The editorial team of *Circulation Journal* has recently confirmed that the manuscript written by Shinzo Kimura et al, *Circ J* 2012 September 12 [Epub ahead of print] and that by Jun Shiraishi et al, published in the April 2011 issue of the *Circulation Journal* (*Circ J* 2011; 75: 806–814) contain a number of serious errors in data analysis.


Therefore, we have decided to retract the papers from *Circulation Journal*.

As the Editor-in-Chief, I regret the time that peer reviewers and others spent evaluating these papers.

I sincerely hope and trust that there will be no repetition of this kind in the future.

Hiroaki Shimokawa, MD, PhD
Editor-in-Chief
*Circulation Journal*
(Released online December 28, 2012)
Enhanced Cardiovascular Protective Effects of Valsartan in High-Risk Hypertensive Patients With Left Ventricular Hypertrophy
– Sub-Analysis of the KYOTO HEART Study –

Jun Shiraishi, MD, PhD; Takahisa Sawada, MD, PhD; Shinzo Kimura, MD, PhD; Hiroyuki Yamada, MD, PhD; Hiroaki Matsubara, MD, PhD
for the KYOTO HEART Study Group

**Background:** The objective of the present study was to examine whether baseline electrocardiographically diagnosed left ventricular hypertrophy (ECG-LVH) influenced the angiotensin II receptor blocker (ARB) valsartan add-on effects on the cardio-cerebrovascular morbidity and mortality in the high-risk hypertensive patients who participated in the KYOTO HEART Study.

**Methods and Results:** The primary endpoint was the same as in the main study: a composite of defined cardiovascualr and cerebrovascular events. The median follow-up period was 3.27 years. The study group was divided into 2 groups according to the presence of ECG-LVH: with LVH, n=803; without LVH, n=2,228. The primary endpoint events occurred more frequently in patients with LVH than in patients without LVH (9.3% vs. 7.3%; hazard ratio [HR], 1.33; 95% confidence interval [CI]: 1.01–1.75). Valsartan add-on significantly decreased the occurrence of primary endpoint events in both LVH-positive patients (5.8% vs. 12.9%; HR, 0.45; 95% CI: 0.28–0.72) and LVH-negative patients (5.5% vs. 9.2%; HR, 0.59; 95% CI: 0.44–0.81) compared with non-ARB treatment. The reduction in combined cardiovascular events (composite of acute myocardial infarction, angina pectoris, and heart failure) due to valsartan treatment in patients with LVH was significantly larger than that in patients without LVH (P<0.0001). Changes in blood pressure during the follow-up period did not differ significantly among the study subgroups.

**Conclusions:** High-risk hypertensive patients with ECG-LVH might gain more cardiovascular benefits from valsartan add-on treatment, compared with patients without ECG-LVH. (Circ J 2011; 75: 806–814)

**Key Words:** Angiotensin II receptor blocker; Left ventricular hypertrophy; Prognosis

Left ventricular hypertrophy (LVH) is a well-established sign of subclinical cardiovascular disease and an independent predictor of cardiovascular events, such as myocardial infarction, stroke, and cardiovascular death in hypertensive patients, and the general population. The frequency of cardiovascular events is 2–4-fold higher in the presence of LVH, independent of blood pressure and other conventional risk factors. Besides chronic exposure to pressure overload, the local renin–angiotensin–aldosterone system (RAAS) plays a major role in the development of LVH. Some experimental and clinical studies have shown that blocking RAAS by angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blocker (ARB) could reverse LVH and might confer cardiovascular benefits beyond lowering blood pressure in hypertensive patients. The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial demonstrated that in hypertensive patients with LVH diagnosed on electrocardiogram (ECG-LVH), the ARB losartan more effectively prevented cardiovascular morbidity and death and concomitantly caused greater reduction in ECG voltage than atenolol. It remains to be determined, however, whether the presence of ECG-LVH affects ARB-mediated cardiovascular protection in hypertensive patients.
The KYOTO HEART Study has demonstrated that ARB valsartan add-on treatment prevents more cardiovascular and cerebrovascular events than conventional non-ARB treatment in high-risk hypertensive patients. The purpose of the present sub-analysis was therefore to examine whether the presence of ECG-LVH influences valsartan add-on effects on cardio-cerebrovascular morbidity and mortality in high-risk hypertensive patients, using data from the KYOTO HEART Study.

