Inflammation as a Cardiovascular Risk Factor

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***Abstract*—** Inflammation occurs in the vasculature as a response to injury, lipid peroxidation, and perhaps infection. Various risk factors, including hypertension, diabetes, and smoking, are amplified by the harmful effects of oxidized low-density–lipoprotein cholesterol, initiating a chronic inflammatory reaction, the result of which is a vulnerable plaque, prone to rupture and thrombosis. Epidemiological and clinical studies have shown strong and consistent relationships between markers of inflammation and risk of future cardiovascular events. Inflammation can potentially be detected locally by imaging techniques as well as emerging techniques, such as identification of temperature or pH heterogeneity. It can be detected systemically by measurement of inflammatory markers. Of these, the most reliable and accessible for clinical use is currently high-sensitivity C-reactive protein. A combination of methods may provide the best identification of persons at risk for cardiovascular events who would benefit from treatment. In randomized, controlled trials, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, in the form of statins, have been shown to provide effective therapy for lowering CRP, in conjunction with their lipid-lowering effects. Although the magnitude of risk reduction associated with statin use appears to be largest for those with the highest serum levels of CRP, whether CRP reduction per se lowers cardiovascular risk is unknown. **(*Circulation*. 2004;109[suppl II]:II-2–II-10.)**

Key Words: inflammation ■ C-reactive protein ■ local detection ■ systemic detection

Although enormous progress has been made in the prevention and treatment of cardiovascular disease (CVD), it remains the leading cause of death throughout the Western world and the second most common cause worldwide.[1] By the year 2020, it is estimated that nearly 40% of all deaths worldwide will be due to CVD, more than twice the percentage of deaths from cancer. In the last 30 years, hyperlipidemia has been identified as a major modifiable risk factor for CV death, yet half of all coronary events occur in persons without overt hyperlipidemia.[1] The search for new and better predictors of risk has led researchers to an in-depth understanding of inflammation in atherogenesis and thrombosis, and to several novel methods for risk reduction and treatment.

Role of the Inflammatory Process in Atherosclerosis

Inflammation plays a role in all stages of atherothrombosis, the underlying cause of approximately 80% of all sudden cardiac death (SCD).[2] Early in the process, in response to oxidized low-density–lipoprotein cholesterol (LDL-C), injury, or infection, resident or circulating leukocytes bind monocytes to the site of a developing lesion. As they continue to ingest chemically modified lipids and lipoproteins, monocytes become macrophages, become foam cells, and initiate fatty streaks. More than half of all cells at the immediate site of plaque rupture are macrophages; they are the dominant type of atherosclerotic inflammatory cell infiltrates.[3] At the same time, other inflammatory mediators, including activated T cells and mast cells, also attach themselves to the endothelium. All of these inflammatory cells eventually contribute to the formation of the atheromatous lesion, which consists of a lipid pool protected by a fibrous cap. The monocyte-macrophages release metalloproteinases. These proteolytic enzymes can break down collagen in the fibrous cap, leaving it prone to rupture, and exposing the tissue factor and atherosclerotic debris beneath to arterial blood, inducing thrombosis. At the same time, smooth muscle cells (SMCs) secrete factors that recruit additional monocytes.[4] Local stimulation of SMCs in the artery wall can amplify the inflammatory response and promote a local procoagulant effect.[4,5]

Activation of macrophages, T lymphocytes, and SMCs leads to the release of additional mediators, including adhesion molecules, cytokines, chemokines, and growth factors, all of which play important roles in atherogenesis (Figure 1).[6] Interleukin-6 (IL-6) is the principal procoagulant cytokine. It can increase plasma concentrations of fibrinogen, plasminogen activator inhibitor type 1,[5,7] and C-reactive protein (CRP), which amplify inflammatory and procoagulant responses.[8–10] Inflammatory cytokines, including IL-1, tumor necrosis factor (TNF), and CRP induce the expression of cellular adhesion molecules, which mediate adhesion of leukocytes to the vascular endothelium.[8,10,11] CRP can also induce monocytes to express tissue factor, a glycoprotein that plays an important role in coagulation.[12]

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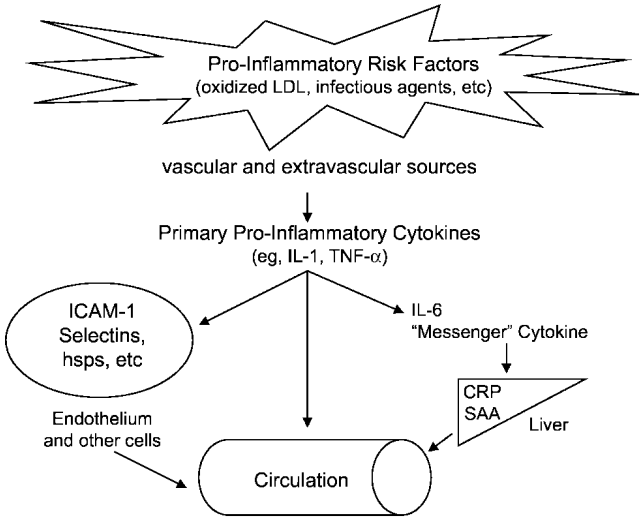

