Acute Coronary Syndromes: Risk Stratification and Initial Management
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In the United States, there are approximately 1.68 million patients admitted every year to hospitals with acute coronary syndromes (ACSs) [1]. Of these, one quarter present with acute myocardial infarction (MI) associated with ECG ST-segment elevation (STEMI), whereas three quarters, or approximately 1.3 million patients, have unstable angina/non–ST elevation MI (UA/NSTEMI) [1]. The former is most commonly caused by acute total occlusion of a coronary artery and therefore urgent reperfusion is the mainstay of therapy, whereas UA/NSTEMI is usually associated with a nonocclusive thrombus [2]. Among patients who have UA/NSTEMI, between 40% and 60% will have evidence of myocardial necrosis with elevated troponin, and are thus diagnosed with a NSTEMI [3,4].

In the past several years, there have been many advances in the diagnosis and management of this patient population, as summarized in part in the 2002 update of the American College of Cardiology (ACC) and the American Heart Association (AHA) UA/NSTEMI guidelines, and the 2004 ACC/AHA STEMI guidelines.

The approach to the patient, especially at the first presentation in the emergency department (ED) or chest pain unit, involves careful risk stratification. This assessment actually involves two steps: assessment of the likelihood that the patient's symptoms represent ACS (as opposed to noncardiac chest pain), and risk stratification of the patients who have ACS to identify high-versus lower-risk patients. The guidelines recommend that specific therapies and treatment can be targeted to only high-risk patients, with other treatments recommended for all patients. The treatments recommended include anti-ischemic, antithrombotic therapy and what strategy should be followed (ie, whether to pursue an invasive versus conservative approach), and reperfusion therapy for STEMI.

Assessment of likelihood of coronary artery disease
Approximately 6 to 7 million persons per year in the United States present to EDs or chest pain units with a complaint of chest pain or other symptoms suggestive of possible ACS. Of these, approximately 20% to 25% have a final diagnosis of unstable angina or MI [5,6]. Thus, the first step in evaluating patients who have possible UA/NSTEMI is to determine the likelihood that coronary artery disease (CAD) is the cause of the presenting symptoms. The 2002 ACC/AHA guidelines list factors associated with increased likelihood that the patient actually has unstable angina (Table 1).

Numerous prediction rules using clinical and ECG variables have also been developed to assess the likelihood of CAD in patients presenting to the ED with chest pain [7–14]. One algorithm, the acute cardiac ischemia time-insensitive prediction instrument (ACI-TIPI) has been integrated into ECG devices. It provides a quantitative likelihood of the patient having ACSs (ie, STEMI and UA/NSTEMI) [12,13]. One randomized trial has shown that ACI-TIPI reduced unnecessary hospital and coronary care unit admissions [13]. Other studies have suggested that good clinical judgment is as good as the computer algorithms [9,10], emphasizing the importance of obtaining a good...
clinical history when assessing patients who have chest pain.

**Risk stratification**

Based on data from a global registry, the outcomes of patients who have ACS fall on a spectrum of risk, ranging from 30-day mortality of 1.7% for patients who have unstable angina to 7.4% for those who have NSTEMI and 11.1% for those who have STEMI [15]. Within clinical trials in which inclusion criteria select higher-risk patients, rates of death by 30 days ranged from 3.5% to 4.5% and of new MI from 6% to 12% [16–18]. However, patients who have UA/NSTEMI constitute a wide spectrum of patients and risk [19–21]; thus, the ACC/AHA guidelines strongly recommend risk stratification as important to characterize the patient’s prognosis and to select appropriate therapy. Boxes 1 through 3 list the three recommended stratifications for risk of death/MI in UA/NSTEMI.

The rationale for risk stratification is to target some of the more aggressive therapies to the higher-risk patients. This approach has been seen in multiple studies with several of the agents for management of UA/NSTEMI. In STEMI, most of the treatments are similar based on the patient’s risk, beginning with reperfusion therapy and including antithrombotic and anti-ischemic therapies, which are similar to that of UA/NSTEMI.

