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C-REACTIVE PROTEIN, INFLAMMATION, AND CORONARY RISK

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Despite progress in the prevention of cardiovascular disease, a significant proportion of first cardiovascular events occurs among individuals without traditional risk factors. Given the usual absence of associated symptoms, the identification of patients with preclinical atherosclerosis is a challenging task. As reviewed elsewhere,[43] however, with the advancement in understanding of the pathobiology of atherosclerotic vascular disease have come new insights regarding potential indicators of underlying atherosclerosis and cardiovascular risk. In particular, as the contribution of inflammation to atherogenesis has attained increased recognition, attention has focused on a number of key mediators and markers of the inflammatory process, including the prototypical acute-phase reactant, C-reactive protein (CRP). High sensitivity assays for CRP (hs-CRP) have now been developed and enable detection of mild elevation of hs-CRP within the normal range. With the application of these assays, the past 5 years have witnessed an accumulation of epidemiologic data documenting associations between mild elevation of hs-CRP and cardiovascular risk among those without clinical vascular disease as well as those for whom the focus is on secondary prevention. In addition, data have revealed interactions between baseline concentrations of hs-CRP and the efficacy of common pharmacologic therapies in primary and secondary prevention, suggesting not only that it may be possible to modify the increased risk associated with elevated hs-CRP, but also that inflammatory markers may be useful in targeting preventive therapies. On the basis of available evidence, it is thus possible that inflammatory markers may become a valuable component of routine cardiovascular risk assessment.

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INFLAMMATION IN ATHEROGENESIS

Pathologic and clinical data suggest a prominent role for inflammation at every stage of atherogenesis.[67] The vascular endothelium is a complex synthetic organ subject to injury from numerous potential insults, including oxidative stress,[19, 30] modified lipoproteins,[73] and hemodynamic forces.[18] Injured endothelial cells initiate a largely stereotyped, initially protective response.[67] Endothelial dysfunction is marked by the up-regulation of cellular adhesion molecules, such as vascular adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), that in concert with chemokines mediate increased adhesion of mononuclear leukocytes and subsequent migration into the subendothelial space.[10, 45–47, 49, 50, 52] The concurrent uptake of low-density lipoproteins (LDLs) by monocyte-derived macrophages transforms them into the lipid-laden foam cells that constitute a key element of the fatty streak, the first recognizable progenitor of the advanced atherosclerotic lesion (Fig. 1).[3, 72, 74, 84]

Mononuclear cells within this inflammatory infiltrate release cytokines, including interleukin (IL)-1[32, 37, 53] and IL-6,[68, 75] that reinforce the process of cellular recruitment and promote the oxidation and uptake of LDL.[50, 74] In addition, these

