Unstable Angina

Current Concepts of Pathogenesis and Treatment

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During the past 15 years, we have learned an enormous amount about the pathogenesis and treatment of unstable angina. In most cases of unstable rest angina, the pathogenesis is a mural thrombus formation on a ruptured or eroded atherosclerotic plaque. However, any process that acutely changes the supply-demand ratio (decreased supply or increased demand in the presence of a decrease in supply) can precipitate the clinical presentation of unstable angina. Standard acute antithrombotic drug therapy is effective in decreasing progression to infarction. Newer agents (low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibitors) are more effective, and their use is evolving. Percutaneous intervention and bypass surgery can reduce symptoms and multiple hospitalizations, in most cases without a decrease in the long-term mortality rate. Because the cost of hospitalization is extremely high and the clinical presentation and outcome are heterogeneous, better triage methods are required.

Unstable angina is a common cardiovascular disorder, accounting for at least 500,000 to 750,000 hospital admissions per year in the United States. Although in the era of modern medical therapy the in-hospital mortality rate is low (<3%) in randomized trials, in-hospital morbidity is still considerable.

DEFINITION OF UNSTABLE ANGINA

The term unstable angina was first used in the early 1970s to define a condition referred to in earlier publications as preinfarction angina, crescendo angina, acute coronary insufficiency, or intermediate coronary syndrome. There have been several classifications of unstable angina. In the commonly used Braunwald classification, unstable angina was defined first in terms of its severity. Class I included the new onset of severe or accelerated angina of less than 2 months’ duration without rest pain. Class II included rest pain during the preceding month but not within the last 48 hours. Class III included angina at rest within the preceding 48 hours.

Unstable angina was further classified into the clinical circumstances under which it occurred, the amount of cardiac medication being taken at presentation, and whether electrocardiographic changes were present (Table 1). Although the large number of categories might detract from its practical utility in clinical cardiology practice, results of 2 prospective studies validate the major subdivisions of this classification in its ability to risk stratify patients who are admitted to the hospital.

As unstable angina implies, the condition is intermediate between stable angina and myocardial infarction (MI). This seems appropriate because unstable angina is a common forerunner to MI; in some studies, most patients report that in the week before infarction, they experienced chest discomfort consistent with unstable angina.

PATHOGENIC MECHANISMS IN UNSTABLE ANGINA

In the mid-1980s, several researchers suggested that unstable angina was linked to non-Q and Q wave MI, and that these conditions represented a spectrum of disease in which plaque disruption or fissuring led to thrombus formation and the acute coronary syndrome. Intracoronary thrombus formation was thought to explain the pathogenesis in most patients with unstable angina. As opposed to MI...
with ST-segment elevation in which the thrombus was usually occlusive, the thrombus in unstable angina was mural and did not result in total coronary occlusion in 80% to 90% of patients (Figure 1).15 Non–Q wave infarction is positioned between the other 2 conditions because there was more frequent total occlusion of the culprit artery than in unstable angina but less than in Q wave MI.14,15

Nearly all pathologic evidence in acute syndromes originates from autopsy studies.16 Because short-term mortality of unstable angina is low, autopsy data in unstable angina represent a highly select population. Aside from these, pathologic material in unstable angina has been obtained mainly from atheromatous plaque that is excised during directional atherectomy of the culprit lesion.17,18 This analysis is subject to sampling error because only a portion of the plaque is removed. Accordingly, our understanding of its pathogenesis derives mainly through other methods, including angiography, angioscopy, and biochemical studies.

Thrombus Formation in Unstable Angina

Results of angiographic studies10,19,20 suggest that intracoronary thrombus formation or a complex lesion (ulcerated or irregular plaque) is found in 50% to 80% of culprit lesions, particularly if the presentation is rest pain. Serial angiograms performed before and after an episode of unstable angina, without an intervening coronary intervention, have shown progression of coronary artery disease in about 75% of patients.21,22

Recently, Dangas et al23 correlated coronary morphologic features of the culprit lesion to the Braunwald classification. There were significant (P < .05) positive correlations between severity of the unstable angina presentation and presence of an intracoronary thrombus or complex lesion. Results of angioscopic studies24 also indicate that intracoronary thrombus or yellow plaque is found in most unstable culprit arteries but infrequently in stable angina. The thrombus in unstable angina has been characterized as grayish-white and presumably platelet-rich, whereas in MI it was red.25 Because the coronary artery is usually totally occluded in MI, this red thrombus is rich in fibrin and red blood cells, superimposed on the platelet component and potenti ated by stasis of blood flow. Although angiography is commonly used to detect thrombus, it has low sensitivity relative to angioscopy.26,27 However, angiography is relatively specific (80%-90%) for the detection of thrombus or a complex lesion.26,27 Small thrombi or mural thrombi that do not cause luminal irregularity probably cannot be detected angiographically. In conclusion, thrombus formation on a presumed disrupted, fissured, or eroded plaque is the most common pathophysiological mechanism in unstable angina, particularly when the presentation is that of acute rest pain. However, it is unrealistic to assume that thrombus formation can explain all unstable presentations. For patients without rest pain, there are less convincing data that thrombus is the predominant cause. In our opinion, these patients require further evaluation.

