Inflammation and Atherosclerosis

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Abstract—Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein, prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease, but also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance. **(*Circulation*. 2002;105:1135-1143.)**

Key Words: endothelium ■ inflammation ■ atherosclerosis ■ proteins

Over the last dozen years, appreciation of the role of inflammation in atherosclerosis has burgeoned. Although it was formerly considered a bland lipid storage disease, substantial advances in basic and experimental science have illuminated the role of inflammation and the underlying cellular and molecular mechanisms that contribute to atherogenesis. Compelling evidence for the importance of inflammation and atherosclerosis at both the basic and clinical level has evolved in parallel. Accumulating data indicate that insights gained from the link between inflammation and atherosclerosis can yield predictive and prognostic information of considerable clinical utility. This review summarizes the experimental and clinical evidence for inflammation in atherosclerosis, and assesses the current state of knowledge regarding the triggers for inflammation in this disease. We will evaluate the participation of inflammation in the acute coronary syndromes (ACS) and review the data supporting the use of inflammatory markers as prognostic and predictive instruments in the context both of ACS and of prediction of risk for various complications of atherosclerosis. Finally, we will consider how new insights into inflammation in atherosclerosis may identify innovative therapeutic strategies to improve outcomes of individuals at risk for or affected by this scourge of growing worldwide importance.

The Scientific Basis of Inflammation in Atherogenesis

In a variety of animal models of atherosclerosis, signs of inflammation occur hand-in-hand with incipient lipid accumulation in the artery wall. For example, blood leukocytes, mediators of host defenses and inflammation, localize in the earliest lesions of atherosclerosis, not only in experimental animals but in humans as well. The basic science of inflammation biology applied to atherosclerosis has afforded considerable new insight into the mechanisms underlying this recruitment of leukocytes. The normal endothelium does not in general support binding of white blood cells. However, early after initiation of an atherogenic diet, patches of arterial endothelial cells begin to express on their surface selective adhesion molecules that bind to various classes of leukocytes (Figure 1A). In particular, vascular cell adhesion molecule-1 (VCAM-1) binds precisely the types of leukocytes found in early human and experimental atheroma, the monocyte and T lymphocyte. Not only does VCAM-1 expression increase on endothelial cells overlying nascent atheroma,[1] but mice genetically engineered to express defective VCAM-1 show interrupted lesion development.[2]

Interestingly, the foci of increased adhesion molecule expression overlap with sites in the arterial tree particularly prone to develop atheroma. Considerable evidence suggests that impaired endogenous atheroprotective mechanisms occur at branch points in arteries, where the endothelial cells

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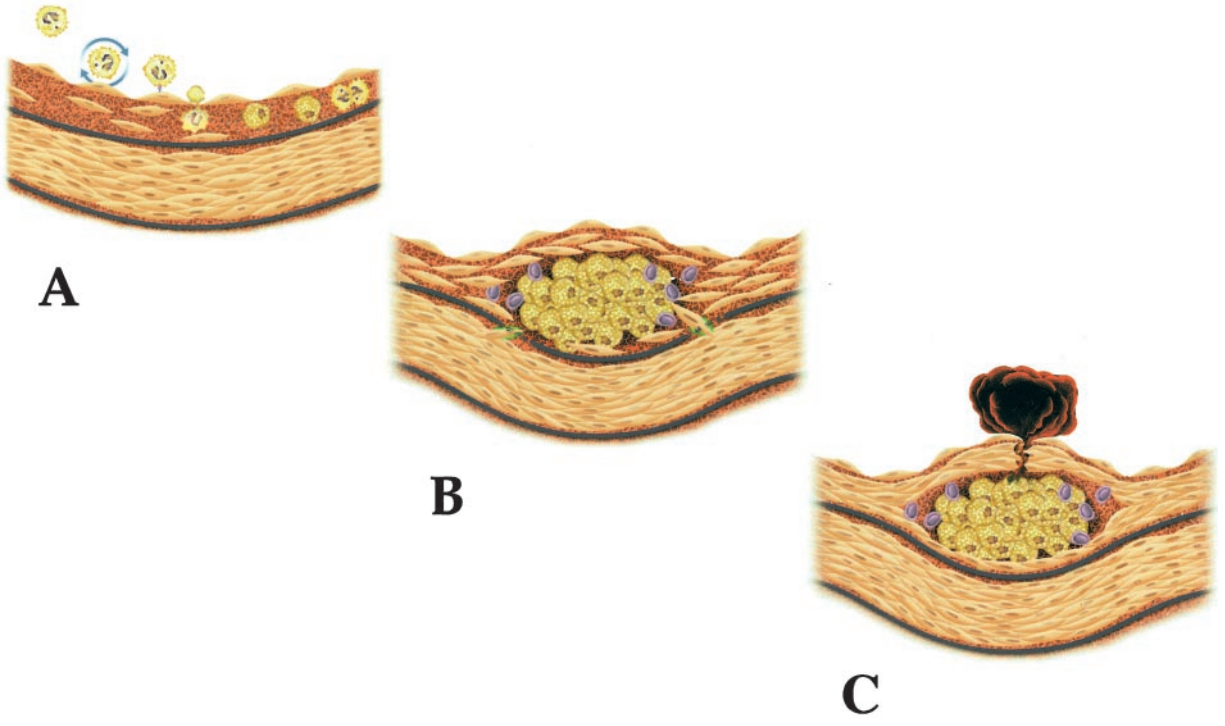