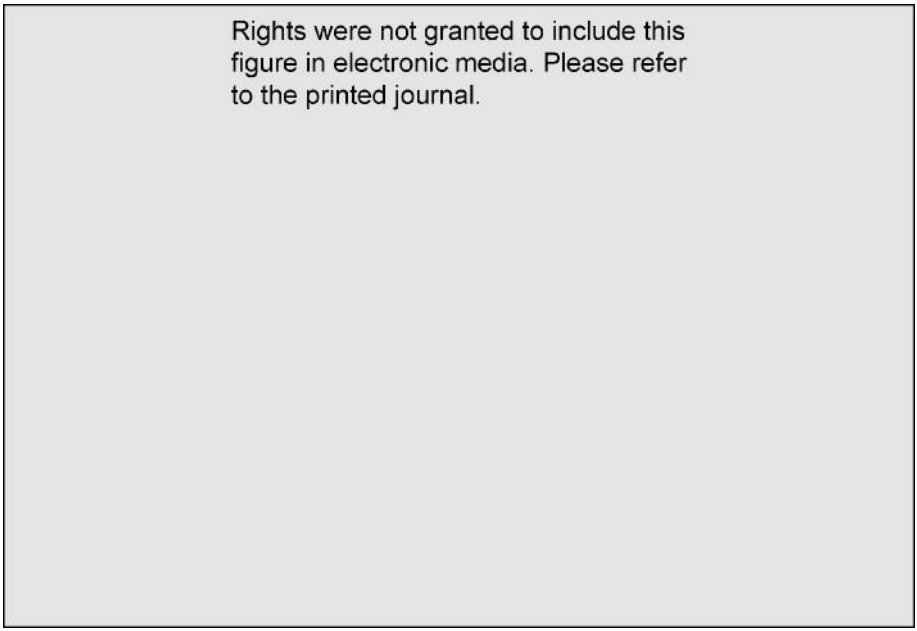

Figure 1. Inflammation and formation of the fatty streak. ICAM-1 = intercellular adhesion molecule 1; MCP-1 = monocyte chemotactic protein-1; M-CSF = macrophage colony stimulating factor; IL = interleukin. Key stages in early atherogenesis (refer to text for details): 1. Endothelial injury and dysfunction; 2. Expression of adhesion molecules; 3. Release of chemokines; 4. Recruitment of inflammatory monocytes; 5. Increased leukocyte adhesion and migration; 6. Incorporation of ox-LDL by macrophages via scavenger receptors to become foam cells; 7. Release of cytokines and mitogens by activated monocytes; 8. Smooth muscle cell migration and proliferation. (From Morrow DA, Ridker PM: Inflammation in cardiovascular disease. *In* Topol E (ed): Textbook of Cardiovascular Medicine Updates, vol. 2, no. 4. Cedar Knolls, NJ, Lippincott-Williams & Wilkins; 1999; with permission.)

cells release mitogens that stimulate the proliferation of smooth muscle cells and contribute to the maturation of the fatty streak into an intermediate atherosclerotic lesion.[22, 33, 40, 70, 83] A resilient fibrous cap forms over this developing mixture of inflammatory and smooth muscle cells, intracellular and extracellular lipid, and necrotic cellular debris, which eventually becomes recognizable as an advanced, complex atherosclerotic plaque.[11, 72] This fibrous cap is composed of a dense extracellular matrix that derives its tensile strength from types I and III collagen as well as elastin and forms a barrier between the highly procoagulant contents of the atheroma core and circulating blood.[23, 31] Erosion or frank rupture of this barrier results in exposure of the contents of the atheroma core and the promotion of thrombus formation. Although in some cases the overlying thrombus is nonocclusive and may incorporate into the maturing plaque,[6, 12, 64] when the forming thrombus leads to rapid compromise of arterial flow, acute myocardial ischemia or infarction may result.[12]

Laboratory and clinical data demonstrating the importance of plaque rupture or erosion in the onset of unstable ischemic syndromes,[1, 8, 13, 15, 29] in conjunction with angiographic data showing discordance between the degree of angiographic stenosis and the risk of acute coronary events, have supported a shift in the prevailing view of the pathobiology of acute coronary syndromes.[31] This evolution in understanding has redirected emphasis from the arterial lumen visualized at angiography toward the characteristics of the underlying atherosclerotic lesion and the factors that influence its *vulnerability* to rupture.[14, 31] Pathologic data have focused particular attention on the fibrous cap[14] at the edge of the atheromatous lesion or *shoulder* region, where inflammatory cells accumulate[42, 78] and plaque rupture most frequently occurs.[8, 14, 54] Macrophages and T lymphocytes have been shown to dominate at the site of plaque compromise regardless of the overall lesion morphology.[7, 13, 42, 78] Although the precise mechanisms by which these inflammatory cells contribute to plaque disruption are not defined, several potential links have emerged.[31]

First, inflammatory cytokines stimulate smooth muscle cells and macrophages to produce collagenases and elastases, which may degrade the protective extracellular matrix.[16, 17, 34, 69] Second, interferon-γ, a cytokine produced by T lymphocytes in the atheroma core, has been found to decrease the production of collagen by smooth muscle cells.[2, 31] In addition to these potential effects on the maintenance of fibrous cap integrity, inflammatory cells and mediators may also contribute to thrombus formation and vessel occlusion via modulation of platelet activation,[82] the coagulation cascade,[41, 48, 80] and vasomotor function.[25, 71] Laboratory and clinical data demonstrate the participation of inflammatory processes at every stage of atherothrombosis, including the initiation of the fatty streak, maturation of the advanced atherosclerotic lesion, thinning of the fibrous cap with plaque compromise, and platelet aggregation and thrombosis.

