

# 2007 Update to the ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction: Implications for Emergency Department Practice

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The American College of Cardiology and American Heart Association have updated their guidelines for the management of non–ST-segment-elevation acute coronary syndrome for the first time since 2002. In the interim, several important studies affecting choices of therapy potentially begun in the emergency department have been completed, and care patterns have changed and matured significantly. In this review, we present the new recommendations that are pertinent to emergency medicine practice and comment on their potential implementation into an evidence-based, multidisciplinary approach to the evaluation and management of this challenging patient population. [Ann Emerg Med. 2008;51:591-606.]

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## INTRODUCTION

The American College of Cardiology (ACC) and the American Heart Association (AHA) have jointly published practice guidelines for various aspects of cardiovascular disease since 1980. Throughout the years, these guidelines have become increasingly based on specific clinical trial data, allowing clinicians to relate their practice preferences objectively to the pertinent strengths and weaknesses of published experience. In September 2000<sup>1</sup> and in a March 2002 update,<sup>2</sup> the ACC and AHA published a practice guideline that addressed the evaluation and management of unstable angina and non–ST-segment-elevation myocardial infarction (NSTEMI) (collectively, “non–ST-segment-elevation acute coronary syndrome”). The aspects of these guidelines most relevant to emergency medicine practice were summarized and discussed in previous issues of *Annals of Emergency Medicine*.<sup>3-5</sup> On August 6, 2007, the ACC/AHA Joint Task Force released an update to the 2002 non–ST-segment-elevation acute coronary syndrome guidelines on their respective Web sites, <http://www.acc.org> and <http://www.americanheart.org>.<sup>6</sup> Review of the changes and additions in that document reveals a number of issues that will affect the emergency department (ED) aspect of practice in the non–ST-segment-elevation acute coronary syndrome continuum of care, and it is our conviction that emergency physicians should remain current on the evidence base underlying such recommendations. We therefore review and comment on them here.

## DEFINITIONS AND WEIGHTING OF EVIDENCE

Non–ST-segment-elevation acute coronary syndrome comprises a clinical syndrome that presents as anginal chest pain or its equivalent (eg, dyspnea, jaw or arm pain, weakness) as the manifestation of decreased coronary blood flow. Non–ST-segment-elevation acute coronary syndrome is generally but not always caused by atherosclerotic coronary artery disease and is associated with an increased risk of transmural myocardial infarction and cardiac death. At ED presentation, non–ST-segment-elevation acute coronary syndrome may be difficult to differentiate from other forms of acute coronary syndrome and from chest pain caused by noncoronary pathology. Furthermore, patients with non–ST-segment-elevation acute coronary syndrome tend to be more heterogeneous (atypical symptomatology, older, higher likelihood of renal insufficiency, challenging electrocardiograms) than those who present with ST-segment-elevation myocardial infarction (STEMI).<sup>6</sup>

The term “acute coronary syndrome” refers to the constellation of symptoms manifesting as a result of acute myocardial ischemia. Acute coronary syndrome encompasses unstable angina, NSTEMI, and STEMI. Generally accepted standards of care are in place for patients with STEMI and involve urgent reperfusion therapy either by means of fibrinolysis (with a target door-to-needle time of 30 minutes) or direct (or primary) percutaneous coronary intervention (with a target door-to-balloon inflation time of 90 minutes)<sup>7,8</sup>; the guidelines described and discussed here are limited to unstable

angina/NSTEMI. In these guidelines, unstable angina and NSTEMI are considered to be the same clinical syndrome but of differing severities. NSTEMI is diagnosed on the basis of abnormal levels of serum biomarkers of myocardial necrosis—usually cardiac troponin I, cardiac troponin T, or the MB band of creatine phosphokinase (CK-MB)—and is considered more severe. Patients with acute coronary syndrome but without positive markers have unstable angina. Unstable angina might present as rest angina, new-onset angina, or accelerating angina.

Evidence used in developing recommendations in the guidelines was classified as follows<sup>6</sup>:

- Class I: There is evidence or general agreement that a specific procedure or treatment is useful and effective; procedure or treatment should be performed or administered.
- Class II: There is conflicting evidence or divergence of opinion about the utility or efficacy of a procedure or treatment. In a class IIa evaluation, the weight of the evidence or opinion is in favor of utility-efficacy, and it is reasonable to perform the procedure or administer the treatment. In class IIb, the utility-efficacy is less well established by evidence or opinion, and the procedure or treatment may be considered.
- Class III: There is evidence or general agreement that a specific procedure or treatment is neither useful nor effective, and it might be harmful in some cases; the procedure or treatment should not be performed or administered.

Recommendations made in the guidelines were based on expert analyses of published data. The weight of the evidence was then ranked according to the aggregate source or sources of that data<sup>6</sup>:

- A (highest): The data were derived from multiple randomized clinical trials that involved large numbers of patients; there is a general consistency of the direction and magnitude of effect.
- B (intermediate): The data were derived from a limited number of randomized trials that involved small numbers of patients or from analysis of nonrandomized studies or observational registries. This would include limited evidence from a single randomized trial or nonrandomized studies or registries.
- C (lowest): The primary basis for the recommendation is a consensus of expert opinion, case studies, or accepted standard of care.

Thus, each recommendation made in the guidelines is cited as class I, IIa, IIb, or III (reflecting the Task Force's analysis of evidence) and weighted as A, B, or C (reflecting the quality and extent of the evidence that was analyzed).

## ED-PERTINENT CHANGES IN GUIDELINE RECOMMENDATIONS

In this article, we are not addressing evaluation and treatment recommendations that have not been substantively updated since 2002. Changes from the 2002 guidelines that are pertinent to ED management of non-ST-segment-elevation acute coronary syndrome can be summarized as follows<sup>6</sup>:

- Initial Evaluation and Management
  - The recommendation for nitroglycerin use has changed.
  - There is increased emphasis on out-of-hospital 12-lead ECG acquisition and out-of-hospital destination protocols.
- Risk Stratification
  - More specific guidance is offered about serial ECG and biomarker testing.
  - Specific risk-prediction models are recommended in early assessment.
  - A specific discussion of chest pain units is offered from the cardiology perspective.
- Anti-Ischemic Therapy
  - The recommendations for  $\beta$ -blocker therapy have been updated according to experience from recent trials.
  - Specific caveats about the use of nonsteroidal anti-inflammatory drugs in patients with acute coronary syndrome are issued.
  - Specific caveats about the use of nitrates in patients exposed to phosphodiesterase inhibitors are made.
- Initial Inpatient Management Strategy
  - The relative evidence supporting an “early invasive” acute coronary syndrome management strategy is compared with that supporting an “initial conservative” strategy. Because it drives decisionmaking with regard to upstream antithrombotic and antiplatelet therapy (see below), this distinction is vital to the collaborative approach to acute coronary syndrome management between emergency medicine, cardiology, and sometimes surgery.
- Anticoagulation Therapy
  - New recommendations for bivalirudin and fondaparinux are made, according to recent clinical trials, but they are (as with enoxaparin and unfractionated heparin) linked to specific management strategies.
- Antiplatelet Therapy
  - Updated recommendations for the use of clopidogrel and platelet glycoprotein IIb/IIIa receptor antagonists are made and are linked to specific management strategies.

