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Optimizing Lipid Lowering in Patients at Risk

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Summary: The efficacy of statins in lowering low-density lipoprotein cholesterol (LDL-C) and reducing coronary heart disease risk is well established; however, recent evidence suggests that more aggressive lipid management, even beyond achievement of currently recommended LDL-C goals, may provide additional clinical benefits. A novel approach to the aggressive lowering of LDL-C is the combination of statins with agents that affect different aspects of cholesterol metabolism. Because absorption of cholesterol is an important contributor to cholesterol balance, the simultaneous inhibition of cholesterol absorption and cholesterol synthesis is an attractive approach to achieving greater LDL-C reductions. In clinical trials, the combination of the cholesterol absorption inhibitor ezetimibe with a statin resulted in greater improvements in lipids than statin monotherapy and allowed a greater percentage of patients to achieve treatment goals. In addition, this combination may offer benefits through reduction of phytosterols, chylomicron remnants, and C-reactive protein. Several ongoing trials are evaluating whether the benefit of simultaneously blocking cholesterol synthesis and intestinal cholesterol absorption translates into better clinical outcomes.

Introduction

Numerous clinical trials demonstrate that lowering low-density lipoprotein cholesterol (LDL-C) significantly reduces the risk of coronary heart disease (CHD);[1–5] nevertheless, treated patients retain a substantial degree of residual CHD risk.[1–5] This finding may be related to less-than-optimal control of risk factors, including dyslipidemia. Poor control of dyslipidemia is supported by surveys conducted in clinical practice that showed that many patients, particularly those at highest CHD risk, did not achieve the current target LDL-C levels. In three different studies, 77 to 82% of patients with CHD and 55 to 81% of patients with more than two risk factors failed to achieve their LDL-C target goal.[6–8]

Furthermore, recent clinical trials demonstrate that reduction of LDL-C to targets below those currently recommended may be needed to provide the greatest clinical benefit. In the Heart Protection Study (HPS), simvastatin reduced the risk of a major vascular event by 24% ($p < 0.001$), even among patients whose baseline LDL-C levels were already at the Adult Treatment Panel (ATP) III goal of < 100 mg/dl.[9] Nevertheless, the rate of vascular events in patients treated with simvastatin was 19.8%, demonstrating that more aggressive treatment of risk factors, including greater LDL-C reduction, may be needed to provide greater CHD prevention.

Two very recent studies, Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)[10] and Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL),[11] provide further evidence, suggesting that the optimal benefits from lipid lowering are achieved at levels well below those recommended by current guidelines.

How Can Greater Low-Density Lipoprotein Cholesterol Reductions Be Achieved?

Achieving greater LDL-C reductions can be approached by either titrating the statin dose or by combining statins with other LDL-C-lowering agents. Statin dose titration is limited by the fact that most LDL-C reduction with these agents is accomplished with the starting dose, with each dose titration (doubling) thereafter yielding only a small incremental 3 to 7% LDL-C reduction.[12] In clinical practice, statin dose titration is often ineffective in achieving LDL-C target goals. In a recent prospective, observational study,[13] physicians (mostly cardiologists) were instructed to treat their patients with CHD and diabetes according to guidelines, follow prescribing information for the statin, and titrate the dose as needed to achieve an LDL-C goal < 100 mg/dl. Of these patients, 52% did not achieve their target goal on the starting statin dose, and only 45% of patients not at goal had their dose titrated. Of those patients whose statin doses were titrated, 90% were titrated only

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once and only 31% (14% of the total population) attained their LDL-C goal within 6 months of starting treatment.[13]

More effective lowering of LDL-C can be achieved by the combination of statins with other agents that affect cholesterol balance. The LDL-C lowering effect of statins is mediated by reducing hepatic cholesterol content by inhibiting hepatic cholesterol synthesis. The liver responds to this decrease by increasing LDL-receptor expression and clearing greater amounts of LDL-C from the plasma. Reduction of hepatic cholesterol levels and the resultant clearance of LDL-C from the plasma can also be induced by reducing the amount of dietary/biliary cholesterol that is absorbed and delivered to the liver via the intestine or by increasing the amount of cholesterol that is eliminated from the liver into the bile. These cholesterol pathways can be targeted by intestinal-acting agents (Fig. 1). Cholesterol absorption inhibitors, such as ezetimibe, inhibit the absorption of cholesterol at the brush border of the small intestine,[14] leading to a decrease in the delivery of cholesterol to the liver. The combination of a statin and cholesterol absorption inhibitor therapies has the advantage of inhibiting both major sources of net cholesterol gain. Statins can also be combined with bile acid sequestrants (BAS), which lower hepatic cholesterol by stimulating conversion of hepatic cholesterol to bile acids.

