INSTRUCTIONS

The following article, “Management of Patients with Acute Coronary Syndrome without Persistent ST Elevation,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 291.

OBJECTIVES

After participating in the continuing education activity, primary care physicians should be able to:
1. Understand the definition of acute coronary syndrome (ACS) and the conditions this term encompasses
2. Develop a method for risk-stratifying patients with chest pain in the emergency department
3. Understand the benefits and risks of therapies for patients with ACS without persistent ST elevation, including newer antiplatelet and antithrombotic therapies
4. Determine which therapies should be started acutely as a function of patient risk
5. Understand the rationale and role for early invasive management, including early coronary angiography and revascularization
6. Review the appropriate medical strategies for secondary prevention in patients with ACS

Ischemic heart disease is the leading cause of death in both women and men in the United States, accounting for nearly 1 million deaths annually [1]. Furthermore, the international prevalence of ischemic heart disease is rising as the population’s longevity increases. Within 20 years, it is projected that ischemic heart disease will account for up 36% of all deaths worldwide [2].

Patients with ischemic heart disease often present with acute coronary syndrome (ACS). ACS describes a spectrum of syndromes that may present when myocardial ischemia occurs, ranging from unstable angina to acute myocardial infarction (MI) [3–5]. Over the past decade, multiple advances have been made in the diagnosis and treatment of ACS. Many of these advances have been evaluated in large-scale randomized clinical trials that have provided the evidence supporting their use in clinical practice. In response to these findings, the American College of Cardiology (ACC) and the American Heart Association (AHA) recently published updated national ACS practice guidelines [3,4]. In the following case study, we will discuss the management of a patient presenting with chest pain as a means of reviewing these recent guidelines for evidence-based ACS care.

CASE STUDY

Initial Presentation and History

A 73-year-old man is brought to the emergency department by ambulance after complaining of chest pain. After breakfast, the patient developed chest pain, which he described as a substernal burning sensation. The pain substantially subsided after sublingual nitroglycerin was administered. His past history is significant for diabetes controlled by diet and hypertension. He does not smoke and takes hydrochlorothiazide as his only medication. As the emergency department personnel perform an initial assessment, electrocardiography is ordered for evaluation of a suspected ACS.

• What is the pathophysiology of conditions included in the ACS spectrum?

ACS typically results from the rupture of a vulnerable plaque in a coronary artery. When plaque rupture occurs, platelets and thrombin aggregate at the site of endothelial disruption, forming a soft thrombus. If this thrombus completely occludes the vessel, an acute injury pattern is usually seen on the electrocardiogram (ECG). In patients with ST segment elevation, myocardial damage will occur unless reperfusion therapy (fibrinolytic therapy or percutaneous coronary intervention) is rapidly delivered.

Patients with plaque rupture can also form a nonocclusive thrombus, which can result in myocardial ischemia, and this is often seen as ST segment depression or flipped T waves on...
ACUTE CORONARY SYNDROME

Presentation

Ischemic discomfort at rest

No ST segment elevation

ST segment elevation

Unstable angina

Non-Q wave MI

Q wave MI

Figure 1. Spectrum of acute coronary syndromes. MI = myocardial infarction.

an ECG. If these patients develop elevated biochemical markers (creatine kinase subfractions or troponin I or T), they are classified as having a non–ST elevation MI. Finally, if all myocardial markers are negative, the patient may still be diagnosed with unstable angina (Figure 1). While these conditions are described as separate diagnoses, it should be appreciated that they represent a spectrum of events. After plaque rupture, thrombus formation can progress from unstable angina to non–ST elevation MI or even ST elevation MI. Further, the thrombus itself is soft and friable and clot microembolization can result in recurrent chest pain, evolving ECG changes, and repeated peaks in biochemical markers.

