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# Comparison of rosuvastatin 10 mg plus ezetimibe versus rosuvastatin 20 mg in atherosclerotic cardiovascular disease and type 2 diabetes

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**Studies comparing efficacy and safety of moderate-intensity statin plus ezetimibe versus high-intensity statin in patients with atherosclerotic cardiovascular disease (ASCVD) and type 2 diabetes (T2DM) are scarce. In this multicenter non-inferiority randomized trial, 223 ASCVD patients with T2DM were randomly assigned to receive either rosuvastatin 20 mg once daily or single-pill combination of rosuvastatin 10 mg plus ezetimibe 10 mg once daily for 24 weeks. Laboratory parameters and clinical events were evaluated at 12 and 24 weeks. Primary efficacy endpoint was the least square mean percent (LSM %) change of low-density lipoprotein cholesterol (LDL-C) level at 24 weeks from baseline. At 24 weeks, the LDL-C LSM % change from baseline was −13.5 in the high-intensity rosuvastatin group and −20.5 in the combination group, with the between-group difference remaining within the predefined non-inferiority margin ($p = 0.06$). Decrease in apolipoprotein B level at 24 weeks from baseline was significantly greater in the combination group than in the high-intensity rosuvastatin group (−15.6% vs. −9.9%, $p$-value = 0.008). Rates of achieving LDL-C < 55 mg/dL were higher in the combination group than in the high-intensity rosuvastatin group, with a significant difference at 12 weeks ($p = 0.01$), though the difference at 24 weeks was not statistically significant ($p = 0.09$). Incidence of total adverse events was lower in the combination groups than in the high-intensity rosuvastatin group ($p = 0.048$). Single-pill combination of moderate-intensity rosuvastatin plus ezetimibe was non-inferior to high-intensity rosuvastatin in LDL-C lowering efficacy with good safety profile in ASCVD patients with T2DM.**

**Keywords** Cardiovascular disease, Diabetes mellitus, Ezetimibe, Randomized controlled trial, Rosuvastatin calcium

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Hypercholesterolemia is a well-known risk factor for atherosclerotic cardiovascular disease (ASCVD)[1]. Statin-based trials, whether for primary or secondary prevention, have demonstrated a reduction in the risk of future cardiovascular events[2]. Recent guidelines recommend a low-density lipoprotein cholesterol (LDL-C) reduction of > 50% from baseline and an LDL-C target of 70 mg/dL for patients at high risk and an LDL-C reduction of > 50% from baseline with an LDL-C target of 55 mg/dL for secondary prevention in very-high-risk patients[3–5]. To achieve these targets, maximally tolerated statin therapy is recommended. However, in some patients, the target goal may not be reached with high-intensity statin alone[3,4] or they may be intolerant to high-intensity statin[6,7]. Statin-associated muscle symptoms (SAMS) are the most prevalent adverse effects with a dose-dependent relationship[8]. For these reasons, high-intensity statins tend to be underutilized in real-world practice[9–11]. Recent studies have reported on coronary plaque regression and reduction in major adverse cardiovascular events (MACE) associated with ezetimibe as a non-statin combination therapy[12,13]. As a result, the need for ezetimibe combination therapy in addition to high-intensity statin monotherapy is increasing in clinical practice to lower LDL-C. East Asian populations, including Chinese and Korean individuals, exhibit increased sensitivity to statins due to differences in Cytochrome P450 2C9 (CYP2C9) genetic polymorphisms and lower average body mass index (BMI), leading to a higher incidence of statin-associated adverse effects[12]. Given this increased sensitivity, major lipid guidelines, including the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and 2022 American Heart Association (AHA)/American College of Cardiology (ACC) recommendations, recognize rosuvastatin 20 mg as an appropriate high-intensity dose for East Asian populations, providing potent LDL-C lowering efficacy with a lower risk of adverse events compared to 40 mg[3,13]. Patients with type 2 diabetes (T2DM) exhibit poorer outcomes following acute coronary syndrome (ACS) and are at an increased risk of developing coronary artery disease. As a result, they require more intensive LDL-C lowering therapy[14]. However, studies on ezetimibe combination therapy in T2DM patients are mostly subgroup studies[15,16]. It remains unclear whether single-pill combination of moderate-intensity statin plus ezetimibe is as effective and safe as high-dose statin monotherapy for ASCVD patients with T2DM. The purpose of this study was to compare the efficacy and safety of moderate-intensity rosuvastatin plus ezetimibe to those of high-intensity rosuvastatin monotherapy in patients with ASCVD and T2DM.

