Endothelial function, antihyperlipidemics, statins, angiotensin-converting enzyme inhibitors also have antiatherogenic properties. Early, aggressive lipid intervention interacting oxidative and inflammatory processes. Angiotensin-converting enzyme levels, as well as by stabilizing plaques, restoring endothelial function, and countering oxidative and inflammatory processes. Angiotensin-converting enzyme inhibitors also have antiatherogenic properties. Early, aggressive lipid intervention is the key to primary and secondary prevention of CHD.

(Key words: atherosclerosis, atherosclerotic plaque, coronary heart disease, endothelial function, antihyperlipidemics, statins, angiotensin-converting enzyme inhibitors)

Recent years have witnessed significant advances in our understanding of the natural history and pathophysiology of coronary heart disease (CHD). Cardiovascular events were once thought to result primarily from arterial stenosis and occlusion due to accumulation of intraluminal atherosclerotic plaque in later life. Today, the vascular endothelium is recognized as a key factor in development of heart disease, and the endothelial changes predisposing to CHD are known to begin much earlier in life than previously thought. Major risk factors for CHD such as hyperlipidemia (particularly high levels of low-density lipoprotein cholesterol [LDL-C]), diabetes mellitus, hypertension, and smoking are all known to cause inflammatory changes that damage the endothelium or interfere with its ability to repair itself after injury.

The type and degree of endothelial damage can now be better appreciated with the use of computed tomography and magnetic resonance imaging, as well as newer techniques such as intravascular ultrasound (IVUS). Clinical studies using IVUS show that pathologic processes in the coronary arteries occur long before symptoms appear, and even before vascular changes can be seen angiographically. For example, the Pathobiology Determinates of Atherosclerosis in Youth (PDAY) study, which included 2000 autopsied persons, showed that fatty streaks and raised lesions in the coronary arteries and abdominal aorta can occur in both male and female adolescents with no known risk factors, highlighting the importance of maintaining a healthy lifestyle. In another study, the presence, extent, and distribution of atherosclerosis in the donor coronary arteries of 262 heart transplant recipients were determined using IVUS studies within weeks of transplantation. Based on measurement of intimal thickness, evidence of atherosclerosis was present in 17% of donors younger than 20 years and 71% of donors 40 to 49 years of age. The prevalence of atherosclerosis was higher than anticipated in these subjects, because the transplant donors were without overt evidence of heart disease. Results from these two recent clinical studies emphasize the need to manage risk factors for CHD in adolescence and young adulthood to prevent atherosclerosis.1,2

Results from IVUS studies suggest that angiography can greatly underestimate the extent of atherosclerosis and may not reveal important pathologic changes in arterial structure, atherosclerotic lesions, and vascular wall status.3 Manifestations of these pathologic changes evidenced by IVUS may explain why the degree of stenosis does not predict disease severity and why small increases in luminal caliber may be associated with dramatic reductions in acute cardiovascular events.3 These events are now thought to be related more to the composition and stability of atherosclerotic plaques than to luminal narrowing.3

Unstable plaques are particularly likely to rupture, leading to thrombosis. Plaque stability is influenced by many factors in addition to size. In fact, acute coronary syndromes are frequently attributable to small, lipid-laden plaques found in vessels with minimal stenosis.4 In addition to a large lipid core, unstable plaques have a thin (versus thick) fibrous cap (Figure 1) with low concentrations of smooth muscle cells and collagen.5,6 The...
integrity of this protective cap can be further affected by matrix metalloproteinas, which are collagen-degrading enzymes released by macrophages that can weaken the fibrous cap and lead to plaque rupture.5,7

Plaque stability may also be affected by the renin-angiotensin system. Patients with hyperlipidemia often have high levels of angiotensin II. This hormone facilitates oxidation and uptake of LDL by monocytes, macrophages, and endothelial cells.8 The interaction between angiotensin II and oxidized LDL is critical for the induction of endothelial dysfunction and atherogenesis.8 In addition, angiotensin-converting enzyme (ACE) activity is exaggerated in culprit lesions from patients with acute coronary syndromes, suggesting that this enzyme plays a pathophysiologic role in atherogenesis.9 Because so many factors influence plaque stability, efforts to prevent coronary events by stenting are likely to fail, as stents merely displace the fat and liquid content of plaque rather than targeting the source of the instability. As a metabolic disease, CHD generally requires drug therapy to stabilize plaques and reduce the risk of plaque rupture and thrombosis.