Figure 1. Participation of inflammation in all stages of atherosclerosis. A, Leukocyte recruitment to the nascent atherosclerotic lesion. Blood leukocytes adhere poorly to the normal endothelium. When the endothelial monolayer becomes inflamed, it expresses adhesion molecules that bind cognate ligands on leukocytes. Selectins mediate a rolling, or saltatory, interaction with the inflamed luminal endothelium. Integrins mediate firmer attachment. Proinflammatory cytokines expressed within atheroma provide a chemotactic stimulus to the adherent leukocytes, directing their migration into the intima. Inflammatory mediators such as M-CSF can augment expression of macrophage scavenger receptors leading to uptake of modified lipoprotein particles and formation of lipid-laden macrophages. M-CSF and other mediators produced in plaques can promote the replication of macrophages within the intima as well. B, T lymphocytes join macrophages in the intima during lesion evolution. These leukocytes, as well as resident vascular wall cells, secrete cytokines and growth factors that can promote the migration and proliferation of SMCs. Medial SMCs express specialized enzymes that can degrade the elastin and collagen in response to inflammatory stimulation. This degradation of the arterial extracellular matrix permits the penetration of the SMCs through the elastic laminae and collagenous matrix of the growing plaque. C, Ultimately, inflammatory mediators can inhibit collagen synthesis and evoke the expression of collagenases by foam cells within the intimal lesion. These alterations in extracellular matrix metabolism thin the fibrous cap, rendering it weak and susceptible to rupture. Cross-talk between T lymphocytes and macrophages heightens the expression of the potent procoagulant tissue factor. Thus, when the plaque ruptures, as shown here, the tissue factor induced by the inflammatory signaling triggers the thrombus that causes most acute complications of atherosclerosis.

experience disturbed flow.[3] For example, absence of normal laminar shear stress may reduce local production of endothelium-derived NO. This endogenous vasodilator molecule also has anti-inflammatory properties and can limit expression of VCAM-1.[4] In addition to inhibiting natural protective mechanisms, disturbed flow can augment the production of certain leukocyte adhesion molecules (eg, intercellular adhesion molecule-1 [ICAM-1]).[5] Augmented wall stresses may also promote the production by arterial smooth muscle cells (SMCs) of proteoglycans that can bind and retain lipoprotein particles, facilitating their oxidative modification and thus promoting an inflammatory response at sites of lesion formation.[6]

Once adherent to the endothelium, the leukocytes penetrate into the intima (Figure 1A). Recent research has identified candidate chemoattractant molecules responsible for this transmigration. For example, monocyte chemoattractant protein-1 (MCP-1) appears responsible for the direct migration of monocytes into the intima at sites of lesion formation.[7,8] A family of T-cell chemoattractants may likewise call lymphocytes into the intima.[9] Once resident in the arterial wall, the blood-derived inflammatory cells participate in and perpetuate a local inflammatory response (Figure 1B). The macrophages express scavenger receptors for modified lipoproteins, permitting them to ingest lipid and become foam cells. In addition to MCP-1, macrophage colony-stimulating factor (M-CSF) contributes to the differentiation of the blood monocyte into the macrophage foam cell.[10,11] T cells likewise encounter signals that cause them to elaborate inflammatory cytokines such as γ-interferon and lymphotoxin (tumor necrosis factor [TNF]–β) that in turn can stimulate macrophages as well as vascular endothelial cells and SMCs.[12] As this inflammatory process continues, the activated leukocytes and intrinsic arterial cells can release fibrogenic mediators, including a variety of peptide growth factors that can promote replication of SMCs and contribute to elaboration by these cells of a dense extracellular matrix characteristic of the more advanced atherosclerosis lesion.[13]

