

# Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination With Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study)

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Patients at risk of coronary heart disease may not achieve recommended low-density lipoprotein (LDL) cholesterol goals on statin monotherapy. This study was designed to investigate the efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe 10 mg in patients at high risk of coronary heart disease. Four hundred sixty-nine patients were randomly assigned to rosuvastatin alone or in combination with ezetimibe for 6 weeks. The primary end point was the percentage of patients achieving the Adult Treatment Panel III (ATP III) LDL cholesterol goal (<100 mg/dl) at week 6. Secondary end points included the percentage of patients achieving other ATP III and 2003 European lipid goals, changes from baseline in lipid, lipoprotein, and inflammatory parameters, and safety and tolerability. Significantly more patients receiving rosuvastatin/ezetimibe than rosuvastatin alone achieved their ATP III LDL cholesterol goal (<100 mg/dl, 94.0% vs 79.1%,  $p < 0.001$ ) and the optional LDL cholesterol goal (<70 mg/dl) for very high-risk patients (79.6% vs 35.0%,  $p < 0.001$ ). The combination of rosuvastatin/ezetimibe reduced LDL cholesterol significantly more than rosuvastatin (-69.8% vs -57.1%,  $p < 0.001$ ). Other components of the lipid/lipoprotein profile were also significantly ( $p < 0.001$ ) improved with rosuvastatin/ezetimibe. Both treatments generally were well tolerated. Rosuvastatin 40 mg was effective at improving the atherogenic lipid profile in this high-risk population. Combination rosuvastatin with ezetimibe 10 mg enabled greater decreases in LDL cholesterol and allowed more patients to achieve LDL cholesterol goals. In conclusion, rosuvastatin plus ezetimibe may improve the management of high-risk patients who cannot achieve goal on maximal statin monotherapy. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:673-680)

Achievement of the low-density lipoprotein (LDL) cholesterol goals in patients at high risk of coronary heart disease (CHD)<sup>1,2</sup> presents a challenge, especially with regard to achieving the optional LDL cholesterol goal of <70 mg/dl if patients have severely elevated LDL cholesterol levels at baseline. The aim of the EXamination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone (EXPLORER) study (D3569C00006) is to compare the efficacy and safety of the most effective and highest marketed dose of rosuvastatin (40 mg) alone or in combination with ezetimibe 10 mg for 6 weeks in high-risk patients with hypercholesterolemia.

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## Methods

**Trial design:** This 6-week, open-label, randomized, parallel-group study was conducted in 58 centers in the United States, Germany, Austria, Switzerland, and South Africa. Patients were required to discontinue lipid-lowering therapy before entering a 6-week dietary lead-in period, during which they were instructed to follow the National Cholesterol Education Program Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes diet.<sup>3</sup> Eligible patients then were randomly assigned (1:1) to treatment with rosuvastatin 40 mg monotherapy or rosuvastatin 40 mg/ezetimibe 10 mg combination therapy. Combination therapy was administered as a single tablet of each medication; both monotherapy and combination therapy were taken once daily. The trial was conducted in accordance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonization of Good Clinical Practice guidelines, and appropriate regulatory requirements. Written informed consent was received from all patients before enrollment.

**Patients:** Men and women aged  $\geq 18$  years with hypercholesterolemia and a history of CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year CHD risk score >20%) were eligible for randomization if the mean of

their 2 most recent fasting LDL cholesterol levels was  $\geq 160$  mg/dl and  $< 250$  mg/dl and the 2 measurements were within 15% of each other. Eligible patients were also required to have a fasting triglyceride (TG) concentration of  $< 400$  mg/dl.

Main exclusion criteria were a history of statin-induced myopathy or serious hypersensitivity reaction to statins and/or ezetimibe; patients considered unstable after a myocardial infarction, unstable angina, myocardial revascularization, coronary artery bypass graft, transient ischemic attack, or stroke; severe congestive heart failure (New York Heart Association class IIIb or IV); patients awaiting a planned myocardial revascularization before entering the study; history of malignancy, with the exception of basal cell or squamous cell carcinoma of the skin; patients with uncontrolled hypothyroidism (thyroid-stimulating hormone  $> 1.5$  times the upper limit of normal) history of homozygous familial hypercholesterolemia, current active liver disease (alanine aminotransferase [ALT] or serum glutamic-pyruvic transaminase  $> 2$  times the upper limit of normal), or severe hepatic impairment; unexplained serum creatine kinase (CK)  $\geq 1$  times the upper limit of normal; serum creatinine  $> 176$   $\mu\text{mol/L}$  (2.0 mg/dl); and use of prohibited concomitant medications. Women who were pregnant or breast-feeding, or of childbearing potential, but not using contraception, were also excluded from the study. Subjects taking hormone replacement therapy or oral contraceptives initiated or changed within 3 months before enrollment in the dietary lead-in were also excluded.

