Inhibitory Effect of Valsartan Against Progression of Left Ventricular Dysfunction After Myocardial Infarction

T-VENTURE Study

Hiroshi Suzuki, MD; Eiichi Geshi, MD; Shuji Nanjyo, MD*; Hajime Nakano, MD*; Jyunichi Yamazaki, MD*; Naoki Sato, MD**; Keiji Tanaka, MD**; Teruo Takano, MD†; Hidenori Yagi, MD††; Takahiro Shibata, MD††; Seibu Mochizuki, MD††; Takashi Katagiri, MD

Background: Angiotensin-converting enzyme inhibitors (ACEI) reduce the mortality in the chronic phase of myocardial infarction (MI), and similar effects of angiotensin receptor blockers (ARB) have been reported. However, these effects of ARB have not yet been established in Japanese patients. A multicenter randomized study was designed for the present study to examine the effect of valsartan as compared to that of ACEI against left ventricular dysfunction after MI.

Methods and Results: Patients with acute MI were randomly allocated to either the valsartan group (n=120; mean age 63±1.0) or the ACEI group (n=121; mean age 62.9±1.0) and followed up until 6 months. Left ventriculography was performed during hospital admission and at 6 months. The blood pressure was similar in the 2 groups throughout the study. The incidences of cardiovascular events and target vessel revascularization were similar, although that of adverse events was significantly higher in the ACEI (12.4%) than in the valsartan group (3.3%; P<0.05). There were no differences in left ventricular ejection fraction and left ventricular end-diastolic volume index between the groups.

Conclusions: Valsartan exhibits similar efficacy effective to that of ACEI in preventing left ventricular dysfunction in Japanese patients with acute MI, and is, in addition, better tolerated than ACEI. (Circ J 2009; 73: 918–924)

Key Words: Angiotensin-converting enzyme inhibitor; Angiotensin receptor blocker; Myocardial infarction; Myocardial remodeling

Advances in coronary care and coronary interventional therapies have reduced the in-hospital mortality rate to less than 10% and improved myocardial remodeling in cases of acute myocardial infarction (AMI). However, AMI patients successfully treated by coronary interventions within a few hours of the onset sometimes develop severe myocardial dysfunction in the chronic stage as a result of myocardial remodeling. Left ventricular (LV) remodeling after AMI limits the long-term prognosis of these patients and remains an important predictor of mortality. Therefore, research to discover novel therapeutic strategies for limiting LV remodeling and preventing heart failure is very important.

Editorial p820

Angiotensin-converting enzyme inhibitors (ACEI) have been shown in randomized trials to reduce the morbidity and improve survival in chronic heart failure and post-AMI patients, especially in selected high-risk patients. Enalapril treatment initiated soon after the occurrence of myocardial infarction (MI) and continued for 6 months was shown to attenuate LV dilatation and produce a greater reduction in the LV volume as compared with placebo treatment after 1 month and 6 months of the occurrence of MI in a substudy of the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) using echocardiography. However, ACEI do not completely block the production of angiotensin II, therefore, blockade of angiotensin II via a non-ACE-dependent pathway through chymase has also been shown to be important in humans. Incomplete inhibition of angiotensin II production by ACEI has been reported with low-dose and long-term treatment. Therefore, use of angiotensin receptor blockers (ARB) might represent a
better strategy for completely inhibiting the deleterious actions of angiotensin II at the level of the type 1 receptor. The use of ARB to increase the levels of angiotensin II is also known to confer favorable effects on the cardiovascular function and structure via stimulation of the type 2 receptor. Furthermore, in experimental post MI heart failure model, it has been shown that ARB attenuated MCP-1 expression and macrophage infiltration in the border zone, resulting in less myocardial fibrosis.