Further History and Physical Examination

The patient reports no prior history of heart disease. He states that he had a similar substernal and epigastric burning sensation earlier in the week. The pain was associated with exertion and was worse after dinner. There was no associated shortness of breath, palpitations, or diaphoresis. The patient plays tennis once a week and has not had any difficulty with this. He eats a low-carbohydrate, low-fat diet and checks his blood glucose once a day. He denies smoking, drinking alcohol, or using recreational drugs. His father had a MI at age 70 years.

On physical examination, the patient appears overweight. His blood pressure is 144/83 mm Hg and his heart rate is 88 bpm and regular. His jugular venous pressure is not elevated, no carotid bruits are present, and his lungs sound clear. On cardiovascular examination, the point of maximal impulse is in normal position, and he has a regular rate and rhythm without any murmurs. Abdominal examination reveals central obesity without any hepatosplenomegaly. His extremities show no edema and have pulses that are strong and equal. Neurologic examination is normal.

- Which evaluations must be performed in the emergency department to help diagnose patients with ACS and determine their level of risk?
- What are high-risk features of ACS?

Risk Stratification

Acute risk stratification of patients with chest pain in the emergency department should stimulate a rapid triage and treatment process. The goals of this emergency department evaluation are to identify those who need to be admitted, the level of monitoring they require, and their need for pharmacologic and interventional therapies. These care decisions should be guided by the patient’s underlying risk. Specifically, the risk-stratification process revolves around addressing 2 important questions: What is the patient’s likelihood of ischemic heart disease? And, if likely, what are the patient’s odds for acute MI and cardiovascular death?

Pretest Probability of Heart Disease

Understanding a patient’s pretest probability of acute ischemic heart disease helps put other diagnostic results (ECG, biochemical markers) into an appropriate context. Traditionally, the Framingham risk score, which incorporates age, sex, cholesterol level, tobacco use, hypertension, and diabetes, is used. With more than 10 years of follow-up, the Framingham risk score has recently been validated in populations with different ethnic groups [6]. Alternatives to this risk score include a series of models based on the Duke Database for Cardiovascular Disease that allow one to estimate a symptomatic patient’s likelihood of significant or severe coronary disease [7].

In addition to the history, the patient’s physical examination can provide important diagnostic and prognostic information. High-risk features include signs of hemodynamic instability (hypotension, tachycardia) and congestive heart failure (elevated jugular venous distention, pulmonary rales, S3 on cardiac examination, and lower extremity edema).

Electrocardiogram

The ECG adds important diagnostic and prognostic information to the evaluation of the ACS patient. Based on the ECG findings, one may quickly determine whether the patient has ST elevation, which is diagnostic of an acute evolving MI. Patients with ST elevation MI must be rapidly screened to determine whether they are candidates for acute reperfusion therapy (fibrinolytics or percutaneous coronary intervention).
Among those without ST segment elevation, the presence and degree of ST depression has been correlated with an increased risk of MI and death at 30 days and 6 months [8]. ST depression measurements of 0.5 mm, 1.0 mm, and 2 mm are incrementally associated with worse clinical outcomes. An analysis of ECGs from patients presenting with acute chest pain in the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb trial highlights the prognostic significance of ECG changes [9]. T wave inversions did not portend as poor a prognosis as ST depression or ST elevation (Figure 2). While those with ST elevation had the highest acute mortality rates, those with ST depression had a higher rate of downstream events, giving them the worst 6-month outcomes. Clearly, an early ECG should be obtained for all patients seen with suspected ischemic chest pain. The level and manner of ST segment deviation from the presenting ECG provides both diagnostic and prognostic information (Table 1).

Cardiac Markers
In addition to having electrocardiographic testing, all patients with suspected ACS without persistent ST segment elevation should undergo testing for serum cardiac markers, both creatine kinase (CK) and its subfractions (CK-MB) and cardiac troponins (I or T). The recent consensus statement on the definition of acute MI includes myocardial necrosis detected by either CK-MB or troponins [5]. Furthermore, serum troponin levels are associated with increasing mortality at 30 days in patients with ACS without persistent ST segment elevation [10–13] (Table 2). Therefore, serum levels of cardiac troponin T or I provide both diagnostic and prognostic information. Bedside point-of-care cardiac marker assays now available allow for more rapid information translation compared with sending samples for local laboratory processing [14].

