

Comparison of effects of azelnidipine and trichlormethiazide in combination with olmesartan on blood pressure and metabolic parameters in hypertensive type 2 diabetic patients

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ABSTRACT

Aims/Introduction: Angiotensin II type 1 receptor blockers (ARB) are regarded as first-line treatment for type 2 diabetes with hypertension. However, lowering blood pressure to the target level often requires more than one antihypertensive agent as recommended by the guideline. In this open-label, prospective, crossover clinical trial, we compared the effects of combination treatment of ARB with a calcium channel blocker (CCB) or with a low-dose thiazide diuretic on blood pressure (BP) and various metabolic parameters in hypertensive patients with type 2 diabetes.

Materials and Methods: A total of 39 Japanese type 2 diabetics with hypertension treated with olmesartan (20 mg/day) for at least 8 weeks were recruited to this study. At study entry, treatment was switched to either olmesartan (20 mg/day)/azelnidipine (16 mg/day) or olmesartan (20 mg/day)/trichlormethiazide (1 mg/day) and continued for 12 weeks. Then, the drugs were switched and treatment was continued for another 12 weeks. We measured clinical blood pressure and various metabolic parameters before and at the end of each study arm.

Results: Compared with the olmesartan/trichlormethiazide treatment, treatment with olmesartan/azelnidipine achieved superior clinical blood pressure and pulse rate control. In contrast, the treatment with olmesartan/trichlormethiazide resulted in increased HbA_{1c}, serum uric acid and worsening of estimated glomerular filtration rate, though there were no differences in other metabolic parameters including urine 8-hydroxy-2'-deoxyguanosine, C-reactive protein and adiponectin between the two treatments.

Conclusions: Our results show that the combination of ARB with azelnidipine is more beneficial with regard to blood pressure control and metabolic outcome than the combination of olmesartan with low dose trichlormethiazide. This trial was registered with UMIN clinical trial registry (no. UMIN000005064). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00135.x, 2011)

KEY WORDS: Calcium channel blocker, Thiazide diuretic, Angiotensin II type 1 receptor blockers

INTRODUCTION

Patients with type 2 diabetes are at high risk of developing cardiovascular diseases, which are also the most common causes of death in these patients. In type 2 diabetes, the prevalence of hypertension is higher than the general population¹, and hypertension associated with diabetes increases the incidence of cardiovascular disease². Thus, treatment of hypertension in

addition to glycemic control is important in order to reduce cardiovascular events in patients with type 2 diabetes^{2,3}, as it was emphasized in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7)⁴. According to that report, the target clinical arterial blood pressure for hypertensive patients with diabetes mellitus is <130/80 mmHg and the use of blockers of the renin-angiotensin system (RAS), either angiotensin II type I receptor blockers (ARB) or angiotensin-converting enzyme (ACE) inhibitors, are recommended as the primary antihypertensive drugs^{4,5}.

The wide use of ARB in the treatment of hypertension is based on their beneficial effects on hypertension-related cardiovascular end-organ damage, at least in part, through reduction of oxidative stress and inflammation in addition to their blood pressure lowering effects^{6,7}. In particular, among the clinically

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available ARB, olmesartan has potent blood pressure lowering effects at a regular dose, compared with other agents⁸⁻¹⁰. However, in the majority of patients, the use of one kind of first-line antihypertensive agent is insufficient to achieve a strict target blood pressure level, and a combination of multiple antihypertensive drugs is required to induce an adequate fall in blood pressure. Generally, ARB or ACE inhibitors are often used in combination with a small dose of thiazide diuretics or calcium channel blockers (CCB).

Thiazide diuretics are beneficial for patients with hypertension, as they reduce cardiovascular morbidity and mortality^{11,12}. In addition, they are commonly used in combination with ARB or ACE inhibitors, as they promote Na excretion and hence enhance the blood lowering effects of ARB or ACE inhibitors¹³. However, thiazide diuretics are known to cause various metabolic abnormalities, such as insulin resistance, new-onset diabetes mellitus, hypokalemia and hyperuricemia^{14,15}. In contrast, CCB can also reduce cardiovascular events in patients with coronary disease or high-risk hypertensives^{16,17}. Furthermore, the combination of CCB with ARB or ACE inhibitors effectively lowers blood pressure without any metabolic adverse effects¹⁸.

The recent ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial compared the relative merits of the combination of ACE inhibitors with those two types of antihypertensive agents. The results showed that the combination of CCB with ACE inhibitors is more effective in reducing cardiovascular events compared to the combination of thiazide diuretics with ACE inhibitors in high-risk hypertensive patients¹⁹. However, the effects of ARB combined with CCB or thiazide diuretics have not been fully evaluated in type 2 diabetic patients with hypertension.

