

**ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction—2002: Summary Article: 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)**

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## ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction—2002: Summary Article

### 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)

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The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI) were published in September 2000.<sup>1</sup> Since then, a number of clinical trials and observational studies have been published or presented that, when taken together, alter significantly the recommendations made in that document. Therefore, the ACC/AHA Committee on the Management of Patients With Unstable Angina, with the concurrence of the ACC/AHA Task Force on Practice Guidelines, revised these guidelines. These revisions were prepared

in December 2001, reviewed and approved, and then published on the ACC World Wide Web site ([www.acc.org](http://www.acc.org)) and AHA World Wide Web site ([www.americanheart.org](http://www.americanheart.org)) on March 15, 2002. The present article describes these revisions and provides further updates in this rapidly moving field. Minor clarifications in the wording of three recommendations that now appear differently from those that were previously published on the ACC and AHA Web sites are noted in footnotes.

The ACC/AHA classifications I, II, and III are used to summarize indications as follows:

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**Class I:** Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.

**Class II:** Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

**IIa:** Weight of evidence/opinion is in favor of usefulness/efficacy.

**IIb:** Usefulness/efficacy is less well established by evidence/opinion.

**Class III:** Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

The weight of the evidence was ranked highest (A) if the data were derived from multiple randomized clinical trials that involved large numbers of patients and intermediate (B) if the data were derived from a limited number of randomized trials that involved small numbers of patients or from careful analyses of nonrandomized studies or observational registries. A lower rank (C) was given when expert consensus was the primary basis for the recommendation.

## Risk Assessment

### Clinical Features

Unstable angina and NSTEMI are heterogeneous disorders in which patients have widely varying risks. Risk is an important “driver” of management decisions, and accurate yet simple methods of risk assessment are important for patient care.

Risk was assessed by multivariable regression techniques in patients presenting with UA/NSTEMI in several large clinical trials. Boersma et al analyzed the relation between baseline characteristics and the incidence of death and the composite of death or myocardial (re)infarction at 30 days in patients who entered the PURSUIT (Platelet IIB/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trial.<sup>2</sup> The most important baseline features associated with death were age, heart rate, systolic blood pressure, ST-segment depression, signs of heart failure, and elevation of cardiac biomarkers. From this analysis, a simple risk estimation score was developed.

Antman et al developed a 7-point risk score, the “TIMI Risk Score,” (age greater than or equal to 65 years, more than 3 coronary risk factors, prior angiographic coronary obstruction, ST-segment deviation, more than 2 angina events within 24 hours, use of aspirin (ASA) within 7 days, and elevated cardiac markers).<sup>3</sup> The score was defined as the simple sum of these individual prognostic variables. The risk of developing an adverse outcome—death, (re)infarction, or recurrent severe ischemia that required revascularization—ranged from 5% with a score of 0 or 1 to 41% with a score of 6 or 7. The score was derived from data in the TIMI 11B (Thrombolysis In Myocardial Infarction 11B) trial<sup>4</sup> and then validated in 3 additional trials—ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events study),<sup>5</sup> and PRISM-PLUS (Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited by

Unstable Signs and symptoms)<sup>6</sup> and prospectively in one TACTICS-TIMI 18 (Treat angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis In Myocardial Infarction) 18.<sup>7</sup> A progressively greater benefit from newer therapies such as low-molecular-weight heparin (LMWH),<sup>4,5</sup> platelet glycoprotein (GP) IIB/IIIa receptor antagonists,<sup>6</sup> and an invasive strategy<sup>7</sup> with increasing risk score have been reported.

### Biomarkers

The Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction<sup>8</sup> emphasized the use of troponins as critical markers of the presence of myocardial necrosis. Although troponins are accurate in identifying myocardial necrosis, the latter is not always secondary to atherosclerotic coronary artery disease. Therefore, in establishing the diagnosis of NSTEMI, cardiac troponins should be used in conjunction with appropriate clinical features and electrocardiographic changes. Myocardial injury of diverse origins (eg, myocarditis, trauma, or cardioversion) may cause necrosis and release of troponins. Although these may be considered instances of NSTEMI, they should be distinguished on clinical grounds from the more common form of NSTEMI secondary to coronary atherosclerosis.