Thus, ST segment deviation on ECG and serum cardiac markers should be used in conjunction with the standard history and physical examination to help identify high-risk patients with ACS without persistent ST elevation. This approach will help the clinician to categorize patients into low-risk, intermediate-risk, and high-risk groups [3,4] (Table 3).

Composite Risk Scores
Several composite strategies have been developed for integrating the patient's history, ECG, and cardiac markers into a quantitative ACS risk assessment. The TIMI risk score (from the Thrombolysis in Myocardial Infarction IIIB and Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave MI [ESSENCE] trials [15,16]) established 7 variables as predictors of a composite of death, nonfatal MI, and recurrent ischemia in patients with ACS without persistent ST elevation [17]. These variables included age greater than 65 years, at least 3 risk factors for coronary artery disease, prior coronary stenosis greater than 50%, ST segment deviation on admission ECG, at least 2 anginal events in the prior 24 hours, use of aspirin in the prior 7 days, and elevated serum cardiac markers. Each variable was valued at 1 point and patients were assigned an overall score. The TIMI risk score directly correlated with the risk of death and cardiac events at 14 days for patients with...
ACS without ST elevation in the TIMI 11B and ESSENCE (low-molecular-weight heparin) trials [17].

The databases from the Platelet Glycoprotein IIb/IIa in Unstable Angina: Receptor Suppression Using Integrilin (epitibatide) Therapy (PURSUIT) trial and the GUSTO IIb trial have also been used to establish risk models [18,19]. Unlike the TIMI risk score, these risk models included continuous variables like heart rate and systolic blood pressure and focused on death or a composite of death or nonfatal MI. The characteristics that consistently identified high-risk patients in these 2 studies included age, systolic blood pressure, pulse rate, ST segment depression, signs of congestive heart failure, and positive cardiac markers. Together, the PURSUIT, the GUSTO IIb, and the TIMI risk models highlight the importance of age, electrocardiographic changes, and serum cardiac markers for predicting the short-term risk of patients presenting with ACS without persistent ST segment elevation [20].

### Table 1. Major Clinical Outcomes During the 30-Day and 6-Month Follow-up by Electrocardiographic Category*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ST Segment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolated T Wave Inversion</td>
</tr>
<tr>
<td></td>
<td>(n = 2723)</td>
</tr>
<tr>
<td>30 Days</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.7 (1.3–2.3)</td>
</tr>
<tr>
<td>Reinforcement</td>
<td>4.2 (3.4–5.0)</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>5.5 (4.7–6.4)</td>
</tr>
<tr>
<td>Angioplasty</td>
<td>22.3 (20.8–24.0)</td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>14.2 (13.0–15.6)</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>35.6 (33.8–37.4)</td>
</tr>
<tr>
<td>6 Months</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3.4 (2.8–4.2)</td>
</tr>
<tr>
<td>Reinforcement</td>
<td>5.4 (4.6–6.4)</td>
</tr>
<tr>
<td>Death or reinfarction</td>
<td>8.1 (7.1–9.3)</td>
</tr>
</tbody>
</table>

*All values are presented as percentages (95% confidence interval). The \(P\) value is < 0.001 for all outcomes except any revascularization, which is < 0.02. The \(P\) values are a test of differences across the 4 electrocardiographic categories and based on likelihood ratio \(\chi^2\) test. (Adapted with permission from Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707–13.)

