Original Article

An Angiotensin Receptor Blocker Reduces the Risk of Congestive Heart Failure in Elderly Hypertensive Patients with Renal Insufficiency

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We examined the efficacy of candesartan in reducing cardiovascular events in hypertensive patients with coexisting chronic kidney disease and cardiovascular diseases. This open-label, prospective study was conducted from 1999 to 2002, and 141 hypertensive subjects 60 to 75 years old with non-diabetic chronic renal insufficiency were enrolled. Before randomization of the patients, we examined their past medical history and found that 69 patients had been hospitalized due to myocardial infarction (MI) or stroke. Therefore, the patients were divided into 2 groups, one with previous histories of MI or stroke and the other with no previous history of MI or stroke. The patients were randomized to receive either the angiotensin receptor blocker candesartan or conventional treatment. The mean duration of follow-up was 3.1±0.4 years. The primary outcome was a primary cardiovascular event (MI, stroke, or heart failure) verified by hospitalization. At the end of the study, in the patients with past history of cardiovascular diseases, blood pressure was reduced from 146.4±7.2/79.2±5.1 to 134.4±6.1/72.3±4.0 mmHg in the candesartan group and from 145.3±5.1/80.1±3.8 to 133.4±5.8/73.8±4.2 mmHg in the conventional treatment group. In the patients without past history of cardiovascular diseases, blood pressure was reduced from 143.2±4.3/78.3±4.8 to 133.8±5.3/73.1±3.8 mmHg in the candesartan group and from 143.9±6.8/78.1±4.2 to 132.6±5.4/74.5±4.4 mmHg in the conventional treatment group at the end of the study. There were no significant differences between the candesartan group and the conventional treatment group in the reduction of blood pressures. Among patients with a past history of cardiovascular disease, the serum creatinine concentration increased from 1.49±0.38 to 1.58±0.42 by candesartan treatment and from 1.50±0.32 to 1.89±0.37 by conventional treatment. On the other hand, in patients with no past history of cardiovascular disease, the serum creatinine concentration increased from 1.44±0.42 to 1.46±0.40 by candesartan treatment and from 1.46±0.44 to 1.51±0.38 by conventional treatment. Although, there was no significant difference in the incidence of cardiovascular events between the 2 groups with the candesartan-based and conventional-based antihypertensive treatment, in patients without cardiovascular events (12/36 *vs.* 7/34: these figures indicate events per total participated persons per 3 years; following figures are the same as this), treatment with candesartan reduced the incidence of cardiovascular events in the patients with past history of cardiovascular diseases (20/33 *vs.* 32/38). In particular, candesartan-based treatment reduced the incidence of congestive heart failure by 66.4%

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in these patients. In conclusion, this prospective, open-labeled randomized study suggests that 1) previous history of cardiovascular diseases is a major risk factor for cardiovascular events; and 2) candesartan is effective for reduction of cardiovascular events in hypertensive patients with coexisting chronic kidney disease and cardiovascular diseases, especially for prevention of congestive heart failure. (*Hypertens Res* 2005; 28: 415–423)

***Key Words*: angiotensin type 1 receptor blocker, renal dysfunction, stroke, myocardial infarction, congestive heart failure**

Introduction

A recent report from the ongoing Cardiovascular Health Study, which includes 5,808 men and women over the age of 65 years, showed that elevated serum creatinine level was associated with an approximately two-fold higher risk of overall and cardiovascular disease (CVD) mortality (*1*). Similarly, the Second National Health and Nutrition Examination Survey Mortality Follow-Up Study revealed that the risk of death from CVD was 1.8 times greater for persons with an estimated glomerular filtration rate (GFR) of less than 70 ml/min per 1.73 m^2 than for those with a GFR of 90 ml/min per 1.73 m^2 or more after adjustment for age, race, sex, systolic blood pressure (SBP), serum total cholesterol level, body mass index, diabetes, history of CVD, level of physical inactivity, and level of education (*2*). Although it has been well documented in both large-scale clinical trials (*3*, *4*) and a meta-analysis (*5*) that blockade of the renin-angiotensin system using angiotensin converting enzyme (ACE) inhibitors reduces the risk of development of end-stage renal disease (EDRD) in patients with non-diabetic chronic kidney disease (CKD), Japanese general physicians have been reluctant to prescribe ACE inhibitors (*6*), mainly because of the adverse effect of dry cough (*7*) and the fear of worsening renal dysfunction (*8*). Angiotensin II receptor blockers (ARBs), which modulate the renin-angiotensin system, reduce blood pressure and microalbuminuria/proteinuria and prevent progression of diabetic nephropathy (*9*, *10*) and non-diabetic CKD (*11*). In addition to the renoprotective effects of ARBs, recent clinical megatrials have demonstrated that ARBs have a cardiorenal protective effect in patients with congestive heart failure (CHF) (*12*) and patients with recent onset of myocardial infarction (*13*).

