

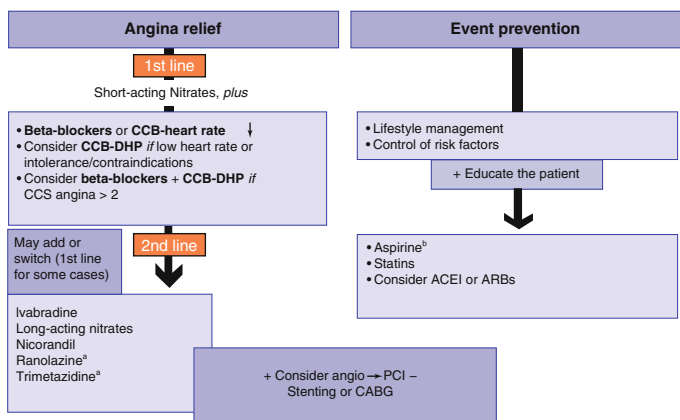


FIGURE 2.1 Summary of ESC guidelines for stable angina management (Figure adapted from Task Force Members et al. [1]).

^aData for patients with diabetes

^bIf intolerance, consider using clopidogrel

Treatment of Atherosclerosis and Event Prevention

The prognosis of stable angina is generally good, and carries annual mortality rate of 1.2–2.4 % and an annual non-fatal myocardial infarction rate of 0.6–2.7 % [1]. Moreover, only 18 % of cardiac events occur in patients with a prior stable angina [10]. This is largely due to the fact that chronic fibro-atheromatous plaques are less prone to rupture, as the thrombogenic lipid core tends to be smaller and shielded from the lumen by a thick fibrous cap, which is devoid of inflammatory cells and often heavily calcified [11–13]. That being said, atherosclerosis is a systemic, multi-focal disease and therefore the presence of stable coronary plaques may serve as a marker for more vulnerable disease elsewhere. Furthermore, for many patients with stable angina the risk of major cardiac events and death is increased due to co-morbidities, including diabetes and previous myocardial infarction [14]. Therefore

secondary preventative measures are hugely important for all patients with stable angina due to atherosclerosis, to slow disease progression and improve long-term outcome.

Lifestyle modification, in the form of healthy eating, exercise, weight reduction and smoking cessation is fundamental. Aside from the positive effects on lowering blood pressure and cholesterol, these interventions alone can result in modest, but measurable, differences in coronary artery stenosis severity and improved myocardial perfusion (probably through changes in the microcirculation) [15]. From the physician's perspective, stringent treatment of hypertension, dyslipidaemia and diabetes is the cornerstone of atherosclerosis management; currently recommended target thresholds for these are blood pressure <140/90 mmHg, LDL <1.8 mmol/L (<70 mg/dL) or 50 % reduction, and HbA1c <7 % (<53 mmol/mol).

Lower BP targets may benefit certain high-risk patients with angina, such as those with diabetes, however these are often impractical to achieve. There is also a theoretical risk that excessive lowering of diastolic BP can lead to impaired coronary perfusion in patients with angina, and some evidence to suggest that this can lead to an increase in cardiac events [16].

Role of Anti-platelet Therapy

The role of anti-platelets for prevention of death, myocardial infarction and stroke in high-risk patients was demonstrated by a large meta-analysis conducted by the Antithrombotic Trialists' Collaboration, which included data from 287 studies and reported a 25 % reduction in serious cardiovascular events [17]. The SAPAT (Swedish Angina Pectoris Aspirin Trial) was the first prospective study to evaluate the use of aspirin in patients with angina; this showed a 34 % reduction in myocardial infarction and sudden death over a 50 month period [18].

Aspirin acts as an irreversible cyclo-oxygenase inhibitor to prevent production of thromboxane, platelet aggregation and arterial thrombosis. Long-term aspirin is recommended for

all patients with angina and evidence of atherosclerosis. For patients with an allergy or intolerance to aspirin, clopidogrel is recommended. Clopidogrel is a thienopyridine derivative that inhibits platelet aggregation through irreversible inhibition of ADP P2Y₁₂ receptors. In CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events), clopidogrel showed marginally superiority to aspirin with a similar safety profile [19]. However, patients with variants of the CYP2C19 gene may have a reduced anti-platelet response to clopidogrel, and point-of-care screening is not currently widely available (or recommended) [20].

Dual anti-platelet therapy with aspirin and clopidogrel is not indicated for stable angina alone, but is common practice in the first year following myocardial infarction and/or coronary artery stenting (to reduce the risk of subsequent events, in-stent thrombosis and early re-stenosis). Newer anti-platelets agents, including prasugrel and ticagrelor, have not yet been evaluated for use in stable angina, and may be associated with increased risk of bleeding. Dipyridamole causes vasodilation of coronary resistance vessels and can provoke exercise-induced ischaemia [2]; it is not recommended for use in stable angina.

Statins: Lipid Lowering and Pleiotropic Effects

Statins inhibit HMG-CoA reductase to lower LDL cholesterol on average by 40–60 %, depending on the drug and dosage [21]. Large meta-analyses performed by the Cholesterol Treatment Trialists' Collaborative have shown that this translates into roughly a 10 % reduction in all cause mortality and 20 % reduction in major vascular events for every 1.0 mmol/L decrease; irrespective of age, sex, baseline LDL cholesterol or previous cardiovascular disease [22, 23].

The benefits of statins are greater than can be explained by their lipid lowering effects alone. Pleiotropic effects of statins can help to stabilize lesions by decreasing inflammation and altering plaque composition, and can also result in small reductions in plaque volume, improved endothelial function and less reversible ischemia [24]. Statins are recommended for all patients with atherosclerotic coronary artery

disease, irrespective of serum cholesterol. When statins cannot be used, other lipid lowering agents such as fibrates, resins, nicotinic acid and ezetimibe may help to lower LDL cholesterol, but the benefit on clinical outcomes with these alternative agents has not yet been shown [1].

High-Risk Patients

For those with stable angina and previous history of myocardial infarction, or left ventricular impairment with ejection fraction $\leq 40\%$, beta-blockers and angiotensin converting enzyme (ACE) inhibitors improve long-term outcome [25, 26], and are recommended along with other cardiac treatments specific to these conditions. ACE inhibitors are also recommended for those with stable angina and diabetes, hypertension or chronic kidney disease, unless contraindicated. Furthermore, combined analysis of the HOPE (Heart Outcomes Prevention Evaluation), EUROPA (European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease) and PEACE (Prevention of Events with ACE inhibition) trials showed a significant reduction in total mortality and fatal and non-fatal cardiovascular events with ACE inhibitors for patients with stable coronary disease without heart failure [27]. This suggests a role for ACE inhibitors in all patients with coronary atherosclerosis. The guidelines also advise influenza vaccination for all patients with atherosclerotic coronary artery disease.

Treatment of Ischaemia and Symptoms

Drugs effective in relieving the symptoms of angina act to restore the balance between myocardial oxygen supply and demand, by reducing myocardial work, improving flow, or both. This is achieved mainly by modulating heart rate, blood pressure, myocardial loading or contractility, vascular tone and diastolic wall tension; these mechanisms alter the threshold at which an angina episode is triggered. See Table 2.1 for summary of recommended anti-angina drugs.

TABLE 2.1 Summary of anti-angina drugs recommended by ESC*, ACC-AHA† and NICE‡

Drug class	Therapeutic target	Mechanism of action	Side-effects	Contraindications	Notes
<i>First-line drugs</i>					
Beta-blockers*†‡	β-adrenergic receptor antagonist	Reduces heart rate, blood pressure and contractility Prolongs diastolic filling time	Fatigue Depression Bradycardia Hypotension Bronchospasm Hyper/hypoglycaemia Impotence	Bradycardia, heart block or other conduction disorder Cardiogenic shock, hypotension Asthma Peripheral vascular disease	May worsen angina due to coronary spasm Cardioselective beta-blockers preferable for angina Prognostic benefit for patients with myocardial infarction and/or heart failure

Calcium channel antagonists*†‡	L-type Ca^{2+} channel antagonist	Acts as systemic and coronary vasodilator Rate-limiting agents also reduce heart rate, blood pressure and contractility, and prolong diastole	Dizziness Headache Fatigue Nausea Constipation Peripheral oedema Bradycardia (rate limiting agents) Hypotension	Cardiogenic shock, First-line for hypotension Bradycardia (rate-limiting agents) Dose adjustment required for liver and renal impairment Co-administration of rate-limiting calcium channel blockers with beta-blockers, or other CYP3A4 enzymes Interacting with interfering drugs agents
<i>Second-line drugs</i>				
Long-acting nitrates*†‡	Nitric oxide donor, activates cGMP pathway	Acts as systemic and coronary vasodilator	Headache Flushing Hypotension Dizziness	Hypotension Co-administration with PDE-5-inhibitors Nitrate-free interval necessary to avoid tolerance Aortic stenosis Hypertrophic cardiomyopathy

(continued)

TABLE 2.1 (continued)

Drug class	Therapeutic target	Mechanism of action	Side-effects	Contraindications	Notes
Nicorandil*†‡	Nitric oxide donor and K^+_{ATP} channel opener	Acts as a balanced systemic and coronary vasodilator	Headache Dizziness Flushing Nausea Malaise Skin, mucosal and gastro-intestinal tract ulcers (rare)	Cardiogenic shock, hypotension Co-administration with PDE-5-inhibitors Aortic stenosis Hypertrophic cardiomyopathy	Cardio-protection due to ischaemic pre-conditioning K^+_{ATP} channel opening antagonized by sulphonylureas
Ranolazine*†‡	Inhibitor of late inward Na^+ current	Reduces diastolic wall tension	Dizziness Constipation Nausea Abdominal pain Headache QT prolongation	Prolonged QT-interval, QT-interval prolonging drugs Liver or renal failure Previous ventricular tachycardia	Improves HbA1c in diabetic patients Dose adjustment for elderly, renal and liver impairment Interaction with CYP3A4, CYP2D6 enzyme and P-glycoprotein substrate interfering drugs

Ivabradine*‡	If channel inhibitor	Reduces heart rate	Flashing lights Blurred vision Headache Dizziness Bradycardia First degree heart block	Heart block, bradycardia Atrial fibrillation Acute MI or HF Liver or renal failure Pregnancy and breast-feeding	Contraindicated during pregnancy and breast-feeding (due to risk of teratogenicity) Interaction with CYP3A4 enzyme interfering drugs
Trimetazidine*	Mitochondrial long-chain 3-ketoacyl CoA thiolase inhibitor	Improves myocardial metabolic efficiency by preventing β -oxidation of free fatty acid, thus increasing glucose usage	Heartburn Nausea Headache Diarrhoea Movement disorders	Parkinson's disease, movement disorders Severe renal impairment	Dose reduction required for renal impairment

Treatment of Acute Angina Episodes

Episodes of angina are treated with sublingual glyceryl-trinitrate (GTN). GTN is rapidly absorbed and acts as a nitric oxide donor to cause systemic and coronary vasodilatation, improving myocardial blood flow, and providing relief of symptoms within several minutes. GTN is recommended for all patients with symptoms of angina, without contraindication. There is a risk of profound hypotension with GTN if administered within 24 h of a phosphodiesterase-5 inhibitor (e.g. sildenafil), are therefore these two medications should not be prescribed together. Other contraindications include aortic stenosis and hypertrophic cardiomyopathy, again due to the risk of acute hypotension (in the presence of significant outflow tract gradient). Common side-effects are headache, flushing and dizziness. When prescribing GTN, patients should be counseled on how and when to use GTN, to anticipate potential side-effects, and to seek medical attention if their symptoms persist despite treatment.

First-Line Agents

β -adrenergic receptor antagonists (beta-blockers) and L-type calcium channel receptor antagonists (calcium channel blockers) are recommended first-line agents to prevent myocardial ischaemia and the symptoms of angina. ACC-AHA guidance supports beta-blockers over calcium channel blockers as the first option where possible, whereas ESC and NICE do not. Evidence for the use of beta-blockers and calcium channels blockers in stable angina comes from studies such as TIBET (Total Ischemic Burden European Trial) and APSIS (Angina Prognosis Study in Stockholm) [28, 29]. Beta-blockers (e.g. bisoprolol) and non-dihydropyridines calcium channel blockers (e.g. diltiazem) reduce myocardial work through negative chronotropic and inotropic actions. These agents also act by prolonging diastole to

improve myocardial oxygen supply. In addition, calcium channel blockers act as systemic and coronary vasodilators.

The type of angina, co-morbidities, contra-indications and patient preference guides the choice of first-line agent. Beta-blockers are recommended for all patients with previous myocardial infarction and/ or heart failure as these have proven prognostic benefit in this context. Longer acting formulations that lack intrinsic sympathomimetic activity are preferred, at a dose titrated to achieve a target heart rate of 50–60 beats per minute. The potential prognostic benefit of beta-blockers in patients with angina alone has been extrapolated from post-myocardial infarction studies and current evidence is lacking [30]. For patients with asthma (or other contra-indications to beta-blockers), and those with primary vasospastic angina, calcium channel blockers are recommended. When a beta-blocker and a calcium channel blocker are used together in combination therapy, a non-rate limiting dihydropyridine (e.g. nifedipine) is advised.

Second-Line Agents

If beta-blockers and calcium channel blockers are contra-indicated, not tolerated or not successful in controlling symptoms of angina, there are a number of effective second-line options. Selection of the appropriate second-line agent to meet the needs of an individual patient can significantly improve the chance of successful treatment. Each of the agents described below are included in the most recent ESC guidelines. Several of these (nicorandil, ivabradine and trimetazidine) are not available in the US, and are therefore not addressed in the AHA-ACC guidelines. Trimetazidine is also not available in the UK, and not included in NICE guidance.

Long-Acting Nitrates

Long-acting nitrates (e.g. isosorbide mononitrate) are effective in reducing the frequency and severity of angina symptoms,

but do not alter long-term prognosis. Mechanisms of action and side-effects are similar to GTN. Establishing a treatment regime that incorporates a nitrate-free interval (of 8–10 h) is necessary to prevent tolerance. Recent evidence suggests that development of nitrate tolerance may be associated with increased oxidative stress, endothelial dysfunction and sympathetic activation—thus challenging the traditional use of long-acting nitrates as the default second-line agent [31] (Table 2.1).

Nicorandil

Nicorandil improves symptoms of angina in a similar manner to nitrates, through its actions as a nitric oxide donor and sarcolemmal K-ATP dependant channel agonist. It may have added prognostic benefit by preventing cardiac events through mechanisms leading to mitochondrial ischaemic pre-conditioning, as shown by the IONA (Impact Of Nicorandil in Angina) study [32]. Nicorandil is a logical choice for patients whose symptoms respond well to nitrates, however significant haemodynamic side-effects may preclude its use in some patients; it can also rarely cause gastro-intestinal tract ulceration.

Ivabradine

Ivabradine lowers heart rate on average by 10 beats per minute through selective inhibition of *If* channels controlling the intrinsic pacemaker cells, reducing sino-atrial node activity. Its safety and efficacy for use in angina was shown by INITIATIVE (INTERNational TRIAl on the Treatment of angina with IVabradinE vs. atenolol) and other studies [33, 34]. In BEAUTIFUL (morBidity-mortality EvAlUaTION of the *If* inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction), significantly lower rates of admission for fatal and non-fatal myocardial infarction and revascularization were observed in a sub-group of patients with stable angina and resting heart rate ≥ 70 beats per minute [35].

Ivabradine does not affect blood pressure, atrio-ventricular node conduction or contractility, but is only effective in patients

who are in sinus rhythm. Ivabradine is indicated for patients with stable angina who cannot take conventional heart-rate lowering agents, and for those whose heart rate is sub-optimally controlled. Common side-effects are mild luminous visual disturbance (phosphenes) during the first 2 months of treatment, headache and dizziness. There is a potential for interactions with drugs that interfere with CYP3A4 liver enzymes.

Ranolazine

Ranolazine helps treat symptoms of angina by reducing diastolic wall tension and oxygen consumption through inhibition of ischaemic late inward sodium currents. Its efficacy as monotherapy and in combination with other anti-angina drugs was shown in the MARISA (Monotherapy Assessment of Ranolazine in Stable Angina), CARISA (Combination Assessment of Ranolazine in Stable Angina), and ERICA (Efficacy of Ranolazine in Chronic angina) trials [36–38]. Ranolazine does not significantly affect heart rate or blood pressure, and is therefore an attractive option for patients who have persistent angina despite optimal doses of heart-rate lowering agents, and for those who are intolerant of the haemodynamic side-effects of nitrates or nicorandil. There is, however, a dose-dependant effect on QT interval prolongation (resulting in a mean increase of 6 ms at maximal recommended dosing), and the potential for interaction with drugs that interfere with CYP3A4 and CYP2D6 liver enzymes. Common side-effects are dizziness, nausea, constipation and abdominal discomfort. In patients with diabetes and angina, ranolazine may have the added benefit of lowering HbA_{1c} levels in patients without previous hyperglycaemia [39].

Trimetazidine

Trimetazidine is another drug used to treat angina in many European countries, which acts by inhibiting β -oxidation of fatty acids to improve efficiency of myocardial metabolism. A Cochrane review of 23 studies performed in 2005 showed

that trimetazidine successfully reduces the number of weekly angina attacks, nitrate usage and exercise time compared to placebo [40]; however, its use in angina has not yet been evaluated in large outcome studies. Trimetazidine is contraindicated in Parkinson's disease and other movement disorders. It is not currently available in the US or UK.

Role of Myocardial Revascularization in Stable Angina

Percutaneous coronary intervention (PCI) and coronary artery by-pass grafting surgery (CABG) are considered in patients with persistent symptoms despite optimal medical therapy, and for those with prognostically significant lesions (i.e. left main stem or three vessel disease). For those with persistent symptoms on medical therapy, NICE recommends adding a third drug only when two anti-angina drugs do not satisfactorily control symptoms and the patient is awaiting revascularization, or in patients for whom revascularization is not appropriate [3]. The decision to offer myocardial revascularization is based on a number of factors, including the presence of significantly obstructive disease with related ischaemia, and the expected benefits for prognosis and/ or symptoms, balanced against the risk of the proposed intervention. The role of revascularization in stable angina patients is further discussed in other chapter.

Special Considerations and Refractory Angina

Microvascular Angina and Cardiac Syndrome X

Empirical treatment of symptoms with conventional anti-angina drugs provides the mainstay of therapy for patients with microvascular angina and/ or cardiac syndrome X. Secondary preventative measures, including aspirin and statins, are also important, primarily for those with risk factors

for atherosclerosis. Roughly half of patients respond to nitrates, and so it is reasonable to try GTN in the first instance. Other anti-anginals, particularly beta-blockers, are also helpful for effort-induced symptoms. ACE inhibitors may improve microvascular function, and are especially recommended for patients with hypertension and/or diabetes. Nicorandil and other second-line anti-angina agents, and novel treatments for refractory angina, may be effective in selected patients.

Vasospastic and Prinzmetal's Variant Angina

Angina at rest can occur due to epicardial artery vasospasm associated with transient ST-segment elevation in Prinzmetal's variant angina. Variable threshold (mixed) angina occurs when coronary spasm is superimposed on diseased arterial segments. Treatment of angina due to coronary vasospasm includes risk factor control, importantly smoking cessation (as this can trigger episodes), and aspirin, plus other secondary preventative measures where appropriate. All potential causes, including illicit drugs (e.g. cocaine), should be excluded. Calcium channel blockers are effective in 90 % of cases, and nitrates may also be helpful. Beta-blockers are avoided due to the risk of worsening vasoconstriction due to unopposed action on alpha-adrenergic arterial receptors.

Refractory Angina

Refractory angina is defined as a chronic condition (>3 months) caused by reversible myocardial ischaemia due to coronary artery disease, which cannot be adequately controlled by a combination of medical therapy, angioplasty and/ or coronary artery bypass grafting surgery [41]. This occurs in roughly 5–10 % of patients undergoing coronary angiography [42]. In this situation, when medical therapy is not sufficient, and revascularization options are limited by unsuitable coronary

anatomy, co-morbidities or other factors, there are several additional therapies that may help to improve quality of life that are included in the practice guidelines. These are external counterpulsation therapy and neurostimulatory techniques. Transmyocardial laser revascularisation has not been shown to be effective and is not currently recommended. Other therapies, such as cardiac rehabilitation and selective serotonin re-uptake inhibitors (for patients with mental stress induced myocardial ischaemia) may also be helpful.

Concluding Remarks

Successful treatment of chronic stable angina relies on a precise, considered approach, to match appropriate pharmacological agents, and revascularization strategies, to individual patient characteristics and mechanisms; in order to restore dynamic coronary physiology, prevent ischaemic symptoms and clinical events. The prevailing underlying pathogenic mechanism leading to symptoms of angina can often be uncovered from the details of the clinical history, and is not always obstructive epicardial artery atherosclerosis. Indeed multiple factors may contribute, necessitating a combination of agents acting on distinct ischaemic pathways. Availability of newer agents supported by clinical practice guidelines, such as ranolazine and ivabradine, which are more specifically targeted and do not disturb the systemic circulation, may increase the efficacy of medical therapy. This has the potential to eliminate the need for invasive coronary procedures, and to provide important symptomatic relief and improved quality of life for many patients with refractory symptoms and no options for revascularization.

References

1. Task Force Members, Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery

- disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–164.
 3. National Institute for Health and Clinical Excellence. Management of stable angina. 2011. <http://guidance.nice.org.uk/CG126>.
 4. Campeau L. Letter: grading of angina pectoris. *Circulation*. 1976;54:522–3.
 5. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–95.
 6. Jespersen L, Hvelplund A, Abildstrøm SZ, Pedersen F, Galatius S, Madsen JK, Jørgensen E, Kelbæk H, Prescott E. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–44.
 7. Herrmann J, Kaski JC, Lerman A. Coronary microvascular dysfunction in the clinical setting: from mystery to reality. *Eur Heart J*. 2012;33:2771–2782b.
 8. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High prevalence of a pathological response to acetylcholine testing in patients with stable angina pectoris and unobstructed coronary arteries. The ACOVA Study (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries). *J Am Coll Cardiol*. 2012;59:655–62.
 9. Maseri A, Chierchia S, Kaski JC. Mixed angina pectoris. *Am J Cardiol*. 1985;56:30E–3.
 10. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–292.
 11. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull W, Rosenfeld ME, Schwartz CJ, Wagner WD, Wissler RW. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the

- Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1995;92:1355–74.
12. Narula J, Nakano M, Virmani R, Kolodgie FD, Petersen R, Newcomb R, Malik S, Fuster V, Finn AV. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. *J Am Coll Cardiol*. 2013;61:1041–51.
 13. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657–71.
 14. Steg PG, Bhatt DL, Wilson PWF, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–206.
 15. Gould KL. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA*. 1995;274:894.
 16. Messerli FH, Mancia G, Conti CR, Hewkin AC, Kupfer S, Champion A, Kolloch R, Benetos A, Pepine CJ. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006;144:884–93.
 17. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
 18. Juul-Möller S, Edvardsson N, Jahnmatz B, Rosén A, Sørensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. *Lancet*. 1992;340:1421–5.
 19. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329–39.
 20. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. *JAMA*. 2009;302:849–57.
 21. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
 22. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering

- of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–81.
23. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380:581–90.
 24. Lee CW, Park S-J. Statins for treating stable angina: can statins improve the plaque morphology and angina? *Future Cardiol*. 2013;9:155–8.
 25. Olsson G, Rehnqvist N, Sjögren A, Erhardt L, Lundman T. Long-term treatment with metoprolol after myocardial infarction: effect on 3 year mortality and morbidity. *J Am Coll Cardiol*. 1985;5:1428–37.
 26. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651–8.
 27. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet*. 2006;368:581–8.
 28. Fox KM, Mulcahy D, Findlay I, Ford I, Dargie HJ. The Total Ischaemic Burden European Trial (TIBET). Effects of atenolol, nifedipine SR and their combination on the exercise test and the total ischaemic burden in 608 patients with stable angina. The TIBET Study Group. *Eur Heart J*. 1996;17:96–103.
 29. Rehnqvist N, Hjemdahl P, Billing E, Björkander I, Eriksson SV, Forslund L, Held C, Näsman P, Wallén NH. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J*. 1996;17:76–81.
 30. Bangalore S, Steg G, Deedwania P, et al. β -Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. *JAMA*. 2012;308:1340–9.
 31. Gori T, Parker JD. Nitrate-induced toxicity and preconditioning: a rationale for reconsidering the use of these drugs. *J Am Coll Cardiol*. 2008;52:251–4.
 32. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002;359:1269–75.
 33. Tardif J-C, Ford I, Tendera M, Bourassa MG, Fox K, INITIATIVE Investigators. Efficacy of ivabradine, a new selective I(f) inhibitor,

- compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005;26:2529–36.
34. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs*. 2007;67:393–405.
 35. Fox K, Ford I, Steg PG, Tendera M, Ferrari R, BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;372:807–16.
 36. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol*. 2004;43:1375–82.
 37. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA, Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291:309–16.
 38. Stone PH, Gratsiansky NA, Blokhin A, Huang I-Z, Meng L, Investigators ERICA. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol*. 2006;48:566–75.
 39. Morrow DA, Scirica BM, Chaitman BR, McGuire DK, Murphy SA, Karwowska-Prokopczuk E, McCabe CH, Braunwald E, MERLIN-TIMI 36 Investigators. Evaluation of the glycometabolic effects of ranolazine in patients with and without diabetes mellitus in the MERLIN-TIMI 36 randomized controlled trial. *Circulation*. 2009;119:2032–9.
 40. Ciapponi A, Pizarro R, Harrison J. Trimetazidine for stable angina. *Cochrane Database Syst Rev*. 2005;(4):CD003614.
 41. Mannheimer C, Camici P, Chester MR, et al. The problem of chronic refractory angina; report from the ESC Joint Study Group on the Treatment of Refractory Angina. *Eur Heart J*. 2002;23:355–70.
 42. Henry TD, Satran D, Jolicœur EM. Treatment of refractory angina in patients not suitable for revascularization. *Nat Rev Cardiol*. 2013;11:78–95.

Chapter 3

Beta-Blockers

Esteban López-de-Sá and José López-Sendón

Introduction

The development of beta-blockers (BB) and their subsequent clinical application represents one of the greatest advances in the pharmacological treatment of cardiovascular disease. No other class of drug has shown such diverse therapeutic utility for the treatment and prevention of cardiovascular diseases. The improvement in exercise tolerance, found following sympathectomy in patients with angina pectoris [1] together with the hypothesis from Ahlquist [2], suggesting that there were two types of receptors that modulate a variety of different adrenergic-controlled functions; inspired Black and colleagues to try to find an effective way of blocking these receptors [3, 4].

It was thought that this then “hypothetical” drug could have a possible therapeutic role in cardiac disorders such as angina pectoris. Propranolol was the first successful BB developed, that demonstrated its value in exertional angina [5] and represented a rational approach for preventing anginal attacks in stable angina (SA). Sir James Black was awarded the Nobel

E. López-de-Sá (✉) • J. López-Sendón
Cardiology Department, Hospital Universitario La Paz,
Madrid, Spain
e-mail: e.lopezdesa@terra.com; jlsendon@gmail.com

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_3,
© Springer International Publishing Switzerland 2015

Prize for Medicine in 1988, for the work leading to the development of propranolol (and cimetidine). Regardless of its effect on SA, BB have demonstrated to be effective in several other clinical disorders, many of them frequently present also in patients with chronic ischemic heart disease, such as hypertension, arrhythmias, and heart failure.

Mechanism of Action

The mechanisms of action differ among different BB and some are not yet completely understood. The prevention of the cardiotoxic effects of catecholamines BB is at the centre of their mode of action. The physiologic effects of catecholamines (norepinephrine, epinephrine and dopamine) are mediated by activation of specific alpha and beta adrenergic and dopaminergic receptors, respectively. Beta-receptors are found in the cardiomyocyte, smooth muscle cells, the airways, the arterial wall, the kidneys, and other tissues that are responsive to the effects of the sympathetic nervous system and the stress response. Activation of beta-receptors trigger physiological reactions, such as relaxation of the bronchial muscles, increased heart rate and increased cardiac inotropism. BB competitively inhibit catecholamine binding to beta-receptors, and weaken the effects of stress hormones. At least three different types of beta receptors have been identified [6].

- *Beta-1*, located mainly in the heart and in the kidneys. The stimulation of these receptors produces an increase in heart rate, contractility, and atrioventricular conduction. In the kidneys it inhibits the release of renin from juxtaglomerular cells and thereby reduce the activity of the renin-angiotensin-aldosterone system.
- *Beta-2*, located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. Activation of these receptors results mainly in vasodilatation and bronchodilatation.
- *Beta-3*, which are found in adipose tissue and the heart. Activation of these receptors may mediate catecholamine-induced thermogenesis and may reduce cardiac contractility.

Angina is the clinical manifestation of an imbalance between myocardial oxygen supply and its metabolic requirements. In SA, three main mechanisms influence the occurrence of symptoms: increased heart rate, increased left ventricular wall stress and increased myocardial contractility. In the daily life of patients with SA, exercise and emotional stress precipitate an increased catecholamine release. The release of noradrenaline and adrenaline and their effects on cardiac beta-receptors, in conjunction to reduced activation of the parasympathetic nervous system can trigger attacks of angina. This effect is, at least partially, counterbalanced by the administration of BB, being this the main mechanism whereby BB improve symptoms in patients with SA. The decreased oxygen requirements associated with the administration of BB is mainly due to the bradycardic effect of these agents, which results in a prolongation of the diastole thus improving myocardial perfusion. In addition to their effect on heart rate BB also reduce blood pressure elevation and myocardial contractility during exercise. The mode of action whereby BB lower blood pressure remains controversial. Conventionally, the antihypertensive action of BB is attributed to their cardiac effects. However, long-term reductions in blood pressure appear greater in individuals with high renin forms of hypertension, suggesting that the renal effects of the BB may be important and these are mediated by their action on the beta-1 receptor.

Less beneficial is the fact that the coronary blood flow can be reduced by BB through the blockade of adrenergically-mediated coronary vasodilation [7].

However, this potentially deleterious effect is generally overcome, in patients with SA, by the reductions in heart rate and myocardial oxygen demand. However, it may be relevant in patients with vasospastic angina.

Other proposed mechanisms of action involve an anti-inflammatory effect with the long-term use of BB in patients with chronic stable ischaemic heart disease. A nonrandomized study documented significantly lower levels of circulating C-reactive protein in patients receiving BB therapy compared with controls [8].

There are many additional properties that several BB may have and different pharmacokinetics, which clinicians should consider when choosing a particular agent (Table 3.1):

- *Selectivity*: Since the desired effects in angina are mediated by blockade of beta1-receptors, which predominate in the heart, beta-1 “cardioselective” agents are generally preferred. However, receptor selectivity is not absolute and is lost at high doses. There are also BB with alpha-adrenergic receptors blocker activity such as carvedilol.
- *Intrinsic sympathomimetic activity (ISA)*: Paradoxically, some BB can exert a weak agonist response. This manifests as a beta-stimulant effect when background adrenergic activity is low (e.g. during sleep) but BB occurs when adrenergic activity is increased (e.g. during exercise) (Table 3.1).
- *Membrane-stabilising activity*: This confers a local anaesthetic and anti-arrhythmic effect.

At least from a theoretical point of view, and as far as the treatment of SA is concerned, it would be appropriate to use selective beta-1 blockers. The characteristics of the most commonly used BB are shown on Table 3.1.

It has to be considered that it has been suggested that there may be an impact of beta-1 receptor polymorphisms on the individual susceptibility to heart failure, the individual response to BB therapy and heart failure prognosis [9].

This individual susceptibility has not been so far shown to affect the efficacy of these drugs in the treatment of SA and hypertension.

Pharmacokinetics

BB vary in their gastrointestinal absorption, first-pass hepatic metabolism, lipid solubility, protein binding, body distribution, blood-brain barrier permeability, concentration in the heart, rate of hepatic biotransformation, pharmacologic activity of metabolites, and renal clearance of the drug and its

TABLE 3.1 Properties of beta-blocking drugs

Drug	Partial agonist activity	Lipid solubility	Active metabolites	Peripheral vasodilatation
<i>I. Non-selective beta-blocker (beta-1 and beta-2)</i>				
Alprenolol	+	Moderate	Yes	
Carteolol	+	Low	Yes (weak)	
Nadolol	0	Low	No	
Oxprenolol	++	Moderate	No	
Penbutolol	+	Moderate	Yes (weak)	
Pindolol	++	High	No	
Propranolol	0	High	Yes	
Sotalol	0	Low	No	
Timolol	0	High	No	
<i>II. Selective beta-blocker (beta-1)</i>				
Acebutolol	+	Moderate	Yes	
Atenolol	0	Low	No	
Betaxolol	0	Moderate	No	
Bisoprolol	0	Moderate	No	
Celiprolol	+	Moderate	No	+
Esmolol	0	Low	No	
Metoprolol	0	High	Yes (weak)	
Nebivolol	0	High	Yes	+
<i>III. Alfa and beta-blocker (alfa-1, beta-1 and beta-2)</i>				
Bucindolol	+	Moderate	Yes	+
Carvedilol	0	Moderate	Yes	+
Labetalol	+	Low	No	+

metabolites. On the basis of their pharmacokinetic properties, BB can be classified into two broad categories differentiated on the basis of lipophilicity or hydrophilicity [10].

The lipid-soluble group are completely absorbed by the small intestine, metabolized by the liver and penetrate the brain easily and rapidly in high concentrations. This results in low bioavailability, substantial interpatient variability in 'steady-state' plasma drug concentrations, rapid elimination half-lives and the possibility of drug interactions with other drugs that affect hepatic enzymes. The blood-brain permeability may result in centrally mediated adverse effects such as vivid dreams. This group of BB is represented by propranolol, timolol, metoprolol and oxprenolol. On the contrary water-soluble BB are incompletely absorbed through the gut, are cleared, unchanged, by the kidney, and penetrate the central nervous system less easily, causing less central side-effect. They show less interpatient variation in bioavailability, have longer elimination half-lives and do not interact with drugs affecting hepatic enzymes. Atenolol, sotalol and nadolol are examples of water-soluble BB [10].

Between these two extremes, there are several drugs like betaxolol, bisoprolol and pindolol, which are cleared partly by the liver and partly by the kidney. Their clearance is only altered by severe renal or hepatic disease, and they do not appear to interact with enzyme inducers or inhibitors.

Adverse Effects

Generally, BB are well tolerated, but like most pharmacological agents they are not exempt from side effects, sometimes severe. These effects are usually manifest when high doses are used.

Cardiovascular

The cardiovascular adverse effects of BB result from their mechanism of action. They may cause bradycardia and AV block. These effects are seen mainly in patients with impaired

sinus node function and some degree of AV-node conduction impairment. Although its use is beneficial in patients with heart failure, in patients with acute decompensation or those with severe ventricular dysfunction, BB may exacerbate symptoms due to its negative inotropic effect. For this reason, in patients with associated heart failure the starting dose of BB should be very low and up-titration should be carried out cautiously, in small dose increments.

The increased peripheral vascular resistance, induced by non-selective agents, can cause or worsen symptoms of peripheral artery disease i.e. claudication [11].

In the presence of peripheral vascular disease, the use of beta-1 selective BB, should be preferred. A meta-analysis of published studies in patients with mild to moderate peripheral vascular disease, mainly treated with beta-1 selective BB, found no exacerbation of symptoms by these agents [12].

Therefore, the traditional clinical concerns may be exaggerated, especially in patients with mild to moderate peripheral vascular disease receiving selective beta-1 blockers.

Metabolic

The BB do not modify glucose or insulin levels in non-diabetic patients, or the incidence of hypoglycaemia in diabetic patients treated with insulin or oral hypoglycaemic agents. However, non-selective BB reduce the symptoms associated with hypoglycaemia (tremor, anxiety, sweating and tachycardia) and delay the recovery of blood glucose following administration of insulin. Beta-1 selective BB produce less interference with glucose recovery to normal levels, so that they will be preferred at least in insulin dependent patients. In any case, the clinical benefit of treatment with BB outweighs the risk, at least after myocardial infarction [13].

Newer vasodilating BB have a more favourable metabolic profile; carvedilol, a combined non-selective and alpha-1 blocker, also prevents lipid peroxidation. In a small study comparing the metabolic effects of carvedilol and metoprolol [14] the mean HbA1c insulin sensitivity improved with

carvedilol (-9.1% ; $P=0.004$) but not with metoprolol (-2.0% ; $P=0.48$); the between-group difference was -7.2% (95 % CI, -13.8% to -0.2% ; $P=0.004$). Blood pressure was similar between groups. Progression to microalbuminuria was less frequent with carvedilol than with metoprolol (6.4% vs 10.3% ; odds ratio, 0.60; 95 % CI, 0.36–0.97; $P=0.04$) [14].

The administration of BB interfere with lipid metabolism and are associated with alteration of serum triglyceride and HDL-cholesterol concentrations. The effect of beta blockers on serum lipids varies with the profile of each individual agent, and may be more prominent among smokers [15].

With the exception of the non-selective BB sotalol, BB therapy has little influence on the serum total cholesterol or LDL-cholesterol concentrations [16].

The magnitude of these changes in serum lipids does not significantly differ between beta-1 selective or not. Two BB possessing ISA, acebutolol and pindolol, did not increase serum triglycerides and serum total cholesterol or LDL-cholesterol. The BB, selective or not, increase plasma levels of triglycerides and VLDL cholesterol and decrease of HDL cholesterol; levels of total cholesterol and LDL cholesterol usually remain unchanged or even increased. Carvedilol seems to have a better profile on lipids at least in diabetic patients [17].

The GEMINI (Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensive) trial compared the effects of carvedilol and metoprolol on lipids after 5 months of therapy on 1,235 participants with type 2 diabetes and hypertension who were receiving renin-angiotensin system blockers [17].

In the metoprolol group, triglycerides and non-HDL cholesterol increased and both the LDL and the HDL cholesterol levels decreased. In the carvedilol group, total LDL and HDL cholesterol decreased, non-HDL cholesterol was unchanged and triglycerides increased. Comparing the carvedilol and metoprolol tartrate groups, there was no statistically significant difference in LDL and HDL cholesterol levels, but there was a significantly greater decrease with carvedilol in total cholesterol

[−2.9 %, 95 % confidence interval (CI) −4.60 to −1.15, $p < 0.001$], triglycerides (−9.8 %, 95 % CI −13.7, −5.75 %, $p < 0.001$) and non-HDL cholesterol (−4.03 %, 95 % CI −6.3 to −1.8, $p < 0.0006$). At the end of the study, significantly more participants in the metoprolol tartrate group had had initiation of statin therapy or the statin dose increased than those in the carvedilol group (11 vs. 32 %, $p = 0.04$) [17].

Pulmonary

The blockade of the beta-2 receptor can lead to an increase of airway resistance and are contraindicated in patients with asthma or chronic obstructive pulmonary disease. A history of asthma, should be considered a contraindication to the use of any BB, but chronic obstructive pulmonary disease is not a contraindication unless there is a significant reactive airway disease [18].

Other Adverse Events

Central effects (headache, depression, sleep disturbances, insomnia and vivid dreams), less common with hydrophilic drugs, may appear after treatment with BB [19].

Some male patients treated with BB may suffer an aggravation of erectile dysfunction and loss of libido.

Abrupt discontinuation of BB after chronic treatment can lead to rebound symptoms (i.e., hypertension, arrhythmias, exacerbated angina). This increased risk is related with upregulation of beta-receptors during chronic treatment.

Clinical Efficacy in Stable Angina

The two aims of the pharmacological treatment of patients with chronic SA are to improve symptoms and to prevent adverse events. The first demonstrated efficacy of BB in the

clinical setting was in the early 60s, when Sir James Black, tested nethalide and proved its effectiveness in controlling symptoms of SA [3].

Subsequent studies of Prichard and Warren tested the effect of propranolol and its dose-dependent action on the treatment of SA [20, 21].

Shortly, other agents with different degrees of selectivity for beta-1 receptors, showed also improvement of symptoms, increase in exercise tolerance and a delayed onset of ST depression on the stress test compared with placebo in patients with SA [22, 23].

Effectiveness Versus Placebo

BB are highly effective to control exercise induced angina. They have demonstrated improvement in exercise capacity in several small placebo controlled trials, and to reduce or suppress both symptomatic and asymptomatic ischaemic episodes [5, 20, 24, 25].

No clear clinical differences have been verified, however, between different BB. Evidence has shown that the BB do not modify the threshold of rate pressure product of appearance of angina, but they delay the reaching of that stage. Decreased exercise heart rate, wall stress and myocardial contractility caused by BB keep oxygen demand below the threshold at which angina occur. The effect of reducing the rate of events in patients with SA has not been specifically studied in large trials, and most of the information comes from studies in the post-infarction period. Nevertheless, in the ASIST trial (Atenolol Silent Ischemia Study) 306 outpatients patients with Canadian Cardiovascular Society class I or II SA, and inducible ischemia were randomized to receive either atenolol (100 mg/day) or placebo during 1 year of follow-up [25].

In this trial the event-free survival (death, resuscitated ventricular arrhythmia, myocardial infarction, hospitalization for unstable angina, aggravation of angina, or revascularization)

improved in atenolol-treated patients ($P < 0.007$), who had an prolonged time to onset of first adverse event (120 versus 79 days) and fewer total first events compared with placebo (relative risk, 0.44; 95 % confidence intervals, 0.26–0.75; $P = 0.001$).

The main objective of the Beta-Blocker Pooling Project was to collect and analyse data from the major long-term secondary prevention trials in order to determine whether there are subsets of post-infarction patients who benefit to a greater or lesser extent from BB therapy than the average patient population [26].

The overall, 1-year mortality, in the nine trials involving 13,679 patients analysed, was 24 % lower in the BB group compared to placebo. Subgroups in the placebo arms with high mortality (e.g. patients with a history of previous myocardial infarction, angina pectoris, mechanical or electrical complications, and digitalis usage) seemed to be particularly benefited under treatment with BB. Patients in the lower risk subgroups also appeared to benefit from BB, but this benefit was smaller in absolute terms and inconsistent across the trials. Based on these findings it is recommended to treat patients with prior myocardial infarction and SA to prevent death, especially sudden cardiac death, and myocardial infarction (Table 3.2) [27, 28].

Its use is also recommended in the absence of prior myocardial infarction, in patients with systolic ventricular dysfunction, given the improved prognosis associated with BB usage in patients with heart failure [29].

Effectiveness of BB Versus Other Antiischemic Drugs

There are therapies that improve prognosis and treatments that only improve symptoms. Regarding prognosis, there are no studies that demonstrate an advantage of BB over other anti-anginal drugs. However, in patients with stable coronary heart disease with previous myocardial infarction and patients

TABLE 3.2 Use of BB in chronic, stable ischaemic heart disease: ESC guidelines

Setting	Class	Evidence
<i>Previous infarction.</i>		
To improve survival	I	A
To reduce reinfarction	I	A
To prevent/control ischaemia	I	A
<i>No previous infarction</i>		
To improve survival	I	C
To reduce reinfarction	I	B
To prevent/control ischaemia	I	A

with heart failure and depressed systolic function, there is evidence for improved prognosis with BB treatment [30, 31].

A meta-analysis conducted over a decade ago, of 90 clinical trials that directly compared antianginal agents, including long-acting nitrates, beta-blockers, and calcium antagonists regarding their relative efficacy on exercise tolerance [32].

Regarding the comparison between BB and calcium channel blockers, only the TIBET [33] and APSIS [34] trials were relatively long-term (>6 months) studies and accounted for 103 of the 116 cardiac events recorded in all trials. The pooled odds ratio (OR) for beta-blockers was 0.98 (95 % confidence interval [CI], 0.66–1.47). Analysis of the 59 shorter term trials, showed no difference in cardiac death or myocardial infarction (OR, 0.90; 95 % CI, 0.40–2.00) among agents. When both long- and short-term follow up trials were assessed together, there were 57 events in the BB and 59 in the calcium antagonist groups. The OR for risk with BB was 0.97 (95 % CI, 0.67–1.38). No significant differences were found when the trials were grouped by type of calcium antagonist (nifedipine vs non-nifedipine agents) or duration of action. Compared with calcium antagonists, BB were associated with 0.31 (95 % CI, 0.00–0.62) fewer episodes of angina per week ($P=0.05$). When the comparison was restricted to trials comparing BB

with nifedipine, there were 0.63 (95 % CI, 0.23–1.00) fewer angina events per week with beta-blockers. Despite the differences in the frequency of angina, nitroglycerin tablet use per week and exercise tolerance (time to ischemia) between calcium antagonists and BB was not significantly different [32].

On the other hand, patients were less likely to discontinue BB than calcium antagonists due to adverse effects. In the above mentioned meta-analysis only 6 studies compared BB with long-acting nitrates [32].

There were no significant differences between BB and long-acting nitrates in any of the outcomes measured. Nevertheless, a trend ($P=0.08$) toward higher nitroglycerin use per week was noted for patients who were taking long-acting nitrates.

Regarding other antianginal drugs, in the double-blind INITIATIVE trial, 939 patients with SA were randomized to receive atenolol or ivabradine [35].

The effect on treadmill exercise tests and number of anginal attacks were similarly reduced by both drugs. The efficacy of propranolol was compared with those of trimetazidine in the Trimetazidine European Multicenter Study [36].

After 3 months, similar anti-anginal efficacy was observed in the propranolol and trimetazidine, groups. There was however, a decreased in ischaemic episodes on Holter monitoring in the 46 % patients who experienced ambulatory ischaemia in the group assigned to atenolol. Taken all of the above together, BB remain, to be first-line treatment for patients with chronic SA [27].

Betablockers in Combination with Other Antianginal Drugs

The CLARIFY registry studied 33,280 patients with chronic ischemic heart disease from 45 countries [37].

This registry showed that although 56 % of patients had previously undergone percutaneous coronary intervention and 23 % coronary surgery, 22 % of the patients continued to

have anginal episodes, with a functional class II in 12 % and class III in 4 % according to Canadian Cardiovascular Society classification (CCS). Over the last two decades the results of percutaneous coronary intervention have improved [38].

Probably the better results are in part related with improved management of drug therapy and an increased use of BB after the procedure. It has been reported that, even with a BB use in 83 % of the cases, at least 18 % of the patients suffer episodes of angina during the first year after the procedure [38].

Therefore even in patients who have no side effects with BB combination therapy with different antianginals is often required.

Early studies in the 1960s showed that the association of propranolol with isosorbide dinitrate increased exercise tolerance, decreased attacks of angina and increased time to onset of ischemic ECG changes compared with placebo [39].

During the 1970s several studies showed a synergistic effect of nitrates and BB. However, there is no randomized trial evidence that combination therapy improves symptoms and long-term nitrate treatment seems to be less effective than BB treatment [40].

BB are often given in association with calcium channel blockers, especially with dihydropyridine calcium antagonists. The association of BB with non-dihydropyridine calcium antagonists such as diltiazem or verapamil can improve symptoms but produce a very high rate of complications. A recent meta-analysis examined 28 studies (37 comparisons) of calcium channel blockers added to a BB ($n=2,468$) and 12 studies (12 comparisons) of a BB added to a calcium channel blocker ($n=1,489$) [41].

Thus, the addition of a calcium channel blocker to BB may be expected to yield nearly a 18 % reduction in angina frequency and approximately a 30 % reduction when the BB is added to a calcium channel blocker (Fig. 3.1).

The ASSOCIATE study [42] explored the effect of ivabradine versus placebo in association with BB in 889 patients with chronic ischemic heart disease in sinus rhythm,

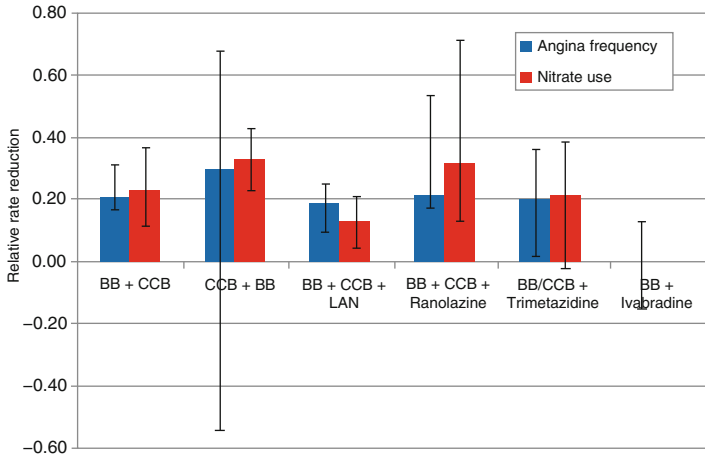


FIGURE 3.1 Relative rate reduction $\pm 95\%$ confidence interval in clinical outcomes obtained from a meta-analysis of clinical trials studying the effect of adding other antianginal drugs to a beta-blocker or a calcium channel blocker. *BB* beta-blocker, *CCB* calcium channel blocker, *LAN* long-acting nitrate [46]

heart rate at rest ≥ 60 bpm and positive symptom-limited exercise tolerance tests. The addition of ivabradine increased significantly all stress test parameters, but did not reduce significantly the frequency of spontaneous angina attacks compared with placebo. By contrast, in a post hoc analysis of the BEAUTIFUL trial, the effect of adding ivabradine to conventional treatment (90 % on BB) was studied in patients with CCS classes II and III and baseline heart rate ≥ 70 bpm offered positive results regarding to outcome [43].

In this analysis there was a significant reduction of 24 % in the incidence of the primary endpoint (cardiovascular death or hospitalization for myocardial infarction or heart failure) and a significant 42 % reduction in the hospitalization for myocardial infarction ($p=0.02$).

The metabolic modulators such as trimetazidine and ranolazine have been assessed as add on therapy to BB in several

trials. The TRIMPOL II trial in 426 patients with stable, effort-induced angina and documented coronary artery disease received either placebo or trimetazidine 20 mg three times daily in addition to metoprolol 50 mg twice daily [44].

Therapy with trimetazidine plus metoprolol produced significant improvements in exercise stress tests and symptoms of angina compared with metoprolol alone. Regarding the association of BB with ranolazine, the CARISA trial, which included 823 patients with severe angina treated with BB or calcium antagonists [45], showed a reduction in number of angina attacks from 4.5 to 3.3 ± 0.2 weeks ($p < 0.05$) without hemodynamic effects.

Summary

BB are the cornerstone of SA treatment. Their effects are particularly suited for the management of effort induced angina as they reduce myocardial oxygen demand. The clinical benefits of BB in SA are highly reproducible. Despite the availability of other antianginal agents in the past few years, treatment guidelines continue to recommend the use of BB as first line. Although BB therapy has not shown to improve prognosis in SA patients in general, some subgroups of patients at higher risk (infarction, ventricular dysfunction, failure heart) may also show an improved outcome with BB.

