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Efficacy and safety of combination therapy with telmisartan, rosuvastatin, and ezetimibe in patients with dyslipidemia and hypertension: A randomized, double-blind, multicenter, therapeutic confirmatory, phase III clinical trial

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Abstract

This study aimed to compare and evaluate the efficacy of the blood pressure (BP) control and cholesterol-lowering effects and safety of combination therapy with

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telmisartan, rosuvastatin, and ezetimibe versus rosuvastatin and ezetimibe double therapy or telmisartan single therapy in dyslipidemia patients with hypertension. After a wash-out/therapeutic lifestyle change period of ≥4 weeks, a total of 100 eligible patients were randomized and received one of three treatments for 8 weeks: (1) telmisartan 80 mg/rosuvastatin 20 mg/ezetimibe 10 mg (TRE), (2) rosuvastatin 20 mg/ezetimibe 10 mg (RE), or (3) telmisartan 80 mg (T). The primary endpoint was the efficacy evaluation of TRE by comparing changes in mean sitting systolic blood pressure (msSBP) and mean percentage change in low-density lipoprotein-C (LDL-C) from baseline after 8 weeks of treatment.

The least square (LS) mean (SE) changes in msSBP at 8 weeks compared with baseline were −23.02 (3.04) versus −7.18 (3.09) mmHg in the TRE and RE groups, respectively ($p < .0001$), and −25.80 (2.74) versus −14.92 (2.65) mmHg in the TRE and T groups, respectively ($p = .0005$). The percentage changes in the mean (SD) LDL-C at 8 weeks compared with baseline were −54.97% (3.49%) versus −0.17% (3.23%) in the TRE and T groups, respectively ($p < .0001$). No serious adverse events occurred, and no statistically significant differences in the incidence of overall AEs and adverse drug reactions occurred among the three groups.

TRE therapy significantly decreased msSBP and LDL-C compared to RE or T therapy with comparable safety and tolerability profiles.

KEYWORDS
combination therapy, dyslipidemia, ezetimibe, hypertension, rosuvastatin, telmisartan

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, representing 32% of all global deaths, according to the World Health Organization report in 2021.[1] The two most significant risk factors for CVD morbidity and mortality, hypertension and dyslipidemia, are frequently accompanied.[2,3] In Korea, 59.9% of people with hypertension have dyslipidemia,[4] and 34.6% of people received combination treatments for hypertension and dyslipidemia in 2018.[5] Managing hypertension and dyslipidemia is essential for reducing the overall risk of CVD. This often requires taking multiple medications to control both chronic conditions.[6] Additionally, fixed-dose combinations (FDC) of antihypertensive and lipid-lowering medication could increase adherence by easing the pill burden.[7,8]

Triple combination therapy of telmisartan, amlodipine, and rosuvastatin has become an effective method for treating high-risk hypertension and dyslipidemia. Triple therapy can successfully target various pathways involved in BP regulation and lipid control by using three drugs with various mechanisms of action, leading to greater control.[9–11] Additionally, the FDC treatment of aspirin, ramipril, and atorvastatin had higher adherence and was more effective for secondary cardiovascular prevention than usual care.[12]

Angiotensin II receptor blockers (e.g., Telmisartan) are one of the preferred first-line treatments for hypertension.[13] Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (hereafter statin), the first-line treatment for dyslipidemia, prevents adverse cardiovascular events by reducing mainly low-density lipoprotein cholesterol (LDL-C) and its pleiotropic effects.[14–16] Ezetimibe reduces cholesterol transport from the small intestine to the liver by preventing cholesterol absorption in the small intestine. Ezetimibe reduces blood cholesterol in a complementary way to statin.[17]

Recent evidence indicated that rosuvastatin/ezetimibe (RE) combination therapy effectively lowered LDL-C levels compared to statin monotherapy, and more patients with combination medication achieved their goal LDL-C levels.[18]

The aim of this study was to compare and evaluate the efficacy of the BP control and cholesterol-lowering effect and safety of combination therapy with telmisartan, rosuvastatin, and ezetimibe (TRE) versus RE double or telmisartan (T) single therapy in dyslipidemia patients with hypertension.

2 | PATIENTS AND METHODS

2.1 | Study patients

Persons who met the inclusion/exclusion criteria were randomly assigned to either the TRE, RE, or T groups and were treated for 8 weeks.

