Comparative Efficacy and Safety Profile of Amlodipine 5 mg/Losartan 50 mg Fixed-Dose Combination and Amlodipine 10 mg Monotherapy in Hypertensive Patients Who Respond Poorly to Amlodipine 5 mg Monotherapy: An 8-Week, Multicenter, Randomized, Double-Blind Phase III Noninferiority Study

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ABSTRACT

Background: The number of hypertensive patients achieving treatment targets is not ideal with therapies that engage a single mechanism of action, and combination therapies using different mechanisms of action can increase drug efficacy in a synergistic way.

Objective: This noninferiority study compared the clinical efficacy and safety profile of fixed-dose combination of amlodipine/losartan 5/50 mg and amlodipine 10 mg monotherapy in essential hypertensive patients who respond poorly to amlodipine 5 mg monotherapy.

Methods: This was a double-blind, multicenter, randomized trial of hypertensive patients (N = 185) aged ≥18 years taking amlodipine 5 mg during the run-in treatment period but failed to achieve sitting diastolic blood pressure (DBP) <90 mm Hg. After randomization into the amlodipine/losartan 5/50 mg fixed-dose combination group (n = 92) and the amlodipine 10 mg monotherapy group (n = 93), treatment was maintained without dose escalation for 8 weeks. The noninferiority margin was prespecified as 4 mm Hg after 8 weeks of treatment for the difference of the average change in DBP between treatments. The primary efficacy evaluation of noninferiority was tested using a confidence interval approach with a 97.5% 1-sided lower confidence limit using the average difference in DBP measured at baseline and 8 weeks.

Results: After 8 weeks, the DBP of both groups decreased from baseline by 8.9 (6.1) and 9.4 (7.5) mm Hg, respectively (difference = −0.5 [6.9] mm Hg, 95% CI: −2.5 to 1.5). Secondary end points of reductions in

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DBP after 4 weeks (−8.1 [6.7] vs −9.9 [7.3] mm Hg, difference = −1.8 mm Hg, 95% CI: −3.9 to 0.2) and sitting systolic blood pressure after 4 (−10.2 [11.8] vs −12.8 [10.2] mm Hg, difference = −2.6 mm Hg, 95% CI: −5.9 to 0.6) and 8 weeks (−12.2 [11.0] vs −13.4 [11.3] mm Hg, difference = −1.2 mmHg, 95% CI: −4.4 to 2.1) were comparable between the 2 treatment groups. There were 38 adverse events in 20 patients (21.7%) in the amlodipine/losartan 5/50 mg fixed-dose combination group and 31 in 24 patients (26.1%) in the amlodipine 10 mg monotherapy group; most were mild. There were 7 adverse events in 6 patients (6.5%) related to treatment in the fixed-dose combination group and 13 in 10 patients (10.9%) in the monotherapy group ($P = 0.30$).

Conclusions: Fixed-dose combination amlodipine/losartan 5/50 mg was not inferior in terms of reductions in DBP after 8 weeks of treatment and had comparable safety profile to amlodipine 10 mg in patients who did not respond to amlodipine 5 mg monotherapy. ClinicalTrials.gov identifier: NCT00940667.
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Key words: amlodipine, hypertension, losartan.

INTRODUCTION

Because hypertension itself is asymptomatic and every drug has the potential for side effects, outpatients with hypertension are often poorly compliant with drug therapy. This problem is exacerbated when patients have to take many different kinds of drugs, either because of uncontrolled hypertension or other diseases.[1,2] Fixed-dose combination therapy might be one way of improving patients' compliance. Fixed-dose combination therapy is also cost-effective because it reduces prescription and dispensing costs. Moreover, combining therapies with different mechanisms of action may have greater efficacy and better tolerability, thereby potentially preventing cardiovascular events more effectively than when the same drugs are delivered separately.[3–7]

Antihypertensive combination therapy generally involves different classes of drugs that maximize the blood pressure–lowering effects of each component while minimizing the overall side effects. Such complementary therapies increase efficacy in a synergistic fashion. One of the antihypertensive drugs that is commonly used in combination therapy is losartan,[3,8,9] a selective and competitive angiotensin II receptor antagonist. When angiotensin II, which is a very potent vasoconstrictive substance (ie, a vasopressor), is inhibited, the concentration of blood renin increases, veins are dilated, and blood pressure is effectively reduced. In addition, secretion of aldosterone decreases, which slows the progression to albuminuria and diabetic neuropathy. Therefore, losartan is frequently used as the first-line drug in combination drugs for patients with renal disease and diabetic hypertension.[3,6,8,9]

