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ORIGINAL RESEARCH ARTICLE

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Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of ROsuvastatin and eZEtimibe)

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Summary

Aim: We aimed to compare the effects of fixed-dose combinations of ezetimibe plus rosuvastatin to rosuvastatin alone in patients with primary hypercholesterolemia, including a subgroup analysis of patients with diabetes mellitus (DM) or metabolic syndrome (MetS).

Method: This multicenter eight-week randomized double-blind phase III study evaluated the safety and efficacy of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin, compared with rosuvastatin alone in patients with primary hypercholesterolemia. Four hundred and seven patients with primary hypercholesterolemia who required lipid-lowering treatment according to the ATP III guideline were randomized to one of the following six treatments for 8 weeks: fixed-dose combinations with ezetimibe 10 mg daily plus rosuvastatin (5, 10, or 20 mg daily) or rosuvastatin alone (5, 10, or 20 mg daily).

Results: Fixed-dose combination of ezetimibe plus rosuvastatin significantly reduced LDL cholesterol, total cholesterol, and triglyceride levels compared with rosuvastatin alone. Depending on the rosuvastatin dose, these fixed-dose combinations of ezetimibe plus rosuvastatin provided LDL cholesterol, total cholesterol, and triglyceride reductions of 56%–63%, 37%–43%, and 19%–24%, respectively. Moreover, the effect of combination treatment on cholesterol levels was more pronounced in patients with DM or MetS than in non-DM or non-MetS patients, respectively, whereas the effect of rosuvastatin alone did not differ between DM vs non-DM or MetS vs non-MetS patients.

Conclusion: Fixed-dose combinations of ezetimibe and rosuvastatin provided significantly superior efficacy to rosuvastatin alone in lowering LDL cholesterol, total cholesterol, and triglyceride levels. Moreover, the reduction rate was greater in patients with DM or MetS.

KEYWORDS

Cholesterol, Diabetes mellitus, Ezetimibe, Hypercholesterolemia, Metabolic syndrome, Rosuvastatin

1 | INTRODUCTION

Cardiovascular disease is a leading cause of significant morbidity and mortality. Dyslipidemia is a major modifiable risk factor for the development of cardiovascular disease, and one of the cornerstones in the prevention of cardiovascular events is a reduction in the level of low-density lipoprotein (LDL) cholesterol.[1,2]

The most effective class of drugs for lowering the serum LDL cholesterol levels is 3-hydroxy-3-methylglutaryl coenzyme reductase inhibitors, also known as statins.[3] Aggressive therapy to lower LDL cholesterol levels with various statins or the same statin at various doses has been reported to be associated with reduced rates of cardiovascular events.[4–8] However, despite the efficacy of statins having been established, the number of patients who achieve the lipid targets is still suboptimal,[9,10] and increasing the dose of statin leads only to a limited reduction in the LDL cholesterol levels and is associated with a higher incidence of side effects.[11,12] Therefore, further reducing the LDL cholesterol levels to the target goal using novel compounds or combination drug therapy with currently available drugs is of interest.[8,13]

Ezetimibe is a novel cholesterol absorption inhibitor that prevents cholesterol absorption by binding to the Niemann–Pick C1-like 1 (NPC1L1) protein.[10,14] NPC1L1 is an intestinal cholesterol transporter,[15] expressed in the brush border membrane of enterocytes in the small intestine.[16] Moreover, the NPC1L1 transporter is also expressed in the liver, where it reabsorbs cholesterol from bile.[17] Hence, ezetimibe decreases the plasma cholesterol levels by preventing cholesterol from being taken up by intestinal enterocytes and absorbed from the intestinal lumen and also restoring biliary cholesterol excretion.[15–18]

Previous studies have reported the efficacy of combined therapy with ezetimibe and variable statins, with resulting reductions in the LDL

cholesterol levels of 12%–19%.[10,13,19,20] Moreover, the IMPROVE-IT study recently demonstrated that the addition of ezetimibe to statin therapy resulted in a significantly lower risk of cardiovascular events. Therefore, combined therapy with ezetimibe and statins may achieve not only incremental reductions in the LDL cholesterol levels, but may also improve the cardiovascular outcomes.[21]

To date, a fixed-dose combination of ezetimibe and rosuvastatin has not yet been developed and tested. Therefore, the objective of this study was to compare the LDL cholesterol-lowering effects of fixed-dose combinations of ezetimibe 10 mg plus rosuvastatin 5, 10, or 20 mg, as compared with rosuvastatin alone in patients with primary hypercholesterolemia. We also performed a subgroup analysis of safety and efficacy in patients with diabetes mellitus and metabolic syndrome.

2. | METHODS

2.1. | Study design

The present Multicenter Randomized Study of ROsuvastatin and eZEtimibe (MRS-ROZE) was an eight-week, double-blind, parallel-group study conducted in 19 centers in South Korea (clinical trials.gov identifier: NCT002205606) from June 24, 2014, to September 21, 2015. The study protocol was approved by institutional review boards at each participating center, and all study participants provided written informed consent. Subjects with primary hypercholesterolemia and age over 19 years were screened. At the first visit, subjects with initial levels of LDL cholesterol ≤250 mg/dL and triglyceride (TG) <400 mg/dL were selected. These patients discontinued lipid-lowering therapy and followed the National Cholesterol Education Program Adult Treatment Panel III (ATP III) Therapeutic Lifestyle Changes [22] diet during a four-week dietary lead-in period. After the lead-in period, the levels of LDL cholesterol and TG were assessed again and the patients who required lipid-lowering treatment according to the ATP III guidelines were finally enrolled in the study. Eligible patients were also required to have LDL cholesterol levels ≤250 mg/dL and TG levels <400 mg/dL at the second visit. The main exclusion criteria included (1) history of significant statin and/or ezetimibe-induced myopathy or rhabdomyolysis; (2) history of serious hypersensitivity reaction to rosuvastatin or ezetimibe; (3) history of unstable angina, myocardial infarction, myocardial revascularization, coronary artery bypass surgery, transient ischemic attack, or stroke within 3 months of the rosuvastatin run-in period; (4) severe congestive heart failure (New York Heart Association III or IV); (5) current active liver disease (alanine aminotransferase and/or aspartate aminotransferase >3 times the upper limit of normal); (6) serum creatinine ≥3 times the upper limit of normal; (7) creatine kinase levels >5 times the upper limit of normal; (8) the use of prohibited concomitant therapies; (9) history of malignancy within the last 5 years; (10) disorders of the digestive system, including galactose intolerance, Lapp lactase deficiency, or glucose–galactose malabsorption, which might limit the study evaluation; and (11) women who were of childbearing potential without contraception, pregnant, or breastfeeding.

