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Original Research

Efficacy and Safety of Triple Therapy of Telmisartan/Amlodipine/Rosuvastatin in Patients with Dyslipidemia and Hypertension: A Multicenter Randomized Clinical Trial

Sungjoon Park, MD[1,†], Doyeon Hwang, MD[1,†], Jeehoon Kang, MD[1], Jung-Kyu Han, MD[1], Han-Mo Yang, MD[1], Kyung Woo Park, MD[1], Hyun-Jae Kang, MD[1], Bon-Kwon Koo, MD[1], Jin-Man Cho, MD[2], Byung-Ryul Cho, MD[3], Sung Gyun Ahn, MD[4], Seok-Min Kang, MD[5], Jung-Hoon Sung, MD[6], Ung Kim, MD[7], Namho Lee, MD[8], Hyo-Soo Kim, MD[1,*]

[1] *Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital and Seoul National University College of Medicine, Seoul, Korea*
[2] *Division of Cardiology, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Seoul, South Korea*
[3] *Division of Cardiology, Department of Internal Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon, South Korea*
[4] *Division of Cardiology, Department of Internal Medicine, Wonju Severance Christian Hospital, Wonju, South Korea*
[5] *Division of Cardiology, Department of Internal Medicine, Severance Hospital, Seoul, South Korea*
[6] *Department of Cardiology, CHA Bundang Medical Center, Seongnam, South Korea*
[7] *Division of Cardiology, Department of Internal Medicine, Yeung-nam University Hospital, Daegu, South Korea*
[8] *Division of Cardiology, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, South Korea*

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ABSTRACT

Background: Hypertension and dyslipidemia significantly contribute to cardiovascular disease development. Their coexistence poses challenges in managing multiple medications, influencing treatment adherence.

Objective: This study aimed to assess the efficacy and safety of a combined treatment approach using a fixed-dose combination therapy.

Methods: This multicenter, 8-week, randomized, double-blind, Phase IV trial was named Telmisartan/Amlodipine/Rosuvastatin from Samjin Pharmaceuticals and evaluated the efficacy and safety of fixed-dose combination treatment in patients with essential hypertension and dyslipidemia. They were randomly assigned to 2 fixed-dose combination therapy groups, telmisartan 40 mg/amlodipine 5 mg/rosuvastatin 10 mg (TEL/ALD/RSV) or amlodipine 5 mg/atorvastatin 10 mg (ALD/ATV) after washout/run-in period. The primary outcomes were the change in mean sitting systolic blood pressure and the percentage change of LDL-C after 8 weeks of medical treatment. Adverse drug reactions and events were assessed.

Results: Of a total of 304 patients who underwent screening, 252 were randomized to the TEL/ALD/RSV group (125 patients) and the ALD/ATV group (127 patients). The mean (SD) ages of the TEL/ALD/RSV group and the ALD/ATV group were 67.4 (11.3) and 68.2 (10.6) years, respectively ($P = 0.563$). The least-squares mean (SE) in mean sitting systolic blood pressure changes between the 2 groups were −16.27 (0.93) mm Hg in the TEL/ALD/RSV group, −6.85 (0.92) mm Hg in the ALD/ATV group (LSM difference = −9.42 mm Hg; 95% CI, −11.99 to −6.84; $P < .001$). For LDL-C level changes, a significant difference was noted between the 2 groups: −50.03% (1.18%) in the TEL/ALD/RSV group, −39.60% (1.17%) in the ALD/ATV group (LSM difference = −10.43%; 95% CI, −13.70 to −7.16; $P < .001$). No severe adverse events were observed.

* Address correspondence to: Hyo-Soo Kim, MD, PhD, Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul 03080, Republic of Korea.
E-mail address: hyosoo@snu.ac.kr (H.-S. Kim).
† These authors contributed equally to this work.

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Conclusions: TEL/ALD/RSV proved to be more efficient than ALD/ATV in lowering blood pressure and reducing LDL-C levels among patients with hypertension and dyslipidemia, with no notable safety concerns. (*Curr Ther Res Clin Exp*. 2024; XX:XXX–XXX). ClinicalTrials.gov identifier: NCT03860220.

