Inflammation and Atherothrombosis

From Population Biology and Bench Research to Clinical Practice

Peter Libby, MD,*‡ Paul M Ridker, MD, MPH*†‡
Boston, Massachusetts

The concept that inflammation governs atherosclerosis and its complications has provided a new unifying hypothesis of the links between risk factors and the cellular and molecular alterations that underlie this disease. This new mechanistic insight has already begun to translate into changes in clinical practice. The preponderance of available data supports the predictive power of biomarkers of inflammation such as high-sensitivity C-reactive protein (hsCRP) in broad categories of individuals, both those who are apparently well and those with already-manifest atherosclerotic cardiovascular disease. The demonstrated clinical utility of hsCRP and potentially of other inflammatory biomarkers has engendered intense interest in evaluating their cost-effectiveness as predictive tools beyond conventional risk markers and as goals for therapy. The rapid translation of inflammation biology in cardiovascular disease from the laboratory to the clinic serves as a gratifying example of bench-to-bedside research. Ultimately, the insight that inflammation plays a fundamental role in atherosclerosis may lead to novel therapies that target aspects of the inflammatory process smoldering within the atheroma. (J Am Coll Cardiol 2006;48:A33–46) © 2006 by the American College of Cardiology Foundation

Our view of atherosclerosis has evolved strikingly over the last several decades. For over 50 years, the medical community regarded atherosclerosis as a cholesterol storage disease characterized by passive deposition of lipid in the arterial wall. According to this concept, continuing accumulation of fatty debris encrusted the artery, causing progressive stenosis that ultimately provoked occlusive thrombosis. Accumulating data and evolution in our thinking cast doubt on this simple concept of atherothrombosis over the last quarter century. Today, we increasingly understand atherogenesis as an active process that involves altered cellular behavior in response to defined molecular signals. We no longer regard the blood vessel as an inert tube, but rather as a living structure composed of cells such as endothelium and smooth muscle (Fig. 1). We possess increasingly detailed knowledge of the interactions between blood components, including cells, proteins, and small molecules, and the intrinsic cells that populate the normal artery wall as contributors to the pathogenesis of this disease.

Current thinking accords a primordial role to inflammation as a common unifying mechanism that links risk factors to lesion formation and their tendency to provoke thrombotic complications. We provide here an overview of the basic and population science that underlies this newfound understanding of this ubiquitous disease. Advances in our understanding of the pathogenesis of atherothrombosis have implications beyond theory and now cross the threshold to clinical practice. This article explores further the translation of basic and population science to clinical practice.

For convenience, we often consider atherogenesis in distinct chronologic phases (Figs. 1 to 4). In contemporary society, the first phase, initiation, occurs all too frequently in childhood or adolescence (Figs. 1 and 2). The nascent lesion then enters a phase of progression, generally considered to occur during young adulthood through middle life (Fig. 3). Ultimately, atherosclerotic disease becomes manifest with either chronic, stable symptoms or thrombotic complications such as acute myocardial infarction or ischemic stroke (Fig. 4). Traditionally, the latter phase of atherothrombosis, complication, occurs in the middle-age or elderly individual. Clearly, this timeline of atherogenesis greatly oversimplifies a complex process. Indeed, individuals with atherosclerosis have lesions with anatomopathological characteristics of more than one stage that coexist, often close proximity. For example, aortae of individuals with atherosclerotic disease can often harbor within centimeters a fatty streak, a fibrous plaque, a calcified lesion, and an ulcerated plaque with thrombosis in situ. Nonetheless, for pedagogical purposes, separating the discussion of atherosclerosis into the phases of lesion initiation, progression, and complication proves convenient.