### Antiplatelet Therapy

Antiplatelet therapy is a cornerstone in the management of UA/NSTEMI. Three classes of antiplatelet drugs (ASA, thienopyridines, and GP IIB/IIIa antagonists) have been found useful in the management of these patients and are the subject of continued intensive investigation and analysis.

#### Clopidogrel

Given its more rapid onset of action<sup>9,10</sup> and better safety profile compared with ticlopidine, clopidogrel is now the preferred thienopyridine. The CURE (Clopidogrel in Unstable angina to prevent Recurrent ischemic Events) trial<sup>11</sup> randomized 12 562 patients with UA/STEMI who presented within 24 hours to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed them for 3 to 12 months; all patients were given aspirin. Cardiovascular death, myocardial infarction (MI), or stroke occurred in 11.5% of patients assigned to placebo and 9.3% of those assigned to clopidogrel (relative risk [RR] 0.80; *P* less than 0.001). Looking at the individual components of the primary composite and end point, there was a trend in favor of clopidogrel for cardiovascular death and stroke (5.5% and 1.4%, respectively, for placebo vs 5.1% and 1.2% for clopidogrel), and there was a significant reduction in MI (6.7% vs 5.2% RR = 0.77, *P* less than 0.001). However, there was no significant difference in the incidence of non-Q-wave MI (3.8% vs 3.5%). A reduction in recurrent ischemia was noted within the first few hours after randomization. These salutary results were observed across all subgroups of patients. There was, however, a significant excess of major bleeding (2.7% in the placebo group versus 3.7% in the clopidogrel group; *P* = 0.003) and of minor bleeding, as well as a (nonsignificant) trend for an increase in life-threatening bleeding. The risk of

bleeding was increased in patients who underwent coronary artery bypass grafting (CABG) within the first 5 days after clopidogrel was discontinued.

The CURE trial was performed in hospitals in which there was *no* routine policy of early invasive procedures, and therefore, revascularization was performed during the initial admission in only 23% of the patients, a substantially lower percentage than currently receive this therapy at most US hospitals. Although the addition of a GP IIb/IIIa antagonist appeared to be well tolerated in patients who were given ASA, clopidogrel, and heparin in CURE, fewer than 10% of patients received this combination. Therefore, additional information on the safety of “quadruple therapy” (heparin [unfractionated or low molecular weight], ASA, clopidogrel, and a GP IIb/IIIa antagonist) should be obtained.

The CURE trial provides strong support for the addition of clopidogrel to ASA on admission in the management of patients with UA and NSTEMI. Clopidogrel appears to be especially useful in hospitals that do not have a routine policy of early invasive procedures and in patients who are not candidates or who do not wish to be considered for revascularization. The optimal duration of therapy with clopidogrel has not been determined. The major benefits in CURE were observed at 30 days, with small additional benefits observed over the subsequent treatment period, which averaged 8 months.

In PCI-CURE, a substudy of CURE, 2658 patients who underwent percutaneous coronary intervention (PCI) had been randomly assigned to double-blind treatment with clopidogrel ( $n=1313$ ) or placebo ( $n=1345$ )<sup>12</sup>; all patients also received ASA. Patients were pretreated with placebo or study drug for a median of 10 days before PCI. After the procedure, most patients received open-label thienopyridine (clopidogrel or ticlopidine) for approximately 4 weeks, after which the study drug (placebo or clopidogrel) was again administered for an average of 8 months. The primary end point, a composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI, occurred in 86 patients (6.4%) in the placebo group compared with 59 (4.5%) in the clopidogrel group (RR 0.70;  $P=0.03$ ). When events that occurred before and after PCI were considered, there was a 31% reduction in cardiovascular death or MI with assignment to clopidogrel ( $P=0.002$ ). Thus, in patients with UA and NSTEMI who are given ASA and are undergoing PCI, a strategy of clopidogrel pretreatment followed by at least 1 month and probably longer-term therapy is beneficial in reducing major cardiovascular events.<sup>12</sup>

