Original Article

In Half of Hypertensive Diabetics, Co-Administration of a Calcium Channel Blocker and an Angiotensin-Converting Enzyme Inhibitor Achieved a Target Blood Pressure of <130/80 mmHg: The Azelnidipine and Temocapril in Hypertensive Patients with Type 2 Diabetes (ATTEST) Study

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We conducted a multicenter, randomized, open-label, ascending dose study to investigate the efficacy and safety of combination therapy using the calcium channel blocker azelnidipine and angiotensin-converting enzyme (ACE) inhibitor temocapril in hypertensive diabetics. Patients received monotherapy with 8 mg azelnidipine (group A, *n*=112) or 2 mg temocapril (group T, *n*=111) for 4 weeks. If the target blood pressure (<130/80 mmHg) was not achieved, doses were doubled. If it was still not achieved, both drugs were coadministered at week 8, and, if needed, another antihypertensive drug was added after week 16. The treatment period was 52 weeks. Blood pressure was decreased significantly beginning at week 8 (*p*<0.0001 in both groups), and the systolic and diastolic blood pressure at the end of the treatment period was 128.2±11.1/76.4±8.1 mmHg. Overall, 53.8% (113/210) of patients achieved the target blood pressure by the end of the study. The effect during the monotherapy period (through week 8) was greater in group A than in group T (systolic, *p*=0.0475; diastolic, *p*=0.0001). Laboratory tests showed significant decreases in the urine albumin:creatinine ratio (*p*=0.0006), high-sensitivity C-reactive protein concentration (*p*=0.0073), and urine 8-isoprostane concentration (*p*=0.0215) at the end of the treatment period, as compared with baseline values. No adverse events caused safety problems. In conclusion, combination therapy using azelnidipine and temocapril is an effective treatment for hypertensive diabetics. (*Hypertens Res* 2008; 31: 1499–1508)

***Key Words*: combination therapy, hypertensive diabetics, target blood pressure, azelnidipine, temocapril hydrochloride**

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Introduction

For the antihypertensive treatment of patients with hypertension and diabetes, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommends angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists, which improve insulin sensitivity, as first-choice drugs, in addition to long-acting dihydropyridine-type calcium channel blockers (*1*). This recommendation is based on the results of large-scale clinical studies such as the UK Prospective Diabetes Study (UKPDS) (*2*) and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (*3*). Moreover, the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004) also recommend these three types of antihypertensive drug as initial therapy (*4*). The target blood pressure in hypertensive diabetics is $<$130 mmHg (systolic)/ $<$80 mmHg (diastolic), which necessitates rigid blood pressure control (*5*, *6*). Coadministration of two or more drugs with different pharmacological actions is generally used to achieve this target blood pressure.

The Fosinopril *versus* Amlodipine Cardiovascular Events Randomized Trial indicated that in hypertensive diabetics, the development of cardiovascular diseases is inhibited more by coadministration of a calcium channel blocker and an ACE inhibitor than by monotherapy with these drugs (*7*). Accordingly, the concomitant use of a calcium channel blocker and an ACE inhibitor is considered desirable for prognosis, as well as for blood pressure control and the reduction of adverse reactions.

With reference to the recent findings described above, azelnidipine was selected as the calcium channel blocker and temocapril hydrochloride as the ACE inhibitor, for patients with mild to moderate hypertension complicated by type 2 diabetes mellitus. The present study was conducted to investigate the rate at which patients achieve the JNC 7 target blood pressure ($<$130/ 80 mmHg) upon receiving monotherapy or combination therapy with these drugs.

Calcium channel blockers have less influence on glucose and lipid metabolism, whereas ACE inhibitors improve glucose metabolism (*8*). However, the influence of the concomitant use of these drugs on glucose and lipid metabolism has not been fully investigated. Thus, the influence of combination therapy with a calcium channel blocker and an ACE inhibitor on these processes was investigated. The influence of tight blood pressure control on renal function and the long-term safety of the drugs were also examined.

Methods

Subjects

The subjects enrolled in this study were male and female patients (30–80 years old) who visited 24 centers nationwide between May 1, 2004, and June 30, 2006, and who displayed mild to moderate hypertension (systolic blood pressure of 140–180 mmHg and diastolic blood pressure of 90–110 mmHg, both determined in the sitting position) associated with type 2 diabetes mellitus.

