Statins as cardioprotective agents

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Several processes contribute to the initiation and progression of atherosclerosis, including plaque formation, endothelial dysfunction, vascular inflammation, and uptake of low-density lipoprotein (LDL) cholesterol by receptors and macrophages. LDL cholesterol ultimately constitutes the lipid core of atherosclerotic plaques. HMG-CoA reductase inhibitors (statins) reduce LDL by directly inhibiting the key enzyme in synthesis of cholesterol—HMG-CoA reductase—and upregulating the expression of LDL receptors, which facilitate clearing LDL from the circulation. Statins have also been shown to reduce levels of total cholesterol, increase levels of high-density lipoprotein (HDL) cholesterol, and lower triglycerides.[1-5]

Reducing levels of LDL cholesterol with statins as a primary or secondary preventive measure reduces coronary events and death from coronary heart disease (CHD).[3,4] Because of the clear association between hypercholesterolemia and CHD, the assumption that the benefits seen in CHD patients treated with statins is primarily due to LDL-lowering effects is reasonable. Multiple studies have shown that a decrease in elevated LDL cholesterol results in decreased cardiovascular morbidity and mortality in patients with elevated serum cholesterol with or without atherosclerosis.[3,4,6,7]

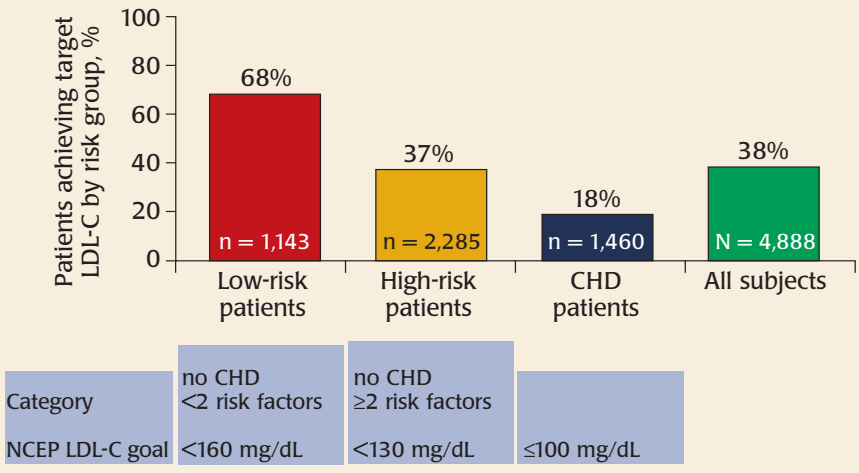
Despite the clear benefits associated with lipid-lowering therapy, many dyslipidemic patients are not adequately treated. The Lipid Treatment Assessment Project (L-TAP) investigators concluded that more aggressive lipid-lowering treatment is needed. In L-TAP, only 38% of hyperlipidemic patients achieved target LDL levels after at least 3 months of treatment (Figure). Only 18% of those with documented CHD and 37% of those with more than two CHD risk factors achieved LDL cholesterol goals. Among low-risk patients, or those with fewer than two CHD risk factors, 68% reached LDL target levels.[8]

The third report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) guidelines state that an LDL cholesterol level below 100 mg/dL is optimal.[9]

Yet practical considerations, in-

FIGURE

The Lipid Treatment Assessment Project (L-TAP): Patients on nondrug and drug therapy who reached target LDL-C goals



LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; NCEP = National Cholesterol Education Program.
Source: Pearson TA et al. *Arch Intern Med* 2000;160:459.

cluding cost, indicate that not everyone can achieve such a low LDL cholesterol level. ATP III specifies goals for several levels of risk to help health professionals counsel patients on goals appropriate for their level of risk. Those at highest risk clearly deserve the most intensive efforts.