References

1. Lindgren I. Angina pectoris; a clinical study with special reference to neurosurgical treatment. *Acta Med Scand Suppl.* 1950;243:1–203.
2. Ahlquist RP. A study of the adrenotropic receptors. *Am J Physiol.* 1948;153(3):586–600.
3. Black JW, Stephenson JS. Pharmacology of a new adrenergic beta-receptor-blocking compound (Nethalide). *Lancet.* 1962;2(7251):311–4.
4. Black JW, Crowther AF, Shanks RG, Smith LH, Dornhorst AC. A new adrenergic betareceptor antagonist. *Lancet.* 1964;1(7342):1080–1.

5. Hamer J, Grandjean T, Melendez L, Sowton GE. Effect of propranolol (inalderal) in angina pectoris: preliminary report. *Br Med J*. 1964;2(5411):720–3.
6. Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown Jr TG. Differentiation of receptor systems activated by sympathomimetic amines. *Nature*. 1967;214(5088):597–8.
7. Jackson CV, Pope TK, Lucchesi BR. Coronary artery vasodilation in the canine: physiological and pharmacological roles of beta-adrenergic receptors. *J Cardiovasc Pharmacol*. 1987;10(2):196–204.
8. Jenkins NP, Keevil BG, Hutchinson IV, Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med*. 2002;112(4):269–74.
9. Liu WN, Fu KL, Gao HY, Shang YY, Wang ZH, Jiang GH, Zhang Y, Zhang W, Zhong M. beta1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to beta-blocker therapy and prognosis. *PLoS One*. 2012;7(7):e37659.
10. Frishman WH. beta-Adrenergic blockade in cardiovascular disease. *J Cardiovasc Pharmacol Ther*. 2013;18(4):310–9.
11. Frohlich ED, Tarazi RC, Dustan HP. Peripheral arterial insufficiency. A complication of beta-adrenergic blocking therapy. *JAMA*. 1969;208(13):2471–2.
12. Paravastu SC, Mendonca DA, Da Silva A. Beta blockers for peripheral arterial disease. *Cochrane Database Syst Rev*. 2013;(9):CD005508.
13. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med*. 1998;339(8):489–97.
14. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright Jr JT, Oakes R, Lukas MA, Anderson KM, Bell DS, GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292(18):2227–36.
15. Vyssoulis GP, Karpanou EA, Pitsavos CE, Toutouza MA, Paleologos AA, Toutouzas PK. Dyslipidemic effects of cigarette smoking on beta-blocker-induced serum lipid changes in systemic hypertension. *Am J Cardiol*. 1991;67(11):987–92.
16. Lehtonen A. Effect of beta blockers on blood lipid profile. *Am Heart J*. 1985;109(5 Pt 2):1192–6.

17. Bell DS, Bakris GL, McGill JB. Comparison of carvedilol and metoprolol on serum lipid concentration in diabetic hypertensive patients. *Diabetes Obes Metab.* 2009;11(3):234–8.
18. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol.* 2001;37(7):1950–6.
19. Salem SA, McDevitt DG. Central effects of beta-adrenoceptor antagonists. *Clin Pharmacol Ther.* 1983;33(1):52–7.
20. Warren SG, Brewer DL, Orgain ES. Long-term propranolol therapy for angina pectoris. *Am J Cardiol.* 1976;37(3):420–6.
21. Prichard BN. Propranolol in the treatment of angina: a review. *Postgrad Med J.* 1976;52 Suppl 4:35–41.
22. Hernandez-Canero A, Gonzalez A, Cardonne A, Perez-Medina T, Garcia-Barreto D. Effect of atenolol in angina pectoris of effort. *Cor Vasa.* 1972;20(2):99–103.
23. Keyrilainen O, Uustialo A. Effects of the cardioselective beta-blocker metoprolol in angina pectoris. A subacute study with exercise tests. *Ann Clin Res.* 1975;7(6):433–41.
24. Gillam PM, Prichard BN. Use of propranolol in angina pectoris. *Br Med J.* 1965;2(5457):337–9.
25. Pepine CJ, Cohn PF, Deedwania PC, Gibson RS, Handberg E, Hill JA, Miller E, Marks RG, Thadani U. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST). *Circulation.* 1994;90(2):762–8.
26. The Beta-Blocker Pooling Project (BBPP): subgroup findings from randomized trials in post infarction patients. The Beta-Blocker Pooling Project Research Group. *Eur Heart J.* 1998;9(1):8–16.
27. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabate M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, ESC Committee for Practice Guidelines, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, HAMILIOS M, Hasdai D, Husted S, James SK, Kervinen

- K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Ryden L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirim A, Zamorano JL (2013) 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949–3003.
28. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C, Task Force on Beta-Blockers of the European Society of Cardiology. Expert consensus document on beta-adrenergic receptor blockers. *Eur Heart J*. 2004;25(15):1341–62. doi:[10.1016/j.ehj.2004.06.002](https://doi.org/10.1016/j.ehj.2004.06.002).
 29. Abraham WT, Singh B. Ischemic and nonischemic heart failure do not require different treatment strategies. *J Cardiovasc Pharmacol*. 1999;33 Suppl 3:S1–7.
 30. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D (2012) ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 33(20):2569–619. doi:[10.1093/eurheartj/ehs215](https://doi.org/10.1093/eurheartj/ehs215).
 31. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2012;33(14):1787–847.
 32. Heidenreich PA, McDonald KM, Hastie T, Fadel B, Hagan V, Lee BK, Hlatky MA. Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina. *JAMA*. 1999;281(20):1927–36.

33. Dargie HJ, Ford I, Fox KM. Total Ischaemic Burden European Trial (TIBET). Effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome in patients with chronic stable angina. The TIBET Study Group. *Eur Heart J*. 1996;17(1):104–12.
34. Rehnqvist N, Hjemdahl P, Billing E, Björkander I, Eriksson SV, Forslund L, Held C, Nasman P, Wallen NH. Effects of metoprolol vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J*. 1996; 17(1):76–81.
35. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K, INITIATIVE Investigators. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J*. 2005;26(23):2529–36.
36. Detry JM, Sellier P, Pennaforte S, Cokkinos D, Dargie H, Mathes P. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina. Trimetazidine European Multicenter Study Group. *Br J Clin Pharmacol*. 1994;37(3):279–88.
37. Ferrari R, Abergel H, Ford I, Fox KM, Greenlaw N, Steg PG, Hu D, Tendera M, Tardif JC, CLARIFY Investigators. Gender- and age-related differences in clinical presentation and management of outpatients with stable coronary artery disease. *Int J Cardiol*. 2013;167(6):2938–43.
38. Venkitachalam L, Kip KE, Mulukutla SR, Selzer F, Laskey W, Slater J, Cohen HA, Wilensky RL, Williams DO, Marroquin OC, Sutton-Tyrrell K, Bunker CH, Kelsey SF, NHLBI-Sponsored Dynamic Registry Investigators. Temporal trends in patient-reported angina at 1 year after percutaneous coronary revascularization in the stent era: a report from the National Heart, Lung, and Blood Institute-sponsored 1997–2006 dynamic registry. *Circ Cardiovasc Qual Outcomes*. 2009;2(6):607–15.
39. Russek HI. Propranolol and isosorbide dinitrate synergism in angina pectoris. *Am J Cardiol*. 1968;21(1):44–54.
40. Lemos KF, Rabelo-Silva ER, Ribeiro LW, Cruz LN, Polanczyk CA. Effect of nitrate withdrawal on quality of life and adherence to treatment in patients with stable angina: evidence from a randomized clinical trial. *Coron Artery Dis*. 2014;25(3):215–23.
41. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2014 pii: 2047487314533217. [Epub ahead of print].

42. Tardif JC, Ponikowski P, Kahan T, ASSOCIATE Study Investigators. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J*. 2009;30(5):540–8.
43. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, BEAUTIFUL Investigators. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur Heart J*. 2009;30(19):2337–45.
44. Szwed H, Sadowski Z, Elikowski W, Koronkiewicz A, Mamcarz A, Orszulak W, Skibinska E, Szymczak K, Swiatek J, Winter M. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). *TRIMetazidine in POLand*. *Eur Heart J*. 2001;22(24):2267–74.
45. Chaitman BR, Pepine CJ, Parker JO, Skopal J, Chumakova G, Kuch J, Wang W, Skettino SL, Wolff AA, Combination Assessment of Ranolazine in Stable Angina Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial. *JAMA*. 2004;291(2):309–16. doi:[10.1001/jama.291.3.309](https://doi.org/10.1001/jama.291.3.309).
46. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2014. doi:[10.1177/2047487314533217](https://doi.org/10.1177/2047487314533217).

Chapter 4

Calcium Channel Blockers

Peter Ong and Udo Sechtem

Background and Pharmacology

Calcium channel blockers (CCB) were first described in the 1960s by the German pharmacologist Albrecht Fleckenstein. The pharmacological mechanism of action lies in the blockage of calcium flow through calcium channels that are embedded in the membrane of many cells including vascular smooth muscle cells and cardiomyocytes. There are several types of calcium channels, and a number of different classes of calcium channel blockers, but almost all of them preferentially block the L-type voltage-gated calcium channel. The latter is responsible for excitation-contraction coupling of skeletal, smooth, and cardiac muscle. Moreover, L-type voltage-gated calcium channels are also involved in the conduction of the pacemaker signal in the heart. Three different classes of CCBs have been described with different properties. The class of CCBs known as dihydropyridines mainly affects

The authors declare that no conflict of interest exists in conjunction with the preparation of this book chapter.

P. Ong, MD (✉) • U. Sechtem, MD
Department of Cardiology, Robert-Bosch Krankenhaus,
Auerbachstr. 110, Stuttgart 70376, Germany
e-mail: Peter.Ong@rbk.de; Udo.Sechtem@rbk.de

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_4,
© Springer International Publishing Switzerland 2015

arterial vascular smooth muscle cells to lower blood pressure by causing vasodilation (e.g. amlodipine). The phenylalkylamine class of CCBs (e.g. verapamil) mainly acts on cardiac cells and has negative inotropic and negative chronotropic effects. The benzothiazepine class of CCBs (e.g. diltiazem) combines effects of the previous two classes.

Dihydropyridine CCBs

Dihydropyridine calcium channel blockers are derived from the molecule dihydropyridine and are often used to reduce systemic vascular resistance and arterial pressure. As a side effect they can cause hypotension which may lead to reflex tachycardia, which can be detrimental for patients with ischemic symptoms because of the increase in myocardial oxygen demand. This CCB class can easily be identified by the suffix “-dipine” (see Table 4.1) and side effects of these drugs may include but are not limited to dizziness, headache, facies rubra, legs and ankle swelling, constipation or gingival overgrowth (Table 4.2).

Non-dihydropyridine CCBs

Phenylalkylamine calcium channel blockers (e.g. verapamil) are rather selective for the myocardium and reduce myocardial oxygen demand. They have minimal vasodilatory effects

TABLE 4.1 Frequently used CCBs and their usual dose

Name of drug	Type of CCB	Standard dose
Amlodipine	Dihydropyridine	Up to 10 mg per day
Lercanidipine	Dihydropyridine	Up to 20 mg per day
Nifedipine	Dihydropyridine	Up to 60 mg per day
Nitrendipine	Dihydropyridine	Up to 40 mg per day
Verapamil	Phenylalkylamine	Up to 480 mg per day
Diltiazem	Benzothiazepine	Up to 360 mg per day

TABLE 4.2 Major side-effects, contra-indications, drug–drug interactions of CCBs

CCB class	Major side effects	Contraindications	Drug–drug interactions
Non-dihydro-pyridines	Bradycardia Heart conduction defect Low ejection fraction Constipation Gingival hyperplasia	Low heart rate or heart rhythm disorder Sick sinus syndrome Congestive heart failure Low blood pressure	Cardiodepressant (β -blockers, flecainide) CYP3A4 substrates
Dihydro-pyridines	Headache Ankle swelling Fatigue Flushing Reflex tachycardia	Cardiogenic shock Severe aortic stenosis Obstructive cardiomyopathy	CYP3A4 substrates

Adapted from ESC 2013 SCAD Guidelines [8]

compared with dihydropyridines and therefore cause less reflex tachycardia, making it appealing for treatment of angina. Their major mechanism of action is causing negative inotropy. Benzothiazepine calcium channel blockers (e.g. diltiazem) belong to the benzothiazepine class of compounds and are an intermediate class between phenylalkylamine and dihydropyridines in their selectivity for vascular calcium channels. By having both cardiac depressant and vasodilator actions, benzothiazepines are able to reduce arterial pressure without producing the same degree of reflex cardiac stimulation caused by dihydropyridines.

CCBs for Treatment of Chronic Stable Angina

Dihydropyridines

Nifedipine is a strong arterial vasodilator with a favorable side-effect profile. The substance has especially been tested

in hypertensive anginal patients when added to β -blockade [1]. In a large placebo-controlled trial long-acting nifedipine in patients with stable coronary artery disease was shown to be safe and significantly reduced the need for coronary angiography and cardiovascular interventions (ACTION trial). There are only few contra-indications to nifedipine (i.e. severe aortic stenosis, obstructive cardiomyopathy, or heart failure) and combination with β -blockade is advisable. Vasodilatory side-effects of nifedipine include headache and ankle swelling (Table 4.2). Amlodipine has a long half-life and is well tolerated. It is therefore an attractive once-a-day anti-anginal and antihypertensive agent compared to other CCBs that need to be taken twice or three times daily. In patients with coronary artery disease and normal blood pressure ($n=1,991$), amlodipine reduced cardiovascular events in a 24-month trial compared to placebo (CAMELOT trial, [2]).

Non-dihydropyridine

The phenylalkylamine calcium channel blocker verapamil has a wide range of approved indications such as exercise induced angina, vasospastic angina, unstable angina pectoris, supraventricular tachycardias and hypertension. Although good safety is suggested, there may be a risk of heart block, bradycardia or heart failure. Compared with metoprolol, the anti-anginal properties were similar [3]. Compared with atenolol in patients with hypertension and coronary artery disease, verapamil caused less new onset of diabetes mellitus, fewer anginal attacks [4], and less depression [5]. It should, however be noted, that β -Blockade combined with verapamil is not recommended due to the risk of heart block. In such instances, β -blockers should be combined with dihydropyridine CCBs. Due to its low side-effect profile, diltiazem has advantages, compared with verapamil, in the treatment of exercise induced angina pectoris [6]. As mentioned above, diltiazem combines the properties of verapamil and dihydropyridines (i.e. negative inotropic effect and peripheral

vasodilation). Outcome studies comparing diltiazem and verapamil are currently not available. Diltiazem should not be used in combination with a β -blocker and the use is also not recommended in patients with coronary artery disease and impaired left ventricular function. The concomitant use of a dihydropyridine CCB together with a β -blocker has been shown to be beneficial in patients with chronic stable angina. This has recently been confirmed in a meta-analysis by Belsey et al. [7]. Moreover, the current ESC guidelines on the management of patients with stable coronary artery disease recommend using CCBs as first-line treatment to control heart rate and symptoms [8].

Calcium Channel Blockers for Treatment of Vasospastic Angina

CCBs have effectively been used in the treatment of vasospastic angina [9] and the available evidence for CCBs for the treatment of vasospastic angina has resulted in a class I recommendation by the Japanese Circulation Society [10]. Studies have shown efficacy for nifedipine, verapamil, diltiazem and amlodipine and these drugs can be used safely at usual doses ([11], Table 4.1). Early studies have shown efficacy for nifedipine in a dose between 40 and 160 mg per day. In this study by Antman et al. [12], nifedipine reduced the mean weekly rate of anginal attacks from 16 to 2 and also led to a significant reduction in nitroglycerin consumption. Angina attacks were controlled in 63 % of all 127 patients in this study. In another study by Pesola et al., diltiazem was tested against placebo in a dose of 60 mg twice daily. In this double-blind crossover study, diltiazem significantly reduced the frequency of angina attacks during 72 h of treatment from 43 to 5 [13]. Amlodipine has also been shown to be effective in the treatment of vasospastic angina. In this randomized placebo-controlled trial of amlodipine by Chahine et al. patients were treated with either 10 mg of amlodipine once

daily or placebo for 4 weeks. The rate of anginal episodes decreased significantly with amlodipine treatment compared with placebo and the intake of nitroglycerin tablets showed a similar trend [14]. Recently, there is cumulating evidence that benidipine is more efficacious in the treatment of vasospastic angina compared to other CCBs. Nishigaki et al. performed a meta-analysis in patients who were treated with either benidipine (n=320), amlodipine (n=308), nifedipine (n=182) or diltiazem (n=960) and found that the rate of major cardiovascular events (cardiac death, myocardial infarction, admission for heart failure, stroke and aortic aneurysm) was lowest in the patients treated with benidipine. This favorable effect may be due to the fact that benidipine has been shown to attenuate endothelial cell injury leading to increased cardiac nitric oxide levels. It should however be noted that to the best of our knowledge, benidipine is currently not available outside Asia. Independent of the CCB used for treating vasospastic angina it is often sensible to start with a low dose and increase the dose when the drug is well tolerated. Moreover, the choice of CCB should be tailored to the patients individual preferences and comorbidities.

References

1. Poole-Wilson PA, Lubsen J, Kirwan BA, van Dalen FJ, Wagener G, Danchin N, Just H, Fox KA, Pocock SJ, Clayton TC, Motro M, Parker JD, Bourassa MG, Dart AM, Hildebrandt P, Hjalmarson A, Kragten JA, Molhoek GP, Otterstad JE, Seabra-Gomes R, Soler-Soler J, Weber S. Effect of long-acting nifedipine on mortality and cardiovascular morbidity in patients with stable angina requiring treatment (ACTION trial): randomised controlled trial. *Lancet*. 2004;364:849–57.
2. Nissen SE, Tuzcu EM, Libby P, Thompson PD, Ghali M, Garza D, Berman L, Shi H, Buebendorf E, Topol EJ. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–25.
3. Rehnqvist N, Hjemdahl P, Billing E, Bjorkander I, Eriksson SV, Forslund L, Held C, Nasman P, Wallen NH. Effects of metoprolol

- vs verapamil in patients with stable angina pectoris. The Angina Prognosis Study in Stockholm (APSIS). *Eur Heart J*. 1996;17:76–81.
4. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, Mancina G, Cangiano JL, Garcia-Barreto D, Keltai M, Erdine S, Bristol HA, Kolb HR, Bakris GL, Cohen JD, Parmley WW. A calcium antagonist vs a noncalcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003;290:2805–16.
 5. Ried LD, Tueth MJ, Handberg E, Kupfer S, Pepine CJ. A Study of Antihypertensive Drugs and Depressive Symptoms (SADD-Sx) in patients treated with a calcium antagonist versus an atenolol hypertension Treatment Strategy in the International Verapamil SR-Trandolapril Study (INVEST). *Psychosom Med*. 2005;67:398–406.
 6. Steffensen R, Grande P, Pedersen F, Haunso S. Effects of atenolol and diltiazem on exercise tolerance and ambulatory ischaemia. *Int J Cardiol*. 1993;40:143–53.
 7. Belsey J, Savelieva I, Mugelli A, Camm AJ. Relative efficacy of antianginal drugs used as add-on therapy in patients with stable angina: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2014. doi:[10.1177/2047487314533217](https://doi.org/10.1177/2047487314533217).
 8. Montalescot G, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
 9. Kimura E, Kishida H. Treatment of variant angina with drugs: a survey of 11 cardiology institutes in Japan. *Circulation*. 1981;63:844–8.
 10. JCS Joint Working Group. Guidelines for diagnosis and treatment of patients with vasospastic angina (coronary spastic angina) (JCS 2008): digest version. *Circ J*. 2010;74:1745–62.
 11. Mauritsen DR, Johnson SM, Winniford MD, Cary JR, Willerson JT, Hillis LD. Verapamil for unstable angina at rest: a short-term randomized, double-blind study. *Am Heart J*. 1983;106:652–8.
 12. Antman E, Muller J, Goldberg S, MacAlpin R, Rubenfire M, Tabatznik B, et al. Nifedipine therapy for coronary-artery spasm. Experience in 127 patients. *N Engl J Med*. 1980;302:1269–73.

13. Pesola A, Lauro A, Gallo R, Madeo A, Cosentino G. Efficacy of diltiazem in variant angina: results of a doubleblind crossover study in CCU by Holter monitoring. The possible occurrence of a withdrawal syndrome. *G Ital Cardiol.* 1987;17:329–39.
14. Chahine RA, Feldman RL, Giles TD, Nicod P, Raizner AE, Weiss RJ, Vanov SK. Randomized placebo-controlled trial of amlodipine in vasospastic angina. Amlodipine Study 160 Group. *J Am Coll Cardiol.* 1993;21:1365–70.

Chapter 5

Nitrates

Amelia Carro and Pablo Avanzas

Introduction

Nitroglycerin was the first medication used – by William Murrell in 1879 – for the treatment of angina pectoris and, in its immediate release formulation i.e. sublingual spray, still continues to be considered a first-line agent for the treatment of angina [1, 2]. Nitrates have a dilatory effect on the venous system and are also coronary vasodilators. They also have a modest arteriolar dilatory action. They are useful drugs for the management of effort induced angina as they decrease myocardial oxygen demand via their systemic vasodilatory action, which reduces left ventricular systolic wall stress. In patients with stable, effort-induced, angina, nitrates improve exercise tolerance, time to onset of angina, and ST segment depression during exercise testing. In combination with beta blockers or calcium channel blockers, nitrate administration results in greater antianginal and

A. Carro, MD, PhD (✉)

Department of Cardiology, Hospital de Jove, Gijón, Spain

e-mail: achevia@gmail.com

P. Avanzas, MD, PhD, FESC

Cardiac Catheterization Laboratories, Area del Corazón,

Hospital Universitario Central de Asturias, Oviedo, Spain

e-mail: avanzas@secardiologia.es

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_5,

© Springer International Publishing Switzerland 2015

TABLE 5.1 Nitrates: classification and characteristics

Compound	Usual dose	Onset of action (min)	Duration of action	Activation
Glycerol Trinitrate (GTN)	Sublingual 0.3–0.6 mg	2–5	10–30 min	Mitochondrial activation
	Spray 0.4 mg 1–2 sprays as needed	2–5	10–30 min	
	Transdermal patch 0.2–0.4 mg/h	30	8–14 h	
Isosorbide Dinitrate (ISDN)	Oral 5–8 mg Twice to thrice daily	15–30	3–6 h	Cytochrome p450 biotrans- formation
Isosorbide Mononitrate (ISMN)	Oral 20 mg Twice daily (7 h apart)	30–60	12–14 h	Cytochrome p450 biotrans- formation
Pentaerythrityl tetranitrate (PETN)	Oral 50–80 mg Twice to thrice daily	20–30	10–12 h	Mitochondrial activation

anti-ischemic effects. The use of sublingual nitrates results in the rapid improvement of acute episodes of angina in both patients with effort induced chest pain and those with angina caused by dynamic mechanisms such as coronary artery spasm and are therefore considered by International guidelines to represent first line therapy for the management of anginal pain. Oral nitrates, however, are associated with the development of tolerance, and therefore the National Institute for Health and Care Excellence (NICE) in the United Kingdom recommend that oral nitrates should be used as second line therapy after β blockers and calcium channel blockers [3]. This chapter reviews the mechanisms of action of nitrates and current evidence regarding their efficacy as antianginal agents (Table 5.1).

Mechanisms of Action

Nitrates dilate veins, arteries, and coronary arteries by relaxing vascular smooth muscle [4]. Among the currently available compounds, the organic nitrates glyceryl trinitrate (GTN) and pentaerythrityl tetranitrate (PETN) are pro-drugs metabolized by the mitochondrial and cytosolic aldehyde dehydrogenase (ALDH-2); ALDH-2 acts as a GTN-reductase that catalyzes the bioactivation of GTN into 1,2-GTN through a NO-independent pathway (Table 5.1). Isosorbide dinitrate (ISDN) and isosorbide mononitrate (ISMN) undergo denitrication through an as yet unknown mechanism, which is not affected by ALDH-2 inhibition (or genetic deletion) [5, 6] ISDN major metabolites, isosorbide-2-mononitrate and isosorbide-5-mononitrate, are both biologically active, with half-lives of approximately 2 and 4 h, respectively. ISMN does not undergo first-pass hepatic metabolism and is completely bioavailable. The vasodilation which follows the administration of organic nitrates is mediated by the activation of soluble guanylate cyclase, followed by increased formation of cyclic guanosine-3',-5'-monophosphate (cGMP) and activation of cGMP-dependent protein kinases and/or cyclic nucleotide-gated ion channels [7, 8] (Fig. 5.1)

Effect on Systemic Hemodynamics

Organic nitrates exert their maximal vasodilatory effect at the level of venous capacitance vessels, large and medium-sized coronary arteries and collateral vessels, while arterioles with a diameter <100 μ m are relatively less affected (Table 5.2). Venodilation lowers preload (left ventricular end-diastolic pressure) and therefore reduces wall stress, resulting in a decrease in myocardial oxygen demand, which is of benefit in subjects affected by effort induced angina caused by severe coronary artery disease. The fall in preload is more pronounced with sitting or standing and this may lead to postural hypotension.

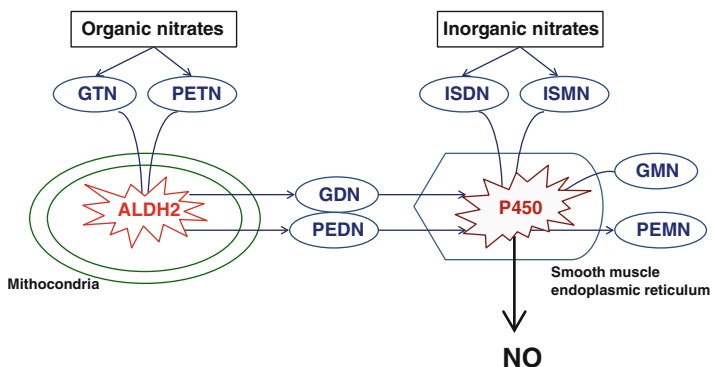


FIGURE 5.1 Organic (high potency) nitrates (GTN, PETN) are bioactivated by mitochondrial and cytosolic ALDH-2. The reductase activity converts the organic nitrates to the denitrated metabolites (GDN, PEDN). The low-potency nitrates (ISDN, ISMN, GDN, PEDN, and their respective mononitrates (GMN and PEMN) are bioactivated by P450 enzymes in the endoplasmic reticulum directly yielding NO. The latter mechanism also accounts for the high potency nitrates used at high doses. *GTN* glyceryl trinitrate, *PETN* pentaerythrityl tetranitrate, *ALDH* aldehyde dehydrogenase, *GDN* glyceryl dinitrate, *PEDN* pentaerythrityl dinitrate, *ISDN* isosorbide dinitrate, *ISMN* isosorbide mononitrate, *GMN* glyceryl mononitrate, *PEMN* pentaerythrityl mononitrate, *NO* nitric oxide

At low doses, nitrates cause a lesser degree of arterial and arteriolar dilation, leading to little or no change in systemic vascular resistance or blood pressure [4]. As the dose is increased, the blood pressure falls, often accompanied by reflex tachycardia. Wall stress is reduced at the lower blood pressure, resulting in a further decrease in myocardial oxygen demand.

Effect on Coronary Hemodynamics

A nitrate-induced increase in coronary blood flow has been proposed as a potential mechanism for relieving ischemia. Animal and human studies have shown that nitrates dilate

TABLE 5.2 Nitrates: mechanism of action

Hemodynamic actions			Non-hemodynamic actions	
Preload reduction	Improvement of myocardial oxygen supply	Afterload reduction	Preconditioning-like effect	Platelet inhibition
Venous return (-)	Dilation of collaterals	Systolic pressure (-)		
LV and RV EDP (-)	Dilation of eccentric coronary stenosis	Systolic stress (-)		
Diastolic wall stress (-)		Aortic compliance (+)		

Antiischemic effects

LV left ventricular, *RV* right ventricular, *EDP* end-diastolic pressure

both normal and abnormal coronary arteries [9]; this response is preserved in saphenous vein grafts [10]. The effect of nitrates on the arteriolar system is uncertain because the coronary arterioles in patients with severe flow-limiting coronary stenoses are already maximally dilated in an attempt to maintain resting blood flow at an appropriate level. There are, however, settings in which a direct effect of nitrates on coronary hemodynamics is clearly beneficial. For example, in the acute coronary syndromes, the dilation of coronary collaterals and conductance arteries can increase oxygen supply [11]. Similar hemodynamic effects provide a background for the benefit of organic nitrates in patients with congestive heart failure. In this setting, the redistribution of blood from the central circulation into large capacitance veins decreases right atrial pressure, and the dilation of large conduit arteries improves the impedance to the left ventricular ejection. The ensuing reduction in left ventricular end-diastolic pressure and left ventricle wall tension concurs to the hemodynamic stabilization of decompensated heart failure [12].

Nitrates can also reduce or reverse coronary artery vasospasm [13]. Thus, patients with primarily vasospastic angina or a large vasoconstrictor component to their angina can benefit from the direct coronary action of nitrate therapy.

Non-hemodynamic, Anti-ischemic Effects of Organic Nitrates: Preconditioning-Like Phenomena and Platelet Inhibition

The term ‘ischemic preconditioning’ describes a protective phenotype that is characterized by a reduced sensitivity to ischemia and reperfusion injury. While this protective phenomenon is, in its traditionally accepted form, triggered by the exposure to a short period of ischemia (such as angina), some drugs have also been shown to possess similar effects, suggesting that the pharmacological manipulation of the ischemic threshold at a cellular and whole organ level could be used as a tool in the prevention or reduction of ischemic events (Table 5.2). Several lines of evidence from both animal and human studies have now clearly demonstrated that the administration of nitroglycerin is associated, independently of any vasodilator effects, with an increased ischemic threshold, as manifested by reduced infarct size, reduced ECG changes in the setting of percutaneous angioplasty, and reduced endothelial dysfunction after ischemia and reperfusion [14–18]. These observations might have direct clinical implications: for instance in the setting of angioplasty or coronary artery bypass grafting, but possibly also during chronic therapy, as shown in a recent post hoc analysis of the GRACE trial and in another smaller retrospective study [19, 20].

Besides these effects, nitrates also reduce platelet aggregability *ex vivo* in healthy volunteers and, to a lesser extent, in patients with coronary artery disease, which might be particularly useful in the setting of acute coronary syndromes. Whether the antiaggregant effects of nitrates have an additional clinical impact in the therapy of coronary artery

disease, particularly in light of the introduction and systematic use of targeted antiplatelet agents such as aspirin, and thienopyridines is, however, unclear.

Nitrate Tolerance

The clinical use of nitrates is limited by the development of tolerance, i.e., the loss of hemodynamic and symptomatic effects that invariably occurs upon prolonged (>12 h) treatment. In the setting of coronary artery disease, this also translates in the loss of antianginal effects. Another phenomenon, this time caused by the withdrawal of chronic nitrate therapy i.e. ‘rebound’ effect [21] results in the worsening of the patient’s anginal symptoms.

Mechanisms of Tolerance

The mechanism responsible for nitrate tolerance is incompletely understood. Tolerance appears to be a complex phenomenon involving vascular, biochemical, and autonomic changes with oxidative stress playing a central role [22, 23], as demonstrated by the fact that administration of vitamin C prevents or reverses these modifications [24, 25]. Tolerance is due to attenuation of the vascular effect of nitrates, but not to altered pharmacokinetics, with at least three (not mutually exclusive) proposed mechanisms [1]:

1. Impaired nitroglycerin bioconversion to 1,2-glyceryl dinitrate with decreased formation of NO. This effect is nitrate-specific and is not seen with non-nitrate sources of NO such as nitroprusside [26]. Consistent with this theory are the experimental observations that there is no tolerance to the effect of S-nitrosothiols and that the activity of mitochondrial aldehyde dehydrogenase-2 (mtALDH), the enzyme required for metabolism of nitrates to 1,2 glyceryl dinitrate is markedly reduced [5]. The same findings can be induced by inhibitors of ALDH [5].

2. Reduced bioactivity of NO [27]. This is supported by the finding that vascular and hemodynamic tolerance to nitrates occurs in animals despite high levels of NO and rates of NO formation that were similar in those animals that were not tolerant [28]. In addition, transgenic animals that overexpress endothelial NO synthase have chronically elevated NO release, which is associated with reduced vascular reactivity to NO-mediated vasodilators [29].
3. Activation of the renin-angiotensin-aldosterone system and sympathetic nervous system in response to nitrate-induced vasodilation [30, 31]. The increased peripheral sensitivity to these vasoconstrictors can be reversed by angiotensin converting enzyme inhibition [30].

Abnormal coronary vasoconstrictor responses have also been described with continuous nitrate exposure [32].

Prevention

Although the mechanisms of nitrate tolerance remain unknown, several approaches to its prevention have been studied. The only widely accepted and most effective method of preventing tolerance is the use of a dosing strategy that provides an interval of low nitrate exposure during each 24-h period. It is thought that a **nitrate-free interval** permits the regeneration of reduced sulfhydryl groups, thereby restoring vascular responsiveness to nitrates (Table 5.3).

There are, however, two concerns regarding intermittent therapy:

1. A time-zero effect, which refers to a deterioration in exercise performance relative to placebo prior to the morning dose of nitrates. In a study of 215 patients given nitroglycerin or placebo patches, the time spent walking on the treadmill in the morning increased before application of the patch in the placebo group but not in the nitroglycerin group, suggesting that withdrawal of nitroglycerin had an adverse effect on exercise performance [33]. This effect was confirmed in other studies of transdermal nitroglycerin

therapy [21, 34]. Adverse effects on exercise tolerance have not been reported in studies of other long-acting nitrates given once daily or in eccentric dosing regimens [9, 35].

2. Rebound angina, which refers to an increase in angina during the nitrate-free interval. There may result from a supersensitivity of the vessel wall to vasoconstrictors [36] or an increased vasomotor response to acetylcholine, suggesting the development of endothelial dysfunction [37].

Whether these effects occur to a clinically significant degree remains unclear and no firm conclusions can be drawn concerning the risk of acute ischemic events during intermittent nitrate therapy [21, 38–40]. Despite this uncertainty, patients and their physicians should be aware of the

TABLE 5.3 Nitrates: side effects and precautions of therapy

Side effect	Comment	Contraindications
Headache	It often responds after several days of therapy Resolution of headache does not necessarily mean loss of efficacy	
Postural hypotension	Initiate treatment with small doses and increase as necessary	Coadministration of phosphodiesterase-5 inhibitors
Light-headedness	Dose reduction may be required	Hypertrophic cardiomyopathy
Syncope	Caution in the elderly, severe aortic stenosis or volume depletion	Right ventricular infarction
Flushing	Initiate treatment with small doses and increase as necessary	Allergic reactions to organic nitrates
Local redness Mild inflammation	Vary application site	Allergic reactions to organic nitrates

(continued)

TABLE 5.3 (continued)

Side effect	Comment	Contraindications
Tolerance	Several strategies have been proposed to avoid tolerance: Nitrate-free interval N-acetylcysteine Folic acid L-arginine Hydralazine Antioxidants: vitamin E, vitamin C, carvedilol Statins Angiotensin converting enzyme inhibitors Diuretics	
Nitrate rebound	These occur during nitrate-free period. Research Some lines of research provide a potential role of PETN in these cases.	Caution in the early days of acute coronary syndrome
Time zero effect		

PETN Pentaerythritol tetranitrate

fact that the nitrate-free period during intermittent dosing regimens should be associated with increased angina.

Other pharmacologic interventions have been tested to reduce nitrate tolerance, although none is as yet used clinically:

- Chronic therapy with **N-acetylcysteine**, a sulfhydryl donor, does not appear to be effective in patients with stable angina [41], in contrast to its acute benefit with intravenous nitroglycerin in subjects with unstable angina.

- **Folic acid** can reverse endothelial dysfunction, possibly by restoring the bioavailability of tetrahydrobiopterin, a cofactor for NO synthase and/or arginine, its substrate. This suggests a possible role for folic acid in preventing nitrate tolerance. This was examined in a study of 18 subjects who were randomly assigned to folic acid (10 mg/day) or placebo for 1 week; all patients received continuous transdermal nitroglycerin (0.6 mg/h) [42]. Compared to placebo, folic acid prevented the development of both endothelial dysfunction and nitrate tolerance.
- Treatment for 5–10 days with **L-arginine**, the substrate for NO synthesis, can modify or prevent the development of nitrate tolerance during continuous transdermal nitroglycerin use [43].
- **Hydralazine** may attenuate nitrate tolerance, perhaps by preventing superoxide generation [44]. This relationship could contribute to the efficacy of combined nitrate-hydralazine therapy in patients with heart failure. In patients with angina pectoris, hydralazine should be given in combination with a beta blocker because of the reflex sympathetic activation.
- Other antioxidants may be helpful, at least from a theoretical perspective, such as **vitamin E** [45] and **vitamin C** [46, 47]. In addition, **carvedilol**, a beta and alpha blocker that also has antioxidant activity, may prevent nitrate tolerance [48]. The importance of antioxidant activity was suggested by a second report which compared carvedilol with another beta and alpha blocker (arotinolol) that was devoid of antioxidant properties; only carvedilol prevented nitrate tolerance [49].
- Therapy with **statins** has been associated with a number of benefits that are independent of their effect on lipid levels. In animal studies, both pravastatin and atorvastatin prevented nitrate tolerance and vascular superoxide formation induced by subcutaneous GTN injections [50] an effect that was associated with increased basal cGMP levels and was abolished when the rats received an inhibitor of the eNOS concomitantly

with GTN. Therapy with statins also appears to improve platelet reactivity to GTN in patients with stable or unstable coronary syndromes [51].

- Other drugs have had variable or no effect. These include **angiotensin converting enzyme (ACE) inhibitors** [30, 52–54], and **diuretics**, which may have some antianginal activity by reducing the plasma volume [54, 55].

Commonly Used Nitrate Preparations

Numerous nitrate preparations are commercially available, including sublingual, buccal, oral, spray, ointment, and transdermal preparations (Table 5.1).

Glyceril Trinitrate

Sublingual Administration

Sublingual nitroglycerin dilates capacitance veins and conduit arteries, relieving symptoms of angina and decreasing cardiac oxygen demand. These effects are so consistent and reproducible that a symptomatic improvement immediately after the administration of sublingual nitroglycerin or isosorbide dinitrate is considered to represent valuable information in the differential diagnosis of chest pain [56]. Similarly, the use of sublingual nitrates in settings where angina is anticipated (i.e. in the symptomatic prophylaxis) is also strongly recommended, and physicians should educate and encourage patients to self-administer nitrates before performing physical activity, or in cases of emotional stress.

The onset of action is within 2–5 min and the duration of action is 10–30 min. Tolerance is not a problem with sublingual nitroglycerin because of its intermittent administration, even in patients on chronic nitrate therapy [57].

The recommended nitroglycerin dose is 0.3 mg (1/200 grains) to 0.6 mg (1/100 grains). One half the dose (0.15 mg

or 1/400 grains) can be used if the patient becomes hypotensive or develops symptoms such as headache or flushing with the higher doses. Elderly patients should be warned about potential lightheadedness, especially in warm weather.

The traditional recommendation is for patients to take one nitroglycerin dose sublingually every 5 min for up to three doses before calling for emergency medical services (EMS) evaluation. However, studies suggest that this approach may result in significant delays in obtaining EMS assistance [58, 59]. As a result, the 2004 College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend contacting EMS if chest pain or discomfort is unimproved or worsening 5 min after one nitroglycerin dose has been taken [60]. No change to this approach was made in the 2007 focused update of the 2004 ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction [61]. For patients known to their providers to have frequent angina, physicians may consider a selected, more tailored message that takes into account the frequency and character of the patient's angina and their typical time course of response to nitroglycerin.

If the sublingual nitroglycerin is potent, a slight tingling sensation should be felt under the tongue. Tablets that crumble easily should not be used. The sublingual mucosa should be moist for adequate dissolution and absorption of the tablet. A drink of water in patients with dry sublingual mucosa prior to ingestion of the tablet may be necessary.

Nitroglycerin tablets are both heat and light sensitive. They should therefore be stored in a tightly capped dark bottle in the refrigerator with only a small supply being carried by the patient. Nitroglycerin tablets in an opened bottle should be discarded after 12 months.

Patient education is extremely important for the proper use of sublingual nitroglycerin. A survey of 50 patients revealed a surprising lack of knowledge concerning the administration, storage, and side effects of this preparation [62]. Only 12 % knew the maximum dose in a 15 min period, 28 % knew the proper storage conditions for sublingual tablets, and 52 % knew the most common side effects.

Sublingual Spray

An equally effective means of administering sublingual nitroglycerin is by metered dose spray. The spray dispenses of 0.4 mg of nitroglycerin. One to two sprays can be used at the start of an attack and up to three sprays can be used in a 15 min period. It has a shelf life of 2–3 years [63].

Transdermal Patch

Transdermal nitroglycerin patches obtained US Food and Drug Administration (FDA) approval in 1981 and gained wide acceptance for its convenience. These patches have either a polymer matrix or a silicone gel impregnated with nitroglycerin; a semipermeable membrane between the drug reservoir and the skin results in a constant delivery of nitroglycerin. Onset of action is 30 min with duration of action in the region of 8–14 h. The usual dose is 0.2–0.8 mg/h [64]. Once again, continuous therapy is associated with nitrate tolerance. In one report, for example, patches of 5, 10, 15, 30, and 45 mg were given continuously and treadmill walking time was examined after 2, 4, and 24 h. With the exception of the 45 mg dose, antianginal effects were seen at 2 and 4 h but were absent at 24 h on the first day. Daily therapy with 15 mg patches for 1–2 weeks was associated with antianginal and hemodynamic effects that were not different from placebo patches. Similar findings were noted in a multicenter, randomized, placebo controlled trial involving 562 patients examined the efficacy of 8 weeks of continuous transdermal nitroglycerin [65]. In doses ranging from 15 to 105 mg/day, there was no difference in exercise tolerance or anginal frequency between active drug and placebo; this effect was noted within 24 h. As a result of these findings, intermittent transdermal regimens have been evaluated. A recent trial evaluated the efficacy of three dose levels of transdermal nitroglycerin (0.2, 0.4, and 0.8 mg/h) applied for 12 h daily for 30 days in 291 patients with chronic stable angina. After 30 days of therapy, treadmill-walking time until the onset of

angina or 1 mm ST depression was significantly improved in all treatment groups when compared to placebo. In addition, there was no evidence of rebound angina or partial tolerance when the antianginal effects on day 30 were compared to those on day [21]. This trial did not directly compare patch-on and patch-off periods and hence the problem of rebound angina after transdermal nitroglycerin withdrawal was not adequately addressed. However, another study, directly evaluated the effect of intermittent transdermal nitroglycerin on the occurrence of ischemia during patch-off hours in 72 patients who were randomized to 12 h of transdermal nitroglycerin or placebo [66]. After 2 weeks of therapy, patients crossed over to the alternative treatment. Compared to placebo, transdermal nitroglycerin significantly reduced the magnitude of ST segment depression at angina onset during exercise testing, but did not alter total angina frequency. Angina frequency and silent ischemia increased by 14 % during patch-off hours compared to patch-on hours.

Isosorbide Dinitrate

Isosorbide dinitrate (ISDN) has an onset of action within 15–30 min and the duration of action is 3–6 h. Low bioavailability from hepatic metabolism has necessitated relatively large doses of 10–40 mg three times daily. The beneficial effects of a single dose of ISDN (15, 30, 60, 120 mg) were demonstrated in 12 patients with chronic stable angina [57]. There was a dose-related reduction in systolic blood pressure that persisted for 8 h. Exercise duration improved up to 8 h after the 15 and 30 mg dose; there was no added benefit with the 60 and 120 mg doses. Unfortunately, tolerance has limited the usefulness of ISDN as a chronic antianginal agent. In the study above, ISDN was given four times daily for 2 weeks [67]: both the blood pressure and exercise responses were attenuated. In particular, exercise duration was only increased for 2 h after a dose and doses above 15 mg four times daily produced no added benefit. The development of tolerance occurred despite higher plasma

concentrations of ISDN during maintenance therapy. Several studies have altered the drug regimen in an attempt to prevent the development of tolerance. One study, for example, examined the effect of 30 mg of ISDN given two (7 am and 12 pm), three (7 am, 12 pm, and 5 pm), and four (7 am, 12 pm, 5 pm, and 11 pm) times daily for 1 week [68]. Exercise duration until the onset of angina was assessed before and 1, 3, and 5 h after the morning dose. After a single initial dose, exercise duration significantly increased versus placebo over the 5 h observation period. After 1 week of therapy, two and three (but not four) times daily dosing was associated with improved exercise tolerance compared placebo; however, the benefit was less pronounced late in the day, indicating partial tolerance. One limitation to the clinical utility of these results is that the response was measured only to the morning dose of ISDN.

The antianginal efficacy of three times daily ISDN has been questioned by a study involving very few patients [69]. Eight patients with chronic stable angina were given ISDN at 8 am, 1 pm, and 6 pm. Exercise time increased 3 h after the morning and afternoon dose but not after the evening dose. It was concluded that ISDN given three times daily offered antianginal protection for at most 6 h.

Isosorbide Mononitrate

Isosorbide mononitrate (ISMN) has been for years now the most commonly used oral nitrate. While important differences exist between ISMN and GTN (first of all the fact that the ALDH-2 is not involved in ISMN biotransformation), the complications associated with chronic therapy are similar, with the only exception of rebound phenomena, which are less manifest with ISMN probably due to the fact that changes in the bioavailability of the drug follow a shallower curve after oral administration of ISMN when compared with the transdermal on-off administration of GTN [49]. As a matter of fact, however, chronic continuous therapy with ISDN and ISMN is also associated with nitrate tolerance,

oxidative stress (of cytosolic, extra-mitochondrial origin), renin production, and plasma volume expansion, and intermittent therapy has been associated with endothelial dysfunction [52–55]. Further, probably because of the absence of changes in mitochondrial reactive oxygen species production, ISMN is devoid of protective preconditioning-mimetic effects and of antiaggregant effects, two phenomena that are thought to concur with the benefit of GTN in the setting of acute coronary syndromes [52, 55].

The use of the rapid-release preparations given approximately 7 h between doses (e.g., 8 am and 3 pm hours) [35] or with the extended release preparation when given once daily in doses of either 120 and 240 mg [70] have been effective strategies when dealing with the problem of tolerance.

Pentaerythrityl Tetranitrate (PETN)

In contrast other nitrate preparations, no endothelial dysfunction has been observed in subjects receiving PETN, a peculiarity likely due to the fact that this nitrate causes upregulation of the antioxidant enzyme hemeoxygenase I (HO-I) [71, 72]. PETN does not induce vascular tolerance, which means that vasodilator potency is preserved during continuous treatment [73, 74]. In addition, it does not cause an increase in vascular production of reactive oxygen species as seen with GTN therapy. Therefore, the tetranitrate PETN appears to be devoid of tolerance, endothelial dysfunction and oxidative stress, while maintaining the preconditioning-like protective properties of other nitrates [75].

While these data provide a strong biological rationale for the superiority of PETN against other nitrates, the lack of clinical data on the antianginal effects of this compound has limited its use. PETN was marketed until the early 1990s in North America and Europe, but it was then removed from the pharmacopeia essentially due to the absence of efficacy data. For the same reason, PETN was removed in 2012 from the list of reimbursable drugs in Germany, the major market for this drug. The recently concluded Cleopatra study addressed

this issue by randomizing 655 patients with coronary artery disease to receive placebo or two daily doses of 80 mg of PETN, demonstrating a benefit of PETN on exercise tolerance during a 12-weeks treatment [76]. These data will hopefully lead to reconsider the use of (and further research on) this drug in clinical practice worldwide.

Side Effects and Precautions

Although nitrate therapy is generally safe, side effects must be taken into account when prescribing these agents (Table 5.3):

1. **Headache** is the most common side effect of nitrates; often dose-related and reported by up to 82 % of patients in placebo-controlled trials.

Two different types of nitrate-induced headaches have been described, not only in terms of their timing and symptoms, but with different causal mechanisms:

- (a) Headaches that develop within the first hour after administration, are usually the result of vasodilation caused by NO release. These are mild or medium severity headaches without characteristic symptoms for migraine, and ease spontaneously. A lower starting dose and then titration to optimal daily dose are likely to minimize these undesirable effect. It is important to stress that the nitrate-induced headache usually disappears within 1–2 weeks during continuous treatment. Nitrate-induced headache was assessed in patients receiving treatment with 5-ISMN over 1–2 years. During the initial 2 weeks, one-third of the patients reported some degree of headache, whereas after this time point headache was only occasionally reported by patients [77, 78]. Similar findings were also observed in a large study using transdermal nitroglycerin 15–105 mg daily. During an 8 week treatment period headache was reported more frequently in actively

treated patients during the initial 1–2 weeks. After 4 weeks, however, headache reporting was similar in placebo-treated patients and nitroglycerin-treated patients.

- (b) Delayed, moderate or severe migraine-type headaches (occurring mainly in subjects with personal or family history of migraine), that develop 3–6 h after the intake of nitrates, with debilitating, long-lasting symptoms including nausea, vomiting, photo- and/or phono-phobia. These are triggered by the release of calcitonin gene-related peptide or glutamate, or changes in ion channel function mediated by cyclic guanosine monophosphate or S-nitrosylation. Migraines usually need anti-attack medication, such as triptans, but these drugs are contraindicated in most medical conditions that are treated using nitrates.

2. **Nitrate-induced hypotension** is common, but often asymptomatic.

This risk may be particularly magnified in patients who are extremely sensitive to the arteriolar effect of nitrates, such as the elderly -due to natural declines in autonomic nervous system regulation [79], those who are volume depleted (e.g., diuretic therapy), or with low systolic blood pressure (i.e., <90 mmHg). A profound drop in systolic blood pressure can aggravate myocardial ischemia. Problems can also occur with excessive venodilation. This can result in a marked decrease in venous return, which induces cardiac emptying that activates mechanical receptors in the heart, possibly leading to hypotension and bradycardia, consistent with the Bezold-Jarisch reflex (vasovagal response) [80]. Use of nitrates in patients who experience syncope after administration of nitrates is contraindicated. Administration of nitrates is also contraindicated with concomitant use of phosphodiesterase-5 inhibitors, used for the treatment of erectile dysfunction, as combination therapy may lead to profound hypotension and even death. Other contraindications related to this mechanism include:

- Patients with hypertrophic cardiomyopathy in whom nitrates can induce or increase outflow tract obstruction, even in those not known to have a resting gradient.
 - Patients with suspected right ventricular infarction, because of the increased risk of inducing hypotension.
 - In patients with severe aortic stenosis or volume depletion, nitrate therapy should be used cautiously.
3. **Flushing** usually develops because of arteriolar dilatation.
 4. Transdermal preparation may cause **local redness** and sometimes mild **inflammation** of the skin.
 5. Coronary dilation rarely causes coronary steal and **myocardial ischaemia**. However, all forms of nitroglycerin should be used cautiously during the early days of **acute myocardial infarction**. In the event that treatment is initiated under this condition, particular attention must be paid to hemodynamic monitoring and clinical status. In addition, **nitrate rebound** may occur and patients may experience nocturnal anginal episodes during intermittent therapy with nitroglycerin patches.
 6. **Reduced response in Asians:** a polymorphism in the enzyme (ALDH2*2), implicated in NO formation, is present in 30–50 % of Asians. Consequently, mtALDH activity and NO production are virtually eliminated [81]. In a series of 80 patients from China who were being treated with nitroglycerin for angina, 33 (41 %) had at least one ALDH2*2 allele [81]. These patients were significantly less likely to respond to nitroglycerin for relief of angina (58 vs 85 %). The lack of response in all patients with the ALDH2*2 allele and the failure of all patients without this allele indicates that other factors are also important determinants of the efficacy of nitroglycerin. An investigator-observed flushing response to alcohol may be both highly sensitive specific for the presence of the ALDH2*2 allele [82].
 7. Both short- and long-acting nitrate formulations are contraindicated in patients with **allergic reactions to organic nitrates**.

