Comparison Between Valsartan and Amlodipine Regarding Cardiovascular Morbidity and Mortality in Hypertensive Patients With Glucose Intolerance

NAGOYA HEART Study

Takashi Muramatsu, Kunihiro Matsushita, Kentaro Yamashita, Takahisa Kondo, Kengo Maeda, Satoshi Shintani, Satoshi Ichimiyi, Miyoshi Ohno, Takahito Sone, Nobuho Ikeda, Masato Watarai, Toyoaki Murohara, for the NAGOYA HEART Study Investigators

Abstract—It has not been fully examined whether angiotensin II receptor blocker is superior to calcium channel blocker to reduce cardiovascular events in hypertensive patients with glucose intolerance. A prospective, open-labeled, randomized, controlled trial was conducted for Japanese hypertensive patients with type 2 diabetes mellitus or impaired glucose tolerance. A total of 1150 patients (women: 34%; mean age: 63 years; diabetes mellitus: 82%) were randomly assigned to receive either valsartan- or amlodipine-based antihypertensive treatment. Primary outcome was a composite of acute myocardial infarction, stroke, coronary revascularization, admission attributed to heart failure, or sudden cardiac death. Blood pressure was 145/82 and 144/81 mmHg, and glycosylated hemoglobin was 7.0% and 6.9% at baseline in the valsartan group and the amlodipine group, respectively. Both of them were equally controlled between the 2 groups during the study. The median follow-up period was 3.2 years, and primary outcome had occurred in 54 patients in the valsartan group and 56 in the amlodipine group (hazard ratio: 0.97 [95% CI: 0.66–1.40]; P=0.85). Patients in the valsartan group had a significantly lower incidence of heart failure than in the amlodipine group (hazard ratio: 0.20 [95% CI: 0.06–0.69]; P=0.01). Other components and all-cause mortality were not significantly different between the 2 groups. Composite cardiovascular outcomes were comparable between the valsartan- and amlodipine-based treatments in Japanese hypertensive patients with glucose intolerance. Admission because of heart failure was significantly less in the valsartan group. (Hypertension. 2012;59:580-586.) ● Online Data Supplement

Key Words: angiotensin II type 1 receptor blocker ● calcium channel blocker ● cardiovascular disease ● diabetes mellitus ● hypertension ● impaired glucose tolerance

Hypertension and type 2 diabetes mellitus (T2DM) are major risk factors for cardiovascular diseases (CVDs), and a combination of those further increases CVD.1-3 Activation of the renin-angiotensin system exacerbates not only hypertension but also insulin resistance and diabetic vascular complications.4-6 Indeed, various renin-angiotensin system blockers (ie, angiotensin-converting enzyme inhibitor [ACEI] or angiotensin II type 1 receptor blocker [ARB]) have been shown to suppress new onset of T2DM and to reduce the progression of diabetic nephropathy.7-10 Hence, many guidelines worldwide recommend ACEI/ARB as the first-line antihypertensive medications for diabetic hypertensive patients.11-14 Several clinical trials previously assessed head-to-head comparisons between ACEI/ARB and calcium channel blocker (CCB) regarding the efficacies on CVD.15-21 In diabetic hypertensive patients, some small-sample trials showed that ACEI significantly reduced the risk of CVD compared with CCB,15,16 whereas another large-scale trial showed no difference.17 The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) and Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) trials, which recruited 5250 (34%) and 2018 patients (43%) with T2DM, respectively,18,19 showed that ARB significantly reduced new onset of T2DM but failed to reduce total CVD compared with CCB. The Irbesartan Diabetic Nephropathy Trial (IDNT) also compared ARB and CCB in...
diabetic patients with nephropathy. Although the IDNT revealed better renal protection by ARB than CCB as a primary outcome, ARB and CCB had similar efficacies on composite CVD as a secondary outcome. Among the components, ARB was more protective against heart failure (HF), whereas CCB tended to be more protective against myocardial infarction (MI) and stroke.

Epidemiologically, CV events in East Asia are different from those in Western countries. Age-adjusted incidence of ischemic heart disease is 80% lower, but cerebrovascular mortality is 2-to 3-fold higher in Japan compared with those in the United States. In addition, mean body mass indices in East Asians are lower than that of Western population. ARB is less protective against new onset of T2DM in lean patients compared with the obese, and CCB has a beneficial property for preventing stroke. Thus, CCBs are still frequently used in hypertensive patients with T2DM in East Asia.