Introduction

Cardiovascular disease (CVD) is now the leading cause of mortality and morbidity worldwide.[1] The simultaneous presence of hypertension and dyslipidemia, which play a pivotal role in the development of CVD, is frequently observed.[1,2] Furthermore, preceding studies have shown that a significant number of patients with hypertension also have dyslipidemia.[3] Previous studies have shown that when hypertension and dyslipidemia coexist, the risk of coronary heart disease is greater than simply adding up the individual risks associated with each of these factors.[4] Due to the interrelated nature of cardiovascular risk factors such as high blood pressure and abnormal cholesterol levels, it is crucial to manage both to reduce the likelihood of future cardiovascular events.[5,6]

The ideal treatment approach should address all these factors simultaneously, which may lead to an increase in the quantity of medications prescribed. However, an increase in the number of pills required for treatment could potentially lead to reduced patient adherence, possibly resulting in the failure of therapy.[7,8] To deal with this problem, a single fixed-dose combination (FDC) medication has the capability to simplify patient adherence by decreasing the tablet count while maintaining effective control over both blood pressure (BP) and cholesterol levels.[9]

In previous studies of combination therapy, telmisartan plus rosuvastatin and amlodipine plus rosuvastatin showed good efficacy and safety profiles in patients with both hypertension and dyslipidemia.[10,11] Although these medications are already being prescribed as combination therapies in clinical settings, research on their efficacy, safety, and comparative studies involving the 3-drug combination are quite limited. In this study, we aim to compare and evaluate the efficacy and safety of the 3-drug regimen consisting of telmisartan 40 mg/amlodipine 5 mg/rosuvastatin 10 mg (TEL/ALD/RSV) against the 2-drug regimen or amlodipine 5 mg/atorvastatin 10 mg (ALD/ATV).

Patients and Methods

Study design and protocol

This Phase IV, 8-week, multicenter, randomized, double-blind study was conducted at 16 hospitals in South Korea from April 2019 to July 2023 under the name Telmisartan/Amlodipine/Rosuvastatin from Samjin Pharmaceuticals Co randomized controlled trial. Before commencing the study, written informed consent was obtained from all participants. If an individual qualified as an eligible patient after the initial screening test (visit 1), he underwent a 6-week period of therapeutic lifestyle change before his baseline visit (visit 2). During this time, both treatment-naïve individuals and those already taking hypertension medication were given a daily 5-mg dose of amlodipine to ensure uniformity (washout period). Also, patients ceased the intake of antidyslipidemia drugs if they were previously using them. At visit 2, the patients who met the final eligibility criteria for participation were randomly assigned to 1 of 2 groups: TEL/ALD/RSV group or ALD/ATV group, with an allocation ratio of 1:1. All patients were given 1 of the 2 drugs at a fixed time once daily for 8 weeks (treatment period). The study participants underwent a total of 3 regular visits at 4-week intervals, including the baseline visit, as well as 2 additional visits (visit 3 and visit 4). After the final administration of the investigational drug in the clinical trial, observation and monitoring of adverse reactions were conducted through either telephone calls or on-site visits at the 2-week posttreatment point (Figure 1). The protocol and informed consent were approved by relevant authorities, and the study adhered to the Declaration of Helsinki and Korean Good Clinical Practice guidelines.

Inclusion and Exclusion Criteria

Eligible participants were adults aged 19 years or older with essential hypertension and dyslipidemia who demonstrated good adherence to therapeutic lifestyle change during the clinical trial period were included. At the baseline visit, patients who met all 3 laboratory findings were enrolled: 140 mm Hg $<$ mean sitting systolic blood pressure (msSBP) $<$190 mm Hg (for patients with chronic kidney disease or diabetes mellitus, 130 mm Hg $\leq$ msSBP $<$ 180 mm Hg), triglyceride (TG) level $<$500 mg/dL, LDL-C level $\leq$250 mg/dL; however, they must meet the specified LDL-C levels according to the risk group classification as Supplemental Table 1. All patients provided informed consent. Exclusion criteria are described in the Supplemental Methods.

Efficacy and tolerability evaluation

The primary outcomes were a change in msSBP and a percentage change in LDL-C in the TEL/ALD/RSV group and ALD/ATV group from baseline to the end of week 8. The secondary outcomes were percentage changes from baseline in LDL-C at week 4, changes from baseline at week 4 and 8 in variables, including total cholesterol (TC) level, TG level, HDL-C level, non-HDL-C level, apolipoprotein B-100 (Apo B) level, apolipoprotein A-1 (ApoA-1) level, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, Apo B/ApoA-1 ratio, and high sensitivity C-reactive protein level, the proportions of study patients who achieved the LDL-C treatment goals at the 8-week time point according to the stratified 4 risk groups: risk group 1: $<$160 mg/dL; risk group 2: $<$130 mg/dL; risk group 3: $<$100 mg/dL; risk group 4: $<$70 mg/dL, changes in msSBP at week 4 from the baseline, changes from baseline in mean sitting diastolic BP at week 4 and 8, the proportion of study patients who achieved target BP $<$140/90 mm Hg, the proportion of study patients who achieved target BP $<$130/90 mm Hg, the percentage of patients with a 8-week BP reduction $\geq$20 mm Hg systolic and $\geq$10 mm Hg diastolic compared with baseline.