Another frequently used antihypertensive drug is amlodipine,[10–13] which is a long-acting dihydropyridine calcium channel blocker (CCB). Amlodipine, like losartan, can be used with a broad range of other drugs. However, amlodipine, like other dihydropyridine CCBs, induces capillary edema (especially ankle edema) because it blocks extracellular calcium input into arterial smooth muscle, which in turn causes the veins to contract and the fluids in the capillaries to leak. This edema cannot be treated by diuretics due to whole-body fluid drainage rather than specifically acting on the edema due to vein contraction.[10–13] To reduce this side effect and increase the blood pressure–lowering effects of amlodipine and other dihydropyridine CCBs, the US Food and Drug Administration has approved 2 combinations of dihydropyridine CCBs with angiotensin-converting enzyme−inhibiting drugs that block the renin-angiotensin-aldosterone system, namely benazepril/amlodipine* and enalapril/felodipine.† [4,14,15] However, because angiotensin-converting enzyme inhibitors affect kinin metabolism, they are associated with a high incidence of dry cough.[9,16] In addition, in rare cases, they can induce angioedema and syncope after the first administration, so special precautions are required. These observations, together with the individual advantages of amlodipine and losartan, suggest that an amlodipine/losartan combination therapy can have excellent blood pressure–lowering effects and a relatively low incidence of side effects.[4,7,14,17]

In this study, we conducted a double-blind, multicenter, randomized Phase III trial to compare the efficacy and safety profile of amlodipine 5 mg/losartan 50 mg fixed-dose combination therapy and amlodipine 10 mg monotherapy in hypertensive patients who failed to respond appropriately to amlodipine 5 mg mono-

*Trademark: Lotrel™ Lotrel (Novartis Pharmaceuticals Corp., East Hanover, New Jersey).

†Trademark: Lexxel® Lexxel (AstraZeneca Pharmaceuticals, Wilmington, Delaware).

therapy. The hypothesis being tested was that the fixed-dose combination of amlodipine 5 mg/losartan 50 mg was at least as effective as amlodipine 10 mg monotherapy in lowering blood pressure, as suggested by the average change in diastolic blood pressure (DBP) after 8 weeks of therapy relative to baseline.

METHODS

Participants, Study Design, and Randomization

Men and women aged ≥18 years with essential hypertension were recruited from the cardiology departments of 13 hospitals in Korea between May 2008 and September 2008 to study the effects of the amlodipine 5 mg/losartan 50 mg fixed-dose combination on essential hypertension. In accordance with the principles of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in 2003,[1] patients were included if they had essential hypertension that could not be controlled before the Phase III trial (ie, a DBP while sitting of ≥90 mm Hg for drug-treated patients and ≥95 mm Hg for drug-naïve patients) and the run-in phase of the current trial revealed that they did not respond to 4 weeks of treatment with open-labeled amlodipine 5 mg monotherapy (ie, their DBP was ≥90 mm Hg). We excluded patients who exhibited systolic blood pressure (SBP) ≥20 mm Hg or DBP ≥10 mm Hg of variations upon blood pressure measurement, as well as those who had been treated with systemic steroid or hormones, anesthetics, tri-tetra-cyclic antidepressants, nonsteroidal anti-inflammatory drugs, and oral contraceptives for 3 months. For each patient, blood pressure was measured in both arms 3 times and the arm with the higher average DBP was selected. Patients who satisfied the inclusion criteria at the screening visit (visit 1) were then treated with amlodipine 5 mg for 4 weeks ± 4 days to allow the patient to visit their hospital for visit 2. Patients stopped taking any previous antihypertensive drugs before receiving study medication during the run-in period. During these 4 weeks, the patients took 1 tablet daily in the morning.

At visit 2, the patients did not take amlodipine in the morning and the blood pressure of each patient was measured from one arm 3 times and the average was calculated. If the patients continued to meet the inclusion criteria on visit 2, they were randomly assigned to the test group or the control drug group and prescribed a 32-day course of the treatment drug (28 days ± 4 additional days to allow the patient to visit their hospital for visit 3). In order to maintain this study double-blinded, each of the patients in either the test group or the control group was required to take 3 tablets once daily, which consisted of 1 amlodipine 5 mg/losartan 50 mg tablet + 2 placebo tablets, or 2 Amodipine tablets (amlodipine 5 mg) + 1 placebo tablet, respectively, in accordance to their assigned group. The drugs were to be taken orally in the morning.

