David R. Brooks

An Introduction to PHP

for Scientists and Engineers

Beyond JavaScript

Springer

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Preface

The best way to become acquainted with a subject is to write a book about it.—Benjamin Disraeli

i. Background

The purpose of this book is provide an introduction to using a server-side programming language to solve some kinds of computing problems that cannot be solved with a client-side language such as JavaScript. The language is PHP (originally created in 1994 by Danish/Icelandic programmer Rasmus Lerdorf as "Personal Home Page Tools" for dealing with his own web site). The PHP language does not have a formal specification, as C does, for example. It is developed and maintained by a User Group of volunteers and is, essentially, defined by the most recently available free download. Although this might seem to be a shaky foundation on which to make a commitment to learning a programming language, PHP has a very large world-wide base of users and applications, which ensures its role into the foreseeable future.

This book should not be considered as a PHP reference source and it does not deal exhaustively even with those elements of the PHP language used in the book. (This should be considered a blessing by the casual programmer.) If you need more information, there is a huge amount of information online about PHP. Hopefully, this book will help you filter this information to focus on solving typical science and engineering problems. An excellent online source for information about PHP is http://www.php.net/manual/en/index.php, maintained by the PHP Documentation Group.[1]

This book is also definitely not intended as an introduction to programming. It is addressed not to professional programmers, actual or potential, but to a technical audience with occasional needs to solve computational problems. It assumes a working knowledge of programming concepts and HTML/JavaScript in particular, such as that provided by my book, *An Introduction to HTML and JavaScript for Scientists and Engineers* (Springer, 2007, ISBN-13: 978-1-84628-656-8,

[1] As with all URL references in this book, this URL was available at the time the book was written, but there can be no guarantee that it will exist in the future.

e-ISBN-13: 978-1-84628-657-5). Occasionally, this book uses examples drawn from the HTML/JavaScript book, but they are presented as stand-alone examples, so you do not need to own the HTML/JavaScript book to use this one.

Although PHP syntax is not that different from JavaScript, the file access syntax will be new to JavaScript programmers who have not previously programmed in a language such as C. C programmers will find there are some similarities between the file access syntax of PHP and C. However, the similarities are sometimes superficial and require that PHP be learned on its own terms, despite the temptation to conclude, "Oh, this works just like C (or JavaScript)."

As is often the case when I learn something new, I had a very specific goal when I started to learn about PHP: I needed to be able to create and access data files stored on a remote server. This is a capability that scientists and engineers always need, but which JavaScript simply cannot provide.

As with other texts I have written over the years, I followed the advice given in the quote at the beginning of this Preface. I wrote the book basically first for myself, and as a result this book will guide you through essentially the same steps I followed. As I began writing it, I had just finished publishing the HTML/JavaScript book mentioned above, so this book starts precisely where the previous one ended—with a knowledge of JavaScript sufficient for writing the online applications I needed, within the limitations of that client-side language.

Chapter 1 deals with the HTML/PHP interface that allows you to pass information from your local computer to a "remote" server, regardless of whether that server is really remote or exists on your own desktop. Chapter 2 deals with the basic elements of the PHP language, from the perspective of someone who is already familiar with programming concepts and JavaScript. If you have no idea what a "for loop" is, you will not be happy with this book!

Chapter 3 deals with arrays, which are a major topic because PHP's implementation of arrays is much richer and more complex than JavaScript's. Chapter 4 presents a summary of some elements of the PHP language used in the book. It is a *very* small subset of the language, but one that I have found meets my own needs. As you begin to apply this language to your own applications, you will no doubt want to make your own additions to my compilation of essentials. Chapter 5 provides a brief introduction to using PHP from a text-based command line interface. This bypasses the need to run PHP on a server and offers some basic facilities for providing user input to a PHP application from the keyboard.

There are many code examples in this book, most of them very short. They are "PHP applications" only in the most primitive sense. Their purpose is to illuminate a specific approach to a particular problem, such as reading a data file or producing properly formatted output. For anyone who, like me, does not make his or her living by programming and does not use a programming language every day, it is very easy to forget the details of how to achieve even simple tasks. I return to my own code examples again and again whenever I need to solve a new computing problem. So, I hope this book and its examples will save you as much time as they do me!

PHP is often used in conjunction with formal databases. However, that topic is not discussed at all in this book. Coming from a C background, I am used to more ad hoc and decidedly more primitive methods of creating and accessing my own data files. The specialized and constantly changing applications I need for my own work would only rarely benefit from a formal database structure.

Another omission that some programmers might find egregious is the lack of any mention of user-defined objects. Again, this is a decision based on my own needs. The additional capabilities that might be provided by creating objects are far outweighed by the practice and programming overhead required to use them correctly and efficiently. I believe this is equally true for this book's intended audience, as well.

A significant benefit of PHP relative to JavaScript is that, from a user's perspective, it appears to be a much more stable language. The language is supported by its own User Group, although it is not possible to predict the future of this support. Rather than being embedded in a browser, as JavaScript is, a PHP programming environment must be downloaded (at no cost) from essentially a single source, so it does not suffer from the many browser-dependent inconsistencies found in HTML/JavaScript.

Finally, a brief comment on the specialized nature of the main example addressed in the first two chapters: I have used it both because it was of interest to me when I first started to write this book and because I believe it represents a generic class of scientific and engineering computing problems. Because there are a lot of calculations, it provides many examples of how to use PHP's math functions; these, of course, are critical in science and engineering applications.

ii. Some typographic conventions used in this book

The code found in documents in this book is always copied directly from the editor used to create them (Visicomm Media's AceHTML freeware

editor), as this is the best way to minimize errors and ensure that the code in the book actually works as intended. This editor displays some language elements in bold and/or italicized font and color-codes them, too. Of course, the color-coding is lost in this book, but the boldface and italicized fonts remain. When code examples in the text are not copied directly from AceHTML code, I have usually not bothered to reproduce that editor's font styles. In any case, those styles, including their presence or absence in the numerous code examples, have no significance relative to the PHP language.

Code and references to code elements in the text, such as function names, are always displayed in `Courier font`. In some code examples, user-supplied text is shown as *{Times Roman text enclosed in curly brackets}*. In some examples, including function parameter lists, variable names are given italicized "generic" names such as *$fileName* which the user can replace with some other application-specific name as needed.

Because of the format of this book, it was sometimes necessary to break lines of code in places where that wouldn't normally be necessary or desirable. I have tried to insert breaks in places where they won't create mischief with the code, but there may remain some cases where line breaks reproduced exactly as they appear in the text may produce a syntax error and prevent a script from executing.

The book contains a glossary with definitions of key terms, and the first appearance of each term appearing in the glossary is printed in **bold font**.

iii. Acknowledgments

I am yet again indebted to my wife Susan for her support and patient editing of this manuscript, especially considering how closely this chore followed my previous book on HTML and JavaScript. In the fall of 2007, I included PHP along with HTML and JavaScript in an introductory programming course I taught to graduate students in Drexel University's School of Biomedical Engineering, Science and Health Systems. Of course, it is always instructive to teach from a manuscript before submitting it, and I thank those students for their feedback!

Finally, I acknowledge relying on descriptions of PHP constructs and functions found online, in particular (but not exclusively) from the online PHP manual written and maintained by the PHP Documentation Group, found at us2.php.net/manual/en/. Especially when a succinct formal definition is available for a function or construct, from a definitive source, it is often difficult and pointless to try to be "original" about how

such a description should be worded. However, I have tried to reword descriptions in a way that is consistent with the coverage provided in this book and with the needs of its intended audience, as I perceive it.

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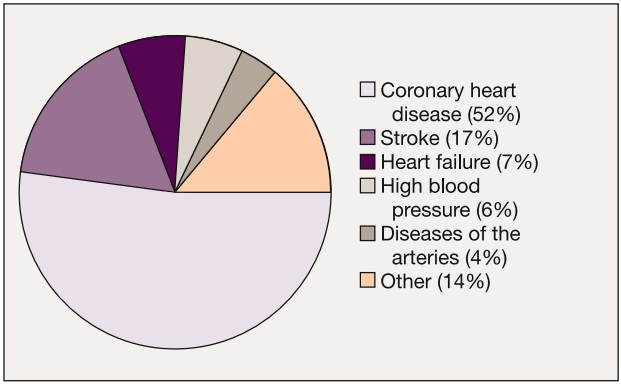
Institute for Earth Science Research and Education
January, 2008

Contents

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



Reproduced with permission from the AHA [1].

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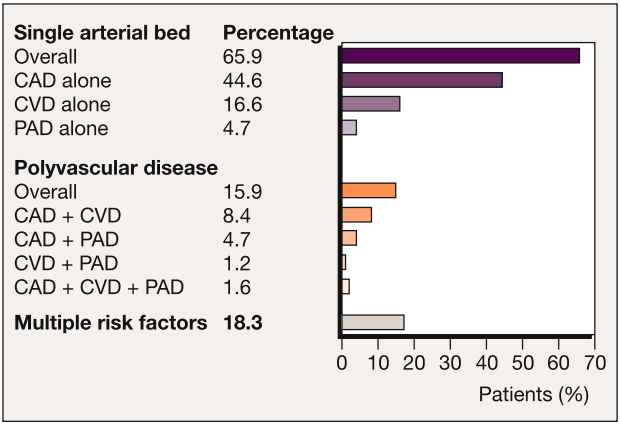
Figure 1.2 Prevalence and overlap of various forms of cardiovascular disease



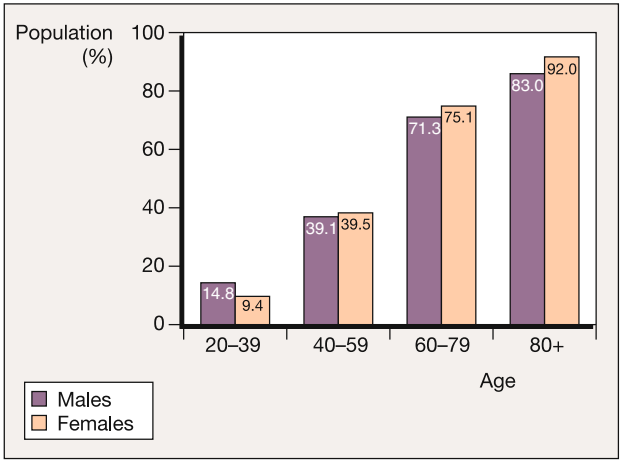
CAD, coronary artery disease; CVD, cerebrovascular disease; PAD, peripheral arterial disease. Reproduced with permission from Bhatt *et al.* [2].

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].

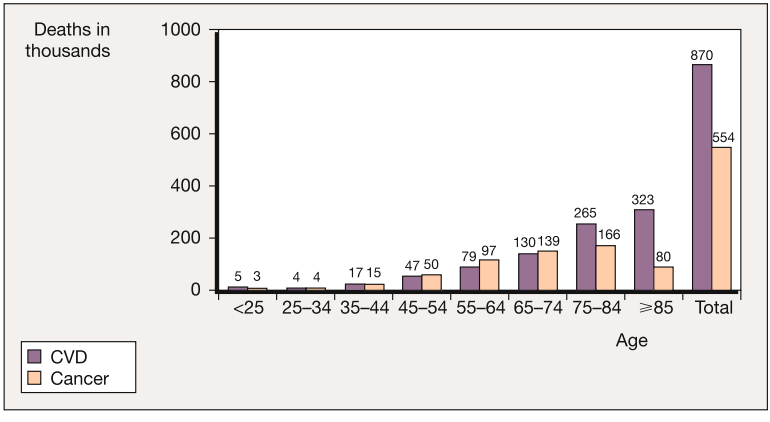
age, so that the mean age of first myocardial infarction is 66 years for men and 70 years for women. Globally, the WHO reported that deaths from cardiovascular diseases are highest for Finnish men and women from the United Kingdom [5].

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



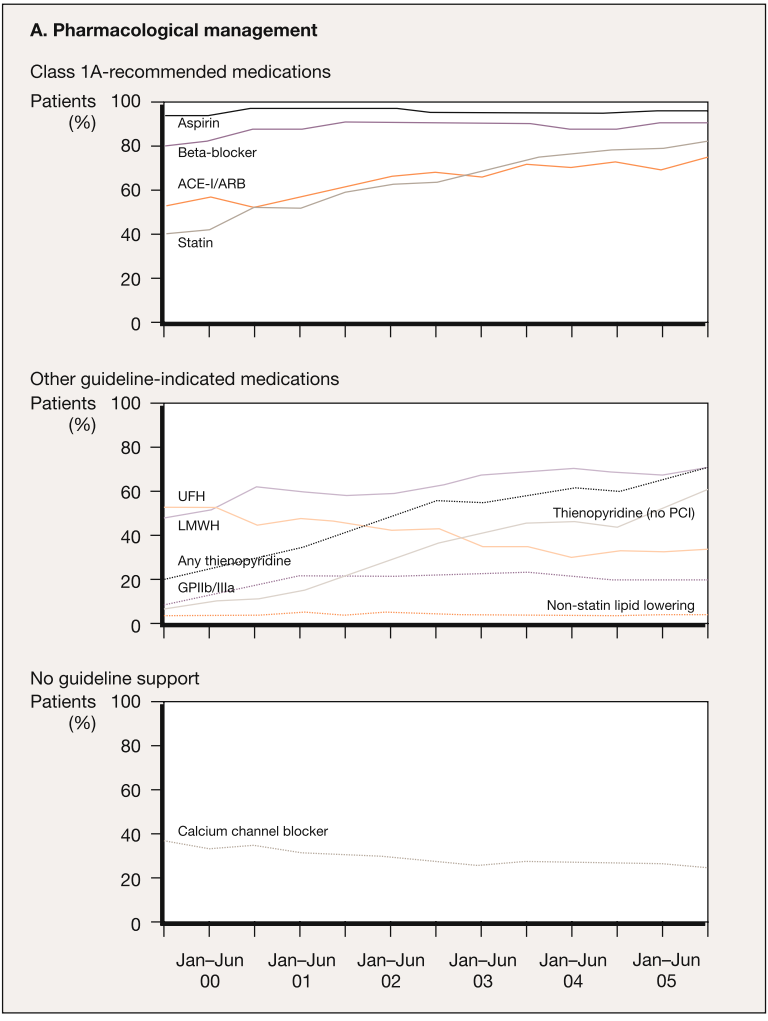
CVD, cardiovascular disease. Reproduced with permission from the AHA [1].

