Inhibitory Effect of Candesartan Cilexetil on Left Ventricular Remodeling After Myocardial Infarction

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SUMMARY

Although angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce left ventricular remodeling after acute myocardial infarction (AMI), the effects of angiotensin receptor blockers have yet to be established. This study was conducted to examine the effects of candesartan on left ventricular remodeling after AMI. Consecutive AMI patients were assigned to a candesartan group or ACEI group after successful coronary intervention. The patients in the candesartan group (n = 77, mean age, 62.8 ± 1.3) received candesartan and the patients in the ACEI group (n = 80, mean age, 63.3 ± 1.2) received lisinopril, enalapril, ortrandolapril. Four mg was the most frequent dose in the candesartan group at 6 months. Lisinopril, enalapril, and trandolapril were administered to 52%, 27%, and 21% of the patients in the ACEI group, respectively. No significant differences in the incidences of cardiac death, nonfatal MI, or hospitalization for heart failure (P = NS) were found between the groups. The candesartan group exhibited a somewhat higher percent increase in left ventricular ejection fraction and significantly lower percent increases in left ventricular end-diastolic volume index and left ventricular end-systolic volume index compared to the ACEI group (P < 0.05, P < 0.05, respectively). Candesartan is more effective than ACEI in preventing left ventricular remodeling after AMI. (Int Heart J 2006; 47: 715-725)

Key words: Myocardial remodeling, Angiotensin receptor blocker, Angiotensin-converting enzyme inhibitor

In-hospital mortality in acute myocardial infarction (AMI) has been reduced to less than 10% due to ongoing advances in coronary care and coronary interventional therapies. Even so, left ventricular remodeling after AMI still limits the long-term prognosis and remains an important predictor of mortality.1,2) Early and successful coronary intervention not only limits the amount of muscle necrosis but also protects cardiac collagen,3) however, we sometimes encounter AMI

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patients who have developed severe myocardial dysfunction in the chronic stage due to myocardial remodeling even after being successfully treated by coronary interventions within a few hours from onset.

Randomized trials have shown that angiotensin-converting enzyme inhibitors (ACEI) reduce morbidity and improve survival in chronic heart failure and post-AMI, especially among selected, high-risk patients. A substudy of the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II) using echocardiography demonstrated that enalapril treatment initiated soon after MI and continued for 6 months can attenuate left ventricular dilatation and thereby elicit a greater reduction in the LV volume compared to that in a placebo-treated group after 1 and 6 months. Incomplete inhibition of angiotensin II production by ACEI has been reported using low-dose and long-term treatment. The blocking of angiotensin II via a non-ACE-dependent pathway through chymase is also important in humans. Therefore, angiotensin receptor blocker (ARB) administration may be the best strategy for completely inhibiting the deleterious actions of angiotensin II at the type 1 receptor. The use of an ARB to increase the levels of angiotensin II is also known to confer favorable effects on cardiovascular function and structure via stimulation of type 2 receptors.

The results of trials on the use of ARBs have not been overly encouraging. The OPTIMAAL (Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan) trial reported in 2002 failed to show a significant difference in total mortality in favor of captopril in patients after complicated AMI. The VALIANT (Valsartan in Acute Myocardial Infarction) trial of 2003 was a double-blind trial using the ARB valsartan in patients with AMI complicated by left ventricular 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 VALIANT findings did not prove it to be in any way superior to captopril.

Candesartan cilexetil is a newly developed ARB from Japan with a high affinity for the angiotensin II type 1 receptor subtype (AT1). In a short-term dose-finding study, candesartan cilexetil improved exercise capacity and alleviated signs and symptoms in patients with congestive heart failure. While candesartan is expected to confer stronger preventive effects against myocardial remodeling than other ARBs, no reports have actually documented its effects on myocardial remodeling after AMI. In the present study we tested whether candesartan would prove more efficacious than ACEI in preventing left ventricular remodeling after AMI.
METHODS

Patient population: Men and women aged 20 to 80 years who had experienced their first AMI were eligible. The enrolled patients were successfully treated with coronary intervention within 24 hours after onset. AMI was defined by the following criteria: chest pain for longer than 30 minutes, ST segment elevation on electrocardiography, and at least a two-fold increase in creatine kinase from the normal range. Successful coronary intervention was defined as a TIMI III flow at the final coronary angiography in the culprit coronary artery. Major criteria for exclusion were cardiogenic shock, hemodynamically significant valvular diseases, and clinically significant hematologic or hepatic disorders. Patients with a systolic blood pressure of less than 100 mmHg or a serum creatinine concentration of more than 2.5 mg/dL were also excluded. Written informed consent for the study was obtained from each patient and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in an a priori approval by the human research committee of our university.