Methods

Study Design and Patient Group

The KYOTO HEART Study was designed as a multicenter, prospective, randomized, open-labeled, blinded endpoints (PROBE), and 2-arm parallel treatment group comparison study with a response-dependent dose titration to evaluate the efficacy of ARB valsartan add-on treatment and conventional non-ARB treatment for reducing the cardio-cerebrovascular morbidity and mortality in high-risk hypertensive patients. The detailed design, organization, clinical measurements, and endpoint definitions of the KYOTO HEART Study have been previously reported. Briefly, we recruited a total of 3,031 Japanese high-risk patients with uncontrolled hypertension from Kyoto Prefectural University School of Medicine-collaborating hospitals led by cardiologists specialists between January 2004 and June 2007. Uncontrolled hypertension was defined as a mean sitting systolic blood pressure ≥140 mmHg, and/or a mean sitting diastolic blood pressure ≥90 mmHg at 2 consecutive measurements in the outpatient clinic. High risk was defined as the presence of at least one of the following factors: coronary artery disease (angina pectoris or a history of myocardial infarction >6 months before the screening), cerebrovascular disease (history of stroke or transient ischemic attack [TIA] >6 months before the screening), peripheral arterial occlusive disease, and/or 1 or more of the following cardiovascular risk factors and none of the exclusion criteria. The cardiovascular risk factors included type-2 diabetes mellitus, current smoking, dyslipidemia, obesity (defined as body mass index [BMI] ≥25 kg/m²), and/or LVH confirmed on ECG. The exclusion criteria were treatment with ARB before randomization, or history of worsening heart failure, unstable angina, myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting within the preceding 6 months. The detailed exclusion criteria of the KYOTO HEART Study have been previously reported. The protocol was approved by the Ethics committee at each participating hospital and written consent was obtained from each patient.

Procedure

After confirming, eligible patients were randomly assigned, in accordance with the minimization method using 8 factors (age, gender, dyslipidemia, diabetes mellitus, smoking, obesity, history of coronary artery disease and/or cerebrovascular disease, and history of congestive heart failure), either to the valsartan add-on group or to the conventional treatment group. For the valsartan add-on group, valsartan 80 mg/day was administered as an initial dose and the dose was doubled after 4 weeks if the initial dose did not achieve the target blood pressure of <140/90 mmHg. After 8 weeks, an additional administration of other anti-hypertensive drugs except for ARBs and ACE inhibitors was allowed. For the conventional treatment group, the anti-hypertensive drugs excluding ARBs and ACE inhibitors were provided. The detailed titration schedule has been described previously. In the present sub-analysis, the KYOTO HEART Study group was divided into 2 groups according to the presence of ECG-LVH at baseline (with LVH, n=803; without LVH, n=2,228; Figure 1). LVH was defined as Sokolow–Lyon voltage (SV1+RV5) >38 mm, irrespective of strain patterns and left-axis deviation. Periodic follow-up examinations were performed every 6 months after setting the durable dose. Study measurements and data management have been described in the design paper.

Endpoint Measurements

The primary endpoint in this sub-analysis was the same as in the main study: new onset and/or worsening of cardiovascular and cerebrovascular events. They included the following events: stroke (hospitalization, and diagnosis on computed tomography [CT] and/or magnetic resonance imaging [MRI]); new or recurrent TIA (hospitalization, diagnosis on CT and/or MRI, and sudden onset of neurological deficit persisting <24 h without a history of atrial arrhythmia causing embolism); new or recurrent acute myocardial infarction (hospitalization, ECG change, and biomarkers for myocardial infarction); occurrence of new or exacerbation of angina pectoris (hospitalization, and diagnosis on ECG changes coinciding with chest symptoms and on coronary angiography showing >75% stenosis according to the American Heart Association [AHA]/American College of Cardiology [ACC] guidelines); occurrence of new or exacerbation of heart failure (hospitalization and clinical symptoms concomitant with left ventricular dysfunction on echocardiography according to the AHA/ACC guidelines); dissecting aneurysm of the aorta (hospitalization, and diagnosed on imaging); lower limb arterial obstruction; emergency thrombosis; transition to dialysis; and doubling of plasma Cr levels. The secondary endpoints included all-cause mortality, worsening of cardiac function, occurrence of new or exacerbation of arrhythmias, occurrence of new or exacerbation of diabetes mellitus or impaired glucose tolerance, and uncontrolled blood pressure. In the present sub-analysis, besides primary and secondary endpoints, we set up a composite of new or recurrent acute myocardial infarction, occurrence of new or exacerbation of angina pectoris, and occurrence of new or exacerbation of heart failure as combined cardiovascular event to elucidate the cardioprotective effect of valsartan add-on treatment. The event evaluation was performed independently by the Endpoint Committee.