The effect of these cardioprotective medications on patients with CKD has been described in longitudinal and retrospective studies (*14*); however, prospective data on the effects of treatment of CKD on CVD or vice versa are still lacking. In addition, although the need to reduce the incidence of adverse cardiovascular outcomes in patients with CKD has been emphasized (*15*), there have been few trials on the use of ARBs on patients—and particularly elderly patients—with CKD in Japan. The present study was conducted to examine the additional effects of candesartan, an ARB, on the outcome of cardiovascular incidents in hypertensive patients with coexisting CKD and CVDs.

Methods

Study Design and Organization

The Efficacy of Candesartan on Outcome in Saitama Trial in Renal Disease (E-COST-R) study was an investigator-initiated, prospective, multicenter, open-label, randomized, active-control, parallel group study that was performed in conjunction with the E-COST study (*16*). The primary objective of this study was to evaluate the long-term effects of once-daily candesartan-based therapy in comparison with conventional therapy in hypertensive patients with mild renal impairment. The trial protocol was approved by the ethics committees of all participating institutions, was conducted in accordance with the Declaration of Helsinki, and was overseen by an independent data and safety monitoring board.

Target Population and Treatment Schedule

This study included 141 patients aged 60 to 75 years with previously treated or untreated hypertension who had renal insufficiency. The entry criteria for arterial hypertension were SBP >140 mmHg and diastolic blood pressure (DBP) >90 mmHg in the sitting position in the office, and a serum creatinine level of more than 1.2 mg/dl and less than 2.0 mg/dl. In addition, the estimated glomerular filtration rate (GFR) was calculated (*17*). Before entry into this study, patients' medical records were checked by individual investigators, and previous hospitalizations due to myocardial infarction or stroke were recorded. Patients randomized to receive candesartan- or conventional-based regimens, after a 2–4 week run-in period, were selected to be included in this analysis if their trough sitting blood pressures were 140–180 mmHg for SBP and/or 90–110 mmHg for DBP. There were no stratifications as part of the randomization process. From the beginning of September 1999 to the end of December 1999, a total of 141 patients with hypertension were randomly assigned to the two groups. The randomization was performed by the envelope method. Patients were followed up for 3 or more years with regular visits and upward titration of medication to reach a goal SBP of less than 130 mmHg and a goal DBP of less than 80 mmHg. We excluded patients with a history of diabetes, which we defined as a fasting blood glucose level >126 mg/dl and/or a postprandial glucose level >200 mg/dl. Patients with secondary hypertension, including patients on dialysis

Table 1. Clinical Profiles of the Patients at Registration

	Candesartan treated		Conventional treated	
	With past history	Without past history	With past history	Without past history
Patient number	33	36	38	34
Age (years)	66.8±3.4	67.4±3.3	67.2±3.8	66.1±2.9
Sex (male/female)	19/14	22/14	23/15	19/15
History of stroke	29		34	
History of MI	4		4	
Systolic BP	146.4±7.2	143.2±4.3	145.3±5.1	143.9±6.8
Diastolic BP	79.2±5.1	78.3±4.8	80.1±3.8	78.1±4.2
Serum creatinine (mg/dl)	1.49±0.38	1.44±0.42	1.50±0.32	1.46±0.44
Estimated GFR (ml/min)	43.4±6.3	45.1±8.0	43.6±5.5	44.8±6.1
BUN (mg/dl)	28.3±6.6	30.3±4.8	30.6±6.2	29.4±5.1
Hemoglobin (g/dl)	11.2±1.3	11.6±2.1	10.8±1.1	11.4±1.3
Total cholesterol (mg/dl)	178±27	183±31	180±29	182±25

MI, myocardial infarction; BP, blood pressure; GFR, glomerular filtration rate; BUN, blood urea nitrogen.

