REVIEW ARTICLE

MECHANISMS OF DISEASE

Mechanisms of Acute Coronary Syndromes and Their Implications for Therapy

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Atherosclerotic lesions in humans typically form over the course of years to decades, one of the longest incubation periods among human diseases. Despite the chronicity of atherosclerosis, thrombotic complications — the most dreaded clinical consequences of this disease — occur suddenly, and often without warning. Our familiarity with the disease has generally led us to accept this apparent paradox without wonder. What mechanisms explain the abrupt transition from stable ischemic heart disease or asymptomatic atherosclerosis to acute coronary syndromes? This review examines our current understanding of the mechanisms underlying these syndromes. According to the traditional view, progressive stenosis narrows the lumen of an atherosclerotic coronary artery to such an extent that a small platelet thrombus could occlude the vessel completely. Thus, an occlusive thrombus complicating a high-grade stenosis would arrest flow and cause ST-segment elevation myocardial infarction. Acute coronary syndromes without ST-segment elevation would result from an incomplete or transient obstruction of flow in the culprit coronary artery at a site of critical stenosis.

These concepts have governed our traditional approaches to atherosclerosis therapy. Our diagnostic tools generally evaluate the ischemia that results from established, fixed stenosis (e.g., stress testing and perfusion scanning) or visualize the stenosis itself by means of arteriography. Our treatments have targeted the stenosis with the use of percutaneous intervention or bypass surgery.

PATHOGENESIS OF ACUTE CORONARY SYNDROMES

Findings from clinical and pathological studies have challenged these commonly held notions of the pathophysiological features of coronary atherosclerosis and its treatment.[1-4] Surprisingly, serial angiographic studies have revealed that the plaque at the site of the culprit lesion of a future acute myocardial infarction often does not cause stenosis that, as seen on the antecedent angiogram, is sufficiently severe to limit flow. Angiographic monitoring of responses to thrombolytic therapy has shown that after lysis of the offending thrombus, the underlying stenosis is often not the cause of the critical stenosis of the artery. In a prospective angiographic study involving patients undergoing percutaneous intervention for coronary artery disease, only half the subsequent events arose from lesions with sufficient stenosis to have warranted intervention at the time of revascularization.[5] Computed tomographic (CT) angiography, which permits evaluation of the arterial wall (not just the lumen), has shown that the characteristics of plaque associated with acute coronary syndromes include low attenuation (i.e., little or no calcification) and outward expansion of the artery wall, a process that tends to accommodate the growth of plaque while minimizing luminal encroachment.[6-8] Intravascular ultrasonography has shown that in acute coronary syndromes, the culprits often lie proximal to the sites of maximal stenosis — the traditional targets of revascularization therapies.[9]

This dissociation between the degree of stenosis and the propensity to provoke an acute coronary syndrome helps to explain why myocardial infarction often occurs without being heralded by the demand-induced symptoms of angina that would result from a high-grade stenosis.

Technologies that permit cross-sectional imaging of the coronary arteries, such as intravascular ultrasonography or CT angiography, underscore the pathological observation that the outward expansion of atherosclerotic arteries accommodates the growth of plaque for much of its life history.[2] Luminal stenosis occurs relatively late in the process of atherogenesis, when plaque growth outstrips the ability of the artery to compensate by expanding outward.[10,11] These findings support the distinction between the degree of stenosis and the size of a plaque. Compensatory enlargement (outward expansion) of the artery during plaque growth can conceal a considerable burden of atheroma by preventing stenosis and thereby obscuring signs and symptoms of ischemia. Sizable plaques can reside in the walls of affected arteries without being detected on arteriograms and without issuing any warning to the patient or physician.

Clinical data acquired during the current era of medical management of atherosclerosis have affirmed that invasive procedures for the treatment of stenoses generally do not prevent future thrombotic events more effectively than noninvasive treatments. The Occluded Artery Trial concluded that restoring coronary flow in the subacute phase of an acute coronary syndrome did not improve outcomes.[12] Similarly, the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed overall that medical therapy provided as much protection from future acute coronary syndromes as did mechanical revascularization.[13] This assemblage of clinical data challenges the traditional view of the pathogenesis of acute coronary syndromes, which ascribes a leading role to critically stenotic lesions.

