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Comparison of efficacy and safety between third-dose triple and third-dose dual antihypertensive combination therapies in patients with hypertension

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Abstract

We compared the efficacy and safety of third-standard-dose triple and third-standard-dose dual antihypertensive combination therapies in patients with mild to moderate hypertension. This was a phase II multicenter, randomized, double-blind, parallel-group trial. After a 4-week placebo run-in period, 245 participants were randomized to the third-dose triple combination (ALC group; amlodipine 1.67 mg + losartan potassium 16.67 mg + chlorthalidone 4.17 mg) or third-dose dual combination (AL group; amlodipine 1.67 mg + losartan potassium 16.67 mg, LC group; losartan potassium 16.67 mg + chlorthalidone 4.17 mg, AC group; amlodipine 1.67 mg + chlorthalidone 4.17 mg) therapy groups and followed up for 8 weeks. The mean systolic blood pressure (BP) reduction was -18.3 ± 13.2, -13.0 ± 13.3, -16.3 ± 12.4, and -13.8 ± 13.2 mmHg in the ALC, AL, LC, and AC groups, respectively. The ALC group showed significant systolic BP reduction compared to the AL and AC groups at weeks 4 ($P = .010$ and $P = .018$, respectively) and 8 ($P = .017$ and $P = .036$, respectively). At week 4, the proportion of systolic BP responders was significantly higher in the ALC group (42.6%) than in the AL (22.0%), LC (23.3%), and AC (27.1%) groups ($P = .013$, $P = .021$, and $P = .045$, respectively). At week 8, the proportion of systolic and diastolic BP responders was significantly higher in the ALC group (59.7%) than in the AL (39.3%) and AC (42.4%) groups ($P = .022$ and $P = .049$, respectively) at week 8. Third-standard-dose triple antihypertensive combination therapy demonstrated early effective BP control compared to third-standard-dose dual combination therapies, without increasing adverse drug reactions in patients with mild-to-moderate hypertension.

KEYWORDS
combination therapy, hypertension, low-dose

1 | INTRODUCTION

High blood pressure (BP) is the most important risk factor for cardiovascular disease. However, the current global treatment rate is less than 40% in men and less than 50% in women. Moreover, the global control rate of hypertension is approximately 20%.[1] Many barriers such as physicians, patients, and system factors, contribute to poor BP control. Therapeutic inertia, failure of physicians to initiate or intensify antihypertensive medication in patients with high or uncontrolled BP, frequently prevents proper management of hypertension.[2] Adverse drug reactions (ADRs), poor BP control, and high pill burden unfavorably affect patients' confidence in the management of hypertension and lead to patient discontinuation of medication.[3] In low-income countries, limited access to healthcare systems and medication are problems causing poor BP control.

Considering the complex mechanism of hypertension and individual variability in response to antihypertensive drugs, it is difficult to properly control BP using a single antihypertensive drug.[4] The stepped-care approach of up-titrating monotherapy takes time to reach optimal BP, and high doses of a single antihypertensive drug cause more adverse events.[5,6] Therefore, recent guidelines recommend a simplified regimen using single-pill combinations with different classes of antihypertensive drugs rather than monotherapy as an initial treatment to achieve early BP control and better long-term adherence to prescribed medication.[7,8] Despite guidelines recommendations, an initial monotherapy strategy remains common, and concerns about ADRs associated with standard dose combinations, such as excessive BP lowering, are barriers to optimal BP control.[9]

These obstacles can be overcome using single-pill combinations of low-dose antihypertensive drugs. In several studies and meta-analyses, combinations of low-dose antihypertensive drugs showed promise in minimizing side effects while exerting the desired BP-lowering effect.[9–11] In this context, we planned to develop low-dose triple antihypertensive combination therapy as the first-line therapy (HM-APOLLO project). As a first step, a phase II study (HM-APOLLO-201, NCT03897868) was conducted to determine the appropriate doses of low-dose triple combinations of antihypertensive drugs as the initial therapy for patients with mild-to-moderate hypertension. We selected a combination of third-standard-dose triple antihypertensive drugs

