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Cholesterol absorption inhibition: filling an unmet need in lipid-lowering management

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International guidelines specify target concentrations of low-density lipoprotein cholesterol (LDL-C) to reduce the risk of coronary heart disease. Although statins are the most widely prescribed cholesterol-lowering drugs, they have a number of limitations. A significant number of statin-treated patients do not reach recommended LDL-C target levels, even with high-dose therapy. Each doubling of the statin dose results in only a 6% reduction in LDL-C. Elevation of liver transaminase levels and muscle toxicity have been associated with high statin doses. Currently available agents that are co-administered with statins are not well tolerated due to gastrointestinal intolerance or are associated with an increased risk of myopathy. The limitations of statin monotherapy and currently available combination therapy warrant the need for more safe, effective and convenient approaches to combination therapy. Co-administration of statins and cholesterol absorption inhibitors may overcome some of these limitations and effectively target both the endogenous and exogenous pathways of cholesterol metabolism. Ezetimibe, a novel selective cholesterol absorption inhibitor, has demonstrated an excellent safety and tolerability profile and a LDL-C-lowering effect that is additive with statins. Co-administration of ezetimibe and a statin may therefore fill an unmet need in lipid-lowering management and provide broader lipid control.

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Key Words: Cholesterol absorption inhibitor, ezetimibe, statins, hypercholesterolaemia, low-density lipoprotein cholesterol, target cholesterol levels.

Introduction

Results from primary and secondary prevention trials with statins have shown that the use of cholesterol-lowering drugs is associated with a reduced risk of coronary-related events, resulting in reduced cardiovascular morbidity and mortality[1–6]. Such clinical trial data strongly support the target low-density lipoprotein cholesterol (LDL-C) levels recommended in the European[7] and American[8] guidelines for the prevention of coronary heart disease (Table 1). The statins are the most widely prescribed drugs for the treatment of hypercholesterolaemia. The question remains whether there is a role for additional drugs in the treatment of patients with hypercholesterolaemia when we already have the very potent statins, which are usually very efficacious in these patients. Why do we need something other than a statin?

Statins lower cholesterol concentrations more effectively than any previously available medication, but their efficacy is not consistently maximized in practice. Despite formal guidelines, only a small percentage of patients eligible for cholesterol-lowering drug therapy receive treatment[9–12]. Secondary prevention studies suggest that the lower the LDL-C attained, the greater the clinical benefit, and underscore the need for more aggressive treatment of hyperlipidaemia[5,13,14]. However, only a small fraction of those receiving treatment achieves the recommended target LDL-C levels[9,11,12,15]. Optimum doses may not be used routinely because of the need for multiple dosage adjustments and safety concerns with high doses. Furthermore, some individuals do not respond optimally to statins.

Combinations of drugs that act by different mechanisms can provide additive effects in reduction of LDL-C levels[16,17]. Combination of two, or sometimes three, lipid-modifying drugs may be needed to meet target LDL-C plasma levels recommended by the European Second Joint Task Force[7] and the U.S. National Cholesterol Education Program (NCEP)[8], especially in patients with mixed dyslipidaemia or moderate-to-severe hypercholesterolaemia. However, combination therapy with statins and nicotinic acid, fibric acid derivatives or bile acid sequestrants is limited by the increased potential for side effects, intolerance and drug interactions[18–22]. These issues can lead to decreased compliance with the treatment regimen and

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Table 1 Recommended target low-density lipoprotein cholesterol (LDL-C) levels

	Europe (EAS) LDL-C [mmol . l^{-1} (mg . dl^{-1})]	U.S.A. (NCEP-ATPII) LDL-C [mmol . l^{-1} (mg . dl^{-1})]
Macrovascular disease (CHD-positive)	3·0–3·5 (115–135)	≤2·6 (100)
No macrovascular disease (CHD-negative)		
≥two risk factors or genetic hyperlipidaemia	3·5–4·0 (135–155)	<3·4 (130)
Lipid risk factor (no non-lipid risk factor)	4·0–4·5 (155–175)	<4·1 (160)

EAS=European Atherosclerosis Society; NCEP-ATPII=National Cholesterol Education Panel — Adult Treatment Panel II; CHD=coronary heart disease.

can preclude the long-term treatment schedule needed to reduce the risk of cardiovascular disease.

