# Ezetimibe and Rosuvastatin Combination Treatment Can Reduce the Dose of Rosuvastatin Without Compromising Its Lipid-lowering Efficacy

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## ABSTRACT

**Purpose:** The goal of this study was to compare the lipid-lowering efficacy of the combination of ezetimibe and low- or intermediate-intensity statin therapy versus that of high-intensity statin monotherapy.

**Methods:** This study is a post hoc analysis of an 8-week, randomized, double-blind, Phase III trial. Patients who had hypercholesterolemia and required lipid-lowering treatment were randomly assigned to 1 of 6 treatment groups: rosuvastatin 5 mg (R5, n = 68), rosuvastatin 10 mg (R10, n = 67), rosuvastatin 20 mg (R20, n = 69), and ezetimibe 10 mg combined with rosuvastatin 5 mg (R5 + E10, n = 67), rosuvastatin 10 mg (R10 + E10, n = 68), and rosuvastatin 20 mg (R20 + E10, n = 68) daily. The effects of coadministration of ezetimibe and a low dose of rosuvastatin on lipid parameters and the target achievement rate were compared between the R5 + E10 and R10 treatment groups, the R5 + E10 and R20 treatment groups, and the R10 + E10 and R20 treatment groups.

**Findings:** Reductions in total cholesterol, LDL-C, apolipoprotein B, the apolipoprotein B/A1 ratio, and non−HDL-C were not different between the R5 + E10 and R10 treatment groups (all, $P > 0.017$), the R5 + E10 and R20 treatment groups (all, $P > 0.017$), and the R10 + E10 and R20 treatment groups (all, $P > 0.017$). R5 + E10 treatment showed efficacy comparable to that of R10 or R20 in affording LDL levels <50% of the baseline level (R5 + E10 vs R10, 73.13% vs 62.69% [$P = 0.1952$]; R5 + E10 vs R20, 73.13% vs 73.91% [$P = 0.9180$]), LDL-C levels <70 mg/dL (R5 + E10 vs R10, 64.18% vs 55.22% [$P = 0.2906$]; R5 + E10 vs R20, 64.18% vs 62.32% [$P = 0.8220$]), and LDL-C levels <50% of the baseline level or <70 mg/dL (R5 + E10 vs R10, 77.61% vs 70.15% [$P = 0.3255$]; R5 + E10 vs R20, 77.61% vs 78.26% [$P = 0.9273$]). The R10 + E10 treatment group was better than the R20 treatment group in achieving the target LDL-C level <70 mg/dL (83.82% vs 62.32%; $P = 0.0046$), even among participants with a baseline LDL-C level >135 mg/dL (77.5% vs 48.8%, respectively; $P = 0.0074$).

**Implications:** Ezetimibe combined with low- or intermediate-intensity statin therapy has lipid-lowering efficacy comparable to or better than that of high-intensity rosuvastatin monotherapy. The results of the present study indicate that the combination treatment with ezetimibe is advantageous in that it permits dose reduction of rosuvastatin without compromising the lipid-lowering efficacy of rosuvastatin. ClinicalTrials.gov identifier: NCT02205606. (*Clin Ther*. 2019;41:2571−2592) © 2019 Published by Elsevier Inc.

**Key words:** Combination therapy, Ezetimibe, Hypercholesterolemia, Rosuvastatin.

## INTRODUCTION

Hypercholesterolemia is a major risk factor for cardiovascular diseases, and lowering of LDL-C levels with statin treatment is an effective method to prevent cardiovascular events.[1–3] Based on accumulating evidence for the effectiveness of statin treatment, moderate- to high-intensity statin therapy for patients with hypercholesterolemia has been recommended to prevent cardiovascular events.[4] For patients with a very high risk of developing cardiovascular events, recent guidelines recommend intensive statin therapy to lower the level of LDL-C to <70 mg/dL or to reduce the level at least 50% if the baseline level is between 70 and 135 mg/dL.[3,5] To reach this target goal, high-dose statin treatment is needed. However, in a previous study, high-dose statin treatment could not effectively reduce the level of LDL-C to the target level in some patients.[6] Compared with statin monotherapy, coadministration of ezetimibe with statin therapy reduced LDL levels more efficiently,[7] and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) has shown that the addition of ezetimibe to statin therapy reduces cardiovascular events.[8] Therefore, recent guidelines recommend the use of ezetimibe when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients who are unable to tolerate statin therapy or for whom statins are contraindicated.[3]

With regard to statin-related adverse drug reactions, intensive statin treatment may increase the incidence rate of such reactions in Asian populations,[9,10] leading to frequent statin down-titration or discontinuation. Suboptimal statin doses may be a barrier to achieving target LDL-C levels. However, one study has shown that the combination of ezetimibe and statins may reduce the statin doses required while affording better LDL-C reduction.[11]

The present study therefore evaluated whether coadministration of ezetimibe and rosuvastatin treatment could reduce the dose of rosuvastatin required without compromising the lipid-lowering efficacy of rosuvastatin monotherapy.

## PATIENTS AND METHODS

### Study Design

The present study is a post hoc analysis of the MRS-ROZE (Multicenter Randomized Study of Rosuvastatin and Ezetimibe; clinical trials.gov identifier: NCT02205606) trial. The design and participants of the primary study have been described elsewhere in detail.[7] Briefly, the study was an 8-week,

Table I. Inclusion criteria associated with randomization per LDL level.

| Risk Category | Cardiovascular Risk Factors* | Randomization Criteria: LDL-C (mg/dL) |
|---|---|---|
| Low risk | 0 risk factors | ≥160 and ≤ 250 |
| Moderate risk | ≥2 risk factors and 10-year risk <10% | ≥160 and ≤ 250 |
| Moderate high risk | ≥2 risk factors and 10-year risk from 10% to 20% | ≥130 and ≤ 250 |
| High risk | CHD† and CHD risk equivalent‡ | ≥100 and ≤ 250 |

* Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medication), low HDL-C level (<40 mg/dL), a family history of premature coronary heart disease (CHD; CHD in male first-degree relative aged <55 years; CHD in female first-degree relative aged <65 years), and age (men aged ≥45 years; women aged ≥55 years).
† CHD includes a history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia.
‡ CHD risk equivalents include clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and ≥2 risk factors with a 10-year risk for hard CHD of >20%.

multicenter, double-blind, parallel-group trial. The study protocol was approved by the institutional review boards of each participating center, and written informed consent was provided by all study participants. Participants aged >19 years, with a history of hypercholesterolemia and/or who received lipid-lowering drug treatment, were screened. Those with LDL-C levels ≤250 mg/dL and triglyceride (TG) levels <400 mg/dL were included in a 4-week dietary lead−in period. Participants who were receiving lipid-lowering drug treatment were asked to discontinue the treatment before inclusion in the dietary lead−in period.

The participants followed the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet. After the dietary lead−in period, study eligibility was reassessed by measuring LDL-C and TG levels. Participants with LDL-C levels ≤250 mg/dL and TG levels <400 mg/dL and who required lipid-lowering treatment according to the National Cholesterol Education Program Adult Treatment Panel III guidelines were finally enrolled in the study (Table I). The exclusion criteria have been described elsewhere in detail.[7] Of the 583 screened participants who entered the dietary lead−in period, 412 were randomly assigned to 1 of the following 6 treatment groups equally: R5 + E10, eight weeks of combination treatment with rosuvastatin 5 mg daily and ezetimibe 10 mg daily; R10 + E10, eight weeks of combination treatment with rosuvastatin 10 mg daily and ezetimibe 10 mg daily; R20 + E10, eight weeks of combination treatment with rosuvastatin 20 mg daily and ezetimibe 10 mg daily; R5, eight weeks of treatment with rosuvastatin 5 mg alone daily; R10, eight weeks of treatment with rosuvastatin 10 mg alone daily; and R20, eight weeks of treatment with rosuvastatin 20 mg alone daily. All study personnel and participants were blinded to the treatment allocation throughout the study. Total cholesterol, TG, HDL-C, LDL-C, apolipoprotein (Apo) B, Apo A1, Apo B/A1 ratio, and non−HDL-C were measured as lipid parameters.

### Statistical Analysis

Among the participants, data from 407 were analyzed (full analysis set).[7] Data from the per-protocol set (PPS) were also analyzed; the results of this analysis are shown in the Supplemental Table VI - XI in Appendix section.

To evaluate the lipid-lowering efficacy of the combination of ezetimibe and low- or intermediate-intensity statin therapy compared with that of higher intensity statin monotherapy, the effects on changes in lipid parameters and the target achievement rate were compared between the R5 + E10 and R10 treatment groups, the R5 + E10 and R20 treatment groups, and the R10 + E10 and R20 treatment groups. Target achievement rate was defined as: (1) lowering of LDL-C to a level <70 mg/dL; and/or (2) at least a 50% reduction in the LDL-C level compared with its baseline level, which is recommended in very-high-risk patients according to recent guidelines.[3,5] For a subgroup analysis, the study population was divided into 2 groups according to the baseline LDL-C level (≤135 mg/dL and >135 mg/dL) as the treatment target differed according to the level of baseline LDL-C level.[3]

Changes in lipid parameters were compared between the groups by using an ANCOVA model adjusted with the baseline values of each lipid parameter. The comparison of the target achievement rate between the groups was performed by using the $\chi^2$ test. $P$ values <0.05 were considered statistically significant. All statistical analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina). Although an overall experiment−wise type I error level was set at alpha = 0.05, the alpha level was set at 0.017 by the Bonferroni correction method when the pairwise comparisons among the experimental groups were repeated 3 times.

## RESULTS

Baseline and demographic characteristics of the analyzed population are presented in Table II. Intergroup differences in age, sex, and number of current smokers were not significant. Furthermore, there were no intergroup differences in the prevalence of diabetes mellitus, hypertension, or coronary heart disease.