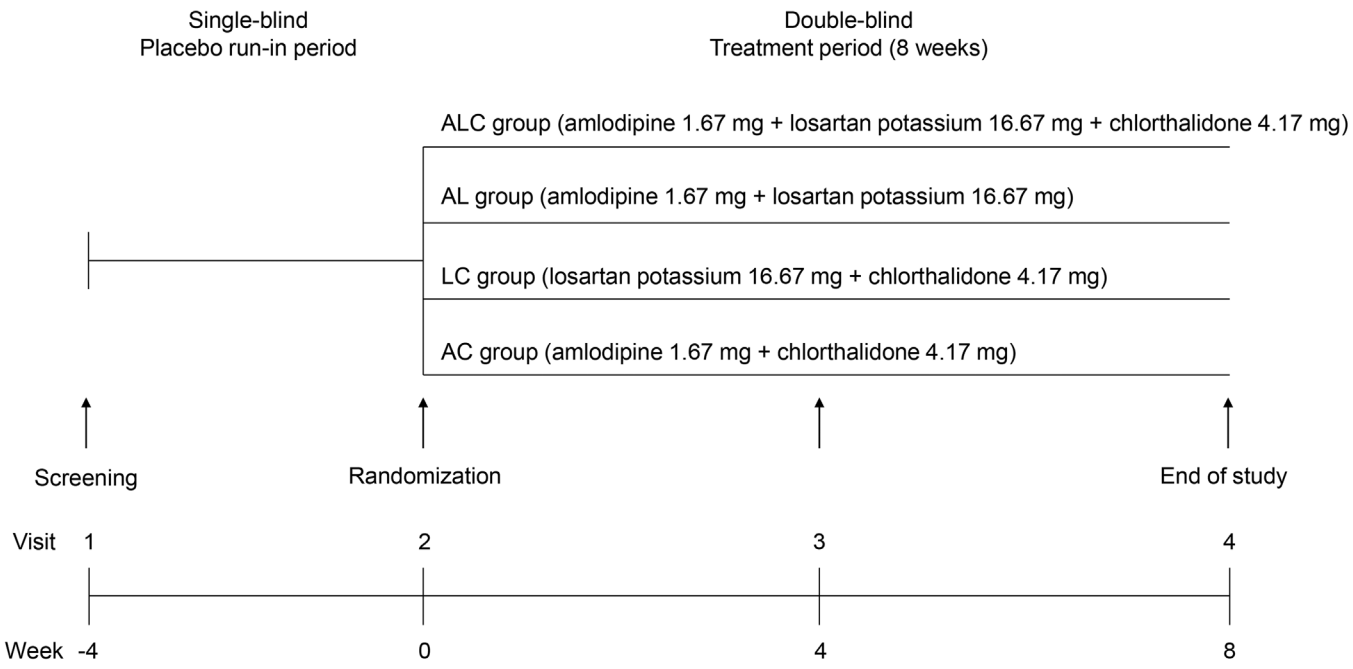

FIGURE 1 Study flow.

(amlodipine 1.67 mg, losartan 16.67 mg, and chlorthalidone 4.17 mg) based on the results of the HM-APOLLO-201 study.[12]

This phase II study (HM-APOLLO-202) aimed to evaluate the contributing effect of each component drug within a fixed combination of third-standard-dose triple antihypertensive drugs according to the scientific guidelines for clinical development of fixed combination medical products from the European Medical Agency.[13] The BP-lowering efficacy of third-standard-dose triple combination therapy was compared with that of third-standard-dose dual combination therapy in patients with mild-to-moderate hypertension.

2 | METHODS

2.1 | Study design

This phase II study was a multicenter, randomized, double-blind, parallel-group trial. This study was conducted in 23 hospitals in the Republic of Korea. The study protocol and informed consent form were approved by the regulatory authority of the Korean Ministry of Food and Drug Safety and the Institutional Review Board of each participating institution (Supplements). Figure 1 illustrates the flow of the study. After a 4-week placebo run-in period, 245 participants were randomized to the third-standard-dose triple combination (ALC group: amlodipine 1.67 mg + losartan potassium 16.67 mg + chlorthalidone 4.17 mg) and third-standard-dose dual combination (AL group: amlodipine 1.67 mg + losartan potassium 16.67 mg, LC group: losartan potassium 16.67 mg + chlorthalidone 4.17 mg, or AC group: amlodipine 1.67 mg + chlorthalidone 4.17 mg) therapy groups and followed up for 8 weeks. We selected combinations of third-standard dose amlodipine, losartan potassium, and chlorthalidone, which had been proven effective in the previous phase II study.[12] At the screening visit (visit 1), participants who satisfied the inclusion/exclusion criteria participated in a 4-week placebo run-in period. At the randomization visit (visit 2), participants who satisfied the eligibility criteria were randomly allocated to one of the four treatment groups and administered the assigned study drug for 8 weeks. This trial has been registered at ClinicalTrials.gov (NCT04959305).

2.2 | Study population

Participants were eligible if they were aged ≥19 years and had a mean sitting systolic BP (SBP) < 180 mmHg and mean sitting diastolic BP (DBP) < 110 mmHg for participants who were already taking antihypertensive drugs or the mean sitting SBP ≥140 to < 180 mmHg and mean sitting DBP < 110 mmHg for participants who were not taking antihypertensive drugs at screening (visit 1). After the 4-week run-in period, participants with a mean sitting SBP ≥140 to < 180 mmHg and mean sitting DBP < 110 mmHg were randomized into 4 different groups (Visit 2). The important exclusion criteria were as follows: a difference > 20 mmHg for the mean sitting SBP or 10 mmHg for the mean sitting DBP between the two arms; confirmed or suspected secondary hypertension; use of three or more classes of antihypertensive drugs within 4 weeks of visit 1 or the necessity of taking contraindicated medication during the trial period; serious cardiovascular or ischemic heart disease within 6 months before the trial; severe heart disease (New York Heart Association class III-IV heart failure); clinically significant renal (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) or hepatic diseases (aspartate transaminase or alanine transaminase level > 3 times the upper limit of normal); a history of hypersensitivity to amlodipine, losartan, chlorthalidone, dihydropyridines, angiotensin

II receptor blockers, or thiazide diuretics; and women who were pregnant, breastfeeding, or of childbearing age unwilling to practice adequate contraception throughout the study. Participants with a mean sitting SBP ≥180 mmHg or DBP ≥110 mmHg, at any visit after randomization and/or with a mean sitting SBP < 100 mmHg or DBP < 60 mmHg, at any visit during the study were withdrawn. The online supplement contains additional exclusion and withdrawal criteria[12] All participants provided written informed consent prior to participation in the study.

2.3 | Randomization and masking

Participants were randomly assigned to one of the four treatment groups at a 1:1:1:1 ratio. Randomization was stratified based on sitting SBP (< 160 or ≥160 mmHg at visit 2). Participants were randomly assigned centrally using an interactive web response system. The randomization list was generated using the PROC PLAN procedure in SAS software (version 9.4; SAS Institute, Cary, North Carolina, USA) and contained information about the study drug administration group to which each patient was allocated according to their randomization number.