Selective cholesterol absorption inhibitors, such as ezetimibe, represent a new option for controlling dietary and biliary cholesterol. Inhibition of cholesterol absorption with ezetimibe combined with inhibition of cholesterol synthesis with a statin may provide greater reduction in LDL-C levels than previously achieved, given the complementary targets of the exogenous and endogenous pathways of cholesterol metabolism. Pharmacokinetic and pharmacodynamic drug-interaction trials have demonstrated that ezetimibe co-administered with a low-dose statin provides greater reductions in LDL-C level than statin monotherapy and also a safe profile[23–25]. Co-administration therapy with a statin and ezetimibe represents a new approach to lipid management that offers great promise in overcoming many of the limitations of current therapeutic strategies.

Limitations of statin monotherapy

The rule of six

A substantial number of patients do not reach recommended LDL-C levels with statin monotherapy, even at high doses. The dose needed to decrease plasma LDL-C levels to a similar degree varies substantially among the six approved statins, and the dose-response relationship is not proportional[26]. Most of the LDL-C-reducing effect is achieved at the starting dose[17]. In general, the statin dose needs to be doubled for each 6% incremental reduction in LDL-C level over the baseline level achieved with the starting dose[26]. Clinical evidence substantiates this 'rule of six,' which is a characteristic of all of the statins. Figure 1 shows the mean percentage reductions in LDL-C level with the recommended starting doses and the maximum approved doses of the six statins[27]. An initial dosage of 10 mg of atorvastatin, for example, reduces the LDL-C level an average of 37%; however, at the maximum dosage of 80 mg daily (three steps of doubled dosage), the additional reduction in LDL-C level is only 18%.

Barter and O'Brien recently reported a study of increasing doses of atorvastatin and simvastatin in 1028 patients with primary hypercholesterolaemia and baseline total cholesterol levels ranging from 5·2 mmol . l^{-1} (201 mg . dl^{-1}) to >9·5 mmol . l^{-1} (367 mg . dl^{-1})[28]. The target level of total cholesterol in the plasma was <5·0 mmol . l^{-1} (193 mg . dl^{-1}). The authors report that the changes in plasma total cholesterol level were largely a reflection of changes in LDL-C level. After 6 weeks of treatment, 38% of patients achieved the target level with 10 mg of atorvastatin daily. It was only when the dose was increased to the maximum of 80 mg that 83% of patients achieved the target level after 24 weeks of therapy.

Attainment of target cholesterol levels also depends on the baseline levels. Among patients whose baseline level was 5·2 mmol . l^{-1} (201 mg . dl^{-1}) to 6.5 mmol . l^{-1} (251 mg . dl^{-1}), 71% achieved the target total cholesterol level with 10 mg of atorvastatin, and 95% achieved it with doses of up to 80 mg daily for 24 weeks. As expected, higher baseline total cholesterol levels were associated with smaller percentages of patients achieving target levels, even with escalation of the statin dose (Fig. 2). Less than 43% of atorvastatin-treated patients with a baseline total cholesterol level >6·6 mmol . l^{-1} (255 mg . dl^{-1}) reached the target level with the 10-mg dose, indicating that most patients

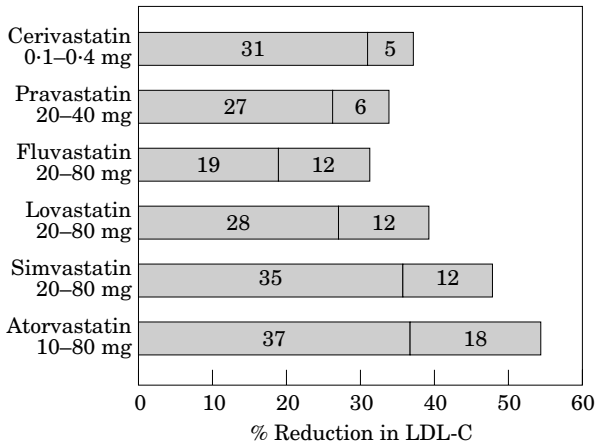

Figure 1 **Mean percentage reductions in low-density lipoprotein cholesterol (LDL-C) levels with the customary starting dose and with the maximum approved dose of the six statins. The maximum dose for lovastatin and fluvastatin is b.i.d. (Reproduced with permission[27].)**

