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Inflammation in Atherosclerosis and Implications for Therapy

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Abstract—Atherosclerosis is now understood to be a disease characterized by inflammation that results in a host of complications, including ischemia, acute coronary syndromes (unstable angina pectoris and myocardial infarction), and stroke. Inflammation may be caused by a response to oxidized low-density lipoproteins, chronic infection, or other factors; and markers of this process, such as C-reactive protein, may be useful to predict an increased risk of coronary heart disease. Thus, we believe that inflammatory processes may be potential targets of therapy in preventing or treating atherosclerosis and its complications. (***Circulation***. 2004;109[suppl III]:III-20–III-26.)

Key Words: atherosclerosis ■ coronary heart disease ■ C-reactive protein ■ inflammation ■ risk factors

Atherosclerosis is an inflammatory disease, not merely the passive accumulation of lipids within artery walls. The chronic inflammatory process involving the arterial endothelium that ultimately results in the complications of atherosclerosis may be caused by a response to the oxidative components of modified low-density lipoprotein (LDL), or to chronic infection, free radicals, or other factors. The association of inflammation with the initiation and progression of atherosclerosis suggests that markers of inflammation, eg, acute phase reactants such as C-reactive protein (CRP), may be useful in predicting an increased risk of coronary heart disease (CHD). Inflammatory processes are also potential targets of therapy in preventing or treating CHD.

Atherosclerosis as an Inflammatory Process

Inflammation Mediates All Stages of Atherosclerosis

Atherosclerosis is a multifactorial, multistep disease that involves chronic inflammation at every stage, from initiation to progression and, eventually, plaque rupture.[1] In atherosclerosis, the normal homeostatic functions of the endothelium are altered, promoting an inflammatory response.[2,3] For example, adhesion molecules expressed by inflamed endothelium recruit leukocytes, including monocytes, which then penetrate into the intima, predisposing the vessel wall to lipid accretion or vasculitis. Inflammatory mediators enhance uptake of modified lipoprotein particles and formation of lipid-filled macrophages. T cells also enter the intima and secrete cytokines, which subsequently amplify the inflammatory response and promote the migration and proliferation of intimal smooth muscle cells. Later in the process, inflammatory mediators can weaken the protective fibrous cap of the atheroma, possibly leading to thrombosis and the occurrence

of acute coronary syndromes such as unstable angina pectoris and myocardial infarction (MI).[1,4]

Inflammatory Mechanisms

Oxidized LDL and Lipoprotein-Derived Products of Lipid Peroxidation. Oxidized LDL is one hypothetical risk factor for atherosclerotic inflammation.[5] It is believed that oxidation of LDL may be modulated by nitric oxide (NO) and its products, as well as by myeloperoxidase and ceruloplasmin.[6,7] In one study, levels of oxidized LDL were significantly higher in patients with acute MI than in patients with angina or in controls, although lipid profiles did not differ among these groups.[8] In atherectomy specimens, the surface area containing macrophages that were positive for oxidized LDL was greater in patients with unstable angina than in those with stable angina.[8] In another study, plasma levels of oxidized LDL were significantly higher in patients with CHD than in controls, and were not correlated with other major risk factors.[9] Natural antioxidants (ie, β-carotene, vitamin C, and vitamin E) have been used as a potential strategy to reduce damage caused by oxidized LDL in patients with or at high risk for CHD, but the majority of clinical trials have not shown reductions in CHD events with this approach.[10] More clinically reliable markers of oxidative stress or the development of more effective antioxidant therapies might make this strategy more useful.[11]

High-Density Lipoprotein. The protective effect of high-density lipoprotein (HDL) against the development of atherosclerosis may result partly from its antiinflammatory and antioxidant properties. HDL inhibits oxidative modification of LDL and blocks the proinflammatory effects of oxidized LDL. Paradoxically, HDL can also have proinflammatory effects; for example, in the presence of the acute-phase