Inflammatory processes not only promote initiation and evolution of atheroma, but also contribute decisively to precipitating acute thrombotic complications of atheroma (Figure 1C). Most coronary arterial thrombi that cause fatal

acute myocardial infarction arise because of a physical disruption of the atherosclerotic plaque. The activated macrophage abundant in atheroma can produce proteolytic enzymes capable of degrading the collagen that lends strength to the plaque's protective fibrous cap, rendering that cap thin, weak, and susceptible to rupture. γ-Interferon arising from the activated T lymphocytes in the plaque can halt collagen synthesis by SMCs, limiting its capacity to renew the collagen that reinforces the plaque.[14,15] Macrophages also produce tissue factor, the major procoagulant and trigger to thrombosis found in plaques. Inflammatory mediators regulate tissue factor expression by plaque macrophages, demonstrating an essential link between arterial inflammation and thrombosis.[16]

Triggers for Inflammation in Atherogenesis

Oxidized Lipoproteins and Inflammation

For almost a century, many have regarded lipids as the *sine qua non* of atherosclerosis. Over the last few decades, a plausible model linking lipids and inflammation to atherogenesis has emerged. According to the oxidation hypothesis, low-density lipoprotein (LDL) retained in the intima, in part by binding to proteoglycan, undergoes oxidative modification.[17,18] Lipid hydroperoxides, lysophospholipids, carbonyl compounds, and other biologically active moieties localize in the lipid fraction of atheroma.[19] These modified lipids can induce the expression of adhesion molecules, chemokines, proinflammatory cytokines, and other mediators of inflammation in macrophages and vascular wall cells. The apoprotein moieties of the lipoprotein particles can also undergo modification in the artery wall, rendering them antigenic and capable of inciting T-cell responses, thus activating the antigen-specific adaptive limb of the immune response.[20] In some experimental situations, administration of antioxidants can retard the progression of atherosclerotic lesions that develop in the face of hyperlipidemia.

Although attractive, theoretically compelling, and supported by a considerable body of experimental evidence, the relevance of the LDL oxidation hypothesis to human atherosclerosis remains unproven. Chemical analysis of the types of modified lipids and proteins extracted from human atheroma do not necessarily correspond to the compounds derived from lipoproteins oxidized in vitro that have furnished much of the evidence linking oxidized lipoproteins to inflammation. Most cell culture studies of the biological effects of oxidized LDL have used material generated by transition metal–mediated oxidation, conditions that some find of dubious in vivo relevance. Hypochlorous acid–mediated derivation of lipoprotein constituents may bear closer relationship to human atherosclerosis than oxidative modification catalyzed by transition metals.[21,22] The leukocyte enzyme myeloperoxidase produces hypochlorous acid within the atheroma. Clinical trials have repeatedly failed to validate the concept that antioxidant vitamin therapy can improve clinical outcomes. Thus, "the jury is still out" on the applicability of the LDL oxidation hypothesis to patients.

Dyslipidemia and Inflammation

Other lipoprotein particles such as very low–density lipoprotein (VLDL) and intermediate-density lipoprotein also have considerable atherogenic potential. These lipoprotein particles can undergo oxidative modification like that of LDL. In addition, some evidence suggests that beta VLDL particles may themselves activate inflammatory functions of vascular endothelial cells.[23,24] High-density lipoprotein (HDL) protects against atherosclerosis. Reverse cholesterol transport effected by HDL likely accounts for some its atheroprotective function. However, HDL particles also can transport antioxidant enzymes such as platelet-activating factor acetylhydrolase and paraoxonase, which can break down oxidized lipids and neutralize their proinflammatory effects.

Hypertension and Inflammation

Hypertension follows closely behind lipids on a list of classical risk factors for atherosclerosis. Increasing evidence supports the view that, like atherosclerosis itself, inflammation may participate in hypertension providing a pathophysiological link between these two diseases. Angiotensin II (AII), in addition to its vasoconstrictor properties, can instigate intimal inflammation. For example, AII elicits the production of superoxide anion, a reactive oxygen species, from arterial endothelial cells and SMCs.[25] AII can also increase the expression by arterial SMCs of proinflammatory cytokines such as interleukin (IL)–6 and MCP-1 and of the leukocyte adhesion molecule VCAM-1 on endothelial cells.[26–28] Some of the clinical benefits of angiotensin-converting enzyme inhibitor therapy may derive from interrupting such proinflammatory pathways.

