Unstable Angina and Non-Q Wave Myocardial Infarction: Does the Clinical Diagnosis Have Therapeutic Implications?

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Objectives. The goal of this review is to reevaluate the unstable coronary syndromes in the setting of new therapies and biochemical markers.

Background. Patients with acute coronary syndromes comprise a large subset of many cardiology practices. Patients with unstable angina (UA) and non-Q wave myocardial infarction (NQMI) may sustain a small amount of myocardial loss but have significant amounts of viable, yet ischemic, myocardium, placing them at high risk for future cardiac events. In the past, enzyme differentiation of NQMI from UA was considered important to assess prognosis and direct therapy.

Methods. Manuscripts published in peer-reviewed journals over the past three decades were reviewed and selected for this review. Recent abstracts were also considered and cited where appropriate.

Results. In the late 1990’s, although UA and NQMI remain parts of a spectrum, it is apparent that the distinction between these two entities is no longer sufficient to identify high risk patients; rather, specific electrocardiographic changes, aspects of the clinical history, newer biochemical markers, and angiographic findings help to better distinguish higher risk individuals from a large patient population with unstable coronary syndromes and these factors usually determine therapy.

Conclusions. Based on these results, it is likely that newer therapies such as glycoprotein IIb/IIIa receptor antagonists, low molecular weight heparins, and coronary stents will be directed toward these high risk patients.

Pathophysiology of Unstable Ischemic Syndromes

Unstable angina (UA). Pathoanatomy. The inciting event underlying the development of all acute ischemic syndromes is
rupture of an atherosclerotic plaque in a coronary artery (9). The lipid core of a plaque is composed of oxidized LDL cholesterol and macrophages and is separated from the vascular lumen by a fibrous cap. The thinnest part of the cap lies at its junction with normal endothelium along the edges of the cap. The combination of enzyme degradation and external mechanical shear forces in the artery results in rupture of the fibrous cap and exposure of the underlying highly procoagulant atheromatous material to the bloodstream. Macrophage deposition and infiltration ensues with release of enzymes, resulting in digestion of the fibrous cap’s collagen and elastin (10). Recent evidence suggests that cytokines released from inflammatory cells within the cap at the attachment to the atheroma enhance the process of plaque destabilization by inhibiting collagen synthesis. The mechanical force of systole acts at the edges of the fibrous cap, which are locations of high circumferential stress, to cause further plaque breakdown. Other factors such as hypertension, smoking, catecholamine release, and vasospasm also predispose to plaque rupture (1,2).

The ruptured plaque is irregular in shape with an exposed underlying surface that favors thrombus formation, the second step in development of an unstable ischemic syndrome (11). A dynamic process produces simultaneous thrombosis and thrombolysis locally, with the resultant equilibrium between the two determining the particular ischemic syndrome (12). Platelets deposit initially but the platelet clump may not stay apposed to the disfigured plaque unless stabilized by fibrin. Secretion of thromboxanes, serotonin, and other vasoactive substances promote further platelet aggregation (13–15). The reduction in blood flow and the irregular surface of the platelet aggregate enhance the buildup of thrombus by way of thromboxane B2, and release of leukotrienes from leukocytes. Vasospasm likely also contributes both to plaque rupture and thrombus formation (16).

Recent studies have shown that in UA, plaque morphology may correlate directly with clinical presentation. Increasing severity of UA by Braunwald classification has been associated with increasing prevalence of thrombus, cellularity, atheroma, and neovascularure in plaque fragments obtained from directional atherectomy (17). Plaque fragments from patients with stable angina are mainly fibrous in composition and are without the complexity noted with UA. These findings further support a pathoanatomic distinction between UA and stable angina.

**Coronary angiographic findings.** The angiographic appearance of a ruptured plaque with superimposed thrombus is one of a “complex” lesion. Ambrose et al. referred to these as “eccentric type II” lesions consisting of asymmetric, convex obstructions with a narrow neck, containing scalloped or overhanging edges (18,19). They are now characterized as complex or complicated lesions (20). The associated thrombus is suggested by a hazy filling defect on contrast arteriography. These lesions are seen in more than 70% of patients with unstable coronary syndromes and in only 10–20% of patients with stable syndromes (21). By use of intravascular ultrasound, it has been estimated that angiography may not detect as many as 50% of thrombi when present (21). Similar to pathoanatomic findings, the angiographic results of patients with UA may vary depending on the specific clinical presentation.

In UA, the complex plaque usually progresses over several weeks, in contrast to NQMI in which complex plaques actually appear more simple on restudy, probably after thrombolysis (22). The majority of coronary stenoses are initially less than 70% in UA patients (23). The presence of associated thrombus depends on the specific clinical presentation and the timing of coronary angiography in relation to presentation and initiation of medical therapy. Some studies have determined that a shorter duration of pain free interval (<1 hour) and a longer duration of pain (>15 minutes) correlate well with lesion complexity and in-hospital events (24,25).