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.

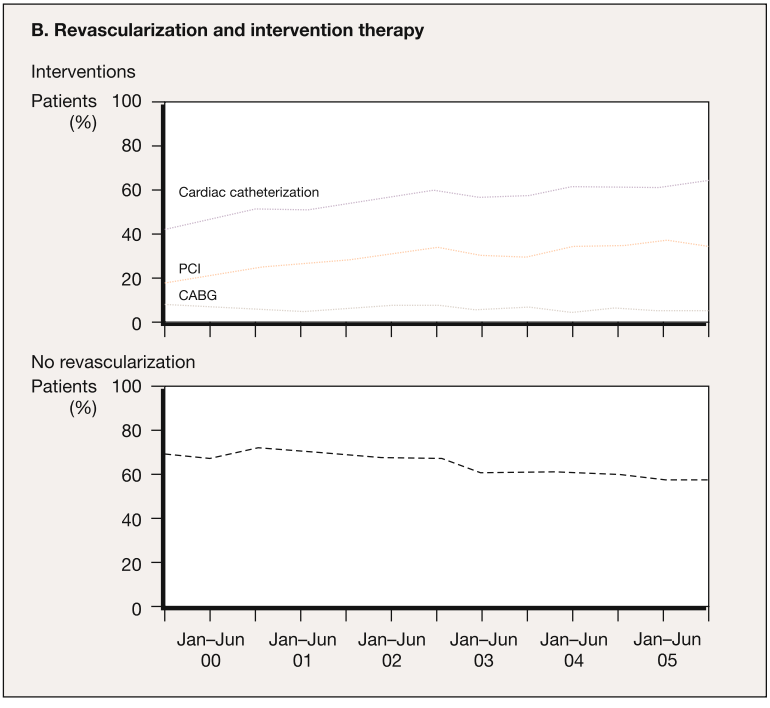
In summary, cardiovascular disease, especially ACS, represents one of the most significant public health priorities across the globe. In the last several decades, improvements have been made in reducing the prevalence of smoking and hypertension, although unfortunately obesity and diabetes have increased 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].

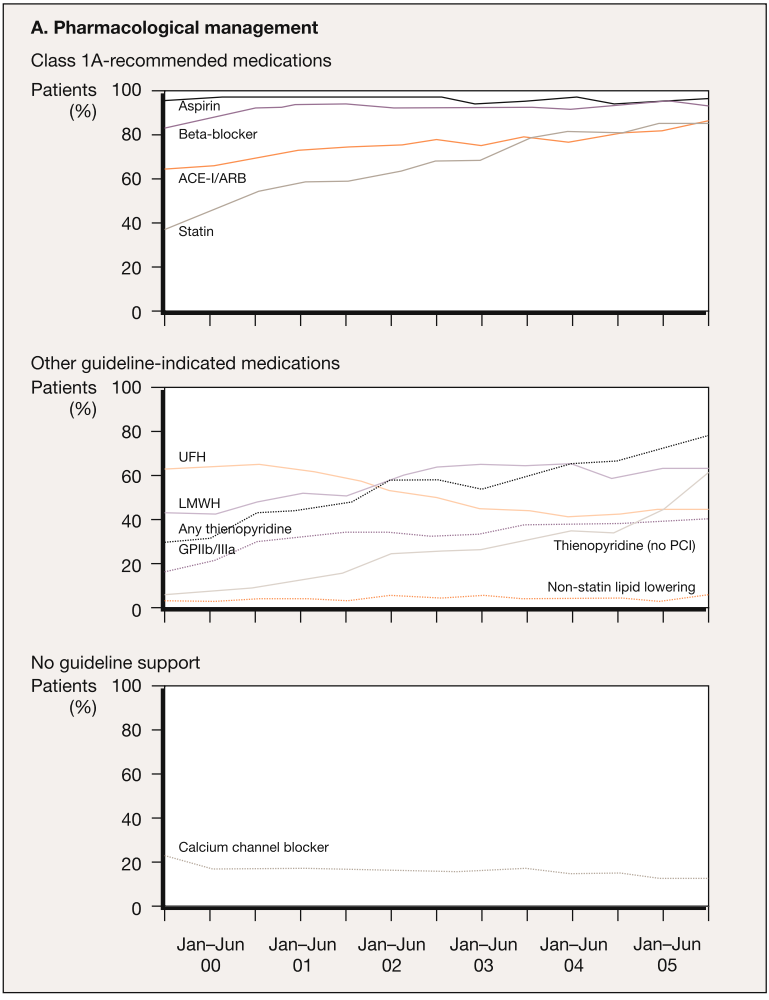
Figure 1.5 *Continued*. The use of guideline-recommended therapies and frequency of revascularization for non-ST-elevation myocardial infarction



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.

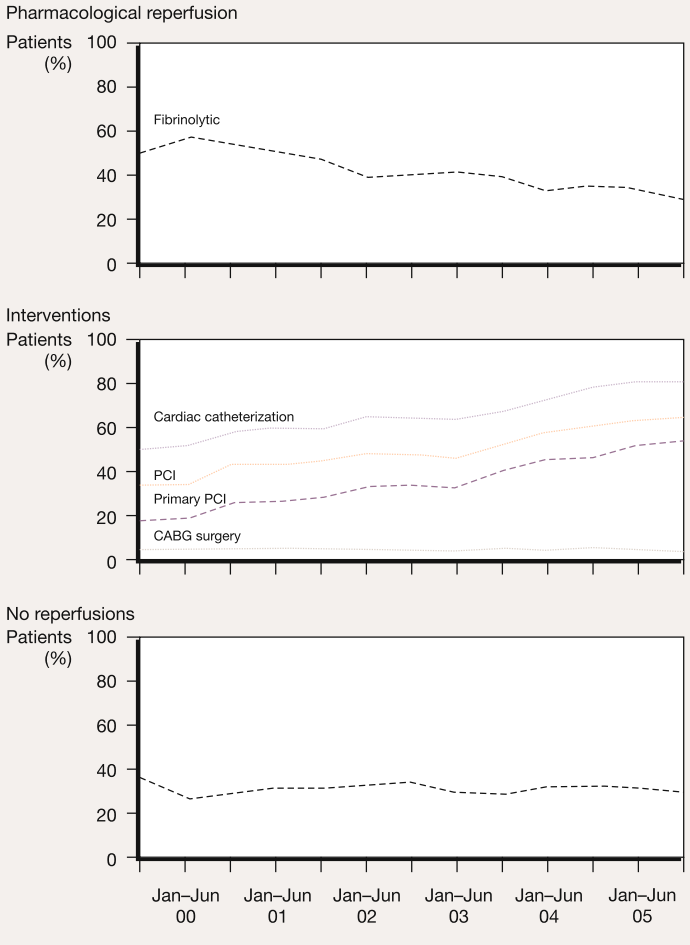
Figure 1.6 The use of guideline-recommended therapies and frequency of mechanical or pharmacological reperfusion for ST-elevation myocardial infarction



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

B. Reperfusion and intervention therapy



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

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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,

A.A. Bavry, D.L. Bhatt (eds.), Acute Coronary Syndromes in Clinical Practice
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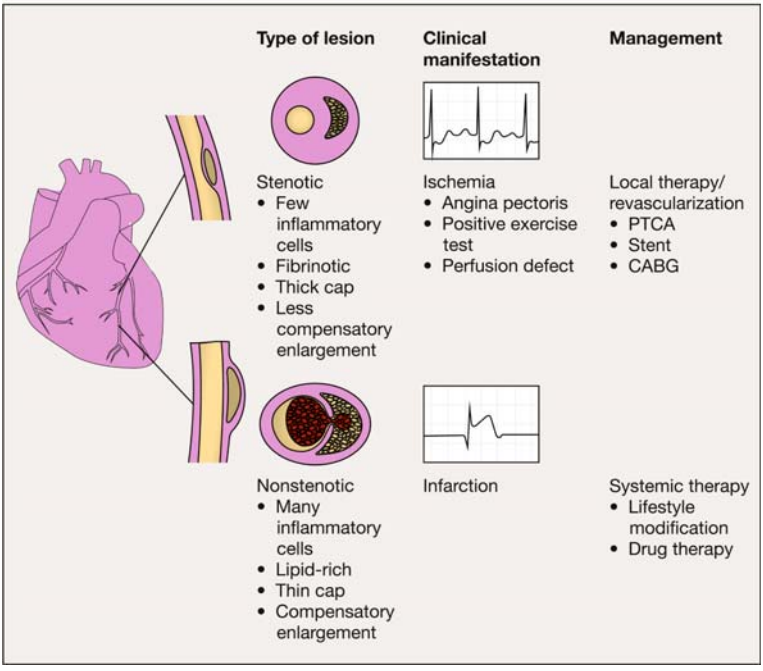
which preserves the luminal area. This is in contrast to patients with stable coronary artery disease who usually display negative remodeling or luminal narrowing. A rupture that leads to coronary occlusion is termed a ST-elevation myocardial infarction, while partial occlusion is a non-ST-elevation 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

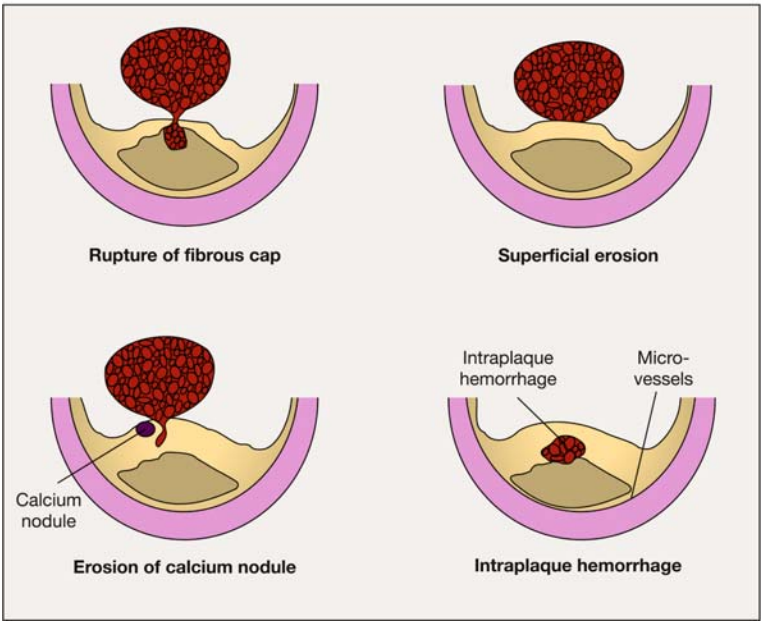
Figure 2.1 Stenotic versus nonstenotic lesions



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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Clinical manifestations

There is a short window of opportunity with ACS, where the prompt establishment of reperfusion therapy dramatically reduces left ventricular dysfunction and improves survival [1]. Accordingly, the initial aim with ACS is to expeditiously make the correct diagnosis. While this may seem overly simplistic, many patients are slow to seek medical attention or there is a long delay in establishing a correct diagnosis. Even when a correct diagnosis is made, delays may exist in bringing optimal therapy to patients who are most in need. Moreover, many patients who present to emergency departments with ACS are incorrectly diagnosed [2]. Attempts to diagnose every case of ACS can lead to excess false positive diagnoses with resultant high healthcare costs and unnecessary patient anxiety [3]. High-risk populations include late presenters, women, people with diabetes, and the elderly, where signs and symptoms of ACS may be protean [4]. Women with typical anginal symptoms and angiographically normal coronaries can still suffer from poor prognosis due to microvascular dysfunction [5]. Additionally, individuals presenting with left bundle branch block or paced rhythms, renal insufficiency, ACS within the peri-operative period and post-myocardial infarction angina are all important populations that require extra vigilance for adverse outcomes. This section will discuss the standard diagnosis of ACS that consists of signs and symptoms, biomarkers, and electrocardiograms, but will also focus on the special populations that need heightened awareness and the different strategies that can be used to make a prompt and accurate diagnosis.

Symptoms and signs

Traditionally, the diagnosis of ACS centers on symptoms, biomarkers and electrocardiograms. Symptoms are one of the most important means by which to make a diagnosis of ACS as they are usually the first opportunity to make the correct diagnosis and initiate prompt therapy. Unfortunately, this is also the area where misdiagnosis can cause a misappropriation of resources and result in poor outcomes. Therefore, it is important that practitioners have a good knowledge of ACS symptomatology [6]. The likelihood that anginal symptoms are attributable to obstructive coronary disease is increased in patients with prior coronary artery revascularization or previously documented coronary

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artery disease. Typical ACS symptoms are described as substernal chest heaviness, although there is great variation beyond this initial brief description that includes the location and quality of angina. Chest pain that is sharp, stabbing or pleuritic is uncommon, although it can be seen in some cases of ACS [7].