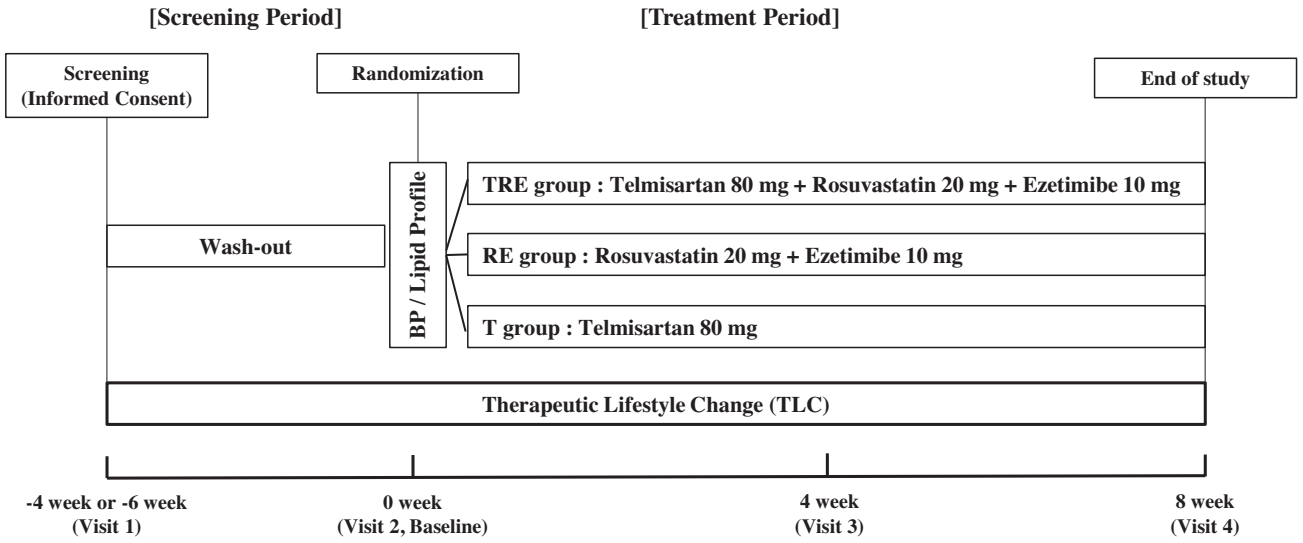


FIGURE 1 Study design. BP, blood pressure; RE, rosuvastatin/ezetimibe; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.

Men or women aged over 19 years with dyslipidemia accompanied by essential hypertension and requiring medical treatment were included. After a ≥4-week wash-out/therapeutic lifestyle change (TLC) period, patients with mean sitting systolic blood pressure (msSBP) ≥ 140 mmHg and mean sitting diastolic blood pressure (msDBP) < 110 mmHg were eligible for the trial. Additionally, patients who met the LDL-C criteria for CVD risk as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[19] were included in the study.

Patients with severe hypertension (msSBP ≥ 180 mmHg or msDBP ≥ 110 mmHg), a BP difference between both arms of msSBP ≥ 20 mmHg or msDBP ≥ 10 mmHg, fasting LDL-C > 250 mg/dL or triglycerides (TG) ≥ 500 mg/dL were excluded.

2.2 | Study design

This study was a randomized, double-blind, multicenter, therapeutic confirmatory, phase III clinical trial. The enrollment of persons was conducted at 18 nationwide sites in the Republic of Korea from September 2019 to June 2021. This study was conducted by the International Conference on Harmonisation–Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. Additionally, the Institutional Review Boards (IRBs) of each participating center approved the study protocol.

The study design is presented in Figure 1. Eligible persons were instructed to follow at least 4 weeks of washout/TLC before randomization. All lipid-modifying and antihypertension medications were prohibited for at least 4 weeks (6 weeks for fibrates). Persons were instructed on patient education for the lifestyle change and underwent diet and exercise therapy for at least 4 weeks (screening period). They maintained TLC during the treatment period. The cardiovascular risk group criteria of the NCEP ATP III[19] were used as a stratification factor; Group1: no other risk factors and LDL-C ≥160 mg/dL, Group2: ≥1 major risk factors and a 10-year CVD risk indicated by Framingham risk score < 10% (LDL-C ≥160 mg/dL), Group3: ≥1 major risk factors and a 10-year risk score 10%–20% (LDL-C ≥130 mg/dL), Group4: coronary artery disease (CAD) or CAD equivalents or ≥1 major risk factors and a 10-year risk score > 20% (LDL-C ≥100 mg/dL).

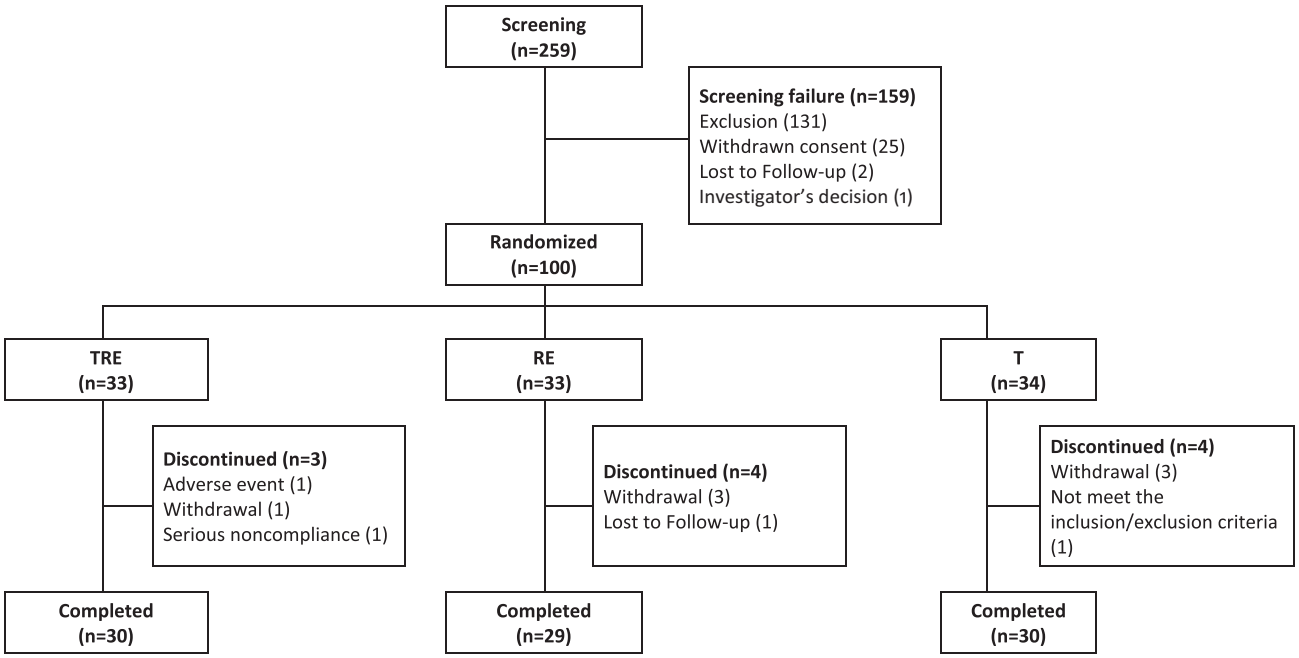
At randomization, persons were re-evaluated for eligibility criteria, and if satisfactory, they were randomly assigned to one of three groups in a 1:1:1 ratio within strata. All persons received three investigational drugs, including a placebo to maintain double-blinding. The TRE group received three active tablets, telmisartan 80 mg (Micardis, Boehringer Ingelheim Pharma Co, Seoul, Korea), rosuvastatin 20 mg (Crestor, AstraZeneca Pharma Co, Seoul, Korea), and ezetimibe 10 mg (Ezetrol, MSD Technology Singapore Pte Ltd.). The RE group received two active tablets, rosuvastatin 20 mg (Crestor, AstraZeneca Pharma Co, Seoul, Korea) and ezetimibe 10 mg (Ezetrol, MSD Technology Singapore Pte Ltd.) and a placebo tablet for telmisartan (ChongKunDang Pharm. Co, Seoul, Korea). The T group received one active tablet, telmisartan 80 mg (Micardis, Boehringer Ingelheim Pharma Co, Seoul, Korea) and two placebo tablets for rosuvastatin and ezetimibe (ChongKunDang Pharm. Co, Seoul, Korea). The placebo tablets had the same appearance as each active tablet.

