

Ezetimibe in the Treatment of Patients with Metabolic Diseases

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Abstract

Dyslipidemia is an established risk factor for cardiovascular disease. While statin therapy remains the most important component of dyslipidemia management, a substantial proportion of patients on statin monotherapy fails to achieve guideline-recommended lipid levels. Ezetimibe is a second-line lipid-lowering agent that reduces sterol absorption, and has a favorable effect on lipid profile. This article reviews studies examining the role of ezetimibe on lipid profile, metabolic biomarkers, and cardiovascular outcomes in individuals with metabolic diseases. Special focus is given to studies in patients with dyslipidemia, Type 2 diabetes, and the metabolic syndrome. The controversy surrounding the role of ezetimibe in mitigating atherosclerosis is also highlighted. The article concludes that the ezetimibe–statin combination improves lipid parameters and helps attain guideline-recommended lipid goals in patients with metabolic diseases. However, further research is needed to better understand the role of ezetimibe monotherapy, and the impact of ezetimibe on clinical cardiovascular outcomes.

Keywords

Dyslipidemia, ezetimibe, metabolic diseases, atherosclerosis

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Dyslipidemia along with hypertension, obesity, and cigarette smoking are established risk factors for premature heart disease.¹ The third report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) recommends a low-density lipoprotein cholesterol (LDL-C) goal of <2.6 mmol/l (<100 mg/dl) for patients with high risk for coronary artery disease (CAD) or CAD risk equivalent and <3.4 mmol/l (<130 mg/dl) for patients with moderate risk for CAD.^{2,3} Although statins have been shown to be effective in lowering LDL-C and decreasing mortality,⁴ 40–80 % of individuals on statin monotherapy fail to achieve guideline-recommended LDL-C levels, with the lowest success rate for LDL-C goal achievement seen in patients with the highest risk for CAD.^{5,6} Heterogeneity in response may partly be due to genetic variation, with poor statin responders having a higher baseline cholesterol absorption,⁷ or increased compensatory cholesterol absorption during therapy.⁸ Although statins can reduce LDL-C levels by 30–50 %, doubling of dose, for those who do not attain a goal LDL-C, only yields an additional reduction of 5–7 %.⁹ In addition, there is a residual risk for CAD despite statin therapy even in individuals who have achieved the recommended LDL-C level. This residual risk may be from a low high-density lipoprotein cholesterol (HDL-C) level, high triglyceride level, high baseline apolipoprotein B (ApoB) level, or from the influence of other co-existing vascular risk factors.^{10–14}

It is also important to note that while only a small proportion of patients on statins do not tolerate treatment,¹⁵ some subgroups have a higher risk for drug toxicity and statin-induced myopathy,¹⁶ particularly patients with chronic kidney disease or patients with HIV receiving protease inhibitors.^{17,18}

Therefore, adding a second-line lipid-lowering agent such as ezetimibe may help in reducing the dose of statin, lowering the risk for side effects, attaining the recommended LDL-C goals, and ameliorating the residual cardiovascular risk in patients on statin monotherapy. In this article, we will look at studies examining the use of ezetimibe in metabolic diseases.

What is Ezetimibe?

Ezetimibe is a lipid-lowering agent that prevents sterol absorption by selectively inhibiting the Niemann Pick C1 Like 1 Protein (NPC1L1) at the jejunal brush border.¹⁹ Decreased sterol absorption leads to the over-expression of hepatic LDL-C receptors with further reduction in the blood LDL-C level.²⁰ A combination therapy of 10 mg of ezetimibe and 10 mg of simvastatin results in a similar degree of LDL-C lowering as an 80 mg simvastatin monotherapy.²¹ In addition, ezetimibe has been shown to increase the HDL-C level,²² and decrease triglyceride and ApoB levels.^{23–25} Ezetimibe also has a favorable metabolic profile with limited drug–drug interactions as it does not induce nor inhibit cytochrome P450 system. It is primarily metabolized by the liver and excreted in feces, and usually no severe side effects are noted with its use. Despite these salutary effects and the approval for use by regulatory agencies based on its efficacy in improving lipid profile,²⁶ evidence from recent trials examining carotid intima-media thickness (CIMT) as a surrogate for atherosclerosis have raised questions about the added beneficial role of ezetimibe in the treatment of atherosclerotic vascular diseases.^{27,28} Tables 1, 2 and 3 summarize clinical studies examining the impact of ezetimibe treatment in various populations.

