

Inflammation and Coronary Heart Disease: An Overview

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About half of the patients presenting with myocardial infarction do not have the classic risk factors. This finding has stimulated a search for other factors that may be responsible and, when present, may help to predict which patients are at greatest risk for myocardial infarction and other cardiovascular events. With improved understanding of the pathogenesis of ischemic heart disease, new insights into potential markers of underlying atherosclerosis and cardiovascular risk have been gained. In recent years, data have accumulated demonstrating that certain markers of inflammation—both systemic and local—play a key role in the development of atherosclerosis. Specifically, elevated levels of one systemic marker of inflammation, C-reactive protein, are associated with an increased risk of cardiovascular disease events. Moreover, potentially important associations have been established between elevated markers of inflammation, such as C-reactive protein and increased efficacy of established therapies; and, in particular, lipid-lowering therapy with the hepatic hydroxymethylglutaryl coenzyme A reductase inhibitor pravastatin. This article discusses the pathogenesis of atherosclerosis, the role of endothelial dysfunction and plaque rupture, and evidence for the role of inflammation and reviews how therapy might reduce vascular inflammation.

Key Words: *Coronary heart disease, Inflammation, Prediction, Therapeutic implications*

Traditionally, it has been theorized that acute myocardial infarctions (MIs) and other acute coronary events that are precipitated by atherosclerosis are due to arterial blockage from fatty deposits. Coronary interventions have focused on identifying angiographically high-grade “culprit” stenoses that are amenable to intervention. It is now known, however, that atherosclerosis involves more than just lipids. In fact, more than half of MIs originate in vessels with <50% stenosis. Furthermore, cholesterol is fundamentally a poor predictor of cardiovascular risk. This is shown in the Framingham Heart Study 26-year follow-up data, which reveal that more than one-third of patients with coronary heart disease have total cholesterol levels <200 mg/dL (1). So, how can prediction of cardiovascular risk be improved? The Framingham Heart Study showed that endogenous factors such as hypertension, dyslipidemia, and diabetes increase risk, as do behavioral factors such as smoking (1). During the 1990s, however, it became clear that a variety of other factors, such as hemostatic and thrombotic mechanisms, inflammatory markers, and genetic factors, also may have great influence (2–19).

Pathogenesis of Atherosclerosis and Thrombosis

Any discussion of how coronary atherosclerosis produces symptoms and cardiovascular events must begin with plaque (4). The arterial wall is not a static structure; it can remodel itself by increasing its external diameter to accommodate plaque development without narrowing the lumen (14). It is not necessarily the size of the plaque

but rather its impaired stability that renders the patient vulnerable to an atherothrombotic event (4). Several factors can lead to the instability of a plaque and a subsequent acute coronary event (2–5) (Fig. 1). Some of the proposed mechanisms, such as impaired endothelial function, can result in the loss of endothelial cells, the exposure of collagen and tissue factor, and superficial thrombosis over a plaque (12). If the area of cell loss is large enough, a large, clinically significant thrombus can form. Impaired plaque stabilization is marked by the presence of a large lipid core and a thin fibrous cap with few smooth muscle cells. Inflammatory activity of T lymphocytes and macrophages contributes to plaque rupture. Exposure of platelets to the lipid core initiates thrombus formation. All of these events together may contribute to the patient’s risk of coronary events. Not surprisingly, the risk of vascular events in patients with stable atherosclerotic plaques is lower than that for patients with unstable plaque (2). Stable plaques are marked by a small lipid core protected by a thick fibrous cap. An overexpression of smooth muscle cells helps to prevent damage to the lipid core and reduces the risk of plaque rupture and thrombus formation. Blood flow through the atherosclerotic area is uninhibited, and platelets do not accumulate.

