Adjuvant Therapy for Incremental Low-Density Lipoprotein Cholesterol Reduction With Ezetimibe

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ABSTRACT: Atherosclerotic cardiovascular disease (CVD) remains the major cause of premature death in developing countries, even though CVD mortality has fallen considerably over recent decades in many countries. Low-density lipoprotein (LDL) cholesterol is an important cause of coronary heart disease. Ezetimibe is a nonstatin agent that was approved in 2003 as an adjunctive therapy in combination with statins because of its ability to decrease plasma cholesterol levels. However, during a period of 12 years, this drug has been used without evidence of any positive effect in terms of morbidity and mortality. The purpose of this review is to briefly discuss the data that seem pertinent regarding the role of ezetimibe in therapy. The precise role of ezetimibe relative to other lipid-lowering drugs is unclear. Similar reductions in LDL cholesterol can often be achieved simply by maximizing the dose of statins. Ezetimibe plus atorvastatin also produced a greater reduction in serum C-reactive protein than atorvastatin alone.

KEYWORDS: ezetimibe, anticholesteremic agents, cholesterol, LDL cholesterol, therapeutic use, adverse effects

Introduction

Atherosclerotic cardiovascular disease (CVD) remains the major cause of premature death in Europe and in the United States, even though CVD mortality has fallen considerably over recent decades in many countries. It is estimated that more than 80% of all CVD mortality now occurs in developing countries.1-2

Cardiovascular disease is the main cause of death in developed countries. In addition, it is associated with higher morbidity, high health-related costs, and decreased quality of life of patients. The healthy lifestyles (with a varied diet and practice exercise) and the control of cardiovascular risk factors (lipid and glucose levels, blood pressure, etc) have proven to be effective in the prevention of CVD.1-2

High low-density lipoprotein cholesterol (LDL-C) levels are a major risk factor for coronary heart disease. Some studies have shown a positive association between LDL-C levels and risk of coronary heart disease.3

Lipid-lowering drugs are a heterogeneous group of drugs with different mechanisms of action that improve the lipid profile due to the decline of some lipid fractions (cholesterol and triglycerides) and improved cholesterol transport by high-density lipoprotein (HDL). These lipid-lowering drugs are initially used as monotherapy. If necessary, treatment can be combined, in order to reduce cardiovascular disease. Multiple clinical trials have shown this effect for some lipid-lowering drugs in primary and secondary prevention.4

Ezetimibe monotherapy is indicated as adjunctive therapy to diet in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) in which a statin is considered inappropiate or nontolerated. In addition, ezetimibe is indicated as adjunctive therapy to diet in patients with familial homozygous sitosterolemia.5

Ezetimibe in combination with a statin, as adjunctive therapy to diet, is indicated in patients with homozygous familial hypercholesterolemia (HoFH) and in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) who are not adequately controlled with a statin alone.5

Ezetimibe is a nonstatin agent that was approved in 2003 as an adjunctive therapy in combination with statins because of its ability to decrease plasma cholesterol levels. However, during a period of 12 years, this drug has been used without evidence of any positive effect in terms of morbidity and mortality.6

In September 2008, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial raised concerns about the safety of ezetimibe because there was an increased incidence of cancer in the active treatment group. This came from a subsidiary analysis; the overall incidence of cancer was not prespecified as a primary outcome or even a secondary outcome in the SEAS trial. In the analysis of Study of Heart and Renal Protection (SHARP) and IMPROved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), there was no significant excess incidence of cancer, either overall or at any particular site, and there was no suggestion of an emerging trend with longer treatment and follow-up periods.7 However, the limited evidence which exists as regards lower mortality...
rates, together with doubts about its safety, mean that its role in therapeutics is being questioned.

The purpose of this review is to briefly discuss the data that seem pertinent regarding the role of ezetimibe in therapy.

**Mechanism of Action, Metabolism, and Pharmacokinetic Profile**

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients. By inhibiting cholesterol absorption at the level of the brush border of the intestine (most probably by interacting with the Niemann–Pick C1-Like 1 protein), ezetimibe reduces the amount of lipoprotein cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDL, which in turn leads to increased clearance of LDL from the blood.5,8

After oral intake, ezetimibe is rapidly absorbed and extensively conjugated to a phenolic glucuronide which is pharmacologically active (ezetimibe-glucuronide). The mean peak plasma concentrations ($C_{\text{max}}$) occur between 1 and 2 hours ($T_{\text{max}}$) in the case of ezetimibe-glucuronide and between 4 and 12 hours ($T_{\text{max}}$) in the case of ezetimibe. The absolute bioavailability of ezetimibe could not be determined because the compound is practically insoluble in aqueous media suitable for injection.5,9