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reactant serum amyloid A (SAA), HDL may elicit such a response in macrophages. In contrast with normal HDL, HDL isolated from coronary artery disease patients without diabetes and with average lipid levels did not protect LDL against oxidation in cells from artery walls.[12,13] HDL from mice genetically predisposed to diet-induced atherosclerosis and fed an atherogenic diet, mice injected with LDL-derived oxidized phospholipids, mice infected with influenza A virus, and hyperlipidemic mice on a normal diet also became proinflammatory. These results suggest that proinflammatory HDL might be useful as a marker of susceptibility to atherosclerosis.[12]

In summary, oxidative modification of lipoproteins can generate a broad array of products of lipid peroxidation, which can affect the vessel wall. During atherogenesis, inflammatory cells (eg, monocyte-derived macrophages) accumulate in arteries, releasing growth factors/cytokines (eg, platelet-derived growth factor [PDGF], transforming growth factor-beta [TGF-β], granulocyte-macrophage colony-stimulating factor). Whereas PDGF may stimulate cholesteryl ester (CE) hydrolysis in cells, TGF-β appears to cause a decrease in lysosomal CE hydrolysis. The latter could lead to a transient reduction in intracellular free cholesterol.[43,44] Growth factors/cytokines also enhance LDL-receptor activity, perhaps in part because of the reduction in intracellular free cholesterol, because LDL-receptor activity varies inversely with cellular cholesterol levels.[43-45] As a result of enhanced LDL-receptor activity, increased amounts of cholesterol/CE are delivered to the cell. When plasma LDL concentrations become elevated, the vessel wall eventually becomes lipid-engorged because it is unable to traffic the large amounts of endocytosed LDL-CE.[45] In addition, lipoprotein entrapment by the extracellular matrix can lead to the progressive oxidation of LDL because of the action of lipoxygenases, reactive oxygen species, peroxynitrite, and/or myeloperoxidase found in oxidized LDL particles. A range of oxidized LDL species is thus generated, ultimately resulting in their delivery to vascular cells through several families of scavenger receptors.[45] These "molecular Trojan horses" and "cellular saboteurs," once formed or deposited in the cell, can contribute to, and participate in, formation of macrophage- and smooth muscle–derived foam cells. A lipid-enriched fatty streak along the vessel wall can develop. In addition to playing a role in foam cell formation, LDL oxidation may activate endothelial cells, increase smooth muscle mitogenesis, or induce apoptosis because of the effects of oxysterols and other products of lipid peroxidation. Because antioxidant defenses may be limited in the microenvironment of the cell or within LDL, the oxidation process continues to progress. Enzymes associated with HDL such as PAF acetylhydrolase and paraoxonase can participate in the elimination of biologically active lipids, but diminished cellular antioxidant activity coupled with low levels of HDL may allow acceleration of the clinical course of vascular disease.

Infectious Agents. Epidemiological studies have suggested an association between some pathogens and atherosclerosis. Two infectious agents, *Chlamydia pneumoniae* (*C pneumoniae*) and cytomegalovirus, have been detected in human atherosclerotic lesions.[14] Seropositivity to *C pneumoniae* was

associated with risk for premature MI in current and former smokers. Elevated antibody titers to both *C pneumoniae* and cytomegalovirus conferred a higher risk for premature MI even after adjustment for other risk factors. Patients who were seropositive for both agents had a 5 times greater risk for premature MI than patients who were seropositive for one agent, and a 12 times greater risk than those who were seropositive for neither agent. Doubly seropositive patients also had increased levels of inflammatory markers, including CRP.[15] The issue is not without controversy: in another study showing an association of CRP with CHD, there were no strong associations of four inflammatory markers, including CRP, with *Helicobacter pylori* or *C pneumoniae* seropositivity.[16]

In a study of mice infected with influenza A, HDL lost its antiinflammatory properties during the acute-phase response. In vitro analyses found that the ability of HDL to inhibit LDL oxidation and LDL-induced monocyte chemotactic activity in human arterial cell cocultures decreased with time after infection. These changes were not associated with a direct effect of the virus on HDL, but were thought to result from a systemic response.[17] A recent study found that infection with multiple pathogens (bacteria and viruses) could contribute to coronary artery disease by precipitating inflammation and endothelial cell injury.[14] Or, it has been suggested that herpes viruses may infect vascular cells, inducing a proinflammatory phenotypic change in the vessel wall which can, in turn, predispose it to cellular degeneration (foam cell appearance) and atherosclerosis.

