



# Comparison of the Efficacy and Safety of Rosuvastatin/Ezetimibe Combination Therapy and Rosuvastatin Monotherapy on Lipoprotein in Patients With Type 2 Diabetes: Multicenter Randomized Controlled Study

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## ABSTRACT

**Introduction:** Ezetimibe/statin combination therapy has been reported to provide additional cardioprotective effects compared to statin monotherapy. The apolipoprotein B/A1 (apoB/A1) ratio is an effective predictor of cardiovascular diseases. The aim of this study was to compare the efficacy and safety of rosuvastatin/ezetimibe

combination therapy versus rosuvastatin monotherapy using the apoB/A1 ratio in patients with diabetes and hypercholesterolemia.

**Methods:** In this randomized, multicenter, open-label, parallel-group study, patients were randomly assigned to receive the combination therapy of rosuvastatin 5 mg/ezetimibe 10 mg once daily ( $n = 68$ ) or monotherapy with rosuvastatin 10 mg once daily ( $n = 68$ ), for 8 weeks.

**Results:** After the 8-week treatment, percentage change (least-square means  $\pm$  standard error) in the apoB/A1 ratio in the rosuvastatin/ezetimibe group was significantly decreased compared to the rosuvastatin group ( $-46.14 \pm 1.58\%$  vs.  $-41.30 \pm 1.58\%$ , respectively;  $P = 0.03$ ). In addition, the proportion of patients achieving  $> 50\%$  reduction in low-density lipoprotein-

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cholesterol (LDL-C) and in the comprehensive lipid target (LDL-C < 70 mg/dL, non-HDL-cholesterol [non-HDL-C] < 100 mg/dL, and apoB < 80 mg/dL) was significantly different between the two groups (76.5 and 73.5% in the rosuvastatin/ezetimibe group and 47.1 and 45.6% in the rosuvastatin group, respectively;  $P < 0.001$ ). The reduction in total cholesterol, non-HDL-C, LDL-C, and apoB were greater in the rosuvastatin/ezetimibe group than in the rosuvastatin group. Both treatments were well tolerated, and no between-group differences in drug-related adverse events were observed.

**Conclusion:** The apoB/A1 ratio was significantly reduced in patients receiving combination therapy with ezetimibe and rosuvastatin compared to those receiving rosuvastatin monotherapy. Both treatments were well tolerated in patients with type 2 diabetes and hypercholesterolemia.

**Trial Registration:** NCT03446261.

**Keywords:** Apolipoprotein A1; Apolipoprotein B; Ezetimibe; Rosuvastatin

### Key Summary Points

#### Why carry out this study?

Statin–ezetimibe combination therapy has been reported to provide additional cardioprotective effects compared to statin monotherapy.

The apolipoprotein B (apoB)/apolipoprotein A1 (apoA1) ratio is considered to be a predictor of future cardiovascular disease; however, to date few studies have compared the change in the apoB/A1 ratio in patients on statin–ezetimibe combination therapy versus those on statin therapy.

The aim of our study was to compare the efficacy and safety of the combination rosuvastatin 5 mg/ezetimibe 10 mg with rosuvastatin 10 mg monotherapy, including the apoB/A1 ratio, in patients with type 2 diabetes (T2DM).

### What was learned from the study?

In persons with T2DM, the addition of ezetimibe to rosuvastatin monotherapy resulted in significant reductions in the apoB/A1 ratio, a predictor of incident cardiovascular disease, and also in the lipid parameters, compared to rosuvastatin monotherapy.

Both rosuvastatin/ezetimibe combination therapy and rosuvastatin monotherapy were generally well tolerated in patients with T2DM, with no significant side effects.

## INTRODUCTION

The use of statins by patients with type 2 diabetes (T2DM) and hypercholesterolemia decreases low-density lipoprotein cholesterol (LDL-C) levels and the risk of cardiovascular events [1–3]. However, many patients remain above the targeted lipid range, despite the recognized efficacy of statins to reduce cholesterol levels [4]. In addition, high-intensity statin therapy has been shown to have limited efficacy to reduce LDL-C levels and is associated with safety concerns [5, 6]. Hence, there is a growing interest in developing supplementary or additional lipid-lowering drugs.

Ezetimibe is a lipid-lowering drug that targets the Niemann–Pick C1-like 1 (NPC1L1) protein, leading to inhibited cholesterol absorption in the small intestine [7]. A previous study that investigated the efficacy and safety of ezetimibe added as adjunct to statin therapy versus statin monotherapy found that the ezetimibe/statin combination decreased LDL-C levels and improved cardiovascular outcomes relative to statin monotherapy [8].

