Chapter 244. Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

Christopher P. Cannon; Eugene Braunwald

Unstable Angina and INon-ST-Segment Elevation Myocardial Infarction: Introduction

Patients with ischemic heart disease fall into two large groups: patients with chronic coronary artery disease (CAD) who most commonly present with stable angina (Chap. 243) and patients with acute coronary syndromes (ACSs). The latter group, in turn, is composed of patients with acute myocardial infarction (MI) with ST-segment elevation on their presenting electrocardiogram (ECG) (STEMI; Chap. 245) and those with unstable angina (UA) and non-ST-segment elevation MI (UA/NSTEMI; Fig. 245-1). Every year in the United States, approximately 1 million patients are admitted to hospitals with UA/NSTEMI as compared with ~300,000 patients with acute STEMI. The relative incidence of UA/NSTEMI compared to STEMI appears to be increasing. More than one-third of patients with UA/NSTEMI are women, while less than one-fourth of patients with STEMI are women.

Definition

The diagnosis of UA is based largely on the clinical presentation. *Stable* angina pectoris is characterized by chest or arm discomfort that may not be described as pain but is reproducibly associated with physical exertion or stress and is relieved within 5–10 minutes by rest and/or sublingual nitroglycerin (Chaps. 12 and 343). UA is defined as angina pectoris or equivalent ischemic discomfort with at least one of three features: (1) it occurs at rest (or with minimal exertion), usually lasting >10 minutes; (2) it is severe and of new onset (i.e., within the prior 4–6 weeks); and/or (3) it occurs with a crescendo pattern (i.e., distinctly more severe, prolonged, or frequent than previously). The diagnosis of NSTEMI is established if a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected in elevated cardiac biomarkers.

Pathophysiology

UA/NSTEMI is most commonly caused by a reduction in oxygen supply and/or by an increase in myocardial oxygen demand superimposed on a lesion that causes coronary arterial obstruction, usually an atherothrombotic coronary plaque. Four pathophysiologic processes that may contribute to the development of UA/NSTEMI have been identified: (1) plaque rupture or erosion with a superimposed nonocclusive thrombus, believed to be the most common cause; in such patients, NSTEMI may occur with downstream embolization of platelet aggregates and/or atherosclerotic debris; (2) dynamic obstruction [e.g., coronary spasm, as in Prinzmetal's variant angina (PVA) (p. 2020)]; (3) progressive mechanical obstruction [e.g., rapidly advancing coronary atherosclerosis or restenosis following percutaneous coronary intervention (PCI)]; and (4) UA secondary to increased myocardial oxygen demand and/or decreased supply (e.g., tachycardia, anemia). More than one of these processes may be involved.

Among patients with UA/NSTEMI studied at angiography, approximately 5% have stenosis of the left main coronary artery, 15% have three-vessel CAD, 30% have two-vessel disease, 40% have single-vessel disease, and

10% have no apparent critical epicardial coronary artery stenosis; some of the latter may have obstruction of the coronary microcirculation. The "culprit lesion" may show an eccentric stenosis with scalloped or overhanging edges and a narrow neck on angiography. Angioscopy has been reported to show "white" (platelet-rich) thrombi, as opposed to "red" (fibrin- and cell-rich) thrombi; the latter are more often seen in patients with acute STEMI. Patients with UA/NSTEMI frequently have multiple plaques at risk of disruption (vulnerable plaques).

Clinical Presentation

History and Physical Examination

The clinical hallmark of UA/NSTEMI is chest pain, typically located in the substernal region or sometimes in the epigastrium, that radiates to the neck, left shoulder, and/or the left arm (Chap. 12). This discomfort is usually severe enough to be described as frank pain. Anginal "equivalents" such as dyspnea and epigastric discomfort may also occur, and these appear to be more frequent in women. The physical examination resembles that in patients with stable angina (Chap. 243) and may be unremarkable. If the patient has a large area of myocardial ischemia or a large NSTEMI, the physical findings can include diaphoresis; pale, cool skin; sinus tachycardia; a third and/or fourth heart sound; basilar rales; and, sometimes, hypotension, resembling the findings of large STEMI.

Electrocardiogram

In UA, ST-segment depression, transient ST-segment elevation, and/or T-wave inversion occur in 30 to 50% of patients. In patients with the clinical features of UA, the presence of new ST-segment deviation, even of only 0.05 mV, is an important predictor of adverse outcome. T-wave changes are sensitive for ischemia but less specific, unless they are new, deep T-wave inversions (≥0.3 mV).

Cardiac Biomarkers

Patients with UA/NSTEMI who have elevated biomarkers of necrosis, such as CK-MB and troponin (a much more specific and sensitive marker of myocardial necrosis), are at increased risk for death or recurrent MI. Elevated levels of these markers distinguish patients with NSTEMI from those with UA. There is a direct relationship between the degree of troponin elevation and mortality. However, in patients *without* a clear clinical history of myocardial ischemia, minor troponin elevations have been reported and can be caused by congestive heart failure (CHF), myocarditis, or pulmonary embolism, or they may be false-positive readings. Thus, in patients with an *unclear* history, small troponin elevations may not be diagnostic of an ACS.