As shown previously,[7] coadministration of ezetimibe and rosuvastatin more effectively reduced

Table II. Baseline clinical and demographic characteristics of the study subjects (full analysis set evaluation).

| Changes | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | *P** |
|---|---|---|---|---|---|---|---|
| All | | | | | | | |
| n | 68 | 67 | 69 | 67 | 68 | 68 | |
| Age, y | 64.16 (9.16) | 65.49 (8.46) | 63.16 (10.14) | 63.49 (8.18) | 64.43 (8.09) | 64.69 (7.35) | 0.6647 |
| BMI, kg/m$^2$ | 25.09 (2.49) | 25.6 (3.18) | 24.78 (2.71) | 24.14 (3.04) | 25.12 (2.88) | 25.07 (2.8) | 0.0882 |
| Men | 32 (47.1%) | 38 (56.7%) | 48 (69.6%) | 37 (55.2%) | 38 (55.9%) | 38 (55.9%) | 0.1976 |
| Current smoker | 5 (7.4%) | 8 (11.9%) | 15 (21.7%) | 13 (19.4%) | 13 (19.1%) | 9 (13.2%) | 0.3113 |
| Diabetes mellitus | 16 (23.5%) | 17 (25.4%) | 18 (26.1%) | 12 (17.9%) | 13 (19.1%) | 17 (25.0%) | 0.8044 |
| Hypertension | 50 (73.5%) | 45 (67.2%) | 46 (66.7%) | 49 (73.1%) | 44 (64.7%) | 49 (72.1%) | 0.8032 |
| CHD | 55 (80.9%) | 55 (82.1%) | 56 (81.2%) | 55 (82.1%) | 58 (85.3%) | 58 (85.3%) | 0.9667 |
| LDL >135 mg/dL | | | | | | | |
| N | 39 | 42 | 41 | 40 | 40 | 43 | |
| Age, y | 62.79 (9.97) | 65.67 (8.64) | 62.78 (11.13) | 62.28 (7.61) | 64.08 (7.49) | 64.12 (7.29) | 0.5262 |
| BMI, kg/m$^2$ | 25.18 (2.71) | 26.22 (2.661)† | 24.42 (2.60) | 24.07 (3.331)† | 25.08 (2.74) | 25.19 (3.10) | 0.0189 |
| Men | 16 (41.0%) | 21 (50.0%) | 24 (58.5%) | 19 (47.5%) | 18 (45.0%) | 21 (48.8%) | 0.7343 |
| Current smoker | 4 (10.3%) | 6 (14.3%) | 9 (22.0%) | 7 (17.5%) | 5 (12.5%) | 6 (14.0%) | 0.9161 |
| Diabetes mellitus | 8 (20.5%) | 9 (21.4%) | 7 (17.1%) | 7 (17.5%) | 9 (22.5%) | 12 (27.9%) | 0.8554 |
| Hypertension | 29 (74.4%) | 24 (57.1%) | 26 (63.4%) | 26 (65.0%) | 27 (67.5%) | 30 (69.8%) | 0.6786 |
| CHD | 27 (69.2%) | 31 (73.8%) | 30 (73.2%) | 30 (75.0%) | 31 (77.5%) | 36 (83.7%) | 0.7496 |
| LDL ≤135 mg/dL | | | | | | | |
| N | 29 | 25 | 28 | 27 | 28 | 25 | |
| Age, y | 66.00 (7.73) | 65.20 (8.32) | 63.71 (8.65) | 65.30 (8.81) | 64.93 (8.99) | 65.68 (7.50) | 0.9389 |
| BMI, kg/m$^2$ | 24.97 (2.21) | 24.57 (3.72) | 25.31 (2.82) | 24.25 (2.61) | 25.17 (3.11) | 24.88 (2.23) | 0.7556 |
| Men | 16 (55.2%) | 17 (68.0%) | 24 (85.7%) | 18 (66.7%) | 20 (71.4%) | 17 (68.0%) | 0.2664 |
| Current smoker | 1 (3.5%) | 2 (8.0%) | 6 (21.4%) | 6 (22.2%) | 8 (28.6%) | 3 (12.0%) | 0.1803 |

(*continued on next page*)

Table II. (*Continued*)

| Changes | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | *P** |
|---|---|---|---|---|---|---|---|
| Diabetes mellitus | 8 (27.6%) | 8 (32.0%) | 11 (39.3%) | 5 (18.5%) | 4 (14.3%) | 5 (20.0%) | 0.2695 |
| Hypertension | 21 (72.4%) | 21 (84.0%) | 20 (71.4%) | 23 (85.2%) | 17 (60.7%) | 19 (76.0%) | 0.3188 |
| CHD | 28 (96.6%) | 24 (96.0%) | 26 (92.9%) | 25 (92.6%) | 27 (96.4%) | 22 (88.0%) | 0.7788 |

BMI = body mass index; CHD = coronary heart disease; R5 = eight weeks of treatment with rosuvastatin 5 mg alone daily; R10 = eight weeks of treatment with rosuvastatin 10 mg alone daily; R20 = eight weeks of treatment with rosuvastatin 20 mg alone daily; R5 + E10 = eight weeks of combination treatment with rosuvastatin 5 mg daily and ezetimibe 10 mg daily; R10 + E10 = eight weeks of combination treatment with rosuvastatin 10 mg daily and ezetimibe 10 mg daily; R20 + E10 = eight weeks of combination treatment with rosuvastatin 20 mg daily and ezetimibe 10 mg daily.

*$P$ values were obtained by using the $\chi^2$ test for categorical variables and ANOVA for continuous variables.

†$P$ values <0.05, statistically significant, post hoc analysis by Tukey's test.

total cholesterol, LDL-C, Apo B, the Apo B/A1 ratio, and non− HDL-C compared with those achieved with the same dose of rosuvastatin alone in the study population (see Supplemental Tables I–III in Appendix section).

The efficacy of coadministration of ezetimibe and a low dose of rosuvastatin against changes in lipid parameters compared with that of rosuvastatin monotherapy at a higher dose is presented in Figure 1 and Supplemental Table IV in Appendix section. There were no intergroup differences in the reduction of total cholesterol, LDL-C, Apo B, the Apo B/A1 ratio, and non−HDL-C between the R5 + E10 and R10 treatment groups, the R5 + E10 and R20 treatment groups, and the R10 + E10 and R20 treatment groups. Among participants whose baseline LDL-C level was >135 mg/dL, those in the R10 + E10 treatment group exhibited a greater percent reduction in total cholesterol and non−HDL-C than those in the R20 treatment group (−43.13% vs −37.99% [$P$ = 0.0404] and −57.13% vs −50.75% [$P$ = 0.0375], respectively), although the finding was insignificant at the adjusted alpha level of 0.017. Among participants whose baseline LDL-C level was ≤135 mg/dL, there was no difference in the changes in lipid parameters between the 2 groups.

Combination treatment with ezetimibe and rosuvastatin afforded a better goal achievement rate than the same dose of rosuvastatin monotherapy (Figure 2A). Furthermore, combination treatment with a low dose of rosuvastatin resulted in a similar or better goal achievement rate with regard to the LDL-C level compared with that associated with rosuvastatin monotherapy at a higher dose (Figure 2B). The target achievement rate associated with the R5 + E10 treatment was comparable to those associated with the R10 and R20 treatments. The R10 + E10 treatment group reported a better achievement rate than the R20 treatment group (83.82% vs 62.32% for the target LDL-C level <70 mg/dL; $P$ = 0.0046) (see Supplemental Table V in Appendix section). Among the participants with a baseline LDL-C level >135 mg/dL (Figure 3A), those in the R5 + E10 treatment group reported a higher achievement rate than those in the R10 treatment group (57.5% vs 35.7%, respectively [$P$ = 0.0480], although this finding was insignificant at the adjusted alpha level of 0.017); the R10 + E10