Concomitant administration of foods (foods with/without high-fat content) had no effect on the oral bioavailability of ezetimibe in its administration as ezetimibe 10 mg tablets. Ezetimibe can be administered with or without food.5,9

Ezetimibe and the ezetimibe-glucuronide complex are bound 99.7% and 88% to 92% to human plasma proteins, respectively. Ezetimibe is primarily metabolized in the small intestine and liver through its conjugation with glucuronides, with posterior biliary excretion. Ezetimibe and the ezetimibe-glucuronide complex are the major compounds derived from the drug that is detected in plasma, representing approximately 10% to 20% and 80% to 90% of the total drug in plasma, respectively. Both ezetimibe and the ezetimibe-glucuronide complex are slowly removed from the plasma, with evidence of significant enterohepatic recirculation. The half-life of ezetimibe and the ezetimibe-glucuronide complex is approximately 22 hours.5,9

**Clinical Trials**

The efficacy and safety of ezetimibe have been studied in many studies in different indications, especially in patients with dyslipidemia (185 studies on hypercholesterolemia, sitosterolemia, hyperlipidemia, and hyperlipoproteinemia), CVD (61 studies on heart disease, coronary artery disease, vascular disease, valvular heart disease, and arrhythmias), and endocrine disorders (there are some studies on diabetes mellitus and metabolic syndrome).10

In cardiovascular prevention (see Table 1), ezetimibe plus atorvastatin was compared with atorvastatin alone, ezetimibe plus simvastatin was compared with simvastatin alone and with placebo, and ezetimibe plus statin was compared with niacin. In aortic stenosis, ezetimibe plus simvastatin was compared with placebo. In acute coronary syndrome and in familial hypercholesterolemia, ezetimibe plus simvastatin was compared with simvastatin alone.

In dyslipidemia, ezetimibe has been compared in monotherapy with placebo or atorvastatin. Combination therapy has been evaluated with fenofibrate, simvastatin, fluvastatin, atorvastatin, rosvastatin and compared with fibrate, statin alone, or with placebo. In patients with cardiovascular disease or with diabetes mellitus, the monotherapy and combination therapy with simvastatin, atorvastatin, or rosvastatin have been evaluated.10

In patients with metabolic syndrome (with or without diabetes) and high LDL-C levels, ezetimibe (combined with simvastatin, atorvastatin, or fenofibrate or alone) has demonstrated beneficial changes in lipid profiles (total cholesterol, LDL-C, apolipoproteins A-I and A-II, triglycerides, and high-sensitivity C-reactive protein) in a similar magnitude than in patients without metabolic syndrome.19–30

These trials are included in meta-analysis concerning cholesterol-lowering interventions in all chronic situations, in high-risk patients with or without LDL-C elevation, in patients with related disease, and in patients with renal insufficiency (on hemodialysis or transplant) and niacin in all types of patients (summarized in Table 1).10–31

**Safety**

Ezetimibe has been well tolerated in some clinical trials.32,33 The overall incidence of adverse reactions was similar between ezetimibe and placebo. Similarly, the rate of discontinuation due to adverse events (AEs) was also comparable between ezetimibe and placebo.5

There have been reports of myalgia, rhabdomyolysis, hepatitis, acute pancreatitis, and thrombocytopenia in patients taking ezetimibe.34 Some of the patients who developed rhabdomyolysis were apparently taking ezetimibe without a statin.35 The risk may be increased with concomitant use of a statin or fibrate. Discontinue ezetimibe and statin or fibrate immediately if myopathy is suspected or confirmed (symptomatic patient with creatine phosphokinase [CPK] >10× upper limit normal).

In September 2008, an association between ezetimibe and increased risk for cancer was reported in a trial evaluating the use of simvastatin with ezetimibe on the progress of aortic stenosis (SEAS).14

Cancer occurred more frequently in the simvastatin with ezetimibe vs simvastatin group (105 [11.1%] vs 70 [7.5%], $P = .01$). Because of this concern, an interim analysis of 2 other trials on simvastatin and ezetimibe (IMPROVE-IT and SHARP) was performed.7 This analysis found no increased risk of incident cancer but a trend toward an increase in cancer deaths. Data were reviewed a total of 7 times between 2008 and the end of the IMPROVE-IT. It appears most likely that the observed effects on cancer and cancer deaths are due to chance because an early increase in cancer deaths in a trial without an
Table 1. Summary of trial included in meta-analysis concerning cholesterol-lowering intervention in all chronic situations, in high-risk patients with or without LDL-C elevation, in patients with related disease, and in patients with renal insufficiency (on hemodialysis or transplant) and niacin in all types of patients.

