Original Research

Effects of Fixed-dose Combination of Low-intensity Rosuvastatin and Ezetimibe Versus Moderate-intensity Rosuvastatin Monotherapy on Lipid Profiles in Patients With Hypercholesterolemia: A Randomized, Double-blind, Multicenter, Phase III Study

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ABSTRACT

Purpose: We investigated whether the combination therapy of low-intensity rosuvastatin and ezetimibe is an useful alternative to moderate-intensity rosuvastatin monotherapy in patients requiring cholesterol-lowering therapy.

Methods: This was a multicenter randomized, double-blind study to investigate the safety and efficacy

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of a fixed-dose combination of rosuvastatin 2.5 mg and ezetimibe 10 mg (R2.5+E10) compared to those of ezetimibe 10 mg monotherapy (E10), rosuvastatin 2.5 mg (R2.5), and rosuvastatin 5 mg monotherapy (R5) in patients with hypercholesterolemia. A total of 348 patients at 15 centers in Korea were screened, and 279 patients were randomized to different groups in the study. Clinical and laboratory examinations were performed at baseline and 4 and 8 weeks after intervention. The primary endpoint was the percentage change of low-density lipoprotein (LDL) cholesterol levels at the 8-week follow-up.

Findings: Baseline characteristics were similar among the four groups. There were significant changes in lipid profiles at the 8-week follow-up. A greater decrease in the LDL cholesterol levels (primary endpoint) were found in the R2.5+E10 group (−45.7±18.6%) than in the E10 group (−16.7±14.7%, $p<0.0001$), R2.5 group (−32.6±15.1%, $p<0.0001$), and R5 group (−38.9±13.9%, $p=0.0003$). Similar outcomes were observed regarding the decrease in total cholesterol, non-high-density lipoprotein (HDL) cholesterol, and apolipoprotein B protein. In addition, changes in the triglyceride and HDL levels in the R2.5+E10 group were significantly different compared with those in the E10 group; however, the changes were similar to those in the other treatment groups. In patients with low and moderate risk, all patients achieved the target LDL cholesterol levels in the R2.5+E10 group (100%) compared to 13.0% in the E10 group, 47.6% in the R2.5 group, and 65.2% in the R5 group. Adverse effects were rare and similar in the four groups.

Implications: Fixed-dose combination of low-intensity rosuvastatin and ezetimibe was more effective in lowering LDL cholesterol and achieving LDL cholesterol goals than moderate-intensity rosuvastatin monotherapy. These findings suggest that the combination therapy of low-intensity rosuvastatin and ezetimibe is an useful alternative to moderate-intensity rosuvastatin monotherapy for cholesterol management, particularly in patients with low and moderate risk. ClinicalTrials.gov identifier: NCT04652349. (*Clin Ther.* 2021;43:1573–1582.)

Key words: ezetimibe, hypercholesterolemia, LDL-C, rosuvastatin calcium.

INTRODUCTION

Statin therapy has been shown to reduce cardiovascular events in both primary and secondary prevention.[1,2] Current guidelines recommend either a high- or moderate-intensity statin therapy according to the risk of atherosclerotic cardiovascular disease.[3,4] High-intensity statins decrease LDL-C levels by ≥50%, whereas moderate-intensity statins reduce LDL-C levels by 30% to 49%. Statins are generally well tolerated and have an excellent safety profile. However, statin-associated adverse effects are not uncommon; in particular, statin-associated muscle symptoms or hepatic toxicity are usually dose dependent.[5,6] Ezetimibe inhibits the uptake of biliary and dietary cholesterol into the enterocytes, and the combination therapy of statins and ezetimibe synergistically lowers LDL-C levels.[7,8] In real-world clinical practice, low-intensity statins combined with ezetimibe are occasionally used due to concerns regarding statin-associated adverse effects. However, it remains unclear whether this combination therapy has similar effects on lipid profiles and fewer adverse effects compared with standard-intensity statin therapy.

In the present study, we compared the effects of a fixed-dose combination of low-intensity rosuvastatin and ezetimibe (2.5/10 mg) with those of ezetimibe 10 mg, low-intensity rosuvastatin 2.5 mg, or moderate-intensity rosuvastatin 5 mg on the lipid profiles of patients requiring cholesterol-lowering therapy.

PATIENTS AND METHODS

Study Design

This multicenter, randomized, double-blind Phase III clinical trial was conducted to compare the effect of combination therapy with rosuvastatin and ezetimibe (2.5/10 mg) versus that of ezetimibe 10 mg, rosuvastatin 2.5 mg, or rosuvastatin 5 mg on lipid levels and their safety profile in patients with hypercholesterolemia (ClinicalTrials.gov identifier, NCT04652349). Patients who voluntarily signed the consent form at Visit 1 and satisfied

the inclusion/exclusion criteria during screening were advised therapeutic lifestyle changes, including diet, exercise, and weight loss for at least 4 weeks (see Supplemental Figure 1 in the online version at doi:10.1016/j.clinthera.2021.07.016). During this period, the subjects had a washout period with no lipid medications (at least 4 weeks from Pre–Visit 2 for statins and omega-3 supplements, and at least 6 weeks from Pre–Visit 2 for fibrates). At Pre–Visit 2, the patients were screened again based on their fasting serum lipid levels and the inclusion/exclusion criteria. Eligible patients were stratified according to the cardiovascular risk category at Visit 2 (see Supplemental Table I in the online version at doi:10.1016/j.clinthera.2021.07.016) and randomly assigned to 1 of 4 treatment groups (1:1:1:1).

The risk of cardiovascular diseases was determined based on the 10-year risk calculated by using the Systematic Coronary Risk Evaluation (SCORE) method and other risk factors (diabetes, chronic renal disease, lipid level, atherosclerotic cardiovascular disease, and familial dyslipidemia). Patients were prescribed the investigational drugs corresponding to their treatment group. They visited the research institution every 4 weeks for efficacy and safety assessments.

Participants

Patients aged ≥19 years were eligible if they provided written informed consent, had fasting serum levels of LDL-C ≤250 mg/dL and triglyceride levels <500 mg/dL at Visit 1, and had appropriate ranges of LDL-C levels according to the defined risk category at Visit 2 (see Supplemental Tables I and II in the online version at doi:10.1016/j.clinthera.2021.07.016). We excluded patients with acute coronary syndrome, advanced heart failure, history of percutaneous coronary intervention, or coronary bypass graft surgery within the last 6 months; history of stroke; type 1 diabetes or uncontrolled type 2 diabetes (glycosylated hemoglobin values >9%); uncontrolled hypertension; comorbidities such as active liver disease, chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2), hyperthyroidism, hypothyroidism, or malignant tumors within the last 5 years; impaired drug absorption or history of alcohol abuse; history of fibromyalgia, myopathy, or rhabdomyolysis; and female patients who were pregnant or breastfeeding.

Study Treatment

Participants were randomly assigned in a 1:1:1:1 ratio to the following groups: combination therapy of rosuvastatin (2.5 mg) and ezetimibe (10 mg), ezetimibe 10 mg, rosuvastatin 2.5 mg, and rosuvastatin 5 mg. The randomization was performed by using a Web-based interactive response system. The allocation to each treatment group was computer generated and stratified according to the cardiovascular risk categories. The packaging manager of Hanmi Pharmaceutical Co, Ltd packaged the investigational drugs according to the randomization list. The patients were prescribed oral administration of the appropriate investigational drugs daily (4 pills: 1 actual medication, 3 placebos) for 8 weeks. Patients and researchers were double-blinded to the group allocation using a placebo throughout the treatment period. All patients underwent therapeutic lifestyle changes throughout the study period.