A recent prospective study of 284 patients with UA undergoing cardiac catheterization has correlated clinical presentation with angiographic findings (26). New onset rest angina had the highest association with complex lesions, intracoronal thrombus, and total occlusion. Postinfarction angina was strongly associated with intracoronary thrombus, complex lesions, and reduced TIMI flow compared with other Braunwald subgroups. In a separate analysis, the Braunwald classes were found to be independent correlates of angiographic morphology; that is, Class III (recent onset rest angina) was an independent correlate of complex lesions, total occlusions, and TIMI flow grade <3. Postinfarction angina correlated with intracoronary thrombus, total occlusions, and TIMI flow grade <3. This study resulted in data linking clinical presentation and complex coronary anatomy in patients with unstable coronary syndromes.

**Coronary angioscopic findings.** Unstable plaque appears yellow and friable compared to the smooth, white surface of stable plaques (27). There are also dark, purple areas of subintimal hemorrhage. In patients with UA, the overlying thrombus appears white in contrast to the red thrombi in acute myocardial infarction. The white color is primarily due to platelet clumps and the red color is due to an accumulation of red blood cells (10,28).

However, a recent histopathophysiologic study examining pathologic specimens of culprit lesions in UA, MI, and stable angina obtained by directional coronary atherectomy noted little difference in plaque morphology in UA and NQMI (29).
Plaques from both contained platelets and red thrombus, perhaps explaining why heparin and the new antiplatelet agents are equally effective in both patient groups. Thrombolysis tends to predominate in UA and clotting predominates in NQMI patients (20). This is important evidence that UA and NQMI are not pathophysiologically distinct entities but rather exhibit overlapping features.

**Non Q-wave myocardial infarction (NQMI). Pathoanatomy.** Rupture of an atheromatous plaque is the initial step in the development of NQMI as it is in UA. Non-Q wave myocardial infarction often occurs after a rapid progression of atherosclerotic lesions at a site which was recently minimally diseased or as transient occlusion at the site of severe stenosis in the presence of extensive collateral circulation (21). Fuster et al. proposed the following explanation for differences between NQMI and UA (1,2): in UA, mild plaque injury allows for formation of a labile thrombus which occludes the artery for 10 to 20 min. Superimposed vasoconstriction, probably secondary to endothelial dysfunction, further assists in vessel occlusion. In NQMI, the duration of occlusion is longer, likely due to a higher degree of plaque damage than in the UA setting, resulting in CPK leakage from the myocardium. Reperfusion usually occurs within two hours preventing QMI, as in 75% of patients with NQMI, the infarct related artery is patent with an extensive collateral circulation.

**Coronary angiographic findings.** DeWood et al. performed early studies examining angiographic findings in NQMI (30). Using serial angiography, they observed that as few as 25% of NQMI patients had total occlusions in the first 24 h and 85% of these patients had collaterals to the occluded segment. Others have found that many of the coronary arterial segments that later become the site of NQMI have either minimal plaques with little or no angiographic evidence of atherosclerotic disease or else contain severe stenoses of variable angiographic morphology (31).

Some subtle distinctions differentiate NQMI from UA angiographically. The presence of total occlusion is approximately 20–40% in NQMI and less in UA, averaging 10–20% (30). In either case, though, complete occlusion may be followed by recanalization. Further, thrombi and multiple filling defects are more likely to be present in NQMI than in UA; however, the timing of angiography in relation to presentation in UA may determine identification of thrombus (20). It appears that the complexity of lesions in UA on serial angiography actually progresses with time, while in NQMI complex-appearing lesions actually resolve over the course of two to three months (22). Uferated plaques with overhanging edges seen more commonly in UA may become more obvious in NQMI patients after gradual thrombolysis (32,33).

**Clinical Presentations**

The clinical presentations of patients with unstable syndromes encompass a wide spectrum. For example, UA patients may present with new onset angina, a changing pattern of angina, angina at rest or with decreasing workloads, and postinfarction angina. Each of these patterns likely represents different pathoanatomic stages. The electrocardiographic findings vary from being entirely normal to demonstrating significant ST segment depression, ST segment elevation, or T wave abnormality.

Myocardial infarction is primarily distinguished from UA by the presence of CPK-MB enzyme elevation, but serum markers are not evident until several hours after presentation. History, physical examination, and initial ECG are unable to allow, in many cases, the clinician to make a distinction with confidence. Because of this consideration, a recent study from the TIMI III trial examined 50 clinical and electrocardiographic variables as predictors of development of NQMI in those presenting with anginal symptoms and ECG changes (34). Four factors were predictive, including: 1) the absence of prior PTCA, 2) duration of pain more than 60 minutes, 3) ST segment deviation on the qualifying ECG, and 4) recent onset of angina. Approximately 50% of patients who had three of four characteristics had a NQMI and 70% of patients with four characteristics had a NQMI. Thus, even when three of four distinguishing characteristics are present, there is still a 50% chance of misclassification as UA or NQMI.