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<tr>
<th>STUDY</th>
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<tr>
<td>ZETELD&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Ezetimibe 10 mg plus atorvastatin 10 mg for 12 wk vs uptitration to atorvastatin 20 mg for 6 wk followed by uptitration to atorvastatin 40 mg for an additional 6 wk</td>
<td>Subjects &gt;65 y with hyperlipidemia and at high risk of coronary heart disease</td>
<td>After stabilization of atorvastatin 10-mg therapy, 1053 patients, &gt;65 y, at high risk of coronary heart disease, with and without atherosclerotic vascular disease and an LDL-C level that was not &lt;70 or &lt;100 mg/dL, respectively, were randomized to receive ezetimibe added to atorvastatin 10 mg for 12 wk vs uptitration to atorvastatin 20 mg for 6 wk followed by uptitration to atorvastatin 40 mg for an additional 6 wk Follow-up: 12 wk</td>
<td>Changes at week 6 in LDL-C: ezetimibe + atorvastatin 10 mg: significantly greater (P &lt; .001) decrease In patients with atherosclerotic vascular disease significantly more percentage achieving an LDL-C level of &lt;70 mg/dL (P &lt; .001) In patients without atherosclerotic vascular disease significantly more percentage achieving an LDL-C level of &lt;100 mg/dL (P &lt; .001) at weeks 6 and 12 compared with atorvastatin 20 mg or atorvastatin 40 mg Ezetimibe plus atorvastatin 10 mg resulted in significantly greater changes at week 6 in total cholesterol, triglycerides, non–HDL-C, apolipoprotein B (all P &lt; .001), and HDL-C (P = .021) compared with atorvastatin 20 mg Significantly greater changes at week 12 in LDL-C, non–HDL-C, apolipoprotein A-I (P = .001), total cholesterol, apolipoprotein B (P &lt; .030), and HDL-C (P &lt; .001) compared with atorvastatin 40 mg Both treatments were generally well tolerated, with comparable safety profiles</td>
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<th>STUDY</th>
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| ENHANCE               | Ezetimibe 10 mg + simvastatin daily vs simvastatin 80 mg daily | 720 patients with familial hypercholesterolemia | Double blind Europe | The mean (±SE) change in the carotid artery intima-media thickness (primary outcome): 0.0058 ± 0.0037 mm (ezetimibe plus simvastatin) vs 0.0111 ± 0.0038 mm (simvastatin) (P = .29)  
Secondary outcomes (other variables regarding the intima-media thickness of the carotid and femoral arteries) did not differ significantly between the 2 groups. Mean (±SD) LDL-C level: 141.3 ± 52.6 mg/dL vs 192.7 ± 60.3 mg/dL (P < .01). Differences in reductions in triglycerides and C-reactive protein levels were 6.6% and 25.7%, respectively (P < .01 for both comparisons)  
Side effect and safety profiles were similar in the 2 groups |
| SEAS                  | Simvastatin 40 mg plus ezetimibe 10 mg daily vs placebo      | Patients with mild-to-moderate asymptomatic aortic stenosis | Double blind | The incidence of composite of major cardiovascular events, including death from cardiovascular causes, aortic valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke (primary outcome), 333 patients (35.3%; ezetimibe plus simvastatin) vs 355 patients (38.2%) in the placebo group (HR: 0.96; 95% CI: 0.83-1.12; P = .59). Aortic-valve replacement: 28.3% (ezetimibe plus simvastatin) vs 29.9% (placebo) (HR: 1.00; 95% CI: 0.84-1.18; P = .97). Ischemic cardiovascular events: HR: 0.78; 95% CI: 0.63 to 0.97; P = .02  
Cancer occurred more frequently in the ezetimibe plus simvastatin (105 vs 70, P = .01) |
| SHARP                 | Simvastatin 20 mg/ezetimibe 10 mg vs placebo                 | 9270 patients with established chronic kidney disease (dialysis or predialysis) | Double blind 20 countries | Reduction in major atherosclerotic events (526 [11.3%]; ezetimibe plus simvastatin) vs 619 [13.4%; placebo]; RR: 0.83, 95% CI: 0.74-0.94; P = .0021  
Nonfatal myocardial infarction or died from coronary heart disease: (213 [4.6%] vs 230 [5.0%]; RR: 0.92, 95% CI: 0.76-1.11; P = .37)  
