Efficacy and Tolerability of Telmisartan/Amlodipine and Rosuvastatin Coadministration in Hypertensive Patients with Hyperlipidemia: A Phase III, Multicenter, Randomized, Double-blind Study

Tae-Seok Kim [1,2]; Seung-Woon Rha [3]; Seok-Yeon Kim [4]; Dae-Gyun Park [5]; Ki-Chul Sung [6]; Myung-Ho Yoon [7]; Kye-Hoon Kim [8]; Han-Cheol Lee [9]; Woo-Sik Kim [10]; Yong-Jin Kim [11]; Jeong-Cheon Ahn [12]; Moo-Yong Rhee [13]; Dong-Hun Cha [14]; Byung-Su Yoo [15]; Sang-Ho Park [16]; Ki-Dong Yoo [17]; Dong-Woon Jeon [18]; Young-Won Yoon [19]; Sang-Kyoon Cho [20]; and Yong-Seog Oh [1,2]

[1]Daejeon St. Mary's Hospital, Daejeon, Korea; [2]Seoul St. Mary's Hospital of the Catholic University, Seoul, Korea; [3]Korea University Guro Hospital, Seoul, Korea; [4]Seoul Medical Center, Seoul, Korea; [5]Kangdong Sacred Heart Hospital, Seoul, Korea; [6]Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Korea; [7]Ajou University Medical Center, Suwon, Korea; [8]Chonnam National University Hospital, Gwangju, Korea; [9]Pusan National University Hospital, Busan, Korea; [10]Kyunghee University Medical Center, Seoul, Korea; [11]Seoul National University Hospital, Seoul, Korea; [12]Korea University Ansan Hospital, Ansan, Korea; [13]Dongguk University Ilsan Hospital, Goyang, Korea; [14]CHA Bundang Medical Center CHA University, Seongnam, Korea; [15]Wonju Severance Christian Hospital, Wonju, Korea; [16]Sooncheonhyang University Hospital Cheonan, Cheonan, Korea; [17]Catholic University of Korea St. Vincent's Hospital, Suwon, Korea; [18]Health Insurance Service Ilsan Hospital, Goyang, Korea; [19]Gangnam Severance Hospital, Seoul, Korea; and [20]Daejin Medical Center, Seongnam, Korea

ABSTRACT

Purpose: Dyslipidemia and hypertension increase the risk for cardiovascular disease. Combination therapy improves patient compliance. This study was conducted to compare the efficacy and tolerability of the combination therapies telmisartan/amlodipine + rosuvastatin, telmisartan/amlodipine, and telmisartan + rosuvastatin in patients with hypercholesterolemia and hypertension.

Methods: In this Phase III, multicenter, 8-week randomized, double-blind study, participants with hypertension and dyslipidemia (defined as a sitting systolic blood pressure [sitSBP] of ≥140 mm Hg, a low-density lipoprotein-cholesterol [LDL-C] level of ≤250 mg/dL, and a triglyceride level of ≤400 mg/dL) were screened. After a 4-week washout/run-in period involving therapeutic lifestyle changes and telmisartan 80 mg once a day, eligible patients had a sitSBP of ≥140 mm Hg and met the LDL-C level criteria according to the National Cholesterol Education Program Adult Treatment Panel III cardiovascular disease risk category. Patients were randomly assigned to 1 of 3 groups: (1) telmisartan/amlodipine 80/10 mg + rosuvastatin 20 mg (TAR group); (2) telmisartan/amlodipine 80/10 mg (TA group); or (3) telmisartan 80 mg + rosuvastatin 20 mg (TR group). The primary efficacy end points were the percentage changes from baseline in LDL-C in the TAR and TA groups and the mean changes in sitSBP in the TAR and

Accepted for publication February 19, 2019
https://doi.org/10.1016/j.clinthera.2019.02.013
0149-2918/$ - see front matter

TR groups at week 8 compared to baseline. Continuous variables were compared using the unpaired *t* test or the Wilcoxon rank sum model, and categorical variables were compared using the χ^2 or Fisher exact test. Tolerability was assessed based on adverse events found on physical examination including vital sign measurements, laboratory evaluations, and 12-lead ECG.

Findings: A total of 134 patients were enrolled. The least squares mean percentage changes in LDL-C at 8 weeks after administration of the drug compared to baseline were −51.9% (3.0%) in the TAR group and −3.2% (2.9%) in the TA group ($P < 0.001$). At 8 weeks after baseline, the least squares mean (SE) changes sitSBP were −28.3 (2.4) mm Hg in the TAR group and −10.7 (2.1) mm Hg in the TR group ($P < 0.001$). The prevalence rates of treatment-emergent adverse events were 15.0%, 25.0%, and 12.2% in the TAR, TA, and TR groups, respectively; those of adverse drug reactions were 15.0%, 22.7%, and 10.2%. None of the differences in rates were significant among 3 groups.

Implications: Triple therapy with TAR can be an effective treatment in patients with dyslipidemia and hypertension. The TAR combination has value for hypertensive patients with hyperlipidemia in terms of convenience, tolerability, and efficacy. ClinicalTrials.gov identifier: NCT03566316. (*Clin Ther.* 2019;41:728−741)

Key words: amlodipine, dyslipidemia, hypertension, rosuvastatin, telmisartan, triple combination.

INTRODUCTION

Many patients with hypertension also have hypercholesterolemia and are treated simultaneously for the 2 conditions.[1−3] Cardiovascular disease (CVD) still causes the greatest number of deaths, even though age-related mortality has decreased. Hypertension is the most important risk factor for CVD, and the risk is further increased in patients with both hypercholesterolemia and hypertension, even if the latter is mild.[4−6]

Among hypertensive patients, the blood pressure (BP)-lowering effect of combination therapy is considered to be more significant than that achieved by increasing the dosage of monotherapy.[7] Various antihypertensive agents can contribute to the prevention of cardiovascular events and improvement in BP control in hypertensive patients.[8,9] The combination of an angiotensin II receptor blocker and a calcium channel blocker for BP control and CVD prevention have been reported to be more clinically effective compared with monotherapy.[10−12]

Telmisartan is an angiotensin II receptor blocker with a strong selectivity for the angiotensin II type I receptor, with a long half-life, making it an effective once-daily drug for BP control.[13] Telmisartan is equivalent to ramipril, and has been shown to improve CVD with particular success among Asian patients.[14] It has been found to be well tolerated and effective in reducing the risks for CVD and mortality in high-risk patients.[15,16] Unlike other angiotensin II receptor blockers, telmisartan also has pleomorphic effects on the cardiovascular system through partial activation of peroxisome proliferator-activated receptor ɣ.[16] It is effective against hyperglycemia and can decrease inflammatory reactions in cardiovascular cells.[15,17]

