Original Research

A Phase III, Multicenter, Randomized, Double-blind, Active Comparator Clinical Trial to Compare the Efficacy and Safety of Combination Therapy With Ezetimibe and Rosuvastatin Versus Rosuvastatin Monotherapy in Patients With Hypercholesterolemia: I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) Randomized Controlled Trial

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Accepted for publication December 22, 2017.
https://doi.org/10.1016/j.clinthera.2017.12.018
0149-2918/$ - see front matter

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ABSTRACT

Purpose: Combination therapy with ezetimibe and statins is recommended in cases of statin intolerance or insufficiency. The objective of this study was to compare the efficacy and safety of combination therapy with ezetimibe and rosuvastatin versus those of rosuvastatin monotherapy in patients with hypercholesterolemia.

Methods: I-ROSETTE (Ildong ROSuvastatin & ezETimibe for hypercholesTElolemia) was an 8-week, double-blind, multicenter, Phase III randomized controlled trial conducted at 20 hospitals in the Republic of Korea. Patients with hypercholesterolemia who required medical treatment according to National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for participation in the study. Patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg in a 1:1:1:1:1:1 ratio. The primary end point was the difference in the mean percent change from baseline in LDL-C level after 8 weeks of treatment between the ezetimibe/rosuvastatin and rosuvastatin treatment groups. All patients were assessed for adverse events (AEs), clinical laboratory data, and vital signs.

Findings: Of 396 patients, 389 with efficacy data were analyzed. Baseline characteristics among 6 groups were similar. After 8 weeks of double-blind treatment, the percent changes in adjusted mean LDL-C levels at week 8 compared with baseline values were –57.0% (2.1%) and –44.4% (2.1%) in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively ($P < 0.001$). The LDL-C–lowering efficacy of each of the ezetimibe/rosuvastatin combinations was superior to that of each of the respective doses of rosuvastatin. The mean percent change in LDL-C level in all ezetimibe/rosuvastatin combination groups was >50%. The number of patients who achieved target LDL-C levels at week 8 was significantly greater in the ezetimibe/rosuvastatin group (180 [92.3%] of 195 patients) than in the rosuvastatin monotherapy group (155 [79.9%] of 194 patients) ($P < 0.001$). There were no significant differences in the incidence of overall AEs, adverse drug reactions, and serious AEs; laboratory findings, including liver function test results and creatinine kinase levels, were comparable between groups.

Implications: Fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with rosuvastatin monotherapy. All groups treated with rosuvastatin and ezetimibe reported a decrease in mean LDL-C level >50%. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy. Clinical Trials.gov identifier: NCT02749994. (*Clin Ther.* 2018;40:226–241) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: ezetimibe, hypercholesterolemia, rosuvastatin, singe-pill combination.

INTRODUCTION

The American College of Cardiology/American Heart Association guide for the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults in 2013 recommended treatment with moderate- to high-intensity statins for patients with hypercholesterolemia.[1] However, some patients cannot attain LDL-C goals, even with maximal doses of a statin.[2] In addition, increasing the statin dose increases the risk

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of side effects in the liver and muscle. Those patients of Asian ethnicity experience more side effects from higher doses of statins because of variations in drug metabolism and clearance.[3,4] Consequently, Health Canada and the US Food and Drug Administration refer to individuals of Asian ethnicity as a higher risk group for statin-induced myopathy and recommend using a lower dose of statin for these individuals.[5,6] Moreover, adherence to statin therapy is generally poor.[7] Suboptimal adherence to statin therapy is a major barrier to achieving LDL-C targets.[8] Statin down-titration or discontinuation occurs more frequently among patients with statin intolerance. The European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guideline for the management of dyslipidemias in 2016 recommended combination therapy with statins and other lipid-lowering drugs in cases of statin intolerance or insufficiency.[9]

Ezetimibe inhibits cholesterol absorption from the small intestine.[10] Several studies have indicated that treatment with statins in combination with ezetimibe has significant LDL-C–lowering effects and prevents cardiovascular events.[11–13] Results of the Gauging the lipid effects of RosuvAstatin plus ezetimibe Versus sImvastatin plus ezetimibe TherapY (GRAVITY) (12-Week Open-label, Phase IIIb Comparing Efficacy and Safety of Rosuvastatin [CRESTOR™] in Combination With Ezetimibe) study indicated an additional LDL-C reduction of 13.2% when ezetimibe was coadministered with rosuvastatin.[14] Rosuvastatin is a cost-effective and efficient agent for the treatment of hypercholesterolemia compared with other statins, even in patients who are at a high risk for cardiovascular events.[15] Consequently, the addition of ezetimibe to rosuvastatin therapy was expected to result in good efficacy and safety. In addition, fixed-dose combinations of ezetimibe and rosuvastatin are expected to improve compliance in patients with hypercholesterolemia. The objective of the present double-blind, multicenter, randomized Phase III study was to compare the efficacy and safety of combination therapy with ezetimibe and rosuvastatin versus rosuvastatin monotherapy in patients with hypercholesterolemia.

PATIENTS AND METHODS

Study Patients

Korean men and women aged between 19 and 79 years with hypercholesterolemia requiring medical treatment according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines were eligible for participation in the study. After >4 weeks of therapeutic lifestyle changes, patients who fulfilled the following criteria were eligible: (1) patients with coronary artery disease or a 10-year cardiovascular disease (CVD) risk indicated by a Framingham risk score >20% with LDL-C levels ≥100 mg/dL; (2) patients with ≥2 major risk factors and a 10-year CVD risk ≤10% but ≤20% with LDL-C levels ≥130 mg/dL; (3) patients with ≥2 major risk factors and a 10-year CVD risk <10% with LDL-C levels ≥160 mg/dL; or (4) patients with ≤1 major risk factor and LDL-C levels ≥160 mg/dL; and (5) patients with a triglyceride (TG) level <400 mg/dL. Patients previously treated with lipid-modifying agents were included after a 6-week washout period. A total of 605 patients were screened for inclusion in the study. Patients (n = 209) who did not fulfill the inclusion criteria or who met any of the exclusion criteria were excluded. Eligible patients were included in the study from April 2016 through February 2017 (Figure 1).

Patients with known histories of statin-induced myopathy, rhabdomyolysis, or hypersensitivity to a statin or ezetimibe were excluded. Patients were also excluded if they had a history of alcohol abuse (>25 units per week), serum creatinine level ≥2.0 mg/dL, hepatic dysfunction with active liver diseases (serum aspartate or alanine aminotransferase levels more than twice the upper limit of normal), elevated creatinine phosphokinase level more than twice the upper limit of normal, uncontrolled diabetes mellitus (glycosylated hemoglobin value ≥9% or fasting blood glucose level ≥160 mg/dL), thyroid dysfunction (thyroid-stimulating hormone ≥1.5 times the upper limit of normal), or were HIV-positive. Patients with unstable angina pectoris, myocardial infarction, cerebrovascular disease, or percutaneous coronary intervention within the past 12 weeks were excluded. Patients were also excluded if they had uncontrolled hypertension, galactose intolerance, Lapp lactase deficiency, glucose-galactose malabsorption, a gastrointestinal disorder such as Crohn's disease, or malignancies. Pregnant women, breastfeeding women, and women of childbearing potential who were not using appropriate contraception were also excluded from the study. Patients with any condition that in the opinion of the investigator would make their participation in this study unsafe or unsuitable were excluded. Use of

