Blood Pressure

ISSN: 0803-7051 (Print) 1651-1999 (Online) Journal homepage: informahealthcare.com/journals/iblo20

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To cite this article: Tsuyoshi Shiga, Hiroshi Kasanuki, Nobuhisa Hagiwara, Tetsuya Sumiyoshi, Takashi Honda, Kazuo Haze, Atsushi Takagi, Masatoshi Kawana, Hideki Origasa, Hiroshi Ogawa & For The Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (Hij-Create) Investigators (2010) Angiotensin receptor blocker-based therapy and cardiovascular events in hypertensive patients with coronary artery disease and impaired renal function, Blood Pressure, 19:6, 359-365, DOI: 10.3109/08037051003802475

To link to this article: https://doi.org/10.3109/08037051003802475

Blood Pressure. 2010; 19: 359–365

informa
healthcare

ORIGINAL ARTICLE

Angiotensin receptor blocker-based therapy and cardiovascular events in hypertensive patients with coronary artery disease and impaired renal function

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Abstract

The aim of this study was to assess the effects of angiotensin receptor blocker (ARB)-based therapy on cardiovascular events in high-risk hypertensive patients with coronary artery disease (CAD) and impaired renal function in *post hoc* analysis of HIJ-CREATE (Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease). Patients (n=2049) were randomly assigned to candesartan-based or non-ARB treatment arms; 1022 patients (age 70±6 years, 28% female) with impaired renal function, defined as creatinine clearance <60 ml/min at baseline. There was no difference in 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 between the two arms in patients without impaired renal function. However, there was a lower incidence of MACE in the candesartan-based treatment arm than in the non-ARB treatment arm (HR=0.79, 95% CI 0.63–0.99, p=0.039) in patients with impaired renal function. Among the MACE, candesartan-based treatment reduced hospitalization for unstable angina (HR=0.71, 95% CI 0.52–0.96, p=0.028). Although candesartan-based treatment was not superior to non-ARB treatment in prevention of cardiac mortality, ARB-based therapy may be beneficial in reducing risk of coronary events in hypertensive patients with CAD and impaired renal function.

Key Words: *Angiotensin receptor blocker, coronary artery disease, hypertension, renal function*

Introduction

Impaired renal function is an independent risk factor of death and cardiovascular events (1–3). Blockade of the renin–angiotensin system has a renoprotective benefit and delays the progression of renal disease (4,5). The 2007 European Society of Hypertension (ESH)–European Society of Cardiology (ESC) guidelines recommended strict blood pressure control and lowering of proteinuria in hypertensive patients with renal dysfunction, and that the combination therapy should include either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) to reach target blood pressure (6). However, it is unclear whether ARB reduces cardiovascular morbidity or mortality in high-risk hypertensive patients with impaired renal function.

Impaired renal function is frequent in the hypertensive patients with coronary artery disease (CAD) (7). In the Heart Institute of Japan Candesartan Randomized Trial for Evaluation in Coronary Artery Disease (HIJ-CREATE), a reduction in the frequency of primary endpoint, a composite of fatal and non-fatal cardiovascular events, was observed in patients with impaired renal function randomly assigned to ARB-based therapy compared with those assigned to non-ARB-based standard therapy (8).

The present investigation is a *post hoc* analysis of HIJ-CREATE to assess the effects of the ARB-based

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(Received 25 January 2010; accepted 18 March 2010)

ISSN 0803-7051 print/ISSN 1651-1999 online
DOI: 10.3109/08037051003802475

therapy on cardiovascular events in high-risk hypertensive patients with CAD and impaired renal function.

Materials and methods

Subjects

HIJ-CREATE was a multicentre, prospective, randomized, open-label, blinded-endpoint trial with an active control design (9), comparing ARB-based and non-ARB treatment strategies in Japan. A total of 2049 enrolled patients with angiographically documented CAD and hypertension were randomly assigned to the candesartan-based treatment arm or non-ARB treatment arm including ACE inhibitors. 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 a history of having received treatment for hypertension at the time of enrolment. Patients with acute myocardial infarction within the past week or with cerebrovascular disorders were excluded. Details of the study design, inclusion and exclusion criteria, endpoints, randomization, treatment, data collection and data analysis have been reported (8). The protocol was approved by the institutional review boards of the participating hospitals. Written informed consent was obtained from all patients.

