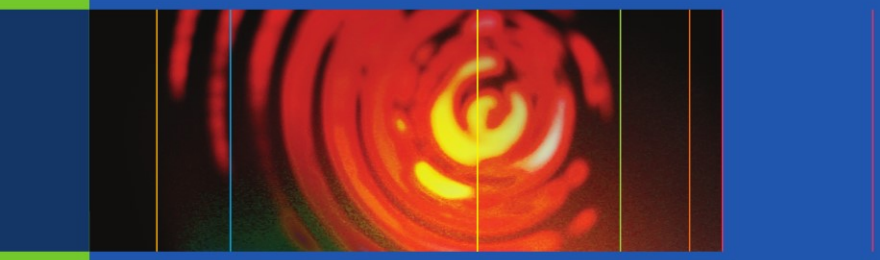
Anthony A. Bavry
Deepak L. Bhatt
Editors



Acute Coronary Syndromes in Clinical Practice

Springer

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To the interventional fellows I have worked with: Drs Chacko, Chhatriwalla, Christofferson, de Oliveiro, Duffy, Filby, Jefferson, Karha, Kelly, Overly, Rajagopal, Shishehbor, and Simpfendorfer. I am honored to have trained with such an exceptionally talented group of individuals.

AAB

To my wife Shanthala and to my sons Vinayak, Arjun, and Ram, for allowing me to spend time at the hospital caring for patients with acute coronary syndromes and at home writing about acute coronary syndromes.

DLB

Contents

Author biographies

Anthony A Bavry MD, MPH, is an Assistant Professor of Medicine at the University of Florida. He received his medical degree from the University of Florida and a masters in public health from Harvard University. He completed his internal medicine residency at the University of Arizona, and general cardiology and interventional cardiology fellowship at the Cleveland Clinic.

Deepak L Bhatt MD, FACC, FSCAI, FESC, FACP, FCCP, FAHA, is Chief of Cardiology of the VA Boston Healthcare System and Director of the Integrated Interventional Cardiovascular Program at Brigham and Women's Hospital and the VA Boston Healthcare System. He is also a Senior Investigator in the TIMI Group and on the faculty of Harvard Medical School.

After graduating as valedictorian from the Boston Latin School, Dr Bhatt obtained his undergraduate science degree as a National Merit Scholar at the Massachusetts Institute of Technology, while also serving as a research associate at Harvard Medical School. He received his medical doctorate from Cornell University. His internship and residency in internal medicine were performed at the Hospital of the University of Pennsylvania, and his cardiovascular training was completed at the Cleveland Clinic. He also completed fellowships in interventional cardiology and cerebral and peripheral vascular intervention, as well as serving as chief interventional fellow at the Cleveland Clinic, where he went on to spend several years as an interventional cardiologist and Associate Professor of Medicine. He served for many years as the Director of the Interventional Cardiology Fellowship and as Associate Director of the Cardiovascular Medicine Fellowship. Dr Bhatt was listed in Best Doctors in America in 2005, 2006, 2007, and 2008.

Dr Bhatt's research interests include preventive cardiology, as well as the optimal management of patients with acute coronary syndromes. He also has research interests in advanced techniques in cardiac, cerebral, and peripheral intervention. He has authored or co-authored over 200 articles, including in *Circulation Research*, *Journal of the American Medical Association*,

Lancet, *Nature Reviews Drug Discovery*, and *New England Journal of Medicine*. He is on the editorial boards of *Acute Coronary Syndromes*, *American Heart Journal*, *Cardiosource* (Associate Editor, Clinical Trials), *CCI*, *Circulation*, *Indian Heart Journal*, *Journal of the American College of Cardiology* (named an Elite Reviewer in 2004, 2005, and 2006), and *Journal of Thrombosis and Thrombolysis*, and is Section Editor of Adjunctive Therapy for the *Journal of Invasive Cardiology*. He is the editor of *Essential Concepts in Cardiovascular Intervention* and *Guide to Peripheral and Cerebrovascular Intervention*, as well as co-editor of the *Handbook of Acute Coronary Syndromes*. He is the international principal investigator for the CHARISMA and CRESCENDO trials and co-principal investigator of the CHAMPION and LANCELOT trials. He serves as the co-chair of the REACH registry. He is also on the steering committees of ARCHIPELAGO, APPRAISE, ATLAS ACS-TIMI 46, CRUSADE, and SEPIA-PCI.

