Comparison of Fixed-dose Combinations of Amlodipine/Losartan Potassium/Chlorthalidone and Amlodipine/Losartan Potassium in Patients With Stage 2 Hypertension Inadequately Controlled With Amlodipine/Losartan Potassium: A Randomized, Double-blind, Multicenter, Phase III Study

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ABSTRACT

Purpose: The goal of this study was to compare the efficacy and safety of fixed-dose combinations of amlodipine/losartan potassium/chlorthalidone (A/L/C) and A/L in Korean patients with stage 2 hypertension inadequately controlled by A/L.

Methods: This study was an 8-week, randomized double-blind, multicenter, phase III clinical trial. Three hundred forty volunteer patients with stage 2 hypertension were randomized to receive A/L/C or A/L. The primary end point was a change in sitting systolic blood pressure (SitSBP) after 8 weeks of treatment. As secondary end points, the change in SitSBP after 2 weeks of treatment and the change in sitting diastolic blood pressure (SitDBP) were compared between treatment groups. All patients were assessed for adverse events, clinical laboratory data, and vital signs.

Findings: Of 330 patients from 33 medical centers, 328 patients who had available efficacy data were analyzed. After 8 weeks of double-blind treatment, the mean (SD) changes in SitSBP at 8 weeks were –16.4 (0.9) mm Hg and –6.9 (1.0) mm Hg in the A/L/C and A/L groups, respectively. A/L/C had a statistically superior blood pressure–lowering effect compared with that of A/L (mean [SD] difference, 9.5 [1.3] mm Hg; $P < 0.001$). The mean (SD) change in SitDBP at 8 weeks was significantly greater with A/L/C (–8.0 [0.6] mm Hg) than with A/L (–3.6 [0.6] mm Hg) ($P < .001$). In terms of the mean (SD) change in SitDBP at 2 weeks compared with baseline, A/L/C (–5.9 [0.5] mm Hg) was statistically different from A/L (–2.9 [0.5] mm Hg) ($P < .001$). Mean (SD) SitSBP change from baseline to week 2 was –13.2 (0.9) and –5.5 (0.9) in the A/L/C and A/L groups, respectively, with a statistically significant blood pressure–lowering effect ($P < 0.001$). The number of participants who achieved target blood pressure at week 8 was significantly higher in the A/L/C group (93 patients [55.7%]) than in the A/L group (48 [29.8%]) ($P < 0.001$). Adverse drug reactions were observed in 23 patients (7.0%), and the incidence of dizziness was significantly higher in the A/L/C group than in the A/L group (4.8% vs 0.6%, $P = 0.037$) There were no serious adverse events associated with the study drugs.

Implications: The results of this study suggest that A/L/C had a significantly increased blood pressure–lowering efficacy compared with that of A/L and had a good safety profile. ClinicalTrials.gov identifier: NCT02916602. (*Clin Ther.* 2017;39:2049–2060) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: amlodipine, chlorthalidone, hypertension, losartan, single-pill combination.

INTRODUCTION

Hypertension (HTN) is a major risk factor for cardiovascular diseases and chronic kidney disease, with a prevalence rate of 25% to 45%.[1,2] Previous trials have found that antihypertensive drug treatment improves cardiovascular outcomes.[3,4] Unfortunately, of the individuals who have HTN, only 25% to 75% are aware of it, and only 11% to 66% are receiving treatment.[5] In addition, the control rate of HTN with antihypertensive medications varies widely from 5% to 58%.[6,7]

Proper blood pressure (BP) control at an early stage is essential for high-risk patients with HTN. However, unless it is mild, HTN is not easily controlled with only a single agent. The 2013 European Society of Hypertension/European Society of Cardiology guideline recommends the use of 2 antihypertensive drugs in patients with a high cardiovascular risk.[3] In addition, the 2014 HTN guideline from the Joint National Committee 8 recommended the initial use of 2 antihypertensive drugs among the thiazide-type diuretic, angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), and calcium channel blocker (CCB) classes in patients with systolic BP >160 mm Hg or diastolic BP >100 mm Hg.[8] Instead of >2 pills of antihypertensive drugs, fixed-dose combinations of 2 antihypertensive drugs in a single tablet are recommended because these combinations minimize inconveniences, improve adherence, and consequently increase the BP control rate.[9,10] In this context, various types of fixed-dose combinations have recently been developed and used, revealing improved patient adherence with their convenient regimen.