The present study is an open label crossover trial in hypertensive type 2 diabetic patients treated with a combination of ARB (olmesartan 20 mg/day) and azelnidipine or low-dose thiazide diuretic (trichlormethiazide 1 mg/day). Blood pressure, pulse rate, various metabolic parameters and renal function were assessed throughout the study.

MATERIALS AND METHODS

Subjects

All patients with type 2 diabetes mellitus who visited Juntendo University Hospital (Tokyo, Japan), Juntendo Tokyo Koto Geriatric Medical Center (Tokyo, Japan), Juntendo University Urayasu Hospital (Urayasu, Japan), Juntendo University Sizuoka Hospital (Shizuoka, Japan), and Juntendo University Nerima Hospital (Tokyo, Japan) between January 2008 and March 2010 were invited to participate in the study. The inclusion criteria were patients with type 2 diabetes mellitus and hypertension in whom the target clinic blood pressure (<130/80 mmHg) could not be achieved despite treatment with olmesartan 20 mg once daily for at least 8 weeks. Patients with HbA_{1c} higher than 8.4% were excluded from the study. In addition, patients with severe renal (estimated glomerular filtration rate [eGFR] <30) or hepatic

disease, overt cardiovascular disease and malignancy were excluded. The presence of diabetic retinopathy was determined by an ophthalmologist using funduscopy. Diabetic nephropathy was defined as an albumin to creatinine ratio ≥ 30 mg/g creatinine by examination of a spot urine sample. Diabetic neuropathy was defined by the recommendation of the Japan Diabetes Society (JDS) using sensory symptoms in the bilateral lower limbs including tingling, pain, allodynia or unusual sensations, or bilateral absence of the Achilles tendon reflex, or in case of diminished sensitivity. A total of 45 Japanese subjects were recruited for the present study. This study was registered with UMIN clinical trial registry (no. UMIN000005064). The ethics committees of the participating hospitals approved the study protocol and informed consent was obtained from each subject.

Study Design

An open label crossover design was applied to the present study. At the end of the monotherapy of olmesartan 20 mg once-daily as the antihypertensive drug, blood pressure was measured and fasting blood samples were collected as baseline data. Then, the participants were randomized into one of two treatment groups who received either 16 mg azelnidipine or 1 mg trichlormethiazide once daily in the morning in addition to olmesartan 20 mg/day. After 12 weeks of azelnidipine/olmesartan treatment, blood pressure was again measured and fasting blood samples were collected. Then, the subjects on azelnidipine were switched to trichlormethiazide, whereas the subjects on trichlormethiazide were switched to azelnidipine, and each continued the treatment for another 12 weeks, after which blood pressure was measured with fasting blood sampling (Figure 1). Blood pressure and pulse rate were recorded at the outpatient clinic, and the reported values represented the average of triplicate measurements taken at intervals of 1 min with the cuff on the left arm in a sitting position after a 5-min rest. All subjects were advised to consume their usual diet and exercise during the study period. Each patient was reviewed as to their general health and

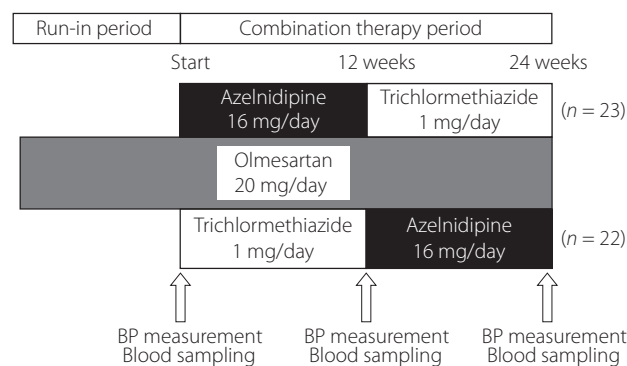


Figure 1 | Study protocol. Schematic diagram of the study protocol. Blood sampling and blood pressure (BP) measurement were carried out at week 0 for basal data. Blood samples obtained at week 12 and 24 were used for evaluation of the effects of each drug.