Conclusion

More than a century after their first clinical use, nitrates continue to be used for the management of angina pectoris. Nitrates represent a heterogeneous group of substances that differ greatly with respect to side effects, including the induction of nitrate tolerance and endothelial dysfunction. This consideration must be taken into account to ensure that an optimal plasma concentration profile is achieved during antianginal treatment with nitrates. Proposed strategies include the asymmetric pattern of effective nitrate concentrations during the daytime followed by a nitrate-poor/nitrate free interval during the night.

Oral nitrates are commonly used as add-on therapy in patients who remain symptomatic despite administration of beta-blockers or calcium-channel antagonists. Patients should be educated on the use of short-term sublingual formulations for prophylaxis of angina. Self administration of nitroglycerin or ISDN before undertaking physical stress or when the patient is under emotional stress, may improve both exercise tolerance and quality of life. Finally, more research is necessary to understand the role of alternative NO-based therapies, for instance the administration of nitrite/nitrate or PETN. While basic science has provided more answers to the still unresolved question of nitrate tolerance, the most important question, i.e. whether this therapy change patient prognosis, “remains unanswered”.

References

1. Parker JD, Parker JO. Nitrate therapy for stable angina pectoris. *N Engl J Med.* 1998;338(8):520–31.
2. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Chronic Stable Angina). *Circulation.* 2003;107(1):149–58.

3. Henderson RA, O'Flynn N. Management of stable angina: summary of NICE guidance. *Heart*. 2012;98(6):500–7.
4. Abrams J. Hemodynamic effects of nitroglycerin and long-acting nitrates. *Am Heart J*. 1985;110(1 Pt 2):216–24.
5. Chen Z, Zhang J, Stamler JS. Identification of the enzymatic mechanism of nitroglycerin bioactivation. *Proc Natl Acad Sci U S A*. 2002;99(12):8306–11.
6. Daiber A, Oelze M, Coldewey M, et al. Oxidative stress and mitochondrial aldehyde dehydrogenase activity: a comparison of pentaerythritol tetranitrate with other organic nitrates. *Mol Pharmacol*. 2004;66(6):1372–82.
7. Munzel T, Feil R, Mulsch A, Lohmann SM, Hofmann F, Walter U. Physiology and pathophysiology of vascular signaling controlled by guanosine 3',5'-cyclic monophosphate-dependent protein kinase [corrected]. *Circulation*. 2003;108(18):2172–83.
8. Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature*. 1987;327(6122):524–6.
9. Brown BG, Bolson E, Petersen RB, Pierce CD, Dodge HT. The mechanisms of nitroglycerin action: stenosis vasodilatation as a major component of the drug response. *Circulation*. 1981;64(6):1089–97.
10. Berglund H, Luo H, Nishioka T, et al. Preserved vasodilatory response to nitroglycerin in saphenous vein bypass grafts. *Circulation*. 1996;94(11):2871–6.
11. Cohen MV, Downey JM, Sonnenblick EH, Kirk ES. The effects of nitroglycerin on coronary collaterals and myocardial contractility. *J Clin Invest*. 1973;52(11):2836–47.
12. Bache RJ, Ball RM, Cobb FR, Rembert JC, Greenfield Jr JC. Effects of nitroglycerin on transmural myocardial blood flow in the unanesthetized dog. *J Clin Invest*. 1975;55(6):1219–28.
13. Ginsburg R, Lamb IH, Schroeder JS, Hu M, Harrison DC. Randomized double-blind comparison of nifedipine and isosorbide dinitrate therapy in variant angina pectoris due to coronary artery spasm. *Am Heart J*. 1982;103(1):44–9.
14. Banerjee S, Tang XL, Qiu Y, et al. Nitroglycerin induces late preconditioning against myocardial stunning via a PKC-dependent pathway. *Am J Physiol*. 1999;277(6 Pt 2):H2488–94.
15. Hill M, Takano H, Tang XL, Kodani E, Shirk G, Bolli R. Nitroglycerin induces late preconditioning against myocardial infarction in conscious rabbits despite development of nitrate tolerance. *Circulation*. 2001;104(6):694–9.

16. Jneid H, Chandra M, Alshaher M, et al. Delayed preconditioning-mimetic actions of nitroglycerin in patients undergoing exercise tolerance tests. *Circulation*. 2005;111(20):2565–71.
17. Leeser MA, Stoddard MF, Dawn B, Jasti VG, Masden R, Bolli R. Delayed preconditioning-mimetic action of nitroglycerin in patients undergoing coronary angioplasty. *Circulation*. 2001;103(24):2935–41.
18. Dragoni S, Gori T, Lisi M, et al. Pentaerythrityl tetranitrate and nitroglycerin, but not isosorbide mononitrate, prevent endothelial dysfunction induced by ischemia and reperfusion. *Arterioscler Thromb Vasc Biol*. 2007;27(9):1955–9.
19. Timoteo AT, Mamede A, de Lurdes FM, et al. Is chronic nitrate therapy associated with a different clinical presentation of acute coronary syndrome? *Rev Port Cardiol*. 2007;26(2):135–43.
20. Ambrosio G, Del PM, Tritto I, et al. Chronic nitrate therapy is associated with different presentation and evolution of acute coronary syndromes: insights from 52,693 patients in the Global Registry of Acute Coronary Events. *Eur Heart J*. 2010;31(4):430–8.
21. Parker JD, Parker AB, Farrell B, Parker JO. Intermittent transdermal nitroglycerin therapy. Decreased anginal threshold during the nitrate-free interval. *Circulation*. 1995;91(4):973–8.
22. Daiber A, Wenzel P, Oelze M, Munzel T. New insights into bioactivation of organic nitrates, nitrate tolerance and cross-tolerance. *Clin Res Cardiol*. 2008;97(1):12–20.
23. Gori T, Dragoni S, Di SG, et al. Tolerance to nitroglycerin-induced preconditioning of the endothelium: a human in vivo study. *Am J Physiol Heart Circ Physiol*. 2010;298(2):H340–5.
24. Bassenge E, Fink N, Skatchkov M, Fink B. Dietary supplement with vitamin C prevents nitrate tolerance. *J Clin Invest*. 1998;102(1):67–71.
25. Thomas GR, DiFabio JM, Gori T, Parker JD. Once daily therapy with isosorbide-5-mononitrate causes endothelial dysfunction in humans: evidence of a free-radical-mediated mechanism. *J Am Coll Cardiol*. 2007;49(12):1289–95.
26. Sage PR, de la Lande IS, Stafford I, et al. Nitroglycerin tolerance in human vessels: evidence for impaired nitroglycerin bioconversion. *Circulation*. 2000;102(23):2810–5.
27. Mangione NJ, Glasser SP. Phenomenon of nitrate tolerance. *Am Heart J*. 1994;128(1):137–46.
28. Laursen JB, Mulsch A, Boesgaard S, et al. In vivo nitrate tolerance is not associated with reduced bioconversion of nitroglycerin to nitric oxide. *Circulation*. 1996;94(9):2241–7.

29. Ohashi Y, Kawashima S, Hirata K, et al. Hypotension and reduced nitric oxide-elicited vasorelaxation in transgenic mice overexpressing endothelial nitric oxide synthase. *J Clin Invest.* 1998;102(12):2061–71.
30. Heitzer T, Just H, Brockhoff C, Meinertz T, Olschewski M, Munzel T. Long-term nitroglycerin treatment is associated with supersensitivity to vasoconstrictors in men with stable coronary artery disease: prevention by concomitant treatment with captopril. *J Am Coll Cardiol.* 1998;31(1):83–8.
31. Parker JO, Parker JD. Neurohormonal activation during nitrate therapy: a possible mechanism for tolerance. *Am J Cardiol.* 1992;70(8):93B–7.
32. Caramori PR, Adelman AG, Azevedo ER, Newton GE, Parker AB, Parker JD. Therapy with nitroglycerin increases coronary vasoconstriction in response to acetylcholine. *J Am Coll Cardiol.* 1998;32(7):1969–74.
33. DeMots H, Glasser SP. Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina. *J Am Coll Cardiol.* 1989;13(4):786–95.
34. Parker JD, Parker JO. Effect of therapy with an angiotensin-converting enzyme inhibitor on hemodynamic and counterregulatory responses during continuous therapy with nitroglycerin. *J Am Coll Cardiol.* 1993;21(6):1445–53.
35. Parker JO. Eccentric dosing with isosorbide-5-mononitrate in angina pectoris. *Am J Cardiol.* 1993;72(12):871–6.
36. Hebert D, Lam JY. Nitroglycerin rebound associated with vascular, rather than platelet, hypersensitivity. *J Am Coll Cardiol.* 2000;36(7):2311–6.
37. Azevedo ER, Schofield AM, Kelly S, Parker JD. Nitroglycerin withdrawal increases endothelium-dependent vasomotor response to acetylcholine. *J Am Coll Cardiol.* 2001;37(2):505–9.
38. Freedman SB, Daxini BV, Noyce D, Kelly DT. Intermittent transdermal nitrates do not improve ischemia in patients taking beta-blockers or calcium antagonists: potential role of rebound ischemia during the nitrate-free period. *J Am Coll Cardiol.* 1995;25(2):349–55.
39. Parker JO, Amies MH, Hawkinson RW, et al. Intermittent transdermal nitroglycerin therapy in angina pectoris. Clinically effective without tolerance or rebound. Minitran Efficacy Study Group. *Circulation.* 1995;91(5):1368–74.
40. Thadani U, Maranda CR, Amsterdam E, et al. Lack of pharmacologic tolerance and rebound angina pectoris during twice-daily

- therapy with isosorbide-5-mononitrate. *Ann Intern Med.* 1994;120(5):353–9.
41. Munzel T, Holtz J, Mulsch A, Stewart DJ, Bassenge E. Nitrate tolerance in epicardial arteries or in the venous system is not reversed by N-acetylcysteine in vivo, but tolerance-independent interactions exist. *Circulation.* 1989;79(1):188–97.
 42. Gori T, Burstein JM, Ahmed S, et al. Folic acid prevents nitroglycerin-induced nitric oxide synthase dysfunction and nitrate tolerance: a human in vivo study. *Circulation.* 2001;104(10):1119–23.
 43. Parker JO, Parker JD, Caldwell RW, Farrell B, Kaesemeyer WH. The effect of supplemental L-arginine on tolerance development during continuous transdermal nitroglycerin therapy. *J Am Coll Cardiol.* 2002;39(7):1199–203.
 44. Gogia H, Mehra A, Parikh S, et al. Prevention of tolerance to hemodynamic effects of nitrates with concomitant use of hydralazine in patients with chronic heart failure. *J Am Coll Cardiol.* 1995;26(7):1575–80.
 45. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of supplemental vitamin E on attenuation of the development of nitrate tolerance. *Circulation.* 1997;96(8):2545–50.
 46. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of the preventive effect of supplemental oral vitamin C on attenuation of development of nitrate tolerance. *J Am Coll Cardiol.* 1998;31(6):1323–9.
 47. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of ascorbate on the preventive effect of nitrate tolerance in patients with congestive heart failure. *Circulation.* 1998;97(9):886–91.
 48. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Randomized, double-blind, placebo-controlled study of carvedilol on the prevention of nitrate tolerance in patients with chronic heart failure. *J Am Coll Cardiol.* 1998;32(5):1194–200.
 49. Watanabe H, Kakihana M, Ohtsuka S, Sugishita Y. Preventive effects of carvedilol on nitrate tolerance—a randomized, double-blind, placebo-controlled comparative study between carvedilol and arotinolol. *J Am Coll Cardiol.* 1998;32(5):1201–6.
 50. Fontaine D, Otto A, Fontaine J, Berkenboom G. Prevention of nitrate tolerance by long-term treatment with statins. *Cardiovasc Drugs Ther.* 2003;17(2):123–8.

51. Chirkov YY, Holmes AS, Willoughby SR, et al. Stable angina and acute coronary syndromes are associated with nitric oxide resistance in platelets. *J Am Coll Cardiol*. 2001;37(7):1851–7.
52. Katz RJ, Levy WS, Buff L, Wasserman AG. Prevention of nitrate tolerance with angiotension converting enzyme inhibitors. *Circulation*. 1991;83(4):1271–7.
53. Dakak N, Makhoul N, Flugelman MY, et al. Failure of captopril to prevent nitrate tolerance in congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1990;66(5):608–13.
54. Cotter G, Metzkor-Cotter E, Kaluski E, et al. Usefulness of losartan, captopril, and furosemide in preventing nitrate tolerance and improving control of unstable angina pectoris. *Am J Cardiol*. 1998;82(9):1024–9.
55. Parker JD, Parker AB, Farrell B, Parker JO. Effects of diuretic therapy on the development of tolerance to nitroglycerin and exercise capacity in patients with chronic stable angina. *Circulation*. 1996;93(4):691–6.
56. Qaseem A, Fihn SD, Dallas P, Williams S, Owens DK, Shekelle P. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. *Ann Intern Med*. 2012;157(10):735–43.
57. Lee G, Mason DT, De Maria AN. Effects of long-term oral administration of isosorbide dinitrate on the antianginal response to nitroglycerin. Absence of nitrate cross-tolerance and self-tolerance shown by exercise testing. *Am J Cardiol*. 1978;41(1):82–7.
58. Leslie WS, Urie A, Hooper J, Morrison CE. Delay in calling for help during myocardial infarction: reasons for the delay and subsequent pattern of accessing care. *Heart*. 2000;84(2):137–41.
59. Simon AB, Feinleib M, Thompson Jr HK. Components of delay in the pre-hospital phase of acute myocardial infarction. *Am J Cardiol*. 1972;30(5):476–82.
60. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44(3):671–719.

61. Antman EM, Hand M, Armstrong PW, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation*. 2008;117(2):296–329.
62. Bailie GR, Kay EA. Patients' knowledge of sublingual glyceryl trinitrate. *BMJ*. 1988;297(6640):32.
63. NitroMist nitroglycerin spray for angina. *Med Lett Drugs Ther*. 2011;53(1360):23–4.
64. Parker JO, Fung HL. Transdermal nitroglycerin in angina pectoris. *Am J Cardiol*. 1984;54(6):471–6.
65. Acute and chronic antianginal efficacy of continuous twenty-four-hour application of transdermal nitroglycerin. Steering Committee, Transdermal Nitroglycerin Cooperative Study. *Am J Cardiol*. 1991;68(13):1263–73.
66. Pepine CJ, Lopez LM, Bell DM, Handberg-Thurmond EM, Marks RG, McGorray S. Effects of intermittent transdermal nitroglycerin on occurrence of ischemia after patch removal: results of the second transdermal intermittent dosing evaluation study (TIDES-II). *J Am Coll Cardiol*. 1997;30(4):955–61.
67. Thadani U, Fung HL, Darke AC, Parker JO. Oral isosorbide dinitrate in angina pectoris: comparison of duration of action and dose-response relation during acute and sustained therapy. *Am J Cardiol*. 1982;49(2):411–9.
68. Parker JO, Farrell B, Lahey KA, Moe G. Effect of intervals between doses on the development of tolerance to isosorbide dinitrate. *N Engl J Med*. 1987;316(23):1440–4.
69. Bassan MM. The daylong pattern of the antianginal effect of long-term three times daily administered isosorbide dinitrate. *J Am Coll Cardiol*. 1990;16(4):936–40.
70. Chrysant SG, Glasser SP, Bittar N, et al. Efficacy and safety of extended-release isosorbide mononitrate for stable effort angina pectoris. *Am J Cardiol*. 1993;72(17):1249–56.
71. Jurt U, Gori T, Ravandi A, Babaei S, Zeman P, Parker JD. Differential effects of pentaerythritol tetranitrate and nitroglycerin on the development of tolerance and evidence of lipid

- peroxidation: a human in vivo study. *J Am Coll Cardiol*. 2001;38(3):854–9.
72. Schnorbus B, Schiewe R, Ostad MA, et al. Effects of pentaerythritol tetranitrate on endothelial function in coronary artery disease: results of the PENTA study. *Clin Res Cardiol*. 2010;99(2):115–24.
 73. Fink B, Bassenge E. Unexpected, tolerance-devoid vasomotor and platelet actions of pentaerythrityl tetranitrate. *J Cardiovasc Pharmacol*. 1997;30(6):831–6.
 74. Oberle S, Abate A, Grosser N, et al. Endothelial protection by pentaerythrityl trinitrate: bilirubin and carbon monoxide as possible mediators. *Exp Biol Med (Maywood)*. 2003;228(5):529–34.
 75. Gori T, Daiber A. Non-hemodynamic effects of organic nitrates and the distinctive characteristics of pentaerythrityl tetranitrate. *Am J Cardiovasc Drugs*. 2009;9(1):7–15.
 76. Munzel T, Meinertz T, Tebbe U, et al. Efficacy of the long-acting nitro vasodilator pentaerythrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial. *Eur Heart J*. 2014;35(14):895–903.
 77. Meffert M, Paackelmann IM. Experience of long term treatment and different dosage regimens of isosorbide 5-mononitrate. *Drugs*. 1987;33 Suppl 4:104–10.
 78. Uusitalo A. Long term efficacy of a controlled-release formulation of isosorbide 5-mononitrate (Imdur) in angina patients receiving beta-blockers. *Drugs*. 1987;33 Suppl 4:111–7.
 79. Hart EC, Wallin BG, Barnes JN, Joyner MJ, Charkoudian N. Sympathetic nerve activity and peripheral vasodilator capacity in young and older men. *Am J Physiol Heart Circ Physiol*. 2014;306(6):H904–9.
 80. Aerts A, Dendale P, Strobel G, Block P. Sublingual nitrates during head-up tilt testing for the diagnosis of vasovagal syncope. *Am Heart J*. 1997;133(5):504–7.
 81. Li Y, Zhang D, Jin W, et al. Mitochondrial aldehyde dehydrogenase-2 (ALDH2) Glu504Lys polymorphism contributes to the variation in efficacy of sublingual nitroglycerin. *J Clin Invest*. 2006;116(2):506–11.
 82. Wall TL, Thomasson HR, Ehlers CL. Investigator-observed alcohol-induced flushing but not self-report of flushing is a valid predictor of ALDH2 genotype. *J Stud Alcohol*. 1996;57(3):267–72.

Chapter 6

Nicorandil

Jason M. Tarkin and Juan Carlos Kaski

Introduction

Nicorandil (*N*-[2-(Nitro-oxy)ethyl]-3-pyridine carboxamide) is an anti-angina agent that acts as both an nitric oxide (NO) donor and adenosine triphosphate-dependant potassium (K^+_{ATP}) channel opener. Nicorandil helps to prevent myocardial ischaemia and the symptoms of angina through its vaso-relaxant affects on the systemic and coronary vasculature, which offload the ventricles and improve myocardial oxygen supply; it may also offer cardio-protective benefit due to activation of endogenous ischaemic preconditioning mechanisms. This chapter will provide an overview of the pharmacological properties of nicorandil and evidence for its clinical use in stable angina.

J.M. Tarkin, MBBS, MRCP
Division of Cardiovascular Medicine,
University of Cambridge, Cambridge, UK

London Deanery, London, UK

J.C. Kaski, MD, DSc, FRCP, FESC, FACC, FAHA (✉)
Cardiovascular and Cell Sciences Research Institute,
St George's, University of London, London, UK
e-mail: jkaski@sgul.ac.uk

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_6,
© Springer International Publishing Switzerland 2015

Pharmacological Profile of Nicorandil

Chemical Composition

The chemical structure of nicorandil (Fig. 6.1) consists of a nicotinamide derivative combined with a nitrate moiety. Its molecular formula is $C_8H_9N_3O_4$ and molecular weight 211.18 g/mol.

Mechanism of Action

Anti-Angina Actions

Nicorandil has two distinct anti-angina mechanisms (Fig. 6.2) [1–3]. The nitrate component acts mainly on systemic venous (capacitance) vessels to reduce preload, and also dilates epicardial coronary arteries. In this context, vasodilatation occurs due to activation of soluble guanylate cyclase, resulting in increased cGMP, activation of protein kinase G, and subsequent lowering of intracellular Ca^{2+} and inhibition of myosin light-chain kinase activity; ultimately leading to relaxation of vascular smooth muscle cells [4]. The nitrate-like effect of nicorandil on the cGMP pathway accounts for the majority of its anti-angina effects at therapeutic concentrations [5].

Nicorandil is also a K^+_{ATP} channel opener. K^+_{ATP} channels control cell excitability, and by opening these channels, nicorandil causes vascular smooth cell depolarization and

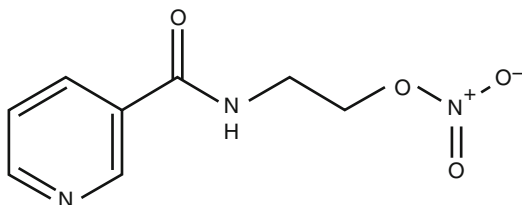


FIGURE 6.1 Chemical structure of nicorandil

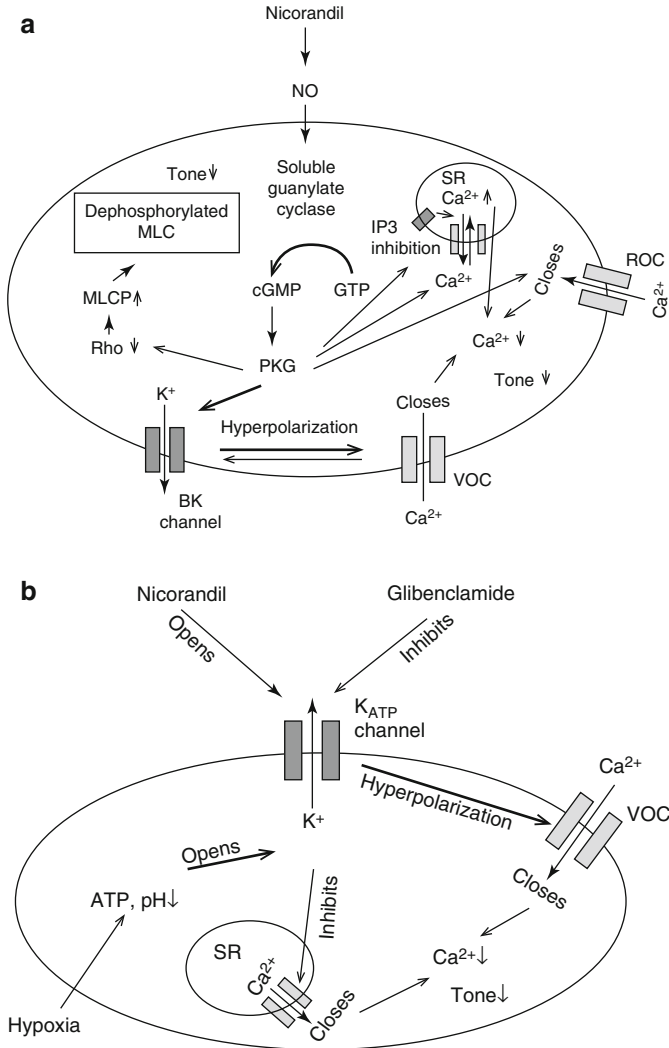


FIGURE 6.2 Molecular actions of nicorandil, showing activation of both *cGMP* Cyclic GMP (guanosine monophosphate) (a) and K^+_{ATP} (b) signaling pathways. *MLC* myosin light chain, *ROC* receptor-operated channels, *VOC* voltage-operated channels, *BK* big potassium, *ATP* adenosine triphosphate, *IP₃* inositol triphosphate, *SR* sarcoplasmic reticulum, *GTP* guanosine-5'-triphosphate, *PKG* protein kinase G (Figure adapted from Horinaka [20])

indirect closure of L-type voltage gated calcium channels resulting in arterial dilatation (similarly to calcium channel blockers) [6, 7]. This affects peripheral and coronary arterial resistance vessels (primarily the coronary microcirculation), resulting in decreased afterload and improved coronary flow [8–10].

Unlike nitrates, tolerance does not develop with nicorandil, probably due to its dual mode of action [11]. This is of particular importance in view of the long-term deleterious effects on endothelial function reported due to free radical accumulation in the context of nitrate tolerance [12]. Sekiya et al. studied the long-term effects of nicorandil and isosorbide dinitrate on endothelial function in 42 patients with ischaemic heart disease in 2005 [13]. In this study, isosorbide dinitrate was associated with significantly worse flow mediated dilatation (a marker of endothelial function) and carotid intima-medial thickness at 3 months, whereas nicorandil showed improved endothelial function and no progression of atherosclerosis.

Cardio-Protective Mechanisms

The actions of nicorandil on K_{ATP}^{+} channels confer cardio-protection through activation of pathways linked to ischaemic preconditioning, however the exact mechanism for this remains unclear [14, 15]. During periods of myocardial ischaemia, K_{ATP} channels are opened due to decreased ATP, cellular acidosis and actions of adenosine mediated via A1 receptors. Hypoxic dilatation of the coronary arteries is mediated by K_{ATP} channels [16]. Activation of K_{ATP} channels also shortens myocardial cell action potentials (seen as electrocardiographic shift in ST-segments), reduces Ca^{2+} overload and cellular energy demands; this has been proposed as an endogenous anti-ischaemic mechanism that may, in part, explain the cardio-protective properties of nicorandil [17]. However, more recently, attention has focused on the role of mitochondrial K_{ATP} channels in mediating ischemic preconditioning due to nicorandil [18, 19], and in particular its potential to

reduce oxidative stress through inhibition of mitochondrial permeability transition pore (mPTP) activation during ischaemic reperfusion injury [20, 21].

Haemodynamic Effects

The haemodynamic effects of nicorandil have been studied in patients undergoing coronary angiography, which overall result in balanced offloading of the ventricles through reduction in preload and afterload, and improved coronary flow due to lowered coronary arterial resistance. A mild transient, dose-dependant sympathetically mediated baroreceptor reflex tachycardia can also occur, but nicorandil does not directly affect cardiac conduction or contractility [22].

Nicorandil dilates coronary arteries on average by 10–20 % in patients with coronary artery disease, which is mostly due to its nitrate-like effect [23]. Significant reduction in coronary arterial resistance is also observed [24, 25]. Coltart et al. showed in a study of 15 patients undergoing routine angiography in 1989, that administration of 40 mg of nicorandil decreased preload (left ventricular end diastolic pressure lowered 4.8 mmHg and mean pulmonary artery pressure 5.7 mmHg), afterload (total peripheral resistance lowered 19 %) and blood pressure (systolic pressure lowered 34 % and diastolic 21 %) [26]. In other angiographic studies, 20 mg of nicorandil decreased left ventricular systolic pressure by 12–13 %, and increased non-stenotic and stenotic epicardial artery diameter by 14 % [27]. Nicorandil has also been shown to significantly improve cardiac index in patients with congestive heart failure [28], and regional wall motion abnormalities following myocardial stunning [29].

Pharmacokinetics

Nicorandil is rapidly and almost completely absorbed via the gastrointestinal tract, reaching maximal plasma concentration after 30–60 min, and steady-state levels following 4–5 days of

standard therapy. Gastrointestinal absorption is delayed, but not decreased by food. Its half-life is 52 ± 13 min. Nicorandil does not undergo first-pass metabolism, and displays a linear dose-to-plasma concentration relationship at doses of 5–40 mg. The oral bioavailability is 75 ± 23.6 %. Metabolism is mainly via denitration into the nicotinamide pathway, with less than 20 % of the administered dose excreted in the urine. Nicorandil circulates largely unbound to albumin or other plasma proteins. Its anti-angina effects last approximately 12 h, necessitating twice-daily dosage. Pharmacokinetic properties are unchanged in the elderly, and in chronic liver and/or renal disease. Plasma levels are not significantly altered by any known drug interactions [30, 31].

Practical Considerations

Dosage

The recommended starting dose of nicorandil is 10 mg twice daily (Table 6.1). In particular patients susceptible to headache, a starting dose of 5 mg twice daily may be used, with subsequent up-titration to achieve clinical response. The usual therapeutic dose is 10–20 mg twice daily, although up to 30 mg twice daily may be used if necessary. As a general principle the lowest effective dose is recommended to avoid potential side-effects, especially in the elderly; although no specific dose adjustments appear to be required for age, or with hepatic or renal impairment.

Safety and Tolerability

The safety of nicorandil, as monotherapy and when combined with other anti-angina agents, has been demonstrated by numerous clinical trials, including a large Prescription Event Monitoring (PEM) study [32]. There is a theoretical risk of arrhythmia due to shortening of the myocardial action potential,

TABLE 6.1 Nicorandil prescribing

Indications

To prevent symptoms of stable angina (second-line drug)

To prevent cardiac events in patients with stable angina and atherosclerosis

Dose

Starting dose: 10 mg twice daily

Maintenance dose: 10 to 20 mg twice daily

No dose adjustment required for hepatic or renal impairment

Side-effects

Common: headache, dizziness, flushing, malaise, nausea/vomiting

Rare: gastro-intestinal tract, skin and mucosal ulcers

Contraindications

Hypotension/cardiogenic shock

Aortic stenosis

Not to be co-administered with phosphodiesterase-5-inhibitors (e.g. sildenafil); may cause profound hypotension

Caution advised when combining with other drugs that potentially lower blood pressure

however no adverse effect on rhythm has been observed in clinical studies and nicorandil may, in fact, protect against ischaemic-induced arrhythmias in patients with unstable coronary disease [33].

Nicorandil is reasonably well-tolerated by most patients; less than 10 % of patients report side-effects at 30 days, and on average 70 % continue to take the medication at 1 year [34]. The side-effect profile is mostly related to its action as a vasodilator. Headache is the most common side-effect, and main reason patients stop taking nicorandil. Headaches are reported by 36 % of patients, usually within the first few days

of therapy, and can often be prevented when using a lower starting dose with slow up-titration. Indeed, symptomatic lowering of blood pressure tends only to occur with starting doses ≥ 40 mg. Other common side-effects are dizziness, flushing, malaise and gastro-intestinal upset, which occur in ≤ 3 %. Rarely, gastrointestinal, skin and mucosal ulcers may develop [35, 36]; these may be refractory to treatment and respond only to withdrawal of nicorandil, which should be stopped in this context. Overall, the incidence of side-effects is similar to other anti-angina agents, including beta-blockers, calcium channel blockers and long-acting nitrates. Nicorandil does not cause worsening of angina, and there is no rebound phenomenon when discontinued abruptly [37].

Cautions and Contraindications

Nicorandil is contraindicated in patients who are allergic to the drug or its constituents. It must not be used in cardiogenic shock, hypotension, or left ventricular failure with low filling pressure, and is also contraindicated by aortic stenosis. Due to the risk of profound hypotension, nicorandil should not be used in conjunction with phosphodiesterase-5-inhibitors (e.g. sildenafil), and caution should be taken when co-administered with other agents that potentially lower blood pressure. As there is a small, but potential risk of gastro-intestinal ulceration due to nicorandil, caution is advised when prescribing for patients also taking corticosteroids. There are no other specific drug warnings, however it is important to note that sulphonylureas have the potential to close K^{+}_{ATP} channels and thus may antagonize the effects of nicorandil.

The effects of nicorandil during pregnancy, breast-feeding and on fertility have not been studied in humans; although no teratogenicity or negative effects on fertility have been observed in animal studies. Therefore, the risks versus benefits of prescribing during pregnancy must be carefully considered. Nicorandil is not recommended while breast-feeding, as it is not known whether it is excreted into human milk.

Clinical Indications and Guidelines

Nicorandil is available in many European countries and the United Kingdom, but is not yet licensed in the United States. Clinical indications are: (1) prevention and long-term treatment of chronic stable angina, and (2) reduction in risk of acute coronary syndrome in patients with stable angina and (a) previous myocardial infarction, (b) coronary artery bypass grafting surgery, and/ or (c) angiographic evidence of coronary artery disease, or (d) positive exercise test together with cardiovascular risk factors.

ESC (European Society of Cardiology) guidance lists a class I (*is recommended*) indication for nicorandil for patients with intolerance, or contra-indication to beta-blockers and calcium channel blockers (level of evidence C), and class IIa (*should be considered*) for those with symptoms despite treatment with first agents (level of evidence B) [38]. NICE (National Institute for Health and Clinical Excellence), similarly, recommend the use of nicorandil for these purposes [39].

Clinical Efficacy

Nicorandil is effective in treating the symptoms of stable angina; both typical, effort-induced symptoms originating from obstructive epicardial artery atherosclerosis (and/or microvascular disease), and angina at rest due to coronary spasm. Its cardio-protective properties offer additional prognostic benefit, to help prevent cardiac events in patients with stable angina; and possibly to protect against ischemic-reperfusion injury and arrhythmia in those with unstable coronary disease.

Effort-Induced Angina

The clinical efficacy of nicorandil to improve symptoms of *effort-induced angina* has been evaluated by a number of clinical trials over the past several decades, which overall

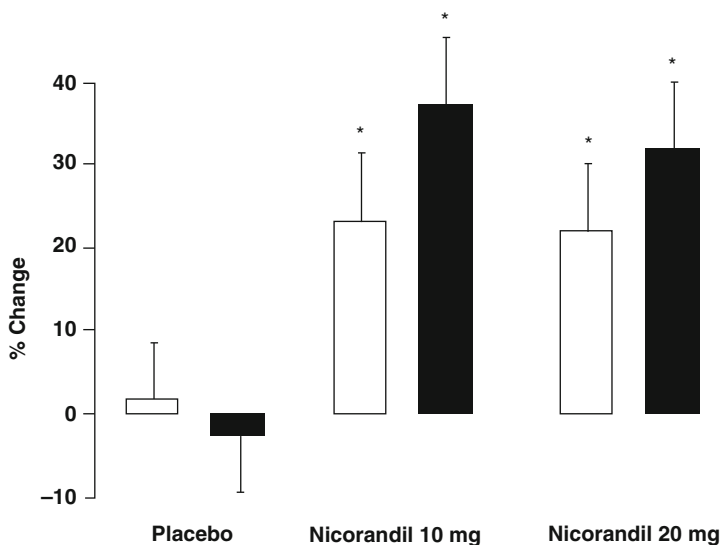


FIGURE 6.3 Effect of nicorandil after 2 weeks of twice-daily therapy, showing significantly increased time-to-onset of angina during exercise at baseline (*light bars*) and 2-h post dose (*black bars*). * $p < 0.05$ (Figure adapted from Meany et al. [47])

have shown similar results to conventional anti-angina drugs, with equal (or potentially less) side-effects and without development of tolerance. The overall efficacy in effort-induced angina is reportedly 71 % [40, 41].

Initial non-comparative studies [42, 43], and prospective randomized, double-blinded studies comparing nicorandil to placebo showed significant improvement on exercise testing from baseline in patients with stable angina [44–48]. In the largest of the placebo-controlled studies, which included 46 patients with stable angina, Meany et al. observed significantly increased time-to-angina in the study group following 2 weeks of nicorandil at 2 h (38 % vs. 2 %, $p < 0.05$) and 12 h (23 % vs. 2 %, $p < 0.05$) after administration (Fig. 6.3). In comparison to long-acting nitrates (isosorbide mononitrate and isosorbide dinitrate) [49–51], calcium channel blockers (nifedipine, amlodipine and diltiazem) [52–54], and

beta-blockers (atenolol, propranolol and metoprolol) [55–57], nicorandil has shown consistently similar short-term anti-ischaemic efficacy.

Among the larger trials to evaluate nicorandil, were the SNAPE (Study of Nicorandil in Angina Pectoris in the Elderly) and SWAN (Comparison of the anti-ischaemic and anti-anginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris) studies, carried out in 2000 and 1999 respectively [50, 53]. The SNAPE study, which included 194 patients with stable angina, reported a similar increase in time-to-ischaemia and time-to-angina, and decrease in maximum ST-segment depression on symptom-limited bicycle exercise test after 4 weeks of treatment with nicorandil versus isosorbide mononitrate [50]. The SWAN study was a multi-centre, double-blind, randomized study comparing nicorandil and amlodipine in 121 patients with stable angina from 25 centres in Austria and Switzerland over 8 weeks [53]. In this study, time-to-symptoms and total exercise duration was again similarly increased among the two study groups. Nicorandil also resulted in improved quality of life variables (similar to amlodipine), and a marginally more favourable tolerability profile.

For patients with effort-induced angina and evidence of inducible myocardial ischaemia, despite angiographically unobstructed coronary arteries (i.e. Cardiac syndrome X), nicorandil may also be used. In these patients, nicorandil augments coronary flow reserve by dilating the coronary microvasculature, ameliorating exercise-induced ischemia and related symptoms [58]. Nicorandil may also help to prevent against iatrogenic microvascular damage in patients with stable angina undergoing percutaneous coronary intervention [59].

Coronary Spasm

Nicorandil is particularly useful in the treatment of coronary spasm, which may arise due to *variant (Prinzmetal's) angina*, *mixed (variable-threshold) angina*, or in the context of an acute coronary syndrome [60]. Its dual mode of action confer

efficacy for both epicardial artery and microvascular spasm. Moreover, patients with variant angina show greater vasodilatory response to nicorandil, than those with effort-induced or post-myocardial infarction symptoms [61].

In a study of 32 patients with variant angina performed in 1987, Kisheda et al. found that nicorandil significantly reduced the frequency of angina episodes and ST-segment changes compared to placebo after 3 days [62]. Angina attacks disappeared completely in 24 of the 32 patients, and overall the average number of angina episodes decreased from 3.6 ± 0.4 per day to 0.7 ± 0.2 per day in the study group, and subsequently increased after stopping nicorandil. Nicorandil can also reverse coronary spasm induced by ergonovine [63], and is at least as effective in preventing coronary spasm as nifedipine [64]. Anecdotal evidence from several case reports suggests that intracoronary nicorandil may be more effective than other agents for relieving acute epicardial artery spasm [65, 66], and for improving coronary slow-flow phenomenon due to microvascular spasm [67–69].

Cardio-Protection

The cardio-protective role of nicorandil in the clinical setting was shown in the IONA (Impact of Nicorandil in Angina) and JCAD (Japanese Coronary Artery Disease) studies [70, 71]. In IONA, 5,126 patients with stable angina were randomized to receive 20 mg of nicorandil or placebo; this showed a significant reduction in cardiac events (composite end-point of death from coronary heart disease, nonfatal myocardial infarction, or hospital readmission for chest pain) in the study group after a mean follow-up of 1.6 years (hazard ratio 0.83, $p=0.014$) [70]. The results of IONA were reported in 2002, and subsequent sub-group analyses showed no evidence of any qualitative or quantitative interactions between nicorandil treatment benefit and subgroup status (including age, sex, risk factors, previous cardiac history, angina status, other medications and overall assessment of risk) [72].

JCAD was a multi-centre prospective observational study published in 2010, which included 2,558 patients with ischaemic

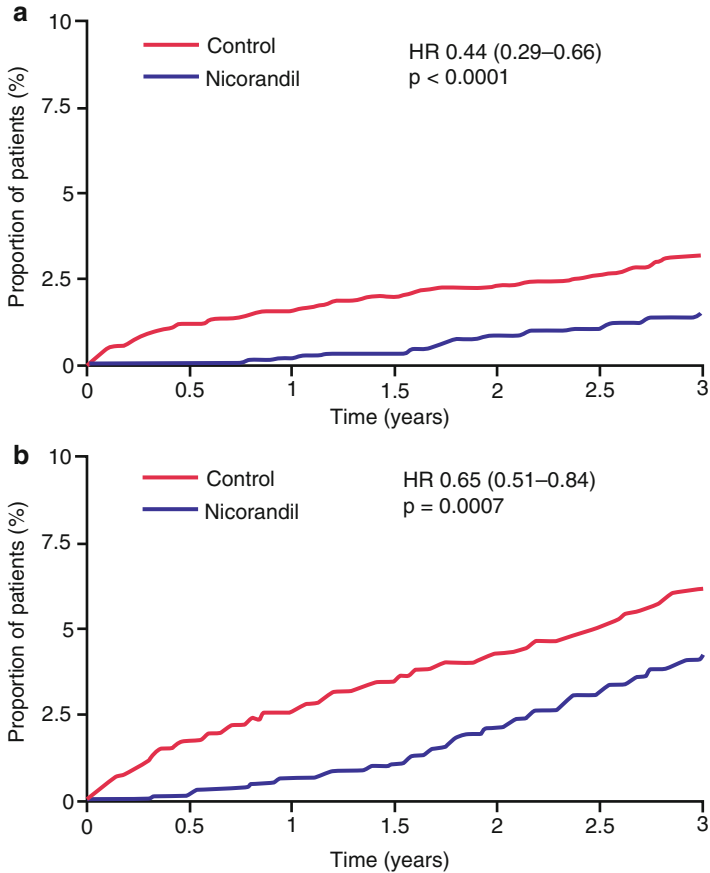


FIGURE 6.4 Cumulative incidence of all causes deaths (a) and cardiac deaths (b) among patients with ischemic heart disease treated with nicorandil vs. placebo, showing significant reduction for both in the study group (Figure adapted from Horinaka et al. [71])

heart disease and ≥ 75 % organic epicardial coronary artery stenosis treated with nicorandil, and the same number of matched controls, followed-up over 2.7 years. JCAD showed a 35 % reduction in all cause mortality (hazard ratio 0.65, $p=0.0008$) and 56 % reduction in cardiac death (hazard ratio 0.44, $p<0.0001$) in the study group (Fig. 6.4) [71]. For patients with *unstable angina*, nicorandil was shown in the CESAR 2

(Clinical European Studies in Angina and Revascularization) study to reduce non-sustained ventricular and supraventricular arrhythmias compared to placebo [33].

Concluding Remarks

Nicorandil is a second-line anti-angina agent, with similar clinical efficacy and tolerability to beta-blockers, calcium channel antagonists and long-acting nitrates. It acts partly as a nitrate, but also as a K^{+}_{ATP} channel opener, targeting multiple angina pathways. Activation of K^{+}_{ATP} channels also helps to circumvent the problem of nitrate tolerance, and may trigger endogenous mitochondrial ischaemic-preconditioning mechanisms, offering protection against future cardiac events. Nicorandil is particularly well-suited for patients with stable angina due to atherosclerosis or coronary spasm, who are not overtly sensitive to its haemodynamic side-effects, and whose symptoms cannot be adequately controlled with conventional therapy.

References

1. Yanagisawa T, Satoh K, Taira N. Circumstantial evidence for increased potassium conductance of membrane of cardiac muscle by 2-nicotinamidoethyl nitrate (SG-75). *Jpn J Pharmacol.* 1979; 29:687–94.
2. Holzmänn S. Cyclic GMP as possible mediator of coronary arterial relaxation by nicorandil (SG-75). *J Cardiovasc Pharmacol.* 1983;5:364–70.
3. Taira N. Nicorandil as a hybrid between nitrates and potassium channel activators. *Am J Cardiol.* 1989;63:18J–24.
4. Goldschmidt M, Landzberg BR, Frishman WH. Nicorandil: a potassium channel opening drug for treatment of ischemic heart disease. *J Clin Pharmacol.* 1996;36:559–72.
5. Kukovetz WR, Holzmänn S, Pösch G. Molecular mechanism of action of nicorandil. *J Cardiovasc Pharmacol.* 1992;20:S1–7.
6. Sumimoto K, Domae M, Yamanaka K, Nakao K, Hashimoto T, Kitamura K, Kuriyama H. Actions of nicorandil on vascular smooth muscles. *J Cardiovasc Pharmacol.* 1987;10 Suppl 8:S66–75.

7. Gomma AH, Purcell HJ, Fox KM. Potassium channel openers in myocardial ischaemia. *Drugs*. 2001;61:1705–10.
8. Brodmann M, Lischnig U, Lueger A, Stark G, Pilger E. The effect of the K⁺ agonist nicorandil on peripheral vascular resistance. *Int J Cardiol*. 2006;111:49–52.
9. Akai K, Wang Y, Sato K, Sekiguchi N, Sugimura A, Kumagai T, Komaru T, Kanatsuka H, Shirato K. Vasodilatory effect of nicorandil on coronary arterial microvessels: its dependency on vessel size and the involvement of the ATP-sensitive potassium channels. *J Cardiovasc Pharmacol*. 1995;26:541–7.
10. Berdeaux A, Drieu la Rochelle C, Richard V, Giudicelli JF. Differential effects of nitrovasodilators, K(+) -channel openers, and nicorandil on large and small coronary arteries in conscious dogs. *J Cardiovasc Pharmacol*. 1992;20 Suppl 3:S17–21.
11. Wagner G. Selected issues from an overview on nicorandil: tolerance, duration of action, and long-term efficacy. *J Cardiovasc Pharmacol*. 1992;20 Suppl 3:S86–92.
12. Gori T, Parker JD. Nitrate-induced toxicity and preconditioning: a rationale for reconsidering the use of these drugs. *J Am Coll Cardiol*. 2008;52:251–4.
13. Sekiya M, Sato M, Funada J, Ohtani T, Akutsu H, Watanabe K. Effects of the long-term administration of nicorandil on vascular endothelial function and the progression of arteriosclerosis. *J Cardiovasc Pharmacol*. 2005;46:63–7.
14. Markham A, Plosker GL, Goa KL. Nicorandil. An updated review of its use in ischaemic heart disease with emphasis on its cardioprotective effects. *Drugs*. 2000;60:955–74.
15. Matsubara T, Minatoguchi S, Matsuo H, et al. Three minute, but not one minute, ischemia and nicorandil have a preconditioning effect in patients with coronary artery disease. *J Am Coll Cardiol*. 2000;35:345–51.
16. Daut J, Maier-Rudolph W, von Beckerath N, Mehrke G, Günther K, Goedel-Meinen L. Hypoxic dilation of coronary arteries is mediated by ATP-sensitive potassium channels. *Science*. 1990;247:1341–4.
17. Caverio I, Djellas Y, Guillon JM. Ischemic myocardial cell protection conferred by the opening of ATP-sensitive potassium channels. *Cardiovasc Drugs Ther*. 1995;9 Suppl 2:245–55.
18. Sato T, Sasaki N, O'Rourke B, Marbán E. Nicorandil, a potent cardioprotective agent, acts by opening mitochondrial ATP-dependent potassium channels. *J Am Chem Soc*. 2000;35: 514–8.

19. Szewczyk A, Marbán E. Mitochondria: a new target for K channel openers? *Trends Pharmacol Sci.* 1999;20:157–61.
20. Horinaka S. Use of nicorandil in cardiovascular disease and its optimization. *Drugs.* 2011;71:1105–19.
21. Hausenloy DJ, Maddock HL, Baxter GF, Yellon DM. Inhibiting mitochondrial permeability transition pore opening: a new paradigm for myocardial preconditioning? *Cardiovasc Res.* 2002;55: 534–43.
22. Treese N, Erbel R, Meyer J. Acute hemodynamic effects of nicorandil in coronary artery disease. *J Cardiovasc Pharmacol.* 2006; 20 Suppl 3:S52–6.
23. Knight C, Purcell H, Fox K. Potassium channel openers: clinical applications in ischemic heart disease—overview of clinical efficacy of nicorandil. *Cardiovasc Drugs Ther.* 1995;9:229–36.
24. Aizawa T, Ogasawara K, Kato K. Effects of nicorandil on coronary circulation in patients with ischemic heart disease: comparison with nitroglycerin. *J Cardiovasc Pharmacol.* 1987;10 Suppl 8:S123–9.
25. Falase B, Easaw J, Youhana A. The role of nicorandil in the treatment of myocardial ischaemia. *Expert Opin Pharmacother.* 2001;2:845–56.
26. Coltart DJ, Signy M. Acute hemodynamic effects of single-dose nicorandil in coronary artery disease. *Am J Cardiol.* 1989;63: 34J–9.
27. Suryapranata H, MacLeod D. Nicorandil and cardiovascular performance in patients with coronary artery disease. *J Cardiovasc Pharmacol.* 1992;20 Suppl 3:S45–51.
28. Solal AC, Jaeger P, Bouthier J, Juliard JM, Dahan M, Gourgon R. Hemodynamic action of nicorandil in chronic congestive heart failure. *Am J Cardiol.* 1989;63:44J–8.
29. Thormann J, Schlepper M, Kramer W, Gottwik M, Kindler M. Effectiveness of nicorandil (SG-75), a new long-acting drug with nitroglycerin effects, in patients with coronary artery disease: improved left ventricular function and regional wall motion and abolition of pacing-induced angina. *J Cardiovasc Pharmacol.* 1983;5:371–7.
30. Frydman AM, Chapelle P, Diekmann H, Bruno R, Thebault JJ, Bouthier J, Caplain H, Ungethuem W, Gaillard C, Le Liboux A. Pharmacokinetics of nicorandil. *Am J Cardiol.* 1989;63: 25J–33.
31. Frydman A. Pharmacokinetic profile of nicorandil in humans: an overview. *J Cardiovasc Pharmacol.* 1992;20 Suppl 3:S34–44.