Other Pathogenic Mechanisms in Unstable Angina

Other mechanisms might explain the clinical syndromes of unstable angina. Inflammation has been implicated. Inflammation plays a role in plaque rupture, contributing to destabilization of the fibrous cap of so-called vulnerable plaques by secretion of matrix metalloproteinases.26 Results of directional atherectomy analysis of culprit lesions in unstable angina show a higher percentage of the excised plaque area infiltrated by inflammatory cells compared with stable angina. One difficulty with understanding the role of inflammation is the interrelationship between thrombus formation and inflammation. Tissue factor is found more commonly in unstable vs stable plaques, and results of histopathologic analysis29,30 of atherectomy specimens show a strong association between macrophage infiltration and tissue factor localization. Local expression of tissue factor by macrophages can lead to activation of the coagulation cascade. Furthermore, activation of platelets might lead to inflammatory reactions at the site of vascular lesions.31 Another link between inflammation and thrombosis might be lipoprotein(a). Recent data32 suggest that lipoprotein(a), which is considered atherosclerotic and thrombogenic, also localizes in macrophage-rich areas in unstable plaques. At the molecular

Table 1. Classification of Unstable Angina According to Braunwald*

| I. Severity | Class I. New onset of severe or accelerated angina |
| Class II. Angina at rest, subacute (≥48 h from presentation) |
| Class III. Angina at rest, acute (≤48 h from presentation) |
| II. Clinical circumstances | Class A. Secondary unstable angina |
| Class B. Primary unstable angina |
| Class C. Postinfarction unstable angina (≥2 wk after infarction) |
| III. Intensity of treatment | 1. Absence of therapy |
| 2. Standard therapy |
| 3. Maximal therapy, including intravenous nitroglucorine |
| IV. Electrocardiographic changes | 1. ST-T abnormalities present |
| 2. ST-T abnormalities absent |

*Data from Braunwald.5
level, the apolipoprotein A portion of the lipoprotein(a) molecule has been shown to be responsible for macrophage chemotraction.

Another potential nonthrombotic mechanism for unstable angina might be smooth muscle cell proliferation. In lesions without angiographic evidence of thrombus, some patients have an abundant proliferation of smooth muscle cells on directional atherectomy analysis of excised plaque similar to that found in restenotic lesions. Again, excluding a role for thrombus is difficult because one third of lesions had thrombus demonstrated on tissue analysis, although the angiogram suggested no thrombus. Furthermore, thrombus might be a potent stimulus for smooth muscle cell proliferation, along with cytokines or growth factors released from inflammatory cells or other stimuli, including infectious agents like Chlamydia pneumoniae and cytomegalovirus. Smooth muscle cell proliferation without thrombus might play a role in unstable angina in the restenotic lesion. Restenotic lesions do not usually contain thrombus, yet their presentation might be that of rest pain with or without enzyme level elevation, indicating non-Q wave MI (Figure 2).

Finally, occasionally there are patients who present with rest ischemia and ST-segment elevation in whom vasospasm on an angiographically normal-appearing vessel is present. However, most patients with so-called Prinzmetal variant angina have fixed and severe atherosclerotic lesions with superimposed thrombus.

**Pathogenic vs Ischemic Mechanisms in Unstable Angina**

In general, the pathogenesis of coronary disease relates to the slow or rapid progression of atherosclerosis. Ischemic mechanisms, on the other hand, reflect an imbalance between myocardial blood supply and oxygen demand. As physicians, we evaluate patients with silent or clinical ischemia. In unstable angina, transient decreases in blood supply or even small increases in myocardial demand in the presence of a new significant lesion might precipitate ischemic manifestations of the disease, namely, angina, by altering this balance. Transient decreases in supply related to intracoronary thrombus formation with spontaneous lysis or embolization, or transient increases in vasomotor tone, might lead to rest pain. Activated platelets release several vasoactive substances that, in the presence of endothelial dysfunction (impaired vasodilation), can result in vasoconstriction at or distal to the lesion and a transient decrease in blood flow. Although a thrombus is usually present to explain or contribute to decreases in blood supply, any process (thrombotic or otherwise) that significantly perturbs this balance can lead to unstable angina.

**NATURAL HISTORY AND PROGNOSIS**

**Natural History of Unstable Angina**

Before the era of modern medical therapy, a few studies assessed clinically long-term outcomes. In 1973, Gazes et al followed up patients with recurrent rest pain in the hospital with ischemic ST and T wave changes. At 1 year their mortality was 43%, whereas at 10 years it was 81%. In 1985, Mulcahy et al reported the natural history in patients who were not treated with angioplasty or bypass surgery. One-year mortality was 8% to 10%, with a 12% to 14% incidence of nonfatal infarction. With antiplatelet drug therapy, there have been significant reductions of 50% to 70% in the incidence of in-hospital death or MI in placebo-controlled randomized trials. However, even in the most recent randomized trials, the incidence of MI in the hospital or at short-term follow-up during aspirin or antiplatelet drug therapy was about 5% to 10%, whereas the incidence of refractory angina was 10% to 20%.

**Prognosis in Unstable Angina**

Several factors have been identified that increase morbidity or mortality, including clinical presentation, electrocardiographic changes at rest, enzymatic evidence of necrosis or inflammation, certain angiographic findings, and Holter evidence of ischemia (Table 2).

