RYAN C. NEAL, MD*
Assistant Professor of Medicine,
Baylor College of Medicine,
Houston, Texas

PETER H. JONES, MD†
Associate Professor of Medicine,
Baylor College of Medicine,
Houston, Texas

Lipid-lowering: Can ezetimibe help close the treatment gap?

ABSTRACT

Most patients who should be on lipid-lowering therapy are not receiving it, and most patients who are receiving it are not reaching their appropriate low-density lipoprotein (LDL) goals. This is in part because physicians and patients fear side effects of statins and other lipid-lowering agents. Ezetimibe (Zetia), a new lipid-lowering drug, may help physicians close this "treatment gap" in more patients, especially in combination with a statin.

KEY POINTS

Ezetimibe works by inhibiting cholesterol absorption. It has a favorable side-effect profile; in particular, it does not cause hepatotoxicity or myositis, which, although uncommon, are concerns with statin therapy.

Ezetimibe lowers LDL levels by about 18% when used as monotherapy and by an additional 25% when added to statin therapy.

The most practical use of ezetimibe will be in combination with ongoing statin therapy in patients who have not reached their LDL goals. Ezetimibe monotherapy may be used when the patient cannot tolerate statin therapy or does not wish to use a statin.

Goal LDL levels are less than 100 mg/dL for patients at high risk, less than 130 for patients at moderate risk, and less than 160 for patients at low risk.

*Dr. Neal has indicated that he is on the speakers' bureaus of AstraZeneca Pharmaceuticals, Merck, and Schering Plough companies and has received grant or research support from Astra Zeneca and Kos Pharmaceuticals, Inc..

†Dr. Jones has indicated that he has received grant or research support from the Pfizer, AstraZeneca, and GlaxoSmithKline companies.

EZETIMIBE (Zetia) is an important new drug for lowering total cholesterol and low-density lipoprotein (LDL) cholesterol levels, and may help overcome some of the barriers to reaching therapeutic goals.

Although existing drugs, especially statins, are safe and effective, most patients still do not achieve goal levels of LDL. One of the chief causes of this "treatment gap" is that many clinicians are concerned about the potential side effects of higher doses of statins or combination therapy with fibrates, niacin, or bile acid resins, resulting in the use of suboptimal therapy.

Ezetimibe, with its lower side-effect profile, provides a new option for potentially more effective lipid-lowering, especially in combination with a statin. Nonetheless, trials with surrogate vascular and clinical end points need to be done.

This paper reviews the goals of lipid-lowering therapy, the magnitude of the treatment gap and the reasons for it, the current lipid-lowering drugs, and the clinical role of ezetimibe.

SCOPE OF THE PROBLEM

More than 12 million people in the United States have coronary heart disease (CHD), and elevated cholesterol is one of the major risk factors for it.

Almost half of men and women in the United States have elevated levels of total cholesterol and LDL, and an estimated 36 million US adults will require lipid-lowering drug therapy to achieve the target LDL goals set by the latest guidelines from the National Cholesterol Education Program's Adult Treatment Panel III (ATP III).[1]

TABLE 1

Not available for online publication.
See print version of the
Cleveland Clinic Journal of Medicine

An estimated 36 million Americans are candidates for lipid-lowering therapy

GOALS ARE BASED ON RISK

The intensity of lipid-lowering treatment should be based on the patient's risk of CHD events. The ATP III guidelines define three risk categories: high, moderate, and low (TABLE 1).

High risk

Those at high risk have either known CHD or conditions that put them at equivalent risk of a cardiovascular event, ie, a 10-year risk greater than 20%. These conditions are:

- Diabetes mellitus
- Noncoronary atherosclerosis (ie, peripheral arterial disease, abdominal aortic aneurysm, or significant carotid artery disease)
- Any combination of two or more major risk factors that add up to a 10-year risk of 20% or higher by Framingham risk-prediction calculations. (To calculate risk, see the ATP III report,[1] or use the calculator online at **http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype-prof.**)

This "CHD risk-equivalent" group comprises more than 20 million US adults, many of whom are diabetic.

Goal of treatment in this group: an LDL level lower than 100 mg/dL.

Moderate risk

The moderate-risk category consists of people with two or more risk factors whose 10-year risk is less than 20%. This group is subdivided into those with a 10-year risk of 10% to 20% (moderate high risk) and those with a 10-year risk of less than 10% (moderate low risk).

Goal: an LDL level lower than 130 mg/dL.

Low risk

Those considered to be at low risk have one or no risk factors. Their 10-year risk is less than 10%.

Goal of treatment: an LDL level lower than 160 mg/dL.