Table 1 | Baseline characteristics of study subjects

<i>n</i>	39
Age (years)	63.2 ± 13.3
Sex (male/female)	26/13
Body weight (kg)	68.0 ± 11.6
Body mass index (kg/m ²)	26.0 ± 3.9
Mean duration of diabetes (years)	6.7 ± 4.9
Current smokers	13
Diabetic retinopathy	7
Diabetic nephropathy	12
Diabetic neuropathy	15
Medications	
Other antihypertensive medication	0
Hypoglycemic agents	
Sulfonylurea	14
Glinide	10
α-Glucosidase	7
Thiazolidinedione	6
Metformin	8
Insulin	5
Statin	12
Fibrate	2
Antiplatelets	7

Data are mean ± SD or number of subjects.

compliance with the medication, which was assessed by tablet counts and checking of blood pressure, bodyweight, and diet and exercise status at each visit. During the study period, the doses of drugs other than antihypertensive drugs were not altered. The clinical characteristics of the study patients are listed in Table 1.

Biochemical Tests

Blood samples were obtained between 08.00 and 10.00 hours after overnight fast. Serum lipids (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), glucose, HbA_{1c}, creatinine, uric acid, sodium and potassium were measured with standard techniques. The value for HbA_{1c} (%) is estimated as a National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the formula $HbA_{1c} (\%) = HbA_{1c} (JDS) (\%) + 0.4\%$, considering the relational expression of HbA_{1c} (JDS) (%) measured by the previous Japanese standard substance and measurement methods and HbA_{1c} (NGSP)²⁰. Insulin and adiponectin were measured by enzyme immunoassay. Measurement of highly sensitive C-reactive protein (hs-CRP) by latex nephelometry was outsourced to a private laboratory (SRL Laboratory, Tokyo, Japan). Homeostasis model assessment of insulin resistance (HOMA-IR) represented the product of fasting plasma insulin (μU/mL) and fasting plasma glucose levels (mmol/L) divided by 22.5. The eGFR was calculated by the formula for Japanese patients: $eGFR (mL/min \text{ per } 1.73 \text{ m}^2) = 194 \times \text{Age}^{-0.287} \times \text{serum creatinine}^{-0.1094} (\times 0.739 \text{ for females})$ ²¹. Urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) was measured by enzyme-linked immunosorbent assay (ELISA)

using a spot urine sample (SRL Laboratory), and the results are expressed relative to creatinine (per mg Cr).

Statistical Analysis

Results are presented as mean ± SD or median (range 25–75%). Differences between groups were examined for statistical significance using the two-tailed paired Student's *t*-test or Wilcoxon signed-rank test when data did not show normal distribution. A *P*-value <0.05 denoted the presence of a statistically significant difference.

RESULTS

A total of 45 diabetic patients with hypertension were randomly assigned to the azelnidipine administered first group (*n* = 23) and trichlormethiazide administered first group (*n* = 22). Of these, 39 patients completed this trial. Six patients dropped out because of loss to follow up (*n* = 3 of the olmesartan/azelnidipine group and *n* = 2 of the olmesartan/trichlormethiazide group) and poor compliance (*n* = 1 of the olmesartan/trichlormethiazide group). No serious adverse effects were observed in all study patients including the six drop-out cases. The demographic characteristics and mean baseline anthropometric data are shown in Tables 1–3. The subjects were relatively obese (body mass index 26.0 ± 3.9 kg/m²) and their blood glucose, blood pressure and serum lipids were well controlled. The anthropometric data under the administration of olmesartan only were compared with those under olmesartan/azelnidipine and olmesartan/trichlormethiazide.

Table 2 shows clinical blood pressure under treatment with each drug. Blood pressure decreased after treatment with olmesartan/azelnidipine and olmesartan/trichlormethiazide. Compared with olmesartan/trichlormethiazide treatment, the combination of olmesartan/azelnidipine significantly reduced systolic and diastolic blood pressures by 5.5 and 3.0 mmHg, respectively. The pulse rate tended to be lower during the combination therapy period with olmesartan/azelnidipine than in the monotherapy period. In addition, the pulse rate in the olmesartan/azelnidipine group was significantly lower than that in the olmesartan/trichlormethiazide group.

Table 3 lists the metabolic markers at baseline and the end of each combination therapy. No significant change in bodyweight was observed throughout the study. Lipids and serum K did not change significantly with either of the combination therapies. With regard to glucose metabolism, HbA_{1c} was significantly lower in the olmesartan/azelnidipine group than the olmesartan/trichlormethiazide group. However, fasting blood glucose, serum insulin and HOMA-IR were comparable between the two groups. Serum uric acid and serum creatinine significantly increased in the olmesartan/trichlormethiazide group, but not in the olmesartan/azelnidipine group. Reflecting these changes, eGFR was significantly increased after olmesartan/azelnidipine treatment compared with olmesartan/trichlormethiazide treatment. In contrast, urinary 8-OHdG, hs-CRP and adiponectin were comparable between the two treatments.

