Over the past 33 years, percutaneous coronary intervention (PCI) has evolved from a somewhat tenuous and experimental procedure to a durable and mainstream therapy, and as a result, the clinical indications for PCI have broadened to include patients with both stable angina pectoris and acute coronary syndrome (ACS).1,2 Acute coronary syndrome refers to the spectrum of clinical signs and symptoms that occur as a result of acute myocardial ischemia, and it is classified as an NSTE-ACS or an ST-segment-elevation ACS (STE-ACS). NSTE-ACS includes patients with unstable angina (UA, negative cardiac biomarkers) or non–ST-segment elevation myocardial infarction (NSTEMI, positive cardiac biomarkers), and STE-ACS includes patients with ST-segment-elevation myocardial infarction (STEMI).3 Over the last 10 years, the incidence rates of STEMI have decreased significantly, and STEMI now makes up less than one third of all MIs in the United States. Thus NSTE-ACS currently accounts for over two-thirds of all acute coronary syndromes. These strategies have been proposed for the management of NSTE-ACS patients, and more recent guidelines and clinical trials increasingly support an invasive strategy for high-risk ACS patients and a less invasive, more conservative strategy for patients deemed to be at lower risk.5

In this chapter, we discuss PCI for patients with NSTE-ACS and focus on the pathophysiology, risk stratification, adjunctive treatment during PCI, early invasive versus ischemia-guided strategy, and the most recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of patients with NSTE-ACS.7

KEY POINTS

- Risk assessment at admission is vitally important and should be repeated during hospitalization.
- Patients presenting with hemodynamic instability, severe left ventricular dysfunction or overt heart failure, recurrent or persistent rest angina despite intensive medical therapy, mechanical complications, and those with significant electrical instability are deemed to be at extremely high risk for death or a complicated myocardial infarction and should undergo urgent coronary angiography.
- Stable patients are managed by one of two strategies: an early invasive strategy and an ischemia-guided strategy.
- An early invasive strategy is recommended for high-risk patients. This includes intensive medical therapy followed by coronary angiography and revascularization as appropriate.
- An ischemia-guided strategy is recommended for low- or intermediate-risk patients. Patients are treated with medical therapy unless they develop refractory or recurrent ischemia or hemodynamic instability.
- When drug-eluting stents are used for revascularization in non–ST-elevation acute coronary syndrome (NSTE-ACS), aspirin should be continued indefinitely. In addition, dual antiplatelet therapy consisting of clopidogrel, prasugrel, or ticagrelor should be continued for 1 year.

BACKGROUND AND RATIONALE FOR PERCUTANEOUS CORONARY INTERVENTION IN PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Coronary atherosclerosis is a chronic disease in which atheromatous material generally evolves silently over time and may eventually result in the development of a high-risk (i.e., vulnerable) plaque (Fig. 19-1).4 Rupture or erosion of this high-risk plaque triggers the formation of intracoronary thrombosis, which can lead to a critical stenosis or occlusion of the coronary artery, as well as associated vasospasm. Although the initial stenosis may evolve silently, healing of a ruptured or eroded plaque may lead to more rapid progression of the stenosis; this may remain clinically silent or may cause angina pectoris. Thus ACS may present with different clinical presentations: UA, NSTEMI, STEMI, and sudden death. All ACS clinical manifestations share a common pathophysiologic pathway—plaque rupture/erosion and some degree of thrombosis and vasospasm—but the duration (i.e., transient or permanent) and severity (i.e., subtotal or total coronary occlusion) are different and are either associated with myocardial necrosis (STEMI and NSTEMI) or no evidence of myocardial necrosis (UA) as manifest by negative cardiac biomarkers. It is important to note that within the first few months after an initial episode of coronary instability, the tendency is strong for repeat instability caused by progression in the severity of the culprit stenosis or by progression of remote lesions.

Although plaque rupture or erosion with associated thrombosis is the most common cause of ACS, it may also be caused by dynamic obstruction (i.e., Prinzmetal’s angina or vasospasm secondary to drug abuse), spontaneous coronary artery dissection (most commonly occurring in peripartum women), severe coronary narrowing without thrombus or spasm (i.e., advanced progressive atherosclerosis or severe restenosis from prior PCI), or a precipitating condition extrinsic to the coronary circulation (i.e., fever, sepsis, tachycardia, hypotension, anemia, hypoxemia, etc.).5 Thus when evaluating individual patients with ACS, it is important to consider the most likely etiology; especially if an invasive strategy is being considered, given that PCI is not necessarily an appropriate therapy for all causes of ACS.

Patients with NSTE-ACS have long-term outcomes similar to patients with STE-ACS and worse than patients with UA.6 NSTE-ACS patients have a similar prognosis to STE-ACS patients likely due to a high prevalence of multivessel disease as well as a higher incidence of recurrent ischemia (35% vs. 23% at 1 year in the Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes [GUSTO-Ill] trial).7 The optimal management of UA or NSTEMI, therefore, is twofold: immediate relief of ischemia and the prevention of progression to acute MI or cardiac death. This can be achieved by a combination of antiischemic, antiplatelet, and anti-thrombotic therapies with or without PCI (see Fig. 19-1).
19-2 SECTION 3 CORONARY INTERVENTION

PATHOPHYSIOLOGY

Asymptomatic atherosclerosis

High-risk/vulnerable plaque

Rupture
Erosion
Platelet aggregation
Thrombosis
Vasoconstriction

Clinically silent

• Stenosis progression
• Stable angina

Acute coronary syndrome

• UA
• NSTEMI
• STEMI
• Sudden death

Thrombosed plaque

Coronary artery disease

TREATMENT

Primary prevention

• Lifestyle
• Aspirin
• Statins

Medical management

• Vasodilators
• Antiplatelet agents
• Antiischemic agents

Revascularization

Critical coronary stenosis or occlusion

Medical management

• Aspirin
• Statins
• Antiplatelet agents
• Antiischemic agents
• Anticoagulation

Long term

• Aspirin
• Statins
• Medical therapy
• Lifestyle modification

Risk Stratification

Although risks of individual patients who present with NSTE-ACS vary widely, several risk scores have been devised to risk-stratify patients, and help identify those who may benefit from an early invasive strategy. The Thrombolysis in Myocardial Infarction (TIMI) risk score, which predicts the risk of 14-day all-cause mortality and new or recurrent MI, is a validated risk-prediction model based on data from the TIMI-IIB and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trials and is the system most commonly used. Seven variables at presentation were independently predictive of outcome (Fig. 19-2):11

1. Age 65 years or older
2. At least two anginal events over the previous 24 hours
3. ST-segment deviation
4. Elevated serum cardiac markers
5. Three or more risk factors for coronary artery disease
6. Aspirin use within the previous week
7. Known history of CAD (stenosis >50%)

The Global Registry of Acute Coronary Events (GRACE) developed a risk calculator for bedside risk estimation of 6-month mortality for patients after hospitalization for ACS.11 The overall 6-month mortality rate was 4.8%, and nine predictive variables were identified (Fig. 19-3, A and B):

1. Older age
2. Previous MI
3. History of heart failure
4. Increased heart rate
5. Lower systolic blood pressure

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Incidence death/MI (%)</th>
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<tr>
<td>0/1</td>
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<td>6/7</td>
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</table>

FIGURE 19-1 Physiopathologic mechanisms underlying acute coronary syndromes. ACE, Angiotensin-converting enzyme; CABG, coronary artery bypass grafting; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; UA, unstable angina.