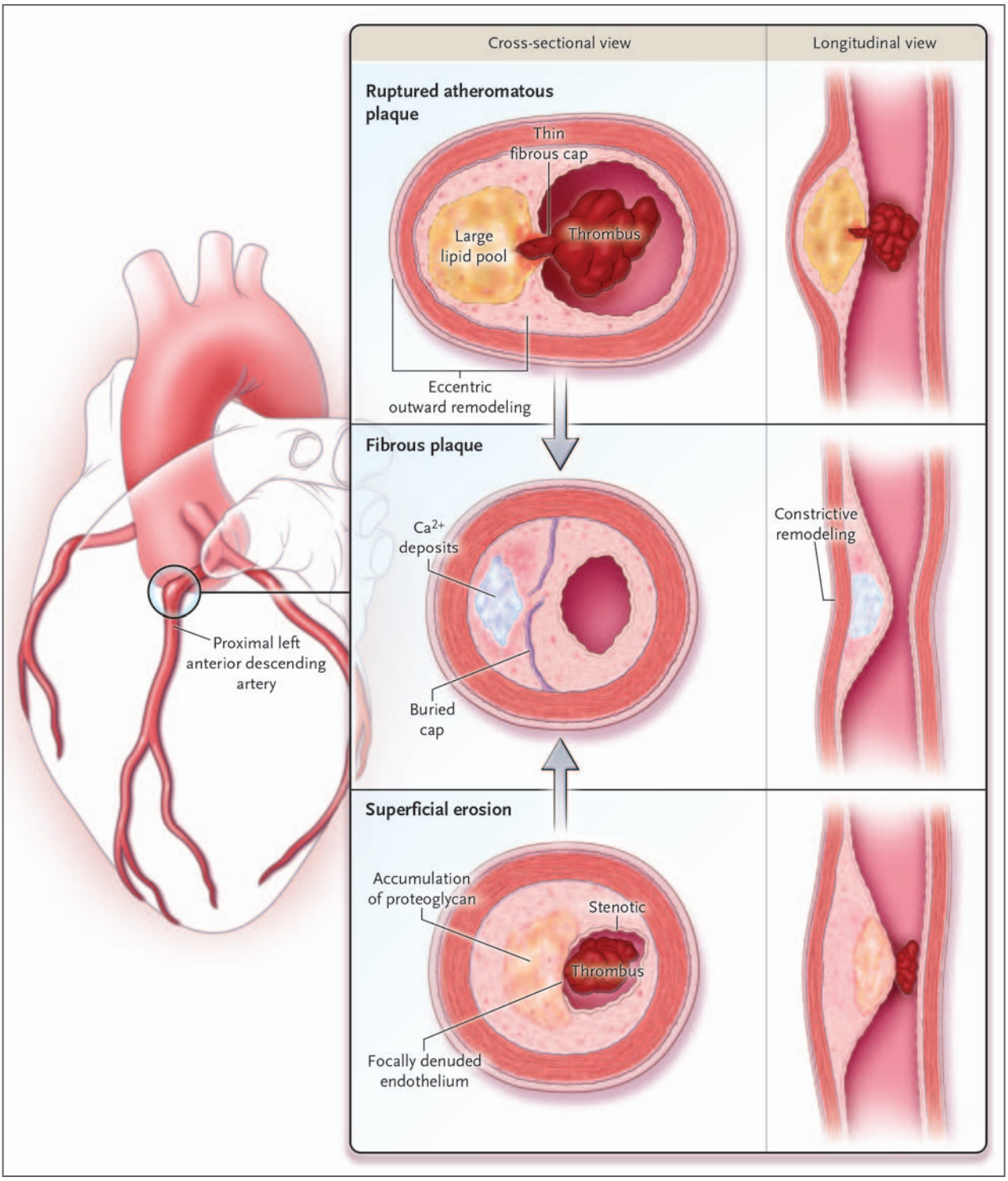
THROMBOTIC COMPLICATIONS OF ATHEROSCLEROSIS

If the progression of luminal stenosis to a critical narrowing does not cause many acute coronary syndromes, what mechanism produces these dramatic and sudden manifestations of chronic atherosclerosis? The long-standing focus on stenosis has diverted attention from autopsy studies conducted by generations of pathologists that have ascribed most fatal coronary events to a physical disruption of coronary arterial plaques (Fig. 1). Frank rupture of the plaque's fibrous cap causes the majority of these deaths; superficial erosion of a coronary artery accounts for most of the balance of fatal events. Autopsy studies have shown that erosion through the intima of a calcified nodule and intraplaque hemorrhage each trigger only a small percentage of acute coronary syndromes.[2,14]

Much of the work addressing the mechanisms of coronary thrombosis has focused on plaque rupture, the most common cause of fatal acute coronary syndromes. A fibrous cap typically overlies the lipid-rich center — also known as the necrotic core — of an atheromatous plaque (Fig. 1). This fibrous cap stands between the blood compartment, with its latent coagulation factors, and the lipid core, a portion of the plaque filled with thrombogenic material. Quantitative morphometric studies have identified the characteristics of plaques that have ruptured and caused a fatal myocardial infarction. Such plaques often, but not always, have thin fibrous caps (50 to 65 μm thick).[2,15] Ruptured plaques also tend to have large lipid cores and abundant inflammatory cells, as well as punctate or spotty calcification.[7,16] In a recent autopsy study,[17] a fibrous-cap thickness of less than 55 μm was identified as the best morphologic indicator of plaques that had caused fatal ruptures. More than 30% of these plaques were associated with a luminal stenosis of less than 75%, even when studied post mortem at pressures below physiological levels. Typically, the sites where plaques rupture and provoke fatal coronary events have few smooth-muscle cells.[18]

INFLAMMATION, COLLAGEN METABOLISM, AND PLAQUE RUPTURE AND THROMBOSIS

Extensive research has focused on the fibrous cap of the plaque because of its importance in the majority of fatal acute myocardial infarctions. This structure, which protects the plaque from rupture, owes its tensile strength to interstitial forms of collagen synthesized primarily by arterial smooth-muscle cells. The association between thinning of the fibrous cap and fatal plaque rupture led to the hypothesis that a defect in plaque collagen metabolism contributes to the



depletion of this extracellular matrix protein, which has a critical role in strengthening the fibrous cap.[1] These considerations have engendered much interest in molecular mediators of collagen metabolism that may operate during atherogenesis. Since inflammatory cells accumulate at the site of ruptured plaques, and since biomarkers of inflammation predict acute coronary

Figure 1 (facing page). Characteristics of Atherosclerotic Plaques Associated with Various Presentations of Coronary Artery Disease.

Characteristic morphologic features of coronary atherosclerotic plaques are depicted in association with three clinical presentations. The anterior surface of the heart (left) shows a representative atherosclerotic plaque at a typical location in the proximal left anterior descending coronary artery. The cross-sectional and longitudinal views of the artery depict details of the lesion types, shown at the level of the plaque. The pair of images at the top shows an eccentric, positively remodeled atheromatous plaque with a thin fibrous cap that has ruptured and provoked the formation of a thrombus. The healing of such disrupted atheromatous plaques can promote evolution to a more fibrous plaque (shown in the middle pair of images). Such a stenotic, fibrous plaque can cause stable ischemic syndromes (e.g., demand angina pectoris) as a result of narrowing of the arterial lumen. In this situation, plaques can contain strata that show "buried caps," which result from a prior disruption of the fibrous cap that provoked the formation of thrombus, followed by healing, fibrosis, and often constrictive (inward) remodeling. This process can promote the progression of a nonocclusive, atheromatous, lipid-rich plaque to a stenotic, more fibrous, calcified plaque. The bottom pair of images shows a proteoglycan-rich plaque that has caused an occlusive thrombus as a result of superficial erosion of the intimal surface.

syndromes, studies (discussed below) have focused on the hypothesis that macrophages — and the mediators that they produce and that regulate their function — disrupt the collagen in the plaque in a manner that may jeopardize the integrity of the fibrous cap, thus precipitating an acute coronary syndrome.

