



JOURNAL OF THE AMERICAN HEART ASSOCIATION

#### **Pathophysiology of Coronary Artery Disease** Peter Libby and Pierre Theroux Circulation 2005;111;3481-3488 DOI: 10.1161/CIRCULATIONAHA.105.537878 Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514 Copyright © 2005 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

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### **Pathophysiology of Coronary Artery Disease**

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Abstract—During the past decade, our understanding of the pathophysiology of coronary artery disease (CAD) has undergone a remarkable evolution. We review here how these advances have altered our concepts of and clinical approaches to both the chronic and acute phases of CAD. Previously considered a cholesterol storage disease, we currently view atherosclerosis as an inflammatory disorder. The appreciation of arterial remodeling (compensatory enlargement) has expanded attention beyond stenoses evident by angiography to encompass the biology of nonstenotic plaques. Revascularization effectively relieves ischemia, but we now recognize the need to attend to nonobstructive lesions as well. Aggressive management of modifiable risk factors reduces cardiovascular events and should accompany appropriate revascularization. We now recognize that disruption of plaques that may not produce critical stenoses causes many acute coronary syndromes (ACS). The disrupted plaque represents a "solid-state" stimulus to thrombosis. Alterations in circulating prothrombotic or antifibrinolytic mediators in the "fluid phase" of the blood can also predispose toward ACS. Recent results have established the multiplicity of "high-risk" plaques and the widespread nature of inflammation in patients prone to develop ACS. These findings challenge our traditional view of coronary atherosclerosis as a segmental or localized disease. Thus, treatment of ACS should involve 2 overlapping phases: first, addressing the culprit lesion, and second, aiming at rapid "stabilization" of other plaques that may produce recurrent events. The concept of "interventional cardiology" must expand beyond mechanical revascularization to embrace preventive interventions that forestall future events. (Circulation. 2005;111:3481-3488.)

Key Words: atherogenesis ■ inflammation ■ ischemia ■ plaque ■ acute coronary syndromes

During the past decade, our understanding of the pathophysiology of coronary artery disease (CAD) has undergone a remarkable evolution. As patients with CAD generally present with either chronic or acute manifestations, this discussion will consider in turn these distinct modes of presentation.

### The Pathophysiology of Chronic CAD

#### **Lesion Formation**

Previously considered a cholesterol storage disease, we currently understand atherogenesis as a complex interaction of risk factors including cells of the artery wall and the blood and molecular messages that they exchange. A useful organizing theme, which emerged first from laboratory studies and has now gained currency in the clinic, accords inflammation a major role in all stages of atherogenesis.<sup>1</sup> Inflammation also participates in the local, myocardial, and systemic complications of atherosclerosis.

When the arterial endothelium encounters certain bacterial products or risk factors as diverse as dyslipidemia, vasoconstrictor hormones inculpated in hypertension, the products of glycoxidation associated with hyperglycemia, or proinflammatory cytokines derived from excess adipose tissue, these cells augment the expression of adhesion molecules that promote the sticking of blood leukocytes to the inner surface of the arterial wall. Transmigration of the adherent leukocytes depends in large part on the expression of chemoattractant cytokines regulated by signals associated with traditional and emerging risk factors for atherosclerosis. Once resident in the arterial intima, the blood leukocytes-mainly mononuclear phagocytes and T lymphocytes-communicate with endothelial and smooth muscle cells (SMCs), the endogenous cells of the arterial wall. Major messages exchanged among the cell types involved in atherogenesis depend on mediators of inflammation and immunity, including small molecules that include lipid mediators such as prostanoids and other derivatives of arachidonic acid, eg, the leukotrienes. Other autacoids, such as histamine, classically regulate vascular tone and increase vascular permeability. Recently, much attention has focused on protein mediators of inflammation and immunity, including the cytokines and complement components. Virtually unknown by cardiologists a mere decade ago, the cytokines have joined the mainstream of our specialty.