Nonhemorrhagic stroke (131 [2.8%] vs 174 [3.8%]; RR: 0.75, 95% CI: 0.60-0.94; P = .01)  
Arterial revascularization procedures (284 [6.1%] vs 352 [7.6%]; RR: 0.79, 95% CI: 0.68-0.93; P = .0036)  
Excess risk of myopathy: 2 per 10 000 patients per year: 9 [0.2%] vs 5 [0.1%])  
Excess risks of hepatitis (21 [0.5%] vs 18 [0.4%])  
Excess of death from any nonvascular cause (668 [14.4%] vs 612 [13.2%], P = .13) |
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<td>Ezetimibe vs niacin</td>
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<td><strong>ARBITER-HALTS</strong>&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Addition of ezetimibe (10 mg/daily) to statin therapy vs extended-release niacin 2000 mg/daily</td>
<td>315 patients with coronary heart disease (CHD) with LDL-C &lt; 100 mg/dL and HDL-C &lt; 50 mg/dL for men or 55 mg/dL for women while receiving stable statin treatment</td>
<td>Follow-up: 14 mo Open</td>
<td>Change in carotid intima-media thickness (CIMT; main outcome) Reduction vs baseline in mean CIMT: (-0.0102 \pm 0.0026) mm (N: (P &lt; 0.001)) vs (-0.0016 \pm 0.0024) mm; (ezetimibe; (P = .88)) ((P = .016) between groups) Reduction vs baseline in maximal CIMT: (-0.0124 \pm 0.0036) mm (N: (P &lt; 0.001)) vs (-0.0005 \pm 0.0029) mm (E; (P = .88))</td>
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<td>Niacin + ezetimibe vs simvastatin + ezetimibe</td>
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<td><strong>Guyton et al</strong>&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Ezetimibe/simvastatin (10/20 mg/d) + niacin (titrated to 2 g/d) vs niacin (titrated to 2 g/d) vs ezetimibe/simvastatin (10/20 mg/d)</td>
<td>1220 patients with type IIa or IIb hyperlipidemia</td>
<td>Follow-up: 24 wk Multicenter, randomized, double-blind study</td>
<td>Changes from baseline in LDL-C (primary outcome) ezetimibe plus simvastatin plus niacin resulted in significantly greater reductions in LDL-C, non-HDL-C, triglycerides, apolipoprotein B, and lipid/lipoprotein ratios, compared with either agent alone ((P &lt; .001)) ezetimibe plus simvastatin plus niacin increased levels of apolipoprotein AI and HDL-C significantly more than ezetimibe plus simvastatin ((P &lt; .001)) ezetimibe plus simvastatin plus niacin reduced high-sensitivity C-reactive protein levels significantly more than niacin ((P = .005)) Patients who discontinued: niacin (25.0%) vs ezetimibe plus simvastatin plus niacin (23.3%) vs E/S (9.6%, (P &lt; .001)) Clinical adverse experiences with niacin: flushing</td>
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<td>Aortic stenosis</td>
<td>Ezetimibe + simvastatin vs placebo</td>
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<td><strong>SEAS</strong>&lt;sup&gt;14&lt;/sup&gt; NCT00092677</td>
<td>Simvastatin 40 mg plus ezetimibe 10 mg daily vs placebo</td>
<td>Patients with mild to moderate asymptomatic aortic stenosis</td>
<td>Follow-up: 52.2 mo Double blind Europe</td>
<td>Aortic-valve replacement: 28.3% (ezetimibe plus simvastatin) vs 29.9% (placebo) (HR: 1.00; 95% CI: 0.84-1.18; (P = .97))</td>
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<td>Acute coronary syndrome</td>
<td>Ezetimibe vs control</td>
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<td><strong>IMPROVE-IT</strong>&lt;sup&gt;12&lt;/sup&gt; NCT00202878</td>
<td>10 mg/d of ezetimibe and 40 mg/d of simvastatin vs simvastatin 40 mg/d</td>
<td>18 144 subjects who had been hospitalized for an acute coronary syndrome within the preceding 10 d and had LDL-C levels of 50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not receiving lipid-lowering therapy</td>
<td>Follow-up: 5.68 y Double blind 39 countries</td>
<td>Composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization (&gt;30 d after randomization), or nonfatal stroke (primary end point): the Kaplan-Meier event rate 32.7% (ezetimibe plus simvastatin) vs 34.7% (simvastatin) (HR: 0.936; 95% CI: 0.89-0.99; (P = .016))</td>
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### Familial hypercholesterolemia