Study End Points

The primary efficacy end point was the percent change in LDL-C levels at the 8-week follow-up. Secondary efficacy end points were the percent changes in the following variables: (1) LDL-C at 4-week follow-up; and (2) total cholesterol, HDL-C, triglyceride, non–HDL-C, apolipoprotein A1, apolipoprotein B (apoB), high-sensitivity C-reactive protein, and LDL-C goal achievement at 4- and 8-week follow-up. The treatment goal of LDL-C was individualized according to the risk category (see Supplemental Table II in the online version at doi:10.1016/j.clinthera.2021.07.016). Safety was assessed by monitoring adverse events, clinical evaluation, and laboratory data. All investigator-reported adverse events were adjudicated by a core laboratory. All adverse events were classified into preexisting adverse events and treatment-emergent adverse events based on the time of occurrence; the findings were summarized in a list.

Statistical Analysis

This trial was designed to show the superiority of combination therapy with rosuvastatin and ezetimibe (2.5/10 mg) over low-dose rosuvastatin (2.5 mg) and ezetimibe (10 mg) on the percent reduction in LDL-C levels. Rosuvastatin 5 mg as the reference standard of moderate-intensity statin was used to assess the utility of the combination of rosuvastatin and ezetimibe (2.5/10 mg) in lowering LDL-C levels. A sample size of 240 subjects (60 per group) was calculated to have 98% power to detect a change of –13.8% in LDL-

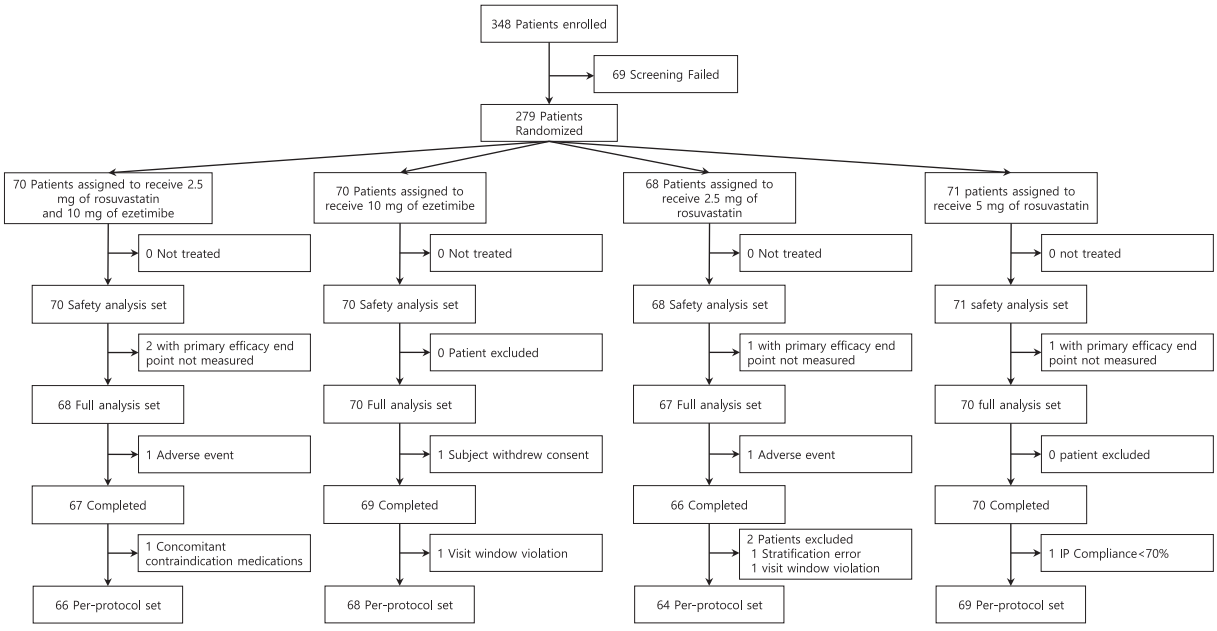

Figure 1. Study flow.

C levels from the baseline between the combination therapy and ezetimibe 10 mg with a 5% significance level,[7,9,10] assuming an SD of 17.3% and a 20% dropout rate. The significance of differences in the baseline characteristics among groups was assessed by analysis of variance (Kruskal-Wallis test) for the continuous variables and the χ^2 test or Fisher's exact test for the categorical variables.

The full analysis set was used for the efficacy assessment and the safety analysis set for the safety assessment. The full analysis set included patients who have undergone a primary end point assessment at least once after administration of an investigational drug, and the safety analysis set included those who have undergone a safety assessment at least once after the administration of an investigational drug. Type I error for the primary end point was controlled by using a stepwise, hierarchical testing procedure (overall power, 94%). Comparisons were made between rosuvastatin and ezetimibe (2.5/10 mg) in the first step and between the combination of rosuvastatin and ezetimibe (2.5/10 mg) and rosuvastatin 2.5 mg in the next step. The percent changes in LDL-C and other lipid parameters among the groups were evaluated by using ANCOVA or Wilcoxon rank-sum tests according to the normality distribution. The last-observation-carried-forward was used to impute missing values for the primary and secondary end points in the full analysis set. Statistical significance was defined as a two-sided P value <0.05. All statistical analyses were conducted by using SAS version 9.4 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Baseline Characteristics

From June 2020 through October 2020, a total of 348 patients at 15 centers in the Republic of Korea were screened, and 279 patients were randomized to the 4 treatment groups (68 received 2.5/10 mg of rosuvastatin and ezetimibe, 70 received 10 mg of ezetimibe, 67 received 2.5 mg of rosuvastatin, and 70 received 5 mg of rosuvastatin). Three patients did not continue the follow-up laboratory examination because of withdrawal of informed consent (n = 1) or the occurrence of adverse events (n = 2). The remaining 276 patients (98.9%) completed the follow-up to assess the efficacy outcomes (Figure 1). The mean (SD) age of the patients was 62.3 (10.5) years, and men comprised 60.4% of the patient population. At the time of randomization, 83 patients (30.2%) had diabetes, 167 (60.7%) had hypertension, and 180 (67.6%) belonged to the high- or very-high-risk group. Baseline demographic characteristics and risk categories were not significantly different between the groups (Table I).

Table I. Baseline characteristics.

Characteristic	Rosuvastatin 2.5 mg and Ezetimibe 10 mg (n = 68)	Ezetimibe 10 mg (n = 70)	Rosuvastatin 2.5 mg (n = 67)	Rosuvastatin 5 mg (n = 70)
Age, mean (SD), y	63.8 (9.4)	62.0 (10.5)	63.1 (10.7)	60.5 (11.4)
Male sex	44 (64.7%)	46 (65.7%)	30 (44.8%)	46 (65.7%)
BMI, mean (SD), kg/m^2	25.0 (2.5)	25.0 (3.0)	25.9 (3.2)	25.0 (2.6)
Risk factors				
Current smoker	12 (17.7%)	7 (10%)	8 (11.9%)	12 (17.1%)
Diabetes mellitus	21 (30.9%)	20 (28.6%)	21 (31.3%)	21 (30.0%)
Hypertension	43 (63.2%)	45 (64.3%)	41 (61.2%)	38 (54.3%)
Medical history				
Asymptomatic CAD	5 (7.4%)	7 (10.0%)	4 (6.0%)	5 (7.1%)
Angina pectoris	11 (16.2%)	19 (27.1%)	10 (14.9%)	14 (20.0%)
Myocardial infarction	4 (5.9%)	3 (4.3%)	7 (10.5%)	3 (4.3%)
Cerebrovascular attack	0 (0%)	1 (1.4%)	2 (3.0%)	2 (2.9%)
Peripheral artery disease	1 (1.5%)	1 (1.4%)	2 (3.0%)	2 (2.9%)
Carotid artery stenosis	1 (1.5%)	0 (0%)	0 (0%)	1 (1.4%)
Risk category				
Low	8 (11.8%)	4 (5.7%)	5 (7.5%)	11 (15.7%)
Moderate	14 (20.6%)	19 (27.1%)	16 (23.9%)	12 (17.1%)
High	22 (32.4%)	16 (22.9%)	20 (29.9%)	18 (25.7%)
Very high	24 (35.3%)	31 (44.3%)	26 (38.8%)	29 (41.4%)

BMI = body mass index; CAD = coronary artery disease.

