J Cardiovasc Imaging. 2020 Jul;28(3):174-182
https://doi.org/10.4250/jcvi.2020.0005
pISSN 2586-7210·eISSN 2586-7296

Journal of Cardiovascular Imaging JCVI

Original Article

Check for updates

# Addition of Amlodipine or Valsartan for Improvement of Diastolic Dysfunction Associated with Hypertension

**Jin Kyung Oh, MD[1,2], Jeong-Sook Seo, MD, PhD[3], Yong Hyun Park, MD, PhD[4], Jae-Hyeong Park, MD, PhD[2], Seung-Ah Lee, MD[1], Sahmin Lee, MD, PhD[1], Dae-Hee Kim, MD, PhD[1], Jong-Min Song, MD, PhD[1], and Duk-Hyun Kang, MD, PhD[1]**

[1]Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, Korea
[2]Division of Cardiology, Department of Internal Medicine, Chungnam National University Hospital, Chungnam National University College of Medicine, Daejeon, Korea
[3]Division of Cardiology, Inje University Busan Paik Hospital, Busan, Korea
[4]Division of Cardiology, Pusan National University Yangsan Hospital, Yangsan, Korea

OPEN ACCESS

**Received:** Jan 20, 2020
**Revised:** Mar 12, 2020
**Accepted:** Apr 16, 2020

**Address for Correspondence:**
**Duk-Hyun Kang, MD, PhD**
Division of Cardiology, Asan Medical Center, College of Medicine, University of Ulsan, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: dhkang@amc.seoul.kr



**ORCID iDs**
Jin Kyung Oh
https://orcid.org/0000-0001-8371-9704
Jeong-Sook Seo
https://orcid.org/0000-0001-6724-4227
Yong Hyun Park
https://orcid.org/0000-0001-6122-214X
Jae-Hyeong Park
https://orcid.org/0000-0001-7035-286X
Seung-Ah Lee
https://orcid.org/0000-0002-4093-7928
Sahmin Lee
https://orcid.org/0000-0003-2250-7948
Dae-Hee Kim
https://orcid.org/0000-0002-8275-4871
Jong-Min Song
https://orcid.org/0000-0002-6754-8199

## ABSTRACT

**BACKGROUND:** Hypertensive patients are at increased risk of diastolic dysfunction. The hypothesis of this study was that addition of amlodipine would be superior to valsartan in improving diastolic dysfunction associated with hypertension.
**METHODS:** In this randomized trial, we randomly assigned 104 controlled, hypertensive patients with diastolic dysfunction to receive either amlodipine 2.5 mg or valsartan 40 mg, in addition to antihypertensive therapy. The primary end point was the change in the ratio of early mitral inflow velocity to early mitral annular relaxation velocity (E/E′) from baseline to the 6-month follow-up. Secondary end points included changes in systolic blood pressure (SBP), left ventricular (LV) mass index, and left atrial volume index.
**RESULTS:** SBP decreased significantly from baseline in both treatment groups ($p < 0.001$). E/E′ decreased significantly from 13.0 ± 2.2 to 12.0 ± 2.7 in the amlodipine arm and from 14.4 ± 4.3 to 12.7 ± 3.7 in the valsartan arm ($p < 0.01$ in both groups). The change of E/E′ was not significantly different between treatment groups ($p = 0.25$). There were also no significant between-group differences regarding the changes in SBP, LV mass index, and left atrial volume index. Two patients (3.8%) in the amlodipine group and 1 (16%) in the valsartan group had serious adverse event.
**CONCLUSIONS:** In this randomized trial involving controlled hypertensive patients, addition of amlodipine or valsartan was associated with an improvement of diastolic dysfunction, but the effects on diastolic dysfunction did not differ significantly between the treatment groups.

