Cardiovascular Drugs

Current Perspectives on Statins

David J. Maron, MD; Sergio Fazio, MD, PhD; MacRae F. Linton, MD

Abstract—Statins (HMG-CoA reductase inhibitors) are used widely for the treatment of hypercholesterolemia. They inhibit HMG-CoA reductase competitively, reduce LDL levels more than other cholesterol-lowering drugs, and lower triglyceride levels in hypertriglyceridemic patients. Statins are well tolerated and have an excellent safety record. Clinical trials in patients with and without coronary heart disease and with and without high cholesterol have demonstrated consistently that statins reduce the relative risk of major coronary events by ~30% and produce a greater absolute benefit in patients with higher baseline risk. Proposed mechanisms include favorable effects on plasma lipoproteins, endothelial function, plaque architecture and stability, thrombosis, and inflammation. Mechanisms independent of LDL lowering may play an important role in the clinical benefits conferred by these drugs and may ultimately broaden their indication from lipid-lowering to antiatherogenic agents. (Circulation. 2000;101:207-213.)

Key Words: statins ■ hypercholesterolemia ■ trials ■ atherosclerosis ■ coronary disease

The advent of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, has revolutionized the treatment of hypercholesterolemia. Statins are the most commonly prescribed agents for the treatment of hypercholesterolemia because of their efficacy in reducing LDL and their excellent tolerability and safety. This review examines the pharmacology, clinical trials, and proposed mechanisms of clinical benefits of statins.

Mechanism of Action
Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis.1 The resultant reduction in hepatocyte cholesterol concentration triggers increased expression of hepatic LDL receptors, which clear LDL and LDL precursors from the circulation.2 Statins may inhibit hepatic synthesis of apolipoprotein B-100 and decrease the synthesis and secretion of triglyceride-rich lipoproteins.3,4 Although the primary mechanism of action for LDL lowering is enhanced clearance of LDL via LDL receptors, reduced hepatic production and secretion of lipoproteins may explain the observation that atorvastatin and simvastatin are capable of lowering LDL in patients with homozygous familial hypercholesterolemia who have no functional LDL receptors.5,6

Pharmacology
Lovastatin, pravastatin, and simvastatin are derived from fungal fermentation. Fluvastatin, atorvastatin, and cerivastatin are entirely synthetic. Lovastatin, simvastatin, atorvastatin, and cerivastatin utilize the cytochrome P 450 (CYP) 3A4 pathway for metabolism or biotransformation.7 Fluvastatin metabolism occurs via CYP2C9, and pravastatin does not use the CYP pathway significantly.8 Pravastatin is extremely hydrophilic compared with other statins except for fluvastatin, which has intermediate physicochemical properties. This difference in hydrophilicity has not been demonstrated to have clinical significance.

Effects on Plasma Lipids and Lipoproteins
Statins are highly effective in reducing LDL and modestly effective in raising HDL. Triglyceride lowering is directly proportional to the baseline triglyceride level and to the LDL-lowering potency of the drug.9,10 Table 1 shows the comparative efficacy and potency of statins on lipids and lipoproteins in patients without hypertriglyceridemia. In general, LDL is reduced an additional 7% with each doubling of the dose.11 Statins do not lower lipoprotein(a) [Lp(a)] concentration.16 Statins are also ineffective in modifying the size and density of LDL.17

Adverse Effects
As a class, statins are well tolerated, and there are no known differences in safety. The most important adverse effects are liver and muscle toxicity. The incidence of transaminase increases greater than 3-fold is ~1% for all statins and is dose related.18–22 If this occurs, the drug should be stopped; transaminase levels generally return to baseline within 2 to 3 months.19

The major adverse effect of statins is myopathy, defined as muscle pain or weakness associated with creatine kinase (CK) levels higher than 10 times the upper limit of normal. Myopathy with statin monotherapy occurs in ~1 in 1000 patients and is dose related. Symptoms may include fever and malaise, and cases have been associated with elevated serum statin drug levels. Rhabdomyolysis and acute renal failure may result if myopathy is not recognized and the drug is
continued.23 If recognized promptly and the drug is stopped, the myopathy is reversible, and acute renal failure is unlikely to ensue.