**End points:** The primary end point was the percentage of patients achieving the ATP III LDL cholesterol goal ( $< 100$  mg/dl) after 6 weeks of treatment. Secondary efficacy end points included the percentage of patients achieving the ATP III non-high-density lipoprotein (non-HDL) cholesterol goal (non-HDL cholesterol  $< 130$  mg/dl and LDL cholesterol  $< 100$  mg/dl when baseline TG  $\geq 200$  mg/dl)<sup>1</sup>; 2003 European<sup>4</sup> LDL cholesterol goals ( $< 2.5$  or 3.0 mmol/L [100 or 115 mg/dl], depending on risk category); combined 2003 European LDL cholesterol and total cholesterol (TC) goals (LDL cholesterol  $< 2.5$  or 3.0 mmol/L [ $< 100$  or 115 mg/dl] and TC  $< 4.5$  or 5.0 mmol/L [ $< 175$  or 190 mg/dl], depending on risk category); and percent change from baseline in LDL cholesterol, HDL cholesterol, TC, TG, non-HDL cholesterol, lipid ratios (LDL/HDL cholesterol, TC/HDL cholesterol, and non-HDL/HDL cholesterol), apolipoprotein A-I, apolipoprotein B, and apolipoprotein B/apolipoprotein A-I ratio, and changes in high-sensitivity C-reactive protein (hs-CRP) at week 6. The frequency and severity of adverse events and abnormal laboratory values were also examined. ATP III recommendations were updated during the course of this study to include an optional goal of LDL cholesterol  $< 70$  mg/dl for very high-risk patients.<sup>1</sup> The non-HDL cholesterol target was also updated, with a target  $< 100$  mg/dl for these very high-risk patients. Analysis of these updated goals was added to the statistical plan before unblinding of study data.

A post hoc analysis was performed to compare effects of treatment on hs-CRP levels in patients with increased hs-CRP ( $> 3$  mg/L) at baseline. hs-CRP levels  $> 3$  mg/L are categorized as high risk in the Centers for Disease Control and Prevention/American Heart Association guidelines.<sup>5</sup>

**Assessments:** Fasting blood samples were collected at weeks  $-6$  (beginning of the dietary lead-in period),  $-2$ ,  $-1$ , 0 (randomization), and 6 for lipid profile analysis at a central laboratory. LDL cholesterol levels were determined using the Friedewald formula, with the exception of visits in which TG levels were  $> 400$  mg/dl, when a  $\beta$  quantification measurement of LDL cholesterol was used. Blood samples for clinical chemistry, including ALT, aspartate aminotransferase, CK, and serum creatinine, were collected at weeks  $-1$ , 0, and 6. Estimated glomerular filtration rate was determined in a post hoc analysis using the abbreviated Modification of Diet in Renal Disease formula: estimated glomerular filtration rate =  $186 \times (\text{serum creatinine in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$ . Safety was assessed by frequency of adverse events and abnormal laboratory data. Adverse events were identified using a standard question ("Have you had any health problems since the previous visit?"). The patient was asked to assess whether the event was mild, moderate, or severe in intensity. Each investigator was required to make a causality assessment of the relation of the event to the study drugs and whether it constituted a serious adverse event. Compliance was assessed at week 6 by counting the number of returned tablets; patients were considered non-compliant if they used  $< 80\%$  of the prescribed number of tablets.

**Statistical analyses:** With the aim of detecting a statistically significant between-group difference of 12% (83% vs 95%) in the primary end point, it was calculated that 190 assessable patients would be required per treatment arm to achieve 95% power at a 2-sided significance level of 5%. Assuming a dropout rate of 10%, 420 patients were required to be randomly assigned.

Efficacy was evaluated by randomized treatment in the intention-to-treat population, which consisted of all patients with a baseline lipid measurement and  $\geq 1$  lipid measurement after baseline and who had used  $\geq 1$  dose of study medication. Analyses used the last-available-observation-carried-forward approach for patients with missing data. Logistic regression analyses with treatment and region (as factors) and baseline LDL cholesterol (as a covariate) were used to compare the percent of patients achieving goals.