Participating subjects were centrally randomized in a 1:1 ratio to either fixed-dose combinations of ezetimibe 10 mg daily plus rosuvastatin or rosuvastatin alone. Specifically, eligible subjects were randomly assigned to one of the following six treatments for 8 weeks: fixed-dose combinations of ezetimibe 10 mg daily plus rosuvastatin (5, 10, or 20 mg daily) (combo therapy) or rosuvastatin alone (5, 10, or 20 mg daily) (monotherapy). Randomization was performed via a web-based online randomization system. All study personnel including the investigators, study site personnel, participants, monitors, and central laboratory personnel were blinded to the treatment allocation throughout the study.

2.2. | Efficacy and safety assessments

The primary efficacy endpoint was the percentage change from baseline in LDL cholesterol in the overall study population. Secondary efficacy endpoints included the percent changes from baseline in other lipids, including total cholesterol, high-density lipoprotein (HDL) cholesterol, TG, non-HDL cholesterol, apolipoprotein A1, and apolipoprotein B. Another secondary efficacy endpoint was the percentage of patients reaching prespecified goals of LDL cholesterol levels depending on coronary heart disease (CHD) risk factors according to the ATP III guideline. Briefly, the LDL cholesterol goals for the three risk levels are as follows: (1) patients with coronary heart disease (CHD) and CHD risk equivalent, LDL cholesterol <100 mg/dL; (2) patients with multiple (≥2) risk factors, LDL cholesterol <130 mg/dL, except for patients with a 10-year risk >20%, for whom the goal is LDL cholesterol <100 mg/dL; and (3) patients with no or one risk factor, LDL cholesterol <160 mg/dL.[1] The efficacy analyses included the full analysis set population.

Additionally, subgroup analyses of subjects with diabetes mellitus (DM) or metabolic syndrome (MetS) were performed. The percentage changes from baseline to 8 weeks in LDL cholesterol and other lipids in the prespecified subgroups were analyzed. The definition of DM was a fasting serum glucose level ≥126 mg/dL or HbA1c ≥6.5% [23] or self-reported use of antihyperglycemic medications. The definition of MetS was the presence of at least three of the following five factors: elevated blood pressure (systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg), abdominal obesity (waist circumference ≥90 cm in men, ≥80 cm in women), elevated TG (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in men, <50 mg/dL in women), and elevated fasting glucose (≥100 mg/dL or receiving treatment for elevated glucose).[24]

Safety was evaluated by monitoring of clinical adverse events (AEs) and laboratory AEs using the all-patients-as-treated population by the investigators' observations, patient-reported adverse symptoms/signs, and various laboratory tests. The investigators of the individual centers rated the AEs in terms of their relationship to the study medication (definitely, probably, possibly, and probably not related), seriousness (death or life-threatening events, prolonged hospitalization, and/or disability/incapacitation), and intensity (mild, moderate, or severe), while blinded to the treatment allocation.

2.3. | Statistical analysis

The target enrollment was 396 patients to result in 354 assessable patients for the primary endpoint. With this number of patients, assuming a within-group standard deviation of 15%, there was 90% power to detect 9% difference between the treatment groups (α=.05, two-sided). The significance of differences in the baseline characteristics between the combo therapy and monotherapy groups was assessed by Student's *t*-test for continuous variables and the chi-square test (Fisher's exact test) for categorical variables. The percentage changes in LDL cholesterol and other lipids between the groups were evaluated using analysis of covariance with terms for the CHD risk factors according to the ATP III guideline and baseline levels of lipid parameters, resulting in the least-squares mean for each treatment. The significance of another key secondary endpoint, the difference in percentage of patients reaching the prespecified goals of LDL cholesterol levels according to the ATP III guideline, was estimated using the Cochran–Mantel–Haenszel test for pooled data and Fisher's exact test for each risk group. For all analyses, a *P* value <.05 was considered statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

3. | RESULTS

3.1. | Baseline characteristics

Of the 583 screened patients who entered the dietary lead-in period, 412 were randomly assigned the study drug(s) and 407 patients were analyzed (Figure 1). A total of 204 patients (50%) received rosuvastatin alone (rosuvastatin 5, 10, or 20 mg daily) and 203 patients (50%) received fixed-dose combination of rosuvastatin and ezetimibe [ezetimibe 10 mg daily plus rosuvastatin (5, 10, or 20 mg daily)]). Overall, 3.9% and 2.5% of subjects who received combo therapy and monotherapy, respectively, discontinued the study treatment due to the withdrawal of consent. The compliance was similar between the treatment groups; at the end of the study, the compliance was 97% in the rosuvastatin-alone group and 96% in the combo therapy group.

The baseline characteristics were similar between the treatment groups in terms of demographic and clinical data (Table 1). Overall, the mean age was 64 years and 56% of patients were men. A total of 135 (33%) patients had DM, 135 (33%) patients had MetS, 77 (19%) patients had both DM and MetS, 288 (70%) had hypertension, and 337 (82%) had a history of coronary artery disease.

The baseline lipid parameters were generally similar between the treatment groups (Table 1). Overall, the mean LDL cholesterol levels were 147.7±31.3 mg/dL, which were similar between the combo therapy and monotherapy groups (147.7±31.3 mg/dL vs 147.7±30.6 mg/dL, *P*=.993). Other lipids including total cholesterol, TG, HDL cholesterol, non-HDL cholesterol, apolipoprotein B, and apolipoprotein A1 did not differ between the two treatment groups (Table 1).

3.2. | Efficacy

The fixed-dose combination of rosuvastatin and ezetimibe achieved significantly greater reductions in LDL cholesterol levels than rosuvastatin alone in the pooled data analysis, as well as in the comparisons for each rosuvastatin dose at weeks 4 and 8 (Figure 2) (pooled data: −88.3 mg/dL vs −74.4 mg/dL at week 8; the difference between the two groups: −13.9 mg/dL) (least-squares mean percent change: −59.1% vs −49.4% at week 8, *P*<.001, Table 2).

