Clinical Cardiology: New Frontiers

Acute Coronary Syndromes
Unstable Angina and Non–Q-Wave Myocardial Infarction

Pierre Théroux, MD; Valentin Fuster, MD, PhD

Ischemic heart disease includes a wide spectrum of conditions, ranging from silent ischemia and exertion-induced angina, through unstable angina, to acute MI. Unstable angina occupies the center of this spectrum, causing disability and risk greater than that of chronic stable angina but less than that of acute MI (Fig 1). Although non–Q-wave MI for many years was considered prognostically similar to unstable angina, recent longitudinal studies indicate that it is similar to Q-wave infarction (Fig 2).

The concept of unstable angina has emerged from observations of frequent symptoms preceding acute MI, followed by prospective documentation that unstable symptoms frequently culminated in acute MI. The syndrome was rapidly accepted as a well-defined clinical entity as specific clinical manifestations, pathophysiological mechanisms, laboratory findings, and treatment became better characterized. Unstable angina is currently one of the leading causes of hospital admission for CAD, and non–Q-wave MI accounts for >30% of admissions for acute MI. Yet, the diagnosis of unstable angina remains clinical, based on symptom recognition. The physician caring for patients with unstable angina is in a privileged position of recognizing rapidly evolving CAD and being able to intervene to prevent irreversible left ventricular damage and progression of CAD.

Unstable angina is classically described as a heterogeneous disease, referring to a wide spectrum of clinical manifestations from stable angina to MI, of disease processes from coronary vasospasm to thrombus formation, and of extent of CAD from no significant stenosis to severe three-vessel disease. Not surprisingly, therefore, the prognosis of unstable angina is quite variable. Despite all these heterogeneous features, the recent progress made in knowledge and management of unstable angina and acute MI has driven the acute coronary syndromes to the forefront of modern cardiology, helping shape future research and development. The new concepts are active coronary plaque and triggers and promoters of inflammation and of thrombus formation. The new therapeutic goals are plaque stabilization and prevention of accelerated atherosclerosis.

Clinical Presentations and Pathophysiology
In 1994, the Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute published a practice guideline: “Unstable Angina: Diagnosis and Management.” This guideline defined unstable angina as follows: “...as having three possible presentations: symptoms of angina at rest (usually prolonged >20 minutes), new-onset (<2 months) exertional angina of at least Canadian Cardiovascular Society Classification (CCSC) class III in severity, or recent (<2 months) acceleration of angina as reflected by an increase in severity of at least one CCSC class to at least CCSC class III. In most, but not all, of these patients, symptoms will be caused by significant coronary artery disease (CAD). Variant angina, non–Q-wave myocardial infarction (MI), and post-MI (>24 hours) angina are part of the spectrum of unstable angina” (Table 1).

Thus, the diagnosis of unstable angina implies recognition of aggravating symptoms of myocardial ischemia of new onset or departing from the usual pattern of chest pain, the reference baseline being the patient’s previous status. By definition, symptoms of unstable angina may have atypical features compared with classic angina. The diagnosis requires discriminative clinical judgment to integrate clinical and laboratory elements orienting to the likelihood of CAD and to the ischemic nature of the chest pain and its severity (Table 2). Patients with a previous history of CAD are more likely to experience an ischemic pain; presence of risk factors and older age increase the likelihood of disease, and ST-T ischemic changes magnify the specificity of the diagnosis. Elevation of plasma levels of CK with presence of CK-MB is diagnostic of myocardial necrosis; troponin I and troponin T are sensitive markers of myocardial cell ischemia and necrosis, and elevated levels are associated with a more serious prognosis. Studies have also documented that systemic markers of an inflammatory state, such as C-reactive protein, can provide independent prognostic information.

Because angina is the clinical manifestation of an imbalance between oxygen demand and supply, extracardiac or cardiac factors that lead to excess demand must be ruled out when instability is recognized (Table 1). These are an inappropriate tachycardia (anemia, fever, hypoxia, tachyarrhythmias, thyrotoxicosis), a high afterload (aortic valve stenosis, left ventricular hypertrophy) or preload (cardiac chamber dilatation, high cardiac output), or inotropic state (sympathomimetic drugs, cocaine intoxication). When no precipitating factors are identified, a primary intracoronary
A disease process limiting coronary blood flow is the likely cause of unstable angina.

Non-Q-wave MI is often diagnosed a posteriori when the results of the cardiac enzymes become available. The clinical presentation, however, is often suggestive of the diagnosis; the chest pain is prolonged, sometimes accompanied by symptoms originating from the autonomic nervous system, and frequently by ST-segment depression persisting well after the resolution of pain. Prinzmetal’s variant angina is diagnosed when transient ST-segment elevation is documented during an episode of chest pain; coronary angiography is required to determine the severity of the underlying stenosis. Diagnostic clinical clues are intermittent episodes of chest pain, often repetitive, usually at rest, typically in the early morning hours, and rapidly relieved by nitroglycerin; syncope during pain is infrequent but highly suggestive of the diagnosis, as are other manifestations of spastic disease, such as migraine headache and Raynaud’s phenomenon. Postinfarction angina (Table 1), recognized by recurrent pain 24 hours to 4 weeks after MI, denotes impaired prognosis; the ischemia can be located at a distance or at the site of infarction. The former is more frequent in inferior MI and is associated with multivessel disease; the latter occurs mainly in anterior MI. Inclusion of these patients within the diagnosis of unstable angina has helped management.