Efficacy End Point

Changes in the lipid parameters and high-sensitivity C-reactive protein levels during treatment are summarized in Figure 2, Supplemental Figure 2 (in the online version at doi:10.1016/j.clinthera.2021.07.016), and Supplemental Table III (in the online version at doi:10.1016/j.clinthera.2021.07.016). The decrease in LDL-C levels at the 8-week follow-up (primary end point) was significantly greater in the combination therapy group than in the other groups. Similar findings were observed regarding the decrease in total cholesterol, non–HDL-C, and apoB protein levels. In addition, changes in the triglyceride and HDL levels in the combination therapy group were significantly different compared with those in the ezetimibe group but were similar compared with those in the other treatment groups. No significant change was observed in high-sensitivity C-reactive protein levels in any of the groups during the study period. In the subgroup analysis according to sex, the change in LDL-C level at 8 weeks of treatment was also notably greater in the combination therapy group than in the other groups, as shown in Supplemental Figure 3 (see the online version at doi:10.1016/j.clinthera.2021.07.016).

The percentage of patients achieving LDL-C goals at the 8-week follow-up according to the SCORE risk category is shown in Figure 3. Overall, the target achievements were significantly higher in the combination therapy group (51.5%) than in the ezetimibe 10-mg (5.7%; $P < 0.0001$), rosuvastatin 2.5-mg (22.4%; $P < 0.0001$), or rosuvastatin 5-mg (32.9%; $P = 0.0092$) group. In patients with low and moderate risk, all patients achieved target LDL-C levels in the combination therapy group (100%) compared with those in the ezetimibe 10-mg (13.0%),

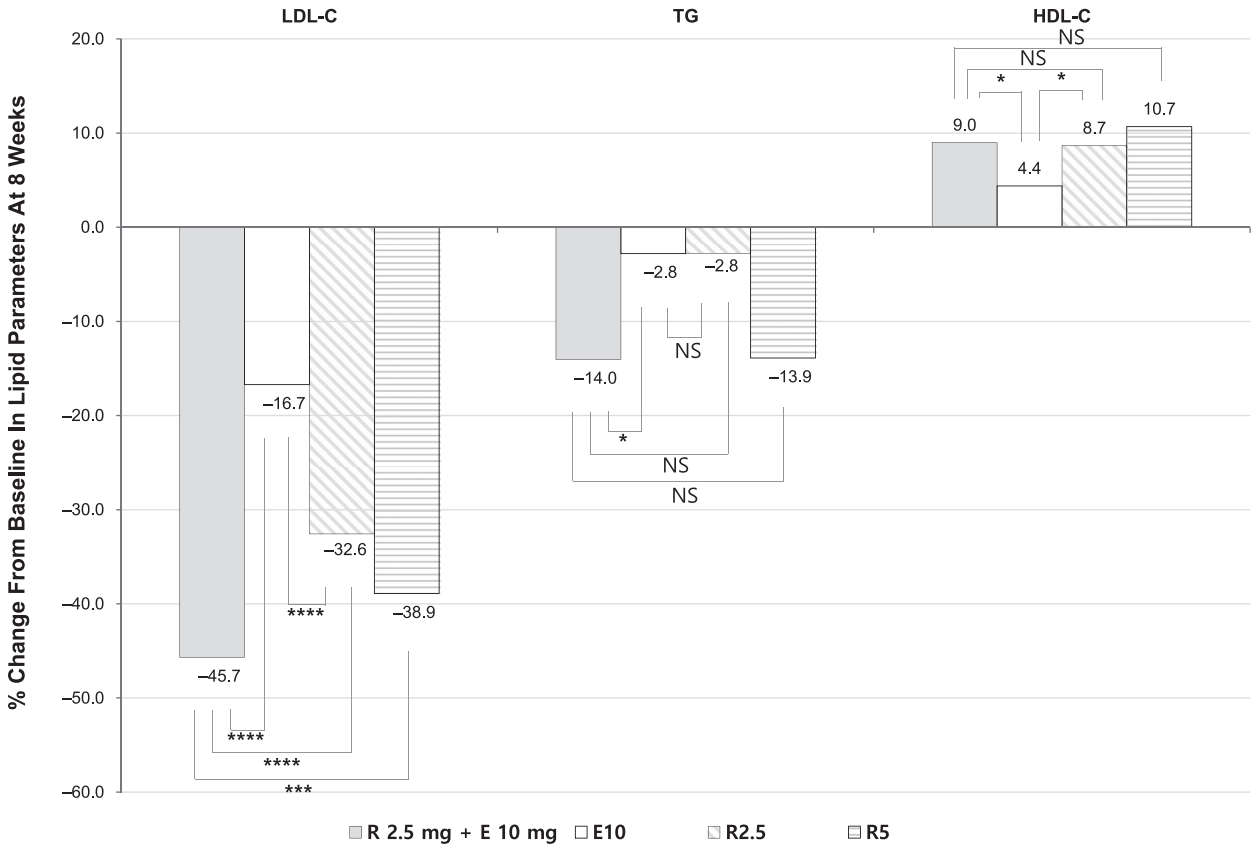

Figure 2. Percent changes in the lipid parameters. E = ezetimibe; NS = not significant ($P \geq 0.05$); R = rosuvastatin; TG = triglyceride. $^{****}P < 0.0001$; $^{***}P < 0.001$; $^{**}P < 0.01$; $^{*}P < 0.05$.

rosuvastatin 2.5-mg (47.6%), and rosuvastatin 5-mg (65.2%) groups. The percentage of patients achieving LDL levels <70 mg/dL or a reduction of LDL ≥50% was significantly higher in the combination therapy group than other groups ($P < 0.001$) (see Supplemental Figure 4 in the online version at doi:10.1016/j.clinthera.2021.07.016).

Safety End Point

Adverse events occurred in 7 (2.5%) patients, and there were no differences in adverse effects between the treatment groups (Table II). Most adverse events were mild, and the most common adverse effects were dyspepsia and pruritus in 2 patients each. Adverse events leading to treatment discontinuation occurred in 1 patient (1.4%) in the combination therapy group and 1 (1.5%) in the rosuvastatin 2.5-mg group. One patient each in the rosuvastatin 5-mg group experienced a significant elevation in liver transaminase (>3 upper limits of normal) and creatine kinase (>10 upper limits of normal) levels during the study.