At visit 3, blood pressure was measured from one arm 3 times and the average was recorded in the morning without taking the treatment drug. Another 32-day course of treatment drug (28 days ± 4 additional days to allow the patient to visit their hospital for visit 4) were prescribed at visit 3. At visit 4, blood pressure was also measured in the morning without taking the treatment drug. Thereafter, adverse events, laboratory data, physical examination, and ECG were evaluated. All patients provided written informed consent. The study protocol was approved by the Korean Food and Drug Administration and the local ethical review boards of each hospital.

Study Objectives

The primary end point of this study was the change in the DBP after 8 weeks of treatment relative to the baseline (visit 2) value. Secondary end points were the changes in sitting SBP after 4 and 8 weeks of treatment relative to baseline, the change in DBP after 4 weeks of treatment relative to baseline, and the blood pressure response rates. Blood pressure response rate is the percentage of patients who achieved the target blood pressure (SBP <140 mm Hg or DBP <90 mm Hg) or achieved a change in the SBP or DBP that exceeded 20 mm Hg and 10 mm Hg relative to baseline, respectively. Adverse events, medical history, and concomitant medications were coded using the Medical Dictionary for Drug Regulatory Affairs 10.0 (International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland) and Anatomical Therapeutic Chemical Code (2008). A safety profile evaluation was performed on all patients who were randomly assigned and administered the investigational products at least once.

Statistical Analysis

The hypothesis being tested was that the fixed-dose combination of amlodipine 5 mg/losartan 50 mg was at least as effective as amlodipine 10 mg monotherapy in lowering blood pressure, as suggested by the average change in DBP after 8 weeks of therapy relative to baseline. It was estimated that a sample size of 156 patients, 78 per treatment group, would be required to show a study power of 0.80 in a one-sided test for

noninferiority at a significance level of 0.025. A previous trial used an inferiority margin of −5 mm Hg[18]; and in this trial, a more conservative approach was applied by prespecifying the noninferiority margin as −4 mm Hg for the difference of the average change in DBP between treatments. The primary efficacy evaluation of noninferiority was tested using a confidence interval approach with a 97.5% one-sided lower confidence limit using the average difference in DBP measured at baseline and 8 weeks. That is to say, noninferiority was established if the lower limit of the confidence interval was above the a prior threshold of −4 mmHg. Secondary end points were tested with a 5% level of significance because they were used as ex-