Impaired renal function was defined as a decrease in creatinine clearance calculated using the Cockcroft–Gault formula (10) to <60 ml/min. A total of 1022 patients had impaired renal function at baseline. In the candesartan-based treatment arm, patients received candesartan at 4–12 mg daily under the Japanese regulations related to pharmacotherapy. Doses of all antihypertensive drugs, including candesartan, were based on the guidelines of the Japanese Hypertension Society. Combined antihypertensive agents, excluding ACE inhibitors, were allowed in order to achieve the desired level of blood pressure. In the non-ARB-based treatment arm, patients received other classes of antihypertensive agents, including ACE inhibitors. 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.

Endpoints

The primary endpoint was the time to first major adverse cardiac event (MACE, a composite of cardiovascular death, non-fatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, hospitalization for stroke and hospitalization for other cardiovascular events). Cardiovascular death was defined as death related to myocardial or cerebral infarction or documented sudden cardiac death. Unstable angina was defined according to the Braunwald criteria (11). 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 and coronary artery bypass grafting.

These event records were provided to an endpoint committee. Although treatment strategies, such as those 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.

Statistical analysis

HIJ-CREATE 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 (12,13). 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.

Time-to-first-occurrence of events was analysed using the Kaplan–Meier method with the log-rank test and the 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 employing the Cox regression model, utilizing tests for interaction to examine the consistency of the results. An independent statistical data centre (STATZ Institute, Tokyo, Japan) performed the analysis using SAS system ver. 9.1 software (SAS Institute, Cary, NC, USA).

Results

Of the 1024 patients in the candesartan-based treatment arm, 509 patients (49.7%) had impaired renal

dysfunction at baseline, and of the 1025 patients in the non-ARB treatment arm, 513 patients (50.0%) had impaired renal function at baseline. Three patient (0.3%) in the candesartan-based treatment arm and five (0.5%) in the non-ARB treatment arm were lost to follow-up. Baseline characteristics of patients are shown in Table I. Of these patients with impaired renal function, 33.1% had acute coronary syndrome and the remainder had stable CAD. Percutaneous coronary intervention and coronary artery bypass grafting had been performed before randomization in 82.2% and 15.4% of patients, respectively. The two treatment arms were well balanced in terms of baseline characteristics. However, left ventricular ejection fraction in the candesartan-based treatment arm was lower than that in the non-ARB treatment arm. As regards medications at baseline, use of ACE inhibitors, calcium-channel blockers and beta-blockers was more prevalent in patients in the non-ARB treatment arm.

Kaplan–Meier curves for primary endpoint (MACE) in the two treatment arms are shown in Figure 1. There was no difference in MACE in patients without impaired renal function between the two arms. On the other

Table I. Clinical characteristics.