A study of the control of collagen biosynthesis by human vascular smooth-muscle cells in culture revealed that exposure to interferon-γ, a product of activated T cells, strongly inhibited the ability of smooth-muscle cells to make the new collagen required to repair and maintain the integrity of the fibrous cap.[19] Even in smooth-muscle cells maximally stimulated with transforming growth factor β to produce interstitial collagen, interferon-γ reduced collagen synthesis to baseline levels or lower. Another study showed an inverse correlation between T-cell accumulation in human atherosclerotic plaques and the messenger RNA that encodes the precursor of interstitial collagen, an observation that supports the relevance in vivo of the profound inhibition of new collagen synthesis by a T-cell–derived mediator.[20]

The level of any macromolecule depends not only on its rate of synthesis but also on the rate at which it breaks down. Interstitial collagen is usually very stable and resists degradation by most proteolytic enzymes. Only a handful of human proteinases have interstitial collagenase activity capable of catalyzing the initial attack on fibrillar collagen. These enzymes belong to the matrix-metalloproteinase (MMP) family. The macrophage, a cell type that abounds in lesions that have caused fatal thrombi, overproduces all three human MMP interstitial collagenases — MMP-1, MMP-8, and MMP-13 — in plaques.[21-25] Moreover, plaques with features similar to those that have caused thrombotic complications display biochemical signatures of collagen cleavage in situ in macrophage-rich regions.[24] Studies of the regulation of MMP production by human macrophages have shown that the T-cell–derived cytokine CD40 ligand (CD154) boosts the production of interstitial collagenase by human macrophages.[26] Thus, cross-talk between adaptive immune cells (T cells) and the more numerous innate immune effector cells (macrophages) inhibits the synthesis and augments the degradation of interstitial collagen. These observations in human tissues and in isolated human cells provide a cellular and molecular mechanism linking inflammation to the thinning and weakening of the fibrous cap, which can precipitate plaque rupture, thrombosis, and acute coronary syndromes. Recent experiments show that the systemic inflammatory reaction to acute myocardial infarction can aggravate inflammation in the plaque, including increased protease activity.[27] This finding helps explain why recurrent thrombotic events tend to cluster in the aftermath of an acute coronary syndrome and often involve lesions not deemed responsible for the initial presentation.[5] It also clarifies why immediate revascularization, by limiting myocardial injury and consequent systemic inflammation, may reduce the risk of recurrent events, whereas revascularization after completion of an infarct does not generally confer such a benefit.

Another recently recognized regulator of plaque proteinase expression, local endothelial shear stress, also has clinical relevance to the formation of lesions prone to rupture. In pigs, regions of the coronary vasculature with low endothelial shear stress colocalize with coronary atheromata with thin fibrous caps and exhibit enhanced expression of matrix-degrading proteinases, in-

Table 1. Interventions That Increase Collagen Content of Atherosclerotic Lesions in Studies in Animals.*

Intervention	Species	Source of Data
Reduction of dietary lipids	Rabbit	Aikawa et al.[31]
Treatment with statins	Rabbit	Fukumoto et al.[32]
Introduction of a mutation that renders resistance to collagenase	Mouse	Fukumoto et al.[33]
Induction of MMP-13 deficiency	Mouse	Deguchi et al.[34]
Induction of MMP-14 deficiency	Mouse	Schneider et al.[35]
Treatment with MMP-13 inhibitor	Mouse	Quillard et al.[36]

* MMP denotes matrix metalloproteinase.

cluding interstitial collagenases.[28,29] In humans, regions of low shear stress in coronary arteries are more likely to cause acute coronary events than regions of high shear stress.[30]

Despite their appeal, the initial data that supported the contribution of proteinases to the pathogenesis of acute coronary syndromes depended primarily on association, and evidence that altered collagen metabolism determines the collagen content of the fibrous cap remained speculative. Insights furnished by the study of experimental preparations that permit gain-of-function and loss-of-function manipulation now support a causal role for altered collagen metabolism in the collagen content of plaque (Table 1). In mice with a genetic susceptibility to diet-induced atherosclerosis, further mutation of a gene that encodes the precursor of interstitial collagen, rendering it resistant to MMP collagenases, yielded an accumulation of collagen in the plaque.[33] In other experiments, genetic inactivation of collagenolytic enzymes or their activators increased the collagen content of plaque.[34,35] Although such germline manipulations permit exquisite selectivity, the congenital absence of an enzyme could confound the interpretation of the results owing to the possibility of compensatory changes in other pathways. Moreover, the genetic approach does not permit analysis of the influence of collagenolysis on aspects of plaque structure that relate to rupture in lesions that have already formed. A recent study has therefore used pharmacologic inhibition of interstitial collagenase to test this hypothesis. Indeed, oral administration of a selective inhibitor of a principal interstitial collagenase, MMP-13, in mice yielded an increase in the collagen content of the fibrous cap in established atherosclerotic plaques.[36]

The combined studies of plaque in humans and animals support the concepts formulated in the early 1990s.[1] Decreased synthesis and increased breakdown of collagen, controlled by inflammatory signals, reduce the content of this critical extracellular matrix macromolecule in plaques. The resultant friable fibrous cap may render plaques susceptible to rupture and thrombosis (Fig. 2). Yet, a weakened fibrous cap alone does not suffice to precipitate plaque rupture, and not all plaques that rupture have thin fibrous caps.[37] Additional contributors to the triggering of plaque rupture may include coronary vasospasm and punctate calcifications. Recent computational analyses indicate that microcalcifications within the atherosclerotic intima can result in a striking increase in circumferential stress and could thus contribute to plaque rupture.[16]

When the fibrous cap ruptures, allowing blood to come into contact with thrombogenic material in the plaque's lipid core, thrombosis can ensue. When a plaque is disrupted, tissue factor, a potent procoagulant produced by macrophages in the plaque's core, triggers thrombin generation and platelet activation and aggregation.[38,39] The same proinflammatory signal that augments collagenase production — CD154 — also induces the expression of tissue factor in human mononuclear phagocytes (Fig. 2).[26] Thus, inflammatory cells and mediators not only regulate collagen synthesis and breakdown but also increase the thrombogenic potential of the atherosclerotic plaque. These dual actions explain the strong links between inflammation and the thrombotic complications of atherosclerosis.[40]

SUPERFICIAL EROSION OF PLAQUES

Superficial erosion of coronary atheromata causes approximately 20 to 25% of cases of fatal acute myocardial infarctions.[2] Observations made with the use of optical coherence tomography support the relevance of findings in autopsy studies to clinical acute coronary syndromes.[41-44] This anatomical substrate for coronary thrombosis occurs more frequently in women than in men and in persons with certain risk factors, such as hypertriglyceridemia. Many lesions that cause coronary thrombosis because of superficial erosion lack prominent inflammatory infiltrates; such plaques exhibit proteoglycan accumulation (Fig. 1).