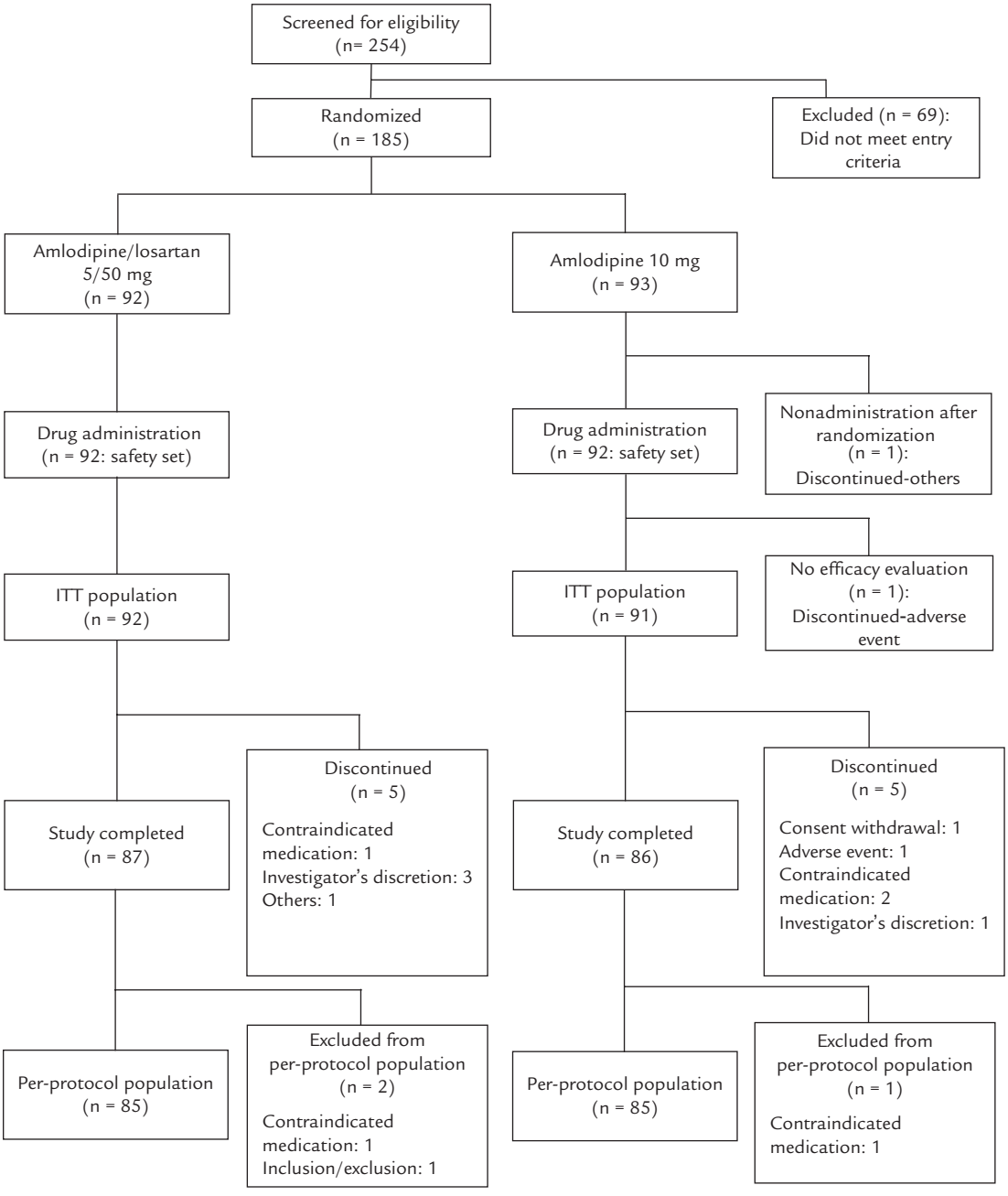

Figure. Summary of patient disposition. ITT = intention-to-treat.

ploratory end points only and not to determine noninferiority. An additional ANCOVA model with the baseline DBP as the covariate was performed to investigate the between-group difference in the reduction in DBP at 4 and 8 weeks. The absolute and relative frequencies of SBP <140 mm Hg, DBP <90 mm Hg, SBP >20 mm Hg, DBP >10 mm Hg, and responder rate in terms of changes after 4 and 8 weeks of treatment relative to baseline were compared using the χ^2 test. The 2 treatment groups were compared in terms of demographic characteristics, including gender, age, height, and weight. For continuous variables, mean (SD), and minimum and maximum values were determined and compared by using a *t* test. For categorical variables, absolute and relative frequencies were determined and compared by using the χ^2 test. The change from baseline in SBP in the subgroup of patients with Stage II hypertension was analyzed using a *t* test. A computer program that could regularly check the completeness, accuracy, and accordance with the protocol based on the Data Management Plan was used. Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Participants

In total, 254 patients were screened in 13 hospitals and 33 patients failed the first screening. Consequently, 221 patients participated in the active run-in period. Thirty-six patients then failed the second screening and 185 patients could be randomly assigned: 92 patients were placed in the amlodipine 5 mg/losartan 50 mg fixed-dose combination group and 93 patients were placed in the amlodipine 10 mg monotherapy group. Of the 185 randomly assigned patients, 1 in the amlodipine 10 mg group did not receive the drug. Thus, there were 92 patients included in the fixed-dose combination therapy group and 92 patients in the monotherapy group: in total, 184 patients received treatment and 183 patients were included in the intention-to-treat (ITT) population. Of these 183 patients, 87 patients in the fixed-dose combination group and 86 patients in the monotherapy group completed the trial. Three patients either violated inclusion/exclusion criteria or made a serious

Table I. Demographic characteristics and baseline blood pressure of the intention-to-treat population (n = 183).