Role of oxidative stress and inflammation

One common denominator among the many factors that contribute to atherogenesis is oxidative stress on the endothelium, which impairs its ability to release nitric oxide, a molecule that normally acts as a kind of “nonstick coating” to prevent lipids and white blood cells from adhering to the endothelium. Without nitric oxide, endothelial injury provokes an inflammatory response that attracts macrophages and lipids, setting the stage for the development of an atherosclerotic plaque (Figure 2).

In general, risk factors for CHD can produce oxidative stress in endothelial cells by raising the intracellular concentration of free radicals. Among the classic risk factors for CHD, high cholesterol levels can inhibit nitric oxide synthesis and shift the cellular balance toward a more pro-oxidant state. This pro-oxidant state amplifies proliferation of vascular smooth muscle cells, impairs vasodilation, promotes inflammation, and activates collagen-degrading enzymes.10-12 Even in the absence of obstructive coronary artery disease, severe endothelial dysfunction is a predictor of myocardial infarction, revascularization procedures, and cardiac death.13

Novel risk factors that have been identified as endothelial cell stressors include high levels of angiotensin II, tumor necrosis factor, and oxidized LDL.11,14 Oxidative stress can be coun-
teracted by drug therapy, but another effective antioxidant is regular exercise. Although patients tend to resist it as a way of preventing heart disease, physical activity should be strongly encouraged for its wide-ranging benefits and cost-effectiveness.

The importance of inflammation in CHD is suggested by the link between the risk of a coronary event and elevated levels of C-reactive protein (CRP), an inflammatory marker. Data from the Physicians’ Health Study show that the risk of a future myocardial infarction is increased about threefold in apparently healthy men with high CRP levels. Even more striking is the fivefold increase in risk among men with an elevated CRP level and an abnormal ratio of total cholesterol to high-density lipoprotein cholesterol (HDL-C). Although the clinical applicability of CRP remains to be clarified, a high CRP level might tip the balance in favor of drug treatment in a patient with a borderline LDL-C concentration.

Inflammation is also implicated by the apparent link between chronic infections and risk of cardiovascular disease. A recent 5-year study of 826 men and women found that chronic infections increased the risk of carotid atherosclerosis, especially in those with a pronounced inflammatory response. This link is further supported by a prospective study of 890 patients with significant CHD at baseline, in which the adjusted prevalence of immunoglobulin G (IgG) antibodies to cytomegalovirus, hepatitis A virus, herpes simplex, Chlamydia pneumoniae, and Helicobacter pylori was proportional to the risk of myocardial infarction or death. After a mean of 3 years, patients with antibodies to four pathogens had a significantly lower event-free survival rate than that of those with antibodies to three or fewer pathogens. Furthermore, CRP levels were proportional to pathogen burden. Pathogen burden may be an important factor to consider when evaluating patients for risk for CHD, particularly in those with multiple risk factors.

Figure 3. Antatherogenic properties of statins.

Benefits of pharmacologic therapy
Because atherogenesis is typically silent, patients at risk must be identified and treated early in the course of the disease. Changes in diet and exercise habits are a key first step, but even patients who are most committed to maintaining a healthy diet and lifestyle often fail to normalize lipid levels and reduce risk. A multifactorial metabolic disease such as CHD warrants drug therapy that has an impact on lipid levels and other risk factors as well.

Intensive therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) reduces the incidence of CHD-related morbidity and mortality. Statins may counteract atherogenesis by several mechanisms, including plaque stabilization, improved endothelial function, and reduced thrombogenicity of endothelial cells (Figure 3). ACE inhibitors are usually thought to protect against coronary events by reducing blood pressure, yet their benefits may also be related to antioxidant or antiplatelet effects (or both), strengthening of the plaque’s fibrous cap, and improvement in endothelial function.

Plaque stabilization
Statins modestly reduce plaque size and may also strengthen the fibrous cap by preventing the death of smooth muscle cells, resulting in collagen accumulation. Lipid-lowering therapy has also been shown to secure the fibrous cap by blocking the release of tissue factor and matrix metalloproteinases (the enzymes that dissolve fibrous caps), as well as by stabilizing the plaque itself through reduction of its core lipid content. In animals fed a high-fat diet, the vascular endothelium shows tremendous macrophage infiltration with abundant matrix metalloproteinases, whereas those treated with statins are protected from both outcomes.

ACE inhibitors may help to shrink and stabilize plaques by limiting endothelial LDL uptake and attenuating proinflammatory processes, and fortifying the fibrous cap by inhibiting smooth muscle cell proliferation and migration away from the plaque.

