Add-On Angiotensin Receptor Blocker in Patients Who Have Proteinuric Chronic Kidney Diseases and Are Treated with Angiotensin-Converting Enzyme Inhibitors

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The benefit of the add-on angiotensin II receptor blocker candesartan to angiotensin-converting enzyme (ACE) inhibitors in inhibition of progression of nephropathy in hypertensive patient with nondiabetic renal disease compared with monotherapy with ACE inhibitors remains controversial. All patients were previously treated with ACE inhibitors. Urinary protein excretion of patients exceeded 1.0 g/d despite treatment with ACE inhibitors. Ninety hypertensive patients with chronic renal insufficiency were randomly assigned to one of two groups. One group received ACE inhibitor plus candesartan (2 to 12 mg/d), and a control group received only ACE inhibitor. The target BP was ≤130/80 mmHg. The primary outcome was the changes in serum creatinine and the reduction of proteinuria. The mean duration of follow-up was 3.1 ± 0.4 yr. At years 2 and 3, systolic and diastolic BP were reduced from 140 ± 3/84 ± 2 to 129 ± 1/78 ± 2 mmHg (candesartan group) and from 135 ± 2/85 ± 2 to 130 ± 2/80 ± 2 mmHg (ACE inhibitors group). In both groups, both systolic and diastolic BP decreased significantly from the beginning to the end of the study (P < 0.01). The serum creatinine concentration increased from 3.02 ± 0.27 to 3.38 ± 0.49 mg/dl (candesartan plus ACE inhibitor group) versus 3.00 ± 0.37 to 4.48 ± 0.57 mg/dl (ACE inhibitor group; P < 0.01) at year 3. Although the level of proteinuria significantly declined in each group (P < 0.05), the degree of reductions in proteinuria was greater in the candesartan group than in the ACE inhibitors group (P < 0.01). In the patients who were treated with candesartan and ACE inhibitor or ACE inhibitor alone, pretreatment proteinuria correlated significantly with decline of renal function, whereas reduction of proteinuria negatively correlated with decline in renal function in the patients who were treated with candesartan. Candesartan with an ACE inhibitor is effective in slowing the progression of renal insufficiency in hypertensive patients with nondiabetic renal disease through reduction of proteinuria.

tigators of this study are listed in the Appendix. The primary objective was to evaluate the long-term effects on renal function and reduction of proteinuria in hypertensive patients who had impaired renal function and were being treated with an ACE inhibitor and compare the addition (or not) of once-daily candesartan to their current ACE inhibitor. The trial protocol was approved by the ethics committees of all participating institutions and was conducted in accordance with the principles of the Declaration of Helsinki, overseen by an independent data and safety monitoring board.

Patients were instructed to follow a diet with a daily protein intake of <0.7 g/kg body wt and a daily salt intake of <9 g. In addition, when a patient had a serum potassium of >6 mEq/L, an ion exchanger was administered.