During the clinical trial period, all persons were recommended to take the prescribed investigational drugs once a day, at a fixed time every day, if possible. No dose adjustment was performed during the entire clinical trial period.

2.3 | Outcomes

The primary endpoints were the mean changes in msSBP compared between the TRE and RE groups and the mean percentage change in LDL-C compared between the TRE and T groups at week 8 compared to the baseline for each.

The secondary endpoints were the mean changes in msSBP and msDBP and the achievement rate of target BP



TRE = Telmisartan/Rosuvastatin/Ezetimibe; RE = Rosuvastatin/Ezetimibe; T = Telmisartan

FIGURE 2 Flowchart describing person disposition.

(msSBP/msDBP < 140/90 mmHg) from baseline to 4 and 8 weeks of treatment compared between the TRE and RE groups; the mean percentage change and the mean change in LDL-C, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), and the LDL-C treatment goal achievement rate according to the NCEP ATP III Guideline[19] (Group 1: < 160 mg/dL, Group 2, 3: < 130 mg/dL, Group 4: < 100 mg/dL) from baseline to 4 and 8 weeks of treatment compared between the TRE and T groups.

In addition, the exploratory endpoints were BP evaluation compared between the TRE and T groups and lipid profile evaluation compared between the TRE and RE groups.

BP was evaluated after the person relaxed for at least 5 min, using the same arm and sphygmomanometer (HEM-7080IC; Omron Health Care, Tokyo, Japan). BP was measured twice after screening, and mean SBP and DBP were calculated from the average of the two measurements. The central laboratory analyzed the lipid profiles.

Adverse events (AEs), laboratory tests, concomitant drugs, vital signs, and physical examination were evaluated for safety endpoints.

2.4 | Statistical analysis

This study was designed under assumptions that TRE therapy is superior to RE combination in reducing BP and superior to T alone in lowering LDL-C levels. The expected difference in mean change (SD) in BP from baseline between the TRE and RE groups was −15.4 mmHg (16.9 mmHg), and the expected difference in mean percent change (SD) in LDL-C from baseline between the TRE and T groups was −62.7% (22%).[20] Sample sizes were calculated for each estimate with 90% power and a two-sided level set at 5%; the larger number was selected, which was the size to assess the change in BP. A sample size of 99 patients was produced considering a 20% drop-off rate and the randomization ratio of 1:1:1 (33 patients in each group).

The major analysis set for evaluation of efficacy was full analysis sets (FAS). Changes in BP and percent changes in LDL-C from baseline were compared between groups and analyzed using an analysis of covariance (ANCOVA) model, considering the baseline and stratification factors (risk group). The achievement rate of the BP target and the target LDL-C level were compared between groups using the Cochran–Mantel–Haensqel test, in which the stratification factor (risk group) was corrected as a covariate. Comparison within each group for changes compared to the baseline was performed through the paired-samples *t*-test. Wilcoxon signed-rank test was performed for non-normal data. The mean msSBP and LDL-C from baseline to 4 and 8 weeks of treatment were compared between groups and analyzed using the Independent t-test. All analyses were two-sided, and *p* values < .05 were considered statistically significant. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Inc, Cary, North Carolina, USA).

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

One hundred participants were randomly assigned to receive TRE (n = 33), RE (n = 33), or T (n = 34) therapy (Figure 2). Furthermore, 11

TABLE 1 Baseline demographic and clinical characteristics of the study participants.