Benefits of Combination Therapy in Optimizing Lipid Lowering: Evidence from Clinical Trials

Combination Therapy with Statins plus Bile Acid Sequestrants

Combination therapy with simvastatin and the BAS colesevelam was evaluated in a multicenter study of patients with primary hypercholesterolemia.[15] In all, 251 patients with baseline LDL-C ≥ 160 mg/dl and triglycerides ≤ 300 mg/dl were randomized to simvastatin 10 or 20 mg, colesevelam 2.3 or 3.8 g, simvastatin 10 mg plus colesevelam 3.8 g, simvastatin 20 mg plus colesevelam 2.3 g, or placebo. Additive reductions in LDL-C were seen with each combination regimen relative to monotherapy with each component. Both combination regimens reduced LDL-C from baseline by a mean of 42% ($p < 0.0001$), compared with the LDL-C reductions of 26 and 34% with simvastatin 10 mg and 20 mg, respectively. Changes in high-density lipoprotein cholesterol (HDL-C) and triglycerides with combination therapy were not significantly improved relative to simvastatin alone. Although the use of a statin plus a BAS produced additive effects on LDL-C, this combination approach may be associated with low compliance due to gastrointestinal intolerability and the need to take numerous pills; colesevelam doses of 2.3 and 3.8 g require 6 and 10 capsules per day, respectively.

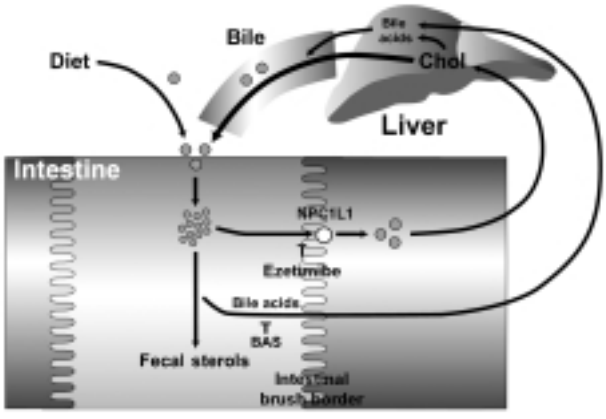

FIG. 1 Mechanism of intestinal-acting agents. Chol = cholesterol, BAS = bile acid sequestrants.

Inhibition of Cholesterol Absorption and Synthesis

The benefit of inhibition of both cholesterol absorption and cholesterol synthesis was demonstrated in large, randomized clinical trials with statin therapy and the cholesterol absorption inhibitor ezetimibe.[16–20] More recently, the benefit of simultaneous inhibition of cholesterol absorption and synthesis by administration of ezetimibe/simvastatin versus simvastatin alone was reported in a large, randomized, double-blind, placebo-controlled multicenter study of patients with primary hypercholesterolemia.[21] Following a 4-week, single-blind, lead-in period, 887 eligible patients with LDL-C levels of 145 to 250 mg/dl and triglycerides ≤ 350 mg/dl during the lead-in were assigned to one of 10 treatment groups: ezetimibe 10 mg; simvastatin 10, 20, 40, or 80 mg; ezetimibe 10 mg/simvastatin 10, 20, 40, or 80 mg; or placebo. Each treatment was administered once daily for 12 weeks. The primary efficacy variable was the percent change from baseline in LDL-C.

