Application of Current Guidelines to the Management of Unstable Angina and Non-ST-Elevation Myocardial Infarction

Eugene Braunwald, MD

Abstract—Unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) is a common but heterogeneous disorder with patients exhibiting widely varying risks. Early risk stratification is at the center of the management program and can be achieved using clinical criteria and biomarkers, or a combination. In addition to anti-ischemic therapy and aspirin, the thienopyridine clopidogrel is indicated except in patients who are potential candidates for urgent coronary artery bypass grafting (CABG). Platelet glycoprotein (GP) IIb/IIIa antagonists are indicated in high-risk patients likely to undergo percutaneous coronary intervention (PCI) but are not indicated in the management of lower-risk patients who do not undergo PCI. There is a growing body of evidence to support the substitution of the low-molecular-weight heparin (LMWH) enoxaparin for unfractionated heparin (UFH). Three recent trials have demonstrated the benefit of an early invasive strategy with catheterization followed by revascularization in patients at high and intermediate risk. Lower-risk patients should undergo early noninvasive stress testing. An intensive program of secondary prevention is mandatory and should be begun before hospital discharge. (Circulation. 2003;108[suppl III]:III-28-III-37.)

Key Words: angina ■ angioplasty ■ antioxidants ■ myocardial infarction ■ platelets

Unstable angina was first defined and named in 1971.1,2 For the past decade, it has been appreciated that UA and NSTEMI form a continuum, with similar pathophysiologic and clinical features, and are logically considered together as UA/NSTEMI. The most common presenting symptom is chest pain, which is one of the most common complaints of patients coming to emergency departments, estimated at 5.3 million visits/year. Approximately one third of these are caused by UA/NSTEMI, resulting in 1.4 million admissions to United States hospitals each year, by far the most common cause of admission for cardiac disorders.3,4 Interestingly, the number of hospital admission for patients with UA/NSTEMI has been rising, while the number with ST-elevation myocardial infarction (STEMI) has leveled off or has actually been declining. The management of UA/NSTEMI has been summarized in guidelines sponsored by the Agency for Health Care Policy and Research, and the National Heart, Lung, and Blood Institute,5 as well as the American College of Cardiology (ACC) and the American Heart Association (AHA). The latter, which are referred to in this article,4,5 were prepared for physicians practicing in the United States, to most of whom an invasive therapy is available. The guidelines for the management of UA/NSTEMI prepared by the European Society of Cardiology6 are quite similar to the American guidelines.

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III-28
MANAGEMENT OF UA/NSTEMI

**Algorithm for the management of patients with UA/NSTEMI.** Patients in whom this diagnosis is confirmed or suspected are treated with aspirin [ASA, heparin (enoxaparin preferred to UFH), β-blockade, nitrates, and clopidogrel]. They are then risk stratified, and their subsequent management is dictated by their risk category.

Although the typical presentation of ischemic chest discomfort in UA/NSTEMI as described above is well known, atypical presentation with dyspnea, nausea, diaphoresis, syncope, or pain in the arms, epigastrium, shoulder, or neck occurs in a large fraction of patients and in as many as one half of patients ≥65 years of age.5 This issue will become even more pressing in the future with the rapid escalation of the proportion of the population age >65.10

A table of high-, intermediate-, and low-risk features was proposed in the first practice guidelines for UA developed under the auspices of the Agency for Health Care Practice and Research3 and was subsequently adopted in modified form by the ACC/AHA4 (Table). Although this risk stratification is based on substantial clinical experience and is widely employed, it has not been independently validated.

**ECG**

The ECG, specifically the presence of ST-segment deviation, is an important determinant of risk. In the Thrombolysis in Myocardial Infarction (TIMI) III Registry new ST-segment depression of as little as 0.05 mV was a predictor of adverse outcomes.11 More recently, Kaul et al. showed that the increased risk of adverse outcome rose progressively with the severity of ST-segment depression, and that both ST-segment depression and troponin T determinations provide complementary prognostic information in patients with UA/NSTEMI.12

**Platelet GP IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin (PURSUIT) Risk Score**

The relation between baseline characteristics and adverse outcomes (death and death or myocardial [re]infarction) was determined by Boersma et al. from the patients enrolled in the PURSUIT trial.13 The principal features associated with adverse outcomes were older age, high heart rate, low systolic blood pressure, ST-segment depression, signs of heart failure, and elevation of cardiac biomarkers. These features were incorporated into a simple, convenient scoring system.