Amlodipine is a long-acting dihydropyridine calcium channel blocker, widely used in the treatment of hypertension. It has little effect on atrioventricular nodal conduction and minimal inotropic effects due to its high selectivity for the peripheral vascular system.[18] Several studies have demonstrated that the drug is effective in inhibiting the progression of arteriosclerosis and preventing stroke,[19−21] as well as ameliorating cardiovascular complications in patients with primary hypertension by inhibiting sympathetic nervous system hyperactivity and increasing parasympathetic activity. Through these effects, amlodipine minimizes the risk for CVD.[22,23]

Rosuvastatin is a water-soluble drug with a relatively long half-life and a low risk for adverse events due to its high tissue selectivity and poor permeability through cellular membranes.[24] It is less expensive and well tolerated compared with other statin medications.[25,26] Some studies have shown that rosuvastatin is more effective in lowering the levels of low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) compared with other statins.[25,26] Among patients without CVD but with an elevated C-reactive protein level and a normal LDL-C level, rosuvastatin at a dosage of 20 mg/d was associated with a significant reduction in the prevalence of CVD compared to placebo (−44%).[27]

Telmisartan and amlodipine have been approved for use in the domestic market in Korea, and one study has demonstrated that they are well tolerated as a 2-drug combination.[28] Atorvastatin/amlodipine combinations have also been prescribed.[29] The use of 2 or more single agents in combination reduces the patient's pill burden and thus increases medication adherence.[30]

The design of this study involved the administration of several permutations of a 3-drug combination, telmisartan/amlodipine + rosuvastatin, in patients with dyslipidemia and hypertension. The purpose of this study was to determine whether telmisartan/amlodipine + rosuvastatin combination therapy has advantages over telmisartan/amlodipine treatment for dyslipidemia and telmisartan/rosuvastatin treatment for hypertension, and to evaluate the efficacy and tolerability of the 3-drug combination in patients with dyslipidemia and hypertension.

PATIENTS AND METHODS

Study Design

This Phase III, 8-week, multicenter, randomized, double-blind study was conducted at 19 institutions in Korea from November 2015 to June 2017. The protocol was approved by the Ministry of Food and Drug Tolerability, and by the institutional review board at each center (approval number 12633). The study and its protocol conformed with the Declaration of Helsinki and the Korean Good Clinical Practice guideline, and all patients provided written informed consent.

Inclusion and Exclusion Criteria

Male or female patients aged over 19 years with hypertension and dyslipidemia (defined as a sitting systolic blood pressure [sitSBP] of ≥140 mm Hg, an LDL-C level of ≤250 mg/dL, and a triglyceride level of ≤400 mg/dL) were screened. After a 4-week washout/run-in period with therapeutic lifestyle changes and administration of telmisartan (80 mg) once a day, patients with a sitSBP of ≥140 mm Hg and who met the LDL-C criterion for CVD risk as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) were included in the study.

The exclusion criteria were as follows: severe hypertension (a sitSBP of ≥180 mm Hg or a sitting diastolic blood pressure [sitDBP] of ≥110 mm Hg); a minimum−maximum difference of ≥20 mm Hg for sitSBP or ≥10 mm Hg for sitDBP in the chosen arm; severe heart failure (defined as New York Heart Association class III or IV); symptomatic orthostatic hypotension; secondary hypertension; acute coronary syndrome, cerebrovascular disease within the prior 6 months (including cerebral infarction or hemorrhage and transient ischemic attack); severe atrial fibrillation, atrial flutter, ventricular tachycardia, or uncontrolled arrhythmia; clinically significant valvular heart disease; severe eye-related disorders within the prior 6 months (retinal hemorrhage, visual disturbances, retinal microaneurysm); uncontrolled diabetes (glycosylated hemoglobin concentration of ≥9%); uncontrolled thyroid disease (a thyroid-stimulating hormone level ≥1.5 times the upper limit of normal [× ULN]); a serum creatinine concentration of ≥2 mg/dL; a history of myopathy or rhabdomyolysis; a creatinine kinase level of ≥3 × ULN; an aspartate aminotransferase or alanine aminotransferase level of ≥2.5 × ULN; primary aldosteronism; obstructive cholangiopathy; clinically significant electrolyte imbalance; persistent hypo- or hyperkalemia; chronic inflammatory disease (eg, rheumatic inflammation); hypersensitivity to telmisartan, amlodipine, or rosuvastatin; inherited galactose intolerance; alcohol abuse; history of cancer within the prior 5 years (including leukemia or lymphoma); pregnancy; childbearing age and not using a contraceptive (in women); and breast-feeding (in women).

Procedure

After a 4-week washout/run-in period during which telmisartan (80 mg) was administered once a day (period I), patients were treated for 8 weeks (period II: treatment). Patients maintained therapeutic lifestyle changes for 12 weeks. Before entering period I, patients were instructed to discontinue all antihypertensive and lipid-modifying agents. At the second visit (visit 2; after period I, defined as 0 weeks, baseline), patients with both BP and lipid-level criteria were randomly assigned to 1 of the following 3 groups (1:1:1): (1) telmisartan/amlodipine 80/10 mg* + rosuvastatin 20 mg† + telmisartan 80 mg−matching placebo (Ildong Pharmaceutical Co

* Trademark: Twynsta® (Boehringer Ingelheim, Seoul, Korea).

† Trademark: Crestor® (AstraZeneca Korea, Seoul, Korea).

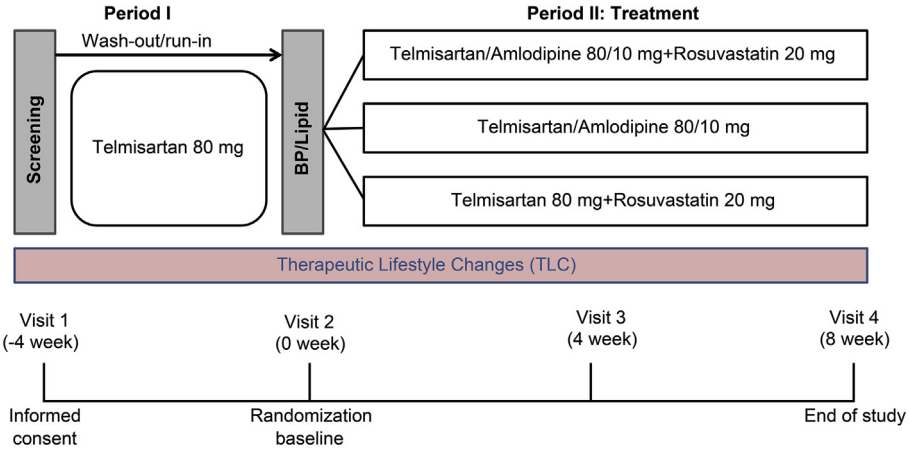

Figure 1. Study design. BP = blood pressure.

