Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients*

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Abstract

Objective: To assess the lipid-altering efficacy and safety of ezetimibe/simvastatin single tablet product compared with rosuvastatin at the approved usual starting, next highest, and maximum doses.

Research design and methods: Double-blind, multicenter, 6-week, parallel-group study in hypercholesterolemic patients (n = 2959). Patients were randomized based on stratification by low-density lipoprotein cholesterol (LDL-C) levels to ezetimibe/simvastatin or rosuvastatin, respectively, at the usual starting (10/20 or 10 mg/day), the next highest (10/40 or 20 mg/day), and maximum doses (10/80 or 40 mg/day).

Results: At all doses and across doses, ezetimibe/simvastatin reduced LDL-C levels significantly more (52–61%) than rosuvastatin (46–57%; p ≤ 0.001). Significantly greater percentages of all patients (p < 0.001) and high risk patients (p < 0.005) attained LDL-C levels < 70 mg/dL (1.8 mmol/L) following ezetimibe/simvastatin treatment compared with rosuvastatin at the prespecified doses and across doses. Ezetimibe/simvastatin also produced significantly greater reductions in total cholesterol (p < 0.001), non-high-density lipoprotein cholesterol (p < 0.001), lipid ratios (p < 0.003), and apolipoprotein B (p < 0.05). Reductions in triglycerides were significantly greater with ezetimibe/simvastatin than rosuvastatin at the usual starting (p = 0.004) and next highest (p = 0.006) doses, and across all doses (p < 0.001). Increases in high-density lipoprotein cholesterol, and decreases in high sensitivity C reactive protein (hsCRP) were similar between treatment groups. Safety profiles were comparable for both treatments; however, the percent of patients with proteinuria was significantly higher following rosuvastatin treatment than ezetimibe/simvastatin, respectively at 10 mg versus

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Introduction

Multiple independent risk factors predict the development and progression of atherosclerosis, and among the most important is hypercholesterolemia, particularly increased concentrations of low-density lipoprotein cholesterol (LDL-C). Epidemiological studies have demonstrated a continuous and graded relationship between concentrations of LDL-C or total cholesterol (TC) and risk of death due to coronary heart disease (CHD)\(^1,2\).

Certain cholesterol-lowering treatments have been shown to provide substantial reductions in cardiovascular morbidity and mortality, progressively lowering the targets for LDL-C reduction\(^3,4\). A log-linear relationship exists between LDL-C levels and CHD risk, such that a 1% reduction in LDL-C is predicted to reduce the risk of CHD by approximately 1%\(^5\). Recent studies confirmed empirically that this relationship extends to an LDL-C level of ≤ 70 mg/dL (1.8 mmol/L) in high-risk patients and that such a low level is attainable\(^5,7\). The importance of lowering LDL-C to reduce CHD risk is emphasized in national and international guidelines\(^8,9\). The aggressive treatment of individuals with established CHD or CHD risk equivalents, or a 10-year CHD risk of > 20%, is exemplified by the current United States guidelines issued by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), which recommends LDL-C lowering to < 100 mg/dL (2.6 mmol/L), with an option to seek levels < 70 mg/dL (1.8 mmol/L)\(^3,4\) in patients considered to be at very high risk.

The effectiveness of statins in reducing LDL-C and providing patients the ability to attain ATP III goals has been well-studied in hypercholesterolemic patients. At commonly prescribed doses, statins can reduce LDL-C levels below 100 mg/dL (2.6 mmol/L) in about 50% of patients, and in the remaining patients, either the statin dose must be increased, or an additional LDL-C-lowering drug must be added to the treatment regimen\(^1\). In patients at high risk, the importance and benefits of statin therapy in achieving these very low levels of LDL-C has been demonstrated\(^10–12\). However, because a large percent of these patients do not reach an LDL-C goal of < 100 mg/dL (≤ 2.6 mmol/L), more effective therapies that can achieve very low levels of LDL-C are needed\(^13\). In addition, the potential impact of such a therapy is significant, considering that the latest estimate of the prevalence of CHD in the United States is 6.9% of the population\(^14\). Moreover, statin therapy has also been shown to be beneficial in lowering plasma LDL-C to achieve reductions in cardiovascular events in patients with type 2 diabetes\(^15\). Type 2 diabetes, considered to be a high-risk factor for CHD by NCEP ATP III\(^1\), is also on the rise in the United States, where it is estimated that 20.8 million people, or 7.0% of the population, have diabetes\(^16\).

The pursuit of more effective lipid control measures has stimulated the identification and development of higher-potency statins, such as rosuvastatin, shown to be more effective in reducing LDL-C compared to other statins\(^17–19\). An alternative approach has been to identify agents with effects complementary and/or incremental to those of statins. This includes ezetimibe, which inhibits the uptake of intestinal biliary and dietary cholesterol\(^20\), by binding to Niemann-Pick C1-Like 1 protein\(^21\). Ezetimibe (10 mg/day), when used as monotherapy, effectively lowers LDL-C (~ 18%); and when added to statin therapy, consistently provides a significantly higher LDL-C-lowering effect\(^22,23\). In the EASE study\(^23\), in which patients received either ezetimibe 10 mg or placebo in addition to their ongoing statin therapy, ezetimibe reduced the LDL-C level by an additional 25.8% as compared to an additional 2.7% reduction with placebo. Ezetimibe in combination with simvastatin was approved by the US Food and Drug Administration as a single tablet formulation (Vytorin, Merck/Schering-Plough Pharmaceuticals, West Point, PA) and has proven to be highly effective in reducing LDL-C through the dual inhibition of cholesterol absorption and biosynthesis for the treatment of hypercholesterolemia\(^24–26\).

