ORIGINAL RESEARCH ARTICLE

A Randomized, Multicenter, Double-blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Quadruple Combination of Amlodipine, Losartan, Rosuvastatin, and Ezetimibe in Patients with Concomitant Essential Hypertension and Dyslipidemia

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Abstract

Background Few data are available regarding the efficacy and safety of a single-pill combination (SPC) consisting of four medications in patients with concomitant hypertension and dyslipidemia.

Objective We aimed to determine the efficacy and tolerability of a fixed-dose SPC consisting of 5 mg amlodipine, 100 mg losartan, 20 mg rosuvastatin, and 10 mg ezetimibe (A/L/R/E) in patients with concomitant hypertension and dyslipidemia.

Methods This was a 14-week, randomized, multicenter, double-blind, placebo-controlled, phase III clinical trial. In total, 145 patients were randomized to receive A/L/R/E, A/L, or L/R/E. The primary endpoints were the average change in the low-density lipoprotein cholesterol (LDL-C) level in the A/L/R/E and A/L groups and the sitting systolic blood pressure (sitSBP) in the A/L/R/E and L/R/E groups. The numbers of patients with adverse drug reactions (ADRs) were compared as safety variables.

Results The average percentage change in the LDL-C level as the least squares mean (LSM) from the baseline LDL-C level at the end of the 8-week treatment was − 59.0% in the A/L/R/E group and 0.2% in the A/L group (LSM difference − 59.2, 95% confidence interval [CI] − 68.1 to − 50.4; $p < 0.0001$). The average change in the sitSBP as the LSM was − 15.8 mmHg in the A/L/R/E group and −4.7 mmHg in the L/R/E group (LSM difference − 11.1, 95% CI − 16.8 to − 5.4; $p = 0.0002$). No ADRs occurred in the A/L/R/E group.

Conclusions A/L/R/E as an SPC could be an effective treatment for patients with hypertension and dyslipidemia without significant safety issues.

Clinical Trials Registration NCT04074551 (registered 30 August 2019).

Extended author information available on the last page of the article

Graphical Abstract

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PEER-REVIEWED FEATURE

A Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of a Quadruple Combination of Amlodipine, Losartan, Rosuvastatin, and Ezetimibe in Patients with Concomitant Essential Hypertension and Dyslipidemia

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AIM

To determine **the efficacy and tolerability of a fixed-dose SPC consisting of amlodipine, losartan, rosuvastatin, and ezetimibe** in patients with concomitant hypertension and dyslipidemia

STUDY DESIGN

Run-in | 8 weeks Treatment

Control 1 (A5mg + L100mg)
Experimental (A5/ L100/ R20/ E10mg)
Control 2 (L100mg + R20/ E10mg)

LDL-C Lowering
sitSBP Lowering

S — L 100mg — R

← At least 4W TLC → Pre V2

V1 (-6W) | V2 (1d) (~ -7d) | V3 (4w±4d) | V4 (8w±4d)

PRIMARY OUTCOMES

% Change from Baseline in LDL-C (A/L/R/E vs. A/L) ↓ 59%

% Change from Baseline in sitSBP (mmHg) (A/L/R/E vs. L/R/E) ↓ 16 mmHg

Week 4 | Week 8

% Change from baseline in LDL-C: 1.31, 0.20, -61.16***, -59.04***

☐ A/L/R/E ☐ A/L
***: P<0.0001 compared with A/L

LS Mean Percentage Change from baseline in SBP: Week 4, Week 8, -5.55, -4.74, -13.59, -15.84*

☐ A/L/R/E ☐ L/R/E
*: P<0.05 , compared with L/R/E

CONCLUSIONS

A/L/R/E as an SPC could be an effective treatment for patients with concomitant hypertension and dyslipidemia

A amlodipine, *E* ezetimibe, *L* losartan, *LDL* low-density lipoprotein, *LS* least square, *R* rosuvastatin, *SBP* systolic blood pressure, *SPC* single pill combination

△ Adis

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Key Points

A dose of 5 mg amlodipine (A), 100 mg losartan (L), 20 mg rosuvastatin (R), and 10 mg ezetimibe (E) as a single-pill combination (A/L/R/E) significantly reduced low-density lipoprotein cholesterol (LDL-C) compared with the A/L group, and reduced blood pressure compared with the L/R/E group.

The average percentage change in the LDL-C level from baseline at the end of the 8-week treatment was -59.0% in the A/L/R/E group and 0.2% in the A/L group (least squares mean [LSM] difference -59.2, 95% confidence interval [CI] -68.1 to -50.4; $p < 0.0001$), and the average change in sitting systolic blood pressure was -15.8 mmHg in the A/L/R/E group and -4.7 mmHg in the L/R/E group (LSM difference -11.1, 95% CI -16.8 to -5.4; $p = 0.0002$).

Eighteen adverse events (AEs) were reported in 14 patients (9.9%) among the total study patients, of which seven AEs (in four patients, 8.5%) occurred in the A/L/R/E group. No adverse drug reactions and nearly all AEs were mild.

This randomized, multicenter, double-blind, placebo-controlled study showed the efficacy and safety of a fixed dose of a single-pill combination with A/L/R/E in patients with hypertension and dyslipidemia.

1 Introduction

The burden of cardiovascular disease (CVD) has steadily increased for several decades, and CVD is now the leading cause of mortality and morbidity worldwide [1]. Hypertension and hypercholesterolemia are the most prevalent modifiable risk factors for CVD and tend to occur together [2]. More than half of patients with hypertension have dyslipidemia, and one study showed inadequate control of risk factors in patients with combined hypertension and dyslipidemia [2–4]. In patients with both hypertension and dyslipidemia, these two diseases should not be managed individually because one condition may affect the other and vice versa [5].

A combination of medications is necessary to effectively treat both hypertension and dyslipidemia. Although a combination of antihypertensive medications can lower blood pressure more effectively than a single medication [6], about 40% of patients with hypertension, including those with uncontrolled blood pressure, still receive antihypertensive monotherapy [7]. Furthermore, a more active regimen with a quadruple low-dose antihypertensive single-pill combination (SPC) can be used as an initial treatment to achieve optimal blood pressure control [8–12]. The rationale underlying the benefits of combination therapy is that combination therapy can effectively activate different complementary pathophysiological pathways, and the incidence of adverse events (AEs) following combination therapy may be reduced because the effects of each agent are reciprocally counterbalanced [13].