Ltd, Seoul, Korea) (TAR group); (2) telmisartan/amlodipine 80/10 mg + rosuvastatin 20 mg—matching placebo (Ildong Pharmaceutical Co Ltd) + telmisartan 80 mg—matching placebo (TA group); and (3) telmisartan 80 mg‡ + rosuvastatin 20 mg + telmisartan/amlodipine 80/10 mg—matching placebo (Ildong Pharmaceutical Co Ltd) (TR group) (Figure 1). Randomization was performed according to a stratified block randomization method using SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina). An independent biostatistician generated the random assignment code. Randomization for this trial was conducted by each institution, and the patients were randomized in the order in which they were enrolled. To maintain the double-blinding, placebos were produced with an appearance identical to that of the respective study drug (color, size, and shape). Because double-blinding was applied to the assigned group, the random assignment code was to be disclosed only in cases of a medical event that the investigator deemed significant enough to disclose the dosage of the clinical trial drug for safe treatment of the patient. At the third and fourth visits (weeks 4 and 8 in period II), patients presented to the institution for efficacy and tolerability assessments.

‡ Trademark: Micardis® (Boehringer Ingelheim).

Efficacy and Tolerability Variables

The primary end points were the percentage changes in LDL-C level in the TAR and TA groups, and the mean changes in sitSBP in the TAR and TR groups at week 8 compared to baseline. The secondary end points at 8 weeks were the percentage changes in total cholesterol (TC), triglyceride (TG), and HDL-C levels; mean change in sitDBP; percentage of patients achieving BP-control goals according to the 8th Joint National Committee (JNC 8) guideline[1] (sitSBP/sitDBP <140/<90 mm Hg, or sitSBP/sitDBP <150/<90 mm Hg in patients aged ≥60 years without current chronic kidney disease or diabetes); and the percentage of patients achieving an LDL-C goal, according to the NCEP ATP III guideline, of <160, <130, or <100 mg/dL, depending on the number of risk factors.

At every visit, BP was checked by the same investigator at each site using an electronic sphygmomanometer (HEM-7080IC; Omron Health Care, Tokyo, Japan) supplied by the sponsor. The arm that showed the higher sitSBP at visit 1 was chosen for subsequent measurements. The BP measurements were performed 3 times at intervals of 2 min or more, and the mean of the 3 values was used.

At visit 1 (screening), all laboratory tests were conducted in the laboratory at each institution. After visit 2 (baseline, randomization), lipid tests (TC, TG, LDL-C, HDL-C) were performed at a central laboratory.

The tolerability assessment variables were treatment-emergent adverse events (TEAEs), vital sign measurements (pulse rate, body temperature, and body weight), and laboratory test results (performed at visits 2, 3, and 4). The causality and severity of AEs were evaluated by the investigators.

Statistical Analysis

Assuming mean differences of 10 (11) mm Hg in sitSBP[31,32] and of 40% (20%) in LDL-C[33] among the treatment groups, the sample size calculation indicated that 32 patients per group would satisfy a significance level of 2.5% and a power of 95%. The total sample size was 126 (43 per group), allowing for a 22% dropout rate. Continuous variables were compared using the unpaired *t* test or Wilcoxon rank sum test, and categorical variables were compared using either the χ^2 test or Fisher exact test. The effects of treatments on the primary and secondary efficacy variables were compared using ANCOVA, with baseline BP as the covariate. End points are expressed as least-squares (LS) means (SE) for continuous variables. The response rates in each treatment group were summarized and analyzed using the Pearson χ^2 test or Fisher exact test. A *P* value of <0.05 (2-sided) was considered statistically significant. The Pearson χ^2 test or Fisher exact test was used to test the differences in frequencies of AEs likely resulting from the study drugs. Subgroup analysis was performed to identify factors associated with changes in SBP and LDL-C. All statistical analyses were performed using SAS software version 9.4 (SAS Institute).

RESULTS

Study Population

A total of 296 patients were screened at 19 institutions. Of those, 162 patients who were ineligible for the study were excluded before the washout/run-in period, and 134 patients who met the inclusion criteria were randomly assigned to the 3 groups (Figure 2). The mean age of the patients was 65.6 (10.3) years, and 93 (70.5%) were men. There were no significant differences in CVD history, diabetes mellitus, drug therapy before enrollment, or lipid and BP baseline measurements among the groups (Table I).

Efficacy Outcomes

The primary variable relating to efficacy in lipid management was the percentage change in LDL-C after 8 weeks compared with baseline between the TAR and TA groups. The LS mean (SE) percentage changes in LDL-C were −51.9% (3.0%) in the TAR group and −3.2% (2.9%) in the TA group ($P < 0.001$). However, the difference in the percentage changes in LDL-C at 8 weeks between the TAR and TR groups was not significant (Table II).

The primary variable with regard to efficacy in BP management was the change in sitSBP after 8 weeks compared to baseline between the TAR and TR groups. The LS mean (SE) changes in sitSBP at 8 weeks after baseline were −28.3 (2.4) mm Hg in the TAR group and −10.7 (2.1) mm Hg in the TR group ($P < 0.001$). There was a significant difference in the change in sitSBP after 8 weeks between the TAR and TA groups (−28.3 [2.4] vs −18.3 [2.3] mm Hg; $P = 0.003$) (Table III).

Secondary lipid efficacy end points included the LS mean (SE) percentage changes in TC, TG, and HDL-C levels at 8 weeks. The LS mean percentage changes from baseline in TC level in the TAR and TA groups were −35.8% (2.1%) and 0.0% (2.1%), respectively ($P < 0.001$); TG, −24.3% (5.4%) and +9.6% (5.2%) ($P < 0.001$); and HDL-C, +14.2% (2.6%) and +7.7% (2.5%) (P = NS). In contrast, the TAR and TR groups did not show significant differences in the LS mean percentage changes in TC, TG, and HDL-C levels at week 8 (Table II).

The secondary BP efficacy end point was the mean change in sitDBP. Compared with baseline values, the LS mean (SE) changes in sitDBP were −17.2 (1.5) mm Hg in the TAR group and −4.8 (1.4) mm Hg in the TR group ($P < 0.001$) (Table III). There was a significant difference in the changes in sitDBP at 8 weeks between the TAR and the TA groups (−17.2 [1.5] and −11.0 [1.5] mm Hg, respectively; $P = 0.003$) (Table III).

The percentages of patients who achieved the LDL-C therapy goal (according to the NCEP ATP III guideline) at 8 weeks after the start of administration of the clinical trial drug were 92.5% (37/40) in the TAR group and 18.6% (8/43) in the TA group ($P < 0.001$). However, the difference between the TAR and TR groups was not significant (92.5% [37/40] vs 81.6% [40/49]) (Figure 3A).