Patients fulfilling the exclusion criteria were those with secondary hypertension or malignant hypertension; those who had onset of myocardial infarction, had received coronary bypass graft, or had undergone percutaneous coronary intervention in the 3 months before giving their informed consent; those with unstable angina pectoris and severe heart failure; those with grade II to III atrioventricular block, atrial fibrillation, or serious arrhythmia; those using a pacemaker; those who had onset of cerebrovascular disorder in the 3 months prior to giving their informed consent; those requiring treatment for malignant tumor or receiving immunosuppressants; those with hepatic function disorder; those with renal function disorder; those with type 1 diabetes mellitus or receiving insulin treatment; those with poor glycemic control (human hemoglobin A1c protein [HbA1c] $\geq$8% despite treatment with oral hypoglycemic drugs); and those whose concentration of the inflammatory marker high-sensitivity C-reactive protein (hs-CRP) might be affected by other conditions (patients who had a bacterial infection, a collagen disorder, or significant trauma or extensive heat burn).

The study was conducted according to the Declaration of Helsinki and complied with good clinical practice. Before the study, the approval of the institutional review boards of the participating medical institutions was obtained. Written informed consent was also obtained from each patient before the study began.

Study Design

The study was designed as a multicenter, randomized, open-label, ascending dose study. When patients were taking an antihypertensive drug before giving their informed consent, a 4-week washout period preceded the observation period.

During the 4-week observation period, blood pressure and heart rate were determined at least twice. Further tests (hematologic tests, serum chemistry, glucose and lipid metabolism, renal function, and concentrations of inflammatory and oxidative stress markers) were conducted, and patients who qualified for the study were enrolled.

The enrolled patients were assigned to either the azelnidipine group (group A) or the temocapril hydrochloride group (group T) (Fig. 1). Patient allocation was carried out by the permuted block method using the institution as a stratum so as to assign a balanced number of patients to the two groups.

Eight milligrams of azelnidipine and 2 mg temocapril hydrochloride were administered to patients in group A and group T, respectively. Each drug (one tablet daily) was taken orally after breakfast. If the patient failed to achieve the target blood pressure after 4 weeks, the doses of azelnidipine and

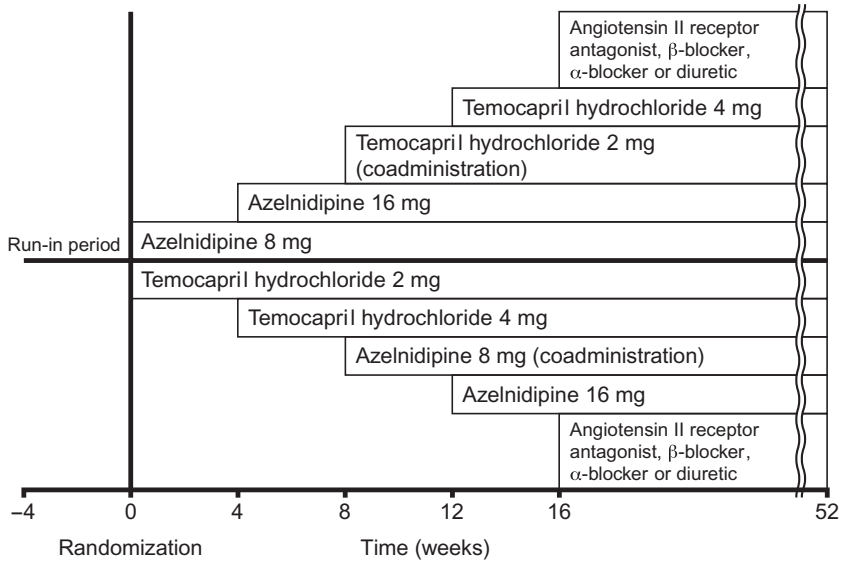

Fig. 1. *Study design.*

temocapril hydrochloride were increased to 16 and 4 mg, respectively. If the target blood pressure was not achieved by week 8, temocapril was coadministered to the patients in group A and azelnidipine to those in group T. When the effect was still insufficient at week 16 despite treatment with the maximum doses of these drugs, a new antihypertensive drug (other than a calcium channel blocker or an ACE inhibitor) was used in combination, and the patients were observed until week 52.

Patients were asked to visit their hospital every 4 weeks during the 52-week treatment period, and their blood pressure and heart rate were determined at each visit. Fasting blood and urine were collected and tests were carried out at weeks 8, 16, 28, and 52, or the time of discontinuation. Using the urine sample, albumin and creatinine concentrations were determined to calculate the urine albumin:creatinine ratio (ACR).

