Original Article

Effects of Monotherapy of Temocapril or Candesartan with Dose Increments or Combination Therapy with Both Drugs on the Suppression of Diabetic Nephropathy

Susumu OGAWA[1)], Kazuhisa TAKEUCHI[1)], Takefumi MORI[1)], Kazuhiro NAKO[1)], Yoshitaka TSUBONO[2),3)], and Sadayoshi ITO[1)]

We examined the effects of increasing the recommended initial doses of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), or of switching to combination therapy with both drugs, on diabetic nephropathy. Hypertensive type 2 diabetic patients with urinary albumin excretion (ACR) between 100 and 300 mg/g creatinine (Cre) were assigned to the following five groups in which an antihypertensive drug was administered at a recommended initial dose for 48 weeks, and then either the dose was doubled or an additional drugs was added to regimen for the following 48 weeks: N, nifedipine-CR (N) 20 mg/day (initial dose); T, ACEI temocapril (T) 2 mg/day; C, ARB candesartan (C) 4 mg/day; T+C, T first and then addition of C; C+T, C first and then addition of C. ACR decreased in the T (*n*=34), C (*n*=40), T+C (*n*=37) and C+T (*n*=35) groups, but not in the N group (*n*=18). However, the anti-proteinuric effect was less in the T than in the C, T+C or C+T groups, while no differences existed among the latter three. In each group, there were significant linear relationships between attained BP and ACR; however, the regression lines were shifted toward lower ACR level in the renin-angiotensin system–inhibition groups compared with the N group. These results indicate that an ACEI and/or ARB is superior to a CCB in retarding diabetic nephropathy, while the combination of low doses of ACEI and ARB has effects similar to those of high-dose ARB. Even among patients treated with an ACEI and/or ARB, lowering BP is important. (*Hypertens Res* 2007; 30: 325–334)

***Key Words*: microalbuminuria, diabetic nephropathy, hypertension, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers**

Introduction

The renin-angiotensin system (RAS) plays an important role in the pathophysiology of diabetic nephropathy. Numerous studies have shown that inhibition of the RAS delays the progression of diabetic nephropathy (*1–4*). At present, two types of RAS inhibitors with different mechanisms of action are commonly used: angiotensin-converting enzyme inhibitor (ACEI), and angiotensin type 1 receptor blocker (ARB). It has been shown that both ACEIs and ARBs confer renal protection by reducing blood pressure (BP) and also by certain other mechanisms independent of their BP-lowering action. It has also been reported that low-dose combination therapy with ACEI temocapril and ARB losartan reduced proteinuria in normotensive patients with immunoglobulin

From the [1)]Division of Nephrology, Endocrinology and Vascular Medicine and [3)]Division of Clinical Epidemiology, Tohoku University School of Medicine, Sendai, Japan; and [2)]Division of Health Policy, School of Public Policy, Tohoku University, Sendai, Japan.

Address for Reprints: Susumu Ogawa, M.D., Ph.D., Division of Nephrology, Endocrinology, and Hypertension, Tohoku University Hospital, Seiryo-machi 1–1, Aoba-ku, Sendai 980–8574, Japan. E-mail: ogawa-s@mail.tains.tohoku.ac.jp

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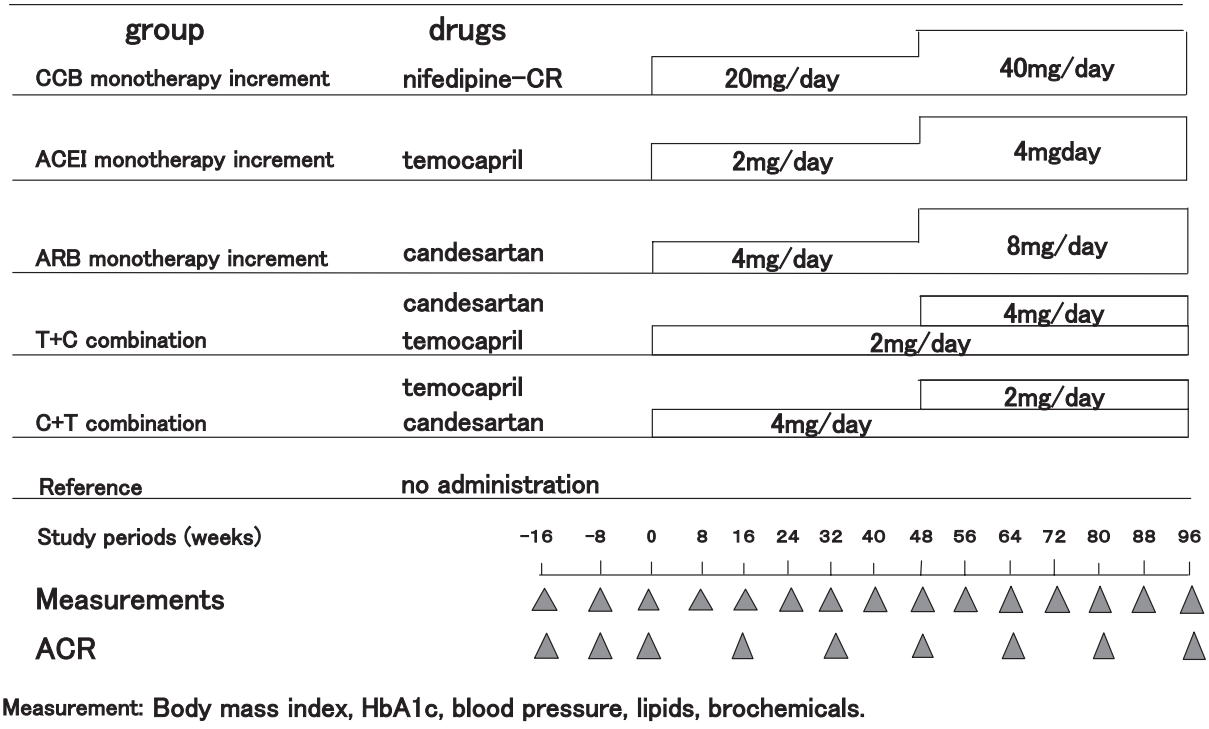