Study protocol: Consecutive patients admitted to Showa University Hospital were randomly assigned to treatment with candesartan at an initial dose of 2-4 mg per day or with one of 3 ACEIs (lisinopril, enalapril, or trandolapril) within 3 days from admission using an envelope method. The selection of an ACEI and the doses of candesartan and the ACEI were left to the discretion of each attending physician. The initial doses of lisinopril, enalapril, and trandolapril were 5-10 mg, 2.5-5 mg, and 0.5-1 mg, respectively. When patients were tolerant of the candesartan cilexetil dose and confirmed to be free of hypotension-related symptoms, the dose was increased 2-4 mg per day every 2 weeks, up to a maximum dose of 12 mg. The doses of the ACEIs were also increased by the initial daily dose or by double the initial dose per day every 2 weeks, up to doses of 20 mg, 10 mg, and 2 mg, respectively. Whenever a patient showed signs of intolerance to an increased dose, the dose was decreased to the level at which the patient's clinical status returned to normal. Blood pressure was determined in a supine position during hospitalization and in a sitting position in an outpatient office using the conventional cuff method. Both groups were administered additional antihypertensive agents when necessary for adequate blood pressure control. The combination of ARB and ACEI was not allowed, however, a calcium antagonist was mandatory when there was suspected involvement of coronary spasm in the AMI.

Left ventriculography: Left ventriculography was performed just after coronary intervention at AMI and at 6 months after MI. Left ventricular ejection fraction (LVEF), left ventricular end-diastolic (LVEDVI), and end-systolic volume index (LVESVI) were calculated using the area-length method in order to evaluate left ventricular function and remodeling. All measurements were made by 2
experienced observers who were blinded to all clinical data. The results are expressed as an average of the data obtained by the 2 observers.

**Statistical analysis:** All data are expressed as the mean ± SEM. Student's *t* test was used to analyze the differences in factors and parameters between the candesartan and ACEI groups, and between the acute stage and follow-up. A *P* value of < 0.05 was considered significant.

## RESULTS

### (1) Study patients: A total of 160 patients were enrolled from January 2001 to March 2003. Seventy-nine patients were allocated to the candesartan group and 81 patients were allocated to the ACEI group. Two patients in the candesartan group and 1 patient in the ACEI group were unavailable for follow-up for a full 6 months after MI. Therefore, we obtained data on 77 patients in the candesartan group (mean age, 62.8 ± 1.3 years) and 80 patients in the ACEI group (mean age, 63.3 ± 1.2 years) for analysis (Table I). There were no differences in the mean age, sex, reperfusion time, peak CK, Killip III, or rates of anterior infarction, stent use, and multivessel disease between the groups (*P* = NS). The rates of 4 risk factors, ie, hypertension, hyperlipidemia, diabetes mellitus, and smoking were also similar between the 2 groups (*P* = NS).

### (2) Follow-up (six months after MI): The most frequent candesartan dose administered during the follow-up was 4 mg, followed by 8 mg. Lisinopril, enalapril, and trandolapril were administered to 52%, 27%, and 21% of the patients in the

| Table 1. Clinical and Angiographic Characteristics of Patients in the Candesartan Group and ACEI Group |
|-----------------|-----------------|-----------------|
|                 | Candesartan group (*n* = 77) | ACEI group (*n* = 80) | *P* |
| Age (years)     | 62.8 ± 1.3       | 63.3 ± 1.2       | NS  |
| Male/female     | 62/15            | 67/13            | NS  |
| Infarcted area (anterior) | 40/77 (52%)       | 43/80 (54%)       | NS  |
| Reperfusion time | 6.0 ± 5.6        | 6.1 ± 6.0        | NS  |
| Peak CK         | 3447 ± 244       | 3259 ± 327       | NS  |
| Killip 3        | 15/77 (19%)      | 20/80 (25%)      | NS  |
| Stent           | 62/77 (81%)      | 68/80 (85%)      | NS  |
| Multivessel disease | 30/77 (39%)     | 29/80 (36%)      | NS  |
| Risk factor     |                 |                 |     |
| Hypertension    | 48/77 (62%)      | 44/80 (55%)      | NS  |
| Hyperlipidemia  | 49/77 (64%)      | 46/80 (58%)      | NS  |
| Diabetes mellitus | 24/77 (31%)   | 21/80 (26%)      | NS  |
| Smoking         | 43/77 (56%)      | 52/80 (65%)      | NS  |

CK indicates creatine kinase.
ACEI group at follow-up, respectively (Table II). Blood pressure at follow-up was similar between the candesartan and ACEI groups ($P = \text{NS}$).