INFLAMMATION AND THE INITIATION OF ATHEROSCLEROSIS

Recent research has forged major advances in defining the molecular mediators of classical and emerging risk factors for atherosclerosis. Our knowledge of the links between risk factors and pathobiology remains incomplete. Current concepts will doubtless undergo expansion and revision. Yet, data obtained to date point strongly to inflammation as a
final common pathway for transducing the effects of risk factors into changes in the biology of the arterial wall (1–3). For example, laboratory and population studies conducted over the last century consistently have identified cholesterol as a potent risk factor for atherosclerosis and its complications. Considerable evidence has established the presence of oxidized components of low-density lipoprotein (LDL) in atherosclerotic lesions. Oxidized phospholipids, some with chemically defined structures, can act as proinflammatory stimuli that alter the behavior of intrinsic vascular wall cells and leukocytes alike (4,5). Certain oxidized phospholipids can elicit the expression on the surface of vascular endothelial cells (EC) of well-characterized adhesion molecules that mediate leukocyte adherence to the luminal surface of these cells (Fig. 1). Likewise, constituents of oxidized LDL can stimulate the expression of chemoattractant molecules, including chemokines such as monocyte chemoattractant protein-1, that beckon the attached leukocyte to migrate through the endothelial monolayer and enter the arterial intima. Angiotensin II can also stimulate the expression of vascular cell adhesion molecule-1 on the endothelial surface (6). Other cytokines regulated by components of oxidized LDL can activate the leukocytes within the intimal layer, provoking their production of further inflammatory mediators (i.e., proinflammatory cytokines and small lipid molecules such as the leukotrienes and prostaglandins). Moreover, these activated leukocytes can generate reactive oxygen species that augment oxidant stress, the constant companion of inflammation in atherosclerosis (6). Concordant population studies support a relationship between hypertension and atherosclerotic cardiovascular disease consistently and convincingly. Considerable evidence now links high blood pressure to inflammation in the artery wall. In particular, angiotensin II,

**Figure 1.** The transition from the normal artery wall to the nascent atherosclerotic lesion. The normal muscular artery has a trilaminar structure. A monolayer of endothelial cells overlies the intimal layer and abuts a basement membrane. In human arteries, the intima normally contains a few resident smooth muscle cells and a layer of extracellular matrix. The internal elastic lamina constitutes the boundary between the intimal layer and the tunica media, normally filled with quiescent smooth muscle cells embedded in an elastin-rich extracellular matrix. When molecules associated with risk factors stimulate oxidative or inflammatory stress, they induce the expression of adhesion molecules for leukocytes and chemoattractants that draw the bound leukocytes into the intimal layer. This diagram does not depict the adventitia, the outermost layer of the blood vessel.
considered a major mediator of hypertension, can act as a proinflammatory stimulus. For example, angiotensin II can stimulate the expression of the proinflammatory cytokine interleukin (IL)-6 and the chemokine monocyte chemotactant protein-1 from arterial smooth muscle cells (SMC) (7,8). Angiotensin II augments the activity of the adenine dinucleotide phosphate oxidases by vascular wall cells. Such enzymes give rise to superoxide anion, a major contributor to oxidative stress in atherosclerotic lesions (9).

Once resident in the artery wall, mononuclear phagocytes transition from a peripheral blood monocyte to a tissue macrophage (Fig. 2). In the artery wall, macrophages accumulate lipid derived from modified lipoproteins internalized through scavenger receptors. However, lipid accumulation in the artery wall depends on a balance between entry and egress. Population studies have consistently established an inverse relationship between high-density lipoprotein (HDL) levels and atherosclerotic cardiovascular disease. One major antiatherosclerotic role of HDL likely results from its ability to accept cholesterol from lipid-engorged macrophages and then ferry it out of the artery wall for catabolism and excretion (10). This process, commonly referred to as reverse cholesterol transport, seems to be only one of the anti-atherosclerotic actions of HDL. Indeed, HDL particles can harbor antioxidant enzymes such as paraoxonase-1, an enzyme that can inactivate potentially proinflammatory phospholipids (11). The HDL particles can mitigate EC expression of cytokine-induced leukocyte adhesion molecules. Thus, low levels of circulating HDL deprive the atheroma’s microenvironment of an endogenous antioxidant and anti-inflammatory particle.