Dr Bhatt has been a visiting lecturer at a number of institutions, including Baylor College of Medicine, Boston University, Emory University, Massachusetts General Hospital/Harvard, Mayo Clinic, Penn State, University of Alabama, University of Massachusetts, University of North Carolina, University of Pennsylvania, University of Virginia, and Yale. He has also lectured internationally, including at the Brazilian Society of Cardiology, French Society of Cardiology, Japanese Society of Thrombosis and Hemostasis, Italian Society of Cardiology, Indonesian Heart Association, McGill University, McMaster University, Montreal Heart Institute, and Swiss Cardiac Society. He has been interviewed extensively by news agencies such as CBS, CNN, FOX, NBC, the *New York Times*, NPR, and the *Wall Street Journal* on topics ranging from premature coronary artery disease to the role of inflammation and genetics in heart attacks.

Preface

Acute coronary syndromes affect millions of individuals annually by causing considerable morbidity and mortality. In developed countries this disease remains the number one killer, despite significant improvements in its management over the last several decades. Acute coronary syndromes are challenging, as the field is a fast moving one with a rapid proliferation of drug and device trials. These new studies become incorporated into separate guideline recommendations by both American and European writing committees, which are frequently updated. Moreover, there are separate guideline recommendations for stable angina, non-ST-elevation acute coronary syndrome, ST-elevation myocardial infarction, and percutaneous coronary intervention. This may make it relatively difficult for practitioners to keep up-to-date with the field. Unfortunately, there is often a gap between the guideline recommendations and the care that is delivered in the 'real world.'

In this book we have attempted to distil the considerable literature on this topic into an accurate, succinct and up-to-date review of acute coronary syndromes. Many specialties are involved in the diagnosis and management of these syndromes; therefore, our audience includes a variety of practitioners: cardiologists, general practitioners, emergency medicine physicians, nurses, nurse practitioners, nursing students, physician trainees, medical students, pharmacists, and paramedics. We take the reader through the epidemiology and prognosis, diagnosis and clinical manifestations, risk stratification, and percutaneous and medical therapies across the entire spectrum of acute coronary syndromes. We end with a discussion on current controversies and future approaches to the treatment of acute coronary syndromes.

In short, we have taken pride and diligence in producing a review that we hope will provide our audience with the necessary knowledge to provide optimal evidence-based care for the acute coronary syndrome patient.

Anthony A Bavry
Deepak L Bhatt

Definition, epidemiology, and prognosis

Cardiovascular disease is an all-encompassing term that includes diseases of the heart and coronary arteries, as well as diseases in other vascular beds. It is a major cause of death and disability in the United States, Europe, and worldwide (*see* Figure 1.1) [1]. Cardiovascular disease that is present in vascular beds outside of the coronary arteries is broadly termed peripheral arterial disease, and patients frequently have disease in such overlapping locations (*see* Figure 1.2) [2]. Examples include carotid and cerebrovascular disease, which are responsible for stroke and transient ischemic attack. Aortoiliac and femoral artery disease are responsible for limb ischemia and claudication. Cardiovascular disease can also manifest itself in stable or unstable forms. Stable coronary artery disease is characterized by stable angina or silent ischemia detected by stress testing, while unstable coronary artery disease (categorized, more generally, as coronary heart disease) includes myocardial infarction and unstable angina. An increasingly used and preferred term for an unstable event is acute coronary syndrome (ACS). ACS encompasses the spectrum from unstable angina to non-ST-elevation myocardial infarction and, finally, ST-elevation myocardial infarction. This

Figure 1.1 Percentage of deaths attributable to cardiovascular disease in the United States

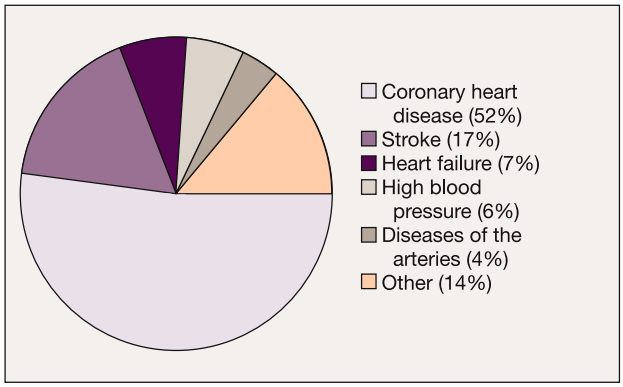

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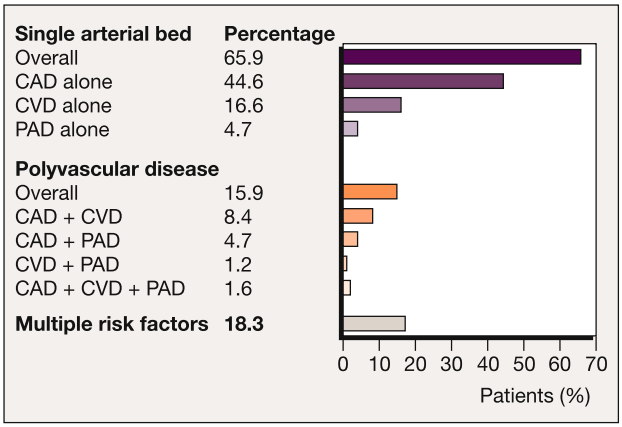
Figure 1.2 Prevalence and overlap of various forms of cardiovascular disease