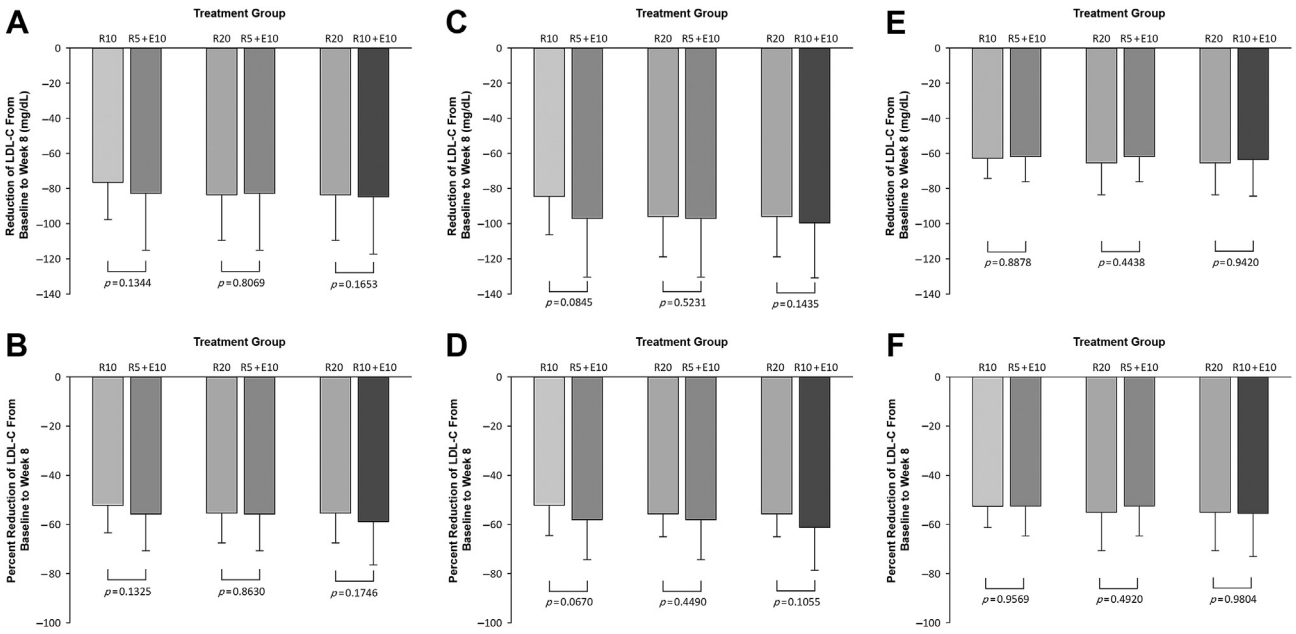


Figure 1. Comparison of LDL changes between statin monotherapy and combination treatment with ezetimibe and low-dose statin therapy. (A and B) Reduction of LDL-C level from baseline to week 8 in the study population. (C and D) Reduction of LDL-C level from baseline to week 8 in patients with a baseline LDL level >135 mg/dL. (E and F) Reduction of LDL-C level from baseline to week 8 in patients with a baseline LDL level ≤135 mg/dL. R10 = eight weeks of treatment with rosuvastatin 10 mg alone daily; R20 = eight weeks of treatment with rosuvastatin 20 mg alone daily; R5 + E10 = eight weeks of combination treatment with rosuvastatin 5 mg daily and ezetimibe 10 mg daily; R10 + E10 = eight weeks of combination treatment with rosuvastatin 10 mg daily and ezetimibe 10 mg daily.

treatment group reported a higher achievement rate than the R20 treatment group (77.5% vs 48.8%; $P = 0.0074$).

The PPS analysis also showed that the efficacy of the ezetimibe and rosuvastatin combination treatment was better than that of rosuvastatin monotherapy. Among participants with a baseline LDL-C level >135 mg/dL, those in the R10 + E10 treatment group reported a greater reduction in total cholesterol, TG, LDL-C, Apo B, the Apo B/A1 ratio, and non−HDL-C than those in the R20 treatment group (see Supplemental Table X in Appendix section). Furthermore, the R5 + E10 and R10 + E10 treatment groups reported better target achievement rates than the R10 and R20 treatment groups, respectively (see Supplemental Table XI in Appendix section).

## DISCUSSION

In the present study, the combination of low-intensity rosuvastatin 5 mg with ezetimibe 10 mg showed efficacy comparable to that of high-intensity rosuvastatin 20-mg monotherapy in terms of lipid lowering and target achievement rate. Furthermore, in participants with a baseline LDL-C level >135 mg/dL, the combination treatment resulted in a better target achievement rate (defined as the achievement

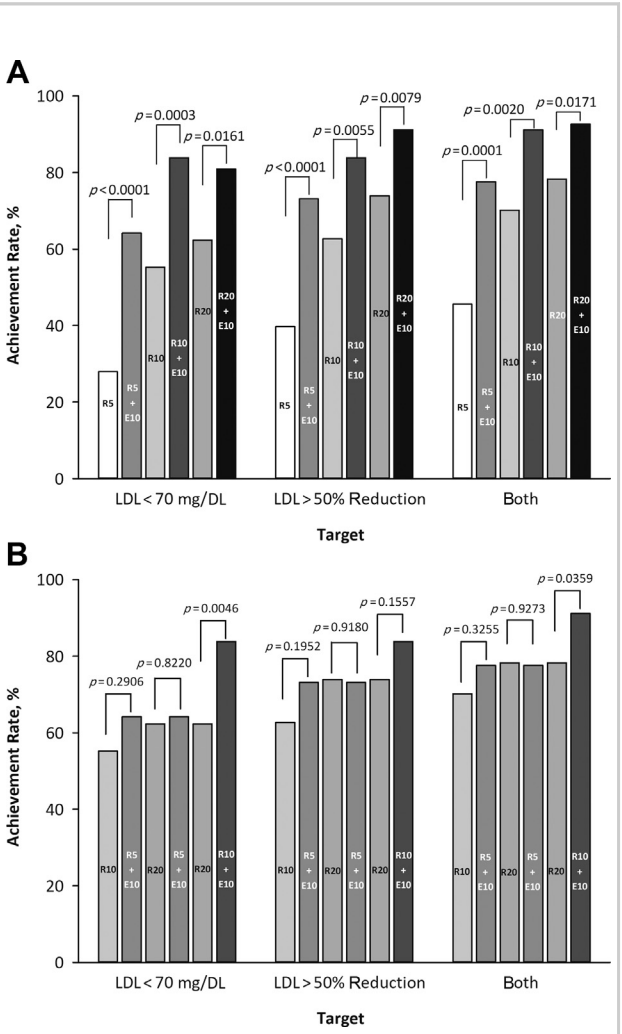


Figure 2. Comparison of target achievement rate. (A) Comparison of ezetimibe and rosuvastatin combination treatment with rosuvastatin monotherapy administered at the same dose. (B) Comparison of ezetimibe and rosuvastatin combination treatment versus higher dose of rosuvastatin monotherapy. R5 = eight weeks of treatment with rosuvastatin 5 mg alone daily; R10 = eight weeks of treatment with rosuvastatin 10 mg alone daily; R20 = eight weeks of treatment with rosuvastatin 20 mg alone daily; R5 + E10 = eight weeks of combination treatment with rosuvastatin 5 mg daily and ezetimibe 10 mg daily; R10 + E10 = eight weeks of combination treatment with rosuvastatin 10 mg daily and ezetimibe 10 mg daily; R20 + E10 = eight weeks of combination treatment with rosuvastatin 20 mg daily and ezetimibe 10 mg daily.

of an LDL-C level <70 mg/dL or a reduction of at least 50% of the baseline level) compared with the results afforded by rosuvastatin 10-mg monotherapy. The full analysis set evaluation showed that the combination of intermediate-intensity rosuvastatin 10 mg and ezetimibe 10 mg was better than high-intensity rosuvastatin 20-mg monotherapy in lowering total cholesterol and non−HDL-C levels. Furthermore, the PPS analysis showed the superior efficacy of the combination treatment in lowering total cholesterol, LDL-C, Apo B, the Apo B/A1 ratio, and non−HDL-C. The target achievement rate associated with the coadministration of rosuvastatin 10 mg and ezetimibe 10 mg was higher than that associated with rosuvastatin 20-mg monotherapy. These results suggest that the combination treatment of rosuvastatin and ezetimibe has an advantage in reducing the dose of rosuvastatin without compromising its lipid-lowering efficacy.

The use of statins for primary and secondary prevention has been shown to reduce the risk of cardiovascular morbidity and mortality per lowering of LDL-C levels.[12] Lower LDL-C levels were associated with lower rates of major coronary events. A greater reduction in LDL-C was associated with a greater reduction in cardiovascular risk.[13] Therefore, the use of moderate- to high-intensity statins is recommended for patients with hypercholesterolemia.[4] Although evidence is lacking regarding how much LDL-C should be lowered, recent guidelines recommend intensive statin therapy for a target LDL-C level <70 mg/dL or a reduction of at least 50% of baseline level if the baseline is between 70 and 135 mg/dL for patients at very high risk.[3,5]

Although intensive lowering of LDL-C in very-high-risk patients has been recommended, only 21.7% of the patients attained their goals in DYSIS (Dyslipidemia International Study), a cross-sectional study documenting statin-treated outpatients in 30 countries worldwide (across Europe, the Middle

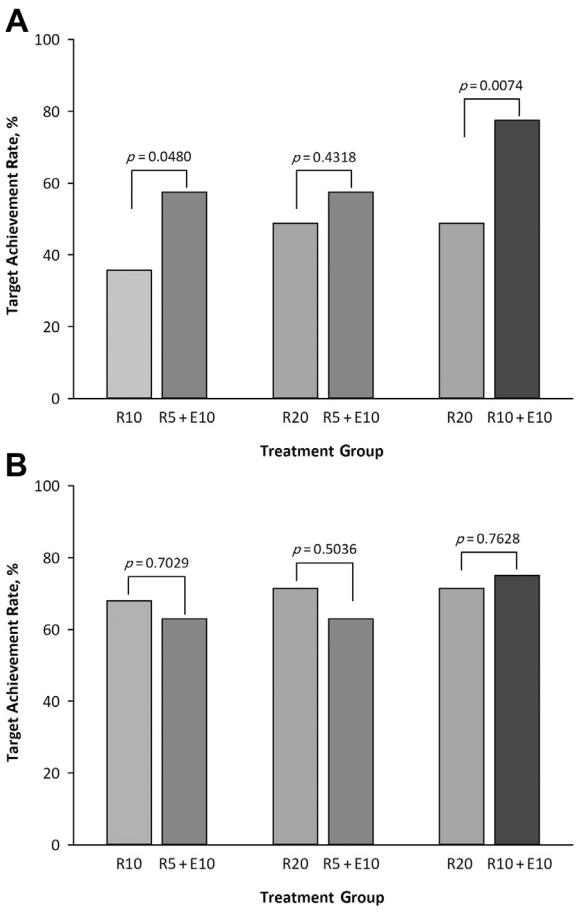


Figure 3. Achievement rate of different targets according to the baseline LDL-C level. (A) Achievement rate of an LDL-C level <70 mg/dL in patients with a baseline LDL-C level >135 mg/dL. (B) Achievement rate of LDL-C to least 50% of baseline LDL-C levels in patients with a baseline LDL-C level ≤135 mg/dL. R10 = eight weeks of treatment with rosuvastatin 10 mg alone daily; R20 = eight weeks of treatment with rosuvastatin 20 mg alone daily; R5 + E10 = eight weeks of combination treatment with rosuvastatin 5 mg daily and ezetimibe 10 mg daily; R10 + E10 = eight weeks of combination treatment with rosuvastatin 10 mg daily and ezetimibe 10 mg daily.