Apolipoprotein B (apoB) is the major apoprotein in all potentially atherogenic lipoprotein particles, and its level is considered to correspond to the number of atherogenic lipoprotein particles. Apolipoprotein A1

(apoA1), on the other hand, is a component of high-density lipoprotein cholesterol (HDL-C) only and is considered to represent the number of antiatherogenic HDL-C particles [9]. Several studies have demonstrated that apoB and apoA1 are markers of atherosclerosis, which in turn is associated with the risk of cardiovascular disease [10–13]. In addition, several large prospective clinical studies have reported that the apoB/apoA1 (apoB/A1) ratio is superior to other lipid parameters as a predictor of cardiovascular disease [10, 12, 14–16].

Therefore, the aim of the present study was to evaluate the efficacy and tolerability of daily rosuvastatin 5 mg/ezetimibe 10 mg combination therapy in comparison to daily rosuvastatin 10 mg monotherapy in terms of the apoB/A1 ratio and other lipid parameters, in patients with T2DM and hypercholesterolemia.

## METHODS

### Study Participants

Adults aged 19–70 years who had been diagnosed with T2DM (glycated hemoglobin [HbA1c] < 8.5%) and hypercholesterolemia (LDL-C > 70 mg/dL) were eligible for inclusion in the study. Patients were excluded if they had: uncontrolled diabetes with HbA1c  $\geq$  8.5%, fasting LDL-C  $\leq$  70 mg/dL, fasting triglyceride (TG)  $\geq$  400 mg/dL, or total cholesterol (TC)  $\geq$  300 mg/dL; history of statin-induced myopathy or rhabdomyolysis; history of hypersensitivity to rosuvastatin or ezetimibe; estimated glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>; alanine aminotransferase and/or aspartate aminotransferase levels > 3-fold the upper limit of normal, or current active liver disease; creatine kinase levels > 3-fold the upper limit of normal. Patients were also excluded if they had received lipid-lowering agents for > 1 week within the 4 weeks immediately preceding the screening visit or received other investigational products within 30 days immediately prior to the screening visit. In addition to the above-mentioned criteria, patients were excluded if deemed by investigators to be ineligible for participation.

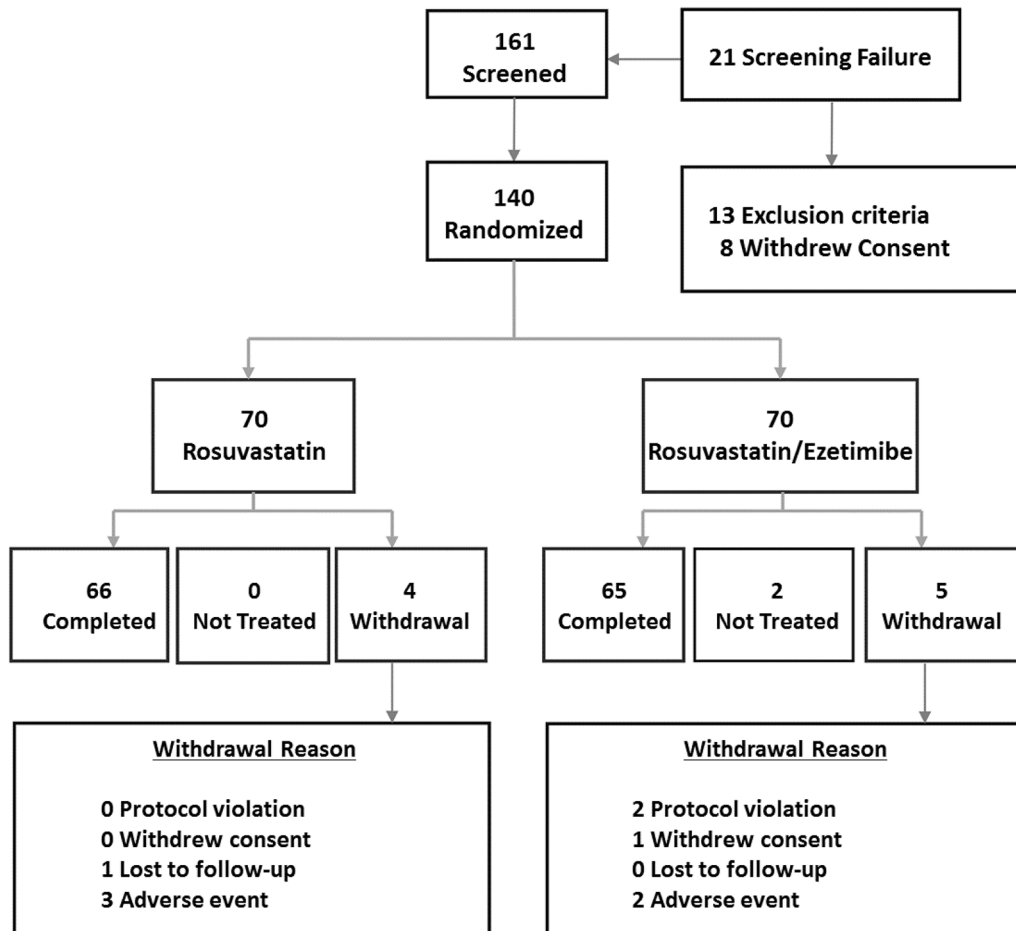
A total of 161 patients were initially screened, of whom 140 were included in the study and randomly assigned to one of the two treatment groups (rosuvastatin/ezetimibe combination therapy group or rosuvastatin monotherapy group) (Fig. 1). Ultimately, 131 patients completed the study (65 in the rosuvastatin/ezetimibe group, 66 in the rosuvastatin group). Four patients were excluded from the efficacy and safety analysis: two patients in the rosuvastatin/ezetimibe group did not take the study medication, and two in the rosuvastatin group were not evaluated for primary efficacy outcome.

