Stronger Effect of Azilsartan on Reduction of Proteinuria Compared to Candesartan in Patients with CKD: A Randomized Crossover Trial

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Keywords

Azilsartan · Candesartan · CKD · Crossover trial · Proteinuria

Abstract

Introduction: Angiotensin receptor blockers (ARBs) are preferably used in hypertensive patients with CKD. Azilsartan is a strong antihypertensive ARB, but its antiproteinuric effects are not well understood. We compared the antiproteinuric effect of azilsartan and candesartan in CKD patients in an open-label, randomized, crossover trial. **Methods:** A total of 111 patients were treated with 20 mg of azilsartan daily for 2 months as a run-in period. After the run-in period, patients were randomized into 2 arms and received either 20 mg of azilsartan or 8 mg of candesartan daily for 3 months in a crossover trial. The primary outcome was the percent change in urinary protein-to-Cr ratio (UPCR). **Results:** Ninety-five patients completed the trial. The mean age was 64.3 years. The estimated glomerular filtration rate (eGFR) and UPCR were

41.5 mL/min/1.73 m² and 1.8 g/gCr, respectively. The baseline systolic and diastolic blood pressures were 131.4 and 71.0 mm Hg, respectively. The mean percent change in the UPCR was –3.8% in the azilsartan group and 30.8% in the candesartan group at the 1st endpoint ($p = 0.0004$), and 6.1% in the azilsartan group and 25.8% in the candesartan group at the 2nd (final) endpoint ($p = 0.029$). The incidence of adverse events, including eGFR levels and serum potassium levels, was not significantly different between the groups. **Conclusion:** A 20 mg azilsartan dose had potent antiproteinuric effects compared with an 8 mg candesartan dose, without an increase in adverse events. Azilsartan may provide renal protection in addition to antihypertensive effects in CKD patients.

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Introduction

Circulating and tissue angiotensin II are associated with the progression of CKD, and angiotensin receptor blockers (ARBs) inhibit the effect of both circulating and tissue angiotensin II [1–3]. In clinical studies, ARBs decreased urinary protein excretion and blood pressure [4, 5], and a reduction in proteinuria was associated with better renal prognosis during ARB treatment. Therefore, ARBs are used as one of the first-line therapies in hypertensive patients with CKD. It was reported that increasing ARB levels above the usual doses produced increased antiproteinuric effects in patients with CKD [6, 7]. However, the doses of ARB used in clinical situations are limited. Furthermore, the addition of angiotensin-converting enzyme (ACE) inhibitors or renin inhibitors to ARBs for further inhibition of the effect of angiotensin II increased adverse events [8, 9]. Therefore, further inhibition of the effect of angiotensin II is difficult to achieve in clinical situations. Azilsartan is reported to have superior antihypertensive effects compared with other ARBs, and this effect might be caused by its strong binding to the angiotensin II receptor compared with other ARBs [10]. We hypothesized that azilsartan has more potent antiproteinuric effects than older ARBs, such as candesartan. We compared azilsartan and candesartan, in a crossover manner, to assess whether azilsartan had stronger antiproteinuric effects in patients with CKD.

Materials and Methods

Study Design

This open-label, randomized, crossover trial comparing the efficacy of azilsartan and candesartan in regard to antiproteinuric and antihypertensive effects was conducted in 12 nephrology centers in Fukuoka, Japan. The renal effect of azilsartan and candesartan was compared. The study design is presented in Figure 1. At the beginning of the study, patients who met the inclusion criteria entered the 2-month run-in period. Patients discontinued any previously used ACE inhibitors or ARBs, and patients were treated using 20 mg of azilsartan once a day. After the run-in period, patients who demonstrated potassium ≥ 5.5 mEq/L, blood pressure $\geq 160/100$ mm Hg, elevated Cr levels $\geq 30\%$, or were judged to be unfit to continue the study by the primary doctor were excluded. The rest of the patients entered the 3-month crossover period. Patients were randomized equally by an independent institution (Mebix Inc., Tokyo, Japan) (via a Web system) into 2 arms and received either 20 mg of azilsartan or 8 mg of candesartan in a crossover manner. Blood pressure, urinary protein-to-Cr ratio (UPCR), age, and the hospital of the study patient were used as stratification factors for randomization.