Characteristic	Amlodipine/Losartan 5/50 mg (n = 92)	Amlodipine 10 mg (n = 91)	Total (N = 183)	*P*
Age, mean (SD), y	54.2 (8.7)	53.2 (10.3)	53.7 (9.5)	0.52*
Male, no. (%)	73 (79.4)	75 (82.4)	148 (80.9)	0.60†
Body weight, mean (SD), kg	72.1 (11.4)	71.2 (10.3)	71.7 (10.8)	0.61*
Medications, no. (%)‡				
ARB	24 (20.3)	30 (26.6)	54 (23.4)	—
ACEI	10 (8.5)	4 (3.5)	14 (6.1)	—
β-blocker	21 (17.8)	22 (19.5)	43 (18.6)	—
CCB	47 (39.8)	51 (45.1)	98 (42.4)	—
Diuretic	12 (10.2)	6 (5.3)	18 (7.8)	—
Other	4 (3.4)	0 (0.0)	4 (1.7)	—
None (treatment naïve)	18 (19.57)	24 (26.37)	42 (22.95)	—
SBP, mean (SD) mm Hg	143.334 (12.30)	145.22 (11.33)	144.327 (11.80)	0.28*
DBP, mean (SD), mm Hg	96.8 (5.3)	97.2 (6.0)	97.0 (5.64)	0.65*

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DBP = diastolic blood pressure; SBP = systolic blood pressure.
*Unpaired *t* test.
†χ^2 test.
‡Overlapping values.

protocol violation. The resulting group of 170 patients (which is a subset of the ITT population) was designated the per-protocol population (**Figure**).

Table I summarizes patient demographic characteristics. Their ages ranged from 27 to 80 years and the 2 groups did not differ significantly in terms of age or gender ($P = 0.52$ and $P = 0.60$, respectively). They also did not differ significantly in terms of weight, height, alcohol-drinking history, or smoking history. The average baseline blood pressure (systolic/diastolic) of the ITT population was 143.3/96.8 mm Hg in the fixed-dose combination group and 145.2/97.2 mm Hg in the monotherapy group. The 2 groups did not differ significantly in baseline SBP and DBP ($P = 0.28$ and $P = 0.65$, respectively).

Blood Pressure–Lowering Efficacy

Analysis of the ITT group revealed that after 8 weeks of treatment, the DBP had decreased relative to baseline by 8.9 (6.1) mm Hg in the fixed-dose combination and 9.4 (7.5) mm Hg in monotherapy group. The mean difference in DBP between the 2 groups was −0.5 (6.9) mm Hg (95% CI: −2.5 to 1.5). Because the lower limit of the confidence interval was above the maximum level of noninferiority (ie, −4 mm Hg), this result suggested that fixed-dose combination of amlo-

Table II. Change in blood pressure end points after 4 or 8 weeks in the intention-to-treat population (n = 183).

Parameter	Amlodipine/Losartan 5/50 mg (n = 92)	Amlodipine 10 mg (n = 91)
Primary end point		
Diastolic blood pressure		
Week 8, mean (SD)	88.0 (7.4)	88.0 (8.3)
Change, mean (SD)	−8.9 (6.1)	−9.4 (7.5)
Difference in mean (SD) change between 2 groups (95% CI)	−0.5 (6.9) (−2.5 to 1.5)	
Analysis with the baseline as the covariate		
Adjusted mean change from baseline	−8.9	−9.3
Estimated difference (95% CI)	−0.4 (−2.4 to 1.5)	
P value*	0.68	
Secondary end points		
Diastolic blood pressure		
Week 4, mean (SD)	88.7 (8.3)	87.3 (9.1)
Change for week 4, mean (SD)	−8.1 (6.7)	−9.9 (7.3)
Difference in mean change between 2 groups (95% CI)	−1.8 (−3.9 to 0.2)	
P value†	0.08	
Systolic blood pressure		
Week 4	133.2 (12.9)	132.4 (11.5)
Change for week 4	−10.2 (11.8)	−12.8 (10.2)
Difference in mean change between 2 groups (95% CI)	−2.6 (−5.9 to 0.6)	
P value‡	0.11	
Week 8	131.1 (12.9)	131.8 (11.8)
Change for week 8	−12.2 (11.0)	−13.4 (11.3)
Difference in mean change between 2 groups (95% CI)	−1.2 (−4.4 to 2.1)	
P value§	0.50	

*Statistical analysis by ANCOVA with the baseline diastolic blood pressure as the covariate.
†Comparison between 2 groups by *t* test.
‡95% CI for difference between groups in mean change after week 4.
§95% CI for difference between groups in mean change after week 8.

dipine 5 mg/losartan 50 mg was at least as effective as amlodipine 10 mg in lowering blood pressure.