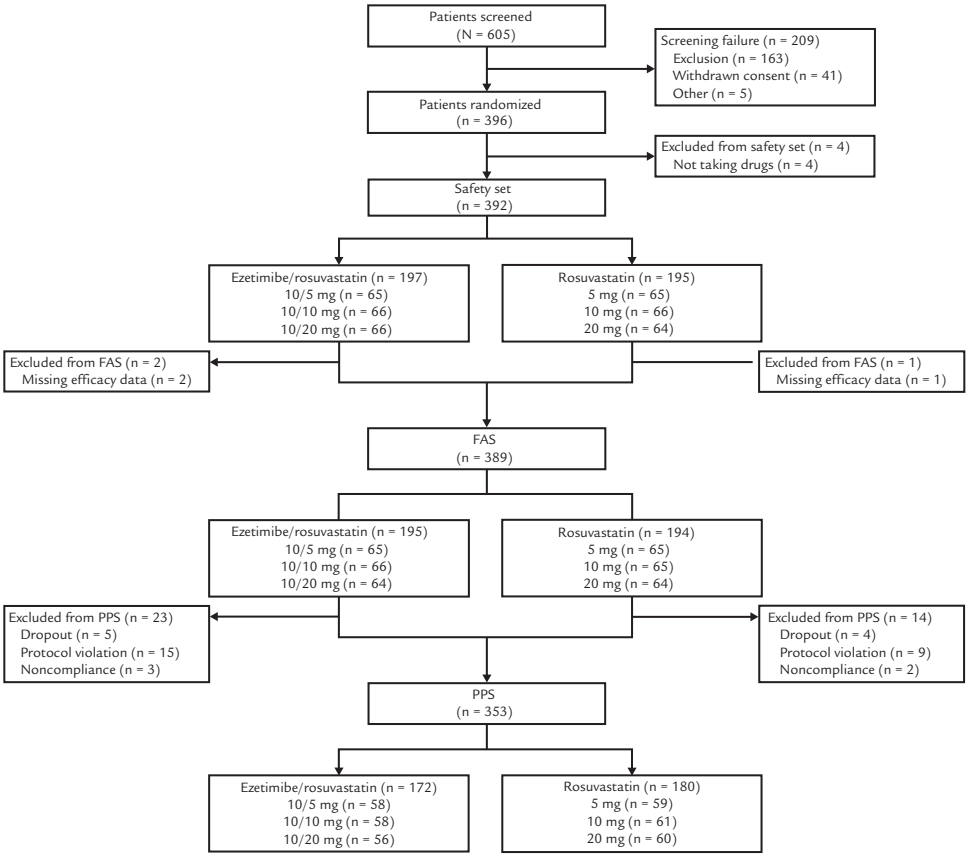

Figure 1. Study flow of the I-ROSETTE (Ildong Rosuvastatin & Ezetimibe for Hypercholesterolemia) randomized controlled trial. FAS = full analysis set; PPS = per-protocol set.

fibrates, niacin, bile acid sequestrants, oral steroids, antiobesity drugs, fish oil, cholestine, fiber-based laxatives, phytosterol margarines, warfarin, cyclosporine, macrolide, and antifungal drugs was not permitted during the study.

Study Design

I-ROSETTE was an 8-week, double-blind, multicenter, Phase III randomized controlled trial conducted at 20 sites in the Republic of Korea (see **Supplemental Table I** in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). During the 4-week run-in period, all patients were instructed to make therapeutic lifestyle changes (see the **Supplemental Figure** in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). At randomization (visit 2, day 0), patients were reevaluated to determine whether they still qualified with respect to the inclusion and exclusion criteria. Patients were randomly assigned to receive 1 of 6 treatments (ezetimibe 10 mg/rosuvastatin 20 mg, ezetimibe 10 mg/rosuvastatin 10 mg, ezetimibe 10 mg/rosuvastatin 5 mg, rosuvastatin 20 mg, rosuvastatin 10 mg, or rosuvastatin 5 mg) and were entered into the 8-week, double-blind treatment period (treatment period). The principal investigators at each center enrolled the patients and assigned the patients to the allocated intervention.

Patients were randomly and sequentially assigned to each treatment or control group in a 1:1:1:1:1:1 ratio by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina) with the stratified block randomization method. Stratification was performed according to NCEP ATP III risk, establishing 3 groups as follows: (1) patients with coronary artery disease or a 10-year CVD risk indicated by a Framingham risk score >20%; (2) patients with ≥2 major risk factors and a 10-year CVD risk ≤20%; or (3) patients with ≤1 major risk factor. Randomization was performed

via a web-based online randomization system. Allocation sequence was generated by an independent statist. All study personnel, including the investigators, study site personnel, participants, monitors, and central laboratory personnel, were blinded to the treatment allocation throughout the study. Doses were not adjusted during the 8-week treatment period, and participants in all groups received 5 tablets (1 real medicine, 1 placebo of different dose, and 3 matched placebos of the other drugs; Ildong Pharma Co, Seoul, the Republic of Korea) once every day to maintain double-blinding.

After the 8-week treatment period, patients who reached their target LDL-C level according to the NCEP ATP III guidelines were assigned to receive each corresponding dose of ezetimibe/rosuvastatin in the rosuvastatin monotherapy group or to continue the original dose of ezetimibe/rosuvastatin in the combination therapy group, and were treated over an additional 12 weeks (follow-up period) (see the **Supplemental Figure** in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). Ideally, participants should have a medication adherence of at least 80% throughout the trial, and those with a medication adherence $<80\%$ were considered to have poor adherence.

The study was approved by the institutional review board of each hospital, and written informed consent was obtained from all participants or their legal guardians before their inclusion in the study. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

End Points and Safety Assessment

The primary end point was to evaluate the efficacy of combination therapy with ezetimibe and rosuvastatin versus rosuvastatin monotherapy by comparing the mean percent change from baseline in LDL-C level after 8 weeks of treatment. The secondary end points were the mean percent change from baseline in the following: (1) total cholesterol (TC), TG, HDL-C, non–HDL-C, apolipoprotein (Apo) B, and Apo A1; (2) high-sensitivity C-reactive protein (hs-CRP); and (3) LDL-C/HDL-C, TC/HDL-C, non–HDL-C/HDL-C, and Apo B/Apo A1 after 4 and 8 weeks of treatment. In addition, the LDL-C control rate, which was defined as the percentage of patients who achieved the target LDL-C level according to their risk factors after 8 weeks of treatment, was compared. For the efficacy analysis, data from the full analysis set (FAS) population were used. The lipid profiles were analyzed in the central laboratory. The level of LDL-C was determined by enzymatic colorimetric assay using standard biochemical procedures on a DDP modular system (Roche, Switzerland).

Safety assessments included monitoring and recording all laboratory tests, vital signs, ECGs, adverse events (AEs), serious AEs, and possible association of AEs with the study drugs. For the safety assessments and follow-up period assessments, data from a safety set population were used. All laboratory tests, except lipid profiles and hs-CRP, were performed in the laboratory of each participating center during all periods of the study. Lipid profiles and hs-CRP were analyzed in the central laboratory. Adverse drug reactions (ADRs) were defined as drug-related AEs and classified as definitely related, probably related, possibly related, probably not related, or unknown to the study drugs. ADRs that were definitely not related to the study drugs were not considered drug-related AEs. Laboratory AEs were assessed by comparing baseline laboratory values with those at follow-up. The severity of AEs was classified as mild for mild symptoms or signs not affecting activities of daily living; moderate for minor limitations in daily living activities; and severe for marked limitations in daily living activities. The investigators at each center decided whether patients with drug-related AEs should be withdrawn from the study.

Statistical Analysis

Data are expressed as mean (SD) for the continuous variables and as number and percentage of patients for the categorical variables. Pearson's χ^2 test or Fisher's exact test was used to analyze categorical variables and independent 2-sample t tests or Wilcoxon's rank sum test was used to analyze continuous variables. The effects of the treatments on the primary and secondary end points were compared by using ANCOVA, which included treatment and stratified factors of CVD risks according to the NCEP ATP III guidelines, with the relevant baseline value as a covariate. End points were expressed as least-squares mean (SE) for the continuous variables. The LDL-C control rate was analyzed by using the

Table I. Demographic and baseline clinical characteristics of the study patients (full analysis set).