As a major consequence of the inflammatory ferment underway in the early atheroma, SMCs migrate from the tunica media into the intima. These cells proliferate and

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**Figure 1.** Simplified schema of diversity of lesions in human coronary atherosclerosis. This schematic depicts 2 morphological extremes of coronary atherosclerotic plaques. Stenotic lesions tend to have smaller lipid cores, more fibrosis, and calcification; thick fibrous caps; and less compensatory enlargement (positive remodeling). They typically produce ischemia appropriately managed by combined medical therapy and often revascularization for symptom relief. Nonstenotic lesions generally outnumber stenotic plaques and tend to have large lipid cores and thin, fibrous caps susceptible to rupture and thrombosis. They often undergo substantial compensatory enlargement that leads to underestimation of lesion size by angiography. Nonstenotic plaques may cause no symptoms for many years but when disrupted can provoke episode of unstable angina or MI. Management of nonstenotic lesions should include lifestyle modification (and pharmacotherapy in high-risk individuals). Enlarged segments of schematic show longitudinal section (left) and cross section (right). Many coronary atherosclerotic lesions may lie between these 2 extremes, produce mixed clinical manifestations, and requires both revascularization and systemic therapy. PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft.

elaborate a rich and complex extracellular matrix. In concert with endothelial cells and monocytes, they secrete matrix metalloproteinases (MMPs) in response to various oxidative, hemodynamic, inflammatory, and autoimmune signals. MMPs, in balance with their endogenous tissue inhibitors, modulate numerous functions of vascular cells, including activation, proliferation, migration, and cell death, as well as new vessel formation, geometric remodeling, healing, or destruction of extracellular matrix of arteries and the myocardium.<sup>2</sup> Certain constituents of the extracellular matrix (notably proteoglycans) bind lipoproteins, prolong their residence in the intima, and render them more susceptible to oxidative modification and glycation (nonenzymaticc conjugation with sugars).<sup>3</sup> These products of lipoprotein modification, including oxidized phospholipids and advanced glycation end products, sustain and propagate the inflammatory response.<sup>4,5</sup> As the lesion progresses, calcification may then occur through mechanisms similar to those in bone formation.<sup>6</sup> In addition to proliferation, cell death (including apoptosis) commonly occurs in the established atherosclerotic lesion.7 The death of lipid-laden macrophages can lead to extracellular deposition of tissue factor (TF), some in particulate form.8 The extracellular lipid that accumulates in the intima can coalesce and form the classic, lipid-rich "necrotic" core of the atherosclerotic plaque.

#### Arterial Remodeling, a Clinically Critical Component of Atherogenesis

From a practical clinical perspective, few aspects of the biology of atherogenesis have had more recent impact than the concept of arterial remodeling (Figure 1). Driven by the ascendancy of angiography and the success of revascularization strategies that target arterial stenoses, the degree of arterial narrowing dominated our thinking about the pathophysiology of CAD for decades. We viewed the risk of events as dependent on the degree of stenosis and envisioned atherosclerosis as a segmental or focal disease.

This traditional viewpoint has undergone radical revisions, thus expanding our sophistication and providing a new perspective for improving patient outcomes. We now recognize that for much of its life history, the atherosclerotic lesion grows outward, or abluminally, rather than inward.<sup>9,10</sup> Thus, a substantial burden of atherosclerosis can exist without producing stenosis.11 Intravascular ultrasound studies have confirmed in vivo older autopsy studies: Stenoses represent the "tip of the iceberg" of atherosclerosis. By the time lesions have progressed to the point of producing stenoses, intimal atherosclerosis usually abounds in a widespread, diffuse distribution.<sup>12</sup> Intravascular ultrasound studies have underscored the unsettling prevalence of atherosclerotic lesions even in adolescent and young adult Americans.13 The recognition of the ubiquity of substantial but non-flow-limiting atherosclerotic lesions has considerable consequences for our current understanding of the acute coronary syndromes (ACS; see following sections).