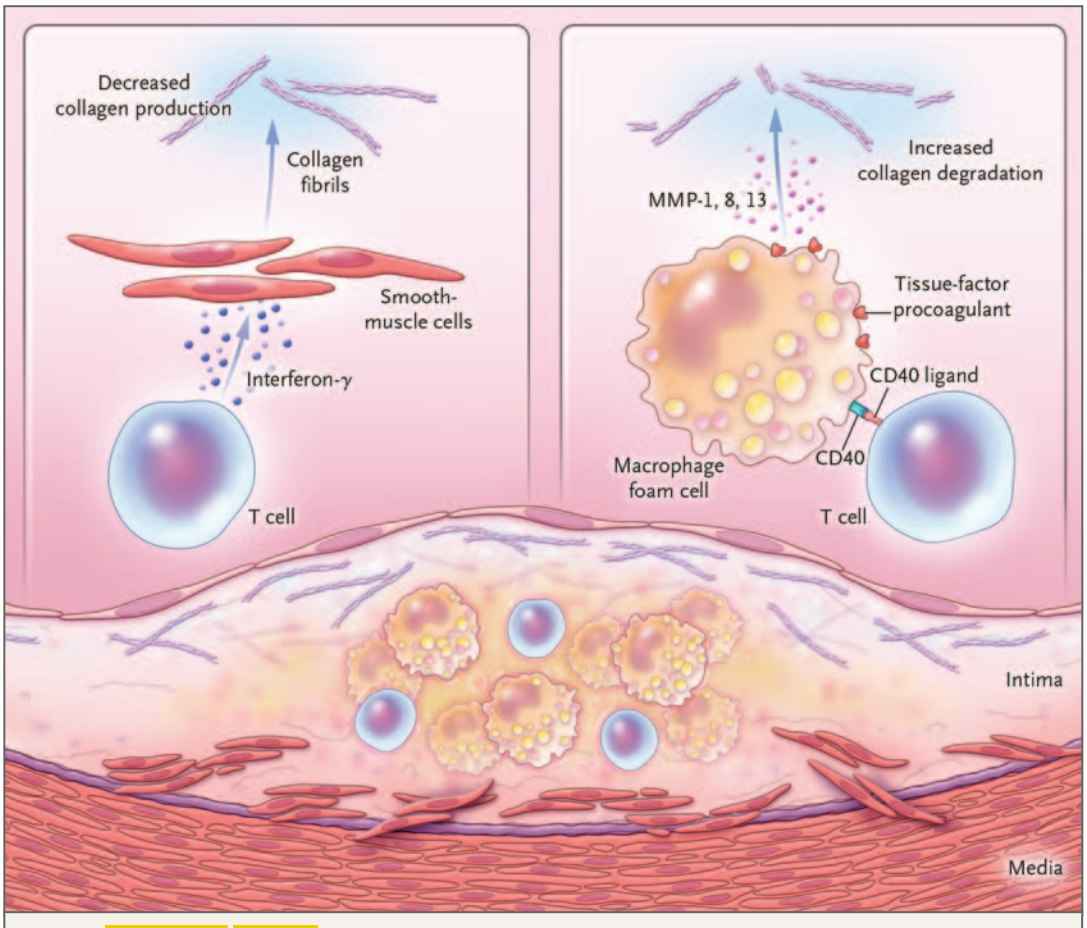


Figure 2. Inflammatory Pathways Predisposing Coronary Arteries to Rupture and Thrombosis.

A cross-section of an atheromatous plaque at the bottom of the figure shows the central lipid core that contains macrophage foam cells (yellow) and T cells (blue). The intima and media also contain arterial smooth-muscle cells (red), which are the source of arterial collagen (depicted as triple helical coiled structures). Activated T cells (of the type-1 helper T-cell subtype) secrete cytokine interferon-γ, which inhibits the production of the new, interstitial collagen that is required to repair and maintain the plaque's protective fibrous cap (upper left). The T cells can also activate the macrophages in the intimal lesion by expressing CD40 ligand (CD154), which engages its cognate receptor (CD40) on the phagocyte. This inflammatory signaling causes overproduction of interstitial collagenases (matrix metalloproteinases [MMPs] 1, 8, and 13) that catalyze the initial rate-limiting step in collagen breakdown (top right). CD40 ligation also causes macrophages to overproduce tissue-factor procoagulant. Thus, inflammatory signaling puts the collagen in the plaque's fibrous cap in double jeopardy — decreasing synthesis and increasing breakdown — rendering the cap susceptible to rupture. Inflammatory activation also boosts tissue-factor production, which triggers thrombus formation in the disrupted plaque. These are the mechanisms through which inflammation in the plaque can precipitate the thrombotic complications of atherosclerosis, including acute coronary syndromes.

The mechanisms of superficial erosion have received much less attention than those involved in the rupture of the fibrous cap. The programmed cell death (i.e., apoptosis) of endothelial cells could contribute to their desquamation.[45] Oxidative stress can promote endothelial apoptosis. In particular, hypochlorous acid — the product of myeloperoxidase, an enzyme released by activated leukocytes associated with atheromata — can initiate apoptosis of endothelial cells.[46] As these cells undergo apoptosis, they produce the procoagulant tissue factor. The oxidant hypochlorous acid may thus initiate or propagate endothelial cell loss and local thrombosis in coronary arteries. Endothelial cells can also express proteinases that may sever their tethers to the underlying base-

Table 2. Favorable Effects of Lipid Lowering in Experimentally Produced Atherosclerotic Plaques.