Taken together, it is still unknown whether ACEI/ARB should be the first-line medication for diabetic hypertensive patients in East Asia for the CVD protection. Accordingly, we carried out the NAGOYA HEART Study (NHS) to compare the efficacies of an ARB valsartan and a CCB amlodipine on cardiovascular morbidity and mortality as a primary outcome in Japanese hypertensive patients with glucose intolerance.

### Materials and Methods

**Study Design**

The rationale and design of the NHS have been described previously. The NHS is an investigator-initiated trial which used a prospective, randomized, open-labeled, blinded endpoints design. Participants were recruited by 171 cardiologists only from 46 board-certified medical centers and hospitals. All of the participants provided their written informed consent. This study was approved by the ethical review committee of the Nagoya University School of Medicine and of participating institutions.

**Inclusion Criteria**

Eligible participants were men and women aged between 30 and 75 years with both hypertension and glucose intolerance (ie, T2DM or impaired glucose tolerance [IGT]). We enrolled hypertensive patients with not only T2DM but also IGT, because IGT has a similarly elevated risk for CVD compared with T2DM. Hypertension was defined as having received any antihypertensive drugs already or blood pressure ≥140/90 mmHg. T2DM was defined as having received any antidiabetic agents or plasma glucose level ≥7.0 mmol/L in fasting state, ≥11.1 mmol/L in nonfasting state, or 2 hours after glycanic load in an oral glucose tolerance test. IGT was defined by plasma glucose level <7.0 mmol/L in fasting state and 7.8 to 11.0 mmol/L as the 2-hour value in an oral glucose tolerance test. For exclusion criteria, please see the online-only Data Supplement.

**Study Outcomes Measure**

Primary outcome was a composite of acute MI (ECG changes, elevation of cardiac enzymes more than twice as high as upper limit of normal levels, and culprit lesion detected by coronary angiogram), stroke (neurological deficit persisting for ≥24 hours and relevant findings in computed tomography or MRI), admission because of HF (new or worsened typical clinical symptoms including dyspnea, shortness of breath, and peripheral edema, together with pulmonary congestion in chest roentgenogram, echocardiographic left ventricular dysfunction according to the guidelines of the American Heart Association/American College of Cardiology, and increased plasma brain natriuretic peptide levels), coronary revascularization (percutaneous coronary intervention or coronary bypass graft surgery unplanned at randomization), or sudden cardiac death (unexpected intrinsic death within 24 hours after the onset of symptoms). All-cause mortality was included as the secondary outcome. All of the reported adverse events were analyzed, and outcomes were strictly adjudicated by an independent End point Evaluation Committee in a blinded manner as for the assigned treatments.

**Procedures and Follow-Up**

Patients were randomly assigned to the valsartan- or the amlodipine-based treatment group. Random allocation was performed by a minimization method with 5 factors of baseline characteristics, such as age, sex, medication for dyslipidemia, current smoking status, and the T2DM/IGT ratio.

As an initial dose, either valsartan 80 mg or amlodipine 5 mg once daily was administered to patients in a respective group. For patients already taking antihypertensive drugs at the enrollment, all of the ACEI/ARB and CCB were once discontinued and the allocated drug was started without a run-in period. During the follow-up, target blood pressure was ≤130/80 mmHg. Physicians could increase the respective dose until 160 mg or 10 mg daily after 4 weeks, and other antihypertensive drugs, such as diuretics, β-blockers, or α-blockers could be added after 8 weeks as needed. Blood glucose control was performed according to the treatment guidelines issued from the Japan Diabetes Society. For additional information, please see the online-only Data Supplement.

**Statistical Analysis**

Data were analyzed on the basis of the intention-to-treat principle. Only the first cardiovascular event was analyzed as a primary outcome in case of multiple events observed in a single patient. Cumulative incidence of cardiovascular events was estimated by the Kaplan-Meier method. The crude hazard ratios (HRs) and 95% CIs were calculated by the Cox proportional hazard model to compare the treatment group differences. The Levene test and repeated-measure ANOVA were used to compare the changes of blood pressure and glycosylated hemoglobin (HbA1c) levels throughout the follow-up.