Figure 1. Inflammation triggers the production of proinflammatory cytokines in the arterial wall. Primary cytokines (interleukin-1 [IL-1], tumor necrosis factor-α [TNF-α]) mediate the attraction and migration of inflammatory cells into vascular tissue. They also induce "messenger" cytokines, which, released into the systemic circulation, cause the liver to increase production of acute phase reactants, including CRP and serum amyloid A (SAA). Hsps indicates heat-shock proteins. Reprinted with permission from Libby P et al.[6]

Finally, endothelium-derived nitric oxide (NO), a vasoactive peptide that helps maintain vascular tone, is reduced at the site of vascular injury. Decreased NO production is implicated in the clinical course of all known CVD.[13] NO inhibits platelet adherence and aggregation, suppresses vasoconstriction, reduces the adherence of leukocytes to the endothelium, and suppresses the proliferation of vascular SMC. Therefore, a reduction in NO activity contributes to a proinflammatory and prothrombotic milieu. CRP may itself play a role in repressing the production of NO and diminishing NO bioavailability.[13]

A risk of plaque rupture exists in plaque with a thin fibrous cap, and inflammatory cells within and under the cap.[14–16] In a quarter of cases, plaque does not rupture; the endothelium is simply replaced by the prothrombotic inflammatory cells.[5,17] These cells also release procoagulant tissue factor, which contributes to thrombogenesis.[5] The final steps in the inflammatory cascade occur when plaque contents—cholesterol, macrophages, tissue factor, necrotic debris, and platelet-derived prothrombotic substances (thromboxane A_2, serotonin, adenosine diphosphate, platelet-activating factor)—come into contact with the blood, and thrombosis ensues. The results may be either coronary or cerebral infarction, depending on the duration of the thrombosis and the location of the associated vasoconstriction.[10]

The risk of plaque rupture correlates poorly with the degree of stenosis: half of all infarctions occur in arteries that have <50% luminal diameter narrowing,[18] a degree of stenosis generally considered hemodynamically insignificant. However, the presence of inflammation in individuals at risk for progressive vascular disease should be detectable in the future, with greater or lesser success, both locally and systemically.

Emerging Diagnostic Techniques: Invasive Techniques

The inflammatory cascade may be occurring, and therefore is potentially capable of being arrested, at various stages and locations in the same patient. Invasive and noninvasive techniques for detecting local inflammation are currently being explored.

Temperature Heterogeneity

Most descriptions of atherosclerotic plaques have been structural, having to do with thickness, density, etc. However, functional characterizations, based on physiological variables such as temperature and pH, may also provide important information.[19] As an example, atherosclerotic plaques at risk for ulceration or rupture display temperature heterogeneity.[17] To determine whether monocytes and inflammatory cells in plaque release heat, intimal surface temperatures were measured at 20 sites in each of 50 carotid arteries taken at endarterectomy from 48 patients.[17] When samples were probed with a thermistor, temperatures varied from 0.2° to 0.3°C up to 2.2°C and correlated positively with the macrophage density, suggesting that heat is generated by the increased metabolism of inflammatory cells. Many specimens contained "hot spots"—foci of increased heat, characteristic of plaques that are denuded and inflamed. To detect whether temperature heterogeneity is observable in vivo, a catheter with an expandable, externally controllable basket with 9 thermosensors was developed.[20] Using this catheter, which is capable of detecting temperature heterogeneity to 0.01°C in various conditions of blood flow, temperature, and luminal stenosis, such temperature heterogeneity has been detected in atherosclerotic dogs and rabbits, in which increased temperature was correlated with increased total macrophage mass.[19,21]

Using a thermography catheter, Stefanadis et al[22] studied 90 subjects, 15 of whom had stable angina, 15 who had unstable angina (UA), and 15 who had acute myocardial infarction (MI). Another 45 patients had normal coronary arteries. Intracoronary temperature was measured with a thermistor probe accurate to 0.05°C. Temperature was constant in the normal arteries, but there was a higher temperature in the atherosclerotic arteries. A progressive temperature increase was seen in plaque from patients with stable angina to acute MI (Figure 2).[22] The acute MI patients were not significantly different from the UA patients in terms of total cholesterol (TC), ratio of TC to high-density–lipoprotein cholesterol (HDL-C), CRP, fibrinogen, and age, indicating that these factors do not account for the differences in plaque temperature.[22]

Catheters containing infrared optical fibers have also been used to detect areas of heat signaling increased inflammation, which, in infrared light, appears yellow. The *r* value relationship between a hand-held thermometer and infrared imaging in a large number of plaques was >0.9.[17] It remains to be seen whether adequate resolution can be achieved using this technique.