## INITIAL EVALUATION AND MANAGEMENT

Consistent with recommendations issued in the 2004 ACC/AHA STEMI guidelines,<sup>7,8</sup> the suggested dosing regimen for nitroglycerin taken by patients before seeking medical attention has been truncated. The new recommendation is that the patient call 911 if no relief of chest pain or related symptomatology is achieved after 1 dose (sublingual or spray) (I-C).<sup>6</sup> In the past, the standard approach was to seek care if 3 successive doses at 5-minute intervals afforded no relief; in the new guidelines, it is recommended that second and third doses be given, as needed, while the patient awaits emergency medical services (EMS) arrival. The guidelines also differentiate between patients with chest pain syndrome consistent with acute coronary syndrome and that of stable angina, for which it is recommended that 911 be called only if pain is not improving with up to 3 successive doses (I-C).<sup>6</sup> These recommendations

**Table 1.** Likelihood that signs and symptoms represent acute coronary syndrome overlying coronary artery disease (adapted from 2007 non-ST-segment-elevation acute coronary syndrome guidelines).<sup>6</sup>

Feature	High Likelihood: Any of	Intermediate Likelihood: In the Absence of High-Likelihood Features, Any of	Low Likelihood: In the Absence of High- or Intermediate-Likelihood Features, May have
History	Chest or left arm discomfort as chief complaint, reproducing known angina Known history of CAD	Chest or left arm discomfort as chief complaint Age >70 y Male Diabetes	Symptoms consistent with myocardial ischemia but not intermediate likelihood Recent cocaine or methamphetamine use
Physical examination	Hypotension, signs of heart failure, transient MR murmur	Extracardiac atherosclerotic vascular disease	Chest discomfort reproduced by palpation
ECG	New ST-segment deviation (1 mm or greater) T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5–1 mm T-wave inversion >1 mm	T-wave flattening or inversion <1 mm in leads with dominant R wave
Cardiac biomarkers	Elevated necrosis marker	Normal	Normal

CAD, Coronary artery disease; MR, mitral regurgitation.

are an important issue for emergency physicians who are discharging to home patients with diagnosed angina and for ED personnel who may receive telephone requests for advice on chest pain treatment. Aspirin is also recommended universally in patients with symptoms potentially referable to acute coronary syndrome, with the exception of known aspirin allergy (I-A).<sup>6</sup>

These 2007 guidelines for non-ST-segment-elevation acute coronary syndrome also reiterate the 2004 STEMI guidelines' emphasis on a more thorough out-of-hospital evaluation of patients with acute coronary syndrome symptoms, including when possible a 12-lead ECG and direction of patients with evidence of acute ischemia to specific receiving hospitals (IIa-B). They specifically recommend that every community have a written protocol to govern selection of destination hospitals from EMS calls.<sup>6,7</sup> Such structure may improve both clinical outcomes and efficiency of care.<sup>9-11</sup>

## RISK STRATIFICATION

Patients presenting to the ED with symptomatology potentially related to acute coronary syndrome should be assessed promptly and consistently in an effort to answer 2 questions simultaneously (I-C):<sup>6</sup>

- What is the likelihood that the presenting symptoms represent acute coronary syndrome as a result of coronary artery disease as opposed to one of the many other differential diagnosis?
- What is the likelihood of an adverse cardiovascular outcome (death, myocardial infarction, stroke, heart failure, recurrent ischemia, or significant arrhythmia)?

Given that the clinical presentation of acute coronary syndrome may be atypical and that the presence or absence of traditional cardiovascular risk factors is an unreliable determinant of the presence of acute coronary syndrome, the

risk stratification process is a challenging but crucial aspect of the ED care of patients with chest pain syndrome. Table 1 lists potential signs and symptoms of acute coronary syndrome categorized by likelihood, and Table 2 identifies features of acute coronary syndrome associated with risks of less versus more adverse outcomes.

Whereas the 2002 guidelines mentioned that "serial" ECGs increased the diagnostic yield in patients being evaluated for possible acute coronary syndrome, they stopped short of a specific recommendation.<sup>2,5</sup> The 2007 guidelines explicitly recommend that nondiagnostic tracings be repeated at 15- to 30-minute intervals, at least initially in patients with persistent symptoms and high clinical suspicion of acute coronary syndrome, to facilitate prompt detection of ST-segment changes (I-B). When available, continuous ST-segment monitoring can be use for ongoing surveillance of patients whose initial ECG is nondiagnostic (IIa-B).<sup>6</sup> The diagnostic yield of serial ECGs is considered lower than that of serial biomarkers,<sup>12-14</sup> but nevertheless the guidelines recommend that both be pursued because diagnostic ECG changes (especially ST-segment elevation) may occur in advance of elevations in markers.<sup>6</sup>

There is further specific guidance on the use of biomarkers of myocardial necrosis. There is a I-B recommendation that markers be assayed in all patients who present with symptomatology consistent with acute coronary syndrome and that troponin (no distinction between T and I) be considered the preferred marker.<sup>6</sup> Increased troponin levels can be detected in the serum as early as 2 to 4 hours after the onset of symptoms but may be delayed for 8 to 12 hours, or even beyond. After myocardial infarction, the increased level may persist for 5 to 14 days. Multiple studies have shown a quantitative relationship between the magnitude of the troponin increase and the risk of death.<sup>15,16</sup> This finding notwithstanding, acute coronary syndrome patients with negative troponin assay results may

**Table 2.** Predictors of greater or lesser short-term risk of death or nonfatal myocardial infarction in patients with non-ST-segment-elevation acute coronary syndrome (adapted from 2007 non-ST-segment-elevation acute coronary syndrome guidelines).<sup>6</sup>

<b>Feature</b>	<b>High Risk: Any One of</b>	<b>Intermediate Risk: In the Absence of High-Risk Features, Any One of</b>	<b>Low Risk: In the Absence of High- or Intermediate-Risk Features, May Have</b>
History	Accelerating tempo of anginal symptoms during preceding 48 h	Previous myocardial infarction or other documented atherosclerotic disease	
Character of pain	Ongoing rest pain >20 min	Rest angina >20 min but now resolved, with intermediate or high likelihood of CAD Angina relieved with rest or NTG Nocturnal angina New-onset angina in past 2 wk, without prolonged or rest pain but with intermediate or high likelihood of CAD	Increased angina severity, frequency, or duration Angina provoked at lower exertion threshold New-onset angina 2 wk to 2 mo before presentation
Clinical findings	Ischemia-related pulmonary edema or S3 New or worsening MR murmur Hypotension Bradycardia or tachycardia Age >75 y	Age >70 y	
ECG	Angina at rest with transient ST-segment changes >0.5 mm New or presumed new BBB Sustained VT	Fixed Q waves in multiple lead groups Resting ST-segment depression <1 mm T wave changes	Normal or unchanged ECG
Cardiac biomarkers	Increased necrosis marker; eg, troponin >0.1 ng/mL	Slightly increased necrosis marker; eg, 0.1<TnT<0.01	Normal

NTG, Nitroglycerin; BBB, bundle branch block; VT, ventricular tachycardia; TnT, cardiac troponin T.

experience adverse outcomes.<sup>6</sup> Furthermore, increased troponin levels may occur from many other causes besides ischemic necrosis, including trauma, myocarditis, sepsis, pulmonary embolism, and renal insufficiency.<sup>17</sup> Specifically in patients with renal dysfunction, troponin I assay may be preferred over troponin T; otherwise, the information obtained with either is considered equivalent.<sup>18</sup>

The 2007 guidelines recommend that patients whose biomarkers are negative within 6 hours of the onset of qualifying symptoms have that assay repeated 8 to 12 hours after symptom onset (I-B) while acknowledging that in clinical practice, a reliable time of onset may not be available.<sup>6</sup> In that case, the safest approach is to assume symptom onset at ED arrival, which takes into adequate account the release kinetics of troponin and the limitations of current assay techniques.