### Study Design

This study was a randomized, multicenter, open-label, parallel-group trial conducted in five centers in South Korea from 23 February 2018 to 5 March 2019 (ClinicalTrials.gov Identifier: NCT03446261). The study conformed with the Helsinki Declaration of 1964, as revised in 2013. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Asan Medical Center, Institutional Review Board of Kyung Hee University Hospital at Gangdong, Institutional Review Board of Sanggye Baek Medical Center, Institutional Review Board of Konkuk University Medical Center, and Institutional Review Board of Kangbuk Samsung Hospital.

Patients were randomly assigned to receive either rosuvastatin 5 mg/ezetimibe 10 mg combination therapy once daily or rosuvastatin 10 mg monotherapy once daily, for 8 weeks, in addition to standard care. The duration of the study was 10 consecutive weeks, including a 2-week screening period and an 8-week active-treatment phase. Patients visited the hospital two to three times during the study period and were scheduled for follow-up visits at 8 weeks for assessment of the efficacy and safety of the therapeutic regimen.

Coexisting conditions were presented using terms from the Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 22.0 (<https://www.meddra.org/>) based on



**Fig. 1** Flow chart of patient distribution

patient medical records for the 3-month period immediately before the screening visit. Coronary artery disease was defined as the presence of  $\geq 1$  of the following: myocardial infarction, coronary artery stenosis, unstable angina, stable angina, or ischemic cardiomyopathy. Peripheral arterial disease was defined as the presence of peripheral arterial occlusive disease or atherosclerosis of arteries.

### Outcomes

The primary efficacy outcome was the percentage change in the apoB/apoA1 ratio from baseline to week 8. The secondary efficacy outcomes at 8 weeks included the proportion patients with  $> 50\%$  reduction in LDL-C; proportion of patients achieving the comprehensive lipid

target (LDL-C  $< 70$  mg/dL, non-HDL-C  $< 100$  mg/dL, and apoB  $< 80$  mg/dL); and changes in lipids and other parameters, including TC, non-HDL-C, LDL-C and HDL-C, TG, apoB, apoA1, apoB48, homeostatic model assessment of insulin resistance (HOMA-IR) level, high-sensitivity C-reactive protein (CRP), HbA1c, and fasting plasma glucose (FPG). Safety outcomes included adverse events (AEs), laboratory measures, and vital signs as evaluated by investigators' observations, patient-reported symptoms/signs of AEs, and results of laboratory testing.