The participants, investigators, clinical research pharmacists at each institution, and sponsors were masked to the assigned drugs until the end of the study. The combination drugs and placebo were manufactured as finished pharmaceutical products by Hanmi Pharmaceutical Co. Ltd. A placebo was used to maintain a double-blind status, and participants were administered a total of two tablets of the study drug and a placebo once daily. All study drugs were prepared and packaged at a manufacturing facility licensed with Good Manufacturing Practice certification by the Korean Ministry of Food and Drug Safety.

2.4 | Study procedure

During the 4-week run-in period, one placebo tablet was administered daily to all the participants in a single-blinded manner. During the 8-week treatment period, all participants were instructed to take the assigned study drug once daily every morning for the duration of the study period. During the treatment period, each participant visited the clinical trial institution at weeks 0 (visit 2), 4 (visit 3), and 8 (visit 4) to assess efficacy and safety. At each visit, participants were instructed to refrain from taking the study drug in the morning before trough BP measurement. Office BP was measured by trained study personnel at each clinical trial center by using an electronic sphygmomanometer (WatchBP Office AFIB, Microlife, Taipei, Taiwan) on the morning of each visit.

The online supplement contains the detailed methods of BP measurements. BP was measured twice in both arms simultaneously at 2-min intervals, and the mean value of the two measurements was used. If the difference between two consecutively obtained readings of sitting SBP was > 5 mmHg, the measurement was repeated. BP values with a difference in sitting SBP within 5 mmHg in two consecutive measurements were used to calculate the mean sitting SBP and DBP. The arm with higher SBP at the screening visit (visit 1) was designated as the index arm. During the next visit, the BP was measured in the index arm. All adverse events were assessed at every visit and recorded on an electronic caser report form.

2.5 | Outcomes

The primary outcome was the mean changes in sitting SBP from baseline to week 8. The secondary outcomes were (1) mean changes in sitting SBP from baseline to week 4, (2) mean changes in sitting DBP from baseline to weeks 4 and 8, (3) SBP response rate after 4 and 8 weeks (percentage of participants with a change in sitting SBP ≥20 mmHg from baseline), and (4) SBP or DBP response rate after 4 and 8 weeks (percentage of participants with a change in sitting SBP ≥20 mmHg and/or sitting DBP ≥10 mmHg relative to that at baseline). Safety was assessed based on adverse events, vital signs, clinical laboratory tests, physical examinations, and electrocardiography findings.

2.6 | Statistical analysis

Generally, data are expressed as mean ± standard deviation for continuous variables and as number (percentage) of participants for categorical variables. Efficacy data analyses were performed based on the full-analysis set (FAS) and the per-protocol set (PPS) population. The FAS included all participants who had received the study drug at least once after randomization and had their sitting SBP measured at least once during the treatment period. The PPS included all eligible participants who completed the 8-week regimen according to the clinical trial protocol without serious protocol violations among those in the FAS.

To compare the changes in sitting SBP and sitting DBP from baseline to weeks 4 and 8 between third-dose triple combination (ALC group) and third-dose dual combinations (AL, LC, and AC group) therapy, analysis of covariance (ANCOVA) was performed using the baseline values and stratification variables (except for the variables related to sitting SBP) as covariates. For post-hoc analysis, a contrast test was performed for pairwise comparisons of the third-dose triple combination with each third-dose dual combination. To compare the BP response rate of the third-dose triple combination and each third-dose dual combination after 4 and 8 weeks, the Cochran-Mantel-Haenszel test was performed, and Pearson's chi-square or Fisher's exact test was used to compare by stratification variables. The last-observation-carried-forward approach was applied for participants with missing values.

Safety data were analyzed based on the safety analysis set population, which included participants who had taken the study drug at least once after randomization and underwent the safety assessment at least once during the treatment period. ADRs are presented as the number (percentage) of participants for treatment-emergent

