Acute Ischemic Heart Disease

Guidelines for the diagnosis and management of unstable angina and non-Q-wave myocardial infarction: Proposed revisions

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* A list of contributors to the development of these guidelines appears in the Appendix.

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Background In 1994, the United States Agency for Health Care Policy and Research issued clinical practice guidelines for the diagnosis and management of unstable angina and non-Q-wave myocardial infarction. In the past 5 years, rapid progress has been made in the management of patients with unstable coronary syndromes, yet current guidelines do not necessarily reflect these advances.


27. The FRAX.I.S. study group. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q-wave myocardial infarction: FRAX.I.S. (Fraxiparine in Ischaemic Syndrome). Eur Heart J 1999;20:1553-62. Abstract


Methods and Results An international forum of cardiology investigators reviewed existing guidelines and discussed areas in which the diagnosis and treatment of unstable angina and non-Q-wave myocardial infarction should be modified. It was agreed that there is sufficient evidence to recommend the following changes: (1) use of serum cardiac markers should be expanded to include troponin I and T levels as diagnostic and prognostic tools; (2) low-molecular-weight heparins should replace unfractionated heparin as antithrombotic agents; (3) new classes of antiplatelet agents are recommended in addition to aspirin; and (4) the use of cholesterol-lowering drugs is appropriate in the long-term management of these patients.

Conclusions Evidence from clinical trials within the last 5 years requires that significant changes be made to existing guidelines for the diagnosis and management of unstable angina and non-Q-wave myocardial infarction. The recommendations detailed should be considered in the creation and implementation of updated guidelines. (Am Heart J 2000;139:461-75.)

Unstable angina (UA) and non-ST elevation myocardial infarction (frequently referred to as non-Q-wave myocardial infarction [NQMI]) are acute manifestations of coronary artery disease (CAD) that affect millions of patients annually throughout the world. Patients with UA or NQMI are at risk for subsequent events, including Q-wave infarction and cardiac death. Appropriate therapy is thus essential to relieve the initial myocardial ischemia and reduce the risk of future adverse cardiac events. In 1994, the United States Agency for Health Care Policy and Research (AHCPR) issued clinical practice guidelines for the diagnosis and management of UA; the guidelines are conveniently summarized in a reference guide for clinicians. Although comprehensive at the time, these guidelines do not reflect the rapid progress that has been made in the past 5 years in the diagnosis and treatment of patients with UA/NQMI.

In September 1998, the International Cardiology Forum sponsored workshops to discuss revision of the 1994 guidelines to reflect current international practice and the results of recent clinical trials. In these workshops, participants representing 40 countries identified areas of the guidelines that require updating as well as areas in which further research is needed. The recommended revisions are summarized in Table I.

### Table I. Summary of new recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
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<tr>
<td>1. An initial assay of serum levels of either troponin T or troponin I should</td>
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<td>be made on admission and at least once more in the next 8 to 12 hours.</td>
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<tr>
<td>Patients with elevated troponin levels should be considered at high risk.</td>
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<tr>
<td>2. LMWH should replace unfractionated heparin as the antithrombin of choice.</td>
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<td>If heparin-induced thrombocytopenia is a concern, hirudin may be considered</td>
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<tr>
<td>an option.</td>
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<tr>
<td>3. Clopidogrel is recommended in place of ticlopidine for aspirin-intolerant</td>
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<td>patients. It may also be considered as a substitute for aspirin in those</td>
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<td>patients unresponsive to aspirin.</td>
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<tr>
<td>4. The GP IIb/IIIa inhibitors eptifibatide and tirofiban, used with concomitant</td>
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<td>aspirin and unfractionated heparin, should be considered options for medical</td>
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<tr>
<td>management of UA/NQMI.</td>
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<tr>
<td>5. Patients with UA/NQMI with elevated LDL cholesterol should be started on</td>
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<td>an HMG CoA reductase inhibitor.</td>
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These revisions pertain to new treatments and procedures for which clear evidence of benefit exists.

**Pathogenesis of UA/NQMI**

The acute coronary syndromes of UA, NQMI, and Q-wave MI share a common pathogenic substrate:
Atherosclerotic lesions of the coronary arteries (Figure 1).

(Figure Not Available) **Fig. 1.** Acute coronary syndromes. Patients with ischemic discomfort at rest may or may not have ST-segment elevation on ECG. The majority of patients who do not have ST elevation are ultimately diagnosed with either UA or NQMI (large arrows) based on presence or absence of cardiac markers such as CK-MB in serum. A minority of these patients have Q-wave MI develop (small arrow). The majority of patients with ST elevation ultimately have Q-wave MI develop (large arrow), whereas only a minority (small arrow) have NQMI develop. The spectrum of clinical conditions ranging from UA to NQMI to Q-wave MI is referred to as acute coronary syndromes. (Reproduced with permission from Antman EM, Braunwald E. Acute myocardial infarction. In: Braunwald E, editor. Heart disease: a textbook of cardiovascular medicine. vol 2. Philadelphia: WB Saunders, 1995. p. 1184-288.)

When an unstable atherosclerotic plaque ruptures or erodes, pathophysiologic processes are triggered that result in thrombus formation at the site of arterial injury. When thrombus formation results in abrupt reduction or cessation of blood flow through the affected vessel, the resulting imbalance between oxygen supply and demand produces the clinical manifestations of ischemia. Clinical manifestations of UA and NQMI are similar at the time of presentation; the diagnosis of NQMI is made when serum markers indicative of cardiac necrosis are detected in the peripheral circulation. The traditional marker, creatine kinase-myocardial band isoenzyme (CK-MB), is less sensitive than newer markers such as cardiac troponin I and cardiac troponin T—approximately 30% of patients without CK-MB elevation have detectable troponin I or T levels and thus have NQMI rather than UA. Angiographic studies of NQMI and Q-wave MI have determined that the degree and duration of coronary artery occlusion and the presence or absence of collateral flow are important determinants of the type of infarction that occurs. Thus the acute coronary syndrome spectrum ranging from UA to NQMI and Q-wave MI represents increasingly severe manifestations of the same pathophysiologic processes. UA and NQMI are often considered together because they are not easily distinguishable from one another at the time of patient presentation; however, it should be recognized that the UA/NQMI syndrome encompasses patients who may differ in both quantitative and qualitative aspects of their disease (eg, the extent of vessel occlusion or plaque instability). Identifying different subgroups of patients and designing appropriate therapies for them therefore remains an important aspect of therapeutic decision making.

**AHCPR practice guidelines**

The 1994 recommendations for the diagnosis and management of UA begin by defining UA (encompassing NQMI) on the basis of 3 possible presentations (Table II) and outlining a diagnostic strategy based on distinguishing probable CAD from other possible causes of acute chest pain.