Much recent interest in vascular biology has centered on the endogenous vasodilator molecule nitric oxide (·NO) (12). In addition to its vasorelaxant properties, ·NO can combat thrombosis by inhibiting platelet aggregation. Moreover, ·NO seems to have direct anti-inflammatory actions on EC, in part mediated by antagonism of the proinflammatory transcription regulator nuclear factor-kappa B (13,14). Thus, ·NO exerts a variety of atheroprotective actions. Interestingly shear stress regulates, endothelial nitric oxide synthase, the enzyme that produces ·NO in EC (15,16). Laminar shear stress encountered by EC under
normal circumstances augments endothelial nitric oxide synthase expression and local ·NO production by EC. In contrast, the regional release of ·NO likely decreases in regions of disturbed flow (16). Indeed, areas with high probability of initial atherosclerotic lesion formation, notably branch points and flow dividers, display evidence for inflammatory stimulation (17,18). Thus, the balance between local proinflammatory and anti-inflammatory processes probably participates in the preferential formation of atherosclerotic lesions at certain locations in the arterial tree.

Depiction of leukocyte recruitment to early atherosclerotic lesions generally focuses on the mononuclear phagocyte, the precursor of the most numerous white cell in lesions, the lipid-laden macrophage. Indeed, the mononuclear phagocyte constitutes the primary effector of the innate arm of the inflammatory immune response. However, other classes of leukocytes such as T and B lymphocytes and mast cells also congregate in the arterial intima during atherogenesis (19). For a full discussion of roles for these cells, see Kovanen (20) and Hansson and Libby (21).

**INFLAMMATION AND THE PROGRESSION OF ATHEROSCLEROSIS**

Once established, the atherosclerotic lesion transitions from the fatty streak, composed primarily of macrophage-derived foam cells, to a lesion with a more fibrous character (Figs. 2 and 3). A major cell type involved in the formation of fibrofatty lesions, the arterial SMC, also responds to a myriad of inflammation-associated mediators. Chemoattractants such as platelet-derived growth factor, locally produced by activated leukocytes or elaborated by SMC themselves when appropriately stimulated, can signal SMC to enter the intimal layer from the media, where they reside in a quiescent state in normal arteries (22). The SMC in the intima, some of which may derive from bone marrow as well as from the

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**Figure 3.** Maturation of the atherosclerotic plaque. More mature lesions develop a fibrous cap composed of a dense extracellular matrix containing collagen and elastin. Underneath the fibrous cap, a lipid core forms that contains many macrophages, dead or dying macrophages, cellular debris including apoptotic bodies, and extracellular lipid accumulations. Proinflammatory mediators released from activated white cells and endothelial cells and smooth muscle cells (SMC) can potentiate cell death by apoptosis in the advancing lesion. As SMCs die within lesions, fewer remain to renew the extracellular matrix in the plaque's fibrous cap. In addition, the activated cells in the lesion, notably the macrophages, secrete proteinases that can degrade the macromolecules of the extracellular matrix. In particular, interstitial collagenases can attack the triple helical collagen fragments, weakening the fibrous cap. Elastases can break down elastin required for migration of cells within the lesion, and arterial remodeling occurs during compensatory enlargement, and in the extreme, aneurysm formation. During this phase of atherogenesis neovessels form in the intima, often arising as extensions of vasa vasorum that originate in the adventitial layer. IEL = internal elastic lamina; MFC = macrophage foam cell; ROS = reactive oxygen species.
tunica media, can elaborate extracellular matrix (ECM) molecules that contribute to lesion fibrosis. The arterial SMC manufactures interstitial collagens, elastin, and glycosaminoglycans, principal constituents of the complex ECM characteristic of mature atherosclerotic plaques (23,24). Transforming growth factor-beta, a product of regulatory T cells and other cells associated with atheromatous plaques, potently stimulates ECM gene expression by arterial SMC (25). During this phase of atherosclerotic lesion progression, the lesions assume the characteristic architecture of the established atheroma, including the formation of a fibrous cap that surmounts the typical plaque (Fig. 3).

