Coronary heart disease (CHD) remains a persistent public health burden in the United States, and it is the cause of one of every five deaths each year. The link between lipids and CHD has been firmly established, first by epidemiologic studies and, more recently, by long-term outcomes trials that demonstrated that lowering low-density lipoprotein cholesterol (LDL-C) levels significantly reduced the risk of major coronary events. Based on this evidence, the National Cholesterol Education Program recommends lowering the LDL-C level to reduce CHD risk, particularly for patients at highest risk. Recently, evidence has emerged that suggests that C-reactive protein may be a mediator of atherosclerosis and its presence may be indicative of increased risk of CHD. Although these data are intriguing, their relevance has yet to be established in prospective outcomes trials. Until then, lipid lowering through lifestyle modification and the use of safe and effective modes of therapy should be the emphasis of CHD risk reduction strategies.

Emerging evidence strongly suggests that coronary heart disease (CHD), once considered the result of vessel-occluding deposition of lipids, is a manifestation of a chronic inflammatory response to injury or infection. Elevated plasma cholesterol levels have long been established as risk factors for CHD, and lowering cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C), has been the focus of the prevention of CHD and its sequelae for almost 25 years. However, the complex mechanisms by which these molecules act are only beginning to be appreciated. Evidence suggests that lipid-lowering modes of therapy also reduce inflammation, which may reduce the risk of cardiovascular events, even for individuals with LDL-C levels in the normal range (<130 mg/dL) based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. This article reviews the role of lipids in plaque development, the data supporting atherosclerosis as an inflammatory disease, and the impact of these data on clinical practice.

Role of Lipids in Plaque Development
Injury or infection can disrupt normal endothelial function and initiate formation of atherosclerotic lesions known as fatty streaks. Fatty streaks typically consist of macrophages and T cells embedded in a thin layer of lipids on the arterial wall. Macrophages engulf lipids, becoming activated foam cells that release an array of chemotaxant molecules, cytokines, and growth factors. More lymphocytes are attracted to the lesion and, in turn, add to the pool of effector molecules that expand and perpetuate the inflammatory response. As this cycle is repeated, the plaque develops a fatty core covered by a fibrous matrix that stabilizes the structure.

The frequent presence of fatty streaks in young children is consistent with the chronic nature of atherosclerotic progression. Although the possible events that can initiate fatty streak formation remain controversial, LDL-C, modified by oxidation, glycation, and association with proteoglycans and immune complexes, can become trapped in the arterial wall, injuring the endothelium and vascular smooth muscle. Once trapped, LDL-C particles become progressively more oxidized, form lipid peroxides, and facilitate accumulation of cholesterol esters. Also, modified LDL-C is chemotactic for circulating monocytes and stimulates the proliferation of macrophages already in the lesion. Inflammatory mediators increase the binding of LDL-C to endothelial cells and vascular smooth muscle cells that have migrated into the lesion. As the plaque becomes thicker, the arterial wall responds by “remodeling,” that is, gradually dilating to maintain the diameter of the vessel lumen. Eventually, macrophages may be stimulated to release metalloproteinases that degrade the fibrous cap and render the plaque vulnerable to rupture.

Although several types of plaque can result in serious coronary events, retrospective analyses have demonstrated that 70% of all fatal acute myocardial infarctions and sudden coronary deaths are attributable to plaque rupture or...
plaque erosion (Figure 1). This observation is not surprising because plaque destabilization is often accompanied by release of prothrombotic factors. However, a recently developed consensus document emphasizes that all types of atherosclerotic plaques can result in coronary events and sudden death. Vulnerable plaques are defined as thrombosis-prone or at risk of rapid progression and exhibit some combination of the following: active inflammation, thinning cap with a large lipid core, endothelial denudation with superficial platelet aggregation, fissures, or greater than 90% stenosis. The authors further conclude that the thrombotic status of the blood and the electrical instability of the myocardium are important to the ultimate outcome for the patient.

Although some of these criteria can be visualized with noninvasive procedures such as magnetic resonance imaging or computer-enhanced tomography, none is easily used for routine screening purposes. Thus, the ATP III risk factor assessment based on a 10-year cardiovascular risk remains the best tool to identify patients at high risk.

Inflammation and Atherosclerosis

An accumulating body of evidence suggests that atherosclerotic progression results from microinflammation mediated by proinflammatory cytokines. The observation that monocytes and T lymphocytes are present at all stages of plaque development is consistent with active inflammation. Chronic low-level inflammation increases atherosclerotic plaque deposition in animal models. In addition, heightened levels of the acute-phase reactant C-reactive protein (CRP) is believed to be a marker of inflammatory processes and may also be of value in the prediction of coronary events. A recently published report suggests that CRP is more than a marker and may be a mediator of atherosclerosis. The association between elevated levels of CRP and cardiovascular risk has been the object of extensive research and is the topic of much current debate. Some evidence suggests that CRP is an independent predictor of risk of cardiovascular events. In a study that followed nearly 28,000 apparently healthy women for 8 years, Ridker and colleagues found that the CRP level was a stronger predictor than the LDL-C level for myocardial infarction, ischemic stroke, coronary revascularization, or death due to cardiovascular causes. However, because CRP and LDL-C levels appeared to identify somewhat different risk groups, the combined risk assessment was superior to that of either marker alone.