<table>
<thead>
<tr>
<th>Table II. Principal presentations of UA</th>
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<tr>
<td><strong>Rest angina</strong></td>
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<tr>
<td><strong>New onset angina</strong></td>
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<tr>
<td><strong>Increasing angina</strong></td>
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</table>

Adapted from 1994 AHCPR guidelines.
The likelihood of CAD is determined from the clinical presentation, electrocardiogram (ECG) findings, medical history, and risk factors for atherosclerosis. When a diagnosis of UA is considered likely, these findings are then used to stratify patients into low-, intermediate-, and high-risk groups (Table III).

### Table III. Short-term risk of adverse cardiac events in patients with UA

<table>
<thead>
<tr>
<th><strong>High risk</strong></th>
<th><strong>Intermediate risk</strong></th>
<th><strong>Low risk</strong></th>
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<tbody>
<tr>
<td><strong>Prolonged ongoing (&gt;20 min) ischemic pain</strong></td>
<td>Prolonged (&gt;20 min) rest angina, now resolved, with moderate or high likelihood of CAD</td>
<td>Increased angina frequency, severity, or duration</td>
</tr>
<tr>
<td>Pulmonary edema, most likely related to ischemia</td>
<td>Rest angina (&gt;20 min or relieved with rest or sublingual nitroglycerin)</td>
<td>Angina provoked at a lower threshold</td>
</tr>
<tr>
<td>Angina at rest with dynamic ST changes &gt;1 mm</td>
<td>Nocturnal angina</td>
<td>New onset angina with onset 2 w to 2 mo before presentation</td>
</tr>
<tr>
<td>Angina with new or worsening MR murmur</td>
<td>Angina with dynamic T-wave changes</td>
<td>Normal or unchanged ECG</td>
</tr>
<tr>
<td>Angina with S3 or new/worsening rales</td>
<td>New onset CCSC III or IV angina in the past 2 weeks with moderate or high likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td>Angina with hypotension</td>
<td>Pathologic Q waves or resting ST depression &lt;1 mm in multiple lead groups (anterior, inferior, lateral)</td>
<td>Pathologic Q waves or resting ST depression &lt;1 mm in multiple lead groups (anterior, inferior, lateral)</td>
</tr>
<tr>
<td><strong>Elevated serum troponin I or T level</strong></td>
<td>Age &gt;65 y</td>
<td></td>
</tr>
</tbody>
</table>

In general, final assignment of risk is based on highest risk feature; however, the table should not be interpreted as an inflexible algorithm. Adapted from 1994 AHCPR Guidelines with modifications reflecting 1998 ICF workshops (in boldface).

**CCSC**, Canadian Cardiovascular Society Classification; **MR**, mitral regurgitation.

A diagnosis of non-CAD, stable angina, UA, or acute MI is made from the initial evaluation; in the 1994 guidelines, only the treatment of patients with UA is considered further. Once a diagnosis of UA has been made and patients are stratified according to risk, patients not already taking daily aspirin are begun on this therapy (unless contraindicated) and, for patients at intermediate to high risk, intravenous unfractionated heparin (UH) is begun. Pharmacologic management of symptoms may include the use of nitroglycerin, morphine, beta-blockers, and calcium channel blockers (which are reserved for patients requiring an additional agent beyond nitrates and beta-blockers or when beta-blockers and nitroglycerin are ineffective or not tolerated, and when no pulmonary edema or severe left ventricular dysfunction is present). Patients at low risk should undergo further evaluation and ongoing management on an outpatient basis. High-risk patients are to be admitted to an intensive care unit; intermediate-risk patients may be admitted to an intensive care unit, intermediate coronary care unit, or other appropriate care facility.
Next, intensive medical management for intermediate- and high-risk patients is considered. The aim of this phase is to relieve pain and ischemia and to establish the strategy for further treatment of the underlying disease. Aspirin and intravenous UH are to be continued as well as pharmacologic management of symptoms. During this time, evaluation continues, including noninvasive testing and assessment of the efficacy of medical therapy. When medical therapy has been effective at controlling symptoms, patients can progress to low-risk status in preparation for nonintensive medical management, including further evaluation and eventual discharge.

Cardiac catheterization and myocardial revascularization are discussed in the context of 2 alternative treatment strategies: "early conservative" versus "early invasive." High-risk patients with an acute coronary syndrome (eg, hemodynamic instability, persistent or dynamic ECG abnormalities, positive serum cardiac markers) are generally considered by most clinicians to be candidates for intervention unless coexisting conditions preclude such a therapeutic option. In the early invasive strategy, intermediate- to low-risk patients undergo cardiac catheterization within 48 hours of admission unless contraindicated, and percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is performed whenever significant CAD is found. In the early conservative strategy, routine catheterization is only performed when medical therapy has failed. For either strategy, catheterization is discouraged for patients in whom the benefits of revascularization, in terms of length and quality of life, are not likely to outweigh the risks.

The final guideline discusses the preparation for discharge and postdischarge care of intermediate and high-risk patients receiving UA. This includes planning for clinical follow-up and discussion of lifestyle modifications to reduce risk. Aspirin therapy should continue indefinitely unless contraindications exist.

**Areas needing revision**

The International Cardiology Forum discussed possible revision of the existing guidelines in the following areas: (1) diagnosis and risk stratification, (2) antithrombin therapy, (3) antiplatelet therapy, (4) basic therapy, including acute treatment of ischemic symptoms and long-term management, and (5) interventional management, including catheterization and revascularization, with particular attention to early invasive versus early conservative treatment strategies.

Rapid advances are being made in all these areas, although many new therapies and procedures are still unproven or remain controversial. There was, however, agreement that sufficient evidence exists to support changes in a number of recommendations: (1) the use of serum cardiac markers should be expanded to include troponin I and T levels as diagnostic and prognostic tools; (2) low-molecular-weight heparins (LMWH) should replace UH as antithrombin agents; (3) new classes of antiplatelet agents are recommended in addition to aspirin; and (4) the use of cholesterol-lowering drugs is appropriate in the long-term management of these patients.

**Diagnosis and risk stratification**

To identify appropriate treatment strategies in those patients with UA/NQMI requiring hospitalization, assessment of risk for future adverse events is required. Risk stratification is an ongoing process during the acute treatment phase and includes evaluation of the history of the present illness, medical history, and the ECG. Measurement of serum cardiac-specific markers is diagnostically useful, and the 1994 guidelines recommend that levels of both total CK and CK-MB be measured on admission and every 6 to 8 hours thereafter for 24 hours. These enzymes are released into the circulation when the myocardium is damaged, and they allow detection of MI in the absence of diagnostic changes on the ECG. The 1994 guidelines did not recommend the routine measurement of serum levels of the cardiac-specific troponins.
to detect myocardial damage. Since then, numerous studies have shown that elevated levels of troponin I or troponin T are correlated with adverse outcomes for patients with acute coronary syndromes, including UA.[8]

In a Thrombolysis In Myocardial Infarction (TIMI) IIIB substudy, blood samples taken from 1404 patients with UA/NQMI at enrollment were analyzed for troponin I. The levels of troponin I correlated positively with death at 42 days, and the increased risk was present even in the absence of elevated CK-MB.[9] In the assay used in the TIMI IIIB study, the limit of detection of cardiac troponin I was 0.4 ng/mL, and patients with levels of 0.4 ng/mL or greater had a significantly increased risk of death compared with patients with lower levels (3.7% vs 1.0%, \( P < .001 \)). The risk of death increased further with increasing troponin I levels.