The combination of statins with certain drugs that are CYP3A4 inhibitors or substrates increases the risk of myopathy, presumably by inhibiting the metabolism of the statin and increasing its blood concentration. These drugs include cyclosporine,24 erythromycin,7 clarithromycin,7 nefazodone,7 azole antifungals,7 protease inhibitors, and mibefradil (with lovastatin and simvastatin).25 Fibrates and niacin also increase the risk of statin-induced myopathy via a mechanism that does not increase plasma statin concentrations.26 Myopathy has been reported with pravastatin even though pravastatin is not metabolized significantly by CYP.27 Statins with and without CYP metabolism have been used safely in low doses in combination with cyclosporine in heart transplant patients.28,29 Other risk factors for statin-induced myopathy are hepatic dysfunction, renal insufficiency, hypothyroidism, advanced age, and serious infection.

Monitoring for Liver and Muscle Toxicity
Both baseline and periodic monitoring of liver transaminases are recommended. Baseline measurement of CK may be useful. Small, clinically insignificant increases in transaminases and CK are commonly observed with all statins.12 Routine follow-up CK measurements are generally not recommended, because severe myopathy usually occurs suddenly and is not preceded by chronic elevations of CK.4 Patients should be instructed to contact their physician if they experience muscle pain or weakness, severe malaise, or flu-like symptoms. If this occurs, statin therapy should be discontinued, and the CK level should be measured without delay. Many experts would consider rechallenge with a different statin after the CK level returns to normal, beginning with a low dose and monitoring closely for symptoms and elevated CK.

Combination With Other Lipid-Lowering Drugs
The combination of statins with other lipid-lowering medications is sometimes necessary to achieve recommended target lipoprotein levels. The combination of a statin with a bile acid–binding resin is highly effective for LDL lowering, because these drugs work via different mechanisms to stimulate LDL receptor clearance of LDL.2 On occasion, triple therapy with statin, resin, and niacin is required to achieve satisfactory LDL control. Although the addition of a statin to gemfibrozil or niacin increases the risk of myopathy, statins administered in low doses have been found to be safe in combination with fibrates30 and with niacin.31 Combination drug therapy associated with increased risk of myopathy should not be given unless the indication is compelling (coronary heart disease [CHD] or other high-risk condition) and the patient is reliable and fully informed of the possible side effects. The efficacy of statin-fibrate or statin-niacin combination on clinical events is not known.

Clinical Trials
Secondary-Prevention Studies
The secondary-prevention trials are summarized in Table 2. The Scandinavian Simvastatin Survival Study (4S) demonstrated a convincing reduction in total mortality among the subjects in the simvastatin group.15 The reduction in coronary events in 4S was observed in both men and women, in individuals younger and older than 60 years of age, and in subjects with other risk factors, including smoking, hypertension, and diabetes.32 In addition, 4S reported a 30% reduction in cerebrovascular events.

The Cholesterol And Recurrent Events (CARE) study extended the findings of 4S to individuals with average cholesterol levels.21 Post hoc analysis revealed no reduction in coronary events among patients in the treatment group with baseline LDL levels below 125 mg/dL, which led the authors to suggest that statin treatment of CHD patients with low LDL levels may not be warranted. Diabetic subjects treated with pravastatin (n = 282) had a 25% reduction in major coronary events compared with diabetic subjects taking placebo.21

The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study extended the findings of CARE by including subjects with unstable angina and by using CHD death as the primary end point, which was reduced by 24% in the pravastatin group.33