## Methods

### Study design

This study was a multicenter, open-label, non-inferiority, randomized trial. Adults aged over 19 years who had been diagnosed with T2DM (and had been taking oral hypoglycemic medications for at least 3 months) and ASCVD were eligible for inclusion in this study. ASCVD was defined as one of the followings: stable angina, unstable angina, myocardial infarction (MI), stroke or transient ischemic attack, peripheral artery disease, and history of percutaneous coronary intervention and coronary artery bypass graft surgery. Exclusion criteria were:[1] type 1 diabetes mellitus (DM);[2] uncontrolled DM defined as hemoglobin A1c (HbA1c) > 8.5%;[3] fasting triglyceride (TG) ≥ 400 mg/dL;[4] history of significant statin and/or ezetimibe-induced myopathy or rhabdomyolysis;[5] history of serious hypersensitivity reaction to rosuvastatin or ezetimibe;[6] alanine aminotransferase (AST) and/or aspartate aminotransferase (ALT) > 3 times the upper limit of normal or history of active liver disease;[6] estimated glomerular filtration rate (eGFR; Modification of Diet in Renal Disease (MDRD) equation) < 30 mL/min/1.73m$^2$;[7] creatine kinase (CK) levels > 5 times of the upper limit of normal;[8] those who were participating in other clinical trials; and[9] those who were considered unsuitable for participation in this clinical trial by investigators. The total duration of this study was 28 consecutive weeks, including a 4-week screening period with rosuvastatin 10 mg per day and a 24-week active treatment period. At the time of enrollment, patients were either receiving prior lipid-lowering therapy or were statin-naïve. To standardize treatment before randomization, all participants underwent a 4-week run-in phase with rosuvastatin 10 mg daily, without a specific washout period. Patients were randomly assigned to receive either a single-pill combination of rosuvastatin 10 mg plus ezetimibe 10 mg (R10Z group) once daily or rosuvastatin 20 mg (R20 group) once daily for 24 weeks in addition to standard care (Supplementary Fig. 1). The allocation sequence was securely implemented by automated randomisation, ensuring assignment was concealed until each participant was allocated. Both treatment groups received similar administration procedures and participant instructions to ensure consistency in intervention delivery. This trial was registered at ClinicalTrials.gov with the identifier NCT03597412 on 24/07/2018, with the enrollment of the first participant occurring on 02/10/2018. Between 02/10/2018 and 12/08/2020, a total of 256 patients were screened for eligibility, and 236 patients were randomly assigned to the R10Z group (118 patients) or the R20 group (118 patients) across 10 centers in South Korea (Fig. 1). There were no significant changes to the trial methods or eligibility criteria after the trial commenced. Among them, 111 patients in the R10Z group and 112 patients in the R20 group received study medication and completed the study (full analysis set (FAS)). A total of 195 patients (97 patients in the R10Z group 98 patients in the R20 group) were included in the per protocol (PP) set, excluding 28 patients (14 patients in the R10Z group and 14 patients in the R20 group) with serious violations who were dropped out from FAS. The study protocol was approved by the Institutional Review Board (IRB) of Kangbuk Samsung Hospital (IRB No: KBSMC 2018-05-040) and the IRBs of all participating centers. This study was conducted in accordance with the Declaration of Helsinki and relevant ethical guidelines, and all participants provided written informed consent before enrollment.

### Efficacy and safety measures

The primary efficacy endpoint was the least squares mean (LSM) % change in LDL-C at 24 weeks, calculated from the LDL-C levels measured at randomization rather than at screening. Main secondary efficacy endpoints were LDL-C change at 12 weeks from baseline, changes of total cholesterol, high density lipoprotein cholesterol (HDL-C), TG, fasting plasma glucose (FPG), HbA1c, and homeostasis model assessment-insulin resistance (HOMA-IR) at 12 and 24 weeks from baseline, and changes of apolipoprotein A1 (ApoA1), apolipoprotein B

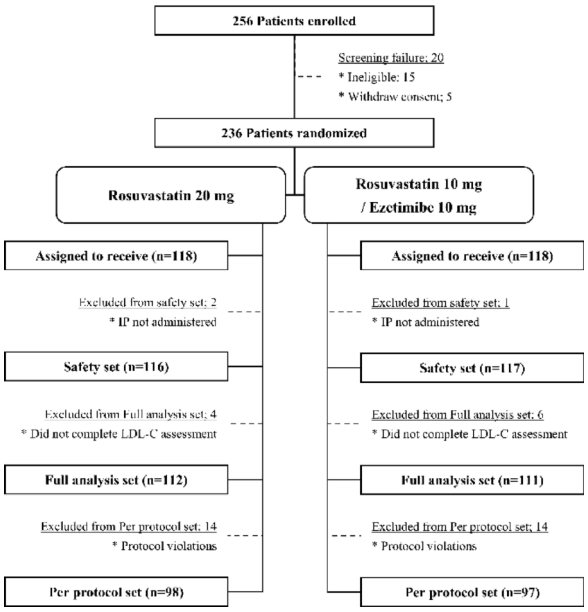


**Fig. 1**. Study flow chart showing the selection of subjects. LDL-C, low-density lipoprotein cholesterol.

(ApoB), apolipoprotein B48 (ApoB48), and apolipoprotein B/apolipoprotein A1 ratio (Apo B/A1) at 24 weeks. All efficacy measures were determined in the central lab after fasting for eight hours. The proportion of those achieving LDL-C < 70 mg/dL and LDL-C < 55 mg/dL at 12 weeks and 24 weeks and the incidence of major adverse cardiovascular and cerebrovascular event (MACCE) during the trial period were assessed. Safety was evaluated through investigator interviews, patient-reported symptoms/signs, and laboratory tests. Adverse events were assessed using predefined criteria, including investigator evaluations of causality (definitely, probably, possibly, or probably not related to study medication), severity (mild, moderate, or severe), and seriousness (death or life-threatening events, prolonged hospitalization, and/or disability/incapacitation). Laboratory parameters, including CK and liver enzyme (AST/ALT) levels, were regularly monitored to support the objective assessment of statin-related adverse effects. Additionally, all adverse event reports were independently reviewed by a safety monitoring board to minimize potential subjectivity in attribution. Pre-specified primary and secondary outcomes remained unchanged throughout the trial.