If target BP is not achieved with 2 drugs, adding a third drug should be considered. The combination of amlodipine (CCB), losartan (ARB), and chlorthalidone (thiazide-type diuretic) (A/L/C) is recommended in the guidelines.[11] Losartan is the first ARB to be introduced for the treatment of HTN and is an active, long-lasting angiotensin II receptor type 1 antagonist.[12] Amlodipine blocks calcium channels located on vascular smooth muscle and causes vasodilation.[13] Chlorthalidone is a thiazide-type diuretic, which differs chemically from thiazide diuretics. The diuretic effect of chlorthalidone occurs in approximately 2.6 hours, and it has a prolonged action of 48 to 72 hours and a mean half-life o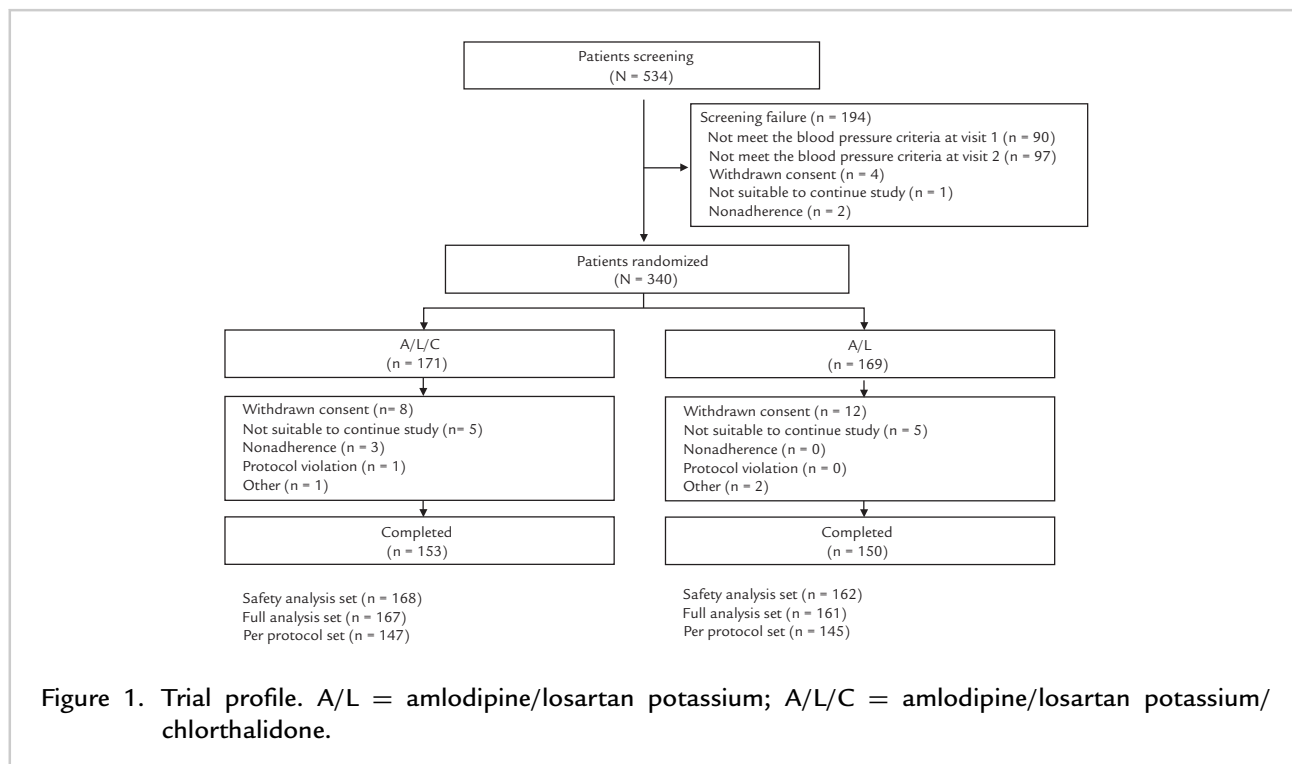f 50 to 60 hours.[14] A major portion of the drug is excreted unmetabolized by the kidneys. In the 2011 National Institute for Health and Care Excellence HTN guideline, chlorthalidone was recommend over hydrochlorothiazide.[11] Chlorthalidone had better BP-lowering effects than hydrochlorothiazide.[15] In addition, chlorthalidone had cardiovascular risk reduction in the ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), MRFIT (Multiple Risk Factor Intervention Trial), and HDFP (Hypertension Detection and Follow-up Program) studies.[16–18] Consequently, the addition of chlorthalidone is expected to have a good efficacy and safety profile in patients with HTN inadequately controlled with amlodipine/losartan potassium (A/L). The objective of this 8-week, double-blind, multicenter, randomized, phase III study was to compare the efficacy and safety of fixed-dose combination of A/L/C) with that of A/L in Korean patients with stage 2 HTN that is inadequately controlled by A/L.