In terms of the other lipids, including total cholesterol, TG, non-HDL cholesterol, and apolipoprotein B, combo therapy showed significantly greater percent reductions than monotherapy in the pooled data analysis, as well as in the comparisons for each rosuvastatin dose, at both weeks 4 and 8 (Table 2, Figure 3). The HDL cholesterol levels increased in both treatment groups, with no difference observed between the two groups (Table 2, Figure 3).

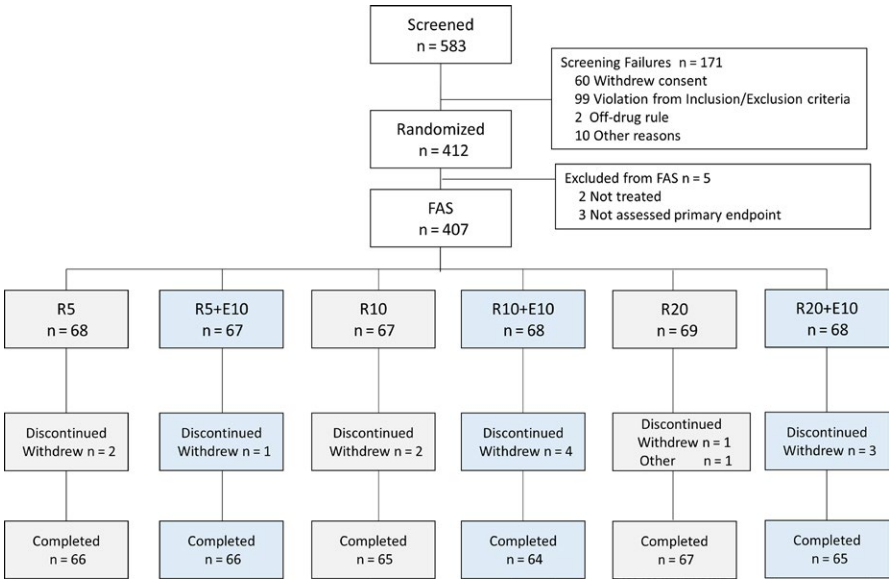

FIGURE 1 Participant distribution. FAS, full analysis set; E10, ezetimibe 10 mg; R5, rosuvastatin 5 mg; R10, rosuvastatin 10 mg; R20, rosuvastatin 20 mg

TABLE 1 Baseline characteristics (full analysis set population)

	R (n=204)	R+E (n=203)	*P* value
Demographic			
Age, y ± SD	64.3±9.3	64.2±7.9	.951
Male, n (%)	118 (57.8)	113 (55.7)	.657
BMI, kg/m^2 ± SD	25.2±2.8	24.7±2.9	.191
Family history of CHD, n (%)	22 (10.8)	28 (13.8)	.355
Current smoker, n (%)	28 (13.7)	35 (17.3)	.612
Diabetes mellitus, n (%)	72 (35.3)	63 (31.3)	.362
Metabolic syndrome, n (%)	69 (33.8)	66 (32.5)	.833
Diabetes and metabolic syndrome, n (%)	40 (19.6)	37 (18.2)	.292
Hypertension, n (%)	141 (69.1)	147 (72.4)	.465
Past history of CHD, n (%)	166 (81.4)	171 (84.2)	.444
Washout information, n (%)			
Statin	119 (58.3)	111 (54.7)	.457
Fibrate	1 (0.5)	2 (1.0)	.623
Bile acid sequestrant	0 (0)	0 (0)	–
Nicotinic acid	0 (0)	2 (1.0)	.248
Combination (statin + other)	16 (7.8)	14 (6.9)	.715
Other	3 (1.5)	9 (4.4)	.077
Baseline lipid profile ± SD			
LDL cholesterol, mg/dL	147.7±30.6	147.7±31.3	.993
Total cholesterol mg/dL	221.2±35.6	221.0±36.5	.975
Triglycerides, mg/dL	152.7±73.1	152.5±69.4	.977
HDL cholesterol, mg/dL	50.1±11.9	49.6±12.9	.646
Non-HDL cholesterol, mg/dL	171.0±35.0	171.5±35.2	.897
Apolipoprotein B, mg/dL	124.1±23.3	124.1±23.3	.989
Apolipoprotein A1, mg/dL	142.6±22.0	142.1±24.5	.828
Lipoprotein(a), mg/dL	39.3±34.1	38.2±35.3	.765

Variables are presented as mean ± SD or n (%); SD, standard deviation; BMI, body mass index; CHD, coronary heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; R, rosuvastatin; E, ezetimibe.

The difference in LDL cholesterol reduction between the combo therapy and monotherapy was significant and greater in patients with DM (n=135, 33%) than in non-DM patients (patients with DM: −64.2% vs −50.2%, difference: −14.0%, *P*<.001; non-DM patients: −57.7% vs −49.8%, difference: −7.9%, *P*<.001; at 8 week; Table 3, Figure 4). In other words, the potency of the combo therapy was greater in patients with DM than in non-DM patients, whereas the potency of the monotherapy was the same in both patients with DM and non-DM patients (combo therapy: patients with DM 64.2% vs non-DM patients −57.7%, *P*=.008). These results were similar to those observed for other lipids, including total cholesterol, non-HDL cholesterol, and apolipoprotein B (Table 3, Figure 4). The TG levels showed greater decreases with combo therapy than with monotherapy, and these decreases were comparable between patients with DM and non-DM patients (Figure S1). No significant differences were observed in HDL cholesterol and apolipoprotein A (Table 3, Figure S1).