Underneath the fibrous cap, a lipid-rich region forms, often known as the necrotic or lipid core. This central structure in the typical atherosclerotic plaque consists of acellular debris, lipid, and macrophage foam cells. Some cells within and surrounding this region of the plaque bear markers of programmed cell death, or apoptosis (Fig. 3) (26). Proinflammatory cytokines can prime cells for apoptotic death after engagement of receptors such as Fas by death signals such as Fas ligand on activated T cells (27). Inflammation participates in plaque progression, as indicated by in vivo experiments that involve interruption of a central proinflammatory signaling pathway mediated by ligation of CD40 as well as circumstantial evidence based on observations of human and experimental plaques in situ (28).

INFLAMMATION AND THE COMPLICATIONS OF ATHEROSCLEROSIS

Atherosclerotic plaques typically develop in the arterial intima over a period of many years, even decades. There, these lesions lurk silently until they either produce a flow-limiting obstruction and provoke ischemia or until they trigger thrombosis. The progression of atherosclerotic lesions to occlusive stenoses preoccupied our pathophysiologic concepts and our diagnostic and therapeutic approaches for most of the 20th century. However, we now recognize that occlusive thrombi more frequently complicate noncritically stenotic plaques than those traditionally deemed the culprit of acute myocardial infarction (Fig. 4). Because of positive remodeling or compensatory enlargement, considerable growth of atheroma can occur without substantial lumenal stenosis (29). Such outwardly remodeled plaques may indeed harbor the most intense inflam-
mation and most likely cause acute thrombotic complications (30).

A physical disruption of atherosclerotic plaques predisposes toward thrombus formation. The plaque’s fibrous cap typically stands between the blood and highly thrombogenic material in the plaque’s lipid core. A thinned fibrous cap can break open, exposing the blood and its coagulation factors to thrombogenic stimuli such as tissue factor that concentrates within the lesion’s central core. Endothelial erosion also can precipitate coronary artery thrombosis (Fig. 4) (31). Convergent experimental results and pathological observation support a tight link between inflammation, plaque disruption, and thrombosis (32). Interferon gamma, a prominent product of the activated T lymphocyte, can limit severely the ability of the SMC to produce new collagen required to repair and maintain the ECM of the plaque’s fibrous cap and hence resist rupture (25). Multiple inflammatory cytokines can augment, alone or in concert, the expression within the plaque of proteinases specialized in degrading the ECM macromolecules that lend strength to the plaque’s fibrous cap (33). Members of the matrix metalloproteinase family, including interstitial collagenases, likely participate in this process. Cysteinyi proteinases such as cathepsin S also can catabolize elastin, a prominent constituent of the arterial ECM in plaques (34). Additionally, serine proteinases, including neutrophil elastase and plasminogen activators, may participate in arterial ECM remodeling and potentially predispose toward plaque disruption and thrombosis (35). Mediators related to inflammation regulate all of these proteolytic enzyme categories.

The plaque’s predominant procoagulant, tissue factor, also undergoes regulation by proinflammatory cytokines, notably CD40 ligand or CD154. In situ studies have colocalized CD40 ligand–positive cells in the vicinity of tissue factor–bearing macrophages in human atherosclerotic lesions (36). Thus, inflammation tightly regulates the procoagulant potential of the atherosclerotic plaque.

Atherothrombotic events, however, depend on not only the “solid state” of procoagulants in the plaque itself but also on the “fluid phase” of the blood (30). Individuals with a systemic proinflammatory burden such as the metabolic syndrome or the diabetic state have elevated levels of fibrinogen, the immediate precursor to fibrin, the major component of thrombi (37). Moreover, the major inhibitor of endogenous fibrinolytic enzymes, plasminogen activator inhibitor–1, also increases in systemic inflammatory states such as those mentioned above (38,39). Thus, in the setting of local inflammation in the plaque or systemic inflammation as reflected by the acute-phase response, inflammatory pathways conspire to promote thrombosis and combat fibrinolysis. Consequently, inflammation promotes clot formation and instability and underlies the thrombotic aspects of atherothrombosis as well as lesion initiation and progression.