Adherence to medications is also important. Increasing the number of pills administered leads to nonadherence [14], which in turn leads to adverse outcomes [15]. For example, the prevalence of resistant hypertension, defined as a blood pressure of $\geq 140/90$ mmHg in patients receiving at least three antihypertensive medications, is relatively high (up to 20%) [16, 17]. Although several novel drugs have been introduced [18–22], adherence to medications is essential for the treatment of resistant hypertension [23].

This problem is magnified if the number of drugs used to control other comorbidities, including dyslipidemia, is considered in this population. To address this, an SPC for managing the above-described risk factors is widely used to treat this patient population and has been advocated as an effective strategy to reduce cardiovascular mortality and morbidity in many studies [24–26].

The present study was designed to establish a basis for the development of an SPC containing amlodipine, losartan, rosuvastatin, and ezetimibe in patients with concomitant hypertension and dyslipidemia compared with coadministration of each pill in the combination of losartan, rosuvastatin, and ezetimibe or the combination of amlodipine and losartan. In this randomized, multicenter, double-blind, placebo-controlled study, we aimed to determine the efficacy and tolerability of this quadruple combination of drugs as an SPC to control blood pressure and the low-density lipoprotein cholesterol (LDL-C) level in patients with hypertension and dyslipidemia.

2 Methods

2.1 Study Design

This 14-week, randomized, multicenter, double-blind, placebo-controlled, phase III clinical trial was performed in 13 medical institutions in South Korea from June 2019 to March 2020. The clinical trial protocol and acquisition of informed consent were approved by the Ministry of Food and Drug Safety and by the Institutional Review Board at each institution. This study was performed in accordance with the Declaration of Helsinki and Korean Good Clinical

Practice. Written informed consent was obtained from all participants before starting the study.

The overall flow of the study is shown in Fig. 1. The 14-week study period consisted of 6 weeks of run-in for therapeutic lifestyle change (TLC) and washout and an 8-week treatment period. Of the 195 screened patients, 145 were enrolled. Eligibility was assessed at the time of screening, and eligible patients participated in the run-in period. During the run-in period, all patients stopped taking previously prescribed antihypertensive and lipid-lowering medications and began treatment with 100 mg losartan once daily. After at least 4 weeks of TLC and washout, eligibility was reassessed at pre-visit 2, and eligible patients were randomized into one of three arms: an SPC consisting of 5 mg amlodipine, 100 mg losartan, 20 mg rosuvastatin, 10 mg ezetimibe, and placebo medication (A/L/R/E [treatment group]); a non-SPC of 5 mg amlodipine, 100 mg losartan, and placebo (A/L [control 1]); and 100 mg losartan with an SPC consisting of 20 mg rosuvastatin, 10 mg ezetimibe, and placebo (L/R/E [control 2]). Four pills of the same shape were provided to the patients in each group to maintain blindness. The randomization was conducted using a stratified block randomization method performed by independent biostatisticians who generated random numbers using a statistical software package (PROC PLAN procedure in SAS version 9.4 software; SAS Institute Inc., Cary, NC, USA). Medication was provided according to the random numbers given at visit 2, and the blindness of the investigators and participants was maintained during the entire study period. All medications were administered orally once daily at the same time for 8 weeks. All participants visited the study institution at 4-week intervals to assess efficacy and safety.

2.2 Study Population

Eligible participants were adults aged $\geq$ 19 years who had a sitting systolic blood pressure (SitSBP) of $\geq$ 130 mmHg and sitting diastolic blood pressure (SitDBP) of < 110 mmHg for those who were taking antihypertensive medications, or a SitSBP of $\geq$ 140 mmHg and SitDBP of < 110 mmHg for those who were not taking antihypertensive medications, as well as an LDL-C level of $\leq$ 250 mg/dL and triglyceride level of < 400 mg/dL at screening (visit 1). All patients provided informed consent.

After at least 4 weeks of TLC and a washout period for treatment with 100 mg losartan only, eligibility was rechecked at pre-visit 2 based on the criteria of 140 mmHg $\leq$ SitSBP < 180 mmHg, SitDBP < 110 mmHg, and a predefined indication for pharmacological treatment of the LDL-C level based on cardiovascular risk, which was generally consistent with the 2016 European Society of Cardiology and European Atherosclerosis Society guidelines (electronic supplementary material [ESM] Table 1) [27].

The full list of exclusion criteria is as follows.