**Keywords:** Amlodipine; Valsartan; Diastolic dysfunction; Hypertension

## INTRODUCTION

Approximately half of hypertensive patients have diastolic dysfunction and diastolic dysfunction is associated with development of congestive heart failure (HF) and increased mortality.[1] The

Journal of Cardiovascular Imaging JCVI

Duk-Hyun Kang
https://orcid.org/0000-0003-4031-8649

**Conflict of Interest**
The authors have no financial conflicts of interest.

Framingham study reported that 51% of patients with HF have a preserved left ventricular (LV) ejection fraction (EF) and hypertension (HT) is the strongest risk factor for HF with preserved EF,[2] also termed diastolic heart failure. The rates of death and morbidity in these patients are as high as in patients with HF and a low LVEF.[3] Hypertensive patients are at increased risk of developing LV hypertrophy and myocardial fibrosis, which cause relaxation abnormality and decreased compliance of LV with a rise in the LV diastolic pressure.[4] Although diastolic HF associated with HT is a clinically significant problem, few clinical trials have been conducted and there is no proven pharmacological therapy to improve outcomes. Because the activation of rennin-angiotensin-aldosterone system (RAAS) has been shown to induce LV hypertrophy and myocardial fibrosis,[5] the RAAS may play a central role in the pathogenic process from HT to diastolic HF. Inhibitors of RAAS have been considered as a treatment option for these patients, and the angiotensin receptor blockers (ARB) have been of interest because they antagonize the effects of angiotensin II more completely.[6] However, the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) trial reported that treatment with irbesartan did not reduce the risk of death or hospitalization for cardiovascular causes among 4,128 patients who had HF with a preserved LVEF.[7]

The degree of improvement of diastolic dysfunction was associated with the extent of systolic blood pressure (BP) reduction, whether a RAAS inhibitor or non-RAAS BP lowering was used.[8][9] Amlodipine is a potent and well-tolerated calcium channel blocker (CCB), and seems to be appropriate for lowering systolic BP more aggressively and improving diastolic dysfunction in hypertensive patients, because amlodipine is clinically very useful for controlling systolic BP. Evaluating the effect of treatments on diastolic dysfunction has been limited by difficulties in non-invasive measure of LV diastolic pressure, but recent advances in echocardiography have made it possible to assess diastolic dysfunction accurately and reproducibly.[10] Thus, assessment of diastolic function by echocardiography would be helpful to determine whether addition of amlodipine or an ARB to standard therapy is more beneficial to hypertensive patients with diastolic dysfunction. To the best of our knowledge, there has been no randomized trial to compare the effect of amlodipine versus an ARB on improving diastolic dysfunction in hypertensive patients. We hypothesized that addition of amlodipine to standard antihypertensive therapy would be superior to addition of valsartan in improving diastolic dysfunction by lowering systolic BP more effectively in hypertensive patients, and tried to examine this hypothesis in a prospective, open-label, randomized comparison study using blinded echocardiographic evaluation for end point.

## METHODS

### Study design

We conducted this prospective, multicenter, open-label, randomized trial at four centers in Korea. The principal investigator designed the trial and oversaw the conduct of the trial and data analyses. The study protocol was approved by the institutional review board at each participating center. All patients provided written informed consent.

Eligibility criteria at screening included an age from 40 to 80 years, controlled HT, and presence of diastolic dysfunction. Controlled HT was defined according to the JNC 8th guideline; systolic BP < 150 and diastolic BP < 90 mmHg in persons aged 60 years or older, systolic BP < 140 and diastolic BP < 90 mmHg in persons 40 through 59 years. Diastolic dysfunction was defined as the ratio of mitral inflow velocity to annular relaxation velocity (E/E′) > 10.[4]


https://doi.org/10.4250/jcvi.2020.0005

Journal of Cardiovascular Imaging JCVI

Exclusion criteria at screening included uncontrolled HT, symptomatic hypotension, a systolic BP of less than 100 mmHg, serum creatinine ≥ 2.5 mg/dL, LVEF < 50%, pregnancy, or a history of intolerance to ARB or amlodipine. Patients were also excluded from the trial if they had moderate or severe valve disease; hypertrophic or restrictive cardiomyopathy; constrictive pericarditis; atrial fibrillation with a heart rate > 120/min; stroke or coronary revascularization within 6 months; cancer within 3 years; a plan of major surgery during the trial.

### Study procedures

We randomly assigned hypertensive patients with diastolic dysfunction in a 1:1 ratio to treatment with either amlodipine or valsartan in addition to standard antihypertensive therapy with the use of a computerized randomization system. After randomization, patients were started on amlodipine 2.5 mg daily or valsartan 40 mg daily. All antihypertensive drug treatment including ARBs, angiotensin converting enzyme (ACE) inhibitors, CCBs, beta blockers and diuretics were continued. Patients were treated for 6 months and evaluated every 2 months.