Stefanadis et al suggested that taking arterial temperature at the site of a lesion may eventually prove to be more useful in clinical practice than measuring acute phase proteins,

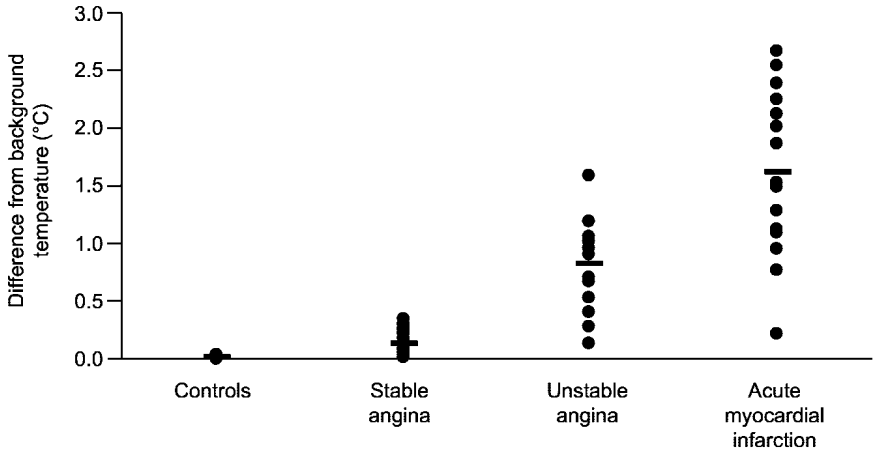

Figure 2. Differences in maximum temperature from background temperature in 4 study groups. Temperature differences increase progressively from stable angina to acute MI patients. This finding is in accordance with the involvement of a localized process, such as clustering of mononuclear infiltrates, in the pathogenesis of plaque rupture. Reprinted with permission from Stefanadis C et al.[22]

because a thermography catheter is clearly measuring heat arising from the plaque alone and not from other parts of the body.[16] Thermal techniques might potentially be combined with intravascular ultrasound or optical coherence tomography to provide both functional and anatomic information.[23]

pH Heterogeneity

Although metalloproteinases are thought to be the principal contributors to plaque degradation, the pH content of plaque may also play a role.[19] As inflammation increases metabolic activity and temperature, it also reduces pH. An acidic, low pH environment can promote apoptosis of SMC, leading to plaque vulnerability. To determine whether pH and temperature would be inversely correlated in unstable plaques, Naghavi and colleagues[19] measured pH in plaques from human carotid and umbilical arteries and Watanabe rabbit aortas (rabbits with intrinsic atherosclerosis). Fluorescence microscopic imaging confirmed pH heterogeneity in both humans and rabbits, but not in human umbilical arteries. In 48 human carotid plaques, there was a bimodal distribution of pH, with marked pH variation ranging from 6.5 to 8.9 in 858 points. pH of lipid-rich areas was significantly lower than pH in calcified areas ($P<0.0001$), and had a higher temperature, reflecting increased metabolic activity and a more acidic environment in the lipid-rich segments (Figure 3).[19] There was a general correlation between increased pH heterogeneity and excessive lactate accumulation. Thus, there may be a role for detection of low pH in determining plaque vulnerability. The potential clinical utility of this measure remains to be evaluated.

Emerging Diagnostic Techniques: Noninvasive Techniques

Although it is useful to be able to measure cap thickness, modified LDL, temperature, and pH, for clinical use, it is important to be able to characterize plaque noninvasively to identify high-risk plaques.[24,25] Two imaging techniques, MRI (MRI) and computed tomography (CT), have been used successfully for this purpose. High-resolution, multicontrast MRI is currently the leading imaging modality for plaque characterization in vivo; it can differentiate plaque components based on both physical and chemical variables, provide high-resolution images of the coronary artery wall, and identify thin fibrous caps and lipid cores of atherosclerotic plaques.[23] In pigs, however, cardiac and respiratory motion artifacts have presented problems.[26] Signal from flowing blood has been eliminated using a high-resolution black-blood sequence. In this method, signal from blood flow is rendered black using preparatory pulses to delineate the vessel wall. Black-blood MRI provides images with excellent flow suppression and high contrast and signal to noise.[24] This technique can be combined with MR angiography.

Superparamagnetic iron oxide (SPIO) techniques have also been used to improve MR angiography of the venous system.[27] SPIO improves contrast and provides a larger temporal window for image acquisition. Using this technique, Ruehm et al were able to show macrophage accumulation in the aorta of rabbits before atherosclerotic lesions were detected.[28] SPIO has been used effectively in apo-E knockout mice; it appears to have potential for use in human carotid arteries.