An alternative approach in this group of patients is the guidelines' recommendation that measurement "2-h  $\Delta$ " CK-MB mass values (ie, the difference between 2 values tested 2 hours apart) in conjunction with serial troponin assay (Ib-B) "may be considered."<sup>12,14,19-21</sup> As assays become more sensitive, detection of small increases in value even while remaining below the upper limit of the normal range may, when combined with clinical judgment, prompt earlier identification of high-risk patients and in turn support the earlier use of more aggressive

medical or interventional management. Although these results are promising, the Task Force clearly believed that more prospective study in this area is needed before this approach earns a higher evidence rank.<sup>6</sup> Likewise, the use of myoglobin as a biomarker earns no recommendations higher than Iib-B,<sup>6</sup> although of particular ED interest is the Iib-B recommendation that, for patients who present within 6 hours of symptom onset, 2 myoglobin (with troponin) assays conducted 90 minutes apart<sup>22</sup> "may be considered" in conjunction with troponin or CK-MB testing.<sup>6</sup> Assay of brain-type natriuretic peptide in patients suspected of having acute coronary syndrome also is recommended at a Iib-B level to "supplement assessment of global risk."<sup>6</sup> The guidelines mention point-of-care marker testing (and specifically bedside multimarker tests) but make no recommendations about their use.

The identification of biomarker-positive patients has therapeutic implications for the emergency physician. Patients with NSTEMI derived increased benefit from platelet glycoprotein Iib/IIIa inhibitors upstream, ie, begun when the diagnosis is established, and at percutaneous coronary intervention,<sup>23-25</sup> low-molecular-weight heparin (versus unfractionated heparin),<sup>26,27</sup> dual antiplatelet therapy with clopidogrel plus aspirin (as opposed to aspirin alone),<sup>28</sup> and an early invasive approach compared with early

**Table 3.** Features used in calculation of the TIMI,<sup>31</sup> GRACE,<sup>33,34</sup> and PURSUIT<sup>35</sup> risk scores for patients with known or suspected non-ST-segment-elevation acute coronary syndrome.

Feature	TIMI	GRACE	PURSUIT
Age	>65 y	Risk increases with each decade	Risk increases with each decade
Anginal history	>2 Events in 24 h		Worst CCS class in previous 6 wk
Cardiac risk profile Examination	>3 CAD risk factors	History of CHF or myocardial infarction	Signs of heart failure
ECG findings	ST deviation	Risk increases with increasing pulse and decreasing blood pressure	ST depression
Biomarkers	Risk increases if positive	ST depression	ST depression
Previous CAD	>50% Stenosis	Risk increases if positive	Risk increases if positive
Other laboratory tests		Risk increases if serum creatinine level is increased	
Medication exposure	Aspirin within 7 days		
Subsequent course		Risk increases if percutaneous coronary intervention not performed	

CCS, Canadian Cardiovascular Society; CHF, congestive heart failure; PCI, percutaneous coronary intervention.

conservative management<sup>29,30</sup> than did patients with “biomarker-negative” unstable angina. This consistency of effect reinforces the need for prospective, risk-adjusted management of NSTEMI in the ED that is aligned with the care that follows.

Another approach to risk stratification is the use of mathematical risk stratification models developed from clinical trials in non-ST-segment-elevation acute coronary syndrome patients. The 2002 guidelines discussed the Thrombolysis in Myocardial Infarction (TIMI) risk score for guiding stratification of both risk and therapy.<sup>2,5,31</sup> Since then, data from an unselected ED chest pain population have validated its utility.<sup>32</sup> The TIMI risk calculator is available for download at <http://www.timi.org>. The 2007 guidelines state that such tools can be useful in clinical decisionmaking in patients with known or suspected acute coronary syndrome (IIa-B) and also suggest that the Global Registry of Acute Coronary Events (GRACE) risk score<sup>33,34</sup> and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model<sup>35</sup> can be used in this fashion. The GRACE score is also used in assessing mortality risk for STEMI patients; it is available for download at <http://www.outcomes-umassmed.org/grace>.

All 3 models are potentially useful in the ED (ie, before diagnostic angiography), although the TIMI score is probably the simplest. A study comparing the 3 showed good predictive accuracy for 1-year death and myocardial infarction in all 3, therefore reinforcing their use in making risk-directed therapeutic decisions.<sup>36</sup> A compilation of the queries involved in calculating each of the 3 scores is presented in Table 3. These models were developed from population-based studies and should not be considered completely reliable for individual patients; therefore, they are to be used to supplement clinical judgment and not to replace it. They also may be used to provide a common terminology in the exchange of information between emergency physicians and cardiologists.

Patients who are not at sufficiently *high* risk to warrant immediate admission with or without intervention, nor at sufficiently *low* risk to warrant discharge without serial testing, may benefit from evaluation in a specialized chest pain unit. These are protocol-driven facilities, often contained within an ED, the goal of which is to reach a decision on the disposition of patients with possible acute coronary syndrome within 24 hours. Usually incorporating a set schedule of ECG and marker assays and culminating (if these are negative) with functional or provocative testing, these units may offer a cost-effective and streamlined approach to the risk stratification of chest pain and related complaints. The potential for cost savings depends on several factors, including (1) the hospital's admission rate of low-risk patients, (2) the extent to which care can be protocolized across specialty lines, and (3) the consistency with which such protocols, once developed, are followed. Typical candidates for chest pain unit evaluation are those with chest pain syndrome whose diagnosis is unclear after initial history-taking, physical examination, 12-lead ECG results, and biomarker assay results. This approach earns a I-B recommendation in the 2007 guidelines.<sup>6</sup> The Task Force also suggests (IIa-B) that coronary computed tomographic (CT) angiography is “reasonable as an alternative” to conventional stress testing.<sup>6</sup> Indeed, early experience with coronary CT angiography in the ED has been positive.<sup>37,38</sup>

### Bottom Line

Risk stratification is a challenging and often subjective exercise that at times may be frustrating. There are many individual indicators of risk—history and character of pain or presumed anginal equivalent, ECG, biomarkers, imaging studies—and some are clear in their indication of high risk, although their absence does not reliably confirm low risk. Chest pain units allow time and consistency to improve risk-stratification performance and safety. Algorithms and models

may prove useful in standardizing the approach but should be used only to supplement clinical judgment, not replace it.

## ANTI-ISCHEMIC THERAPY

The primary changes in the 2007 guidelines about anti-ischemic therapy address the use of  $\beta$ -adrenergic blockers.  $\beta$ -Blockers benefit patients with non-ST-segment-elevation acute coronary syndrome by reducing myocardial oxygen demand and increasing the duration of diastole. Recent findings in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) study<sup>39</sup> called into question the risk:benefit balance of intravenous, then oral (versus oral only) dosing, primarily in patients who were hemodynamically unstable, and the non-ST-segment-elevation acute coronary syndrome guidelines mirror these concerns. Oral  $\beta$ -blocker therapy is recommended to be initiated within the first 24 hours of care for the non-ST-segment-elevation acute coronary syndrome patient, as long as none of the following contraindications are present (I-B)<sup>6</sup>:

- Signs of heart failure or low-output state
- Increased risk for cardiogenic shock (age >70 years, systolic blood pressure <120 mm Hg, sinus tachycardia >110 beats/min, or bradycardia <60 beats/min)
- PR interval greater than 0.24 seconds
- Second- or third-degree heart block
- Active reactive airway disease

Intravenous  $\beta$ -blockade in the same clinical scenario is recommended only at a IIa-B level, representing a more cautious approach than that advocated in 2002, when such use had been level I-B.<sup>2,5,6</sup> Still, studies have shown a moderate net clinical benefit to IV initiation of  $\beta$ -blockers in acute coronary syndrome patients who are stable and at low risk of shock.<sup>39,40</sup> Emergency physicians and cardiologists should reach a consensus prospectively on a consistent approach to  $\beta$ -blocker dosing in individual hospitals.