# The Therapy of Chronic CAD: Perspective for the Future

Until recently, the presence of myocardial ischemia associated with flow-limiting stenoses governed the therapy of CAD (Figures 1 and 2). Various imaging methods performed at rest or during a provocative test allow the monitoring of regional myocardial perfusion and function with a high degree of diagnostic accuracy. Therapy aimed at reduction of



**Figure 2.** Management of atherosclerosis: matching therapy with pathophysiology. This scheme places management of atherosclerosis in context of physiopathology, phase of disease, and intensity of risk (depicted by yellow to red gradient from right to left). Preventive measures apply to entire population. Higher-risk individuals and those with documented disease often warrant drug therapy as well. Antianginal therapy is added when disease becomes symptomatic, and full antithrombotic therapy is added in ACS. ASA indicates aspirin; NTG, nitroglycerin;  $\beta B$ ,  $\beta$ -adrenergic blocking agents; CCB, calcium channel blockers; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; UFH, unfractionated heparin; and LMWH, low-molecular-weight heparin.

myocardial oxygen requirements and/or enhancement of myocardial blood flow (eg, nitroglycerin, nitrates,  $\beta$ -blocking agents, and calcium channel blockers) reduce oxygen requirements by influencing factors such as heart rate and the inotropic and loading conditions of the heart (Figure 2). Drugs that enhance the efficiency of energy production by inhibiting free fatty acid oxidation and that promote glucose utilization are on the horizon. Revascularization procedures can effectively restore forward coronary artery blood flow in the majority of patients. The successive generations of advances in surgical and percutaneous revascularization represent some of the great therapeutic advances of the last century. Emerging revascularization modalities include stimulation of arteriogenesis by gene, protein, or cell therapy.

Beyond treatment of flow-limiting lesions, we also must attend to nonobstructive plaques (Figures 1 and 2). Traditional angiography provides only estimates of the severity of most lesions; ischemia may result from dynamic obstruction superimposed on fixed stenoses, and lesions can progress surprisingly rapidly, heralding a poor prognosis.<sup>14</sup> Indeed, fixed stenoses do not progress in a smooth and continuous fashion but seemingly in sudden spurts.<sup>15,16</sup> This discontinuous progression of plaques probably reflects episodes of acute lesion disruption, thrombosis in situ, and healing that promote sudden increases in the severity of obstruction,<sup>17</sup> a scenario that develops most often on nonseverely obstructing lesions. Appropriately directed revascularization can relieve symptoms for the minority of the atheromata in the coronary tree that actually cause ischemia but may not protect against future acute thrombotic events. Current evidence suggests that measures that modify risk factors can delay disease

progression and even permit its regression. The convergence of these recent findings makes a strong case for combining optimal revascularization strategies with long-term risk reduction in lifestyle, often in conjunction with pharmacological measures in atherosclerotic patients (Figures 1 and 2).

Numerous primary and secondary prevention trials have shown that aggressive management of modifiable risk factors reduces death rates, myocardial infarction (MI), stroke, and other cardiovascular events, including the need for revascularization. A 1-mm Hg decrease in blood pressure lowers the long-term risk of MI by 2% to 3%, whereas a 10% reduction in LDL cholesterol diminishes cardiovascular death by 10% and cardiovascular events by 25%. Similarly, the discontinuation of smoking rapidly reduces the attendant cardiovascular risk. Diabetes mellitus and metabolic syndrome elevate the risk of cardiovascular death 2- to 4-fold and reduce life expectancy by 5 to 10 years. The National Cholesterol Education Program Adult Treatment Panel III report has defined and recently refined guidelines for the primary and secondary prevention of atherosclerosis on the basis of risk scales that account for blood lipids, modifiable and nonmodifiable nonlipid risk factors, and other emerging risk factors.18

Lifestyle measures must remain the foundation for the primary prevention of cardiovascular disease. However, individuals whose risk of cardiovascular events exceeds 2%/y and patients with CAD or CAD equivalents often also merit drug therapy. The Heart Protection Study (HPS) showed unambiguous benefit of statin administration in individuals aged 40 to 80 years with total cholesterol >135 mg/dL and at risk because of a previous MI or other coronary or noncoronary artery occlusive disease, diabetes mellitus, or treated hypertension.<sup>19</sup> The Physicians' Health Study (PHS) showed that aspirin significantly reduced the rates of MI in men aged 40 to 80 years.<sup>20</sup> The Heart Outcomes Prevention Evaluation (HOPE) study enrolled patients 55 years of age or older with evidence of vascular disease or diabetes plus 1 other cardiovascular risk factor randomized to the angiotensin-converting enzyme (ACE) inhibitor ramipril or placebo,<sup>21</sup> and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) studied the effects of perindopril in patients with stable CAD of a lower-risk category.<sup>22</sup> Both studies showed that ACE inhibitor administration significantly reduced cardiovascular events. A recent trial in a lower-risk population showed no advantage of ACE inhibitor therapy over contemporary conventional management, highlighting the role for lifestyle modification in such individuals.23