	Creatinine clearance ≥60 ml/min			Creatinine clearance <60 ml/min		
Variable	Candesartan-based (n=515)	Non-ARB (n=512)	p-value	Candesartan-based (n=509)	Non-ARB (n=513)	p-value
Age (years)	59±9	60±8	0.320	70±6	70±6	0.448
Female sex	50 (9.7%)	68 (13.3%)	0.073	136 (26.7%)	151 (29.4%)	0.334
Diagnosis						
Acute coronary syndrome	185 (36.0%)	199 (38.9%)	0.341	160 (31.4%)	178 (34.7%)	0.268
Revascularization						
PCI	432 (83.9%)	421 (82.2%)	0.479	418 (82.1%)	422 (82.3%)	0.954
CABG	39 (7.6%)	40 (7.8%)	0.885	85 (16.7%)	72 (14.0%)	0.238
Medical history						
Dyslipidaemia	306 (59.4%)	320 (62.5%)	0.311	297 (58.3%)	292 (56.9%)	0.644
Diabetes mellitus	193 (37.4%)	200 (39.1%)	0.601	185 (36.3%)	201 (39.2%)	0.350
Current smoker	167 (32.4%)	155 (30.3%)	0.457	95 (18.7%)	92 (17.9%)	0.763
Family history of CAD	109 (21.2%)	140 (27.3%)	0.021	104 (20.4%)	100 (19.5%)	0.707
Cerebrovascular disease	41 (8.0%)	33 (6.4%)	0.348	70 (13.8%)	61 (11.9%)	0.373
Peripheral vascular disease	12 (2.3%)	7 (1.4%)	0.252	25 (4.9%)	19 (3.7%)	0.342
Atrial fibrillation	24 (4.7%)	31 (6.1%)	0.321	34 (6.7%)	46 (9.0%)	0.174
Previous MI	206 (40.0%)	180 (35.2%)	0.109	199 (39.1%)	193 (37.6%)	0.628
NYHA functional class			0.768			0.056
I	423 (82.1%)	417 (81.4%)		378 (74.3%)	409 (79.7%)	
II	74 (14.4%)	75 (14.6%)		111 (21.8%)	80 (15.6%)	
III	10 (1.9%)	10 (2.0%)		9 (1.8%)	12 (2.3%)	
IV	8 (1.6%)	10 (2.0%)		11 (2.2%)	12 (2.3%)	
Body mass index (kg/m^2)	25.7±2.8	25.8±3.0	0.327	23.5±2.6	23.5±2.7	0.848
Systolic blood pressure (mmHg)	135±18	134±17	0.931	136±19	137±17	0.305
Diastolic blood pressure (mmHg)	77±13	77±11	0.806	74±11	75±12	0.488
Heart rate (beats/min)	70±12	69±10	0.121	69±11	69±11	0.920
LVEF (%)	54±11	55±11	0.146	53±11	55±12	0.019
Total cholesterol (mg/dl)	196±35	196±37	0.822	190±34	189±32	0.533
Triglyceride (mg/dl)*	139 [102–197]	137 [95–194]	0.563	120 [90–175]	115 [85–158]	0.135
HDL-cholesterol (mg/dl)	44±12	44±11	0.760	45±12	45±13	0.914
C-reactive protein (mg/dl)*	0.2 [0.1–0.3]	0.2 [0.1–0.4]	0.856	0.2 [0.1–0.4]	0.2 [0.1–0.4]	0.308
Creatinine clearance (ml/min)	78±16	77±15	0.225	47±8	47±9	0.866
Medications						
ACE inhibitors	1 (0.2%)	361 (70.5%)	<0.001	7 (1.1%)	362 (70.6%)	<0.001
Calcium-channel blockers	225 (43.7%)	269 (52.5%)	0.005	231 (45.4%)	305 (59.5%)	<0.001
Beta-blockers	237 (46.0%)	246 (48.0%)	0.515	226 (44.4%)	260 (50.7%)	0.044
Diuretics	34 (6.6%)	33 (6.4%)	0.919	68 (13.4%)	49 (9.6%)	0.056
Statins	250 (48.5%)	237 (46.3%)	0.469	209 (41.1%)	210 (40.9%)	0.968
Nitrates	240 (46.6%)	250 (48.8%)	0.475	262 (51.5%)	276 (53.8%)	0.456
Aspirin	473 (91.8%)	469 (91.6%)	0.888	473 (92.9%)	466 (90.8%)	0.222
Dose of candesartan						
<8 mg daily	373 (72.4%)			401 (78.3%)		
≥8 mg daily	142 (27.6%)			111 (21.7%)		
Follow-up period (months)*	4.2 [3.5–4.8]	4.1 [3.4–4.9]	0.565	4.3 [3.5–4.9]	4.3 [3.4–4.9]	0.995

Values are n (%) or mean±SD. *Median [interquartile range]. ARB, angiotensin receptor blocker; PCI, Percutaneous coronary intervention; CABG, Coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme.