Safety was assessed based on adverse events (AEs) reported and documented by researchers. An AE was defined as any unintended harmful occurrence, sign (including abnormal lab results), symptom, or disease in a patient receiving an investigational drug, without the necessity of a causal link to the drug. An adverse drug reaction (ADR) was any unintended harmful response at any drug dose that could not be ruled out in relation to the investigational drug. A serious adverse event was identified by criteria such as death or a life-threatening situation, hospitalization or extended hospital stay, severe disability, fetal malformation, or cases requiring treatment to prevent further harm. AEs and ADRs were cate-

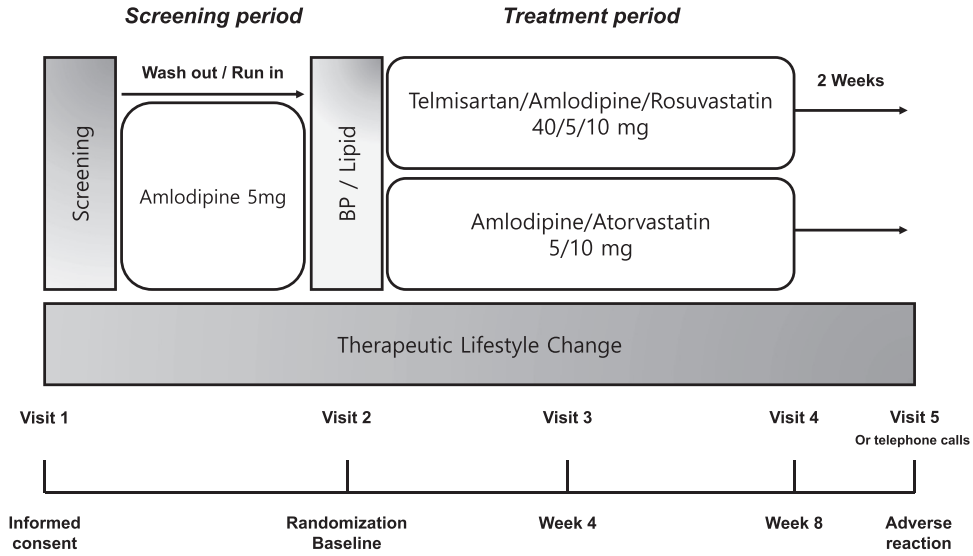

Fig 1. Study design. BP = blood pressure.

gorized as mild (minimal discomfort), moderate (discomfort influencing daily activities but not necessitating study discontinuation), or severe (requiring study discontinuation due to significant discomfort). Treatment-emergent AE is defined as an AE that occurs during the treatment period.

Statistical Analysis

The study aimed to enroll 304 participants, factoring a 10% dropout rate, for a Phase IV clinical trial. It aims to establish the superiority of the TEL/ALD/RSV group over the ALD/ATV group in terms of LDL-C and systolic BP changes in patients with hypertension with dyslipidemia. Based on previous research, effect sizes were conservatively assumed, with a sample size of 112 participants per group to meet statistical criteria. Detailed sample size calculation is described in the Supplemental Methods.

Continuous variables were compared using either the unpaired *t* test or the Wilcoxon rank-sum test, whereas categorical variables were compared using the χ^2 test or Fisher exact test. To evaluate the influence of treatments on primary and secondary efficacy measures, we used Analysis of covariance (ANCOVA) with baseline measurement as the covariate. The results include the least squares mean (LSM) and SE for each administration group, along with LSM for the differences between the 2 groups. Subgroup analysis was conducted to identify factors associated with changes in systolic BP and LDL-C. All applicable *P* values were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed using SPSS version 24.0 (IBM-SPSS Inc, Armonk, NY).

Results

Patient characteristics

A total of 304 patients from the 16 centers were screened, and 252 patients were randomized. A total of 8 (3.2%) patients withdrew from the study, with 4 patients in each of the 2 groups. Three patients dropped out due to withdrawal of consent, and 1 patient experienced a protocol violation in the TEL/ALD/RSV group. In the ALD/ATV group, 3 patients withdrew their consent, and 1 patient had to use contraindicated medication. Thus, the clinical trial was completed by 121 patients in the TEL/ALD/RSV group and 123 patients in the ALD/ATV group (Figure 2). The demographic and baseline characteristics of patients are described in Table 1. The mean (SD) age of the patients was 67.8 (10.9) years, and the mean (SD) body mass index was 26.3 (3.0). One hundred ten (43.7%) patients had diabetes mellitus, and 38 (15.1%) patients were current smokers. The 10-year atherosclerotic CVD risk of total patients was 17.0% (8.1%). There were no significant differences in demographic characteristics between the 2 groups.