There now appears to be an important role for clopidogrel in patients with UA/NSTEMI, both those who are managed conservatively and those who undergo PCI, especially stenting. However, it is not entirely clear how long therapy should be maintained. Because clopidogrel, when added to ASA, increases the risk of bleeding during major surgery in patients who are scheduled for CABG, if possible, clopidogrel should be withheld for at least 5 days<sup>11</sup> and preferably for 7 days before surgery.<sup>13</sup> In many hospitals in which patients with UA/NSTEMI undergo diagnostic catheterization within 24 to 36 hours of admission, clopidogrel is not started until it is clear that CABG will *not* be scheduled within the next several

days. A loading dose of clopidogrel can be given to a patient on the catheterization table if a PCI is to be performed immediately. If PCI is not performed, clopidogrel can be begun after the catheterization.

#### ***Glycoprotein IIb/IIIa Antagonists in PCI***

The introduction of platelet GP IIb/IIIa antagonists represents an important advance in the treatment of patients with UA/NSTEMI who are undergoing PCI. These drugs take advantage of the fact that platelets play an important role in the development of ischemic complications that may occur in patients with UA/NSTEMI during coronary revascularization procedures. The September 2000 guidelines emphasized the value of GP IIb/IIIa antagonists in patients with UA/NSTEMI who were undergoing PCI.<sup>1</sup>

Two trials of GP IIb/IIIa inhibitors have been published since September 2000. The ESPRIT trial (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) was a placebo-controlled trial designed to assess whether eptifibatid improved outcome in patients undergoing stenting.<sup>14</sup> Fourteen percent of the 2064 patients enrolled in ESPRIT had UA/NSTEMI. The primary end point (the composite of death, MI, target-vessel revascularization, and “bailout” GP IIb/IIIa antagonist therapy) was reduced from 10.5% to 6.6% with treatment ( $P=0.0015$ ). There was consistency in the reduction of events in all components of the end point and in all major subgroups, including patients with UA/NSTEMI. Major bleeding occurred more frequently in patients who received eptifibatid (1.3%) than in those who received placebo (0.4%;  $P=0.027$ ); however, no significant difference in the transfusion rate occurred. At 1 year of follow-up, death or MI occurred in 12.4% of patients assigned to placebo and 8.0% of eptifibatid-treated patients (hazard ratio 0.63; 95% confidence interval [CI] 0.48 to 0.83;  $P=0.001$ ).<sup>15</sup>

In the only head-to-head comparison of GP IIb/IIIa antagonists, the TARGET trial (Do Tirofiban and ReoPro Give similar Efficacy? Trial) randomized 5308 patients to tirofiban or abciximab before PCI with the intent to perform stenting.<sup>16</sup> The primary end point, a composite of death, nonfatal MI, and urgent target-vessel revascularization at 30 days, occurred less frequently in those given abciximab than in those given tirofiban (6.0% versus 7.6%;  $P=0.038$ ). There was a similar direction and magnitude for each component of the end point. The difference in outcome between the 2 treatment groups may be related to a suboptimal dose of tirofiban resulting in inadequate platelet inhibition. However, by six months, the primary end point occurred in a similar percentage of patients in each group (14.9% tirofiban versus 14.3% abciximab, NS). Mortality was also similar (1.9% versus 1.7%, NS).<sup>17</sup>

#### ***Glycoprotein IIb/IIIa Antagonists Without Scheduled PCI***

The Global Utilization of Strategies to Open Occluded Coronary Arteries IV-Acute Coronary Syndromes (GUSTO IV-ACS) trial<sup>18</sup> enrolled 7800 patients with UA/NSTEMI who were admitted to the hospital with more than 5 minutes of chest pain and ST-segment depression and/or elevated troponin T or I concentration and in whom early (less than 48 hours) revascularization was not intended to be conducted.