DISCUSSION

In the present study, the fixed-dose combination therapy of low-intensity rosuvastatin 2.5 mg with ezetimibe 10 mg showed a greater decrease in LDL-C, non–HDL-C, and apoB protein, and beneficial changes in lipid ratios, than the moderate-intensity rosuvastatin 5-mg monotherapy in patients with varied profiles, which resulted in a higher percentage of patients attaining the target LDL-C goal. Overall, 100% of the patients in the low- and moderate-risk categories achieved the target levels of LDL-C with a combination of low-intensity rosuvastatin and

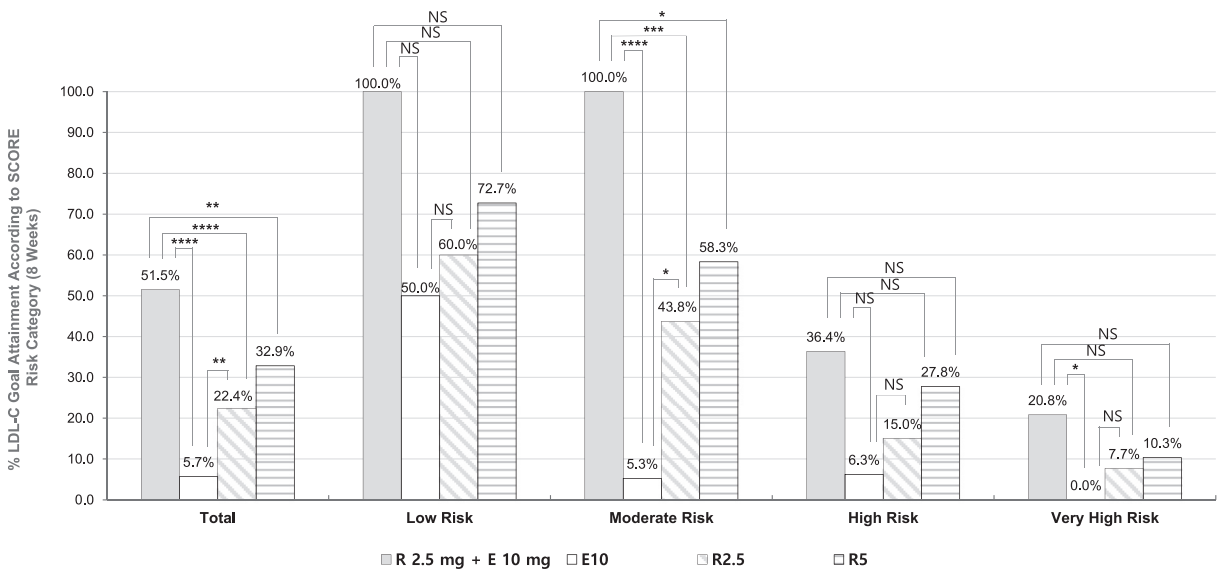

Figure 3. LDL-C goal achievement according to Systematic Coronary Risk Evaluation (SCORE) risk category at 8 weeks. E = ezetimibe; NS = not significant ($P \geq 0.05$); R = rosuvastatin. $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P < 0.001$; $^{\S}P < 0.0001$.

Table II. Treatment-related side effects. Values are given as no. (%).

Variable	Rosuvastatin 2.5 mg and Ezetimibe 10 mg (n = 70)	Ezetimibe 10 mg (n = 70)	Rosuvastatin 2.5 mg (n = 68)	Rosuvastatin 5 mg (n = 71)
Adverse drug reaction	2 (2.9)	1 (1.4)	2 (2.9)	2 (2.8)
Mild	1 (1.4)	1 (1.4)	2 (2.9)	1 (1.4)
Moderate	1 (1.4)	0 (0)	0 (0)	1 (1.4)
Severe	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse drug reaction	0 (0)	0 (0)	0 (0)	0 (0)
Adverse drug reaction leading to withdrawal	1 (1.4)	0 (0)	1 (1.5)	0 (0)
Reported adverse drug reaction				
Abdominal distension	0 (0)	0 (0)	1 (1.5)	0 (0)
Dyspepsia	0 (0)	1 (1.5)	1 (1.5)	0 (0)
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Aspartate aminotransferase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Blood creatine phosphokinase increased	0 (0)	0 (0)	0 (0)	1 (1.4)
Myalgia	1 (1.4)	0 (0)	0 (0)	0 (0)
Headache	0 (0)	0 (0)	0 (0)	1 (1.4)
Pruritus	1 (1.4)	1 (1.5)	0 (0)	0 (0)

ezetimibe; however, this outcome was not seen in those in the high- and very-high-risk category (31.8%). Adverse side effects were largely similar and very low in all treatment groups. These findings suggest that combination therapy with low-intensity rosuvastatin 2.5 mg with ezetimibe 10 mg is a more effective strategy compared with rosuvastatin 5 mg for cholesterol management in patients with low and moderate risk.

Statins are the basis of lipid management due to their proven benefits. They are classified into 3 categories according to cholesterol-lowering efficacy[3]: high-intensity statins (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) achieve at least a 50% reduction in LDL-C; moderate-intensity statins (atorvastatin 10–20 mg or rosuvastatin 5–10 mg) achieve a 30% to 49% reduction in LDL-C; and low-intensity statins (pravastatin 10–20 mg, simvastatin 10 mg, or rosuvastatin 2.5 mg) achieve an LDL-C reduction of <30%. High-intensity statin therapy is recommended for patients with high and very high risk of cardiovascular disease, whereas moderate-intensity statin therapy is indicated for those with low and moderate risk. Although high- and moderate-intensity statins remain the standard therapy to reduce cardiovascular events, some patients are unable to tolerate statin therapy. In fact, the use of statins is considered to be suboptimal in real-world practice, and low-intensity statins are occasionally used, especially for patients with a low risk of cardiovascular disease. Therefore, there is a wide gap between guideline-based optimal care and actual care in clinical practice. These might be due to concerns about the statin-associated adverse effects. Statin-associated muscle symptoms are the most common of the statin-associated adverse effects, which are usually dose dependent.[5,6] However, an adequate reduction (≥30%) in LDL-C levels may be necessary to achieve a clinically meaningful benefit.[11] One rational approach is using 2 cholesterol-lowering agents, such as a low-intensity statin and ezetimibe, which may alleviate the concerns regarding statin-associated adverse effects and lead to achievement of LDL-C goals.

It is recommended to use combination therapy with complementary mechanisms of action to maximize the effect with a lower dose and reduce the risk of several adverse reactions. Inhibition of cholesterol synthesis in the liver by rosuvastatin can enhance cholesterol absorption, while paradoxically decreasing the lipid-lowering effect. The addition of a cholesterol absorption inhibitor, ezetimibe, can provide a complementary action and increase the LDL-C–reducing efficacy of statins.[12] Ezetimibe inhibits cholesterol absorption in the intestine and decreases LDL-C by ~20%. When coadministered with a statin, ezetimibe led to a significant additional reduction in LDL-C levels, with a higher proportion of patients achieving the target goals. In the present study, the low-intensity rosuvastatin/ezetimibe combination therapy decreased LDL-C levels by 45.7%, which was superior to that achieved with moderate-intensity rosuvastatin therapy (ie, 38.9%). These findings are compatible with those of the previous studies showing that adding ezetimibe 10 mg to any statin dose reduced LDL-C levels by an additional 25%, compared with the usual 6% achieved by doubling the statin dose.[9,10,13,14] In addition, low-intensity rosuvastatin/ezetimibe versus moderate-intensity rosuvastatin led to significantly greater improvements in total cholesterol, non–HDL-C, and apoB protein. In contrast, the decrease in LDL-C was <20% with ezetimibe alone, which is considerably below the current recommended limits for cholesterol treatment. The clinical benefit of LDL-C–lowering therapy depends on the intensity of therapy, the baseline LDL-C level, and the baseline risk of cardiovascular disease.[4] LDL-C goals were attained with low-intensity rosuvastatin/ezetimibe combination therapy in most patients with low and moderate risk. However, it did not achieve the target goals in the majority of patients with high risk or very high risk and may not be appropriate in these patient populations. Although the relative efficacy of statin/ezetimibe combination therapy compared with that of equivalent statin monotherapy remains unclear, the risk reduction of cardiovascular events is known to be proportional to the degree of decrease in LDL-C.[1,2,15–17] These findings suggest that the addition of ezetimibe to low-intensity rosuvastatin therapy may be a useful alternative to moderate-intensity rosuvastatin therapy in patients with low and moderate risk.