**TIMI Risk Score**

This represents a simple, convenient method of risk stratification, in which the number of independent risk factors on presentation is determined.14 The incidence of an adverse outcome (death, myocardial [re]infarction, or recurrent severe ischemia) at 14 days ranged from 5% with a risk score of 0–1 to 41% with a risk score of 6–7 (Figure 3). This risk score was derived from an analysis of patients in the TIMI 11B trial, and has been validated in four additional trials14–17 and one registry.18 With an increasing risk score, progressively greater benefits of treatment with LMWH versus UFH,14 of the platelet GP IIb/IIIa receptor blocker tirofiban versus placebo,15 and of an invasive versus a conservative strategy16 were observed. However, patients across all levels of the TIMI risk score showed similar relative reductions in adverse outcomes with clopidogrel.17 The risk score was effective also in predicting postdischarge adverse outcomes.19 This ability of a risk assessment scheme to detect differences in treatment benefit specific to particular therapies greatly enhances the imperative to use the score in practice.

**Serum Creatinine**

There is growing evidence that renal dysfunction is associated with increased risk of adverse outcome.20 It has been

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**Figure 1.** Algorithm for the management of patients with UA/NSTEMI. Patients in whom this diagnosis is confirmed or suspected are treated with aspirin [ASA, heparin (enoxaparin preferred to UFH), β-blockade, nitrates, and clopidogrel]. They are then risk stratified, and their subsequent management is dictated by their risk category.

**Figure 2.** Influence of rest pain on outcome; death or MI at left or death at right of presenting factors in patients with UA. Although rest pain was associated with a distinctly worse outcome, there were substantial risks in patients without rest pain. These should be designated "lower-" rather than "low-" risk patients. (Adapted from: Scirica BM, Cannon CP, McCabe CH, et al. Prognosis in the Thrombolysis in Myocardial Ischemia III Registry according to the Braunwald unstable angina pectoris classification. Am J Cardiol. 2002;90:821–826.)
**Short-term risk of death or nonfatal MI in patients with UA**

<table>
<thead>
<tr>
<th>Feature</th>
<th>High Risk (At Least 2 of the Following Features Must Be Present)</th>
<th>Intermediate Risk (No High-Risk Feature but 1 of the Following Features Must Be Present)</th>
<th>Low Risk (No High- or Intermediate-Risk Feature but the Following Features Must Be Present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Accelerating tempo of ischemic symptoms in preceding 48 h</td>
<td>Prior MI, peripheral or cerebrovascular disease, or CABG:* prior aspirin use</td>
<td>New-onset or progressive CCS Class III or IV angina in the past 2 weeks with moderate or high likelihood of CAD</td>
</tr>
<tr>
<td>Character of pain</td>
<td>Prolonged ongoing (&gt;20 min) rest pain</td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td>Clinical findings</td>
<td>Pulmonary edema, most likely related to ischemia New or worsening MR murmur, S(_1) or new/worsening rales Hypotension, bradycardia, tachycardia Age &gt;75 years</td>
<td>Age &gt;70 years</td>
<td></td>
</tr>
<tr>
<td>ECG findings</td>
<td>Angina at rest with transient ST-segment changes &gt;0.05 mV Bundle-branch block, new or presumed new Sustained ventricular tachycardia</td>
<td>T-wave inversions &gt;0.2 mV Pathological Q-waves</td>
<td>Normal or unchanged ECG during an episode of chest discomfort</td>
</tr>
<tr>
<td>Cardiac markers</td>
<td>Elevated (eg, TnT, or TnI &gt;0.1 ng/mL)</td>
<td>Slightly elevated (eg, TnT &gt;0.01 but &lt;0.1 ng/mL)</td>
<td>Normal</td>
</tr>
</tbody>
</table>