32. Dunn N, Freemantle S, Pearce G, Wilton LV, Mann RD. Safety profile of nicorandil–prescription-event monitoring (PEM) study. *Pharmacoepidemiol Drug Saf.* 1999;8:197–205.
33. Patel DJ, Purcell HJ, Fox KM. Cardioprotection by opening of the K(ATP) channel in unstable angina. Is this a clinical manifestation of myocardial preconditioning? Results of a randomized study with nicorandil. CESAR 2 investigation. Clinical European studies in angina and revascularization. *Eur Heart J.* 1999;20: 51–7.
34. Witchitz S, Darmon JY. Nicorandil safety in the long-term treatment of coronary heart disease. *Cardiovasc Drugs Ther.* 1995;9 Suppl 2:237–43.
35. Agbo-Godeau S, Joly P, Lauret P, Szpirglas R, Szpirglas H. Association of major aphthous ulcers and nicorandil. *Lancet.* 1998;352:1598–9.
36. Watson A, Ozairi OA, Fraser A, Loudon M, O’Kelly T. Nicorandil associated anal ulceration. *Lancet.* 2002;360:546–7.
37. Roland E. Safety profile of an anti-anginal agent with potassium channel opening activity: an overview. *Eur Heart J.* 1993;14 Suppl B:48–52.
38. Task Force Members; Montalescot G, Sechtem U, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J.* 2013;34:2949–3003.
39. National Institute for Health and Clinical Excellence. Management of stable angina. 2011. <http://guidance.nice.org.uk/CG126>.
40. Hanai Y, Mita M, Hishinuma S, Shoji M. Systematic review on the short-term efficacy and safety of nicorandil for stable angina pectoris in comparison with those of β -blockers, nitrates and calcium antagonists. *Yakugaku Zasshi.* 2010;130:1549–63.
41. Kinoshita M, Sakai K. Pharmacology and therapeutic effects of nicorandil. *Cardiovasc Drugs Ther.* 1990;4:1075–88.
42. Awata N, Azuma J, Sawamura A, Harada H, Hamaguchi T, Park S, Kishimoto S. Efficacy of nicorandil on exercise performance in patients with stable effort angina: exercise echocardiography evaluation. *Curr Ther Res.* 1989;45:621–32.
43. Hiasa Y, Hamai K, Wada T, Aihara T, Bando M, Nakai Y, Kataoka Y. Chronic effects of nicorandil on exercise tolerance in patients with stable effort angina pectoris. *Tokushima J Exp Med.* 1989;36:65–70.

44. Kinoshita M, Nishikawa S, Sawamura M, Yamaguchi S, Mitsunami K, Itoh M, Motomura M, Bito K, Mashiro I, Kawakita S. Comparative efficacy of high-dose versus low-dose nicorandil therapy for chronic stable angina pectoris. *Am J Cardiol.* 1986;58:733–8.
45. Hayata N, Araki H, Nakamura M. Effects of nicorandil on exercise tolerance in patients with stable effort angina: a double-blind study. *Am Heart J.* 1986;112:1245–50.
46. Camm AJ, Maltz MB. A controlled single-dose study of the efficacy, dose response and duration of action of nicorandil in angina pectoris. *Am J Cardiol.* 1989;63:J61–5.
47. Meany TB, Richardson P, Camm AJ, Coltart J, Griffith M, Maltz MB, Signy M. Exercise capacity after single and twice-daily doses of nicorandil in chronic stable angina pectoris. *Am J Cardiol.* 1989;63:J66–70.
48. Why HJ, Richardson PJ. A potassium channel opener as monotherapy in chronic stable angina pectoris: comparison with placebo. *Eur Heart J.* 1993;14 Suppl B:25–9.
49. Döring G. Antianginal and anti-ischemic efficacy of nicorandil in comparison with isosorbide-5-mononitrate and isosorbide dinitrate: results from two multicenter, double-blind, randomized studies with stable coronary heart disease patients. *J Cardiovasc Pharmacol.* 1992;20 Suppl 3:S74–81.
50. Ciampricotti R, Schotborgh CE, De Kam PJ, van Herwaarden RH. A comparison of nicorandil with isosorbide mononitrate in elderly patients with stable coronary heart disease: the SNAPE study. *Am Heart J.* 2000;139(5) (abstract).
51. Lai C, Onnis E, Solinas R, Orani E, Lai G, Cadeddu M, Cherchi A. A new anti-ischemic drug for the treatment of stable effort angina pectoris: nicorandil. Comparison with placebo and isosorbide-5-mononitrate. *Cardiologia.* 1991;36:703–11.
52. Ulvenstam G, Diderholm E, Frithz G, Gudbrandsson T, Hedbäck B, Höglund C, Moelstad P, Perk J, Sverrisson JT. Antianginal and anti-ischemic efficacy of nicorandil compared with nifedipine in patients with angina pectoris and coronary heart disease: a double-blind, randomized, multicenter study. *J Cardiovasc Pharmacol.* 1992;20 Suppl 3:S67–73.
53. The SWAN Study Group. Comparison of the antiischaemic and antianginal effects of nicorandil and amlodipine in patients with symptomatic stable angina pectoris: the SWAN study. *J Clin Basic Cardiol.* 1999;2:213–7.
54. Guermontprez JL, Blin P, Peterlongo F. A double-blind comparison of the long-term efficacy of a potassium channel opener and

- a calcium antagonist in stable angina pectoris. *Eur Heart J*. 1993; 14 Suppl B:30–4.
55. Hughes LO, Rose EL, Lahiri A, Raftery EB. Comparison of nicorandil and atenolol in stable angina pectoris. *Am J Cardiol*. 1990;66:679–82.
 56. Meeter K, Kelder JC, Tijssen JG, Buxx JJ, Henneman JA, Kerker JP, Hugenholtz PG. Efficacy of nicorandil versus propranolol in mild stable angina pectoris of effort: a long-term, double-blind, randomized study. *J Cardiovasc Pharmacol*. 1992;20 Suppl 3:S59–66.
 57. Di Somma S, Liguori V, Petitto M, Carotenuto A, Bokor D, de Divitiis O, de Divitiis M. A double-blind comparison of nicorandil and metoprolol in stable effort angina pectoris. *Cardiovasc Drugs Ther*. 1993;7:119–23.
 58. Yamabe H, Namura H, Yano T, Fujita H, Kim S, Iwahashi M, Maeda K, Yokoyama M. Effect of nicorandil on abnormal coronary flow reserve assessed by exercise 201Tl scintigraphy in patients with angina pectoris and nearly normal coronary arteriograms. *Cardiovasc Drugs Ther*. 1995;9:755–61.
 59. Hirohata A, Yamamoto K, Hirose E, et al. Nicorandil prevents microvascular dysfunction resulting from PCI in patients with stable angina pectoris: a randomised study. *EuroIntervention*. 2014;9:1050–6.
 60. Kaski JC. Management of vasospastic angina—role of nicorandil. *Cardiovasc Drugs Ther*. 1995;9:221–7.
 61. Kishida H, Hata N, Kusama Y, Iwahara S, Sasaki Y, Mori N, Yasutake M, Koumi S, Takayama M, Munakata K. Angiographic response to a vasodilating drug, nicorandil, in patients with coronary artery disease. *Jpn Heart J*. 1990;31:135–43.
 62. Kishida H, Murao S. Effect of a new coronary vasodilator, nicorandil, on variant angina pectoris. *Clin Pharmacol Ther*. 1987;42:166–74.
 63. Aizawa T, Ogasawara K, Nakamura F, Hirosaka A, Sakuma T, Nagashima K, Kato K. Effect of nicorandil on coronary spasm. *Am J Cardiol*. 1989;63:75J–9.
 64. Lablanche JM, Bauters C, Leroy F, Bertrand ME. Prevention of coronary spasm by nicorandil: comparison with nifedipine. *J Cardiovasc Pharmacol*. 1992;20 Suppl 3:S82–5.
 65. Hayashi T, Ichikawa M, Iwata A, Nakata T, Lim Y-J, Mishima M. Intracoronary nicorandil relieves multiple coronary vasospasm with hemodynamic collapse. *Circ J*. 2008;72:327–30.
 66. Noguchi T, Nonogi H, Yasuda S, Daikoku S, Morii I, Itoh A, Goto Y, Miyazaki S. Refractory coronary spasm relieved by intracoronary administration of nicorandil. *Jpn Circ J*. 2000;64:396–8.

67. Sadamatsu K, Tashiro H, Yoshida K, Shikada T, Iwamoto K, Morishige K, Yoshidomi Y, Tokunou T, Tanaka H. Acute effects of isosorbide dinitrate and nicorandil on the coronary slow flow phenomenon. *Am J Cardiovasc Drugs*. 2010;10:203–8.
68. Sadamatsu K, Inoue S, Tashiro H. Coronary slow flow phenomenon caused by contrast-induced microvascular spasm. *Intern Med*. 2007;46:1991–3.
69. Kiyooka T, Kobayashi Y, Ikari Y. A case of vasospastic angina in which the ergonovine provocation test with intracoronary isosorbide dinitrate and nicorandil was effective in the diagnosis of microvascular spasm. *Cardiovasc Interv Ther*. 2014. doi:[10.1007/s12928-013-0237-1](https://doi.org/10.1007/s12928-013-0237-1).
70. IONA Study Group. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. *Lancet*. 2002;359:1269–75.
71. Horinaka S, Yabe A, Yagi H, Ishimitsu T, Yamazaki T, Suzuki S, Kohro T, Nagai R; The JCAD Study Investigators. Effects of nicorandil on cardiovascular events in patients with coronary artery disease in The Japanese Coronary Artery Disease (JCAD) Study. *Circ J*. 2010;74:503–9.
72. IONA Study Group. Impact of nicorandil in angina: subgroup analyses. *Heart*. 2004;90:1427–30.

Chapter 7

Ivabradine

Alberto Dominguez-Rodriguez

Introduction

Stable angina pectoris is the most common presenting symptom of coronary artery disease (CAD). While the subjective nature of the symptom complicates epidemiological studies, it has been estimated that between 2 and 4 % of the general population in most European countries suffer from angina, with values as high as 10–20 % for males in the 65- to 74-year age group [1]. Similar values have been reported in the USA [2]. A sizable proportion of patients with angina currently receive inadequate treatment for their condition. This suboptimal management has been linked to the shortcomings of currently available therapy and the presence of comorbidities [3, 4].

These observations have been corroborated by the Euro Heart Survey, which assessed the presenting characteristics and subsequent management of 3,779 patients with stable angina in Europe [5]. The majority comprised men, with a mean age of 61 years. The overall prevalence of concomitant conditions was low; for example, 18 % presented with diabetes, 7 % with peripheral vascular disease, and 8 % with

A. Dominguez-Rodriguez, MD, PhD, FESC
Department of Cardiology, Hospital Universitario de Canarias,
Tenerife, Spain
e-mail: adrvdg@hotmail.com

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_7,
© Springer International Publishing Switzerland 2015

135

chronic respiratory disease. Despite this, the Euro Heart Survey demonstrated that diabetes and other comorbidities, the severity of angina, and left ventricular dysfunction can all affect the prognosis of patients with stable angina [6]. The Euro Heart Survey also indicated that patient characteristics and the presence of a coexisting illness may have an impact on the management of stable angina [5, 6].

The majority of episodes of myocardial ischemia in patients with stable CAD are triggered by an acceleration of heart rate due to exercise or the activities of daily living. Indeed, in such patients, any increase in heart rate during daily activities may be associated with ischemia [7, 8]. Moreover, the variation in ischemic activity is independently associated with a similar circadian variation in heart rate, suggesting that observed circadian ischemic patterns are primarily linked to heart rate patterns [9]. There are many mechanisms through which an elevated heart rate might directly affect cardiovascular risk, including increased myocardial oxygen demand, energy depletion, accelerated atherosclerosis, and increased risk of plaque rupture [10].

Heart rate reduction is a well-recognized strategy for prevention of myocardial ischemia and angina pectoris in patients with stable CAD. Heart rate-lowering therapy can avert excessive increases in heart rate due to the physical and emotional stress associated with daily living, preventing the onset of ischemia and angina. Thus, resting heart rate of 60 bpm is often recommended as a target in CAD patients [11]. Ivabradine is the first member of a new group of drugs, the specific heart rate-lowering agents, to be introduced into clinical use. Ivabradine acts by selectively inhibiting the ionic current I_p , which modulates pacemaker activity in the sinoatrial node, providing pure heart rate reduction [12].

Pharmacodynamic Properties

Heart rate is normally determined by the rate of spontaneous diastolic depolarization of myocytes in the sinoatrial node. The rate of spontaneous diastolic depolarization is

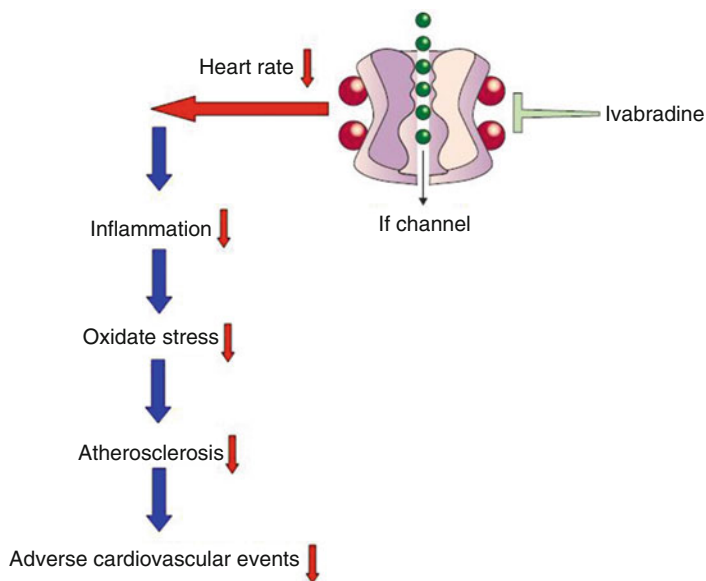


FIGURE 7.1 Role of ivabradine in cardiovascular pathology. I_f channels, in the sinoatrial node, are responsible for an inwardly direct current. The selective binding of ivabradine to I_f channels, makes it a pure heart-rate-reducing agent. The heart rate reduction by ivabradine can reverse accelerated atherosclerosis and therefore a reduction of adverse cardiovascular events

significantly influenced by I_p , a mixed sodium–potassium current involving ion movement across so-called f-channels, which are activated by hyperpolarization, and the opening of which is dependent on the intracellular availability of cyclic adenosine monophosphate [13].

Ivabradine directly and selectively inhibits the I_f current, reducing diastolic depolarization rate and heart rate (Fig. 7.1) [14]. Ivabradine enters and blocks the channel from the cytoplasmic side of the membrane, preferentially when the channel is in the open state [14]. The selective binding of ivabradine to I_f channels, makes it a pure heart-rate-reducing agent. The specificity of ivabradine for the I_f current ensures that ivabradine has no direct effects on myocardial

contractility (or relaxation), ventricular repolarization or intracardiac conduction [15]. The dependence of I_f inhibition with ivabradine on baseline heart rate suggests that heart rate slowing should be greatest in patients with the highest pre-treatment heart rate. This was corroborated by data in 2,351 patients, which showed that the magnitude of heart rate reduction was directly related to baseline heart rate, for each dose of ivabradine [16].

By reducing heart rate, ivabradine reduces myocardial oxygen demand. It also maximizes oxygen supply and myocardial perfusion by prolonging diastolic time and by enabling coronary vasodilation during exercise [17]. In contrast, β -blockers tend to prolong systole because of their negative effect on myocardial contractility. In consequence, diastole is shorter with β -blockers than with ivabradine at rest and during exercise for a similar heart rate reduction [17].

Endothelial dysfunction has been demonstrated in CAD. In experimental studies, ivabradine has been shown to protect endothelial function. Treatment with ivabradine for 3 months prevented deterioration of endothelium-dependent vasodilation in the renal and cerebral arteries in dyslipidaemic mice [18]. Furthermore, recently has been demonstrated that oral ivabradine enhances the resolution of the marked inflammatory response associated with acute coronary syndrome [19, 20]. These data suggest that ivabradine can ameliorate the vascular component of inflammation in line with observations of previous studies in animal models [21, 22].

Pharmacokinetic Properties and Tolerability

Ivabradine exhibits linear pharmacokinetics over an oral dose range of 0.5–24 mg, with rapid absorption after administration of a single oral dose [23]. In fasting conditions, the time to peak drug concentration is approximately 1 h, with an absolute bioavailability of the filmcoated tablets of around 40 % following gastrointestinal and hepatic first-pass metabolism. In fed conditions, the time to peak plasma drug concentration

is prolonged by approximately 1 h and the plasma concentration of ivabradine is increased by 20–30 % [23].

Ivabradine has a half-life of 2 h in plasma and an effective half-life of 11 h. Renal clearance of ivabradine is 70 mL/min, and the total clearance is 400 mL/min. After oral administration, approximately 4 % of the ivabradine dose is excreted unchanged in urine. Compared with younger individuals, no appreciable differences in the pharmacokinetic profile of ivabradine were observed in the elderly (aged ≥ 65 years) or very elderly (≥ 75 years) [23].

Renal impairment (creatinine clearance 15–60 mL/min) has a minimal effect on the pharmacokinetics of both ivabradine and its main metabolite, as renal clearance accounts for a small part (20 %) of the elimination of both products. As regards hepatic impairment and ivabradine, patients with mild hepatic impairment require no dose adjustment. Caution is advocated when treating patients with moderate hepatic impairment, and ivabradine is contraindicated in patients with severe hepatic insufficiency [23].

Ivabradine has a favourable tolerability profile, as observed during its clinical development [24]. It is safe and well tolerated when administered as a monotherapy [25, 26] or when administered in combination with atenolol [27], bisoprolol [28], other β -blockers [29] or other cardiovascular therapies [30]. Ivabradine is also well tolerated in patients with comorbidities including asthma and chronic obstructive pulmonary disease [31] or in patients with diabetes mellitus, without any particular safety concerns or adverse effects on glucose metabolism [32].

The two most common adverse events associated with the recommended doses of ivabradine are bradycardia and visual symptoms [24]. Bradycardia is an expected adverse event of any heart rate-reducing treatment. However, in the clinical programme of ivabradine, only 3–4 % of patients receiving therapeutic doses of ivabradine (5 or 7.5 mg twice daily) experienced symptomatic bradycardia. Furthermore, there were very low rates of discontinuation in these studies due to this adverse event [33, 34]. The visual symptoms associated

with ivabradine are due to the action of ivabradine on retinal ion channels (I_h current), which belong to the same family as those responsible for the I_f current in the sino-atrial node. In the clinical trials of ivabradine, visual symptoms (mainly phosphenes) were reported in a small proportion of patients. These symptoms were generally mild and resolved spontaneously during or after treatment. Less than 1 % of patients receiving ivabradine in clinical trials discontinued treatment because of visual symptoms [25–30, 35].

Efficacy of Ivabradine in CAD with Monotherapy

The anti-anginal and anti-ischemic efficacy of ivabradine has been confirmed in patients with stable angina and monotherapy (Table 7.1).

In a placebo-controlled, randomized, dose-ranging study conducted in 360 patients with stable CAD and chronic stable angina, Borer et al. [25] showed that ivabradine produced dose-dependent improvements in exercise tolerance parameters. This reduction in angina and ischemia was associated with significant reductions in rate-pressure product at peak exercise and increases in total work performed in an exercise tolerance test among ivabradine-treated patients. Furthermore, in the open-label extension phase (2–3 months) of this study, ivabradine reduced angina attacks from 4.14 to 0.95 attacks per week and consumption of short-acting nitrates from 2.28 to 0.50 U per week [25].

Tardif et al., in a double-blind, randomised, active-controlled, parallel-group and multicentre study, demonstrated that after 16 weeks of treatment, patients receiving ivabradine 7.5 or 10 mg twice daily or atenolol 100 mg/day had similar increases in total exercise duration and the number of angina attacks per week. Even though ivabradine was noninferior, after 4 months of treatment, all exercise tolerance test parameters showed a trend toward improvement with ivabradine compared with atenolol [26].

TABLE 7.1 Summary of the main studies of ivabradine in coronary artery disease with monotherapy

Author	Study summary
Borer et al., 2003 [25]	Randomised double-blind, placebo-controlled trial, 360 patients with a ≥ 3 -month history of chronic stable angina were randomly assigned to receive ivabradine (2.5, 5, or 10 mg BID) or placebo for 2 weeks, followed by an open-label 2- or 3-month extension on ivabradine (10 mg BID) and a 1-week randomized withdrawal to ivabradine (10 mg BID) or placebo. In the per-protocol population ($n=257$), time to 1-mm ST-segment depression increased in the 5 and 10 mg BID groups ($P<0.005$); time to limiting angina increased in the 10 mg BID group ($P<0.05$).
Tardif et al., 2005 [26]	Randomised, double-blinded trial, 939 patients with stable angina were randomized to receive ivabradine 5 mg bid for 4 weeks and then either 7.5 or 10 mg bid for 12 weeks or atenolol 50 mg od for 4 weeks and then 100 mg od for 12 weeks. Patients underwent treadmill exercise tests at randomization (M(0)) and after 4 (M(1)) and 16 (M(4)) weeks of therapy. Increases in total exercise duration at trough at M(4) were 86.8 ± 129.0 and 91.7 ± 118.8 s with ivabradine 7.5 and 10 mg, respectively and 78.8 ± 133.4 s with atenolol 100 mg. The number of angina attacks was decreased by two-thirds with both ivabradine and atenolol.
Ruzyllo et al., 2007 [36]	Patients with a ≥ 3 -month history of chronic, stable effort-induced angina were randomised to receive ivabradine 7.5 mg ($n=400$) or 10 mg ($n=391$) twice daily or amlodipine 10 mg once daily ($n=404$) for a 3-month, double-blind period. Bicycle exercise tolerance tests were performed at baseline and monthly intervals. At 3 months, total exercise duration was improved by 27.6 ± 91.7 , 21.7 ± 94.5 and 31.2 ± 92.0 s with ivabradine 7.5 and 10 mg and amlodipine, respectively, both ivabradine groups were comparable to amlodipine (p -value for noninferiority <0.001). Similar results were observed for time to angina onset and time to 1 mm ST-segment depression.

(continued)

TABLE 7.1 (continued)

Author	Study summary
Skalidis et al., 2011 [37]	<p>During diagnostic coronary angiography (baseline), 21 patients with stable coronary artery disease underwent coronary flow velocity measurements in a non-culprit vessel, using a Doppler guidewire, at rest (r) and after adenosine administration to achieve maximal hyperaemia (h). During programmed coronary intervention in the culprit vessel, the same measurements were repeated 1 week after treatment with ivabradine (5 mg twice daily).</p> <p>Ivabradine treatment significantly improves hyperaemic coronary flow velocity and coronary flow reserve in patients with stable coronary artery disease. These effects remain even after heart rate correction indicating improved microvascular function.</p>

Ruzyllo et al., in a large multicentre, international, double-blind, randomized, parallel-group trial in 1,195 patients with stable angina, studied the efficacy of ivabradine versus amlodipine. They demonstrated, that ivabradine was not inferior to amlodipine in improving exercise tolerance as well as increasing time to angina onset, time to limiting angina and time to 1-mm ST-segment depression. Furthermore, ivabradine produced a greater reduction of rate-pressure product than amlodipine [36]. Recently, Skalidis et al. [37] assessed the effect of ivabradine on coronary blood flow velocity and coronary flow reserve in patients with stable CAD. This study showed that ivabradine significantly reduced heart rate and improved hyperaemic and resting coronary flow velocity and coronary flow reserve in these patients after 1 week of treatment.

Efficacy of Ivabradine in CAD with Combination Therapy

The anti-anginal and anti-ischemic efficacy of ivabradine has been confirmed in patients with stable angina and combination therapy (Table 7.2).

The double blind, randomized, multicentre, placebo-controlled ASSOCIATE (evaluation of the aSsociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr) trial was conducted in 889 patients with stable angina already receiving atenolol [27]. All included patients had a positive symptom-limited exercise test while receiving atenolol 50 mg once daily. These patients were randomized to receive either ivabradine 5 mg twice daily for 2 months, which was then

TABLE 7.2 Summary of the main studies of ivabradine in coronary artery disease with combination therapy

Author	Study summary
Lopez-Bescos et al., 2007 [30]	Randomized double-blind, parallel-group study 386 patients with chronic stable angina were randomized to either ivabradine 5 mg b.i.d. (n=198, group 1) or ivabradine 7.5 mg b.i.d. (n=188, group 2) for 12 months. Safety was assessed on the basis of reported adverse events at 1, 3, 6, 9 and 12 months. Ivabradine was well tolerated. Resting heart rate was reduced by 9 bpm in group 1 and 12 bpm in group 2. At month 12 relative to month 0 there was a significant reduction in the number of angina attacks per week.
Tardif et al., 2009 [27]	Randomised double-blinded trial, 889 patients with stable angina receiving atenolol 50 mg/day were randomized to receive ivabradine 5 mg b.i.d. for 2 months, increased to 7.5 mg b.i.d. for a further 2 months, or placebo. Patients underwent treadmill exercise tests at the trough of drug activity using the standard Bruce protocol for randomization and at 2 and 4 months. Total exercise duration at 4 months increased by 24.3 ± 65.3 s in the ivabradine group, compared with 7.7 ± 63.8 s with placebo ($P < 0.001$). Ivabradine was superior to placebo for all exercise test criteria at 4 months ($P < 0.001$ for all) and 2 months (P -values between < 0.001 and 0.018). Ivabradine in combination with atenolol was well tolerated.

(continued)

TABLE 7.2 (continued)

Author	Study summary
Amosova et al., 2011 [28]	<p>Twenty-nine patients with stable angina and moderate left ventricular systolic dysfunction already on bisoprolol 5 mg od were randomized into 2 groups. Group 1 (n=17) received ivabradine (5–7.5 mg bid) in addition to bisoprolol 5 mg od, while in group 2 (n=12) bisoprolol was uptitrated first to 7.5 mg and then 10 mg od. Patients underwent a treadmill test, 6-min walking test, and echocardiography at baseline and after 2 months. Mean resting heart rate decreased in both groups, from 76.6 ± 4.6 to 59.3 ± 2.5 bpm ($P < 0.001$) in group 1 and from 75.9 ± 3.0 to 60.5 ± 2.3 bpm ($P = 0.002$) in group 2. However, more patients became asymptomatic in group 1 than in group 2. Addition of ivabradine also improved exercise capacity. Chronotropic reserve significantly improved with ivabradine, but not with bisoprolol 10 mg.</p>
Werdan et al., 2012 [29]	<p>Non-interventional, multicenter, prospective study included 2,330 patients with stable angina pectoris treated with a flexible dose of ivabradine twice daily in addition to beta-blocker for 4 months. The parameters recorded included heart rate, number of angina attacks, nitrate consumption, tolerance, and quality of life. After 4 months ivabradine reduced heart rate, the number of angina attacks and nitrate consumption was reduced. At baseline (i.e., on beta-blocker), half of the patients (51 %) were classified as Canadian Cardiovascular Society (CCS) grade II; 29 % were CCS grade I. After 4 months' treatment with ivabradine, most of the patients were CCS grade I (68 %).</p>

TABLE 7.2 (continued)

Author	Study summary
Fox et al., 2014 [38]	Randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8 % and 6.4 %, respectively; hazard ratio, 1.08; 95 % confidence interval, 0.96–1.20; $P=0.20$), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina ($P=0.02$ for interaction).

increased to 7.5 mg twice daily for an additional 2 months (449 patients), or placebo (440 patients) and underwent exercise testing at the trough of drug activity at 2 and 4 months. Ivabradine significantly increased the total exercise duration as well as all other exercise test criteria such as time to limiting angina, time to angina onset and time to 1 mm ST-segment depression compared with placebo. Therefore, this study clearly demonstrated that ivabradine treatment in patients with stable angina receiving the β -blocker resulted in a significant long-term improvement in total exercise duration in standardized Bruce protocol exercise testing [27].

Amosova and colleagues studied the anti-anginal and antiischemic efficacy and tolerability of ivabradine (7.5 mg twice daily) in combination with the bisoprolol (5 mg once daily) versus bisoprolol 10 mg/day in 29 patients with stable

angina [28]. After 2 months of therapy, the mean resting heart rate decreased similarly in both groups. However, addition of ivabradine was more efficient for improvement of exercise capacity. Moreover, Lopez-Bescos et al. studied the efficacy and tolerability of add-on ivabradine demonstrating that the initial efficacy observed with ivabradine is maintained over a longer period of time (12 months) in patients with chronic stable angina receiving concomitant therapy with anti-anginal therapies such as long-acting nitrates, nicorandil, and trimetazidine or dihydropyridine calcium-channel blockers [30].

Werdan and colleagues in a multicentre trial of 2,330 German patients with stable angina pectoris, demonstrated that adding ivabradine to standard therapy with a β -blocker significantly reduced heart rate (from 85 to 65.6 bpm after 4 months), the number of angina attacks per week (from 1.7 attacks to 0.3 attacks per week) and nitrate consumption (from 2.3 to 0.4 U per week) over 4 months of treatment [29].

More recently, the SIGNIFY trial [38] a randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy reported findings in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more. The study included 12,049 patients with activity-limiting angina i.e. class \geq II on the Canadian Cardiovascular Society scale. Patients were randomly assigned to receive placebo or ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55–60 beats per minute. The primary end point was a composite of death from cardiovascular causes or nonfatal myocardial infarction. After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8 % and 6.4 %, respectively; hazard ratio, 1.08; 95 % confidence interval, 0.96–1.20; $P=0.20$), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction. One unexpected finding of extreme interest was that Ivabradine

was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina (one of the approved indications for the drug in Europe) but not among those without activity-limiting angina ($P=0.02$ for interaction).

Efficacy of Ivabradine in Patients with CAD and Comorbidities

Ivabradine has been shown to be an effective anti-angina drug in elderly patients, and in those with comorbidities such as patients with asthma or chronic obstructive pulmonary disease, diabetes mellitus or peripheral vascular disease [31, 39] (Table 7.3). Ivabradine is effective in patients with stable angina pectoris comorbidities [31]. In a pooled analysis of five randomized studies investigating the efficacy of ivabradine in patients with angina, the anti-anginal efficacy of ivabradine was similar across a range of subpopulations. These subpopulations were defined according to age, sex, disease characteristics, and comorbidities (history of myocardial infarction, cerebrovascular disease, revascularization status, diabetes, asthma/chronic obstructive pulmonary disease, or peripheral vascular disease) [31].

Koester and colleagues in an open-label, multicentre, non-interventional subanalysis of 382 patients octogenarians with stable angina pectoris receiving ivabradine showed that ivabradine therapy over 4 months significantly reduced angina pectoris episodes, heart rate and the consumption of short-acting [39].

Administration of Ivabradine in Patients with CAD

Ivabradine is available in 5 and 7.5 mg film-coated tablets. For the treatment of CAD, the recommended starting dose of ivabradine is 5 mg twice daily, which can be up-titrated to

TABLE 7.3 Summary of the main studies of ivabradine in patients with coronary artery disease and comorbidities

Author	Study summary
Tendera et al., 2009 [31]	Data on the frequency of angina attacks, short-acting nitrate consumption, and heart rate were pooled from five randomized trials in patients with stable angina pectoris receiving 5, 7.5, or 10 mg of ivabradine b.i.d. for 3 or 4 months. The subpopulations were defined according to age, sex, disease characteristics, and comorbidities (severity of angina, history of myocardial infarction, cerebrovascular disease, revascularization status, diabetes, asthma/chronic obstructive pulmonary disease, or peripheral vascular disease). All subpopulations experienced 51–70 % reductions in the frequency of angina attacks. Ivabradine's efficacy was maintained in the presence of different comorbidities. Ivabradine had a good safety and tolerability profile in all the subpopulations assessed.
Koester et al., 2011 [39]	This group included 382 octogenarians (mean age 83 ± 2.9 years) who were followed up over 4 months. Patients were treated with ivabradine in flexible doses (2.5, 5, or 7.5 mg bid). After 4 months of treatment with ivabradine, heart rate was reduced. Angina pectoris attacks were reduced from 3.0 ± 4.6 to 0.8 ± 1.8 per week ($p < 0.0001$). Consumption of nitrates decreased from 4.2 ± 5.1 to 1.2 ± 2.7 ($p < 0.0001$). Efficacy and tolerance were assessed as 'very good/good' for 95 and 99 %.

7.5 mg twice daily after 3 or 4 weeks if the resting heart rate is still above 60 bpm. The dose of ivabradine can be reduced to 2.5 mg twice daily if the resting heart rate goes below 50 bpm or if the patient experiences symptoms related to bradycardia, such as dizziness, fatigue or hypotension, during treatment with the recommended daily dose of ivabradine [39]. A lower starting dose (2.5 mg twice daily) is recommended in patients aged 75 years or older. No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 mL/min, or in patients with mild hepatic impairment [40].

Conclusions

The antianginal and anti-ischemic efficacy of ivabradine has been confirmed in patients with stable angina in a large-scale clinical study against placebo, and in trials against β -blocker and amlodipine. These studies also documented the good clinical tolerability and safety of ivabradine. The most frequent drug-related adverse effects were visual symptoms, which were generally mild and well tolerated, and had a minimal impact on acceptability. Ivabradine is licensed in Europe for the symptomatic treatment of stable angina pectoris and it is recommended that it is used at the starting dose of 5 mg b.i.d., which can be increased to a maintenance dose of 7.5 mg b.i.d.; however, the results of the SIGNIFY study require that ivabradine is used with extreme caution in within licensed indications. More studies are needed to ascertain the reasons for the harm observed in certain patient subgroups in the SIGNIFY trial.

References

1. Fox K, García MA, Ardissino D, et al. Guidelines on the management of stable angina pectoris. Executive summary. *Rev Esp Cardiol.* 2006;59:919–70.
2. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in U.S. deaths from coronary disease, 1980–2000. *N Engl J Med.* 2007;356:2388–98.
3. Parker JO. Chronic angina pectoris: inadequacies of current therapy. *Am J Geriatr Cardiol.* 2004;13:261–6.
4. Wiest FC, Bryson CL, Burman M, McDonell MB, Henikoff JG, Fihn SD. Suboptimal pharmacotherapeutic management of chronic stable angina in the primary care setting. *Am J Med.* 2004;117:234–41.
5. Daly CA, Clemens F, Sendon JL, et al. The initial management of stable angina in Europe, from the Euro Heart Survey: a description of pharmacological management and revascularization strategies initiated within the first month of presentation to a cardiologist in the Euro Heart Survey of Stable Angina. *Eur Heart J.* 2005;26:1011–22.

6. Daly CA, De Stavola B, Sendon JL, et al. Predicting prognosis in stable angina—results from the Euro heart survey of stable angina: prospective observational study. *BMJ*. 2006;332:262–7.
7. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetière P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med*. 2005;352:1951–8.
8. Kop WJ, Verdino RJ, Gottdiener JS, O’Leary ST, Bairey Merz CN, Krantz DS. Changes in heart rate and heart rate variability before ambulatory ischemic events(1). *J Am Coll Cardiol*. 2001;38:742–9.
9. Andrews TC, Fenton T, Toyosaki N, et al. Subsets of ambulatory myocardial ischemia based on heart rate activity. Circadian distribution and response to anti-ischemic medication. The Angina and Silent Ischemia Study Group (ASIS). *Circulation*. 1993;88:92–100.
10. Dominguez-Rodriguez A, Blanco-Palacios G, Abreu-Gonzalez P. Increased heart rate and atherosclerosis: potential implications of ivabradine therapy. *World J Cardiol*. 2011;3:101–4.
11. Fraker Jr TD, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. *Circulation*. 2007;116:2762–72.
12. DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. *Drugs*. 2004;64:1757–65.
13. DiFrancesco D. Pacemaker mechanisms in cardiac tissue. *Annu Rev Physiol*. 1993;55:455–72.
14. Bucchi A, Baruscotti M, DiFrancesco D. Current-dependent block of rabbit sino-atrial node I(f) channels by ivabradine. *J Gen Physiol*. 2002;120:1–13.
15. Manz M, Reuter M, Lauck G, Omran H, Jung W. A single intravenous dose of ivabradine, a novel I(f) inhibitor, lowers heart rate but does not depress left ventricular function in patients with left ventricular dysfunction. *Cardiology*. 2003;100:149–55.
16. Borer JS, Le Heuzey JY. Characterization of the heart rate-lowering action of ivabradine, a selective I(f) current inhibitor. *Am J Ther*. 2008;15:461–73.
17. Colin P, Ghaleh B, Monnet X, Hittinger L, Berdeaux A. Effect of graded heart rate reduction with ivabradine on myocardial

- oxygen consumption and diastolic time in exercising dogs. *J Pharmacol Exp Ther.* 2004;308:236–40.
18. Drouin A, Gendron ME, Thorin E, Gillis MA, Mahlberg-Gaudin F, Tardif JC. Chronic heart rate reduction by ivabradine prevents endothelial dysfunction in dyslipidaemic mice. *Br J Pharmacol.* 2008;154:749–57.
 19. Dominguez-Rodriguez A, Fard SS, Abreu-Gonzalez P, et al. Randomised, double-blind, placebo-controlled trial of ivabradine in patients with acute coronary syndrome: effects of the If current inhibitor ivabradine on reduction of inflammation markers in patients with acute coronary syndrome--RIVIERA trial study design and rationale. *Cardiovasc Drugs Ther.* 2009;23:243–7.
 20. Dominguez-Rodriguez A, Consuegra-Sanchez L, Blanco-Palacios G, et al. Anti-inflammatory effects of ivabradine in patients with acute coronary syndrome: a pilot study. *Int J Cardiol.* 2012;158:160–2.
 21. Custodis F, Baumhäkel M, Schlimmer N, et al. Heart rate reduction by ivabradine reduces oxidative stress, improves endothelial function, and prevents atherosclerosis in apolipoprotein E-deficient mice. *Circulation.* 2008;117:2377–87.
 22. Baumhäkel M, Custodis F, Schlimmer N, Laufs U, Böhm M. Heart rate reduction with ivabradine improves erectile dysfunction in parallel to decrease in atherosclerotic plaque load in ApoE-knockout mice. *Atherosclerosis.* 2010;212:55–62.
 23. Deedwania P. Selective and specific inhibition of If with ivabradine for the treatment of coronary artery disease or heart failure. *Drugs.* 2013;73:1569–86.
 24. Savelieva I, Camm AJ. If inhibition with ivabradine: electrophysiological effects and safety. *Drug Saf.* 2008;31:95–107.
 25. Borer JS, Fox K, Jaillon P, et al. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. *Circulation.* 2003;107:817–23.
 26. Tardif JC, Ford I, Tendera M, et al. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. *Eur Heart J.* 2005;26:2529–36.
 27. Tardif JC, Ponikowski P, Kahan T, et al. Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. *Eur Heart J.* 2009;30:540–8.
 28. Amosova E, Andrejev E, Zaderey I, Rudenko U, Ceconi C, Ferrari R. Efficacy of ivabradine in combination with Beta-

- blocker versus uptitration of Beta-blocker in patients with stable angina. *Cardiovasc Drugs Ther.* 2011;25:531–7.
29. Werdan K, Ebelt H, Nuding S, Höpfner F, Hack G, Müller-Werdan U. Ivabradine in combination with beta-blocker improves symptoms and quality of life in patients with stable angina pectoris: results from the ADDITIONS study. *Clin Res Cardiol.* 2012;101:365–73.
 30. López-Bescós L, Filipova S, Martos R. Long-term safety and efficacy of ivabradine in patients with chronic stable angina. *Cardiology.* 2007;108:387–96.
 31. Tendera M, Borer JS, Tardif JC. Efficacy of I(f) inhibition with ivabradine in different subpopulations with stable angina pectoris. *Cardiology.* 2009;114:116–25.
 32. Borer JS, Tardif JC. Efficacy of ivabradine, a selective I(f) inhibitor, in patients with chronic stable angina pectoris and diabetes mellitus. *Am J Cardiol.* 2010;105:29–35.
 33. Fox K, Ford I, Steg PG, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet.* 2008;372:817–21.
 34. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010;376:875–85.
 35. Köster R, Kaehler J, Meinertz T, REDUCTION Study Group. Treatment of stable angina pectoris by ivabradine in every day practice: the REDUCTION study. *Am Heart J.* 2009;158:e51–7.
 36. Ruzyllo W, Tendera M, Ford I, et al. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. *Drugs.* 2007;67:393–405.
 37. Skolidis EI, Hamilos MI, Chlouverakis G, et al. Ivabradine improves coronary flow reserve in patients with stable coronary artery disease. *Atherosclerosis.* 2011;215:160–5.
 38. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med.* 2014;371(12):1091–9.
 39. Koester R, Kaehler J, Meinertz T. Ivabradine for the treatment of stable angina pectoris in octogenarians. *Clin Res Cardiol.* 2011;100:121–8.
 40. Ferrari R, Ceconi C. Selective and specific I(f) inhibition with ivabradine: new perspectives for the treatment of cardiovascular disease. *Expert Rev Cardiovasc Ther.* 2011;9:959–73.

Chapter 8

Trimetazidine

**Alda Huqi, Giacinta Guarini, Doralisa Morrone,
and Mario Marzilli**

Abbreviations

ACS	Acute coronary syndrome
ATP	Adenosine triphosphate
BBs	β -blockers
CABG	Coronary artery bypass graft surgeries
CAD	Coronary artery disease
CCBs	Calcium channel blockers
CSA	Chronic stable angina
FAO	Fatty acid oxidation
FMD	Flow-mediated dilation
GAO	Glucose oxidation
HUVECs	Human umbilical vein endothelial cells
IHD	Ischemic heart disease
LC	3-KAT long-chain 3-ketoacyl CoA thiolase
OMT	Optimal medical therapy
PCI	Percutaneous coronary interventions

A. Huqi • G. Guarini • D. Morrone • M. Marzilli, MD (✉)
Cardiovascular Medicine Division,
Cardio-Thoracic and Vascular Department, University of Pisa,
Via Paradisa 2, Pisa (Pi) 56124, Italy
e-mail: mario.marzilli@med.unipi.it

PDH	Pyruvate dehydrogenase enzyme
TRCAG	Transradial coronary artery angiography
TRPCI	Transradial percutaneous coronary intervention
VSMCs	Vascular smooth muscle cells

Introduction

Percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) are revascularization procedures performed daily worldwide for the symptomatic treatment of patients with chronic stable angina (CSA). Nevertheless, angina remains still a relevant clinical problem. In fact, large clinical trials have consistently reported that a significant proportion of patients continue to have symptoms despite “successful and complete” myocardial revascularization (Table 8.1) [1–6]. As many as two thirds of these patients

TABLE 8.1 Percentage of patients with symptom persistence/reoccurrence in main clinical trials

Study	Follow up duration	Type of intervention	% Patients with angina
BARI [1]	1 year	CABG, PCI	10 % CABG, 30 % PCI
COURAGE [2]	5 years	PCI, MT	26 % PCI, 28 % MT
RITA-2 [3]	1 year	PCI, MT	38 % PCI, 57 % MT
MASS-II [4]	1 year	CABG, PCI, MT	12 % CABG, 21 % PCI, 54 % OMT
FAME [5]	2 years	Angiography-guided PCI, FFR-guided PCI	24 % angiography-guided PCI, 20 % FFR-guided PCI

Abbreviations: *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass grafting, *FFR* fractional flow reserve, *MT* medical therapy

may require the use of one or more anti-angina agents despite which symptom control is not optimal in a large proportion [7].

Revascularization procedures (either percutaneous or surgical) are performed with the aim of removing the flow limiting effect of epicardial coronary artery stenoses. This rationale is in line with the accepted pathophysiological mechanism of stable angina i.e., flow limiting epicardial stenosis, and the majority of patients undergoing revascularization benefit from the intervention. However, the situation is not straightforward as at least three main angina patient subgroups exist that deserve special consideration: (1) Patients who are deemed unsuitable for coronary revascularization because of diffuse coronary artery disease (CAD). Importantly, this subset represents an increasing population, particularly among subjects with diabetes and elderly patients; (2) Patients whose symptoms failed to be improved after percutaneous or surgical coronary procedures (recurrent angina). There are several possible causes for this i.e., bypass graft failure, restenosis, atherosclerotic disease progression and incomplete revascularization, among others. (3) Patients who undergo successful revascularization, and in whom none of the above mentioned mechanisms can be identified as a cause for symptom recurrence (persistent angina). In this latter group, factors other than epicardial stenosis, such as microvascular dysfunction, have been suggested as the underlying pathophysiological mechanism for persistent symptoms. While patients in the first subgroup experience a poor quality of life, subjects in the latter two experience the additional burden of having to undergo repeat invasive procedures, which leads to increased patient and physician frustration and, last but not least, increased healthcare costs. Irrespective of the underlying cause, the final common pathophysiological mechanism is a reduced myocardial oxygen supply which is resistant to revascularization and traditional medical therapies.

Over the last 30 years considerable progress has been made in the therapeutic options for ischemic heart disease (IHD). Among these, metabolic modulation therapy, using

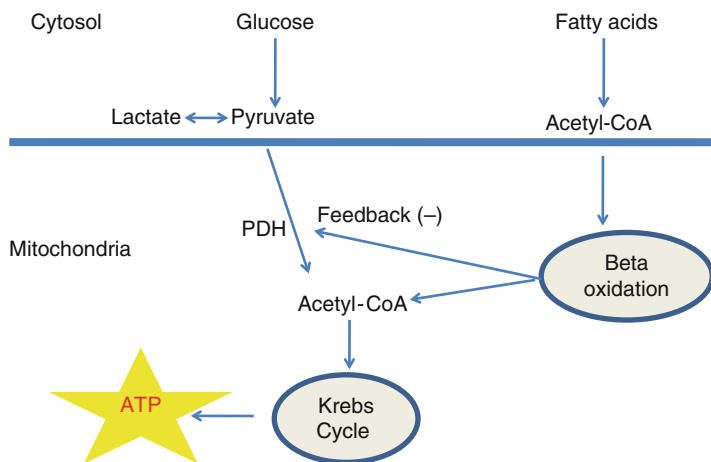


FIGURE 8.1 Schematic representation of main ATP sources in normal conditions (see text for details)

agents such as trimetazidine, has been shown to confer significant symptom relief. The drug can be safely added to ongoing therapy with β -blockers (BBs), calcium channel blockers (CCBs), and nitrates, and has not been shown to display unfavorable drug interactions [8].

Cardiac Metabolism and the Rationale for Metabolic Modulation Therapy

In the adult heart, glycolysis and mitochondrial oxidative metabolism are the principal sources of energy production, with the later accounting for more than 95 % of the total amount required for heart function. Under normal conditions, 50–70 % of the energy produced by mitochondrial oxidative metabolism is derived from fatty acid β -oxidation. The remaining 30–50 % is achieved from the oxidative metabolism of the glycolytic products of glucose (pyruvate) (Fig. 8.1).

Relevance of Myocardial Metabolic Alterations in IHD

In aerobic conditions, fatty acid oxidation (FAO) yields more adenosine triphosphate (ATP) per gram of substrate than glucose oxidation (GO). However, FAO requires about 10–15 % more oxygen to produce an equivalent amount of ATP, thus representing a less efficient energy production pathway [9].

Such a property becomes particularly relevant in of the presence of a reduced oxygen supply such as in flow limiting IHD. Glucose metabolism begins with glycolysis, a cytosolic process that converts glucose to pyruvate. Glycolysis supplies pyruvate to the enzyme pyruvate dehydrogenase (PDH), which is the rate limiting enzyme for GO [9].

When PDH is active, pyruvate enters the mitochondria and is converted to acetyl-CoA, therefore fueling the Krebs cycle for ATP production. Conversely, FAO, which occurs within the mitochondria, is another source of acetyl-CoA for the Krebs cycle. These two sources of acetyl-CoA are highly dependent on and affected from each other, a phenomenon known as the ‘Randle cycle’ [10].

In the presence of large amounts of fatty acids, FAO is stimulated, while GO is directly inhibited through PDH activity [11].

As a consequence, pyruvate cannot enter the mitochondria and therefore cannot fuel oxidative metabolism. This results in the production of only two ATP for each glucose molecule (versus 36 ATP during GO) and conversion of pyruvate to lactate with resultant proton accumulation.

As a consequence of ischemia, less ATP is generated within mitochondria. This triggers accelerated glycolysis and reduces cell pH, leads to calcium accumulation, potassium efflux and adenosine formation [12].

Of interest, pain resulting from myocardial ischemia (angina) is associated with an enhanced catecholamine release and increased lipolysis. This condition is also associated with an increase in circulating fatty acids levels, a

relative increase in FAO and therefore (through the ‘Randle cycle’) a reduced GO rate.

Myocardial ischemia has therefore a prominent role in increasing the uncoupling between glycolysis and GO by contemporaneously increasing glycolysis and reducing GO rates, further reducing cardiac efficiency. The need to use ATP for reestablishing ionic homeostasis instead of supporting contractile function is another cause for reduced cardiac efficiency. In addition, intracellular proton accumulation also directly decreases the efficiency of the contractile proteins and therefore cardiac efficiency [13].

Therefore, therapeutic interventions aimed at shifting myocardial substrate utilization from fatty acid towards glucose metabolism would particularly benefit cardiac efficiency and IHD symptoms. Given the interdependence between FAO and GO oxidation this can be achieved by either inhibiting FAO or stimulating GO. In this chapter we will focus on the use of trimetazidine, a partial inhibitor of FAO, in patients with chronic stable angina.

Beneficial Cellular Effects of Fatty Acid Oxidation Inhibition by Trimetazidine

There are numerous ways of inhibiting cardiac FAO, some of which include the inhibition of fatty acid transport into the cardiac myocyte, the inhibition of fatty acid uptake into the mitochondria, and the inhibition of the enzymatic machinery of the β -oxidative pathway itself.

Trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine dihydrochloride), a metabolic modulator agent that has been used for more than two decades in Europe, inhibits FAO by blocking the β -oxidative enzyme, long-chain 3-ketoacyl CoA thiolase (LC 3-KAT) [14].

This effect results in an increase in PDH activity which compensates the reduced availability of acyl-CoA derived from β -oxidation of fatty acids, by providing them through GO. In this way, stimulation of GO increases glycolysis/

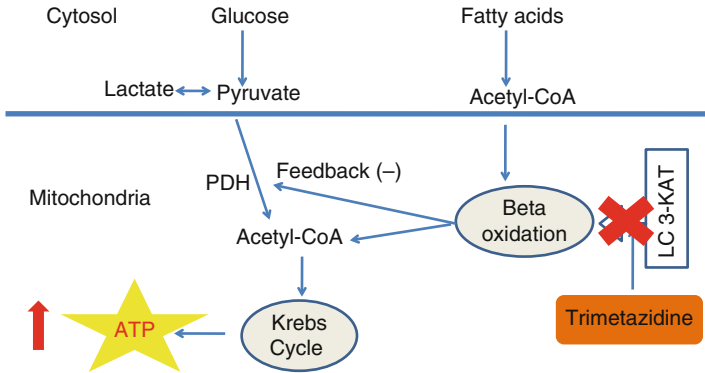


FIGURE 8.2 Trimetazidine inhibits LC-3KAT, one of the enzymes of fatty acid oxidation. In this way there is a reduced production of acetyl-CoA originating from fatty acid oxidation and therefore a relief of PDH activity. This results in increased glucose oxidation and, therefore a higher myocardial efficiency. Abbreviations: ATP (adenosine triphosphate)

glucose oxidation coupling, resulting in a decreased proton production, and a decreased both intracellular calcium overload and free radical production. Finally, these chain effects prevent a significant decrease in ATP and phosphocreatine levels in response to hypoxia or ischemia, preserve ionic pump function and therefore translate into an improved cardiac efficiency and reduced symptoms. Importantly, these effects are not associated with significant alterations in hemodynamic parameters, a fact of particular important for patients who receive anti-ischemic treatment with hemodynamic active agents [14] (Fig. 8.2).

Novel Evidence on the Effects of Trimetazidine on Endothelial Function

Accumulating evidence suggests that trimetazidine has the ability to improve endothelium-dependent relaxation through direct and/or indirect effects on the endothelium itself.

