2002 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

Charles V. Pollack, Jr., MA, MD
Matthew T. Roe, MD, MHS
Eric D. Peterson, MD, MPH

From the Pennsylvania Hospital, University of Pennsylvania Health System, Philadelphia, PA (Pollack), and the Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (Roe, Peterson).

The publication of comprehensive evidence-based guidelines for the management of non–ST-segment elevation acute coronary syndrome by the American College of Cardiology and the American Heart Association in September 2000 marked a sentinel event in the evolution of managing this challenging patient population. Many of the recommendations included in the guidelines have relevance to the emergency department care of patients with non–ST-segment elevation acute coronary syndrome and were summarized in *Annals of Emergency Medicine* in September 2001. New clinical data in this area continue to accumulate at a remarkably rapid rate, prompting the American College of Cardiology and the American Heart Association to publish an update of the 2000 guidelines in October 2002. Several of the modified and new recommendations again potentially affect ED management. These are presented and discussed here.

[*Ann Emerg Med.* 2003;41:355-369.]

0196-0644/2003/$30.00 + 0
doi:10.1067/mem.2003.88

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. Over the years, these guidelines have become increasingly evidence based, allowing clinicians to relate their practice preferences objectively to the strengths and weaknesses of published experience. In September 2000, 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).[1] It was a successor to the 1994 guideline published by the Agency for Healthcare Policy and Research (now the Agency for Healthcare Research and Quality).[2] The aspects of these guidelines most pertinent to emergency medicine practice were specifically summarized and discussed in September 2001 in *Annals of Emergency Medicine*.[3,4] On March 15, 2002, recognizing that a number of important trials involving patients with non–ST-segment elevation (NSTE) acute coronary syndrome had been published or presented since the literature review for the 2000 guidelines had been completed, the ACC/AHA Joint Task Force posted a mark-up update on the Web sites www.acc.org and www.americanheart.org. A summary of the update was published in October 2002.[5] Review of the changes and additions reveals a number of issues of immediate potential pertinence to ED practice, and it is our conviction that emergency physicians should remain current on the evidence basis underlying such recommendations. We therefore review and comment on them here. Other recommendations from the 2000 guidelines and relevant summary[3,4] not discussed in this review should still be considered valid.

DEFINITIONS AND WEIGHTING OF EVIDENCE

Unstable angina/NSTEMI comprises a clinical syndrome that presents as chest pain or its anginal equivalent (eg, dyspnea, jaw or arm pain) as the manifestation of decreased coronary blood flow. Unstable angina/NSTEMI is generally but not always caused by atherosclerotic coronary artery disease and is associated with an increased risk of transmural myocardial infarction (MI) and cardiac death. According to the National Center for Health Statistics, there were 1,433,000 hospitalizations for unstable angina/NSTEMI in the United States in 1996[6]; to put this into perspective, there were 5,315,000 ED visits for chest pain and related complaints in 1997.[7] At ED presentation, unstable angina/NSTEMI is often difficult to differentiate from other forms of acute coronary syndrome and from chest pain caused by noncoronary pathology. Furthermore, patients with NSTE acute coronary syndrome tend to be more heterogeneous (atypical pain patterns, varying ages, higher likelihood of renal insufficiency, difficulty in interpreting biomarker results) than those who present with MI.

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 ST-segment elevation MI (STEMI). Generally accepted standards of care are in place for patients with STEMI and involve urgent reperfusion therapy either by means of fibrinolysis or percutaneous coronary intervention[8]; the subject guidelines and this discussion 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, the MB band of creatine phosphokinase, or, in the appropriate time frame, myoglobin, 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:

- Class I: There is evidence or general agreement that a specific procedure or treatment is useful and effective.
- Class II: There is conflicting evidence or divergence of opinion about the utility or efficacy of a procedure or treatment.

• Class IIa: The weight of the evidence or opinion is in favor of utility-efficacy.

• Class IIb: Utility-efficacy is less well established by evidence or opinion.

• Class III: There is evidence or general agreement that a specific procedure or treatment is neither useful nor effective and might be harmful in some cases.

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:

• A (highest): The data were derived from multiple randomized clinical trials that involved large numbers of patients.

• 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.

• C (lowest): The primary basis for the recommendation is expert opinion.

Thus, each recommendation made in the guidelines is cited as Class I, II, 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

Changes from the 2000 guidelines in March 2002 that are pertinent to ED management of NSTE acute coronary syndrome can be summarized as follows:

• Risk stratification: For diagnosis, the value of clinical risk algorithms (eg, the Thrombolysis In Myocardial Infarction [TIMI] risk score) and the need for rapidly incorporating biomarker information is emphasized.

• Optimal management strategy: There has been a strong shift in favor of the recommendation for early interventional management in high-risk (see the following definition) patients with NSTE acute coronary syndrome. The recommendation for interventional management includes the use of platelet glycoprotein IIb/IIIa antagonists.

• Use of clopidogrel: The recommendations for antiplatelet therapy with clopidogrel (Plavix) have been significantly expanded.

• Use of anticoagulants: The recommendation for anticoagulation has been upgraded in general, and the low-molecular-weight agent enoxaparin (Lovenox) has received specific recommendations for use.

• Use of glycoprotein IIb/IIIa antagonists in noninterventional management: The recommendations for medical management with platelet glycoprotein IIb/IIIa antagonists have been refined.

Risk Stratification

Risk stratification for chest pain in the ED in the absence of diagnostic ECG findings remains an inexact science. Clinical acumen, ECG results, and biomarker assays are largely reliable but still miss 2% to 5% of patients with MI in the ED.[9] Quick and accurate risk stratification of patients with chest pain in the ED is essential to evidence-based initiation of early and aggressive medical and interventional management of NSTE acute coronary syndrome.

Across populations of patients, risk has been assessed by using multivariable regression techniques in patients presenting with unstable angina/NSTEMI in several large clinical trials. These have not yet been validated in large prospective studies of patients with NSTE acute coronary syndrome. Boersma et al[10] analyzed the relationship between baseline characteristics available in the ED and the incidence of death and death-plus-myocardial-reinfarction at 30 days. The most important baseline features associated with death were age, pulse rate, systolic blood pressure, ST-segment depression, signs of pump failure, and increased levels of biomarkers. A risk estimation score was developed from this analysis, but its complexity renders it not particularly amenable to bedside use in the ED.