One cardiac death occurred in each group and 1 patient in each group was hospitalized due to heart failure. No significant differences in the incidences of cardiac death, nonfatal MI, or hospitalization for heart failure ($P = \text{NS}$) were found between the groups. One patient in the candesartan group was unable to continue the study drug due to hypotension, and 3 patients in the ACE group dis-
continued the study drug due to cough ($P = NS$). The incidence of target vessel revascularization was not significantly different between the 2 groups ($P = NS$), and restenosis occurred at similar frequencies in the 2 groups ($P = NS$) (Table III).

Figure 1. Left ventricular ejection fraction (%) (A) and % change in left ventricular ejection fraction (B). *: NS, **: $P < 0.01$.

Figure 2. Left ventricular end-diastolic volume index (mL/m$^2$) (A) and % change in left ventricular end-diastolic volume index (B). *: NS, **: $P < 0.05$, ****: $P < 0.001$. 
(3) **Left ventricular ejection fraction (LVEF):** No follow-up left ventriculographies were performed on the 3 candesartan patients and 5 ACEI patients who experienced the various conditions described above. This left us with data on 74 candesartan patients and 75 ACEI patients for our analysis of left ventricular function at follow-up.

LVEF in the candesartan group was significantly higher in the chronic stage than in the acute stage in the same patients (acute stage 45.8 ± 1.2 versus 50.3 ± 1.3, \( P < 0.01 \)). In the ACEI group, on the other hand, it was similar between the chronic and acute stages (acute stage 48.6 ± 1.4 versus 49.7 ± 1.3, \( P = \text{NS} \)). The percent increase in LVEF tended to be higher in the candesartan group than in the ACEI group (candesartan group, 14.4 ± 4.5% versus ACEI group, 6.3 ± 3.4%, \( P = \text{NS} \))(Figure 1).

(4) **Left ventricular end-diastolic volume index (LVEDVI):** LVEDVI in the candesartan group was similar between the chronic and acute stages in the same patients (acute stage 85.3 ± 2.4 versus 87.7 ± 2.3, \( P = \text{NS} \)). In the ACEI group, it was significantly higher in the chronic stage than in the acute stage (acute stage 82.7 ± 2.5 versus 92.9 ± 2.6, \( P < 0.001 \)). The % increase of LVEDVI was significantly lower in the candesartan group than in the ACEI group (candesartan group, 5.3 ± 2.9% versus ACEI group, 17.2 ± 3.8%, \( P < 0.05 \)), indicating a stronger inhibition of myocardial remodeling in the former (Figure 2).

(5) **Left ventricular end-systolic volume index (LVESVI):** LVESVI in the candesartan group was similar between the chronic and acute stages in the same patients (acute stage 46.9 ± 1.9 versus 44.1 ± 1.8, \( P = \text{NS} \)). In the ACEI group, it
was significantly higher in the chronic stage than in the acute stage (acute stage $43.2 \pm 2.1$ versus $47.3 \pm 2.2$, $P < 0.05$). The percent increase in LVESVI was significantly lower in the candesartan group than in the ACEI group (candesartan group, $-1.3 \pm 4.0\%$ versus ACEI group, $18.2 \pm 5.1\%$, $P < 0.05$), indicating a stronger inhibition of myocardial remodeling in the former (Figure 3).

**DISCUSSION**

This is the first study to demonstrate the superiority of candesartan over ACEI as an inhibitor of myocardial remodeling after AMI. In the comparisons between our candesartan and ACEI groups, the former exhibited a somewhat greater percent increase in LVEF and significantly lower percent increases in LVEDVI and LVESVI. Inhibition of myocardial remodeling after AMI was thus confirmed to be stronger in the candesartan patients.

Candesartan cilexetil, the agent used in the present study, was developed in Japan as a new angiotensin II receptor blocker with a high affinity for the angiotensin II type 1 receptor subtype. Candesartan has been reported to have the highest affinity to the AT1 receptor among the ARBs. Candesartan acts not only as an angiotensin inhibitor, but also as an anti-inflammatory agent and as a therapy for impaired endothelial function. When administered to hypertensive patients, candesartan reverses endothelial dysfunction by improving flow-mediated dilation and fibrinolysis. Candesartan has also been shown to significantly improve the percent flow-mediated dilator response to hyperemia and to significantly reduce plasma levels of plasminogen activator inhibitor type-1 antigen and monocyte chemoattractant protein-1. Another study reported the efficacy of candesartan in improving endothelial dysfunction assessed by forearm blood flow and in reducing monocyte chemoattractant protein-1 and soluble intercellular adhesion molecule-1. In the present study, these additional effects of candesartan may help confer a stronger protection against myocardial remodeling than ACEI.