While the typical location is substernal, angina can often present on the left side of the chest, as well as partially or entirely in the neck, jaw, shoulder, arm, or back. These varied locations for angina can misdirect the diagnostic workup toward other considerations, including aortic dissection, pulmonary embolus, as well as less serious considerations such as costochondritis or musculoskeletal disorders. Moreover, some patients may present with silent or vague symptoms that can make establishing the correct diagnosis especially problematic. Silent or vague symptoms are usually seen in women, the elderly, and patients with diabetes; therefore, ACS should always be considered early in these groups. Relief of angina with administration of nitroglycerin is felt to increase the likelihood of the presence of obstructive coronary disease, although this agent can also improve noncardiac sources of chest pain [8].

Accompanied signs and symptoms of angina include dyspnea, nausea, diaphoresis, and anxiety, which are generally, although not universally, more common with ST-elevation myocardial infarction. With ST-elevation myocardial infarction, symptoms are not relieved with rest or nitroglycerin. Prompt resolution of ST elevation after administration of nitroglycerin is better categorized as non-ST-elevation myocardial infarction or ACS with transient ST-elevation. This should raise the suspicion of coronary spasm, but intermittent occlusion of a coronary artery instead of a persistent thrombotic occlusion is more likely. An important feature of unstable angina and non-ST-elevation myocardial infarction is that symptoms are new onset and usually present at rest unlike stable angina, where rest and/or nitroglycerin characteristically provide symptom relief. Angina that is exertional in nature may also be categorized as unstable if the symptoms represent a worsening from the patient's baseline [6].

Biomarkers

Biomarkers are important for firmly establishing an accurate diagnosis of ACS. They are also useful for risk stratification and prognostication, which can aid in determining the optimal therapy for a patient. Patients without

elevated biomarkers and no other high-risk features can often be managed in a dedicated chest pain unit [9]. The most commonly used biomarkers include troponin I and T, as well as total creatine kinase (CK) and the myocardial band isoenzyme of CK (CK-MB) [10]. Troponin I and T become elevated 6 hours after ischemic injury, and can remain elevated for 2 weeks. Total and CK-MB isoenzyme become elevated 4–6 hours after ischemic injury and are especially useful for detecting re-infarction. Initially, troponin biomarkers were considered highly specific for ACS; however, various disease states and conditions can also elevate troponin levels (*see* Figure 3.1). A troponin level that is found to be elevated in a clinical context that is unlikely to be an ACS should be interpreted with caution. A common example is minimally elevated troponin in a patient with renal insufficiency in septic shock. In such a situation, minimally elevated troponin may not represent a true ACS, but it still portends a poor prognosis and merits aggressive risk factor modification [11]. In patients with renal insufficiency, CK values (total and CK-MB) can be especially useful for diagnosing and managing ACS. Elevated CK-MB levels in the absence of elevated total CK is associated with a poor prognosis [12]. Myoglobin is also sometimes used, although this biomarker suffers from even poorer specificity relative to the aforementioned enzymes. Therefore, myoglobin values are rarely used alone or in combination with CK and troponin values in making a diagnosis of ACS.

Figure 3.1 Conditions that can cause an elevation in troponin I or T values outside of ACS

- Renal insufficiency
- Pulmonary embolus
- (Myo)pericarditis
- Decompensated heart failure
- Tako-tsubo syndrome
- Coronary vasospasm
- Critical illness, including extensive burns and sepsis
- Cardiac contusion, trauma, and surgery
- Electrical cardioversion/defibrillation
- Electrophysiological procedures, including pulmonary vein isolation and arrhythmia ablation procedures

In ST-elevation myocardial infarction, biomarkers have less of an initial role since the working diagnosis is made by symptoms and electrocardiographic findings. In this population, biomarkers are important to gauge the size of an infarct and to risk stratify the patient after reperfusion. Waiting for cardiac biomarkers to return before making a diagnosis of ST-elevation myocardial infarction and starting reperfusion therapy is harmful and contraindicated. In contrast, cardiac biomarkers can help to risk stratify patients who present with chest pain of unclear etiology. Patients with positive biomarkers constitute a high-risk group relative to negative biomarker patients, and should receive appropriately aggressive therapy. By definition, cardiac biomarkers are negative in unstable angina patients, although dynamic and ischemic electrocardiographic changes should be present. Since unstable angina patients are a relatively high-risk group, in general they should receive the same therapy as non-ST-elevation myocardial infarction patients. A patient initially diagnosed with unstable angina based on symptoms and ischemic electrocardiographic findings, who is later found to have elevated biomarkers should be re-classified as non-ST-elevation myocardial infarction.

Electrocardiogram

The electrocardiogram is a central diagnostic test of cardiology since it is inexpensive, readily available, and provides quick and accurate information to risk stratify patients and direct therapy. However, important caveats to the electrocardiogram should be remembered, such as the differential diagnosis for ST-elevation (*see* Figure 3.2) [13]. Historically, myocardial infarctions were categorized as Q-wave or non-Q-wave events, which are terminal findings in a dynamic and evolving electrocardiographic process. Such an approach takes hours to days to make a diagnosis, at which time the window of opportunity to abort the myocardial infarction has largely passed. Presently, the electrocardiogram is used to rapidly triage patients into ST- or non-ST-elevation ACS pathways. This approach immediately risk stratifies patients and identifies those who urgently need reperfusion therapy. The electrocardiogram should be obtained early in patients who present with silent or vague symptoms. Nausea and fatigue in elderly patients with diabetes might be due to ACS and therefore needs to be diagnosed quickly. The electrocardiogram shows a spectrum of risk where combined ST elevation and depression represents the highest risk [14]. On the lower end of the spectrum are small inverted T-waves, while ST depres-

Figure 3.2 ST-segment elevation in normal circumstances and in various conditions

Condition	Features
Normal (so-called male pattern)	Elevation of 1–3 mm Most marked in V2 Concave Seen in approximately 90% of healthy young men; therefore, normal
Early repolarization	Most marked in V4, with notching at J-point Tall, upright T-waves Reciprocal ST depression in aVR, not in aVL, when limb leads are involved
ST elevation of normal variant	Seen in V3 through V5 with inverted T-waves Short QT, high QRS voltage
Left ventricular hypertrophy	Concave Other features of left ventricular hypertrophy
Left bundle branch block	Concave ST-segment deviation discordant from the QRS
Acute pericarditis	Diffuse ST-segment elevation Reciprocal ST-segment depression in aVR, not in aVL Elevation seldom >5 mm PR-segment depression
Hyperkalemia	Other features of hyperkalemia present: • widened QRS and tall, peaked, tented T-waves • low-amplitude or absent P-waves • ST-segment usually downsloping
Brugada syndrome	rSR' in V1 and V2 ST-segment elevation in V1 and V2, typically downsloping
Pulmonary embolism	Changes simulating myocardial infarction seen often in both inferior and anteroseptal leads
Cardioversion	Striking ST-segment elevation, often >10 mm, but lasting only 1–2 minutes immediately after direct-current shock
Prinzmetal's angina	Same as ST-segment elevation in infarction, but transient
Acute myocardial infarction	ST-segment with a plateau or shoulder or upsloping Reciprocal behavior between aVL and III

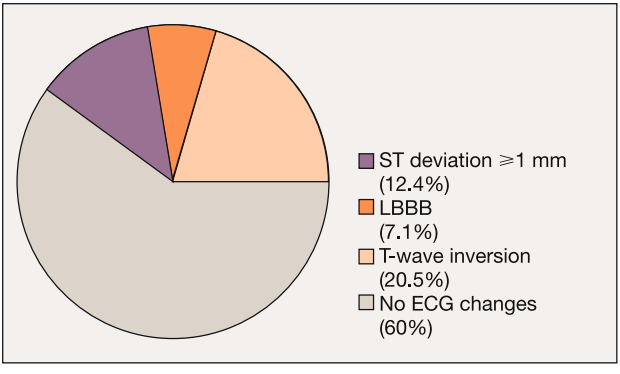
Reproduced with permission from Wang *et al.* [13].

sions are intermediate risk. The magnitude of ST changes as well as the number leads involved are also important. As valuable as the electrocardiogram is, there are special circumstances where it is difficult or impossible to interpret. The electrocardiogram may be negative or nondiagnostic in more than one-half of non-ST-elevation ACS patients (*see* Figure 3.3) [15].

It is still possible to interpret ST changes in patients with right bundle branch block; however, this is much more challenging in patients with a left bundle branch block. Unfortunately, patients who present with a left bundle branch block have worse outcomes when compared with those who have interpretable electrocardiograms. While a left bundle branch block is usually the result of an extensive myocardial infarction, these patients are slow to be diagnosed and therefore experience delays in receiving reperfusion therapy. Other than having a high index of suspicion in patients with a left bundle branch block, there are electrocardiographic criteria that can aid in making the diagnosis of acute myocardial infarction more likely (*see* Figure 3.4) [16]. These consist of:

- 1 mm or more of ST-depression in V1 to V3;
- 5 mm of ST-elevation discordant to the QRS complex;
- 1 mm of ST-elevation concordant to the QRS complex.

Figure 3.3 Proportion of ECG changes among consecutive patients admitted with unstable angina and non-Q-wave myocardial infarction



ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction. Reproduced with permission from Cannon *et al*. [15].

Figure 3.4 Odds ratios and scoring system for predicting myocardial infarction among patients with left bundle branch block

Criterion	Odds ratio (95% CI)	Score
ST-segment elevation ⩾1 mm and concordant with QRS complex	25.2 (11.6–54.7)	5
ST-segment depression ⩾1 mm in lead V1, V2, or V3	6.0 (1.9–19.3)	3
ST-segment elevation ⩾5 mm and discordant with QRS complex	4.3 (1.8–10.6)	2

CI, confidence interval. Reproduced with permission from Sgarbossa *et al.* [16].

Patients with paced rhythms are another group that makes diagnosis of myocardial infarction difficult. In patients who are not pacemaker dependent, the lower rate of the pacemaker can be reset below the patient's native sinus rhythm to allow for interpretation of native ST-segments. While this may help some patients, many will have repolarization abnormalities after reverting to a native sinus rhythm, which still make ST-segments difficult to interpret. Patients with lateral myocardial infarction due to circumflex artery occlusion also deserve special mention since this area can be electrocardiographically silent.

Summary

The diagnosis of ACS patients is critically important in order to improve cardiac outcomes, including patient survival. The art of medicine and the science of diagnostic studies combine to formulate an accurate diagnosis and assess patient risk. Novel biomarkers are under study that may allow even earlier detection of lower thresholds of myonecrosis, while electrocardiograms with greater than 12 leads are also under investigation for the diagnosis of ACS with even more precision.

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Risk stratification

Patients who present with ACS should continually undergo risk stratification throughout their hospitalization. Risk stratification is synonymous with prognosis determination: patients who have the highest risk will also have the poorest prognosis. This process begins at the moment of initial medical contact, proceeds throughout hospitalization and continues thereafter. The process of risk stratification channels intensive medical care to those who are most in need, while reserving more conservative therapy for patients at lower risk. This process is essential since intensive medical care can produce its own side effects. Such side effects may be acceptable in patients at highest risk, although in lower risk populations they will become unattractive.

Risk stratification for ST-elevation myocardial infarction is mainly used to predict prognosis, unlike non-ST-elevation ACS, where risk stratification also helps to guide therapy. For such patients, the decision focuses on deciding if and when invasive therapy through left-heart catheterization and possible revascularization should take place. Patients at low risk will be able to forego invasive therapy and undergo more traditional means of risk stratification, such as stress testing, while the lowest risk patients can usually be managed with early hospital discharge. Risk stratification also identifies which patients will need the most aggressive adjuvant therapies such as anti-platelet and anti-thrombotic medications. ACS are different from stable coronary artery disease in that patients with ACS are at persistently increased risk for recurrent events. Continued risk stratification after stabilization of an ACS therefore works to limit these recurrent events through control of cardiovascular risk factors. The following sections will discuss risk stratification of ACS and focus on popular risk stratification models. Various models are specific to non-ST-elevation ACS, while others apply to ST-elevation myocardial infarction.

Variables, such as electrocardiographic changes and elevated biomarkers, are important, although when used independently they fail to fully predict a patient's risk. For electrocardiographic changes, there is a spectrum of risk where small T-wave inversions predict the lowest risk, and ST-elevation along with areas of depression predict higher risk [1]. Similarly for biomarkers, there is also a spectrum of risk that rises with increasing levels of cardiac biomarkers [2]. Since only looking at one variable may not fully predict

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prognosis, attempts have been made to construct accurate and easy-to-use risk models that incorporate multiple variables.

Non-ST-elevation ACS risk models

The TIMI (Thrombolysis in Myocardial Infarction) risk score is one of the more recognizable scoring systems to assess patient risk [3]. This model was incorporated from the TIMI 11B and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI) trials and is therefore applicable to patients with unstable angina and non-ST-elevation myocardial infarction. The TIMI risk score is also useful in predicting which ACS patients will have a more favorable response to early invasive therapy when compared to medical management. The TACTICS (Treat Angina with Aggrastat and Determine the Cost of Therapy with an Invasive or Conservative Strategy)-TIMI 18 trial identified patients with an intermediate or high TIMI risk score who benefited from early invasive therapy, although the lowest risk patients appeared to do equally well on either approach [4].

The TIMI risk score incorporates seven variables (1 point for each variable) that independently predict a composite of death, myocardial infarction, or urgent revascularization at 14 days. The seven variables used in the scoring system are readily available and therefore allow for quick risk assessment (*see* Figure 4.1). They include the following characteristics [5]:

- age 65 years or greater;
- the presence of three or more traditional risk factors for coronary disease;
- previously documented coronary artery disease (i.e., ⩾50% stenosis);
- the use of aspirin within the last 7 days;
- two or more angina episodes in the previous 24 hours;
- electrocardiographic changes indicative of ischemia;
- elevated cardiac biomarkers.