Experimental and clinical studies have shown that patients with greater oxidative stress and high oxygen free radical production have severe endothelial dysfunction due to high plasma levels of malondialdehyde and lipid hydroperoxides [15].

Trimetazidine improves endothelium-dependent vasodilation, and this effect is correlated with decreased plasma levels of both malondialdehyde and hydroperoxides. Using flow-mediated dilation (FMD) techniques, Park et al. evaluated the effects of sheath induced injury and trimetazidine on endothelial function of the radial artery (RA) after transradial coronary artery angiography (TRCAG) or transradial percutaneous coronary intervention (TRPCI) [16].

Ten weeks after the procedure, FMD was reduced in the control group, whereas no difference was found in the trimetazidine group, suggesting that treatment with trimetazidine improves endothelial function of the cannulated RA.

Following PCI, inflammation, thrombosis, cellular proliferation, and extracellular matrix production, contribute to neointimal hyperplasia and post-procedural luminal narrowing leading to restenosis and delayed re-endothelialization, all of which represent important clinical problems. Yoon et al. showed that 4 weeks of trimetazidine treatment resulted in a dose-dependent reduction in the intima-media thickness ratio of the carotid artery of type 1 and 2 rat model after balloon injury [17].

This effect was accompanied by decreased proliferation of vascular smooth muscle cells (VSMCs) and accelerated re-endothelialization after carotid balloon injury. In vitro experiments with trimetazidine showed decreased VSMCs proliferation and migration, whereas human umbilical vein endothelial cells (HUVECs) displayed increased proliferation and decreased apoptosis. Antioxidative effects of trimetazidine were observed in both VSMCs and HUVECs. The authors concluded that reduction of restenosis by trimetazidine treatment was the net effect of changes in antioxidative and anti-inflammatory properties, which are cell-specific effects on either survival or apoptosis [17].

In line with these results, Chen et al. recently published the results of a randomized study involving 786 patients who

underwent drug eluting stent placement for chronic IHD. At 1 year from the index procedure, treatment with trimetazidine on top of optimal medical therapy significantly reduced in-stent-restenosis and major cardiac adverse events [18].

Clinical Efficacy of Trimetazidine

Treatment with trimetazidine has been shown to confer beneficial effects in various clinical scenarios including chronic stable angina, acute coronary syndromes (ACS), as well as heart failure. In patients with chronic angina, trimetazidine increases exercise capacity and delays the appearance of symptoms and ECG changes during exercise [15, 19, 20]. Importantly, the benefits observed after acute administration are maintained in long term treatment, which is well tolerated by patients [21]. Trimetazidine has no significant negative inotropic effects or vasodilator properties either at rest or during dynamic exercise [22]. The efficacy of trimetazidine as an anti-angina drug has been assessed in randomized, placebo-controlled studies, both as ‘solo’ treatment and in combination or comparison with BBs and CCBs (Table 8.2).

Trimetazidine as Monotherapy

The beneficial effects of trimetazidine as an anti-angina drug were first tested as monotherapy regimens in chronic angina patients who were withdrawn all anti-angina medications at least 8 days before inclusion [20, 21]. The results showed a significant improvement in exercise capacity (increased total work and increase in the duration of exercise) in response to trimetazidine treatment. Similarly, there was a significant reduction in the weekly number of angina attacks in the trimetazidine group as compared with placebo. No differences in blood pressure (BP) and heart rate (HR) were observed between the two groups, confirming the absence of any hemodynamic effect of trimetazidine.

TABLE 8.2 Main trimetazidine studies considered in this review

Author	Year	Study title
Trimetazidine as monotherapy		
Sellier et al. [20]	1986	The effects of trimetazidine on ergometric parameters of exercise-induced angina.
Passeron et al. [21]	1994	Effectiveness of trimetazidine in stable effort angina due to chronic coronary insufficiency.
<i>Trimetazidine with B-blockers</i>		
Szwed et al. [23]	2001	Combination treatment in stable effort angina using trimetazidine and metoprolol. TRIMPOL II study.
Trimetazidine with CCBs		
Monpere et al. [24]	1990	Combination of trimetazidine with nifedipine in effort angina.
Manchanda et al. [25]	1997	Combination treatment with trimetazidine and diltiazem in stable angina pectoris.
Trimetazidine versus nitrates		
Hanania et al. [26]	2002	Comparison between trimetazidine and mononitrate isosorbide for patients receiving B-blockers.
Trimetazidine versus B-blockers		
Detry et al. [27]	1994	Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina.
Trimetazidine versus CCBs		
Dalla-Volta et al. [28]	1990	Comparison of trimetazidine with nifedipine in effort angina: a double-blind, crossover study.

TABLE 8.2 (continued)

Author	Year	Study title
<i>Trimetazidine in elderly and diabetic patients</i>		
Kolbel et al. [29]	2003	Trimetazidine in geriatric patients with stable angina pectoris: the TIGER study.
Marazzi et al. [30]	2009	Effect of trimetazidine on quality of life in elderly patients with ischemic dilated cardiomyopathy
Ribeiro et al. [31]	2007	Trimetazidine added to combined hemodynamic antianginal therapy in patients type 2 diabetes: a randomized crossover trial.
<i>Prognostic effects of trimetazidine</i>		
Iyengar et al. [32]	2009	Effect of antianginal drugs in stable angina on predicted mortality risk after surviving a myocardial infarction: a preliminary study (METRO)
Chen et al. [18]	2014	Chronic treatment with trimetazidine after discharge reduces the incidence of restenosis in patients who received coronary stent implantation: a 1-year prospective follow-up study

Abbreviations: *B-blockers* β -blockers, *CCBs* calcium channel blockers

Trimetazidine in Combination with BBs

TRIMPOL II was a randomized, double-blind, placebo-controlled, multicenter study that recruited 426 patients with stable angina who were randomized to either trimetazidine 20 mg three times a day or placebo on top of metoprolol [23].

The addition of trimetazidine to standard therapy with metoprolol resulted in an improvement in time to ST segment depression on exercise tolerance testing, total exercise workload, mean nitrate consumption, and angina frequency

as compared to patients receiving placebo. Moreover, the drug had a favorable side-effect profile with the most common adverse event being nausea, vomiting, fatigue, and myalgia. In another study, the VASCO trial, patients were randomized to receive 50 mg of atenolol add on trimetazidine (35 mg) or trimetazidine alone 70 mg or placebo b.i.d. for 12 weeks. Trimetazidine showed no benefit in terms of clinical parameters (relief from angina, tolerance exercise) among patients with mild symptoms. However, a sub-study of the trial, in which only patients with severe angina were included, showed the superiority of trimetazidine when compared to placebo in terms of angina relief and exercise tolerance. The short duration of the study (12 weeks) did not allow for the evaluation of the incidence of side effects, which have been recently associated with long-term use of trimetazidine [14].

Trimetazidine in Combination with CCBs

One study evaluated the effects of trimetazidine, compared with placebo, in patients with a persistently positive stress test, despite receiving at least 15 days of treatment with nifedipine [24]. Trimetazidine was associated with an increase in maximal workload, while this parameter remained stable or even slightly deteriorated with placebo. Moreover, mean weekly frequency of angina attacks decreased with the use of trimetazidine as compared with placebo. Subsequent studies of combination therapy with non-dihydropyridines confirmed the beneficial effects of a combination treatment with trimetazidine, in the absence adverse hemodynamic events or increased side effects [25].

Trimetazidine Versus Nitrates

Hanania et al. investigated the efficacy of trimetazidine with that of isosorbide mononitrate in symptomatic angina patients receiving a atenolol 100 mg/day [26]. Both drugs induced significant and comparable clinical benefits in terms of improvement of quality of life and exercise stress test

results. However, as opposed to nitrate use, the addition of trimetazidine to the baseline treatment regimen was not associated with significant hemodynamic or other adverse effects such as headaches.

Trimetazidine Versus BBs

The effects of trimetazidine (20 mg three times daily) were compared with those of propranolol (40 mg three times daily) in a double-blind parallel group multicentre study in 149 men with stable angina [27]. After 3 months of treatment, similar anti-angina efficacy was observed between the trimetazidine and propranolol groups. No significant differences with regard to angina frequency, exercise duration or time to 1 mm ST segment depression were observed between the different treatment groups. However, while heart rate and the product of heart rate and pressure at rest and at peak exercise decreased with propranolol, no significant changes were observed in the trimetazidine group.

Trimetazidine Versus CCBs

Trimetazidine efficacy has also been shown in a head to head, double-blind study with the dihydropyridinic agent nifedipine [28]. The results show that nifedipine and trimetazidine both decreased the number of angina attacks and increased workload parameters without any significant difference between the two drugs. However, at a constant level of work, the rate x pressure product decreased with nifedipine, but remained stable with trimetazidine.

Trimetazidine in Elderly and Diabetic Patients

Elderly patients and patients with diabetes frequently present with refractory angina because of diffuse atherosclerotic disease or other co-morbidities. The use of trimetazidine has been

shown to benefit both of these patient populations. In the TIGER study [29] involving 141 stable angina patients aged 65–86 years, trimetazidine was shown to improve exercise stress tests and angina symptoms. Because of its metabolic effect, free from any hemodynamic action, trimetazidine proved to be beneficial in elderly patients, with an excellent tolerance profile. Another study assessed the effects of trimetazidine in addition to standard cardiovascular therapy on left ventricular function and quality of life parameters in elderly patients with IHD and reduced left ventricular function [30]. This was a randomized placebo controlled study involving 47 elderly symptomatic patients who were already on optimal medical therapy (OMT). At 6 months after randomization, patients on trimetazidine showed a significant improvement in clinical conditions and quality of life. A significant improvement in quality of life and exercise capacity has been also observed in diabetic chronic angina patients presenting with coronary anatomy not amenable to revascularization who were treated with trimetazidine on top of OMT [31].

Trimetazidine in Other Clinical Scenarios

Trimetazidine use is not limited to patients with chronic stable angina. In fact its use has been shown to be beneficial in other settings such as ACS, heart failure, hypertrophic cardiomyopathy. As previously mentioned, trimetazidine improves myocardial energy utilization, a particularly relevant aspect for the failed heart which has been shown to be energy-starved [33]. A recent meta-analysis on 16 randomized controlled trials involving 884 heart failure patients showed that trimetazidine treatment induced improved left ventricular ejection fraction and volumes, total exercise time, NYHA functional class and B-type natriuretic-peptide levels. Although the main findings of this meta-analysis were that the additional use of trimetazidine failed to reduce all-cause mortality, trimetazidine exerted symptomatic benefits and reduced hospitalization for cardiac causes [34].

Potential Prognostic Impact of Trimetazidine on Mortality of Angina Patients

Except for B-blockers administered in post - myocardial infarction patients, most trials on chronic stable angina therapy failed to show benefits in terms of hard clinical outcomes (i.e., survival, cardiovascular death, all cause of mortality) [31,35]. Nonetheless, studies evaluating the prognostic impact of trimetazidine have been ongoing. The METRO (ManagEment of angina: a reTRO-spective cOhort) study assessed the effects that different anti-angina drugs had on subsequent (6 months) mortality risk of patients with stable angina experiencing myocardial infarction [32]. Amongst the use of at least one antianginal drug (nitrates, B-blockers, CCBs, trimetazidine, or nicorandil) over several months prior to a myocardial infarction, trimetazidine was the only agent associated with a mortality benefit. As previously mentioned, benefits on major cardiac adverse events were also shown on a recent randomized controlled study on patients undergoing PCI [18]. However, although the clinical benefits have been documented since early 80s, unfortunately trimetazidine still lacks a widespread clinical use or a guideline recommendation in the management of chronic stable angina patients.

Definition and Explanation of Words and Terms

Fatty acid oxidation

This process is termed β -oxidation since it occurs through the sequential removal of 2-carbon units by oxidation at the β -carbon position of the fatty acyl-CoA molecule. Each round of β -oxidation produces one mole of NADH, one mole of FADH_2 and one mole of acetyl-CoA which then enters the Krebs cycle.

Glycolysis

This is the biochemical pathway that initiates the oxidation of glucose. Glycolysis occurs in the cytoplasm and it splits the six-carbon glucose molecule into two three-carbon molecules of pyruvate. This is accomplished through a series of chemical reactions during which a small amount of ATP and two molecules of pyruvate are formed.

Glucose oxidation

Pyruvate formed in glycolysis is transported into the mitochondria converted to acetyl-CoA by PHD enzyme. Consequently acetyl-CoA originating from glucose exhibits the same metabolic fate as that originating from fatty acid beta oxidation: it enters the Krebs cycle for energy production.

Krebs cycle

This is a series of enzyme-catalysed chemical reactions that occur in the matrix of the mitochondrion. Krebs cycle is part of a fundamental metabolic pathway involved in the chemical conversion of carbohydrates, fats and proteins (namely their acetyl-CoA products) into carbon dioxide and water to generate a form of usable energy such as ATP.

Pyruvate

Is the three carbon end product of glycolysis (two pyruvates for each glucose molecule), which is converted into acetyl-CoA. When the oxygen is insufficient, pyruvate is broken down anaerobically, creating lactate.

Acetyl-CoA

It is the activated acetate, which is composed of two carbon atoms. This important coenzyme is the metabolic product of the oxidation of several amino acids, pyruvate and fatty acids. The acetyl-CoA is then broken down and used by the Krebs cycle for energy production.

Cardiac efficiency

As for a machine, the efficiency of the heart is the ratio of effective work to the energy expended in producing it, i.e., $\text{energy spent for contractile purposes} / \text{energy spent for contractile purposes} + \text{energy spent for metabolic purposes} + \text{energy spent for ionic homeostasis} + \text{energy spent for heat production}$.

Persistent angina

Lack of angina symptom relief for more than 6 months after a coronary revascularization procedure.

Refractory angina

Angina pectoris not responding to standard treatment (revascularization and hemodynamic drug therapy)

Microvascular dysfunction

Presence of signs and/or symptoms of myocardial ischemia in the absence of obstructive CAD and where microvascular abnormalities (increased distal vessel resistance as assessed by invasive coronary angiography) rather than epicardial coronary stenosis can be demonstrated.

References

1. Writing Group for the Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Five-year clinical and functional outcome comparing bypass surgery and angioplasty in patients with multivessel coronary disease. A multicenter randomized trial. *JAMA*. 1997;277(9):715–21.
2. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–16.
3. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol*. 2003;42:1161–70.
4. Hueb W, Soares PR, Gersh BJ, Cesar LA, Luz PL, Puig LB, Martinez EM, Oliveira SA, Ramires JA. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. *J Am Coll Cardiol*. 2004;43:1743–51.
5. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, Van't Veer M, Klauss V, Manoharan G, Engstrom T, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. *J Am Coll Cardiol*. 2010;56(3):177–84.

6. Deligonul U, Vandormael MG, Shah Y, Galan K, Kern MJ, Chaitman BR. Prognostic value of early exercise stress testing after successful coronary angioplasty: importance of the degree of revascularization. *Am Heart J*. 1989;117:509–14.
7. Holubkov R, Laskey WK, Haviland A, Slater JC, Bourassa MG, Vlachos HA, Cohen HA, Williams DO, Kelsey SF, Detre KM. Angina 1 year after percutaneous coronary intervention: a report from the NHLBI Dynamic Registry. *Am Heart J*. 2002;144:826–33.
8. Chazov EI, Lepakchin VK, Zharova EA, Fitilev SB, Levin AM, Rumiantzeva EG, Fitileva TB. Trimetazidine in Angina Combination Therapy – the TACT study: trimetazidine versus conventional treatment in patients with stable angina pectoris in a randomized, placebo-controlled, multicenter study. *Am J Ther*. 2005;12:35–42.
9. Stanley WC, Recchia FA, Lopaschuk GD. Myocardial substrate metabolism in the normal and failing heart. *Physiol Rev*. 2005;85:1093–129.
10. Randle PJ, Garland PB, Hales CN, Newsholme EA. The glucose fatty-acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet*. 1963;1:785–9.
11. Depre C, Vanoverschelde JL, Taegtmeyer H. Glucose for the heart. *Circulation*. 1999;99:578–88.
12. Liu Q, Docherty JC, Rendell JC, Clanachan AS, Lopaschuk GD. High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. *J Am Coll Cardiol*. 2002;39:718–25.
13. El Banani H, Bernard M, Baetz D, Cabanes E, Cozzone P, Lucien A, Feuvray D. Changes in intracellular sodium and pH during ischaemia-reperfusion are attenuated by trimetazidine. Comparison between low- and zero-flow ischaemia. *Cardiovasc Res*. 2000;47:688–96.
14. 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;86:580–8.
15. Sellier P, Audouin P, Payen B, Corona P, Duong TC, Ourbak P. Acute effects of trimetazidine evaluated by exercise testing. *Eur J Clin Pharmacol*. 1987;33:205–7.
16. Park KH, Park DW, Kim MK, Kim HS, Park WJ, Cho GY, Choi YJ. Effects of sheath injury and trimetazidine on endothelial dysfunction of radial artery after transradial catheterization. *J Interv Cardiol*. 2012;25:411–7.

17. Yoon JW, Cho BJ, Park HS, Kang SM, Choi SH, Jang HC, Shin H, Lee MJ, Kim YB, Park KS, et al. Differential effects of trimetazidine on vascular smooth muscle cell and endothelial cell in response to carotid artery balloon injury in diabetic rats. *Int J Cardiol.* 2013;167:126–33.
18. Chen J, Zhou S, Jin J, Tian F, Han Y, Wang J, Liu J, Chen Y. Chronic treatment with trimetazidine after discharge reduces the incidence of restenosis in patients who received coronary stent implantation: a 1-year prospective follow-up study. *Int J Cardiol.* 2014;174(3):634–9.
19. Detry JM. Clinical features of an anti-anginal drug in angina pectoris. *Eur Heart J.* 1993;14(Suppl G):18–24.
20. Sellier P. The effects of trimetazidine on ergometric parameters in exercise-induced angina. Controlled multicenter double blind versus placebo study. *Arch Mal Coeur Vaiss.* 1986;79:1331–6.
21. Passeron J. Effectiveness of trimetazidine in stable effort angina due to chronic coronary insufficiency. A double-blind versus placebo study. *Presse Med.* 1986;15:1775–8.
22. Pornin M, Harpey C, Allal J, Sellier P, Ourbak P. Lack of effects of trimetazidine on systemic hemodynamics in patients with coronary artery disease: a placebo-controlled study. *Clin Trials Metaanal.* 1994;29:49–56.
23. Szwed H, Sadowski Z, Elikowski W, Koronkiewicz A, Mamcarz A, Orszulak W, Skibinska E, Szymczak K, Swiatek J, Winter M. Combination treatment in stable effort angina using trimetazidine and metoprolol: results of a randomized, double-blind, multicentre study (TRIMPOL II). *TRIMetazidine in POLand.* *Eur Heart J.* 2001;22:2267–74.
24. Monpere C, Brochier M, Demange J, Ducloux G, Warin JF. Combination of trimetazidine with nifedipine in effort angina. *Cardiovasc Drugs Ther.* 1990;4 Suppl 4:824–5.
25. Manchanda SC, Krishnaswami S. Combination treatment with trimetazidine and diltiazem in stable angina pectoris. *Heart.* 1997;78:353–7.
26. Hanania G, Haiat R, Olive T, Maalouf B, Michel D, Martelet M, Godard S. Coronary artery disease observed in general hospitals: ETTIC study. Comparison between trimetazidine and mononitrate isosorbide for patients receiving betablockers. *Ann Cardiol Angeiol (Paris).* 2002;51:268–74.
27. Detry JM, Sellier P, Pennaforte S, Cokkinos D, Dargie H, Mathes P. Trimetazidine: a new concept in the treatment of angina. Comparison with propranolol in patients with stable angina.

- Trimetazidine European Multicenter Study Group. *Br J Clin Pharmacol.* 1994;37:279–88.
28. Dalla-Volta S, Maraglino G, Della-Valentina P, Viena P, Desideri A. Comparison of trimetazidine with nifedipine in effort angina: a double-blind, crossover study. *Cardiovasc Drugs Ther.* 1990;4 Suppl 4:853–9.
29. Kolbel F, Bada V. Trimetazidine in geriatric patients with stable angina pectoris: the tiger study. *Int J Clin Pract.* 2003;57:867–70.
30. Marazzi G, Gebara O, Vitale C, Caminiti G, Wajngarten M, Volterrani M, Ramires JA, Rosano G, Fini M. Effect of trimetazidine on quality of life in elderly patients with ischemic dilated cardiomyopathy. *Adv Ther.* 2009;26:455–61.
31. Ribeiro LW, Ribeiro JP, Stein R, Leitao C, Polanczyk CA. Trimetazidine added to combined hemodynamic antianginal therapy in patients with type 2 diabetes: a randomized crossover trial. *Am Heart J.* 2007;154(78):e1–7.
32. Iyengar SS, Rosano GM. Effect of antianginal drugs in stable angina on predicted mortality risk after surviving a myocardial infarction: a preliminary study (METRO). *Am J Cardiovasc Drugs.* 2009;9:293–7.
33. Neubauer S. The failing heart – an engine out of fuel. *N Engl J Med.* 2007;356:1140–51.
34. Zhang L, Lu Y, Jiang H, Sun A, Zou Y, Ge J. Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol.* 2012;59:913–22.
35. de Shu F, Dong BR, Lin XF, Wu TX, Liu GJ. Long-term beta blockers for stable angina: systematic review and meta-analysis. *Eur J Prev Cardiol.* 2012;19:330–41.

Chapter 9

Ranolazine

**Giuseppe M.C. Rosano, Cristiana Vitale,
and Maurizio Volterrani**

Introduction

Angina pectoris is the most common clinical manifestation of ischaemic heart disease [1, 2]. The aims in the choice of pharmacological and non-pharmacological approaches for the treatment of angina should be to improve prognosis and reduce symptoms. Aspirin, lipid-lowering therapy and ACE-inhibitors have been shown to reduce the risk of death and non-fatal MI in both primary and secondary prevention trials. Beta-blockers, ivabradine, calcium channel blockers, trimetazidine, nitrates and nicorandil all improve exercise tolerance and symptoms in patients with ischaemic heart disease but

G.M.C. Rosano (✉) • C. Vitale
Cardiovascular and Cell Sciences Research Institute,
St George's University of London, London, UK

Department of Cardiovascular Rehabilitation,
IRCCS San Raffaele, via di val cannuta 249 - Roma, Rome, Italy
e-mail: giuseppe.rosano@gmail.com; cristiana.vitale@sanraffaele.it

M. Volterrani
Cardiovascular and Cell Sciences Research Institute,
St George's University of London, London, UK
e-mail: maurizio.volterrani@sanraffaele.it

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_9,
© Springer International Publishing Switzerland 2015

none of these agents has been shown to improve prognosis in patients with chronic stable angina [3, 4].

For many years it has been implied that the effect of beta-blockers in reducing cardiac events in post-infarction patients with left ventricular dysfunction was mirrored by an effect in patients with chronic stable angina but recent evidence suggests that this is not the case. In fact there is no evidence, apart from data in heart failure patients, to suggest a prognostic benefit for beta-blockers in patients without a recent myocardial infarction and left ventricular dysfunction. Despite the increasing success of conventional medical therapeutic approaches and the continued development and improvement of mechanical revascularization approaches, a significant number of patients with ischaemic heart disease and angina pectoris are not successfully managed with currently available pharmacological options. In addition, in a substantial proportion of patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) these procedures fail to achieve complete revascularization, and many patients therefore continue to experience residual angina symptoms even despite maximal medical therapy [5].

Ranolazine is the latest of the anti-anginal drugs approved for the treatment of angina pectoris. This molecule exerts its anti-anginal effect via its electrophysiological properties and without affecting heart rate or blood pressure ("non-haemodynamic" mechanism of action).

Pharmacology

Ranolazine is a racemate consisting of a 1:1 ratio of (R) and (S) enantiomers at the secondary alcohol that originates from the secondary carbon of the epoxide ring in guaiacol glycidyl ether (GGE/Ran 3). It has one stable polymorphic form and is very little soluble in water, but freely soluble in buffered solutions at pH levels below 4.82. Ranolazine is formulated as a prolonged release matrix tablet, the drug substance has high solubility in acidic medium and low solubility in basic medium. The prolonged release characteristics are achieved

by using a pH-dependent polymer (methacrylic acid-ethyl acrylate copolymer 1:1) that it is insoluble in low pH but starts dissolving at around pH 5 or higher, resulting in disintegrating tablets. Numerous studies indicate a mechanism of action of ranolazine on the late myocardial sodium currents (I_{Na}), which results in improved myocardial ischaemia and myocardial protection, both in vitro and in animal models. While the concentrations needed to demonstrate an effect on I_{Na} in mechanistic studies ranges from 1 to 100 μ M, the anti-ischaemic effects have been observed at different order of magnitude of concentrations (i.e. 10 nM in the isolated rat heart). Several metabolites of ranolazine have a relevant pharmacodynamic effect; the most abundant in man being CVT-2514 (RS 88390) and CVT 2738 (RS 94287), that inhibit late I_{Na} at least as potently as the parent substance.

Pharmacokinetics

The mean bioavailability of ranolazine after oral administration of slow release tablets varies from 35 to 50 %, and peak plasma concentrations are reached 2–5 h after oral administration; half-life is 7 h. Food does not affect the rate or extent of absorption of ranolazine SR formulation [6]. As a consequence, steady state is achieved within 3 days of twice-daily dosing. Ranolazine undergoes rapid and extensive metabolism. In the liver, ranolazine is metabolised principally by CYP3A4, but also by CYP2D6. Nearly 65 % of ranolazine is bound to plasma proteins and less than 5 % is excreted unchanged. Concomitant administration of CYP3A4 inhibitors results in large increases in ranolazine exposure; three to four-fold increase with a potent CYP3A4 inhibitor like ketoconazole and 2.4-fold increase with a moderate CYP3A4 inhibitor like diltiazem. Ranolazine inhibits simvastatin transport in vitro and increases the plasma concentrations of simvastatin and simvastatin acid in vivo (60 and 39 %, respectively). The mechanism of interaction could be due to CYP3A4 inhibition but may also be related to P-gp inhibition.

Studies in mild hepatic impairment showed no effect on the pharmacokinetics of ranolazine while in moderate hepatic impairment the Area Under the Curve (AUC_{0-12}) was increased by 75 %. Since there are no data available on the pharmacokinetic of ranolazine in severe hepatic impairment, this condition should be considered to represent a contraindication for its use.

Safety and Tolerability

Ranolazine is generally well tolerated with undesirable effects often developing within the first 2 weeks of treatment. The most common adverse events reported in patients receiving ranolazine are constipation, nausea and asthenia. Treatment with ranolazine is associated with small dose-related mean increases in QTc from baseline [6]. However, in the clinical development programme of ranolazine there has been no evidence of an increased risk of torsades de pointes.¹⁸ Furthermore, in the MERLIN-TIMI 36 study a significantly lower incidence of arrhythmias including ventricular tachycardia was detected in patients treated with ranolazine compared to patients receiving placebo.¹⁰

Drug Interactions

Ranolazine is metabolised through CYP3A4, therefore drug-drug interaction must always be considered when ranolazine is co-administered with drugs inhibiting or being metabolised through this enzyme. Ranolazine increases plasma concentrations of simvastatin lactone and simvastatin acid. The concurrent administration of ranolazine with strong CYP3A4 inhibitors (HIV protease inhibitors, clarithromycin, telithromycin, itraconazole, ketoconazole, fluconazole, voriconazole, posaconazole, and nefazodone) should be avoided or low doses used with caution if there is clear need for the use of ranolazine in a given patient. Caution is recommended in

combining ranolazine with moderately potent CYP3A4 inhibitors including diltiazem and erythromycin. Co-administration or Ranolazine with Class Ia (quinidine) or Class III (dofetilide and sotalol) antiarrhythmics, is contraindicated.

Mechanism of Action

The mechanism of action of ranolazine is believed to be the consequence of its effect on the inhibition of sodium entry into myocardial cells through INa channels [7]. Of interest, the effect of ranolazine on the inhibition of sodium entry into cardiac cells favours the sodium and calcium homeostasis and prevents ischaemia-induced diastolic dysfunction.

Following electrical excitation, sodium ions enter the cardiac cells through membrane sodium channels causing the rapid depolarization of the action potential. The opening of the Na channels is very short and it is followed by a closure caused by the temporary inactivation of the channel; Na channels remain then closed until the next membrane depolarization. A small portion of the Na channels, however, do not inactivate completely after the opening phase and continue to open and close during the repolarisation phase of the action potential. This late opening of the Na channels allows a constant current of Na ions (INa) to enter the myocardial cell throughout the early repolarisation phase that coincides with the mechanical systole. Experimental evidence suggests that INa is increased in myocytes exposed to hypoxia [8], and ischaemia [9, 10]. The metabolic changes occurring during myocardial ischaemia are associated with an elevation of intra-myocyte Na concentration [10–12] and the increase in the late INa contributes to the elevation of intracellular sodium that is observed during ischaemia [9, 13].

An intracellular increase of Na concentration leads to an increased exchange of intracellular sodium for extracellular calcium (with Na exit and calcium entry), and a reduced exchange of intracellular calcium for extracellular Na (with calcium exit and Na entry). The increase of the intracellular

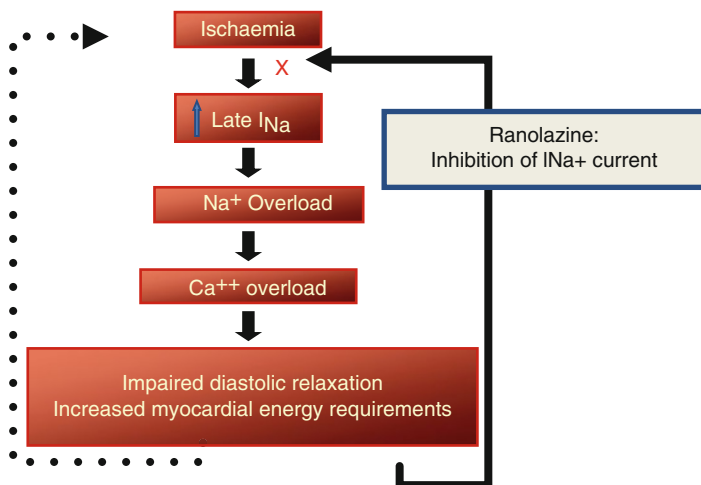


FIGURE 9.1 Effect of myocardial ischemia on late Na current (INa) and activation of the vicious circle of events due to INa. Ranolazine inhibits Calcium overload and thereby improves myocardial ischemia

Na concentration leads to intracellular calcium overload. The myocardial calcium overload causes an increase in actin/myosin interaction and an increase in myocardial oxygen consumption and in the left ventricular diastolic relaxation.

The mechanism of action of Ranolazine is to reduce the late INa in a concentration-, voltage- and frequency-dependent manner [14–16]. During ischaemia, the ranolazine-induced decrease of late INa reduces the ischaemia-induced increase in the intracellular sodium concentration. In this way ranolazine helps to preserve the ionic homeostasis in the myocardium during ischaemia and prevents calcium overload (Fig. 9.1). The effect of ranolazine on the late INa reduces the accumulation of intracellular calcium and the associated increase in ventricular stiffness and increased myocardial oxygen consumption. These effects in turn reduce left ventricular stiffness and reduce myocardial oxygen consumption.

Preclinical Evidence with Ranolazine

The effect of ranolazine on sodium and calcium homeostasis and contractile function has been demonstrated in experimental models of rat hearts in which sodium overloading was caused by increased I_{Na} [17]. Ranolazine has been shown to improve diastolic ventricular relaxation during ischaemia/reperfusion in rabbits [18], in the isolated rat heart in presence of ischaemic metabolites [19], and in ventricular myocytes of dogs with ischaemic left ventricular dysfunction. All these effects have been associated with an amelioration of myocardial ischemia in the models used.

Clinical Use of Ranolazine

Ranolazine was approved for clinical use in the USA in 2006, as add-on therapy for the treatment of chronic angina, and received a first-line indication in November 2008. The maximum dosage approved in the USA is 1 g twice daily. In Europe, ranolazine (prolonged-release tablets) was approved by the European Medicine Agency in July 2008 as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line antianginal therapies (such as beta blockers and/or calcium antagonists). The recommended initial dose in adults is 375 mg twice daily that it can be further up-titrated to the recommended maximum dose of 750 mg twice daily.

Clinical Development Program

The clinical development program of ranolazine includes earlier trials conducted with the immediate-release formulation and later clinical trials that used the sustained-release formulation. The main dose-response study for the demonstration of the efficacy of ranolazine was the Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial [20], which randomised 191 patients to either ranolazine or placebo. The

CARISA study (Combination Assessment of Ranolazine In Stable Angina) [21], assessed the effect of ranolazine 750 mg twice daily or 1 g bd as add on to atenolol, amlodipine or diltiazem in 823 patients with chronic stable angina. In the Efficacy of Ranolazine In Chronic Angina (ERICA) trial, 565 patients were randomised to receive ranolazine 1 g (bd) or placebo in addition to amlodipine 10 mg (od) for 6 weeks [22].

The Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial, randomised 6,560 patients to receive ranolazine (initially intravenously and then 1 g bd orally) or matching placebo within 48 h from the onset of ischaemic symptoms. Patients were followed for a median of 348 days. This study was conducted in patients with acute coronary syndromes and for this reasons will not be reported in this chapter [23].

MARISA Study

This was the main dose-response study. The objectives of the trial were to assess the tolerability of three doses of ranolazine sustained-release compared to placebo and their effects on treadmill exercise performance. It was a double-blind, randomised, placebo-controlled, cross-over study enrolling 191 patients treated with 500, 1,000 and 1,500 mg ranolazine against placebo. Treatment duration was 1 week at each dose level. Improvement of exercise duration was statistically significant compared to placebo for all three doses of ranolazine from 24 s at 500 mg bid. to 46 s at 1,500 mg bid, and showing a clear dose-response pattern. However, the disproportionate increase in adverse events with the 1,500 mg bid dose led to the conclusion that doses above 1,000 mg bid should not be used.

TERISA Study

The TERISA study (Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina) assessed the efficacy of ranolazine versus placebo on weekly angina

frequency and sublingual nitroglycerin use in 949 diabetic patients with coronary artery disease and chronic stable angina despite treatment with up to two anti-anginal agents [24]. Patients were randomized to a parallel 8 week double-blind study of ranolazine (target dose 1 g bid) or placebo. Weekly angina episodes were significantly reduced by ranolazine compared to placebo (3.8 vs. 4.3 episodes, $p=0.008$), as was the weekly use of sublingual nitrates (1.7 vs. 2.1, $p=0.003$). The study showed that among symptomatic patients with diabetes and despite treatment with up to two anti-anginal agents, ranolazine was effective in reducing the occurrence of angina attacks and the use of sublingual nitrates.

CARISA Study

In this study 823 patients were randomised to either ranolazine 750 mg bid. ($n=279$), ranolazine 1 g bid or placebo as add-on treatment to atenolol 50 mg od, amlodipine 5 mg od, or diltiazem 180 mg od. All patients had had chronic stable angina for at least 3 months. The pre-qualifying exercise test had to be symptom-limited and show the usual definite signs of myocardial ischaemia during exercise (0.1 mV ST segment depression). Mean age of included patients was 64 years. Mostly Whites and only about 23 % were females. Twenty-three percent were diabetics and 29 % had a diagnosis of congestive heart failure. Over 60 % were hypertensive and 58 % had suffered a previous myocardial infarction. The objective of the study was to determine the effects of ranolazine at doses of 750 mg bid or 1 g bid compared to placebo on symptom-limited exercise duration among patients with chronic stable angina treated with commonly used anti-anginal drugs. The primary efficacy end point was the change from baseline in exercise duration at trough after 12 weeks on study drugs. At baseline there were no differences between the three treatment arms; all showed an exercise duration of approximately 7 min, since one requirement was the ability to perform an exercise test with a duration of

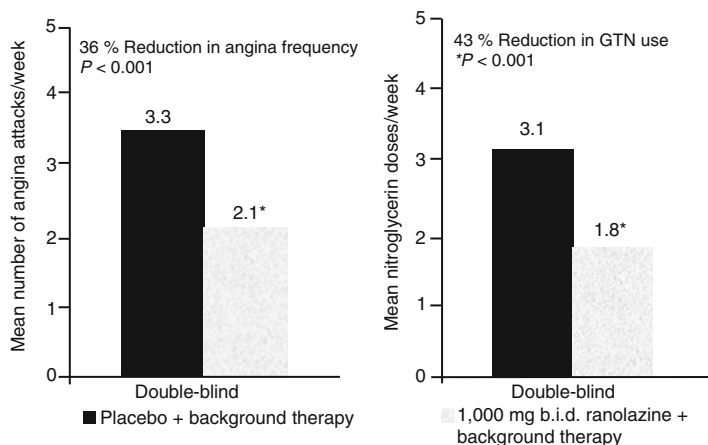


FIGURE 9.2 CARISA study effect of ranolazine on angina frequency and use of sublingual nitrates compared to placebo

3–9 min (modified Bruce protocol). The mean increases in exercise duration at trough were statistically significantly greater for patients treated with either dose of ranolazine SR than with placebo. A significant improvement in the occurrence of anginal episodes and the use of sublingual nitrates was also observed with ranolazine (Fig. 9.2).

ERICA Study

The trial assessed the effect of ranolazine sustained-release in patients with a documented history of coronary artery disease, chronic stable angina for 3 months or longer, and three or more angina episodes a week during the 2-week qualification period despite treatment with amlodipine 10 mg daily. Patients were randomised to receive either ranolazine 500 mg (bd) uptitrated to 1 g after 1 week or placebo on top of Amlodipine 10 mg. Patients were assessed at 2 and 6 weeks after initiation of the full-dose. Out of 565 randomised patients 98 % in each group completed the trial. Patients allocated to ranolazine had a significantly lower incidence of weekly episodes of angina

compared with patients receiving placebo. The effect on angina was mirrored by a significant reduction in the average weekly rate of NTG consumption in patients receiving ranolazine.

Meta-Analysis on Clinical Efficacy

A meta-analysis from our group assessed the effects of ranolazine on anginal symptoms, sublingual nitrate use, functional capacity, electrocardiographic signs of myocardial ischaemia and haemodynamic parameters in patients with chronic ischaemic heart disease [25]. We analysed randomized trials assessing the effects of ranolazine compared to control regarding exercise duration, time to onset of angina, time to 1 mm ST-segment depression, weekly sublingual nitrate use and weekly angina frequency. Of 358 articles identified in the initial search, 28 were retrieved for more detailed evaluation. Thereafter, 22 studies were excluded (i.e. articles reporting data already included in previous reports) and six trials were selected for the analysis.

Compared to placebo Ranolazine treatment was found to significantly improve exercise duration by >31.8 s, time to onset of angina by 37.976 s, and time to 1 mm ST-segment depression by 36.0 s. Ranolazine treatment was found to significantly reduce weekly angina frequency compared to placebo and weekly use of sublingual nitrates. Furthermore, ranolazine treatment significantly reduced HbA1c levels by 0.429 % compared to placebo, in diabetic patients. The results of this meta-analysis have confirmed the anti-anginal and anti-ischaemic properties of ranolazine and have provided an estimate of the magnitude of its effects in clinical practice.

Effects on Glucose Metabolism

A positive effect of ranolazine on glycated haemoglobin (HbA1c) has been shown by the CARISA study (post-hoc analysis) in patients with diabetes [21]. In this study, ranolazine

750 mg and 1 g bid reduced HbA1c compared with placebo (by 0.48 % and 0.70 % respectively). Interestingly, patients receiving insulin showed a greater reduction in HbA1c. A reduction in HbA1c was also observed in the MERLIN-TIMI 36 trial [23]. HbA1c fell from 7.5 to 6.8 % with ranolazine and subjects without diabetes in the ranolazine group were 32 % less likely to develop new hyperglycaemia compared to the placebo group.

Clinical indication for the Use of Ranolazine in Chronic Stable Angina

Despite the growing numbers worldwide of PCI in patients with stable angina the number of patients uncontrolled with single anti-anginal medications is increasing both because of the increasing burden of the disease and because of the failure to modify the natural history of chronic coronary artery disease with percutaneous interventions. Besides antiplatelets, statins and ACE-inhibitors there are no drugs that have been shown to improve prognosis in chronic stable angina. The effect of both beta-blockers and ivabradine in post-infarction patients and/or in those with heart failure cannot be translated to chronic stable coronary artery disease and data from registries and clinical trials do not support the chronic use of these drugs for prognostic benefits in this subset of patients. Therefore, the classification of first and second line anti-anginal drugs for the treatment of angina must be revised and all anti-anginals should be placed on the same level unless a clear prognostic benefit is shown.

There is an unmet need for additional drugs with anti-anginal effects especially for those that act on targets other than the ones commonly used by the classic haemodynamic agents. The extensive clinical development program of ranolazine in chronic stable angina supports its use in combination with anti-anginal drugs for the treatment of patients with chronic stable angina. The absence of any effect on heart rate or on blood pressure make ranolazine a drug extremely easy to use, even in patients with low heart rate or low blood

pressure. Therefore ranolazine appears to have a role in the treatment of chronic stable angina. The absence of haemodynamic effects make this drug extremely useful for the treatment of those patients where blood pressure and heart rate do not allow further intervention with haemodynamic agents. Although there are no clinical trials of combination therapy with other metabolic agents, the mechanism of action of ranolazine suggests that its effects may be potentiated by other metabolic interventions such as trimetazidine. Recent pharmaco-economic studies conducted both in Europe and in the USA have shown ranolazine to be cost-effective in patients with chronic stable angina. A recent study from Spain calculated the incremental cost-utility ratio of using ranolazine compared with a placebo and showed that the incremental cost-utility ratio is 8,455 Euro per quality-adjusted life-year (QALY)/patient in Spain and that the incremental cost-utility ratio is particularly effective in non-hospitalized patients with mild or moderate angina frequency [26].

Conclusions

Ranolazine is a novel anti-anginal agent with a non-haemodynamic mechanism of action. It is effective as adjunctive therapy in patients with chronic stable angina whose symptoms are not controlled by conventional treatment. The clinical development program of ranolazine has shown that the drug improves exercise performance and decreases angina attacks and the use of sublingual nitrates, compared to placebo. Ranolazine is well tolerated with neutral effect on haemodynamics.

References

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498–504.
2. Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary heart disease statistics 2010. British Heart Foundation, London; 2010.

3. Dobre D, Borer JS, Fox K, et al. Heart rate: a prognostic factor and therapeutic target in chronic heart failure. The distinct roles of drugs with heart rate-lowering properties. *Eur J Heart Fail.* 2014;16(1):76–85.
4. Rosano GM, Collins P. Gender differences in treatment of cardiovascular disease: a task force on gender of the ESC proposal on gender specific studies in cardiovascular pharmacology. *Fundam Clin Pharmacol.* 2010;24(6):662–3.
5. Boden W, O'Rourke R, Teo K, et al. Optimal medical therapy with or without PCI for stable coronary disease: the COURAGE trial. *N Engl J Med.* 2007;356:1503–16.
6. Summary of product characteristics. Ranexa® (ranolazine). <http://www.medicines.org.uk/EMC/medicine/21402/SPC/Ranexa%20prolonged-release%20tablets/>.
7. Belardinelli L, Antzelevitch C, Fraser H. Inhibition of late (sustained/persistent) sodium current: a potential drug target to reduce intracellular sodium-dependent calcium overload and its detrimental effects on cardiomyocyte function. *Eur Heart J.* 2004;6(Suppl A):A13–7.
8. Ju YK, Saint DA, Gage PW. Hypoxia increases persistent sodium current in rat ventricular myocytes. *J Physiol.* 1996;497:337–47.
9. Undrovinas AI, Fleidervish IA, Makielski JC. Inward sodium current at resting potentials in single cardiac myocytes induced by the ischemic metabolite lysophosphatidylcholine. *Circ Res.* 1992;71:1231–41.
10. Wu J, Corr PB. Palmitoyl carnitine modifies sodium currents and induces transient inward current in ventricular myocytes. *Am J Physiol.* 1994;266:H1034–46.
11. Ward CA, Giles WR. Ionic mechanism of the effects of hydrogen peroxide in rat ventricular myocytes. *J Physiol.* 1997;500: 631–42.
12. Huang B, El Sherif T, Gidh-Jain M, et al. Alterations of sodium channel kinetics and gene expression in the postinfarction remodeled myocardium. *J Cardiovasc Electrophysiol.* 2001;12: 218–25.
13. Murphy E, Perlman M, London RE, Steenbergen C. Amiloride delays the ischemia-induced rise in cytosolic free calcium. *Circ Res.* 1991;68:1250–8.
14. Song Y, Shryock JC, Wu L, Belardinelli L. Antagonism by ranolazine of the pro-arrhythmic effects of increasing late INa in guinea pig ventricular myocytes. *J Cardiovasc Pharmacol.* 2004;44:192–9.

15. Undrovinas AI, Undrovinas NA, Belardinelli L. Ranolazine inhibits late sodium current in isolated left ventricular myocytes of dogs with heart failure. *J Am Coll Cardiol.* 2004;43:178A.
16. Antzelevitch C, Belardinelli L, Zygmunt AC, et al. Electrophysiological effects of ranolazine, a novel antianginal agent with antiarrhythmic properties. *Circulation.* 2004;110:904–10.
17. Fraser H, Belardinelli L, Wang L, et al. Inhibition of late I_{Na} by ranolazine reduces Ca^{2+} overload and LV mechanical dysfunction in ejecting rat hearts. *Eur Heart J.* 2005;26(abstract suppl):414.
18. Gralinski MR, Black SC, Kilgore KS, et al. Cardioprotective effects of ranolazine (RS-43285) in the isolated perfused rabbit heart. *Cardiovasc Res.* 1994;28:1231–7.
19. Maruyama K, Hara A, Hashizume H, et al. Ranolazine attenuates palmitoyl-L-carnitine induced mechanical and metabolic derangement in the isolated, perfused rat heart. *J Pharm Pharmacol.* 2000;52:709–15.
20. Chaitman BR, Skettino SL, Parker JO, et al.; for the MARISA Investigators. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol.* 2004;43:1375–82.
21. Chaitman BR, Pepine CJ, Parker JO, et al.; for the Combination Assessment of Ranolazine In Stable Angina (CARISA) Investigators. Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina. A randomized controlled trial. *JAMA.* 2004;291:309–16.
22. Stone PH, Gratsiansky NA, Blokhin A, Huang I-Z, Meng L.; for the ERICA Investigators. Antianginal efficacy of ranolazine when added to treatment with amlodipine: the ERICA (Efficacy of Ranolazine in Chronic Angina) trial. *J Am Coll Cardiol.* 2006;48:566–75.
23. Morrow DA, Scirica BM, Karwatowska-Prokopczuk E, et al.; for the MERLIN-TIMI 36 Trial Investigators. Effects of ranolazine on recurrent cardiovascular events in patients with non-ST-elevation acute coronary syndromes. The MERLIN-TIMI 36 randomized trial. *JAMA.* 2007;297:1775–83.
24. Kosiborod M, Arnold SV, Spertus JA, et al. The TERISA study (Type 2 diabetes evaluation of ranolazine in subjects with chronic stable angina). *J Am Coll Cardiol.* 2013;61(20):2038–45. doi:[10.1016/j.jacc.2013.02.011](https://doi.org/10.1016/j.jacc.2013.02.011). Epub 2013 Mar 10.

25. Savarese G, Rosano G, D'Amore C, et al. Effects of ranolazine in symptomatic patients with stable coronary artery disease. A systematic review and meta-analysis. *Int J Cardiol.* 2013;169(4): 262–70.
26. Hidalgo-Vega A, Ramos-Goñi JM, Villoro R. Cost-utility of ranolazine for the symptomatic treatment of patients with chronic angina pectoris in Spain. *Eur J Health Econ.* 2014;15(9): 917–25.

Chapter 10

New Antianginal Drugs Still Not Available for Clinical Use

Juan Tamargo and Eva Delpón

Introduction

Coronary artery disease (CAD) is the leading cause of death in Europe and chronic stable angina pectoris (CSA) is the most common manifestation of the disease, being the initial symptom in up to 70 % of patients [1]. The incidence and prevalence of patients with CSA is anticipated to increase in the coming decade as a result of the aging of the population, better management of acute myocardial infarction (MI), increasing burden of atherosclerosis and obesity, greater use of life-prolonging therapies and limitations of available anti-anginal agents [1]. The aims of pharmacological management of angina pectoris are both to obtain relief of symptoms to improve quality of life and to improve prognosis regarding morbidity and mortality [1]. Current strategies to relieve symptoms aim to reduce myocardial oxygen demand (MVO_2) and/or increase coronary blood flow to the ischemic area with the use of β -blockers, calcium channel antagonists,

J. Tamargo (✉) • E. Delpón
Department of Pharmacology, School of Medicine,
University Complutense, Madrid 28040, Spain
e-mail: jtamargo@med.ucm.es

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment of Chronic Stable Angina Pectoris*, Current Cardiovascular Therapy, DOI 10.1007/978-3-319-17332-0_10,
© Springer International Publishing Switzerland 2015

189

nitrates, K^+ -channel openers, and selective bradycardiac agents, and/or to improve ionic homeostasis (late sodium current inhibitors) in the myocardium. This occurs either by direct cardiac effects or indirectly through complex effects on hemodynamic determinants. Ideally, antianginal drug treatment should be tailored to individual patient's needs, taking into consideration the characteristics and severity of symptoms, the location, severity and functional significance of coronary artery stenosis, the presence of co-morbidities and patient preference [2].

Unfortunately, many patients with CSA remain symptomatic and at risk of major cardiac events despite the combination of two or more conventional drugs at maximum tolerated dosages [3]. Many patients with CSA have concomitant comorbidities (hypertension, bradycardia, heart failure, diabetes mellitus) that make it difficult to uptitrate the dose or contraindicate the use of conventional antianginal drugs (e.g., β -blockers, calcium antagonists) due to fear of inducing dose-related adverse effects such as hypotension, bradycardia and/or atrioventricular block before angina relief is achieved. Additionally, persistent angina occurs in approximately 10–25 % of patients subjected to coronary bypass surgery and/or percutaneous interventions and 60–80 % require antianginal therapy 1 year after the procedure [4–6]. Because of the inability of current antianginal drugs to optimally control episodes of CSA, there is an unmet need for developing new drugs with different, but complementary, mechanisms of action devoid of the limitations of current treatments (e.g., with no or minimal hemodynamic effects) and that can be safely added to the current therapy.

In this chapter we review some of the newest antianginal drugs, Chinese traditional medicines with potential clinical applications, and angiogenic factors under development for the treatment of CSA. The results from randomized clinical trials (RCTs) or meta-analyses are summarized in Tables 10.1, 10.2, and 10.3.