Systemic Inflammation

A variety of recent investigations have indicated that inflammation has a prominent role in the progression of atherosclerotic disease. Researchers have sought to identify inflammatory markers that might improve our ability to predict MI and stroke (15). Several acute phase inflammatory proteins, cytokines, and intercellular adhesion molecules have been examined as potential indicators of underlying atherosclerosis and risk of future cardiovascular events (16–19). C-reactive protein (CRP) is an established marker of inflammation, increasing by

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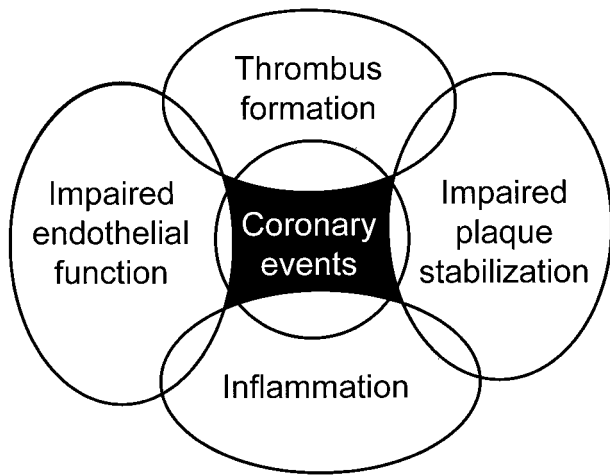


Figure 1. Potential mechanisms for plaque instability and coronary events.

several hundred-fold in response to acute injury, infection, or other inflammatory stimuli (15, 18). The recent development of high-sensitivity assays for CRP (hs-CRP) has led to the belief that CRP is an indicator of microinflammation. It has been shown to be an independent risk factor for future cardiovascular events in apparently healthy individuals (6, 8, 9).

Seminal work by Ridker and colleagues (11) focused on the use of hs-CRP assays to stratify patients with CRP levels within the currently accepted normal range. Using the hs-CRP assay in the Women's Health Study, these investigators found that slight elevations in CRP were associated with an increased risk for cardiovascular events. Those patients in the highest quartile were 5 times more likely to experience a cardiovascular event than were those in the lowest quartile ($p = 0.0001$). This disparity in risk was even more striking among patients with MI or stroke (RR = 5.5) (8).

Even in women considered to be at low risk for a vascular event, hs-CRP levels were predictive (8). In fact, risk estimates were independent of other risk factors, and prediction models that included hs-CRP provided a better method of predicting risk than models that excluded it (all $p < 0.01$). In stratified analysis, hs-CRP assay results were a predictor among women at low risk as well as among those at high risk. Most recent analyses from the same cohort showed hs-CRP assays to be the strongest univariate predictor of cardiovascular risk among 12 markers, including inflammation, lipids and lipoproteins, and homocysteine (20). As part of the Physicians' Health Study (6), Ridker et al. examined levels of CRP in 543 apparently healthy men in whom MI, venous thrombosis, or stroke developed subsequently and in 543 men in whom vascular disease did not develop during a follow-up period of at least 8 years. These patients were assigned to receive a placebo or aspirin at the beginning of the trial. Baseline plasma hs-CRP levels were higher in men who subsequently had a MI (Fig. 2 (6)). The men in the quartile with the highest hs-CRP

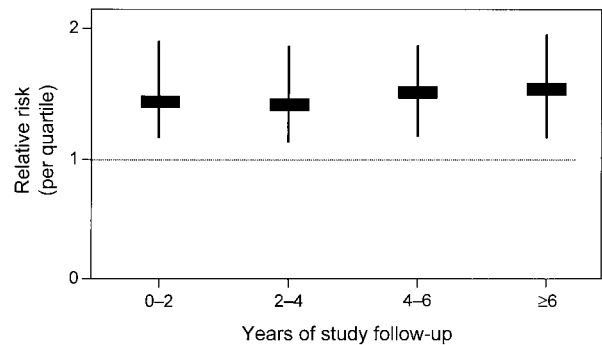


Figure 2. Levels of high-sensitivity C-reactive protein and risk of future MI: Analysis stratified by years of follow-up. (Reprinted with permission from Ridker PM, Cushman M, Stampfer MJ, et al: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973.)

levels had nearly 3 times the relative risk for MI of men in the lowest quartile. The increased risk remained stable during at least 6 years of follow-up. The hs-CRP level also was predictive of stroke in the Physicians' Health Study (6). On an epidemiologic level, cholesterol levels are not predictive of stroke (7). In this study, however, men in the highest quartile of hs-CRP values had nearly 2 times the risk of having a stroke of men in the lowest quartile.