1. A $\geq$ 20 mmHg range in the SitSBP or $\geq$ 10 mmHg range in the SitDBP between blood pressure measurements on both arms.
2. Average SitSBP of $\geq$ 180 mmHg or SitDBP of $\geq$ 110 mmHg at either visit 1 or pre-visit 2.
3. Coadministration of cyclosporine.
4. Galactose intolerance, Lapp lactase deficiency, glucose–galactose malabsorption, or other related genetic disorder.
5. Known intolerance or allergy to angiotensin II receptor blockers (ARBs), 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, calcium channel blockers, or ezetimibe, or a known history of multidrug allergy.
6. Hereditary angioedema or a history of angioedema related to treatment with an angiotensin-converting enzyme inhibitor or ARB.
7. Fibromyalgia, myopathy, rhabdomyolysis, or known history of an adverse drug reaction (ADR) to statins.
8. Serum creatine phosphokinase level of $\geq$ 2 $\times$ the upper normal limit at pre-visit 2.
9. Secondary hypertension or suspicion of secondary hypertension because of coarctation of the aorta, primary aldosteronism, renal artery stenosis, Cushing's syndrome, pheochromocytoma, or polycystic kidney disease.
10. Symptomatic orthostatic hypotension.
11. Uncontrolled primary hyperthyroidism (thyroid-stimulating hormone level of $\geq$ 1.5 $\times$ the upper normal limit at visit 1).
12. Significant liver disease (aspartate transaminase or alanine transaminase level of > 3 $\times$ the upper normal limit at visit 1).
13. Significant renal disease with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 at visit 1.
14. Active gout or symptomatic hyperuricemia (uric acid level of $\geq$ 9.0 mg/dL at visit 1).
15. Type 1 diabetes mellitus (DM) or uncontrolled type 2 DM with a hemoglobin A1C level of > 9.0% at visit 1.
16. Clinically significant ventricular arrhythmia.
17. Medical history including congestive heart failure with New York Heart Association classification III or IV, cerebrovascular accident within 6 months of visit 1, hypertrophic cardiomyopathy, hemodynamically significant aortic or mitral stenosis, coronary artery disease with more than moderate stenosis, ischemic heart disease, or associated procedures within 6 months of visit 1.
18. Retinal disease with more than moderate severity within 6 months of visit 1.
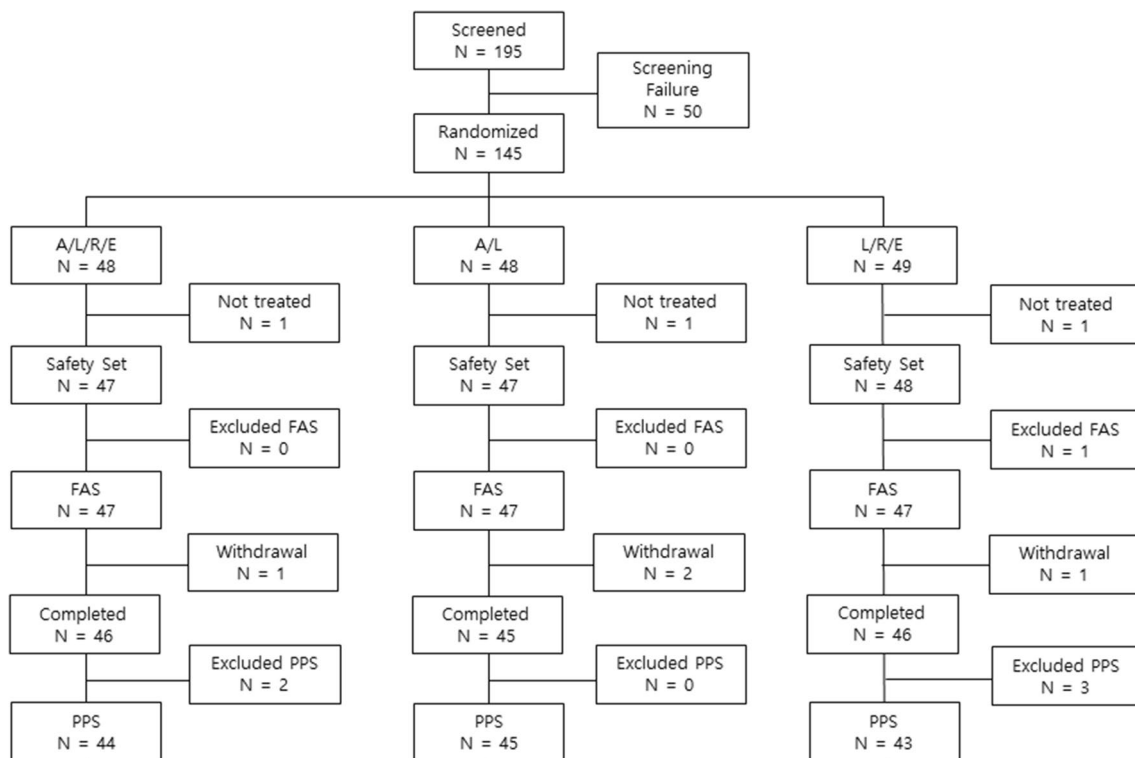19. Pancreatitis or active gall bladder disease.

Fig. 1 Overall study flow. *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan, *FAS* full analysis set, *L/R/E* losartan/rosuvastatin/ezetimibe, *PPS* per protocol set

20. Any disease that could change the absorption, distribution, metabolism, or excretion of drugs.
21. Clinically significant hypovolemia (e.g., strict salt restriction).
22. Chronic inflammatory status requiring treatment or an immune-related disorder (requiring steroids, a nonsteroidal anti-inflammatory drug, or cytotoxic agent for > 7 days).
23. Substance-related disorder, including alcohol use, within 12 months of visit 1.
24. History of malignant tumors, including leukemia and lymphoma, within 5 years of visit 1.
25. Administration of a drug from another clinical trial within 30 days.
26. Pregnant, breastfeeding, or potentially child-bearing woman who is not using adequate contraception.
27. Woman with a positive pregnancy test at visit 1.
28. Any clinically significant reason for a patient to be an inappropriate candidate for a clinical study as judged by the investigator;

Although type 1 DM is a well-known cardiovascular risk factor, it was an exclusion criterion in this study because most cases of type 1 DM occur in children and young adults.

2.3 Efficacy and Safety Variables

The primary efficacy variables were the average change in the LDL-C level (as a percentage change) at the end of the 8-week treatment for the treatment group (A/L/R/E) and control 1 group (A/L), and the average change in the SitSBP (mmHg) for the treatment group and control 2 group (L/R/E). The secondary efficacy variables were the average change (percentage or mmHg according to the variable) in the LDL-C level for the treatment and control 2 groups, and in the SitSBP for the treatment and control 1 groups after 8 weeks of treatment, as well as the average change in the LDL-C level and in the SitSBP after 4 weeks of treatment in all three groups. The secondary efficacy variables also included the total cholesterol level, high-density lipoprotein cholesterol (HDL-C) level, triglyceride level, SitDBP, rate of achieving the target LDL-C level, rate of achieving the target blood pressure (SitSBP of < 140 mmHg and SitDBP of < 90 mmHg), rate of response in blood pressure (≥ 20 mmHg change in SitSBP and ≥ 10 mmHg change in SitDBP), and rate of achieving both the target LDL-C level and blood pressure at the end of the 4- and 8-week treatments in all three groups. The target LDL-C level was defined based on the 2016 European Society of Cardiology/European Atherosclerosis Society guidelines [27].

Blood pressure was measured automatically using a calibrated monitor, and the average of two measurements obtained after at least 5 min of rest in a sitting position within a comfortable environment was used. Factors that may influence the blood pressure measurement, such as coffee, smoking, exercise, or alcohol, were avoided before the measurement was performed.