Reduces inflammation (lowers levels of macrophages, cytokines, and chemokines and expression of leukocyte adhesion molecules)
Reduces expression of interstitial collagenase (MMP-1)
Increases levels of interstitial collagen
Lowers levels of oxidized low-density lipoprotein
Reduces production of reactive oxygen species
Increases expression of endothelial nitric oxide synthase
Reduces thrombotic potential (reduced tissue factor content and activity)
Increases fibrinolytic potential (reduced level of plasminogen activator inhibitor-1)

ment membrane.[45] Modified low-density lipoprotein (LDL), for example, can induce the expression of the enzyme MMP-14 by human endothelial cells.[47] MMP-14 can activate MMP-2, an enzyme that degrades basement-membrane forms of nonfibrillar collagen (type IV). The mechanisms of superficial erosion merit attention in future investigations; they are much less well understood than the mechanisms underlying the fracture of the plaque's fibrous cap.

THERAPEUTIC IMPLICATIONS OF NEW MECHANISTIC INSIGHTS

Although revascularization procedures that target occlusive coronary stenosis relieve anginal symptoms, they have not consistently reduced the risk of an acute coronary syndrome or death from coronary artery disease. In stark contrast, contemporary medical therapy — notably, statin treatment — has prevented both first and recurrent acute coronary syndromes in broad categories of patients. Curiously, even though these medical interventions reduce events, they have little effect on the degree of stenosis as assessed on angiography and result in only modest reductions in atheroma volume as assessed on intravascular ultrasonography.[48] Can the new insights into the mechanisms of acute coronary syndromes, described above, illuminate these clinical findings and explain how medical treatment reduces the thrombotic complications of atherosclerosis?

Event reduction that is out of proportion to the shrinkage of stenoses has led to the hypothesis that lipid lowering alters qualitative characteristics of atheromata — that such treatment causes modest quantitative improvement in lumen caliber but may qualitatively limit the propensity of plaques to rupture and their thrombogenicity. These changes in the biologic features of plaque are now considered to confer "stabilization," a feature that distinguishes lipid-lowering interventions from those that address luminal stenosis without altering the molecular and cellular processes inculpated in the triggering of thrombotic complications.[49] A comprehensive series of studies in rabbits and mice tested this hypothesis. One series of investigations in rabbits with experimentally induced atherosclerosis lowered lipid levels by means of diet alone, a "lifestyle" intervention. A combination of arterial injury and an atherogenic diet provoked the development of fibrofatty aortic plaques in rabbits. After a period of lesion generation, the rabbits were switched to a low-fat, low-cholesterol diet or were kept on a diet that maintained dyslipidemia. The lipid-lowering diet reduced the content of inflammatory cells, augmented interstitial collagen accumulation, and reduced tissue factor antigen and activity in concert with other effects that contrast with the features of human plaques prone to rupture and thrombosis (Table 2).[31,50]

Other studies showed that statin treatment caused similar reductions in inflammatory-cell content and collagenase levels and augmented collagen accumulation in atheromata of Watanabe heritable hyperlipidemic rabbits.[32,51] Because rabbits of this strain — characterized by mutated LDL receptors — have only modestly reduced LDL cholesterol levels when treated with statins, these studies indicate that statins have a stabilizing effect on plaques that extends beyond their lipid-lowering action.[52]

Observations in humans support the concept, established in animals, that lipid lowering can increase the fibrous nature of plaques — a change that should confer resistance to rupture. Imaging studies suggest that plaques have a more fibrous character in patients receiving treatment with statins than in those not receiving such treatment.[53-56] Statin therapy is also associated with reduced lipid content and indexes of macrophage activity and more fibrous atheromata as assessed on magnetic resonance imaging in both rabbits and humans.[57-59] These studies in humans affirm the clinical relevance of the studies in animals described above and the classic observations of Armstrong and colleagues regarding the "regression" of atheroscle-

rotic lesions in nonhuman primates after dietary restriction of lipids.[60]

Despite the remarkable benefits of statin therapy, patients appropriately treated with this class of agents are still at considerable risk for acute coronary syndromes[61] — hence the need to make further inroads against this residual burden of disease. The advent of novel strategies for lowering LDL cholesterol levels below those achievable with statins alone (e.g., inhibition of serum proprotein convertase subtilisin/kexin 9 [PCSK9]) provides considerable promise in this regard.[62,63] Therapies that target other aspects of the lipid profile have proved disappointing when put to the test, despite extensive preclinical and clinical biomarker data. Clinical trials of interventions that address levels of high-density lipoprotein (HDL) cholesterol have shown no benefit (e.g., the cholesteryl ester transfer protein [CETP] inhibitors tested thus far, and niacin).[64-67] Similarly, recent large-scale trials of fibrates, agents that substantially lower triglyceride levels and modestly raise HDL cholesterol levels, in patients with type 2 diabetes mellitus have not shown a reduction in cardiovascular events.[68,69]

Given the role of inflammation in the pathophysiological aspects of plaque rupture, several studies are assessing the use of antiinflammatory therapies other than statins to reduce the risk of a recurrent acute coronary syndrome. A recent clinical trial of low-dose colchicine (0.5 mg per day) in patients with stable ischemic heart disease has shown a reduced incidence of acute coronary syndromes.[70] This trial was relatively small (532 patients, with a total of 55 events), and the investigators did not use a double-blind design and did not report levels of inflammatory biomarkers, which might have provided a glimpse into the possible mechanisms underlying the effects of colchicine. Nevertheless, these encouraging results should prompt a larger-scale, double-blind trial of this inexpensive agent, which has a long history of clinical use and a well-known and acceptable risk profile. Two large clinical trials are testing the use of darapladib, a small molecular inhibitor of a lipoprotein-associated phospholipase, to reduce clinical events.[71,72] Although this intervention has the potential for antiinflammatory actions, in a phase 2 trial it did not reduce levels of C-reactive protein but did limit lipid core size, a characteristic that may render plaques susceptible to rupture.[73] Other interventions under investigation include antibody neutralization of the proinflammatory cytokine interleukin-1β or the use of low-dose methotrexate on a weekly basis, treatments currently used successfully for other inflammatory conditions.[74,75]

