

Statin Treatment in Diabetes Mellitus

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As we mark the tenth anniversary of the publication of the Diabetes Control and Complications Trial and the fifth anniversary of the United Kingdom Prospective Diabetes Study, studies which so clearly demonstrate the role of glycemic control in the prevention and delay of microvascular complications, it is interesting to consider what fundamental new concepts in diabetes care have developed. Since the 1970s, there have been substantial epidemiological data demonstrating that cardiovascular diseases (here defined as ischemic heart disease, stroke, and peripheral vascular disease) constitute the primary cause of morbidity and mortality in patients with diabetes. In fact, at least 60% and arguably 80% of people with diabetes will eventually succumb to cardiovascular disease (CVD).

However, because patients with diabetes were largely excluded from randomized clinical trials that evaluated the role of cardiovascular risk factor intervention to reduce CVD, the evidence that cardiovascular events and death can be prevented or delayed in patients with diabetes by antiplatelet treatment, blood pressure reduction, and lipid-lowering therapy has been slow in developing. Aspirin therapy was demonstrated to reduce CVD events in the Early Treatment Diabetic Retinopathy Study (ETDRS), with a publication in 1992.¹ The most recent issue of *Clinical Diabetes* largely focused on hypertension therapy, stimulated by the publication of the ALLHAT study,² a clinical trial that randomized more than 12,000 patients with diabetes, arguably more hyperten-

sive patients with diabetes than had been studied in all previous trials evaluating the role of blood pressure treatments in reducing CVD.

In this article, we focus on lipid-lowering therapy, more specifically on the hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors or “statins,” stimulated by the publication of the Heart Protection Study (HPS).³ The HPS was a statin trial that randomized almost 6,000 people with diabetes, almost an order of magnitude more people with diabetes than had been reported in CVD outcome trials of lipid-lowering therapy through 2002. (The diabetes portion of the HPS is reviewed in this issue on p. 151.)

Mechanism of Action and Effects⁴

Statins are lipid-lowering agents that specifically, competitively, and reversibly inhibit HMG-CoA reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in the formation of cholesterol. Because synthesis of cholesterol in the liver accounts for some 60–70% of the total cholesterol pool, these compounds are very active in reducing cholesterol levels—much more effective than dietary intervention.

Possibly as a direct effect of decreased cholesterol synthesis, the rate of assembly and secretion of circulating cholesterol-containing particles, particularly LDL and very-low-density lipoprotein (VLDL) is reduced. Furthermore, inhibition of hepatic cholesterol synthesis results in a compensatory increase in the expression of LDL receptors in the liver, which in turn bind circulating LDL

as well as VLDL-remnant particles and remove them from the circulation. These two effects result in a reduction in what is measured clinically as total cholesterol, LDL cholesterol, and triglycerides. Statins are generally also associated with modest increases in HDL cholesterol through unclear mechanisms perhaps related to increases synthesis of apolipoprotein A-I. Finally, of relevance to patients with diabetes, some studies suggest that statins are associated with a modest improvement in LDL particle size or density.

In most patients, statins produce substantial effects in lipid levels within 1–2 weeks, with maximal effects in 4–6 weeks. It should be noted that there have been proposed “pleiotropic” benefits of statin therapy independent of long-term changes in cholesterol levels, including inhibition of arterial smooth muscle cell proliferation, prevention of oxidation of LDL cholesterol, plaque stabilization effects on macrophages, improvement of endothelial function, and possible anti-thrombotic and anti-inflammatory effects.

There are five currently marketed statins: atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin (Table 1). Their relative effectiveness in lowering LDL cholesterol is hotly debated in the marketplace, but by consensus atorvastatin and simvastatin produce greater reductions of LDL cholesterol than the others. All have been demonstrated to reduce CVD events, though there is a substantially greater breadth and depth of clinical trial data for simvastatin and pravastatin. Several recent studies with atorvastatin have been stopped earlier