In the US, ezetimibe/simvastatin (Vytorin) and rosuvastatin (Crestor, AstraZeneca, Wilmington, DE) are widely prescribed, respectively, at the recommended usual starting [10/20 mg/day (44%) and 10 mg/day (63%)], and the next highest [10/40 mg/day (39%)].

Conclusion: Ezetimibe/simvastatin was more effective than rosuvastatin in LDL-C lowering, and provided greater or comparable improvements in other lipid measures and hsCRP at the approved usual starting, next highest, and maximum doses in hypercholesterolemic patients. Although the doses compared in this study were not equivalent on a milligram basis, the results provide clinically relevant information regarding the use of these drugs for initial therapy and for subsequent use at higher doses when appropriate. Both treatments were generally well-tolerated; however, this study was not powered nor of sufficient duration to assess the prevalence of rare clinical adverse effects. Overall, ezetimibe/simvastatin offers an effective and tolerable treatment option for lipid management. An assessment of its full clinical benefit awaits evaluation in longer-term clinical studies.
and 20 mg/day (17%) doses\textsuperscript{27}. Similarly, in Europe, the most commonly prescribed doses of ezetimibe/simvastatin (INEGY, MSD-SP, Hoddesdon, UK) and rosvuastatin (Crestor, AstraZeneca, Macclesfield, UK) prescriptions, respectively, are the usual starting [10/20 mg/day (60.2%) and 10 mg/day (80.8%)] and next higher [10/40 mg/day (23.6%) and 20 mg/day (11.8%)] doses\textsuperscript{28}. This study was undertaken to assess the lipid-altering effectiveness and safety of ezetimibe/simvastatin in comparison to rosvuastatin at the recommended usual starting, next highest, and maximum doses of both drugs.

## Methods

### Study design and participants

Protocol 058 was a multicenter, double-blind, randomized, active-controlled, 6-arm, parallel-group study (10 weeks, with 4-week placebo/diet run-in period, followed by 6 weeks of active treatment) designed to evaluate the efficacy and safety of ezetimibe/simvastatin versus rosvuastatin monotherapy at the recommended usual starting, next highest, and maximum doses of each, in patients with hypercholesterolemia. The protocol was approved by appropriate institutional review boards, and all patients provided written informed consent before initiation of any study procedure.

Men and women 18–81 years of age with LDL-C ≥ 145 mg/dL (3.7 mmol/L) and ≤ 250 mg/dL (6.5 mmol/L) were eligible for enrollment. Other eligibility criteria included fasting serum triglyceride (TG) level ≤ 350 mg/dL (4.0 mmol/L), alanine aminotransferase (ALT), aspartate aminotransferase (AST), or creatine kinase (CK) level ≤ 1.5 times the upper limit of normal (ULN), serum creatinine level ≤ 1.5 mg/dL (133 mmol/L), and hemoglobin A1c < 9.0% in patients with diabetes. Patients discontinued fibrate and all other lipid-lowering therapy at 9 and 7 weeks, respectively, before the start of the study. Patients who met entry criteria and were able to maintain NCEP Therapeutic Lifestyle Changes, or similar diet, were randomized in equal proportions to one of the six treatment groups: ezetimibe/simvastatin at doses of 10/20, 10/40, or 10/80 mg, or rosvuastatin monotherapy at doses of 10, 20, or 40 mg. Patients were centrally randomized using an interactive voice response system and stratified according to LDL-C level [≥ 145 mg/dL (3.8 mmol/L) and < 160 mg/dL (4.1 mmol/L); ≥ 160 mg/dL (4.1 mmol/L); and < 190 mg/dL (4.9 mmol/L); and ≥ 190 mg/dL (4.9 mmol/L)] regardless of ATP III CHD risk category, 1 week before the start of study medication to achieve balance among treatment groups.

### Laboratory methods

Clinical laboratory measurements were performed at a certified central laboratory [Pharmaceutical Product Development, Inc/Medical Research Laboratories International (PPD/MRLI), Highland Heights, Kentucky, USA]. Lipid measurements were performed
according to standards specified by the National Heart, Lung, and Blood Institute, and the Centers for Disease Control and Prevention. LDL-C values were calculated by the method of Friedewald ($LDL-C = TC−(HDL-C + TG/5)$). When TG levels were $> 400$ mg/dL ($> 4.5$ mmol/L), direct LDL-C measurements were obtained using the beta-quantitative method. High-sensitivity CRP was measured by the immunonephelometric method (Dade Behring, Inc., Deerfield, Illinois, USA) from archived serum samples. The percent of patients with proteinuria ($> 1+$ and $> ++$) was assessed by urine protein dipstick analysis (Bayer Atlas), quantitated by automated spectrophotometry (Atlas) (PPD/MRLI). In patients positive for proteinuria, the urine was further assessed by microscopic determination of white and red blood cell numbers. Blood chemistry tests included pre- and post-baseline measurements of serum creatinine.