Diagnostic Evaluation

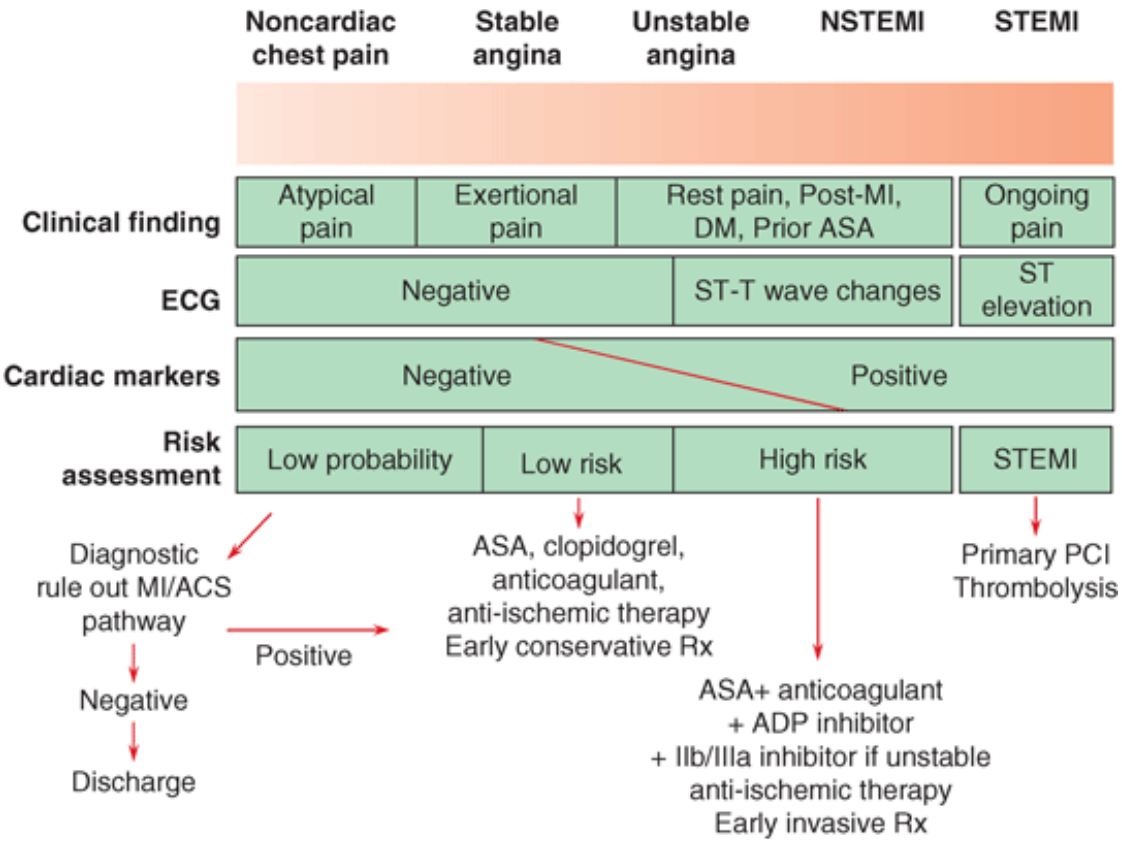
(See also Chap. 12) Approximately six million persons per year in the United States present to hospital emergency departments (EDs) with a complaint of chest pain or other symptoms suggestive of ACS. A diagnosis of an ACS is established in 20 to 25% of such patients. The first step in evaluating patients with possible UA/NSTEMI is to determine the *likelihood* that CAD is the cause of the presenting symptoms. The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines include, among the factors associated with a high likelihood of ACS, a prior history typical of stable angina, a history of established CAD by angiography, prior MI, CHF, new ECG changes, or elevated cardiac biomarkers.

Diagnostic Pathways

Four major diagnostic tools are used in the diagnosis of UA/NSTEMI in the ED: clinical history, the ECG, cardiac markers, and stress testing (coronary imaging is an emerging option). The goals are to: (1) recognize or exclude MI (using cardiac markers), (2) evaluate for rest ischemia (using serial or continuous ECGs), and (3) evaluate for significant CAD (using provocative stress testing). Patients with a low likelihood of ischemia are usually managed

with an ED-based critical pathway (which, in some institutions, is carried out in a "chest-pain unit" **Fig. 244-1)**. Evaluation of such patients includes clinical monitoring for recurrent ischemic discomfort, serial ECGs, and cardiac markers, typically obtained at baseline and at 4–6 h and 12 h after presentation. If new elevations in cardiac markers or ECG changes are noted, the patient should be admitted to the hospital. If the patient remains pain free and the markers are negative, the patient may proceed to stress testing. CT angiography is used with increasing frequency to exclude obstructive CAD (Chap. 229).

