

A multicenter, randomized, and double-blind phase IV clinical trial to compare the efficacy and safety of fixed-dose combinations of amlodipine orotate/valsartan 5/160 mg versus valsartan/hydrochlorothiazide 160/12.5 mg in patients with essential hypertension uncontrolled by valsartan 160 mg monotherapy

Youngkeun Ahn, MD, PhD^a, Yongcheol Kim, MD^a, Kiyuk Chang, MD, PhD^b, Weon Kim, MD, PhD^c, Moo-Yong Rhee, MD, PhD^d, Kwang Soo Cha, MD, PhD^e, Min Su Hyon, MD, PhD^f, Chi Young Shim, MD, PhD^g, Sung Yun Lee, MD, PhD^h, Doo Il Kim, MD, PhDⁱ, Sang Wook Kim, MD, PhD^j, Sang-Wook Lim, MD, PhD^k, Kyoo-Rok Han, MD, PhD^l, Sang-Ho Jo, MD, PhD^m, Nae-Hee Lee, MD, PhDⁿ, Jun Kwan, MD, PhD^o, Taehoon Ahn, MD, PhD^{p,*}

Abstract

Background: To determine whether the effectiveness and safety of fixed-dose combinations (FDCs) of amlodipine orotate/valsartan (AML/VAL) 5/160 mg are noninferior to those of valsartan/hydrochlorothiazide (VAL/HCTZ) 160/12.5 mg in hypertensive patients with inadequate response to valsartan 160 mg monotherapy.

Methods: This 8-week, active-controlled, parallel-group, fixed-dose, multicenter, double-blind randomized controlled, and noninferiority trial was conducted at 17 cardiovascular centers in the Republic of Korea. Eligible patients had mean sitting diastolic blood pressure (msDBP) ≥ 90 mm Hg despite monotherapy with valsartan 160 mg for 4 weeks. Patients were randomly assigned to treatment with AML/VAL 5/160 mg FDC (AML/VAL) group or VAL/HCTZ 160/12.5 mg FDC (VAL/HCTZ) group once daily for 8 weeks. A total of 238 patients were enrolled (AML/VAL group, $n = 121$; VAL/HCTZ group, $n = 117$), of whom 228 completed the study.

Results: At 8 weeks after randomization, msDBP was significantly decreased in both groups (-9.44 ± 0.69 mm Hg in the AML/VAL group and -7.47 ± 0.71 mm Hg in the VAL/HCTZ group, both $P < .001$ vs baseline). Between group difference was -1.96 ± 1.00 mm Hg, indicating that AML/VAL 5/160 mg FDC was not inferior to VAL/HCTZ 160/12.5 mg FDC at primary efficacy endpoint. Control rate of BP defined as the percentage of patients achieving mean sitting SBP (msSBP) < 140 mm Hg or msDBP < 90 mm Hg (target BP) from baseline to week 8 was significantly higher in the AML/VAL group than that in the VAL/HCTZ group (84.3% [$n = 102$] in the AML/VAL group vs 71.3% [$n = 82$] in the VAL/HCTZ group, $P = .016$). At 8 weeks after randomization, mean uric acid level was significantly increased in the VAL/HCTZ group compared to that at baseline (0.64 ± 0.08 mg/dL; $P < .001$). However, it was slightly decreased from baseline in the AML/VAL group (-0.12 ± 0.08 mg/dL; $P = .085$). The intergroup difference was significant ($P < .001$).

Editor: Yan Li.

YA and YK contributed equally as first coauthors.

Data Access and Reponsibility: The principal investigator, Taehoon Ahn, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Trial Registration: This trial is registered at the US National Institutes of Health (ClinicalTrials.gov) #NCT02433119.

Funding/support: This research was sponsored by Dong-A ST Co Ltd, Seoul, Republic of Korea.

The authors have no conflicts of interest to disclose.

^a Department of Cardiovascular Medicine, Chonnam National University Hospital, Gwangju, ^b The Catholic University of Korea, Seoul St. Mary's Hospital, ^c Kyung Hee University Hospital, Seoul, ^d Dongguk University Ilsan Hospital, Goyang, ^e Pusan National University Hospital, Busan, ^f Soonchunhyang University Seoul Hospital, Seoul, ^g Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, ^h Inje University Ilsan Paik Hospital, Goyang, ⁱ Inje University Haeundae Paik Hospital, Busan, ^j Chung-Ang University Hospital, Seoul, ^k CHA Bundang Medical Center, CHA University, Seongnam, ^l Hallym University Kangdong Sacred Heart Hospital, Seoul, ^m Hanlym University Sacred Heart Hospital, Anyang, ⁿ Soonchunhyang University Bucheon Hospital, Bucheon, ^o Inha University Hospital, ^p Heart Center, Gachon University Gil Hospital, Incheon, Republic of Korea.

* Correspondence: Taehoon Ahn, Heart Center, Gachon University Gil Hospital, Namdong-daero 774 beon-gil, Namdong-Gu, Incheon 21565, Republic of Korea (e-mail: encore@gilhospital.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc.

This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2018) 97:37(e12329)

Received: 19 February 2018 / Accepted: 21 August 2018

<http://dx.doi.org/10.1097/MD.00000000000012329>

Conclusion: The effectiveness and safety AML/VAL 5/160mg FDC are noninferior to those of VAL/HCTZ 160/12.5mg FDC in patients with hypertension inadequately controlled by valsartan 160mg monotherapy.