**Statistical methods**

For the efficacy analyses, a modified intent-to-treat (MITT) population was used, which included all randomized patients who had a valid baseline and at least one valid post-baseline measurement. Baseline values for the efficacy variables were the average of the Week –1 and Day 1 (predose) measurements, and study endpoint values were the average of the Week 5 and Week 6 measurements (or the last measurement if only one measurement was available). Treatment comparisons were carried out using an analysis of variance (ANOVA) model with terms for treatment (6 levels: ezetimibe/simvastatin: 10/20, 10/40, and 10/80 mg; and rosuvastatin 10, 20, and 40 mg) and Week –1 LDL-C stratum ($\geq 145$ to $< 160$, $\geq 160$ to $< 190$, and $\geq 190$ mg/dL ($\geq 3.7$ to $< 4.1$, $\geq 4.1$ to $< 4.9$, and $\geq 4.9$ mmol/L)). With appropriate contrasts, this model provided estimates of within-treatment percent changes from baseline and between-treatment differences and 95% confidence intervals (CIs) for the differences.

As prespecified in the data analysis plan, if the primary hypothesis (difference in percent changes from baseline in LDL-C between the ezetimibe/simvastatin and rosuvastatin groups averaged across all doses) was significant at the 0.05 level, then, in a closed testing approach, the secondary hypotheses (differences in percent changes in LDL-C by dose) were tested using the Hochberg procedure. All treatment comparisons on the secondary and other efficacy endpoints were carried out using the ANOVA model described above. Because of the skewed distribution of TG, the ANOVA model was analyzed using Tukey normal scores rank transformations of percent change from baseline. Statistical inferences were based on non-parametric ANOVA results, and medians and 95% CIs for the medians were presented. Since the distribution of hsCRP levels was also skewed, post hoc analyses of hsCRP levels were performed in the same manner as TG.

The percent of patients reaching NCEP ATP III LDL-C goals by risk category, and the percent of all patients and of high-risk patients (CHD or CHD risk-equivalent) reaching LDL-C $< 70$ mg/dL ($< 1.8$ mmol/L) and $< 100$ mg/dL ($< 2.6$ mmol/L), were compared between treatments using logistic regression models with terms for treatment, Week –1 LDL-C stratum, and the percent difference between the LDL-C baseline and NCEP ATP III goal (or treatment to $< 100$ or $< 70$ mg/dL ($< 1.8$ or $< 2.6$ mmol/L), respectively).

All patients who received at least one dose of double-blind study medication were included in the safety analyses. Fisher’s exact test was used for comparisons between the pooled treatment groups on the incidence of adverse experiences (including percentages of patients with $\geq 1$ adverse experiences, drug-related adverse experiences, serious adverse experiences, and discontinuations due to an adverse experience) and on the incidences of the following predefined elevations: consecutive elevations of ALT and/or AST $\geq 3$ times the ULN (this category includes those patients with two consecutive measurements for ALT and/or AST $\geq 3$ times the ULN; a single, last measurement $\geq 3$ times the ULN; or a measurement $\geq 3$ times the ULN that had no follow-up measurements within 2 days of the last dose of study medication), CK elevations $\geq 10$ times the ULN, with or without muscle symptoms.

**Results**

**Patients**

A total of 5269 patients were screened at 214 sites in the United States, of which 2959 were randomized (1478 to ezetimibe/simvastatin and 1481 to rosuvastatin). The disposition of patients is illustrated in Figure 1. A total of 2855 patients were included in the MITT population (1478 to ezetimibe/simvastatin and 1481 to rosuvastatin). The distributions of patient demographics and NCEP ATP III risk categories were comparable across treatment groups (Table 1).

**Efficacy**

The mean percent reduction in LDL-C from baseline across all doses was significantly greater ($p < 0.001$) in
Table 1. Baseline patient characteristics for all randomized patients