Fully satisfactory results have not been obtained from trials of ARB. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial reported in 2002 failed to show any significant difference in the total mortality, although the trend seemed to be in favor of captopril in patients with complicated AMI. The Valsartan in Acute Myocardial Infarction (VALIANT) trial of 2003 was a double-blind trial using the ARB valsartan in patients with AMI complicated by LV systolic dysfunction, heart failure, or both. Valsartan proved to be as effective as captopril in patients at a high risk for cardiovascular events after MI, but the trial was performed mainly in Western countries, and no evidence of the effect of ARB on the progression of LV dysfunction after AMI was reported in Japanese patients.

We conducted the inhibitory effect of valsartan against progression of left ventricular dysfunction after myocardial infarction (T-VENTURE) study to examine whether valsartan might prove more efficacious than ACEI in preventing LV remodeling after AMI.

**Methods**

**Patient Population**

All men and women presenting with their first episode of AMI were eligible. The enrolled patients were successfully treated by coronary intervention within 24 h of onset of the AMI. AMI was diagnosed based on the following criteria: chest pain for longer than 30 min, ST segment elevation on the electrocardiogram, and at least a 2-fold increase from the normal range of the serum concentration of creatine kinase. Successful coronary intervention was defined as the achievement of Thrombolysis In Myocardial Infarction (TIMI) II or III flow at the final coronary angiography in the culprit coronary artery.

The major exclusion criteria were the presence of cardiogenic shock, hemodynamically significant valvular diseases and/or clinically significant hematologic or hepatic disorders at the time of entry into the study. Patients with a systolic blood pressure of less than 100 mmHg or serum creatinine concentration of more than 3.0 mg/dl at the time of entry into the study were also excluded. Furthermore, patients enrolled in other studies were also excluded in this study.

Written informed consent for the study was obtained from each patient and the study protocol conformed to the ethical guidelines set by the 1975 Declaration of Helsinki, as reflected by the *apriori* approval obtained from the human research committee of each of the individual participating hospitals.

**Study Design**

Consecutive patients admitted to Showa University Hospital, Toho University Omori Medical Center, Nippon Medical School Hospital and Jikei University Hospital were randomly assigned to treatment with valsartan at an initial dose of 40–80 mg per day or one of the following ACEI (enalapril maleate, perindopril erbumine, lisinopril, temocapril hydrochloride, alacepril, imidapril hydrochloride, ortrandolapril) within 10 days of admission to the hospital for AMI. The initial doses of enalapril maleate, perindopril erbumine, lisinopril, temocapril hydrochloride, alacepril, imidapril hydrochloride andtrandolapril were 2.5–5.0 mg, 1–2 mg, 5–10 mg, 1–2 mg, 12.5–25.0 mg, 2.5–5.0 mg and 0.25–0.5 mg, respectively. When the patients were found to tolerate the initial valsartan dose and confirmed to be free of hypotension-related symptoms, the dose was increased to a maximum of 160 mg daily. The doses of the ACEI were also increased to their respective maximum doses. Whenever a patient showed signs of intolerance to an increased dose, the dose was decreased to the level at which patient’s clinical status returned to normal. Blood pressure was measured with the patient in the supine position during hospitalization and with the patient in the sitting position at the outpatient office by the conventional cuff method. Both groups were administered additional antihypertensive agents as necessary for adequate blood pressure control. Although the combination of an ARB with ACEI was not allowed, a calcium antagonist was mandatory when involvement of coronary spasm was suspected in the development of AMI in the patient.

**Coronary Angiography and Follow-up**

Patients were followed up clinically, and follow-up coronary angiography was conducted at 6 months after the occurrence of MI. The occurrence of adverse events, including cardiovascular death, non-fatal MI, unstable angina, revascularization and non-fatal stroke, and re-hospitalization because of other cardiovascular diseases was prospectively monitored and analyzed in all the patients until 6 months post MI.

**Left Ventriculography**

Left ventriculography was performed just after coronary intervention within 24 h of the occurrence of AMI and at 6 months after the occurrence of MI. LV ejection fraction (LVEF), LV end-diastolic (LVEDVI) and end-systolic volume index (LVESVI) were calculated using the area-length method in order to evaluate LV function and the occurrence of LV remodeling.