CT may be a more practical alternative to MRI, because it is generally less expensive and takes less time. Noncontrast CT can quantify the site and magnitude of calcium, which is

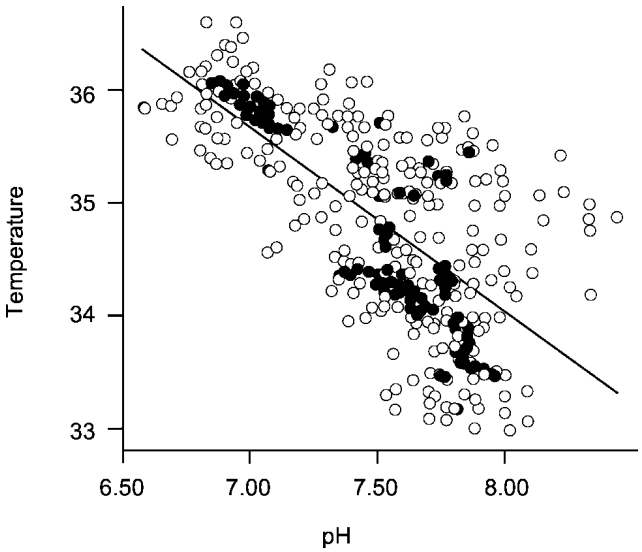

Figure 3. When pH of human endarterectomized carotid artery atherosclerotic plaques was measured in 48 patients, pH was inversely correlated with temperature (°C), suggesting a possible role for detecting low pH in the identification of high-risk plaques. Reprinted with permission from Naghavi M et al.[19]

a component of 60% to 80% of culprit lesions.[29] Potentially, CT of the coronary arteries can provide essential information about the architecture and composition of atherosclerotic plaque.

Raman spectroscopy is an optical technique that characterizes the chemical composition of tissue.[23,30] Raman spectra are obtained by processing collected light that is scattered by a tissue illuminated with a laser. It can potentially quantify cholesterol in plaque and can monitor the effects of atheroma-modifying therapy.[23,31] Raman spectroscopy is limited by the fact that blood absorbs laser light and that it is 1-dimensional.[23] It can, however, be combined with other imaging techniques to provide important information about plaque composition.

Targeted contrast-enhanced ultrasound using microbubble contrast agents is in the early stages of development but also holds potential as a technique that can be used clinically to evaluate vascular inflammation.[32]

Detection of Systemic Inflammation

Predictive Value of Various Inflammatory Markers

Atherosclerosis is a diffuse disease. Raised circulating concentrations of acute phase proteins, cytokines, and cell adhesion molecules suggest that inflammatory processes are occurring systemically. Recently, the role of several markers in the prediction of coronary events has been studied in apparently healthy men and women, as well as among patients with stable angina, acute coronary syndromes, and in secondary prevention. These markers include IL-6,[33,34] serum amyloid A (SAA),[35] TNF-α,[36] soluble intercellular adhesion molecule-1 (sICAM-1),[11,37] macrophage inhibitory cytokine-1,[38] sP-selectin,[39] and CD 40 ligand.[40] Of these various markers, however, only high-sensitivity (hs) CRP, which has a well-standardized assay, is so widely available as to be clinically useful at this time.

Predictive Value of C-Reactive Protein

CRP is an acute-phase reactant that has been shown in prospective cohort studies worldwide to be a reliable measure of underlying systemic inflammation and a strong predictor of future MI and stroke. Although CRP levels may increase up to 1000-fold in response to major infection or trauma, levels are remarkably stable over long periods of time when measured in asymptomatic adults, in whom CRP in the high-normal range has been found to be a potent, independent predictor of future vascular events.[41] When measured with high-sensitivity assays, CRP levels have long-term predictive value. For example, in the Honolulu Heart Study,[42] the odds of MI rose not only in the first few years of follow-up, but also as far as 20 years into the follow-up period. Thus, inflammation plays an early as well as late role in the atherosclerotic process, and the assessment of CRP provides a method to ascertain that risk very early in life.[42]

hs-CRP has also been studied in sera from 302 autopsies from men and women whose only inflammatory condition was atherosclerosis.[43] The lowest elevation of serum hs-CRP was found in those who died of noncardiac causes. Stable plaques showed a modest elevation, erosive plaques a greater elevation, and marked elevations in hs-CRP were seen in ruptured plaques.[43] Plasma concentrations in the highest quartile were associated with a 1.5- to 7-fold increase in relative risk (RR) of symptomatic atherosclerosis. In all cases of SCD, some elevation of hs-CRP was seen, regardless of the presence or absence of thrombosis, suggesting that hs-CRP identifies lesions rich in lipids and macrophages, and that it is associated with a risk of a vascular event, even in patients with clinically stable coronary heart disease (CHD).

More than 50% of those who die suddenly from cardiac causes do not have a history of CHD. In one recent study, baseline levels of hs-CRP were significantly associated with the risk of SCD over a 17-year period (p for trend $=0.001$).[2] This relationship remained significant after controlling simultaneously for multiple cardiac risk factors. Increased risk was seen primarily in men in the highest quartile, who had a 2.78-fold increased risk of SCD. Analyses that controlled for lipid variables, homocysteine, and multiple cardiac risk factors did not significantly alter these results. Neither homocysteine nor lipid levels were significantly associated with risk of SCD.

A nested case-control study was done in post-MI patients as part of the Cholesterol And Recurrent Events (CARE) trial, to determine whether markers of inflammation predict risk of recurrent events among stable patients with a prior history of MI.[44] Blood samples from 391 participants who subsequently developed recurrent nonfatal MI or a fatal event were compared with samples from 391 age- and sex-matched patients who did not have a recurrent event. CRP and SAA levels in prerandomization samples were compared with those at follow up. Levels were higher among cases than controls ($P=0.05$ for CRP; $P=0.006$ for SAA). Those with levels in the highest quartile had a RR of a recurrent events that was 75% higher than those in the lowest quartile ($P=0.02$ for both CRP and SAA).[44] Baseline lipid levels were virtually identical among those with and without evidence of inflammation. Thus, low-grade inflammation as assessed by CRP predicts risk of recurrent events after MI.

