

*Medical Progress***UNSTABLE ANGINA PECTORIS**

YEREM YEGHIAZARIANS, M.D.,
 JOEL B. BRAUNSTEIN, M.D., ARMAN ASKARI, M.D.,
 AND PETER H. STONE, M.D.

UNSTABLE angina accounts for more than 1 million hospital admissions annually¹; 6 to 8 percent of patients with this condition have nonfatal myocardial infarction or die within the first year after diagnosis.^{2,3} Various definitions of unstable angina have been proposed, but in 1989, Braunwald devised a classification system to ensure uniformity of categorization, as well as diagnostic and prognostic information.⁴ This system is used to classify angina according to the severity of the clinical manifestation, defined as acute angina while at rest (within the 48 hours before presentation), subacute angina while at rest (within the previous month but not within the 48 hours before presentation), or new onset of accelerated (progressively more severe) angina; the clinical circumstances in which unstable angina develops, defined as either angina in the presence or absence of other conditions (e.g., anemia, fever, hypoxia, tachycardia, or thyrotoxicosis) or angina within two weeks after an acute myocardial infarction; and whether or not electrocardiographic abnormalities are present. Given the heterogeneity of the clinical manifestations of unstable angina, it is not surprising that the prognosis is quite variable.

Recently, the term “acute coronary syndromes” has been used to describe the spectrum of conditions that includes unstable angina, non-Q-wave myocardial infarction (which generally presents without ST-segment elevation), and Q-wave myocardial infarction (which generally presents with ST-segment elevation). Patients with unstable angina and those with non-Q-wave myocardial infarction often present in a similar manner, and the distinction between the two conditions can be made only many hours or days lat-

er, when the results of cardiac-enzyme tests become available. Since many of the clinical trials discussed in this article enrolled patients before the enzyme values were available, the studies actually investigate both clinical entities. In this article, we will focus on the pathophysiology and management of unstable angina and distinguish it from non-Q-wave myocardial infarction when possible and appropriate.

PATHOGENESIS**Initiation of the Cascade of Plaque Fissure and Rupture**

Disruption of a formed plaque is a complex pathologic process that is central to the initiation of the acute coronary syndromes. Sudden total or near-total arterial occlusion frequently develops in arteries that previously appeared to have minimal stenosis.⁵⁻⁸ Two thirds of arteries with plaques that rupture and in which a totally occlusive thrombus subsequently develops have stenosis of 50 percent or less before plaque rupture, and in 97 percent of patients, stenosis is initially less than 70 percent.⁵ The arterial lesions of patients with unstable angina frequently have complex, eccentric morphologic features on coronary angiography; such features have been found to represent ruptured plaque with superimposed thrombus.⁷⁻¹¹

Mature plaques are made up of two main components: a lipid-rich core and a meshwork of extracellular-matrix proteins that form a fibrous cap.¹²⁻¹⁴ The presence of large, eccentric lipid pools and infiltration of foam cells are the characteristics of the lipid core most frequently associated with fissured or ruptured plaques.¹³⁻¹⁵ The majority of these lesions rupture at the sites of greatest mechanical stress, notably the junction of the plaque cap and the adjacent normal intima or the shoulder regions of the lipid pool.^{13,16} Fissures occurring at weak cap sites and not at sites subject to the greatest mechanical stresses are thought to be initiated by proteinases secreted by macrophages that enzymatically degrade the fibrous cap¹⁷⁻²¹ (Fig. 1).

Acute Thrombosis and Platelet Aggregation

Local thrombosis occurring after plaque disruption results from complex interactions among the lipid core, smooth-muscle cells, macrophages, and collagen.²²⁻²⁴ The lipid core is the most potent substrate for platelet-rich thrombus formation,²² and both smooth-muscle and foam cells within the core correlate with the expression of tissue factor in unstable plaques.²³ Once exposed to blood, tissue factor interacts with factor VIIa to initiate a cascade of enzymatic reactions resulting in the local generation of thrombin and deposition of fibrin. Because of the delicate equilibrium between thrombosis and endog-

From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston. Address reprint requests to Dr. Stone at the Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at pstone@rics.bwh.harvard.edu.

©2000, Massachusetts Medical Society.

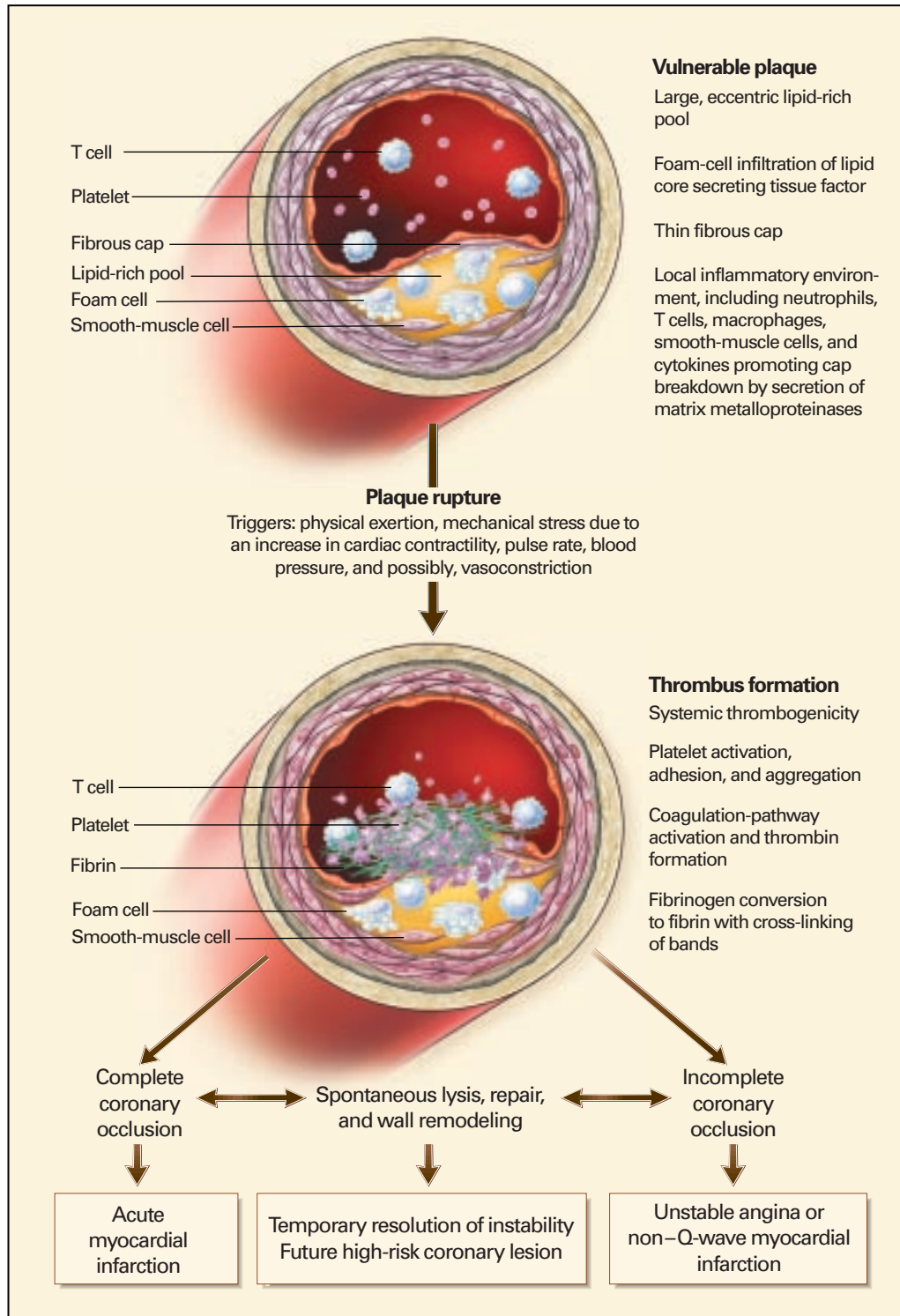


Figure 1. Pathophysiologic Events Culminating in the Clinical Syndrome of Unstable Angina.

Numerous physiologic triggers probably initiate the rupture of a vulnerable plaque. Rupture leads to the activation, adhesion, and aggregation of platelets and the activation of the clotting cascade, resulting in the formation of an occlusive thrombus. If this process leads to complete occlusion of the artery, then acute myocardial infarction with ST-segment elevation occurs. Alternatively, if the process leads to severe stenosis but the artery nonetheless remains patent, then unstable angina occurs.

enous thrombolysis, some acute vascular lesions resolve when fissures are repaired.²⁵

As part of the response to any type of disruption of the endothelial wall, platelets aggregate and release granular contents that further propagate platelet aggregation, vasoconstriction, and thrombus formation (Fig. 1).²⁵ Systemic factors and inflammation also contribute to alterations in the hemostatic and coagulation pathways and may play a part in the initiation of the intermittent thrombosis that is characteristic of unstable angina.²⁶⁻²⁸ Inflammatory acute-phase reactants, cytokines, chronic infections, and catecholaminergic surges may provide a systemic stimulus for enhancing production of tissue factor, procoagulant activity, or platelet hyperaggregability (Fig. 1).^{29,30}

Coronary Vasospasm

Although not central to the underlying pathogenesis of the acute coronary syndromes, episodic vasospasm may contribute to vascular instability by altering preexisting coronary plaques, which causes intimal disruption and penetration of macrophages or aggregation of platelets. These processes — in turn — may lead to the formation of foam cells and the proliferation of smooth-muscle cells.³¹⁻³⁶

Erosion of Coronary Plaque without Rupture

An alternative mechanism of luminal narrowing may involve the rapid proliferation and migration of smooth-muscle cells in response to endothelial injury.³⁷ Rapid conformational changes in the shape and size of a lesion due to the expansion of the smooth muscle may lead to the relatively abrupt onset of luminal narrowing and symptoms of ischemia.³⁸ Current techniques cannot clearly distinguish between patients whose acute symptoms are due to conventional plaque rupture and those whose symptoms are due to minor erosions or conformational changes.