As the primary outcome parameter, the percentage of patients who had achieved the target blood pressure was calculated at the end of the treatment period. As the secondary outcome parameter, a decrease in blood pressure from measurements taken in the observation period was calculated. Concerning glucose and lipid metabolism, renal function, and concentrations of inflammatory and oxidative stress markers, changes at each time point from the baseline values were calculated, and their relationships to blood pressure decrease were investigated.

In week 8 of the treatment period, an assessment similar to that described above was made separately for group A and group T, allowing for intergroup comparison.

For the investigation of glucose metabolism, insulin concentrations were determined by radioimmunoassay, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the equation

$$\text{HOMA-IR} = \text{fasting plasma glucose concentration (mg/dL)} \times \text{insulin concentration (}\mu\text{U/mL)}/405.$$

Concentrations of the inflammatory marker hs-CRP were determined by nephelometry. Concentrations of the oxidative stress markers, urine 8-isoprostane and urine 8-hydroxy-2′-deoxyguanosine (8-OHdG), were determined by enzyme immunoassay and concentrations of malondialdehyde-modified low-density lipoprotein (MDA-LDL) by enzyme-linked immunosorbent assay (ELISA). The urinary albumin concentration was determined by enzyme immunoassay.

Target Number of Patients

When the percentage of patients achieving the target blood pressure by week 52 was assumed to be 70% (group A and group T combined), the number of patients whose 95% confidence interval based on the normal approximation of binominal distribution was calculated at a precision of ±7% was 165. When the significance level and power of detection were assumed to be $\alpha = 5\%$ (two-tailed) and 80%, respectively, and when the percentages of patients in group A and group T achieving the target blood pressure by week 8 were assumed to be 50 and 30%, respectively, the number of patients required per group was 93.

By allowing the percentage of dropout patients to be ~5% by week 8 and ~10% by week 52 of the treatment period, the required number of patients became 200.

Statistical Analysis

A full analysis set was used for the analysis of primary effi-

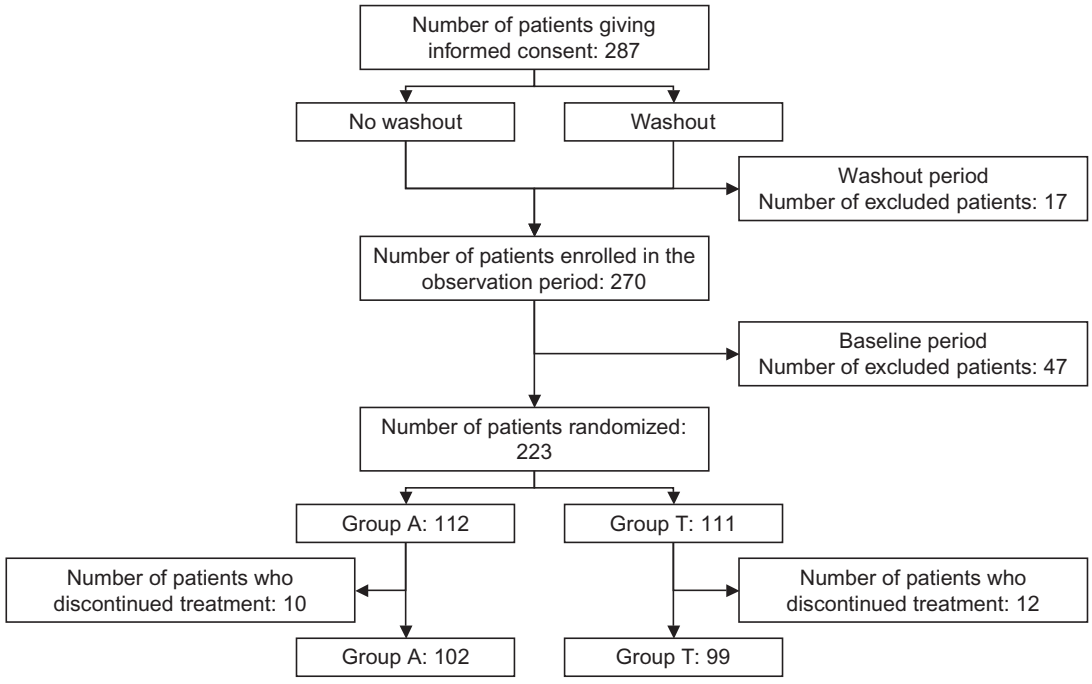

Fig. 2. *Trial profile.*

cacy. All patients who received the study drug even once were included in the safety analysis. The last observation carried forward method was used on the data upon completion of drug administration. Continuous data were expressed as mean±SD, but medians (quartile 1, 25% points, to quartile 3, 75% points) were also used for values that did not conform to the normal distribution hypothesis. Categorical data were expressed as percentages.