Statistical Analysis

All continuous data are expressed as mean±SD. Baseline characteristics were compared between the subgroups using Student’s 2-sample 2-sided test or Mann–Whitney test. Fisher’s exact test or chi-square test was used for categorical variables. Analysis of change in blood pressure was performed on STATA using a 2-way ANOVA with repeated measure. All time-to-event variables were displayed on Kaplan–Meier estimate according to groups. Event rates were adjusted for gender, age, diabetes, smoking, dyslipidemia, obesity, heart failure, statin, and concomitant anti-hypertensive treatment, and Cox’s proportional hazard regression analysis was used to compare the event rate between groups. All tests were 2-sided. P<0.05 was considered statistically significant.

Results

Baseline Characteristics and Medications

The baseline characteristics for all 3,031 patients are summarized in Table 1. During the median follow-up period of 3.27 years, 18 patients in the valsartan add-on arm and 16 patients in the conventional treatment arm met the main study: new onset and/or worsening of cardiovascular and cerebrovascular events. They included the following events: stroke (hospitalization, and diagnosis on computed tomography [CT] and/or magnetic resonance imaging [MRI]); new or recurrent TIA (hospitalization, diagnosis on CT and/or MRI, and sudden onset of neurological deficit persisting <24 h without a history of atrial arrhythmia causing embolism); new or recurrent acute myocardial infarction (hospitalization, ECG change, and biomarkers for myocardial infarction); occurrence of new or exacerbation of angina pectoris (hospitalization, and diagnosis on ECG changes coinciding with chest symptoms and on coronary angiography showing >75% stenosis according to the American Heart Association [AHA]/American College of Cardiology [ACC] guidelines); occurrence of new or exacerbation of heart failure (hospitalization and clinical symptoms concomitant with left ventricular dysfunction on echocardiography according to the AHA/ACC guidelines); dissecting aneurysm of the aorta (hospitalization, and diagnosed on imaging); lower limb arterial obstruction; emergency thrombosis; transition to dialysis; and doubling of plasma Cr levels. The secondary endpoints included all-cause mortality, worsening of cardiac function, occurrence of new or exacerbation of arrhythmias, occurrence of new or exacerbation of diabetes mellitus or impaired glucose tolerance, and uncontrolled blood pressure. In the present sub-analysis, besides primary and secondary endpoints, we set up a composite of new or recurrent acute myocardial infarction, occurrence of new or exacerbation of angina pectoris, and occurrence of new or exacerbation of heart failure as combined cardiovascular event to elucidate the cardioprotective effect of valsartan add-on treatment. The event evaluation was performed independently by the Endpoint Committee.

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Table 1. Baseline Patient Characteristics vs. Presence of LVH

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>LVH+ (n=803)</th>
<th>LVH– (n=2,228)</th>
<th>Comparison between LVH+ and LVH–</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65±12</td>
<td>65±11</td>
<td>0.6312</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>520/283</td>
<td>1,208/1,020</td>
<td>0.0927</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>159±15</td>
<td>156±14</td>
<td>0.0825</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>89±12</td>
<td>88±11</td>
<td>0.5533</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>71±15</td>
<td>70±18</td>
<td>0.3059</td>
</tr>
<tr>
<td>Body mass index (kg/cm²)</td>
<td>24±3</td>
<td>24±4</td>
<td>0.0644</td>
</tr>
<tr>
<td>Waist size (cm)</td>
<td>84±10</td>
<td>86±10</td>
<td>0.4852</td>
</tr>
<tr>
<td>Cardiothoracic ratio (%)</td>
<td>51±6</td>
<td>51±6</td>
<td>0.2302</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>43±9</td>
<td>25±6</td>
<td>1.0000</td>
</tr>
</tbody>
</table>

Echocardiography
- Ejection fraction (%)
- IVS thickness (mm)
- LV PW thickness (mm)
- LDL-cholesterol (mg/dl)
- HDL-cholesterol (mg/dl)
- Triglyceride (mg/dl)
- Hemoglobin A1c (%)
- Fasting plasma glucose (mg/dl)
- Serum creatinine (mg/dl)
- Serum sodium (mEq/L)
- Serum potassium (mEq/L)

Risk factor n (%)
- Current smokers
- Obesity
- Diabetes mellitus
- Dyslipidemia
- Coronary heart disease
- Cerebrovascular disease
- Heart failure