All received ASA and either unfractionated heparin (UFH) or LMWH. They were randomized to placebo, an abciximab bolus and 24-hour infusion, or an abciximab bolus and 48-hour infusion. The primary end point, death or MI at 30 days, occurred in 8.0% of patients given placebo, 8.2% given 24-hour abciximab, and 9.1% given 48-hour abciximab, differences that were not statistically significant. At 48 hours, death occurred in 0.3%, 0.7%, and 0.9% in these groups, respectively (placebo versus abciximab 48 hours,  $P=0.008$ ). The lack of benefit of abciximab was observed in most subgroups, including patients with elevated concentrations of troponin who were at higher risk. Although the explanation for these results is not clear, they indicate that abciximab, at least at the dosing regimen used in GUSTO IV-ACS, is *not* indicated in the management of patients with UA or NSTEMI in whom an early invasive management strategy is not planned.

In the PRISM-PLUS trial, 1069 patients did not undergo early PCI. Although tirofiban treatment was associated with a lower incidence of death, MI or death, and MI or refractory ischemia at 30 days, these reductions were not statistically significant.<sup>19</sup> In a high-risk subgroup of these patients not undergoing PCI (TIMI risk score greater than or equal to 4),<sup>3</sup> tirofiban appeared to be beneficial whether they underwent PCI (odds ratio [OR] 0.60, 95% CI 0.35 to 1.01) or not (OR 0.69, 95% CI 0.49 to 0.99). However, no benefit was observed in the patients at lower risk.<sup>6</sup> In the PURSUIT trial, eptifibatid reduced the incidence of death or MI from 15.7% to 14.2% (RR 0.91; 95% CI 0.79 to 1.00;  $P=0.032$ ).<sup>20</sup>

Boersma et al performed a meta-analysis of GP IIb/IIIa antagonists in all 6 large, randomized, placebo-controlled trials (including GUSTO IV-ACS,<sup>18</sup> which involved 31 402 patients with UA/NSTEMI who were not routinely scheduled to undergo coronary revascularization.<sup>21</sup> A small reduction in the odds of death or MI in the active treatment arm (11.8% versus 10.8%; OR 0.91, 95% CI 0.84 to 0.98;  $P=0.015$ ) was observed. Unexpectedly, no benefit was observed in women (test for interaction between treatment assignment and gender,  $P$  less than 0.0001). However, women with positive troponins derived a treatment benefit that was similar to men. In the meta-analysis, reductions in the end points of death or nonfatal MI considered individually did *not* achieve statistical significance.

Although not scheduled for coronary revascularization procedures, 11 965 of the 31 402 patients (38%) actually underwent PCI or CABG within 30 days, and in this subgroup, the OR for death or MI in patients assigned to GP IIb/IIIa antagonists was 0.89 (95% CI 0.80 to 0.98). In the other 19 416 patients who did not undergo coronary revascularization, the OR for death or MI in the GP IIb/IIIa group was 0.95 (95% CI 0.86 to 1.05,  $P=NS$ ). Major bleeding complications were increased in the GP IIb/IIIa antagonist-treated group compared with those who received placebo (1.4% versus 2.4%,  $P$  less than 0.0001). The authors concluded that in patients with UA/NSTEMI who were not routinely scheduled for early revascularization and who were at high risk of thrombotic complications, "treatment with a GP IIb/IIIa inhibitor might therefore be considered." Thus, GP IIb/IIIa inhibitors are of benefit in high-risk patients with

UA/NSTEMI, and their administration, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned received a Class I recommendation. These agents are of questionable benefit in patients who do not undergo PCI. However, the revised guidelines recommend broader indications for a routine invasive strategy (see following text).

