53 Non–ST Elevation Acute Coronary Syndromes

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BACKGROUND

Definitions

Ischemic heart disease may be manifested clinically as either chronic stable angina (**see Chapter 54**) or an acute coronary syndrome (ACS). The latter, in turn, can be subdivided into ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina (UA) (**Fig. 53-1**). **Chapters 51 and 52** discuss STEMI in detail. Because NSTEMI and UA are indistinguishable at initial evaluation and the entity of UA is receding as the sensitivity of biomarkers of myocardial injury increases, they are often described together as NSTE-ACS and are discussed together in this chapter.

Features that help differentiate ACS from stable angina are (1) onset of symptoms at rest (or with minimal exertion) and lasting longer than 10 minutes unless treated promptly; (2) severe, oppressive pressure or chest discomfort; and (3) an accelerating pattern of symptoms that develop more frequently, occur with greater severity, or awaken the patient from sleep. Symptoms alone do not suffice to distinguish the three types of ACS from one another. Patients without persistent (>20 minutes) ST-segment elevation in two or more contiguous leads but with biomarker evidence of myocardial necrosis are classified as having NSTEMI, whereas in patients without such evidence of myocardial necrosis, UA is diagnosed—a condition generally carrying a better prognosis.

Epidemiology

Globally, ischemic heart disease remains the number one cause of mortality; it was responsible for 7 million of the 53 million deaths reported in 2010.[1] ACS, the acute manifestation of ischemic heart disease, accounted for approximately 1.1 million discharges in the United States in 2009,[2] with approximately twice this number in Europe. The annual number of hospital discharges for ACS in developed countries has declined slowly over the past two decades, accompanied by an increase in nations with developing economies (**see Chapter 1**).[3] In the United States, three recent trends have changed the frequency distribution of the types of ACS: (1) wider use of primary preventive therapies (aspirin, statins, smoking cessation) appears to have resulted in fewer cases of STEMI[4]; (2) aging of the U.S. population, with higher rates of diabetes and chronic kidney disease (CKD), have increased the incidence of NSTE-ACS[5]; and (3) the use of more sensitive assays for myocardial necrosis (i.e., cardiac-specific troponin [cTn]) has shifted the classification of NSTE-ACS away from UA toward NSTEMI[5] (**Fig. 53-2**; also see Fig. 51-2A). Overall, the age- and sex-adjusted incidence rates of NSTEMI have grown slowly since 1999.[4]

PATHOPHYSIOLOGY

The pathogenesis of NSTE-ACS involves four processes: (1) rupture of unstable atheromatous plaque, (2) coronary arterial vasoconstriction, (3) imbalance between the supply and demand of the myocardium for oxygen, and (4) gradual intraluminal narrowing of an epicardial coronary artery because of progressive atherosclerosis or poststent restenosis. These processes are not mutually exclusive and can occur simultaneously in any combination.

Plaque rupture or erosion leads to the formation of superimposed thrombus (typically nonocclusive in NSTE-ACS) along with subsequent impaired myocardial perfusion, which if persistent, leads to myocardial necrosis. Inflammation of the arterial wall and the action of metalloproteinases produced by inflammatory cells in degrading the fibrous wall of plaque contribute to their instability (**see Chapter 41**).

Vasoconstriction causing dynamic obstruction of coronary arterial flow may result from spasm of the epicardial coronary arteries (Prinzmetal angina, see below)—constriction of small, intramural, muscular coronary arteries resulting in increased coronary vascular resistance. This constriction may result from vasoconstrictors released by platelets, endothelial dysfunction (cardiac syndrome X; **see Chapter 77**), or adrenergic stimuli (e.g., the "fight-or-flight" response, cold, cocaine, or amphetamines [**Chapter 68**]). More than one of these mechanisms may be present simultaneously. Insufficient myocardial O_2 supply may also occur in patients with severe anemia and hypotension. When an increase in myocardial O_2 demand (e.g., tachycardia, fever, thyrotoxicosis) occurs in a patient with fixed narrowing of an epicardial coronary artery, secondary NSTE-ACS may develop.

Activation of the coagulation cascade and platelets plays a central role (described in detail in **Chapter 82**) in the formation of thrombus following plaque rupture/erosion. The first step in thrombus formation is vascular injury or endothelial dysfunction, which causes *adhesion* of platelets to the arterial wall via binding of platelet glycoprotein (GP) Ib to subendothelial von Willebrand factor. Exposure of platelets to subendothelial collagen and/or circulating thrombin causes platelet *activation* (**Fig. 53-3**), which induces platelets to change shape and results in degranulation with release of adenosine diphosphate

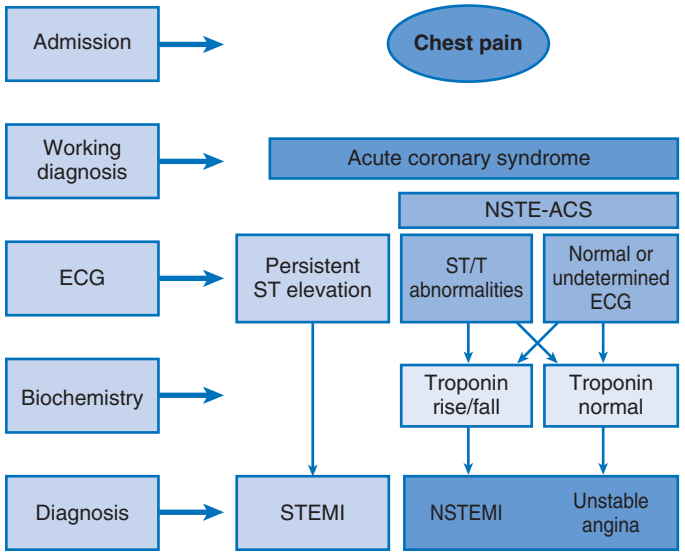


FIGURE 53-1 Spectrum of ACSs. ECG = electrocardiogram. *(Modified from Hamm CW, Bassand JP, Agewall S, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 32:2999, 2011.)*

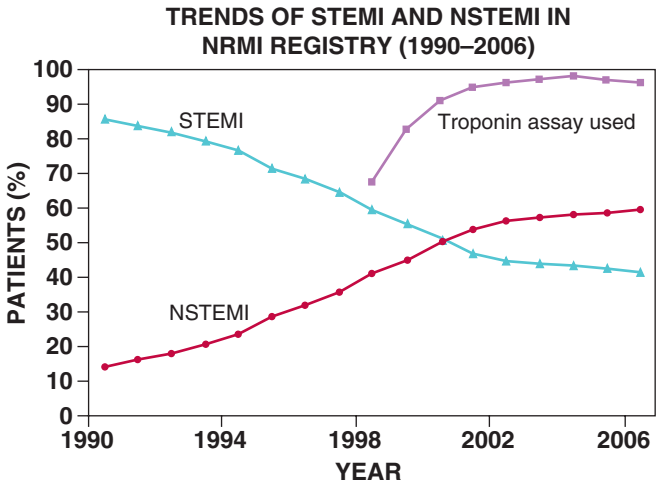


FIGURE 53-2 Trends of STEMI and NSTEMI in National Registry of Myocardial Infarction (NRMI) from 1990 to 2006. The proportion of patients with STEMI or NSTEMI and the proportion of patients in whom a troponin assay was used to diagnose AMI are shown. *(From Rogers WJ, Frederick PD, Stoehr E, et al: Trends in presenting characteristics and hospital mortality among patients with ST elevation and non–ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 156:1026, 2008.) (Also see Figure 51-2.)*

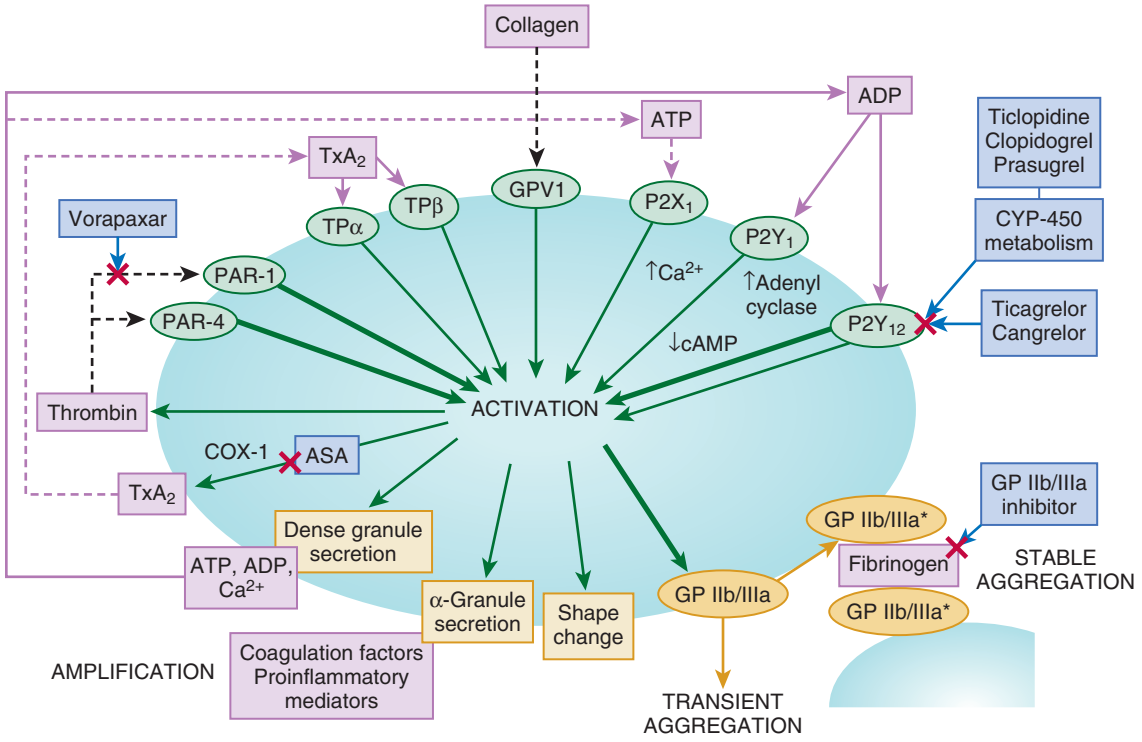


FIGURE 53-3 Platelet activation mechanisms and sites of blockade of antiplatelet therapies. Platelet activation is initiated by soluble agonists such as thrombin, TxA_2, 5-HT (hydroxytryptamine), ADP (via $P2Y_1$ and $P2Y_{12}$), and ATP and by adhesive ligands such as collagen and von Willebrand factor. Consequently, dense granule secretion of platelet agonists and secretion of TxA_2 lead to amplification of platelet activation, which causes a conformational change in the GP IIb/IIIa receptor that leads it to bind to fibrinogen and results in platelet aggregation. The $P2Y_{12}$ receptor plays a major role in the amplification of platelet activation. ASA = acetylsalicylic acid; ATP = adenosine 5′-triphosphate; cAMP = cyclic adenosine monophosphate; COX-1 = cyclooxygenase-1; PAR = protease receptor protein; TP = human thromboxane A2 receptor; TRA = thrombin receptor antagonist; X = sites of action of antiplatelet agents. *(From Braunwald E: Unstable angina and non–ST elevation myocardial infarction. Am J Respir Crit Care Med 185:924, 2012. Modified from Storey RF: Biology and pharmacology of the platelet $P2Y_{12}$ receptor. Curr Pharm Des 12:1255, 2006. From Wallentin L: $P2Y_{12}$ inhibitors: Differences in properties and mechanisms of action and potential consequences for clinical use. Eur Heart J 30:1964, 2009.)*

(ADP) and thromboxane A_2 (TxA2)—which in turn causes further platelet activation and expression of platelet glycoprotein GP IIb/IIIa.

In parallel, tissue factor expressed within the lipid-rich core of atherosclerotic plaque, when exposed to circulating blood, activates the coagulation cascade. A complex of tissue factor and coagulation factors VIIa and Va leads to the formation of activated factor X (factor Xa), which in turn amplifies the production of activated factor IIa (thrombin). The cascade proceeds with thrombin-induced conversion of fibrinogen to fibrin. The platelet and coagulation systems converge in that thrombin is also a potent platelet activator. Platelet

GP IIb/IIIa binds circulating fibrinogen, thereby causing platelet *aggregation* and ultimately producing a platelet-fibrin thrombus, portions of which may embolize distally and cause myocardial necrosis.

The central role of coronary artery thrombosis in the pathogenesis of NSTE-ACS is supported by (1) autopsy findings of thrombi in the coronary arteries typically localized to a ruptured or eroded atherosclerotic plaque; (2) a high incidence of thrombotic lesions in coronary atherectomy specimens in patients with NSTE-ACS in comparison to those with stable angina; (3) observations of plaque ulceration and/or irregularities in the fibrous cap of atherosclerotic plaque consistent with plaque rupture and thrombus formation as visualized by coronary angiography, intravascular ultrasound (IVUS), optimal coherence tomography (OCT), or computed tomographic angiography (CTA); (4) elevation of serum markers of platelet activity, thrombin generation, and fibrin formation; and (5) improvement in clinical outcome with antiplatelet and anticoagulant treatment.

CLINICAL ASSESSMENT

History and Physical Examination

NSTE-ACS resulting from atherosclerosis is relatively uncommon in men younger than 40 years and women younger than 50 years, but the incidence rises steadily thereafter. Although NSTE-ACS may be the initial manifestation of coronary heart disease (CHD), most patients have preceding stable angina or myocardial infarction (MI). Patients with ACS more frequently have traditional risk factors for CHD (**see Chapter 42**) than do normal subjects or those with nonischemic chest pain. Although coronary risk factors can be used to assess risk in populations, they are less helpful in the assessment of individual patients.

The initial symptom is typically described as pressure, heaviness, or frank pain beneath the sternum (**see Chapter 50**), and it resembles stable exertional angina—but is usually more intense and lasts longer (>20 minutes). Associated radiation to the ulnar aspect of the proximal part of the left arm, either shoulder, the neck, or the jaw may occur, but symptoms may be present anywhere between the ear and epigastrum.[6] Symptoms such as diaphoresis, nausea, abdominal pain, dyspnea, and syncope may accompany the pain. Features that support the diagnosis include exacerbation of symptoms by physical exertion; precipitation by severe anemia, infection, inflammation, fever, or metabolic or endocrinologic (e.g., thyroid) disorders; and importantly, relief with rest or nitroglycerin. Atypical manifestations, such as dyspnea without chest discomfort, pain limited to the epigastrium, or indigestion, represent "anginal equivalents." These atypical findings are more prevalent in women, older adults, and patients with diabetes, CKD, or dementia and can lead to underrecognition, undertreatment, and worse outcomes. Chest pain that is pleuritic or described as stabbing is generally noncardiac in origin.

The clinical manifestations may be sudden, with severe, new-onset symptoms occurring during minimal exertion (Canadian Cardiovascular Society class[7] [CCSC] III) or at rest (CCSC IV), an accelerating pattern of angina (more frequent, more intense, longer lasting), or angina occurring shortly after a completed MI.[8]

Physical Examination

Findings on physical examination may be normal, although patients with large territories of myocardial ischemia may have audible third and/or fourth heart sounds. Rarely, hypotension, pale cool skin, sinus tachycardia, or frank cardiogenic shock can occur; these findings are far more common with STEMI than with NSTE-ACS. The examination can also be important in that potential precipitating causes of ACS can be identified, such as fever, resistant hypertension, tachycardia, profound bradycardia, thyroid disease, or gastrointestinal bleeding. Finally, findings on physical examination such as pulse deficits, tachypnea, and tachycardia in the presence of clear lung fields and pulsus paradoxus with jugular venous distention may lead to alternative life-threatening diagnoses such as aortic dissection, pulmonary embolism, or cardiac tamponade.

Electrocardiography

The most common abnormalities on the 12-lead electrocardiogram (ECG) are ST-segment depression and T wave inversion; they are more likely to be present while the patient is symptomatic. Comparison with a recent ECG is important because dynamic ST-segment depressions as little as 0.05 mV are a sensitive (albeit not very specific) marker for NSTE-ACS. Greater degrees of ST-segment depression predict poorer outcomes, however, even when adjusted for other prognostic factors.[9,10] Transient ST-segment elevation lasting less than 20 minutes occurs in up to 10% of patients and suggests either coronary vasospasm or an aborted infarction. Deep (>0.2 mV) T wave inversions are compatible with, but not necessarily diagnostic of NSTE-ACS, whereas isolated T wave inversions of lesser magnitude are not particularly helpful given their low specificity. In patients with definite NSTE-ACS, findings on the ECG may be normal or nondiagnostic in more than half of patients. Because ischemia may occur in a territory that is not well represented on the standard 12-lead ECG (see below) or because the patient may have episodic ischemia that is missed on the initial ECG, tracings should be repeated every 20 to 30 minutes until the symptoms resolve, the diagnosis of MI is established or excluded, or an alternative diagnosis is made.

Coronary angiography identifies a culprit lesion in the circumflex coronary artery in a third of patients with high-risk NSTE-ACS.[11] Because the standard 12-lead ECG does not represent this territory well, assessment of posterior leads V_7 through V_9 should be considered in patients with a history suggestive of ACS and a nondiagnostic initial ECG. Similarly, ACS caused by isolated involvement of an acute marginal branch of the right coronary artery is often not apparent on the standard 12-lead ECG but may be suspected from leads V_3R and V_4R.[12] Therefore it is useful to obtain these extra leads in patients suspected of having ACS but with normal findings on a 12-lead ECG.

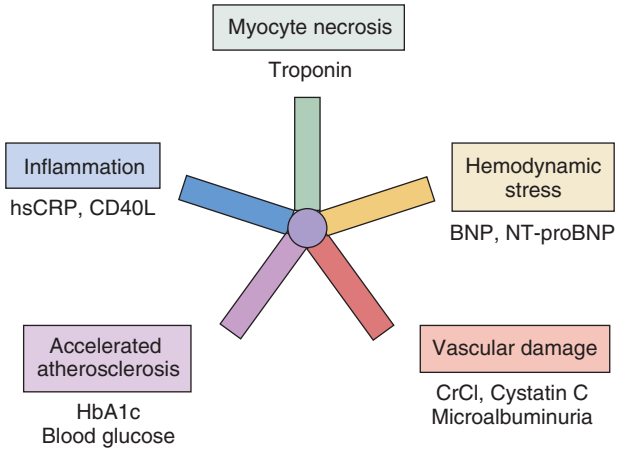
Continuous monitoring of the ECG in the days following NSTE-ACS can identify patients at higher risk for recurrent events. ST-segment depressions noted on such monitoring within the first week after NSTE-ACS are associated with an increased risk for reinfarction and death.[13]

Laboratory

Biomarkers reflecting the pathogenesis of NSTE-ACS aid in diagnosis and prognosis. They include markers of myocyte necrosis, hemodynamic perturbation, vascular damage, accelerated atherosclerosis, and inflammation (**Fig. 53-4**). During the past decade, cardiac-specific troponins (cTnI and cTnT) have become the biomarkers of choice to identify myocardial necrosis and hence distinguish NSTEMI from UA. Several pathobiologic mechanisms can lead to the release of detectable levels of cTn in blood (**Table 53-1**). Because of differences among assays, there is consensus that the diagnosis of acute MI requires an elevation in cTnI or cTnT above the 99th percentile of the normal range for the specific assay used,[14] a typical temporal rise and decline when serial samples are tested, and a clinical picture consistent with ACS.