Data given as mean±SD or n (%).
LVH, left ventricular hypertrophy; ARB, angiotensin II receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; IVS, interventricular septum; LV, left ventricle; PW, posterior wall; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Figure 1. Study flowchart. ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy.
patients in the conventional non-ARB arm were lost because of consent withdrawal or loss of follow-up. In the present sub-analysis, the study group was divided into 2 groups according to the presence of LVH, and further divided into valsartan add-on treatment and non-ARB treatment, respectively (Figure 1). From the echocardiography data at baseline, interventricular septal thickness and left ventricular posterior wall thickness were significantly greater in the patients with LVH (Table 1). Overall, the patients with LVH had a higher prevalence of male gender, current smoking, and heart failure as well as a lower prevalence of obesity (BMI $\geq 25$) and dyslipidemia than those without LVH (Table 1). Except for the prevalence of heart failure in the LVH-negative patients, in the presence or absence of LVH, the baseline clinical char-

<table>
<thead>
<tr>
<th>Baseline medication</th>
<th>All (n=803)</th>
<th>Valsartan (n=399)</th>
<th>Non-ARB (n=404)</th>
<th>P value</th>
<th>All (n=2,228)</th>
<th>Valsartan (n=1,118)</th>
<th>Non-ARB (n=1,110)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB</td>
<td>429 (53)</td>
<td>205 (51)</td>
<td>224 (55)</td>
<td>0.5054</td>
<td>1,228 (55)</td>
<td>620 (55)</td>
<td>608 (55)</td>
<td>0.7464</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>158 (20)</td>
<td>74 (19)</td>
<td>84 (21)</td>
<td>0.2480</td>
<td>436 (20)</td>
<td>215 (19)</td>
<td>221 (20)</td>
<td>0.1630</td>
</tr>
<tr>
<td>β-blocker</td>
<td>153 (19)</td>
<td>78 (20)</td>
<td>75 (19)</td>
<td>0.4235</td>
<td>388 (17)</td>
<td>186 (17)</td>
<td>202 (18)</td>
<td>0.9440</td>
</tr>
<tr>
<td>α-blocker</td>
<td>26 (3)</td>
<td>13 (3)</td>
<td>13 (3)</td>
<td>0.7225</td>
<td>70 (3)</td>
<td>32 (3)</td>
<td>38 (3)</td>
<td>0.4477</td>
</tr>
<tr>
<td>Thiazide</td>
<td>25 (3)</td>
<td>14 (4)</td>
<td>11 (3)</td>
<td>0.9743</td>
<td>72 (3)</td>
<td>38 (3)</td>
<td>34 (3)</td>
<td>0.6540</td>
</tr>
<tr>
<td>Anti-aldosterone</td>
<td>20 (2)</td>
<td>13 (3)</td>
<td>7 (2)</td>
<td>0.5214</td>
<td>37 (3)</td>
<td>18 (2)</td>
<td>19 (2)</td>
<td>0.8510</td>
</tr>
<tr>
<td>Other diuretics</td>
<td>46 (6)</td>
<td>26 (5)</td>
<td>21 (5)</td>
<td>0.5210</td>
<td>116 (5)</td>
<td>51 (5)</td>
<td>65 (6)</td>
<td>0.1692</td>
</tr>
<tr>
<td>Statin</td>
<td>215 (27)</td>
<td>103 (26)</td>
<td>112 (28)</td>
<td>0.5415</td>
<td>779 (35)</td>
<td>388 (35)</td>
<td>391 (35)</td>
<td>0.7968</td>
</tr>
<tr>
<td>Fibrate</td>
<td>13 (2)</td>
<td>4 (1)</td>
<td>9 (2)</td>
<td>0.1690</td>
<td>52 (2)</td>
<td>31 (3)</td>
<td>21 (2)</td>
<td>0.1672</td>
</tr>
<tr>
<td>Other anti-hyperlipidemic agents</td>
<td>12 (1)</td>
<td>8 (2)</td>
<td>4 (1)</td>
<td>0.2359</td>
<td>62 (3)</td>
<td>37 (3)</td>
<td>25 (2)</td>
<td>0.1293</td>
</tr>
<tr>
<td>Sulfonyl urea</td>
<td>83 (10)</td>
<td>41 (10)</td>
<td>42 (10)</td>
<td>0.9553</td>
<td>264 (12)</td>
<td>133 (12)</td>
<td>131 (12)</td>
<td>0.9450</td>
</tr>
<tr>
<td>Other oral hyperglycemic agents</td>
<td>73 (9)</td>
<td>41 (10)</td>
<td>32 (8)</td>
<td>0.2458</td>
<td>211 (9)</td>
<td>100 (9)</td>
<td>111 (10)</td>
<td>0.3949</td>
</tr>
<tr>
<td>Insulin</td>
<td>15 (2)</td>
<td>8 (2)</td>
<td>7 (2)</td>
<td>0.7756</td>
<td>67 (3)</td>
<td>30 (3)</td>
<td>37 (3)</td>
<td>0.3691</td>
</tr>
</tbody>
</table>

Data given as n (%).