Table 2 | Blood pressure and pulse rate at baseline, olmesartan/azelnidipine and olmesartan/trichlormethiazide treatment

	Baseline (olmesartan alone)	Olmesartan + azelnidipine	Olmesartan + trichlormethiazide	P-value*
Systolic blood pressure (mmHg)	149.8 ± 11.6	135.2 ± 14.5	140.7 ± 15.2	0.017
Diastolic blood pressure (mmHg)	84.0 ± 10.1	77.2 ± 10.6	80.2 ± 12.8	0.023
Pulse rate (b.p.m.)	77.1 ± 10.7	71.2 ± 11.0	76.4 ± 11.6	<0.001

Data are mean ± SD.

*Comparison between olmesartan/azelnidipine and olmesartan/trichlormethiazide groups by two-tailed paired Student's *t*-test.

Table 3 | Biochemical data at baseline, olmesartan/azelnidipine and olmesartan/trichlormethiazide treatment

	Baseline (olmesartan alone)	Olmesartan + azelnidipine	Olmesartan + trichlormethiazide	P-value*
Bodyweight (kg)	68.5 ± 11.6	68.6 ± 11.7	69.0 ± 11.9	NS
HbA _{1c} (%)	7.18 ± 1.03	7.19 ± 0.98	7.40 ± 1.14	0.014
Fasting blood glucose (mmol/L)	6.66 (5.56–8.24)	6.60 (5.62–8.70)	6.71 (5.73–8.48)	NS
Insulin (μU/mL)	7.80 (4.60–11.10)	6.65 (5.00–12.40)	8.30 (5.70–10.80)	NS
HOMA-IR	1.97 (0.99–4.07)	1.99 (1.44–4.11)	2.75 (1.53–3.30)	NS
HDL (mmol/L)	1.31 ± 0.27	1.30 ± 0.25	1.27 ± 0.25	NS
LDL (mmol/L)	2.86 ± 0.70	2.99 ± 0.79	2.96 ± 0.78	NS
Triglyceride (mmol/L)	6.52 (4.85–10.3)	6.63 (5.66–10.38)	7.50 (5.45–10.15)	NS
Creatinine (μmol/L)	72.5 ± 17.6	72.4 ± 19.3	75.1 ± 19.5	0.037
eGFR (mL/min/1.73 m ²)	71.1 ± 18.4	72.0 ± 21.6	68.0 ± 17.6	0.011
Uric acid (mmol/L)	0.35 ± 0.09	0.35 ± 0.08	0.38 ± 0.09	0.005
Na (mmol/L)	61.6 ± 0.8	61.2 ± 0.8	61.2 ± 0.9	NS
K (mmol/L)	1.11 ± 0.09	1.08 ± 0.09	1.10 ± 0.11	NS
Adiponectin (μg/mL)	5.38 ± 2.53	5.41 ± 2.22	5.09 ± 2.36	NS
hs-CRP (mg/dL)	0.055 (0.030–0.108)	0.059 (0.031–0.109)	0.068 (0.035–0.113)	NS
8-OHdG (ng/mg creatinine)	4.03 ± 1.79	3.89 ± 2.65	3.99 ± 2.43	NS

Data are mean ± SD or median (range 25–75%). Plasma insulin level and homeostasis model assessment of insulin resistance (HOMA-IR) were not measured in patients on insulin therapy (*n* = 5).

8-OHdG, 8-hydroxy-2'-deoxyguanosine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, highly-sensitive C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

*Comparison between olmesartan/azelnidipine and olmesartan/trichlormethiazide groups by two-tailed Student's *t*-test or Wilcoxon signed-rank test.

DISCUSSION

Our data showed that the combination therapy of olmesartan with azelnidipine had a more potent blood pressure lowering effect without affecting the metabolic parameters compared to that with trichlormethiazide.

The present study showed that clinical systolic and diastolic blood pressures were significantly lower in the olmesartan/azelnidipine group than in the olmesartan/trichlormethiazide group by 5.5 and 3.0 mmHg, respectively. Recently, several large trials showed that strict blood pressure control could reduce the onset of cardiovascular diseases in patients with type 2 diabetes^{2,3}. For example, a 4-mmHg fall in diastolic blood pressure in the HOT study was found to equate with a 51% decrease in the onset of cardiovascular diseases². Similarly, a 1.92-mmHg decrease in systolic blood pressure in the HOPE study was found to equate to a 25% reduction in cardiovascular mortality in type 2 diabetic patients³. Considered together with the aforementioned studies, the fall in arterial pressure recorded in the present study was clinically significant and more than a subtle change. Although

increasing the dose of trichlormethiazide might achieve further reduction in blood pressure, we only used a low dose of trichlormethiazide, because the adverse effects on metabolism are more common with higher doses of thiazide diuretics^{14,22}.