Characteristic	TRE[a] (No. = 33)	RE[a] (No. = 31)	T[a] (No. = 32)	p[b]
Age, mean (SD), y	63.64 (10.65)	62.58 (10.76)	60.75 (9.73)	.4169[K]
Male	26 (78.79)	24 (77.42)	22 (68.75)	.6017[C]
BMI, mean (SD), kg/m^2	26.19 (2.76)	26.50 (3.50)	25.73 (2.51)	.5830[A]
NCEP ATP III risk category				
≥1 risk factor	29 (87.88)	29 (93.55)	24 (75.00)	.1076[F]
CHD and CHD risk equivalents	15 (45.45)	17 (54.84)	15 (46.88)	.7237[C]
Group category[c]				
Group1	3 (9.09)	2 (6.45)	3 (9.38)	.9876[F]
Group2	2 (6.06)	3 (9.68)	4 (12.50)	
Group3	8 (24.24)	8 (25.81)	7 (21.88)	
Group4	20 (60.61)	18 (58.06)	18 (56.25)	
Drug therapy before enrollment				
Antihypertensive	28 (84.85)	24 (77.42)	27 (84.38)	.6879[C]
Lipid-lowering	25 (75.76)	21 (67.74)	25 (78.13)	.6170[C]
Lipid and BP baseline, mean (SD)				
LDL-C, mg/dL	162.79 (35.17)	155.68 (28.11)	156.56 (34.48)	.5862[K]
Total cholesterol, mg/dL	227.94 (37.86)	219.61 (33.09)	225.72 (38.39)	.6451[A]
Triglyceride, mg/dL	183.58 (82.67)	180.35 (83.65)	175.03 (70.84)	.9898[K]
HDL-C, mg/dL	45.42 (9.73)	44.61 (7.36)	48.84 (12.39)	.3810[K]
SiSBP, mmHg	154.68 (10.79)	152.77 (9.84)	153.53 (9.30)	.7855[K]
SiDBP, mmHg	91.18 (9.22)	89.61 (9.10)	94.03 (7.21)	.1208[A]

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; SiDBP, sitting diastolic blood pressure; SiSBP, sitting systolic blood pressure; RE, rosuvastatin/ezetimibe; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.

[a]Data are presented as the number (percentage) of patients unless otherwise noted.

[b]*p* values between telmisartan/rosuvastatin/ezetimibe and rosuvastatin/ezetimibe and telmisartan group. [ANOVA (A) or Kruskal–Wallis Test (K) or Chi-square test (C) or Fisher's exact test (F)].

[c]Group1:no other risk factors and LDL-C ≥160 mg/dL, Group2: ≥1 major risk factors and a 10-year cardiovascular disease (CVD) risk indicated by Framingham risk score < 10% (LDL-C ≥160 mg/dL), Group3: ≥1 major risk factors and a 10-year risk score 10%–20% (LDL-C ≥130 mg/dL), Group4: coronary artery disease (CAD) or CAD equivalents or a 10-year risk score > 20% (LDL-C ≥100 mg/dL).

participants dropped out of the study, and 89 completed treatments. Among the enrolled 100 persons, one person had not administered study drugs, and 99 were analyzed for safety evaluation. For efficacy, 96 persons were analyzed as the FAS, excluding four persons whose BP or lipid profile had not been evaluated during the clinical trial. The demographic and baseline clinical characteristics, including baseline BP and lipid profiles, were similar among all groups (Table 1). No significant differences were observed.

3.2 | Efficacy

The LS mean (SE) changes in msSBP from baseline after 8 weeks of treatment were −23.02 (3.04) and −7.18 (3.09) mmHg in the TRE and RE groups, respectively (Table 2). Treatment with TRE resulted in a greater reduction in BP than treatment with RE (differences, −15.85 mmHg [95% CI, −23.00 to −8.69 mmHg], $p < .0001$). The LS mean (SE) changes in msSBP from baseline to after 8 weeks of treatment were −25.80 (2.74) and −14.92 (2.65) mmHg in the TRE and T groups, respectively. The differences between the TRE and the T groups were also statistically significant (differences, −10.88 mmHg [95% CI, −17.40 to −4.36 mmHg], $p = .0015$) (Table 2). The LS mean (SE) change in msDBP from baseline to 8 weeks was −10.89 (1.49) and −1.15 (1.50) mmHg in the TRE and the RE groups, respectively. The differences between the TRE and the RE groups were −9.74 mmHg [95% CI, −13.24 to −6.24 mmHg] and it was statistically significant ($p < .0001$) (Table 2). A significantly higher number of persons achieved target BP at week 8 in the TRE group (69.70%, 23 persons) compared to the RE group (25.81%, eight persons, $p = .0005$) (Figure 3A). The mean (SD) msSBP from baseline to 4 and 8 weeks of treatment was from 154.68 (10.79) mmHg to 134.44 (13.02) mmHg and 130.88 (12.76) mmHg in the TRE group, which was a more significant reduction than in the RE group, from 152.77 (9.84) mmHg to 149.72 (16.69) mmHg and 145.60 (17.09) mmHg ($p = .0001$ at 4 weeks and $p < .0001$ at 8 weeks)

TABLE 2 Changes in blood pressure from baseline to week 8.

