Angiotensin II receptor blocker-based vs. non-angiotensin II receptor blocker-based therapy in patients with angiographically documented coronary artery disease and hypertension: the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE)

Hiroshi Kasanuki¹, Nobuhisa Hagiwara¹, Saichi Hosoda², Tetsuya Sumiyoshi², Takashi Honda³, Kazuo Haze⁴, Michitaka Nagashima¹, Jun-ichi Yamaguchi¹, Hideki Origasa⁵, Mitsuyoshi Urashima⁶, and Hiroshi Ogawa* for the HIJ-CREATE Investigators

¹The Heart Institute of Japan, Tokyo Women’s Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan; ²Sakakibara Heart Institute, Tokyo, Japan; ³Saisei-kai Kumamoto Hospital, Kumamoto, Japan; ⁴Osaka City General Hospital, Osaka, Japan; ⁵Division of Clinical Epidemiology and Biostatistics, Toyama University, Toyama, Japan; and ⁶Division of Clinical Research and Development, Jikei University School of Medicine, Tokyo, Japan

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Aims
To test whether angiotensin II receptor blockers (ARBs) therapy can reduce the incidence of cardiovascular events compared with non-ARB-based standard pharmacotherapy in coronary artery disease (CAD) patients with hypertension.

Methods and results
Angiographically documented CAD patients with hypertension were randomly assigned to receive either candesartan-based (n = 1024) or non-ARB-based pharmacotherapy including angiotensin-converting enzyme-inhibitors (n = 1025). The primary endpoint was the occurrence of a first major adverse cardiovascular event (MACE). There were 552 primary events during a median follow-up of 4.2 years: 264 (25.8%) in the candesartan group and 288 (28.1%) in the non-ARB group (hazard ratio, 0.89; 95% confidence interval, 0.76–1.06). No significant differences existed between groups in terms of cardiovascular death (2.7 vs. 2.4%, 1.14; 0.66–1.95), non-fatal myocardial infarction (2.8 vs. 2.5%, 1.12; 0.66–1.88), or heart failure (3.9 vs. 4.3%, 0.91; 0.59–1.40). New-onset diabetes was diagnosed significantly less frequently with candesartan than with non-ARBs (0.37; 0.16–0.89). Incidence of study drug discontinuation due to adverse events was lower with candesartan than with non-ARBs (5.7 vs. 12.2%, P < 0.001).

Conclusion
Although candesartan showed no significant differences in MACE compared with the non-ARB treatment group, the drug significantly reduced the incidence of new-onset diabetes and was better tolerated. This study is registered as International Standard Randomised Controlled Trial No. UMIN000000790.

Keywords
Randomized controlled trial • Coronary artery disease • Hypertension • Candesartan

* Corresponding author. Tel: +81 3 3353 8111, Fax: +81 3 3356 0441, Email: mogawa@hij.twmu.ac.jp
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Introduction

Conventional factors including hypertension account for most of the risks of myocardial infarction. Evidence from clinical trials indicates the beneficial effects of various classes of blood pressure-lowering regimens on cardiovascular event rates in hypertensive patients. Several classes of antihypertensive agent have demonstrated benefits in patients with coronary artery disease (CAD). Angiotensin II receptor blocker therapy is an alternative therapeutic approach that attenuates the renin–angiotensin system more specifically than angiotensin-converting enzyme-inhibitors (ACE-Is). Angiotensin II receptor blocker therapy might therefore exert stronger effects on the reduction of cardiac morbidity beyond blood pressure-lowering effects compared with other antihypertensive agents, including ACE-Is. Furthermore, ARBs may have protective clinical effects similar to those of ACE-Is, but may be better tolerated. However, this notion has recently been challenged. In ONTARGET, a recent randomized trial, the investigators clearly demonstrated that the ARB telmisartan is equivalent to ramipril in high-risk patients with vascular disease. Nonetheless, the effects of ARBs for secondary prevention of CAD in patients with hypertension who are receiving current standard therapy have yet to be determined.