MEDICAL THERAPY

Antiplatelet Therapy

Aspirin

Aspirin blocks platelet cyclooxygenase by irreversible acetylation, thus preventing the formation of thromboxane A₂. The Veterans Administration Cooperative Study,³⁹ the Canadian Multicenter Trial,⁴⁰ and the Montreal Heart Institute Study⁴¹ confirmed that aspirin reduces the risk of death from cardiac causes and fatal and nonfatal myocardial infarction by 51 to 72 percent in patients presenting with unstable angina. Given aspirin's ability to inhibit platelet aggregation over a wide range of doses,⁴²⁻⁴⁶ treatment with an initial dose of at least 160 mg per day, followed by a dose of 80 to 325 mg per day for an indefinite period,⁴⁷ is currently recommended, with the understanding that higher doses of aspirin are associated with more frequent gastrointestinal side effects. Aspirin is limited in its ability to reduce plate-

let aggregation since it provides insufficient blockade of the platelet activation that is induced by adenosine diphosphate (ADP), collagen, and low concentrations of thrombin and provides no inhibition of platelet adhesion.

Ticlopidine

Ticlopidine, a thienopyridine derivative, appears to be an effective second-line alternative to aspirin in the treatment of unstable angina and also has a role as adjunctive therapy with aspirin to prevent thrombosis after the placement of intracoronary stents. By a mechanism different from that of aspirin, ticlopidine blocks both ADP-mediated platelet aggregation and transformation of the platelet fibrinogen receptor into a high-affinity form.^{25,48} The Studio della Ticlopidina nell'Angina Instabile trial demonstrated a 46.3 percent reduction in the incidence of the primary composite end point of death and nonfatal myocardial infarction at six months (incidence, 7.3 percent for those receiving ticlopidine vs. 13.6 percent for those receiving placebo; $P=0.009$) in patients treated with ticlopidine in addition to conventional therapy.⁴⁸ Clinical practice guidelines⁴⁷ suggest that ticlopidine may be substituted for aspirin in patients with hypersensitivity to aspirin or gastrointestinal intolerance, although the 2.4 percent incidence of serious granulocytopenia, typically reversible after the discontinuation of the drug, limits its widespread use.

Clopidogrel

Clopidogrel is a new thienopyridine derivative related to ticlopidine. It affects the ADP-dependent activation of the glycoprotein IIb/IIIa complex and effectively inhibits platelet aggregation.⁴⁹ Clopidogrel has fewer side effects than ticlopidine and has not been reported to cause neutropenia. In a 1996 trial, 19,185 patients with atherosclerotic vascular disease, manifested as ischemic stroke, myocardial infarction, or symptomatic peripheral vascular disease, were randomly assigned to receive either clopidogrel or aspirin.⁴⁹ After a mean follow-up period of 1.9 years, clopidogrel proved to be more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or death from vascular disease (risk, 5.3 percent vs. 5.8 percent; $P=0.04$). However, a lack of benefit was shown in an independent analysis of the subgroup with myocardial infarction (risk, 5.0 percent vs. 4.8 percent; $P=0.66$).

In addition, the combination of clopidogrel and aspirin appears to be a promising and safer alternative to the combination of ticlopidine and aspirin in preventing coronary-stent thrombosis.⁵⁰

Platelet Glycoprotein IIb/IIIa Receptor Antagonists

Unlike antiplatelet agents that target only one of many individual pathways involved in platelet aggregation, antagonists of glycoprotein IIb/IIIa, a re-

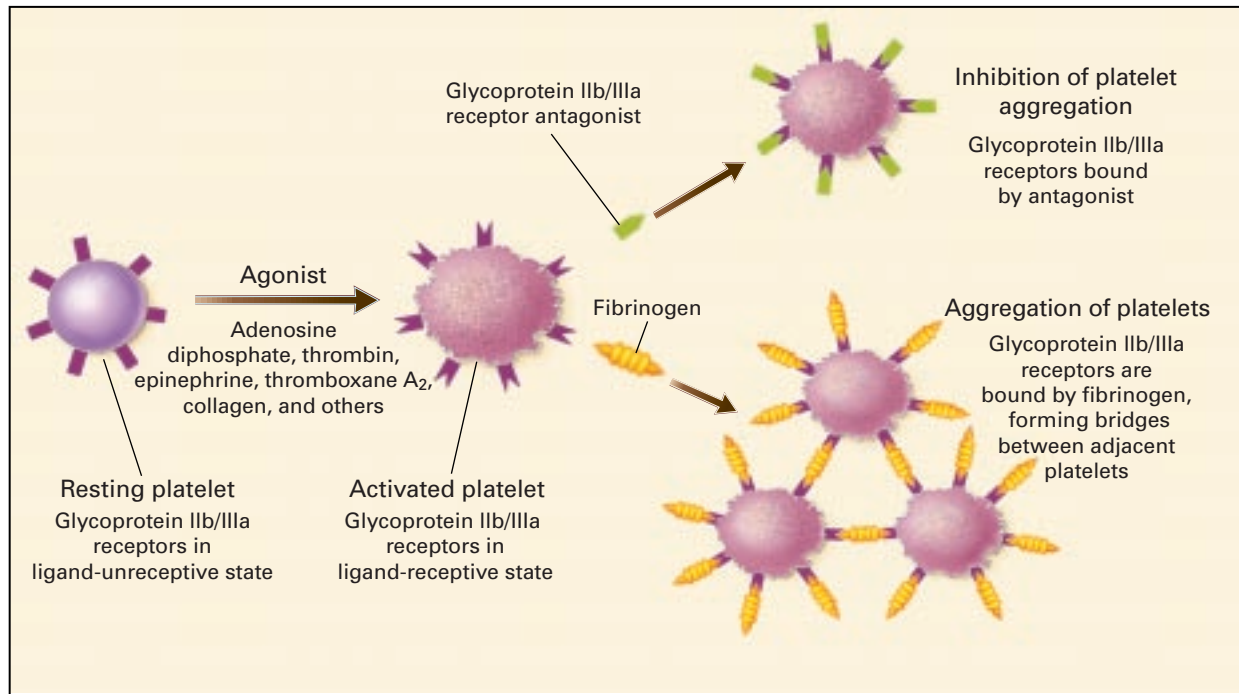


Figure 2. Processes of Platelet Activation and Aggregation and Inhibition of Platelet Aggregation by Inhibitors of Glycoprotein IIb/IIIa Receptors.

Activation causes changes in the shape of platelets and conformational changes in glycoprotein IIb/IIIa receptors, transforming the receptors from a ligand-unreceptive state to a ligand-receptive state. Ligand-receptive glycoprotein IIb/IIIa receptors bind fibrinogen molecules, which form bridges between adjacent platelets and facilitate platelet aggregation. Inhibitors of glycoprotein IIb/IIIa receptors also bind to glycoprotein IIb/IIIa receptors, blocking the binding of fibrinogen and thus preventing platelet aggregation. Adapted from Madan et al.,⁵¹ with the permission of the publisher.

ceptor on the platelet for adhesive proteins such as fibronectin and von Willebrand factor (Fig. 2),⁵² maximally inhibit the final common pathway involved in platelet adhesion, activation, and aggregation. Three classes of glycoprotein IIb/IIIa inhibitors have been developed: murine-human chimeric antibodies (e.g., abciximab), synthetic peptide forms (e.g., eptifibatid), and synthetic nonpeptide forms (e.g., tirofiban and lamifiban).^{51,52}

Use as an adjunct to invasive coronary interventions. The glycoprotein IIb/IIIa antagonists consistently reduce the 30-day relative risk of the composite end point of death, myocardial infarction, or the need for repeated revascularization by 22 to 56 percent when they are administered with unfractionated heparin and aspirin, but they have no effect on mortality alone.⁵³⁻⁶⁰ The magnitude of benefit varied among the trials.

In the Evaluation of 7E3 for the Prevention of Ischemic Complications trial,⁵³ patients at high risk for abrupt vessel closure were randomly assigned to receive a bolus of abciximab alone, a bolus of abciximab followed by a 12-hour infusion, or placebo. As compared with placebo, treatment with the abciximab bolus plus infusion resulted in a 35 percent reduction

in the incidence of the composite end point at 30 days (8.3 percent vs. 12.8 percent, $P=0.008$), a 23 percent reduction at 6 months (27 percent vs. 35.1 percent, $P=0.001$), and a 13 percent reduction at 3 years (41.1 percent vs. 47.2 percent, $P=0.009$),^{51,53-55} although the rate of major bleeding was twice as high in this group as in the placebo group. Mortality at 30 days was similarly low (1.7 percent) in each group, but at 3 years, evolving myocardial infarction or unstable angina was 60 percent less common (5.1 percent vs. 12.7 percent) among the high-risk patients who received the abciximab bolus plus infusion than among those who received placebo.