Variable	TRE (No. = 33)	RE (No. = 31)	T (No. = 32)
MSSBP			
Mean (SD)	−23.80 (12.82)	−7.18 (15.94)	−12.97 (15.28)
Treatment difference			
LS mean (SE)	−23.02 (3.04)	−7.18 (3.09)	–
LS mean (SE)	−25.80 (2.74)	–	−14.92 (2.65)
LS mean difference [95% CI]	–	−15.85 [−23.00, −8.69]	−10.88 [−17.40, −4.36]
$p^{\dagger}$	–	<.0001	.0015
MSDBP			
Mean (SD)	−11.00 (7.87)	−0.50 (8.63)	−6.56 (7.22)
Treatment difference			
LS mean (SE)	−10.89 (1.49)	−1.15 (1.50)	–
LS mean (SE)	−12.27 (1.50)	–	−6.58 (1.46)
LS mean difference [95% CI]	–	−9.74 [−13.24, −6.24]	−5.68 [−9.31, −2.06]
$p^{\dagger}$	–	<.0001	.0026

Treatment difference was calculated as telmisartan/rosuvastatin/ezetimibe group minus rosuvastatin/ezetimibe group or telmisartan group.
Abbreviations: CI, Confidence Interval; LS mean, Least Square Mean; MSSBP, mean sitting systolic blood pressure; MSDBP, mean sitting diastolic blood pressure; SD, Standard Deviation; SE, Standard Error; RE, rosuvastatin/ezetimibe; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.
$^{\dagger}p$ value for ANCOVA, with Group(stratification variable) as a covariate.

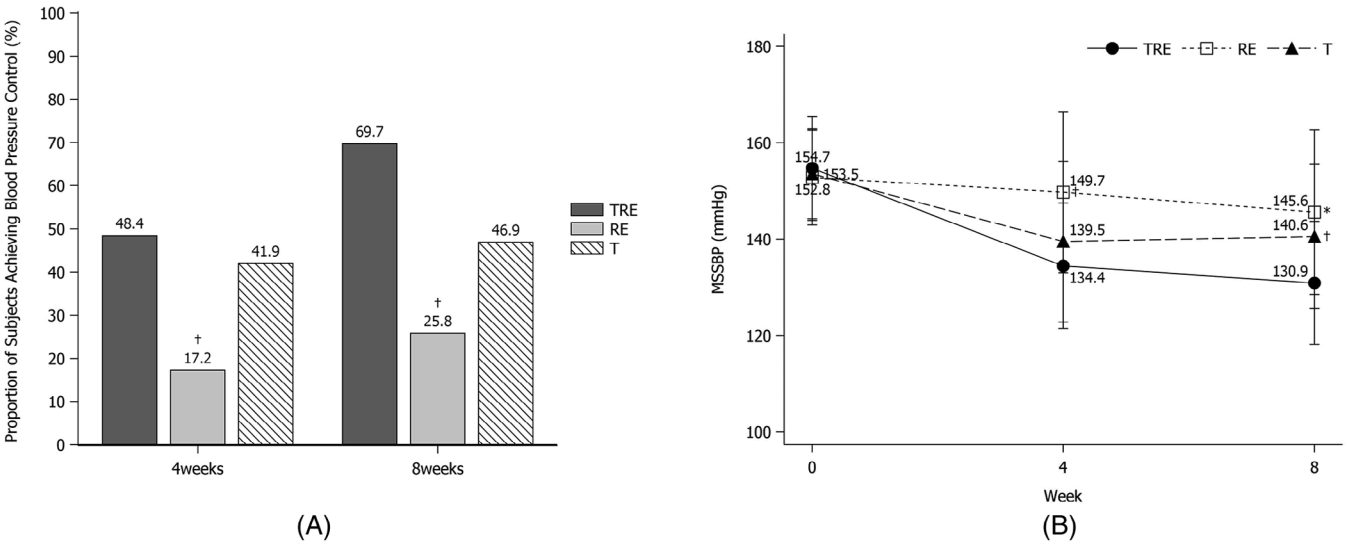


FIGURE 3 (A) Achievement rate of the BP target (msSBP/msDBP < 140/90 mmHg) at 4 and 8 weeks of treatment ($^{\dagger}p < .05$ vs. TRE by Cochran-Mantel- Haensqel test). (B) The mean msSBP from baseline to 4 and 8 weeks ($^{*}p < .0001$ and $^{\dagger}p < .05$ vs. TRE by independent *t*-test). msDBP, mean sitting diastolic blood pressure; msSBP, mean sitting systolic blood pressure; RE, rosuvastatin/ezetimibe; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.

(Figure 3B). The effects of lowered msSBP were comparable at 4 and 8-week follow-ups.

The LS mean (SE) percentage changes in mean LDL-C at 8 weeks compared with baseline values were −54.97% (3.49%) and −0.17% (3.23%) in the TRE and T groups, respectively (Table 3). Treatment with TRE had a more effect on the lipid control than T alone (differences, −54.80% [95% CI, −62.76% to −46.83%], $p < .0001$). The LS mean (SE) percentage changes in TC after the 8-week treatment were −40.31% (2.53%) and 1.40% (2.40%) in the TRE and T groups, respectively. The difference between the TRE and the T groups was −41.72% [95% CI, −47.56% to −35.87%], and it was statistically significant ($p < .0001$) (Table 3). TG levels were significantly decreased in the TRE group than the T group (differences, −45.00% [95% CI, −63.96% to −26.05%], $p < .0001$) (Table 3). The percentage changes

TABLE 3 Percent changes in lipid variables from baseline to week 8.