East, Canada, Africa, and Asia).[14] Based on the data from different European countries, LDL-C control is better for those receiving a high-intensity lipid-lowering therapy than those receiving low- or moderate-intensity lipid-lowering therapy.[15] Rosuvastatin 40 mg is rarely recommended in Asian subjects because of safety issues.[3] The goal achievement rate associated with rosuvastatin 20-mg treatment for very-high-risk patients was 68.5% in the analysis of the VOYAGER (An Individual Patient Data Meta-Analysis of Statin Therapy in At Risk Groups: Effects of Rosuvastatin, Atorvastatin, and Simvastatin) database.[6] As reported in a previous study, combination treatment with ezetimibe and rosuvastatin was associated with a better LDL-C–lowering effect.[7]

The major concern related to statin treatment is treatment-related adverse events.[16] Myopathy is not uncommon and is one of the major barriers in the use of statin treatment. It is dose dependent, and European Society of Cardiology/European Atherosclerosis Society guidelines recommend alternative dosing; examples of such dosing include every other day or twice a week with atorvastatin or rosuvastatin in high-risk patients who cannot tolerate daily doses of statin treatment, even though no clinical endpoint trials are available,[3] because several studies have shown a considerable LDL-C–lowering effect with alternate dosing of statins.[17] However, there is no evidence that such treatment decreases cardiovascular events or death.[18] Moreover, statin treatment has been shown to increase the risk of developing type 2 diabetes. The statin-related risk of diabetes seems to be dose or potency dependent.[19,20] Therefore, reducing the dose of statins is expected to help reduce the incidence of statin treatment–related type 2 diabetes. Although it is not yet proven, coadministration of ezetimibe with statins does not seem to increase the risk of developing statin-related type 2 diabetes, even with further LDL-C lowering. In a study comparing statin treatment alone and the combination of ezetimibe and statin treatment, high-intensity statin treatment was associated with a higher risk of incident diabetes in prediabetic individuals, whereas the addition of ezetimibe to statin therapy did not increase the risk of incident diabetes.[21] The fact that the combination of ezetimibe and low-dose rosuvastatin afforded an LDL-C–lowering effect

equivalent to that of higher dose rosuvastatin monotherapy and a greater target achievement rate than that associated with the latter in the present study may be beneficial in reducing the side effects of high-intensity statin treatment; it may also be considered a possible advantage of combination treatment with ezetimibe over rosuvastatin monotherapy.

The present study has several limitations. First, the primary study was not designed to evaluate the effect of ezetimibe and rosuvastatin combination treatment in high- or very-high-risk patients although these individuals were included in the study. The sample size of high- or very-high-risk patients was not adequate. We therefore performed the analysis in the entire study population, including low-risk patients. Second, this study was a post hoc analysis, and thus the analysis was not confirmatory but exploratory. Third, the study yielded a short-term result in a small population. The sample size may not be adequate to have enough statistical power for comparing efficacy between groups. There was no difference in the incidence of treatment-related adverse events. A long-term study in a larger population involving head-to-head comparisons with statin monotherapy is therefore needed to show the beneficial effects of combination treatment with ezetimibe and low-dose statins on the reduction of statin-related side effects and equal or greater reduction of cardiovascular events.

## CONCLUSIONS

Combination treatment with ezetimibe and low-dose statins showed equal or superior efficacy compared with that of higher intensity statin monotherapy. The results of the present study indicate an advantage of the combination treatment with ezetimibe and statins, in that it permitted dose reduction of rosuvastatin without compromising the lipid-lowering efficacy of rosuvastatin. The results suggest a possibility that the combination treatment with ezetimibe and statins may reduce the incidence of statin-related side effects.

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## DISCLOSURES

Dr. Rhee has received lecture honoraria from Pfizer Inc, LG Life Sciences Ltd, Boehringer Ingelheim Pharma GmbH & Co KG, Hanmi Pharm. Co Ltd, Yuhan Co Ltd, and Boryung Pharmaceutical Co Ltd; fees for consulting from Hanmi Pharm. Co Ltd; and research grants from Boryung Pharmaceutical Co Ltd and Dong-A Pharmaceutical Co, Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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## APPENDIX. SUPPLEMENTARY TABLES

Supplement Table 1. Changes of lipid parameters from baseline to week 8 between treatments (FAS analysis)

| Changes | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
|---|---|---|---|---|---|---|---|---|---|
| Total Cholesterol | | | | | | | | | |
| mg/dL | −64.24 ± 32.98 | −76.49 ± 22.56 | −83.68 ± 27.52 | −82.55 ± 33.58 | −86.00 ± 35.08 | −99.35 ± 35.39 | 0.0001 | 0.0081 | 0.0013 |
| % change | −28.28 ± 13.18 | −34.94 ± 8.23 | −36.97 ± 9.48 | −36.65 ± 11.29 | −39.80 ± 13.27 | −43.68 ± 12.76 | <0.0001 | 0.0085 | 0.0007 |
| Triglyceride | | | | | | | | | |
| mg/dL | −20.32 ± 57.32 | −34.30 ± 56.03 | −32.80 ± 63.22 | −28.61 ± 50.11 | −45.07 ± 56.24 | −60.19 ± 69.15 | 0.0244 | 0.0478 | 0.0372 |
| % change | −6.43 ± 41.69 | −13.86 ± 32.27 | −14.28 ± 37.78 | −13.59 ± 34.49 | −21.85 ± 33.53 | −27.00 ± 31.54 | 0.0772 | 0.0820 | 0.1027 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | 1.81 ± 7.78 | 5.54 ± 8.70 | 4.71 ± 9.68 | 3.94 ± 8.81 | 5.16 ± 8.63 | 6.01 ± 7.98 | 0.0465 | 0.7190 | 0.5994 |
| % change | 4.69 ± 15.57 | 12.17 ± 17.92 | 11.79 ± 24.28 | 10.10 ± 19.52 | 12.82 ± 19.29 | 14.23 ± 18.97 | 0.0151 | 0.9805 | 0.8116 |
| LDL | | | | | | | | | |
| mg/dL | −63.10 ± 29.94 | −76.42 ± 21.33 | −83.57 ± 25.90 | −82.90 ± 32.28 | −84.74 ± 32.66 | −97.22 ± 33.30 | <0.0001 | 0.0117 | 0.0013 |
| % change | −42.11 ± 17.30 | −52.29 ± 11.09 | −55.43 ± 12.13 | −55.78 ± 14.96 | −58.84 ± 17.63 | −64.32 ± 16.90 | <0.0001 | 0.0107 | 0.0006 |
| Apo B | | | | | | | | | |
| mg/dL | −44.65 ± 20.68 | −54.93 ± 14.60 | −59.52 ± 19.58 | −56.63 ± 21.42 | −60.96 ± 22.28 | −67.90 ± 22.64 | <0.0001 | 0.0253 | 0.0070 |
| % change | −35.78 ± 14.23 | −44.73 ± 9.46 | −46.67 ± 10.88 | −46.46 ± 12.56 | −49.47 ± 14.24 | −53.02 ± 13.70 | <0.0001 | 0.0244 | 0.0035 |
| Apo A1 | | | | | | | | | |
| mg/dL | 4.63 ± 16.58 | 8.61 ± 19.11 | 8.93 ± 20.43 | 8.27 ± 18.12 | 9.44 ± 17.63 | 7.39 ± 13.88 | 0.1196 | 0.9287 | 0.5160 |
| % change | 3.53 ± 11.29 | 6.80 ± 14.15 | 7.23 ± 15.29 | 6.86 ± 13.76 | 7.80 ± 12.52 | 5.96 ± 10.23 | 0.0531 | 0.8111 | 0.4572 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | −0.33 ± 0.15 | −0.43 ± 0.13 | −0.47 ± 0.27 | −0.43 ± 0.19 | −0.49 ± 0.20 | −0.52 ± 0.21 | <0.0001 | 0.0237 | 0.0286 |
| % change | −37.57 ± 13.80 | −47.49 ± 10.36 | −49.26 ± 12.77 | −49.37 ± 12.54 | −52.41 ± 15.17 | −54.97 ± 15.55 | <0.0001 | 0.0405 | 0.0168 |
| Non-HDL | | | | | | | | | |
| mg/dL | −66.04 ± 31.49 | −82.03 ± 22.04 | −88.39 ± 29.13 | −86.49 ± 33.61 | −91.16 ± 35.28 | −105.37 ± 36.72 | <0.0001 | 0.0103 | 0.0013 |
| % change | −38.20 ± 16.37 | −48.27 ± 9.37 | −50.58 ± 11.95 | −51.12 ± 13.93 | −54.02 ± 16.44 | −59.10 ± 16.24 | <0.0001 | 0.0120 | 0.0007 |