**Evaluation of Risk and Prognosis**

Various classifications of unstable angina have been proposed, accounting for clinical presentation, pathophysiological mechanisms, and, most importantly, risk or prognosis. The classification proposed by Braunwald has become frequently used. This classification considers pathophysiology and clinical background and the severity of manifestations. The pathophysiological clinical situations are (A) a condition extrinsic to the coronary vascular bed intensifying myocardial ischemia, (B) primary unstable angina with no extrinsic condition to intensify ischemia, and (C) unstable angina within 2 weeks after MI. The severity grading is as follows: I, new onset of severe angina or significant aggravation of previous angina, without rest pain; II, angina at rest within the past month but not within 48 hours; and III, angina at rest within 48 hours. Subclassifications address the intensity of previous treatment from 1, none; to 2, standard treatment for chronic stable angina; and to 3, maximal anti-ischemic drug therapy. This classification is based on a large, diverse number of observations on the natural history of unstable angina. Collectively, these have demonstrated that patients with new-onset, severe angina (class I) have a better prognosis than those with rest pain (classes II and III); among the latter, patients who have experienced ischemia at rest in the immediate past (class III) are at higher risk than those who have “cooled off” (class II). Similarly, patients with secondary unstable angina, in whom a clearly identifiable precipitating cause of unstable angina can be identified (class A), have a better prognosis (insofar as unstable angina is concerned) than do patients in whom intrinsic CAD is responsible (class B), because in the former, simple removal of the precipitating cause usually returns them to their preexisting state. Patients who develop unstable angina early in their recovery from acute MI (class C) are at high risk of developing additional myocardial damage.

**Selected Abbreviations and Acronyms**

- CAD = coronary artery disease
- CCSC = Canadian Cardiovascular Society Classification
- CK = creatine kinase
- GP = glycoprotein
- MI = myocardial infarction
- TF = tissue factor

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**Figure 1.** Cumulative 6-month mortality from ischemic heart disease. Diagnosis on admission to hospital (n = 21,761; 1985 to 1992). From Duke Cardiovascular Database. Reproduced with permission from Reference 1.

**Figure 2.** Top, Cumulative 1-year combined death or MI among patients with Q-wave and non–Q-wave MI treated with fibrinolysis. Reproduced with permission from Reference 2. Bottom, Risk of subsequent cardiac events in stable convalescing patients after first non–Q-wave and Q-wave MI. Reproduced with permission from Reference 3.
TABLE 1. Unstable Angina: General Understanding

<table>
<thead>
<tr>
<th>Presentation</th>
<th>A. Extracardiac</th>
<th>B. Primary</th>
<th>C. Post MI</th>
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</thead>
<tbody>
<tr>
<td>I Exertional, &lt;2 mo, CCSC III</td>
<td>1 Trigger—A.A.</td>
<td>4 A.A.</td>
<td>7 E.I.</td>
</tr>
<tr>
<td>II Resting, &gt;48 hours</td>
<td>2 Trigger—A.A.</td>
<td>5 A.A.</td>
<td>8 E.I.</td>
</tr>
<tr>
<td>III Resting, &lt;48 hours</td>
<td>3 Trigger—A.A.</td>
<td>6 A.A.—E.I.</td>
<td>9 E.I.</td>
</tr>
</tbody>
</table>

A.A. indicates antithrombotic, antianginal; E.I., early intervention. Numbers 1 through 9 indicate risk. Modified from Reference 11.

According to this understanding, Table 1 presents an unstable angina risk score of 1 to 9, with 1 being the mildest and 9 being the most severe, but certain variants have also been examined. For example, the classification described above has been correlated with the underlying coronary anatomy in patients with unstable angina and with chronic stable angina. An “unstable angina score” was established by denoting the severity of unstable angina (class I=1, class II=2, and class III=3) and the clinical circumstances in which it occurs (class A=1, class B=2, and class C=3). Thus, patients with unstable angina received scores of 2 to 6; patients with chronic stable angina were assigned a score of 0. In this and other subsequent prospective studies, multi-variate analysis identified the unstable angina score to be the most important predictor of coronary lesion complexity and intracoronary thrombus.

A further stratification of risk (Tables 2 and 3) is suggested, based on absence or presence of ST-T-wave changes during pain and on absence or presence of elevation of troponin levels and CK-MB levels and of the magnitude of changes when present. Hemodynamic deterioration during pain with pulmonary edema, new mitral regurgitation or third heart sound, or hypotension also predicts a more serious prognosis. Other predictors are factors relevant to prognosis at any stage in the evolution of CAD, such as left ventricular dysfunction and extensive CAD, age, and comorbid conditions such as diabetes mellitus, obstructive pulmonary disease, renal failure, and malignancy.

Pathogenesis

Unstable angina is a complex condition. The most important pathophysiological mechanism of ischemia is a primary reduction of myocardial oxygen supply due to plaque disruption with associated thrombosis and vasoconstriction (Fig 3).

Plaque Disruption

The process of atherogenesis, lipid accumulation, cell proliferation, and extracellular matrix synthesis is neither linear nor predictable. New high-grade lesions often appear in segments of artery that were normal only months earlier at angiographic examination. Indeed, mild coronary lesions may be associated with significant progression to severe stenosis or total occlusion; these lesions may account for as many as two thirds of the patients in whom unstable angina or other acute coronary syndromes develop. This unpredictable and episodic progression is most likely caused by plaque disruption with subsequent thrombus, which changes the plaque geometry, leading to intermittent plaque growth and acute occlusive coronary syndromes.