**Target Population and Treatment Schedule**

This study included Japanese hypertensive patients who were between the ages of 35 and 79 yr and had renal dysfunction that previously was treated with ACE inhibitors. Inclusion criteria were a serum creatinine concentration of between 1.2 and 5.0 mg/dl, systolic BP (SBP) of >130 and <180 mmHg, diastolic BP (DBP) >80 and <120 mmHg, and a daily urinary protein excretion of >1.0 g. From the beginning of September 1999 to the end of December 1999, we randomly assigned 90 hypertensive patients who had chronic renal insufficiency and were receiving an ACE inhibitor to additional treatment with candesartan (2 to 12 mg/d) or to a control group that received continuously ACE inhibitors without candesartan. There was no stratification as part of the randomization process. The randomization was carried out by the envelope method: The physicians picked up the envelopes in which the allocated groups were indicated. All patients were followed for 3 yr or until death or referral for renal replacement therapy, including dialysis therapy or renal transplantation, whichever occurred first. The following patients were excluded: Patients with secondary hypertension, including patients who were on dialysis therapy or receiving renal transplantation; patients who had chronic renal diseases and were receiving corticosteroid hormone; patients with myocardial infarction or stroke within the previous 6 mo or angina pectoris that required treatment with β blockers or calcium channel blocker; and patients with heart failure or left ventricular ejection fraction of 40% or less or with a disorder that in the treating physician’s opinion for other types of ARB. BP was measured in each clinic beginning of September 1999 to the end of December 1999, we randomly assigned 90 hypertensive patients who had chronic renal insufficiency and were receiving an ACE inhibitor to additional treatment with candesartan (2 to 12 mg/d) or to a control group that received continuously ACE inhibitors without candesartan. There was no stratification as part of the randomization process. The randomization was carried out by the envelope method: The physicians picked up the envelopes in which the allocated groups were indicated. All patients were followed for 3 yr or until death or referral for renal replacement therapy, including dialysis therapy or renal transplantation, whichever occurred first. The following patients were excluded: Patients with secondary hypertension, including patients who were on dialysis therapy or receiving renal transplantation; patients who had chronic renal diseases and were receiving corticosteroid hormone; patients with myocardial infarction or stroke within the previous 6 mo or angina pectoris that required treatment with β blockers or calcium channel blocker; and patients with heart failure or left ventricular ejection fraction of 40% or less or with a disorder that in the treating physician’s opinion for other types of ARB. BP was measured in each clinic between 9 and 11 a.m. using a mercury sphygmomanometer; the first and the fifth Korotkoff sounds were used to identify systolic and diastolic values, respectively. Two measurements were performed with the patient in the sitting position for 5 and 10 min, respectively, and the average of the two values was taken as the clinical BP for the purpose efficacy analysis. Patients were followed up for 3 yr or more with regular visits and upward titration of medication to reach a target SBP of <130 mmHg and DBP of <80 mmHg. The main ACE inhibitors used were benazepril 2.5 to 10 mg/d or trandolapril 2 to 4 mg/d. Doses of benazepril and trandolapril were determined on the basis of previous studies (11,17,18). Calcium channel antagonist, diuretics, β blockers, and other antihypertensive agents were used when the BP level was above the predetermined limit. The record of renal biopsy revealed that 47 of 90 patients had IgA nephropathy, 16 had chronic glomerulonephritis, and six had membranous nephropathy. The remaining 21 patients without a biopsy had underlying renal disease of unknown origin.

**Outcome Measures**

The primary outcome was the rate of decline of renal function, which was evaluated using the changes in serum creatinine and reduction of proteinuria. Routine laboratory tests were performed in four central laboratories. Serum creatinine (specific enzyme assay); hematologic and serum tests, including uric acid, blood urea nitrogen (BUN), electrolytes, and 24-h urinary excretion of protein (dye-binding method using pyrogallol red-molybdate complex); and creatinine were measured at the beginning and at the end of the baseline period and subsequently during the follow-up period every 3 mo.

Adverse events (AE) were monitored throughout the study. The study was completed and end point follow-up was stopped on December 31, 2002.

**Statistical Analyses**

Results were expressed as mean ± SEM. Statistical significance of the results was determined using t test for unpaired samples or Mann-Whitney test, when applicable. Differences among treatment groups in postrandomization measures were evaluated by analysis of covariance (ANCOVA) and with the χ² test. Pearson product moment correlation coefficients were used to evaluate whether baseline proteinuria or reduction of proteinuria was correlated with decline of estimated GFR. ANCOVA was also used to compare the difference between two groups. P < 0.05 was considered statistically significant. All calculations were made with statistical software Stat View Version 5.0 (SAS Institute Inc., Cary, NC) and Dr. SPSS II for Windows (SPSS Japan Inc., Tokyo, Japan).

**Results**

The demographic data are shown in Table 1. There were no significant differences in age, gender ratio, levels of BUN, hematocrit, and underlying renal diseases between candesartan-based and ACE inhibitor groups.

<table>
<thead>
<tr>
<th>Table 1. Demographic data of patientsa</th>
<th>Candesartan + ACE Inhibitor (n = 45)</th>
<th>ACE Inhibitors (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.3 ± 11.9</td>
<td>59.9 ± 12.0</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>27/18</td>
<td>27/18</td>
</tr>
<tr>
<td>Underlying renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA nephropathy</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>glomerular nephritis</td>
<td>8</td>
<td>8</td>
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<tr>
<td>membranous nephropathy</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>unknown origin of renal disease</td>
<td>10</td>
<td>11</td>
</tr>
</tbody>
</table>