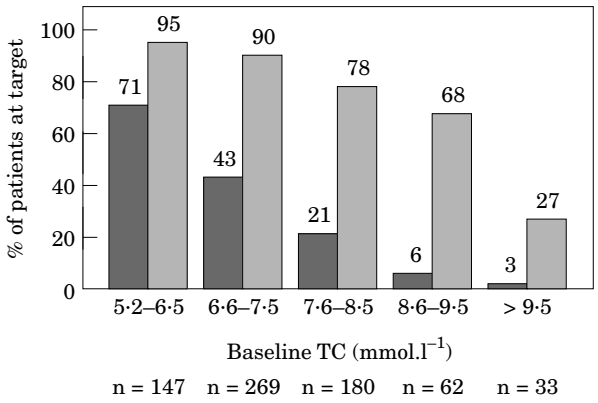

Figure 2 **Treatment-to-target effect of baseline total cholesterol (TC): atorvastatin (■) 10 mg, (□) 10–80 mg. (Reproduced with permission[28].)**

(about two-thirds) need to have the statin dose increased to reach optimal target cholesterol levels. Among patients with baseline levels of 7·6 mmol . l^{-1} (293 mg . dl^{-1}) to 8·5 mmol . l^{-1} (329 mg . dl^{-1}), only 78% achieved target levels with up to 80 mg daily. In practice, this suggests that more than 20% of patients with moderate baseline total cholesterol levels will not reach target levels, even with maximum doses of atorvastatin. Patients with familial hypercholesterolaemia have excessive baseline total cholesterol levels. Of the patients with a baseline total cholesterol level >9·5 mmol . l^{-1} (367 mg . dl^{-1}), 3% attained target levels with atorvastatin 10 mg and 27% reached target levels with doses to 80 mg. These patterns were similar with simvastatin treatment, but even fewer patients achieved target levels with simvastatin.

Statin escape phenomenon

Well known to physicians who treat hypercholesterolaemic patients with statins, the 'escape phenomenon' refers to the slow increase in LDL-C levels that can occur after the initial response during prolonged periods of drug administration[29]. Barter and O'Brien have reported evidence of this phenomenon in patients given 10-mg daily doses of atorvastatin (Fig. 3a) or simvastatin (Fig. 3b)[28]. After week 6, 38% of patients treated with atorvastatin reached the target level, but at week 12 only 27% (more than two-thirds of the atorvastatin-treated patients) maintained the desired levels; in this treatment group, the mean cholesterol levels gradually increased from 4·5 mmol . l^{-1} (174 mg . dl^{-1}) to 4·8 mmol . l^{-1} (186 mg . dl^{-1}) during the 24-week study (Fig. 3a). Similarly, in the simvastatin group, 26% of patients reached the target level after week 6, but only 12–16% (roughly half of the simvastatin-treated patients) maintained it throughout the study. The mean plasma total cholesterol level for the simvastatin group increased from 4·6 mmol . l^{-1} (178 mg . dl^{-1}) initially to 5·1 mmol . l^{-1} (197 mg . dl^{-1}) at the end of the