CLINICAL IMPLICATIONS OF INFLAMMATION BIOLOGY IN ATHEROSCLEROSIS

The inflammatory hypothesis of atherothrombosis has major implications for clinical practice. First, inflammatory biomarkers possess substantial clinical utility for improving vascular risk detection beyond that achieved with hyperlipidemia and traditional risk factors (40). Second, the recognition of atherosclerosis as an inflammatory disease provides impetus to seek novel anti-inflammatory therapies with the potential to treat and prevent acute thrombosis (41).

RISK PREDICTION

Multiple studies in primary and secondary prevention as well as acute coronary ischemia have determined that a diverse set of proinflammatory biomarkers can furnish prognostic information beyond that available from traditional risk factors. Current analyses of fibrinogen (37); the cytokines IL-1, IL-6, and IL-18 (42–44); myeloperoxidase (45); metalloprotease-9 (46); sCD40L (47,48); lipoprotein–associated phospholipase A2 (49); the adhesion molecules soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, and P-selectin (50–52); and the adipokines leptin and adiponectin (53,54) have determined an association between each of these biomarkers and the risk of initial or recurrent vascular events; similar observations pertain to incident hypertension, even among currently normotensive individuals (55). However, clinical application of these findings largely focuses on high-sensitivity C-reactive protein (hsCRP), a pentraxin biomarker of innate immunity with analytical chemistry characteristics favorable to standard outpatient clinical settings. As outlined below, such effects prove relevant in primary and secondary prevention and acute coronary ischemia; they also enhance our understanding of the mechanisms and underlying agents commonly used to treat vascular disease (Fig. 5).

THE USE OF hsCRP IN PRIMARY AND SECONDARY PREVENTION

More than 24 prospective epidemiologic studies of initially healthy individuals have evaluated the role of hsCRP as a determinant of vascular risk, and all reported positive findings. Of these studies, 10 were adequately powered to evaluate the risk prediction role of hsCRP beyond that associated with traditional factors included in global assessment algorithms such as the Framingham Risk Score (49,56–64). When evaluated as a group and despite highly diverse patient populations, each study showed the importance of inflammation beyond traditional approaches to risk prediction (Fig. 6); as shown, these studies consistently find that the risk for subjects in the top tertile of hsCRP is approximately twice that of those in the lowest tertile. On this basis, the U.S. Centers for Disease Control and Prevention and the American Heart Association endorsed hsCRP as an adjunct to risk prediction in primary preven-
tion, particularly among individuals at “intermediate” risk (65). Broadly, blood levels of hsCRP <1, 1 to 3, and >3 mg/l correspond to low, moderate, and high vascular risk across all levels of LDL cholesterol (LDL-C), the Framingham Risk Score, and the metabolic syndrome. More recent analyses show that these clinical cut points for hsCRP add relevant prognostic information across all levels of the total/HDL cholesterol and apolipoprotein B/apolipoprotein A ratios, not only after adjustment for traditional covariates but also after controlling for diabetes and obesity (66) (Fig. 7). Contrary to prior assumptions, the rare individuals who chronically show markedly elevated levels of hsCRP (>10 mg/l) do not seem to represent false-positive cases. Rather, such individuals likely have markedly increased vascular risk, suggesting that inflammation from several sources can be pathogenic in the vascular endothelium (67). Despite the frequent citation of a few studies as not showing independent predictive value, the data they report actually agree with the overall effect estimates seen in larger studies. For example, the Rotterdam Study reported an age-adjusted relative risk for those in the highest compared with the lowest quartile of hsCRP of 2.0 (95% confidence interval 1.1 to 3.4), fully consistent with other data (68). Similarly, data from the Framingham Heart Study regarding CRP show strong positivity for stroke (69).