**Multiple Biomarker Risk Assessment**

Two approaches have been employed. Newby et al. demonstrated that a bedside strategy using myoglobin, creatine kinase-MB, and troponin I provides more accurate risk stratification than a single-marker, laboratory-based approach. Sabatine et al. considered three pathophysiologic factors that operate in UA/NSTEMI: (1) plaque instability and the myonecrosis resulting from microembolization; (2) vascular inflammation; and (3) left ventricular damage. Each could be assessed independently from an assessment of biomarkers, i.e., cardiac-specific troponin, C-reactive protein, and brain natriuretic peptide, respectively. In a retrospective analysis of Orbifiban in Patients with Unstable Coronary Syndromes (OPUS)-TIMI 16, we observed that each elevated biomarker was independently associated with adverse outcomes. These findings were then validated prospectively in TACTICS-TIMI 18 in which the relative 30-day mortality risks for patients with 0, 1, 2, and 3 biomarkers were multiplicative at 1, 2.1, 5.7, and 13.0, respectively. In the future, incorporation of these three markers into a single cassette should prove useful in “point-of-care” risk assessment.

It is likely that even more proteins will be added into a “protein-guided” strategy or therapy so that treatment can be matched to the particular risk markers in the individual patient.
calibration of risk scores should greatly enhance their ability to risk-stratify and to identify patients who are likely to benefit from particular therapies.

Management

Four major components of therapy must be considered in every patient with UA/NSTEMI: (1) anti-ischemic therapy; (2) antiplatelet/anticoagulant therapy; (3) invasive therapy (early catheterization and revascularization); and (4) predischarge and posthospital care.

Anti-ischemic therapy consists of sublingual followed by intravenous nitroglycerin, intravenous followed by oral β-blockade, and nondihydropyridine calcium blockers in patients with ischemia refractory to or who cannot tolerate the former drugs. This therapy has not changed in the past 15 years and is described in detail elsewhere.3,4

Subtotal thrombotic coronary occlusion plays a central pathogenetic role in UA/NSTEMI and both platelet aggregation and thrombin-activated fibrin formation are responsible for clot development. Therefore, both antiplatelet and antithrombin therapy are key components of care.

Antiplatelet Therapy

Aspirin

The important role played by this cyclooxygenase-1 inhibitor is well established from multiple clinical trials and several meta-analyses,4,25,30 and based on these, aspirin has become a cornerstone in the management of UA/NSTEMI. A syndrome of “aspirin-resistance” has emerged recently. This syndrome has been variously described as relative failure to inhibit platelet aggregation and/or failure of prolongation of the bleeding time, or the development of a clinical event while on aspirin therapy.27 Patients with aspirin resistance appear to be at higher risk of recurrent events, and although prospective randomized trials have not yet been reported in these patients, it is logical to treat them with clopidogrel, although aspirin should not be discontinued. Furthermore, Alexander et al. demonstrated both a high event rate and a large treatment effect of epifibatide in patients with an acute coronary syndrome (ACS) despite prior aspirin therapy.28

Clopidogrel

This thienopyridine blocks the P2Y12 adenosine diphosphate receptor on the platelet surface and thereby inhibits platelet activation. Its use in UA/NSTEMI is based primarily on the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO) trials. The former randomized 12,562 patients with UA/NSTEMI (all of whom were receiving aspirin) to clopidogrel (300-mg loading dose followed by 75 mg daily) or placebo.29 After a follow-up averaging 9 months, the primary prespecified “hard” endpoints of cardiovascular death, MI, and stroke were reduced significantly by 20% from 11.5% in the placebo group to 9.3% in the clopidogrel group (Figure 4). A reduction of recurrent ischemia was already present within 6 h of randomization.30 The salutary effects were noted across all of the subgroups, including those without ST-segment deviation or troponin release and those with a low TIMI risk score.19,17