**ENHANCE 13**

**Ezetimibe 10 mg + simvastatin daily vs simvastatin 80 mg daily**

- **720 patients with familial hypercholesterolemia**
- **Follow-up: 24 mo**
- **Double blind**

**Primary outcome:**

The mean (±SE) change in the carotid-artery intima-media thickness: 0.0058 ± 0.0037 mm (ezetimibe plus simvastatin) vs 0.0111 ± 0.0038 mm (simvastatin) (P = .29)

**Secondary outcomes:**

- Mean (±SD) LDL-C level: 141.3 ± 52.6 mg/dL vs 192.7 ± 60.3 mg/dL; P < .01
- Differences in reductions of triglycerides and C-reactive protein levels were 6.6% and 25.7%, respectively (P < .01 for both comparisons)

**Side effect and safety profiles:**

Similar in the 2 groups

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### Metabolic syndrome

**Ezetimibe/simvastatin vs atorvastatin**

**Rosen et al 19**

**Ezetimibe 10 mg/simvastatin 20 mg vs ezetimibe 10 mg/simvastatin 40 mg vs atorvastatin 20 mg vs atorvastatin 40 mg**

- **1128 patients with hypercholesterolemia, metabolic syndrome factors (abdominal obesity, depleted HDL-C and elevated triglycerides, blood pressure, and fasting glucose), and moderate/high risk of coronary heart disease**
- **Follow-up: 6 wk**
- **Double blind**

**Ezetimibe/simvastatin** and atorvastatin efficacy was generally consistent across MetS factor subgroups

**Percent change from baseline in LDL (LDL-C) at week 6**

- Ezetimibe10/simvastatin20 mg: −36.5%
atorvastatin20: −49.6%
atorvastatin40: −39.4%
atorvastatin40: −53.9%

**Ezetimibe/simvastatin treatment (vs atorvastatin) was a significant predictor for change in most efficacy variables** (LDL-C, non-HDL-C, apolipoprotein B, total cholesterol, triglycerides, and very-LDL-C)
### Table 1. (Continued)

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<tr>
<td>Jimenez et al&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Ezetimibe/simvastatin 10/20 mg vs simvastatin 40 mg or atorvastatin 20 mg or rosuvastatin 10 mg</td>
<td>617 patients with metabolic syndrome, cardiovascular disease, diabetes mellitus, and LDL-C (≥70 and ≤160 mg/dL)</td>
<td>Follow-up: 6 wk Randomized, double blind</td>
<td>Switching to ezetimibe/simvastatin 10/20 mg was more effective at reducing LDL-C, total cholesterol, and Apo B vs doubling the baseline statin dose to simvastatin 40 mg or atorvastatin 20 mg or switching to rosuvastatin 10 mg. Mean percent changes in LDL-C were as follows: −22.5% ezetimibe/simvastatin, −9.6% doubled baseline statin, and −19.2% rosuvastatin</td>
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<tr>
<td>Averna et al&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Switching to ezetimibe/simvastatin 10/20 mg or rosuvastatin 10 mg</td>
<td>368 high-risk hypercholesterolemic patients with metabolic syndrome</td>
<td>6 wk Randomized, double blind</td>
<td>Treatment with ezetimibe/simvastatin was significantly more effective than rosuvastatin at lowering LDL-C, total cholesterol, non-HDL-C, and apolipoprotein B (all P &lt; .001)</td>
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<tr>
<td>Westerink et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Simvastatin 80 mg vs simvastatin/ezetimibe 10/10 mg</td>
<td>100 abdominal obese patients with the metabolic syndrome</td>
<td>6 wk treatment Multicenter; double blind, crossover</td>
<td>Fasting LDL-C levels (3.57 mmol/L at baseline) were reduced to 1.79 mmol/L following treatment with simvastatin 80 mg and 1.81 mmol/L with simvastatin/ezetimibe 10/10 mg</td>
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<tr>
<td>Takase et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Ezetimibe (10 mg/d) or nothing for 6 mo</td>
<td>78 patients with metabolic syndrome</td>
<td>6 mo treatment</td>
<td>Visceral fat was decreased 7.2% (from 161.3 ± 58.6 to 148.4 ± 52.7 cm; P &lt; .05), and adiponectin was increased 7.7% (from 3.61 ± 3.10 to 3.86 ± 3.62 µg/mL; P &lt; .05) after ezetimibe therapy</td>
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Abbreviations: CI, confidence interval; ENHANCE, Enhances Atherosclerosis Regression; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; RR, risk ratio; SE, standard error; SEAS, Simvastatin and Ezetimibe in Aortic Stenosis; SHARP, Study of Heart and Renal Protection; ZETELD, ZETia in the ELDerly.