### Table 2. Troponin Level and Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Troponin T</th>
<th>Cohort Studies</th>
<th>Troponin I</th>
<th>Cohort Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical Trials</td>
<td>(n = 5)</td>
<td>Cohort Studies</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>2904</td>
<td>2255</td>
<td>4912</td>
<td>1491</td>
</tr>
<tr>
<td>Mean age, yr</td>
<td>64</td>
<td>60</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male, %</td>
<td>68</td>
<td>66</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Troponin positive, %</td>
<td>40</td>
<td>21</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>Death rate troponin positive, %</td>
<td>3.8</td>
<td>11.6</td>
<td>4.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Death rate troponin negative, %</td>
<td>1.3</td>
<td>1.7</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Median follow-up, wk</td>
<td>4</td>
<td>18</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Summary OR, 95% CI</td>
<td>3.0 (1.6–5.5)</td>
<td>5.1 (3.2–8.4)</td>
<td>2.6 (1.8–3.6)*</td>
<td>8.5 (3.5–21.1)†</td>
</tr>
<tr>
<td>Study heterogeneity (P) value</td>
<td>0.28</td>
<td>0.11</td>
<td>0.28</td>
<td>0.16</td>
</tr>
</tbody>
</table>

\(CI =\) confidence interval; \(OR =\) odds ratio. (Adapted with permission from Heidenreich PA, Alloggiamento T, Melsop K, et al. The prognostic value of troponin in patients with non-ST elevation ACS: a meta-analysis. J Am Coll Cardiol 2001;38:478–85.)

*\(P = 0.01\) for difference between trial and nontrial troponin I results.

†A \(P\) value < 0.05 indicates significant heterogeneity between trials in the mortality odds ratio for a positive troponin.
Above all, it is important to realize that risk stratification is not limited to the initial evaluation. Rather, it should be a continuous assessment that is updated as more data are available, such as sequential ECGs, serum cardiac markers, and hemodynamic information. Based on these initial and subsequent studies, patients can be efficiently diagnosed and appropriately triaged for further medical intervention over their first 12 to 18 hours of hospital observation (Figure 3).

Results of Initial Testing

The patient’s ECG shows sinus rhythm with normal axis, no Q waves, and 1 to 2 mm of anterior ST depression in V1–4. Chest radiograph shows normal lung fields, normal heart size, and no signs of congestive heart failure. Results of standard blood work, including complete blood count, Chem 7, and CK and CK-MB levels, are within normal limits. On initial measurement, the troponin T level is elevated at 0.35 ng/mL.

**Table 3. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD**

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Likelihood</th>
<th>Intermediate Likelihood</th>
<th>Low Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Presence of any of the following</td>
<td>Absence of high-likelihood features and presence of any of the following</td>
<td>Absence of high- or intermediate-likelihood features but may have</td>
</tr>
<tr>
<td>Examination</td>
<td>Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina</td>
<td>Chest or left arm pain or discomfort as chief symptom</td>
<td>Probably ischemic symptoms in absence of any of the intermediate likelihood characteristics</td>
</tr>
<tr>
<td></td>
<td>Known history of CAD, including MI</td>
<td>Age &gt; 70 years</td>
<td>Recent cocaine use</td>
</tr>
<tr>
<td>ECG</td>
<td>Transient MR, hypotension, diaphoresis, pulmonary edema, or rales</td>
<td>Extracardiac vascular disease</td>
<td>Chest discomfort reproduced by palpation</td>
</tr>
<tr>
<td></td>
<td>New or presumably new transient ST segment deviation (≥ 0.05 mV) or T wave inversion (≥ 0.2 mV) with symptoms</td>
<td>Fixed Q waves</td>
<td>T wave flattening or inversion in leads with dominant R waves</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Elevated cardiac TnI, TnT, or CK-MB</td>
<td>Normal ST segments or T waves not documented to be new</td>
<td>Normal ECG</td>
</tr>
</tbody>
</table>


- Into which risk strata does this patient fall?
- Which therapeutic agents should he receive at this time?