These data in secondary prevention complement evidence in primary prevention that indicates that hs-CRP levels are a strong predictor of cardiac events, even after adjustment for traditional risk factors. This effect was initially described in the Physicians' Health Study in which apparently healthy men were monitored for more than 8 years for the development of first ever MI, stroke, or venous thrombosis.[45] In that study, baseline hs-CRP levels were found to be higher among men who developed MI or stroke than among those who remained free of disease. Moreover, the men in the quartile with the highest CRP values had 3 times the risk of MI of the men in the lowest quartile, whereas the risk of stroke was approximately doubled. Risks were stable over long periods and were independent of other lipid and nonlipid risk factors.[45]

In women, hs-CRP levels have also been found to be highly predictive of future vascular risk and also to have implications for the use of hormone replacement therapy (HRT). For example, as part of the Women's Health Initiative, a prospective, nested case-control study was conducted to assess the association between baseline levels of CRP,

TABLE 1. Relative Risks (95% CIs) of Future Cardiovascular Events According to CRP Levels >3.0 mg/L or <3.0 mg/L and According to the Presence or Absence of the Metabolic Syndrome

	All Cardiovascular Events			Coronary Events
	Total Cohort (n=14 719)	LDL <160 mg/dL (n=12 453)	LDL <130 mg/dL (n = 8500)	Total Cohort (n=14 719)
CRP <3 mg/L, no metabolic syndrome	1.0	1.0	1.0	1.0
CRP >3 mg/L, no metabolic syndrome	1.5 (1.0–2.2)	1.3 (0.8–2.2)	1.2 (0.6–2.3)	1.6 (0.9–2.7)
CRP <3 mg/L, metabolic syndrome present	2.3 (1.6–3.3)	2.2 (1.4–3.5)	2.5 (1.4–4.4)	3.1 (2.0–4.9)
CRP >3 mg/L, metabolic syndrome present	4.0 (3.0–5.4)	4.4 (3.1–6.3)	4.4 (2.8–7.1)	5.5 (3.8–8.0)

Data are shown for all cardiovascular events (n=255) and for coronary events only (n=163). CI indicates confidence interval; CRP, C-reactive protein; and LDL, low-density lipoprotein.

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IL-6, and CHD, and to examine the relationship between baseline use of HRT, CRP, and IL-6 levels and subsequent risk.[46] Among >75 000 women nationwide with no history of CVD, 304 women who subsequently developed CHD events were matched by age, smoking status, and ethnicity with 304 women who did not develop CHD. Median baseline levels of CRP and IL-6 were significantly higher among cases versus controls ($P<0.001$ for both). Both inflammatory markers were significantly associated with a 2-fold increase in odds for CHD events. However, despite the observation that HRT use elevated CRP levels, a positive graded relationship was also seen between plasma CRP levels and the odds ratio for CHD among users and nonusers of HRT across the spectrum of baseline CRP. Thus, the blood level of hs-CRP was more important in predicting subsequent vascular risk than was the use or nonuse of HRT.[46]

Metabolic Syndrome

The metabolic syndrome refers to the presence of at least 3 of the following: abdominal obesity, elevated triglycerides, reduced levels of HDL-C, high blood pressure (BP), and high fasting glucose. All of these characteristics are also modestly associated with elevated levels of CRP. Moreover, CRP levels correlate with other components of the metabolic syndrome that are not easily measured in clinical practice, including fasting insulin, microalbuminuria, and impaired fibrinolysis.[47] Based on data from the Third National Health and Nutrition Examination Survey (NHANES III), approximately 24% of US adults now qualify as having the metabolic syndrome.[48] To address the role of hs-CRP in the setting of the metabolic syndrome, a recent study evaluated interrelationships between CRP, the metabolic syndrome, and incident CV events among 14 719 apparently healthy women, 24% of whom had the metabolic syndrome, who were followed-up for an 8-year period for MI, stroke, coronary revascularization, or CV death. In brief, at all levels of the metabolic syndrome, levels of CRP improved risk prediction for future CV events. Furthermore, CRP levels were highly predictive even among those with the full metabolic syndrome at study entry (Table 1).[47] In addition to predicting thrombotic events, CRP also predicted type 2 diabetes, which shares common inflammatory processes with atherosclerosis.[49] These findings have implications for therapies targeting insulin resistance and diabetes as well as CVD.