Percent change from baseline in lipid and lipoprotein levels was compared between treatment groups using analysis of variance, with a separate model fitted for each lipid parameter. Models included treatment and region as factors. Analysis of hs-CRP was performed using nonparametric Wilcoxon rank-sum test and a robust regression technique known as MM estimation.<sup>6</sup> Safety data were summarized by actual treatment received for the safety population, which included all randomized patients who used  $\geq 1$  dose of study medication. No formal statistical analysis was performed on safety data.

## Results

**Study population:** Of 1,197 patients who entered the dietary lead-in period, 469 were randomly assigned (230 to rosuvastatin 40-mg monotherapy and 239 to rosuvastatin 40-mg plus ezetimibe 10-mg combination therapy) (Fig-

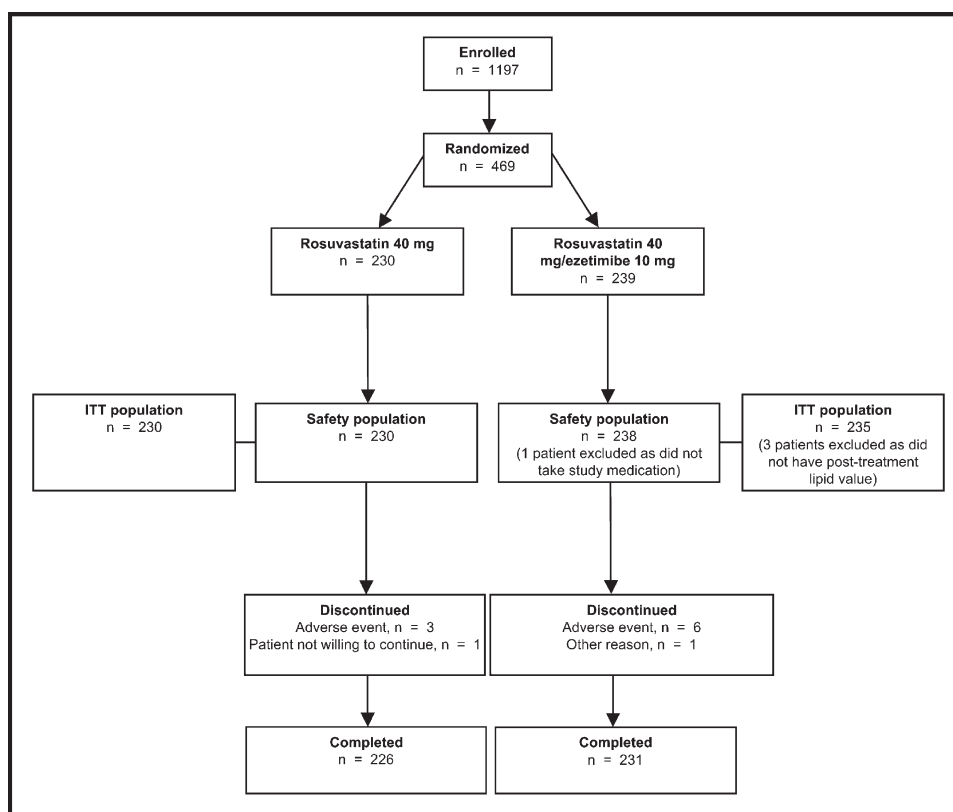


Figure 1. Patient flow and statistical analysis sets. ITT = intention to treat. LDL-C = LDL cholesterol; non-HDL-C = non-HDL cholesterol.

ure 1). Four patients were excluded from the intention-to-treat population ( $n = 465$ ); 1 patient was randomly assigned but did not take study medication and was excluded from the safety population ( $n = 468$ ), and 3 patients had no lipid values after baseline. Treatment groups were similar at baseline in terms of demographic and clinical variables (Table 1). At the end of the study, 95% and 97% of patients were compliant with rosuvastatin in the monotherapy and combination therapy groups, respectively. Compliance with ezetimibe was also high, with 97% of patients in the combination therapy group taking  $\geq 80\%$  of the medication.

**Efficacy:** Significantly more patients achieved the ATP III LDL cholesterol goal ( $<100$  mg/dl) at week 6 with combination therapy versus monotherapy (94.0% vs 79.1%,  $p < 0.001$ ; Figure 2). The ATP III non-HDL cholesterol ( $<130$  mg/dl) and LDL cholesterol ( $<100$  mg/dl) goals for patients with baseline TGs  $\geq 200$  mg/dl (88 patients [37.4%] in the combination therapy group; 80 patients [34.8%] in the monotherapy group) were achieved by a significantly higher percentage of patients in the combination therapy than monotherapy group ( $p < 0.001$ ; Figure 2). In addition, at week 6, significantly more very high-risk patients (196 in the combination therapy group and 197 in the monotherapy group) achieved the optional LDL cholesterol goal of  $<70$  mg/dl in the combination therapy than monotherapy group (79.6% vs 35.0%,  $p < 0.001$ ). Significantly more patients achieved both updated goals (non-HDL cholesterol  $<100$  mg/dl and LDL cholesterol  $<70$  mg/dl, or non-HDL cholesterol  $<130$  mg/dl and LDL cholesterol  $<100$  mg/dl, depending on risk category, for patients with