FIGURE 19-2 The Thrombolysis in Myocardial Infarction (TIMI) risk score for death or myocardial infarction (MI) at 14 days, derived by assigning a value of 0 when a factor is absent and 1 when a factor is present. CAD, Coronary artery disease.
1. Age
   Years
   30–39 .............. 0
   40–49 ............. 18
   50–59 ............. 36
   60–69 ............. 55
   70–79 ............. 73
   80–89 ............. 91
   ≥90 ............... 100

2. History of congestive heart failure ........... 24

3. History of myocardial infarction .......... 12

4. Resting heart rate
   Beats/min
   50–70 ......................... 3
   70–90 ......................... 9
   90–110 ..................... 14
   110–150 ................. 23
   150–200 ................. 35
   ≥200 ...................... 43

5. Systolic blood pressure
   mm Hg
   ≤79.9 ......................... 24
   80–99.9 ..................... 22
   100–120 .................. 18
   120–140 ................. 14
   140–160 ................. 10
   160–200 .................. 4
   ≥200 ...................... 0

6. ST-segment depression

7. Initial serum creatinine
   mg/dL
   0–0.39 ..................... 1
   0.4–0.79 .................. 3
   0.8–1.19 ................. 5
   1.2–1.59 ............... 7
   1.6–1.99 ............... 9
   2.3–3.99 ............... 15
   ≥4 ..................... 20

8. Elevated cardiac enzymes ............... 15

9. No in-hospital percutaneous coronary intervention ....... 14

A limitation of the use of the TIMI risk score in identifying patients at higher risk who present with NSTE-ACS is that some patients may initially present with negative cardiac biomarkers, only to demonstrate elevation in these markers 12 hours later. Of 1342 patients who were enrolled in the TIMI-IIIB trial, 200 (14.9%) were troponin negative at baseline but developed an elevated troponin I level (≥0.4 ng/mL) at 12 hours. Six independent predictors were identified (Table 19-1), and a score was derived to identify patients with the highest likelihood to become troponin positive later during hospital admission (Fig. 19-4). The derived score was tested in 855 patients in the GUSTO IIA study and similarly predicted a late rise in troponin T levels. This score, therefore, may be useful to further assist in risk stratification of patients who present with NSTE-ACS and initially unremarkable troponin levels.

PREDICTING A LATE POSITIVE SERUM TROPOinin LEVEL IN INITIALLY TROPOinin-NEGATIVE PATIENTS WITH NON-ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

A limitation of the use of the TIMI risk score in identifying patients at higher risk who present with NSTE-ACS is that some patients may initially present with negative cardiac biomarkers, only to demonstrate elevation in these markers 12 hours later. Of 1342 patients who were enrolled in the TIMI-IIIB trial, 200 (14.9%) were troponin negative at baseline but developed an elevated troponin I level (≥0.4 ng/mL) at 12 hours. Six independent predictors were identified (Table 19-1), and a score was derived to identify patients with the highest likelihood to become troponin positive later during hospital admission (Fig. 19-4). The derived score was tested in 855 patients in the GUSTO IIA study and similarly predicted a late rise in troponin T levels. This score, therefore, may be useful to further assist in risk stratification of patients who present with NSTE-ACS and initially unremarkable troponin levels.

ADJUNCTIVE TREATMENT DURING PERCUTANEOUS CORONARY INTERVENTION FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

Antiplatelet Treatment

Aspirin

The activation and aggregation of platelets after the rupture of a vulnerable plaque are key components in the pathophysiology of ACS. Aspirin inhibits the cyclooxygenase (COX) pathway in platelets and in the
Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial enrolled 12,562 patients and demonstrated a 20% reduction in cardiovascular death, MI, and stroke. A subset of this population that underwent PCI was studied in the PCI-CURE trial, and this showed that pretreatment with clopidogrel for a median of 6 days before PCI was associated with a 31% reduction in cardiovascular death or MI. A loading dose of 600 mg achieves maximal antiplatelet inhibition faster than 150 mg or 300 mg and has lasting benefit of up to 30 days in low-to intermediate-risk patients undergoing elective PCI. In higher-risk patients, use of glycoprotein (GP) IIb/IIIa inhibitors may have an added benefit.

An important consideration for the use of clopidogrel in ACS patients is the substantial variability in individual patient response to clopidogrel. Multiple potential hypotheses have been proposed to explain this “clopidogrel resistance,” such as differences in clopidogrel dosage, intestinal absorption problems, and varying availability and clearance of the active metabolite. Genetic factors such as polymorphisms of the hepatic CYP pathway, which is responsible for metabolizing clopidogrel’s produg into an active metabolite, are becoming increasingly well understood, and at least three major genetic polymorphisms of the CYP2C19 isoenzyme—CYP2C19*1, CYP2C19*2, and CYP2C19*3—have been attributed with loss of function and diminished responsiveness to clopidogrel. However, considerable debate persists regarding management strategies for clopidogrel resistance. Though platelet function testing is available to direct individual patient care, genetic testing thus far has not been shown to improve clinical outcomes in patients with clopidogrel resistance.

The Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial randomized patients with clopidogrel resistance to high-dose versus standard-dose clopidogrel but found no differences in cardiovascular outcomes between the two groups. The Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety (GRAVITAS) trial26 randomized patients taking aspirin and clopidogrel to omeprazole or placebo. Although this trial found no clinical difference in cardiovascular outcomes between patients taking aspirin and those taking placebo, the U.S. Food and Drug Administration (FDA) has nevertheless issued a warning against the concomitant use of clopidogrel with the PPIs esomeprazole and omeprazole.

**Prasugrel**

Prasugrel is a second-generation irreversible P2Y12 inhibitor that is more potent and more consistent with respect to platelet inhibition. The Trial to Assess Improvement in Therapeutic Outcomes By Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON–TIMI 38) trial evaluated 13,608 patients with moderate- to high-risk ACS (NSTE-ACS and STE-ACS) after randomly receiving either prasugrel or clopidogrel during PCI. In this study, prasugrel significantly reduced the composite end point of cardiovascular death, nonfatal MI, or nonfatal stroke by 19% compared with clopidogrel (Fig. 19-5). A subgroup analysis showed that prasugrel was associated with a 24% reduction in MI, a 34% reduction in the need for urgent revascularization, and a 52% reduction in stent thrombosis. These benefits, however, were also associated with a 0.5% absolute increase in non–coronary artery bypass graft surgery (CABG)–related TIMI major bleeding and a 0.3% absolute increase in fatal bleeding. A landmark analysis of this trial revealed that patients with a previous transient ischemic attack (TIA) or stroke, those who were 75 years of age or older, or those who weighed less than 60 kg were at especially high risk of bleeding. These patient subgroups are therefore relatively contraindicated for treatment with prasugrel.

In the setting of NSTE-ACS, prasugrel can be given at the time of PCI but should not be given upstream of PCI. In a Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients With Non–ST-Elevation

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**FIGURE 19-4** The TIMI-IIIb score used to identify patients who become troponin-positive later during hospital admission. MI, Myocardial infarction; PCI, percutaneous coronary intervention.

*Endothelium*, which prevents thromboxane A2 (TXA2) production and therefore inhibits platelet aggregation. Because COX-1 inhibition is irreversible, the antiplatelet effects of aspirin last through the entire lifetime of the platelets (7 to 10 days). Multiple studies have shown the benefit of aspirin therapy in CAD with reduction in angina, death, and MI by 30%. In the setting of NSTE-ACS, the ACC/AHA guidelines recommend an initial loading dose of at least 162 mg in order to achieve an immediate clinical antithrombotic effect; thereafter a maintenance dose of 81 mg aspirin daily is sufficient for cardioprotection. Higher doses of aspirin have not been shown to have added cardiovascular benefit and are associated with higher risks of bleeding.