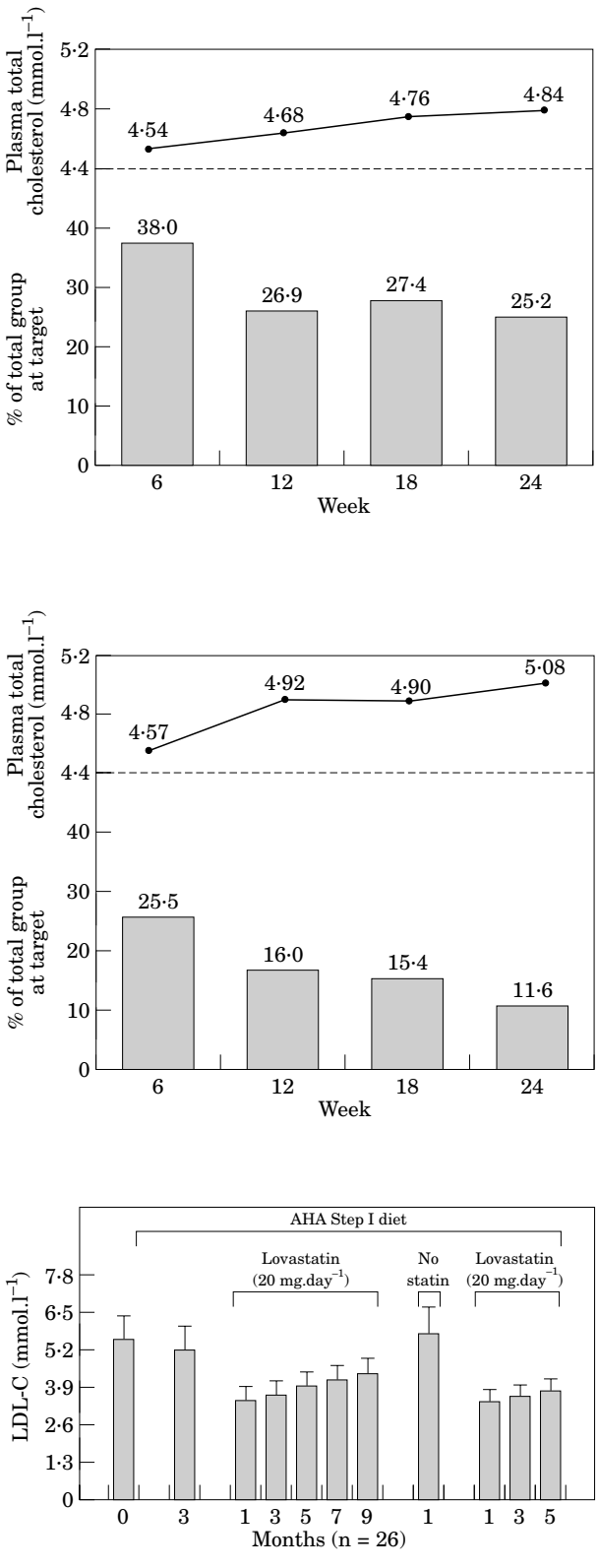

Figure 3 **The escape phenomenon that occurs with HMG-CoA reductase inhibitors, demonstrated with (top) atorvastatin (10 mg), (middle) simvastatin (10 mg), and (bottom) lovastatin (20 mg) therapy. AHA = American Heart Association; LDL-C = low-density lipoprotein cholesterol. (Reproduced with permission[28,29].)**

study. Thirty-three per cent of the atorvastatin and 55% of the simvastatin patients who were at the target cholesterol level at week 6 were no longer at target during week 24 of therapy.

Rubenstein and Weintraub reported the escape phenomenon of LDL-C during lovastatin treatment[29]. Twenty-six patients received 20 mg of lovastatin and were instructed to follow the American Heart Association Step I diet. Patients followed these dietary recommendations throughout the study. The maximum decrease in LDL-C occurred after 1 month of lovastatin therapy, followed by a slow increase in LDL-C over 9 months (Fig. 3c). At that point, lovastatin was discontinued for 1 month, and then restarted. The escape phenomenon was again evident, with a small but consistent increase in LDL-C levels over the next 5 months.

Possible explanations for this escape phenomenon include patient non-compliance with statin therapy or dietary recommendations. Short-term compliance can be improved, but attempts to improve long-term adherence to dietary restrictions have had limited success. Escape phenomenon may also be due to reduced efficacy of the statins by induction of HMG-CoA reductase, cytochrome P450 enzymes or by another yet undiscovered mechanism[29].

Hepatotoxicity and myopathy concerns

Increasing the statin dose may cause elevation of liver aminotransferase levels with concomitant hepatotoxicity, and elevation of creatine kinase levels with concomitant myotoxicity. In the Expanded Clinical Evaluation of Lovastatin (EXCEL) study, for example, an increase in lovastatin dose (20 mg to 80 mg) increased the incidence of persistent aminotransferase elevations (to greater than three times the upper limit of normal) from 0·1–1·5%[30]. This study included 8245 patients treated with 20 mg or 40 mg of lovastatin once daily, 20 mg or 40 mg twice a day, or placebo. The percentages of individuals with aminotransferase elevations three times the upper limit of normal on successive measures were similar in the placebo and 20-mg daily (0·1%) groups. However, the percentages of patients with significant aminotransferase elevations progressively increased as the lovastatin dose increased, and reached 1·5% in patients receiving 80 mg daily ($P<0·001$). The percentages of patients who had single increases in aminotransferase values followed the same trend. For the placebo group, 1·2% of patients had a single aminotransferase elevation greater than three times the upper limit of normal, whereas 3·2% of patients given the highest dose of lovastatin had a single elevation.