Diabetes and Inflammation

Diabetes is yet another risk factor for atherosclerosis of growing importance. The hyperglycemia associated with diabetes can lead to modification of macromolecules, for example, by forming advance glycation end products (AGE).[29] By binding surface receptors such as RAGE (receptor for AGE), these AGE-modified proteins can augment the production of proinflammatory cytokines and other inflammatory pathways in vascular endothelial cells. Beyond the hyperglycemia, the diabetic state promotes oxidative stress mediated by reactive oxygen species and carbonyl groups.[30] As in the case of hypertension, inflammation links diabetes to atherosclerosis.

Obesity and Inflammation

Obesity not only predisposes to insulin resistance and diabetes, but also contributes to atherogenic dyslipidemia. High levels of free fatty acids originating from visceral fat reach the liver through the portal circulation and stimulate synthesis of the triglyceride-rich lipoprotein VLDL by hepatocytes. The resulting elevation in VLDL can lower HDL cholesterol by augmenting exchange from HDL to VLDL by cholesteryl ester transfer protein. Adipose tissue can also synthesize cytokines such as TNF-α and IL-6.[31] In this way obesity itself promotes inflammation and potentiates atherogenesis independent of effects on insulin resistance or lipoproteins.

Infection

Infectious agents might also conceivably furnish inflammatory stimuli that accentuate atherogenesis.[32,33] Acute infections can alter hemodynamics and the clotting and fibrinolytic systems in ways that can precipitate ischemic events. Chronic extravascular infections (eg, gingivitis, prostatitis, bronchitis, etc) can augment extravascular production of inflammatory cytokines that may accelerate the evolution of remote atherosclerotic lesions. Intravascular infection might also provide a local inflammatory stimulus that could accelerate atherogenesis. Many human plaques show signs of infection by microbial agents such *Chlamydia pneumoniae. Chlamydiae*, when present in the arterial plaque, may release lipopolysaccharide (endotoxin) and heat shock proteins that can stimulate the production of proinflammatory mediators by vascular endothelial cells and SMCs and infiltrating leukocytes alike.[34] Epidemiological studies of infection, however, have yielded mixed results, with little prospective evidence that antibodies directed against *Chlamydia pneumoniae, Helicobacter pylori,* herpes simplex virus, or cytomegalovirus predict vascular risk.

Inflammation and the ACS

The mechanisms of ACS encompass elements of thrombosis and vasoconstriction superimposed on atherosclerotic lesions. Thrombosis frequently persists, detectable by angiography, by angioscopy, or at autopsy. In contrast, vasospasm presents challenges to quantification because of its transient nature. Reduction of stenoses by administration of nitrates[35] or use of provocative maneuvers[36,37] provides evidence for arterial spasm. Indeed, thrombosis may beget vasospasm. Local thrombus formation generates serotonin, thromboxane A_2, and thrombin. Each of these thrombosis-associated mediators can cause vasoconstriction not only at the site of thrombosis, but also downstream. In this manner, a proximal thrombus in an epicardial conduit coronary artery might propagate spasm to the distal smaller vessels. Thrombi present a more tractable therapeutic target than vasoconstriction, as vasodilator drugs, when given systemically, seldom overcome the effect of locally produced constrictor substances.[35]

Yet, even with aggressive thrombolytic, anticoagulant, and/or antiplatelet agents or interventional therapy, patients with ACS still have a 12% to 16% incidence of major cardiac events at 4 to 6 months after hospital discharge.[38,39] Novel treatments based on increased understanding of the underlying mechanisms of plaque instability should yield further improvements in outcomes. Growing evidence indicates that in ACS, elevated circulating inflammatory markers, in particular C-reactive protein (CRP), predict an unfavorable course, independent of the severity of the atherosclerotic or ischemic burden. Thus, inflammation represents one potential novel pathophysiological mechanism of the ACS that may furnish such a new target for therapy.