CCB, calcium channel blocker; ACE, angiotensin-converting enzyme. Other abbreviations see in Table 1.

Figure 2. Changes in blood pressure during the study period. ARB, angiotensin II receptor blocker; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.
Figure 3. Kaplan–Meier curves and effect of left ventricular hypertrophy (LVH) at baseline on primary endpoints. CI, confidence interval.

Figure 4. Kaplan–Meier curves and effect of valsartan on primary endpoints in hypertensive patients with or without left ventricular hypertrophy (LVH) at baseline. ARB, angiotensin II receptor blocker; CI, confidence interval; HR, hazard ratio.
Characteristics did not differ significantly between the patients with valsartan add-on treatment and the patients with conventional non-ARB treatment (Table 1). The baseline medications before randomization are summarized in Table 2. Except for statin and other anti-hyperlipidemic agents, the distribution of the baseline medications did not differ significantly between the patients with LVH and those without LVH. In the presence of LVH as well as in the absence of LVH, it did not differ significantly between the patients with valsartan add-on treatment and the patients with conventional non-ARB treatment.

Changes in Blood Pressure
Figure 2 shows the time course of blood pressure during the study period. Blood pressure was well controlled to levels below 140/80 mmHg in the 4 categories. Irrespective of LVH or valsartan add-on treatment, systolic blood pressure and diastolic blood pressure did not differ significantly among the 4 categories throughout the study period.

Clinical Outcome
During the median follow-up period of 3.27 years, primary endpoint events occurred in 75 patients (9.3%) with LVH and in 163 patients (7.3%) without LVH, and the cumulative incidence of primary endpoint adjusted for baseline characteristics and baseline medications showed that the presence of LVH was an independent risk of new onset and/or worsening of cardiovascular and cerebrovascular events (primary endpoint; hazard ratio [HR], 1.33; 95% confidence interval [CI]: 1.01–1.75; Figure 3). The patients with LVH had a higher prevalence of new or exacerbation of heart failure (2.0% vs. 1.0%; HR, 2.22; 95%CI: 1.12–4.40), and combined cardiovascular events (composite of acute myocardial infarction, angina pectoris, and heart failure; 5.2% vs. 3.6%; HR, 1.59; 95%CI: 1.03–2.23) than did the patients without LVH. Kaplan–Meier curves for primary endpoint and the HR and 95%CI assessing effects of valsartan add-on treatment in the presence or absence of LVH are given in Figure 4. In the presence of LVH, the patients with valsartan add-on treatment had significantly smaller prevalence of primary endpoints (5.8% vs. 12.9%; HR, 0.45; 95%CI: 0.28–0.72), new or exacerbation of angina pectoris (1.0% vs. 4.0%; HR, 0.25; 95%CI: 0.09–0.75), and combined cardiovascular events (2.5% vs. 7.9%; HR, 0.25; 95%CI: 0.12–0.56) than those with non-ARB treatment. In contrast, in the absence of LVH, the patients with valsartan add-on treatment had lower prevalence of primary endpoints (5.5% vs. 9.2%; HR, 0.59; 95%CI: 0.44–0.81) as well as stroke (1.5% vs. 3.0%; HR, 0.51; 95%CI: 0.29–0.91) than those with non-ARB treatment. Among the subgroup receiving valsartan, there was no significant difference in primary endpoints between patients with LVH and patients without LVH, while among the subgroup receiving non-ARB treatment, patients with LVH had a higher prevalence of primary endpoints than patients without LVH (Figure 4). Moreover, based on the heterogeneity test, the combined cardiovascular event reduction by the valsartan add-on treatment in the presence of LVH was significantly larger than that in the absence of LVH (P<0.001; Figure 5).