CLINICAL APPLICATIONS

In concert with laboratory data, prospective clinical studies have evaluated several acute-phase proteins, cytokines, and intercellular adhesion molecules as potential novel markers for cardiovascular risk assessment.[4, 5, 38, 59, 60] CRP has several characteristics that render this inflammatory marker particularly attractive for this purpose. CRP is well described as a marker of systemic inflammation and is documented to rise several hundredfold in response to acute injury, infection, or other inflammatory stimuli.[51] Its concentration remains stable over long periods of time in the absence of new stimuli and depends almost entirely

on the rate of hepatic production rather than factors influencing protein clearance.[36, 51] Further, in contrast to many other inflammatory markers, assay techniques for hs-CRP are reliable, fully automated, and now highly sensitive, providing a simple clinical tool for the careful assessment of systemic inflammation.[28, 76, 81]

C-Reactive Protein High Sensitivity Assays and Cardiovascular Risk

Observational epidemiologic data document a positive association between hs-CRP and prevalence of coronary artery disease (CAD). In a population-based study derived from general practice registers in Great Britain, the prevalence of CAD among 388 men aged 50 to 69 years was observed to increase 1.5-fold for each doubling of hs-CRP concentration (95% confidence interval [CI], 1.25 to 1.92).[39] Increased concentrations of hs-CRP were also associated with increasing age, smoking, body mass index, and exposure to certain infectious pathogens.[39] Cross-sectional data cannot adequately account for the effects of these potential confounders, and they cannot discriminate whether the observed relationship between hs-CRP and symptomatic CAD is due to cause or effect. A series of prospective epidemiologic studies, however, have shown that elevated baseline levels of hs-CRP are correlated with higher risk of future cardiovascular morbidity and mortality among those with and without clinical evidence of vascular disease even after adjustment for the effects of many of these potential confounders (Fig. 2).

With regard to patients with established vascular disease, investigators of the prospective European Concerted Action on Thrombosis and Disabilities Study (ECAT) found that among 2121 patients with angina, each standard deviation increase in baseline hs-CRP was associated with a 45% increase in the relative risk of nonfatal myocardial infarction (MI) or sudden cardiac death (95% CI for relative risk [RR], 1.15 to 1.83) over 2 years of follow-up.[20] Further, in a nested case-control analysis of stable post-MI patients in the Cholesterol and Recurrent Events (CARE) trial, hs-CRP was predictive of significantly higher risk for recurrent nonfatal MI or fatal coronary events (75% higher RR in the highest versus lowest quintile of hs-CRP).[62]

Two studies have demonstrated extension of this prognostic capacity from individuals with active ischemic heart disease to include those with risk factors but free of clinical atherosclerosis.[58] The Multiple Risk Factor Intervention Trial (MRFIT) Research Group followed a cohort of men recognized as high risk on the basis of traditional cardiovascular risk factors and documented a direct positive association between hs-CRP and coronary heart disease mortality over a 17-year period (RR, 2.8; 95% CI, 1.4 to 5.4).[26] This association was not evident among nonsmokers.[26] Similarly, among elderly patients with evidence of preclinical atherosclerosis followed prospectively in the Cardiovascular Health Study and the Rural Health Promotion Project, increased levels of hs-CRP were associated with increased risk for subsequent coronary events.[77]