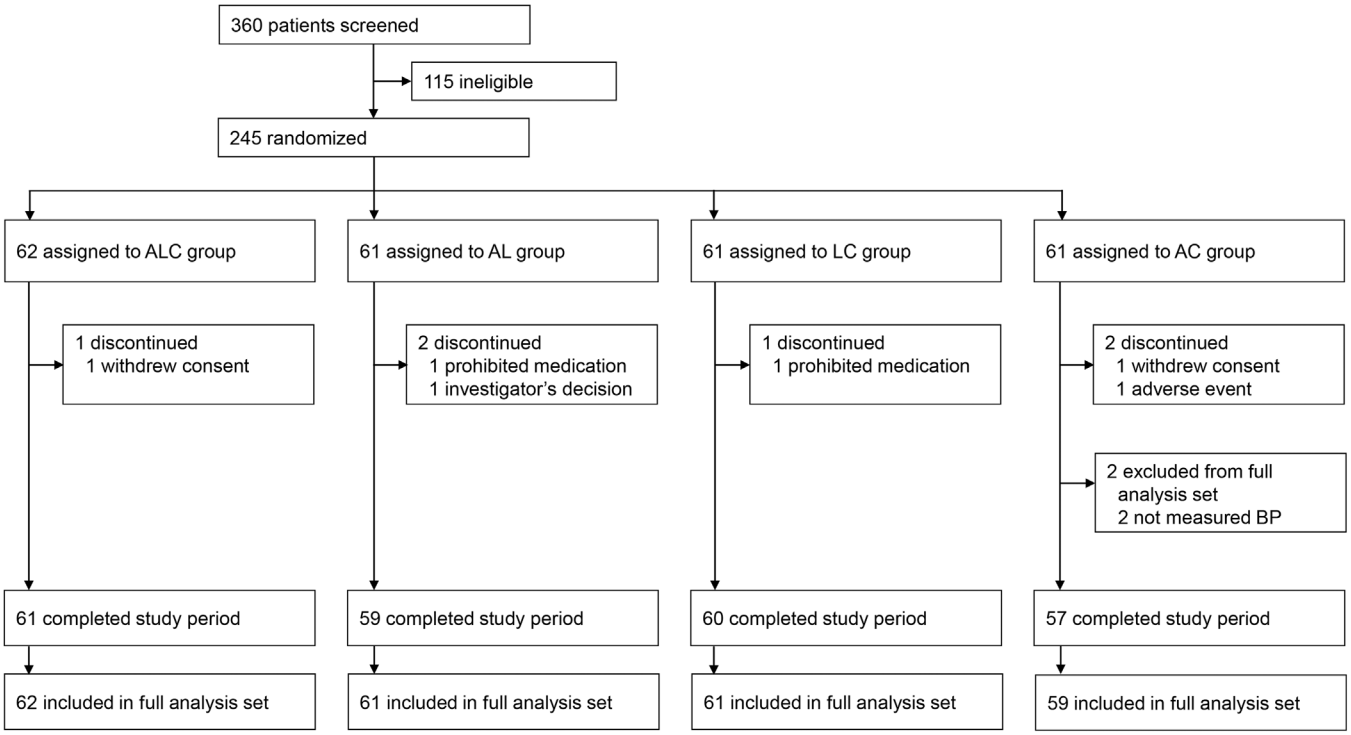

FIGURE 2 Patients disposition.

adverse events occurring after randomization. For changes in laboratory parameters after 8 weeks relative to baseline, ANCOVA or the Kruskal-Wallis test was used for between-group comparisons.

The difference in BP-lowering effect between low-dose triple and low-dose dual antihypertensive combinations could not be predicted as there is no previous study evaluating the effect of third-dose dual antihypertensive drug combinations. Therefore, considering the exploratory characteristics of phase II clinical trials, the sample size was determined to be 50 per group. Considering a 10% dropout rate, 224 patients were planned to randomize into four groups (56 patients in each group).

SAS software (version 9.4; SAS Institute, Cary, North Carolina, USA) was used for the statistical analyses.

3 | RESULTS

Between April 2021 and December 2021, 360 participants were screened, and 245 eligible for the trial were randomized into 4 groups. In total, 243 participants were included in the FAS (Figure 2). Baseline patient characteristics such as mean age, sex, height, body weight, and rates of current smoking, drinking, and prevalence of diabetes, did not differ among the four groups. There were no differences in baseline SBP and DBP among the 4 groups (Table 1).

The mean SBP reduction was −18.3 ± 13.2, −13.0 ± 13.3, −16.3 ± 12.4, and −13.8 ± 13.2 mmHg at week 8 from baseline, in the ALC, AL, LC and AC groups, respectively (Figure 3A, Supplement Table S1). SBP reduction at week 8 was significantly greater in the ALC group than in the AL (LS mean difference [standard error], −5.1 [2.1], 95% confidence interval [CI] −9.2 to −0.9, $P = .017$) and the AC (LS mean difference [standard error] −4.5 [2.1], 95% CI −8.7 to −0.3, $P = .036$) groups. The difference in SBP reduction at week 4 was also significantly greater in the ALC group than in the AL (LS mean difference [standard error] −5.3 [2.0], 95% CI −9.2 to −1.3, $P = .010$) and the AC (LS mean difference [standard error] −4.8 [2.0], 95% CI −8.8 to −0.8, $P = .018$) groups, and there was a marginal but insignificant difference in SBP reduction between the ALC and LC groups (LS mean difference [standard error] −3.8 [2.0], 95% CI −7.8 to 0.1, $P = .057$). The mean DBP reduction was −7.9 ± 7.0, −5.0 ± 8.0, −7.6 ± 8.0, and −5.4 ± 8.0 mmHg at week 8 from baseline, in the ALC, AL, LC, and AC groups, respectively (Figure 3B, Supplement Table S2). DBP reduction at week 8 was significantly greater in the ALC group than in the AL group (LS mean difference [standard error] −2.9 [1.3], 95% CI −5.4 to −0.3, $P = .031$).

The proportion of SBP responders in the ALC group (43.5%) was not significantly different from that in the AL (27.9%; $P = .058$), LC (39.3%; $P = .652$), and AC (30.5%; $P = .109$) groups at week 8. However, at week 4, it was significantly greater in the ALC group (42.6%) than in the AL (22.0%; $P = .013$), LC (23.3%; $P = .021$), and AC (27.1%; $P = .045$) groups (Figure 4A, Supplementary Table S3). Notably, the proportion of SBP or DBP responders at week 8 was significantly greater in the ALC group (59.7%) than in the AL (39.3%; $P = .022$) and AC (42.4%, $P = .049$) groups, but not in the LC group (57.4%, $P = .818$). Moreover, the proportion of SBP or DBP responders at week 4 (52.5% for ALC, 35.6% for AL, 36.7% for LC and 33.9% for AC) was significantly greater in the ALC group than in the AC group ($P = .030$) (Figure 4B, Supplementary Table S4).