Fig. 1. Study design. #, collected urine and blood samples, and measured blood pressure and pulse rate.

Addition of ACE inhibitors, ARBs, and renin inhibitors was not permitted. A change of antihypertensive medications, except for changes to ACE inhibitors, ARBs, and renin inhibitors, was permitted if the primary doctor assessed that it was required. Target blood pressure was under 130/80 mm Hg, in accordance with the guidelines of the Japanese Society of Nephrology [11].

This study was performed in accordance with the Declaration of Helsinki and was approved by the Independent Review Board of Kyusyu University Hospital (Approval number 24-023) and registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; the trial identification number: UMIN000008597) in Japan. This study was also approved by an Ethics Committee in each study center. Patients were required to provide written informed consent. The discontinuation criteria included marked high and low blood pressure, cases where the primary doctor assessed that it was impossible to continue the study because of worsening of coexisting disorders or adverse events, hospitalization over 1 month, drug noncompliance, marked infrequent visits, withdrawal of consent, and any case where the primary doctor assessed that it was inappropriate to continue the study.

Patients

The inclusion criteria included patients who required antihypertensive drugs (defined as clinic systolic blood pressure ≥ 130 mm Hg and/or diastolic blood pressure ≥ 80 mm Hg or receiving antihypertensive drugs), UPCR ≥ 0.3 g/gCr, estimated glomerular filtration rate (eGFR) ≥ 15 mL/min/1.73 m², age more than 20 years, and outpatient status. The exclusion criteria included patients with known hypersensitivity to azilsartan or candesartan, myocardial infarction or stroke in the previous 6 months, serum potassium ≥ 5.5 mEq/L, significant hepatic dysfunction (alanine aminotransferase was over 3 times the healthy upper limit), IgA nephropathy who were treated with steroid therapy during the previous year, known renal artery stenosis, severe nephrotic syndrome (serum albumin < 2.0 g/dL), severe infection, malignancy, pregnancy, and lactation.

Fig. 2. Study flow diagram.

Study Procedures

During the crossover period, patient urine samples and blood samples were collected, and blood pressure and pulse rates were measured at 0, 1, 3, 4, and 6 months. For patients who needed to visit the hospital once a month for therapy, samples and data were also collected at 2 and 5 months. Systolic and diastolic blood pressures were evaluated in a sitting position after rest. The pulse rate was simultaneously assessed. Urine samples were collected to measure the UPCR, and blood samples were collected to measure hematological and biochemical parameters. All assays were performed using commercially available laboratory equipment. Renal function was assessed using a modified eGFR for Japanese patients [12].

Study Outcomes

We treated the data of 1 and 4 months as the first endpoint (1EP). To prevent variation in proteinuria, we averaged the UPCR and blood pressure data at 2 and 3 months and 5 and 6 months, and we treated the data as the UPCR and blood pressure at the second (final) endpoint (2EP). The primary outcome was the percent change in the UPCR at 1EP and 2EP. The secondary outcomes were the UPCR, systolic and diastolic blood pressures, the percent changes in systolic and diastolic blood pressures, and eGFR at 1EP and 2EP.

Statistical Analysis

Data from previous studies were used for sample size calculations. We expected that our patients would present with a mean proteinuria of approximately 1.7 g/day during ARB treatment [13]. On the basis of previous studies assessing additional renin-angiotensin system (RAS) inhibition, we assumed a 15% reduction

in proteinuria mediated by azilsartan compared with candesartan [6, 14–17]. We expected that the standard deviation of the percent change in the UPCR was 45, based on our previous studies and studies of ARBs. We selected 80% as the power, and we used a significance level of $\alpha = 0.05$. From these data, we estimated that 160 patients, including a 10% predicted dropout, were required to complete the crossover study to detect a statistically significant difference. To prevent errors resulting from the crossover design, the treatment periods were decided in random order. Because of this randomization and the short half-life of the intervention drugs (azilsartan: 11 h, candesartan: 9 h), the study protocol did not include washout periods [18, 19].