FIGURE 244-1

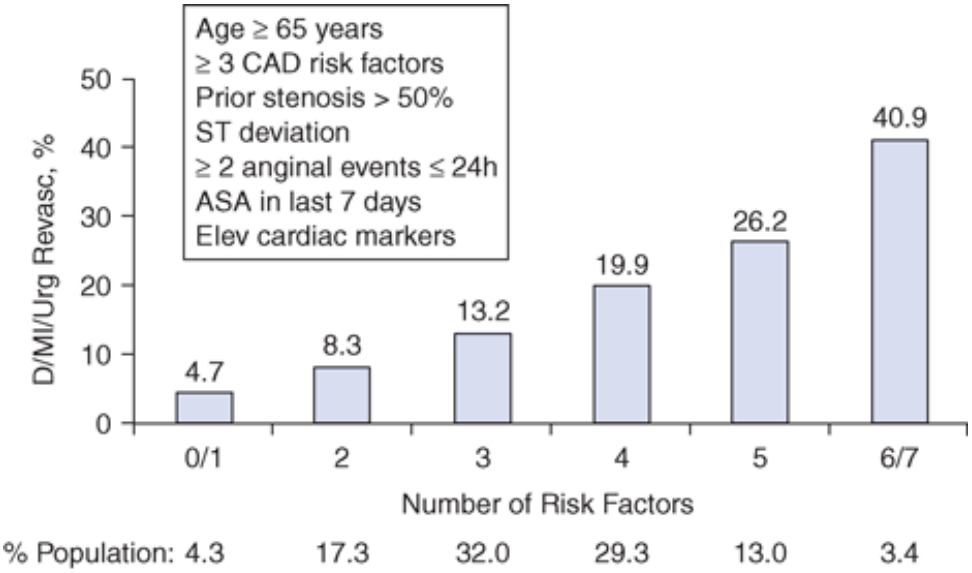


Algorithm for risk stratification and treatment of patients with suspected coronary artery disease. Using the clinical history of the type of pain and medical history, the ECG, and cardiac markers, one can identify patients who have a low likelihood of UA/NSTEMI, for whom a diagnostic "ruleout myocardial infarction (MI) or acute coronary syndrome (ACS)" is warranted. If this is negative, the patient may be discharged, but if positive, the patient is admitted and treated for UA/NSTEMI. On the other end of the spectrum, patients with acute ongoing pain and ST-segment elevation are treated with percutaneous coronary intervention (PCI) or fibrinolysis (Chap. 245). For those with UA/NSTEMI, risk stratification is used to identify patients at medium to high risk, for whom an early invasive strategy is warranted. Antithrombotic therapy should include aspirin, an anticoagulant, an ADP antagonist (clopidogrel or prasugrel), with GP IIb/IIIa inhibition considered for use during PCI. For patients at low risk, treatment with aspirin, clopidogrel, an anticoagulant such as unfractionated or low molecular–weight heparin (LMWH) or fondaparinux and anti-ischemic therapy with beta blockers and nitrates, and a conservative strategy are indicated. ASA, aspirin; DM, diabetes mellitus; ECG, electrocardiogram; MI, myocardial infarction; Rx, treatment; STEMI, ST-segment elevation myocardial infarction. (*Adapted from CP Cannon, E Braunwald, in Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 9th ed, R Bonow et al (eds). Philadelphia, Saunders, 2011.*)

Risk Stratification and Prognosis

Patients with documented UA/NSTEMI exhibit a wide spectrum of early (30 days) risk of death, ranging from 1 to 10%, and of new or recurrent infarction of 3–5% or recurrent ACS (5-15%). Assessment of risk can be accomplished by clinical risk scoring systems such as that developed from the Thrombolysis in Myocardial Infarction (TIMI) Trials, which includes seven independent risk factors: age ≥ 65 years, three or more risk factors for CAD, documented CAD at catheterization, development of UA/NSTEMI while on aspirin, more than two episodes of angina within the preceding 24 h, ST deviation ≥0.5 mm, and an elevated cardiac marker **(Fig. 244-2)**. Other risk factors include diabetes mellitus, left ventricular dysfunction, renal dysfunction and elevated levels of brain natriuretic peptides and C-reactive protein. Multimarker strategies involving several biomarkers are now gaining favor, both to define more fully the pathophysiologic mechanisms underlying a given patient's presentation and to stratify the patient's risk further. Early risk assessment (especially using troponin, ST-segment changes, and/or a global risk-scoring system) is useful both in predicting the risk of recurrent cardiac events and in identifying those patients who would derive the greatest benefit from antithrombotic therapies more potent than unfractionated heparin, such as low molecular–weight heparin (LMWH) and glycoprotein IIb/IIIa inhibitors, and from an early invasive strategy. For example, in the TACTICS-TIMI 18 Trial, an early invasive strategy conferred a 40% reduction in recurrent cardiac events in patients with a positive troponin level, whereas no benefit was observed in those without detectable troponin.