Although elevated cTn usually reflects myocardial necrosis, it does not always reflect MI. Abnormal elevations have been observed with a number of conditions, including heart failure, pulmonary embolism, myocarditis, pericarditis, transplant rejection, chemotherapy, and direct or indirect cardiac trauma. Furthermore, cTnI may be elevated chronically at a low-grade level in patients with severe CKD (stages IV and V), and all cTn is cleared more slowly in patients with impaired renal function. Therefore interpretation of the clinical significance of elevated cTn in such patients requires care. In fact, an estimated 60% to 70% of individuals with chest discomfort seen in an emergency department will have measurable cTn concentrations,[15] but only a minority of them are experiencing acute MI.

Patients with clinical findings suggestive of NSTE-ACS should have serial measurements of cTn beginning at initial evaluation. Newer high-sensitivity assays available in Europe (but not in the United States as of 2012) can exclude myocardial necrosis if two values measured 3 hours apart are both normal.[16] However, the specificity of high-sensitivity cTn assays in the diagnosis of NSTE-ACS may be as



Biomarker	Independent predictor of risk	Useful as a component in a multimarker strategy	Therapeutic implication
Troponin	+++	++	+++
BNP	+++	++	0
Renal dysfunction	++	+	+
Glucose metabolism*	+	0	+
CRP	++	++	++

FIGURE 53-4 Multimarker approach for risk stratification in ACSs. *Glucose metabolism = hyperglycemia or elevated HbA1C. BNP = brain natriuretic peptide; CD40L = CD40 ligand; CrCl = creatine clearance; CRP = C-reactive protein; HbA1c = glycated hemoglobin; hsCRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal brain natriuretic peptide. *(Modified from Morrow DA, Braunwald E: Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. Circulation 108:250, 2003.)*

TABLE 53-1 Mechanisms of Troponin Release

TYPE	EXAMPLES/EXPLANATION
Myocyte* necrosis	Ischemia, infarction, inflammation, infiltration, trauma, toxic/metabolic (e.g., sepsis)
Apoptosis	Programmed cell death because of activation of caspases
Normal myocyte turnover	Natural low-grade annual turnover of myocytes (unclear whether this can be detected in the systemic circulation with current assays)
Cellular release of proteolytic troponin degradation products	Creation of small fragments that pass through the intact myocyte membrane without cell death
Increased cellular wall permeability	Reversible injury to myocyte membranes resulting in altered permeability (e.g., secondary to stretch, ischemia)
Formation and release of membranous blebs	Active secretion of vesicles or membrane expression with shedding (e.g., secondary to hypoxia)

*Diseased skeletal muscle may also cause increases in circulating cTnT (but not in cTnI).
From White HD: Pathobiology of troponin elevations: Do elevations occur with myocardial ischemia as well as necrosis? J Am Coll Cardiol 57:2406, 2011.

low as 60%, even in patients with established CHD.[17] The fourth-generation cTn assays currently used in the United States are less sensitive than the so-called high-sensitivity assays, and two negative cTn assays at least 6 to 9 hours apart are needed to exclude MI. The change in cTn between measurements appears to be more important than the actual concentration and can help distinguish MI from other processes that cause elevated cTn.[18] In addition, normal early cTn levels are useful in the identification of patients at very low risk for cardiovascular events over the next 6 months[19]; they are useful in long-term prognostication as well (**Fig. 53-5**).

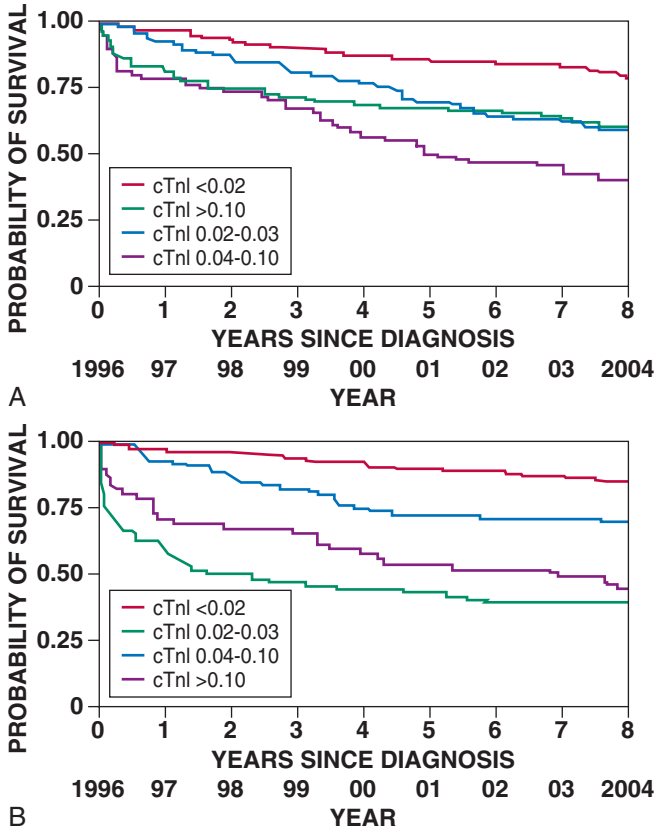


FIGURE 53-5 Survival of patients with MI according to baseline troponin. **A,** Mortality. **B,** MI and congestive heart failure. Individuals with a possible MI and low levels of cTnI (0.02 to 0.04 ng/mL), which are below the 99th percentile for this assay, had more subsequent events than did those with undetectable values. *(From Kavsak PA, Newman AM, Lustig V, et al: Long-term health outcomes associated with detectable troponin I concentrations. Clin Chem 53:220, 2007.)*

As already noted, an important consequence of the use of increasingly sensitive cTn assays is that the fraction of NSTE-ACS patients with UA has decreased in favor of NSTE-MI. This reclassification is important because even minor elevations in cTn are associated with poorer outcomes than in patients without evidence of myonecrosis. Reclassification from UA to NSTEMI can lead to more aggressive treatment of patients with a low-level, "positive" cTn assay.[20]

Other biomarkers also increase in the days to weeks following NSTE-ACS. Natriuretic peptides (i.e., brain natriuretic peptide [BNP] and N-terminal pro-BNP) rise in proportion to the degree of ventricular distention and correlate with the risk for adverse events.[21,22] In patients with NSTE-ACS, a baseline BNP measured on average 40 hours after the onset of symptoms correlated strongly with risk for death, heart failure, and MI through 10 months in a graded fashion.[21] Baseline natriuretic peptide levels also help identify patients more likely to benefit from more aggressive treatments, including intensive anti-ischemic regimens,[22] aggressive statin therapy,[23] and early coronary revascularization.[24]

C-reactive protein (CRP) is a marker of inflammation that is elevated following ACS, and persistently elevated levels after discharge are associated with increased long-term cardiovascular risk. Elevated levels of fasting blood glucose and glycosylated hemoglobin indicate the presence of diabetes mellitus or metabolic syndrome and portend accelerated atherosclerosis and an increased risk for cardiovascular events in both the short and long term.[25] Renal dysfunction, as reflected by elevated levels of cystatin C and creatinine, is associated with an increase in cardiovascular events, including cardiovascular mortality, in patients with NSTE-ACS.

Several novel biomarkers can help improve prognostication in patients with NSTE-ACS (**Table 53-2**). These biomarkers tend to fall

TABLE 53-2 Emerging Biomarkers in Acute Coronary Syndromes

MARKER NAME	DESCRIPTION	REFERENCE
Markers That Predict Death and/or Ischemic Events		
Growth differentiation factor-15	Member of the transforming growth factor-beta cytokine superfamily that is released from cardiomyocytes after ischemia and reperfusion injury	26
Heart-type fatty acid–binding protein	Cytoplasmic protein involved in intracellular uptake and buffering of free fatty acids in the myocardium	27
Myeloperoxidase	A hemeprotein released during degranulation of neutrophils and some monocytes	28
Pregnancy-associated plasma protein A	Zinc-dependent matrix metalloproteinase abundantly expressed in eroded and ruptured plaque but only minimally expressed in stable plaque	29
Placental growth factor	Member of the vascular endothelial growth factor family that is strongly upregulated in atherosclerotic lesions and acts as a primary inflammatory instigator of atherosclerotic plaque instability	30
Secretory phospholipase A_2	Hydrolyzes phospholipids to generate lysophospholipids and fatty acids, thereby enhancing susceptibility of the vessel to atherogenesis	31
Interleukin-6	Stimulator of hepatic synthesis of C-reactive protein	32
Chemokine ligand-5 and ligand-18	Mediators of monocyte recruitment induced by ischemia	33
Markers That Predict Heart Failure		
Midregional proadrenomedullin	Peptide fragment of the vasodilatory peptide adrenomedullin	34
Neopterin	Marker of monocyte activation	35
Osteoprotegerin	Modulator of immune function and inflammation	36

into two general categories: (1) markers that predict death and/or ischemic events[26-33] and (2) markers that predict heart failure.[34-36]

Multimarker approaches involving biomarkers that are independent predictors of outcome are increasingly being used.[37] One such approach uses three common biomarkers (cTn, CRP, and BNP), with an increasing number of abnormal markers correlating with a stepwise higher risk for subsequent ischemic complications.[38]

Measurement of serum lipids, including low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol and triglyceride, is useful in identifying important, treatable risk factors for coronary atherothrombosis (**see Chapter 45**). The first available sample should be used to guide therapy. Evaluation for other secondary causes of NSTE-ACS[39] may also be appropriate in selected patients (e.g., determining the presence of hypoxemia, anemia, and disturbed thyroid function) because such "secondary" NSTE-ACS can often be treated and recurrences prevented.

Noninvasive Testing

Goals of noninvasive testing in patients with suspected NSTE-ACS include (1) determining the presence or absence of coronary artery disease (CAD); (2) establishing CAD as the cause of the elevated cTn in patients with other possible explanations; (3) evaluating the extent of residual ischemia after medical therapy has been initiated, thus guiding further therapy; (4) localizing the ischemia before a planned percutaneous coronary intervention (PCI) in patients with multivessel disease; and (5) assessment of left ventricular function.

The safety of early stress testing in patients with NSTE-ACS has been debated, but pharmacologic or symptom-limited stress testing appears to be safe after a period of at least 24 hours of stabilization without symptoms of active ischemia[40]; contraindications include active ischemia or other signs of hemodynamic or electrical instability.

The merits of various modalities of stress testing have been compared (**see Chapter 13**). Exercise stress myocardial perfusion imaging with sestamibi (**Chapter 16**) and stress echocardiography with dobutamine have slightly more sensitivity than electrocardiographic exercise stress testing does alone. A useful approach is to individualize the choice based on patient characteristics, local availability, and expertise in interpretation. For most patients, electrocardiographic exercise stress testing is recommended if the ECG at rest lacks ST-segment abnormalities. If ST abnormalities exist at rest or if the patient is unable to exercise or cannot achieve a significant workload during exercise, pharmacologic stress perfusion or echocardiographic imaging is recommended. Findings consistent with high risk (e.g., severe ischemia as reflected by ST-segment depression ≥0.2 mV, hypotension, ventricular tachyarrhythmia, new or worsening left ventricular dysfunction) are indications to proceed rapidly with coronary angiography with the intent of performing revascularization if the coronary anatomy is appropriate.

Echocardiography is useful in the assessment of left ventricular systolic and diastolic function and can also be used to identify left atrial dilation,[41] functional mitral regurgitation,[42] tricuspid annular plane systolic excursion,[43] diastolic dysfunction,[44] ventricular mechanical dyssynchrony,[45] and ultrasound lung comets[43] (extravascular lung fluid observed on thoracic ultrasound scanning)—each of which has been associated with an adverse prognosis in patients with NSTE-ACS.

Contrast-enhanced coronary CTA (CCTA) in patients with or suspected of having NSTE-ACS can help establish the diagnosis of epicardial CAD in patients with equivocal signs and symptoms and identify unstable plaque at high risk for rupture. Detailed analysis of plaque morphology has identified two characteristics—positive vessel remodeling and low-attenuation plaque of lipid-rich lesions (**Fig. 53-6**)—that were associated with plaque rupture and ACS in 1059 patients observed for clinical events for an average of 27 months after imaging.[46]

CCTA can be used to exclude ACS rapidly in hospital emergency departments in patients with suspected ACS. Three randomized trials[47-49] (**see Chapter 18**) examined the value of early CCTA in assessment of patients in the emergency department. Whether a CCTA approach to patients suspected of having ACS will be superior to judicious outpatient clinical follow-up of low-risk patients with normal cTn levels remains to be determined.

Cardiac magnetic resonance (CMR) using a rapid-scan protocol can provide precise measurements of ventricular function and volumes, evaluate ventricular wall edema, identify areas of infarction versus hibernating myocardium, establish the presence of myocardial perfusion, quantify wall motion and the ejection fraction, and identify myocardium at risk in patients with NSTE-ACS.[50] These detailed assessments can then help guide PCI, particularly when the culprit lesion is uncertain—such as in patients with multivessel disease or with borderline stenoses.

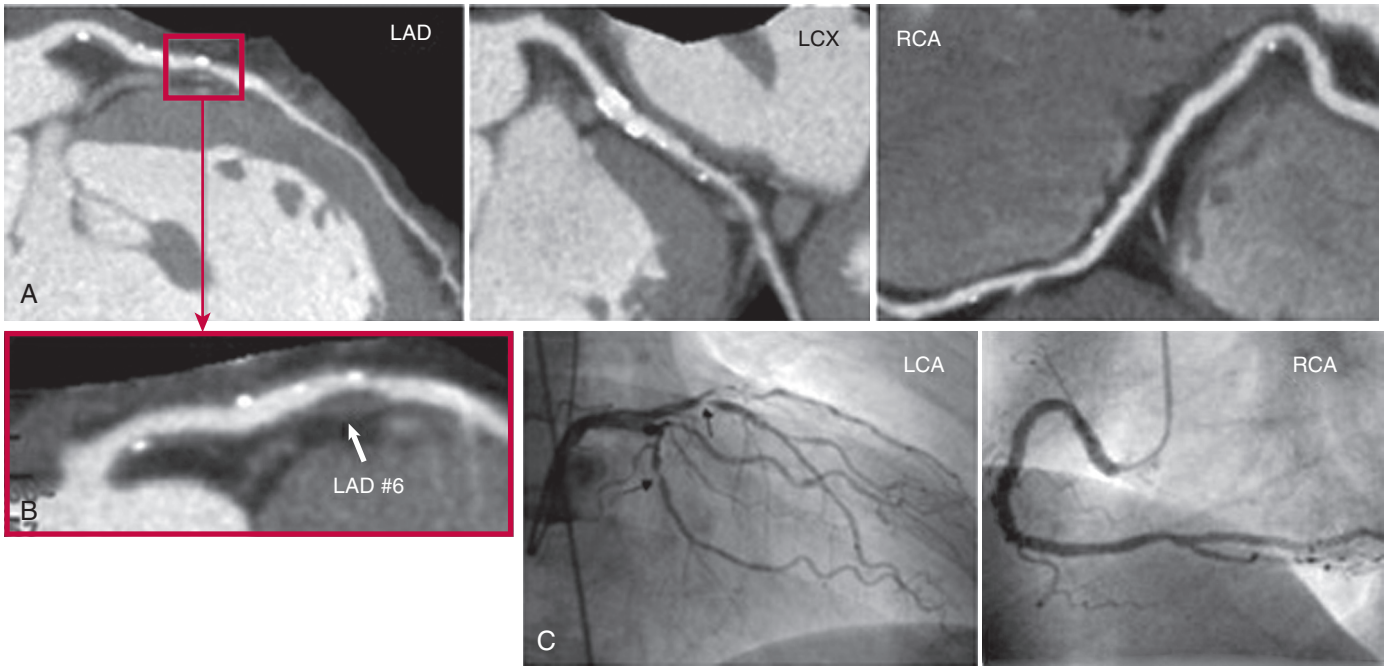


FIGURE 53-6 Angiographic characteristics of high-risk plaque. **A,** Curved multiplanar reformatted images of the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). **B,** Positive remodeling, low-attenuation plaque, and spotty calcification were detected in the LAD on CTA. **C,** An ACS involving the high-risk plaque seen earlier in the LAD *(arrow)* occurred 6 months after CTA. *(From Motoyama S, Sarai M, Harigaya H, et al: Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 54:49, 2009.)*

Invasive Imaging

Invasive coronary angiography has been the reference technique for imaging the coronary arterial tree for more than five decades. The culprit lesion in NSTE-ACS typically exhibits an eccentric stenosis with scalloped or overhanging edges and a narrow neck (**see Chapter 20**). These angiographic findings may represent disrupted atherosclerotic plaque and/or thrombus. Features suggesting thrombus include globular intraluminal masses with a rounded or polypoid shape. "Haziness" of a lesion suggests the presence of thrombus, but this finding is not specific.

Approximately 85% of patients with a clinical diagnosis of NSTE-ACS have significant coronary obstruction (i.e., >50% stenosis of the luminal diameter) in at least one major coronary artery. Most have obstructive disease involving multiple epicardial arteries (≈10% with left main coronary artery, ≈35% with three-vessel disease, ≈20% with two-vessel disease), whereas only approximately 20% have isolated single-vessel disease.[51] The remaining 15% have no evidence of significant coronary obstruction on angiography; this finding occurs more frequently in women and nonwhite individuals. In such patients, NSTE-ACS, if present, may be related to microvascular coronary obstruction, endothelial dysfunction, or coronary artery spasm and is generally associated with a more favorable prognosis. The absence of coronary obstruction on angiography, however, should prompt a search for causes of the symptoms other than coronary atherosclerosis.

Two invasive cross-sectional imaging techniques—IVUS and OCT—can provide additional detail regarding plaque morphology and are sometimes used clinically to visualize the deployment of intracoronary stents. A large necrotic core visualized by IVUS in culprit lesions undergoing intracoronary stenting can predict the no-reflow phenomenon after stenting.[52] OCT of plaque in patients with ACS has demonstrated its lipid content, calcification, and thrombus.[53] Plaque with a thin fibrous cap is associated with a high risk for rupture if the hemoglobin A1c content is 8.0% or higher.[53]

Even though several other invasive techniques—including angioscopy, intravascular magnetic resonance imaging (MRI), near-infrared spectroscopy, palpography, thermoscopy, and shear stress imaging—have been developed, large-scale prospective evaluation of these diagnostic techniques is needed to assess and compare their clinical usefulness and cost-effectiveness.