In a more recent study evaluating the effects of increasing doses of atorvastatin compared with placebo in 4704 patients, increases of aminotransferase levels with the lowest doses of atorvastatin (10 mg or 20 mg daily) were similar to those in the placebo group[31]. With the higher doses of atorvastatin (40 mg or 80 mg daily), however, 2·3% of patients had significant elevations of aminotransferase levels. An increase in atorvastatin dose from 40 mg to 80 mg decreased LDL-C level from 51–57% of placebo, but also increased the incidence of elevated aminotransferases nearly fourfold (from 0·6–2·3% of patients).

The prescribing information for atorvastatin, lovastatin and simvastatin shows a 60% reduction in LDL-C level with 80 mg of atorvastatin compared with a 50% reduction with 40 mg of atorvastatin, but this dose increase results in a fourfold increase in the percentage of patients with significantly elevated aminotransferase levels (Fig. 4). With the highest recommended dose of lovastatin (80 mg daily), there is a 1·7-fold increase in the percentage of patients with elevated aminotransferase levels. With high-dose simvastatin, the comparable increase is 2·3-fold relative to the starting dose. It would therefore be preferable to avoid high doses of statins.

The EXCEL study also showed creatine kinase elevations in each group; the trend was similar to that with aminotransferase elevations. The percentages of single creatine kinase elevations greater than 10 times the upper limit of normal were similar in the placebo group and in each of the lovastatin-treated groups, except the group treated with 80 mg daily. In the latter high-dose group, the percentage of patients with creatine kinase elevations (3·5%) was much greater than that in the placebo group (1·6%) and in each of the other lovastatin treatment groups (range 1·0–2·1%). Myopathy occurred in one patient (0·1%) receiving 40 mg of lovastatin once daily and in four patients (0·2%) receiving the 80-mg dose. It has been recently estimated that 0·1–0·5% of patients taking cholesterol-lowering drugs will have a drug-related elevation in serum creatine kinase[32]. The incidence of the more serious rhabdomyolysis is about 0·04%[33].

Currently available combination therapy for dyslipidaemia

More than one lipid-regulating drug is often required to treat patients with hypercholesterolaemia to target cholesterol levels recommended by the European and American guidelines, particularly for patients with multiple lipid abnormalities. Combination therapy with current lipid-modifying agents is limited by issues such as poor tolerance, safety and compliance[18]. Bile acid sequestrants co-administered with statins are not well tolerated due to gastrointestinal intolerance. The potential for increased hepatotoxicity and myopathy may increase if a statin is given in combination with a fibrate or niacin[34]. Contraindications to statin–fibrate and statin–niacin combination therapy include renal failure or other severe debilitating illness; these combinations are not recommended for older patients >70 years of age, non-compliant patients and patients taking multiple medications[19]. The limitations of statin monotherapy and statin combinations with these agents warrant the