Echocardiographic evaluation was performed at randomization and at the 6-month follow-up or early termination visits. Experienced sonographers who are unaware of the patients' clinical characteristics and treatment assignments, performed a standard two-dimensional and Doppler echocardiographic examination on all patients using a commercial echocardiography system. The primary and secondary echocardiographic efficacy analyses were done on off-line digital computerized review system by investigators who are blinded to treatment allocation and previous echocardiographic measures. Doppler tissue interrogation of early diastolic mitral annular relaxation velocity (E′) was recorded at the septal annulus,[10] and additional echocardiographic assessments include the peak velocity of early mitral inflow (E), and the ratio of E/E′. In addition to the Doppler variables, the end-systolic volume, end-diastolic volume, and EF of the LV were calculated with the biplane Simpson method.[11] LV mass and left atrial (LA) volume were also measured and corrected for body surface area.

### End points

The primary end point was change in the ratio of E velocity to E′ velocity from baseline to 24 weeks follow-up. Secondary end points included changes in systolic BP, LV mass index, and LA volume index.

### Statistical analysis

We assumed a baseline mean E/E′ ratio of 10.0 and a common standard deviation of 2.7.[8] Given these assumptions, we calculated that a sample size of 102 patients randomly assigned to two groups, would provide 80% power to detect a 15% difference in the E/E′ ratio between groups, using a two-sided t test with an alpha level of 0.05. The primary analysis was prespecified as measurement of a change between baseline and 6-month follow-up or the last assessment, and included all randomized patients who had a baseline and at least one follow-up assessment, according to the intention-to-treat principle. Baseline clinical and echocardiographic characteristics were compared in the two treatment groups with the use of the Student t test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables as appropriate. The null hypothesis was that there would be no between-group difference regarding the change in E/E′ ratio from baseline to 6-month follow-up. This hypothesis was tested in an intention-to-treat analysis. For the primary and secondary end points, we used the t-test methods for differences between groups as described in the protocol. The correlation of the secondary endpoints with the


https://doi.org/10.4250/jcvi.2020.0005

Journal of Cardiovascular Imaging JCVI

primary endpoint (E/E′ ratio) and their respective changes were also be analyzed. All reported p values were 2 sided, and a p value < 0.05 was considered statistically significant.

## RESULTS

Between December 2016 and November 2018, we enrolled a total of 104 patients; 52 patients were randomly assigned to amlodipine and 52 to valsartan. The numbers of patients who were screened, randomly assigned to a treatment group and included in the primary analysis are shown in **Figure 1**. Baseline characteristics of enrolled patients are listed in **Table 1**. The mean age of the patients was 66.0 ± 9.4 years and 65% were men. Mean systolic BP/diastolic BP was 138 ± 12 / 80 ± 7 mmHg. Ninety-nine patients (95%) had been taking either an ARB or CCB, and 61 patients (59%) were on both ARB and CCB before enrollment. By design, all of the study patients had evidence of diastolic dysfunction, with mean E/E′ of 13.4 ± 3.3. Mean LV mass index was 101.5 ± 20.3 g/m$^2$ and mean LA volume index was 34.6 ± 11.8 mL/m$^2$. E/E′ was not related to BP or LV mass index, but related to LA volume index (r = 0.26, p = 0.010). There were no significant differences in any baseline characteristics between treatment groups.

Follow-up clinical and echocardiographic examination was performed on 87 patients (84%) and not performed on 17 (16%) who withdrew from therapy. Systolic BP decreased significantly from baseline in both treatment groups (p < 0.001; **Table 2**), but decreases in diastolic BP were not significant. In the amlodipine arm, BP was changed from 139 ± 11 / 81 ± 7 to 129 ± 14 / 78 ± 9 mmHg and from 138 ± 12 / 80 ± 8 to 129 ± 14 / 80 ± 12 mmHg in the valsartan arm. The difference in BP reduction did not significantly differ between treatment groups.