Thus, clopidogrel (in addition to aspirin and heparin or low molecular weight heparin) is recommended for patients with UA/NSTEMI in whom a noninterventional approach is planned (Class I recommendation). In patients in whom an interventional approach is planned, a GP IIb/IIIa inhibitor (in addition to aspirin and heparin or low molecular weight heparin) is recommended (Class I recommendation). No head-to-head comparison of clopidogrel, a GP IIb/IIIa inhibitor, and their combination has been reported. The addition of a GP IIb/IIIa inhibitor to a subset of patients in the CURE trial who were receiving aspirin, clopidogrel, and heparin appeared to be well tolerated, and current practice frequently involves the use of this combination of drugs. However, until further information on the safety and efficacy of such quadruple therapy becomes available, a Class IIa recommendation is made for the addition of a GP IIb/IIIa inhibitor for patients with UA/NSTEMI who are receiving aspirin, clopidogrel, and unfractionated or low molecular weight heparin and who are referred for an invasive strategy. A Class I recommendation is made for a GP IIb/IIIa inhibitor at the time of PCI in patients receiving heparin and aspirin. Specific updated recommendations for the use of antiplatelet regimens in the revised guidelines are as follows:

#### Class I

1. **Antiplatelet therapy should be initiated promptly. ASA should be administered as soon as possible after presentation and continued indefinitely. (Level of Evidence: A)**
2. **Clopidogrel should be administered to hospitalized patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. (Level of Evidence: A)**
- \*3. **In hospitalized patients in whom an early noninterventional approach is planned, clopidogrel should be added to ASA as soon as possible on admission and administered for at least 1 month (Level of Evidence: A), and for up to 9 months. (Level of Evidence: B)**
- \*4. **A platelet GP IIb/IIIa antagonist should be administered, in addition to ASA and heparin, to patients in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: A)**
- \*†5. **In patients for whom a PCI is planned and who are not at high risk for bleeding, clopidogrel should be started and continued for at least 1 month (Level of Evidence: A) and for up to 9 months. (Level of Evidence: B)**
- \*6. **In patients taking clopidogrel in whom elective CABG is planned, the drug should be withheld for 5 to 7 days. (Level of Evidence: B)**

**Class IIa**

- \*1. Eptifibatide or tirofiban should be administered, in addition to ASA and LMWH or UFH, to patients with continuing ischemia, an elevated troponin, or with other high-risk features in whom an invasive management strategy is *not* planned. (Level of Evidence: A)
- \*2. A platelet GP IIb/IIIa antagonist should be administered to patients already receiving heparin, ASA, and clopidogrel in whom catheterization and PCI are planned. The GP IIb/IIIa antagonist may also be administered just prior to PCI. (Level of Evidence: B)

**Class IIb**

- \*1. Eptifibatide or tirofiban, in addition to ASA and LMWH or UFH, to patients without continuing ischemia who have no other high-risk features and in whom PCI is *not* planned. (Level of Evidence: A)

**Class III**

- 1. Intravenous fibrinolytic therapy in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block. (Level of Evidence: A)
- \*2. Abciximab administration in patients in whom PCI is *not* planned. (Level of Evidence: A)

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\*New indication, not included in September 2000 guidelines.

†Minor clarification different from full-text version on web site.

**Anticoagulant Therapy**

The September 2000 guidelines<sup>1</sup> reviewed the evidence regarding the use of intravenous UFH or subcutaneous LMWH. It provided the following Class I recommendation:

**“Parenteral anticoagulation with intravenous UFH or subcutaneous LMWH should be added to antiplatelet therapy with ASA or a thienopyridine. (Level of Evidence: B)”**

In the interim, a number of studies have appeared that support the use of enoxaparin. In the EVET trial (Enoxaparin Versus Tinzaparin in the management of unstable coronary artery disease), 2 LMWHs, enoxaparin and tinzaparin, administered for 7 days, were compared in 438 patients with UA/NSTEMI. A preliminary report stated that both the recurrence of unstable angina and the need for revascularization were significantly lower in the enoxaparin group.<sup>22</sup> Because the level of anticoagulant activity cannot be easily measured in patients given LMWH (eg, activated partial thromboplastin time or activated clotting time), interventional cardiologists have expressed concern about the substitution of LMWH for UFH in patients scheduled for catheterization with possible PCI. However, Collet et al<sup>23</sup> have shown in a small nonrandomized observation study in 293 patients that PCI can be performed safely with UA/NSTEMI patients who received the usual dose of enoxaparin. In NICE-1 (National Investigators Collaborating on Enoxaparin), an observational study, intravenous enoxaparin (1.0 mg/kg) was used in 828 patients undergoing elective PCI without an intravenous GP

IIb/IIIa antagonist.<sup>24</sup> The rates of bleeding (1.1% major bleeding and 6.2% minor bleeding in 30 days) were comparable to those observed in historical controls with UFH.