History taking, physical examination, laboratory tests (including measurement of the thyroid-stimulating hormone level), and electrocardiography were performed to evaluate tolerability and AEs at each visit (visit 1, pre-visit 2, visit 3, and visit 4).

An AE was defined as any symptom or sign that was not intended to be harmful, and an ADR was defined as an AE in which a relationship with the investigational drug could not be ruled out. An AE or ADR was considered serious if one of the following criteria was met: death or risk of death, hospitalization or extension of the hospital stay if already hospitalized, life-long or severe disability, fetal malformation, drug dependence, drug abuse, hematological disorder, or other clinically important events. The severity of the AEs or ADRs was graded as mild, moderate, or severe. A mild AE or ADR was considered when the patient had only minimal discomfort that did not affect daily activities or require treatment. A moderate AE or ADR was considered when the patient had substantial discomfort that affected daily activities and required treatment or hospitalization but did not require discontinuation of the study. A severe AE or ADR was considered when the patient had more severe discomfort that required discontinuation of the study.

2.4 Statistical Analysis

An assessment was performed according to the intention-to-treat principle. An analysis of demographic, baseline, and efficacy variables was performed in all patients who took the study medication and were assessed for the efficacy variable at least once until the end of the study. A per-protocol analysis was conducted in the patients who finished the study without deviating from the protocol (e.g., unfulfilled inclusion or exclusion criteria, drug adherence rate of < 80% or > 120%, or administration of drugs that possibly affected the efficacy or safety assessment). An analysis of the safety variables was performed in patients who took the study medication, and patients were assessed for safety variables at least once until the end of the study.

For demographic and baseline data, continuous variables were analyzed using analysis of variance or the Kruskal–Wallis test according to the normality of distribution, and categorical variables were analyzed using the Chi-square test or Fisher's exact test. The efficacy assessment was performed using analysis of covariance adjusted for each baseline value and risk stratum as a covariate for continuous variables. The Cochran–Mantel–Haenszel test was performed using the CVD risk category as a stratum for categorical variables. All statistical analyses were performed using SAS version 9.4 software, and a two-tailed p-value of < 0.05 was considered significant.

A sample size of 129 patients (43 per group) was calculated to attain 81% power to detect a − 9.75 mmHg difference between the A/L/R/E and L/R/E groups for the average change in SitSBP with a 5% significance level, assuming a 15 mmHg standard deviation (SD) and a 10% withdrawal rate.

3 Results

3.1 Demographics and Baseline Characteristics

Among the 195 patients, 145 fulfilled the enrollment criteria. A total of 137 patients completed the study, and 8 withdrew. The reasons for withdrawing from the study included withdrawal of consent ($n = 5$, 3.4%), a mean SitSBP of ≥180 mmHg or mean SitDBP of ≥ 110 mmHg at any visit ($n = 2$, 1.4%), and a judgment by the investigator that it would be harmful for the patient to continue to participate in the trial ($n = 1$, 0.7%).

The demographics and baseline characteristics of the study participants are summarized in Table 1. The demographic characteristics were obtained at the time of screening, and the lipid profile and blood pressure measurements were obtained at pre-visit 2. The baseline characteristics were comparable among the three groups. The mean patient age was 65.7 years, and 67.4% of the patients were male. Of all patients, 70.2% and 93.6% were taking antidyslipidemics and antihypertensives, respectively. In total, 65.2% of patients were categorized as very high risk according to the predefined criteria (ESM Table 1), and no patient was categorized as low risk. The LDL-C level after washout was comparable among the three groups, with an average (SD) of 140.1 (33.7) mg/dL. The average (SD) SitSBP and SitDBP was 153.1 (11.8) and 88.1 (9.9) mmHg, respectively.

3.2 Efficacy Outcomes

The treatment group (A/L/R/E) and control 1 group (A/L) were compared to assess the primary outcomes related to the LDL-C level. The mean (SD) percentage change in the LDL-C level from baseline to the end of the 8-week treatment was greater in the treatment group (− 59.5% [21.6]) than in the control 1 group (0.7% [23.8]). The least squares mean (LSM) of the percentage change in the LDL-C level from baseline to 8 weeks was larger in the treatment group than in the control 1 group (− 59.0% vs. 0.2%; $p < 0.0001$) (Table 2 and Fig. 2). The primary SitSBP outcome was

determined for the treatment group (A/L/R/E) and control 2 group (L/R/E). The mean (SD) change in the SitSBP from baseline to 8 weeks was −16.0 (14.4) mmHg in the treatment group and − 4.6 (14.8) mmHg in the control 2 group. The LSM of the change in the SitSBP from baseline was −15.8 mmHg in the treatment group and − 4.7 mmHg in the control 2 group ($p = 0.0002$) (Table 3 and Fig. 3).

The detailed results for the secondary outcomes are shown in the ESM. The percentage change in the LDL-C level at 8 weeks between the treatment group and control 2 group and the change in the SitSBP at 8 weeks between the treatment group and control 1 group were not significantly different between the respective groups (ESM Tables 2 and 3). The results of the percentage changes in the LDL-C level at 4 weeks in the three groups revealed a significant difference between the treatment group and control 1 group (LSM of 61.2% vs. 1.3%; $p < 0.0001$) but not between the treatment group and control 2 group (ESM Table 4). With respect to the change in the SitSBP at 4 weeks in the three groups, a significant difference was found between the treatment and control 2 groups (− 13.6 vs. − 5.6 mmHg; $p = 0.0067$) but not between the treatment and control 1 groups (ESM Table 5). The percentage changes in the total cholesterol, HDL-C, and triglyceride levels were significantly higher in the treatment group than in the control 1 group, but there were no differences between the treatment group and the control 1 group at both 4 and 8 weeks (ESM Tables 6–11). The change in the SitDBP was consistent with the change in the SitSBP between the treatment group and control 2 group, but the change was comparable between the treatment group and control 1 group at both 4 and 8 weeks (ESM Tables 12 and 13).