Abbreviations: ADR = adverse drug reaction, AE = adverse event, AML/VAL = amlodipine orotate/valsartan, ARB = angiotensin II receptor blocker, BP = blood pressure, CCB = calcium channel blocker, CI = confidence interval, FDC = fixed-dose combination, msDBP = mean sitting diastolic blood pressure, msSBP = mean sitting systolic blood pressure, PP = per protocol, SAE = serious adverse event, VAL/HCTZ = valsartan/hydrochlorothiazide.

Keywords: amlodipine orotate, fixed-dose combination, hypertension, valsartan

1. Introduction

Hypertension is a leading cause of death and the most important risk factor for cardiovascular disease, cerebrovascular disease, and renal disease.^[1–3] Its prevalence is expected to increase from 972 million people in the year of 2000 to 1.56 billion by 2025.^[4] Korean National Health and Nutrition Examination Survey have revealed that age-standardized prevalence of hypertension is approximately 30% among adults over 30 years of age.^[5] In patients with hypertension, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), and diuretics are all suitable for initial antihypertensive treatment.

Valsartan is a nonpeptide ARB used orally to treat hypertension. It inhibits angiotensin type II receptor involved in reducing aldosterone secretion.^[6] This causes arteriolar and venous dilation, resulting in a decrease in blood pressure (BP). Amlodipine is one of the most widely used long-acting dihydropyridine CCB, ensuring sustained antihypertensive effect over 24 hours after a single dose.^[7] Amlodipine orotate was developed based on amlodipine besylate. The BP reducing effect of amlodipine orotate treatment is similar to that of amlodipine besylate in patients with mild to moderate hypertension.^[8]

However, antihypertensive monotherapy does not provide adequate BP control in two-thirds of patients.^[9] A combination of antihypertensive drugs is a useful and appropriate treatment option because it can be more effective in lowering BP than high-dose monotherapy in hypertensive patients unless BP control is achieved by monotherapy.^[10,11] Combination therapy chosen from angiotensin-converting-enzyme inhibitors, ARBs, CCBs, and diuretics is recommended first because it has shown relatively good results.^[12,13] However, direct comparison studies on which drugs are useful in combination therapy for hypertensive patients who are not effectively treated with ARB monotherapy are limited.

Therefore, the objective of this study was to determine whether the efficacy and safety of amlodipine orotate/valsartan (AML/VAL) 5/160mg fixed-dose combination (FDC) were noninferior to those of valsartan/hydrochlorothiazide (VAL/HCTZ) 160/12.5mg FDC for hypertensive patients with not quite effective response to valsartan 160mg monotherapy.

2. Patients and methods

2.1. Study design and patients population

This 8-week, active-controlled, parallel-group, fixed-dose, multicenter, double-blind randomized controlled, and noninferiority trial was conducted at 17 cardiovascular centers in the Republic of Korea between March 2015 and November 2016. This study was approved by the Institutional Review Board of each participating study center (ClinicalTrials.gov registry number: NCT02433119). It was conducted in accordance with the

Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients prior to participation.

List of the Institutional Review Board: Chonnam National University Hospital, Seoul St. Mary's Hospital, Kyung Hee University Hospital, Dongguk University Ilsan Hospital, Pusan National University Hospital, Soon Chun Hyang University Hospital Seoul, Severance Cardiovascular Hospital, Inje University Ilsan Paik Hospital, Inje University Haeundae Paik Hospital, Chung-Ang University Hospital, CHA Bundang Medical Center, Hallym University Kangdong Sacred Heart Hospital, Hanlym University Sacred Heart Hospital, Soon Chun Hyang University Hospital Bucheon, Inha University Hospital, Gachon University Gil Hospital.

The present study included subjects aged ≥ 19 years who were diagnosed with essential hypertension at the first visit. Subjects with medical history or evidence of a secondary hypertension or history of hypersensitivity to CCB, ARB, or sulfonamide were excluded from this study. Additionally, subjects with severe hypertension defined as mean sitting systolic blood pressure (msSBP) ≥ 200 mmHg or mean sitting diastolic blood pressure (msDBP) ≥ 120 mmHg and those with difference in BP (msSBP ≥ 20 mmHg or msDBP ≥ 10 mmHg) between right and left arm at screening evaluation were excluded. The subjects were excluded from the study if they had uncontrolled diabetes (fasting glucose ≥ 200 mg/dL or HbA1c $\geq 9.0\%$), severe heart failure (New York Heart Association Functional class III, IV), ischemic heart disease (angina pectoris, myocardial infarction within 6 months), peripheral vascular disease, second and third degree atrioventricular block, past history of percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, clinically significant arrhythmia, past history of severe cerebrovascular event (within 6 months), transient ischemic attack (within 1 year), moderate to malignant retinopathy, abnormal renal function test result (creatinine clearance < 30 mL/min or serum creatinine ≥ 2 mg/dL), abnormal liver function test result (aspartate transaminase and alanine transaminase ≥ 3.0 times the upper limit of normal), hyperkalemia or hypokalemia, and past history of liver disease.

After screening, eligible patients who had msDBP ≥ 90 mmHg despite monotherapy with valsartan 160mg for 4 weeks were randomly assigned to receive either group AML/VAL 5/160mg FDC (AML/VAL) or VAL/HCTZ 160/12.5mg FDC (VAL/HCTZ) once daily for another 8 weeks without dose adjustment, using block-randomization (Fig. 1).