In the 135 patients with MetS (33%), the difference in the efficacy between combo therapy and monotherapy was more pronounced than in non-MetS patients (patients with MetS: −63.9% vs −47.6%, difference: −16.3%, *P*<.001; non-MetS patients: −57.6% vs −51.2%, difference: −6.5%, *P*=.001 at week 8; Table 4, Figure 5). In other words, the potency of the combo therapy was greater in patients with MetS than in non-MetS patients, whereas the potency of the monotherapy was similar between patients with MetS and non-MetS patients (combo therapy: patients with MetS −63.9% vs non-MetS patients −57.6%, *P*=.013). These results were also similar to those observed for other lipids, including total cholesterol, non-HDL cholesterol, and apolipoprotein B (Table 4, Figure 5). Combo therapy was more potent than monotherapy in reducing the TG levels and in elevating the HDL cholesterol levels, both in patients with and without MetS (Figure S2). Interestingly, the potencies of both combo therapy and monotherapy on the TG and HDL cholesterol levels were greater in patients with MetS than in non-MetS patients (Figure S2). No significant differences were observed in the apolipoprotein A levels (Table 4).

The target LDL achievement rate was higher in patients treated with combo therapy than in patients treated with monotherapy (Table 5). In the pooled data analysis, 367 patients (90.1%) achieved the prespecified goals of LDL cholesterol levels depending on CHD risk factors according to the ATP III guideline, and more patients treated with combo therapy achieved the LDL cholesterol targets when compared with patients treated with monotherapy (94.1% vs 86.3%, *P*=.009). Moreover, patients with CHD/CHD risk equivalents or a 10-year risk >20% treated with combo therapy showed a higher achievement rate of the LDL cholesterol target than those treated with monotherapy (94.4% vs 84.7%, *P*=.003) (Table 5).

3.3. | Safety

No serious drug-related adverse events (AEs) were reported. There were three serious AEs, including one in the monotherapy group (breast cancer) and two in the combo therapy group (left ulnar fracture and epigastric pain), although these were not considered drug-related AEs by the investigators. The incidence of prespecified AEs was generally comparable between the two groups, with no clinically meaningful differences or statistical significance (Table S1). Consecutive elevations ≥3 times the upper normal limits in alanine aminotransferase or aspartate aminotransferase occurred in 1 (0.5%) of 204 patients receiving monotherapy and 1 (0.5%) of 206 patients receiving combo therapy. Elevations ≥5 times the upper normal limits in creatine kinase occurred only in 1 (0.5%) of 204 patients receiving combo therapy, with no significant differences between the groups.

4. | DISCUSSION

This study sought to evaluate the effects of fixed-dose combination of rosuvastatin and ezetimibe compared to rosuvastatin alone in the

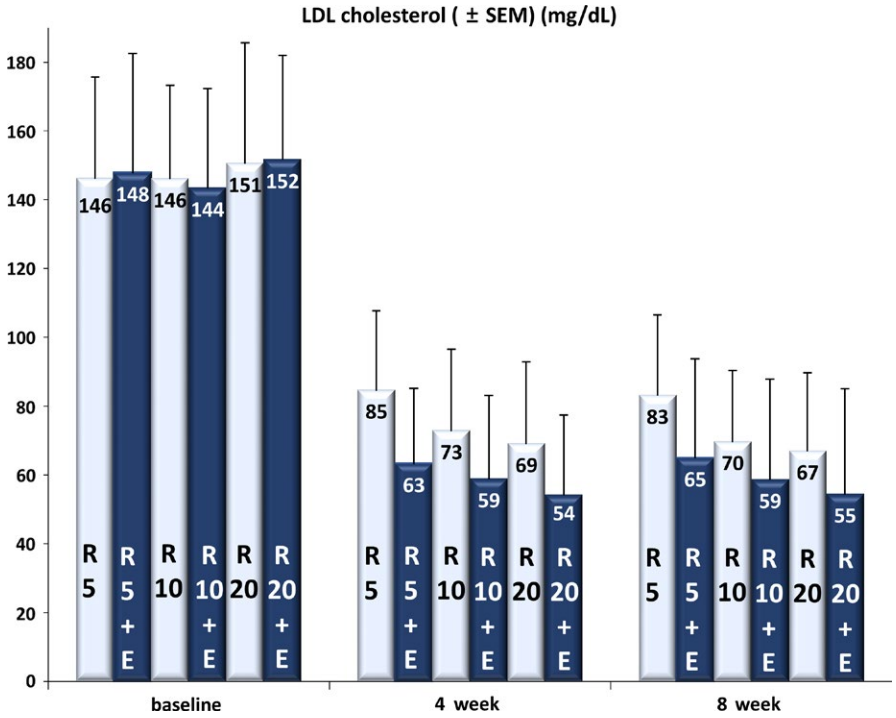

FIGURE 2 LDL cholesterol levels at baseline and after treatment. Bars represent standard errors; LDL, low-density lipoprotein; E, ezetimibe 10 mg; R5, rosuvastatin 5 mg; R10, rosuvastatin 10 mg; R20, rosuvastatin 20 mg

TABLE 2 Percentage change in lipid parameters from baseline at weeks 4 and 8 (full analysis set population)

	R (n=204)	R+E (n=203)	Difference	95% CI for difference	*P* value
Week 4		%±SEM			
LDL cholesterol	−50.0±1.8	−60.9±1.8	−10.9±1.5	−13.8, −8.0	<.001
Total cholesterol	−33.0±1.3	−40.8±1.3	−7.7±1.1	−9.9, −5.6	<.001
Triglycerides	−13.9±3.4	−24.4±3.4	−10.5±2.9	−16.2, −4.7	<.001
HDL cholesterol	11.4±2.1	14.9±2.1	3.5±1.8	−0.1, 7.0	.054
Non-HDL cholesterol	−46.1±1.6	−56.6±1.6	−10.6±1.4	−13.3, −7.9	<.001
Apolipoprotein B	−43.4±1.4	−51.3±1.4	−7.9±1.2	−10.3, −5.5	<.001
Apolipoprotein A1	7.7±1.4	9.0±1.4	1.3±1.2	−1.1, 3.6	.290
Lipoprotein(a)	12.5±7.0	21.9±6.9	9.4±6.0	−2.4, 21.3	.117
Week 8					
LDL cholesterol	−49.4±1.9	−59.1±1.8	−9.7±1.6	−12.8, −6.6	<.001
Total cholesterol	−32.9±1.4	−39.6±1.4	−6.7±1.2	−9.0, −4.4	<.001
Triglycerides	−13.4±3.5	−22.7±3.5	−9.3±3.1	−15.4, −3.3	.003
HDL cholesterol	11.7±2.1	14.1±2.0	2.5±1.8	−1.1, 6.0	.171
Non-HDL cholesterol	−45.8±1.7	−54.9±1.7	−9.0±1.5	−11.9, −6.1	<.001
Apolipoprotein B	−42.8±1.5	−50.0±1.5	−7.3±1.3	−9.8, −4.7	<.001
Apolipoprotein A1	8.2±1.4	9.1±1.3	0.8±1.2	−1.5, 3.2	.476
Lipoprotein(a)	14.1±7.5	25.0±7.4	10.9±6.5	−2.0, 23.8	.096