In a substudy of Global Use of Strategies to Open Occluded Arteries (GUSTO) IIa, cardiac troponin T levels were evaluated for their use in risk stratification in 885 patients with acute myocardial ischemia.[10] Elevated troponin T levels, defined as >0.1 ng/mL, were positively correlated with death at 30 days (11.8% vs 3.9%, \( P < .001 \)). The correlation between elevated troponin T and death was independent of CK-MB levels.

The use of rapid testing for cardiac troponin I or T for risk stratification in the emergency department was investigated in a prospective study of 773 patients with acute chest pain.[11] Troponin T tests were positive in 94% percent of patients with evolving MI and 22% of patients with UA; troponin I was positive in 100% of patients with evolving MI and 36% of patients with UA. The rate of major cardiac events was only 1.1% in patients with negative troponin T and 0.3% in patients with negative troponin I.

The increased risk for an adverse event in patients with elevated troponins is manifested early and persists for months after the initial hospitalization.[12] Because cardiac troponins are detectable in the peripheral circulation 8 to 12 hours after the onset of MI, it is therefore now recommended that an initial assay of serum levels of either troponin T or troponin I be made on admission and at least once more in the next 8 to 12 hours. At this time, there is no clear advantage to choosing either troponin I or T. Because assays are continually being refined, limits of detection change, making it difficult to define appropriate cutoff levels. A normal value in the range of 0.1 to 0.2 ng/mL is well accepted for troponin T; for troponin I, the normal level may vary with the assay used, and it is recommended that clinicians follow the manufacturers’ recommendations. Patients with elevated troponin levels should be considered high-risk even in the absence of other high-risk criteria. Conversely, the absence of elevated troponin levels is not by itself indicative of low risk. It is therefore important to conduct a full risk assessment before discharge.

**Antithrombin therapy**

Plaque disruption triggers the extrinsic pathway of blood coagulation[13] by exposing tissue factor, an integral membrane protein with an extracellular domain, to plasma proteins. Tissue factor activates circulating factor VII and then forms a complex with the activated factor VIIa to activate factor X. Factor Xa and platelet-derived factor Va interact on phospholipid membrane surfaces in the presence of calcium to form the prothrombinase complex, which cleaves prothrombin, generating thrombin. Thrombin then cleaves fibrinogen to yield fibrin monomer, which polymerizes and cross-links, forming fibrin. Thrombin also positively regulates its own synthesis by activating factors V and VIII, thus leading to the production of additional factor Xa. Thrombin also activates platelets. Inhibition of thrombin activity is therefore central in the medical management of patients with UA/NQMI.

The classic antithrombin agent for therapy in acute coronary syndromes is UH, a heterogeneous mixture
of sulfated glycosaminoglycans of varying chain length (Table IV).

### Table IV. Summary of antithrombin agents available for treatment of UA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical condition</th>
<th>Contraindications*</th>
<th>Usual dose †</th>
</tr>
</thead>
<tbody>
<tr>
<td>UH</td>
<td>Intermediate- and high-risk UA</td>
<td>Active major bleeding, severe thrombocytopenia, prior HIT subsequent to UH, patients for whom it is not possible to monitor coagulation status at appropriate intervals</td>
<td>IV bolus: 70-80 U/kg; infusion: 15-18 U/kg per hour, titrated to maintain aPTT at 1.5-2.0 times control; aPTT determinations 6 h after initiation of treatment or any dosage adjustment</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox, Clexane)</td>
<td>Intermediate- and high-risk UA</td>
<td>Active major bleeding, prior HIT subsequent to UH or LMWH therapy, hypersensitivity to heparin or pork products</td>
<td>1 mg/kg SC injections twice daily for 48 h or until the patient is stable; for high-risk patients, an initial additional IV bolus (30 mg) may be considered</td>
</tr>
<tr>
<td>Dalteparin§ (Fragmin)</td>
<td>Intermediate- and high-risk UA</td>
<td>Same as for enoxaparin</td>
<td>120 IU/kg body weight SC injection every 12 h for up to 6 d</td>
</tr>
<tr>
<td>Nadroparin§ (Fraxiparin, Fraxiparine)</td>
<td>Intermediate- and high-risk UA</td>
<td>Same as for enoxaparin</td>
<td>0.1 mL/10 kg body weight (88 IU/kg) SC injection every 12 h for up to 6 d</td>
</tr>
</tbody>
</table>

*IV, Intravenous; SC, subcutaneous; HIT, heparin-induced thrombocytopenia.

*For all agents, allergy and prior intolerance or hypersensitivity are contraindications.

† Refer to manufacturers' prescribing information for detailed discussion of contraindications, warnings, and dosages.

- Enoxaparin has been demonstrated to be superior to UH. [28](#) [31](#)

- Dalteparin and nadroparin have been demonstrated to be equivalent to UH. [25](#) [27](#)

When heparin-induced thrombocytopenia is a concern, the hirudin lepirudin (Refludan) should be considered an alternative to UH or enoxaparin; however, it has not been approved for prophylactic use in UA/NQMI. For lepirudin, the dose used in OASIS-2 is recommended: 0.4 mg/kg body weight (up to 110 kg) intravenous bolus over a 15- to 20-second period followed by 0.15 mg/kg (up to 110 kg) per hour as a continuous intravenous infusion for 72 hours or until the patient is stable. The infusion should be adjusted to maintain an aPTT of 1.5 to 2.5 times control. Desirudin (Revasc) was used at the following dose in GUSTO-IIb: 0.1 mg/kg body weight intravenous bolus, followed by an infusion of 0.1 mg/kg per hour for a minimum of 72 hours. [82](#)

Its anticoagulant effect derives from its ability to bind and accelerate the activity of antithrombin.
(formerly called antithrombin III), a plasma protein that inactivates both thrombin (factor IIa) and factor Xa. The 1994 AHCPR guidelines recommend the use of UH as an anticoagulant in all intermediate- and high-risk patients receiving UA, with the infusion to be initiated as soon as the diagnosis is made and continued for 2 to 5 days or until revascularization is performed.