Data are expressed as mean $\pm$ SD or number (percentage), if not otherwise mentioned. Treatment effect, carryover effect, and period effect were assessed using a repeated measures ANOVA. Linear regression analysis was performed to examine the correlation of 2 parameters. A difference was considered significant at $p < 0.05$. Data were evaluated using JMP version 13.0 (SAS Institute, Cary, NC, USA).

Results

Study Population

A patient flow diagram is shown in Figure 2. We obtained informed consent from 111 patients who started the run-in period. During the run-in period, 8 patients discontinued. Of the 103 patients who were randomized,

Table 1. Baseline characteristics of study subjects ($n = 95$)

Age, years	64.3±12.9
Male, n (%)	64 (67.3)
Systolic blood pressure, mm Hg	131.4±18.3
Diastolic blood pressure, mm Hg	71.0±12.5
Pulse, per minute	72.3±11.2
BMI, kg/m ²	24.6±5.8
Diabetes mellitus, n (%)	35 (36.8)
Cardiovascular disease, n (%)	12 (12.6)
Renal diagnosis, n (%)	
Chronic glomerulonephritis	50 (52.6)
Diabetic kidney disease	13 (13.7)
Hypertensive nephropathy	27 (28.4)
Others	5 (5.3)
Medications, n (%)	
Other antihypertensive medication	
Calcium antagonist	68 (71.6)
Diuretic	25 (26.3)
β blocker	14 (14.7)
$\alpha\beta$ blocker	7 (7.3)
α blocker	6 (6.3)
Aldosterone antagonist	2 (2.1)
Lipid-lowering agent, n (%)	47 (49.5)
Hemoglobin, g/dL	12.6±1.9
Serum Cr, mg/dL	1.6±0.7
eGFR, mL/min/1.73 m ²	41.5±19.7
Serum sodium, mmol/L	140.8±2.4
Serum potassium, mmol/L	4.6±0.5
UPCR, g/gCr	1.8±1.8
Uric acid, mg/dL	7.0±1.5
Cr kinase, IU/L	163.5±226.8
Alanine aminotransferase, IU/L	19.9±10.6

GFR, estimated glomerular filtration rate; UPCR, urinary protein-to-Cr ratio. Data are presented as mean $\pm$ SD or value (percentage).

8 patients discontinued the study. Finally, 95 patients completed the study and were included in the analysis. The baseline characteristics of the study subjects are summarized in Table 1.

Percent Change in Proteinuria (Primary Outcome)

For the primary outcome, the mean percent change in the UPCR from baseline was $-3.8 \pm 7.9\%$ in the azilsartan group and $30.8 \pm 7.9\%$ in the candesartan group at 1EP ($p = 0.0004$), and $6.1 \pm 8.5\%$ in the azilsartan group and $25.8 \pm 8.5\%$ in the candesartan group at 2EP ($p = 0.029$) (Fig. 3). No significant period effect or carryover effect was detected.

Secondary Outcomes

Systolic blood pressure at 1EP was lower in the azilsartan group (129.6 ± 1.9 mm Hg) than in the candesartan group (134.8 ± 1.9 mm Hg) ($p = 0.0007$). The mean percent change in systolic blood pressure at 1EP was lower in the azilsartan group ($-0.6 \pm 1.3\%$) than in the candesartan group ($3.5 \pm 1.3\%$) ($p = 0.0006$). Diastolic blood pressure at 1EP was lower in the azilsartan group (71.3 ± 1.3 mm Hg) than in the candesartan group (73.5 ± 1.3 mm Hg) ($p = 0.02$). The mean percent change in diastolic blood pressure at 1EP was lower in the azilsartan group ($1.5 \pm 1.5\%$) than in the candesartan group ($5.1 \pm 1.5\%$) ($p = 0.01$). The mean UPCR at 1EP was lower in the azilsartan group (1.6 ± 0.2 g/gCr) than in the candesartan group (1.9 ± 0.2 g/gCr) ($p = 0.01$) (Fig. 4).