Fig. 1. *The protocol of this study.*

A nephropathy (*5*).

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA 2) has shown that the effects of ARB in reducing proteinuria and suppressing the progression to overt nephropathy are dose-dependent (*6*). It has also been reported that very high doses of ARB exert better antialbuminuric effects than the more commonly used doses (*7*). Moreover, recent studies indicate that dual blockade of the RAS with an ACEI and an ARB is superior to either drug alone in reducing proteinuria in diabetic patients (*8–11*). However, only a few studies have examined which of the two dosing regimens—monotherapy featuring dose increments or combination therapy—is more effective (*12*). In addition, the order of combination therapies, namely, adding an ARB to an ACEI (ACEI+ARB), or adding an ACEI to an ARB (ARB+ACEI), may be an important factor that influences the outcome in short term studies.

We therefore compared the albuminuria-reducing effects between monotherapy with dose increments and combination therapy of ACEI and ARB, and between ACEI+ARB therapy and ARB+ACEI therapy in hypertensive type 2 diabetic patients with microalbuminuria.

Methods

This is a single-blind randomized clinical study. Type 2 diabetic outpatients who met the following criteria were enrolled: 1) previously untreated moderate hypertension (130/80–200/110 mmHg); 2) microalbuminuria with a urinary albumin-to-creatinine ratio (ACR) of 100–300 mg/g creatinine (Cre) in all three measurements during the observation period; 3) glycated hemoglobin A1c (HbAlc)<8.0%; 4) no changes in medications or hospitalization during the past 3 years; 5) body mass index (BMI)<30 kg/m^2; 6) serum Cre<1.2 mg/dl; 7) no other renal diseases; 8) no severe cerebral or cardiovascular diseases or liver dysfunction; and 9) no active retinopathy. All the procedures were approved by the ethics committees of Tohoku University Hospital, and informed consent was obtained from all patients.

The study protocol is shown in Fig. 1. After a 16-week observation period, subjects were assigned to one of five groups: 1) a calcium channel blocker (CCB) nifedipine-CR (N) monotherapy group, in which 20 mg of N was administered for 48 weeks, and then the dose was increased to 40 mg for the following 48 weeks; 2) an ACEI temocapril (T) monotherapy group in which 2 mg of T was administered for 48 weeks, and then the dose was increased to 4 mg for the following 48 weeks; 3) an ARB candesartan (C) monotherapy group, in which 4 mg of C was administered for 48 weeks, and then the dose was increased to 8 mg for the following 48 weeks; 4) a T+C combination group in which 2 mg of T was administered for 48 weeks, and then 4 mg of C was added for the following 48 weeks; and 5) a C+T combination group in which 4 mg of C was administered for 48 weeks, and then 2 mg of T was added for the following 48 weeks (Fig. 1).

Routine examinations such as body weight (BMI), BP,

Table 1. Baseline Characteristics of the Subjects

Drugs	Monotherapy			Combination theapy		Control
	Nifedipine-CR	Temocapril (T)	Candesartan (C)	T+C	C+T	
Numbers	18	34	40	37	35	10
Sex (M/F)	8/10	16/18	19/21	18/19	17/18	5/5
Age (years)	63.9±3.3	60.9±2.4	62.2±2.5	61.8±2.4	62.5±2.5	61.1±2.3
Duration (years)	16.1±1.4	16.6±1.3	15.7±1.8	16.9±1.5	16.7±1.9	16.4±1.0
BMI (kg/m^2)	23.8±0.8	24.3±0.9	23.5±0.8	24.1±0.9	23.9±0.8	23.3±1.1
FPG (mg/dl)	139±12.2	124±7.9	133±9.4	134±7.9	137±9.4	135±7.4
HbA1c (%)	6.8±0.8	6.7±0.3	6.8±0.2	6.8±0.3	6.9±0.2	7.1±0.2
SBP (mmHg)	155±6.4	153±4.5	151±3.9	155±4.6	150±4.9	149±5.4
DBP (mmHg)	90.6±3.0	90.6±2.6	89.9±2.3	91.7±2.5	89.8±2.8	89.4±3.8
Cre (mg/dl)	0.66±0.05	0.77±0.05	0.78±0.04	0.72±0.05	0.70±0.04	0.88±0.44
TC (mg/dl)	190±9.6	210±7.4	204±5.8	199±7.4	188±5.8	213±10.0
TG (mg/dl)	116±12.9	115±12.1	96.8±9.6	97.6±12.1	108±9.6	119±16.5
HDL-C (mg/dl)	52.5±3.3	59.5±3.3	65.1±3.9	53.9±3.3	55.4±3.9	62.9±4.5

Mean±SEM. Control: no administration. M, male; F, female; BMI, body mass index; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; Cre, creatinine; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol.