Although useful in the treatment of UA/NQMI, UH has several limitations. These are primarily a consequence of an unpredictable dose-response relation that results, in part, from the variable binding of UH to plasma proteins and endothelial cells and from inactivation of UH by platelet factor 4. Because the anticoagulant response in individual patients is unpredictable, it is difficult to achieve a therapeutic anticoagulant status rapidly, and the activated partial thromboplastin time (aPTT) must be periodically monitored. Heparin can also stimulate platelet aggregation and thus thrombus formation, and prolonged use can provoke thrombocytopenia, which may be accompanied by life-threatening sequelae in a small fraction of patients. There is therefore a need for safer and more effective antithrombin agents. Newer antithrombin agents include LMWHs, which, like heparin, require antithrombin as a cofactor and the direct antithrombins, such as hirudin, which do not require antithrombin (Table IV).

LMWHs are derived from UH by chemical or enzymatic cleavage and, like their parent compound, are mixtures of polysaccharides of varying chain length. The shorter average chain length is accompanied by enhanced bioavailability relative to UH after subcutaneous administration and is associated with a longer plasma half-life and greater resistance to inhibition by activated platelets. In contrast to UH, LMWHs have a more predictable anticoagulant effect, and routine laboratory monitoring is not required to assess anticoagulant efficacy. An additional consequence of the shortened chain length is an increase in the ratio of factor Xa to factor IIa (thrombin) inactivation. Although LMWHs are similar in many respects, the differences in molecular weight distribution and slight differences in molecular structure result in differences in relative anti-factor Xa to anti-factor IIa activity and in pharmacokinetic properties. These compounds should therefore be considered to be distinct therapeutic agents.

Three LMWHs, dalteparin, enoxaparin, and nadroparin, have been evaluated as replacements for UH in the treatment of patients with UA/NQMI in clinical trials. They have proven to be at least equivalent to UH in terms of reduction of major composite end points. It is recommended that the standard for medical management of UA/NQMI be revised to replace UH with a LMWH as the antithrombin of choice. Although all LMWHs share the advantages of ease of administration, predictable pharmacokinetic response, and lack of need for drug monitoring, enoxaparin is the only LMWH demonstrated to be superior to UH in patients with UA/NQMI.

Enoxaparin should be given at a dose of 1 mg/kg body weight (equivalent to 100 IU/kg) twice daily, as subcutaneous injection. Clinical trials of enoxaparin for UA/NQMI administered the drug for 2 to 5 days during the acute phase of management. For high-risk patients, an initial additional intravenous bolus (30 mg) has been shown to be safe and may be considered. However, the efficacy of this dose has not been directly tested. The doses of other LMWHs used in CAD trials were 120 IU/kg dalteparin and 0.1 mL/10 kg (87 to 95 IU/kg) nadroparin, both given twice daily as subcutaneous injections for 5 to 7 days.

**The ESSENCE trial of enoxaparin**

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events (ESSENCE) study was a randomized, double-blind, placebo-controlled study comparing the clinical efficacy and safety of enoxaparin versus UH in 3170 patients with UA/NQMI. The trial compared 1 mg (100 IU/kg) body weight subcutaneous enoxaparin every 12 hours with UH given as an initial 5000 IU bolus followed by continuous infusion, with the UH dose adjusted to maintain the aPTT at 55 to 85 seconds.
Patients receiving enoxaparin also received placebo UH infusion, and the UH group received subcutaneous placebo injections. All patients also received 100 to 325 mg aspirin daily. The prespecified treatment duration was a minimum of 48 hours to a maximum of 8 days; the resulting average treatment period was 3.1 days.

Enoxaparin significantly reduced the occurrence of death, MI, and recurrent angina at 14 days relative to UH (16.6% vs 19.8%, \( P = .019 \)) and at 30 days (19.8% vs 23.3%, \( P = .016 \)). Enoxaparin also reduced the frequency of revascularization procedures (27.0% vs 32.2%, \( P = .001 \)) at 30 days. At 30 days, there was no significant difference in major bleeding complications; however, the incidence of minor bleeding with enoxaparin, primarily ecchymoses at injection sites, was significantly higher (18.4% vs 14.2%, \( P = .001 \)). In a 1-year follow-up study, it was shown that the benefit of enoxaparin observed at 30 days was maintained; the incidence of the composite of death, MI, and recurrent angina was still significantly lower in the enoxaparin group (32% vs 35.7%, \( P = .022 \)).

The TIMI 11B trial of enoxaparin

TIMI 11B, like the ESSENCE study, was a randomized, double-blind, controlled study comparing enoxaparin with UH in the treatment of UA/NQMI. The treatment strategies consisted of an initial bolus of either UH (70 IU/kg intravenous) or enoxaparin (30 mg intravenous), followed by either intravenous UH for at least 72 hours (15 U/kg per hour, adjusted to maintain an aPTT of 1.5 to 2.0 times control) or subcutaneous injections of 1.0 mg/kg enoxaparin every 12 hours for up to 8 days or until hospital discharge. Patients also received aspirin and either placebo infusion or subcutaneous placebo injections. At day 8 or hospital discharge, twice-daily injections of either enoxaparin (40 mg for patients <65 kg or 60 mg for patients \( \geq 65 \) kg) or placebo were continued for a total treatment duration of 43 days.

The primary efficacy end point of TIMI 11B was the composite of death, MI, or severe recurrent ischemia requiring urgent revascularization and was evaluated at 14 and 43 days after enrollment. At 14 days, the frequency of the composite end point was reduced from 16.6% with UH to 14.2% with enoxaparin (\( P = .03 \)). Although this benefit was maintained at 43 days, there was no additional benefit of continued treatment. During the period of hospitalization, there were no significant differences between groups in the frequency of bleeding complications. During the outpatient phase, enoxaparin use was correlated with a small but significant increase in spontaneous and instrumented major hemorrhage when compared with placebo (1.5% vs 2.9%, \( P = .02 \)).

The FRIC trial of dalteparin

The Fragmin in Unstable Coronary Artery Disease (FRIC) trial was a 2-phase, randomized, controlled study of dalteparin in 1482 patients with UA/NQMI. In the open-label acute phase, patients received aspirin plus either subcutaneous dalteparin (120 IU twice daily) or UH. UH was given initially as a 5000 IU/kg intravenous bolus followed by a continuous infusion at 1000 IU/h, with dosage adjustment to maintain the aPTT at 1.5 times control. After 48 hours, conversion to subcutaneous UH (12,500 IU twice daily) was permitted. After 6 days, conversion to subcutaneous UH (12,500 IU twice daily) was permitted. After 6 days, 69 (9.3%) of 751 patients treated with dalteparin died or had MI or recurrent angina develop compared with 55 (7.6%) of 731 patients who were treated with UH (\( P = .35 \)). There was also no significant difference in the rates of adverse events. This study indicated that the acute-phase treatment regimens with either dalteparin or UH were equivalent in efficacy and safety. In the extended treatment phase from days 6 to 45, dalteparin plus aspirin was no better than aspirin alone.