CRP Versus Other Risk Markers

Data from the Women's Health Study have also been important in understanding the role of hs-CRP in risk detection. Among 28 263 apparently healthy postmenopausal women who were monitored prospectively for future vascular events, 4 inflammatory markers (hs-CRP, SAA, IL-6, and sICAM-1) were all found to be significant predictors of risk; hs-CRP, however, was the most significant predictor in univariate analysis, outperforming homocysteine, lipoprotein(a), and LDL-C (Figure 4).[50,51] A subgroup analysis was limited to women with LDL-C <130 mg/dL, the National Cholesterol Education Program (NCEP) goal for primary prevention.[52] In this analysis, women with elevated baseline levels of hs-CRP, SAA, IL-6, or sICAM-1 were at increased risk for CV events, but the effect remained strongest for hs-CRP and SAA.

In a long-term follow-up of participants in the Women's Health Study, CRP proved to be a stronger predictor of risk

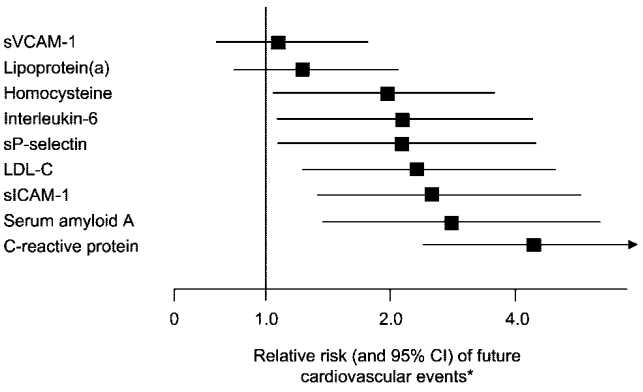

Figure 4. Prognostic value of various cardiovascular biomarkers in healthy women in the Women's Health Study. The combination of high-sensitivity CRP with the total cholesterol:high-density–lipoprotein cholesterol (TC:HDL-C) ratio provided a stronger predictor than either CRP or TC:HDL-C alone. Relative risks and 95% confidence interval (CI) are shown for individuals in the top versus the bottom quartile for each factor. sICAM-1 indicates soluble intracellular adhesion molecule-1; and sVCAM-1, soluble vascular adhesion molecule-1. *Top versus the bottom quartile, after adjustment for age and smoking. Reprinted with permission from Ridker PM.[51]

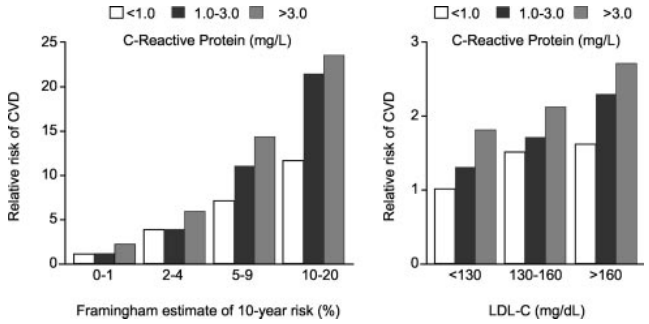

Figure 5. Multivariable-adjusted relative risks of cardiovascular disease according to levels of high-sensitivity C-reactive protein (hs-CRP) and categories of low-density–lipoprotein cholesterol (LDL-C). hs-CRP levels add prognostic information at all levels of LDL-C and at all levels of the Framingham Risk Score. Reprinted with permission from Ridker PM.[53]

than LDL-C.[53] CRP and LDL-C were minimally correlated (r=0.08), but baseline levels of each had a strong linear relation with the incidence of CV events. Specifically, after adjustment for age, smoking, diabetes, BP, and use or nonuse of HRT, the RRs of first CV events in increasing quintiles of CRP versus those in the lowest quintile were 1.4, 1.6, 2.0, and 2.3 (P<0.001). The corresponding RRs in increasing quintiles of LDL-C as compared with the lowest were 0.9, 1.1, 1.3, and 1.5 (P<0.001). Overall, 77% of events occurred among women with LDL-C <160 mg/dL, and 46% occurred among those with LDL-C <130 mg/dL. Patients with elevated levels of both LDL-C and CRP had nearly 8 times the CV risk of those with low levels of both markers. Both the area under the receiver operating characteristic curve (0.64 versus 0.60) and the population attributable risk (40% versus 19%) were significantly greater for CRP than for LDL-C. This suggests that if it were possible to reduce all levels of LDL-C to the lowest quintile, population attributable risk for CVD would be reduced by 19%, whereas if inflammation could be reduced to the lowest levels, there would theoretically be a 40% reduction in CVD. These data suggest that, in primary prevention, CRP may be a stronger predictor of CV events than is LDL-C, and that measurement of hs-CRP adds important prognostic information to that delineated in the Framingham Risk Score (Figure 5).[53]

Treating Inflammation

COX-2 Inhibitors

In the atherosclerotic process, several products are generated that play a key role in inflammation and therefore may be therapeutic targets. Among these, the enzyme cyclooxygenase (COX), converts arachidonic acid to prostaglandins. COX has 2 isoforms: COX-2 is an inducible form that is upregulated in atherosclerotic plaques. COX-2 may contribute to early atherosclerosis by inducing metalloproteinases.[54] The selective inhibition of COX-2, therefore, may have antiinflammatory effects. By decreasing vascular inflammation, it may, in turn, potentially reduce mononuclear cell infiltration, improve NO availability, and enhance plaque stability.[55] There is, in fact, evidence for these effects in animal models.[54] Moreover, in the Nonsteroidal AntiInflammatory Drugs in Unstable Angina Treatment (NUT-2) pilot study, meloxicam, a COX-2 inhibitor, decreased the occurrence of angina and revascularization in patients with acute coronary syndrome without ST-segment elevation.[56] It is important to recognize, however, that COX-2 inhibitors do not have significant antiplatelet activity, and some studies have suggested that these agents are associated with a net hazard when compared with the use of aspirin.[56] Thus, large-scale clinical trials using COX-2 inhibitors are needed to better understand the potential risks and benefits of these agents in preventing CV risk.