TABLE 1 Demographics and baseline characteristics (full analysis set).

	Total	ALC group	AL group	LC group	AC group	*P* *
No.	243	62	61	61	59	
Age, years	61.8 (11.4)	61.8 (13.0)	61.6 (11.7)	60.0 (10.7)	63.9 (10.0)	.320[a)]
Sex, no. (%)						
Male	153 (63.0)	40 (64.5)	37 (60.7)	38 (62.3)	38 (64.4)	.966[b)]
Female	90 (37.0)	22 (35.5)	24 (39.3)	23 (37.7)	21 (35.6)	
Height, cm	164.6 (9.1)	165.2 (10.6)	163.6 (9.0)	164.7 (8.6)	164.9 (8.1)	.784[a)]
Weight, kg	69.7 (13.1)	70.5 (15.6)	69.1 (13.5)	70.6 (11.9)	68.6 (11.0)	.798[a)]
Smoker, no. (%)	43 (17.7)	15 (24.2)	12 (19.7)	9 (14.8)	7 (11.9)	.296[b)]
Drinker, no. (%)	109 (44.9)	32 (51.6)	24 (39.3)	25 (41.0)	28 (47.5)	.489[b)]
Diabetes mellitus, no. (%)	61 (25.1)	15 (24.2)	16 (26.2)	12 (19.7)	18 (30.5)	.584[b)]
Strata, no. (%)						
SBP < 160 mmHg	174 (71.6)	44 (71.0)	44 (72.1)	44 (72.1)	42 (71.2)	.998[b)]
SBP≥160 mmHg	69 (28.4)	18 (29.0)	17 (27.9)	17 (27.9)	17 (28.8)	
SBP, mmHg	152.6 (10.7)	152.6 (11.2)	152.3 (10.9)	152.9 (10.7)	152.6 (10.3)	.990[a)]
DBP, mmHg	92.1 (9.1)	92.6 (8.6)	92.2 (9.3)	93.0 (8.4)	90.7 (10.0)	.524[a)]

Data are expressed as number (percent) or mean (standard deviation).
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; ALC, combination of amlodipine (1.67 mg), losartan (16.67 mg) and chlorthalidone (4.17 mg); AL, combination of amlodipine (1.67 mg) and losartan (16.67 mg); LC, combination of losartan (16.67 mg) and chlorthalidone (4.17 mg); AC, combination of amlodipine (1.67 mg) and chlorthalidone (4.17 mg); 95% CI, 95% confidence interval.
*P-value by [a)] ANOVA, and [b)] Pearson's Chi-square test.

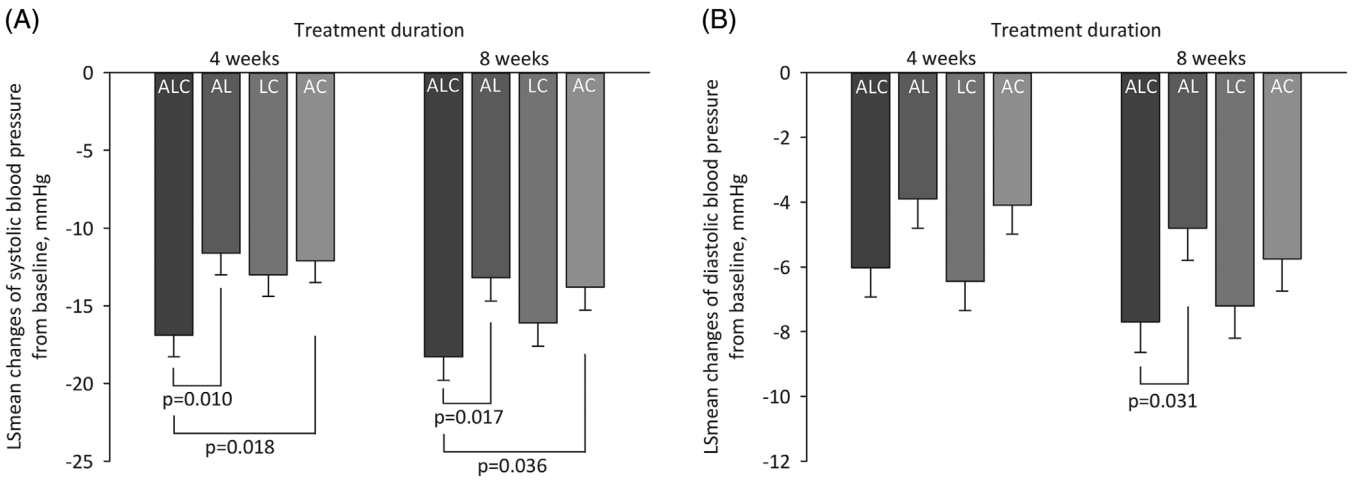

FIGURE 3 Changes in sitting (A) systolic and (Bb) diastolic blood pressure at week 4 and 8 from baseline. ALC, combination of amlodipine (1.67 mg), losartan (16.67 mg), and chlorthalidone (4.17 mg); AL, combination of amlodipine (1.67 mg) and losartan (16.67 mg); LC, combination of losartan (16.67 mg) and chlorthalidone (4.17 mg); AC, combination of amlodipine (1.67 mg) and chlorthalidone (4.17 mg).