Patients were instructed to take the study drug once daily at the same time in the morning. At the screening visit, BP was measured in both arms 3 times and the arm with the higher average SiDBP was selected. At each visit, after at least 5 minutes of rest in a sitting position, siSBP, siDBP, and pulse rate were measured 3 times with a 2-minute interval between measurements in the same arm using a semi-automated sphygmomanometer (WatchBP

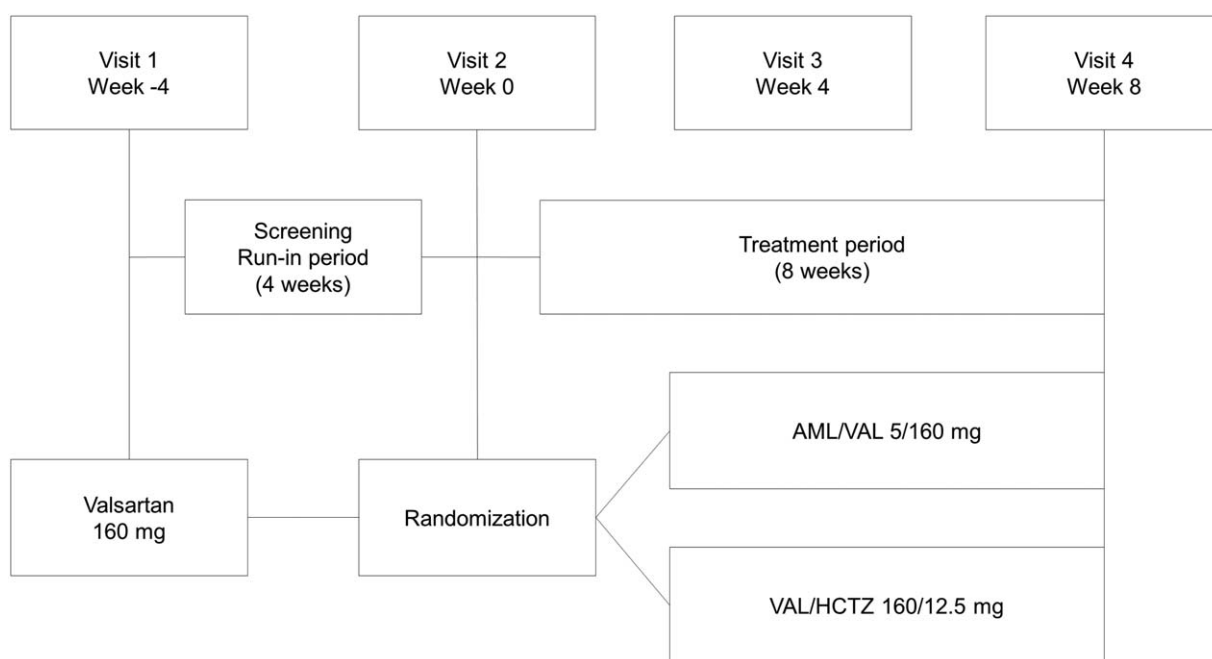


Figure 1. Study design. AML/VAL = amlodipine orotate/valsartan; VAL/HCTZ = valsartan/hydrochlorothiazide.

Office TWIN200, Microlife AG Corporation, Widnau, Switzerland). The average of the 3 sitting BP measurements was used. Thereafter, adverse events (AEs), laboratory data, and physical examination were evaluated.

2.2. Randomization and masking

Randomization code was generated by a statistician using SAS (Ver. 9.3, SAS Institute, Cary, NC) and was stratified by center with a 1:1 ratio. The size of block was 2 or 4. When a patient was eligible for the study by the opinion of investigator, a subject screening number was provided at the visit 1, and subject enrollment number was provided when the subject satisfying enrollment criteria at the visit 2. Drugs corresponding to that the enrollment number were dispensed by a pharmacist. Both patients and investigators were blinded to the group assignment. In addition to the active medication, either AML/VAL or VAL/HCTZ, patients received identical matching placebo.

2.3. Efficacy evaluations

The primary efficacy endpoint was the reduction in msDBP from baseline to week 8. The secondary and other efficacy endpoints were to compare the following: reduction in msDBP from baseline to week 4, reductions in msSBP from baseline to weeks 4 and 8, control rate which was defined as the percentage of patients achieving msSBP <140 mmHg or msDBP < 90 mmHg (target BP) at week 8, response rate defined as the percentage of patients achieving msSBP ≥20 mmHg and msDBP ≥10 mmHg at week 8, and changes in laboratory parameters (total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glucose, creatinine, and uric acid) at week 8.

2.4. Safety assessments

Safety assessments consisted of measuring vital signs, physical examinations, and recording all AEs and adverse drug reaction

(ADRs) at each visit. Laboratory testing included routine hematological and biochemistry parameters at 8 weeks.

2.5. Statistical analysis

The primary efficacy endpoint was the change in msDBP from baseline to 8 weeks after treatment. A sample size of 115 in each group was estimated to be able to provide 80% power to noninferiority between AML/VAL 5/160mg FDC and VAL/HCTZ 160/12.5 mg FDC at 2.5% significance level, assuming a standard deviation of 7.97 for AML/VAL 5/160mg FDC and 8.22 for VAL/HCTZ 160/12.5mg FDC with a noninferiority margin of 3 mmHg. Considering drop-out rate at 10%, a total of 256 patients were enrolled to be randomized.

Efficacy analysis was based on full analysis set (consisted of all randomized patients who received at least 1 dose of study medication and who had at least 1 evaluable primary measurement) and per protocol (PP) set (consisted of all randomized patients who completed the study without any major protocol violation). Last-Observation-Carried-Forward approach was used to impute missing data for the full analysis set. Safety analyses included all randomized patients who received at least 1 dose of study drug and had a measurement of the safety endpoint.