A variety of biomarkers linked to inflammation predict recurrence of short-term coronary events in patients after ACS as well as or better than do conventional risk factors.<sup>24</sup> These markers include acute-phase reactants, pro- and antiinflammatory cytokines, MMPs, shed cell adhesion molecules, and other markers of activation of platelets and white cells, including soluble CD40 ligand and the leukocyte enzyme myeloperoxidase. Because these markers often foretell cardiovascular events in normal populations as well as in patients with stable CAD, they likely reflect fundamental mechanisms of the disease. Current guidelines do not recommend routine clinical assessment of such emerging markers



Figure 3. Microanatomy of coronary arterial thrombosis and acute occlusion. Rupture of fibrous cap (upper left) causes some two thirds to three quarters of fatal coronary thromboses. Superficial erosion (upper right) occurs in one fifth to one guarter of all cases of fatal coronary thromboses. Certain populations such as diabetic individuals and women appear more susceptible to superficial erosion as mechanism of plaque disruption and thrombosis. Erosion of a calcium nodule may also cause plaque disruption and thrombosis (lower left). In addition, friable microvessels in base of atherosclerotic plaque may rupture and cause intraplaque hemorrhage. Consequent local generation of thrombin may stimulate SMC proliferation, migration, and collagen synthesis, promoting fibrosis and plaque expansion on subacute basis. Severe intraplaque hemorrhage can cause sudden lesion expansion by mass effect acutely as well.

of risk. However, a combination of some of these markers with others, such as genetic variants, may provide new insights into the underlying mechanisms of the initiation and progression of atherosclerosis and plaque vulnerability and eventually may guide therapy. Thus, analysis of several databases determined that individuals who profited most from aspirin and statin therapy in primary prevention trials were also those with elevated C-reactive protein values at baseline.<sup>25,26</sup> Statins and peroxisome proliferator activated receptor agonists (both  $\alpha$ - and  $\gamma$ -) can reduce the blood levels of C-reactive protein and other markers of inflammation. These reductions support the importance of the antiinflammatory effects of these drugs as well as the eventual benefits of antiinflammatory or immune system–modulating therapy aimed specifically at atherosclerosis. However, we presently lack proof that pharmacological lowering of inflammatory markers confers clinical benefit.

#### The Pathophysiology of the ACS

As recently as the 1980s, some uncertainty prevailed with regard to the causative role of thrombosis in ACS.<sup>27</sup> In vivo imaging techniques applied in humans and the success of antithrombotic and fibrinolytic therapy in ACS established in practice the role of thrombosis in their pathogenesis. A number of microanatomic mechanisms underlie acute coronary thrombosis (Figure 3). According to autopsy studies—clearly biased toward fatal outcomes—a through-and-through rupture of the plaque's protective fibrous cap most commonly causes lethal coronary thrombosis.<sup>28,29</sup> Other mechanisms that account for a minority of fatal coronary thromboses include superficial erosion, intraplaque hemorrhage, and the erosion of a calcified nodule (Figure 3).<sup>30</sup> Thus, physical disruption of the atherosclerotic plaque accounts for almost all acute coronary thromboses.

Disrupted plaques provoke thrombosis in several ways. First, contact with collagen in the plaque's extracellular matrix can trigger platelet activation. Second, TF produced by macrophages and SMCs activates the coagulation cascade.<sup>31</sup> The disrupted plaque thereby represents a "solidstate" stimulus to both thrombosis and coagulation; these pathways reinforce each other, as thrombin generation amplifies the activation of platelets and other cells in the lesion (Figure 4). Conversion of fibrinogen to fibrin and release of von Willebrand factor from activated platelets can provide the cross-linking molecular bridges between platelets that yield the dense, 3-dimensional network of platelets entrapped in fibrin characteristic of the "white" arterial thrombus.