A panel of experts convened by the Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute developed guidelines for the treatment of unstable angina in 1994. These guidelines were based on a review of the literature and expert opinion. The guidelines recommend that patients with unstable angina be treated with aspirin and other antiplatelet drugs, and that patients with high-risk features be treated with a combination of antiplatelet drugs and a thienopyridine. The guidelines also recommend that patients be referred for percutaneous coronary intervention or coronary artery bypass surgery based on the results of coronary angiography.

**Table 2. Factors Associated With Increased Morbidity or Mortality in Unstable Angina**

<table>
<thead>
<tr>
<th>Clinical presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged rest pain, recurrent rest pain in the hospital, postinfarction rest pain, heart failure, or hypotension with chest pain</td>
</tr>
<tr>
<td>Electrocardiographic changes</td>
</tr>
<tr>
<td>ST-segment deviation ≥0.5 mm, left bundle branch block, or symmetrical T inversions</td>
</tr>
<tr>
<td>Enzyme evidence of myocardial necrosis or inflammation</td>
</tr>
<tr>
<td>Elevated troponin T or I, creatine kinase–MB, or C-reactive protein result</td>
</tr>
<tr>
<td>Angiographic findings</td>
</tr>
<tr>
<td>Significant left main coronary artery disease, left ventricular dysfunction intracoronary thrombus, or a complex-appearing lesion</td>
</tr>
<tr>
<td>Holter evidence of ischemia</td>
</tr>
<tr>
<td>Silent ischemia of &gt;60 min on 24-h monitoring after hospital admission</td>
</tr>
</tbody>
</table>

* Each of these factors usually compared with the absence of the clinical presentation, electrocardiographic change, enzyme level increase, etc.
Table 3. Likelihood of Significant CAD in Patients With Symptoms Suggesting Unstable Angina*

<table>
<thead>
<tr>
<th>High Likelihood</th>
<th>Intermediate Likelihood</th>
<th>Low Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any of the following features:</td>
<td>Abundance of high-likelihood features and any of the following:</td>
<td>Abundance of high-likelihood and intermediate-likelihood features:</td>
</tr>
<tr>
<td>Known history of CAD</td>
<td>Definite angina: men $\geq 60$ y or women $\geq 70$ y</td>
<td>Chest pain, probably not angina</td>
</tr>
<tr>
<td>Definite angina: men $\geq 60$ y or women $\geq 70$ y</td>
<td>Probable angina: men $\geq 60$ y or women $\geq 70$ y</td>
<td>One risk factor but not diabetes</td>
</tr>
<tr>
<td>Hemodynamically changes or ECG changes with pain</td>
<td>Probably not angina in diabetic or nondiabetic patients with $\geq 2$ other risk factors†</td>
<td>T wave flat or inverted $&lt;1$ mm in leads with dominant R waves</td>
</tr>
<tr>
<td>Variant angina</td>
<td>Extracardiac vascular disease</td>
<td>Normal ECG findings</td>
</tr>
<tr>
<td>ST increase or decrease $\geq 1$ mm</td>
<td>ST depression of $0.05$ to $1.00$ mm</td>
<td></td>
</tr>
<tr>
<td>Marked symmetrical T wave inversion in multiple precordial leads</td>
<td>T wave inversion $\geq 1$ mm in leads with dominant R waves</td>
<td></td>
</tr>
</tbody>
</table>

*CAD indicates coronary artery disease; ECG, electrocardiographic.
†CAD risk factors include diabetes, smoking, hypertension, and elevated cholesterol level. Reprinted with permission from Clinical Practice Guideline, Unstable Angina (AHCPR) Publication 94-0602: Agency for Health Care Policy and the NHLBI, 1994.

Table 4. Short-term Risk of Nonfatal Myocardial Infarction in Patients With Symptoms Suggesting Unstable Angina*

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any of the following features must be present:</td>
<td>No high-risk features but must have any of the following:</td>
<td>No high- or intermediate-risk features but may have any of the following:</td>
</tr>
<tr>
<td>Prolonged ongoing ($\geq 20$ min) rest pain</td>
<td>Rest angina now resolved but not low likelihood of CAD</td>
<td>Increased angina frequency, severity, or duration</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>Rest pain ($\geq 20$ min or relieved with rest or nitrerglycerin therapy)</td>
<td>Angina provoked at a lower threshold</td>
</tr>
<tr>
<td>Angina with new or worsening mitral regurgitation murmurs</td>
<td>Angina with dynamic T wave changes</td>
<td>New-onset angina within 2 wks to 2 mos</td>
</tr>
<tr>
<td>Angina with S$_2$ or rales</td>
<td>Nocturnal angina</td>
<td>Normal or unchanged ECG findings</td>
</tr>
<tr>
<td>Angina with hypotension</td>
<td>New-onset CCSC III or IV angina in past 2 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>but not low likelihood of CAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Q wave or ST depression $\geq 1$ mm in multiple leads</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age $&gt;65$ y</td>
<td></td>
</tr>
</tbody>
</table>

*CAD indicates coronary artery disease; CCSC, Canadian Cardiovascular Society Class; ECG, electrocardiographic. Reprinted with permission from Clinical Practice Guideline, Unstable Angina (AHCPR) Publication 94-0602: Agency for Health Care Policy and the NHLBI, 1994.