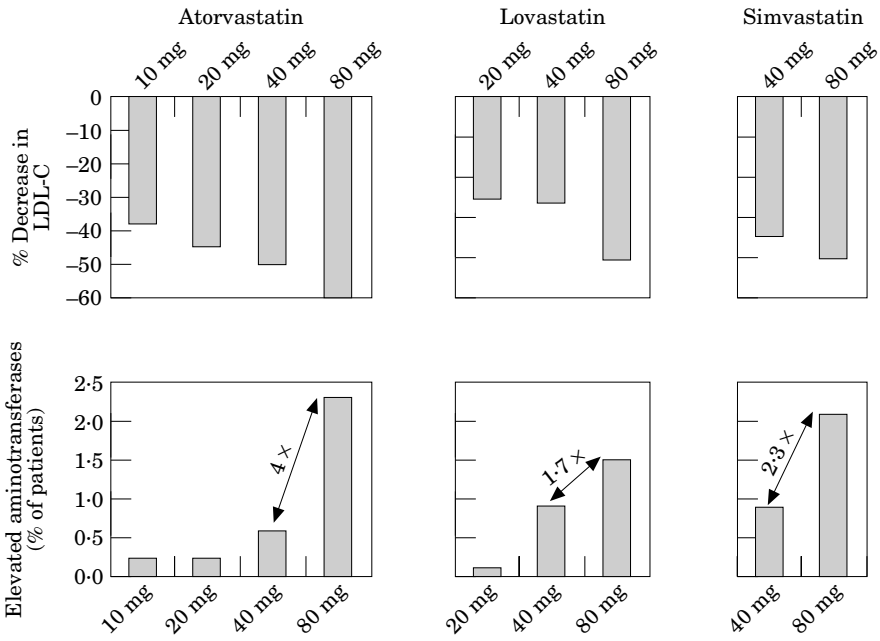

Figure 4 **Percentage reduction of low-density lipoprotein cholesterol (LDL-C) levels expected with incremental dose increases with atorvastatin, lovastatin and simvastatin relative to the risk of aminotransferase levels increasing to greater than three times the upper limit of normal. (Data from prescribing information.)**

need for more safe, effective and convenient approaches to combination therapy.

Cholesterol absorption inhibitors: a new concept in lipid management

Ezetimibe is the first member of a novel class of highly selective cholesterol absorption inhibitors that effectively and potently prevent the absorption of cholesterol by inhibiting the passage of dietary and biliary cholesterol across the intestinal wall[35,36]. Pre-clinical studies with an ezetimibe analogue revealed a potential decreased atherogenic propensity of chylomicrons by reducing their cholesteryl ester content[37]. Statins exclusively target the endogenous pathway of cholesterol synthesis and cannot control dietary and biliary cholesterol that is absorbed via the exogenous cholesterol pathway. Statins may increase the clearance of chylomicron remnants; however, they may not decrease cholesterol content. Therefore, combination of a statin with ezetimibe should be highly effective in reducing the atherogenic potential of the chylomicrons.

Ezetimibe has been shown to decrease significantly ($P<0{\cdot}05$) LDL-C levels in hypercholesterolaemic patients either as monotherapy[38,39] or when combined with a statin[23–25]. Ezetimibe also increases HDL-C level and may also reduce elevated triglyceride concentrations[39]. Three studies in which 10 mg of ezetimibe was co-administered with 10 mg of simvastatin[23], 20 mg of simvastatin[24], or 20 mg of lovastatin[25] resulted in additive LDL-C reductions of 16–18% compared with the statin monotherapy group. Ezetimibe has demonstrated an excellent safety and tolerability profile with an adverse event profile similar to that of placebo[23–25,38,39].

Co-administration of a statin and ezetimibe targets both pathways of cholesterol metabolism, thereby offering a new model of lipid management. Ezetimibe represents an efficient option to lower LDL-C levels in one step of 16–18% compared with a sequential doubling of doses of the various statins. More patients should be able to reach their LDL-C target with ezetimibe and statin combination therapy than with statin monotherapy. Furthermore, patients will be more likely to get to their target and stay on target.

Conclusions

A substantial percentage of patients treated with statins do not achieve or maintain the recommended target levels of LDL-C without taking high doses of these agents. For a fraction of patients, the need for dose increases is due to the escape phenomenon, characterized by an initial response to the statin followed by a return toward pre-treatment LDL-C levels with continued therapy. However, high-dose therapy is associated with a greater risk of hepatotoxicity and myopathy. Currently available agents co-administered with statins increase reductions of LDL-C levels but are not well tolerated or carry the risk of increased toxicity. Thus safer, more effective and convenient treatment options are needed.

Combination therapy with newer agents, such as ezetimibe, may bring more patients to target cholesterol levels more conveniently. Combination therapy with ezetimibe and a statin effectively targets both the endogenous and exogenous pathways of cholesterol metabolism, and offers the possibility of managing the escape phenomenon without resorting to the use of high doses of statins. Co-administration of ezetimibe and a statin may also help to compensate for the rule of six. Also, this combination therapy can achieve greater LDL-C level reductions than statin monotherapy and should be more convenient with less need for statin dosage adjustments. Therefore, co-administration of ezetimibe with statins may fill an unmet need in lipid-lowering management and offer broader lipid control.

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