PATIENTS AND METHODS
Study Patients

Korean men and women aged ≥19 years with essential HTN were eligible for participation in the study. Both previously treated and untreated patients were included. A total of 534 patients were screened for inclusion in the study. Patients (n = 194) who could not fulfill the inclusion criteria or satisfied any of the exclusion criteria were excluded. The eligible patients were included in the study from May 2015 through September 2016 (Figure 1). To be included in the study, previously untreated patients were required to have a sitting systolic BP (SitSBP) of ≥160 and <200 mm Hg. Previously treated patients were required to have a SitSBP of ≥140 and <200 mm Hg. SitBP was measured 3 times from each arm, and the arm with the higher mean BP was selected.

We excluded patients with resistant HTN who were taking more than 4 drugs or who had unstable angina pectoris, myocardial infarction, cerebrovascular disease, or uncontrolled arrhythmia within the past 6 months. Patients with a minimum-maximum difference of ≥20 mm Hg in SitSBP or ≥10 mm Hg in sitting diastolic BP (SitDBP) in the chosen arm at screening were excluded. Patients were also excluded if they had secondary HTN, heart failure (New York

Figure 1. Trial profile. A/L = amlodipine/losartan potassium; A/L/C = amlodipine/losartan potassium/ chlorthalidone.

Heart Association class III-IV), significant valvular heart disease, uncontrolled diabetes mellitus (glycosylated hemoglobin level ≥9%), type 1 diabetes mellitus, hepatic dysfunction (serum aspartate or alanine aminotransferase levels >3 times the upper limit of normal), serum creatinine level ≥2.0 mg/dL, anuria, shock, symptomatic hyperuricemia, untreated Addison disease, symptomatic orthostatic hypotension, connective tissue diseases, gastrointestinal disorder (such as Crohn disease), alcohol abuse, significant electrolyte imbalance, or known hypersensitivity to amlodipine, losartan, chlorthalidone, dihydropyridine, angiotensin II receptor blocker classes, thiazide diuretics, or sulfonamides. The use of antihypertensive medications other than the study agents, oral steroids, nonsteroidal anti-inflammatory drugs, cytotoxic agents, or antipsychotic agents was not permitted during the study. Pregnant women, breastfeeding women, and women of childbearing potential who were not using appropriate contraception were also excluded from the study. Any patient with a condition that, in the opinion of the investigator, would make his/her participation in this study unsafe or unsuitable was excluded. All patients were not permitted to participate in other clinical trials.

Study Design

This was an 8-week, randomized, double-blind, multicenter, phase III clinical trial conducted at 33 sites in Korea. The Korean Food and Drug Administration and the Institute Review Board of each hospital approved the study protocol. The study was conducted in accordance with the ethical principles of the current Declaration of Helsinki, and participants or their legal guardians signed informed consent forms before any relevant laboratory tests were conducted. In the initial 4-week run-in period (period 1), all patients received a fixed-dose combination of A/L 5/50 mg/d via open label. At randomization (visit 2, day 0), patients with SitSBP ≥140 mm Hg were reevaluated to determine whether they still met the inclusion/exclusion criteria. Patients were excluded if they had severe HTN (SitSBP ≥200 mm Hg or SitDBP ≥120 mm Hg). Participants were randomly assigned to receive A/L/C 5/50/12.5 mg or A/L 5/50 mg and then entered the 2-week, double-blind treatment period (period 2). Participants were randomly assigned to each treatment group in a 1:1 ratio via an interactive web response system using a stratified randomization method. The dose was not adjusted during the 2-week treatment period, and participants in all groups received 2 tablets (the real medicine and

a matched placebo of the other drug; Hanmi Pharma Co, Seoul, Korea) once a day in the morning to maintain double-blinding. After the 2-week treatment period, the doses were escalated to A/L/C 5/100/25 mg or A/L 5/100 mg for an additional 6 weeks (period 3), and participants in all groups received 2 tablets of the real medicine and a matched placebo. Participants were required to have a medication adherence of ≥80% throughout the trial, and those with an adherence <80% were considered to have poor adherence.

End points and Safety Assessment

The primary end point was to evaluate the efficacy of fixed-dose combinations of A/L/C and A/L by comparing the mean change from baseline in SitSBP after 8 weeks of treatment. The secondary end points compared (1) the mean change from baseline in SitDBP after 2 and 8 weeks of treatment, (2) the mean change from baseline in SitSBP after 2 weeks of treatment, and (3) the BP response rate, which was defined as the percentage of patients who achieved the target BP (SitSBP/DBP <140/90 mm Hg) after 2 and 8 weeks of treatment. For the efficacy analysis, data from the full analysis set population were used.