Because these were consensus-based rather than evidence-based guidelines, no prospective validation had been attempted at the time of publication. Preliminary data from an analysis$^{26}$ of emergency department visits for chest pain in Olmstead County, Minnesota, suggest that the Agency for Health Care Policy and Research assessment of high, intermediate, and low risk for subsequent coronary events could stratify patients evaluated in this setting. Other studies are in progress to attempt to prospectively validate these findings.

**MEDICAL THERAPY IN UNSTABLE ANGINA**

Antianginal Therapy

As mentioned previously, ischemia, whether silent or clinically evident, is related to an imbalance between myocardial blood supply and oxygen demand. Antianginal drugs, including organic nitrates, β-adrenergic blocking agents, and calcium channel blockers, are commonly prescribed. Results of several studies$^{26-61}$ indicate that, used alone or in combination, they reduce ischemia. However, there are few data that use of these drugs reduces the incidence of subsequent MI. Only in meta-analysis$^{62}$ has it been shown that use of β-adrenergic blocking agents significantly reduces subsequent MI. This reduction was small (13%) compared with a much larger benefit afforded by antithrombotic drug therapy.

Ordinarily, in the setting of rest pain, β-adrenergic blocking agents and organic nitrates (usually intravenous nitrerglycerin) are prescribed and titrated until heart rate is 50 to 60 beats/min and blood pressure is well controlled. Calcium channel blockers are generally not first-line therapy. In patients with a contraindication to β-adrenergic blocking agents or with refractory pain, calcium channel blockers can be used. In patients with Prinzmetal angina and rest pain, calcium channel blockers and nitrates are first-line therapy; β-adrenergic blocking agents should not be prescribed because they can potentiate spasm.$^{63}$

**Antithrombotic Drug Therapy**

The modern era of antithrombotic drug therapy in unstable angina began in 1983 with publication of the Veterans Administration Cooperative Study,$^{36}$ showing the beneficial effects of short-term aspirin therapy on reducing the in-hospital and 1-year event rates compared with placebo. Previous studies$^{64,65}$ with anticoagulant drugs in unstable angina were flawed by initial study design or by treatment violations. In placebo-controlled randomized trials$^{36,41}$ of aspirin in doses of 75 to 1300 mg/d, all dosages were effective in reducing the incidence of MI or death by about 50% to 70% (Table 5).
Intravenous, unfractionated heparin therapy has also been compared against or in combination with aspirin therapy. Results of some studies indicated that heparin therapy was superior to aspirin therapy in reducing cardiac events, particularly refractory angina, whereas others suggested it was at least as good as aspirin therapy. However, with heparin therapy alone, Theroux et al found re-

Table 5. Antithrombotic Drug Therapy in Unstable Angina

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, No.</th>
<th>Follow-up</th>
<th>Aspirin Dose, mg/d</th>
<th>Heparin Dose, per day</th>
<th>Aspirin</th>
<th>Heparin</th>
<th>Aspirin + Heparin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis et al</td>
<td>1266</td>
<td>3 mo</td>
<td>324</td>
<td>...</td>
<td>5†‡</td>
<td>...</td>
<td>...</td>
<td>10.1</td>
</tr>
<tr>
<td>Cairns et al</td>
<td>555</td>
<td>18 mo</td>
<td>1300</td>
<td>...</td>
<td>6.6†</td>
<td>...</td>
<td>...</td>
<td>17.1</td>
</tr>
<tr>
<td>Theroux et al</td>
<td>479</td>
<td>6 d</td>
<td>650</td>
<td>5000-U bolus + 1000 U/h</td>
<td>3.3†</td>
<td>0.8‡</td>
<td>1.6†</td>
<td>13.6</td>
</tr>
<tr>
<td>Wallentin</td>
<td>794</td>
<td>3 mo</td>
<td>75</td>
<td>5000 U IV qid × 5 d</td>
<td>7.4†‡</td>
<td>16.6‡</td>
<td>5.7†</td>
<td>17.6</td>
</tr>
<tr>
<td>Theroux et al</td>
<td>484</td>
<td>6 d</td>
<td>650</td>
<td>5000-U bolus + 1000 U/h</td>
<td>3.7†‡</td>
<td>0.8‡</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Cohen et al</td>
<td>214</td>
<td>3 mo</td>
<td>162.5</td>
<td>PTT 2X control = warfarin§</td>
<td>8.5</td>
<td>...</td>
<td>6‡</td>
<td>...</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; IV, intravenous; qid, 4 times daily; and PTT, partial thromboplastin time.
†P < .05 vs placebo.
‡P < .05 aspirin vs heparin.
§Prothrombin time 1.5-2X control for 3 months.

or heparin therapy, and MI or death, although reduced, has not been completely prevented.