Changes in systolic and diastolic blood pressure, heart rate, glucose metabolism, lipid metabolism, renal function, and concentrations of inflammatory and oxidative stress markers at each time point within the group were analyzed using the paired *t*-test. Since changes in renal function and hs-CRP concentration did not conform to the normal distribution hypothesis, intragroup comparisons were also made using the Wilcoxon signed rank test. For intergroup comparisons of systolic and diastolic blood pressure, heart rate, glucose and lipid metabolism, and oxidative stress markers at week 8 of the treatment period, the *t*-test was used. For intergroup comparisons of renal function and concentrations of hs-CRP, the Wilcoxon signed rank sum test was used. For the achievement of the target blood pressure, the percentage of patients who achieved the target blood pressure and its 95% confidence interval at each time point were calculated. For intergroup comparisons at week 8, the Fisher exact test was used.

The Medical Dictionary for Regulatory Activities/J version 9.0 was used for the coding of adverse events and adverse reactions. SAS version 8.2 (SAS Institute Inc., Cary, USA) was used in the analysis.

Results

Disposition of Patients

Figure 2 shows the numbers of patients at each stage of the study. Major reasons for discontinuation were the onset of adverse events (four patients in group A and five in group T), withdrawal of informed consent (two and one, respectively), and other reasons given by patients (two and one, respectively).

On completion of the study, the management of the randomized 223 patients was investigated. Thirteen patients (five in group A and eight in group T) were excluded from the analysis because both their fasting plasma glucose and HbA1c concentrations in the 6 months before the start of the study or during the observation period were below the concentrations necessary to fulfill the diagnostic criteria for diabetes mellitus. As a result, 210 patients were included in the analysis of efficacy. All randomized patients were included in the safety analysis.

Patient Characteristics

Table 1 summarizes the characteristics of the patients who participated in the study. The two groups were comparable.

Table 1. Patient Characteristics

	Group A	Group T	Total
n	107	103	210
Age (years)	60.3±9.5	58.2±10.2	59.3±9.9
No. of men	78 (72.9%)	66 (64.1%)	144 (68.6%)
Height (cm)	162.55±9.17	161.83±8.41	162.20±8.80
Body weight (kg)	69.16±12.89	68.88±13.63	69.02±13.23
Body mass index	26.11±3.91	26.18±4.06	26.14±3.97
Duration of hypertension (years)[a]	6.35±6.05	6.83±8.55	6.59±7.39
Baseline systolic blood pressure (mmHg)	154.8±9.5	155.5±9.5	155.2±9.5
Baseline diastolic blood pressure (mmHg)	95.3±4.9	94.8±4.4	95.1±4.7
Baseline heart rate (beats/min)	73.1±7.8	72.8±7.8	72.9±7.8
HbA1c (%)	6.48±0.81	6.44±0.75	6.46±0.78
Fasting plasma glucose (mg/dL)	133.9±31.1	130.7±26.7	132.3±29.0
LDL-cholesterol (mg/dL)	128.7±30.5	128.5±31.3	128.6±30.8
Triglyceride (mg/dL)	153.0±117.8	157.3±111.7	155.1±114.5
Albumin:creatinine ratio (mg/g creatinine)	106.10±246.71	178.74±603.61	141.73±458.26
High-sensitivity C-reactive protein (ng/mL)	1,350.1±1,625.2	1,322.8±2,049.0	1,336.5±1,843.8
No. of smoker	24 (22.4%)	32 (31.1%)	56 (26.7%)

Data expressed as mean±SD, unless otherwise indicated. [a]For 90 patients in each group (total 180). Patients for whom the duration of hypertension was uncertain are excluded. LDL, low-density lipoprotein; group A, azelnidipine group; group T, temocapril hydrochloride group.