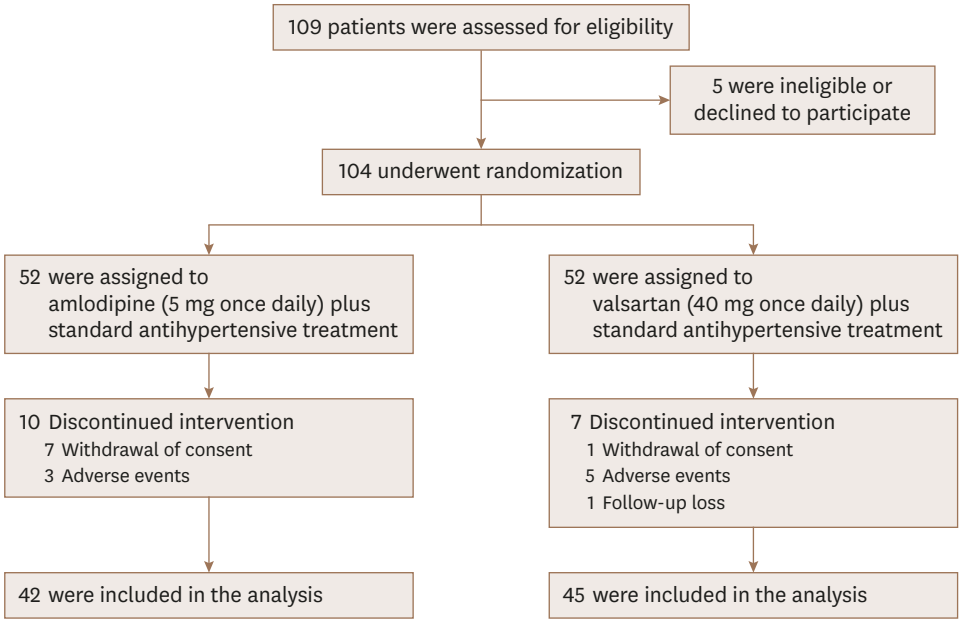


**Figure 1.** Eligibility, randomization, and follow-up. Of the 109 patients who were assessed for eligibility, 5 were excluded. Of the 104 patients who underwent randomization, 52 were assigned to amlodipine group and 52 to the valsartan group; Follow-up clinical and echocardiographic examination was not performed on 17 who withdrew from therapy, and 87 were included in the analysis.


https://doi.org/10.4250/jcvi.2020.0005

Journal of Cardiovascular Imaging JCVI

**Table 1.** Baseline clinical characteristics

| Variables | Amlodipine group (n = 52) | Valsartan group (n = 52) |
|---|---|---|
| Age (years) | 65.3 ± 9.6 | 66.7 ± 9.2 |
| Male gender | 35 (67.3) | 33 (63.5) |
| Body mass index (kg/m$^2$)* | 26.7 ± 3.7 | 26.2 ± 3.5 |
| Systolic blood pressure (mmHg) | 136.9 ± 11.7 | 138.8 ± 11.7 |
| Diastolic blood pressure (mmHg) | 80.4 ± 6.9 | 80.5 ± 7.9 |
| Heart rate | 69.6 ± 12.8 | 67.1 ± 10.9 |
| Medical history | | |
| Diabetes mellitus | 16 (30.8) | 14 (26.9) |
| Hyperlipidemia | 35 (69.2) | 35 (67.3) |
| Chronic kidney disease† | 5 (11.6) | 4 (9.1) |
| Coronary artery disease | 14 (26.9) | 15 (28.8) |
| Previous history of PCI or CABG | 10 (19.2) | 8 (15.4) |
| Stroke or transient ischemic attack | 2 (3.8) | 1 (1.9) |
| Atrial fibrillation or flutter | 0 (0.0) | 2 (3.8) |
| Antihypertensive medication | | |
| ACE inhibitor | 0 (0.0) | 3 (5.8) |
| ARB | 44 (86.3) | 43 (82.7) |
| Calcium-channel blocker | 40 (78.4) | 33 (63.5) |
| Beta-blocker | 18 (35.3) | 24 (46.2) |
| Diuretic | 9 (17.3) | 9 (17.3) |
| Others | 4 (7.8) | 0 (0.0) |
| Not using antihypertensive agent | 0 (0.0) | 0 (0.0) |
| Echocardiographic variables | | |
| Medial E/E′ ratio | 12.9 ± 2.2 | 14.0 ± 4.1 |
| E (cm/s) | 64.8 ± 13.5 | 68.6 ± 15.4 |
| E′ (cm/s) | 5.1 ± 1.0 | 5.2 ± 1.5 |
| E/A ratio | 0.85 ± 0.22 | 0.87 ± 0.23 |
| Deceleration time (ms) | 237.4 ± 64.4 | 220.2 ± 50.8 |
| LV mass index (g/m$^2$) | 104.2 ± 23.3 | 99.1 ± 17.0 |
| LA volume index (mL/m$^2$) | 33.8 ± 10.6 | 35.6 ± 12.9 |
| LV end-systolic volume (mL) | 37.0 ± 15.5 | 35.8 ± 10.4 |
| LV end-diastolic volume (mL) | 95.3 ± 30.2 | 95.3 ± 24.0 |
| Ejection fraction (%) | 62.4 ± 4.5 | 62.6 ± 4.5 |
| LV posterior wall thickness (mm) | 10.0 ± 1.4 | 9.6 ± 1.1 |
| LV septal wall thickness (mm) | 10.2 ± 1.6 | 9.8 ± 1.2 |
| TR velocity (m/s) | 2.4 ± 0.3 | 2.3 ± 0.2 |
| Laboratory measurements | | |
| Hemoglobin (g/dL) | 13.9 ± 1.5 | 13.8 ± 1.5 |
| AST (IU/L) | 29.2 ± 12.0 | 25.2 ± 6.7 |
| ALT (IU/L) | 28.6 ± 14.3 | 23.7 ± 7.8 |
| Fasting total cholesterol (mg/dL) | 162.6 ± 31.1 | 160.2 ± 23.4 |
| Fasting plasma glucose (mg/dL) | 135.9 ± 53.6 | 124.7 ± 30.9 |
| Creatinine (ng/dL) | 0.89 ± 0.28 | 0.87 ± 0.22 |
| Estimated GFR (mL/min/1.73 m$^2$) | 84.6 ± 19.7 | 84.0 ± 18.4 |
| Potassium (mmol/L) | 4.2 ± 0.5 | 4.3 ± 0.6 |