### Statistical Analysis

All analyses were performed based on the intention-to-treat population. Continuous

**Table 1** Baseline characteristics

Variable	Rosuvastatin 10 mg monotherapy ( <i>n</i> = 68)	Rosuvastatin 5 mg/ezetimibe 10 mg combination therapy ( <i>n</i> = 68)	<i>P</i>
Age (year)	56.9 ± 8.9	53.7 ± 9.7	0.05
Male	38 (55.9%)	37 (54.4%)	0.86
Current smoking	18 (26.5%)	14 (20.6%)	0.42
Alcohol drinking	35 (51.5%)	36 (52.9%)	0.86
Height (cm)	163.2 ± 9.7	163.7 ± 9.1	0.78
Weight (kg)	70.2 ± 12.9	68.2 ± 10.9	0.33
Body mass index (kg/m <sup>2</sup> )	25.4 ± 3.2	26.2 ± 3.3	0.16
DM duration (month)	71.2 ± 74.4	75.7 ± 78.9	0.93
Hypercholesterolemia duration (month)	31.0 ± 46.8	38.3 ± 56.8	0.74
Systolic blood pressure (mmHg)	125.7 ± 14.9	129.1 ± 13.8	0.06
Diastolic blood pressure (mmHg)	76.8 ± 10.3	79.0 ± 9.1	0.18
HbA1c (%)	6.9 ± 0.8	7.0 ± 0.8	0.43
FPG (mg/dL)	127.3 ± 29.2	133.2 ± 24.4	0.05
Total cholesterol (mg/dL)	205.3 ± 30.1	200.6 ± 24.6	0.52
Triglycerides (mg/dL)	154.9 ± 73.7	178.9 ± 80.2	0.06
HDL cholesterol (mg/dL)	51.0 ± 12.9	47.5 ± 13.3	0.07
LDL-cholesterol (mg/dL)	140.0 ± 28.1	133.5 ± 27.3	0.17
Non-HDL cholesterol (mg/dL)	154.3 ± 31.0	153.1 ± 25.4	0.80
Apolipoprotein B (mg/dL)	119.3 ± 22.0	116.0 ± 20.3	0.36
Apolipoprotein A1 (mg/dL)	139.9 ± 25.2	137.9 ± 22.7	0.46
Apolipoprotein B/A1 ratio	0.9 ± 0.2	0.9 ± 0.2	0.71
Apolipoprotein B48 (mg/dL)	3940.4 ± 3673.0	4628.2 ± 4292.8	0.20
HOMA-IR	2.6 ± 2.4	3.0 ± 1.9	0.17
High-sensitivity CRP (mg/dL)	1.7 ± 2.7	1.3 ± 1.4	0.90
Coexisting conditions			1.00
Hypertension	17 (25.0%)	15 (22.1%)	
Coronary artery disease	1 (1.5%)	0 (0.0%)	
Peripheral arterial disease	4 (5.9%)	5 (7.4%)	

Data are presented as the mean ± standard deviation or as a number (*n*) with the percentage in parenthesis  
*CRP* C-reactive protein, *DM* diabetes mellitus, *FPG* fasting plasma glucose, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model assessment for insulin resistance, *LDL* low-density lipoprotein

variables were expressed as the mean  $\pm$  standard deviation, and categorical variables were expressed as percentages. Student's *t* tests were used to compare the means of continuous variables, and the  $\chi^2$  test (Fisher's exact test) was used to compare categorical variables. For the adjusted mean difference between groups, we used the analysis of covariance model, with the results presented as least-square mean (LSM)  $\pm$  standard error (SE) values. The paired *t* test was used to compare the changes in lipid and other parameters. For all analyses, a *P* value  $< 0.05$  was considered to be statistically significant. All statistical analyses were performed using the SAS version 9.4 statistical package (SAS, Inc., Cary, NC, USA).

## RESULTS

### Baseline Characteristics

A total of 136 patients were analyzed at five medical centers, with 68 patients randomly assigned to the rosuvastatin monotherapy treatment arm of the study and 68 randomly assigned to the rosuvastatin/ezetimibe combination therapy arm. The baseline characteristics of the study patients in these two groups are given in Table 1. The average age of the patients was 55.3 years, 55.2% were male, mean duration of diabetes was 73.4 months, and mean duration of hypercholesterolemia was 34.7 months. The baseline characteristics of the study population were balanced between groups.