All of the statistical analyses were performed by an independent statistical analysis board, and a *P* value <0.05 was considered statistically significant.

**Results**

**Patient Characteristics**

A total of 1168 patients were considered to be eligible for the present study, but 6 patients who met exclusion criteria and 12 patients who withdrew their consent were excluded. Consequently, 1150 patients were randomly assigned to the valsartan group (n=575) or the amlodipine group (n=575), and a total of 1117 patients (97%) completed the follow-up throughout the study (Figure S1). Please see the online-only Data Supplement.
Baseline characteristics of enrolled patients are shown in Table 1. All of the patients were diagnosed as hypertensive, and 82% and 18% had T2DM and IGT, respectively. In overall samples, mean age was 63 years, and 66% were men. Mean blood pressure and HbA1c were 145/82 mmHg and 7.0%, respectively. There were no significant differences in baseline characteristics between the 2 groups. Table 2 shows the prescribed medications during the follow-up. Immediately after the random allocation, 77% of patients in both groups were prescribed only the assigned regimen as an antihypertensive medication. The concomitant antihypertensive drugs were mainly β-blockers in both groups. Antihypertensive and hypoglycemic agents showed no differences in use between the 2 groups.

### Blood Pressure Changes and HbA1c Levels During the Study

Changes in blood pressure and HbA1c levels are shown in Figure 1. Blood pressure was reduced to 131/73 mmHg in the valsartan group and 132/74 mmHg in the amlodipine group at 54 months. The Levene test for equality of variances showed no differences between the 2 groups. Blood pressure did not differ between the 2 groups throughout the trial (P=0.653 in systolic BP and P=0.658 in diastolic BP by repeated-measure ANOVA). HbA1c levels were shown to decrease steadily to 6.7% in both groups, and the changes did not differ between the 2 groups.

### Clinical Outcomes

The median follow-up period reached 3.2 years (interquartile range: 2.6–4.7 years), and the Data and Safety Monitoring Board suggested finishing the follow-up at that point. A total of 202 clinical adverse events from 148 patients (26%) in the valsartan group and 204 events from 162 patients (28%) in the amlodipine group were reported to the end point evaluation committee. Figure 2 shows the incidence of adjudicated primary composite cardiovascular outcomes. A total of 56 events from 54 patients (9.4%) in the valsartan group and 64 events from 56 patients (9.7%) in the amlodipine group were adjudicated as primary outcomes, and time-to-event curves did not significantly differ between the 2 groups (HR: 0.97 [95% CI: 0.66–1.40]; P=0.85). Table 3 shows HRs for each component ascertained in this study, and there were no significant differences in the risk of MI, stroke, coronary revascularization, or sudden cardiac death between the 2 groups. However, incidence of admission because of HF was significantly less in the valsartan group than in the amlodipine group (3 versus 15 patients; HR: 0.20 [95% CI: 0.06–0.69]; P=0.012). Figure S2 shows the time-dependent curves of the incidence of admission attributed to worsening of HF. Please see the online-only Data Supplement. All-cause mortality, as a secondary outcome, did not significantly differ between the 2 groups (22 versus 16 patients; HR: 1.37 [95% CI: 0.72–2.61]; P=0.34; Table 3).

### Adverse Events

With respect to the safety outcome, we confirmed 106 adverse events of 94 patients in the valsartan group and 112 events of 94 patients in the amlodipine group during the follow-up (Table S1). However, any serious adverse events were not observed. There were no significant differences in the incidence of each adverse event, including the definite solid cancer (22 in the valsartan group and 23 in the amlodipine group) between the 2 groups. Please see the online-only Data Supplement.
Discussion