HbA1c, and lipids (triglyceride; total cholesterol; high density lipoprotein cholesterol were conducted every 8 weeks, and ACR measurements were made every 16 weeks. The patients were followed up until 96 weeks of treatment. BP was measured with a mercury sphygmomanometer after the subject had rested at least 10 min and was determined by averaging the last two measurements. For urine collection, the subjects emptied their bladders completely at the outpatient clinic, after which they maintained a sitting position for 1 h or longer, and the urine was collected for measurement of ACR.

This study was carried out after providing the subjects with thorough information and obtaining their consent. Although we advised then to take antihypertensive drugs as needed, some wished to take the tests but not the medications, and expressed their desire to be followed up with dietary and exercise treatments only. Of these, 10 subjects whom we could follow up for 96 weeks were regarded as a reference group (the "No administration" group). Since this group was not randomized, however, no simple comparisons could be made, so we decided to feature them only as reference data.

Statistical Analysis

Baseline characteristics of the subjects were expressed as the mean±SEM, and their differences among the treatment groups were tested by ANOVA. Correlations were determined by the Spearman rank correlation test. ACR values were log-transformed. Temporal changes in systolic BP (SBP), diastolic BP (DBP), and ACR within each treatment group were tested with Wilcoxon signed rank test, and the differences among the treatment groups were tested by ANOVA with Tukey's multiple comparison. To examine the intergroup differences in the associations between ACR and SBP at week 96, multiple linear regression was used in which the outcome variable was ACR and the predictor variables were SBP and dummy variables for treatment groups. Values of $p<0.05$ were considered significant. All analyses were performed with Statview 5.0 (SAS Institute, Cary, USA).

Results

Table 1 shows the demographics of each group at randomization (week 0). In the N group, 20 subjects began taking the drug but only 18 managed to reach week 96. Dropout cases included 1 patient who complained of dizziness and palpitations immediately after starting the drug, and 1 who complained of similar symptoms immediately after dose increment. In the T group, 40 patients began taking the drug, with 34 reaching week 96. Dropout cases included 2 patients who complained of coughing immediately after starting the drug, 1 who complained of coughing immediately after dose increment, 1 who complained of dizziness and wooziness, and 2 who had their diabetes treatment changed. The C group had no dropout cases. In the T+C group, 3 out of 40 subjects dropped out of the study, because of coughing immediately after the administration of T (2 patients), or change in diabetes treatment (1 patient). In the C+T group, 5 out of 40 subjects dropped out of the study. Reasons for dropout were dizziness during administration of C (1 patient), coughing while taking T in combination (2 patients), change in diabetes treatment (1 patient) and hospitalization during the course (1 patient). No significant differences were seen among the six groups, including the reference group. The number of patients in each group who took oral hypoglycemic drugs was 7 in the N group, 15 in the T group, 16 in the C group, 14 in the T+C group, 14 in the C+T group, and 3 in the reference group. The

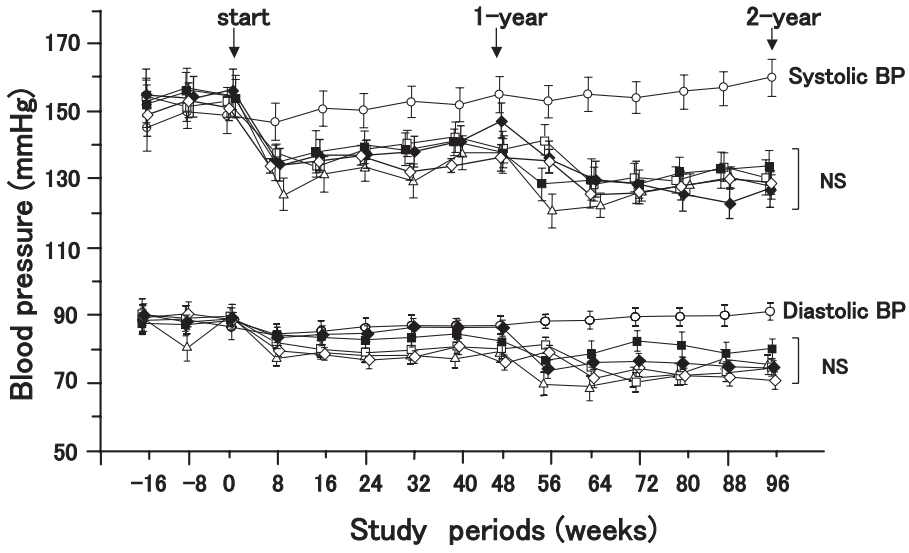

Fig. 2. *The lines represent changes of blood pressure (BP, mmHg). Patients were randomized to a nifedipine-CR monotherapy group (open triangles), temocapril monotherapy group (open squares), candesartan monotherapy group (open diamonds), temocapril+candesartan combination group (closed squares), or candesartan+temocapril combination group (closed diamonds) at 0 months after the 16-week observation period. The no treatment group is indicated by open circles. The data are expressed as the mean±SEM.*