A simpler approach that is potentially consistent with typical ED practice was published by Antman et al.[11] The TIMI investigators developed a 7-point risk score (Figure 1) that appears to be predictive of the risk of development of an adverse cardiac outcome (death, reinfarction, or urgent target vessel revascularization)

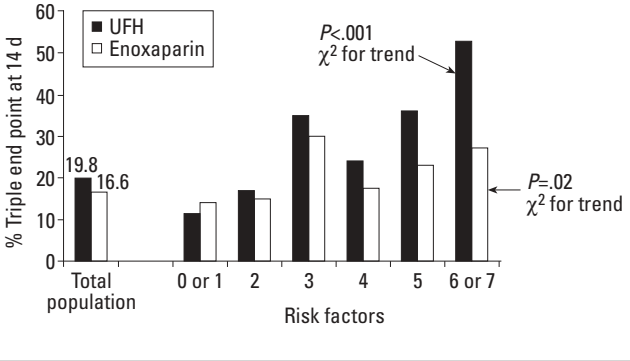
at 14 days after presentation. The TIMI risk score, the arithmetic sum of the 7 individual variables, relates to a risk of adverse outcomes ranging from 5% to 41% when applied retrospectively to large NSTEMI acute coronary syndrome databases. The score was derived from data in the TIMI-11B trial[12] and has been validated to date in 3 additional trials: Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE),[13] Treat Angina with aggrastat + determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18,[14] and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS).[15] Patients with NSTE acute coronary syndrome appear to derive progressively greater benefit from newer therapies, such as low-molecular-weight heparin,[12,13] platelet glycoprotein IIb/IIIa inhibition,[16] and an interventional strategy[14] with increasing risk score (Figure 2).[11] The TIMI risk score can easily be used to supplement other ED risk stratification approaches and is available for download into a palmtop computer.[17] Coupled with recommendations for risk-directed therapy (below), simplified risk stratification approaches are likely to improve ED care and facilitate management of patients with NSTE acute coronary syndrome by cardiology consultants.

One of the components of the TIMI risk score is the troponin level. As discussed previously,[3] troponin assay is an ED-accessible test for the presence of myocardial necrosis. Anecdotal reaction to the 2000 guidelines indicated that a considerable number of emergency physicians and cardiologists question the absolute reliability of currently available troponin assays for indicating the presence of a significant coronary artery lesion at coronary angiography (authors' experience, Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines [CRUSADE] Initiative regional educational meetings, 2001 to 2002). The updated guidelines specifically point out that, although troponins are accurate in identifying myocardial necrosis,[18] such necrosis is not necessarily caused by atherosclerotic coronary artery disease; troponin levels can also be increased in patients with myocarditis, cardiomyopathy, circulatory shock, and myocardial contusion. Furthermore, currently available troponin assays vary widely in their sensitivity and specificity. Therefore, in making the diagnosis of NSTEMI, cardiac troponins should be considered in the overall context of the patient's presentation; for example, the presence of

Figure 1.
The TIMI risk score uses features typically available in the ED to determine relative risk. Derived from the TIMI-11B study,[11] the score is additive without weighting (0 to 7). The features are shown.

- Age >65 y
- Documented prior coronary artery stenosis >50%
- Three or more conventional cardiac risk factors (eg, age, sex, family history, hyperlipidemia, diabetes, smoking, hypertension, obesity)
- Use of aspirin in the preceding 7 d
- Two or more anginal events in the preceding 24 h
- ST-segment deviation (transient elevation or persistent depression)
- Increased cardiac biomarkers

Figure 2.
Treatment effect for enoxaparin in relation to risk factors. The TIMI risk score was applied to the ESSENCE population; note that the response to enoxaparin improves as the risk level increases.[11] Similar benefit related to increasing risk has been shown for glycoprotein IIb/IIIa receptor blockade[16] and for interventional (versus noninterventional) therapy.[14,24] The triple end point (y-axis) is the composite of death, myocardial infarction, and urgent revascularization. ***UFH,*** *Unfractionated heparin.*



ST-segment depression on the ECG can magnify the diagnostic value of a borderline troponin level. On the other hand, although the old axiom "treat the patient, not the lab value" clearly applies to patients with chest pain, the presence of an increased troponin level across populations of patients with NSTE acute coronary syndrome is clearly associated with a higher risk of morbidity and mortality.[19-22] Levels of the MB band of creatine phosphokinase-MB, although not emphasized as much in the guidelines as troponin levels, remain useful in risk stratification of patients with chest pain and in defining MI. A reliable biomarker suggestive of myocardial ischemia instead of necrosis would clearly enhance early risk stratification; one such test, for ischemia-modified albumin, is currently on the market in Europe and Canada.[23] Markers of ischemia might indicate subtler risk and outcome levels of acute coronary syndrome, just as troponin improves sensitivity for detecting AMI. These markers are not currently recommended by the guidelines.

The bottom line for emergency medicine is that rapid and accurate risk stratification of patients with chest pain, particularly those without ST-segment elevation, is essential to optimal ED management. Risk stratification should be comprehensive and tailored to the capabilities of the individual institution and the preferences of the evaluating and consulting physicians. Chest pain risk stratification should be consistent in the ED to improve communication between the emergency medicine and cardiology services. Tools such as the TIMI risk score should be considered a systematic means of enhancing clinical judgment in the evaluation of these patients, although it should be noted that no studies have yet been published showing that decision tools change clinical decisionmaking when used in practice. Emergency physicians and cardiologists should work closely with their colleagues in the clinical laboratory to maximize the accuracy and turnaround time of troponin assays.

Optimal Management Strategy

In the 2000 guidelines, an early invasive strategy was recommended for patients with high-risk features (see the following text) at a Class I, Level B level. "Invasive" (or "interventional") strategy refers to coronary angiography, followed by revascularization (percutaneous coronary intervention or coronary artery bypass grafting), as dictated by the anatomy of the culprit lesion or lesions. The time parameter implied by the term "early" is not specifically defined in the guidelines but has generally been interpreted as "within 24 hours" (page 48, 2002 guidelines) or "within 24-36 hours" (page 35). "Medical management" is defined as management that does not include even diagnostic coronary angiography.

The 2002 guidelines more strongly recommend (Class I, Level A) an early interventional strategy in patients with unstable angina/NSTEMI and any of the following high-risk indicators:

- recurrent angina-ischemia at rest or with low-level activities despite intensive anti-ischemic therapy;
- increased troponin level;
- new or presumably new ST-segment depression;
- recurrent angina-ischemia with congestive heart failure symptoms, an S3 gallop, pulmonary edema, worsening rales, or new or worsening mitral valve regurgitation;
- high-risk findings on noninvasive stress testing;
- decreased left ventricular systolic function (eg, ejection fraction <40% on noninvasive study);
- hemodynamic instability;
- sustained ventricular tachycardia;
- history of percutaneous coronary intervention within 6 months; or
- history of coronary artery bypass grafting.