The Heart Institute of Japan Candesartan Randomised Trial for Evaluation in CAD (HIJ-CREATE) was designed to test the hypothesis that long-term use of candesartan is more effective in reducing major cardiovascular events than non-ARB-based standard pharmacotherapy in angiographically documented CAD patients with hypertension, with equivalent blood pressure control.

Methods

Study design

The HIJ-CREATE was a multicentre, prospective, randomized, open-label, blinded-endpoint trial with an active control design comparing two antihypertensive treatment strategies involving 14 medical centres in Japan. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The institutional review board or relevant Ethics Committee of each participating medical centre approved the protocol, and all patients provided written informed consent prior to trial enrolment. A steering committee was responsible for the scientific conduct and publication of the trial results, and a working group was responsible for daily administration of the trial. This investigation was funded by the Japan Research Promotion Society for Cardiovascular Diseases, which played no role in the conduct of the study.

Inclusion and exclusion criteria

The HIJ-CREATE included specifically targeted hospitalized patients with CAD and hypertension between 20 and 80 years old. The protocol requires coronary angiography to be performed for the diagnosis of CAD when patients are enrolled. Even if no apparent stenotic lesion was observed on angiography at enrolment, patients with a history of revascularization procedures or with coronary spastic angina documented by acetylcholine provocation test were eligible to participate in the trial. Blood pressure was measured using a standard cuff mercury sphygmomanometer after 5 min of rest in the sitting position. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or history of having received treatment for hypertension at the time of enrolment.

Patients with secondary hypertension were excluded. Patients with acute myocardial infarction (AMI) within the past week or cerebrovascular disorders within the past 3 months were also excluded. Acute myocardial infarction was defined by the presence of typical clinical symptoms, electrocardiographic findings, and release of cardiac enzymes. Other major exclusion criteria included severe aortic valve stenosis; obstructive hypertrophic cardiomyopathy; serum creatinine level >2.0 mg/dL; potassium >5 mmol/L; female sex; and childbearing potential and not using contraception; history of serious or hypersensitivity reactions to other antihypertensive agents; acute liver disease or hepatic dysfunction (hepatic transaminases or bilirubin >1.5× the upper limit of normal); known malignant neoplasm; and current condition requiring ACE-Is or ARBs.

The primary endpoint of HIJ-CREATE was the time to first major adverse cardiac event (MACE; a composite of cardiovascular death, non-fatal myocardial infarction, unstable angina, heart failure, stroke, and other cardiovascular events requiring hospitalization). Cardiovascular death was defined as death due to myocardial or cerebral infarction or documented sudden cardiac death. Unstable angina was defined according to the Braunwald criteria. Heart failure was defined on the basis of symptoms (such as dyspnoea), clinical signs (such as rales or ankle oedema), and the need for treatment with diuretics, vasodilators, or antihypertensive drugs. Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 h. Stroke was further classified as the result of intracranial haemorrhage, ischaemia (if results of computed tomography or magnetic resonance imaging were available), or uncertain cause. Other cardiovascular events include peripheral artery diseases, dissecting aneurysm of the aorta, and increased size of aortic aneurysm. Secondary endpoints included angioplasty, stenting or coronary artery bypass grafting, and new onset of diabetes. Pre-existing diabetes was defined as fasting blood glucose level ≥126 mg/dL or treatment with hypoglycemic agents at the time of enrolment. New-onset diabetes was defined by two or more post-randomization fasting glucose measurements ≥126 mg/dL or commencement of hypoglycemic agents and/or evidenced by poor glycaemic control defined as glycohaemoglobin A1c ≥6.5%. These event records were provided to the Endpoint Classification Committee (consisting of three experienced cardiologists who were not study investigators, see Appendix) and were then determined in a blinded fashion. An endpoint committee whose members were blinded to treatment group assignments adjudicated all potential endpoints. Adverse events were determined by Endpoint Classification Committee on the basis of the information volunteered by patients. Although treatment strategies such as requiring hospitalization and revascularization treatment were used at the discretion of the responsible physician at each hospital, all potential endpoints were adjudicated by an endpoint committee whose members were blinded to treatment group assignments.

