Efficacy and Safety of Triple Therapy With Telmisartan, Amlodipine, and Rosuvastatin in Patients With Dyslipidemia and Hypertension: The Jeil Telmisartan, Amlodipine, and Rosuvastatin Randomized Clinical Trial

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ABSTRACT

Purpose: Fixed-dose combination therapy with telmisartan, amlodipine, and rosuvastatin is needed in patients with hypertension and dyslipidemia for better adherence and cost-effectiveness than free—equivalent combination therapies. This study aimed to compare the efficacy and safety of combination therapy with telmisartan, amlodipine, and rosuvastatin versus telmisartan plus amlodipine or telmisartan plus rosuvastatin in patients with hypertension and dyslipidemia.

Methods: The Jeil Telmisartan, Amlodipine, and Rosuvastatin Randomized Clinical Trial (J-TAROS-RCT) was an 8-week, multicenter, randomized, double-blind, parallel, Phase III clinical trial

conducted at 9 hospitals in Korea. After a run-in period of >4 weeks, patients who fulfilled the criteria of the National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for randomization to receive 1 of 3 treatments for 8 weeks: (1) telmisartan/amlodipine 80 mg/10 mg plus rosuvastatin 20 mg, (2) telmisartan/amlodipine 80 mg/10 mg, or (3) telmisartan 80 mg plus rosuvastatin 20 mg. The primary end point was efficacy evaluation of combination therapy with telmisartan/amlodipine/rosuvastatin by comparing the change in mean sitting systolic blood pressure (msSBP) and mean percentage change in LDL-C from baseline after 8 weeks of treatment. Adverse events (AEs),

clinical laboratory data, and vital signs were assessed in all patients.

Findings: Among 148 patients, the changes in msSBP from baseline after 8 weeks of treatment were a mean (SD) of –24.41 (2.38) versus –9.31 (2.36) mm Hg in the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin groups, respectively. Significantly more participants achieved the target BP at week 8 in the telmisartan/amlodipine/rosuvastatin group (41 patients [87.2%]) than in the telmisartan/rosuvastatin group (24 [50.0%], $P < 0.001$). The changes in mean (SD) LDL-C at 8 weeks compared with baseline values were –57.59% (11.59%) versus 6.08% (20.98%) in the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine groups, respectively. The percentages of patients who achieved the target LDL-C according to their risk factors after 8 weeks of treatment were 97.87% vs 6.12% in the telmisartan/amlodipine/rosuvastatin and the telmisartan/amlodipine groups ($P < 0.0001$), respectively. No significant differences were found in the incidence of overall AEs and adverse drug reactions, and serious AEs were comparable among 3 groups.

Implications: Fixed-dose combinations of telmisartan, amlodipine, and rosuvastatin decreased BP and LDL-C in patients with hypertension and dyslipidemia. The safety and tolerability profiles of fixed-dose telmisartan, amlodipine, and rosuvastatin combination therapy were comparable with those of telmisartan plus amlodipine or telmisartan plus rosuvastatin. ClinicalTrials.gov identifier: NCT03088254. (*Clin Ther*. 2019;41:233–248) © 2018 Published by Elsevier Inc.

Key words: amlodipine, hypercholesterolemia, rosuvastatin, singe–pill combination, telmisartan.

INTRODUCTION

The 2017 American College of Cardiology/American Heart Association guideline for hypertension in adults recommended using 2 antihypertensive drugs of different classes in stage 2 hypertension, which is defined as a blood pressure (BP) $\geq$140/90 mm Hg.[1] According to previous diagnostic criteria of hypertension, its prevalence was 38.6%–46.9% from 2011 to 2012.[2] Nonetheless, control rates of hypertension were only 20.3%–54.7%. On the basis of these poor control rates, guidelines recommended the commencement of antihypertensive drugs by separate agents or in a fixed-dose combination to reduce the mean BP by > 20/10 mm Hg. Among cotherapies, angiotensin receptor blockers (ARBs) with calcium channel blockers were the recommended first–line combination. Although the incidence of angiotensin-converting enzyme inhibitor–induced cough has been reported to be in the range of 5%–44%, with an especially high incidence in Asians, telmisartan is well tolerated compared with angiotensin-converting enzyme inhibitors.[3,4] In addition, telmisartan modestly reduced the risk of cardiovascular death, myocardial infarction, or stroke. Among ARBs, telmisartan is structurally unique and has a long duration of action with consistent and sustained BP control of >24 h.[5] In a previous study, combination therapy with telmisartan plus amlodipine produced good BP control rates of up to 76.5% by reducing the systolic BP (SBP) and diastolic BP (DBP) by 26.4 and 20.1 mm Hg, respectively.[6] In addition, telmisartan exhibited additional pleiotropic effects on insulin sensitivity and antiatherosclerosis by partially acting on peroxisome proliferator–activated receptor γ, thereby reducing glucose, insulin, and triglyceride levels.[7] In addition, telmisartan increased nitric oxide activity of the renal endothelium.[8]

The prevalence of dyslipidemia has also increased, ranging from 42.7% to 56.8%.[9] The proportion of patients with dyslipidemia who also have hypertension is 2.1 times higher than those who are normotensive. In patients with hypertension, the rate of LDL-C $\geq$130 mg/dL was reported to be up to 71.0%. For controlling dyslipidemia, rosuvastatin is an effective agent with an acceptable safety profile, which has been proven in many previous trials.[10] However, dyslipidemia has not been adequately controlled in many patients, and the addition of more pills to the regimen worsened the patient adherence. Thus, once-daily dosing and fixed-dose combination therapy, which decreases the absolute number of pills, could improve adherence and efficacy.[11] Consequently, the addition of rosuvastatin to telmisartan with amlodipine was expected to result in excellent efficacy, tolerability, and adherence in patients with hypertension and dyslipidemia. Therefore, the objective of this double-blind, multicenter, randomized, Phase III study was to compare the efficacy and safety of combination

therapy with telmisartan, amlodipine, and rosuvastatin versus telmisartan plus amlodipine or telmisartan plus rosuvastatin in patients with hypertension and dyslipidemia.

PATIENTS AND METHODS
Study Patients

Korean men and women aged >19 years with primary hypertension and hypercholesterolemia requiring medical treatment were eligible for participation in the study. Patients who fulfilled the criteria of mean sitting SBP (msSBP) < 180 mm Hg, mean sitting (msDBP) < 110 mm Hg, LDL-C ≤250 mg/dL, and triglycerides<400 mg/dL were enrolled and started the run-in period with telmisartan 80 mg once daily together with therapeutic lifestyle changes. After a >4-week run-in period, patients who fulfilled the following criteria of the National Cholesterol Education Program Adult Treatment Panel III guidelines were eligible for the treatment period: (1) patients with no other risk factors and LDL-C ≥160 mg/dL (group 1), (2) patients with ≥1 major risk factors and a 10-year cardiovascular disease (CVD) risk indicated by Framingham risk score <10% with LDL-C ≥ 160 mg/dL (group 2A), (3) patients with ≥1 major risk factors and a 10-year CVD risk ≥10% but ≤20% with LDL-C ≥130 mg/dL (group 2B), or

(4) patients with coronary artery disease or a 10-year CVD risk >20% with LDL-C ≥100 mg/dL (group 3).

A total of 216 patients were screened for inclusion in the study, and those (n = 68) who did not fulfill the inclusion criteria or who met any of the exclusion criteria were excluded. Eligible patients were included in the study from September 2016 through July 2017 (Figure 1) at 9 Korean tertiary hospitals.