The NHS is a randomized, prospective clinical trial comparing the efficacies on cardiovascular outcomes between ARB and CCB in hypertensive patients with glucose intolerance. The present study has a novelty to evaluate the cardiovascular events as a primary outcome exclusively in non-Western patients with glucose intolerance.24 East Asians are generally less obese than Western population, although they had similar prevalence of T2DM.24 This epidemiological data suggest that East Asians could have some different substrates in glucose intolerance. Furthermore, the incidence of CVD in East Asia is much different from Western countries. However, there was little clinical evidence that supports therapeutic guidelines for the treatment of diabetic hypertensive patients in East Asia. In this study, both blood pressure and glycemic status were equally controlled between the 2 treatment groups, and there was no difference in a primary composite cardiovascular outcome. Our result was generally in line with the data of the Western IDNT Trial for which the number of patients were almost similar to ours, whereas the cardiovascular outcome was measured as a secondary outcome.21 The VALUE and CASE-J trials enrolled a larger number of diabetic patients than ours, but they also showed no difference in composite cardiovascular outcomes between the ARB- and CCB-based treatments.18,19 Consequently, any evidence in clinical advantage of ARB against CCB regarding composite CVD has not been yielded regardless of the race.

In the present study, the valsartan-based treatment significantly reduced the risk of HF as compared with the amlodipine-based treatment. One may argue that more frequent use of thiazides in the valsartan group possibly attributed to better protection against HF. However, this effect on HF in valsartan-

![Figure 1](image1.png)

Figure 1. Changes in blood pressure and glyemic control throughout the study. SBP indicates systolic blood pressure; DBP, diastolic blood pressure.

![Figure 2](image2.png)

Figure 2. Kaplan-Meier curves for the incidence of primary composite outcome. Time to the first cardiovascular event was used for the analysis.
Based treatment was statistically significant even in those who never received thiazides throughout the study \((n=967; HR: 0.21; \text{95\% CI: 0.05–0.96}; P=0.04)\), and test of heterogeneity in thiazides use showed no statistical significance \((P=0.50)\). Thus, our study suggested the more protective efficacy of valsartan against HF regardless of the use of thiazides, and our findings confirm the results of the IDNT Trial, as well as a meta-analysis in diabetic patients in Western countries.\(^{21,33}\) In contrast, both the original VALUE Trial and CASE-J Trial showed significant difference of blood pressure throughout the follow-up and no difference in the risk of HF.\(^{18,19}\) However, a modified analysis of the VALUE Trial indicated that, when blood pressure effects of valsartan and amlodipine were adjusted equally, the only difference in outcomes between the 2 groups was a lower incidence of HF in the valsartan group.\(^{18}\) Our study showed considerably lower HR \((0.20)\) for HF than previous trials because of the small number of cases, whereas there may be several possible explanations for this finding. First, given the fact that T2DM leads to renal damage and sodium retention, our patients could be more likely to develop HF than those with hypertension only.\(^{5}\) Indeed, a subanalysis of the HEART Studies that clearly showed reduced risk of stroke in the valsartan group compared with the non-ARB group,\(^{33}\) and head-to-head comparison trials not only in Asians\(^{19}\) but also in whites.\(^{18,21}\) However, it is quite in contrast to the 2 recent Japanese trials, the JIKEI HEART and KYOTO HEART Studies that clearly showed reduced risk of stroke in the add-on group with valsartan compared with the non-ARB group, who mainly received CCB.\(^{37,38}\) In these 2 trials, \(>50\%\) of patients in the ARB add-on group also received CCB, so that these trials might suggest the superiority of combined therapy with ARB and CCB against the control group (mainly CCB-based without ARB). Thus, the discrepancy between the NHS and the JIKEI/KYOTO HEART Studies may partially be explained by the difference in the concomitant medications and the study design.

We showed that CCB had a tendency to reduce the risk of MI compared with ARB similar to the IDNT findings.\(^{21}\) The VALUE Trial demonstrated that MI was significantly lower in the CCB group compared with the ARB group.\(^{18}\) However, it requires careful interpretation, because this finding might be yielded by the difference in blood pressure control \((\approx 4/2 \text{ mmHg})\) during the follow-up in the VALUE Trial. However, when the effect of blood pressure was adjusted, the difference of MI risk disappeared.\(^{14}\) Furthermore, an updated meta-analysis demonstrated that ARB and CCB showed equivalent MI risk.\(^{36}\)

In the risk of stroke, we found no difference between ARB and CCB. This finding is also in line with a previous meta-analysis in diabetic patients\(^{33}\) and head-to-head comparison trials not only in Asians\(^{19}\) but also in whites.\(^{18,21}\) However, it is quite in contrast to the 2 recent Japanese trials, the JIKEI HEART and KYOTO HEART Studies that clearly showed reduced risk of stroke in the add-on group with valsartan compared with the non-ARB group, who mainly received CCB.\(^{37,38}\) In these 2 trials, \(>50\%\) of patients in the ARB add-on group also received CCB, so that these trials might suggest the superiority of combined therapy with ARB and CCB against the control group (mainly CCB-based without ARB). Thus, the discrepancy between the NHS and the JIKEI/KYOTO HEART Studies may partially be explained by the difference in the concomitant medications and the study design.