aACE, angiotensin-converting enzyme.
Follow-Up and BP Control

The mean follow-up time (from randomization through death, loss to follow-up, or end of study) was 3.1 ± 0.4 yr. Patients in the candesartan plus ACE inhibitor and ACE inhibitor only groups continued study therapy 92 and 89% of the entire follow-up time, respectively. The mean final candesartan dose was 8.5 ± 1.2 mg/d, and 80% of all patients received 8 mg/d. In the candesartan plus ACE inhibitor treatment group, 68% of the patients took more than two additional drugs, and 45% took three additional drugs. In contrast, 75% of the patients who received ACE inhibitors only took more than two additional drugs, and 65% took more than three additional drugs. The average dose of ACE inhibitor was 4.5 ± 1.1 mg in the candesartan plus ACE inhibitor group, 4.2 ± 0.9 mg in the ACE inhibitor group of benazepril, 2.4 ± 0.9 mg in the candesartan plus ACE inhibitor group, and 2.8 ± 1.2 mg in the ACE inhibitor group of trandolapril. There were no significant differences in the mean dose of ACE inhibitors between the candesartan plus ACE inhibitor and ACE inhibitor only groups. The mean sitting BP at the end of follow-up or at the last visit before a primary end point was reduced from 140 ± 3/84 ± 2 to 129 ± 1/78 ± 2 mmHg (candesartan plus ACE inhibitor group) and from 135 ± 2/85 ± 2 to 130 ± 2/80 ± 2 mmHg (ACE inhibitors group; Figure 1). At years 2 and 3, there were significant differences in DBP between the group that received candesartan plus ACE inhibitor and the ACE inhibitor only group. A BP of <130/80 mmHg was achieved for 82% of those who were taking candesartan plus ACE inhibitor and 80% of those who were taking ACE inhibitors only. Additive antihypertensive drugs were used as in Table 2. Calcium channel antagonists (mainly amlodipine) were used in >60% of the patients in both groups. The frequency of antihypertensive drug usage was not significantly different between the two groups.

Figure 1. Effects of antihypertensive treatment on systolic and diastolic BP in the patients with nondiabetic chronic kidney disease (CKD). ○, patients who received candesartan and angiotensin-converting enzyme (ACE) inhibitor; ●, patients who received ACE inhibitors only. Values represent means ± SEM. **P < 0.01 versus the baseline value; †P < 0.05 versus ACE inhibitors group.

Table 2. Combined antihypertensive drugs

<table>
<thead>
<tr>
<th></th>
<th>Candesartan + ACE Inhibitor (%; n = 45)</th>
<th>ACE Inhibitors (%; n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>15.5</td>
<td>17.8</td>
</tr>
<tr>
<td>β blockers</td>
<td>6.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Ca antagonists</td>
<td>66.7</td>
<td>62.2</td>
</tr>
<tr>
<td>Others</td>
<td>17.8</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Effects of Candesartan on the Rate of Decline of Renal Function

In the first 2 yr of the study, there were similar increases in the level of serum creatinine in the two groups; however, at year 3, the level of serum creatinine was significantly different between the two groups (P < 0.05). Twenty-four-hour creatinine clearance that was calculated from serum and urine creatinine and urine volume showed similar changes as observed with serum creatinine (Figures 2 and 3).

Urinary Protein Excretion

Treatment with candesartan resulted in a significant decrease in urinary protein excretion from a basal value of 1.78 ± 0.10 to 0.62 ± 0.15 g/d at year 1, 0.56 ± 0.16 g/d at year 2, and 0.55 ± 0.16 g/d at year 3 (P < 0.01). From year 1 to year 3, the magnitude of decreases in urinary protein excretion was greater in the candesartan group than in the ACE inhibitors group (P < 0.01). In the patients who were not treated with candesartan, urinary excretion of protein decreased significantly from a basal value of 1.61 ± 0.11 to 1.21 ± 0.17 g/d at year 3 (Figure 4).