TABLE 10.1 Major randomized clinical trials with drugs under development in patients with chronic stable angina pectoris

Acronyms [reference]/NTC	Study design	Treatment/ comparator	Primary end points	Outcomes
Allopurinol				
[7]/ISRCTN 82040078	60 R, DB, PC, CO	Allopurinol (600 mg/day) or placebo for 6 weeks	Time to ST depression	Allopurinol significantly prolonged the time to ST depression, TED and the time to angina
[8]/ISRCTN15253766	80 R, DB, PC, CO	Allopurinol (300 mg/d for 4 weeks and 600 mg/ day for 4 weeks) or placebo	Whether XO inhibition improves endothelial dysfunction and XO-induced OS	Allopurinol abolished vascular OS and improved endothelium- dependent vasodilation and flow-mediated dilation
[9]	40, ST elevation MI R, PC	Allopurinol (400 mg loading dose followed by 100 mg/day 1 month) or placebo	Effect on cardiac biomarkers, ST-E recovery, and clinical outcomes	Allopurinol resulted in a more effective ST-E recovery and lower peak values of troponin I, CPK and CK-MB

(continued)

TABLE 10.1 (continued)

Acronyms [reference]/NTC	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
Febuxostat					
NCT01549977		R, DB, PA	Febuxostat (80 mg/day) or placebo for up to 12 weeks	Change in ETT at week 12	Terminated (business decision)
NCT01763996	30	R, DB, CO	Febuxostat (80 mg/day) or placebo for up to 6 weeks	Change in coronary artery flow from rest to isometric handgrip exercise at 6 and 12 weeks	Ongoing
Cardiac metabolic modulators (Glucagon-like peptide-1)					
GLP-1 [65]	21, AMI and LVEF <40 % after primary CABG	Non-R, pilot	GLP-1 (1.5 pmol/ kg/min for 72 h) or placebo	Effect of GLP-1 on global and regional LV function in the early post-MI period	GLP-1 improved LVEF, global and regional wall motion scores

[66]	20, undergoing CABG	GLP-1 (1.5 pmol/kg/min for 60 h) or placebo	Effect of GLP-1 on LV function during dobutamine stress and postischemic stunning	GLP-1 decreased need for inotropic support and vasodilator drugs
Sitagliptin Read ISRCTN78649100	14, CAD and normal LV function	Sitagliptin (100 mg) or placebo		Alogliptin improved global and regional LV performance and mitigated postischemic stunning
Dantonic® (T-89)				
NCT00797953	120	R, DB, PC, PG	T89 (2 × 75 or 3 × 75 mg bid) or placebo for 8 weeks	Completed, but not reported
NCT01659580	960	R, DB, PC, PA	T-89 150, 225 and mg b.i.d. for 6 weeks	Ongoing
			Change of symptom-limited TED	
				(continued)

(continued)

TABLE 10.1 (continued)

Acronyms [reference]/NTC	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
Endothelin-receptor antagonists					
Bosentan [10]	28	R, DB, PC	Bosentan, 200 mg i.v. or placebo	Effects on systemic and coronary hemodynamics	Bosentan increased coronary diameter, particularly in segments with no or mild angiographic changes
BQ-123 [11]	30, patients undergoing CA	SB	Intracoronary BQ-123 (6 µmol/L over 20 min) or saline	Effects on myocardial ischemia during coronary angioplasty	BQ-123 prevented the reduction in myocardial ischemia on repeated balloon inflations
Fasudil (Rho kinase inhibitor) [12]	Effort angina		Fasudil (300 µg/ min for 15 min)		Fasudil improved pacing-induced angina

[13]	45	OL	Fasudil (5, 10, and 20 mg tid) for 2 weeks each dose	Anginal attacks per week, MET and the time to the onset of 1-mm ST segment depression	Fasudil reduced the number of attacks and prolonged MET and time to 1-mm ST segment depression
	22	OL	Fasudil 20 mg tid for 2 weeks, then 40 mg tid for 2 weeks	Anginal attacks per week, MET and time to the onset of 1-mm ST segment depression	Fasudil reduced the number of angina attacks and the use of sublingual NTG and prolonged the MET
	125	R, DB	Fasudil (5, 10, 20, or 40 mg tid) for 4 weeks.	MET and time to the onset of 1-mm ST segment depression	Fasudil prolonged MET and time to 1-mm ST segment depression

(continued)

TABLE 10.1 (continued)

Acronyms [reference]/NTC	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
[14]	84	R, DB, PC	Fasudil (20 mg tid titrated to 80 mg tid) or placebo	Change from baseline in total ETT duration at peak after 2, 4, 6 and 8 weeks of treatment	Fasudil increased the time to ≥ 1 mm ST-segment depression at both peak and trough compared with placebo
Testosterone					
[15]	46 men	R, DB	Testosterone (5 mg/day by transdermal patch) or placebo	Time to 1-mm ST-segment depression and ETT at 4 and 12 weeks	Testosterone reduces exercise-induced myocardial ischemia.

[16]	18 men	R	Testosterone (2.5 mg IV in 5 min) or placebo	Effect of acute i.v. testosterone on exercise- induced myocardial ischemia	Testosterone improves exercise-induced myocardial ischemia
------	--------	---	--	---	--

AMI acute myocardial infarction, *CA* coronary angioplasty, *CABG* coronary artery bypass grafting, *CO* cross-over, *DB* double-blind, *ETT* exercise treadmill testing, *LVEF* left ventricular ejection fraction, *MET* maximum exercise time, *MI* myocardial infarction, *NTC* ClinicalTrials.gov, *NTG* nitroglycerine, *OL* open label, *OS* oxidative stress, *PA* parallel-assignment, *PC* placebo-controlled, *PG* parallel-group, *R* randomized, *TED* total exercise duration

TABLE 10.2 Systematic reviews evaluating the efficacy and safety of traditional Chinese medicines in patients with coronary artery disease

Study [reference]	RCTs/ patients	Treatment	Results
Compound salvia pellet (CSP) in SCA [17]	17/ uncertain	CSP vs nitrate ester preparations	CSP relieved angina and improved ECG better than nitrates with less adverse reactions and no tolerance
T89 [18]	27/3722	T89 vs nitrates	T89 significantly improved angina symptoms and ECG changes, produced less adverse events and no tolerance was observed.
T89 [19]	60/6931	T89 vs ISDN	T89 was apparently more effective than ISDN in improving angina symptoms and ECG parameters.
Panax notoginseng [20]	17/1747	Panax notoginseng vs no intervention	Panax notoginseng alleviate angina symptoms (number and duration of angina and dosage of NTG and ECG changes) but did not show benefit on major CV events
Sanqi Panax Notoginseng (SPN) injection [21]	10/969	SPN alone or plus conventional drugs	SPN was effective and safe and combined with western medications appeared to be more effective than conventional drugs alone. No serious adverse effects were reported.

T89 in patients with AMI [22]	7/1215	T89 vs no intervention, placebo, or conventional western medicine	T89 reduced the risk of cardiac death and heart failure compared with no intervention, and improved quality of life and impaired LVEF. Drug safety was unproven for the limited data
Suxiao jiu xin wan [23]	15/1776	Suxiao jiu xin wan vs nitrates	Compared with NTG improved ECG changes, reduced symptoms, frequency of attacks and use of NTG. No differences vs ISDN for symptoms and ECG changes. No serious side effects were identified
<hr/>			
Suxiao jiu xin wan: its main components include tetramethylpyrazine (extracted from <i>Ligusticum chuanxiong</i>) and borneol (<i>Borneolum Syntheticum</i>) <i>AMI</i> acute myocardial infarction, <i>CV</i> cardiovascular, <i>ISDN</i> isosorbide dinitrate, <i>NTG</i> nitroglycerine, <i>RCT</i> randomized clinical trials			

TABLE 10.3 Randomised controlled trials with proangiogenic factors in patients with chronic stable angina

Acronyms [reference](NTC)	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
FGF-4 and FGF-2					
AGENT-1 [24]	79, CCS class II-III	R, DB	IC injection of Ad5FGF-4 (3.3×10^8 – 10^{11} vp) or placebo	Safety and anti-ischemic effects of Ad5- FGF4 gene transfer	Improved exercise time in patients with baseline ETT ≤ 10 min
AGENT-2 [25]	52, CCS class II-IV	R, DB, PC	IC injection of Ad5FGF-4 (10^{10} vp or placebo)	Decrease in adenosine- induced ischemic LV perfusion defect size	Ad5FGF-4 significantly improved myocardial perfusion at 8 weeks
AGENT-3 and 4 (NCT00346437, NCT00185263) [26]	416 and 116, CCS class II-IV	R, DB, PC, PA	Low (1×10^9 vp) and high IC doses of Ad5FGF-4 (1×10^{10} vp) or placebo	Change from baseline in total ETT time at 12 weeks	Stopped prematurely. Improved exercise time and tolerance with high dose, only in women

[27]	24, CCS III-IV for CABG	R, DB, PC	rFGF-2 (10 or 100 µg) or placebo via sustained-release heparin-alginate microcapsules	Safety and efficacy of local FGF as an adjunct to CABG surgery	The high dose improved angina symptoms and cardiac perfusion after 3 months
FIRST trial [28]	337, CCS III-IV	R, DB, PC	Single IC infusion of rFGF2 at 0, 0.3, 3, or 30 µg/kg	Safety and efficacy of rFGF2 in patients with advanced CAD	No improvement in exercise tolerance or myocardial perfusion.
VEGF					
NCT01002430	30, no option -patients	R, SB, PA	Endocardial injection (10 ⁹ , 10 ¹⁰ and 10 ¹¹ vp) of AdVEGF-D into 10 sites of the myocardium	Safety and tolerability at 1 year	Ongoing

(continued)

TABLE 10.3 (continued)

Acronyms [reference](NTC)	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
AWARE (NCT000438867)	Women with angina not candidates for revascularization	R, DB, PC	Ad5FGF-4 or placebo	Time to onset of ischemia ECG changes during ETT after 6 months	Recruitment status is unknown
VIVA trial [29]	178, CCS II–III	DB, PC	IC infusion of low or high-doses (17 and 50 ng/kg/min) of rhVEGF followed by i.v. infusions on days 3, 6, and 9.	Safety and efficacy of intracoronary and intravenous rhVEGF	High-dose improved CCS class. A nonsignificant trend in ETT and angina frequency

REVASC trial [30]	67, CCS II-IV	R	AdVEGF121 (4×10^{10} pu) administered IM via mini-thoracotomy	Time to 1 mm ST-segment depression at 12 and 26 weeks	Improved time to 1 mm ST-segment depression, TED and angina symptoms at 26 weeks, but not myocardial perfusion
EUROINJECT- ONE trial [31]	80, CCS III-IV	R, DB, PC	Percutaneous IM phVEGF-A ₁₆₅ gene transfer (0.5 mg) or placebo	Myocardial perfusion, LV function, and clinical symptoms after 3 months	No difference in myocardial perfusion

(continued)

TABLE 10.3 (continued)

Acronyms [reference](NTC)	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
NORTHERN trial [32]	93, CCS III-IV	DB, PC	VEGF165 plasmid (2000 mcg) vs placebo via endocardial route	Change in myocardial perfusion from baseline to 3 or 6 months	No improvement in myocardial perfusion
NOVA trial [33]	17/129, CCS II-IV	R, DB, PC	12 IM injections of VEGF121 or placebo	TED and time to 1 mm ST depression during exercise at 12, 26 and 52 weeks	Negative effect. Premature termination
KAT trial [34, 35]	103, CCS II-III	R, DB, PC	IC AdVEGF165 (2×10^{10} pfu), VEGF plasmid liposome (mcg) or placebo	Minimal lumen diameter and percent diameter stenosis at 6 months	No effect on postangioplasty restenosis, but improved myocardial perfusion. After 8 years did not increase the risk of MACEs

ASPIRE trial (NCT01550614)	100	R, C, PG	IC infusion of Ad5- FGF4, delivered during induced transient ischemia	Myocardial perfusion, angina functional class, symptoms, and quality of life	Ongoing
KAT30 trial (NCT01002430)	30, CCS II-III	R, SB, PA	AdVEGF-D (10 ⁹ , 10 ¹⁰ , and 10 ¹¹ vp) injected into 10 sites of the myocardium	Safety and efficacy of catheter mediated endocardial adenovirus VEGF-D gene therapy in patients with severe coronary heart disease.	Recruiting

(continued)

TABLE 10.3 (continued)

Acronyms [reference](NTC)	Patients (n)	Study design	Treatment/ comparator	Primary end points	Outcomes
HGF					
[36]	9, CAD	Phase I	VM202 (0.5–2.0 mg) injected into the right coronary artery (RCA) territory	Global myocardial functions after 6 months	Improved global myocardial functions (wall motion score index and stress perfusion)
NCT01925352	40	OL	HGF, 5×10^9 vp by transcatheter injection into five LV sites	Death, new myocardial infarction or stroke 6 months after treatment	Recruiting

ATP adenosine triphosphate, *CABG* coronary artery bypass grafting, *CCS* Canadian Cardiovascular Society, *DB* double-blind, *ETT* exercise treadmill testing, *IC* intracoronary, *IM* intramyocardial, *MACEs* major adverse cardiovascular events, *MET* maximum exercise time, *MI* myocardial infarction, *NTC* ClinicalTrials.gov, *OL* open label, *PA* parallel assignment, *PC* placebo-controlled, *PG* parallel-group, *R* randomized, *SB* single blind, *TED* total exercise duration, *Vp* viral particles

Antianginal Drugs

Xanthine Oxidase Inhibitors

Allopurinol

Inactivation of nitric oxide (NO) by superoxide anions ($O_2^{\cdot-}$) contributes to impaired endothelium-dependent vasodilation in patients with CAD. Xanthine oxidase (XO) is a major source of $O_2^{\cdot-}$ and its activity is abundant in both vascular endothelium and plasma of CAD patients. Increased activity of XO in human coronary arteries has been shown to reduce vascular NO availability and increase vascular oxidative stress (OS) and endothelial dysfunction in CAD patients [37]. Conversely, XO inhibition reduced the levels of OS in the circulation and improved endothelial function and cardiac contractility in patients with CAD [38, 39]. Allopurinol, a XO inhibitor, reduces OS and improves endothelial/vascular dysfunction in patients with CAD [8, 40]. These effects of allopurinol are independent from changes induced by the agent on plasma uric acid and tend to persist when given in addition to conventional optimal antianginal therapy, including statins and ACE inhibitors [41]. These findings raise the possibility that allopurinol may be a useful agent for treatment of CSA.

The effects of high-dose allopurinol were assessed in patients with angiographically documented stable CAD and left ventricular ejection fraction (LVEF) >45 % [7]. Compared with baseline, allopurinol significantly prolonged the time to ST depression (43-s, 95 % CI 31–58), total exercise time (58-s, 95 % CI 45–77), and time to chest pain (38-s, 95 % CI 17–55). Baseline urate plasma concentration did not correlate with the effects of allopurinol on exercise variables. Diastolic blood pressure during exercise was significantly lower, while maximum tolerated rate pressure product was significantly higher on allopurinol compared with placebo. The observed absolute increase in median time to ST depression was similar to that previously described with other antianginal drugs including amlodipine, nitrates, ivabradine, atenolol and ranolazine. In

another study from the same group of investigators, patients with CSA treated with conventional anti-ischemic and vasculoprotective agents were randomized to receive high-dose allopurinol (600 mg/day) or placebo [8]. Allopurinol was shown to abolish vascular OS and improved endothelial-dependent vasodilation and central augmentation index, as assessed by pulse wave velocity analysis. These findings confirm that XO is a major source of vascular OS and XO inhibitors improve vascular OS and endothelial function which results in increased coronary blood flow in patients already receiving treatment with optimal conventional CAD therapy. Of interest, as the anti-ischemic effect of allopurinol is not associated to haemodynamic changes this agent could be used safely in combination with conventional antianginal drugs or as an alternative therapy when conventional agents cannot be tolerated because of adverse hemodynamic or electrophysiological effects.

In the acute coronary setting, i.e., patients undergoing primary coronary intervention, allopurinol treatment improved ST segment recovery (reflecting improved epicardial coronary flow and perfusion at microvascular level) and reduced troponin I, CPK and CK-MB elevations [9]. In addition, allopurinol significantly reduced (13 %) major adverse cardiac events (MACE) at 1-month follow-up.

Mechanism of Action

The mechanism of the anti-ischemic effects of allopurinol remains to be fully elucidated, but it can be related to a reduction in OS, an improvement in endothelial function which increases coronary perfusion and decreases LV afterload, and an increase in cardiac adenine nucleotide levels [40, 42]. Substrates for adenosine triphosphate (ATP), such as AMP, are broken down by XO and thus, inhibition of XO would increase the adenine nucleotide pool (ATP and creatine phosphate) that would protect and improve cardiac function during ischemia [39, 42]. ATP synthesized in the mitochondria is converted to phosphocreatine (PCr) by the mitochondrial creatine kinase and PCr is exported to the cytosol where it converts adenosine diphosphate (ADP) to ATP through the activity of

cytosolic creatine kinase (cCK). Allopurinol decreases OS which indirectly activates CKc activity and the synthesis of ATP. Additionally, XO inhibition with allopurinol enhances calcium sensitivity in stunned trabeculae [43] and exerts a positive inotropic effect. In pacing-induced heart failure models, allopurinol enhances baseline LV contractile performance and decreases myocardial oxygen consumption leading to a near normalization of myocardial energetics [39, 44, 45].

Pharmacokinetics and Adverse Effects

Allopurinol is well absorbed but rapidly and completely metabolized in the liver to oxipurinol, a XO inhibitor which is excreted by the kidneys. The half-lives of allopurinol and oxipurinol are 1–2 and ~15 h, respectively. Oral allopurinol can cause stomach upset, nausea, diarrhea, and a cutaneous rash. Some patients can develop a hypersensitivity syndrome with fever, skin rash, eosinophilia, hepatitis and worsened renal function. Rarely, it can cause Stevens-Johnson syndrome and toxic epidermal necrolysis, two life-threatening conditions. As oxipurinol is eliminated only by the kidney, its half-life increases in patients with chronic kidney disease (CKD).

Interestingly, high-dose allopurinol was well-tolerated in trials of patients with CSA and a mean estimated glomerular filtration rate (eGFR) of 59 mL/min (stage III CKD) [7, 8]. The dose of allopurinol used for management of angina is similar to the highest dose used for moderately severe gout i.e., 400–600 mg/day, and therefore the risk of hypersensitivity and serious cutaneous adverse reactions can increase in patients with CKD. Thus, the long-term safety of high-dose allopurinol in patients with CSA, a population characterised by advanced age, multiple drug treatments, comorbidities, and CKD needs to be assessed carefully.

Febuxostat

This is a more potent and selective XO inhibitor than allopurinol [46, 47]. Febuxostat is rapidly absorbed (bioavailability 49 %) after oral administration, reaching peak

plasma levels within 0.5–1.3 h. It binds to plasma proteins (99 %), is extensively metabolized in the liver [by conjugation via uridine diphosphate glucuronosyl transferases (UGT1A1, 1A3, 1A9 and 2B7) and oxidation via CYP1A2, CYP2C8, and CYP2C9 and non-P450 enzymes] and is eliminated (mostly as metabolites) by both hepatic and renal pathways with a half-life of 5–8 h. The main adverse effects of febuxostat include cutaneous rashes, headache, arthralgia, abdominal pain, nausea and liver function abnormalities. A phase 2 trial designed to assess the effect of febuxostat as an add on to stable anti-anginal therapy on exercise treadmill testing in subjects with CSA and a serum urate ≥ 5 mg/dl (NCT01549977) was prematurely terminated and an ongoing phase 4 study assesses the effects of febuxostat on coronary artery endothelial dysfunction in patients with CSA (NCT01763996). Thus, at present, the role of febuxostat in the management of patients with CSA is uncertain.

Newer Inhibitors of the Late Sodium Current

F15845

F15845 is a new selective I_{NaL} blocker with anti-ischemic properties. In atrial and ventricular muscle cells and in Purkinje fibres, the rapid upstroke (phase 0) of the action potential (AP) is due to the activation-opening of Na^+ channels generating the peak inward Na^+ current (I_{Na}) which determines the initiation and propagation of the cardiac AP. Under normal conditions, most cardiac Na^+ channels open transiently (1–3 ms) upon membrane depolarization but rapidly inactivate-close and remain closed during the plateau phase of the AP. However, a small percentage of Na^+ channels either fail to inactivate properly, or close and then reopen during the plateau phase, generating the so-called late Na^+ current (I_{NaL}) [48]. The amplitude of the I_{NaL} is ~ 1 % of the peak I_{Na} , but because it persists hundreds of milliseconds, the amount of Na^+ carried by the I_{NaL} can be of the same

order as that carried by the peak I_{Na} . The amplitude of I_{NaL} markedly increases during both myocardial ischemia and increased OS. The increase in I_{NaL} enhances Na^+ influx and intracellular Na^+ concentration ($[Na^+]_i$) which leads to an increase in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via the reverse mode of the Na^+ - Ca^{2+} exchanger [48, 49]. This increase in cytosolic Na^+ and Ca^{2+} concentrations during ischemia is a major contributor to the impairment of ventricular relaxation, leading to an increase in diastolic wall tension and MVO_2 and a decrease in subendocardial coronary blood flow during the diastole [48]. Moreover, the increase in cytosolic Na^+ during ischemia and the kinetics of $[Na^+]_i$ recovery are key determinants of the recovery of LV function during reperfusion [50] and enhanced Na^+ influx, directly or through Ca^{2+} overload, increases ATP consumption and decreases ATP production. Thus, an increase in I_{NaL} plays a key role in the contractile and metabolic disturbances observed in the ischemic myocardium.

In HEK293 cells transfected with the SCN5A gene, which encodes the α -subunit of $hNa_v1.5$, F15845 inhibited veratridine-induced I_{NaL} (IC_{50} 5.3–9.3 μM) and shifted the I_{NaL} inactivation curve towards hyperpolarized potentials without interfering with activation kinetics [51, 52]. F15845 blocked the Na^+ channel in a voltage-dependent manner, being more effective at depolarized potentials, i.e., in ischemic cardiac tissues. However, F15845 did not affect the I_{Na} responsible of the upstroke, the L-type Ca^{2+} and several K^+ channels activated during the cardiac AP, which confirmed its selectivity towards I_{NaL} and explain why it did not affect shape of the cardiac AP [51, 52]. In rat isolated left atria F15845 inhibited the diastolic contracture elicited by activators of the I_{NaL} (ischemia, veratrine or lysophosphatidylcholine) [53]. In isolated hearts from diabetic (*db/db*) mice no-flow ischemia produced a rapid increase in $[Na^+]_i$ which persisted elevated upon reperfusion. F15845 significantly inhibited the increase in $[Na^+]_i$ and in diastolic pressure during ischemia/reperfusion (I/R). In rats subjected to a 15-min occlusion of left coronary artery followed by 24-h reperfusion F15845 reduced myocardial infarct size and troponin I plasma levels; in rats

subjected to 14-day reperfusion, F 15845 significantly reduced the expansion of infarct size [53]. In guinea pig isolated and perfused hearts F 15845 did not modify affect coronary blood flow, heart rate and left ventricular function, but reduced the increase in LV end-diastolic pressure (diastolic contracture) induced by global ischemia [51]. In rabbits subjected to 5 min coronary artery occlusion and in dogs with coronary stenosis and subjected to left atrial pacing F15845 dose-dependently inhibited ischemia-induced ST segment elevation [51]. The myocardial protection afforded by F15845 was assessed in two pig models of I/R [54]. In the first model, the left circumflex coronary artery (LCCA) was ligated for 60-min and then reperfused for 48-h and F15845 administered i.v. before ischemia. In the second model a ligation of the LCCA was applied for 15 min 1 week before the actual 60 min occlusion. In both models, F15845 significantly reduced infarct size and lowered plasma myoglobin and troponin I levels. Of note, in both models the protective effects of F15845 were not associated with significant hemodynamic effects, confirming a direct cardiac anti-ischemic activity. However, the pharmacokinetic properties, safety and clinical development of F 15845 are unknown and require further assessment.

Cardiac Metabolic Modulators

The normal heart derives ~60–100 % of its energy from free fatty acid (FFA) oxidation and the remainder from glucose and lactic acid [55]. However, FFA oxydation requires 10–15 % more oxygen for a given quantity of ATP produced [56]. Furthermore, FFA and their metabolites inhibit pyruvate dehydrogenase and glucose oxidation, increase OS and lactate and proton accumulation (intracellular acidosis), impair Ca^{2+} handling and LV contractility (diastolic dysfunction), and increase the risk of arrhythmias [55, 56]. During myocardial ischemia the heart shifts its preference from FFA to glucose to minimize the extra O_2 consumption associated with FFA oxidation. Metabolic modulators are drug that

augment glucose uptake and shift myocardial substrate of utilization from FFA to glucose oxidation enhancing oxygen efficiency during myocardial ischemia [55, 56]. These drugs have the potential to relieve symptoms in patients with refractory angina receiving optimal medical therapy but who are not amenable to revascularization.

Glucagon-like peptide-1-[7–36] amide (GLP-1) released from intestinal L cells in a glucose- dependent manner increases glucose-stimulated pancreatic insulin secretion and myocardial glucose uptake via the translocation of glucose-transporting vesicles (GLUT-1 and -4) to the sarcolemma [57]. Some cardiac effects GLP-1 depend on the direct stimulation of G protein-coupled receptors (GLP-1R) coupled to adenylyl cyclase (positive inotropism, glucose uptake, ischemic preconditioning); however, postischemic recovery of cardiac function and vasodilation, depend on rapid metabolism of GLP-1 to GLP-1(9–36) [58]. However, the half-life of native GLP-1 is 1–2 min as it is rapidly degraded *in vivo* by the ubiquitous dipeptidyl peptidase-4 (DPP-4). GLP-1 mimetics and analogs and DPP-4 inhibitors that increase GLP-1 levels might overcome this problem, but clinical studies with all these agents in angina pectoris are limited in number and scope, so that their long-term effects are unknown. DDP-IV inhibitors can also exert incretin-independent cardioprotective effects as they attenuate the degradation of chemokine stromal cell derived factor (SDF-1) and substance P [59]. SDF-1 enhances angiogenesis via vascular endothelial growth factor/NOS3-related pathway and stimulates endothelial and cardiac progenitor cell migration to the heart improving cardiac function after myocardial infarction, whereas substance P stimulate endothelium-derived NO release.

In animal models of ischemia-reperfusion, DPP-4 inhibitors (DPP-4i) reduced infarct size (38–64 %) and ameliorated cardiac dysfunction by attenuating cardiac mitochondrial dysfunction (reduced OS and mitochondrial swelling) and cardiomyocyte apoptosis (increased Bcl-2 and pro-caspase-3 expression in the ischemic area) [60–62]. GLP-1 (1.5 pmol/kg/

min) attenuated myocardial stunning after brief periods of myocardial I/R in conscious dogs, so that regional wall motion recovery occurred earlier and was complete in GLP-1-treated dogs; this effect was accompanied by improvement in LV diastolic relaxation [63]. GLP-1 increased myocardial glucose uptake and decreased creatine phosphokinase release following reperfusion but it had no direct effects on myocardial contractility, heart rate, or coronary blood flow.

In a pilot study in 14 patients with CAD and preserved LV function awaiting revascularization, the DPP-IVi sitagliptin, improved global and regional LV performance and attenuated post-ischemic stunning during dobutamine stress echocardiography [64]. In another pilot study in ten patients with AMI and LVEF <40 % after successful primary angioplasty the i.v. infusion of GLP-1 (1.5 pmol/kg/min for 72 h) significantly improved LVEF and regional and global wall motion score indexes in both diabetic and non-diabetic patients and was well tolerated, with only transient gastrointestinal effects [65]. Moreover, the in-hospital mortality rate and hospital length of stay were reduced in the GLP-1 treated group. Furthermore, in patients with CAD and preserved LVEF undergoing CABP the perioperative use of GLP-1 (1.5 pmol/kg/min beginning 12 h before grafting and continuing for 48 h) did not modify the LVEF but achieved better glycemic control and reduced the use of inotropic and vasoactive infusions and arrhythmic drugs in the postoperative period [66]. All these evidences suggest that GLP-1 may represent a new approach to improve myocardial glucose uptake and regional and global LV function, limit myocardial stunning and improve clinical outcomes in patients with CAD, particularly in diabetic patients.

Several ongoing trials are evaluating whether: (1) GLP-1 modulates cardiac metabolism (NCT01607450) or reduces reperfusion injury after myocardial ischemia (NCT00835848) and its effects on endothelial and metabolic effects in coronary circulation (NCT00923962) or in microvascular myocardial function in patients with type 2 diabetes (DM2) (NCT01931982), or its effects on cardiac function and epicar-

dial adipose tissue (NCT02042664); (2) the cardioprotective effects of liraglutide, a GLP-1 agonist, on reperfusion injury (NCT02001363) or on cardiovascular endpoints in patients with DM2 (NCT01761318); (3) the effects of sitagliptin in combination with lenograstim on the improvement of myocardial function in patients undergoing routine percutaneous coronary revascularisation for acute MI (NCT00650143) and on beta-cell function in patients with acute MI or unstable angina pectoris. (NCT00627744); (4) the effects of the DPP-4i alogliptin in addition to standard of care on cardiovascular outcomes in patients with DM2 and acute coronary syndromes (NCT00968708).

Traditional Chinese Herbal Remedies

Salvia Pellet (T89)

This Chinese remedy is currently approved in 26 countries for the treatment and prevention of CSA and other cardiovascular conditions. T89 consists of extracts of Danshen root (dried root of *Salviae Miltiorrhizae*) and Sanqi (root of *Panax notoginseng*) with borneol (*Cinnamomum camphora*) in a capsule form (Dantonic[®], Dantonic[®] dripping pill, Cadiotonic[®] Pill). Danshen has been used extensively in Chinese medicine for many years in the treatment of cardiovascular diseases. In experimental studies the dried root of *Salvia miltiorrhizae* blocks L-type Ca²⁺ channels and produces coronary vasodilation. It has been reported to reduce infarct size in experimental animal models, to inhibit platelet aggregation and thrombosis by inhibiting the synthesis and release of thromboxane A₂, to improve endothelial dysfunction, scavenge free radicals and exert antiinflammatory effects [67]. Moreover, in a rat model of MI (left anterior descending coronary artery ligation) tanshinone IIA, a major active component of Danshen, was shown to have cardio-protective, antifibrotic and antiinflammatory effects, by reducing expression of monocyte chemoattractant protein-1 (MCP-1), TGF-β1 and

macrophage infiltration [68]. Danshen also appears to be effective in relieving angina caused by coronary artery spasm [67] and a meta-analysis suggested that compound salvia pellet is more effective than nitrates to improve angina symptoms and ECG changes [17]. *Panax notoginseng* also produces coronary vasodilation, inhibits vascular smooth muscle cell proliferation, platelet activation and aggregation, reduces heart rate and exerts antioxidant, anti-inflammatory and angiogenic effects [69]. Borneol has antithrombotic, anti-inflammatory and antioxidative effects [70, 71].

A randomized, open label, dose-escalation phase I study was performed in 46 Chinese volunteers to determine the maximum tolerance dose (MTD) of T89 and support a proposed dose regimen change [72]. Doses of T89 were progressively increased from 540 to 3,510 mg but the MTD value was not reached, so it must be higher than 3,510 mg, i.e., 13 times higher than its current clinical dose. Thirteen subjects reported adverse events which resolved spontaneously within 30 min and only one moderate adverse effect (muscle damage) was observed at 2,970 mg. Another dose-escalation trial assessed the tolerability of a single dosage of 6–16 T89 capsules in non-Asian people [73]. T89 up to 16 capsules was not associated with abnormalities in clinical laboratory tests or ECG parameters. Only minor and transient adverse effects (dizziness, stomach discomfort, diarrhea, involuntary muscular contraction) were observed. The incidence of adverse effects was low (3.3 %) up to 13 capsules (i.e., 4 times the therapeutic dosage) and increased (38.9 %) at higher doses, but no defined dose-limiting toxicity events occurred.

A phase II study evaluated the efficacy and safety of T89 in 120 patients with CSA, but results were not reported (NCT00797953). An ongoing phase III evaluates the safety and efficacy of T89 in patients with CSA (NCT01659580). The primary efficacy outcome is the change of symptom-limited total exercise duration (TED) at trough drug levels at the end of treatment, although the contribution of the main herb Danshen to and the difference of various production batches in the overall efficacy and safety profiles are also explored.

Several recent reviews which analyzed the efficacy and safety of some traditional Chinese medicines following the steps of systematic review recommended by the Cochrane group are summarized in Table 10.2 [17–23]. However, the overall evidence is limited because the methodological and reporting quality of the trials was generally low. Furthermore, effects on quality of life and clinical outcomes were underreported and the safety profile unproven because of limited data. Thus, high-quality RCTs are required to provide the scientific evidence supporting the long-term effective and safe use of traditional Chinese medicines in patients with CAD.

Other Agents

Bosentan, an Endothelin-1 Blocker

Endothelin-1 (ET-1), acting via the ET_A receptor, increases vascular tone in epicardial coronary arteries of patients with CAD [10], and accounts for nearly all the resting tone in atherosclerotic coronary arteries, especially at stenoses [74]. Elevated ET-1 plasma levels are associated with reduced coronary vasomotor responses in patients with angina and normal coronary arteriograms [75] and with rapid coronary artery disease progression [76]. In patients with CSA the ET_A/ET_B endothelin-receptor antagonist bosentan decreased systolic blood pressure, but increased heart rate and coronary diameter, particularly in vessels with no or mild angiographic changes [10]. The intracoronary infusion of BQ-123 (6 $\mu\text{mol/L}$ over 20 min), a selective ET_A receptor antagonist, also increased by 10 % distal coronary artery diameter, but not the coronary blood flow velocity. In patients undergoing coronary angioplasty BQ-123 prevented the normal reduction of myocardial ischemia on repeated balloon inflations during angioplasty, possibly secondary to a “steal” effect through coronary collaterals [11]. Unfortunately, the use of endothelin-receptor antagonists is markedly limited by their adverse effect profile (headache, edema, flushing, and elevated liver transaminases).

Fasudil, a Rho-Kinase Inhibitor

Contractile activity of vascular smooth muscle cells (VSMCs) following stimulation of G-protein-coupled receptors by various agonists (noradrenaline, ET-1, angiotensin II) is regulated by $[Ca^{2+}]_i$ and Ca^{2+} sensitization of contractile proteins [77]. Following the increase in $[Ca^{2+}]_i$, this cation binds to calmodulin and the complex Ca^{2+} -calmodulin activates the myosin light-chain kinase (MLCK), which phosphorylates the 20-kDa myosin light chain (MLC20) and promotes its interaction with actin and subsequent VSMC contraction. Conversely, MLC20 is dephosphorylated by myosin light chain phosphatase (MLCPh), which inhibits the actin-myosin II interaction and promotes VSMC relaxation. Thus, inhibition of MLCPh increases the extent of MLC20 phosphorylation and enhances the sensitivity of VSMCs to cytosolic $[Ca^{2+}]_i$, a process known as “ Ca^{2+} sensitization”. This can occur following phosphorylation of MLCPh by Rho-kinase (ROCK), a Ser/Thr protein kinase, activated by the small monomeric G-protein RhoA.

In VSMCs, RhoA-Rho kinase pathway is up-regulated by angiotensin II, OS and inflammatory stimuli and increased activity of Rho-kinase plays a central role in the genesis of increased coronary artery tone in patients with vasospastic angina and microvascular angina [78–82]. Fasudil selectively inhibits Rho-kinase ($K_i=0.33$) by competing with the ATP-binding site on the enzyme, induces VSMC relaxation, improves endothelial dysfunction, normalizes endothelial NAD(P)H oxidase activity and OS and in animal models of coronary artery spasm effectively suppresses vasoconstriction [10, 11, 20–23, 74–82].

In patients with vasospastic angina (either angiographically detectable or microvascular) intracoronary infusion of fasudil markedly attenuated coronary constriction induced by acetylcholine (ACh) and prevented the occurrence of chest pain and ischemic ECG changes without changes in systemic hemodynamics or baseline coronary blood flow [81]. Fasudil further dilated the site of ACh-induced coronary vasospasm in patients with vasospastic angina already treated

with NTG [83] and prevented the occurrence of myocardial ischemia in patients with microvascular angina [82]. Moreover, in patients with effort angina, intracoronary administration of fasudil significantly increased oxygen saturation in the coronary sinus vein and ameliorated pacing-induced myocardial ischemia, including symptoms, ischemic ST-segment depression and lactate production [12]. The effects of fasudil (5, 10, 20 and 40 mg tid) were evaluated in three phase II trials in patients with CSA [13]. Fasudil significantly reduced the number of angina attacks, prolonged dose-dependently the maximum exercise time (MET) and the time to the onset of 1-mm ST segment depression on treadmill compared with baseline, while blood pressure and heart rate during exercise remained unchanged at rest or during exercise. Fasudil was well tolerated in these trials and the most frequent adverse event was headache. All these results confirmed the role Rho-kinase in the regulation of coronary artery tone and confirmed the antianginal effects of fasudil. Another study evaluated the efficacy and safety of fasudil in patients with CSA [14]. Fasudil increased peak exercise duration and time to ≥ 1 mm ST-segment depression at both peak and trough and improved Seattle Angina Questionnaire scores compared with placebo. However, no significant differences in CCS class, time to angina, or frequency of angina or nitroglycerin use were noted between groups. These data suggest that the optimum oral dose of fasudil for patients with CSA may be >80 mg tid. Fasudil is well absorbed after oral administration (bioavailability 95 %) and is rapidly metabolized (half-life 0.8 h) to its active metabolite hydroxyfasudil which has a half-life of 5 h [13, 80]. However, although fasudil is used in Japan for the treatment of cerebral vasospasm associated to subarachnoid hemorrhage, it has not been approved for the treatment of angina pectoris.

Testosterone

The higher incidence of CAD in men compared with premenopausal women suggested a possible causal role of testosterone.

Testosterone improves coronary endothelium-dependent relaxation in men with established CAD [84, 85]. In a pilot study, transdermal testosterone, in addition to their current medication, significantly increased the time to 1 mm ST-segment depression on treadmill exercise testing [15]. In another study, testosterone significantly increased time to 1-mm ST-segment depression and total exercise time [16]. However, large, well designed trials are required before testosterone can be considered as a therapy for angina in clinical practice.

Therapeutic Angiogenesis

Despite significant advances in medical, interventional, and surgical therapy for CAD, the burden remains high. Therapeutic angiogenesis represents an attractive therapeutic approach that includes sprouting and growth of new blood vessels from pre-existing vasculature following the delivery of angiogenic growth factors [86]. Specific criteria need to be fulfilled for angiogenic gene therapy to be successful included: the gene selected should code for a protein with angiogenic activity, the vector should provide high gene-transfer efficiency, the delivery technique should target the ischemic tissue, and the procedure should be safe, both in the short and long term [25]. Results with angiogenic growth factors are summarized in Table 10.3.

Fibroblast Growth Factor (FGF)

In preclinical models of CAD the intracoronary gene transfer of FGF-4 and FGF-5 stimulated angiogenesis, enhanced collateral blood flow, and relieved stress-induced ischemia evidenced by increased LV blood flow and function [87, 88]. The Angiogenic GENE Therapy (AGENT-1) trial evaluated the safety and anti-ischemic effects of 5 ascending doses of Ad5-FGF4 gene in patients with CSA [24]. Patients receiving Ad5-FGF4 did not show an improvement in exercise time at 4 weeks (NS). However, a protocol-specified, subgroup analysis showed a significant improvement in patients with baseline exercise treadmill testing (ETT) ≤ 10 min. The

AGENT-2 trial enrolled patients with CSA and reversible ischemia comprising >9 % of the LV on adenosine SPECT imaging [86]. At 8 weeks, the intracoronary administration of Ad5FGF-4 significantly reduced the ischemic defect size and more patients treated with Ad5FGF-4 than with placebo reported complete resolution of angina (30 % vs 13 %) and no nitroglycerin use (43 % vs 17 %). In both trials there were no deaths, MI, myocarditis, allergic reactions, or symptomatic hypotension during Ad5FGF-4 administration or at follow-up. Based on these results, the phase 2b/3 AGENT-3 and AGENT-4 trials were designed but both studies were prematurely finished because an interim analysis of the AGENT-3 trial revealed that the primary end point would not reach significance. However, in a pooled analysis, the incidence of angina/worsening angina was statistically less in patients treated with Ad5FGF-4 (17.7 %) as compared to placebo (25.4 %) [26]. Surprisingly, beneficial effects on total ETT time, time to 1 mm ST-segment depression, time to angina, and CCS class were observed only in females, but the reasons for the different effect between men and women are unknown. There were no hemodynamic or hematologic changes or adverse events associated with intracoronary administration of Ad5FGF-4. The ongoing AWARE trial studies the effects of FGF-4 in women with angina not candidates for revascularization. The intracoronary injection of recombinant FGF-2 (rhFGF-2) improved angina symptoms and myocardial perfusion after 3 months in patients undergoing CABG [27]. In patients with stable angina pectoris it did not improve exercise tolerance or myocardial perfusion; a trend towards symptomatic improvement was seen at 30 but not at 180 days [28].

Vascular Endothelial Growth Factor

The injection of VEGF₁₆₅, an isoform of VEGF, into the dysfunctional cardiac wall to dogs with chronic MI increased vascular density in the border zone and coronary perfusion and improved fractional shortening and LVEF and decreased

MI size [89–92]. The mechanism involved in infarct size reduction included an increase in angiogenesis and arteriogenesis, a decrease in peri-infarct fibrosis and in myofibroblast proliferation and enhanced cardiomyoblast proliferation due to activation of endogenous cardiac stem cells and/or indirect paracrine activity of *VEGF* [89–92].

In the VIVA (Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis) trial, patients with CSA unsuitable for standard revascularization the intracoronary infusion followed by i.v. injection of rhVEGF did not modify exercise tolerance, quality of life or myocardial perfusion at 60 days as compared with placebo, but at 120 days high-dose rhVEGF resulted in significantly improved angina and favorable trends in ETT time and angina frequency [29]. The Randomized Evaluation of VEGF for Angiogenesis (REVASC) study randomized patients with intractable angina and no option of revascularisation to either AdVEGF-A₁₂₁ or maximal medical therapy. There were significant improvements in exercise tolerance and QoL in the AdVEGF-A₁₂₁-treated patients compared with controls [30]. AdVEGF121 improved exercise time to 1 mm ST-segment depression at 26 weeks, but not at 12 weeks. At 26 weeks VEGF gene transfer improved TED, time to moderate angina and angina symptoms as measured by the CCS Angina Class and Seattle Angina Questionnaire. However, a placebo effect cannot be ruled out in this trial as patients in the control group did not have a thoracotomy or receive placebo. However, two studies enrolling patients with advanced CAD and no other treatment option found that VEGF₁₆₅ did not improve myocardial perfusion abnormalities compared with placebo [31, 32]. In one of the trials, after 3 months, VEGF gene transfer improved the local wall motion disturbances, assessed both by NOGA and contrast ventriculography, which may suggest a favorable anti-ischemic effect [31]. In another trial, the direct intramyocardial injection of AdGVVEGF121.10NH in patients with advanced refractory CAD did not improve exercise capacity, time to ischaemic threshold or myocardial perfusion compared to sham injection in a 52-week follow-up [33]. Finally,

Kuopio Angiogenesis Trial (KAT) showed that VEGF-A₁₆₅ expressed transiently in either an adenoviral vector or a plasmid significantly improved myocardial perfusion but did not have any effects on the percentage of luminal stenosis or minimal lumen diameter at 6-month follow-up [34]. The 8.1-years follow-up of these patients found that intracoronary VEGF gene transfer did not increase the risk of MACE, arrhythmias, cancer, diabetes or other diseases [35].

The ongoing ASPIRE trial evaluates whether a single intracoronary infusion of Ad5-FGF4, delivered during induced transient ischemia, improving myocardial perfusion, angina class, patient symptoms and quality of life. Both short-term (8 weeks) and long-term (12 month) safety of Ad5FGF-4 will also be evaluated. The phase I ongoing KAT301 study evaluates the safety and efficacy of intramyocardial injection of AdVEGF-D (Ad-VEGF-D^{ΔNΔC}) in patients with chronic ischemia and no option of revascularisation (NCT01002430).

Hepatocyte Growth Factor (HGF)

It presents combined angiogenic, antiapoptotic and antifibrotic effects [93–96]. HGF induces proliferation and inhibits apoptosis of endothelial cells [97] and stimulates the migration of VSMCs to the sprouting new vessels [94]. HGF decreases collagen I and III synthesis and myocardial fibrosis through the inhibition of TGF- β expression and stimulates extracellular matrix degradation via the activation of matrix metalloprotease-1 and urokinase-like plasminogen activator [95, 98, 99]. HGF also increases the small leucine-rich proteoglycans biglycan and decorin by ERK1/2- and p38 MAPK-mediated pathways, which bind to active TGF- β and inhibit its actions on cell proliferation [100]. Furthermore, HGF suppresses myofibroblast activation [99], an effect related to a mitogen-activated protein kinase-dependent blockade of Smad-2/3 nuclear translocation [100].

In preclinical models of I/R and OS, HGF gene transfer into the ischemic myocardium reduced infarct size, increased capillary density and regional myocardial perfusion and

improved LV systolic and diastolic function through multiple beneficial actions, such as increased angiogenesis, Bcl-2 and Bcl-XL overexpression, decreased production of oxygen free radicals and antiapoptotic and antifibrotic actions [97, 100–104]. These effects can explain the decrease in infarct transmural extent in the infarcted-treated group and strongly suggest that HGF might have a potential utility in patients with CAD.

VM202 is a naked DNA expressing two isoforms of HGF (VM202RY and pCK-HGF-X7). It was injected into periinfarction and infarction sites in pigs following the occlusion of the left anterior descending coronary artery distal to the first diagonal branch, followed by reperfusion [105]. At 50 days, VM202 increased LVEF in infarcted animals to the level of controls without infarction; two-dimensional strain improved in remote, peri-infarcted and infarcted myocardium and infarct size was smaller in infarcted treated animals compared with infarcted controls, indicating that VM202 prevented LV remodeling associated with MI. VM202 also increased maximum signal intensity and upslope at first-pass perfusion imaging, while reduced delayed-enhancement imaging and LV end-diastolic and end-systolic volumes [106]. This improvement in regional and global perfusion and function and the decreased extent of hypoenhanced ischemic myocardium and scar tissue were attributed to an increase in the number of capillaries and arterioles and the formation of islands/peninsulas of viable myocytes in infarcted and peri-infarcted regions as HGF modified cardiac progenitor cells behavior to form new viable myocytes, coronary arterioles, and capillaries [107].

A phase I trial evaluated the safety, tolerability and potential efficacy of VM202 injected into the right coronary artery (RCA) territory following completion of CABG for the left coronary artery territory in nine patients with CAD [36]. After 6-month follow-up period global myocardial functions (wall motion score index and stress perfusion) improved. In the injected region VM202 improved regional myocardial perfusion and wall thickness of the diastolic and systolic phases. No serious complications or generation of anti-HGF antibodies were observed.

In conclusion, therapeutic angiogenesis using vascular growth factors represents an interesting option in patients with CAD. Preclinical studies and initial small unblinded studies demonstrated both clinical improvement and evidence of angiogenesis with an acceptable safety profile. However, in RCTs FGF or VEGF failed to unequivocally demonstrate a beneficial effect. Thus, well-designed RCTs should be encouraged to provide definitive answers in patients with severe CAD, which cannot be treated effectively with current therapeutic strategies.

Acknowledgements This work was supported by Instituto de Salud Carlos III (Red RIC, and PI11/01030) and Comunidad de Madrid (S2010/BMD-2374).

References

1. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003.
2. Kaski JC, Chester MR, Chen L, et al. Rapid angiographic progression of coronary artery disease in patients with angina pectoris. The role of complex stenosis morphology. *Circulation*. 1995;92:2058–65.
3. Daly CA, Clemens F, López-Sendón JL, et al., Heart Survey Investigators. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. *Eur Heart J*. 2005;26:996–1010.
4. Serruys PW, Unger F, Sousa JE et al., Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117–24
5. Scirica BM, Morrow DA. Ranolazine in patients with angina and coronary artery disease. *Curr Cardiol Rep*. 2007;9:272–27.
6. Gibbons RJ, Abrams J, Chatterjee K, et al. 2002 guideline update for the management of patients with chronic stable angina – summary article: a report of the American College of Cardiology/

- American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol*. 2003;41:159–68.
7. Noman A, Ang DS, Ogston S, et al. Effect of high-dose allopurinol on exercise in patients with chronic stable angina: a randomised, placebo controlled crossover trial. *Lancet*. 2010;365:2161–7.
 8. Rajendra NS, Ireland S, George J, et al. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. *J Am Coll Cardiol*. 2011;58:820–8.
 9. Rentoukas E, Tsarouhas K, Tsitsimpikou C, et al. The prognostic impact of allopurinol in patients with acute myocardial infarction undergoing primary percutaneous coronary intervention. *Int J Cardiol*. 2010;145:257–8.
 10. Wenzel RR, Fleisch M, Shaw S, et al. Hemodynamic and coronary effects of the endothelin antagonist bosentan in patients with coronary artery disease. *Circulation*. 1998;98:2235–40.
 11. Kyriakides ZS, Kremastinos DT, Kolettis TM, et al. Acute endothelin-A receptor antagonism prevents normal reduction of myocardial ischemia on repeated balloon inflations during angioplasty. *Circulation*. 2000;102:1937–43.
 12. Fukumoto Y, Mohri M, Inokuchi K, et al. Anti-ischemic effects of Fasudil, a specific Rho-kinase inhibitor, in patients with stable effort angina. *J Cardiovasc Pharmacol*. 2007;49:117–21.
 13. Shimokawa H, Hiramori K, Iinuma H, et al. Anti-anginal effect of Fasudil, a Rho-kinase inhibitor, in patients with stable effort angina: a multicenter study. *J Cardiovasc Pharmacol*. 2002;40:751–61.
 14. Vicari RM, Chaitman B, Keefe D, et al. Efficacy and safety of Fasudil in patients with stable angina: a double-blind, placebo-controlled, phase 2 trial. *J Am Coll Cardiol*. 2005;46:1803.
 15. English KM, Steeds RP, Jones TH, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102:1906–11.
 16. Rosano GM, Leonardo F, Pagnotta P, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation*. 1999;99:1666–70.
 17. Wang L, Xiong ZY, Wang G. Systematic assessment on randomized controlled trials for treatment of stable angina pectoris by compound salvia pellet. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2004;24:500–4.

