Acute Coronary Syndrome

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Faculty

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Faculty Disclosure

Contributing faculty, Lori L. Alexander, MTPW, ELS, MWC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians, physician assistants, and nurse practitioners to enhance their knowledge of the diagnosis, assessment, management, and secondary prevention of acute coronary syndrome.

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Course Objective

The pace at which acute coronary syndrome guidelines are updated make it challenging for clinicians to remain current with the recommendations that lead to improved outcomes for this substantial patient population. The purpose of this course is to reduce the widening gap between care according to guidelines and actual care delivered by providing healthcare professionals with knowledge necessary to implement the most appropriate approach to diagnosis and treatment.

Learning Objectives

Upon completion of this course, you should be able to:

1. Discuss the prevalence and definition of coronary heart disease (CHD) and acute coronary syndrome (ACS).
2. Explain the pathophysiology of ACS, including the role of plaque formation and rupture.
3. Devise a strategy for screening and evaluation of asymptomatic individuals at risk for ACS.
4. Describe the various clinical presentations of ACS and the differential diagnosis of chest pain, including considerations for non-English-proficient patients.
5. More effectively utilize ECG and cardiac biomarkers in the diagnosis of ST-segment elevation myocardial infarction (STEMI) and unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI).
6. Discuss the factors involved in risk stratification of individuals with suspected ACS.
7. Assess the consistency of your and your team's adherence to guidelines for the acute treatment of UA/NSTEMI.
8. Select the optimal anti-ischemic, antiplatelet, and anticoagulant agents for the treatment of UA/NSTEMI.
9. Distinguish between the clinical indications for an ischemia-guided or invasive strategy for patients with UA/NSTEMI.
10. Discuss the issue of timing in selecting reperfusion therapy for patients with STEMI.
11. Describe the role of percutaneous coronary intervention (PCI) for STEMI.
12. Identify contraindications and cautions for fibrinolysis in the treatment of STEMI.
13. List other reperfusion therapies used in the treatment of STEMI, and identify the appropriate therapy for individual patients.
14. Outline appropriate secondary prevention measures for patients with ACS.
15. Discuss the relationship between guideline adherence in practice and patient outcomes.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Cardiovascular disease (CVD) is comprised of coronary heart disease (CHD), heart failure, stroke, and hypertension. On the basis of national health data from 2017–2020, the prevalence of CVD in adults older than 20 years of age is 48.6% overall (127.9 million persons in 2020) and increases with age [1]. CVD prevalence excluding hypertension is 9.9% overall (28.6 million in 2020). The average annual direct and indirect cost of CVD in the United States was an estimated $407.3 billion in 2018–2019 [1].

CHD, which encompasses angina pectoris (stable angina), coronary insufficiency (unstable angina or UA), and myocardial infarction (MI) affects an estimated 20.5 million Americans 20 years of age and older [1]. CHD is the leading cause of death from CVD in the United States, accounting for 41.2% of all CVD deaths [1]. According to data from 5,680 hospitals reporting to the Centers for Medicare and Medicaid Services, the average 30-day mortality after acute MI was 12.4% in 2020 [1]. As a chronic disease, CHD has a significant impact on quality of life, negatively affecting physical, psychologic, and social well-being. CHD also carries a tremendous economic burden: an estimated direct and indirect cost of $239.9 billion. This figure is expected to grow to nearly $400 billion by 2035 [1].

Atherosclerosis, the underlying condition of CHD, is progressive, with periods of stable and nonstable disease. Periods of instability can cause the occurrence of acute coronary syndrome (ACS), a spectrum of life-threatening disorders that includes UA, non-ST-segment elevation MI (NSTEMI), and ST-segment elevation MI (STEMI). In 2019, there were 673,000 hospitalizations associated with a principal diagnosis of ACS [1].

Advances in the understanding of the pathophysiology of ACS have led to the identification of UA/NSTEMI and STEMI as distinct clinical entities, with differences in prevalence, etiology, clinical features, treatment, and outcomes [2; 3; 4]. In addition, the development and evaluation of pharmacologic therapies and reperfusion procedures in a multitude of large-scale trials have resulted in a redefinition of the diagnosis and treatment of acute MI. The results of these trials have formed the evidence base for clinical practice guidelines developed by the American College of Cardiology (ACC) and the American Heart Association (AHA), in conjunction with other specialty organizations [2; 3; 5; 6]. Despite the widespread dissemination of these guidelines and documentation of better outcomes and decreased risk for subsequent events with guideline-driven treatment, adherence to many aspects of guideline-directed treatment could be improved [7; 8; 9; 10]. Variations in practice have resulted in reports of disparities in assessment, treatment, and outcomes across subgroups according to age, gender, race/ethnicity, risk level, type of MI, and practice setting [7; 11; 12; 13; 14; 15; 16; 17; 18]. For example, a 2018 review found significant gender differences in age, symptom profile, quality and timeliness of guideline-based medical care, and clinical outcomes in patients with acute MI [19]. Women with MI are older, more likely to report atypical symptoms, and often present with heart failure and cardiogenic shock. Lack of clinical recognition prolongs ischemia time and delays definitive treatment, which may partly explain why women are less likely to receive guideline-based

pharmacologic therapies and revascularization than men with acute MI. The analysis also found that women suffer higher risk-adjusted rates of bleeding, vascular complications, and short-term mortality, although risk-adjusted rates of long-term mortality remain similar between men and women following acute MI [19]. Highlighting the different needs of different populations of patients and the disparities in care, as well as emphasizing the appropriate use of treatment guidelines, can help to reduce the gap between evidence-based care and actual care delivered.

The novel therapies for ACS developed over the past few years have reduced its associated morbidity and mortality [1]. However, treatment strategies can be complex, leaving many clinicians unsure of the most appropriate approach to diagnosis and treatment. Optimizing patient outcomes in ACS depends on several factors, including:

- Timely access to care
- Appropriate use of diagnostic tools, including cardiac biomarkers
- Systematic and accurate risk stratification
- Knowledge of the risks and benefits of treatment options (e.g., pharmacologic therapies, revascularization procedures)
- Appropriate follow-up care
- Adherence to secondary prevention measures

Primary care clinicians, emergency healthcare professionals, and cardiologists should understand these factors, especially as they relate to care in their specific settings, and should become familiar with evidence-based strategies for assessment, diagnosis, treatment, and prevention. Primary care clinicians are in a unique position to identify patients who may be at risk for CHD (and thus the potential for ACS) and to educate these patients regarding the benefits of lowering their risk profile through changes in health behaviors, such as smoking cessation, diet, exercise, and compliance with medications. However, adherence to guideline-recommended prevention strategies has been a challenge, in part because of frequently changing guidelines and gender disparities [20; 21; 22; 23]. Primary care providers also play a crucial role in the care of patients after ACS, managing secondary prevention strategies.

Several registries have been developed to collect data on the use of guideline-directed treatment and patient outcomes. These initiatives include Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation? (CRUSADE) and the Acute Coronary Treatment and Intervention Outcome Network (ACTION)-Get With the Guidelines (GWTG) [24; 25]. Data from these initiatives have shown that adherence to guidelines enhances outcomes [7; 26; 27].

Data related to CHD and ACS are taken from several sources, and differences in the source populations (e.g., age, gender, health status), and the dates of study should be considered when interpreting the findings (***Table 1***). Data from community surveillance programs enable the calculation of the prevalence and incidence of CHD, angina, and MI among identified populations. Individuals in these programs are asymptomatic and usually do not have CHD at the beginning of the study. Several registries have been established to collect information from multiple institutions on individuals with ACS, and these registries, along with data from quality improvement initiatives and large-scale, multi-institutional clinical trials, have served to provide demographic profiles of individuals with CHD and ACS, temporal patterns in treatment practices, and overall adherence to evidence-based guidelines.

SOURCES OF DATA ON CORONARY ARTERY DISEASE AND ACUTE CORONARY SYNDROME (ACS)			
Data Source	**Years**	**Population**	**Purpose**
Community Surveillance Programs			
Framingham Heart Study (http://www.framinghamheartstudy.org)	1948 to present	5,209 men and women (original cohort) 5,124 adult children (and spouses) of original participants (1971) 4,095 grandchildren of original cohort (2002) Age at entry: 30 to 62 years (original cohort)	Identify common factors or characteristics contributing to cardiovascular disease by following its development over a long period of time
Atherosclerosis Risk in Communities (https://www2.cscc.unc.edu/aric)	1987–1989 to present	15,792 men and women in four U.S. communities Age at entry: 45 to 64 years	Investigate the etiology and natural history of atherosclerosis, the etiology of clinical atherosclerotic diseases, and variation in cardiovascular risk factors, medical care, and disease by race, gender, location, and date
Cardiovascular Health Study (http://www.chs-nhlbi.org)	1989 through 1999	5,201 men and women (687 Black men and women added in 1992–1993) Age at entry: 65 years or older	Observe risk factors for cardiovascular disease in individuals 65 years of age or older
Data Registries			
National Registry of Myocardial Infarction (NRMI) 1-4	1990–2006	2.2 million men and women with acute myocardial infarction (MI)	Tracked the characteristics, treatment, and outcomes for patients with acute MI (largest observational registry of ACS)
National Cardiovascular Data Registries (NCDR) (https://cvquality.acc.org/NCDR-Home)	1997	>2,400 hospitals >8,500 outpatient providers >60 million patient records	Provides data on evidence-based cardiovascular care, patient outcomes, and healthcare costs
Global Registry of Acute Coronary Events (GRACE)	1999 to 2009	102,341 men and women with ACS at 247 hospitals in 30 countries	Ongoing international registry
Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry and Get With the Guidelines (GWTG)	2007 to present	More than 2,500 hospitals and more than 3 million patients	A national surveillance system to assess patients with STEMI and NSTEMI to provide data on patient outcomes and adherence to evidence-based guidelines
Source: [28; 29; 30]			*Table 1*

When reviewing data from registries, it is important to consider several factors, including differences in the composition of the populations (according to age, gender, and race/ethnicity), the type of ACS (UA, NSTEMI, or STEMI), variations in treatment according to the timeframe of the study (because of advances in treatment options), and better outcomes in quality improvement initiatives and clinical trials than in registries (because of level of care). Lastly, the National Hospital Care Survey provides information on discharge diagnoses, as well as national patterns of healthcare delivery in hospital-based settings and ambulatory surgery centers. Although information on discharge diagnoses can help provide a better understanding of the prevalence of the different components of ACS, because the survey is event-driven (rather than person-driven), the number of hospitalizations does not necessarily correlate to the number of individuals.

This course begins by providing a context for ACS through a discussion of the epidemiology of CHD and ACS and the pathophysiology of ACS, as well as the primary prevention of CHD, which helps to lower the prevalence of ACS. The diagnostic evaluation of patients suspected of having ACS and risk stratification in the emergency department setting are presented in detail. Although many of the same classes of drugs are used to treat UA/NSTEMI and STEMI, the therapeutic approaches vary considerably. The treatment of ACS is a complex issue because of the wide scope of related cardiac disease and the extensive treatment decisions involved. As such, this course is limited to provide an overview of an uncomplicated course of ACS. Clinicians are encouraged to consult the evidence-based guidelines related to the diagnosis, treatment, and secondary prevention of ACS.

OVERVIEW OF ACUTE CORONARY SYNDROME

Since the early 1990s, an enhanced understanding of the pathogenesis of CHD has helped to create a framework for defining ischemic heart disease. The AHA/ACC define ACS as "a spectrum of conditions compatible with acute myocardial ischemia and/or infarction that are usually due to an abrupt reduction in coronary blood flow" [3]. The concept of ACS is helpful, as the initial clinical presentations of UA, NSTEMI, and STEMI often appear similar. However, UA/NSTEMI and STEMI differ in many ways, including their prevalence, severity, pathophysiology, clinical presentation, treatment, and prognosis.

DEFINITION OF TERMS

In patients with CHD, transient imbalances can occur in the supply and demand of oxygen to the myocardium. This ischemia can manifest as precordial chest discomfort, or angina pectoris. Angina is considered stable when it is precipitated by stress or exertion and rapidly resolves with rest or the use of nitrates. Angina is considered unstable when it occurs suddenly (without a precipitating factor); it may occur at rest and may increase in frequency or severity. With both stable angina and UA, ischemia is fully reversible, with no evidence of myocardial necrosis as indicated by elevated levels of serum cardiac biomarkers (e.g., cardiac troponin) [3]. UA may or may not be associated with signs of ischemic changes on electrocardiography (ECG), such as ST-segment depression or new T-wave inversion [3].

UA is closely related to NSTEMI, and the two entities are often indistinguishable from each other, especially during the initial evaluation of a patient [3]. Recognizing the continuum of UA and NSTEMI, the authors of the 2014 AHA/ACC guideline for the management of the conditions created the term NSTE-ACS (non-ST-elevation acute coronary syndromes) to replace "UA/NSTEMI" [3]. Unlike UA, NSTEMI is associated with myocardial necrosis and resultant release of cardiac biomarkers. In addition, the ECG usually shows ST-segment depression, transient ST-elevation, and/or prominent T-wave inversions, but these findings are not required for a diagnosis of NSTEMI [3]. In contrast, STEMI is associated with myocardial damage, with both elevated serum cardiac biomarker levels and persistent ST-segment elevation on ECG [2].

An MI was once defined according to symptoms, ECG abnormalities, and serum cardiac enzyme levels. The advent of more sensitive and specific cardiac biomarkers and imaging studies has led to an ability to detect smaller amounts of myocardial necrosis and, in turn, a need for a more precise definition of MI. While myocardial injury, defined as an elevation in serum cardiac troponin, is a prerequisite for the diagnosis of MI, there must also be clinical evidence of myocardial ischemia to distinguish MI from cardiac troponin elevation caused by nonischemic myocardial injury (e.g., myocarditis, sepsis, chronic kidney disease). The European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the AHA, and the World Heart Federation jointly developed a Universal Definition of MI Consensus Document, last updated in 2018, which states: "the clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia" [31]. Detection of an elevated cardiac troponin value above the 99th percentile of the upper reference limit is the preferred diagnostic indicator of myocardial injury. The injury is considered acute if there is a rise and/or fall of troponin value. Myocardial ischemia in a clinical setting is most often determined from the patient's history, the EKG, or cardiac imaging studies, as evidenced by any one of the following [31]:

- Symptoms of ischemia
- New or presumed new significant ST-segment elevations in two contiguous leads, T wave changes or new left bundle branch block
- Development of pathologic Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of an intracoronary thrombus by angiography or autopsy

The consensus document further classifies MI according to clinical context, pathologic findings, and prognostic differences in conjunction with different treatment strategies [31]. Myocardial injury caused by atherothrombotic coronary artery disease and precipitated by atherosclerotic plaque disruption (rupture, ulceration, erosion, or dissection), resulting in intraluminal thrombus in one or more of the coronary arteries is designated type 1 MI. The dynamic thrombotic component may lead to distal coronary embolization with ensuing myocyte necrosis [31]. Ischemic myocardial injury in the context of a mismatch between oxygen supply and demand, in the absence of atheromatous plaque disruption, is classified as type 2 MI. Such patients usually have stable known or presumed CAD, and the MI is precipitated by acute stressors such as coronary emboli, vasospasm, gastrointestinal bleeding, or sustained tachyarrhythmia. Other types are defined as occurring in conjunction with percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), stent thrombosis, or sudden cardiac death [31].

PREVALENCE AND MORTALITY OF NSTEMI AND STEMI

The overall prevalence of CHD among adults is 7.1%, with a higher prevalence among men compared with women (8.7% vs. 5.8%) [1]. The prevalence increases with age, with the highest rates found among people 80 years and older [1]. It is estimated that about 60% of hospital admissions for ACS are in patients older than 65 years of age, and 85% of ACS-related deaths occur in this age group [19]. Global and national registries of acute coronary events show that ACS of older adults are more likely to present as NSTE-ACS than STEMI and are more likely to be women and to have higher prevalence of such comorbidities as hypertension, heart failure, atrial fibrillation, stroke, anemia, and renal disease [32; 33]. Women tend to be older than men at the time of a first cardiac event [14; 34; 35].

PREVALENCE OF CORONARY HEART DISEASE (CHD), MYOCARDIAL INFARCTION (MI), AND ANGINA AMONG ADULTS 20 YEARS AND OLDER ACCORDING TO RACE/ETHNICITY						
Condition	**Men**			**Women**		
	White	**Black**	**Hispanic**	**White**	**Black**	**Hispanic**
CHD	9.4%	6.2%	6.8%	5.9%	6.3%	6.1%
MI	4.8%	4.0%	3.1%	2.2%	2.3%	1.9%
Angina	4.7%	2.7%	3.6%	3.5%	4.1%	4.3%
Source: [1]						*Table 2*

PREVALENCE OF NON-ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AND ST-ELEVATION MYOCARDIAL INFARCTION (STEMI) ACCORDING TO RACE/ETHNICITY						
Type of MI	**White**	**Black**	**Asian**	**AI/AN**	**Hawaiian/ PI**	**Hispanic or Latino Ethnicity**
NSTEMI (111,535)	83.4%	13.0%	1.9%	0.9%	0.2%	6.6%
STEMI (71,368)	85.7%	10.1%	2.5%	0.7%	0.2%	6.7%
AI = American Indian, AN = Alaskan Native, PI = Pacific Islander.						
Source: [37]						*Table 3*

The prevalence of CHD, MI, and angina vary according to gender and race/ethnicity. The CHD prevalence estimates are 5.7% among White people, 5.4% among Black people, 8.6% among American Indian/Alaska Native people, and 4.4% among Asian people older than 18 years of age [1]. The prevalence rate is highest among White men (9.4%) and lowest among White women (5.9%); similarly, the prevalence of MI is highest for White men (4.8%) and lowest for Hispanic and White women (1.9% and 2.2%, respectively) (***Table 2***) [1]. The prevalence of angina is highest for White men (4.7%) and lowest for Black men (2.7%) [1].

Of the unique hospitalizations for ACS in 2019 (1,266,000), 1,248,000 were for MI alone, 18,000 were for UA alone [1]. Data from a report on the population characteristics of patients with MI in the ACTION Registry-GWTG provide insight on racial/ethnic variations in MI [36]. Among 182,903 patients, approximately 84% were White, 12% were Black, and 2% were Asian; 0.8% and 0.2% were American Indian/Alaskan or Hawaiian/Pacific Islander, respectively [36]. In addition, approximately 7% were of Hispanic or Latino ethnicity [37].

The incidence of STEMI has decreased since 2003, while the incidence of NSTEMI has increased [2]. STEMI continues to be less prevalent than NSTEMI, accounting for 29% to 39% of MIs documented in various registries [36; 37]. However, STEMI is more common than NSTEMI among younger patients, with a rate of nearly 30% among patients younger than 55 years and of 30% among patients 55 to 64 years old [37]. STEMI is also more common among some racial/ethnic groups; for example, STEMI accounted for the highest proportion (86%) of the MIs among White individuals (***Table 3***) [37].

As noted, CHD-related mortality rates continue to decrease. From 2010 to 2020, the annual death rate attributable to CHD declined 19.2% and the actual number of deaths declined 0.9% [1]. This decline in CHD mortality rates in part reflects the shift in pattern of clinical presentations of AMI. Eight-year mortality was higher for NSTEMI (67%) than for STEMI (53%) [1]. Heart disease is still the overall leading cause of death in the United States and represents a similar proportion of all deaths for men and women (20.9% vs 19.1%) [1; 38]. CHD-related mortality increases with age, with CHD accounting for about 18% of all deaths among people 45 to 64 years of age, 22% of all deaths among people 65 years of age and older, and 26% of all deaths among people 85 years of age and older [38].

With regard to race, (and not including deaths in 2021 attributed to COVID-19), heart disease is the leading cause of death among all racial/ethnic populations (***Table 4***) [38]. Heart disease is the leading cause of death among non-Hispanic White and Black populations, but the second leading cause of death in the Hispanic populations.

Improved adherence to evidence-based guidelines has been associated with decreased mortality rates after ACS events. Rates of short-term morbidity mortality are higher for STEMI than for NSTEMI. Review of data in the National Cardiovascular Data Registry ACTION Registry-GTWG showed in-hospital mortality rates of approximately 5% to 7% for STEMI and rates of approximately 3% to 5% for NSTEMI [36; 39]. The rate of in-hospital cardiogenic shock has also been higher among patients with STEMI (4.5% vs 1.8%), whereas the rates of in-hospital reinfarction, heart failure, and stroke have been similar (0.9% vs 0.6%, 5.3% vs 5.5%, and 0.5% vs 0.6%, respectively) [36]. At one year, however, the risk of mortality is similar for STEMI and NSTEMI [40].