Estimated GFR

Because inulin and nonradiolabeled iothalamate are not available for determination of GFR in Japan, we usually use 24-h creatinine clearance for estimation of GFR. In this study, estimated GFR was calculated by using the Modification of Diet in Renal Disease (MDRD) equation GFR = 186 × serum creatinine (mg/dl)^−1.154 × age^−0.203 × (0.742 if female) (19) and compared with 24-h creatinine clearance. These values correlated with each other (MDRD GFR = −0.482 + 0.982 × 24-h creatinine clearance [R = 0.869, P < 0.0001 (total)]; MDRD GFR = −1.549 + 1.039 × 24-h creatinine clearance [R = 0.862 (ACE inhibitors group)]; MDRD GFR = 0.188 + 0.941 × 24 h creatinine clearance [R = 0.880 (candesartan plus ACE inhibitor group)])

Correlations between Proteinuria and 24-h Creatinine Clearance

These data prompted us to examine the relationship between the basal levels of protein excretion and reduction of 24-h creatinine clearance, and a correlation index was calculated. Figure 5 shows the relationship between the basal levels of urinary protein excretion and reduction of 24-h creatinine clearance in both groups (r = 0.104, P = 0.0260, candesartan plus ACE inhibitor group; r = 0.465, P = 0.0012, ACE inhibitors group; P < 0.0001 between two groups by ANCOVA). Therefore, it is suggested that
compared with the ACE inhibitor group, the reduction in creatinine clearance was smaller in candesartan group. Also, in the patients who were treated with candesartan and ACE inhibitor, there was a significant correlation between the reduction of urinary protein excretion and the decline of 24-h creatinine clearance ($r = 0.405, P < 0.05$). Conversely, there were no correlations between these two factors in the patients who were not treated with candesartan (Figure 6).

**AE and Safety Profile**

Both candesartan and ACE inhibitors were well tolerated, with few discontinuations as a result of AE and discontinuations as a result of drug-related AE.

**Doubling of Serum Creatinine Levels and Dialysis Therapy**

Doubling of serum creatinine levels was defined as the first serum creatinine value that was twice the baseline value, as confirmed by a second serum creatinine value that was obtained at least 4 wk after the initial finding of doubling. Serum creatinine levels increased two-fold during the study period in seven patients of the ACE inhibitors group and none of the candesartan plus ACE inhibitor group. Two patients who were treated with candesartan plus ACE inhibitor and two patients who were treated with ACE inhibitor alone were started on dialysis therapy. Two patients dropped out of the candesartan and ACE inhibitors group, and three patients dropped out of the ACE inhibitor group. We also investigated the serum creatinine levels of the patients before entry into our study. Reciprocal of serum creatinine were $0.64 \pm 0.05$ ($-12 \text{ mo}, n = 43$), $0.60 \pm 0.05$ ($-6 \text{ mo}, n = 43$), $0.51 \pm 0.04$ (on registration), $0.48 \pm 0.05$ (year 1), $0.44 \pm 0.04$ (year 2), and $0.37 \pm 0.04$ (year 3) in the ACE inhibitors group ($P < 0.01$ month $0.554 \left[r^2 = 0.941\right]$) and $0.67 \pm 0.05$ ($-12 \text{ mo}, n = 41$), $0.63 \pm 0.05$ ($-6 \text{ mo}, n = 41$), $0.53 \pm 0.04$ (on registration), $0.53 \pm 0.04$ (year 1), $0.52 \pm 0.05$ (year 2), and $0.52 \pm 0.04$ (year 3) in the candesartan plus ACE inhibitor group ($n = 41; \sim0.003 \times \text{ month} + 0.592 \left[r^2 = 0.636\right]$). The slope of the candesartan plus ACE inhibitors group was significantly gentler than that in the ACE inhibitors group ($P < 0.05$).

**Laboratory Findings**

There were no significant differences in the two treatment groups in the levels of BUN, hematocrit, and serum potassium at the start of the study. However, the levels of BUN and serum potassium increased significantly at 3 yr compared with the basal values in both groups. Moreover, hematocrit decreased significantly in the patients in both treatment groups (Table 3).
Discussion