18. Wang G, Wang L, Xiong ZY, et al. Compound salvia pellet, a traditional Chinese medicine, for the treatment of chronic stable angina pectoris compared with nitrates: a meta-analysis. *Med Sci Monit.* 2006;12:SR1–7.
19. Jia Y, Huang F, Zhang S, et al. Is Danshen (*Salvia miltiorrhiza*) dripping pill more effective than isosorbide dinitrate in treating angina pectoris? A systematic review of randomized controlled trials. *Int J Cardiol.* 2012;157:330–40.
20. Shang Q, Xu H, Liu Z, et al. Oral *Panax notoginseng* preparation for coronary heart disease: a systematic review of randomized controlled trials. *Evid Based Complement Alternat Med.* 2013;2013:940125.
21. Yang X, Xiong X, Wang J. Sanqi panax notoginseng injection for angina pectoris. *Evid Based Complement Alternat Med.* 2014; 2014:963208.
22. Luo J, Xu H, Chen K. Systematic review of compound Danshen dropping pill: a Chinese patent medicine for acute myocardial infarction. *Evid Based Complement Alternat Med.* 2013; 2013:808076.
23. Duan X, Zhou L, Wu T, Liu G, Qiao J, Wei J, Ni J, Zheng J, Chen X, Wang Q. Chinese herbal medicine Suxiao jiu xin wan for angina pectoris. *Cochrane Database Syst Rev.* 2008;(1):CD004473.
24. Grines CL, Watkins MW, Helmer G, et al. Angiogenic Gene Therapy (AGENT) trial in patients with stable angina pectoris. *Circulation.* 2002;105:1291–7.
25. Grines CL, Watkins MW, Mahmarian JJ, et al. A randomized, double-blind, placebo-controlled trial of Ad5FGF-4 gene therapy and its effect on myocardial perfusion in patients with stable angina. *J Am Coll Cardiol.* 2003;42:1339–47.
26. Henry TD, Grines CL, Watkins MW, et al. Effects of Ad5FGF-4 in patients with angina: an analysis of pooled data from the AGENT-3 and AGENT-4 trials. *J Am Coll Cardiol.* 2007;50: 1038–46.
27. Laham RJ, Sellke FW, Edelman ER, et al. Local perivascular delivery of basic fibroblast growth factor in patients undergoing coronary bypass surgery: results of a phase I randomized, double-blind, placebo-controlled trial. *Circulation.* 1999;100: 1865–71.
28. Simons M, Annex BH, Laham RJ, et al. Pharmacological treatment of coronary artery disease with recombinant fibroblast growth factor-2: double-blind, randomized, controlled clinical trial. *Circulation.* 2002;105:788–93.

29. Henry TD, Annex BH, McKendall GR, et al. The VIVA trial: vascular endothelial growth factor in ischemia for vascular angiogenesis. *Circulation*. 2003;107:1359–65.
30. Stewart DJ, Hilton JD, Arnold JM, et al. Angiogenic gene therapy in patients with nonrevascularizable ischemic heart disease: a phase 2 randomized, controlled trial of AdVEGF(121) (AdVEGF121) versus maximum medical treatment. *Gene Ther*. 2006;13:1503–11.
31. Kastrup J, Jorgensen E, Ruck A, et al. Direct intramyocardial plasmid vascular endothelial growth factor-A165 gene therapy in patients with stable severe angina pectoris A randomized double-blind placebo-controlled study: the Euroinject One trial. *J Am Coll Cardiol*. 2005;45:982–8.
32. Stewart DJ, Kutryk MJ, Fitchett D, et al. VEGF gene therapy fails to improve perfusion of ischemic myocardium in patients with advanced coronary disease: results of the NORTHERN trial. *Mol Ther*. 2009;17:1109–15.
33. Kastrup J, Jorgensen E, Fuchs S, et al. A randomised, double-blind, placebo-controlled, multicentre study of the safety and efficacy of BIOBYPASS (AdGVVEGF121.10NH) gene therapy in patients with refractory advanced coronary artery disease: the NOVA trial. *EuroIntervention*. 2011;6:813–8.
34. Hedman M, Hartikainen J, Syvanne M, et al. Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene transfer in the prevention of postangioplasty and in-stent restenosis and in the treatment of chronic myocardial ischemia: phase II results of the Kuopio Angiogenesis Trial (KAT). *Circulation*. 2003;107:2677–83.
35. Hedman M, Muona K, Hedman A, et al. Eight-year safety follow-up of coronary artery disease patients after local intracoronary VEGF gene transfer. *Gene Ther*. 2009;16:629–34.
36. Kim JS, Hwang HY, Cho KR. Intramyocardial transfer of hepatocyte growth factor as an adjunct to CABG: phase I clinical study. *Gene Ther*. 2013;20:717–22.
37. Spiekermann S, Landmesser U, Dikalov S, et al. Electron spin resonance characterization of vascular xanthine and NAD(P)H oxidase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. *Circulation*. 2003;107:1383–9.

38. Baldus S, Müllerleile K, Chumley P, et al. Inhibition of xanthine oxidase improves myocardial contractility in patients with ischemic cardiomyopathy. *Free Radiac Biol Med*. 2006;41:1282–128.
39. Hirsch GA, Bottomley PA, Gerstenblith G, et al. Allopurinol acutely increases adenosine triphosphate energy delivery in failing human hearts. *J Am Coll Cardiol*. 2012;59:802–8.
40. George J, Carr E, Davies J, et al. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation*. 2006;114:2508–16.
41. Higgins P, Dawson J, Lees KR, et al. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. *Cardiovasc Ther*. 2012;30:217–26.
42. Khatib SY, Farah H, El-Migdadi F. Allopurinol enhances adenine nucleotide levels and improves myocardial function in isolated hypoxic rat heart. *Biochemistry (Mosc)*. 2001;66:328–33.
43. Perez NG, Gao WD, Marban E. Novel myofilament Ca^{2+} -sensitizing property of xanthine oxidase inhibitors. *Circ Res*. 1998;83:423–30.
44. Ekelund UEG, Harrison RW, Shokek O, et al. Intravenous allopurinol decreases myocardial oxygen consumption and increases mechanical efficiency in dogs with pacing-induced heart failure. *Circ Res*. 1999;85:437–45.
45. Ukai T, Cheng CP, Tachibana H, et al. Allopurinol enhances the contractile response to dobutamine and exercise in dogs with pacing-induced heart failure. *Circulation*. 2001;103:750–5.
46. Schumacher Jr HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum*. 2008;59:1540–154.
47. Becker MA, Schumacher Jr HR, Wortmann RL, et al. Febuxostat compared with allopurinol in subjects with hyperuricemia and gout. *N Engl J Med*. 2005;343:2450–61.
48. Zaza A, Belardinelli L, Shryock JC. Pathophysiology and pharmacology of the cardiac “late sodium current”. *Pharmacol Ther*. 2008;119:326–39.
49. Hale SL, Shryock JC, Belardinelli LS, et al. Late sodium current inhibition as a new cardioprotective approach. *J Mol Cell Cardiol*. 2008;44:954–67.

50. Imahashi K, Kusuoka H, Hashimoto K, et al. Intracellular sodium accumulation during ischemia as the substrate for reperfusion injury. *Circ Res.* 1999;84:1401–6.
51. Vacher B, Pignier C, Létienne R, et al. F 15845 inhibits persistent sodium current in the heart and prevents angina in animal models. *Br J Pharmacol.* 2009;156:214–25.
52. Pignier C, Rougier JS, Vié B, et al. Selective inhibition of persistent sodium current by F 15845 prevents ischaemia-induced arrhythmias. *Br J Pharmacol.* 2010;161:79–91.
53. Vié B, Sablayrolles S, Létienne R, et al. 3-(R)-[3-(2-Methoxyphenylthio-2-(S)-methylpropyl)amino-3,4-dihydro-2H-1,5-benzoxathiepine bromhydrate (F 15845) prevents ischemia-induced heart remodeling by reduction of the intracellular Na⁺ Overload. *J Pharmacol Exp Ther.* 2009;330:696–703.
54. Létienne R, Bel L, Bessac AM, et al. Myocardial protection by F 15845, a persistent sodium current blocker, in an ischemia-reperfusion model in the pig. *Eur J Pharmacol.* 2009;624:16–22.
55. Lopaschuk GD, Ussher JR, Folmes CD, et al. Myocardial fatty acid metabolism in health and disease. *Physiol Rev.* 2010;90:207–58.
56. Lee L, Horowitz J, Frenneaux M. Metabolic manipulation in ischaemic heart disease, a novel approach to treatment. *Eur Heart J.* 2004;25:634–41.
57. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev.* 2012;33:187–215.
58. Ban K, Noyan-Ashraf MH, Hoefer J, et al. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. *Circulation.* 2008;117:2340–50.
59. Murohara T. Dipeptidyl peptidase-4 inhibitor: another player for cardiovascular protection. *J Am Coll Cardiol.* 2012;59:277–9.
60. Davidson M. Cardiovascular effects of glucagonlike peptide-1 agonists. *Am J Cardiol.* 2011;108:33B–41.
61. Timmers L, Henriques JP, de Kleijn DP, et al. Exenatide reduces infarct size and improves cardiac function in a porcine model of ischemia and reperfusion injury. *J Am Coll Cardiol.* 2009;53:501–10.
62. Bose AK, Mocanu MM, Carr RD, et al. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes.* 2005;54:146–51.

63. Nikolaidis LA, Elahi D, Hentosz T, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. *Circulation*. 2004;110:955–61.
64. Read PA, Khan FZ, Heck PM, et al. DPP-4 inhibition by sitagliptin improves the myocardial response to dobutamine stress and mitigates stunning in a pilot study of patients with coronary artery disease. *Circ Cardiovasc Imaging*. 2010;3:195–201.
65. Nikolaidis LA, Mankad S, Sokos GG, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation*. 2004;109:962–5.
66. Sokos GG, Bolukoglu H, German J, et al. Effect of glucagon-like peptide-1 (GLP-1) on glycemic control and left ventricular function in patients undergoing coronary artery bypass grafting. *Am J Cardiol*. 2007;100:824–9.
67. Cheng TO. Cardiovascular effects of Danshen. *Int J Cardiol*. 2007;121:9–22.
68. Ren ZH, Tong YH, Xu W, et al. Tanshinone II A attenuates inflammatory responses of rats with myocardial infarction by reducing MCP-1 expression. *Phytomedicine*. 2010;17:212–8.
69. Lau AJ, Toh DF, Chuab TK. Anti-platelet and anticoagulant effects of *Panax notoginseng*: comparison of raw and steamed *Panax notoginseng* with *Panax ginseng* and *Panax quinquefolium*. *J Ethnopharmacol*. 2009;125:380–6.
70. Li YH, Sun XP, Zhang YQ, et al. The antithrombotic effect of borneol related to its anticoagulant property. *Am J Chin Med*. 2008;36:719–27.
71. Liu R, Zhang L, Lan X, et al. Protection by borneol on cortical neurons against oxygen-glucose deprivation/reperfusion: involvement of anti-oxidation and anti-inflammation through nuclear transcription factor kappaB signaling pathway. *Neuroscience*. 2011;176:408–19.
72. Zhou Y, Cui Y, Zhao X, et al. The safety and tolerance of herbal anti-angina drug compound Danshen droplet pill in healthy volunteers. *Pharmacol Pharm*. 2013;4:490–5.
73. Ling S, Luo RZ, Nheu L, et al. A phase I dose-escalation study to evaluate tolerability in a Western population to T89, a modern cardiovascular herbal medicine. *J Cardiovasc Pharmacol*. 2012;60:513–9.
74. Kinlay S, Behrendt D, Wainstein M, et al. Role of endothelin-1 in the active constriction of human atherosclerotic coronary arteries. *Circulation*. 2001;104:1114–8.

75. Cox ID, Bøtker HE, Bagger JP, et al. Elevated endothelin concentrations are associated with reduced coronary vasomotor responses in patients with chest pain and normal coronary arteriograms. *J Am Coll Cardiol*. 1999;34:455–60.
76. Zouridakis EG, Schwartzman R, Garcia-Moll X, et al. Increased plasma endothelin levels in angina patients with rapid coronary artery disease progression. *Eur Heart J*. 2001;22:1578–84.
77. Somlyo AP, Somlyo AV. Signal transduction by G-proteins, rho-kinase and protein phosphatase to smooth muscle and non-muscle myosin II. *J Physiol*. 2000;522:177–85.
78. Wetschureck N, Offermanns S. Rho/Rho-kinase mediated signaling in physiology and pathophysiology. *J Mol Med*. 2002;80:629–38.
79. Kandabashi T, Shimokawa H, Miyata K, et al. Inhibition of myosin phosphatase by upregulated rho-kinase plays a key role for coronary artery spasm in a porcine model with interleukin-1beta. *Circulation*. 2000;101:1319–23.
80. Shimokawa H, Seto M, Katsumata N, et al. Rho-kinase-mediated pathway induces enhanced myosin light chain phosphorylations in a swine model of coronary artery spasm. *Cardiovasc Res*. 1999;43:1029–39.
81. Masumoto A, Mohri M, Shimokawa H, et al. Suppression of coronary artery spasm by the Rho-kinase inhibitor Fasudil in patients with vasospastic angina. *Circulation*. 2002;105:1545–7.
82. Mohri M, Shimokawa H, Hirakawa Y, et al. Rho-kinase inhibition with intracoronary Fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. *J Am Coll Cardiol*. 2003;41:15–9.
83. Otsuka T, Ibuki C, Suzuki T, et al. Administration of the Rho-kinase inhibitor, Fasudil, following nitroglycerin additionally dilates the site of coronary spasm in patients with vasospastic angina. *Coron Artery Dis*. 2008;19:105–10.
84. Chou TM, Sudhir K, Hutchison SJ, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. *Circulation*. 1996;94:2614–9.
85. Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999;100:1690–6.
86. Chu H, Wang Y. Therapeutic angiogenesis: controlled delivery of angiogenic factors. *Ther Deliv*. 2012;3:693–714.
87. Giordano FJ, Ping P, McKirnan MD, et al. Intracoronary gene transfer of fibroblast growth factor-5 increases blood flow and

- contractile function in an ischemic region of the heart. *Nat Med.* 1996;2:534–9.
88. Gao MH, Lai NC, McKirnan MD, et al. Increased regional function and perfusion after intracoronary delivery of adenovirus encoding fibroblast growth factor 4: report of preclinical data. *Hum Gene Ther.* 2004;15:574–87.
 89. Ferrarini M, Arsic N, Recchia FA, et al. Adeno-associated virus-mediated transduction of VEGF165 improves cardiac tissue viability and functional recovery after permanent coronary occlusion in conscious dogs. *Circ Res.* 2006;98:954–61.
 90. Saeed M, Saloner D, Martin A, et al. Adeno-associated viral vector-encoding vascular endothelial growth factor gene: effect on cardiovascular MR perfusion and infarct resorption measurements in swine. *Radiology.* 2007;243:451–60.
 91. Su H, Joho S, Huang Y, et al. Adeno-associated viral vector delivers cardiac-specific and hypoxia-inducible VEGF expression in ischemic mouse hearts. *Proc Natl Acad Sci U S A.* 2004;101:16280–5.
 92. Vera Janavel G, Crottogini A, Cabeza Meckert P, et al. Plasmid-mediated VEGF gene transfer induces cardiomyogenesis and reduces myocardial infarct size in sheep. *Gene Ther.* 2006;13:1133–42.
 93. Azuma J, Taniyama Y, Takeya Y, et al. Angiogenic and antifibrotic actions of hepatocyte growth factor improve cardiac dysfunction in porcine ischemic cardiomyopathy. *Gene Ther.* 2006;13:1206–13.
 94. Morishita R, Aoki M, Hashiya N, et al. Therapeutic angiogenesis using hepatocyte growth factor (HGF). *Curr Gene Ther.* 2004;4:199–206.
 95. Taniyama Y, Morishita R, Nakagami H, et al. Potential contribution of a novel antifibrotic factor, hepatocyte growth factor, to prevention of myocardial fibrosis by angiotensin II blockade in cardiomyopathic hamsters. *Circulation.* 2000;102:246–52.
 96. Taniyama Y, Morishita R, Auki M, et al. Angiogenesis and antifibrotic action by hepatocyte growth factor in cardiomyopathy. *Hypertension.* 2002;40:47–53.
 97. Guo Y, He J, Wu J, et al. Locally overexpressing hepatocyte growth factor prevents post-ischemic heart failure by inhibition of apoptosis via calcineurin-mediated pathway and angiogenesis. *Arch Med Res.* 2008;39:179–88.
 98. Tomita N, Morishita R, Taniyama Y, et al. Angiogenic property of hepatocyte growth factor is dependent on upregulation of essential transcription factor for angiogenesis, ets-1. *Circulation.* 2003;107:1411–7.

99. Mizuno S, Kurosawa T, Matsumoto K, et al. Hepatocyte growth factor prevents renal fibrosis and dysfunction in a mouse model of chronic renal disease. *J Clin Invest.* 1998;101:1827–34.
100. Yang J, Dai C, Liu Y. Hepatocyte growth factor suppresses renal interstitial myofibroblast activation and intercepts Smad signal transduction. *Am J Pathol.* 2003;163:621–32.
101. Kitta K, Day RM, Ikeda T, et al. Hepatocyte growth factor protects cardiac myocytes against oxidative stress-induced apoptosis. *Free Radic Biol Med.* 2001;31:902–10.
102. Chen XH, Minatoguchi S, Kosai K, et al. In vivo hepatocyte growth factor gene transfer reduces myocardial ischemia-reperfusion injury through its multiple actions. *J Card Fail.* 2007;13:874–83.
103. Kondo I, Ohmori K, Oshita A, et al. Treatment of acute myocardial infarction by hepatocyte growth factor gene transfer: the first demonstration of myocardial transfer of a “functional” gene using ultrasonic microbubble destruction. *J Am Coll Cardiol.* 2004;44:644–53.
104. Shirakawa Y, Sawa Y, Takewa Y, et al. Gene transfection with human hepatocyte growth factor complementary DNA plasmids attenuates cardiac remodeling after acute myocardial infarction in goat hearts implanted with ventricular assist devices. *J Thorac Cardiovasc Surg.* 2005;130:624–32.
105. Carlsson M, Osman NF, Ursell PC. Quantitative MR measurements of regional and global left ventricular function and strain after intramyocardial transfer of VM202 into infarcted swine myocardium. *Am J Physiol Heart Circ Physiol.* 2008;295:H522–32.
106. Saeed M, Martin A, Ursell P, et al. MR assessment of myocardial perfusion, viability, and function after intramyocardial transfer of VM202, a new plasmid human hepatocyte growth factor in ischemic swine myocardium. *Radiology.* 2008;249:107–18.
107. Gonzalez A, Rota M, Nurzynska D. Activation of cardiac progenitor cells reverses the failing heart senescent phenotype and prolongs lifespan. *Circ Res.* 2008;102:597–606.

Chapter 11

Medical Therapy Versus Revascularization in the Management of Stable Angina Pectoris

**Isaac Pascual, Pablo Avanzas, Raquel del Valle,
and César Morís**

Introduction

The optimal strategy for the management of patients with stable coronary artery disease (SCAD) remains a matter for scientific debate as it has been over the past decades. In the past few years, technical advances in revascularization therapies and the development of many new effective pharmacological agents have helped in the management of SCAD. There is universal agreement that optimal medical therapy (OMT) should be the first step to manage SCAD unless prognostic considerations, usually based on angiographic findings, come into play. Evidence exists regarding

I. Pascual, MD, PhD, FESC • P. Avanzas, MD, PhD, FESC (✉)
R. del Valle, MD • C. Morís, MD, PhD, FESC
Cardiac Catheterization Laboratories, Area del Corazón,
Hospital Universitario Central de Asturias, Oviedo, Spain
e-mail: ipascua@live.com; avanzas@secardiologia.es

P. Avanzas, J.C. Kaski (eds.), *Pharmacological Treatment
of Chronic Stable Angina Pectoris*, Current Cardiovascular
Therapy, DOI 10.1007/978-3-319-17332-0_11,
© Springer International Publishing Switzerland 2015

235

both symptomatic improvement and increased survival rates with this approach. There is also agreement that invasive procedures constitute complementary therapies that play a major role in management. When OMT is insufficient to control symptoms, percutaneous or surgical revascularization therapies should be considered to improve clinical outcomes. This chapter reviews the role of revascularization procedures, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), in the management of SCAD patients and addresses the current controversy regarding comparisons with medical treatment.

CABG and Medical Treatment

Comparative studies between medical treatments and CABG were carried out many years ago [1–3], which makes it difficult to extrapolate those findings to current medical practice. Indeed, studies conducted in the '70s and '80s, were carried out without the routine use of antiplatelet agents, ACE inhibitors or statins. Major improvements have taken place in recent years regarding both the availability of a diversity of pharmaceutical agents and the development of more effective surgical techniques. The three initial main trials that shed light into the role of CABG in SCAD patients were the Veterans Administration Cooperative Study, the Coronary Artery Surgery Study (CASS) and the European Coronary Surgery Study (ECSS). All of them randomized patients with significant SCAD to medical treatment alone or surgery. In the three studies, the surgical-revascularization-therapy group showed a marked improvement in relation to angina symptoms, exercise tolerance and quality of life, in contrast to the group that received medical treatment alone [1–3]. Despite the difficulties in applying these results to current clinical practice, a consistent message of these studies is the identification of high-risk angiographic patterns. Left ventricular

dysfunction, together with certain patterns of coronary artery disease, have been associated with poor prognosis. Significant stenosis ($>50\%$) of the left main coronary artery (LMCA); two or three vessels coronary artery disease, including the proximal left anterior descending (LAD) artery and three vessel disease, with ventricular dysfunction and with or without disease of the proximal LAD are considered to require surgical revascularization. The DUKE registry has shown that the long-term benefit of bypass surgery over medical treatment concerning mortality was only limited to high-risk patients. For low-risk patients i.e. those with single-vessel disease, CABG resulted in angina improvement but not in better survival rates [4]. These findings were also confirmed in the meta-analysis carried out by the Bypass Trialists Collaboration Study. During a 5 year follow-up period, there were no significant differences in AMI rates (24.4 % with bypass surgery and 30.7 % with medical treatment), but survival rates were higher in patients who underwent revascularization therapy for LMCA disease and two or three vessel disease including proximal involvement of the LAD. In the study, an increase in survival rates became evident on the second year after CABG and the difference was not significant after the tenth year of follow-up, mainly because of problems with the saphenous-vein grafts and the need to operate patients initially allocated to medical treatment. The study also showed that the presence of severe ventricular dysfunction or an early positive result of the stress test predicted an absolute-benefit of CABG over medical treatment [5]. All these studies show that CABG reduces symptoms and ischemia, and improves quality of life of patients with chronic angina, but it is necessary to analyse risks and benefits in the individual patient. Total surgical mortality in bypass surgery is between 1 and 4 %, depending on the population under study and the institutions considered. Risk-stratification models are available and should be used to assess the individual risk in each patient.

Impact of Type of Procedure

The most common procedure is the use of the internal mammary artery (IMA) to LAD (85 % permeability at 10 years) and saphenous-vein grafts for other arteries. Using the IMA has been shown to increase survival rates and to reduce the incidence of late myocardial infarction, recurrent angina and subsequent heart surgery. Arterial grafting with the use of the right IMA [6, 7] or radial arteries has shown permeability indexes >90 % after 3 years. Another technical factor to consider is the use of cardiopulmonary bypass. Studies comparing conventional surgery and off-pump surgery have shown no significant differences in mortality rates between groups during the first 1–3 years. Kahn's study [8] comparing on- and off-pump bypass grafting results in patients with multi-vessel coronary artery disease found a significant reduction of graft permeability in the off-pump-bypass-grafting group [8]. Current data from recent studies have reported non-statistically significant lower post-operative mortality and myocardial infarction MI in the off-pump group but a clinically and statistically significant one-third reduction in the incidence of stroke, from 2.1 % in the on-pump group to 1.4 % in the off-pump group (relative risk 0.7; 95 % CI 0.49–0.99) [9]. Moreover, the use of off-pump CABG has been related to low rates of transfusion, re-operation for peri-operative bleeding, respiratory complications and acute kidney injury. However, it resulted in an increased risk of early revascularization from 0.2 % in the on-pump group to 0.7 % in the off-pump group. In view of these results, it seems that both strategies should be carefully evaluated, with indications depending on patient's profile and the experience of the surgical team [10].

Percutaneous Coronary Intervention

The evolution of coronary angioplasty, from its introduction by Andreas Gruentzig, in 1977 to the recent years, has been vertiginous. Technical developments, versatile devices, and

the improvement and refining of technical procedures, has contributed to the exponential use of this treatment and the spread and broadening of its indications. The initial limitation of the procedure to single-vessel coronary-artery disease has become obsolete. Currently, angioplasty and stenting can be used for treatment of both single and multi-vessel coronary artery disease with <1 % mortality. Data from clinical trials in recent years show that angioplasty reduces events and symptoms, and improves quality of life. The incorporation of stenting to PCI has represented a turning point regarding the reduction of restenosis rates. Indeed two well-defined periods can be identified in this regard: the pre- and post-stent era. During the *pre-stent* period, studies such as ACME, RITA-2 and AVERT, showed a superiority of PCI over pharmacological therapy for symptom control in patients with chronic stable coronary-artery disease. However no increase in survival rates was shown, and there was even a higher rate of adverse events in patients undergoing PCI [11–14]. At 7 years of follow up, RITA-2 showed that an initial strategy of PCI improved angina and exercise tolerance but did not influence the risk of death or MI [15]. According to the Bucher meta-analysis [16], PCI compared to medical treatment, did not increase survival rates in stable angina patients (Fig. 11.1). Some studies were also conducted that compared pharmacological therapy with revascularization procedures, both bypass surgery and PCI. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study randomized patients with stable ischemic heart disease and asymptomatic ischemia but who had coronary anatomy suitable for revascularization to three treatment strategies: angina-guided drug therapy, angina plus ischemia-guided drug therapy, and revascularization by PCI or bypass surgery [17]. Two years after randomization, the total mortality was 6.6 % in the angina-guided strategy, 4.4 % in the ischemia-guided strategy, and 1.1 % in the revascularization strategy. Interestingly, PCI was associated with a reduction in mortality as follows: 2-year event rates were 1.1 % for mortality; 5.5 % for death or MI; and 31.7 % for death, MI, or recurrent hospitalization. In the TIME and

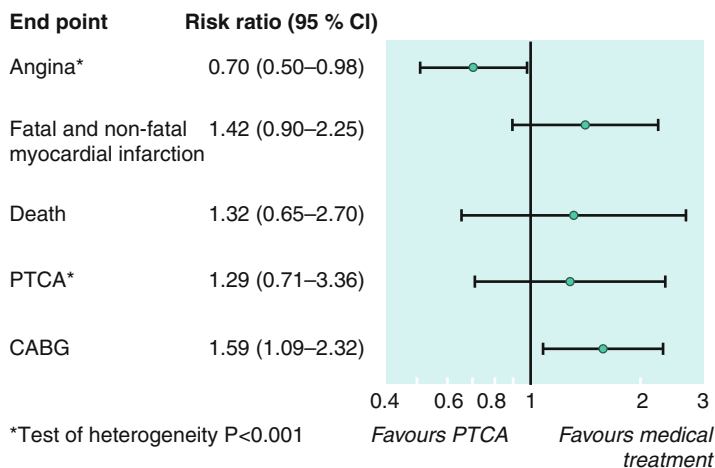


FIGURE 11.1 Pooled risk ratios for various end points from six randomised controlled trials comparing percutaneous transluminal coronary angioplasty (PTCA) with medical treatment in patients with non-acute coronary heart disease; (CABG: coronary artery bypass grafting; $n=953$ for PTCA and 951 for medical treatment) (*Reproduced with permission from Bucher et al. [16])

MASS trials, involving elderly patients and patients with proximal-LAD disease, respectively, PCI proved to be superior to medical treatment for symptom control [18, 19].

The *post-stent* period led to a dramatic decrease in restenosis rates and the need for repeat PCI [20–22]. This is one of the key reasons that explain the exponential growth and use of interventional techniques in recent years. Importantly though, there have also been advances during this period, in the pharmacological treatment of patients with chronic ischemic heart disease [16, 21]. Two studies are ground breaking in this regard: the BARI 2D [23] and COURAGE [24] trials (Table 11.1). BARI 2D was designed to compare, in patients with type 2 diabetes mellitus, the effects of PCI versus coronary-artery bypass grafting (CABG), both on top of optimal medical therapy (OMT), versus OMT alone. 2,368 patients with documented ischemia who were either

TABLE 11.1 Baseline clinical characteristics in COURAGE and BARI-2D trials

	Courage	BARI-2D
Year of initial publication	2008	2009
Period of recruitment	1999–2004	2001–2005
Entry criteria	CAD by catheter plus positive stress or angina	CAD by catheter plus T2DM plus positive stress or angina
Type of revascularization and randomization	PCI+OMT vs OMT	PCI+OMT vs OMT CABG+OMT vs OMT
Primary end point	Death/nonfatal MI	Death
Secondary end point	Death/MI/stroke/hospitalization for unstable angina	Death/MI/stroke
Follow-up, y	4.6	5
Patients, <i>n</i>	2,287	2,368
OMT patients, <i>n</i>	1,149	1,192
Revascularization patients, <i>n</i>	1,138	1,176 (798 for PCI, 378 for CABG)
Mean age, y	61	62
Previous MI	38 %	32 %
T2DM	34 %	100 %
Angina CCS classification	78 % with 0–II 21 % with III	60 % with 0–II 9 % with III–IV
Mean LVEF	61 %	57 % (82 % were normal)
Crossover (medically treated and revascularized during follow-up)	33 %	42 %

Reproduced with permission from Fernandez and Boden [26]

CABG coronary artery bypass graft, *CAD* coronary artery disease, *CCS* Canadian Cardiovascular Society, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *OMT* optimal medical therapy, *PCI* percutaneous coronary intervention, *T2DM* type 2 diabetes mellitus

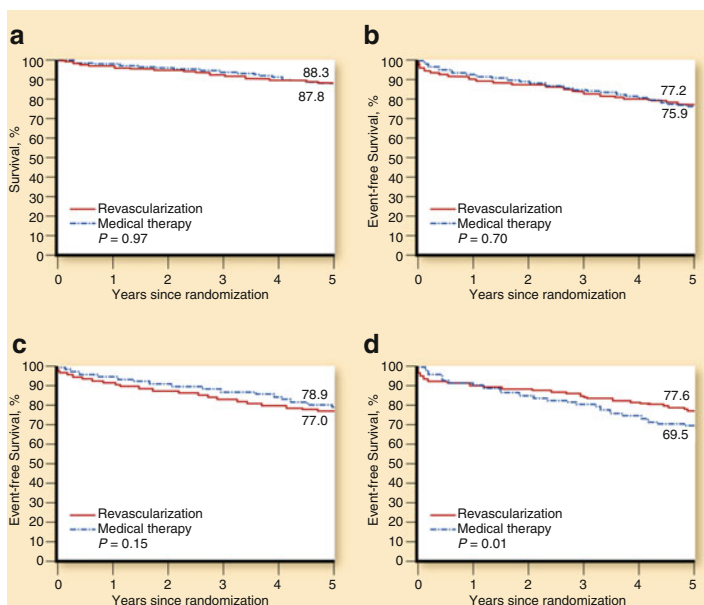


FIGURE 11.2 Major clinical endpoints in the BARI-2D trial. **(a)** Survival: revascularization vs medical therapy. **(b)** Freedom from major cardiovascular events: revascularization vs medical therapy. **(c)** Freedom from cardiovascular events in the PCI stratum. **(d)** Freedom from cardiovascular events in the CABG stratum (Reproduced with permission from Fernandez and Boden [26])

asymptomatic or who had mild to moderate symptoms were included in the study. No difference was seen regarding 5-year mortality between revascularization and OMT alone (11.7 % versus 12.2 %; $P=0.97$) (Fig. 11.2). Similarly, no difference was observed in 5-year rates of the combined end point of death, myocardial infarction, and stroke (22.8 % versus 24.1 %; $P=0.70$) [23]. The COURAGE trial [24] is the largest study so far comparing the results of interventional therapy combined with optimal medical therapy (intensive pharmacological treatment and lifestyle change) with optimal medical therapy alone in patients with chronic ischemic heart disease. The trial involved 2,287 patients, who were randomized to PCI combined with medical treatment (1,149) and to medical treatment alone (1,138). The primary outcome

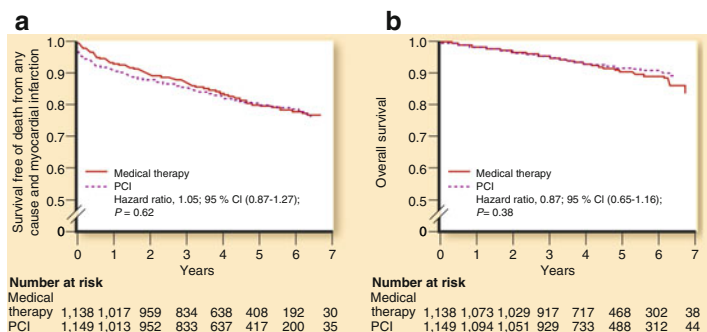


FIGURE 11.3 Major clinical end points in the COURAGE trial. (a) Survival free of death from any cause and myocardial infarction. (b) Overall survival (Reproduced with permission from Fernandez and Boden [26])

was death from any cause or non-fatal infarction during the follow-up period (Fig. 11.3). The 4.6-year cumulative rates showed no significant differences in the primary outcome between the PCI group and the medical-therapy-alone group (19–18.5 %; $P=0.62$). This similarity remained when periprocedural myocardial infarction was excluded (16.2–17.9 %; $P=0.29$). No differences were observed either in the incidence of hospitalization for acute coronary syndrome or in the mortality rates of both groups. Between the first and third year of follow-up, there was a substantial reduction of the prevalence of angina in both groups, but there was a significant difference in favour of the PCI group (55–66 % after 1 year, and 67–72 % after 3 years). These differences disappeared during the fifth year of follow-up (approximately 73 % of patients in both groups were free from angina). Patients who underwent PCI had less need for additional revascularization (21.1 % of patients in the PCI group had to undergo bypass surgery, as compared with 32.6 % of the medical-therapy group; $P<0.001$). In summary, the COURAGE trial suggested that, in comparison with medical therapy alone, optimal medical therapy combined with PCI (mainly with conventional stents) showed similar death and infarction rates, but with less need for revascularization and a better initial control of angina [24, 25]. Thus the BARI-2D

and COURAGE trials addressed a crucial question, with both trials demonstrating that revascularization is not superior to OMT regarding reductions in mortality or major cardiovascular events [26].

Limitations of These Studies

These two trials have limitations that should be considered. One of these is the percentage of crossover towards revascularization in the medical treatment group. In COURAGE, crossover over 5 years of follow up occurred in 33 % of cases while it was expected to occur in only 5 %. In the BARI 2D trial, rate of crossover to revascularization was 42 %. Another important point is the lack of quantification of the ischemic area. Moreover, drug-eluting stents were not widely available when these studies started, so bare metal stents mainly were used. We can only speculate that this could have had an impact on clinical outcomes. Finally, many high- risk patients were directly sent to revascularization after coronary angiography without randomization.

Revascularization Options: PCI Versus CABG

Before the more recent evolution of stents, several randomized studies (SoS, MASS-II, BARI, AWSOME, ARTS) compared the efficacy of PCI and CABG in patients with multivessel SCAD [27–31]. Similar rates of mortality were observed with both strategies, except in diabetic patients, who had better results with surgery in the BARI trial. According to these studies, stroke and non-fatal myocardial infarction rates were also similar in both treatment arms, with patients undergoing PCI needing more repeat revascularization procedures. In the drug eluting stent (DES) era, the ARTS I study was designed to compare CABG with stenting in patients with multivessel disease. At 5 years of follow up there were no differences in mortality between stenting and

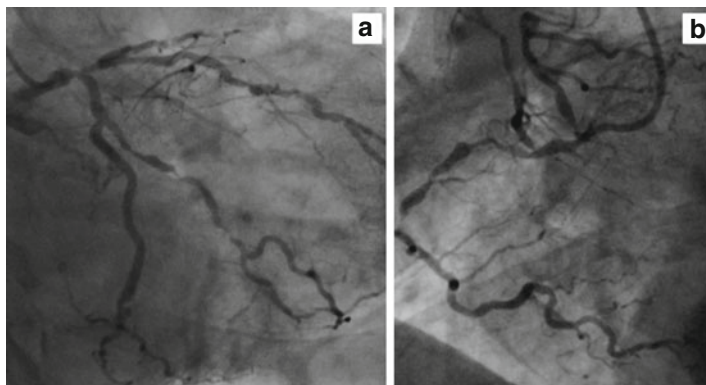


FIGURE 11.4 Angiographic view of a high SINTAX score case (>33). (a) Left coronary artery. (b) Right coronary artery

CABG. The ARTS II study studied the 5-year safety and effectiveness of the sirolimus eluting stent in patients with multivessel disease and compared the outcomes of ARTS II with the outcomes of the 2 historical arms of ARTS I. At 5 years, sirolimus eluting stent had a safety record comparable to CABG and superior to bare metal stents, and a MACE rate that was higher than that in patients treated with CABG, but lower than that in patients treated with bare metal stents. There were no differences in mortality between stenting and CABG [32, 33].

The SYNTAX trial randomized 1,800 patients with three-vessel disease or left main coronary artery disease to CABG or paclitaxel DES. One novelty introduced in this study was the use of an angiography score to grade the complexity of coronary artery disease; the “SYNTAX score” (Fig. 11.4). The SYNTAX algorithm consists of twelve questions (Table 11.2). Rates of major adverse cardiac or cerebrovascular events at 12 months were significantly higher in the PCI group (17.8 %, vs. 12.4 % for CABG; $P=0.002$), in large part because of an increased rate of repeat revascularization (13.5 % vs. 5.9 %, $P<0.001$). At 12 months, the rates of death and myocardial infarction were similar between the two groups; stroke was

TABLE 11.2 The SYNTAX score algorithm

1. Dominance
2. Number of lesions
3. Segments involved per lesion
4. Total occlusion
(a) Number of segments involved
(b) Age of the total occlusion (>3 months)
(c) Blunt Stump
(d) Bridging collaterals
(e) First segment beyond the occlusion visible by antegrade or retrograde filling
(f) Side branch involvement
5. Trifurcation
6. Bifurcation
(a) Type
(b) Angulation between the distal main vessel and the side branch <70°
7. Aorto-ostial lesion
8. Severe tortuosity
9. Length >20 mm
10. Heavy calcification
11. Thrombus
12. Diffuse disease/small vessels

significantly more likely to occur with CABG (2.2 %, vs. 0.6 % with PCI; $P=0.003$). Results of SINTAX trial at 5 years of follow up (Fig. 11.5) showed Kaplan-Meier estimates of MACCE rates to be 26.9 % for the CABG group versus 37.3 % in the PCI group ($p<0.0001$). The rates of myocardial infarction, the

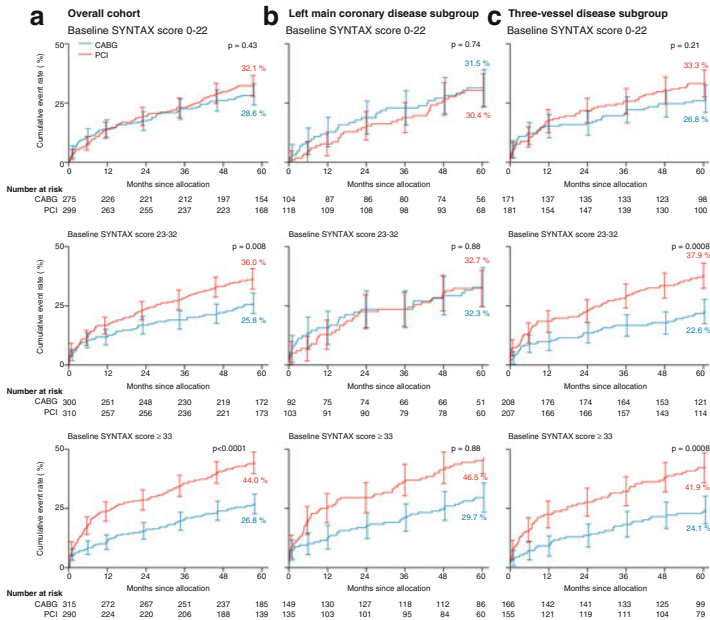


FIGURE 11.5 Kaplan-Meier cumulative event curves for MACCE by baseline SYNTAX score tercile. (a) Overall cohort; (b) left main coronary disease subgroup; and (c) three-vessel disease subgroup (Reproduced with permission from Mohr et al. [34])

combination of death or stroke or myocardial infarction, and repeat revascularization were significantly higher in patients who were assigned to PCI than in those who were assigned to CABG. The rates of all-cause mortality and stroke, however, were not significantly different between groups. 28.6 % of patients in the CABG group with low SYNTAX scores had MACCE versus 32.1 % of patients in the PCI group ($p=0.43$) and 31 % in the CABG group with left main coronary disease had MACCE versus 36.9 % in the PCI group ($p=0.12$); however, in patients with intermediate or high SYNTAX scores, MACCE was significantly increased with PCI (intermediate score, 25.8 % of the CABG group vs 36.0 % of the PCI group; $p=0.008$; high score, 26.8 % vs 44 %; $p<0.0001$). The authors

concluded that CABG should remain the standard of care for patients with high or intermediate SYNTAX scores. For patients with less complex disease (low SYNTAX scores) or left main coronary disease (low or intermediate SYNTAX scores), PCI was an acceptable alternative. One of the main implications derived from SYNTAX trial was the usefulness of the SYNTAX score, as a measure of the anatomical severity of coronary artery disease, and the assessment of the Heart Team in the revascularization decision-making process [34].

In the left main setting, we have now the results of some studies comparing PCI and CABG. The PRECOMBAT trial was a prospective, open label, randomized trial conducted at 13 sites in Korea. The authors randomly assigned patients with unprotected left main coronary artery stenosis to CABG (300 patients) or PCI with sirolimus-eluting stents (300 patients). Both groups were compared with respect to the primary composite end point of major adverse cardiac or cerebrovascular events (death from any cause, myocardial infarction, stroke, or ischemia-driven target-vessel revascularization) at 1 year. Event rates at 2 years were also reported. PCI with sirolimus-eluting stents was shown to be noninferior to CABG with respect to the primary composite end point [35]. Results from DELTA registry showed that PCI for ostial/midshaft lesions in unprotected left main coronary artery was associated with clinical outcomes comparable to those observed with CABG at long-term follow-up, despite the use of older first-generation DES [36]. PCI for ostial/midshaft lesions has been also associated with better clinical outcomes compared to distal bifurcation lesions in unprotected left main coronary artery, due to the lower need for repeat revascularization in ostial/mid-shaft lesions [37]. Regarding the type of stent, no differences have been recently reported between the use of zotarolimus versus everolimus eluting stents in the left main PCI [38].

Revascularization therapy should be carefully assessed in an individualized fashion by the “Heart Team”, a group of different physicians involving clinical cardiologists, interventional cardiologists, and cardiac surgeons not directly implicated in

the clinical case, who should report a global evaluation of each case. Many different factors should be taken in account to reach a decision regarding revascularization. The anatomical complexity of coronary artery disease (SYNTAX score), biological characteristics of the patient (i.e. age, diabetes, cerebrovascular disease, renal failure), surgical risk estimated by validated scores, the possibility of therapeutic fulfilment and the preference of the patient must be determinant factors.

Effect of Revascularization on Left Ventricular Function

Complete revascularization is considered to be one of the strongest predictors of improved clinical outcome [39–47]. While reduced left ventricular ejection fraction (LVEF) is known to be a powerful prognostic predictor of adverse clinical outcome, it remains unclear whether patients with SCAD and preserved left ventricular function who receive revascularization are more likely to preserve left ventricular systolic function as compared with those who receive OMT alone [39]. The results of several prospective randomized trials, which rigorously compared ‘hard’ clinical endpoints i.e. death and MI in SIHD patients who had undergone revascularization or OMT have failed to show superiority of either management strategy. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, the evaluation of left ventricular function (initially preserved) was performed in 1,220 subjects with multivessel coronary heart disease. After 5 years from randomization (PTCA or CABG) there were no significant differences in left ventricular ejection fraction between groups [48]. In MASS II (Multivessel disease randomized for CABG, PCI and medical treatment) there were no differences in the evolution of left ventricular function between patients in the medical treatment group and those who underwent surgical or percutaneous revascularization [31]. Similar findings were reported in a sub analysis of COURAGE trial. The COURAGE nuclear sub study assessed ventricular

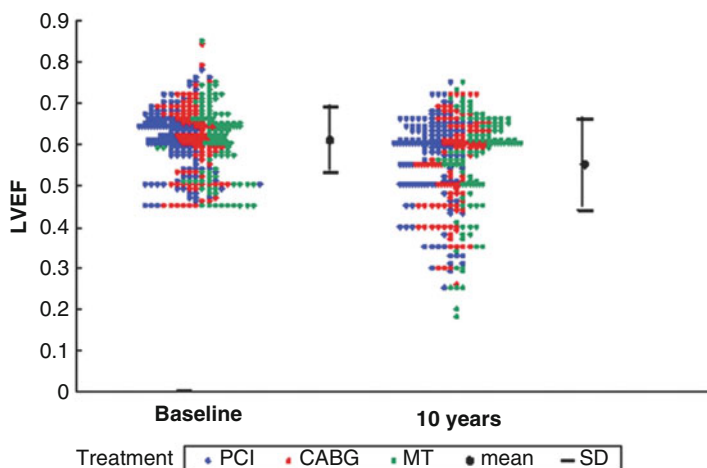


FIGURE 11.6 Left ventricular ejection fraction at baseline and the 10th year, according to treatment assigned: $p=0.675$: mean left ventricular ejection fraction similar among groups in the beginning and end of the follow-up; $p=0.641$: similar evolution among the groups; $p=0.001$: left ventricular ejection fraction decrease over time (Reproduced with permission from Garzillo et al. [50])

function at baseline and 6–18 months after intervention. Similar rest and post-stress LVEF values were found in OMT treated patients, with or without PCI [49].

In a recently published post-hoc analysis of the MASS II Trial, Garzillo et al. [50] evaluated long-term findings of serial left ventricular ejection fraction measurements in stable ischemic heart disease patients with multivessel CAD at baseline and at 10 years following randomization to PCI, CABG, or OMT using transthoracic echocardiography. The principal finding of this post-hoc analysis [50] was that regardless of the therapeutic strategy applied, left ventricular function remained preserved in the absence of major adverse cardiac events, except for an obvious decrease in LVEF among the subset of SCAD patients who sustained an MI either prior to or after revascularization (Fig. 11.6). LV systolic function

remained preserved at the end of the 10-year follow-up period with each of the three treatment strategies and declined minimally in all three groups. In conclusion, there was no statistically significant difference in the decline in LVEF between OMT and revascularization in this stable ischemic heart disease population. These data suggest that, in patients with multivessel stable coronary artery disease and preserved left ventricular systolic function at baseline, there is no measurable difference in left ventricular ejection fraction with or without revascularization [50]. Further studies are necessary for a deeper knowledge about the real influence of complete or incomplete revascularization in SCAD patients for preservation of left ventricular function.

Ischemia-Guided Percutaneous Revascularization

Revascularization therapy for SCAD guided by tests of ischaemia is one of the principal hot topics of the actual guidelines. The presence and extent of inducible ischemia is one of the most important factors related to outcome [51]. In patients with SCAD, several studies have analyzed the role of ischemia-guided percutaneous revascularization, using non invasive and invasive methods. Non invasive imaging studies with exercise echocardiography suggest that treatment of non ischemic coronary lesions may be safely deferred with an annual estimated incidence of death or MI of 0.6 %, as reported in the meta-analysis of Meltz et al [52]. The study of Hachamovitch et al. [53] emphasized the relationship between inducible ischemia on SPECT and the presence of short-term survival benefits with early revascularization vs. medical therapy. 10,627 patients without a prior history of MI or revascularization were included and underwent SPECT imaging. Revascularization was associated with a reduction in mortality for patients having moderate to severe ischemia. The cut-off level of ischemic myocardium, assessed by summed stress scores, to predict lower mortality using revascularization was

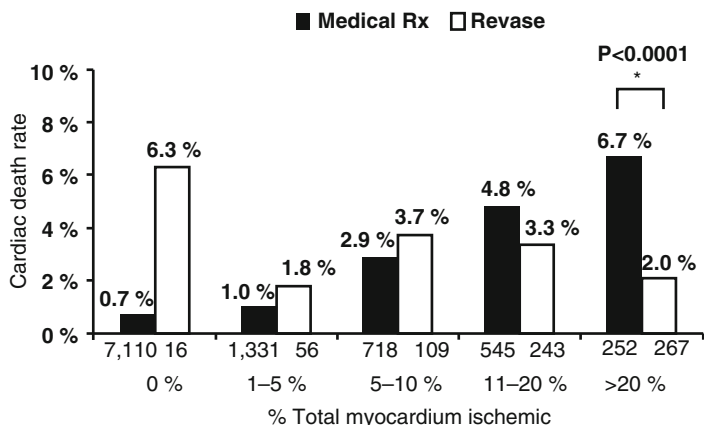


FIGURE 11.7 Observed cardiac death rates over the follow-up period in patients undergoing revascularization (Revasc) vs medical therapy (Medical Rx) as a function of the amount of inducible ischemia. Increase in cardiac death frequency as a function of inducible ischemia, (* $P < 0.0001$) (Reproduced with permission from Hachamovitch et al. [53])

approximately 10–12.5 % (Fig. 11.7) [53]. Kim et al. supported the benefit of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary artery disease. The outcomes of ischemia-guided revascularization were retrospectively compared with those of non ischemia-guided revascularization in a registry of 5,340 patients with multivessel coronary disease comprising 2,587 percutaneous coronary interventions (PCIs) with drug-eluting stents and 2,753 coronary artery bypass graft (CABG) surgeries. The incidence of major adverse cardiac and cerebrovascular events (MACCE) including death, myocardial infarction, stroke, or repeat revascularization was significantly lower in the ischemia-guided than in the non ischemia-guided group (16.2 % vs. 20.7 %; adjusted hazard ratio [aHR]: 0.73; 95 % confidence interval [CI]: 0.60–0.88; $p = 0.001$), primarily driven by the lower repeat revascularization rate (9.9 % vs. 22.8 %; aHR: 0.66; 95 % CI: 0.49–0.90; $p = 0.009$). Subgroup analysis

showed that ischemia-guided reduced the risk of MACCE in PCI (17.4 % vs. 22.8 %; aHR: 0.59; 95 % CI: 0.43–0.81; $p=0.001$) but not in CABG (16.0 % vs. 18.5 %; aHR: 0.87; 95 % CI: 0.67–1.14; $p=0.31$) patients [54]. Regarding diagnostic procedures, several diagnostic modalities are available for use as tools to establish the initial diagnosis, assess disease severity, and select the appropriate treatment strategy in symptomatic patients suspected of having CAD. In relation to this point, a multicenter study performed in Japan hypothesised that the choice of the initial diagnostic test might influence the treatment strategy. They showed that patients receiving initial SPECT had a lower rate of revascularization than those receiving coronary angiography (odds ratio, 5.36; 95 % CI, 4.07–7.05) [55].