BENEFIT OF TREATMENT

We have abundant evidence from clinical trials (primarily with statins) that when LDL levels are lowered, the rate of cardiovascular events declines significantly. Statins have been shown to be effective and safe in both the primary and secondary prevention of cardiovascular disease.

Primary prevention trials such as the West of Scotland Coronary Prevention Study (WOSCOPS)[2] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[3] have shown the benefit of statin treatment in patients with either very high LDL levels or average LDL and below-average high-density lipoprotein cholesterol (HDL) levels.

The recent Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm[4] demonstrated a significant 36% risk reduction in cardiovascular events in high-risk hypertensive patients treated with atorvastatin 10 mg/day.

Secondary prevention trials such as the Heart Protection Study (HPS),[5] the Scandinavian Simvastatin Survival Study (4S),[6] Cholesterol and Recurrent Events (CARE),[7] and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)[8] have shown consistent benefit in patients with CHD or at equivalent risk who have LDL levels that were elevated (4S) or average (HPS, CARE, LIPID). These trials showed significant reductions in both cardiovascular events and all-cause mortality.

THE TREATMENT GAP

Nevertheless, most patients who should be on lipid-lowering therapy are not receiving it, and most patients who are receiving it are not reaching their appropriate LDL goals.

The Quality Assurance Program[9] evaluated more than 48,500 CHD patients from more than 140 medical practices, many of them cardiology practices. Although nearly all patients with CHD should be on lipid-lowering therapy, only 39% of the patients were currently on lipid-lowering therapy, and, surprisingly, only 44% had an LDL level documented in the chart. Moreover, of the 44% who had an LDL measurement in their chart, only 25% had achieved a target level of below 100 mg/dL.

Similarly, the Lipid Treatment Assessment Project[10] found that only 18% of CHD patients undergoing treatment achieved LDL levels below 100 mg/dL. Of the 82% of CHD patients who did not achieve the treatment goal, approximately 17% had LDL levels above 160 mg/dL.

The National Registry for Myocardial Infarction[11] reported that only one third of patients discharged from a hospital after an acute myocardial infarction were placed on lipid-lowering therapy.

Narrowing the gap

To narrow the treatment gap, we need to:

- Identify patients in the primary care setting who are at high risk for CHD
- Educate health care professionals about the optimal methods to achieve target lipid goals and about the safety of current therapies
- Develop new therapies that enhance the ability to achieve LDL goals.

OBSTACLES TO ATTAINING GOALS

The reasons for not achieving lipid goals are numerous and include failure to titrate drug therapy after the initial dose, infrequent follow-up evaluations, and physician and patient concerns about drug safety at higher doses or in combination therapy.

Concerns about safety

Despite the proven safety profile of statins and other lipid-lowering therapies, many clinicians are reluctant to treat aggressively. Concerns over safety were heightened by a greater-than-expected incidence of rhabdomyolysis with cerivastatin (Baycol), which led to its withdrawal from the market.

Adjusting the regimen

At the lowest doses, statins reduce LDL levels by approximately 17% to 38%,[12] which is often not enough to reach target levels, especially in the highest-risk patients. In such cases, the options are to:

- **Increase the statin dose.** The reduction in LDL levels with statin therapy is predictable, such that doubling the dose results in a 6% further reduction in LDL.
- **Change to another statin** of higher potency. At the 10-mg dose, statins rank in potency from least to greatest as follows: fluvastatin, lovastatin, pravastatin, simvastatin, and atorvastatin.
- **Add another, complementary drug** such as a bile acid resin to statin therapy.

Even in cardiology practices, high LDL levels often go untreated

CURRENT DRUG THERAPIES

Statins

Statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) competitively inhibit HMG-coenzyme A reductase, the rate-limiting step of cholesterol synthesis. This results in upregulation of LDL receptors on the liver surface, which increases LDL uptake from the plasma.

TABLE 2

At present, most patients do not reach goal LDL levels

Effect on lipids. Using one of the five available statins by itself at a dosage ranging from 10 to 80 mg per day, LDL levels can be reduced from 17% to 51% (TABLE 2).[12]

Side effects. While the side-effect profile of statins is very favorable, all statins can cause hepatotoxicity and myopathy.

Hepatotoxicity, defined as an aspartate aminotransferase concentration three or more times the upper limit of normal, is reported to occur in 0.1% of patients at the start of statin therapy at usual doses. The incidence increases either as the dosage is increased (to approximately 2% to 2.5% at an 80-mg dose of any statin) or when niacin or a fibrate is added. Hepatotoxicity reverses when the statin or combination is discontinued.