Safety assessments included monitoring and recording all laboratory tests, vital signs, adverse events (AEs), serious AEs, and possible association with the study. All laboratory tests, including blood tests, urinalysis, serum biochemistry, and pregnancy tests, were analyzed in the laboratory of each participating center during all periods of the study. Adverse drug reactions (ADRs) were defined as drug-related AEs only if they were definitely related, probably related, or possibly related to the study drugs or unknown. AEs that were probably not related or definitely not related were not considered drug-related AEs. Laboratory AEs were assessed by comparing baseline laboratory values with those at follow-up. The severity of AEs was classified as mild for mild symptoms or those that did not affect daily activities, moderate for symptoms that produced minor limitations of daily activities, and severe for symptoms that produced marked limitations of daily activities. The investigators at each center decided whether patients with drug-related AEs should be withdrawn from the study.

Statistical Analysis

Data are expressed as the mean (SD) for continuous variables and as number (percentage) of patients for categorical variables. The Pearson χ^2 tests or Fisher exact tests were used for categorical variables, and unpaired t tests or Wilcoxon rank sum tests were used for continuous variables. The effects of treatments on the primary and secondary end points (except BP control rate) were compared using ANCOVA, with baseline BP as covariate. End points were expressed as least-squares mean (SE) for the continuous variables. BP control rate were analyzed using the Pearson χ^2 test. The full analysis set included all randomized patients who received at least one dose of double-blind study medication during periods 2 and 3 and provided at least one SitSBP measurement after randomization in periods 2 and 3. The sample size of the study was determined based on the estimation of the primary end point of SitSBP obtained in a previous trial.[19] We assumed that the decrease in SitSBP by adding chlorthalidone would be 4.9 (13.0) mm Hg. Using a 2-sided test for differences with an α level of 0.05, we calculated that 148 patients in each group would have to undergo randomization for the study to have a 90% power to detect a difference in SitSBP between the 2 groups; therefore, we enrolled 164 patients in each group to account for 10% loss. $P < .05$ was considered statistically significant. SAS software, version 9.4 (SAS Institute, Cary, North Carolina) was used for statistical analysis.

RESULTS
Patient Disposition and Baseline Characteristics

Five hundred thirty-four patients were screened in the beginning of the study, and 90 patients who did not meet the inclusion criteria were excluded before the run-in period and 104 patients before randomization. Ninety-seven patients among the 104 patients had HTN controlled with A/L and were excluded. Three hundred forty patients were randomly assigned to receive A/L/C (n = 171) or A/L (n = 169) (Figure 1). After excluding 10 patients who were coassigned to other trials, 330 patients were analyzed for safety profile. For efficacy profile, 328 patients, excluding 2 patients whose BP had never been measured during the trial, were analyzed as a full analysis set. Of the randomized patients, there were

37 dropout patients, and the remaining 303 patients completed the study. The demographic and baseline clinical characteristics of patients in the 2 treatment groups are summarized in Table I. Baseline patient characteristics of sex, mean age, weight, height, diabetes mellitus, and medications on admission were similar between the 2 groups. No significant differences were found between the groups in baseline SitSBP and SitDBP. Median drug adherence of A/L/C and A/L was 100%.

Efficacy

After 8 weeks of double-blind treatment, the mean (SE) changes in SitSBP relative to baseline SitSBP were –16.4 (0.9) mm Hg and –6.9 (1.0) mm Hg in the A/L/C and A/L treatment groups, respectively (Table II and Figure 2). A/L/C had a statistically superior BP-lowering effect compared with that of A/L (mean [SE] difference, 9.5 [1.3] mm Hg; $P < 0.001$). In the per-protocol set analysis, the adjusted mean (SE) SitSBP at 8 weeks compared