HEART DISEASE AS A PERCENTAGE OF ALL DEATHS ACCORDING TO RACE AND HISPANIC ORIGIN

Racial/Ethnic Population	CHD as Percentage of All Deaths
Hispanic	15.0%
Non-Hispanic White	20.8%
Non-Hispanic Black	20.1%
Asian	18.4%
Native Hawaiian/Other Pacific Islander	19.2%
American Indian/Alaska Native	13.9%

Source: [38] *Table 4*

PATHOPHYSIOLOGY OF ACS

The most common cause of ACS is atherosclerotic CAD, a multi-decade process augmented by aging and acquired factors that impact the degree of atherosclerosis. Atherogenesis proceeds by sequential pathologic change within the vessel wall that leads to formation of an atheromatous plaque. Further progression of the atheroma results in a necrotic core beneath a fibrous cap, accompanied by some degree of plaque instability. ACS is most often precipitated by plaque rupture (especially in men) and acute thrombosis as vascular endothelium is exposed to highly thrombogenic necrotic core material [32; 41]. Plaque erosion or fissuring may also lead to ACS [41]. The mechanisms underlying plaque erosion are not as well understood as those for plaque rupture, but inflammation plays a central role in both [41; 42; 43].

Other causes of ACS include dynamic obstruction (coronary artery spasm or vasoconstriction), spontaneous coronary dissection, infection, hypercoagulability states, or progressive mechanical obstruction. However, these causes are rare [44].

Plaque Formation

The gradual process of atherosclerosis usually causes no symptoms over the course of many years, with most plaques causing no symptoms [41]. However, the condition renders vessels susceptible to the formation of plaque through damage to the vascular endothelium. This damage is brought about by the primary risk factors for atherosclerosis, including high plasma levels of low-density lipoprotein (LDL), low plasma levels of high-density lipoprotein (HDL), cigarette smoking, hypertension, diabetes mellitus, male sex, and family history [41]. The process of plaque formation begins when monocytes infiltrate a damaged endothelial wall by binding to endothelial adhesion molecules. The monocytes then undergo differentiation and become macrophages. Macrophages become foam cells by digesting LDL that has also penetrated the arterial wall, helping to create a lipid-filled plaque. Macrophages produce inflammatory cell mediators, such as tumor necrosis factor alpha (TNF-α), interleukins, and metalloproteinases, which can lead to the infiltration of a high number of inflammatory cells at the site of the plaque.

A system for classifying the severity of atherosclerotic plaques (lesions) was developed in the 1990s, with lesions categorized into several types according to their histologic composition and structure [45; 46; 47; 48]. A simpler classification, based on morphologic characteristics, was later introduced [49]. According to this system, lesions are defined in seven categories: intimal xanthoma (so-called fatty streak), intimal thickening, pathologic intimal thickening, fibrous cap atheroma, thin-cap fibroatheroma (TCFA), calcified nodule, and fibrocalcific plaque [49]. Pathologic intimal thickening or a thick-cap fibroatheroma is usually involved in plaque erosion [43]. Erosion is often the cause of thrombosis in young patients, particularly women younger than 50 years of age [34; 43]. The least often cause of thrombosis is a calcified nodule, which is usually found in older patients with substantially calcified and tortuous arteries [43].

Plaque Rupture

The stability of plaque is a crucial factor in the potential for rupture. Plaque that is at high risk of rupture is referred to as vulnerable plaque [50]. Vulnerable plaque has the following hallmark characteristics [41; 51]:

- Large lipid core (more than 40% of the total lesion area)
- Thin, fibrous cap (usually less than 65 micrometers)
- High infiltration of macrophages
- Few smooth muscle cells
- Expansive remodeling preserving the lumen
- Neovascularization from the vasa vasorum
- Adventitial/perivascular inflammation
- Spotty calcification

Because of its high lipid content, vulnerable plaque is associated with the progressive development of ischemic disease [41]. The high level of macrophage infiltration reflects the important role of inflammation in plaque rupture as well as early plaque formation. Plaque rupture generally begins where the cap is thinnest and has the highest infiltration of macrophages, which release lytic enzymes and toxic metabolites that act to degrade the cap, leading to rupture [41]. Plaque rupture triggers the formation of a thrombus when thrombogenic elements of the lipid core are exposed to circulating blood; rupture and thrombosis may occur at the same time, but a temporary increase in stress (emotional or physical) may be the trigger for a cardiac event [41]. However, a life-threatening luminal thrombus develops only occasionally; it is theorized that other factors are involved, such as thrombogenicity of the exposed plaque material, local flow disturbances, and systemic thrombotic propensity [41]. The presence of plaque material interspersed in a thrombus indicates that severe thrombosis developed immediately after plaque rupture; more often, however, the thrombus develops over several days before an ACS event [41].

In one study, the thrombus was days or weeks old in 49% of patients with STEMI [52]. Researchers have used a variety of imaging techniques to determine the distribution of TCFAs, and the lesions are most often found in the proximal third of the major coronary arteries, although the left circumflex and right coronary arteries were affected evenly throughout their length in one study [53; 54; 55]. The findings of another study suggest that TCFAs causing ACS events are also more likely to be found in proximal locations and that the left main coronary artery was less commonly affected [56].

Why some plaque ruptures cause an ACS event and most do not is unclear. Plaque rupture in nonculprit lesions has been found in approximately 14% of patients with ACS, and among these lesions, plaque burden was significantly greater in lesions with plaque rupture than in lesions without plaque rupture [57]. Plaque rupture in combination with large plaque burden and luminal narrowing appears to lead to ACS [4]. Lipid-rich plaque and intracoronary thrombus have been found significantly less often in patients with asymptomatic CHD compared with patients with NSTEMI [58].

It was once thought that the degree of occlusion caused by a thrombus differentiated STEMI from NSTEMI, with complete and sustained occlusion resulting in STEMI, and incomplete or transient occlusion resulting in NSTEMI [59]. However, research is challenging this theory; for example, studies have shown that the degree of stenosis in some cases of acute MI is not severe enough to limit blood flow [59]. Other studies have demonstrated that ACS is often associated with plaque with little or no calcification and positive vessel remodeling (outward expansion of the artery wall) and that plaque rupture, TCFAs, and red thrombus are significantly more common with STEMI than with NSTEMI [60; 61].

RISK FACTORS FOR CHD

Some risk factors for CHD were established many years ago, and researchers continue to seek to identify other risk factors that add predictive value to traditional risk factors.

Traditional Risk Factors

The Framingham Heart Study identified the first risk factors, and these factors were integrated into a risk-assessment tool, the Framingham Risk Score [62]. The factors in the Framingham Risk Score include age, total cholesterol level, HDL level, systolic blood pressure, treatment for hypertension, and cigarette smoking, and the score is used to determine the 10-year risk of so-called hard CHD (defined as MI or coronary-related death) among asymptomatic adults. The Framingham risk score is one of several scores that involve several traditional risk factors for assessing risk; other scores recommended include the Systematic Coronary Risk Evaluation (SCORE), PROCAM (men) and Reynolds (separate scores for men and women) [63]. The use of one of these risk calculators is a class IB recommendation from the American College of Cardiology Foundation and American Heart Association [63]. It is important to consider the populations on which these risk scores are based. For example, the Framingham Risk Score was developed on the basis of risk factors identified in the Framingham Heart Study, which involved a primarily White, middle-aged population. When the risk score has been evaluated in other populations, it has been found to underestimate the risk of CHD among older (mean age: 73.5 years) Black and White individuals, especially women [64]. ACC/AHA guidelines published in 2013 recommend that race- and sex-specific Pooled Cohort Equations be used to predict 10-year risk of a first hard atherosclerotic cardiovascular disease event in non-Hispanic Black and non-Hispanic White individuals (class IB) [65].

These equations were developed on the basis of data on participants from several large racially and geographically diverse studies [65]. The guidelines also note that the sex-specific pooled cohort equations for non-Hispanic White individuals may be considered to estimate risk for people other than Black and non-Hispanic White individuals (class IB) [65].

Primary care clinicians are also encouraged to routinely evaluate the presence of individual CHD risk factors, and the U.S. Preventive Services Task Force (USPSTF) has recommended routine screening for hypertension and dyslipidemia as well as counseling and pharmacologic interventions for smoking cessation [66; 67; 68]. The adult prevalence of hypertension in the United States is 46.7% and the prevalence of hypercholesterolemia (total cholesterol >200 mg/dL) is 33.9% [1].

Nontraditional Risk Factors

Many nontraditional risk factors have been evaluated for their usefulness in enhancing the estimation of CHD risk, and the ACC/AHA has issued evidence-based recommendations according to individual risk (***Table 5***) [63; 65]. A positive family history is considered a nontraditional risk factor for CHD, and approximately 14% of adults report having a parent or sibling who had a heart attack or angina before 50 years of age [1]. Family history of premature angina, MI, angioplasty, or bypass surgery increases the lifetime risk about 50% for both heart disease (from 8.9% to 13.7%) and CVD mortality (from 14.1% to 21%) [1]. Other nontraditional risk factors lend themselves to quantitative measure that may be used to predict risk. Those that have been evaluated most often are inflammatory markers, lipid-related markers, other biochemical markers, testing for subclinical atherosclerosis, electrocardiography (ECG), and imaging studies.

Inflammatory Markers

The recognition of the important role of inflammation in the development of CHD has led to increased research on the value of inflammatory markers in predicting risk. C-reactive protein (CRP) is the marker that has been most rigorously studied. The USPSTF found moderate, consistent evidence that adding a CRP level to a risk algorithm improves risk stratification for individuals at intermediate risk, and the 2010 ACCF/AHA guideline subsequently noted that measuring the CRP level may be reasonable for asymptomatic men (50 years of age or younger) or women (60 years of age or younger) who are at intermediate risk for cardiovascular disease [63; 69]. The ACCF/AHA guideline does not recommend a CRP level for asymptomatic adults at high risk [63]. One study suggested improved 10-year risk prediction when a CRP or fibrinogen level was added to a traditional risk score [70]. A later ACCF/AHA guideline notes that a high-sensitivity CRP may be considered when a risk-based treatment decision is uncertain after quantitative risk assessment [65].

The USPSTF found no evidence that homocysteine levels or leukocyte counts were useful in further stratifying risk among individuals at intermediate risk [71].

Lipid-Related Markers

The 2010 ACCF/AHA guideline for assessment of cardiovascular risk does not recommend assessment of lipoprotein or apolipoprotein levels [63]. Measurement of a lipoprotein-associated phospholipase A2 level "might be reasonable" for asymptomatic adults at intermediate risk [63]. In a study published after the ACCF/AHA guideline, the prediction of CHD improved slightly when information on apolipoprotein B and A-I, lipoprotein(a), or lipoprotein-associated phospholipase A2 mass was added to risk scores that included total cholesterol and HDL levels [72]. However, the 2013 ACCF/AHA guideline notes that the contribution of apolipoprotein B is uncertain [65].

EVIDENCE-BASED RECOMMENDATIONS FOR USE OF NONTRADITIONAL RISK FACTORS TO EVALUATE CHD RISK IN ASYMPTOMATIC ADULTS	
Nontraditional Risk Factor	**Recommendation (Class, Level of Evidence)**
Family history of CHD	Recommended for all asymptomatic women (IB) May be considered if risk-based treatment decision is uncertain after quantitative risk assessment (IIbB)[a]
Family history of atherothrombotic CHD	Recommended for all asymptomatic adults (IB)
Genomic testing	Not recommended (IIIB)
Lipoprotein and apolipoprotein assessments	Not recommended (IIIC)
Natriuretic peptides	Not recommended (IIIB)
C-reactive protein	May be considered if a risk-based treatment decision is uncertain (after quantitative risk assessment IIbB)[a] Not recommended for asymptomatic adults at high risk (IIIB) May be reasonable for asymptomatic men (50 years of age or younger) or women (60 years of age or younger) who are at intermediate risk (IIbB)
Hemoglobin A1C	May be reasonable for risk assessment in asymptomatic adults who do not have diabetes (IIbB) May be considered for asymptomatic adults with diabetes (IIbB)
Testing for microalbuminuria	Utility is uncertain[a] Reasonable for asymptomatic adults with hypertension or diabetes (IIaB) Might be reasonable for asymptomatic adults at intermediate risk who do not have hypertension or diabetes (IIbB)
Lipoprotein-associated phospholipase A2	Might be reasonable for asymptomatic adults at intermediate risk (IIbB)
Resting electrocardiography (ECG)	Reasonable for asymptomatic adults with hypertension or diabetes (IIaC) May be considered for asymptomatic adults who do not have hypertension or diabetes (IIbC)
Transthoracic echocardiography (to detect left ventricular hypertrophy)	May be considered for asymptomatic adults who have hypertension (IIbB) Not recommended for asymptomatic adults who do not have hypertension (IIIC)
Measurement of carotid intima-media thickness	Not recommended (IIIB)[a] Reasonable for asymptomatic adults at intermediate risk (IIaB)[b]
Brachial/peripheral flow-mediated dilation	Not recommended (IIIB)
Measurement of arterial stiffness	Not recommended outside of research settings (IIIC)
Measurement of ankle-brachial index	May be considered if a risk-based treatment decision is uncertain after quantitative risk assessment (IIbB)[a] Reasonable for asymptomatic adults at intermediate risk (IIaB)
Exercise ECG	May be considered for asymptomatic adults at intermediate risk (IIbB)[c]
Stress echocardiography	Not indicated for asymptomatic adults at low or intermediate risk (IIIC)
Stress myocardial perfusion imaging	Not indicated for asymptomatic adults at low or intermediate risk (IIIC) May be considered for assessment of advanced cardiovascular risk in asymptomatic adults who have diabetes or asymptomatic adults with a strong family history of CHD or when previous risk assessment suggests high risk of CHD (IIbC)

Table 5 continues on next page.

EVIDENCE-BASED RECOMMENDATIONS FOR USE OF NONTRADITIONAL RISK FACTORS TO EVALUATE CHD RISK IN ASYMPTOMATIC ADULTS *(Continued)*	
Nontraditional Risk Factor	**Recommendation (Class, Level of Evidence)**
Coronary artery calcium scoring	May be considered if a risk-based treatment decision is uncertain after quantitative risk assessment(IIbB)[a] Not recommended for persons at low risk (10-year risk <6%) (IIIB) Reasonable for asymptomatic adults at intermediate risk (10-year risk of 10% to 20%) (IIaB) Reasonable for asymptomatic adults (40 years and older) who have diabetes (IIaB) May be reasonable for persons at low to intermediate risk (10-year risk of 6% to 10%) (IIbB)
Coronary computed tomography angiography	Not recommended for asymptomatic adults (IIIC)
Magnetic resonance imaging of plaque	Not recommended for asymptomatic adults (IIIC)
[a]Recommended in the 2014 guideline. [b]Published recommendations on required equipment, technical approach, and operator training and experience for performance of the test must be carefully followed to achieve high-quality results. [c]May also be considered for sedentary adults who plan to start a vigorous exercise program.	
Source: [63; 65]	*Table 5*

Other Biochemical Markers

According to the 2010 ACCF/AHA guideline, natriuretic peptide levels are not recommended for the evaluation of risk among asymptomatic adults [63]. A hemoglobin A1C "may be reasonable" for assessing risk in asymptomatic adults without diabetes and "may be considered" for asymptomatic adults with diabetes [63]. This guideline also notes that testing for microalbuminuria is reasonable for asymptomatic adults with hypertension or diabetes and "might be reasonable" for asymptomatic adults with hypertension or diabetes who are at intermediate risk [63]. However, in its 2013 guideline, the ACCF/AHA expert panel notes that the contribution of albuminuria is uncertain [65].

Testing for Subclinical Atherosclerosis

Historically, screening for atherosclerosis has been done through measurement of lipid levels as surrogate markers. Now, coronary artery calcium scoring has become a strong risk predictor, improving risk classification of asymptomatic adults when the score is combined with traditional risk factors [73; 74]. The 2010 ACCF/AHA guideline notes that calcium scoring is reasonable for asymptomatic adults at intermediate risk (10-year risk of 10% to 20%), and for asymptomatic adults (40 years and older) who have diabetes and "may be reasonable" for individuals at low-to-intermediate risk (10-year risk of 6% to 10%) [63]. The test is not recommended for persons at low risk (10-year risk of less than 6%). Similarly, 2010 appropriate use criteria state that determination of a coronary calcium score with noncontrast CT is appropriate for individuals with a family history of premature CHD and for asymptomatic individuals with no known CHD who are at intermediate risk [75]. Subsequent systematic reviews have confirmed that coronary artery calcium scoring has additional predictive value (in combination with traditional risk factors), primarily for asymptomatic individuals at intermediate risk [76; 77]. The 2013 ACCF/AHA guideline notes that a CAC score may be considered if a risk-based treatment decision is uncertain after quantitative risk assessment [65].

The clinical utility of other tests for identifying subclinical disease is not as clear. In 2009, the USPSTF found no evidence that measurement of carotid intima-media thickness or ankle-brachial index were useful in further stratifying risk among individuals at intermediate risk [71]. However, the 2010 ACCF/AHA guideline notes that measurement of carotid intima-media thickness and ankle-brachial index is reasonable for asymptomatic adults at intermediate risk; however, the 2013 ACCFR/AHA guideline does not recommend routine measurement of carotid intima-media thickness and states that ankle-brachial index may be considered if a risk-based treatment decision is uncertain after quantitative risk assessment [63; 65]. The 2010 ACCF/AHA guideline does not recommend measurement of flow-mediated dilation or arterial stiffness as part of risk assessment [63]. Still more recently, systematic reviews have shown that measurement of flow-mediated dilation and carotid intima-media thickness had additional predictive value (in combination with traditional risk factors), primarily for asymptomatic individuals at intermediate risk [76; 77]. Magnetic resonance imaging of plaque is not recommended [63].

ECG

The ACC/AHA, ACP, and USPSTF have all recommended against routine screening with resting ECG and exercise treadmill test for asymptomatic individuals at low risk [63; 78; 79; 80]. The 2010 ACCF/AHA guideline notes that exercise ECG "may be considered" for asymptomatic adults at intermediate risk, but the USPSTF notes that there is insufficient evidence to assess the balance of benefits and harms of such screening among asymptomatic adults at intermediate or high risk [63; 80].

Imaging Studies

The 2010 ACCF/AHA guideline and the ACP screening guideline note that stress echocardiography is not indicated for asymptomatic adults at low or intermediate risk [63; 79]. Transthoracic echocardiography (to detect left ventricular hypertrophy) is not recommended for asymptomatic adults but "may be considered" for asymptomatic adults with hypertension. Coronary CT angiography is not recommended for asymptomatic adults. Stress myocardial perfusion imaging is not indicated for asymptomatic adults at low or intermediate risk but "may be considered" for assessment of advanced cardiovascular risk in asymptomatic adults with diabetes or with a strong family history of CHD [63; 79].

Primary Prevention Interventions Based on Risk Assessment

Primary prevention interventions should be implemented when a patient has one or more risk factors. Recent guideline updates have created shifts away from established goals and thresholds for interventions, especially with regard to hypertension and dyslipidemia.

The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease was commissioned to consolidate existing recommendations and clinical practice guidelines into a single document for primary prevention of CVD [81]. The document includes new guidance for aspirin use, exercise/physical therapy, and tobacco use, and recommendations for interprofessional team-based care, shared decision-making, and assessment of social determinants of health. Calculation of an age-specific 10-year CVD risk assessment should guide decision making, matching the intensity of preventive interventions to the patient's absolute risk. Effective prevention strategies promote a healthy lifestyle throughout life emphasizing optimal diet, physical activity, and avoidance of tobacco and exposure to secondhand smoke. Other major points of emphasis include the following [81]:

- Adults 40 to 75 years of age with traditional risk factors for CVD should undergo 10-year risk assessment and have a clinician-patient risk discussion before beginning pharmacologic therapy such as a statin or antihypertensive therapy.
- All adults should consume a heart-healthy diet, and overweight patients should be offered counseling to achieve and maintain weight loss.

- Adults should engage in at least 150 minutes per week of accumulated moderate-intensity physical activity or 75 minutes of vigorous-intensity physical activity.
- Guidance specific to management of adults with type 2 diabetes is provided.
- All adults should be assessed at every healthcare visit for tobacco use.
- Aspirin should be used infrequently for primary prevention of CVD because of lack of net benefit.
- Statin therapy is first-line treatment for primary prevention of CVD in patients with elevated low-density lipoprotein cholesterol levels (≥190 mg/dL), in those with diabetes who are 40 to 75 years of age, and those determined to be at sufficient risk of CVD after a clinician-patient discussion.
- Nonpharmacologic interventions are recommended for adults with elevated blood pressure, and the target blood pressure for those requiring pharmacologic therapy should generally be 130/80 mm Hg.