The major benefit was a reduction in MI; although death and stroke trended in favor of clopidogrel, the reduction in these events did not achieve statistical significance.31 However, clopidogrel was associated with significant increases in major bleeding (3.7% versus 2.7%) and minor bleeding, as well as with a trend toward increases in life-threatening bleeding. Excess bleeding was greater in patients on higher doses of aspirin or who underwent CABG within 5 days of discontinuing clopidogrel.29 The increased risk of bleeding with the combination of aspirin and clopidogrel in patients undergoing CABG has been confirmed.32

In an observational substudy in CURE in 2658 patients undergoing PCI a median of 10 days after randomization (the PCI-CURE Study), most of the patients received open-label thienopyridine for about 4 weeks after the procedure.33 Pretreatment with clopidogrel was associated with a 30% lower relative risk of cardiovascular death, MI, or revascularization within 30 days (6.4% versus 4.5%). Continuing benefit of clopidogrel was observed during the 8 months after blinded study medication (clopidogrel or placebo) was resumed 1 month after PCI. The benefit of pretreatment and long-term follow-up treatment with clopidogrel was also observed in CREDO, a trial in 2116 patients, 55% of whom had UA/NSTEMI and were to undergo PCI.34

Based on these trial results, it is recommended that clopidogrel be considered a first-line drug in UA/NSTEMI and added to aspirin in patients with UA/NSTEMI, except those at high risk for bleeding and those in whom the need for urgent CABG cannot be excluded.5 Thus, clopidogrel should be administered to patients with UA/NSTEMI: (1) in whom an early noninvasive approach is planned; (2) who are known not to be candidates for urgent coronary bypass surgery based on previous knowledge of the coronary anatomy or who have contraindications to surgery; and (3) in whom catheterization will be deferred for >24–36 h. In patients in whom a diagnostic catheterization is planned within 24–36 h after presentation, it is reasonable to withhold clopidogrel until the findings on a coronary angiogram exclude the need for urgent...
bypass surgery. The loading dose of clopidogrel can then be administered in the catheterization laboratory prior to PCI or it may be started immediately after the catheterization. Because clopidogrel (like aspirin) is an irreversible inhibitor of platelet function, it is recommended that the drug be discontinued for 5 or preferably 7 days before elective surgery, including CABG.4,5

An alternative view is that the extra risk of bleeding is tolerable in patients in whom angiography has not yet been performed because of the prevention of ischemic events during the waiting period. This view is bolstered by the observations within CREDO that pretreatment >6 h before PCI tended to enhance the benefit of the drug,34 and that the combination of clopidogrel and GP IIb/IIIa inhibition appeared to be at least additive for benefit without enhancing the risk of bleeding.

Platelet GP IIb/IIIa Antagonists

There is strong evidence from multiple trials that GP IIb/IIIa antagonists reduce the incidence of death or MI in patients with UA/NSTEMI undergoing PCI, and that their use in this setting is indicated clearly.4 However, little data are available from trials in which the strategy of purposefully not undergoing PCI was employed. One notable exception is the GUSTO IV-ACS trial, which was designed specifically to examine the potential benefit of abciximab in patients with UA/NSTEMI in whom PCI was not intended. No benefit was observed; indeed a secondary endpoint, i.e., death within 48 h, favored placebo.35 The situation is less clear for the small-molecule agents, eptifibatide and tirofiban. A retrospective analysis of the PRISM-PLUS trial showed that tirofiban reduced the incidence of adverse outcomes in patients at high risk (TIMI risk score ≥4) who did not undergo PCI.15

