EDITORIAL COMMENT

Low-Density Lipoprotein Lowering Therapy: An Analysis of the Options*

Frank M. Sacks, MD
Boston, Massachusetts

The hydromethylglutaryl coenzyme A (HMG CoA) reductase inhibitors, “statins,” have been remarkably effective in reducing low-density lipoprotein (LDL) cholesterol concentration, decreasing the incidence of coronary heart disease (CHD) and stroke, and extending survival (1–5). Statins inhibit the synthesis of cholesterol primarily in the liver. The hepatocyte, as its content of cholesterol decreases, responds in two ways: it decreases the production of very low-density lipoprotein (VLDL), the atherogenic precursor of LDL, and increases the production of LDL receptors that take up VLDL and LDL from plasma. These actions substantially lower the VLDL and LDL concentrations in plasma. The statin class reduces LDL cholesterol 30% to 55% from starting to maximal doses.

Inhibitors of sterol absorption. The liver’s exquisite sensitivity to a reduction in its content of cholesterol can be exploited further for additional therapeutic benefit in patients who are being treated with statins. Reducing cholesterol or bile acid absorption by the intestine has a downstream effect of reducing hepatocyte cholesterol, and it is a time-tested means of lowering plasma LDL concentration. It is an important fact that agents that block intestinal sterol absorption lower LDL concentration just as much if they are taken with or without statins. This additivity provides the opportunity to lower LDL cholesterol concentration more than can be accomplished by statins alone. However, this approach has had limited clinical success because of mild efficacy, inconvenient administration, or side effects. Bile acid sequestering resins, cholestyramine and colestipol, have potential for 25% to 35% lowering of LDL cholesterol at the highest dose (6), which is rarely reached because of their gastrointestinal side effects, the need to dissolve the resin in a beverage, and unpleasant texture and taste. For these reasons, these resins are uncommonly prescribed, and adherence to even a low dose is generally unsatisfactory.

Plant sterols and stanols, themselves nonabsorbable, reduce intestinal cholesterol absorption and lower LDL cholesterol by about 10% to 15% (7). Their clinical effectiveness is limited by the requirement to eat special supplemented foods, such as margarine 20 to 30 g daily. Dietary soluble fiber reduces sterol absorption, which may account for some of its modest action to lower LDL cholesterol, about 2 mg/dl per g soluble fiber (8). A synthetic soluble fiber, colesvelam (WelChol, Sankyo Pharma, Piscataway, New Jersey), has recently been marketed in a tablet. Colesevelam, a hydrophilic gel, is well tolerated and reduces LDL cholesterol by 10% to 16% for 3.8 g (9,10), double or triple the potency of natural dietary fiber (8). The advantages of colesevelam are that it is not absorbed from the intestine and the incidence of side effects is similar to placebo. One would expect it to be as safe as fiber in food. The principal drawback to treatment with colesevelam is that six tablets per day taken with meals are needed to achieve the 3.8 g daily dose. Thus, a truly convenient LDL-lowering therapy with an intestinal mechanism of action has not been available.

Ezetimibe: mechanism and efficacy. Into this therapeutic gap enters ezetimibe (Zetia, Merck Schering Plough, North Wales, Pennsylvania), an inhibitor of intestinal absorption of cholesterol (11–16). Ezetimibe reduced cholesterol absorption from 50% to 23%, and among individuals the reductions in cholesterol absorption and plasma LDL were correlated (16). The well-conducted trial of Davidson et al. (12) in this issue of the Journal demonstrates that a 10 mg single daily dose lowers LDL cholesterol by 14%, in addition to the effects of simvastatin. The study population had moderately elevated LDL cholesterol averaging 180 mg/dl before treatment. Ezetimibe produced similar additional LDL reduction throughout the simvastatin dose range, 10 to 80 mg. In patients with homozygous familial hypercholesterolemia, a notoriously difficult condition to treat pharmacologically, ezetimibe added a 20% LDL reduction to the effects of simvastatin or atorvastatin (13).

Pharmacologically, ezetimibe is truly a novel agent. Unlike previous LDL-lowering agents with an intestinal action that are not absorbed, ezetimibe is rapidly absorbed by the intestinal cell, extensively glucuronidated, and produces systemic concentrations of unmodified and glucuronidated forms (14,15). Ezetimibe recirculates enterohepatically several times a day in coordination with meals. The systemic concentration of ezetimibe at any given dose varies considerably among patients, fluctuates throughout the day, and is directly related to the extent of LDL reduction (15). Systemic trough levels of ezetimibe over 15 ng/ml were found to produce consistent LDL lowering, and this was achieved in most people with a single 10 mg daily dose. The site of action is thought to be inside the enterocyte and not in the intestinal lumen like all other agents that block intestinal absorption of sterols. The mechanism by which ezetimibe decreases cholesterol absorption is unknown.
Ezetimibe has little effect on high-density lipoprotein (HDL) cholesterol and triglycerides. Ezetimibe did not produce adverse effects in combination with statin therapy, and has minimal potential for interactions with other drugs.