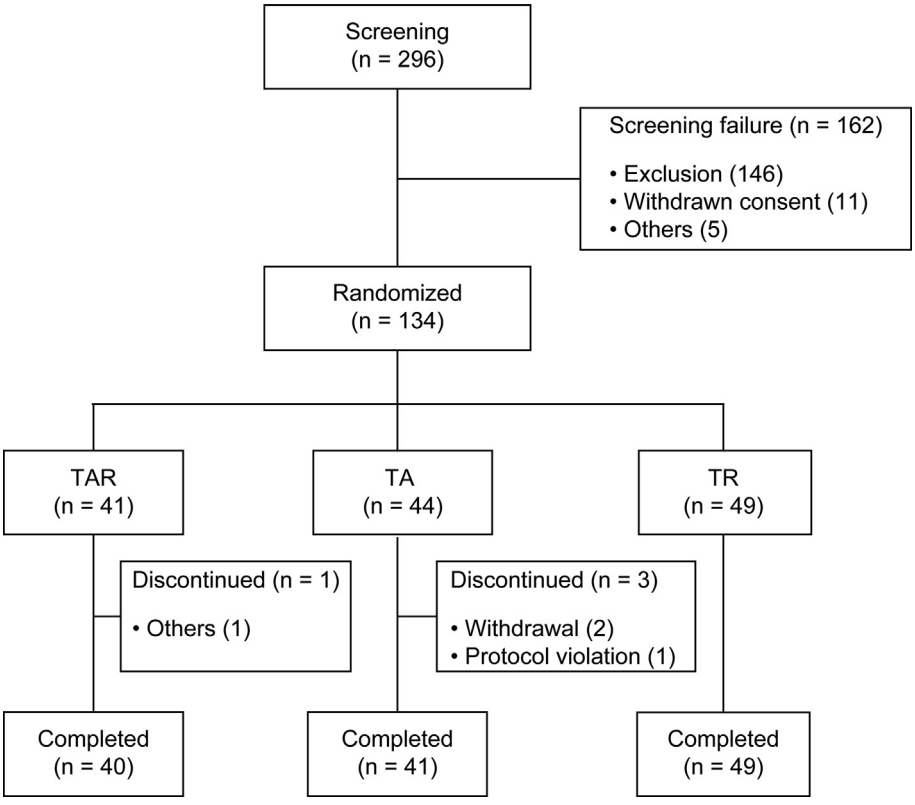

Figure 2. Patient disposition. FAS = full analysis set; IP = investigational product; PPS = per protocol set; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin.

The percentages of patients who reached the BP control goal (according to the JNC 8 guideline) at 8 weeks after the start of administration of the clinical trial drug in the TAR, TA, and TR groups were 85.0% (34/40), 62.8% (27/43), and 46.9% (23/49), respectively. There were significant differences between the TAR and TA groups ($P = 0.022$) and the TAR and TR groups ($P = 0.0002$) (Figure 3B). The percentages of patients who reached both the LDL-C and BP treatment goals at 8 weeks in the TAR, TA, and TR groups were 80.0% (32/40), 16.3% (7/43), and 38.8% (19/49), respectively (Figure 3C). There were significant differences between the TAR and TA groups ($P < 0.001$) and between the TAR and TR groups ($P < 0.001$) (Figure 3C). The mean LDL-C levels and sitSBP at weeks 0−8 are illustrated in Figure 4.

Subgroup analysis revealed significant differences between the TAR and TA groups in terms of the percentage changes in LDL-C, and between the TAR and TR groups in terms of the changes in sitSBP, with the exception of the subgroup of patients aged >75 to <85 years. No significant differences were observed among the subgroups except in the case of comparisons between patients <75 years and patients >75 years in the TAR group ($P = 0.002$) (Figure 5).

Compliance and Tolerability

The mean rates of compliance with the clinical trial drugs was 95% or more in all treatment groups in the prerandomization period (95.76% [16.09%] in TAR, 95.99% [6.80%] in TA, and 96.36% [9.15%] in TR). The mean compliance rates during the treatment

Table I. Baseline demographic and clinical characteristics of the study patients.

Characteristic	TAR (n = 40)	TA (n = 43)	TR (n = 49)	All Patients (n = 132)
Age, mean (SD), y	67.4 (10.0)	66.4 (11.0)	63.4 (9.7)	65.6 (10.3)
Sex, no. (%)				
Men	29 (72.5)	27 (62.8)	37 (75.5)	93 (70.5)
Women	11 (27.5)	16 (37.2)	12 (24.5)	39 (29.6)
NCEP ATP III risk category, no. (%)				
0−1 risk factor	4 (10.0)	0 (0.0)	3 (6.1)	7 (5.3)
≥2 risk factors and 10-year risk for <10%	1 (2.5)	4 (9.3)	1 (2.0)	6 (4.6)
≥2 risk factors and 10-year risk for 10%−20%	7 (17.5)	10 (23.3)	8 (16.3)	25 (18.9)
IHD or IHD risk equivalents or 10-year risk for >20%	28 (70.0)	29 (67.4)	37 (75.5)	94 (71.2)
Risk factors, no. (%)				
Diabetes mellitus	15 (37.5)	16 (37.2)	15 (30.6)	46 (34.8)
Coronary heart disease history	14 (35.0)	15 (34.9)	17 (34.7)	46 (34.8)
Drug therapy before enrollment, no. (%)				
Antihypertensive	33 (82.5)	33 (76.7)	38 (77.6)	104 (74.8)
Lipid-lowering	22 (55.0)	18 (41.9)	22 (44.9)	62 (47.0)
Lipids and BP baseline, mean (SD)				
LDL-C, mg/dL	155 (29.2)	155.7 (23.1)	160 (32.0)	—
Total cholesterol, mg/dL	223.5 (36.1)	221.6 (28.9)	228.5 (36.5)	—
HDL-C, mg/dL	50.2 (14.5)	46.3 (10.7)	46.9 (10.3)	—
Triglyceride, mg/dL	174.7 (100.7)	174.5 (79.4)	188.8 (78.0)	—
sitSBP, mm Hg	156.8 (13.7)	154.8 (10.6)	154.8 (10.6)	—
sitDBP, mm Hg	89.4 (10.8)	90.3 (8.1)	91 (9.8)	—

BP = blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III; sitDBP = sitting diastolic blood pressure; sitSBP = sitting systolic blood pressure; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin.

period were 98% or more in all of the treatment groups (data not shown).

Among the 133 patients in the safety set groups, the prevalences of TEAEs in the present trial were 15.0% (6/40 patients, 7 cases) in the TAR group, 25.0% (11/44 patients, 13 cases) in the TA group, and 12.2% (6/49 patients, 8 cases) in the TR group. There was no statistically significant difference between the safety set and TEAE groups ($P = 0.2408$) (Table IV). The prevalences of adverse drug reactions (ADRs), which could not be negated with the clinical trial drugs, were 15.0% (6/40 patients, 7 cases) in the TAR group, 22.7% (10/44 patients, 11 cases) in the TA group, and 10.2% (5/49 patients, 5 cases) in the TR group; and there was no statistically significant difference between the tolerability set and TEAE groups ($P = 0.2514$). None of the patients in the TAR and TR groups experienced a serious AE (SAE), and there was no statistically significant difference between the 2 groups ($P = 0.6316$). No significant TEAEs and ADRs were observed in this trial, and none of the patients discontinued the trial due to an AE. There were no statistically significant differences in the prevalence rates of TEAEs, ADRs, or SAEs. The differences in the prevalences of AEs, ADRs, and SAEs in the subgroups of all ages, sexes, and underlying diseases were nonsignificant between the groups. An SAE occurred in 1 patient (2.3%, 1 case) as a "toxicity to various agents" in the TA group. The result of the SAE was classified as "recovered," the severity was "severe," and the investigator

Table II. Least squares (LS) mean percentage changes from baseline in lipid variables from baseline to 8 weeks (full analysis set). Data are given as %.