**Statistical Analysis**

All data were expressed as mean±SEM. Categorical variables were compared by Fisher’s exact probability test. Student’s t-test was used to analyze the differences between the valsartan and ACEI groups, and between the results in the acute stage and at 6 months after the occurrence of MI. In all tests, P values of <0.05 were considered to be significant.

The differences in the blood pressure changes between the valsartan and ACEI groups were analyzed by repeated-measures ANOVA, followed by the unpaired t-test. Differences within groups were analyzed by repeated-measures ANOVA followed by the post-hoc Bonferroni Test.

**Results**

**Study Patients**

A total of 256 patients were enrolled in the study from January 2001 to March 2003. One-hundred and twenty-eight patients were allocated to the valsartan group and 128 to the ACEI group. Eight patients in the valsartan group and
7 patients in the ACEI group were excluded from the analysis, because the reperfusion intervention was undertaken more than 24 h after the onset of MI. Thus, finally, the data of 120 patients in the valsartan group (mean age, 63.0 ± 1.0 years) and 121 patients in the ACEI group (mean age, 62.9 ± 1.0 years) were included for the analysis of the adverse drug reactions (intention-to-treat population (ITT)). The test drug needed to be discontinued because of adverse drug reactions in 3 patients of the valsartan group and 8 patients of the ACEI group. There were no significant differences between the groups in terms of the mean age, sex distribution, reperfusion time, peak creatine kinase (CK) concentration, frequency of stent use, or frequency of multivessel disease. The prevalence rates of 4 risk factors, ie, hypertension, hyperlipidemia, diabetes mellitus and smoking, were also similar between the 2 groups (Table 1). The number of orally administered drugs at discharge was similar between the 2 groups (Table 2).

### Table 1. Clinical and Angiographic Characteristics of Patients in the Valsartan Group and ACEI Group

<table>
<thead>
<tr>
<th></th>
<th>Valsartan group (n=120)</th>
<th>ACEI group (n=121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0±1.0</td>
<td>62.9±1.0</td>
<td>0.964</td>
</tr>
<tr>
<td>M/F</td>
<td>101/19</td>
<td>99/22</td>
<td>0.628</td>
</tr>
<tr>
<td>Culprit (RCA/LAD/LCX)</td>
<td>44/2/62/12</td>
<td>58/0/56/7</td>
<td>0.131</td>
</tr>
<tr>
<td>Reperfusion time</td>
<td>6.1±0.5</td>
<td>5.9±0.5</td>
<td>0.719</td>
</tr>
<tr>
<td>Peak creatine kinase (mg/dl)</td>
<td>3.085±196</td>
<td>3.096±192</td>
<td>0.871</td>
</tr>
<tr>
<td>Stent</td>
<td>109 (90.8%)</td>
<td>106 (87.6%)</td>
<td>0.658</td>
</tr>
<tr>
<td>Vessel disease 1/2/3</td>
<td>73/32/15</td>
<td>77/30/14</td>
<td>0.904</td>
</tr>
</tbody>
</table>

Risk factor

- Hypertension
  - Valsartan group: 73 (60.8%)
  - ACEI group: 65 (53.7%)
- Hyperlipidemia
  - Valsartan group: 54 (45.0%)
  - ACEI group: 53 (43.8%)
- Diabetes mellitus
  - Valsartan group: 41 (34.2%)
  - ACEI group: 41 (33.9%)
- Smoking
  - Valsartan group: 81 (67.5%)
  - ACEI group: 67 (55.4%)

ACEI, angiotensin-converting enzyme inhibitors.