Pathological studies have revealed that such atherosclerotic plaques prone to rupture are commonly composed of a crescentic mass of lipids separated from the vessel lumen by a fibrous cap. Plaques that undergo disruption tend to be relatively soft and have a high concentration of cholesteryl esters rather than of free cholesterol monohydrate crystals. In addition, plaques rich in extracellular matrix and smooth muscle cells, not necessarily considered vulnerable or lipid rich, may have a superficial erosion with complicated thrombosis also leading to unstable angina and other acute coronary syndromes. Moreover, in addition to this rather “passive” phenomenon of plaque disruption, a better understanding of an “active” phenomenon related to macrophage activity is evolving.

Passive Plaque Disruption

Related to physical forces, passive plaque disruption occurs most frequently where the fibrous cap is thinnest, most heavily infiltrated by foam cells, and therefore weakest. For eccentric plaques, this is often the shoulder or between the plaque and the adjacent vessel wall. Pathoanatomic examination of intact and disrupted plaques and in vitro mechanical testing of isolated fibrous caps from aorta indicate that vulnerability to rupture depends on three factors: circumferential wall stress or cap “fatigue”; location, size, and consistency of the atheromatous core; and blood flow characteristics, particularly the impact of flow on the proximal aspect of the plaque (ie, configuration and angulation of the plaque). Active Plaque Disruption

An active phenomenon of plaque disruption is probably important. Thus, atherectomy specimens from patients with acute coronary syndromes revealed macrophage-rich areas. Macrophages can degrade extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasmino-
gen activators and a family of matrix metalloproteinases (collagenases, gelatinases, and stromelysins) that may weaken the fibrous cap, predisposing it to rupture.16,20

Acute Thrombosis
Disruption of a vulnerable or unstable plaque with a subsequent change in plaque geometry and thrombosis results in a complicated lesion.18 Such a rapid change in the atherosclerotic plaque geometry may result in acute occlusion or subocclusion with clinical manifestations of unstable angina or other acute coronary syndromes. More frequently, however, the rapid changes appear to result in mural thrombus without evident clinical symptoms, which, by self-organization, may be a main contributor to the progression of atherosclerosis. More specifically, at the time of coronary plaque disruption, a number of local and thrombogenic factors may influence the degree and the duration of thrombus deposition (Table 4).16,18 Such a thrombus may then either be partially lysed or become replaced in the process of organization by the vascular repair response.18

Vulnerable Plaque Substrate and TF-Dependent Thrombus
Various human atherosclerotic plaques (by American Heart Association classification) were exposed to flowing blood at high shear rate, and their thrombogenicity was evaluated. In a disrupted vulnerable plaque with ulceration, as occurs in approximately two thirds of acute coronary syndrome, the lipid-rich core abundant in cholesteryl ester displayed the highest thrombogenicity and the most intense TF staining compared with other arterial components.21 Colocalization analysis of coronary atherectomy specimens (culprit lesions) from patients with unstable angina demonstrated a strong relationship between TF and macrophages.19 As a result of these recent observations, one of us (V.F.) is investigating whether TF content and activity in the atheromatous gruel is mediated by macrophages, thus suggesting a cell-mediated thrombogenicity in patients with unstable angina and acute coronary syndrome, based on the observation that thrombus formation in lipid-rich plaques can be prevented by recombinant TF pathway inhibition.

Systemic Hypercoagulable State–Dependent Thrombosis
We also investigated whether systemic factors, such as the circulating monocyte, may be involved in TF expression and thrombogenicity, triggered by infection, hypercholesterolemia, or other systemic factors (Table 4). Thus far, preliminary evidence confirms that in a disrupted plaque with only an erosion, as occurs in approximately one third of acute coronary syndromes (exposing collagen or smooth muscle cells), thrombosis may occur only in the presence of some of the circulating or systemic factors mentioned above.16

Vasoconstriction
Although many episodes of unstable angina and acute MI are caused by the disruption or erosion of plaque with superimposed thrombosis, other mechanisms that alter myocardial oxygen supply and demand must be considered. Original studies by Maseri et al9 have suggested that coronary vaso-
constriction plays an important role. In the acute coronary syndromes, vasoconstriction either may occur as a response to a mildly dysfunctional endothelium near the culprit lesion or, more likely, may be a response to deep arterial damage or plaque disruption of the culprit lesion itself. Thus, in regard to this second type of vasoconstriction, it appears that a predisposition exists for platelet-dependent and thrombin-dependent vasoconstriction at the site of plaque disruption and thrombosis that may be very significant but transient. Thus, platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A2, and thrombin-dependent vasoconstriction occur if the vascular wall has been significantly damaged with de-endothelialization, suggesting the direct interaction of these substances with the vascular smooth muscle cells.

Vasoconstriction and Prinzmetal’s Variant Angina

In Prinzmetal’s variant angina, there is a transient, abrupt, marked reduction in the diameter of a proximal epicardial coronary artery, resulting in myocardial ischemia in the absence of any preceding increases in myocardial oxygen demand (reflected in elevations of heart rate or blood pressure). This reduction in diameter can usually be reversed by nitroglycerin and can occur in either normal or diseased coronary arteries. The striking reduction in lumenal diameter is usually focal and involves one site or occasionally more than one. Sites of spasm in Prinzmetal’s angina are often adjacent to atheromatous plaques. Potential mechanisms include endothelial injury (which reverses the dilator response to a variety of stimuli, eg, acetylcholine) and hypercontractility of vascular smooth muscle due to vasoconstrictor mitogens, leukotrienes, serotonin, and higher local concentrations of blood-borne vasoconstrictors in areas of neovascularized atherosclerotic plaques. Moreover, several studies suggest that magnesium ions play a role in the pathogenesis of attacks of variant angina. In patients with variant angina, magnesium sulfate has been shown to terminate stressor-induced variant anginal attacks.