PPAR-γ Agonists

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that act as transcription factors controlling the expression of target genes that in turn regulate various cellular functions.[57] The subfamily member PPAR-γ is a key regulator of lipoprotein metabolism, coordinating the uptake of oxidized LDL and the processing of cholesterol in macrophages. PPAR-γ is highly expressed by macrophages and foam cells.[58] In vitro, PPAR-γ agonists may inhibit production of cytokines and expression of adhesion molecules in endothelial cells.[59] They may also reduce production of metalloproteinases and prevent them from homing to plaques.[58] Using high-resolution MRI, plaque regression and stabilization have been observed in the atherosclerotic rabbit treated with a selective PPAR-γ activator.[60] These agents have recently been found to reduce levels of CRP in human subjects with type 2 diabetes,[61] in whom they were associated with declines in levels of plasminogen activator inhibitor-1 and possible reduced CV risk.

Aspirin

Aspirin has been shown to reduce the risk of first CV events; in the Physicians' Health Study, risk reduction with aspirin therapy was 44%.[62] The magnitude of RR reduction attributable to aspirin in primary prevention is greatest in persons with the highest levels of CRP and declines in direct relation to CRP levels, suggesting that the benefit of aspirin may be at least partially due to its inflammatory effects.[45] However, aspirin itself appears to have minimal effect on plasma CRP levels.

Other Pharmacological Agents

A variety of agents have been reported to reduce CRP. These include the lipid-lowering agents niacin, fibrates, and gemfibrozil. Benefit has also been reported for clopidogrel[63] and abciximab.[64]

3 Hydroxy-3-Methylglutaryl Coenzyme A (HMG CoA) Reductase Inhibitors (Statins)

Statins are the most effective agents available today for the reduction of vascular inflammation. In addition to lowering lipids, these drugs exhibit potent antiinflammatory effects mediated by inhibition of macrophage function. The inhibition of endogenous cholesterol synthesis in macrophages has the potential to reduce macrophage activation and foam cell formation. Statin treatment has been associated with reduced thermal heterogeneity in atherosclerotic lesions.[65] In a rabbit model of atherosclerosis, atorvastatin decreased neointimal

TABLE 2. Age-Specific Gains in Life Expectancy Resulting From Statin Therapy in Men and Women in the Low LDL/High CRP Group

Outcome	Men Age (yrs)					Women Age (yrs)				
	35	45	55	65	75	35	45	55	65	75
Life expectancy without treatment (yr)	38.6	29.93	21.88	14.96	9.51	44.77	35.43	26.57	18.69	12.16
Gain in life expectancy with treatment (months)	10.2	9.4	7.4	5.3	3.4	7.9	7.7	7.0	5.8	3.8

CRP indicates C-reactive protein; and LDL, low-density lipoprotein.
Reprinted with permission from Blake GJ et al.[73]

inflammation and arterial macrophage infiltration.[66] Statins may also prevent degradation of the extracellular matrix by matrix metalloproteinases,[57] reduce levels of tissue factor,[57] and induce expression of PPAR-γ. In one study, human monocytes were incubated with 0.1 to 10 μmol/L of atorvastatin for up to 24 hours. Exposure to the statin activated PPAR-γ and inhibited the production of TNF-α, a proinflammatory molecule.[67] The authors suggest that atorvastatin possesses properties that can reduce inflammation in activated monocytes and possibly prevent the degradation of the extracellular matrix by metalloproteinases. Statins are also modulators of endothelial function, and have the ability to upregulate synthesis of NO.[68]

Statins reduce CRP levels rapidly and for extended periods. In post-MI patients in the CARE study, long-term treatment with pravastatin was associated with a reduction in serum CRP levels and with better clinical outcome.[69] CRP levels were measured at baseline and at 5 years in 472 randomly selected participants who remained free of events during the follow-up period. Statistically significant differences were seen at 5 years between the statin and placebo groups in median CRP levels. Among survivors of MI on standard therapy and placebo, CRP levels tended to increase over 5 years, whereas statin treatment resulted in significantly lower levels of CRP, which were unrelated to the magnitude of lipid lowering.[69] Patients on active therapy had median CRP levels 21.6% lower than those on placebo at the end of the treatment period ($P=0.007$). The risk reduction attributable to treatment was greater among those with evidence of inflammation (54%) than without such evidence (25%) and was present even though baseline lipid levels were similar in the two groups. Because most participants in CARE were taking aspirin, the effect of statin treatment in reducing CRP levels appears to be additive to that of aspirin.[70]