Thus, among patients who have been identified as having a moderate or high likelihood of having an ACS, the ACC/AHA guidelines highlight risk stratification as a key step that can target the intensity of medical and interventional therapies to higher-risk patients. Factors associated with a high risk for death or nonfatal MI in patients who have UA/NSTEMI are prolonged rest pain, ST-segment changes, elevated cardiac biomarkers (eg, troponin), diabetes, evidence of congestive heart failure, and age over 75 years. Low-risk patients present without rest pain [22], ECG changes, or evidence of heart failure (see Box 3). Other factors are highlighted as markers of long-term risk, such as extent of CAD, left ventricular dysfunction, and elevated markers of inflammation.

In UA/NSTEMI, use of troponin alone has been a powerful tool for risk stratification and targeting of therapies. Studies have found that high-risk patients benefit from the more aggressive treatments. For low molecular weight heparin (LMWH), glycoprotein (GP) IIb/IIIa inhibitors, and an early invasive strategy, there is a greater benefit of these interventions in patients who have a positive troponin, and almost no benefit in patients who have a negative troponin [3,23–26]. For example, with the GP IIb/IIIa inhibitors, there was a 50% to 70% reduction in death or MI in patients who were troponin-positive and were receiving GP IIb/IIIa inhibitors compared with patients not receiving these agents, with no benefit of GP IIb/IIIa inhibitors in those who did not have a positive troponin [24,25]. A different pattern has been seen with the oral antiplatelet agents, in that aspirin and clopidogrel benefit low-, intermediate-, and high-risk patients and those who have positive or negative cardiac markers [27–29]. Thus, aspirin and clopidogrel have been recommended for all patients regardless of risk, whereas GP

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**Table 1**

<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>Typical angina; known history of coronary artery disease including myocardial infarction</td>
<td>Probable angina; age &gt;70 years; male diabetes mellitus</td>
<td>Atypical symptoms</td>
</tr>
<tr>
<td>Examination</td>
<td>Congestive heart failure</td>
<td>Peripheral vascular disease, cerebrovascular accident</td>
<td>Pain on palpation</td>
</tr>
<tr>
<td>ECG</td>
<td>New ECG changes</td>
<td>Old ECG abnormalities</td>
<td>Normal</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Positive</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

IIb/IIIa inhibitors are recommended for use only in high-risk patients or those undergoing percutaneous coronary intervention (PCI) (Fig. 1).

### Risk scores

Integrating all the risk factors identified in the ACC/AHA guidelines as low-, intermediate-, or high-risk, comprehensive risk scores have been developed using clinical variables and ECG and initial serum cardiac marker data [30,31]. The Thrombolysis in Myocardial Infarction (TIMI) risk score was developed using multivariate analysis to predict the occurrence of death, MI, or recurrent ischemia leading to urgent revascularization in the TIMI 11B trial. Seven independent risk factors emerged: age over 65 years, more than three risk factors for CAD, documented CAD at

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**Box 1. Short-term high risk for death/myocardial infarction in unstable angina/NSTEMI**

*At least one of:*

**History**
- Accelerating tempo of ischemic symptoms in preceding 48 hours

**Character of pain**
- Prolonged ongoing (>20 min) rest pain

**Clinical findings**
- Pulmonary edema, most likely caused by ischemia
- New or worsening mitral regurgitation murmur
- S₃ or new/worsening rales
- Hypotension, bradycardia, tachycardia
- Age over 75 years

**ECG**
- Rest angina with transient ST changes greater than 0.05 mV
- Bundle branch block
- New sustained ventricular tachycardia

**Cardiac markers**
- Markedly elevated (eg, Troponin T or Troponin I >0.1 ng/mL)


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**Box 2. Short-term intermediate risk for death/myocardial infarction in unstable angina/NSTEMI**

*No high-risk features, but must have one of:*

**History**
- Prior myocardial infarction, peripheral vascular disease, or cerebrovascular disease
- Coronary artery bypass grafting
- Prior aspirin use