Eptifibatid at two doses was compared with placebo in patients scheduled to undergo an elective, urgent, or emergency percutaneous procedure.⁵⁶ The rates of the composite outcome at 30 days tended to be more favorable in the eptifibatid groups (incidence, 9.2 percent for those receiving the lower dose, 9.9 percent for those receiving the higher dose, and 11.4 percent for those receiving placebo; $P=0.06$), but the mortality rate was similarly low in each group (0.5 percent, 0.8 percent, and 1.1 percent, respectively).⁵⁶

Tirofiban was administered as a bolus followed by infusion to patients at high risk for abrupt vessel closure,⁵⁷ and although the drug reduced the incidence of the composite end point by 39 percent at 2 days as compared with placebo (2.7 percent vs. 4.4 percent, $P=0.005$), there was no significant effect at 30 days (8.0 percent vs. 10.4 percent, $P=0.052$). The mortality rates were similar in the two groups at 30 days (tirofiban, 0.8 percent; placebo, 0.7 percent) and at 60 days (1.8 percent and 1.4 percent, respectively).³

Recent studies have tried to enhance the safety of these agents and identify the patients most likely to benefit from their use. As compared with placebo, abciximab administered with low-dose unfractionated heparin (initial bolus, 70 U per kilogram of body weight) was as effective as abciximab plus a standard dose of unfractionated heparin (initial bolus, 100 U per kilogram) in reducing the incidence of the 30-day composite end point (5.2 percent for abciximab plus low-dose unfractionated heparin vs. 5.4 percent for abciximab plus the standard dose of unfractionated heparin and 11.7 percent for placebo plus the standard dose of unfractionated heparin, $P<0.001$) and caused less bleeding than abciximab plus the standard dose of unfractionated heparin.⁵⁸ These benefits were sustained at one year.⁶¹ However, the mortality rates were not significantly improved at 30 days (0.4 percent vs. 0.3 percent and 0.8 percent, respectively; P not significant) or at 1 year (1.8 percent vs. 1.7 percent and 2.6 percent, P not significant).⁶¹ The greatest benefit of abciximab may be in high-risk patients with refractory unstable angina and elevated troponin levels.⁶²

Use as primary medical therapy. Treatment with the combination of tirofiban, aspirin, and unfractionated heparin resulted in a significant reduction in the incidence of new myocardial infarction or death, as compared with the combination of aspirin and unfractionated heparin, at 7 days (4.9 percent vs. 8.3 percent, $P=0.006$) and at 30 days (8.7 percent vs. 11.9 percent, $P=0.03$), but not at 6 months (12.3 percent vs. 15.3 percent, $P=0.06$).⁶³ The six-month mortality rates (6.9 percent vs. 7.0 percent, $P=0.85$) and the rates of major bleeding complications were similar in the two groups. The Platelet Receptor Inhibition in Ischemic Syndrome Management study found a 36 percent lower 30-day mortality rate among patients treated with tirofiban and aspirin than among those treated with unfractionated heparin and aspirin (2.3 percent vs. 3.6 percent, $P=0.02$),⁶⁴ but the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms study did not show a benefit with tirofiban and aspirin in the absence of unfractionated heparin.⁶³

The largest study of unstable angina and non-Q-wave myocardial infarction was the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy trial, which showed that the combination of eptifibatide, unfractionated

heparin, and aspirin significantly reduced the incidence of death or myocardial infarction at 30 days, as compared with the combination of unfractionated heparin and aspirin (incidence, 14.2 percent vs. 15.7 percent; $P=0.04$), although there was no significant effect on mortality (3.5 percent vs. 3.7 percent, $P=0.53$).⁶⁵ Although the benefits became apparent after only 96 hours of therapy, these reductions were observed only in men. In addition, eptifibatide was associated with increased bleeding and a more frequent need for transfusions. Moreover, among the patients who underwent revascularization, there was a significant reduction in the incidence of the composite end point even before the procedure was performed (incidence, 1.7 percent vs. 5.5 percent; $P<0.001$). This difference was not significant 30 days after the intervention (10.2 percent vs. 12.4 percent, $P=0.24$).

Similar beneficial effects of other glycoprotein IIb/IIIa antagonists in the treatment of unstable angina have recently been reported.⁶³⁻⁶⁶ These and other emerging data suggest that early, potent antiplatelet therapy leads to better outcomes. Several clinical issues are still unresolved, however, including the dosage that provides the maximal platelet inhibition and entails the minimal risk of bleeding, the duration of therapy that provides the best long-term clinical outcome, the route of administration that optimizes the bioavailability of the drugs, the most effective agent overall, and the optimal combination of drugs with low-molecular-weight heparins, thrombolytic drugs, or other agents.

Antithrombin Therapy

Unfractionated Heparin

Unfractionated heparin is a glycosaminoglycan made up of polysaccharide chains ranging in molecular weight from 3000 to 30,000.⁶⁷ These polysaccharide chains bind to antithrombin III and cause a conformational change that accelerates the inhibition of thrombin and factor Xa by antithrombin III. A meta-analysis showed a 33 percent lower incidence of myocardial infarction or death among patients who received combination therapy with aspirin and unfractionated heparin than among those who received aspirin alone.⁶⁸ Current practice guidelines support the use of the combination of unfractionated heparin and aspirin for the treatment of unstable angina.⁴⁴ The maximal duration of continuous infusion in patients without symptoms is 48 hours after admission, since longer treatment may result in a higher incidence of death or myocardial infarction than shorter treatment⁶⁹; if symptoms persist, however, the infusion is continued until an invasive intervention can be performed.

Despite its extensive use in treating the acute coronary syndromes, unfractionated heparin has the disadvantage of variability in its dose-response curve. This variability is due to the fact that unfractionated

TABLE 1. PREPARATIONS OF LOW-MOLECULAR-WEIGHT HEPARIN AND THEIR ANTI-FACTOR Xa:ANTI-FACTOR IIa RATIOS.*

PREPARATION	MEAN MOLECULAR WEIGHT	ANTI-FACTOR Xa: ANTI-FACTOR IIa RATIO
Ardeparin	6000	1.9
Dalteparin	6000	2.7
Enoxaparin	4200	3.8
Nadroparin	4500	3.6
Reviparin	4000	3.5
Tinzaparin	4500	1.9

*Adapted from Weitz.⁶⁷

heparin binds competitively to plasma proteins other than antithrombin.⁶⁶ Both the resistance of clot-bound thrombin to inhibition by heparin and the sensitivity of heparin to platelet factor 4 contribute to a further reduction in the antithrombotic efficacy of the drug. In addition, the potential occurrence of the idiosyncratic and unpredictable serious side effect of heparin-induced thrombocytopenia creates a compelling need for other antithrombin agents.⁷⁰

Low-Molecular-Weight Heparins

Unlike unfractionated heparin, preparations of low-molecular-weight heparin have in common a predictable pharmacokinetic profile, high bioavailability, a long plasma half-life, and an easy means of administration (subcutaneous injection) without the need to monitor activated partial-thromboplastin time.⁶⁷ Short-chain (<18 saccharides) fragments of low-molecular-weight heparin have been formulated, with varying anti-factor Xa:anti-factor IIa ratios (Table 1). Higher ratios of anti-factor Xa to anti-factor IIa activity provide for potent inhibition of thrombin generation as well as inhibition of thrombin activity (Fig. 3).

The efficacy of low-molecular-weight heparins in the treatment of unstable angina has been variable, depending on the particular preparation used.⁷²⁻⁷⁶ The varying efficacy probably reflects differences in the anti-factor Xa:anti-IIa ratios.⁵³ Low-ratio preparations are associated with outcome data that are similar to those of unfractionated heparin, whereas high-ratio preparations produce superior results. The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events study demonstrated that the incidence of the composite end point of death, myocardial infarction, or recurrent angina was lower with enoxaparin than with unfractionated heparin, at 14 days (incidence, 16.6 percent vs. 19.8 percent; $P=0.016$) and at 30 days (19.8 percent vs. 23.3 percent, $P=0.016$), although there was no significant difference in the rate of death alone (2.2 percent vs. 2.3 percent at 14 days, $P=0.92$; 2.9 percent vs. 3.6

percent at 30 days, $P=0.25$).⁷⁷ The recent Thrombolysis in Myocardial Infarction (TIMI) 11B study confirmed that enoxaparin is superior to unfractionated heparin in reducing the composite end point of myocardial infarction and emergency revascularization without causing a significant increase in the rate of major bleeding. There was, however, no significant difference in mortality.⁷⁸

There are a number of unresolved issues regarding the use of low-molecular-weight heparins in the treatment of acute coronary syndromes, including the choice of agents, appropriate dosages,⁷⁹ timing (short-term vs. long-term), and cost effectiveness. The value of these agents in combination with glycoprotein IIb/IIIa receptor antagonists or thrombolytic therapy is an especially important issue, since such combinations may lower the overall risks of bleeding and improve clinical outcomes.

Direct Antithrombins

Unlike indirect thrombin inhibitors (e.g., unfractionated heparin or low-molecular-weight heparins), which bind both factor IIa and factor Xa, the direct antithrombins inhibit thrombin formation in a manner that is independent of antithrombin III activity and primarily decrease thrombin activity (Fig. 3). Direct antithrombins, which include hirudin, hirulog, argatroban, efegatran, and inogatran, may inhibit clot-bound thrombin more effectively than indirect thrombin inhibitors.⁶⁷ In the recent Organisation to Assess Strategies for Ischemic Syndromes trial, therapy with recombinant hirudin in patients with acute myocardial ischemia without ST-segment elevation seemed to be superior to therapy with unfractionated heparin in preventing death, myocardial infarction, and refractory angina, both at 72 hours and at 7 days (incidence of the composite end point at 7 days, 5.6 percent in the hirudin group and 6.7 percent in the unfractionated-heparin group; $P=0.01$), although there was a higher rate of major bleeding in the hirudin group (1.2 percent vs. 0.7 percent, $P=0.01$).⁸⁰ In contrast, the effect of inogatran on the composite end point of death, myocardial infarction, or refractory angina was not significantly different from that of unfractionated heparin.⁸¹ To date, the efficacy and safety of direct antithrombins as primary antithrombotic therapy in patients with unstable angina have not been widely accepted.