There are also new drug-drug interaction concerns expressed in the 2007 guidelines that have become evident since the 2002 guidelines were published. Nitrates should not be administered to non-ST-segment-elevation acute coronary syndrome patients who have taken a phosphodiesterase inhibitor for erectile dysfunction within 24 hours of sildenafil use or 48 hours of tadalafil use (III-C).<sup>6</sup> Nitrate-mediated vasodilation is both exaggerated and prolonged in the presence of these drugs.<sup>41-43</sup> It is important for the emergency physician to query patients specifically about the use of such drugs, rather than relying on voluntary disclosure.

There is a new caution (III-C) about the use of nonsteroidal anti-inflammatory drugs (excluding aspirin) during the acute management of patients with non-ST-segment-elevation acute coronary syndrome. Whether nonselective or cyclooxygenase-2-selective drugs, the guidelines cite increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with the use of these drugs.<sup>6</sup> It is recommended that these drugs be discontinued immediately on diagnosis of acute coronary syndrome.<sup>44-46</sup>

Finally, the use of morphine sulfate for ischemic discomfort uncontrolled by nitrates is recommended at a IIa-B level.<sup>6</sup> It received a I-C recommendation in 2002.<sup>2</sup> Data published since then from the CRUSADE Registry showed that the 30% of 57,039 high-risk non-ST-segment-elevation acute coronary syndrome patients who received morphine sulfate had a higher unadjusted and adjusted likelihood of inhospital mortality (propensity-adjusted odds ratio=1.41; 95% confidence interval [CI] 1.26 to 1.57).<sup>47</sup> Although subject to the usual limitations of registry data analysis, this finding at least raises a new safety concern and should be considered during ED patient management.

## Bottom Line

$\beta$ -Blockers are an important component of the ED management of patients with acute coronary syndrome. New data suggest that unless the patient has refractory angina or is markedly hypertensive or tachycardic, oral  $\beta$ -blockade is probably sufficient without intravenous loading. Nonsteroidal anti-inflammatory drugs such as ibuprofen and ketorolac should not be given when acute coronary syndrome is suspected. A thorough history of medication use should be obtained before nitroglycerin is administered, and although there are no prospective data on alternative drugs for analgesia, morphine sulfate should perhaps be reserved for significant pain unrelieved by both nitrates and  $\beta$ -blockers.

## INITIAL MANAGEMENT STRATEGY

The 2002 non-ST-segment-elevation acute coronary syndrome guidelines recommended (I-A) that patients with any high-risk feature optimally undergo diagnostic angiography and revascularization as indicated within 48 hours of arrival; there was a I-B recommendation for interventional management even in the absence of a high-risk finding.<sup>2,5</sup> In 2007, the guidelines use new terminology: an “initial invasive,” “early invasive,” or simply “invasive” strategy, in which patients being treated with evidence-based anti-ischemic, antithrombotic, and antiplatelet medications will undergo coronary angiography from 4 to 24 hours after admission is differentiated from an “initial conservative” or “selectively invasive” strategy. For simplicity, we refer herein to early invasive strategy and selectively invasive strategy because the guidelines refer to a base strategy of invasive risk stratification and treatment as indicated, with a lesser degree of evidentiary support (see below) for delaying the invasive approach. In the selectively invasive strategy, patients are taken for an invasive evaluation only if they fail intensive medical management (refractory angina, angina at rest) or have objective evidence of ongoing ischemia (dynamic ST-segment changes, high-risk stress test, or, variably, positive biomarkers).<sup>6</sup>

The 2007 recommendations are as follows:<sup>6</sup>

- I-A: An early invasive strategy is indicated in initially stabilized unstable angina/NSTEMI patients who have an increased risk for clinical events.
- I-B: Unless there are significant comorbidities or contraindications, an early invasive strategy is indicated for

patients with refractory angina or hemodynamic or electrical instability.

- IIb-B: In initially stabilized patients, a selectively invasive strategy *may be considered* [our emphasis] in patients with an increased risk for clinical events.
- III-C: An early invasive strategy is not recommended in patients with acute chest pain syndrome and a low likelihood of acute coronary syndrome, nor in patients who will not consent to revascularization regardless of the findings.

Recent data supporting the early invasive strategy include several meta-analyses,<sup>48-50</sup> long-term results from the Third Randomized Intervention Treatment of Angina (RITA-3) Study,<sup>50</sup> the Intracoronary Stenting with Antithrombotic Regimen Cooling-off (ISAR-COOL) Trial,<sup>51</sup> and the Value of First Day Angiography/Angioplasty in Evolving Non-ST Segment Myocardial Infarction: Open Multicenter Randomized (VINO) Trial.<sup>52</sup> An early invasive strategy provides a definitive (ie, angiographic) assessment of risk and can quickly identify the 10% to 20% of patients with no significant disease and the 20% who have 3-vessel or left main disease, allowing earlier surgical revascularization for the latter.<sup>6</sup> Previous concerns about the hazards of early percutaneous coronary intervention have been ameliorated by the use of aggressive, risk-directed, upstream, medical therapy. A formal meta-analysis of early invasive strategy versus a selectively invasive strategy has concluded that the former results in an 18% relative reduction in death or myocardial infarction and a significant reduction in the single death endpoint, along with improved quality of life.<sup>48</sup>

The RITA-3 trial compared early invasive strategy with the selectively invasive strategy in 1,810 moderate-risk non-ST-segment-elevation acute coronary syndrome (NSTEMI patients were excluded) patients. A reduction in refractory angina drove a slight early benefit to the early invasive strategy, but in longer follow-up at 5 years, the early invasive strategy–managed patients had lower death and myocardial infarction rates.<sup>50</sup> The smaller VINO trial randomized 131 NSTEMI patients to catheterization on the day of admission versus selectively invasive strategy. Even though 40% of the selectively invasive strategy patients received revascularization by 6 months, there was a significant reduction (6% versus 22%) in death or repeated myocardial infarction in the early invasive strategy patients.<sup>52</sup> Both moderate- and high-risk patients were enrolled in ISAR-COOL (n=410) and were randomized to either very early or delayed angiography. Intensive medical therapy (aspirin, heparin, clopidogrel [including a 600-mg loading dose], and tirofiban) was administered to all patients.<sup>51</sup> Times to catheterization were 2.4 versus 86 hours, and the most informative finding in the study was that there was a significant reduction in events occurring before catheterization in the early invasive strategy group, suggesting that “cooling down” acute coronary syndrome patients is not routinely beneficial. Overall, the very early invasive strategy was associated with better 30-day death and myocardial infarction rates (5.9% versus 11.6%).<sup>51</sup>

Important to the emergency medicine perspective, these 3 studies cross the risk spectrum from moderate to high and show a consistency of benefit to the combination of aggressive medical management and prompt angiography.