An alternative approach is to use LMWH during the period of initial stabilization and to withhold the dose on the morning of the procedure. If an intervention is required and more than 8 hours has elapsed since the last dose of LMWH, UFH can be used for PCI according to usual practice patterns. Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 hours.

The September 2000 guidelines reflected concern regarding the combined use of LMWH and GP IIb/IIIa antagonists. Although the data are not definitive, it now appears that GP IIb/IIIa antagonists can be used with LMWH. In the ACUTE II (Anti-thrombotic Combination Using Tirofiban and Enoxaparin II) study,<sup>25</sup> UFH and enoxaparin were compared in patients with UA/NSTEMI who were given tirofiban. The frequencies of both major and minor bleeding were similar, and there was a trend to fewer adverse events in the patients given enoxaparin. A number of other open-label studies have examined the safety of combining enoxaparin, with abciximab, eptifibatide, or tirofiban in patients with UA/NSTEMI who are treated with PCI or conservatively; of combining enoxaparin with abciximab in patients undergoing elective PCI<sup>26</sup>; and of combining dalteparin with abciximab in patients with UA/NSTEMI who are treated conservatively and during PCI.<sup>27</sup> Although the majority of these studies relied on historical controls, none suggested that the combination of enoxaparin and a GP IIb/IIIa antagonist was associated with excess bleeding, whether or not the patient also underwent PCI.

Specific recommendations for the use of heparins in the revised guidelines are as follows:

**Class I**

- \*1. Anticoagulation with subcutaneous LMWH or intravenous UFH should be added to antiplatelet therapy with ASA and/or clopidogrel. (Level of Evidence: A)

**Class IIa**

- \*†1. Enoxaparin is preferable to UFH as an anticoagulant in patients with UA/NSTEMI, in the absence of renal failure and unless CABG is planned within 24 hours. (Level of Evidence: A)

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\*New indication, not included in the September 2000 guidelines.

†Minor clarification different from full-text version on web site.

**Early Conservative vs Early Invasive Strategies**

The September 2000 guidelines indicated that 2 different treatment strategies, termed “early conservative” and “early invasive,” may be used in patients with UA/NSTEMI.<sup>1</sup> In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest or with minimal activity or dynamic ST-segment changes) or a strongly positive stress test despite vigorous

medical therapy. In the *early invasive strategy*, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and angiographically directed revascularization, if possible.

Several trials comparing these 2 strategies were reviewed, but greatest attention was paid to the then-most-recent trial, FRISC II (Fragmin and Fast Revascularization during InStability in Coronary artery disease II).<sup>28</sup> At 1 year, the mortality rate in the invasive strategy group was 2.2% compared with 3.9% in the noninvasive strategy group ( $P=0.016$ ).<sup>29</sup> However, in FRISC II, the invasive strategy involved treatment for an average of 6 days in the hospital with LMWH, ASA, nitrates, and beta-blockers before coronary angiography, an approach that would be difficult to adopt in US hospitals.