**TABLE 4. Thrombogenic Risk Factors**

<table>
<thead>
<tr>
<th>Local factors</th>
<th>Systemic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of plaque disruption</td>
<td>Cholesterol, lipoprotein(a)</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>Catecholamines (ie, smoking, stress, cocaine)</td>
</tr>
<tr>
<td>Tissue substrate</td>
<td>Fibrinogen, impaired fibrinolysis (ie, plasminogen activator inhibitor-1), activated platelets and clotting (ie, factor VII, thrombin generation—prothrombin fragment 1 + 2, or activity—fibrinopeptide A)</td>
</tr>
<tr>
<td>Surface of residual thrombus</td>
<td>Infections (C pneumoniae, cytomegalovirus, H pylori)</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td></td>
</tr>
</tbody>
</table>

*High risk: occlusion (acute coronary syndrome)—low risk: mural (progression). Adapted with permission from References 16 and 18.
Integrated Pathogenesis of the Various Coronary Syndromes and of Unstable Angina

Having discussed plaque disruption and thrombus formation, we will summarize the current views on the pathophysiology of acute coronary syndromes. In patients with stable CAD, angina or silent ischemia commonly results from increases in myocardial oxygen demand that outstrip the ability of stenosed coronary arteries to increase its delivery. In contrast, unstable angina or ischemia, non–Q-wave MI, and Q-wave MI (on occasion these acute syndromes may also be silent) present a continuum of the disease process and are usually characterized by an abrupt reduction in coronary flow. Thus, the presence of local and systemic thrombogenic risk factors at the time of plaque disruption may modify the extent and duration of thrombus deposition and account for the variety of pathological and acute clinical manifestations (Table 4).

In unstable angina, a relatively small erosion or fissuring of an atherosclerotic plaque may lead to an acute change in plaque structure and a reduction in coronary blood flow, resulting in exacerbation of angina. Transient episodes of thrombotic vessel occlusion at the site of plaque injury may occur, leading to angina at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10 to 20 minutes. In addition, release of vasoactive substances by platelets and vasoconstriction secondary to endothelial vasodilator dysfunction may contribute to a reduction in coronary flow. Overall, alterations in perfusion and myocardial oxygen supply probably account for two thirds of episodes of unstable angina; the rest may be caused by transient increases in myocardial oxygen demand.

In non–Q-wave MI, more severe plaque damage would result in more persistent thrombotic occlusion, perhaps lasting up to 1 hour. Approximately one fourth of patients with non–Q-wave MI may have an infarct-related vessel occluded for >1 hour, but the distal myocardial territory is usually supplied by collaterals. ST-segment elevation in the ECG, an early peak in plasma CK concentration, and a high rate of angiographic patency of the involved vessel in early angiograms support these speculations. Resolution of vasoconstriction may be also pathogenically important in non–Q-wave MI. Therefore, spontaneous thrombolysis, vasoconstriction resolution, and presence of collateral circulation are important in preventing the formation of Q-wave MI by limiting the duration of myocardial ischemia.

In Q-wave MI, larger plaque fissures may result in the formation of a fixed and persistent thrombus. This leads to an abrupt cessation of myocardial perfusion for >1 hour, resulting in transmural necrosis of the involved myocardium. The coronary lesion responsible for the infarction and the other acute coronary syndromes is frequently only mildly to moderately stenotic, which suggests that plaque rupture with superimposed thrombus rather than the severity of the underlying lesion is the primary determinant of acute occlusion. Some cases of sudden coronary death probably involve a rapidly progressive coronary lesion in which plaque rupture and resultant thrombosis lead to ischemic and fatal ventricular arrhythmias in the absence of collateral flow. Platelet microemboli may contribute to the development of sudden ischemic death.

Approach to Early Management

Initial Orientation

Guidelines have been published for the management of patients with unstable angina (Table 3). Patients at low risk with new-onset exertion angina or minor exacerbation of chest pain during exercise, which is promptly relieved by nitroglycerin, can be safely managed as outpatients, assuming close follow-up and rapid investigation. Patients with prolonged pain and a ruled-out diagnosis of MI are observed in the emergency room or in a chest pain unit, where clinical status, ECG, cardiac enzymes, and whenever possible, troponin T or troponin I plasma levels are monitored. Blood tests are obtained at admission and repeated 8 to 12 hours after the onset of chest pain to rule out myocardial damage. Patients with a more definite diagnosis and one or more features of high risk, including repetitive pain, hemodynamic compromise, ST-segment shift, or elevation in cardiac enzymes or troponin T or I levels are best monitored in a coronary care unit setting. Management of patients with an intermediary risk is directed by the physician's judgment, often dictated by local facilities and pattern of practice.

General Medical Management: Anti-ischemic and Antithrombotic

In any suspected case of unstable angina, medical treatment is initiated early. Treatment targets control of symptoms of myocardial ischemia and prevention of MI and death. The former is achieved by optimizing balance between myocardial oxygen need and myocardial oxygen supply and the latter by controlling the ongoing disease process of thrombus formation. (See Tables 1, 3, and 5.)