Recent data supporting the selectively invasive strategy include the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial<sup>53</sup> and several observational studies.<sup>54</sup> In the European ICTUS study, 1,200 high-risk non-ST-segment-elevation acute coronary syndrome patients were randomized to receive a selectively invasive strategy or an early invasive strategy; the former group received aspirin, clopidogrel, low molecular weight heparin, and lipid-lowering therapy, and those who underwent percutaneous coronary intervention also received abciximab,<sup>53</sup> reflecting an intensity of medical management not often achieved in contemporary US practice.<sup>55</sup> The ability to detect a reproducible difference between the 2 arms was doubtless affected by the fact that 47% of the selectively invasive strategy patients eventually underwent revascularization. This being said, however, the 1-year and 3-year rates of death, myocardial infarction, and rehospitalization for acute coronary syndrome were not different.<sup>53</sup> This finding is inconsistent with the long-term follow-up results of RITA-3.<sup>50</sup> Finally, a Cochrane analysis of early invasive strategy versus selectively invasive strategy in the stent era concluded that there is a long-term morbidity and mortality benefit of the early invasive strategy.<sup>56</sup> However, an advantage of the selectively invasive strategy is that many patients, particularly those at lower risk, will stabilize on optimal medical management and will not require angiography, resulting in a cost savings, although not necessarily a shorter hospital stay.<sup>6</sup>

### Bottom Line

Although contemporary data (with the exception of ICTUS) favor on balance the early invasive approach, all of the early versus delayed studies have used aggressive medical therapy as a foundation approach for all patients. Therefore, regardless of the ultimate management strategy chosen by the treating cardiologist, optimal outcomes can be expected only when the emergency physician provides evidence-based medical stabilization to non-ST-segment-elevation acute coronary syndrome patients before transition of care. This involves not only anti-ischemic therapy but also the use of antithrombotic and antiplatelet agents, administered according to a clinical assessment of risk *before* angiography.

### ANTICOAGULATION THERAPY

There have been several important studies of anticoagulation therapy for non-ST-segment-elevation acute coronary syndrome completed since the publication of the 2002 guidelines. These have prompted a number of new recommendations in the 2007 guidelines, which are summarized in Table 4.

Anticoagulation is appropriate for patients deemed to be at intermediate or higher acute coronary syndrome ischemic risk.

**Table 4.** Recommendations for antithrombotic therapy in non–ST-segment-elevation acute coronary syndrome patients in the 2002<sup>2,5</sup> and 2007<sup>6</sup> ACC/AHA guidelines.\*

Agent	2002 Guidelines	Level	2007 Guidelines	Level
UFH	Initiate for treatment	I-A	EIS: initiate SIS: initiate	I-A I-A
Enoxaparin	Initiate for treatment Preferred over UFH	I-A IIa-A	EIS: initiate SIS: initiate SIS: preferred over UFH	I-A I-A IIa-B
Fondaparinux	Not rated		EIS: initiate SIS: initiate SIS with increased bleeding risk: initiate SIS: preferred over UFH	I-B I-B I-B IIa-B
Bivalirudin	Not rated		EIS: initiate	I-B

EIS, Early invasive management strategy; SIS, selectively invasive management strategy; UFH, unfractionated heparin.

\*The 2007 guidelines differentiate drug choice by management strategy (early invasive versus selectively invasive).

There are many options for anticoagulation in the upstream environment, and the choice is informed by many issues, including (1) emergency physician preference, (2) cardiologist preference, (3) perceived level of ischemic risk, (4) concern for hemorrhagic risk, (5) likely duration of therapy before angiography and possible revascularization, (6) logistical issues such as US Food and Drug Administration (FDA) labels and formulary inclusion, and (7) local standard of care. There are more options than ever for anticoagulation in the acute coronary syndrome patient, including both indirect antithrombin agents (unfractionated heparin, low-molecular-weight heparins, and anti-Xa inhibitors) and direct antithrombins. Comparing these options head to head is frequently problematic because trials are often designed or executed in a fashion that makes uncertain (1) the equivalent potency of drugs being compared, (2) the impact of prerandomization anticoagulation therapy (often administered in the ED), (3) the inconsistency and impact of concomitant antiplatelet therapy, (4) the intensity of procedures received by patients, and (5) basic study design issues, such as superiority versus noninferiority endpoints.

The 2007 guidelines also place an increased emphasis on the avoidance of bleeding complications in the management of non–ST-segment-elevation acute coronary syndrome.<sup>6</sup> Because of a relationship between bleeding events and increased risk of ischemic events and death,<sup>57</sup> there are new recommendations for anticoagulation and antiplatelet therapy that link choices among agents to the attenuation of bleeding risk. In the ED, bleeding risk may be assumed to be higher than average in patients who are older, are female, have diminished renal function, and are anemic at presentation.<sup>6,58</sup>

The major new studies of anticoagulants considered in the 2007 guidelines are the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) Trial,<sup>59</sup> the Organization to Assess Strategies for Ischaemic Syndromes (OASIS)-5 Study,<sup>60</sup> and the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) Trial.<sup>61</sup> SYNERGY was a study that compared enoxaparin with unfractionated heparin in patients with non–

ST-segment-elevation acute coronary syndrome and high-risk features who were to be treated with an early invasive strategy. The dose of enoxaparin was 1 mg/kg subcutaneously every 12 hours, with a supplemental intravenous dose (0.3 mg/kg) given in the event of percutaneous coronary intervention more than 8 (but less than 12) hours after the last subcutaneous dose. The dose of unfractionated heparin was an intravenous bolus of 60 U/kg (up to 5000 U) and then an initial infusion of 12 U/kg per hour (up to 1000 U/hour), further adjusted with a goal-activated partial thromboplastin time of 50 to 70 seconds. Patients with an estimated creatinine clearance of less than 30 mL/minute were excluded. Patients may have received no anticoagulation or treatment with either enoxaparin or unfractionated heparin before randomization. All other treatment (clopidogrel, glycoprotein IIb/IIIa inhibitors,  $\beta$ -blockers, statins, etc) was left to the discretion of the treating physician, although compliance with the 2002 guidelines was encouraged.<sup>59</sup>

Overall, 92% of the patients underwent diagnostic angiography, and roughly half of those underwent percutaneous coronary intervention; 19% of the 10,027 patients underwent coronary artery bypass grafting surgery, a high proportion probably attributable to the advanced age of the subject population (one quarter were aged 75 years and older). There were no baseline or procedural intensity differences between the 2 groups. Median time from randomization to catheterization was 22 hours, although some 8 to 10 hours typically elapsed between presentation and randomization. The primary efficacy endpoint failed to show superiority of enoxaparin, although noninferiority criteria (at a 10% margin) were satisfied; 14.0% of the enoxaparin patients had death or myocardial infarction by 30 days, whereas 14.5% of the unfractionated heparin patients met the endpoint (hazard ratio 0.96; 95% CI 0.86 to 1.06). The safety endpoint was less clear cut, with the enoxaparin patients experiencing a statistically significant increase in TIMI major bleeding (9.1% versus 7.6%;  $P=.008$ ) but a nonsignificant excess of Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries severe bleeding (2.7% versus 2.2%;  $P=.08$ ) and RBC

$$\text{Estimated creatinine clearance in males} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times \text{serum creatinine (mg/dl)}}$$

$$\text{Estimated creatinine clearance in females} = \frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}$$

**Figure 1.** Formula for estimating creatinine clearance.

transfusions (17.0% versus 16.0%;  $P=.16$ ).<sup>59</sup> At least some of the excess bleeding was attributable to crossover from enoxaparin to unfractionated heparin at percutaneous coronary intervention in this unblinded study,<sup>62</sup> once more reinforcing the need for good communication and collaboration between emergency physicians and cardiologists. At 6 months' follow-up, patients who received only enoxaparin had statistically lower death and myocardial infarction rates than those who received only unfractionated heparin (hazard ratio 0.85; 95% CI 0.75 to 0.95;  $P=.006$ ), and at 12 months, mortality between the 2 groups was similar.<sup>63</sup> The 2007 guidelines give enoxaparin a I-A recommendation for use as an anticoagulant in non-ST-segment-elevation acute coronary syndrome, whether in early invasive strategy- or selectively invasive strategy-managed patients (Table 4).<sup>6</sup> The dosing interval for enoxaparin should be doubled from 12 to 24 hours if creatinine clearance, which can be readily estimated in the ED (Figure 1), is less than 30 mL/minute.