In current practice, the earliest objective features of patients with suspected acute coronary syndromes are the presenting electrocardiographic changes. Many patients presenting with NQMI may have ST segment elevation but more commonly will have ST segment depression and/or associated T wave inversions. UA may similarly present with ST segment elevation. Although not as common as with QMI and NQMI, ST segment elevation has been reported in as many as 16% of UA patients in one series (35). Combinations of ST segment elevation and depression or ST segment depression alone may occur. Therefore, ST segment shifts are not specific to any of the three coronary syndromes. The further development of Q waves is not predictable, so the most significant early distinction lies in evaluation of the ST segments and T waves. The significance of this differentiation is that thrombolytic therapy has been shown to be of benefit in patients with ST segment elevation but not in those with ST segment depression or isolated T wave changes (36).

**Risk Stratification and Prognosis—the Clinical History and Initial Electrocardiogram (Table 1)**

In both UA and NQMI, the most important adverse electrocardiographic prognostic indicator is the presence of ST segment depression. Several studies have shown that the most significant indicator of future clinical events including recurrent angina, reinfarction, or death is the presence of ST segment depression (37). In a recent study by Nyman et al. evaluating the ECGs of 911 men with UA or NQMI admitted to the CCU, patients were followed for the endpoints of cardiac death, myocardial infarction, or severe angina for up to one year (38). Those patients with admission ST depression on
Table 1. Early Indicators of High Risk Patients With Unstable Coronary Syndromes

<table>
<thead>
<tr>
<th>Category</th>
<th>Indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrocardiographic findings</td>
<td>ST segment depression</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Braunwald Class III or C</td>
</tr>
<tr>
<td></td>
<td>Need for I.V. nitrates</td>
</tr>
<tr>
<td></td>
<td>Increased age</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Biochemical markers</td>
<td>Elevated troponin I or T</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td>Reduced left ventricular function</td>
</tr>
<tr>
<td></td>
<td>Anterior wall involvement</td>
</tr>
<tr>
<td>Angiographic findings</td>
<td>Complex lesions</td>
</tr>
<tr>
<td></td>
<td>Thrombus</td>
</tr>
<tr>
<td>PredischARGE noninvasive testing</td>
<td>Reversible perfusion defects on nuclear imaging</td>
</tr>
<tr>
<td></td>
<td>Wall motion abnormalities by echocardiography</td>
</tr>
<tr>
<td></td>
<td>Increased lung/myocardial uptake on nuclear imaging</td>
</tr>
</tbody>
</table>

the ECG were at highest risk (18%) of future MI or recurrent angina. Of note, cardiac enzyme levels did not predict out of hospital cardiac events nor did location of ECG changes. In another study evaluating subgroups of patients with NQMI, ST segment depression was associated with lower LV ejection fraction, more hospital complications, and a higher mortality rate at one year than ST segment elevation (39). It appears that persistent ST depression places the patient at very high risk. Schechtman et al. found a one year mortality rate of 22.2% when ST segment depression persisted after hospital discharge (40). Further, the location of changes, particularly leads V1–V4, suggests a large area of myocardium at increased risk of adverse events independent of CPK level at presentation.

The ECG provides easily obtainable prognostic information, but it is well known that the extent of coronary artery disease (CAD) and resting ejection fraction in UA patients also contribute. Certainly, severe three vessel CAD or significant stenosis in the left main coronary artery or left anterior descending artery may result in at least a twofold higher mortality rate than disease in the right coronary artery and/or left circumflex coronary artery (41). Similarly, patients presenting with pulmonary edema in UA have a high incidence of severe CAD and a poor prognosis, which is dramatically lessened by revascularization procedures (42). In general, coronary bypass grafting can be performed with low perioperative mortality in patients with UA and markedly depressed left ventricular function (43).

In an effort to assess other clinical factors and risk stratify a very heterogeneous UA group, Braunwald proposed a classification system in 1989 based on the severity of symptoms and clinical circumstances at the time of presentation (44). A prospective validation of this system was performed in a cohort of 393 consecutive patients with UA (45). Five variables-postinfarction angina, the need for intravenous nitroglycerin on admission, the absence of beta-blocker or rate-lowering calcium channel blocker prior to admission, and baseline ST segment depression were predictive of major in-hospital complication. In addition, increasing age and coexistent diabetes were also predictive. A subsequent prospective study in 417 consecutive patients with the diagnosis of UA in regard to six month outcome similarly found that postinfarction angina and intravenous nitroglycerin therapy were the most predictive of adverse outcome along with advanced age and presence of ECG changes on admission (46).