Systolic blood pressure at 2EP was lower in the azilsartan group (128.8 ± 1.9 mm Hg) than in the candesartan group (132.4 ± 1.9 mm Hg) ($p = 0.01$). The mean percent change in systolic blood pressure at 2EP was lower in the azilsartan group ($-1.4 \pm 1.2\%$) than in the candesartan group ($1.2 \pm 1.2\%$) ($p = 0.02$). Diastolic blood pressure at 2EP was not significantly different between the azilsartan group (71.4 ± 1.3 mm Hg) and the candesartan group (72.9 ± 1.3 mm Hg) ($p = 0.1$). The mean percent change in diastolic blood pressure at 2EP was not significantly different between the azilsartan group ($1.6 \pm 1.7\%$) and the candesartan group ($3.6 \pm 1.7\%$) ($p = 0.2$). The mean UPCR at 2EP was not significantly different between the azilsartan group (1.7 ± 0.2 g/gCr) and the candesartan group (1.9 ± 0.2 g/gCr) ($p = 0.096$) (Fig. 5).

The sequential changes in systolic blood pressure, diastolic blood pressure, and UPCR are shown in Figure 6. The participants of the solid line were treated with azilsartan for 3 months and then switched to candesartan. The participants of the dotted line were treated with candesartan for 3 months and then switched to azilsartan. The systolic blood pressures of the azilsartan- and candesartan-treated participants were 131.3 ± 2.5 and 130.5 ± 2.3 mm Hg at 3 months, and 126.4 ± 2.6 and 134.4 ± 3.3 mm Hg at 6 months, respectively. The diastolic blood pressures of the azilsartan- and candesartan-treated participants were 70.9 ± 1.9 and 73.1 ± 1.8 mm Hg at 3 months, and 71.9 ± 1.9 and 72.7 ± 2.0 mm Hg at 6 months, respectively. The UPCR levels of the azilsartan- and candesartan-treated participants were 1.9 ± 0.3 and 1.7 ± 0.3 g/gCr at 3 months, and 1.5 ± 0.3 and 2.1 ± 0.3 g/gCr at 6 months, respectively. The sequential changes in the percent changes in systolic blood pressure, diastolic blood pressure, and UPCR are shown in Figure 7. The mean percent changes in the systolic blood pressure of the azil-

Fig. 3. Percent change in the UPCR in the azilsartan and candesartan groups from baseline at 1EP (**a**) and 2EP (**b**). * $p < 0.05$ versus candesartan group. Data are expressed as mean $\pm$ SEM. 1EP, the first endpoint; 2EP, the second endpoint; UPCR, urinary protein-to-Cr ratio.

Fig. 4. Values at 1EP of the systolic blood pressure (**a**), percent change in systolic blood pressure (**b**), diastolic blood pressure (**c**), percent change in diastolic blood pressure (**d**), and UPCR (**e**) in the azilsartan and candesartan groups. * $p < 0.05$ versus candesartan group. Data are expressed as mean $\pm$ SEM. 1EP, the first endpoint; UPCR, urinary protein-to-Cr ratio.

Fig. 5. Values at 2EP of the systolic blood pressure (a), percent change in systolic blood pressure (b), diastolic blood pressure (c), percent change in diastolic blood pressure (d), and UPCR (e) in the azilsartan and candesartan groups. * $p < 0.05$ versus candesartan group. Data are expressed as mean $\pm$ SEM. 2EP, the second endpoint; UPCR, urinary protein-to-Cr ratio.

Fig. 6. Sequential changes in systolic blood pressure (a), diastolic blood pressure (b), and UPCR (c) of the azilsartan- and candesartan-treated participants. Data are expressed as mean $\pm$ SEM. UPCR, urinary protein-to-Cr ratio.

Fig. 7. Sequential changes in the percent changes in systolic blood pressure (a), diastolic blood pressure (b), and UPCR (c) of the azilsartan- and candesartan-treated participants. Data are expressed as mean $\pm$ SEM. UPCR, urinary protein-to-Cr ratio.