The OASIS-5 study compared fondaparinux to enoxaparin in patients with non-ST-segment-elevation acute coronary syndrome and high-risk features.<sup>60</sup> Fondaparinux is an indirect (mediated by antithrombin III, as with UFH and LWMHs) inhibitor of factor Xa. Inhibition at the Xa step of the coagulation cascade blocks the amplification of downstream coagulation reactions and therefore impedes the generation of thrombin, although there is no action against thrombin that is already formed or that is produced despite fondaparinux's action. This agent has been shown to be an effective anticoagulant and is indicated for the treatment of deep venous thrombosis and pulmonary embolism.<sup>64,65</sup>

The OASIS-5 investigators compared a control strategy of enoxaparin 1.0 mg/kg subcutaneously twice daily (once daily if creatinine clearance was <30 mL/minute), coupled with UFH at percutaneous coronary intervention if performed more than 6 hours after the last enoxaparin dose, versus a strategy of fondaparinux 2.5 mg subcutaneously daily (one third the venous thrombosis treatment dose), with more fondaparinux or UFH at percutaneous coronary intervention. OASIS-5 was designed and powered as a noninferiority trial. After enrollment of about 60% of the 20,078 non-ST-segment-elevation acute coronary syndrome patients in the study, the protocol was amended to allow more UFH in the catheterization laboratory in response to the finding that catheter-associated thrombus was reported 3 times more frequently (0.9% versus 0.3%) in the fondaparinux arm than in the enoxaparin arm,<sup>60</sup> but given the findings of increased bleeding in the SYNERGY study

among patients who received both enoxaparin and UFH,<sup>62</sup> the change may have negatively affected the safety profile of enoxaparin in this double-blind, double-dummy study.

In OASIS-5, only about two thirds of the patients underwent diagnostic angiography; just over half of these had percutaneous coronary intervention, and the coronary artery bypass graft rate overall was under 10%. The primary ischemic outcome (death, myocardial infarction, or refractory ischemia) at 9 days showed no difference between the 2 groups (5.8% with fondaparinux, 5.7% with enoxaparin; hazard ratio for fondaparinux 1.01; 95% CI 0.90 to 1.13) but met the noninferiority margin of 18.5%. At 30 days and at 6-month follow-up, patients receiving fondaparinux experienced a nonsignificant trend toward better composite ischemic outcomes, although the single endpoints of death at 30 days ( $P=.02$ ) and 180 days ( $P=.05$ ) and of stroke at 180 days ( $P=.04$ ) significantly favored fondaparinux. In the safety analysis of OASIS-5, major bleeding was much less common in the fondaparinux arm at 9 days (2.2% versus 4.1%; hazard ratio 0.52;  $P<.001$ ), driving a net benefit (primary ischemic composite plus major bleeding) that favored fondaparinux (7.3% versus 9.0%; hazard ratio 0.81; 95% CI 0.73 to 0.89;  $P<.001$ ).<sup>60</sup>

The 2007 guidelines recommend fondaparinux at a I-B level, with particular emphasis on choosing it for patients at increased risk for bleeding (Table 4).<sup>6</sup> Emergency physicians must be aware that patients treated with upstream fondaparinux should receive an additional anticoagulant with antithrombin (specifically, anti-IIa) activity at percutaneous coronary intervention, making it essential that the choice of fondaparinux for initial management be clearly communicated to the interventional team, if applicable.

The ACUTY study was more complex than SYNERGY and OASIS-5, involving a subrandomization for antiplatelet therapy, as well as a comparison between anticoagulation strategies.<sup>61</sup> The study drug in ACUTY was bivalirudin, a direct (ie, not requiring antithrombin III) anti-IIa anticoagulant. Bivalirudin is a synthetic analog of hirudin that binds bivalently and reversibly to both circulating and clot-bound thrombin. It therefore interferes directly with coagulation and inhibits the thrombin-mediated activation of platelets. In ACUTY, bivalirudin with or without upstream glycoprotein IIb/IIIa inhibitor was compared with "a heparin" (UFH or enoxaparin), with or without upstream glycoprotein IIb/IIIa inhibitor, and to bivalirudin with glycoprotein IIb/IIIa inhibitor given only provisionally in 13,819 patients destined for an early invasive strategy. The randomization was unblinded and could occur after treatment with a heparin or glycoprotein IIb/IIIa inhibitor had already been initiated. The study was designed and powered for noninferiority, with a large margin of 25%. The dose of bivalirudin used upstream was 0.1 mg/kg intravenous bolus (about one seventh the labeled bolus for percutaneous coronary intervention) and then 0.25 mg/kg per hour; there was a second bolus and a higher infusion dose if the patient

**Table 5.** Recommendations for antiplatelet therapy in non–ST-segment-elevation acute coronary syndrome patients in the 2002<sup>2,5</sup> and 2007<sup>6</sup> ACC/AHA guidelines.\*

Agent	2002 Guidelines	Level	2007 Guidelines	Level
ASA	Initiate promptly	I-A	Initiate promptly	I-A
Clopidogrel	Initiate promptly in ASA-allergic patients (dose not specified)	I-A	Initiate promptly in ASA-allergic patients; give loading dose	I-A
	Initiate promptly in non–ST-segment-elevation acute coronary syndrome; give loading dose	I-A	EIS: initiate with loading dose as soon as possible OR give small-molecule GPI	I-A
	Hold if coronary artery bypass graft is planned within 5-7 days	I-B	Hold if coronary artery bypass graft is planned within 5-7 days	I-B
			SIS: initiate with loading dose as soon as possible SIS with later high risk: initiate with loading dose as soon as possible OR give small-molecule GPI	I-A
Small-molecule GPI	Initiate for treatment if catheterization and percutaneous coronary intervention are planned	I-A	EIS: initiate OR give loading dose of clopidogrel	I-A
			EIS: initiate AND give loading dose of clopidogrel	IIa-B
	Initiate as medical management in high-risk patients	IIa-A	SIS with later high risk: initiate upstream	IIa-C
	Initiate in addition to ASA and anticoagulation and clopidogrel if catheterization and percutaneous coronary intervention are planned	IIa-B	EIS: may omit upstream GPI if patient receives bivalirudin and at least 300 mg clopidogrel <6 h before catheterization and percutaneous coronary intervention	IIa-B
	Initiate as medical management in non–high-risk patients when catheterization and percutaneous coronary intervention are not planned	IIb-A		
Large-molecule GPI	Initiate if catheterization and percutaneous coronary intervention are planned	I-A	EIS: initiate	I-A
	Not appropriate for medical management when percutaneous coronary intervention not planned <24 h	III-A	Not appropriate for medical management when percutaneous coronary intervention not planned <24 h	III-A

ASA, Aspirin; CABG, coronary artery bypass graft; GPI, glycoprotein IIb/IIIa inhibitor.