Anti-ischemic Therapy

Restricted activities are indicated. Although caregivers should be attentive to patient need and comfort, the medical environment should not create an climate of undue fear or dependency. Nitroglycerin and, if required, intravenous morphine are administered for pain relief. A long-acting nitrate preparation is routinely prescribed, based on the clinical efficacy of nitroglycerin to relieve pain and on results of many small studies that have suggested efficacy for prophylaxis of pain. Nitroglycerin is administered as an intravenous infusion in patients with a higher risk or with recurrent chest pain. Nitroglycerin can also prevent silent ischemia, control hypertension, and improve left ventricular dysfunction. Tolerance to the hemodynamic effects develops rapidly, and a period without drug administration is recommended after the first 24 to 48 hours. β-Blockers are also widely accepted for the management of unstable angina on the basis of their efficacy in lowering the angina threshold and preventing recurrent ischemia and death after MI. They are particularly useful when clinical evidence of a high sympathetic tone is present, such as inappropriate tachycardia or hypertension. A bolus intravenous administration may result in stabilization of evolving or repetitive chest pain. Calcium antagonists, and more particularly the rate-limiting agents, are effective in preventing recurrent ischemia. Nifedipine is not recommended without concomitant β-blockade, because it may increase the event rate. Triple antianginal therapy, with the...
addition of calcium antagonists to nitroglycerin and \( \beta \)-blockers, is useful to prevent recurrence of angina.\(^{27}\)

**Antithrombotic Therapy**

Antithrombotic and anticoagulant treatment is cause-specific therapy for unstable angina. Thrombolytic agents are not indicated, as opposed to MI with ST-segment elevation. Rapid lysis of an occluding thrombus is required in the latter condition and control of ongoing thrombotic activity in the former. Thus, lytic agents may stimulate the thrombogenic process and result in a paradoxical aggravation of ischemia and in MI.\(^{38}\)

The efficacy of antiplatelet therapy has been conclusively documented in clinical trials. Aspirin is the gold standard. The drug reduces the risk of fatal or nonfatal MI by 71\% during the acute phase,\(^{29,30}\) by 60\% at 3 months,\(^{30,31}\) and by 52\% at 2 years.\(^{32}\) Aspirin possesses numerous physiological effects, many of which are potentially beneficial. The mechanism accounting for the benefit in unstable angina is believed to be irreversible inhibition of the cyclooxygenase pathway in platelets, blocking formation of thromboxane \( A_2 \) and platelet aggregation. Drugs that selectively inhibit thromboxane synthase, the thromboxane receptor, or both have not shown an advantage over aspirin. A bolus dose of 160 to 325 mg is recommended to rapidly achieve full inhibition of thromboxane \( A_2 \) generation by platelets, followed by maintenance doses of 80 to 160 mg/d. Low doses of aspirin, 75 mg/d, appear to be as effective as high doses and cause fewer side effects. The thienopyridines ticlopidine and clopidogrel, unlike aspirin, block platelet aggregation induced by ADP and the transformation of GP IIb/IIIa into its high-affinity state. They are effective antiplatelet agents. In one open-label, randomized study in patients with unstable angina, ticlopidine 250 mg twice a day reduced by 46\% the risk of fatal or nonfatal MI at 6 months.\(^{33}\) Control patients in this study received no aspirin. The benefits of ticlopidine became apparent after only 10 days of therapy, in compliance with the known delay of the drug to reach full antiplatelet activity. Ticlopidine is an acceptable alternative therapy for secondary prevention in patients with poor tolerance to aspirin. Clopidogrel has a longer half-life, is administered once a day, and has a favorable side-effect profile. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial documented the efficacy of the drug for secondary prevention in patients with previous stroke or MI or with peripheral vascular disease.\(^{34}\) No excess leukopenia or thrombocytopenia and no more frequent gastrointestinal side effects than aspirin were observed in the study. The drug has not been evaluated in acute situations.

Development of pharmacological agents inhibiting the GP IIb/IIIa inhibitors has represented an important breakthrough in antiplatelet therapy.\(^{35}\) Direct occupancy of the receptor by a monoclonal antibody or by synthetic compounds mimicking the RGD sequence for fibrinogen binding prevents platelet aggregation. Drugs available for intravenous use are abciximab, a monoclonal antibody against the receptor; eptifibatide, a peptidic inhibitor; and the nonpeptides lamifiban and tirofiban. The effects are highly specific at therapeutic doses and rapidly reversible, but abciximab also inhibits the vitronectin receptor (\( \alpha_{\text{IIb}}\beta_3 \)) and binds tightly to the receptor. Trials with abciximab have conclusively documented the efficacy of the therapeutic approach in preventing death, MI, and abrupt vessel closure associated with coronary angioplasty. In one of these trials, abciximab was administered in patients with refractory angina for 20 to 24 hours before the procedure and for 1 hour after.\(^{36}\) The Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial randomized patients with unstable angina and non–Q-wave MI to tirofiban alone, heparin alone, or a combination of the two on a background of aspirin.\(^{37}\) Medical therapy was applied for the initial 48 hours, followed by angiography and, when clinically indicated, angioplasty on study drug infusion; 31\% of patients had angioplasty. The combination of tirofiban, aspirin, and intravenous heparin reduced the risk of death and MI at 48 hours from 2.6\% to 0.9\%, a 66\% reduction compared with heparin alone, and at 30 days from 11.9\% to 8.7\%, a 30\% risk reduction. The tirofiban-alone arm was dropped prematurely because of an excess mortality, without, however, any excess in rates of MI or refractory angina. The Platelet Receptor Inhibition for Ischemic Syndrome Management (PRISM) trial showed no excess mortality with tirofiban alone compared with heparin alone and a significant risk reduction in the rate of death, MI, or refractory ischemia during the 48-hour infusion of the drug.\(^{38}\) Eptifibatide, evaluated in the Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Trial (PURSUIT), significantly reduced the risk of death and MI at 30 days from 15.7\% to 14.2\%, a 9\% risk reduction.\(^{39}\) Heparin was also used in this trial to suggest that optimal clinical benefits in acute coronary syndromes could require combined inhibition of platelets and of thrombin. More effective inhibition of thrombin generation with newer anticoagulants may further potentiate the gain derived from platelet inhibition.