We excluded patients with SBP/DBP differences ≥20/10 mm Hg between both arms, symptomatic orthostatic hypotension, or secondary dyslipidemia. Patients with unstable angina pectoris, myocardial infarction, cerebrovascular disease, percutaneous coronary intervention, and uncontrolled arrhythmia within the past 3 months were excluded. Patients with known histories of severe ocular diseases within the past 6 months, hereditary angioedema, myopathy, rhabdomyolysis, or autoimmune diseases were excluded. Patients were also excluded if they had a history of alcohol abuse, major psychiatric disorders, or malignant tumor within the past 5 years. Patients with severe aortic stenosis, biliary stenosis, secondary hypertension, thyroid dysfunction (thyroid-stimulating hormone ≥1.5 times the upper limit of normal), uncontrolled diabetes mellitus (glycosylated hemoglobin ≥9%), severe heart failure (New York Heart Association III/IV), creatinine clearance <30 mL min^{-1}·1.73 m$^{(2)-1}$, hepatic dysfunction (serum
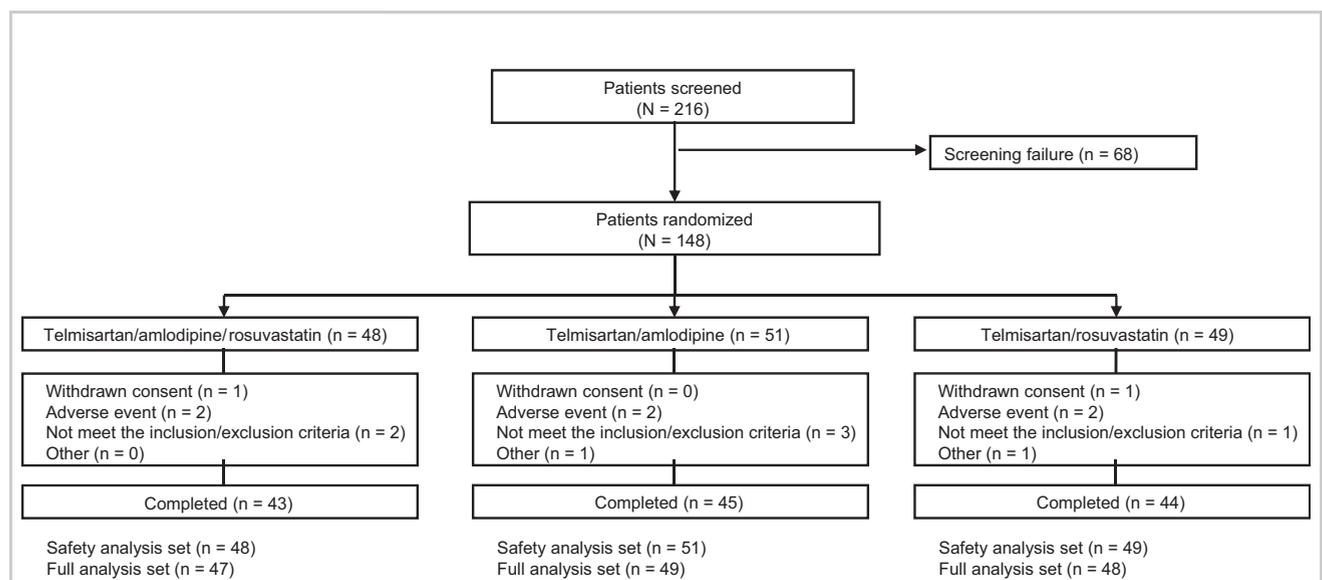

Figure 1.   Study design of the Jeil Telmisartan Amlodipine Randomized Clinical Trial.

aspartate or alanine aminotransferase levels more than twice the upper limit of normal), elevated creatinine phosphokinase level more than twice the upper limit of normal, potassium >5.5 mEq/L, uncontrolled sodium deficiency, or HIV positive. Patients were also excluded if they had gastrointestinal disorder, such as Crohn disease or a history of gastrointestinal surgery. Women who were pregnant, breastfeeding, or of childbearing potential who were not using appropriate contraception were also excluded from the study. The use of other antihypertensive drugs, antilipidemic drugs, oral steroids, oral contraceptives, fish oil, cholestine, antipsychotics, phytosterol margarines, and vasodilators was not permitted during the study. Patients with any condition that in the opinion of the investigator would make their participation in this study unsafe or unsuitable were excluded.

Study Design

This trial was an 8-week, multicenter, randomized, double-blind, parallel, Phase III clinical trial conducted at 9 sites in Korea. During the 4-week run-in period, all patients were instructed to make therapeutic lifestyle changes. At randomization, patients were reevaluated to determine whether they were still eligible with respect to the inclusion and exclusion criteria. Patients were randomly assigned to receive 1 of 3 treatments, telmisartan/amlodipine 80 mg/10 mg plus rosuvastatin 20 mg, telmisartan/amlodipine 80 mg/10 mg, or telmisartan 80 mg plus rosuvastatin 20 mg, and commenced the 8-week, double-blind treatment period. The principal investigators at each center enrolled and assigned the patients to the allocated intervention. Randomization was performed using a web-based online randomization system in a 1:1:1 ratio. All study personnel, including the investigators, study site personnel, participants, monitors, and central laboratory personnel, were blinded to the treatment allocation throughout the study. Doses were not adjusted during the 8-week treatment period, and participants in all groups received 4 tablets once daily to maintain double-blinding. Experimental drug was 2 pills of telmisartan 40 mg/amlodipine 5 mg and rosuvastatin 20 mg. The telmisartan/amlodipine/ rosuvastatin group received 2 active tablets of telmisartan 40 mg/amlodipine 5 mg from Boehringer Ingelheim Pharma Co, Seoul, Korea, 1 placebo tablet of telmisartan, and 1 active tablet of rosuvastatin

20 mg from AstraZeneca Pharma Co, Seoul, Korea. The telmisartan/amlodipine group received 2 active tablets of telmisartan 40 mg/amlodipine 5 mg from Boehringer Ingelheim Pharma Co, Seoul, Korea, 1 placebo tablet of telmisartan, and 1 placebo tablet of rosuvastatin from Jeil Pharma Co, Seoul, Korea. The telmisartan/rosuvastatin group received 2 placebo tablets of telmisartan/amlodipine from Jeil Pharma Co, Seoul, Korea, 1 active tablet of telmisartan 80 mg from Boehringer Ingelheim Pharma Co, Seoul, Korea, and 1 active tablet of rosuvastatin 20 mg from AstraZeneca Pharma Co, Seoul, Korea.

Ideally, participants were expected to have a medication adherence of at least 70% throughout the treatment period, and those with <70% or >125% were considered to have poor adherence. The study was approved by the institutional review board of each hospital, and written informed consent was obtained from all participants or their legal guardians before their inclusion in the study. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

End Points and Safety Assessment

The primary end point was to evaluate the efficacy of combination therapy with telmisartan/amlodipine/ rosuvastatin versus telmisartan/rosuvastatin by comparing the mean change in msSBP and the mean percentage change in LDL-C from baseline after 8 weeks of treatment. The secondary end points were the mean percentage change from baseline in (1) LDL-C after 4 weeks of treatment; (2) total cholesterol, triglycerides, HDL-C, non−HDL-C, apolipoprotein (Apo) B, and Apo A1; (3) LDL-C/ HDL-C and Apo B/Apo A1; and (4) high-sensitivity C-reactive protein (hs-CRP) after 4 and 8 weeks of treatment. In addition, we compared (5) the LDL-C control rate, which was defined as the percentage of patients who achieved the target LDL-C according to their risk factors after 8 weeks of treatment, the mean change from baseline in (6) msSBP after 4 weeks of treatment and (7) msDBP after 4 and 8 weeks of treatment, achieving (8) the BP target rate of <140/90 mm Hg after 8 weeks of treatment, (9) the BP controlling rate <130/90 mm Hg, and (10) the BP-lowering response rate, which was defined as the percentage of patients whose SBP decreased ≥20 mm Hg or DBP ≥10 mm Hg after 8 weeks of treatment.

For the efficacy analysis, data from the full analysis set (FAS) population were used. Blood samples were drawn from each patient after 12 h of fasting. The lipid profiles and hs-CRP were analyzed at the central laboratory. The BP was measured when the patient was relaxed for at least 5 min using the same arm and sphygmomanometer (HBP-9020, Omron-Healthcare, Kyoto, Japan). BP was measured twice at the interval of >2 min in the selected arm. If the gap of DBP was >5 mm Hg, BP was measured once more. Mean SBP was calculated from 2 or 3 measured SBPs.

Safety assessments included monitoring and recording adverse events (AEs), all laboratory tests (except lipid profiles), electrocardiograms, vital signs of the heart and pulse rate, consecutive hepatic dysfunction rate (serum aspartate or alanine aminotransferase levels >3 times the upper limit of normal), and myopathy rate. For the safety and follow-up period assessments, data from a safety set population were used. Adverse drug reactions (ADRs) were defined as drug-related AEs and classified as certain, probably, possible, unlikely, none, or not assessable for the study drugs. ADRs that were unrelated to the study drugs were not considered study drug–related AEs. Laboratory AEs were assessed by comparing baseline laboratory values with those at follow-up. The severity of AEs was classified as mild for mild symptoms or signs not affecting activities of daily living, moderate for minor limitations in daily living activities, and severe for marked limitations in daily living activities. The investigators at each center decided whether patients with ADRs should be withdrawn from the study.

Statistical Analysis

Data are expressed as mean (SD) for the continuous variables and number (percentage) of patients for the categorical variables. The Pearson χ^2 test or Fisher exact test was used to analyze the categorical variables, and independent 2-sample t tests or Wilcoxon rank sum test was used to analyze continuous variables. The effects of the treatments on the primary and secondary end points were compared using an ANCOVA, which included treatment and stratified factors according to the groups, with the relevant baseline value as a covariate. The control and response rates were analyzed using the Cochran–Mantel–Haenszel test.

Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group minus the telmisartan/amlodipine group or telmisartan/rosuvastatin group.

The FAS included all randomized patients who received at least 1 dose of the double-blind study medication and provided at least 1 end-point measurement after randomization. This was a combination therapy study to verify the superiority of telmisartan/amlodipine/rosuvastatin treatment in terms of mean percentage change in LDL-C (from baseline to week 8) over telmisartan/amlodipine therapy and mean change in msSBP over telmisartan/rosuvastatin therapy. Overall, statistical power of the whole hypothesis was set to 80%, and the 2-sided significance level of each hypothesis was set to 5%. The statistical power of each hypothesis was set to 95% without adjusting for multiplicity. The sample size of the study was determined based on the estimation of mean change in msSBP obtained in previous trials.[12] We assumed that the mean (SD) change in msSBP after adding amlodipine would be 7.96 (11.05) mm Hg. Required sample sizes were at least 33 patients per group. A total of 126 patients (42 in each of the 3 groups) were considered to meet the sample size cutoff, under the assumption of a dropout rate of 20%. $P < 0.05$ was considered statistically significant. SAS software version 9.3 (SAS Institute, Cary, North Carolina) was used for the statistical analysis.