Randomization and treatment

Figure 1 shows the trial profile. The present study used an independent statistical data centre to manage patient registration, which included the confirmation of eligibility criteria, operation of the randomization scheme, and data management. During the index hospitalization, eligible patients were allocated to either the candesartan-based treatment arm or the non-ARB-based treatment arm according to a computer-generated, stratified, permuted-block randomization code. We used permuted-block randomization with a block size of four. Blocks were assigned according to the number of participants enrolled.
at each centre. For safety and ethical reasons, all patients underwent essential revascularization before randomization and continued to receive any prior antihypertensive agents until administration of the randomized medications, and before discharge were switched from the previous agents under close supervision with no run-in period. In the candesartan-based treatment arm, patients already receiving ARBs other than candesartan discontinued the previous agents and started receiving candesartan at 4–12 mg/day under the Japanese regulations related to pharmacotherapies. Doses of all antihypertensive drugs, including candesartan, were based on the guidelines of the Japanese Hypertension Society. Therapeutic modalities were consistent with the established standard pharmacotherapy. Combined antihypertensive agents excluding ACE-Is were allowed in order to achieve the desired level of blood pressure. In the non-ARB-based treatment arm, patients already receiving ARBs discontinued the previous agents and began receiving other classes of antihypertensive agents, including ACE-Is. In both treatment arms, titration of antihypertensive agents or combined medications was performed at the discretion of the responsible physician to reach the target blood pressure of 130/85 mmHg.

Follow-up
Participants were followed by hospital doctors or other general practitioners. Incidence of endpoint events in addition to drug safety information was determined during the scheduled 6, 12, 24, 36, 48, and 60 month visits, through contact with each patient, or via access to certificates issued by administrative authorities if necessary. All patients were followed for ≥36 months. In patients who underwent percutaneous coronary intervention during index hospitalization, follow-up coronary angiography was performed. Angiograms were sent to the angiographic core laboratory for analysis. All trial data were processed at a statistical data centre. In this study, the safety monitoring committee only evaluated safety information.

Statistical analysis
We set an accrual period of 2 years and a maximum duration of follow-up of 5 years. Since the control non-event rate at 1 year was assumed to be 0.9, the hazard in the control group was estimated to be 0.0088 per month under an assumption of exponential distribution. In addition, the hazard in the ARB intervention group was estimated to be 0.0070 per month (corresponding to a 1 year non-event rate of 0.92), since the hazard ratio (HR) was supposed to be 0.8.

The present study was designed to detect a 20% reduction in events in the candesartan arm compared with the control group. A primary endpoint event rate of approximately 100 events/1000 person-years in the control group was estimated from previous data. To detect this difference at a two-tailed 5% level of significance with 80% power, 1015 patients per group (2030 in total) were required during an enrolment period of 2 years and a mean follow-up period of ≥3 years. The intention-to-treat approach was used for efficacy and safety analyses, and all randomized patients were included in all analyses, regardless of protocol violations. Time-to-first-occurrence of events was analysed using the Kaplan–Meier method with the log-rank test and conventional Cox proportional hazards model. Furthermore, to evaluate effects within specific time intervals, the time-dependent extension of the Cox model using internal covariates was used. Analysis for consistency of treatment effects in pre-specified subgroups was explored with respect to the primary and secondary endpoints by the Cox regression model, utilizing tests for interaction to examine consistency of the results. The pre-specified subgroups were gender, age (<65 vs. ≥65 years), BMI, C-reactive protein, renal function, presence or absence of ACS, blood pressure, disease...
several studies have shown that impaired renal function is associated with a higher risk of cardiovascular events. In the current study, we evaluated the effects of candesartan-based therapy in patients with impaired renal function.