Variable	TAR (n = 40)	TA (n = 43)	TR (n = 49)
LDL-C			
LS mean (SE)	−51.9 (3.0)	−3.2 (2.9)	−47.9 (2.7)
LS mean difference	—	−48.7*	−4.0†
Total cholesterol			
LS mean (SE)	−35.8 (2.1)	0.0 (2.1)	−33.8 (1.9)
LS mean difference	—	−35.8*	−2.0†
Triglycerides			
LS mean (SE)	−24.3 (5.4)	9.6 (5.2)	−24.9 (4.9)
LS mean difference	—	−33.9*	0.6†
HDL-C			
LS mean (SE)	+14.2 (2.6)	+7.7 (2.5)	+13.2 (2.4)
LS mean difference	—	6.5†	1.0†

HDL-C = high- density lipoprotein cholesterol; LDL-C = low- density lipoprotein cholesterol; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin.
* $P < 0.001$ (ANCOVA, with baseline as a covariate).
† P = NS (ANCOVA, with baseline as a covariate).

Table III. Least squares (LS) mean changes from baseline in blood pressure (BP) from baseline to 8 weeks (full analysis set). Data are given as %.

Variable	TAR (n = 40)	TA (n = 43)	TR (n = 49)
sitSBP			
LS mean (SE), mm Hg	−28.3 (2.4)	−18.3 (2.3)	−10.7 (2.1)
LS mean difference, mm Hg	—	−10.0*	−17.6†
sitDBP			
LS mean (SE), mm Hg	−17.2 (1.5)	−11.0 (1.5)	−4.8 (1.4)
LS mean difference, mm Hg	—	−6.3*	−12.5†

sitDBP = sitting diastolic blood pressure; sitSBP = sitting systolic blood pressure; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR, telmisartan + rosuvastatin.
* $P = 0.003$ (ANCOVA, with baseline as a covariate).
† $P < 0.001$ (ANCOVA, with baseline as a covariate).

determined that the relevance of this SAE to the clinical trial drug was "not clearly related." The patient's consent was withdrawn, the patient discontinued the trial, and the study drug was discontinued. No indications of abnormal vital signs or ECG changes were observed. None of the patients were evaluated as having any abnormality after the administration of the drugs for clinical trial.

DISCUSSION

The present study evaluated the efficacy and tolerability of TAR, a triple−drug combination therapy, in hypertensive patients with hyperlipidemia. Therapy with TAR resulted in the achievement of both the BP-lowering effect of telmisartan/amlodipine and the lipid profile−modifying effects of rosuvastatin. Telmisartan/amlodipine + rosuvastatin therapy showed efficacy in lipid modification similar to that of TR therapy; however, a comparison of the changes in BP between the TAR and TA groups indicated the change to be greater in the TAR group. With regard to tolerability, most AEs reported in this study were mild to moderate in severity, and no differences were observed between the groups.

We found that TAR therapy provided additional, statistically significant BP-lowering effects compared with TA therapy (LS mean changes: SBP, −28.5 vs −18.7 mm Hg [$P = 0.0035$]; DBP, −17.2 vs −10.4 mm Hg [$P = 0.0011$] for TAR vs TA, respectively). We tried to identify the factors including sex, age (≥65 or <65 years), baseline BP/lipid levels, concurrent medications, underlying disease (diabetes, CVD), as well as NCEP ATP III

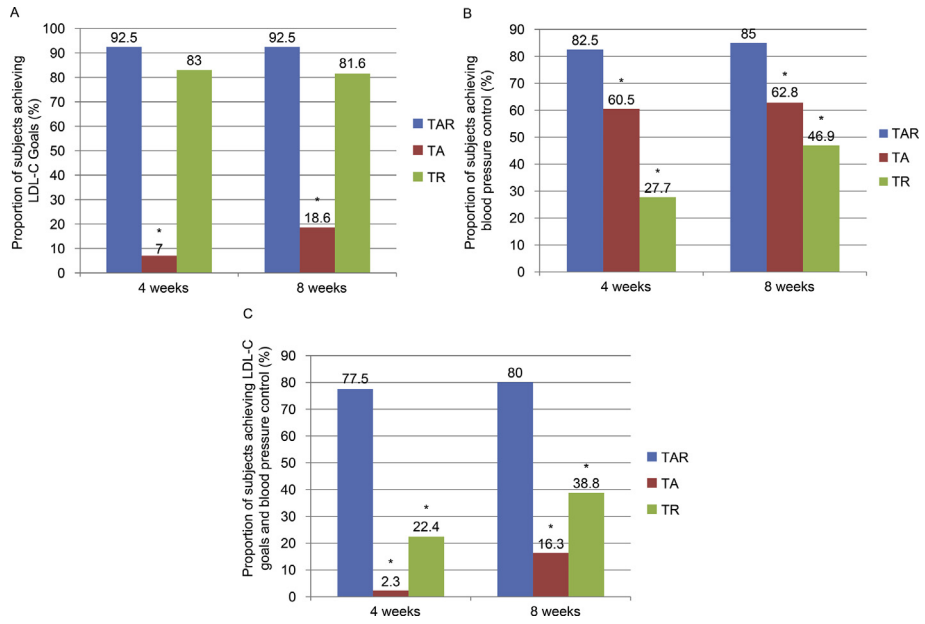

Figure 3. Rates patients achieving LDL-C (A), BP control (B), and LDL-C and BP (C) goals after 4 and 8 weeks of treatment. LDL-C = low-density lipoprotein cholesterol; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin. *$P < 0.05$ versus TAR (Pearson χ^2 test).

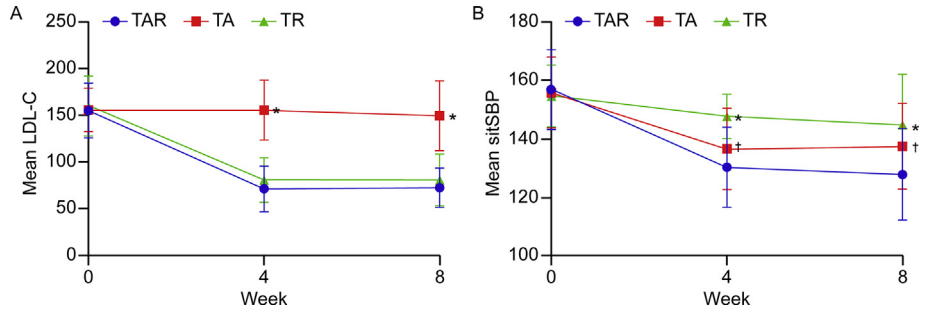

Figure 4. Mean LDL-C (A) and sitSBP (B) after 4 and 8 weeks of treatment. LDL-C = low-density lipoprotein cholesterol; sitSBP = sitting systolic blood pressure TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin. *$P < 0.001$ and $^{\dagger}P < 0.05$ versus TAR (2-sample t test).

risk groups, that may have caused the significant reduction in BP in the TAR group (data not shown). However, we found no factors other than the administration of rosuvastatin that could have explained this effect.