Heparin is recommended in the management of unstable angina whenever one risk feature is identified. The recommendation is based on documented efficacy in many trials of moderate size, supported by meta-analyses.\(^{40,41}\) Heparin is given as an intravenous bolus followed by an infusion titrated to activated partial thromboplastin time values two times the upper limit of normal. Low-molecular-weight heparins have better bioavailability and produce more reproducible anticoagulation. They also induce less platelet activation and are conveniently administered subcutaneously once or twice daily with no need for monitoring. The various low-molecular-weight heparins have a different ratio of inhibition of factor Xa to thrombin and may have different biological properties and efficacy. The FRISC study showed a superiority of dalteparin over placebo,\(^{42}\) and the FRIC study showed some equivalence between the drug and unfractionated heparin.\(^{43}\) The Efficacy and Safety of Subcutaneous Enoxaparin in non–Q-Wave Coronary Events Study (ESSENCE) trial documented a reduction of 20.4\% in the rate of death and MI at 30 days and of 15\% in the rate of death, MI, and refractory ischemia with enoxaparin administered for a median of 2.6 days (48 hours to 7 days) compared with standard heparin (Fig 4).\(^{44}\) Additional clinical investigation is currently ongo-
ing with the low-molecular-weight heparins, extending the period of treatment to many weeks after hospital discharge.

The direct thrombin inhibitors, and more particularly hirudin, the prototype of this class of agents, have been widely investigated in recent years. Trials with doses of 0.6 mg/kg bolus and 0.2 mg · kg\(^{-1}\) · h\(^{-1}\) infusion were prematurely discontinued because of an unacceptable risk of bleeding.\(^{45}\) The low doses of 0.2 mg/kg bolus and 0.1 mg · kg\(^{-1}\) · h\(^{-1}\) infusion subsequently investigated, although effective during the acute phase, resulted in a gain at 30 days of marginal significance in patients with an acute coronary syndrome without ST-segment elevation.\(^{46}\) Other trials of moderate sample size with synthetic direct thrombin inhibitors also failed to show benefit.\(^{46}\) A large trial is now evaluating a moderate dose of hirudin (0.4 mg/kg bolus and 0.15 mg · kg\(^{-1}\) · h\(^{-1}\) infusion), on the basis of favorable results observed in a pilot study.\(^{47}\)

Although anticoagulants are highly effective during the acute phase, their benefit is most often partly lost in the long term. This is partly explained by a reactivation of the clinical manifestation of the disease once the drugs are discontinued, suggesting that the disease process remains active.\(^{48}\) Strategies currently being investigated to maintain the early gain are more prolonged administration of low-molecular-weight heparins, warfarin, the combination of aspirin and clopidogrel, and oral inhibitors of the GP IIb/IIIa receptor.

**Medical Management Versus Coronary Interventions**

In an effort to define better therapeutic modalities, intervention therapy has been compared with medical therapy. The two main trials that have compared bypass surgery with medical therapy, the National Cooperative Study\(^{49}\) and the Veterans Administration Cooperative Study,\(^{26}\) have shown similar survival rates with the two therapeutic modalities. In the former study, mortality at 1 year was 8% in surgical patients and 7% in medical patients. In the latter, the rates of MI after 2 years were 11.7% and 12.2%, respectively. Rates of crossover to surgery were 19% at 1 year in the National Cooperative Study and 34% at 2 years in the Veterans Administration study. Importantly, subsets of patients in the Veterans Administration study benefited in the long term from surgery. Thus, the 5-year survival rate in patients with three-vessel disease was 89% with surgery compared with 75% with medical treatment \((P=.02)\), and mortality in patients with an ejection fraction between 30% and 49% was reduced from 27% to 14%.

With the development of percutaneous procedures for myocardial revascularization, trials have been reoriented to the comparison of an early invasive strategy with an early conservative strategy. The TIMI 3B trial was the prototype of these trials.\(^{28}\) By study design, patients in the early invasive strategy arm had coronary angiography within 24 to 48 hours after randomization, followed by coronary angioplasty or bypass surgery in the presence of suitable anatomy. These procedures were performed in the conservative strategy arm with failure of medical therapy, defined by recurrent chest pain with ST-T changes, a ≥20-minute period of ischemic ST-segment shifts on a 24-hour Holter monitor, a predischARGE positive stress thallium exercise test before completion of stage 2 of the Bruce protocol, rehospitalization for unstable angina, or angina class III or IV with a positive exercise test during follow-up. A total of 1473 patients with unstable angina or non–Q-wave MI were randomized. The primary end point included death, MI, or a positive treadmill test at 6 weeks; it occurred in 18.1% of patients assigned to the conservative strategy and in 16.2% of patients assigned to invasive strategy \((P=NS)\). Death or MI occurred in 7.8% and 7.2% of patients at 6 weeks \((P=NS)\) and in 12.2% and 10.8% at 1 year \((P=NS)\). A large proportion (64%) of patients assigned to medical treatment crossed over to invasive treatment because of recurrent angina or an early positive test for ischemia. Also, the average length of initial hospital stay, the incidence of rehospitalization within 6 weeks, and the number of days of rehospitalization were all decreased with invasive treatment. The Veterans Affairs non–Q-wave Infarction Strategies in Hospital (VANQWISH) study recently reported a better outcome at hospital discharge and at 1 year with an initial conservative strategy in patients with non–Q-wave MI randomized to medical or invasive strategy.\(^{51}\) Rates of death and MI at hospital discharge were 3% and 8%, and at 1 year, they were 18.5% and 24%, respectively. The evaluation of these results awaits publication of the report.