Risk Assessment

Residual Risk

The risk for recurrent ischemic events following an episode of ACS depends as much on the presence and stability of multifocal lesions as on the culprit lesion responsible for the initial event.[54] Thus because aggressive interventional approaches are increasingly being successful in the treatment of culprit lesions, aggressive medical management of the remaining plaque is required to prevent recurrent events.[54] The percentage of patients with more than one active plaque on angiography has been correlated with the level of high-sensitivity CRP (hsCRP).[55] These findings provide an important pathophysiologic link between inflammation, more diffuse active CAD, and recurrent cardiac events in the months to years following a clinical ACS event.

Natural History

Patients with UA, defined as NSTEMI-ACS without abnormal elevation of cTn, have lower short-term mortality (<2.0% at 30 days) than do those with NSTEMI or STEMI.[56] The early mortality risk with NSTEMI is related to the extent of myocardial damage and resulting hemodynamic compromise and is lower than in patients with STEMI, who usually have larger infarcts.[4,56] In contrast, long-term outcomes with respect to both mortality and nonfatal events are worse in patients with NSTE-ACS than in those with STEMI.[57] This finding probably results from the greater age, extent of CAD, previous MI, comorbid conditions (such as diabetes and impaired renal function), and likelihood of recurrence of ACS in patients with NSTE-ACS than in those with STEMI.

Combined Risk Assessment Scores

Several risk scores that integrate clinical variables and findings on the ECG and/or from serum cardiac markers have been developed for patients with NSTE-ACS.[58-60] The TIMI (Thrombolysis In Myocardial Ischemia) risk score (**Fig. 53-7**) identifies seven independent risk factors; their sum correlates directly with death or recurrent ischemic events.[58] This simple, rapid assessment of risk at initial evaluation identifies high-risk patients who can derive benefit from an early invasive strategy and more intensive antithrombotic therapy. This risk score also predicts the severity of angiographic findings, including

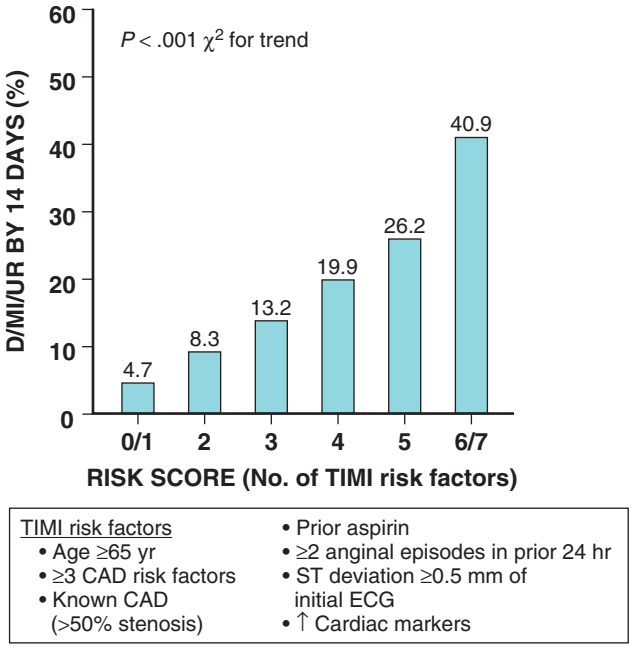


FIGURE 53-7 TIMI risk score for NSTE-ACS. The number of risk factors present is counted. *(From Antman EM, Cohen M, Bernink PJ, et al: The TIMI risk score for unstable angina/non–ST elevation MI: A method for prognostication and therapeutic decision making. JAMA 284:835, 2000.)*

the extent of CAD,[61] thrombus burden, and flow impairment.[62] An even simpler score, the TIMI risk index (age in decades × heart rate/systolic blood pressure), predicts mortality in patients with NSTEMI.[63]

The GRACE (Global Registry of Acute Coronary Events) risk score[60] has also identified risk factors that are independently associated with increased mortality. Although perhaps more accurate, it is more complex than the TIMI risk score and is not easily calculated by hand.

MANAGEMENT

Treatment of NSTE-ACS consists of two phases: acute management directed at the clinical symptoms and stabilization of the culprit lesion or lesions and longer-term therapy aimed at preventing progression of the underlying disease and future plaque rupture/erosion. In a prospective natural history study of patients with NSTE-ACS who successfully underwent PCI of the culprit lesion, 20% had a second ACS event over a mean of 3.4 years, with half of these events being ascribed to the original culprit lesion and the other half to a new lesion.[54]

General

Patients with new or worsening chest discomfort or an anginal equivalent symptom suggestive of ACS should be transported rapidly to the emergency department of a hospital by an ambulance, if possible, and evaluated immediately (**Fig. 53-8**).[64] The initial evaluation should include a directed history and physical examination and an ECG performed within 10 minutes of arrival.[65] Blood specimens for cTn assay should be obtained with expedited assessment via either a point-of-care device or laboratory measurement that can provide results within 60 minutes. Additional laboratory studies, such as a complete blood count, serum electrolytes, creatinine, and glucose, can help guide early management treatments and strategy.

Patients with elevated cTn or new ST-segment abnormalities or deemed to be at moderate or high risk based on a validated risk score should be admitted to a specialized cardiovascular or intensive care unit. Patients with UA but without elevated cTn and ischemic electrocardiographic changes should generally be admitted to a monitored bed, preferably in a cardiovascular step-down unit.[6] In these settings, continuous electrocardiographic monitoring with telemetry detects tachyarrhythmias, alterations in atrioventricular and intraventricular conduction, and changes in ST-segment deviation. Patients should be placed at bed rest, arterial O_2 saturation should be assessed continuously by oximetry, and supplemental O_2 is advisable in patients with reduced arterial O_2 saturation (<90%) and/or in those with heart failure and pulmonary rales. Ambulation, as tolerated, is permitted if the patient has been stable without recurrent chest discomfort or changes on the ECG for at least 12 to 24 hours. Patients with atypical symptoms and low risk or those who have symptoms more consistent with another noncardiac cause may be observed in the emergency department or a short-stay unit. A second cTn assay should be performed 3 to 6 hours after the first, and/or further assessment with noninvasive imaging or stress testing may be considered to permit rapid exclusion of ACS.

Anti-Ischemic Therapy

A primary goal in the management of NSTE-ACS is relief of ischemic symptoms and prevention of the severe short- and long-term sequelae, including recurrent MI, heart failure, and death.

Nitrates

Nitrates are endothelium-independent vasodilators that both increase myocardial blood flow by coronary vasodilation and reduce myocardial oxygen demand by lowering cardiac preload through venodilation and reduce cardiac afterload by inducing arterial dilation and thereby diminishing ventricular wall stress.

Sublingual (or buccal) nitroglycerin (0.3 to 0.6 mg up to three times at 5-minute intervals) should be administered to patients without hypotension, beginning even before hospital arrival whenever possible. If ischemic symptoms persist and/or the patient is hypertensive or in heart failure, intravenous nitroglycerin (5 to 10 μg/min, with the dose increased gradually to 200 μg/min as needed) should be initiated as long as systolic blood pressure remains higher than 100 mm Hg. Topical or long-acting oral nitrates can be used if the patient has been free of pain for 12 to 24 hours. Tolerance to the antiischemic effects of nitrates may develop within 12 to 24 hours and can be ameliorated by nitrate-free intervals. If symptoms do not allow nitrate-free intervals, increasing the dose may be effective. Discontinuation of high doses of nitrates, particularly when administered intravenously, should be performed in a gradual manner to prevent recurrent ischemia.

Contraindications to nitrate use are hypotension or the use of phosphodiesterase type 5 (PDE-5) inhibitors (e.g., sildenafil, tadalafil, vardenafil) within the previous 24 to 48 hours. PDE-5 inhibitors reduce the breakdown of cyclic guanosine monophosphate (cGMP) and thereby cause an exaggeration and prolongation of the vasodilator effects of nitrates, which can result in severe hypotension, myocardial ischemia, or even death. Nitrates should be used with caution in patients with severe aortic valve stenosis, hypertrophic cardiomyopathy with left ventricular outflow obstruction at rest, right ventricular infarction, or hemodynamically significant pulmonary embolism.

Beta-Adrenergic Receptor Blocking Agents

Much of the evidence supporting the use of beta-adrenergic receptor blockers (beta blockers) for NSTE-ACS has been extrapolated from clinical trials, predominantly in patients with STEMI, in which it was demonstrated that beta blockers reduce reinfarction, ventricular fibrillation, and death (**see Chapter 52**). A systematic review pooling data on patients with UA from trials performed more than 25 years ago (in the pre-cTn era) suggested that beta blockers reduce the risk for progression to MI.[66] Whether beta blockers have similar efficacy in the modern era of intensive pharmacologic management and early revascularization is not clear.

Oral beta-blocking agents in doses used for chronic stable angina (**see Chapter 54**) should be initiated within the first 24 hours,[6,66] with the following exceptions: (1) signs of decompensated heart failure; (2) evidence of a low–cardiac output state; (3) increased

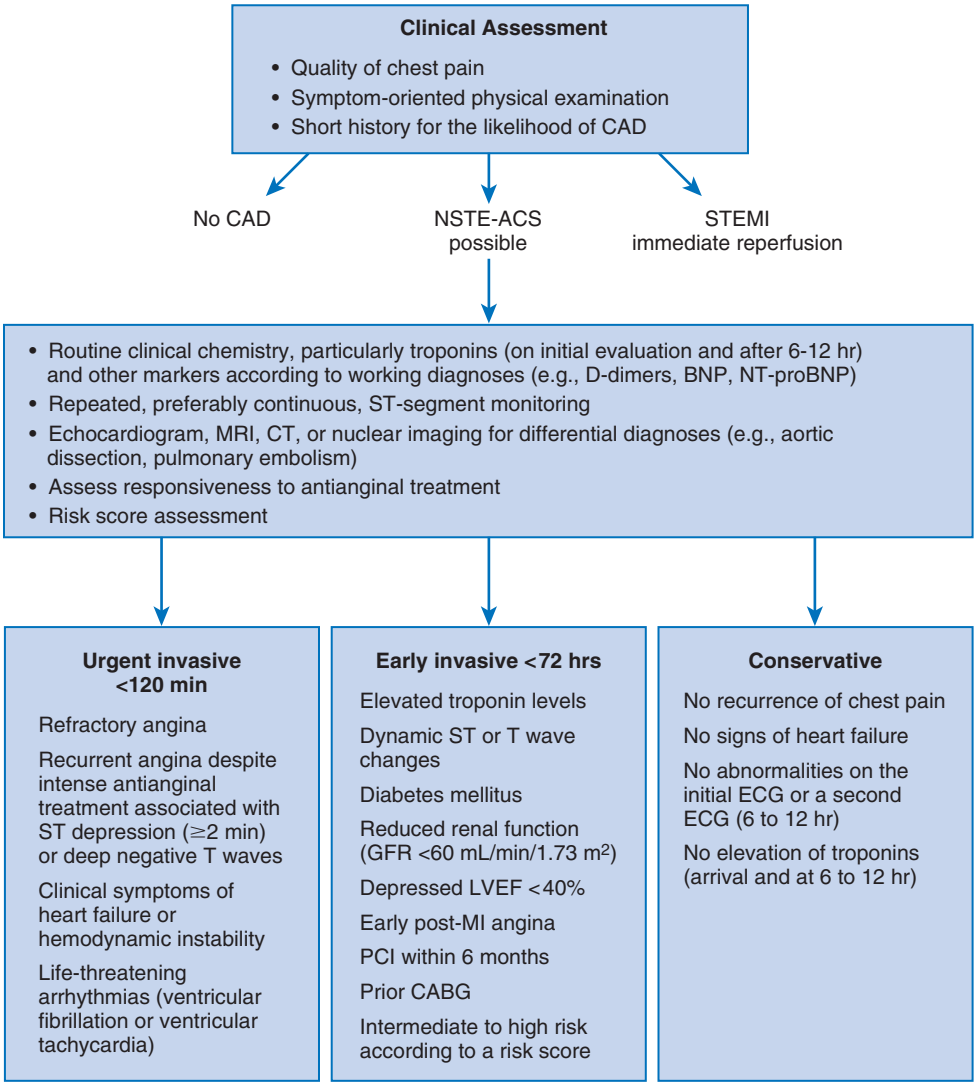


FIGURE 53-8 Decision-making algorithm for the management of NSTE-ACS. CABG = coronary artery bypass grafting; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction. *(From Bassand JP, Hamm CW: Diagnosis and treatment of non–ST-segment elevation acute coronary syndromes: European Society of Cardiology guidelines. Eur Heart J 32:369, 2011.)*

risk for cardiogenic shock; or (4) atrioventricular block, asthma, or reactive airway disease. Beta blockers can be administered to patients with heart failure once their condition has stabilized. If ischemia and/or chest pain persists despite intravenous nitrate therapy, intravenous beta blockers may be used cautiously, followed by oral administration. Intravenous beta blockers should be avoided in patients with acute MI and heart failure at initial evaluation.[67] The choice of beta blockers can be individualized by taking into account the drug's pharmacokinetics, physician familiarity, and cost, but beta blockers with intrinsic sympathomimetic activity, such as pindolol, should generally be avoided.

Morphine

In patients with persistent pain despite therapy with nitrates and beta blockers (see below), intravenous boluses of morphine sulfate at doses of 2 to 5 mg may be administered every 10 minutes for up to three times while carefully monitoring blood pressure, respiration, and mental status.[6] Morphine may act as both an analgesic and an anxiolytic, and its venodilator effects may be beneficial by reducing ventricular preload. The latter action is especially useful in patients with pulmonary congestion. However, morphine may also cause hypotension, and if it occurs, supine positioning and intravenous saline should be used to restore blood pressure; pressors are rarely needed. If respiratory depression develops, naloxone (0.4 to 2.0 mg) may be given. Contraindications include hypotension and allergy to morphine, for which meperidine can be substituted.

Calcium Channel Blockers

These agents have vasodilator effects and reduce arterial pressure. Some, such as verapamil and diltiazem, also slow the heart rate, reduce myocardial contractility, and thereby reduce O_2 requirements. Early studies suggested that diltiazem may reduce the incidence of recurrent MI.[68] Calcium channel blockers have been effective in reducing ischemia in patients with NSTE-ACS and persistent ischemia despite treatment with full-dose nitrates and beta blockers, as well as in patients with contraindications to beta blockers (see above) and in those with hypertension.[65,69] Such patients should receive nondihydropyridine calcium channel–blocking agents that lower the heart rate. The short-acting formulation of the dihydropyridine nifedipine, which accelerates the heart rate, can cause harm in patients with ACS when not coadministered with a beta blocker. No harm has been observed with long-term treatment with the long-acting dihydropyridines—amlodipine or felodipine—in patients with documented left ventricular dysfunction and CAD,[70] thus indicating that these agents may be safe in patients with NSTE-ACS and left ventricular dysfunction.[71]

Ranolazine

This novel antianginal agent exerts its effects without altering the heart rate or blood pressure. Its predominant mechanism of action is inhibition of the late sodium current in myocardial cells, thereby reducing some of the deleterious effects attributed to the overload of intracellular sodium and calcium during ischemia (**see Chapter 21**). Ranolazine reduces ischemic episodes and the need for nitroglycerin in patients with chronic stable angina, both as monotherapy and in combination with calcium channel blockers or beta blockers. Ranolazine underwent evaluation in a placebo-controlled trial of 6560 patients with NSTE-ACS who were monitored for an average of almost 1 year.[72] In the overall trial population, ranolazine did not reduce the primary composite outcome of cardiovascular death, MI, or recurrent ischemia but did decrease the incidence of recurrent ischemia. The primary outcome, however, was reduced significantly in the subgroups of patients with elevated natriuretic peptides (by 21%) and in those with previous stable angina (by 14%).[73]

Antiplatelet Therapy

Given the central role of platelet activation and aggregation in the pathogenesis of ACS, it comes as no surprise that antiplatelet therapy represents a key component of treatment in patients with NSTE-ACS (**Table 53-3**; also see Fig. 53-3).

Aspirin (Acetylsalicylic Acid)

Acetylsalicylic acid (ASA) acetylates platelet cyclooxygenase-1 (COX-1), which blocks the synthesis and release of TxA_2, a platelet activator,

TABLE 53-3 Recommendations for Oral Antiplatelet Agents[65]

RECOMMENDATIONS	CLASS	LEVEL
Aspirin should be given to all patients without contraindications at an initial loading dose of 150-300 mg and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy	I	A
A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over a period of 12 months unless there are contraindications such as excessive risk for bleeding	I	A
A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal hemorrhage or peptic ulcer and is appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, ≥65 years, concurrent use of anticoagulants or steroids)	I	A
Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically indicated	I	C
Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate to high risk for ischemic events (e.g., elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is commenced)	I	B
Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for $P2Y_{12}$ inhibitor–naïve patients (especially diabetic individuals) in whom the coronary anatomy is known and who are proceeding to PCI unless there is a high risk for life-threatening bleeding or other contraindications‡	I	B
Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel	I	A
A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option	I	B
A higher maintenance dose of clopidogrel, 150 mg daily, should be considered for the first 7 days in patients managed with PCI and without increased risk for bleeding	IIa	B
Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine but may be considered in selected cases	IIb	B
Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used	IIb	B
In patients pretreated with $P2Y_{12}$ inhibitors who need to undergo nonemergency major surgery (including CABG), postponing surgery for at least for 5 days after cessation of ticagrelor or clopidogrel and for 7 days for prasugrel should be considered if clinically feasible and if the patient is not at high risk for ischemic events	IIa	C
Starting (or restarting) ticagrelor or clopidogrel after CABG should be considered as soon as considered safe	IIa	B
The combination of aspirin with an NSAID (selective COX-2 inhibitors and nonselective NSAID) is not recommended	III	C

*Class of recommendation.
†Level of evidence.
‡Prasugrel is given a IIa recommendation as the overall indication, including clopidogrel-pretreated patients and/or unknown coronary anatomy. The class I recommendation here refers to the specifically defined subgroup.
CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; NSAID = nonsteroidal anti-inflammatory drug.
From Hamm CW, Bassand JP, Agewall S, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 32:2999, 2011.

thereby decreasing platelet aggregation and arterial thrombus formation. Because the inhibition of COX-1 by aspirin is irreversible, the antiplatelet effects last for the lifetime of the platelets—approximately 7 to 10 days. Several placebo-controlled trials have demonstrated the benefit of aspirin in patients with NSTE-ACS.[74] In addition to reducing adverse clinical events early in the course of treatment, aspirin also reduces the frequency of ischemic events in secondary prevention. It is a cornerstone of antiplatelet therapy in patients with all forms of ACS.[75]

Even though doses of ASA in randomized trials have ranged from 50 to 1300 mg/day, there does not appear to be a dose-response effect on efficacy, but gastrointestinal bleeding is increased at higher doses.[74] The CURRENT OASIS-7 (Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Symptoms)[76] trial randomly assigned 25,086 patients with ACS to receive high-dose (300 to 325 mg/day) or low-dose (75 to 100 mg/day) ASA for 30 days (and to high-dose versus regular-dose clopidogrel; see below). No difference in the risk for cardiovascular death, MI, or stroke was observed between the two doses, but gastrointestinal bleeding increased with the higher dose. Guidelines recommend that in patients with NSTE-ACS in whom continual ASA therapy has not been prescribed, the initial loading dose should be 162 to 325 mg, followed by a maintenance dose of 75 to 100 mg daily.[6] Data from PLATO (Study of Platelet Inhibition and Patient Outcomes), a large trial of ticagrelor (**see Chapter 82**), an oral antiplatelet agent that inhibits the $P2Y_{12}$ receptor, provides another reason to favor low-dose ASA.[77]

So-called ASA resistance may occur during chronic therapy,[78] with 2% to 8% of patients exhibiting a limited antiplatelet effect (i.e., minimal change in inhibition of platelet aggregation). These patients tend to have a greater risk for recurrent cardiac events.[79] Causes of ASA resistance are varied and include poor compliance (pseudoresistance), reduced absorption, interaction with ibuprofen, overexpression of COX-2 mRNA, and use of enteric-coated dosage forms. Rarely, a genetic or other intrinsic reason for minimal response to ASA is present. There is no evidence, however, that routine monitoring of antiplatelet effects with adjustment of the dose is a clinically effective strategy.