Methods
A total of 5005 participants were evaluated for eligibility in 14 clinical centres in Japan (see Appendix). Between June 2001 and April 2004, a total of 2049 patients were randomized in this trial. Among these, 1024 patients were allocated to the candesartan-based treatment arm, and 1025 to the non-ARB-based treatment arm. Follow-up was completed in June 2007. During the median follow-up period of 4.2 years (inter-quartile range, 3.5–4.9 years), three patients in the candesartan arm and five patients in the non-ARB arm were lost to follow-up, resulting in a follow-up rate of 99.6%. Table 1 shows baseline characteristics of the two groups of participants. The two treatment groups were well balanced with respect to baseline characteristics. Mean [+ standard deviation (SD)] age was 65 ± 9 years and mean blood pressure upon enrolment was 135 ± 18/76 ± 12 mmHg. Percutaneous coronary intervention and coronary artery bypass grafting had been performed before randomization in 82.8 and 11.5% of patients, respectively. Before randomization, ACE-I, calcium-channel blockers, β-blockers, and ARBs had been prescribed in 37.0, 55.8, 41.9, and 21.6% of patients, respectively.

Clinical outcome
Figure 2 illustrates mean systolic and diastolic blood pressures for the two groups. Mean blood pressure at baseline was 135.5/75.8 mmHg in the non-ARB group and 135.0/75.6 mmHg in the candesartan group. Mean blood pressure during follow-up was reduced by 3.3/1.1 mmHg in the non-ARB group and by 4.3/2.7 mmHg in the candesartan group. Blood pressures did not differ significantly between groups throughout the trial (systolic blood pressure, \( P = 0.379 \); diastolic blood pressure, \( P = 0.194 \)).

Incidence of the primary endpoint was 28.1% in the non-ARB group and 25.8% in the candesartan group. The reduction in the incidence of MACEs did not achieve statistical significance [HR, 0.89; 95% confidence interval (CI), 0.76–1.06; \( P = 0.19 \); Figures 3 and 4]. Furthermore, no significant differences were noted between the candesartan and non-ARB groups in terms of cardiovascular death (2.7 vs. 2.4%; HR, 1.14; 95% CI, 0.66–1.95); non-fatal myocardial infarction (2.8 vs. 2.5%; HR, 1.12; 95% CI, 0.66–1.88); heart failure (3.9 vs. 4.3%; HR, 0.91; 95% CI, 0.59–1.40); or stroke (4.4 vs. 4.8%; HR, 0.92; 95% CI, 0.61–1.37) (Figure 4).

In terms of secondary endpoints, angioplasty, stenting, or coronary artery bypass grafting was performed in 271 patients (26.4%) in the non-ARB group and in 256 patients (25.0%) in the candesartan group (HR, 0.93; 95% CI, 0.78–1.10; \( P = 0.41 \)). New-onset diabetes was diagnosed in fewer of the patients assigned to the candesartan-group compared with controls (HR, 0.37; 95% CI, 0.16–0.89; \( P = 0.03 \); Figure 4).

Figure 5 shows relative risks and 95% CIs for the primary endpoint according to selected demographics and background treatments. Most point estimates demonstrated similar HRs, and no statistical heterogeneity was identified among subgroups. Although candesartan treatment was associated with a significant reduction of 21% (HR, 0.79; 95% CI, 0.63–0.99; \( P = 0.04 \)) in the frequency of primary endpoint in patients with impaired renal function defined as creatinine clearance < 60 mL/min, no significant interactions were noted between patient characteristics. Further investigations are needed into the mechanisms underlying the beneficial effects of candesartan-based therapy in patients with renal impairment, but not in patients with normal renal function.

Table 2 shows the occurrence of pre-specified adverse experiences. The difference in adverse events is driven by ‘cough’ and anaemia in the non-ARB group. Consequently, study drug discontinuation decided by attending physicians because of an adverse event arose more frequently in the non-ARB-based standard therapy group than in the candesartan group (12.2 vs. 5.7%; \( P < 0.001 \)). In the candesartan group, 2.5% of patients were prescribed ACE-I by the end of the study period. Conversely, 23.0% of patients in the non-ARB-based group were prescribed ARBs at the end of the study.