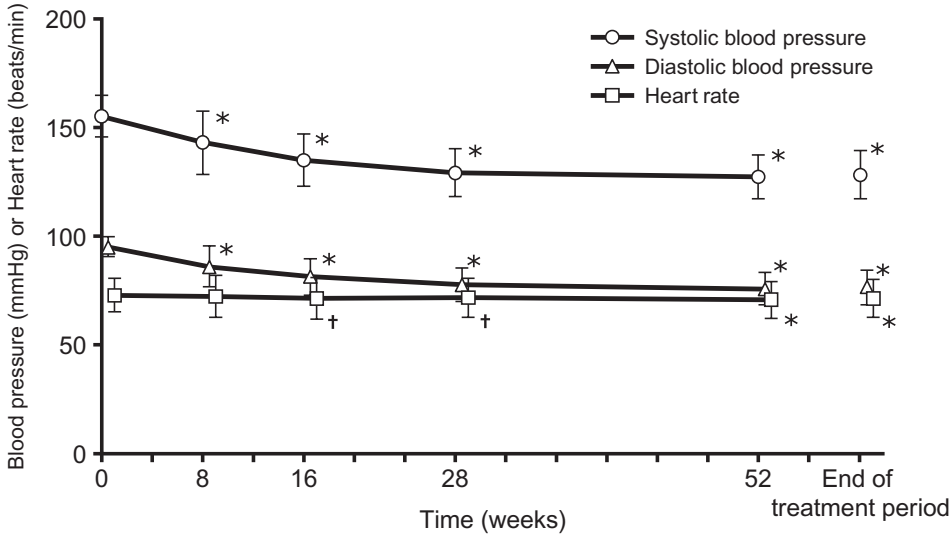

Fig. 3. *Changes in blood pressure and heart rate (mean±SD). *p<0.001; †p<0.05.*

Blood Pressure and Heart Rate

Figure 3 shows changes in blood pressure throughout the study in all patients analyzed. A significant decrease in blood pressure was observed from week 8 of the treatment period onward. The systolic and diastolic blood pressure at the end of the treatment period was 128.2±11.1/76.4±8.1 mmHg. Heart rate decreased significantly beginning in week 16 in all patients analyzed and at the end of the treatment period was 71.2±8.7 beats/min (Fig. 3).

When the systolic and diastolic blood pressure was compared between groups A and T, the measurements at week 8 and at the end of the treatment period were 140.8±13.2/84.3±9.7 mmHg and 126.9±10.9/75.9±7.8 mmHg, respectively, in group A, and 145.0±15.8/87.8±8.5 mmHg and 129.6±11.1/77.0±8.5 mmHg, respectively, in group T. The results of intragroup comparison indicated a significant decrease at both week 8 and the end of the treatment period,

Table 2. Control Rate of Blood Pressure (<130/80 mmHg)

	Week				End of treatment period
	8	16	28	52	
All patients	10.5% (22/210)	23.9% (48/201)	41.3% (81/196)	58.2% (110/189)	53.8% (113/210)
Group A	13.1% (14/107)	—	—	—	58.9% (63/107)
Group T	7.8% (8/103)	—	—	—	48.5% (50/103)

Group A, azelnidipine group; group T, temocapril hydrochloride group.

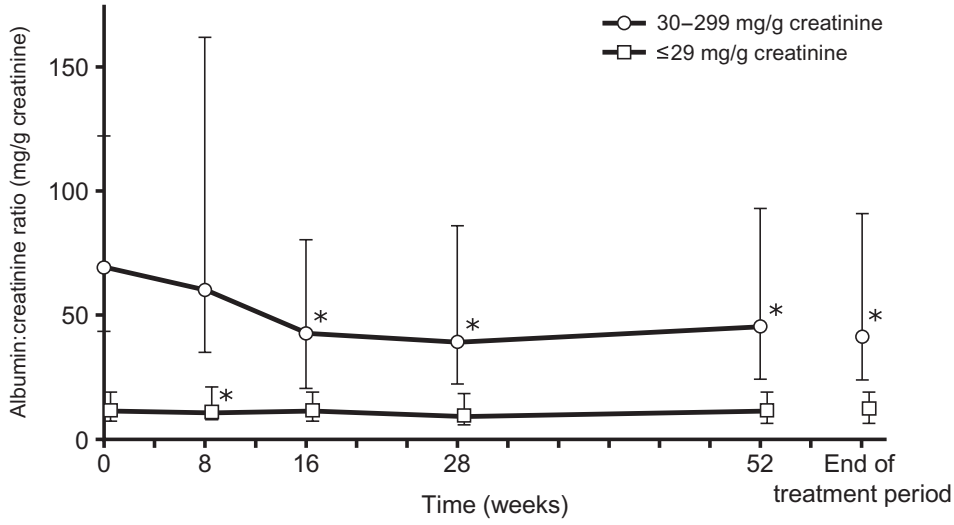

Fig. 4. *Changes in albumin:creatinine ratio (median: quartile 1 to quartile 3) stratified by classification stage of diabetic nephropathy in patients with ≤29 mg/g creatinine (n=105) and 30–299 mg/g creatinine (n=84). *p<0.05.*

in comparison with baseline measurements ($p<0.0001$ in both groups).