Table 2. The Prevalence of Antihypertensive Drugs at Start of the Study (Number of Patients)

	Candesartan treated		Conventional treated	
	With past history (n=33)	Without past history (n=36)	With past history (n=38)	Without past history (n=34)
ACE inhibitor	9	8	10	8
β-Blocker (including α-β blocker)	2	2	3	1
Calcium channel blocker	29	28	30	28
Diuretics	6	4	6	3
Others	2	0	1	1

ACE, angiotensin converting enzyme.

therapy or those who had received renal transplantation, were excluded. Also excluded were patients with chronic renal disease receiving corticosteroid hormone, myocardial infarction or stroke within the previous 6 months, angina pectoris requiring treatment with β-blockers or calcium channel blockers (CCBs), heart failure or left ventricular ejection fraction of 40% or less, or a disorder that in the treating physician's opinion required treatment with candesartan or other types of ARBs. In this study, continuous use of ACE inhibitors was not prohibited when physicians judged necessity of this treatment for his or her treatment.

Outcome Measures

The primary outcome was a primary cardiovascular event (hospitalization due to myocardial infarction, stroke, or CHF). Routine laboratory tests were performed in four central laboratories. Adverse events were monitored throughout the study. The study ran its full course and end point follow-up was stopped on December 31, 2002.

Statistical Methods

The baseline characteristics of the two treatment groups and the patients with or without renal dysfunction were compared by Student's t-test, χ^2 test, and a nonparametric test (Wilcoxon test). All analyses were performed according to the intent to treat principle. Differences between treatment groups and past history of cardiovascular events in post-randomization measures or events were evaluated by analysis of variance and with the χ^2 test. Results of the primary endpoint analysis were independently validated by experts from the statistics laboratories (Fields Works Co., Ltd., Hyogo, Japan). All data are reported as the means±SEM. Statistical significance was set at $p<0.05$. SPSS software, version 11.0.1 (SPSS Inc., Chicago, USA) was used for statistical analyses (*18*).

Results

Follow-Up and Blood Pressure Control

Patients assigned to receive either candesartan- or conventional-based treatment were similar in characteristics. There

Table 3. Changes in Blood Pressure

	Year			
	0	1	2	3
Changes in systolic blood pressure (mmHg)				
Candesartan treated				
With past history	146.4±7.2	137.3±6.2	135.3±5.3	134.4±6.1
Without past history	143.2±4.3	132.6±4.9	134.2±6.2	133.8±5.3
Conventional treated				
With past history	145.3±5.1	134.1±5.8	135.6±5.0	133.4±5.8
Without past history	143.9±6.8	131.9±5.9	133.1±5.1	132.6±5.4
Changes in diastolic blood pressure (mmHg)				
Candesartan treated				
With past history	79.2±5.1	74.6±4.1	72.6±3.4	72.3±4.0
Without past history	78.3±4.8	73.6±3.9	72.3±4.4	73.1±3.8
Conventional treated				
With past history	80.1±3.8	74.2±4.6	73.0±5.1	73.8±4.2
Without past history	78.1±4.2	73.3±4.4	73.8±3.8	74.5±4.4

Table 4. Changes in Heart Rate (Beats/min)

	Year			
	0	1	2	3
Candesartan treated				
With past history	72.3±10.4	74.8±8.4	72.4±10.2	70.1±9.3
Without past history	76.8±9.8	76.2±7.8	70.8±9.7	72.1±10.4
Conventional treated				
With past history	73.8±11.2	77.3±10.1	72.0±9.1	74.8±9.6
Without past history	75.4±10.0	76.8±9.6	71.2±8.4	72.7±8.7

was no significant difference in the levels of blood pressure and serum creatinine between the patients with or without past history of cardiovascular events (Table 1). The mean follow-up time (from randomization through death or end of study) was 3.1±0.4 years. The mean final candesartan dose was 7.12±1.56 mg or 6.99±1.22 mg daily in the patients with or without past history of CVD, respectively, and 82% and 71% of patients in the respective groups received 8 mg daily. Eighty-four percent of the patients who received candesartan-based treatment were taking more than two additional drugs, and 95% of the patients who received conventional-based treatment were taking more than two drugs. Twenty-five percent of patients with a past history of cardiovascular events and 12% of patients without past history of cardiovascular events were receiving ACE inhibitors. The average dosage of ACE inhibitors in the patients with mild renal dysfunction was 4.5±1.1 mg of benazepril and 2.2±0.9 mg of trandolapril. The prevalence of antihypertensive drugs at the start of the study is shown in Table 2.