Trials of nadropan
In a small, single-blind trial of 219 patients with UA, nadroparin plus aspirin significantly reduced the risk of MI, recurrent angina, and revascularization relative to UH plus aspirin. These early results were not confirmed by the subsequent Fraxiparine in Ischemic Syndrome (FRAXIS) study. FRAXIS was a double-blind, randomized clinical trial comparing nadroparin with UH in patients with UA/NQMI. A total of 3468 patients were randomly assigned to a regimen of UH for 6 days, nadroparin for 6 days, or nadroparin for 14 days. After initial administration of an intravenous bolus (5000 IU), UH was continued as an infusion and adjusted to maintain aPTT values of 1.5 to 2.5 times control values. Nadroparin was given as subcutaneous injection, 0.1 mL/10 kg (86 IU/kg), every 12 hours. No significant differences in the occurrence of the primary end point, the composite of cardiovascular death, MI, or refractory or recurrent angina after 14 days, were demonstrated. The incidence was 18.1% in patients who received UH, 17.8% with the 6-day nadroparin regimen, and 20.0% with the 14-day nadroparin regimen. An increase in bleeding complications was noted in the group that received nadroparin for 14 days.

Under some circumstances, other antithrombins might be used. Hirudin, a small peptide, has been investigated as an antithrombin in CAD. A recombinant hirudin, lepirudin, was shown to be superior to UH for the treatment of UA/NQMI in a large, randomized, controlled clinical trial, the Organization to Assess Strategies for Ischemic Syndromes (OASIS-2). At 7 days, the incidence of death, MI, or refractory angina was reduced from 6.7% with UH to 5.6% with hirudin ($P = .012$). However, in OASIS-2 there was a significant increase in the frequency of bleeding incidents classified as major but not life-threatening (0.8% for hirudin vs 0.3% for UH, $P = .001$). Hirudin also shares some of the disadvantages of UH, namely the requirement for intravenous delivery and the monitoring of aPTT values. In addition, aPTT measurements reflect the anticoagulant response to hirudin less reliably than for UH. However, if heparin-induced thrombocytopenia is a concern, particularly type II, hirudin should be considered. The dose used in OASIS-2, an initial bolus of 0.4 mg/kg followed by an infusion of 0.15 mg/kg per hour for 3 days, is recommended. Although LMWHs are less likely to cause heparin-induced thrombocytopenia in patients, they do share antigenicity with UH. Thus patients who are sensitized for heparin-induced thrombocytopenia who receive LMWHs are at risk for complications, and use of LMWHs in these patients should be avoided.

Antiplatelet therapy

Injury to the blood vessel wall or plaque disruption exposes elements of the subendothelial matrix, including proteins that support attachment of circulating platelets. Platelets adhering to matrix proteins are activated and release agonists such as adenosine diphosphate and thromboxane A2 that activate and recruit additional platelets. Platelet activation results in a conformational change of the cell-surface fibrinogen receptor glycoprotein (GP) IIb/IIIa. This conformational change is a critical step in the process of platelet aggregation because it increases the affinity of this extremely abundant adhesion protein for its principal ligand, fibrinogen. A fibrinogen molecule can bind to more than one receptor, thereby cross-linking adjacent platelets and stabilizing the platelet plug.

Aspirin, an inhibitor of the thromboxane A2 pathway, is the most widely used antiplatelet agent (Table V).

**Table V. Summary of antiplatelet agents available for treatment of UA**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical condition</th>
<th>Contraindications*</th>
<th>Usual dose†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Diagnosis of UA</td>
<td>Active bleeding</td>
<td>160-324 mg initial, reducing to 80-324 mg/d</td>
</tr>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>UA and aspirin</td>
<td>Active bleeding,</td>
<td>250 mg twice daily</td>
</tr>
<tr>
<td>IV, Intravenous</td>
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<tr>
<td>----------------</td>
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<tr>
<td><strong>Tirofiban (Aggrastat)</strong></td>
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<tr>
<td>As adjunct to PCI: Use for intermediate- and high-risk UA.</td>
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<td>IV, Intravenous</td>
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<tr>
<td><strong>Abciximab (ReoPro)</strong></td>
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<tr>
<td>As adjunct to PCI: Use for UA and aspirin intolerance or allergy, or failure of aspirin therapy.</td>
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<tr>
<td>IV, Intravenous</td>
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<tr>
<td><strong>Eptifibatide (Integrilin)</strong></td>
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<td>IV, Intravenous</td>
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<tr>
<td><strong>Clopidogrel (Plavix, Iscover)</strong></td>
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<tr>
<td>As adjunct to PCI: Use for UA and aspirin intolerance or allergy, or failure of aspirin therapy.</td>
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</tbody>
</table>

| **Thrombocytopenia, Thrombotic Thrombocytopenic Purpura, or Thrombocytopenia, Hypersensitivity to Abciximab or Murine Proteins, Use of IV Dextran Before or During PCI, or Any Condition Incompatible with Increased Bleeding Risk** |
| 135 mg/kg IV bolus immediately before start of PCI, followed by 24 h IV infusion of 10 mg/min, concluding 1 h after PCI. |
| **Thrombocytopenia, Serum Creatinine ≥ 2.0 mg/dL, Dependency on Renal Dialysis, Current or Planned Use of Another Parenteral GP IIb/IIIa Inhibitor, or Any Condition Incompatible with Increased Bleeding Risk** |
| 10-60 mg/kg IV bolus followed by 24 h IV infusion of 0.125 mg/kg per min (to a maximum of 10 mg/min) for 12 h; for UA when PCI planned, 0.25 mg/kg IV bolus followed by 18 to 24 h IV infusion of 10 mg/min, concluding 1 h after PCI. |
| **Thrombocytopenia, History of Thrombocytopenia After Exposure to Tirofiban, Current or Planned Use of Another Parenteral GP IIb/IIIa Inhibitor, or Any Condition Incompatible with Increased Bleeding Risk** |
| Initial infusion of 0.4 mg/kg per min IV infusion for 30 min, reducing to 0.1 mg/kg per min, or a minimum of 48 h, if angiography planned or PCI planned within 96 h. |

<table>
<thead>
<tr>
<th>IV, Intravenous</th>
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<tr>
<td><strong>Tirofiban (Aggrastat)</strong></td>
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| 10-60 mg/kg IV bolus followed by 24 h IV infusion of 0.125 mg/kg per min (to a maximum of 10 mg/min) for 12 h; for UA when PCI planned, 0.25 mg/kg IV bolus followed by 18 to 24 h IV infusion of 10 mg/min, concluding 1 h after PCI. |
| **Thrombocytopenia, History of Thrombocytopenia After Exposure to Tirofiban, Current or Planned Use of Another Parenteral GP IIb/IIIa Inhibitor, or Any Condition Incompatible with Increased Bleeding Risk** |
| Initial infusion of 0.4 mg/kg per min IV infusion for 30 min, reducing to 0.1 mg/kg per min, or a minimum of 48 h, if angiography planned or PCI planned within 96 h. |
Its efficacy and relative safety have been demonstrated; however, it does not inhibit platelet activation by thromboxane A2-independent pathways and is associated with an increased risk of bleeding complications, primarily gastrointestinal in origin. Additionally, a significant percentage of patients (30% to 40% in some studies) do not respond to moderate (80 to 325 mg) doses of aspirin. Therefore the need for safer and more effective antiplatelet agents exists.