\*The 2007 Guidelines differentiate drug choice by management strategy (early invasive versus selectively invasive).

underwent percutaneous coronary intervention. The doses of heparin and enoxaparin were the same as those used in SYNERGY.<sup>61</sup>

There was a second randomization for timing of glycoprotein IIb/IIIa inhibitor administration in first 2 arms defined above, between initiation at randomization (by definition, upstream of catheterization) and at percutaneous coronary intervention, if performed (see below). Patients enrolled were at moderate to high risk with non–ST-segment-elevation acute coronary syndrome, and in this manner ACUITY differs from SYNERGY and OASIS-5, which evaluated only high-risk patients. The primary outcome in ACUITY was the composite of ischemic complications (death, myocardial infarction, unplanned revascularization) and major bleeding (inclusive of, but not limited to, TIMI major criteria), termed “net clinical benefit.” At 30 days, bivalirudin plus glycoprotein IIb/IIIa inhibitor showed similar outcomes to heparin plus glycoprotein IIb/IIIa inhibitor. Comparing the latter with

bivalirudin monotherapy, bivalirudin resulted in noninferior rates of composite ischemia (7.8% versus 7.3%;  $P=.32$ ; relative risk 1.08; 95% CI 0.93 to 1.42), significantly reduced major bleeding (3.0% versus 5.7%;  $P<.001$ ; relative risk 0.53; 95% CI 0.43 to 0.65), and significantly improved net clinical outcome (10.1% versus 11.7%,  $P=.015$ ; relative risk 0.86; 95% CI 0.77 to 0.97).<sup>61</sup>

Subgroup analysis revealed that much of the ischemic benefit of the bivalirudin monotherapy arm was lost if patients did not also receive a thienopyridine before angiography or percutaneous coronary intervention. This is a consideration if bivalirudin is initiated as an anticoagulant in the ED. The median time from randomization to catheterization in ACUITY was only 4 hours,<sup>61</sup> substantially faster than the presentation-to-catheterization interval in contemporary practice (CRUSADE: 22 hours<sup>55</sup>). The 2007 guidelines recommend that bivalirudin be used (I-B) in the patient undergoing an early invasive strategy and (IIa-B) that, when given with a clopidogrel loading dose at least 6

hours before catheterization, it be used without a glycoprotein IIb/IIIa inhibitor (Table 5).<sup>6</sup>

### Bottom Line

Nowhere is it more clear than with anticoagulant therapy that “one size does *not* fit all.” Heparin and enoxaparin, already in widespread use in the ED for patients with non-ST-segment-elevation acute coronary syndrome across a range of risks, continue to be recommended at a I-A level, whether the patient is treated with an early invasive strategy or a selectively invasive strategy. New recommendations pertinent to the emergency physician include fondaparinux and bivalirudin, both of which carry the advantage of lower bleeding risk and therefore are pertinent when the acute coronary syndrome patient is female, older, or anemic or has diminished renal function. The former has the disadvantage of requiring an additional agent in the catheterization laboratory. The latter has been studied primarily in the patient who is rapidly transitioned to the catheterization laboratory, may require supplemental antiplatelet therapy (in which case agent cost may become an issue), and trends towards poorer ischemic outcomes. The use of either of these new agents will require close cooperation between the ED, the treating cardiologist, and the catheterization laboratory.

### ANTIPLATELET THERAPY

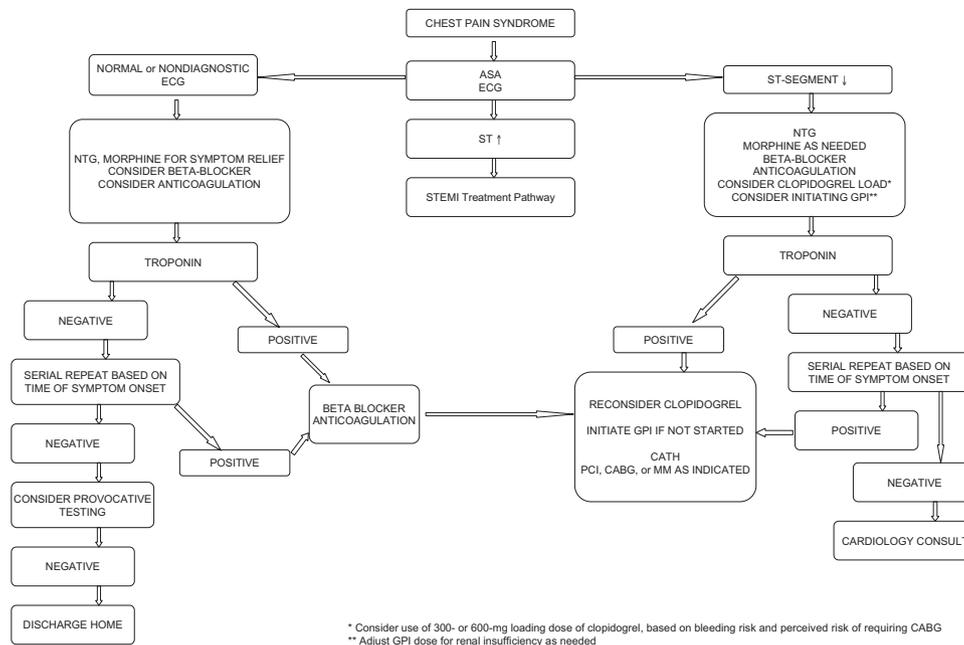
Unlike the approach to optimal anticoagulation therapy for non-ST-segment-elevation acute coronary syndrome, there has been a relative paucity of new data on antiplatelet therapy since release of the 2002 guidelines. The 2007 guidelines’ recommendations for antiplatelet therapy are summarized in Table 5. There are no new data for the use of aspirin, which has been considered to be standard of care for many years. There are scant new data on clopidogrel, but a combination of broad clinical experience,<sup>66</sup> its ease of administration, the use of drug-eluting stents, and its linkage to new antithrombotic regimens (see discussion of the ACUITY trial, above) has resulted in wider recommendations for its use.

There has been a clarification of the dose of clopidogrel to be used as an aspirin substitute; the recommended approach is to give a loading dose of 300 mg in the ED for those occasional patients with allergy or hypersensitivity to aspirin.<sup>6</sup> This is the FDA-labeled loading dose for clopidogrel in all indications pertinent to the ED, but many emergency physicians will collaborate with interventional cardiologists who often load non-ST-segment-elevation acute coronary syndrome patients with 600 mg before percutaneous coronary intervention. A small trial has shown favorable outcomes with this approach,<sup>67</sup> but it has not been sufficiently studied in large-scale studies. The entire issue of clopidogrel loading is problematic for the emergency physician, who must be concerned that the acute coronary syndrome patient may require coronary artery bypass graft after diagnostic catheterization and that a recent load of clopidogrel will delay or complicate surgery. It may be reasonably assumed that a 600-mg loading dose would engender

even more enmity from cardiothoracic surgeons should the need for surgery ensue. The 2007 guidelines retain the caveat issued in 2002 that clopidogrel be withheld if coronary artery bypass graft is anticipated in 5 to 7 days, but in the ED there is no valid predictive tool for the need for coronary artery bypass graft. This issue once more highlights the need for cross-disciplinary collaboration among emergency physicians, cardiologists, and cardiothoracic surgeons to determine an optimal approach for their institution. In contemporary practice, the rate of near-term (during the index hospitalization) coronary artery bypass graft among high-risk non-ST-segment-elevation acute coronary syndrome patients is approximately 12%,<sup>55</sup> and among patients without high-risk features it is much lower, with the rate of truly emergency coronary artery bypass graft procedures at only about 1%.<sup>68</sup> It is important that the stakeholders in each facility be aware of their own incidence of coronary artery bypass graft in these patients because its low frequency may support broader upstream use of clopidogrel, accepting the increased risk of bleeding if coronary artery bypass graft ensues, to improve protection from ischemic events.

Of note, the European Society of Cardiology also updated its non-ST-segment-elevation acute coronary syndrome guidelines in 2007 and, though citing the same studies, recommends at a I-A level that at least 300 mg of clopidogrel be given as early as possible to all patients characterized as having non-ST-segment-elevation acute coronary syndrome, regardless of further risk differentiation.<sup>69</sup> These guidelines then go on to recommend that coronary artery bypass graft be delayed by 5 days if indicated, thereby taking the opposite approach to the problem as the ACC/AHA document, which recommends withholding clopidogrel until the risk of coronary artery bypass graft has been addressed.<sup>6</sup> In fact, the ESC guidelines state that “the approach of postponing clopidogrel administration until coronary anatomy is known in patients submitted to very early invasive angiography is not based on evidence.”<sup>69</sup> Recognizing the 2 starkly different interpretations of clinical trial data expressed in these documents may offer emergency physicians some insight into what many view anecdotally as the inconsistency and seeming unpredictability about the use of clopidogrel loading in individual non-ST-segment-elevation acute coronary syndrome patients by individual cardiologists.