Table 1  
Patient characteristics at baseline (randomized population)

Variable	Rosuvastatin 40 mg Group ( $n = 230$ )	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group ( $n = 239$ )
Age (yrs) (mean $\pm$ SD)	63.5 $\pm$ 10.6	63.1 $\pm$ 10.2
Men	55.7%	58.6%
Caucasian	91.7%	93.3%
Body mass index (kg/m <sup>2</sup> ) (mean $\pm$ SD)	29.7 $\pm$ 4.9	28.8 $\pm$ 4.7
Creatinine clearance		
>80 ml/min	49.1%	51.0%
50 to $\leq 80$ ml/min	43.5%	42.7%
30 to $< 50$ ml/min	7.0%	6.3%
$< 30$ ml/min	0%	0%
Metabolic syndrome at baseline*	63.5%	59.0%
Diabetes mellitus	39.6%	34.4%
Men $\geq 45$ yrs, women $\geq 55$ yrs	92.6%	91.6%
Hypertension ( $\geq 140/90$ mm Hg or on antihypertensive medication)	87.0%	86.6%
HDL cholesterol $< 40$ mg/dl (1.0 mmol/L)	18.7%	24.3%

\* According to NCEP ATP III definition.

baseline TGs  $\geq 200$  mg/dl) with combination therapy than monotherapy (79.5% vs 27.5%,  $p < 0.001$ ).

Analyses according to the 2003 European LDL cholesterol goals (LDL cholesterol  $< 2.5$  or  $3.0$  mmol/L [ $< 100$  or  $115$  mg/dl], depending on risk category) and combined LDL

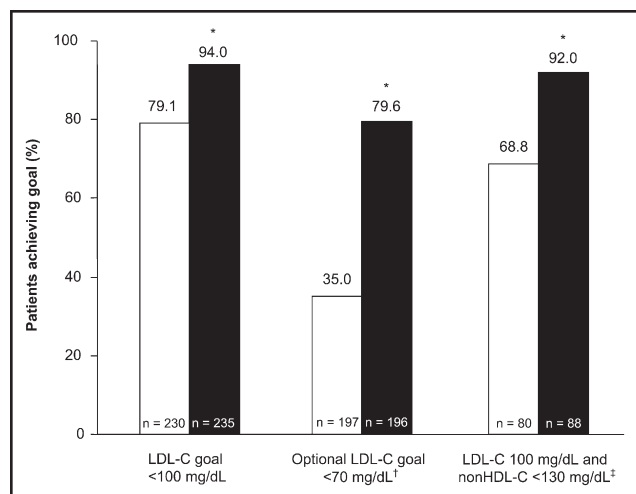


Figure 2. Patients (percent) achieving ATP III LDL cholesterol, updated ATP III LDL cholesterol, and non-HDL cholesterol goals after 6 weeks of treatment (intention-to-treat [ITT] population). \* $p < 0.001$  versus rosuvastatin 40 mg. <sup>†</sup>For very high-risk patients only. <sup>‡</sup>For patients with baseline TGs  $\geq 200$  mg/dl. White bars, rosuvastatin 40 mg; black bars, rosuvastatin 40 mg plus ezetimibe 10 mg. LDL-C = LDL cholesterol; non-HDL-C = non-HDL cholesterol.

cholesterol and TC goals (LDL cholesterol  $<2.5$  or  $3.0$  mmol/L [ $<100$  or  $115$  mg/dl] and TC  $<4.5$  or  $5.0$  mmol/L [ $<175$  or  $190$  mg/dl], respectively, depending on risk category) indicated that a significantly higher percent of patients in the combination therapy group achieved goal compared with those in the monotherapy group at week 6 (LDL cholesterol 93.6% vs 74.3%, LDL cholesterol and TC 90.6% vs 68.3%,  $p < 0.001$  for both).