The Seventh Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-7) trial randomized 25,086 patients with ACS undergoing an early invasive strategy (70.8% with UA/NSTE-ACS) to low-dose (75 to 100 mg) versus high-dose (300 to 325 mg) aspirin and found no significant difference in cardiovascular death, MI, or stroke at 30 days. In OASIS-7, no significant difference in bleeding was reported with higher doses of aspirin; however, an analysis of 192,036 patients in 31 clinical trials showed that higher doses of aspirin (>200 mg) were associated with substantially higher rates of major, minor, and gastrointestinal bleeding. Although aspirin is certainly an important pharmacologic therapy in ACS patients, it does not prevent all thrombotic events.

**Thienopyridines**

Thienopyridines—such as ticlopidine, clopidogrel, and prasugrel—exert their antiplatelet effects by irreversibly blocking the P2Y12 receptor and its associated signaling pathway, thereby inhibiting platelet activation for the entire lifespan of the platelet. Thienopyridines are administered as an initial loading dose followed by a maintenance dose because they take several hours to exhibit their irreversible antiplatelet effect. It is important to note that their mechanism of action is entirely independent of and complementary to that of aspirin, and the combination of aspirin and a thienopyridine is superior to the use of aspirin alone.

**Clopidogrel**

Clopidogrel is the most widely studied of the thienopyridine class. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPR) trial studied 19,185 patients with atherosclerotic vascular disease and revealed a 9% relative risk reduction in vascular death, MI, or ischemic stroke without a significant increase in bleeding. The
Myocardial Infarction (ACCOAST), upstream therapy with prasugrel increased bleeding complications but did not improve cardiovascular outcomes.32

Ticagrelor

Ticagrelor is the newest P2Y12 inhibitor on the market, and it has several distinct characteristics compared with previous P2Y12 inhibitors. First, it is a non-thienopyridine, a cyclopentyltriazolopyrimidine that is a noncompetitive inhibitor of the P2Y12 receptor.33 Second, it is a reversible platelet inhibitor with a short half-life of 7.2 hours and therefore requires twice-daily dosing. Ticagrelor was compared with clopidogrel in the Study of Platelet Inhibition and Platelet Outcomes (PLATO),34 which randomized 18,624 patients with ACS to either ticagrelor or clopidogrel. Of these, 11,598 had UA/NSTE-ACS. The primary end point was a composite of cardiovascular death, MI, or stroke. Ticagrelor was found to have a 1.9% absolute reduction and 16% relative reduction in the primary end point (9.8% vs. 11.7%). The absolute risk reduction of cardiovascular mortality for ticagrelor was 1.1%. Subgroup analysis showed that the significant reduction in the primary end point held true for NSTE-ACS patients but not among UA patients. Rates of all-cause major bleeding were similar between groups, but non-CABG-related TIMI major bleeding was significantly higher with ticagrelor. This multicenter study was notable for significant geographic variances in outcome; surprisingly, patients in North America randomized to ticagrelor were not found to have the same benefit. Compared with clopidogrel, no significant difference was found in the primary end point. Subsequent analyses attributed this variation to a dose-related aspirin effect on ticagrelor, because patients in North America were found to be taking significantly higher maintenance doses of aspirin (>300 mg) during the study. Doses of aspirin greater than 100 mg may attenuate the effects of ticagrelor; for this reason, patients receiving ticagrelor should only take low-dose aspirin (81 mg daily).

Dual-antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (clopidogrel or ticagrelor) is considered standard pretreatment of patients with NSTE-ACS undergoing PCI with or without stent implantation (ACC/AHA guidelines class IIB recommendation, level of evidence [LOE] A).32 The preference for ticagrelor instead of clopidogrel is a class Ila recommendation.3 However, the optimal timing for initiation of a P2Y12 inhibitor may still pose a dilemma in actual clinical practice. The frequency of adverse cardiac events is reduced within the first hours of treatment with a P2Y12 inhibitor, but if the patient is referred for urgent or emergent surgery, this approach may be associated with more perioperative blood loss.34 However, given the fact that CABG is less likely to be necessary in the contemporary stent era even for high-risk NSTE-ACS patients, early P2Y12 inhibition is recommended unless urgent CABG is deemed to be very likely.

Anticoagulant Treatment

Heparin

Since the beginning of PCI, unfractionated heparin (UFH) has been given to prevent thrombosis during intracoronary instrumentation and to minimize thrombosis at the site of the plaque, which is damaged by balloon angioplasty and/or stent implantation. Treatment with UFH in addition to aspirin usually is given based on the data from a meta-analysis that demonstrated a reduction of the combined death and MI rate of 7.9% for those treated with UFH compared with 10.3% for those treated with aspirin alone.35 UFH is given as an initial intravenous (IV) bolus of 60 IU/kg followed by a 12 IU/kg/h infusion, and guided by an activated clotting time (ACT) in the range of 250 to 300 seconds. If combined with a GP IIb/IIIa inhibitor, the dose of UFH should be lower: an initial IV bolus of 50 to 60 IU/kg and ACT in the range of 200 to 250 seconds to prevent excessive bleeding complications.

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) has also been used in the setting of PCI for NSTE-ACS. In the Fast Revascularization During Instability in Coronary Artery Disease (FRISC) trial,36 1506 patients were randomly assigned to receive dalteparin (120 IU/kg twice daily, with a maximal dose of 10,000 IU) or UFH during the first 5 to 7 days of hospitalization followed by dalteparin (7500 IU subcutaneously, daily) or placebo for 35 to 45 days. Dalteparin was associated with a 6.5% relative risk reduction in death or MI during the first 6 days (1.8% in the treatment group vs. 4.8% in the placebo group), with persistence of these differences at 40 days. The ESSENCE trial37 evaluated 3171 UA/NSTE-ACS patients who were randomly assigned to receive enoxaparin (1 mg/kg subcutaneously [SC] twice daily) or continuous infusion of UFH (minimum of 48 hours to a maximum of 8 days). The dose of enoxaparin should be reduced to 1 mg/kg SC daily in patients with a creatinine clearance (CrCl) < 30 mL/min. The risk of recurrent angina, MI, or death was significantly lower in the enoxaparin patients than in the UFH patients at 14 days (16.6% vs. 19.8%). The benefit persisted at 30 days, but at the cost of increased minor bleeding with no significant difference in major bleeding (6.5% vs. 7%).38

The TIMI-IIB trial39 randomized 3910 patients with UA/NSTE-ACS to receive either enoxaparin or UFH for 3 to 8 days while hospitalized followed by either enoxaparin or placebo through day 43 as an outpatient. At 8 days, a 14.6% risk reduction in the composite end point of MI, death, and need for urgent revascularization was noted, and at 43 days, a 12.3% risk reduction in the same end point was reported. Bleeding was similar in both groups during initial hospitalization, but the risk of major bleeding during the outpatient phase of the study was doubled in the enoxaparin group compared with placebo. These data suggest that enoxaparin may be more effective than UFH at reducing the risk of ischemic events during the acute management of NSTE-ACS patients without an important increase in major bleeding events. A meta analysis of nearly 22,000 patients with UA/NSTE-ACS enrolled in six randomized trials reported a relative risk reduction of 9% in the composite end point of death or MI at 30 days for patients treated with enoxaparin compared with those treated with UFH and found no significant difference in major bleeding at 7 days.40 These results demonstrate that use of enoxaparin was beneficial when an ischemia-guided strategy was utilized for patient management.

More recent trials have compared UFH and enoxaparin when an early invasive strategy is implemented. The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial41 studied 10,027 patients with high-risk

![Figure 19-5](image-url)
UA/NSTE-ACS who were treated using an early invasive strategy. In this study, no significant difference was found in the primary end point of all-cause mortality or nonfatal MI at 30 days, but patients who received enoxaparin exhibited a 20% increase in TIMI major bleeding in association with invasive procedures, especially CABG. When considered as a whole, the data presented above support the notion that treatment with enoxaparin, compared with UFH, appears to be more efficacious at reducing ischemic events in UA/NSTE-ACS patients who are treated with an ischemia-guided strategy. However, interpretation of data from the SYNERGY trial, as well as from other trials (such as the Aggrastat to Zocor [A-to-Z] trial), comparing UFH and enoxaparin in UA/NSTE-ACS patients treated with an early invasive strategy, must be interpreted carefully because many of the patients in these trials had already received other antithrombotic agents before being randomized to a given treatment arm. Thus the high rate of patient crossover is an important confounding factor. The most recent ACC/AHA guidelines consider enoxaparin to be a reliable alternative to UFH for patients treated both with an early invasive and an ischemia-guided strategy (class I, LOE A).