Variables are presented as the least-squares means ± SEM; SEM, standard error of the mean; CI, confidence interval; LDL, low-density lipoprotein; HDL, high-density lipoprotein; R, rosuvastatin; E, ezetimibe.

treatment for primary hypercholesterolemia patients with LDL cholesterol levels above the ATP III recommended treatment targets. To our knowledge, the MRS-ROZE study is the first trial evaluating the safety and efficacy of fixed-dose combinations of rosuvastatin and ezetimibe in subjects with hypercholesterolemia.

The reduction in LDL cholesterol by fixed-dose combination therapy was significantly greater than that of rosuvastatin monotherapy in the pooled group, as well as in the subgroup comparisons for each rosuvastatin dose, at both weeks 4 and 8. Combo therapy produced an additional significant reduction in the baseline LDL cholesterol of

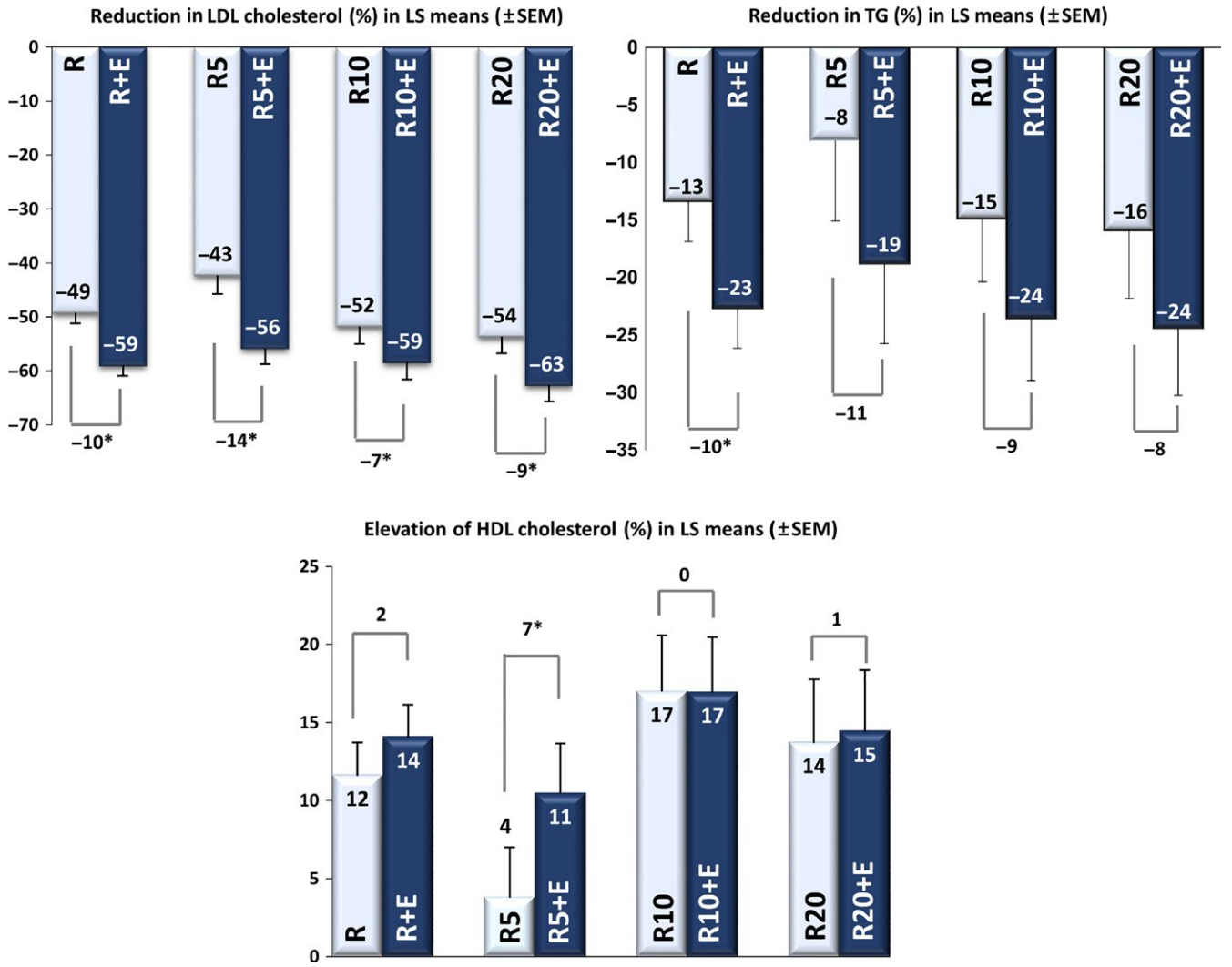

FIGURE 3 Comparison of the percent changes in LDL cholesterol, TG, and HDL cholesterol between monotherapy and combo therapy for 8 wk: pooled data and data of the three different doses. Bars represent standard errors; LDL, low-density lipoprotein; TG, triglyceride; HDL, high-density lipoprotein; LS means, least-squares means; R, rosuvastatin (pooled); E, ezetimibe 10 mg; R5, rosuvastatin 5 mg; R10, rosuvastatin 10 mg; R20, rosuvastatin 20 mg. *P<.05 for the specified between-treatment difference

9.7%. Moreover, significantly more subjects reached the ATP III LDL cholesterol goals with combo therapy compared with monotherapy, and combo therapy resulted in significantly greater reductions in the total cholesterol, TG, non-HDL cholesterol, and apolipoprotein B levels, as early as after 4 or 8 weeks. The changes in HDL cholesterol also tended to be greater by combo therapy than by monotherapy, although this did not reach statistical significance.