In the interim, the TACTICS-TIMI 18 trial was reported.<sup>7</sup> In this trial, 2220 patients with UA or NSTEMI were treated with ASA, heparin, and the GP IIb/IIIa antagonist tirofiban. They were then randomized to an early invasive strategy with routine coronary angiography within 48 hours followed by revascularization if the coronary anatomy was deemed suitable, or to a more conservative strategy. In the latter, catheterization was performed only if the patient had recurrent ischemia or a strongly positive stress test. Death, myocardial (re)infarction, or rehospitalization for an acute coronary syndrome at 6 months occurred in 19.4% of patients assigned to the conservative strategy versus 15.9% assigned to the invasive strategy (OR 0.78; 95% CI 0.62 to 0.97;  $P=0.025$ ). Occurrence of death or MI was also reduced at 6 months (9.5% versus 7.3%;  $P$  less than 0.05). The beneficial effects on outcome were particularly evident in medium- and high-risk patients, as defined by an elevation of troponin T greater than 0.01 ng/mL or of troponin I greater than 0.1 ng/mL, the presence of ST-segment deviation, or a TIMI risk score greater than or equal to 3.<sup>7,30</sup> In the absence of these high-risk features, outcomes in patients assigned to the 2 strategies were similar. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy. The benefits of the invasive strategy were achieved at no significant increase in the cost of care over the 6-month follow-up period.

Thus, both the FRISC II<sup>28,29</sup> and TACTICS-TIMI 18<sup>7,30</sup> trials, the 2 most recent trials comparing invasive versus conservative strategies in patients with UA/NSTEMI, showed a benefit in patients assigned to the invasive strategy. In contrast to earlier trials, a large majority of patients undergoing PCI in these 2 trials received coronary stents as opposed to balloon angioplasty alone. In TACTICS-TIMI 18, treatment included the GP IIb/IIIa antagonist tirofiban, which was administered for an average of 22 hours before coronary angiography. The routine use of the GP IIb/IIIa antagonist in this trial may have eliminated the excess risk of early (within 7 days) acute MI in the invasive arm, an excess risk that was observed in FRISC II and other trials in which there was no routine "upstream" use of a GP IIb/IIIa antagonist. Therefore, an invasive strategy is associated with a better outcome in UA/NSTEMI patients at high risk who receive a GP IIb/IIIa antagonist.<sup>7</sup> Although the benefit of GP IIb/IIIa antagonists is well established for patients with UA/NSTEMI who undergo

PCI, the optimum time of commencing these drugs—as early as possible after presentation, ie, "upstream," as in TACTICS TIMI 18, or just before the PCI—has not been established.

Specific recommendations for the use of an invasive strategy in the revised guidelines are as follows:

#### Class I

†1. **An early invasive strategy in patients with UA/NSTEMI without serious comorbidity and who have any of the following high-risk indicators: (Level of Evidence: A)**

- \*(a) **Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy.**
- \*(b) **Elevated TnT or TnI**
- \*(c) **New or presumably new ST-segment depression**
- (d) **Recurrent angina/ischemia with CHF symptoms, an S<sub>3</sub> gallop, pulmonary edema, worsening rales, or new or worsening MR**
- (e) **High-risk findings on noninvasive stress testing**
- (f) **Depressed LV systolic function (eg, EF less than 0.40 on noninvasive study)**
- (g) **Hemodynamic instability**
- (h) **Sustained ventricular tachycardia**
- (i) **PCI within 6 months**
- (j) **Prior CABG**

2. **In the absence of any of these findings, either an early conservative or an early invasive strategy may be offered in hospitalized patients without contraindications for revascularization. (Level of Evidence: B)**

\*New indication, not included in the September 2000 guidelines.

†Minor clarification different from full-text version on web site.

#### Risk Factor Modification

The September 2000 guidelines pointed out that despite the overwhelming evidence for the benefits of beta-hydroxy-beta-methylglutaryl-coenzyme A (HMG-CoA) reductase (statin) therapy in patients with elevated low-density lipoprotein (LDL) cholesterol levels, almost no data existed about the timing of initiation of therapy in patients with acute coronary syndromes.<sup>1</sup> Indeed, the secondary prevention trials of statins specifically excluded patients with UA/NSTEMI in the acute phase. Fewer than 300 patients had been entered into the trials within 4 months of an acute coronary syndrome.