Inflammatory Markers

Established risk factors for CHD do not fully account for all risk of disease or adequately explain the etiology of the disease process. Therefore, identifying novel risk factors and markers warrants continued investigation. Among the inflammatory markers for CHD risk that have received attention are interleukins and CRP. It is not yet known whether these markers have a causal relation to CHD or if the association of these markers with CHD simply reflects an underlying disease process.

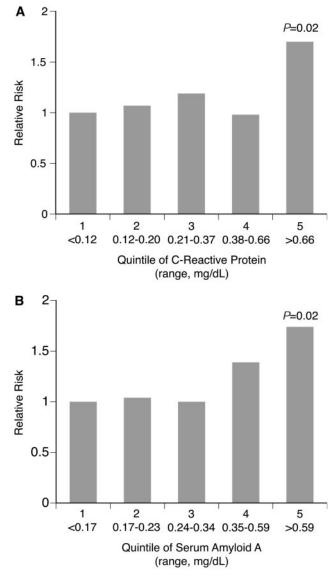### *Predictive Value of Inflammatory Markers*

Interleukin-6 (IL-6), a circulating cytokine, has been identified as a marker of inflammation in coronary atherosclerotic plaques. Serum levels of IL-6 increase in response to acute MI, unstable angina, percutaneous coronary intervention, and late restenosis. IL-6 stimulates platelet aggregation and the expression of tissue factor, macrophage LDL receptors, CRP, and fibrinogen. IL-6 also regulates the expression of other inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α).[18]

CRP, one of many human acute-phase reactants, is produced in the liver in response to IL-6, IL-1β, and TNF-α. It activates the classic complement cascade, mediates phagocytosis, regulates inflammation, and is a nonspecific but sensitive marker of infection and tissue inflammation.[19] Prospective studies have shown that an elevated level of CRP is associated with increased risk for cardiovascular events in apparently healthy persons.[20] Studies also support the prog-

nostic value of CRP in patients with a prior history of cardiovascular disease.[21] CRP might directly promote vascular disease; alternatively, it may indicate the presence of a chronic infection associated with an increased risk for CHD or an already identified CHD risk factor such as smoking, obesity, or preexisting atherosclerosis.[16,19] Because of their interrelationship, CRP could simply be a surrogate marker for IL-6 or some other factor.[22]

One study[16] prospectively measured four circulating markers of inflammation, CRP, SAA, leukocyte count, and albumin, to determine whether an underlying inflammatory process was related to CHD. The study monitored 5661 British men over a 12-year period for all-cause mortality and cardiovascular morbidity.[16] After adjustment for confounding factors, men in the top third of baseline CRP levels had an odds ratio for CHD of 2.13 compared with men in the bottom third. The adjusted odds ratios were 1.65 for SAA, 1.12 for leukocyte count, and 0.67 for albumin.[16] The investigators concluded that baseline values of all four markers were associated with each other as well as with the future risk for CHD, suggesting that some underlying inflammatory process is associated with CHD.

CRP and SAA were measured post hoc in the Cholesterol and Recurrent Events (CARE) trial, which prospectively monitored stable post-MI men and women who were randomized to either pravastatin or placebo.[21] Patients experiencing recurrent MI or death from CHD (cases) were matched to patients who remained free of these events over the 5-year follow-up period (controls). Levels of CRP and SAA were significantly higher among cases than among controls. Furthermore, patients in the highest quintiles of CRP and SAA had a relative risk for recurrent coronary events that was 75% higher than those in the lowest quintiles (Figure). The overall relative risk for a recurrent coronary event in patients with elevated levels of CRP and SAA was 1.77 and 1.74, respectively.[21] Placebo patients with CRP and SAA levels at or above the 90th percentile had the highest relative risk for recurrent coronary events (RR=2.81; P=0.007). In addition, the combined risk was greater than the product of the individual risks associated with either inflammation or placebo treatment alone. These data suggest that CRP and SAA levels predict an increased risk for recurrent coronary events among stable patients with a history of MI.[21]