Any of these findings might be determined or might manifest during the evaluation of a patient with chest pain in the ED or an associated chest pain observation unit. Although emergency physicians control neither the availability of nor the access to interventional cardiology care, it is important that they understand the data supporting this approach in patients objectively identified as high risk in the ED.

As previously mentioned, this recommendation for an early interventional strategy represents an upgrade of the assessment of supporting data since the 2000 guidelines. After the publication of that document, 2

large and important studies were published: Fragmin and Fast Revascularisation during Instability in Coronary Artery Disease (FRISC) II[24] and TACTICS-TIMI 18.[14] Both of these studies, which compared invasive and conservative strategies, showed a benefit in patients with NSTE who underwent invasive management. Previous trials had been inconclusive, but a large majority of patients undergoing percutaneous coronary intervention in these 2 studies received coronary stenting as opposed to balloon angioplasty alone, and this technical advancement might be largely responsible for improved outcomes. In the European FRISC II study, the interventional strategy followed prolonged (mean 6 days) medical management with β-blockers, aspirin, nitrates, and the low-molecular-weight heparin dalteparin; this approach is not feasible in the US system. In TACTICS-TIMI 18, treatment included medical "stabilization" with the glycoprotein IIb/IIIa antagonist tirofiban for an average of 22 hours before coronary angiography, which might have reduced the excess risk of MI in the interventional arm during the first 7 days after presentation. This excess risk, observed in FRISC II and other trials in which there was no routine upstream use of a glycoprotein IIb/IIIa blocker and termed the "early hazard factor," has been cited as an argument against early intervention in the past. The use of upstream medical management with advanced anticoagulants and antiplatelet agents for high-risk patients in the ED has been previously advocated.[4]

An interventional strategy with glycoprotein IIb/IIIa receptor blockade is therefore associated with an improved outcome in high-risk patients with unstable angina/NSTEMI.[14] Although the benefit of intravenous glycoprotein IIb/IIIa inhibitors is established for patients with unstable angina/NSTEMI undergoing percutaneous coronary intervention, the optimum time to initiate this therapy has not been clearly established. In the Platelet glycoprotein IIb/IIIa in Unstable angina Receptor Suppression Using Integrilin Therapy (PURSUIT) trial,[25] there appeared to be a time-to-treatment benefit to the prompt initiation of eptifibatide, as would be feasible in the ED.[26] Furthermore, in patients with unstable angina/NSTEMI who were admitted to community hospitals in the PURSUIT trial, the administration of eptifibatide was associated with a reduced need for transfer to tertiary referral centers and with improved outcomes.[27] Similar benefit was found to accrue to the use of tirofiban in PRISM-PLUS.[28]

As in the 2000 guidelines, triple therapy (antiischemic, antithrombotic, antiplatelet) is recommended in 2002 for patients undergoing invasive management. There is a Class I, Level A recommendation for a platelet glycoprotein IIb/IIIa antagonist, aspirin, and a heparin compound in patients for whom catheterization and percutaneous coronary intervention are planned.[1,5] The 2002 guidelines state that the glycoprotein IIb/IIIa agent might "also be administered just prior to percutaneous coronary intervention," begging the question of whether the agent should be administered in the ED for patients in whom interventional management is planned. This is an issue that is optimally decided prospectively in each institution through multidisciplinary collaboration and planning that results in a chest pain pathway, so that the transition of care for patients with NSTE acute coronary syndrome from the ED to the cardiology service is consistent and seamless.

Guidelines such as the ACC/AHA document do not purport to represent the standard of care; they merely present, analyze, and rate the best evidence regarding care. Emergency physicians and their noninterventional cardiology colleagues who work in hospitals that do not provide ready access to interventional management of patients with NSTE acute coronary syndrome (either in house or by rapid transfer) can clearly provide efficacious medical management for these patients. The recommendations in the guidelines should, however, prompt an interdisciplinary review of each institution's capabilities and preferences in this regard. Regardless of the usual approach to cardiology management for patients with NSTE acute coronary syndrome in their institutions, emergency physicians should focus on rapid and accurate risk stratification of patients with chest pain and focus on aggressive medical therapy, such as antithrombin and antiplatelet therapy, for which a time-to-treatment benefit has been demonstrated.[4]

The bottom line for emergency medicine is that patients with NSTE acute coronary syndrome and high-risk features should optimally be managed interventionally with glycoprotein IIb/IIIa receptor blockade. In institutions with ready catheterization laboratory availability, emergency physicians can expedite this management by quickly identifying high-risk patients, initiating aggressive medical therapy, and involving interventional cardiologists early on in the patient's course. In institutions without ready catheterization laboratory availability, the dissemination of these guidelines should prompt a careful and thorough multidisciplinary reevaluation of optimal treatment pathways within the institution. Issues for discussion should include potential transfer arrangements and optimization of medical therapy, such as use of aggressive antiplatelet therapy before transfer for catheterization.

Use of Clopidogrel

One of the more important studies published since the release of the 2000 guidelines was the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial.[29] In this study, published in August 2001, 12,562 patients with unstable angina/NSTEMI presenting within 24 hours of onset of chest pain or chest pain equivalent were randomized to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) for 3 to 12 months. All patients received aspirin (75 to 325 mg daily). Patients with recent percutaneous coronary intervention, coronary artery bypass grafting, or both, and patients who had already received glycoprotein IIb/IIIa agents were excluded. The composite efficacy end point of cardiovascular death, MI, or stroke occurred in 11.5% of patients assigned to placebo and 9.3% assigned to clopidogrel (relative risk=0.80; $P<.001$). A reduction in recurrent ischemia was noted within the first few hours after randomization, but the single end point of mortality was not improved in the short or long term.[29]

Along with this efficacy benefit, there was an excess of major bleeding (2.7% in the placebo group versus 3.7% in the clopidogrel group; $P=.003$) and minor bleeding but not of life-threatening bleeding. This is not unexpected because clopidogrel is an effective and irreversible inhibitor of the platelet adenosine diphosphate receptor. Furthermore, the risk of bleeding was increased in patients undergoing coronary artery bypass grafting within the first 5 days of stopping clopidogrel. It should be noted that the CURE study was conducted at centers in which there was no routine policy of early intervention, and therefore, the protocol was not consistent with the latest guidelines. In CURE, revascularization was performed during the index admission in only 23% of the patients overall, and the median time to percutaneous coronary intervention was 6 days, reflecting a dearth of US enrollments in the study.[29]