increase in incident cancer would be unusual. In a preliminary report of the final analysis of the SHARP trial, there continued to be no increase in cancer incidence with ezetimibe, but there was a statistically nonsignificant increase in cancer deaths (3.2% vs 2.8%),\textsuperscript{16} and the final analysis of IMPROVE-IT showed no increase in cancer.\textsuperscript{12,36}

The incidence of any new relapsing and progressing malignancy was 10.03% (or 909 events) in the simvastatin plus ezetimibe arm vs 10.08% (or 915 events) in the simvastatin arm. The hazard ratios (HRs) for these end points are all very close to 1.0 (range: 0.993-1.032) with the upper bound of the 95% confidence interval (CI) between 1.09 and 1.22.

The percentages of patients with other AEs of special interest were very similar between treatment arms: myopathy/rhabdomyolysis, CPK elevations, liver enzyme elevations, gallbladder-related events, and cholecystectomies. A summary of AEs is presented in Table 2.

In patients receiving simvastatin 40 mg, the exposure-adjusted rate of the combined end point of myopathy/rhabdomyolysis is slightly higher in the patients taking simvastatin plus ezetimibe 40 mg compared with those taking simvastatin 40 mg (7.2 per 10 000 patient-years compared with 4.7 per 10 000 patient-years).

Safety analyses were also conducted for new-onset diabetes, pancreatitis, acute renal failure, interstitial lung disease, and hypersensitivity reactions in the IMPROVE-IT trial.

### Efficacy

In cardiovascular prevention, in old patients with hyperlipidemia and high risk of coronary heart disease, the addition of ezetimibe to a statin treatment significantly decreased LDL-C levels and other outcomes (total cholesterol, triglycerides, HDL cholesterol, and apolipoprotein B).\textsuperscript{11} The results are not consistent in cardiovascular morbimortality\textsuperscript{12,14,15} or in the carotid artery intima-media thickness change.\textsuperscript{13,17}

In familiar hypercholesterolemia, the Enhances Atherosclerosis Regression (ENHANCE) trial (April 2008)\textsuperscript{13} was conducted in 720 patients. Ezetimibe 10 mg was compared with placebo. At 2 years, changes in the thickness of the intima-media carotid artery (primary end point) showed no statistically significant differences.

In aortic stenosis, the SEAS trial (September 2008)\textsuperscript{14} was performed in 1873 patients with mild-to-moderate asymptomatic aortic stenosis. Ezetimibe/simvastatin (10/40 mg) was

### Table 2. A summary of adverse events of ezetimibe/simvastatin from the intention-to-treat population in the IMPROVE-IT trial.

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<tr>
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<th>SIMVASTATIN</th>
<th>P VALUE</th>
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<tr>
<td>ALT and/or AST &gt;3× ULN, consecutive</td>
<td>2.50</td>
<td>2.30</td>
<td>.429</td>
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<tr>
<td>CK &gt;10× ULN</td>
<td>0.70</td>
<td>0.70</td>
<td>.866</td>
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<tr>
<td>CK &gt;10× ULN with symptoms</td>
<td>0.30</td>
<td>0.30</td>
<td>.887</td>
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<tr>
<td>Myopathy/rhabdomyolysis\textsuperscript{a}</td>
<td>0.30</td>
<td>0.30</td>
<td>.896</td>
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<tr>
<td>Cholecystectomy hospitalizations</td>
<td>1.50</td>
<td>1.50</td>
<td>.958</td>
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<tr>
<td>Gallbladder-related AEs</td>
<td>3.10</td>
<td>3.50</td>
<td>.109</td>
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<tr>
<td>Biliary duct disorders</td>
<td>0.50</td>
<td>0.50</td>
<td>.595</td>
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<tr>
<td>Gallstone disorders</td>
<td>2.80</td>
<td>3.20</td>
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<tr>
<td>Gallbladder hospitalization</td>
<td>2.20</td>
<td>2.40</td>
<td>.378</td>
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Abbreviations: AEs, adverse events; ALT, alanine aminotransferase; CK, creatine kinase; IMPROVE-IT, IMProved Reduction of Outcomes: Vytorin Efficacy International Trial; ULN, upper limit normal.

\textsuperscript{a}Adjudicated events.