RESULTS

Patient Disposition and Baseline Characteristics

We randomly assigned 148 patients to receive telmisartan/amlodipine/rosuvastatin (n = 48), telmisartan/amlodipine (n = 51), or telmisartan/rosuvastatin (n = 49) (Figure 1). Furthermore, 16 of the randomized patients dropped out, whereas the remaining 132 completed the treatment. Among the enrolled 148 patients, no patients had not taken any study drugs, and they were all analyzed for safety parameters. For efficacy parameters, 144 patients, excluding 4 whose lipid profile or BP had not been measured during the trial, were analyzed as the FAS.

The demographic and baseline clinical characteristics of age, sex, body mass index, hypertension, diabetes mellitus, and medications on admission were similar among 3 groups (Table I). No significant differences in the baseline lipid profiles were found among the groups. However, baseline

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

Characteristic	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)	$P^{\dagger}$
Age, mean (SD), y	67.96 (9.44)	66.63 (10.22)	65.88 (9.13)	0.471
Male	33 (70.21)	31 (63.27)	34 (70.83)	0.674
BMI, mean (SD), kg/m^2	26.52 (3.12)	26.55 (2.92)	27.67 (3.41)	0.128
Comorbidities				
Stable angina	26 (55.32)	26 (53.06)	28 (58.33)	0.872
Previous or prior myocardial infarction	1 (2.13)	1 (2.04)	1 (2.08)	1.000
Diabetes mellitus	15 (31.91)	16 (32.65)	13 (27.08)	0.813
Percutaneous coronary intervention	16 (34.04)	18 (36.73)	19 (39.58)	0.855
Prior medications				
Statin	38 (80.85)	39 (79.59)	40 (83.33)	0.891
ACEi or ARB	39 (82.98)	40 (81.63)	42 (87.50)	0.712
β-Blockers	10 (21.28)	12 (24.49)	15 (31.25)	0.524
Calcium channel blockers	8 (17.02)	4 (8.16)	9 (18.75)	0.284
Diuretics	5 (10.64)	3 (6.12)	2 (4.17)	0.427
Antithrombotic agents	36 (76.60)	34 (69.39)	40 (83.33)	0.270
Lipid profiles, mean (SD)				
LDL-C, mg/dL	150.51 (31.78)	153.12 (35.18)	158.92 (30.62)	0.256
Total cholesterol mg/dL	216.38 (31.68)	219.84 (37.88)	225.69 (32.84)	0.411
Triglycerides, mg/dL	157.62 (50.84)	145.08 (70.21)	156.25 (75.24)	0.296
HDL-C, mg/dL	46.17 (12.36)	49.76 (13.60)	47.44 (11.98)	0.316
Non−HDL-C, mg/dL	170.21 (32.39)	170.08 (38.76)	178.25 (30.57)	0.408
Apolipoprotein B, mg/dL	130.47 (26.19)	131.22 (29.93)	134.50 (22.40)	0.562
Apolipoprotein A, mg/dL	134.13 (23.02)	140.80 (22.75)	138.58 (23.83)	0.160
Highly sensitive CRP, mg/dL	1.16 (1.18)	1.10 (1.18)	1.80 (3.46)	0.624
Patients by CHD risk factor				0.134
Group 3 (CHD/CHD risk equivalents [10-y risk >20%])	40 (85.11)	38 (77.55)	44 (91.67)	
Group 2B (risk factors ≥2 [10% ≤ 10-y risk ≤20%])	6 (12.77)	9 (18.37)	2 (4.17)	
Group 2A (Risk factors ≥2 [10-y risk <10%])	1 (2.13)	1 (2.04)	0 (0.00)	
Group 1 (risk factors 0−1)	0 (0.00)	1 (2.04)	2 (4.17)	

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CHD = coronary heart disease.
* Data are given as number (percentage) of patients unless otherwise noted.
† P values between telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine and telmisartan/rosuvastatin group.

msSBP had significant mean (SD) differences between the telmisartan/amlodipine/rosuvastatin combination therapy and telmisartan/amlodipine groups (149.49 [12.09] vs 144.29 [11.09] mm Hg, P = 0.029) (Table II). The baseline msSBP of the telmisartan/amlodipine/rosuvastatin combination therapy and telmisartan/rosuvastatin groups was similar (149.49 [12.09] vs 147.08 [13.69] mm Hg, P = 0.242).

Table II. Changes in blood pressure from baseline after 8-week follow-up.

Variable	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)
msSBP at baseline, mm Hg			
Mean (SD)	149.49 (12.09)	144.29 (11.09)	147.08 (13.69)
Median	147.00	142.00	144.50
Range	130.00 to 175.00	130.00 to 178.00	130.00 to 177.00
msSBP at 4-week follow-up, mm Hg			
Mean (SD)	126.04 (12.56)	125.27 (10.47)	140.52 (21.24)
Median	126.00	127.00	140.50
Range	96.00 to 156.00	96.00 to 150.00	102.00 to 183.00
Change in msSBP baseline at week 4			
Mean (SD)	−23.45 (12.64)	−19.02 (13.34)	−6.56 (16.38)
Median	−20.00	−19.00	−5.50
Range	−60.00 to −1.00	−71.00 to 8.00	−50.00 to 35.00
P	<0.0001	<0.0001	0.008
Treatment difference LS mean (SE)*	−21.76 (1.59)	−20.64 (1.56)	—
LS mean (SE)	−23.17 (2.11)	—	−6.83 (2.09)
LS mean difference (95% CI)	—	−1.13 (−5.61 to 3.36)	−16.34 (−22.25 to −10.43)
P	—	0.619	<0.0001
msSBP at 8-week follow-up			
Mean (SD)	124.87 (13.70)	122.57 (12.41)	137.98 (23.72)
Median	124.00	125.00	137.50
Range	97.00 to 164.00	93.00 to 149.00	92.00 to 203.00
Change in msSBP from baseline at week 8, mm Hg			
Mean (SD)	−24.62 (13.80)	−21.71 (14.93)	−9.10 (18.54)
Median	−23.00	−24.00	−10.50
Range	−50.00 to 3.00	−59.00 to 11.00	−50.00 to 40.00
P	<0.0001	<0.0001	0.001
Treatment difference LS mean (SE)*	−22.93 (1.84)	−23.33 ± 1.80	—
LS mean (SE)	−24.41 (2.38)	—	−9.31 (2.36)
LS mean difference (95% CI)		0.41 (−4.76 to 5.57)	−15.10 (−21.77 to −8.43)
P	—	0.877	<0.0001
msDBP at baseline, mm Hg			
Mean (SD)	81.74 (12.52)	77.84 (12.78)	83.33 (12.89)
Median	81.00	77.00	82.50
Range	59.00 to 109.00	48.00 to 109.00	60.00 to 107.00
msDBP at 4-week follow-up, mm Hg			
Mean (SD)	70.83 (10.84)	70.24 (9.52)	81.13 (13.24)
Median	70.00	70.00	80.00
Range	54.00 to 98.00	49.00 to 94.00	54.00 to 103.00

Table II. (*Continued*)

Variable	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)
Change in msDBP from baseline at week 4, mm Hg			
Mean (SD)	–10.91 (8.99)	–7.59 (9.80)	–2.21 (7.62)
Median	–11.00	–10.00	–1.00
Range	–29.00 to 12.00	–24.00 to 32.00	–24.00 to 10.00
P	<0.0001	<0.0001	0.1741
Treatment difference LS mean (SE)*	–10.01 (1.10)	–8.46 (1.08)	—
LS mean (SE)	–11.12 (1.12)	—	–2.00 (1.11)
LS mean difference (95% CI)	—	–1.55 (–4.63 to 1.53)	–9.12 (–12.26 to –5.98)
P	—	0.319	<0.0001
msDBP at 8-week follow-up, mm Hg			
Mean (SD)	70.17 (10.87)	68.41 (9.21)	79.58 (13.72)
Median	69.00	68.00	81.50
Range	54.00 to 96.00	51.00 to 86.00	45.00 to 114.00
Change in msDBP from baseline at week 8, mm Hg			
Mean (SD)	–11.57 (8.71)	–9.43 (10.01)	–3.75 (9.20)
Median	–11.00	–11.00	–4.50
Range	–29.00 to 7.00	–32.00 (18.00)	–21.00 to 16.00
P	<0.0001	<0.0001	0.007
Treatment difference LS mean (SE)*	–10.66 (1.09)	–10.31 (1.07)	—
LS mean (SE)	–11.79 (1.21)	—	–3.54 (1.20)
LS mean difference (95% CI)	—	–0.35 (–3.39 to 2.70)	–8.26 (–11.65 to –4.86)
P	—	0.820	<0.0001

LS = least-squared; msSBP = mean sitting systolic blood pressure, msDBP = mean sitting diastolic blood pressure.

*Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group minus telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Mean (SD) drug adherence for telmisartan/amlodipine/rosuvastatin, telmisartan/rosuvastatin, and telmisartan/rosuvastatin was 99.42% (14.26%), 96.54% (20.29%), and 95.98% (20.16%), respectively.

Efficacy

The mean (SD) changes in msSBP from baseline after 8 weeks of double-blind treatment were –24.41 (2.38) versus –9.31 (2.36) mm Hg in the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin groups, respectively (Table II and Figure 2A and B). Treatment with telmisartan/amlodipine/rosuvastatin resulted in a statistically greater BP-lowering effect than that of treatment with telmisartan/rosuvastatin (differences, –15.10 mg/dL [95% CI, –21.78 to –8.43 mg/dL], $P < 0.0001$). In the per-protocol analysis, the msSBP at 8 weeks was also significantly lower in the telmisartan/amlodipine/rosuvastatin group than it was in the telmisartan/rosuvastatin group (–24.69 [12.77] vs –9.97 [17.46] mm Hg, $P < 0.0001$). The secondary end point, msSBP change at 4 weeks, was significantly greater in the telmisartan/amlodipine/rosuvastatin group than it was in the telmisartan/rosuvastatin group (–23.45 [12.64] vs –6.56 [16.38] mm Hg, $P < 0.0001$) (Table II and Figure 2A and B). The effects of decreasing the msSBP were comparable at 4-week follow-up and 8-

(A)

Mean SD changes of msSBP after 4- and 8-week treatment

(B)   **LS mean SD change of msSBP after 4- and 8-week treatment**

(C)

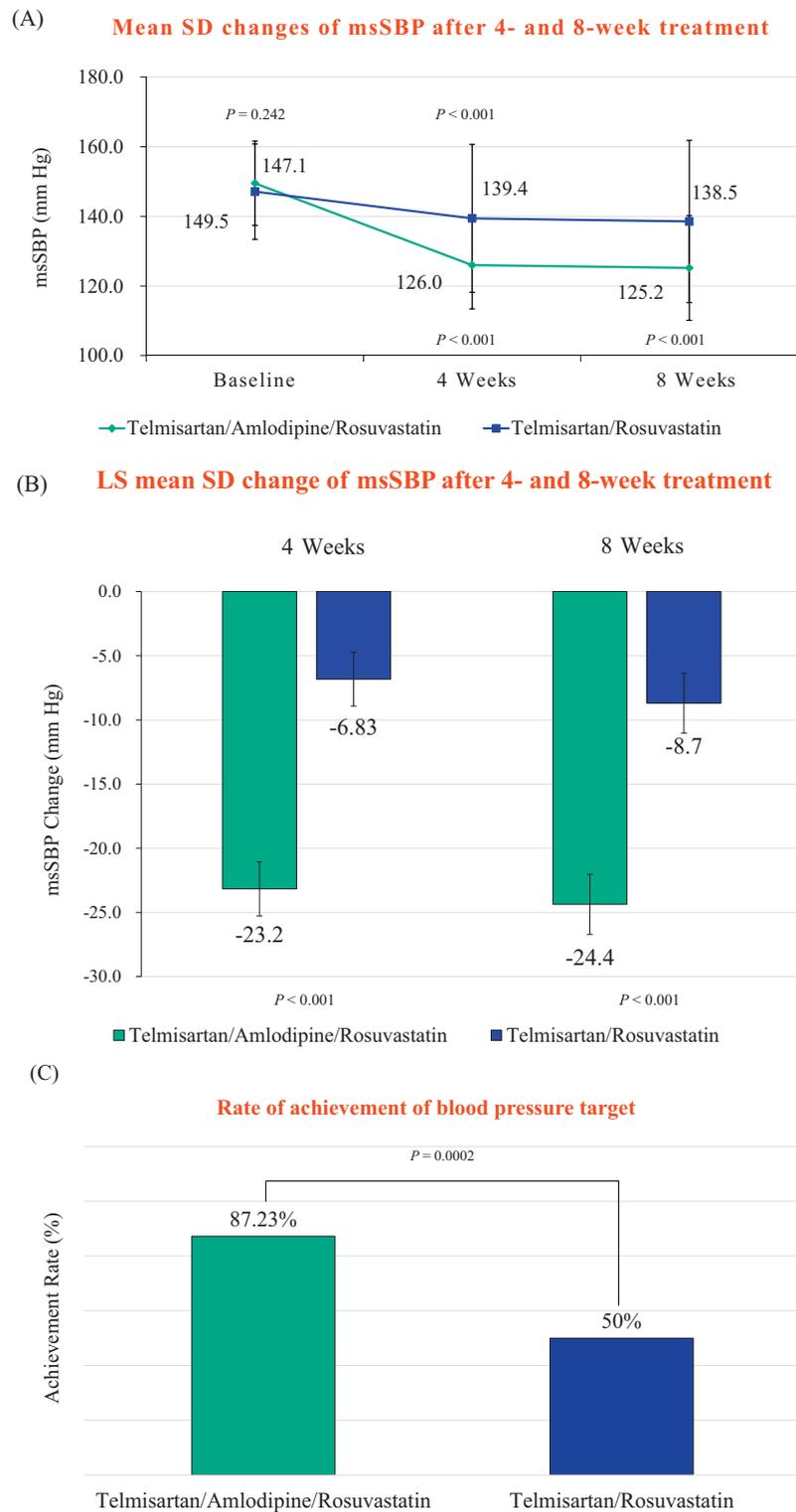**Rate of achievement of blood pressure target**

Figure 2.   Changes in mean (SD) sitting systolic blood pressure (msSBP) from baseline after 4 and 8 weeks of double-blind treatment. (A) Forest plot showing msSBP between groups. (B) Least-squared (LS) mean (SD) percentage change in msSBP after 8 weeks of treatment. (C) Rate of achievement of blood pressure target.

Table III. Rate of achievement of BP target.

Variable	No. (%) of Patients			$P*$	$P^{\dagger}$
	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)		
Achievement rate of <140/90 mm Hg goal	41 (87.23)	46 (93.88)	24 (50.00)	0.262	<0.001
Controlling rate of < 130/90 mmHg goal	32 (68.09)	36 (73.47)	18 (37.50)	0.497	0.005
BP-lowering response rate of msSBP ≥20 mm Hg or msDBP ≥10 mm Hg	36 (76.60)	35 (71.43)	17 (35.42)	0.726	<0.0001

BP = blood pressure; msDBP = mean sitting diastolic blood pressure; msSBP = mean sitting systolic blood pressure.
*P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine groups.
†P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin groups.

week follow-up. In terms of the change in msDBP at 4 weeks relative to baseline msDBP, a significant difference was found between the telmisartan/amlodipine/rosuvastatin and the telmisartan/rosuvastatin groups (–10.91 [8.99] vs –2.21 [7.62] mm Hg, $P < 0.0001$) (Table II). The msDBP change from baseline to 8 weeks was –11.57 (8.71) and –3.75 (9.20) mm Hg in the telmisartan/amlodipine/rosuvastatin and the telmisartan/rosuvastatin groups, respectively ($P < 0.0001$). The number of participants who achieved target BP at week 8 was significantly higher in the telmisartan/amlodipine/rosuvastatin group (41 patients [87.2%]) than in the telmisartan/rosuvastatin group (24 [50.0%], $P < 0.001$) (Table III and Figure 2C). The BP controlling rate of <130/90 mm Hg after 8 weeks of treatment was significantly higher in the telmisartan/amlodipine/rosuvastatin group than telmisartan/rosuvastatin group (68.9% vs 37.5%, $P = 0.005$). The BP-lowering response rate was also considerably higher in the telmisartan/amlodipine/rosuvastatin group than telmisartan/rosuvastatin group (76.6% vs 35.4%, $P < 0.0001$).

The mean (SD) percentage changes in mean LDL-C at 8 weeks compared with baseline values were –57.59% (11.59%) vs 6.08% (20.98%) in the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine groups, respectively (Table IV and Figure 3A and B). Treatment with telmisartan/amlodipine/rosuvastatin resulted in a statistically greater lipid-lowering effect than treatment with telmisartan/amlodipine (differences, –63.93% [95% CI, –70.75% to –57.10%], $P < 0.0001$). The secondary end point, percentage changes in mean LDL-C at 4 weeks, was significantly greater in the telmisartan/amlodipine/rosuvastatin group than it was in the telmisartan/amlodipine group (–57.22% [9.76%] vs 5.00% [17.59%], $P < 0.0001$) (Table IV and Figure 3A and B). The effects of decreasing the LDL-C were comparable at 4-week follow-up and 8-week follow-up. The percentage of patients who achieved the target LDL-C according to their risk factors after 8 weeks of treatment were 97.87% and 6.12% in the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine groups, respectively ($P < 0.0001$) (Table V and Figure 3C).