The reductions in LDL cholesterol were 43%, 52%, and 54% by rosuvastatin 5, 10, and 20 mg, respectively. Specifically, the reduction in LDL cholesterol in our study with rosuvastatin 10 mg was 52%, which is relatively higher than in previous studies that mainly evaluated Western populations: 44.6% to 47%.[25–27] Although previous large-scale clinical trials have consistently demonstrated the statin efficacy and safety in a variety of populations, few clinical trials have examined the efficacy of statins in different ethnic and racial groups; especially, on the basis of Asian ethnicity, most studies have been carried out in Asia.[28] A few previous studies evaluated the effect of rosuvastatin in Japanese population. The reductions in LDL cholesterol with rosuvastatin 10 mg in these studies were 49.7% [29] and 49.2%,[30] which were comparable to our result (52%) and also higher than the results of Western populations. Liao described that genetically based differences at the level of drug transporters and hepatic enzymes in the metabolism of statins would be the potential mechanisms of enhanced response to statins in Asians.[28]

The incremental reduction in LDL cholesterol by ezetimibe in our study was 9.7%. Previous studies reported the reduction in LDL cholesterol differed according to the study design. Previous factorial studies reported the incremental reduction in LDL cholesterol with the addition of ezetimibe: 12.1% – 13.8%.[10,13,20] Moreover, previous add-on studies reported higher incremental reduction in LDL cholesterol: 18.2 – 25.2%.[19,31,32] The differences in baseline LDL cholesterol levels that might be affected by previously receiving statin therapy in add-on studies might explain the difference. The present study is a factorial study that compared the efficacy of combo therapy vs

TABLE 3 Percentage changes in lipid parameters from baseline to week 8 (full analysis set population)

	Diabetes					Nondiabetes				
	R (n=72)	R+E (n=63)	Difference	95% CI of difference	*P* value	R (n=132)	R+E (n=140)	Difference	95% CI of difference	*P* value
Demographics										
Age, y ± SD	66.1±7.9	64.9±7.6	1.2±7.8		.372	63.2±9.8	63.9±8.0	−0.6±8.9		.555
Male, n (%)	44 (61.1)	38 (60.3)	–		.925	74 (56.1)	75 (53.6)	–		.680
BMI, kg/m^2 ± SD	26.0±2.8	25.8±3.2	0.2±3.0		.689	24.7±2.7	24.3±2.7	0.4±2.7		.263
Average R dose, mg[a]	11.6±6.1	12.1±6.3				11.8±6.3	11.1±6.0			
Week 8		%±SEM					%±SEM			
LDL cholesterol	−50.2±1.8	−64.2±2.0	−14.0±2.7	−19.3, −8.7	<.001	−49.8±1.4	−57.7±1.3	−7.9±1.9	−11.7, −4.1	<.001[b]
R5	−42.3±4.2	−63.6±4.9	−21.3±6.5	−34.4, −8.2	.002	−42.0±2.0	−53.1±1.9	−11.0±2.7	−16.5, 5.6	<.001[b]
R10	−52.0±2.3	−63.9±2.8	−12.0±3.6	−19.3, −4.8	.002	−52.6±2.5	−57.1±2.3	−4.6±3.4	−11.3, 2.1	.179
R20	−56.4±2.8	−64.8±2.6	−8.4±3.9	−16.2, −0.7	.034	−55.1±2.3	−63.8±2.4	−8.7±3.3	−15.3, −2.0	.011
Total cholesterol	−34.4±1.4	−43.8±1.5	−9.5±2.0	−13.5, −5.5	<.001	−32.8±1.0	−38.4±1.0	−5.6±1.4	−8.3, −2.8	<.001[b]
Triglycerides	−11.9±3.5	−21.9±3.7	−10.0±5.1	−20.1, 0.1	.051	−11.4±2.8	−20.3±2.7	−8.9±3.9	−16.6, −1.3	.023
HDL cholesterol	11.3±2.3	9.0±2.5	−2.3±3.4	−9.0, −4.5	.511	8.9±1.5	13.6±1.4	4.7±2.1	0.7, 8.7	.022[b]
Non-HDL cholesterol	−46.6±1.7	−58.3±1.8	−11.7±2.5	−16.7, −6.7	<.001	−45.2±1.3	−53.2±1.3	−8.0±1.8	−11.5, −4.4	<.001[b]
Apolipoprotein B	−42.3±1.5	−53.2±1.6	−10.9±2.2	−15.1, −6.6	<.001	−42.4±1.2	−48.1±1.1	−5.7±1.6	−8.8, −2.5	.001[b]
Apolipoprotein A1	6.5±1.5	4.4±1.6	−2.1±2.2	−6.5, 2.3	.346	5.7±1.0	7.9±1.0	2.2±1.4	−0.5, 4.9	.109[b]
Lipoprotein(a)	29.0±11.0	41.2±11.8	12.3±16.1	−19.6, 44.2	.447	15.1±4.1	25.9±3.9	10.8±5.7	−0.3, 22	.057
Glucose, mg/dL	0.9±3.3	3.8±3.5	2.9±4.8	−6.6, 12.5	.544	0.1±1.4	−1.3±1.4	−1.4±2.0	−5.3, 2.5	.479[b]

Variables are presented as mean ± SD or least-squares means ± SEM. SD, standard deviation; SEM, standard error of the mean; CI, confidence interval; R, rosuvastatin; E, ezetimibe; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]Average doses of rosuvastatin in the pooled patients: R, 11.7 mg; R+E, 11.7 mg.

[b]*P* value <.05 by ANCOVA between R+E in patients with diabetes vs R+E in nondiabetic patients.