### Table 3. The main findings of safety analyses for new-onset diabetes, pancreatitis, acute renal failure, interstitial lung disease, and hypersensitivity reactions in the IMPROVE-IT trial.

<table>
<thead>
<tr>
<th></th>
<th>EZETIMIBE/ SIMVASTATIN, %</th>
<th>SIMVASTATIN, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>New-onset diabetes</td>
<td>7.20</td>
<td>7.30</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.53</td>
<td>0.64</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>2.86</td>
<td>2.59</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>0.37</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypersensitivity reaction</td>
<td>8.11</td>
<td>8.24</td>
</tr>
</tbody>
</table>


Modified from Westerink et al.\textsuperscript{23}
compared with placebo. At 4 years, the results in the primary end point (cardiovascular mortality, replacement aortic valve, nonfatal stroke, hospitalization for unstable angina, heart failure, coronary revascularization, percutaneous coronary intervention, or nonhemorrhagic stroke) did not achieve statistically significant differences.

In chronic kidney disease, the SHARP trial (June 2011)\textsuperscript{15,16} was performed in 9270 patients. Ezetimibe/simvastatin (10/20 mg) was compared with placebo. At 5 years of treatment, the results in the primary end point (nonfatal myocardial infarction [MI], coronary mortality, hemorrhagic stroke, or arterial revascularization) showed a risk reduction (11.3% vs 13.4%; risk ratio = 0.85, 95% CI: 0.74-0.94) which was statistically significant. The absolute risk reduction was 2.1% (0.43% annually). No benefits were obtained on cardiovascular mortality or total mortality.

For coronary artery disease, IMPROVE-IT trial (June 2015)\textsuperscript{12} was conducted in 18 144 patients hospitalized for acute coronary syndrome in the previous 10 days with associated cardiovascular risk factors (diabetes mellitus, previous coronary angiography, or percutaneous coronary intervention during the last entry) who were ≥50 years with LDL-C between 50 and 125 mg/dL (100 mg/dL for those treated with lipid-lowering drugs). This is a randomized, multicenter, double-blind study conducted in 39 centers in countries in North America, Europe, Australia, New Zealand, Asia, and Latin America clinical trial.

For 2.5 or more years, they received simvastatin (40 mg/d) plus ezetimibe (10 mg/d) or simvastatin (40 mg/d) plus placebo. Simvastatin dose was 80 mg/d if LDL-C was greater than 79 mg/dL until the Food and Drug Administration (FDA) alert; from this moment, the dose was reduced to 40 mg/d. If values were not getting LDL-C ≤ 100 mg/dL, treatment was stopped and a more potent statin was prescribed. The main composite variable was cardiovascular death, nonfatal MI, unstable angina requiring admission hospital, coronary revascularization (≥30 days after randomization), and nonfatal stroke. At 6 years, 42% of patients in each group had abandoned the treatment. At 7 years of follow-up (median follow-up = 6 years), the incidence of cardiovascular death or coronary event or nonfatal stroke was 32.7% vs 34.7% (HR: 0.936, 95% CI: 0.89-0.99). There were no differences compared with placebo in total mortality or cardiovascular mortality. The results of IMPROVE-IT trial are not applicable to patients at high-risk primary prevention, other cardiovascular patients with an old coronary syndrome, or patients on secondary prevention in patients with a different pathology coronary syndrome. The original protocol was amended on 5 occasions. The expected duration of the trial was around 2.5 years. For almost 7 years, differences between ezetimibe and placebo in the 2 planned interim analyses are not observed. A third analysis that was performed was unjustifiable. So, the study had to be extended from 2.5 to 7 years of follow-up, and the sample size was increased by 80% finally to obtain statistically significant differences in the primary end point.

There are doubts about the real effectiveness of ezetimibe as the advisory committee of the FDA seriously questioned the statistical analysis; there are many patients with incomplete data (11% of patients had no information on the primary end point, which was charged with a dummy data similar to those observed in reality in a group of similar patients in the trial).

### Patient Preferences

All clinical decisions related to lipid-lowering therapy (initiation, monitoring, and dose adjustment) should be shared and agreed with the patient, taking into account their opinion and preferences, to improve compliance, effectiveness, and safety of the treatment.

It is necessary to consider other comorbidities of the patients prior to initiating the treatment with ezetimibe.