We applied the prospective, randomized, open-labeled, blinded endpoints method to assess outcomes. The prospective, randomized, open-labeled, blinded endpoints design is relatively vulnerable to reporting bias, because allocated drugs are open to both patients and physicians. In this regard, softer end points should be adjudicated with a special care. In the present study, an independent clinical research nurse coordinator group managed to follow up patient records and to collect the data in \(>90\%\) of patients, and all of the reported adverse events were strictly adjudicated by an independent end point evaluation committee under a blinded manner as to the drug assignment. In fact, among 386 provisional reports, only 120 \((31.1\%)\) were adjudicated.

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**Table 3. Primary Outcome and Overall Cardiovascular Event**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Valsartan Group ((n=575))</th>
<th>Amlodipine Group ((n=575))</th>
<th>HR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite cardiovascular event</td>
<td>54 (9.4)</td>
<td>56 (9.7)</td>
<td>0.97 (0.66–1.40)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Components</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>7 (1.2)</td>
<td>3 (0.5)</td>
<td>2.33 (0.60–9.01)</td>
<td>0.22</td>
</tr>
<tr>
<td>Stroke</td>
<td>13 (2.3)</td>
<td>16 (2.8)</td>
<td>0.81 (0.39–1.68)</td>
<td>0.57</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>10 (1.7)</td>
<td>11 (1.9)</td>
<td>0.90 (0.38–2.12)</td>
<td>0.81</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>2 (0.3)</td>
<td>4 (0.7)</td>
<td>2.00 (0.50–9.27)</td>
<td>0.43</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>1.00 (0.06–16.1)</td>
<td>0.997</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>29 (5.0)</td>
<td>26 (4.5)</td>
<td>1.12 (0.66–1.90)</td>
<td>0.68</td>
</tr>
<tr>
<td>Admission because of heart failure</td>
<td>3 (0.5)</td>
<td>15 (2.6)</td>
<td>0.20 (0.06–0.69)</td>
<td>0.012</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4 (0.7)</td>
<td>4 (0.7)</td>
<td>1.00 (0.25–3.99)</td>
<td>0.997</td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>22 (3.8)</td>
<td>16 (2.8)</td>
<td>1.37 (0.72–2.61)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Admission because of heart failure included 4 adjudicated heart failure patients who rejected hospital admission because of personal reasons and received additional medications. Cardiovascular death included fatal stroke and sudden cardiac death. HR indicates hazard ratio. Incident rates are presented as per 1000 patient-years.
as the primary end point by the committee. Therefore, we believe that the bias would be highly unlikely to account for the differences. Rather, prospective, randomized, open-labeled, blinded endpoints design is close to daily clinical practice and less stressful to patients.24

Our patients were relatively well controlled in both blood pressure and glycemic status. A recent international cohort study reconfirmed that the incidence of CVD was significantly lower in Japan compared with other countries.25 These underlying conditions might result in quite lower incidence of primary outcomes (3.1% per year) than we anticipated. In addition, the sample size (n=1150) was less than the initially planned number of samples (n=3000), and that the present study was underpowered to determine our initial hypothesis that ARB might be more effective in preventing major CV events than CCB. However, postcensored analysis indicated acceptable statistical power (84.9%), the risk of primary outcome in each group was almost even (HR: 0.97), and our results were consistent with previous clinical evidence.18,19,21,33,34

Perspectives

The NHS is the first randomized, controlled trial comparing the clinical efficacies of ARB and CCB in Japanese hypertensive patients with glucose intolerance. Composite major CV events were similarly observed between ARB-based and CCB-based antihypertensive treatment. However, HF was more significantly reduced by ARB regimen. The NHS results echo those of the IDNT CV event trial and confirm the efficacy of ARB in this patient population in diabetic hypertensive patients in East Asia. Our results will highlight the safety and efficacy of ARB and support the current therapeutic guidelines for the treatment of diabetic hypertensive patients.