In this same study, multivariate analysis indicated that increasing CRP levels were associated with increased risk of cardiovascular events at all levels of estimated risk based on the Framingham risk score and NCEP ATP III risk categories. Although the women in this study who had high CRP and low LDL-C levels were at higher absolute risk than those with low CRP and high LDL-C levels, only the latter group would be considered eligible for aggressive therapy.

Danesh et al recently reported data from a study of circulating inflammatory markers that evaluated the relevance of CRP to the prediction of CHD. These investigators prospectively observed 18,569 individuals enrolled in the Reykjavik Heart Study and measured inflammatory markers in blood samples obtained at baseline from up to 2459 patients who had a nonfatal myocardial infarction or died of CHD during the study and from up to 3969 control subjects without CHD. Results of the study suggested that CRP was not as strong a predictor for CHD as more traditional risk factors such as total cholesterol level or cigarette smoking. Therefore, the authors concluded that recommendations regarding the use of the CRP level in predicting the likelihood of CHD may need to be reviewed.

Newer information reveals that CRP is a modulator of inflammation and may have both proinflammatory and anti-inflammatory actions, which may directly contribute to endothelial dysfunction by inducing cytokine release and surface expression of adhesion molecules. Through a conformational rearrangement in CRP from a pentameric to a monomeric structure, the atherogenic effects of CRP are noted on human endothelial cells. C-reactive protein now appears to be more than a marker of cardiovascular events.

The Emerging Concept of the Vulnerable Patient

Vulnerable plaques are not the only culprit factors for the development of acute coronary syndromes, myocardial infarction, and sudden cardiac death. Vulnerable blood (prone to thrombosis) and vulnerable myocardium (prone to fatal arrhythmia) play an important role in the outcome. Therefore, the term vulnerable patient may be more appropriate and is proposed now for the identification of subjects with high likelihood of having cardiac events develop in the near future.
Markers and Modulators

- Inflammation
- Matrix matters
- Intraplaque
  - Hemorrhage
  - Angiogenesis
- Endothelial cells
- Matrix Metalloproteinases
  - Tissue inhibitors of matrix metalloproteinases
  - Cathepsins
  - Transforming growth factor-β
- Platelets
- Tissue factor
- Tissue factor pathway inhibitor
- Tissue plasminogen activator
- Plasminogen activator inhibitor-1
- Fibrinogen
- von Willebrand factor

Systemic Biology

- Inflammation
- Blood rheology
- Coagulation
- Infecion
- Multiple complex plaques

**Figure 2.** Factors contributing to the “vulnerable patient.”

**Prevention and Treatment of Cardiovascular Disease**

Clinical data have clearly established the efficacy of lipid-lowering modes of therapy in reducing cardiovascular risk. First-line lipid-lowering therapy for most individuals is the initiation of therapeutic lifestyle changes (TLC). Components of TLC that have been shown to be effective in lowering LDL-C levels include dietary changes, commencement of regular physical activity, smoking cessation, and weight loss. Although a number of pharmacologic agents are available to modify lipid levels, data from multiple prospective outcomes trials have demonstrated that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the most effective agents to reduce risk of CHD. An in-depth discussion of these agents is provided elsewhere in this supplement.

Although the primary mechanism by which statins reduce CHD risk is via LDL-C reduction, the anti-inflammatory activity associated with statins may explain some of their efficacy, particularly in patients who do not have elevated cholesterol levels. The anti-inflammatory effect of statins has been demonstrated in a number of recent trials. Statins have been noted to induce activation of peroxisome proliferator-activated receptor α and increase HDL-C.

In the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, patients receiving aggressive statin therapy had a sevenfold greater reduction in CRP compared with patients receiving the more moderate regimen. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, patients had fourfold higher baseline CRP levels than those in REVERSAL (12.3 mg/L vs 2.9 mg/L). However, CRP levels still decreased by more than 80% during the 18 to 30 months of follow-up. In the acute setting, however, the decrease was not significantly different between treatment groups. The cholesterol absorption inhibitor ezetimibe, coadministered with a statin significantly reduced markers of cardiovascular risk, including CRP. This result suggests that statins with or without cholesterol absorption inhibitors demonstrate enhanced anti-inflammatory effects.

**Comment**

Lipids, particularly cholesterol, play a fundamental role in the development of CHD. A substantial volume of evidence indicates that reducing cholesterol levels reduces the risk of CHD in both primary...
and secondary prevention populations. Despite the emergence of new markers of CHD (such as CRP), LDL-C currently remains the primary target for reduction of risk of CHD. However, emerging evidence suggests the intriguing notion that the anti-inflammatory activities of lipid-lowering modes of therapy such as statins may have a more significant role in reducing risk of CHD than previously believed. However, until the relevance of these nontraditional risk factors is established in well-designed prospective outcomes trials, physicians and patients should strive to decrease CHD risk by reducing lipids through the initiation of therapeutic lifestyle changes and use of appropriate modes of lipid therapy.

References