Low-Molecular-Weight Heparin. Low-molecular-weight heparins have potential advantages over unfractionated heparin, including a more predictable anticoagulant effect with a higher ratio of anti–factor Xa to anti–factor IIa, thus inhibiting the generation of thrombin at a higher point in the coagulation cascade. They also require no monitoring of anticoagulation, are administered subcutaneously, and are resistant to inhibition by activated platelets. Results of several randomized clinical trials demonstrated that low-molecular-weight heparins were at least comparable to unfractionated heparin in preventing deep vein thrombosis after surgery. The FRISC study evaluated therapy with combination aspirin and subcutaneous dalteparin sodium vs aspirin in unstable angina or non–Q wave MI. Dalteparin was given subcutaneously twice daily for up to 6 days, followed by a single injection daily for the next 35 to 45 days vs placebo injections. In 1506 randomized patients, there was a significant 6% reduction in the combined end point of death or infarction in the dalteparin group vs the aspirin group. The control group did not receive standard unfractionated heparin. In the FRISC study, a direct comparison with unfractionated heparin was carried out. Dalteparin therapy was as effective as unfractionated heparin therapy during short-term management of unstable angina or non–Q wave infarction. Prolonged treatment (≥45 days) did not confer any additional benefit over aspirin therapy alone. In the Efficacy and Safety of Subcutane Enoxaparin in Non–Q Wave Coronary Events (ESSENCE) trial, 3171 patients with rest angina or non–Q wave infarction were randomized to receive low-molecular-weight heparin (enoxaparin sodium, 1 mg/kg) subcutaneously twice daily vs continuous intravenous unfractionated heparin for 48 hours to a maximum of 8 days, with a reduction in the primary end point of death or MI at 14 days from 19.8% to 16.6%, respectively (P < .02). These statistically significant reductions in composite end points were maintained at 30 days and at 1 year. A similar positive result for enoxaparin therapy in unstable angina was recently shown in the Thrombolysis in Myocardial Infarction (TIMI) IIB trial. Why the results of the ESSENCE and TIMI XIB trials were positive whereas the FRISC study showed no added benefit for low-molecular-weight heparin therapy is speculative, but might be related to trial design or to intrinsic differences between low-molecular-weight heparin compounds (ie, the higher ratio of anti–factor Xa to anti–factor IIa of enoxaparin to dalteparin).

Direct Thrombin Inhibitors. Unlike heparins, direct thrombin inhibitors do not require a cofactor (anti–thrombin III) for their effect. There are also no circulating inhibitors, and they are not inactivated by platelet factor IV. They are also effective against circulating and clot-bound throm-
bin. Because they are resistant to binding by endothelial cells and other plasma proteins, direct thrombin inhibitors more predictably prolong the partial thromboplastin time than does unfractionated heparin.

In the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb trial,12 142 patients with an acute syndrome were randomly assigned to 72 hours of therapy with intravenous heparin or hirudin. More than 8000 patients had no ST elevation and a diagnosis of unstable angina or non-Q wave MI. The primary end point of death or nonfatal infarction or reinfarction at 30 days was insignificantly reduced by hirudin therapy from 9.8% to 8.9%. In patients without ST elevation, the results were even less impressive. On the other hand, at 24 hours there were fewer adverse events during hirudin infusion. There was no increase in the incidence of serious or lifethreatening bleeding complications, although moderate bleeding was increased with hirudin therapy. It is unclear why results of this trial were not positive at 30 days for hirudin, but it has been suggested that, like most thrombin inhibitors, rebound might occur once drug administration is stopped. In addition, hirudin therapy might not effectively block thrombin generation. Therefore, there is the potential for a small amount of thrombin to be generated in an area hidden from the effects of hirudin that might lead to subsequent thrombus formation.71

Platelet Glycoprotein IIb/IIIa Receptor Antagonists. In unstable angina, the thrombus is platelet rich, and interfering with platelet aggregation seems to be the most important strategy for reducing clinical events. This is suggested by several lines of evidence: (1) biologic and rheologic evidence of thrombus formation without total coronary occlusion, (2) angiographic data showing white thrombi or ulcerated plaques in unstable angina vs red thrombi and total occlusion in MI, (3) the effects of aspirin use in decreasing adverse events in unstable angina and the lack of efficacy of using thrombolytic agents, and (4) the importance of platelet activation and aggregation after arterial vessel wall injury in the process of subacute stent thrombosis.

In the past few years, a new class of drug has been developed that interferes with the final common pathway of platelet aggregation—exposure of the GPIIb/IIIa receptor on the platelet (Figure 3). Nearly all randomized trials in the short-term management of unstable angina have involved these competitive antagonists, which are small peptide or nonpeptide molecules that bind the receptor and block fibrinogen binding.

In 1998, data from 4 large, randomized trials16–18 (>17 000 patients) were published (Table 6). All involved infusion of one of these agents for 48 hours or longer. In 3 studies heparin was given in the placebo group, and in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM PLUS) trial, the treatment group also received heparin. In the Platelet Glycoprotein IIb/IIIa in Unstable Angina Receptor Suppression Using Integrilin Therapy (PURSUIT) study, heparin was given only at the physician’s discretion, although nearly all patients received it. The PRISM PLUS trial had an arm that received only the nonpeptide GPIIb/IIIa inhibitor (tirofiban hydrochloride), whereas another arm received tirofiban and heparin. All placebo patients received aspirin. Results of 3 of the 4 trials were positive, with a significant difference for their primary end point between the study drug and control groups. In early 1999, tirofiban and eptifibatide were approved by the Food and Drug Administration for use in patients with unstable angina or non–ST-segment elevation infarction. Because the agents are more expensive than conventional unfractionated heparin and might also increase bleeding complications, it remains unclear in which patients these agents should be used. Until the cost-benefit ratio of the newer strategies can be determined, it makes sense to limit their use in the short-term management of unstable angina to patients at high risk for adverse events. Thus, patients in the high-risk category by American College of Cardiology/American Heart Association guidelines should be included. Patients with refractory angina or recurrent rest pain after MI should also be treated with these drugs. Perhaps patients with rest pain and evidence of myocardial necrosis (elevated creatine kinase–MB or an elevated troponin) should also be considered candidates for therapy.