### Statistical analysis

The primary efficacy analysis was conducted using an intention-to-treat (ITT) approach based on the FAS, which included all randomized participants except those with major protocol violations. Additionally, a PP analysis was performed as a supplementary analysis, including only participants who adhered to the study protocol without major deviations. No interim analyses or specific stopping guidelines were applied, as the trial was completed as planned. Efficacy analyses were conducted for the FAS population ($n = 223$). Continuous variables are expressed as mean ± standard deviation or median [interquartiles]. Categorical variables are expressed as numbers and percentages. Student's t-test (or Mann-Whitney U test) was used to compare means of continuous variables and Chi-square test or Fisher's exact test was used to compare categorical variables depending on the distribution of values. The non-inferiority margin was an absolute difference of 9% in least square mean (LSM) % change in LDL-C at 24 weeks. For continuous variables among primary and secondary efficacy endpoints, analysis of covariance (ANCOVA) was performed using baseline value and stratification factor (LDL-C ≤ 100 mg/dL and > 100 mg/dL at screening) as covariates. All correlation analyses were performed in the FAS population ($n = 223$). Correlations were assessed using Pearson's or Spearman's correlation coefficients as appropriate. For correlation analyses involving changes in variables, the differences between baseline and Week 24 values (Δ change = Week 24 – Baseline) were used. P-values < 0.05 were considered statistically significant. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc, Cary, NC, USA). The full trial protocol is available upon request from the corresponding author.

## Results

### Patient characteristics

The trial was completed as scheduled, with no early termination or stopping due to adverse events or other reasons. In the overall population, mean age was 65 years and the proportion of males was 81.6%. Baseline characteristics (Table 1) were not significantly different between the two groups except for current smoking status. The proportion of previous history of ACS was 74.4% and mean DM duration was 7.2 years. Baseline mean LDL-C level at randomization was 72.1 ± 23.1 mg/dL in the R10Z group and 69.8 ± 17.9 mg/dL in the R20 group ($p = 0.65$). Other lipid parameters, HbA1c, FPG, HOMA-IR, and medications were not significantly different between the two groups.

| | R20 *N* = 112 | R10Z *N* = 111 | Total *N* = 223 | *p*-value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, years | 64.9 ± 10.0 | 65.0 ± 9.1 | 64.9 ± 9.6 | 0.99 |
| Male, n (%) | 97 (86.6) | 85 (76.6) | 182 (81.6) | 0.05 |
| BMI, kg/m$^2$ | 25.5[23.8,27.2] | 25.0[23.2,27.1] | 25.3[23.6,27.1] | 0.28 |
| Systolic BP, mmHg | 129.9 ± 13.5 | 128.2 ± 18.4 | 129.0 ± 16.1 | 0.43 |
| Diastolic BP, mmHg | 75.7 ± 9.2 | 74.3 ± 12.0 | 75.0 ± 10.7 | 0.35 |
| Heart rate, beats/min | 72.5 [65.0,79.0] | 72.0[67.0,78.5] | 72.0[66.0,79.0] | 0.43 |
| Comorbidity | – | – | – | – |
| Current smoking, n (%) | 35 (31.3) | 19 (17.1) | 54 (24.2) | 0.01 |
| Hypertension, n (%) | 67 (59.8) | 70 (63.1) | 137 (61.4) | 0.62 |
| Heart failure, n (%) | 4 (3.6) | 1 (0.9) | 5 (2.2) | 0.37 |
| COPD, n (%) | 2 (1.8) | 1 (0.9) | 3 (1.4) | 0.99 |
| CKD*, n (%) | 2 (1.8) | 1 (0.9) | 3 (1.4) | 0.99 |
| Type of ASCVD | – | – | – | – |
| Stable Angina, n (%) | 23 (20.5) | 14 (12.6) | 37 (16.6) | 0.11 |
| Unstable Angina, n (%) | 31 (27.7) | 30 (27.0) | 61 (27.4) | 0.91 |
| Non-STEMI, n (%) | 21 (18.8) | 28 (25.2) | 49 (22.0) | 0.24 |
| STEMI, n (%) | 30 (26.8) | 26 (23.4) | 56 (25.1) | 0.56 |
| History of PCI, n (%) | 78 (69.6) | 80 (72.1) | 158 (70.9) | 0.69 |
| History of CABG, n (%) | 1 (0.9) | 1 (0.9) | 2 (0.9) | 0.99 |
| Stroke or TIA, n (%) | 6 (5.4) | 4 (3.6) | 10 (4.5) | 0.75 |
| DM duration, year | 7.3[3.4,13.1] | 7.1[3.1,13.7] | 7.3[3.3,13.6] | 0.88 |
| ASCVD duration, year | 6.7[2.0,10.2] | 5.1[2.5,8.3] | 5.5[2.3,9.6] | 0.19 |
| Laboratory data | | | | |
| LDL-Cholesterol, mg/dL† | 69.8 ± 17.9 | 72.1 ± 23.1 | 71.0 ± 20.7 | 0.65 |
| Total-Cholesterol, mg/dL | 128.0 ± 23.5 | 131.6 ± 25.9 | 129.8 ± 24.7 | 0.28 |
| HDL-Cholesterol, mg/dL† | 43.9 ± 10.6 | 44.3 ± 10.3 | 44.0 ± 10.4 | 0.75 |
| Triglyceride, mg/dL† | 140.5 ± 59.3 | 151.1 ± 80.4 | 145.8 ± 70.6 | 0.69 |
| Apolipoprotein A1, mg/dL† | 140.2 ± 26.6 | 139.3 ± 24.1 | 139.7 ± 25.3 | 0.98 |
| Apolipoprotein B, mg/dL | 74.0 ± 16.1 | 76.2 ± 17.9 | 75.1 ± 17.0 | 0.35 |
| Apolipoprotein B48, mg/dL | 0.6[0.3,0.9] | 0.5[0.4,1.2] | 0.6[0.3,1.0] | 0.79 |
| Apolipoprotein B/ A1 ratio | 0.5[0.5,0.6] | 0.5[0.5,0.6] | 0.5[0.5,0.6] | 0.34 |
| HbA1c, % | 6.7[6.3,7.1] | 6.9[6.5,7.4] | 6.8[6.4,7.2] | 0.01 |
| FPG, mg/dL | 130.0[116.0,144.0] | 128.0[113.0,149.0] | 128.0[116.0,147.0] | 0.83 |
| HOMA-IR | 2.8[1.8,4.8] | 2.8[1.4,5.4] | 2.8[1.5,4.9] | 0.84 |
| Medication | | | | |
| Aspirin, n (%) | 69 (61.6) | 63 (56.8) | 132 (59.2) | 0.46 |
| Beta-blocker, n (%) | 79 (70.5) | 80 (72.1) | 159 (71.3) | 0.80 |
| RASiACEi/ARB, n (%) | 53 (47.3) | 51 (46.0) | 104 (46.6) | 0.84 |
| Calcium channel blocker, n (%) | 14 (12.5) | 10 (9.0) | 24 (10.8) | 0.40 |
| Nitrates, n (%) | 43 (38.4) | 36 (32.4) | 79 (35.4) | 0.35 |
| Combination (ACEi/ARB and Calcium channel blocker), n (%) | 12 (10.7) | 13 (11.7) | 25 (11.2) | 0.81 |