Total cholesterol was significantly decreased after 8-week treatment with telmisartan/amlodipine/rosuvastatin than with telmisartan/amlodipine (–39.27% [8.09%] vs 2.77% [15.65%], $P < 0.001$) (Supplemental Table I). The telmisartan/amlodipine/rosuvastatin group also had a significant decrease in mean (SD) triglyceride level than the telmisartan/amlodipine group (–28.34% [24.73%] vs 3.25% [51.97%], $P = 0.001$) (Supplemental Table II). Moreover, mean (SD) HDL-C was significantly increased in the telmisartan/amlodipine/rosuvastatin group than it was in the telmisartan/amlodipine group (16.36% [21.13%] vs 2.67% [16.33%],

Table IV.   Changes in LDL-C after 8-week follow-up.

Variable	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)
Baseline LDL-C, mg/dL			
Mean (SD)	150.51 (31.78)	153.12 (35.18)	158.92 (30.62)
Median	148.00	148.00	164.00
Range	100.00 to 241.00	101.00 to 242.00	100.00 to 242.00
LDL-C at 4-week follow-up, mg/dL			
Mean (SD)	63.77 (17.74)	159.57 (41.60)	70.79 (17.76)
Median	62.00	150.00	67.00
Range	35.00 to 109.00	103.00 to 295.00	34.00 to 133.00
Change from baseline at week 4, %[*]			
Mean (SD)	–57.22 (9.76)	5.00 (17.59)	–54.89 (10.09)
Median	–58.54	2.63	–56.28
Range	–72.09 to –33.00	–23.87 to 77.71	–68.78 to –25.28
P	<0.0001	0.128	<0.0001
Treatment difference LS mean (SE)[†]	–57.33 (2.06)	5.11 (2.02)	—
LS mean (SE)	–57.56 (1.42)	—	–54.56 (1.40)
LS mean difference (95% CI)	—	–62.44 (–68.17 to –56.72)	–3.00 (–6.97 to 0.98)
P	—	<0.0001	0.138
LDL-C at 8-week follow-up, mg/dL			
Mean (SD)	63.55 (20.72)	160.61 (43.25)	71.54 (17.62)
Median	60.00	153.00	70.00
Range	30.00 to 114.00	95.00 to 315.00	36.00 to 129.00
Change from baseline at week 8, %[*]			
Mean (SD)	–57.59 (11.59)	6.08 (20.98)	–53.99 (12.08)
Median	–59.34	4.82	–54.83
Range	–75.78 to –24.39	–44.77 to 89.76	–71.43 to –17.00
P	<0.0001	0.056	<0.0001
Treatment difference LS mean (SE)[†]	–57.72 (2.45)	6.21 (2.40)	—
LS mean (SE)	–58.01 (1.69)	—	–53.58 (1.67)
LS mean difference (95% CI)	—	–63.93 (–70.75 to –57.10)	–4.42 (–9.15 to 0.31)
P	—	<0.0001	0.067

LS = least-Squared.
[*] Change rate was calculated as [(Each Visit − Baseline)/Baseline] × 100.
[†] Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group minus telmisartan/amlodipine group or telmisartan/rosuvastatin group.

P = 0.002) (Supplemental Table III). The percentage changes in non−HDL-C, Apo B, Apo A1, LDL-C/ HDL-C, total cholesterol, and Apo B/Apo A1 were significantly greater with telmisartan/amlodipine/ rosuvastatin treatment than with telmisartan/ amlodipine (Supplemental Table IV−VIII). The changes in highly sensitive C-reactive protein after 4 and 8 weeks were similar between the telmisartan/ amlodipine/rosuvastatin and telmisartan/amlodipine groups (Supplemental Table IX).
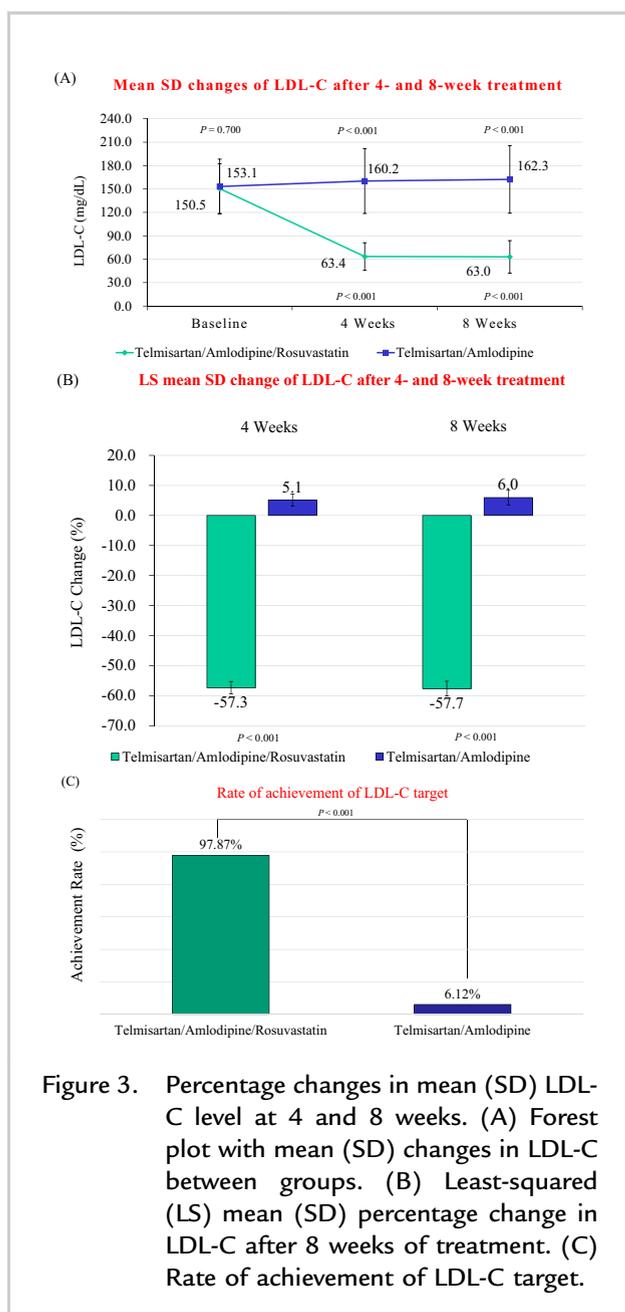
Figure 3. Percentage changes in mean (SD) LDL-C level at 4 and 8 weeks. (A) Forest plot with mean (SD) changes in LDL-C between groups. (B) Least-squared (LS) mean (SD) percentage change in LDL-C after 8 weeks of treatment. (C) Rate of achievement of LDL-C target.

Safety

Among the 148 patients in the safety analysis set, 13 (8.8%) experienced at least 1 ADR after treatment (Table VI). The most common ADR was peripheral edema. No significant differences were found in the overall incidence of AEs, ADRs, and serious AEs. Laboratory findings, including liver function test results and creatinine kinase levels, were comparable among the 3 groups. Two patients in each group dropped out because of AEs.

DISCUSSION

In this double-blind, multicenter, randomized, Phase III study, triple combination therapy with telmisartan/amlodipine/rosuvastatin significantly decreased the mean sSBP and LDL-C compared with telmisartan/rosuvastatin or telmisartan/amlodipine therapy, respectively, without increasing the overall AEs. Furthermore, achievements of the target BP or LCL-C rates were also significantly higher in the telmisartan/amlodipine/rosuvastatin group than the other groups during the 8-week follow-up.

Hypertension is a well-known risk factor for CVDs, whose prevalence is gradually increasing with dyslipidemia,[13] and large number of patients up to 80% have both hypertension and dyslipidemia at the same time.[14] In these patients, antihypertensive therapy could reduce 20%−50% of the cardiovascular events, including stroke, myocardial infarction, and heart failure.[15] In addition, current guidelines emphasize the use of statins to attain desired LDL-C for primary and secondary prevention.[16] However, in real-world clinical practice, only half of patients with hypertension are receiving treatment, and only 34% of are adequately controlled.[17] Statin therapy discontinuation rates were reported to be up to 60% after 1 year of treatment, and only a quarter of patients met their therapeutic LDL-C goal.[18,19] Nonadherence with a medication regimen is one of the major causes of treatment failure,[20] and poor adherence contributes to the practice-outcome gap. Recognized reasons for nonadherence include problems with polypharmacy and regimen complexity. Patients with multiple risk factors, such as hypertension and dyslipidemia, need to take several medications to control BP and LDL-C, especially in elderly patients who have multiple comorbidities.[21] Several antihypertensive and lipid-lowering medications lead to a sharp decrease in the adherence to both treatments of <50% just after 3 months.[22] Thus, administration of antihypertensive and lipid-lowering therapy via fixed-dose combinations could improve adherence by reducing the pill burden.[23] One of the potential limitations of the polypill strategy is inconvenience of dose adjustments. When the therapeutic target was not reached, fine-tuning with the polypill strategy may be difficult. In addition, patients who experienced an AE with any of the components had a chance to discontinue use of all drugs. Nonetheless, the long-