Table 1: Ezetimibe and Cardiovascular Outcomes

Study	Design	Duration	Population	Intervention	Comparator	Main Finding
Rossebo et al., 2008 ²⁹	Randomized, blinded	4 years	Asymptomatic AS n=1,873	S 40 mg+E 10 mg	S 40 mg+P	Composite of atherosclerotic events: No difference (35 % in S+E group vs 38 % in S+P group)
Baigent et al., 2011 ¹⁷	Randomized, blinded	5 years	CKD n=9,270	S 20 mg+E 10 mg	P	Composite of atherosclerotic events: Benefits in S+E group (17 % proportional reduction in S+E group vs P group)

AS = aortic stenosis; CKD = chronic kidney disease; E = ezetimibe; P = placebo; S = simvastatin.

Ezetimibe and Cardiovascular Events

Two trials (see *Table 1*) have assessed the efficacy of ezetimibe and statin combination therapy in reducing major cardiovascular events. No trial has evaluated the impact of ezetimibe monotherapy on clinical outcomes.

Intensive lipid lowering was seen in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial—a randomized double-blind trial involving 1,873 participants with mild-to-moderate asymptomatic aortic stenosis.²⁹ The participants received either 10 mg of ezetimibe plus 40 mg simvastatin or placebo daily. After a median follow up of 52 months, the primary outcome of a composite of major cardiovascular events was not different in the two groups.

However, fewer patients in the ezetimibe–simvastatin group had ischemic cardiovascular events (hazard ratio [HR], 0.78; 95 % confidence interval [CI] 0.63–0.97). This positive result was mostly contributed by fewer coronary artery bypass procedures in the intervention group than the placebo group (7.3 versus 10.8 %), suggesting that the intervention may have favorably impacted coronary atherosclerosis and resulted in the lower need for surgical coronary interventions.³⁰

The Study of Heart and Renal Protection (SHARP) was a randomized double-blind trial involving 9,270 participants with the wide range of advanced chronic kidney disease.¹⁷ Participants were assigned to receive either 10 mg of ezetimibe plus 20 mg simvastatin or placebo daily and followed for a median of approximately five years. Major atherosclerotic events occurred in 11.3 % of participants in the intervention group compared with 13.4 % of participants in the placebo group, corresponding to a 17 % lower rate of events in the intervention group (risk ratio 0.83; 95 % CI 0.74–0.94), with the reductions in ischemic stroke (2.5 versus 3.5 %) and coronary revascularizations (3.2 versus 4.4 %) driving the difference between groups.

While these two trials examining clinical endpoints have not tested the ezetimibe–statin combination with another lipid-lowering agent, or ezetimibe or simvastatin monotherapy. The ongoing IMPROVED Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is expected to determine whether the addition of ezetimibe to statin therapy improves cardiovascular outcomes compared with statin alone.³¹ IMPROVE-IT is designed to enroll up to 18,000 moderate- to high-risk patients stabilized after acute coronary syndrome. Participants are randomized into groups receiving 10 mg of ezetimibe plus 40 mg simvastatin, or 40 mg of simvastatin, and the occurrence of major cardiovascular events is assessed during a minimum follow up of 2.5 years.

Ezetimibe in Dyslipidemia

A landmark trial published in 2002 by Davidson and colleagues assessed the efficacy of ezetimibe–statin combination compared with statin monotherapy on improving lipid-profile in patients with primary hypercholesterolemia.²¹ Ezetimibe–statin combination provided an incremental 13.8 % reduction in LDL-C level, a 2.4 % increase in HDL-C level and a 7.5 % reduction in triglyceride level compared with statin monotherapy. More trials have since examined this question in different populations, and, recently, a large meta-analysis looking at participant-level data from 27 randomized trials (n=21,794) comparing the efficacy of the ezetimibe–statin combination with statin monotherapy on improving lipid levels has been published.²² The meta-analysis concluded that the ezetimibe–statin combination resulted in significantly greater reductions in LDL-C, non-HDL-C, total cholesterol, triglyceride, ApoB, and high-sensitivity C-reactive protein (hs-CRP), and an increase in HDL-C than statin monotherapy. The combination ezetimibe–statin therapy also yielded a greater percent achievement of LDL-C, non-HDL-C, and ApoB goals.²² This benefit in lipid profile was seen in the general population with dyslipidemia, and in subgroups of patients with Type 2 diabetes and CAD.