**Bivalirudin**

Bivalirudin is a direct thrombin inhibitor and a synthetic analogue of hirudin that reversibly binds thrombin and inhibits clot-bound thrombin. The Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2 (REPLACE-2) trial demonstrated that bivalirudin could be used as an alternative to UFH plus GP IIb/IIIa blockade in low-risk patients who undergo PCI. The efficacy of bivalirudin was further evaluated in the Acute Catheterization and Urgent Intervention Triage Strategy (ACUTY) trial. It randomized 13,800 patients with moderate- to high-risk UA/NSTE-ACS undergoing an invasive strategy into three treatment groups: group I received UFH or enoxaparin plus GP IIb/IIIa inhibitor, group II received bivalirudin plus GP IIb/IIIa inhibitor, and group III received bivalirudin alone. The primary end point at 30 days was a net clinical outcome based on an ischemic composite (i.e., death from any cause, MI, or unplanned revascularization for ischemia) or major bleeding. The net outcome was lower with the bivalirudin-alone strategy, which could be ascribed to a significant reduction in major bleeding in the bivalirudin group (Table 19-2).

**Fondaparinux**

Fondaparinux is a synthetic polysaccharide that leads to indirect inhibition of activated factor X (FXa), and it was evaluated in the Fifth Organization to Assess Strategies for Ischemic Syndromes (OASIS-5) trial. In this study 20,078 patients were randomized to treatment with either fondaparinux (2.5 mg/day) or enoxaparin (1 mg/kg twice daily) for a mean of 6 days. Approximately 40% of patients underwent PCI and 15% underwent CABG in both groups. Fondaparinux was equivalent to enoxaparin in terms of the primary efficacy end point at 9 days—composite of death, MI, or refractory ischemia—and major bleeding at 9 days was significantly lower with fondaparinux than with enoxaparin (2.2% vs. 4.1%; P < .001). However, fondaparinux was associated with an increased rate of guide catheter thrombosis; therefore it should be administered concurrently with an additional anticoagulant that has anti-IIa activity.

**Glycoprotein IIb/IIIa Inhibitors**

The final common pathway of platelet activation and aggregation is mediated by a conformational change in the GP IIb/IIIa receptor from an inactive to an active state. GP IIb/IIIa inhibitors interfere with the ability of the GP IIb/IIIa receptor to bind with target ligands, and thus they are potent inhibitors of platelet aggregation. All three currently used GP IIb/IIIa inhibitors—abciximab, eptifibatide, and tirofiban—exhibit different pharmacodynamic and pharmacokinetic properties, different clinical trial outcomes, and as a result have different recommendations for clinical use.

**Abciximab**

Abciximab (formerly c7E3) was the first of the three currently used GP IIb/IIIa inhibitors to be subjected to large-scale clinical trial testing and was first evaluated in the present era of the early 1990s. The Evaluation of abciximab for the Prevention of Ischemic Complications (EPIC) trial studied high-risk patients with UA, evolving MI, or complex coronary lesion anatomy and showed a 35% reduction in the composite end point of death, MI, or recurrent ischemia compared with placebo. The C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial studied 1265 patients with UA who underwent PCI. In this study, a 30% relative reduction in the primary end point of all-cause mortality, MI, or recurrent ischemia requiring urgent revascularization was reported at 30 days. The rate of MI was noted to be lower before, during, and after PCI in patients treated with abciximab, and a subgroup analysis revealed that abciximab facilitated thrombus resolution and prevented recurrent ischemia. Abciximab therefore has clearly been shown to be efficacious in the setting of UA/NSTE-ACS patients undergoing PCI. The Global Use of Strategies to Open Occluded Coronary Arteries—IV–Acute Coronary Syndromes (GUSTO-IV–ACS) trial, however, studied 7800 patients with UA/NSTE-ACS who were not scheduled to undergo an early invasive strategy. Patients in this study were randomized to receive an abciximab bolus followed by infusion for either 24 or 48 hours or placebo. In this trial abciximab provided no benefit as it relates to the primary composite end point of death or MI at 30 days, even in a subgroup of patients with elevated troponin levels. The current ACC/AHA guidelines reflect these results; abciximab is not recommended for the treatment of patients with UA/NSTE-ACS for whom an ischemia-guided strategy is planned.

**Tirofiban**

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial, in which 3322 patients with UA were randomized to receive either UFH or tirofiban for 48 hours. A 32% reduction in the rate of death, MI, or refractory ischemia was noted at 48 hours, but no significant difference was noted at 30 days. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial randomized UA and NSTE-ACS patients to receive aspirin plus either heparin, tirofiban, or both. The tirofiban-only arm was stopped early because of excess death at 7 days (4.6% vs. 1.1% in the heparin-only arm). Patients who received both heparin and tirofiban exhibited

### Table 19-2 ACUTY Trial Results

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<th>End Point (30 Days)</th>
<th>UFH/Enox + GPI (n = 4603)</th>
<th>Bivalirudin + GPI (n = 4604)</th>
<th>Bivalirudin Alone (n = 4612)</th>
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<tr>
<td>Major bleeding (%)</td>
<td>5.7</td>
<td>5.3</td>
<td>3.0</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

the greatest benefit in terms of a reduction in the composite end point at 7 days of death, MI, or refractory ischemia. This benefit was sustained at 30 days and at 6 months (27.2% vs. 32% in the heparin-only arm).

**Eptifibatide**

Eptifibatide was studied in 9461 patients with NSTE-ACS in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. In this study, treatment with eptifibatide was associated with a 10% reduction in the relative risk of death and MI at 30 days. A meta-analysis confirmed the utility of GP IIb/IIIa inhibitors in the management of patients with moderate to high-risk UA/NSTE-ACS. This analysis pooled 31,402 patients from six different GP IIb/IIIa trials involving ACS patients and showed a 9% reduction in the odds ratio of death or MI for patients treated with a GP IIb/IIIa inhibitor compared with those who received a placebo. Subgroup analysis revealed a significant benefit in the treatment of patients with moderate to high-risk UA/NSTE-ACS. This analysis showed a 9% reduction in the odds ratio of death or MI, recurrent ischemia requiring urgent revascularization, or MI for troponin-positive patients and showed no such reduction in troponin-negative patients. Reduction in the odds ratio of death or MI was also noted to be greater in patients who underwent PCI within 5 days. The Do Tirofiban and Reopro Give Similar Efficacy Outcomes Trial (TARGET) was a direct comparison between abciximab and tirofiban. It demonstrated that the primary end point—a composite of death, nonfatal MI, or urgent revascularization at 30 days—was significantly higher in the tirofiban group compared with those receiving abciximab (7.6% vs. 6.0%), but at 6 months, this difference was no longer statistically significant.

Most recently, the Early Versus Delayed Provisional Eptifibatide in Acute Coronary Syndromes (EARLY-ACS) trial compared early routine versus delayed provisional administration of eptifibatide in 9492 patients with NSTE-ACS who were randomly assigned to an invasive strategy. The primary end point was the composite of death, MI, recurrent ischemia requiring urgent revascularization, or thrombotic bailout at 96 hours. No difference in the primary end point was observed between the two groups at 96 hours; however, use of early routine PCI was associated with higher rates of non-life-threatening bleeding and transfusions.