The 2017 Guideline for High Blood Pressure in Adults sets goals for systolic and diastolic blood pressure and provides evidence-based recommendations on treatment approaches [82]. These recommendations are included and adapted in the ACC/AHA 2019 Guideline on Primary Prevention of Cardiovascular Disease [81]. The authors of a meta-analysis found that, although antihypertension treatment provides similar benefit for individuals at all levels of baseline risk of CHD, the absolute risk reductions are progressively greater as baseline risk increases [83; 84].

With regard to the treatment of cholesterol levels, ACC/AHA guidelines published in 2013, and updated in 2018, differ greatly from the National Cholesterol Education Program (NCEP) guideline in 2001, with a substantially greater number of people eligible for treatment with cholesterol-lowering drugs, especially within the population of individuals at moderate risk of CHD [23; 85; 86; 87]. The new guideline matches statin assignment to total plaque burden better than the NCEP guideline, according to a study in which plaque burden was determined by CT angiography [88]. A clinician-patient risk discussion is recommended to ensure that patients understand the benefits of risk-reduction interventions, potential adverse effects, drug-drug interactions, and patient preferences [89]. This approach also has the potential to enhance patient adherence to medication. The 2018 guideline recommendations for management of blood cholesterol are included and adopted in the ACC/AHA Guideline on Primary Prevention of Cardiovascular Disease [81].

Increased emphasis has been placed on better management of lifestyle habits as primary prevention of CHD. Lifestyle risk factors such as obesity, poor diet, and physical inactivity have a great influence on traditional risk factors such as blood pressure and cholesterol levels, as well as on novel risk factors, such as inflammation and endothelial function [90]. Lifestyle management is a key component of the new guidelines for the treatment of cholesterol levels and hypertension, and several other guidelines have addressed issues related to lifestyle behaviors, such as obesity, diet, and physical activity. The ACC/AHA/TOS (The Obesity Society) developed a guideline on the management of overweight and obesity, and some members of the Expert Panel authored a separate review on the evidence statements related to cardiovascular risk [91; 92]. The AHA/ACC also published a guideline on lifestyle management to reduce cardiovascular risk in 2013 [93]. The decision to offer or refer adults without cardiovascular risk factors to behavioral counseling should be individualized by the primary care physician [94].

Another aspect of prevention that warrants increased attention is the role of complementary and alternative medicine. Approximately 33% of adults use complementary and alternative medicine therapy (including dietary supplements), and 40% to 70% do not tell their doctors about the therapy [95; 96]. Systematic reviews have shown that there is insufficient evidence to support the primary prevention of cardiovascular disease with multivitamins, co-enzyme Q10, selenium supplement, green or black tea, or tai chi [97; 98; 99; 100; 101]. Studies have shown that a Mediterranean diet has a beneficial effect on cardiovascular risk factors, although the evidence is limited [102]. The USPSTF recommends against vitamin E supplements and ß-carotene for the prevention of cardiovascular disease [97].

Adherence to guidelines for management of CHD risk and to prevent cardiovascular disease has been suboptimal, especially among patients at low risk for disease [20; 21; 103]. Clinicians have noted several barriers to adhering to CHD prevention guidelines, including [20; 21]:

- Cost of medications
- Lack of reimbursement, especially for lifestyle interventions
- Lack of adequate time for counseling
- Lack of patient education tools
- Existence of multiple guidelines
- Lack of knowledge and skills to recommend dietary changes and facilitate patient adherence

Efforts should be directed at alleviating these barriers to enable healthcare professionals to evaluate patients' risk factors adequately and to develop ways to help patients understand their risk and the importance of prevention strategies. A multidisciplinary team approach is needed to provide expertise in all areas. In addition, initiatives should emphasize the risk of CHD among women.

DIAGNOSIS AND RISK STRATIFICATION

Chest pain is the second most common reason for seeking care in the emergency department, accounting for approximately 5.6% of visits [104]. Patients with chest pain present a tremendous diagnostic challenge for many reasons, including a substantial overlap between characteristics of noncardiac and cardiac pain, misinterpretations of ECG and cardiac biomarker levels, and the lack of typical clinical presentation in many individuals.

Most emergency department clinicians err on the side of caution when evaluating patients with chest pain because of the serious consequences of a missed diagnosis of ACS, in terms of adverse patient outcome as well as threat of medical malpractice [105]. As a result, fewer than 10% of patients who are evaluated for chest pain are ultimately found to have ACS [106].

Both the overdiagnosis and underdiagnosis of ACS have unique consequences. Overdiagnosis leads to unnecessary treatments and high costs, and underdiagnosis has the more serious consequence of increased mortality (compared with hospitalized patients) [105]. The high rate of overdiagnosis indicates that a greater understanding is needed about several aspects of ACS:

- Which individuals are at highest risk for ACS
- How clinical signs and symptoms reflect the likelihood of ACS
- How age, gender, and race/ethnicity are related to differences in signs and symptoms
- How signs, symptoms, and diagnostic testing results should be factored into accurate risk stratification

Not only does a diagnosis of ACS need to be accurate, but it should be timely, as appropriate treatment given early substantially reduces morbidity and mortality [2; 3].

To help standardize the diagnosis of patients with chest pain and ACS-related symptoms, the AHA and ACC have jointly developed guidelines on the management of suspected UA/NSTEMI and STEMI, which are updated frequently as new evidence becomes available [2; 3]. The approach to diagnosing UA/NSTEMI and STEMI is primarily the same, but each has some unique features. The diagnosis of UA/NSTEMI can be more complex because it lacks the definitiveness of a specific ECG finding. With the diagnosis of STEMI, time is a crucial factor because of the need for reperfusion within tight timeframes. Both guidelines include recommendations for initial evaluation in the emergency department as well as the prehospital setting. The focus here is on initial evaluation in the emergency department setting, and the emphasis throughout is on class I recommendations.

It is imperative to quickly identify patients with chest pain and other symptoms suggestive of ACS, and registration staff and triage nurses should be familiar with their institution's chest pain protocol. High priority should be given to patients with chest pain. Ideally, the emergency department will be notified that a patient with chest pain is arriving, as such patients should be transported by emergency medical services (EMS). Use of EMS transport is associated with substantial decreases in ischemia time and in treatment delays [107]. Unfortunately, studies have shown that 40% to 80% of patients with ACS symptoms do not use emergency medical services, with high rates of self-transport among minority populations [107; 108; 109].

The two primary goals of the initial evaluation in the emergency department are to determine the likelihood that an individual has ACS and to estimate the short-term risk of adverse outcome(s) [3]. The findings of the history, physical examination, ECG, and cardiac troponin levels have been integrated into risk assessment scores and clinical prediction algorithms to help identify patients at increased risk of adverse outcomes. Identifying patients at high risk is most important, as these patients will gain the greatest absolute benefit from appropriate therapy [2; 3]. Because timely, appropriate treatment depends on results of the clinical findings and diagnostic testing, it is essential that this information is obtained as quickly as possible.

Studies have shown that adherence to guidelines for the diagnosis and management of ACS has improved since the early 2000s, but can still be improved [28; 110; 111; 112]. Improving adherence to guideline-directed diagnosis calls for system-wide involvement in quality improvement initiatives. The ACC/AHA recommends participation in a standardized quality-of-care registry that tracks and measures outcomes, complications, and performance measures because of its benefit in improving the quality of care for patients with ACS [3].

HISTORY AND PHYSICAL EXAMINATION

The ACC/AHA guidelines begin with recommendations for a carefully taken history and physical examination. A carefully taken history and physical examination are essential to elicit the details needed to make an accurate diagnosis. The medical history should focus on the type of pain the individual is having, accompanying symptoms, and risk factors that may predispose the patient to ACS. The primary goal of the physical examination is to identify any precursors of acute ischemia and to rule out noncardiac causes of pain, many of which are life-threatening. It is important to determine the time of symptom onset, as timely treatment is essential, especially for patients with STEMI. Other helpful information includes the presence of contraindications to any potential treatment and a history of related events, such as previous episodes of ischemia, MI, CABG, or PCI [2; 3].

Given the importance of the patient's history in determining a diagnosis of ACS, it is essential to ensure accurate communication between the patient and healthcare providers, with attention to addressing language and cultural needs. However, the potential for communication challenges can be high. In a London study involving patients with ACS who were of Afro-Caribbean or South East Asian descent, three primary impediments to effective

communication were identified: leading questions to define chest pain, patient-clinician conflict related to poor communication, and frank miscommunication as a result of language barriers and translational difficulties [113].

Such communication challenges are prevalent in the United States, as the population of non-English-speaking individuals grows. According to the U.S. Census Bureau, more than 46 million Americans are foreign-born, and 26.5 million Americans say they speak English less than "very well" [114]. It has been suggested that patients should be asked what language is spoken at home and what language they prefer for their medical care information, as some patients prefer their native language even though they can understand and discuss symptoms in English [115].

Many studies have demonstrated that the lack of an interpreter for patients with limited English proficiency compromises the quality of care [116; 117]. In addition, the use of professional interpreters is associated with improvements in communication (e.g., errors, comprehension), healthcare use, clinical outcomes, and patient satisfaction with care [116; 118]. Despite these findings, professional interpreters are underused in healthcare settings, including the emergency department [117].

"Ad hoc" interpreters (e.g., untrained staff members, family members, friends, or strangers in the hospital) are often used instead of professional interpreters for a variety of reasons, including convenience and cost. However, clinical consequences are more likely with ad hoc interpreters than with professional interpreters [116]. A systematic review of the literature has shown that the use of professional interpreters provides better clinical care than the use of ad hoc interpreters, with the former improving the quality of care for patients with limited English language skills to a level equal to that for patients with no language barriers [118]. In addition, individuals with limited English language skills have indicated a preference for professional interpreters rather than family members [119].

Chest Pain

Chest pain is the most commonly reported symptom in all patients with ACS, regardless of age, gender, race/ethnicity, or the presence of comorbid conditions [11; 120]. Despite this fact, up to one-third of patients with ACS have no chest pain or discomfort [120; 121]. Thus, the lack of chest pain should not rule out ACS as a diagnosis, especially in the presence of other indicators.

The first step in evaluating chest pain is to determine whether the pain is cardiac or noncardiac. Many other conditions can cause chest pain that is similar to cardiac pain, and the physical examination and imaging tests can aid in the differential diagnosis (***Table 6***) [3; 122]. When discussing chest pain with the patient, the clinician should focus on several aspects of the pain or discomfort, including [105]:

- Characteristics (i.e., severity, location, radiation)
- Time of onset
- Duration
- Alleviating and exacerbating factors

So-called classic ACS-related chest pain has been described as diffuse pain or pressure in the substernal or epigastric area that frequently radiates to the neck, throat, jaw, back, shoulder, and left arm [123]. Chest pain related to ACS usually begins abruptly and lasts at least 15 to 20 minutes; however, the duration of pain varies among patients [123; 124]. The intensity of classic ACS chest pain increases over time, reaching maximal intensity after a few minutes [123]. Pain is usually worse with activity and improves with rest.

Several descriptors are used most often to describe ACS-related chest pain, including [105; 123]:

- Tightness
- Pressure
- Heaviness
- Crushing
- Squeezing

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN
Life-Threatening Causes
Aortic dissection
Pulmonary embolism
Pneumothorax
Expanding aortic aneurysm
Other Causes
Pneumonia
Pleuritis
Pericarditis
Costochondritis
Cervical disc disease
Peptic ulcer disease
Gastroesophageal reflux
Biliary disease
Pancreatitis
Panic attack
Source: [3; 122] *Table 6*

The characteristics of ACS-related chest pain are similar to those of stable angina, which has been noted to be deep, poorly localized discomfort of the chest or arm [3]. ACS-related chest pain differs from stable angina in that ACS-related pain occurs at rest, is of new onset, or is of increasing intensity, duration, and/or frequency [3]. An important distinction between stable angina and UA is that the former is exacerbated by activity or emotional stress and relieved by rest and/or nitroglycerin; in contrast, UA occurs at rest [3]. Pain associated with UA may also be pain previously diagnosed as angina that has increased in frequency, duration, or severity or that is prompted by less exertion than in the past [3].

Pain features that are not generally characteristic of ACS-related pain include [3; 123; 125; 126; 127]:

- Sharp, stabbing pain
- Pain reproduced with movement or palpation of the chest wall or arms
- Pain of several hours' duration
- Fleeting pain (episodes lasting for a few seconds or less)
- Pain that is of greatest intensity at the onset
- Discomfort primarily (or only) in the middle or lower abdomen

However, the possibility of ACS should not be dismissed because of the presence of atypical pain characteristics. ACS has been diagnosed in 22% of patients who had sharp or stabbing pain and in 13% of patients with pleuritic-type pain, in as many as 15% of patients who had reproducible pain, and in 5% of patients with sharp, stabbing, fleeting pain [3; 125].

An increasing number of studies have demonstrated that atypical chest pain occurs more often in several subgroups of patients, especially women, older individuals, and people with diabetes [11; 120; 128; 129; 130; 131; 132]. In addition, the findings of several studies and literature reviews have demonstrated that women with ACS are more likely to have pain or discomfort in the jaw, neck, throat, arm/shoulder, and back [128; 133; 134].

In the past, it was thought that cardiac pain could be distinguished from some types of noncardiac pain by assessing the relief of chest pain with use of specific drugs, such as nitroglycerin or antacids. However, relief of chest pain after administration of either of these drugs should not be used to distinguish pain as cardiac or noncardiac in nature. Studies have shown that nitroglycerin may relieve both cardiac and noncardiac chest pain [3]. In one study, nitroglycerin relieved chest pain in 35% of patients with ACS and 41% of patients without ACS [3]. Similarly, a gastrointestinal cause of pain should not be assumed if the chest pain is relieved by antacids, as some patients with ACS have reported relief after use of such a drug [3; 126].

Associated Symptoms

The classic presentation of ACS includes some symptoms in addition to chest pain, primarily dyspnea, diaphoresis, nausea, abdominal pain, or syncope [2; 3]. Again, there is wide variation in the symptoms reported by patients with ACS, as well as differences in subgroups of patients. Patients with STEMI more commonly report nausea, cold sweats, and vomiting [134]. Diaphoresis occurs more often in men with ACS compared with women [128]. In contrast, the likelihood of nonspecific symptoms is greater for women with ACS, with higher rates of fatigue,

RISK FACTORS FOR CHD ACCORDING TO RACE/ETHNICITY AMONG PATIENTS WITH ACS					
Patient Characteristics	**White**	**Black**	**Hispanic**	**Native American**	**Asian**
Age	63.9 years ±13	59.4 years ±13	61.3 years ±13	58.7 years ±12	63.7 years ±12
Male sex	62%	50%	61%	62%	61%
Risk Factors					
Family history of CHD	42%	38%	37%	42%	28%
Hypertension	69%	81%	71%	70%	75%
Diabetes	28%	40%	44%	54%	37%
Current smoker	26%	31%	22%	38%	16%
ACS = acute coronary syndrome; CHD = coronary heart disease.					
Source: [138]					*Table 7*

nausea and/or vomiting, indigestion, palpitations, dyspnea, and dizziness, and lightheadedness [128; 129; 133; 134; 135; 136]. Among older individuals, dyspnea and fatigue have been noted to be the most common symptoms and diaphoresis has been reported less often [11; 125; 126].

Patient History

Typically, the patient history can aid in the diagnosis of a current disease. However, in a study of the influence of traditional cardiac risk factors on a diagnosis of ACS, the cardiac risk factor burden (defined as the number of risk factors) had limited value in predicting the likelihood of ACS, especially in patients older than 40 years of age [130]. Research has shown that a history of traditional cardiac risk factors varies among some subgroups. Women with ACS are more likely than men to have a history of diabetes, hypertension, or hyperlipidemia [24; 123; 133]. (Women are less likely to be smokers, to have a history of angina or MI, and to have had PCI or CABG, regardless of the cardiac history [24; 128; 137]. According to data from the NCDR, the prevalence of risk factors varies across racial/ethnic subgroups of individuals with ACS (***Table 7***) [138].

The five most important history-related factors that relate to the likelihood of ischemia due to CHD are (in order of importance) [139]:

- Nature of the chest pain
- History of CHD
- Sex/gender
- Age
- Number of traditional risk factors

Physical Examination

Most often, the physical examination is normal for patients being evaluated for possible ACS. Thus, the physical examination is important not to establish a diagnosis of ACS but rather to rule out an alternate diagnosis, identify any precursors of acute ischemia, identify any comorbidities that may have an impact on treatment decisions, and add prognostic information [2; 3]. Ruling out a noncardiac cause of chest pain is especially important given the severity of some potential conditions [3; 122].

The physical examination should include the following [3]:

- Measurement of vital signs
- Determination of the presence of stroke, pulses, or absence of jugular venous distention
- Pulmonary auscultation for rales
- Cardiac auscultation for murmurs and gallops
- Neurologic evaluation
- Evaluation for signs of cardiogenic shock (hypotension and organ hypoperfusion)
- Identification of contraindications to antiplatelet or fibrinolytic therapy

The presence of bruits or pulse deficits (which would suggest extracardiac disease) is associated with a higher likelihood of significant CHD [3]. Similarly, significant CHD is more likely in a patient who has an S3 or S4 gallop, a new mitral insufficiency murmur, or signs of congestive heart failure (pulmonary rales and elevated jugular venous pressures) [125]. Cardiogenic shock is associated more often with STEMI than NSTEMI, and mortality rates are high [3]. Physical examination should also identify contraindications to antiplatelet or fibrinolytic therapy, which include any prior intracranial hemorrhage, known malignant intracranial neoplasm, suspected aortic dissection, active bleeding or bleeding diathesis (excluding menses), or significant closed-head or facial trauma within the previous three months [2].

DIAGNOSTIC EVALUATION

The integration of the clinical presentation and history with ECG findings, cardiac biomarker levels, and results of cardiac imaging is essential for determining an accurate diagnosis, assessing risk, and guiding subsequent therapy.

ECG

ECG has historically been used to assess myocardial ischemia, and it continues to be an essential diagnostic tool in ACS and an important component in risk stratification. The ECG not only provides documentation of an acute MI but also differentiates between UA/NSTEMI and STEMI. Both UA and NSTEMI are characterized by a lack of ST-segment elevation on ECG. The distinction between the two conditions relies on troponin levels.

New ST-segment depression and symmetrical inverted T-waves both suggest acute ischemia or NSTEMI, and the likelihood is higher for ST-segment depression [3]. As noted, STEMI is associated with complete occlusion (more than 90%) of a coronary artery, and such occlusion is indicated by ST-segment elevation, ranging from less than 1 mm in a single lead to 10 mm in multiple leads [124]. An emergency physician experienced in reading ECGs or a cardiologist should interpret the findings, especially when STEMI is suspected [2]. A diagnosis of acute MI is confirmed with results of serial cardiac biomarker measurements in 90% of patients who have ST-segment elevation of 1 mm or more in at least two contiguous leads [3]. The resultant area of irreversible infarction with STEMI can be large, and immediate reperfusion therapy is needed. Therefore, ECG is essential for therapeutic decision making, and its findings are the primary determinant for treatment of STEMI [2].

The ACC/AHA guidelines recommend that a 12-lead ECG be done and interpreted by an experienced physician within 10 minutes after arrival for patients who have chest pain or other signs suggestive of ACS [2; 3]. The diagnostic accuracy of ECG is improved if it is done while the patient is symptomatic, as acute ischemia (and underlying CHD) is strongly suggested by the transient ST-segment changes that occur during symptoms at rest and resolve when symptoms disappear [3]. A 12-lead ECG performed by EMS personnel is recommended for patients who have symptoms consistent with STEMI [2].

A single ECG cannot capture the entire dynamic process of ischemia. As a result, the initial ECG for patients with acute MI can be normal or nondiagnostic in 20% to 55% of cases [123]. Among patients with chest pain and a normal ECG, approximately 1% to 6% will subsequently be found to have MI and about 4% will be found to have UA [3]. Nondiagnostic ECGs are more likely in older patients; according to trial data, the rate of nondiagnostic ECGs was 23% for patients younger than 65 years of age and was 43% for patients 85 years of age and older [11]. In addition, ST-segment elevation on the ECG at presentation has been shown to decrease with age, from 96.3% for patients younger than 65 years of age to 69.9% for patients 85 years of age or older [11].