On this basis, the following new recommendations relative to platelet adenosine diphosphate receptor inhibition were promulgated in the 2002 guidelines update:

- Antiplatelet therapy should be initiated promptly in patients with NSTE acute coronary syndrome. Aspirin should be administered as soon as possible after presentation and continued indefinitely (Class I, Level A, no change from 2000 guidelines).
- Clopidogrel should be administered to hospitalized patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance (Class I, Level A).
- In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to aspirin as soon as possible *on admission* (italics added) and administered for at least 1 month (Class I, Level A) and for up to 9 months (Class I, Level B).
- In patients for whom an interventional approach is planned, clopidogrel should be started and continued for at least 1 month (Class I, Level A) and up to 9 months in patients who are not at high risk for bleeding (Class I, Level B).
- In patients taking clopidogrel in whom coronary artery bypass grafting is planned, if possible, the drug should be withheld for at least 5 days and preferably for 7 days (Class I, Level A).

How are these recommendations to be implemented in the ED? Figure 3 outlines an approach consistent with the 2002 guidelines. In summary, patients sus-

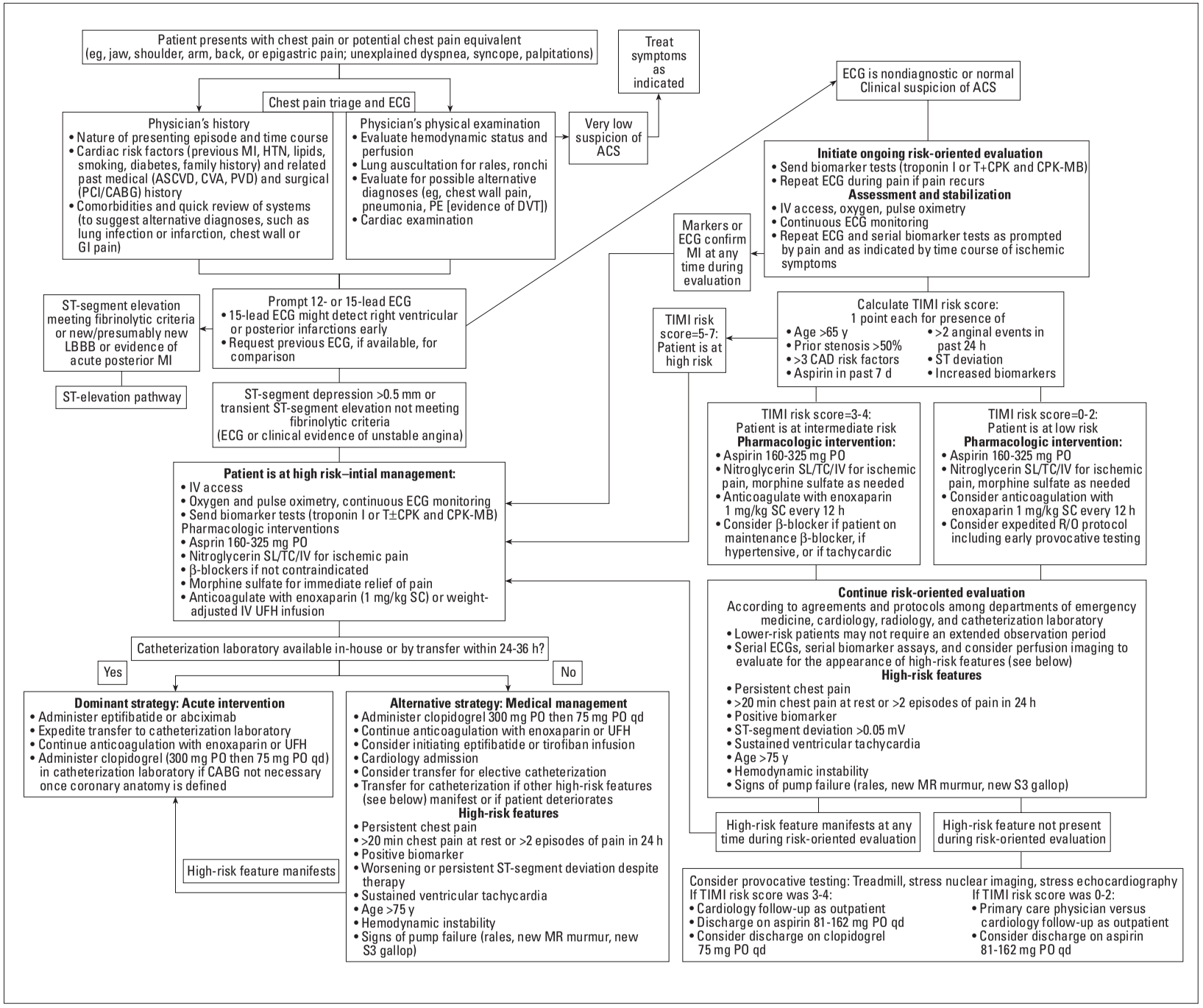


Figure 3.
Evidence-based approach[1] to patients with acute coronary syndrome in the ED from the Centers of Excellence in Venous and Arterial Thrombosis (CEVAT) Initiative.[45] Objective risk stratification is an essential component of the evaluation. In this flow chart, the TIMI risk score[11] is used to illustrate this process. The TIMI risk score has yet to be studied prospectively as a decisionmaking tool in an acute coronary syndrome trial. ***HTN,*** *hypertension;* ***ASCVD,*** *atherosclerotic cardiovascular disease;* ***CVA,*** *cerebrovascular accident (stroke);* ***PVD,*** *peripheral vascular disease (including carotid disease);* ***PCI,*** *percutaneous coronary intervention;* ***CABG,*** *coronary artery bypass grafting;* ***GI,*** *gastrointestinal;* ***PE,*** *pulmonary embolism;* ***DVT,*** *deep vein thrombosis;* ***ACS,*** *acute coronary syndrome;* ***LBBB,*** *left bundle-branch block;* ***CPK,*** *creatine phosphokinase;* ***CPK-MB,*** *creatine phosphokinase, MB band;* ***UFH,*** *unfractionated heparin;* ***CAD,*** *coronary artery disease;* ***PO,*** *oral;* ***SC,*** *subcutaneous;* ***SL,*** *sublingual;* ***TC,*** *transcutaneous;* ***IV,*** *intravenous;* ***R/O,*** *rule out;* ***qd,*** *every day;* ***MR,*** *mitral regurgitation.*

pected of having acute coronary syndrome should be given aspirin (162 to 325 mg) as soon as possible at home, in the emergency medical services setting, or in the ED. Patients with true aspirin allergy should receive clopidogrel, presumably at a loading dose (300 mg, although this is not specified in the guidelines), instead of aspirin.