With the multitude of antplatelet therapies being administered to ACS patients, some had concerns that the efficacy of GP IIb/IIIa inhibitors might be reduced in patients pretreated with clopidogrel. The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR–REACT-2) trial addressed this issue. ISAR–REACT-2 was a randomized, double-blind trial that compared treatment with abciximab (n = 1012) or placebo (n = 1010) in patients with NSTE-ACS who were treated with a 600-mg loading dose of clopidogrel. The primary end point was a composite of death, MI, recurrent ischemia requiring urgent revascularization, or MI at 30 days. The reduction in the primary end point was significant in favor of abciximab in all patients with NSTE-ACS (8.9% vs. 11.9%), and this was achieved with no difference in TIMI-defined major bleeding (Fig. 19-6). As seen in several other trials, abciximab was highly effective in high-risk NSTE-ACS patients (i.e., troponin-positive patients) but was not effective in troponin-negative patients.

Despite the demonstrated advantages of GP IIb/IIIa inhibitors in the treatment of patients with UA/NSTE-ACS undergoing PCI, most of these studies were done before the benefits of clopidogrel were clearly established. The optimal timing of GP IIb/IIIa initiation is therefore still being clarified. Early routine use of GP IIb/IIIa inhibitors has been associated with a significantly higher risk of major bleeding. Contemporary trials are therefore needed to define the role and timing of GP IIb/IIIa inhibitors in NSTE-ACS and to assess whether the benefits of triple-antiplatelet therapy outweigh the risks of bleeding in this setting. Several trials are currently ongoing that will help address this question. The most recent ACC/AHA guidelines recommend the use of GP IIb/IIIa inhibitors in patients with NSTE-ACS and high-risk features such as an elevated troponin. It is a class I recommendation in patients not adequately pretreated with clopidogrel or ticagrelor and a class IIa recommendation in patients who have been pretreated.

ACS patients who present with hemodynamic instability, severe left ventricular dysfunction or overt heart failure, recurrent or persistent rest angina despite intensive medical therapy, mechanical complications (e.g., acute mitral regurgitation and ventricular septal defect), or sustained ventricular tachycardia are at extremely high risk for death or a complicated MI. For this reason, unless they have been deemed inappropriate for revascularization, these patients should undergo urgent coronary angiography. For the management of other less overtly ill patients who present with NSTE-ACS, two strategies have emerged: an ischemia-guided strategy (previously called an initial conservative strategy) and an early invasive strategy. The ischemia-guided strategy entails the use of intensive medical therapy, which includes aspirin, antiplatelet therapy (clopidogrel, ticagrelor), anticoagulation (UFH, LMWH, or fondaparinux), beta-blockers, statins, and/or nitroglycerin (if not contraindicated; Fig. 19-7). Patients who become asymptomatic on this regimen are typically observed for 48 to 72 hours and then undergo cardiac stress testing, usually with some form of myocardial imaging (nuclear imaging or echocardiography). Patients who manifest signs or symptoms of ongoing ischemia at any time during observation or who demonstrate high- or intermediate-risk findings on stress testing are then referred for coronary angiography and subsequent revascularization as appropriate. Patients with low-risk stress test findings are treated medically with aspirin indefinitely, clopidogrel or ticagrelor for up to 12 months, statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors. Prior to coronary angiography and revascularization, patients managed with an early invasive strategy are also treated with intensive medical therapy that includes aspirin, anticoagulation (UFH, LMWH, bivalirudin, or fondaparinux), and a P2Y12 inhibitor. GP IIb/IIIa inhibitors can be considered if high-risk features are present.

Initial studies—TIMI IIIB, Veterans Affairs Non-Q-Wave Myocardial Infarction Strategies In Hospital (VANQWISH), and Medicine Versus Angiography in Thrombolysis Exclusion (MATE)—did not show superiority for either an early invasive or an ischemia-guided strategy. However, these trials were done before the advent of stents, adjunctive anticoagulation, and antiplatelet therapy, which have all significantly improved PCI outcomes. Five important randomized trials have been done in the contemporary PCI era: Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II); Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction (TACTICS–TIMI 18); Value of First-Day Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction (VIANO); and Randomized Intervention Trial of Unstable Angina 3
(RITA-3)\textsuperscript{61}, and Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS).\textsuperscript{62}

With an early invasive strategy, early revascularization (in-hospital) was achieved in 44% to 76% of patients (Fig. 19-8). Even with an ischemia-guided strategy, the need to cross over with early revascularization ranged from 9% to 40%. The contrast in the frequencies of early revascularization between the early invasive and ischemia-guided strategies varied from as low as 24% (TACTICS-TIMI 18) to as high as 62% (FRISC-II). Revascularization after hospital discharge was predominantly performed in the patients randomized to an early conservative strategy. The primary end point of these trials was defined as a composite of death and MI with or without rehospitalization. All trials with the exception of RITA-3 and ICTUS found a statistically significant advantage with an early invasive strategy (Table 19-3). The in-hospital mortality rates are shown in Figure 19-9. The mortality rates at the end of follow-up are presented in Figure 19-10. The RITA-3 trial reported the outcome at a median follow-up of 5 years (Table 19-4).\textsuperscript{61} At 1 year, the death and nonfatal MI rates were not different between the early invasive strategy and the conservative strategy, but at 5 years, there was a significant difference in favor of the early invasive strategy (Fig. 19-11).

**Optimal Timing of Intervention**

In patients with NSTE-ACS who are undergoing an early invasive strategy, the optimal timing of intervention has not yet been defined.\textsuperscript{63} During an NSTE-ACS, early or immediate revascularization of the culprit lesion may decrease the time for recurrent ischemic events. On the other hand, allowing these patients to be treated first with aggressive antithrombotic therapy prior to angiography may help stabilize the lesion and may thereby reduce periprocedural complications during revascularization. The Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) study\textsuperscript{64} investigated whether the outcomes of early catheterization and later catheterization were different. A total of 56,352 patients were treated at 310 U.S. hospitals and were entered into the CRUSADE registry. The patients were retrospectively classified as having very early (23.4-hr) or later (46.3-hr) catheterization. The in-hospital adverse cardiac events that occurred in the two groups are presented in Table 19-5. No difference was found between the two groups, but the investigators warned cautiously that they could not exclude an important risk reduction, particularly for early catheterization within 12 hours of presentation.

**TABLE 19-3 Early Invasive Versus Conservative Strategies in Five Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary End Point</th>
<th>Early Invasive</th>
<th>Conservative</th>
<th>RR or OR</th>
<th>CI 95%, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRISC-II\textsuperscript{58}</td>
<td>Death/MI at 1 yr</td>
<td>10.4%</td>
<td>14.1%</td>
<td>RR = 0.74</td>
<td>0.60 to 0.92, P = .005</td>
</tr>
<tr>
<td>TACTICS\textsuperscript{59}</td>
<td>Death/MI/rehosp. for ACS at 6 mo</td>
<td>15.9%</td>
<td>19.4%</td>
<td>OR = 0.78</td>
<td>0.62 to 0.97, P = .025</td>
</tr>
<tr>
<td>VINO\textsuperscript{60}</td>
<td>Death/MI at 6 mo</td>
<td>6.2%</td>
<td>22.3%</td>
<td></td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>RITA-3\textsuperscript{61}</td>
<td>Death/MI at 1 yr</td>
<td>7.6%</td>
<td>8.3%</td>
<td>RR = 0.91</td>
<td>0.67 to 1.25, P = .58</td>
</tr>
<tr>
<td>ICTUS\textsuperscript{62}</td>
<td>Death/MI/rehosp. &lt;1 yr</td>
<td>22.7%</td>
<td>21.2%</td>
<td>RR = 1.07</td>
<td>0.87 to 1.33, P = .53</td>
</tr>
</tbody>
</table>