Blood Pressure Follow-Up

In the patients without past history of cardiovascular events, the mean sitting blood pressure at the end of follow-up or at the last visit preceding a primary end point was reduced from 143.2±4.3/78.3±4.8 to 133.8±5.3/73.1±3.8 mmHg in the candesartan group and from 143.9±6.8/78.1±4.2 to 132.6±5.4/74.5±4.4 mmHg in the conventional treatment group. In the patients with past history of cardiovascular events, the mean sitting blood pressure at the end of follow-up or at the last visit preceding a primary end point was reduced from 146.4±7.2/79.2±5.1 to 134.4±6.1/72.3±4.0 mmHg in the candesartan group and from 145.3±5.1/80.1±3.8 to 133.4±5.8/73.8±4.2 mmHg in the conventional treatment group (Table 3). Among patients without a past history of cardiovascular events, a blood pressure of less than 130/80 mmHg was achieved for 75% of those taking candesartan and 71% of those taking conventional antihypertensive drugs. In the conventional treatment group, CCBs were the most commonly administered antihypertensive drugs in the conventional treatment group. However, in the patients with past history of cardiovascular events, a blood pressure of less than 130/80 mmHg was achieved for 68% of those taking candesartan, and in the patients without past history of cardiovascular events, 66% of those taking conventional antihypertensive drugs achieved the same target blood pressure.

Table 5. Changes in Blood Urea Nitrogen, Serum Creatinine Level, and Estimated GFR

	Year			
	0	1	2	3
Changes in blood urea nitrogen (mg/dl)				
Candesartan treated				
With past history	28.3±6.6	26.7±6.3	29.4±6.6	31.5±7.0
Without past history	30.3±4.8	31.2±5.8	31.1±4.8	33.4±6.7
Conventional treated				
With past history	30.6±6.2	32.7±7.1	36.2±7.4	40.2±6.6*
Without past history	29.4±5.1	28.6±6.1	30.7±5.5	32.4±4.9
Changes in serum creatinine level (mg/dl)				
Candesartan treated				
With past history	1.49±0.38	1.49±0.40	1.58±0.31	1.58±0.42
Without past history	1.44±0.42	1.45±0.33	1.48±0.36	1.46±0.40
Conventional treated				
With past history	1.50±0.32	1.58±0.33	1.78±0.48*	1.89±0.37*
Without past history	1.46±0.44	1.44±0.35	1.47±0.44	1.51±0.38
Changes in estimated GFR (ml/min)				
Candesartan treated				
With past history	43.4±6.3	43.3±7.2	40.4±7.1	40.1±6.4
Without past history	45.1±8.0	43.8±6.4	42.1±6.6	42.3±5.4
Conventional treated				
With past history	43.6±5.5	40.2±4.8	36.5±5.8*	34.3±4.9*
Without past history	44.8±6.1	43.6±6.6	42.6±6.0	41.0±5.8

GFR, glomerular filtration rate. *$p<0.05$ *vs.* basal value.

During follow-up, the achieved SBP and DPB values were not different between patients with and those without past history of cardiovascular events. There was no significant change in heart rate in any of the groups during the study (Table 4).

Renal Function Measurement

No significant changes were seen in serum creatinine values or in estimated GFR at the end of the 3.1-year treatment period in the patients without past history of cardiovascular events regardless of treatment modality. However, in the patients with past history of cardiovascular events, the levels of serum creatinine and blood urea nitrogen increased significantly in those treated with conventional-based therapy compared to those who received candesartan-based therapy; the estimated GFR also decreased significantly in patients who received conventional therapy (Table 5).

Figures 1 and 2 provide a comparison of cardiovascular events between patients with and without past history of cardiovascular events.

The incidence of cardiovascular events was reduced by 20/33 *vs.* 32/38 ($p<0.05$) with the candesartan-based treatment compared with the conventional treatment in the patients with past history of cardiovascular events (these figures indicate events per total participated persons per 3 years; following figures are the same as this). There were no significant differences in the incidence of stroke and myocardial infarction; however, a significant reduction was found in the incidence of CHF between the candesartan-based treatment group and the conventional treatment group (4/33 *vs.* 13/38, Fig. 1). In the patients without past history of cardiovascular events, however, there were no significant differences in the incidence of stroke, myocardial infarction, or CHF between the candesartan-based treatment and conventional treatment groups (Fig. 2).