Warfarin

Warfarin monotherapy appears to be at least as effective after myocardial infarction as aspirin in preventing death or recurrent myocardial infarction,⁸² but whether warfarin and aspirin as combination therapy for the acute coronary syndromes actually improve prognosis remains unclear. The Antithrombotic Therapy in Acute Coronary Syndromes study showed that combination therapy with aspirin and anticoagulants (heparin followed by warfarin, with a

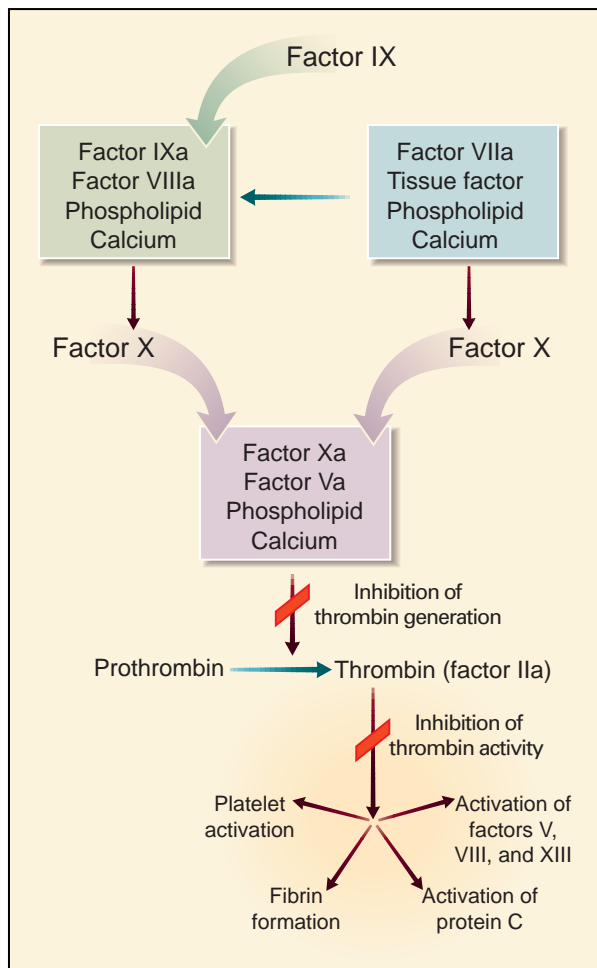


Figure 3. Role of Factors Xa and IIa (Thrombin) in Coagulation. Indirect antithrombins, such as low-molecular-weight heparins, bind both factors IIa and Xa, thus reducing both thrombin activity and thrombin generation. In contrast, direct thrombin inhibitors are less efficacious clinically, because they inhibit the action of thrombin (factor IIa) only. Adapted from Eisenberg,⁷¹ with the permission of the publisher.

target international normalized ratio [INR] of 2.0 to 3.0) for 12 weeks resulted in a reduction of approximately 60 percent in the primary end points of recurrent angina with electrocardiographic changes, myocardial infarction, death, or all three at 14 days, as compared with aspirin alone.⁸³ A nearly 50 percent reduction in ischemic events continued to be observed at three months, and the rate of bleeding complications was only slightly higher in the combination-therapy group than in the aspirin-alone group.⁸³ The Coumadin Aspirin Reinfarction Study, however, failed to show any additional benefit from a combination of aspirin plus fixed-dose warfarin (1 or 3 mg, not adjusted to a prothrombin time), as compared with aspirin alone.⁸⁴

More recently, attention has turned to moderate-

intensity warfarin therapy plus aspirin as treatment for the acute coronary syndromes. Combination therapy with a target INR of 2.0 to 2.5 for 10 weeks after the initial presentation of unstable angina produced a significantly better clinical and angiographic outcome than aspirin monotherapy, but there was no difference in the frequency of bleeding.⁸⁵ A more recent report from the Organization to Assess Strategies for Ischemic Syndromes pilot study⁸⁶ suggested that aspirin combined with long-term, moderate-intensity warfarin therapy (with a target INR of 2.0 to 2.5), rather than with low-intensity warfarin therapy (with an INR of 1.5), produced lower rates of death, new myocardial infarction, and stroke than aspirin alone at three months (incidence of composite end points, 5.1 percent in the group given aspirin plus moderate-intensity warfarin and 13.1 percent in the group given aspirin plus low-intensity warfarin; $P=0.05$). This benefit, however, occurred at the expense of an appreciable increase in bleeding in the group receiving moderate-intensity warfarin therapy (major bleeding, 2 percent vs. 1 percent, $P=0.56$; minor bleeding, 28.6 percent vs. 12.1 percent, $P=0.004$).⁸⁶ The benefits observed were limited to patients in whom effective anticoagulation was maintained, since about half of the patients receiving warfarin discontinued therapy because of a concern about bleeding, a lack of compliance, or a need for interventions.

The evidence remains inconclusive regarding the incremental value of incorporating long-term anticoagulant therapy into the standard aspirin regimen for patients with unstable angina. Furthermore, the availability of oral glycoprotein IIb/IIIa antagonists will generate only more questions concerning safer and more efficacious combination regimens.

Thrombolytic Therapy

Despite the fact that initial small studies suggested that there is a benefit associated with thrombolysis in patients with unstable angina, more recent and larger clinical trials have clearly demonstrated that this therapy should be avoided. The TIMI IIIB trial demonstrated an actual increase in the rates of death, myocardial infarction, and bleeding in patients categorized as having unstable angina or non-Q-wave myocardial infarction.^{87,88} Other trials have confirmed the lack of benefit from the use of thrombolytic therapy in the acute coronary syndromes that are not associated with ST-segment elevation.⁸⁹⁻⁹²

Conventional Antianginal Therapy

Beta-Blockers

Beta-blockers provide convincing benefits with respect to mortality for patients with acute myocardial infarction,⁴⁷ and much of this beneficial effect is thought to be mediated through the ability of these agents to decrease myocardial oxygen demand. Evidence supporting the use of beta-blockers in unstable

angina, however, is based on limited data from randomized trials.⁹³⁻⁹⁵ The meta-analysis of studies involving 4700 patients with unstable angina by Yusuf and colleagues demonstrated a 13 percent reduction in the risk of myocardial infarction among patients treated with beta-blockers ($P < 0.04$).⁹⁶ A strong pathogenic link between unstable angina and acute myocardial infarction has led to the uniform recommendation that these medications be used as first-line agents in all acute coronary syndromes.⁴⁷

The various preparations of beta-blockers (oral or intravenous, long-acting or short-acting) appear to have equal efficacy.⁹⁷ Caution should be exercised in prescribing beta-blockers to patients with contraindications to such therapy, however, and short-acting agents should be tried before long-acting agents are used.

Nitrates

Like beta-blockers, nitrates are widely used in the management of unstable angina, despite the lack of convincing data that show that nitrates reduce mortality or the rate of new myocardial infarction.⁹⁸ The antiischemic effects of nitrates are mediated by a number of mechanisms, which include their reduction of myocardial oxygen demand as a result of decreases in ventricular preload and afterload, their moderate effect on arterial vasodilatation, their augmentation of collateral coronary blood flow, their reduction in the frequency of coronary vasospasm, and potentially, their inhibition of platelet aggregation.⁹⁹

Intravenous nitroglycerin is considered the first-line therapy for unstable angina because of the ease of administration and titration and the rapid resolution of effects once the infusion is discontinued.⁴⁷ Nonparenteral routes of administration are not recommended in the short-term treatment of unstable angina, because they cannot be readily adjusted. The concern with the use of continuous nitrate therapy, however, is that tolerance may develop after 24 hours of administration. The mechanisms responsible for the development of nitrate tolerance remain poorly understood but probably involve intrinsic abnormalities of the vasculature, including enhanced vascular superoxide and endothelin production.¹⁰⁰ If tachyphylaxis occurs, efficacy can be maintained by increasing the dose or changing the method of administration to a nonparenteral form and allowing for a six-to-eight-hour nitrate-free interval.⁴⁷ Recent studies have also demonstrated that the supplemental use of antioxidants, especially vitamin C, appears to prevent nitrate tolerance.¹⁰¹

Calcium-Channel Blockers

There are two main categories of calcium-channel blockers — the dihydropyridines (including nifedipine) and the non-dihydropyridines (including verapamil and diltiazem).¹⁰²⁻¹⁰⁴ Both types cause coro-

nary vasodilatation and reduce blood pressure. As compared with the non-dihydropyridines, the dihydropyridines exert a greater effect on vascular vasodilatation, have a smaller inhibitory effect on both the sinus and atrioventricular nodes, and have a smaller negative inotropic effect.

A meta-analysis of studies in which patients with unstable angina were treated with calcium-channel blockers found no effect of the drugs on the incidence of death or myocardial infarction.⁹⁶ In patients who were not previously receiving beta-blockers, conventional nifedipine was associated with a 16 percent higher risk of myocardial infarction or recurrent angina than was placebo, whereas the combination of metoprolol and nifedipine was associated with a 20 percent lower incidence of these events (neither effect reached statistical significance).⁹⁵ The probable explanation for the increased mortality among patients treated with nifedipine alone is that such therapy leads to reflex tachycardia and an increase in oxygen demand.¹⁰² A number of second-generation vascular-selective dihydropyridines are now available, but these have not been studied in patients with unstable angina.