### Table 2. Medical Therapy at Discharge After MI in the Valsartan Group and ACEI Group

<table>
<thead>
<tr>
<th></th>
<th>Valsartan group (n=120)</th>
<th>ACEI group (n=121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>66 (55.0%)</td>
<td>76 (62.8%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetic drugs</td>
<td>27 (22.5%)</td>
<td>26 (21.5%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>71 (59.2%)</td>
<td>70 (57.9%)</td>
<td>0.836</td>
</tr>
<tr>
<td>Nitrates</td>
<td>21 (17.5%)</td>
<td>26 (21.5%)</td>
<td>0.435</td>
</tr>
<tr>
<td>β-blockers</td>
<td>29 (24.2%)</td>
<td>37 (30.6%)</td>
<td>0.264</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>33 (27.5%)</td>
<td>30 (24.8%)</td>
<td>0.633</td>
</tr>
<tr>
<td>Diuretics</td>
<td>23 (19.2%)</td>
<td>22 (18.2%)</td>
<td>0.844</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>10 (8.3%)</td>
<td>10 (8.3%)</td>
<td>0.985</td>
</tr>
<tr>
<td>Aspirin</td>
<td>118 (98.3%)</td>
<td>120 (99.2%)</td>
<td>0.622</td>
</tr>
<tr>
<td>Warfarin potassium</td>
<td>11 (9.2%)</td>
<td>11 (9.1%)</td>
<td>0.984</td>
</tr>
</tbody>
</table>

MI, myocardial Infarction. Other abbreviation see in Table 1.

### Table 3. Cardiovascular Events at 6 Months After MI in the Valsartan Group and ACEI Group

<table>
<thead>
<tr>
<th></th>
<th>Valsartan group (n=120)</th>
<th>ACEI group (n=121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined events</td>
<td>17 (14.2%)</td>
<td>21 (17.3%)</td>
<td>0.597</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Revascularization</td>
<td>9 (7.5%)</td>
<td>11 (9.0%)</td>
<td>0.647</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (1.7%)</td>
<td>3 (2.5%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>3 (2.5%)</td>
<td>4 (3.3%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hospitalization for peripheral artery disease</td>
<td>1 (0.8%)</td>
<td>0</td>
<td>0.498</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1,2.

### Follow-up Data (6 Months After MI)

The drugs were started at an average of 1.7±0.3 days after the onset of MI in the valsartan group, and 2.0±0.4 days after the onset in the ACEI group (P=NS). The initial dose of valsartan was 56.3±2.2 mg, which was 0.70±0.03 of adjusted dose to the regular approved dose in Japan, and the 0.74±0.04 of adjusted dose to regular approved dose in Japan of ACEI group was similar. However, the adjusted dose to the regular approved dose in Japan of the ACEI was 0.87±0.04, which was significantly higher than that in the valsartan group (0.75±0.03) at discharge (P<0.01). At 6 months after MI, the dose of valsartan increased to 0.81±0.04 of adjusted dose to regular approved dose in Japan (64.3±3.0 mg), which was significantly lower than the corresponding value in the ACEI group (0.92±0.04) (P<0.05). Enalapril maleate, perindopril erbumine, lisinopril, temocapril hydrochloride, imidapril hydrochloride, alacepril and trandolapril were administered to 65 (53.7%), 22 (18.2%), 19 (15.7%), 6 (5.0%), 4 (3.3%), 3 (2.5%) and 2 (1.7%) of the patients in the ACEI group, respectively, at 6 months.
The blood pressure at the start of medication was similar in the valsartan (129±2/73±1 mmHg) and ACEI (127±2/72±1 mmHg) groups (P=NS). At discharge, the blood pressure was significantly lower at 114±1/65±1 mmHg in the valsartan group and at 114±1/66±1 mmHg in the ACEI group, as compared with the initial values (P<0.05, P<0.05, respectively). At 6 months after the occurrence of MI, the blood pressure recovered to the initial values in both groups, and there was no significant difference in the blood pressure at this time-point between the 2 groups (P=NS).