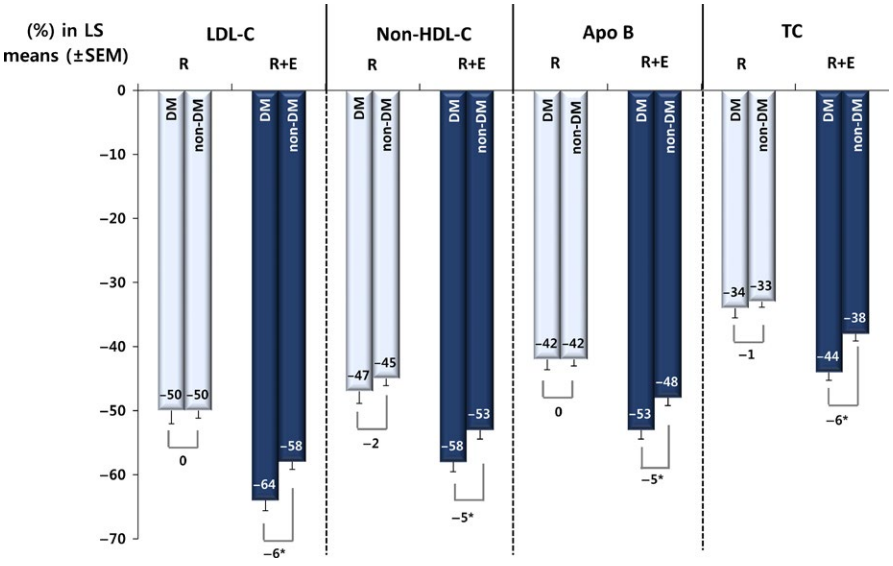

FIGURE 4 Greater reduction in cholesterol observed in patients with DM than in non-DM patients receiving combo therapy. Among patients receiving combo therapy, patients with DM exhibited greater reductions in cholesterol compared to non-DM patients, whereas patients with DM and non-DM patients receiving monotherapy showed comparable levels of cholesterol reduction. Bars represent standard errors; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; TC, total cholesterol; R, rosuvastatin; E, ezetimibe. *P<.05 for the specified between-treatment difference

TABLE 4 Percentage changes in lipid parameters from baseline to week 8 (full analysis set population)

	Metabolic syndrome					Nonmetabolic syndrome				
	R (n=69)	R+E (n=66)	Difference	95% CI for difference	*P* value	R (n=135)	R+E (n=137)	Difference	95% CI for difference	*P* value
Demographics										
Age, y ± SD	64.9±9.4	64.7±7.6	−0.2±8.6		.372	63.9±9.2	64.0±8.0	0.1±8.6		.960
Male, n (%)	38 (55.1)	35 (53.0)	–		.925	80 (59.3)	78 (56.9)	–		.698
BMI, kg/m^2 ± SD	26.4±2.9	26.0±2.9	−0.4±2.9		.689	24.5±2.6	24.2±2.8	−0.3±2.8		.341
Average R dose, mg[a]	11.5±6.2	13.6±6.2				11.8±6.3	10.8±6.0			
Week 8		%±SEM					%±SEM			
LDL cholesterol	−47.6±1.7	−63.9±1.8	−16.3±2.5	−21.3, −11.4	<.001	−51.2±1.4	−57.6±1.4	−6.5±2.0	−10.4, −2.6	.001[b]
R5	−39.0±3.7	−54.9±4.7	−15.80±6.0	−28.0, −3.6	.013	−44.1±2.2	−55.7±2.1	−11.6±3.1	−17.7, 5.6	<.001
R10	−49.3±2.4	−65.3±2.6	−16.0±3.6	−23.2, −8.8	<.001	−53.9±2.4	−56.0±2.3	−2.1±3.3	−8.7, 4,5	.529[b]
R20	−55.1±2.2	−66.6±1.9	−11.5±2.9	−17.3, −5.7	<.001	−55.3±2.5	−62.8±2.8	−7.5±3.7	−14.9, −0.1	.046
Total cholesterol	−33.5±1.2	−45.0±1.3	−11.5±1.8	−15.0, −8.0	<.001	−33.4±1.0	−37.7±1.0	−4.3±1.5	−7.2, −1.4	.003
Triglycerides	−23.6±2.6	−38.5±2.7	−14.9±3.7	−22.3, −7.5	.051	−5.9±3.0	−11.8±2.9	−5.9±4.2	−14.1, 2.3	.161
HDL cholesterol	15.6±2.6	19.9±2.6	4.3±3.7	−3.0, 11.6	.511	6.9±1.4	8.4±1.4	1.5±2.0	−2.3, 5.4	.437
Non-HDL cholesterol	−44.5±1.4	−59.2±1.5	−14.8±2.1	−18.8, −10.7	<.001	−46.4±1.4	−52.6±1.4	−6.2±1.9	−10.0, −2.4	.001[b]
Apolipoprotein B	−41.0±1.4	−53.7±1.4	−12.7±2.0	−16.7, −8.7	<.001	−43.1±1.2	−47.7±1.2	−4.6±1.7	−7.9, −1.4	.005[b]
Apolipoprotein A1	8.4±1.5	8.8±1.6	0.4±2.2	−3.9, 4.7	.855	4.7±1.0	5.9±1.0	1.2±1.4	−1.6, 3.9	.409
Lipoprotein(a)	17.3±8.0	41.1±8.2	23.8±11.5	1.1, 46.4	.040	21.4±5.7	25.6±5.6	4.2±8.0	−11.6, 19.9	.603
Glucose, mg/dL	1.9±3.0	0.1±3.1	−1.8±4.3	−10.4, 6.8	.676	−0.5±1.6	0.4±1.6	0.9±2.3	−3.7, 5.4	.713

Variables are presented as mean ± SD or least-squares means ± SEM. SD, standard deviation; SEM, standard error of the mean; R, rosuvastatin; E, ezetimibe; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]Average dose of rosuvastatin in the pooled patients: R, 11.7 mg; R+E, 11.7 mg.

[b]*P* value <.05 by ANCOVA test between R+E in patients with metabolic syndrome vs R+E in nonmetabolic syndrome patients.

monotherapy after 4 weeks of therapeutic lifestyle changes and washout period. Based on this information, the incremental LDL cholesterol of 9.7% was comparable to previous results.

In our study, the efficacy of combo therapy in comparison with monotherapy on lowering LDL cholesterol was even greater in patients with DM than in non-DM patients. Diabetes has been listed as a CHD risk equivalent by ATP III.[22] Therefore, the LDL cholesterol goal for patients with diabetes is equivalent to that of patients with known CHD.[2] Previous studies have reported the improved effects of adding ezetimibe to simvastatin or rosuvastatin compared to statin monotherapy in patients with DM.[33–36] In our study, we reproduced these phenomena using fixed-dose combinations of ezetimibe and rosuvastatin in patients with DM. Patients with DM have a unique pathophysiology in terms of the intestinal cholesterol absorption. They have higher expression of the NPC1L1 gene, which facilitates the cholesterol absorption in the small intestine,[36,37] while they have lower expression of ATP-binding cassette transporters G5 and G8, which normally facilitate the excretion of cholesterol from the intestinal epithelial cells to the small bowel lumen,[38] resulting in an enhanced cholesterol absorption. Ezetimibe selectively inhibits cholesterol absorption from the intestine by binding to the NPC1L1 receptor. Therefore, combo therapy with ezetimibe might be more effective in patients with DM.