ACS, Acute coronary syndrome; CI, confidence interval; FRISC-II, Fast Revascularization During Instability of Coronary Artery Disease; ICTUS, Invasive Versus Conservative Treatment in Unstable Coronary Syndromes; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; TACTICS, Treat Angina With Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy; VINO, Value of First-Day Angiography/Angioplasty in Evolving Non–ST-Segment Elevation Myocardial Infarction: An Open Multicenter Randomized Trial.
TABLE 19-4 RITA-3 Trial Outcomes at a Median Follow-up of 5 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Early Intervention (n = 895)</th>
<th>Conservative Strategy (n = 915)</th>
<th>RR, 95% CI, and P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year death/MI</td>
<td>11.2%</td>
<td>16.9%</td>
<td>0.64 (0.56 to 0.72), P = 0.04</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>7.3%</td>
<td>10.6%</td>
<td>0.69 (0.59 to 0.80), P = 0.02</td>
</tr>
<tr>
<td>Cardiovascular death of MI</td>
<td>12.2%</td>
<td></td>
<td>0.74 (0.65 to 0.87), P = 0.03</td>
</tr>
</tbody>
</table>


This issue was addressed in the Intracoronary Stenting With Anti-thrombotic Regimen Cooling-Off (ISAR-COOL) trial, which randomized 410 patients who had symptoms of UA plus ST-segment depression or elevated cardiac troponin T levels. Patients were randomized to antithrombotic pretreatment for 3 to 5 days (the cooling-off strategy) or very early intervention after pretreatment for less than 6 hours. Antithrombotic pretreatment consisted of heparin, aspirin, clopidogrel, and tirofiban. The outcome is presented in Table 19-6. The reduction was significant in the combined death and MI rate in favor of the very early intervention strategy. This favorable outcome was predominantly attributable to adverse events occurring before catheterization.

The Early or Late Intervention in Unstable Angina (ELISA) pilot study investigated whether pretreatment with a GP IIb/IIIa inhibitor, tirofiban, was beneficial compared with no pretreatment. A total of 229 patients with NSTE-ACS were randomized to an early strategy (i.e., early angiography without tirofiban pretreatment) or to a late strategy (i.e., delayed angiography after pretreatment with tirofiban). The primary end point was enzymatic infarct size (LDH48) as assessed by the area under the lactate dehydrogenase release curve up to 48 hours after symptom onset (LDH48). The infarct size and clinical outcome at 30 days are presented (Table 19-7). The study showed that delayed angiography with pretreatment with tirofiban was associated with a smaller enzymatic infarct size. No differences in clinical outcome were reported at 30 days.

The CRUSADE quality improvement initiative investigated the use of an early invasive management within 48 hours in 17,926 high-risk NSTEMI patients (Table 19-8). A total of 8037 patients (44.8%) underwent early cardiac catheterization, and of these, 75% were revascularized: 4733 (58.9%) underwent PCI, and 1296 (16.1%) underwent CABG. The unadjusted incidence of in-hospital mortality and postmission MI was significantly lower for patients who underwent early invasive management than for those who did not, and patients who underwent early invasive management were younger and had less comorbidity (Table 19-7). The adjusted risks for death and MI were therefore lower for patients who underwent early invasive management, and in a propensity-matched pair analysis, the mortality rate remained lower for patients who underwent early invasive management (2.5% vs. 3.7%, P = 0.01).

The Optimal Timing of Coronary Angiography and Potential Intervention in Non–ST-Elevation Acute Coronary Syndromes (OPTIMA) trial randomized patients with NSTE-ACS undergoing PCI to either immediate PCI or PCI within 24 to 48 hours. Medical therapy was the
same for both groups and consisted of triple-antplatelet therapy with aspirin, clopidogrel, and a GP IIb/IIIa inhibitor. The primary end point was a composite of death, nonfatal MI, and revascularization at 30 days. This small study (n = 142) was terminated early because of poor enrollment. However, it demonstrated that the primary end point was significantly higher in the immediate PCI group, and this was driven by significantly higher rates of MI in the immediate PCI group.

In a similar fashion, the Angioplasty to Blunt the Rise of Troponin (ABOARD) trial 69 randomly assigned 352 patients with high-risk NSTE-ACS (TIMI risk >3) to receive immediate versus delayed coronary angiography (between 8 and 60 hr post randomization). Over 96% of patients received aspirin and clopidogrel; GP IIb/IIIa inhibition was used in 65% in the immediate intervention group, compared to 57% in the delayed intervention group. In this study, the difference was not significant either in the primary outcome of peak hospital troponin I value or the secondary combined outcome of death, MI, or urgent revascularization at 1 month.

The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial 76 was a larger study that randomized 3031 patients with NSTE-ACS to early PCI (within 24 hr) or delayed PCI (at least 36 hr). In this trial, aspirin and clopidogrel was used in over 85% of patients, and GP IIb/IIIa inhibitors were used in 23% of patients. The primary end point was a composite of death, MI, and stroke at 6 months. In this trial, no significant difference was found between the two groups. However, when stratified by risk according to the GRACE score, the highest risk patients in the trial (highest tertile, GRACE risk score >140) did have a substantial and significant reduction in the primary end point with an early intervention strategy (13.9% vs. 21.0%, HR 0.65, P = .006). This difference was not seen in patients in the lower two risk tertiles (Table 19-9, Fig. 19-12).

The secondary end point of the TIMACS trial was a composite of death, MI, and refractory ischemia, and here there was significant benefit in early intervention across the entire study population, including in low-risk patients (9.5% vs. 12.9%, P = .003). A 28% relative reduction in the secondary end point in the early intervention group was driven mainly by a significant reduction in refractory ischemia (1.0% vs. 3.3% in the early vs. delayed groups, P <.001; Table 19-10).77

### Patients Who Derive Benefit from an Early Invasive Strategy

Patients with elevated troponin levels (data from FRISC-II and TACTICS–TIMI 18), ST-segment depression (data from FRISC-II, TACTICS–TIMI 18, and TIMI IIIB), the degree of and number of ECG leads with ST-segment depression (data from FRISC-II), and age greater than 65 years (data from TIMI IIIB and TACTICS–TIMI 18) have been clearly shown to benefit from an early invasive strategy. The TIMI risk score applied to TACTICS–TIMI 18 showed that patients at low risk (TIMI risk score 0 to 2) demonstrated no difference in outcome—that is, a composite of death, MI, or rehospitalization for ACS at 6 months—whether they were treated with an early invasive or an early conservative strategy.77 Patients at intermediate risk (TIMI risk score 3 to 4), however, showed better outcomes when treated with an invasive strategy.
Insulin resistance is associated with a prothrombotic and proinflammatory state, and cardiovascular disease remains the leading cause ofcardiac biomarker elevation and magnitude of ST-segment depression were each independent predictors of poorer outcomes and that these patients benefited from an early invasive strategy. A recent meta-analysis combining pooled data from the ABOARD, ELISA, ISAR-COOL, and TIMACS trials showed that early coronary angiography and intervention significantly reduced the risk of recurrent ischemia and the length of hospital stay. Based on the evidence, it appears that use of an early invasive strategy for high-risk patients with NSTE-ACS is superior to reduce major adverse cardiac events (MACEs) than use of an ischemia-guided strategy. The overall mortality or combined mortality at the end of follow-up of the pooled data from the FRISC, TACTICS, VINO, RITA-3 (1-year follow-up), and ICTUS trials were 3.6% for the early invasive strategy versus 4.7% for the conservative strategy. Rates of MI were 10.6% for the early invasive and 12.4% for the conservative strategy. In particular, patients with elevated troponin levels or with high-risk indicators benefit from an early invasive approach in combination with adjunctive treatment with a platelet GP IIb/IIIa inhibitor before, during, and after PCI. Lower-risk patients have similar outcomes with either strategy.