The effect of rosuvastatin on BP remains controversial because no large-scale and well-designed confirmatory clinical trials have proven the BP-lowering efficacy of rosuvastatin as a primary end point in hypertensive patients. Some studies have

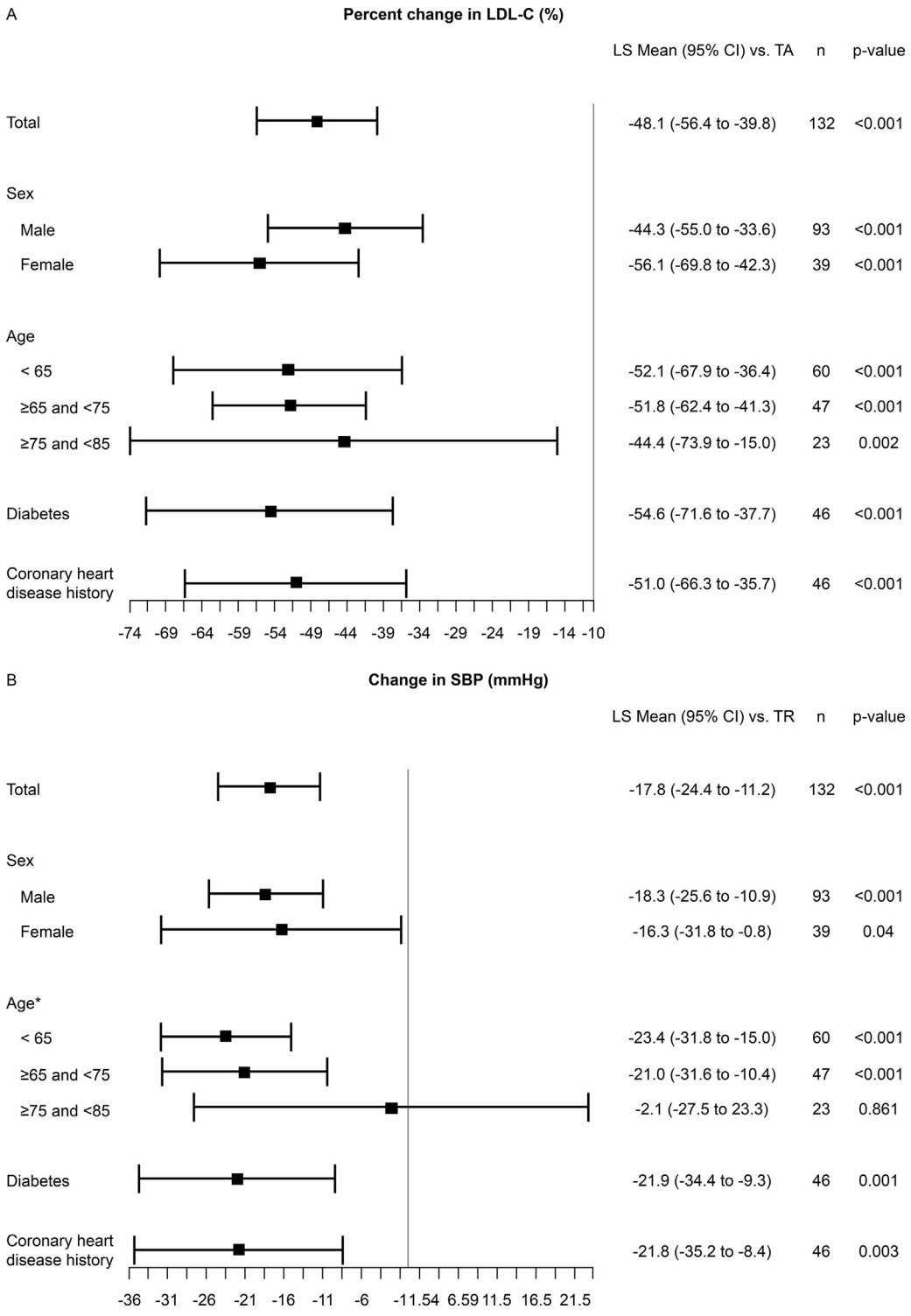

Figure 5. Changes from baseline in LDL-C with TAR versus TA (A) and in SBP with TAR versus TR (B), by subgroup. LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TR = telmisartan + rosuvastatin. **P* between age subgroups in the TAR group (ANCOVA model adjusted for baseline).

Table IV. Summary of treatment-emergent adverse events in the study. Data are given as number of patients (%) [number of cases].

Variable	TAR (n = 40)	TA (n = 44)	TR (n = 49)	P value (between)
TEAEs	6 (15.0), [7]	11 (25.0), [13]	6 (12.2), [8]	0.2408†
Intensity				
Mild	6 (15.0), [7]	10 (22.7), [10]	6 (12.2), [8]	—
Moderate	0	1 (2.3), [1]	0	—
Severe	0	1 (2.3), [2]	0	—
SAEs	0	1 (2.3), [1]	0	0.6316‡
ADRs	6 (15.0), [7]	10 (22.7), [11]	5 (10.2), [5]	0.2514†
Serious ADRs	0	0	0	—
Common TEAEs				
Viral upper respiratory tract infection	2 (5.0), [2]	3 (6.8), [3]	0	—
Edema, peripheral	1 (2.5), [1]	2 (4.6), [2]	0	—
Blood creatine phosphokinase increase	0	1 (2.3), [1]	1 (2.0), [1]	—

ADRs = adverse drug reactions; SAEs = serious adverse events; TA = telmisartan/amlodipine; TAR = telmisartan/amlodipine + rosuvastatin; TEAEs = treatment-emergent adverse events; TR = telmisartan + rosuvastatin.
† Pearson χ^2 test.
‡ Fisher exact test.

suggested a pleiotropic effect of statins in hypertensive patients with hypercholesterolemia.[34–38] Based on meta-analysis reports that have reviewed randomized controlled trials,[39] statins cause significant reductions in SBP; and the BP-lowering effects are greater when baseline BP is high, unrelated to age, changes in serum cholesterol, or length of the trial. Briasoulis et al[40] performed a meta-analysis evaluating data from a total of 40 prospective randomized controlled trials of statin therapy. They found small but statistically significant reductions in SBP (–2.62 and –3.07 mm Hg in patients taking statins and in hypertensive patients, respectively). Although the mechanism(s) involved and the extent of BP reduction with statin use have not been clearly elucidated, it is believed that statins lower BP by increasing nitric oxide bioavailability and improving arterial compliance.[40]

To the best our knowledge, our study identified the greatest difference in BP decrease between TAR and TA groups compared with those from all previous studies of similar design conducted in Korean patients with the essential comorbidities of hypertension and hyperlipidemia.[34,41–43] It is plausible that arterial compliance was improved because of reductions in BP due to rosuvastatin administration, and/or that vascular endothelial cell remodeling activity increased the susceptibility to the antihypertensive agent (telmisartan, amlodipine). However, we cannot rule out the possibility that the reduction in BP during TAR therapy may have been exaggerated by chance due to the small sample size of this study. We also looked closely at unexpected hypotensive AEs to investigate how the significant reductions in BP affected the tolerability of TAR treatment. There were no AEs associated with hypotension in either the TAR or TA group, and the pulse rates were not significantly different between those 2 groups. Therefore, the results of this study show that the 3 medications included in TAR combination therapy act synergistically to reduce BP, and that the magnitude of reduction does not affect tolerability.