Recent mega trials to compare the effects of ARBs and ACEIs in AMI patients did not find the former to be superior. In the OPTIMAAL trial, losartan was neither superior nor noninferior to captopril in patients with evidence of heart failure or left ventricular dysfunction after AMI. There was no significant difference in total mortality in favor of captopril, leading to the interpretation that ACEIs should remain the first-choice treatment in patients after complicated AMI. The incidences of reinfarction, revascularization, and all-cause hospital admission were essentially identical between the 2 groups. In the recently published VALIANT trial, valsartan proved to be as effective as captopril in improving survival and reducing cardiovascular morbidity in patients at high risk.
for cardiovascular events after AMI. The VALIANT study contradicted the OPTIMAAL data by proving the noninferiority of valsartan relative to captopril, but it did not prove the superiority of the former. The present study was consistent with the above two mega trials in finding no significant differences in the incidences of cardiac death, nonfatal MI, or hospitalization for heart failure between the candesartan and ACEI groups. However, the present study was the only one to demonstrate the superiority of an ARB over ACEIs as an inhibitor of myocardial remodeling after AMI using left ventriculography. No left ventriculography analyses were performed in the OPTIMAAL and VALIANT trials.

Our study also differed from the mega trials in 3 other respects: the time of the initial ARB administration, the patient population enrolled, and the type of ARB used. The drugs were commenced within 10 days after the onset of MI in the mega trials, whereas we commenced administration by as early as the third day. The OPTIMAAL and VALIANT trials included only AMI patients complicated with heart failure, whereas our population also included AMI patients with mild left ventricular dysfunction.

The doses of candesartan and ACEI used in this study were relatively low. Fifty-seven percent of the patients received 2-4 mg of candesartan and 34% received 8-12 mg of candesartan. Japanese patients generally need lower drug doses than patients in the West. The ARCH-J study, a trial conducted in Japanese patients only, convincingly showed the effectiveness of 8 mg of candesartan cilexetil compared with placebo in a population of patients with moderate congestive heart failure.17 In CHARM,18 a trial similar in design to the ARCH-J study but conducted chiefly in Europe and the United States, the mean daily dose of candesartan was 24 mg. It thus appears that even low doses of ARB inhibit myocardial remodeling after MI and slow the progression of congestive heart failure in Japanese patients. The effects of low-dose candesartan on cardiovascular events have also been reported in Japanese patients with coronary artery disease.19 Even when administered at a dose (4 mg/day) too low to elicit a blood pressure response for as long as 2 years after the start of treatment, candesartan began to noticeably inhibit cardiac events relatively soon after the start of the treatment. The appearance of inhibitory effects on cardiovascular events without changes in BP indicates that candesartan confers cardioprotective effects via mechanisms unrelated to BP reduction. The effectiveness of low-dose candesartan has also been reported in other organs.20 Low-dose candesartan cilexetil has prevented early kidney damage in Japanese type 2 diabetic patients with mildly elevated BP.20 Even the 4 mg/day dose of candesartan decreased systolic BP to a level similar to that in the control group, suggesting that the preventive effect on early kidney damage was also obtained via mechanisms separate from the hypotensive action of the drug.
Beta-blockers are not frequently used for the treatment of Japanese patients after AMI and heart failure. The rates of beta-adrenergic blocker use in candesartan groups differ markedly between the ARCH-J trial performed in Japanese patients with congestive heart failure (18.9%) and the CHARM trial (55.3%). A similar difference can be found in the rates of beta-adrenergic blocker use in studies of ARB after MI (OPTIMAAL) and VALIANT, 78.6% and 70%; Japanese study, 25-47%). The discrepancy is mainly a consequence of the involvement of coronary spasms in AMI. If coronary spasm is suspected, the administration of a calcium antagonist is mandatory in Japan. This contraindicates the use of beta-blockers, a class of agents which can aggravate coronary spasms. In comparison with whites, Japanese patients exhibited a 3-fold higher incidence of coronary spasm and a higher incidence of vasoconstriction of non-spastic segments after acetylcholine soon after AMI. A multicenter, prospective, randomized trial to compare the effects between beta-blockers and calcium antagonists post-AMI has shown a substantially lower cardiovascular event rate in Japanese patients than in the Western patients, and a similar cardiovascular event rate between beta-blocker and calcium antagonist groups. However, the incidences of heart failure and coronary spasm were significantly higher in the beta-blocker group than in the calcium antagonist group.

**Limitations of the study:** Three types of ACEIs selected by the physicians in the ACE group were administered in consecutively enrolled patients in this clinical trial to compare the efficacies of candesartan cilexetil and ACEIs on left ventricular remodeling after MI. We did take steps, however, to confirm that the blood pressure at 6 months after MI was similar among the patients administered candesartan cilexetil and the 3 ACEIs.

**Conclusions:** The angiotensin receptor blocker candesartan is a more effective inhibitor of left ventricular remodeling after myocardial infarction than angiotensin converting enzyme inhibitors.

**REFERENCES**