Table 2. Urinary Albumin-to-Creatinine Ratio at Baseline and during Follow-Up in Subjects

Week	Monotherapy			Combination theapy		Control
	Nifedipine-CR	Temocapril (T)	Candesartan (C)	T+C	C+T	
−32	183 (109–283)	173 (117–277)	215 (129–294)	222 (101–286)	254 (144–285)	228 (150–243)
−16	220 (105–297)	227 (135–273)	209 (103–291)	220 (145–266)	203 (109–292)	208 (107–218)
Baseline (0)	235 (124–297)	245 (108–286)	238 (134–285)	235 (123–282)	261 (126–267)	247 (136–291)
16	156 (65–227)	136 (34–242)	108 (18–245)	139 (27–231)	125 (25–219)	228 (85–245)
32	208 (89–348)	156 (56–326)	139 (23–278)	169 (54–298)	129 (38–306)	309 (126–411)
48	225 (119–486)	188 (44–408)	147 (57–378)	180 (49–421)	164 (51–344)	289 (120–404)
64	181 (34–431)	121 (22–312)	68.9 (11–214)	104 (15–267)	50.2 (14–227)	347 (169–533)
80	217 (35–419)	138 (18–377)	83.9 (22–315)	66.5 (18–353)	54.3 (17–305)	364 (206–722)
96	228 (27–487)	145 (20–389)	73.5 (15–350)	60.3 (14–328)	47.3 (15–342)	354 (218–941)

Values are geometric mean (range). Control: no administration.

number of patients who underwent insulin therapy was 4 in the N group, 7 in the T group, 10 in the C group, 9 in the T+C group, 8 in the C+T group, and 0 in the reference group.

HbA1c levels, BMI and lipids levels did not change over the study period (96 weeks) in any treatment group.

Figure 2 shows the changes in BP. In the reference group, there were no reductions in either SBP or DBP, but elevation was observed from week 64 to 96. In all groups treated with antihypertensive drugs, SBP fell significantly (about 18 mmHg, $p<0.01$) with the initial dose, and dropped further (about 9 mmHg, $p<0.01$) after dose increments or combination treatment. DBP did not decrease significantly with the initial dose, but it dropped significantly (about 10 mmHg, $p<0.01$) after either dose increment or combination treatment. The BP values at week 96 were 127±5.0/78.8±3.4, 130±4.5/78.5±3.3, 128±4.7/74.3±3.9, 126±4.9/78.4±3.1, and 134±5.1/77.5±2.3 mmHg in the N, T, C, C+T and T+C group, respectively. There were no differences in BP among these five drug treatment groups. BP was 157±6.5/93.5±2.8 mmHg in the reference group.

Table 2 shows the absolute values of ACR from week 0 to 96. Figure 3 shows the changes in ACR value after logarithmic conversion in each group. Because ACR after logarithmic conversion showed a normal distribution, the values were expressed as the mean±SEM. The following studies were made using the post-logarithmic conversion figures.

In the reference group, ACR did not decrease; instead, it increased significantly, starting at week 32, and changed to

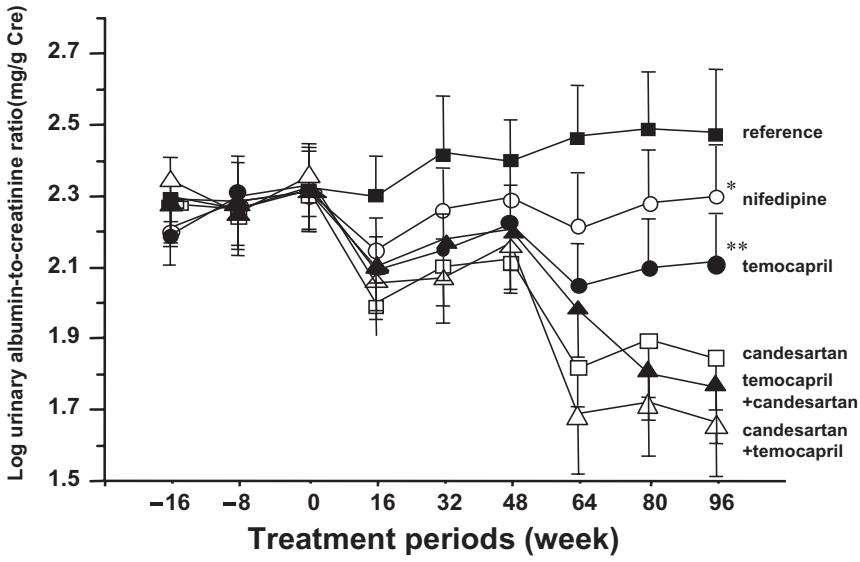

Fig. 3. *Changes in the logarithmic-converted albumin-to-creatinine ratio (ACR) in each group. Values are shown as the mean±SEM.*