Intergroup differences in the study drug-related ADRs were not significant among the four groups, and all ADRs were mild in intensity (Table 2). One participant (1.6%) in the AL group reported peripheral edema, which was considered related to the study treatment. Changes in serum creatinine and uric acid levels from baseline after the 8-week treatment period were significantly different among the four groups (Table 3). The change in serum creatinine levels in the ALC group was significantly lower than that in the LC group ($P = .038$) and insignificant compared to that in the AC group ($P = .051$). The change in uric acid levels was also significantly lower in the ALC group than in the LC and AC groups ($P = .005$ and $P = .011$, respectively). However, there were no cases of clinically significant elevation in serum creatinine or uric acid levels. Changes in serum blood urea nitrogen, calcium, sodium, and potassium levels did not differ among the four groups.

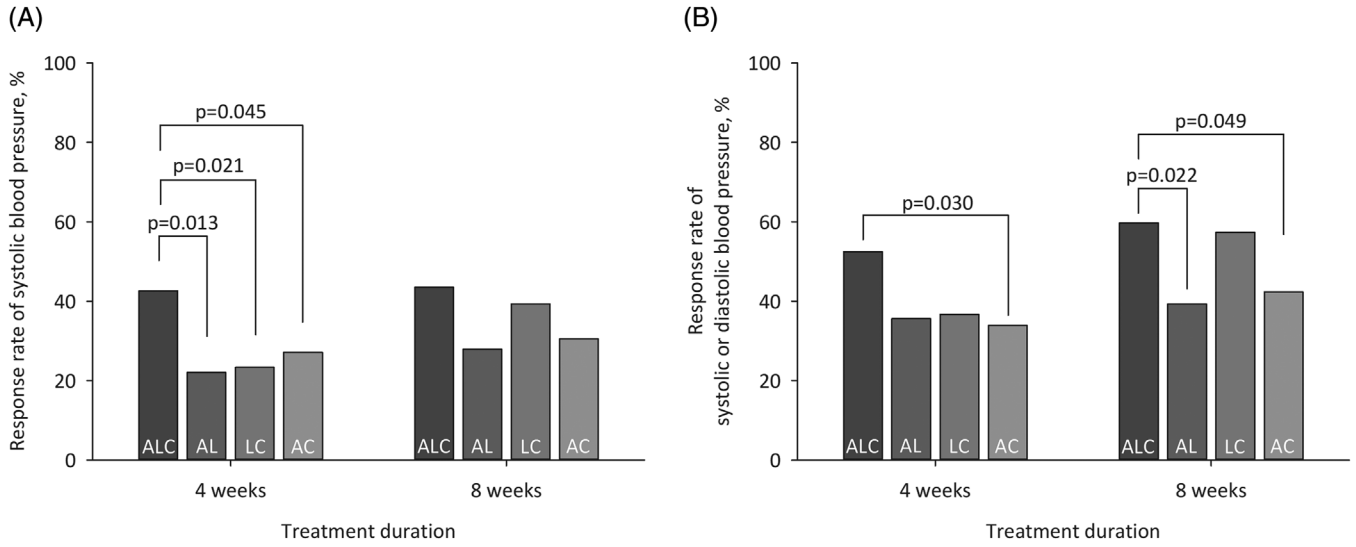

FIGURE 4 Proportion of (A) systolic blood pressure responders and (B) systolic or diastolic blood pressure responders at week 4 and week 8. ALC, combination of amlodipine (1.67 mg), losartan (16.67 mg), and chlorthalidone (4.17 mg); AL, combination of amlodipine (1.67 mg) and losartan (16.67 mg); LC, combination of losartan (16.67 mg) and chlorthalidone (4.17 mg); AC, combination of amlodipine (1.67 mg) and chlorthalidone (4.17 mg).

TABLE 2 Study drug-related adverse drug reactions (Safety analysis set, no. = 245).

	ALC Group	AL Group	LC Group	AC Group
No.	62	61	61	61
Abdominal pain upper	1 (1.6)	–	–	–
Nausea	2 (3.2)	–	–	–
Edema peripheral	–	1 (1.6)	–	–
Swelling	–	1 (1.6)	–	–
Dizziness	–	1 (1.6)	1 (1.6)	–
Headache	1 (1.6)	–	–	–

Data are number of patients (percent).
ALC, combination of amlodipine (1.67 mg), losartan (16.67 mg) and chlorthalidone (4.17 mg); AL, combination of amlodipine (1.67 mg) and losartan (16.67 mg); LC, combination of losartan (16.67 mg) and chlorthalidone (4.17 mg); AC, combination of amlodipine (1.67 mg) and chlorthalidone (4.17 mg).

4 | DISCUSSION

In our study, SBP reduction at week 4 was greater in the third-standard-dose triple antihypertensive combination therapy than in the third-standard-dose dual combination therapies, and these differences were maintained until week 8, except for the combination of third-dose losartan and chlorthalidone. The proportion of SBP responders was significantly higher in the third-dose triple antihypertensive combination therapy group than in the third-dose dual combination therapy groups at week 4. These results indicate that each component drugs have a relevant contribution within the third-dose combination drug. In addition, the greater and earlier BP reduction observed with the third-dose triple antihypertensive combination therapy was the principal finding of our study.