In addition, clopidogrel should be administered in the ED (per the guidelines, "as soon as possible on admission") to patients who are not expected to undergo catheterization over the ensuing 24 to 36 hours and to those who are not eligible for coronary artery bypass grafting because it is concern over coronary artery bypass grafting–related bleeding that is most serious. Patients who are anticipated to be sent to the catheterization laboratory within 24 to 36 hours should receive clopidogrel during their hospital course, but consideration should be given to withholding clopidogrel in the ED because the coronary anatomy is not yet known. Only after determining the nature of the culprit coronary lesion or lesions is it clear whether patients with NSTE acute coronary syndrome will require urgent or emergency coronary artery bypass grafting (in clinical trials, the incidence of this ranges from 10% to 25%[25,30]), and the risk of bleeding with a loading dose of clopidogrel on board before coronary artery bypass grafting might well outweigh the benefit of this additional level of antiplatelet therapy.[29,31] It is not currently feasible to predict reliably in the ED which patients with acute coronary syndrome will be found to require urgent or emergency coronary artery bypass grafting. Emergency physicians who hold that the administration of clopidogrel is the standard of care in patients with acute coronary syndrome can remedy their concerns by contributing to the development of a multidisciplinary acute coronary syndrome pathway, by which they know that patients undergoing intervention will receive the drug once the coronary anatomy is defined and the need for coronary artery bypass grafting has been excluded. Still another alternative is for the emergency physician to leave the entire issue of clopidogrel use to the consulting cardiologist, at least until there are more complete data on bleeding risk in patients managed interventionally with the drug on board.

Although the addition of a platelet glycoprotein IIb/IIIa inhibitor in patients receiving aspirin, clopidogrel, and heparin in CURE was well tolerated, fewer than 10% of patients received this combination. Therefore, additional information on the safety of the addition of heparin (low-molecular-weight heparin or unfractionated heparin) and a glycoprotein IIb/IIIa inhibitor in patients already receiving aspirin and clopidogrel should be obtained. Also, it is not yet clear whether clopidogrel improved the outcome in patients who received glycoprotein IIb/IIIa antagonists after randomization. The 2002 guidelines give a positive Class IIa, Level B recommendation to the addition of a glycoprotein IIb/IIIa agent to heparin, aspirin, and clopidogrel in patients in whom an interventional approach is planned.

The bottom line for emergency medicine is that the CURE results offer powerful support for the use of clopidogrel in NSTE acute coronary syndrome. Neither the data nor the guidelines, however, offer much specific guidance on optimal timing of administration. Taking into account the risk-benefit characteristics of clopidogrel and the likelihood of unanticipated coronary artery bypass grafting after catheterization in high-risk patients, the strategy outlined in Figure 3 optimizes the use of this important antiplatelet therapy, including administration of clopidogrel in the ED to patients who are not catheterization or coronary artery bypass grafting candidates. In each hospital, emergency physicians, cardiologists, and cardiovascular surgeons should develop a consistent strategy for addressing the use of clopidogrel in NSTE acute coronary syndrome. Furthermore, the CURE data, although compelling, do not compare the results of platelet adenosine diphosphate receptor blockade with clopidogrel with glycoprotein IIb/IIIa receptor blockade; there is currently no foundation for the suggestion that clopidogrel can be used in lieu of glycoprotein IIb/IIIa therapy.

Use of Anticoagulants

Antithrombin therapy is considered an integral component of the upstream management of NSTE acute coronary syndrome. In the 2000 guidelines, anticoagulation with unfractionated heparin or low-molecular-

weight heparin was recommended as Class I, Level B. Although anticoagulation is clearly considered the standard of care in the management of these patients, a Level A recommendation was withheld because of the paucity of randomized, controlled data supporting the use of unfractionated heparin and uncertainty about the use of low-molecular-weight heparin in the catheterization laboratory and in combination with glycoprotein IIb/IIIa agents. In the 2002 update, these recommendations are issued regarding the use of anticoagulants:

- Anticoagulation with subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin should be added to antiplatelet therapy with aspirin, clopidogrel, or both (Class I, Level A).
- Enoxaparin is preferable to unfractionated heparin as an anticoagulant in patients with unstable angina/NSTEMI, unless coronary artery bypass grafting is planned within 24 hours (Class IIa, Level A).

The upgrade of the anticoagulation recommendation and the unusual step of singling out a specific agent within the low-molecular-weight heparin class resulted from the inclusion of several recent studies of enoxaparin and perhaps a reconsideration of the strengths of the ESSENCE[13] and TIMI-11B[12] analyses.

The issue of performing percutaneous coronary intervention in patients anticoagulated with low-molecular-weight heparin and, therefore, whose activated partial thromboplastin time or activated clotting time cannot be used to measure the extent of anticoagulation on demand was addressed by Collet et al,[32] who showed, in a study of 293 patients with NSTE acute coronary syndrome, that percutaneous coronary intervention can be performed safely with the usual dose of enoxaparin compared with that of historical control patients. In one of the observational National Investigators Collaborating on Enoxaparin registries, intravenous enoxaparin (1.0 mg/kg) was used in 828 patients undergoing elective percutaneous coronary intervention without glycoprotein IIb/IIIa receptor blockade.[33] The rate of bleeding (1.1% for major bleeding, 6.2% for minor bleeding at 30 days) was again comparable with that of historical control patients given unfractionated heparin.

An alternative approach specifically recommended in the 2002 guidelines is to use low-molecular-weight heparin during the period of initial stabilization (ie, during the ED care of the patient with NSTE acute coronary syndrome). If desired, the dose can be withheld by the cardiologist on the morning of the procedure, and unfractionated heparin can then be used for percutaneous coronary intervention according to usual practice patterns. Because the anticoagulant effect of unfractionated heparin can be more readily reversed than that of low-molecular-weight heparin, unfractionated heparin is preferred in patients likely to undergo coronary artery bypass grafting within 24 hours, although the need for coronary artery bypass grafting cannot reliably be predicted in the ED.