FIGURE 244-2



The TIMI Risk Score for UA/NSTEMI, a simple but comprehensive clinical risk stratification score to identify increasing risk of death, myocardial infarction, or urgent revascularization to day 14. CAD, coronary artery disease; ASA, aspirin. *(Adapted from Antman et al.)*

Treatment: Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction

Medical Treatment

Patients with UA/NSTEMI should be placed at bed rest with continuous ECG monitoring for ST-segment deviation and cardiac arrhythmias. Ambulation is permitted if the patient shows no recurrence of ischemia (discomfort or ECG changes) and does not develop a biomarker of necrosis for 12–24 h. Medical therapy involves simultaneous anti-ischemic treatment and antithrombotic treatment.

Anti-Ischemic Treatment

(Table 244-1) To provide relief and prevention of recurrence of chest pain, initial treatment should include bed rest, nitrates, and beta blockers.

Table 244–1. Drugs Commonly Used in Intensive Medical Management of Patients with Unstable Angina and Non-ST Segment Elevation MI

Drug Category	Clinical Condition	When to Avoid[a]	Dosage
Nitrates	Administer sublingually, and, if symptoms persist, intravenously	Hypotension Patient receiving sildenafil or other PDE-5 inhibitor	Topical, oral, or buccal nitrates are acceptable alternatives for patients without ongoing or refractory symptoms 5–10 μg/min by continuous infusion titrated up to 75–100 μg/min until relief of symptoms or limiting side effects (headache or hypotension with a systolic blood pressure <90 mmHg or more than 30% below starting mean arterial pressure levels if significant hypertension is present)
Beta blockers[b]	Unstable angina	PR interval (ECG) >0.24 s 2° or 3° atrioventricular block Heart rate <60 beats/min Systolic pressure <90 mmHg Shock Left ventricular failure Severe reactive airway disease	Metoprolol 25–50 mg by mouth every 6 h If needed, and no heart failure, 5-mg increments by slow (over 1–2 min) IV administration
Calcium channel blockers	Patients whose symptoms are not relieved by adequate doses of nitrates and beta blockers, or in patients unable to tolerate adequate	Pulmonary edema Evidence of left ventricular dysfunction	Dependent on specific agent

	doses of one or both of these agents, or in patients with variant angina	(for diltiazem or verapamil)	
Morphine sulfate	Patients whose symptoms are not relieved after three serial sublingual nitroglycerin tablets or whose symptoms recur with adequate anti-ischemic therapy	Hypotension Respiratory depression Confusion Obtundation	2–5 mg IV dose May be repeated every 5–30 min as needed to relieve symptoms and maintain patient comfort

[a]Allergy or prior intolerance is a contraindication for all categories of drugs listed in this chart.

[b]Choice of the specific agent is not as important as ensuring that appropriate candidates receive this therapy. If there are concerns about patient intolerance owing to existing pulmonary disease, especially asthma, left ventricular dysfunction, risk of hypotension or severe bradycardia, initial selection should favor a short-acting agent, such as propranolol or metoprolol or the ultra-short-acting agent esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease should prompt a trial of a short-acting agent at a reduced dose (e.g., 2.5 mg IV metoprolol, 12.5 mg oral metoprolol, or 25 μg/kg per min esmolol as initial doses) rather than complete avoidance of beta-blocker therapy.

Note: Some of the recommendations in this guide suggest the use of agents for purposes or in doses other than those specified by the U.S. Food and Drug Administration. Such recommendations are made after consideration of concerns regarding nonapproved indications. Where made, such recommendations are based on more recent clinical trials or expert

consensus. IV, intravenous; ECG, electrocardiogram; 2°, second-degree; 3°, third-degree.

Source: Modified from E Braunwald et al: Circulation 90:613, 1994.

Nitrates

Nitrates should first be given sublingually or by buccal spray (0.3–0.6 mg) if the patient is experiencing ischemic pain. If pain persists after 3 doses given 5 min apart, intravenous nitroglycerin (5–10 μg/min using nonabsorbing tubing) is recommended. The rate of the infusion may be increased by 10 μg/min every 3–5 min until symptoms are relieved or systolic arterial pressure falls to <100 mmHg. Topical or oral nitrates (Chap. 243) can be used once the pain has resolved or they may replace intravenous nitroglycerin when the patient has been pain-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the use of sildenafil or other drugs in that class within the previous 24–48 h.

Beta Adrenergic Blockers and Other Agents

Beta blockers are the other mainstay of anti-ischemic treatment. Oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended as first-line treatment. A caution has been raised in the new ACC/AHA guidelines for use of intravenous beta blockade in patients with any evidence of acute heart failure, where they could increase the risk of cardiogenic shock. Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent or recurrent symptoms after treatment with full-dose nitrates and beta blockers and in patients with contraindications to beta blockade. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibition and HMG-CoA reductase inhibitors (statins) for long-term secondary prevention. Early administration of intensive statin therapy (e.g., atorvastatin 80 mg) prior to percutaneous coronary intervention (PCI) has been shown to reduce complications, suggesting that high-dose statin therapy should be started at the time of admission.