Variable	TRE (No. = 33)	RE (No. = 31)	T (No. = 32)
LDL-C			
Mean (SD)	−61.38 (14.25)	−58.18 (22.17)	−4.49 (19.09)
Treatment difference			
LS mean (SE)	−62.56 (4.16)	−59.93 (4.06)	–
LS mean (SE)	−54.97 (3.49)	–	−0.17 (3.23)
LS mean difference [95% CI]	–	−2.63 [−12.08, 6.82]	−54.80 [−62.76, −46.83]
$p^{\dagger}$	–	.5790	<.0001
Total cholesterol			
Mean (SD)	−45.24 (12.41)	−41.75 (16.73)	−2.32 (13.60)
Treatment difference			
LS mean (SE)	−45.33 (3.27)	−42.71 (3.18)	–
LS mean (SE)	−40.31 (2.53)	–	1.40 (2.40)
LS mean difference [95% CI]	–	−2.62 [−9.97, 4.73]	−41.72 [−47.56, −35.87]
$p^{\dagger}$	–	.4784	<.0001
Triglyceride			
Mean (SD)	−27.37 (30.11)	−29.21 (30.11)	18.38 (45.94)
Treatment difference			
LS mean (SE)	−24.29 (5.55)	−26.42 (5.60)	–
LS mean (SE)	−27.13 (7.97)	–	17.87 (7.70)
LS mean difference [95% CI]	–	2.13 [−10.85, 15.11]	−45.00 [−63.96, −26.05]
p†	–	.7436	<.0001
HDL-C			
Mean (SD)	3.04 (14.93)	8.54 (14.55)	−3.12 (12.75)
Treatment difference			
LS mean (SE)	3.09 (3.08)	7.64 (3.05)	–
LS mean (SE)	1.69 (2.79)	–	−3.20 (2.77)
LS mean difference [95% CI]	–	−4.55 [−11.33, 2.22]	4.89 [−1.82, 11.61]
p†	–	.1836	.1500

Treatment difference was calculated as telmisartan/rosuvastatin/ezetimibe group minus rosuvastatin/ezetimibe group or telmisartan group.
Abbreviations: CI, Confidence Interval; LS mean, Least Square Mean; RE, rosuvastatin/ezetimibe; SD, Standard Deviation; SE, Standard Error; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.
†p value for ANCOVA, with Group(stratification variable) as a covariate.

in mean HDL-C were 1.69% (2.79%) and −3.20% (2.77%) in the TRE and T groups, respectively. There was no statistically significant difference in HDL-C level (differences, 4.89% [95% CI, −1.82% to 11.61%], $p = .1500$), but it showed a tendency to increase after administration of the investigational drug.

The percentage of persons who achieved the target LDL-C after 8 weeks of treatment was 96.97% and 12.50% in the TRE and T groups, respectively ($p < .0001$) (Figure 4A). The mean (SD) LDL-C from baseline to 4 and 8 weeks of treatment were from 162.79 (35.17) mg/dL to 58.94 (22.47) mg/dL and 61.48 (21.35) mg/dL in the TRE group, which was more significant than in the T group, from 156.56 (34.48) mg/dL to 151.71 (42.49) mg/dL and 149.38 (43.59) mg/dL ($p < .0001$) (Figure 4B).

3.3 | Safety

Safety analysis was performed on persons who took at least one dose of the investigational drug. Among the 99 persons in the safety analysis set, 16 (16.16%) experienced 24 treatment-emergent adverse events (TEAE). In the TRE group, six persons (18.18%, 10 cases) were reported, four (12.12%, six cases) in the RE group and six (18.18%, eight cases) in the T group. There was no significant difference among the three groups ($p = .7422$). Most of the 24 cases were lower than moderate in severity (20 mild, 3 moderate, and 1 severe). A severe AE reported in the TRE group was "Large intestine polyp" (one person, 3.03%, one case), but it was judged as "not related" to the investigational drug, and the person recovered. Thirteen persons (13.13%) experienced 17