The comparative studies have not shown a real contrast between treatment groups in rates of interventions. In the TIMI study, cardiac catheterization was performed in 98% of patients randomized to the early invasive group and in 65% randomized to the early conservative strategy; angioplasty in 38% and 26%, respectively; and surgery in 25% and 24%. In the VANQWISH trial, revascularization rates at 1.5 years were 44% with early aggressive management and 33% with early medical treatment \((P=NS)\). Currently available data therefore suggest that medical management and percutaneous or surgical interventions are more additive and complementary than conflicting. The respective advantages and disadvantages of the various treatment strategies are known. Unstable angina is a medical situation associated with a buildup of multiple pathophysiological processes culminating in myocardial ischemia. Interventions are often required as an adjunct to medical treatment to relieve recurrent ischemia and
severe obstruction. Conversely, aggressive medical treatment is required as an adjunct to invasive procedures to prevent the enhanced risk of abrupt vessel closure associated with the presence of a thrombus. The procedures, at times, may be life-saving. Whether percutaneous or surgical procedures should be performed is a matter of coronary anatomy, benefit and risk of the respective procedures, and often, patient choice guided by physician experience. Percutaneous intervention first targets correction of the culprit lesion, and bypass surgery targets more complete revascularization. Angioplasty is usually preferred in one-vessel disease. Comparison of the respective merits of bypass surgery versus angioplasty in patients with multivessel disease has in general provided similar results. Left main artery disease is an indication for bypass surgery, and proximal left anterior descending coronary artery stenosis is also often best treated by internal mammary artery graft surgery. In the Bypass Angioplasty Revascularization Investigation (BARI) trial, treated diabetic patients with multivessel disease had a significantly better 5-year survival with bypass surgery than with balloon angioplasty when at least one internal mammary graft implant was performed.

The technical advances and increased safety of percutaneous interventions with adjunctive GP IIb/IIIa inhibition, stent implantation, and a search for optimal angiographic results have significantly reduced the previously reported high failure rates of early interventions. A new era in bypass surgery has also opened with minimally invasive surgery. This procedure has also included minimally invasive surgery. This progress has led to more timely use of interventions, greater expertise, development of widespread facilities, and networks for patient referral to tertiary centers. The relative advantage of medical therapy versus intervention therapy is best evaluated at present in the context of risk and benefit for individual patients and optimal use of medical resources. These resources differ between countries and between regions in the same country. One approach generally recommended consists of initial medical therapy tailored to risk, with rapid progression to invasive management when ischemia is not adequately controlled.

**Tailoring Therapeutic Modalities and Intensity to Risk Profile**

The majority of patients with unstable angina are well controlled with medical therapy, with no recurrent ischemia, and have a favorable risk profile (Tables 1 and 3). These patients do not need routine angiography and are adequately stratified with provocative testing, including imaging techniques when available. A negative exercise test rules out ischemia associated with severe stenosis and is associated with a low event rate during follow-up. ST-segment depression or a transient perfusion defect indicates significant stenosis. Treatment may be medical if the modifications are not severe or are manifested at a high level of exercise or invasive if more severe or occurring at low level of exercise.

As discussed in the section “Evaluation of Risk and Prognosis,” patients with angina in the early phase of MI or those with persistence of instability on medical treatment are at high risk. They should have early coronary angiography with the goal of identifying a critical coronary stenosis suitable for correction by an intervention. Recurrent ischemia indicates lack of control of the disease state, presence of a critical coronary stenosis, or more extensive disease. Intra-aortic balloon counterpulsation is indicated to stabilize the more unstable patients and as a bridge to more definitive correction.

**Medical Management After Initial Therapy: Plaque Passivation**

Issues that need consideration past the acute phase are prevention of recurrent events and quality of life. The presence of limiting angina on medical treatment is an indication to investigate options for revascularization procedure. Follow-up studies have also documented that the risk of recurrence is high after unstable angina and non-Q-wave MI. Modern trials that have included aspirin, heparin, antithrombotic therapy, and coronary revascularization as standard treatment reported rates of death and MI of 8% to 14% after 4 to 6 weeks and of death, MI, or refractory ischemia of 15% to 25%.

The period of higher risk extends during the following 3 months and beyond. Recurrence may represent incomplete healing and may also suggest that unstable angina is not only an acute, self-limited process but also an acute exacerbation of a more persistent underlying disease process. The plaque, whatever the causative factor(s), is exceedingly inflammatory in unstable angina, and reactivation of the process and new plaque rupture may trigger new thrombus. New dimensions on antithrombotic treatment are emerging with the goal of passivation of the active plaque to prevent reactivation and recurrence and possibly also rapid progression of atherosclerosis.

**Future Directions**

New methods are being developed to investigate the unstable patient and the unstable plaque. Such methods are external magnetic resonance imaging of the components of the plaque and thermal detection of the inflammatory process. The scope of potential beneficial therapy is rapidly expanding as pathophysiological mechanisms become better defined. Promising new therapeutic avenues include control of triggers to plaque activation, plaque inflammation, and rupture; better antithrombotic drugs; and prevention of cell death during ischemia (Table 5).