Thus, the ACC/AHA guidelines state that if the initial ECG is not diagnostic or if the patient remains symptomatic and ACS is suspected, serial ECGs should be done at intervals of 15 to 30 minutes during the first hour [3].

ST-segment and T-wave changes are not specific for ACS and may be the result of another disease or condition. Left ventricular aneurysm, pericarditis, myocarditis, Prinzmetal angina, Takotsubo cardiomyopathy, early repolarization, and Wolff-Parkinson-White syndrome may cause ST-segment elevation [3]. T-wave inversion can be caused by central nervous system events and treatment with tricyclic antidepressants or phenothiazines.

Adherence to the ACC/AHA guidelines for obtaining ECG has been suboptimal, with ECG being performed up to 73% of the time [140; 141]. Delay in obtaining the first ECG has been associated with female gender and older age [11; 24; 142]. This delay may be related to the high rate of atypical presentation of ACS in these populations [11; 143]. Increasing the number of nurses or ECG technicians during peak hours and training additional staff to perform ECGs may help to improve timeliness [28; 144].

Cardiac Biomarkers

Cardiac biomarkers are detectable intracellular macromolecules released into the circulation after cardiomyocyte injury and death. The biomarkers once used—creatinine kinase (CK)-MB and myoglobin—have been replaced by cardiac-specific troponin (troponin I or T) because of the latter's high concentration in myocardium, near-absolute specificity for myocardial tissue, absence in the blood of healthy individuals, and high clinical sensitivity [2; 3; 31]. Measurement of CK-MB or myoglobin levels was not useful or cost-effective [145].

Cardiac Troponins

As noted, cardiac troponin I and T are sensitive and specific biomarkers of myocardial injury, and serum measurements are used to identify whether patients with ACS have had an MI. A variety of troponin assays are in use. Contemporary ("sensitive") troponin assays have been in use for many years, while "highly sensitive" assays were only approved in 2017 for use in the United States. The Fourth Universal Definition of MI recommends using highly sensitive troponin assays when available [31]. The time to initial elevation of cardiac troponin levels following MI is 2 to 12 hours when measured by sensitive assays, with peak elevation at 24 hours (troponin I) and 12 to 48 hours (troponin T) [3; 146]. Levels may remain elevated for 5 to 10 days (troponin I) or up to 14 days (troponin T) after an MI [146]. Highly sensitive assays detect significant elevations of cardiac troponin within one hour, which has the advantage of more rapid diagnosis and triage. The sensitivity of cardiac troponin for the diagnosis of MI is relatively low during the first six hours, especially in patients who present shortly after symptom onset [146]. However, for most patients with ACS, MI can be ruled out or confirmed within six hours, in part because of the high rate of delayed presentation associated with chest pain [3].

For the diagnosis of MI, the Fourth Universal Definition of MI defines myocardial injury as a rise and/or fall in cardiac troponin of at least one level above the 99th percentile of the upper reference level (URL) for normal values, including evidence of serial increases or decreases of troponin levels [31]. Similarly, the recommendations based on the findings of a Laboratory Medicine Best Practices systematic review are the use of cardiac troponin assays only (no additional biomarkers), with the 99th percentile URL used as the clinical diagnostic threshold for a diagnosis of NSTEMI [147].

It is important to bear in mind that chronic elevations of troponin are present in some patients unrelated to acute events, which is why a rise or fall of troponin is required to establish the diagnosis of MI. Baseline troponin levels are often higher in the elderly than in younger adults; 20% of adults older than 70 years of age have, as baseline, a cardiac troponin level above the 99th percentile URL [32]. Troponin assays are not standardized; the value reported will vary depending on the assay used, and comparison of reported results across different laboratories may not be reliable for diagnostic purposes [31]. Clinicians should familiarize themselves with the specific assay used in their own clinical facility.

The ACC/AHA guideline for UA/NSTEMI states that troponin levels should be measured at the time of presentation and three to six hours after the onset of symptoms in all patients suspected of having ACS [3]. If the time of symptom onset is unclear, the time of presentation should be used instead. When initial serial troponin levels are normal but ECG changes and/or clinical features increase the suspicion for ACS, additional troponin levels should be measured beyond six hours [3]. The lack of elevated troponin levels at the time of presentation should not rule out an MI, as the initial level is normal in as many as 23% of patients with MI [148]. Troponin levels appear to have value in ruling out an MI; the negative predictive value of undetectable troponin levels has been reported to be 99% to 100%.

A diagnosis of MI should not be made on the basis of a single elevated troponin level, as elevated levels may be associated with other cardiac conditions, including tachyarrhythmia, high or low blood pressure, cardiac trauma, heart failure, myocarditis, and pericarditis [3].

Other Markers

As noted earlier, CK-MB, myoglobin, and other biomarkers are no longer useful in diagnosing ACS. B-type natriuretic peptide (BNP) and N-terminal proBNP are also not useful as an aid to diagnosing ACS, but they have demonstrated strong predictive value for short-term and long-term mortality for patients with ACS, and the ACC/AHA guideline notes that these biomarkers may be considered to assess risk in patients in whom ACS is suspected (class IIbB) [3; 149; 150].

COMPREHENSIVE RISK SCORE AND PROGNOSIS

Risk stratification is an integral component of diagnosis, especially for patients with UA/NSTEMI. The risk of cardiac death and ischemic events varies widely in the UA/NSTEMI population, and the prognosis can help inform decision making regarding treatment [3]. The ACC/AHA guidelines for UA/NSTEMI and STEMI recommend risk assessment with either the Thrombolysis in Myocardial Infarction (TIMI) risk score or the GRACE risk model [2; 3]. The TIMI risk score predicts 30-day and 1-year mortality and was developed in a population of patients with STEMI; the GRACE model predicts in-hospital and six-month mortality for all patients with ACS [2; 3].

The TIMI risk score is based on seven independent risk factors [151]:

- Advanced age (65 years or older)
- At least three risk factors for CHD
- Previous coronary artery stenosis of 50% or more
- ST-segment deviation on initial ECG

- At least two episodes of angina in the past 24 hours
- Use of aspirin in the past seven days
- Elevated levels of cardiac biomarkers

One point is given for each factor, and the total score corresponds to the risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 days [151]. That risk ranges from 4.7% for a TIMI risk score of 0 or 1 to 40.9% for a score of 6 or 7. Patients with a higher TIMI score will derive greater benefit from an invasive strategy [3]. The TIMI risk calculator can be accessed online at https://timi.org.

The GRACE risk model includes eight variables [152]:

- Age
- Killip class
- Systolic blood pressure
- ST-segment deviation
- Cardiac arrest during presentation
- Serum creatinine level
- Elevated cardiac biomarkers
- Heart rate

Points are assigned to each factor, and the sum total corresponds to a probability of in-hospital death, ranging from 0.2% or less for up to 60 points to more than 52% for a sum of 250 points or more [152]. As with the TIMI score, patients with a higher score gain greater benefit from an invasive strategy [3]. The GRACE risk tool is also available online (https://www.outcomes-umassmed.org/grace).

Clinical features, ECG findings, and troponin levels may also be used to determine both early- and long-term prognosis and direct treatment. For example, patients with elevated troponin levels will gain benefit from intensive management and early revascularization [3]. In addition, elevated troponin levels have been associated with an estimation of infarct size and the risk of death [3]. With regard to ECG findings, after confounding ECG patterns (i.e., bundle-branch block, paced rhythm, left ventricular hypertrophy), the highest risk for death has been associated with ST-segment deviation (elevation or depression) [3]. Isolated T-wave inversion or normal ECG findings were associated with intermediate and low risk, respectively [3]. In another study, the incidence of death or MI at one year was significantly higher for patients who had ST-segment deviation of at least 1 mm and an elevated troponin level (18%) compared with patients who had deviation of less than 1 mm (11%) [153].

FINAL DIAGNOSIS

Four diagnoses are possible after complete evaluation for possible ACS: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS.

Risk assessment factors are used to help identify people who are at low risk of ACS and can thus be discharged safely. In one study, short-term clinically relevant adverse cardiac events were rare among patients who had "nonconcerning" vital signs, nonischemic findings on ECG, and no elevated troponin levels on serial testing [154]. Accelerated diagnostic protocols have been developed to help identify patients who can be safely discharged. According to one such protocol, a TIMI score of 0, no new ECG changes, and nonelevated troponin levels at 0 and 2 hours after the time of presentation indicates a low risk of ACS, with no major adverse cardiac events occurring within 30 days after discharge [155; 156]. Another risk stratification tool, the HEART score (consisting of history, ECG findings, age, risk factors, and troponin levels) has been validated in the Netherlands [157]. The HEART score has been shown to identify patients at low risk for ACS and major adverse cardiac events [157]. When compared with care according to ACC/AHA guidelines, a protocol consisting of the HEART score and troponin levels at 0 and 3 hours, led to an increased number of early discharges, with no major adverse cardiac events at 30 days; shorter lengths of stay, and a decrease in objective cardiac testing over 30 days [106].

The ACC/AHA guideline for UA/NSTEMI includes no class I recommendations for discharge from the emergency department. For patients with possible ACS but normal ECG and troponin levels, the guideline notes that it is reasonable to [3]:

- Observe in a chest pain unit or telemetry unit and perform serial ECGs and cardiac troponin levels at intervals of three and six hours (class IIaB)
- Order a treadmill ECG (IIaA), stress myocardial perfusion imaging, or stress echocardiography (IIaB) before discharge or within 72 hours after discharge
- Perform coronary CT angiography to assess coronary artery anatomy (IIaA) or rest myocardial perfusion imaging with a technetium-99m radiopharmaceutical to exclude myocardial ischemia (IIaB)

Patients with chronic stable angina should be treated according to the ACC/AHA guidelines [158]. Patients who are discharged from the emergency department should be told to see their primary care physician as soon as possible, preferably within 72 hours [3]. The results of all diagnostic testing in the emergency department should be sent to the primary care physician to ensure continuity of care. Patients with definite ACS should be treated according to the type of MI.

TREATMENT OF UA/NSTEMI

According to data from several studies and quality improvement initiatives, adherence to ACC/AHA guidelines has improved since the early 2000s, but is still not optimal. In addition, time is needed for clinicians to become familiar with updates to clinical practice guidelines.

The ACC/AHA guideline, updated in 2014, reflects the research advances made in ACS. Many more treatment options are available, and clinicians should be familiar with the choices in order to select a strategy on the basis of an individual's status and preference. The most substantial changes in the updated guideline relate to the following issues [3]:

- More potent antiplatelet and anticoagulant therapy
- Benefit of guideline-directed medical therapy for low-risk patients
- Proper selection of older individuals and women for interventional therapy
- Expanded recommendations on discharge, including patient education, dual antiplatelet therapy, and referral to cardiac rehabilitation

GENERAL CARE

The general care of patients with UA/NSTEMI is directed at the severity of symptoms. Bed rest is recommended while patients have ischemic pain. After symptoms have subsided, patients may move to a chair. The ACC/AHA guideline notes that there is no benefit to the routine use of supplemental oxygen, and it may, in fact, even be harmful [3]. Instead, supplemental oxygen should be given only to patients who have an arterial oxygen saturation of less than 90%, respiratory distress, or other high-risk features of hypoxemia. Continuous ECG monitoring should also be carried out, not only to detect ECG changes that may provide additional diagnostic and prognostic information but also because sudden ventricular fibrillation is the primary preventable cause of death during this initial period [3].

ANALGESIC AND ANTI-ISCHEMIC THERAPY

The goal of immediate treatment for patients with UA/NSTEMI is to provide relief of ischemia and to prevent recurrent adverse ischemic events [3]. This goal is initially achieved through anti-ischemic, antiplatelet, and anticoagulant therapies (***Table 8***).

Analgesic and anti-ischemic therapy for UA/NSTEMI involves the use of nitroglycerin, morphine, beta blockers, calcium-channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. These agents will help alleviate pain through their mechanisms of action. No nonsteroidal anti-inflammatory drugs (NSAIDs) should be given because of the documented increased risk of major adverse cardiovascular events [3].

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Analgesia			
Nitroglycerin	All patients, unless contraindicated (class IC)	No recommendation	Contraindicated for patients with hypotension or who have used sildenafil or vardenafil within previous 24 hours or tadalafil within previous 48 hours (class IIIB).
	All patients, unless contraindicated (class IB)	No recommendation	
Morphine	Reasonable for patients who have chest pain unrelieved by maximally tolerated anti-ischemic medications (class IIbB)	Not specifically recommended. Narcotics should be considered if high-dose aspirin fails to relieve pain (class IIbC)	—
Anti-Ischemia Therapy			
Beta blocker	All patients, unless contraindicated (class IA) Continue during and after hospitalization, unless contraindicated (class IC) Re-evaluate patients with initial contraindications to beta blockers for subsequent use (class IC)	All patients, unless contraindicated (class IB) Continue during and after hospitalization, unless contraindicated (class IB) Re-evaluate patients with initial contraindications to beta blockers for subsequent use (class IC)	Administer in the first 24 hours. Contraindicated for patients with signs of heart failure, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to beta blockers.
ACE inhibitor	Started and continued in all patients with left ventricular ejection fraction less than 40% and in patients with hypertension, diabetes, or stable CKD, unless contraindicated (class IA)	All patients (within the first 24 hours) with anterior location, HF, or ejection fraction less than or equal to 0.40, unless contraindicated (class IA)	Contraindicated for patients with hypotension (systolic blood pressure of <100 mm Hg or <30 mm Hg below baseline). An angiotensin receptor blocker should be used for patients intolerant of ACE inhibitors.
Calcium-channel blocker	Patients with continued or recurrent ischemia or with contraindications to beta blockers (class IB)	No recommendation	—
Antiplatelet Therapy			
Aspirin (non-enteric coated, chewable)	All patients (class IA) Continued indefinitely	All patients (class IA) Continued indefinitely	Should be given as soon as possible at time of evaluation. Contraindicated for patients who have aspirin allergy or active bleeding. Lower dose is reasonable during initial period post-stent implantation in patients at risk of bleeding. Consider clopidogrel or warfarin if aspirin is contraindicated. Monitor closely.
Clopidogrel	All patients (class IB) Administer to patients who are unable to take aspirin (class IB) Maintenance dose daily, continued preferably for up to one year (class IB)	All patients (in addition to aspirin), before or at the time of PCI, if not already started and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (class IC) Daily dose should be continued for one year (class IC)	Loading dose not recommended for older (>75 years of age) patients with STEMI. Should be withheld for five days in patients to have CABG (class IB). Monitor closely when used in conjunction with warfarin.

Table 8 continues on next page.

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI *(Continued)*			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Antiplatelet Therapy *(Continued)*			
Prasugrel	Not recommended for initial platelet therapy. All patients undergoing PCI with stenting should be given a loading dose and at least one year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	All patients undergoing PCI with stenting should be given a loading dose and at least one year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB). Should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non-fibrin-specific agent (classIIaB)	Should be withheld for at least seven days in patients to have CABG (class IB). Should not be administered to patients with history stroke or transient ischemic attack (classIIIB).
Ticagrelor	All patients undergoing PCI with stenting should be given a loading dose and at least one year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	All patients (in addition to aspirin) undergoing PCI with stenting should be given a loading dose and at least one year of maintenance therapy with this or other P2Y inhibitor if not given clopidogrel (class IB).	Should be withheld for at least five days in patients to have CABG (class IB). May only be used with lower doses (81 mg) of aspirin. Requires twice daily administration.
Glycoprotein IIb/IIIa inhibitor	Patients selected for early invasive treatment, along with dual-antiplatelet therapy, who are at intermediate or high risk (high troponin levels) (class IIbB)	Reasonable for selected patients who are receiving unfractionated heparin to have abciximab with primary PCI (class IIaA); eptifibatide or tirofiban may also be considered with primary PCI (class IIaB) May be reasonable to administer in emergency department to patients selected for primary PCI (class IIbB)	The rate of IV infusion of eptifibatide or tirofiban should be reduced by 50% for patients with estimated creatinine clearance <50 mgL/min. Eptifibatide or tirofiban should be discontinued two to four hours before CABG (class IB).
Anticoagulant Therapy			
Unfractionated heparin (UFH)	Option for patients selected for early invasive treatment (class IB) and early conservative treatment (class IB) Dose adjusted according to hospital protocol to maintain therapeutic anticoagulation for 48 hrs or until PCI (class IB)	Option for patients selected for primary PCI (class IC) or fibrinolytic therapy (class IC); administer for at least 48 hours or until revascularization	The UFH dose should be reduced when a glycoprotein IIb/IIIa inhibitor is also given (class IC). For patients undergoing PCI after receiving anticoagulant regimen, administer additional boluses of UFH as needed to support procedure (class IC).
Enoxaparin	Option for patients selected for early invasive treatment (class IA) and early conservative treatment (class IA)	Option for patients selected for fibrinolytic therapy (class IA); administer for at least 48 hours; for use up to eight days or until revascularization	Discontinue enoxaparin 12 to 24 hours before CABG (class IB). Reduce dose for creatinine clearance less than 30 mL/min and/or ≥75 yrs of age.

Table 8 continues on next page.

ADJUNCTIVE TREATMENT INDICATIONS FOR PATIENTS WITH UA/NSTEMI OR STEMI *(Continued)*			
Adjunctive Therapy	**UA/NSTEMI**	**STEMI**	**Comments**
Anticoagulant Therapy *(Continued)*			
Bivalirudin	Option for patients selected for early invasive treatment (class IB)	Preferred over UFH with glycoprotein IIb/IIIa inhibitor in patients selected for PCI at high risk of bleeding (class IIaB) Useful supportive measure for primary PCI with/without prior treatment with UFH (class IB)	Reduce dose for creatinine clearance less than 30 mL/min. Discontinue bivalirudin three hours before CABG (class IB).
Fondaparinux	Option for patients selected for early invasive treatment (class IB) and early conservative treatment (IB)	Option for patients selected for fibrinolytic therapy (class IB)	Should not be used as sole anticoagulant to support PCI in patients with NSTE-ACS due to an increased risk of catheter thrombosis. Avoid for creatinine clearance less than 30 mL/min. Discontinue 24 hrs before CABG.
ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; CKD = chronic kidney disease; HF = heart failure; PCI = percutaneous coronary intervention.			
Source: [2: 3]			*Table 8*

SIZE OF TREATMENT EFFECT FOR RECOMMENDED INTERVENTIONS	
Class	**Predicted Treatment Effect**
I	Benefit >>> Risk Procedure/treatment should be performed/administered.
IIa	Benefit >> Risk (Additional studies with focused objectives needed) It is reasonable to perform procedure/administer treatment.
IIb	Benefit ≥ Risk (Additional studies with broad objectives needed; additional registry data would be helpful) Procedure/treatment may be considered.
III	No Benefit (Procedure/test not helpful; no proven benefit) OR Harm (Procedure/test excess cost without benefit or harmful; treatment harmful to patients)

LEVEL OF EVIDENCE	
Level	**Supporting Evidence**
A	Multiple randomized clinical trials or meta-analyses
B	Single randomized trial or nonrandomized studies
C	Consensus opinion of experts, case studies, or standard-of-care

Nitroglycerin

Nitroglycerin is a vasodilator that relieves ischemic-related pain by reducing myocardial oxygen demand and enhancing oxygen delivery. Nitroglycerin can be given as sublingual tablets every five minutes for up to three doses. The indications for intravenous nitroglycerin are persistent ischemia, hypertension, or heart failure, following administration of sublingual nitroglycerin and a beta blocker [3]. The administration of intravenous nitroglycerin should be discontinued within 24 hours after the patient's condition has stabilized, at which point oral nitroglycerin can be given. Discontinuation of intravenous nitroglycerin should be gradual, as the abrupt cessation has been associated with exacerbation of ischemic changes on ECG [3]. Nitroglycerine and all nitrates are contraindicated when a phosphodiesterase inhibitor has been used recently [3]. Nitrates are used with caution in patients with right ventricular infarction.

Morphine

The 2014 guideline states that morphine is an option for patients who do not have relief of ischemia-related symptoms during treatment with intravenous nitroglycerin or for patients who have recurrence of symptoms during anti-ischemic therapy [3]. If morphine is used in conjunction with intravenous nitroglycerin, the patient's blood pressure should be closely monitored, as hypotension is a potential adverse effect.

Beta Blockers

The inhibition of beta-1 adrenergic receptors by beta blockers acts to decrease cardiac work and myocardial oxygen demand. Beta blockers also slow the heart rate, which helps enhance coronary blood flow. A beta blocker should be given orally to all patients (unless contraindicated) within 24 hours after presentation [3]. This use of beta blocker therapy has been associated with significantly lower in-hospital mortality [159]. The evidence for the benefit of beta-blocker therapy is well established, but it diminishes as the time from the index cardiac event elapses [160]. Contraindications include signs of heart failure, low-output state, increased risk of cardiogenic shock, or other relative contraindications to beta blockade.