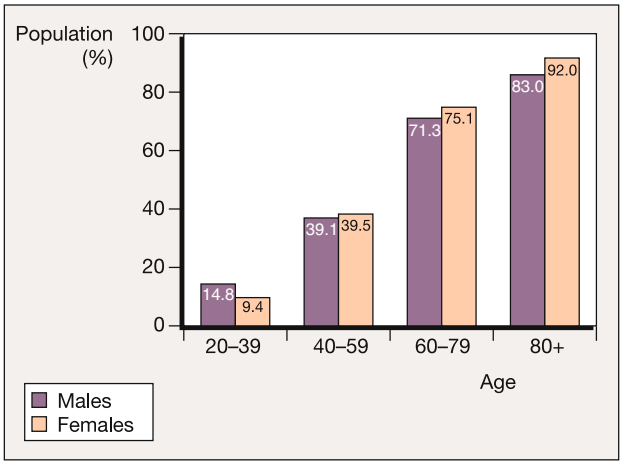
CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease. Reproduced with permission from Bhatt *et al.* [2].

chapter will review the epidemiology and prognosis of cardiovascular disease in general, with a special focus on ACS.

In the United States, cardiovascular disease will affect nearly 80 million individuals at some point in their lives. Approximately one-half of these individuals are 65 years of age or older. In fact, the lifetime risk of cardiovascular disease is more than 70–80% (*see* Figure 1.3) [1]. Globally, approximately 10–15 million individuals die each year from cardiovascular disease, accounting for approximately one-third of all deaths [3,4]. The World Heath Organization (WHO) has projected that the number of deaths attributable to cardiovascular disease will continue to increase to the year 2030, while deaths from communicable causes will continue to decline [5].

There are nearly 8 million Americans who have had a myocardial infarction, with an incidence of approximately 1.5 million ACS per year and nearly 200,000 silent myocardial infarctions per year [1]. Of the ACS, two-thirds are due to unstable angina or non-ST-elevation myocardial infarction, while one-third is due to ST-elevation myocardial infarction. The incidence of ACS, similar to cardiovascular disease in general, increases with advanced

Figure 1.3 Prevalence of cardiovascular disease stratified by age and gender



Data include unstable coronary syndromes (myocardial infarction and unstable angina), heart failure, stroke and hypertension. Reproduced with permission from the AHA [1].

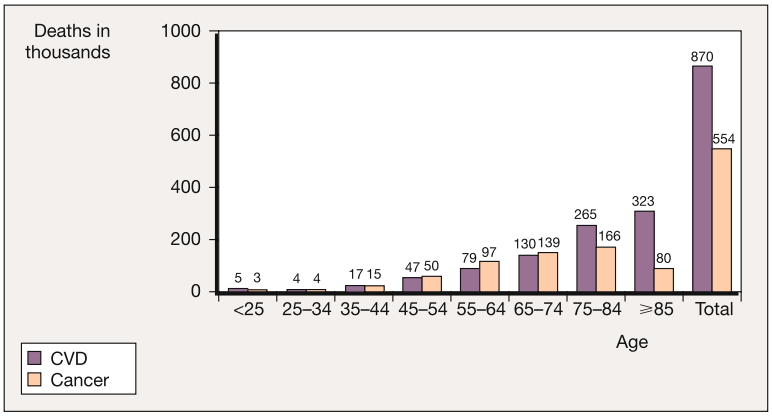
age, so that the mean age of first myocardial infarction is 66 years for men and 70 years for women. Globally, the WHO reported that deaths from cardiovascular diseases are highest for Finnish men and women from the United Kingdom [5].