Variable	Ezetimibe/Rosuvastatin 10/5 mg (n = 65)	Ezetimibe/Rosuvastatin 10/10 mg (n = 66)	Ezetimibe/Rosuvastatin 10/20 mg (n = 64)	Ezetimibe/Rosuvastatin Total (N = 195)	Rosuvastatin 5 mg (n = 65)	Rosuvastatin 10 mg (n = 65)	Rosuvastatin 20 mg (n = 64)	Rosuvastatin Total (N = 194)
Demographic								
Age, mean (SD), y	63.3 (9.0)	62.5 (8.9)	61.6 (10.7)	62.5 (9.5)	62.4 (9.3)	63.3 (8.6)	64.2 (8.3)	63.3 (8.7)
Male	41 (63.1%)	39 (59.1%)	39 (60.9%)	119 (61.0%)	40 (61.5%)	46 (70.8%)	40 (62.5%)	126 (65.0%)
BMI, mean (SD), kg/m^2	25.2 (2.8)	26.3 (4.3)	25.0 (2.5)	25.5 (3.4)	25.9 (3.7)	25.4 (2.8)	25.0 (3.2)	25.4 (3.3)
Medical history								
Hypertension	38 (58.5%)	50 (75.8%)	39 (60.9%)	127 (65.1%)	44 (67.7%)	49 (75.4%)	45 (70.3%)	138 (71.1%)
Unstable angina	15 (23.1%)	8 (12.1%)	13 (20.3%)	36 (18.5%)	5 (7.7%)	6 (9.2%)	8 (12.5%)	19 (9.8%)
Myocardial infarction	10 (15.4%)	6 (9.1%)	6 (9.4%)	22 (11.3%)	14 (21.5%)	10 (15.4%)	9 (14.1%)	33 (17.0%)
Diabetes mellitus	20 (30.8%)	25 (37.9%)	14 (21.9%)	59 (30.3%)	26 (40.0%)	24 (36.9%)	21 (32.8%)	71 (36.6%)
Previous medications								
Statin	45 (69.2%)	48 (72.7%)	36 (56.3%)	129 (66.2%)	48 (73.8%)	46 (70.8%)	42 (65.6%)	136 (70.1%)
Fibrate	0	1 (1.5%)	2 (3.1%)	3 (1.5%)	2 (3.1%)	0	0	2 (1.0%)
Bile acid sequestrant	0	0	0	0	0	0	0	0
Nicotinic acid	0	0	0	0	0	0	0	0
Combination (statin + other)	3 (4.6%)	3 (4.5%)	5 (7.8%)	11 (5.6%)	3 (4.6%)	3 (4.6%)	2 (3.1%)	8 (4.1%)
Other	3 (4.6%)	1 (1.5%)	2 (3.1%)	6 (3.1%)	2 (3.1%)	2 (3.1%)	1 (1.6%)	5 (2.6%)
Lipid profiles, mean (SD)								
LDL-C, mg/dL	160.7 (40.6)	146.5 (28.4)	153.5 (31.2)	153.5 (34.1)	156.1 (33.5)	146.0 (33.4)	152.8 (31.4)	151.6 (32.9)
Total cholesterol mg/dL	234.1 (45.6)	219.6 (36.5)	227.8 (33.9)	227.1 (39.3)	230.8 (36.5)	218.0 (38.4)	226.1 (37.3)	225.0 (37.6)
Triglycerides, mg/dL	152.0 (65.2)	161.3 (67.5)	165.3 (71.3)	159.5 (67.9)	173.2 (80.3)	148.6 (65.8)	145.5 (70.9)	155.8 (73.3)
HDL-C, mg/dL	49.6 (13.3)	45.5 (9.9)	49.1 (13.4)	48.1 (12.4)	47.4 (10.1)	49.1 (12.9)	51.4 (14.2)	49.3 (12.5)
Non–HDL-C, mg/dL	184.5 (42.8)	174.1 (34.8)	178.7 (31.1)	179.1 (36.7)	183.3 (35.8)	168.8 (35.9)	174.8 (34.0)	175.6 (35.6)
Apolipoprotein B, mg/dL	132.0 (30.6)	125.6 (25.6)	126.9 (19.6)	128.5 (25.7)	131.6 (24.5)	123.3 (24.8)	125.7 (23.5)	126.9 (24.4)
Apolipoprotein A1, mg/dL	138.1 (23.0)	133.3 (20.2)	139.5 (24.4)	136.9 (22.6)	136.3 (20.0)	138.3 (22.6)	140.0 (23.9)	138.2 (22.2)
Patients by CHD risk factors								
CHD/CHD risk equivalents (10-y risk >20%)	54 (83.1%)	55 (83.4%)	54 (84.4%)	163 (83.6%)	55 (84.6%)	53 (81.5%)	54 (84.4%)	162 (83.5%)
Risk factors ≥2 (10% ≤10-y risk ≤20%)	3 (4.6%)	2 (3.0%)	3 (4.1%)	8 (4.1%)	2 (3.1%)	5 (7.7%)	1 (1.6%)	8 (4.1%)

(continued)

Table I. (continued).

Variable	Ezetimibe/Rosuvastatin				Rosuvastatin			
	10/5 mg (n = 65)	10/10 mg (n = 66)	10/20 mg (n = 64)	Total (N = 195)	5 mg (n = 65)	10 mg (n = 65)	20 mg (n = 64)	Total (N = 194)
Risk factors ≥2 (10-y risk < 10%)	1 (1.5%)	3 (4.6%)	1 (1.6%)	5 (2.6%)	2 (3.1%)	1 (1.5%)	3 (4.7%)	6 (3.1%)
Risk factors 0–1	7 (10.8%)	6 (9.1%)	6 (9.4%)	19 (9.7%)	6 (9.2%)	6 (9.2%)	6 (9.4%)	18 (9.3%)

BMI = body mass index; CHD = coronary heart disease.

Cochran-Mantel-Haenszel test. The FAS included all randomized patients who received at least 1 dose of the double-blind study medication and provided at least 1 LDL-C measurement after randomization.

This trial was a combination therapy study to verify the superiority of ezetimibe/rosuvastatin treatment in terms of percent change in LDL-C level (from baseline to week 8) over rosuvastatin alone for each rosuvastatin dose (5, 10, and 20 mg) and in total. Overall statistical power for the whole hypothesis was set to 80%, and the 2-sided significance level of each hypothesis was set to 5%. The statistical power for each hypothesis was set to 95% without adjusting for multiplicity. The sample size of the study was determined based on the estimation of mean percent changes of LDL-C level obtained in previous trials.[16–18] We assumed that the mean percent change in LDL-C level after adding ezetimibe would be 10.5% (14.9%). Required sample sizes were at least 53 patients per group. A total of 354 patients (59 patients each for 6 groups) were considered to meet the sample size cutoff, working under the assumption of a 10% dropout rate. P values <0.05 were considered statistically significant. SAS software was used for statistical analysis.

RESULTS

Patient Disposition and Baseline Characteristics

A total of 605 patients were screened at the beginning of the study, and 209 patients who failed to meet the inclusion criteria were excluded before the run-in treatment period. A total of 396 patients were randomly assigned to receive ezetimibe 10 mg/rosuvastatin 20 mg (n = 67), ezetimibe 10 mg/rosuvastatin 10 mg (n = 67), ezetimibe 10 mg/rosuvastatin 5 mg (n = 65), rosuvastatin 20 mg (n = 65), rosuvastatin 10 mg (n = 66), or rosuvastatin 5 mg (n = 66) (**Figure 1**). Of the randomized patients, 16 dropped out, and the remaining 380 patients completed the treatment period. During the follow-up period, an additional 9 patients dropped out (see the **Supplemental Figure** in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). After excluding 4 patients who had not taken any study drugs among the enrolled 396 patients, 392 were analyzed for safety parameters. For efficacy parameters, 389 patients excluding 3 patients whose lipid profile had never been measured during the trial were analyzed as an FAS.