<table>
<thead>
<tr>
<th></th>
<th>Rosuva 10 mg</th>
<th>EZ/simva 10/20 mg</th>
<th>Rosuva 20 mg</th>
<th>EZ/simva 10/40 mg</th>
<th>Rosuva 40 mg</th>
<th>EZ/simva 10/80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 492, n (%)</td>
<td>N = 492, n (%)</td>
<td>N = 495, n (%)</td>
<td>N = 493, n (%)</td>
<td>N = 494, n (%)</td>
<td>N = 493, n (%)</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>55.6 ± 10.3</td>
<td>54.9 ± 10.4</td>
<td>55.8 ± 10.4</td>
<td>56.2 ± 10.4</td>
<td>55.4 ± 10.6</td>
<td>55.9 ± 10.0</td>
</tr>
<tr>
<td>Sex men</td>
<td>206 (41.9)</td>
<td>237 (48.2)</td>
<td>215 (43.4)</td>
<td>221 (44.8)</td>
<td>203 (41.1)</td>
<td>220 (44.6)</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>427 (86.8)</td>
<td>431 (87.6)</td>
<td>421 (85.1)</td>
<td>429 (87.0)</td>
<td>425 (86.0)</td>
<td>426 (86.4)</td>
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<tr>
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<td>38 (7.7)</td>
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<td>Hispanic</td>
<td>25 (5.1)</td>
<td>20 (4.1)</td>
<td>24 (4.8)</td>
<td>19 (3.9)</td>
<td>19 (3.8)</td>
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<td>Other</td>
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<td>11 (2.2)</td>
<td>15 (3.0)</td>
<td>15 (3.0)</td>
<td>12 (2.4)</td>
<td>14 (2.8)</td>
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<td>NCEP ATP III risk category</td>
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<td>CHD/CHD risk equivalent</td>
<td>130 (26.4)</td>
<td>123 (25.0)</td>
<td>122 (24.6)</td>
<td>119 (24.1)</td>
<td>107 (21.7)</td>
<td>130 (26.4)</td>
</tr>
<tr>
<td>2+ CHD risk factors</td>
<td>154 (31.3)</td>
<td>156 (31.7)</td>
<td>174 (35.2)</td>
<td>150 (30.4)</td>
<td>189 (38.3)</td>
<td>167 (33.9)</td>
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<tr>
<td>0–1 risk factors</td>
<td>208 (42.3)</td>
<td>213 (43.3)</td>
<td>199 (40.2)</td>
<td>224 (45.4)</td>
<td>198 (40.1)</td>
<td>196 (39.8)</td>
</tr>
<tr>
<td>Visit 2 LDL-C Strata</td>
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<tr>
<td>≥145–&lt;160 mg/dL (≥3.7–&lt;4.1 mmol/L)</td>
<td>166 (33.7)</td>
<td>166 (33.7)</td>
<td>167 (33.7)</td>
<td>166 (33.7)</td>
<td>167 (33.8)</td>
<td>166 (33.7)</td>
</tr>
<tr>
<td>≥160–&lt;190 mg/dL (≥4.1–&lt;4.9 mmol/L)</td>
<td>211 (42.9)</td>
<td>211 (42.9)</td>
<td>212 (42.8)</td>
<td>212 (43.0)</td>
<td>212 (42.9)</td>
<td>212 (43.0)</td>
</tr>
<tr>
<td>≥190 mg/dL (≥4.9 mmol/L)</td>
<td>115 (23.4)</td>
<td>115 (23.4)</td>
<td>116 (23.4)</td>
<td>115 (23.3)</td>
<td>115 (23.3)</td>
<td>115 (23.3)</td>
</tr>
<tr>
<td>Body mass index (mean kg/m² ± SD)</td>
<td>29.6 ± 5.5</td>
<td>29.9 ± 5.9</td>
<td>29.8 ± 5.9</td>
<td>29.2 ± 5.6</td>
<td>29.7 ± 6.1</td>
<td>29.6 ± 6.0</td>
</tr>
</tbody>
</table>

EZ/simva = ezetimibe/simvastatin; rosuva = rosuvastatin; CHD = coronary heart disease

†Metabolic syndrome defined as having 3 of the following characteristics: (1) waist circumference > 102 cm (males) or > 80 cm (females); (2) TG ≥ 150 mg/dL (≥1.7 mmol/L); (3) HDL-C < 40 mg/dL (<1.0 mmol/L) (males) or < 50 mg/dL (<1.3 mmol/L) (females); (4) Blood pressure ≥ 130/85 mmHg or on antihypertensive medication; (5) Fasting glucose ≥ 110 mg/dL or diabetic
patients treated with ezetimibe/simvastatin (55.8%) than with rosuvastatin (51.6%) (Figure 2 and Table 2). Similarly, significantly greater reductions in LDL-C were also observed at the usual starting ($p < 0.001$), the next highest ($p = 0.001$), and the maximum ($p < 0.001$) doses of ezetimibe/simvastatin compared with rosuvastatin.

As summarized in Table 2, patients receiving ezetimibe/simvastatin had statistically significantly greater reductions, at all dose comparisons and across doses in TC ($p < 0.001$), non-HDL-C ($p < 0.001$), apo B ($p < 0.05$), LDL-C:HDL-C ratio ($p < 0.002$), and TC:HDL-C ratio ($p < 0.003$). Reductions in TGs were statistically significantly greater for the dose comparisons of ezetimibe/simvastatin 10/20 mg and rosuvastatin 10 mg ($p = 0.004$), ezetimibe/simvastatin 10/80 mg and rosuvastatin 40 mg ($p = 0.006$), and when averaged across all doses ($p < 0.001$), and were comparable at ezetimibe/simvastatin 10/40 mg and rosuvastatin 20 mg ($p = 0.121$). Changes in HDL-C and hsCRP were similar for both study medications at all dose comparisons.