Data from the Physicians Health Study (PHS) further extend this relationship between hs-CRP and cardiovascular risk to individuals at low risk with low rates of cigarette consumption and no prior history of CAD. In a prospective, nested, case-control analysis, apparently healthy men who subsequently developed MI, stroke, or peripheral vascular disease were paired with an equal number of participants matched for age and smoking status who remained free of vascular events over an 8-year period of follow-up.[59] Baseline concentrations

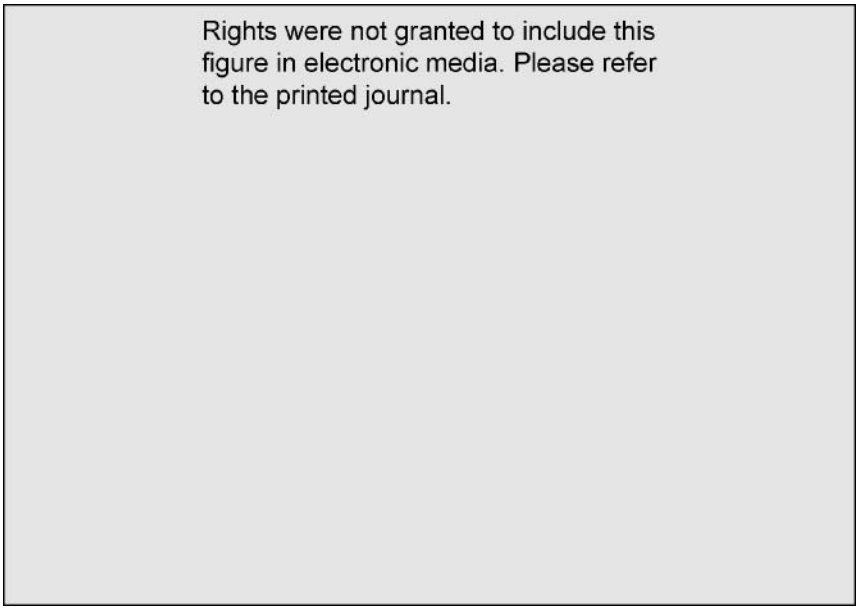

Figure 2. Prospective studies of C-reactive protein as a risk factor for cardiovascular disease among apparently healthy individuals. (From Ridker P, Haughie P: Prospective studies of C-reactive protein as a risk factor for cardiovascular disease. J Invest Med 46:391–395, 1998; with permission.)

of hs-CRP were significantly elevated among those who suffered vascular events compared with those who did not (Fig. 3). Specifically, those with highest baseline levels of hs-CRP had two times the risk of future stroke (RR, 1.9; 95% CI, 1.1 to 3.3),[59] three times the risk of future MI (RR, 2.9; 95% CI, 1.8 to 4.6),[59] and four times the risk of developing severe peripheral arterial disease (RR, 4.1; 95% CI, 1.2 to 6.0).[56] These risk estimates were not modified by smoking status and persisted in multivariate analyses adjusted for other cardiovascular risk factors, including total and high-density lipoprotein cholesterol, triglycerides, fibrinogen, and lipoprotein Lp(a).[59] In additional analyses, multivariate models that included hs-CRP and lipid parameters showed superior risk prediction compared with those based on lipids alone.[57] Notably, elevated hs-CRP predicted higher risk of MI for men at low as well as high risk on the basis of lipid parameters (Fig. 4).[57] Finally, data from the European MONICA-Augsberg study offer consistent observations regarding the prognostic capacity of hs-CRP among individuals without clinical evidence of CAD. In this prospective study of 936 middle-aged men, an overall 19% increase in risk of future nonfatal or fatal coronary events was observed for each standard deviation increase in baseline hs-CRP after adjustment for multiple risk factors, including smoking status.[24]

At least one prospective study has demonstrated an association between hs-CRP and cardiovascular risk in women. In data derived from the Women's Health Study (WHS), baseline levels of hs-CRP were significantly higher in 122 postmenopausal women who subsequently developed a first cardiovascular event compared with 244 age-matched and smoking-matched control subjects,