Beta blockers with intrinsic sympathomimetic activity should be avoided; otherwise, the choice of beta blocker is up to the physician, as no studies have been done to compare single agents with each other. The ACC/AHA guideline recommends the use of sustained-release metoprolol, carvedilol, or bisoprolol as beta-blocker therapy for patients with UA/NSTEMI, stabilized heart failure, and reduced systolic function.

Adherence to guidelines for beta-blocker therapy has ranged from a concordance rate of 56 to 91 (with 100 representing perfect concordance) [8; 140]. Patients are more likely to be treated with beta blockers if they have a history of beta-blocker use, a higher systolic blood pressure or lower heart rate on presentation, no signs of heart failure, and have been under the care of a cardiologist [159]. Lower rates of beta blocker therapy have been found for older individuals and women, especially women younger than 55 years of age (compared with men of the same age) [12; 161].

Calcium-Channel Blockers

Calcium-channel blockers act to inhibit contraction of myocardial and smooth muscle and to cause vasodilation, although the agents in this drug class vary in the degree of vasodilation and myocardial contractility they produce [3]. They also relieve (or prevent) signs and symptoms of ischemia by decreasing heart rate and blood pressure.

The strongest evidence for a benefit of calcium-channel blockers in the setting of UA/NSTEMI primarily relates to symptom control. Calcium-channel blockers are indicated for patients who have UA/NSTEMI and [3]:

- Ongoing or recurring ischemia-related symptoms despite adequate doses of nitroglycerin and beta blockers
- Intolerance of adequate doses of nitroglycerin or beta blockers

The four agents used most commonly are nifedipine, amlodipine, verapamil, and diltiazem. Although data on comparisons of these four drugs are limited, verapamil and diltiazem are recommended because of their negative inotropic actions and negative chronotropic and dromotropic effects [3]. The ACC/AHA guideline recommends that a nondihydropyridine calcium channel blocker (verapamil or diltiazem) be given to patients with UA/NSTEMI who have continuing or frequently recurring ischemia and a contraindication to beta blockers, provided that clinically significant left ventricular dysfunction, increased risk for cardiogenic shock, a PR interval greater than 0.24 second, or second- or third-degree atrioventricular block without a cardiac pacemaker are not present [3]. In addition, oral nondihydropyridine calcium antagonists are recommended (unless contraindicated) for patients who have recurrent ischemia after appropriate use of beta blockers and nitrates. Immediate-release nifedipine is not recommended for routine use because of a dose-related increase in mortality [3].

Angiotensin-Converting Enzyme (ACE) Inhibitors

An ACE inhibitor should be administered orally within the first 24 hours (unless contraindicated) to patients who have pulmonary congestion or a left ventricular ejection fraction (LVEF) less than 0.40, and to patients who have hypertension, diabetes mellitus, or stable chronic kidney disease [3]. The guidelines also note that an angiotensin-receptor blocker (ARB) should be given to patients who cannot tolerate an ACE inhibitor and have signs of heart failure or LVEF of less than 0.40. The benefits of ACE inhibitors have been demonstrated primarily in the long-term setting after MI, with significant reductions in adverse outcomes, including survival at 30 days [3; 162; 163]. ARBs have been shown to be noninferior to ACE inhibitors in the prevention of clinical endpoints, including MI and stroke, in high-risk patients [164].

The rate of ACE inhibitor use has been reported to be approximately 77% among patients with UA/NSTEMI [8]. Use has been lower among older individuals and women, especially women younger than 55 years of age (compared with men of the same age) [12; 161].

Other Anti-Ischemic Interventions

The ACC/AHA guideline does not make evidence-based recommendations for other anti-ischemic interventions, but does note two additional interventions for persistent or recurrent ischemia [3]. One is ranolazine, an antianginal agent that is indicated for the treatment of chronic angina [165]. The drug has been found to reduce recurrent ischemia in the ACS setting [166; 167]. The other intervention is intra-aortic balloon pump counterpulsation, which has historically been used for refractory ischemia. The findings of observational studies have led to its use in the ACS setting, with rigorous randomized controlled trials showing no reduction in adverse events or mortality [3].

Cholesterol Management

Among patients with UA/NSTEMI, treatment with statins has been shown to be associated with lower rates of recurrent MI, CHD-related mortality, need for myocardial revascularization, and stroke [3]. These benefits have been greater with a high-intensity statin (such as atorvastatin) than with low- or moderate-intensity statins. Thus, the 2014 ACC/AHA guideline recommends that all patients receive high-intensity statin therapy, unless contraindicated [3]. Adherence to this recommendation should be improved; in a study in a tertiary care center, 52% of patients eligible for intensive statin therapy received it during hospitalization [168].

ANTIPLATELET THERAPY

Aspirin continues to be a key element of therapy for patients with UA/NSTEMI as part of overall antiplatelet therapy and reduces rates of recurrent MI and death [3]. Antiplatelet therapy reduces platelet formation and aggregation, integral components in the formation of a thrombus after plaque disruption.

Aspirin

The ACC/AHA guideline recommends that aspirin be given as soon as possible after a patient arrives in the emergency department and continued indefinitely in patients who tolerate it [3]. However, adherence by emergency medical personnel to guidelines recommending prompt prehospital aspirin administration is only 45% [169]. Aspirin is contraindicated for patients who are allergic to the drug or who have active bleeding; clopidogrel is recommended for patients who cannot tolerate aspirin [3]. Aspirin should be nonenteric-coated and chewable, and the recommended dose is 162 mg to 325 mg. A maintenance dose of aspirin should be continued indefinitely, at a daily dose of 81 mg to 325 mg. Adherence to the recommended use of aspirin has been better than for other drug therapies for patients with UA/NSTEMI, with rates of 97% to 99% [8; 141]. Rates of aspirin use have been reported to be lower for older individuals and women, especially women younger than 55 years of age [12; 161].

P2Y12 Inhibitors

P2Y12 inhibitors are added to aspirin as dual-antiplatelet therapy for patients who are managed medically as well as patients treated with PCI. Three inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for use in UA/NSTEMI: clopidogrel, prasugrel, and ticagrelor. In addition, cangrelor is approved for patients treated with PCI [161].

Clopidogrel

Clopidogrel was the first antiplatelet agent to become standard therapy in the ACS setting. The drug was approved by the FDA in 2002 on the basis of the findings of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, in which 12,562 patients with UA/NSTEMI were randomly assigned to treatment with aspirin with or without clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed up for 3 to 12 months, regardless of the treatment strategy used (conservative or invasive) [170]. The risk of cardiovascular-related death, MI, or stroke was significantly lower for patients who received clopidogrel. The results were similar in many subgroups of patients.

The ACC/AHA guideline recommends clopidogrel as one of two P2Y12 inhibitors to be given in addition to aspirin to all patients (unless contraindicated) with UA/NSTEMI who are to be treated with either an early invasive or ischemia-guided strategy [3]. The recommended dose of clopidogrel is a loading dose of 300 mg or 600 mg, followed by 75 mg daily for up to 12 months. Clopidogrel is also recommended for patients who are unable to take aspirin [3].

Prasugrel

Prasugrel has been shown to be more effective than clopidogrel for patients treated with PCI with stenting. In a comparison of the two drugs in patients with moderate-to-high-risk ACS who were scheduled for PCI, prasugrel was given as a 60-mg loading dose, followed by 10 mg daily, and clopidogrel was given as a 300-mg loading dose, followed by 75 mg daily. Both drugs were given for 6 to 15 months. Prasugrel was associated with a significantly lower rate of the primary composite endpoint of cardiovascular-related death, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%) [171]. However, the risk of major bleeding was increased with prasugrel (2.4% vs. 1.8%). Overall mortality did not differ significantly between the two drugs [171].

Prasugrel has also been compared with clopidogrel in patients with UA/NSTEMI who are managed medically. In this study, prasugrel was not associated with a decrease in the primary composite endpoint of cardiovascular-related death, MI, or stroke (13.9% vs. 16%) [172]. The rates of major bleeding were similar.

The ACC/AHA guideline recommends prasugrel as one of three options for maintenance antiplatelet therapy (with aspirin) for patients who have PCI and coronary stenting, but prasugrel is not recommended for patients treated with an early-invasive or ischemia-guided strategy [3].

Ticagrelor

Ticagrelor, the first in a new class of antiplatelets known as cyclopentyl-triazolo-pyrimidines, was approved by the FDA in 2011 [173]. Its mechanism of action differs from that of clopidogrel and prasugrel in that it does not require hepatic metabolism for activation and its action is reversible. Ticagrelor achieves greater and more consistent platelet inhibition than clopidogrel [173].

Ticagrelor was compared with clopidogrel in the Study of Platelet Inhibition and Patient Outcomes (PLATO), a randomized, controlled trial involving 18,624 patients, most of whom had UA/NSTEMI [174]. After 12 months, the rate of the primary composite endpoint (i.e., cardiovascular-related death, MI, or stroke) was lower in the ticagrelor and aspirin group than in the clopidogrel and aspirin group (9.8% vs. 11.7%) [174]. In addition, the all-cause death rate was lower in the ticagrelor group than in the clopidogrel group. Although the overall rates of major bleeding did not differ between the two groups, ticagrelor was associated with a higher rate of major bleeding in a subgroup of patients who did not have CABG.

The ACC/AHA guideline recommends ticagrelor as an option (with aspirin) as maintenance antiplatelet therapy for up to 12 months after initial treatment with either an early invasive or ischemia-guided strategy [3]. As a class IIaB recommendation, the ACC/AHA note a preference for ticagrelor over clopidogrel. The recommended dose is 180 mg as a loading dose, followed by 90 mg twice daily. The benefit of ticagrelor compared with clopidogrel is limited to an aspirin dose of 75–100 mg [175].

Adherence to guidelines on the use of a P2Y12 inhibitor has been low, especially for patients with UA/NSTEMI, with rates of 10% to 57% [10]. Rates of use have been lower among women [14]. In addition, some inhibitors have been used inappropriately; for example, in one study, 3% of patients with prior stroke received prasugrel despite its contraindication in that setting [10].

Glycoprotein IIb/IIIa Inhibitors

Glycoprotein IIb/IIIa inhibitors are potent inhibitors of platelet aggregation. Three intravenous glycoprotein IIb/IIIa inhibitors have been approved for clinical use: abciximab, eptifibatide, and tirofiban. Intravenous glycoprotein IIb/IIIa inhibitors are recommended, as oral agents in this class have been associated with increased risk for bleeding and mortality [3].

A meta-analysis (48 trials, 33,513 patients) demonstrated that glycoprotein IIb/IIIa inhibitors were associated with a lower all-cause mortality at 30 days after PCI but not at six months, compared with placebo or usual care [176]. The rate of severe bleeding was increased with glycoprotein IIb/IIIa inhibitors. Less benefit was found when clopidogrel was used. When glycoprotein IIb/IIIa inhibitors were used as part of initial medical treatment of UA/NSTEMI (12 trials, 33,176 patients), there was no decrease in mortality at 30 days, although the rate of death or MI was slightly lower at 30 days and six months [176]. Again, the risk of severe bleeding was higher with glycoprotein IIb/IIIa inhibitors.

The ACC/AHA guideline recommends a glycoprotein IIb/IIIa inhibitor for patients at intermediate-to-high risk (i.e., elevated troponin levels) who are to be treated with an early invasive strategy and dual-antiplatelet therapy [3]. Eptifibatide and tirofiban are the preferred inhibitors (class IIb, B) [3].

The recommended use of glycoprotein IIb/IIIa inhibitors is suboptimal in two ways. First, guideline-recommended use is low, especially among women [14; 177; 178]. Despite the clear benefit of glycoprotein IIb/IIIa inhibitors for high-risk patients, studies have shown that treatment with the drugs are directed toward patients at lower risk, with its use in high-risk patients ranging from 18% to 35% [179; 180]. Use of glycoprotein IIb/IIIa inhibitors has also been suboptimal with respect to dosing; in one study, an excess dose was given to 26.8% of patients [181]. Excess dosing was more likely among older individuals, women, and patients with renal insufficiency, diabetes mellitus, heart failure, or low body weight [181]. Increased risk of major bleeding and mortality were associated with an excess dose.

ANTICOAGULANT THERAPY

Parenteral anticoagulant therapy (in addition to antiplatelet therapy) is recommended for patients with definite or likely UA/NSTEMI, regardless of the initial treatment strategy (early invasive or ischemia-guided) [3].

The anticoagulants used in the UA/NSTEMI setting are enoxaparin, bivalirudin, fondaparinux, and unfractionated heparin [3].

Enoxaparin

Enoxaparin is a low-molecular-weight heparin that offers many pharmacologic advantages compared with unfractionated heparin [44]:

- More predictable anticoagulant effect
- Greater bioavailability
- Lower incidence of heparin-induced thrombocytopenia
- Routine monitoring not required
- Given as a fixed-weight base dose

Compared with unfractionated heparin, enoxaparin has been associated with lower rates of recurrent ischemic events and of invasive procedures in the short term, as well as at one year among patients with UA [182]. Among high-risk patients with UA/NSTEMI treated with an early invasive strategy, the rate of death or MI at 30 days did not differ significantly between enoxaparin and unfractionated heparin, and enoxaparin was associated with an increased risk of major bleeding [183; 184]. A 2023 assessment of bleeding and associated risk factors among a cohort of 602 patients treated with enoxaparin found that the incidence of bleeding was 15.8%; 5.7% involved major bleeding. The risk factors associated with bleeding were age 65 years or older, history of bleeding, and history of oral anticoagulant exposure [185].

The ACC/AHA guideline recommends enoxaparin as an option for all patients with NSTE-ACS [3]. The recommended dose is 1 mg/kg, given subcutaneously, every 12 hours, and the drug is continued throughout the hospitalization or until PCI is done [3]. The dose should be decreased to 1 mg/kg daily for patients with a creatinine clearance less than 30 mL/min.

Studies have shown that 14% to 19% of patients with UA/NSTEMI have received an excess dose of low-molecular-weight heparin [181; 186]. A higher dose was significantly associated with major bleeding and death [186]. The patients who received excess doses were more likely to be older, smaller, and female [181; 186].

Bivalirudin

Bivalirudin is a direct thrombin inhibitor, and it has shown little benefit in lowering the risk of adverse outcomes compared with unfractionated heparin. Bivalirudin has been evaluated only in patients being considered for an early invasive strategy. In a study of 13,819 moderate-risk and high-risk patients, bivalirudin alone was compared with two other regimens: bivalirudin plus a glycoprotein IIb/IIIa inhibitor, and heparin (unfractionated heparin or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor.

Bivalirudin plus a glycoprotein IIb/IIIa inhibitor was noninferior to heparin plus a glycoprotein IIb/IIIa inhibitor with respect to composite endpoint (death, MI, or unplanned revascularization) at 30 days [187]. Bivalirudin alone was also noninferior to heparin plus a glycoprotein IIb/IIIa inhibitor, but it offered a significant benefit in terms of major bleeding [187]. At one year, there was no significant difference in the composite endpoint among the three groups [188]. A meta-analysis of 15 trials that included more than 25,000 patients undergoing PCI found that bivalirudin was associated with an increased risk of stent thrombosis, MI, all-cause mortality, and major adverse cardiac events and a reduced risk of major bleeding [189]. When the dose of heparin in the control arm was more than 100 units/kg, bivalirudin was associated with a reduction in major bleeding; when the dose of heparin was less than 75 units/kg, bivalirudin was not associated with reduced major bleeding [189].

The ACC/AHA guideline recommends bivalirudin only for patients who are to have an early invasive strategy [3]. The recommended dose is 0.10 mg/kg as a loading dose, followed by 0.25 mg/kg/hr, to be continued until diagnostic angiography or PCI is performed [3].

Fondaparinux

Fondaparinux is a synthetic polysaccharide molecule that is a selective inhibitor of activated Factor X. It has been compared with enoxaparin in patients with NSTE-ACS and found to have similar efficacy in terms of a primary endpoint of ischemic events, but offering benefit in terms of a significantly lower rate of major bleeding [190; 191; 192; 193]. The ACC/AHA guideline recommends fondaparinux, 2.5 mg subcutaneously daily, for the duration of hospitalization or until PCI is done [3]. When fondaparinux is used alone in this setting, an additional anticoagulant with anti-IIa activity should be given to help prevent catheter thrombosis [3].

Unfractionated Heparin

Unfractionated heparin has been used in the ACS setting since the early 1960s. Heparin prevents the formation of thrombi by accelerating the action of the proteolytic enzyme antithrombin that inactivates Factors IIa, IXa, and Xa [44]. An early meta-analysis (six trials, 1,353 patients) showed that unfractionated heparin plus aspirin reduced the risk for death or MI by 33% compared with aspirin alone among patients with UA [194]. These studies preceded the era of dual-antiplatelet therapy and early catheterization and revascularization.

The ACC/AHA guideline recommends giving unfractionated heparin for 48 hours or until PCI is performed [3]. A weight-adjusted dose is preferred to a fixed initial dose, as anticoagulation is more predictable with such dosing [3]. The recommended dose in the ACC/AHA guideline is an initial loading dose of 60 IU/kg (to a maximum of 4,000 IU) and an initial infusion of 12 IU/kg/h (to a maximum of 1,000 IU/hr), which is adjusted to a therapeutic activated partial thromboplastin time range [3].

CHOICE OF TREATMENT STRATEGY: EARLY INVASIVE VS. ISCHEMIA-GUIDED STRATEGY

As stated, risk stratification is essential to determine the level of treatment: an early invasive or an ischemia-guided strategy. An early invasive approach involves diagnostic angiography, with revascularization performed if appropriate based on coronary anatomy [3]. The procedure is typically done within 24 hours (early invasive) or 25 to 72 hours (delayed invasive) [3]. The optimal timing of angiography has not been established [3]. With an ischemia-guided strategy (previously referred to as a conservative approach or medical management), noninvasive testing is done and angiography is performed only when this testing demonstrates evidence of ischemia. The ACC/AHA guideline provides direction for appropriately selecting an early invasive or ischemia-guided strategy (***Table 9***) [3].

FACTORS ASSOCIATED WITH APPROPRIATE SELECTION OF EARLY INVASIVE STRATEGY OR ISCHEMIA-GUIDED STRATEGY IN PATIENTS WITH NSTE-ACS	
Treatment Strategy	**Factors Guiding Selection**
Immediate invasive (within two hours)	Refractory angina Signs or symptoms of HF or new or worsening mitral regurgitation Hemodynamic instability Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy Sustained VT or VF
Ischemia-guided strategy	Low-risk score (e.g., TIMI [0 or 1], GRACE [<109]) Low-risk, Tn-negative female patients Patient or clinician preference in the absence of high-risk features
Early invasive (within 24 hours)	None of the above, but GRACE risk score >140 Temporal change in Tn New or presumably new ST depression
Delayed invasive (within 25 to 72 hours)	None of the above, but diabetes mellitus Renal insufficiency (GFR <60 mL/min/1.73 m^2) Reduced LV systolic function (EF <40%) Early postinfarction angina PCI within six months Prior CABG GRACE risk score 109–140; TIMI score ≥2
CABG = coronary artery bypass graft; EF = ejection fraction; GFR = glomerular filtration rate; GRACE = Global Registry of Acute Coronary Events; HF = heart failure; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; Tn = troponin; VF = ventricular fibrillation; VT = ventricular tachycardia.	
Source: [3]	*Table 9*

Early Invasive Strategy

The findings of most studies have indicated that a routine early invasive strategy is superior to an ischemia-guided strategy in terms of reducing the rate of cardiovascular-related death or MI, as well as of angina and rehospitalization [15; 195; 196]. However, a meta-analysis found insufficient evidence to support either approach as having a survival benefit for patients with NSTE-ACS [197]. The greatest advantage of an early invasive strategy has been found among patients at high risk.

An urgent or immediate invasive strategy is recommended for patients with NSTE-ACS with refractory angina or hemodynamic or electrical instability who do not have serious comorbidities or contraindications [3]. An early invasive strategy is recommended for patients with NSTE-ACS who are initially stabilized and at elevated risk for clinical events [3]. The guideline recommends against an early invasive strategy for patients with acute chest pain and a low likelihood of ACS (normal troponin levels) as well as for patients with extensive comorbidities (class III: no benefit).