Analysis of the secondary end points revealed that the 2 groups in the ITT population were also similar in terms of change in DBP after 4 weeks of treatment relative to the baseline values (−8.1 [6.7] vs −9.9 [7.3] mm Hg, difference = −1.8 mm Hg, 95% CI: −3.9 to 0.2; Table II). This was also true for the change in SBP after 4 weeks (−10.2 [11.8] vs −12.8 [10.2] mm Hg, difference = −2.6 mm Hg, 95% CI: −5.9 to 0.6) and 8 weeks (−12.2 [11.0] vs −13.4 [11.3] mm Hg, difference = −1.2 mm Hg, 95% CI: −4.4 to 2.1) of treat-

Table III. Responder rates in the intention-to-treat population (n = 183).

Parameter	Amlodipine/ Losartan 5/50 mg, no. (%)	Amlodipine 10 mg, no. (%)	Total, no. (%)	*P**
Week 4				
SBP < 140 mm Hg				
Responder	65 (70.7)	74 (81.3)	139 (76.0)	0.09
Nonresponder	27 (29.4)	17 (18.7)	44 (24.0)	
DBP < 90 mm Hg				
Responder	55 (59.8)	56 (61.5)	111 (60.7)	0.81
Nonresponder	37 (40.2)	35 (38.5)	72 (39.3)	
Mean change in SBP exceeds baseline by >20 mm Hg				
Responder	18 (19.6)	20 (22.0)	38 (20.8)	0.69
Nonresponder	74 (80.4)	71 (78.0)	145 (79.2)	
Mean change in DBP exceeds baseline by >10 mm Hg				
Responder	39 (42.4)	42 (46.2)	81 (44.3)	0.61
Nonresponder	53 (57.6)	49 (53.9)	102 (55.7)	
All parameters (=responder rate)				
Responder	78 (84.8)	77 (84.6)	155 (84.7)	0.97
Nonresponder	14 (15.2)	14 (15.4)	28 (15.3)	
Week 8				
SBP < 140 mm Hg				
Responder	73 (79.4)	71 (78.0)	144 (78.7)	0.83
Nonresponder	19 (20.7)	20 (22.0)	39 (21.3)	
DBP < 90 mm Hg				
Responder	59 (64.1)	53 (58.2)	112 (61.2)	0.41
Nonresponder	33 (35.9)	38 (41.8)	71 (38.8)	
Mean change in SBP exceeds baseline by >20 mm Hg				
Responder	19 (20.7)	24 (26.4)	43 (23.5)	0.36
Nonresponder	73 (79.4)	67 (73.6)	140 (76.5)	
Mean change in DBP exceeds baseline by >10 mm Hg				
Responder	37 (40.2)	37 (40.7)	74 (40.4)	0.95
Nonresponder	55 (59.8)	54 (59.3)	109 (59.6)	
All parameters (=responder rate)				
Responder	82 (89.1)	80 (87.9)	162 (88.5)	0.80
Nonresponder	10 (10.9)	11 (12.1)	21 (11.5)	

DBP = diastolic blood pressure; SBP = systolic blood pressure.
*χ^2 test.

ment relative to baseline values. The per-protocol population results were similar to those of the ITT population (data not shown).

A response to treatment was defined as achievement of the target blood pressure, as shown in Table III. The responder rates for the fixed-dose combination and monotherapy groups in the ITT population after 4 weeks of treatment were 84.8% (78 of 92) and 84.6% (77 of 91), respectively, which did not differ significantly ($P = 0.97$). After 8 weeks of treatment, the responder rates were 89.1% (82 of 92) and 87.9% (80 of 91), respectively, which did not differ significantly ($P = 0.80$). Similarly, the responder rates of the fixed-dose combination and monotherapy groups in the per-protocol population after 4 and 8 weeks of treatment did not differ significantly (data not shown). In the subgroup analysis of patients who had Stage II hypertension (SBP >160 mm Hg), additional BP reductions of −24.6 (10.5) mm Hg on amlodipine 5 mg/losartan 50 mg at 8 weeks ($P < 0.001$) and −18.8 (9.6) mm Hg on amlodipine 10 mg at 8 weeks ($P < 0.001$) were observed (Table IV). The between-treatment difference in reductions (−5.8 mm Hg) was not statistically significant ($P = 0.19$).