Ezetimibe was approved by the Food and Drug Administration on October 25, 2002. The key question for clinicians is how ezetimibe should be incorporated into current practice to prevent and treat cardiovascular disease (CVD).

**Statins for first-line LDL treatment.** Ezetimibe has little potential as a first-line treatment for hyperlipidemia, as it cannot compete with the clinical efficacy of statins on LDL and CVD. There are over 50,000 patients who have participated in placebo-controlled trials of five years or more in duration, using pravastatin 40 mg, simvastatin 20 to 40 mg, or lovastatin 20 to 40 mg. All-cause mortality (1,2,4) and virtually all cardiovascular events (1–5) are reduced. Extended follow-up of two trials, Scandinavian Simvastatin Survival Study (4S) (17) and Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) (18), showed that the survival benefit persisted and even increased over two years in the groups that had been randomized to active drug. In the pravastatin (19) and simvastatin (4) trials, no increase in liver transaminases occurred over that found with placebo, even in patients with elevated transaminase concentrations before treatment. There was no statistically significant increase in myalgia, myositis, myopathy, or high serum creatine phosphokinase level with either drug. There was no excess risk of myopathy with pravastatin 40 mg (19), and with simvastatin 40 mg it was minuscule and not statistically significant: six to seven cases per 10,000 treated patients in five years, and no case was fatal (4).

These megatrials of pravastatin and simvastatin also vanquished all the old shibboleths of lipid treatment related to safety (20,21). There was no increase in any cause of morbidity or mortality, most importantly cancer, to counter the CVD benefits. In fact, on extended follow-up of the LIPID and 4S trials, cancer rates were lower in the pravastatin and simvastatin groups, with statistical significance nearly achieved (17,18). Furthermore, in a randomized trial of patients with hepatocellular carcinoma, pravastatin 40 mg significantly improved median survival (22). Inhibition of HMG CoA reductase could suppress tumor growth by reducing farnesyl isoprenoid formation, which affects signal transduction by oncogenic products. These observations on cancer are particularly important, because once initiated, lipid treatment needs to be given for decades if not lifelong, and cancer incidence markedly increases with age.

Now we will consider specific clinical situations, in a typical population with CHD or other high-risk conditions and with mean LDL cholesterol between 130 and 150 mg/dl, a starting dose of a statin would achieve the LDL cholesterol goal of <100 mg/dl in the majority of patients, and increasing to the next dose should suffice to bring most of the other patients to this level. Flat pricing above starting doses for some of the statins, such as pravastatin and simvastatin, makes this approach economically attractive.

**What to do when the LDL goal is not reached?** Let us now proceed to a more challenging patient with CVD who has hypercholesterolemia, for example, with LDL cholesterol before treatment of 190 mg/dl, the average pretreatment level in the 4S trial (1). An initial dose of a statin would lower LDL to about 125 mg/dl (34% from baseline). Let us evaluate the risk reduction at this point and after additional lipid therapies. The statin trials in the aggregate suggest that relative risk reduction of 25% is achieved by a 40 mg/dl decrease in LDL cholesterol (1–4). Thus, a 40% reduction in risk would be expected for this patient, consistent with the actual results of 4S trial (1). Each doubling of a statin dose reduces LDL cholesterol by about 6% (23). As an example, increasing simvastatin from 20 to 80 mg would lower LDL by another 12% (15 mg/dl), and this projects to an additional 10% reduction in CHD. The result with the ezetimibe strategy would be similar: a 14% reduction in LDL cholesterol (12) and a projected 11% reduction in CHD. It is clear that both strategies together would have to be employed to reach the LDL goal <100 mg/dl, and this would achieve about a 20% additional reduction in CHD risk beyond the initial 40% reduction. Another option is to add niacin 1.5 g daily, which will reduce LDL by 10% to 15%; HDL increasing with niacin is an added benefit in patients with low HDL accompanying high LDL (24). Perhaps the simplest option is to switch to atorvastatin 80 mg, which would produce a 53% to 56% reduction in LDL, easily achieving the goal, although the potential for adverse effects increases slightly (25,26), as discussed subsequently.