**Character of pain**
- Prolonged (>20 min) rest angina, now resolved, with moderate or high likelihood of coronary artery disease
- Rest angina (<20 min) or relieved with rest or sublingual nitroglycerin

**Clinical findings**
- Age over 70 years

**ECG**
- T-wave inversions greater than 0.2 mV
- Pathologic Q waves

**Cardiac markers**
- Slightly elevated (eg, Troponin T >0.01 ng/mL but <0.1 ng/mL)

Box 3. Short-term low risk for death/myocardial infarction in unstable angina

No high or intermediate risk feature, but may have any of:

History
None indicated

Character of pain
New-onset Canadian Cardiovascular Society class III or IV angina in past 2 weeks without prolonged (>20 min) rest pain, but with moderate or high likelihood of coronary artery disease

Clinical findings
None indicated

ECG
Normal or unchanged ECG during chest discomfort

Cardiac markers
Normal


catheterization, prior ASA, more than two episodes of angina in the last 24 hours, ST deviation more than 0.5 mm, and elevated cardiac markers. This scoring system was able to risk stratify patients across a ten-fold gradient of risk, from 4.7% to 40.9% ($P < .001$) [31]. More importantly, the relative benefit of enoxaparin as compared with unfractionated heparin increased as the risk increased [31]. Similar findings have now been seen using the TIMI risk score to predict the benefit of GP IIb/IIIa inhibitors [32] and an early invasive strategy [3]. Thus, these findings support the ACC/AHA guideline recommendations that risk stratification be the first task in evaluating patients who present with UA/NSTEMI [33].

Fig. 1. 2002 American College of Cardiology/American Heart Association guideline recommendations for antithrombotic therapy for unstable angina/non–ST elevation acute coronary syndrome. (From Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2000;36:970–1062; with permission.)

Antithrombotic and medical therapy

Initial treatment for patients who have UA/NSTEMI should include aspirin, which leads to a 50% to 70% reduction in death or MI as compared with placebo [34]. Current data on aspirin indicate the drug is beneficial for long-term treatment at doses as low as 75 mg/d [27]. New data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial indicates that lower doses of aspirin (eg, 81 mg) are associated with a 50% lower rate of major bleeding over 1 year of treatment than doses of 200 to 325 mg [35]. Thus, for acute management in-hospital, 160 to 325 mg daily is recommended, but at hospital discharge and during follow-up, the new data suggest a dose of 81 mg may be safer.

The 2002 ACC/AHA guideline included a new Class I recommendation for the use of clopidogrel in addition to aspirin. Clopidogrel blocks the ADP pathway by blocking the P$_2$Y$_{12}$ component of the ADP receptor, which in turn decreases platelet activation and aggregation. The CURE trial found that clopidogrel plus aspirin led to a 20% relative risk reduction in cardiovascular death, MI, or stroke compared with aspirin alone [28]. This benefit was seen in low- and high-risk patients [29] and was seen as early as 24 hours [36], with the Kaplan-Meier curves for event rate in the two treatment groups diverging after just 2 hours.
This benefit has also been seen in two other trials. In the CREDO trial of patients undergoing PCI, clopidogrel was associated with a significant 27% relative reduction in the combined risk for death, MI, or stroke at 1 year ($P = .02$) [37]. Similarly, in the CAPRIE trial, clopidogrel alone had a significant reduction in these events versus aspirin through 3 years of follow-up in patients who had prior atherothrombotic disease [38]. Thus, there is strong evidence from large double-blind, randomized trials that clopidogrel plus aspirin is the new optimal long-term antithrombotic regimen.

Intravenous GP IIb/IIIa inhibitors have also been shown to be beneficial in treating UA/NSTEMI [39]. For “upstream” management (ie, initiating therapy when the patient first presents to the hospital), the small molecule inhibitors epifibatide and tirofiban clearly show benefit, whereas abciximab was of no benefit in an unselected UA/NSTEMI patient population [40] and is in fact contraindicated for patients approached with a noninvasive strategy [41].