Our study demonstrated that candesartan added on background ACE inhibitor therapy provided superior renoprotection as compared with treatment with an ACE inhibitor alone, as reflected by decreases in urinary excretion of protein and slowing of the deterioration of renal function in hypertensive patients with moderate to severe renal impairment. It is widely known that chronic ACE inhibitor therapy reduces proteinuria and slows the progression of chronic kidney disease (CKD) (1). Jafar et al. (4) demonstrated that urinary protein excretion of $\geq 2.0$ g/dl is strongly associated with a low risk for kidney disease progression. Similar observations have been noted by several investigators about the effects of ACE inhibitors on reduction of proteinuria in patients with CKD (20). In our study, the patients who had urinary protein excretion $>1.0$ g/d despite treatment with ACE inhibitors were selected. There has been little information about the effects of ACE inhibitors on progression of CKD when these drugs fail to reduce proteinuria. In these cases, it is claimed that the dose of ACE inhibitors is not maximized and these two drugs’ working on the same hormonal system can be called additive only when one of them is at the top of the dose response (16). In this study, the doses of ACE inhibitors (benazepril and trandolapril) were not always maximized because of AEs such as dry cough, unexpected increased serum creatinine, elevation of serum potassium, etc. However, the dose of benazepril was determined by using the previously published data (17), and that of trandolapril was used by the suggestions of Nakao et al. (11). In addition, in our study, the levels of SBP were similar between the patients in the candesartan plus ACE inhibitor group and the ACE inhibitors group. Despite comparable BP values, combination therapy with candesartan decreased proteinuria more than ACE inhibitors alone. There are only limited data available from large-scale clinical studies on the renoprotective effects of dual blockade of the RAS, as compared with a single use of either ACE inhibitor or ARB. The COOPERATE trial, conducted by Nakao et al. (11), demonstrated for the first time the long-term effect of dual blockade of the RAS on urinary excretion of protein as well as doubling of serum creatinine or reaching ESRD. Recently, Kincaid-Smith et al. (21) demonstrated that standard ACE inhibitors plus candesartan is more effective in reducing SBP and proteinuria than a 50% increase in ACE inhibitor dose alone in patients with proteinuric nephropathies. More recently, Wolf and Ritz (22) proposed the hypothesis that patients who had optimal BP control under monotherapy with RAS blockers with proteinuria $>1$ g/d would benefit from therapy with ACE inhibitor and ARB in combination. Our findings that add-on ARB in the patients who previously were treated ACE inhibitors reduced urinary protein excretion to $<1.0$ g/d and prevented the progression of renal dysfunction may support their hypothesis.

Previously, the antiproteinuric effect of ACE inhibitors and ARB was reported to be more than could be expected from BP reduction alone (4). However, recently, an animal study demonstrated that treatment with benazepril provides renoprotection in the rat remnant kidney model of progressive glomerulosclerosis, primarily through BP-dependent mechanisms (23). In addition, similar data have been presented suggesting that the effect of losartan, an angiotensin receptor antagonist, on proteinuria has little to do without the BP reduction (24).

In this study, two patients in each group developed ESRD irrespective of whether they were treated with candesartan. In the COOPERATE study, the number of patients who reached
ESRD was one (1%) in the combination group and seven (8%) in the ACE inhibitor group. Although our data are compatible with these findings, the number of the patients who reached ESRD in the group that received ACE inhibitor only and had been treated previously was extremely low. These suggest that starting treatment with ACE inhibitors at a stage of kidney damage that corresponds to a mildly decreased GFR is renoprotective. In our study, at year 3, there were significant differences in the levels of serum creatinine between the patients who were treated with add-on candesartan and those who were not treated with candesartan, suggesting that in the long term, add-on ARB with ACE inhibitors is likely to reduce the risk for ESRD when patients had higher levels of urinary protein excretion despite treatment with ACE inhibitors. In addition to the changes in GFR, the doubling of serum creatinine also was calculated. As the data of estimated GFR was reflected, the reciprocal curve became slow after the add-on angiotensin II blockade. However, because we did not include this evaluation in the outcome of our study, the data were omitted from the decision of conclusion. The efficacy of candesartan in the treatment of patients with renal disease reported here offers the opportunity to expand further the use of this drug to the patients with complications related to hypertension.

In our study, an unexpected finding was a small, nonsignificant increase in serum potassium levels. Previously, one of the adverse effects of dual blockade therapy was considered to be hyperkalemia (25). However, the increase in serum potassium levels was thought to be a result of the progression of renal dysfunction, not a complication of add-on therapy. However, we did not measure the plasma aldosterone levels. The reasons that the levels of serum potassium did not reach dangerous levels are as follows. First, there is no significant difference between the two groups in the frequency of use of diuretics, which would influence the serum potassium levels. The reasons that the levels of serum potassium did not increase in serum potassium to the same degree as ACE inhibitor in the presence of renal insufficiency. These differential effects on serum potassium were related to a relatively smaller reduction in plasma aldosterone as a result of the ARB and were not related to changes in GFR. Also, another factor of independent blood pressure or albuminuria may contribute to these results as in other studies (27).