In addition to the solid state of the disrupted plaque, the "fluid phase" of blood can predispose toward coronary thrombosis (Figure 4). Plasminogen activator inhibitor-1 (PAI-1) extinguishes the body's natural fibrinolytic mecha-



Figure 4. Determinants of thrombosis in coronary atherosclerotic plaques. Formation, extent, and duration of coronary thrombi produced by mechanisms such as those outlined in Figure 3 depend on both solid-state factors in plaque itself and fluid-phase determinants in blood. See text for further explanation.

nism that combats the persistence and accumulation of thrombi by inhibiting urokinase-like and tissue-type plasminogen activators. Circulating levels of PAI-1 increase in diabetes and obesity, and mediators of hypertension such as angiotensin II can augment PAI-1 expression by various cell types.<sup>32</sup> Furthermore, disrupted plaques can elaborate particulate TF, which can heighten the thrombogenicity of blood.<sup>31</sup>

These fluid-phase changes led to the concept of the "vulnerable patient," thus augmenting our appreciation of the so-called "vulnerable plaque."<sup>33,34</sup> In the context of ACS, the distal embolization of TF-rich debris spewing into the bloodstream from the core of the suddenly disrupted plaque may promote distal thrombosis in the microcirculation.<sup>35,36</sup> Such distal embolization explains in part the "no-reflow" phenomenon that can complicate both spontaneous and iatrogenic plaque disruption and prevent effective reperfusion of the distal microcirculation.

#### The Vulnerable Plaque: Fact or Fancy?

The ascendancy of the concept of the so-called vulnerable plaque launched a quest for methods to identify plaques at high risk of causing thrombotic complications. Anatomicopathological studies established characteristics of the ruptureprone plaque, including a thin, fibrous cap and a large lipid core populated by numerous inflammatory cells and relatively lacking in SMCs.<sup>28</sup> Recent results, however, point to the multiplicity of such "high-risk" plaques and the widespread nature of inflammation in patients prone to develop ACS. As noted earlier, both autopsy and intravascular ultrasound studies have underscored the diffuse nature of intimal disease in patients with ACS. Even portions of the coronary arterial tree that appear perfectly normal by angiographic criteria often harbor a substantial burden of atherosclerosis. In particular, plaques with substantial outward remodeling, or "compensatory enlargement," can have thin, fibrous caps and large lipid pools without encroaching on the lumen (Figure 1). As previously noted, such "hidden" lesions not only evade angiographic detection but also produce no symptoms until they trigger thrombosis, as they do not produce ischemia. Even using relatively insensitive angiographic criteria for plaque disruption, patients with ACS often present with more than one ulcerated plaque.<sup>37</sup> A multiplicity of active lesions portends a worse prognosis on follow-up. Systematic intravascular ultrasound studies of patients with ACS have shown that many have more than one disrupted plaque<sup>38</sup>; angioscopic observations yield similar findings.<sup>39</sup> Furthermore, the use of markers of inflammation such as myeloperoxidase indicates a transmyocardial step-up in levels of this inflammatory marker, even in the effluent of regions not perfused by the culprit artery.<sup>40</sup> Thus, although clinical presentations often involve focal lesions, arterial inflammation driving the underlying biology that predisposes to the local complications appears diffuse.

These recent findings challenge our traditional view of coronary atherosclerosis as a segmental or localized disease simply righted by local therapies such as bypass surgery or percutaneous revascularization. Newer imaging technologies such as optical coherence tomography, thermography, Raman/near-infrared spectroscopy, electron beam computed tomography, magnetic resonance imaging, and multidetector or multislice spiral computed tomography should provide additional information related to the risk of progression and cardiovascular events with regard to the atherosclerotic burden and its activity. Such novel imaging strategies will likely prove most useful and cost-effective in selected higher-risk individuals rather than in indiscriminate screening of unselected, asymptomatic populations.

## Treatment of the ACS: Perspective on the Future

In view of the appropriateness of local therapies to relieve angina and acute ischemia associated with an angiographically detectable culprit lesion and the prolongation of life and prevention of MI by systemic therapies that address risk factors, the current approach in treating ACS should involve 2 overlapping phases: the acute phase and the rapid stabilization of culprit lesions.