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

Characteristic[*]	A/L/C (n = 167)	A/L (n = 161)	Total (N = 328)	P
Sex, no. (%)				
Male	132 (79.0)	129 (80.1)	261 (79.6)	0.808[†]
Female	35 (21.0)	32 (19.9)	67 (20.4)	
Age, y				
Mean (SD)	59.3 (11.3)	61.2 (10.9)	60.2 (11.1)	0.085[‡]
Range	22–80	25–79	22–80	
Weight, kg				
Mean (SD)	74.1 (12.7)	71.9 (11.7)	73.0 (12.2)	0.087[‡]
Range	49.0–132.0	50.0–115.0	49.0–132.0	
Height				
Mean (SD)	166.5 (8.0)	166.1 (8.0)	166.3 (8.0)	0.431[‡]
Range	146.0–188.0	134.6–185.0	134.6–188.0	
Smoker, no. (%)				
Current smoker	37 (22.2)	23 (14.3)	60 (18.3)	0.182[†]
Never smoker	87 (52.1)	93 (57.8)	180 (54.9)	
Ex-smoker	43 (25.8)	45 (28.0)	88 (26.8)	
Drinker, no. (%)				
Current drinker	106 (63.5)	98 (60.9)	204 (62.2)	0.886[†]
Never drinker	53 (31.7)	55 (34.2)	108 (32.9)	
Ex-drinker	8 (4.8)	8 (5.0)	16 (4.9)	
SitSBP, mm Hg				
Mean (SD)	150.8 (10.1)	150.6 (9.0)	150.7 (9.6)	0.670[‡]
Range	140.0–183.7	139.7–182.0	139.7–183.7	
SitDBP, mm Hg				
Mean (SD)	92.9 (8.5)	91.9 (7.6)	92.4 (8.1)	0.246[‡]
Range	71.7–114.0	75.7–113.3	71.7–114.0	
Previous use of antihypertensives, no. (%)	138 (82.6)	135 (83.9)	273 (83.2)	0.768[†]
Type 2 diabetes mellitus, no. (%)	28 (16.8)	28 (17.4)	56 (17.1)	0.881[†]

A/L = amlodipine/losartan potassium; A/L/C = amlodipine/losartan potassium/chlorthalidone; SitDBP = sitting diastolic blood pressure; SitSBP = sitting systolic blood pressure.
[*]Percentages are based on the subjects within each treatment group. Age is the age on the date of informed consent.
[†]Pearson χ^2 test.
[‡]Wilcoxon rank sum test.

Table II. Changes from baseline in blood pressure after treatment with fixed-dose combinations of A/L/C and A/L potassium in patients with stage 2 hypertension.

Variable	A/L/C (n = 167)	A/L (n = 161)
SitSBP, mm Hg		
Baseline (week 0)	150.8 (10.1)	150.6 (9.0)
At week 2	137.5 (12.6)	145.1 (12.7)
Change from baseline, LS mean (SE)	−13.2 (0.9)	−5.5 (0.9)
Difference vs A/L	−7.8 (1.3)	–
95% CI	−10.3 to −5.2	–
P vs A/L	<0.001	–
End of treatment (week 8)	134.4 (12.5)	143.8 (13.5)
Change from baseline, LS mean (SE)	−16.4 (0.9)	−6.9 (1.0)
Difference vs A/L	−9.5 (1.3)	–
95% CI	−12.1 to −6.9	–
P vs A/L	<0.001	–
SitDBP, mm Hg		
Baseline (week 0)	92.9 (8.5)	91.9 (7.6)
At week 2	86.9 (8.7)	89.2 (8.4)
Change from baseline, LS mean (SE)	−5.9 (0.5)	−2.9 (0.5)
Difference vs A/L	−3.0 (0.7)	–
95% CI	−4.5 to −1.5	–
P vs A/L	<0.001	–
End of treatment (week 8)	84.8 (8.6)	88.4 (9.5)
Change from baseline, LS mean (SE)	−8.0 (0.6)	−3.6 (0.6)
Difference vs A/L	−4.3 (0.8)	–
95% CI	−5.9 to −2.7	–
P vs A/L	<0.001	–

A/L = amlodipine/losartan potassium; A/L/C = amlodipine/losartan potassium/chlorthalidone; LS, least squares; SitDBP = sitting diastolic blood pressure; SitSBP = sitting systolic blood pressure.

with at baseline was −17.8 (1.0) mm Hg and −7.3 (1.0) mm Hg in the A/L/C and A/L groups, respectively ($P < 0.001$).

As the secondary end point, the mean (SE) SitDBP change at 8 weeks was significantly greater in the A/L/C group (−8.0 [0.6] mm Hg) than in the A/L group (−3.6 [0.6] mm Hg) ($P < 0.001$) (Table II and Figure 3). In terms of the change in mean SitDBP at 2 weeks relative to baseline SitDBP, there was a significant difference between the A/L/C group (−5.9 [0.5] mm Hg) and the A/L/ group (−2.9 [0.5] mm Hg) ($P < 0.001$). The mean (SE) SitSBP change from baseline to week 2 was −13.2 (0.9) and −5.5 (0.9) in the A/L/C and A/L groups, respectively, with a statistically significant BP-lowering effect ($P < 0.001$).