Table V. Rate of achievement of LDL-C cholesterol target.*

Variable	Telmisartan/ Amlodipine/ Rosuvastatin (n = 47)	Telmisartan/ Amlodipine (n = 49)	Telmisartan/ Rosuvastatin (n = 48)
Patients achieving LDL-C goal			
Total No. (%)	46 (97.87)	3 (6.12)	46 (95.83)
P		< 0.0001[†]	0.616[‡]
Patients by CHD risk factors, No. (%)			
Group 3 (CHD/CHD risk equivalents [10-y risk >20%])	39 (97.50)	2 (5.26)	42 (95.50)
Group 2 (risk factors ≥2 [10% ≤ 10-y risk ≤20% or 10-y risk <10%])	7 (100.00)	1 (10.00)	2 (100.00)
Group 1 (risk factors 0−1)	0 (0.00)	0 (0.00)	2 (100.00)

CHD = coronary heart disease.
*Targets were LDL-C <160 mg/dL (group 1), LDL-C <130 mg/dL (group 2A and 2B), and LDL-C <100 mg/dL (group 3).
[†]P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine group.
[‡]P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin group.

term studies found better risk factor control by better adherence to the polypill strategy. Actually, fixed-dose combinations improved the adherence by 20%−24% compared with free−equivalent combination regimen, thereby contributing to higher target goal achievement and fewer complications.[11,24]

The 2017 guideline for high BP in adults recommended the use of combination therapy in those with BP ≥ 140/90 mm Hg.[1] Because single antihypertensive therapy met the BP goal in only 50% of patients, many patients with hypertension required ≥2 antihypertensive medications to achieve target BP goals.[25] The use of antihypertensive agents with complementary action mechanisms could be more efficacious than increasing a single antihypertensive agent to the maximal dose.[26] Telmisartan, an angiotensin II receptor antagonist, and amlodipine, a calcium channel antagonist, are well established agents for hypertension with complementary action mechanisms.[27] As individual agents, telmisartan reduces the risk of cardiovascular events, whereas amlodipine effectively treats angina and reduces the risk of hospitalization attributable to angina and the risk of coronary revascularization procedures in patients with coronary artery disease. In a previous study, combination therapy with

telmisartan and amlodipine found a strong BP-lowering effect (msSBP/msDBP, −26.4/−20.1 mm Hg).[28] Control rates of msSBP/msDBP were 54%−77%/69%−85%, and response rates of msSBP/msDBP were 80%−91%/82%−93%. Those results were comparable to the findings of this study with the msSBP/sDBP-lowering effects of −24.4/−11.6 mm Hg, respectively, and the BP control rate in this study was 87.2%.

The robust efficacy of rosuvastatin, which was used in this trial, has been proven in many previous studies.[29,30] In the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), administration of rosuvastatin 20 mg significantly lowered LDL-C levels by >50%.[29] Furthermore, the proportion of patients who achieved the Adult Treatment Panel III LDL-C target was higher in the rosuvastatin group than other statins groups when compared in equivalent doses.[30] In our trial, the percentage reduction in mean LDL-C at 8 weeks was 57.59%, and the percentage of patients who achieved the target LDL-C according to their risk factors was 97.87%. Thus, fixed-dose combination therapy with telmisartan/amlodipine/rosuvastatin had efficacy in controling BP and LDL-C comparable to that of

Table VI. Summary of AEs and frequency of drug-related AEs in treated set.

Variable	No. (%) of AEs			P^*	$P^\dagger$
	Telmisartan/ Amlodipine/ Rosuvastatin (n = 48)	Telmisartan/ Amlodipine (n = 51)	Telmisartan/ Rosuvastatin (n = 49)		
Total AEs	11 (22.92)	8 (15.69)	9 (18.37)	0.361	0.580
Total drug-related AEs	7 (14.58)	4 (7.84)	2 (4.08)	0.286	0.091
Serious AEs	0 (0.00)	0 (0.00)	0 (0.00)	NA	NA
Severity				0.576	>0.99
Mild	7 (14.58)	3 (5.88)	2 (4.08)		
Moderate	1 (2.08)	0 (0.00)	0 (0.00)		
Severe	0 (0.00	1 (1.96)	0 (0.00)		
Action taken with IP				>0.99	0.556
Maintenance dose	4 (8.33)	3 (5.88)	0 (0.00)		
Permanent dechallenge	3 (6.25)	1 (1.96)	2 (4.08)		
ADRs according to system organ class					
General disorders and administration site conditions	5 (10.42)	2 (3.92)	1 (2.04)	0.260	0.112
Edema peripheral	5 (10.42)	2 (3.92)	1 (2.04)	0.260	0.112
Nervous system disorders	1 (2.08)	1 (1.96)	0 (0.00)	>0.99	0.495
Dizziness	1 (2.08)	1 (1.96)	0 (0.00)	>0.99	0.495
Gastrointestinal disorders	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Dyspepsia	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Frequent bowel movements	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Infections and infestations	0 (0.00)	1 (1.96)	0 (0.00)	>0.99	NA
Viral upper respiratory tract infection	0 (0.00)	1 (1.96)	0 (0.00)	>0.99	NA
Metabolism and nutrition disorders	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Diabetes mellitus	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Psychiatric disorders	0 (0.00)	0 (0.00)	1 (2.04)	NA	>0.99
Anxiety	0 (0.00)	0 (0.00)	1 (2.04)	NA	>0.99
Respiratory, thoracic and mediastinal disorders	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Rhonchi	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Skin and subcutaneous tissue disorders	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Urticaria	1 (2.08)	0 (0.00)	0 (0.00)	0.485	0.495
Liver function tests ≥3 times ULN	0 (0.00)	0 (0.00)	0 (0.00)	NA	NA
Myopathy	0 (0.00)	1 (1.96)	0 (0.00)	>0.99	NA

ADR = adverse drug reaction; AE = adverse event; IP = investigational product; NA = not available; ULN = upper limit of normal.
*P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/amlodipine group.
†P values between the telmisartan/amlodipine/rosuvastatin and telmisartan/rosuvastatin group.

individual therapy with telmisartan, amlodipine, and rosuvastatin in this trial.

Although 14.58% of patients experienced ADRs, combination therapy with telmisartan/amlodipine/rosuvastatin was generally well tolerated in this trial compared wth previous studies.[6,31] The most common ADR was peripheral edema, which is one of the common AEs of the dihydropyridine calcium antagonists.[32] Amlodipine has been reported to cause dose-dependent pedal edema in up to 25% of patients.[33] However, coadministration of an ARB could attenuate this intracapillary hypertension by causing postcapillary venous dilatation. In addition, adding rosuvastatin to telmisartan/amlodipine did not increase AEs, such as myopathy or elevated liver enzyme levels, in our study. Consequently, combination therapy with telmisartan/amlodipine/rosuvastatin produced good efficacy in lowering BP and LDL-C levels in patients with hypertension and dyslipidemia with a good safety profile and tolerability.

CONCLUSIONS

Fixed-dose combinations of telmisartan, amlodipine, and rosuvastatin decreased BP and LDL-C levels in patients with hypertension and dyslipidemia. The safety and tolerability profiles of fixed-dose telmisartan, amlodipine, and rosuvastatin combination therapy were comparable with those of telmisartan plus amlodipine or telmisartan plus rosuvastatin therapy.

CONFLICT OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article. There was no roles of study sponsors in the study design, data collection, data analysis, and preparation of the manuscript.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary Table I.   Changes in total cholesterol from baseline after treatment

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	216.38 ± 31.68	219.84 ± 37.88	225.69 ± 32.84
Median	215.00	215.00	225.50
Min, Max	162.00, 306.00	163.00, 315.00	164.00, 317.00
Week 4			
Mean ± SD	131.40 ± 19.99	225.78 ± 45.48	136.50 ± 20.71
Median	127.00	212.00	133.50
Min, Max	100.00, 180.00	169.00, 382.00	104.00, 213.00
Week 8			
Mean ± SD	130.87 ± 22.74	224.88 ± 47.42	138.92 ± 20.65
Median	129.00	218.00	135.00
Min, Max	94.00, 185.00	145.00, 388.00	104.00, 207.00
% Change from Baseline at Week 4			
Mean ± SD	-38.85 ± 7.76	3.05 ± 13.21	-38.94 ± 8.76
Median	-40.61	0.79	-39.20
Min, Max	-50.20, -17.28	-20.66, 62.55	-51.46, -17.12
p-value	< 0.0001	0.196	<0.0001
Treatment Difference			
LS Mean ± SE	-38.97 ± 1.56	3.17 ± 1.52	-
LS Mean ± SE	-39.36 ± 1.11	-	-38.44 ± 1.09
LS Mean difference [95% CI]		-42.15 [-46.48, -37.82]	-0.93 [-4.03, 2.18]
p-value		<0.0001	0.555
% Change from Baseline at Week 8			
Mean ± SD	-39.27 ± 8.09	2.77 ± 15.65	-37.51 ± 11.23
Median	-41.67	0.88	-37.67
Min, Max	-51.64, -18.75	-35.56, 65.11	-57.73, 1.22
p-value	<0.0001	0.323	<0.0001
Treatment Difference			
LS Mean ± SE	-39.39 ± 1.81	2.89 ± 1.77	-
LS Mean ± SE	-39.89 ± 1.30	-	-36.90 ± 1.29
LS Mean difference [95% CI]		-42.28 [-47.30, -37.25]	-2.98 [-6.65, 0.68]
p-value		< 0.0001	0.109