Ischemia-Guided Strategy

The objective of an ischemia-guided strategy is to avoid unnecessary treatment (and associated costs) for patients at low risk for significant CHD. The ACC/AHA guideline notes that an ischemia-guided strategy may be considered for patients with NSTE-ACS who are initially stabilized and at elevated risk for clinical events (class IIbB) [3]. It is also reasonable to consider clinician and patient preference in decision making about an ischemia-guided strategy (class IIbC). Patients at low or intermediate risk who have had no ischemia at rest or with low-level activity for at least 12 to 24 hours should have noninvasive stress testing (class IB) [3]. Factors to consider when selecting a stress test are the patient's resting ECG and ability to exercise, as well as local resources. An exercise stress test is the easiest, most cost-effective test and should be the choice unless the patient is unable to exercise or has ST changes on resting ECG (class IC) [3]. ST changes on the resting ECG may interfere with interpretation of the stress test findings, and for patients with ST changes, stress testing with an imaging modality (such as cardiac radionuclide imaging or stress echocardiography) is recommended (class IB). Pharmacologic stress testing with imaging should be done for patients who have limited ability to exercise (class IC). Exercise stress testing should be done and interpreted according to the ACC/AHA guidelines, and the results will dictate the need for further therapy [198].

Many factors other than risk influence the use of an early invasive strategy. Such a strategy has been used more often, regardless of patients' risk, when a cardiac catheterization laboratory is available or the treating physician is a cardiologist [179; 199; 200]. Patient demographic characteristics, such as age, race, and gender, are also factors. Data from trials indicate that an early invasive strategy is used less frequently for older patients, Black patients, and women [7; 11; 138; 196; 199; 201].

The benefit of an early invasive strategy for women is unclear [15; 196]. However, when women have high-risk features, such as elevated troponin levels, an early invasive approach does lead to better outcomes; women at low-risk have better outcomes from an ischemia-guided approach [22; 202]. These findings led the ACC/AHA to emphasize that an immediate invasive strategy should be used for women who are eligible for that approach and that an early invasive strategy should not be used for women at low risk for ACS [3].

Revascularization Procedures

CABG was once the primary revascularization procedure, but advances in less invasive techniques have contributed to a decline in CABG rates and an increase in the use of PCI for NSTE-ACS [7; 203].

A comprehensive comparison of CABG and PCI was carried out in the Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) study, and the findings were considered in the formulation of the 2011 ACC/AHA/Society for Cardiac Angiography and Interventions (SCAI) guideline recommendations for PCI [5]. In a meta-analysis (31 trials, 15,004 patients) published after the guideline, among patients eligible for either PCI or CABG, the latter procedure was associated with lower rates of repeat revascularization, and death; the rate of MI was similar, and the rate of stroke was higher with CABG [204]. Class I recommendations for the use of PCI include patients who have refractory angina or hemodynamic or electrical instability (without comorbidities or contraindications), and initially stabilized patients who have an elevated risk for clinical events [5]. PCI is preferred for patients with discrete lesions, in large-caliber vessels, or one or two vessels, whereas CABG is recommended for more extensive CHD, including left main disease, three-vessel disease, or two-vessel disease with severe involvement of the proximal left anterior descending coronary artery [6]. For patients with multivessel disease, CABG has been associated with higher adjusted rates of long-term survival and lower rates of MI and repeat vascularization compared with PCI with stenting [205; 206]. CABG is also recommended for patients with left ventricular systolic dysfunction [6].

TREATMENT OF STEMI

Advances in revascularization procedures and antiplatelet and anticoagulant therapies have improved outcomes for patients with STEMI, with significant decreases in the rates of mortality and morbidity [2; 207]. The reported mortality rates are approximately 5% to 6% (in-hospital) and 7% to 18% (one-year) [2]. Morbidity includes heart failure, pulmonary edema, reinfarction, cardiogenic shock, and stroke, and rates of these events have also declined significantly [207].

When ECG demonstrates ST-segment elevation, the goal of treatment is to immediately obtain normal coronary perfusion through the occluded infarct-related artery, thus decreasing ischemic time [2]. Re-establishing blood flow through the occluded artery is crucial for limiting the size of the infarct, minimizing myocardial damage, preserving left ventricular function, decreasing morbidity, and improving survival [2; 208].

Reperfusion therapy is the cornerstone in the management of STEMI, and antiplatelet and anticoagulant agents are necessary as ancillary therapy. The options for reperfusion include revascularization procedures and/or pharmacologic (fibrinolytic) therapy. As with the treatment for NSTEMI, the use of PCI has become the primary approach to revascularization; approximately 80% to 90% of patients have PCI revascularization based on angiographic findings [209]. In addition, PCI is the preferred strategy for reperfusion because of its superior outcomes compared with fibrinolytic therapy [2; 209]. However, gaining the optimal benefit from PCI depends on many factors, and timing is the most important variable in selecting a reperfusion therapy [2; 208]. Care should also be taken to evaluate patients for contraindications to fibrinolytic therapy [5].

The ACCF/AHA guideline on the management of STEMI was most recently updated in 2013. The guideline notes that patients with STEMI should be treated in either a coronary care unit or a stepdown unit [2]. Care provided in a coronary care unit should be structured according to evidence-based protocols, and nursing staff should be certified in critical care. Patients who are admitted to a coronary care unit may be transferred to a stepdown unit once they have been clinically stable for 12 to 24 hours [2]. Low-risk patients who have had successful PCI may be admitted directly to a stepdown unit.

TIMING

A familiar adage associated with STEMI is "time is muscle," and every effort should be made to shorten the ischemic time as much as possible. The timing of reperfusion therapy is a complex issue involving the time from the onset of symptoms and the time from presentation to treatment. The time for transfer to another hospital is also a factor for most patients, as most hospitals do not have a cardiac catheterization laboratory and a skilled, readily available PCI team.

The 2013 ACCF/AHA guideline indicates that PCI is preferred over fibrinolytic therapy for patients with STEMI when it can be performed in a timely manner by experienced operators [2]. PCI should be done within less than 90 minutes after the patient's first medical contact [2]. If PCI cannot be done within 90 minutes, fibrinolytic therapy should be initiated as the reperfusion strategy within 120 minutes of the first medical contact.

As a systems goal, EMS transport directly to a PCI-capable hospital for primary PCI is the recommended triage strategy for patients with STEMI, with an ideal first medical contact-to-device time system goal of 90 minutes or less.

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Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

The most significant factor in achieving an optimal outcome from PCI is timing. Findings from hospitals reporting to the Centers for Medicare and Medicaid Services have shown an improvement in the number of patients treated with primary PCI within the recommended 90-minute window, from 44.2% in 2005 to 91.4% in 2010 [210]. In addition, the median door-to-balloon or door-to-device time declined from 96 minutes in 2005 to 64 minutes in 2010 [210].

Improvements in door-to-balloon time have been attributed to national initiatives focused on identification of barriers to appropriate care and implementation of innovative protocols. These initiatives successfully addressed physician and organizational barriers with efforts to develop systems of care that increase patient access to primary PCI based on whether the patient presents to a PCI-capable or non-capable facility [2].

Strategies to Improve Timing of Therapy

Specific strategies that have improved the door-to-device time interval focus on three key components: door-to-ECG time, ECG-to-catheterization laboratory time, and laboratory arrival-to-device time. The ACCF/AHA provides the following steps as a general protocol in improving door-to-device times [2]:

- A prehospital ECG to diagnose STEMI is used to activate the PCI team while he patient is en route to the hospital.
- Emergency physicians activate the PCI team.
- A single call to a central page operator activates the PCI team.
- A goal is set for the PCI team to arrive in the catheterization laboratory within 20 minutes after being paged.
- Timely data feedback and analysis are provided to members of the STEMI care team.

PCI

As noted, PCI has become more commonly used than CABG for revascularization. PCI for STEMI can be subcategorized according to when the procedure is done and whether it is done in conjunction with fibrinolytic therapy. Primary PCI refers to PCI that is done alone as primary treatment after diagnostic angiography [2]. (As will be described, ancillary treatment with anticoagulant and antiplatelet agents should be given to support PCI.) Facilitated PCI was once a strategy of full- or half-dose fibrinolysis (with or without glycoprotein IIb/IIIa inhibitors) and immediate transfer for planned PCI within 90 to 120 minutes [2]. However, no net clinical benefit has been found with this strategy, and it is not recommended [2]. Rescue PCI refers to transfer for PCI after fibrinolysis has failed. A pharmacoinvasive strategy is the administration of fibrinolytic therapy, in either the prehospital setting or at a non-PCI-capable hospital for early coronary angiography and PCI when appropriate [2].

Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population.

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Strength of Recommendation/Level of Evidence: IIaB (It is reasonable to perform the procedure based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

Primary PCI

Primary PCI is preferred because of the many advantages it offers compared with fibrinolytic therapy, including wider eligibility, better rates of reperfusion, lower risks, and improved outcomes [209; 211; 212]. PCI is especially preferred for high-risk patients, specifically patients 75 years of age and older, patients with an unclear diagnosis, and

patients with cardiogenic shock, heart failure, or ventricular arrhythmias [2]. However, analysis of data has shown that PCI has been done less often among patients at high risk (41%) than among patients at low risk (60%) or intermediate risk (54%) [179].

Class I indications for primary PCI include the following [5]:

- STEMI symptoms within 12 hours (level A)
- Severe heart failure or cardiogenic shock (level B)
- Contraindications to fibrinolytic therapy with ischemic symptoms less than 12 hours (level B)

The ACC/AHA guideline notes that PCI is reasonable for patients with clinical and/or ECG evidence of ongoing ischemia 12-24 hours after onset of symptoms (class IIaB) and might be considered for asymptomatic patients with STEMI and higher risk who presented between 12 and 24 hours after the onset of symptoms (IIbC) [5].

The use of coronary stents during PCI reduces the rates of adverse events such as re-occlusion, restenosis, and target-vessel revascularization [5; 209; 211]. Drug-eluting stents have been associated with lower long-term rates of target-vessel revascularization and restenosis compared with bare-metal stents, but the reduction has varied among the many types of drug-eluting stents and stent thrombosis was originally a complication [213; 214]. Subsequent-generation drug-eluting stents were developed to overcome this complication, and thin-strut fluoropolymer-coated cobalt chromium everolimus-eluting stents have been associated with rates of stent thrombosis that are lower than those for other types of drug-eluting stents or bare-metal stents [214]. One small study that included 372 patients compared the efficacy of drug-eluting stents with drug-coated balloons for use during PCI [215]. The primary outcome was a composite of major adverse cardiovascular events (e.g., cardiac death, MI, target lesion revascularization) at one year [215]. Major adverse events occurred in 10 patients (12%) in the drug-coated balloon group and in 50 patients (13.4%) in the drug-eluting stent group. Other studies have confirmed the potential benefit of using drug-coated balloons during PCI [216; 217].

The complications of primary PCI include adverse reactions to the contrast medium, volume loading, difficulty with arterial access, and technical complications [211]. Reperfusion injury and hemorrhagic transformation of a bland infarction and hemorrhagic stroke are rare after primary PCI [209].

Primary PCI is supported by antiplatelet and antithrombin therapy. Class I recommendations for this therapy in patients with STEMI include the following [5]:

- Aspirin (level B)
- P2Y12 inhibitors (level A)
- Unfractionated heparin (level C)
- Bivalirudin (level B)

The aspirin dose before PCI should be 325 mg for patients who had not been taking aspirin therapy and 81 mg to 325 mg for patients who had already been taking daily aspirin [5]. If stents are to be implanted during PCI, a loading dose of a P2Y12 inhibitor should be given (clopidogrel, 600 mg; prasugrel, 60 mg; or ticagrelor, 180 mg) [5]. For clopidogrel, a 300-mg loading dose is recommended for patients who have PCI within 24 hours after receiving fibrinolytic therapy; a 600-mg loading dose is recommended for patients who have PCI more than 24 hours after receiving fibrinolytic therapy [5]. This recommendation is based on the results of several investigations to explore various loading doses of clopidogrel before or during PCI. A meta-analysis of seven studies demonstrated that a 600 mg loading of clopidogrel reduces the rate of adverse cardiovascular events without an increase in major bleeding compared with 300 mg [5]. The findings of another study suggested that a 600-mg loading dose

(compared with a 300-mg dose) is associated with improvements in procedural angiographic endpoints and one-year clinical outcomes in patients with STEMI who undergo primary PCI [5]. No benefit is derived from increasing the loading dose to 900 mg compared with 600 mg [5]. The guideline acknowledges that the safety and efficacy of pretreatment with clopidogrel remains controversial [5].

EVIDENCE-BASED PRACTICE RECOMMENDATION

After PCI for STEMI, aspirin should be continued indefinitely.

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Strength of Recommendation/Level of Evidence: IA (Procedure/treatment should be performed based on data derived from multiple randomized clinical trials or meta-analyses evaluating multiple populations.)

When compared with clopidogrel, prasugrel was associated with a 2.2% reduction in a composite endpoint of cardiovascular-related death, nonfatal reinfarction, or nonfatal stroke [5]. Prasugrel is contraindicated in patients with active pathologic bleeding or history of transient ischemic attack or stroke. Its use is not recommended for patients older than 75 years of age because of increased risk of fatal intracranial bleeding [5].

If unfractionated heparin is used, it is reasonable to give a glycoprotein IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-bolus tirofiban), regardless of whether patients are pretreated with clopidogrel [5]. The ACCF/AHA guideline for STEMI states that it is reasonable to begin treatment with abciximab before or at the time of primary PCI (with or without stenting) [2]. The precise timing of administration has not been defined. Treatment with tirofiban or eptifibatide may also be considered at the time of primary PCI [2].

With regard to anticoagulant therapy, unfractionated heparin is recommended but should not be given to patients already receiving therapeutic enoxaparin (subcutaneously) (class III: harm) [5]. Bivalirudin is also a recommended anticoagulant, with or without previous treatment with unfractionated heparin (class IB) [5]. Bivalirudin or argatroban should be used instead of unfractionated heparin in patients with heparin-induced thrombocytopenia (class IB). Fondaparinux should not be used as the only anticoagulant with PCI (class III: harm) [5]. An additional anticoagulant with anti-Ha activity should be used because of the risk of catheter thrombosis.

FIBRINOLYTIC THERAPY

The benefit of fibrinolytic therapy is its potential to establish reperfusion quickly. The re-establishment of coronary blood flow within the first 30 minutes after occlusion can abort infarction [218]. Reperfusion within 30 minutes to 2 hours can salvage myocardial tissue substantially, and fibrinolytic therapy administered within this timeframe has reduced mortality [219].

Although the focus of treatment for patients presenting with STEMI is often given to PCI, fibrinolytic therapy is the treatment of choice for some patients. If a patient arrives at or is transported by EMS to a non-PCI-capable facility, the decision whether to immediately transfer to a PCI-capable facility or administer fibrinolytic therapy must be made. Factors that affect this decision include the time from onset of symptoms, the risk of complications related to STEMI, the risk of bleeding with fibrinolysis, the presence of shock or severe heart failure, and the time required for transfer to a PCI-capable hospital. The ACCF/AHA guideline recommends that, in the absence of contraindications, fibrinolytic therapy should be given to patients with STEMI and onset of ischemic symptoms within the previous 12 hours when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact [2].

COMPARISON OF FIBRINOLYTIC AGENTS FOR TREATMENT OF STEMI				
Characteristic	**Streptokinase**	**Alteplase**	**Reteplase**	**Tenecteplase**
Dose	1.5 MU	Up to 100 mg	10 U + 10 U	30–50 mg
Administration	Infusion (over 30 to 60 minutes)	Bolus and infusion (over 90 minutes)	Bolus (over 2 minutes) given 30 minutes apart	Bolus
Weight-based dosing	No	Yes	No	Yes
Antigenic	Yes	No	No	No
Patency rate[a]	60% to 68%	73% to 84%	84%	85%
Fibrin specificity[b]	No	Yes (++)	Yes (++)	Yes (++++)

TIMI = Thrombolysis in Myocardial Infarction.
[a]90-minute grade 2 or 3 TIMI blood flow.
[b]++++ is stronger than ++.

Source: [46] *Table 10*

CONTRAINDICATIONS AND CAUTIONS FOR FIBRINOLYSIS USE IN ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)[a]
Absolute Contraindications
Any prior intracranial hemorrhage
Known structural cerebral vascular lesion (e.g., arteriovenous malformation)
Known malignant intracranial neoplasm (primary or metastatic)
Ischemic stroke within three months EXCEPT acute ischemic stroke within 4.5 hours
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menses)
Significant closed-head or facial trauma within three months
Intracranial or intraspinal surgery within two months
Severe uncontrolled hypertension (unresponsive to emergency therapy)
For streptokinase, prior treatment within the previous six months
Relative Contraindications
History of chronic, severe, poorly controlled hypertension
Substantial hypertension on presentation (systolic greater than 180 mm Hg or diastolic greater than 110 mm Hg)
History of prior ischemic stroke (greater than three months)
Dementia
Known intracranial pathology not covered in absolute contraindications
Traumatic or prolonged (greater than 10 minutes) CPR
Major surgery (within less than three weeks)
Recent (within two to four weeks) internal bleeding
Noncompressible vascular punctures
Pregnancy
Active peptic ulcer
Oral anticoagulant therapy

[a]Viewed as advisory for clinical decision making and may not be all-inclusive or definitive.
CPR = cardiopulmonary resuscitation, INR = international normalization ratio.

Source: [2] *Table 11*

Prehospital fibrinolytic therapy may reduce the time delay from symptom onset to treatment and can be administered by a trained EMS unit either with a physician on board or with a hospital-based physician in direct contact. A meta-analysis (six trials) showed a 60-minute reduction in time from symptom onset to treatment with prehospital compared to hospital-based initiation of fibrinolytic therapy [220]. Data from several trials indicate that prehospital fibrinolytic therapy may lower STEMI mortality rates and is considered to be of particular benefit in rural areas [220; 221].

Four fibrinolytic agents have been evaluated and approved in the STEMI setting: tenecteplase, reteplase, alteplase (tPA), and streptokinase (***Table 10***) [2]. Of these agents, only streptokinase is non-fibrin-specific, and a fibrin-specific agent is preferred [2]. Each agent is associated with risks and benefits, and the choice of an agent is based on several factors, including preferences in the hospital formulary, cost, ease of administration, and the possibility of subsequent PCI. Although streptokinase is the least expensive agent, it is rarely used and no longer marketed in the United States because it is not fibrin-specific and has been shown to be less effective than the other three drugs [2].

Alteplase is inconvenient to administer, as it must be given as an initial intravenous bolus over 30 minutes followed by 60 minutes of infusion [2; 222]. Reteplase and tenecteplase have both been compared with alteplase. Both have resulted in similar mortality as alteplase, and reteplase has led to better total patency rates or complete perfusion [223; 224; 225; 226]. TIMI 3 flow at 90 minutes has been similar for tenecteplase and alteplase [227]. The use of alteplase has thus declined because of the availability of these more convenient drugs with similar or improved outcomes [222].

The most common complication of fibrinolytic therapy is major bleeding, which occurs in approximately 5% to 6% of patients [208]. Adverse outcomes after fibrinolytic therapy are generally more common among women and older patients [228; 229]. Many instances of bleeding can be traced to incorrect dosing, particularly with weight-based agents [222]. In addition, patients who receive an improperly high dose of fibrinolytic agents have increased 30-day mortality.

Repeat fibrinolytic therapy after failed fibrinolytic therapy has not led to significant clinical improvement in terms of all-cause mortality or nonfatal reinfarction and has been associated with an increased risk for bleeding [230]. Rescue PCI is the preferred strategy for failed fibrinolytic therapy, as it has been shown to offer benefit when compared with repeat fibrinolytic therapy [230; 231; 232].

Contraindications to Fibrinolytic Therapy

Another factor in selecting a reperfusion approach is whether the patient has contraindications to fibrinolytic therapy. Regardless of timing, PCI should be strongly considered for patients who are at high risk for bleeding complications, especially intracranial hemorrhage. There are several absolute and relative contraindications to fibrinolytic therapy; absolute contraindications include a history of intracranial hemorrhage or of substantial closed head or facial trauma within the past three months, suspected aortic dissection, or active bleeding (***Table 11***) [2]. Relative contraindications include history of poorly controlled hypertension, recent internal bleeding, and oral anticoagulant therapy [2].

Ancillary Therapy

As described, a STEMI-associated thrombus consists of a fibrin-rich core and a platelet-rich cap. Because of this, both antiplatelet and anticoagulant therapies play important roles in supporting reperfusion therapy by helping to maintain patency of the infarct-related artery and preventing re-occlusion [2].