In contrast with monotherapy with nifedipine, treatment with diltiazem and verapamil may impart an advantage in terms of survival and reduced rates of reinfarction to patients with the acute coronary syndromes who have a normal ejection fraction and no evidence of pulmonary congestion on x-ray films (30 percent lower rates of mortality and reinfarction among patients treated with diltiazem than among those who received placebo after a mean follow-up period of 25 months).¹⁰⁴⁻¹⁰⁶ Lowered heart rate, reduced myocardial contractility, and reduced afterload may be responsible for some of the observed benefits seen with the non-dihydropyridine agents in patients without impaired systolic function. The use of calcium-channel blockers, especially the non-dihydropyridines, should be reserved for patients in whom beta-blockers are contraindicated or those with refractory symptoms despite aggressive treatment with aspirin, nitrates, and beta-blockers.

CORONARY REVASCULARIZATION

In the era before coronary stenting and glycoprotein IIb/IIIa receptor inhibition, coronary-artery bypass grafting (CABG) was indicated for patients with unstable angina who had high-risk coronary anatomy: luminal obstruction of 50 percent or more of the left main coronary artery or three-vessel disease and either a reduced ejection fraction (< 50 percent) or diabetes mellitus.^{107,108} CABG was also considered for patients with anatomical features associated with moderate risk (i.e., two-vessel disease, proximal subtotal stenotic lesions, and depressed left ventricular function). Although a meta-analysis of the randomized trials in which conventional angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) was compared

with CABG in moderate-risk patients found no difference in terms of prognosis between these strategies, patients undergoing PTCA had 10 times the risk of requiring repeated revascularization procedures and 1.6 times the risk of recurrent angina at one year.¹⁰⁹

PTCA in patients with refractory unstable angina is associated with a substantial risk of the following complications: death (up to 5.4 percent), myocardial infarction (up to 9 percent), need for emergency surgery (up to 12 percent), and restenosis (up to 42 percent).¹¹⁰⁻¹¹³ The introduction of intracoronary stents, however, has improved both short-term and long-term outcomes. As compared with PTCA alone, stenting is associated with a higher rate of initial procedural success (96 percent vs. 90 percent, $P=0.01$), larger luminal diameter after the procedure (2.5 mm vs. 2.0 mm, $P<0.001$), a lower rate of restenosis at six months (16 percent vs. 31 percent, $P<0.001$), and an improved rate of event-free survival at six months (89 percent vs. 79 percent, $P=0.004$).^{113,114} The risk of abrupt vessel closure, myocardial infarction, or the need for urgent surgery may now be less than 2 percent.¹¹⁵⁻¹¹⁷ However, as compared with PTCA, stenting has been associated with a higher cost per patient.¹¹⁴ The newer adjunctive pharmacologic therapies enhance even further the benefits associated with the use of stents. The more potent antiplatelet agents, ticlopidine and clopidogrel, used with aspirin for two to four weeks after stent placement, may be optimal for the prevention of acute in-stent thrombosis.^{118,119}

The decision regarding the specific revascularization procedure to be used (e.g., CABG, PTCA, stent placement, or atherectomy) is based on the coronary anatomy, the left ventricular function, the experience of the medical and surgical personnel, the presence or absence of coexisting illnesses, and the preferences of both the patient and the physician.

RISK STRATIFICATION AND SELECTION OF MANAGEMENT STRATEGIES

About 80 percent of patients who present with unstable angina have conditions that stabilize within 48 hours after the initiation of aggressive medical therapy.¹²⁰ Many of these patients then undergo tests to stratify risk (e.g., exercise testing, perfusion scintigraphy, or Holter monitoring) in order to determine which patients can be safely treated medically and which require cardiac catheterization and myocardial revascularization.

Laboratory Markers

In addition to the commonly used quantitative measurements of creatine kinase (CK) and its MB isoenzyme (CK-MB), several studies have evaluated the use of cardiac troponins (troponin T and troponin I) in patients undergoing risk stratification.¹²¹⁻¹²⁴ Measurement of troponin levels may be of greatest value in patients with a normal CK-MB level.^{122,123}

In such patients, the presence of an elevated troponin T value is associated with an odds ratio of 3.9 for coronary events within the following six months.¹²¹

Among patients with unstable angina or non-Q-wave myocardial infarction, there is an increased risk of death within six weeks in those with a troponin I level of 0.4 ng per milliliter or higher (3.7 percent, vs. 1 percent in those with a troponin I level of <0.4 ng per milliliter; $P<0.001$), and the risk of death continues to increase as the troponin level increases.¹²⁴ The risk of death associated with elevated troponin levels persists after adjustments are made for other base-line characteristics that are independently predictive of mortality.

More recent studies evaluated the role of C-reactive protein in assessing risk in patients with unstable angina or non-Q-wave myocardial infarction. A TIMI 11A substudy¹²⁵ showed that the mortality rate at 14 days was highest among patients with both a positive troponin test and an elevated C-reactive protein level (1.55 mg per deciliter or more), as compared with patients with either a positive troponin test or an elevated C-reactive protein level or those with a negative troponin test and a low C-reactive protein level (9.1 percent vs. 4.65 percent and 0.36 percent, respectively; $P<0.001$). Among patients with a negative troponin test, the mortality rate was higher in those who had an elevated C-reactive protein level (5.8 percent vs. 0.36 percent, $P=0.006$). It has recently been reported that levels of C-reactive protein may remain elevated for at least three months after discharge from the hospital and that patients with persistent elevations may be at a higher risk for recurrent instability and myocardial infarction.¹²⁶

Electrocardiographic Findings

New or reversible ST-segment deviation of 0.5 mm or more from base line or left bundle-branch block noted on the electrocardiogram obtained at the time of admission is associated with an increase in the incidence of death or myocardial infarction at one year (15.8 percent, vs. 8.2 percent in patients without electrocardiographic changes).^{127,128} In the TIMI IIIB study, reversible ST-segment depression was associated with an increase by a factor of three to six in the likelihood of death, myocardial infarction, ischemia at rest, or provokable ischemia during a test to stratify risk.¹²⁹ Isolated T-wave inversion, however, does not appear to be a marker of adverse prognosis.¹³⁰⁻¹³²

Exercise Stress Testing and Nuclear Imaging

Exercise^{133,134} or pharmacologic¹³⁵ stress testing provides important information about a patient's risk, and the use of nuclear imaging improves both the study's sensitivity and its specificity.¹³⁴ Abnormal thallium uptake by the lungs, represented by an increased ratio of the amount of thallium in the lung to the amount in the heart (≥ 0.50) on stress imaging, is a marker

of stress-induced left ventricular dysfunction and has been shown to provide independent prognostic information.¹³⁶ Patients with abnormal lung uptake have lower left ventricular function, lower exercise capacity, and a higher prevalence of angina on exercise than patients without abnormal lung reuptake and, after one year of follow-up, have a higher rate of cardiac events (18 percent vs. 10 percent, $P=0.001$) despite having a higher revascularization rate (28 percent vs. 15 percent, $P<0.001$).

Dipyridamole sestamibi tomography, like thallium-201 imaging, helps distinguish between low-risk and high-risk patients with unstable angina in a population at intermediate clinical risk before testing.¹³⁵ A normal result on dipyridamole sestamibi scanning was associated with a lower rate of cardiac events during a two-year follow-up period than an abnormal result (10 percent vs. 69 percent, $P<0.01$). The presence of either a reversible or a fixed perfusion defect had independent predictive value for future cardiac events.

Ambulatory Electrocardiographic (Holter) Monitoring

The widespread use of aggressive antithrombotic and antianginal regimens has decreased the incidence of episodes of ST-segment deviation, which are generally asymptomatic, from 60 to 80 percent to 10 to 15 percent.¹³⁷ The vast majority of patients with episodes of ischemia on ambulatory monitoring also have ischemic abnormalities on other tests used to assess level of risk (exercise test or stress perfusion scintigraphy).¹²⁹ Thus, ambulatory electrocardiographic monitoring to assess risk among patients with unstable angina cannot be recommended.

Early Identification of the Optimal Strategy

Although the conditions of the majority of patients with unstable angina will stabilize with effective antiischemic medications, approximately 50 to 60 percent of such patients will require coronary angiography and revascularization because of the "failure" of medical therapy, defined by either recurrent ischemia at rest while the patient is in the hospital or provokable ischemia during a test to assess risk before discharge.^{87,127,138} Investigations have attempted to identify early the patients in whom medical therapy would probably fail, since the assignment of such patients to a more appropriate management strategy could then be handled expeditiously. The early and accurate triage of high-risk patients could lead to better outcomes for patients as well as a more economical use of hospital resources.^{88,125}

Among 733 patients randomly assigned to an early conservative strategy in the TIMI Phase IIIB trial, a number of the characteristics of the patients on admission were predictive of those in whom medical therapy was subsequently most likely to fail: the presence of reversible ST-segment deviation, a history of angina, prior use of aspirin or heparin, a family his-

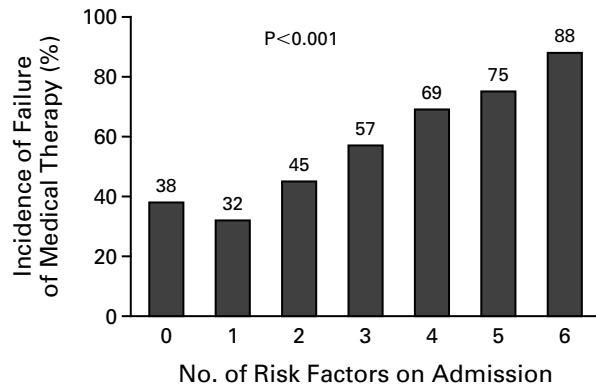


Figure 4. Incidence of the Failure of Medical Therapy According to the Number of Risk Factors Present on Admission.