Discussion
The major findings of the present sub-analysis of the

<table>
<thead>
<tr>
<th>EndPoint</th>
<th>LVH</th>
<th>Valsartan</th>
<th>Non-ARB</th>
<th>0.13</th>
<th>0.25</th>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
<th>Hazard ratio (95%CI)</th>
<th>p</th>
<th>Heterogeneity p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>+</td>
<td>23.5%</td>
<td>52</td>
<td>12.9%</td>
<td>0.45 (0.28–0.72)</td>
<td>0.00097</td>
<td>0.3079</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>61.5%</td>
<td>102</td>
<td>9.2%</td>
<td>0.59 (0.44–0.81)</td>
<td>0.00042</td>
<td></td>
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<tr>
<td>Stroke</td>
<td>+</td>
<td>8.2%</td>
<td>13</td>
<td>3.2%</td>
<td>0.62 (0.26–1.49)</td>
<td>0.28097</td>
<td></td>
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<td></td>
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<tr>
<td>-</td>
<td>17.1%</td>
<td>33</td>
<td>3.0%</td>
<td>0.51 (0.29–0.91)</td>
<td>0.01904</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Angina pectoris</td>
<td>+</td>
<td>4.1%</td>
<td>16</td>
<td>4.0%</td>
<td>0.25 (0.09–0.75)</td>
<td>0.00782</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>28.1%</td>
<td>48</td>
<td>2.5%</td>
<td>0.64 (0.36–1.15)</td>
<td>0.12844</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>+</td>
<td>0.3%</td>
<td>6</td>
<td>1.2%</td>
<td>0.20 (0.02–1.73)</td>
<td>0.17069</td>
<td></td>
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<td>-</td>
<td>3.2%</td>
<td>6</td>
<td>0.5%</td>
<td>0.99 (0.52–1.87)</td>
<td>0.84058</td>
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<tr>
<td>Heart failure</td>
<td>+</td>
<td>8.4%</td>
<td>23</td>
<td>13.7%</td>
<td>0.12 (0.07–0.21)</td>
<td>0.00328</td>
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<tr>
<td>-</td>
<td>17.5%</td>
<td>34</td>
<td>13.0%</td>
<td>0.37 (0.19–0.71)</td>
<td>0.03902</td>
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<tr>
<td>Lower limb arterial obstruction</td>
<td>+</td>
<td>2.5%</td>
<td>4</td>
<td>1.0%</td>
<td>1.01 (0.25–4.02)</td>
<td>0.98886</td>
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<tr>
<td>-</td>
<td>1.4%</td>
<td>4</td>
<td>0.3%</td>
<td>0.87 (0.32–2.39)</td>
<td>0.74892</td>
<td></td>
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<tr>
<td>Transition to dialysis or doubling of serum creatinine levels</td>
<td>+</td>
<td>0.4%</td>
<td>10</td>
<td>0.9%</td>
<td>0.40 (0.12–1.26)</td>
<td>0.13579</td>
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<tr>
<td>-</td>
<td>3.2%</td>
<td>8</td>
<td>0.4%</td>
<td>0.74 (0.17–3.32)</td>
<td>0.68824</td>
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<tr>
<td>Dissecting aneurysm of aorta</td>
<td>+</td>
<td>0.0%</td>
<td>1</td>
<td>0.2%</td>
<td>0.72 (0.12–0.46)</td>
<td>0.36691</td>
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<tr>
<td>-</td>
<td>3.2%</td>
<td>7</td>
<td>0.4%</td>
<td>0.72 (0.12–0.46)</td>
<td>0.36691</td>
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<tr>
<td>Combined cardiovascular event</td>
<td>+</td>
<td>10.5%</td>
<td>32</td>
<td>7.9%</td>
<td>0.25 (0.12–0.56)</td>
<td>0.00015</td>
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<tr>
<td>-</td>
<td>32.9%</td>
<td>48</td>
<td>4.3%</td>
<td>0.72 (0.46–1.12)</td>
<td>0.13691</td>
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<tr>
<td>All cause mortality</td>
<td>+</td>
<td>9.3%</td>
<td>12</td>
<td>3.0%</td>
<td>0.76 (0.32–1.78)</td>
<td>0.53404</td>
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<tr>
<td>-</td>
<td>13.1%</td>
<td>20</td>
<td>1.8%</td>
<td>0.65 (0.32–1.29)</td>
<td>0.23347</td>
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<tr>
<td>Cardiovascular death</td>
<td>+</td>
<td>2.0%</td>
<td>6</td>
<td>1.5%</td>
<td>0.34 (0.07–1.66)</td>
<td>0.20662</td>
<td></td>
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<tr>
<td>-</td>
<td>6.0%</td>
<td>7</td>
<td>0.6%</td>
<td>0.85 (0.29–2.52)</td>
<td>0.76707</td>
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Figure 5. Effects of valsartan on cardiovascular and cerebrovascular outcomes in hypertensive patients with or without left ventricular hypertrophy (LVH) at baseline. Hazard ratio and 95% confidence intervals (CIs) adjusted for gender, age, diabetes, smoking, dyslipidemia, obesity, heart failure, statin, and concomitant anti-hypertensive treatment. Combined cardiovascular events: composite of acute myocardial infarction, angina pectoris, and heart failure. ARB, angiotensin II receptor blocker.
KYOTO HEART Study are as follows: (1) among high-risk Japanese hypertensive patients, baseline ECG-LVH was a risk for cardiovascular and cerebrovascular events; (2) irrespective of ECG-LVH, valsartan add-on treatment prevented more cardio- and cerebrovascular events than conventional non-ARB treatment; (3) compared with non-ARB treatment, valsartan add-on treatment significantly reduced occurrence of new or exacerbation of angina pectoris in the presence of LVH, while it suppressed stroke in the absence of LVH; (4) the reduction of combined cardiovascular event (composite of acute myocardial infarction, angina pectoris, and heart failure) by the valsartan add-on treatment in the presence of LVH was significantly larger than that in the absence of LVH; and (5) the time course of blood pressure lowering was similar among the 4 subgroups.