A post hoc analysis of the primary prevention Air Force/ Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS) evaluated CRP at baseline and after 1 year of therapy with lovastatin versus placebo, using the high-sensitivity assay for this protein. CRP data were available for 5742 male and female participants with average levels of total cholesterol and below-average levels of HDL who had been monitored for 5 years.[23] Lovastatin therapy reduced CRP levels by 14.8% (P<0.001). As would be expected, lovastatin was associated with a reduced risk for coronary events in patients whose baseline LDL cholesterol was higher than the median value, regardless of the CRP level. However, among patients whose LDL cholesterol was lower than the median, CRP measurement provided additional information. For those with both LDL cholesterol and CRP lower than the median values, there was no benefit of therapy. For the group whose

Relative risks for recurrent coronary events among post-MI patients in the Cholesterol and Recurrent Events study (post hoc analysis) according to baseline plasma concentrations of C-reactive protein (top) and serum amyloid A (bottom). Reprinted from Ridker PM et al. *Circulation*. 1998;98:839–844.

LDL cholesterol was lower than the median, but whose CRP was higher than the median, the relative risk for an acute coronary event with lovastatin versus placebo was 0.58 (95% confidence interval: 0.34 to 0.98) and the number needed to treat to prevent one event was 48. Therefore, using the high-sensitivity CRP (hsCRP) assay in addition to standard lipid evaluation may improve our ability to identify patients at high risk.

A substudy of the West of Scotland Coronary Prevention Study (WOSCOPS) examined blood markers of inflammation as predictors of risk in hypercholesterolemic men with no history of heart attack who were treated with either pravastatin or placebo.[24] A total of 580 men who had had a coronary event (nonfatal MI, CHD death, or a revascularization procedure) were each matched for age and smoking status with 2 control subjects (total: 1160) from the same cohort who had

not had a coronary event. Lipoprotein-associated phospholipase A_2, CRP, fibrinogen levels, and the white-cell count were measured at baseline, along with other traditional risk factors. All four measurements demonstrated significant positive associations with the risk for coronary events. However, only lipoprotein-associated phospholipase A_2 remained a strong predictor when the analyses were adjusted for age, systolic blood pressure, and lipoprotein levels in multivariate models.

In some populations, even patients with CRP levels in the lower ranges may be at increased risk. For example, a study of patients <50 years of age with stable premature coronary artery disease found that those with CRP levels in the currently accepted upper normal range or higher were at increased long-term risk for future cardiovascular events such as cardiac death, acute MI, or revascularization.[25]

Epidemiological data support the predictive ability of inflammatory markers such as IL-6, SAA, CRP, and others. Unlike the first two, CRP is attractive for clinical use because its high-sensitivity assay is standardized and widely available, with a low cost compared with other risk-assessment innovations such as vascular imaging technologies. Despite these features, the general recommendation for using CRP as a novel CHD risk factor still faces several challenges.[26] In the meanwhile, CRP measurement may be useful as an adjunct to traditional measures of lipids, especially for the purpose of detecting enhanced risk in patients whose lipid values may not be severely elevated, but who are at intermediate risk based on scoring systems that account for multiple established risk factors. In fact, the latest guidelines of the National Cholesterol Education Program's third Adult Treatment Panel recommend that the presence of emerging risk factors such as CRP may be used to justify intensification of lipid-modifying therapy in patients who appear to be at borderline risk based on traditional risk factors alone.[27]

Effects of Drugs and Diet on Inflammation

The association of inflammatory markers with increased risk for CHD suggests the use of antiinflammatory treatment to reduce the risk for future CHD events. However, no prospectively designed studies have so far assessed clinical benefits after specific treatment of these markers. Such studies would indicate whether inflammatory markers could be used not only in risk stratification but also to determine therapeutic efficacy.

