UNSTABLE ANGINA, FROM PATHOLOGY TO CLINICAL OUTCOME: AN OVERVIEW

SAMIR ALAM, MD, FACC

Acute coronary syndromes represent sudden, unexpected, potentially fatal expression of atherosclerotic coronary disease. Additionally, they comprise an important pathologic mechanism responsible for acceleration of the disease and rapid expansion of the plaque. LDL-oxidation, monocyte transformation, triggering of acute inflammation, and thinning of the plaque are viewed, at present, as key metabolic and pathologic events responsible for plaque rupture, thrombosis, and acute ischemia. Growth factors elicited by macrophages, platelets, and endothelial cells contribute to plaque growth and subsequent high clinical coronary event rate observed over short term. Strategies for prevention and management of acute coronary syndromes must take into account the elements and triggers involved. Aggressive management is warranted, especially in the presence of specific injury markers. Currently, proposed classification of unstable angina incorporates relevant clinical pathologic considerations that constitute a predictable framework for identifying high-risk clinical targets. The clinical, angiographic, and outcome experience of 100 consecutive patients with unstable angina demonstrate the effectiveness of a comprehensive protocol of antithrombotic therapy and early revascularization.

ATHEROSCLEROSIS is a chronic inflammatory condition that is often suddenly expressed into an acute event by a thrombotic process superimposed on plaque rupture.1-12 Acute coronary syndromes thus comprise the clinical pathologic link connecting atherosclerosis, commonly a dormant benign condition with fatal or near-fatal clinical syndromes.

Mechanical and biomechanical3,4 properties of the plaque primarily influence the behavior of the plaque. The paradigms linking volume and severity of plaque stenosis to clinical events are disputed at present. 5 In this communication, we review the recent evidence implicating chemical and inflammatory factors leading to biomechanical plaque vulnerability, rupture and disruption,

From the Department of Medicine, Division of Cardiology, American University of Beirut, Beirut, Lebanon.

Address reprint requests and correspondence to Dr. Alam: Department of Medicine, Division of Cardiology, American University of Beirut, Beirut, Lebanon.

thrombosis, and consequent clinical events. The relation of these pathological events to acceleration of the disease will be discussed, and strategies derived from our tertiary center experience as well as from other clinical trials will be proposed.

Plaque Pathology

Results of recent studies indicate that rapidly evolving atherothrombotic lesions are the culprit in patients who suffer fatal coronary events. Characteristically, these injured plaques are rich in lipid with abundance of macrophages and low in smooth-muscle cell content with scarce collagen matrix. Vulnerable plaques had frequently suffered an inflammatory process which has eroded the matrix, leading to disruption.1-4 The origin of the plaque starts with intracellular and extracellular trapping of LDL-cholesterol in the subintimal compartment of the arterial wall.6 Oxidative
modification of the LDL-molecule results in the shift of LDL recognition by LDL cell receptor to recognition by scavenger receptors and/or oxidized-LDL receptor. The result is a massive and uncontrolled accumulation of free cholesterol and foam cells. Additionally, oxidized-LDL induces gene expression, leading to enhanced monocyte adherence, migration, and transformation into macrophages. P selectin, endothelial-derived monocytes, chemo-attractant protein MCP-1, and monocyte-colony stimulating factor (MCSF) are released. Interestingly, HDL-associated enzymes have been found to protect against LDL modification. The activation of monocytes affect local changes by the release of inflammatory, cytotoxic, and growth mediators including interleukin I, interleukin 6, as well as platelet-derived growth factor (PDGF). Additionally, LDL-oxidation affects T-lymphocyte attraction and subsequent release of adhesion molecules VCAM, ICAM1, and PDGF from endothelial cells and smooth-muscle cells. Oxidized-LDL also inhibits endothelial cell migration and impairs the repair of ulcerated plaques. Highly oxidized-LDL has been shown to be toxic to macrophages and may thus further amplify the inflammatory process and formation of the necrotic core. The above-described molecular events underscore the importance of lipid oxidation in the formation, complication, and progression of atheromatous plaque. Conversely, pharmacological manipulation of lipid oxidation has been demonstrated to favorably influence the clinical outcome of patients with coronary disease.