The proportion of patients who achieved the target LDL-C level was significantly higher in the treatment group than in the control 1 group at both 4 and 8 weeks. This difference was consistent in all patients in all CVD risk categories (no patients were classified as low risk in this study). No significant difference in the proportion of patients who achieved the target LDL-C level was observed between the treatment and control 2 groups at 4 or 8 weeks. The rate of achieving the target LDL-C level in the treatment group was similar among the CVD risk categories (89.3% for very high-risk patients vs. 100.0% for moderate- and high-risk patients at week 4, and 82.1% for very high-risk patients vs. 88.9% for high-risk patients vs. 90.0% for moderate-risk patients at week 8) [ESM Tables 14 and 15). The proportions of patients who achieved the target blood pressure (55.3% vs. 25.5%; $p = 0.0033$) and responders in changes from baseline blood pressure (27.7% vs. 10.6%; $p = 0.0036$) were significantly different between the treatment group and control 2 group at 8 weeks. The proportions of patients who achieved the target blood pressure and

responders in changes from baseline blood pressure in the treatment group and control 1 group were comparable at 4 or 8 weeks (ESM Tables 16 and 17). The proportion of patients who achieved the target LDL-C level and blood pressure at 4 weeks was highest in the treatment group (44.7%) among the three groups (44.7% vs. 2.1% vs. 19.1%). The same comparisons at 8 weeks also revealed the highest target rate in the treatment group compared with the control 1 and control 2 groups (44.7% vs. 2.1% vs. 17.0%) [ESM Tables 18 and 19).

3.3 Safety Outcomes

Safety outcomes were analyzed in the safety analysis set of patients. A summary of the safety outcomes is shown in Tables 4 and 5. The average (SD) exposure period was similar among the three groups: 54.4 (3.7) days in the treatment group, 54.1 (5.1) days in the control 1 group, and 53.3 (8.8) days in the control 2 group.

The number of patients with treatment-emergent AEs, defined as AEs occurring during the treatment period, was 14 (9.9%) among the 142 patients, while the rates in the treatment group, control 1 group, and control 2 group were 8.5% (4/47 patients, 7 events), 17.0% (8/47 patients, 8 events), and 4.2% (2/48 patients, 3 events), respectively (Table 4). The most frequent AEs were a high aspartate aminotransferase level (three patients) and a high alanine aminotransferase level (three patients). Most AEs were mild (13/142 patients). Only one moderate AE (ureterolithiasis) was considered serious, resulting in hospitalization. However, this AE did not have a causal relationship with the investigational drug.

Among these AEs, three patients (four events) were considered to have ADRs: two patients (two events) in the control 1 group and one patient (two events) in the control 2 group. All ADRs were mild (Table 5).

4 Discussion

In this randomized, multicenter, double-blind, placebo-controlled study, we showed the efficacy of A/L/R/E as an SPC for lowering the LDL-C level and blood pressure after 8 weeks of treatment by comparing this SPC with A/L or L/R/E at the same doses. After the 8-week treatment, A/L/R/E was more effective than L/R/E in lowering the SBP by around 15 mmHg, and more effective than A/L in lowering the LDL-C level by around 60%. Thus, A/L/R/E was more effective than the control combinations in achieving both the target LDL-C level and target blood pressure without any significant safety problems.

The study participants, all of whom had both hypertension and dyslipidemia with an LDL-C level that required

Table 1 Demographics and baseline characteristics of the study patients (full analysis set)

Characteristics	A/L/R/E [*n* = 47]	A/L [*n* = 47]	L/R/E [*n* = 47]	Total [*n* = 141]	*p*-Value
Age, years					0.451[a]
Mean (SD)	64.0 (11.7)	66.8 (8.5)	66.2 (12.8)	65.7 (11.1)	
Range	23–83	40–84	27–89	23–89	
Sex [*n* (%)]					0.303[b]
Male	35 (74.5)	32 (68.1)	28 (59.6)	95 (67.4)	
Female	12 (25.5)	15 (31.9)	19 (40.4)	46 (32.6)	
Height, cm					0.064[a]
Mean (SD)	164.9 (7.7)	160.6 (7.8)	163.0 (10.7)	162.8 (9.0)	
Range	148.1–179.0	139.0–181.1	145.4–191.0	139.0–191.0	
Weight, kg					0.123[a]
Mean (SD)	71.9 (10.8)	66.8 (10.7)	70.9 (16.1)	69.9 (12.9)	
Range	46.8–100.8	40.0–93.7	46.5–124.5	40.0–124.5	
Current smoker [*n* (%)]					0.732[b]
Yes	9 (19.1)	8 (17.0)	11 (23.4)	28 (19.9)	
No	38 (80.9)	39 (83.0)	36 (76.6)	113 (80.1)	
Drinker [*n* (%)]					0.578[b]
Yes	29 (61.7)	24 (51.1)	27 (57.4)	80 (56.7)	
No	18 (38.3)	23 (48.9)	20 (42.6)	61 (43.3)	
Prior use of antidyslipidemics [*n* (%)]					0.145[b]
Yes	31 (66.0)	30 (63.8)	38 (80.9)	99 (70.2)	
No	16 (34.0)	17 (36.2)	9 (19.1)	42 (29.8)	
Prior use of antihypertensives [*n* (%)]					0.909[c]
Yes	45 (95.7)	43 (91.5)	44 (93.6)	132 (93.6)	
No	2 (4.3)	4 (8.5)	3 (6.4)	9 (6.4)	
Risk category [*n* (%)][d]					0.804[b]
Moderate risk	10 (21.3)	9 (19.1)	9 (19.2)	28 (19.9)	
High risk	9 (19.1)	7 (14.9)	5 (10.6)	21 (14.9)	
Very high risk	28 (59.6)	31 (66.0)	33 (70.2)	92 (65.2)	
Total cholesterol, mg/dL					0.223[a]
Mean (SD)	200.0 (38.5)	195.2 (30.0)	208.1 (39.4)	201.1 (36.3)	
Range	120.0–282.0	135.0–261.0	140.0–304.0	120.0–304.0	
Triglyceride, mg/dL					0.664[a]
Mean (SD)	167.6 (64.1)	167.2 (70.8)	156.5 (66.1)	163.8 (66.8)	
Range	77.0–317.0	68.0–397.0	59.0–398.0	59.0–398.0	
LDL-C, mg/dL					0.128[a]
Mean (SD)	138.1 (34.1)	134.3 (26.9)	148.0 (38.2)	140.1 (33.7)	
Range	77.0–213.0	81.0–203.0	82.0–245.0	77.0–245.0	
HDL-C, mg/dL					0.542[a]
Mean (SD)	46.8 (11.1)	47.4 (111.1)	49.3 (11.8)	47.8 (11.3)	
Range	28.0–79.0	28.0–74.0	28.0–84.0	28.0–84.0	
SitSBP, mmHg					0.245[a]
Mean (SD)	152.3 (12.4)	155.4 (12.4)	151.5 (10.4)	153.1 (11.8)	
Range	130.0–177.0	132.5–179.0	133.5–178.5	130.0–179.0	
SitDBP, mmHg					0.846[a]
Mean (SD)	88.6 (10.0)	87.4 (9.9)	88.2 (10.0)	88.1 (9.9)	
Range	67.5–109.0	56.5–109.5	66.5–104.0	56.5–109.5	