For the primary endpoint, to demonstrate the noninferiority of AML/VAL 5/160mg FDC to VAL/HCTZ 160/12.5mg FDC, if the upper boundary of 2-sided 95% confidence interval (CI) for LS mean difference between the 2 groups was less than the pre-defined noninferiority margin of 3 mmHg, AML/VAL 5/160mg FDC was considered to be noninferior to VAL/HCTZ 160/12.5 mg FDC. An analysis of covariance (ANCOVA) model with baseline BP as a covariate was used to compare the primary endpoint and the secondary endpoints (msDBP reductions from baseline to week 4, msSBP reductions from baseline to weeks 4 and 8) between treatment groups. For the primary endpoint and the secondary endpoints (msDBP reductions from baseline to

week 4, msSBP reductions from baseline to weeks 4 and 8), Chi-square test or Fisher exact test was used to compare control rates and response rates between the 2 groups.

For safety endpoints, frequencies and percentages of patients who experienced AEs were summarized and chi-square test or Fisher exact test was used for comparisons between treatment groups. For continuous variables, intergroup comparisons were performed using 2 sample *t*-test or Wilcoxon rank sum test.

Two-sided *P* values of less than .05 were considered to be statistically significant. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Among 367 patients with hypertension after screening, a total of 238 eligible patients were randomly assigned to the AML/VAL group (*n* = 121) or the VAL/HCTZ group (*n* = 117), of whom 228 completed the study (Fig. 2). Baseline demographic and clinical characteristics of these patients are shown in Table 1.

3.2. Efficacy

Regarding primary efficacy endpoint, the reductions in msDBP from baseline to week 8 were -9.44 (0.69) mmHg in the AML/VAL group and -7.47 (0.71) mmHg in the VAL/HCTZ group (both $P < .001$ vs baseline) (Fig. 3A). The mean difference of the reduction in msDBP from baseline to 8 weeks was -1.96 mmHg between the 2 groups (95% confidence interval [CI]: -3.93 to 0.00 mmHg). The upper limit of 95% CI (at 0.00 mmHg) was less than the predefined noninferiority margin (3 mmHg), confirming that AML/VAL 5/160 mg FDC was not inferior to VAL/HCTZ 160/12.5 mg FDC. Similar results were obtained in the PP set. Reductions in msDBP after 8 weeks of study medication were -9.39 (0.70) mmHg in the AML/VAL group and -7.42 (0.73) mmHg in the VAL/HCTZ group (both $P < 0.001$ vs baseline). The mean difference of the reduction in msDBP from baseline to 8 weeks was -1.97 mmHg between the 2 groups (95% CI: -3.98 to 0.03 mmHg). The upper limit of 95% CI (at 0.03 mmHg) was less than 3 mmHg.

Regarding secondary efficacy endpoint, reductions in msDBP from baseline to week 4 were -9.23 (0.73) mmHg in the AML/VAL group and -7.97 (0.74) mmHg in the VAL/HCTZ group (both $P < .001$ vs baseline) (Fig. 3A). These msDBP reductions at

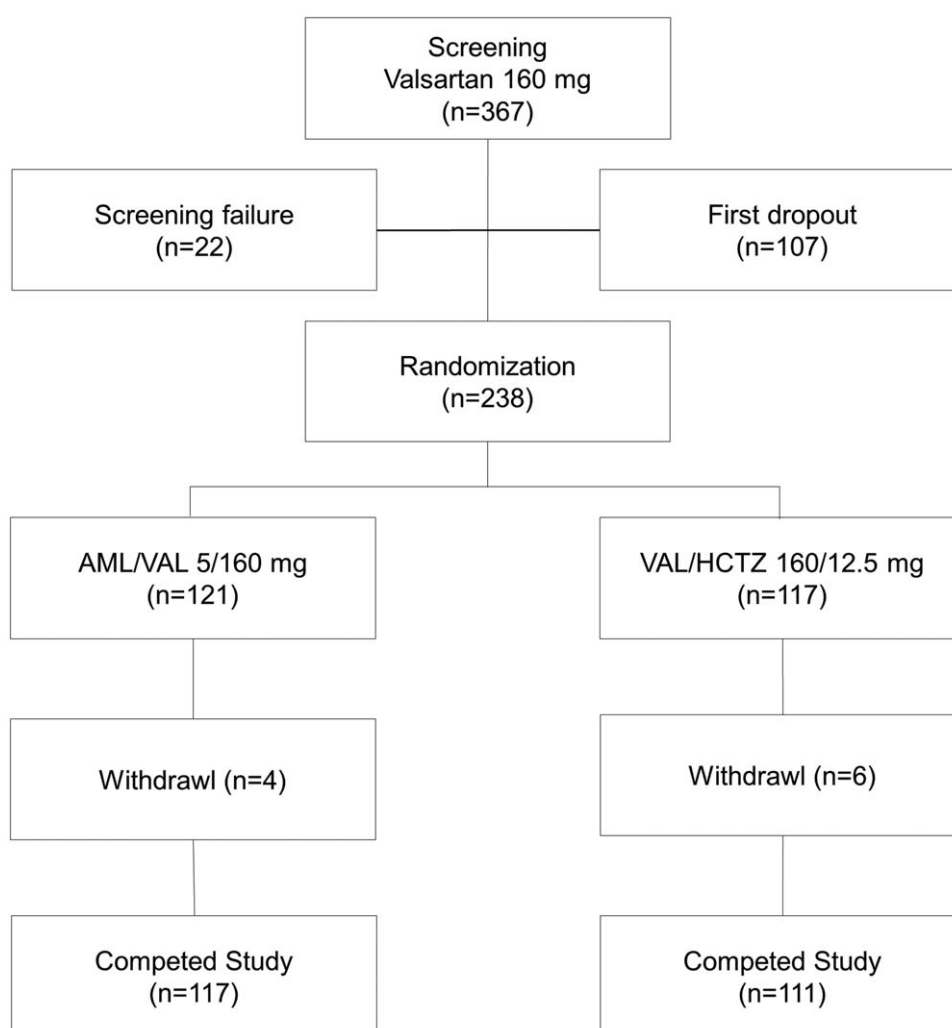


Figure 2. Flow chart of the patients through the study. AML/VAL = amlodipine orotate/valsartan; VAL/HCTZ = valsartan/hydrochlorothiazide.