In this trial,[21] the administration of ezetimibe/simvastatin reduced LDL-C by 46.2 to 60.8% over the 10 to 80 mg dose range, compared with LDL-C reductions of 31.3 to 45.6% with 10 to 80 mg simvastatin alone (Fig. 2). Across all doses, the additional reduction in LDL-C achieved with ezetimibe/simvastatin was statistically significant versus simvastatin (−53.1 vs. −38.3%, $p \leq 0.001$). The lowest combination therapy dose (ezetimibe 10 mg/simvastatin 10 mg) was as effective in lowering LDL-C as simvastatin 80 mg. Of importance is the finding that treatment with ezetimibe/simvastatin allowed 82.4% of patients to achieve their LDL-C goal of < 100 mg/dl compared with 42.9% of patients treated with simvastatin alone ($p < 0.001$) (Fig. 3). In addition to the beneficial effects on LDL-C, ezetimibe/simvastatin produced a significant 13% reduction in triglycerides (−28.0 vs. −15.2%, $p \leq 0.001$) and a significant 14% reduction in non-HDL-C (−48.5 vs. 34.1%, $p < 0.001$) relative to simvastatin monotherapy. Ezetimibe/simvastatin was well tolerated, with an overall safety profile comparable with simvastatin alone.[21]

Another recently completed trial directly compared the efficacy of coadministration of ezetimibe and simvastatin versus atorvastatin alone.[22] In this large, randomized trial, patients treated with ezetimibe/simvastatin showed LDL-C reductions of 46.1 to 59.4% when titrated over the 10 to 80 mg simvastatin dose range, compared with 37.2 to 52.5% with 10 to 80 mg

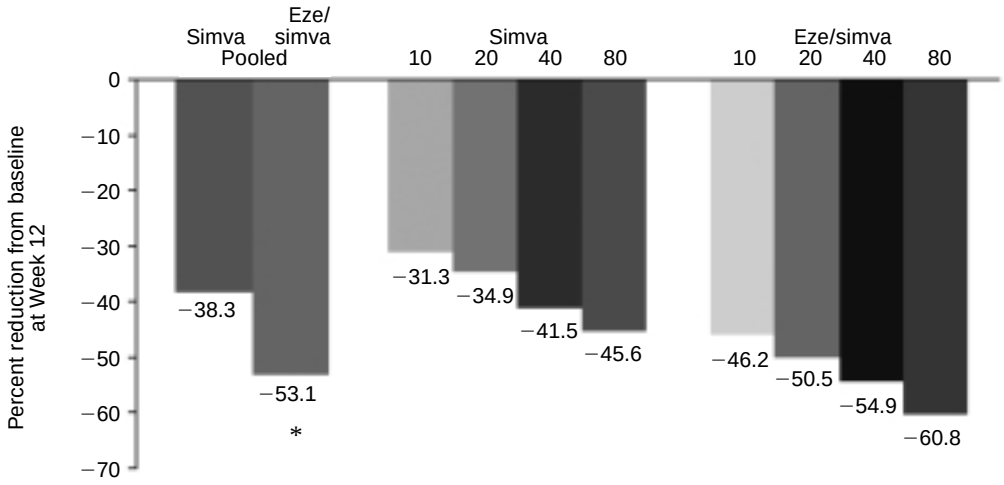

FIG. 2 Effect of coadministration of ezetimibe (Eze) 10 mg with simvastatin (Simva) at 10 mg to 80 mg in patients with primary hypercholesterolemia. Results for pooled ezetimibe/simvastatin versus pooled simvastatin groups are shown on the left. Results are presented as mean percent change from baseline. *p ≤ 0.001 versus placebo. Data are from Ref. No. 21.

atorvastatin alone. Reductions in LDL-C were significantly greater with ezetimibe/simvastatin versus atorvastatin at each corresponding statin dose (p ≤ 0.01). The effect of ezetimibe/simvastatin versus atorvastatin alone on HDL-C was particularly evident, with significantly greater increases at 10 mg (8.0 vs. 5.1%), 20 mg (9.0 vs. 6.9%), 40 mg (11.4 vs. 7.8%), and 80 mg (12.3 vs. 6.5%) of each respective statin dose.