The rate of all-cause mortality in the patients with past history of CVD was 4 subjects in each group; 3 deaths in the candesartan group and 2 in the conventional group were due to stroke, 1 in the candesartan group was due to myocardial infarction, and 2 in the conventional group were due to CHF. There was no death in the patients without past history of cardiovascular events in either group.

Adverse Events and Safety Profile

Candesartan was better tolerated with fewer overall and drug-related discontinuations.

Discussion

E-COST and E-COST-R are the first intervention trials to assess the effects of an ARB on cardiovascular morbidity and mortality in Japanese hypertensive patients. In the E-COST

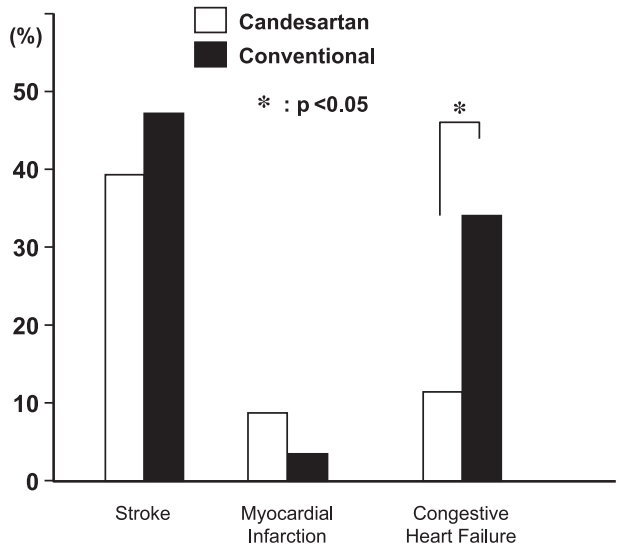

Fig. 1. *Incidence of cardiovascular events in patients with past history of cardiovascular diseases. Candesartan significantly reduced the overall incidence of cardiovascular events, and congestive heart failure.* *p < *0.05* vs. *the conventionally treated group.*

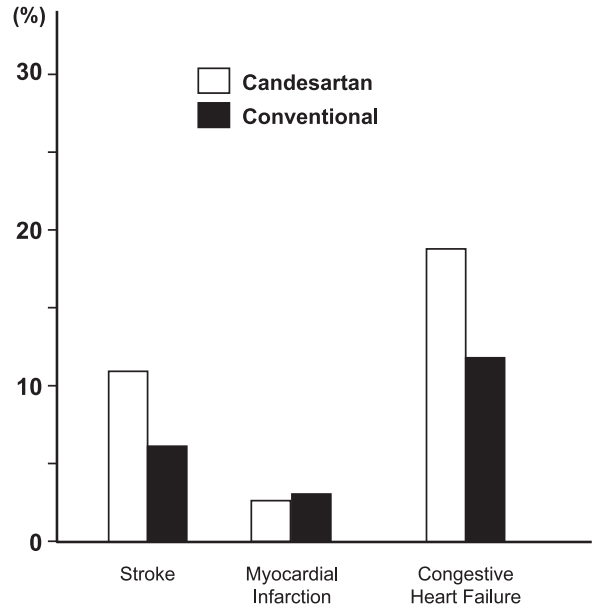

Fig. 2. *Incidence of cardiovascular events in patients without past history of cardiovascular diseases. There was no significant difference in the incidence of cardiovascular diseases between the two groups.*

study, we found that candesartan effectively reduced the incidence of cardiovascular events compared to conventional treatment (*16*).