Studies included in the meta-analysis that examined ezetimibe’s role in patients at moderate-to-high risk for CAD showed that the combination ezetimibe–statin therapy produced a significantly greater reduction in LDL-C level than the doubling of statin (atorvastatin or simvastatin) dose.^{32–34} Similar results were observed in a trial that examined the role of ezetimibe in elderly population with moderate-to-high risk for CAD.³⁵

Ezetimibe in Diabetes

Diabetes is considered as a CAD risk equivalent and the management of dyslipidemia is a major component of diabetes care. A pooled analysis of 27 trials that included more than 6,000 patients with diabetes and more than 1,500 patients without diabetes showed that while patients with diabetes and without diabetes both had a more favorable lipid outcomes with the ezetimibe–statin combination than with statin monotherapy, patients with diabetes achieved significantly larger reductions in LDL-C, total cholesterol and non-HDL-C compared with patients without diabetes.³⁶ An earlier study comparing ezetimibe–simvastatin to atorvastatin in patients with Type 2 diabetes showed that ezetimibe 10 mg plus simvastatin 20 mg reduced LDL-C 15.3 % more than atorvastatin 10 mg, and ezetimibe 10 mg plus simvastatin 40 mg reduced LDL-C 6.7 % more than atorvastatin 40 mg.³⁷ Similarly, ezetimibe–statin combination therapy yielded significantly greater reductions in triglyceride and hs-CRP levels, and an increase in HDL-C level than atorvastatin monotherapy. The combination therapy also resulted in more patients achieving their LDL goals.

Table 2: Ezetimibe and Metabolic Diseases

Study	Design	Duration	Population	Intervention	Comparator	Main Finding
Davidson et al., 2002 ²¹	Randomized, blinded	12 weeks	Primary HC n=131	S 10, 20, 40, 80 mg+E 10 mg	E 10 mg; S 10, 20, 40, 80; P	Incremental 13.8 % LDL-C reduction in the pooled S+E groups vs pooled S groups
Morrone et al., 2012 ²²	Meta-analysis of randomized, blinded, active or P controlled trials	4–24 weeks	Population from 27 clinical trials from 1999–2008 n=21,794	Statin+E 10 mg	Statin	Greater reductions in LDL-C and higher achievement of LDL-C goal with S+E vs statin monotherapy
Feldman et al., 2004 ³²	Randomized, blinded	5 weeks	Primary HC with CAD or CAD risk equivalent n=710	S 10, 20, 40 mg+E 10 mg	S 20 mg	75, 83 and 87 % of patients on S+E 10, 20 and 40 mg attained NCEP ATP III LDL-C goal <100 mg/dl vs 46 % patients on S 20 mg
Conard et al., 2008 ³³	Randomized, blinded	6 weeks	Moderate risk CAD n=196	A 20 mg+E 10 mg	A 40 mg	31 % reductions in LDL-C and 84 % LDL-C goal attainment in patients on A 20 mg+E vs 11 and 49 % in patients on A 40 mg, respectively
Leiter et al., 2008 ³⁴	Randomized, blinded	6 weeks	High-risk CAD n=579	A 40 mg+E 10 mg	A 80 mg	27 % reduction in LDL-C goal attainment in patients on A 40 mg+E vs 11 and 32 % in patients on A 80 mg, respectively
Foody et al., 2010 ³⁵	Randomized, blinded	12 weeks	Moderate or higher risk CAD ≥65 years old n=1,289	S 20 mg+E 10 mg S 40 mg+E 10 mg	A 10, 20 mg A 40 mg	54.2 % decrease in LDL-C with S 20 mg+E vs 39.5 and 46.6 % with A 10 mg and A 20 mg, respectively. 59.1 % decrease in LDL-C with S 40 mg+E vs 50.8 % with A 40 mg, and higher achievement of recommended goals with S+E vs A
Leiter et al., 2011 ³⁶	Meta-analysis of randomized, blinded, active or P-controlled trials	4–24 weeks	Population from 27 clinical trials from 1999–2008 n=21,794; with DM2 n=6,541 and without DM2 n=15,253	Statin+E 10 mg	Statin	Statin+E more effective in improving LDL-C and other lipids vs statin monotherapy
Goldberg et al., 2006 ³⁷	Randomized, blinded	6 weeks	DM2 n=1,229	S 20+E 10 mg S 40+E 10 mg	A 10, 20 mg A 40 mg	53.6 and 57.6 % reduction in LDL-C with S 20 mg+E and S 40 mg+E vs 38 % with 10 mg, 44.6 with A 20 mg and 50.9 % with A 40 mg, respectively. Higher achievement of LDL-C goals with S+E vs A
Robinson et al., 2009 ⁴⁵	Randomized, blinded	6 weeks	MetS n=1,128	S 20+E 10 mg S 40+E 10 mg	A 10, 20 mg A 40 mg	13.1 %, 10.2 % greater reduction in LDL-C with S 20 mg+E vs A 10 mg and A 20 mg, respectively, 8 % greater reduction in LDL-C with S+E vs A
Pearson et al., 2005 ⁴⁶	Randomized, blinded	6 weeks	HC n=3,030	Statin+E 10 mg	Statin+P	25.8 % greater reduction in LDL-C in statin+E vs 2.7 % in statin+P. Higher achievement of LDL-C goals with statin+E vs statin+P
Deneke et al., 2006 ⁴⁷	Post hoc analysis of randomized trial	6 weeks	HC n=3,030	Statin+E 10 mg	Statin+P	Reduction in LDL-C by 28 % in DM2, 24 % in MetS and 26 % in neither with statin+E vs 3 % with P for each group. Higher achievement of LDL-C goals with statin+E vs statin+P