Clopidogrel and Aspirin

Recommended antiplatelet therapy has traditionally involved aspirin and clopidogrel. The 2013 ACCF/AHA guideline for STEMI includes a recommendation for clopidogrel (75 mg per day for at least 14 days and up to one year) to be added to aspirin for patients with STEMI, regardless of whether reperfusion with fibrinolytic therapy has been initiated [2].

Although prasugrel has been approved by the FDA for use in patients with STEMI and may be incorporated into the supportive treatment of these patients in place of clopidogrel, it is no longer recommended for use as an adjunct to fibrinolytic therapy [2].

Glycoprotein IIb/IIIa Inhibitor

A glycoprotein IIb/IIIa inhibitor may also be considered as an ancillary agent for patients who receive fibrinolytic therapy. The 2013 ACCF/AHA guideline for STEMI notes that the use of a glycoprotein IIb/IIIa inhibitor (abciximab, tirofiban, or eptifibatide) is reasonable at the time of primary PCI for selected patients with STEMI; routine use is not recommended [2].

It may be reasonable to administer intravenous glycoprotein IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended.

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Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

Two meta-analyses of randomized trials that support this recommendation involved a comparison of glycoprotein IIb/IIIa inhibitors in patients with STEMI who had primary PCI. In each case, there was no significant difference in 30-day mortality, reinfarction, TIMI flow grade 3, or ST-segment resolution among the agents [233; 234].

Heparin, Fondaparinux, Enoxaparin, or Bivalirudin

Anticoagulant therapy is associated with bleeding complications, so care must be taken in selecting an appropriate agent, with attention paid to the patient's renal function status, the time to an invasive procedure, and overall bleeding risk [235]. Unfractionated heparin, enoxaparin, and fondaparinux are the recommended anticoagulant agents based on studies demonstrating their efficacy [2]. The 2013 ACCF/AHA guideline recommends bivalirudin as an acceptable anticoagulant for primary PCI or for patients undergoing rescue PCI for failed fibrinolysis. Bivalirudin may be useful as a supportive measure for patients undergoing PCI either with or without prior treatment with unfractionated heparin and is particularly useful if patients develop heparin-induced thrombocytopenia and still require anticoagulation [2]. Anticoagulation should be continued for the duration of the index hospitalization (up to eight days) or until revascularization. Enoxaparin is recommended over unfractionated heparin when anticoagulant therapy will extend beyond 48 hours [2].

Unfractionated heparin should be used for patients with severe impairment of renal function, and unfractionated heparin or enoxaparin may be used for patients who are at increased risk of bleeding and who are likely to have early angiography [235]. Researchers reviewed data on 20,479 patients to compare outcomes for unfractionated heparin and enoxaparin [236]. Significantly fewer patients in the enoxaparin group had subsequent PCI within 30 days after fibrinolytic therapy [236]. There were no differences between the two agents with respect to major bleeding in this study, whereas a more recent meta-analysis found enoxaparin to be superior to unfractionated heparin in reducing the incidence of major bleeding [237]. In patients with obesity, enoxaparin was associated with significantly lower risks of in-hospital venous thromboembolism and in-hospital mortality, major bleeding, mortality related to pulmonary embolism, and hospitalization costs when compared with unfractionated heparin [238].

Fondaparinux may also provide benefit for patients who receive fibrinolytic therapy [239; 240]. In one trial, 12,092 patients with STEMI were randomly assigned to fondaparinux (2.5 mg once daily for up to eight days) or to placebo. Analysis of a subgroup of 5,436 patients who received fibrinolytic therapy (primarily streptokinase) showed that fondaparinux was associated with significantly lower rates of death

or nonfatal MI at 30 days and severe bleeding, yielding a significant overall benefit [239]. As noted, an additional anticoagulant (with anti-IIa activity) should be used in addition to fondaparinux when PCI is to be done after fibrinolytic therapy, and fondaparinux should not be used when creatinine clearance is less than 30 mL/min [2].

NO REPERFUSION THERAPY

Despite the clear benefit of reperfusion, a significant percentage of eligible patients with STEMI do not receive reperfusion therapy and some are mistakenly considered "ineligible" [207; 208; 241; 242]. One study of 8,578 patients with STEMI found that more than 7% of all individuals with no contraindications to reperfusion were not given fibrinolysis or PCI [243]. Patients who are less likely to receive reperfusion therapy are older than 65 years of age, are female, have an atypical clinical presentation, and have a history of cardiovascular disease [208; 243; 244]. Another study found that 45% of eligible patients with diabetes on dialysis were not treated with reperfusion (i.e., mistakenly considered ineligible) [2]. Compared with in-hospital mortality rates for patients who do receive therapy, the mortality rates are substantially higher for patients who are eligible for reperfusion but do not receive it, and rates have been higher and more discrepant for women, older patients, and patients with prior congestive heart failure, MI, or CABG surgery [241; 242; 243; 245].

Patients with no contraindications to reperfusion should be selected for primary PCI or fibrinolysis. Patients who lack access to PCI or have absolute contraindications to fibrinolysis should receive antithrombotic therapy in the hope of restoring TIMI grade 3 flow to the occluded vessel and preventing complications [246]. Older ACC/AHA guidelines for STEMI included recommendations for the treatment of patients who do not receive reperfusion therapy, including administration of aspirin, clopidogrel, and anticoagulants (low-molecular-weight heparin or fondaparinux rather than unfractionated heparin) to be given for the duration of hospitalization [247]. The 2013 guideline for STEMI does not include a specific recommendation for the treatment of patients who do not receive reperfusion therapy [2]. Despite this, it may be reasonable to administer the additional recommended medications (in the absence of contraindications) in these patients.

Acting on the theory that late revascularization of an infarct-related artery may improve left ventricular function and survival, some researchers have explored the value of late PCI for patients who have not had reperfusion therapy. However, the results of such studies have shown that elective PCI of an occluded infarct-related artery 3 to 28 days after MI offered no incremental benefit (beyond optimal medical therapy) for stable patients. The ACCF/AHA guideline for STEMI includes a recommendation that PCI of a totally occluded infarct-related artery more than 24 hours after STEMI should not be done in asymptomatic, stable patients with one- or two-vessel disease [2].

CABG

Although PCI is performed more frequently, several situations call for the use of CABG. The ACCF/AHA guideline for STEMI and the ACC/AHA guideline for CABG surgery recommend emergent or urgent CABG when PCI has failed, for coronary anatomy not amenable to PCI, and at the time of surgical repair of a mechanical defect (e.g., ventricular septal, papillary muscle, free-wall rupture) [2; 6].

The ACC/AHA/SCAI recommend that treatment decisions regarding coronary revascularization in patients with coronary artery disease should be based on clinical indications, regardless of sex, race, or ethnicity, because there is no evidence that some patients benefit less than others, and efforts to reduce disparities of care are warranted.

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CABG results in a longer average recovery time and hospital stay compared with PCI (9.2 days and 3.2 days, respectively), and the in-hospital mortality is higher for CABG than for PCI (5.0% to 6.0% and 3.0% to 3.5%, respectively) [245]. However, long-term outcomes, including survival, have been similar for the two procedures. The mortality risk associated with emergent or urgent CABG is greater than that for elective CABG [211]. In addition, there is an increased risk of bleeding associated with clopidogrel and prasugrel given within five to seven days before CABG [211]. Thus, when CABG is planned, clopidogrel should be withheld for at least five days (seven days for prasugrel) unless the urgency for the procedure outweighs the increased risk for bleeding [2; 6]. The use of CABG should follow the ACC/AHA guideline for this procedure [6].

NONINVASIVE TESTING

Exercise testing in patients with STEMI is useful for risk stratification and assessment of functional capacity and should be performed to assess the presence and extent of inducible ischemia in patients who have not had angiography and do not have high-risk features [2]. The optimum time to exercise testing after STEMI has not been clearly defined. Exercise testing before discharge can provide reassurance to patients about their functional capacity and can also be used to establish exercise parameters for cardiac rehabilitation [2]. On the other hand, deferring exercise testing until three weeks after discharge in clinically low-risk patients appears to be safe and reasonable [2]. The ACCF/AHA guideline for STEMI suggests that exercise testing should be done before discharge in patients who may be candidates for a revascularization procedure and who have not undergone coronary angiography [2]. The use of exercise testing and the interpretation of its results should follow the guideline developed for this modality [198].

Echocardiography is also recommended for assessing left ventricular function in patients with STEMI who have not had coronary angiography and can be useful for evaluation of RV infarction in patients with inferior STEMI and initial nondiagnostic findings [2]. Patients who have baseline abnormalities that may compromise interpretation of the ECG findings should have stress echocardiography (or myocardial perfusion imaging) to assess inducible ischemia [2]. Echocardiography and stress echocardiography should be performed according to guidelines or criteria developed for their use [248].

GENERAL CARE AND ADJUVANT THERAPIES

In addition to either catheter-based or pharmacologic reperfusion, treatment of patients with STEMI involves the use of some of the same general care principles (such as those regarding bed rest and the use of oxygen) and drugs as those recommended for patients with NSTE-ACS. Adjuvant therapy involves the use of dual-antiplatelet therapy, nitroglycerin, morphine, beta blockers, ACE inhibitors, calcium-channel blockers, and statins; the drugs used depend on whether the patient is treated with PCI or fibrinolytic agents [2].

Antiplatelet Therapy

The 2013 ACCF/AHA guideline for the management of STEMI recommends aspirin at a dose of 162–325 mg as a loading dose before either PCI or fibrinolytic therapy [2]. A P2Y12 inhibitor is used along with aspirin as dual-antiplatelet therapy. For patients treated with PCI, clopidogrel (600 mg), prasugrel (60 mg), or ticagrelor (180 mg) should be given as a loading dose as early as possible or at the time of the PCI [2]. Treatment with a P2Y12 inhibitor is continued for one year. Clopidogrel is the recommended P2Y12 inhibitor to support fibrinolytic therapy; a loading dose of 300 mg is used for patients 75 years of age or younger, and no loading dose is used for patients older than 75 years of age [2]. Treatment with clopidogrel is continued for at least 14 days and up to one year.

Nitroglycerin/Morphine

The benefit of nitroglycerin for patients with STEMI has been modest, but the drug can be given sublingually (0.4 mg every five minutes up to three doses) for persistent or recurrent ischemic discomfort [2]. The use of nitroglycerin should not preclude the use of other drugs that have been shown to have more benefit, such as ACE inhibitors.

The drug of choice to manage the pain associated with STEMI is intravenous morphine sulfate [2]. Morphine sulphate is indicated to relieve ongoing ischemic discomfort, control hypertension, ameliorate anxiety, or manage pulmonary edema. The initial dose should be 4–8 mg, with lower doses in the elderly. Additional doses of 2–8 mg may be given at intervals of 5 to 15 minutes [2].

Beta Blockers

The use of beta blockers has been an established recommendation for patients with STEMI because of the drugs' association with lower mortality [2]. The recommendation was modified in the 2007 focused update of the ACC/AHA guideline because of safety issues related to the use of intravenous beta blockers in conjunction with fibrinolytic therapy as well as emerging data on a lack of survival benefit [247]. The findings were confirmed in the 2013 ACCF/AHA guideline, and it is still recommended that oral beta blockers be used within the first 24 hours, except for those subsets of patients at high risk for complications with use of beta blockers [2]. Beta blockers should not be used in patients with signs of heart failure, evidence of a low output state, increased risk of cardiogenic shock, or other relative contraindications to beta blockade.

ACE Inhibitors

The use of an oral ACE inhibitor is a strong recommendation for all patients recovering from STEMI, including those with anterior infarction, pulmonary congestion, or LVEF of less than 0.40, as well as those with normal LVEF in whom cardiovascular risk factors are well controlled [2]. Adherence to this recommendation has increased since the late 1990s but remains low [179; 249; 250]. Results of a 2022 study of 260 patients indicated adherence to guideline recommendations was achieved in less than 71% of study subjects, with women less likely to receive guideline-directed treatment. During the one-year follow-up, 23 patients died; adherence to guideline-directed therapy was associated with fewer deaths [251]. In addition, the doses used in clinical practice have been lower than the target doses used in clinical trials [249].

A meta-analysis of several major trials (more than 100,000 patients) demonstrated that use of an ACE inhibitor was associated with a significant overall odds reduction in mortality of 6.5% [252]. Early treatment is optimal, as reductions in mortality have been greatest within the first five days after the MI [252; 253]. The ACCF/AHA guideline for STEMI notes that it is preferable to initiate treatment with an ACE inhibitor within 24 hours [2]. Treatment should start at a low dose that is gradually increased to a full dose within 24 to 48 hours.

ACE inhibitors are of most benefit for patients who are 55 to 74 years of age, have had an anterior infarct, or have a heart rate of at least 80 beats per minute [254]. Contraindications include a systolic blood pressure of less than 100 mm Hg (or more than 30 mm Hg below baseline), the presence of clinically relevant renal failure, a history of bilateral stenosis of the renal arteries, or known allergy. Patients who cannot tolerate an ACE inhibitor should be treated with an ARB [2]. Data indicate that ARBs might be associated with lower all-cause mortality and hospitalization for heart failure compared with ACE inhibitors among patients with acute MI [255].

Calcium-Channel Blockers

Early treatment with dihydropyridine calcium antagonists (nifedipine and nicardipine) has not been found to improve rates of mortality or reinfarction [2]. Nifedipine is contraindicated in the treatment of STEMI. Although verapamil and diltiazem may be useful to relieve ongoing or recurrent ischemia, lower

OUTCOMES WITHIN FIVE YEARS AFTER FIRST MYOCARDIAL INFARCTION IN PATIENTS 45 YEARS OF AGE OR OLDER		
Outcome	**Prevalence**	
	Men	**Women**
Recurrent MI or fatal CHD	17%	21%
Heart failure	16%	22%
Stroke	4%	7%
CHD = coronary heart disease, MI = myocardial infarction.		
Source: [1]		*Table 12*

blood pressure, or control the ventricular response rate to atrial fibrillation when beta blockers are contraindicated (and the patient has well-preserved left ventricular function and no clinical evidence of congestive heart failure or pulmonary congestion), no specific recommendation for their use exists in the 2013 STEMI guideline [2; 3]. Both drugs have been associated with significantly reduced mortality and major cardiovascular events [256; 257]. Verapamil should not be used for patients with heart failure or bradyarrhythmias, and diltiazem should not be used for patients with left ventricular dysfunction [2].

DISCHARGE PLANNING AND SECONDARY PREVENTION

Appropriate discharge planning and secondary prevention measures are essential, as the morbidity and mortality after UA/NSTEMI or STEMI are high (***Table 12***). A multidisciplinary team should be involved in preparing the patient for discharge, and detailed discharge instructions should be given to both the patient and family [2]. Discharge instructions should be easily understood, culturally sensitive, given in the patient's preferred language, and reinforced with written instructions. Instructions should include detailed information on the comprehensive care plan, including [2; 3]:

- Scheduling the first follow-up visit
- Return to normal activities (driving, work, physical/sexual activities)
- Recommended secondary prevention measures
- Medication dosing, frequency, and adherence
- Plans to obtain prescribed medications immediately after discharge
- Referral to cardiac rehabilitation

CARDIAC REHABILITATION

Exercise-based cardiac rehabilitation and secondary prevention programs have been shown to reduce repeat hospital admissions and improve health-related quality of life and function [258; 259]. Referral to a cardiac rehabilitation or secondary prevention program is a recommendation in the ACC/AHA guidelines for NSTE-ACS and STEMI [2; 3].

SECONDARY PREVENTION STRATEGIES

Substantial evidence has demonstrated that aggressive risk-reduction therapies enhance patient outcomes after ACS, and the 2014 AHA/ACC Guideline for NSTE-ACS, the 2013 ACCF/AHA guideline for STEMI, and the 2011 update of the AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients With Coronary and Other Atherosclerotic Vascular Disease guideline have made several recommendations for secondary prevention focusing on lifestyle modifications and medications.

Lifestyle Modifications

After an ACS event, patients must address modifiable risk factors associated with atherogenesis by changing certain behaviors. Lifestyle modifications will include improvements in diet and physical activity levels, smoking cessation, blood pressure control, lipid management, and diabetes management [2; 260]. Clinicians should involve other healthcare professionals in helping patients to achieve goals and should reinforce patients' positive efforts toward reaching these goals.

Smoking Cessation

Quitting smoking has been described as "probably the most important thing a smoker with acute MI can do to improve future health" [261]. Mortality after an ACS event for a patient who smokes cigarettes is twice that for a patient who does not, but cessation of smoking reduces reinfarction and death rates at one year [2]. Clinicians should use the in-hospital period after MI and each office visit as an opportunity to ask patients who were smokers if they have quit or are ready to quit and should offer counseling, pharmacologic support, and information on formal quit programs. The in-hospital period is unique because many patients are motivated to quit and are typically unable to smoke for three to nine days. Randomized controlled trials have shown that repeated contacts during the hospital stay and at and beyond three months (typically by telephone) are more likely to result in smoking cessation [2]. An updated Cochrane review showed that only intensive counseling programs work and that nicotine replacement further increases the rates of successful cessation among patients in intensive programs [262]. Another Cochrane review found high-quality evidence for a benefit of combined pharmacotherapy (with any type of nicotine-replacement therapy, bupropion, nortriptyline, or varenicline) and behavioral treatment compared to usual care, brief advice, or less intensive behavioral support [263]. However, many clinicians are reluctant to add another drug to the multitude of medications prescribed after MI.

Diet

Obesity is another well-documented risk factor for CHD, and weight management programs and information on healthy eating/caloric intake should be promoted as appropriate [260]. The patient's body mass index and waist circumference should be measured at each visit. The goal is to attain a body mass index of 18.5–24.9 and a waist circumference of 35 inches (women) or 40 inches (men) [260]. When weight reduction is needed, the initial goal is weight loss of 5% to 10% from baseline [260].

Exercise

The level of exercise should be prescribed according to risk, previous level of exercise, and possibly the results of a stress test [260]. The minimum goal is 30 minutes of aerobic exercise (e.g., walking, cycling, jogging) five times per week, with an optimal goal of 30 to 60 minutes every day [260]. Resistance training two times per week is reasonable to prescribe. Patients should also be encouraged to increase their routine daily activities (such as house cleaning and gardening).

Exercise-based secondary prevention programs are recommended for patients with STEMI and UA/NSTEMI.

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Strength of Recommendation/Level of Evidence: IB (Procedure/treatment should be performed based on data derived from a single randomized clinical trial or nonrandomized studies evaluating limited populations.)

Medications

Four classes of medications are recommended after an ACS event: antiplatelet/anticoagulant agents (aspirin, warfarin, and a P2Y12 inhibitor), beta blockers, ACE inhibitors (or ARBs), and lipid-lowering agents [2; 3; 260; 264]. Treatment with these four classes has been associated with one-year mortality that is significantly lower than that for patients

treated with none or one of the medications with a positive impact most apparent at 24 months postdischarge, regardless of revascularization therapy [263; 265]. In addition, nitroglycerin should be prescribed for all patients, and they should be instructed on its use for ischemic pain [2]. The medication profile should be tailored to each patient on the basis of the in-hospital events and procedures, risk factors, and drug tolerability.

Antiplatelet/Anticoagulant Agents

The recommended antiplatelet therapy after discharge is a combination of aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) [2; 260; 264]. The findings of studies have suggested that low-dose aspirin is as effective as higher doses but has a better safety profile [170; 266; 267]. The recommended daily dose of aspirin is 75–162 mg for all patients, and the ACC/AHA guidelines for the management of STEMI and NSTE-ACS state that it is reasonable to a use an 81-mg dose [2; 3; 264; 267]. However, despite the better safety profile of low-dose aspirin, data have indicated that 325 mg is the most common dose, prescribed for 55.7% of patients with UA/NSTEMI [268].

The addition of clopidogrel to aspirin as maintenance therapy has been found to enhance outcomes for patients [267; 269]. Among 12,562 patients with ACS who were taking aspirin (at a dose of 75–325 mg daily) in one trial, one year of treatment with clopidogrel was associated with a lower rate of a composite endpoint of cardiac death, MI, or stroke, regardless of the aspirin dose [267]. Clopidogrel was also associated with an increased risk for major bleeding, but bleeding risks increased with increasing aspirin dose, with or without clopidogrel [267; 269]. The 2013 update of the ACCF/AHA guideline for the management of STEMI includes modified recommendations for maintenance therapy with a P2Y12 inhibitor [2]. The guideline indicates that patients with a stent should receive clopidogrel (75 mg daily), prasugrel (10 mg daily), or ticagrelor (90 mg twice a day) for at least one year. Patients not receiving a stent should be treated with clopidogrel (75 mg daily); it is reasonable to prescribe prasugrel (10 mg daily) in patients not receiving a stent and without a history of stroke or transient ischemic attack [2].