Supplement Table 2. Changes of lipid parameters from baseline to week 8 between treatments in subjects with a baseline LDL level of >135 mg/dL (FAS analysis)

| Changes | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
|---|---|---|---|---|---|---|---|---|---|
| Total Cholesterol | | | | | | | | | |
| mg/dL | −77.41 ± 28.95 | −85.38 ± 22.18 | −94.73 ± 24.59 | −96.68 ± 34.86 | −101.28 ± 33.64 | −109.79 ± 37.37 | 0.0028 | 0.0060 | 0.0082 |
| % change | −31.61 ± 10.10 | −35.99 ± 8.46 | −37.99 ± 8.00 | −39.71 ± 11.93 | −43.13 ± 12.89 | −44.78 ± 13.48 | 0.0017 | 0.0041 | 0.0065 |
| Triglyceride | | | | | | | | | |
| mg/dL | −17.26 ± 49.53 | −33.62 ± 62.19 | −34.17 ± 59.54 | −31.63 ± 51.42 | −50.78 ± 52.08 | −58.51 ± 73.57 | 0.0227 | 0.0015 | 0.1076 |
| % change | −5.26 ± 32.50 | −10.75 ± 33.29 | −16.89 ± 32.81 | −15.56 ± 33.16 | −27.09 ± 30.32 | −25.07 ± 30.52 | 0.0556 | 0.0017 | 0.3650 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | −0.03 ± 8.02 | 5.17 ± 7.76 | 4.95 ± 9.61 | 3.55 ± 8.66 | 5.05 ± 7.91 | 5.58 ± 7.22 | 0.0303 | 0.8786 | 0.8052 |
| % change | 0.86 ± 15.50 | 11.46 ± 16.95 | 12.15 ± 20.85 | 8.95 ± 19.10 | 12.03 ± 16.76 | 13.07 ± 16.95 | 0.0165 | 0.9523 | 0.6081 |
| LDL | | | | | | | | | |
| mg/dL | −74.82 ± 28.07 | −84.57 ± 21.73 | −96.00 ± 22.89 | −97.10 ± 33.37 | −99.63 ± 31.23 | −107.49 ± 35.90 | 0.0005 | 0.0115 | 0.0201 |
| % change | −44.25 ± 14.25 | −52.14 ± 12.40 | −55.68 ± 9.27 | −58.01 ± 16.33 | −61.19 ± 17.50 | −63.72 ± 18.38 | 0.0002 | 0.0079 | 0.0151 |
| Apo B | | | | | | | | | |
| mg/dL | −52.18 ± 19.98 | −60.46 ± 14.58 | −67.97 ± 17.86 | −65.98 ± 21.76 | −70.23 ± 21.72 | −74.15 ± 24.67 | 0.0007 | 0.0148 | 0.0552 |
| % change | −37.37 ± 12.86 | −44.95 ± 10.46 | −47.79 ± 8.44 | −49.00 ± 13.27 | −52.19 ± 14.56 | −53.24 ± 15.18 | 0.0002 | 0.0107 | 0.0429 |
| Apo A1 | | | | | | | | | |
| mg/dL | 2.12 ± 17.48 | 9.58 ± 19.98 | 9.87 ± 22.09 | 6.29 ± 18.26 | 9.00 ± 16.82 | 7.60 ± 13.59 | 0.2429 | 0.7653 | 0.3541 |
| % change | 1.79 ± 11.80 | 7.49 ± 15.17 | 7.90 ± 15.59 | 5.31 ± 13.80 | 7.38 ± 11.67 | 5.98 ± 9.69 | 0.1696 | 0.8383 | 0.2504 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | −0.37 ± 0.16 | −0.46 ± 0.13 | −0.54 ± 0.32 | −0.49 ± 0.20 | −0.55 ± 0.20 | −0.56 ± 0.23 | 0.0001 | 0.0262 | 0.1860 |
| % change | −37.81 ± 13.89 | −47.99 ± 10.95 | −50.55 ± 10.91 | −51.03 ± 13.19 | −54.82 ± 15.54 | −55.08 ± 17.35 | <0.0001 | 0.0261 | 0.1185 |
| Non-HDL | | | | | | | | | |
| mg/dL | −77.38 ± 28.81 | −90.55 ± 21.38 | −99.68 ± 27.03 | −100.23 ± 34.59 | −106.33 ± 33.94 | −115.37 ± 39.52 | 0.0003 | 0.0069 | 0.0119 |
| % change | −40.20 ± 12.60 | −48.44 ± 10.12 | −50.75 ± 9.40 | −53.10 ± 14.37 | −57.13 ± 16.62 | −58.82 ± 17.09 | <0.0001 | 0.0055 | 0.0097 |

*p* values were obtained by ANCOVA, adjusted for baseline values.

Supplement Table 3. Changes of lipid parameters from baseline to week 8 between treatments in subjects with a baseline LDL of ≤135 mg/dL (FAS analysis)

| Changes | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
|---|---|---|---|---|---|---|---|---|---|
| Total Cholesterol | | | | | | | | | |
| mg/dL | −46.52 ± 29.98 | −61.56 ± 13.73 | −67.50 ± 23.56 | −61.63 ± 16.66 | −64.18 ± 24.09 | −81.40 ± 22.81 | 0.0162 | 0.6018 | 0.0870 |
| % change | −23.80 ± 15.53 | −33.17 ± 7.67 | −35.47 ± 11.31 | −32.12 ± 8.60 | −35.03 ± 12.54 | −41.77 ± 11.45 | 0.0158 | 0.5878 | 0.0682 |
| Triglyceride | | | | | | | | | |
| mg/dL | −24.45 ± 67.09 | −35.44 ± 44.98 | −30.79 ± 69.33 | −24.15 ± 48.72 | −36.93 ± 61.76 | −63.08 ± 62.14 | 0.3403 | 0.3192 | 0.1952 |
| % change | −8.00 ± 52.16 | −19.07 ± 30.41 | −10.47 ± 44.44 | −10.68 ± 36.81 | −14.36 ± 36.91 | −30.31 ± 33.62 | 0.4796 | 0.2353 | 0.1846 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | 4.28 ± 6.83 | 6.16 ± 10.23 | 4.36 ± 9.96 | 4.52 ± 9.16 | 5.32 ± 9.72 | 6.76 ± 9.25 | 0.5735 | 0.7594 | 0.3554 |
| % change | 9.83 ± 14.36 | 13.36 ± 19.74 | 11.26 ± 28.97 | 11.80 ± 20.37 | 13.94 ± 22.71 | 16.22 ± 22.26 | 0.3011 | 0.9964 | 0.4620 |
| LDL | | | | | | | | | |
| mg/dL | −47.34 ± 25.04 | −62.72 ± 11.52 | −65.36 ± 18.29 | −61.85 ± 14.27 | −63.46 ± 20.97 | −79.56 ± 18.08 | 0.0062 | 0.5899 | 0.0137 |
| % change | −39.24 ± 20.63 | −52.54 ± 8.69 | −55.06 ± 15.59 | −52.47 ± 12.21 | −55.47 ± 17.57 | −65.35 ± 14.29 | 0.0054 | 0.5507 | 0.0131 |
| Apo B | | | | | | | | | |
| mg/dL | −34.53 ± 17.22 | −45.65 ± 8.93 | −47.15 ± 15.02 | −42.76 ± 10.98 | −47.73 ± 15.54 | −57.15 ± 13.22 | 0.0251 | 0.7878 | 0.0321 |
| % change | −33.64 ± 15.86 | −44.36 ± 7.69 | −45.02 ± 13.71 | −42.71 ± 10.57 | −45.59 ± 13.06 | −52.64 ± 10.97 | 0.0183 | 0.7414 | 0.0286 |
| Apo A1 | | | | | | | | | |
| mg/dL | 8.00 ± 14.94 | 6.98 ± 17.85 | 7.56 ± 18.03 | 11.21 ± 17.84 | 10.08 ± 19.03 | 7.02 ± 14.65 | 0.2511 | 0.5941 | 0.8741 |
| % change | 5.87 ± 10.29 | 5.65 ± 12.45 | 6.25 ± 15.06 | 9.16 ± 13.63 | 8.40 ± 13.85 | 5.92 ± 11.30 | 0.1303 | 0.5053 | 0.8306 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | −0.27 ± 0.12 | −0.37 ± 0.11 | −0.38 ± 0.15 | −0.34 ± 0.13 | −0.41 ± 0.18 | −0.45 ± 0.16 | 0.0039 | 0.5910 | 0.0414 |
| % change | −37.26 ± 13.91 | −46.65 ± 9.44 | −47.36 ± 15.10 | −46.91 ± 11.29 | −48.96 ± 14.18 | −54.78 ± 12.19 | 0.0048 | 0.7163 | 0.0609 |
| Non-HDL | | | | | | | | | |
| mg/dL | −50.79 ± 28.74 | −67.72 ± 14.67 | −71.86 ± 24.02 | −66.15 ± 18.77 | −69.50 ± 24.46 | −88.16 ± 23.33 | 0.0059 | 0.6509 | 0.0407 |
| % change | −35.52 ± 20.30 | −47.98 ± 8.14 | −50.34 ± 15.12 | −48.18 ± 12.95 | −49.59 ± 15.39 | −59.59 ± 14.99 | 0.0064 | 0.6227 | 0.0338 |

*P* values were obtained by ANCOVA, adjusted for baseline values.