**Table 1**. Baseline characteristics of full analysis set population. R20, rosuvastatin 20 mg group; R10Z, rosuvastatin 10 mg with ezetimibe 10 mg; n, number; BMI, body-mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ASCVD, atherosclerotic cardiovascular disease; STEMI, ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; TIA, transient ischemic attack; DM, diabetes mellitus; LDL-cholesterol, low density lipoprotein cholesterol; HDL-cholesterol; hs-CRP, high sensitivity C-reactive protein; FPG, fasting plasma glucose; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker. Variables with a normal distribution are presented as mean ± standard deviation and those with a non-normal distribution are presented as median [interquartile]. Categorical variables are presented as n (%). *CKD was denied as serum creatinine > 2 mg/dL. †Although mean ± standard deviation values were provided to facilitate comprehension, statistics were calculated using a non-parametric method.

| Items | | | Rosuvastatin ($N=112$) | Rosuvastatin/Ezetimibe ($N=111$) | LSM Difference between groups | $p$-value† |
|---|---|---|---|---|---|---|
| LDL-Cholesterol | Baseline | Mean ± SD, mg/dL | 69.8 ± 17.9 | 72.1 ± 23.1 | | |
| | Week 12 | Mean ± SD, mg/dL | 62.2 ± 21.4‡ | 56.4 ± 22.8‡ | | |
| | Week 24 | Mean ± SD, mg/dL | 60.0 ± 21.1‡ | 55.1 ± 21.6‡ | | |
| | Week 12 | LSM ± SE change, % | −9.0 ± 3.1 | −18.3 ± 3.1 | 9.3 ± 4.4 | 0.04 |
| | Week 24 | LSM ± SE change, % | −13.5 ± 2.6 | −20.5 ± 2.6 | 7.0 ± 3.7 | 0.06 |
| Total-Cholesterol | Baseline | Mean ± SD, mg/dL | 128.0 ± 23.5 | 131.59 ± 25.9 | | |
| | Week 12 | Mean ± SD, mg/dL | 121.6 ± 27.6‡ | 116.3 ± 27.7‡ | | |
| | Week 24 | Mean ± SD, mg/dL | 119.7 ± 25.6‡ | 115.1 ± 25.1‡ | | |
| | Week 12 | LSM ± SE change, % | −6.8 ± 3.4 | −12.7 ± 3.4 | 5.9 ± 2.4 | 0.01 |
| | Week 24 | LSM ± SE change, % | −8.2 ± 3.0 | −13.1 ± 2.9 | 4.9 ± 2.1 | 0.02 |
| HDL-Cholesterol | Baseline | Mean ± SD, mg/dL | 43.9 ± 10.6 | 44.3 ± 10.3 | | |
| | Week 12 | Mean ± SD, mg/dL | 42.4 ± 10.2§ | 43.9 ± 10.6 | | |
| | Week 24 | Mean ± SD, mg/dL | 42.3 ± 10.2 | 44.0 ± 9.1 | | |
| | Week 12 | LSM ± SE change, % | −0.06 ± 2.7 | 2.7 ± 2.6 | −2.7 ± 2.0 | 0.18 |
| | Week 24 | LSM ± SE change, % | −0.7 ± 2.5 | 2.6 ± 2.4 | −3.3 ± 1.9 | 0.08 |
| Triglyceride | Baseline | Mean ± SD, mg/dL | 140.5 ± 59.3 | 151.1 ± 80.4 | | |
| | Week 12 | Mean ± SD, mg/dL | 144.1 ± 66.0 | 137.9 ± 69.9 | | |
| | Week 24 | Mean ± SD, mg/dL | 138.7 ± 60.8 | 130.6 ± 62.5§ | | |
| | Week 12 | LSM ± SE change, % | 3.3 ± 6.9 | −1.9 ± 6.8 | 5.2 ± 5.2 | 0.32 |
| | Week 24 | LSM ± SE change, % | −3.7 ± 6.0 | −10.4 ± 5.8 | 6.7 ± 4.5 | 0.14 |

**Table 2**. Percent change* of lipid parameters from baseline at 12 weeks and 24 weeks. LSM, least square mean; LDL-cholesterol, low-density lipoprotein cholesterol; SD, standard deviation; SE, standard error; HDL-cholesterol, high-density lipoprotein cholesterol. *Percent change (%) = [(value at week 12 or 24)- (baseline value)]/ (baseline value) × 100. †The $p$-value shows difference between the two groups in the amount of reduction for each cholesterol level from baseline at 12 and 24 weeks. ‡$p$-value < 0.0001 for difference from baseline values. §$p$-value < 0.05 for difference from baseline values.