Myalgia without elevation of creatine kinase occurs in clinical practice in 5% to 10% of patients on statin therapy. However, myositis, defined as muscle symptoms with a creatine kinase value of 10 or more times the upper limit of normal, is reported in fewer than 0.1% of patients at usual starting doses. Again, the risk increases with dose and in combination therapy, particularly with fibrates.

The incidence of fatal rhabdomyolysis due to progressive myositis is thought to be less than 1 in 10,000 patients and to occur with less than 1 of every 10 million written prescriptions.

Since statins have proven to reduce cardiovascular events by 24% to 40%, their benefits in high-risk patients outweigh this risk.[13]

Fibrates

The fibrates (gemfibrozil and fenofibrate) affect lipid metabolism as agonists of peroxisome proliferator-activated receptor alpha. This results in increased peripheral lipolysis of triglyceride-rich lipoproteins through a stimulation of lipoprotein lipase, a reduction in apoprotein C-III, and an increase in apoprotein A1 production.[14]

Effect on lipids. Clinically, fibrates increase HDL levels by 10% to 20% and lower triglyceride levels by 20% to 50%, with variable effects on LDL levels. They reduce CHD events in primary prevention (as shown in the Helsinki Heart Study[15]) and in secondary prevention (as shown in the VA-HDL Intervention Trial[16]).

Side effects. Although fibrates are generally well tolerated, their side effects include myopathy, cholelithiasis, and gastrointestinal discomfort.

Niacin

Niacin or nicotinic acid is believed to exert its lipid effects by reducing the catabolism of HDL and reducing free fatty acid substrate, thereby reducing hepatic production of very-low-density lipoprotein cholesterol.

Effect on lipids. Depending on the dose, niacin reduces LDL levels by 15% to 25%, increases HDL levels by 15% to 20%, and reduces triglyceride levels by 20% to 50%.[17]

Side effects include cutaneous flushing,

itching, dyspepsia, hepatotoxicity, and glucose intolerance. Flushing occurs in more than 50% of patients taking immediate-release preparations. These symptoms can be significantly improved by titrating the dosage slowly and adding aspirin.

Elevated transaminase levels are most often seen with sustained-release forms.[18]

Despite niacin's tendency to worsen glucose intolerance, a recent study found it to have negligible glucose effects in patients with well-controlled type 2 diabetes.[19]

Bile acid resins

Bile acid resins inhibit bile salt absorption in the terminal ileum, which interrupts their enterohepatic recirculation. This results in an increase in hepatic bile acid synthesis from cholesterol and an increase in hepatic LDL receptor expression.

Effect on lipids. Resins can lower LDL levels by 15% to 30% and can increase HDL levels by 3% to 5%, but they may elevate triglyceride levels.

Side effects are primarily gastrointestinal, ie, constipation, bloating, and dyspepsia.

Because they can increase triglycerides, resins are contraindicated as monotherapy if baseline triglyceride levels are greater than 400 mg/dL.[20]

Combination therapy

Combination therapy may be necessary in some patients, particularly those with heterozygous familial hypercholesterolemia and mixed dyslipidemias. For patients with high LDL, low HDL, and high triglyceride levels, the combination most often used is a statin plus niacin or a fibrate.

Despite the small but added risk of hepatotoxicity or myositis, use of a statin in combination with either niacin or a fibrate can be both safe and effective for achieving goal LDL levels and improving HDL and triglyceride levels, particularly for patients with CHD or at equivalent risk. Unfortunately, many clinicians opt for monotherapy to avoid the potential added risk.

For patients at highest risk of a CHD event, it is desirable to have another drug that can be used safely in combination with statins to achieve target LDL levels.

THE CLINICAL ROLE OF EZETIMIBE

Ezetimibe received US Food and Drug Administration approval as a lipid-lowering agent in 2002. It is approved for the treatment of primary hypercholesterolemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia.

Mechanism of action

Ezetimibe is a selective cholesterol absorption inhibitor that blocks a yet-unidentified sterol transporter that moves cholesterol into the wall of the small intestine.[21]

Normally, dietary and biliary cholesterol are absorbed in the proximal small intestine. This cholesterol is packaged with dietary triglyceride into chylomicrons, which undergo intravascular lipolysis by lipoprotein lipase to form chylomicron remnants, which are subsequently removed by LDL receptors on the surface of the liver.

Ezetimibe blocks the intestinal absorption of dietary and biliary cholesterol and decreases the cholesterol content of chylomicrons, which in turn reduces the amount of cholesterol delivered to the liver. This reduced hepatic cholesterol results in a compensatory increase in LDL-receptor expression and enhanced clearance of LDL particles.