Supplement Table 4. Comparison of lipid parameters changes from baseline to week 8 between statin monotherapy and combination of ezetimibe with lower dose of statin. (FAS analysis)

| | All | | | LDL> 135 mg/dL | | | LDL≤135 mg/dL | | |
|---|---|---|---|---|---|---|---|---|---|
| | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 |
| Total Cholesterol | | | | | | | | | |
| mg/dL | 0.3086 | 0.9833 | 0.0920 | 0.1293 | 0.4150 | 0.0546 | 0.8233 | 0.1645 | 0.8423 |
| % change | 0.3833 | 0.9183 | 0.0864 | 0.1244 | 0.4157 | 0.0404 | 0.7748 | 0.1873 | 0.9450 |
| Triglyceride | | | | | | | | | |
| mg/dL | 0.4140 | 0.4417 | 0.0966 | 0.2706 | 0.6565 | 0.0306 | 0.8202 | 0.4232 | 0.9347 |
| % change | 0.4276 | 0.5422 | 0.1678 | 0.1636 | 0.8426 | 0.0684 | 0.6450 | 0.4782 | 0.9211 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | 0.7609 | 0.9697 | 0.8076 | 0.6410 | 0.4269 | 0.5864 | 0.9903 | 0.2513 | 0.8639 |
| % change | 0.7296 | 0.8976 | 0.6999 | 0.8976 | 0.3839 | 0.4297 | 0.5313 | 0.2495 | 0.9000 |
| LDL | | | | | | | | | |
| mg/dL | 0.1344 | 0.8069 | 0.1653 | 0.0845 | 0.5231 | 0.1435 | 0.8878 | 0.4438 | 0.9420 |
| % change | 0.1325 | 0.8630 | 0.1749 | 0.0670 | 0.4490 | 0.1055 | 0.9569 | 0.4920 | 0.9804 |
| Apo B | | | | | | | | | |
| mg/dL | 0.3736 | 0.9264 | 0.1847 | 0.1678 | 0.8193 | 0.1558 | 0.3999 | 0.3912 | 0.8814 |
| % change | 0.3638 | 0.9847 | 0.1570 | 0.1214 | 0.6376 | 0.1016 | 0.5086 | 0.4349 | 0.8751 |
| Apo A1 | | | | | | | | | |
| mg/dL | 0.4841 | 0.7538 | 0.8682 | 0.6582 | 0.3962 | 0.5403 | 0.0785 | 0.0596 | 0.6484 |
| % change | 0.3728 | 0.6597 | 0.8648 | 0.7442 | 0.384 | 0.4729 | 0.0458 | 0.0541 | 0.6199 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | 0.2353 | 0.7823 | 0.2225 | 0.2794 | 0.9268 | 0.2938 | 0.4530 | 0.7155 | 0.5183 |
| % change | 0.2651 | 0.6596 | 0.1551 | 0.2611 | 0.6588 | 0.1167 | 0.5026 | 0.8835 | 0.7353 |
| Non-HDL | | | | | | | | | |
| mg/dL | 0.1799 | 0.7947 | 0.1086 | 0.1245 | 0.5224 | 0.0516 | 0.9680 | 0.5778 | 0.8962 |
| % change | 0.1668 | 0.7718 | 0.1267 | 0.0877 | 0.3970 | 0.0375 | 0.8956 | 0.6125 | 0.8984 |

Supplement Table 5. Comparison of proportion of subjects achieving low-density lipoprotein cholesterol levels below 50%, 70 mg/dL and either of below 50% or 70 mg/dL (FAS analysis)

| | R5 | R5/E10 | R10 | R10/E10 | R20 | R20/E10 | p* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 | R10 vs R5 + E10 | R20 vs R5 + E10 | R20 vs R10 + E10 |
| All | | | | | | | | | | | | |
| ≥50% | 27 (39.71) | 49 (73.13) | 42 (62.69) | 57 (83.82) | 51 (73.91) | 62 (91.18) | <0.0001 | 0.0055 | 0.0079 | 0.1952 | 0.9180 | 0.1557 |
| <70 mg/dL | 19 (27.94) | 43 (64.18) | 37 (55.22) | 57 (83.82) | 43 (62.32) | 55 (80.88) | <0.0001 | 0.0003 | 0.0161 | 0.2906 | 0.8220 | 0.0046 |
| ≥50% or <70 mg/dL | 31 (45.59) | 52 (77.61) | 47 (70.15) | 62 (91.18) | 54 (78.26) | 63 (92.65) | 0.0001 | 0.0020 | 0.0171 | 0.3255 | 0.9273 | 0.0359 |
| LDL≤135 mg/dL | | | | | | | | | | | | |
| ≥50% | 10 (34.5) | 17 (62.96) | 17 (68.0) | 21 (75.00) | 20 (71.43) | 23 (92.0) | 0.0331 | 0.5723 | 0.0560 | 0.7029 | 0.5036 | 0.7628 |
| LDL>135 mg/dL | | | | | | | | | | | | |
| <70 mg/dL | 5 (12.8) | 23 (57.5) | 15 (35.7) | 31 (77.5) | 20 (48.8) | 31 (72.1) | <0.0001 | 0.0001 | 0.0288 | 0.0480 | 0.4318 | 0.0074 |

*$p$ value by Chi-square test.

Supplement Table 6. Baseline clinical and demographic characteristics of study subjects (PP set analysis)

| | Treatment groups | | | | | | p[a)] |
|---|---|---|---|---|---|---|---|
| | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | |
| All | | | | | | | |
| n | 63 | 61 | 67 | 59 | 62 | 61 | |
| Age, years | 64.29 ± 9.24 | 65.61 ± 8.8 | 63.04 ± 10.23 | 63.8 ± 8.38 | 64.34 ± 8.1 | 64.39 ± 7.32 | 0.713 |
| BMI, kg/m$^2$ | 25.18 ± 2.51 | 25.61 ± 3.24 | 24.69 ± 2.61 | 24 ± 2.97 | 25.02 ± 2.96 | 24.96 ± 2.75 | 0.058 |
| Men (%) | 31 (49.2) | 34 (55.7) | 46 (68.7) | 36 (61) | 34 (54.8) | 35 (57.4) | 0.333 |
| Current smoker (%) | 5 (7.9) | 7 (11.5) | 15 (22.4) | 12 (20.3) | 11 (17.7) | 8 (13.1) | 0.188 |
| Diabetes mellitus (%) | 16 (25.40) | 16 (26.33) | 17 (25.37) | 10 (16.95) | 13 (20.97) | 13 (21.31) | 0.8144 |
| Hypertension (%) | 47 (74.60) | 43 (70.49) | 44 (65.67) | 45 (76.27) | 39 (62.90) | 42 (68.85) | 0.5736 |
| CHD (%) | 53 (84.1) | 51 (83.6) | 55 (82.1) | 52 (88.1) | 53 (85.5) | 52 (85.3) | 0.9621 |
| LDL > 135 mg/dL | | | | | | | |
| n | 35 | 36 | 40 | 34 | 36 | 39 | |
| Age, years | 62.77 ± 10.09 | 65.89 ± 9.22 | 62.80 ± 11.27 | 62.91 ± 7.83 | 63.97 ± 7.39 | 63.82 ± 7.42 | 0.6715 |
| BMI, kg/m$^2$ | 25.24 ± 2.79 | 26.34 ± 2.67 | 24.44 ± 2.63 | 23.71 ± 3.20 | 25.07 ± 2.88 | 25.09 ± 3.10 | 0.007 |
| Men (%) | 15 (42.86) | 17 (47.22) | 23 (57.50) | 19 (55.88) | 16 (44.44) | 20 (51.28) | 0.7513 |
| Current smoker (%) | 4 (11.43) | 5 (13.89) | 9 (22.50) | 6 (17.65) | 5 (13.89) | 6 (15.38) | 0.8551 |
| Diabetes mellitus (%) | 8 (22.86) | 8 (22.22) | 7 (17.50) | 6 (17.65) | 9 (25.00) | 10 (25.64) | 0.9289 |
| Hypertension (%) | 26 (74.29) | 22 (61.11) | 25 (62.50) | 23 (67.65) | 23 (63.89) | 26 (66.67) | 0.8774 |
| CHD (%) | 26 (74.29) | 27 (75.00) | 29 (72.50) | 29 (85.29) | 28 (77.78) | 32 (82.05) | 0.7657 |
| LDL $\geq$ 135 mg/dL | | | | | | | |
| n | 28 | 25 | 27 | 25 | 26 | 22 | |
| Age, years | 7.81 ± 0.00 | 8.32 ± 0.00 | 8.66 ± 0.00 | 9.10 ± 0.00 | 9.12 ± 0.00 | 7.20 ± 0.00 | 0.9015 |
| BMI, kg/m$^2$ | 25.09 ± 2.14 | 24.57 ± 3.72 | 25.07 ± 2.57 | 24.40 ± 2.64 | 24.95 ± 3.12 | 24.73 ± 2.04 | 0.9294 |
| Men (%) | 16 (57.14) | 17 (68.00) | 23 (85.19) | 17 (68.00) | 18 (69.23) | 15 (68.18) | 0.3921 |
| Current smoker (%) | 1 (3.57) | 2 (8.00) | 6 (22.22) | 6 (24.00) | 6 (23.08) | 2 (9.09) | 0.2889 |
| Diabetes mellitus (%) | 8 (28.57) | 8 (32.00) | 10 (37.04) | 4 (16.00) | 4 (15.38) | 3 (13.64) | 0.2277 |
| Hypertension (%) | 21 (75.00) | 21 (84.00) | 19 (70.37) | 22 (88.00) | 16 (61.54) | 16 (72.73) | 0.2835 |
| CHD (%) | 27 (96.43) | 24 (96.00) | 26 (96.30) | 23 (92.00) | 25 (96.15) | 20 (90.91) | 0.9127 |

[a)] *p* values were obtained by the chi-square test for categorical variables and ANOVA for continuous variables.
LDL, low density lipoprotein; BMI, body mass index; CHD, coronary heart disease.