Fig. 8. eGFR in the azilsartan and candesartan groups at 1EP and 2EP. Data are expressed as mean $\pm$ SEM. 1EP, the first endpoint; 2EP, the second endpoint; eGFR, estimated glomerular filtration rate.

sartan- and candesartan-treated participants were -1.3 ± 1.7 and $1.8 \pm 1.5\%$ at 3 months and -1.5 ± 1.7 and $0.6 \pm 2.0\%$ at 6 months, respectively. The mean percent changes of the diastolic blood pressure of the azilsartan- and candesartan-treated participants were 1.3 ± 2.4 and $3.2 \pm 2.1\%$ at 3 months and 2.0 ± 2.5 and $4.1 \pm 2.6\%$ at 6 months, respectively. The mean percent changes in the UPCR of

the azilsartan- and candesartan-treated participants were 14.7 ± 9.7 and $8.1 \pm 8.3\%$ at 3 months and -2.5 ± 12.3 and $43.4 \pm 16.5\%$ at 6 months, respectively.

The mean eGFR levels at 1EP and 2EP were not significantly different between the azilsartan group (40.1 ± 2.1 , 38.7 ± 2.0 mL/min/1.73 m², respectively) and the candesartan group (41.3 ± 2.1 , 39.8 ± 2.0 mL/min/1.73 m², respectively) ($p = 0.12$, $p = 0.10$) (Fig. 8). The percent change in UPCR was associated with the percent changes in systolic blood pressure ($r = 0.33$, $p < 0.0001$) and diastolic pressure ($r = 0.4$, $p < 0.0001$) at 1EP. The percent change in UPCR was also associated with the percent changes in systolic blood pressure ($r = 0.2$, $p = 0.01$) and diastolic pressure ($r = 0.34$, $p < 0.0001$) at 2EP.

Side Effects and Change in Antihypertensive Drugs

During the run-in period, 2 patients demonstrated increased Cr levels, 2 patients demonstrated decreased blood pressure, and 1 patient demonstrated drug eruption produced by azilsartan treatment. During the crossover period, 1 patient demonstrated increased Cr levels and 1 patient demonstrated drug eruption produced by candesartan treatment. One patient required hospitalization during both azilsartan and candesartan treatments. The study treatments were well tolerated by the majority of the study patients, and there was no apparent difference in the frequency of side effects between the azilsartan and candesartan groups during the crossover period. He-

Table 2. Adverse effects during the study period

	20 mg azilsartan	8 mg candesartan	<i>p</i> value
Hemoglobin, g/dL	12.6±0.2	12.6±0.2	0.6
Serum Cr, mg/dL	1.65±0.1	1.62±0.1	0.3
Serum sodium, mmol/L	140.7±0.3	140.7±0.3	0.9
Serum potassium, mmol/L	4.6±0.1	4.5±0.1	0.1
Uric acid, mg/dL	6.7±0.1	6.7±0.1	0.5
Cr kinase, IU/L	176.8±18.1	146.7±18.1	0.2
Alanine aminotransferase, IU/L	19.3±1.1	19.9±1.1	0.6

Data are presented as mean ± SEM.

matological and biochemical parameters related to adverse effects of ARBs were not significantly different between the azilsartan and candesartan groups during the study period (Table 2).

Antihypertensive drugs and diuretic drugs were changed during the crossover period. Antihypertensive drugs were decreased in 3 patients and increased in 1 patient during azilsartan treatment, and these drugs were increased in 3 patients during candesartan treatment. Diuretic drugs were decreased in 3 patients and increased in 1 patient during azilsartan treatment, and increased in 7 patients and decreased in 1 patient during candesartan treatment.

Discussion

The current study demonstrated that azilsartan (20 mg daily) treatment significantly decreased proteinuria and blood pressure compared with candesartan (8 mg daily) in patients with CKD who required hypertensive drugs. These significant reductions in proteinuria and blood pressure during azilsartan treatment were not associated with significant increases in side effects compared with candesartan. To the best of our knowledge, this is the first study of azilsartan in which the primary outcome is proteinuria. Furthermore, the level of proteinuria in the current study was higher than that in another study using azilsartan [18, 20–24]. We demonstrated that azilsartan had beneficial antiproteinuric and antihypertensive effects in patients with proteinuric CKD compared with candesartan, an older ARB.