According to the intergroup comparison, differences in the decreases in systolic and diastolic blood pressure at week 8 of the treatment period, expressed as measurements for group A minus those for group T (95% confidence interval), were −3.4 (−6.8 to 0.0) and −4.1 (−6.1 to −2.1) mmHg, respectively, indicating a significantly larger decrease in group A than in group T (systolic blood pressure, $p=0.0475$; diastolic blood pressure, $p=0.0001$). The group A minus group T difference (95% confidence interval) in heart rate was −1.1 (−3.3 to 1.1) beats/min. Although there was no significant difference between the groups, the heart rate decreased more in group A than in group T ($p=0.3398$).

Table 2 shows the percentages of patients who achieved the target blood pressure at each time point assessed during the study. More patients achieved the target blood pressure as the study progressed, with more than half achieving the target by the end of the treatment period.

More patients in group A than in group T had achieved the target blood pressure at week 8 (*i.e.*, during the monotherapy period) and by the end of the treatment period, although the difference between the two groups was non-significant.

Patients were taking an average of 2.2 antihypertensive drugs at the end of the treatment period. Hypertension was controlled in 20.5% of patients by monotherapy with azelnidipine or temocapril hydrochloride (in 11.9 and 8.6%, respectively) through the end of the study. When monotherapy failed to achieve the target blood pressure, azelnidipine and temocapril hydrochloride were used concomitantly. Hypertension was controlled by these drugs alone in 47.1% of all patients, while 31.4% required treatment with three or more drugs. An angiotensin II receptor antagonist was most frequently used as the third drug (20.5% of all patients).

Glucose and Lipid Metabolism, Renal Function, and Other Tests

Compared with baseline levels, concentrations of fasting plasma glucose and HbA1c were higher at all the assessment times following the start of drug administration. Fasting plasma glucose increased significantly, from 132.3±29.0 mg/dL at the baseline period to 141.4±36.7 mg/dL at the end of the treatment period. HbA1c also increased significantly, from 6.46±0.78% to 6.90±1.05% (intragroup comparison; fasting plasma glucose, $p=0.0003$; HbA1c, $p<0.0001$). How-

Table 3. Change in Stage Classification of Diabetic Nephropathy (by Albumin:Creatinine Ratio) before and after Treatment

	n	ACR at end of treatment period (mg/g creatinine)		
		≤29	30–299	≥300
Baseline ACR (mg/g creatinine) ≤29	105	92	12	1
30–299	84	32	46	6
≥300	21	0	9	12

ACR, albumin:creatinine ratio.

Table 4. Changes in the Concentration of High-Sensitivity C-Reactive Protein and 8-Isoprostane throughout the Study

	n	Mean±SD	Median[a]	Changes from baseline	95% confidence interval[b]	*p*[c]
High-sensitivity C-reactive protein (ng/mL)						
Baseline	207	1,336.5±1,843.8	732.0	—	—	—
Week 8	195	1,230.4±2,261.2	661.0	−65.0	−140.0 to 2.0	0.0053
Week 16	185	1,258.6±2,070.2	634.0	−68.0	−132.0 to −9.0	0.0105
Week 28	183	1,104.8±1,524.5	617.0	−87.0	−128.0 to −23.0	0.0024
Week 52	176	1,202.8±1,640.0	684.5	−38.5	−90.0 to 25.0	0.0311
End of treatment period	195	1,173.9±1,587.6	690.0	−55.0	−95.0 to 8.0	0.0073
8-Isoprostane (U/L)						
Baseline	30	179.70±102.64	170.00	—	—	—
Week 8	28	145.7±84.7	135.00	−24.5	−73.44 to −5.49	0.0244
Week 16	27	175.96±109.07	130.00	−14.22	−50.74 to 22.29	0.4306
Week 28	27	147.52±85.52	120.00	−42.67	−82.06 to −3.27	0.0349
Week 52	27	139.63±86.03	130.00	−50.56	−89.73 to −11.39	0.0134
End of treatment period	30	135.80±83.91	120.00	−43.90	−80.84 to −6.96	0.0215

[a]Median for high-sensitivity C-reactive protein and mean for 8-isoprostane. [b]Confidence interval of the median for high-sensitivity C-reactive protein and confidence interval of the mean for 8-isoprostane. [c]Wilcoxon signed rank test for high-sensitivity C-reactive protein and intragroup comparison by paired *t*-test for 8-isoprostane.

ever, no changes occurred in the insulin concentration or HOMA-IR during the baseline period or at all time points during the treatment period. In addition, no specific trends were observed in the serum lipid concentrations.