ANGIOGRAPHY

Role and Timing of Angiography

Because the diagnosis of unstable angina is clinical, it is not uncommon that some patients might have other
noncardiac causes for their clinical complaints of chest pain. In most studies74 of unstable angina, normal or insignificant coronary disease is found in 10% to 20% of patients. Even in TIMI IIIB,75 in which patients with rest pain and new electrocardiographic changes or a previous history of coronary disease underwent angiography, the incidence of insignificant disease was 11% to 19%. Angiography also identifies left main coronary disease or significant multivessel disease and left ventricular dysfunction that surgical therapy is likely to benefit. Therefore, coronary angiography helps identify which form of therapy is most beneficial (ie, medical therapy, interventional therapy, or bypass surgery).

When is the proper time for angiography in unstable angina? In the TIMI IIIB trial,72 patients with unstable angina or non–Q wave infarction (the latter represented about one third of the trial) were randomized to (1) an invasive strategy whereby cardiac catheterization was performed less than 48 hours after presentation or (2) an early conservative strategy whereby only patients with recurrent ischemia at rest, a positive predischarge stress thallium test result, or recurrent significant angina after discharge would undergo catheterization. In more than 1400 patients at 6 weeks, there was no significant difference between invasive (98% catheterization rates) and conservative (64% catheterization rates) strategies in the incidence of the primary end point of death or MI. The incidence of bypass surgery or angioplasty in the conservative group vs the invasive group was 50% vs 63%.

Until recently, the TIMI IIIB trial was the only randomized comparison of these 2 strategies. The high rate of catheterization and revascularization in the conservative strategy might have been responsible for lessening the benefit of an invasive strategy, as carried out in TIMI IIIB. Recently, the Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial76 randomized 920 patients within 24 to 72 hours of experiencing an acute non–Q wave MI to invasive vs conservative approaches using criteria similar to that of TIMI IIIB. Catheterization rates in VANQWISH were lower in the conservative arm (29% at 30 days) than were rates in TIMI IIIB (64% at 42 days); rates in the invasive strategy arm were similar to those in TIMI IIIB (>95%). Revascularization procedures in VANQWISH were 44% in the invasive arm vs 33% in the conservative arm. Mortality or nonfatal MI (the primary end point) or mortality alone was significantly higher in the invasive strategy at hospital discharge, at 1 month, and at 1 year (P < .05 for all). In this trial, the difference in mortality between the 2 strategies was primarily related to the higher mortality rate for coronary bypass surgery in the invasive arm (11.6%) than in the conservative arm (3.4%).

Similar data questioning the role of early catheterization and revascularization in unstable angina and non–Q wave infarction was reported in the Organisation to Assess Strategies for Ischaemic Syndromes (OASIS) Registry.77 Nearly 8000 consecutive patients with unstable angina or MI without ST-segment elevation were prospectively recruited from 95 hospitals in 6 countries and followed up for 6 months. Overall, 48% underwent angiography and 33% underwent a revascularization procedure. Hospitals with vs without catheterization facilities had higher catheterization (60% vs 30%) and revascularization (40% vs 20%) rates during follow-up. There was no significant difference in cardiovascular mortality or MI among countries, and a lower mortality rate was present in hospitals without vs with routine catheterization facilities (10.6% vs 12.5%; P = .05) at 6 months.

How does one interpret these new data, which question the role of an early invasive approach in unstable angina? Surely, the data cast some doubt on the usual practice of early angiography commonly performed in many countries, such as the United States. However, there are limitations to these new studies. The surgical mortality rate in VANQWISH was high, and multivessel disease was routinely managed with bypass surgery rather than con-
Complication rate in refractory and postinfarction angina, with a slightly lower success rate compared with patients already stabilized. In comparison, studies during this same period in angioplasty in stable angina showed higher success rates and lower complication rates than all 3 groups of patients with unstable angina (Table 7). In the 1990s, use of adjunctive agents like abciximab (ReoPro, c7E3 Fab; Centocor Inc, Malvern, Pa), in addition to intracoronary stents, has markedly increased success rates and decreased short-term complications. Angiographic success can now be achieved in many laboratories in more than 95% of lesions. Patients with significant multivessel disease can be revascularized in a single setting, or the culprit lesion can be intervened on early and the remaining lesions at a later date.