### Hepatic impairment

Systemic exposure is increased in hepatic impairment. Use ezetimibe with caution in patients with mild hepatic impairment (Child-Pugh class A); use is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh classes B and C).\textsuperscript{5}

### Renal impairment

Use ezetimibe with caution in patients with severe renal impairment (CrCl ≤ 30 mL/min/1.73 m\textsuperscript{2}); systemic exposure is increased ~1.5-fold. If using concurrent simvastatin in patients with moderate-to-severe renal impairment (CrCl < 60 mL/min/1.73 m\textsuperscript{2}), the manufacturer of ezetimibe recommends that simvastatin doses exceeding 20 mg be used with caution and AEs (eg, myopathy) be monitored closely.\textsuperscript{5}

### Pregnancy

Ezetimibe should not be prescribed during pregnancy as it lacks safety data. An anion exchange resin such as cholestyramine is the drug of choice because it is not absorbed by the gastrointestinal tract.\textsuperscript{40}

### Lactation

No toxic effects on the infant have been reported with the use of many of these drugs, including ezetimibe. Lipid reducers should not be used during breastfeeding because there is no enough information about their safety. If the drug is taken, there are no limitations to breastfeeding. If there is an urgent indication, cholestyramine or pravastatin would be worth considering.\textsuperscript{40}

### Contraindications

Contraindications include hypersensitivity to ezetimibe or any component of the formulation, concomitant use with a
3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) in patients with active hepatic disease or unexplained persistent elevations in serum transaminases, and pregnancy and breastfeeding (when used concomitantly with a statin).5

Place in Therapy
Ezetimibe in monotherapy is not considered a drug of first choice because although it has demonstrated effectiveness in reducing hypercholesterolemia, it is not effective in the prevention of cardiovascular events. Statins are considered the drugs of choice for the treatment of dyslipidemia when non-pharmacological measures on the lifestyle of the patient are ineffective. Specifically, simvastatin is the recommended choice as statin, and its clinical efficacy has been established in cardiovascular prevention and presents more favorable cost-effectiveness ratio.41,42

According to the guidelines of National Institute for Health and Care Excellence, ezetimibe in monotherapy is recommended as an option only in adults in whom initial statin therapy is contraindicated or who cannot tolerate statin therapy.43,44

Patients with dyslipidemia, particularly those with established CVD, diabetes, or asymptomatic high-risk individuals, may not always reach treatment targets. Therefore, combination treatment may be needed.45

Combinations of a statin and a bile acid sequestrant or a combination of a statin and an ezetimibe can be used for greater reduction of LDL-C than can be achieved with either drug alone. Another advantage of combination therapy is that lower doses of statins can be used, thus diminishing the risk of adverse effects associated with high doses. However, statins should be used in the highest tolerable doses to reach the LDL-C target level before combination therapy.45

Ezetimibe, coadministered with initial statin therapy, is recommended as an option for treating primary (heterozygous familial or nonfamilial) hypercholesterolemia in adults who have started statin therapy when serum total or LDL-C concentration is not appropriately controlled either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to the initial statin therapy and when a change from initial statin therapy to an alternative statin is being considered. Intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.45,46

Ezetimibe may also be prescribed for 2 very rare inherited disorders (prevalence: 1 in 1 000 000 births) that are usually specialist managed: HoFH and homozygous sitosterolemia.46

Conclusions
The precise role of ezetimibe relative to other lipid-lowering drugs is unclear. Similar reductions in LDL-C can often be achieved simply by maximizing the dose of statins. As an example, 1 randomized trial found that the reduction in LDL-C concentration was the same with atorvastatin 10 mg plus ezetimibe as with atorvastatin 80 mg alone; however, adding ezetimibe to atorvastatin 80 mg did result in an additional 9% reduction in LDL-C concentration. Ezetimibe plus atorvastatin also produced a greater reduction in serum C-reactive protein than atorvastatin alone.

Ezetimibe may be helpful in avoiding high doses of statins (and potentially increased susceptibility to muscle injury) in patients who do not meet cholesterol goals on low-dose statin therapy alone.

Ezetimibe has been well tolerated in clinical trials. When administered alone, the incidence of either myopathy or serum transaminase elevations was similar to that of placebo, and when coadministered with a statin, the incidence of serum transaminase elevation has been slightly higher than with statin therapy alone. The manufacturer suggests measurement of liver function tests prior to initiating treatment with ezetimibe plus a statin.

Author Contributions
EFL, EB, GB, MR, and JAV conceived and designed the experiments, analyzed the data, wrote the first draft of the manuscript, contributed to the writing of the manuscript, agreed with manuscript results and conclusions, jointly developed the structure and arguments for the paper, and made critical revisions and approved the final version. All authors reviewed and approved the final manuscript.

Disclosures and Ethics
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