Discussion
In patients with angiographically documented CAD and hypertension who are receiving current standard therapy, although no significant reduction was seen in events for the primary outcome, candesartan was significantly better tolerated, with fewer discontinuations due to drug-related adverse events. Furthermore, candesartan significantly reduced the incidence of new-onset diabetes in comparison with controls.

Previous studies have confirmed clear benefits of ACE-IIs in patients with stable CAD.1,2 On the other hand, the effects of ARBs in patients with stable CAD remain to be determined under contemporary management, including high prevalence of coronary revascularizations. In ONTARGET, a recent randomized trial, the investigators provided evidence to physicians that the ARB telmisartan is equivalent to ramipril in high-risk patients with vascular disease. The present HIJ-CREATE was not a direct head-to-head comparison of an ACE-I and an ARB, but was the first trial to examine whether candesartan treatment would be more effective than non-ARB-based standard pharmacotherapy in reducing cardiovascular events in hypertensive patients with angiographically documented CAD. Our results provide evidence to cardiologists of the value of broader use of ARB-based strategies for CAD patients at risk of developing diabetes and/or chronic kidney disease. Since patients in the present study were treated sufficiently with revascularization and optimal pharmacotherapy, rates of adverse events were lower in the present study than in previous studies. Candesartan did not show any significant difference in MACE in favour of non-ARB treatment group, but did significantly reduce the incidence of new-onset diabetes in comparison with non-ARB treatment and was also better tolerated.
### Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard therapy (n = 1025)</th>
<th>Candesartan-based-therapy (n = 1024)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>219 (21.4%)</td>
<td>186 (18.2%)</td>
<td>0.069</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 ± 8.9</td>
<td>64.5 ± 9.4</td>
<td>0.272</td>
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<td>Diagnosis</td>
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<tr>
<td>Acute coronary syndrome</td>
<td>378 (36.9%)</td>
<td>346 (33.8%)</td>
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<tr>
<td>Number of diseased vessels</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>146 (14.2%)</td>
<td>149 (14.5%)</td>
<td>0.623</td>
</tr>
<tr>
<td>1</td>
<td>437 (42.6%)</td>
<td>436 (42.5%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>277 (27.0%)</td>
<td>294 (28.7%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>165 (16.1%)</td>
<td>145 (14.1%)</td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>844 (82.3%)</td>
<td>852 (83.2%)</td>
<td>0.606</td>
</tr>
<tr>
<td>During enrolment hospitalization</td>
<td>542 (52.9%)</td>
<td>538 (52.5%)</td>
<td>0.878</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>112 (10.9%)</td>
<td>124 (12.1%)</td>
<td>0.402</td>
</tr>
<tr>
<td>During enrolment hospitalization</td>
<td>31 (3.0%)</td>
<td>35 (3.4%)</td>
<td>0.614</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>612 (59.7%)</td>
<td>604 (59.0%)</td>
<td>0.739</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>401 (39.1%)</td>
<td>379 (37.0%)</td>
<td>0.325</td>
</tr>
<tr>
<td>Current smoker</td>
<td>377 (36.8%)</td>
<td>401 (39.2%)</td>
<td>0.194</td>
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<tr>
<td>Family history</td>
<td>240 (23.4%)</td>
<td>213 (20.8%)</td>
<td>0.154</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>94 (9.2%)</td>
<td>111 (10.8%)</td>
<td>0.208</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>26 (2.5%)</td>
<td>38 (3.7%)</td>
<td>0.127</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>77 (7.5%)</td>
<td>58 (5.7%)</td>
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<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td>0.129</td>
</tr>
<tr>
<td>I</td>
<td>826 (80.6%)</td>
<td>801 (78.2%)</td>
<td>0.231</td>
</tr>
<tr>
<td>II</td>
<td>155 (15.1%)</td>
<td>185 (18.1%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>22 (2.1%)</td>
<td>19 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>22 (2.1%)</td>
<td>19 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.7 ± 3.1</td>
<td>24.6 ± 2.9</td>
<td>0.585</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.5 ± 17.5</td>
<td>135.0 ± 18.5</td>
<td>0.522</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.8 ± 11.7</td>
<td>75.6 ± 12.1</td>
<td>0.802</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55.1 ± 11.3</td>
<td>53.9 ± 11.2</td>
<td>0.022</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>192.4 ± 34.9</td>
<td>193.5 ± 34.7</td>
<td>0.488</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)*</td>
<td>126.5 (89.0–179.0)</td>
<td>128.5 (94.5–187.5)</td>
<td>0.129</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>44.5 ± 11.8</td>
<td>44.6 ± 12.0</td>
<td>0.828</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>62.0 ± 19.3</td>
<td>62.6 ± 19.9</td>
<td>0.469</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)*</td>
<td>0.2 (0.1–0.4)</td>
<td>0.2 (0.1–0.4)</td>
<td>0.356</td>
</tr>
<tr>
<td>Medications before randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Is</td>
<td>389 (38.0%)</td>
<td>370 (36.1%)</td>
<td>0.394</td>
</tr>
<tr>
<td>Diuretics</td>
<td>79 (7.7%)</td>
<td>99 (9.7%)</td>
<td>0.115</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td>586 (57.2%)</td>
<td>557 (54.4%)</td>
<td>0.206</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>440 (42.9%)</td>
<td>418 (40.8%)</td>
<td>0.334</td>
</tr>
<tr>
<td>ARBs</td>
<td>224 (21.9%)</td>
<td>218 (21.3%)</td>
<td>0.756</td>
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<tr>
<td>Medications at discharge</td>
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<tr>
<td>ACE-Is</td>
<td>723 (70.5%)</td>
<td>8 (0.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>82 (8.0%)</td>
<td>103 (10.1%)</td>
<td>0.104</td>
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<tr>
<td>Calcium-channel blockers</td>
<td>574 (56.0%)</td>
<td>457 (44.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ß-Blockers</td>
<td>506 (49.4%)</td>
<td>464 (45.3%)</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Continued
Table 1 Continued