Table II. Percent changes from baseline in LDL-C levels after treatment with ezetimibe/rosuvastatin combination therapy and rosuvastatin monotherapy in patients with hypercholesterolemia.

Variable	Ezetimibe/ Rosuvastatin 10/5 mg (n = 65)	Rosuvastatin 5 mg (n = 65)	Ezetimibe/ Rosuvastatin 10/10 mg (n = 66)	Rosuvastatin 10 mg (n = 65)	Ezetimibe/ Rosuvastatin 10/20 mg (n = 64)	Rosuvastatin 20 mg (n = 64)	Ezetimibe/ Rosuvastatin, Total (N = 195)	Rosuvastatin, Total (N = 194)
Baseline								
Mean (SD)	160.7 (40.6)	156.1 (33.5)	146.5 (28.4)	146.0 (33.4)	153.5 (31.2)	152.8 (31.4)	153.5 (34.1)	151.6 (32.9)
Median	160.0	156.0	146.5	138.0	148.5	148.0	150.0	145.5
Minimum, maximum	101.0, 251.0	103.0, 259.0	101.0, 211.0	102.0, 229.0	104.0, 247.0	103.0, 232.0	101.0, 251.0	102.0, 259.0
4-Week follow-up								
Mean (SD)	72.8 (27.9)	93.0 (27.3)	67.2 (30.4)	77.5 (27.7)	53.5 (22.0)	75.2 (29.5)	64.5 (28.1)	81.9 (29.1)
Median	69.0	92.0	60.0	73.0	46.5	71.0	61.0	75.5
Minimum, maximum	29.0, 180.0	47.0, 176.0	28.0, 157.0	37.0, 177.0	19.0, 129.0	27.0, 195.0	19.0, 180.0	27.0, 195.0
Percent changes from baseline at 4 weeks								
Mean (SD)	–54.0 (16.7)	–39.8 (15.0)	–53.9 (19.6)	–46.6 (15.0)	–64.6 (13.9)	–50.3 (19.7)	–57.5 (17.6)	–45.5 (17.2)
Median	–58.1	–44.3	–59.8	–50.9	–67.2	–55.3	–62.2	–49.6
Minimum, maximum	–77.7, 22.9	–62.3, 4.8	–77.4, 5.6	–73.6, 5.3	–85.7, –27.1	–79.2, 58.5	–85.7, 22.9	–79.2, 58.5
Adjusted mean (SE)	–55.0 (2.9)	–41.2 (2.9)	–52.3 (3.2)	–45.0 (3.1)	–65.3 (3.2)	–51.0 (3.2)	–57.7 (1.8)	–45.9 (1.8)
P	<0.001		0.020		<0.001		<0.001	
8-Week follow–up								
Mean (SD)	76.9 (34.6)	92.0 (26.2)	62.9 (31.3)	78.5 (28.1)	53.1 (22.0)	75.4 (34.0)	64.4 (31.3)	82.0 (30.3)
Median	68.0	90.0	58.0	75.0	49.0	67.5	57.0	75.0
Minimum, maximum	24.0, 198.0	46.0, 161.0	23.0, 186.0	32.0, 210.0	26.0, 149.0	24.0, 257.0	23.0, 198.0	24.0, 257.0
Percent changes from baseline at 8 weeks								
Mean (SD)	–51.6 (19.5)	–39.9 (18.2)	–57.1 (18.5)	–45.7 (16.1)	–64.4 (15.5)	–49.2 (27.1)	–57.7 (18.6)	–44.9 (21.2)
Median	–56.6	–43.2	–61.4	–49.6	–69.7	–55.4	–61.5	–49.7
Minimum, maximum	–80.8, 19.3	–69.8, 31.0	–82.7, 6.0	–70.7, 5.0	–82.6, –7.1	–81.5,108.9	–82.7, 19.3	–81.5,108.9
Adjusted mean (SE)	–51.8 (3.4)	–40.5 (3.4)	–55.8 (3.2)	–44.4 (3.1)	–62.2 (4.1)	–47.1 (4.1)	–57.0 (2.1)	–44.4 (2.1)
P	<0.001		<0.001		<0.001		<0.001	

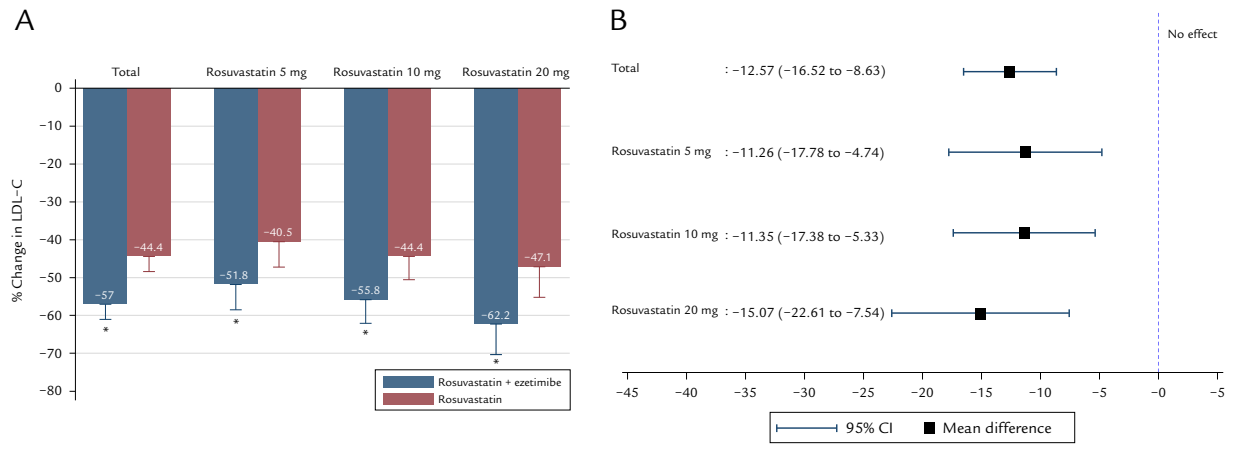

Figure 2. (A) Least squares mean percent change in LDL-C after 8 weeks of treatment with ezetimibe/rosuvastatin and rosuvastatin. (B) Forest plot with mean differences in LDL-C between groups. *$P < 0.001$ versus rosuvastatin group.

The demographic and baseline clinical characteristics of patients in each of the treatment groups are summarized in Table I. The baseline patient characteristics of sex, mean age, weight, height, diabetes mellitus, and medications on admission were similar between groups. No significant differences were found between the groups in the baseline lipid profiles. Mean drug compliance for ezetimibe/rosuvastatin combinations and rosuvastatin monotherapy was 95.3% (11.5%) and 96.2% (7.1%), respectively.

Table III. Percent changes from baseline in lipid profiles after treatment with ezetimibe/rosuvastatin combination therapy and rosuvastatin monotherapy in patients with hypercholesterolemia. Values are given as mean (SE).