Antithrombotic Therapy

(Table 244-2) This is the other main component of treatment for UA/NSTEMI. Initial treatment should begin with the platelet cyclooxygenase inhibitor aspirin **(Fig. 244-3)**. The typical initial dose is 325 mg/d, with lower doses (75–162 mg/d) recommended for long-term therapy. The OASIS-7 trial randomized 25,087 ACS patients to receive high-dose (300–325 mg/d) vs. low-dose (75-100 mg/d) aspirin for 30 days and reported no differences in the risk of major bleeding or in efficacy over this period of time. "Aspirin resistance" has been noted in 5–10% of patients and more frequently in patients treated with lower doses of aspirin, but frequently has been related to noncompliance.

Table 244–2. Clinical Use of Antithrombotic Therapy

Oral Antiplatelet Therapy	
Aspirin	Initial dose of 162–325 mg nonenteric formulation followed by 75–162 mg/d of an enteric or a nonenteric formulation
Clopidogrel	Loading dose of 300-600 mg followed by 75 mg/d

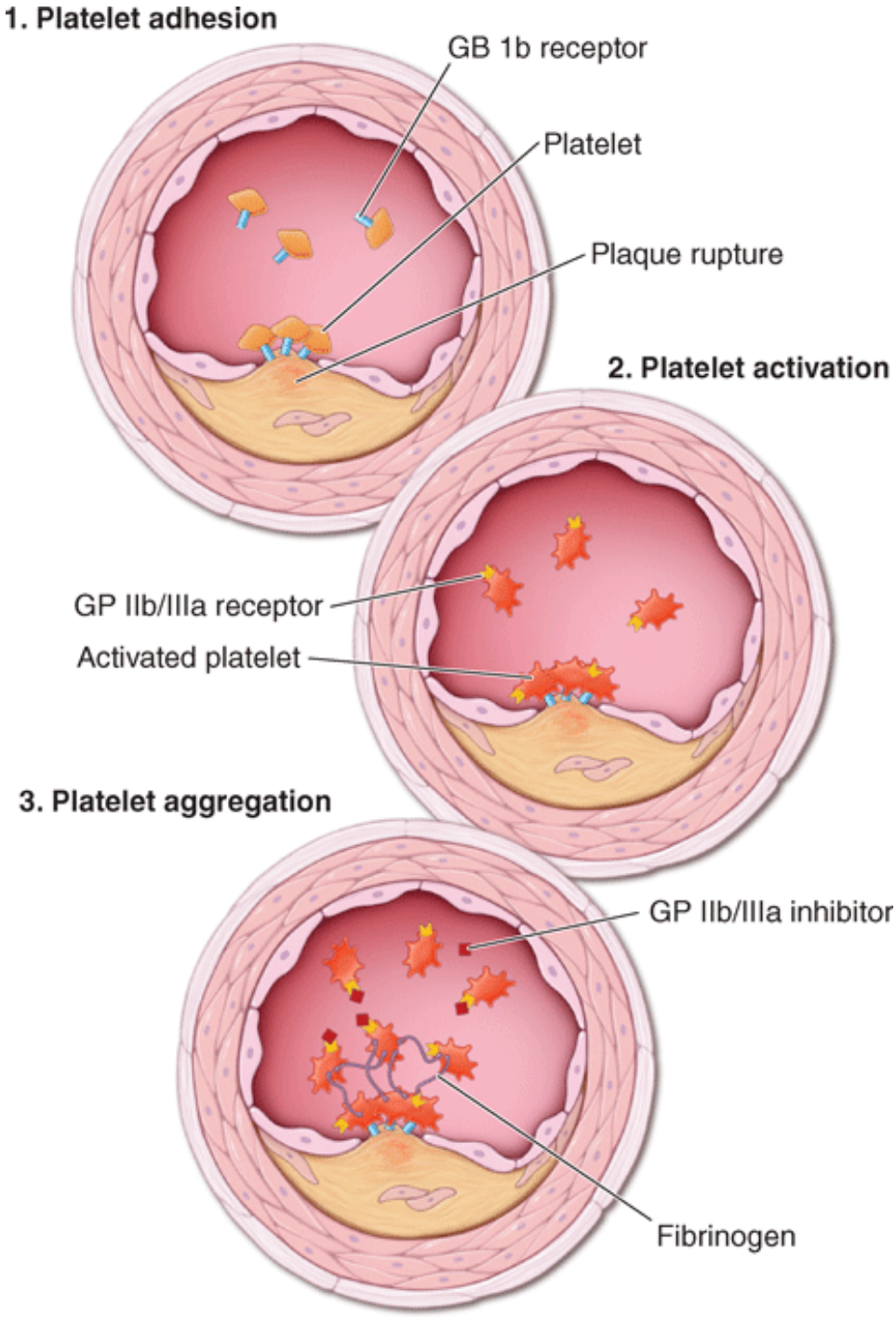
Prasugrel	Pre-PCI: Loading dose 60 mg followed by 10 mg/d
Intravenous Antiplatelet Therapy	
Abciximab	0.25 mg/kg bolus followed by infusion of 0.125 μg/kg per min (maximum 10 μg/min) for 12 to 24 h
Eptifibatide	180 μg/kg bolus followed by infusion of 2.0 μg/kg per min for 72 to 96 h
Tirofiban	0.4 μg/kg per min for 30 min followed by infusion of 0.1 μg/kg per min for 48 to 96 h
Heparins*	
Unfractionated Heparin (UFH)	Bolus 60–70 U/kg (maximum 5000 U) IV followed by infusion of 12–15 U/kg per h (initial maximum 1000 U/h) titrated to a PTT 50–70 s
Enoxaparin	1 mg/kg SC every 12 h; the first dose may be preceded by a 30-mg IV bolus; renal adjustment to 1 mg/kg once daily if creatine Cl < 30 cc/min
Fondaparinux	2.5 mg SC qd
Bivalirudin	Initial bolus intravenous bolus of 0.1 mg/kg and an infusion of 0.25 mg/kg per hour. Before PCI, an additional intravenous bolus of 0.5 mg/kg was administered, and the infusion was increased to 1.75 mg/kg per hour.