Patients with the highest risk (seven out of seven variables) have a composite event rate of 40%, compared with an event rate of 4.7% for the lowest risk

Figure 4.1 Variables used to construct the GRACE, TIMI and PURSUIT risk scores

	Risk score
GRACE (0–258)	
Age (years)	
<40	0
40–49	18
50–59	36
60–69	55
70–79	73
⩾80	91
Heart rate (bpm)	
<70	0
70–89	7
90–109	13
110–149	23
150–199	36
⩾200	46
Systolic blood pressure (mmHg)	
<80	63
80–99	58
100–119	47
120–139	37
140–159	26
160–199	11
⩾200	0
Creatinine (mg/dL)	
0–0.39	2
0.4–0.79	5
0.8–1.19	8
1.2–1.59	11
1.6–1.99	14
2–3.99	23
⩾4	31

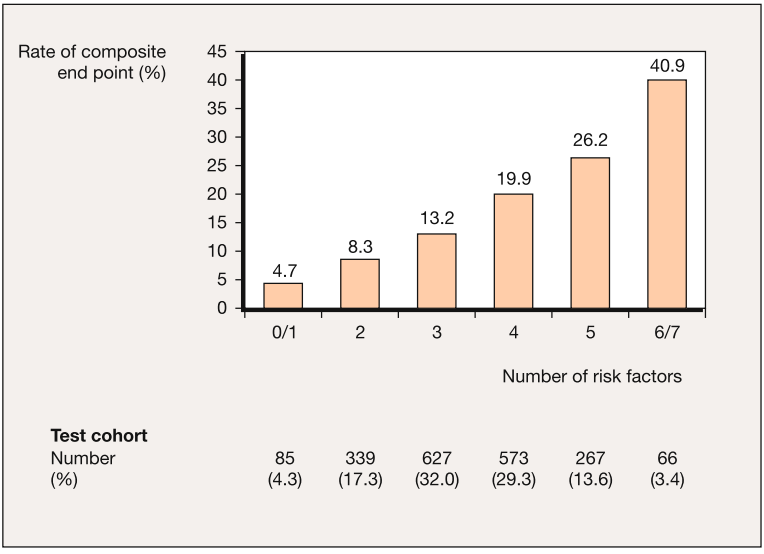
CCS, Canadian Cardiovascular Society Functional Classification of Angina; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; PURSUIT, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina. Reproduced with permission from de Araujo Goncalves [5]. *Continued overleaf*.

Figure 4.1 *Continued*. Variables used to construct the GRACE, TIMI and PURSUIT risk scores

	Risk score
Killip class	
Class I	0
Class II	21
Class III	43
Class IV	64
Cardiac arrest at admission	43
Elevated cardiac markers	64
ST-segment deviation	30
TIMI (0–7)	
Age ⩾65 years	1
⩾3 risk factors for coronary artery disease	1
Use of aspirin (last 7 days)	1
Known coronary artery disease (stenosis ⩾50%)	1
>1 episode of rest angina in <24 hours	1
ST-segment deviation	1
Elevated cardiac markers	1
PURSUIT (0–18)	
Age [separate points for enrollment diagnosis, UA (MI)]	
50–59	8 (11)
60–69	9 (12)
70–79	11 (13)
⩾80	12 (14)
Sex	
Male	1
Female	0
Worst CCS class in previous 6 weeks	
No angina or CCS I/II	0
CCS III/IV	2
Signs of heart failure	2
ST-depression on presenting electrocardiogram	1

patients (*see* Figure 4.2). The incidence of individual outcomes is similarly increased with increased risk scores (*see* Figure 4.3). The TIMI risk score has been validated to be accurate and it is easy to use; however, several important

Figure 4.2 TIMI risk score

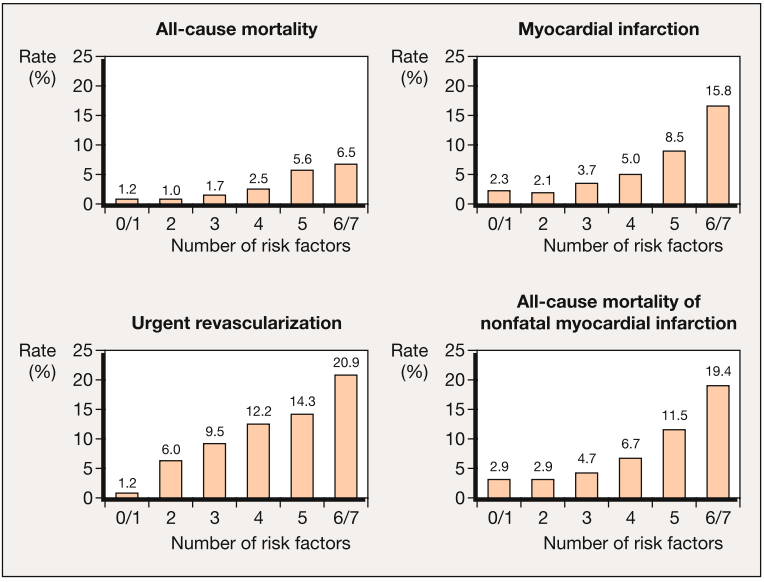


MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction. Reproduced with permission from Antman *et al.* [3].

caveats associated with its use should be highlighted. Patients who present with elevated biomarkers (i.e., non-ST-elevation myocardial infarction) without any other TIMI risk score variables should still receive early invasive therapy, even though this model would have predicted low risk for future events. Accordingly, for this model to effectively predict which patients will benefit from invasive therapy, it is likely best reserved for individuals with unstable angina and those with chest pain of unclear etiology. Among these individuals, the TIMI risk score can provide excellent prognostic information that can be used to determine the degree of anti-platelet and anti-thrombin therapy as well as the need for early invasive therapy. Another concern is that this model does not incorporate heart or renal failure into the scoring system, which are known to be poor prognosticators.

The PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin [eptifibatide] Therapy) trial studied 9461

Figure 4.3 Incidence of individual outcomes based on the TIMI risk score

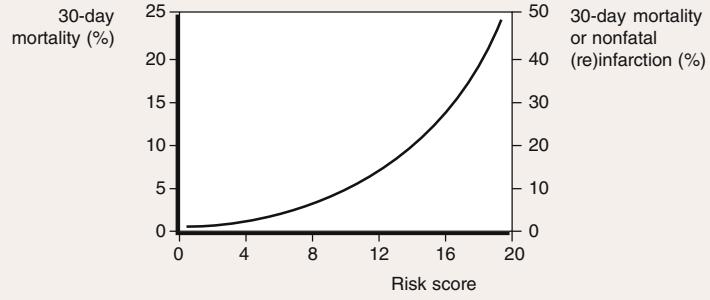


TIMI, Thrombolysis In Myocardial Infarction. Reproduced with permission from Antman *et al.* [3].

patients with non-ST-elevation ACS. This trial was used to construct the PURSUIT risk score that predicts death as well as death or myocardial infarction at 30 days (*see* Figure 4.4) [6]. A strength of the PURSUIT scoring system is that unlike the TIMI risk score, heart failure is included as an important prognosticator (*see* Figure 4.1) [5].

The GRACE (Global Registry of Acute Coronary Events) registry enrolled 11,389 patients across the spectrum of ACS, including ST-elevation myocardial infarction. This registry was used to construct the GRACE risk score, which predicts in-hospital adverse cardiac events through the use of eight variables (*see* Figure 4.5) [7]. Similar to the TIMI and PURSUIT risk models, GRACE incorporates advanced age and signs of heart failure, but it is unique in that it additionally adds renal insufficiency as an important prognosticator of risk (*see* Figure 4.1) [5]. This model is somewhat more cumbersome than the TIMI risk model in that there is a wide range of possible points for each variable.

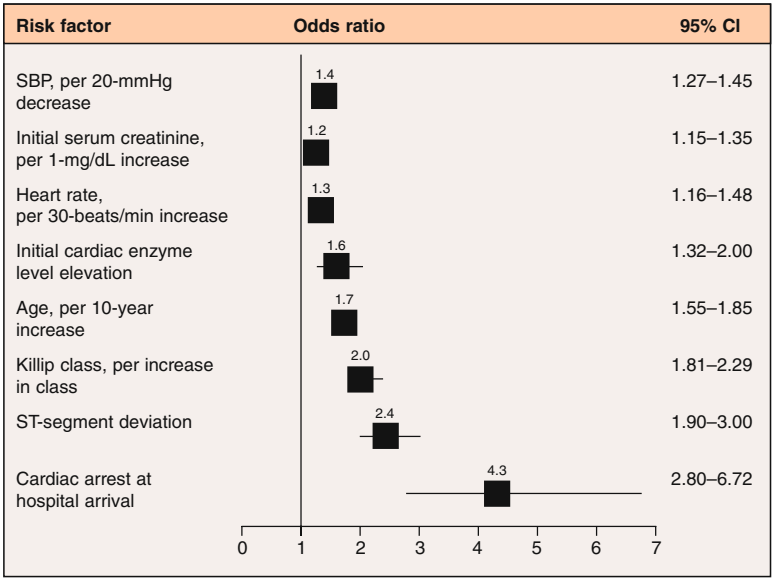
Figure 4.4 PURSUIT risk score for predicting short-term adverse outcomes among patients with non-ST-elevation ACS



	Score	
	Mortality only	Mortality or infarction
Age		
50	0	8 (11)
60	2(3)	9 (12)
70	4 (6)	11 (13)
80	6 (9)	12 (14)
Gender		
Female	0	0
Male	1	1
Worst CCS-class in previous 6 weeks		
No angina; I or II	0	0
III or IV	2	2
Heart rate (bpm)		
80	0	0
100	1 (2)	0
120	2 (5)	0
Systolic blood pressure (mmHg)		
No	0	0
Yes	3	1
Signs of heart failure (rales)		
No	0	0
Yes	3	2
ST depression on presenting ECG		
No	0	0
Yes	3	1

bpm, beats per minute; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; PURSUIT, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. Reproduced with permission from Boersma *et al.* [6].

Figure 4.5 Prediction of in-hospital mortality across the spectrum of ACS according to various risk factors



CI, confidence interval; SBP, systolic blood pressure. Reproduced with permission from Granger *et al.* [7].

The TIMI, PURSUIT and GRACE models have been compared to each other for their ability to predict short-term as well as long-term adverse events [5]. All three models were found to have good discriminatory ability in the short term, which is not surprising since this is the time period for which they were designed to predict. There were differences, however, in the discriminative ability of these models to predict long-term events. The GRACE model was found to most accurately predict long-term events, which may be due to the inclusion of renal insufficiency as an important prognosticator. Similar to the analysis from the TACTICS-TIMI 18 trial, patients with the highest risk were found to derive the most benefit from invasive therapy.

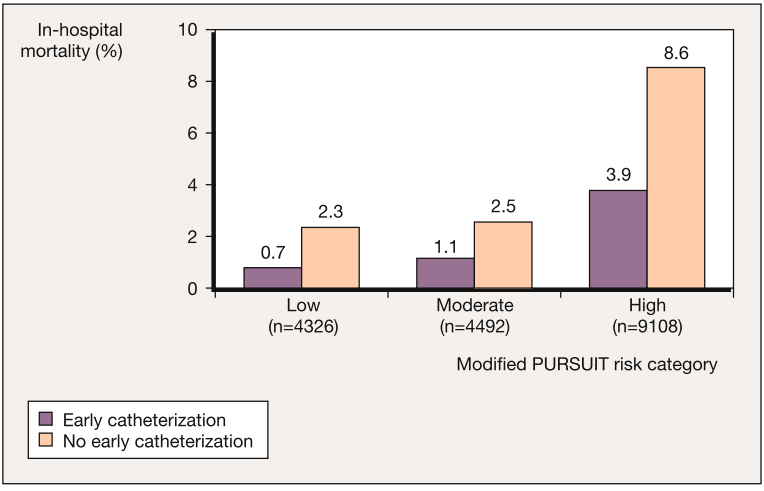
In the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA

Guidelines) registry, fewer than 50% of the patients with an ACS underwent invasive therapy within 48 hours of hospital presentation. Patients who underwent early invasive therapy were shown to have improved survival (*see* Figure 4.6) [8,9]. Unfortunately, research has shown that patients with the poorest prognosis are less likely to receive invasive therapy even though they are most in need of it (*see* Figure 4.7) [10]. For example among non-ST-elevation ACS, 40% of the lowest risk patients received percutaneous coronary intervention in contrast to 25% of the highest risk patients.

ST-elevation risk models

As mentioned previously, the GRACE risk score can be applied across the spectrum of ACS; however, there are additional models designed specifically for ST-elevation myocardial infarction. One of the earliest models of risk stratification within the modern era of reperfusion therapy for acute myocardial

Figure 4.6 In-hospital mortality rates stratified by time to catheterization among risk categories determined from presenting clinical characteristics



PURSUIT, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy. Reproduced with permission from Bhatt *et al*. [9].