In the present study, we demonstrated that coexisting CVDs and mild renal dysfunction in patients were associated with an increased risk of stroke and myocardial infarction. Compared to the patients without mild renal dysfunction, the incidence of previous myocardial infarction and stroke was doubled (71/141 *vs.* 233/1,630) in spite of the similar age distribution in the groups (mean age, 68 *vs.* 65 years old). In a prior epidemiologic study, renal insufficiency was associated independently with CVD incidence and mortality (*19*). It is clear from the above that people with mild renal dysfunction should be regarded as having increased cardiovascular risk even in the absence of classic risk factors. Generally, there have been few prospective treatment studies of cardiovascular outcomes in samples with mild renal dysfunction. In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibition with ramipril was shown to be beneficial because it reduced the high cardiovascular risk associated with mild renal dysfunction (*20*). Our present study has clearly demonstrated that even in Japanese hypertensive patients, renal insufficiency is a strong risk factor for CVD. Moreover, in the present study, patients with diabetes were excluded. These findings have important implications because of the recent rise in the prevalence of diabetes in Japan as well as European countries and the USA; that is, the incidence of cardiovascular events will increase substantially by considering patients with diabetes. Also, in this study, the patients with coexisting renal insufficiency and CVDs were found to have lower proteinuria compared to other large scale clinical trials such as Ramipril Efficacy in Nephropathy (REIN) (*21*) and Angiotensin-converting-enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) (*3*). The average age of patients participating in the aforementioned studies was lower than that of patients in the present study (56 *vs.* 68 years). This was probably due to several factors related to the care of the patients, since in Japan, subjects with moderate to severe proteinuria are usually cared for by physicians in the hospital rather than by general practitioners. On the other hand, elderly subjects with mild proteinuria and mild renal insufficiency mostly due to hypertensive nephrosclerosis are cared for by general practitioners. Most investigators who participated in the present study were general practitioners, and it is likely that a large proportion of the patients with renal insufficiency in the present study were suffering from nephrosclerosis but not from glomerulonephritis. This might be a reflection of the levels of blood pressure and the course of renal dysfunction, because several studies have revealed that, in spite of higher blood pressure levels, in patients with hypertensive nephrosclerosis, those with lower proteinuria and renal dysfunction deteriorated more gradually than those with hypertensive glomerulonephritis or diabetic nephropathy (*3*).

In the present study, treatment with candesartan significantly reduced the incidence of CHF, but did not produce significant differences in the incidence of stroke and myocardial infarction in patients with mild renal dysfunction and preexisting CVD.

Among CVD, CHF is most closely associated with CKD

(*19*). Since CHF is associated with a reduction in renal blood flow and GFR (*22*), it is not unreasonable to conclude that the heart damage itself may contribute to the progressive renal insufficiency. Based on experimental data and clinical trials, the renin-angiotensin system seems to promote CKDs and CHF, and both ACE inhibitors and ARBs are equipotent in reducing adverse end-organ effects associated with overactivation of the renin-angiotensin system (*23*). A number of reviews on the association between CKD and CHF have appeared recently (*22*). In a recent study of the incidence of CKD and CHF after an acute myocardial infarction (*24*), the loss of GFR in the patients treated with ACE inhibitors was slower than that in patients not treated with ACE inhibitors, indicating that the fall in renal function can be prevented to some extent by ACE inhibitors. Another recent study similarly reported that mild renal diseases were a major risk for cardiovascular complication after myocardial infarction (*13*). In the present study, the rate of decline of GFR in the patients with mild renal dysfunction treated with candesartan was slower than that in the patients not treated with candesartan. This would be a favorable effect for the prevention of CHF. Recently, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial has shown that the addition of candesartan to ACE-inhibitor or other treatment leads to a further clinically important reduction in relevant cardiovascular events in patients with CHF (*25*). More than 20% of the patients enrolled in this study had been treated with ACE inhibitors; this might have been the reason that candesartan treatment was more effective than regular treatment for preventing CHF. Compared to the beneficial effects of a single blockade of cardioprotection and renal protection (*26*), the potential cardio-renal benefit of dual blockade of the renin-angiotensin system pathways with ACE inhibitors and ARBs is an area of interest to clinicians. In addition, mechanistic studies have shown favorable neurohormonal, hemodynamic, and left ventricular remodeling effects when an ARB was added in patients already treated with ACE inhibitors (*27*). In their community-based population study, Abramson *et al*. showed that the combination of CKD and anemia was associated with a substantial increase in stroke risk (*28*). In our study, there were no significant differences in the degree of anemia among the 4 groups throughout the study. Moreover, the levels of hemoglobin were on average higher in our study (average 11.3 g/dl) than in the study of Abramson *et al*. (less than 10.0 g/dl). It is therefore reasonable that in patients with mild renal dysfunction anemia becomes important as a risk factor for stroke if the levels of hemoglobin are less than 10 g/dl. In the present study, although candesartan had the additional benefit of reducing the incidence of stroke in patients without renal impairment, this added benefit was not seen in the patients with renal impairment. In the CHARM trial, candesartan treatment did not produce favorable effects on risk reduction of stroke in the patients with CHF (*29*). The reasons for the substantially higher incidence of stroke in the patients with mild renal dysfunction treated with candesartan are not entirely clear. Until now, there have been no decisive trials showing a significant reduction in the incidence of stroke in hypertensive patients after the dual blockade of the renin-angiotensin system. Moreover, the incidence of CHF in the present study was also higher than expected. No similar findings as higher incidence of these two events observed in the present study were reported so far, indicating that our patients were more severely damaged by both cardiovascular diseases and renal insufficiency.