The 1994 guidelines recommended ticlopidine as an alternative to aspirin in patients with aspirin sensitivity or major gastrointestinal intolerance. Ticlopidine is an oral antiplatelet agent that irreversibly inhibits adenosine diphosphate-induced platelet-fibrinogen binding (Table V). It has not been directly compared with aspirin in patients with UA/NQMI and therefore was not recommended as first-line antiplatelet therapy. Ticlopidine was shown to be effective in reducing clinical end points in patients undergoing PCI followed by placement of an intracoronary stent. Use of ticlopidine, however, is associated with an increased incidence of rash, gastrointestinal intolerance, neutropenia, thrombocytopenia, and, rarely, thrombotic thrombocytopenic purpura. A chemically similar compound, clopidogrel, was shown in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study to be superior to aspirin in preventing ischemic events in a long-term (1 to 3 years) study involving patients with ischemic stroke, CAD, or peripheral arterial disease. Clopidogrel has not been associated with an increase in neutropenia or thrombocytopenia. Although not directly tested, it is reasonable to extrapolate the results of CAPRIE to the UA/NQMI population; thus clopidogrel is recommended in place of ticlopidine for aspirin-intolerant patients. It may also be considered as a substitute for aspirin in those patients unresponsive to aspirin.

Because multiple platelet activation pathways converge at GP IIb/IIIa, this receptor is an obvious target for antiplatelet therapies. Two classes of GP IIb/IIIa inhibitors are available: an antibody fragment that recognizes the fibrinogen receptor and a ligand mimic that competitively inhibits fibrinogen binding by occupying the ligand-recognition site on the receptor (Table V). These classes of inhibitor differ in several aspects. Compared with antibody, the small-molecule competitive inhibitors have shorter half-lives, and thus their activity is more rapidly reversible. The competitive inhibitors are specific for GP IIb/IIIa, whereas the antibody also recognizes related proteins, in particular the vitronectin receptor. Abciximab, a monoclonal antibody Fab fragment, is used in the setting of UA/NQMI in patients undergoing PCI or when the procedure is planned within 24 hours. Although the efficacy of abciximab in this setting was demonstrated in the Evaluation of 73E in Preventing Ischemic Complications (EPIC), Evaluation of PTCA to Improve Long-Term Outcome by C7E3 GP IIb/IIIa Receptor Blockade (EPILOG), and C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trials, it has not been directly tested as an antiplatelet agent in the medical management of patients with UA/NQMI.

Two ligand mimics, eptifibatide and tirofiban, have demonstrated efficacy in the treatment of patients with UA/NQMI in the absence of revascularization. It is recommended that these agents, used
with concomitant aspirin and UH, be considered as options for medical management of UA/NQMI. Eptifibatide is a cyclic heptapeptide designed to occupy the fibrinogen binding site on the GP IIb/IIIa receptor with higher affinity than the natural ligand, thereby preventing platelet aggregation. Tirofiban is a nonpeptide compound that blocks platelet aggregation through a similar mechanism. An additional nonpeptide inhibitor of GP IIb/IIIa, lamifiban, is not yet available commercially; however, evidence indicates that lamifiban may also be effective in the treatment of UA/NQMI.

The PURSUIT trial of eptifibatide

The Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial was a randomized, double-blind study comparing intravenous eptifibatide with placebo in the treatment of UA/NQMI. Initially, 2 dosages of eptifibatide were compared with placebo; however, when the higher dosage proved safe, the lower dosage arm of the trial was discontinued. The completed trial included 4722 patients receiving eptifibatide (180 μg/kg bolus followed by an infusion of 2.0 μg/kg per minute) and 4739 receiving placebo (bolus plus infusion). The study drug was infused for 72 hours or until discharge from the hospital; in the case of coronary interventions, the infusion could be continued for a total of 96 hours. Most patients also received aspirin and UH.

The primary end point, the composite of death or nonfatal MI at 30 days, was significantly lower in the eptifibatide group (14.2% vs 15.7%, \( P = .04 \)). At 7 days, there was also a significant reduction in mortality rate (1.5% vs 2.0%, \( P = .05 \)) and in the composite end point (10.1% vs 11.6%, \( P = .02 \)). A recently reported post hoc analysis suggests that the benefit of eptifibatide was realized only in patients who received heparin. The use of eptifibatide was correlated with an increased risk of mild to severe bleeding; however, there was no significant difference in the rate of stroke.

The PRISM-PLUS trial of tirofiban

The Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study compared tirofiban plus UH with UH alone in the treatment of UA/NQMI. PRISM-PLUS originally included a treatment arm with tirofiban alone; however, this arm was discontinued because of excess mortality rate at 7 days. The study was completed with 773 patients receiving tirofiban (0.4 μg/kg per minute loading dose for 30 minutes followed by an infusion of 0.1 μg/kg per minute) plus adjusted-dose UH and 797 patients receiving adjusted-dose UH plus placebo. In both groups UH was administered as an intravenous bolus (5000 U) followed by an infusion of 1000 U/h, adjusted to maintain an aPTT of twice the control. All patients received aspirin. The study drugs were infused for a minimum of 48 hours and a maximum of 96 hours, with an average treatment duration of 71 hours.

The primary end point of PRISM-PLUS was the composite of death, new MI, or refractory ischemia within 7 days of enrollment. In the tirofiban plus UH group, the frequency of the end point was significantly lower than in the group receiving UH alone (12.9% vs 17.9%, \( P = .004 \)). The composite of death plus MI was also significantly lower in the tirofiban group at 7 days and at 30 days (4.9% vs 8.3%, \( P = .006 \), and 8.7% vs 11.9%, \( P = .03 \)). The incidence of major bleeding was similar in the 2 groups.

The PARAGON trial of lamifiban

The Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) study randomly assigned 2282 patients with UA/NQMI to receive lamifiban and heparin according to a 2 × 2 factorial design: low- and high-dose lamifiban (1 and 5 μg/min, respectively), both with and without heparin, or placebo plus heparin. All patients received
aspirin. At 30 days there were no significant differences in the frequency of ischemic events among treatment groups, but after 6 months the frequency of death or MI was lowest for those who received low-dose lamifiban plus heparin (12.6% vs 17.9% in the placebo group, \( P = .025 \)). The incidence of bleeding was similar in the placebo and low-dose lamifiban groups. High-dose lamifiban plus heparin resulted in a similar rate of death or MI compared with control at 6 months (18% for both groups) and more major or intermediate bleeding (12.1% vs 5.5%, \( P = .002 \)) after 30 days.