ACS portends a poor prognosis. It is estimated that myocardial infarction results in 15 years of life lost to the individual, and translates into a 5-year mortality of 50% in patients greater than 70 years of age [1]. Data from a contemporary randomized clinical trial of patients admitted with a non-ST-elevation ACS found 30-day mortality to be 3% and death or myocardial infarction to be 14% [6]. Registry data also revealed the 30-day mortality for non-ST-elevation myocardial infarction to be 5.1%, which was similar to or slightly less than the mortality for ST-elevation myocardial infarction (5.1%), or ST-elevation myocardial infarction with reciprocal ST-depression (6.6%) [7]. In a nonselected population of patients with ST-elevation myocardial infarction undergoing lytic therapy, 30-day mortality may be as high as 10% [8]. Although early outcomes are similar across the ACS spectrum, patients

with non-ST-elevation myocardial infarction have a higher late mortality (8.9% at 6 months), compared with ST-elevation myocardial infarction (6.8% at 6 months) [7]. Not surprisingly, cardiovascular disease is responsible for the most deaths in the United States at a rate of approximately one death every minute (*see* Figure 1.4) [1].

Although the burden of cardiovascular disease is tremendous, mortality from myocardial infarction has been declining for the last several decades after peaking in the early 1970s [9]. In the United States, the death rate from coronary heart disease in men declined from 540 deaths per 100,000 population to 267 deaths per 100,000 population during the period 1980–2000. In women, the death rate declined from 263 deaths per 100,000 population to 134 deaths per 100,000 population over the same time period [10]. It is estimated that approximately half of this reduction is attributable to improved cardiovascular treatments. Examples in acute myocardial infarction include the use of cardiopulmonary resuscitation, aspirin, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, thrombolysis, and primary angioplasty. The use of angioplasty has increased dramatically, although the utilization of this therapy is still far from optimal among eligible individuals [11]. The other half of the reduction in mortality is attributable to cardiovas-

Figure 1.4 Cardiovascular disease deaths compared to cancer deaths stratified by age



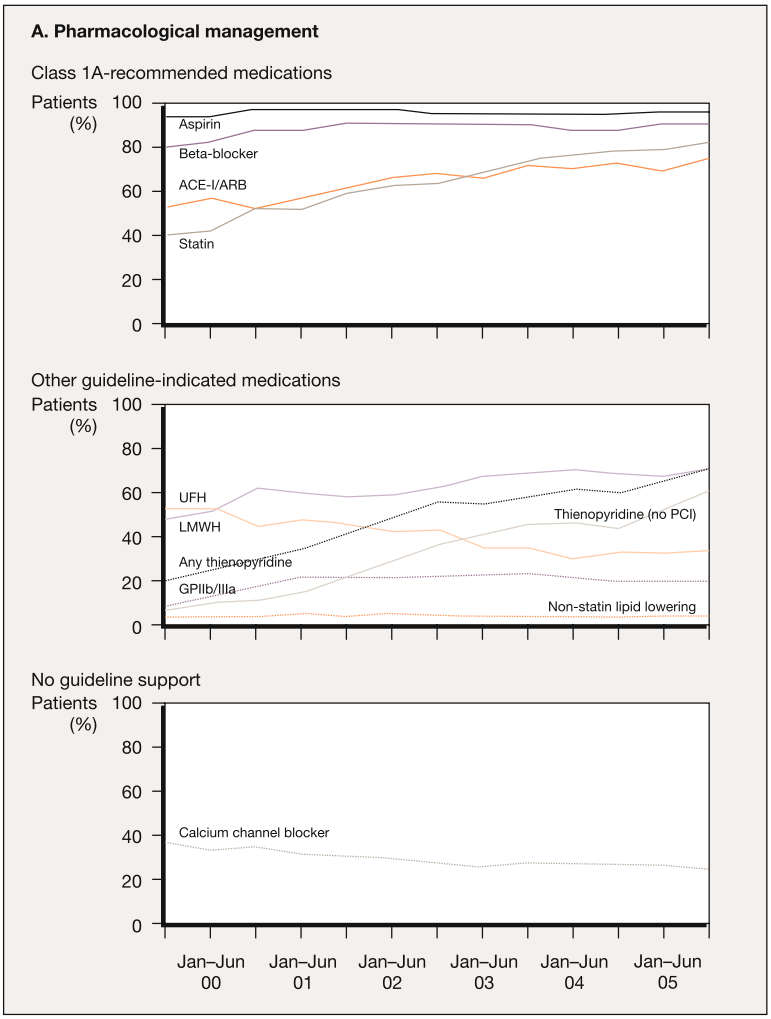
CVD, cardiovascular disease. Reproduced with permission from the AHA [1].

cular risk factor modification. From 1980 to 2000, the prevalence of smoking and physical inactivity was reduced by 32% and 8%, respectively. Systolic blood pressure was reduced by an absolute of 4 mmHg and total cholesterol declined by an absolute of 6 mmol/L. The change in risk factors may have also changed the landscape of ACS since there are now proportionately more non-ST ACS relative to ST-elevation events [12]. Unfortunately, part of this benefit has been offset by increases in diabetes and body mass index. Moreover, the population-wide decline in modifiable risk factors is likely attenuated due to the global underutilization of anti-hypertensive and statin medications [2]. A reduction in coronary mortality has also been documented in other developed countries such as England and Wales [13], Finland [14], and the Netherlands [15]. While this is reassuring, the reality is that more people are living longer with cardiovascular disease after having suffered an acute event [16].