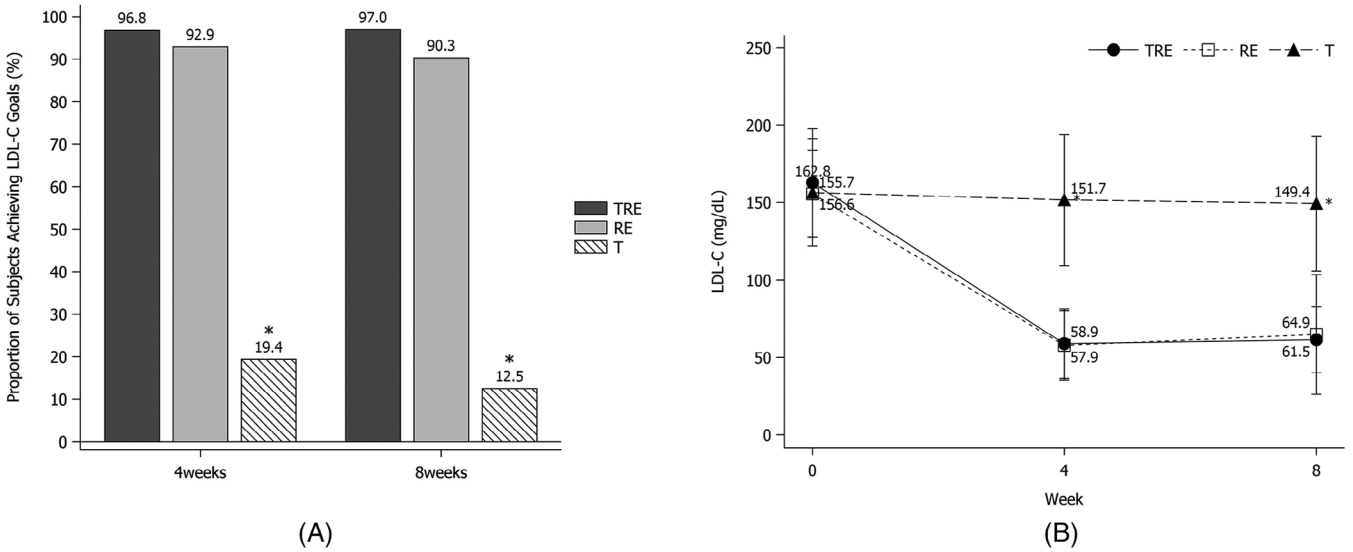


FIGURE 4 (A) The LDL-C treatment goal achievement rate according to the NCEP ATP III Guideline (Group 1: < 160 mg/dL, Group 2, 3: < 130 mg/ dL, Group 4: < 100 mg/dL) at 4 and 8 weeks of treatment (*p < .0001 vs. TRE by Chi-square test). (B) The mean LDL-C from baseline to 4 and 8 weeks of treatment (*p < .0001 vs. TRE by independent t-test). LDL-C, low-density lipoprotein cholesterol; RE, rosuvastatin/ezetimibe; T: telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe.

ADRs after treatment (Table 4). In the TRE group, five persons (15.15%, six cases) were reported, four (12.12%, six cases) in the RE group, and four (12.12%, five cases) in the T group. There was no significant difference among the three groups (p = 1.000). The most common ADR was "Headache" (four persons, 4.04%, four cases), followed by "Alanine aminotransferase increased" and "Aspartate aminotransferase increased." The most reported ADRs were "Nervous system disorders" and "Investigations" in the TRE and RE groups and "Gastrointestinal Disorders" in the T group. Most ADRs were previously reported for each agent. No SAE was reported. One person (3.03%) dropped out owing to "Alanine aminotransferase increased" in the TRE group. This AE was mild, and the person recovered.

4 | DISCUSSION

This study was a randomized, double-blind, multicenter, therapeutic confirmatory, phase III study to compare and evaluate the efficacy and safety of combination therapy with TRE in dyslipidemia patients with hypertension. The LS mean (SE) change in msSBP and percentage change in LDL-C from baseline to 8 weeks of treatment were significantly decreased in the TRE group compared to the RE and T groups, respectively. Furthermore, the rate of achievement of the target BP or LDL-C level was also significantly higher in the TRE group during the 8-week follow-up. Safety analysis revealed no significant differences among the three groups.

The combination of an angiotensin II receptor blocker (ARB) and lipid-lowering agents is frequently prescribed for their additive risk reduction of CVD.[10] FDC with ARB and statins could have additional beneficial effects other than apparent BP reduction and lipid profile control.

Telmisartan is an ARB with potent selectivity for the angiotensin II type I receptor. Once daily administration of this medication efficiently lowers BP because of its long half-life.[21] Moreover, it is well tolerated and effectively lowers CVD risks and mortality in high-risk patients.[21,22] In the ONTARGET (The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) investigation, telmisartan demonstrated comparable effectiveness to ramipril in individuals with vascular disease or high-risk diabetes.[23]

Rosuvastatin is an HMG-CoA reductase inhibitor with a high tissue selectivity. It inhibits cholesterol synthesis by inhibiting the conversion of HMG-CoA to mevalonic acid. The HMG-CoA reductase inhibitory effect lasts for 24 h because of its long half-life and has the highest potency among statins on the market to date.[24–26] However, there are reports that the rate of renal excretion with rosuvastatin is higher than with atorvastatin, a lipophilic statin, and that atorvastatin is more helpful in preserving renal function than rosuvastatin.[27,28] However, rosuvastatin has high hepatic selectivity, exhibits higher binding interactions with HMG-CoA reductase, and displays a notable affinity for the enzyme's active site. Furthermore, rosuvastatin has pleiotropic effects independent of HMG-CoA reductase inhibition, including anti-inflammatory, improvements in endothelial function, and antithrombotic and antioxidant effects.[29] The JUPITER study and HOPE-3 study indicated that rosuvastatin significantly reduced the risk of CVD by reducing the inflammatory biomarkers such as high-sensitivity C-reactive protein (CRP) in healthy participants with elevated CRP and in participants with intermediate risk of CVD.[30,31]

In this study, the TRE group showed a substantial BP-lowering effect compared with the T group. The results showed that TRE combination therapy showed additional BP-lowering effects without serious AEs. In a previous study, the combination of telmisartan/amlodipine and rosuvastatin provided statistically significant BP-lowering effects

TABLE 4 Summary of treatment-emergent adverse events (TEAE) in the study

Variable	TRE (No. = 33)	RE (No. = 33)	T (No. = 33)	$p^{\dagger}$
TEAEs	6 (18.18)[10]	4 (12.12)[6]	6 (18.18)[8]	.7422[C]
Intensity				
Mild	6 (18.18)[9]	3 (9.09)[5]	5 (15.15)[6]	–
Moderate	0	1 (3.03)[1]	2 (6.06)[2]	–
Severe	1 (3.03)[1]	0	0	–
SAEs	0	0	0	–
ADRs	5 (15.15)[6]	4 (12.12)[6]	4 (12.12)[5]	>.999[F]
Gastrointestinal disorders	1 (3.03)[1]	0	3 (9.09)[3]	.3196[F]
Conspiration	0	0	1 (3.03)[1]	>.999[F]
Dyspepsia	0	0	1 (3.03)[1]	>.999[F]
Epigastric discomfort	0	0	1 (3.03)[1]	>.999[F]
Vomiting	1 (3.03)[1]	0	0	>.999[F]
Nervous system disorders	2 (6.06)[2]	2 (6.06)[2]	0	.5418[F]
Headache	2 (6.06)[2]	2 (6.06)[2]	0	.5418[F]
Investigations	2 (6.06)[3]	1 (3.03)[3]	0	.7709[F]
Alanine aminotransferase increased	2 (6.06)[2]	1 (3.03)[1]	0	.7709[F]
Aspartate aminotransferase increased	1 (3.03)[1]	1 (3.03)[1]	0	>.999[F]
Blood creative phosphokinase increased	0	1 (3.03)[1]	0	>.999[F]
Ear and labyrinth disorders	0	1 (3.03)[1]	0	>.999[F]
Vertigo positional	0	1 (3.03)[1]	0	>.999[F]
General disorders and administration site	0	0	1 (3.03)[1]	>.999[F]
Chest discomfort	0	0	1 (3.03)[1]	>.999[F]
Skin and subcutaneous tissue disorders	0	0	1 (3.03)[1]	>.999[F]
Pruritus	0	0	1 (3.03)[1]	>.999[F]
Serious ADRs	0	0	0	–