Perhaps the most light that has been shed on this question comes from a meta-analysis of GP IIb/IIIa antagonists of six large trials involving 31,402 UA/NSTEMI patients who were not scheduled to undergo PCI conducted by Boersma et al.36 A significant, albeit small (−9% relative, −1% absolute), reduction in the odds for the combined endpoint of death or MI was observed in the GP IIb/IIIa antagonist group, while bleeding was increased significantly from 1.4% in the placebo group to 2.4% in the GP IIb/IIIa antagonist group. On additional analysis, it was found that 5847 of the 31,402 (19%) patients actually underwent early (within 5 days) revascularization, and the observed benefit of GP IIb/IIIa antagonists, i.e., reduction of death or MI, was largely confined to this subgroup (−21%). These findings include and are bolstered by detailed analyses of the PURSUIT trial within the United States, in which the early invasive strategy was used frequently. In this United States subgroup, 35 events/1000 patients treated were averted.37 On the other hand, the majority of patients, 25,555 (81%), in the Boersma meta-analysis did not undergo early revascularization and the reduction in death or MI (−3%) was not significant. Baseline troponin measurements were available in 16,151 patients, albeit not from all of the trials. As anticipated, adverse outcomes in this subgroup were substantially more frequent in those with troponin elevation (10.9%) than in those without (6.6%). Assignment to a GP IIb/IIIa antagonist was associated with a relative reduction of death or MI in the former (−14%) but not in the latter (−11%) group.

Although caution must be exercised in the interpretation of results obtained from such nonrandomized subgroups, based on the totality of evidence, it was concluded by the ACC/AHA Guideline Committee5 that high-risk patients, especially troponin-positive patients who are likely to undergo angiography, should receive a GP IIb/IIIa antagonist. The two small-molecule agents, eptifibatide and tirofiban, may be started “upstream,” i.e., 1 or 2 days before, and continued during the procedure. Any of the three available GP IIb/IIIa antagonists may be started immediately before or in the course of the procedure. However, in accord with the findings of GUSTO-IV ACS, abciximab is not indicated in patients in whom PCI is not planned.33 None of the GP IIb/IIIa antagonists appear to be effective or indicated in the routine management of low-risk, troponin-negative patients in whom early angiography is not intended. It would now be useful to compare prospectively “upstream” early treatment with a small-molecular GP IIb/IIIa antagonist in patients with UA/NSTEMI with the commencement of therapy just before PCI.

Based on observations in PCI-CURE33 and CREDO,34 clopidogrel does not appear to add to the bleeding risk of GP IIb/IIIa antagonists; however, additional observations on the interaction between these drugs is warranted. The efficacies of thienopyridine and GP IIb/IIIa antagonists appear to be additive, and triple antiplatelet therapy (aspirin, clopidogrel, and a GP IIb/IIIa antagonist) are indicated in high-risk patients in whom PCI is planned and who do not have an excessive risk of bleeding.

Anticoagulant Therapy

UFH

The benefit of UFH when added to aspirin has been established in seven randomized trials, and the combination of UFH and aspirin has been used in the management of UA/NSTEMI for >15 years.3,23 Moreover, the aforementioned trials demonstrating the benefits of clopidogrel and the GP IIb/IIIa inhibitors have all been carried out on a background of aspirin and UFH. Nonetheless, there are many disadvantages of UFH.3,35 These include its nonspecific binding to and resulting inactivation by platelets, vascular endothelium, fibrin, platelet factor 4, and a variety of circulating proteins. The production of antistrep antibodies may be associated with heparin-induced thrombocytopenia. This binding leads to an uncertain and erratic anticoagulant effect, requiring frequent monitoring of the activated partial thromboplastin time, dose adjustments, and requirement for continuous intravenous infusion.

LMWH

Given these problems with UFH, attention has focused on the LMWHs in which these disadvantages have largely been overcome. Importantly, monitoring of the anticoagulant effect is not necessary, and the incidence of heparin-induced thrombocytopenia is reduced. LMWHs are potent inhibitors not only of circulating thrombin but also of factor Xa. Therefore, these agents interfere not only with the action of
circular thrombin (their anti-factor IIa effect), as does UFH, but they also reduce the formation of thrombin (their anti-factor Xa effect). Another practical advantage of LMWHs is their rapid and predictable absorption after subcutaneous administration. Their prolonged elimination makes twice-daily administration feasible. Two double-blind, randomized trials, Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) and TIMI 11B, comprising a total of 7081 patients, showed a significant benefit of enoxaparin over UFH, and a prespecified meta-analysis showed a significant reduction of death or MI.