The GRACE (Global Registry of Acute Coronary Events) registry tracks detailed information including cardiovascular outcomes across the spectrum of ACS [17]. From 1999 to 2006 the use of guideline-recommended medications increased among non-ST-elevation myocardial infarction (*see* Figure 1.5) and ST-elevation myocardial infarction (*see* Figure 1.6). The proportion of patients who did not receive any form of revascularization therapy for non-ST-elevation ACS decreased from 69% to 58% ($p<0.001$) due to a significant increase in the use of percutaneous coronary intervention (from 17% to 35%; $p<0.001$). In ST-elevation myocardial infarction, the use of mechanical reperfusion increased from 32% to 64%, while pharmacological reperfusion decreased from 50% to 28%; therefore, the proportion of patients that did not receive any reperfusion therapy remained constant at approximately one-third. Over this follow-up period, early and late death, early myocardial infarction and late stroke were reduced among non-ST-elevation myocardial infarction patients, while, in-hospital death, cardiogenic shock, myocardial infarction and late stroke were reduced among ST-elevation myocardial infarction patients.

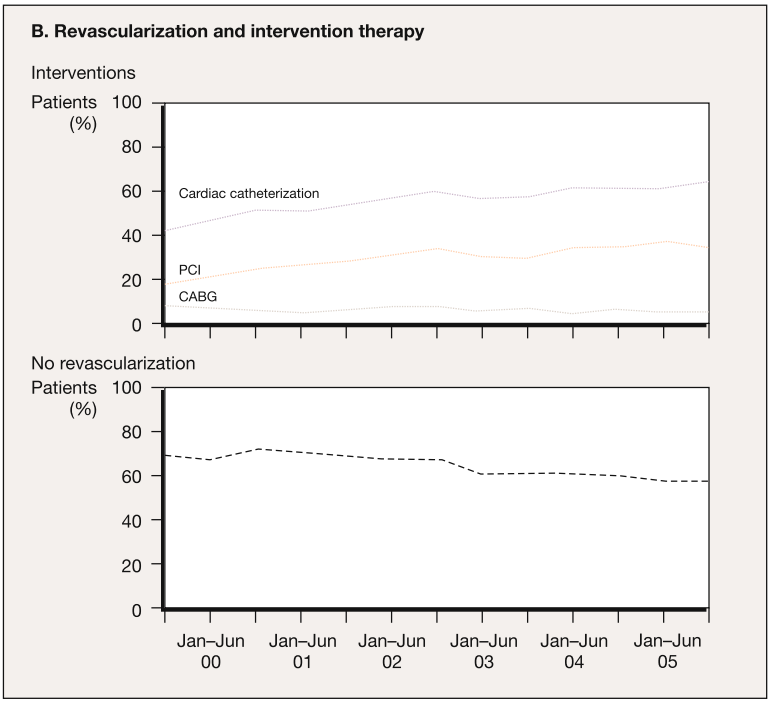
In summary, cardiovascular disease, especially ACS, represents one of the most significant public health priorities across the globe. In the last several decades, improvements have been made in reducing the prevalence of smoking and hypertension, although unfortunately obesity and diabetes have increased during this time. As a result of the change in risk factors, the proportion of ST-elevation myocardial infarction has declined relative

Figure 1.5 The use of guideline-recommended therapies and frequency of revascularization for non-ST-elevation myocardial infarction



ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GP, glycoprotein; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. Reproduced with permission from Fox *et al.* [17].