overt albuminuria (mean value of ACR>300) after week 64. In the N group, ACR decreased at week 16 but subsequently increased, and the significant difference from baseline (week 0) disappeared at week 32 and 48. With dose increments, ACR decreased significantly ($p<0.01$) at week 64 as compared with both week 0 and 48. However, it rose again at week 80 and 96 with no significant differences compared with baseline (week 0) or week 48. The ACR values in the T, C, C+T and T+C groups decreased at week 16 as compared with week 0. However, they gradually increased at week 32 and 48, although the ACR value at week 48 remained significantly lower ($p<0.05$) than those at week 0 in all groups. After dose increment or combination, the ACR values in the T, C, C+T and T+C groups at week 64, 80 and 96 were significantly lower ($p<0.01$) than those at either week 0 or 48. In the T monotherapy group, the ACR value decreased after dose increment then tended to increase thereafter. In contrast, in the other three groups, namely, the C, C+T and T+C groups, ACR remained reduced. At week 48, no differences in ACR were seen among the N, T, C, C+T and T+C groups. At week 96, the N group showed a higher ACR value than the other four groups (*N groups *vs*. the other four groups), and the T group showed a higher ACR value than the C, C+T, and T+C groups (**T group *vs*. the other three groups).

The % changes in ACR at week 48 were −23.3±8.0%, −38.2±9.3%, −37.2±11.3%, and −23.2±8.4% in the T, C, C+T and T+C groups, respectively, and the differences among them were not significant. However, in the N group, the % change in ACR was −4.3±6.8%, a significantly smaller decrease as compared with the other groups ($p<0.001$). In the reference group, ACR increased by 19.9±4.5%. The % changes in ACR from baseline to week 96 were −40.8±10.7%, −69.1±11.3%, −81.9±13.5%, and −74.3±9.4% in the T, C, C+T and T+C groups, respectively. There were no significant differences among the C, T+C and C+T groups. However, the % decrease in ACR was significantly smaller in the T group as compared with the other three groups ($p<0.05$). In the N group, the % change in ACR was −3.0±7.9%, a significantly smaller decrease than in the other four groups ($p<0.01$). In the reference group, ACR increased by 46.9±7.9%.

Percent changes in ACR from week 48 to 96, *i.e.*, % changes in ACR attributable to either dose increment or combination. The % changes in ACR were −50.0±9.0%, −71.2±12.7%, and −66.6±9.2% in the C, C+T and T+C groups, and the differences among them were not significant. In contrast, in the T group, the % change in ACR was −22.9±10.9%, a decrease which was significantly ($p<0.05$) smaller than those observed in the above three groups, and was significantly larger than those observed in the T and reference groups.

The proportion of subjects who had progressed to overt albuminuria (ACR>300) at week 96 was 27.8% (5/18) in the N group, 17.7% (6/34) in the T group, 10.0% (4/40) in the C group, 8.6% (3/35) in the C+T group, 8.7% (3/37) in the T+C group, and 80.0% (8/10) in the reference group. The BP values of these subjects were 148±7.0/88.9±1.8, 151±8.5/88.4±1.2, 149±7.4/88.3±1.1, 146±3.9/88.4±1.6, and 149±7.1/87.3±1.2 mmHg in the N, T, C, C+T and T+C groups, respectively, with all of these subjects showing higher values than the average of each group during the same period. In the reference group, BP was 164±6.6/91.4±1.8 mmHg. The proportion of subjects who had improved to normoalbuminuria (ACR<30) at week 96 was 11.1% (2/18) in the N group, 14.7% (5/34) in the T group, 27.5% (11/40) in the C group, 22.9% (8/35) in the C+T group, 24.3% (9/37) in the