At 6 weeks, LDL cholesterol decreased to 56.9 and 81.5 mg/dl in the combination and monotherapy groups, respectively. Significantly greater percent decreases in LDL cholesterol levels were achieved with combination therapy than monotherapy (mean percent decrease  $-69.8\%$  vs  $-57.1\%$ ,  $p < 0.001$ ; Table 2). Significantly ( $p < 0.001$ ) greater decreases in TC, non-HDL cholesterol, and TG were also observed at week 6 in the combination therapy group compared with the monotherapy group (Table 2). Both treatments increased HDL cholesterol to a similar extent at week 6 (Table 2). LDL/HDL cholesterol, TC/HDL cholesterol, and non-HDL/HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared with those receiving monotherapy (all  $p < 0.001$ ; Table 2). Mean week-6 value for the LDL/HDL cholesterol ratio was 1.1. Significant decreases in apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio were observed in the combination therapy group compared with the monotherapy group ( $p < 0.001$  for both). Apolipoprotein A-I increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively ( $p = 0.202$ ; Table 2).

After 6 weeks of treatment, median percent decrease in hs-CRP was significantly higher with combination therapy than monotherapy ( $-46.4\%$  vs  $-28.6\%$ ,  $p < 0.001$ ; Table 2). Of 183 patients with median hs-CRP  $>3$  mg/L at baseline (90 in the combination therapy group, 93 in the monotherapy group), a higher proportion of those treated with combination therapy than monotherapy achieved hs-CRP

levels  $<3$  mg/L (56.7% vs 37.6%) and  $<1$  mg/L (14.4% vs 6.5%).

**Safety:** Both treatments were well tolerated, and the overall frequency and type of adverse events were similar between treatment groups. Adverse events were experienced by 31.5% and 33.5% of patients receiving combination therapy or monotherapy, respectively (Table 3).

Frequencies of liver, muscle, and renal adverse events were low in both groups. Myalgia was the most frequently reported adverse event in both treatment groups (Table 4). Most adverse events were mild to moderate in intensity. The most frequently reported treatment-related adverse event was increased ALT in the combination therapy group ( $n = 6$  [2.5%]) and myalgia in the monotherapy group ( $n = 5$  [2.2%]). The percent of patients who discontinued treatment as a result of any adverse event was low (combination therapy group 2.5%, monotherapy group 1.3%; Table 3). Treatment-related adverse events were the reason for discontinuation in 2 patients (0.8%) in the combination therapy group and in 3 patients (1.3%) in the monotherapy group. The frequency of serious adverse events was low (combination therapy group 2.1%, monotherapy group 1.7%; Table 3), and no treatment-related serious adverse events were reported in either treatment group. One death occurred during the study (combination therapy group; acute myocardial infarction), and this was not considered to be related to study treatment.

A total of 14 patients had myalgia (combination therapy group,  $n = 7$  [2.9%]; monotherapy group,  $n = 7$  [3.0%]), which was considered treatment related in 8 patients (combination therapy group,  $n = 3$  [1.2%]; monotherapy group,  $n = 5$  [2.2%]). Myalgia was the cause for treatment withdrawal in 1 patient from each treatment group; neither event was categorized as serious and neither patient had a CK value outside the normal range. No patient in the study had clinically important increases in CK (i.e.,  $>10$  times the upper limit of normal). There were no reported cases of myopathy, myositis, or rhabdomyolysis. Changes from baseline to the end of treatment for all serum chemistry parameters were small and similar across treatment groups.

Clinically relevant changes in laboratory values are listed in Table 5. ALT increases ( $>3$  times the upper limit of normal) were recorded in 3 patients, all in the combination therapy group. None of these adverse events led to premature discontinuation, and none was serious.

Mean baseline serum creatinine was  $94.0 \mu\text{mol/L}$  in the monotherapy group and  $92.1 \mu\text{mol/L}$  in the combination therapy group. The percent of patients with serum creatinine increases  $>50\%$  from baseline was low in both treatment groups; no increases in serum creatinine  $>100\%$  from baseline were recorded (Table 5). At week 6, proteinuria (change in dipstick-positive urine protein from none or trace at baseline to ++ or greater) was detected in 11 patients (combination therapy group,  $n = 1$  [0.4%]; monotherapy group,  $n = 10$  [4.5%]; Table 5) and hematuria (increase in dipstick-positive urine blood from none or trace at baseline to + or greater) in 14 patients (combination therapy group,  $n = 6$  [2.6%]; monotherapy group,  $n = 8$  [3.6%]). Concurrent proteinuria and hematuria were detected in 1 patient (0.4%) in the combination therapy group and 4 patients

Table 2  
Percentage change from baseline in lipid, lipoprotein and inflammatory marker levels after six weeks of treatment (intention-to-treat population)