Because of the difficulty in determining therapeutic anticoagulant levels, there has been concern about the appropriate dose of LMWH in patients undergoing PCI, and the safety of LMWH in patients receiving GP IIb/IIIa inhibitors has been questioned. These concerns are being allayed by a number of observational studies and registries using enoxaparin. Importantly, enoxaparin was compared with UFH in 746 patients with UA/NSTEMI receiving aspirin and epifibatide in the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial. The primary endpoint, non-CABG-associated major bleeding, was significantly lower in the enoxaparin compared to the UFH groups (1.8% versus 4.6%), although the relative incidence of minor bleeding was reversed. Also, the rate of death or nonfatal MI at 30 days and of ischemia on a continuous Holter monitor were each reduced almost by half in the enoxaparin group.

Thus, based on the available evidence it is advisable to use enoxaparin in place of UFH in patients with UA/NSTEMI. There are two caveats. First, the results of two large trials are awaited. In Superior Yield of New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY), UFH and enoxaparin are being compared in patients in whom an invasive strategy is planned, whereas (SYNERGY), UFH and enoxaparin are being compared in patients with UA/NSTEMI receiving aspirin and epifibatide in the Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment (INTERACT) trial. The primary endpoint, non-CABG-associated major bleeding, was significantly lower in the enoxaparin compared to the UFH groups (1.8% versus 4.6%), although the relative incidence of minor bleeding was reversed. Also, the rate of death or nonfatal MI at 30 days and of ischemia on a continuous Holter monitor were each reduced almost by half in the enoxaparin group.

An early invasive strategy (early coronary arteriography followed by revascularization as indicated by the arteriographic findings) versus an early conservative strategy (catheterization, and if indicated, revascularization, only in the event of failure of medical therapy) has been studied in five large, prospective, randomized trials. The first two of these were carried out before routine stenting was used. The TIMI IIIB trial showed no significant difference in the outcomes between these two strategies, although a retrospective analysis identified high-risk factors, which could be used to predict failure of the conservative strategy and the superiority of the invasive strategy. The other “early” trial, the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial, showed an excess of deaths, as well as of death or MI, with the invasive strategy. However, this discrepant result appeared to be related to an unusually high mortality rate associated with CABG.

The three trials conducted more recently, i.e., during the “stent era,” have all shown superiority of the invasive strategy (Figure 5). The Fragmin and Fast Revascularization during
Instability in Coronary Artery Disease (FRISC) II trial showed a significant reduction in total mortality and in death or MI at 1 year in the patients assigned to the invasive strategy. However, because the patients in the invasive arm of this trial were treated in the hospital with an intensive regimen that included LMWH for an average of 6 days before catheterization, the applicability of the results of this trial, at least for United States practice, is limited. In the TACTICS-TIMI 18 trial all of the patients received not only aspirin and UFH but also the “up-front,” i.e., immediate, administration of the GP IIb/IIIa inhibitor tirofiban. In contrast with FRISC II, cardiac catheterization in the invasive arm was carried out relatively early, i.e., a mean of 22 h after randomization. Death or infarction at 6 months was reduced significantly by 23% from 9.5% in the conservagroup to 7.3% in the invasive group. The benefit was confined to patients at high or intermediate risk, defined as TIMI risk score ≥3, any elevation of troponin T (>0.01 mg/mL), or ST-segment deviation. In patients without these risk features, the outcomes with the two strategies were similar. Importantly, the length of hospital stay was reduced with the invasive strategy, and the overall costs of implementing the two strategies were similar.

The Randomized Intervention Trial of Unstable Angina (RITA) 3 trial enrolled patients with UA/NSTEMI, all of whom were treated with aspirin and enoxaparin. In patients assigned to the invasive arm, coronary angiography was performed an average of 2 days after randomization. At 4 months, there was a 34% reduction in the primary endpoint of death, (re)infarction, or refractory angina (from 14.5% to 9.6%) with the invasive strategy, and at 12 months a significant difference was sustained. The “harder” endpoints of death or (re)infarction, as defined by the European Society of Cardiology/ACC criteria, also showed a significant 27% reduction at 1 year with the invasive strategy.