Table 1**Baseline demographic and clinical characteristics of both groups.**

Characteristics	AML/VAL (n = 121)	VAL/HCTZ (n = 117)	All patients (n = 238)	P [*]
Demographic				
Age, y	56.14 (9.97)	57.74 (11.29)	56.92 (10.65)	.249
Male, no., %	90 (74.4)	96 (82.1)	186 (78.2)	.152
Height, cm	166.08 (7.44)	167.39 (8.26)	166.73 (7.87)	.293
Weight, kg	72.82 (11.68)	72.23 (12.59)	72.53 (12.11)	.450
SBP, mmHg	144.58 (10.62)	148.43 (12.34)	146.47 (11.64)	.011
DBP, mmHg	96.26 (5.43)	97.66 (6.92)	96.95 (6.23)	.291
Pulse rate, beat/min	72.07 (9.33)	72.62 (10.81)	72.34 (10.07)	.571
Clinical				
Smoking history, no., %				.083
None	19 (15.7)	29 (24.8)	48 (20.1)	
Ex-smoker	34 (28.1)	38 (32.5)	72 (30.3)	
Smoker	68 (56.2)	50 (42.7)	118 (49.6)	
Alcohol intake, no., %				.303
None	79 (65.3)	84 (71.8)	163 (68.5)	
Past	7 (5.8)	9 (7.7)	16 (6.7)	
Current	35 (28.9)	24 (20.5)	59 (24.8)	

Data are presented as mean (SD) unless otherwise indicated. AML/VAL, AML/VAL 5/160 mg FDC group; VAL/HCTZ, VAL/HCTZ 100/12.5 mg FDC group. AML/VAL = amlodipine orotate/valsartan, FDC = fixed-dose combination, SD = standard deviation, VAL/HCTZ = valsartan/hydrochlorothiazide.

*AML/VAL vs VAL/HCTZ.

week 4 were not significantly different between the 2 groups ($P=.23$). Reductions of msSBP from baseline to weeks 4 and 8 were -11.81 (0.99) mmHg and -12.17 (1.05) mmHg, respectively, in the AML/VAL group (both $P<.001$). They were -11.43 (1.01) mmHg and -11.24 (1.08) mmHg, respectively, in the VAL/HCTZ group (both $P<.001$) (Fig. 3B). These reductions in msSBP at week 4 or week 8 between the 2 groups were not significantly different ($P=.786$, $P=.54$, respectively). In PP analysis, reductions in msDBP from baseline to week 4 were -9.27 (0.73) mmHg in the AML/VAL group ($P<.001$) and -8.12 (0.76) mmHg in the VAL/HCTZ group ($P<.001$). These msDBP reductions at week 4 were not significantly different

between the 2 groups ($P=0.23$). Reductions of msSBP from baseline to week 4 and week 8 were -11.85 (0.96) mmHg and -12.05 (1.06) mmHg, respectively, in the AML/VAL group (both $P<.001$). They were -11.76 (1.00) mmHg and -11.25 (1.10) mmHg, respectively, in the VAL/HCTZ group (both $P<.001$). These reductions in msSBP at week 4 or week 8 between the 2 groups were not significantly different ($P=.474$, $P=.604$, respectively).

Control rate showed significant difference (84.3% in the AML/VAL group vs 71.3% in the VAL/HCTZ group, $P=.016$). However, response rate was not significantly different between the 2 groups (18.2% in the AML/VAL group vs 22.6% in the