Cardiovascular events occurred in 17 patients (14.2%) in the valsartan group, but in 21 patients (17.3%) in the ACEI group (P=NS). One sudden death was encountered in the ACEI group and there were no deaths in the valsartan group (P=NS). The incidence of target vessel revascularization did not differ significantly between the 2 groups (P=NS) (Table 3).

Cardiovascular events occurred in 17 patients (14.2%) in the valsartan group, but in 21 patients (17.3%) in the ACEI group (P=NS). One sudden death was encountered in the ACEI group and there were no deaths in the valsartan group (P=NS). The incidence of target vessel revascularization did not differ significantly between the 2 groups (P=NS) (Table 3). However, the overall incidence of adverse drug reactions was significantly higher in the ACEI group (15 patients; 12.4%) than in the valsartan group (4 patients; 3.3%) (P<0.05). The study drug needed to be discontinued in 3 patients of the valsartan group as a result of the development of hypotension or liver dysfunction, and in 8 patients of the ACEI group because of the development of cough, hypertension, heart failure or angina pectoris (Table 4).

**Left Ventriculography**

Left ventriculography was undertaken in both the acute phase and at 6 months after MI occurrence in a total of 96 patients in the valsartan group and a total of 78 patients in the ACEI group.

The LVEF was significantly higher at 6 months after the occurrence of MI than in the acute phase in the valsartan group (acute phase 50.7±1.2 in the acute phase vs 54.9±1.2 at 6 months after MI; P<0.05). In the ACEI group, however, the values of this parameter measured in the acute phase and at 6 months after the occurrence of MI were similar (53.5±1.1 in the acute phase vs 56.2±1.3 at 6 months after MI, P=NS). The LVEF was similar in the valsartan and ACEI groups, both in the acute phase and at 6 months after the occurrence of MI. The percentage increase of the LVEF was also similar between the 2 groups (14.0±3.7% in the valsartan group vs 7.0±3.6% in the ACEI group; P=NS) (Figure 1).

The LVEDVI was significantly higher at 6 months after the occurrence of MI than in the acute phase in the valsartan group (72.5±2.4 in the acute phase vs 82.2±2.4 at 6 months after MI; P<0.01). However, the value measured at 6 months after the occurrence of MI was similar to that measured in the acute phase in the ACEI group (76.1±3.0 in the acute phase vs 81.9±3.0 at 6 months after MI; P=NS). The LVEDVI was similar in the valsartan and ACEI groups, both in the acute phase and at 6 months after the occurrence of MI. Furthermore, the percentage increase of the LVEDVI was also similar in the valsartan group and ACEI groups (21.8±5.4% in the valsartan group vs 20.7±5.7% in the ACEI group; P=NS) (Figure 2).

The values of the LVESVI measured in the acute phase and at 6 months after the occurrence of MI were similar in the valsartan group (36.7±1.7 in the acute phase vs 38.5±1.9

---

**Table 4. Adverse Drug Reactions at 6 Months After MI in the Valartan Group and ACEI Group**

<table>
<thead>
<tr>
<th></th>
<th>Valsartan group (n=120)</th>
<th>ACEI group (n=121)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined adverse reactions</td>
<td>4 (3.3%)</td>
<td>15 (12.4%)</td>
<td>0.018</td>
</tr>
<tr>
<td>Dry cough</td>
<td>0</td>
<td>7 (5.8%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (0.8%)</td>
<td>2 (1.7%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (1.7%)</td>
<td>1 (0.8%)</td>
<td>0.992</td>
</tr>
<tr>
<td>Uncontrollable hypertension</td>
<td>0</td>
<td>2 (1.7%)</td>
<td>0.499</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>1 (0.8%)</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>0</td>
<td>1 (0.8%)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Abbreviations see in Tables 1, 2.