Ezetimibe does not affect the absorption of fatty acids, triglycerides, bile acids, or lipid-soluble vitamins.

Ezetimibe dosage: 10 mg once daily, with or without food

Pharmacokinetics and metabolism

Ezetimibe is glucuronidated in the liver and enterohepatically circulated via the portal circulation and biliary tract. More than 95% of ezetimibe and its glucuronidated metabolite localize in the brush border of the small intestine.

Since both ezetimibe and its metabolite are active, its half-life is approximately 24 hours, so it needs to be taken only once a day. It can be taken with or without food.

Ezetimibe does not inhibit or induce the cytochrome P450 system and has low systemic exposure, which could decrease the potential for drug-drug interactions and adverse effects. At present, there are no suspected long-term safety concerns with this drug.

Effect on lipids

In clinical studies in patients with familial hypercholesterolemia, ezetimibe 10 mg once daily lowered LDL levels by 17% as monotherapy,[22] and further lowered levels up to 25% when added to ongoing statin therapy.[23]

As monotherapy, ezetimibe has only minimal effects on HDL and triglyceride levels, but when combined with a statin it appears to further increase HDL levels and lower triglyceride levels.[23] Added to ongoing statin therapy, ezetimibe has been shown to raise HDL levels by 3% and lower triglyceride levels by an additional 14%.[23]

We have very little clinical data about the use of ezetimibe in combination with other lipid-altering drugs. Ezetimibe combined with fenofibrate was studied in 32 patients: the combination lowered LDL levels by 36% in eight patients, whereas fenofibrate alone lowered levels by 22% in eight patients (data presented at the European Atherosclerosis Society Meeting, Glasgow, Scotland, May 2001). There were no significant improvements in HDL or triglyceride levels.

While we have no clinical trial evidence of the efficacy of ezetimibe in combination with colesevelam, we have used this combination in several patients in our comprehensive lipid clinic (Center for Cardiovascular Disease at Baylor College of Medicine, Houston, Tex). In theory, the different mechanisms of action of these drugs should be complementary in LDL-lowering, and it is unlikely that colesevelam would interfere with ezetimibe's activity.

The side-effect profile of ezetimibe is similar to that of placebo

Role of ezetimibe: Primarily in combination therapy

In clinical settings, the most practical use of ezetimibe will be in combination with ongoing statin therapy in patients who have not reached their LDL goals. Occasionally, ezetimibe monotherapy may be used when the patient cannot tolerate statin therapy or does not wish to use a statin.

Because patients sometimes cannot tolerate maximum doses of statins or a combination of a statin and a fibrate or a statin and niacin, clinicians may choose moderate-dose statin monotherapy or low-dose statin therapy plus an agent less likely to increase the risk of hepatotoxicity and myopathy. Ezetimibe may have a role in such cases: in studies evaluating ezetimibe in combination with statin therapy, there appears to be no significant increase in the side effects compared with placebo.

Side effects

Clinical trials of ezetimibe as monotherapy have involved more than 1,700 patients, and trials of ezetimibe in combination with statins have included more than 2,300 patients. The most common complaints in both types of therapy were gastrointestinal and musculoskeletal symptoms, and headache.

In phase 3 trials of ezetimibe as monotherapy, the incidence of elevated serum transaminase levels (three or more times the upper limit of normal) was less than 1.0%. No creatine kinase elevations of 10 or more times the upper limit of normal were noted.

In studies of combination therapy (a statin plus ezetimibe), ezetimibe had no effect on the pharmacokinetics of simvastatin, atorvastatin, or lovastatin.

The overall safety profile of ezetimibe in combination with statins is comparable to that of statin monotherapy. The incidence of elevated serum transaminase levels of three or more times the upper limit of normal was 0.4% for a statin alone and 1.3% for ezetimibe plus a statin. Creatine kinase elevations of greater than five times the upper limit of normal occurred in fewer than 1.0% of subjects.

Angioedema. A warning was recently added to the ezetimibe label about the risk of angioedema as a side effect. At present, there are no absolute numbers as to the frequency of angioedema, which was not seen during clinical trials prior to the drug's approval.

Cost-effectiveness of ezetimibe

Cost-effectiveness studies of ezetimibe have not been done yet, but at an approximate retail cost of $72 for 30 pills, it is clearly more expensive to add ezetimibe to ongoing statin therapy than to titrate statin therapy to a higher dose. On the other hand, the risk of adverse effects is higher with maximal statin dosing, and physicians are reluctant to prescribe statins at those doses.

Ezetimibe's cost-effectiveness may be improved when the manufacturer carries out

its plan to develop a single pill that contains simvastatin and ezetimibe.