Clinical interest in hsCRP also links in part to the observation that its baseline levels associate with increased risk of developing type 2 diabetes mellitus, even after adjustment for obesity and other population-based determinants of diabetogenesis (70). Multiple studies show that hsCRP levels predict vascular events beyond the components of the metabolic syndrome (as defined by Adult Treatment Panel III criteria) or the presence of frank diabetes (71–73). Although partly caused by associations between CRP and insulin resistance, such effects are consistent across patient groups with and without
overt evidence of altered glucose homeostasis (74) (Fig. 8). Although the American Diabetes Association recently challenged the existence of the metabolic syndrome (75), the concerns largely addressed the controversy surrounding syndrome definition. If the definition of patients with metabolic syndrome aims to identify those with the highest risk of developing both vascular events and type 2 diabetes, and given the practical difficulty of measurement of insulin resistance and hypo- fibrinolysis in clinical settings, we and others suggest that inclusion of hsCRP in formal definitions of metabolic syndrome may help achieve this goal (76).

Beyond primary prevention, multiple studies have found that hsCRP levels in stable patients after myocardial infarction can predict recurrent infarction and cardiovascular death (77,78), a finding consistent with data from patients...
undergoing elective percutaneous intervention (79) or surgical revascularization (80). However, inflammatory mechanisms of atherothrombosis occur in multiple vascular beds, and hsCRP levels predict incident peripheral arterial disease (81) as well as incident and recurrent stroke (69,82). Such predictive ability may reach beyond large-vessel disease. The Rotterdam Scan Study recently reported that higher CRP levels are associated with the presence and progression of cerebral white matter lesions in the periventricular and subcortical regions, data with implications for small-vessel disease progression (83). Supporting the selectivity for CRP as a predictor of cardiovascular disease, this marker does not correlate with either the development of cancer (84) or with noncardiovascular disease events (85).

**hsCRP in Acute Coronary Ischemia**

The role of hsCRP in cardiovascular events emerged initially from observations on patients with acute ischemia and unstable angina (86–88). Multiple studies have determined that hsCRP levels at the time of presentation or at hospital discharge provide prognostic information on both short-term and long-term risk, even in the absence of troponin elevation (89,90). As such, a component of plaque vulnerability may not depend on myocardial cell death, an issue likely relevant for the development of targeted anti-inflammatory agents for acute myocardial ischemia.

When used in conjunction with other biomarkers, including brain natriuretic peptide and myeloperoxidase, hsCRP levels also provide incremental evidence of vulnerability to acute ischemia. Compared with any 1 biomarker used in isolation, investigators for the TIMI (Thrombolysis In Myocardial Infarction) 16 and TIMI 18 trials showed that combinations of these emerging biomarkers may provide a superior method for the detection of vascular risk, at least in the setting of acute ischemia (91) (Fig. 9).

**hsCRP and Therapeutic Interventions**

Although hsCRP is clearly an effective clinical tool for risk stratification in multiple clinical settings, currently no data directly link hsCRP reduction to lower rates of vascular events. Nonetheless, diet and exercise—therapies proven to lower the risk of both heart disease and diabetes—are associated with decreased hsCRP in obese and modestly overweight patients (92,93). Interestingly, insulin resistance is associated not only with elevated baseline levels of hsCRP but also with greater hsCRP reduction during weight loss. Although patients have sustained hsCRP reductions after gastric bypass surgery, intensive lifestyle modifications that combine both caloric restriction and moderate-intensity physical exercise produce reductions of approximately 30% (94). Agents commonly used to treat diabetes, including insulin, metformin, and the peroxisome proliferator-activated receptor-gamma agonists rosiglitazone and pioglitazone, also lower CRP (95). Whether these effects result

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**Figure 8.** Odds ratios of cardiovascular disease (CVD) in U.S. patients with diabetes mellitus, metabolic syndrome, and elevated high-sensitivity C-reactive protein (hsCRP) in NHANES (National Health and Nutrition Evaluation Survey). Adapted with permission from Malik et al. (74).

**Figure 9.** Prognostic utility of combining high-sensitivity C-reactive protein, troponin, and brain natriuretic peptide in the setting of acute coronary ischemia in the TIMI 16 and TIMI 18 clinical trials. Adapted with permission from Sabatine et al. (91); OPUS-TIMI = Orbofiban in Patients With Unstable Coronary Syndromes–Thrombolysis In Myocardial Infarction Trial; TACTICS = Treat Angina With Aggrastat and Determine Costs of Therapy With Invasive or Conservative Strategies.
from improvements in insulin resistance and/or do not depend on improved glycemic control remains controversial.