Table 1. Characteristics of Available Statins

Generic Name	Trade Name	Tablet sizes (mg)	Initial dose (mg)	Equipotent dose ¹⁹ (mg)	Cost of max-sized tablet (\$) ²⁰	Cost of equipotent dose (\$)
Atorvastatin	Lipitor	10, 20, 40, 80	10, 20, 40	10	3.00	1.94
Fluvastatin	Lescol	20, 40	20 or 40 in evening	80*	1.56	3.12
Fluvastatin extended release	Lescol XL	80	80 in evening	80*	1.97	1.97
Lovastatin	Generic	10, 20, 40	20 in evening	60*	1.97	2.95
Lovastatin	Mevacor	10, 20, 40	20 in evening	60*	3.94	5.91
Lovastatin extended release	Altacor	10, 20, 40, 60	20, 40, or 60 at bedtime	40* ²¹	1.83	1.81
Pravastatin	Pravachol	10, 20, 40, 80	40	60*	3.76	2.52
Simvastatin	Zocor	5, 10, 20, 40, 80	20 (40 in diabetes)	20–30*	3.73	3.72

*Difficult to assess precisely from available data.

than planned because of significantly lower event rates among treated patients than among those randomized to placebo. A somewhat outdated meta-analysis of data from trials in which several statins were evaluated for effects in primary prevention, secondary intervention, and/or reducing progression of atherosclerotic plaques indicated similar reductions in death and major cardiovascular events among statins.⁵ Certainly, a suggestion of the HPS is that cardiovascular risk burden and LDL level achieved during therapy determine the absolute risk of CVD events.

The statins vary substantially in price. In general, if modest cholesterol-lowering is required (~30% from baseline), several options are available in the \$2/day range. If substantially higher LDL reductions are necessary, they can only be achieved with higher doses of atorvastatin or simvastatin at \$3–4/day. However, substantial savings are possible if patients are willing to split large tablets of the more potent agents. It should be noted that pill splitting has not been formally studied or approved by the Food and Drug Administration (FDA)

and does result in some risk of confusion and the possibility that patients may take excessive doses by accident.

Absorption, Metabolism, and Adverse Effects⁴

Statins are rapidly absorbed following oral administration. There are no clinically meaningful effects of food on the anti-hyperlipemic effects of the statins, though modest and variable effects on absorption have been demonstrated. Except for atorvastatin, which seems to have a longer effective half-life, there is a marginally greater lipid-lowering effect when statins are administered in the evening. Statins undergo extensive first-pass metabolism in the liver, largely through the cytochrome P-450 (CYP) enzyme system. Atorvastatin, lovastatin, and simvastatin are primarily metabolized by CYP3A4; fluvastatin is metabolized principally by CYP2C9 with some involvement of CYP2C8 and CYP3A4. Pravastatin is unique in that its metabolism is independent of the CYP enzyme system. There is some evidence that statins may accumulate in patients with hepatic insufficiency or cirrhosis. It is

unknown whether statins are removed by dialysis.

Statins are generally well tolerated. In controlled clinical trials, 0.3–4.6% of patients receiving statins discontinued therapy because of adverse effects, generally rash, musculoskeletal pain, asymptomatic increases in serum aminotransferases (AST and/or ALT) concentrations and mild, nonspecific gastrointestinal disturbances.

Increases in AST and ALT to more than three times the upper limit of normal that occurred on at least two (not necessarily consecutive) occasions were reported in ~0.1–3% of patients receiving statins for at least 11 months. These increases were generally dose-dependent but, importantly, were not associated with jaundice. Severe liver injury related to statin therapy is extremely rare if it occurs at all. Elevated liver enzymes generally return to normal following either dose reduction (50–75%) or cessation of therapy. Interestingly, increases in liver enzymes generally do not recur with rechallenge, whether with the same or another statin.

Muscle aches with or without weakness occur in 1–6% of patients receiving statins in controlled clinical trials. Myopathy characterized by symptoms as well as serum creatine kinase (CK) levels greater than ten times the upper limit of normal occurred in < 0.7% of people treated with statins in clinical trials. The risk of myopathy appears to be somewhat dose-dependent and increased in the setting of renal or hepatic impairment, hypothyroidism, and in the elderly (particularly the frail) and those with serious illness. Rhabdomyolysis, effectively myopathy with increased serum creatinine, has been reported as a rare serious occurrence with each of the statins and can be fatal. In August 2001, cerivastatin was withdrawn from worldwide markets as a result of substantially higher reporting rates of fatal rhabdomyolysis.

An excellent recent review points out that in randomized controlled trials of statin therapy involving more than 80,000 subjects, there were essentially identical rates of myositis and rhabdomyolysis among statin-treated and placebo-treated patients.⁶ Nevertheless, patients should be instructed on the possibility of these adverse events and advised to discontinue therapy and present for evaluation promptly if unexpected muscle pain, weakness, or discoloration of urine occurs. Routine screening with CK measurements is not necessary. In symptomatic patients, a CK measurement should be performed and the drug discontinued if levels exceed ten times the upper limit of normal without explanation or other possible cause.