Additional Benefits of Combining a Cholesterol Absorption Inhibitor and a Statin: Beyond Low-Density Lipoprotein Cholesterol

Chylomicron cholesterol: Intestinally absorbed cholesterol is transported to the liver via chylomicrons and chylomicron remnants. Chylomicron remnants have been shown to penetrate into the arterial wall, where they may contribute to the atherosclerotic process.[23] Diabetes and other lipid disorders are associated with an impaired clearance of chylomicrons.[24]

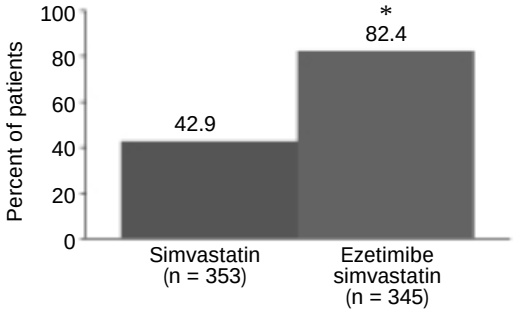

FIG. 3 Percentage of patients attaining National Cholesterol Education Program-Adult Treatment Panel (NCEP ATP) III low-density lipoprotein cholesterol (LDL-C) goal of < 100 mg/dl with ezetimibe/simvastatin versus simvastatin alone. *p < 0.001 for statin plus ezetimibe versus statin plus placebo. Data are from Ref. No. 21.

Thus, the reduction in chylomicron cholesterol by ezetimibe[25] may represent an additional mechanism by which ezetimibe may reduce atherogenic potential.

Phytosterols: Phytosterols are structurally related to cholesterol and are found in the diet at levels near those of cholesterol, although they are absorbed less efficiently. Patients who have the inherited disease β-sitosterolemia have very high plasma concentrations of phytosterols and develop premature atherosclerosis and CHD. Other studies have demonstrated that moderately elevated levels of phytosterols in normal individuals may also be associated with increased CHD risk.[26, 27] Like cholesterol, phytosterol absorption in the intestine is inhibited by ezetimibe, and ezetimibe treatment has been shown to decrease plasma concentrations of phytosterols significantly in patients with and without β-sitosterolemia. In patients with β-sitosterolemia, those who received ezetimibe 10 mg had significant reductions in campesterol and sitosterol of 24 and 21%, respectively, versus placebo at the end of the 8-week treatment period (p = 0.001).[28] Recently, in a placebo-controlled study in patients with primary hypercholesterolemia, administration of ezetimibe/simvastatin reduced levels of campesterol and sitosterol by 61 and 52%, respectively, at the end of the 12-week study period (p < 0.001).[29] Thus, by virtue of the cholesterol absorption inhibitor component, inhibition of cholesterol absorption and synthesis offers the additional benefit of reducing phytosterols, the clinical benefit of which remains to be determined.

High-Sensitivity C-Reactive Protein: Several investigations have demonstrated the central role of inflammation in atherosclerosis and cardiovascular risk. High-sensitivity C-reactive protein (hs-CRP) is an inflammatory marker that has been associated with increased cardiovascular risk. Notably, in the Women's Health Study, higher hs-CRP levels were associated with greater cardiovascular risk at all LDL-C concentrations and at all Framingham estimates of 10-year CHD risk.[30] Re-