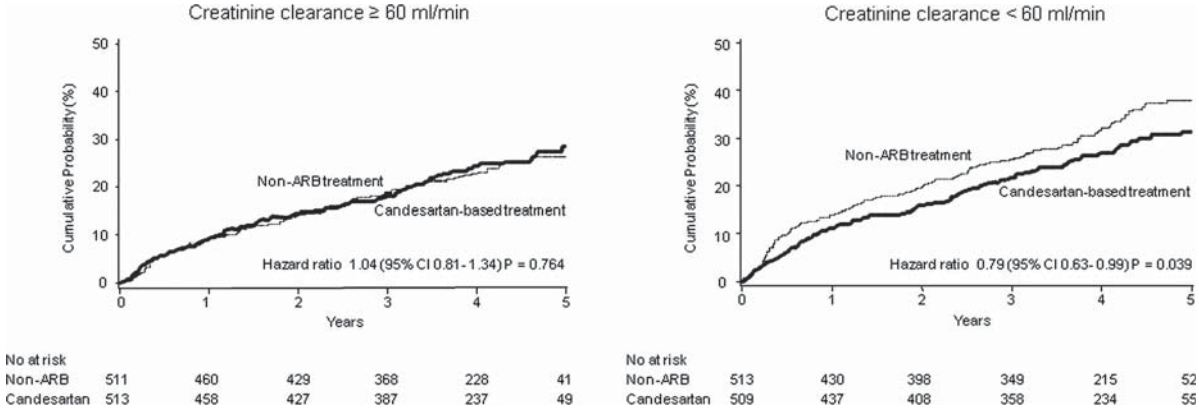

Figure 1. Kaplan–Meier curve for primary endpoint (major adverse cardiovascular event) in patients with creatinine clearance ≥60 ml/min and with creatinine clearance <60 ml/min.

hand, there was a lower incidence of MACE in the candesartan-based treatment arm in patients with impaired renal function.

Figure 2 shows mean systolic and diastolic blood pressures in the two treatment arms during the follow-up period in patients with impaired renal function. Mean blood pressure at baseline was 136/74 mmHg in the candesartan-based therapy group and 137/75 mmHg in the non-ARB treatment arm. Blood pressures did not differ between the two arms throughout the trial (systolic blood pressure, $p=0.127$; diastolic blood pressure, $p=0.084$).

In addition, when each of MACE in patients with impaired renal function was analysed separately, candesartan-based treatment reduced the risk of hospitalization for unstable angina by 29%. However, no significant differences were observed between the two arms in terms of cardiovascular death and non-fatal myocardial infarction, hospitalization for heart failure, hospitalization for stroke or hospitalization for other cardiovascular events (Figure 3). There was no difference in the rate of secondary endpoints between the two arms (Figure 3).

Discussion

HIJ-CREATE tested whether ARB candesartan-based therapy can reduce the incidence of cardiovascular events compared with non-ARB standard pharmacotherapy in hypertensive patients who had angiographically documented CAD, but showed no significant difference in MACE between the two arms (8). It is increasingly recognized that impaired renal function, chronic kidney disease of any degree, portends a worsened prognosis for CAD patients (14). Mortality after myocardial infarction and after undergoing percutaneous coronary intervention or coronary bypass grafting is higher in patients with impaired renal function than in those without impaired renal function (15–18). This *post hoc* analysis of HIJ-CREATE focused on high-risk hypertensive patients with CAD and impaired renal function. There was a lower incidence of MACE, especially hospitalization for unstable angina, in the candesartan-based treatment arm than in the non-ARB treatment arm in patients with impaired renal function, but not in patients without impaired renal function. However, candesartan-based treatment did not improve