Consistent with previous reports, ECG-LVH was an independent risk of cardiovascular and cerebrovascular events among hypertensive patients in the present sub-analysis of the KYOTO HEART Study.\(^2,3\) Additionally, ECG-LVH was strongly associated with occurrence of new or exacerbation of heart failure and combined cardiovascular events (composite of acute myocardial infarction, angina pectoris, and heart failure). It is well recognized that electrocardiographically or echocardiographically documented LVH is one of the indicators of target organ damage in hypertensive patients. Persistent exposure to high blood pressure causes cardiac myocyte hypertrophy and extracellular matrix collagen deposition, leading to LVH as an adaptive reaction at the early stage, and advancing from LVH to cardiovascular diseases such as coronary heart disease, malignant arrhythmia, and congestive heart failure at the later stage in the cardiovascular continuum,\(^4\) in which the RAAS system, angiotensin II in particular, plays a crucial role. Thus, LVH is a silent and pre-clinical cardiovascular disease and could be a significant predictor of subsequent cardiovascular disease in hypertensive patients. In contrast, regression of electrocardiographic or echocardiographic LVH by anti-hypertensive treatment is associated with lower frequency of cardiovascular events, independent of blood pressure lowering.\(^5,12\) Previous studies and recent meta-analysis-oriented reports have demonstrated that ARBs, ACE inhibitors, and calcium channel blockers are superior to \(\beta\)-blockers and diuretics in reducing echocardiographic left ventricular mass.\(^13-17\) Moreover, aldosterone blocker in addition to ARB and direct renin inhibitor have also recently been reported to be effective in promoting LV mass reduction, indicating the priority of the RAAS inhibitors in the treatment of hypertensive patients with LVH.\(^18,19\)

Apart from the LIFE study, however, beneficial effects of the RAAS inhibitors on clinical outcome in hypertensive patients with LVH, a subgroup of high-risk hypertensive patients, have not been fully investigated in detail.

The present sub-analysis of the KYOTO HEART Study is the first to investigate whether baseline ECG-LVH influences the valsartan add-on effects on the cardiovascular or cerebrovascular morbidity and mortality in the high-risk hypertensive patients. Although, irrespective of LVH, valsartan add-on treatment prevented more primary endpoints (composite of cardiovascular and cerebrovascular event) than conventional non-ARB treatment, the primary endpoint reduction ratio by the valsartan add-on treatment in the presence of LVH was much larger than that in the absence of LVH. In addition, compared with non-ARB treatment, valsartan add-on treatment reduced occurrence of new or exacerbation of angina pectoris in hypertensive patients with LVH, but not in those without LVH. Moreover, based on the heterogeneity test, the combined cardiovascular event (composite of acute myocardial infarction, angina pectoris, and heart failure) reduction by the valsartan add-on treatment in the presence of LVH was significantly larger than that in the absence of LVH and, based on Cox’s proportional hazard model analysis, the valsartan add-on treatment might cancel the LVH-associated risk of cardio- and cerebrovascular event. Taken together, it is reasonable to propose that high-risk hypertensive patients with LVH might gain more cardiovascular benefits by valsartan add-on treatment, compared with those without LVH. Additionally, to a lesser extent, high-risk hypertensive patients without LVH might also acquire cardiovascular benefits from valsartan add-on treatments. Because the degree of beneficial effect from valsartan treatment partly depends on the background risks such as LVH, other risks, such as coronary artery disease, cerebrovascular disease, diabetes and so on, which were considered to be high risk in the inclusion criteria, may be similarly important. The additional sub-analyses for the involvement of these high risks are in progress.