Variable	Ezetimibe/Rosuvastatin (n = 195)	Rosuvastatin (n = 194)	Difference	95% CI for Difference	*P*
At 4-week follow-up					
LDL-C, mg/dL	−57.7 (1.8)	−45.9 (1.8)	−11.8 (1.8)	−15.3 to −8.4	<0.001
Total cholesterol mg/dL	−39.0 (1.3)	−30.8 (1.3)	−8.2 (1.2)	−10.7 to −5.8	<0.001
Triglycerides, mg/dL	−19.5 (3.7)	−12.7 (3.7)	−6.8 (3.8)	−14.2 to 0.6	0.072
HDL-C, mg/dL	12.6 (1.7)	10.2 (1.8)	2.4 (1.7)	−1.0 to 5.9	0.162
Non–HDL-C, mg/dL	−53.2 (1.7)	−42.4 (1.6)	−10.8 (1.6)	−14.0 to −7.6	<0.001
Apolipoprotein B, mg/dL	−47.8 (1.4)	−38.4 (1.4)	−9.5 (1.4)	−12.2 to −6.7	<0.001
Apolipoprotein A1, mg/dL	7.7 (1.1)	7.1 (1.1)	0.6 (1.1)	−1.6 to 2.9	0.584
At 8-week follow-up					
LDL-C, mg/dL	−57.0 (2.1)	−44.4 (2.1)	−12.6 (2.0)	−16.5, to −8.6	<0.001
Total cholesterol mg/dL	−38.8 (1.4)	−30.2 (1.4)	−8.6 (1.4)	−11.3 to −5.8	<0.001
Triglycerides, mg/dL	−19.2 (3.2)	−11.9 (3.2)	−7.3 (3.2)	−13.7 to −1.0	0.024
HDL-C, mg/dL	13.6 (1.8)	11.3 (1.8)	2.3 (1.8)	−1.2 to 5.9	0.200
Non–HDL-C, mg/dL	−53.2 (1.9)	−42.2 (1.8)	−11.1 (1.8)	−14.6 to −7.5	<0.001
Apolipoprotein B, mg/dL	−46.7 (1.5)	−37.7 (1.5)	−8.9 (1.5)	−11.9 to −5.9	<0.001
Apolipoprotein A1, mg/dL	9.6 (1.2)	9.1 (1.2)	0.4 (1.2)	−2.0 to 2.8	0.736

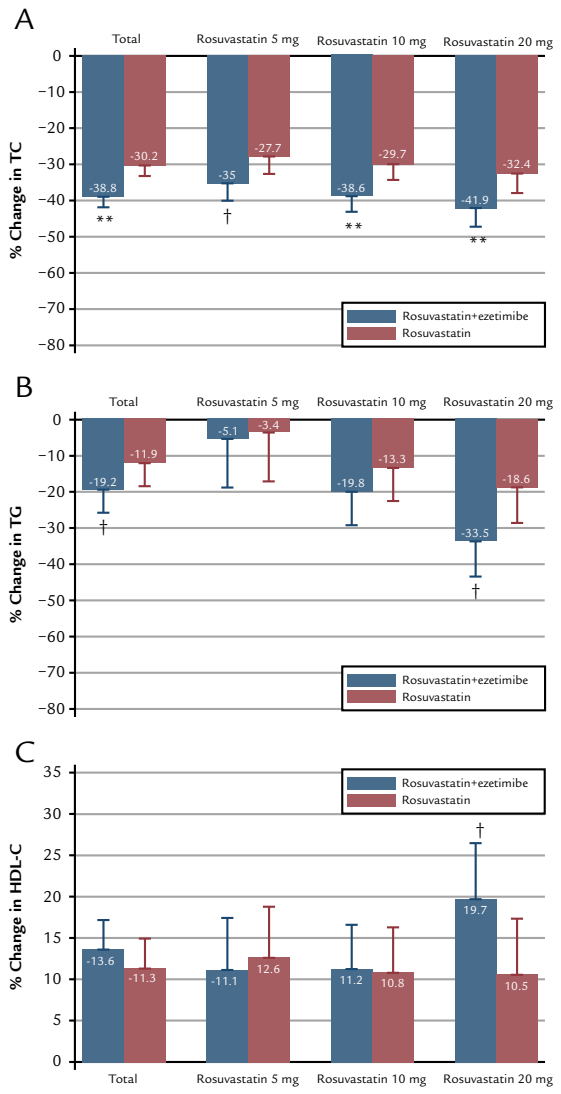

Figure 3. Least squares (LS) mean percent change in other lipid profiles after 8 weeks of treatment with ezetimibe/rosuvastatin and rosuvastatin. (A) LS mean percent change in TC; (B) LS mean percent change in TG; and (C) LS mean percent change in HDL-C. TC = total cholesterol; TG = triglycerides. $^{*}P < 0.001$, $^{\dagger}P < 0.05$ versus rosuvastatin group.

Efficacy

After 8 weeks of double-blind treatment, the percent changes in adjusted mean LDL-C level at 8 weeks compared with baseline values were –57.0% (2.1%) and –44.4% (2.1%) in the total ezetimibe/rosuvastatin and total rosuvastatin groups, respectively (Table II and Figure 2). Treatment with ezetimibe/rosuvastatin resulted in a statistically greater lipid-lowering effect compared with treatment with rosuvastatin alone (differences, –12.6 mg/dL [95% CI, –16.5 to –8.6]; $P < 0.001$). The LDL-C–lowering efficacy of each dose of ezetimibe/rosuvastatin combination therapy was superior to that of the corresponding dose of rosuvastatin alone. In the heterogeneity analysis, significant heterogeneity according to rosuvastatin dose was found (see Supplemental Table II in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). The mean percent reductions in LDL-C level in all ezetimibe/rosuvastatin combination groups were >50% from baseline. Treatment with combination therapy reduced LDL-C levels by –51.8% (3.4%), –55.8% (3.2%), and –62.2% (4.1%) in the 10/5 mg, 10/10 mg, and 10/20 mg ezetimibe/rosuvastatin combination groups, respectively.

The percent changes in TC, TG, non–HDL-C, and Apo B were also greater in the total ezetimibe/rosuvastatin group than in the total rosuvastatin alone group (Table III and Figures 3A–3C). The changes in HDL-C and Apo A1 levels were not significantly different between the combination and monotherapy groups. The changes after 4 and 8 weeks in hs-CRP were similar between the combination and monotherapy groups (see Supplemental Table III in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018). The number of patients who achieved their target LDL-C level at week 8 was significantly greater in the total ezetimibe/rosuvastatin group (180 [92.3%] of 195 patients) than in the total rosuvastatin monotherapy group (155 [79.9%] of 194 patients) ($P < 0.001$) (Table IV and Figure 4).

Safety

Among the 392 patients in the safety profile set, 44 (11.2%) experienced at least 1 AE after randomization (Table V). The most common AEs were gastrointestinal disorders, followed by investigations and musculoskeletal and connective tissue disorders. There were no significant differences in the overall incidence of AEs, ADRs, or serious AEs. Laboratory findings, including liver function test results and creatinine kinase levels, were comparable

Table IV. Rate of achievement of LDL-C target. Values are given as no. (%).

Variable	Ezetimibe/ Rosuvastatin 10/5 mg (n = 65)	Rosuvastatin 5 mg (n = 65)	Ezetimibe/ Rosuvastatin 10/10 mg (n = 66)	Rosuvastatin 10 mg (n = 65)	Ezetimibe/ Rosuvastatin 10/20 mg (n = 64)	Rosuvastatin 20 mg (n = 64)	Ezetimibe/ Rosuvastatin, Total (N = 195)	Rosuvastatin, Total (N = 194)
Total no. of patients achieving LDL-C goal	56 (86.2)	44 (67.7)	62 (93.9)	58 (89.2)	62 (96.9)	53 (82.8)	180 (92.3)	155 (79.9)
Patients according to CHD risk factors								
CHD/CHD risk equivalents (10-y risk >20%)	46 (85.2)	34 (61.8)	52 (94.5)	48 (90.6)	52 (96.3)	44 (81.5)	150 (92.0)	126 (77.8)
Risk factors ≥2 (10%≤10-y risk ≤20%	2 (66.7)	2 (100.0)	2 (100.0)	5 (100.0)	3 (100.0)	0	7 (87.5)	7 (87.5)
Risk factors ≥2 (10-y risk <10%)	1 (100.0)	2 (100.0)	3 (100.0)	0	1 (100.0)	3 (100.0)	5 (100.0)	5 (83.3)
Risk factors 0–1	7 (100.0)	6 (100.0)	5 (83.3)	5 (83.3)	6 (100.0)	6 (100.0)	18 (94.7)	17 (94.4)

CHD = coronary heart disease.