However, the urine ACR (median: quartile 1 to quartile 3) decreased significantly, from 31.0 (11.2–88.0) mg/g creatinine during the baseline period to 23.3 (10.9–66.5) mg/g creatinine at the end of the treatment period (intragroup comparison; $p=0.0006$). When a subgroup analysis was conducted according to nephropathy disease stage, a marked decrease in urine ACR was observed in patients with microalbuminuria whose urine ACR during the baseline period was 30–299 mg/g creatinine (Fig. 4).

The urine ACR at the end of the treatment period was further investigated by stratifying patients into those with normoalbuminuria, microalbuminuria, and proteinuria based on their urine ACR at the start of treatment. As shown in Table 3, the measurements were normalized (normoalbuminuria) in 32 (38.1%) of the 84 patients who had microalbuminuria at the start of the study, while proteinuria at the start of treatment was improved to microalbuminuria in 9 (42.9%) of the 21 patients.

The hs-CRP concentration decreased significantly, from 732 (400–1,470) ng/mL (median: quartile 1, 25% points, to quartile 3, 75% points) during the baseline period to 690 (351–1,150) ng/mL at the end of the treatment period (intragroup comparison; $p=0.0073$) (Table 4).

Of the oxidative stress markers, the concentration of urine 8-isoprostane decreased significantly, from 179.70±102.64 U/L during the baseline period to 135.80±83.91 U/L at the end of the treatment period (intragroup comparison; $p=0.0215$) (Table 4). However, no specific changes occurred in the concentration of urine 8-OHdG or MDA-LDL during the baseline period or at all time points during the treatment period.

No significant differences between group A and group T were observed for any of the above-mentioned variables.

When the relation between achievement or non-achievement of the target blood pressure and glucose and lipid metabolism, renal function, and concentrations of hs-CRP and oxidative stress markers was investigated, no special relation was observed for any of these variables. In addition, when the relationship between the decrease in blood pressure and changes in each of these variables was investigated using regression analysis, no significant correlation was observed for any of the variables.

Safety

Subjective symptoms and objective findings were noted in 81.2% (181/223) of patients, and adverse events directly attributable to either of the drugs occurred in 19.7% (44/223). There were no deaths, but serious adverse events occurred in 15 patients. Only two of these events (stomach cancer and atrioventricular block) could be directly attributable to the drugs and therefore judged as adverse reactions. The most frequently reported adverse reaction was cough (16.1%; 36/223 patients). All these cases were judged to be adverse reactions to temocapril hydrochloride.

When stratified by drug, subjective symptoms and objective findings were observed in 72.7% (149/205) of patients and adverse reactions occurred in 2.4% (5/205) after the start of azelnidipine administration, while they were 76.5% (156/204) and 21.1% (43/204), respectively, in the temocapril hydrochloride group.

Abnormal changes in laboratory test results occurred in 58.1% (129/222) of patients overall and adverse reactions in 2.7% (6/222). The most frequently reported adverse reaction was an increase in blood potassium concentration (0.9%; 2/222). When stratified by drug, abnormal changes in laboratory test results occurred after the start of administration in 50.7% (104/205) of patients and adverse reactions in 1.5% (3/205) in the group administered azelnidipine, while they were 55.4% (112/202) and 3.0% (6/202) of patients in the group administered temocapril hydrochloride.

Discussion

Antihypertensive Effect, Control Rate of Blood Pressure, and Heart Rate

According to JSH 2004, the American Diabetes Association recommendations, JNC 7, and the European Society of Hypertension–European Society of Cardiology recommendations, the target blood pressure for antihypertensive treatment for patients with hypertension and diabetes is $<130/80$ mmHg (systolic/diastolic blood pressure), necessitating strict blood pressure control. Because the control of blood pressure in hypertensive diabetics is generally difficult, it is considered necessary to concomitantly administer two or more drugs with different pharmacological actions to achieve the target blood pressure (*4*).

In the present study, patients were treated concomitantly for 52 weeks with the long-acting dihydropyridine-type calcium channel blocker and an ACE inhibitor, which are both recommended as initial antihypertensive drugs for hypertensive diabetics. As a result, the percentage of patients who achieved the target blood pressure by the end of the treatment period was 53.8% overall, and their final blood pressure was decreased to 128.2/76.4 mmHg, which is below the target blood pressure. The mean number of antihypertensive drugs required to lower the blood pressure was 2.2, and it was confirmed that there were no safety problems with the number of drugs used. JSH 2004, JNC 7, and other studies established $<130/80$ mmHg as the target blood pressure in hypertensive diabetics based on the inhibition of cardiovascular events and safety in lowering blood pressure observed in the Hypertension Optimal Treatment study (*9*) and UKPDS (*2*). The result achieved in the present study was below this target, and the percentage of patients who achieved the target blood pressure exceeded 50%, a better result than has been reported by previous studies (*10–12*). Thus, the results of the present study show the utility of combination therapy based on azelnidipine and temocapril hydrochloride.