In our previous study, SBP reduction after 8 weeks of monotherapy with amlodipine 5 mg and losartan 100 mg was −12.4 ± 13.1 and −11.1 ± 15.9 mmHg, respectively.[12] In this study, the mean SBP reductions (at week 8 from baseline) were −18.3 ± 13.2, −13.0 ± 13.3, −16.3 ± 12.4, and −13.8 ± 13.2 mmHg in the ALC, AL, LC and AC groups, respectively. The level of BP reduction by third-dose triple antihypertensive combination therapy is expected to be superior to that of monotherapy at a standard dose. Therefore, we believe that a third-dose triple antihypertensive combination in a single-pill is an effective initial antihypertensive treatment option in patients with mild-to-moderate hypertension, with relatively greater and rapid BP-lowering efficacy and low ADRs as shown in our present and previous studies.[12] We are conducting a Phase III study to show greater BP reduction and comparable tolerability of third-dose triple combination

TABLE 3 Change of laboratory values from baseline at week 8 (Safety analysis set).

	ALC Group	AL Group	LC Group	AC Group	*P*
No.	62	61	61	61	
Creatinine					
Baseline	0.80 (0.14)	0.83 (0.18)	0.80 (0.21)	0.83 (0.23)	
Week 8	0.80 (0.14)	0.83 (0.18)	0.82 (0.20)	0.86 (0.25)	
Mean changes from baseline at week 8	−0.00 (0.08)	−0.01 (0.11)	0.02 (0.09)	0.02 (0.08)	.022[v]
Median changes from baseline at week 8	0.00	−0.01	0.02	0.02	
Min, Max	−0.16, 0.33	−0.28, 0.26	−0.30, 0.17	−0.24, 0.26	
BUN					
Baseline	14.6 (3.7)	14.6 (4.6)	14.0 (3.3)	14.6 (4.4)	
Week 8	15.9 (4.1)	15.1 (3.7)	15.9 (4.4)	15.9 (5.7)	
Mean changes from baseline at week 8	1.2 (4.3)	0.4 (4.1)	2.0 (3.9)	1.3 (3.9)	.213[†]
Median changes from baseline at week 8	1.0	1.0	2.0	1.0	
Min, Max	−13.0, 13.0	−12.0, 12.0	−6.0, 11.0	−10.0, 13.0	
Ca					
Baseline	9.27 (0.43)	9.23 (0.38)	9.21 (0.40)	9.23 (0.37)	
Week 8	9.29 (0.43)	9.19 (0.42)	9.24 (0.38)	9.25 (0.35)	
Mean changes from baseline at week 8	0.01 (0.29)	−0.04 (0.34)	0.05 (0.28)	0.03 (0.27)	.402*
Median changes from baseline at week 8	0.00	−0.05	0.00	0.00	
Min, Max	−0.70, 0.70	−0.90, 0.60	−0.80, 0.60	−0.90, 0.70	
Na					
Baseline	141.0 (1.8)	141.2 (1.8)	141.2 (1.6)	141.1 (1.8)	
Week 8	140.9 (2.0)	141.4 (1.9)	140.8 (1.6)	140.7 (2.0)	
Mean changes from baseline at week 8	−0.2 (1.5)	0.1 (1.8)	−0.3 (1.6)	−0.4 (2.1)	.545[†]
Median changes from baseline at week 8	0.0	0.0	0.0	0.0	
Min, Max	−4.0, 4.0	−3.0, 4.0	−4.0, 3.0	−10.0, 3.0	
K					
Baseline	4.38 (0.32)	4.39 (0.33)	4.37 (0.35)	4.42 (0.36)	
Week 8	4.31 (0.41)	4.32 (0.36)	4.28 (0.40)	4.29 (0.43)	
Mean changes from baseline at week 8	−0.07 (0.34)	−0.08 (0.33)	−0.11 (0.37)	−0.13 (0.39)	.655[†]
Median changes from baseline at week 8	−0.10	−0.10	−0.10	−0.10	
Min, Max	−0.80, 0.80	−0.90, 0.70	−1.10, 0.80	−0.90, 1.40	
Uric acid					
Baseline	5.77 (1.67)	5.48 (1.47)	5.16 (1.40)	5.50 (1.21)	
Week 8	5.81 (1.53)	5.22 (1.47)	5.47 (1.48)	5.71 (1.20)	
Mean changes from baseline at week 8	0.04 (0.92)	−0.27 (0.74)	0.31 (0.65)	0.21 (0.70)	<.001[†]
Median changes from baseline at week 8	0.00	−0.30	0.35	0.20	
Min, Max	−1.70, 3.90	−2.00, 1.60	−1.30, 1.90	−2.70, 1.60	

Data are expressed as mean (SD). Min, minimum; Max, maximum.

P value: *ANCOVA and [†]Kruskal-Wallis test.

ALC, combination of amlodipine (1.67 mg), losartan (16.67 mg) and chlorthalidone (4.17 mg); AL, combination of amlodipine (1.67 mg) and losartan (16.67 mg); LC, combination of losartan (16.67 mg) and chlorthalidone (4.17 mg); AC, combination of amlodipine (1.67 mg) and chlorthalidone (4.17 mg); BUN, blood urea nitrogen; Ca, calcium; Na, sodium; K, potassium.

therapy to amlodipine 5 mg monotherapy after 8 weeks of treatment (HM-APOLLO-301, NCT05362110). In addition, since the third-dose dual antihypertensive combinations show SBP reduction comparable to that of monotherapy, third-dose dual antihypertensive combinations (especially, a combination of third-dose losartan and chlorthalidone) also might be an effective alternative as a first-line drug for the treatment of hypertension, although this should be evaluated further in future studies.