The use of hsCRP to improve patient selection for cardiovascular therapies is best shown with regard to 3-hydroxy-3-methylglutaryl reduction with statins. Originally developed solely as a means to lower LDL-C, statin agents may possess additional anti-inflammatory properties. As recently reviewed, statins may be directly immunomodulatory, may inhibit expression of cell adhesion molecules, can induce thrombomodulin and tissue plasminogen activator and thus favorably alter hemostatic balance, and may have direct beneficial effects on platelets and smooth muscle proliferation (96,97).

Initial observations from the CARE (Cholesterol and Recurrent Events) trial showed clinically that statins lower CRP levels (98); additionally, the benefit of statin therapy seemed greater among individuals with higher levels of the inflammatory biomarkers hsCRP or serum amyloid A protein (77). We now recognize that statins as a class lower hsCRP levels. However, the mechanisms of this effect remain uncertain, because IL-6 levels do not decline consistently with statin therapy. Indeed, statins can reduce the production of CRP by isolated hepatocytes (99,100). Further, the magnitude of hsCRP reduction expected from the initiation of statin therapy cannot be gleaned from the magnitude of LDL reduction in individual patients (101).

Provocative data now suggest the utility of hsCRP in monitoring the effectiveness of statins in primary prevention, after stent placement, and in high-risk acute coronary syndromes. Data regarding apparently healthy patients in the AFCAPS-TexCAPS (Air Force Coronary Atherosclerosis Prevention Study–Texas Coronary Atherosclerosis Prevention Study) primary prevention trial showed that lovastatin decreases hsCRP levels, and suggested that individuals with low levels of LDL-C and concomitant elevations of hsCRP might benefit substantially from statin treatment (102). By contrast, the AFCAPS-TexCAPS trial found no evidence of statin efficacy among individuals with low levels of both LDL-C and hsCRP. These analyses led to the initiation of the ongoing large-scale JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) (right) of primary prevention with rosuvastatin among individuals with native LDL-C levels <130 mg/dl, who thus do not qualify for statin therapy but are at increased risk because of CRP levels >2 mg/l (103). The hard end points of the JUPITER trial will make its results important not only regarding the inflammatory hypothesis of atherosclerosis but also for the conceptual basis of extending beyond LDL-C as the sole method for determining those likely to benefit from statin therapy. With regard to coronary stent placement in patients with stable angina, statins reduce the increased risk of recurrent events associated with elevated CRP levels, independent again of underlying levels of LDL-C (104,105).

Recent data from the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infections Therapy–TIMI 22 and the REVERSAL (Reversal of Atherosclerosis with Lipitor) trials further suggest that hsCRP levels achieved by statin therapy may rival LDL-C levels achieved with these agents. Specifically, in the PROVE IT–TIMI 22 trial of patients with acute coronary syndrome treated with either atorvastatin (80 mg) or pravastatin (40 mg), the survival rate of individuals who achieved LDL-C levels below the study median (70 mg/dl) improved significantly, data consistent with clinical recommendations to aggressively lower lipid levels in high-risk patients (106) (Fig. 10, left). However, that same trial determined that the survival rate of individuals with hsCRP levels below the median (2 mg/l) improved significantly as well, regardless of the LDL-C level achieved (Fig. 10, right). Perhaps more importantly, the magnitude of benefit associated with low levels of hsCRP equaled that of low LDL, even though the effect was almost entirely independent of lipid lowering. Thus, the greatest clinical benefit of statin therapy within the PROVE IT–TIMI 22 trial occurred among patients who lowered both LDL-C (<70 mg/dl) and hsCRP (<2 mg/l) (Fig. 11). Post-hoc analyses of these data showed even greater risk reductions at hsCRP levels <1 mg/l.