Ezetimibe combination with low-intensity rosuvastatin was well tolerated, with an excellent safety profile. Most of the adverse events were mild, and no serious adverse events were reported in any patients. The adverse event profiles observed in the low-intensity rosuvastatin/ezetimibe group were similar to those in the low-intensity rosuvastatin group and the ezetimibe

group. Few patients discontinued treatment as a result of adverse events. In the combination therapy group, 1 patient experienced myalgia without an elevation of creatine kinase level during the study. For the most part, abnormal laboratory test results were unremarkable.

Several potential limitations need to be addressed. First, the small sample size and the use of surrogate markers are significant drawbacks of our study. It remains uncertain whether our findings would ultimately translate into reduced cardiovascular events in clinical practice, and this needs to be verified through trials with large sample sizes. Second, patients with a broad range of baseline risks were included in this study. The fixed-dose combination of low-intensity rosuvastatin and ezetimibe has a moderate potency to decrease LDL-C by 30% to 50%, and our findings may not be applicable for patients with high or very high risk. Third, the incidence of adverse events and discontinuation was low in each group, and there were no statistically significant differences between groups. This study was not designed with sufficient statistical power to prove the tolerability of a low-dose statin versus a standard dose of statin, and larger scale studies are needed. Finally, our study only involved an Asian population; thus, the extrapolation of these data to other ethnic groups may be limited. Overall, the rate of LDL goal attainment was lower in the high- and very-high-risk groups. The lower rate could have originated from insufficient validation of the SCORE risk algorithm in the Asian population, and the possibility of ethnic or geographic differences cannot be ruled out.

CONCLUSIONS

Low-intensity rosuvastatin (2.5 mg) with ezetimibe 10 mg resulted in more significant reductions in LDL-C and beneficial changes in lipid ratios than moderate-intensity rosuvastatin 5 mg monotherapy among a broad range of patients requiring cholesterol-lowering therapy.

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Cheol Whan Lee contributed to the design and implementation of this study, the analysis of the results, the writing and critical revision of the manuscript, and obtaining the fund and supervision of this research. Seung-Ah Lee carried out the acquisition, analysis, and interpretation of data, participated in statistical analysis, and drafted the manuscript with support from Cheol Whan Lee. All listed authors have performed the data collection and supervised this trial, and revised the manuscript for important intellectual content.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

REFERENCES

1. Cholesterol Treatment Trialists CollaborationEfficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: 1. Evidence from genetic, epidemiologic, and clinical studies. *Eur Heart J*. 2017;38:2459–2472.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary. *J Am Coll Cardiol*. 2019;73:3168–3209.
4. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188.
5. Riphagen IJ, van der Veer E, Muskiet FA, DeJongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. *Curr Med Res Opin*. 2012;28:1247–1252.
6. Nguyen KA, Li L, Lu D, et al. A comprehensive review and meta-analysis of risk factors for statin-induced myopathy. *Eur J Clin Pharmacol*. 2018;74:1099–1109.
7. Yu M, Liang C, Kong Q, Wang Y, Li M. Efficacy of combination therapy with ezetimibe and statins versus a double dose of statin monotherapy in participants with hypercholesterolemia: a meta-analysis of literature. *Lipids Health Dis*. 2020;19:1.
8. Sudhop T, Lutjohann D, Kodal A, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation*. 2002;106:1943–1948.
9. Kim KJ, Kim SH, Yoon YW, et al. Effect of fixed-dose combinations of ezetimibe plus rosuvastatin in patients

with primary hypercholesterolemia: MRS-ROZE (Multicenter Randomized Study of Rosuvastatin and Ezetimibe). *Cardiovasc Ther*. 2016;34:371–382.
10. Torimoto K, Okada Y, Mori H, et al. Efficacy of combination of ezetimibe 10 mg and rosuvastatin 2.5 mg versus rosuvastatin 5 mg monotherapy for hypercholesterolemia in patients with type 2 diabetes. *Lipids Health Dis*. 2013;12:137.
11. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research GroupMajor outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998–3007.
12. Strilchuk L, Tocci G, Fogacci F, Cicero AFG. An overview of rosuvastatin/ezetimibe association for the treatment of hypercholesterolemia and mixed dyslipidemia. *Expert Opin Pharmacother*. 2020;21:531–539.
13. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90:1084–1091.
14. Denke M, Pearson T, McBride P, Gazzara RA, Brady WE, Tershakovec AM. Ezetimibe added to ongoing statin therapy improves LDL-C goal attainment and lipid profile in patients with diabetes or metabolic syndrome. *Diab Vasc Dis Res*. 2006;3:93–102.
15. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
16. Ference BA, Majeed F, Penumetcha R, Flack JM, Brook RD. Effect of naturally random allocation to lower low-density lipoprotein cholesterol on the risk of coronary heart disease mediated by polymorphisms in NPC1L1, HMGCR, or both: a 2 x 2 factorial Mendelian randomization study. *J Am Coll Cardiol*. 2015;65:1552–1561.
17. Lee SH, Lee JY, Kim GH, et al. Two-sample Mendelian randomization study of lipid levels and ischemic heart disease. *Korean Circ J*. 2020;50:940–948.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria
At Visit 1

1) Participants aged ≥ 19 years
2) Participants who voluntarily provided written consent to participate in this clinical trial
3) Participants with the following fasting serum lipid measurements at Visit 1:
   a) LDL-C ≤ 250mg/dL
   b) Triglycerides < 500 mg/dL

At Visit 2

4) Participants who belong to one of the following risk groups based on the risk of cardiovascular diseases determined by their fasting serum lipid levels at Pre-Visit 2, after at least four weeks of the therapeutic lifestyle changes period:

Exclusion criteria

Risk category		LDL-C[a] (mg/dL)	TG[b](mg/dL)
Low-risk group	10-year risk* <1%	116 - 250	< 500
Moderate-risk group	1% ≤10-year risk <5%	100 - 250	
High-risk group	5% ≤10 year risk <10% or has at least 1 of the high risk factor (See below)†	70 - 190	
Very high-risk group	10% ≤10 year risk or has at least 1 of the very high risk factor (See below)‡	55 - 190	