Figure 4.7 The management of patients with ACS based on their GRACE risk score

	Unstable angina/NSTEMI				STEMI			
	Low risk	Medium risk	High risk	*p*-value	Low risk	Medium risk	High risk	*p*-value
Number	3944	5440	5704		4119	2623	2359	
Cardiac catheterization	2836 (72%)	3689 (68%)	2894 (51%)	<0.001	3236 (79%)	1937 (74%)	1342 (57%)	<0.001
PCI	1554 (40%)	1907 (35%)	1426 (25%)	<0.001	2466 (60%)	1421 (54%)	959 (41%)	0.98
CABG	298 (7.6%)	425 (7.9%)	361 (6.4%)	0.006	162 (4.0%)	108 (4.2%)	86 (3.7%)	0.67
Fibrinolytics	113 (2.9%)	103 (1.9%)	108 (1.9%)	0.001	1538 (38%)	828 (32%)	445 (19%)	<0.001
Exercise tolerance test	977 (25%)	1205 (23%)	915 (16%)	<0.001	807 (20%)	414 (16%)	238 (10%)	<0.001
Echocardiography	2096 (54%)	2784 (52%)	3250 (58%)	<0.001	2985 (74%)	1982 (76%)	1815 (78%)	0.002
In-hospital drugs								
Aspirin	3705 (94%)	5080 (93%)	5136 (90%)	<0.001	3948 (96%)	2490 (95%)	2147 (91%)	<0.001
Thienopyridine	2009 (52%)	2627 (49%)	2292 (41%)	<0.001	2543 (62%)	1485 (57%)	1013 (44%)	<0.001
UFH	1956 (50%)	2496 (47%)	2627 (47%)	0.001	2552 (63%)	1527 (59%)	1280 (55%)	<0.001
LMWH	2263 (58%)	3145 (58%)	3160 (56%)	0.016	2052 (50%)	1447 (56%)	1251 (54%)	<0.001
GPIIb/IIIa inhibitor	1008 (26%)	1197 (22%)	1002 (18%)	<0.001	1669 (41%)	914 (35%)	659 (28%)	0.099
ACE inhibitor	2157 (55%)	2911 (54%)	3234 (57%)	0.004	2796 (68%)	1861 (71%)	1589 (68%)	0.01
Beta-blocker	3352 (85%)	4533 (84%)	4251 (75%)	<0.001	3706 (90%)	2217 (85%)	1615 (69%)	<0.001
Calcium antagonist	1120 (29%)	1745 (32%)	1936 (34%)	<0.001	578 (14%)	490 (19%)	425 (18%)	<0.001

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; GP, glycoprotein; GRACE, GLobal Registry of Acute Coronary Events; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; UFH, unfractionated heparin. Reproduced with permission from Fox *et al.* [10].

infarction came from the GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial [11]. This landmark trial examined the effect of various thrombolytic regimens on patients with ST-elevation myocardial infarction. This model showed that five variables can predict 90% of patient mortality at 30 days. These variables include:

- advanced age (i.e., greater than 75 years);
- Killip class III or IV heart failure;
- low systolic blood pressure;
- elevated heart rate;
- anterior myocardial infarction.

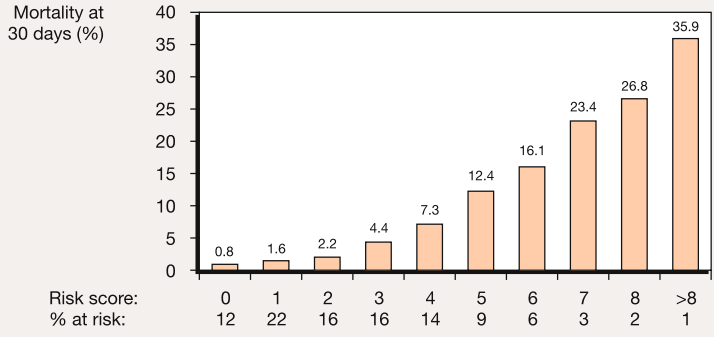
Of these variables, age is the strongest predictor of mortality. Patients younger than 45 years of age have a mortality of 1.1%, compared with 20.5% for patients older than 75 years. The theme of advanced age and hemodynamic instability as strong predictors of mortality and adverse events is also seen in more recent risk models.

The TIMI risk score for ST-elevation myocardial infarction accurately predicts 30-day mortality through the use of eight variables. Mortality among the lowest risk patients is less than 1%, although it is as high as 36% among the highest risk patients. Just as in the non-ST-elevation risk models, age and signs of heart failure predict most of the risk, although the location of the event (i.e., anterior myocardial infarction), low body weight (i.e., <67 kg), and a delay in time until treatment (i.e., >4 hours) are also important (*see* Figure 4.8) [12].

Given the emergent nature of ST-elevation myocardial infarction, a complete risk assessment that requires the assessment of multiple variables may be somewhat problematic. A pared down risk score with only three variables has recently been proposed [13], although this may not be ideal in all circumstances [14]. The three variables are: advanced age (i.e., greater than 80 years), presence of cardiogenic shock, and presence of heart failure.

Patients with ACS are not only at risk for short-term events, but they are also at increased risk for future events. The index hospitalization is an excellent opportunity to emphasize risk-factor modification, healthy diet, and exercise, which together can act to reduce these late events. Pharmacologically, it is now appreciated that the initiation of statin therapy

Figure 4.8 TIMI risk score for STEMI for predicting 30-day mortality



1. Age 65–74/≥75 years	2/3 points
2. Systolic blood pressure <100 mmHg	3 points
3. Heart rate >100 bpm	2 points
4. Killip II–IV	2 points
5. Anterior STE or LBBB	1 point
6. Diabetes, h/o HTN, or h/o angina	1 point
7. Weight <67 kg	1 point
8. Time to treatment >4 hours	1 point
Risk score	**0–14 possible points**

h/o, history of; HTN, hypertension; LBBB, left bundle branch block; STE, ST-elevation; STEMI, ST-elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction. Reproduced with permission from Morrow *et al.* [12].

during hospitalization and its continued use is associated with improved survival as well as reduced episodes of unstable angina and need for revascularization [15].

Summary

There is no perfect risk score for ACS since there is a balance between being comprehensive and completely predictive of risk versus being quick and

simple, which may be accurate, although lack in discriminative ability. For non-ST-elevation ACS, the TIMI, PURSUIT and GRACE models all work well in predicting risk in the short term. The TIMI risk score is the easiest to use and can be committed to memory or referenced with a pocket card, although this model does not incorporate important variables such as heart failure and renal insufficiency. For finer estimation of risk, the GRACE score performs very well, especially for the prediction of long-term events. For ST-elevation myocardial infarction, both the TIMI and GUSTO risk scores are excellent, although if time does not allow for complete risk assessment, age and signs of cardiogenic shock or heart failure provide a good snapshot of risk.

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Anti-platelet therapies

Anti-platelet drugs are one of the fundamental therapies for improving cardiovascular outcomes among ACS patients. Medications are used adjunctively along with mechanical or chemical reperfusion. Patients who are not candidates for revascularization may only receive medical treatment for their ACS. Cardiovascular drugs are given with the expectation that they will produce a significant beneficial effect. For some drugs in certain groups of patients, the goal is to improve survival and reduce infarct size, while for other drugs the goal is the amelioration of ischemic symptoms. Drugs, like aspirin, are widely used across the spectrum of ACS, although other agents like fibrinolytics are only used in ST-elevation myocardial infarction. It is also important to understand that each drug comes with the potential for side effects. Accordingly, the risk–benefit profile for each cardiovascular drug should be known, and the side effects minimized where possible. For some patients, the risk of a drug will outweigh its expected benefit, and should therefore not be used. This chapter will review the important anti-platelet cardiovascular drugs across the spectrum of ACS and emphasize the benefits and side effects of each agent.

Aspirin

Aspirin is the unequivocal cornerstone of cardiovascular drugs. This agent acts by irreversibly blocking platelet cyclooxygenase, which subsequently blocks thromboxane A_2 production. It is also one of the most widely studied agents. The Anti-Platelet Trialists' Collaboration studied the use of aspirin for the secondary prevention of cardiovascular events in over 100,000 patients with various forms of vascular disease [1]. Among acute myocardial infarction patients, the use of aspirin results in a 33% reduction in vascular events [1] and a 25% reduction in vascular death [2] when compared to placebo. This analysis also found that aspirin benefits patients who had remote myocardial infarction, as well as patients with stable or unstable angina, peripheral arterial disease, or history of transient ischemic attack or stroke, although low-risk patients did not clearly benefit [1]. Other findings from this analysis were that low-dose aspirin (i.e., 75–150 mg/day) is effective [1], which supports the current recommendation of low-dose aspirin for chronic therapy.

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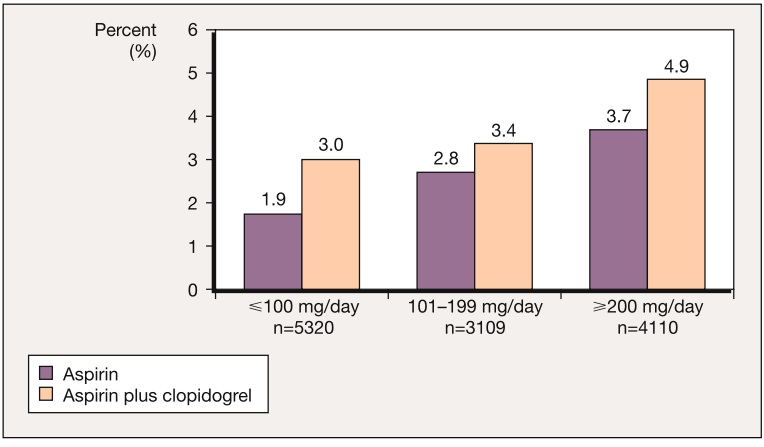
Aspirin can result in serious bleeding in a significant proportion of patients. An important substudy from the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial studied the effect of various doses of aspirin [3]. This study found that major bleeding was associated with increased doses of chronic aspirin (i.e., greater than 200 mg versus less than 100 mg) whether aspirin was used alone or in combination with clopidogrel (*see* Figure 5.1). Additionally, there was some suggestion of potentially diminished efficacy with increasing doses of chronic aspirin.

Aspirin recommendation

Patients across the spectrum of ACS, from unstable angina to ST-elevation myocardial infarction, should receive 162–325 mg/day of aspirin upon hospital presentation [4,5]. Low-dose (i.e., 75–162 mg/day) should be used long term to minimize bleeding complications. New guidelines recommend aspirin 162–325 mg/day among patients who receive a coronary stent (3 months for a sirolimus stent and 6 months for a paclitaxel stent), then decrease to 75–162 mg/day [4,6]. The use of ibuprofen is discouraged due to an interaction with aspirin; however, if this medicine is used it should be given at least 8 hours before or 30 minutes after the administration of aspirin [4].

Figure 5.1 Incidence of major bleeding according to aspirin dose among patients with ACS

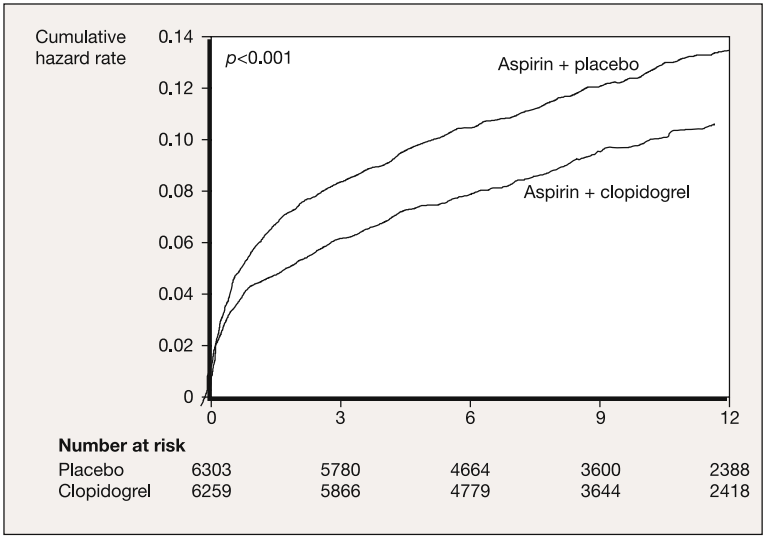


Reproduced with permission from Peters *et al.* [3].

Clopidogrel

Clopidogrel is a relatively new cardiovascular agent that acts by irreversibly blocking the platelet adenosine diphosphate (ADP) receptor, thus preventing platelet aggregation. The CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) trial documented the superiority of clopidogrel compared with aspirin in nearly 20,000 patients with vascular disease at reducing a composite of vascular death, myocardial infarction, or stroke [7,8]. Additionally, the CURE trial found that aspirin and clopidogrel (75 mg/day after a 300-mg loading dose) were superior to aspirin alone in reducing adverse cardiovascular events among patients with non-ST-elevation ACS (*see* Figure 5.2) [9]. It is important to note that the CURE trial predominately studied conservatively treated patients with ACS who were infrequently treated with glycoprotein IIb/IIIa inhibitors (<10% of study

Figure 5.2 Benefit of clopidogrel in reducing ischemic events in patients with non-ST-elevation ACS



Primary outcome is a composite of death, nonfatal myocardial infarction, or stroke. Reproduced with permission from Yusuf *et al*. [9].

population) or received invasive therapy (<25% of study population); however, the patients that did undergo intervention also derived benefit from this therapy [10]. The precise role of this agent in patients with ACS who are treated aggressively with a glycoprotein IIb/IIIa inhibitor and early invasive therapy is unknown. Clopidogrel has also been shown to be beneficial in the ST-elevation myocardial infarction population [11,12]. The COMMIT (Clopidogrel and Metroprolol in Myocardial Infarction) trial studied over 45,000 patients with ST-elevation myocardial infarction, of whom half received fibrinolytic therapy (the remainder were conservatively treated) [12]. Patients randomized to clopidogrel received 75 mg/day without a loading dose for a mean of 15 days. Aspirin and clopidogrel significantly improved survival and reduced ischemic events when compared with aspirin alone. It is interesting that even though no loading dose of clopidogrel was used in this trial, the event curves began to separate early, favoring the use of clopidogrel. A meta-analysis also documented that the addition of clopidogrel to aspirin produces a small, yet significant survival advantage that is mainly restricted to the highest risk patients [13].