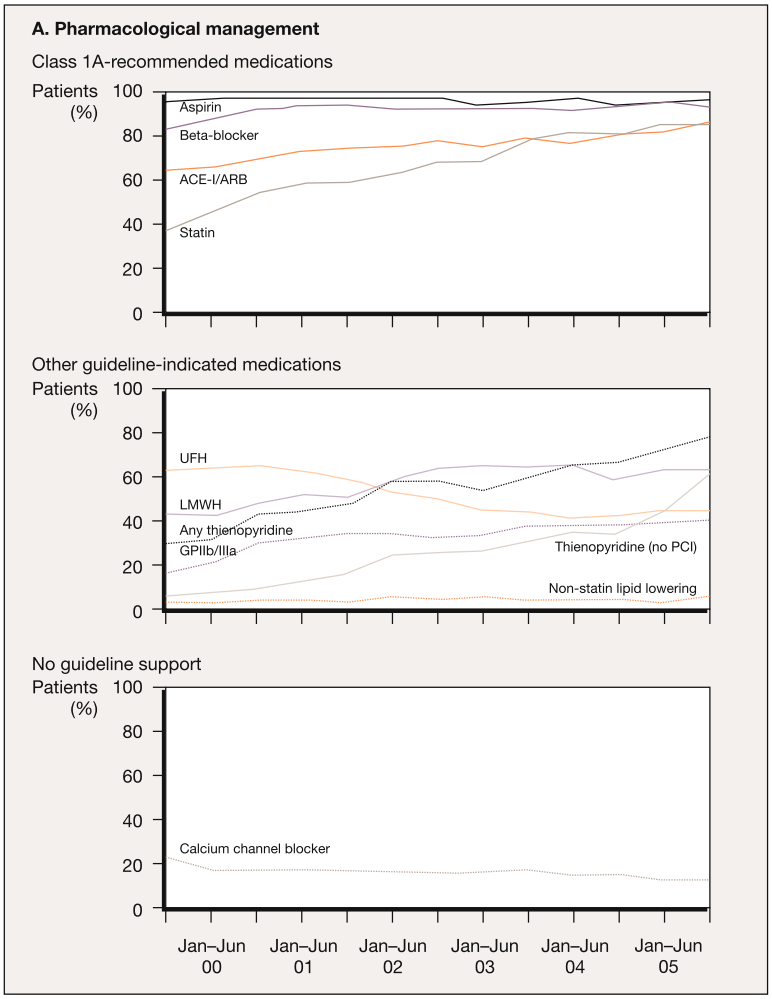
Figure 1.5 *Continued*. The use of guideline-recommended therapies and frequency of revascularization for non-ST-elevation myocardial infarction



CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Reproduced with permission from Fox *et al.* [17].

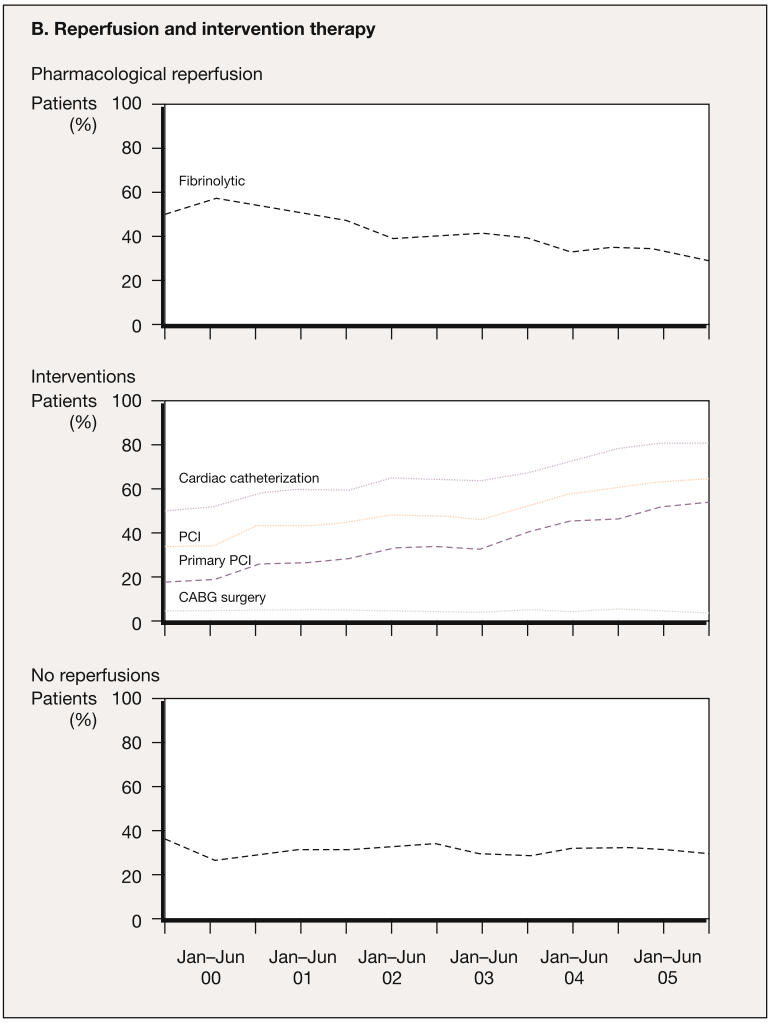
to non-ST-elevation ACS. While this is good, the long-term prognosis of non-ST-elevation ACS remains poor. The last several decades have also seen improvements in reperfusion, revascularization, and adjuvant medical therapies, which have translated into decreased case-fatality for acute myocardial infarction. Thus, while we can applaud the significant achievements that have taken place, there is much room for improvement in the care of ACS patients.