A/L/R/E amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan, *L/R/E* losartan/rosuvastatin/ezetimibe, *SitDBP* sitting diastolic blood pressure, *SitSBP* sitting systolic blood pressure, *SD* standard deviation, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *ANOVA* analysis of variance

[a]ANOVA

[b]Pearson's Chi-square test

[c]Fisher's exact test

[d]There were no patients with low risk

Table 2 Change in LDL-C from baseline at 8 weeks after treatment with fixed-dose combinations of A/L/R/E and A/L in the full analysis set

LDL-C (mg/dL)	A/L/R/E [n = 47]	A/L [n = 47]
Baseline		
Mean (SD)	138.1 (34.1)	134.3 (26.9)
Range	77.0–213.0	81.0–203.0
At week 8		
Mean (SD)	54.5 (29.6)	131.9 (29.5)
Range	22.0–170.0	74.0–181.0
Change from baseline	− 83.6 (37.6)	− 2.4 (34.3)
Percentage change from baseline	− 59.5 (21.6)	0.7 (23.8)
Percentage change from baseline, LSM (SE)	− 59.0 (3.1)	0.2 (3.1)
Difference vs. A/L, LSM (SE)	− 59.2 (4.56)	
95% CI[a]	− 68.1 to − 50.4	
P-value vs. A/L[a]	< 0.0001	

LSM least squares mean, *LDL-C* low-density lipoprotein cholesterol, *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan, *SD* standard deviation, *SE* standard error, *CI* confidence interval, *ANCOVA* analysis of covariance

[a]ANCOVA
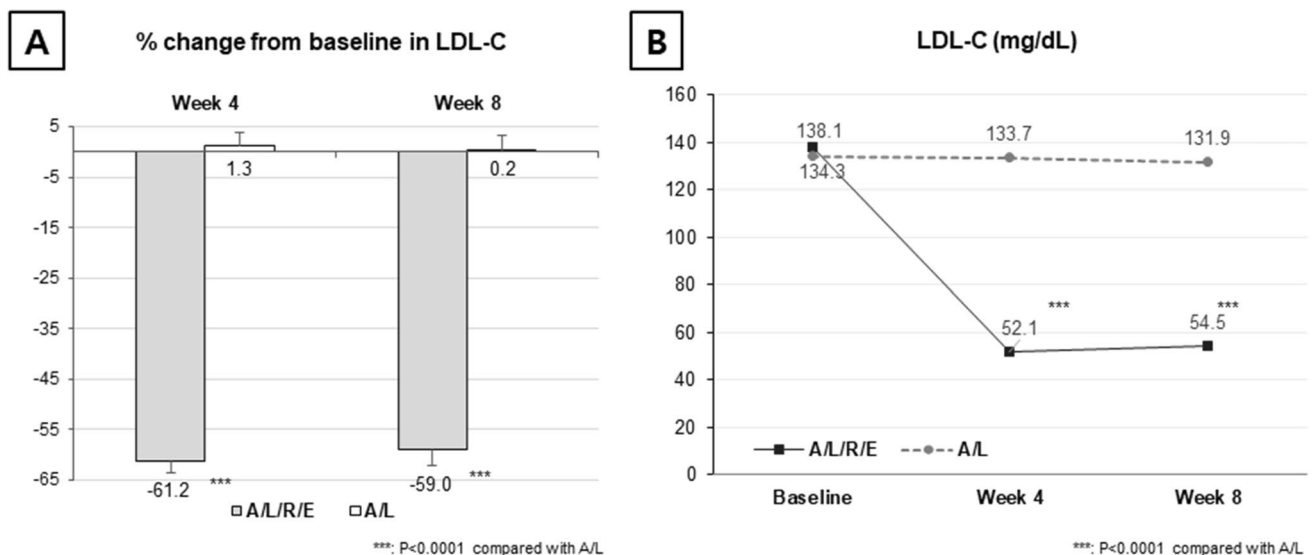
Fig. 2 Average percentage change from baseline in LDL-C at week 4 and week 8. **A** The values were provided as least squares mean, a result of the analysis of covariance test. **B** The average of LDL-C (mg/dL) at week 4 and week 8. *A/L/R/E* amlodipine/losartan/rosuvas-tatin/ezetimibe, *A/L* amlodipine/losartan, *LDL-C* low-density lipoprotein cholesterol, *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan

pharmacological intervention, represent a population with important modifiable CVD risk factors [1]. According to the analysis of the 2019 Global Burden of Disease Study, ischemic heart disease is responsible for approximately half of CVD deaths, and hypertension and dyslipidemia are the first- and third-ranked factors for CVD burden, respectively. These pathological conditions tend to co-occur [2, 3, 28, 29]. The proportion of adults with both conditions ranges from 16.0% to 18.3% [2, 29], and this population is prone to a higher risk of CVD [28, 29] than the population with

only one of the conditions. To the best of our knowledge, the current study is the first study worldwide to show the efficacy and safety of a fixed dose of an SPC with A/L/R/E in patients with concomitant hypertension and dyslipidemia. We expect improvements in both medication adherence and efficacy using an SPC with A/L/R/E in real clinical practice as shown in our study.