Correlation of Elevated Inflammatory Markers With Adverse Prognosis

Elevated values of circulating inflammatory markers such as CRP, serum amyloid A, IL-6, and IL-1 receptor antagonist commonly accompany ACS. Such elevations correlate with in-hospital and short-term adverse prognosis[40–47] and may reflect not only a high prevalence of myocardial necrosis, ischemia-reperfusion damage, or severe coronary atherosclerosis but also a primary inflammatory instigator of coronary instability. The contribution of each of the inflammatory processes mentioned above to prognosis may vary in different groups of patients according to the criteria used for their selection. In turn, the short-term prognostic role of elevated CRP values in ACS may correlate at least in part with the long-term prognostic role of CRP values within the normal range in normal individuals[48,49] and of elevated values in chronic coronary disease.[50,51] Of note, the degree of elevation in CRP discussed here in the context of the ACS exceeds the relative increases within the normal range measured by the high-sensitivity assay discussed below in relation to prospective coronary risk stratification.

Inflammation and Myocardial Necrosis and Ischemia

Liuzzo et al[41] demonstrated early on that elevated CRP correlates with adverse short-term prognosis in selected patients with unstable angina, Braunwald class IIIb, who lacked evidence of myocardial necrosis and had an ischemic burden similar to that of patients without CRP elevation. Half of patients with ACS have persistently elevated CRP after discharge, a finding associated with recurrent episodes of instability and infarction.[47] Patients with variant angina and large ischemic burden, or stable angina pectoris and severe coronary artery disease, have a very low incidence of elevated CRP, affirming the specificity of systemically detectable inflammation in ACS.[52] Indeed, the elevation of CRP in unstable patients does not appear to relate merely to the extent and severity of atherosclerosis, as only about 20% of patients with chronic stable angina and a high prevalence of multivessel disease have elevated CRP values compared with 70% of patients with unstable angina.[41] Moreover, CRP values in patients with peripheral vascular disease severe enough to require revascularization do not differ significantly from those observed in unstable angina and single-vessel disease[53] (E. Rossi et al, unpublished data, 2001).

Not all patients with unstable angina and elevated CRP develop infarction. But practically all patients with infarctions preceded by unstable angina have elevated CRP on admission. The final sustained coronary occlusion leading to infarction may result from a coexistent prothrombic diathesis or from enhanced coronary vasoreactivity.[54] Inflammation might not only mark increased risk of infarction, but also participate in precipitating occlusive events. In addition, aspects of the acute-phase inflammatory response may directly influence thrombosis. Although CRP serves as a convenient marker of inflammation, the other proteins augmented during the acute-phase response include fibrinogen and plasminogen activator inhibitor-1. Thus, inflammation can promote thrombus formation and can enhance clot stability by inhibiting endogenous fibrinolysis.

Prevalence of Inflammation in the ACS and Interindividual Variability

In patients with ACS, the prevalence of a primary inflammatory pathogenic component of coronary instability, as detect-

able by elevated CRP, varies considerably. Elevated CRP (>3 mg/L) is found in <10% of normals, in <20% of patients with chronic stable or variant angina, but in >65% of patients with unstable angina, Braunwald class IIIb, and in >90% of patients with acute infarction preceded by unstable angina, but in <50% of those in whom the infarction was totally unheralded (in samples taken before elevation of markers of necrosis).[41,47,55]

The absence of elevated CRP in >30% of patients with severe unstable angina and in >50% of those with acute MI not preceded by unstable angina suggests an important heterogeneity of the role of inflammatory triggers of the clinical syndromes of coronary instability.[56] Individuals may vary in their response to inflammatory stimuli. The increase in CRP and IL-6 observed in response to the vascular trauma caused by coronary angioplasty or by uncomplicated cardiac catheterization[51] and that observed after acute infarction[57] correlates linearly with baseline CRP and IL-6 levels. In vitro, the IL-6 production by isolated monocytes from unstable patients with elevated CRP and IL-6 significantly exceeds that produced by monocytes from patients with normal values.[47] These individual differences in the degree of response to given inflammatory stimuli may have a genetic basis. For example, certain haplotypes in the IL-1/IL-1 receptor agonist gene complex correlate with heightened inflammatory responses and incidence of ACS.[58]

Inflammatory Biomarkers and Risk of First Cardiovascular Events: Implications for Prevention

The above discussion reviewed the role of inflammatory mediators and markers in ACS. However, inflammation contributes across the spectrum of cardiovascular disease, including the earliest steps in atherogenesis. This recognition has had a profound impact on our understanding of atherothrombosis as more than a disease of lipid accumulation, but rather as a disorder characterized by low-grade vascular inflammation. Practically, we can use this concept to predict future cardiovascular risk.