Data shown are number (%) not otherwise specified.
*The body-mass index is the weight in kilograms divided by the square of the height in meters.
†Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL per minute per 1.73 m$^2$ of body-surface area.
ACE: angiotensin-converting enzyme, ALT: alanine aminotransferase, ARB: angiotensin receptor blocker, AST: aspartate aminotransferase, CABG: coronary-artery bypass grafting, GFR: estimated glomerular filtration rate, LA: left atrium, LV: left ventricle, PCI: percutaneous coronary intervention, TR: tricuspid regurgitation.

Echocardiographic measures at baseline and 24 weeks follow-up, and changes in echocardiographic measures are shown in **Table 2**. E′ significantly increased in both treatment groups from baseline to follow-up ($p < 0.01$), whereas E did not change significantly in both groups. The ratio of E/E′, the primary end point, decreased significantly from 13.0 ± 2.2 to 12.0 ± 2.7 in the amlodipine arm and from 14.4 ± 4.3 to 12.7 ± 3.7 in the


https://doi.org/10.4250/jcvi.2020.0005

**Table 2.** Hemodynamic data at baseline and 24weeks, and change between treatment groups

| | Baseline | | | 24 weeks | | | Change (24 weeks-baseline) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Amlodipine (n = 42) | Valsartan (n = 45) | p value | Amlodipine (n = 42) | Valsartan (n = 45) | p value | Amlodipine (n = 42) | p value* | Valsartan (n = 45) | p value* | p value |
| Systolic blood pressure (mmHg) | 138.6 ± 10.8 | 137.8 ± 12.1 | 0.769 | 129.4 ± 13.7 | 128.6 ± 14.2 | 0.772 | −9.14 ± 12.93 | < 0.001 | −9.29 ± 14.30 | < 0.001 | 0.960 |
| Diastolic blood pressure (mmHg) | 80.8 ± 6.7 | 80.3 ± 8.0 | 0.757 | 78.1 ± 8.9 | 80.0 ± 11.9 | 0.400 | −2.64 ± 8.60 | 0.053 | −0.24 ± 9.16 | 0.859 | 0.212 |
| Medial E/E′ ratio | 13.0 ± 2.2 | 14.4 ± 4.3 | 0.070 | 12.0 ± 2.7 | 12.7 ± 3.7 | 0.367 | −0.99 ± 1.87 | 0.001 | −1.68 ± 3.44 | 0.002 | 0.254 |
| E (cm/s) | 63.6 ± 14.0 | 69.3 ± 13.5 | 0.057 | 63.1 ± 14.7 | 67.5 ± 14.1 | 0.159 | −0.56 ± 9.74 | 0.712 | −1.87 ± 13.25 | 0.349 | 0.603 |
| E′ (cm/s) | 4.9 ± 1.0 | 5.1 ± 1.4 | 0.517 | 5.3 ± 1.1 | 5.6 ± 1.5 | 0.257 | 0.39 ± 0.83 | 0.004 | 0.55 ± 0.87 | < 0.001 | 0.411 |
| E/A ratio | 0.85 ± 0.24 | 0.86 ± 0.23 | 0.768 | 0.82 ± 0.21 | 0.85 ± 0.19 | 0.505 | −0.03 ± 0.11 | 0.137 | −0.01 ± 0.18 | 0.635 | 0.715 |
| Deceleration time (ms) | 242.6 ± 64.3 | 218.1 ± 53.5 | 0.057 | 240.5 ± 53.3 | 219.0 ± 37.8 | 0.032 | −2.18 ± 69.41 | 0.840 | 0.48 ± 54.92 | 0.957 | 0.843 |