The earliest priority should limit loss of cardiomyocytes by addressing the thrombotic process that restricts flow and/or distal embolization of plaque debris and thrombotic material. The clinical correlates of severe ischemia include unstable clinical status, ischemic ST-T segment abnormalities, and the release of troponin T or I. These findings all indicate a relatively poor prognosis. An aggressive management approach that combines inhibition of platelets and thrombin generation with coronary angiography aiming at percutaneous or surgical revascularization of suitable culprit lesion(s) can improve outcomes in such high-risk patients.<sup>41</sup> A combination of oral aspirin, clopidogrel, and an intravenous glycoprotein IIb/IIIa antagonist during angioplasty currently affords the most effective antiplatelet therapy for such highrisk patients. Future antiplatelet therapy may offer a more complete blockade of the  $P2Y_1$  and  $P2Y_{12}$  ADP receptors and also inhibit the von Willebrand factor-glycoprotein Ib/IX complex that mediates platelet adhesion and platelet aggregation at high shear rates. This inhibition of platelet activation may provide benefits beyond preventing aggregation and thrombus progression by attenuating the platelet release of potent prothrombotic and proinflammatory products and the formation of platelet-monocyte aggregates, thus breaking some of the links that exist between thrombosis and inflammation.42,43 Anticoagulation in ACS currently uses unfractionated heparin or low-molecular-weight heparins. Antithrombotic agents in development include specific inhibitors of specific thrombin and factor Xa, acting either by mouth or parenterally, with variable half-lives, and inhibitors of the TF-factor VIIa complex that initiates thrombus formation.

Application of advances in knowledge of the biology of ACS and the role of inflammation afford new opportunities for attenuating plaque thrombogenicity, achieving more rapid control of the disease process, and preventing early recurrence. Early institution of statin therapy after ACS likely improves outcomes in part due to antiinflammatory effects attributable to both cholesterol lowering and direct antiinflammatory actions.<sup>44–46</sup> The potential of other agents that target inflammation per se requires further investigation. Some experimental studies have shown that inhibition of cyclooxygenase-2 or the thromboxane recep-

tor retards atherosclerosis.47 So far, only a few phase 2 trials in humans with ACS have tested antiinflammatory agents, with no conclusive efficacy achieved. A 48-hour course of intravenous methylprednisolone therapy did not improve the short-term outcome of patients with unstable angina.<sup>48</sup> A recombinant, soluble P-selectin glycoprotein ligand-1-immunoglobulin and 2 different antibodies to leukocyte integrin CD11b/CD18 showed no reduction of infarct size in patients treated with either fibrinolysis<sup>49</sup> or primary angioplasty.<sup>50</sup> Pexelizumab, a monoclonal antibody against C5, also failed in 2 trials to influence infarct size as estimated by creatine kinase-MB release, the primary outcome. The drug, however, strikingly reduced mortality and cardiogenic shock in the primary angioplasty trial, Compliment Inhibition in Myocardial Infarction Treated with Percutaneous Transluminal Coronary Angioplasty (COMMA).<sup>51</sup> The dissociation between infarct size and mortality benefit challenges traditional concepts and suggests a role for complement and inflammation in mortality and morbidity associated with ACS. Pexelizumab prevents the formation of C5a, a potent anaphylatoxin associated with leukocyte recruitment and expression of proinflammatory mediators, including cytokines, inducible nitric oxide synthase, and C5b, which promote cell death and apoptosis owing to the membrane attack complex. A substudy showed that levels of inflammatory markers predicted occurrence of death/cardiogenic shock and that these levels fell with pexelizumab in association with reduced rates of these adverse outcomes.1 These observations and others from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial<sup>52</sup> that death in patients with cardiogenic shock is not correlated with hemodynamic status and significantly improves short- and long-term survival with reperfusion therapy also support the clinical importance of inflammation in ACS.53 Indeed, preliminary studies in patients with refractory cardiogenic shock have shown improved hemodynamic status and survival with N<sup>G</sup>-monomethyl-L-arginine, a nitric oxide synthase inhibitor.54 Considering their likely role in plaque destabilization and in vascular and myocardial remodeling, MMPs represent another potential therapeutic target. Inhibitors of MMPs are currently being investigated in acute MI, although it is unlikely that chronic, broad-spectrum MMP inhibitors will have a favorable tolerability profile.