SD = Standard Deviation, Min = minimum, Max = maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as '([Each visit-Baseline]/Baseline) × 100'
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table II. Changes in triglyceride (TG) from baseline after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	157.62 ± 50.84	145.08 ± 70.21	156.25 ± 75.24
Median	159.00	132.00	133.50
Min, Max	59.00, 256.00	49.00, 347.00	47.00, 385.00
Week 4			
Mean ± SD	107.11 ± 34.17	143.80 ± 50.48	107.10 ± 41.05
Median	106.00	134.00	103.50
Min, Max	43.00, 193.00	59.00, 296.00	46.00, 226.00
Week 8			
Mean ± SD	110.53 ± 49.82	134.61 ± 62.94	120.13 ± 48.25
Median	100.00	116.00	109.50
Min, Max	40.00, 284.00	54.00, 282.00	29.00, 267.00
Change from Baseline at Week 4 (%)			
Mean ± SD	-28.87 ± 20.66	14.98 ± 59.35	-23.97 ± 31.06
Median	-32.05	0.00	-32.17
Min, Max	-64.07, 19.29	-53.67, 248.98	-63.93, 112.12
p-value	< 0.0001	0.240	< 0.0001
Treatment Difference			
LS Mean ± SE	-26.42 ± 5.60	12.63 ± 5.49	-
LS Mean ± SE	-28.73 ± 3.35	-	-24.11 ± 3.31
LS Mean difference [95% CI]		-39.04 [-54.65, -23.43]	-4.62 [-13.98, 4.74]
p-value		< 0.0001	0.329
Change from Baseline at Week 8 (%)			
Mean ± SD	-28.34 ± 24.73	3.25 ± 51.97	-14.00 ± 36.98
Median	-32.73	-7.69	-23.22
Min, Max	-74.47, 39.90	-72.16, 250.00	-74.86, 76.92
p-value	< 0.0001	0.566	0.008
Treatment Difference			
LS Mean ± SE	-26.80 ± 5.62	1.77 ± 5.50	-
LS Mean ± SE	-28.20 ± 4.19	-	-14.14 ± 4.14
LS Mean difference [95% CI]		-28.57 [-44.21, -12.92]	-14.06 [-25.77, -2.36]
p-value		0.001	0.019

SD = Standard Deviation, Min = minimum, Max = maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as "[(Each visit - Baseline)/Baseline] × 100"
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table III.   Changes in high-density lipoprotein cholesterol (HDL-C) from baseline after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	46.17 ± 12.36	49.76 ± 13.60	47.44 ± 11.98
Median	43.00	49.00	45.50
Min, Max	30.00, 85.00	23.00, 85.00	27.00, 80.00
Week 4			
Mean ± SD	53.87 ± 13.13	49.92 ± 12.64	52.40 ± 11.90
Median	52.00	48.00	52.50
Min, Max	34.00, 85.00	31.00, 90.00	31.00, 78.00
Week 8			
Mean ± SD	52.96 ± 13.86	50.53 ± 14.18	52.67 ± 12.96
Median	51.00	49.00	51.50
Min, Max	32.00, 93.00	28.00, 90.00	30.00, 83.00
Change from Baseline at Week 4 (%)			
Mean ± SD	17.99 ± 15.53	1.89 ± 14.05	12.36 ± 17.83
Median	14.29	3.13	10.64
Min, Max	-4.65, 46.81	-31.37, 34.78	-18.18, 75.00
p-value	< 0.0001	0.350	< 0.0001
Treatment Difference			
LS Mean ± SE	17.23 ± 2.03	2.63 ± 1.98	-
LS Mean ± SE	17.66 ± 2.27	-	12.69 ± 2.25
LS Mean difference [95% CI]		14.60 [8.94, 20.26]	4.97 [-1.38, 11.33]
p-value		<0.0001	0.123
Change from Baseline at Week 8 (%)			
Mean ± SD	16.36 ± 21.13	2.67 ± 16.33	12.66 ± 18.96
Median	14.29	0.00	10.99
Min, Max	-15.79, 85.37	-28.21, 56.52	-29.31, 75.00
p-value	< 0.0001	0.438	< 0.0001
Treatment Difference			
LS Mean ± SE	15.63 ± 2.67	3.37 ± 2.61	-
LS Mean ± SE	16.02 ± 2.79	-	13.00 ± 2.76
LS Mean difference [95% CI]		12.27 [4.82, 19.72]	3.02 [-4.77, 10.81]
p-value		0.002	0.443

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean=Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit-Baseline)/Baseline] × 100
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table IV.	Changes from baseline in non-high-density lipoprotein cholesterol (HDL-C) after 8-week follow-up		
	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	170.21 ± 32.39	170.08 ± 38.76	178.25 ± 30.57
Median	171.00	167.00	175.50
Min, Max	112.00, 266.00	107.00, 277.00	119.00, 265.00
Week 4			
Mean ± SD	77.53 ± 18.48	175.86 ± 46.97	84.10 ± 17.29
Median	75.00	160.00	82.00
Min, Max	43.00, 128.00	111.00, 343.00	53.00, 135.00
Week 8			
Mean ± SD	77.91 ± 23.63	174.35 ± 49.79	86.25 ± 16.78
Median	75.00	160.00	82.50
Min, Max	38.00, 150.00	100.00, 345.00	55.00, 124.00
Change from Baseline at Week 4 (%)			
Mean ± SD	-54.20 ± 8.23	3.82 ± 15.89	-52.19 ± 9.52
Median	-55.38	2.38	-54.25
Min, Max	-66.84, -33.60	-24.87, 78.65	-65.79, -27.75
p-value	< 0.0001	0.162	< 0.0001
Treatment Difference			
LS Mean ± SE	-54.19 ± 1.85	3.82 ± 1.81	-
LS Mean ± SE	-54.52 ± 1.26	-	-51.88 ± 1.25
LS Mean difference [95% CI]		-58.01 [-63.16, -52.87]	-2.64 [-6.18, 0.89]
p-value		<0.0001	0.140
Change from Baseline at Week 8 (%)			
Mean ± SD	-54.32 ± 10.47	2.92 ± 18.57	-50.50 ± 11.76
Median	-55.02	0.00	-53.54
Min, Max	-70.77, -19.35	-37.10, 79.69	-71.70, -14.29
p-value	<0.0001	0.653	<0.0001
Treatment Difference			
LS Mean ± SE	-54.32 ± 2.22	2.91 ± 2.17	-
LS Mean ± SE	-54.70 ± 1.58	-	-50.12 ± 1.56
LS Mean difference [95% CI]		-57.23 [-63.40, -51.06]	-4.59 [-9.02, -0.15]
p-value		<0.0001	0.043

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit-Baseline)/Baseline] × 100'
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table V.   Changes in apolipoprotein B (APO B) from baseline after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	130.47 ± 26.19	131.22 ± 29.93	134.50 ± 22.40
Median	128.00	131.00	133.50
Min, Max	81.00, 210.00	85.00, 215.00	91.00, 183.00
Week 4			
Mean ± SD	67.85 ± 15.12	132.65 ± 35.02	71.79 ± 12.58
Median	65.00	123.00	70.50
Min, Max	39.00, 116.00	85.00, 261.00	49.00, 112.00
Week 8			
Mean ± SD	66.91 ± 17.70	132.90 ± 35.77	71.21 ± 11.20
Median	65.00	125.00	72.00
Min, Max	39.00, 123.00	81.00, 257.00	43.00, 103.00
Change from Baseline at Week 4 (%)			
Mean ± SD	-47.60 ± 8.17	1.49 ± 15.17	-45.82 ± 9.96
Median	-47.62	1.00	-47.45
Min, Max	-60.71, -27.01	-21.15, 82.52	-58.89, -17.04
p-value	< 0.0001	0.679	< 0.0001
Treatment Difference			
LS Mean ± SE	-47.63 ± 1.78	1.51 ± 1.74	-
LS Mean ± SE	-47.88 ± 1.25	-	-45.55 ± 1.23
LS Mean difference [95% CI]		-49.14 [-54.08, -44.20]	-2.33 [-5.82, 1.16]
p-value		< 0.0001	0.188
Change from Baseline at Week 8 (%)			
Mean ± SD	-48.55 ± 9.77	1.76 ± 16.83	-46.05 ± 10.34
Median	-48.36	0.00	-47.31
Min, Max	-64.06, -19.00	-28.87, 79.72	-67.76, -15.38
p-value	<0.0001	0.876	< 0.0001
Treatment Difference			
LS Mean ± SE	-48.57 ± 2.02	1.78 ± 1.97	-
LS Mean ± SE	-48.83 ± 1.40	-	-45.78 ± 1.38
LS Mean difference [95% CI]		-50.36 [-55.96, -44.75]	-3.05 [-6.96, 0.86]
p-value		< 0.0001	0.125

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit − Baseline)/Baseline] × 100
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table VI.   Changes in apolipoprotein A1 (APO A1) from baseline after 8-week follow-up