An important change between the 2002 and 2007 guidelines is a new “either/or” approach to clopidogrel and glycoprotein IIb/IIIa inhibitors in upstream management of non-ST-segment-elevation acute coronary syndrome<sup>6</sup> (Table 5). For patients undergoing early invasive strategy, there is a new I-A recommendation that patients receive a loading dose of clopidogrel *or* a small-molecule glycoprotein IIb/IIIa inhibitor and a new IIA-B recommendation that patients treated with an early invasive strategy receive *both* clopidogrel and a glycoprotein IIb/IIIa inhibitor.<sup>6</sup> The latter approach is actually more intuitive, given that the 2 antiplatelet agents have different mechanisms (clopidogrel inhibits platelet activation, whereas glycoprotein IIb/IIIa inhibitors inhibit aggregation of platelets that are already activated) and sites



**Figure 2.** Early assessment and management of the patient with NSTEMI ACS. *NTG*, nitroglycerin; *GPI*, glycoprotein IIb/IIIa inhibitor; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass grafting surgery; *MM*, medical management.

(adenosine diphosphate versus glycoprotein IIb/IIIa receptors) of action, but should be pursued with great caution in patients with untoward bleeding risk or when there is increased likelihood (by whatever measure) of near-term coronary artery bypass graft. Should this be the case, the safer approach is to use a small-molecule glycoprotein IIb/IIIa inhibitor, the effects of which are short lived (clopidogrel's action is irreversible) and can be discontinued if coronary artery bypass graft is required. The clopidogrel-or-glycoprotein-IIb/IIIa-inhibitor approach is more difficult to support from the emergency medicine perspective, given that patients with symptoms of acute coronary syndrome in the ED can be assumed already to have activated platelets, and glycoprotein IIb/IIIa inhibitors are the only class of drugs that inhibit their aggregation. Furthermore, the 2 antiplatelet therapies have never been compared directly in a prospective study.

A recent clinical trial, Intracoronary Stenting with Antithrombotic Regimen-REACT-2 (ISAR-REACT-2),<sup>25</sup> illustrates this concept. In this study, 2,022 patients undergoing percutaneous coronary intervention received aspirin, UFH, 600 mg clopidogrel, and either abciximab (12-hour infusion) or placebo. Overall, the patients receiving abciximab experienced a lower rate of death or myocardial infarction (8.9% versus 11.9%), but the benefit was entirely confined to those patients who had increased troponin levels (ie, were at higher risk). Further, there was no difference between the 2 groups in bleeding complications.<sup>25</sup> This study, then, supports the addition of a glycoprotein IIb/IIIa inhibitor to even high-dose clopidogrel in non-ST-segment-elevation acute coronary syndrome patients who are at high risk.

Besides ISAR-REACT-2, the only new trial data on upstream glycoprotein IIb/IIIa inhibitor use in non-ST-segment-elevation acute coronary syndrome since the 2002 guidelines come from the secondary randomization of the ACUITY study (see above); there are also recent data on glycoprotein IIb/IIIa inhibitor use in contemporary practice in CRUSADE.<sup>70</sup> From ACUITY, as discussed above, one might reasonably conclude that upstream glycoprotein IIb/IIIa inhibitor therapy may not be necessary in patients who are not at high risk.<sup>61</sup> However, even in the moderate- to high-risk study population of ACUITY, bivalirudin monotherapy failed to meet generous noninferiority criteria for ischemic endpoints against a heparin plus upstream glycoprotein IIb/IIIa inhibitor therapy, although its use was associated with less major bleeding.<sup>71</sup> Furthermore, patients randomized in ACUITY to receive percutaneous coronary intervention-only glycoprotein IIb/IIIa inhibitor who subsequently did not undergo percutaneous coronary intervention never received glycoprotein IIb/IIIa inhibitor therapy, confounding the interpretation of these results. The 2007 guidelines IIA-B recommendation (Table 5) for the omission of upstream glycoprotein IIb/IIIa inhibitor in lieu of bivalirudin plus clopidogrel is in fact not supported by the ACUITY data in *high-risk* patients, although for percutaneous coronary intervention in those patients, bivalirudin is an effective anticoagulant (IIA-B). When given with glycoprotein IIb/IIIa inhibitor, bivalirudin loses some of its safety advantage, but ischemic efficacy trends toward improvement. It appears that patients who begin receiving UFH or enoxaparin in the ED can be safely transitioned to

bivalirudin in the catheterization laboratory,<sup>72</sup> and if an upstream glycoprotein IIb/IIIa inhibitor has been started as well, there are no data to suggest glycoprotein IIb/IIIa inhibitor therapy should not be continued with bivalirudin.

Contemporary registry data from the CRUSADE Initiative confirm the utility of glycoprotein IIb/IIIa inhibitor therapy in high-risk non-ST-segment-elevation acute coronary syndrome therapy.<sup>55</sup> They also demonstrate the potential for adverse effects of glycoprotein IIb/IIIa inhibitor therapy, bleeding, which is often associated with inappropriately high doses.<sup>73</sup> The small-molecule glycoprotein IIb/IIIa inhibitors are excreted through the kidneys, and doses should be adjusted both for creatinine clearance and actual body weight.<sup>74,75</sup> When this is done, the likelihood of major bleeding with appropriate dosing in contemporary practice diminishes significantly.<sup>55</sup>

### Bottom Line

Emergency physicians and cardiologists must address proper patient selection, timing of initiation, dose adjustments, and expected management strategy in reaching an evidence-based, consistent, and risk-appropriate multidisciplinary protocol for antiplatelet therapy in non-ST-segment-elevation acute coronary syndrome. Aspirin should be given as soon as possible after even potential acute coronary syndrome is recognized. Oral antiplatelet therapy with clopidogrel is simple and offers ischemic benefit but is associated with substantially increased bleeding risk if the patient requires near-term coronary artery bypass graft that cannot be delayed 5 days, because its effects on platelets are irreversible. Small-molecule glycoprotein IIb/IIIa inhibitor therapy is reversible and offers ischemic protection when platelets are already activated but is also associated with bleeding risk, although this can be minimized with proper dosing based on weight and estimated creatinine clearance. Patients at no untoward bleeding risk and unlikely to require coronary artery bypass graft may benefit from “triple” antiplatelet therapy with aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitor.

### SUMMARY

Evidence and opinions about the optimal management of non-ST-segment-elevation acute coronary syndrome are constantly in flux. The 2007 ACC/AHA guidelines offer a foundation on which substantive discussions among all the stakeholders in acute coronary syndrome care—emergency physicians, noninterventional cardiologists, hospitalists, internists, interventionalists, and cardiothoracic surgeons—can be held. It is essential to best patient outcomes that a coherent, evidence-based, and consistent approach or protocol be developed at each institution that maximizes an institution’s capabilities and minimizes its limitations in acute coronary syndrome care. These guidelines offer a convenient source for much of the information on which these often challenging decisions can be made, but for optimal impact, they must be coupled with knowledge of the institution’s own data on catheterization use and timing, ischemic outcomes, bleeding outcomes, incidence of near-term coronary artery bypass graft, etc. These institution-specific data, coupled with information from clinical

trials, should weigh more heavily in protocol development than personal preference for one agent or another, making the emergency physician’s management of acute coronary syndrome less problematic, more consistent, and ultimately more successful.

A guidelines-based flow chart for the management of non-ST-segment-elevation acute coronary syndrome is shown in [Figure 2](#).

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