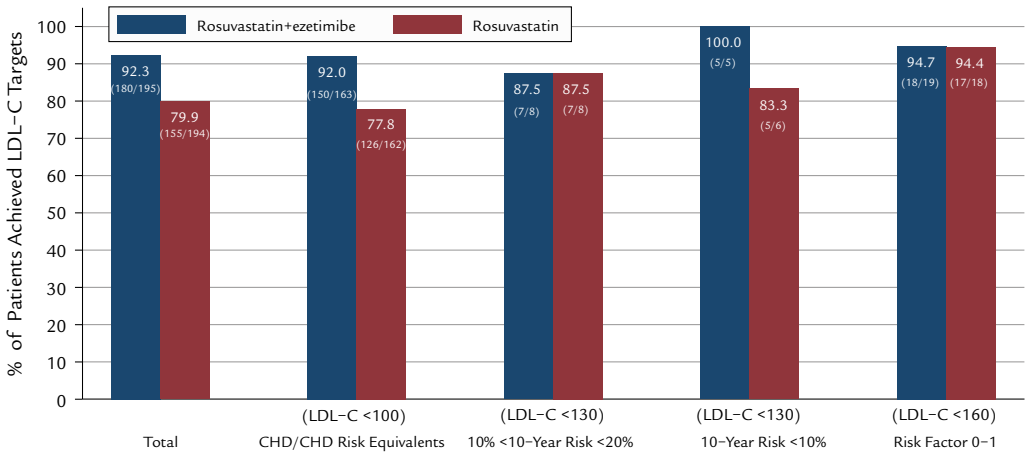

Figure 4. LDL-C target achievement rates in subgroups. The LDL-C target in patients with coronary heart disease (CHD)/CHD risk equivalents (10-year risk >20%) was <100 mg/dL; with risk factors ≥2 (10% ≤10-year risk ≤20%), it was <130 mg/dL; with risk factors ≥2 (10-year risk <10%), it was <130 mg/dL; and with risk factors 0 to 1, it was <160 mg/dL.

between groups. No patients in the ezetimibe/rosuvastatin group dropped out because of AEs.

DISCUSSION

This confirmatory clinical trial compared the efficacy and safety of combination therapy with ezetimibe and rosuvastatin versus rosuvastatin monotherapy in patients with hypercholesterolemia. In this multicenter, randomized, double-blind, Phase III study, the addition of ezetimibe to rosuvastatin found significantly reduced LDL-C levels compared with the respective rosuvastatin monotherapy, with no increase in overall AEs. Remarkably, more patients treated with the combination of ezetimibe and rosuvastatin achieved their LDL-C target during the 8-week follow-up.

Intensive statin therapy in previous studies efficiently lowered LDL-C levels and improved cardiovascular outcomes.[11] Nevertheless, suboptimal statin therapy owing to reduced compliance has been problematic.[19] In real-world data, adherence to statin therapy is only 55% to 60%, even over short-term follow-up periods.[20] One reason for such a low compliance rate are the side effects of intensive statin therapy. Although intensive statin therapy reduced cardiovascular events, it increased the risk of statin-related AEs.[21] Common side effects caused by statins include asymptomatic elevated liver enzyme levels and creatinine kinase, pruritus, rash, gastrointestinal discomfort, and statin-related myopathy.[22] The incidence of muscle-related adverse reactions from statin therapy was reported to be up to 15%.[23] Intensive statin therapy significantly increased AEs requiring discontinuation of therapy, the risk of abnormal liver function test results, and the incidence of myopathy.[24]

Because intensive statin therapy provoked statin intolerance, low compliance, or statin insufficiency, the use of additional lipid-modifying therapies has been required.[25] In a previous study, combination therapy with ezetimibe and a statin significantly lowered LDL-C levels and improved cardiovascular outcomes compared with statin monotherapy.[26] The addition of ezetimibe to a moderate-dose statin is likely to result in 17 fewer myocardial infarctions and 6 fewer strokes per 1000 treated patients over 6 years.[27] In this study, the mean percent change in LDL-C level at 8 weeks was >50% for all doses of ezetimibe/rosuvastatin combination therapy. According to the 2016 ESC/EAS guideline for management of dyslipidemia, a reduction in LDL-C level of at least 50% is recommended in patients with more than high risk.[9] We have therefore shown that combination therapy with ezetimibe and rosuvastatin could effectively decrease LDL-C levels in high-risk patients according to the current updated guideline. In addition, lower doses of statin combined with ezetimibe showed effective LDL-C–lowering efficacy equivalent to that of intensive statin therapy and did not increase AEs,

Table V. Summary of adverse events (AEs) and frequency of drug-related AEs experienced by ≥2% of patients in any 1 of the treatment groups in the treated set. Values are given as no. (%) of patients reporting an AE.

	Ezetimibe/Rosuvastatin				Rosuvastatin				
AE	10/5 mg (n = 65)	10/10 mg (n = 66)	10/20 mg (n = 66)	Total (N = 197)	5 mg (n = 65)	10 mg (n = 66)	20 mg (n = 64)	Total (N = 195)	*P*
All AEs	6 (9.2)	4 (6.1)	12 (18.2)	22 (11.2)	11 (16.9)	5 (7.6)	6 (9.4)	22 (11.3)	0.971[*]
Drug-related	4 (6.2)	2 (3.0)	5 (7.6)	11 (5.6)	0	2 (3.0)	4 (6.3)	6 (3.1)	0.223[*]
Serious	1 (1.5)	0	0	1 (0.5)	0	1 (1.5)	0	1 (0.5)	0.999[†]
Serious drug-related	0	0	0	0	0	1 (1.5)	0	1 (0.5)	0.497[†]
Deaths	0	0	0	0	0	0	0	0	NA
Discontinuation due to AEs	0	0	0	0	0	1 (1.5)	1 (1.6)	2 (1.0)	0.247[†]
Drug-related	0	0	0	0	0	1 (1.5)	1 (1.6)	2 (1.0)	0.247[†]
Serious	0	0	0	0	0	1 (1.5)	0	1 (0.5)	0.497[†]
Serious drug-related	0	0	0	0	0	1 (1.5)	0	1 (0.5)	0.497[†]
AEs occurring in ≥2% of patients									
Gastrointestinal disorders	0	2 (3.0)	4 (6.1)	6 (3.0)	0	1 (1.5)	0	1 (0.5)	0.121[†]
Investigations	1 (1.5)	1 (1.5)	3 (4.6)	5 (2.5)	1 (1.5)	0	1 (1.6)	2 (1.0)	0.449[†]
Infections and infestations	0	1 (1.5)	0	1 (0.5)	4 (6.2)	0	1 (1.6)	5 (2.6)	0.121[†]
Musculoskeletal and connective tissue disorders	1 (1.5)	0	3 (4.6)	4 (2.0)	0	0	1 (1.6)	1 (0.5)	0.372[†]
Nervous system disorders	1 (1.5)	0	1 (1.5)	2 (1.0)	3 (4.6)	1 (1.5)	1 (1.6)	5 (2.6)	0.283[†]
Skin and subcutaneous tissue disorders	1 (1.5)	0	1 (1.5)	2 (1.0)	1 (1.5)	1 (1.5)	0 (0.0)	2 (1.0)	0.999[†]
Liver function test results ≥3 × ULN									
Alanine aminotransferase	0	0	1 (1.7)	1 (0.6)	0	0	0	0	0.499[†]
Aspartate aminotransferase	0	0	1 (1.7)	1 (0.6)	0	0	0	0	0.489[†]
Creatine kinase ≥5 × ULN	0	0	0	0	0	0	0	0	NA

NA = not available; ULN = upper limit of normal.
[*]Per the χ^2 test.
[†]Fisher's exact test compared pooled data of ezetimibe/rosuvastatin versus pooled data of rosuvastatin.

which was consistent with previous studies.[28–30] Another study also found greater LDL-C–lowering efficacy and similar safety profiles of rosuvastatin 5 or 10 mg combined with ezetimibe than those of rosuvastatin 10 or 20 mg monotherapy.[31]

In previous research, administration of ezetimibe and rosuvastatin increased the target LDL-C goal from 67% to 96%.[32] In our study, the target achievement rate increased from 86.2% to 96.9% in accordance with the increases in rosuvastatin doses. This rate is relatively higher than that of other studies performed in the Republic of Korea and of that in non-Asian subjects.[14,31] In patients with a high risk for CVD, the 2016 ESC/EAS guideline recommended treatment with a statin in combination with a cholesterol absorption inhibitor or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor. However, ezetimibe is considered as the first add-on therapy to a statin for achieving the LDL-C target goal until now, and the economic burden of treatment with ezetimibe is lower than with a PCSK9 inhibitor.[32] From these findings, combination therapy with ezetimibe and rosuvastatin effectively lowered LDL-C levels and contributed to a reduction in subsequent adverse cardiovascular events.