	Telmisasrtan/Amlodipine/Rosuvastatin n = 47	Telmisartan/Amlodipine n = 49	Telmisartan/Rosuvastatin n = 48
Baseline			
Mean ± SD	134.13 ± 23.02	140.80 ± 22.75	138.58 ± 23.83
Median	126.00	138.00	137.00
Min, Max	102.00, 209.00	83.00, 202.00	94.00, 203.00
Week 4			
Mean ± SD	145.21 ± 23.97	142.24 ± 25.00	146.13 ± 23.44
Median	143.00	142.00	142.00
Min, Max	108.00, 216.00	97.00, 194.00	106.00, 201.00
Week 8			
Mean ± SD	142.19 ± 22.64	139.63 ± 25.23	148.02 ± 24.45
Median	139.00	137.00	147.50
Min, Max	108.00, 202.00	92.00, 197.00	95.00, 198.00
Change from Baseline at Week 4 (n)			
Mean ± SD	8.75 ± 9.93	1.28 ± 9.90	6.49 ± 14.17
Median	7.69	0.78	5.88
Min, Max	-12.90, 27.59	-21.21, 20.45	-24.86, 52.17
p-value	< 0.0001	0.370	0.003
Treatment Difference			
LS Mean ± SE	8.42 ± 1.42	1.60 ± 1.39	-
LS Mean ± SE	8.31 ± 1.67	-	6.93 ± 1.65
LS Mean difference [95% CI]		6.82 [2.84, 10.80]	1.38 [-3.29, 6.06]
p-value		0.001	0.559
Change from Baseline at Week 8 (%)			
Mean ± SD	6.96 ± 13.51	-0.57 ± 10.65	7.70 ± 14.38
Median	5.80	-0.74	5.31
Min, Max	-21.34, 56.03	-17.96, 28.79	-16.67, 52.17
p-value	0.001	0.709	0.001
Treatment Difference			
LS Mean ± SE	6.42 ± 1.71	-0.06 ± 1.67	-
LS Mean ± SE	6.43 ± 1.89	-	8.21 ± 1.87
LS Mean difference [95% CI]		6.48 [1.71, 11.26]	-1.78 [-7.07, 3.51]
p-value		0.008	0.506

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit − Baseline)/Baseline] × 100
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table VII. Changes in low-density lipoprotein/high-density lipoprotein cholesterol ratio (LDL-C/HDL-C) after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	3.47 ± 1.10	3.31 ± 1.16	3.52 ± 0.98
Median	3.45	3.22	3.43
Min, Max	1.52, 6.03	1.40, 6.37	1.64, 6.52
Week 4			
Mean ± SD	1.26 ± 0.45	3.42 ± 1.31	1.41 ± 0.43
Median	1.24	3.25	1.34
Min, Max	0.57, 2.35	1.40, 7.56	0.63, 2.65
Week 8			
Mean ± SD	1.30 ± 0.61	3.45 ± 1.42	1.42 ± 0.43
Median	1.18	3.36	1.38
Min, Max	0.44, 3.50	1.40, 7.42	0.64, 2.89
Change from Baseline at Week 4 (%)			
Mean ± SD	-63.28 ± 8.82	4.36 ± 20.13	-58.92 ± 11.40
Median	-64.82	2.83	-62.11
Min, Max	-79.12, -47.21	-26.63, 95.94	-75.78, -21.77
p-value	< 0.0001	0.379	< 0.0001
Treatment Difference			
LS Mean ± SE	-63.10 ± 2.27	4.19 ± 2.22	-
LS Mean ± SE	-63.35 ± 1.44	-	-58.85 ± 1.42
LS Mean difference [95% CI]		-67.29 [-73.59, -60.98]	-4.50 [-8.52, -0.48]
p-value		<0.0001	0.029
Change from Baseline at Week 8 (%)			
Mean ± SD	-62.18 ± 13.80	4.61 ± 21.21	-58.22 ± 12.28
Median	-64.77	0.27	-60.64
Min, Max	-82.64, -14.19	-33.15, 89.76	-77.82, -21.77
p-value	< 0.0001	0.268	<0.0001
Treatment Difference			
LS Mean ± SE	-62.09 ± 2.63	4.53 ± 2.58	-
LS Mean ± SE	-62.25 ± 1.86	-	-58.15 ± 1.84
LS Mean difference [95% CI]		-66.62 [-73.95, -59.29]	-4.10 [-9.30, 1.11]
p-value		< 0.0001	0.121

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit − Baseline)/Baseline] × 100
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table VIII.   Changes in apolipoprotein B/Apolipoprotein A1 ratio (APO B/APO A1) after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/ Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	1.01 ± 0.29	0.96 ± 0.28	1.00 ± 0.25
Median	0.96	0.93	0.98
Min, Max	0.51, 1.76	0.50, 1.74	0.52, 1.75
Week 4			
Mean ± SD	0.48 ± 0.13	0.97 ± 0.34	0.50 ± 0.12
Median	0.45	0.92	0.49
Min, Max	0.26, 0.81	0.53, 2.06	0.29, 0.80
Week 8			
Mean ± SD	0.48 ± 0.16	0.99 ± 0.36	0.49 ± 0.11
Median	0.45	0.93	0.47
Min, Max	0.24, 1.05	0.53, 2.11	0.27, 0.82
Change from Baseline at Week 4 (%)			
Mean ± SD	-51.35 ± 9.12	1.21 ± 19.32	-48.28 ± 11.79
Median	-50.78	-1.83	-52.12
Min, Max	-68.93, -28.59	-26.65, 101.20	-66.11, -17.04
p-value	< 0.0001	0.586	< 0.0001
Treatment Difference			
LS Mean ± SE	-51.15 ± 2.21	1.02 ± 2.16	-
LS Mean ± SE	-51.30 ± 1.41	-	-48.32 ± 1.40
LS Mean difference [95% CI]		-52.17 [-58.31, -46.03]	-2.98 [-6.92, 0.96]
p-value		< 0.0001	0.137
Change from Baseline at Week 8 (%)			
Mean ± SD	-50.85 ± 13.13	3.29 ± 19.49	-49.34 ± 10.49
Median	-53.60	-0.51	-50.59
Min, Max	-72.61, -4.91	-32.06, 87.77	-68.94, -21.36
p-value	< 0.0001	0.553	< 0.0001
Treatment Difference			
LS Mean ± SE	-50.68 ± 2.43	3.12 ± 2.38	-
LS Mean ± SE	-50.80 ± 1.62	-	-49.39 ± 1.60
LS Mean difference [95% CI]		-53.80 [-60.57, -47.03]	-1.41 [-5.93, 3.11]
p-value		< 0.0001	0.537

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit − Baseline)/Baseline) × 100]
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.

Supplementary Table IX. Changes in high sensitivity C-reactive protein (hs-CRP) from baseline after 8-week follow-up

	Telmisasrtan/Amlodipine/ Rosuvastatin n = 47	Telmisartan/Amlodipine n = 49	Telmisartan/ Rosuvastatin n = 48
Baseline			
Mean ± SD	1.16 ± 1.18	1.10 ± 1.18	1.80 ± 3.46
Median	0.72	0.77	0.91
Min, Max	0.19, 4.75	0.21, 7.11	0.20, 23.40
Week 4			
Mean ± SD	0.89 ± 1.23	1.73 ± 2.59	0.95 ± 1.07
Median	0.48	0.89	0.63
Min, Max	0.10, 8.11	0.14, 13.01	0.20, 6.93
Week 8			
Mean ± SD	0.94 ± 1.11	1.52 ± 2.49	1.06 ± 1.75
Median	0.57	0.80	0.52
Min, Max	0.08, 5.93	0.10, 17.30	0.18, 9.03
Change from Baseline at Week 4 (%)			
Mean ± SD	6.99 ± 137.77	124.48 ± 392.43	6.57 ± 112.93
Median	-29.78	3.81	-25.12
Min, Max	-89.83, 624.11	-90.77, 2182.46	-97.05, 586.14
p-value	0.047	0.173	0.264
Treatment Difference			
LS Mean ± SE	8.27 ± 42.93	123.25 ± 42.04	-
LS Mean ± SE	3.76 ± 18.12	-	9.73 ± 17.93
LS Mean difference [95% CI]		-114.98 [-234.31, 4.36]	-5.96 [-56.78, 44.85]
p-value		0.059	0.816
Change from Baseline at Week 8 (%)			
Mean ± SD	16.52 ± 193.64	113.83 ± 448.20	-4.15 ± 129.75
Median	-18.10	5.50	-31.23
Min, Max	-86.44, 1247.73	-84.85, 2989.29	-96.24, 713.51
p-value	0.039	0.101	0.002
Treatment Difference			
LS Mean ± SE	17.99 ± 50.37	112.42 ± 49.33	-
LS Mean ± SE	13.90 ± 24.01	-	-1.59 ± 23.76
LS Mean difference [95% CI]		-94.43 [-234.46, 45.61]	15.49 [-51.85, 82.82]
p-value		0.184	0.649

SD = Standard Deviation, Min = Minimum, Max = Maximum
LS Mean = Least Square Mean, SE = Standard Error, CI = Confidence Interval
Change rate (%) was calculated as [(Each visit-Baseline)/Baseline] × 100
Treatment difference was calculated as telmisartan/amlodipine/rosuvastatin group − telmisartan/amlodipine group or telmisartan/rosuvastatin group.