In patients treated conservatively, the incidence of the failure of medical therapy, which led to prompt coronary angiography and revascularization, increased substantially as the number of base-line risk factors increased. These factors included the presence of ST-segment depression on admission, a history of angina, older age, a family history of coronary artery disease, and the use of aspirin or heparin. $P<0.001$ for the comparison among the groups. Adapted from Stone et al.,¹²⁹ with the permission of the publisher.

tory of premature coronary disease, and older age.¹²⁹ If none of these characteristics were present, the risk of the failure of medical therapy was only 38 percent, whereas if all of the characteristics were present the risk of failure rose to almost 90 percent ($P<0.001$) (Fig. 4).¹²⁹ Early triage would be enhanced by a thorough assessment of the patients' characteristics at the time of presentation; such an assessment would include a detailed history and physical examination, electrocardiogram, and measurement of laboratory markers, such as troponin. The potential value of early stratification of risk is supported by recent observations that the administration of either abciximab⁶² or dalteparin¹³⁹ reduced the incidence of death or myocardial infarction only in patients with unstable angina who had an elevated troponin T level. The appropriate use of medications and procedures may be enhanced by an individualized risk assessment.

SUMMARY

On the basis of clinical characteristics and laboratory markers on admission, patients can generally be categorized as at low risk, intermediate risk, or high risk^{4,47,140} (Fig. 5). Patients at low or intermediate risk (i.e., those without pain at the time of evaluation, those who have an unchanged or normal electrocardiogram, and those whose condition is hemodynamically stable) should be treated with aspirin and assessed further.⁴⁷ If they have been asymptomatic for more than 24 hours, they may undergo evaluation on an outpatient basis if the evaluation can be completed within 72 hours after discharge.⁴⁷ High-risk patients

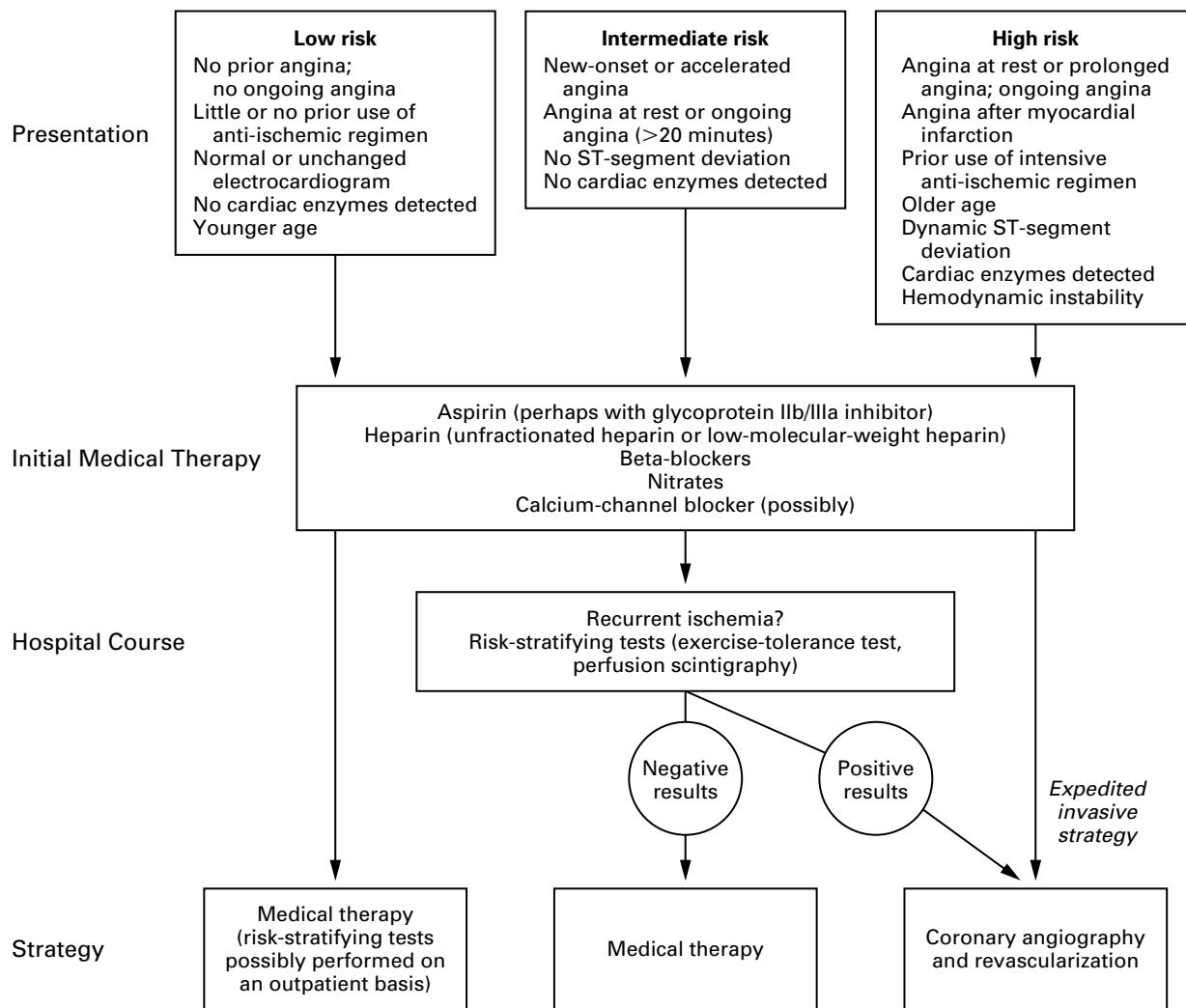


Figure 5. Treatment Strategy for Patients Who Present with Unstable Angina.

are those who have had angina at rest, prolonged angina, or persistent angina with dynamic ST-segment changes or hemodynamic instability, and they urgently require simultaneous evaluation and treatment.⁴⁷ Medical therapy should be adjusted rapidly to relieve manifestations of ischemia and should include antiplatelet therapy (aspirin, or ticlopidine or clopidogrel if aspirin is contraindicated), antithrombotic therapy (unfractionated heparin or low-molecular-weight heparin), beta-blockers, nitrates, and possibly calcium-channel blockers. Early administration of glycoprotein IIb/IIIa inhibitors may be particularly important, especially in high-risk patients with positive troponin tests or those in whom implantation of coronary stents is anticipated. The safety and efficacy of combined, intensive antiplatelet therapies (glycoprotein IIb/IIIa inhibitors) and antithrombotic therapies (low-molecular-weight heparins) have yet to be clarified.

The condition of the vast majority of patients stabilizes rapidly with aggressive medical management, and such patients can then undergo tests to assess their level of risk.⁴⁷ If manifestations of ischemia recur, either spontaneously or during testing, patients should undergo coronary angiography and revascularization. Patients whose condition remains stable and who are considered to be at low risk may be suitable for continued medical management. Use of an early, reliable risk-stratification process may permit the appropriate and economical allocation of medical resources and the optimal outcomes for patients.

REFERENCES

1. Graves E. National Hospital Discharge Survey. Annual survey 1996. Series 13, no. 4. Washington, D.C.: National Center for Health Statistics, 1998.
2. Lincoff AM, Tcheng JE, Califf RM, et al. Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa

- blockade with abciximab: one-year outcome in the EPILOG trial. *Circulation* 1999;99:1951-8.
3. Gibson CM, Goel M, Cohen DJ, et al. Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. *J Am Coll Cardiol* 1998;32:28-34.
 4. Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410-4.
 5. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;78:1157-66.
 6. Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? *Circulation* 1996;94:2662-6.
 7. Ambrose JA, Winters SL, Arora RR, et al. Angiographic evolution of coronary artery morphology in unstable angina. *J Am Coll Cardiol* 1986;7:472-8.
 8. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;12:56-62.
 9. Alison HW, Russell RO Jr, Mantle JA, Kouchoukos NT, Moraski RE, Rackley CE. Coronary anatomy and arteriography in patients with unstable angina pectoris. *Am J Cardiol* 1978;41:204-9.
 10. Fuster V, Frye RL, Connolly DC, Danielson MA, Elveback LR, Kurland LT. Arteriographic patterns early in the onset of coronary syndromes. *Br Heart J* 1975;37:1250-5.
 11. Ambrose JA, Winters SL, Stern A, et al. Angiographic morphology and the pathogenesis of unstable angina pectoris. *J Am Coll Cardiol* 1985;5:609-16.
 12. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993;69:377-81.
 13. Richardson PD, Davies MJ, Born GVR. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989;2:941-4.
 14. Fuster V, Lewis A. Conner Memorial Lecture: mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994;90:2126-46. [Erratum, *Circulation* 1995;91:256.]
 15. Thérault P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998;97:1195-206.
 16. Cheng GC, Loree HM, Kamm RD, Fishbein MC, Lee RT. Distribution of circumferential stress in ruptured and stable atherosclerotic lesions: a structural analysis with histopathological correlation. *Circulation* 1993;87:1179-87.
 17. Henney AM, Wakeley PR, Davies MJ, et al. Localization of stromelysin gene expression in atherosclerotic plaques by in situ hybridization. *Proc Natl Acad Sci U S A* 1991;88:8154-8.
 18. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-50.
 19. Moreno PR, Falk E, Palacios IF, Newell JB, Fuster V, Fallon JT. Macrophage infiltration in acute coronary syndromes: implications for plaque rupture. *Circulation* 1994;90:775-8.
 20. Welgus HG, Campbell EJ, Cury JD, et al. Neutral metalloproteinases produced by human mononuclear phagocytes: enzyme profile, regulation, and expression during cellular development. *J Clin Invest* 1990;86:1496-502.
 21. Galis ZS, Sukhova GK, Kränzhöfer R, Clark S, Libby P. Macrophage foam cells from experimental atheroma constitutively produce matrix-degrading proteinases. *Proc Natl Acad Sci U S A* 1995;92:402-6.
 22. Fernández-Ortiz A, Badimón JJ, Falk E, et al. Characterization of the relative thrombogenicity of atherosclerotic plaque components: implications for consequences of plaque rupture. *J Am Coll Cardiol* 1994;23:1562-9.
 23. Moreno PR, Bernardi VH, Lopez-Cuellar J, et al. Macrophages, smooth muscle cells, and tissue factor in unstable angina: implications for cell-mediated thrombogenicity in acute coronary syndromes. *Circulation* 1996;94:3090-7.
 24. Wilcox JN, Smith KM, Schwartz SM, Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. *Proc Natl Acad Sci U S A* 1989;86:2839-43.
 25. Patrono C, Renda G. Platelet activation and inhibition in unstable coronary syndromes. *Am J Cardiol* 1997;80:17E-20E.
 26. Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM. C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. *Blood* 1993;82:513-20.
 27. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation* 1998;97:2007-11.
 28. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. *Circulation* 1998;97:425-8.
 29. Cannon CP, McCabe CH, Stone PH, et al. Circadian variation in the onset of unstable angina and non-Q-wave acute myocardial infarction (the TIMI Registry and TIMI IIIB). *Am J Cardiol* 1997;79:253-8.
 30. Curfman GD. Is exercise beneficial — or hazardous — to your heart? *N Engl J Med* 1993;329:1730-1.
 31. Alpert JS. Coronary vasomotion, coronary thrombosis, myocardial infarction and the camel's back. *J Am Coll Cardiol* 1985;5:617-8.
 32. Meredith IT, Yeung AC, Weidinger FF, et al. Role of impaired endothelium-dependent vasodilation in ischemic manifestations of coronary artery disease. *Circulation* 1993;87:Suppl V:V-56-V-66.
 33. Wiecek I, Haynes WG, Webb DJ, Ludlam CA, Fox KAA. Raised plasma endothelin in unstable angina and non-Q wave myocardial infarction: relation to cardiovascular outcome. *Br Heart J* 1994;72:436-41.
 34. Watanabe T, Suzuki N, Shimamoto N, Fujino M, Imada A. Contribution of endogenous endothelin to the extension of myocardial infarct size in rats. *Circ Res* 1991;69:370-7.
 35. Ross R. The pathogenesis of atherosclerosis — an update. *N Engl J Med* 1986;314:488-500.
 36. Nobuyoshi M, Tanaka M, Nosaka H, et al. Progression of coronary atherosclerosis: is coronary spasm related to progression? *J Am Coll Cardiol* 1991;18:904-10.
 37. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996;93:1354-63.
 38. Flugelmann MY, Virmani R, Correa R, et al. Smooth muscle cell abundance and fibroblast growth factors in coronary lesions of patients with nonfatal unstable angina: a clue to the mechanism of transformation from the stable to the unstable clinical state. *Circulation* 1993;88:2493-500.
 39. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina: results of a Veterans Administration cooperative study. *N Engl J Med* 1983;309:396-403.
 40. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina: results of a Canadian multicenter trial. *N Engl J Med* 1985;313:1369-75.
 41. Thérault P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
 42. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106. [Erratum, *BMJ* 1994;308:1540.]
 43. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;2:349-60.
 44. Eisenberg MJ, Topol EJ. Prehospital administration of aspirin in patients with unstable angina and acute myocardial infarction. *Arch Intern Med* 1996;156:1506-10.
 45. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30.
 46. Wallentin L, Research Group on Instability in Coronary Artery Disease in Southeast Sweden. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. *J Am Coll Cardiol* 1991;18:1587-93.
 47. Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Clinical practice guideline. No. 10. Rockville, Md.: Department of Health and Human Services, 1994. (AHCPR publication no. 94-0602.)
 48. Balsano F, Rizzon P, Viola F, et al. Antiplatelet treatment with ticlopidine in unstable angina: a controlled multicenter clinical trial. *Circulation* 1990;82:17-26.
 49. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
 50. Moussa I, Oetgen M, Roubin G, et al. Effectiveness of clopidogrel and aspirin versus ticlopidine and aspirin in preventing stent thrombosis after coronary stent implantation. *Circulation* 1999;99:2364-6.
 51. Madan M, Berkowitz SD, Tchong JE. Glycoprotein IIb/IIIa integrin blockade. *Circulation* 1998;98:2629-35.
 52. Lefkowitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;332:1553-9.
 53. The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.
 54. Topol EJ, Califf RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994;343:881-6.
 55. Topol EJ, Ferguson JJ, Weisman HF, et al. Long-term protection from

- myocardial ischemic events in a randomized trial of brief β_3 blockade with percutaneous coronary intervention. *JAMA* 1997;278:479-84.
56. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatid on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997;349:1422-8.
57. The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;96:1445-53.
58. The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689-96.
59. The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. *Lancet* 1997;349:1429-35. [Erratum, *Lancet* 1997;350:744.]
60. The EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet* 1998;352:87-92.
61. Lincoff AM, Tcheng JE, Califf RM, et al. Sustained suppression of ischemic complications of coronary intervention by platelet GP IIb/IIIa blockade with abciximab: one-year outcome in the EPILOG trial. *Circulation* 1999;99:1951-8.
62. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;340:1623-9.
63. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488-97. [Erratum, *N Engl J Med* 1998;339:415.]
64. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498-505.
65. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436-43.
66. The PARAGON Investigators. An international, randomized, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin, or both in unstable angina. *Circulation* 1998;97:2386-95.
67. Weitz JI. Low-molecular-weight heparins. *N Engl J Med* 1997;337:688-98. [Erratum, *N Engl J Med* 1997;337:1567.]
68. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA* 1996;276:811-5.
69. Klein LW, Wahid F, VandenBerg BJ, Parrillo JE, Calvin JE. Comparison of heparin therapy for < or = 48 hours to > 48 hours in unstable angina pectoris. *Am J Cardiol* 1997;79:259-63.
70. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med* 1995;332:1330-5.
71. Eisenberg PR. Novel antithrombotic strategies for the treatment of coronary artery thrombosis: a critical appraisal. *J Thromb Thrombolysis* 1995;1:237-49.
72. Gurfinkel EP, Manos EJ, Mejail RI, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. *J Am Coll Cardiol* 1995;26:313-8.
73. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;347:561-8.
74. Klein W, Buchwald A, Hillis WS, et al. Fragmin in unstable angina pectoris or in non-Q-wave acute myocardial infarction (the FRIC study). *Am J Cardiol* 1997;80(5A):30E-34E.
75. Swahn E, Wallentin L. Low-molecular-weight heparin (Fragmin) during instability in coronary artery disease (FRISC). *Am J Cardiol* 1997;80(5A):25E-29E.
76. Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease: Fragmin in unstable coronary artery disease study. *Circulation* 1997;96:61-8. [Erratum, *Circulation* 1998;97:413.]
77. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-52.
78. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) IIB trial. *Circulation* 1999;100:1593-601.
79. The Thrombolysis in Myocardial Infarction (TIMI) IIA Trial Investigators. Dose-ranging trial of enoxaparin for unstable angina: results of TIMI IIA. *J Am Coll Cardiol* 1997;29:1474-82.
80. Organisation to Assess Strategies for Ischemic Syndromes (OASIS-2) Investigators. Effects of recombinant hirudin (lepirudin) compared with heparin on death, myocardial infarction, refractory angina, and revascularisation procedures in patients with acute myocardial ischaemia without ST elevation: a randomised trial. *Lancet* 1999;353:429-38.
81. Thrombin Inhibition in Myocardial Ischaemia (TRIM) Study Group. A low molecular weight, selective thrombin inhibitor, inogatran, vs heparin, in unstable coronary artery disease in 1209 patients: a double-blind, randomized, dose-finding study. *Eur Heart J* 1997;18:1416-25.
82. Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990;323:147-52.
83. Cohen MC, Adams PC, Parry G, et al. Combination antithrombotic therapy in unstable rest angina and non-Q-wave infarction in nonprior aspirin users: primary end points analysis from the ATACS Trial. *Circulation* 1994;89:81-8.
84. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. *Lancet* 1997;350:389-96.
85. Williams MJA, Morison IM, Parker JH, Stewart RAH. Progression of the culprit lesion in unstable coronary artery disease with warfarin and aspirin versus aspirin alone: preliminary study. *J Am Coll Cardiol* 1997;30:364-9.
86. Anand SS, Yusuf S, Pogue J, Weitz JI, Flather M. Long-term oral anticoagulant therapy in patients with unstable angina or suspected non-Q-wave myocardial infarction: Organization to Assess Strategies for Ischemic Syndromes (OASIS) pilot study results. *Circulation* 1998;98:1064-70.
87. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545-56.
88. Bovill EG, Tracy RP, Knatterud GL, et al. Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, phase IIIB trial). *Am J Cardiol* 1997;79:391-6.
89. Ambrose JA, Almeida OD, Sharma SK, et al. Adjunctive thrombolytic therapy during angioplasty for ischemic rest angina: results of the TAUSA Trial. *Circulation* 1994;90:69-77.
90. Bar FW, Verheugt FW, Col J, et al. Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome: results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. *Circulation* 1992;86:131-7.
91. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1 000 patients. *Lancet* 1994;343:311-22. [Erratum, *Lancet* 1994;343:742.]
92. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesbro J. Insights into the pathogenesis of the acute ischemic syndromes. *Circulation* 1988;77:1213-20.
93. Telford AM, Wilson C. Trial of heparin versus atenolol in prevention of myocardial infarction in intermediate coronary syndrome. *Lancet* 1981;1:1225-8.
94. Gottlieb SO, Weisfeldt ML, Ouyang P, et al. Effect of the addition of propranolol to therapy with nifedipine for unstable angina pectoris: a randomized, double-blind, placebo-controlled trial. *Circulation* 1986;73:331-7.
95. Lubsen J, Tijssen JG. Efficacy of nifedipine and metoprolol in the early treatment of unstable angina in the coronary care unit: findings from the Holland Interuniversity Nifedipine/metoprolol Trial (HINT). *Am J Cardiol* 1987;60:18A-25A.
96. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary prevention with aspirin, and risk factor modification. *JAMA* 1988;260:2259-63.
97. Prisant LM, Houghton JL, Bottini PB, Carr AA. Unstable angina: pharmaceutical versus invasive therapy. *Postgrad Med* 1994;96:88-95.
98. Thadani U, Opie LH. Nitrates for unstable angina. *Cardiovasc Drugs Ther* 1994;8:719-26.
99. Fitzgerald DJ, Roy L, Robertson RM, Fitzgerald GA. The effects of organic nitrates on prostacyclin biosynthesis and platelet function in humans. *Circulation* 1984;70:297-302.
100. Munzel T, Kurz S, Heitzer T, Harrison DG. New insights into mechanisms underlying nitrate tolerance. *Am J Cardiol* 1996;77:24C-30C.
101. Bassenge E, Fink N, Skatchkov M, Fink B. Dietary supplement with vitamin C prevents nitrate tolerance. *J Clin Invest* 1998;102:67-71.
102. Ferrari R. Prognosis of patients with unstable angina or acute myocardial infarction treated with calcium channel antagonists. *Am J Cardiol* 1996;77:22D-25D.