SUMMARY

Our understanding of the pathogenesis of acute coronary syndromes has undergone a veritable revolution in the past 20 years. We now understand in molecular and cellular terms how most serious thrombotic complications of coronary atherosclerosis occur. In particular, inflammatory pathways have emerged as important drivers of plaque disruption and thrombosis. This insight into the pathophysiological features of acute coronary syndromes expands the scope of treatment of this disease beyond the traditional focus on reducing stenoses. The laboratory and clinical data summarized here should help us both to understand how contemporary therapies can reduce the risk of these events and to make further inroads against the residual burden of disease in the future.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Libby P. The molecular bases of the acute coronary syndromes. Circulation 1995;91:2844-50.
2. Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. Acute coronary events. Circulation 2012;125:1147-56.
3. Crea F, Liuzzo G. Pathogenesis of acute coronary syndromes. J Am Coll Cardiol 2013;61:1-11.
4. Falk E, Nakano M, Benton JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J 2013;34:719-28.
5. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-35. [Erratum, N Engl J Med 2011;365:2040.]
6. Hoffmann U, Moselewski F, Nieman K, et al. Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syndrome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol 2006;47:1655-62.
7. Motoyama S, Sarai M, Harigaya H, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol 2009;54:49-57.
8. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for noninvasive imaging. Nat Clin Pract Cardiovasc Med 2008;5:Suppl 2:S2-S10.
9. Schoenhagen P, Stone GW, Nissen SE, et al. Coronary plaque morphology and frequency of ulceration distant from culprit lesions in patients with unstable and stable presentation. Arterioscler Thromb Vasc Biol 2003;23:1895-900.

10. Glagov S, Weisenberg E, Zarins C, Stankunavicius R, Kolletis G. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371-5.
11. Clarkson TB, Prichard RW, Morgan TM, Petrick GS, Klein KP. Remodeling of coronary arteries in human and nonhuman primates. JAMA 1994;271:289-94.
12. Hochman JS, Lamas GA, Buller CE, et al. Coronary intervention for persistent occlusion after myocardial infarction. N Engl J Med 2006;355:2395-407.
13. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-16.
14. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation 2005;111:3481-8.
15. Yonetsu T, Kakuta T, Lee T, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. Eur Heart J 2011;32:1251-9.
16. Maldonado N, Kelly-Arnold A, Vengrenyuk Y, et al. A mechanistic analysis of the role of microcalcifications in atherosclerotic plaque stability: potential implications for plaque rupture. Am J Physiol Heart Circ Physiol 2012;303:H619-H628.
17. Narula J, Nakano M, Virmani R, et al. Histopathologic characteristics of atherosclerotic coronary disease and implications of the findings for the invasive and noninvasive detection of vulnerable plaques. J Am Coll Cardiol 2013;61:1041-51.
18. Davies MJ, Richardson PD, Woolf N, Katz DR, Mann J. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. Br Heart J 1993;69:377-81.
19. Amento EP, Ehsani N, Palmer H, Libby P. Cytokines and growth factors positively and negatively regulate interstitial collagen gene expression in human vascular smooth muscle cells. Arterioscler Thromb 1991;11:1223-30.
20. Rekhter MD, Zhang K, Narayanan AS, Phan S, Schork MA, Gordon D. Type I collagen gene expression in human atherosclerosis: localization to specific plaque regions. Am J Pathol 1993;143:1634-48.
21. Galis ZS, Sukhova GK, Lark MW, Libby P. Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. J Clin Invest 1994;94:2493-503.
22. Nikkari ST, O'Brien KD, Ferguson M, et al. Interstitial collagenase (MMP-1) expression in human carotid atherosclerosis. Circulation 1995;92:1393-8.
23. Herman MP, Sukhova GK, Libby P, et al. Expression of neutrophil collagenase (matrix metalloproteinase-8) in human atheroma: a novel collagenolytic pathway suggested by transcriptional profiling. Circulation 2001;104:1899-904.
24. Sukhova GK, Schonbeck U, Rabkin E, et al. Evidence for increased collagenolysis by interstitial collagenases-1 and -3 in vulnerable human atheromatous plaques. Circulation 1999;99:2503-9.
25. Shah PK, Falk E, Badimon JJ, et al. Human monocyte-derived macrophages induce collagen breakdown in fibrous caps of atherosclerotic plaques: potential role of matrix-degrading metalloproteinases and implications for plaque rupture. Circulation 1995;92:1565-9.
26. Mach F, Schöenbeck U, Bonnefoy J-Y, Pober J, Libby P. Activation of monocyte/macrophage functions related to acute atheroma complication by ligation of CD40: induction of collagenase, stromelysin, and tissue factor. Circulation 1997;96:396-9.
27. Dutta P, Courties G, Wei Y, et al. Myocardial infarction accelerates atherosclerosis. Nature 2012;487:325-9.
28. Chatzizisis YS, Baker AB, Sukhova GK, et al. Augmented expression and activity of extracellular matrix-degrading enzymes in regions of low endothelial shear stress co-localize with coronary atheromata with thin fibrous caps in pigs. Circulation 2011;123:621-30.
29. Koskinas KC, Sukhova GK, Baker AB, et al. Thin-capped atheromata with reduced collagen content in pigs develop in coronary arterial regions exposed to persistently low endothelial shear stress. Arterioscler Thromb Vasc Biol May 2 (Epub ahead of print).
30. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation 2012;126:172-81.
31. Aikawa M, Rabkin E, Okada Y, et al. Lipid lowering by diet reduces matrix metalloproteinase activity and increases collagen content of rabbit atheroma: a potential mechanism of lesion stabilization. Circulation 1998;97:2433-44.
32. Fukumoto Y, Libby P, Rabkin E, et al. Statins alter smooth muscle cell accumulation and collagen content in established atheroma of Watanabe heritable hyperlipidemic rabbits. Circulation 2001;103:993-9.
33. Fukumoto Y, Deguchi JO, Libby P, et al. Genetically determined resistance to collagenase action augments interstitial collagen accumulation in atherosclerotic plaques. Circulation 2004;110:1953-9.
34. Deguchi JO, Aikawa E, Libby P, et al. Matrix metalloproteinase-13/collagenase-3 deletion promotes collagen accumulation and organization in mouse atherosclerotic plaques. Circulation 2005;112:2708-15.
35. Schneider F, Sukhova GK, Aikawa M, et al. Matrix-metalloproteinase-14 deficiency in bone-marrow-derived cells promotes collagen accumulation in mouse atherosclerotic plaques. Circulation 2008;117:931-9.
36. Quillard T, Tesmenitsky Y, Croce K, et al. Selective inhibition of matrix metalloproteinase 13 (MMP-13) increases collagen content of established mouse atheromata. Arterioscler Thromb Vasc Biol 2011;31:2464-72.
37. Ohayon J, Finet G, Gharib AM, et al. Necrotic core thickness and positive arterial remodeling index: emergent biomechanical factors for evaluating the risk of plaque rupture. Am J Physiol Heart Circ Physiol 2008;295:H717-H727.
38. Drake TA, Morrissey JH, Edgington TS. Selective cellular expression of tissue factor in human tissues: implications for disorders of hemostasis and thrombosis. Am J Pathol 1989;134:1087-97.
39. Wilcox JN, Smith KM, Schwartz SM, Gordon D. Localization of tissue factor in the normal vessel wall and in the atherosclerotic plaque. Proc Natl Acad Sci U S A 1989;86:2839-43.
40. Croce K, Libby P. Intertwining of thrombosis and inflammation in atherosclerosis. Curr Opin Hematol 2007;14:55-61.
41. Kubo T, Imanishi T, Takarada S, et al. Assessment of culprit lesion morphology in acute myocardial infarction: ability of optical coherence tomography compared with intravascular ultrasound and coronary angioscopy. J Am Coll Cardiol 2007;50:933-9.
42. Ozaki Y, Okumura M, Ismail TF, et al. Coronary CT angiographic characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy. Eur Heart J 2011;32:2814-23.
43. Holmes DR Jr, Lerman A, Moreno PR, King SB III, Sharma SK. Diagnosis and management of STEMI arising from plaque erosion. JACC Cardiovasc Imaging 2013;6:290-6.
44. Braunwald E. Coronary plaque erosion: recognition and management. JACC Cardiovasc Imaging 2013;6:288-9.
45. Libby P. The molecular mechanisms of the thrombotic complications of atherosclerosis. J Intern Med 2008;263:517-27.
46. Sugiyama S, Kugiyama K, Aikawa M, Nakamura S, Ogawa H, Libby P. Hypochlorous acid, a macrophage product, induces endothelial apoptosis and tissue factor expression: involvement of myeloperoxidase-mediated oxidant in plaque erosion and thrombogenesis. Arterioscler Thromb Vasc Biol 2004;24:1309-14.
47. Rajavashisth TB, Liao JK, Galis ZS, et al. Inflammatory cytokines and oxidized low density lipoproteins increase endothelial cell expression of membrane type 1-matrix metalloproteinase. J Biol Chem 1999;274:11924-9.