Efficacy outcomes

The change in msSBP and percent change in LDL-C from the baseline to week 8 after the treatment are shown in Table 2. The baseline mean (SD) msSBP was 145.5 (9.3) mm Hg in the TEL/ALD/RSV group and 145.4 (9.5) mm Hg in the ALD/ATV group ($P = 0.983$). By the eighth week, mean (SD) msSBP decreased to 129.2 (12.4) mm Hg in the TEL/ALD/RSV and 138.6 (11.6) mm Hg in the ALD/ATV group ($P < 0.001$). The LSM (SE) in msSBP from baseline to 8 weeks were −16.27 (0.93) mm Hg in the TEL/ALD/RSV group and −6.85 (0.92) mm Hg in the ALD/ATV group, respectively. A significant difference was observed in LSM (SE) between the 2 groups (9.42 [1.31] mm Hg; 95% CI, −11.99 to −6.84; $P < .001$) (Figure 3).

Regarding LDL-C levels, at baseline, the TEL/ALD/RSV group and ALD/ATV group had mean (SD) LDL-C values of 146.6 (30.2) mg/dL and 149.7 (34.3) mg/dL, respectively ($P = 0.456$). After 8 weeks, these values changed to 72.7 (21.6) mg/dL in the TEL/ALD/RSV group and 88.2 (22.2) mg/dL in the ALD/ATV group ($P < 0.001$). The percentage change in LDL-C from baseline to the end of the 8-week treatment was more pronounced in the TEL/ALD/RSV group (−50.03%) than in the ALD/ATV group (−39.60%) (LSM difference = −10.43 mg/dL; 95% CI, −13.70 to −7.16; $P < .001$) (Figure 4).

Supplemental Tables 2 through 8 present a detailed analysis of the secondary outcomes. Analyzing the percentage changes in LDL-C levels after 4 weeks between the 2 groups, a significant difference emerged between the TEL/ALD/RSV group and the ALD/ATV group in LSM (SE) (−12.30% [1.51%]; 95% CI, −15.28 to −9.32; $P < 0.001$) (Supplemental Table 2). The TEL/ALD/RSV group exhibited notably higher percentage changes in TC, TG, non-HDL-C, ApoB, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, and ApoB/ApoA-1 ratio levels at both the 4-week and 8-week marks in comparison to the baseline, compared with the ALD/ATV group. However, no significant differences were found in HDL-C, ApoA-1, and high-sensitivity C-reactive protein between the 2 groups at any measurement intervals (Supplemental Table 3). Supplemental

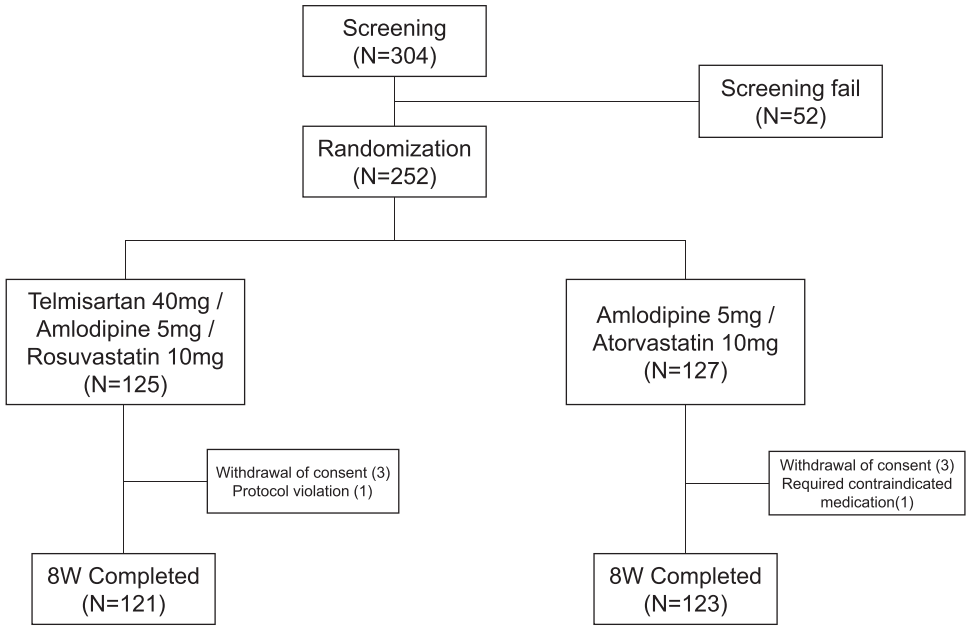

Fig 2. Overall study flow chart.