---

**Figure 1.** (a) Left ventricular ejection fraction (%) and (b) percentage change of left ventricular ejection fraction between the valsartan group and angiotensin-converting enzyme inhibitor (ACEI) group. *P<0.05 vs acute stage.
at 6 months after MI; P=NS). In the ACEI group also, the values of this parameter measured in the acute phase and at 6 months after the occurrence of MI were similar (36.2±1.9 in the acute phase vs 37.4±2.4 at 6 months after MI; P=NS). The LVESVI values were similar in the valsartan and ACEI groups, both in the acute phase and at 6 months after the occurrence of MI. Furthermore, the percentage increase of the LVESVI was also similar in the 2 groups (16.2±6.8% in the valsartan group vs 22.0±8.3% in the ACEI group; P=NS) (Figure 3).

**Figure 2.** (a) Left ventricular end-diastolic volume index (ml/m²) and (b) percentage change of left ventricular end-diastolic volume index between the valsartan group and angiotensin-converting enzyme inhibitor (ACEI) group. *P<0.05 vs acute stage.

**Figure 3.** (a) Left ventricular end-systolic volume index (ml/m²) and (b) percentage change of left ventricular end-systolic volume index between valsartan group and angiotensin-converting enzyme inhibitor (ACEI) group.

**Figure 4.** Percentage change of left ventricular ejection fraction (LVEF), percentage change of left ventricular end-diastolic volume index (LVEDVI), and percentage change of left ventricular end-systolic volume index (LVESVI) between low and high creatine kinase-MB groups. *P<0.05 vs low group, **P<0.01 vs low group.
We subdivided the study patients according to the area of myocardial infarction, reperfusion time (within/after 12 h), median CK concentrations and median CK-MB concentrations to compare the differences in the LVEF, LVEDVI, LVESVI, percentage change of LVEF, percentage change of LVEDVI, and percentage change of LVESVI between the valsartan and ACEI groups. There were no significant differences in the area of myocardial infarction, reperfusion time (within/after 12 h), median CK or median CK-MB concentrations between the 2 groups.

We compared the differences in the LVEF, LVEDVI, LVESVI, percentage change of LVEF, percentage change of LVEDVI, and percentage change of LVESVI among the ACEI administered in the ACEI group. There were no significant differences in all parameters among the ACEI.

We compared the percentage change of LVEF, percentage change of LVEDVI, and percentage change of LVESVI between the low CK-MB group and high CK-MB groups divided by the median CK-MB value in all patients. The percentage increase of LVEF was significantly higher in the low CK-MB group (18.3±4.0%) than in the high CK-MB group (3.7±3.5%; P<0.01), and the percentage increase of LVESVI was also significantly lower in the low CK-MB group (7.0±7.5%) than in the high CK-MB group (30.6±7.5%; P<0.05); however, the percentage increase of LVEDVI was similar in the 2 groups (17.5±5.4% in the low CK-MB group vs 25.2±5.9% in the high CK-MB group; P=NS) (Figure 4).

**Discussion**

This is the first study to show the similar efficacy of valsartan to that of ACEI in preventing myocardial remodeling after AMI in Japanese patients. The occurrence rate of cardiovascular events was similar, whereas that of adverse drug reactions was significantly lower in the valsartan group than in the ACEI group.

Recent mega trials performed to compare the effects ofARB and ACEI in AMI patients did not find the former agents to be superior. In the OPTIMAAL trial, losartan was neither superior nor non-inferior to captopril in patients with evidence of heart failure or LV dysfunction after AMI11 There was no significant difference in the total mortality rate, although the trend was in favor of captopril, leading to the interpretation that ACEI should remain the treatment of first choice for patients with complicated AMI. The incidences of reinfarction, revascularization and all-cause hospital admission were essentially identical between the 2 groups.Valsartan has been shown to inhibit the binding of angiotensin II to the AT1 receptors in the aortic smooth muscle cells, with a 30,000-fold higher affinity than that for the angiotensin II receptors in the human myometrium (AT2-receptor subtype).14 Valsartan showed a 5-fold greater affinity, on average, for the AT1 receptor than losartan15 In the recently published VALIANT trial, valsartan proved to be as effective as captopril in improving the survival and reducing cardiovascular morbidity in patients at a high risk for cardiovascular events after AMI12 The results of the VALIANT study contradicted the data from the OPTIMAAL study by showing the non-inferiority of valsartan to captopril, although it also did not prove superiority of the former. Furthermore, a study to examine the class effect of angiotensin II receptor blockers on mortality in patients with heart failure who were aged 65 years or older has been carried out16 The study showed that irbesartan, valsartan, and candesartan were associated with better survival rates than losartan. Although our data did not compare the effect of valsartan to other angiotensin II receptor blockers, it is possible that the effect of valsartan after AMI is not a class effect.