**Atherosclerosis**

The importance of an aggressive program of control of risk factors needs to be stressed with each patient. Discontinuation of smoking, control of hypertension, aggressive lowering of LDL cholesterol values, and physical fitness prevent death, MI, and the need for coronary angiography in later years, suggesting modification in plaque constitution and decreased thrombogenicity. New risk factors are emerging; their independent contributing roles in atherosclerosis and in acute coronary syndrome, as well as the potential benefit associated with their control, need better definition. Some of these are associated with endothelial dysfunction, such as estrogen deficiency, and high homocysteine, P-selectin, and von Willebrand factor plasma levels. Others, such as fibrinogen, TF, and factor VII, mark a thrombogenic state. Levels of tissue
TABLE 5. Buildup of Disease Processes Leading to Unstable Angina and Cell Necrosis, and the Multifactorial Therapeutic Approach to Control of Disease

<table>
<thead>
<tr>
<th>Pathophysiological Process</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Control of established and new risk factors</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Anti-inflammatory drugs*</td>
</tr>
<tr>
<td>&quot;Active&quot; plaque</td>
<td>Antibiotics*</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Antithrombic therapy</td>
</tr>
<tr>
<td>Acute ischemia</td>
<td>Aspirin</td>
</tr>
<tr>
<td>Calcium entry</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>Acute ischemia</td>
<td>GP IIb/IIIa inhibitors</td>
</tr>
<tr>
<td>Cell necrosis</td>
<td>Na&quot;-H&quot; exchange blockers*</td>
</tr>
</tbody>
</table>

*At a clinical investigation stage.

plasminogen activator inhibitor and of lipoprotein(a) can also be elevated. Markers of an inflammatory state, such as C-reactive protein, interleukin, P-selectin and other cell adhesion molecules, activated circulating leukocytes, and platelet-leukocyte aggregates, are found in unstable angina.7 The value of these markers to identify the high-risk patients and to evaluate response to treatment needs further investigation. Of interest, the protective effect of aspirin against occurrence of a first MI in the Physicians’ Health Study appears to be related to baseline levels of C-reactive protein, raising the possibility that anti-inflammatory agents may have clinical benefits in preventing cardiovascular disease.56 The doses of aspirin in the study were 325 mg on alternate days.

Antithrombotic Therapy

The field of antithrombotic therapy is rapidly evolving as more selective and more effective drugs are developed. Benefit derived from the combination of aspirin and clopidogrel could be additive. Platelet adhesion can be inhibited by monoclonal antibody against GP 1b/IX and by inactive fragments of von Willebrand factor. Oral GP IIb/IIIa inhibitors may prolong the benefit observed with intravenous agents and are currently being evaluated in large-scale trials.

Anticoagulants under investigation target inhibition of the coagulation cascade at specific levels, such as the TF–factor VII complex (recombinant TF pathway inhibitor), the tenase complex (direct inhibitors of factor Xa), thrombin (intravenous and oral direct inhibitors), and amplification of effects of natural anticoagulants (heparin cofactor 2, recombinant activated protein C).

Anti-Inflammatory and Anti-Infectious Therapy

Control of the inflammatory process may prevent plaque activation and thrombus formation. Potentially useful interventions are inhibitors of leukotrienes, cyclooxygenase-2, metalloproteinases, monocyte/macrophages, cytokines and adhesive molecules, and modulation of promoters of gene transcription such as nuclear factor-κB.20 There is also a large potential for correcting the triggers to inflammation and the biological offenders, such as oxidized LDL, free radicals, and viruses and bacteria. Candidates for an infectious process are Helicobacter pylori, Chlamydia pneumoniae, cytomegalovirus, and other herpesviruses. Compelling evidence exists for a role of Chlamydia pneumoniae, such as high titters of antibodies in patients with CAD and an acute manifestation, and the presence of elementary bodies, DNA, and antigens in atherosclerotic arterial wall.27 The infectious process can be a distant infection that induces immune activation, cross-reactive antibodies, cytokine release, endothelial damage and thrombogenesis, or a local infection of endothelial cells, smooth muscle cells, or macrophages and lymphocytes resulting in endothelial injury, cell proliferation, and inflammation. Alternatively, the bacteria can be an innocent bystander. Two pilot studies, however, have suggested that antibiotic therapy with a macrolide could improve prognosis after an acute coronary syndrome. Gupta et al58 screened 220 men after MI and randomized the 80 patients with antibody titers >1/64 to azithromycin or placebo for 5 or 6 days. The odds of an event in patients with placebo was 4 times higher than in nonrandomized patients with negative titers and than in treated patients with positive titers. In the other trial, roxithromycin administered for 30 days in 202 patients with unstable angina or non–Q-wave MI reduced the 6-month rate of death or MI from 4% to 0% and of death, MI, or recurrent ischemia from 9% to 2%.59

Prevention of Cell Necrosis

Left ventricular damage is the strongest independent predictor of short- and long-term prognosis after an acute coronary syndrome. Attempts to reduce left ventricular damage in humans have been few in the past because of lack of an effective therapy but are now reviving with the availability of new agents. Ischemic myocardial injury initiates an acute inflammatory response, with neutrophil activation and release of cytokines, leukotrienes, proteases, and free radicals. The interruption of these processes with free radical scavengers and inhibitors of cytokines, lipoxygenase, cyclooxygenase, and various adhesive proteins may be effective in limiting the size of infarction. It is also now possible to prevent the calcium overload associated with myocardial cell ischemia and reperfusion, leading to cell contracture, rupture of sarcosomes, and cell death by inhibiting the sodium-hydrogen antiport system.60 Such a potent and relatively selective inhibitor of the Na"-H" exchange system is presently being investigated in clinical situations with risk of necrosis.

In summary, the pathophysiology of unstable angina involves numerous pathways building up to result in intravascular thrombosis, ischemia, and cell death. The multifactorial etiology requires a multifactorial approach. The road to effective control has been marked by definition of the cellular mechanisms; development of effective antithrombotic therapy with aspirin, heparin, and the GP IIb/IIIa inhibitors; and progress in revascularization procedures. The road to future progress is rich in new working hypotheses and therapeutic strategies.

References