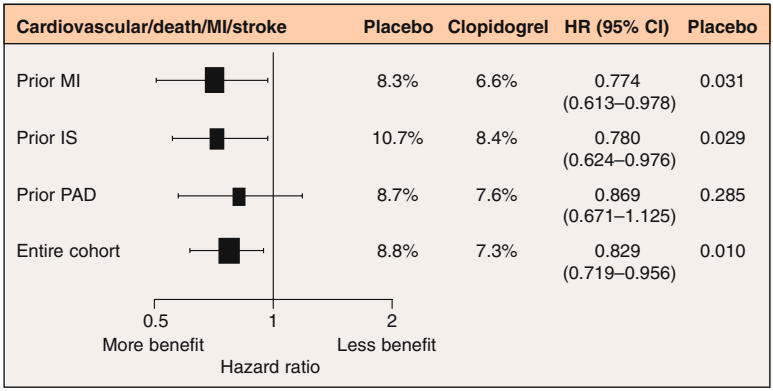
Clopidogrel recommendation

Clopidogrel should be used instead of aspirin in patients with ACS who have a significant allergy to aspirin [4,5]. For other patients, clopidogrel should be used in addition to aspirin early during the hospitalization [4,5]. This is especially true among patients with ACS [4], including patients with ST-elevation myocardial infarction [5]. Revascularized patients should receive 9–12 months of clopidogrel [4,5,14], or even longer for some patients (*see* Figure 5.3) [15,16], including those with a drug-eluting stent [17]. A minority of patients will require surgical revascularization, which makes the upstream use of clopidogrel (i.e., before coronary angiography) somewhat problematic, although not prohibitive, due to concerns of surgical bleeding [18]. Patients who need coronary artery bypass grafting should have clopidogrel discontinued at least 5 days before surgery is performed [4].

Prasugrel

Prasugrel is a new ADP receptor inhibitor that has been shown to be more potent and have more rapid anti-platelet effects than clopidogrel (see

Figure 5.3 Benefit of long-term dual anti-platelet therapy in important subgroups of patients



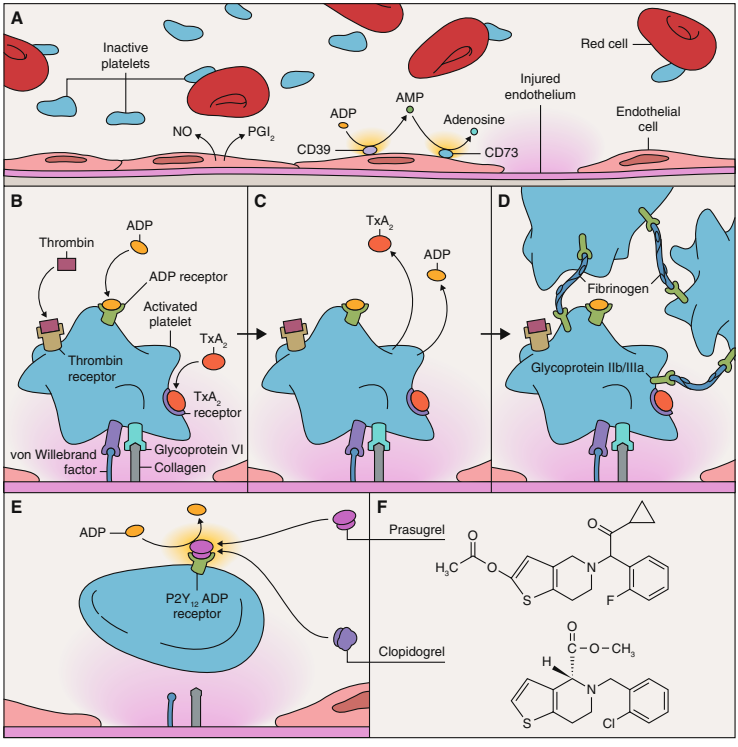
Mean 28 months. CI, confidence interval; HR, hazard ratio; IS, ischemic stroke; MI, myocardial infarction; PAD, peripheral arterial disease. Reproduced with permission from Bhatt *et al*. [16].

Figure 5.4) [19]. This agent was investigated in the TRITON-TIMI 38 (TRial to assess Improvement in Thera peutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38) trial [20]. This trial randomized 13,608 moderate- to high-risk patients with ACS who underwent percutaneous coronary intervention to prasugrel or clopidogrel. Prasugrel resulted in reduced myocardial infarction, urgent target vessel revascularization, and stent thrombosis when compared to clopidogrel (see Figure 5.5) [20]. This efficacy was partially offset by increased major and life-threatening bleeding. The investigators identified three variables that produced increased bleeding with prasugrel:

- age >75 years;
- weight >60 kg;
- a history of transient ischemic attack or cerebrovascular accident.

Among patients without any of these variables, there was increased efficacy without additional major bleeding with prasugrel. Therefore, a patient's ischemic and bleeding risks will need to be assessed prior to administration of prasugrel [21].

Figure 5.4 Role of platelet activation and aggregation in ischemic syndromes



(**A**) Platelets flow in the blood in their inactive state. (**B**) Several different agonists can lead to platelet activation. (**C**) The activated platelet then itself secretes prothrombotic factors. (**D**) Platelet aggregation factors. (**E**) The adenosine diphosphate (ADP) receptor plays a central role in platelet activation. (**F**) Clopidogrel and prasugrel are both thienopyridines whose active metabolites bind to the ADP receptor. AMP, adenosine monophosphate; NO, nitric oxide; PGI_2, prostacyclin; TxA_2, thromboxane A_2. Reproduced with permission from Bhatt [21].

Glycoprotein IIb/IIIa inhibitors

Glycoprotein IIb/IIIa inhibitors are agents that prevent platelet aggregation by terminally blocking platelet fibrinogen receptors. Unlike oral glycoprotein IIb/IIIa inhibitors, which have been shown to increase mortality when compared with placebo [22,23], the intravenous agents are effective in select

Figure 5.5 Major efficacy and bleeding end points in the overall TRITON-TIMI 38 cohort at 15 months

Outcome	Incidence with prasugrel (%)	Incidence with clopidogrel (%)	Hazard ratio (95% CI)
Efficacy end points			
Cardiovascular death, myocardial infarction, or stroke	9.9	12.1	0.81 (0.73–0.90)
Myocardial infarction	7.3	9.5	0.76 (0.67–0.85)
Urgent target vessel revascularization	2.5	3.7	0.66 (0.54–0.81)
Stent thrombosis	1.1	2.4	0.48 (0.36–0.64)
Bleeding end points			
Major bleeding	2.4	1.8	1.32 (1.03–1.68)
Life-threatening bleeding	1.4	0.9	1.52 (1.08–2.13)
Fatal bleeding	0.4	0.1	4.19 (1.58–11.11)
Death, myocardial infarction, stroke, or major bleeding	12.2	13.9	0.87 (0.79–0.95)

CI, confidence interval. Adapted from Wiviott *et al.* [20].

patients [24]. These are now a relatively mature group of cardiovascular drugs that have been studied in numerous trials in tens of thousands of patients. Boersma and colleagues reported the use of glycoprotein IIb/IIIa inhibitors versus placebo in over 30,000 patients with ACS who were not routinely scheduled to undergo early coronary revascularization [25]. There was no difference in mortality; however, glycoprotein IIb/IIIa inhibition reduced nonfatal myocardial infarction by 17% at 5 days, and by 8% at 30 days. While there was no survival benefit in unselected patients, glycoprotein IIb/IIIa inhibitors may improve survival in conservatively treated patients with diabetes [26]. Karvouni and colleagues restricted their analysis to 20,137 patients with non-ST-elevation ACS treated with glycoprotein IIb/IIIa inhibitors versus placebo who routinely underwent percutaneous coronary intervention [27]. In this population, the adjunctive use of glycoprotein IIb/IIIa inhibitors during coronary revascularization produced a long-term survival advantage. In ST-elevation myocardial infarction, the use of abciximab compared with placebo was also associated with an early and long-term survival advantage [28]. Glycoprotein IIb/IIIa inhibitors increase major bleeding, although this can be attenuated by using lower doses of heparin and stopping heparin

after percutaneous coronary intervention [27]. Hemorrhagic strokes do not appear to be increased with glycoprotein IIb/IIIa inhibition, unless combined with fibrinolytic therapy [29]; however, with the recent findings of the FINESSE trial, this practice should become infrequent [30].

Special issues with glycoprotein IIb/IIIa inhibitors

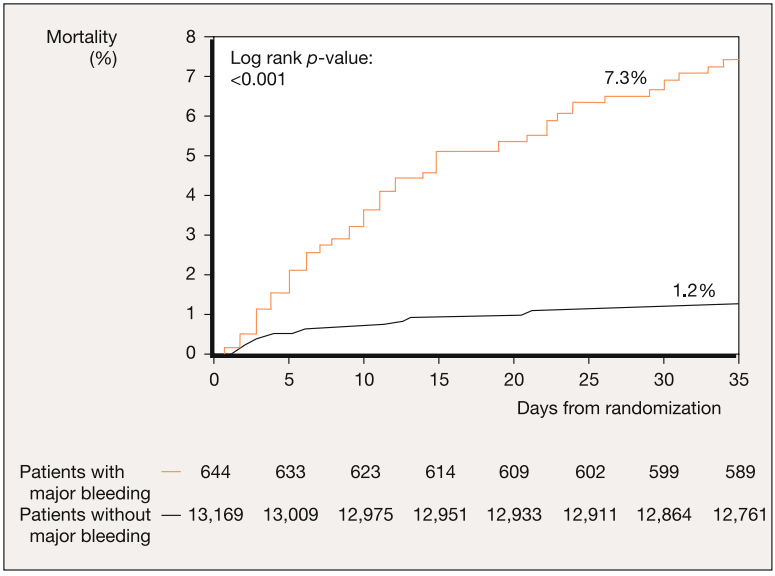
In the above analyses, the most commonly studied agents were abciximab, eptifibatide, and tirofiban. The TARGET (Do Tirofiban and ReoPro Give Similar Efficacy Trial) study documented the superiority of abciximab in reducing death, nonfatal myocardial infarction, or urgent revascularization compared with tirofiban [31]. The reduction in the composite end point was primarily driven by a reduction in nonfatal myocardial infarction.

Glycoprotein IIb/IIIa inhibitors can be given prior to cardiac catheterization (i.e., 'upstream') or at the time of coronary intervention. In fact, there is evidence that intracoronary administration of a glycoprotein IIb/IIIa inhibitor may reduce adverse cardiac events [32] compared with intravenous administration. The ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) timing trial documented a composite ischemia rate of 7.1% with upstream administration of a glycoprotein IIb/IIIa inhibitor compared with 7.9% with deferred use (p=0.13) [33]. Unfortunately, major bleeding was increased with upstream use (6.1%), compared to deferred use (4.9%; p=0.009). The importance of this finding cannot be overstated since major bleeding significantly increases short-term mortality (*see* Figure 5.6) [34]. Further study of upstream versus deferred use of eptifibatide is underway in the EARLY ACS trial.

Glycoprotein IIb/IIIa inhibitor recommendation

Glycoprotein IIb/IIIa inhibitors are best suited for patients with ACS who undergo percutaneous coronary intervention [4,5]; however, conservatively treated patients with diabetes may also derive benefit from their use [26]. Abciximab appears to be preferred to the other agents when initiated in the catheterization laboratory and should be continued for 12 hours after intervention [31]. When eptifibatide and tirofiban are used, they should be continued for 18–24 hours after intervention, although if these agents are initiated upstream, eptifibatide may be preferred as it has better data for use in percutaneous coronary intervention than tirofiban [4,5]. Glycoprotein IIb/IIIa inhibitors increase major bleeding, which is a potent predictor of short-term mortality [34]. Mechanisms to reduce major bleeding include:

Figure 5.6 The impact of major bleeding on mortality from the ACUITY trial



ACUITY, Acute Catheterization and Urgent Intervention Triage Strategy. Reproduced with permission from Manoukian [34].

proper dosing (especially for the elderly and patients with renal insufficiency) [4,5]; termination of anti-thrombin agents after revascularization [27]; and administration of glycoprotein IIb/IIIa inhibitors in the catheterization laboratory (intracoronary administration may be preferable) after arterial access has been obtained [32].

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Appendices

A.1 List of HTML and PHP Document Examples

A.2 ASCII Characters for Windows PCs

The first 127 ASCII character codes are standardized and the remaining characters are system-dependent. The values shown are for Windows-based PCs. These characters can be displayed from a Windows computer keyboard by pressing and holding the Alt key and pressing the corresponding base-10 (Dec) code on the numerical keypad ("locked" with the NumLock key).