Drug Safety Profile

There were 184 patients who were randomly assigned into treatment groups, took at least 1 dose of study drug, and were checked for tolerability by the investigator by phone or during a visit after assignment. As shown in Table V, the numbers of adverse events that occurred after random assignment were 38 in 20 patients (21.7%) in the amlodipine 5 mg/losartan 50 mg fixed-dose combination group and 31 in 24 patients (26.1%) in the amlodipine 10 mg monotherapy group; most of them were mild. The numbers of adverse events related to the treatment drugs were 7 in 6 patients (6.5%) in the fixed-dose combination group and 13 in 10 patients (10.9%) in the monotherapy group; and these differences were not significantly different. The major adverse event related to the treatment drugs was headache, with similar rates of occurrence between the 2 groups. Three serious adverse events occurred during the trial: One case in the fixed-dose combination group (herniated lumbar disk), another case in the monotherapy group (cerebral infarction), and another serious adverse event (a fibular fracture) occurred during the active run-in period. None of the serious adverse events were considered related to the study drugs. Two patients in the monotherapy group discontinued due to adverse events. One patient reported a mild skin rash and the other reported a severe cerebral infarction.

There were statistically significant differences in neutrophils ($P = 0.0482$), eosinophils ($P = 0.0052$), and total bilirubin ($P = 0.0215$) between treatment groups; however, the differences were minimal, within normal ranges, and were judged to be without clinical significance by the investigators. There was a significant difference in pulse from baseline at 4 weeks in the amlodipine 10 mg group ($P = 0.0009$) and at 8 weeks in the amlodipine/losartan 5/50 mg group ($P = 0.0093$). However, there were no significant differences between treatment groups ($P = 0.7108$ and $P = 0.2181$). One patient in the monotherapy group had an increase in glucose, total cholesterol, triglyceride, and low-density lipoprotein cholesterol, and another pa-

Table IV. Change from baseline in mean systolic blood pressure in patients with Stage II hypertension (systolic blood pressure ≥ 160 mm Hg) after 8 weeks of treatment.

Parameter	Amlodipine/Losartan 5/50 mg (n = 12)	Amlodipine 10 mg (n = 11)
Baseline, mean (SD), mm Hg	168.0 (5.8)	166.7 (6.8)
Week 8, mean (SD), mm Hg	143.4 (12.9)	147.9 (11.0)
Mean change (SD), mm Hg	−24.6 (10.5)	−18.8 (9.6)
Change from baseline, 95% CI	−31.3 to −17.9	−25.2 to −12.4
P value* for change from baseline	<0.001	<0.001
Between-treatment difference, mm Hg	−5.8 (*P* = 0.19)	

*Unpaired *t* test.

Table V. Overall incidence of adverse events (AEs) in all randomized patients who received at least 1 treatment drug dose (n = 184).

Parameter	Amlodipine/Losartan 5/50 mg (n = 92), no. (%)	Amlodipine 10 mg (n = 92), no. (%)	*P**
Patients with AE	20 (21.7)	24 (26.1)	0.49
No. of AE	38	31	—
No. of serious AE	1 (1.1)	1 (1.1)	1.00
Severity of AE			0.69
Mild	15 (16.3)	21 (22.8)	
Moderate	3 (3.3)	2 (2.2)	
Severe	2 (2.2)	1 (1.1)	
AE that resulted in drop-out	0 (0.00)	2 (2.2)	0.50
Drug-related AE†	6 (6.5)	10 (10.9)	0.30
Dizziness	0 (0.0)	1 (1.1)	—
Headache	2 (2.2)	4 (4.4)	—
Somnolence	0 (0.0)	2 (2.2)	—
Face edema	0 (0.0)	1 (1.1)	—
Fatigue	0 (0.0)	1 (1.1)	—
Edema peripheral	0 (0.0)	1 (1.1)	—
Skin rash	0 (0.0)	2 (2.2)	—
Urticaria generalized	1 (1.1)	0 (0.0)	—
Dyspnea	1 (1.1)	0 (0.0)	—
Libido decreased	0 (0.0)	1 (1.1)	—
Pollakiuria	1 (1.1)	0 (0.0)	—
Orthostatic hypotension	1 (1.1)	0 (0.0)	—
Death	0 (0.0)	0 (0.0)	—

*Statistical analysis by χ^2 test or Fisher's exact test.
†Overlapped calculation.

tient in the fixed-dose combination therapy group had an increase in urinary leukocyte level after treatment. However, these abnormalities were judged to be not related to the treatment drugs. The physical examination results were normal except for 1 patient in the fixed-dose combination therapy group with a paresthesia of the right arm, which was not considered related to the study drug and was reported as an adverse event. None of the ECGs taken at screening and at study completion were clinically significantly abnormal.