Despite being conducted in different countries with different practice patterns and background therapies, all three of the trials reached similar conclusions. Thus, in the absence of specific contraindications, an early invasive strategy is now recommended for patients with UA/NSTEMI who are at high or intermediate risk (Figure 6). These patients should receive aspirin and a heparin, probably enoxaparin. As stated above, clopidogrel should be started immediately if the catheterization is to be deferred by >24–36 h, or at the catheterization table if it is carried out within this time period and the initial angiogram rules out the need for urgent CABG.

The question has been raised as to how the 2002 update of the ACC/AHA guidelines will affect the use of GP IIb/IIIa antagonists. On the one hand, their use is likely to be enhanced if, as recommended, the early invasive strategy is more widely adopted because this strategy includes the use of these agents in patients with UA/NSTEMI undergoing PCI. On the other hand, their use is likely to be curbed by the recommendation that they are not indicated in patients who are not at high risk and in whom PCI is not planned. Most probably, the adoption of these two recommendations will result in little overall change in the use of these agents, but it is hoped that the care of patients with UA/NSTEMI will be improved by their application to patients who are most likely to benefit.

Gender Differences

Differences in the presentation of women and men with UA/NSTEMI have been noted consistently. Thus, in the TIMI IIIb registry, we noted that women, compared with men, were older, more likely to have a history of hypertension and diabetes mellitus, and more likely to have a family history of hypertension, but were less likely to have had a prior MI or a history of smoking. On angiography, they had less severe and extensive coronary artery disease. They were also less likely than men to undergo angiography or revascularization. Similar gender differences have been observed in the TIMI IIIb and TACTICS-TIMI 18 trials. The responses to therapy may also differ. Thus, both the PUR-SUIT trial and the meta-analysis of all of the large trials of GP IIb/IIIa antagonists in ACS suggest that the benefit does not occur in women. These findings may be confounded by the difficulties in recognizing women with UA/NSTEMI secondary to coronary atherosclerosis. The benefit of GP IIb/IIIa administration in women with elevated troponin concentrations were similar to those in men.

The relation between gender and the benefit of an early invasive management strategy has been examined in four studies. A significant interaction between gender and the treatment effect of an invasive strategy was observed in FRISC II and RITA 3, with absence of benefit in women. Yet in TACTICS-TIMI 18 and in a prospective cohort study, no difference in response was observed. Whereas the explanation for these differences is not entirely clear, it is inappropriate to withhold an invasive strategy from women at high or intermediate risk who have obstructed coronary arteries that are suitable for revascularization.

Care of the Low(er)-Risk Patient

Although the preceding discussion has focused on patients at high or intermediate risk, the majority of patients with UA are at low risk. As already pointed out, “low risk” is probably a misnomer, and patients with UA without rest pain should
The diagnosis of an ACS should serve as a "wake-up call" (Figure 2). Although these patients need not be hospitalized, they should receive intensive anti-ischemic therapy, as well as aspirin and clopidogrel. Attention should also be directed immediately to the correction of extracardiac factors that may have disturbed the balance between myocardial oxygen supply and demand, such as fever, anemia, arrhythmias, severe hypertension, unrecognized pulmonary embolism, and thyrotoxicosis, any of which can greatly intensify the severity of ischemia.

In the absence of troponin elevation, ST-segment deviation, or rest pain within 12 h, these lower-risk patients should be managed like those with severe stable angina (Figure 7). A noninvasive stress test should be carried out, and patients with tests showing high-risk features should promptly undergo coronary arteriography and, depending on the anatomic findings, revascularization. Coronary arteriography is optional in patients with a positive test but without high-risk findings. Consideration of an alternative diagnosis, including variant angina, and/or continued observation are indicated in patients with a negative noninvasive stress test.