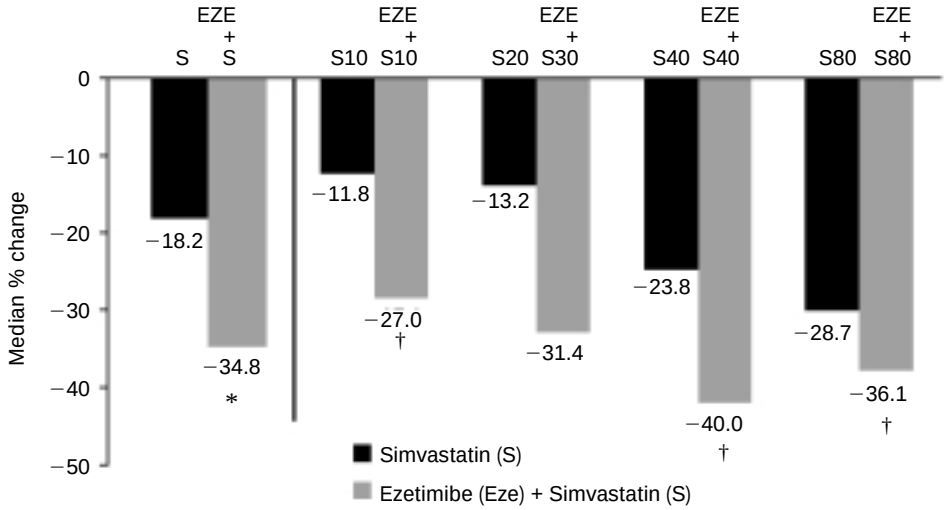

FIG. 4 Median percent change from baseline in high-sensitivity C-reactive protein (hs-CRP) following treatment of primary hypercholesterolemic patients with simvastatin alone, or ezetimibe plus simvastatin. The results are pooled for patients treated with simvastatin 10, 20, 40, or 80 mg, and for ezetimibe 10 mg plus simvastatin 10, 20, 40, or 80 mg. *$p < 0.01$ versus simvastatin monotherapy; †$p < 0.05$ versus simvastatin monotherapy. Abbreviations as in Figure 1. Reprinted from Ref. No. 32 with permission from Excerpta Medica Inc.

cently, a causal role for CRP in atherosclerosis was demonstrated in mice,[31] suggesting the possibility that CRP reduction may reduce CHD events. In a study of combination ezetimibe/simvastatin therapy,[32] ezetimibe coadministered with simvastatin nearly doubled the median reduction in hs-CRP versus simvastatin alone (34.8 vs. 18.2%, $p < 0.01$) (Fig. 4). At each simvastatin dose, ezetimibe provided additional reductions in hs-CRP versus simvastatin alone ($p < 0.05$ at 10, 40, and 80 mg, $p = 0.09$ at 20 mg), and ezetimibe plus 10 mg simvastatin was as effective in reducing hs-CRP as 80 mg simvastatin alone. Given the potential role of CRP in atherosclerosis,[30] the large effects of cholesterol absorption inhibitor/statin therapy on hs-CRP may attenuate the detrimental effects of inflammation on cardiovascular risk.

Ongoing Trials

Several ongoing trials are evaluating whether the beneficial effects of ezetimibe plus simvastatin translate into superior clinical outcomes. Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) is a 2-year study that is evaluating whether combination therapy with ezetimibe plus simvastatin 80 mg is more effective than simvastatin 80 mg alone in reversing carotid atherosclerosis in patients with heterozygous familial hypercholesterolemia.[33] Simvastatin and Ezetimibe in Aortic Stenoses (SEAS) is a 4-year, placebo-controlled study that is conducted in patients with aortic stenosis. This study is evaluating whether ezetimibe plus simvastatin 40 mg affects progression of aortic stenosis and risk of major cardiovascular events.[33] Finally, the Study of Heart and Renal Protection (SHARP) is a 4-year trial that will compare ezetimibe plus simvastatin with simvastatin alone in patients with chronic kidney disease.[34] The SHARP trial plans to enroll 9,000 patients, including 3,000 patients on dialysis, and will evaluate major vascular events and the rate of loss in renal function. The results of these trials will provide critical information regarding the clinical impact of this novel approach to lipid management and are eagerly awaited.

Conclusions

Although statin therapy has a well-established clinical benefit, recent clinical trials have demonstrated that more aggressive LDL-C lowering than currently achieved with statin monotherapy may be necessary for optimal benefit. Greater LDL-C reductions can be achieved by combining statins with agents that target other aspects of cholesterol metabolism. The simultaneous inhibition of hepatic cholesterol synthesis and intestinal cholesterol absorption has emerged as an attractive approach to LDL-C lowering, and clinical trials show that the coadministration of the cholesterol absorption inhibitor ezetimibe with a statin results in greater improvements in lipid parameters and greater attainment of LDL-C goals than those achieved with statin monotherapy. This approach also offers the additional benefits of reduction of phytosterols, chylomicron cholesterol, and hs-CRP. The results of ongoing clinical trials will determine whether the benefits of simultaneously blocking cholesterol synthesis and intestinal cholesterol absorption will translate into superior clinical outcomes.

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