The first lesson from this exercise is that, after the initial risk reduction from a starting dose of a statin, tinkering with statin dose increases of one or two doublings or adding ezetimibe or other inhibitor of intestinal sterol absorption would be expected to produce rather modest effects on CHD. These effects are also just projections; proof that high doses of statins produce meaningful added reduction in CHD awaits the results of several large trials that compare simvastatin 80 mg with 20 mg (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH]) (27), atorvastatin 80 mg with 10 mg (Treating to New Targets [TNT]), atorvastatin 80 mg with simvastatin 20 to 40 mg (Incremental Decrease in End points through Aggressive Lipid-lowering [IDEAL]), and atorvastatin 80 mg with pravastatin 40 mg (Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE-IT]) (28). Thus, exercising any of these options for additional LDL therapy beyond pravastatin 40 mg (2), simvastatin 40 mg (1,4), and lovastatin 40 mg (3) takes us outside the reassuring envelope of evidence-based medicine. Two distinct perspectives for adhering to such principles and essentially to “leave well enough alone” pharmacologically have been advanced recently in this Journal (29) and elsewhere (30).
Safety and the balance between benefit and harm. Although efficacy of intensifying LDL lowering treatment eventually may be borne out, safety and the balance between benefit and harm is less easy to parse at this time. Adverse effects of statin therapy are dose-dependent and have occurred in trials primarily at the highest dose. For example, atorvastatin 80 mg increased the incidence of serum transaminase abnormalities during 16 weeks to 2.5% (38/1,538) compared with 0.6% (9/1,548) on placebo (26). Two of the patients were hospitalized for jaundice, which resolved. In a study that compared atorvastatin 80 mg with simvastatin 80 mg in 826 patients for 30 weeks, atorvastatin was associated with a higher incidence of serum transaminase abnormalities (3.8% vs. 0.5%), including four cases with hyperbilirubinemia, and of gastrointestinal symptoms (10% vs. 3%) (31). No cases of myopathy were reported for either drug (31). In another trial of simvastatin 80 mg, there were two cases of myopathy among 314 patients during 24 weeks; a link to the drug was confirmed by the finding of high serum simvastatin concentrations, 5- and 10-fold more than expected (32). In a pooled analysis of four controlled trials comparing simvastatin 80 mg and 40 mg, confirmed transaminase increases occurred in 1.5% (23/1,586) with 80 mg compared to 0.7% (4/543) with 40 mg, and myopathy in 0.6% (9/1,586) with 80 mg and 0.2% (1/543) with 40 mg (33). The differences between doses were not statistically significant. Lovastatin 80 mg was associated with an increased incidence of high serum transaminase and creatine kinase (34). The hepatic and muscular abnormalities reported for the 80 mg dose of atorvastatin, simvastatin, and lovastatin all were in excess of what occurred with lower doses (32–35). Although these rates of adverse events are low, we need to keep in mind that the 80-mg doses have been evaluated only in short-term trials of 4 to 11 months duration. The long-term safety is undetermined, pending results from the large-scale longer-term studies in progress. Thus, using these highest approved doses of statins requires added caution. The recent American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute clinical advisory on statin use (36) describes clinical settings in which closer monitoring may be prudent, such as in patients who are taking medications that increase the serum concentration of certain statins, elderly or frail patients, and those with multisystem disease.

Ezetimibe or statin dose escalation? Thus, with concerns about high doses of statins, is ezetimibe a more attractive option? Low-density lipoprotein lowering is modest but reliable, the drug is conveniently taken, and no important adverse effects or drug–drug interactions have come to light. Nonetheless, several caveats are in order. First, the number of patients who have been treated with ezetimibe is many fewer than with high-dose statins. Second, the duration of ezetimibe treatment in reported studies has been but 12 weeks (11–13). Third, the drug is absorbed and produces serum concentrations that are related to its LDL lowering effect (14,15). Finally, a “wild card” is that the molecular action of ezetimibe is unknown. We do not know whether the molecular target of ezetimibe is expressed in vivo in tissues outside the intestine, and what the clinical effect might be of interaction with ezetimibe. This could be meaningful because systemic concentrations of ezetimibe are maintained continually during therapy. For these reasons, ezetimibe, the first of its class, needs careful scrutiny after it is made available. Thus, to reach the goal for LDL, I judge statin dose escalation to be the preferred option at this time because the adverse effects are uncommon, well known, and amenable to monitoring (36), and I would reserve ezetimibe for patients who experience true adverse effects from high-dose statins. Finally, we must persistently reinforce and intensify nutrition and other therapeutic lifestyle changes which have substantial, largely unrealized potential to prevent CVD, diabetes, and other chronic diseases.

Reprint requests and correspondence: Dr. Frank M. Sacks, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115. E-mail: fsacks@hsph.harvard.edu.

REFERENCES