There are specific features of NQMI as well which are predictive of adverse outcome. Posthospital reinfarction and recurrent angina are higher in NQMI than QMI, offsetting the higher early risk with QMI. Anterior location, persistent ST segment depression, and associated congestive heart failure (CHF) are independent predictors of increased early mortality in NQMI patients up to three months post event (47). Late mortality is higher in older patients, those with diabetes, and those suffering reinfarction (48). As with UA, the presence of ischemic, yet viable, myocardium suggested by recurrent angina or reinfarction portends higher risk. However, the occurrence of NQMI also indicates myocardial necrosis, and so anterior location and history of CHF likely also predispose to increased likelihood of life-threatening arrhythmias and sudden cardiac death.

The Contribution of Biochemical Markers to Prognosis and Risk Stratification

A number of biochemical markers have been studied in the setting of ischemic syndromes. The primary focus of the past three decades has been to identify cellular markers that reliably and rapidly diagnose myocardial injury to provide more rapid treatment for a higher risk subset of patients. CKMB levels are often obtained at initial presentation of patients with suspected ischemic syndromes and are checked serially every 4–6 h until they reach a peak. Increases in plasma levels occur between 6 to 10 h after the onset of infarction but may occur sooner in NQMI or “smaller” infarctions as recanalization increases the rapidity with which CKMB appears in the plasma (49). Resolution usually occurs within 36 to 72 h but may be prolonged in patients with renal dysfunction or hypothyroidism. While ECG changes and clinical presentation often overlap, CKMB levels are utilized to distinguish between UA and NQMI. A prospective study performed in 199 patients with UA in which frequent CPK serum levels were obtained showed that total CKP levels may also be elevated in as many as 19% of patients with UA, somewhat reducing the specificity of enzyme sampling (50). Of particular importance was that patients with elevated CPK levels had a higher rate of reinfarction than those without elevations. It has been generally felt, though, that elevated CKMB levels, when present, indicate myocyte injury and reduced left ventricular dysfunction, placing the patient at higher risk for future events.

Myoglobin is a low molecular weight protein present in cardiac and skeletal muscle that is a sensitive but not specific marker of myocardial injury (51). It is rapidly released from necrotic myocardium and subsequently rapidly cleared by the
kidneys. The rate of rise of serum myoglobin levels is more rapid during reperfusion of previously occluded coronary vessels as may occur with NQMI. Elevated levels of myoglobin are also found in patients with UA, perhaps released from skeletal muscle in severely ill patients and may obscure differentiation of UA from NQMI. Myoglobin, then, is a very nonspecific marker in unstable ischemic syndromes.

Recently, the troponins have been studied extensively and were approved for clinical use by the Food and Drug Administration in 1994. Troponin I, C, and T form a complex that regulates the calcium-modulated interaction of actin and myosin in striated muscle (51). Monoclonal antibodies to troponin I have been developed which have no cross-reactivity with noncardiac skeletal muscle isoforms, as may occur with troponin T. Troponin I is more specific for myocardial cell injury and elevations do not occur in patients with skeletal muscle injury (e.g., in the perioperative setting) or in patients with renal failure, unless concomitant cardiac damage has occurred (52).

Given that troponins are reliable markers of myocardial cell injury, recent studies have focused on the prognostic information they provide. When analyzing patients presenting with UA, the subgroup of patients with elevated troponin T levels appears to define a group at higher risk of adverse outcome. Specifically, in a study by Hamm et al. (53), the risk of in-hospital MI or cardiac death among patients with UA and normal CKMB levels was significantly higher in those with detectable troponin T levels in the range of 0.2 to 3.64 mcg/L despite standard medical therapy. Further, in a group of 240 patients with documented myocardial infarction (Q wave or NQMI) by WHO criteria, Stubbs et al. (54) found that an admission troponin T level of greater than or equal to 0.2 mcg/L, especially in association with ST segment elevation, identified a group at high risk of MI or cardiac death within three years.

It appears that the prognostic information provided by these proteins is independent of the classification of the patient’s presentation as UA or acute MI. Ohman et al. (55) studied 855 patients in the GUSTO-IIa study group presenting within 12 h of the onset of symptoms consistent with myocardial ischemia. Approximately 5 of patients had an elevated troponin level (>0.1 mcg/L) and mortality was significantly higher in these patients than in patients who had lower levels of troponin at 30 days. Troponin T level was more strongly correlated with 30 day survival than electrocardiographic category or CKMB level. A retrospective analysis by Antman et al. (56) of 1404 patients in the TIMI IIIb study found that levels of troponin I greater than 0.4 mcg/L were associated with a significantly higher mortality within 42 days than lower levels and that mortality increased for each 0.1 mcg/L rise in troponin levels. Troponin I level was an independent risk factor for death even when adjusting for baseline characteristics such as ST depression and age, which were also predictive of mortality.