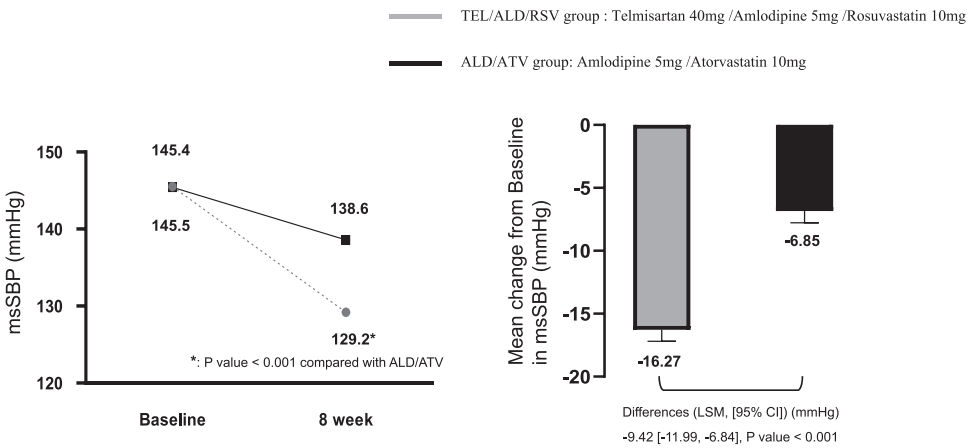

Fig. 3. Changes from baseline in mean sitting systolic blood pressure (msSBP) at week 8 between the telmisartan 40 mg/amlodipine 5 mg/rosuvastatin 10 mg (TEL/ALD/RSV) group and amlodipine 5 mg/atorvastatin 10 mg (ALD/ATV) group. LSM = least-square mean.

Table 1
Baseline characteristics of the study populations.

	Telmisartan/amlodipine/ rosuvastatin (n = 125)	Amlodipine/atorvastatin (n = 127)	Total (N = 252)	*P* value
Age*, y	67.4 ± 11.3	68.2 ± 10.6	67.8 ± 10.9	0.576
Female†	48 (38.4)	54 (42.5)	102 (40.5)	0.505
Height*, cm	161.8 (8.9)	162.1 (9.2)	162.0 (9.0)	0.821
Weight*, kg	68.8 (10.8)	69.6 (13.2)	69.2 (12.0)	0.595
BMI†	26.2 (2.8)	26.3 (3.1)	26.3 (3.0)	0.697
DM†	53 (42.4)	57 (44.9)	110 (43.7)	0.691
Smoking†	18 (14.4)	20 (15.7)	38 (15.1)	0.765
CAD†	98 (78.4)	105 (82.7)	203 (80.6)	0.391
CVA†	8 (6.4)	6 (4.7)	14 (5.6)	0.562
PAD†	2 (1.6)	2 (1.6)	4 (1.6)	0.987
Carotid disease†	2 (1.6)	3 (2.4)	5 (2.0)	0.664
AAA†	0 (0)	3 (2.4)	3 (1.2)	0.084
CAD family history†	5 (4.0)	5 (3.9)	10 (4.0)	0.980
10-y ASCVD risk*	16.8 (7.8)	17.3 (8.5)	17.0 (8.1)	0.650
Age: Male ≥45 y, Female ≥55 y	119 (95.2)	121 (95.3)	240 (95.2)	0.978
HDL < 40	18 (14.4)	19 (15.0)	37 (14.7)	0.900
Risk factor number*	2.28 (0.55)	2.30 (0.55)	2.29 (0.55)	0.782

AAA = abdominal aorta aneurysm; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAD = coronary artery disease; CVA = cerebrovascular accident; DM = diabetes mellitus; PAD = peripheral arterial disease.

* Values are presented as mean (SD).

† Values are presented as n (%).

Table 2
Changes from baseline in mean sitting systolic blood pressure (msSBP) and LDL-C level at week 8.

	Telmisartan/amlodipine/rosuvastatin (n = 121)	Amlodipine/atorvastatin (n = 123)
msSBP, mm Hg		
Baseline		
Mean (SD)	145.5 (9.3)	145.4 (9.5)
Week 8		
Mean (SD)	129.2 (12.4)	138.6 (11.6)
LSM (SE), %	−16.27 (0.93)	−6.85 (0.92)
LSM difference (SE), %	−9.42 (1.31)	
95% CI	−11.99 to −6.84	
P value	< 0.001	
LDL-C, mg/dL		
Baseline		
Mean (SD)	146.6 (30.2)	149.7 (34.3)
Week 8		
Mean (SD)	72.7 (21.6)	88.2 (22.2)
LSM (SE) change from baseline, mm Hg	−50.03 (1.18)	−39.60 (1.17)
LSM (SE) change difference, mm Hg	−10.43 (1.66)	
95% CI	−13.70 to −7.16	
P value	< 0.001	

LSM = least-square mean.