The best human data relating inflammation to the prospective development of vascular events have come from large-scale, population-based studies. To date, elevated levels of several inflammatory mediators among apparently healthy men and women have proven to have predictive value for future vascular events. In particular, prospective epidemiological studies have found increased vascular risk in association with increased basal levels of cytokines such as IL-6 and TNF-α[49,59–61]; cell adhesion molecules such as soluble ICAM-1, P selectin, and E selectin[62–64]; and downstream acute-phase reactants such as CRP, fibrinogen, and serum amyloid A.[48,49,65–70a] Several traditional cardiovascular risk factors track with these inflammatory biomarkers, in particular central obesity and body mass index. These observations have considerable importance because, as discussed above, adipocytes can produce inflammatory cytokines, and a common underlying disorder of innate immunity may well link obesity, accelerated atherosclerosis, and insulin resistance.[71b] In support of this hypothesis, very recent observations show that elevated levels of both IL-6 and CRP associate not only with the subsequent development of atherosclerosis, but also with the development of type II diabetes, even among individuals with no current evidence of insulin resistance.[72]

For clinical purposes, the most promising inflammatory biomarker appears to be CRP, a classical acute-phase marker and a member of the pentraxin family of innate immune response proteins.[73] The clinical appeal of CRP stems from several analytic properties. Unlike upstream cytokines, CRP has a long half-life, affording stability of levels with no observable circadian variation.[74] Further, CRP is easily measured in usual outpatient settings, and standardized high-sensitivity assays commercially available provide similar results in fresh, stored, and frozen plasma.[75] Functionally, in addition to providing a downstream integration of overall cytokine activation, CRP has several direct effects that may affect vascular disease progression. These reported functions include an ability to bind and activate complement, induce expression of several cell adhesion molecules as well as tissue factor, mediate LDL uptake by endothelial macrophages, induce monocyte recruitment into the arterial wall, and enhance production of MCP-1.[76–80]

More than a dozen population-based studies have demonstrated that baseline CRP levels predict future cardiovascular events. CRP testing may thus have a major adjunctive role in the global assessment of cardiovascular risk.[81] Available prospective epidemiological studies have included elderly as well as middle-aged individuals, and show consistency for the endpoints of first-ever myocardial infarction or stroke as well as for the development of symptomatic peripheral arterial disease[53] (Figure 2). In one recent overview analysis that included 2557 cases with an average follow-up of 8 years, individuals with basal CRP levels in the top third exhibited a 2-fold increase in future vascular events even after adjustment for all other available vascular risk factors.[69] Perhaps of equal clinical impact, both men and women with elevated levels of CRP consistently show high vascular risk, even in the absence of hyperlidipidemia.[49,82] Algorithms that combine CRP and lipid screening to improve risk assessment may have clinical utility for outpatient use[81] (Figure 3).

In addition to providing a simple method to assess low-grade inflammation and improve global risk prediction, CRP screening may also provide a novel method of targeting statin therapy, particularly in the primary prevention of myocardial infarction and stroke. Both experimental and clinical outcome data now support the hypothesis that statins, in addition to being potent LDL-lowering agents, also attenuate plaque inflammation and influence plaque stability. Both pravastatin and cerivastatin can reduce macrophage content within experimental atherosclerotic plaques,[83–85] whereas simvastatin, fluvastatin, and atorvastatin appear to reduce intimal inflammation[86] and suppress the expression of tissue factor and matrix metalloproteinases both in vivo and in vitro.[87,88] Statins may also inhibit expression of adhesion molecules critical for monocyte attachment and adhesion to the vascular endothelium.[89]

The first data to link the utility of CRP as a marker of inflammation with potential utility in targeting statin therapy emerged from the Cholesterol and Recurrent Events (CARE) trial, a secondary prevention study in which elevated CRP