### SPECIAL POPULATIONS

#### Diabetes

Insulin resistance is associated with a prothrombotic and proinflammatory state, and cardiovascular disease remains the leading cause of
death among diabetics. With rates of obesity across the globe rising to epidemic proportions, the prevalence of diabetes is expected to double by the year 2030. Diabetic patients who have acute coronary syndrome have significantly worse outcomes compared with the general population. Mortality rates for diabetic patients are significantly higher across the board for both UA/NSTE-ACS and STE-ACS than for the general population. Diabetes is associated with a mortality difference even at 30 days for both UA/NSTE-ACS (2.1% vs. 1.1%, diabetics vs. nondiabetics, \( P < 0.001 \)) and STE-ACS (8.5% vs. 5.4%, diabetics vs. nondiabetics, \( P < 0.001 \)). At 1 year, diabetic patients continue to have a significantly higher mortality risk (HR 1.65 for UA/NSTE-ACS, HR 1.22 for STE-ACS). In particular, at 1 year, diabetic patients who present with UA/NSTE-ACS have mortality rates that are almost as high as nondiabetics who present with STE-ACS (7.2% vs. 8.1%).

Diabetic patients who present with an ACS are therefore a high-risk group. As such, in the 2010 American College of Cardiology Foundation (ACCF)/AHA Focused Update, diabetic patients who present with UA/NSTE-ACS were designated as a subgroup for whom an early invasive strategy would be preferred. Subgroup analysis of diabetic patients in both the FRISC-II and TACTICS–TIMI 18 trial showed a significant risk reduction in MI and death with an invasive strategy. In addition to an early invasive strategy, current guidelines recommend maintaining glucose levels below 180 mg/dL, but this must be done with caution to avoid hypoglycemia.

**Chronic Kidney Disease**

Patients with chronic kidney disease (CKD) have worse outcomes after MI than the general population. In patients with end-stage renal disease, the 2-year mortality rate after an MI is 50%—twice that of the general population. However, a worse mortality risk is seen even at 30 days for both UA/NSTE-ACS and STE-ACS. The mortality difference at 30 days for both UA/NSTE-ACS and STE-ACS is significantly higher across the board for both UA/NSTE-ACS (2.1% vs. 1.1%, diabetics vs. nondiabetics, \( P < 0.001 \)) and STE-ACS (8.5% vs. 5.4%, diabetics vs. nondiabetics, \( P < 0.001 \)). At 1 year, diabetic patients continue to have a significantly higher mortality risk (HR 1.65 for UA/NSTE-ACS, HR 1.22 for STE-ACS). In particular, at 1 year, diabetic patients who present with UA/NSTE-ACS have mortality rates that are almost as high as nondiabetics who present with STE-ACS (7.2% vs. 8.1%).

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**Women**

The benefit of using an early invasive strategy for treating women is achieved primarily in women with high-risk features such as ST-segment changes or elevated troponin levels. Women who were managed with very early aggressive revascularization had a better long-term outcome than men. The combined end point of death and nonfatal MI was significantly reduced at a follow-up of 20 months for women compared with men (OR 0.65; 95% CI, 0.28 to 0.92).

**RADIAL PERCUTANEOUS CORONARY INTERVENTION**

Patients undergoing an invasive approach for ACS are concurrently treated with antithrombotic and antiplatelet therapy and are therefore at higher risk for bleeding than those undergoing elective PCI. These bleeding complications are associated with a significant mortality risk. PCI via radial arterial access is associated with significantly lower rates of bleeding compared with femoral arterial access, and increasingly more operators are utilizing radial arterial PCI during ACS, including STEMI. The Trial of Trans-Radial Versus Trans-Femoral Percutaneous Coronary Intervention (PCI) Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy (RIVAL) randomized 7021 patients with STEMI (\( n = 1958 \)) or NSTE-ACS (\( n = 5063 \)) to radial versus femoral PCI. The primary end point was a composite of death, MI, stroke, and non–CABG-related major bleeding. A significant reduction was seen in mortality (1.3% vs. 3.2%, radial vs. femoral, \( P = 0.006 \)) and in the primary end point (3.1% vs. 5.2%, radial vs. femoral, \( P = 0.026 \)) with radial PCI in patients with STEMI. However, in NSTE-ACS patients, the difference was not significant in either the mortality or primary end point. Preliminary data from the Radial Versus Femoral Access in Mortality Reduction in Non-ST-Elevation Myocardial Infarction (REALITY-NSTEMI) study was presented at the Transcatheter Cardiovascular Therapeutics (TCT) 2013 Scientific Sessions. This observational cohort study enrolled 10,095 patients who presented with NSTE-ACS and found that transradial access was associated with significantly lower rates of bleeding (0.23% vs. 0.97%, radial vs. femoral, \( P = 0.001 \)) and access-site complications (0.33% vs. 1.00%, radial vs. femoral, \( P = 0.003 \)). Preliminary data also found a mortality benefit with transradial access in patients with NSTE-ACS at 30 days (HR 0.35; 95% CI, 0.31 to 0.97; \( P = 0.041 \)), at 6 months (HR 0.59; 95% CI, 0.41 to 0.87; \( P = 0.007 \)), and at 1 year (HR 0.74; 95% CI, 0.55 to 0.99; \( P = 0.042 \)). Full details of REALITY-NSTEMI had not been published at the time of printing.

**REvascularization of Multivessel Disease in Non-ST-Segment Elevation Acute Coronary Syndrome**

When patients undergo coronary angiography for NSTE-ACS and are found to have multivessel disease, the interventionalist must decide on an appropriate strategy for revascularization: PCI versus CABG and multivessel PCI versus culprit-vessel PCI. CABG was compared with PCI in patients who were candidates for either procedure. The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEPHEART) study was an observational, nonrandomized study that found a 36% lower mortality rate with early revascularization in patients with mild to moderate CKD but not with severe CKD (stage 4). A subsequent meta-analysis of randomized controlled trials in patients with CKD did not find a significant benefit in mortality or MI with an invasive strategy, although an invasive strategy was associated with significantly lower rates of rehospitalization compared with a conservative strategy. When patients undergo coronary angiography for NSTE-ACS and are found that transradial access was associated with significantly lower rates of bleeding (0.23% vs. 0.97%, radial vs. femoral, \( P = 0.001 \)) and access-site complications (0.33% vs. 1.00%, radial vs. femoral, \( P = 0.003 \)). Preliminary data also found a mortality benefit with transradial access in patients with NSTE-ACS at 30 days (HR 0.35; 95% CI, 0.31 to 0.97; \( P = 0.041 \)), at 6 months (HR 0.59; 95% CI, 0.41 to 0.87; \( P = 0.007 \)), and at 1 year (HR 0.74; 95% CI, 0.55 to 0.99; \( P = 0.042 \)). Full details of REALITY-NSTEMI had not been published at the time of printing.

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PCI. In making this decision, it is always important to consider from a practical standpoint that it may not always be overtly obvious which lesion is the clear culprit for the ACS event. This is especially the case when a patient has been treated with anticoagulant and antiplatelet therapy for many hours prior to angiography, which may decrease the intracoronary thrombus burden associated with a recently ruptured plaque and may make it difficult or impossible to identify. A retrospective analysis of the safety and efficacy of multivessel stenting versus culprit vessel-only stenting utilizing bare-metal stents in 1240 patients with NSTE-ACS revealed that multivessel stenting was associated with a significantly reduced in-hospital complication or TVR, the presence of unstable CAD was not reported as a predictive factor. In a subanalysis of the in-hospital complications or TVR, the presence of unstable CAD. However, because of delayed healing after DES and the complexity of the lesions present, amount of myocardium supplied by the lesions in question, amount of fluoroscopy time used, and amount of contrast used, which leads to concerns over renal toxicity. In many cases, because of one or more of the previously mentioned factors, an interventionalist may choose to bring a patient back for a staged PCI procedure, either during the same hospitalization or at a later time, in order to complete the task of total revascularization.