Fractional flow reserve (FFR) is nowadays considered the goldstandard for invasive assessment of physiological stenosis significance and a tool for decision making in coronary revascularization. The recently published ESC guidelines on the management of stable coronary artery disease endorse the use of FFR for risk stratification. FFR is calculated as the ratio of distal coronary pressure to aortic pressure measured during maximal hyperaemia. A normal value for FFR is 1.0. Stenoses with a FFR >0.80 are hardly ever associated with exercise-induced ischaemia [56]. The principal utility of FFR is in certain situations when it is not clear whether an intermediate angiographic lesion causes ischaemia. The use of FFR in the catheterization laboratory accurately identifies which lesions should be revascularized and improves the outcome in most elective clinical and angiographic conditions, as compared with the situation where revascularization decisions are simply made on the basis of angiographic appearance of the lesion [56]. The DEFER study evaluated the 5-year outcomes in 325 patients assigned to three groups: deferred group (FFR ≥ 0.75 without PCI), PCI group (FFR ≥ 0.75 with PCI), and a control group (FFR <0.75 with PCI). 5-year event-free survival rates were similar in the deferred and PCI groups, with a risk of cardiac death or MI in patients with normal FFR inferior to 1 % per year [57]. FAME study

evaluated angio-guided versus FFR-guided percutaneous revascularization in patients with multivessel disease. Routine measurement of FFR in patients with multivessel coronary artery disease who were undergoing PCI with drug-eluting stents significantly reduced the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year of follow up [58]. The 2-year outcome report of the FAME study supported the safety of deferring PCI for nonischemic lesions [59]. Of interest, a sub-analysis of the FAME study also showed that angiography is inaccurate in assessing the functional significance of a coronary stenosis when compared with the FFR in the 50–70 % category but also in the 70–90 % angiographic severity category [60]. The FAME-2 trial tested the benefits, for SCAD, of FFR-guided PCI plus optimal medical therapy with optimal medical treatment alone. It showed that 4.3 % of patients in the PCI group compared with 12.7 % in the medical therapy group (HR, 0.32; 95 % CI, 0.19–0.53; $P < 0.001$) had a primary endpoint event of death, MI, or urgent revascularization. There was a lower rate of urgent revascularization in the PCI group than in the medical therapy group (1.6 % vs. 11.1 %; HR, 0.13; 95 % CI, 0.06–0.30; $P < 0.001$) [61].

Other nonrandomized observational studies have also shown the benefits of ischemia-guided revascularization. In the post acute coronary syndrome setting, once the culprit lesion has been treated, the severity of different stable lesions can also be assessed by FFR. Non-invasive stress testing immediately after the acute phase may be not possible, and furthermore, non-conclusive or contraindicated. In stabilized patients with recent acute coronary syndrome, FFR of non-culprit lesions can be safely evaluated, either during the index procedure or in a staged procedure [62].

The usefulness of FFR-guided revascularization strategy have been consistently demonstrated in different angiographic scenarios like left main, isolated left anterior descending coronary artery, small vessels or bifurcation lesions. Hamilos et al. reported that angiography alone did not allow appropriate individual decision making about the need for

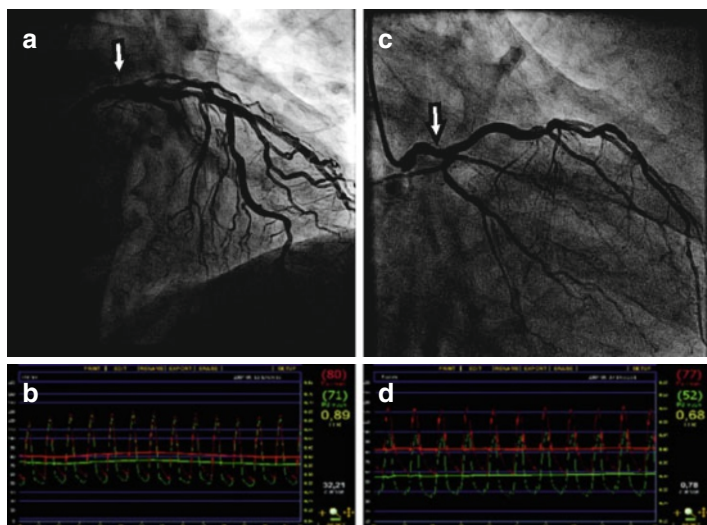


FIGURE 11.8 Examples of discordance between the angiographic appearance and the FFR values of left main lesions. (a) An angiographically tight left main stenosis (white arrow) with an FFR value of 0.89 (b). (c) An angiographically mild left main stenosis with an FFR value of 0.68 (d) (Reproduced with permission from Hamilos et al. [63])

revascularization in patients with equivocal stenosis of the left main coronary artery (Fig. 11.8). Moreover, this study supported that angiography often underestimates the functional significance of the stenosis of the left main. The favourable outcome of an FFR-guided strategy suggests that FFR should be assessed in such patients before taking the decision about the need for revascularization [63]. Muller et al proposed the usefulness of FFR-guiding percutaneous revascularization of isolated proximal left anterior descending coronary artery. This study concluded that the medical treatment of patients with a hemodynamically nonsignificant stenosis ($\text{FFR} \geq 0.80$) in the proximal LAD was associated with an excellent long-term clinical outcome with survival at 5 years similar to an age- and sex-matched control population [64]. In a study

reported by Puymirat et al. FFR-guided percutaneous revascularization of small coronary arteries was safe and resulted in better clinical outcome when compared with an angio-guided PCI [65]. The utility of FFR in percutaneous intervention for bifurcation lesions has been evaluated by Kumsars et al. The usefulness of FFR in this situation was to identify the functional grade of stenosis of the side branch [66].

All these studies indicate that ischemia guided PCI may reduce the cost, radiation exposure and procedural complications by avoiding unnecessary, complex procedures and consequently improving long-term prognosis. In addition, several studies have suggested that patients with more extensive ischaemia benefit from revascularization therapy, and this benefit could achieve long-term survival benefit if the ischaemia is severe and if significant reduction of ischaemia is achieved.

Future Directions

The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial was designed to answer some questions raised by the COURAGE and BARI 2D trials. The results of these two trials demonstrated that in patients with stable ischemic heart disease (SIHD), an initial management strategy of revascularization plus optimal medical therapy (OMT) did not reduce the risk of death or MI as compared with OMT alone. Both trials randomized patients after cardiac catheterization. Following the evidence provided by COURAGE and BARI 2D, a clinical trial that randomizes SIHD patients at a uniformly higher risk prior to cardiac catheterization is needed to determine optimal management for patients with SIHD. ISCHEMIA trial is planned for at least 150 sites in more than 30 countries and will compare angiography and revascularization plus optimal medical therapy with the conservative strategy of optimal medical therapy only. ISCHEMIA's primary end point is time to cardiovascular

death, MI, or hospitalization for unstable angina, resuscitated cardiac arrest, or heart failure. The secondary end points include angina-related quality of life and cost-effectiveness. This trial will target patients with more severe ischemia than those included in the COURAGE trial. This trial will better clarify the benefits of ischemia-guided revascularization for stable CAD patients.

Conclusions

As an initial strategy, all patients with SIHD should receive optimal medical therapy in addition to prescription of a healthy lifestyle. Revascularization exerts favourable effects on symptoms, quality of life, exercise capacity, and survival in some cases. The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, the amount of related ischaemia and the expected benefit regarding prognosis. Revascularization can offer survival benefits in high-risk, stable-angina patients, who are formally defined as those with multivessel coronary artery involvement or left main CAD, LVEF dysfunction and extensive ischemia. Stable-angina patients who are low risk on the basis of these criteria should not undergo revascularization procedures unless they experience significant angina, in which case revascularization can improve quality of life.

References

1. Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and baseline characteristics, including experience with medical treatment. By the Veterans Administration Cooperative Group for the Study of Surgery for Coronary Arterial Occlusive Disease. *Am J Cardiol.* 1977;40(2):212–25.
2. Myocardial infarction and mortality in the coronary artery surgery study (CASS) randomized trial. *N Engl J Med.* 1984;310(12):750–8.

3. European Coronary Surgery Study Group. Long-term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet*. 1982;2(8309):1173–80.
4. Mark DB, Shaw L, Harrell Jr FE, Hlatky MA, Lee KL, Bengtson JR, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med*. 1991;325:849–53.
5. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344(8922):563–70.
6. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2010;31(20):2501–55.
7. Task Force Members, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949–3003.
8. Khan NE, De Souza A, Mister R, Flather M, Clague J, Davies S, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med*. 2004;350:21–8.
9. Afilalo J, Rasti M, Ohayon SM, Shimony A, Eisenberg MJ, et al. Off-pump vs. on-pump coronary artery bypass surgery: an updated meta-analysis and meta-regression of randomized trials. *Eur Heart J*. 2012;33:1257–67.
10. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*. 2012;366:1489–97.
11. Parisi AF, Folland ED, Hartigan P. A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. Veterans Affairs ACME Investigators. *N Engl J Med*. 1992;326:10–6.
12. Folland ED, Hartigan PM, Parisi AF. Percutaneous transluminal coronary angioplasty versus medical therapy for stable angina pectoris: outcomes for patients with double-vessel versus single

- vessel coronary artery disease in a Veterans Affairs Cooperative randomized trial. Veterans Affairs ACME Investigators. *J Am Coll Cardiol.* 1997;29:1505–11.
13. RITA-2 trial participants. Coronary angioplasty versus medical therapy for angina: the second Randomised Intervention Treatment of Angina (RITA-2) trial. *Lancet.* 1997;350:461–8.
 14. McCormick LS, Black DM, Waters D, Brown WV, Pitt B. Rationale, design, and baseline characteristics of a trial comparing aggressive lipid lowering with Atorvastatin Versus Revascularization Treatments (AVERT). *Am J Cardiol.* 1997;80(9):1130–3.
 15. Henderson RA, Pocock SJ, Clayton TC, Knight R, Fox KA, Julian DG, Chamberlain DA. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol.* 2003;42:1161–70.
 16. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomised controlled trials. *BMJ.* 2000;321:73–7.
 17. Davies RF, Goldberg AD, Forman S, Pepine CJ, Knatterud GL, Geller N, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study 2 year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. *Circulation.* 1997;95:2037–43.
 18. Pfisterer M. Long-term outcome in elderly patients with chronic angina managed invasively versus by optimized medical therapy: four-year follow-up of the randomized Trial of Invasive versus Medical therapy in Elderly patients (TIME). *Circulation.* 2004;110:1213–8.
 19. Hueb WA, Bellotti G, De Oliveira SA, Arie S, De Albuquerque CP, Jatene AD, et al. The Medicine, Angioplasty or Surgery Study (MASS): a prospective, randomized trial of medical therapy, balloon angioplasty or bypass surgery for single proximal left anterior descending artery stenoses. *J Am Coll Cardiol.* 1995;26:1600–5.
 20. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med.* 2003;138:777–86.
 21. Cassar A, Holmes Jr DR, Rihal CS, Gersh BJ. Chronic coronary artery disease: diagnosis and management. *Mayo Clin Proc.* 2009;84:1130–46.
 22. Fuster V, Farkouh ME. General cardiology perspective: decision making regarding revascularization of patients with type 2 diabetes mellitus and cardiovascular disease in the Bypass

- Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Circulation*. 2010;121(22):2450–2.
23. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–15.
 24. Boden WE, O'Rourke RA, Teo KK, et al.; for the COURAGE trial Co-principal Investigators and Study. Coordinators: the evolving pattern of symptomatic coronary artery disease in Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. *J Am Coll Cardiol* 2007;99:208–12.
 25. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007; 356:1503–16.
 26. Fernandez SF, Boden WE. Strategies in stable ischemic heart disease: lessons from the COURAGE and BARI-2D trials. *Curr Atheroscler Rep*. 2010;12:423–31.
 27. Serruys PW, Unger F, Sousa JE, Jatene A, Bonnier HJ, Schonberger JP, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med*. 2001;344:1117–24.
 28. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med*. 1996;335:217–25.
 29. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet*. 2002;360:965–70.
 30. Morrison DA, Sethi G, Sacks J, Grover F, Sedlis S, Esposito R, et al. A multicentre, randomized trial of percutaneous coronary intervention versus bypass surgery in high-risk unstable angina patients. The AWESOME (Veterans Affairs Cooperative Study #385, angina with extremely serious operative mortality evaluation) investigators from the Cooperative Studies Program of the Department of Veterans Affairs. *Control Clin Trials*. 1999;20:601–19.
 31. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. *Circulation*. 2010;122:949–57.

32. Serruys PW, Onuma Y, Garg S, Vranckx P, De Brune B, et al. 5-Year clinical outcomes of the ARTS II (Arterial Revascularization Therapies Study II) of the sirolimus-eluting stent in the treatment of patients in the treatment of patients multivessel de novo coronary artery lesions. *J Am Coll Cardiol*. 2010;55:1093–101.
33. Serruys PW, Ong AT, van Herwerden LA, Sousa JE, Jatene A, Bonnier JJ, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. *J Am Coll Cardiol*. 2005;46(4): 575–81.
34. Mohr FW, Morice MC, Kappetein AP, Feldman TE, Ståhle E, Colombo A, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet*. 2013;381(9867):629–38.
35. Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718–27.
36. Naganuma T, Chieffo A, Meliga E, Capodanno D, Park SJ, Onuma Y, et al. Long-term clinical outcomes after percutaneous coronary intervention versus coronary artery bypass grafting for ostial/midshaft lesions in unprotected left main coronary artery from the DELTA registry: a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv*. 2014;7(4): 354–61.
37. Naganuma T, Chieffo A, Meliga E, Capodanno D, Park SJ, Onuma Y, et al. Long-term clinical outcomes after percutaneous coronary intervention for ostial/mid-shaft lesions versus distal bifurcation lesions in unprotected left main coronary artery: the DELTA Registry (drug-eluting stent for left main coronary artery disease): a multicenter registry evaluating percutaneous coronary intervention versus coronary artery bypass grafting for left main treatment. *JACC Cardiovasc Interv*. 2013;6(12):1242–9.
38. Mehilli J, Richardt G, Valgimigli M, Schulz S, Singh A, Abdel-Wahab M, et al. Zotarolimus- versus everolimus-eluting stents for unprotected left main coronary artery disease. *J Am Coll Cardiol*. 2013;62(22):2075–82.
39. Sidhu SS, Boden WE. Optimal medical therapy vs. revascularization on long-term LV function. *Eur Heart J*. 2013;34:3339–41.

40. van den Brand MJ, Rensing BJ, Morel MA, Foley DP, de Valk V, Breeman A, et al. The effect of completeness of revascularization on event-free survival at one year in the arts trial. *J Am Coll Cardiol*. 2002;39:559–64.
41. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, et al. Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961–72.
42. Hannan EL, Wu C, Walford G, Holmes DR, Jones RH, Sharma S, et al. Incomplete revascularization in the era of drug-eluting stents: impact on adverse outcomes. *JACC Cardiovasc Interv*. 2009;2:17–25.
43. Hannan EL, Racz M, Holmes DR, King 3rd SB, Walford G, Ambrose JA, et al. Impact of completeness of percutaneous coronary intervention revascularization on long-term outcomes in the stent era. *Circulation*. 2006;113:2406–12.
44. Tamburino C, Angiolillo DJ, Capranzano P, Dimopoulos K, La Manna A, Barbagallo R, et al. Complete versus incomplete revascularization in patients with multivessel disease undergoing percutaneous coronary intervention with drug-eluting stents. *Catheter Cardiovasc Interv*. 2008;72:448–56.
45. Head SJ, Mack MJ, Holmes Jr DR, Mohr FW, Morice MC, Serruys PW, et al. Incidence, predictors and outcomes of incomplete revascularization after percutaneous coronary intervention and coronary artery bypass grafting: a subgroup analysis of 3-year SYNTAX data. *Eur J Cardiothorac Surg*. 2012;41:535–41.
46. Wu C, Dyer AM, King 3rd SB, Walford G, Holmes Jr DR, Stamato NJ, et al. Impact of incomplete revascularization on long-term mortality after coronary stenting. *Circ Cardiovasc Interv*. 2011;4:413–21.
47. Genereux P, Palmerini T, Caixeta A, Rosner G, Green P, Dressler O, et al. Quantification and impact of untreated coronary artery disease after percutaneous coronary intervention: The residual SYNTAX. (Synergy Between PCI With Taxus and Cardiac Surgery) score. *J Am Coll Cardiol*. 2012;59:2165–74.
48. Gibbson RJ, Miller DD, Liu P, Guo P, Brooks MM, Schwaiger M. Similarity of ventricular function in patients alive 5 years after randomization to surgery or angioplasty in the BARI trial. *Circulation*. 2001;103:1076–82.
49. Shaw LJ, Berman DS, Maron DJ, Mancini GB, Hayes SW, Hartigan PM, et al. Optimal medical therapy with or without percutaneous coronary intervention to reduce ischemic burden:

- results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy. *Circulation*. 2008;117:1283–91.
50. Garzillo CL, Hueb W, Gersh BJ, Lima EG, Rezende PC, Hueb AC, et al. Longterm analysis of left ventricular ejection fraction in patients with stable multivessel coronary disease undergoing medicine, angioplasty, or surgery: 10-year follow-up of the MASS II trial. *Eur Heart J*. 2013;34:3370–7.
 51. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. 27th Bethesda conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:1007–19.
 52. Metz LD, Beattie M, Hom R, Redberg RF, Grady D, Fleischmann KE. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol*. 2007;49:227–37.
 53. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900–7.
 54. Kim YH, Ahn JM, Park DW, Song HG, Lee JY, Kim WJ, et al. Impact of ischemia-guided revascularization with myocardial perfusion imaging for patients with multivessel coronary disease. *J Am Coll Cardiol*. 2012;60:181–90.
 55. Yamauchi T, Tamaki N, Kasanuki H, Kimura T, Uemura Y, Iimuro S. Optimal initial diagnostic strategies for the evaluation of stable angina patients: a multicenter, prospective study on myocardial perfusion imaging, computed tomographic angiography, and coronary angiography. *Circ J*. 2012;76:2832–9.
 56. Pijls NH, Sels JW. Functional measurement of coronary stenosis. *J Am Coll Cardiol*. 2012;59:1045–57.
 57. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, Bar F, Hoorntje J, Koolen J, Wijns W, de Bruyne B. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. *J Am Coll Cardiol*. 2007;49:2105–11.
 58. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van't Veer M, et al.; FAME Study Investigators. Fractional flow reserve

- versus angiography for guiding percutaneous coronary intervention. *N Engl J Med*. 2009;360(3):213–24.
59. Pijls NHJ, Fearon WF, Tonino PA, Siebert U, Ikeno F, Bornschein B, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) Study. *J Am Coll Cardiol*. 2010;56:177–84.
 60. Tonino PA, Fearon WF, De Bruyne B, Oldroyd KG, Leeser MA, Ver Lee PN, Maccarthy PA, Van't Veer M, Pijls NH. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010;55:2816–21.
 61. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al.; FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med*. 2012;367:991–1001.
 62. Ntalianis A, Sels JW, Davidavicius G, Tanaka N, Muller O, Trana C, et al. Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction. *JACC Cardiovasc Interv*. 2010;3:1274–81.
 63. Hamilos M, Muller O, Cuisset T, Ntalianis A, Chlouverakis G, Sarno G, et al. Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically equivocal left main coronary artery stenosis. *Circulation*. 2009;120(15):1505–12.
 64. Muller O, Mangiacapra F, Ntalianis A, Verhamme KM, Trana C, Hamilos M, et al. Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior descending coronary artery stenosis. *JACC Cardiovasc Interv*. 2011;4(11):1175–82.
 65. Puymirat E, Peace A, Mangiacapra F, Conte M, Ntarladimas Y, Bartunek J, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary revascularization in patients with small-vessel disease. *Circ Cardiovasc Interv*. 2012;5(1):62–8.
 66. Kumsars I, Narbute I, Thuesen L, Niemelä M, Steigen TK, Kervinen K, et al. Side branch fractional flow reserve measurements after main vessel stenting: a Nordic-Baltic Bifurcation Study III substudy. *EuroIntervention*. 2012;7(10):1155–61.

Index

A

- Abnormal COronary
 VAseomotion
 (ACOVA), 36–37
- Acetylcholine (ACh), 15, 16, 19,
 20, 37, 218
- Acetyl-CoA
 - ATP sources, 156
 - Krebs cycle, 157, 168
 - PHD enzyme, 168
 - trimetazidine inhibits
 LC-3KAT, 159
- ACIP study. *See* The
 Asymptomatic Cardiac
 Ischemia Pilot (ACIP)
 study
- Acute coronary syndrome (ACS)
 - GTN, 103
 - inflammatory response, 138
 - nitrates, anti-aggregant
 effects, 92
 - trimetazidine, 161
- Adenosine, 8, 11, 115, 118
- Adenosine triphosphate (ATP)
 - allopurinol, 208–209
 - glycolytic products, 156
 - Krebs cycle, 157
 - phosphocreatine levels, 159
- β -Adrenergic receptor
 - antagonists. *See*
 Beta-blockers (BBs)
- AGENT-1 trial. *See* Angiogenic
 GENe Therapy
 (AGENT-1) trial
- Aldehyde dehydrogenase-2
 (ALDH-2), 89, 90, 102
- Allopurinol
 - acute coronary
 setting, 208
 - adverse effects, 209
 - CAD patients, 207
 - diastolic blood pressure, 207
 - LVEF, 207
 - mechanism of action, 208–209
 - nitric oxide, inactivation, 207
 - in patients with chronic stable
 angina, 192
 - pharmacokinetics, 209
 - ST depression, 207
 - vascular OS, 208
 - xanthine oxidase, 207
- American College of Cardiology-
 American Heart
 Association (ACC-
 AHA), 37, 42–45
- Amlodipine, 142, 149, 181, 182

Angina

- activity-limiting, 147
- anti-angina drug, 161
- anti-anginal efficacy, 140, 142, 145, 149
- CARISA study, 180–182
- CSA, 154
- diabetic chronic, 166
- ERICA trial, 180, 182–183
- MARISA trial, 179, 180
- mortality (*see* Mortality, angina patients)
- myocardial ischemia, 157
- persistent angina, 155, 168
- ranolazine, in chronic stable angina, 184–185
- recurrent angina, 155
- refractory angina, 169
- stable angina pectoris, 135, 147, 149
- TERISA study, 180–181
- Angina pectoris. *See also* Myocardial ischemia
- CABG (*see* Coronary artery bypass graft surgery (CABG))
- coronary steal, 10–11
- CSA (*see* Chronic stable angina (CSA))
- endogenous opioids, release, 2
- MVA (*see* Microvascular angina (MVA))
- pain signals, 2
- PCI (*see* Percutaneous coronary intervention (PCI))
- and silent ischemia, 2
- Angina Prognosis Study in Stockholm (APSIS), 46, 68
- Angiogenic GENE Therapy (AGENT-1) trial, 220
- Angiotensin converting enzyme (ACE) inhibitors, 51, 98, 184, 236
- allopurinol, 207

- coronary atherosclerosis, 41
- myocardial infarction, 41
- ranolazine, 173

Antianginal drugs

- BB, 69–72
- cardiac metabolic modulators, 212–215
- chronic stable angina
 - clinical trials, 191–197
 - proangiogenic factors, 200–206
- conventional, 190
- CSA, 181, 189
- fatty acid oxidation, 167
- glycolysis, 167
- I_{Na} (*see* Na^+ current (I_{Na}))
- microvascular dysfunction, 169
- myocardial oxygen demand, 189
- persistent angina, 168
- prognostic benefit, 184
- pyruvate, 168
- ranolazine, 174
- traditional Chinese herbal remedies
 - efficacy and safety, evaluation, 198–199
 - endothelin-1 blocker, 217
 - FGF, 220–221
 - HGF, 223–225
 - Rho-kinase inhibitor, 218–219
 - salvia pellet (T89), 215–217
 - testosterone, 219–220
 - therapeutic angiogenesis, 220
 - VEGF, 221–223
- trimetazidine, 167
- xanthine oxidase inhibitors
 - allopurinol, 207–209
 - febuxostat, 209–210
- Anti-angina mechanisms
 - cGMP pathway, 116
 - endothelial function, 118

guanylate cyclase, 116
 ISDN, 118
 K^{+}_{ATP} channels, 116
 MLC, 116, 117
 Anti-ischemic drugs, 67–69
 Anti-platelet therapy
 aspirin, 39–40
 clopidogrel, 40
 prasugrel and ticagrelor, 40
 SAPAT, 39
 The Asymptomatic Cardiac
 Ischemia Pilot (ACIP)
 study, 239
 ATP. *See* Adenosine triphosphate
 (ATP)

B

BARI 2D trial. *See* Bypass
 Angioplasty
 Revascularization
 Investigation 2 Diabetes
 (BARI 2D) trial

Beta-blockers (BBs)
 adverse events, 65
 and antianginal drugs, 69–72
 vs. anti-ischemic drugs, 67–69
 cardiovascular, 62–63
 in chronic and stable ischaemic
 heart disease, 68
 drugs, properties, 61
 effectiveness vs. placebo,
 66–67
 hypothetical drug, 57
 mechanism of action, 58–60
 metabolic, 63–65
 pharmacokinetics, 60–62
 pulmonary, 65
 in stable angina, 65–66
 sympathectomy, 57
 vs. trimetazidine, 165
 Bradycardia, 139, 148
 Bypass Angioplasty
 Revascularization
 Investigation 2 Diabetes
 (BARI 2D) trial

clinical characteristics,
 240–242
 clinical endpoints, 242
 and ISCHEMIA trial, 256
 left ventricular function,
 evaluation, 249
 limitations, 244
 patients with angina, in
 clinical trials, 154

C

CABG. *See* Coronary artery
 bypass graft surgery
 (CABG)

CAD. *See* Coronary artery
 disease (CAD)

Calcium channel blockers
 (CCBs)
 and BB, 46–47, 68, 70
 benzothiazepine, 80, 81
 cardiac depressant, 81
 dihydropyridine, 80
 dosage, 80
 myocardium, 80
 pharmacology
 benzothiazepine, 80
 cardiomyocytes, 79
 phenylalkylamine
 class, 80
 vascular smooth muscle
 cells, 79
 vs. trimetazidine, 146, 164, 165

Canadian Cardiovascular
 Society (CCS), 66, 70,
 146, 220, 221

Cardiac pain pathway, 2, 3

Cardiac syndrome X, 20, 36,
 50–51, 125

Cardio-protective mechanisms
 coronary artery
 stenosis, 127
 IONA, 126
 JCAD, 126
 supraventricular arrhythmias,
 127–128

- CARISA study. *See* Combination Assessment of Ranolazine In Stable Angina (CARISA) study
- Ca²⁺ sensitization, 218
- CCBs. *See* Calcium channel blockers (CCBs)
- cCK. *See* Cytosolic creatine kinase (cCK)
- CCS. *See* Canadian Cardiovascular Society (CCS)
- Chronic kidney disease (CKD), 209
- Chronic nitrate therapy, 93, 98
- Chronic stable angina (CSA)
- allopurinol, effects, 207, 209
 - CARISA study, 181
 - CCB with β -blocker, 83
 - clinical trials, 191–197
 - definition, 35
 - dihydropyridines, 81–82
 - phenylalkylamine, 82
 - proangiogenic factors, 200–206
 - ranolazine, use, 184–185
 - symptoms, 35
 - TERISA study, 180–181
 - as ‘tight/constricting’ pain, 35
 - trimetazidine use, 166
 - verapamil, 82
- CKD. *See* Chronic kidney disease (CKD)
- Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial
- clinical characteristics, 240–242
 - clinical end points, 242–243
 - and ISCHEMIA trial, 256
 - limitations, 244
 - vs. medical therapy, 243
 - patients with angina, in clinical trials, 154
- Clopidogrel, 40
- Cold pressor test (CPT), 16, 19
- Collateral blood circulation, 9–10
- Combination Assessment of Ranolazine In Stable Angina (CARISA) study, 72, 180–182
- Contrast stress echocardiography, 19
- Coronary angiography
- collateral circulation, 9
 - haemodynamic effects, 119
 - limitations, 6–7
 - MVA, 17, 19, 22
 - refractory angina, 51
- Coronary artery bypass graft surgery (CABG), 174, 221, 224
- clinical trials, 154
 - conventional and off-pump surgery, 238
 - IMA, use, 238
 - myocardial revascularization, 50
 - on-and off-pump, 238
 - vs. PCI
 - ARTS I and ARTS II, 244–245
 - PRECOMBAT trial, 248
 - SYNTAX trial, 245–248
 - risk-stratification models, 237
 - in SCAD patients, trials, 236
- Coronary artery disease (CAD)
- bradycardia, 148
 - combination therapy
 - activity-limiting angina, 147
 - anti-anginal and anti-ischemic efficacy, 142, 145
 - ASSOCIATE trial, 143
 - Bruce protocol exercise test, 145
 - chronic stable angina, 146
 - ivabradine, 143–145
 - multicentre trial, 146
 - nonfatal myocardial infarction, 146

- SIGNIFY trial, 146
- stable angina pectoris, 146
- comorbidities, 147, 148
- endothelial dysfunction,
 - 138, 207
- endothelin-1, 227
- FGF, 220
- left coronary artery territory,
 - 224
- monotherapy
 - amlodipine vs. ivabradine,
 - 142
 - angina attacks, 140
 - anti-anginal and anti-ischemic efficacy, 140
 - dose-ranging study, 140
 - ivabradine, 141–142
 - open-label extension
 - phase, 140
 - placebo-controlled,
 - randomized study, 140
 - myocardial ischemia, 136
 - traditional Chinese medicines,
 - 198–199
- Coronary artery spasm (CAS)
 - acetylcholine, 16
 - causes and mechanisms, 13, 14
 - hyperventilation, 16
 - mechanical damage,
 - endothelium and vessel
 - wall, 12
 - occlusive and subocclusive
 - spasm, 12, 14
 - Prinzmetal's variant angina,
 - 12, 13
 - Rho-kinase, 15
 - SMC hyper-reactivity, 15
 - spasmogenic vascular
 - changes, 16
 - sublingual nitrates, use, 88
 - susceptibility, 15–16
 - vasospastic mechanism, 12
- The Coronary Artery Surgery Study (CASS), 236
- Coronary blood flow (CBF)
 - CFR impairment, 5
 - ivabradine effect, 142
 - less beneficial, BB reduction, 59
 - nitrate-induced increasing,
 - 90–91
 - and pressure gradient, 5
 - TTE-DR, 19
- Coronary flow reserve (CFR)
 - cardiac work, level, 4
 - CBF reduction, 5
 - ivabradine effect, 142
 - stenosis, 8
- Coronary hemodynamics
 - artery vasospasm, 92
 - congestive heart failure, 91
 - ischemia, 90
 - saphenous vein grafts, 90
- Coronary microvascular dilator
 - function, 19
- Coronary microvascular
 - dysfunction (CMVD)
 - acetylcholine, dosage, 20
 - adrenergic stimulation, 21
 - chest pain, mechanism, 22
 - classification, 17, 18
 - contrast stress
 - echocardiography, 19
 - CPT, 19
 - microvascular dilator
 - function, 19
 - MVA (*see* Microvascular
 - angina (MVA))
 - resistance coronary arteries,
 - abnormalities of, 17
 - risk factors, 21–22
 - TTE-DR, 19
- Coronary steal, 10–11
- Coronary stenosis
 - coronary artery diameter,
 - reduction of, 5
 - hemodynamic significance, 8
 - intraventricular pressure and
 - extravascular forces, 6, 7
 - ischemic threshold, 4
 - limitations, angiography, 6–7
 - myocardial oxygen demand, 3–4
 - perfusion pressure, 4

- Coronary stenosis (*cont.*)
 - subendocardial layers, 6
 - vessel lumen, reduction of, 4
- Corrected TIMI frame count (cTFC), 22, 23
- COURAGE trial. *See* Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial
- CSA. *See* Chronic stable angina (CSA)
- CYP3A4 inhibitors, 176–177
- Cytosolic creatine kinase (cCK), 208–209

D

- Dihydropyridine CCBs
 - amlodipine, 82
 - antihypertensive agent, 82
 - coronary artery disease, 82
 - hypotension, 80
 - ischemic symptoms, 80
 - nifedipine, 81
- Dipeptidyl peptidase-4 (DPP-4), 213, 215
- Dipyridamole, 11, 19, 40
- Drug eluting stent (DES), 244, 245, 248, 252

E

- Efficacy of Ranolazine In Chronic Angina (ERICA) trial, 180, 182–183
- Emergency medical services (EMS), 99
- Epicardial artery atherosclerosis, 123
- Estimated glomerular filtration rate (eGFR), 209
- ETT. *See* Exercise treadmill testing (ETT)

- The European Coronary Surgery Study (ECSS), 236
- The European Society of Cardiology (ESC)
 - anti-angina drugs, recommended, 42–45
 - BB, use, 68
 - class I and class IIa indication, 123
 - guidelines, 37, 38
 - recommendations, 37
- Evaluation of the Antianginal efficacy and Safety of the aSSociation Of the If Current Inhibitor ivAbradine with a beTa-blockEr (ASSOCIATE) trial, 70, 143
- Exercise treadmill testing (ETT), 210, 220, 221

F

- Fatty acid oxidation (FAO), 157–159, 167
- FFA. *See* Free fatty acid (FFA)
- Fibroblast growth factor (FGF), 220–221
- First-line agents
 - beta-blockers and calcium channel blockers, 46–47
 - CMVD detection, 19
- Fractional flow reserve (FFR)
 - ischemia-guided percutaneous revascularization vs. angio-guided PCI, 256
 - decision making, 254–255
 - DEFER study, 253
 - FAME study, 253–254
 - principal utility, 253
 - risk stratification, 253
 - measurements, 7–8
 - myocardial oxygen consumption, 8
- Free fatty acid (FFA), 212–213

G

- GGE. *See* Guaiacol glycidyl ether (GGE)
- Glucagon-like peptide-1-amide (GLP-1), 192–193, 213, 214
- Glucose oxidation (GO), 157–159, 168, 212
- Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensive (GEMINI) trial, 64
- Glyceril trinitrate (GTN), 46, 48
 chest pain, 98
 chronic nitrate therapy, 98
 EMS, 99
 myocardial infarction, 99
 sublingual mucosa, 99
 sublingual nitroglycerin, 98
 transdermal nitroglycerin patches, 100–101
- GO. *See* Glucose oxidation (GO)
- Guaiacol glycidyl ether (GGE), 174

H

- Heart rate (HR)
 β -blocker, 146
 blood pressure, 165, 174, 184–185
 CAD, 136
 ivabradine, 137, 138
 reduction, 136
- Hepatocyte growth factor (HGF), 206, 223–225
- Human umbilical vein endothelial cells (HUVECs), 160

I

- IHD. *See* Ischemic heart disease (IHD)

- Impact Of Nicorandil in Angina (IONA) study, 126
- Internal mammary artery (IMA), 238
- International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial, 256–257
- Intrinsic sympathomimetic activity (ISA), 60
- Ischemic heart disease (IHD), 157–158, 173–174
 BB, use, 67, 68
 ranolazine effects, 183
- Ischemic threshold, 4
- Isosorbide dinitrate (ISDN)
 angina onset, 102
 antianginal efficacy, 102
 chronic antianginal agent, 101
 exercise duration, 102
 hepatic metabolism, 101
- Isosorbide mononitrate (ISMN), 89, 102–103
- Ivabradine
 antianginal and anti-ischemic efficacy, 149
 CAD (*see* Coronary artery disease (CAD))
 concomitant conditions, 135
 the Euro Heart Survey, 135, 136
 heart rate, 136
 myocardial ischemia, 136
 pharmacodynamic properties (*see also* Tolerability, ivabradine)
 baseline heart rate, 138
 β -blockers, 138
 cardiovascular pathology, 137
 dyslipidaemic mice, 138
 endothelial dysfunction, 138

Ivabradine (*cont.*)

- f-channels, 137
- heart rate, 136
- spontaneous diastolic depolarization, 136–137
- SIGNIFY trial, 149
- stable angina pectoris, 135
- suboptimal management, 135

J

- Japanese Coronary Artery Disease (JCAD) studies, 126–127

K

- Krebs cycle, 157, 168
- Kuopio Angiogenesis Trial (KAT), 223

L

- LC 3-KAT. *See* Long-chain 3-ketoacyl CoA thiolase (LC 3-KAT)
- Left circumflex coronary artery (LCCA), 212
- Left ventricular ejection fraction (LVEF)
 - GLP-1 infusion, 214
 - high-dose allopurinol, effects, 207
 - in infarcted animals, VM2020 injection, 224
 - revascularization effect, 249, 250
- Long-chain 3-ketoacyl CoA thiolase (LC 3-KAT), 158, 159
- L-type calcium channel receptor antagonists. *See* Calcium channel blockers (CCBs)

M

- Major adverse cardiac and cerebrovascular events (MACCE), 246, 247, 252–253
- Major adverse cardiac events (MACE), 208, 223
- Management of angina: a reTROspective Ohort (METRO) study, 167
- Management, stable angina
 - ACOVA, 36–37
 - acute angina episodes, treatment, 46
 - anti-atherosclerosis and anti-angina therapies, 34
 - anti-platelet therapy, 39–40
 - effort-induced angina, 35–36
 - first-line agents, 46–47
 - guidelines, ESC/ACC-AHA/NICE, 37, 38, 42–45
 - high-risk patients, 41
 - ischaemia, treatment, 41
 - lifestyle modification, 39
 - lower BP targets, 39
 - microvascular angina/cardiac syndrome X, 50–51
 - myocardial revascularization, 50
 - pattern of symptoms, 36
 - Prinzmetal's variant angina, 51
 - prognosis, 38–39
 - refractory angina, 51–52
 - second-line agents, 47–50
- MARISA trial. *See* Monotherapy Assessment of Ranolazine In Stable Angina (MARISA) trial
- Maximum tolerance dose (MTD), 216
- MCP-1. *See* Monocyte chemoattractant protein-1 (MCP-1)

- Medical treatment
 - CABG, 236–237
 - PCI, 239, 242
 - ventricular function, 249
- Metabolic Efficiency With
 - Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes (MERLIN)-TIMI 36 trial, 176, 180, 184
- METRO study. *See* Management of angina: a retrospective cohort (METRO) study
- MI. *See* Myocardial infarction (MI)
- Microvascular angina (MVA)
 - and cardiac syndrome X, 50–51
 - definition, 17
 - diagnosis, 17
 - primary, 17
 - secondary, 17
 - stable and unstable, 18
- MLCK. *See* Myosin light chain kinase (MLCK)
- MLCPh. *See* Myosin light chain phosphatase (MLCPh)
- Monocyte chemoattractant protein-1 (MCP-1), 215–216
- Monotherapy Assessment of
 - Ranolazine In Stable Angina (MARISA) trial, 179, 180
- Mortality, angina patients
 - acetyl-CoA, 168
 - antianginal drug, 167
 - BB, 167
 - cardiac adverse events, 167
 - cardiac efficiency, 168
 - fatty acid oxidation, 167
 - glucose oxidation, 168
 - glycolysis, 167
 - Krebs cycle, 168
 - METRO study, 167
 - microvascular dysfunction, 169
 - persistent angina, 168
 - pyruvate, 168
 - refractory angina, 169
- MTD. *See* Maximum tolerance dose (MTD)
- Myocardial infarction (MI)
 - acute, 189, 215
 - BB therapy, 66–68
 - cardiovascular death/hospitalization, 71
 - mortality risk, 167
 - nonfatal, 146
 - stable coronary heart disease, 67–68
- Myocardial ischemia
 - amelioration, 179
 - CMVD (*see* Coronary microvascular dysfunction (CMVD))
 - coronary steal, 10–11
 - differences, 20, 21
 - glycolysis and GO, 158
 - heart rate reduction, 136
 - late Na (INa)
 - current, 178
 - mechanisms, 1
 - Randle cycle, 157–158
 - signs and symptoms, 169
 - silent ischemia, 2
 - stable CAD, 136
 - subendocardial layers, 6
- Myocardial oxygen
 - demand, 1, 3, 6, 21, 80, 89, 138
- Myocardial revascularization, 50, 154
- Myosin light chain (MLC), 116, 117
- Myosin light chain kinase (MLCK), 218
- Myosin light chain phosphatase (MLCPh), 218

N**Na⁺ current (I_{Na})**

- definition, 210
- F15845, 210–212
- intra-myocyte, 177
- mechanistic studies, 175
- ranolazine, 178

The National Institute for health and Clinical Excellence (NICE) guidance

- anti-angina drugs, recommended, 42–45
- guidelines, 37, 38
- nicorandil, use, 123
- oral nitrates, 88
- recommendations, 37

Nicorandil

- anti-angina actions, 116–118
- anti-ischaemic efficacy, 125
- aortic stenosis, 122
- arrhythmias, 121
- cardio-protective mechanisms, 118–119
- CCBs, 123
- coronary spasm, 125–126
- corticosteroids, 122
- dosage, 120
- haemodynamic effects, 119
- headache, 121
- ischaemic preconditioning, 115
- monotherapy, 120
- myocardial ischaemia, 115, 125
- nicotinamide, 116
- pharmacokinetics, 119–120
- placebo-controlled studies, 124

Nitrates

- antianginal agents, 88
- coronary vasodilators, 87
- endoplasmic reticulum, 89, 90
- folic acid, 97
- GTN, 89
- headaches, 104–105
- hydralazine, 97
- hypotension, 105–106

- intermittent nitrate therapy, 95
- myocardial ischaemia, 106
- N-acetylcysteine, 96
- NO formation, 94
- oral nitrates, 88, 107
- oxidative stress, 93
- PETN, 89
- pravastatin and atorvastatin, 97
- rebound angina, 95
- S-nitrosothiols, 93
- statins therapy, 97
- sulfhydryl groups, 94
- systemic hemodynamics, 89–90
- vasoconstrictor responses, 94
- venous system, 87

Nitric oxide (NO) donor, 46, 48, 115**O****Obstructive coronary**

- atherosclerosis
- collateral circulation, 9–10
- dynamic changes, 8–9
- pathophysiology, coronary stenosis (*see* Coronary stenosis)

Optimal medical therapy

- (OMT), 161, 166, 213
- vs.* PCI effects, 240
- post-stent period, 240
- and revascularization, 242, 251
- SIHD patients, 256

Organic nitrates

- acute coronary syndromes, 92
- GTN and PETN, 89
- ischemic preconditioning, 92
- vasodilator effects, 92

P**PCr. *See* Phosphocreatine (PCr)****PDH. *See* Pyruvate dehydrogenase (PDH)****Pentaerythrityl tetranitrate (PETN)**

- GTN therapy, 103

hemeoxygenase I (HO-I), 103
 vasodilator potency, 103
 Percutaneous coronary
 intervention (PCI)
 BARI-2D trials (*see* Bypass
 Angioplasty
 Revascularization
 Investigation 2 Diabetes
 (BARI 2D) trial)
 and CABG, 154, 174
 DES, 244–245
 PRECOMBAT trial, 248
 SYNTAX trail, 245, 246, 248
 CLARIFY registry, 69
 coronary angioplasty, 238–239
 COURAGE trials (*see* Clinical
 Outcomes Utilizing
 Revascularization and
 Aggressive Drug
 Evaluation
 (COURAGE) trial)
 myocardial revascularization,
 50
 pre-stent period
 ACIP study, 239
 ACME, RITA-2 and
 AVERT, 239
 TIME and MASS trials,
 239–240
 stenting, 239
 survival rates, 239, 240
 symptom persistence/
 reoccurrence, 154
 TRPCI, 160
 Phosphocreatine (PCr), 159, 208
 Poiseuille law, 5
 Potassium (K)⁺_{ATP} channel
 opener, 115, 116, 128,
 190–191
 PRECOMBAT trial, 248
 Prescription Event Monitoring
 (PEM) study, 120
 Prinzmetal's variant angina, 12,
 13, 36, 51, 125
 Pyruvate dehydrogenase (PDH),
 157–159, 212

R

Randle cycle, 157–158
 Randomized Evaluation of
 VEGF for
 Angiogenesis
 (REVASC) study, 222
 Ranolazine
 ACE-inhibitors, 173
 adjunctive therapy, 185
 angina pectoris, 173
 anti-anginal drugs, 174
 aspirin, 173
 CARISA study, 181–182
 chronic stable angina, 174,
 184–185
 clinical use, 179
 CYP3A4 inhibitors, 176–177
 death and non-fatal MI, 173
 diastolic ventricular
 relaxation, 179
 dose-response study, 179
 ERICA study, 182–183
 glucose metabolism, 183–184
 ischaemic heart disease, 173
 left ventricular dysfunction, 174
 lipid-lowering therapy, 173
 MARISA study, 180
 mechanism of action, 177–178
 meta-analysis, 183
 non-haemodynamic
 mechanism, 174, 185
 non-pharmacological
 approach, 173
 non-ST-elevation acute
 coronary syndromes,
 180
 PCI and CABG, 174
 pharmacokinetics, 175–176
 pharmacology, 174–175
 safety and tolerability, 176
 sodium and calcium
 homeostasis, 179
 TERISA study, 180–181
 Refractory angina, 51–52, 165, 213
 Renin-angiotensin-aldosterone
 system, 94

REVASC study. *See* Randomized Evaluation of VEGF for Angiogenesis (REVASC) study

Revascularization

- acute MI, 215
- AdVEGF-A₁₂₁, 222
- chronic stable angina, 154
- coronary, 155, 215
- epicardial stenosis, 155
- and hemodynamic drug therapy, 169
- ischemia-guided
 - percutaneous
 - cardiac death rates, 251–252
 - FFR, 253–256
 - MACCE, 252–253
 - non invasive imaging, 251
 - PCIs with drug-eluting stents, 252
- on left ventricular function
 - BARI trial, 249
 - COURAGE nuclear sub study, 249–250
 - LVEF, 249, 250
 - MASS II trial, 249, 250
 - systolic function, 250–251
- maximal medical therapy, 222
- PCI and CABG, 174
- Rho-kinase (ROCK) inhibitor, 15, 218–219

S

- SA. *See* Stable angina (SA)
- Salvia pellet (T89), 198, 215–217
- Second-line agents
 - ivabradine, 48–49
 - long-acting nitrates, 47–48
 - nicorandil, 48
 - ranolazine, 49
 - trimetazidine, 49–50
- Silent ischemia
 - and angina frequency, 101
 - ASIST trial, 66
 - definition, 2

Stable angina (SA)

- and BB, 58, 72
- clinical efficacy, 65–66
- double-blind INITIATIVE trial, 69
- in Europe, 135
- management (*see* Management, stable angina)
- monotherapy, 140
- myocardial infarction, 67
- placebo, 66
- symptomatic
 - treatment, 149

Stable coronary artery disease (SCAD)

- CABG role, 236
- OMT, 235–236
- revascularization
 - ischemia-guided
 - percutaneous, 251
 - in LVEF, 250

Statins

- lipids lowering and pleotropic effects, 40–41
- pravastatin and
 - atorvastatin, 97

Stents

- and angioplasty, 239
- DES, 244–245
- PCI
 - post-stent period, 240–243
 - pre-stent period, 239–240
 - with sirolimus-eluting, 248, 254

Swedish Angina Pectoris Aspirin Trial (SAPAT), 39

Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) trial

- left and right coronary artery, angiography, 245
- MACCE rates, Kaplan-Meier estimation, 246, 247
- score algorithm, 245, 246

T

- Takotsubo disease, 22, 23
- TERISA study. *See* Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) study
- Testosterone, 196–197, 219–220
- Therapeutic angiogenesis, 220, 225
- Thrombosis, 9, 22, 24–25, 160, 215
- Tolerability, ivabradine
 - bradycardia, 139
 - fasting conditions, 138
 - fed conditions, 138–139
 - hepatic impairment, 139
 - ivabradine, 139
 - renal impairment, 139
 - sino-atrial node, 140
- Total Ischemic Burden European Trial (TIBET), 46, 68
- Transdermal nitroglycerin therapy, 94–95
- Transradial coronary artery angiography (TRCAG), 160
- Transradial percutaneous coronary intervention (TRPCI), 160
- Transthoracic echocardiographic Doppler recording (TTE-DR), 19
- Trimetazidine
 - angina patient subgroups, 155
 - anti-angina drug, 161
 - vs.* β -blockers, 156, 163–165
 - B-type natriuretic-peptide level, 166
 - vs.* calcium channel blockers, 156, 164, 165
 - chronic angina, 161
 - CSA, 154
 - elderly and diabetic patients, 165–166
 - endothelial function, 159–161
 - epicardial stenosis, 155
 - failed heart, 166

- fatty acid oxidation inhibition, 158–159
 - glycolytic products, 156
 - ischemic heart disease, 155–156
 - mitochondrial oxidative metabolism, 156
 - monotherapy, 161–163
 - mortality (*see* Mortality, angina patients)
 - myocardial metabolic alterations, in IHD, 157–158
 - myocardial revascularization, 154–155
 - vs.* nitrates, 164–165
 - NYHA functional class, 166
 - pathophysiological mechanism, 155
 - PCI and CABG, 154
 - treatment, 161
 - TRPCI. *See* Transradial percutaneous coronary intervention (TRPCI)
 - Type 2 Diabetes Evaluation of Ranolazine in Subjects With Chronic Stable Angina (TERISA) study, 180–181
- V**
- Vascular endothelial growth factor (VEGF), 201–205, 222, 223
 - Vascular endothelial growth factor in Ischemia for Vascular Angiogenesis (VIVA) trial, 222
 - Vascular smooth muscle cells (VSMCs)
 - beta-2, 58
 - contractile activity, 218
 - HGF, 223
 - HUVECs, 160
 - RhoA-Rho kinase pathway, 218

Vasoconstriction. *See also*
 Coronary artery spasm
 (CAS)
 definition, 12
 fasudil, 218
 intracoronary infusion,
 endothelin-1/fLMP, 17
 and thrombosis, 24
 vasoconstrictor stimuli, 14, 15

Vasodilator
 CCBs, 80
 dipyridamole, 40
 endothelium, 15
 GTN, 46
 nifedipine, 81
 PETN, 103
 trimetazidine, 161

Vasospastic angina
 amlodipine, 83
 benidipine, 84
 diltiazem, 83
 endothelial cell injury, 84
 nifedipine, 83

VEGF. *See* Vascular endothelial
 growth factor (VEGF)

The Veterans Administration
 Cooperative Study, 236

VIVA trial. *See* Vascular
 endothelial growth
 factor in Ischemia for
 Vascular Angiogenesis
 (VIVA) trial

VSMCs. *See* Vascular smooth
 muscle cells (VSMCs)

X

Xanthine oxidase inhibitors
 allopurinol, 207–209
 febuxostat, 209–210

Xanthines, 11, 207

Z

Zotarolimus *vs.* everolimus
 eluting stents, 248