A = atorvastatin; CAD = coronary artery disease; DM2 = diabetes mellitus Type 2; E = ezetimibe; HC = hypercholesteremia, LDL-C = low-density lipoprotein cholesterol; MetS = the metabolic syndrome; NCEP ATP = National Cholesterol Education Program Adult Treatment Panel; P = placebo; S = simvastatin.

Table 3: Ezetimibe and Carotid Intima-media Thickness

Study	Design	Duration	Population	Intervention	Comparator	Main Finding
Kastelein et al., 2008 ²⁷	Randomized, blinded	2 years	FH n=720	S 80 mg+E 10 mg	S 80 mg+P	Change in CIMT: No difference (0.0111±0.0038 mm in S+E group vs 0.0058±0.0037 mm with S+P group)
Howard et al., 2008 ⁶⁰ Fleg et al., 2008 ⁶¹	Randomized, blinded	36 months	Native Americans, age ≥40 years with DM2, n=499	Aggressive treatment: statin, statin+E 10 mg	Standard treatment: statin	Change in CIMT: Benefit in aggressive treated group (−0.012 mm in aggressive treatment group vs +0.038 mm in standard treatment group)
Meaney et al., 2009 ⁶²	Randomized, blinded	1 year	CAD n=90	Statin+E 10 mg	Statin	Change in CIMT: 25–30% decrease in CIMT in all treatment groups
Taylor et al., 2009 ²⁸	Randomized, blinded	1 month	4 CAD and CAD-risk equivalent n=208	Statin+E 10 mg	Statin+niacin	Change in CIMT: Benefit in statin+niacin group (−0.0102±0.0026 mm change in maximum CIMT in statin+niacin group vs −0.0016±0.0024 mm and −0.0005±0.0029 mm in statin+E group, respectively)

CAD = coronary artery disease; CIMT = carotid intima-media thickness; E = ezetimibe; FH = familial hypercholesterolemia; P = placebo; S = simvastatin.