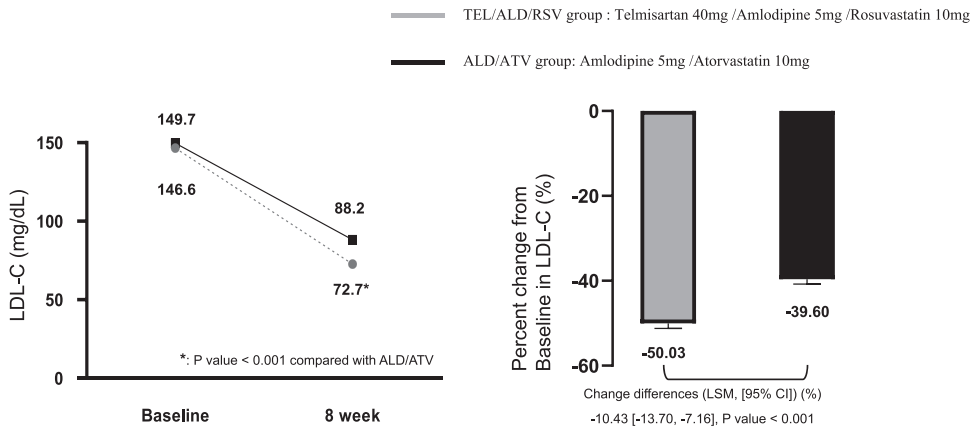

Fig 4. Percent change from baseline in LDL-C at week 8 between the telmisartan 40 mg/amlodipine 5 mg/rosuvastatin 10 mg (TEL/ALD/RSV) group and amlodipine 5 mg/atorvastatin 10 mg (ALD/ATV) group. LSM = least-square mean.

Tables 4 and 5 demonstrated the alterations in msSBP from the baseline at week 4 after treatment and the changes in mean sitting diastolic BP from the baseline at week 4 and 8. The proportion of patients in the risk group 4 who achieved the target LDL-C level below 70 mg/dL was significantly higher in the TEL/ALD/RSV group than in the ALD/ATV group at 8 weeks (TEL/ALD/RSV group: 52 out of 98 (53.1%) vs ALD/ATV group: 23 out of 100 (23.0%); $P < 0.001$). However, there were no significant differences in the proportion of patients achieving the target LDL-C level between the 2 groups in the risk stratified groups 1, 2, and 3 (Supplemental Table 6). After 8 weeks, there were significant differences between the TEL/ALD/RSV group and ALD/ATV group in the proportions of patients achieving the target BP of 140/90 mm Hg (71.9% vs 51.2%; $P = 0.001$), 130/90 mm Hg (53.7% vs 20.3%; $P < 0.001$), and responders showing adequate changes from baseline BP (20.7% vs 2.4%; $P < 0.001$) (Supplemental Tables 7 and 8).

Safety outcomes

The occurrence of treatment-emergent AEs was observed in 23 patients, which accounted for 9.1% of the total patient population, with a total of 32 events (Table 3). Eight (6.4%) patients were attributed to patients in the TEL/ALD/RSV group, and 15 (11.8%) patients were associated with the ALD/ATV group. Notably, no severe ADR was reported, with 22 events in 16 patients classified as mild and 10 events in 9 patients classified as moderate in severity. Chest discomfort was the most common, occurred in 5 patients. Severe AE was observed in 1 patient from the ALD/ATV group who had to discontinue the trial due to the necessity of using a contraindicated medication for newly diagnosed heart failure with reduced ejection fraction. However, it was not directly related to the treatment drug. Additionally, ADRs occurred in 2 patients as hypotension and headache, which were classified as mild severity. These reactions did not necessitate the cessation or reduction of the treatment drug.

Discussion

In this randomized, multicenter, double-blind, placebo-controlled study, we showed the efficacy of TEL/ALD/RSV for lowering BP and LDL-C level after 8 weeks of treatment by comparing this with ALD/ATV in South Korean patients with both hypertension and dyslipidemia. After the 8-week treatment period, TEL/ALD/RSV was more effective than ALD/ATV in lowering SBP by 9.42 mm Hg and in lowering LDL-C level by 10.4%. Thus, TEL/ALD/RSV was more effective than ALD/ATV in achieving both the target BP and LDL-C level without any significant safety problems.

Previous studies have demonstrated the efficacy of telmisartan in reducing BP in patients with hypertension.[12,13] Our research

Table 3
Summary of treatment-emergent adverse events (TEAEs).