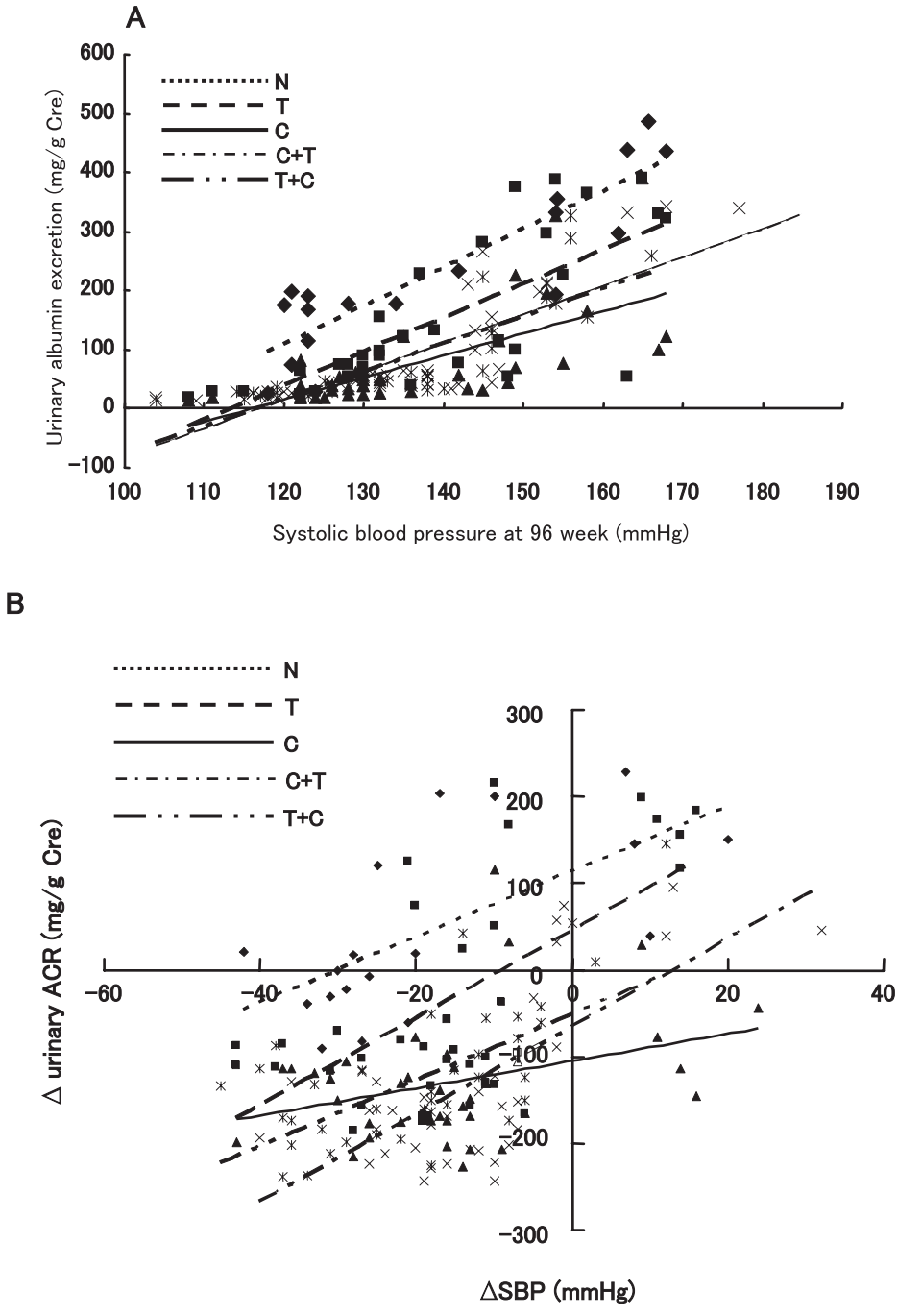

Fig. 4. *A: Relationship between the absolute value of achieved blood pressure (mmHg) and urinary albumin-to-creatinine ratio (ACR) at week 96. There was a significant relationship in each group. However, the regression line for the nifedipine-CR (N) group was shifted upward. N, nifedipine-CR monotherapy; T, temocapril monotherapy; C, candesartan monoterapy; C+T, candesartan+temocapril combination therapy; T+C, temocapril+candesartan combination therapy.* ◆*: N,* $y = 6.4995x - 670.84$, $r^2 = 0.742$, $p < 0.001$; ■*:T,* $y = 5.7542x - 651.42$, $r^2 = 0.563$, $p < 0.001$; ▲*:C,* $y = 3.7318x - 431.95$, $r^2 = 0.445$, $p < 0.001$; ×*: C+T,* $y = 4.8274x - 564.68$, $r^2 = 0.693$, $p < 0.001$; ✻*: T+C,* $y = 3.7855x - 433.15$, $r^2 = 0.564$, $p < 0.001$. *B: Relationship between the change in BP (ΔBP) and the change in the urinary albumin-to-creatinine ratio (ΔACR).* ◆*: N,* $y = 3.7703x + 113.61$, $r^2 = 0.425$, $p < 0.001$; ■*: T,* $y = 5.0245x + 45.028$, $r^2 = 0.390$, $p < 0.001$; ▲*: C,* $y = 1.5723x - 105.16$, $r^2 = 0.113$, $p < 0.001$; ×*: C+T,* $y = 5.0465x - 65.522$, $r^2 = 0.464$, $p < 0.001$; ✻*: T+C,* $y = 3.8103x - 50.981$, $r^2 = 0.406$, $p < 0.001$.

T+C group, and 0.0% (0/10) in the reference group. The BP values of these subjects were 118/76 or 124/78, 119±3.5/78.2±0.8, 120±2.8/74.0±0.6, 118±2.9/76.2±0.6, and 119±4.5/77.0±0.6 mmHg in the N, T, C, C+T and T+C groups respectively, with all of them showing lower values than the average for each group during the same period.