The combination of rosuvastatin and ezetimibe may have a safety advantage regarding statin-related side effects compared with the equivalent dose of other statins owing to variations in their metabolism. Statins, including atorvastatin and simvastatin, are primarily metabolized by hepatic cytochrome P450 (CYP) enzymes, especially CYP3A4/5. Many other drugs are also metabolized by hepatic CYP and, therefore, when administered together with statins, they could potentially cause drug-related AEs. However, rosuvastatin is not significantly metabolized by CYP3A4 and is partially metabolized by CYP2C9. Unmetabolized drug is excreted via the bile into the feces, thereby reducing the potential for drug–drug interactions.[33] Ezetimibe is also not metabolized by CYP and has no known significant drug–drug interactions. Consequently, the combination of rosuvastatin and ezetimibe causes few drug–drug interactions, which contributes to the low incidence of AEs.[34] Until now, safety data of the combination of rosuvastatin have scarcely included Asian patients. One study reported that the incidence of AEs after addition of ezetimibe to statin therapy was 40% for total AEs.[35] However, administration of a single-pill combination with ezetimibe and rosuvastatin, even high-dose rosuvastatin with ezetimibe, did not increase AEs but did lower LDL-C levels by an additional 15% in this study. Although there is no report of a direct comparison with other combination lipid-lowering therapies, our study suggests that the single-pill ezetimibe/rosuvastatin combination was advantageous because of its tolerability, efficacy, and safety profiles. In addition, we found that all doses of rosuvastatin combined with ezetimibe lowered mean LDL-C levels $>50\%$ from baseline. Because statin intolerance and statin insufficiency are major hindrances to achieving LDL-C target goals, tolerable and efficient lipid-lowering combination therapy is essential in clinical practice. In this regard, fixed-dose, single-pill combinations of ezetimibe and rosuvastatin may have the additional benefit of improving drug adherence. Therefore, ezetimibe/rosuvastatin combination therapy could play a major role in lowering LDL-C levels in patients with hypercholesterolemia.

CONCLUSIONS

Treatment with fixed-dose combinations of ezetimibe/rosuvastatin significantly improved lipid profiles in patients with hypercholesterolemia compared with treatment with rosuvastatin alone. In all groups treated with a rosuvastatin/ezetimibe combination, mean LDL-C levels were reduced by $>50\%$. The safety and tolerability of ezetimibe/rosuvastatin therapy were comparable with those of rosuvastatin monotherapy.

ACKNOWLEDGEMENTS

SJ Hong and HS Jeong wrote the manuscript, analyzed data and created figures. SJ Hong, JC Ahn, DH Cha, KH Won, W Kim, SK Cho, SY Kim, BS Yoo, KC Sung, SW Rha, JH Shin, KR Han, WS Chung, MS Hyon, HC Lee, JH Bae, MY Rhee, J Kwan, DW Jeon, and KD Yoo contributed to collecting and analyzing clinical data. HS Kim contributed to study design and collected and analyzed clinical data.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest of grants, honoraria, consultancies, speakers' bureau or advisory-board positions, or significant stock holdings received from industry or organizations regarding the content of this article.

The sponsor supported the supply of the investigational products, laboratory tests, and clinical research coordinator expenses.

SUPPLEMENTARY MATERIAL

Supplemental tables and a figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clinthera.2017.12.018.

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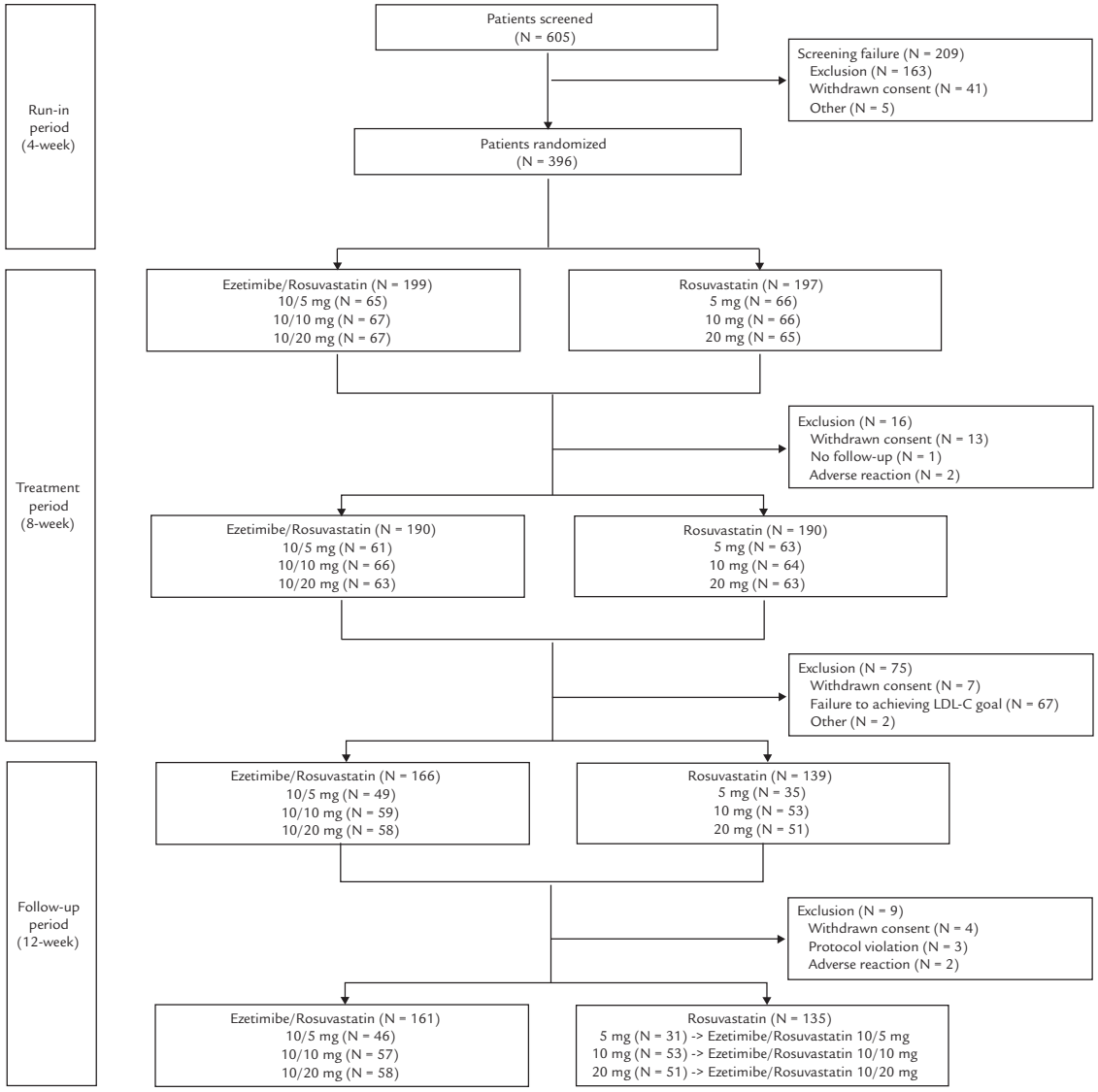
SUPPLEMENTARY MATERIAL

Supplemental Figure.