**Figure 1.** Flow of patients through each stage of the trial. *Includes one patient randomized to EZ/simva 10/80 mg/day, but mistakenly treated with rosuvastatin 20 mg/day. AE = adverse experience; EZ/simva = ezetimibe/simvastatin; LDL-C = low-density lipoprotein cholesterol; MITT = modified intent-to-treat

**LDL-C treatment goal attainment**

A significantly greater percent of patients attained NCEP ATP III LDL-C goals [$< 100$, $< 130$, $< 160$ mg/dL ($< 2.6$, $< 3.4$, $< 4.1$ mmol/L) for high, moderate, and low risk subjects, respectively] when treated with ezetimibe/simvastatin than with rosuvastatin at the lowest dose comparison of ezetimibe/simvastatin 10/20 mg (94.7%) versus rosuvastatin 10 mg (90.1%, $p = 0.009$) and when averaged across all doses respectively (95.9% versus 93.0%, $p = 0.001$; Figure 3). There was no significant difference in attainment of ATP III goal at the other dose comparisons. Similarly, significantly higher percentages of patients achieved LDL-C levels of $< 100$ mg/dL (2.6 mmol/L) with ezetimibe/simvastatin versus rosuvastatin, respectively, at the lowest (84.0% versus 72.0%, $p < 0.001$) and maximum (93.2% versus 89.1%, $p = 0.031$) doses, and across doses (88.2% versus 81.9%, $p < 0.001$), and with ezetimibe/simvastatin 40 mg and rosuvastatin 20 mg, the percentages were comparable (87.2% and 84.7%, respectively, $p = 0.132$). Additionally, significantly higher percentages of patients (24.2%, 40.7%,

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Ezetimibe/simvastatin versus rosuvastatin for lipids
Table 2. Summary of efficacy results for lipoproteins and hsCRP (MITT population), by treatment group

<table>
<thead>
<tr>
<th>Parameter statistics</th>
<th>Rosuva 10 mg</th>
<th>EZ/simva 20 mg</th>
<th>Rosuva 20 mg</th>
<th>EZ/simva 40 mg</th>
<th>Rosuva 40 mg</th>
<th>EZ/simva 80 mg</th>
<th>All rosuva</th>
<th>All EZ/simva</th>
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<tr>
<td>LDL-C</td>
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<tr>
<td>Baseline mean (mg/dL)</td>
<td>172 (4.5)</td>
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<td>172 (4.5)</td>
<td>173 (4.5)</td>
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<td>(mmol/L)</td>
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<tr>
<td>% change from baseline</td>
<td>-45.8 (0.5)</td>
<td>-51.5 (0.5)</td>
<td>-52.3 (0.5)</td>
<td>-54.8 (0.5)</td>
<td>-56.7 (0.5)</td>
<td>-61.0 (0.5)</td>
<td>-51.6</td>
<td>-55.8</td>
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<tr>
<td>(SE)†</td>
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<tr>
<td>Treatment difference</td>
<td>-5.7***</td>
<td>-2.5**</td>
<td>-4.3***</td>
<td>-4.3***</td>
<td>-4.2***</td>
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<tr>
<td>(SE)‡</td>
<td>(0.8)</td>
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<td>HDL-C</td>
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<td>Baseline mean, mg/dL</td>
<td>51 (1.3)</td>
<td>51 (1.3)</td>
<td>50 (1.3)</td>
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<td>50 (1.3)</td>
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<td>(mmol/L)</td>
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<tr>
<td>% change from baseline</td>
<td>6.7 (0.5)</td>
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<td>8.1 (0.5)</td>
<td>8.3 (0.5)</td>
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Table 2 (continued)

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**LDL-C:HDL-C**

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**Total-C:HDL-C**

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<td>(SE)†</td>
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**Apo B**

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<td>–3.2***</td>
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**hsCRP§**

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<td>% change from baseline</td>
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<td>(–30.0, –20.0)</td>
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<td>(95% CI) §</td>
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<td>(–6.1, 0.0)</td>
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EZ = ezetimibe 10 mg; all rosuva = Rosuvastatin (10, 20, and 40 mg) pooled across all doses
All EZ/simva = ezetimibe/simvastatin (10/20, 10/40, and 10/80 mg) pooled across all doses
*p < 0.05; **p = 0.001 (LDL-C); 0.004 (TG, rosuva 10 and EZ/simva 20 mg); 0.006 (TG, rosuva 40 and EZ/simva 80 mg), 0.002 (LDL-C:HDL-C), 0.003 (Total C:HDL-C); ***p < 0.001 for specified between-treatment difference
†Percent changes from baseline and between-treatment differences are LS means and differences in LS means
‡Treatment differences are EZ/simva 10/20 mg minus rosuva 10 mg, EZ/simva 10/40 mg minus rosuva 20 mg, and EZ/simva 10/80 mg minus rosuva 40 mg
§Percent changes from baseline and between-treatment differences are medians and differences in medians
¶Nonparametric results (medians) are presented for TG and CRP
65.8%, and 43.5%) attained LDL-C levels < 70 mg/dL (1.8 mmol/L) with ezetimibe/simvastatin 20, 40, 80 mg, and across doses respectively, compared to the percent of patients (9.3%, 29.7%, 49.5%, and 29.5%) with rosuvastatin 10, 20, 40 mg, and across doses, respectively (p < 0.001).