Before the abciximab era, there was much enthusiasm for using intracoronary thrombolytic agents during intervention for unstable angina. Results of several uncontrolled studies suggested benefit in short-term closure or with high-risk procedures. To ascertain whether there was a role for prophylactic urokinase therapy during angioplasty in unstable angina, the Thrombolysis and Angioplasty in Unstable Angina (TAUSA) trial was performed. This randomized, multicenter, double-masked, placebo-controlled trial ascertainment whether intracoronary urokinase therapy improved the short-term results of angioplasty and decreased the inhospital complication rate. The major findings of the trial in nearly 500 randomized patients were a higher short-term closure rate in patients treated with urokinase and a significantly higher composite clinical end point (MI, bypass surgery, or ischemia) compared with the placebo group. As a result of this trial and the equally dismal results of systemic or intracoronary thrombolytic therapy in the short-term management of unstable angina, emphasis has turned to the role of platelet activation and the use of newer and more powerful antiplatelet agents to prevent complications during percutaneous intervention.
Two large trials evaluated direct thrombin inhibitors during angioplasty, the Hirulog Angioplasty Trial and the Hirudin Trial (HELVETICA), which directly compared the newer agents with heparin. In the hirulog trial, bivalirudin (Hirulog; Biogen Inc, Cambridge, Mass) was given usually for 24 hours during and after angioplasty, whereas in the hirudin trial, patients received either intravenous hirudin for 24 hours during or after angioplasty or intravenous hirudin plus 3 days of subcutaneous hirudin after intervention. Results of the hirulog trial revealed no overall benefit for hirulog vs heparin therapy in diminishing adverse clinical events after angioplasty, although there was a significant reduction in adverse clinical events in patients undergoing intervention for postinfarction unstable angina with hirulog. In the HELVETICA trial, hirudin therapy decreased the incidence of adverse clinical events at 96 hours after angioplasty vs heparin therapy. However, at 7 months there was no difference between groups in the incidence of recurrent symptoms, clinical events, or restenosis rates.

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Several drugs of this kind have been evaluated (Table 8). The most impressive results with adjunctive therapy during intervention have been with the use of abciximab—the chimeric monoclonal antibody against the platelet GPIIb/IIIa receptor—a noncompetitive inhibitor of this receptor that remains on the platelet until the platelet is removed from the circulation. Furthermore, significant amounts of abciximab are still present in the circulation 7 to 10 days after administration. Thus, the platelet inhibitory effects are more prolonged compared with the competitive blockers after therapy is terminated. In addition, compared with the competitive blockers, abciximab binds to the GPIIb/IIIa receptor and the vitronectin receptor on smooth muscle cells and platelets. This latter receptor might be important in smooth muscle cell proliferation. However, unlike the synthetic, competitive inhibitors of the GPIIb/IIIa receptor, abciximab has the potential to elicit an antibody response, possibly because of its murine origin or its comparatively large size. Bleeding risk might also be higher because of the more prolonged inhibition of platelet function than with other compounds.

In the Evaluation of 7E3 for the Prevention of Ischemic Complications trial, a subgroup of nearly 500 patients with unstable angina was randomized. The composite 30-day end point of death, MI, or emergency revascularization was reduced by 62% in the bolus plus 12-hour infusion group vs the placebo group (4.5% vs 12.8%; P = .01). This reduction was even greater than that seen in the entire trial (62% vs 35% with abciximab). However, abciximab therapy increased bleeding. Because bleeding events were higher in smaller patients but efficacy was not affected by body size, a second trial was initiated to evaluate whether weight adjustment of the heparin administered with abciximab might retain efficacy while decreasing bleeding. In the Evaluation in PTCA to Improve Long-Term Outcome With Abciximab GPIIb/IIIa Blockade (EPILOG) trial, such a result was obtained. In patients given weight-adjusted heparin plus abciximab, there were significant decreases in adverse end points without significant increases in bleeding rates compared with those given placebo. In the third reported study using abciximab in unstable patients, the Reduction of Recurrent Ischemia With Abciximab During Continuous ECG-Ischemia Monitoring in Patients With Unstable Angina Refractory to Standard Treatment (CAPTURE) trial randomized 1265 patients with refractory unstable angina after angiography to abciximab vs placebo therapy begun 18 to 24 hours before their scheduled intervention. Drug administration was continued until 1 hour after intervention. After an interim analysis of 1050 patients (1400 patients were randomized and 1265 were ultimately treated), the trial was stopped because efficacy was significantly enhanced with abciximab therapy. Infarction rates were lower in the abciximab group vs the placebo group before angioplasty (0.6% vs 2.1%; P = .03) and during angioplasty (2.6% vs 5.5%; P = .009). Bleeding was

### Table 8. GPIIb/IIIa Antagonists During Coronary Interventions

<table>
<thead>
<tr>
<th>Trial†</th>
<th>Patients, No.</th>
<th>Heparin Bolus</th>
<th>Agent</th>
<th>30-d End Point, %‡</th>
<th>Major Bleeding, %</th>
<th>6-mo End Point, %§</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPIC59</td>
<td>2099</td>
<td>10 000-12 000 IU</td>
<td>Abciximab</td>
<td>8.3; 12.8</td>
<td>14; 7</td>
<td>27.0; 35.1</td>
</tr>
<tr>
<td>EPLOG83</td>
<td>2792</td>
<td>70 or 100 U/kg</td>
<td>Abciximab</td>
<td>5.2; 5.4</td>
<td>2; 3.5</td>
<td>22.8; 22.3</td>
</tr>
<tr>
<td>CAPTURE84</td>
<td>1265</td>
<td>≤100 U/kg</td>
<td>Abciximab</td>
<td>11.3; 15.9</td>
<td>3.8</td>
<td>19; 31</td>
</tr>
<tr>
<td>IMPACT I88</td>
<td>4010</td>
<td>100 U/kg</td>
<td>Epifibatide</td>
<td>9.2; 9.9</td>
<td>11.4</td>
<td>5.1; 5.2</td>
</tr>
<tr>
<td>RESTORE89</td>
<td>2139</td>
<td>150 U/kg (≤10 000 U)</td>
<td>Tirofiban</td>
<td>8</td>
<td>10.5</td>
<td>5.3</td>
</tr>
</tbody>
</table>