**Treatment**

**Low-Risk Patients**

Low-risk patients are patients younger than 70 years of age, without a prior history of cardiovascular disease, without any ECG changes, and with normal serum cardiac markers (Table 3). The distinction between patients with ACS and non-cardiac chest pain remains an important clinical challenge. Many gastrointestinal, pulmonary, and musculoskeletal disorders present with chest pain. The patient’s cardiovascular risk factors in addition to a careful history and physical examination will be needed to differentiate non-cardiac chest pain. Ultimately, many patients with non-cardiac chest pain will be treated with medications for low-risk ACS for both therapeutic and diagnostic reasons.

All patients with suspected ACS should be given aspirin therapy. Aspirin irreversibly acetylates the cyclooxygenase enzyme in platelets, preventing the formation of thromboxane A2. This process blocks the pathway of platelet activation, a key step in the pathophysiology of ACS. Aspirin has been shown to improve clinical outcomes for ACS patients with ST segment elevation and patients without ST elevation. Aspirin reduces the risk of early death by 25% in those with ST segment MI [21] and by more than 51% in those with non-ST elevation ACS when compared with placebo [22–24]. Given the robust benefits, low costs, and relatively safe side-effect profile of aspirin, it should be administered immediately to all patients who present with chest pain and who have no clear contraindications until their etiology is proven not to be cardiac in origin. The recommended dose of aspirin is between 162 and 325 mg [21,25]. For patients with aspirin allergy, the thienopyridine clopidogrel can be considered as an alternative.

Anti-ischemic therapy is also an important component of care for patients presenting with chest discomfort and possible
ACS. The goal of anti-ischemic therapy is to relieve symptoms and prevent future ischemic episodes. These goals are usually accomplished by decreasing the myocardial metabolic demand and by limiting catecholamine surges that can precipitate ischemia. β Blockers are considered first-line anti-ischemic agents for patients with ACS without ST elevation. β Blockers bind to adrenergic cell surface receptors and competitively inhibit the actions of catecholamines. They are contraindicated in severe reactive airway disease, advanced AV block, or decompensated congestive heart failure. Several large-scale clinical trials demonstrated that β blockers reduce short-term mortality and (re)infarction following presentation with acute ST segment elevation MI [26–28]. The effectiveness of acute β-blocker therapy has been tested less completely in those with non–ST segment elevation ACS; however, given their low side-effect profile and benefits in acute MI patients, β blockers were favored in the ACC/AHA guidelines as first-line anti-ischemic therapy in all ACS patients without contraindications.

Nitrites exert their anti-ischemic effects by decreasing myocardial oxygen demand and by increasing myocardial flow. Nitrites are available in sublingual, oral, topical, and intravenous preparations. The major side effect of nitrites is hypotension. Large-scale clinical trials with oral and transdermal nitrites following acute ST segment elevation MI have not shown a mortality benefit [29,30]. Therefore, nitrites should be used to provide early and sustained symptom relief for patients presenting with ACS, with the knowledge that clinical outcomes will not be improved.

Calcium channel blocking (CCB) agents provide an alternative for patients with ACS who have contraindications to β blockers. Multiple CCB agents have been tested in ACS populations, yet the results from these trials have been
mixed. A meta-analysis of all agents found no significant overall survival benefit [31,32]. Short-acting dihydropyridine calcium antagonists (eg, nifedipine) were demonstrated to result in harm. Longer-acting agents (eg, verapamil, diltiazem, or amiodipine) appear safe to most ACS patients, except those with ventricular dysfunction or heart failure, in whom they cause increased mortality.

Intermediate-Risk Patients
Intermediate-risk patients have normal serum cardiac markers, no significant ST segment ECG changes, and 1 or more of the following: age greater than 70 years, prior history of cardiovascular disease, diabetes, or prolonged chest pain.

In addition to the previously mentioned therapies, patients with intermediate risk should also be considered for anticoagulant therapy. Unfractionated heparin was the first anticoagulant therapy studied for patients with ACS without ST segment elevation. Two meta-analyses have summarized several smaller trials involving unfractionated heparin plus aspirin and found that the combination reduced the short-term risk of death or MI compared with aspirin alone (P = 0.05) [33,34]. These findings have led the ACC/AHA to recommend the use of unfractionated heparin, dosed with a weight-based nomogram designed to target an activated partial thromboplastin time of 1.5 to 2 times normal, in ACS patients without ST segment elevation.