Dec	Hex		Dec	Hex		Dec	Hex	
0	0	(1)	30	1E	▲	61	3D	=
1	1	☺	31	1F	▼	62	3E	>
2	2	☻	32	20	(2)	63	3F	?
3	3	♥	33	21	!	64	40	@
4	4	♦	34	22	"	65	41	A
5	5	♠	35	23	#	66	42	B
6	6	♠	36	24	$	67	43	C
7	7	•	37	25	%	68	44	D
8	8	◘	38	26	&	69	45	E
9	9	○	39	27	'	70	46	F
10	A	◙	40	28	(	71	47	G
11	B	♂	41	29	)	72	48	H
12	C	♀	42	2A	*	73	49	I
13	D	♪	43	2B	+	74	4A	J
14	E	♫	44	2C	,	75	4B	K
15	F	☼	45	2D	-	76	4C	L
16	10	►	46	2E	.	77	4D	M
17	11	◄	47	2F	/	78	4E	N
18	12	↕	48	30	0	79	4F	O
19	13	‼	49	31	1	80	50	P
20	14	¶	50	32	2	81	51	Q
21	15	§	51	33	3	82	52	P
22	16	▬	52	34	4	83	53	S
23	17	↨	53	35	5	84	54	T
24	18	↑	54	36	6	85	55	U
25	19	↓	55	37	7	86	56	V
26	1A	→	56	38	8	87	57	W
27	1B	←	57	39	9	88	58	X
28	1C	∟	58	3A	:	89	59	Y
29	1D	↔	59	3B	;	90	5A	Z
			60	3C	<	91	5B	[

92	5C	\	134	86	å	176	B0	
93	5D	]	135	87	ç	177	B1	
94	5E	^	136	88	ê	178	B2	
95	5F	_	137	89	ë	179	B3	
96	60	`	138	8A	è	180	B4	
97	61	a	139	8B	ï	181	B5	
98	62	b	140	8C	î	182	B6	
99	63	c	141	8D	ì	183	B7	
100	64	d	142	8E	Ä	184	B8	
101	65	e	143	8F	Å	185	B9	
102	66	f	144	90	É	186	BA	
103	67	g	145	91	æ	187	BB	
104	68	h	146	92	Æ	188	BC	
105	69	i	147	93	ô	189	BD	
106	6A	j	148	94	ö	190	BE	
107	6B	k	149	95	ò	191	BF	
108	6C	l	150	96	û	192	CO	
109	6D	m	151	97	ù	193	C1	
110	6E	n	152	98	ÿ	194	C2	
111	6F	o	153	99	Ö	195	C3	
112	70	p	154	9A	Ü	196	C4	
113	71	q	155	9B	¢	197	C5	
114	72	r	156	9C	£	198	C6	
115	73	s	157	9D	¥	199	C7	
116	74	t	158	9E	Pts	200	C8	
117	75	u	159	9F	*f*	201	C9	
118	76	v	160	A0	á	202	CA	
119	77	w	161	A1	í	203	CB	
120	78	x	162	A2	ó	204	CC	
121	79	y	163	A3	ú	205	CD	
122	7A	z	164	A4	ñ	206	CE	
123	7B	{	165	A5	Ñ	207	CF	
124	7C	|	166	A6	ª	208	D0	
125	7D	|	167	A7	º	209	D1	
126	7E	}	168	A8	¿	210	D2	
127	7F	⌂	169	A9	⌐	211	D3	
128	80(3)	Ç	170	AA	¬	212	D4	
129	81	ü	171	AB	½	213	D5	
130	82	é	172	AC	¼	214	D6	
131	83	â	173	AD	¡	215	D7	
132	84	ä	174	AE	«	216	D8	
133	85	à	175	AF	»	217	D9	

218	DA	┌	231	E7	τ	244	F4	⌠
219	DB		232	E8	Φ	245	F5	⌡
220	DC		233	E9	Θ	246	F6	÷
221	DD		234	EA	Ω	247	F7	≈
222	DE		235	EB	δ	248	F8	°
223	DF		236	EC	∞	249	F9	∙
224	E0	α	237	ED	φ	250	FA	·
225	E1	ß	238	EE	ε	251	FB	√
226	E2	Γ	239	EF	∩	252	FC	^{n}
227	E3	π	240	F0	≡	253	FD	^{2}
228	E4	Σ	241	F1	±	254	FE	■
229	E5	σ	242	F2	≥	255	FF	[4]
230	E6	μ	243	F3	≤			

[1] ASCII 0 is a null character.
[2] ASCII 32 is a space (as produced by pressing the space bar on your keyboard).
[3] Because the Euro did not exist when the ASCII character sequence was standardized, its symbol, €, does not have a representation in the standard sequence (although it is available as a special character for many fonts in Microsoft Word, for example). On some European computer systems, it may take the place of Ç, the character for ASCII code 128.
[4] ASCII 255 is a blank character.

Exercises

These exercises, while not keyed to specific chapters, are nonetheless presented roughly in order relative to the material presented in Chapters 1 through 3, and 5. (Chapter 4 is a summary of PHP elements and contains just syntax examples rather than new applications.)

1. Rewrite Document 2.5 (`windspd.php`) so that it uses the *`$array = file($filename)`* function to copy all the wind speed data into an array. Each line in the file will become an array element, and the `explode()` function can then be used to access the data. This approach can be used to eliminate the long format specifier string required in Document 2.5. To use the `explode()` function, the only requirement is that you know exactly how the values in the file are separated. In the sample file shown in the problem statement for Document 2.5, there is a header line with values separated by a space. Each wind speed value is followed by a comma and a space. Does it matter if the delimiter given in the `explode()` function is `", "` or `","`? The documentation for the `explode()` function says that it "returns an array of strings consisting of substrings of the string" specified as a parameter. Does it matter that the contents of the arrays returned by `explode()` should be treated as numbers and not strings?

2. Create a file of names and densities of various materials. Write an HTML/PHP application that will display all materials and densities for which the density is greater than or less than some value specified in the HTML document. (Use a radio button to select.)

3. Create a file of unit conversions that lists a "from" unit, a "to" unit, and the number by which the "from" unit must be multiplied to get the value of the "to" unit. For example, to convert from feet to yards, multiply by 0.33333. Write an HTML/PHP application that will allow the user to specify a name and value for a "from" unit and the name of a "to" unit, and will display the equivalent value for the "to" unit.

One problem with such an application is that your HTML document will not "know" which units are included in the data file, and that file can be accessed only through the PHP application. You do not

want to "hard code" all possible unit names into your HTML document. There is no simple solution to this problem. The PHP application could search the file entries based on only the first few letters of the unit names passed from the HTML document, which would prevent problems with a user specifying "meters" in the HTML document when the data file contained only "meter."

4. Write a PHP application that uses one or more functions to find the minimum, maximum, mean, median, and standard deviation of numerical values stored in a file. Note that to find the median, the values need to be sorted. For an odd number of sorted values, the median is the middle value. For an even number of values, the median is the average of the two middle numbers.

The mean of a list of n numbers is:

$$m = \sum_{x=1}^{n} x_i$$

and the standard deviation is:

$$s = \sqrt{\frac{\sum_{i=1}^{n} x_i^2 - \left(\sum_{i=1}^{n} x_i\right)^2 / n}{n-1}}$$

5. Simulation studies in science and engineering often require random numbers drawn from a normal ("bell-shaped") distribution rather than from a uniform distribution. By definition, a set of normally distributed numbers should have a mean of 0 and a standard deviation of 1. PHP has a random number function that generates uniformly distributed values in the range [0,1). That is, the generator could produce a value of 0, but it should never produce a value of 1.

There is a simple way to generate a pair of normally distributed numbers x_1 and x_2 (or at least numbers that *look* like they are normally distributed in some statistical sense) from a pair of uniformly distributed numbers u_1 and u_2 in the range (0,1]:

$x_1 = [-2 \ln(u_1)]^{1/2} \cdot \cos(2\pi u_2)$
$x_2 = [-2 \ln(u_1)]^{1/2} \cdot \sin(2\pi u_2)$

where ln() is the natural (base e) logarithm.

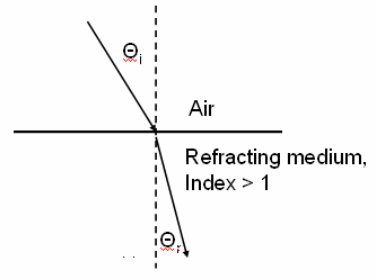
Write a PHP application to create a file containing 100 normally distributed values. When you do this in a for… loop, remember that each "trip" through the loop calculates two values, x_1 and x_2, not just one. If you like, you can write a simple HTML interface to specify the number of normally distributed values to be generated.

Because ln(0) is undefined, your code will have to check every value of u_1 to make sure it is not 0. If it is, replace u_1 with some arbitrary small value. This should happen only rarely, if ever, so it will not bias the statistics of even a fairly small sample. Note that PHP's random number generator is not supposed to produce a value of exactly 1, for which ln(1) = 0, but if it does it will cause no problems with these calculations.

Calculate the mean and standard deviation of the numbers you have generated. You can do this by summing the values of x_i and x_i^2 as you generate them. Then use the formulas given in the previous exercise. The mean and standard deviation of these 100 normally distributed values should be close to 0 and 1, but not exactly equal to these values for this finite set. There are other ways to check whether a set of numbers is really normally distributed, but that is beyond the scope of this problem. It is even possible that the numbers generated with this algorithm would pass such tests even though they are not really randomly normal.

6. Snell's law of refraction relates the angle of incidence θ_i of a beam of light to the angle of refraction θ_r of the beam as it enters a different medium:

$$n_i \sin(\theta_i) = n_r \sin(\theta_r)$$



The table gives the refractive index for four materials. Assuming that the incident material is always air, create a table that shows incident angles from 10° to 90° in steps of 10°. The angle of refraction corresponding to an incident angle of 90° is the angle beyond which light incident from within the refracting material is reflected back into that medium, rather than exiting into air.

Material	Index of refraction
Air	1.00
Water	1.33
Glass	1.50
Diamond	2.42

7. A circuit containing an inductance of L henrys and a capacitance of C farads has a resonant frequency f given by:

$$f = \frac{1}{2\pi\sqrt{LC}} \text{ Hz}$$

Write an HTML/PHP application that allows the user to input a range of inductances and capacitances along with a "step size" for each component, and generates a table containing the resonant frequency for each LC pair of values.

For example, the output could generate a table for inductances in the range from 20-100 μh in steps of 20 μh and capacitances from 100-1000 μf in steps of 100 μf. It does not make any difference which of these components are the rows in the table and which are the columns.

8. In a materials testing experiment, samples are given random doses of radiation R every hour. The maximum total radiation exposure R_{max} is specified and the experiment is stopped if the next radiation dose will cause R_{max} to be exceeded. The units for the radiation do not matter for this problem.

Write an HTML document that will provide, as input to a PHP application, the maximum total dose and the maximum individual dose. The PHP application should then generate a table summarizing the random doses delivered to the sample. It could look something like this:

Maximum cumulative radiation = 1000
Maximum individual dose = 200

Dose	Amount	Cumulative
1	144	144
2	200	344
3	73	417
4	59	476
5	168	644
6	119	763
7	99	862
8	177	not delivered

9. Modify Document 3.12 (`histo.php`) so that the code will accommodate any arbitrary range of input values, with those values distributed in the specified number of equal-size bins. For example, the occurrences of numbers from –30 to +30 could be counted in 12 bins of size 5. It should be up to the user to define the number of bins in a way

that makes sense relative to the range of values to be represented by the histogram. The code should save the histogram data in a file.

10. Create a data file containing an unspecified number of values between 0 and 100. Define an array with letter grades as keys:

```
$a = array("A" => 90, "B" => 80, …);
```

This array defines cutoff points for each letter grade.

Define another array with the same character keys. The elements of this array should be initialized to 0. Then, when you read through your data file, increment the appropriate grade "box" by 1. (This could be done with multiple if... statements, for example.) When you are finished, display the keys and contents of the second array in a table that shows the number of A's, B's, etc.; for example:

```
A 3
B 7
C 5
D 2
F 1
```

This is just another version of the histogram problem, but the box limits are defined by the elements of `$a`, rather than by allocating the values into a specified number of identically sized boxes.

11. Write a PHP application that will read a text file and count the number of occurrences of each letter in the file. (Use the `fgetc()` function to read one character at a time from the file.) Upper- and lowercase letters count as the same character. Store the results in an array with 26 upper- or lowercase character keys and display the contents of the array when all characters have been read from the file. If you like, you can make this an application that runs from a command line, so you can specify the name of the input text file when you execute the application.

12. Write an HTML/PHP application that will calculate and display a monthly loan repayment schedule. The user specifies the loan amount, the annual interest rate, and the duration of the loan in years. Payments are made monthly.

For n loan payments, where n is the number of years times 12, the monthly payment P for a loan amount A at annual interest rate r (expressed as a decimal fraction, not a percent) is

$$P = (A \cdot r/12)/[1 - 1/(1 + r/12)^n]$$

At the end of the loan repayment schedule, display the total amount received in loan payments.

Suppose you were thinking about lending this money yourself. The alternative is to deposit the money in an interest-bearing account. What APY (annual percent yield) would that account have to pay in order for you to have the same amount of money at the end of y years as you would have received from the loan repayments?

If you don't reinvest the loan payments as you receive them, calculate the APY from:

$$A_{final} = A_{start} \cdot (1 + r_{APY})^y$$

If you immediately reinvest each loan payment in an account paying an annual rate R (presumably lower than rate r) then at the end of y years (n months) that account will hold

$$A_{final} = A_{start} \cdot [(1 + R/12)^n - 1]/(R/12)$$

Here is an example. The monthly payments for a two-year, 8% loan of $200,000 are $9045.46. The total amount paid is 24 × $9045.46 = $217,091. The APY for an account with an initial deposit of $200,000 that would yield this amount is $(A_{final}/A_{start})^{(1/y)} - 1 = 4.19\%$. Suppose you reinvest the monthly payments as you receive them at 4%, compounded monthly. When the loan is repaid, you will have a total of $225,620, which is equivalent to an APY of 6.21% on a two-year investment of the $200,000.