Primary-Prevention Studies
The primary-prevention trials are summarized in Table 2. The West of Scotland Coronary Prevention Study (WOSCOPS)
found a significant reduction in the primary end point of coronary death and nonfatal myocardial infarction after 5 years.20 Because of the lower baseline risk in the WOSCOPS population, the number needed to treat (NNT) to prevent 1 major coronary event (NNT=100/absolute risk reduction) was higher (NNT=42) than that found in 4S (NNT=15), CARE (NNT=33), or LIPID (NNT=28). In a subgroup analysis, high-risk individuals (>2% event rate per year) were those younger than 55 years of age and with vascular disease, smoking, or minor ECG abnormalities, or older hypercholesterolemic individuals with any additional risk factor.36 If treatment had been focused on these high-risk individuals, the NNT would have been reduced from 42 to 17.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) found that lovastatin prevented first acute major coronary events in men and women with average LDL levels and low HDL levels.32 Individuals in the 2 lowest HDL tertiles (HDL <40 mg/dL) benefited the most. This study raises the question of whether the position of the National Cholesterol Education Program (NCEP) should be altered to recommend statin treatment in patients whose risk profile includes HDL lower than 40 mg/dL.

Effects of Statins on Cerebrovascular and Peripheral Vascular Disease

Analysis of 45 prospective observational cohorts that reported 13 397 strokes in 450 000 people demonstrated no independent association of baseline total cholesterol level and risk of stroke, except perhaps in individuals younger than 45 years of age.35 Two meta-analyses found secondary-prevention trials produced a significant reduction in cerebrovascular events, whereas primary prevention resulted in a nonsignificant reduction in stroke rate.36,37 Trials that used serial B-mode carotid ultrasound in patients with and without CHD showed that statins slow progression and induce regression of carotid atherosclerosis.38,39

Although pravastatin did not affect femoral atherosclerosis in a primary-prevention setting,39 it significantly reduced the intima-media thickness of the common femoral artery in subjects with coronary artery disease.39a Simvastatin was also shown to be beneficial in intermittent claudication.40

Angiographic Trials

Statins slow the progression and induce the regression of coronary atherosclerosis, reduce the formation of new lesions, and reduce the incidence of coronary events.41 Although the absolute change in arterial narrowing is relatively small, the frequency of cardiovascular events is decreased substantially in most of these studies. This apparent disparity between the small degree of angiographic change and the relatively large differences in clinical event rates led to the concept of plaque stabilization and a profound change in our understanding of the biology of the atherosclerotic plaque.42

Mechanisms for Clinical Benefits

Effects on Endothelial Function

Hypercholesterolemia reduces endothelial production and increases degradation of nitric oxide (NO).43 Cholesterol lowering by statins44,45 results in significant improvement in endothelial function. Both pravastatin and lovastatin significantly reduce the frequency and intensity of ischemic episodes as detected by 48-hour Holter monitoring after as little as 4 months of therapy.46,47 The effects of statins on endothelial function may be partially independent of cholesterol lowering. Both simvastatin and lovastatin induce transcriptional activation of the NO synthase gene in human endothelial cells in vitro.48 Endothelial function improves in primates receiving a dose of pravastatin that does not reduce LDL.49 Furthermore, both simvastatin and lovastatin exert a dose-dependent protective effect in an experimental stroke model, mediated by increased production of endothelial NO synthase rather than cholesterol lowering.50

Another relevant observation comes from 4S and CARE, in which simvastatin and pravastatin reduced LDL to different degrees (35% and 28%, respectively) with different effects on major coronary events (32% versus 23% reduction, respec-

<table>
<thead>
<tr>
<th>TABLE 2. Clinical Outcome Studies Using Statins</th>
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<tr>
<td>Study, n (% Women)</td>
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<td>---------------------</td>
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<tr>
<td>Secondary-prevention trials</td>
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<tr>
<td>4S,15 4444 (19) Simvastatin 20–40 mg/d</td>
</tr>
<tr>
<td>CARE,21 4159 (14) Pravastatin 40 mg/d</td>
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<tr>
<td>LIPID,33 9014 (17) Pravastatin 40 mg/d</td>
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<tr>
<td>Primary-prevention trials</td>
</tr>
<tr>
<td>WOSCOPS,20 6595 (0) Pravastatin 40 mg/d</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS,22 6605 (15) Lovastatin 20–40 mg/d</td>
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*On-trial LDL-C values are calculated from published data.†Results for CABG; the need for PTCA was reduced by 19% (P=0.024).

NNT indicates number needed to treat to prevent 1 major coronary event (100/absolute risk reduction).
tively), yet the effect on stroke and transient ischemic attack was similar (28% and 31% reduction, respectively). These observations argue in favor of a direct, non–LDL-mediated effect of statins on endothelial function.