Persistence of a beneficial effect after discontinuation of therapy was also observed in the EPIC trial evaluating abciximab in angioplasty.\(^{48} \) \(^{50} \) The term passivation has been used to describe this long-term clinical effect of GP IIb/IIIa inhibitors, which may be the result of limiting platelet-driven vasoconstriction in the short term and diminishing the levels of platelet-derived growth factors and their local effects in the long term.\(^{49} \) \(^{50} \)

Eptifibatide and tirofiban are also beneficial in the treatment of UA/NQMI in patients undergoing PCI as well as those managed medically. In the PURSUIT and PRISM-PLUS trials, large subcohorts underwent PCI early during the course of management, and post hoc analysis indicates that these patients received the largest benefit from GP IIb/IIIa blockade. The use of reversible GP IIb/IIIa inhibitors in PCI was more directly investigated in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT-II) (eptifibatide) and Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) (tirofiban) trials.\(^{57} \) \(^{58} \) In these studies, patients were also maintained on a regimen of intravenous heparin during and after their interventions. Although the use of new antiplatelet agents in conjunction with UH has therefore been extensively examined and found to be safe, the efficacy and safety of using a GP IIb/IIIa receptor antagonist in conjunction with LMWH therapy are still being evaluated. Likewise, data on the use of LMWH with PCI although promising, are limited at this time. Therefore, it is recommended that if PCI is imminent, therapy be initiated with UH and a GP IIb/IIIa inhibitor. If CABG is planned, GP IIb/IIIa inhibitors should be discontinued before revascularization.

There is no direct evidence supporting a choice of a GP IIb/IIIa inhibitor plus UH and aspirin versus a LMWH plus aspirin. Workshop participants believed that because of the large proportion of patients undergoing intervention in trials of the competitive GP IIb/IIIa inhibitors, it was premature to recommend the use of these agents unconditionally when no intervention is planned. It was, however, suggested that patients with UA/NQMI already taking aspirin could be considered to have had unsuccessful aspirin therapy and therefore should be considered candidates for one of the newer antiplatelet agents, particularly the GP IIb/IIIa inhibitors. Similarly, when patients receiving LMWH and aspirin have refractory ischemia and catheterization facilities are not readily available, the use of GP IIb/IIIa blockade might be indicated. Finally, GP IIb/IIIa inhibitors might be considered for the highest risk patient subsets. This will continue to be a rapidly moving field, and evidence to guide these decisions should be available in the future.

**Postdischarge medical management**

After the acute treatment phase, management of the patient with UA/NQMI progresses to nonintensive medical therapy before hospital discharge. Although the acute ischemia precipitated by plaque rupture will have resolved, the underlying CAD persists and, even with optimum medical care, many patients will have an acute MI in the years after the initial hospitalization. Therefore aspirin or other antiplatelet therapy should continue indefinitely, and continued antianginal therapy may also be required. Secondary preventative measures should be taken to reduce risk, including appropriate lifestyle changes such as quitting smoking, modifying diet to reduce weight if needed, and lowering cholesterol. Diabetes mellitus, hypertension, and hyperlipidemia, conditions associated with increased risk of adverse outcomes, should be aggressively managed. Diabetics are particularly susceptible to progressive vascular disease, and risk factor reduction for secondary prevention should be rigorously pursued in this
Medical therapy to reduce serum cholesterol is now an additional option to be strongly considered. Lovastatin, the first hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor, was introduced in the late 1980s. Since then, a number of other statins have become available. Several of them have been intensively studied for long-term therapy in patients with CAD and moderately to highly elevated LDL cholesterol.

In the Scandinavian Simvastatin Survival Study (4S), 4444 patients with angina or prior MI and a serum cholesterol level of 5.5 to 8.0 mmol/L (213 to 309 mg/dL) were randomly assigned to treatment with placebo or simvastatin. The 5-year mortality rate in the simvastatin group was significantly lower (8% vs 12%, $P = .0003$), as was the risk of undergoing a major coronary event (19% vs 28%, $P < .00001$). There was also a highly significant 37% reduction in risk of undergoing a revascularization procedure.

In the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, pravastatin was compared with placebo in patients with coronary disease and a broad range of initial cholesterol levels. Over a period of 6.1 years, there was a 24% reduction in mortality rate from cardiac causes (8.3% to 6.4%, $P < .001$) and similar reductions in other adverse cardiovascular events. The reduction in risk of coronary events with pravastatin therapy was similar among those with previous MI and among those who had been hospitalized with UA. A meta-analysis of 4 trials in which pravastatin was compared with placebo over a 2- to 3-year course of therapy in patients with coronary disease and moderate to severely elevated serum cholesterol found that with pravastatin there was a 62% reduction in the risk of MI ($P = .001$). In the West of Scotland Coronary Prevention Study (WOSCOPS), a primary prevention study, pravastatin was also shown to reduce the incidence of adverse coronary events in men with no history of MI but with moderate hypercholesterolemia (mean 272 mg/dL [7.0 mmol/L]). Over an average follow-up period of 4.9 years, there was a 31% reduction in the incidence of death from coronary heart disease or nonfatal MI.

The effectiveness of long-term statin therapy for secondary prevention in CAD is thus well established. The potential benefit of aggressive lipid-lowering therapy as an early intervention in patients with UA/NQMI is currently being investigated in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study. In this trial, the efficacy of statin therapy, initiated at hospitalization, will be examined during a 4-month follow-up period.

In 1994, it was recommended that baseline cholesterol levels be determined from blood samples taken at admission. These levels were then to be used as guidelines to establish goals for cholesterol-reducing lifestyle changes. Given the results of clinical trials of statins, it is now recommended that patients with UA/NQMI with elevated LDL cholesterol be started on an HMG CoA reductase inhibitor. An advantage of starting such therapy during hospitalization is that patient compliance is likely to be higher than if such therapy is postponed. Several statins are now available, and all reduce serum cholesterol levels; however, only pravastatin, simvastatin, and recently lovastatin have been shown to reduce the risk of adverse cardiac events in long-term clinical studies. The target level for LDL cholesterol is still subject to debate, as is the effectiveness of cholesterol-lowering medications in patients with heart disease with average cholesterol levels. The Cholesterol And Recurrent Events (CARE) trial found that patients with cholesterol levels considered to be within the average range, with plasma total cholesterol levels <240 mg/dL (6.2 mmol/L) and LDL cholesterol in the range of 115 to 174 mg/dL (3.0 to 4.5 mmol/L), benefitted from pravastatin treatment after an acute MI. The European Society of Cardiology recommends target levels of total cholesterol <5.0 mmol/L (190 mg/dL) with LDL cholesterol <3.0.
mmol/L (115 mg/dL) for secondary prevention in all classes of patients who have symptoms of coronary disease. Similarly, the American National Cholesterol Education Project guidelines recommend that LDL cholesterol be reduced to <100 mg/dL (2.6 mmol/L) and total cholesterol <200 mg/dL (5.2 mmol/L) in patients with coronary heart disease. In 1997, the American Heart Association recommended that LDL cholesterol levels of >130 mg/dL (3.4 mmol/L) should be reduced with medication. For patients with LDL cholesterol levels between 100 and 129 mg/dL (2.6 and 3.4 mmol/L), lowering cholesterol through diet modification may be attempted; if this is unsuccessful the decision to progress to drug therapy is left to the judgement of the treating physician.