ARBs reduce proteinuria in patients with CKD and have a reno-protective effect [16]. Therefore, ARBs are recommended for hypertensive patients with CKD by

clinical guidelines. The reno-protective effect of azilsartan has not been well assessed. Shiga et al. [20] and Takami et al. [21] demonstrated that azilsartan (20 mg) and olmesartan medoxomil (20 mg) decreased blood pressure equally, and both drugs decreased the urinary albumin-to-Cr ratio equally. Kakio et al. [22] demonstrated that azilsartan (20 mg) and olmesartan medoxomil (20 mg) decreased blood pressure equally but only azilsartan significantly decreased urinary albumin. They suspected that the effect on glomerular efferent arterioles in the azilsartan group might be stronger than that in the olmesartan group. Takahara et al. [18] compared the blood pressure-lowering effects of azilsartan (10 mg) and candesartan (8 mg). They demonstrated that the blood pressure-lowering effects of azilsartan were noninferior to those of candesartan, and the urinary albumin-to-Cr ratio was not different between the 2 groups. Other results have varied depending on drug doses or the drugs which have been compared with azilsartan [23–25]. The present study demonstrated that azilsartan (20 mg) significantly reduced the percent change in proteinuria as well as systolic blood pressure compared with candesartan (8 mg). Proteinuria is an important biomarker of renal function, and a reduction in proteinuria during ARB treatment is associated with reno-protective effects in hypertensive patients with CKD [5]. Our results suggest that azilsartan may be useful in the treatment of CKD patients with proteinuria.

In the present study, the differences in the percent changes in the UPCR between the azilsartan and candesartan groups were 34.6% at 1EP and 19.7% at 2EP, respectively. Azilsartan reduced proteinuria compared with candesartan during the course of the study. We demonstrated that the significant reduction in proteinuria induced by azilsartan was associated with reduced blood pressure. The antiproteinuric effect may be associated with both the antihypertensive and azilsartan-mediated direct effects on the kidney. Azilsartan has an original component, a 5-oxo-1,2,4 oxadiazole in a tetrazole ring, and this structure has been reported to induce strong inverse agonism in and bind tightly to angiotensin II type 1 receptors compared with other ARBs [10, 20]. In vitro, the inhibitory effects of azilsartan mediated through binding to angiotensin II and angiotensin II type 1 receptors were stronger than those of other ARBs [10]. This strong binding of azilsartan to angiotensin II type 1 receptors is thought to be associated with long and strong antihypertensive effects in a clinical setting. ARBs demonstrate reno-protective effects, and these effects are partially mediated by direct effects on the kidney which are

independent of antihypertensive effects [16]. Takami et al. [21] demonstrated that the changes in urinary angiotensinogen, which is a biomarker of intrarenal RAS activation [26], were associated with the changes in the urinary albumin-to-Cr ratio; however, they were not associated with the changes in blood pressure. In a study in Zucker diabetic fatty rats, azilsartan decreased proteinuria compared with candesartan, although these drugs did not affect blood pressure [27]. We demonstrated that azilsartan decreased proteinuria and blood pressure significantly compared with candesartan, and our results are consistent with those of previous studies. These effects might be associated with the strong inhibitory effect to angiotensin II type 1 receptors by azilsartan compared to the other ARBs. However, further studies are needed to clarify direct effects in the kidney produced by strong RAS inhibition of azilsartan.

Azilsartan (20 mg) significantly reduced blood pressure compared with candesartan in the current study. This result is consistent with that of previous studies of azilsartan and azilsartan medoxomil, a prodrug of azilsartan, which showed that the blood pressure-reducing effects of azilsartan and azilsartan medoxomil might be even stronger than those of other ARBs [20–22, 28–34]. In the current study, the differences in systolic blood pressure changes produced by azilsartan and candesartan were 5.2 and 3.6 mm Hg at 1EP and 2EP, respectively. These differences were small, but important. A 10 mm Hg reduction in systolic blood pressure led to a 13% reduction in all-cause mortality, in a meta-analysis [35]. Even a 2 mm Hg reduction in systolic blood pressure was associated with a 4% lower risk of coronary death and a 6% lower risk of stroke death [36]. The association between a reduction in blood pressure and proteinuria varied because of differences in baseline blood pressure levels in previous studies [4, 16, 37–42]. In studies in which the average baseline blood pressure was not in the hypertensive range and an RAS inhibitor was used, a 1 mm Hg reduction in mean blood pressure was associated with a 4.9–18.2% reduction in proteinuria [37–42]. In the current study, a 1 mm Hg increase in mean blood pressure was associated with an 8.2% increase in proteinuria in the candesartan group, and this result was consistent with previous studies. These results indicated that a small change in blood pressure had a major impact on a change in proteinuria in patients within a hypertensive blood pressure range. Furthermore, the significant lower blood pressure in the azilsartan group compared to the candesartan group observed at 1EP is also important in the present study. The stabilization times of systolic blood pres-