The present study was conducted using the main inclusion criteria of the OPTIMAAL and VALIANT trials, including the time of the initial ARB administration; however, the study differed from these mega trials in 3 respects: in the racial distribution, in the cardiac functions of the enrolled patients, and in the type and dose of the ARB used. The major difference was in the racial distribution of the patients; our study only contained Japanese patients, whereas mainly Caucasians were enrolled in the 2 mega trials referred to above. Furthermore, the OPTIMAAL and VALIANT trials included only AMI patients with complicating heart failure, whereas our study population also included AMI patients with mild LV dysfunction. The doses of valsartan and ACEI used in the present study were relatively low. The average initial dose of valsartan was 56.3±2.2 mg and the dose at follow-up was 64.3±3.0 mg. In general, Japanese patients require lower doses of these drugs than Western patients. The mean dose of valsartan in VALIANT was 247±105 mg, much higher than that indicated above in the present study. It would appear that even low doses of ARB might be sufficient to inhibit myocardial remodeling after MI and slow the progression of congestive heart failure in Japanese patients. However, we need to pay attention to the fact that there have been no studies in Japan, showing significant benefit of ACEI administered after MI. The JAMP study, which examined the effect of ACE after MI in Japan, failed to show the improvement of long-term survival.17 However, in the JAMP study the participants were selected from discharged patients who had been admitted to the hospital within 14 days after onset of an initial AMI. The start date of ACE was an average of 14 days after the onset, which could be considered late. The benefits of ACE might be related to early initiation of the drugs as shown by many studies from Western countries.3,4

Some reports have indicated a rather high prevalence of LV dilatation in AMI patients treated successfully by PCI.18 Impaired microvascular reperfusion has been reported to be associated with LV remodeling and the development of congestive heart failure in patients with AMI.19 The reperfusion phenomenon has also been reported to be a strong predictor of LV remodeling after AMI.20 However, the most reliable predictor of remodeling after MI reported from previous experimental and clinical studies is the infarct size.21–23 Most previous studies were performed retrospectively and not all patients received coronary reperfusion therapy along with ACEI or ARB administration. In the present study, the patient group with high peak concentrations of CK-MB exhibited a lesser increase of the EF and greater increase of the LVESVI, suggestive of exaggerating LV remodeling. Our present study was a prospective study and all patients received coronary reperfusion therapy following ACEI or ARB administration. The present study results also indicate that the infarct size is still the most reliable predictor of remodeling, even in the present era of advanced treatment techniques for AMI.

**Study Limitations**

Seven types of ACEI selected at the physician’s discretion choice were administered in randomly enrolled patients in the ACE group in this clinical trial conducted to compare
the preventive efficacies of valsartan and ACEI on LV remodeling after MI. It is possible that there are some differences in the efficacy among ACEI; however, patients in both groups showed similar blood pressure control throughout the study and hypotension-related adverse events were also similar between the 2 study groups. Therefore, the administered dose of valsartan was at least as effective as the doses of ACEIs used in the present study.

Conclusions

Valsartan exhibits similar efficacy effective to that of ACEI in preventing LV dysfunction in Japanese patients with AMI, and is, in addition, better tolerated than ACEI.

References