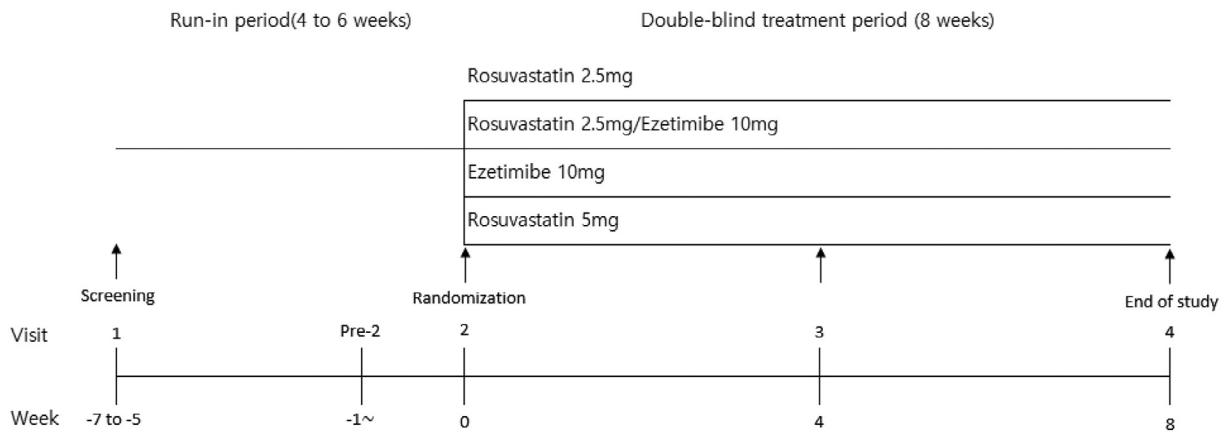
* Based on the 2019 ESC/EAS Guidelines. Refer to Appendix 4 for more details on the classification method.
† High risk factors; [a]LDL-C, low-density lipoprotein cholesterol; [b] TG, Triglycerides.
• Markedly elevated single risk factors,
e.g.) Total cholesterol > 310 mg/dL or LDL-C > 190 mg/dL
BP ≥ 180/110 mmHg
• Familial hyperlipidemia without other major-risk factors§
• Diabetes without target organ damage,
with diabetes duration ≥ ten years or accompanied by major risk factor§
• Moderate to severe chronic renal disease (eGFR 30-59 mL/min/1.73 m^2)
‡ Very high-risk factors
• Documented atherosclerotic cardiovascular disease (ASCVD), either clinical or unequivocal on imaging
• Diabetes with peripheral organ damage such as microalbuminuria, retinopathy, and neuropathy or accompanied by at least three major-risk factors§
• Severe chronic renal disease (eGFR < 30 mL/min/1.73 m^2)
• Familial hyperlipidemia accompanied by major-risk factors§
§ Major risk factors: smoking, hypertension, dyslipidemia, family history of premature ASCVD, chronic kidney disease, metabolic syndrome, conditions specific to women (e.g., preeclampsia, premature menopause, inflammatory disease

At Visit 1

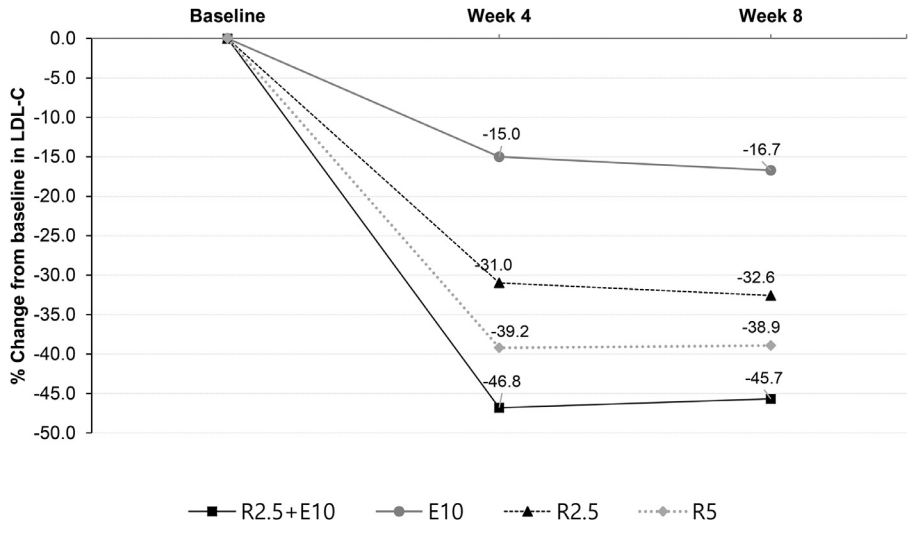
1) Patients with active liver disease and severe liver impairment (patients with an idiopathic and consistent increase in serum AST and ALT levels or with serum ALT and AST levels three times the upper limit of normal at Visit 1)
2) Patients with advanced renal failure (eGFR < 30 mL/min/1.73 m^2 at Visit 1)
3) Patients with type I diabetes or uncontrolled type 2 diabetes (HbA1c > 9% at Visit 1)
4) Patients with acute hypertension or uncontrolled hypertension (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg at Visit 1)
5) Patients with symptomatic orthostatic hypotension
6) Patients with the following medical history within six months before screening at Visit 1:
   - NYHA class III~IV heart failure
   - CCSA class III~IV angina
   - Ventricular arrhythmia
7) Patients with severe hemorrhagic (intracranial or subarachnoid bleeding, etc.) or ischemic (intracranial atherosclerosis, serious carotid artery stenosis, etc.) cerebrovascular diseases, hypertensive encephalopathy, transient ischemic attacks (TIAs), acute coronary syndrome (acute myocardial infarction, unstable angina, etc.), or a history of angioplasty, percutaneous coronary intervention, or coronary artery bypass surgery within six months before screening at Visit 1
8) Patients who were diagnosed with a malignant tumor within five years before Visit 1 or currently have an active malignant tumor (with an exception to cervical cancer, skin basal cell carcinoma, and skin squamous cell carcinoma)
9) Patients with a history of substance or alcohol abuse within six months before Visit 1
10) Patients with a medical or family history of fibromyalgia, myopathy, rhabdomyolysis, or hereditary myopathy or patients with a history of HMG-CoA reductase inhibitor- or fibrate-induced muscular toxicity
11) Patients with impaired drug absorption due to a history of gastrointestinal surgery, gastrointestinal impairment, or surgical or internal conditions
12) Patients resistant or hypersensitive to the ingredients of the investigational drug or having a history of multi-drug allergy
13) Patients with hereditary conditions such as galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption
14) Pregnant or breastfeeding female patients or patients whose partners are planning to conceive; female or male patients not using appropriate contraceptive methods
15) Patients administered a different investigational drug within 30 days before Visit 1
16) Patients deemed ineligible for participation in the clinical trial based on clinical findings by investigators