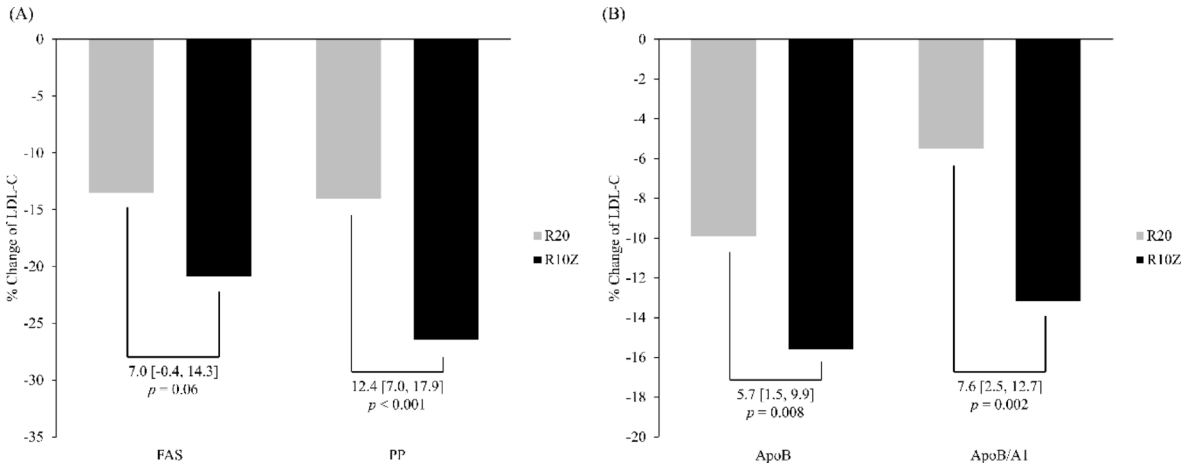


**Fig. 2**. Percent change of LDL-cholesterol (**A**) and apolipoprotein (**B**) at 24 weeks. $p$-values for analysis of covariance (ANCOVA) test. LDL-C, low-density lipoprotein cholesterol.

## Efficacy

Medication adherence was similar between the two groups (94.3% in the R10Z group and 95.4% in the R20 group, $p=0.73$). After 24 weeks of treatment, LDL-C was significantly decreased from baseline in both groups (-20.5% in R10Z group and − 13.5% in R20 group, $p$-value < 0.001 in both groups, Table 2; Fig. 2A). The LSM % difference between R10Z and R20 groups was 7.0% ($p$ for non-inferiority = 0.06). In the PP Set, the R10Z group showed greater reduction in LDL-C than the R20 group (− 14.1% vs. −26.5%, $p<0.001$; the LSM difference between the two groups: 12.4%, Fig. 2A).

The % change from baseline in secondary efficacy endpoints at 12 and 24 weeks of treatment as well as between group difference were summarized for the FAS population. Results are shown in Tables 2 and 3. At 12 weeks, the difference in LDL-C change between the R10Z group and the R20 group was 9.33% ($p$-value = 0.035).