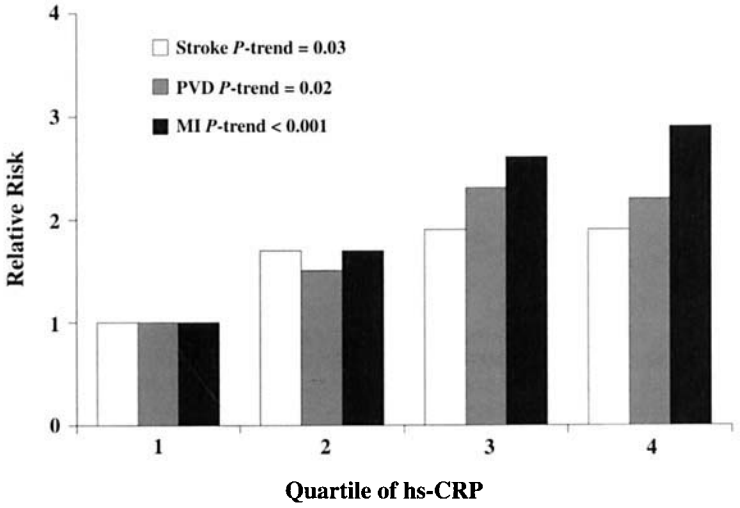

Figure 3. Relative risk for vascular events in apparently healthy men. (*Data from* Ridker et al: Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 336:973–979, 1997; and Ridker PM, et al: Plasma concentration of C-reactive protein and risk of developing peripheral vascular disease. Circulation 97:425–428, 1998.)

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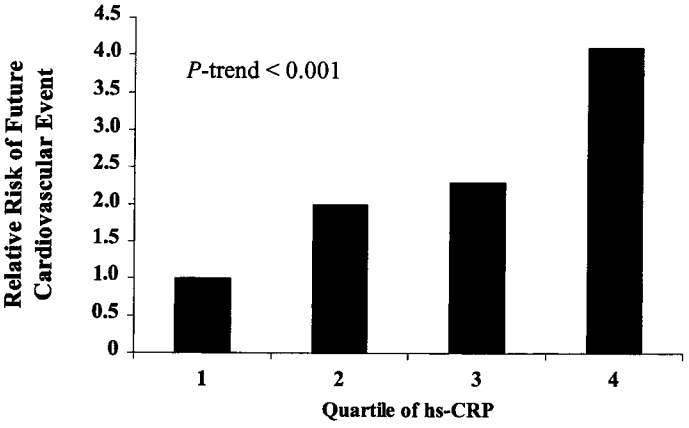
Figure 4. Adjusted relative risks of first myocardial infarction (MI) stratified by baseline hs-CRP and total cholesterol above and below the 75th percentile in the control group. Chol = cholesterol. Open bar = total chol <75th percentile; solid bar = total chol >75th percentile. (*Adapted from* Ridker PM, et al: C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. Circulation 97:2007–2011, 1998; with permission.)

who remained free of vascular disease during 3 years of follow-up.[55] Those with levels of hs-CRP in the highest quartile were at nearly five times the risk of any vascular event (RR, 4.8; 95% CI, 2.3 to 10.1) and seven times the risk of MI or stroke (RR, 7.3; 95% CI, 2.7 to 19.9).[55] Consistent with findings in men, these risk estimates were independent of other recognized cardiovascular risk factors and persisted among multiple low-risk subgroups examined (Fig. 5).[55] Models that included hs-CRP in addition to the lipid profile had a prognostic advantage over those that did not.[55] Moreover, the predictive value of hs-CRP in the WHS was significantly larger than that associated with homocysteine, another emerging *novel* risk factor.[61]

Inflammation and Preventive Therapies

Based on epidemiologic data demonstrating a prognostic capacity of hs-CRP for cardiovascular risk independent of traditional risk factors, it has been suggested that this inflammatory marker may have a role in routine cardiovascular risk assessment.[76] This consideration raises the important question as to whether the increased risk associated with elevation of inflammatory markers can be reduced through preventive intervention. Several prospective studies have addressed this issue.