However, treatment of patients with diabetes may be more complicated as diabetic dyslipidemia is often associated with lower LDL-C levels and higher levels of small-dense LDL (sd-LDL), triglyceride, and ApoB levels,³⁸ which is now emerging as a potentially important cardiovascular risk mediator,^{39–41} and ezetimibe has had inconsistent effects on sd-LDL levels. A recent small randomized study of six-week duration involving 40 patients with diabetes showed that the sd-LDL level decreased by 20 %, 24 %, and 33 % with ezetimibe 10 mg, simvastatin 20 mg and the combination of ezetimibe 10 mg plus simvastatin 20 mg, respectively.⁴² Contrary to this observation, another small randomized study of 2-week duration involving 72 healthy men showed that ezetimibe monotherapy altered LDL subfraction distribution towards a more atherogenic profile by significantly increasing the sd-LDL level.⁴³ Further research is needed to better elucidate the clinical importance of LDL subfractions and it is currently unclear if ezetimibe induced sd-LDL particles behave differently from normal LDL particles.⁴⁴

Ezetimibe in the Metabolic Syndrome

The metabolic syndrome, as defined as having three or more of the following five characteristics: waist circumference >102 cm (>40 inches) in men, or >89 cm (>35 inches) in women; triglyceride >1.7 mmol/l (>150 mg/dl); HDL-C <1.0 mmol/l (<40 mg/dl) in men or <1.3 mmol/l (<50 mg/dl) in women; hypertension (blood pressure [BP] ≥130/85 mmHg or on antihypertensive medication); and fasting glucose ≥6.1 mmol/l (≥110 mg/dl) or a history of diabetes, is associated with cardiovascular disease and is designated as a moderate-risk category for CAD.

In a randomized trial by Robinson and colleagues assessing the lipid-lowering efficacy of the ezetimibe–simvastatin combination and atorvastatin monotherapy in more than 1,000 subjects with hypercholesterolemia and the metabolic syndrome, significantly greater improvements in the levels of LDL-C, non-HDL-C, ApoB, and lipid/lipoprotein ratios were observed with ezetimibe–simvastatin therapy compared with atorvastatin monotherapy.⁴⁵ HDL-C levels were also significantly increased in the ezetimibe–simvastatin group and more participants in ezetimibe–simvastatin group achieved their LDL-C goal.

The Ezetimibe Add-on to Statin for Effectiveness (EASE) trial similarly found significant improvement in lipid profile and LDL-C goal attainment with ezetimibe–simvastatin combination therapy than with statin monotherapy in hypercholesterolemic patients.⁴⁶ A post hoc analysis of the EASE trial showed that 67 % of participants with the metabolic syndrome and 71 % of participants with Type 2 diabetes attained the recommended LDL-C goal with ezetimibe–statin combination therapy compared with only 22 % of participants with the metabolic syndrome and 21 % of participants with Type 2 diabetes who attained LDL-C goals with statin monotherapy.⁴⁷ There was also a more favorable apolipoprotein profile and a significantly lower LDL-C and hs-CRP levels with ezetimibe–statin combination therapy across all subgroups.

There is emerging evidence suggesting ezetimibe’s positive impact on a number of the metabolic syndrome-related parameters and biomarkers. It has been postulated that ezetimibe may improve insulin resistance and increase serum adiponectin levels.^{48,49} Ezetimibe monotherapy has also been observed to be associated with an improvement in visceral fat area, fasting insulin level, homeostasis model assessment of insulin resistance and hs-CRP level in patients with fatty liver.⁵⁰ hs-CRP is an important inflammatory biomarker related to adverse cardiovascular outcomes,^{51,52} and studies have consistently shown a significant reduction in hs-CRP levels with ezetimibe–statin combination therapy.²² Whether these improvement in surrogate endpoints result in clinical benefit needs further research.

Ezetimibe Safety and Tolerability

Ezetimibe is generally well tolerated. A large meta-analysis with 14,497 patients from 18 randomized trials showed that the overall safety profile of ezetimibe–statin combination is similar to that of statin monotherapy.⁵³ However, subsidiary analysis of the SEAS trial data did raise a concern about the risk for cancer with ezetimibe–statin combination therapy as the combination therapy group had a significantly higher incidence of cancers than the placebo group (11.1 versus 7.5 %).²⁹ This was an unexpected finding that had not been observed in other studies,

but, nonetheless, subsequent meta-analysis by Peto and colleagues examining incident cancers in the much larger SHARP and IMPROVE-IT trials (total n=20,617) did not reveal excess cancer incidence in the ezetimibe–statin combination group compared with placebo (risk ratio 0.96, 95 % CI 0.82–1.12).⁵⁴

Ezetimibe and Carotid Intima-media Thickness

Ezetimibe has been shown in animal studies to reduce vascular inflammation and atherosclerosis.⁵⁵ CIMT is a commonly used surrogate measure of atherosclerotic vascular disease in clinical studies. CIMT predicts coronary atherosclerosis,⁵⁶ and is independently associated with adverse cardiovascular outcomes.⁵⁷ The relative risk for CAD increases two- to threefold with each 0.03 mm increase per year in CIMT.⁵⁸ Thus, studies evaluating the role of ezetimibe on CIMT deserve special mention (see Table 3).