Our study has certain limitations. The study had an open-label design, which may introduce some degree of bias in the data. These kinds of flaws in methods might induce some preference bias in the two groups; however, no significant differences between the two groups were noted at the beginning of the study. It therefore seems that assessments that used an open-label, randomized design to evaluate the effects of candesartan on slowing the progression of renal insufficiency in this study are valid. Second, the dose of the drugs used in this study was lower than that used elsewhere in the world. However, these dosages are commonly used in Japan, and the maximum dose of each drug (10 mg for benazepril, 2 mg for trandolapril, and 12 mg for candesartan) is strictly restricted by the Ministry of Health, Labor and Welfare. We could not overrule the possibility that these smaller doses might have an impact on our results. However, the rate of decline in patients with nondiabetic nephropathy using this dose of ACE inhibitors in the COOPERATE study was similar to that reported for studies that were conducted in the United States and Europe. It therefore seems that, in our study, these doses would be suitable for Japanese patients. Third, we used 24-h creatinine clearance as an indicator of renal function. Recently, iothalamate clearance was used as a novel method to measure GFR (28); however, many studies have used the Cockcroft-Gault formula (9) or the MDRD formula (29) for estimation of GFR. Conceivably, using these formulas would over- or underestimate the true value of GFR; however, iothalamate still is not approved to use clinically in Japan. For comparison, we calculated the 24-h creatinine clearance and estimated GFR using the MDRD equation. The correlation index was $r = 0.86$ to 0.88, indicating that renal dysfunction was evaluated adequately.

### Table 3. Baseline values and changes in BUN, hematocrit, and serum potassium

<table>
<thead>
<tr>
<th></th>
<th>Before Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
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<tr>
<td>BUN (mg/dl)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>candesartan + ACE inhibitor</td>
<td>40.6 ± 6.0</td>
<td>43.1 ± 4.1</td>
<td>49.1 ± 7.7b</td>
<td>51.7 ± 5.9c</td>
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<tr>
<td>ACE inhibitors</td>
<td>39.0 ± 5.6</td>
<td>45.9 ± 4.8b</td>
<td>54.9 ± 5.1bd</td>
<td>60.2 ± 8.3c,d</td>
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<tr>
<td>Hematocrit (%)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>candesartan + ACE inhibitor</td>
<td>37 ± 6</td>
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<td>31 ± 7b</td>
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<tr>
<td>ACE inhibitors</td>
<td>37 ± 5</td>
<td>35 ± 6</td>
<td>31 ± 7</td>
<td>30 ± 5b</td>
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<td>Serum potassium (mEq/L)</td>
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<tr>
<td>candesartan + ACE inhibitor</td>
<td>4.7 ± 0.5</td>
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<td>5.4 ± 0.7b</td>
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<tr>
<td>ACE inhibitors</td>
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<td>4.7 ± 0.6</td>
<td>5.2 ± 0.6</td>
<td>5.3 ± 0.7b</td>
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</table>

* BUN, blood urea nitrogen.

b $P < 0.05$ and c $P < 0.01$, significant difference versus the basal values.

d $P < 0.05$, significant difference versus the other group.
Conclusion
The add-on candesartan with ACE inhibitors is effective in slowing the progression of renal insufficiency in hypertensive patients with nondiabetic renal disease through reduction of proteinuria.

Appendix: Study Investigators
The following investigators from the following institutions participated in this study: Tatsuhiko Kanno, Musashi Ranzan Hospital; Junko Shoda, Chichibu Hospital; Hiromichi Suzuki, Yoshihiko Kanno, and Tsumeo Takenaka, Saitama Medical School; Soichi Sugahara, Ikebukuro Hospital; Keiko Kaneko, Irumadai Clinic; and Tsukasa Nakamara, Shinماتudo Central General Hospital.

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Parts of this study were presented at the 38th annual meeting of the American Society of Nephrology, 2005, Philadelphia, PA; and the 28th annual meeting of the Japanese Society of Hypertension, September 15, 2005, Asahikawa, Japan.

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