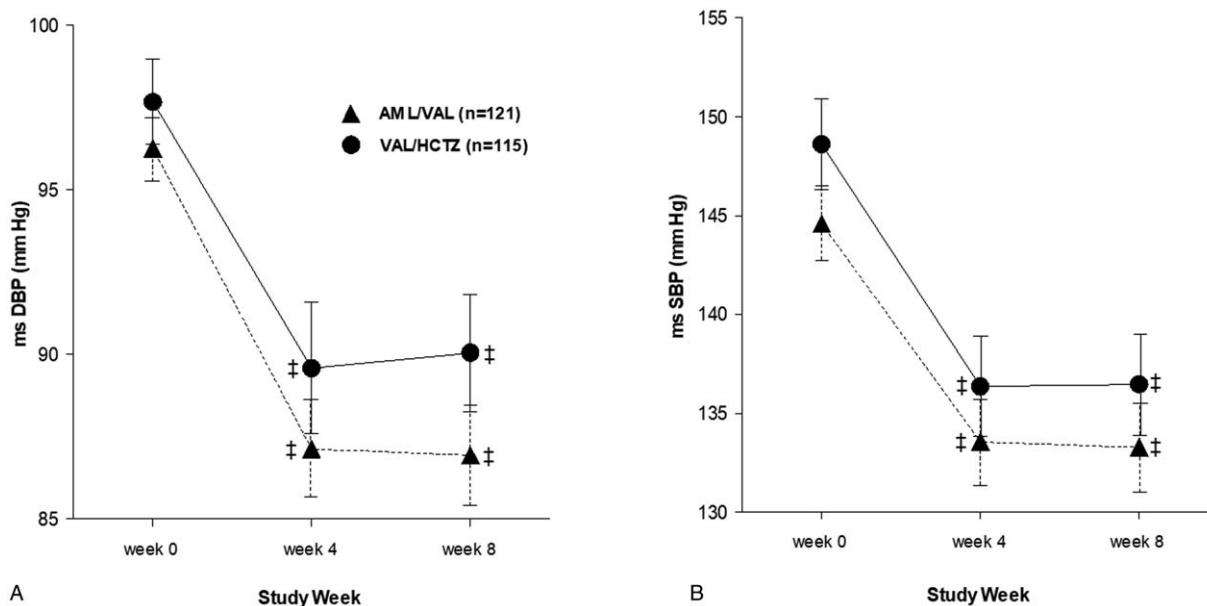


Figure 3. Mean blood pressure change from baseline through 8-week follow-up. (A) msDBP and (B) msSBP. AML/VAL, AML/VAL 5/160mg FDC; VAL/HCTZ, VAL/HCTZ 160/12.5 mg FDC. * $P<.001$ versus baseline. AML/VAL = amlodipine orotate/valsartan, FDC = fixed-dose combination, msDBP = mean sitting diastolic blood pressure, msSBP = mean sitting systolic blood pressure, VAL/HCTZ = valsartan/hydrochlorothiazide.

Table 2**Control and Normalization rate and response rate by group.**

Parameter	AML/VAL (n = 121)	VAL/HCTZ (n = 115)	P
Control rate, no., %			
msDBP < 90 mmHg or msSBP < 140 mmHg	102 (84.3)	82 (71.3)	.016
Response rate, no., %			
Δ msDBP > 10 mmHg and Δ msSBP > 20 mmHg	22 (18.2)	26 (22.6)	.398

AML/VAL, AML/VAL 5/160 mg FDC group; VAL/HCTZ, VAL/HCTZ 100/12.5 mg FDC group. AML/VAL = amlodipine orotate/valsartan, FDC = fixed-dose combination, msDBP = mean sitting diastolic blood pressure, msSBP = mean sitting systolic blood pressure, VAL/HCTZ = valsartan/hydrochlorothiazide.

VAL/HCTZ group, $P = .398$) (Table 2). In PP analysis, response rate at week 8 was not significantly different between the 2 groups either (18.3% in the AML/VAL group vs 20.6% in the VAL/HCTZ group, $P = .665$).

Regarding changes of laboratory parameters at week 8, the mean uric acid level was significantly increased from baseline in the VAL/HCTZ group (0.64 [0.98] mg/dL, $P < .001$). However, it was slightly decreased from baseline in the AML/VAL group (-0.12 [0.08] mg/dL, $P = .085$). The intergroup difference was significant ($P < .001$) (Fig. 4). Lipid, glucose, or creatinine did not show significant changes in either group (Table 3)

3.3. Safety

A total of 236 patients (121 in the AML/VAL group and 115 in the VAL/HCTZ group) were included in the safety set. There were no significant differences in incidence of overall AEs or ADRs between the 2 groups. No serious AEs or serious ADRs were found in either group (Table 4).

4. Discussion

Therapeutic efficacy of combination therapy has been well established. A meta-analysis of 42 randomized trials has shown a 5-fold reduction in BP with a combined use of 2 antihypertensive drugs of different classes compared to doubling the dose of 1 drug alone.^[14] Guidelines have recommended both combination therapies of ARB with an HCTZ and an ARB with a CCB to achieve target BP.^[15,16] In addition, FDC regimens have been well investigated to improve drug compliance in hypertension.^[17] Which ARB-based fixed combination therapy is useful for hypertension uncontrolled by ARB monotherapy remains unclear. Combination therapy with ARB and CCB is one of the preferred regimens. It is the most widely used 2-drug combination for BP reduction.^[15] AML/VAL FDC has clinically demonstrated significant BP lowering effect. It is also well-tolerated in several clinical trials.^[18,19] Furthermore, combination of fixed-dose amlodipine orotate and ARB has demonstrated