Although predictive of short term outcome, troponin T also has long term prognostic value as studied by Lindahl et al. (57); 976 patients presenting with ischemic symptoms and/or electrocardiographic changes consistent with myocardial ischemia were followed for five months after presentation. The maximum troponin T level in the first 24 h was an independent predictor of future MI or cardiac death in the ensuing 5 months, and increasing troponin levels were proportional to a higher event rate. In addition, there was considerable overlap of maximum troponin T levels in patients with MI or UA especially in the intermediate 0.06 to 0.18 mcg/L range.

As discussed, it has been suggested that the specificity of troponin I may be higher for myocardial tissue than troponin T. Accordingly, Galvani et al. (58) studied 106 patients presenting with chest discomfort within 48 h of admission with the primary endpoints at 30 days and one year being death or nonfatal MI. A troponin I level greater than 3.1 mcg/L was an independent risk factor for death or nonfatal MI within 30 days and the prognostic value was maintained at one year. Only 68% of patients with troponin I elevations were free of cardiac events as compared with 90% of those without elevations.

Though higher levels of troponins seem to indicate increased risk, are low levels enough to obviate further evaluation and allow discharge of patients with unstable coronary syndromes? The answer to this question is still under investigation (59), although a study of 773 consecutive patients with chest pain and without ST segment elevation on the ECG attempted to answer this question (60). Event rates in patients with negative troponin T or I tests were only 1.1% and 0.3%, respectively, leading the authors to conclude that negative test results are associated with low risk and allow for safe discharge of patients from the emergency room. More recently, however, in a more heterogeneous cohort of more than 1,000 patients presenting with chest pain, a negative test result (low troponin I level) did not assure a good prognosis (61).

In summary, the current evidence shows that both troponins T and I can be easily measured and are independent markers of adverse outcome in both the short and long term followup of patients with unstable ischemic syndromes. They may also be more specific indicators than the traditional electrocardiographic changes or CKMB enzyme elevations. There is early evidence that elevated troponin levels may indicate complex lesion morphology (62). However, further investigation is needed to determine the appropriate treatment strategy, such as early angiography and/or angioplasty, for patients with elevated troponin levels and whether such intervention results in better, more cost-effective outcomes.

The Timing of Coronary Angiography

Whether or not routine coronary angiography should be employed in the setting of UA or NQMI has been the subject of considerable debate in recent years. In addition, the optimal timing of intervention has also been controversial. The belief that patients with UA or NQMI have significant amounts of jeopardized myocardium has pushed many cardiologists to seek invasive evaluation early (63,64). Others have adopted a more conservative strategy in which they have pursued angiography only if significant ischemia is present on noninvasive stress testing.
Table 2. Therapeutic Options for Patients With Unstable Coronary Syndromes

<table>
<thead>
<tr>
<th>Medication</th>
<th>Recommendation:</th>
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<tbody>
<tr>
<td>Aspirin*</td>
<td>Class I</td>
</tr>
<tr>
<td>Heparin*</td>
<td>Class I</td>
</tr>
<tr>
<td>Nitrates*</td>
<td>Class I</td>
</tr>
<tr>
<td>Calcium antagonists*</td>
<td>Class I</td>
</tr>
<tr>
<td>Beta blockers*</td>
<td>Class I</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa antagonists†</td>
<td>Class IIa</td>
</tr>
<tr>
<td>Coronary intervention with or without stents‡</td>
<td>Class IIa</td>
</tr>
<tr>
<td>Low molecular weight heparin§</td>
<td>Class IIa</td>
</tr>
</tbody>
</table>

*: see reference 110; †: see references 85–94; ‡: see references 101–103; §: see references 81–84.

Early, retrospective studies (64) suggested benefit with an aggressive invasive approach, but large randomized studies have shown no reduction in nonfatal reinfarction or death with that strategy (65–67). In the recent VANWISH study (66), patients admitted to 15 Veterans Affairs Medical Centers from April 1993 to December 1995 with NQMI were screened and 920 patients were actually enrolled. These patients were randomized to an early invasive strategy which consisted of coronary angiography shortly after admission followed by angioplasty, if indicated, or an early conservative strategy with coronary angiography only if symptom-limited stress testing was positive. The incidence of in-hospital adverse events in the early invasive arm was higher than in the conservative strategy as was the average length of stay. All-cause mortality and nonfatal reinfarction in patients randomized to the invasive arm were significantly higher at discharge and during followup of 12 to 44 months. No subgroup of NQMI patients in the early invasive arm appeared to benefit from that strategy and there were no cost savings or shorter hospitalizations. Therefore, a routine early invasive strategy may not be warranted in NQMI as once believed, and the overall approach may not differ significantly from that in UA where either strategy has been followed. This should not be surprising, because most patients with NQMI or UA have patent arteries at the time of angiography soon after presentation, in contrast to those with QMI, who have occluded vessels. Coronary intervention may be more safely performed after the patient has been more carefully evaluated and perhaps stabilized with medical therapy.