Figure 4A shows the relationship between the absolute value of attained SBP and ACR at week 96 in each group, while Fig. 4B shows the relationship between changes in BP (ΔSBP) and changes in ACR (ΔACR). In each treatment group, there was a significant positive linear correlation between attained SBP and ACR at week 96 as well as between ΔSBP and ΔACR. However, in the N group, the regression line was shifted upward as compared with the other treatment groups, indicating that, at the same BP, the RAS inhibitors can suppress ACR more powerfully than N. The regression lines did not differ significantly among the T, C, T+C, and C+T groups.

Discussion

The present study demonstrated that RAS inhibition with C and/or T was more effective than the calcium antagonist N for retarding nephropathy in hypertensive patients with early diabetic nephropathy. We found that a combination of the recommended initial doses of ACEI and ARB had effects similar to those by higher-dose ARB monotherapy. In addition, at the final observation, the lower the attained BP, the lower the ACR, even among patients treated with RAS inhibitors. Our results indicate that both achieving tight BP control and RAS inhibition are important in the management of patients with diabetic nephropathy.

In the reference group, 80% of the subjects progressed to overt nephropathy within 2 years. This clearly shows that unless antihypertensive treatment is provided, hypertensive type 2 diabetic patients with microalbuminuria carry a high risk of advancing to overt nephropathy in the present study was higher than the values previously reported (*6*, *13*). This may have been due to our selection criteria since we enrolled patients with a relatively high ACR range (100–300) within microalbuminuria.

Tight BP control is essential in order to prevent the development and progression of diabetic nephropathy. Based on the results of various large scale clinical trials, RAS inhibitors are now recommended as first-line drugs for the treatment of diabetic nephropathy (*14*). Studies suggest that RAS inhibitors may have renoprotective mechanisms independent of their BP-lowering action (*4*). On the other hand, a recent meta-analysis has indicated that the renoprotective effect of RAS inhibition may be largely explained by decreases in BP (*15*). However, demonstration of BP-independent renoprotective actions may depend on the achieved BP and the dose of RAS inhibitors. Indeed, a recent study by Rossing showed that reduction of ACR by irbesartan was greater at a dose of 900 mg than 300 mg, while there were no differences in 24 hour, daytime or nighttime BP levels (*6*). In the present study, we observed linear relationships between achieved BP and achieved ACR at the end of the study in all RAS inhibition groups. In addition, there were significant relationships between ΔSBP and ΔACR. Thus, up to the doses examined here, reduction of BP seems to play an important role in the anti-proteinuric mechanisms of RAS inhibition. It is possible that higher doses of ACEI, ARB or their combination would reduce proteinuria independently of BP levels.

It remains controversial whether CCBs confer renal protection in diabetes (*16*). Studies have shown that both CCBs and ACEIs were equally effective in blunting the decay of the glomerular filtration rate (GFR) in diabetic patients who did not have overt proteinuria (*17*). On the other hand, in patients with overt nephropathy the renal endpoints (end-stage renal disease and doubling of serum creatinine) were reduced significantly in the ARB group as compared with the CCB or placebo group, while no difference existed between the CCB and placebo group (*3*). The reason for such discrepant results is not apparent at present: however, it may be related to the level of BP, the stage of nephropathy and/or the duration of follow up. However, it seems clear that RAS inhibition more markedly reduced urinary albumin excretion in the range of both microalbuminuria and macroalbuminuria. Finally, Ruggenenti *et al*. have recently reported that trandolapril reduced the onset of nephropathy in type 2 diabetic patients, while verapamil had no effect (*18*). Consistent with these previous studies, we also observed that ACR did not change in the group treated with N (CCB), while great reductions were seen in the groups with RAS inhibition. However, further analysis of the N group revealed that ACR was reduced in those whose BP was tightly controlled, with a linear relationship between ΔSBP and ΔACR. Thus, the anti-albuminuric effect of CCBs may merely be due to their BP-lowering action. When compared with the N group, the RAS inhibition groups attained lower ACR at similar degrees of BP reduction. This may suggest that RAS inhibition may reduce urinary albumin excretion by mechanisms other than lowering BP.

According to large-scale clinical studies, the anti-albuminuric or anti-proteinuric effects of low-dose ACEIs and ARBs attenuate in the long run (*3*, *6*, *19*). On the other hand, IRMA 2 has shown that high-dose ARBs maintained anti-albuminuric effects for extended periods (*6*). Our studies are consistent with these previous studies in the anti-albuminuric effects of the low-dose ACEI and ARB waned over the period of 48 weeks. After the dose of the ARB was raised to a high level, however, its anti-albuminuric effects became stronger and persistent. On the other hand, the effects achieved by dose increment of the ACEI were much less pronounced, and the reason for this is not clear from the present study. It may be possible that even higher doses are needed for further reduction in ACR by an ACEI. Alternatively, an angiotensin II–producing pathway mediated by other than ACE and/or the

aldosterone breakthrough phenomenon may be involved (*20*–*22*).