In a post-hoc subgroup analysis of high-risk patients (i.e., patients with CHD or CHD risk equivalent by NCEP ATP III), significantly higher proportions of patients treated with ezetimibe/simvastatin reached the LDL-C goal of < 100 mg/dL (< 2.6 mmol/L) than rosuvastatin when averaged across all doses (p = 0.011) (Figure 4A); however, the individual dose comparisons did not reach statistical significance. Significantly higher proportions of patients also achieved an LDL-C level of < 70 mg/dL (< 1.8 mmol/L), at the lowest and maximum doses, across doses (p < 0.001) and at the ezetimibe/simvastatin 10/40 mg versus rosuvastatin 20 mg dose comparison (p = 0.005; Figure 4B).

**Safety**

The percentages of patients with clinical and laboratory adverse experiences were comparable between the two treatments. Similar percentages of patients in the pooled ezetimibe/simvastatin and the pooled rosuvastatin groups had one or more clinical adverse experience (29.2% versus 31.1%), drug-related adverse experiences (8.1% versus 7.4%), and serious adverse experiences (1.2% versus 1.1%). There were
no statistically significant differences in the frequency of any category of pre-specified clinical adverse experiences between the treatment groups, including drug-related and/or serious, gastrointestinal-, gallbladder-, hepatitis-, rash-, or allergy-related clinical adverse experiences. Sixty-six patients (2.2%) discontinued the study due to clinical adverse experiences in each of the pooled ezetimibe/simvastatin and rosuvastatin groups. There were no deaths during the study.

The incidences of consecutive elevations in hepatic transaminase levels (ALT and/or AST) ≥ 3 times the ULN were not statistically significantly different between the pooled ezetimibe/simvastatin and the pooled rosuvastatin monotherapy groups (Table 3). In the ezetimibe/simvastatin groups, nine (0.6%) patients (one on 10/20 mg, two on 10/40 mg and six on 10/80 mg) and in the rosuvastatin monotherapy group three (0.2%) patients (two on 20 mg and one on 40 mg) had consecutive elevations in ALT and/or AST (≥ 3 × ULN). Among the patients with consecutive ALT and/or AST elevations, none had concurrent total bilirubin levels of > 1.5 mg/dL. There were no differences in the incidences of consecutive elevations of CK ≥ 10 × ULN, or CK ≥ 10 × ULN with or without muscle symptoms between the treatment groups. One (0.1%) patient in the rosuvastatin 40 mg group had CK elevations ≥ 10 × ULN, of which the one rosuvastatin patient and two of the ezetimibe/simvastatin patients experienced muscle symptoms.

The percent of patients with ≥ 1+ proteinuria was statistically significantly higher at rosuvastatin 10 mg (5.4%) versus ezetimibe/simvastatin 10/20 mg (1.7%; p = 0.004; difference –3.6%; 95% CI –6.2, –1.2), and at rosuvastatin 40 mg (9.2%) versus ezetimibe/simvastatin 10/80 mg (3.6%; p < 0.001; difference –5.5%; 95% CI –8.8, –2.4). Proteinuria in the rosuvastatin 20 mg group (5.4%) did not differ from the ezetimibe/simvastatin 10/40 mg group (5.3%). However, when pooled across doses, the percent of patients with proteinuria in the rosuvastatin group (6.6%) was significantly greater than the ezetimibe/simvastatin group (3.5%; p < 0.001; difference –3.1%; 95% CI –4.7, –1.4). Similarly, the percent of patients with no, trace, or > ++ baseline proteinuria with ≥ ++ proteinuria at follow-up was greater at rosuvastatin 40 mg (3.4%) versus ezetimibe/simvastatin 10/80 mg (0.4%; p < 0.001; difference –3.0%; 95% CI –5.0, –1.3), and in the pooled rosuvastatin (1.9%) versus the pooled ezetimibe/simvastatin (0.8%; p = 0.023; difference –1.0%; 95% CI –2.0, –0.2), but there was no difference at rosuvastatin 10 mg (1.3%) versus ezetimibe/simvastatin 10/20 mg (0.6%) or at rosuvastatin 20 mg (1.0%) versus ezetimibe/simvastatin 10/40 mg (1.5%). Post-baseline levels of serum creatinine increased in one (0.1%) patient in the rosuvastatin 40 mg group and none were observed in the ezetimibe/simvastatin groups.