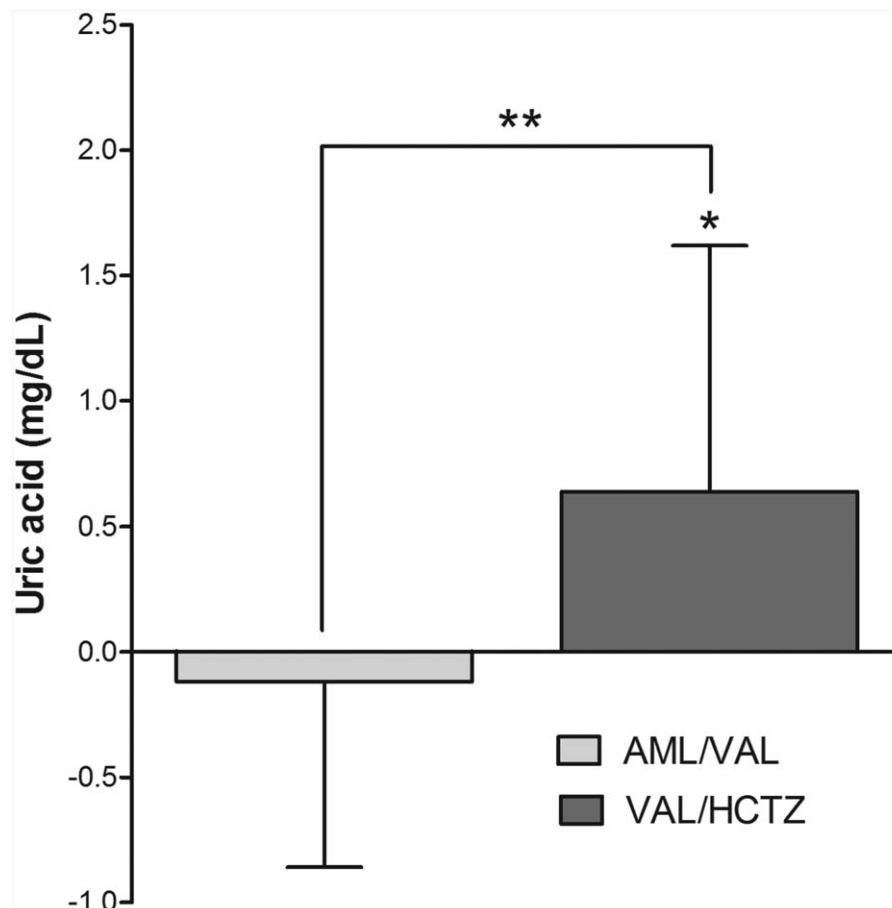


Figure 4. Uric acid level change after 8 weeks of medication. AML/VAL, AML/VAL 5/160 mg FDC; VAL/HCTZ, VAL/HCTZ 160/12.5 mg FDC. * $P < .001$ versus baseline. ** $P < .001$ in intergroup difference. AML/VAL = amlodipine orotate/valsartan, FDC = fixed-dose combination, VAL/HCTZ = valsartan/hydrochlorothiazide.

Table 3**Changes of laboratory parameters at week 8 of both groups.**

Parameter	AML/VAL (n = 121)	VAL/HCTZ (n = 115)	P for treatment difference
Total cholesterol	0.15 (2.40)	4.12 (2.47)	.250
TG	8.23 (9.45)	4.12 (9.73)	.762
HDL-C	-0.7 (0.66)	0.61 (0.68)	.166
LDL-C	-0.01 (2.16)	2.84 (2.23)	.347
Uric acid	-0.12 (0.08)	0.64 (0.08)	<.001
Glucose	1.50 (1.42)	1.00 (1.46)	.807
Creatinine	-0.00 (0.01)	0.02 (0.01)	.072

Data are presented as LS mean (SE). AML/VAL = amlodipine orotate/valsartan, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, VAL/HCTZ = valsartan/hydrochlorothiazide.

the safety and biocompatibility of amlodipine besylate (first marketed as amlodipine) and ARB FDC.^[20]

In our study, FDC of amlodipine orotate and valsartan 5/160 mg significantly decreased BP in patients with hypertension uncontrolled by valsartan 160 mg monotherapy. The DBP lowering effect of FDC of amlodipine orotate and valsartan 5/160 mg was not significantly different from that of FDC of valsartan and HCTZ 160/12.5 mg. In addition, FDC of amlodipine orotate and valsartan 5/160 mg provided rapid and significant BP reduction after only 4 weeks of medication. Although response rates did not differ significantly between the 2 groups, control rate (defined as achieving both target DBP or target SBP at msDBP <90 mmHg and msSBP <140 mmHg) at week 8 was significantly greater in the AML/VAL group compared to those in the VAL/HCTZ group. In terms of effectiveness, our data suggest that the FDC of amlodipine orotate and valsartan 5/160 mg has a rapid, significant BP lowering effect and high achievement rate of the target BP as well.

Hydrochlorothiazide selectively enhances urate reabsorption by acting as a counter-ion for urate transport.^[21] Valsartan does not have a molecular effect of uricosuric action through inhibition of uric acid transporter 1 in hypertensive patients when compared to losartan.^[22] Some studies have shown that valsartan can result in significant increase of serum uric acid level.^[23] In our study, uric acid level was significantly increased

from baseline in the VAL/HCTZ group. However, FDC of amlodipine orotate and valsartan 5/160 mg did not increase serum uric acid level. Instead, it slightly decreased serum uric acid level. The cause of uric acid reduction in AML/VAL group might be due to amlodipine because amlodipine can significantly increase the clearance rate of uric acid.^[24] Furthermore, amlodipine orotate can decrease uric acid level as much as amlodipine besylate after 8 weeks of treatment^[8]. Therefore, FDC of amlodipine orotate and valsartan 5/160 mg might be especially useful for hypertensive patients with hyperuricemia.

Our study has some limitations that are worth mentioning. First, the follow-up period was relatively short (only for 8 weeks). Second, it is difficult to generalize the results of this study because the population studied is different from the population treated in practice. Therefore, a large-scale study is needed to evaluate the long-term efficacy of FDC of amlodipine orotate and valsartan 5/160 mg.

5. Conclusions

The efficacy and safety of FDC with AML/VAL 5/160 mg were found to be noninferior to those of FDC with VAL/HCTZ 160/12.5 mg in patients with hypertension inadequately controlled by valsartan 160 mg monotherapy. In addition, treatment with FDC of AML/VAL 5/160 mg resulted in significantly higher control rate (achieving both target SBP and target DBP) compared to FDC of VAL/HCTZ 160/12.5 mg. In terms of safety, there were no serious AEs and serious ADRs in either group. FDC of AML/VAL 5/160 mg did not increase serum uric acid level either, although FDC of VAL/HCTZ 160/12.5 mg significantly increased serum uric acid level.

Author contributions

All authors were involved in revising the original draft of the manuscript and approved the final draft. All authors were involved in the decision to submit this manuscript for publication. The research sponsor was involved in the design of the study, data collection, and data analysis.