*Other LMWH exist beyond those listed.

Abbreviations: IV, intravenous; SC, subcutaneously.

Source: Modified from J Anderson et al: JACO 50:e1, 2007.

FIGURE 244-3



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Platelets initiate thrombosis at the site of a ruptured plaque with denuded endothelium: *platelet adhesion* occurs via (1) the GP 1b receptor in conjunction with von Willebrand factor. This is followed by *platelet activation* (2), which leads to a shape change of the platelet, degranulation of the alpha and dense granules, and expression of glycoprotein IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is *platelet aggregation* (3), in which fibrinogen (or von Willebrand factor) binds to the activated GP IIb/IIIa receptors. Aspirin (ASA) and clopidogrel act to decrease platelet activation, whereas the GP IIb/IIIa inhibitors inhibit the final step of platelet aggregation. GP, glycoprotein. [*Modified from CP Cannon, E Braunwald, in Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed, R Bonow et al (eds). Philadelphia, Saunders, 2008.*]

The thienopyridine, clopidogrel, an inactive prodrug that is converted into an active metabolite, which blocks the

platelet $P2Y_{12}$ component or the adenosine diphosphate receptor, in combination with aspirin, was shown in the CURE trial to confer a 20% relative reduction in cardiovascular death, MI, or stroke, compared with aspirin alone in both low- and high-risk patients, but to be associated with a moderate (absolute 1%) increase in major bleeding. Pretreatment with clopidogrel (a 300 or 600 mg loading dose, followed by 75 mg qd) is recommended prior to PCI. The OASIS-7 trial reported that one week of a higher dose of clopidogrel (600 mg loading dose and 150 mg/d for one week) did not result in an overall improvement in outcomes in ACS patients, but did so in patients receiving 325 mg of aspirin, especially those who underwent PCI.

Continued benefit of one year of treatment with the combination of clopidogrel and aspirin has been observed both in patients treated conservatively and in those who underwent PCI and should certainly continue for at least one year in patients with a drug-eluting stent. Up to one-third of patients have low response to clopidogrel, and a substantial proportion of these are related to a genetic variant of the cytochrome P450 system. A variant of the 2C19 gene leads to reduced conversion of clopidogrel into its active metabolite, which, in turn, causes lower platelet inhibition and a higher risk of cardiovascular events. Alternate agents, such as prasugrel, should be considered for ACS patients who are hyporesponsive to clopidogrel as identified by platelet and/or genetic testing, although such testing is not yet widespread.

A recently approved thienopyridine, prasugrel, has been shown to achieve a more rapid onset, and higher level of platelet inhibition than clopidogrel. It has been used in ACS patients following angiography in whom PCI is planned at a dose of 60 mg load followed by 10 mg/d for up to 15 months. The TRITON-TIMI 38 trial showed that relative to clopidogrel, prasugrel reduced the risk of cardiovascular death, MI, or stroke significantly by 19%, albeit with an increase in major bleeding. Stent thrombosis was also reduced by 52%. This agent is contraindicated in patients with prior stroke or transient ischemic attack. Ticagrelor is a novel, *reversible* ADP inhibitor that has recently been reported to reduce the risk of cardiovascular death, MI, or stroke by 16% compared with clopidogrel in a broad population of ACS patients. This agent also reduced mortality and did not increase the risk of total bleeding; it is not yet FDA approved at the time of this writing.