Lipids/lipoproteins	Rosuvastatin 40 mg Group (n = 230)			Rosuvastatin 40 mg/Ezetimibe 10 mg Group (n = 235)			p Value <sup>†</sup>
	Mean at		Mean Change from Baseline	Mean at		Mean Change from Baseline	
	Baseline	Wk 6		Baseline	Wk 6		
LDL cholesterol (mg/dl)*	191	82	-57%	189	57	-70%	<0.001
TC (mg/dl)*	278	162	-42%	276	134	-51%	<0.001
HDL cholesterol (mg/dl)*	50	53	+9%	49	54	+11%	0.151
Non-HDL cholesterol (mg/dl)*	228	109	-52%	226	80	-65%	<0.001
TGs (mg/dl)*	186	138	-25%	186	114	-35%	<0.001
LDL/HDL cholesterol	4.1	1.6	-60%	4.1	1.1	-72%	<0.001
TC/HDL cholesterol	5.9	3.2	-45%	5.9	2.6	-56%	<0.001
Non-HDL/HDL cholesterol	4.9	2.2	-55%	4.9	1.6	-67%	<0.001
Apolipoprotein B (mg/dl)	173	95	-45%	176	76	-56%	<0.001
Apolipoprotein A-I (mg/dl)	166	169	+3%	166	167	+2%	0.202
Apolipoprotein B/apolipoprotein A-I	1.1	0.6	-46%	1.1	0.5	-57%	<0.001
hs-CRP (mg/L) (median)	2.4	1.7	-29%	2.5	1.2	-46%	<0.001

\* To convert milligrams per deciliter to millimoles per liter, multiply by 0.02586 for cholesterol and 0.01129 for TGs.

<sup>†</sup> For percentage change from baseline with rosuvastatin 40 mg/ezetimibe 10 mg group versus rosuvastatin 40 mg group at week 6.

Table 3  
Number of patients with adverse events (randomized safety population)

Variable	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 238)
Any adverse event	77 (33.5%)	75 (31.5%)
Rosuvastatin-related adverse event only	21 (9.1%)	2 (0.8%)
Rosuvastatin- and ezetimibe-related adverse event*	N/A	16 (6.7%)
Serious adverse event	4 (1.7%)	5 (2.1%)
Rosuvastatin-related serious adverse event only	0	0
Rosuvastatin- and ezetimibe-related serious adverse event*	N/A	0
Adverse event leading to death	0	1 (0.4%)
Rosuvastatin-related adverse event only, leading to death	0	0
Rosuvastatin- and ezetimibe-related adverse event leading to death*	N/A	0
Discontinuation due to adverse event	3 (1.3%)	6 (2.5%)
Rosuvastatin-related adverse event only, leading to discontinuation	3 (1.3%)	0
Rosuvastatin- and ezetimibe-related adverse event, leading to discontinuation*	N/A	2 (0.8%)

\* No event was considered related only to ezetimibe.

(1.8%) in the monotherapy group at week 6. None of the patients who developed proteinuria or hematuria by these definitions had creatinine increases of >50%.

In a post hoc analysis, the glomerular filtration rate increased between baseline and 6 weeks in both treatment

Table 4  
Most frequent reported ( $\geq 2.0\%$  in any group) adverse events (randomized safety population)

Variable	No. (%) of Patients With Adverse Events	
	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/ Ezetimibe 10 mg Group (n = 238)
Myalgia	7 (3.0%)	7 (2.9%)
Nausea	5 (2.2%)	6 (2.5%)
ALT increased	1 (0.4%)	6 (2.5%)
Angina pectoris	6 (2.6%)	1 (0.4%)

groups, from a mean  $\pm$  SD of  $70.3 \pm 13.0$  to  $72.3 \pm 14.3$  ml/min/1.73 m<sup>2</sup> in the combination therapy group and  $68.5 \pm 14.4$  to  $68.9 \pm 15.5$  ml/min/1.73 m<sup>2</sup> in the monotherapy group. At week 6, mean percent increase in the combination therapy group was significantly different from baseline (3.4%, 95% CI 1.8 to 4.9); percent change in the monotherapy group was not statistically significant (0.8%, 95% CI -0.8 to 2.5).

## Discussion

EXPLORER is the first large-scale study to evaluate the efficacy and safety of rosuvastatin, the most efficacious of the currently available statins, in combination with ezetimibe, a lipid-lowering compound that inhibits intestinal cholesterol absorption,<sup>7</sup> in patients with hypercholesterolemia and at high risk of CHD. Although rosuvastatin was initiated at 40 mg/day in this research study, the recommended starting doses are 5 or 10 mg, with an optional starting dose of 20 mg/day in patients with marked hypercholesterolemia (LDL cholesterol >190 mg/dl) and aggressive lipid targets.