### Efficacy

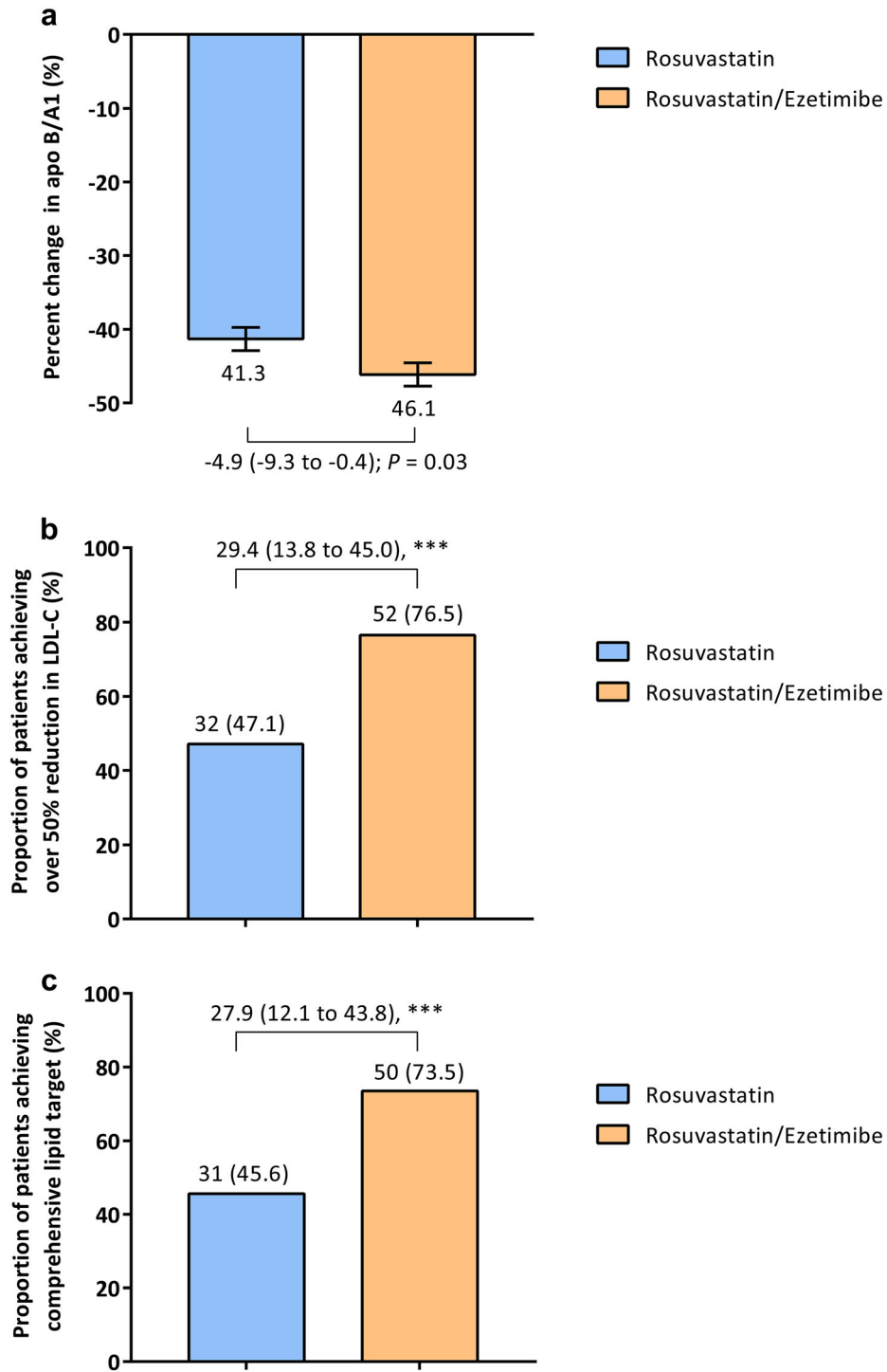
After 8 weeks of treatment, the percentage changes in the LSM  $\pm$  SE from baseline in the apoB/A1 ratio were  $-46.14 \pm 1.58\%$  ( $P < 0.001$ ) for the rosuvastatin/ezetimibe group and  $-41.30 \pm 1.58\%$  ( $P < 0.001$ ) for the rosuvastatin group. Reductions in the apoB/A1 ratios in the rosuvastatin/ezetimibe group were significantly greater than those in the rosuvastatin group, with a between-group difference of  $-4.93\%$  (95% confidence interval [CI]  $-9.39$