Contraindications to ASA include documented allergy (e.g., ASA-induced asthma), nasal polyps, active bleeding, or a known platelet disorder. Dyspepsia or other gastrointestinal symptoms with long-term ASA therapy (i.e., ASA intolerance) does not usually preclude therapy in the short term. In patients who have an allergy or who cannot tolerate ASA, desensitization or substituting clopidogrel, prasugrel, or ticagrelor is recommended.[75]

$P2Y_{12}$ (Adenosine Diphosphate) Inhibitors

Management of ACS now routinely includes dual antiplatelet therapy (DAPT), which consists of ASA and a $P2Y_{12}$ inhibitor (see Fig. 53-3). The latter falls into two groups: thienopyridines (ticlopidine,

clopidogrel, and prasugrel) and a cyclopentyl-triazolopyrimidine (ticagrelor). Thienopyridines act by irreversibly blocking binding of ADP to the platelet surface $P2Y_{12}$ receptor, thereby interfering with both platelet activation and aggregation by ADP. They are prodrugs that require oxidation by the hepatic cytochrome P-450 (CYP) system to form active metabolites.[80] Thienopyridines also reduce fibrinogen, blood viscosity, and erythrocyte deformability and aggregability through mechanisms that appear to be independent of ADP. In contrast, ticagrelor acts directly as a reversible blocker of the $P2Y_{12}$ receptor. Drugs that inhibit the CYP system do not affect ticagrelor.

Clopidogrel

This drug largely avoids the hematologic complications (neutropenia and, rarely, thrombotic thrombocytopenic purpura) associated with ticlopidine, the first widely used thienopyridine. When clopidogrel is absorbed, approximately 85% is hydrolyzed by circulating esterase and thus rendered inactive. The remaining clopidogrel must be oxidized by the hepatic CYP system to generate the active metabolites that inhibit the $P2Y_{12}$ receptor.

The addition of clopidogrel to ASA was studied in the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial of 12,562 patients with NSTE-ACS in which patients were treated with ASA, unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH), and other standard therapies and were randomly assigned to receive a 300-mg loading dose of clopidogrel followed by 75 mg daily or placebo.[81] The addition of clopidogrel to ASA reduced cardiovascular death, MI, or stroke by 20% in both low- and high-risk patients with NSTE-ACS, regardless of whether they were managed with medical therapy, PCI, or coronary artery bypass grafting (CABG) (**Fig. 53-9**). Benefit was seen as early as 24 hours, with Kaplan-Meier curves beginning to diverge after just 2 hours.[82] Moreover, the benefit continued throughout the trial's 1-year treatment period. Benefit of treatment before PCI was also observed, with a 31% reduction in cardiac events at 30 days and 1 year in patients with NSTE-ACS randomly assigned to DAPT versus ASA alone.[83]

These and similar findings in other trials led to a class IA recommendation in the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for clopidogrel treatment before PCI.[84] In patients undergoing CABG, those who had received clopidogrel within 5 days of surgery had an increased risk for major bleeding and the need for reoperation, which led to the recommendation that use of clopidogrel be discontinued at least 5 days before surgery, if possible.[6]

In NSTE-ACS, the initial loading dose of 300 to 600 mg clopidogrel is followed by a maintenance dose of 75 mg daily. Use of a 600-mg loading dose achieves a steady-state level of platelet inhibition after just 2 hours, more rapidly than the 300 mg dose. In the CURRENT OASIS 7 trial, high-dose clopidogrel (600-mg loading dose, 150-mg maintenance dose for 7 days, then 75 mg thereafter) did not reduce the composite of cardiovascular death, MI, or stroke in patients with NSTE-ACS, although it increased major bleeding and the need for red cell transfusions.[76] However, an analysis of the subgroup of patients in CURRENT OASIS-7 who underwent PCI[85] and a meta-analysis of more than 25,000 patients undergoing PCI[86] both demonstrated that a 600-mg loading dose of clopidogrel reduces cardiovascular events following PCI when compared with 300 mg. Thus 600 mg clopidogrel is the preferred loading dose for patients with NSTE-ACS undergoing PCI.[75,84]

Two strategies for initiating clopidogrel therapy in patients with NSTE-ACS have evolved: (1) starting clopidogrel at the time of arrival or hospital admission or (2) delaying treatment with clopidogrel until after coronary angiography and then administering the drug on the catheterization table if PCI is performed. The early treatment strategy is preferred because it affords the benefits of reducing early ischemic events, albeit at the cost of an increase in bleeding in the minority of patients who undergo CABG instead of or immediately after PCI.[87]

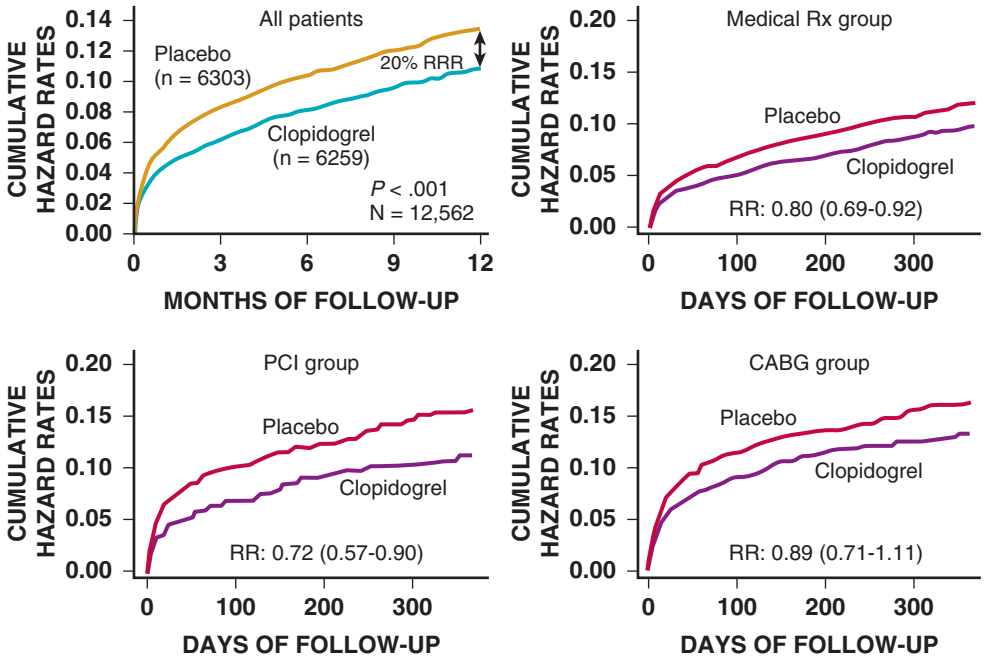


FIGURE 53-9 Clopidogrel for NSTE-ACS. The benefit of clopidogrel in reducing cardiovascular death, MI, or stroke in patients with NSTE-ACS in the CURE trial and in patients managed medically or with PCI or CABG is shown. RR = relative risk; Rx = drug. *(From Yusuf S, Zhao F, Mehta SR, et al: Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 345:494, 2001; and Fox KA, Mehta SR, Peters R, et al: Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non–ST-elevation acute coronary syndrome: The Clopidogrel in Unstable angina to prevent Recurrent ischemic Events [CURE] trial. Circulation 110:1202, 2004.)*

As with ASA, hyporesponders to clopidogrel have been identified[88] and have higher rates of recurrent cardiac events, including stent thrombosis, MI, and death.[89] The incidence of patients not achieving the expected pharmacologic response to clopidogrel varies from 5% to 30%, depending on the population and the definition used to assess response.[89] Hyporesponsiveness to clopidogrel is more common in patients with diabetes, as well as in those with obesity, of advanced age, and with a genetic polymorphism of the CYP system.[90] Patients with a minimal antiplatelet response to clopidogrel have lower concentrations of the active metabolite, thus indicating failure of this necessary conversion.

Several polymorphisms of the gene encoding for the CYP2C19 enzyme have been associated with reduced production of the active metabolite of clopidogrel (**see also Chapters 7, 52, and 82**).[69] These polymorphisms (especially the reduced-function *C2 allele) occur in approximately a third of white individuals and up to half of Asians and have been associated with increased adverse clinical outcomes in patients treated with clopidogrel.[91] In other studies, reduced-function alleles have been associated with increased stent thrombosis.[92] Testing for these polymorphisms in patients who are candidates for thienopyridine treatment can identify those who are likely to be unresponsive or hyporesponsive to the standard dose of clopidogrel and are candidates for alternative antiplatelet regimens (**Fig. 53-10**). Three randomized trials that evaluated more aggressive antiplatelet regimens in patients with high platelet reactivity after standard doses of aspirin and clopidogrel, however, did not show a significant reduction in clinical cardiovascular events with higher doses of antiplatelet drugs versus standard doses.[93-95] Data from a study of

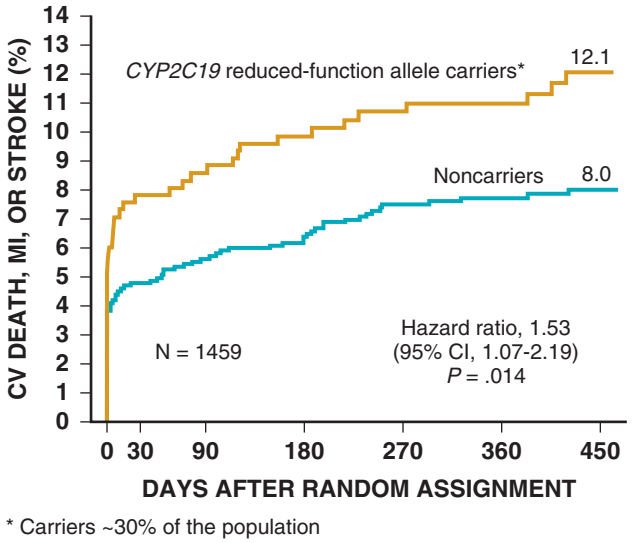


FIGURE 53-10 CYP2C19 and clinical outcomes. The association between status as a carrier of a CYP2C19 reduced-function allele and the primary efficacy outcome or stent thrombosis is shown in subjects receiving clopidogrel in the TRITON–TIMI 38 trial. Among 1459 subjects who were treated with clopidogrel and could be classified as CYP2C19 carriers or noncarriers, the rate of the primary efficacy outcome (a composite of death from cardiovascular [CV] causes, MI, or stroke) was significantly higher in carriers than in noncarriers. *(From Mega JL, Close SL, Wiviott SD, et al: Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 360:354, 2009.)*

patients with UA undergoing PCI showed that a daily maintenance dose of 225 mg or more of clopidogrel (at least three times the standard dose) is necessary in heterozygote carriers of the CYP2C19*2 allele to achieve the same level of platelet inhibition as that in noncarriers who receive 75 mg daily.[96] Thus the reason that these three trials failed to show clinical benefit with more intensive antiplatelet regimens in patients with high platelet reactivity may be due in part to insufficiently high doses of antiplatelet therapy.

Proton pump inhibitors (PPIs) modestly reduce the antiplatelet effect of clopidogrel when assessed by platelet function assays[97] because of competition for metabolism by the CYP3A4 enzyme. Observational studies have raised concern that this effect may lead to ischemic complications in patients receiving such an inhibitor, especially omeprazole, as opposed to clopidogrel without a PPI. However, a randomized, double-blind trial[98] and an analysis of ticagrelor (which is not metabolized via the CYP system) versus clopidogrel[99] indicated that a clinically significant interaction between clopidogrel and PPIs is unlikely.

Prasugrel

This thienopyridine is a prodrug like clopidogrel, and its active metabolite is an irreversible inhibitor of the platelet $P2Y_{12}$ receptor and thereby an inhibitor of platelet aggregation. However, unlike clopidogrel, prasugrel is oxidized rapidly in one step to its active metabolite and becomes active within 30 minutes of ingestion. Although the active metabolites of clopidogrel and prasugrel exert equal antiplatelet effects when studied in vitro, generation of the prasugrel metabolite is approximately 10 times as great as generation of the clopidogrel metabolite, which results in roughly 10 times greater potency.

TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction)[100] randomly assigned 13,608 patients with ACS (10,074 with NSTE-ACS) in whom PCI was planned to receive either prasugrel (60-mg loading dose, 10-mg daily maintenance dose) or what was then the Food and Drug Administration (FDA)-approved dose of clopidogrel (300-mg loading dose, 75-mg daily maintenance dose)—which had been shown in the CURE trial to be beneficial in NSTE-ACS patients who underwent PCI. All patients also received ASA.[83] The primary efficacy endpoint (cardiovascular death, MI, and stroke) was reduced significantly by 19% with prasugrel (**Fig. 53-11A**). The benefit was particularly striking (30%) in patients with diabetes.[101] In the 12,844 patients who received coronary stents at the time of PCI, prasugrel reduced the incidence of stent thromboses by half in comparison to clopidogrel. This relative reduction in stent thrombosis was similar in bare-metal and drug-eluting stents.[102]

These findings of the superiority of prasugrel over clopidogrel agrees with the aforementioned concept that the limited efficacy of clopidogrel versus prasugrel is related to the slower and less effective generation of the active metabolite of clopidogrel.[103] Indeed, in a crossover study of patients undergoing PCI for stable angina, Wiviott and coauthors reported that a 60-mg loading dose of prasugrel resulted in greater platelet inhibition than did a 600-mg loading dose of clopidogrel.[104] The same was observed during maintenance therapy, for which the comparison was made between 10 mg prasugrel and 150 mg clopidogrel daily.

Not unexpectedly, the greater platelet inhibitory effect of prasugrel was associated with increased bleeding. In TRITON–TIMI 38, there was a 0.6% absolute (32% relative) higher incidence of major (including fatal) bleeding. The risk for bleeding was especially high in elderly adults (≥75 years of age), in whom the use of prasugrel should be limited to those at high risk and in those with reduced body weight (<60 kg, 132 lb). Avoidance of treating such patients with prasugrel unless they are at high risk for thrombosis is advisable, and if prasugrel is used, they should be treated with a 5-mg instead of a 10-mg maintenance dose. Patients with a history of stroke or transient ischemic attack (TIA) have a prohibitive incidence of intracranial hemorrhage. Therefore prasugrel is indicated in patients with NSTE-ACS immediately before PCI but is contraindicated in those with a history of stroke or TIA.[100] In patients who were younger than 75 years, weighed at least 60 kg, and had no previous history of stroke or TIA (i.e., the "core" group of patients for whom the FDA approved use of the drug), prasugrel was associated with a robust 26% reduction in the primary endpoint. Use of prasugrel should be discontinued at least 7 days before surgery is performed, whenever possible.[75] DAPT with ASA and a $P2Y_{12}$ receptor inhibitor should be continued for 1 year following PCI.

Prasugrel (10 mg daily) was compared with clopidogrel (75 mg daily) in 7243 patients younger than 75 years who were being managed medically following NSTE-ACS in the TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial.[105] No difference occurred in the primary composite endpoint of cardiovascular death, MI, or stroke, nor in severe bleeding.

Ticagrelor

In contrast to the thienopyridines, whose active metabolites are irreversible platelet inhibitors, ticagrelor is a reversible blocker of the $P2Y_{12}$ platelet receptor that acts directly on the platelet and has a half-life of approximately 12 hours.[106] Although it has an active metabolite, the potency of the latter is similar to that of the parent drug; both are excreted into bile. Like prasugrel, ticagrelor can inhibit $P2Y_{12}$-mediated platelet aggregation almost completely.

A phase III pivotal trial (PLATO) compared ticagrelor (180-mg loading dose, followed by 90 mg twice daily) with clopidogrel (a 300- or 600-mg loading dose, followed by a 75-mg daily maintenance dose); both groups also received ASA. The PLATO trial enrolled 18,624 patients, 11,067 (59%) of whom had NSTE-ACS.[106] The primary endpoint, a composite of cardiovascular death, MI, and stroke, fell significantly by 16% (Fig. 53-11B). A significant 16% reduction in MI, a 21% reduction in cardiovascular death, and a 22% relative (1.4% absolute) reduction in total mortality also occurred. The rate of stent thrombosis was reduced significantly, from 1.9% to 1.3%. A broad array of subgroups showed greater clinical efficacy of ticagrelor than clopidogrel, including those who had previously received clopidogrel, in patients treated with a noninvasive strategy, as well as in patients with STEMI.

PLATO showed no benefit of ticagrelor in the subgroup of patients enrolled in the United States, in whom the dose of aspirin was higher on average than in other countries.[77] Whether this finding is related to chance, to more frequent use of ASA at 325 mg daily, or to some

other aspect of care in the United States remains uncertain. The FDA has recommended that low-dose (75 to 100 mg) ASA be used for maintenance with ticagrelor. Regardless of which $P2Y_{12}$ inhibitor is selected as the second antiplatelet agent, the dose of aspirin should be decreased to 75 to 100 mg after the initial loading dose, and patients should be monitored for bleeding while receiving DAPT for 1 year following NSTE-ACS.[75] PLATO showed a 0.7% absolute (19% relative) higher incidence of non–CABG-related major bleeding ($P = 0.03$) with ticagrelor than with clopidogrel. Episodes of moderate or minor dyspnea and ventricular pauses exceeding 5 seconds occurred more frequently in patients treated with ticagrelor than in those treated with clopidogrel.

The PLATO investigators calculated that if 1000 hospitalized patients with ACS were treated with ticagrelor and ASA and compared with a similar group treated with clopidogrel and ASA, there would be 14 fewer deaths, 11 fewer MIs, 6 to 8 fewer cases of stent thrombosis, and 7 more patients with non–CABG-related major bleeding, with 9 patients switching to a thienopyridine because of dyspnea. Because ticagrelor is a reversible agent, it can be started at the time of arrival at the emergency department and be continued for 1 year in medically managed patients or those undergoing PCI.[75] Although ticagrelor achieves a higher level of platelet inhibition than clopidogrel does, it has a shorter effective half-life and should be discontinued 5 days before CABG.[75] However, the shorter half-life mandates twice-daily administration of this drug and may therefore reduce compliance.