Low-molecular-weight (LMW) heparins are composed of polysaccharide chains that are shorter than those in unfractionated heparin preparations. The LMW heparins are more potent inhibitors of factor Xa, have a longer half-life, and have more pharmacologic activity than unfractionated heparin. Three major LMW heparins have been studied in patients with ACS without ST segment elevation: dalteparin and nadroparin were evaluated in 2 ACS trials and found to have no benefits on reducing death, MI, or refractory symptoms compared with unfractionated heparin [35,36]. In contrast, enoxaparin was found to be superior to unfractionated heparin in the ESSENCE and TIMI 11B trials [15,16]. Therefore, enoxaparin currently is the only LMW heparin with an indication for ACS without persistent ST segment elevation. In fact, the AHA/ACC guidelines recommend enoxaparin over unfractionated heparin in patients with unstable angina or non-ST elevation MI unless coronary artery bypass grafting (CABG) is planned within 24 hours.

High-Risk Patients
High-risk patients are defined as those with ST segment depression or transient ST segment elevation, positive serum cardiac markers, recurrent ischemia despite medical therapy, and signs of hemodynamic instability (Table 3). The case patient meets these high-risk criteria since he has ECG changes (lateral ST depression) and a positive troponin T level.

In addition to receiving aspirin and heparin, high-risk ACS patients should be considered for treatment with an intravenous glycoprotein IIb/IIIa receptor antagonist (GP IIb/IIIa inhibitor) and clopidogrel, an oral antiplatelet agent. GP IIb/IIIa inhibitors block a receptor on the platelet surface that undergoes a conformational change following platelet activation. Without GP IIb/IIIa receptor inhibition, the receptor is free to bind to circulating proteins such as fibrinogen and may lead to cross-linking and aggregation of platelets [37]. GP IIb/IIIa receptor antagonists also occupy the fibrinogen-binding site and competitively inhibit fibrinogen binding and the process of platelet aggregation.

Two GP IIb/IIIa inhibitors, eptifibatide and tirofiban, have been approved by the U.S. Food and Drug Administration for initial therapy for high-risk ACS patients. Both drugs are renally cleared, and the dose must be adjusted in patients with renal insufficiency. In the PURSUIT trial, eptifibatide used in conjunction with unfractionated heparin (versus heparin alone) was demonstrated to result in a significant 10% reduction in 30-day risk of death or recurrent MI in high-risk ACS patients [38]. Tirofiban, a synthetic, nonpeptide GP IIb/IIIa antagonist, was associated with a similar risk reduction when evaluated in high-risk ACS in the PRISM Plus trial [39]. Most recently, a meta-analysis of 6 large ACS trials involving more than 31,000 patients found that eptifibatide and tirofiban significantly reduce the risk of death or MI at 30 days (composite odds ratio, 0.88 [95% confidence interval, 0.82–0.95]). This effect was larger in those with positive initial cardiac markers and in those who underwent percutaneous coronary intervention [40–42]. Clopidogrel is a thienopyridine that inhibits adenosine diphosphate release–dependent platelet aggregation through a novel receptor. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial recently evaluated clopidogrel plus aspirin versus aspirin alone in 12,562 patients with ACS without persistent ST elevation [43]. Patients were treated within 24 hours of presentation with a 300 mg loading dose of clopidogrel followed by 75 mg/day for an average of 9 months. The patients who received clopidogrel and aspirin had a significant absolute decrease of 2.1% in a composite of death from cardiovascular cause, nonfatal MI, and stroke. This benefit was counterbalanced by an increased risk of major bleeding. The risk of bleeding was particularly evident among patients who underwent CABG.