The REVERSAL trial treated coronary disease patients with the same statin agents and doses as PROVE IT. Atherosclerotic progression, as measured by intravascular ultrasound, slowed primarily among individuals who lowered both LDL-C and hsCRP (107). Similar to the PROVE IT trial, individuals who achieved aggressive reductions in both LDL-C and hsCRP experienced the highest degree of disease regression. Taken together, these clinical data strongly suggest that dual goals of therapy for high-risk patients treated with statins should include LDL-C <70 mg/dl as well as hsCRP <2 mg/l. On this
basis, clinicians may need to measure and monitor hsCRP in a manner analogous to the methods currently used to measure and monitor LDL-C, at least if the goal is to maximize patient benefit with statin therapy.

**IS CRP MORE THAN A CLINICAL MARKER OF DISEASE?**

For a biomarker to be clinically useful, it need only improve the clinician’s ability to detect disease risk and assist in therapeutic decision making. As previously outlined, hsCRP has overwhelmingly proven to have these characteristics. Whether or not a biomarker is in the causal pathway of disease and can formally fulfill the Koch postulates is ultimately not relevant for decisions regarding these important clinical applications. Nonetheless, it has been of interest to examine the possibility that CRP might play a direct role in the atherothrombotic process.

Commonly, CRP localizes in atherosclerotic plaques, where it can bind to modified LDL, contribute to complement activation, increase monocyte recruitment, and lead to lesion progression (108,109); CRP also reduces NO synthesis, increases the release of endothelin-1, and augments the function of adhesion molecules and chemokines within vascular SMC and EC (110,111). In transgenic mice, CRP may heighten thrombosis after arterial injury (112). Yet, overexpression of CRP in atherosclerosis-prone mice has little effect on lesion progression. Additionally, controversy remains regarding any direct pathogenic effects mediated by monomeric rather than pentameric CRP (113).

Based on currently available data, we believe that CRP has potential as a relevant target for therapy, but also recognize that evidence to date is both controversial and incomplete. Indeed, research on the possible pathogenic mechanisms of CRP must proceed carefully to answer questions regarding the potential role of CRP as a target for therapy. Recently released studies indicate at least 7 common single-nucleotide polymorphisms in the CRP gene, including one tri-allelic single-nucleotide polymorphism; haplotypes based on these single-nucleotide polymorphisms, however, are responsible for only a tiny fraction of the population variance in CRP, confirming the major importance of environmental factors on inflammatory processes (114,115). Recently completed human CRP infusion studies suggest induction of a substantial proinflammatory and prothrombotic state, albeit with limitations (116). The development of agents that specifically lower CRP without effecting platelet function or lipid levels will assist in understanding these issues.

As previously described, the clinical application of hsCRP is a mature practice, and abundant evidence shows that hsCRP can assist physicians as they evaluate cardiovascular risk and monitor therapeutic interventions. Whether or not hsCRP ultimately proves to be a direct mediator of vascular disease will not alter its role as a useful clinical tool.

**Conclusions.** The concept that inflammation governs atherosclerosis and its complications has provided a new unifying hypothesis regarding the links between risk factors and the cellular and molecular alterations that underlie this disease. This construct not only furnishes new mechanistic insight into the disease process but also has begun to translate into changes in clinical practice. The preponderance of present data support the predictive power of biomarkers of inflammation in broad categories of individuals, both those who are apparently well and those with already-manifest atherosclerotic cardiovascular disease. The clinical utility of inflammatory biomarkers has engendered intense interest and ongoing investigation to evaluate cost-effectiveness as a predictive tool beyond conventional risk markers. The proposition that hsCRP levels should become a guide for and/or a goal of therapy has received support from large-scale clinical trials.

The rapid translation of inflammation biology in cardiovascular disease from the laboratory to the clinic serves as a gratifying example of bench-to-bedside research. Yet, many questions remain unsettled in this regard, and we can look forward to considerable excitement in the future as experimental and clinical studies emerge to help settle the unresolved and/or controversial issues. The application of inflammation biology to atherosclerosis has already afforded new insight into how current interventions, both pharmacologic and lifestyle, may reduce cardiovascular risk. Ultimately, the insight that inflammation plays a fundamental role in atherosclerosis may lead to novel therapies that target aspects of the inflammatory process smoldering within the atheroma.
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