Our A/L/R/E SPC has many advantages. First, in terms of its antihypertensive effect, the treatment efficacy of combinations of different drug classes has been supported by large

Table 3 Change in blood pressure from baseline at 8 weeks after treatment with fixed-dose combinations of A/L/R/E and L/R/E in the full analysis set

SitSBP (mmHg)	A/L/R/E [n = 47]	L/R/E [n = 47]
Baseline		
Mean (SD)	152.3 (12.4)	151.5 (10.4)
Range	130.0–177.0	133.5–178.5
At week 8		
Mean (SD)	136.3 (15.8)	146.9 (14.7)
Range	101.0–173.5	119.0–185.5
Change from baseline	− 16.0 (14.4)	− 4.6 (14.8)
Change from baseline, LSM (SE)	− 15.8 (2.0)	− 4.7 (2.0)
Difference vs. L/R/E, LSM (SE)	− 11.1 (2.9)	
95% CI[a]	− 16.8 to − 5.4	
P-value vs. L/R/E[a]	0.0002	

LSM least squares mean, *SitSBP* sitting systolic blood pressure, *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *L/R/E* losartan/rosuvastatin/ezetimibe, *SD* standard deviation, *CI* confidence interval, *ANCOVA* analysis of covariance

[a]ANCOVA

amounts of evidence. For example, a combination of antihypertensive medications is associated with a larger blood pressure reduction [6], a higher rate of achieving the target blood pressure [30], a lower rate of treatment discontinuation regardless of the classes of drugs combined [31], and a potentially reduced CVD risk [32, 33]. The combination of an ARB and calcium channel blocker is effective and well tolerated for managing hypertension. Compared with monotherapy using either a calcium channel blocker or ARB alone [34], the combination of these two drugs produces a greater blood pressure-lowering effect with a lower rate of AEs, as shown in our study.

Second, as a lipid-lowering agent, the combination of rosuvastatin and ezetimibe has many known advantages. Statins play a central role in reducing the LDL-C level and thereby the cardiovascular risk [35, 36]. However, it has become more difficult to achieve the target LDL-C level because of the emerging tougher LDL-C goal, particularly in the high-risk and very high-risk groups [37, 38]. The combination of a statin with ezetimibe is useful for further reducing the LDL-C level, as recommended in the current guidelines [36], when statin monotherapy is insufficient for achieving the LDL-C goal. One meta-analysis showed that adding ezetimibe to statin therapy was more effective than a double dose of statin monotherapy [39].

Third, by combining four drugs for two different but closely related diseases, the SPC contained both antihypertensives and antidyslipidemics to reduce the CVD risk. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) Legacy Study and the ASCOT–Lipid Lowering Arm (ASCOT-LLA), treatment for blood pressure and cholesterol were associated with long-term clinical benefits in terms of cardiovascular outcomes [40, 41]. However, patients with both conditions are undertreated in the real-world clinical setting. For example, a report published in the mid-2000s showed that only 29% of patients were treated for both conditions, and only 9% achieved the target blood pressure and LDL-C level [2]. The control rate for both conditions
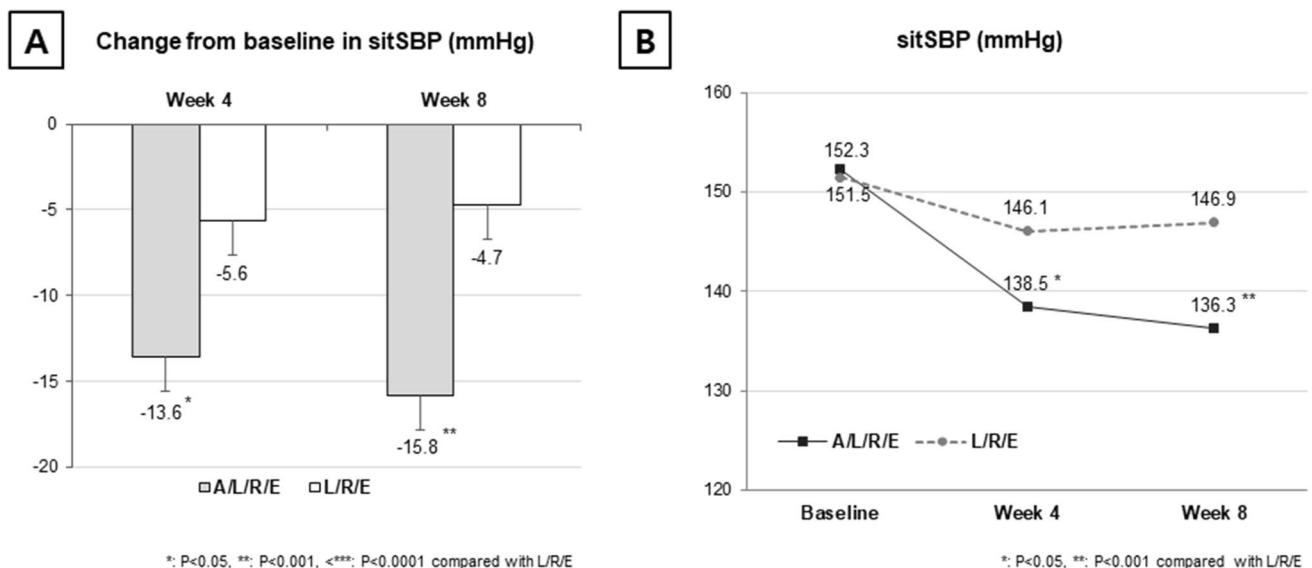

Fig. 3 Average change from baseline in sitSBP at week 4 and week 8. **A** The values were provided as least squares mean, a result of the analysis of covariance test. **B** The average of sitSBP at week 4 and week 8. *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *L/R/E* losartan/rosuvastatin/ezetimibe, *sitSBP* sitting systolic blood pressure