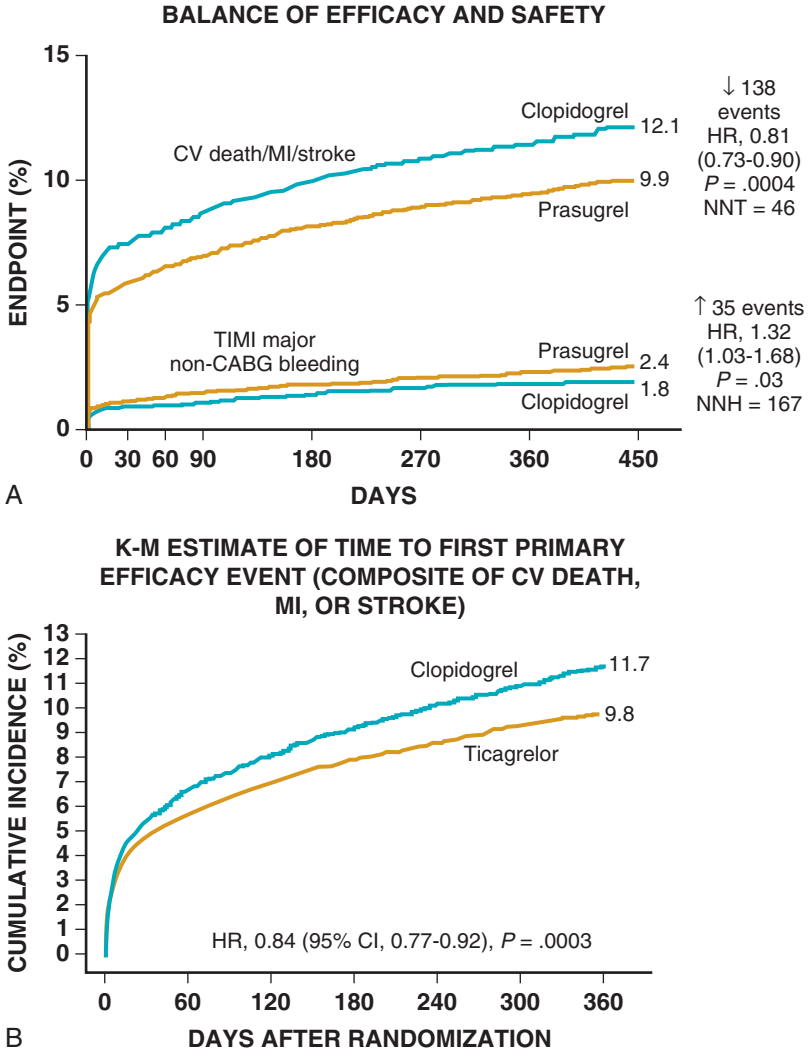


FIGURE 53-11 **A,** Comparison of the efficacy and safety of prasugrel versus clopidogrel in the TRITON–TIMI 38 trial in patients with ACSs undergoing PCI. HR = hazard ratio; NNT = number of patients needed to prevent one primary endpoint event; NNH = number of patients needed to be treated to cause harm (TIMI major bleeding). **B,** The primary endpoint of the PLATO trial—a composite of death from vascular causes, MI, or stroke—occurred significantly less often in the ticagrelor group than in the clopidogrel group. CV = cardiovascular; KM = Kaplan-Meier. (***A,*** *From Wiviott SD, Braunwald E, McCabe CH, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357:2001, 2007;* ***B,*** *from Wallentin L, Becker RC, Budaj A, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 361:1045, 2009.)*

Protease-Activated Receptor-1 Antagonists

The oral protease-activated receptor-1 (PAR-1) antagonist vorapaxar, an investigational drug that inhibits thrombin-mediated platelet activation, has been studied in patients with ACS. It did not reduce the primary efficacy endpoint significantly, but major bleeding was increased, including intracranial hemorrhage.[107] Thus vorapaxar does not appear to have a role early after ACS. In the TRA-2P–TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction) trial of 26,449 stable patients with a history of MI, ischemic stroke, or peripheral vascular disease, the addition of vorapaxar to standard therapies reduced ischemic events while increasing bleeding in comparison to placebo.[108] Patients 2 weeks to 1 year after MI who were enrolled in TRA-2P had a 20% reduction in cardiovascular death, MI, or stroke. The drug may thus play a role in secondary prevention in patients with NSTEMI.

Glycoprotein IIb/IIIa Inhibitors

These drugs block the final common pathway of platelet aggregation, fibrinogen-mediated cross-linkage of platelets, caused by a variety of stimuli (e.g., thrombin, ADP, collagen, serotonin) (see Fig. 53-3). Three agents in this class are available: abciximab, a monoclonal antibody approved only in patients undergoing PCI; eptifibatide; and tirofiban (the latter two are reversible small-molecule inhibitors). Each of these agents is administered as an intravenous bolus followed by continuous infusion. The activity of the small-molecule receptor blockers and the accompanying bleeding risk subside promptly after discontinuation of the infusion. Tirofiban and eptifibatide have short half-lives (≈2 hours), with restoration of platelet function in about 4 hours; thus they should be discontinued 2 to 4 hours before major surgery. Abciximab has prolonged action (≈12 hours) and cannot be reversed rapidly, so major surgery should be deferred until at least 24 hours after administration.

Several trials have shown benefit of GP IIb/IIIa inhibition in the management of patients with NSTE-ACS, with an overall significant 9% relative reduction in death or MI at 30 days in a large meta-analysis.[109] Tirofiban plus heparin and aspirin significantly reduced the rate of death, MI, or refractory ischemia at 7 days when compared with heparin plus ASA.[110] In a trial involving 10,948 patients, eptifibatide also significantly reduced the rate of death or MI at 30 days.[111] However, no benefit and higher early mortality were found with the use of abciximab in patients with NSTE-ACS in whom an early conservative strategy was planned.[112]

The benefit of GP IIb/IIIa inhibition appears to be greater when used in high-risk patients with NSTE-ACS, such as those with ST-segment changes and/or elevated troponin concentration or diabetes.[109,113] These subgroups have more thrombus at coronary angiography and thus have higher risk for microvascular embolization. The benefit of GP IIb/IIIa inhibition has been confirmed even in patients with a background of clopidogrel pretreatment.[113,114]

In a meta-analysis of placebo-controlled trials, rates of major hemorrhage were significantly higher in patients treated with GP IIb/IIIa inhibitors—occurring in 2.4% as opposed to 1.4% of those given placebo.[109] The rate of severe thrombocytopenia (<50,000/mm^3) was approximately 0.5% in patients treated with a GP IIb/IIIa

inhibitor and heparin versus 0.3% in those receiving heparin alone. Thrombocytopenia is associated with increased bleeding and recurrent thrombotic events, thus indicating a need to monitor the platelet count daily during the GP IIb/IIIa infusion.

Two large trials have examined the timing of initiation of GP IIb/IIIa inhibitors: routine early administration at initial evaluation versus delayed provisional use just before PCI.[115,116] No difference was seen in the primary efficacy outcome between these two strategies, although routine early administration of GP IIb/IIIa inhibitors was associated with an increased risk for bleeding. A meta-analysis of 12 clinical trials involving 46,374 patients with NSTE-ACS treated with a GP IIb/IIIa inhibitor at initial encounter and before angiography demonstrated a significant 11% reduction in death or MI at 30 days versus control patients (either no GP IIb/IIIa inhibitor or deferred use just before PCI), although the benefit of early routine use appeared to be modest when compared with a strategy of deferred use before PCI.[117] Furthermore, there was no reduction in mortality and a 23% relative increase in major bleeding with routine early use of GP IIb/IIIa inhibitors.

Based on the totality of the evidence, a strategy of routine administration of GP IIb/IIIa inhibitors to patients with NSTE-ACS who receive DAPT with ASA and a $P2Y_{12}$ inhibitor (i.e., triple antiplatelet therapy) is not recommended. However, selective use in patients at high risk for ischemic complications (such as patients with diabetes or angiographic evidence of thrombus) and at low risk for bleeding who are to undergo PCI appears to be more prudent. GP IIb/IIIa inhibitors are also useful in the management of thrombotic complications during PCI.

Anticoagulant Therapy

In addition to antiplatelet therapy, as described above, an anticoagulant should be administered to patients with NSTE-ACS as soon as possible. Several anticoagulants are available (**see Chapter 82**).

Heparin

UFH is a mixture of polysaccharide chains of different length that prevents coagulation by blocking thrombin (factor IIa) and factor Xa. It also binds to circulating plasma proteins, acute-phase reactants, and endothelial cells and thus has an unpredictable anticoagulant effect. Because of its short half-life, UFH must be administered as an intravenous infusion to ensure a stable level of anticoagulation in patients with ACS.

Despite these limitations, treatment with intravenous UFH has been an important component of therapy for patients with NSTE-ACS.[118] A meta-analysis showed a 33% reduction in death or MI with UFH plus aspirin versus aspirin alone.[119] Variability in the anticoagulant effects of UFH, which is quite common, is thought to result from the heterogeneity of UFH and from neutralization of heparin by circulating plasma factors and by proteins released by activated platelets.[120] Daily monitoring of the anticoagulant response via the activated partial thromboplastin time (APTT) is recommended, with titrations being made according to a standardized nomogram to achieve an APTT of 50 to 70 seconds or 1.5 to 2.5 times control.[65] Based on the data available, the ACC/AHA guidelines recommend a weight-adjusted dose of UFH (60-unit/kg bolus and 12-unit/kg/hr infusion), as well as frequent monitoring of the APTT (every 6 hours until the target range is reached and every 12 to 24 hours thereafter) and adjustment of the dose if necessary.[75] Adverse effects include bleeding, especially when the APTT is elevated. Immunogenic heparin-induced thrombocytopenia (HIT) is an infrequent but serious complication that can cause thrombosis and bleeding and may even be fatal.

Heparin Reversal

Protamine sulfate binds heparin to form a stable salt, thus quickly reversing the anticoagulant effect of UFH. Approximately 1 mg of protamine is required to neutralize 100 units of UFH. Because the half-life of UFH is approximately 1 to 1.5 hours, the dose of protamine necessary to reverse an infusion of UFH should be based on the total UFH dose administered in the previous 2 to 3 hours. After administration of protamine, the APTT can be used to assess the efficacy of reversal of the anticoagulant effect of UFH. A slow intravenous injection is recommended to avoid hypotension or bradycardia. Other common, but transient adverse reactions include flushing, feeling of warmth, and dyspnea. Protamine reverses approximately 60% of the anticoagulant effect of LMWH (see below) but does not completely neutralize its anti-Xa activity.

Low-Molecular-Weight Heparin

These forms of heparin are enriched with shorter polysaccharide chains, which results in a more predictable anticoagulant effect than that of UFH. LMWH has several potential advantages over UFH: (1) its greater anti–factor Xa activity (relative to factor IIa) inhibits thrombin generation more effectively; (2) LMWH induces greater release of tissue factor pathway inhibitor than UFH does, and it is not neutralized by platelet factor 4; (3) LMWH less frequently causes HIT[121]; (4) the high and consistent bioavailability of LMWH allows subcutaneous administration; (5) monitoring of the anticoagulation level is not necessary; and (6) LMWH binds less avidly to plasma proteins than UFH does and therefore has a more consistent anticoagulant effect.

Because renal dysfunction affects LMWH more than UFH, the dose of LMWH should be reduced in patients with a creatinine clearance lower than 30 mL/min. The standard dose of enoxaparin is 1 mg/kg subcutaneously every 12 hours, with dosing only once daily for patients with a creatinine clearance lower than 30 mL/min. Administration of enoxaparin for up to 8 days (or until hospital discharge) was found to be effective in patients with ACS, whereas extending therapy to 6 weeks did not further reduce ischemic events in patients with NSTE-ACS.[122] UFH should not be administered in the catheterization laboratory within 10 hours of treatment with enoxaparin, 1 mg/kg, unless factor Xa activity is known to be low because concomitant administration of UFH can result in supratherapeutic anti-Xa and anti-IIa levels and cause excess bleeding.[123] In the event of bleeding, the anticoagulant effect of LMWH can be reversed with protamine, but less effectively than reversal of UFH (see above).

In patients with NSTE-ACS treated with ASA, LMWH reduced the odds of death or MI by 66% when compared with placebo.[119] Although several LMWHs have been approved, the weight of evidence supports the choice of enoxaparin.[6,65] In a meta-analysis of 21,945 patients from six trials of patients with NSTE-ACS in which enoxaparin was compared with UFH, however, new or recurrent MI occurred less frequently with enoxaparin, whereas the rate of major bleeding was similar between the drugs.[124]

Direct Thrombin Inhibitors

These drugs have a potential advantage over indirect thrombin inhibitors such as UFH or LMWH in that they do not require antithrombin and can inhibit clot-bound thrombin. They do not interact with plasma proteins, they provide a very stable level of anticoagulation, and they do not cause thrombocytopenia—thus making them an excellent choice for anticoagulation in patients with a history of HIT.

Bivalirudin, the most widely used direct thrombin inhibitor in patients with ACS or undergoing PCI, binds reversibly to thrombin and has a half-life of approximately 25 minutes. In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial,[125] patients with NSTE-ACS managed with an early invasive strategy were randomly assigned in an open-label fashion to one of three treatments: (1) UFH or enoxaparin with or without a GP IIb/IIIa inhibitor, (2) bivalirudin with a GP IIb/IIIa inhibitor, and (3) bivalirudin alone. The key findings were that bivalirudin alone reduced bleeding in comparison to either strategy that included a GP IIb/IIIa inhibitor, there were no differences in major bleeding between anticoagulants (UFH or enoxaparin versus bivalirudin) in patients taking a GP IIb/IIIa inhibitor, and there were no differences in ischemic events between the three treatment arms.[125] Thus the use of bivalirudin monotherapy (with ASA and a $P2Y_{12}$ inhibitor but without a GP IIb/IIIa inhibitor) is now considered an acceptable alternative in patients with NSTE-ACS managed with an early invasive strategy and may be preferred in patients with increased risk for bleeding who are undergoing PCI.[6,65,75]

In patients with NSTE-ACS before angiography, the recommended dose of bivalirudin is a 0.1-mg/kg intravenous bolus followed by an infusion at 0.25 mg/kg/hr. If started during the procedure, a 0.75-mg/kg bolus dose of bivalirudin should be administered, followed by an infusion at 1.75 mg/kg/hr during PCI. It may be discontinued shortly after PCI to permit removal of arterial access sheaths. In patients with renal dysfunction, the infusion should be modified as follows: (1) if the creatinine clearance is lower than 30 mL/min and the patient is not being managed with hemodialysis, the infusion rate should be reduced to 1 mg/kg/hr, and (2) in patients undergoing hemodialysis, the infusion rate should be reduced to 0.25 mg/kg/hr.

Factor Xa Inhibitors

Fondaparinux

This synthetic pentasaccharide is an indirect Xa inhibitor and requires the presence of antithrombin for its action. The OASIS-5 trial compared daily subcutaneous fondaparinux (2.5 mg) with standard-dose enoxaparin in 20,078 patients with high-risk NSTE-ACS.[126] No difference was found in the primary ischemic composite through 9 days, although fondaparinux did reduce major bleeding by nearly half and mortality at 30 days tended to be lower with fondaparinux. In patients undergoing PCI, however, fondaparinux was associated with more than a threefold increased risk for catheter-related thrombi. Supplemental UFH at the time of catheterization (85 units/kg if no GP IIb/IIIa inhibitor was used; 60 units/kg with a concomitant GP IIb/IIIa inhibitor) appeared to minimize the risk for this problem with fondaparinux.[127] Thus fondaparinux is an alternative for patients with NSTE-ACS managed noninvasively and, in particular, for patients at higher risk for bleeding.[6,65]

Otamixaban

At infusions of 0.105 and 0.140 mg/kg/hr, the investigational direct factor Xa inhibitor otamixaban is associated with fewer ischemic complications and similar safety as UFH plus eptifibatide in patients with ACS.[128] A large phase III trial of otamixaban is under way.[129]

Oral Anticoagulation

Several trials have examined oral anticoagulation with warfarin following ACS because of the rationale that prolonged treatment might extend the benefit of early anticoagulation with a parenteral antithrombin agent. Although the combination of ASA plus warfarin was more effective than aspirin alone for long-term secondary prevention of MI, this combination is associated with increased serious bleeding.[130] In patients without a coronary stent but with another indication for warfarin, such as chronic atrial fibrillation or severe left ventricular dysfunction, who are at high risk for systemic embolization, the combination of ASA and warfarin may be useful for long-term antithrombotic management.

Triple therapy (i.e., the combination of aspirin, a $P2Y_{12}$ inhibitor, and warfarin) is sometimes required in patients with NSTE-ACS after stenting who have atrial fibrillation or another strong indication for warfarin. It may be associated with a high bleeding risk, especially with long-term administration,[131] but it has not been tested prospectively to date against DAPT in a large randomized trial. When such triple therapy is deemed essential, the combination of low-dose aspirin (75 to 81 mg daily), warfarin (titrated meticulously to an international normalized ratio [INR] of 2.0 to 2.5), and the use of clopidogrel for as short a time as necessary is recommended.[6] Use of bare-metal stents rather than drug-eluting stents may be preferable because they can reduce the duration of $P2Y_{12}$ therapy required. The 2010 European Society of Cardiology (ESC) guidelines for the management of patients with atrial fibrillation in whom NSTE-ACS has been treated with a stent recommend shortened courses of triple therapy (aspirin, clopidogrel, a vitamin K antagonist [VKA]), followed by long-term *single* antiplatelet therapy and a VKA.[132]

Two potent oral direct factor Xa inhibitors (rivaroxaban and apixaban) have been studied in phase III trials of patients with ACS. In the ATLAS ACS 2–TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction) trial, low-dose rivaroxaban (5 mg twice daily) and very low-dose rivaroxaban (2.5 mg twice daily)—which are 50% and 25%, respectively, of the approved dose of this drug in patients with atrial fibrillation—were compared with placebo as an add-on to standard DAPT therapy (ASA and clopidogrel in 92% of patients) in 15,527 patients with recent ACS.[133] Rivaroxaban (doses combined) reduced the primary composite of death, MI, or stroke significantly by 16% when compared with antiplatelet therapy without an anticoagulant. In addition, rivaroxaban substantially reduced overall mortality and stent thrombosis, although excessive bleeding, including higher rates of intracerebral hemorrhage, were observed. The 2.5-mg twice-daily dose of rivaroxaban had a more favorable profile in that it reduced cardiovascular mortality (**Fig. 53-12**) by 34% and total mortality by 32% and resulted in less bleeding than the 5 mg twice-daily dose of rivaroxaban.