In the PHS, researchers randomly assigned initially healthy men to low-dose aspirin (325 mg orally every other day) or placebo and found that the use of aspirin was associated with an overall 44% reduction in the risk of a first MI



Subgroup	RR	RR	RR	RR	*P*-trend
No hyperlipidema	1.0	1.7	2.0	3.9	0.002
No hypertension	1.0	1.7	2.0	2.8	0.04
No current smoking	1.0	2.0	2.3	4.5	0.0004
No diabetes	1.0	2.5	2.6	4.9	0.0001

Figure 5. Adjusted relative risk (RR) of future cardiovascular events among apparently healthy women stratified by quartile of baseline hs-CRP concentration both among all subjects (top) and among specific low-risk subgroups (bottom). (*Data from* Ridker PM, et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation 98:731–733, 1998.)

($P<.0001$).[59] Although the risk of future MI was lower for those taking aspirin in all quartiles of hs-CRP, the relative preventive efficacy of aspirin therapy increased in magnitude with each rising quartile of this inflammatory marker (Fig. 6, *top*). Specifically, those with the highest levels of hs-CRP realized a 55.7% reduction in the risk of future MI ($P=.02$), whereas those in the lowest quartile showed only a 13.9% risk reduction ($P=.77$).[59] Although the pathophysiologic reasons for this observed relationship are not defined, it is intriguing to speculate as to whether the efficacy of aspirin in cardiovascular prevention may be, in part, due to its influence on inflammatory pathways, in addition to its recognized effects on platelet aggregation. These observations also raise the possibility that

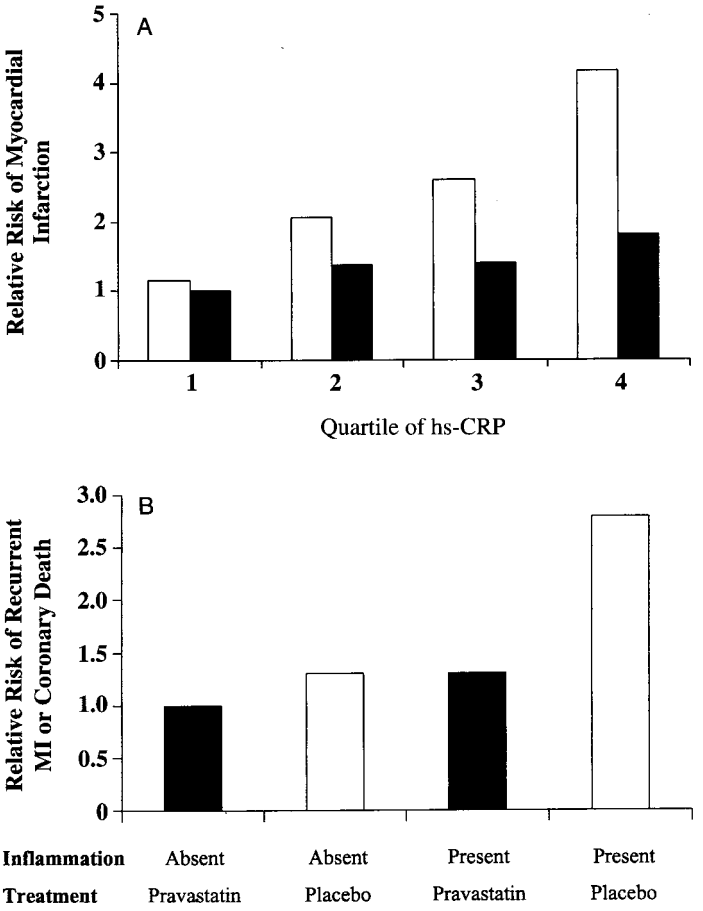


Figure 6. Efficacy of aspirin *(A)* and pravastatin *(B)* therapy and interaction with evidence of inflammation. hs = CRP-high-sensitivity C-reactive protein. Open bar = placebo; solid bar = aspirin. (*Data from* Ridker PM, et al: Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 336:973–979, 1997; and Ridker PM, et al: Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol. Circulation 98:839–844, 1998.)

the increase in vascular risk associated with evidence of inflammation might be modified by other anti-inflammatory therapies.