Four options are available for anticoagulant therapy to be added to aspirin and clopidogrel. Unfractionated heparin (UFH) is the mainstay of therapy. The low-molecular-weight heparin (LMWH), enoxaparin, has been shown in several studies to be superior to UFH in reducing recurrent cardiac events, especially in conservatively managed patients. The indirect Factor Xa inhibitor, fondaparinux, is equivalent for early efficacy compared with enoxaparin but appears to have a lower risk of major bleeding. Bivalirudin, a direct thrombin inhibitor, is similar in efficacy to either UFH or LMWH among patients treated with a GP IIb/IIIa inhibitor, but use of bivalirudin alone causes less bleeding than the combination of heparin and a GP IIb/IIIa inhibitor in patients with UA/NSTEMI undergoing catheterization and/or PCI.

Prior to the advent of clopidogrel, many trials had shown the benefit of intravenous GP IIb/IIIa inhibitors. The benefit, however, has been small, i.e., only a 9% reduction in death or MI, with a significant increase in major bleeding. Two recent studies also failed to show a benefit for early initiation compared with use only for PCI. The use of these agents may be reserved for unstable patients with recurrent rest pain and ECG changes who undergo PCI.

Excessive bleeding is the most important adverse effect of all antithrombotic agents, including anticoagulants and antiplatelet agents. Therefore, attention must be directed to the doses of antithrombotic agents, accounting for weight, creatinine clearance, and a previous history of excessive bleeding, as a means of reducing the risk of bleeding.

Invasive versus Conservative Strategy

Multiple clinical trials have demonstrated the benefit of an early invasive strategy in high-risk patients, i.e., patients

with multiple clinical risk factors, ST-segment deviation, and/or positive biomarkers **(Table 244-3)**. In this strategy, following treatment with anti-ischemic and antithrombotic agents, coronary arteriography is carried out within ~48 h of admission, followed by coronary revascularization (PCI or coronary artery bypass grafting), depending on the coronary anatomy.

Table 244–3. Class I Recommendations for Use of an Early Invasive Strategy*

Class I (Level of Evidence: A) Indications
Recurrent angina at rest/low-level activity despite Rx
Elevated TnT or TnI
New ST-segment depression
Rec. angina/ischemia with CHF symptoms, rales, MR
Positive stress test
EF < 0.40
Decreased BP
Sustained VT
PCI < 6 months, prior CABG
High-risk score

*Any one of the high-risk indicators.

Abbreviations: BP, blood pressure; CABG, coronary artery bypass grafting; CHF, congestive heart failure; EF, ejection fraction; MR, mitral regurgitation; PCI, percutaneous coronary intervention; Rec, recurrent; TnI, troponin I; TnT, troponin T; VT, ventricular tachycardia.

Source: J Anderson et al: JACO 50:e1, 2007.

In low-risk patients, the outcomes from an invasive strategy are similar to those obtained from a conservative strategy, which consists of anti-ischemic and antithrombotic therapy followed by "watchful waiting," and in which coronary arteriography is carried out only if rest pain or ST-segment changes recur or there is evidence of ischemia on a stress test.

Long-Term Management

The time of hospital discharge is a "teachable moment" for the patient with UA/NSTEMI, when the physician can review and optimize the medical regimen. Risk-factor modification is key, and the caregiver should discuss with the patient the importance of smoking cessation, achieving optimal weight, daily exercise following an appropriate diet, blood-pressure control, tight control of hyperglycemia (for diabetic patients), and lipid management, as recommended for patients with chronic stable angina (Chap. 243).

There is evidence of benefit with long-term therapy with five classes of drugs that are directed at different components of the atherothrombotic process. Beta blockers, statins (at a high dose, e.g., atorvastatin 80 mg/d), and ACE inhibitors or angiotensin receptor blockers are recommended for long-term plaque stabilization. Antiplatelet therapy, now recommended to be the combination of aspirin and clopidogrel (or prasugrel in post PCS patients) for one year, with aspirin continued thereafter, prevents or reduces the severity of any thrombosis that would occur if a plaque were to rupture.

Observational registries have shown that patients with UA/NSTEMI at high risk, including women and the elderly as well as racial minorities, are less likely to receive evidence-based pharmacologic and interventional therapies with resultant poorer clinical outcomes and quality of life.

Prinzmetal's Variant Angina

In 1959 Prinzmetal et al. described a syndrome of severe ischemic pain that occurs at rest but not usually with exertion and is associated with transient ST-segment elevation. This syndrome is due to focal spasm of an epicardial coronary artery, leading to severe myocardial ischemia. The cause of the spasm is not well defined, but it may be related to hypercontractility of vascular smooth muscle due to vasoconstrictor mitogens, leukotrienes, or serotonin.