- *Highest risk.* Those with CHD and CHD "equivalents" (composed of those with equivalent 10-year risk for hard CHD, patients with diabetes, atherosclerotic vascular disease, multiple risk factors with 10-year hard CHD risk >20%). For these patients, the LDL cholesterol goal is < 100 mg/dL.
- *Those with two or more risk factors and 10-year hard CHD risk of 10% to 20%.* For these patients, the LDL cholesterol goal is < 130 mg/dL and drug treatment is considered if LDL cholesterol remains above 130 mg/dL despite 3 months of therapeutic lifestyle change.
- *For those with two or more risk factors and 10-year hard CHD risk of < 10%.* For these patients, the LDL cholesterol goal is < 130 mg/dL, but drug treatment is considered only if LDL cholesterol remains above 160 mg/dL despite 3 months of therapeutic lifestyle change.
- *Low near-term risk.* Those with 10-year hard CHD risk of < 10% (usually those with 0-1 risk factor).

Effects of statin treatment

The majority of acute myocardial infarctions (MIs) arise from atherosclerotic lesions that are mild to moderate in severity. Statins have been shown to decrease mortality from coronary events 25% to 30%.[5] Statins possess a variety of proven benefits, as summarized in Table 1.

In the Scandinavian Simvastatin Survival Study (4S) and the recently presented Heart Protection Study, patients with the lowest baseline LDL level benefited from simvastatin treatment as much as those with higher levels of LDL.[2] The Cholesterol and Recurrent Events (CARE) trial showed a significant benefit from statin therapy in CHD patients compared with subjects with comparable serum cholesterol levels receiving placebo.[4] In an analysis of the role of high-sensitivity C-reactive protein in the primary prevention trial known as the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), Ridker and colleagues found that C-reactive protein predicted benefit from lovastatin, even in those with cholesterol/HDL ratios below the median.[10] Brown and colleagues found that patients treated with statins had a significantly decreased risk of MI compared with patients receiving other cholesterol-lowering treatments, despite similar decreases in cholesterol.[11]

Several clinical trials have also shown that lipid-lowering therapy leads to only moderate changes in arterial narrowing and that the reduction in clinical events seen with such therapy is much greater than would be expected with these changes alone.[2,6,11] Protective effects have been seen well in advance of evidence of plaque regression, indicating that mechanisms other than a reduction in lesion size and vessel stenosis may be responsible.[12]

Proposed cardioprotective effects of statins

Potential mechanisms by which statins may contribute to decreased cardiovascular events include atherosclerotic plaque stabilization and repair, suppression of the inflammatory response, improved endothelial function, and antithrombotic effects (Table 2).

Atherosclerotic plaque stabilization and repair. Atherosclerotic plaque rupture resulting in thrombotic occlusion of a vessel is a major factor in the precipitation of cardiovascular events. Characteristics that make plaques increasingly likely to rupture include a large lipid pool, an increased number of inflammatory cells in the vulnerable shoulder region of plaques, increased neovascularization, and a thin fibrous cap with few smooth muscle cells and collagen fibers.[13,14] Because the fibrous cap separates the lipid-filled core of the plaque from circulating blood, it plays a critical role in plaque stability. Cap strength depends on the presence and organization of connective tissue proteins synthesized by smooth muscle cells, including collagen, elastin, and proteoglycans.[13] Macrophages release matrix metalloproteinases, which degrade the collagen fibers that are largely responsible for fibrous cap strength.

Statins appear to stabilize atherosclerotic plaques by inhibiting several processes that contribute to plaque vulnerability. Studies have shown that statins modify the properties of the lipid core, decreasing lipid and inflammatory cell content in plaques.[12,15] These processes are slow, however, and have a minimal effect on lumen size.[11] Corti and colleagues showed that lipid lowering with simvastatin was associated with significant regression of atherosclerotic lesions, with effects seen after 12 months of therapy.[16] Although subjects had significant reductions in vessel wall thickness and area in both aortic and carotid arteries, there were no changes in lumen area.