Baseline levels of hs-CRP have also been demonstrated to modify the beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition in a trial of secondary prevention (see Fig. 6, *bottom*). In the CARE trial, individuals with stable ischemic heart disease after prior MI randomized to treatment with pravastatin, 40 mg/d, experienced a 24% reduction in the rate of recurrent MI or fatal coronary events compared with those taking placebo.[62] Although the risk of recurrent coronary events was reduced by therapy with pravastatin among individuals both with and without evidence of inflammation, the relative risk reduction was greater for those with consistent evidence of inflammation (54% versus 25%) even though baseline lipid levels were virtually identical in each population.[62] In addition, the association between inflammation and risk of recurrent events was attenuated among those treated with pravastatin (RR, 1.29; $P = .5$) as compared with a persistent elevation of risk for those taking placebo (RR, 2.1; $P = .048$).[62] These data provide evidence as to the possible clinical relevance of laboratory observations demonstrating nonlipid effects of the HMG-CoA reductase inhibitors, such as modulation of immune function,[27, 79] antiproliferative effects on vascular smooth muscle,[44, 65] and antithrombotic properties.[9, 66] Follow-up data from the CARE trial support this hypothesis because pravastatin appears to reduce plasma hs-CRP concentration in an LDL-independent manner.[63]

The search for other interventions that might ameliorate the risk associated with increased indicators of inflammation is ongoing. For example, inhibition of the interaction between endothelial cellular adhesion molecules and integrins on the surface of circulating monocytes might interrupt the onset of atherogenesis at its earliest stages.[21, 35] Acting later in the process, interventions aimed at modulating smooth muscle cell proliferation might be successful in slowing or preventing maturation of the fatty streak into the intermediate atheromatous plaque.[31] Alternatively, pharmacologic stimulation of the production of structural proteins by smooth muscle cells or inhibition of the competing degrading enzymes released by inflammatory cells might favorably alter the integrity of the protective fibrous cap. Carefully designed laboratory and clinical studies are needed to explore these potential directions for novel therapy as well as evaluate the multiple interdependent effects of manipulating complex inflammatory pathways.

CONCLUSIONS

Advancements in understanding of the pathobiology of atherothrombosis have implicated inflammation as a central contributor to the progression of atherosclerotic vascular disease. Epidemiologic data demonstrate an association between the inflammatory marker hs-CRP and risk of future cardiovascular morbidity and mortality among those at high risk or with documented vascular disease. Moreover, a series of prospective studies provides consistent data documenting that mild elevation of baseline levels of hs-CRP among apparently healthy individuals is associated with higher long-term risk for future cardiovascular events. Among men and women, this predictive capacity of hs-CRP is independent of traditional cardiovascular risk factors and offers a prognostic advantage over measurement of lipids alone. Further, observations from the PHS and CARE trial suggest that the increased risk associated with systemic inflammation may be modified with certain preventive therapies and that in-

flammatory markers such as hs-CRP may help to identify those who would benefit most from these pharmacologic interventions.

Given that high-throughput assays for inflammatory markers, including hs-CRP, are likely to become available for clinical use, carefully designed studies are needed to evaluate the clinical efficacy of hs-CRP as a new marker to stratify cardiovascular risk. Further, prospective, randomized trials are important to test directly the value of inflammatory markers in targeting specific preventive therapies. Finally, it is still undetermined as to whether elevation of these inflammatory markers reflects the degree of underlying atherosclerosis or plaque *vulnerability* or rather results from some other environmental or infectious stimulus or even has direct effects on platelet aggregation or coagulation.[43] Ongoing and future investigation will clarify the specific pathophysiologic relationships through which these markers correlate with adverse prognosis.

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