In the present study, the pulse rate in the olmesartan/azelnidipine group was significantly lower than in the olmesartan/trichlormethiazide group, consistent with previous reports^{23,24}. Azelnidipine reduces the pulse rate in essential hypertension, unlike other dihydropyridine CCB such as amlodipine^{25,26}, because it inhibits sympathetic nerve activity²⁷. In contrast, diuretics are likely to increase pulse rate as a result of their action of reducing plasma volume. Epidemiological studies suggest that increased pulse rate is a predictor for cardiovascular disease and a poor prognosis^{28–30}, thus our data point to better beneficial effects for azelnidipine compared with thiazide diuretics.

Thiazide diuretics are well known to induce hyperuricemia, even at low doses²². The present study showed that serum uric acid was also significantly higher in the olmesartan/

trichlormethiazide group than in the olmesartan/azelnidipine group. Recent studies have shown that thiazide-induced hyperuricemia correlates with increased cardiovascular events in hypertensive patients^{31,32}. Thus, care should be taken regarding uric acid monitoring during thiazide treatment, even when combined with ARB.

Previous studies reported that thiazide diuretics increase the risk for developing hyperglycemia³³. Indeed, we found that HbA_{1c} levels were significantly higher in the olmesartan/trichlormethiazide group than in the olmesartan/azelnidipine group. Several studies suggested that thiazide-induced hyperuricemia and hypokalemia might mediate insulin resistance^{15,34}. However, we found that the change in HbA_{1c} level correlated neither with changes in serum uric acid level nor with serum potassium level (data not shown). Further studies are needed to clarify the mechanism of the adverse effects of thiazide diuretic on glucose metabolism.

We also found that renal function assessed by serum creatinine and eGFR deteriorated in the olmesartan/trichlormethiazide group. Although the mechanisms responsible for thiazide-associated renal dysfunction remain unclear, certain mechanisms, such as the chronic effects of thiazides on metabolic abnormalities like hyperuricemia, hyperglycemia or volume depletion, could be considered to impair renal function^{14,35–37}. In contrast, azelnidipine was considered to provide renal protection and to reduce proteinuria^{26,38}. In contrast to our findings, the GUARD (The gauging Albuminuria Reduction With Lotrel in Diabetic Patients with Hypertension) study showed that the treatment using ACE with thiazide diuretic resulted in a greater reduction in albuminuria without thiazide-associated renal dysfunction compared with the group using ACE and CCB, although the blood pressure reduction was better in the ACE and CCB group³⁹. We could not show exact reasons for these differences, because we did not evaluate the effect on albuminuria. Thus, further clinical study is required.

Recent studies have shown that azelnidipine have anti-inflammatory and anti-oxidative stress effects and can increase serum adiponectin levels^{24,26,27,40}. We evaluated the effects of azelnidipine and trichlormethiazide on inflammation, oxidative stress markers and serum adiponectin. However, our results showed no differences in these parameters between the two treatment groups. The reason for the lack of effect of azelnidipine on metabolic parameters in the present study is not clear at present. It is possible that a longer duration of drug treatment is required before the appearance of these unique effects of azelnidipine.

In the present study, just nine of the olmesartan/azelnidipine group and seven of the olmesartan/trichlormethiazide group achieved the target blood pressure of <130/80 mmHg. In general, a combination of more than three antihypertensive drugs is needed to achieve this goal⁴¹. Thus, it is important to treat hypertension more intensively with a combination of more than three antihypertensive drugs, including thiazide diuretics, to reduce both diabetic microvascular and macrovascular compli-

cations in case of poor control with a combination of ARB and CCB.

The limitation of the present study is the relatively small number of patients and the crossover design. Considering the practical performance with clinical patients, we could not set up a washout period. In addition, we compared the effect of drugs at only one point, thus time-course changes in blood pressure and pulse rate during the combination study could not be evaluated. Regarding order effects, there were no differences between the azelnidipine-trichlormethiazide group and the trichlormethiazide-azelnidipine group by two-way analysis of variance for repeated measurements.

In conclusion, our data suggested that compared with the combination of olmesartan and trichlormethiazide, that of olmesartan and azelnidipine had superior blood pressure lowering effects, as well as superior effects on glucose and uric metabolism, and renal function in patients with type 2 diabetes. Our results suggest that the combination of olmesartan/azelnidipine can be considered ideal agents to provide better cardiovascular protection than the combination of olmesartan/trichlormethiazide in type 2 diabetic patients with hypertension.

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