Two low-molecular-weight heparin compounds are approved by the US Food and Drug Administration for the treatment of NSTE acute coronary syndrome: enoxaparin and dalteparin. Dalteparin (Fragmin) was shown in the FRIC study[34] to be noninferior in safety and efficacy to unfractionated heparin, whereas in the ESSENCE[13] and TIMI-11B[12] studies, enoxaparin was shown to be superior to unfractionated heparin, with similar rates of major bleeding. After the publication of the 2000 guidelines, the Enoxaparin Versus Tinzaparin trial, which compared enoxaparin and the low-molecular-weight heparin tinzaparin (Innohep) administered for 7 days in 438 patients, was published. The recurrence of angina and the need for revascularization were significantly less in the enoxaparin group.[35] The advantages of low-molecular-weight heparin preparations vis-à-vis the ease of subcutaneous administration and the absence of a need for monitoring are particularly appealing in the ED. Furthermore, the low-molecular-weight heparins stimulate platelets less than unfractionated heparin[36] and are less frequently associated with heparin-induced thrombocytopenia.[37] Finally, the response to enoxaparin might be magnified in patients who present at higher risk (Figure 2). These considerations resulted in the new recommendations specifically for enoxaparin. Concern over the ability to control anticoagulation tightly during percutaneous coronary intervention and over optimal timing for sheath re-

moval in patients given low-molecular-weight heparin is currently being addressed in large-scale studies. In the meantime, some emergency physicians have opted to use unfractionated heparin as a matter of routine, especially in institutions in which consulting cardiologists have not reached a consensus on a standard approach to anticoagulation.

Although the data to date are not definitive, it appears that glycoprotein IIb/IIIa inhibitors can be used safely and efficaciously with low-molecular-weight heparin. A number of studies have examined this issue in the interventional setting, and none has suggested that the combination of low-molecular-weight heparin and glycoprotein IIb/IIIa agents is associated with excessive bleeding.[38-41] Furthermore, the anticipated use of a glycoprotein IIb/IIIa agent should not prevent the use of enoxaparin in the ED management of patients with NSTE acute coronary syndrome. This has been reinforced by the findings of the INtegrilin and Enoxaparin Randomized assessment of Acute Coronary syndrome Treatment (INTERACT) study,[41] which was presented after release of the guidelines update. In INTERACT, 746 patients who met guidelines-defined high-risk criteria were all given full-dose eptifibatide. Patients were then randomized to receive either enoxaparin (1 mg/kg administered subcutaneously every 12 hours for ≥4 doses) or weight-adjusted unfractionated heparin by means of intravenous infusion. In this Canadian study, 60% of patients underwent cardiac catheterization; 30% underwent percutaneous coronary intervention, and 12% underwent coronary artery bypass grafting. The risk of major bleeding at 48 and 96 hours was significantly lower for enoxaparin-treated patients than for unfractionated heparin–treated patients. More striking was the finding that ischemic events (detected by means of continuous 12-lead ST-segment trend monitoring) were much less common in patients treated with enoxaparin (14.1% and 12.7% at 0 to 48 and 48 to 96 hours, respectively) than in patients treated with unfractionated heparin (25.1% and 25.9%, both *P* values less than .002).[41] This is the largest randomized study of the combination of a low-molecular-weight heparin and a glycoprotein IIb/IIIa agent to date.

The bottom line for emergency medicine is that the use of a low-molecular-weight heparin in the ED is convenient and, in the case of enoxaparin, is associated with strong data showing safety and efficacy. Enoxaparin should become standard therapy for anticoagulation in patients with NSTE acute coronary syndrome being medically managed. Some interventional cardiologists are not yet comfortable with using low-molecular-weight heparin in the catheterization laboratory because of the relative difficulty of assessing the extent of anticoagulation before intervention or pulling sheaths. Once again, this is a topic that should be prospectively discussed by a multidisciplinary group at each institution so that an appropriate clinical pathway can be designed. Data supporting the use of enoxaparin in interventional management continue to accrue.

Use of Glycoprotein IIb/IIIa Agents in Noninterventional Management

The strong (Level I, Class A) recommendation for the use of glycoprotein IIb/IIIa agents for high-risk NSTE acute coronary syndrome in the 2000 guidelines was not met with universal acceptance.[42] Since the publication of those recommendations, however, data on the use of these agents in patients managed both interventionally and conservatively have continued to accumulate. The recommendations for platelet glycoprotein IIb/IIIa receptor antagonists in the 2002 guidelines update are as follows:

- A platelet glycoprotein IIb/IIIa antagonist should be administered, in addition to aspirin and a heparin compound, to patients in whom catheterization and percutaneous coronary intervention are planned. The glycoprotein IIb/IIIa antagonist can also be administered just before percutaneous coronary intervention (Class I, Level A, discussed above).
- Eptifibatide or tirofiban should be administered, in addition to aspirin and a heparin compound, to patients with continuing ischemia, an increased troponin level, or other high-risk features (see above) in whom an interventional strategy is not planned (medical management; Class IIa, Level A).

• Eptifibatide or tirofiban should be administered, in addition to aspirin and a heparin compound, to patients without continuing ischemia who have no other high-risk features and in whom an intervention is not planned (medical management; Class IIb, Level A).

• Abciximab should be administered to patients in whom percutaneous coronary intervention is not planned (medical management; Class III, Level A).

These changes can be summarized as follows: the recommendation for glycoprotein IIb/IIIa receptor blockade in patients being managed interventionally remains strong and unchanged; medical therapy of high-risk patients with NSTE acute coronary syndrome with a small-molecule (eptifibatide or tirofiban) glycoprotein IIb/IIIa agent is recommended but with a lower level of support than in the 2000 guidelines; medical therapy for patients not at high risk with a glycoprotein IIb/IIIa agent is not supported by strong data; and the use of abciximab in patients being managed without intervention is not recommended. These changes reflect synthesis of the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO-IV) acute coronary syndrome[43] results and reevaluation of medical therapy in previous large glycoprotein IIb/IIIa agent trials.

The GUSTO-IV acute coronary syndrome trial[43] enrolled 7,800 patients with unstable angina/NSTEMI who presented with at least 5 minutes of suggestive chest pain and either ST-segment depression or increased troponin levels. All patients received aspirin and a heparin compound and then were randomized to 1 of 3 arms (placebo, an abciximab bolus and 24-hour infusion, or an abciximab bolus and 48-hour infusion), all as part of forced medical management. At 30 days, the composite of death or MI ranged from 8.0% to 9.1%, with no differences across the 3 groups, although at 48 hours, death occurred more commonly in the 48-hour abciximab group than in the placebo group (0.3% versus 0.9%, *P*=.008). The lack of benefit of abciximab was observed in most subgroups, including patients with increased concentrations of troponin, who were therefore objectively at higher risk.