Effects of Statins on CRP

In several trials, the effects of statins on CRP levels appeared unrelated to their effects on lipid levels, suggesting that statins may exert an antiinflammatory action.[21,23] The well-documented lipid-regulating effects of statins in conjunction with their possible antiinflammatory properties may therefore provide a theoretical double benefit.[28]

In a study of atorvastatin in high-risk patients with combined hyperlipidemia, CRP concentrations decreased significantly with statin treatment. These reductions were unrelated to decreases in total cholesterol and LDL cholesterol, but were directly related to triglyceride changes and inversely related to changes in HDL cholesterol levels.[28] The effects of

pravastatin, simvastatin, and atorvastatin were compared in a crossover study of a small number of patients (N=22) with elevated triglycerides and LDL cholesterol. The three drugs were equally effective in significantly decreasing CRP, and none reduced plasma levels of IL-6 or its soluble receptor. Changes in CRP levels were correlated with changes in triglycerides but not with changes in LDL cholesterol or HDL cholesterol. During the washout period between treatments, LDL cholesterol increased but CRP did not, providing further evidence of the dual activity of statins.[29] In another small study, atorvastatin decreased CRP and SAA, whereas simvastatin did not. Both statins decreased the inflammatory marker soluble phospholipase A_2, but they had no reproducible effect on intercellular adhesion molecule-1 or IL-6.[30] A recent study with simvastatin showed a reduction in CRP within 14 days, an effect that was independent of LDL-cholesterol reduction.[31]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial was a randomized, open-label study comparing the effect of atorvastatin 80 mg/d versus pravastatin 40 mg/d on carotid intima-media thickness in 161 patients.[32] During 12 months of therapy, atorvastatin induced mean regression of carotid intima-media thickness versus stabilization with pravastatin ($P=0.03$). In addition, atorvastatin produced significantly greater reductions in levels of LDL cholesterol ($P<0.001$) and CRP ($P=0.005$) compared with pravastatin. This finding of greater CRP reductions in patients treated with atorvastatin who achieved lower LDL-cholesterol levels differs from results of other statin trials, in which CRP reductions were independent of an effect on LDL cholesterol. However, the markedly different lipid-lowering potencies of these two drugs make it difficult to discern the potential role of their respective nonlipid effects. This study points to the need for future clinical outcome trials to determine the utility of using both CRP and LDL as measures of the success of statin therapy.

In the 16-week, randomized, double-blind Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, 3086 patients received atorvastatin 80 mg/d or placebo within 24 to 96 hours after hospitalization for unstable angina or non–Q-wave acute MI.[33] Atorvastatin reduced the relative risk for a primary combined end point event by 16% ($P=0.048$), based on a significant reduction in the risk for recurrent symptomatic myocardial ischemia. There were no significant reductions in the other components of the primary end point (death, nonfatal acute MI, cardiac arrest). In these patients, CRP, SAA, and IL-6 levels were markedly elevated at baseline, and these elevations were greater in subjects with LDL-cholesterol levels below the study median of 125 mg/dL.[34] Because a decrease in LDL cholesterol represents an acute-phase response after a coronary event, the inverse relation suggests that CRP, SAA, and IL-6 levels are higher in patients who are sicker. After 16 weeks of therapy, atorvastatin produced significantly greater reductions in CRP (34%; $P<0.0001$) and SAA (13%; $P=0.0006$) levels compared with placebo. There was a nonsignificant trend toward lower levels of IL-6. These results suggest that CRP can serve as a marker of decreased

inflammation with atorvastatin; however, the relation to reduction in risk for clinical events is not clear and requires further study.

The Pravastatin Inflammation/CRP Evaluation (PRINCE) study prospectively examined the effect of pravastatin 40 mg/d versus placebo on CRP in a cohort of 1702 men and women with no prior history of cardiovascular disease and 1182 with known cardiovascular disease.[35] After 24 weeks, CRP was reduced by ≈16.9% ($P<0.001$) in primary-prevention patients treated with pravastatin compared with placebo. The absolute change in CRP in the pravastatin group was 0.02 mg/dL. Similar changes were seen in the secondary-prevention arm. There was no clear correlation in this study between the changes in LDL cholesterol or HDL cholesterol and the reductions in hsCRP, and allocation to pravastatin and baseline CRP levels were the best predictors of change in CRP ($P<0.001$ for both).