Table 4 Summary of TEAEs in the safety analysis set

Variables	A/L/R/E [n = 47]	A/L [n = 47]	L/R/E [n = 48]	Total [n = 142]
TEAEs, n (%) [mild/moderate/severe]	4 (8.5) [7/0/0]	8 (17.0) [7/1/0]	2 (4.2) [3/0/0]	14 (9.9) (17/1/0)
Tinnitus	0	0	1 (2.1) [1/0/0]	1 (0.7) [1/0/0]
Dyspepsia	0	0	1 (2.1) [1/0/0]	1 (0.7) [1/0/0]
Hordeolum	0	1 (2.1) [1/0/0]	0	1 (0.7) [1/0/0]
Nasopharyngitis	0	2 (4.3) [2/0/0]	0	2 (1.4) [2/0/0]
ALT increased	3 (6.4) [3/0/0]	0	0	3 (2.1) [3/0/0]
AST increased	3 (6.4) [3/0/0]	0	0	3 (2.1) [3/0/0]
Blood creatine kinase increased	0	1 (2.1) [1/0/0]	0	1 (0.7) [1/0/0]
C-reactive protein increased	0	1 (2.1) [1/0/0]	0	1 (0.7) [1/0/0]
Pain in extremity	0	1 (2.1) [1/0/0]	0	1 (0.7) [1/0/0]
Dizziness	0	0	1 (2.1) [1/0/0]	1 (0.7) [1/0/0]
Ureterolithiasis	0	1 (2.1) [0/1/0]	0	1 (0.7) [0/1/0]
Dermatitis	1 (2.1) [1/0/0]	0	0	1 (0.7) [1/0/0]
Urticaria	0	1 (2.1) [1/0/0]	0	1 (0.7) [1/0/0]

AEs with a start date on or after administration of the study drug or pre-existing conditions that worsened on or after

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan, *L/R/E* losartan/rosuvastatin/ezetimibe, *AE* adverse event, *TEAEs* treatment-emergent adverse events, *ALT* alanine transaminase, *AST* aspartate transaminase

Table 5 Summary of ADRs in the safety analysis set

System Organ Class Preferred Terms	A/L/R/E [n = 47]	A/L [n = 47]	L/R/E [n = 48]	Total [n = 142]
Total event, n (%) [mild/moderate/severe]	0 (0.0) [0/0/0]	2 (4.3) [2/0/0]	1 (2.1) [2/0/0]	3 (2.1) [4/0/0]
Tinnitus	0 (0.0) [0/0/0]	0 (0.0) [0/0/0]	1 (2.1) [1/0/0]	1 (0.7) [1/0/0]
C-reactive protein increased	0 (0.0) [0/0/0]	1 (2.1) [1/0/0]	0 (0.0) [0/0/0]	1 (0.7) [1/0/0]
Pain in extremity	0 (0.0) [0/0/0]	1 (2.1) [1/0/0]	0 (0.0) [0/0/0]	1 (0.7) [1/0/0]
Dizziness	0 (0.0) [0/0/0]	0 (0.0) [0/0/0]	1 (2.1) [1/0/0]	1 (0.7) [1/0/0]

TEAEs that have the relationship to study drug as 'yes' are regarded as ADRs

ADRs adverse drug reactions, *A/L/R/E* amlodipine/losartan/rosuvastatin/ezetimibe, *A/L* amlodipine/losartan, *L/R/E* losartan/rosuvastatin/ezetimibe, *TEAEs* treatment-emergent adverse events

remains at < 33% of all cases [3, 4]. We showed a higher rate of target achievement for both conditions in the treatment group (44.68%) compared with the above-mentioned rate, suggesting the usefulness of treatment with a combination of antihypertensive and antidyslipidemic agents. Although several reports have shown the antidyslipidemic effects of blood pressure-lowering agents (and vice versa), their pleiotropic effects are controversial [42–45]. In the current study, there were no significant differences in the changes in the LDL level between the A/L/R/E and L/R/E groups (ESM Table 2) or in the changes in the SitSBP between the A/L/R/E and A/L groups (ESM Table 3). A further large study is warranted to explore this issue. Drug compliance was not an objective of this study, and a placebo was provided to maintain the blindness of the investigators and patients. However, the combination of four effective drugs as a single pill might be helpful to enhance drug adherence, as shown by previous studies [24–26, 46].

Our study had several limitations. First, the number of patients was relatively low, and the follow-up duration was too short to observe the long-term efficacy and safety outcomes of the study drug. This limitation could be overcome by postmarketing surveillance in the future. Second, the patients were limited to the Korean population. Considering the potential differences in pharmacodynamics or kinetics among races, it may be necessary to assess this drug combination in more heterogeneous populations. Finally, the main limitation of our study is the lack of a real-world comparator arm. Although the tolerability was excellent across all three groups in the current study, the efficacy and tolerability must be further evaluated by adding a comparator group receiving individual pills.

5 Conclusion

In the present study, the A/L/R/E SPC was effective for achieving the target blood pressure and LDL-C level in patients with hypertension and dyslipidemia without significant safety issues.

Declarations

Conflict of Interest Min Chul Kim, Youngkeun Ahn, Moo Hyun Kim, Seok-Yeon Kim, Taek Jong Hong, Moo-Yong Rhee, Sang-Hyun Kim, Soon-Jun Hong, Hyungseop Kim, Weon Kim, In Ho Chae, Duk-hyun Kang, Byeong-Keuk Kim, and Hyo Soo Kim declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval This study was approved by the Institutional Review Board of each institute.

Consent to Participate Written informed consent was obtained from all participants before starting the study.

Data Availability Statement The data used and/or analyzed during the current study are available from Hanmi Pharmaceutical Company, but restrictions apply to the availability of these data, which were used under the license of the current study. Data are available from the authors upon reasonable request and with the permission of Hanmi Pharmaceutical Company.

Consent for Publication Not applicable.

Code Availability Not applicable.

Authors' Contributions Conceptualization: MCK and H-SK. Data curation; MCK, YA and H-SK. Analysis: MCK, YA and H-SK. Funding acquisition: H-SK. Investigation: MCK and H-SK. Methodology: MCK and H-SK. Project administration: YA and H-SK. Resources: MCK and H-SK. Supervision: YA, MHK, S-YK, TJH, M-YR, S-HK, HK, WK, IHC, DK, B-KK and H-SK. Validation: MCK and YA. Visualization: MCK and H-SK. Writing: MCK and H-SK. Reviewing: MCK, YA, MHK, S-YK, TJH, M-YR, S-HK, S-JH, HK, WK, IHC, DK, B-KK and H-SK. All authors read and approved the final manuscript.

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