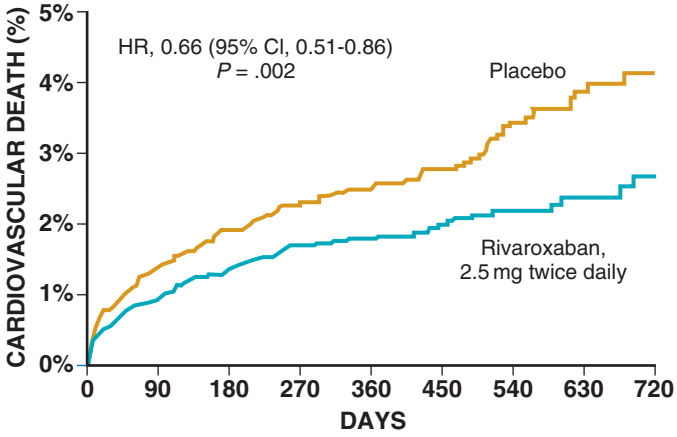


FIGURE 53-12 Rivaroxaban and cardiovascular mortality after ACS. The cumulative incidence of cardiovascular death is shown in patients after ACS who received aspirin and a thienopyridine and were randomly assigned to placebo (n = 5114) versus rivaroxaban, 2.5 mg twice daily (n = 5113). *(Modified from Mega JL, Braunwald E, Wiviott SD, et al: Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 366:9, 2012.)*

In the APPRAISE-2 (Apixaban for Prevention of Acute Ischemic Events 2) trial,[134] apixaban, 5 mg twice daily (a full dose of Xa inhibitor with properties similar to those of rivaroxaban), was compared was placebo in 7392 patients with recent ACS (60% had NSTE-ACS) who were being treated with aspirin and clopidogrel. The trial was stopped prematurely because of excess major bleeding with no apparent reduction in recurrent ischemic events in patients randomly assigned to apixaban. The difference in outcome between APPRAISE-2 and ATLAS-2–TIMI 51 might be related to the higher dose of the Xa inhibitor in APPRAISE-2; in contrast to ATLAS-2–TIMI 51, it included patients with a history of stroke.

Bleeding—Risk Assessment, Prevention, and Treatment

Severe bleeding is the most common nonischemic complication of antithrombotic therapy and is associated with poorer outcomes in patients with ACS,[135] but controversy has surrounded the independent contribution of bleeding to mortality.[136,137] Whether the increase in mortality and other adverse events observed in patients who have had serious bleeding is a result of the bleeding per se or the higher risk for adverse outcomes from the ACS in patients who are more likely to experience bleeding is unclear. Both mechanisms probably contribute.

Regardless, strong effort must be made to minimize bleeding. European guidelines[65] recommend assessment of bleeding risk (as well as risk for ischemia) in all patients with NSTE-ACS via an established risk score (**Table 53-4**).[138] Practical steps to reduce the risk for bleeding in patients with NSTE-ACS include the use of (1) weight-adjusted (instead of fixed) doses of anticoagulants; (2) modified dosing of antithrombotics in patients with renal dysfunction; (3) selection of

TABLE 53-4 CRUSADE Bleeding Risk Score for Estimating In-Hospital Risk for Major Bleeding

PREDICTOR	SCORE
Baseline Hematocrit (%)	
≤31	9
31-33.9	7
34-36.9	3
37-39.0	2
≥40	0
Creatine Clearance* (mL/min)	
≤15	39
>15-30	35
>30-60	28
>60-90	17
>90-120	7
>120	0
Heart Rate (beats/min)	
≤70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
≥121	11
Sex	
Male	0
Female	8

PREDICTOR	SCORE
Signs of Congestive Heart Failure at Initial Evaluation	
No	0
Yes	7
Previous Vascular Disease†	
No	0
Yes	6
Diabetes Mellitus	
No	0
Yes	6
Systolic Blood Pressure (mm Hg)	
<90	10
91-100	8
101-120	5
121-180	1
181-200	3
≥201	5

RISK FOR BLEEDING	
Total Score (Range, 1-100)	**Predicted Risk for Bleeding (%)**
≤20 (very low)	3.1
21-30 (low)	5.6
31-40 (moderate)	8.6
41-50 (high)	13.4
≥50 (very high)	22.6

*Creatinine clearance was estimated with the Cockcroft-Gault formula.
†Previous vascular disease was defined as a history of peripheral artery disease or previous stroke. To calculate the CRUSADE bleeding score, total the points associated with the above eight factors and use the bottom part of the table to predict the risk for bleeding.
‡In patients managed by an invasive strategy.
Modified from Giugliano RP, Braunwald E: The year in non–ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 54:1544, 2009; modified from Subherwal S, Bach RG, Chen AY, et al: Baseline risk of major bleeding in non–ST-segment-elevation myocardial infarction: The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) bleeding score. Circulation 119:1873, 2009.

anticoagulants with a lower-risk bleeding profile (e.g., fondaparinux in patients managed conservatively, bivalirudin with an early invasive strategy) in patients at higher bleeding risk; (4) low-dose aspirin (75 to 100 mg daily) after the initial loading dose[76]; (5) gastrointestinal protective agents in patients at high risk for gastrointestinal bleeding[98]; (6) minimization of concomitant therapies (such as nonsteroidal anti-inflammatory drugs) that increase the risk for gastrointestinal bleeding; (7) radial arterial access, smaller sheath sizes, and timely removal of sheaths for coronary angiography and PCI[139]; and (8) use of bare-metal (instead of drug-eluting) stents, which permits a shorter course of DAPT (1 month instead of 6 to 12 months).

Among the key recommendations included in the Working Group on Thrombosis of the ESC[140] are (1) interruption and/or neutralization of antithrombotic therapy in the case of major bleeding, unless adequate hemostasis is achieved by other specific measures; (2) withholding of transfusions in stable patients with a hemoglobin level higher than 8 g/dL if bleeding has stopped; and (3) continuation of antithrombotic therapy without interruption in the case of minor bleeding.

Invasive Versus Conservative Management

Two general approaches to the use of cardiac catheterization and revascularization can be taken in patients with NSTE-ACS: (1) an early invasive strategy involving routine early (within 48 hours of initial evaluation) cardiac catheterization, followed by PCI, CABG, or continuing medical therapy, depending on the coronary anatomy, and (2) a more conservative approach, with initial medical management and catheterization being reserved for patients with recurrent ischemia either at rest or on a noninvasive stress test, followed by revascularization if the anatomy is suitable.

A meta-analysis of seven recent trials confirmed an overall significant 25% reduction in mortality and a 17% reduction in nonfatal MI after 2 years of follow-up in patients managed with an early invasive strategy.[141] These findings favoring an early invasive strategy were also observed in key subgroups who traditionally are less likely to undergo early angiography, including older adults,[142,143] patients with CKD,[144] and women,[145] although one analysis in women did not show benefit.[146] The apparently conflicting results in women may be reconciled by considering the risk of the women who were included in the studies inasmuch as a sex-specific collaborative meta-analysis[147] demonstrated benefit of an invasive strategy in all men and in high-risk women but not in low-risk women.

Thus an early invasive strategy is recommended in patients with NSTE-ACS who have ST-segment changes and/or positive troponin on admission or in whom these high-risk features develop over the subsequent 24 hours. Other high-risk indicators, such as recurrent ischemia or evidence of congestive heart failure, are indications for an early invasive strategy.[6,65,75] An early invasive strategy is also advised in patients with NSTE-ACS previously treated with CABG[6] and in patients who have had NSTE-ACS within 6 months of a previous PCI and in whom restenosis may be the cause.[65] Indications for an initial

conservative strategy include patients with life-threatening comorbid conditions or in whom the risks outweigh the benefits, patients who do not wish to undergo an invasive procedure, and low-risk patients without recurrent symptoms.[65,75]

Timing of an Invasive Approach

A meta-analysis of four trials involving 4013 patients with NSTE-ACS compared an early invasive strategy (average time to angiography ranging from 1.2 to 14 hours) with a delayed invasive strategy (average time to angiography of 21 to 86 hours). Mortality and MI rates in the two strategies did not differ,[148] but the early invasive approach was associated with significant reductions in recurrent ischemia (41%) and duration of hospital stay (28%) and with favorable trends with respect to bleeding and the composite of cardiovascular death, MI, or stroke. This analysis lends support to an early invasive strategy, especially in high-risk patients such as those with continuing ischemia despite intensive medical therapy, as well as in patients with acute heart failure and ventricular tachyarrhythmias.

Percutaneous Coronary Intervention (See Chapter 55)

Angiographic success (TIMI epicardial grade 2 or 3 flow) can be achieved in the vast majority (95%) of patients with NSTE-ACS who undergo PCI, even in those considered to be at high risk.[149] However, the development of intraprocedural complications, such as transient or sustained loss of a side branch, abrupt closure, distal embolization, or development of the no-reflow phenomenon, has been associated with a fourfold to fivefold increase in the risk for ischemic complications and death over the next 30 days.[149,150] Use of GP IIb/IIIa inhibitors improves acute outcomes following PCI. Although use of a drug-eluting stent reduces the risk for restenosis, there is a risk for late stent thrombosis following implantation of a drug-eluting stent, especially when DAPT (i.e., ASA and a $P2Y_{12}$ inhibitor) is discontinued. This serious complication can be reduced in the long term (at least 6 to 12 months) in patients treated with drug-eluting stents.

The third-generation stents coated with everolimus have demonstrated consistent benefits in comparison to earlier-generation stents coated with sirolimus or paclitaxel[151,152] and in comparison to bare-metal stents.[153] Given reductions in stent thrombosis and other ischemic events following placement of an everolimus-eluting stent, the need for prolonged (≥12 months) DAPT is less clear, and shorter durations of DAPT may be possible.[154]

Percutaneous Coronary Intervention Versus Coronary Artery Bypass Grafting

Several trials have compared PCI and CABG in patients with ischemic heart disease, many of whom had NSTE-ACS. Based on the results, CABG is recommended for patients with disease of the left main coronary artery, as well as for those with multivessel disease (involving all three major epicardial vessels or the proximal left anterior descending artery plus a second artery) and a left ventricular ejection fraction lower than 40% and/or diabetes mellitus. In a recent study of 1900 patients with diabetes and multivessel CAD (27% of whom had NSTE-ACS), CABG significantly reduced the composite endpoint of death, MI, or stroke in comparison to PCI.[155] However, as experience with multivessel and left main PCI grows, an increasing number of nondiabetic patients with this more complex coronary anatomy may also be suitable for PCI. For other patients with less severe CAD, PCI is ordinarily performed if the coronary anatomy is suitable. PCI is associated with slightly lower initial morbidity and mortality and lower rates of stroke[155] than CABG is, but a higher need for repeated PCI[155-157] and somewhat less relief of angina.[158]

Lipid-Lowering Therapy

Long-term treatment with lipid-lowering therapy, especially with statins, has shown benefit in patients following acute MI and NSTE-ACS (**see also Chapters 42 and 45**).[159] In a prespecified subgroup of more than 3200 patients with UA in the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) trial, pravastatin therapy led to a significant 26% reduction in total mortality.[160] Initiation of statins in the hospital at the time of an ACS has been associated with long-term benefits in outcome when compared with placebo.[161]

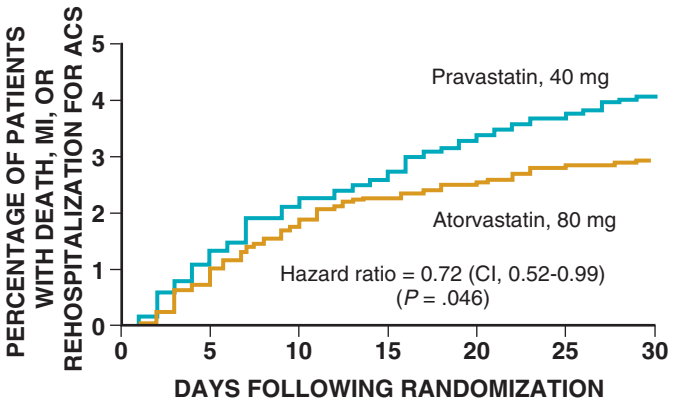


FIGURE 53-13 Effect of intensive statin therapy following NSTE-ACS. The benefit of intensive statin therapy initiated early after ACS in the PROVE IT–TIMI 22 trial is shown. A significant reduction in events occurred in the first 30 days. *(From Ray KK, Cannon CP, Cairns R, et al: The timing of benefits of intensive statin therapy in ACS: A PROVE IT–TIMI 22 substudy. J Am Coll Cardiol 46:1405, 2005.)*

In the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) trial, conducted in 4162 patients who were enrolled an average of 7 days following an ACS, intensive lipid-lowering therapy with atorvastatin, 80 mg, versus moderate lipid-lowering therapy with pravastatin, 40 mg (**Fig. 53-13**), resulted in a 16% reduction (median LDL levels achieved in the two arms were 62 and 95 mg/dL, respectively) in the primary endpoint (a composite of cardiovascular death, MI, stroke, revascularization, or unstable angina leading to hospitalization) and a 25% reduction in death, MI, or urgent revascularization.[162] Benefits began to emerge only 2 weeks after random assignment,[163] thus highlighting the importance of early initiation of intensive statin therapy after ACS. Based in part on these results, the National Cholesterol Education Program (NCEP) recommended an optional therapeutic LDL goal of less than 70 mg/dL in high-risk patients with CHD, such as those with a history of an ACS.[164] Regression of CAD after ACS was observed with intensive lipid-lowering therapy in diabetic patients with NSTE-ACS when LDL lower than 70 mg/dL was achieved.[165]

Four additional trials of intensive versus moderate (standard) statin therapy followed PROVE IT–TIMI 22, one involving post-ACS patients and three involving patients with stable CAD. A meta-analysis of the five published trials, including 39,612 patients monitored for a median of 5.1 years, showed highly significant reductions of 15% in major vascular events and a 13% reduction in coronary death or MI with intensive versus standard statin therapy.[166] Of note, no adverse effects of ultra-low LDL (below 40 to 50 mg/dL) have emerged,[167] and thus statin doses should not be routinely titrated downward in asymptomatic patients who are tolerating high-dose statins after ACS.

Intensive statin therapy for patients with an ACS should start, at the latest, at the time of hospital discharge,[6] but benefit of intensive statin therapy before PCI with a 44% reduction in both peri-PCI MI and other adverse events through 30 days was demonstrated in a meta-analysis of 13 randomized trials[168]—thus suggesting a benefit if high-dose statin therapy is started at the time of admission. Although epidemiologic studies have shown that patients with higher HDL cholesterol levels have a lower incidence of CHD, no pharmacologic therapies directed at raising HDL have yet demonstrated an improvement in clinical outcomes in patients with or after ACS in the statin era (**see also Chapters 42 and 45**).

Discharge and Posthospital Care

The time of hospital discharge following ACS affords a "teachable moment" for the patient,[169] when the physician and staff can review and optimize the medical regimen for long-term treatment. Patients

with NSTE-ACS and those with STEMI should receive secondary prevention approaches as described in **Chapters 42, 47, and 52**.

SUBGROUPS OF SPECIAL INTEREST

Older Adults

The incidence of ACS increases with age, and given the current demographic trends, elderly patients (≥75 years of age) will represent an increasing proportion of those with ACS. Yet evidence-based therapies are underused in older as opposed to younger patients,[170] even when considering comorbid conditions and contraindications.[171]

Elderly patients with NSTE-ACS present challenges to diagnosis and management, including a greater likelihood of atypical symptoms (e.g., dyspnea, confusion); noncoronary cause of ACS, such as hypertension, myocardial hypertrophy, and diastolic dysfunction; hepatic and renal dysfunction resulting in impaired metabolism and decreased clearance of drugs; and comorbid conditions that predispose to adverse reactions, such as bleeding and renal failure and higher risk for ischemic complications.[172] The combination of these comorbid conditions and a greater tendency to use polypharmacy in older adults increases the risk for drug-drug interactions and side effects.

In general, pharmacologic treatment of NSTE-ACS in older adults should parallel the recommended therapies for younger patients, albeit with greater anticipation of and surveillance for adverse drug events.[173] The high prevalence of reduced renal function in elderly individuals, despite an apparently "normal" serum creatinine level, may lead to excess dosing of antithrombotics such as enoxaparin and GP IIb/IIIa inhibitors.[174] Guidelines recommend assessment of renal function (by estimation of either creatinine clearance or the glomerular filtration rate) in all patients with ACS to permit proper dosing and selection of medications.[65,75,175]

Elderly patients are more likely than younger ones to have severe CAD that could benefit from invasive management leading to revascularization. However, because elderly patients also often have medical comorbid conditions that increase the risk for adverse outcomes and because patients and physicians exercise more caution regarding invasive procedures, elderly patients have lower rates of invasive procedures. Analyses comparing invasive and conservative management provide support for the use of an early invasive strategy in elderly patients who do not have contraindications to angiography,[176] particularly if the troponin level is elevated at initial evaluation, whereas an early conservative strategy may be preferred in elderly patients without troponin elevation.[143] Barring comorbid medical conditions that prove to be contraindications, advanced age should not deter otherwise indicated comprehensive treatment of NSTE-ACS.

Women (See also Chapter 77)

Women are accounting for an increasingly larger proportion of patients with ACS, now approaching 50%.[177] On average, women with NSTE-ACS tend to be a decade older than men, but management of NSTE-ACS should be similar regardless of sex.[178] What is considered to be the "typical" manifestation of ACS is based on previous studies that were conducted predominantly in men—such manifestations can differ from the more varied findings in women, in whom the chest discomfort associated with ACS is more commonly atypical. Nonatherosclerotic causes of angina, such as microvascular dysfunction[179] in the coronary circulation without associated epicardial obstructive disease and superimposed thrombosis, are more frequent in women.

Women with ACS are also more likely than men to have abnormal BNP and hsCRP levels,[180] vascular reactivity,[181] and functional capacity,[182] probably because of the more complex and varied pathophysiology underlying ACS in women.[183] Nonetheless, women with elevated circulating troponin or with high-risk noninvasive test results should be referred for coronary angiography, with the understanding that they may be at higher risk for bleeding complications. Because women with ACS are on average older than men, have lower body weight, and are more likely to have impaired renal function, they are at particular risk for medication overdose of therapies such as LMWH or GP IIb/IIIa inhibitors.[184]

Studies investigating the usefulness of intensive DAPT,[185] an early invasive strategy,[147] and the use of high-intensity statins[186] in patients with NSTE-ACS have challenged the concept that women fare less well than men with the use of standard intensive therapies. These findings underscore the view that women and men with NSTE-ACS as a result of obstructive CAD should receive similar management.

Diabetes Mellitus and Glucose Intolerance (See also Chapter 61)

Diabetes mellitus and glucose intolerance are epidemic in the United States. An estimated 25.6 million (11.3%) U.S. adults (≥20 years of age) have diabetes mellitus,[187] and it is undiagnosed in approximately 7 million of them. The annual incidence of new cases of diabetes in 2010 was 1.9 million—double the rate 30 years ago. An estimated additional 35% (79 million) of U.S. adults, as well as half of adults 65 years or older, have prediabetes (based on elevated fasting glucose or hemoglobin A1c levels). Despite advances in management over the past three decades, patients with diabetes mellitus continue to experience a threefold increased risk for age-adjusted cardiovascular mortality when compared with those without diabetes, and almost five of six patients older than 65 years with diabetes die of some form of heart or blood vessel disease.[177] Thus patients with diabetes in whom NSTE-ACS develops deserve special consideration.