**Areas of divergent practice or controversy**

Among workshop participants there was general agreement with the 1994 recommendations for basic therapy, including the use of aspirin and antianginal drugs, with minor modifications. It was agreed that the appropriate dosage of aspirin is currently an area of uncertainty, with recommended initial doses ranging from 160 to 325 mg and maintenance doses from 75 to 160 mg/d. The higher initial dose should be considered for patients not previously taking aspirin. For relief of symptoms of ischemia, nitrate therapy should be initiated with either sublingual tablets or sprays, progressing to intravenous nitrates if 3 tablets or applications of spray do not relieve symptoms. If symptoms persist, therapy with beta-blockers should be added, either simultaneously or after intravenous nitrates. The optimal duration of nitrate therapy remains controversial given unanswered questions regarding tolerance. The 1994 guidelines on beta-blockers were considered acceptable. For patients already taking beta-blockers with unrelieved symptoms, an increase in dosage might be considered if the heart rate is >60 beats/min. Alternatively, and for all patients with heart rates in the range of 60 to 65 beats/min, a calcium channel blocker could be added. No consensus could be reached, however, on the relative benefits of long-acting dihydropyridines versus nondihydropyridine agents. If beta-blockers are contraindicated, then nondihydropyridine calcium channel blockers might be used. Changes in these aspects of UA/NQMI management could not be supported by available data, and further research is needed.

It was clear from workshop discussions that certain aspects of diagnosis and management of UA/NQMI vary widely from country to country, and even within regions of the United States. The choice of pharmacologic agents and the approach to intervention is determined in part by the drugs and facilities available to a particular physician and in part by personal and institutional preference. In 1994, cardiac catheterization and revascularization were discussed in terms of early invasive and early conservative treatment strategies. These strategies differ primarily in how they define the population undergoing early intervention; the early conservative strategy prefers to reserve intervention for high-risk patients and patients who do not respond to medical therapy. At that time, no recommendation favoring one particular treatment strategy was made. Although success rates in coronary interventions have improved significantly since 1994, associated with the increased use of coronary artery stents and GP IIb/IIIa inhibitors, the question of when and in whom to intervene remains controversial.

TIMI IIIB was the first study to directly compare the outcomes of invasive versus conservative management of patients with UA/NQMI. The invasive strategy dictated routine angiography and revascularization if appropriate within 48 hours of randomization; patients in this group also received standard medical therapy. Patients in the conservative group were managed medically and underwent catheterization and revascularization only if medical therapy failed. The primary end point was the composite of death, nonfatal MI, and failed exercise treadmill testing 6 weeks after enrollment. In the invasive treatment group, 16.2% of patients had an end point event compared with 18.1% of patients in the conservative management group, a statistically insignificant difference. However, patients in the conservative management group required longer hospitalization and used larger amounts of antianginal medications. Thus the results of TIMI IIIB suggest a minor advantage to the invasive approach.
In the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) study, conservative and invasive treatment strategies were compared in 920 patients with NQMI. The protocol was similar to that of TIMI IIIB, except revascularization of stenotic vessels detected during diagnostic angiography was not mandated. The primary end point was the composite of death and nonfatal MI during a long-term follow-up of 23 months. After 1 month and 1 year, the frequency of adverse events was significantly higher in the invasive management group, although the majority of adverse events in patients managed invasively occurred in those undergoing CABG and in those who had no revascularization performed. After 23 months the difference between groups was no longer statistically significant. The outcome of VANQWISH suggests that a conservative approach is equivalent to an invasive one. The low rate of revascularization, however, among patients undergoing an invasive strategy was an issue of concern in generalizing the results of VANQWISH.

Another method of comparing invasive and conservative strategies is to look at clinical practices and outcomes in different countries. In some countries, such as Brazil and the United States, routine cardiac catheterization and revascularization is preferred over more conservative strategies, whereas in other countries, such as Hungary and Poland, conservative management strategies are favored. In Canada and Austria, the rates of intervention are intermediate. The OASIS registry compared the outcomes for patients with UA/NQMI in these 6 countries and found no significant differences in the composite end point of death and MI. The rates of refractory angina and rehospitalization were lowest in countries with higher rates of intervention; however, this was accompanied by an increase in rates of stroke and major bleeding. No clear advantage of either strategy could be shown.

The choice of invasive versus conservative strategies will continue to be subject to debate. It is probably no longer useful, however, to consider these as discrete approaches to patient management, for several reasons. First, the decision to perform cardiac catheterization and subsequent angioplasty within 48 hours is not practical in many regions; nevertheless, many workshop participants believed that medium- or high-risk patients should not be discharged without at some time undergoing angiography. Second, a clear distinction between diagnostic angiography and routine revascularization is necessary because a strategy might be preferred that recommends routine angiography but reserves revascularization for those patients not responding to optimal medical therapy. In the absence of evidence strongly favoring one strategy or the other, the decision to intervene will undoubtedly continue to be based primarily on practical considerations, cost, philosophy, and the needs of the individual patient.

**Application of treatment guidelines**

The publication of treatment guidelines has a measurable effect on clinical practice, yet adherence to recommendations remains incomplete. Further effort should be made to encourage application of guidelines to a larger proportion of the population. There is evidence that the elderly and women are less likely to receive optimal treatment for acute coronary syndromes; similarly, particular attention should be given to ensure that minority groups receive adequate care. Investigation of behavior modification patterns for patients as well as physicians is needed to enhance the use of treatments known to reduce morbidity and mortality.

**Summary**

The optimal diagnostic and treatment strategies for patients with UA/NQMI will continue to be redefined as rapid progress is made in the understanding and treatment of this syndrome. The recommendations presented here reflect, in part, discussions at the International Cardiology Forum in September 1998. Although areas of controversy remain, we have summarized major points on which a consensus could be reached and for which the weight of the clinical evidence supports a change in
practice.

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Appendix

The following people contributed to the preparation of these recommendations.

*International Cardiology Forum (ICF) Co-chairs*

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*ICF Members*

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