Figure 1.6 The use of guideline-recommended therapies and frequency of mechanical or pharmacological reperfusion for ST-elevation myocardial infarction



ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GP, glycoprotein; LMWH, low-molecular-weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin. Reproduced with permission from Fox *et al.* [17].

Figure 1.6 *Continued*. The use of guideline-recommended therapies and frequency of mechanical or pharmacological reperfusion for ST-elevation myocardial infarction



CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. Reproduced with permission from Fox *et al.* [17].

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Chapter 2

Pathophysiology

This chapter reviews the key elements in the pathophysiology and natural history of atherosclerosis. The interaction between the coagulation cascade and platelet physiology will also be discussed. Our understanding of the complex pathophysiology of atherosclerosis, the coagulation cascade, and platelet physiology is important in order to optimize pharmaceutical and device therapy.

Atherosclerosis

The development of atherosclerosis is influenced by an individual's risk factors: hypertension, hyperlipidemia, diabetes, and smoking. Atherosclerosis progresses over many decades until it is clinically detected [1]. Intimal thickening is present early in life; however, this is not felt to be pathologic. In the second to third decade of life, monocytes infiltrate the subintima. Once in the subintima, monocytes become macrophages, which become foam cells upon the ingestion of cholesterol. This is called a fatty streak or fatty dot and occurs early in the atherosclerotic disease process, although it progresses to an advanced plaque as a necrotic core develops. Expansion of this lipid content into a necrotic core occurs along with degradation of the extracellular matrix by matrix metalloproteinases and other inflammatory cytokines. Hemorrhage from the vasa vasorum may also contribute to the enlargement of the necrotic core. This process is more likely to occur at arterial branch points, which are areas of low shear stress. At this point, a vulnerable plaque may be present, characterized by a large necrotic lipid core underlying a thin fibrous cap. This is also referred to as a thin cap fibroatheroma and it is prone to rupture at its shoulder. The thin fibrous cap is composed of macrophages, lymphocytes, type I collagen, and relatively few smooth muscle cells [2].

Plaque rupture

Plaque rupture is responsible for most causes of sudden death and acute coronary syndromes [3]. Microscopically, plaques that rupture have decreased smooth muscle cells and increased macrophages and inflammatory cells. Macroscopically, vulnerable plaques are usually characterized by expansion of the external elastic media, referred to as positive remodeling,

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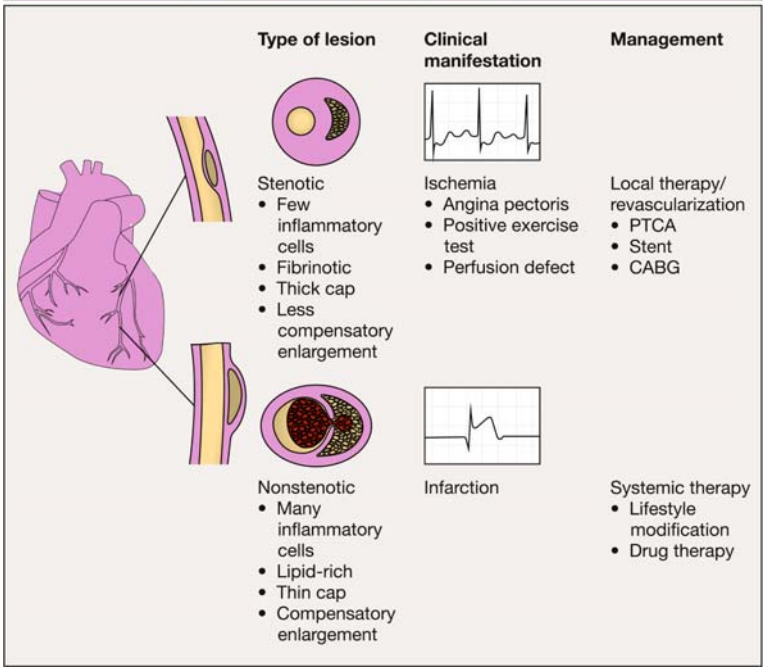
which preserves the luminal area. This is in contrast to patients with stable coronary artery disease who usually display negative remodeling or luminal narrowing. A rupture that leads to coronary occlusion is termed a ST-elevation myocardial infarction, while partial occlusion is a non-ST-elevation acute coronary syndrome (*see* Figure 2.1) [4]. Plaque rupture is more common in older individuals.