*GP indicates glycoprotein; MI, myocardial infarction; and NA, not applicable.
†See the “New Adjunctive Antithrombotic Therapy for Intervention in Unstable Angina” section for expansion of trial names. EPIC indicates Evaluation of FE3 for the Prevention of Ischemic Complications.
‡Death, MI, or urgent revascularization.
§Death, MI, or any revascularization, except IMPACT II data (only death or MI).
¶P < .05 vs placebo. Double entries signify 2 subgroups within the study who received G P.
‖By treatment, 9.1% received analysis (P = .05 vs placebo).
higher than in the EPILOG trial but less than in the Evaluation of 7E3 for the Prevention of Ischemic Complications trial.92

Other GPIIb/IIIa inhibitors have been studied. In the Randomized Ef-
cacy Study of Tirofiban for Out-
comes and Restenosis (RESTORE)93 and Integrin to Minimise Platelet Ag-
gregation and Coronary Thrombo-
sis (IMPACT) II94 trials, the competi-
tive GPIIb/IIIa agents tirofiban and 
eptifibatide, respectively, were used. 
Both trials demonstrated beneficial re-
sults vs placebo therapy, although 
they were not as significant as those 
seen with abciximab therapy. The less 
than optimal benefit seen in the 
IMPACT II trial with eptifibatide 
therapy might have been related to an 
insufficient dose of drug to effect-
tively block the GPIIb/IIIa receptor. 
The inhibitory effects of eptifibatide 
on the receptor are strongly affected 
by plasma calcium levels. Use of cit-
rates as an anticoagulant for platelet 
aggregation studies might have arti-
ficially overestimated the in vivo an-
tiplatelet effects of eptifibatide therapy 
in this trial because citrate binds cal-

Surgical Revascularization in Unstable Angina

Established indications for aorto-
coronary bypass surgery include ob-
structive (>50%) left main coronary 
disease or 3-vessel disease with decreased left ventricular systolic 
function.101-104 These have been es-

tablished from prospective, random-
tized trials that found surgery to be 
superior to medical therapy in stable 
and unstable patients. Two large, 
randomized trials105-108 of bypass sur-
gery vs medical therapy in unstable 
angina have been performed. The 
Veterans Administration Cooperative 
Study randomized 468 patients. 
Although 3-year mortality was simi-
lar in both groups, patients with 
3-vessel disease, alone and with de-
creased ventricular function (<50% 
ejection fraction), had a survival ad-
vantage with surgery. The high op-
erative mortality and limited use of 
the internal thoracic artery as a by-
pass conduit limited the value of this 
study. Medical therapy was also sub-
optimal by today's standards be-
cause antithrombotic drugs were not 
used. In the National Heart, Lung, 
and Blood Institute trial105,106 of by-
ypass surgery vs medical therapy in 
unstable angina performed in the 
early 1970s, there was no benefit for 
surgery over medical therapy in the 
hospital or in the 1- and 2-year in-
cidence of death or MI. The long-
term results of both studies were 
clouded by the high crossover rate 
from medical therapy to bypass sur-
gery, which was 31% at 2 years in the 
National Heart, Lung, and Blood 
Institute Study, and 34% in the Veter-
ans Administration Study. 

With preserved left ventricular 
function, the presence of significant 
left main stenosis still warrants sur-

Stenting in Unstable Angina

Stents are commonly used in un-
stable angina, although no random-
ized trials, to our knowledge, have 
shown benefit in this group, per se. 
However, a recently published re-

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Despite reservations regarding 
the immediate postoperative 
course of unstable angina in pa-
ients undergoing aortocoronary by-
pass surgery, long-term outcome 
seems favorable. Rahimtoola et al112 
reported the 5- and 10-year actu-
arial survival of patients with un-
stable rest angina after MI to be 92% 
and 83%, respectively, similar to the 

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portant pathogenic mechanism is an intracoronary platelet-rich thrombus on a disrupted, ulcerated, or eroded atherosclerotic plaque leading to partial coronary occlusion. Medical therapy is aimed at preventing total coronary occlusion (antithrombotic and anticoagulant drug therapy), reducing myocardial oxygen demands, and preventing vasospasm (nitrate, β-adrenergic blocking agent, and sometimes calcium channel blocker therapy). New antithrombotic drug approaches have been developed that seem somewhat more effective than standard antithrombotic drug therapy, but at a higher cost. Angiography is often performed and is useful in identifying patients in need of interventional therapy by percutaneous techniques or bypass surgery, although newer studies question its routine use. Furthermore, because this clinical diagnosis is so common and because of the enormous cost of hospitalization, strategies are being developed to better triage patients into those in whom a noninvasive approach would be appropriate vs those in whom the more aggressive approach is warranted.

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