| LV end-systolic volume (mL) | 37.7 ± 16.5 | 36.7 ± 10.8 | 0.439 | 39.2 ± 17.4 | 37.6 ± 10.0 | 0.641 | 1.63 ± 9.20 | 0.302 | 0.97 ± 6.97 | 0.394 | 0.731 |
| LV end-diastolic volume (mL) | 95.6 ± 31.3 | 97.0 ± 24.9 | 0.833 | 99.7 ± 37.5 | 101.2 ± 24.3 | 0.836 | 4.54 ± 23.59 | 0.262 | 4.16 ± 17.89 | 0.160 | 0.973 |
| Ejection fraction (%) | 62.3 ± 4.6 | 62.3 ± 4.6 | 0.969 | 62.4 ± 5.3 | 62.3 ± 4.7 | 0.915 | 0.07 ± 4.00 | 0.907 | −0.01 ± 4.04 | 0.993 | 0.928 |
| LV mass index (g/m$^2$) | 104.8 ± 21.8 | 99.7 ± 17.2 | 0.249 | 101.5 ± 22.7 | 99.8 ± 16.7 | 0.696 | −3.77 ± 7.70 | 0.006 | 0.03 ± 10.08 | 0.986 | 0.067 |
| LA volume index (mL/m$^2$) | 34.1 ± 10.4 | 35.9 ± 12.9 | 0.484 | 33.9 ± 9.7 | 39.0 ± 16.8 | 0.096 | −0.50 ± 6.49 | 0.629 | 3.15 ± 10.17 | 0.043 | 0.055 |
| LV posterior wall thickness (mm) | 10.1 ± 1.4 | 9.7 ± 1.1 | 0.126 | 9.7 ± 1.7 | 9.6 ± 1.1 | 0.721 | −0.40 ± 0.67 | 0.001 | −0.08 ± 0.66 | 0.413 | 0.038 |
| LV septal wall thickness (mm) | 10.3 ± 1.7 | 9.8 ± 1.3 | 0.173 | 10.1 ± 1.7 | 9.7 ± 1.1 | 0.244 | −0.24 ± 0.82 | 0.089 | −0.15 ± 0.73 | 0.170 | 0.636 |
| TR velocity (m/s) | 2.4 ± 0.3 | 2.3 ± 0.2 | 0.428 | 2.3 ± 0.2 | 2.4 ± 0.2 | 0.406 | −0.01 ± 0.24 | 0.712 | 0.07 ± 0.23 | 0.057 | 0.124 |

*p values changes reflect within-group differences.
LA: left atrium, LV: left ventricle, TR: tricuspid regurgitation.

valsartan arm (p < 0.01 in both groups) (**Figure 2**). E/E′ was decreased in patients (76.2%) in the amlodipine arm and patients (77.8%) in the valsartan arm, respectively, and the difference was not significant (p = 1.000). The change of E/E′ from baseline to 24 weeks follow-up was -0.99 ± 1.87 in the amlodipine arm and -1.68 ± 3.44 in the valsartan arm, and was not significantly different between treatment groups (p = 0.25). There were also no significant differences between the treatment groups in the secondary end points, changes in LV mass index (p = 0.067) and LA volume index (p = 0.055). In the exploratory correlation analysis, change of systolic BP was not related to change in E′ or E/E′, but related to change in LV mass index (r = 0.85) and change in LA volume index (r = 0.69) (p < 0.001 for both).

Both amlodipine 2.5 mg and valsartan 40 mg regimens were well tolerated. During follow-up, 2 patients (3.8%) had serious adverse events in the amlodipine group; 1 (1.9%) had serious adverse event in the valsartan group (**Table 3**).