Recently, it has been discovered that vulnerable plaques can undergo frequent asymptomatic rupture with healing. Healing is characterized by

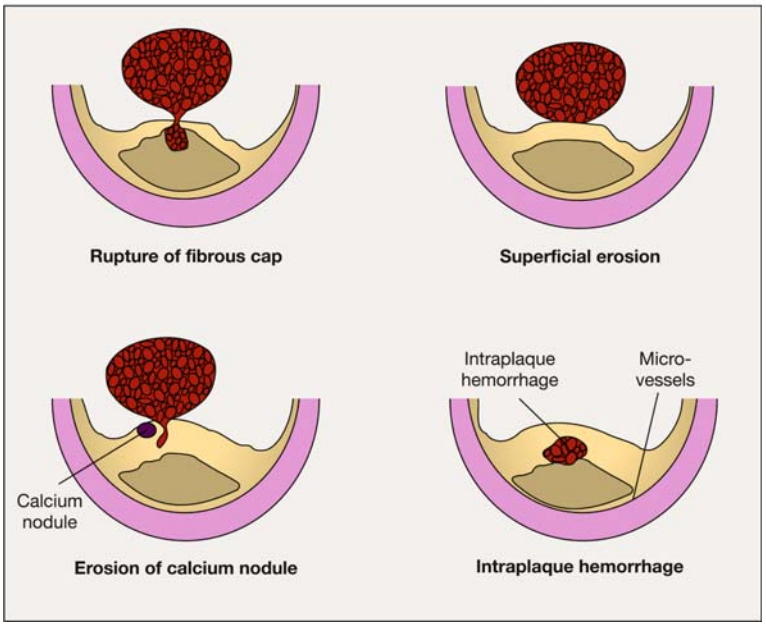
Figure 2.1 Stenotic versus nonstenotic lesions



Stenotic lesions tend to be associated with thick fibrous caps and produce stable angina, while vulnerable plaques have a large lipid cores with thin caps and produce unstable coronary events. CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty, Reprinted with permission from Libby & Theroux [4].

progressive thickening of the fibrous cap. While it is possible that each rupture can be subclinical, over time this process may result in luminal narrowing and cause stable angina [5]. An important finding is that most unstable coronary events originate from nonflow-limiting lesions (e.g., less than 70% stenosis) [6]. The implication is that revascularization of a severe coronary stenosis is usually done with the intent of symptom relief, rather than reduction in myocardial infarction or death. The next most common cause of unstable coronary events is plaque erosion, characterized by increased smooth muscle cells and decreased macrophages. Plaque erosion is frequently seen in younger individuals. The least common cause of an unstable coronary event is a calcified nodule (*see* Figure 2.2) [4].

Figure 2.2 Causes of unstable coronary events



The most common cause of an unstable coronary event is rupture into a vulnerable plaque, although other mechanisms are possible. Reprinted with permission from Libby & Theroux [4].

The coagulation cascade

The coagulation cascade is accelerated on the surface of platelets. This process can be initiated from multiple points; however, binding of the platelet glycoprotein VI receptor to subendothelial collagen is one of the important steps after plaque rupture. This results in platelet adhesion to the subendothelium followed by platelet activation. Fibrinogen mediates the aggregation of activated platelets through the cross-linking of the glycoprotein IIb/IIIa receptor. This is called the final common pathway of platelet aggregation. Glycoprotein IIb/IIIa inhibitors act by preventing the binding of fibrinogen to this receptor. Aspirin blocks cyclooxygenase, which prevents the conversion of arachidonic acid to prostaglandin G_2 and thromboxane A_2. These two agents cause potent platelet aggregation and vasoconstriction. Thienopyridines (e.g., clopidogrel) prevent platelet activation and aggregation by blocking the platelet adenosine diphosphate receptor. Aggregated platelets combine with fibrin to form thrombus. A platelet-rich thrombus forms at areas of high shear stress and is called a white thrombus, while a fibrin-rich thrombus is called a red thrombus. A red thrombus forms at areas of relative hemostasis, and can therefore trap red blood cells within the fibrin mesh. Fibrin is the final product of the coagulation cascade, which is the meeting point of the extrinsic and intrinsic pathways. Exposure of tissue factor after plaque rupture initiates the process that converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. Tissue factor is the main stimulus for thrombin generation after plaque disruption.

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