The mechanism by which the cardioprotective effect of valsartan was enhanced in the presence of LVH remains unclear. Accumulating clinical evidence has indicated that hypertensive patients with LVH are at higher risk of cardiovascular events.\(^5,3\) and the present study has found a higher prevalence of heart failure and combined cardiovascular events consisting of angina pectoris, acute myocardial infarction, and heart failure in high-risk hypertensive patients with LVH. In addition, based on the findings from the experimental studies, angiotensin II type 1 (AT1) receptor is locally activated in cardiac hypertrophy and heart failure, and angiotensin II induces hypertrophic change in cardiac myocytes as well as stimulates cell proliferation and collagen synthesis in cardiac fibroblasts through AT1 receptor, leading to LVH.\(^20-22\) Although the role of angiotensin II type 2 (AT2) receptor in the pathogenesis of LVH remains uncertain,\(^23\) AT2 receptor activation could block coronary artery thickening and perivascular fibrosis.\(^24\) Because valsartan has the highest selectivity for AT1 receptor over AT2 receptor among ARBs,\(^25\) valsartan might be not only a strong blocker of AT1 receptor but also a potent stimulator of AT2 receptor. Indeed, AT2 receptor is present in atherosclerotic lesions,\(^26\) and valsartan suppresses wall thickening and perivascular fibrosis in coronary arteries after pressure overload.\(^27\) Another recent report has also shown that mean blood volume measured on myocardial contrast echocardiography, an indicator of the myocardial microvascular narrowing, is decreased in hypertensive patients with LVH, and valsartan corrects the decreased mean blood volume in those patients.\(^28\) These facts might therefore account for the enhanced reduction of cardiovascular events, particularly angina pectoris, by valsartan in hypertensive patients with LVH.

With regard to stroke prevention, the usefulness of ACE inhibitor and ARB has already been established in hypertensive patients.\(^7,29,30\) The LIFE study has shown that losartan prevented more fatal or non-fatal stroke than atenolol in hypertensive patients with LVH on ECG.\(^7\) In the KYOTO HEART Study valsartan add-on treatment significantly reduced stroke more than conventional non-ARB treatment in high-risk hypertensive patients,\(^8\) and, in the present sub-analysis, compared with conventional non-ARB treatment, the valsartan add-on treatment reduced stroke in the absence of LVH, but not in the presence of LVH. In contrast, a previous study has shown that LVH is an independent predictor of acute cerebrovascular events in hypertensive patients.\(^31\)

We cannot explain the relationship between the presence/
absence of LVH and stroke prevention by valsartan add-on treatment precisely, but, besides the effect of study limitations such as the post-hoc analysis, there is a possibility that LVH, one of the causes of subclinical cardiovascular damage, might not be highly associated with stroke. Indeed, among patients with non-ARB treatment in the present study, the prevalence of stroke in patients with LVH was almost equal to that in patients without LVH, while the frequency of cardiovascular events, such as angina pectoris, acute myocardial infarction, or heart failure in patients with LVH was greater than that in patients without LVH. These data might contribute in part to the cancelled cerebrovascular protective effect of valsartan in the presence of LVH.

Study Limitations
There were a number of limitations to the present study. First, this study was a post-hoc analysis. Differences in patient characteristics among the groups cannot be completely excluded and the present study might contain undetected bias, except for those described in the results. Second, because the main study was performed using the PROBE design, we could not exclude possible bias in event reporting, particularly for softer endpoints such as angina pectoris and TIA. Another possible bias is that treatment and examination strategies such as hospitalization and coronary angiography depend on the decision of the responsible cardiologist specialist at each hospital. All coronary culprit lesions, however, were confirmed on coronary angiography, and cerebrovascular events were diagnosed based on CT and/or MRI, and the investigators were kept blinded to the diagnostic criteria for softer endpoints, which had been determined by the endpoint committee. In cases in which the provisional report was uncertain, the endpoint committee requested further information and revised the endpoint judgment. Among 558 provisional reports, only 238 (42.7%) were confirmed as the primary endpoint. The prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990; 322: 1561–1566.


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Conclusion
Irrespective of ECG-LVH, valsartan add-on treatment prevented more cardio- and cerebrovascular events than conventional non-ARB treatment in high-risk hypertensive patients. In addition, the cardiovascular event reduction by the valsartan add-on treatment in the presence of LVH was significantly larger than that in the absence of LVH, suggesting that high-risk hypertensive patients with ECG-LVH might obtain more cardiovascular benefits from valsartan add-on treatment, compared with those without ECG-LVH.

Acknowledgment
The authors declare no conflict of interest.

References

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