In GRACE (Global Registry of Acute Coronary Events), more than a fourth of patients with NSTE-ACS had diabetes.[188] Even after multivariate adjustment for higher comorbid conditions, diabetes itself confers a 65% increase in the odds for death following NSTE-ACS.[189] Even milder forms of impaired glucose metabolism entail increased cardiovascular risk. Metabolic syndrome was present in 25% of patients admitted to the hospital with an ACS in an Israeli national survey, and these patients had a doubling of adjusted mortality.[190]

Patients with diabetes should receive established medical therapies for NSTE-ACS, as do nondiabetic patients, with additional attention directed toward control of blood glucose and prevention of acute kidney injury. Four key recommendations from an AHA scientific statement on the management of hyperglycemia in patients with ACS[191] are that (1) plasma glucose should be measured in all patients with ACS; (2) in patients in an intensive care or coronary care unit, glucose should be monitored closely and intravenous insulin considered in patients with blood glucose levels higher than 180 mg/dL; (3) outside the unit, blood glucose should be maintained at levels lower than 180 mg/dL with subcutaneous insulin; and (4) glucose metabolism should be reassessed after discharge in patients without previous known diabetes mellitus who demonstrated hyperglycemia during hospitalization.

Because patients with diabetes derive similar benefit with an early invasive strategy as nondiabetic patients do, diabetes is included among the characteristics that should prompt adoption of an early invasive strategy.[69,75] Patients with diabetes have a worse long-term outcome after revascularization than do nondiabetic patients, particularly after PCI,[192] because they have a higher risk for restenosis and progression of disease in nonculprit lesions. Use of GP IIb/IIIa inhibitors appears to have special benefit in diabetic patients who undergo coronary stenting.[193] In particular, diabetic patients with elevated baseline glucose levels may merit the use of more potent platelet inhibitors such as prasugrel[101] (**Fig. 53-14**) because these patients have more severe platelet dysfunction.[194]

Chronic Kidney Disease (See also Chapter 88)

The Centers for Disease Control and Prevention estimated that as of 2010, the prevalence of CKD had increased to 14% in U.S. adults older than 20 years.[195] Patients with CKD (including those with even minor reductions in renal function[196]) represent a group of special interest because the risk for recurrent ischemic events is higher following ACS,[197] as is treatment-related complications.

Unfortunately, most major cardiovascular clinical trials exclude patients with severe CKD, and thus the evidence base for treatment recommendations in patients with CKD is limited. A meta-analysis of five trials of patients with NSTE-ACS and CKD (three of the trials excluded patients with severe renal dysfunction) demonstrated trends toward more favorable outcomes with an early invasive strategy than with conservative management.[144] Thus coronary angiography should be considered in patients with CKD, and the benefits of prompt revascularization should be weighed against the risk for bleeding and contrast-induced nephropathy.

Patients with CKD have a greater risk for bleeding because of impaired platelet function[198] and because of overdosing with antithrombotic therapy[199] (**Table 53-5**; also see Table 88-1). In addition, patients with CKD have increased risk for contrast-induced nephropathy and acute kidney injury. Current guidelines recommend that the risk for contrast-induced nephropathy be assessed by measurement of the ratio of contrast volume to creatinine clearance[175] and that this ratio not exceed 3.7.[75] Adequate hydration in the periprocedural period is essential,[175] but the evidence that isomolar agents are superior to low-osmolar agents is not compelling.[75] Physicians should assess renal function in all patients with NSTE-ACS.[6,75] In patients with CKD, the dosage of medications that are cleared renally should be adjusted; such medications include enoxaparin, bivalirudin, eptifibatide, and tirofiban.

Prinzmetal Variant Angina

In 1959, Prinzmetal and colleagues described a syndrome of ischemic pain that occurred at rest, accompanied by ST-segment elevation.[200] Prinzmetal variant angina (PVA) may be associated with acute MI, ventricular tachycardia or fibrillation, and sudden cardiac death. Spasm of a proximal coronary artery with resultant transmural ischemia and abnormalities in left ventricular function are the diagnostic hallmarks of PVA. The precise mechanisms responsible for the spasm have not been established, but a reduction in nitric oxide production by the coronary arterial endothelium or an imbalance between endothelium-derived relaxing and contracting factors may contribute.[201] The finding of elevated levels of serum hsCRP in many patients supports a contribution of inflammation to the condition.[202] Polymorphisms of the alpha$_2$ presynaptic and the beta$_2$ postsynaptic receptors may also be associated with PVA.[203]

Patients with PVA tend to be younger than those with NSTE-ACS attributable to coronary atherosclerosis, and many do not exhibit the classic coronary risk factors except that they are frequently heavy cigarette smokers. The anginal pain is often extremely severe and may be accompanied by syncope related to atrioventricular block, asystole, or ventricular tachyarrhythmia.[204] Attacks of PVA tend to cluster between midnight and 8:00 AM.[205]

Approximately a third of patients with PVA also exhibit severe fixed coronary obstruction and may have a combination of exertion-induced angina with ST-segment depression and episodes of angina at rest with ST-segment elevation. Rarely, PVA appears to be a manifestation of a generalized vasospastic disorder associated with migraine and/or Raynaud phenomenon. PVA can also develop in association with aspirin-induced asthma and administration of 5-fluorouracil and cyclophosphamide. The ergot derivatives used to treat migraine headache and serotonin antagonists (e.g., serotonin reuptake inhibitors used to treat depression) can

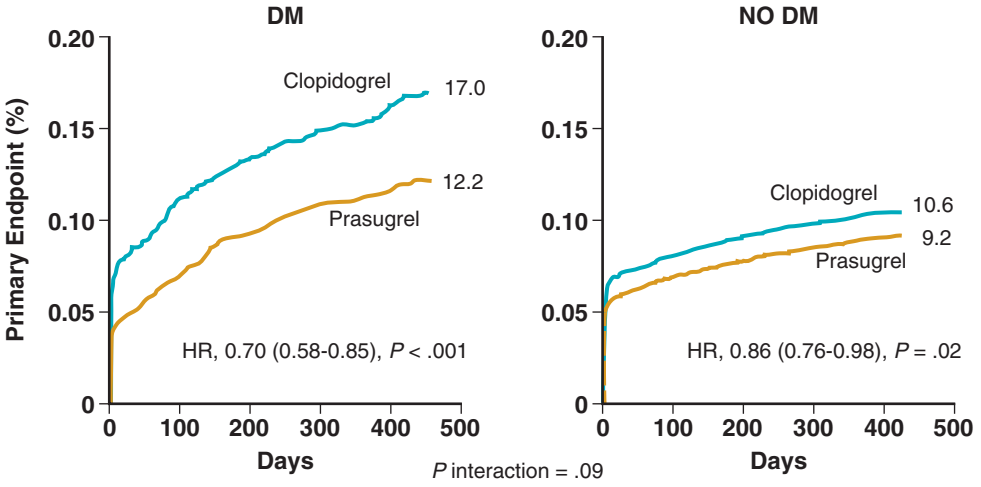


FIGURE 53-14 Prasugrel versus clopidogrel in patients with diabetes. Kaplan-Meier curves for prasugrel versus clopidogrel stratified by diabetes status in TRITON–TIMI 38 are shown. The primary efficacy endpoint was a composite of cardiovascular death, nonfatal MI, or nonfatal stroke. DM = diabetes mellitus. *(From Wiviott SD, Braunwald E, Angiolillo DJ, et al: Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel—Thrombolysis in Myocardial Infarction 38. Circulation;118:1626, 2008.)*

TABLE 53-5 Recommendations for the Use of Anticoagulant and Antiplatelet Drugs in Chronic Kidney Disease[65]

DRUG	RECOMMENDATIONS
Enoxaparin	Dose reduction to 1 mg/kg once daily in the case of severe renal failure (CrCl <30 mL/min) Consider monitoring anti-Xa activity
Fondaparinux	Contraindicated in severe renal failure (CrCl <20 mL/min). Drug of choice in patients with moderately reduced renal function (CrCl 30-60 mL/min)
Bivalirudin	Patients with moderated renal impairment (30-59 mL/min) should receive an infusion of 1.75 mg/kg/hr. If the creatinine clearance is <30 mL/min, reduction of the infusion rate to 1 mg/kg/hr should be considered. No reduction in the bolus dose is needed. If a patient is being maintained on hemodialysis, the infusion rate should be reduced to 0.25 mg/kg/hr
Abciximab	No specific recommendations for the use of abciximab or for dose adjustment in the case of renal failure. Careful evaluation of risk for hemorrhage is needed before using the drug in patients with renal failure
Eptifibatide	The infusion dose should be reduced to 1 µg/kg/min in patients with CrCl <50 mL/min. The bolus dose remains unchanged at 180 µg/kg/min. Eptifibatide is contraindicated in patients with CrCl <30 mL/min
Tirofiban	Dose adaptation is required in patients with renal failure; 50% of the bolus dose and infusion is administered if CrCl is <30 mL/min

Recommendations for the use of drugs listed in this table may vary depending on the exact labeling of each drug in the country where it is used. See also Table 88-1.
CrCl = creatinine clearance.
Modified from Hamm CW, Bassand JP, Agewall S, et al: ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 32:2999, 2011.

precipitate episodes of PVA.[206] The incidence of PVA has always been greater in Japan than in Western countries, but across the world, the incidence appears to have fallen markedly over the past three decades; this decline may be related in part to the more aggressive use of calcium antagonists for hypertension.[207]

The key to diagnosis of PVA lies in the detection of episodic ST-segment elevation often accompanied by severe chest pain, usually occurring at rest (**Fig. 53-15A**) Multiple asymptomatic episodes of (silent) ST-segment elevation occur in many patients. ST-segment deviations may be present in any leads, depending on the artery involved. Sometimes serious ventricular arrhythmias[208] or transient conduction disturbances[209] may occur during periods of ST-segment elevation and result in syncope. Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with PVA and associated severe obstructive lesions.[210]

Provocative Testing

Three provocative tests for coronary spasm can be performed at the time of coronary angiography—hyperventilation (Fig. 53-15B), intracoronary acetylcholine, and intracoronary ergonovine—although the third test is no longer available in the United States. These provocative maneuvers should be performed only in patients without obstructive CAD and in whom PVA is suspected, but not yet confirmed. Their use has been declining over the past two to three decades, in part related to the induction of rare but sometimes fatal arrhythmias. Hyperventilation may also be performed with electrocardiographic monitoring outside the catheterization laboratory, but its sensitivity is low unless the attacks are very frequent (more than five times per week).

Management

Patients with PVA should be strongly urged to discontinue smoking. The mainstay of therapy is a calcium antagonist, alone or usually in combination with a long-acting nitrate. Sublingual or intravenous nitroglycerin often abolishes attacks of PVA promptly, and long-acting nitrates are useful in preventing attacks. The response to beta blockade in patients with PVA is variable.[211] Some patients, particularly those with associated fixed obstructions, exhibit a reduction in the frequency of exertion-induced angina caused primarily by augmentation of myocardial oxygen requirements. In others, however, nonselective beta-blocking agents may actually be detrimental because blockade of $beta_2$ receptors, which mediate coronary dilation, allows unopposed alpha receptor–mediated coronary vasoconstriction to occur.

PCI and occasionally CABG may be helpful in patients with PVA and discrete, proximal fixed obstructive lesions, but revascularization is contraindicated in patients with isolated coronary artery spasm without accompanying fixed obstructive disease. Patients who have experienced ischemia-associated ventricular fibrillation and continue to manifest ischemic episodes despite maximal medical treatment should receive an implantable cardioverter-defibrillator.[212,213]

Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events occurring during the first 6 months after diagnosis. The extent and severity of the underlying CAD and the tempo of the syndrome have a major effect on the incidence of late mortality and MI. Remission occurs more frequently in patients without significant fixed coronary artery stenoses and in those who have discontinued smoking.[214] For reasons that are not clear, some patients, after a relatively quiescent period of months or even years, experience a recrudescence of vasospastic activity with frequent and severe episodes of ischemia. Fortunately, these patients generally respond to retreatment with calcium antagonists and nitrates. Clinical outcomes are excellent in patients with isolated coronary spasm and no underlying CAD, with no cardiac death or MI occurring in 76 patients monitored for 3 years in the CASPAR (Coronary Artery Spasm in Patients with Acute Coronary Syndrome) study, although about half of the patients frequently experienced angina.[215]

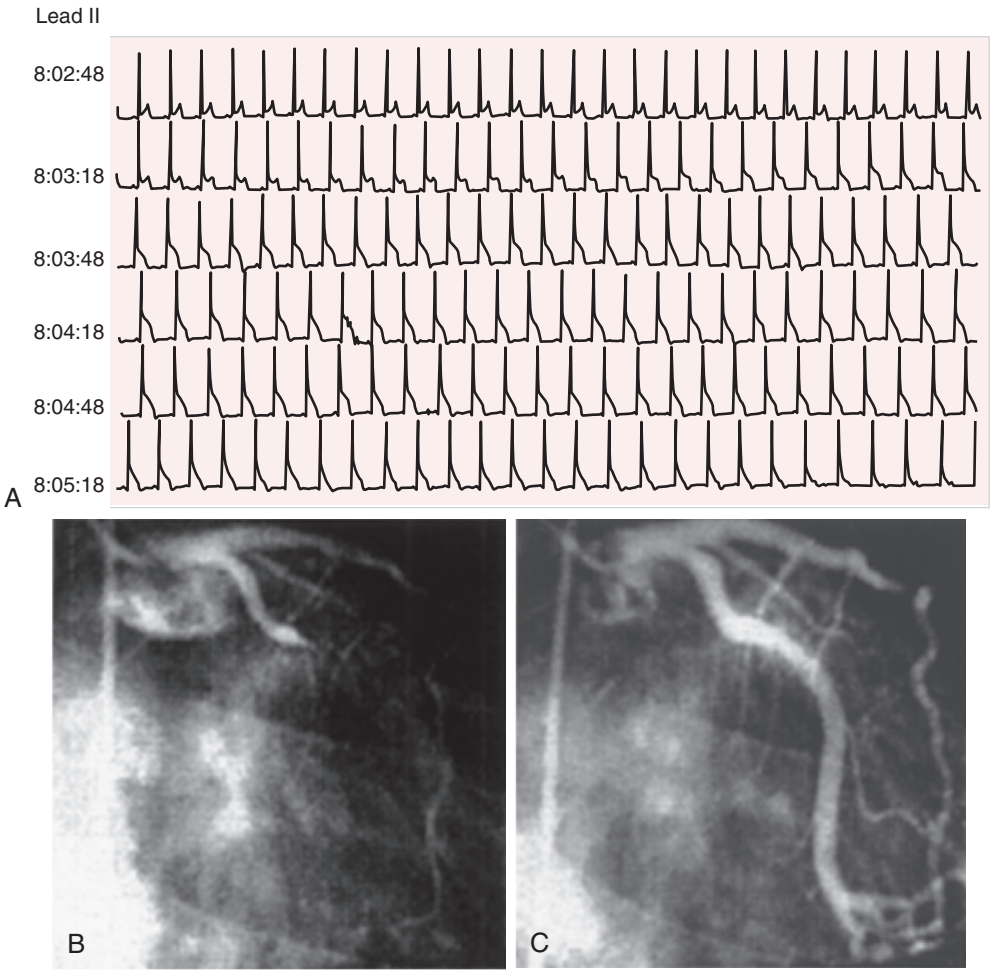


FIGURE 53-15 Observations in a 39-year-old man with Prinzmetal angina. **A,** Continuous electrocardiography during an episode of angina; transient ST-segment elevation (in lead II) was noted on continuous telemetry. **B,** Hyperventilation-induced total occlusion of the proximal left circumflex artery (visible on angiography with the right anterior oblique caudal view). **C,** Spasm that resolved with the administration of intracoronary nitroglycerin and diltiazem. The patient's symptoms were controlled with oral nitrates and calcium channel blockade during a follow-up of 2 years. *(From Chen HSV, Pinto DS: Prinzmetal angina. N Engl J Med 349:e1, 2003.)*

Cardiac Syndrome X

Approximately 15% of patients with NSTE-ACS have no obstructive epicardial disease, although they may have electrocardiographic evidence of myocardial ischemia. This condition, commonly referred to as cardiac syndrome X, is described in **Chapter 77**. It must be distinguished from metabolic syndrome X, discussed in **Chapter 42**.

Cocaine and Amphetamines (See also Chapter 68)

Cocaine use causes a marked increase in sympathetic tone by blocking the reuptake of norepinephrine from synapses by preganglionic neurons, thereby resulting in increased myocardial oxygen demand and decreased supply.[216] This may cause acute myocardial ischemia and be manifested as an ACS. This condition, which has similar findings as amphetamine abuse, occurs more frequently in younger persons and should be especially considered in males younger than 30 years.[217] The use of psychoactive "street" drugs known as "bath salts" that contain synthetic cathinones with cocaine-like actions may also cause cardiovascular complications, including ACS.[218]

FUTURE PERSPECTIVES

Several aspects of the diagnosis and management of NSTE-ACS will continue to advance rapidly and will probably affect numerous aspects of patient care, including the classification, risk assessment, prognostication, and management of patients with NSTE-ACS. With future development and more widespread use of more sensitive assays of cTn, it is likely that some myocardial necrosis will be detected in a large majority of patients with NSTE-ACS. Hence the frequency of diagnosis of UA will continue to decline and more of these patients will meet the criteria for NSTEMI. Newer biomarkers emerging from proteomic techniques will allow identification of specific causes of NSTE-ACS, which in turn will result in more specific and individualized treatment (**see Chapter 10**). Improvements in noninvasive plaque imaging will lead to the rapid exclusion of ACS when the diagnosis is uncertain and to more rapid and accurate assessment of coronary obstruction and detection of vulnerable plaque.

As new pharmacologic agents that target different aspects of the clotting cascade and platelet function are developed, additional therapeutic options will become available and allow clinicians to select more effective and safer combinations directed toward individual patients' needs. Newer generations of intracoronary stents under development, including totally resorbable stents, may further reduce the risk for restenosis and stent thrombosis—thereby leading to shorter periods of antithrombotic therapy, which will reduce the incidence of bleeding.

Several new therapies are now undergoing phase III trials. These include new, powerful drugs to reduce LDL cholesterol and raise the HDL cholesterol concentration profoundly (**see Chapters 42 and 45**). Similarly, new interventions are under evaluation for the treatment of resistant hypertension (**see Chapter 44**). Judicious use of these new treatments will probably further reduce the development of initial and recurrent episodes of NSTE-ACS.