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<thead>
<tr>
<th>Variables</th>
<th>Standard therapy (n = 1025)</th>
<th>Candesartan-based-therapy (n = 1024)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>447 (43.6%)</td>
<td>459 (44.8%)</td>
<td>0.58</td>
</tr>
<tr>
<td>Nitrates</td>
<td>526 (51.3%)</td>
<td>503 (49.1%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Aspirin</td>
<td>935 (91.2%)</td>
<td>948 (92.6%)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; NYHA, New York Heart Association. Values represent mean ± SD.
*Median (25th–75th percentile).

Figure 2 Systolic and diastolic blood pressures in treatment groups during follow-up. Blood pressure did not differ significantly between groups throughout the trial (systolic blood pressure, $P = 0.379$; diastolic blood pressure, $P = 0.194$). Error bars indicate standard deviation. $P$-values were obtained by a test of trend profile using a mixed model.

Figure 3 Kaplan–Meier curve for primary endpoint (major adverse cardiovascular event).
Figure 4  Hazard ratio for primary and secondary endpoints.

Figure 5  Subgroup analyses for primary endpoint. *Participants who underwent repeat PCIs for several years before randomization were excluded. †By tertiles of mean blood pressure. PCI, percutaneous coronary intervention.
In terms of practical management, high-risk CAD patients with hypertension often require combination therapy from the early stages, and administration of a single antihypertensive agent is unlikely. Patients at very high risk of subsequent cardiovascular events, such as HIJ-CREATE participants, deserve access to all available treatment strategies, including blockade of the renin–angiotensin system as used in the control group. This requirement for administration of the best available pharmacotherapy is only possible in a society in which all individuals have health insurance and thus equal access to the same medications and the same level of care in medical institutions. We recognize that several controversies remain with regard to this issue. Other large-scale trials of antihypertensive agents in CAD patients with hypertension have been completed since our study began, but whether the apparent benefits of certain classes of antihypertensive agents are class-specific or merely reflect the impact of blood pressure reduction has not been determined. Achieving equivalent blood pressure levels when adhering to a strict treatment protocol appears difficult using specific agents alone. Accordingly, HIJ-CREATE was pragmatic, but had methodological limitations in comparing individual antihypertensive agents.