Supplement Table 7. Changes of lipid parameters from baseline to week 8 between treatments (PP set analysis)

| | Treatment groups | | | | | | P | | |
|---|---|---|---|---|---|---|---|---|---|
| | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
| Total Cholesterol | | | | | | | | | |
| mg/dL | −64.98 ± 31.13 | −76.21 ± 21.14 | −84.40 ± 26.82 | −80.66 ± 29.90 | −89.71 ± 32.78 | −101.54 ± 33.24 | 0.0005 | <0.0001 | 0.0004 |
| % change | −28.93 ± 12.62 | −35.08 ± 7.56 | −37.31 ± 9.17 | −36.59 ± 10.68 | −41.32 ± 11.44 | −44.36 ± 11.08 | 0.0002 | 0.0002 | 0.0002 |
| Triglyceride | | | | | | | | | |
| mg/dL | −19.57 ± 58.55 | −34.70 ± 54.25 | −33.42 ± 63.99 | −27.93 ± 47.45 | −47.13 ± 57.39 | −62.72 ± 71.16 | 0.0118 | 0.0214 | 0.0338 |
| % change | −5.51 ± 42.86 | −14.99 ± 29.19 | −14.42 ± 38.28 | −14.74 ± 33.72 | −23.16 ± 34.32 | −27.70 ± 31.94 | 0.0257 | 0.0709 | 0.1097 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | 1.57 ± 7.91 | 5.52 ± 8.49 | 4.73 ± 9.75 | 4.39 ± 9.18 | 5.44 ± 8.96 | 6.33 ± 8.11 | 0.0124 | 0.8923 | 0.5465 |
| % change | 4.44 ± 15.95 | 12.18 ± 17.51 | 11.95 ± 24.49 | 11.29 ± 20.29 | 13.52 ± 19.97 | 15.06 ± 19.35 | 0.0032 | 0.7801 | 0.7651 |
| LDL | | | | | | | | | |
| mg/dL | −64.05 ± 27.48 | −76.57 ± 19.15 | −84.19 ± 24.90 | −81.76 ± 29.07 | −88.31 ± 30.21 | −99.05 ± 31.77 | <0.0001 | <0.0001 | 0.0004 |
| % change | −43.37 ± 16.02 | −52.82 ± 9.14 | −55.94 ± 11.43 | −56.19 ± 13.91 | −61.00 ± 14.60 | −65.15 ± 14.82 | <0.0001 | 0.0002 | 0.0001 |
| Apo B | | | | | | | | | |
| mg/dL | −45.25 ± 18.96 | −54.50 ± 12.85 | −60.01 ± 19.09 | −55.46 ± 19.74 | −63.29 ± 20.58 | −69.33 ± 21.84 | 0.0002 | <0.0001 | 0.0041 |
| % change | −36.76 ± 13.08 | −44.85 ± 8.02 | −47.13 ± 10.39 | −46.47 ± 12.27 | −51.40 ± 11.72 | −53.69 ± 12.43 | <0.0001 | 0.0004 | 0.0017 |
| Apo A1 | | | | | | | | | |
| mg/dL | 4.83 ± 16.90 | 8.93 ± 17.43 | 8.97 ± 20.53 | 8.90 ± 18.95 | 9.75 ± 18.30 | 8.20 ± 13.96 | 0.1153 | 0.9133 | 0.6681 |
| % change | 3.71 ± 11.48 | 6.95 ± 12.73 | 7.32 ± 15.38 | 7.41 ± 14.41 | 8.08 ± 13.00 | 6.56 ± 10.35 | 0.0514 | 0.7432 | 0.5797 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | −0.33 ± 0.14 | −0.43 ± 0.13 | −0.48 ± 0.27 | −0.42 ± 0.19 | −0.50 ± 0.19 | −0.53 ± 0.21 | <0.0001 | 0.0003 | 0.0240 |
| % change | −38.71 ± 12.13 | −47.79 ± 9.17 | −49.79 ± 11.99 | −49.59 ± 12.16 | −54.36 ± 12.60 | −155.96 ± 13.94 | <0.0001 | 0.0016 | 0.0077 |
| Non-HDL | | | | | | | | | |
| mg/dL | −66.56 ± 29.34 | −81.74 ± 20.78 | −89.13 ± 28.19 | −85.05 ± 29.58 | −95.15 ± 32.62 | −107.87 ± 34.36 | <0.0001 | <0.0001 | 0.0003 |
| % change | −39.04 ± 15.70 | −48.52 ± 8.48 | −51.07 ± 11.28 | −51.69 ± 12.84 | −56.28 ± 13.68 | −60.06 ± 13.97 | <0.0001 | 0.0001 | 0.0001 |

*p* values were obtained by ANCOVA, adjusted for baseline value. HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein.

Supplement Table 8. Changes of lipid parameters from baseline to week 8 between treatments in subjects with LDL> 135 mg/dL (PP set analysis)

| | Treatment groups | | | | | | p | | |
|---|---|---|---|---|---|---|---|---|---|
| | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
| Total Cholesterol | | | | | | | | | |
| mg/dL | −78.29 ± 26.42 | −86.39 ± 19.41 | −94.68 ± 24.90 | −93.88 ± 31.56 | −109.03 ± 23.10 | −111.51 ± 36.59 | 0.0087 | <0.0001 | 0.0052 |
| % change | −32.29 ± 9.32 | −36.42 ± 7.30 | −37.99 ± 8.10 | −39.59 ± 11.76 | −46.41 ± 7.26 | −45.17 ± 12.84 | 0.0051 | <0.0001 | 0.0039 |
| Triglyceride | | | | | | | | | |
| mg/dL | −15.86 ± 50.14 | −34.19 ± 60.47 | −34.30 ± 60.29 | −26.79 ± 49.42 | −56.06 ± 51.53 | −58.36 ± 77.07 | 0.0271 | 0.0002 | 0.1174 |
| % change | −4.05 ± 33.39 | −12.16 ± 28.40 | −16.75 ± 33.21 | −14.49 ± 34.62 | −30.38 ± 29.82 | −24.04 ± 31.79 | 0.0339 | 0.0004 | 0.4534 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | −0.40 ± 8.26 | 5.08 ± 7.16 | 4.80 ± 9.68 | 3.94 ± 9.18 | 5.42 ± 8.21 | 5.49 ± 7.32 | 0.0161 | 0.9449 | 0.8081 |
| % change | 0.36 ± 16.06 | 11.35 ± 16.02 | 11.94 ± 21.07 | 10.01 ± 20.24 | 13.04 ± 17.30 | 12.98 ± 17.27 | 0.0087 | 0.758 | 0.6135 |
| LDL | | | | | | | | | |
| mg/dL | −75.94 ± 24.75 | −86.19 ± 17.47 | −95.75 ± 23.13 | −96.09 ± 29.34 | −106.61 ± 20.90 | −109.05 ± 35.04 | 0.0009 | <0.0001 | 0.0135 |
| % change | −45.47 ± 12.72 | −53.01 ± 9.56 | −55.62 ± 9.38 | −58.89 ± 15.25 | −65.48 ± 9.70 | −64.11 ± 17.32 | 0.0002 | <0.0001 | 0.0087 |
| Apo B | | | | | | | | | |
| mg/dL | −52.73 ± 18.09 | −60.64 ± 11.56 | −67.92 ± 18.09 | −64.78 ± 19.76 | −74.95 ± 15.05 | −75.42 ± 24.31 | 0.0025 | <0.0001 | 0.0486 |
| % change | −38.18 ± 11.97 | −45.19 ± 8.34 | −47.84 ± 8.54 | −49.24 ± 13.05 | −55.82 ± 8.05 | −53.56 ± 14.66 | 0.0008 | <0.0001 | 0.0362 |
| Apo A1 | | | | | | | | | |
| mg/dL | 2.34 ± 17.96 | 10.29 ± 17.25 | 9.52 ± 22.25 | 6.83 ± 19.42 | 9.41 ± 17.49 | 8.17 ± 13.43 | 0.2755 | 0.6493 | 0.5048 |
| % change | 2.00 ± 12.10 | 7.85 ± 13.02 | 7.71 ± 15.74 | 5.81 ± 14.72 | 7.78 ± 12.13 | 6.37 ± 9.67 | 0.1976 | 0.7679 | 0.3651 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | −0.38 ± 0.14 | −0.47 ± 0.12 | −0.54 ± 0.32 | −0.49 ± 0.19 | −0.58 ± 0.16 | −0.57 ± 0.23 | 0.0003 | <0.0001 | 0.1781 |
| % change | −38.86 ± 12.10 | −48.59 ± 9.02 | −50.49 ± 11.04 | −51.49 ± 12.53 | −58.50 ± 9.10 | −55.65 ± 16.46 | <0.0001 | <0.0001 | 0.0858 |
| Non-HDL | | | | | | | | | |
| Mg/dL | −77.89 ± 25.57 | −91.47 ± 18.84 | −99.48 ± 27.34 | −97.82 ± 30.88 | −114.44 ± 22.29 | −117.00 ± 38.79 | 0.0007 | <0.0001 | 0.0097 |
| % change | −40.96 ± 11.47 | −48.89 ± 8.81 | −50.68 ± 9.51 | −53.60 ± 14.00 | −61.45 ± 9.03 | −59.10 ± 16.30 | 0.0001 | <0.0001 | 0.0069 |

*P* values were obtained by ANCOVA, adjusted for baseline value. HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein.