Unfractionated heparin (UFH) or LMWH is recommended for patients who have UA/NSTEMI [42]. Comparative trials of enoxaparin (a LMWH) versus UFH have demonstrated superiority of enoxaparin in reducing recurrent cardiac events [43,44]. Based on these data, the 2002 Updated ACC/AHA UA/NSTEMI practice guidelines have made a Class IIA recommendation that enoxaparin is the preferred antithrombin over UFH [41].

Anti-ischemic therapy with nitrates is also recommended, with the use of intravenous nitrates for ongoing ischemic pain and beta-blockade early and during long-term follow-up [33].

In STEMI, benefits of early angiotensin-converting enzyme inhibition are considerable. In the GISSI-3 [45] trial, early initiation of lisinopril was associated with a 12% mortality reduction, and in ISIS-4 [46], captopril therapy resulted in a 7% mortality reduction. Benefits were more pronounced in patients who had anterior MI. However, in patients who had NSTEMI, no benefit was observed in the ISIS-4 study.

### Invasive versus conservative strategy: non–ST elevation acute coronary syndrome

For patients who have UA/NSTEMI, nine randomized trials have assessed the merits of an invasive strategy involving routine cardiac catheterization with revascularization (if feasible) versus a conservative strategy where angiography and revascularization are reserved for patients who have evidence of recurrent ischemia either at rest or on provocative testing. Of these, six of the last seven have all shown a significant benefit of the invasive strategy (Fig. 2), especially in higher-risk patients [3,35,47]. Accordingly, the 2002 ACC/AHA guideline has added ST-segment changes and positive troponin to the list of high-risk indicators that would lead to a Class I recommendation for an early invasive strategy, as shown in Box 4 [41]. With regard to the timing of an invasive strategy, the results from the Intracoronary Stenting with Antithrombotic Regimen Cooling-Off study found a benefit of an immediate invasive strategy with an average time to catheterization of 2 hours, compared with a delayed invasive strategy with an average time to catheterization of 4 days [48]. Randomized studies have not yet evaluated whether an immediate invasive approach is better than catheterization 24 to 48 hours postadmission.

### Summary—acute therapy for non–ST elevation acute coronary syndrome

Summarizing the ACC/AHA guidelines, there are now five baseline therapies for all patients: aspirin; clopidogrel; heparin or LMWH (with enoxaparin the preferred antithrombin); beta-blockers; and nitrates (Fig. 3) [23]. Then there are two treatments that are best targeted by risk

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**Fig. 2.** The “weight of the evidence” showing benefit of an invasive versus conservative strategy in patients who have unstable angina/non–ST elevation acute coronary syndrome. The size of the boxes for each of the nine randomized trials corresponds to the number of patients enrolled. (*Modified from* Cannon CP, Turpie AG. Unstable angina and non-ST-elevation myocardial infarction: initial antithrombotic therapy and early invasive strategy. *Circulation* 2003;107:2640–5; with permission.)
**Box 4. ACC/AHA guideline recommendations for an early invasive strategy for unstable angina/non–ST elevation myocardial infarction**

**Class I**

Any of the high-risk indicators (level of evidence: A)
- Recurrent angina at rest/low-level activity despite treatment
- Elevated Troponin T or Troponin I
- New ST-segment depression
- Recurrent angina/ischemia with congestive heart failure symptoms, rales, mitral regurgitation
- Positive stress test
- EF less than 0.40
- Decreased blood pressure
- Sustained tidal volume
- PCI less than 6 months, prior coronary artery bypass grafting


stratification: the invasive strategy and the IIb/IIIa inhibitor, where the benefit is in the higher-risk patients.

**ECG ST-segment elevation: reperfusion therapy**

In STEMI, the coronary artery is in most cases 100% occluded with a fresh thrombus at the site of a ruptured plaque. To restore perfusion to the myocardium, immediate reperfusion of the infarct-related artery is needed.

There are two approaches: use of fibrinolytic therapy or primary PCI. Time is critical with either therapy, where the sooner reperfusion is achieved, the greater the chance of reducing morbidity and increasing survival.