**Therapy (Table 2)**

**Antithrombotic medications.** Therapy for UA and NQMI have traditionally been similar because the initial clinical presentations are often difficult to separate. The anticoagulant regimen and need for interventional therapy have been studied extensively in recent years. Aspirin and intravenous heparin therapy are currently the mainstay of initial treatment strategy for NQMI and UA. Theroux et al. performed a double-blind, randomized study involving 479 patients with UA in the late 1980's showing that either aspirin or heparin alone, or the combination of the two, significantly reduced the incidence of MI and refractory angina (68). However, early withdrawal of heparin may reactivate the disease process within hours of discontinuation; combination therapy with aspirin attenuates this response (69).

Although numerous studies have evaluated aspirin’s efficacy in unstable coronary syndromes, the Veterans Administration study was the first to prospectively determine the benefit of aspirin therapy in reduction of cardiac events in patients with UA (70). The RISC investigators proved benefit of aspirin in patients with either NQMI or UA (71). Subsequently, Cohen et al. performed a multicenter investigation of antithrombotic therapy in UA and NQMI patients admitted within 48 h of the onset of chest pain (72). The overall ischemic event rate was 27% in both groups, but patients with NQMI had a higher reinfarction and death rate, despite maximal antianginal and antithrombotic medication. The addition of warfarin is not of benefit and can only be recommended in NQMI associated with LV thrombus. Further, the optimal duration of antithrombotic medication is felt to be approximately 48 h for UA and NQMI; a more lengthy administration may result in adverse outcome (73).

Beta blockers also appear to provide benefit in UA by reducing myocardial oxygen demand and cardiac work to reduce ischemia. Long term administration of beta blockers without intrinsic sympathomimetic activity in a metaanalysis of trials of patients with UA showed a 13% reduction in risk of developing MI (5). Calcium channel blockers may effectively control symptoms although there is no clear beneficial effect on survival. Intravenous nitrates have peripheral and coronary vascular effects, decreasing myocardial preload and left ventricular end-diastolic volume. No randomized placebo controlled trials have been performed in UA addressing the efficacy of the drug for symptom relief or reduction of cardiac events.

The focus in patients with NQMI has been on the role of calcium channel blockers. The Diltiazem Reinfarction Study prospectively evaluated 576 patients receiving diltiazem or placebo beginning 24 to 72 h after NQMI and continuing for 14 days (74). There was significant reduction of reinfarction and postinfarction angina with diltiazem. The Multicenter Diltiazem Post Infarction Trial (75) found a significant reduction of adverse cardiac events in patients receiving diltiazem who did not have pulmonary edema on presentation. Similar favorable findings cannot be extrapolated to include other calcium channel blockers such as verapamil and nifedipine, which have not been found to reduce reinfarction or mortality (76–78). Diltiazem’s unique effect on prevention of coronary vasoconstriction and decrease in myocardial oxygen requirements by reducing heart rate and contractility have led to its widespread use.

The role of beta blockers in NQMI has been controversial and routine use for NQMI cannot be advocated. Although the Beta Blocker Heart Attack Trial (BHAT) reported significant advantages in patients with acute MI, retrospective subgroup analysis of NQMI patients receiving propranol after two years
showed no reduction in death rates or need for revascularization (79). These findings were criticized by some for lack of statistical power. Another trial, though, suggested an even higher mortality rate in NQMI patients taking metoprolol as compared to placebo (80).

Low molecular weight heparins (LMWH) are increasingly finding new applications in certain patients (81). The FRISC study found a significant reduction in death and MI with dalteparin in patients with UA already on aspirin (82). A larger study, Fragmin in Unstable Coronary Artery Disease Study (FRIC) randomized 1482 patients with UA or NQMI to dalteparin or dose-adjusted unfractionated heparin for six days in phase I and for 45 days in phase II (83). The combined endpoint of death, myocardial infarction, recurrence of angina, and need for revascularization procedures in both groups were comparable, suggesting that LMWH may be an acceptable alternative to heparin in the acute treatment of unstable coronary syndromes. The recently published ESSENCE trial in which over 3180 patients with UA or NQMI were randomized to enoxaparin or standard heparin suggested an advantage of LMWH over standard heparin (84). The data, though, are not conclusive that LMWH should replace standard heparin, as heparin treated patients were not always adequately anticoagulated in the studies. LMWH could be administered to thrombocytopenic patients or those requiring long-term therapy.

**Glycoprotein IIb/IIIa receptor blockers.** New antiplatelet therapies have made the distinction between NQMI and UA less relevant from the standpoint of therapy. Activation of the platelet glycoprotein (GP) IIb/IIIa receptor to bind fibrinogen, fibronectin or VWF is the final step in platelet aggregation. Several trials, complete or ongoing, have evaluated the efficacy of new antiplatelet therapies (85–94) (Table 3). Recent trials in acute coronary syndromes lump unstable angina with non-Q wave MI ostensibly because these non ST segment syndromes do not exhibit improved outcome with thrombolysis or early intervention, and may be deleterious. Several glycoprotein IIb/IIIa receptor blockers offer some short-term improvement, both as stand alone therapy and in conjunction with intervention at 48–72 h, but at substantial cost.