Plaque Disruption

Accumulated experimental and clinical data suggest dissociation between coronary events and plaque size. Acute coronary syndromes and outcome of coronary artery disease are demonstrably related to plaque rupture, platelet aggregation, and thrombosis. The propensity of a plaque for rupture is determined by the interaction between triggers (such as hemodynamic factors and smoking) and biomechanical characteristics of the plaque, regardless of size. A rupture-prone plaque is characterized by a lipid-rich core with an abundance of thrombotic tissue factor and disproportionately thin fibrous cap with reduced matrix and smooth-muscle cell content; plaque stress is increased, rendering the plaque deformable and prone to rupture, often at the junction of the normal vessel segments with the plaque. A dysfunctional endothelium further promotes thrombosis and vasoactivity at the site of the plaque and hence facilitates thrombotic and occlusive tendency of the vessel. Platelets play key mediating role in acute coronary syndromes. Dysfunctional or superficially-injured endothelium promotes platelet aggregation and degranulation, resulting in mechanical plugging, prostaglandin-mediated vasoconstriction, and superimposed thrombosis. PDGF further affects plaque growth and expansion. Experimental, metabolic, and clinical evidence confirm the participation of platelets in all phases of unstable angina.

Prior aspirin therapy has been shown to improve outcome. Antiplatelet therapy is the mainstay of unstable angina therapy. The traditional concept that thrombo-occlusive complications of the plaque are primarily the result of exposure of corpuscular elements of the circulating blood to subintimal lipids and the collagen of mechanically-injured plaque is no longer tenable in light of current observations, implicating a decisive inflammatory process mediated by predominance of macrophages and T-lymphocytes. These cells express important cytotoxic and inflammatory pathways mediated by several cytokines (interferon gamma, tissue necrosis factor, interleukin I, and MCSF), resulting in impaired maintenance and repair of the collagen framework of the cap, activation of matrix-degrading proteinases originating from macrophages, as well as switching of program of cell death (apoptosis) of macrophages and smooth-muscle cells. Plaque stability or vulnerability should then be viewed as a complex interaction of forces related to lipid core and metabolic and genetic factors affecting oxidative potentials, inflammatory state, and fibrotic/calcification activity within the plaque. These factors determine the cellular and matrix components of the fibrous plaque, hence its stress resistance. Additionally, endothelial function and existing extrinsic metabolic and thrombotic forces inclusive of lipoprotein LDL, Lp(a), hemodynamic condition, and smoking constitute triggering and/or confounding factors which influence the outcome of plaque injury. The final event in plaque rupture is
platelet aggregation, plaque hemorrhage, thrombosis, expansion, and/or thrombotic occlusion. The pathologic severity depends on the depth of plaque injury and the existing balance between the procoagulant and fibrinolytic state. The clinical syndrome is determined by thrombus friability, pre-existing collaterals, and other prevailing metabolic factors. Repeated cycles of thrombosis, inclusion, organization, and accelerated plaque growth are implicated in many clinical situations and have been demonstrated in pathologic specimens and angiographic observations.

Clinical Pathologic Correlations

The above-described pathologic events help place in perspective, important and relevant clinical syndromes and observations: (1) abrupt change of the clinical course and unexpected ischemic events, regardless of the severity of plaque stenosis; (2) accelerated, non-linear progression of clinical and angiographic diseases following unstable syndromes, with demonstrable significant incidence of total occlusion of culprit lesions despite "stabilizing medical" therapy; (3) dissociation between reduction of plaque size by lipid-lowering treatment and reduction of coronary events; (4) failure of revascularization of significantly obstructive disease to prevent fatal events.