Improved endothelial function
Research into prevention of CHD is now focusing on pathobiological processes in the endothelium, with emphasis on how classic and novel risk factors can alter endothelial cell function. As described earlier, endothelial cells under oxidative stress develop high concentrations of free radicals. This process distorts their effect on vasoactive molecules, growth regulators, matrix modulators, and extracellular matrix receptors, ultimately producing endothelial dysfunction and atherosclerosis. Fortunately, statins and ACE inhibitors appear to exert a protective effect on the endothelium.

Therapy with lipid-lowering drugs can reverse coronary artery endothelial dysfunction. This therapy appears to improve endothelial function by promoting nitric oxide synthesis, which enhances vasodilation.
enhanced vasodilation translates into a significant increase in myocardial perfusion.24

Endothelial dysfunction is partly attributable to inactivation of nitric oxide and angiotensin I (AT1) receptor stimulation by angiotensin II. In one study, an AT1-receptor antagonist administered to animals fed a diet containing 0.5% cholesterol improved endothelial function, decreased macrophage infiltration, and reduced early plaque formation.25

Decreased thrombogenicity

Based on animal studies, statins have the ability to counteract thrombogenicity and enhance the fibrinolytic potential of endothelial cells by stimulating the release of tissue plasminogen activator.26 These properties may help to both prevent progression of atherosclerosis26 and reduce the risk of recurrent thrombosis in the setting of acute coronary syndrome. In addition, statins have anti-inflammatory effects, resulting in reductions in levels of CRP among hyperlipidemic patients with CHD and reductions in macrophage proliferation and activation.27,28

Other potential benefits

Another mode of action observed with statin therapy involves the reduction of the thickness of the carotid intima media, a measurement that may correlate to cardiovascular risk factors and may be predictive of both CHD and brain infarction.29,30 In the Atorvastatin versus Simvastatin in Atherosclerosis Progression (ASAP) study,39 325 patients with familial hypercholesterolemia were randomly assigned to 2 years of intensive therapy with high-dose atorvastatin calcium (80 mg/d) or standard therapy with a conventional dose of simvastatin (40 mg/d). Thickness of the carotid intima media decreased significantly in those who received intensive lipid-lowering therapy and increased significantly in those who received standard therapy.29

In addition, antihyperlipemic agents show potential benefit in the management of left ventricular hypertrophy (LVH). High lipid levels may induce or worsen LVH by stimulating the release of angiotensin II, which is a growth factor for heart muscle. In one 20-year follow-up of 475 men from the general population, dyslipidemia and high dietary fat intake at age 50 years predicted the prevalence of LVH at age 70 years.31 In theory, lipid-lowering drugs might arrest or reverse these processes.

Finally, long-term statin therapy has recently been shown to significantly reduce the risk of diabetes in men, probably as a result of its triglyceride-lowering effects, anti-inflammatory properties, and endothelial benefits.32 This finding emphasizes the need for treating the many interrelated factors in the cluster of disorders known as the metabolic syndrome.

Comment

Coronary heart disease is now understood to be a lifelong process rooted in inflammation, thrombosis, and plaque instability. Pathogenic changes occur well before the appearance of symptoms and may be undetectable even on angiography. Strategies for treatment and prevention of future events must include management of risk factors—most important, lowering LDL-C levels to or below those recommended in the National Cholesterol Education Program (NCEP) Expert Panel (Adult Treatment Panel III [ATP III]) guidelines.33 However, as primary care providers, it is important to assess and manage a patient's global risk—the sum of his or her risk factors—on an individual basis, meaning that all the patient’s risk factors should be taken into consideration when developing a comprehensive treatment plan (that is, stop smoking, lose weight, decrease lipids, control blood pressure)

Lifestyle modification is essential for all patients, and they should be encouraged to adhere to dietary and exercise regimens even if drug therapy is ultimately required. Early intervention with drug therapy (particularly statins) is a key component in the care of patients at risk for CHD. Effective drug therapy addresses both classic and novel risk factors by improving plaque stability, endothelial function, and other vascular activities. The interaction of the vascular mechanisms associated with statin therapy has formed the basis of a novel therapeutic strategy for early lipid intervention immediately after acute coronary syndromes to prevent recurrent ischemic events. In combination with lifestyle modification and management of coexisting risk factors such as hypertension and diabetes, intensive medical therapy should significantly reduce the risk of ischemic events and CHD-related mortality.

References