In addition, in our study, the potency of combo therapy was found to be more effective in patients with MetS compared with non-MetS patients. Previous studies have reported that the combination of ezetimibe with a statin produced a greater reduction in LDL cholesterol in patients with MetS,[39,40] especially for simvastatin.[41,42] In this study using fixed-dose combinations, we confirmed that combo therapy is useful for patients with MetS, similar to patients with DM.

The results of other lipids, including total cholesterol, non-HDL cholesterol, and apolipoprotein B, also revealed that the differences

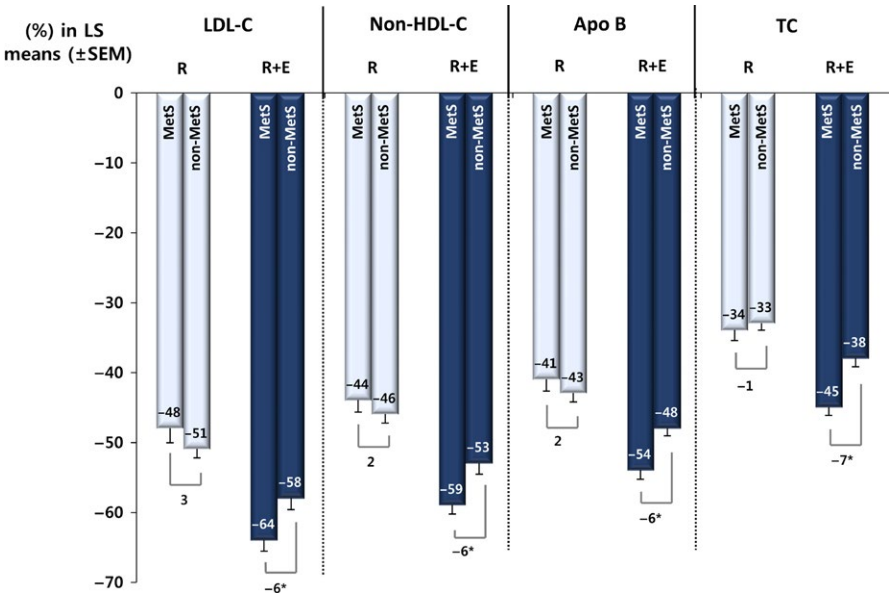

FIGURE 5 Greater reduction in cholesterol in patients with MetS vs non-MetS patients receiving combo therapy. Among patients receiving combo therapy, patients with MetS showed greater reductions in cholesterol compared to non-MetS patients, whereas comparable reductions in cholesterol were observed in patients with MetS vs non-MetS patients receiving monotherapy. Bars represent standard errors; MetS, metabolic syndrome; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; Apo B, apolipoprotein B; TC, total cholesterol; R, rosuvastatin; E, ezetimibe. *P<.05 for the specified between-treatment difference

TABLE 5 Proportion of subjects achieving low-density lipoprotein cholesterol goals by cardiovascular risk category (full analysis set population)

	Rosuvastatin (n=204)	Rosuvastatin + ezetimibe (n=203)	R5 (n=68)	R5+E10 (n=67)	R10 (n=67)	R10+E10 (n=68)	R20 (n=69)	R20+E10 (n=68)
Total patients achieving LDL cholesterol goal, n (%)	176 (86.3)	191 (94.1)[a]	50 (73.5)	65 (97.0)[a]	63 (94.0)	62 (91.2)	63 (91.3)	64 (94.1)
Patients by CHD risk factors, n (%)								
Risk factors 0–1	11 (100)	12 (92.3)	4 (100.0)	5 (100.0)	3 (100.0)	3 (75.0)	4 (100.0)	4 (100.0)
Risk factors ≥2- and 10-y risk ≤20%	10 (100)	10 (90.9)	3 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)	3 (75.0)
CHD/CHD risk equivalents or 10-y risk >20%	155 (84.7)	169 (94.4)[b]	43 (70.5)	57 (96.6) [b]	56 (93.3)	55 (91.7)	56 (90.3)	57 (95.0)

LDL, low-density lipoprotein; CHD, coronary heart disease; R, rosuvastatin; E, ezetimibe.
[a]P value <.05 by the Cochran–Mantel–Haenszel test, with the CHD risk factors defined according to the National Cholesterol Education Program Adult Treatment Panel III.
[b]P value <.05 by Pearson's chi-square test.

in efficacy of combo therapy compared with monotherapy were more effective in patients with DM or MetS than in those without.

The safety and tolerability profiles observed in this study were generally comparable between the two groups and to those of previous studies of ezetimibe and rosuvastatin of similar duration. No drug-related serious AEs were observed, and the incidence of muscle, liver, hepatitis-related, gastrointestinal-related, and allergic AEs was generally low and comparable between the two treatment groups and with other previous studies. However, although the results of this study showed comparative safety and efficacy of fixed-dose combination of rosuvastatin and ezetimibe vs rosuvastatin alone, the duration of the study was relatively short, limiting the ability to generalize these results to longer-term therapy.

In conclusion, the results of this study support the safety and efficacy of fixed-dose combination of rosuvastatin (5, 10, or 20 mg) and ezetimibe (10 mg) compared with rosuvastatin alone in patients with hypercholesterolemia. The benefits of fixed-dose combination treatment were more pronounced in DM and MetS patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS

This study was approved by Seoul National University Hospital Institutional Review Board (date of approval: July 31, 2014).

AUTHOR CONTRIBUTIONS

KJK, SHK, IHC, and HSK were involved in the conception and design of the study. All the authors were involved in the analysis or interpretation of data. KJK, SHK, IHC, and HSK were involved in the drafting of the manuscript. All the authors were involved in the critical review and revision of the manuscript. All the authors approved the final version of the manuscript, including the authorship list.

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SUPPORTING INFORMATION

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