Some limitations to this study need to be mentioned. First, the study was conducted by voluntary physicians with voluntary patients, and a large number of the voluntary physicians were general practitioners. This may have influenced the fact that the cause of of underlying renal disease in a relatively large number of patients was nephrosclerosis rather than glomerulonephritis. This may be one of the reasons why candesartan did not produce a significant reduction in the incidence of cardiovascular events in hypertensive patients with mild renal insufficiency and mild proteinuria when they did not have a previous history of CVDs. Our previous multicenter trial which examined the effect of benidipine, a CCB, on blood pressure, renal dysfunction and outcomes in hypertensive elderly patients did not show any significant differences between the groups with and those without addition of ACE inhibitors (*30*). Furthermore, the study was not carried out in a double-blinded manner but rather in open-labeled fashion. This design may have led to bias in the four groups. However, in the patients with mild renal dysfunction, there were no significant differences in the levels of serum creatinine and blood pressure compared with baseline measurements. It therefore appears that assessment of the effects of candesartan on cardiovascular mortality and morbidity using an open-labeled randomized study such as this might be valid. Second, potential type II errors may be present due to the lower incidence of CVD in Japanese people. Third, in the present study, diabetes was excluded, but in the other studies patients with diabetes were included since diabetes is a well known risk factor. Forth, since a diagnosis of CHF is usually based on symptoms and physical examinations in combination, the criteria for diagnosis and hospitalization may have differed among the participating physicians, thereby resulting in the greater incidence in CHF. However, the authors checked individual cases by corresponding with the physicians who reported the incidence, and it is therefore less likely that the diagnosis for CHF differed widely among the participating physicians. Lastly, the initial design of this study was that of an outcome study to evaluate the relationship between elevated serum creatinine and cardiovascular events. Originally, the numbers of patients needed in the present study were statistically calculated as below. The incidence of cardiovascular events, including myocardial infarction, stroke, and congestive heart failure, has been reported as about 5% in elderly hypertensive patients with elevated serum creatinine >1.5 mg/dl (*1*). To earn significant difference between the

present 2 groups in primary endpoint, numbers needed to treat were calculated as 33.4 (*31*) with error probabilities limits 0.2 and 0.05. We set the number of patients in each group as 40, in consideration of potential drop-out for non-medical reasons, and the enrollment period as 5 years. However, this study was discontinued at year 3 because of the rapidly increasing prevalence of ARBs in Japan. Again, this study was conducted by volunteer patients and physicians and they freely switched from the conventional treatment to ARBs, including candesartan. The reason above is associated with renouncing our claim for outcome study.

In summary, this study suggests that a previous history of CVD is a major risk factor for hospitalization due to cardiovascular events; in addition, this is the first prospective study to demonstrate that candesartan, an angiotensin receptor blocker, is effective for reduction of cardiovascular events in hypertensive patients with coexisting CKD and CVDs, especially for prevention of CHF.