Data are presented as the number of patients (%) [number of cases].
Abbreviations: ADR, adverse drug reaction; RE, rosuvastatin/ezetimibe; T, telmisartan; TRE, telmisartan/rosuvastatin/ezetimibe; SAE, serious adverse event.
*TEAEs: AE with a start date on or after administration of study drug or preexisting conditions that worsened on or after study drug administration.
$^{\dagger}p$ value for Chi-square test (C) or Fisher's exact test (F).

compared with telmisartan/amlodipine therapy.[17] These additional BP-lowering effects are assumed to be caused by rosuvastatin.

Previous studies have suggested that statins can amplify the BP-lowering effects of ARBs.[10,32,33] In a recent retrospective observational study, statin use was associated with better ambulatory BP control,[34] and a meta-analysis of prospective randomized, controlled trials of statin therapy showed that significant reduction of SBP in patients taking statins compared to control group.[35] The mechanism by which statin reduces BP is presumed to be due to pleiotropic effects such as suppression of vascular smooth muscle cell proliferation, reduction of angiotensin II-type 1 receptor, and vasodilation by increasing nitric oxide bioavailability.[15,36] A study using a rabbit model of high cholesterol diet-induced atherosclerosis demonstrated that the combination of statins and ARBs synergistically exerted an early antiatherosclerotic effect compared to administering each drug individually by reducing plaque burden.[37] The combination of statins with ARBs have also been reported to prevent atherosclerosis activities[38] and reduce carotid intimal thickness.[39] Compared to each single medication therapy, FDC therapies with ARB and statins have shown equivalent efficacies with no additional AEs.[40,41]

Statins are widely used for preventing atherosclerotic CVDs, and high-dose statins are more commonly recommended because the current guidelines lower target LDL-C compared to previous ones.[15–17] However, the maximum dose of rosuvastatin often does not reduce LDL-C levels to the target range.[42] In addition, clinical trials have reported that rosuvastatin doses above a certain point are associated with an increased risk of AEs, including myopathy.[43] Therefore, additional lipid-lowering medications are frequently used to reach target LDL-C levels.[44]

Ezetimibe selectively reduces cholesterol absorption in the small intestine with a low incidence of AEs.[45,46] IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) has proven that the statin/ezetimibe combination not only lowers LDL-cholesterol compared to statin monotherapy but also reduces CVD.[47]

Therefore, ezetimibe is recommended in combination with statins. In a previous study, patients who received ezetimibe in addition to statins had an additional 15.2% reduction in LDL-C levels compared to those who received a statin alone.[48] The combination therapy of ezetimibe and statin can effectively lower LDL-C even at low doses of statins, so it is a good strategy to avoid side effects of high doses of statins.[49,50] A previous study showed that RE together significantly lowered LDL-C levels compared to rosuvastatin alone.[49] In this study, TRE significantly lowered LDL-C levels compared to RE at 8 weeks. Thus, the combination of TRE can reduce LDL-C efficiently without serious AEs.

Furthermore, a previous study showed that ezetimibe-rosuvastatin with telmisartan therapy is effective and safe compared to either ezetimibe-rosuvastatin double therapy or telmisartan monotherapy.[51] The triple combination yielded improvements in the primary endpoints of msSBP and LDL-C levels compared to their respective control groups. The efficacy results were consistent with this study, and no clinically significant differences were observed in the safety outcomes in both studies.

There are a few limitations to this study. The study duration was not long enough to evaluate lipid profiles, and a relatively small number of Korean patients were enrolled. Thus, this study limited the generalization of these results to prolonged treatment periods and other ethnic. Despite these limitations, the data show that TRE for 8 weeks in dyslipidemia patients with essential hypertension significantly improved BP and lipid profile.

5 | CONCLUSIONS

Combination therapy of TRE was superior in lowering BP and improving lipid profiles compared to RE combination or T alone. No significant difference was observed among the three groups in safety evaluation; thus, the combination of TRE can be safely administered. Therefore, the combined administration of TRE in dyslipidemia patients with essential hypertension controls BP and improves lipid metabolism more effectively.

AUTHOR CONTRIBUTIONS

C.J. Lee and S. M. Kang wrote and revised the manuscript. S. M. Kang contributed to the study design and S.M. Kang, W.C. Kang, S.H. Ihm, I.S. Sohn, J.S. Woo, J.W. Kim, S.J. Hong, J.H. Choi, J.W. Suh, J.B. Seo, J.H. Doh, J.W. Son, J.H. Park, J.H. Lee, Y.J. Hong, J.H. Heo, and J.H. Shin contributed to data collection and analysis.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The data are the property of the authors and can be made available upon reasonable request to the corresponding author.

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