Supplemental Figure. Study protocol of I-ROSETTE RCT (Ildong ROSuvastatin & ezETimibe for hypercholesTElolemia Randomized Clinical Trial).

Supplemental Table I–III.

Supplemental Table I. List of centers, local PI, and the number of patients recruited at each center.

No.	Principal investigator	Affiliation	Enrolled patients
1	Soon Jun Hong	Department of Cardiology, Cardiovascular Center, Korea University Anam Hospital, Seoul, Republic of Korea	65
2	Hyo-Soo Kim	Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea.	59
3	Jeong Cheon Ahn	Division of Cardiology, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Korea.	58
4	Dong-Hun Cha	Division of Cardiology, Department of Internal Medicine, Bundang CHA Hospital, CHA University College of Medicine, Seongnam, Korea.	36
5	Kyung Heon Won	Division of Cardiology, Department of Internal Medicine, Seoul Medical Center, Seoul, Korea	34
6	Weon Kim	Cardiovascular Department of Internal Medicine, Kyung Hee University Hospital, Seoul, Korea.	25
7	Sang Kyoon Cho	Division of Cardiology, Department of Internal Medicine, Bundang Jesaeng Hospital, Seongnam, Korea.	18
8	Seok-Yeon Kim	Division of Cardiology, Department of Internal Medicine, Seoul Medical Center, Seoul, Korea	16
9	Byung-Su Yoo	Division of Cardiology, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea	15
10	Ki Chul Sung	Division of Cardiology, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea	14
11	Seung-Woon Rha	Cardiovascular Center, Korea University Guro Hospital, Seoul, Korea	9
12	Joon-Han Shin	Department of Cardiology, Ajou University Medical Center, Suwon, Korea.	9
13	Kyoo Rok Han	Division of Cardiology, Department of Internal Medicine, Kangdong Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, Korea.	9
14	Wook Sung Chung	Division of Cardiology, Department of Internal Medicine, The catholic University, Seoul, Korea.	8
15	Min Su Hyon	Division of Cardiology, Department of Internal Medicine, Soonchunhyang University Hospital, Seoul, Korea	7
16	Han Cheol Lee	Division of Cardiology, Department of Internal Medicine, Medical Research Institute, Pusan National University Hospital, Busan, Korea	4
17	Jang-Ho Bae	Division of Cardiology Heart Center, Konyang University Hospital, Daejeon, Korea	4
18	Moo-Yong Rhee	Cardiovascular Center, Dongguk University Ilsan Hospital, Goyang, Korea.	3
19	Jun Kwan	Division of Cardiology, Department of Internal Medicine, Inha University Hospital, Incheon, Korea	3
20	Dong Woon Jeon	Division of Cardiology, Department of Internal Medicine, NHIS Ilsan Hospital, Goyang, Korea	0
21	Ki Dong Yoo	Division of Cardiology, Department of Internal Medicine, The Catholic University of Korea St. Vincent's Hospital, Suwon, Korea	0

Supplemental Table II. Heterogeneity analysis according to rosuvastatin dose.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Baseline value	1	382	13.01	0.0004
Stratified factors (NCEP ATP III group)	2	382	0.21	0.8108
Treatment	1	382	41.4	<.0001
Rosuvastatin Dose	2	382	12.06	<.0001

Supplemental Table III. Changes from baseline in high sensitivity C-reactive protein after treatment with ezetimibe/rosuvastatin combination therapy and rosuvastatin monotherapy in hypercholesterolemia patients.

Variables		Ezetimibe/ Rosuvastatin 10/5mg N=65	Rosuvastatin 5mg N=65	Ezetimibe/ Rosuvastatin 10/10mg N=66	Rosuvastatin 10mg N=65	Ezetimibe/ Rosuvastatin 10/20mg N=64	Rosuvastatin 20mg N=64	Ezetimibe/ Rosuvastatin Total N=195	Rosuvastatin Total N=194
Baseline	Mean ± SD	0.22 ± 0.69	0.18 ± 0.23	0.16 ± 0.24	0.21 ± 0.47	0.14 ± 0.20	0.17 ± 0.25	0.18 ± 0.43	0.19 ± 0.34
	Median	0.07	0.11	0.09	0.07	0.08	0.07	0.07	0.08
	Min, Max	0.01, 5.36	0.01, 1.16	0.01, 1.41	0.01, 2.86	0.01, 1.22	0.01, 1.48	0.01, 5.36	0.01, 2.86
4-week follow-up	Mean ± SD	0.07 ± 0.07	0.12 ± 0.15	0.13 ± 0.20	0.17 ± 0.57	0.07 ± 0.08	0.16 ± 0.35	0.09 ± 0.13	0.15 ± 0.40
	Median	0.05	0.08	0.06	0.06	0.05	0.05	0.05	0.06
	Min, Max	0.01, 0.36	0.01, 0.78	0.01, 1.09	0.01, 4.57	0.01, 0.56	0.01, 2.23	0.01, 1.09	0.01, 4.57
Percentage changes from baseline at 4 weeks	Mean ± SD	−4.35 ± 123.29	7.84 ± 112.76	32.06 ± 276.62	21.47 ± 169.66	12.13 ± 122.13	152.54 ± 701.59	13.38 ± 189.00	60.14 ± 422.72
	Median	−40.00	−25.00	−25.66	−20.00	−29.17	−33.81	−33.33	−25.00
	Min, Max	−96.88, 800.00	−98.28, 609.09	−92.31, 2080.00	−95.83, 1233.33	−94.87, 600.00	−95.00, 4360.00	−96.88, 2080.00	−98.28, 4360.00
	Adjusted Mean ± SE	−17.95 ± 20.55	−7.94 ± 20.78	21.10 ± 39.27	14.46 ± 38.49	12.14 ± 89.88	159.78 ± 89.74	5.85 ± 32.73	54.01 ± 32.67
	P-value	0.627		0.870		0.099		0.146	
8-week follow-up	Mean ± SD	0.12 ± 0.14	0.16 ± 0.26	0.20 ± 0.70	0.16 ± 0.56	0.08 ± 0.15	0.18 ± 0.59	0.13 ± 0.43	0.17 ± 0.49
	Median	0.06	0.08	0.05	0.06	0.06	0.05	0.06	0.06
	Min, Max	0.01, 0.77	0.01, 1.70	0.02, 5.55	0.01, 4.57	0.01, 1.13	0.01, 4.72	0.01, 5.55	0.01, 4.72
Percentage changes from baseline at 8 weeks	Mean ± SD	43.80 ± 182.25	20.02 ± 111.77	307.04 ± 2274.0	10.21 ± 100.59	14.80 ± 196.13	152.86 ± 1176.6	123.38 ± 1331.7	60.56 ± 680.91
	Median	0.00	−25.00	−26.79	−14.29	−33.33	−27.88	−25.00	−25.00
	Min, Max	−97.01, 820.00	−95.83, 542.86	−91.30, 18400.0	−93.75, 440.00	−92.31, 1333.33	−91.30, 9340.00	−97.01, 18400.0	−95.83, 9340.00
	Adjusted Mean ± SE	30.71 ± 26.33	4.10 ± 26.63	661.80 ± 266.96	367.18 ± 261.67	−22.14 ± 152.13	123.89 ± 151.90	216.10 ± 105.69	156.67 ± 105.50
	P-value	0.314		0.287		0.333		0.578	

SD = standard deviation
SE = standard error