In terms of improvements in the lipid profile, the groups that received TAR and TR showed 51.9% and 47.9% decreases in LDL-C, respectively, which are similar to the 47%–53% reductions reported in previous clinical trials of rosuvastatin

administration.[44] In previous research, the administration of rosuvastatin achieved NCEP ATP III and/or European Society of Cardiology (ESC) LDL-C goal attainment ranging from 53% to 94%.[38] The LDL-C–lowering effects of rosuvastatin were more apparent in patients defined as being in the low-risk category according to NCEP ATP III.[38] In our study, the observed LDL-C goal attainment in the TAR group is in line with rates reported in previous studies, although it appeared to be somewhat high considering that many patients classified as being in the high-risk NCEP ATP III category were included (5.3%, 4.6%, 18.9, and 71.2% for the ATP III risk categories I, II [<10% of 10-year risk], II [10%e20% of 10-year risk], and III, respectively).

Subgroup analyses were conducted to identify differences in efficacy between subgroups according to sex, age, history of diabetes, and history of coronary heart disease. Among the subgroups, smaller reductions in SBP were observed in the older age group (≥75 and ‘85 years) who received TAR compared to the TR group. To the best of our knowledge, differences in the effects of amlodipine according to age have not been reported. Considering the size of the present trial, a subgroup analysis in elderly patients would be needed in postmarketing surveillance or in an observational study in clinical practice in order to draw firm conclusions.

In a 2003 report on medication adherence,[45] the World Health Organization quoted the following statement by Haynes et al[45]: "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments." In other words, compliance with medication can be regarded as an indicator of treatment progress. Given the usual coexistence of hypertension and hyperlipidemia and the multifactorial nature of CVD, physicians must rely on multiple drug prescriptions to successfully manage various coexisting pathologies. Fixed-dose combination (FDC), triple-drug, single-pill therapy reduces the overall pill burden and could ultimately provide superior clinical outcomes.

To the best of our knowledge, this is the first study to investigate the efficacy and tolerability of TAR combination therapy in patients with coexisting essential hypertension and hyperlipidemia. We observed a notable effect of rosuvastatin on BP control. The combination therapy presented in this study could provide an effective, well-tolerated, and convenient treatment option for patients with hypertension and hyperlipidemia.

Study Limitations

The relatively small sample size and short follow-up period were the main limitations of the present study. The efficacy and tolerability of TAR need to be evaluated in additional clinical trials of FDC therapy with a single pill. Further long-term investigations of the additive effects of TAR combination therapy on BP control are required to confirm the clinical benefits.

CONCLUSIONS

In this randomized clinical trial conducted in hypertensive patients with hyperlipidemia, 8-week treatment with TAR was found to be superior to the same duration of treatment with TA for the control of hyperlipidemia and hypertension compared with TR treatment. No specific effects on tolerability were observed. Therefore, the development of a TAR combination for use in hypertensive patients with hyperlipidemia will be of value for reasons of convenience as well as tolerability and efficacy.

Conflicts of Interest

This work was supported by Ildong Pharmaceuticals, Co, Ltd, Korea. The sponsor paid for laboratory testing and clinical research coordinator expenses and supplied the investigational products. The funding source had no role in study design, collection, analysis, or interpretation of data.

The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

ACKNOWLEDGMENTS

We thank Editage (www.editage.com) for English language editing and publication support.

S.W. Rha contributed to the conceptualization. S.W. Rha, S.Y. Kim, D.G. Park, K.C. Sung, M.H. Yoon, K.H. Kim, H.C. Lee, W.S. Kim, Y.J. Kim, J.C. Ahn, M.Y. Rhee, D.H. Cha, B.S. Yoo, S.H. Park, K.D. Yoo, D.W. Jeon, Y.W. Yoon, S.K. Cho, and Y.S. Oh contributed to data curation and formal analysis. T.S.

Kim contributed in writing of the manuscript, formal analysis, and generating figures. All of the authors approved the final version of the manuscript.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2019.02.013.

REFERENCES

1. James PA, Oparil S, Carter BL, et al. Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the eighth Joint National Committee (JNC 8). *JAMA*. 2014;2014(311):507–520.
2. National Education Programs Working Group report on the management of patients with hypertension and high blood cholesterol. *Ann Intern Med*. 1991;114:224–237.
3. Meigs JB, D'Agostino Sr RB, Wilson PW, et al. Risk variable clustering in the insulin resistance syndrome. The Framingham Offspring Study. *Diabetes*. 1997;46: 1594–1600.
4. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986;111: 383–390.
5. MacMahon SW, Cutler JA, Furberg CD, et al. The effects of drug treatment for hypertension on morbidity and mortality from cardiovascular disease: a review of randomized controlled trials. *Prog Cardiovasc Dis*. 1986;29(3 Suppl 1): 99–118.
6. Perreault S, Dorais M, Coupal L, et al. Impact of treating hyperlipidemia or hypertension to reduce the risk of death from coronary artery disease. *CMAJ*. 1999;160:1449–1455.
7. Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
8. Ohishi M, Kawai T, Hayashi N, et al. Effect of tablets with a combination of telmisartan and amlodipine on patients with hypertension: the Cotalo study. *Hypertens Res*. 2013;36: 620–626.
9. Gu Q, Burt VL, Dillon CF, et al. Trends in antihypertensive medication use and blood pressure control among United States adults with hypertension: the National Health and Nutrition Examination Survey, 2001 to 2010. *Circulation*. 2012;126:2105–2114.
10. Noh YH, Lim HS, Kim MJ, et al. Pharmacokinetic interaction of telmisartan with s-amlodipine: an open-label, two-period crossover study in healthy Korean male volunteers. *Clin Ther*. 2012;34:1625–1635.
11. Chrysant SG. The role of angiotensin receptor blocker and calcium channel blocker combination therapy in treating hypertension: focus on recent studies. *Am J Cardiovasc Drugs*. 2010;10:315–320.
12. Ishimitsu T, Numabe A, Masuda T, et al. Angiotensin-II receptor antagonist combined with calcium channel blocker or diuretic for essential hypertension. *Hypertens Res*. 2009;32:962–968.
13. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs*. 2006;66:51–83.
14. Dans AL, Teo K, Gao P, et al. A subgroup of high-risk Asians, telmisartan was noninferior to ramipril and better tolerated in the prevention of cardiovascular events. *PLoS One*. 2010;5, e13694.
15. Benndorf RA, Boger RH. Pleiotropic effects of telmisartan: still more to come? *J Hypertens*. 2008;26:854–856.
16. Ruilope LM. Telmisartan for the management of patients at high cardiovascular risk. *Curr Med Res Opin*. 2011;27: 1673–1682.
17. Suksomboon N, Poolsup N, Prasit T. Systematic review of the effect of telmisartan on insulin sensitivity in hypertensive patients with insulin resistance or diabetes. *J Clin Pharm Ther*. 2012;37:319–327.
18. Haria M, Wagstaff AJ. Amlodipine. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. *Drugs*. 1995;50:560–586.
19. Coca A, Mazón P, Aranda P, et al. Role of dihydropyridinic calcium channel blockers in the management of hypertension. *Expert Rev Cardiovasc Ther*. 2013;11:91–105.
20. Wang JG, Li Y, Franklin SS, et al. Prevention of stroke and myocardial infarction by amlodipine and angiotensin receptor blockers: a quantitative overview. *Hypertension*. 2007;50:181–188.
21. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292:2217–2225.
22. Singh M, Mensah GA, Bakris G. Pathogenesis and clinical physiology of hypertension. *Cardiol Clin*. 2010;28:545–559.
23. Radjab Y, Aboudrar S, Milouk FZ, et al. Cardiovascular autonomic response to amlodipine in primary hypertension. *ISRN Cardiol*. 2012;2012:832183.
24. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther*. 2006;80:565–581.
25. McKenney JM, Jones PH, Adamczyk MA, et al. Comparison of the efficacy of rosuvastatin versus atorvastatin, simvastatin, and pravastatin in achieving lipid goals: results from the STELLAR trial. *Curr Med Res Opin*. 2003;19: 689–698.
26. Olsson GO. Safety and efficacy of rosuvastatin. *Lancet*. 2004;364(9429):135.