**Fig. 2** Efficacy of rosuvastatin monotherapy versus rosuvastatin/ezetimibe combination therapy. **a** Percentage change in apolipoprotein B/apolipoprotein A1 (apoB/A1) ratio from baseline to week 8. Data in **a** are presented as least-square mean  $\pm$  standard error; between-group treatment difference is given under the graph with the 95% confidence interval (CI) in parenthesis. **b** Proportion of patients achieving  $> 50\%$  reduction in low-density lipoprotein-cholesterol (LDL-C) at 8 weeks. **c** Proportion of patients achieving comprehensive lipid target (LDL-C  $< 70$  mg/dL, non-high-density lipoprotein-C  $< 100$  mg/dL, and apoB  $< 80$  mg/dL) without any adverse event-related drop-out. **b, c** Values immediately above bars are the number of patients with the percentage in parenthesis; the difference in responder's proportion with the 95% CI in parenthesis are also shown above graphs. \*\*\* $P < 0.001$

to  $-0.47$ ;  $P = 0.03$ ; Fig. 2a). A significantly greater proportion of patients in the rosuvastatin/ezetimibe group (76.47%) versus the rosuvastatin group (47.06%) achieved  $> 50\%$  reduction in LDL-C at 8 weeks. The difference between groups was 29.41% (95% CI 13.84–44.98;  $P < 0.001$ ; Fig. 2b). In addition, there were significant differences in the proportion of patients achieving the comprehensive lipid target without any AE-related drop-out (73.53% in the rosuvastatin/ezetimibe group vs. 45.59% in the rosuvastatin group), with a between-group difference of 27.94% (95% CI 12.13–43.76;  $P < 0.001$ ; Fig. 2c).

### Changes in Lipid Profile, Glucose Metabolism, and Inflammatory Markers

The decreases in the LSM  $\pm$  SE of LDL-C from baseline to 8 weeks were significantly greater in the rosuvastatin/ezetimibe group than in the rosuvastatin group ( $-77.3 \pm 2.6$  vs.  $-63.2 \pm 2.6$  mg/dL, respectively;  $P < 0.001$ ) (Table 2). In addition, after 8 weeks of treatment, TC, non-HDL-C, and apoB levels (comprehensive lipid target) were significantly reduced in the rosuvastatin/ezetimibe group relative to the rosuvastatin monotherapy group, with between-group LSM differences of  $-18.8$ ,  $-13.9$ , and  $-10.3$  mg/dL, respectively ( $P < 0.001$ , respectively; Table 2). On the



**Table 2** Changes in lipid parameters after 8 weeks of treatment

Variable	Rosuvastatin 10 mg monotherapy ( <i>n</i> = 68)	Rosuvastatin 5 mg/ezetimibe 10 mg combination therapy ( <i>n</i> = 68)	<i>P</i>
Total cholesterol (mg/dL)	− 62.6 ± 2.8	− 81.4 ± 2.8	< 0.001
Triglycerides (mg/dL)	− 42.8 ± 5.9	− 41.6 ± 5.9	0.88
HDL-cholesterol (mg/dL)	4.5 ± 0.8	0.4 ± 0.8	< 0.001
LDL-cholesterol (mg/dL)	− 63.2 ± 2.6	− 77.3 ± 2.6	< 0.001
Non-HDL cholesterol (mg/dL)	− 67.5 ± 2.8	− 81.4 ± 2.8	< 0.001
Apolipoprotein B (mg/dL)	− 43.9 ± 2.0	− 54.2 ± 2.0	< 0.001
Apolipoprotein A1 (mg/dL)	9.9 ± 1.7	0.02 ± 1.7	< 0.001
Apolipoprotein B48 (mg/dL)	−149.7 ± 375.0	49.3 ± 375.0	0.79

Data are presented as least-square means (LSM) ± standard error (SE)

**Table 3** Changes in glucose metabolism-related parameters and inflammatory marker after 8 weeks of treatment

Variable	Rosuvastatin 10 mg monotherapy ( <i>n</i> = 68)	Rosuvastatin 5 mg/ezetimibe 10 mg combination therapy ( <i>n</i> = 68)	<i>P</i>
HOMA-IR	0.44 ± 0.26	0.47 ± 0.26	0.94
High-sensitivity CRP (mg/dL)	− 0.25 ± 0.35	− 0.15 ± 0.35	0.84
FPG (mg/dL)	3.9 ± 2.5	6.3 ± 2.5	0.49
HbA1c (%)	0.05 ± 0.06	0.13 ± 0.06	0.34

Data are presented as LSM ± SE

other hand, at 8 weeks, there was a significant increase in HDL-C and apoA1 levels in the rosuvastatin group (4.5 ± 0.8 and 9.9 ± 1.7 mg/dL, respectively) compared with the rosuvastatin/ezetimibe group (0.4 ± 0.8 and 0.02 ± 1.7 mg/dL, respectively). These differences were significant at  $P < 0.001$  (Table 2). However, there were no significant differences in TG, HOMA-IR, high-sensitivity CRP, apoB48, FPG, and HbA1c between the two groups (Tables 2, 3).