Unfortunately, most of the previously mentioned therapeutic trials were carried out in isolation from each other. Thus, we have limited data on which of the potential antiplatelet and anticoagulant therapies combinations is most safe and efficacious. For example, in the CURE trial very few patients received a GP IIb/IIIa agent, so it remains unclear whether clopidogrel has additive benefits in the acute setting.
In summary, decisions regarding the use of acute therapies for patients with ACS without persistent ST segment elevation should be based on the perceived risk of adverse cardiac outcomes in the patient. All patients with suspected ACS should receive aspirin and β blockers unless contraindicated. Intermediate-risk patients should receive antithrombotic therapy with unfractionated heparin or LMW heparin. Patients with high-risk features should also be considered for GP IIb/IIIa inhibitors and clopidogrel (Figure 4).

Initial Therapy

The patient was given aspirin by the emergency medical services personnel in transport to the emergency room. In the emergency room, he was given intravenous then oral β blockers with an appropriate heart rate response. He also had nitroglycerin paste applied. Based on his positive markers and ECG changes, the patient is determined to be at high-risk for non-ST elevation MI and started on unfractionated heparin. After the ECG and laboratory findings are reviewed, a

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Figure 4. Management of patients presenting with symptoms of ischemia. ASA = acetalsalicylic acid; CABG = coronary artery bypass grafting; CK = creatine kinase; ECG = electrocardiogram; IV GPIIb/IIla = intravenous glycoprotein IIb/IIla receptor; LBBB = left bundle branch block; LMWH = low-molecular-weight heparin; NSSTT = nonsignificant ST and T wave; PTCA = percutaneous transluminal coronary angioplasty; TnT/I = troponin T/I.

*C The term “CURE-like” refers to a population similar to that of the CURE trial [43], where early intervention, particularly coronary artery bypass graft, is unlikely.
Further Hospital Management

On hospital day 2, the patient undergoes cardiac catheterization, which demonstrates a 95% stenosis of the proximal left anterior descending artery. Following this procedure, he undergoes stent implantation with an excellent angiographic result.

• What medications should be initiated for the patient prior to hospital discharge?

Patients who undergo stent implantation should receive oral clopidogrel therapy for up to 28 days [50]. The optimal duration of clopidogrel therapy for patients with ACS remains unclear, but results from the CURE trial suggest that high-risk patients with ACS without persistent ST elevation should be treated with clopidogrel and aspirin for up to 9 months.

In addition, all patients with ACS should be placed on appropriate secondary prevention therapies. Significant evidence demonstrates that aspirin decreases long-term cardiovascular death in patients with ACS [51]. β Blockers also reduce postinfarction cardiovascular mortality and should be started in all patients with ACS who do not have contraindications [52].

In addition to aspirin and β blockers, angiotensin-converting enzyme (ACE) inhibitors should also be considered for patients with ACS. Multiple trials have demonstrated that ACE inhibitors reduce rates of death and recurrent heart failure in ACS patients with heart failure or left ventricular dysfunction. Most recently, the Heart Outcomes Prevention Evaluation trial tested the efficacy of the ACE inhibitor ramipril in nearly 10,000 patients with vascular disease. Over 3.5 years of follow-up, treated patients were 20% less likely to die than those not treated. In addition, treated patients had significantly less vascular events, including MI, stroke, heart failure, and progression to diabetes. Given this strongly positive study, all patients with ACS should be considered for long-term ACE inhibitor therapy [53].

A lipid profile should be assessed in patients with ACS. Given that lipid levels can decline following acute ischemic events, this test ideally should be done on admission. Therapy with simvastatin and pravastatin for patients post-MI decreases cardiovascular events and death [54,55]. Based on initial trial results, it was thought that this benefit was limited to those with an elevated low-density lipoprotein (LDL) cholesterol level (eg, exceeding 120 mg/dL). However, preliminary data from the Heart Prevention Study indicates that patients with a normal baseline total and LDL cholesterol level benefited from statin therapy [56]. Therefore, patients with ACS with hyperlipidemia certainly should be given statin therapy prior to discharge, and consideration

- Should the patient undergo early invasive evaluation with cardiac angiography or be treated using a conservative, ischemia-driven strategy within the next 48 hours?