The number of participants who achieved target BP at week 8 was significantly more in the A/L/C group (93 patients [55.7%]) than in the A/L group (48 [29.8%]) ($P < 0.001$).

Safety Profile

Among the 330 patients in the safety profile set, 65 patients (19.7%) experienced at least one AE after randomization, and ADRs were reported in 23 patients (7.0%) (Table III). The most common ADR was dizziness, followed by constipation, increased blood uric acid, headache, and hypotension. The incidence of dizziness was significantly higher in the A/L/C group than in the A/L group (4.8% vs. 0.6% in ADRs, $P = 0.037$). Gastrointestinal disorders,
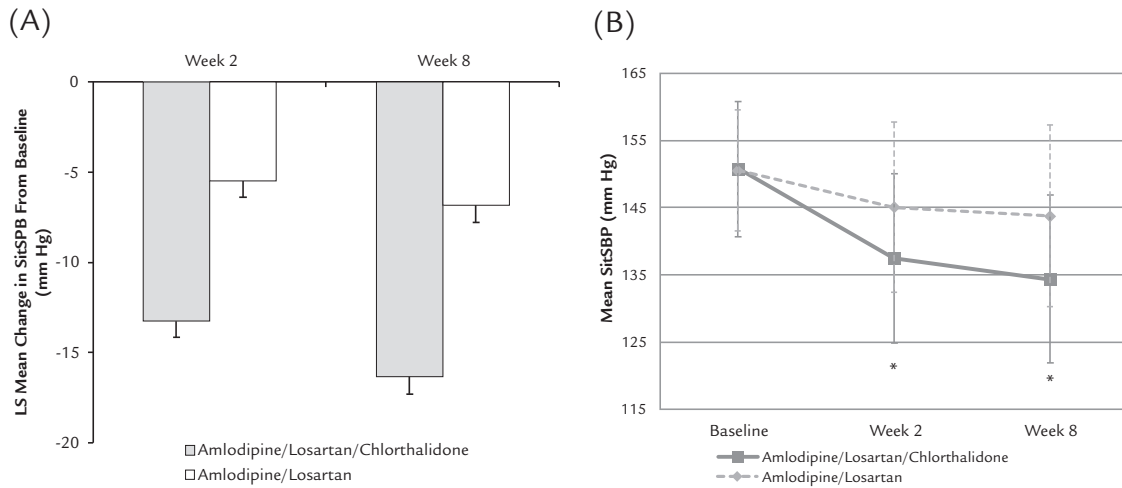
Figure 2. Mean sitting systolic blood pressure (SitSBP) changes from baseline through 8-week follow-up in the full analysis population. (A) Comparison of least-squares (LS) mean SitSBP changes at 2 and 8 weeks. B, Mean SitSBP from baseline to 8 weeks. Error bars indicate SD. $^{*}P < 0.001$.

consisting of abdominal distension, constipation, dyspepsia, epigastric discomfort, and esophagitis, developed more in the A/L/C group than in the A/L group in terms of treatment-emergent AEs (4.8% vs 0.6%, $P = 0.037$) but not in ADRs (1.2% vs 0%, $P = 0.499$). Although one serious AE of arthralgia was noted in the A/L/C group, it was probably not related to the study drug. However, there were no significant differences in other AEs or in weight, pulse,

electrocardiogram, and laboratory findings between the groups. Two patients were dropped from the study, and both were from the A/L/C group. One patient was dropped because of developing atrial fibrillation, which was probably related to the investigational product administration. The second patient was dropped because of mild elevations of uric acid and cholesterol, which were definitely not related to the investigational product administration.
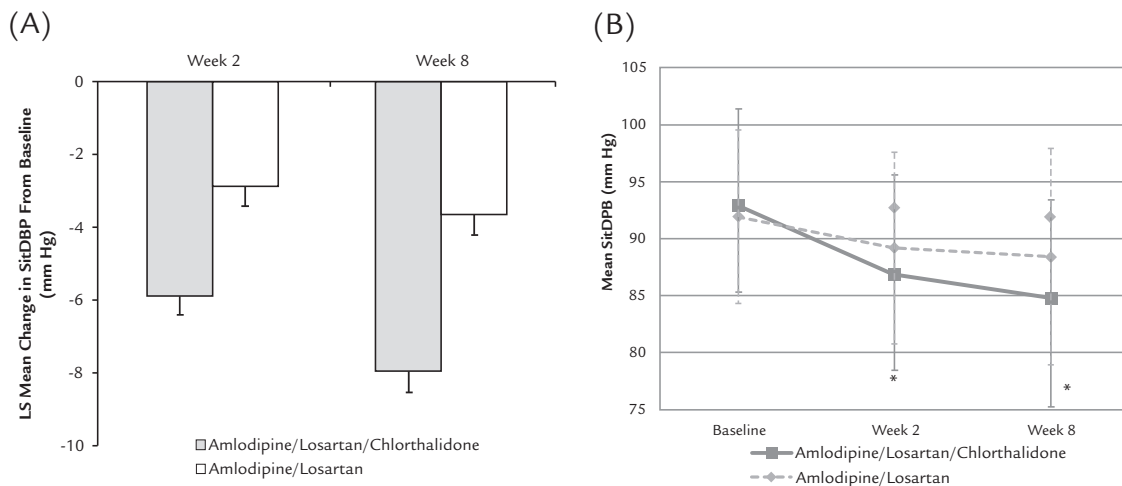