There are literally hundreds of uncommonly reported signs and symptoms documented among the tens of thousands of people who have been evaluated in clinical trials and the tens of millions who have been treated. For any statin-using patient with a symptom, providers should explore whether the statin may be the cause. Given the dramatic data demonstrating the effect of statins in reducing cardiovascular risk,

before labeling a patient as statin-intolerant, it is advisable to rechallenge high-risk patients who suspect they are having adverse events either with a lower dose of the same agent or with a low dose of another statin unless the side effect is potentially life-threatening.

All serious adverse effects associated with use of statins, or any other drug for that matter, should be reported to the FDA MedWatch Program by phone (800-FDA-1088), fax (800-FDA-0178), Internet (<http://www.fda.gov/medwatch>), or mail (MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787)

Drug Interactions⁴

In clinical trials, the risk of developing myopathy and rhabdomyolysis seems to be increased in patients receiving statins concomitantly with other agents metabolized through the CYP3A4 enzyme system, particularly CYP3A4. In all such combinations, keeping statin doses to the minimum required is prudent. The most relevant drug interactions for the average patient with diabetes are those with fibrate drugs and niacin, agents frequently employed to reduce the hypertriglyceridemia and low HDL cholesterol levels commonly encountered in patients with type 2 diabetes and often poorly addressed with statin therapy. Recent studies suggest the possibility that the drug interactions with fibrates may be mediated through effects on statin glucuronidation, another mechanism of drug elimination.⁷ Fenofibrate seems to be much less frequently associated with these adverse events than gemfibrozil.⁸

In the setting of statin therapy, niacin doses should be limited to no more than 1 g or, at most, 2 g/day. The risk of myopathy is almost certainly less with statin-niacin combination therapy than with statin-gemfibrozil combination. In fact, there is now a combination tablet of extended-release niacin with lovastatin available in 500/20, 750/20, and 1,000/20 tablets with a maximum approved dose of 2,000 mg of niacin and 40 mg of lovastatin.⁹

The package inserts of all statins suggest that the concomitant use of statins with niacin and fibrates should be avoided unless the potential benefits outweigh the risks; however, in patients who require fibrate therapy as well as substantial LDL-lowering (> 30%), there may be a modestly lower risk of adverse consequences when atorvastatin is combined with fenofibrate than other statin drug combinations. Extreme caution is necessary when using these combinations in patients with renal insufficiency because of their reduced clearance of drugs and metabolites and higher background risk of rhabdomyolysis.

Drugs and foods known to affect the CYP3A4 system need to be used cautiously in patients treated with atorvastatin, lovastatin, or simvastatin because these agents are largely metabolized through that system. These combinations may result in a higher risk of statin-related adverse events as well as changes in therapeutic levels of both agents. There are poorly explained drug interactions with pravastatin and fluvastatin (specifically acid-reducing agents) as well, despite the fact that they largely do not rely on the CYP3A4 system for metabolism. The package insert of any statin should be consulted when prescribing such products for patients with complex regimens; the details and extent of these interactions are beyond the scope of this review.

Provider should exercise caution in co-administering statin drugs with cyclosporine, certain anti-bacterial agents (erythromycin, clarithromycin, metronidazole), certain anti-fungal agents (itraconazole, fluconazole, ketoconazole), HIV protease inhibitors, rifampin, nefazodone, amiodarone, diltiazem, verapamil, danazol, phenytoin, diclofenac, zileuton, fluvoxamine, warfarin, digoxin, and large quantities (more than 1 quart) of grapefruit juice. Because many of these agents are prescribed for short courses, consideration of temporarily stopping a statin is reasonable as opposed to avoiding the use of a poten-

tially helpful agent or using a potentially harmful combination.

Special Populations⁴

The use of statins in children has not been extensively studied. In general, bile-acid sequestrants are preferred anti-hyperlipidemic drugs in children and adolescents. If they do not exhibit an adequate response, niacin may be added as second-line therapy, preferably with consultation from a lipid specialist. There is clear evidence that statins reduce CVD events in the elderly. Greater caution, particularly in frail older women who are slight of build, is prudent based on reports of greater frequency of myopathy and even related deaths.