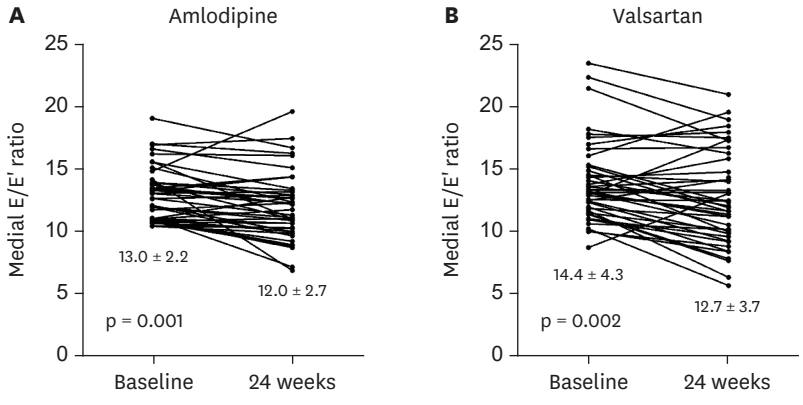


**Figure 2.** Change of medial E/E′ ratio in the two treatment groups over 24 weeks. Medial E/E′ ratio was significantly decreased at 24 weeks in the both amlodipine (A) and valsartan group (B). The change of E/E′ from baseline to 24 weeks follow-up was not significantly different between treatment groups. Graphs depict individual changes of medial E/E′ ratio. Data were analyzed using paired and unpaired Student's t test and shown as means ± SD.


https://doi.org/10.4250/jcvi.2020.0005

Journal of Cardiovascular Imaging JCVI

**Table 3.** Investigator-reported adverse events

| | Amlodipine (n = 52) | Valsartan (n = 52) |
|---|---|---|
| Serious adverse event* | 2 | 1 |
| Hypotension | 0 | 1 |
| Dizziness | 1 | 1 |
| Palpitation | 1 | 0 |
| Edema | 1 | 2 |
| General weakness | 0 | 2 |
| Dyspnea | 0 | 1 |
| Dyspepsia | 0 | 1 |
| Facial flushing | 0 | 1 |
| Itching sense | 1 | 0 |
| Neck pain | 1 | 0 |
| Fracture | 1 | 0 |

*In the amlodipine arm, 2 serious adverse events occurred due to hospitalization for urinary tract infection and diabetic foot. In the valsartan arm, 1 serious adverse event occurred due to hospitalization for femur neck fracture. None of these events were deemed to be treatment related.

## DISCUSSION

We found that addition of low-dose ARB or CCB was associated with small but significant reduction of systolic BP and improvement of diastolic function in patients with HT under control. The extent of BP reduction with amlodipine was similar to that with valsartan, and no difference was observed in changes of echocardiographic measures for diastolic dysfunction between the treatment groups.

In this study, we hypothesized that addition of amlodipine to standard antihypertensive therapy would be superior to addition of valsartan in lowering systolic BP, because previous trials reported that ACE inhibitor or ARB was used more frequently than CCB for antihypertensive therapy at baseline,[9] and additional BP lowering effect of ARB would be smaller in patients who had been taking ACE inhibitor or ARB, whereas combination of CCB with ARB has a synergistic BP-lowering effect. We enrolled patients fulfilling criteria for diastolic dysfunction and age of study patients were relatively older than previous trials.[8][9] Thus, the percentage of patients using ACE inhibitor or ARB for control of HT at baseline was similar to that of patients using CCB and most patients were on combined treatment with a CCB and a RAAS inhibitor during the trial period, which might explain our finding that no difference was observed in reduction of systolic BP between the treatment groups. In an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy, patients receiving treatment with an amlodipine-based regimen had better diastolic function than patients treated with the atenolol-based regimen, independent of BP reduction,[12] and in the VALIDD (Valsartan in Diastolic Dysfunction) study, there was no significant difference in the change in early diastolic relaxation velocity among hypertensive patients who were randomly assigned to valsartan or placebo.[8] Although we hypothesized that amlodipine would be superior to valsartan in improving diastolic dysfunction, changes in the ratio of E/E′ did not differ significantly in this randomized trial comparing amlodipine with valsartan. Because lowering BP was associated with improvement in diastolic dysfunction,[8][9] similar reduction of BP might contribute to no significant differences in changes of echocardiographic variables related to diastolic dysfunction between the treatment groups.