- What is the evidence for the early invasive strategy in combination with the medical therapies started on admission?

Four randomized trials have looked at an early invasive approach, coronary angiography within 72 hours of presentation, versus a conservative approach that reserves coronary angiography for recurrent ischemia on medical therapy, for patients with unstable angina or non–ST elevation MI. These trials include the TIMI IIIb trial, the Veterans Affairs Non-Q Wave Infarction Strategies in Hospital Trial (VANQWISH) trial, the Fragnin and Fast Revascularization during Instability in Coronary artery disease (FRISC II) trial, and the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI-18) trial [44-48].

The former TIMI IIIb and VANQWISH trials found no benefit of an early invasive strategy relative to more conservative care. In contrast, the more recent FRISC II and TACTICS-TIMI-18 trials were performed with contemporary revascularization procedures, including coronary stents and new bypass surgery techniques. In addition, both trials tested a strategy of preemptive antithrombotic treatment, with either LMW heparin (FRISC II Trial) or a GP IIb/IIIa inhibitor (TACTICS-TIMI-18). In contrast to prior studies, FRISC demonstrated a significant absolute risk reduction in death and nonfatal MI in the invasive group. Furthermore, long-term mortality was reduced by close to 50% in patients managed invasively [47]. Similarly, TACTICS-TIMI-18 demonstrated a significant decrease in risk for death, nonfatal MI, or rehospitalization for ACS through 6 months (P = 0.025). Subgroup analyses revealed that those with negative troponins or low clinical risk (based on TIMI score) had no benefit from the early invasive strategy. In contrast, those with positive troponin or intermediate to high clinical risk had enhanced benefit from intervention [49].

small-molecule GP IIb/IIIa inhibitor is given intravenously. The patient is admitted to a telemetry bed in the cardiac step-down unit. He has 1 further episode of chest discomfort that is associated with worsening ST segment depression. The ECG changes and chest pain resolve with intravenous nitroglycerin. Subsequent cardiac markers confirm the diagnosis of non–ST elevation MI, with a peak CK-MB level of 55 ng/dL and a peak troponin T level of 0.56 ng/dL.
should be given to treating all ACS patients with a statin, regardless of their lipid levels [57].

Finally, lifestyle modification interventions should be offered to patients with ACS. These would include smoking cessation counseling for those who smoke, dietary counseling (particularly for those who are overweight), and referral to cardiac rehabilitation.

Case Conclusion

The patient recovers from the percutaneous intervention without difficulty. The GP IIb/IIIa inhibitor is stopped approximately 12 hours after the intervention, and the patient is continued on aspirin, clopidogrel, and a β-blocker. Prior to discharge, he is started on an ACE inhibitor, and after his LDL cholesterol is determined to be 130 mg/dL, a statin for hyperlipidemia is started. The patient is also referred for cardiac rehabilitation after hospital discharge.

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EVALUATION FORM: Management of Patients with Acute Coronary Syndrome without Persistent ST Elevation

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Part 1. Please respond to each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
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<tbody>
<tr>
<td>I was provided with new information pertinent to my practice.</td>
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<td>I reaffirmed a specific skill or knowledge.</td>
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<td>This article will help with clinical decision making.</td>
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<td>Relevant clinical outcomes are addressed.</td>
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<td>The case is communicated in a manner that kept my interest.</td>
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<td>The case presentation is realistic and effective.</td>
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<td>I could easily interpret the tables and figures.</td>
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<td>My attitude about this topic changed in some way.</td>
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Additional comments: ____________________________________________________

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

☑ see no need to change my practice.
☐ will seek more information before modifying my practice.
☐ intend to change the following aspect(s) of my practice: (Briefly describe)


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