Beyond the classic risk markers related to intracoronary thrombus formation such as ST-segment shifts and troponin elevation, emerging ACS risk discriminants relate more to the activity of the underlying atherosclerosis and to metabolic factors than to the actual thrombotic activity of the culprit lesion. For example, diabetes and renal failure strongly predict poor prognosis. Therefore, a second phase in the management of ACS should accompany appropriate revascularization, with the aim to stabilize lesions. Such treatments seek to reduce the patient's overall vulnerability to a recurrent event by addressing systemic factors that influence the multiple potential culprits and also systemic factors that render plaque disruption more likely to produce a persistent and occlusive thrombus. In this regard, substantial evidence and preliminary observations in humans suggest that lipidlowering therapy achieves some of its consistent and marked benefit in reducing recurrent coronary events by affecting the biology of the plaque.<sup>55</sup> Just as inflammation underlies the pathophysiology of plaque formation and complications, successful therapeutic strategies appear to exert their benefit at least in part by combating inflammation.<sup>56</sup> Recent data that a statin-associated decline in C-reactive protein accompanies improved outcomes after ACS, independent of LDL lowering, support this view.<sup>46</sup>

In the previous era, the "Holy Grail" of secondary prevention of CAD was the regression of stenoses. Our current focus should aim to stabilize lesions and improve the systemic factors that render the patient vulnerable to thrombotic complications of atherosclerosis. In conjunction with a body of experimental findings,55 recent intravascular ultrasound evidence indicates that atheromata may shrink in size without necessarily reducing the degree of luminal stenosis.<sup>57,58</sup> Thus, compensatory enlargement appears to operate in reverse, allowing considerable lesion shrinkage without altering the angiogram. We need to expand our concept of the reversibility of atherosclerosis beyond the regression of stenoses to encompass such lesion shrinkage concealed behind the angiographic silhouette. We also must consider not only the quantitative aspect of the atheroma (its size or degree of stenosis) but also the qualitative nature of the lesion-some are susceptible to rupture and more prone to provoke thrombosis, whereas others, with a sturdier extracellular matrix skeleton, will less likely undergo disruption and trigger clot formation.

#### **Conclusions and Clinical Implications**

In the daily practice of cardiology, we confront CAD continually. Despite our quotidian familiarity with its clinical aspects, our views of the pathophysiology of coronary atherosclerosis have changed radically in the past decade. Our understanding of the anatomy and underlying biology of coronary atherosclerosis will likely continue to evolve, driven by advances both at the laboratory bench and in the clinic. We can now link the biology of the blood vessel, the myocyte, and the inflammatory response to our classic hemodynamic approach to achieve a more profound understanding of clinical CAD.

The revision of our classic views of atherosclerosis has important practical implications for patient care. Our revascularization strategies become ever better and more successful. Insights into the mechanisms of thrombosis, both at sites of intervention and in the more distal microcirculation, furnish a foundation for improved concomitant therapy of patients who undergo acute revascularization to reduce complications and preserve myocardium. We appreciate anew the need for systemic treatment to prevent ACS in individuals at risk. Future goals include the need to individualize therapy on the basis of specific patient characteristics. The burgeoning field of biomarkers and the promise of genetic risk stratification and pharmacogenetics should prove fruitful in this regard. Similar approaches may allow us to target preventive therapy in a more efficient and cost-effective manner. We now have excellent tools at hand for reducing LDL. Pharmacological and therapeutic interventions in development may permit us to reach beyond LDL as a target for reducing the risk of atherosclerotic complications. Such approaches include raising HDL levels, angiogenic modalities, and regenerative strategies involving stem cells. We must in parallel seek ways to reverse the epidemic of obesity, metabolic syndrome, and diabetes by lifestyle changes and possibly drug treatment. Should we fail in this regard, the wave of obesity and its complications threaten to undo the advances against atherosclerosis of the past decades.

The concept of "interventional cardiology" should expand beyond mechanical revascularization to encompass preventive interventions that forestall future events. As careful clinical and pathological observations have driven the science of coronary artery biology in the past, the opportunities of translational research to improve insights into pathophysiology and devise new and better treatments for CAD represent a major opportunity to improve patient outcomes in coming years.

#### Acknowledgments

This work was supported in part by grants to Dr Libby from the National Heart, Lung, and Blood Institute (HL-34636, HL-48743, and HL-56985).

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