Clinical Syndrome of Unstable Angina

Unstable angina is a common clinical syndrome and has become the most frequent cause of cardiac unit admissions. Its importance is that it ushers an acute pathologic transformation of the plaque and portends the potential for significant coronary event rates in short and long term. An objective scheme to identify, classify, compare, and evaluate outcome of patients with this entity was recently proposed by Braunwald's classification. This framework has served a useful function in providing standardized parameters of diagnosis and therapy (Table 1). Occurrence of rest angina within 48 h after infarction and manifested reversible EKG changes, despite maximal medical therapy, describe groups at high risk. Conversely, no angina for 48 h and an absence of EKG changes, despite no medical therapy, describe very low-risk groups.

We examined 100 consecutive patients who presented or were referred to our tertiary care facility with unstable angina. Patients with active infarction were excluded. Non-Q infarction patients were not entered in this study.

A total of 81 patients were males while 19 were females; 55 patients had experienced pain within 24 h, 9 within 48 h, and 36 had no pain for more than 48 h. Twenty-six patients had new onset of pain and 41 had rest pain, while 27 had changing patterns of pre-existing angina. Family history of coronary artery disease, hypercholesterolemia, and active smoking were prevalent in 48, 35, and 73 patients, respectively. Forty-three patients had reversible ST changes and 36 had only T changes, while 16 patients had no EKG changes manifested. All patients were treated with variable combinations of heparin, nitrates, beta-blockers, and calcium-blockers, in addition to aspirin. Ninety patients received heparin, 86 received aspirin, and 78 received a combination of both. All patients underwent catheterization 3 to 12 (mean, 3.5) days after admission. Sixty-two patients were considered clinically controlled at time of angiography.

Anatomic findings revealed left anterior descending (LAD) involvement in 78%, left circumflex (LCF) in 61%, right coronary artery (RCA) in 53%, and left main in 7%. LAD was the culprit in 51 %, LCF in 29%, and RCA in 20% while 6% of patients had normal anatomy.

The outcome following the catheterization is summarized: 48 patients were operated, 27 patients received angioplasty, and 27 were treated medically.

Table 1. Clinical classification of unstable angina.

<table>
<thead>
<tr>
<th>Clinical states</th>
<th>Aggravating Plaque as non-cardiac culprit (B) factors (A)</th>
<th>Post MI (C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) New onset, accelerated, no rest pain</td>
<td>IA IB IC</td>
<td></td>
</tr>
<tr>
<td>(II) Angina at rest, none in 48 h</td>
<td>IIA IIB IIC</td>
<td></td>
</tr>
<tr>
<td>(III) Angina at rest, in past 48 h</td>
<td>IIIA IIIB IIIC</td>
<td></td>
</tr>
</tbody>
</table>

MI = myocardial infarction.
UNSTABLE ANGINA

because of insignificant anatomic disease, unsuitable anatomy, or patient-physician preference. Three patients sustained myocardial infarction, and 2 patients died post-bypass surgery. Of the angioplasty group, 25 patients had successful dilatation and 2 patients required emergency bypass surgery.

In contrast to significant short- and long-term event rate reported in the syndrome of unstable angina,29-32 our experience underscores the feasibility and effectiveness of an aggressive medical, revascularization protocol with low risk for myocardial infarction and death. The pathologic events outlined above help explain the progressive nature of unstable angina, especially at the site of ruptured plaques. Kaski et al27 observed 31% incidence of major coronary events, occurring one month to one year following "medical stabilization" of unstable angina among patients waiting for elective angioplasty. Of 72% progressed lesions, 70% were totally occluded. Similarly, Fuster et al and others observed substantial event rate among medically-treated patients following unstable angina and non-Q myocardial infarction. Although the outcome of conservative and invasive strategy groups in unstable angina was comparable in TIMI-IIIB experience, yet there was a significant crossover from conservative to invasive strategy groups prompted by developing clinical events33; 64% and 49% of patients required catheterization and bypass surgery, respectively, within one year. A preemptive intervention strategy, therefore, seems justified.