- 103.** Held PH, Yusuf S, Furberg CD. Calcium channel blockers in acute myocardial infarction and unstable angina: an overview. *BMJ* 1989;299:1187-92.
- 104.** Théroux P, Taeymans Y, Morissette D, Bosch X, Pelletier GB, Waters DD. A randomized study comparing propranolol and diltiazem in the treatment of unstable angina. *J Am Coll Cardiol* 1985;5:717-22.
- 105.** The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988;319:385-92.
- 106.** Effect of verapamil on mortality and major events after acute myocardial infarction. (the Danish Verapamil Infarction Trial II — DAVIT II). *Am J Cardiol* 1990;66:779-85.
- 107.** Luchi RJ, Scott SM, Deupree RH, Principal Investigators and Their Associates of Veterans Administration Cooperative Study No. 28. Comparison of medical and surgical treatment for unstable angina pectoris: results of a Veterans Administration cooperative study. *N Engl J Med* 1987;316:977-84.
- 108.** The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217-25.
- 109.** Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-9.
- 110.** Marzocchi A, Piovaccari G, Marrozzini C, et al. Results of coronary stenting for unstable versus stable angina pectoris. *Am J Cardiol* 1997;79:1314-8.
- 111.** Myler RK, Shaw RE, Stertz SH, et al. Unstable angina and coronary angioplasty. *Circulation* 1990;82:Suppl II:II-88-II-95.
- 112.** Bentivoglio LG, Detre K, Yeh W, Williams DO, Kelsey SF, Faxon DP. Outcome of percutaneous transluminal coronary angioplasty in subtypes of unstable angina pectoris: a report of the 1985-1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *J Am Coll Cardiol* 1994;24:1195-206.
- 113.** Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
- 114.** Serruys PW, van Hout B, Bonnier H, et al. Randomised comparison of implantation of heparin-coated stent with balloon angioplasty in selected patients with coronary artery disease. *Lancet* 1998;352:673-81. [Erratum, *Lancet* 1998;352:1478.]
- 115.** Shimada K, Kawarabayashi T, Komatsu R, Sakamoto T, Shimizu Y, Yoshikawa J. Efficacy and safety of early coronary stenting for unstable angina. *Cathet Cardiovasc Diagn* 1998;43:381-5.
- 116.** Chauhan A, Vu E, Ricci DR, et al. Multiple coronary stenting in unstable angina: early and late clinical outcomes. *Cathet Cardiovasc Diagn* 1998;43:11-6.
- 117.** Madan M, Marquis JF, de May MR, et al. Coronary stenting in unstable angina: early and late clinical outcomes. *Can J Cardiol* 1998;14:1109-14.
- 118.** Hall P, Nakamura S, Maiello L, et al. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. *Circulation* 1996;93:215-22.
- 119.** Leon MB, Baim DS, Popma JJ, et al. Clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998;339:1665-71.
- 120.** Hillis WS. The continuing debate: conservative or interventional therapy for unstable coronary artery disease. *Am J Cardiol* 1997;80:51E-54E.
- 121.** Pettijohn TL, Doyle T, Spiekerman AM, Watson LE, Riggs MW, Lawrence ME. Usefulness of positive troponin-T and negative creatine kinase levels in identifying high-risk patients with unstable angina pectoris. *Am J Cardiol* 1997;80:510-1.
- 122.** Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation* 1996;93:1651-7.
- 123.** Antman EM, Sacks DB, Rifai N, McCabe CH, Cannon CP, Braunwald E. Time to positivity of a rapid bedside assay for cardiac-specific troponin T predicts prognosis in acute coronary syndromes: a Thrombolysis in Myocardial Infarction (TIMI) 11A substudy. *J Am Coll Cardiol* 1998;31:326-30.
- 124.** Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-9.
- 125.** Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. *J Am Coll Cardiol* 1998;31:1460-5.
- 126.** Biasucci LM, Liuzzo G, Grillo RL, et al. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. *Circulation* 1999;99:855-60.
- 127.** Cannon CP, McCabe CH, Stone PH, et al. The electrocardiogram predicts one-year outcome of patients with unstable angina and non-Q wave myocardial infarction: results of the TIMI III Registry ECG Ancillary Study. *J Am Coll Cardiol* 1997;30:133-40.
- 128.** Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;281:707-13.
- 129.** Stone PH, Thompson B, Zaret BL, et al. Factors associated with failure of medical therapy in patients with unstable angina and non-Q wave myocardial infarction: a TIMI-IIIB database study. *Eur Heart J* 1999;20:1084-93.
- 130.** Haines DE, Raabe DS, Gundel WD, Wackers FJ. Anatomic and prognostic significance of new T-wave inversion in unstable angina. *Am J Cardiol* 1983;52:14-8.
- 131.** Sclarovsky S, Davidson E, Lewin RF, Strasberg B, Arditti A, Agmon J. Unstable angina pectoris evolving to acute myocardial infarction: significance of ECG changes during chest pain. *Am Heart J* 1986;112:459-62.
- 132.** Gorgels APM, Vos MA, Mulleneers R, de Zwaan C, Bar FWHM, Wellens HJJ. Value of the electrocardiogram in diagnosing the number of severely narrowed coronary arteries in rest angina pectoris. *Am J Cardiol* 1993;72:999-1003.
- 133.** Stratmann HG, Younis LT, Wittry MD, Amato M, Miller DD. Exercise technetium-99m myocardial tomography for the risk stratification of men with medically treated unstable angina pectoris. *Am J Cardiol* 1995;76:236-40.
- 134.** Madsen JK, Stubgaard M, Utne HE, et al. Prognosis and thallium-201 scintigraphy in patients admitted with chest pain without confirmed acute myocardial infarction. *Br Heart J* 1988;59:184-9.
- 135.** Stratmann HG, Tamesis BR, Younis LT, Wittry MD, Amato M, Miller DD. Prognostic value of predischARGE dipyridamole technetium 99m sestamibi myocardial tomography in medically treated patients with unstable angina. *Am Heart J* 1995;130:734-40.
- 136.** Jain D, Thompson B, Wackers FJT, Zaret BL. Relevance of increased lung thallium uptake on stress imaging in patients with unstable angina and non-Q wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI)-IIIB Study. *J Am Coll Cardiol* 1997;30:421-9.
- 137.** Stone PH. The role of ST-segment monitoring in the management of patients with unstable angina. In: Rutherford JD, ed. *Unstable angina pectoris*. New York: Marcel Dekker, 1991:105-20.
- 138.** Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;338:1785-92. [Erratum, *N Engl J Med* 1998;339:1091.]
- 139.** FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC II) Investigators. Long-term low-molecular-mass heparin in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:701-7.
- 140.** Zaacks SM, Liebson PR, Calvin JE, Parrillo JE, Klein LW. Unstable angina and non-Q wave myocardial infarction: does the clinical diagnosis have therapeutic implications? *J Am Coll Cardiol* 1999;33:107-18.