Variable	Telmisartan/amlodipine/ rosuvastatin (n = 125)	Amlodipine/atorvastatin (n = 127)	Total (N = 252)
patients with AEs	8 (6.4)	15 (11.8)	23 (9.1)
Cases of AEs*	9 [8/1/0]	23 [14/9/0]	33 [22/10/0]
Chest discomfort	1 [1/0/0]	4 [1/3/0]	5 [2/3/0]
Headache	2 [1/1/0]	2 [1/1/0]	4 [2/2/0]
Dizziness	1 [1/0/0]	1 [1/0/0]	2 [2/0/0]
Cough	1 [1/0/0]	1 [1/0/0]	2 [2/0/0]
Foot edema	0	2 [2/0/0]	2 [2/0/0]
Hand edema	0	1 [1/0/0]	1 [1/0/0]
Angioedema	0	1 [1/0/0]	1 [1/0/0]
Elevated creatinine kinase level	0	1 [0/1/0]	1 [0/1/0]
AGE	0	1 [0/1/0]	1 [0/1/0]
GERD	0	1 [1/0/0]	1 [1/0/0]
Fatty liver	0	1 [1/0/0]	1 [1/0/0]
Nausea	1 [1/0/0]	0	1 [1/0/0]
Epigastric pain	0	1 [1/0/0]	1 [1/0/0]
Watery diarrhea	0	1 [0/1/0]	1 [0/1/0]
Other allergic rhinitis	0	1 [1/0/0]	1 [1/0/0]
Numbness of foot	1 [1/0/0]	0	1 [1/0/0]
Tongue pain	1 [1/0/0]	0	1 [1/0/0]
Sputum	0	1 [1/0/0]	1 [1/0/0]
Periodontitis	0	1 [1/0/0]	1 [1/0/0]
Nontuberculous mycobacteria lung disease	0	1 [0/1/0]	1 [0/1/0]
Hypotension*	1 [1/0/0]	0	1 [1/0/0]
Heart failure with reduced ejection fraction	0	1 [0/1/0]	1 [0/1/0]
ADR†			2 [2/0/0]
Headache*	0	1 [1/0/0]	1 [1/0/0]
Hypotension*	1 [1/0/0]	0	1 [1/0/0]
No. of patients with SAEs	0	1 (0.8)	1 (0.4)
ADR leading to drug withdrawn	0	1 (0.8)	1 (0.4)

ADR = adverse drug reaction; AE = adverse events; AGE = Acute gastroenteritis; GERD = gastroesophageal reflux disease; SAE = serious adverse event.
* Values are presented as mild/moderate/severe.
† Values are presented as n (%).

confirmed these findings and consistently observed positive results with the use of telmisartan 40 mg. Additionally, prior studies examined the effect on LDL-C level through different types and doses of statins. The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial reported 6-week change in LDL level of –45.8% with rosuvastatin 10 mg and –36.8% with atorvastatin 10 mg.[14] Strandberg et al[15] demonstrated LDL-C level changes over a 12-week trial, showing –46.92% for rosuvastatin and –38.07% for atorvastatin. In our 8-week randomized controlled trial, we noted consistent efficacy in reducing LDL-C level when comparing atorvastatin and rosuvastatin. Also, regarding safety outcomes, no significant differences were observed between the TEL/ALD/RSV group and the ALD/ATV group. For patients with uncontrolled hypertension or dyslipidemia despite treatment with 2 combination fixed pills, the FDC medication of TEL/ALD/RSV appears to be more effective than ALD/ATV. Strength of our research is the integration of established antihypertension and lipid-lowering medications, each validated through extensive studies, into a single pill. We have not only reaffirmed their efficacy but also demonstrated their safety, establishing their applicability for use in real clinical practice.

The combination of TEL/ALD/RSV, which are the most extensively researched drugs for treating hypertension and dyslipidemia, has demonstrated significant and proven benefits, as demonstrated by a wealth of clinical trials.[16–18] Telmisartan, a specific angiotensin II receptor blocker with a notable preference for the angiotensin II type I receptor and an extended half-life, which renders it a highly efficient once-daily medication for BP management. It has demonstrated excellent tolerability and effectiveness in diminishing the chances of CVD and mortality in individuals at high risk.[19] Distinct from other angiotensin II receptor blockers, telmisartan has exhibited pleiotropic effects on the cardiovascular system by partially activating peroxisome proliferator-activated receptor γ.[20] Amlodipine, categorized as a dihydropyridine-type calcium channel blocker, mainly targets vascular smooth muscle cells and the long-lasting L-type calcium receptors of the myocardium. Its mechanism involves impeding the influx of calcium into these cells, leading to decreased resistance in peripheral blood vessels and, consequently, a lowering of BP.[21] However, they may produce an AE by inducing peripheral vascular constriction, which could lead to edema. Angiotensin II receptor blockers, on the other hand, are believed to block the renin-angiotensin system, encouraging general vascular relaxation and venous expansion. When angiotensin II receptor blockers are combined with calcium channel blockers, they can exhibit a synergistic effect to counteract the venous constriction induced by calcium channel blockers. This leads to a substantial reduction in BP and a mechanism that holds the potential to decrease the occurrence of edema. Rosuvastatin, a water-soluble drug with a relatively long half-life and a low risk for adverse events, is less expensive and well tolerated compared with other statin medications.[22] In particular, it demonstrates the most potent inhibitory effect on this enzyme, largely due to its high affinity for 3-hydroxy-3-methylglutaryl coenzyme A reductase. This leads to a notable decrease in LDL-C levels and an elevation in HDL-C levels.[14] Therefore, the use of the TEL/ALD/RSV combination in this study, presented as FDC, is anticipated to have substantial effects on both hypertension and hyperlipidemia.