### Table 3. Percent of patients with predefined elevations in ALT, AST, and CK

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<tr>
<th>Predefined limits of change</th>
<th>Pooled treatment groups</th>
<th>All rosuva</th>
<th>All EZ/simva</th>
<th>Difference (95% CI)</th>
<th>p-value §</th>
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<tbody>
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<td>ALT</td>
<td></td>
<td>m/n (%)</td>
<td>m/n (%)</td>
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<tr>
<td>≥ 3 × ULN, one or more</td>
<td>2/1447 (0.1)</td>
<td>9/1437 (0.6)</td>
<td>–</td>
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<tr>
<td>≥ 3 × ULN, consecutive†</td>
<td>2/1447 (0.1)</td>
<td>8/1437 (0.6)</td>
<td>0.4 (–0.0, 1.0)</td>
<td>0.064</td>
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<td>AST</td>
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</tr>
<tr>
<td>≥ 3 × ULN, one or more</td>
<td>1/1447 (0.1)</td>
<td>5/1437 (0.3)</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>≥ 3 × ULN, consecutive†</td>
<td>1/1447 (0.1)</td>
<td>5/1437 (0.3)</td>
<td>0.3 (–0.1, 0.7)</td>
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<td>ALT and/or AST</td>
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<td>≥ 3 × ULN, consecutive†</td>
<td>3/1447 (0.2)</td>
<td>9/1437 (0.6)</td>
<td>0.4 (–0.1, 1.0)</td>
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<td>≥ 5 × ULN to &lt; 10 × ULN</td>
<td>5/1447 (0.3)</td>
<td>1/1437 (0.1)</td>
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<td>≥ 10 × ULN</td>
<td>1/1447 (0.1)</td>
<td>4/1437 (0.3)</td>
<td>0.2 (–0.2, 0.6)</td>
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<td>≥ 10 × ULN with muscle symptoms</td>
<td>1/1447 (0.1)</td>
<td>2/1437 (0.1)</td>
<td>0.1 (–0.3, 0.4)</td>
<td>0.624</td>
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</table>

EZ = ezetimibe 10 mg; all rosuva = rosuvastatin (10, 20, and 40 mg) pooled across all doses
All EZ/simva = ezetimibe/simvastatin (10/20, 10/40, and 10/80 mg) pooled across all doses
% = m/n × 100 = (number of patients with elevated test/number of patients tested) × 100
†CI = confidence intervals, calculated using a method based on Wilson’s score method
§p-values were from Fisher’s Exact test
Includes subjects with (a) two consecutive measurements for ALT and/or AST ≥ 3 × ULN, (b) a single, last measurement > 3 × ULN, or (c) a measurement ≥ 3 × ULN, followed by a measurement < 3 × ULN that was taken more than 2 days after the last dose of study medication
Not applicable
Discussion

This study demonstrated the greater LDL-C lowering efficacy of ezetimibe/simvastatin compared to rosvuastatin at the widely prescribed usual starting, next highest, and maximum doses in hypercholesterolemic patients. The results of this study are consistent with the findings of an earlier meta-analysis\(^5\) of 14 randomized trials which indicated that LDL-C lowering with the ezetimibe/simvastatin combination was greater than with rosvuastatin monotherapy, respectively, at the corresponding usual starting (10/20 mg versus 10 mg), the next highest (10/40 mg versus 20 mg) doses, the maximum doses (10/80 mg versus 40 mg), and the lower doses (10/10 mg versus 5 mg). The incremental reductions in LDL-C observed in this study were greater with ezetimibe/simvastatin than with rosvuastatin, respectively, by 5.7% (10/20 mg versus 10 mg), 2.5% (10/40 mg versus 20 mg), and 4.3% (10/80 mg versus 40 mg).

In this study, the respective final LDL-C levels ranged from 84 mg/dL (2.2 mmol/L) at 10/20 mg to 68 mg/dL (1.8 mmol/L) at 10/80 mg for ezetimibe/simvastatin, and 93 mg/dL (2.4 mmol/L) at 10 mg to 75 mg/dL (1.9 mmol/L) at 40 mg for rosvuastatin. Until recently such levels would have been regarded as exceptionally low. Several studies, including The MRC-Heart Protection Study (HPS)\(^10\), Treating to New Targets (TNT)\(^9\), and the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)\(^7\) studies, have demonstrated that these low levels of LDL-C were associated with cardiovascular benefits. Although the average level of LDL-C achieved with ezetimibe/simvastatin in this study was similar to those achieved in the TNT\(^9\) and IDEAL\(^7\) studies, it should be noted that the effect of ezetimibe/simvastatin or rosvuastatin upon the reduction of coronary events in clinical trials has not yet been assessed.

Recently, based on the results of five large clinical trials, the NCEP re-examined the recommendations of the ATP III and reinforced the treatment goal of LDL-C < 100 mg/dL (< 2.6 mmol/L) for high-risk patients, and suggested consideration of reducing LDL-C levels to < 70 mg/dL (< 1.8 mmol/L)\(^3\). The NCEP recognized that to achieve such low levels of LDL-C may require the use of a combination of lipid-lowering drugs. In the study reported here, both study medications brought LDL-C to levels < 100 mg/dL (< 2.6 mmol/L) in a high proportion of patients (> 80%), corroborating previous experience\(^26\). Additionally, larger proportions of all patients (43.5%) and high risk patients (50.1%) achieved LDL-C levels < 70 mg/dL (< 1.8 mmol/L) following treatment with ezetimibe/simvastatin when compared across doses to those treated with rosvuastatin (29.5% and 29.4% for all patients and high-risk patients, respectively).