The beneficial effects of statins on plaque stability are principally attributable to LDL cholesterol lowering. Other benefits may be due to pleotropic effects, but none have been proved to be independent of LDL lowering. These benefits include increased collagen accumulation and reinforcement of the fibrous skeleton, inhibition of lipoprotein oxidation, decreased macrophage

accumulation, and inhibition of enzymes that degrade the extracellular matrix, including matrix metalloproteinases and tissue factor.[12,15,17] By increasing plaque stability and decreasing risk of rupture, these effects of statins may contribute to a decrease in coronary events.

Decreased vascular inflammation. Inflammation of the vessel wall plays a major role in atherosclerosis and, ultimately, atherothrombosis by contributing to vessel constriction, spasm, and thrombus formation.[18] In brief, lipoproteins contribute to atherosclerotic plaque development by promoting the inflammatory response in the vascular endothelium,[18] and this leads to production of proinflammatory cytokines by macrophages and T lymphocytes. T cells produce interferon-gamma, which inhibits smooth muscle cell proliferation, synthesis of collagen in the fibrous cap, and maintenance and repair of the matrix of vulnerable plaques. Matrix metalloproteinases expressed by macrophages also contribute to the degradation of existing collagen and other components of the fibrous cap. Increased inflammatory cells can lead to degradation of the extracellular matrix, diminished endothelial function, and thrombosis.[14,19] Statins are thought to reduce the inflammatory process by decreasing the number of inflammatory cells in atherosclerotic plaques.[1]

Elevated high-sensitivity C-reactive protein, an acute phase reactant that serves as a clinical marker of inflammation, has been shown to be an important predictor of CHD and is elevated in patients with ischemia, MI, and CHD, as well as in patients with risk factors such as diabetes and metabolic syndrome.[20,21] In the Physicians Health Study, high-sensitivity C-reactive protein was a significant predictor of MI, independent of other risk factors, including LDL cholesterol levels.[22] Several studies have shown retrospectively that statins lower high-sensitivity C-reactive protein in hypercholesterolemic patients.[4,7,23] In a post hoc analysis, CARE trial patients with elevated levels of high-sensitivity C-reactive protein who were randomly assigned to placebo had a significantly greater risk of a recurrent coronary event than those with similar levels assigned to pravastatin.[4] The effect of pravastatin was greater among patients with evidence of inflammation than those without, independent of baseline LDL levels. This suggests that statins may inhibit inflammatory processes that promote the acute phase response. Moreover, in AFCAPS/TexCAPS, the large-scale primary prevention trial mentioned previously, in which men and women with elevated LDL cholesterol and low HDL cholesterol were chosen as subjects, elevated high-sensitivity C-reactive protein levels identified those who benefitted from statin therapy, even though the cholesterol/HDL ratio was below median.[10] As Ridker proposed, a large-scale, randomized clinical trial of statins in subjects without overt elevations of LDL cholesterol but with evidence of elevated high-sensitivity C-reactive protein are needed to directly test the hypothesis that statin's anti-inflammatory effects may be beneficial even in the absence of raised LDL cholesterol levels.[24]

Coronary endothelial function and vasodilation. Endothelium-derived nitric oxide plays an important role in endothelial function. Nitric oxide inhibits atherogenesis by inhibiting vasoconstriction, monocyte adhesion to the endothelium, smooth muscle cell proliferation, and platelet aggregation, as well as preventing oxidation of LDL. Decreased nitric oxide production leads to a reduced ability to inhibit oxidative stress within the endothelial cell. Oxidized LDL downregulates endothelial nitric oxide synthase (eNOS), which, in turn, inhibits endothelium-derived relaxing factor. Impairment of the release

TABLE 1

Cardioprotective effects of statins

- Lipids—Statins lower LDL cholesterol levels, increase HDL cholesterol levels, decrease triglycerides, and decrease remnant particles.
- Angiographic changes—Statin treatment results in positive wall remodeling, but the clinical benefit is much greater than expected based on the minimal change in lumen diameter.
- Clinical event reduction—Statins reduce total mortality in those with the highest LDL cholesterol levels, as shown in 4S and LIPID.[2,3] These agents also decrease mortality from fatal and nonfatal MI, as shown in 4S, LIPID, WOSCOPS, and AFCAPS/TexCAPS.[2,3,6,7]

LDL = low-density lipoprotein; HDL = high-density lipoprotein; 4S = Scandinavian Simvastatin Survival Study; LIPID = Long-term Intervention with Pravastatin in Ischaemic Disease; MI = myocardial infarction; WOSCOPS = West of Scotland Coronary Prevention Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study.