After 8 weeks of treatment, 98.5% of patients in the rosuvastatin/ezetimibe group and 88.4% of those in the rosuvastatin group achieved the apoB/A1 ratio of < 0.7 (Electronic Supplementary Material [ESM] Fig. 1). In addition, 77.9% of patients in the rosuvastatin/ezetimibe group

and 46.4% of those in the rosuvastatin group achieved the LDL-C target < 70 mg/dL (ESM Fig. 2).

### Safety

No significant differences were observed between the rosuvastatin/ezetimibe and rosuvastatin groups in terms of the percentage of patients who presented AEs (Table 4). Both treatments were generally well tolerated. Overall, the most common AEs were a mild increase in liver enzyme levels ( $n = 2$ ) and myalgia ( $n = 2$ ). All reports of myalgia originated in the rosuvastatin group. Serious AEs included diabetic retinopathy ( $n = 1$ , in the rosuvastatin/ezetimibe group), angina pectoris ( $n = 1$ , in the



**Table 4** Safety assessment during the 8 weeks of the study

Variable	Rosuvastatin monotherapy 10 mg ( <i>n</i> = 68)	Rosuvastatin 5 mg/ezetimibe 10 mg monotherapy ( <i>n</i> = 68)
ALT or AST $\geq 3 \times$ UNL	2 (2.94)	2 (2.94)
Myalgia	2 (2.94)	0 (0.00)
Abdominal distention	0 (0.00)	1 (1.47)
Abdominal pain	0 (0.00)	1 (1.47)
Urticaria	1 (1.47)	0 (0.00)
Peripheral edema	0 (0.00)	1 (1.47)
Dizziness	0 (0.00)	1 (1.47)
Diabetic retinopathy	0 (0.00)	1 (1.43)
Angina pectoris	1 (1.43)	0 (0.00)
Colon cancer	1 (1.43)	0 (0.00)
Death from any causes	0 (0.00)	0 (0.00)

Data are presented as the number (of patients) with the percentage in parenthesis

ALT Alanine aminotransferase, AST Aspartate aminotransferase, UNL upper normal limit

rosuvastatin group) and colon cancer ( $n = 1$ , in the rosuvastatin group). However, none of these were associated with the study drug. No deaths, as a serious AE, were noted. We recorded seven AEs resulting in permanent discontinuation of the study drugs, namely, myalgia ( $n = 2$ , in the rosuvamibe group), abdominal distension ( $n = 1$ , in the rosuvastatin/ezetimibe group), abdominal pain ( $n = 1$ , in the rosuvastatin/ezetimibe group), peripheral edema ( $n = 1$ , in the rosuvastatin/ezetimibe group), dizziness ( $n = 1$ , in the rosuvastatin/ezetimibe group), and urticaria ( $n = 1$ , in the rosuvamibe group).

## DISCUSSION

In the present study, treatment with rosuvastatin 5 mg/ezetimibe 10 mg combination therapy resulted in significantly greater reductions in the apoB/A1 ratio than did rosuvastatin 10 mg monotherapy after 8 weeks in patients with T2DM and hypercholesterolemia. In addition, the proportion of patients who achieved > 50% reduction in LDL-C and in the comprehensive lipid target was significantly greater in the rosuvastatin/ezetimibe group than in the

rosuvastatin monotherapy group. Moreover, significant reductions in lipid parameters were observed in the rosuvastatin/ezetimibe group compared with the rosuvastatin group. Both therapies were generally well tolerated, and few incidents of elevated liver enzymes or myalgia were reported.

The results of previous studies on ezetimibe/statin combination therapy demonstrate that this combination therapy has significant cholesterol-lowering [17, 18] and cardioprotective effects compared to statin monotherapy [8]. The side effects of statin therapy depend on the prescribed statin dose [19]. Hence, reducing the statin dosage and adding ezetimibe to the therapeutic regimen could be efficacious in the management of cholesterol and cardiovascular disease, without the statin-related AEs [20].