Table 5  
Clinically relevant changes in laboratory values (randomized safety population)

Variable	No. (%) of Patients With Changes in Laboratory Values	
	Rosuvastatin 40 mg Group (n = 230)	Rosuvastatin 40 mg/Ezetimibe 10 mg Group (n = 238)
ALT elevations at any time		
>3 × Upper limit of normal	0 (0.0%)	3 (1.3%)
CK elevations at any time		
>5 × Upper limit of normal	2 (0.9%)	2 (0.8%)
>10 × Upper limit of normal	0 (0.0%)	0 (0.0%)
Serum creatinine increase at any time		
>50%–100% from baseline	3 (1.3%)*	1 (0.4%) <sup>†</sup>
>100% from baseline	0 (0.0%)	0 (0.0%)
Proteinuria at week 6 <sup>‡</sup>	10 (4.5%)	1 (0.4%)

\* Above upper limit of normal in 2 patients.

<sup>†</sup> Above upper limit of normal in this patient.

<sup>‡</sup> Change in dipstick-positive urine protein from none or trace at baseline to ++ or greater.

Decreases in LDL cholesterol from baseline of approximately 40% to 60% were reported with ezetimibe 10 mg in combination with atorvastatin, simvastatin, pravastatin, or lovastatin.<sup>8–13</sup> In this study, at week 6, mean LDL cholesterol levels decreased by 57% (from 191 to 82 mg/dl) in the rosuvastatin 40-mg group and by 70% (from 189 to 57 mg/dl) in the combination therapy group. The addition of ezetimibe to rosuvastatin 40 mg provided an additional approximately 13% decrease in LDL cholesterol compared with rosuvastatin alone. This is similar to the 13% incremental decrease observed with ezetimibe added to maximal-dose simvastatin (80 mg)<sup>9</sup> and higher than the 7% incremental decrease observed with ezetimibe added to maximal-dose atorvastatin (80 mg).<sup>8</sup>

Recent evidence has also suggested that patients at high CHD risk benefit from lowering LDL cholesterol levels to less than current targets, and that the greater the LDL cholesterol decrease, the better the clinical outcome.<sup>14,15</sup> The low mean LDL cholesterol levels achieved in this study are particularly impressive in light of the high baseline LDL cholesterol levels (~190 mg/dl), similar to those in the Scandinavian Simvastatin Survival Study.<sup>16</sup> In patients with established CHD, decreases in LDL cholesterol to 61 mg/dl (similar to that for the combination therapy group and less than currently recommended guideline levels) after treatment with rosuvastatin 40 mg were associated with regression of atherosclerosis.<sup>17</sup>

The significantly greater decreases in LDL cholesterol with rosuvastatin plus ezetimibe compared with rosuvastatin alone enabled more patients in the combination therapy group to achieve ATP III LDL cholesterol goals. The ATP III goal of LDL cholesterol <100 mg/dl for high-risk patients was achieved by 94% of patients in the combination therapy group compared with 79% of patients in the monotherapy group; 92% of combination therapy patients also achieved the non-HDL cholesterol goal of <130 mg/dl compared with 69% of monotherapy

patients. Achieving lipid goals has been associated with improvements in cardiovascular outcomes.<sup>18</sup> Rosuvastatin in combination with ezetimibe may prove valuable in high-risk patients unable to achieve lipid goals with statin monotherapy.

The need for effective LDL cholesterol-lowering therapy is increasingly important as LDL cholesterol goals become more stringent; the updated ATP III guidelines recommend an optional goal of <70 mg/dl for very high-risk patients,<sup>1</sup> and the American Heart Association/American College of Cardiology has recommended LDL cholesterol <70 mg/dl as a “reasonable” option for all patients with CHD.<sup>2</sup> In the National Cholesterol Education Program Evaluation Project Utilizing Novel E-Technology (NEPTUNE) II survey, 75% of patients with cardiovascular disease were classified as at very high risk of CHD, and only 18% met the optional LDL cholesterol goal of <70 mg/dl.<sup>19</sup> In the present study, a significantly greater percentage of very high-risk patients receiving rosuvastatin plus ezetimibe achieved the optional LDL cholesterol goal of <70 mg/dl than patients receiving rosuvastatin alone (80% vs 35%,  $p < 0.001$ ). In a previous trial of high-risk patients with baseline LDL cholesterol levels lower than those in the present study, 64% of patients receiving simvastatin 80 mg plus ezetimibe 10 mg for 6 weeks achieved the optional LDL cholesterol goal of <70 mg/dl.<sup>11</sup>