The social health insurance system gives Japanese patients comprehensive coverage of hospital fees, but provides precise instruction as to therapeutic modalities, including the amounts of medications. For example, the maximum therapeutic dose of candesartan is 12 mg/day. As a result, 73.9% of patients in the candesartan arm of the present study received a maintenance dose <8 mg/day, lower than previously reported. Further investigations of optimal dosing strategies for candesartan are needed to reduce subsequent cardiovascular events in patients with CAD and hypertension. Long-term clinical trials of antihypertensive agents have shown significant differences in the rates of new-onset diabetes between treatment groups. A recent meta-analysis showed that ARB and ACE-Is are the antihypertensive agents least associated with incident diabetes, followed by calcium-channel blockers, β-blockers, and diuretics. Although small numbers of affected patients and relatively short follow-up periods limit the power of existing studies to detect an increased risk of cardiovascular events in patients with new-onset diabetes, as in the present study, longer follow-up might identify associations with increased frequency of cardiovascular events.

### Study strengths and limitations

Previous randomized, controlled trials have applied strict criteria to avoid heterogeneities of treatment effects. As patients eligible for enrolment had to be hospitalized in our trial, HIJ-CREATE appears to involve the most severely affected CAD population compared with previous studies that assessed the effects of antihypertensive agents in CAD patients with hypertension. Conversely, the relatively broad eligibility criteria could lead to the necessity for evaluation of interactions and combined effects of agents in detailed analyses, including post hoc-exploratory attitudes.

Some further limitations of our study suggest possibilities for further investigation. The difficulty of conducting a randomized trial in Japan in a double-blinded fashion is well known, because the Japanese Pharmaceutical Affairs Law heavily restricts the use of placebo in physician-initiated studies. The present study was conducted with the use of a prospective, randomized, open-label design, with blinded assessments of endpoints. Although treatment strategies such as requiring hospitalization and revascularization treatment were used at the discretion of the responsible physician at each hospital, an endpoint committee whose members were blinded to treatment group assignments adjudicated all potential endpoints. Secondly, the present study was underpowered mainly because the actual event rate was much lower than the expected rate. The high usage (71%) of ACE-Is in the non-ARB-based standard therapy group appears likely to have contributed to reduced power compared with that we expected in advance. The rather low dose of candesartan used in the ARB group under the drug-related Japanese regulation also contributed to this finding. Given the low event rate in HIJ-CREATE, our study was underpowered for demonstrating that candesartan had a significant effect on reducing total adverse cardiovascular events. Although our results do not provide any evidence of superiority for ARB over non-ARB-based standard therapy, several pre-defined subgroup analyses were performed in the present study and caution is needed in the interpretation. Nonetheless, our results suggest the superiority of ARB-based therapy for secondary prevention of CAD in hypertensive patients with impaired renal function compared with traditional therapeutic modalities. Finally, participants of the present study were recognized as a high-risk population and were thus started on randomized medication immediately without washout. Consequently, Kaplan–Meier curves for the primary outcome might not separate for the first few months.

In conclusion, candesartan is similar to standard non-ARB pharmacotherapy in reducing rates of cardiovascular events among patients with angiographically documented CAD and hypertension who are receiving current standard therapy. Candesartan-based therapy is better tolerated, mainly due to reduced cough...
comparing with standard therapy, and is associated with a significant reduction in new-onset diabetes.

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**Conflict of interest:** The sponsor played no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The HIJ-CREATE Steering Committee had full access to all data in the study and had final responsibility for the decision to submit for publication.

**Appendix**

**Study organization**

Executive Committee: Hiroshi Kasanuki (Chair), Nobuhsa Hagwara.
Steering Committee: Saichi Hosoda, Tetsuya Sumiyoshi, Takashi Honda, Kazuo Haze, Hiroshi Ogawa.

**Data and Safety Monitoring Committee:** Keiji Ueda (Chair, Japan Pharmaceutical Information Center).

Voting Members: Hiroshi Matsuoi (Saitama Medical University); Hideki Origa (Toyama University).