Supplement Table 9. Changes of lipid parameters from baseline to week 8 between treatments in subjects with LDL≤135 mg/dL. (PP set analysis)

| Changes | Treatment groups | | | | | | p | | |
|---|---|---|---|---|---|---|---|---|---|
| | R5 | R10 | R20 | R5 + E10 | R10 + E10 | R20 + E10 | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 |
| Total Cholesterol | | | | | | | | | |
| mg/dL | −48.36 ± 28.82 | −61.56 ± 13.73 | −69.19 ± 22.23 | −62.68 ± 14.41 | −62.96 ± 24.36 | −83.86 ± 14.89 | 0.0266 | 0.7639 | 0.0261 |
| % change | −24.74 ± 14.95 | −33.17 ± 7.67 | −36.29 ± 10.63 | −32.52 ± 7.46 | −34.28 ± 12.53 | −42.94 ± 7.00 | 0.0247 | 0.7611 | 0.0227 |
| Triglyceride | 2 | | | | | | | | |
| mg/dL | −24.21 ± 68.31 | −35.44 ± 44.98 | −32.11 ± 70.29 | −29.48 ± 45.59 | −34.77 ± 63.61 | −70.45 ± 60.18 | 0.1882 | 0.3773 | 0.1394 |
| % change | −7.33 ± 52.99 | −19.07 ± 30.41 | −10.97 ± 45.21 | −15.07 ± 33.16 | −13.17 ± 38.09 | −34.19 ± 31.88 | 0.2765 | 0.2576 | 0.1442 |
| HDL cholesterol | 3 | | | | | | | | |
| mg/dL | 4.04 ± 6.83 | 6.16 ± 10.23 | 4.63 ± 10.05 | 5.00 ± 9.34 | 5.46 ± 10.06 | 7.82 ± 9.35 | 0.2751 | 0.8045 | 0.2734 |
| % change | 9.53 ± 14.52 | 13.36 ± 19.74 | 11.98 ± 29.27 | 13.03 ± 20.63 | 14.19 ± 23.51 | 18.74 ± 22.54 | 0.1081 | 0.9258 | 0.3945 |
| LDL | 4 | | | | | | | | |
| mg/dL | −49.18 ± 23.44 | −62.72 ± 11.52 | −67.07 ± 16.18 | −62.28 ± 13.11 | −62.96 ± 21.56 | −81.32 ± 12.12 | 0.0115 | 0.6689 | 0.002 |
| % change | −40.76 ± 19.30 | −52.54 ± 8.69 | −56.41 ± 14.12 | −52.51 ± 11.10 | −54.80 ± 17.88 | −66.99 ± 8.90 | 0.0100 | 0.6342 | 0.0027 |
| Apo B | 5 | | | | | | | | |
| mg/dL | −35.91 ± 15.82 | −45.65 ± 8.93 | −48.30 ± 14.01 | −42.80 ± 10.71 | −47.14 ± 15.78 | −58.53 ± 10.09 | 0.0485 | 0.8601 | 0.011 |
| % change | −34.99 ± 14.37 | −44.36 ± 7.69 | −46.08 ± 12.75 | −42.70 ± 10.22 | −45.27 ± 13.31 | −53.94 ± 7.24 | 0.0351 | 0.8089 | 0.0118 |
| Apo A1 | 6 | | | | | | | | |
| mg/dL | 7.95 ± 15.21 | 6.98 ± 17.85 | 8.17 ± 18.07 | 11.72 ± 18.30 | 10.23 ± 19.72 | 8.24 ± 15.17 | 0.2022 | 0.5383 | 0.8568 |
| % change | 5.86 ± 10.48 | 5.65 ± 12.45 | 6.75 ± 15.11 | 9.59 ± 13.98 | 8.50 ± 14.35 | 6.90 ± 11.69 | 0.1008 | 0.4396 | 0.8249 |
| Apo B/A1 | 7 | | | | | | | | |
| mg/dL | −0.28 ± 0.11 | −0.37 ± 0.11 | −0.39 ± 0.14 | −0.34 ± 0.14 | −0.39 ± 0.17 | −0.46 ± 0.15 | 0.0072 | 0.5554 | 0.0182 |
| % change | −38.52 ± 12.38 | −46.65 ± 9.44 | −48.75 ± 13.43 | −47.02 ± 11.36 | −48.63 ± 14.58 | −56.51 ± 8.01 | 0.0093 | 0.6591 | 0.0242 |
| Non-HDL | 8 | | | | | | | | |
| mg/dL | −52.39 ± 27.92 | −67.72 ± 14.67 | −73.81 ± 22.09 | −67.68 ± 16.06 | −68.42 ± 24.94 | −91.68 ± 14.91 | 0.0062 | 0.7451 | 0.0047 |
| % change | −36.63 ± 19.74 | −47.98 ± 8.14 | −51.66 ± 13.67 | −49.10 ± 10.79 | −49.12 ± 15.82 | −61.76 ± 8.50 | 0.0063 | 0.7095 | 0.0046 |

*P* values were obtained by ANCOVA, adjusted for baseline value. HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein.

Supplement Table 10. Comparison of lipid parameters changes from baseline to week 8 between statin monotherapy and combination of ezetimibe with lower dose of statin. (PP set analysis)

| | All | | | LDL> 135 mg/dL | | | LDL≤135 mg/dL | | |
|---|---|---|---|---|---|---|---|---|---|
| | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 | R5 + E10 vs R10 | R5 + E10 vs R20 | R10 + E10 vs R20 |
| Total Cholesterol | | | | | | | | | |
| mg/dL | 0.3669 | 0.8475 | 0.0032 | 0.1918 | 0.5301 | <0.0001 | 0.9216 | 0.1327 | 0.5113 |
| % change | 0.3982 | 0.8008 | 0.0071 | 0.1794 | 0.4754 | <0.0001 | 0.9313 | 0.1468 | 0.5570 |
| Triglyceride | | | | | | | | | |
| mg/dL | 0.2584 | 0.2518 | 0.0471 | 0.2425 | 0.5225 | 0.0072 | 0.8097 | 0.3327 | 0.8713 |
| % change | 0.2858 | 0.2630 | 0.1051 | 0.1687 | 0.5960 | 0.0214 | 0.9720 | 0.3225 | 0.9754 |
| HDL cholesterol | | | | | | | | | |
| mg/dL | 0.9049 | 0.6857 | 0.9145 | 0.9029 | 0.6797 | 0.7639 | 0.8152 | 0.1877 | 0.8859 |
| % change | 0.3995 | 0.6105 | 0.7993 | 0.8092 | 0.6610 | 0.6145 | 0.3449 | 0.1898 | 0.9205 |
| LDL | | | | | | | | | |
| mg/dL | 0.1469 | 0.8849 | 0.0045 | 0.0840 | 0.4911 | <0.0001 | 0.9075 | 0.2525 | 0.5691 |
| % change | 0.1199 | 0.9226 | 0.0201 | 0.0491 | 0.3228 | <0.0001 | 0.9873 | 0.2639 | 0.5541 |
| Apo B | | | | | | | | | |
| mg/dL | 0.4315 | 0.7495 | 0.0061 | 0.2118 | 0.8621 | <0.0001 | 0.3939 | 0.2239 | 0.8282 |
| % change | 0.3954 | 0.8406 | 0.0139 | 0.1447 | 0.6239 | <0.0001 | 0.5064 | 0.2496 | 0.8210 |
| Apo A1 | | | | | | | | | |
| mg/dL | 0.4845 | 0.6711 | 0.9095 | 0.5586 | 0.5199 | 0.6244 | 0.0679 | 0.0688 | 0.6749 |
| % change | 0.3335 | 0.5832 | 0.8998 | 0.6948 | 0.5119 | 0.5532 | 0.0375 | 0.0616 | 0.6377 |
| Apo B/A1 | | | | | | | | | |
| mg/dL | 0.2570 | 0.8407 | 0.0146 | 0.3301 | 0.9505 | 0.0015 | 0.4047 | 0.9635 | 0.7878 |
| % change | 0.2637 | 0.7449 | 0.0193 | 0.2714 | 0.5185 | 0.0003 | 0.4753 | 0.8471 | 0.9917 |
| Non-HDL | | | | | | | | | |
| mg/dL | 0.1612 | 0.8143 | 0.0020 | 0.1662 | 0.4838 | <0.0001 | 0.7764 | 0.425 | 0.5919 |
| % change | 0.1122 | 0.7615 | 0.0093 | 0.1101 | 0.3263 | <0.0001 | 0.6682 | 0.4502 | 0.5721 |

*P* values were obtained by ANCOVA, adjusted for baseline value. HDL, high density lipoprotein; LDL, low density lipoprotein; Apo, apolipoprotein.

Supplement Table 11. Comparison of proportion of subjects achieving low-density lipoprotein cholesterol levels below 50%, 70 mg/dL and one of both (PP set analysis)

| | R5 | R5/E10 | R10 | R10/E10 | R20 | R20/E10 | p* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | R5 vs R5 + E10 | R10 vs R10 + E10 | R20 vs R20 + E10 | R10 vs R5 + E10 | R20 vs R5 + E10 | R20 vs R10 + E10 |
| All | | | | | | | | | | | | |
| ≥50% | 25 (39.68) | 44 (74.58) | 37 (60.66) | 54 (87.10) | 50 (74.63) | 57 (93.44) | 0.0001 | 0.0008 | 0.0041 | 0.1036 | 0.9948 | 0.0734 |
| <70 mg/dL | 19 (30.16) | 41 (69.49) | 34 (55.74) | 55 (88.71) | 43 (64.18) | 50 (81.97) | <0.0001 | <0.0001 | 0.0241 | 0.1197 | 0.5279 | 0.0011 |
| ≥50% or <70 mg/dL | 29 (46.03) | 47 (79.66) | 42 (68.85) | 59 (95.16) | 53 (79.1) | 58 (95.08) | 0.0001 | 0.0001 | 0.0078 | 0.1763 | 0.9386 | 0.0071 |
| LDL≤135 mg/dL | | | | | | | | | | | | |
| ≥50% | 10 (35.71) | 16 (64.00) | 17 (68.00) | 19 (73.08) | 20 (74.07) | 21 (95.45) | 0.0398 | 0.6908 | 0.0440 | 0.7653 | 0.4316 | 0.9344 |
| LDL>135 mg/dL | | | | | | | | | | | | |
| <70 mg/dL | 5 (14.29) | 22 (64.71) | 12 (33.33) | 31 (86.11) | 20 (50.00) | 28 (71.79) | <0.0001 | <0.0001 | 0.0473 | 0.0087 | 0.2032 | 0.0008 |

*$p$ value was obtained by Chi-square test.

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