Effects on the Cellular Components of Atherosclerotic Plaque
Statins can decrease smooth muscle cell growth in vitro at pharmacological doses. Additionally, both simvastatin and pravastatin reduce the proliferation of macrophages induced by oxidized LDL in vitro and reduce the accumulation of cholesteryl esters in macrophages exposed to oxidized LDL. It is well established that statins inhibit the growth of lymphocytes and other blood mononuclear cells via multiple pathways unrelated to cholesterol metabolism, an effect whose therapeutic relevance is currently being investigated in patients with leukemia.

Effects on Thrombosis and Inflammation
Statins may affect thrombus formation, erythrocyte deformability, and levels of plasminogen activator inhibitor-1 and fibrinogen, with possible substantial differences among the different molecules. A recent subanalysis of the CARE trial showed that pravastatin lowers the levels of C-reactive protein and eliminates the higher risk of cardiovascular events associated with this inflammatory marker. Pravastatin also reduced the incidence of organ rejection and the cytotoxicity of natural killer cells in recipients of heart and kidney transplants.

Unresolved Questions
Correlation Between Degree of Cholesterol Lowering and Clinical Benefits
The significant clinical benefits observed in the large clinical trials with statins could be due entirely to the reduction in LDL. Several facts support this position. First, the clinical effects of treatment in 4S (simvastatin lowered LDL by 35%) were much stronger than those observed in CARE (pravastatin lowered LDL by 28%). Second, the Post Coronary Artery Bypass Graft (Post CABG) demonstrated that the aggressive reduction of LDL with lovastatin (to ≈95 mg/dL) produced better angiographic outcomes and reduced the rate of revascularization procedures compared with a more moderate LDL reduction (to ≈135 mg/dL). Also, the magnitude of benefit obtained in these major trials is comparable to that reported in the Program On Surgical Control of Hyperlipidemia (POSCH), in which ileal bypass was used to produce a 37% reduction in LDL levels.

However, attributing the different clinical results in 4S and CARE simply to different degrees of LDL lowering may be misleading because of the much lower baseline LDL level in the CARE subjects and the consequently much higher baseline risk of CHD recurrences and death in the 4S subjects. In fact, when a group of >500 CARE subjects was selected for enrollment characteristics similar to those of the 4S inclusion criteria (higher LDL and higher risk), the effect of pravastatin on clinical outcomes was similar to that of simvastatin, despite a 10 percentage-point smaller reduction in LDL produced in the CARE subjects compared with 4S subjects. Additionally, the better angiographic results obtained by aggressive treatment of LDL in the Post CABG study did not translate into reduction in coronary events or death. Finally, no significant effects on event rates were detected in the first 4 years of POSCH, which suggests that the anatomic changes induced on the plaque by a substantial cholesterol reduction take 5 years to translate into clinical benefits.

The nature of the correlation between the extent of cholesterol reduction with statins and the degree of clinical benefit is controversial. Post hoc analyses of the WOSCOPS, CARE, and 4S studies have resulted in conflicting reports. In WOSCOPS, the reduction in the rate of fatal and nonfatal CHD was related to LDL lowering up to a 24% level, but no additional benefits were observed for reductions in LDL as great as 39%. Similarly, the relative risk of an end point in CARE was progressively reduced with LDL levels declining from 140 to 120 mg/dL, but additional lowering of LDL did not produce additional risk reduction. On the other hand, the relationship between cholesterol reduction and event reduction in 4S was curvilinear and never reached a threshold.