### Table 3. Studies of Glycoprotein IIb/IIIa Receptor Antagonists

<table>
<thead>
<tr>
<th>Trial Acronym</th>
<th>N</th>
<th>Outcome</th>
<th>P Value</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPTURE</td>
<td>1265</td>
<td>11.3 vs 15.9</td>
<td>0.012</td>
<td>abciximab</td>
</tr>
<tr>
<td>PARAGON</td>
<td>2282</td>
<td>10.3 vs 11.7</td>
<td>NS</td>
<td>lamifiban</td>
</tr>
<tr>
<td>PRISM</td>
<td>3252</td>
<td>15.9 vs 17.1</td>
<td>0.340</td>
<td>tirofiban</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>9461</td>
<td>15.9 vs 17.1</td>
<td>0.340</td>
<td>tirofiban</td>
</tr>
<tr>
<td>EPIC†</td>
<td>2099</td>
<td>8.3 vs 12.8</td>
<td>0.008</td>
<td>abciximab</td>
</tr>
<tr>
<td>EPILOG*</td>
<td>2792</td>
<td>5.4 vs 11.7</td>
<td>&lt;0.001</td>
<td>abciximab</td>
</tr>
<tr>
<td>IMPACT II*</td>
<td>4010</td>
<td>9.2 vs 11.4</td>
<td>0.063</td>
<td>eptifibatide</td>
</tr>
<tr>
<td>PRISM-PLUS*</td>
<td>1570</td>
<td>18.5 vs 22.3</td>
<td>0.03</td>
<td>tirofiban</td>
</tr>
<tr>
<td>RESTORE†</td>
<td>2212</td>
<td>10.3 vs 12.2</td>
<td>0.160</td>
<td>tirofiban</td>
</tr>
</tbody>
</table>

N = number of patients; Outcome = 30 day composite outcome of death, nonfatal myocardial infarction, or need for revascularization procedure in treated patients (listed first) versus placebo patients (listed second); *Intervention trials.

In order to evaluate fully the apparent favorable results of the many GPIIb/IIIa antagonists, we performed a metaanalysis to determine whether there was overall benefit of the inhibitors in patients with UA and NQMI (Figure 1). There was significant heterogeneity among the studies, (e.g., drug used, acuity of presentation, number of patients getting interventions) and so a random effects model was utilized. The endpoint examined was the 30 day composite endpoint of death, myocardial infarction, and recurrent ischemia with need for repeat intervention. The number of composite endpoint events was significantly lower for patients receiving GPIIb/IIIa receptor antagonists compared to placebo. The relative risk of events in patients receiving the drug was 0.79 (0.66, 0.94, 95% confidence interval), resulting in an overall 21.3% reduction in risk of events compared with patients receiving only aspirin and heparin. Relative risks and 95% confidence intervals for the 9 trials examined are shown in Fig. 1. We also examined the effects of covariates that may affect outcome, specifically focusing on drug type, number of patients undergoing coronary intervention (CI), and acuity of presentation; at the p = 0.05 level, there was no effect of these variables on overall outcome.
present (26), as suggested by PRISM and PRISM-PLUS. ReoPro may be used when complex anatomy is identified and CI planned, and, if proven effective, oral GPIIb/IIIa antagonists could be used for medically treated patients. However, there is no current evidence that standard heparin and aspirin therapy should be replaced by these agents.

Thrombolytic therapy. Thrombolytic therapy is now used frequently in the acute MI setting. Several studies have demonstrated that early recanalization of the infarct related artery will reduce infarct size and improve prognosis. Large clinical trials have clearly established benefit in the subgroup of patients presenting with ST segment elevation and a history consistent with acute MI. However, patients with non ST segment elevation presentations (UA or NQMI) appear to derive no clinical benefit from thrombolytic therapy (95–98), even when combined with balloon angioplasty (99).

The lack of success with thrombolysis in UA and NQMI compared with favorable results in patients with QMI is intriguing. While thrombolytic therapy clearly promotes clot lysis, it also sets in motion pathophysiological mechanisms favoring further thrombosis (100). One mechanism may be through enhanced thrombin formation as markers of thrombin generation such as fibrinopeptide A and thrombin; AT III levels increase after thrombolysis. Patients with UA and high levels of fibrinopeptide A are known to be at higher risk for adverse events. Thrombolytic agents also activate platelets causing release of the vasoactive substances serotonin and thromboxane A2 which recruit other platelets and induce local vasoconstriction. Furthermore, thrombi in patients in with UA are composed primarily of platelets rather than erythrocytes and are more resistant to thrombolysis than those in patients with evolving QMI and total occlusion due to erythrocyte-rich thrombus. Nonetheless, in NQMI or UA, thrombolytic therapy does not provide clinical benefit for either patient subset.