Figure 3. Mean sitting diastolic blood pressure (SitDBP) changes from baseline through 8-week follow-up in the full analysis population. (A) Comparison of least-squares (LS) mean SitDBP changes at 2 and 8 weeks. (B) Mean SitDBP from baseline to 8 weeks. Error bars indicate SD. $^{*}P < 0.001$.

Table III. Comparison of AEs between the treatment groups.[*]

Variable	A/L/C (n = 168)	A/L (n = 162)	Total (N = 330)	P[†]
AEs				
Total	39 (23.2)	26 (16.1)	65 (19.7)	0.102
Intensity				0.089
Mild	33 (19.6)	23 (14.2)	56 (17.0)	
Moderate	5 (3.0)	3 (1.9)	8 (2.4)	
Severe	1 (0.6)	0 (0.0)	1 (0.3)	
Patients with any serious AEs	1 (0.6)	0 (0.0)	1 (0.3)	0.509
Serious AE type				
Arthralgia	1 (0.6)	0 (0.0)	1 (0.3)	0.509
ADRs				
Patients with any ADRs	16 (9.5)	7 (4.3)	23 (7.0)	0.064
Gastrointestinal disorders	2 (1.2)	0 (0.0)	2 (0.6)	0.499
Constipation	2 (1.2)	0 (0.0)	2 (0.6)	0.499
General disorders and administration site conditions	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Asthenia	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Investigations	1 (0.6)	3 (1.9)	4 (1.2)	0.364
Blood creatinine increased	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Blood uric acid increased	1 (0.6)	1 (0.6)	2 (0.6)	0.999
Liver function test increased	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Metabolism and nutrition disorders	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Hypertriglyceridemia	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Nervous system disorders	10 (6.0)	1 (0.6)	11 (3.3)	0.007
Dizziness	8 (4.8)	1 (0.6)	9 (2.7)	0.037
Headache	2 (2.0)	0 (0.0)	2 (0.6)	0.499
Paresthesia	1 (0.6)	0 (0.0)	1 (0.3)	0.999
Psychiatric disorders	1 (0.6)	0 (0.0)	1 (0.3)	0.999
Insomnia	1 (0.6)	0 (0.0)	1 (0.3)	0.999
Renal and urinary disorders	1 (0.6)	0 (0.0)	1 (0.3)	0.999
Pollakiuria	1 (0.6)	0 (0.0)	1 (0.3)	0.999
Vascular disorders	2 (1.2)	1 (0.6)	3 (0.9)	0.999
Flushing	0 (0.0)	1 (0.6)	1 (0.3)	0.491
Hypotension	2 (1.2)	0 (0.0)	2 (0.6)	0.499

ADR = adverse drug reaction; AE = adverse event; A/L = amlodipine/losartan potassium; A/L/C = amlodipine/losartan potassium/chlorthalidone.

[*]A patient is counted once at the maximum severity if the patient reported one or more events. Percentages are based on the patients within each treatment group. None of the serious AEs are considered related to the antihypertensive treatment.

[†]Pearson χ^2 test or Fisher exact test.

DISCUSSION

This was a confirmatory clinical trial to compare fixed-dose combinations of A/L/C and A/L in patients with stage 2 HTN inadequately controlled with A/L.

In this multicenter, randomized, double-blind, 8-week, phase III study, the addition of chlorthalidone to A/L increased BP-lowering efficacy compared with that of A/L without increasing overall AEs. There was a dose-

escalating effect of A/L/C. After 2 weeks of treatment with A/L/C 5/50/12.5 mg, the dose escalation to A/L/C 5/100/25 mg from 2 to 8 weeks had an additional BP-lowering efficacy (Tables II and Figures 2 and 3). Remarkably, with the combination of A/L/C, we can expect an increase in the BP response rate of approximately 56% in A/L combination therapy–resistant patients with HTN.