The question of whether the combination of an ACEI and an ARB is superior to either drug alone, and if so, whether such effects are related to BP-reduction or dose is under active of investigation. Several studies have reported that dual blockade resulted in larger reductions in both ACR and BP (*8*, *10*). In the design of these studies, an ARB was added to the maximum dose of an ACEI, or high doses of an ACEI and an ARB were combined without dose adjustment. On the other hand, the Candesartan and Lisinopril Microalbuminuria (CALM) II study showed that 40 mg/day of lisinopril and the combination of 20 mg lisinopril and 16 mg candesartan caused similar reductions in both BP and ACR (*9*). In contrast, Fujisawa *et al*. reported that in patients with diabetic nephropathy who had been treated with an ACEI or ARB, halving the dose of the RAS inhibitor and combining it with a half dose of an other RAS inhibitor resulted in a significant reduction in ACR as compared with the value before combination (*23*). Since the BP was not affected by the change in therapy, they suggested that the combination therapy may confer a renal protective effect beyond BP lowering. Cetinkaya *et al*. carried out a study similar to ours but with a shorter follow-up period (24 weeks in total), and found that the combination of losartan 50 mg/day and enalapril 10 mg/day reduced ACR and BP more than monotherapy with enalapril 20 mg/day or losartan 100 mg/day (*12*). While the reasons for the apparent discrepancies among these studies—including the present study—are not clear, they may be due to the differences in the degree of nephropathy, duration of follow up, doses of RAS inhibitors and/or previous treatment. The present study is unique in that we enrolled only patients with both untreated hypertension and late-stage microalbuminuria, and in that we followed these patients for a relatively long period (2 years).

In the present study, addition of an ACEI or ARB at week 48 resulted in further reductions in both BP and ACR. It is worth noting that this combination of initial recommended doses generated anti-albuminuric effects that were comparable to those of high-dose ARB. In addition, the order of combination did not make any difference in either the BP-lowering or the anti-albuminuric effect. The mechanisms responsible for the excellent effects of the combinations may involve more complete blockade of RAS, activation of angiotensin type 2 receptors, and/or increased levels of bradykinins and *N*-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) (*24*–*28*). We have recently shown that in patients with diabetic nephropathy, addition of an ARB to an ACEI reduced both BP and ACR, and the reduction of ACR was closely associated with the reduction of urinary markers of oxidative stress (*29*). It is therefore possible that the combination therapy may have reduced renal oxidative stress significantly more than the initial doses. Yagi *et al*. have reported that combined treatment with an ARB and ACEI has an additive effect on inhibiting neointima formation *via* improvement of nitric oxide production and suppression of oxidative stress (*30*). However, we can speculate on these issues in the present study, since we did not examine urinary markers other than ACR.

In the present study, the rate of progression to overt nephropathy in the N group (27.8%) was higher than that in the C monotherapy or combination groups (8.6–10.0%). The progression rate of the N group was also higher than that of the placebo group (14.9%) in the IRMA 2 study (*6*). The progression rate in the C monotherapy or combination groups of the present study was similar to that reported for the low-dose irbesartan group (9.7%) but higher than that reported for the high-dose group (5.2%) in the IRMA 2 study (*6*). These differences may have been due to differences in the doses used or the demographics of patients, such as the stage of microalbuminuria at enrollment.

In the Microalbuminuria Reduction with Valsartan (MARVAL) study, which compared the anti-albuminuric effect of the CCB amlodipine and the ARB valsartan in diabetic patients with microalbuminuria, the rate of ACR normalization was 14.5% with the CCB and 29.9% with the ARB after a 24-week follow-up period (*4*). In the IRMA 2 study, the normalization rates were 34% and 24% with the high and low doses of irbesartan, respectively, while that in the placebo group was 21% (*6*). In the present study, the normalization rate in the C monotherapy or combination groups (23–28%) was higher than that of the N group (11.1%). The normalization rate in the C monotherapy or combination groups was comparable to that achieved with valsartan in the MARVAL study or with low-dose irbesartan in the IRMA 2 study (*4*, *6*). However, this rate seems somewhat lower than that achieved with high-dose irbesartan in IRMA 2 study. While there are differences in the demographics of the subjects or the protocols among the studies, these results suggest a strong possibility that diabetic microalbuminuria can regress to normoalbuminuria in a decent proportion through active interventions for tight BP control and RAS inhibition. This notion is consistent with the recent report that remission to normoalbuminuria was strongly associated with RAS inhibition and antihypertensive treatment in Steno type 2 randomized Study (*31*). In the light of recent publications suggesting that reduction of ACR reduces the risk of end-stage renal disease and cardiovascular events, it is important to monitor not only BP but also ACR quantitatively (*32*).

Conclusion

In hypertensive patients with early diabetic nephropathy, an ACEI and/or an ARB is superior to a CCB in retarding nephropathy, while the combination of the recommended initial doses of an ACEI and an ARB has effects similar to those by high-dose ARB monotherapy. Even among patients treated with an ACEI and/or ARB, lowering BP is important. Although no generalizations can be made since the systems for medical care differ from country to country, ARBs often

cost more than ACEIs. Thus, using a combination of a low-dose ARB and ACEI would cost less than increasing the dose of the ARB. From an economical point of view, therefore, the combination of low doses of an ACEI and an ARB should be considered before increasing the dose of ARB.

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