TABLE 2

Proposed cardioprotective mechanisms of statins

- Atherosclerotic plaque stabilization and repair
- Anti-inflammatory effects
- Improved coronary endothelial function
- Antithrombotic effects

or activity of endothelium-derived relaxing factor results in endothelial dysfunction, a major contributor to the atherosclerotic process.[1,24-26]

Elevated LDL has been linked to decreased endothelial function; in one study, a significant improvement in endothelial function was observed after a single treatment of LDL apheresis.[27] Improved endothelial function has also been seen with statin treatment. This effect has been attributed primarily to lowered serum cholesterol levels. Several studies, however, indicate that other mechanisms may be partly responsible for these beneficial effects.

Treasure and colleagues demonstrated a significant improvement in endothelial function in the coronary arteries of patients with atherosclerosis after 6 months of lipid-lowering treatment with lovastatin.[28] This study suggested a role for statin therapy in the alleviation of ischemic symptoms by decreasing vasoconstriction and improving the vasodilatory response. Laufs and colleagues showed that simvastatin therapy led to increased eNOS expression and activity in the presence of oxidized LDL, independent of extracellular cholesterol concentration, and prevented downregulation of eNOS by oxidized LDL.[26] Kaesemeyer and colleagues showed that pravastatin stimulated nitric oxide production in cultured endothelial cells within minutes, far sooner than a reduction in cholesterol levels could occur, again suggesting a mechanism independent of LDL lowering.[25]

Other proposed beneficial effects of statins on endothelial function include decreased production of reactive oxygen species, resulting in decreased oxidative stress and enhanced endothelium-dependent relaxation, and inhibited synthesis of endothelin-1 in endothelial cells, leading to decreased vasoconstriction.[14,26,28,29] Statins appear to have multiple beneficial effects on the vascular endothelium, leading to decreased vascular reactivity and improved myocardial perfusion and potentially providing relief from ischemic symptoms.

Antithrombotic effects. Acute coronary syndromes are usually caused by thrombus formation initiated by rupture of atherosclerotic plaques, a process mediated by platelet activity. Platelet reactivity to vascular injury is increased in the presence of high levels of serum lipids.[30] High serum cholesterol levels contribute to increased platelet aggregation, adhesion, and hypercoagulability at sites of plaque rupture. These effects are thought to correlate with increased cholesterol content in the platelet membranes of patients with hypercholesterolemia. Some studies suggest that statins have several inhibitory effects on this process, including decreasing the cholesterol content of erythrocytes and platelets, potentially causing these cells to be less thrombogenic.[31,32]

Although several studies have suggested antithrombotic actions of statins, the evidence is not as compelling as for the other pleiotropic effects proposed.[33] One study showed a 21% decrease in thrombus area after 3 months of treatment with pravastatin and a 34% decrease after 6 months in patients without CHD. Among patients with CHD, thrombus area decreased by 13% after 3 months and 16% after 6 months.[34]

Conclusion

The LDL-lowering effects of statins are well established and of enough benefit to make statins the drugs of choice for lowering lipid levels in patients with CHD or in those at high risk. Treatment to target levels as recommended by ATP III is associated with decreased morbidity and mortality, and this is supported by an extensive clinical trial database of male and female subjects with varying degrees of risk and a wide range of LDL cholesterol values. Although developing evidence suggests a role for statins in reducing CHD risk beyond that of LDL cholesterol lowering, further research is needed to determine whether these effects indeed result in enough cardioprotective benefits to warrant use of statins in patients not specified by ATP III. At a minimum, the increased use of statins as directed by ATP III holds the promise for greatly limiting the CHD epidemic. ■

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