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1. British Society for Antimicrobial Chemotherapy. Resistance surveillance website (http://www.bsacsurv.org/mrsweb/bacteraemia?organism=A&antimicrobial=All&year=All&country=All&summary=SIRSummary&formname=bsac_bacteraemia&submit=Search).

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Mechanisms of Acute Coronary Syndromes

TO THE EDITOR: In his review article about the mechanisms of disease of acute coronary syndromes and their potential therapies, Libby (May 23 issue)[1] does not refer to the role of hyperglycemia, although the association between dysglycemia and atherosclerosis has been clearly shown.[2] Hyperglycemia is an important factor in cardiovascular damage, working through different mechanisms such as the activation of protein kinase C, polyol and hexosamine pathways, and the production of advanced glycation end products.[3] Moreover, hyperinsulinism has been established as an important factor associated with the occurrence of new cardiovascular events in patients with a first myocardial infarction.[4] The common mechanisms that contribute to insulin resistance and endothelial dysfunction also include glucotoxicity, lipotoxicity, and inflammation, which are correlated with oxidative stress and result in an increased risk of cardiovascular events.[5] Hence, appropriate glycemic control, in association with the treatment of dyslipidemia and other pro-oxidative conditions, is necessary to counteract oxidative stress in patients with cardiovascular diseases, such as acute coronary syndromes.

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1. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013;368:2004-13.
2. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 2011;14:575-85.
3. Fiorentino TV, Prioletta A, Zuo P, Folli F. Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. Curr Pharm Des 2013 February 20 (Epub ahead of print).
4. García RG, Rincón MY, Arenas WD, et al. Hyperinsulinemia is a predictor of new cardiovascular events in Colombian patients with a first myocardial infarction. Int J Cardiol 2011;148:85-90.
5. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006;113:1888-904.

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TO THE EDITOR: Libby states, "In humans, regions of low shear stress in coronary arteries are more likely to cause acute coronary events than regions of high shear stress," citing the Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology (PREDICTION) study.[1] Readers will get the impression that the PREDICTION study showed an association of acute coronary events with high shear stress, although high shear stress was not associated with plaque burden, luminal obstruction, or acute coronary events in that study. However, evidence suggests the association of regions of high shear stress with plaque rupture in advanced plaques.[2] Readers may also not appreciate the interplay of biomechanical factors (shear stress and strain) with inflammation and instability of the fibrous cap, which is one of the key determinants in plaque rupture.[2]

Finally, Libby raises concern about unexplained residual risk of acute coronary events among patients treated with statins. This risk can be partly circumvented by prolonged exposure to low levels of low-density lipoprotein cholesterol beginning early in life, as shown in a recent

mendelian randomization analysis[3] from our institution, emphasizing the importance of primary prevention strategies for coronary artery disease.

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1. Stone PH, Saito S, Takahashi S, et al. Prediction of progression of coronary artery disease and clinical outcomes using vascular profiling of endothelial shear stress and arterial plaque characteristics: the PREDICTION Study. Circulation 2012;126:172-81.
2. Seneviratne A, Hulsmans M, Holvoet P, Monaco C. Biomechanical factors and macrophages in plaque stability. Cardiovasc Res 2013;99:284-93.
3. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 2012;60:2631-9.

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TO THE EDITOR: In his presentation of the mechanisms of acute coronary syndromes and their implications for therapy, Libby does not explain why 63% of coronary plaques rupture at the shoulder region and only 37% in the center of the cap.[1] By contrast, 94% of carotid plaques rupture around the midpoint and between the midpoint and the shoulder, and only 6% at the shoulder region.[2] Persons who die during exertion have coronary plaque rupture mainly in the midpoint of the fibrous cap, in contrast to those who die at rest and who have plaque rupture at shoulder regions.[3] Ultrastructurally, the junctions between endothelial cells that line human plaques are often open, whereas the junctions over the normal arterial wall are usually closed.[4] This allows inflammatory cells to penetrate selectively into these particular plaque areas.