At Pre-Visit 2

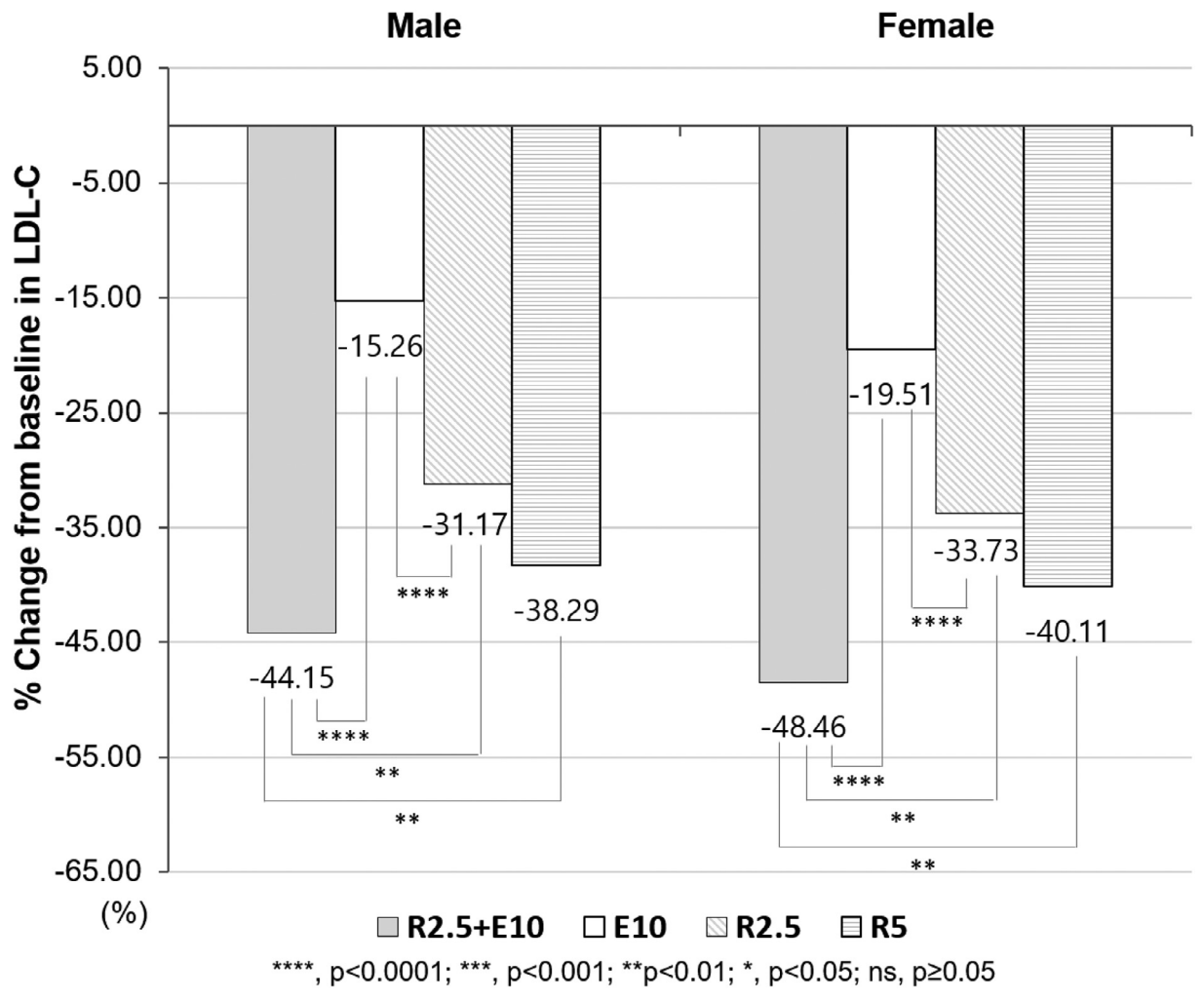
17) Patients with CPK levels more than 5 times higher than the upper limit of normal
18) Patients with uncontrolled hyperthyroidism or hypothyroidism (patients with TSH levels 1.5 times higher than the upper limit of normal)
19) Patients administered dyslipidemia medications within 4 weeks of Pre-Visit 2 (or within six weeks for fibrates)
20) Patients deemed ineligible for participation in the clinical trial based on clinical findings by the investigators



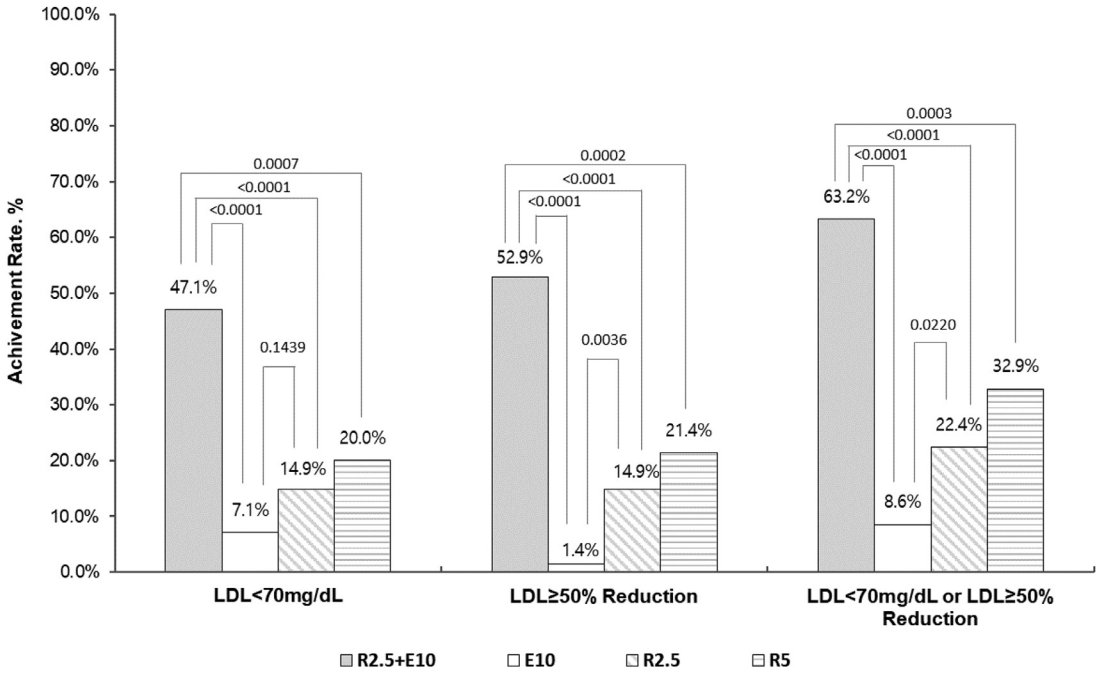
Supplementary Figure 1. Study design



Supplementary Figure 2. Serial changes in LDL cholesterol levels at week 4 and week 8.



Supplementary Figure 3. Subgroup analysis by sex in % change of LDL-C.



Supplementary Figure 4. Achievement of target LDL cholesterol goal at 8 weeks

Supplementary Table 2. Ranges of LDL-C for enrollment and treatment goals by risk category

Risk category		LDL-C[a] and TG[b] for enrollment		LDL-C treatment goal
		LDL	TG	
Low-risk group	10-year risk* <1%	116 – 250	< 500	< 116 mg/dL
Moderate-risk group	1% ≤ 10-year risk <5%	100 - 250		< 100 mg/dL
High-risk group	5% ≤ 10 year risk <10% or has at least 1 of the high risk factors (See below)[†]	70 - 190		≥50% reduction from baseline and < 70 mg/dL
Very high-risk group	10% ≤10 year risk or has at least 1 of the very high risk factors (See below) [†]	55 - 190		≥50% reduction from baseline and < 55 mg/dL

[a] LDL-C, low-density lipoprotein cholesterol
[b] TG, Triglycerides.
[†] The risk of cardiovascular diseases was determined based on the 10-year risk calculated using the Systematic COronary Risk Evaluation (SCORE) method and other risk factors (diabetes, chronic renal disease, lipid level, atherosclerotic cardiovascular disease, familial dyslipidemia etc.)