In addition to LDL-C lowering, ezetimibe/simvastatin also consistently reduced levels of TC, non-HDL-C and apo B to a greater extent than rosvuastatin monotherapy at each dose comparison. Increases in HDL-C of 6.7–8.3% were observed at each dose for both treatments with no statistically significant differences between treatment groups. Reductions in the LDL-C:HDL-C ratio, a proposed index of lipid-related vascular risk\(^34\), were consistently greater with ezetimibe/simvastatin than rosvuastatin, as would be anticipated from the alterations in its constituent parts. Similarly, reductions in the TC:HDL-C ratio, another proposed measure of CHD risk\(^35\), were also consistently favored with ezetimibe/simvastatin. Overall, TG was reduced more favorably with ezetimibe/simvastatin than rosvuastatin at all doses except the rosvuastatin 20 mg versus ezetimibe/simvastatin 10/40 mg dose comparison, at which there was no treatment difference.

Reductions in hsCRP at all dose comparisons were comparable between the two treatment groups, and are consistent with the Vytorin versus Atorvastatin (VYVA) study\(^27\), in which ezetimibe/simvastatin and atorvastatin reduced hsCRP comparably. While hsCRP level is not a CHD risk factor recognized by the NCEP ATP III\(^4\), it is acknowledged to be an emerging risk factor, and measurement of hsCRP is considered optional for assessment of overall CHD risk assessment\(^36\).

The overall safety and tolerability of ezetimibe/simvastatin and rosvuastatin were similar. In general, there were no significant differences between ezetimibe/simvastatin and rosvuastatin in terms of clinically significant elevations in levels of muscle or liver enzymes (Table 3). In regards to the liver enzymes ALT and AST, ezetimibe/simvastatin tended towards a numerically higher frequency of elevated levels, compared with rosvuastatin, partially attributed to differences at the 10/80 mg and 40 mg doses, but not at lower doses. These elevations in liver enzymes all remitted with the discontinuation of drug treatment, and none were associated with increases in bilirubin. In the ezetimibe/simvastatin group, elevations of muscle enzyme, CK ≥ 10 × ULN, with or without muscle symptoms, were numerically higher, but not statistically significantly different from the levels in the rosuvastatin group. As noted in the product inserts for ezetimibe/simvastatin\(^37\) and rosvuastatin\(^38\), myopathy is a rare adverse experience with both agents, and thus patients should be monitored for muscle symptoms. Higher proteinuria was observed in the rosuvastatin groups, particularly at the 40 mg dose. This observation is consistent with the experience described in the rosvuastatin product insert and other studies\(^39\), although the clinical significance of this is not known. It should be noted that while this
was a relatively large study, the incidence of serious adverse experiences was low, and the study was neither powered nor of sufficient duration to accurately assess the prevalence of rare clinical adverse effects.

This study is the first randomized, controlled clinical study which directly compares the single tablet ezetimibe/simvastatin to rosuvastatin. Both drugs were evaluated in this study at the clinically approved usual starting doses and as these agents are also used when more aggressive LDL-lowering therapy is appropriate, at the next highest and maximum doses. Therefore, the results of this study provide clinicians with information regarding the use of these drugs in comparable clinical situations (i.e., for initial therapy and for subsequent use at higher doses as well). The paradigm for this study design was used previously in a comparison of the usual starting, the next highest, and maximum doses of ezetimibe/simvastatin and atorvastatin (VYVA study)\textsuperscript{26}. However, in the current study, the doses compared were not equivalent in terms of milligrams. This situation can arise in clinical practice wherein consideration of therapy is based upon approved doses of drugs which differ on a per milligram basis. Overall, this study demonstrated the greater lipid-lowering efficacy of ezetimibe/simvastatin compared with rosuvastatin at these doses; however, an assessment of its full clinical impact awaits further evaluation in longer-term, clinical trials.

**Conclusion**

In summary, dual inhibition of two sources of cholesterol, absorption and biosynthesis, provided by the single tablet ezetimibe/simvastatin, resulted in greater overall efficacy in lowering LDL-C compared with a potent statin monotherapy agent, rosuvastatin, at the usual starting, next highest, and maximum doses. Furthermore, the greater LDL-C reducing efficacy produced by ezetimibe/simvastatin generally resulted in a higher percent of LDL-C goal attainment, particularly for those high-risk patients who attained LDL-C levels < 70 mg/dL (< 1.8 mmol/L). Patients treated with ezetimibe/simvastatin versus rosuvastatin showed significantly greater improvements in TC, apo B, non-HDL-C, and LDL-C:HDL-C and TC:HDL-C ratios at all dose comparisons, and also in TG at the usual starting doses (10/20 mg versus 10 mg), the maximum doses (10/80 mg versus 40 mg), and when averaged across all doses. Improvements in HDL-C and hsCRP were similar for both study medications at all dose comparisons. Both study drugs were generally well-tolerated; however, a higher percent of patients treated with rosuvastatin had proteinuria compared to ezetimibe/simvastatin. Thus, the ezetimibe/simvastatin tablet offers an effective and tolerable treatment option for lipid management in patients with hypercholesterolemia.

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