| Items | | | R20 ($N=112$) | R10Z ($N=111$) | LSM Difference between groups | $p$-value† |
|---|---|---|---|---|---|---|
| Apolipoprotein A1 | Baseline | Mean ± SD, mg/dL | 140.2 ± 26.6 | 139.3 ± 24.1 | | |
| | Week 24 | Mean ± SD, mg/dL | 134.4 ± 23.8‡ | 137.2 ± 23.1 | | |
| | Week 24 | LSM ± SE change, % | −1.2 ± 2.2 | 0.5 ± 2.1 | −1.8 ± 1.66 | 0.29 |
| Apolipoprotein B | Baseline | Mean ± SD, mg/dL | 74.0 ± 16.1 | 76.2 ± 17.9 | | |
| | Week 24 | Mean ± SD, mg/dL | 68.6 ± 17.0§ | 65.4 ± 16.5§ | | |
| | Week 24 | LSM ± SE change, % | −9.9 ± 3.0 | −15.6 ± 3.0 | 5.7 ± 2.1 | 0.008 |
| Apolipoprotein B48 | Baseline | Mean ± SD, mg/dL | 0.7 ± 0.5 | 0.7 ± 0.5 | | |
| | Week 24 | Mean ± SD, mg/dL | 0.7 ± 0.5 | 0.6 ± 0.5 | | |
| | Week 24 | LSM ± SE change, % | 26.2 ± 19.0 | 6.3 ± 18.6 | 19.9 ± 14.5 | 0.17 |
| Apolipoprotein B/A1 | Baseline | Mean ± SD | 0.5 ± 0.2 | 0.6 ± 0.2 | | |
| | Week 24 | Mean ± SD | 0.5 ± 0.2 | 0.5 ± 0.1§ | | |
| | Week 24 | LSM ± SE change, % | −5.5 ± 3.5 | −13.2 ± 3.4 | 7.6 ± 2.6 | 0.004 |
| HbA1c | Baseline | Mean ± SD, % | 6.8 ± 0.7 | 7.0 ± 0.7 | | |
| | Week 12 | Mean ± SD, % | 6.9 ± 0.9‡ | 7.11 ± 0.8‡ | | |
| | Week 24 | Mean ± SD, % | 7.1 ± 0.9§ | 7.3 ± 1.0§ | | |
| | Week 12 | LSM ± SE change, % | −0.3 ± 1.5 | −0.2 ± 1.4 | −0.07 ± 1.1 | 0.95 |
| | Week 24 | LSM ± SE change, % | 2.9 ± 2.0 | 4.0 ± 2.0 | −1.1 ± 1.5 | 0.47 |
| FPG | Baseline | Mean ± SD, mg/dL | 131.9 ± 23.0 | 136.9 ± 40.0 | | |
| | Week 12 | Mean ± SD, mg/dL | 139.8 ± 32.0 | 135.3 ± 27.9 | | |
| | Week 24 | Mean ± SD, mg/dL | 138.0 ± 33.1 | 140.6 ± 38.5 | | |
| | Week 12 | LSM ± SE change, % | 1.5 ± 4.1 | −0.5 ± 4.0 | 2.0 ± 3.1 | 0.52 |
| | Week 24 | LSM ± SE change, % | 2.2 ± 4.3 | 4.3 ± 4.2 | −2.2 ± 3.2 | 0.51 |
| HOMA-IR | Baseline | Mean ± SD | 3.9 ± 3.6 | 4.7 ± 6.0 | | |
| | Week 12 | Mean ± SD | 4.3 ± 4.2‡ | 3.6 ± 2.5‡ | | |
| | Week 24 | Mean ± SD | 4.7 ± 6.9‡ | 4.5 ± 6.5‡ | | |
| | Week 12 | LSM ± SE change, % | 46.4 ± 52.4 | 2.9 ± 50.9 | 43.6 ± 39.7 | 0.27 |
| | Week 24 | LSM ± SE change, % | 37.1 ± 34.0 | 32.1 ± 33.1 | 5.0 ± 25.8 | 0.85 |

**Table 3**. Percent change* of other laboratory parameters from baseline at 12 and 24 weeks. LSM, least square mean; SD, standard deviation; SE, standard error; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance. *Percent change (%) ={(value at week 12 or 24)- (baseline value)}/ (baseline value) x 100. †The p-value shows difference between the two groups in the amount of reduction for each cholesterol level from baseline at 12 and 24 weeks. ‡$p$-value < 0.05 for difference from baseline values. §$p$-value < 0.0001 for difference from baseline values.

The % change of ApoB (−15.6% vs. −9.9%, $p$-value = 0.008) and that of ApoB/ApoA1 ratio (−13.2% vs. −5.5%, $p$-value = 0.004) at 24 weeks were greater in the R10Z group than in the R20 group (Fig. 2B). A significant positive correlation was observed between ApoB and LDL-C reductions from baseline to Week 24 ($r = 0.9201$, $p < 0.001$). Further details on this correlation analysis are provided in Supplementary Fig. 2 and Supplementary Table 1. However, changes in HDL cholesterol, TG, ApoA1, ApoB48, HbA1c, FPG, and HOMA-IR at 12 and 24 weeks showed no significant differences between the two groups.

Achieving rates for LDL-C < 70 mg/dL at 12 and 24 weeks were excellent in both groups, ranging from 79.5% (R20 group) to 82.9% (R10Z group) (Fig. 3). However, there was no significant difference in the proportion of responders with LDL-C levels below 70 mg/dL (difference in proportion: 2.5% ($p = 0.67$) at 12 weeks and 3.4% ($p = 0.51$) at 24 weeks, Fig. 3A). Meanwhile, achieving rate for LDL-C < 55 mg/dL at 12 weeks was significantly higher in the R10Z group than in the R20 group (difference in proportion: 16.6%, $p = 0.01$, Fig. 3B), which such rate at 24 weeks showed a trend to be higher in the R10Z group (difference in proportion: 11.2%, $p = 0.09$).

## Safety

The incidence of total AEs was lower in the R10Z group than in the R20 group (28.2% vs. 40.5%, $p = 0.048$) (Supplementary Table 2). Abnormalities in laboratory test and musculoskeletal AEs were very low in both groups, showing no significant differences between the two groups. Permanent discontinuation rates due to AEs occurred in 3 (2.6%) subjects in the R10Z group and 5 (4.3%) subjects in the R20 group ($p = 0.50$). Although the sample size was small and the follow-up period was limited to 24 weeks, no significant difference in MACCE incidence was observed between the two groups ($p = 0.50$).