Acknowledgments


The affiliation of Mr Nobuo Shirahashi is Novartis Pharma KK, Tokyo, Japan, and Department of Preventive Medicine and Environmental Health, Osaka City University Medical School, Osaka, Japan.

Sources of Funding

The NAGOYA HEART Study was funded by Nagoya University Graduate School of Medicine, The Department of Cardiology, Nagoya University Graduate School of Medicine, reported receiving research promotion grants (Shougaku Kifukin) from Actelion, Astellas, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Fuji Film, Glaxo, Kaken, Kowa, Kureha, Medtronic, Mitsubishi Tanabe, Motheda, MSD, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, and Takeda. However, the research topics of these donation grants are not restricted.

Disclosures

To M. received lecturer’s fees from Daiichi Sankyo, Novartis Pharma, Pfizer, and Takeda.

References


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_Hypertension_. 2012;59:580-586; originally published online January 9, 2012; doi: 10.1161/HYPERTENSIONAHA.111.184226

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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An erratum has been published regarding this article. Please see the attached page for:
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Data Supplement (unedited) at:
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1. On page 584, Table 3, in the Outcomes column, “Sudden cardiac death” has been changed to read, “Cardiovascular death.” Also, the following information has been added in table legend: “Admission because of heart failure included 4 adjudicated heart failure patients who rejected hospital admission because of personal reasons and received additional medications. Cardiovascular death included fatal stroke and sudden cardiac death.”

2. On page 585, in the Acknowledgments, the following information has been added: “The affiliation of Mr. Nobuo Shirahashi is Novartis Pharma KK, Tokyo, Japan, and Department of Preventive Medicine and Environmental Health, Osaka City University Medical School, Osaka, Japan.”

The authors apologize for these errors.

These corrections have been made to the current online version of the article, which is available at http://hyper.ahajournals.org/content/59/3/580.full.
Comparison between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive patients with glucose intolerance: NAGOYA HEART Study

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Expanded Materials and Methods

Exclusion criteria
Patients with the following conditions were excluded from the study: prior CVD within 6 months; taking CCB for angina pectoris; left ventricular ejection fraction < 40%; atrioventricular block; secondary or severe hypertension (≥200/110 mmHg); serum creatinine ≥221 μmol/L; pregnant women; life expectancy less than 3 years; or other conditions for which physicians judged it inappropriate to enroll patients.

Procedures and follow up
Patients were followed up every month in the first 3 months and then every 1 to 3 months. Pre-specified measurements, prescribed medications, and clinical events were reported to the Data Management Center every 6 months. We also made clinical research coordinators (CRC) visit regularly to collect and reconfirm the reported data. Even when patients had stopped visiting institutions, CRC checked up their health status by either letter or phone call. Finally, the CRC group managed 40/46 institutions (87%) and 1043/1150 patients (91%).

Interim analyses and data monitoring
The interim analyses were assessed immediately after closing the enrollment and every 6 months (four times in total). The Data and Safety Monitoring Board (DSMB) independently monitored every updated result and suggested to continue or to close this study. The prespecified conditions to close this study were as follows: the difference of effects in the two treatment groups were shown to be statistically significant (O’Brien-Fleming stopping boundary); the number of incident CVD reached more than we anticipated (321 cases in total); median follow-up period reached more than 3 years; or any serious adverse events (grade 3 or more) that might threaten the safety of study continuation were observed.
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Valsartan group (n = 575)</th>
<th>Amlodipine group (n = 575)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid cancer</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>4</td>
<td>5</td>
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<tr>
<td>Aortic aneurysm</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Rashes / Zoster</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Benign tumor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fracture</td>
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<tr>
<td>Face flush</td>
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<td>Fatigue</td>
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<td>Hyperkalemia</td>
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<td>Total events</td>
<td>106</td>
<td>112</td>
</tr>
</tbody>
</table>

n indicates number.
Figure S1. Flow diagram of the NAGOYA HEART Study (NHS).
Figure S2. Kaplan-Meier curves for the incidence of admission due to worsening of heart failure. Time to the first event was used for the analysis. CI indicates confidence interval.