The ApoB/A1 ratio, as representative of the total number of atherosclerotic particles, is considered to be a stronger predictor of atherosclerosis and cardiovascular disease than LDL-C [10, 21, 22]. However, few studies have compared the use of a high-dose statin with that of the low-dose statin/ezetimibe combination, with a focus on the changes in the apoB/A1 ratio. To our knowledge, this is the first study to

use apoB/A1 ratios to compare the efficacy of rosuvastatin 5 mg/ezetimibe 10 mg combination therapy and rosuvastatin 10 mg therapy. Our results are consistent with those from a previous study that demonstrated a greater apoB/A1 lowering effect with atorvastatin 5 mg/ezetimibe 5 mg combination therapy than from atorvastatin 20 mg monotherapy [23]. However, another study that compared rosuvastatin 5 mg/ezetimibe 10 mg combination therapy with rosuvastatin 20 mg monotherapy reported no difference between the groups [24]. It is possible that any effects on the apoB/A1 ratio depend on the statin and/or statin or ezetimibe dose prescribed, as well as on the patient population. In our study, a significant reduction in the apoB/A1 ratio with the rosuvastatin/ezetimibe combination was observed; this reduction was due to the decrease in apoB and increase in apoA1 levels. Dual inhibition of cholesterol biosynthesis in the liver and cholesterol absorption in the intestine using a combination of ezetimibe with a statin results in further decreases in apoB [25]. In addition, the observed differences in the apoA1 values between the two groups could be attributed to the favorable effects of rosuvastatin on apoA1, compared to other statins [26].

Previous studies have demonstrated the improved lipid-lowering effects of the ezetimibe/rosuvastatin combination compared to rosuvastatin monotherapy in patients with T2DM [24, 27]. Our study reported similar results, with a significantly higher proportion of patients in the rosuvastatin/ezetimibe group achieving > 50% reduction in LDL-cholesterol and in the comprehensive lipid target compared to the rosuvastatin monotherapy group. Patients with T2DM have an enhanced expression of the NPC1L1 gene, which promotes cholesterol absorption in the small intestine [28, 29]. Ezetimibe binds to the NPC1L1 receptor, thereby selectively preventing cholesterol absorption from the intestine. Therefore, co-administration of ezetimibe and a statin could provide improved efficacy in patients with T2DM.

In contrast, changes in apoB48 levels showed opposite trends between the two groups, although the difference was not statistically

significant. Previous studies have reported that diabetic patients have high apoB48 levels [30] and that ezetimibe might decrease apoB48 levels by inhibiting intestinal cholesterol absorption, but the differences reported were not statistically significant in these studies [30, 31]. In present study, we also could not determine the efficacy of ezetimibe for apoB48 reduction due to the short duration of the follow-up and small sample size. Therefore, future studies are needed to clarify the effect of ezetimibe on apoB48 reduction in diabetes patients.

Several studies have reported an effect of statins on glucose metabolism [23, 31–34] and on the risk of new-onset diabetes [35, 36], but the results remain controversial. Results from earlier studies also suggest that ezetimibe could improve insulin resistance [37–39]. Two studies reported that the addition of ezetimibe to a statin as combination therapy improved insulin resistance and did not increase the risk of diabetes [40, 41]. However, in our study, FPG, HbA1c, and HOMA-IR did not differ between the two groups following the 8-week treatment. Previous reports evaluating the effect of the rosuvastatin/ezetimibe combination on glucose control and insulin resistance are very limited. The exact rationale underlying the reported effects of combination therapy on glucose metabolism remains unknown. Hence, further studies using large samples and longer therapeutic periods may clarify the effect of rosuvastatin and rosuvastatin/ezetimibe combination therapy on glucose metabolism.

In this study, the safety profiles observed were generally tolerable between the two groups. No drug-related serious AEs were reported, and overall the incidence of liver, muscle, gastrointestinal, and allergic AEs was low and comparable between the two treatment groups.

This study has several limitations. First, the duration of this study was relatively short and the patient population was small. Therefore, the results may not adequately represent the long-term efficacy and safety issues related to these drugs. Second, the open-label design might result in bias in the comparison of lipid profiles and affect the assessment of AEs. Third, we did

not evaluate the effects of other doses of rosuvastatin or other statins in combination with ezetimibe. Finally, the clinical impact of apoB/A1 changes was not reported in our study. Further studies to evaluate the implication of the apoB/A1 ratio on clinical outcomes in larger patient populations are needed.

## CONCLUSION

An 8-week combination therapy of rosuvastatin 5 mg/ezetimibe 10 mg showed a significant reduction in the apoB/A1 ratio, a predictor of future cardiovascular disease, compared to rosuvastatin 10 mg monotherapy, in patients with diabetes and hypercholesterolemia. No unexpected safety issues were identified, and both treatments were well tolerated.

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**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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