## Discussion

In the present study, the LDL-C lowering effect of single-pill combination of rosuvastatin 10 mg plus ezetimibe 10 mg was non-inferior to that of rosuvastatin 20 mg after 24 weeks of treatment in ASCVD patients with T2DM. The achievement rate of reducing ApoB, ApoB/ApoA1, and LDL-C to target levels was greater in the single-pill

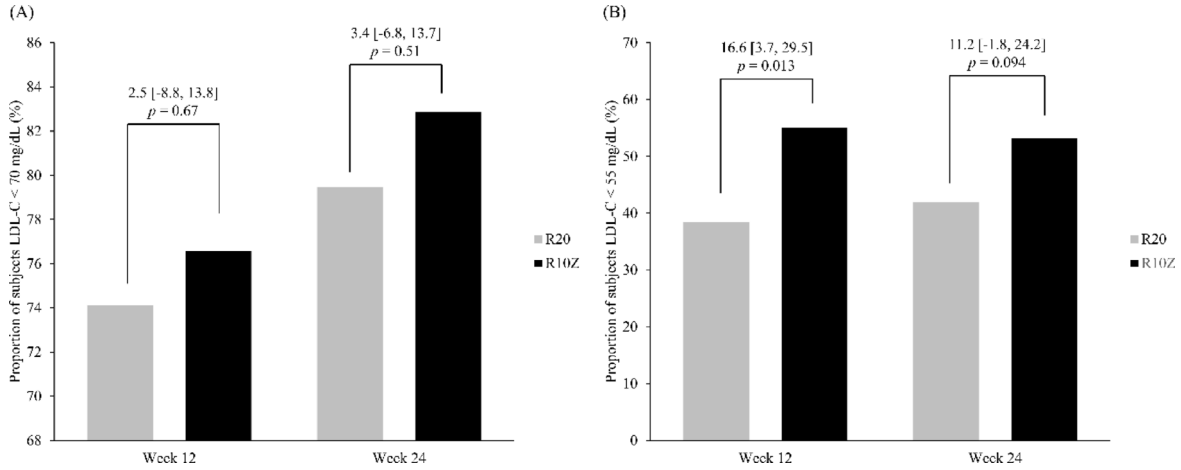


**Fig. 3**. Target achievement for LDL-cholesterol < 70 mg/dL (**A**) and < 55 mg/dL (**B**) at 12 weeks and 24 weeks. *p*-values for Chi-square test. LDL-C, low-density lipoprotein cholesterol.

combination group. Both treatment groups were generally well tolerated, with the single-pill combination group showing fewer overall adverse events.

In patients with T2DM, current guidelines recommend aggressive LDL-C reduction with high-intensity statin as an initial therapy, especially in patients who have already had ASCVD[3,13]. However, safety issues including liver enzyme elevation, statin-associated muscle symptoms, and new-onset diabetes tend to limit the use of high-intensity statins in clinical practice. Recently, a Swedish nationwide cohort study showed that the proportion of patients taking high-intensity statin at post-MI 1-year was just less than half and that ezetimibe was used by 7% after post-MI 6–10 weeks[17]. In another European study, the rate of patients receiving high-intensity statin monotherapy in patients with established ASCVD was 38%[7]. LDL-C goal achievement rates in the high-intensity statin group were 45% for LDL-C < 70 mg/dL and 22% for LDL-C < 55 mg/dL, respectively. Meanwhile, the goal achievement rates in the ezetimibe combination group were 54% and 21%, respectively. However, statin use in the combination group included moderate, high, or unknown intensity[7]. The combination therapy with moderate-intensity statin and ezetimibe is often used to lower LDL-C intensively in individuals who have statin intolerance or do not reach the target goal. In Korea, ezetimibe has been covered by the National Health Insurance in Korea and single-pill combination formulations of statin and ezetimibe have been developed six years ago. Thus, the combination therapy with statin and ezetimibe in Korea has been used as an initial LDL-C lowering drug more frequently than in other countries. In a prospective, randomized trial with non-ST elevation ACS patients, ezetimibe added to rosuvastatin 10 mg exhibited a greater reduction in LDL-C by 15% at week 12 than rosuvastatin 20 mg[18]. In the VOYAGER (an indiVidual patient data meta-analysis Of statin therapY in At risk Groups: Effects of Rosuvastatin, atorvastatin, and simvastatin) database analysis, 62.3% in the rosuvastatin 10 mg group and 79.5% in the rosuvastatin 20 mg group achieved LDL-C goal of either < 70 mg/dl or ≥ 50% reduction in high-risk patients[6]. In our study, the rosuvastatin 20 mg group had a similar goal achievement rate as those of previous studies. By adding ezetimibe, the rosuvastatin 10 mg group could achieve a rate similar to that of the rosuvastatin 20 mg group. Recent European guidelines recommend to lower LDL-C to below 55 mg/dL in patients at very high risk[13]. The LDL-C target in patients with coronary artery disease was reduced to 55 mg/dL in the Korean dyslipidemia guidelines published in 2022[19]. In our trial, 108 (48.4%) patients reached LDL-C below 55 mg/dL at week 24. This proportion was significantly higher in the R10Z group at 12 weeks and numerically higher at 24 weeks, indicating that the combination treatment was more effective in achieving target of < 55 mg/dL of LDL-C.

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) has compared efficacy of moderate-intensity statins and moderate-intensity statins with ezetimibe[20]. It is generally known that ezetimibe add-on therapy is comparable to 3-step statin uptitration in LDL-C lowering by 15–18%[21]. In the IMPROVE-IT study, adding ezetimibe to a moderate statin resulted in a 24% lower LDL-cholesterol at 1 year and a 6.4% reduction in MACE during the study period. In diabetic patients, the clinical benefit of adding ezetimibe to statin was greater than in non-diabetic patients (p for interaction = 0.02)[15]. Furthermore, the RACING (RAndomized Comparison of Efficacy and Safety of Lipid-lowerING With Statin Monotherapy Versus Statin/Ezetimibe Combination for High-risk Cardiovascular Diseases) trial has recently reported that moderate-intensity statin plus ezetimibe is non-inferior to high-intensity statin alone in reducing the risk of cardiovascular events in ASCVD patients[22]. Meanwhile, the combination therapy showed a greater achievement rate of LDL-C goal than the high-intensity statin alone, similar to our results[22]. However, these results may require careful interpretation as follows. First, the concept of 'Lower is Better' in LDL-C is still valid for risk reduction of ASCVD, which is the ultimate goal of LDL-C lowering therapy. In both our study and the RACING study, the group of patients taking high-intensity statin alone had a lower rate in achieving the LDL-C target compared to the group taking moderate-intensity statin and ezetimibe. Therefore, patients who do not reach the target LDL-C level while taking high-intensity statin alone could potentially benefit from adding ezetimibe to their treatment regimen to lower their LDL-C levels further. Currently, guidelines recommend statin as the initial treatment.