The mechanisms by which statins may counteract inflammation are still undergoing investigation. In an animal model of atherosclerosis, atorvastatin reduced inflammation by decreasing the expression of the proinflammatory molecule cyclooxygenase-2 (COX-2). Atorvastatin also decreased the activity of nuclear factor-κB, a transcription factor controlling proinflammatory genes, in circulating mononuclear cells. This finding suggests that atorvastatin may affect the activity of inflammatory mediators in circulating monocytes before they enter the vascular wall, differentiate into macrophages, and contribute to the atherosclerotic process.[36]

However, as with the other so-called pleiotropic effects of statins, investigators have yet to elucidate the contribution of the statins' possible antiinflammatory actions to clinical benefit observed in the large trials. Is evidence of inflammation sufficient grounds to initiate statin treatment, and is CRP an appropriate surrogate measurement for clinical benefit? At present, more research is clearly needed. Until such data become available, the decision to initiate any treatment should continue to be based on the patient's overall risk profile and specific needs, as well as on the physician's clinical judgment.

Angiotensin-Converting Enzyme Inhibition
By interrupting the expression of adhesion molecules and cytokines, angiotensin-converting enzyme (ACE) inhibitors exert antiinflammatory effects on the development of atherosclerosis and on the plaque rupture that initiates acute coronary syndromes.[37] In the future, identification of specific markers of inflammation may identify a subpopulation of high-risk post-MI patients and others for whom therapy with an ACE inhibitor will be more effective than it is for the total patient population.

Biology of PPARs and the Role of Fibrates
Peroxisome proliferator-activated receptors (PPARs) are lipid-activated nuclear receptors that serve as transcriptional regulators of genes encoding for proteins involved in glucose and lipid metabolism. PPARs bind to and are activated by such diverse agents as long-chain fatty acids, arachidonic and linoleic acid metabolites, and the thiazolidinedione class of antidiabetic drugs. Growth factors, such as epidermal growth factor and PDGF, have been shown to phosphorylate PPARs

via the MAP kinase-signaling pathway and to decrease PPAR transcriptional activity.

Several PPAR-responsive genes have been identified, including the protein CD36. CD36, a scavenger receptor, is expressed on platelets, monocyte/macrophages, microvascular endothelial cells, retinal pigment epithelium, striated and smooth muscle, and adipose tissue. CD36 recognizes a broad variety of ligands, including oxidized LDL, anionic phospholipids, apoptotic cells, thrombospondin-1, collagen, effete photoreceptors, fatty acids, and *Plasmodium falciparum*–infected erythrocytes. Incubation of macrophages with PPAR-γ ligands, including oxidized LDL and thiazolidinediones, increases expression of CD36, which has been shown to play an important role in the development of atherosclerosis in animal models by regulating cholesterol trafficking to the vessel wall. It has been shown that oxLDL increases CD36 by elevating PPAR in the cell. Therefore, it has been hypothesized that upregulation of PPAR by its ligands can affect the pathogenesis of the lesion.

In this regard, fibrates, once bound to PPARs, can alter lipoprotein metabolism and inflammation in atherosclerosis. For example, ligand activation prevents IL-1–induced expression of IL-6 and COX-2 in endothelial and smooth muscle cells, monocytes, and macrophages. In addition, fibrates are thought to decrease the risk for coronary events by reducing inflammation and procoagulant factors (eg, fibrinogen) and by modestly improving lipid profiles.[38] However, in a clinical trial, bezafibrate did not significantly reduce CRP, although it did improve lipid profiles.[28] Thus, the role of fibrates and PPAR agonists in general in attenuating the inflammatory response in humans remains controversial.