DISCUSSION

Current guidelines have recommended that patients with SBP >160 mm Hg or DBP >100 mm Hg should be prescribed 2 or more antihypertensive drugs.[1] These recommendations have now been adopted by many physicians when they first encounter a hypertensive patient, even though the validity of this practice remains to be rigorously tested. Outpatients with hypertension who take only 1 pill are frequently noncompliant, and this poor compliance is often worse when patients have to take several drugs.[1,2] Consequently, to improve the convenience of taking several drugs simultaneously, fixed-dose combination therapy has been developed.[3,6,8–10] This fixed-dose combination therapy may have greater efficacy and better tolerability than free combination therapy or high-dose monotherapy.

Dihydropyridine CCBs are the most widely used antihypertensive drugs in Korea. However, there are some common dose-related adverse events, such as headache, flushing, and edema, that are directly related to their vasodilatory effect.[19] To overcome dose-re-

lated adverse events and to improve the overall efficacy of antihypertensive drugs, various fixed-dose combination therapies have been tried. Among them, a combination of CCBs and angiotensin receptor blockers showed a more substantial blood pressure–lowering effect in SBP and DBP compared with monotherapy. Moreover, these results further support the notion that combining an angiotensin receptor blocker with a CCB reduces the incidence of CCB-induced edema.[20,21]

Notably, whereas 8 weeks of amlodipine 5 mg/losartan 50 mg fixed-dose combination therapy reduced mean DBP in this Phase III trial by 8.85 (6.14) mm Hg, in a Phase II dose ranging clinical trial[22] in which 4 amlodipine/losartan fixed-dose combination groups and 4 amlodipine or losartan dose monotherapy groups were compared (amlodipine 5 mg/losartan 50 mg, amlodipine 5 mg/losartan 100 mg, and amlodipine 10 mg/losartan 50 mg fixed-dose combination therapies), the results revealed that the amlodipine 5 mg/losartan 50 mg combination for 8 weeks decreased average DBP by 15.61 (8.33) mm Hg, which was twice as much as the reduction described in this study. A similar finding was observed for the amlodipine 10 mg monotherapy: In the present study, after 8 weeks, the mean DBP decreased by 9.37 (7.50) mm Hg, whereas in the Phase II study, the decrease was 16.43 mm Hg. These disparities might reflect a difference between the 2 study populations: while the current trial was conducted with hypertensive patients whose hypertension could not be controlled by amlodipine 5 mg, the Phase II trial involved newly diagnosed patients with DBP $>$ 95 mm Hg and $<$115 mm Hg).[22] More than 40% of the patients enrolled in this study were taking CCBs, yet had not attained target blood pressure levels. Moreover, all patients who were randomized were taking amlodipine 5 mg and still did not achieve blood their pressure target after 4 weeks of treatment. It is possible that some or all of these patients were resistant to CCBs, which caused attenuation in the overall response to therapy. An alternative explanation may be that blood pressure response and control may be determined by initial treatment. In the Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Ttreatment Strategy for Hypertension Control (ACCELERATE) trial, whether first-line therapy was a monotherapy or combination was shown to be an important factor in determining the magnitude of blood pressure decrease and control over time.[23]

Another interesting result pertains to the subgroup analysis of patients who had Stage II hypertension. After amlodipine 5 mg treatment for 4 weeks, patients experienced additional reductions in blood pressure. The reductions are worth noting considering that patients had already been treated for 4 weeks with amlodipine 5 mg. This post hoc analysis was conducted on small groups, so this limitation should be considered in the interpretation of these subgroup results. In addition, the results of all of the secondary analyses in this trial should be interpreted with caution because the statistical analyses were powered for the primary efficacy end points.

CONCLUSIONS

The results of this study suggest that 8 weeks of amlodipine 5 mg/losartan 50 mg fixed-dose combination therapy was at least as effective as amlodipine 10 mg monotherapy in lowering DBP after 8 weeks of treatment, and exhibited a safety profile generally comparable to amlodipine 10 mg in hypertensive Korean patients who did not respond appropriately to amlodipine 5 mg monotherapy.

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