Recent clinical trials have demonstrated the promise of low-dose triple or quadruple antihypertensive drug combination therapy as a first-line treatment in managing mild-to-moderate hypertension.[12,14,15] The introduction of this approach may benefit from the following effects: early and rapid BP control, and fewer adverse drug reactions. Barriers to effective BP control are multifactorial and can be divided into patient, physician, and healthcare system factors.[16] Therapeutic inertia seems to be a fundamental contributor to this impediment.[2,17,18] As shown in a recent study, therapeutic inertia is very common in primary care patients with uncontrolled hypertension. In that study, the therapeutic inertia was 87% and was similar in men and women.[19] A stepped-care approach that initiates from monotherapy at a standard dose and up-titrates the dose when BP is not lowered to the target is a common approach for managing hypertension. The drawback of this approach is therapeutic inertia, which does not intensify antihypertensive medications in patients with uncontrolled BP.[17,20] Early and greater BP lowering can reduce therapeutic inertia by decreasing the need for intensification.[6] In addition, general physicians in primary care are required to familiarize themselves with dozens of individual guidelines. Physicians' lack of training on how to select appropriate antihypertensive drugs and achieve their goals may play an important role in therapeutic inertia. Moreover, variable responses to different antihypertensive drugs make it difficult for general physicians to determine the initial antihypertensive drug selection.[4,21] The advantage of the combination of triple antihypertensive drugs (amlodipine, losartan, and chlorthalidone) is that it overcomes individual variability in response to antihypertensive drugs by combining drugs with different modes of action. Reduction of ADR and simplification of regimens using single-pill combination drugs can improve treatment adherence in patients. Low-dose triple or quadruple antihypertensive combination therapy may reduce the incidence of ADR associated with a higher dose of monotherapy or a combination of standard-dose drugs.[9] Ultimately, early and rapid BP control is expected to reduce cardiovascular events. The beneficial effect of rapid BP reduction on major cardiovascular events is emphasized in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study.[22] Consistent with the results of the VALUE study, the Antihypertensive and Lipid-Lowering Treatments to Prevent Heart Attack Trial[23] and Anglo-Scandinavian Cardiac Outcomes Trial-BP Lowering Arm[24] suggested that early BP lowering decreased the incidence of cardiovascular events. The beneficial effect of prompt BP reduction, within 1 to 3 months, was also confirmed in patients with type 2 diabetes mellitus.[25]

This study has several limitations. First, the study period was short, and an 8-week treatment period may be insufficient in evaluating the sustained BP-lowering effects and ADRs following long-term treatment. Second, the number of participants was small. This might significantly contribute to a marginal but insignificant difference in SBP reduction between the ALC and LC groups. Herein, the sample size was not predicted because of the exploratory characteristics of this study and no available data for the effect of third-dose dual antihypertensive drug combinations. In a previous study, amlodipine (10 mg)/valsartan (320 mg)/hydrochlorothiazide (25 mg) combination showed −7.6 mmHg greater SBP reduction than valsartan (320 mg)/hydrochlorothiazide (25 mg) combination therapy, and the sample size was 583 and 559, respectively.[26] Considering the administration of two-standard-dose in the above study, a significantly greater SBP reduction in the ALC group than in the AL and AC groups, and a significant difference in the response rate between ALC and LC groups at week 4, a significant BP reduction in the ALC group than in the LC group is expected in a larger study population. Third, this study was limited to Koreans. Furthermore, many hypertensive patients have various characteristics, such as seasonal variation, morning hypertension, comorbid cardiovascular disease, diabetes, obesity, high sodium intake, and chronic kidney disease. Further studies with longer follow-up duration are needed in patients of other races/ethnicities and with various hypertension characteristics.

In conclusion, during an 8-week treatment period, the third-standard-dose triple antihypertensive combination therapy demonstrated early effective BP control than the third-standard-dose dual combination therapies without increasing ADRs in patients with mild-to-moderate hypertension. The results of our study showed each component drug within a fixed combination of third-standard-dose triple antihypertensive drugs had a significant contributing effect of on BP reduction.

5 | PERSPECTIVES

Single-pill third-standard-dose triple antihypertensive combination drug is expected to have earlier and greater BP control than standard-dose monotherapy by addressing variable responses to different classes of antihypertensive drugs and counter-regulatory responses by covering three different modes of BP-lowering action. This did not increase ADRs. Better and earlier BP control may reduce the treatment inertia caused by poor BP control and difficulty in selecting effective drugs. Therefore, a third-standard-dose triple antihypertensive combination drug in a single pill could be effectively and safely used as a first-line treatment in patients with mild-to-moderate hypertension. We are conducting a phase III study to demonstrate the superior BP-lowering effect of third-standard-dose triple antihypertensive combination therapy compared to standard-dose monotherapy.

AUTHOR CONTRIBUTIONS

Conceptualization: MYR; Methodology: MYR and JAJ; Validation: MYR and JAJ; Formal analysis: MYR, KCS, SJH and JAJ; Writing—Original Draft: MYR, KCS and SJH; Writing—Review & Editing: MHJ, DHK, SWL, KP, JBL, SYK, JMC, GYC, JHH, SHK, HYL, WK, DKC, SP, JS, WBP, KK,

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CONFLICT OF INTEREST

Financial interests: Moo-Yong Rhee received lecture honoraria from Hanmi Pharm. Co. Ltd., and Boryung Pharmaceutical Co. Ltd., and consulting fees from Hanmi Pharm. Co. Ltd. Korea. Jin-A Jung is an employee of Hanmi Pharm. Co., Ltd., Korea. The other authors had no financial interests related to the current study.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during this study are available from the corresponding author and Hanmi Pharm. Co., Ltd., Korea on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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