Libby did not refer to the activation of matrix metalloproteinases (MMPs) by mast-cell–derived proteases, which may be an important mechanism in the destabilization of atherosclerotic plaque. Immunocytochemical analyses have identified significantly higher numbers of tryptase-containing mast cells and cells expressing MMP-1 and MMP-3 in the shoulder regions of atherosclerotic plaques than in the tunica media of control nonatherosclerotic arteries.[5]

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1. Maehara A, Mintz GS, Bui AB, et al. Morphologic and angiographic features of coronary plaque rupture detected by intravascular ultrasound. J Am Coll Cardiol 2002;40:904-10.
2. Redgrave JN, Lovett JK, Gallagher PJ, Rothwell PM. Histological assessment of 526 symptomatic carotid plaques in relation to the nature and timing of ischemic symptoms: the Oxford plaque study. Circulation 2006;113:2320-8.
3. Burke AP, Farb A, Malcom GT, Liang Y, Smialek JE, Virmani R. Plaque rupture and sudden death related to exertion in men with coronary artery disease. JAMA 1999;281:921-6.
4. Constantinides P, Harkey M. Electron microscopic exploration of human endothelium in step-serial sections of early and advanced atherosclerotic lesions. Ann N Y Acad Sci 1990;598:113-24.
5. Johnson JL, Jackson CL, Angelini GD, George SJ. Activation of matrix-degrading metalloproteinases by mast cell proteases in atherosclerotic plaques. Arterioscler Thromb Vasc Biol 1998;18:1707-15.

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THE AUTHOR REPLIES: Gómez-Arbeláez and López-Jaramillo consider the role of glycemic control and countering oxidative stress in patients at risk for acute coronary syndromes. Dysglycemia and associated metabolic derangements certainly associate with cardiovascular risk. My review, however, focused primarily on therapeutic opportunities supported by rigorous clinical evidence. Glycemic control indeed limits the microvascular complications of diabetes. Yet, more recent clinical trials — conducted in the statin era — show that strict glycemic control confers at best a slight reduction in the risk of acute coronary syndromes, while augmenting the risk of hypoglycemia.[1] Moreover, despite preclinical evidence pointing to oxidative stress as a therapeutic target in atherosclerosis, a large and well-conducted trial of antioxidant vitamins and of one pharmacologic antioxidant agent did not show a reduction in the risk of cardiovascular events.[2] These results have called into question the role of strict glycemic control or antioxidant therapy in the prevention of acute coronary syndromes.

Reddy and Jagadeesh emphasize the importance of biomechanical factors in the regulation of inflammation and fibrous-cap stability. I agree wholeheartedly. Current data highlight the importance of shear stress in regulating the atheroprotective functions of the endothelium. In regions of disturbed flow, arteries lose these protective

functions and show heightened susceptibility to atheroma development and conditions that would favor thrombus accumulation.[3] I fully endorse their assertion of the importance of primary prevention strategies for coronary artery disease.

Kounis cites the pioneering morphologic studies by Constantinides and Harkey that showed open junctions between endothelial cells over human plaques. Since these classic studies, substantial data have highlighted qualitative abnormalities in endothelial function rather than desquamative injury, or physical discontinuities between junctions, as a mechanism of inflammatory-cell recruitment.[3] The expression of selective adhesion molecules on the surface of endothelial cells that have undergone activation by risk factor–related stimuli, and local elaboration of chemoattractant molecules, lead to leukocyte accumulation in lesions, according to current evidence. I agree completely regarding the potential contributions of mast cells and their proteases to atherogenesis — indeed, genetic studies in mice rigorously implicate mast cells in experimental atherogenesis.[4]

I further concur with the points raised regarding the roles of mast-cell–derived proteases in the activation of MMPs. In addition to the mast-cell–derived enzymes chymase and tryptase, other serine proteases, including some involved in blood coagulation, such as plasmin and thrombin, can also activate the zymogen forms of MMPs.[5]

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1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364-79.
2. Tardif JC, McMurray JJ, Klug E, et al. Effects of succinobucol (AGI-1067) after an acute coronary syndrome: a randomised, double-blind, placebo-controlled trial. Lancet 2008;371:1761-8.
3. Gimbrone MA Jr, García-Cardeña G. Vascular endothelium, hemodynamics, and the pathobiology of atherosclerosis. Cardiovasc Pathol 2013;22:9-15.
4. Sun J, Sukhova GK, Wolters PJ, et al. Mast cells promote atherosclerosis by releasing proinflammatory cytokines. Nat Med 2007;13:719-24.
5. Galis ZS, Kranzhöfer R, Fenton JW II, Libby P. Thrombin promotes activation of matrix metalloproteinase-2 produced by cultured vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 1997;17:483-9.
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Middle East Respiratory Syndrome Coronavirus Infections in Health Care Workers

TO THE EDITOR: A majority of the 94 cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection that have been reported to date have occurred in Saudi Arabia. Patients with this infection have presented with serious respiratory disease and have required hospitalization.[1,2] However, there have been case reports of less severe disease within family[3,4] and hospital[2] clusters, and the clinical spectrum of MERS-CoV infections may extend to asymptomatic and subclinical cases. Therefore, the epidemiologic and clinical characteristics of this infection need further definition. The patterns of the spread of MERs-CoV among family[3,4] or hospital[2] clusters suggest that transmission occurs through droplets or contact. We previously reported two cases of MERS-CoV infection in health care workers,[2] one of which was fatal.

The presence of asymptomatic or subclinical MERS-CoV infections in the community or among health care workers could have important public health implications, since these infections may be sources of transmission to close contacts in the community or to patients with coexisting medical conditions. The close proximity of health care workers to patients and the handling of human biologic material (sputum, respiratory secretions, feces, urine, or blood) may increase the risk of transmission, and health care workers may be particularly at risk for MERS-CoV infections.

The Saudi Arabian Ministry of Health routinely screens all close contacts of patients in whom MERS-CoV infection has been diagnosed, and more than 3000 people have been screened to date. We recently identified seven health care workers with MERS-CoV infection (two of whom were asymptomatic and five of whom had mild upper respiratory tract symptoms) through screening of single sample nasopharyngeal swabs