**Primary percutaneous coronary intervention**

At present, the preferred method of achieving coronary reperfusion is the use of primary PCI.

Many randomized controlled trials have compared pharmacologic and mechanical reperfusion during STEMI. A meta-analysis of 23 of these trials found that primary PCI was superior to thrombolytic therapy in reducing mortality; non-fatal reinfarction; stroke; and the combined end-point of death, nonfatal reinfarction, and stroke [49]. The benefits of PCI in reducing mortality and recurrent MI were particularly striking.

At present, however, only 20% to 25% of hospitals have primary PCI capabilities. Therefore, hospitals that do not have PCI capabilities can either treat patients who have STEMI with immediate thrombolysis, or emergently transfer them to a site where PCI can be performed. Recent clinical trials have also found that if door-to-balloon times are within 2 to 3 hours, that primary PCI is superior to fibrinolysis with a 40% to 50% reduction of the combined end point [50–52].

**Thrombolysis**

Thrombolysis has been shown to reduce mortality in several large placebo-controlled trials using streptokinase (SK) and tissue plasminogen activator (t-PA). These benefits persist through at least 10 years of follow up. The Fibrinolytic Therapy Trials’ overview of all the major placebo-controlled studies showed a 2.6% absolute reduction in mortality for patients who have STEMI treated within the first 12 hours after the onset of symptoms [53]. Patients presenting with new left bundle branch block and a strong clinical history for acute MI also derive a substantial benefit from thrombolysis. Patients who have non–ST
elevation ACS, however, do not benefit from thrombolysis.

SK was the initial fibrinolytic drug, with newer agents later developed. The fibrin-specific thrombolytic agents, such as alteplase (t-PA), were seen in the TIMI-I trial to have twice the rate of infarct-related artery patency as SK [54]. In the GUSTO I trial, accelerated tPA plus heparin led to a highly significant 14% reduction in mortality. Reteplase and tenecteplase are molecular modifications of t-PA designed to have longer plasma half-lives that allow double or single bolus administration, respectively. However, the newer agents did not lead to a further reduction in mortality rates compared with t-PA.

Similarly, use of the combination of half-dose fibrinolysis and GP IIb/IIIa receptor inhibitors did not improve mortality, and this more complicated regimen is not widely used. The use of other adjunctive agents with full-dose fibrinolysis is being actively studied, with enoxaparin being compared with UFH in the EXTRACT-TIMI 25 trial, and clopidogrel being added to standard regimens versus placebo in the CLARITY-TIMI 28 trial.

**Choice of reperfusion therapy**

In summary, although thrombolysis is more widely available, is simple to administer, and produces results that are independent of operator experience, primary PCI in experienced hands is associated with less-recurrent infarction and ischemia; lower short-term mortality; and less stroke and intracranial hemorrhage than thrombolysis. PCI also results in higher early infarct-related artery patency rates and reduced residual stenosis compared with thrombolysis. The current ACC/AHA guidelines recommend invasive strategy with PCI if a timely intervention can be performed; that is, if door-to-balloon time is less than 90 minutes or if the delay to PCI compared with on-site thrombolysis is less than 1 hour. Primary PCI is also generally preferred for patients in cardiogenic shock, who have contraindications to thrombolysis, and in whom thrombolysis is unlikely to produce meaningful benefit (eg, symptom onset more than 3 hours before presentation).

**Summary**

For patients who have ACS, risk stratification is key to initiating appropriate treatment. For STEMI, immediate reperfusion therapy is needed, and thus rapid identification of ST elevation on the ECG is critical. Having a standardized protocol for rapid treatment—with either primary PCI or thrombolysis—is critical. For UA/NSTEMI, one first has to identify the patients who have a higher likelihood of actually having an ACS as opposed to noncardiac chest pain. There are many modalities for this assessment, as reviewed in this issue. Among patients who have a moderate or high likelihood of ACS, stratification to high versus lower risk is needed to choose appropriate therapies. Thus, it is important for risk stratification to be a central part of all management of patients who have ACS.

**References**


[33] Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients...