**DRUG-ELUTING STENTS FOR PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME**

The primary limitation of PCI using bare-metal stents (BMSs) has been the higher rate of repeat revascularization. Drug-eluting stents (DESs) are associated with substantially reduced rates of target-lesion revascularization (TLR) in patients who present with NSTE-ACS. In various randomized trials comparing the efficacy of DESs with that of BMSs to reduce the restenosis and target-vessel revascularization (TVR) rates, the reported proportions of patients with unstable CAD were between 30% and 50%. Although many variables were studied that predicted early in-hospital complications or TVR, the presence of unstable CAD was not reported as a predictive factor. In a subanalysis of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, investigating the safety and efficacy of sirolimus-eluting stents, it was shown that sirolimus stenting in patients with UA and in those with stable angina was associated with an almost similar risk reduction in the need for TVR compared with bare-metal stenting. The hazard ratio at 1 year of clinically driven TVR for DES use was 0.30 (95% CI, 0.13 to 0.71; P = .0006) compared with bare-metal stenting. The Baseil Stent Kosten Effectiviteit Studie (BASESET) demonstrated that there were fewer adverse cardiac events for patients (N = 301) with NSTE-ACS who received a DES than for those given a BMS.

A subgroup analysis of the One-Year Clinical Results With the Slow-Release, Polymer-Based Paclitaxel-Eluting TAXUS Stent (TAXUS IV) trial, which examined 450 patients with ACS (80% UA and 20% NSTE-ACS), revealed a significant reduction in MACEs for patients treated with paclitaxel-eluting stents compared with bare-metal stenting, with a benefit due entirely to a lower rate of TLR. An analysis of the mandated Massachusetts State PCI Registry showed that in 1228 matched pairs, the 2-year risk of death or recurrent MI was significantly lower in patients who received DESs, as was the rate of revascularization. It may be concluded that, then, the safety and efficacy of DES implantation are similar in patients who present with stable or unstable CAD. However, because of delayed healing after DES and the effects of stent implantation in a highly unstable thrombotic milieu, the use of DAPT should be continued for at least 1 year after DES implantation.

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**STATINS AND PERCUTANEOUS CORONARY INTERVENTION FOR NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME**

Early and post-PCI statin therapy is beneficial to reduce adverse coronary events after ACS. The Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering (MIRACL) trial randomized 3086 patients with unstable CAD to early treatment with 80 mg of atorvastatin (n = 1355) or placebo (n = 1384). At 16 weeks, the primary end point—a composite of death, nonfatal myocardial infarction, and revascularization—occurred in 14.8% in the atorvastatin group and 17.4% in the placebo group (P = .01). Only 16% of these patients underwent revascularization.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (LIPPH-22) trial, intensive statin treatment in patients hospitalized for an ACS was compared with standard statin therapy. The combined primary end point was death from any cause, MI, documented UA, rehospitalization, revascularization (performed at least 30 days after randomization), and stroke. The trial randomized 4162 patients to intensive statin treatment (80 mg of atorvastatin daily, n = 2099) or to pravastatin (40 mg, n = 2063). Of these patients, 69% underwent PCI for the treatment of their index ACS before randomization, and 75% underwent an early invasive strategy. The low-density lipoprotein (LDL) cholesterol levels were 106 mg/dL before treatment in each group. The primary end point at the end of follow-up (mean, 24 months) was reached in 22.4% of the intensive atorvastatin group and in 26.3% of the standard-dose pravastatin group (P = .005). The difference in treatment effect started at 30 days, which confirmed the results with statin treatment in the MIRACL trial.

In the Lescol Intervention Prevention Study (LIPS), 1669 patients were randomized to receive 80 mg of fluvastatin or placebo, with treatment starting 2 days after successful PCI. The LIPS study showed that the statin-treated group had a significantly lower incidence of recurrent clinical events (24.1%) than the placebo group (26.7%, P = .01).

The most recently published AHA/ACC guidelines regarding statin therapy are notable for a dramatic departure from recommendations established during previous years. Patients with a history of ACS are at higher risk for recurrent atherosclerotic cardiovascular disease and death. For years, previous guideline recommendations had advocated secondary prevention with statins titrated to a goal LDL less than 100 mg/dL, with an option to titrate to a goal less than 70 mg/dL. With the newest guidelines, target LDL levels have been eliminated. Statin therapy is now categorized as (1) low intensity (lowers LDL-C by less than 30%), (2) moderate intensity (lowers LDL-C by 30% to 50%), and (3) high intensity (lowers LDL-C by 50% or more). The newest guidelines now recommend that all patients with a history of atherosclerotic cardiovascular disease receive statin therapy. In patients with an established history of CAD, those 75 years of age or younger without contraindications to statins should receive high-intensity statin therapy. Patients older than 75 years or those who may be at risk for drug interactions should receive moderate-intensity statin therapy. **High-intensity statin therapy** is defined as atorvastatin 40 or 80 mg or rosuvastatin 20 mg. **Moderate-intensity statin therapy** consists of the following options: (1) atorvastatin 10 to 20 mg, (2) rosuvastatin 5 to 10 mg, (3) simvastatin 20 to 40 mg, (4) pravastatin 40 to 80 mg, (5) lovastatin 40 mg, or (6) fluvastatin 40 mg twice daily. Once the appropriate intensity of statin therapy has been initiated, the current guidelines no longer recommend treating to a target LDL.

**MANAGEMENT OF PATIENTS WITH NON–ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME**

Outlined here is a pragmatic approach consistent with the most recent ACC/AHA and European Society of Cardiology (ESC) guidelines. Patients with NSTE-ACS should receive antithrombotic, antiplatelet, and anticoagulant treatment. An early risk assessment is vitally important
in order to identify those who may benefit from an early aggressive approach. This assessment should be based on clinical presentation, age, electrocardiographic (ECG) changes, cardiac enzymes and biomarkers, and clinical course. The risk level is classified as high, intermediate, or low (Tables 19-12 through 19-14); further management is guided by risk classification. Patients who present with NSTE-ACS and evidence of hemodynamic instability or cardiogenic shock, severe left ventricular dysfunction or overt heart failure, recurrent or persistent angina at rest despite intensive medical therapy, acute mitral regurgitation or ventricular septal defect, or sustained ventricular arrhythmias should undergo urgent coronary angiography and appropriate revascularization. Patients who are stable but have a history of prior CABG or PCI within 6 months, new ST-segment depression, elevated cardiac biomarkers, angina with minimal activity despite intensive medical therapy, left ventricular ejection fraction below 40%, or a TIMI risk score greater than 2 should be managed with an early invasive strategy. Patients with a low TIMI risk score (<2) and no high-risk features should be managed with an ischemia-guided strategy. The findings of coronary angiography largely determine whether patients should be referred for PCI or CABG (see Fig. 19-7). If PCI is the chosen revascularization modality, it may be performed in the same sitting or in a staged fashion as deemed appropriate by the treating physician. Patients undergoing PCI should receive adjunctive treatment with aspirin, a P2Y12 inhibitor (clopidogrel or ticagrelor), and an anticoagulant (UFH, LMWH, bivalirudin, or fondaparinux) with or without a GP IIb/IIIa antagonist. Lifestyle changes and secondary prevention using aspirin, beta-blockers, statins, and ACE inhibitors should be implemented for all survivors of NSTE-ACS as appropriate.
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76. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC); the European Association for Cardio-Thoracic Surgery (EACTS); the European Association for Percutaneous Cardiovascular Interventions (EAPCI); et al. Guidelines on myocardial revascularization. Eur Heart J 35:2031–2053, 2010.