The Lipid-Coronary Artery Disease (L-CAD) study was a small trial that randomized 126 patients with an acute coronary syndrome to early treatment with pravastatin, alone or in combination with cholestyramine or niacin, or to usual care. At 24 months, the patients who received early aggressive treatment had a lower incidence of clinical events (23%) than the usual-care group (52%;  $P=0.005$ ).<sup>31</sup> In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial, 3086 patients were randomized to treatment with an aggressive lipid-lowering regimen of atorvastatin 80 mg per day or placebo 24 to 96 hours after an acute coronary syndrome.<sup>32</sup> At 16 weeks of follow-up, the primary

end point of death, nonfatal MI, resuscitated cardiac arrest, or recurrent severe myocardial ischemia was reduced from 17.4% in the placebo group to 14.8% in the atorvastatin group ( $P=0.048$ ). There were no significant differences between the 2 groups in the risk of the following individual end points: death, nonfatal MI, cardiac arrest, or worsening heart failure; however, there were fewer strokes and a lower risk of severe recurrent ischemia in patients assigned to atorvastatin.

Although the evidence from these 2 trials of a beneficial effect of pre-discharge initiation of lipid-lowering therapy is not yet robust or definitive, observational studies support this policy. In the Swedish Registry of Cardiac Intensive Care of almost 20 000 patients, the adjusted relative risk of mortality was 25% lower in patients in whom statin therapy was initiated before hospital discharge.<sup>33</sup> In addition, patients in whom lipid-lowering therapy is begun in the hospital are much more likely to be undergoing such therapy at a later time. In one demonstration project, the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP), the in-hospital initiation of lipid-lowering therapy was associated with an increased percentage of patients treated with statins 1 year later (from 10% to 91%) and with a higher frequency of patients whose LDL cholesterol was less than 100 mg/dL (from 6% to 58%).<sup>34</sup> Although additional trials are ongoing, there appear to be no adverse effects and substantial advantages to the initiation of lipid-lowering therapy before hospital discharge.<sup>35–37</sup> Such early initiation of therapy has also been recommended in the third report of the National Cholesterol Education Program (NCEP III), which also raised the threshold of high-density lipoprotein cholesterol concentration that required therapy.<sup>38</sup> Similar considerations apply to the early initiation of statin therapy following PCI. In the Lescol Intervention Prevention Study (LIPS), 1669 patients were randomized to receive 80 mg fluvastatin or placebo, beginning two days after PCI. After a follow-up of 3.9 years, the statin-treated group had a lower incidence of clinical events (21.4%) than the placebo group (26.7%),  $P=0.01$ .<sup>39</sup>

In addition to maintaining the original Class I recommendations for LDL cholesterol reduction, specific additional recommendations for the use of lipid-lowering therapy in UA/NSTEMI in the revised guidelines are as follows:

#### Class I

- \*1. A fibrate or niacin if high-density lipoprotein cholesterol is less than 40 mg per dl, occurring as an isolated finding or in combination with other lipid abnormalities. (Level of Evidence: B)

#### Class IIa

- \*1. HMG-CoA reductase inhibitors and diet for LDL cholesterol greater than 100 mg per dl begun 24 to 96 hours after admission and continued at hospital discharge. (Level of Evidence: B)

\*New indication, not included in the September 2000 guidelines.

### Conclusions

These guidelines address the diagnosis and management of patients with UA and the closely related condition NSTEMI.

These life-threatening disorders are a major cause of emergency medical care and are responsible for more than 1.4 million hospitalizations annually in the United States.<sup>40</sup> Nearly 60% of these admissions are among persons greater than 65 years old, and almost half occur in women. In 1997, there were 5 315 000 visits to US emergency departments for the evaluation of chest pain and related symptoms.<sup>41</sup>

Because of the high incidence of UA/NSTEMI and the seriousness of this condition (approximately 15% rate of death or [re]infarction at 30 days),<sup>1,20</sup> continued research in this field is of the greatest importance. It is encouraging that in the 21 months since the publication of the September 2000 guidelines, a considerable body of additional useful information about these conditions has emerged. Indeed, the progress between September 2000 and June 2002 equals that between 1994, when the first guidelines were published,<sup>42</sup> and September 2000.

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