Specific populations at highest risk for NSTE-ACS have been identified. These groups also paradoxically tend to be undertreated with existing proven therapies. We anticipate that special effort will be made to identify these patients and to intensify both primary and secondary prevention.

As treatment plans become more diverse, more sophisticated electronic information systems will help guide care. To ensure optimal, personalized management of patients with NSTE-ACS, appropriate use and analysis of electronic medical records will in turn allow more accurate assessment of outcomes and improve the quality of care.

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GUIDELINES

Unstable Angina and Non–ST Elevation Myocardial Infarction

Robert P. Giugliano and Eugene Braunwald

In 2012 the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) published a focused update on practice guidelines for the management of patients with unstable angina (UA) and non–ST elevation myocardial infarction (NSTEMI),[1,2] also referred to as non–ST elevation acute coronary syndrome (NSTE-ACS). The 2012 update, which replaced the previous year's focused update[3] to the 2007 full guidelines,[4] reflects the rapid accumulation of new information related to antithrombotic therapy, timing of invasive management, secondary prevention, and treatment of special subgroups (specifically in patients with diabetes and chronic kidney disease [CKD]). This guideline summary highlights the major updates

to the guidelines, with the standard ACCF/AHA classification system being used for indications (classes I to III) and level of evidence (A to C).[2]

INITIAL EVALUATION AND MANAGEMENT

Patients who experience symptoms suggestive of ACS should not be evaluated by telephone but instead should be referred to a medical facility that permits examination by a physician, assessment of a 12-lead electrocardiogram (ECG), and laboratory testing for cardiac biomarkers of necrosis *(class I; level of evidence: C)*. **Figure 53G-1** presents an updated detailed algorithm for the initial evaluation, triage, and management of patients with suspected ACS.

EARLY RISK STRATIFICATION

Class I Recommendations

1. Rapid clinical determination of risk for obstructive coronary artery disease (CAD) (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management. *(Level of evidence: C.)*
2. Patients with chest discomfort or other ischemic symptoms should undergo early risk stratification for cardiovascular events (e.g., death or repeated myocardial infarction [MI]) that focuses on the history, including anginal symptoms, findings on the physical examination, findings on the ECG, and biomarkers of cardiac injury, and the results should be considered in patient management. *(Level of evidence: C.)*
3. A 12-lead ECG should be obtained and shown to an experienced emergency physician as soon as possible after arrival at the emergency department (ED), with a goal of 10 minutes within ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of ACS. *(Level of evidence: B.)*
4. If the initial ECG is not diagnostic but the patient remains symptomatic and ACS is highly suspected clinically, serial ECGs, initially at 15- to 30-minute intervals, should be obtained to detect the potential for development of ST-segment elevation or depression. *(Level of evidence: B.)*
5. Cardiac biomarkers should be measured in all patients with chest discomfort consistent with an ACS. *(Level of evidence: B.)*
6. A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients with chest discomfort consistent with an ACS. *(Level of evidence: B.)*
7. Patients with negative cardiac biomarkers within 6 hours of the onset of symptoms consistent with an ACS should have biomarkers remeasured in the time frame of 8 to 12 hours after symptom onset. *(Level of evidence: B.)*
8. The initial evaluation of a patient with a suspected ACS should include consideration of noncoronary causes of the development of unexplained symptoms. *(Level of evidence: C.)*

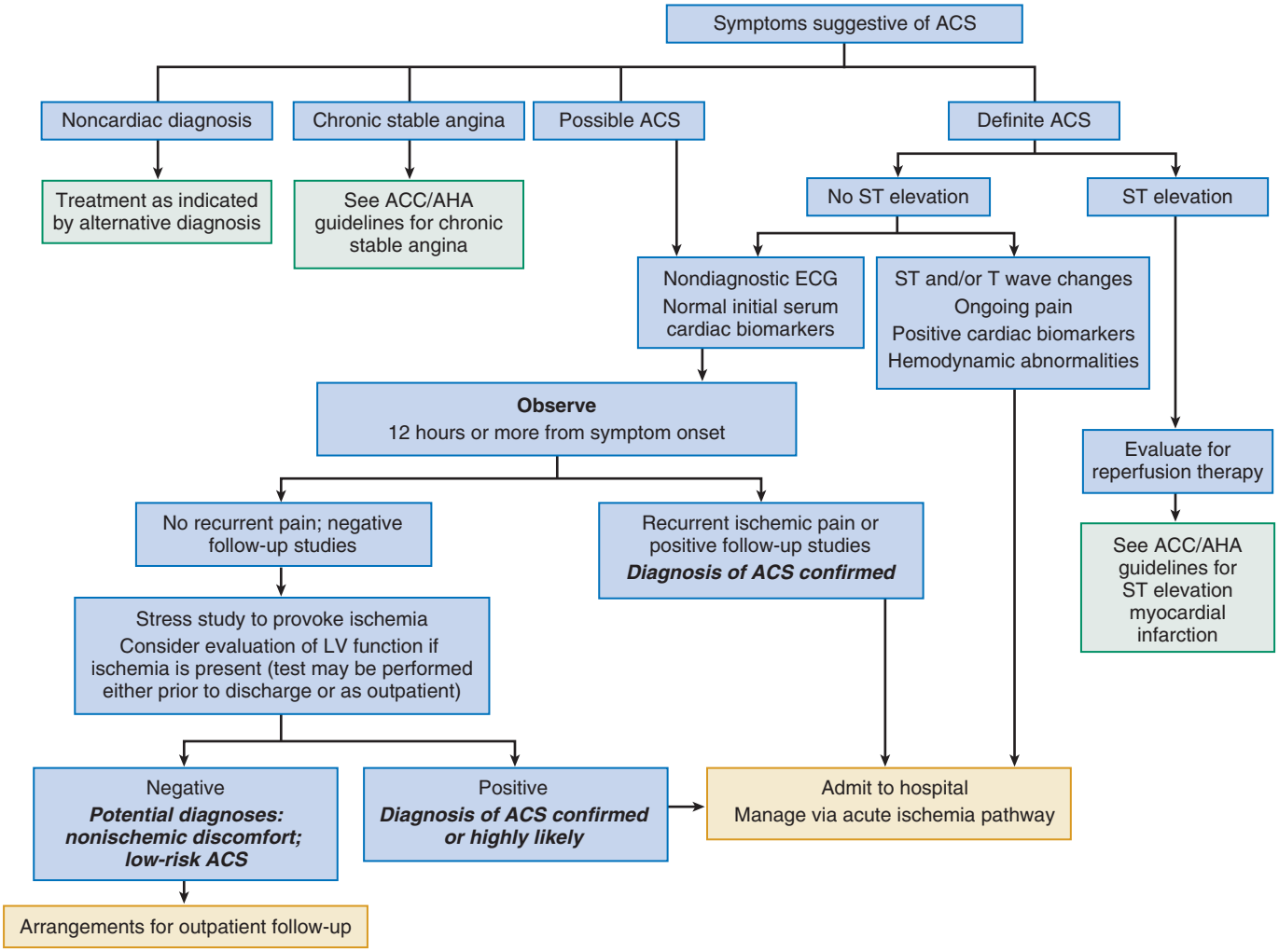

FIGURE 53G-1 Algorithm for the evaluation and management of patients suspected of having an ACS. LV = left ventricular. *(From Anderson JL, Adams CD, Antman EM, et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61:e179, 2013.)*

Class IIa

1. Use of risk stratification models, such as the TIMI (Thrombolysis In Myocardial Infarction) or GRACE (Global Registry of Acute Coronary Events) risk score or the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) risk model, can be useful to assist in decision making with regard to treatment options in patients with a suspected ACS. *(Level of evidence: B.)*
2. It is reasonable to remeasure positive biomarkers at 6- to 8-hour intervals two to three times or until the levels have peaked as an index of infarct size and dynamics of the necrosis. *(Level of evidence: B.)*
3. It is reasonable to obtain supplemental ECG leads V_7 through V_9 in patients whose initial ECG is nondiagnostic to rule out MI secondary to occlusion of the left circumflex artery. *(Level of evidence: B.)*
4. Continuous monitoring of the 12-lead ECG is a reasonable alternative to serial 12-lead recordings in patients whose initial ECG is nondiagnostic. *(Level of evidence: B.)*

Class IIb

1. For patients seen within 6 hours of symptoms suggestive of an ACS, a 2-hour change in the MB fraction of creatine kinase in conjunction with a 2-hour change in troponin may be considered. *(Level of evidence: B.)*
2. Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. *(Level of evidence: B.)*

EARLY HOSPITAL CARE

The class I recommendations for anti-ischemic therapy in the 2012 guideline update are similar to those in previous guidelines and include continuous monitoring of the ECG, supplemental oxygen in selected patients with hypoxemia or respiratory distress, nitrates, beta blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Nonsteroidal anti-inflammatory drugs other than aspirin should not be used because they increase risk for mortality, reinfarction, hypertension, heart failure, and myocardial rupture.

Three important changes were made in the recommendations regarding oral antiplatelet therapy in the guideline update, namely, (1) addition of prasugrel as an option in patients managed by percutaneous coronary intervention (PCI), (2) addition of ticagrelor in patients managed medically or with an invasive strategy, and (3) modification of the duration of $P2Y_{12}$ inhibitor therapy to up to 12 months after an NSTE-ACS. In contrast, recommendations regarding anticoagulation therapy did not change substantially in the 2012 update.

INITIAL CONSERVATIVE VERSUS INVASIVE STRATEGIES

Class I

1. An early invasive strategy is indicated in patients with UA/NSTEMI who have refractory angina or hemodynamic or electrical instability (without serious comorbid conditions or contraindications to such procedures). *(Level of evidence: B.)*
2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in initially stabilized patients with UA/NSTEMI (without serious comorbid conditions or contraindications to such procedures) who have elevated risk for clinical events *(level of evidence: A).* To assess clinical risk, the guidelines endorse the use of a risk stratification model such as the TIMI[5] or GRACE[6] risk score or the PRUSUIT risk model.[7] *(Class IIa, level of evidence: B.)*

Class IIa

1. It is reasonable to choose an early invasive strategy (within 12 to 24 hours of admission) for initially stabilized high-risk patients with UA/NSTEMI. For patients not at high risk, a delayed invasive approach is also reasonable. *(Level of evidence: B.)*

Class IIb

1. In initially stabilized patients, an initially conservative (i.e., a selectively invasive) strategy may be considered as a treatment strategy for patients with UA/NSTEMI (without serious comorbid conditions or contraindications to such procedures) who have elevated risk for clinical events, including those who are troponin positive. *(Level of evidence: B.)*

Class III: No Benefit

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbid conditions (e.g., liver or pulmonary failure, cancer) in whom the risks associated with revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. *(Level of evidence: C.)*
2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with acute chest pain and low likelihood of an ACS. *(Level of evidence: C.)*
3. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) should not be performed in patients who will not consent to revascularization regardless of the findings. *(Level of evidence: C.)*

LATE HOSPITAL CARE, HOSPITAL DISCHARGE, AND POSTHOSPITAL DISCHARGE CARE

Tables 53G-1 and 53G-2 review the recommendations regarding surgical and percutaneous coronary revascularization.

LONG-TERM MEDICAL THERAPY AND SECONDARY PREVENTION

Antiplatelet Therapy

1. For patients with UA/NSTEMI treated medically without stenting, aspirin (or a thienopyridine in patients with aspirin allergy) should be prescribed indefinitely. *(Level of evidence: A.)* Clopidogrel (75 mg/day) or ticagrelor (90 mg twice daily, the aspirin dose should not exceed 100 mg daily) should be prescribed for up to 12 months. *(Level of evidence: B.)*
2. For patients with UA/NSTEMI treated with a stent (bare-metal stent BMS] or drug-eluting stent [DES]), aspirin should be continued indefinitely *(level of evidence: A).* The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows:
   a. Clopidogrel, 75 mg daily, prasugrel, 10 mg daily (consider 5 mg in patients weighing <60 kg), or ticagrelor, 90 mg twice daily, should be given for at least 12 months in patients receiving DESs and up to 12 months for those receiving BMSs. *(Level of evidence: B.)*
   b. If the risk for morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered. *(Level of evidence: C.)*
3. Clopidogrel, 75 mg daily *(level of evidence: B),* prasugrel, 10 mg daily (in PCI-treated patients) *(level of evidence: C),* or ticagrelor, 90 mg twice daily *(level of evidence: C),* should be given to patients recovering from UA/NSTEMI when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (despite the use of gastroprotective agents such as proton pump inhibitors).

Class IIa

1. After PCI it is reasonable to use 81 mg/day of aspirin in preference to higher maintenance doses. *(Level of evidence: B.)*

Class IIb

1. For patients with UA/NSTEMI who have an indication for anticoagulation, addition of warfarin may be reasonable to maintain an

TABLE 53G-1 Revascularization to Improve Survival Versus Medical Therapy

ANATOMIC SETTING	COR	LEVEL OF EVIDENCE
Unprotected Left Main Disease or Complex Coronary Artery Disease		
CABG and PCI	I—Heart team approach recommended	C
CABG and PCI	IIa—Calculation of STS and SYNTAX scores	B
Unprotected Left Main Disease*		
CABG	I	B
PCI	IIa—For SIHD when *both* of the following are present: Anatomic conditions associated with a low risk for PCI procedural complications and a high likelihood of a good long-term outcome (e.g., a low SYNTAX score of <22, ostial or trunk left main CAD) Clinical characteristics that predict significantly increased risk for adverse surgical outcomes (e.g., STS-predicted risk or operative mortality >5%) IIa—For patients with UA/NSTEMI if not candidates for CABG IIa—For patients with STEMI when distal coronary flow is TIMI flow grade <3 and PCI can be performed more rapidly and safely than CABG IIb—For SIHD when *both* of the following are present: Anatomic conditions associated with a low to intermediate risk for PCI procedural complications and an intermediate to high likelihood of a good long-term outcome (e.g., low to intermediate SYNTAX score of <33, bifurcation left main CAD) Clinical characteristics that predict an increased risk for adverse surgical outcomes (e.g., moderate to severe COPD, disability from previous stroke, previous cardiac surgery; STS-predicted risk for operative mortality >2%) III: Harm—For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B B C B B
Three-Vessel Disease with or Without Proximal Left Anterior Descending Artery Disease*		
CABG	I IIa—It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX score >22) who are good candidates for CABG	B B
PCI	IIb—Of uncertain benefit	B
Two-Vessel Disease with Proximal Left Anterior Descending Artery Disease*		
CABG	I	B
PCI	IIb—Of uncertain benefit	B
Two-Vessel Disease Without Proximal Left Anterior Descending Artery Disease*		
CABG	IIa—With extensive ischemia IIb—Of uncertain benefit without extensive ischemia	B C
PCI	IIb—Of uncertain benefit	B
One-Vessel Proximal Left Anterior Descending Artery Disease		
CABG	IIa—With LIMA for long-term benefit	B
PCI	IIb—Of uncertain benefit	B
One-Vessel Disease Without Proximal Left Anterior Descending Artery Disease		
CABG	III: Harm	B
PCI	III: Harm	B
Left Ventricular Dysfunction		
CABG	IIa—EF of 35% to 50% IIb—EF <35% without significant left main CAD	B B
PCI	Insufficient data	
Survivors of Sudden Cardiac Death with Presumed Ischemia-Mediated Ventricular Tachycardia		
CABG	I	B
PCI	I	C
No Anatomic or Physiologic Criteria for Revascularization		
CABG	III: Harm	B
PCI	III: Harm	B

*In patients with multivessel disease who also have diabetes, it is reasonable to choose coronary artery bypass grafting (CABG) (with LIMA) over PCI *(class IIa; level of evidence: B).*

COPD = chronic obstructive pulmonary disease; COR = class of recommendation; EF = ejection fraction; LIMA = left internal mammary artery; SIHD = stable ischemic heart disease; STS, Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

From Anderson JL, Adams CD, Antman EM, et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61:e179, 2013.

TABLE 53G-2 Revascularization to Improve Symptoms with Significant Anatomic (>50% Left Main or >70% Non–Left Main CAD) or Physiologic (FFR <0.80) Coronary Artery Stenoses

CLINICAL SETTING	COR	LEVEL OF EVIDENCE
>1 significant stenosis amenable to revascularization and unacceptable angina despite GDMT	I—PCI I—CABG	A
>1 significant stenosis and unacceptable angina in whom GDMT cannot be implemented because of contraindications to medications, adverse effects, or patient preferences	IIa—CABG IIa—PCI	C
Previous CABG with >1 significant stenosis associated with ischemia and unacceptable angina despite GDMT	IIa—PCI IIb—CABG	C
Complex 3-vessel CAD (e.g., SYNTAX score >22) with or without involvement of the proximal LAD artery and a good candidate for CABG	IIa—CABG preferred over PCI	B
Viable ischemic myocardium perfused by coronary arteries not amenable to grafting	IIb—TMR as an adjunct to CABG	B
No anatomic or physiologic criteria for revascularization	III: Harm—CABG III: Harm—PCI	C

CABG = coronary artery bypass grafting; COR = class of recommendation; FFR = fractional flow reserve; GDMT = guideline-directed medical therapy; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TMR = transmyocardial laser revascularization.
From Anderson JL, Adams CD, Antman EM, et al: 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61:e179, 2013.

international normalized ratio [INR] of 2.0 to 3.0. *(Level of evidence: B.)* A target INR of 2.0 to 2.5 is preferable while giving dual antiplatelet therapy, especially in older patients and those at increased risk for bleeding.

Warfarin

Class I

1. Use of warfarin in conjunction with aspirin and/or $P2Y_{12}$ receptor inhibitor therapy is associated with an increased risk for bleeding, and patients and clinicians should watch for bleeding, especially gastrointestinal bleeding, and seek medical evaluation for evidence of bleeding. *(Level of evidence: A.)*

SPECIAL GROUPS

Diabetes Mellitus

Class I

1. Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus. *(Level of evidence: A.)*

Class IIa

1. For patients with UA/NSTEMI and multivessel disease, coronary artery bypass grafting (CABG) with use of the internal mammary arteries can be more beneficial than PCI in patients being treated for diabetes mellitus. (*Level of evidence: B.*)
2. PCI is reasonable for UA/NSTEMI patients with diabetes mellitus, single-vessel disease, and inducible ischemia. *(Level of evidence: B.)*

Chronic Kidney Disease

Class I

1. Creatinine clearance should be estimated in patients with UA/NSTEMI, and doses of renally cleared medications should be adjusted according to the pharmacokinetic data for specific medications. *(Level of evidence: B.)*
2. Patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration. *(Level of evidence: B.)*
3. Calculation of the contrast volume–to–creatinine clearance ratio is useful to predict the maximum volume of contrast media that can be given without significantly increasing the risk for contrast-induced nephropathy. *(Level of evidence: B.)*

Class IIa

1. An invasive strategy is reasonable for patients with mild (stage 2) and moderate (stage 3) CKD. *(Level of evidence: B.)* (There are insufficient data on the benefit or risk associated with an invasive strategy in patients with UA/NSTEMI and advanced CKD [stages 4 and 5].)

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