Questions about clopidogrel maintenance therapy remain, as the optimal dose and duration of therapy have not been identified [165; 270; 271; 272]. Another concern is the effect of stopping clopidogrel. In a 2008 study of 3,137 patients with ACS (treated either medically or with PCI) who took clopidogrel for a mean of 9 to 10 months, there was a significantly high risk of adverse events in the initial 90 days after stopping treatment with clopidogrel [272]. The reason for this phenomenon is unclear, and the authors suggested that strategies to reduce the incidence of such early events should be identified [272]. Additionally, the response to clopidogrel varies among patients, and diminished responsiveness has been observed [264]. A 2010 retrospective study of 2,017 patients with ACS, conducted to confirm the findings of the 2008 study, found that the 0- to 90-day interval after stopping clopidogrel was associated with higher risk of death/MI compared with the 91- to 360-day interval. There was a similar trend of increased adverse events 0 to 90 days after stopping clopidogrel for various subgroups (i.e., women versus men, medical therapy versus PCI, stent type, and ≥6 months or <6 months of clopidogrel treatment) [273]. Warfarin is recommended as an antithrombotic for patients with UA/NSTEMI or STEMI who are allergic to aspirin [260; 264].

Antiplatelet therapy is preferred over anticoagulant therapy with warfarin (or other vitamin K agonists) for treating patients with atherosclerosis [260]. However, warfarin therapy is reasonable for patients with a prosthetic heart valve, persistent or paroxysmal atrial fibrillation, a documented left ventricular thrombus, concomitant venous thromboembolic disease, or other indication. Warfarin should be given to maintain a specific international normalized ratio (INR) depending on the use of stents, underlying cardiac disease, and the concomitant use of clopidogrel [260]. The risk of bleeding is increased when warfarin is used in conjunction with aspirin and/or clopidogrel, and patients treated with the three medications should be monitored closely [260].

Beta Blockers

Treatment with oral beta blockers is recommended for all patients after UA/NSTEMI or STEMI [2]. Treatment should continue indefinitely.

ACE Inhibitors or ARBs

An ACE inhibitor is also recommended as long-term therapy after UA/NSTEMI or STEMI [2; 260]. ARBs should be used for patients who are unable to tolerate an ACE inhibitor and have clinical or radiographic signs of heart failure or a left ventricular ejection fraction of less than 40% [2].

Lipid-Lowering Agents

Even before the advent of statins, reducing lipid levels through diet and previously available medications led to significant reductions in MIs. Statins are now the preferred medications for lipid-level management, and several studies have demonstrated their effectiveness in reducing atherogenesis. A fasting lipid profile should be determined within 24 hours after admission, and statin therapy should begin during hospitalization, regardless of this baseline level [2]. Intensive statin therapy appears to be of benefit for patients with recent ACS (but not for patients with stable CHD). In a pooled analysis of data on more than 8,600 patients, intensive statin therapy significantly reduced all-cause mortality compared with standard therapy [274]. This benefit was confirmed in an analysis of data from a total of six trials (28,505 patients), with all-cause mortality at two years of 3.5% for intensive therapy compared with 4.6% for standard therapy [275]. A meta-analysis of 20 trials involving 8,750 patients with ACS undergoing PCI found a time-related benefit to the start of statin therapy. By meta-regression, earlier statin administration correlated significantly with lower risk of MI, major adverse cardiac events, and major adverse cardiac and cerebrovascular events [276].

The 2013 ACCF/AHA guideline for STEMI indicates the need to continue or initiate the use of a statin to manage patients' lipoprotein levels [2]. In particular, the guideline makes a sole recommendation for high-dose atorvastatin (80 mg daily), based primarily on results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial. Rates of cardiovascular events did not significantly decrease with tiered simvastatin (40 mg for one month, then 80 mg thereafter), and there are concerns about the safety of the 80-mg dose [2]. The compliance rate of statins may be improved when therapy is initiated before discharge following STEMI.

The goal of statin therapy is to achieve an LDL level less than 100 mg/dL for patients with average risk, and an LDL level of less than 70 mg/dL is reasonable for very-high-risk patients [2]. If the triglyceride level is 200 mg/dL or higher, the non-HDL cholesterol should be less than 130 mg/dL in patients with average risk, whereas a non-HDL cholesterol level of less than 100 mg/dL is reasonable for very-high-risk patients. Statin therapy should be supplemented with dietary modification, weight management, and exercise. Patients should be encouraged to follow a diet with an increase of fresh fruits and vegetables, with less than 7% of total calories as saturated fat, less than 1% of total calories as trans fatty acids, and less than 200 mg per day of cholesterol [2; 260].

If statin therapy fails to control lipid levels or patients do not tolerate statins, treatment with niacin or a bile acid sequestrant is reasonable [260]. Ezetimibe should be considered if patients do not tolerate any of the aforementioned medications [277; 278; 279; 280].

Other Therapies

After discharge, patients may need other treatments to manage blood pressure, depression, or diabetes.

Control of Blood Pressure

In addition, blood pressure should be controlled according to the 2017 Guideline for High Blood Pressure in Adults, which recommends treatment when blood pressure is elevated, defined as 120–129/<80 mm Hg [82]. The guideline recommends initial treatment with nonpharmacologic interventions and lifestyle changes. Initiation of pharma-

cologic treatment is recommended for secondary prevention in patients with clinical CVD and an average systolic blood pressure of 130 mm Hg or greater or an average diastolic blood pressure of 80 mm Hg or greater and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average systolic blood pressure 130 mm Hg or greater or an average diastolic blood pressure 80 mm Hg or greater. The AHA/ACCF recommends initial treatment with a beta blocker and/or an ACE inhibitor as secondary prevention for patients with CHD [260].

Treatment of Depression

An ACS event can be distressing for many patients, leading to a heightened fear of dying and anxiety about adjusting to life with cardiac disease [281]. These emotions can substantially affect a patient's psychosocial status and lead to depression [282; 283]. Some degree of clinically significant depression has been reported to occur in up to half of patients with ACS, with major depression occurring in 15% to 20% of patients [282]. Depression has been found more often in women compared with men and in men with a history of MI [284]. In addition to the negative effect on the patient's quality of life, depression has also been shown to be associated with lack of adherence to secondary prevention measures and with increased mortality [283; 285; 286].

Evaluation of a patient's psychosocial status, with particular attention paid to signs of depression, is a recommendation in the ACCF/AHA guidelines for STEMI and UA/NSTEMI, and screening for depression and referral and/or treatment is a recommendation in the 2011 AHA/ACCF Secondary Prevention and Risk Reduction Therapy guideline [2; 3; 260]. At each visit, clinicians should ask patients about anxiety, sleep disorders, social support, and symptoms of depression. Cognitive behavior therapy, sertraline, and selective serotonin reuptake inhibitors may be useful for enhancing the quality of life for patients with symptoms of depression, though treatment does not directly improve cardiovascular disease outcomes [260; 282].

Management of Diabetes

CHD is responsible for about 75% of deaths in individuals with diabetes, and more than 30% of patients with NSTE-ACS have diabetes [3]. It is now well known that a reduction in blood glucose levels is associated with improved outcomes in patients with diabetes or prediabetes who have experienced UA/NSTEMI or STEMI. This reduction may be achieved as the result of lifestyle changes (including weight management, physical activity, and medical nutrition therapy) or medication therapy [2; 3; 287; 288]. The patient's primary care physician and/or endocrinologist typically handle the management of diabetes, but it is beneficial for treating physicians to coordinate with a primary care physician or specialist [260].

The goal of diabetes management (aside from reversal of the condition though intensive lifestyle change) is tight glycemic control, as both hyperglycemia and hypoglycemia have a profound impact on in-hospital and six-month mortality rates following a cardiac event [3]. Metformin is the recommended first-line diabetes pharmacotherapy for the prevention of cardiovascular complications [260]. The intensity of blood glucose-lowering medications should be closely tailored to each patient's risk of hypoglycemia during treatment. It may be reasonable to initiate treatment with medications to achieve a hemoglobin A1c of 7% or less [260; 289; 290].

Adherence and Compliance

Despite the obvious benefit of secondary prevention strategies, physician adherence to guidelines and patient compliance with cardiac rehabilitation, medication regimens, and lifestyle change recommendations are suboptimal [260; 261; 291; 292; 293; 294; 295; 296]. According to data from several studies, referrals to cardiac rehabilitation range from 64% to 87% by hospital (mean: 81%) [293]. Quality improvement initiatives have increased referrals. Rates of actual enrollment are more important than referral rates, however, and enrollment has been much lower than referral rates [293; 294].

Only 29% of patients with MI who were referred to cardiac rehabilitation enrolled within one month of discharge; this rate raised to just 48.25% after six months [294]. Women are less likely to be enrolled after one month, as are patients with hypertension or peripheral arterial disease and uninsured patients. Older patients are less likely to have participated at six months, as are smokers and patients with economic hardship. White individuals and patients who attained a higher education level were more likely to enroll by six months [294].

Cardiac rehabilitation coordinators have identified several patient-related barriers to participation in rehabilitation programs as well as implementation of other evidence-based guidelines, including coming to terms with a diagnosis of heart disease, challenges in changing behavior, and cost [297]. Others have identified distance from a rehabilitation center (e.g., long travel time, lack of transportation) and high co-pays as significant barriers [294]. Efforts to improve rates of referral to cardiac rehabilitation should continue, and more research is needed to determine how to address barriers to enrollment.

Data have also indicated that rates of dietary change and smoking cessation in patients with ACS need improvement. Research shows that physicians are recommending dietary modification and smoking cessation to patients (91% and 95%, respectively), but rates of compliance are not optimal [261; 295; 298]. Smoking cessation rates following MI (roughly 30% at six months) are greater than in similar-age patients in the general population but are still too low [261].

Reasons provided for not adhering to dietary modification (and exercise) include not being able to see a physical change, and many individuals express that they are dissatisfied with having to make so many lifestyle changes at once [296]. However, the results of a 2014 study indicate that patients with ACS who comply with nonsmoking, diet, and exercise plans have significantly lower mortality and recurrence of MI despite no change to their waist circumference [299]. Therefore, it is important that patients understand that the benefits of dietary modification are internal (not based on appearance) and that obtaining a regular lipid profile will show their progress.

With regard to medications, studies have shown that up to 57% of patients are not managed optimally, defined as receiving all four classes of medications [26; 177; 201; 250; 265; 292; 298; 300]. Optimal medical therapy is less likely among older patients; women; and patients who had CABG during the index hospitalization, had previous heart failure, or had renal dysfunction [265; 301; 302].

The class I guideline recommendations for all secondary prevention strategies can be organized into a simplified "ABCDE" approach to help clinicians implement guideline-based care [303]:

- A: Aspirin, antianginal agents, antiplatelet therapy, and ACE inhibitors (or ARBs)
- B: Beta blockers and blood pressure control
- C: Cardiac rehabilitation, cholesterol treatment, and cigarette smoking cessation
- D: Diet, depression management, and diabetes management
- E: Exercise and education

Critical pathways, protocols, and other quality improvement tools are valuable for helping to increase implementation of guidelines [26; 304]. For example, the GWTG program helps to enhance compliance through a Web-based tool that provides online reminders about discharge management strategies. This tool can be used to send discharge instructions and information on medications to primary care clinicians [26; 28]. The GWTG-Coronary Artery Disease program was implemented in 418 U.S. hospitals and was associated with widespread and prolonged adherence to evidence-based guidelines [304].

Lack of patient compliance with medications is also a serious problem and has been referred to as an unrecognized risk factor for CHD, because of its association with significant increases in adverse events and health costs [305; 306]. Among individuals with CHD (many of whom had experienced a recent ACS event), compliance with guideline-recommended medications has ranged from 18% to 55%. Approximately 54% of individuals have been compliant with all of their initial medications, and compliance decreases over time [305; 307; 308]. One study showed that compliance was 60.3% at one year, 53.7% at two years, and 48.8% at five years [309]. Individuals who discontinue medications are more likely to be older, female, unmarried, and less educated [307]. Several other factors have been found to be associated with noncompliance with medications [305; 307; 308]:

- Choice of medication
- Tolerability
- Duration of treatment
- Dosing frequency
- Higher number of prescribed medications
- Lack of symptoms as indication for the medication
- Uncertainty about how to take the medication
- Lack of transportation to the pharmacy

Patient Education

Patient education is an integral component of treatment for patients with ACS and should begin during hospitalization and continue throughout follow-up care [2]. Adequate time for appropriate education during the index hospitalization has been challenged by shorter hospital stays and reduced staffing [310]. The responsibility of patient education has thus shifted to the healthcare team. Surveys have shown that nearly one-half of individuals are not knowledgeable about ACS-related symptoms or their level of risk, even after having an ACS event [310]. Men, older individuals, and individuals with less formal education were less likely to be knowledgeable about their risk and symptoms [310]. This lack of knowledge can contribute to lack of compliance with recommended secondary prevention strategies.

Research has shown that patient education should focus on the importance of [2; 311]:

- Recognition of symptoms
- Timeliness of care
- Acknowledgment of risk factors for ACS
- Compliance with secondary prevention strategies

Education in these areas should be tailored to individuals, as perceptions of cardiac disease and risk differ across subgroups of patients according to age, gender, and race/ethnicity [311; 312]. As noted, many clinicians do not feel confident in their effectiveness in helping patients understand their disease and comply with preventive measures [20]. Several strategies can help clinicians educate patients effectively (***Table 13***) [313; 314; 315; 316; 317].

Recognition of Symptoms

Many individuals still believe that the onset of an MI will be "dramatic," with chest pain that is severe and crushing [2; 318]. Among individuals who had an acute MI, 40% interpreted their symptoms as cardiac in nature [312]. In addition, chest pain and other ACS-related symptoms were interpreted differently by men and women. Men were more likely to think the symptoms were cardiac in nature if the chest pain was severe and if they had a history of CHD. In contrast, women did not relate severity of chest pain with a cardiac origin [312]. Healthcare professionals should talk to patients about the "real" signs and symptoms of ACS, emphasizing the diversity in symptoms [310].

STRATEGIES TO HELP ENHANCE EFFECTIVENESS OF PATIENT EDUCATION
Ask the patient what language he or she prefers for educational resources and use that language for oral education and written resources (as much as possible).
Assess the patient's baseline understanding of the disease and treatment.
Ask the patient what and how much he or she wants to know.
Discuss epidemiologic and clinical evidence.
Involve other healthcare specialists in the educational process.
Use a variety of educational resources in a variety of media.
Try innovative approaches, such as interactive modules.
Offer online resources to patients (e.g., the AHA website [https://www.heart.org] or the NHLBI website [https://www.nhlbi.nih.gov]).
Ascertain potential barriers to compliance.
Develop an action plan.
Have patient focus on one behavior change at a time, if necessary.
Involve family members in educational efforts.
Reinforce recommendations at all office visits.
Provide positive reinforcement for each step toward goals.
Provide telephone follow-up.
Source: [313; 314; 315; 316; 317] *Table 13*

REASONS FOR DELAY IN SEEKING MEDICAL ATTENTION FOR CHEST PAIN
Expected more severe chest pain
Believed chest pain would resolve
Did not think symptoms were serious
Decided on "wait and see" approach
Thought symptoms were related to another condition (e.g., muscle strain, heartburn)
Was not aware of benefit of rapid action
Feared embarrassment if symptoms were not related to cardiac event
Underestimated personal risk of cardiac event
Source: [2; 318] *Table 14*

Timeliness of Care

On average, individuals wait 1.5–2 hours before seeking medical care for ACS-related symptoms, and this delay has not changed over time, despite many national public campaigns emphasizing the importance of timely care [2]. Furthermore, up to 50% of individuals with ACS-related symptoms are transported to the hospital by means other than emergency medical services, which can increase delays [2; 319]. Individuals have given several reasons for delays in seeking medical care (***Table 14***) [318]. Individuals and their families or caregivers should be told that immediate action is needed for ACS-related symptoms, including calling emergency medical services, taking nitroglycerin for ischemic pain, and taking aspirin.

Acknowledgement of Risk Factors

The need for better understanding of risk among individuals who have had ACS is evidenced by studies that have shown that their perceptions of their personal risk are lower than their actual risk [2; 310; 318]. Healthcare professionals should reinforce information about modifiable risk factors and provide patients with educational resources that describe risk factors and their effect on the potential for future events. Patients' individual risk factors should be discussed in an ongoing manner, with a focus on positive changes through lifestyle modifications and medications.

Compliance with Secondary Prevention Strategies

Compliance with prevention strategies can be enhanced by identifying the barriers for each individual patient and working together to address the problem. Primary care clinicians and other healthcare professionals should ask patients about medication compliance at each office visit and should emphasize the importance of maintaining drug therapy. Ongoing education about the benefit gained from medications as well as lifestyle modifications is vital to ensuring high compliance and low risk of adverse events.

INTERPROFESSIONAL PRACTICE AND COLLABORATION

ACS represents the acute expression (recognition) of a chronic disease, one with pre-event possibilities for primary prevention and post-event need for secondary prevention and management strategies that restore and maintain health. Care of the patient with CVD/ACS is challenging, the clinical issues multifaceted and complex for patient, patient's family, and practitioner alike. Patients with chronic disease are estimated to visit four to nine different healthcare professionals regularly; interprofessional collaboration is an effective way to share the load, facilitate care, and reinforce management goals [320]. Evidence shows that an interprofessional team approach enhances quality of care and improves outcomes for patients with complex illness and diverse needs [321].

Interprofessional practice and collaboration (IPC) is a model of care provided by healthcare professionals with overlapping expertise, committed to shared responsibility, mutual trust, and communication to achieve a common goal [321]. Increasingly, IPC is modeled in the context of medical education. The introduction of IPC to primary care and chronic disease management has been shown to foster patient-centered care and reduce healthcare costs [322; 323].

CONCLUSION

The identification of the pathophysiologic process leading to ACS has redefined the treatment of this spectrum of cardiac disorders, and researchers continue to refine therapeutic options to produce optimal patient outcomes. Despite a shared initiating event (plaque rupture or erosion), UA/NSTEMI and STEMI are distinct clinical entities, with differences in pathophysiology, clinical presentation, treatment, and prognosis. The diagnosis of UA/NSTEMI (also known as NSTE-ACS) relies primarily on elevated levels of cardiac troponins and the lack of ST-segment elevation on ECG. By contrast, the diagnosis of STEMI is made solely on ECG findings. After the type of MI has been determined, complex decision making is required to determine the appropriate course of treatment.

The goal of immediate treatment of NSTE-ACS is relief of ischemia and prevention of recurrent ischemic events. Risk stratification is essential for determining whether an early invasive or ischemia-guided strategy is best for the patient. Antiplatelet therapy, P2Y12 inhibitors, and antithrombotic therapy are adjuncts to treatment. With STEMI, the goal of immediate treatment is re-establishment

of blood flow to the heart. The crucial factor for determining the treatment approach is timing from the onset of symptoms to treatment and from arrival in the emergency department to treatment. The preferred option for reperfusion is PCI, but the recommended 90-minute door-to-balloon time is difficult to achieve in most cases. However, there is an increased emphasis on developing systems of care that increase patient access to primary PCI. The other option for reperfusion, fibrinolytic therapy, has the advantage of immediately re-establishing blood flow, but it is associated with lower rates of reperfusion and higher risks compared with PCI. Ancillary therapy with antiplatelet therapy, P2Y12 inhibitors, and antithrombotic therapy is used to maintain patency of the infarct-related artery and prevent re-occlusion.

Review of data from several large-scale studies, cardiac registries, and quality improvement initiatives has shown that adherence to guideline recommendations for the diagnosis, treatment, and secondary prevention NSTE-ACS and STEMI are suboptimal, particularly for older individuals, women, and minority populations. In addition, an inverse relationship has been found between risk and treatment, with more low-risk patients than high-risk patients receiving aggressive treatment. The data have also demonstrated a clear benefit in survival and outcomes when guideline recommendations are followed. Thus, clinicians should become more familiar with these guidelines and should encourage hospitals to implement system-wide policies and procedures to facilitate guideline-driven care. The use of protocols, clinical pathways, and standardized order forms can help to ensure that all patients receive appropriate care in a timely manner. After discharge, effective communication among the treating physician, the healthcare team, the patient and family, and the patient's primary care clinician is essential for ensuring long-term compliance with lifestyle modifications and medications, which will help to reduce the risk of future cardiac events.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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Evidence-Based Practice Recommendations Citations

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