The Physicians' Health Study also showed that hs-CRP levels can predict the development of peripheral vascular disease (PVD) (7). Using a prospective, nested, case control design, the investigators measured the baseline hs-CRP levels of 144 apparently healthy men in whom PVD subsequently developed and in an equal number of control patients matched by age and smoking habit who remained free of PVD during a 5-year follow-up period. Median baseline hs-CRP levels were significantly higher among those patients in whom PVD subsequently developed. Furthermore, the risk increased significantly with each increasing quartile of hs-CRP level. Patients who had coronary heart disease severe enough to require revascularization surgery had the highest hs-CRP levels. In multivariate analysis, models incorporating hs-CRP and lipid parameters provided a significantly better method of predicting risk than did models using lipids alone. Similar results in women were reported recently (20).

The MONICA-Augsburg Cohort also demonstrated the predictive value of hs-CRP for coronary events (9). This study examined the association of hs-CRP with coronary heart disease in 936 apparently healthy, middle-aged men. The patients were selected from a random sample of the general population and were followed for 8 years. There was a positive, significant linear relationship between hs-CRP and the incidence of coronary events ($n = 53$), even after adjustments were made for major confounders (Fig. 3). Because serum concentrations of hs-CRP predict cardiovascular risk, it has been suggested that this inflammatory marker may have a role in routine cardiovascular risk assessment. Furthermore,

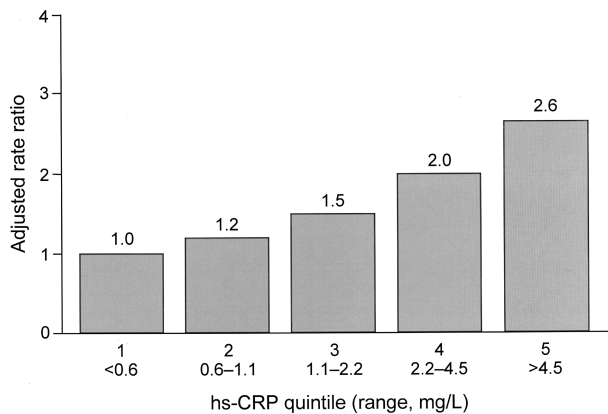


Figure 3. Hs-CRP and coronary heart disease in initially healthy middle-aged men: MONICA-Augsburg cohort (9).

evidence indicating an interaction between certain preventive therapies and baseline hs-CRP levels raises the possibility that inflammatory markers also may have a role in targeting specific therapeutic and preventive interventions (15–18).

Lipid-modifying Interventions Can Reduce Inflammation

Data from the Physicians' Health Study (6) indicate that cardiovascular risk can be modified with antiinflammatory therapy with aspirin. The investigators measured plasma hs-CRP in 543 apparently healthy men in whom cardiovascular events subsequently developed and in 543 control patients who did not report vascular disease during a follow-up period of longer than 8 years. Subjects were randomly assigned to receive aspirin or a placebo at the beginning of the trial. The men in the quartile with the highest levels of hs-CRP had 3 times the risk of MI ($p < 0.001$) and 2 times the risk of ischemic stroke of men in the lowest quartile. The use of aspirin was associated with an overall 44% risk reduction of a first MI. Although the risk was reduced by 56% in patients with the highest levels of hs-CRP, aspirin use minimally and nonsignificantly reduced the risk of future MI by only 14% in patients with the lowest hs-CRP levels.

Ridker et al. also examined the relationship between levels of hs-CRP and hormone replacement therapy (HRT [estrogen alone or estrogen plus progesterone]) in 493 postmenopausal women from the Women's Health Study (21). Median hs-CRP levels in women using HRT were twice as high as they were in women who were not using HRT ($p = 0.001$) (Fig. 4). In addition, no difference was found in hs-CRP levels between women not using HRT and healthy, middle-aged men involved with the Physicians' Health Study (9). Fröhlich et al. (22) reported similar results in 749 postmenopausal women drawn randomly from the general population who participated in the MONICA-Augsburg survey in 1994 and 1995, as did Cushman et al. (23) in participants in the PEPI trial. Thus, the use of HRT is associated with