Among 1,069 patients in the PRISM-PLUS trial who did not undergo early percutaneous coronary intervention, tirofiban appears to have been beneficial in a high-risk subgroup (retrospectively applied TIMI risk score ≥4), whether they underwent later percutaneous coronary intervention (odds ratio [OR]=0.60; 95% confidence interval [CI] 0.35 to 1.01) or not (OR=0.69; 95% CI 0.49 to 0.99).[11,16] However, no benefit was observed in patients at lower risk.[16] Boersma et al[44] carried out a meta-analysis of the effect of medical therapy with glycoprotein IIb/IIIa agents from all 6 large randomized placebo-controlled trials (including the GUSTO-IV acute coronary syndrome trial), involving 31,402 patients with NSTE acute coronary syndrome not routinely scheduled to undergo coronary revascularization. This group can be viewed as patients managed medically from ED evaluation onward. A significant reduction in the likelihood of the composite end point of death or MI was demonstrated in the glycoprotein IIb/IIIa treatment arm (11.8% versus 10.8%; OR=0.91; 95% CI 0.84 to 0.98; *P*=.015). Although not scheduled for coronary revascularization procedures, 11,965 (38%) of the 31,402 patients actually underwent percutaneous coronary intervention or coronary artery bypass grafting within 30 days, and in this late interventional subgroup, the OR for death or MI in the treated patients was 0.89 (95% CI 0.80 to 0.98).

In the 19,416 patients in this analysis who did not undergo percutaneous coronary intervention or coronary artery bypass grafting, the OR for death or MI in the glycoprotein IIb/IIIa group was 0.95 (95% CI 0.86 to 1.05; *P*=not significant). Major bleeding complications were significantly more common in the glycoprotein IIb/IIIa group compared with those in the placebo group (2.4% versus 1.4%; *P*<.0001). The conclusion from this study was that in patients with unstable angina/NSTEMI at high risk who are not routinely scheduled for early revascularization, "treatment with a [glycoprotein] IIb/IIIa inhibitor might therefore be considered."[44] Thus glycoprotein IIb/IIIa inhibitors are of substantial benefit in patients with unstable angina/NSTEMI who undergo percutaneous coronary intervention and may be considered an appropriate component of ED therapy in these patients. The small-molecule glycoprotein IIb/IIIa agents are indicated in the medical management of

patients with high-risk NSTE acute coronary syndrome and should be considered for use in that role in the ED. Because the data supporting the use of glycoprotein IIb/IIIa antagonists are clearly stronger in conjunction with interventional management, emergency physicians might opt to defer this issue entirely to the consulting cardiologist.

The bottom line for emergency medicine is that the updated guidelines continue to support the use of glycoprotein IIb/IIIa agents in high-risk patients being managed interventionally. Institutional pathways designed to expedite interventional cardiac care should include the option for initiation of these agents in the ED. In noninterventional settings, glycoprotein IIb/IIIa agents remain appropriate for ED-cardiology care of high-risk patients but should not be given routinely in low-risk patient groups.

In summary, these ACC/AHA guidelines present the cardiology specialty's assessment of current best practice for the diagnosis and management of NSTE acute coronary syndrome. New or reiterated recommendations in the 2002 update that are pertinent to the ED evaluation and management of these patients include (1) further refinement of the risk stratification process, (2) a decided preference for interventional management strategies in high-risk patients with acute coronary syndrome on the basis of continuing accumulation of data, (3) expansion and clarification of the role of clopidogrel, (4) specific recommendations for the use of the low-molecular-weight heparin enoxaparin, and (5) clarification of the role of glycoprotein IIb/IIIa receptor blockade according to management strategy. The Table summarizes these changes, and Figure 3 provides a practical overall approach to the evidence-based risk stratification and management of patients with NSTE acute coronary syndrome.

Received for publication May 28, 2002. Revisions received August 31, 2002, and September 23, 2002. Accepted for publication September 23, 2002.

All authors have received honoraria, research support (direct or indirect), or both from COR Therapeutics (now part of Millennium Pharmaceuticals), Key Pharmaceuticals, Aventis Pharmaceuticals, Bristol-Myers-Squibb Pharmaceuticals, and Sanofi-Synthelabo, which market therapeutic agents cited in this article.

Address for reprints: Charles V. Pollack, Jr., MA, MD, Department of Emergency Medicine, Pennsylvania Hospital, 800 Spruce Street, Philadelphia, PA 19107; E-mail pollackc@pahosp.com.

Table.
Bottom line summary: ED-pertinent new, revised, or reiterated recommendations from the 2002 guidelines update.

General Recommendation	Revised or Reiterated Recommendation	Upgrade/Downgrade/New/ Unchanged Since September 2000
Risk stratification	Rapid and accurate risk stratification of patients with chest pain is essential.	No change, but TIMI risk score receives special emphasis.
Optimal management strategy	1. Early (24–36 h) interventional strategy when high-risk features present 2. Interventional management includes glycoprotein IIb/IIIa receptor blockade	1. Upgrade (IB→IA) 2. Unchanged
Use of clopidogrel	1. Clopidogrel for patients with acute coronary syndrome and aspirin allergy 2. Clopidogrel in addition to aspirin on admission if noninterventional management planned 3. Clopidogrel continued 1 to 9 mo after intervention 4. Delay or withhold clopidogrel 5 to 7 days if coronary artery bypass grafting is anticipated	1. Upgrade (IB→IA) 2. New 3. New 4. New
Use of anticoagulants	1. Anticoagulation with unfractionated or low-molecular-weight heparin 2. Enoxaparin specifically preferred over unfractionated heparin unless coronary artery bypass grafting is anticipated within 24 h	1. Upgrade (IB→IA) 2. New
Glycoprotein IIb/IIIa agents in medical therapy	1. Small-molecule glycoprotein IIb/IIIa agent in high-risk patients managed without intervention 2. Small-molecule glycoprotein IIb/IIIa agent not indicated in non–high-risk patients being managed without intervention 3. Abciximab not indicated if intervention not planned	1. Refinement (IA→IIaA) 2. New 3. New

REFERENCES

1. 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. Updated March 2002 at http://www.acc.org and http://www.americanheart.org.

2. Braunwald E, Mark DB, Jones RH, et al. *Unstable Angina: Diagnosis and Management.* Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, US Public Health Service, US Department of Health and Human Services; 1994:1. AHCPR publication No. 94-0602.

3. Pollack CV Jr, Gibler WB. 2000 ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a practical summary for emergency physicians. *Ann Emerg Med.* 2001;38:229-240.

4. Pollack CV Jr, Gibler WB. Advances create opportunities: implementing the major tenets of the new unstable angina guidelines in the emergency department. *Ann Emerg Med.* 2001;38:241-248.

5. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction—2002: 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). *Circulation.* 2002;106:1893-1900.

6. National Center for Health Statistics. *Detailed Diagnoses and Procedures: National Hospital Discharge Survey, 1996.* Hyattsville, MD: National Center for Health Statistics; 1996.

7. Nouraj P. *National Hospital Ambulatory Medical Care Survey: 1997 Emergency Department Summary.* Hyattsville, MD: National Center for Health Statistics; 1997.

8. American College of Cardiology Web site. Available at: http://www.acc.org/clinical/guidelines/nov96/1999/index.htm. Accessed January 21, 2003.

9. Storrow AB, Gibler WB. Chest pain centers: diagnosis of acute coronary syndrome. *Ann Emerg Med.* 2000;35:449-461.

10. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcomes in patients with a cute coronary syndromes without persistent ST-segment elevation: results for an international trial of 9461 patients. *Circulation.* 2000;101:2557-2567.

11. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835-842.

12. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non–Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. *Circulation.* 1999;100:1593-1601.

13. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med.* 1997;337:447-452.

14. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med.* 2001;344:1879-1887.

15. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction [published erratum appears in *N Engl J Med.* 1998;339:415]. *N Engl J Med.* 1998;338:1488-1497.

16. Morrow DA, Antman EM, Snapinn S, et al. An integrated clinical approach to predicting the benefit of tirofiban in non-ST elevation acute coronary syndromes: application of the TIMI risk score for UA/NSTEMI in PRISM-PLUS. *Eur Heart J.* 2002;23:223-229.

17. Clinical Trial Results Web site. Available at: http://www.clinicaltrialresults.org. Accessed January 21, 2003.

18. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol.* 2000;36:959-969.

19. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med.* 1996;335:1333-1341.

20. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med.* 1996;335:1342-1349.

21. Pettijohn TL, Doyle T, Spiekerman AM, et al. Usefulness of positive troponin-T and negative creatine kinase levels in identifying high-risk patients with unstable angina pectoris. *Am J Cardiol.* 1997;80:510-511.

22. Lindahl B, Andren B, Ohlsson J, et al. Risk stratification in unstable coronary artery disease: additive value of troponin T determinations and pre-discharge exercise tests. FRISC Study Group. *Eur Heart J.* 1997;18:762-770.

23. Jesse RL, Crosby PA. The role of a biochemical marker for ischemia in the management of acute coronary syndrome patients. Oral presentation at: World Congress of Cardiology; May 2002; Sydney, New South Wales, Australia.

24. Fragmin and Fast Revascularisation During Instability in Coronary Artery Disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet.* 1999;354:708–715.

25. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med.* 1998;339:436-443.

26. Bhatt DL, Marso SP, Houghtaling P, et al. Does earlier administration of eptifibatide reduce death and MI in patients with acute coronary syndromes? *Circulation.* 1998;98(Suppl 1):I560-I561.

27. Greenbaum AB, Harrington RA, Hudson MP, et al. Therapeutic value of eptifibatide at community hospitals transferring patients to tertiary referral centers early after admission for acute coronary syndromes. *J Am Coll Cardiol.* 2001;37:492-498.

28. Theroux P, Alexander J Jr, Dupuis J, et al. Upstream use of tirofiban in patients admitted for an acute coronary syndrome in hospitals with or without facilities for invasive management. *Am J Cardiol.* 2001;87:375-380.

29. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med.* 2001;345:494-502.

30. PARAGON Investigators. Platelet IIb/IIIa antagonism for the reduction of acute coronary syndrome events in a global organizational network. *Circulation.* 1998;97:2386-2395.

31. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet.* 2001;358:527-533.

32. Collet JP, Montalescot G, Lison L, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. *Circulation.* 2001;103:658-663.

33. Kereiakes DJ, Grines C, Fry E, et al. Enoxaparin and abciximab adjunctive pharmacotherapy during percutaneous coronary intervention. *J Invasive Cardiol.* 2001;13:272-278.

34. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. FRagmin In unstable Coronary artery disease study (FRIC) [published erratum appears in *Circulation.* 1998;97:413]. *Circulation.* 1997;96:61-68.

35. Michalis LK, Papamichail N, Katsouras C, et al. Enoxaparin versus tinzaparin in the management of unstable coronary artery disease (EVET Study) [abstract]. *J Am Coll Cardiol.* 2001;37:365a.

36. Xiao Z, Theroux P. Platelet activation with unfractionated heparin at therapeutic concentrations and comparisons with a low-molecular-weight heparin and with a direct thrombin inhibitor. *Circulation.* 1998;97:251-256.

37. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med.* 1995;332:1330-1335.

38. Cohen M, Theroux P, Frey MJ, et al. Anti-thrombotic combination using tirofiban and enoxaparin: the ACUTE II Study [abstract]. *Circulation.* 2000;102(Suppl II):II826.

39. Young JJ, Kereiakes DJ, Grines CL. Low-molecular-weight heparin therapy in percutaneous coronary intervention: the NICE 1 and NICE 4 trials. National Investigators Collaborating on Enoxaparin Investigators. *J Invasive Cardiol.* 2000;12(Suppl E):E14-E18.

40. Kereiakes DJ, Kleiman NS, Fry E, et al. Dalteparin in combination with abciximab during percutaneous coronary intervention. *Am Heart J.* 2001;141:348-352.

41. Goodman SG, Fitchett D, Armstrong PW, et al, for the INTERACT Trial Investigators. Randomized evaluation of the safety and efficacy of enoxaparin versus unfractionated heparin in high-risk patients with non–ST-segment elevation acute coronary syndromes receiving the glycoprotein IIb/IIIa inhibitor eptifibatide. *Circulation.* 2003;107:238-244.

42. Schriger DL, Herbert ME. Platelet glycoprotein inhibitors in patients with medically managed acute coronary syndrome: does the enthusiasm exceed the science? *Ann Emerg Med.* 2001;38:229-240.

43. Simoons ML. Effect of glycoprotein IIb/IIIa receptor blocker abciximab on outcome in patients with acute coronary syndromes without early coronary revascularisation: the GUSTO IV-ACS randomised trial. *Lancet.* 2001;357:1915-1924.

44. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a metaanalysis of all major randomised clinical trials. *Lancet.* 2002;359:189-198.

45. Pollack CV Jr, Cohen M. Outcome-effective management of acute coronary syndromes: guidelines, protocols, and recommendations for emergency medical practice. *CEVAT Panel Reports.* 2002;1:1-20.