Appendix

Members of the E-COST Group

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References

1. Fried L: Renal insufficiency as a predictor of cardiovascular outcomes. *J Am Coll Cardiol* 2003; **41**: 1364–1372.
2. Muntner P, Hamm LL, Kusek JW, Chen J, Whelton PK, He J: The prevalence of nontraditional risk factors for coronary heart disease in patients with chronic kidney disease. *Ann Intern Med* 2004; **140**: 9–17.
3. Maschio G, Alberti D, Janin G, *et al*: Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; **334**: 939–945.
4. Ruggenenti P, Perna A, Gherardi G, *et al*: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999; **354**: 359–364.
5. Jafar TH, Schmid CH, Levey AS: Effect of angiotensin-converting enzyme inhibitors on progression of nondiabetic renal disease. *Ann Intern Med* 2002; **137**: 298–299.
6. Saito I, Kawabe H, Tsujioka M, Hirose H, Shibata H: Trends in pharmacologic management of hypertension in Japan one year after the publication of the JSH 2000 guidelines. *Hypertens Res* 2002; **25**: 175–178.
7. Saruta T, Arakawa K, Iimura O, *et al*: Difference in the incidence of cough induced by angiotensin converting enzyme inhibitors: a comparative study using imidapril hydrochloride and enalapril maleate. *Hypertens Res* 1999; **22**: 197–202.
8. Hiwada K, Ogihara T, Matsumoto M, *et al*: Guidelines for hypertension in the elderly—1999 revised version. Ministry of Health and Welfare of Japan. *Hypertens Res* 1999; **22**: 231–259.
9. Brenner B, Cooper ME, De Zeeuw D, *et al*: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001; **345**: 861–869.
10. Parving H-H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 2001; **345**: 870–878.
11. Iino Y, Hayashi M, Kawamura T, *et al*: Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension—a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in Hypertensive Patients (JLIGHT) study. *Hypertens Res* 2004; **27**: 21–30.
12. Granger CB, McMurray JJ, Yusuf S, *et al*: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003; **362**: 772–776.

13. Anavekar NS, McMurray JJ, Velazquez EJ, *et al*: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; **351**: 1285–1295.
14. Foley RN, Herzog CA, Collins AJ: Blood pressure and long-term mortality in United States hemodialysis patients: USRDS Waves 3 and 4 Study. *Kidney Int* 2002; **62**: 1784–1790.
15. Levey AS: Controlling the epidemic of cardiovascular disease in chronic renal disease: where do we start? *Am J Kidney Dis* 1998; **32**: S5–S13.
16. Suzuki H, Kanno Y, for the Efficacy of Candesartan on Outcome in Saitama Trial (E-COST) Group: Effects of candesartan on cardiovascular outcomes in Japanese hypertensive patients. *Hypertens Res* 2005; **28**: 307–314.
17. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**: 31–41.
18. Armitage P, Berry G, Matthews JNS: Survival analysis, in Statistical Methods in Medical Research, 4th ed. Oxford, Blackwell Science, 2002, pp 568–590.
19. Shlipak MG, Fried LF, Crump C, *et al*: Cardiovascular disease risk status in elderly persons with renal insufficiency. *Kidney Int* 2002; **62**: 997–1004.
20. Mann J, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigation: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril; the HOPE randomized trial. *Ann Intern Med* 2001; **134**: 629–636.
21. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G: Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int* 1998; **53**: 1209–1216.
22. Laskar SR, Dries DL: The prognostic significance of renal dysfunction in patients with chronic systolic heart failure. *Curr Cardiol Rep* 2003; **5**: 205–210.
23. Brewster UC, Setaro JF, Perazella MA: The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states. *Am J Med Sci* 2003; **326**: 15–24.
24. Hillege HL, Girbes ARJ, de Kam PJ, *et al*: Renal function, neurohormonal activation, and survival in patients with chronic heart failure. *Circulation* 2000; **102**: 203–210.
25. McMurray JJ, Ostergren J, Swedberg K, *et al*: Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; **362**: 767–771.
26. Nakamura T, Ushiyama C, Osada S, *et al*: Combination therapy of trandolapril and candesartan cilexetil reduces microalbuminuria and urinary endothelin-1 excretion in patients with type 2 diabetes. *Clin Exp Nephrol* 2002; **6**: 135–139.
27. Baruch L, Anand I, Cohen IS, Ziesche S, Judd D, Cohn JN: Augmented short- and long-term hemodynamic and hormonal effects of an angiotensin receptor blocker added to angiotensin converting enzyme inhibitor therapy in patients with heart failure. *Circulation* 1999; **99**: 2658–2664.
28. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W: Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. *Kidney Int* 2003; **64**: 610–615.
29. Yusuf S, Pfeffer MA, Swedberg K, *et al*: Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.
30. Suzuki H, Saruta T: Effects of calcium antagonist, benidipine, on the progression of chronic renal failure in the elderly: a 1-year follow-up. *Clin Exp Hypertens* 2001; **23**: 189–201.
31. Ardizzoni A: Efficient designs for testing new agents and regimens. *Chest* 1996; **109**: 83S–86S.