27. Mora S, Ridker PM. Justification for the use of statins in primary prevention: an intervention trial evaluating rosuvastatin (JUPITER)–can C-reactive protein be used to target statin therapy in primary prevention? *Am J Cardiol*. 2006;97(2A):33A–41A.
28. Ma L, Wang W, Zhao Y, et al. Combination of amlodipine plus angiotensin receptor blocker or diuretics in high-risk hypertensive patients: a 96-week efficacy and safety study. *Am J Cardiovasc Drugs*. 2012;12:137–142.
29. Park JH, Lee YH, Ko SK, et al. Cost-effectiveness analysis of low-density lipoprotein cholesterol-lowering therapy in hypertensive patients with type 2 diabetes in Korea: single-pill regimen (amlodipine/atorvastatin) versus double-pill regimen (amlodipine+atorvastatin). *Epidemiol Health*. 2015;37:e2015010.
30. Ah YM, Lee JY, Choi YJ, et al. Persistence with antihypertensive medications in uncomplicated treatment-naïve patients: effects of initial therapeutic classes. *J Korean Med Sci*. 2015;30:1800–1806.
31. Telmisartan 80mg Non-responder Trial. Available at: http://clinicaltrials.gov/ct2/show/NCT01222520?term=NCT01222520&rank=1. Accessed March 14, 2019
32. Filtered trial for telmisartan 40mg non-responder. Available at: http://clinicaltrials.gov/ct2/show/NCT00550953?term=NCT00550953&rank=1. Accessed March 14, 2019.
33. Saito Y, Goto Y, Dane A, et al. Randomized dose-response study of rosuvastatin in Japanese patients with hypercholesterolemia. *J Atheroscler Thromb*. 2003;10:329–336.
34. Jang JY, Lee SH, Kim BS, et al. Additive beneficial effects of valsartan combined with rosuvastatin in the treatment of hypercholesterolemic hypertensive patients. *Korean Circ J*. 2015;45:225–233.
35. Borghi C, Prandin MG, Costa FV, et al. Use of statins and blood pressure control in treated hypertensive patients with hypercholesterolemia. *J Cardiovasc Pharmacol*. 2000;35:549–555.
36. Kanbay M, Yildirir A, Bozbas H, et al. Statin therapy helps to control blood pressure levels in hypertensive dyslipidemic patients. *Ren Fail*. 2005;27:297–303.
37. Straznicky NE, Howes LG, Lam W, et al. Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolemia and systemic hypertension. *Am J Cardiol*. 1995;75:582–586.
38. Correa Jr V, Fuchs FD, Moreira LB, et al. Blood pressure-lowering effect of simvastatin: a placebo-controlled randomized clinical trial with 24-h ambulatory blood pressure monitoring. *J Hum Hypertens*. 2014;28:62–67.
39. Strazzullo P, Kerry SM, Barbato A, et al. Do statins reduce blood pressure?: a meta-analysis of randomized, controlled trials. *Hypertension*. 2007;49:792–798.
40. Briasoulis A, Agarwal V, Valachis A, et al. Antihypertensive effects of statins: a meta-analysis of prospective controlled studies. *J Clin Hypertens (greenwich)*. 2013;15:310–320.
41. Park JS, Shin JH, Hong TJ, et al. Efficacy and safety of fixed-dose combination therapy with olmesartan medoxomil and rosuvastatin in Korean patients with mild to moderate hypertension and dyslipidemia: an 8-week, multicenter, randomized, double-blind, factorial-design study (OLSTA-D RCT: OLmesartan rosuvaSTAtin from Daewoong). *Drug Des Devel Ther*. 2016;10:2599–2609.
42. Lee HY, Kim SY, Choi KJ, et al. A randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and the tolerability of a triple combination of amlodipine/losartan/rosuvastatin in patients with comorbid essential hypertension and hyperlipidemia. *Clin Ther*. 2017;39:2366–2379.
43. Oh GC, Han JK, Han KH, et al. Efficacy and safety of fixed-dose combination therapy with telmisartan and rosuvastatin in Korean patients with hypertension and dyslipidemia: TELSTA-YU (TELmisartan-rosuvaSTAtin from YUhan), a multicenter, randomized, 4-arm, double-blind, placebo-controlled, phase III study. *Clin Ther*. 2018;40:676–691.
44. Gandhi SK, Järbrink K, Fox KM, et al. Effectiveness of rosuvastatin in reducing LDL-C and target LDL-C goal attainment in real-world clinical practice. *Curr Med Res Opin*. 2009;25:2817–2828.
45. Sabaté E, ed. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva, Switzerland: World Health Organization; 2003.

Address correspondence to: Yong-Seog Oh, MD, PhD, Department of Internal Medicine, Seoul St. Mary's Hospital of the Catholic University, 222, Banpo-daero, Seocho-gu, Seoul, Republic of Korea. E-mail: oys@catholic.ac.kr