Cyclooxygenase Inhibitors
Cyclooxygenase exists in two isoforms, COX-1 and COX-2, and plays an important role in inflammation. COX-1 is constitutively expressed in most tissues. COX-2 is induced at sites of inflammation and is expressed by cells in human atherosclerotic lesions.[39]

Aspirin. Aspirin, which inhibits both COX isoenzymes,[39] has antiplatelet and antiinflammatory activities. The ability of aspirin to decrease the incidence of a first thrombotic event, including MI, ischemic stroke, and venous thrombosis, was measured with respect to CRP levels. Men with the highest CRP levels had an increased risk for MI and ischemic stroke, but not venous thrombosis, independent of other risk factors. Aspirin significantly reduced the risk for MI among men in the highest quartile of CRP levels, but not among those in the lowest quartile. This result suggests that the relation of CRP-mediated inflammation to vascular risk is confined to the arterial circulation, that aspirin acts as an antiinflammatory agent, and that CRP levels may identify persons who are more likely to respond to aspirin therapy.[22]

Inhibition of COX-2. The expression of COX-2 is induced by cytokines, growth factors, and prostaglandins secreted by macrophages in the vessel wall. COX-2 expression can lead to production of proinflammatory eicosanoids that in turn induce the production of IL-6. COX-2 promotes the development of early atherosclerotic lesions in LDL-receptor–deficient male mice fed a Western diet, whereas inhibition of

COX-2 decreases atherogenesis.[39] In a rabbit model of atherosclerosis and in cultured vascular smooth muscle cells, atorvastatin decreased COX-2 but not COX-1 expression induced by cytokines, suggesting COX-2 as a therapeutic target in atherosclerosis.[36] Selective inhibitors of COX-2 are used clinically as antiinflammatory and analgesic drugs. In patients treated with COX-2 inhibitors for arthritis, cardiovascular events occurred at a higher or equal rate compared with patients treated with other classes of antiinflammatory drugs or placebo. Nevertheless, it is possible that selective use of COX-2 inhibitors combined with an antiplatelet agent might reduce the substrate for thrombotic events and inhibit thrombosis. This hypothesis remains to be tested in clinical trials.[39]

Fish Oil

In animal studies as well as in human populations, consumption of large amounts of fish and of highly unsaturated fatty acids in general (and omega-3 fatty acids [n-3 FA] in particular) reduces the risk of CHD.[40] In a study monitoring 22 071 men with no prior CHD for up to 17 years, higher baseline blood levels of n-3 FA were strongly associated with a reduced risk of sudden death, even after controlling for confounding factors.[41] In a study monitoring 84 688 women over 16 years, a higher intake of fish or n-3 FA was associated with a lower risk for CHD after adjustment for standard risk factors. In secondary prevention trials, increased consumption of fatty fish or dietary supplementation with n-3 FA reduced coronary events.[42]

The cardioprotective effect of n-3 FA may result from reductions in endothelial activation or expression of cell adhesion molecules. In vitro, the n-3 FA docosahexaenoic acid, but not saturated fatty acids, protected human endothelial cells from activation by inflammatory cytokines and inhibited the expression of cell adhesion molecules, including vascular cell adhesion molecule-1 and E-selectin. Effective concentrations of docosahexaenoic acid can be achieved by nutritional supplementation.[40] The protective effect of n-3 FA may also be due in part to an antiarrhythmic effect,[41] reduction of triglycerides, decreased platelet aggregability, and possibly inhibition of COX. However, aspirin is a much stronger COX inhibitor than fish oil.[42]

Conclusions

Inflammation and oxidation are crucial to the pathogenesis of atherosclerosis. Inflammatory markers such as CRP and SAA may predict risk for CHD. The role of inflammation in clinical decision-making related to cardiovascular prevention, however, requires further research. Inflammatory markers, especially CRP, may prove to be useful adjuncts to traditional risk assessment to help determine the intensity of intervention, but should not supplant other risk factors when considering the initiation of treatment. That certain pharmacological interventions reduce inflammatory parameters helps illustrate the biological plausibility of the inflammation hypothesis, but the precise contribution of these effects to clinical benefit has proved difficult to analyze. For now, clinical event data from randomized trials represent the best guides for identifying treatment strategies. By this standard, statins, ACE inhibitors, aspirin, and dietary supplementation with n-3 fatty acids are among the appropriate drug approaches with putative antiinflammatory effects that have been shown to reduce CHD risk.

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Text added to this article in page proofs required adding reference citations out of correct numerical order on page III-21. The new references are listed as numbers 43–45.

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