According to the results of stratified analysis using each group as a factor, the decrease in blood pressure in group A was significantly higher than that in group T until week 8, that is, during the monotherapy period. This result shows the usefulness of azelnidipine in hypertensive diabetics, indicating its strong antihypertensive effect and the rapid onset of its effect. As in the case of blood pressure, the heart rate was decreased significantly in and after week 16 of the treatment period. This result is assumed to be attributable to the effect of concomitant azelnidipine—that is, not caused by reflex sympathetic stimulation (*13*).

Influence on Glucose and Lipid Metabolism, Renal Function, and Other Tests

Considering changes in glucose and lipid metabolism, renal function, and concentrations of oxidative stress and inflammatory markers at the end of the treatment period, concentrations of fasting plasma glucose and HbA1c were increased significantly whereas the urine ACR and urine 8-isoprostane and hs-CRP concentrations were decreased significantly, and therefore improved. Although fasting plasma glucose and HbA1c concentrations were increased significantly, no change occurred in the insulin concentration or insulin resistance indices, including the HOMA-IR, indicating that not all glucose metabolism measurements worsened. As the changes in glucose metabolism variables showed no correlation with the decrease in blood pressure or whether the target blood pressure was achieved, these changes were unrelated to the antihypertensive effect. Because no changes in the treatment of diabetes mellitus were allowed during the study, it is highly likely that the increase in fasting plasma glucose and HbA1c concentrations occurred along with the spontaneous course of the disease. However, because the secondary inefficacy of sulfonylurea drugs over time could also be responsible for these changes, further investigation is necessary.

The urine ACR and urine 8-isoprostane and hs-CRP concentrations showed a trend of decreasing up to week 8, that is, during the monotherapy period. However, this initial decrease was not significant, and these measurements decreased significantly in and after week 16 (the coadministration period). The renoprotective, antioxidative, and anti-inflammatory effects suggested by these changes have been reported in

basic research studies using both azelnidipine and temocapril hydrochloride (*14–18*). A clinical study also showed that urinary protein excretion, urine 8-OHdG concentration, and urinary liver-type fatty acid–binding protein concentration decreased significantly in patients taking azelnidipine (*19*). Moreover, it has been shown that urine 8-isoprostane and hs-CRP concentrations decrease relatively quickly after administration of olmesartan, an angiotensin II receptor antagonist (*20*, *21*). In the present study, azelnidipine and temocapril hydrochloride showed a tendency to decrease these indices of inflammation and oxidative stress. In other words, the significant decrease in these indices caused by coadministration of these drugs is clinically relevant. No definite correlation was observed between the decrease in blood pressure and changes in urine ACR, urine 8-isoprostane concentration, and hs-CRP concentration. Because these changes were unrelated to whether the target blood pressure was achieved, it is assumed that factors other than the antihypertensive effect, such as improvement in renal blood flow (*17*, *18*) and vascular endothelial function (*14*, *16*), might be involved.

When a stratified analysis was conducted using each group as a factor, no significant differences were observed between the groups for glucose and lipid metabolism, renal function, and other variables throughout the study. According to many guidelines, inhibitors of the renin-angiotensin system are recommended as initial antihypertensive agents for hypertensive diabetes. However, based on the results of the present study, particularly the rapid onset of the antihypertensive effect in the azelnidipine group, the dihydropyridine-type calcium channel blocker azelnidipine may also be useful as the initial drug with which to begin treatment of hypertension in diabetes.

Safety

Of the serious adverse reactions in two patients, investigators judged the stomach cancer and atrioventricular block as probably related to azelnidipine or temocapril hydrochloride. However, these adverse reactions could be incidental diseases. The frequently occurring cough recorded as an adverse reaction was noted in 36 patients and was judged to be reaction to temocapril hydrochloride. The remaining adverse events all consisted of mild symptoms, and all patients recovered after discontinuing the study drug or therapeutic drug. No abnormalities that caused serious problems were noted in the laboratory tests.

Based on this, none of the adverse events was considered to present any particular safety problem. Further, there were no problems related to safety with either monotherapy or coadministration of azelnidipine and temocapril hydrochloride.

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