Although average reduction of systolic BP was only 9 mmHg in this study, add-on therapy with either low-dose amlodipine or valsartan was associated with improvement of diastolic dysfunction. The Systolic Blood Pressure Intervention Trial (SPRINT) compared the benefit


https://doi.org/10.4250/jcvi.2020.0005

Journal of Cardiovascular Imaging JCVI

of treatment of systolic BP to a target of less than 120 mmHg with treatment to a target of less than 140 mmHg, and reported that targeting a systolic BP of less than 120 mmHg, as compared with less than 140 mmHg, resulted in lower rates of fatal and nonfatal major cardiovascular events and all-cause death.[13] Though current guidelines do not set the lower target of systolic BP for hypertensive patients with diastolic dysfunction, add-on therapy with low-dose CCB or ARB, might be a well-tolerated treatment option for improvement of diastolic dysfunction in controlled, hypertensive patients with systolic BP in the range of 120 to 140 mmHg.

Echocardiographic assessment of diastolic function allows the diagnosis of HF that are frequently missed, especially in patients with normal LVEF.[14] Tissue Doppler imaging is used for recording the longitudinal velocities of the mitral annulus, and E′ reflects early ATP-dependent, active relaxation of myocardium.[8] A decrease in E′ is the robust echocardiographic measure of diastolic dysfunction and less sensitive to preload than the mitral inflow profiles.[15] Because E′ remains reduced and E increases with higher LV filling pressure, E/E′ correlates well with LV filling pressure and is the best parameter to estimate LA and LV end-diastolic pressure in patients with a normal LVEF.[14][16] Because estimation of LV filling pressure is the most important in assessing the response to treatment of patients with diastolic dysfunction, E/E′ was selected for the primary end point of this study.

### Study limitations

Our trial is a mechanistic study, not an outcome trial. Thus, our results do not suggest that a CCB or ARB should be added to controlled hypertensive patients with diastolic dysfunction.

We tried to perform follow-up echocardiographic evaluation on all of the 104 patients who underwent randomization, but 17 who withdrew from therapy refused to undergo follow-up assessment and primary analysis included only 87 patients with follow-up echocardiographic assessment done.

### Conclusion

In this randomized trial comparing amlodipine with valsartan among controlled hypertensive patients, the effects for diastolic dysfunction did not differ significantly between the treatment groups. Addition of low-dose CCB or ARB was associated with a significant improvement of diastolic dysfunction.

## ACKNOWLEDGMENTS

This work was supported by Yuhan Corporation.

## REFERENCES

1. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;275:1557-62.
PUBMED | CROSSREF
2. Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999;33:1948-55.
PUBMED | CROSSREF


https://doi.org/10.4250/jcvi.2020.0005

3. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-9.
PUBMED | CROSSREF
4. European Study Group. How to diagnose diastolic heart failure. *Eur Heart J* 1998;19:990-1003.
PUBMED | CROSSREF
5. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991;83:1849-65.
PUBMED | CROSSREF
6. Desai A. Current understanding of heart failure with preserved ejection fraction. *Curr Opin Cardiol* 2007;22:578-85.
PUBMED
7. Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. *N Engl J Med* 2008;359:2456-67.
PUBMED | CROSSREF
8. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomised trial. *Lancet* 2007;369:2079-87.
PUBMED | CROSSREF
9. Solomon SD, Verma A, Desai A, et al. Effect of intensive versus standard blood pressure lowering on diastolic function in patients with uncontrolled hypertension and diastolic dysfunction. *Hypertension* 2010;55:241-8.
PUBMED | CROSSREF
10. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quiñones MA. Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol* 1997;30:1527-33.
PUBMED | CROSSREF
11. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.
PUBMED | CROSSREF
12. Tapp RJ, Sharp A, Stanton AV, et al. Differential effects of antihypertensive treatment on left ventricular diastolic function: an ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) substudy. *J Am Coll Cardiol* 2010;55:1875-81.
PUBMED | CROSSREF
13. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;373:2103-16.
PUBMED | CROSSREF
14. Oh JK. Assessment of diastolic function and diastolic heart failure. In: Oh JK, Seward JB, Tajik AJ, editors. The Echo Manual. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2007. p.120-42.
15. Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol* 1997;30:474-80.
PUBMED | CROSSREF
16. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. *Circulation* 2000;102:1788-94.
PUBMED | CROSSREF