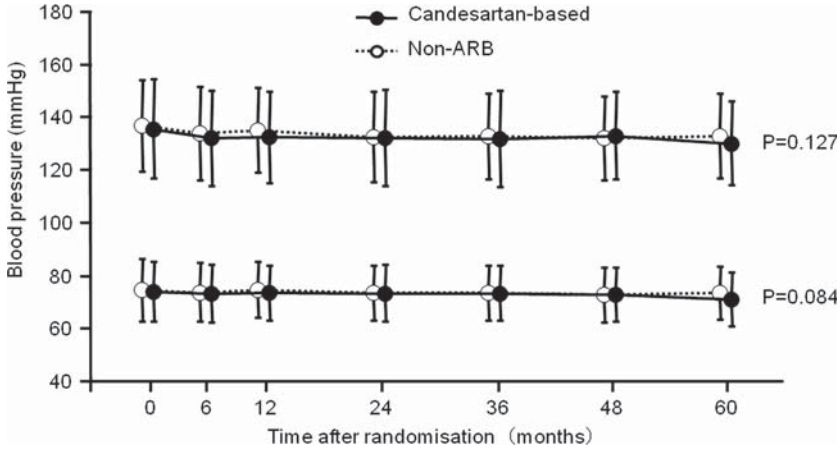

Figure 2. Systolic and diastolic blood pressures in candesartan-based and non-ARB treatment arms in patients with creatinine clearance <60 ml/min. Error bars indicate standard deviation. *p*-values were obtained by a test of trend profile using a mixed model. ARB, angiotensin receptor blocker.

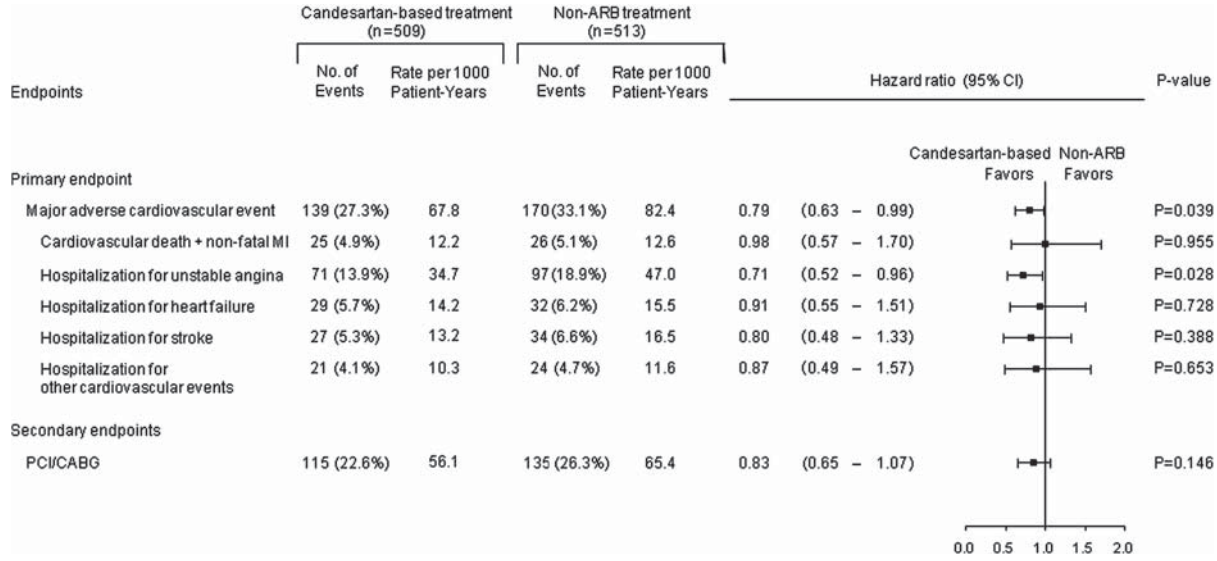

Figure 3. Hazard ratio for primary and secondary endpoints in patients with creatinine clearance <60 ml/min. ARB, angiotensin receptor blocker, PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting, MI, myocardial infarction.

cardiovascular mortality in patients with impaired renal function compared with non-ARB treatment (the use of ACE inhibitors was 70.6%).

Traditional risk factors fail to fully account for the elevated cardiovascular risk in patients with impaired renal function and several emerging risk factors such as inflammation, oxidative stress, nitric oxide availability and endothelial dysfunction have recently received a great deal of attention (15). Activation of the renin–angiotensin system plays a central role in development of hypertension and renal disease (19). Blockers of the renin–angiotensin system, ACE inhibitors and ARBs, have been shown to have renoprotective benefits (4,5). The Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) study did not demonstrate a benefit of the ACE inhibitor trandolapril in reducing cardiovascular mortality or morbidity in patients with stable CAD and preserved left ventricular function (20), which differed from the finding of benefit for stable CAD in other studies, Heart Outcomes Prevention Evaluation (HOPE) (21) and EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) (22). However, a substudy of PEACE showed that trandolapril reduced mortality in CAD patients with impaired renal function (23). These findings suggested that impaired renal function could increase the risk of cardiovascular events, and blockade of the renin–angiotensin system is therefore potentially an important therapeutic strategy in this population.