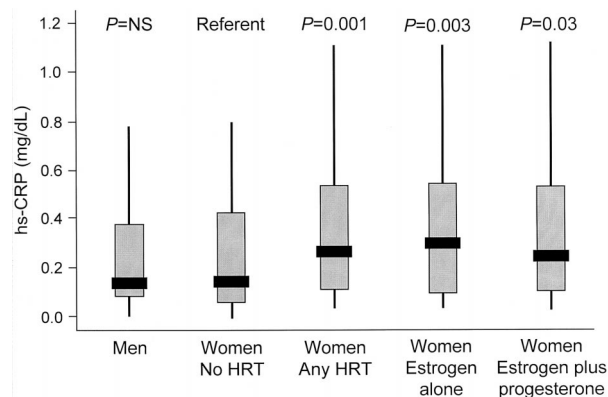


Figure 4. Hs-CRP levels according to sex and HRT status. (Reprinted with permission from Ridker PM, Hennekens CH, Rifai N, et al: Hormone replacement therapy and increased plasma concentration of C-reactive protein. *Circulation* 1999;100:713.)

elevated levels of hs-CRP and may increase cardiovascular risk in this population.

The Cholesterol and Recurrent Events (CARE) study (24) evaluated whether long-term therapy with pravastatin, which reduces cardiovascular risk, might alter levels of hs-CRP. This inflammatory marker was measured at baseline and at 5 years in 472 randomly selected participants who remained free of recurrent coronary events during follow-up. Overall, hs-CRP levels at baseline and at 5 years were highly correlated ($r = 0.60$, $p < 0.001$). The level of hs-CRP, in fact, was better correlated than standard cholesterol screening. In the entire CARE study, random assignment to treatment with pravastatin was associated with a significant 24% reduction in the risk of recurrent MI or coronary death. Similar to results with aspirin therapy in the Physicians' Health Study, the magnitude of risk reduction with therapy in this substudy was greatest in those with evidence of inflammation (risk reduction attributable to pravastatin therapy, 54%) as compared with those without evidence of inflammation (risk reduction, 25%). Moreover, the association between inflammation and risk for recurrent events was significant among those randomized to placebo but was attenuated and no longer significant among those treated with pravastatin (Fig. 5) (10).

Future Directions

The improved understanding of the role of inflammation in atherogenesis offers specific targets for novel therapeutic interventions. For example, interruption of the interaction of key intercellular adhesion molecules might inhibit atherogenesis at its earliest stage: the response to endothelial injury. Antioxidant therapy might alter the course of very early atherogenesis by reducing oxidation of low-density lipoproteins. Pharmacologic interventions targeted at reducing smooth muscle cell proliferation might slow or prevent progression of the fatty streak to the intermediate atheromatous plaque. Well-conducted clinical and laboratory studies are needed to

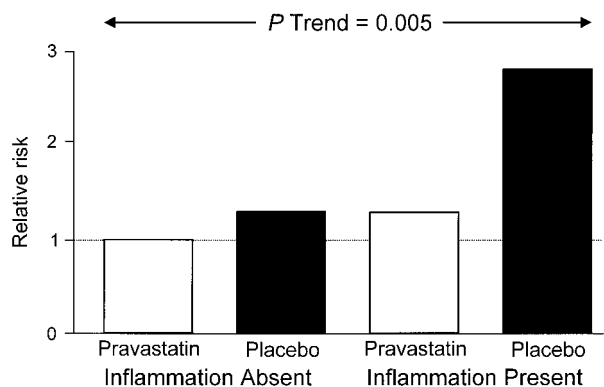


Figure 5. Efficacy of pravastatin therapy in patients with history of MI based on presence of evidence of inflammation. (Reprinted with permission from Ridker PM, Rifai N, Pfeffer MA, et al: Inflammation, pravastatin, and risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation* 1998;98:839.)

evaluate the multiple interdependent effects of modulating inflammatory mediators.

Conclusions

Inflammation is an important contributor to atherothrombosis. Prospective trials show that elevated levels of hs-CRP measured at baseline are associated with adverse cardiovascular prognosis among healthy individuals as well as those at higher risk because of the presence of other risk factors and acute coronary syndromes. The availability of high-sensitivity assays such as for CRP should lead to better prediction of cardiovascular risk—and early institution of preventive or secondary therapy for atherosclerosis.

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