### PredischARGE Management and Secondary Prevention

The diagnosis of an ACS should serve as a “wake-up call” to patients with UA/NSTEMI and to their caregivers, and the latter should commence a vigorous, meticulous program of secondary prevention, including achievement of optimal weight, dietary advice, cessation of smoking, exercise, control of hypertension, intensive management of established diabetes, and detection of previously unrecognized diabetes. One area that is not settled is the timing and intensity of statin therapy. The results of observational studies of the early (predischarge) commencement of statins are mixed. The only large double-blind, placebo-controlled trial, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, while showing a benefit of early statin use, achieved just nominal statistical significance ($P=0.048$), without any benefit in the “hard” prespecified endpoints of death or MI. Two large prospective statin trials in post-ACS patients have completed enrollment, are now in a follow-up phase, and will be reported within the next year. In the A to Z trial, patients with ACS are assigned to commence simvastatin 40 mg/day or placebo before hospital discharge, and at 4 months these two treatment arms are advanced to simvastatin 80 mg/day and 20 mg/day, respectively. The Pravastatin or Atorvastatin Evaluation and Infarction Therapy (PROVE IT)-TIMI 22 trial is comparing marked cholesterol lowering using atorvastatin 80 mg/day with modest cholesterol lowering using pravastatin 40 mg/day (Figure 8), and thereby addresses the question of “how low is low enough” with respect to low-density lipoprotein (LDL) cholesterol. This trial also compares, in a second randomization, gatifloxacin, an oral fluoroquinolone that has potent antichlamydial properties, with placebo.

While awaiting the results of these two trials, there is agreement on several points. First, patients with UA/NSTEMI should be treated, at the very least, in accord with the third report of the National Cholesterol Education Program (NCEP III), and their LDL cholesterol concentrations should be reduced to <100 mg/dL. The Heart Protection Study indicates that the outcome of stable patients with even lower baseline levels can be improved with a statin. Second, early, i.e., predischarge, commencement of a statin is well tolerated. Third, observational studies have shown that patients who commence statin therapy before hospital discharge are much more likely to be taking a statin and to have achieved NCEP III established target levels (<100 mg/dL) of LDL cholesterol than patients who are not treated in this manner. Fourth, in patients with UA/NSTEMI already receiving a statin at the time of presentation, the drug should not be withdrawn. Fifth, the Lescol Intervention Prevention Study (LIPS) compared fluvastatin 80 mg/day with placebo, commencing 2 days after PCI in patients, many with UA/NSTEMI. The clinical event rate in the statin-treated group was reduced significantly by 20%. Therefore, it is logical to include UA/NSTEMI patients who have undergone PCI in early cholesterol reduction program. Last, patients with low high-density lipoprotein cholesterol (<40 mg/dL) should be considered for additional therapy with a fibrate or niacin.

### Future Directions

Despite the substantial improvement in every aspect of the assessment and care of patients with UA/NSTEMI, this condi-
tion remains associated with an unacceptably high incidence of both short- and long-term adverse outcomes. Three current areas of research appear to be quite promising.

The first promising area is the detection of arterial inflammation, using a combination of systemic biomarkers (such as C-reactive protein) and noninvasive imaging (such as high resolution magnetic resonance), in the identification of patients with vulnerable plaques who are at high risk of future development or recurrence of UA/NSTEMI.

The second area is the treatment not only of the culprit lesion but of other vulnerable plaques with multiple drug-eluting stents in patients who have already developed UA/NSTEMI as well as those who have not yet developed a clinical manifestation, but are at high risk, as in the first area, above.

The third area is the use of new, potent systemic anti-inflammatory drugs (in addition to statins, aspirin, and clopidogrel) in patients with vulnerable plaques.

As important as these future approaches are likely to be, it is of the highest priority to apply the wealth of available information to patient care at this time. Registry-based data suggest that the gap between available knowledge and its application remains unacceptably high.

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Braunwald

Unstable Angina and Non-ST-Elevation MI


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