		Payment	Balance	Reinvestment
			200000.00	Rate = 4%
Payment #	1	9045.46	192287.88	9045.46
	2	9045.46	184524.34	18121.07
	3	9045.46	176709.04	27226.93
	4	9045.46	168841.64	36363.14
	5	9045.46	160921.79	45529.81
	6	9045.46	152949.15	54727.04
	7	9045.46	144923.35	63954.92
	8	9045.46	136844.05	73213.56
	9	9045.46	128710.88	82503.06

	10	9045.46	120523.50	91823.53
	11	9045.46	112281.53	101175.07
	12	9045.46	103984.61	110557.78
	13	9045.46	95632.39	119971.76
	14	9045.46	87224.48	129417.13
	15	9045.46	78760.52	138893.98
	16	9045.46	70240.13	148402.41
	17	9045.46	61662.94	157942.55
	18	9045.46	53028.57	167514.48
	19	9045.46	44336.63	177118.32
	20	9045.46	35586.75	186754.17
	21	9045.46	26778.54	196422.14
	22	9045.46	17911.60	206122.34
	23	9045.46	8985.55	215854.88
	24	9045.46	0.00	225619.85
Total Income		217091.00		225619.85
Return		4.19%		6.21%

13. Modify Document 3.13 (`cardShuffle.php`) so that the code will display four shuffled "hands" of 13 cards each, identified by value and suit:

Three of Clubs
King of Clubs
…
Ten of Spades
Deuce of Spades

14. Define a "heat wave" as a condition for which the maximum temperature exceeds 90°F on any three consecutive days. Write a PHP application that will read and display a file of daily maximum high temperatures, including in your output an appropriate message when a heat wave is in progress.

Note that you can define a heat wave only retroactively, because the heat wave is known to be occurring only on the third day. This means that you must store data from at least the two previous days before you can display an appropriate message for the heat wave days.

Here is a sample data file with appropriate output:

07/01/2006 89
07/02/2006 90 heat wave day 1

07/03/2006 93 heat wave day 2
07/04/2006 92 heat wave day 3
07/05/2006 94 heat wave day 4
07/06/2006 89
07/08/2006 91 heat wave day 1
07/09/2006 90 heat wave day 2
07/10/2006 92 heat wave day 3
07/11/2006 89
07/12/2006 87

15. The value of equipment used in manufacturing and other businesses declines as the equipment ages. Businesses must recover the cost of "durable" equipment by depreciating its value over an assumed useful lifetime of n years. At the end of n years, the equipment may have either no value or some small salvage value. Depreciation can be computed three ways:

1. *Straight-line depreciation.* The value of an asset minus its salvage value depreciates by the same amount each year over its useful life of n years.

2. *Double-declining depreciation.* Each year, the original value of an asset minus the previously declared depreciation is diminished by 2/n. (This method does not depend on an assumed salvage value.)

3. *Sum-of-digits depreciation.* Add the integers from 1 through n. For year i, the depreciation allowed is the original value of the asset minus its salvage value, times (n – i) + 1, divided by the sum of the digits.

Write an HTML document that allows the user to enter the original value of an asset, the number of years over which the depreciation will be taken, and its salvage value at the end of the depreciation period. Then write a PHP application that will use these values to print out a depreciation table showing the results for each depreciation method. Here is a sample table.

The code that generated this table used `echo` statements and the `round()` function to generate the output, because that was a little easier to do while the code was being developed. You can gain more control over the output by, for example, having 100 print as 100.00, using `printf()` with appropriate format specifiers.

Businesses often like to "front load" the depreciation of an asset in order to realize the maximum tax deduction in the year that the funds

were actually spent for the equipment. For this reason, they would likely not choose the straight line method even though it is the simplest of the three.

Original value		$1000				
Salvage value		$100				
Lifetime (years)		7				
Year	Straight line	Asset value	Double declining	Asset value	Sum of digits	Asset value
1	128.57	871.43	285.71	714.29	225	775
2	128.57	742.86	204.08	510.2	192.86	582.14
3	128.57	614.29	145.77	364.43	160.71	421.43
4	128.57	485.71	104.12	260.31	128.57	292.86
5	128.57	357.14	74.37	185.93	96.43	196.43
6	128.57	228.57	53.12	132.81	64.29	132.14
7	128.57	100	37.95	94.86	32.14	100

16. When analyzing a time sequence of measurements made on a noisy system, it is often useful to smooth the data so that trends are easier to spot. One simple smoothing technique is a so-called unweighted moving average. Suppose a data set consists of n values. These data can be smoothed by taking a moving average of m points, where m is some number significantly less than n. The average is unweighted because old values count just as much as newer values. The formula for calculating the smoothed average value S_i corresponding to the i^{th} value in the data set, is

$$S_i = \frac{\left(\sum_{j=i-m+1}^{i} x_j \right)}{m}, \quad i \geq m$$

Given a set of n points, an algorithm for calculating a moving average of m values is:

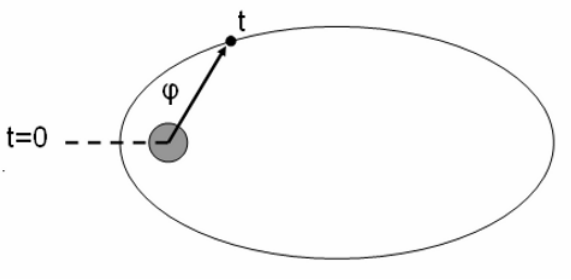
1. Calculate the sum s of the first m points. The first average (S_m) equals s/m.

2. For each value of i = m + 1 to n, add the i^{th} value to s and subtract the $(i - m)^{th}$ value. Then calculate the average for this new sum.

3. Repeat step 2 until i = n.

Write a PHP application that reads a file of numerical values and creates a new file containing the original values and the moving average smoothed values. You may wish to create an HTML interface that specifies the file name and the number of points to be included in the moving average.

17. The orbit of a body rotating around a gravitational center is characterized by its orbital period τ, the time required to complete one complete revolution starting at perigee (the closest approach to the gravitational center), and its eccentricity e, the departure from a circular orbit. Eccentricity is a dimensionless quantity between 0, for a circular orbit, and 1, when the orbit becomes a parabola. For intermediate values of e, the orbit is an ellipse with the gravitational center at one focus of the ellipse. The speed of an orbiting object is maximum at its perigee (t = 0), and minimum at its apogee (t = τ/2).



For a circular orbit, the angular position φ of an object in its orbit is simply related to time $t \leq \tau$:

$\varphi_{e=0} = 2\pi(t/\tau)$ radians

When the orbit is elliptical, the calculation of the angular position of an object in its orbit is much more complicated. The "mean anomaly" M for any orbit is the same as the true angular position for a circular orbit with the same period:

$M = 2\pi(t/\tau)$ radians

But, the actual angular position φ, the "true anomaly," for a non-circular orbit cannot be calculated directly. The mean anomaly is related to the so-called eccentric anomaly E_c through a transcendental equation:

$$M = E_c - e \cdot \sin(E_c)$$

After E_c is found, then the true anomaly φ can be calculated directly:

$$\varphi_{0<e<1} = \arccos\{[\cos(E_c) - e]/[1 - e \cdot \cos(E_c)]\}$$

If M is greater than π radians (that is, if $t/\tau > 0.5$), then let $\varphi = 2\pi - \varphi$. Express your final answer in degrees (degrees = radians·180/π).

To solve for E_c using a recursive function with t, τ, e, and the current guess for E_c as the four parameters:

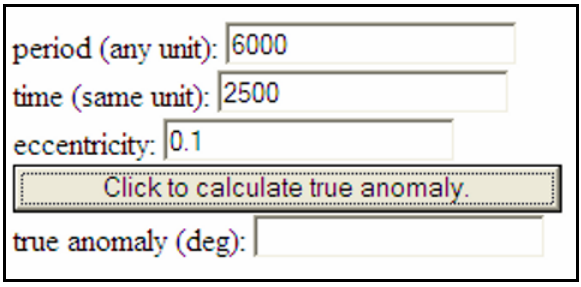
1. As an initial guess, let $E_c = M$ and use this value in the initial call to the function.

2. In the function, calculate $newE_c = M + e \cdot \sin(E_c)$.

3. Recursively call the function with $newE_c$ as the fourth argument.

4. Keep recalculating until the absolute value $|newE_c - E_c|$ is less than some suitably small value—1×10^{-5} is a reasonable choice.

When the terminating condition for recursive calls is satisfied, then calculate φ as defined. Use an HTML interface something like this:



Values of eccentricity very to close to 1 may cause numerical problems, including failure of recursive functions to reach their terminating condition. If eccentricity is equal to 1, then your code should display an appropriate message—that the object's path is a parabola and

not an ellipse. Eccentricity values greater than 1 or less than 0 are simply not allowed as input.

18. Rewrite the PHP application in Document 3.14b so that it does not store data from the file in an array for any of the operations specified in the problem statement.

19. Using Documents 5.3a and 5.3b as a guide, write a PHP application that accepts as input the "weather report" barometric pressure and returns the "station" pressure. Except at a few research sites, the reported barometric pressure value is always corrected to sea level—otherwise it would not be possible to understand maps of high and low pressure associated with weather systems. The actual barometric pressure at a site (station pressure) can be obtained from the reported pressure by adjusting it for site elevation h, in units of kilometers:

$$p_{station} = p_{sea\ level} \cdot \exp(-0.119h - 0.0013h^2)$$

In the United States, barometric pressure is reported in units of inches of mercury. Almost everywhere else in the world, the units are millibars (hectopascals). Values for standard atmospheric conditions at sea level are 1013.25 millibars or 29.921 inches of mercury. Because these two units have such different values associated with them, your code can determine the units in which the pressure was entered. If the sea level pressure value entered is less than 40, assume the units are inches of mercury and convert that value to millibars:

$$p_{millibars} = p_{inches\ of\ mercury} \cdot (1013.25/29.921)$$

As an example, look at an online weather report for Denver, Colorado, USA. Denver is often called the "mile high city" because its elevation is about 5300 ft (1.6 km). The barometric pressure will be reported as a value typically just a little above 1000 millibars, just as it is at sea level. Use your PHP application to calculate the actual barometric pressure in Denver under standard atmospheric conditions.

Glossary

The Chapter and section in which a term first appears is given in parentheses following the term. The first appearance in the text is printed in bold font.

append (text file) (1.1)
A "write-only" access permission that allows new information to be appended to the end of an existing text file.

ASCII character sequence (3.2)
A standardized representation of characters.

client-side language (1.1)
A programming language such as JavaScript that resides on a local browser and can process scripts downloaded to the browser, as opposed to a server-side language such as PHP.

command line interface (CLI) (5.1)
A text-based computer interface that allows a user to type commands, enter data from the keyboard, and display text output from a program.

constructor (3.1)
A means of defining the properties and contents of a built-in or user-defined data object, such as the array constructor in PHP.

escape character (4.4)
A backslash (\), indicating that the following character has a special meaning.

escape sequence (4.4)
A backslash followed by a character.

file handle (1.1)
The "logical" name by which a physical file is identified within a program.

file name extension (1.1)

A set of (usually) three or four characters following a period (.) which identifies the nature of a file and its contents. File extensions are often associated with specific applications, such as `.php` for any file containing text that can be interpreted as a PHP script.

floating-point number (1.1)

A real number, and a particular way of representing such a number within computer memory. Whole numbers can be represented as either integers or floating-point numbers.

format (1.1)

A specification for reading or writing data from or to a file or other resource, such as a keyboard, or a description of how the contents of a file are organized.

format string (1.1)

A string that provides information about the contents and format of values in a file.

header line(s) (1.1)

One or more lines in a file which identify and/or describe the contents of that file, as opposed to the data themselves.

language construct (1.1)

A reserved term or group of terms in a programming language which performs certain operations.

local computer (server) (1.1)

In this book, the term "local computer" usually refers to a user's own computer that is also running a server application.

PHP document (1.1)

Any text document that can be interpreted as a PHP script.

PHP environment (1.1)

A local or remote server that includes a PHP script interpreter, a place to store PHP scripts, and a place where files can be created, read, and modified.

PHP interpreter (1.1)
A computer application that interprets PHP script files.

PHP script (1.1)
A series of statements that follow PHP syntax rules, and that can be executed by a PHP interpreter.

PHP tag (1.1)
`<$php… $>`, an HTML tag which contains PHP statements.

pseudo data type (4.1)
A type specifier such as `(mixed)` used to indicate the data type or types associated with a variable name or other identifier.

random access (4.4)
Pertaining to a data file whose contents can be accessed in any order.

read-only (text file) (1.1)
A text file available for access from within a PHP script in a way that only allows its contents to be read but not modified in any way.

remote server (1.1)
A server running somewhere other than on a local computer.

resource (4.1)
Any data source, such as a data file or a keyboard, that is external to but accessible to a PHP application. Resources are represented by the pseudo data type *`(resource)`*.

sequential access (4.4)
Pertaining to a data file whose contents can be accessed only sequentially, starting at the beginning.

server (1.1)
A software application that provides services such as file access to other computer programs and users on the same computer (a local server) or some other computer (a remote server). A computer on which a server application is running is often referred to as a server even if it is also used for other purposes.

server side (1.1)

Refers to activities taking place on a server or data files residing in folders accessible through a server, even if that server is on a user's local computer.

server-side language (1.1)

A programming language such as PHP which resides on a computer server, as opposed to being available within a local (client-side) browser.

write-only (text file) (1.1)

A text file that be created or overwritten from within a PHP script.

Index

NOTE: For HTML tags and PHP functions and constructs, only first appearances or significant new uses are indexed. PHP math functions are not indexed individually; tables of all math functions are found at the index reference to “math functions” and “functions, math”.