Strategies for Diagnosis and Therapy

Acute coronary syndromes should be managed according to established pathobiological understanding. The elements which participate in the genesis of the syndrome must be selectively targeted and neutralized. Patients at high risk must be identified for aggressive management. Culprit lesions must be carefully evaluated for severity, morphology, and thrombus content. Appropriate revascularization and medical treatment should be initiated promptly.

Medical Treatment

Uniform guidelines for the treatment of unstable syndromes have not been established. The following recommendations are based on trends and results of small clinical trials: (1) heparin and aspirin, in combination, especially for patients who had experienced ischemic pain in the last 48 h22,23 have been shown to be the most effective intervention for the medical control of unstable angina. Platelet aggregation can now be completely inhibited by drugs acting on membrane receptor IIb/IIIa, Blockage of the receptor may aid benefit to aspirin and to heparin in unstable angina. Thrombolytic therapy, however, has not proved effective except in severe and intractable cases; (2) nitrates possess anti-ischemic and antiplatelet effects and have been shown in many trials to reduce the frequency of silent and symptomatic episodes34; (3) β-blockers have anti-ischemic and sympathetic neutralizing properties and have been shown to be superior to calcium blockers, especially nifedipin, in reducing incidence of myocardial infarction and recurrent angina. Diltiazem, in patients with non-Q infarction and preserved ventricular function, has been shown to decrease subsequent fatal and non-fatal events30,35-37; and (4) invasive strategies as noted above, especially in patients at high risk an invasive diagnostic and revascularization strategy is recommended following a period of stabilization with drug therapy.30,31 Clinical data suggest that a treatment period of 3 to 5 days is beneficial and perhaps diminishes procedure-related complications during angioplasty or bypass surgery. It should be appreciated, however, that acute phase angioplasty carries higher risk of abrupt closure, need for emergency bypass surgery, and restenosis than stable angina.30,31,37,38

Risk Stratification

Markers of increased risk for myocardial infarction and recurrent ischemic events are surrogates of continuing plaque instability, as well as progression and plaque expansion. These markers are recurrent pain, EKG changes during pain, pain in the last 48 h, post-myocardial infarction, remote ischemia, elevated serum troponin,39 thrombus in culprit vessel, and positive stress test performed following stabilization.40 The common practice of stress test at an early phase of admission is not recommended because of potential aggravation of plaque injury by increased shear force. Furthermore, because unstable culprit plaques are frequently subocclusive, they are
unlikely to manifest noticeable limitation of regional blood-flow reserve. Stress test data are therefore irrelevant to the pathophysiology of unstable syndrome and can be misleading when used to screen for culprit lesions of unstable angina.

**Preventive Strategies**

Preventive measures aimed at control of risk factors and "stabilizing" of plaque have been shown to be beneficial and cost effective. Pathologic and clinical observations have established that acute coronary syndromes are the results of abrupt transformation and progression of small or moderate-sized plaques, and that the value of lipid-lowering therapy was in the ability to stabilize a subpopulation of lipid-rich, rupture-prone plaques. A comprehensive program of risk factor modification and lipid control should be the prime focus for the reduction of coronary artery disease mortality. The use of HMG-COA reductase inhibitor in the 4S study showed a 40% reduction rate of cardiac events in patients with history of coronary disease.17

**Conclusion**

Acute coronary syndromes, such as unstable angina, non-Q infarction, myocardial infarction, and sudden death, share common pathologic and pathophysiologic mechanisms, with only quantitative differences in the degree of plaque injury, platelet aggregation, dynamic obstruction, and thrombotic occlusion. Limited clinical trials have observed substantial first-year morbidity, even among clinically stabilized patients. Pathologic mechanisms, triggered in unstable angina, readily account for atherosclerotic plaque expansion and remodeling following injury. Early identification, antiplatelet, antithrombin, and timely revascularization seem to be quite effective in improving clinical outcome. Prevention or reduction of ischemic events is possible with aggressive risk modification and lipid-lowering therapy.

**References**