The Pravastatin Inflammation/CRP Evaluation (PRINCE) was a prospective, primary prevention double-blind trial, conducted to determine whether pravastatin has antiinflammatory effects as determined by changes in CRP levels in 1702 men and women with no history of CVD who were randomized to statin or placebo.[70] After 24 weeks, there was a decrease of 16.9% (0.02 mg/dL) in the statin-treated patients, but no change in CRP levels in the placebo group ($P<0.001$). This effect was seen as early as 12 weeks (median reduction in CRP with treatment was 14.7%; $P<0.001$) and was present among all subgroups, regardless of age, smoking status, body mass index, baseline lipid levels, presence of diabetes, and use of aspirin or HRT. No association was observed between CRP and LDL-C levels at baseline and end of study, or changes in those variables over time. In an open-label study in a secondary prevention cohort comprising 1182 patients, similar reductions in CRP levels were seen. Thus, statin treatment reduced CRP levels at both 12 and 24 weeks in an LDL-C–independent manner, again indicating that statins possess antiinflammatory as well as lipid-lowering effects.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS) was a 5-year randomized trial of lovastatin conducted to determine whether statins would prevent acute coronary events in a primary prevention cohort.[71] In that study, the level of CRP was measured at baseline and after 1 year in 5742 participants. Results showed that rates of coronary events increased significantly with increases in baseline levels of CRP. Statin treatment reduced CRP by 14.8% ($P<0.001$), an effect that was not explained by changes in the lipid profile. Most importantly, statin treatment was effective in preventing acute coronary events among those with elevated CRP levels, regardless of baseline levels of LDL-C or the TC:HDL-C ratio.[71]

Magnitude of Risk Reduction With Statin Therapy

Although the ability of statin therapy to reduce CRP levels is clearly a class effect, studies with pravastatin, lovastatin, simvastatin, and atorvastatin have failed to show correlations between the magnitude of LDL-C reduction and the magnitude of CRP reduction. However, post-hoc analyses of both AFCAPS/TexCAPS and CARE indicated that absolute risk reduction effected by statin therapy is largest for persons with elevated CRP levels. In AFCAPS/TexCAPS, absolute risk for persons with elevated CRP and low LDL-C was higher than for those with high LDL-C and low CRP.[41] Results of this trial suggest that in primary prevention the benefit of statin therapy among persons with low cholesterol but high CRP levels may be just as high as that observed among those with hyperlipidemia.[71]

Using a decision-analytic model and evidence from randomized trials, Blake et al[72] estimated gains in life expectancy with statin therapy for persons without overt hyperlipidemia but with elevated levels of CRP. Estimates of prognosis after MI or stroke were derived from population-based studies. Their analysis suggested that projected life-expectancy gain with statin therapy for men and women aged 58 years with LDL-C <149 mg/dL and elevated CRP is 6.5 months, which is similar to that for treated patients with LDL-C ≥ 149 mg/dL (Table 2.).[72] They speculated that projected gains in life expectancy would be similar or larger for treated patients with elevated CRP and LDL-C <160

mg/dL, many of whom do not meet the NCEP guidelines for lipid treatment in primary prevention of CVD.[72]

Thus, at least in theory, statin therapy may be effective in the primary prevention of coronary events among persons with average and below average cholesterol levels but with elevated levels of CRP. This describes one quarter of the population of the United States and Europe, who are not currently being targeted for statin therapy. The recently launched Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) has been designed to directly test this hypothesis among 15 000 healthy men and women with LDL-C levels <130 mg/dL and CRP levels 2 mg/L. Participants will receive either rosuvastatin or placebo and will be monitored for first ever coronary events.

Conclusions

Inflammation plays a critical role in CVD, and the inflammatory cascade is particularly important in the atherosclerotic process. New and more effective techniques for detecting inflammation, both locally and systemically, are emerging.

Elevated levels of CRP are associated with increased risk of CVD even in the absence of hyperlipidemia. Although IL-6 also appears to play an important role in indicating CV risk,[33,73] measures of IL-6 are subject to day-to-day biological variability, making them less reliable. The commercial availability of hs-CRP assays has made screening for this marker simple, reliable, and reproducible; levels of hs-CRP <1, 1 to 3, and >3 mg/L correspond to low, moderate, and high CV risk. Tests for hs-CRP and for LDL-C are likely detecting different high-risk groups and are a more powerful predictive tool when used in combination. hs-CRP has been shown to add prognostic information at all levels of LDL-C, at all levels of the metabolic syndrome, and at all levels of the Framingham Risk Score.

Statin therapy reduces CRP levels independently of any effect on lipid levels. Data indicate that the proportion of CVD that might be prevented by reducing inflammation may possibly exceed that achievable by reducing LDL-C throughout the population. Data also show that, in primary prevention, high CRP/low LDL-C persons are at higher absolute risk than low CRP/high LDL persons, and suggest that such individuals might benefit from statin therapy. A trial of statins versus placebo in this population is needed to resolve this issue.

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