RECOMMENDATIONS

We should look to the evidence-based ATP III guidelines for help in optimizing CHD risk-reduction for our patients at risk, including patients with diabetes, the metabolic syndrome, or hypertension with other risk factors. Our attempts to reduce LDL levels need to be more intensive and should include lifestyle changes and drug treatment.

While statins remain the first line of therapy for most patients, some patients do not tolerate them, so other drugs and combinations should be considered. Concern about potential hepatic or muscle toxicity with maximum-dose statin therapy or with combination therapies such as statin plus fibrates may contribute to undertreatment.

In such cases, ezetimibe may have a role. It has been shown to be safe and effective when given with a statin without increasing adverse events, and it also appears to safely lower LDL levels when used alone. In theory, the mechanism of action of ezetimibe should complement that of fibrates, niacin, and bile acid resins. Further efficacy and safety trials are warranted to confirm this.

In addition, trials of ezetimibe treatment with vascular and clinical end points need to be done. Nonetheless, ezetimibe appears to be effective and well tolerated in lowering LDL levels, both as monotherapy or in combination with a statin.

REFERENCES

1. **Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.** Executive summary of the third report of the National Cholesterol Education Program (NCEP): Adult Treatment Panel III. JAMA 2001; 285:2486–2497.
2. **Shepherd J, Cobbe SM, Ford I, et al.** Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. The West of Scotland Coronary Prevention Study Group. N Engl J Med 1995; 333:1301–1307.
3. **Downs JR, Clearfield M, Weis S, et al.** Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279:1615–1622.
4. **Sever PS, Dahlof B, Poulter NR, et al.** Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA). Lancet 2003; 361:1149–1158.
5. **Collins R, Armitage J, Parish S.** MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised, placebo-controlled trial. Lancet 2002; 360:7–22.
6. **Scandinavian Simvastatin Survival Study Group.** Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease. Lancet 1994; 344:1383–1389.
7. **Sacks FM, Pfeffer MA, Moye LA, et al.** The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Am J Cardiol 1991; 68:1436–1446.
8. **The Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.** Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339:1349–1357.
9. **Sueta CA, Chowdhury M, Boccuzzi SJ, et al.** Analysis of the degree of undertreatment of hyperlipidemia and congestive heart failure secondary to coronary artery disease. Am J Cardiol 1999; 83:1303–1307.
10. **Pearson TA, Laurora I, Chu H, et al.** The Lipid Treatment Assessment Project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemia patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. Arch Intern Med 2000; 160:459–467.
11. **Fonarow GC, French WJ, Parsons LS, et al.** Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: data from the National Registry of Myocardial Infarction 3. Circulation 2001; 103:38–44.
12. **Jones P, Kafonek S, Lauroa I, et al.** Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (The CURVES Study). Am J Cardiol 1998; 81:582–587.
13. **Pasternak RC, Smith SC Jr, Bairney-Merz CN, et al.** ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002; 40:568–573.
14. **Shepherd J.** Fibrates and statins in the treatment of hyperlipidemia: an appraisal of their efficacy and safety. Eur Heart J 1995; 16:5–13.
15. **Frick MH, Elo O, Happa K, et al.** Helsinki Heart Study: primary prevention trial with gemfibrozil in middle aged men with dyslipidemia. N Engl J Med 1987; 317:1237–1245.
16. **Rubins HB, Robins SJ, Collins D, et al.** Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999; 341:410–418.
17. **Goldberg A, Alagona P Jr, Capuzzi DM, et al.** Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. Am J Cardiol 2000; 85:1100–1105.
18. **McKenney JM, Proctor JD, Harris S.** A comparison of efficacy and toxic effects of sustained vs immediate release niacin in hypercholesterolemic patients. JAMA 1994; 271:672–677.
19. **Elam MB, Hunninghake DB, Davis KB, et al.** Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease. The ADMIT Study: a randomized trial. JAMA 2000; 284:1263–1270.
20. **Block DM.** Gut-acting drugs for lowering cholesterol. Curr Atherosclerosis Rep 2002; 4:71–75.
21. **Bays HE, Moore PB, Drehobl MA, et al.** Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001; 23:1209–1230.
22. **Dujovne CA, Ettinger MP, McNeer JF, et al.** Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002; 90:1092–1097.
23. **Gagno C, Bays HE, Weiss SR, et al.** Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; 90:1084–1091.

ADDRESS: *Ryan C. Neal, MD, Assistant Professor of Medicine, Baylor College of Medicine, 6565 Fannin, Suite B160 A, Mailstop A601, Houston, TX 77030; e-mail rneal@bcm.tmc.edu.*