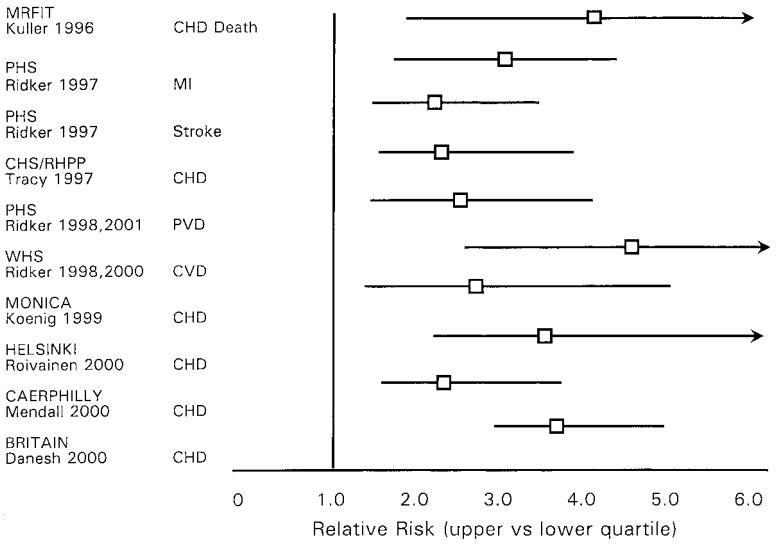

Figure 2. Prospective studies of high-sensitivity CRP as a risk factor for future vascular disease. CHD indicates coronary heart disease; MRFIT, Multiple Risk Factor Intervention Trial; PHS, Physicians' Health Study; CHS/RHPP, Cardiovascular Health Study and the Rural Health Promotion Project; WHS, Women's Health Study; PVD, pulmonary vascular disease; CVD, cardiovascular disease; and MONICA, Monitoring Trends and Determinants in Cardiovascular Disease. Studies cited are the following: Kuller et al,[66] Ridker et al,[48,49,53,68] Tracy et al,[67] Koenig et al,[70a] Danesh et al,[69] Roivanen et al,[70b] and Mendall et al.[71] Adapted from Ridker.[81]

levels correlated with significantly increased risk of recurrent coronary events.[50,90] In a series of hypothesis-generating studies, the CARE investigators then demonstrated that the magnitude of risk reduction attributable to pravastatin was substantially greater among those with evidence of inflammation compared with those without evidence of inflammation. The CARE investigators also reported that random allocation to pravastatin lowered CRP levels in a manner unrelated to the effect of pravastatin on LDL or HDL cholesterol, data that provided strong evidence that statins may have important anti-inflammatory effects.[90]

Although initially controversial, clinical studies with cerivastatin, lovastatin, simvastatin, and atorvastatin have since replicated the reduction in CRP first described in the CARE trial for pravastatin.[91–94] Of these confirmatory studies, the Pravastatin Inflammation CRP Evaluation (PRINCE) was by far the largest, enrolling 2884 patients into two parallel study arms: a secondary prevention cohort (N=1182), which received open-label pravastatin 40 mg daily, and a primary prevention cohort (N=1702), which was randomly allocated to either pravastatin 40 mg daily or to matching placebo.[93] Forty percent of the PRINCE participants were women, and 28% took prophylactic aspirin, a regimen previously shown to attenuate the effect of CRP on vascular risk.[48]

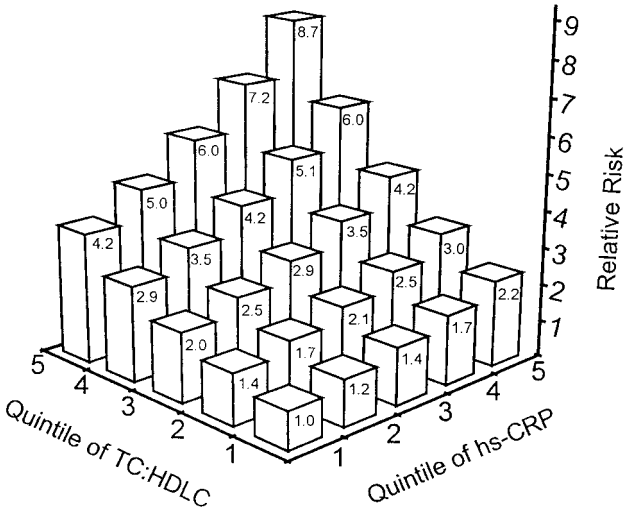

Figure 3. Interactive effects of CRP and lipid testing as determinants of cardiovascular risk. hs-CRP indicates high-sensitivity CRP assay; TC, total cholesterol. Adapted from Ridker.[81]