There are no data on the use of statins in pregnant women. Statin drugs should be discontinued in women who are pregnant or trying to conceive. In fact, in women of child-bearing potential, providers must exercise great caution in evaluating potential risks and benefits of statin therapy. Statins have been demonstrated to be teratogenic in animals, and, theoretically, inhibition of cholesterol biosynthesis should cause fetal toxicity because products of these pathways are critical for the synthesis of steroid hormones and cell membranes. Statins do pass into human milk and thus are contraindicated in the setting of lactation as well.

Statins should be used with caution in people with renal insufficiency, hepatic impairment, active liver disease, and in people who consume large quantities of alcohol.

Clinical Benefits and Use

Statin therapy has been associated with a 19–55% reduction in CVD events in patients with diabetes with and without known vascular disease. The major demonstration of the HPS is that the benefits of statins extend to people with diabetes and no known vascular disease as well as to those with near-normal LDL levels. The lipid entry criteria for the HPS was total cholesterol \geq 135

mg/dl; approximately half of the participants had LDL levels $<$ 116 mg/dl.

There is no class of lipid-lowering therapy that has nearly the breadth or depth of evidence demonstrating benefits on rates of myocardial infarction, need for revascularization, and stroke.³

There are also data to suggest that statins may have benefits on the rate of development of diabetes.^{3,10} Finally, there are more speculative data that indicate that statins may reduce the rate of progression of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy.^{11–13}

Current American Diabetes Association guidelines suggest that all adults with diabetes should be managed to achieve an LDL cholesterol $<$ 100 mg/dl employing statins as first-line therapy.¹⁴ Combination therapy with bile acid resins (cholestyramine, colestevlam, colestipol), cholesterol absorption inhibitors (ezetimibe), plant stanol esters, niacin, and/or fenofibrate can provide even greater lowering when needed. Similarly, those agents can be used as an alternative to statin therapy in patients who are demonstrably intolerant of statins. In light of the novel findings of the HPS, it seems likely that lipid management guidelines will be modified to suggest that people with diabetes who would have qualified for the HPS ($>$ 40 years of age with total cholesterol \geq 135 mg/dl) should be treated with a statin drug. This will constitute virtually all people with diabetes over age 40.

The major question remaining is whether those patients should be treated with simvastatin, 40 mg daily (the dose used in the HPS), or an equivalent dose of another agent. Effectively, the HPS has demonstrated that simvastatin, 40 mg daily, is superior to placebo. We know from other trials in patients with higher levels of LDL cholesterol that simvastatin, 20 mg daily, is effective in reducing CVD events.¹⁵ This is potentially an important clinical question in light of the frequency of high triglycerides and low HDL in patients with diabetes, the demonstrated benefit (admittedly

lesser in depth and breadth) of fibrates and niacin to reduce CVD events, and the relative contraindication to combination of statins with fibrates and niacin, particularly at high doses.

It is remarkable that after 16 years of clinical use and half a dozen clinical trials demonstrating benefit in reducing hard endpoints such as heart attack and stroke that still more than half of people with diabetes are untreated with statin drugs despite clear indications by guidelines. A recent study describing clinical practice in Scotland from 1990 to 1995 demonstrated that of 5,590 patients with an incident myocardial infarction (MI), $<$ 8% used statins. The 5% of patients who were 80% adherent with statin therapy were 81% less likely to have a recurrent MI and 53% more likely to survive the observation period.¹⁶

Based on analyses of the third National Health and Nutrition Examination Survey (NHANES-III), which examined patients between 1988 and 1994, there are 8.2 million people in the United States with diabetes and no clinical evidence of CVD with an LDL cholesterol \geq 100 mg/dl and only 1.6 million with an LDL $<$ 100 mg/dl. If statin therapy were administered to lower LDL $<$ 100 mg/dl, 71,000 major coronary events could be prevented annually including 13,000 among people with LDL levels between 100 and 129 mg/dl at an annual incremental cost per person at risk of \$480–950 for those with LDL 100–129 mg/dl and \$590–1,920 for those with LDL \geq 130 mg/dl.¹⁷

There are data to suggest that patients with diabetes, those treated with statins, those with fewer noncardiovascular medications, and those who saw their health care provider more often were more likely to be adherent to lipid-lowering therapy.¹⁸ The impact of new clinical trials, new agents, and better understanding of the risks and benefits associated with statin therapy will likely improve both initiation rates for lipid-lowering therapy and adherence with the promise of longer and more vibrant life for our patients with diabetes.

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