The randomized double-blind Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia (ENHANCE) trial involving 720 subjects revealed that the ezetimibe–statin combination and simvastatin monotherapy groups did not have significantly different mean change in CIMT after a two-year follow up despite higher reductions in LDL-C in the combination group.²⁷ This apparent disconnect between the change in CIMT and the change in LDL-C is in contrast to observations in multiple other studies where the degree of CIMT regression correlated with the magnitude of LDL-C reduction.^{59–62} Furthermore, the scale of LDL-C lowering may actually be more important than the choice of lipid-lowering therapy as studies in high-risk subjects have shown similar CIMT regression in participants who attain similar LDL-C reductions regardless of whether their treatment assignment was ezetimibe–statin combination or statin monotherapy.^{61,62} The discordance between CIMT change and LDL-C lowering in ENHANCE may be explained by the possibility of a more aggressive pre-trial lipid management and thinner baseline CIMT in ENHANCE participants compared with participants in other trials.⁶³ While the specifics of pre-enrolment lipid-lowering therapy are not available, it has been postulated that ENHANCE participants were likely to have been treated more aggressively prior to recruitment than participants in other trials as usual care for hyperlipidemia had changed several years before the start of ENHANCE. Prior aggressive lipid lowering and control of vascular risk factors may have altered the carotid wall structure making it less likely for an additional therapy to show improvement in CIMT. In addition, lower baseline CIMT in ENHANCE participants may have also hindered the ability of any therapy to provide incremental benefit. This

reasoning is supported by an analogous result on CIMT and LDL-C seen in a prior study involving high-dose statin where the baseline CIMT was similar to ENHANCE.⁶⁴

How do other second-line lipid-lowering agents compare with ezetimibe on CIMT regression? This question was assessed by the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies (ARBITER 6-HALTS) trial where patients on statin therapy with CAD or CAD equivalent and baseline low LDL-C and HDL-C levels were randomized to extended-release niacin (target dose 2,000 mg per day) or ezetimibe 10 mg per day.²⁸ The primary outcome was the between-group difference in the change from baseline in the mean CIMT after 14 months. The trial was terminated early after niacin treatment showed superior efficacy to ezetimibe in reducing mean CIMT. Surprisingly, in a post hoc analysis, a paradoxical increase in CIMT was seen in participants with greater LDL-C reduction in the ezetimibe group. The incidence of major cardiovascular events was also higher in the ezetimibe group (5 versus 1 %). An additional analysis of the study showed that the cumulative exposure to niacin was related to the regression of CIMT whereas cumulative exposure to ezetimibe was related to the progression of CIMT.⁶⁵

Although the results from ENHANCE and ARBITER 6-HALTS raises doubts on ezetimibe's role in mitigating atherosclerosis, it has to be stressed that CIMT is only a surrogate marker for atherosclerotic diseases and it has not been established that reducing CIMT results in lowering of clinical cardiovascular risks.^{66,67} Therefore, the final judgment on the clinical utility of ezetimibe in reducing atherosclerotic cardiovascular events can only be made with an adequately powered trial with hard, clinical cardiovascular endpoints.

Conclusion

There is strong and consistent evidence that ezetimibe–statin combination improves lipid parameters and helps attain guideline recommended lipid goals in patients with metabolic diseases. This is especially important in patients who are unable to tolerate high-dose statin therapy. However, there is a dearth of evidence on ezetimibe monotherapy, and ezetimibe's role in alleviating atherosclerosis remains controversial. The result of the ongoing IMPROVE-IT trial that compares the ezetimibe–simvastatin combination to simvastatin monotherapy after acute coronary syndrome is expected to help further elucidate the role of ezetimibe in cardiovascular risk reduction.³¹ ■

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