Clinical and Angiographic Manifestations

Patients with Prinzmetal's variant angina (PVA) are generally younger and have fewer coronary risk factors (with the exception of cigarette smoking) than patients with UA secondary to coronary atherosclerosis. Cardiac examination is usually unremarkable in the absence of ischemia. The clinical diagnosis of variant angina is made with the detection of transient ST-segment *elevation* with rest pain. Many patients also exhibit multiple episodes of asymptomatic ST-segment elevation (*silent ischemia*). Small elevations of troponin may occur in patients with prolonged attacks of variant angina.

Coronary angiography demonstrates transient coronary spasm as the diagnostic hallmark of PVA. Atherosclerotic plaques, which do not usually cause critical obstruction, in at least one proximal coronary artery occur in the majority of patients, and in them spasm usually occurs within 1 cm of the plaque. Focal spasm is most common in the right coronary artery, and it may occur at one or more sites in one artery or in multiple arteries simultaneously. Ergonovine, acetylcholine, other vasoconstrictor medications, and hyperventilation have been used to provoke focal coronary stenosis on angiography to establish the diagnosis. Hyperventilation has also been used to provoke rest angina, ST-segment elevation, and spasm on coronary arteriography.

Treatment: Prinzmetal's Variant Angina

Nitrates and calcium channel blockers are the main agents used to treat acute episodes and to abolish recurrent episodes of PVA. Aspirin may actually increase the severity of ischemic episodes, possibly as a result of the exquisite sensitivity of coronary tone to modest changes in the synthesis of prostacyclin. The response to beta blockers is variable. Coronary revascularization may be helpful in patients who also have discrete, proximal fixed obstructive lesions.

Prognosis

Many patients with PVA pass through an acute, active phase, with frequent episodes of angina and cardiac events during the first 6 months after presentation. Long-term survival at 5 years is excellent (~90–95%). Patients with no or mild fixed coronary obstruction tend to experience a more benign course than do patients with associated severe obstructive lesions. Nonfatal MI occurs in up to 20% of patients by 5 years. Patients with PVA who develop serious arrhythmias during spontaneous episodes of pain are at a higher risk for sudden cardiac death. In most patients who survive an infarction or the initial 3- to 6-month period of frequent episodes, the condition stabilizes, and there is a tendency for symptoms and cardiac events to diminish over time.

Further Readings

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Wiviott SD et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 357:2001, 2007 [PubMed: 17982182]

Algorithm for risk stratification and treatment of patients with suspected coronary artery disease. Using the clinical history of the type of pain and medical history, the ECG, and cardiac markers, one can identify patients who have a low likelihood of UA/NSTEMI, for whom a diagnostic "ruleout myocardial infarction (MI) or acute coronary syndrome (ACS)" is warranted. If this is negative, the patient may be discharged, but if positive, the patient is admitted and treated for UA/NSTEMI. On the other end of the spectrum, patients with acute ongoing pain and ST-segment elevation are treated with percutaneous coronary intervention (PCI) or fibrinolysis (Chap. 245). For those with UA/NSTEMI, risk stratification is used to identify patients at medium to high risk, for whom an early invasive

strategy is warranted. Antithrombotic therapy should include aspirin, an anticoagulant, an ADP antagonist (clopidogrel or prasugrel), with GP IIb/IIIa inhibition considered for use during PCI. For patients at low risk, treatment with aspirin, clopidogrel, an anticoagulant such as unfractionated or low molecular–weight heparin (LMWH) or fondaparinux and anti-ischemic therapy with beta blockers and nitrates, and a conservative strategy are indicated. ASA, aspirin; DM, diabetes mellitus; ECG, electrocardiogram; MI, myocardial infarction; Rx, treatment; STEMI, ST-segment elevation myocardial infarction. (*Adapted from CP Cannon, E Braunwald, in Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 9th ed, R Bonow et al (eds). Philadelphia, Saunders, 2011.*)

The TIMI Risk Score for UA/NSTEMI, a simple but comprehensive clinical risk stratification score to identify increasing risk of death, myocardial infarction, or urgent revascularization to day 14. CAD, coronary artery disease; ASA, aspirin. *(Adapted from Antman et al.)*

Platelets initiate thrombosis at the site of a ruptured plaque with denuded endothelium: *platelet adhesion* occurs via (1) the GP 1b receptor in conjunction with von Willebrand factor. This is followed by *platelet activation* (2), which leads to a shape change of the platelet, degranulation of the alpha and dense granules, and expression of glycoprotein IIb/IIIa receptors on the platelet surface with activation of the receptor, such that it can bind fibrinogen. The final step is *platelet aggregation* (3), in which fibrinogen (or von Willebrand factor) binds to the activated GP IIb/IIIa receptors. Aspirin (ASA) and clopidogrel act to decrease platelet activation, whereas the GP IIb/IIIa inhibitors inhibit the final step of platelet aggregation. GP, glycoprotein. [*Modified from CP Cannon, E Braunwald, in Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed, R Bonow et al (eds). Philadelphia, Saunders, 2008.*]