Coronary interventions. The presence of thrombus and/or complex lesions in patients with UA and NQMI have made performing coronary interventions in these patients challenging. Although more commonly visualized in NQMI, thrombus plays an important pathophysiological role in UA as well, and increases the risk of performing CI. In particular, angioscopic features of disruption, yellow color, or thrombus at the culprit lesion site can identify patients at high risk of early adverse outcome after CI (1).

New devices and antiplatelet agents have been extensively investigated to counteract these problems. Previous studies have indicated a poorer outcome in coronary lesions containing thrombus undergoing CI. In addition to thrombotic complications, a feature of high risk lesions is their tendency to undergo abrupt closure following CI. Although stents have not been approved for use in the setting of visible thrombus, early results suggest that success rates with stents in thrombotic lesions are favorable. A retrospective study of 231 patients by Marzocchi et al. (101) compared the results of stenting in stable and unstable angina patients and found comparable success rates; there were high (>90%) success rates in both groups with similar in-hospital complications, low (<2%) subacute stent thrombosis, and low incidence of cardiac events at six month followup. Another recent study evaluated new devices such as autoperfusion balloons, stents, and atherectomy in patients with refractory UA and achieved an 88% success rate despite the high risk lesions (102).

These results, combined with the observations from the TIMI IIIB investigators, suggest that the CI may be performed safely and successfully in patients with unstable coronary syndromes with success rates approaching those in patients with stable plaques (103). Angiographic success was observed in 96.1% of patients with UA or NQMI in the TIMI IIIB trial with a low incidence of complications. While these trials did not directly compare outcome in UA versus NQMI, it seems that the advent of stents and glycoprotein IIB/IIIA receptor antagonists may make it less important to distinguish between the two as success rates in the unstable syndromes approach those in the stable, routine CI.

Pre-discharge Diagnostic Testing

In light of the recently published VANQWISH trial (66), predischarge stress testing plays an important role in risk stratification and management of NQMI patients. Patients undergoing stress testing as opposed to routine coronary angiography had better outcomes up to 44 months out from their events. In NQMI, predischarge symptom-limited or maximal exercise testing after an acute event appears to have a higher yield than low level exercise stress testing, and can be performed safely. Symptom limited stress testing in NQMI patients has a greater than 75% positive predictive value for critical stenosis of one vessel or more in the presence of 2 mm ST segment depression. The sensitivity and specificity can be improved with the addition of nuclear SPECT imaging (104).

Perhaps equally important is the presence of postinfarction angina. In a study of 549 patients with acute MI (n = 186 with NQMI), results of exercise stress testing with or without nuclear imaging did not impact on subsequent cardiac risk (105). 16.7% of patients experienced a cardiac event, nonfatal reinfarction, recurrent angina, or cardiac death in the succeeding two month period. Only postinfarction angina and insulin dependent diabetes were independent predictors of cardiac risk.

Similarly, predischarge maximal exercise stress testing with technetium labeled sestamibi in the absence of coronary revascularization was assessed in 126 consecutive men with UA stabilized with medication initially (106). Significantly, cardiac events occurred in 39% of those with abnormal technetium and in 60% of those with a reversible defect compared to 12% in patients with normal scans. 2% of normals had a nonfatal MI or cardiac death versus 25% of those with a reversible defect. In addition, in 128 patients with UA undergoing dipyriramole stress testing who could not exercise (predischarge testing), those with normal scans experienced a 10% cardiac event rate compared with 69% of those with abnormal results at 16 mean followup (107). Furthermore, exercise stress echocardiography and thallium-201 SPECT imaging have been
compared in patients one month out from an event and both were highly sensitive (88% and 81%, respectively) for detecting significant CAD with induction of wall motion abnormality or perfusion defect (108). Long term prognostic information can also be obtained from stress echocardiography in that 56% of patients with a wall motion score index below the median suffered MI or cardiac death in an eight year median followup (109).

In summary, stress testing for patients with UA treated medically and for patients with recent NQMI appears to be safe and provides important prognostic information. The presence of stress induced wall motion defects with echocardiography or a perfusion defect on nuclear imaging suggests the presence of ischemic, yet viable, myocardium at risk. This issue is central to the management of both NQMI and UA patients.

Current recommendations. Current recommendations for management of patients presenting with a suspected unstable coronary syndrome are summarized in Fig. 2. Patients who present with chest pain (without ST segment elevation) need to be rapidly separated into a high, medium, or low risk category as specified by Braunwald et al. (110). See text for details. GPIIb/IIIa RA = Glycoprotein IIb/IIIa receptor antagonist.

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Figure 2. Possible treatment algorithm for patients presenting with a suspected unstable coronary syndrome. Patients presenting to the emergency department with chest pain need to be rapidly separated into a high, medium, or low risk category as specified by Braunwald et al. (110). See text for details. GPIIb/IIIa RA = Glycoprotein IIb/IIIa receptor antagonist.

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