In treating HTN, a major problem is poor treatment adherence. To increase the adherence rate for HTN, fixed-dose combinations of antihypertensive drugs, reducing the necessary number of pills, should be considered.[9,20,21] Furthermore, combining medications offers an additive BP-lowering effect via different mechanisms.[22] Various types of fixed-dose combinations have been developed recently to improve patient adherence. Among the various combinations of antihypertensive medications, renin-angiotensin system inhibitors and CCBs are most commonly used for fixed-dose combination therapy. A combination of ARB and CCB is particularly effective for decreasing BP and is recommended particularly in Asians because ARBs have fewer AEs than ACEis do in this population.[23–25] The incidence of cough has been reported to be >2-fold higher in East Asian patients than in white patients; thus, ACEis are rarely prescribed to control BP in Korea or other East Asian countries.[26] Among various ARBs, losartan-based combination therapies could effectively reduce BP and improve cardiovascular events.[27] Amlodipine is a dihydropyridine class CCB that reduces peripheral vascular resistance, resulting in reduced BP. It is the most frequently used CCB in the fixed-dose combination of a CCB and an ARB. Furthermore, dose-dependent adverse effects of amlodipine, such as ankle edema, can be reduced by combining it with an ARB.[28,29] Chlorthalidone affects the distal convoluted tubule of the nephron, producing diuretic effects. Although head-to-head comparisons of cardiovascular outcomes between chlorthalidone and hydrochlorothiazide have not been conducted, a few studies have suggested that chlorthalidone has superior efficacy compared with that of hydrochlorothiazide.[17] In addition to the MRFIT study, which was the first study to suggest clinical benefits of chlorthalidone, chlorthalidone had higher efficacy to reduce BP in another study.[30] Although there has been no report of a direct comparison with other triple antihypertensive therapies, we believe that the A/L/C combination has an efficacy that is comparable to that of other triple antihypertensive therapies.

The results of this study revealed superior efficacy of the A/L/C triple combination therapy compared with that of the A/L dual combination therapy. Furthermore, dose escalation of A/L/C 5/50/12.5 mg to A/L/C 5/100/25 mg produced additive BP-lowering effects. The mean changes of SitSBP/SitDBP were –13.2/–5.9 (0.9/0.5) mm Hg from baseline to 2 weeks and –16.4/–8.0 (0.9/0.6) mm Hg from baseline to 8 weeks (Table II and Figures 2 and 3). Considering the efficacy and dose escalation effect, the control rate of HTN was significantly higher with triple combination therapy than with dual combination therapy at 8 weeks. In addition, triple combination of A/L/C was tolerable. Overall, 25 ADRs were reported by 23 patients (7.0%) among the 330 participants in the safety profile set, including 18 cases by 16 participants (9.5%) in the A/L/C group and 7 cases by 7 participants (4.3%) in the A/L group. These ADRs were all mild or moderate. Among the ADRs reported in the present study, dizziness is a major AE of A/L/C. A causal relationship between dizziness and the investigational product could not be ruled out. In a previous study, the occurrence rate of dizziness was 7.7% in triple antihypertensive therapy.[31] The incidence rate of dizziness was slightly lower in the present study, with 8 patients (4.8%) in the A/L/C group. Although there is no report of a direct comparison with other triple antihypertensive therapies, we believe that the A/L/C combination has an advantage in terms of its tolerability. In addition, we found that rapid up-titration of A/L/C can be effectively administered. Because delaying the time to BP control is one of the risk factors for cardiovascular AEs, quick and adequate BP control is essential.[32] In this regard, fixed-dose, single-pill combinations have an additional efficacy by improving drug adherence. Triple combination therapy of A/L/C, therefore, has sufficient efficacy and tolerability for patients with HTN inadequately controlled with dual combination therapy.

The present study has a few limitations. Although this study was adequately powered to compare BP-lowering efficacy between the 2 groups, the size of the study population was relatively small for confirming tolerability. Because this study was confined to Korean patients with HTN, extrapolation of our results to other ethnic background should be made cautiously. However, in

consideration that there were no reports of ethnic differences in ARBs, the administration of A/L/C should have same effects in other ethnics.

CONCLUSIONS
The fixed-dose combination of A/L/C was effective in treating patients with stage 2 HTN inadequately controlled with A/L. The tolerability of combined A/L/C treatment was comparable to that of A/L.

CONFLICTS OF INTEREST
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