In addition to reducing LDL cholesterol, improving other components of the lipid profile may be beneficial in reducing global risk in patients with CHD.<sup>3</sup> In this study, compared with rosuvastatin alone, combination therapy significantly decreased other atherogenic lipid components, such as TC, TG, non-HDL cholesterol, and apolipoprotein B. HDL cholesterol levels increased from baseline by 8.5% with rosuvastatin alone and by 10.8% with combination therapy, with no significant difference between treatment groups. A recent analysis from the Treating to New Targets study examined the CHD event rate of patients on atorvastatin therapy and found that patients in the lowest quartile of LDL/HDL cholesterol ratio (<1.3) had the lowest event rate.<sup>20</sup> In the present study, patients treated with rosuvastatin plus ezetimibe had a mean LDL/HDL cholesterol ratio of 1.1 on therapy compared with 1.6 in the monotherapy group, and approximately 40% of patients on combination therapy achieved a LDL cholesterol level less than or equal to their HDL cholesterol level. In contrast to atorvastatin, the HDL cholesterol-increasing effect of rosuvastatin is consistent across its dose range.<sup>21</sup> Increases of 7.7%, 9.5%, and 9.6% were reported in high-risk patients with hypercholesterolemia after 6 weeks of treatment with rosuvastatin 10, 20, and 40 mg, respectively.<sup>21</sup> These are similar to increases reported here. In the present study, the addition of ezetimibe to rosuvastatin therapy did not lead to attenuation of the HDL cholesterol-increasing effects of rosuvastatin.

In addition to improving the atherogenic lipid profile, lipid-modifying therapies may have pleiotropic and anti-inflammatory effects. hs-CRP is an indicator of inflammation and a widely studied marker of cardiovascular risk. In this study, hs-CRP decreases were significantly higher with combination therapy than monotherapy (–46.4% vs

–28.6%). By comparison, in the Vytorin versus Atorvastatin (VYVA) study, decreases in hs-CRP with ezetimibe/simvastatin were not significantly different from those with atorvastatin monotherapy (24.8% vs 25.1%, averaged across statin doses of 10 to 80 mg).<sup>11</sup> similar to that reported in this trial. Decreases up to 62% were reported with atorvastatin 80 mg plus ezetimibe.<sup>8</sup> Patients with hs-CRP levels >3 mg/L are considered at high risk of future cardiovascular events.<sup>5</sup> In the present study, a post hoc analysis showed that compared with monotherapy, more patients in the combination therapy group had hs-CRP levels <3 mg/L (low or moderate risk<sup>5</sup>) or <1 mg/L (low risk<sup>5</sup>) after the 6-week treatment period.

Limitations of the study include short duration, open-label design, measuring safety variables only 3 times, and insufficient power to assess clinical events. Clearly, larger long-term studies are needed to evaluate safety and clinical events. The safety of rosuvastatin alone was studied extensively in a broad range of patients with dyslipidemia.<sup>22,23</sup> Analysis of >12,000 patients from a worldwide clinical development program showed that the safety of rosuvastatin 10 to 40 mg was similar to that of the other statins.<sup>23</sup> In the present study, co-administration of rosuvastatin with ezetimibe was well tolerated, with a safety profile similar to that of rosuvastatin alone. No cases of myopathy or rhabdomyolysis were reported. The frequency of proteinuria was greater in the monotherapy group; however, there appeared to be no obvious association between the development of proteinuria and worsening renal function measured by serum creatinine. Furthermore, as indicated by the post hoc analysis of estimated glomerular filtration rate, laboratory abnormalities were not associated with deterioration in renal function. The effect of short- (6 to 52 weeks) and long-term (up to 3.8 years) treatment with rosuvastatin 5 to 40 mg on renal function, measured using glomerular filtration rate, was assessed in patients enrolled in the rosuvastatin clinical development program.<sup>24,25</sup> In both studies, small but significant ( $p < 0.01$ ) improvements from baseline in glomerular filtration rate were observed across all doses of rosuvastatin (5 to 40 mg). In addition, renal function was unchanged or tended to improve in patients who developed dipstick-positive proteinuria when on treatment.<sup>24,25</sup> In the present study, the addition of ezetimibe to rosuvastatin 40 mg increased lipid-modifying efficacy and goal attainment with a safety profile similar to that of rosuvastatin monotherapy.

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