Both ACE inhibitor and ARB are now first-line therapies, which block the renin–angiotensin system, for protection of the cardiovascular system (24). The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) demonstrated that the ARB telmisartan is equivalent to the ACE inhibitor ramipril in patients with vascular disease or high-risk diabetes (25). The Valsartan in Acute Myocardial Infarction Trial (VALIANT) also showed that the ARB valsartan was as effective as the ACE inhibitor captopril in patients after myocardial infarction (26). Although it was not a head-to-head comparison of an ARB and an ACE inhibitor, HIJ-CREATE found no difference in the reduction of the rates of cardiovascular events between the candesartan-based and non-ARB (71% usage of ACE inhibitor) treatment arms, among patients with CAD and hypertension (8).

In this *post hoc* analysis, lower incidence of hospitalization for unstable angina in candesartan-based treatment arm compared with non-ARB treatment arm was observed. The reason for this difference between the two arms remains unclear. Angiotensin II, angiotensin II type 1 (AT1) receptor and interleukin 6 (IL-6) were reported to be colocalized in coronary plaques from patients with unstable angina (27). A greater amount of angiotensin II was produced from the heart in unstable angina patients than in stable angina patients, and overexpression of AT1 receptor gene was observed in heart biopsy specimens from unstable angina patients (28). Angiotensin II enhances IL-6 production (27,29) and IL-6 induces upregulation of vascular AT1 receptor expression (30). An interesting clinical study showed that the ARB irbesartan, but not the ACE inhibitor enalapril, reduced high-sensitivity C-reactive protein and IL-6 and thromboxane A2-induced platelet aggregation in patients with CAD (31). ACE inhibition may allow for escape generation of angiotensin II by ACE-independent pathways (5). Inhibition of angiotensin II via direct blockade of AT1 receptor by ARB may exert more potent anti-inflammatory and anti-aggregatory effects, which lead to inhibition of the development of unstable angina, compared with other type of antihypertensive drugs in high-risk

hypertensive patients with CAD and impaired renal function. To clarify this clinical significance, further prospective study will be needed.

It has yet been lack of proven cardioprotective effect of ARB in patients with impaired renal function (14). This *post hoc* analysis of HIJ-CREATE suggested that the ARB may be beneficial in reducing risk of coronary events in high-risk hypertensive patients with impaired renal function.

Limitations

There were some limitations in this study. First, the analysis was *post hoc*. We could not clearly define a difference because of drug-effect between the two arms. Secondly, the number of subjects was relatively small. Moreover, patients with serum creatinine level >2.0 mg/dl or end-stage renal disease were excluded from enrolment in HIJ-CREATE. Therefore, categorical assessment or subgroup analysis was not feasible. Thirdly, HIJ-CREATE was based on a prospective, randomized, open-label design, with blinded assessments of endpoints. We could not exclude treatment bias because of the open-label design. An endpoint committee whose members were blinded to each treatment arm adjudicated all potential endpoints. However, we could not completely exclude information bias that investigators consciously or unconsciously withheld. Fourthly, a relative low dose of candesartan used; 78% of patients received a maintenance dose of <8 mg daily in the candesartan-based treatment arm. The Japanese social health insurance system permits a maximum therapeutic dose of candesartan of 12 mg daily. However, even at low doses of 12 mg daily or less, candesartan showed a blood pressure-lowering effect or renoprotective effect in Japanese hypertensive patients (32,33).

Conclusions

The results of a *post hoc* analysis of the data from the HIJ-CREATE suggested that although candesartan-based treatment was not superior to non-ARB treatment in prevention of cardiovascular mortality, ARB-based therapy might be beneficial in reducing the risk of subsequent coronary events in high-risk hypertensive patients with CAD and impaired renal function.

Acknowledgements

This study is registered as International Standard Randomized Controlled Trial No. UMIN000000790. This study was supported by funds from the Japan Research Promotion Society for Cardiovascular Diseases.

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.

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Supplementary material available online

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