However, there is no research comparing the effectiveness of statin and ezetimibe in cardiovascular events with similar LDL-C reductions. Second, both studies found that the high-intensity statin group had more adverse events. However, since these studies were conducted in an open-label design, there might be a bias towards concerns about high-intensity statins causing more side effects. Recent trials suggested a nocebo effect on statin-associated muscle symptoms, meaning that the perception of side effects can be influenced by expectations[23,24].

A greater reduction in ApoB was observed in the R10Z group, which was significantly correlated with the reduction in LDL-C, reinforcing the close relationship between these two lipid parameters. ApoB is a major apolipoprotein present in all potentially atherogenic lipoprotein particles, and its concentration reflects the total number of LDL particles, making it a strong indicator of the adequacy of lipid-lowering therapy[25]. Mendelian randomization studies have suggested that apoB, as a marker of the number of atherogenic particles, may be a more accurate index of the adequacy of LDL lowering therapy than LDL-C[26,27]. Several studies have demonstrated that ezetimibe, whether used alone or in combination with statins, can effectively lower ApoB and chylomicron remnants[28–32]. While our study showed a significant reduction in ApoB levels, the observed decrease in ApoB48 was not statistically significant. Therefore, the potential effect of ezetimibe on ApoB48 reduction requires further investigation. In addition to its LDL-C and ApoB-lowering effects, ezetimibe has also been reported to exert pleiotropic effects, including improvement in endothelial function and reductions in inflammation markers[33,34]. Notably, previous studies have suggested that ezetimibe can reduce small dense LDL-C, a highly atherogenic lipoprotein subfraction that is more prevalent in patients with diabetes and insulin resistance[35]. These findings suggest that the clinical benefit of ezetimibe may extend beyond traditional lipid metrics, supporting its value in high-risk populations such as patients with T2DM.

A number of studies have reported effects of statins on glucose metabolism and the risk of developing new-onset diabetes. Previous studies have suggested that ezetimibe might improve glucose metabolism or insulin resistance[36–38]. However, as previous studies about the effect of ezetimibe added to statin on insulin resistance have reported conflicting results[37,39–41], the effect of ezetimibe on diabetes development or control is not yet conclusive. In our study including only T2DM patients, there were no differences in FPG, HbA1c, or HOMA-IR between the two groups after a 24-week treatment. Further research is needed to determine effects of rosuvastatin and ezetimibe on glucose metabolism.

This study has some limitations. First, our study was not designed to assess effects of moderate-intensity statin plus ezetimibe versus high-intensity statin on cardiovascular events. In addition, it had a small number of subjects with a relatively short duration. Therefore, this study cannot determine the impact of the two treatment strategies on CV events. A larger, long-term study on ASCVD patients with T2DM is needed to define effects of the two strategies on CV outcomes. Second, the present study cannot be extended to other ethnicities because our study only included Asians. Third, as an open-label trial, this study may have introduced potential bias, particularly in the attribution of adverse effects. To minimize subjectivity, adverse events were assessed using predefined criteria, supported by laboratory evaluations, and reviewed by an independent safety monitoring board. Strengths of this study include its randomized design, which directly compares the effects of moderate-intensity statin plus ezetimibe versus high-intensity statin in ASCVD patients with T2DM. This study provides valuable clinical evidence on lipid-lowering strategies in this high-risk population. The primary efficacy endpoint, the LSM % change in LDL-C, was calculated from LDL-C levels measured at randomization rather than at screening, ensuring that the observed differences directly reflect the effects of the assigned treatments. The use of LSM allows for baseline variability adjustment and provides a more precise estimate of LDL-C reduction, minimizing potential confounding effects.

## Conclusion

Single-pill combination of moderate-intensity rosuvastatin plus ezetimibe was non-inferior to high-intensity rosuvastatin in LDL-C lowering effect with more favorable lipid profiles and excellent safety in ASCVD patients with T2DM. However, to consider moderate-intensity statins and ezetimibe combination therapy as an alternative or initial treatment to high-intensity statin monotherapy, further studies are needed to confirm if up-titrating from low-to-moderate-intensity statin with ezetimibe is non-inferior to adding ezetimibe after statin up-titration in terms of cardiovascular outcomes and adverse events.

## Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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## Author contributions
H.I.C, Writing—original draft, Formal analysis, Investigation, Methodology, Visualization; S.J.O., Y.H.J., Y.H.P., Y.H.P., T.H.Y., J.H.D., Y.J.H., K.T.A., J.M.C., Writing—review & editing, Data curation, Methodology, B.J.K., Writing—review & editing, Conceptualization, Funding acquisition, Supervision.

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## Declarations

## Competing interests
The authors declare no competing interests.

## Ethics approval
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards (IRBs) of all participating institutions.

## Informed consent
Informed consent was obtained from all participants involved in the study.

## Additional information
**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-00298-7.

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