Study limitations

Our study had several limitations. First, our study was limited to the Korean population, and given the potential differences in

pharmacodynamics or kinetics among various ethnic groups, further evaluation of this drug combination in more diverse populations may be warranted. Second, the follow-up period was relatively brief to observe the long-term effectiveness and safety outcomes of the study drug. Third, patients with severe hypertension and severe hypercholesterolemia were excluded from the clinical trial. Fourth, despite well-defined LDL-C targets for each risk group, comparing atorvastatin 10 mg and rosuvastatin 10 mg in the control group revealed that many patients did not reach their target LDL-C levels. This is noteworthy considering that, after the randomized controlled trial, some patients achieved the target by increasing the dose or adding other agents such as ezetimibe. However, during the trial period, there was a risk of exposure due to not reaching the target, which could have implications for the patients' overall risk profile. Last, although the tolerability was excellent in 2 groups in our current study, further evaluation of the drug's efficacy and tolerability should be conducted by including a comparison group receiving individual FDCs.

Conclusions

In patients with hypertension and dyslipidemia, the triple combination of TEL/ALD/RSV led to a significant reduction in both blood pressure and LDL-C levels, with no discernible increase in AEs when compared with the ALD/ATV FDC medication.

Declaration of competing interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2024.100735.

References

1. GBD 2019 Diseases and Injuries CollaboratorsGlobal burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;17;396(10258):1204–1222.
2. O'Meara JG, Kardia SL, Armon JJ, Brown CA, Boerwinkle E, Turner ST. Ethnic and sex differences in the prevalence, treatment, and control of dyslipidemia among hypertensive adults in the GENOA study. *Arch Intern Med*. 2004;164:1313–1318.
3. Wong ND, Lopez V, Tang S, Williams GR. Prevalence, treatment, and control of combined hypertension and hypercholesterolemia in the United States. *Am J Cardiol*. 2006;98:204–208.
4. Egan BM, Li J, Qanungo S, Wolfman TE. Blood pressure and cholesterol control in hypertensive hypercholesterolemic patients: national health and nutrition examination surveys 1988-2010. *Circulation*. 2013;128:29–41.
5. Jackson R, Lawes CM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. *Lancet*. 2005;365:434–441.
6. Trimarco V, Izzo R, Morisco C, et al. High HDL (High-Density Lipoprotein) Cholesterol Increases Cardiovascular Risk in Hypertensive Patients. *Hypertension*. 2022;79:2355–2363.
7. Gupta P, Patel P, Štrauch B, et al. Risk Factors for Nonadherence to Antihypertensive Treatment. *Hypertension*. 2017;69:1113–1120.
8. Kolandaivelu K, Leiden BB, O'Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J*. 2014;35:3267–3276.
9. Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med*. 2009;122:290–300.
10. Kim W, Chang K, Cho EJ, et al. A randomized, double-blind clinical trial to evaluate the efficacy and safety of a fixed-dose combination of amlodipine/rosuvastatin in patients with dyslipidemia and hypertension. *J Clin Hypertens (Greenwich)*. 2020;22:261–269.
11. Jin X, Kim MH, Han KH, et al. Efficacy and safety of co-administered telmisartan/amlodipine and rosuvastatin in subjects with hypertension and dyslipidemia. *J Clin Hypertens (Greenwich)*. 2020;22:1835–1845.
12. Song ZY, Kim MH, Lee HC, et al. Efficacy and Safety of Coadministered Ezetimibe-Rosuvastatin plus Telmisartan in South Korean Patients with Dyslipidemia and Hypertension: A Multicenter, Randomized, Double-Blind, Active-Controlled, Phase III Trial. *J Clin Med*. 2023:12.
13. 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 e671.
14. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). *Am J Cardiol*. 2003;92:152–160.
15. Strandberg TE, Feely J, Sigurdsson EL. Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. *Clin Ther*. 2004;26:1821–1833.
16. Sharpe M, Jarvis B, Goa KL. Telmisartan: a review of its use in hypertension. *Drugs*. 2001;61:1501–1529.
17. Wang JG, Palmer BF, Vogel Anderson K, Sever P. Amlodipine in the current management of hypertension. *J Clin Hypertens (Greenwich)*. 2023;25:801–807.
18. White CM. A review of the pharmacologic and pharmacokinetic aspects of rosuvastatin. *J Clin Pharmacol*. 2002;42:963–970.
19. Ruilope LM. Telmisartan for the management of patients at high cardiovascular risk. *Curr Med Res Opin*. 2011;27:1673–1682.
20. Benndorf RA, Böger RH. Pleiotropic effects of telmisartan: still more to come? *J Hypertens*. 2008;26:854–856.
21. Burges R, Moisey D. Unique pharmacologic properties of amlodipine. *Am J Cardiol*. 1994;73:2a–9a.
22. Olsson GO. Safety and efficacy of rosuvastatin. *Lancet*. 2004;364:135.