sure produced by azilsartan and candesartan were shown to be 7.1 and 11.0 days, respectively [43]. It was demonstrated in a clinical study that the prompt achievement of target blood pressure is important for the prevention of cardiovascular events [44]. In the present study, azilsartan lowered blood pressure significantly and rapidly. These results might provide meaningful clinical benefits for patients.

Azilsartan did not produce increased adverse effects compared with candesartan. Laboratory findings did not suggest any clinically severe changes in renal function and potassium status. During the crossover period, 1 patient was hospitalized because of a bone fracture during candesartan treatment, and 1 patient was hospitalized because of an abdominal aortic aneurysm during azilsartan treatment. However, these events are not associated with the study drugs.

The current study had some limitations. First, it was designed to evaluate the short-term effect of azilsartan and candesartan and did not include hard endpoints. Second, we selected a crossover design, which is consistent with previous studies using ARBs [19, 45, 46]. This was mainly because of the sample size. We did not detect a significant carryover and period effect, except for a period effect of the eGFR at 2EP, and we attribute this to the natural history of CKD. Third, the sample size was smaller than we had previously calculated. We had assumed a 15% reduction in proteinuria, but the difference was larger in the study. Fourth, antihypertensive and diuretic drugs were changed in some patients as previously permitted, and significant differences in diastolic blood pressure, the percent change in diastolic blood pressure, and urinary protein excretion at 1EP had disappeared at 2EP. This means that azilsartan rapidly decreased blood pressure and proteinuria, and the primary physician changed antihypertensive and diuretic drugs to achieve target blood pressure. The rapid decrease in blood pressure by azilsartan and dose titration of the other ARBs was also observed in a clinical trial comparing azilsartan medoxomil and other ARBs [23]. Fifth, during the run-in period, we administered azilsartan, and we excluded patients who were intolerant of azilsartan to avoid misleading results. Sixth, the dose of azilsartan and candesartan used in the current study was lower than the dose used in previous studies [47, 48] and Western countries. In Japan, the maximum dose of candesartan permitted for hypertensive patients with renal injury is 8 mg and the maximum dose of azilsartan permitted is 40 mg. In the context of Japan, we chose 20 mg of azilsartan and 8 mg of candesartan in the current study.

Conclusion

The current study demonstrated that azilsartan decreased proteinuria and blood pressure significantly compared with candesartan without severe adverse events. Azilsartan may be superior to candesartan in terms of reno-protective and antihypertensive effects in patients with CKD.

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Statement of Ethics

This study was performed in accordance with the Declaration of Helsinki, approved by the Independent Review Board of Kyusyu University Hospital (Approval number 24-023), and registered at

the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; trial identification number: UMIN000008597) in Japan. This study was also approved by an Ethics Committee in each study center. Patients were required to provide written informed consent.

Conflict of Interest Statement

Ka.T. and T.K. have received honoraria and grants from Takeda Pharmaceutical Co., Ltd. The other authors declare no conflict of interest.

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Author Contributions

Research idea and study design: T.S. and Ka.T.; data acquisition: T.S., Ka.T., H.Y., H.T., S.Y., S.T., A.T., M.E., K.F., Ku.T., and T.N.; data analysis/interpretation: T.S., Ka.T., and H.Y.; statistical analysis: T.S., Ka.T., and H.Y.; supervision or mentorship: T.K. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors reviewed the manuscript and approved the final version for publication. Ka.T. takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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