Supplementary Table 3. Change in lipid parameters

	Rosuvastatin 2.5mg/ Ezetimibe 10mg	Ezetimibe 10mg	Rosuvastatin 2.5mg	Rosuvastatin 5mg
Number of patients on treatment	68	70	67	70
LDL-C[a] (mg/dL)				
Baseline	137.16 (27.70)	137.57 (29.98)	140.15 (28.32)	144.86 (23.94)
Week 4	70.77 (21.69)	114.55 (25.37)	95.89 (22.27)	87.36 (22.44)
Week 8	71.94 (19.91)	113.13 (26.51)	93.21 (23.89)	87.84 (22.95)
% change from baseline				
Week 4	-46.80 (18.65)[2)b,2)d,2)f]	-14.99 (16.90)	-30.99 (14.82)[2)b]	-39.20 (14.72)
Week 8	-45.67 (18.61)[1)b,2)d,2)f]	-16.72 (14.70)	-32.58 (15.08)[1)b]	-38.91 (13.94)
HDL-C[b] (mg/dL)				
Baseline	51.07 (13.70)	50.26 (17.38)	47.39 (11.46)	48.71 (11.72)
Week 4	54.48 (13.75)	52.90 (17.47)	52.48 (12.61)	53.71 (12.49)
Week 8	55.12 (14.68)	51.63 (17.02)	51.07 (11.99)	53.19 (11.71)
% change from baseline				
Week 4	7.30 (13.81)	6.45 (12.36)	11.17 (13.34)[2)a]	10.98 (14.46)
Week 8	8.98 (15.11)[2)a]	4.38 (14.77)	8.66 (13.65)[2)a]	10.69 (16.08)
Non HDL-C (mg/dL)				
Baseline	154.34 (27.87)	154.63 (31.01)	158.52 (31.00)	162.51 (23.71)
Week 4	85.70 (25.81)	128.14 (28.39)	110.80 (24.73)	99.38 (24.21)
Week 8	85.84 (22.29)	127.00 (28.74)	109.64 (28.91)	100.37 (23.67)
% change from baseline				
Week 4	-43.82 (16.38)[2)b,2)d,2)f]	-16.30 (13.36)	-29.74 (13.76)[2)b]	-38.68 (12.49)
Week 8	-43.26 (16.13)[2)b,2)d,2)f]	-17.46 (12.07)	-30.00 (16.36)[2)b]	-38.10 (11.38)
LDL-C/HDL-C Ratio				
Baseline	2.83 (0.82)	2.98 (0.99)	3.10 (0.94)	3.09 (0.67)
Week 4	1.39 (0.58)	2.35 (0.80)	1.92 (0.63)	1.69 (0.54)
Week 8	1.38 (0.48)	2.38 (0.81)	1.92 (0.67)	1.71 (0.52)
% change from baseline				
Week 4	-50.14 (16.88)[2)b,2)d,2)f]	-19.75 (15.45)	-37.43 (14.06)[2)b]	-44.76 (13.53)
Week 8	-49.99 (15.85)[2)b,2)d,2)f]	-19.36 (14.78)	-37.02 (16.69)[2)b]	-43.97 (14.68)
TC[c] **(**mg/dL)				
Baseline	205.41 (30.37)	204.89 (34.92)	205.91 (33.66)	211.23 (27.77)
Week 4	140.18 (25.57)	181.04 (32.13)	163.28 (27.15)	153.09 (27.49)
Week 8	140.96 (25.46)	160.72 (30.70)	178.63 (31.45)	153.56 (27.74)
% change from baseline				
Week 4	-31.21 (12.66)[2)b,2)d,2)f]	-11.03 (10.64)	-20.56 (10.76)[1)b]	-27.41 (10.52)
Week 8	-30.49 (13.74)[2)b,2)d,2)f]	-21.27 (12.64)	-12.33 (9.73)[2)b]	-27.21 (9.27)

(*continued on next page*)

Supplementary Table 3. (*continued*)

	Rosuvastatin 2.5mg/ Ezetimibe 10mg	Ezetimibe 10mg	Rosuvastatin 2.5mg	Rosuvastatin 5mg
TG[d] (mg/dL)				
Baseline	151.19 (85.71)	150.81 (73.15)	154.96 (67.65)	155.44 (89.24)
Week 4	119.88 (60.66)	133.13 (73.74)	135.46 (67.13)	115.58 (56.87)
Week 8	118.44 (59.87)	136.96 (59.73)	142.63 (98.73)	120.20 (54.34)
% change from baseline				
Week 4	-13.68 (34.22)	-6.98 (34.36)	-9.16 (39.70)	-19.23 (25.94)
Week 8	-14.03 (33.09)[2)a]	-2.79 (35.42)	-2.79 (53.92)	-13.88 (32.28)
ApoB[e] (mg/dL)				
Baseline	126.81 (21.70)	126.94 (25.90)	129.85 (23.33)	130.41 (17.80)
Week 4	79.27 (21.77)	108.81 (22.03)	96.46 (19.80)	87.99 (17.53)
Week 8	79.13 (17.63)	109.27 (26.21)	95.40 (21.03)	87.61 (17.13)
% change from baseline				
Week 4	-37.01 (15.56)[2)b,2)d,2)f]	-13.12 (12.35)	-25.45 (12.15)[2)b]	-32.22 (11.56)
Week 8	-36.48 (15.60)[2)b,2)d,2)f]	-13.71 (12.13)	-25.87 (13.02)[2)b]	-32.30 (11.89)
ApoA1[f] (mg/dL)				
Baseline	153.10 (25.54)	151.21 (36.84)	145.16 (25.12)	146.24 (23.01)
Week 4	163.62 (25.89)	159.43 (36.98)	162.03 (28.12)	161.16 (26.66)
Week 8	165.03 (28.90)	157.97 (42.00)	158.54 (25.85)	159.97 (26.08)
% change from baseline				
Week 4	6.95 (10.19)[2)c]	5.95 (9.31)	11.59 (9.58)[2)b]	10.17 (10.59)
Week 8	8.34 (12.68)	5.02 (11.59)	9.88 (10.40)[2)b]	9.80 (11.34)
ApoB/ApoA1				
Baseline	0.85 (0.21)	0.88 (0.27)	0.92 (0.26)	0.91 (0.17)
Week 4	0.50 (0.16)	0.72 (0.22)	0.61 (0.17)	0.56 (0.14)
Week 8	0.49 (0.13)	0.73 (0.22)	0.62 (0.17)	0.56 (0.14)
% change from baseline				
Week 4	-40.87 (14.13)[2)b,2)d,2)e]	-17.58 (12.78)	-32.80 (11.81)[2)b]	-38.11 (11.59)
Week 8	-41.25 (12.81)[2)b,2)d]	-17.23 (12.30)	-31.98 (13.65)[2)b]	-37.64 (13.62)
Hs CRP[g] (mg/l)				
Baseline	2.04 (7.23)	1.27 (1.59)	1.23 (1.00)	1.22 (2.07)
Week 4	1.31 (2.33)	1.17 (1.30)	1.13 (1.45)	0.77 (0.73)
Week 8	0.94 (1.42)	0.94 (0.84)	1.12 (1.61)	0.87 (0.92)
% change from baseline				
Week 4	40.72 (285.2)	17.74 (89.54)	1.69 (62.44)	1.08 (67.30)
Week 8	-1.97 (117.7)	6.42 (102.4)	9.26 (106.3)	6.74 (96.45)

Note: Compared with Rosuvastatin 2.5mg +Ezetimibe 10mg
Note: 1) ANCOVA; 2) Wilcoxon rank-sum test;
[a] *P*: <0.05 vs Ezetimibe 10mg
[b] *P*:<0.01 vs Ezetimibe 10mg
[c] *P*: <0.05 vs Rosuvastatin 2.5mg
[d] *P*:<0.01 vs Rosuvastatin 2.5mg
[e] *P*: <0.05 vs Rosuvastatin 5mg
[f] *P*:<0.01 vs Rosuvastatin 5mg