**Endpoint Committee:** Kazuho Kato (Chair, Cardiovascular Institute Hospital).

Voting Members: Hirokazu Hayakawa (Nippon Medical School), Tadano Aizawa (Cardiovascular Institute Hospital).

Statistical Data Center: Katsunori Shimada (STATZ Institute Inc.).

QCA Core Laboratory: Yasuhiro Ishii, Hiroshi Koganei.

Clinical centres: Tokyo Women’s Medical University; Atsushi Takagi; Sakakibana Heart Institute: Ryuta Asano; Osaka City General Hospital: Akira Ito; Saisei-Kai Kumamoto Hospital: Koichi Nakao; Cardiovascular Center of Sendai: Tatsuro Ueda; Seihi Hamamatsu General Hospital: Toshiaki Oka; Saitama Cardiovascular and Respiratory Center: Kamon Imai; Saisei-Kai Kurihashi Hospital: Yasuhiro Endoh; National Yokohama Medical Center: Katsunori Iwade, Naohide Tanaka; Tokyo Metropolitan Fuchu Hospital: Tatsuro Ueda, Hiroyuki Tanaka; Kosei General Hospital: Masao Kagawuchi; NTT-East Kanto Medical Hospital: Satoshi Ohnishi; Shin-Matsudo Central General Hospital: Yasuhiro Kagawge; Higashi-Nihon Cardiovascular Center: Naoya Fujita, Takao Yamauchi.

**References**


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**CARDIOVASCULAR FLASHLIGHT**

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**Multi-vessel coronary artery spasm**

Hee Hwa Ho*, Chung Wah Siu, and Wai Luen Lee

Division of Cardiology, Department of Medicine, Queen Mary Hospital, Pokfulam Road, Hong Kong

* Corresponding author. Tel: +852 25182111, Fax: +852 25188558, Email: hokai_wah@yahoo.com

A 69-year-old male, a chronic smoker with history of hypertension, presented with chest pain. Electrocardiogram showed marked ST-depression over antero-lateral leads (Panel A). Echocardiogram showed inferior wall hypokinesia. Troponin level was elevated confirming the diagnosis of non-ST-elevation myocardial infarction. He was treated with aspirin, clopidrogel, low molecular heparin, and glycoprotein 2b/3a inhibitors. Coronary angiography the following day (Panel C) showed non-obstructive diffusely diseased vessels over the left anterior descending (LAD) and left circumflex (CIRC) arteries. Right coronary artery (RCA) which was the culprit artery appeared even smaller in calibre and was occluded (Panel E). Our initial reaction was to treat his condition medically. However, we decided to repeat the coronary angiography with intracoronary nitroglycerin with the option of percutaneous coronary intervention of any significant coronary stenoses. After injection of a single bolus of intracoronary nitroglycerin, the LAD and CIRC arteries (Panel D) appeared bigger in calibre and were non-obstructive. The possibility of coronary artery spasm was considered and coronary angiography of RCA was repeated. After three boluses of intracoronary nitroglycerin, a normal looking RCA was unmasked (Panels F and G).

Coronary artery spasm usually develops at the site of coronary stenoses but may also occur in angiographically normal coronary arteries. The prevalence of coronary artery spasm is actually higher in patients with acute coronary syndrome than in patients with stable angina. As illustrated by our case, it is important to be aware of this possibility and the judicious use of intracoronary nitroglycerin during coronary angiography can lead to the correct diagnosis being made.

Panel A. Electrocardiogram at presentation.

Panel B. Electrocardiogram (post-nitroglycerin injection).

Panel C. Coronary angiography of left anterior descending and left circumflex arteries.

Panel D. Coronary angiography of left anterior descending and left circumflex arteries (post-nitroglycerin injection).

Panel E. Coronary angiography of right coronary artery.

Panel F. Coronary angiography of right coronary artery (after the first bolus intracoronary nitroglycerin injection).

Panel G. Coronary angiography of right coronary artery (after three boluses of intracoronary nitroglycerin injection).

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