Overall, random allocation to pravastatin in PRINCE reduced median CRP levels by 16.9% compared with placebo ($P<0.001$). This effect was seen as early as 12 weeks (median reduction in CRP with pravastatin 14.7%, $P<0.001$) and was present among all prespecified subgroups by gender, age, smoking status, body mass index, baseline lipid levels, or the presence of diabetes. This study showed no association between baseline CRP and baseline LDL cholesterol levels or between end-of-study CRP and end-of-study LDL cholesterol levels, such that <2% of the variance in CRP could be explained by lipid levels. As observed in prior hypothesis-generating studies, there was minimal evidence of association between change in LDL cholesterol and change in CRP, data again demonstrating the independent nature of these two effects.[93]

Although provocative, data describing CRP reduction with statins does not in itself establish a role for CRP testing as an adjunct to lipid screening, or as a tool to improve targeting of statin therapy. However, data from the recently released Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) CRP substudy addresses this issue directly.[92] In brief, CRP levels were assessed at baseline among 5742 participants in AFCAPS/TexCAPS, a primary prevention study of lovastatin carried out among low- to moderate-risk individuals. This study showed an overall reduction in primary acute coronary events of 37%.[95] In the inflammation analysis, participants were divided into four groups of equal size on the basis of lipid and CRP levels above or below study median (Table).[92] As expected, random allocation to lovastatin therapy was highly effective in reducing primary acute coronary events among those with baseline levels of LDL cholesterol above 149 mg/dL, the median LDL value in the cohort as a whole. However, lovastatin therapy also reduced coronary event rates among those with lower levels of LDL cholesterol and above-median levels of CRP.

Event Rates and Number Needed to Treat Among Those Allocated to Lovastatin or Placebo in the AFCAPS/TexCAPS Trial, According to Baseline Levels of LDL Cholesterol and CRP

	Event Rates/5 Years		
Patient Group	Lovastatin	Placebo	NNT*
Low LDL, low CRP	0.025	0.022	...
Low LDL, high CRP	0.029	0.051	48
High LDL, low CRP	0.020	0.050	38
High LDL, high CRP	0.038	0.055	58

*NNT indicates number needed to treat to prevent 1 coronary event. The NNT can not be calculated for those in the low LDL, low CRP strata because there was no evidence of efficacy of lovastatin in this subgroup.

Adapted from Ridker et al.[92]

In fact, the event rate in the placebo group (as well as the magnitude of risk reduction associated with lovastatin use) for those with above-median CRP levels and below-median lipid levels was just as high as that observed among those with overt hyperlipidemia. In marked contrast, lovastatin therapy did not benefit participants in the AFCAPS/TexCAPS trial who had below-average LDL levels and below-average CRP levels.[92]

The CRP data from AFCAPS/TexCAPS are important for several reasons. First, they confirm that elevated CRP levels strongly predict future vascular risk and that the addition of CRP to lipid screening helps to predict global risk. Second, the AFCAPS/TexCAPS CRP data raise the possibility that statin therapy may prove highly effective even among apparently healthy individuals who do not have hyperlipidemia, but who have a propensity toward coronary events as detected by elevated levels of CRP. Because half of all heart attacks and strokes in the United States occur among individuals with normal cholesterol levels, these data provide novel biological insights about some patients who may be at higher risk because of elevated CRP levels, although ≈50% of patients who develop an infarction not preceded by unstable angina appear to have normal levels of CRP on admission. As nearly 25 000 000 Americans fit within this low-LDL/high-CRP category yet remain outside current preventive guidelines, more specific understanding of the predictive role of elevated CRP in the presence of low LDL is needed.

Conclusion

Our understanding of atherosclerosis has evolved beyond the view that these lesions consist of a lifeless collection of lipid debris. Current evidence supports a central role for inflammation in all phases of the atherosclerotic process. Substantial biological data implicate inflammatory pathways in early atherogenesis, in the progression of lesions, and finally in the thrombotic complications of this disease. Clinical studies affirm correlation of circulating markers of inflammation with propensity to develop ischemic events and with prognosis after ACS. Intralesional or extralesional inflammation may hasten atheroma evolution and precipitate acute events. Circulating acute-phase reactants elicited by inflammation may not only mark increased risk for vascular events, but in some cases may contribute to their pathogenesis. This new insight into the role of inflammation in the pathobiology of atherosclerosis has initiated important new areas of direct clinical relevance. We can use inflammatory markers today for risk stratification. Future studies will gauge their utility as guides to monitor therapy. Finally, the quest to identify proximal stimuli for inflammation, as one pathogenic process in atherogenesis or trigger to lesion complication, may yield novel therapeutic targets in years to come.

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