Although apparently divergent, these results could be a function of global risk and the baseline LDL level in the populations studied (Figure). The benefit of LDL lowering may be limited by the risk imposed by other factors unrelated to LDL. Thus, the shape of the correlation curve may be mostly a function of the baseline risk in the population studied. If this interpretation is correct, one can postulate that a moderate reduction in LDL (≈25%) will produce maximum benefits in moderate-risk populations, whereas more aggres-
sive reductions in LDL to the levels recommended by the NCEP guidelines or beyond would produce additional benefits in high-risk hypercholesterolemic populations.64

Clinical Recommendations

Patients With Atherosclerosis
It is now accepted as a standard of care to lower LDL to <100 mg/dL in patients with atherosclerosis. Given the relatively small number of CHD patients with untreated LDL below this level and poor physician compliance with NCEP guidelines, and considering that non-LDL effects of statins may confer additional protection, the use of statins in all patients with atherosclerosis should be considered. Treatment in these patients should be initiated at the earliest opportunity, such as the time of diagnosis of an acute coronary or cerebrovascular event.

Patients With Diabetes
The risk of a major coronary event is as high in diabetic subjects without known CHD as in nondiabetic survivors of myocardial infarction.65 Data from both 4S and CARE show that the absolute risk reduction induced by statin treatment was larger in diabetic than in nondiabetic subjects.21,32 For this reason, LDL lowering is now recognized as the first priority in the control of diabetic dyslipidemia,66 and statin treatment should be implemented in the majority of type 2 diabetic patients with LDL >100 mg/dL.

Asymptomatic Patients With Multiple Risk Factors
Statin therapy should be prioritized according to the patient’s global risk. It is evident that among asymptomatic individuals, the absolute benefit of therapy with statins is greatest for subjects with the highest baseline risk. If the level of absolute risk deserving aggressive intervention is ≥2% per year,67 and the expected risk reduction by statin treatment is ≈30%, then the target NNT in practice would be 33 over 5 years or lower. Along this line of thinking, statins may be seen as antithromogenic agents that will affect overall CHD risk even when the LDL level is not the most prominent problem within the risk profile.

Patients With Moderate Hypertriglyceridemia or Combined Hyperlipidemia
A recent consensus statement advocates the use of statins as first-line treatment in high-risk patients with triglyceride levels below 500 mg/dL.4 The combination of low-dose statin with nicotinic acid or fibrates for combined hyperlipidemia is a safe approach when performed with appropriate monitoring and after careful patient education.68 Statins are not appropriate first-line therapy in individuals with severe hypertriglyceridemia.

Patients With Low HDL
Data from 4S,69 CARE,21 and AFCAPS/TexCAPS22 show impressive clinical benefits in subgroups with low levels of HDL. These results suggest that statin treatment may be appropriate for patients with low HDL levels not simply because of the LDL lowering and direct arterial wall effects, but possibly because of the increase in HDL. Given the combined effect of statins on LDL and HDL, it is reasonable to use the ratio of total cholesterol to HDL, as recommended by the Canadian guidelines,70 with a goal of <5 in high-risk and <4 in very-high-risk individuals.

Future Directions
Within the next few years, we will learn whether statins produce a benefit in the setting of acute coronary syndromes and how statin therapy, alone or as a major component of medical therapy, compares with revascularization procedures for patients with stable coronary disease. Indeed, a recent trial71 found that high-dose atorvastatin was at least as effective as angioplasty plus usual care in reducing coronary events in patients with stable CHD. Another important area of inquiry will be the evaluation of statin therapy in the prevention of stroke in subjects at high risk for cerebrovascular events.

Although statins are cost-effective in high-risk groups,72 they are vastly underutilized among patients with coronary disease.73 It is critically important that practices become organized so that high-risk patients are systematically identified and treated. Risk assessment is equally important to identify patients at the lower end of the risk spectrum, when the cost of statin therapy may not be justified.

Our understanding of the pharmacological effects of statins is evolving toward the realization that these agents do more than simply lower cholesterol. Similar to the ACE inhibitors, whose role as antihypertensive agents is now surpassed by their effects on cardiac and renal function, statins may produce benefits both by decreasing cholesterol and by lipid-independent mechanisms, and they are poised to become invaluable tools in the prevention and management of CHD.

Acknowledgments
Dr. Fazio and Linton are Established Investigators of the American Heart Association and are supported by American Heart Association Grants-in-Aid 95011450 and 9750728 and by National Institutes of Health grants HL-57986 and HL-53989.

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Circulation. 2000;101:207-213
doi: 10.1161/01.CIR.101.2.207
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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