Conceptualization: Doo Il Kim, Nae-Hee Lee, Jun Kwan.

Funding acquisition: Taehoon Ahn.

Investigation: Jun Kwan.

Methodology: Sang Wook Kim, Kyoo-Rok Han, Jun Kwan.

Supervision: Sung Yun Lee, Sang-Wook Lim, Kyoo-Rok Han, Sang-Ho Jo, Taehoon Ahn.

Validation: Sang Wook Kim, Nae-Hee Lee, Taehoon Ahn.

Writing – original draft: Youngkeun Ahn, Yongcheol Kim.

Writing – review & editing: Kiyuk Chang, Weon Kim, Moo-Yong Rhee, Kwang Soo Cha, Min Su Hyon, Chi Young Shim, Sang-Wook Lim, Kyoo-Rok Han, Sang-Ho Jo, Nae-Hee Lee.

Table 4**Summary of adverse events during the study period of both groups.**

Parameter	AML/VAL (n=121) n (%), case	VAL/HCTZ (n=115) n (%), case	P
Overall AE	14 (11.6), 20	11 (9.6), 14	.617
SAE	–	–	
SADR	–	–	
ADR	6 (5.0), 7	3 (2.6), 3	.501
Dizziness	1 (0.8), 1	1 (0.9), 1	
Headache		1 (0.9), 1	
Somnolence	1 (0.8), 1		
Abdominal distension	1 (0.8), 1		
Fatigue	1 (0.8), 1		
Serum CPK increased	1 (0.8), 1		
Serum TG increased	1 (0.8), 1		
Erectile dysfunction		1 (0.9), 1	
Urticaria	1 (0.8), 1		

ADR = adverse drug reaction, AE = adverse event, CPK = creatinine phosphokinase, SADR = serious adverse drug reaction, SAE = serious adverse event, TG = triglyceride.

References

- [1] He J, Whelton PK. Epidemiology and prevention of hypertension. *Med Clin North Am* 1997;81:1077–97.
- [2] Whelton PK. Epidemiology of hypertension. *Lancet* 1994;344:101–6.
- [3] Ezzati M, Lopez AD, Rodgers A, et al. Selected major risk factors and global and regional burden of disease. *Lancet* 2002;360:1347–60.
- [4] Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365:217–23.
- [5] Jee SH, Appel LJ, Suh I, et al. Prevalence of cardiovascular risk factors in South Korean adults: results from the Korea Medical Insurance Corporation (KMIC) Study. *Ann Epidemiol* 1998;8:14–21.
- [6] Black HR, Bailey J, Zappe D, et al. Valsartan: more than a decade of experience. *Drugs* 2009;69:2393–414.

- [7] Jeffers BW, Robbins J, Bhambri R, et al. A Systematic review on the efficacy of amlodipine in the treatment of patients with hypertension with concomitant diabetes mellitus and/or renal dysfunction, when compared with other classes of antihypertensive medication. *Am J Ther* 2015;22:322–41.
- [8] Hong SJ, Ahn TH, Baek SH, et al. Comparison of efficacy and tolerability of amlodipine orotate versus amlodipine besylate in adult patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 8-week follow-up, noninferiority trial. *Clin Ther* 2006;28:537–51.
- [9] Elliott WJ. Is fixed combination therapy appropriate for initial hypertension treatment? *Curr Hypertens Rep* 2002;4:278–85.
- [10] Neutel JM. The role of combination therapy in the management of hypertension. *Nephrol Dial Transplant* 2006;21:1469–73.
- [11] Chrysant SG. Using fixed-dose combination therapies to achieve blood pressure goals. *Clin Drug Investig* 2008;28:713–34.
- [12] Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med* 2008;359:2417–28.
- [13] Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829–40.
- [14] Wald DS, Law M, Morris JK, et al. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am J Med* 2009;122:290–300.
- [15] Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;34:2159–219.
- [16] Shin J, Park JB, Kim KI, et al. 2013 Korean Society of Hypertension guidelines for the management of hypertension. Part II-treatments of hypertension. *Clin Hypertens* 2015;21:2.
- [17] Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010;55:399–407.
- [18] Lins R, Aerts A, Coen N, et al. Effectiveness of amlodipine-valsartan single-pill combinations: hierarchical modeling of blood pressure and total cardiovascular disease risk outcomes (the EXCELLENT study). *Ann Pharmacother* 2011;45:727–39.
- [19] Sison J, Assaad-Khalil SH, Najem R, et al. Real-world clinical experience of amlodipine/valsartan and amlodipine/valsartan/hydrochlorothiazide in hypertension: the EXCITE study. *Curr Med Res Opin* 2014;30:1937–45.
- [20] Lee SY, Kim JR, Jung JA, et al. Bioequivalence evaluation of two amlodipine salts, besylate and orotate, each in a fixed-dose combination with olmesartan in healthy subjects. *Drug Des Devel Ther* 2015;9:2811–7.
- [21] Peterzan MA, Hardy R, Chaturvedi N, et al. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012;59:1104–9.
- [22] Nishida Y, Takahashi Y, Susa N, et al. Comparative effect of angiotensin II type I receptor blockers on serum uric acid in hypertensive patients with type 2 diabetes mellitus: a retrospective observational study. *Cardiovasc Diabetol* 2013;12:159.
- [23] Reyes AJ. Cardiovascular drugs and serum uric acid. *Cardiovasc Drugs Ther* 2003;17:397–414.
- [24] Chanard J, Toupance O, Lavaud S, et al. Amlodipine reduces cyclosporin-induced hyperuricaemia in hypertensive renal transplant recipients. *Nephrol Dial Transplant* 2003;18:2147–53.