Original Article

Is Renoprotection by Angiotensin Receptor Blocker Dependent on Blood Pressure?: The Saitama Medical School, Albuminuria Reduction in Diabetics with Valsartan (STAR) Study

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To explore the effects of various antihypertensive regimes on microalbuminuria, an angiotensin II receptor blocker (ARB), valsartan, was substituted for or added to treatment with a calcium channel blocker (CCB). After a 6-month CCB baseline period, 28 Japanese hypertensive patients with incipient diabetic nephropathy (defined as a urinary albumin excretion [UAE] of 30–300 mg/g creatinine), were assigned to two groups according to their blood pressure (BP) levels: in patients with a BP of more than 130/85 mmHg (*n*=17), valsartan was added to the CCB (Group A), while in patients with a BP <130/85 mmHg, valsartan alone was given (Group B: *n*=11) for 12 months. UAE was determined before and at 3, 6 and 12 months after the initiation of ARB. Although the initial BP was significantly higher in Group A (150/83 mmHg) than Group B (127/77 mmHg), BP was decreased to 141/78 mmHg in Group A and slightly, but not significantly, increased to 130/82 mmHg in Group B. In both groups, UAE was significantly decreased after ARB treatment (to 89% of the basal value in Group A and to 40.5% of the basal value in Group B) and did not differ each other and the amount of decrease did not differ significantly between the two groups. These results suggest that combination therapy with an ARB and CCB is very effective in lowering BP and UAE in cases in which BP is not well controlled, while, even in patients with a sufficient BP control of <130/85 mmHg, the use of ARB singly resulted in a significant decrease in UAE without a further decrease in BP, implying that the ARB had a renoprotective action independent of changes in BP. (*Hypertens Res* 2007; 30: 529–533)

***Key Words*: angiotensin receptor blocker, calcium channel blocker, combination therapy, microalbuminuria, target blood pressure**

Introduction

Diabetic nephropathy is the most common cause of end-stage renal disease in many countries, including Japan. In fact, among the 33,935 patients who started hemodialysis in Japan in 2004, 13,920 (41.3%) were diabetic (*1*). It has been demonstrated that the progressive decline in renal function in patients with diabetes is ameliorated by the treatment of hypertension (*2*, *3*). Of all antihypertensive agents, angiotensin converting enzyme (ACE) inhibitors (ACEIs) and angiotensin II type 1 (AT1) receptor blockers (ARBs) have been considered to be particularly effective in limiting the progression of diabetic nephropathy. Lewis *et al*. reported that captopril, one of the ACEIs, reduced the risk of doubling of the baseline serum creatinine level by 48%, and treatment with captopril was associated with a 50% reduction in the risk of the combined end points of death, hemodialysis and renal

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Received September 19, 2006; Accepted in revised form January 25, 2007.

Table 1. Characteristics of Patients in Group A and B before and 12 Months after the Administration of ARB, Valsartan

	Group A		Group B	
	Before	At 12 months	Before	At 12 months
n	17		11	
Age (years)	60.2±15.5		60.2±15.3	
Body weight (kg)	63.1±12.5	64.8±12.6	64.8±15.5	63.8±15.3
SBP (mmHg)	150±16.7	141±9.6	127±13.8	130±10.2
DBP (mmHg)	83±13.4	78±13.0	77±11.0	82±17.1
FPG (mg/dL)	132±27.0	147±38.7	147±35.3	156±38.5
HbA_{1C} (%)	7.3±1.7	7.4±1.6	7.7±2.0	7.4±1.7
TC (mg/dL)	199±34.7	212±36.8	182±31.7	182±33.6
TG (mg/dL)	149±53.1	121±53.5	96±42.3	161±68.0
HDL-C (mg/dL)	55±16.5	57±20.4	50±14.0	47±15.2
Creatinine (mg/dL)	0.63±0.21	0.66±0.21	0.66±0.24	0.73±0.24
eGFR (mL/min/1.73 m^2)	123±45.2	113±35.2	115±37.6	100±23.9
UAE (mg/g creatinine)	76.7±51.4	68.3±69.5	93.9±62.8	38.0±27.7

Each value indicates the mean±SD. ARB, angiotensin II type 1 receptor blocker; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; HDL-C, high density lipoprotein-cholesterol; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion.

transplantation in type 1 diabetics with proteinuria (*4*). ARBs were also found to attenuate the progression of nephropathy in hypertensive type 2 diabetic patients with proteinuria (*5*, *6*) or microalbuminuria (*7*). Microalbuminuria was also decreased with an ARB in hypertensive and normotensive patients with type 2 diabetes mellitus (*8*). These beneficial effects of ACEIs and ARBs have been attributed to amelioration of glomerular capillary hypertension as well as a systemic blood pressure (BP)–lowering effect. In addition, reduction of tissue angiotensin II levels may play an important role in reducing glomerular injury (*9*).

However, the optimal choice of antihypertensive agent for realizing BP reduction and renoprotection has generated considerable controversy. Although dihydropyridine calcium channel blockers (CCBs) lower BP to a comparable degree compared to other drug classes, some studies have reported that they do not slow the progression of diabetic nephropathy. For example, in the IDNT (Irbesartan Diabetic Nephropathy Trial), irbesartan reduced the rate of serum creatinine doubling by 16% in comparison with that by amlodipine in hypertensive proteinuric diabetics (*6*). Moreover, amlodipine was not as effective as valsartan in decreasing microalbuminuria in normotensive and hypertensive diabetics with microalbuminuria (*8*). Thus, there may exist clear differences between CCBs and ARBs in terms of the renoprotective effects in diabetics with proteinuria or microalbuminuria. In the present study, to examine the effects of the two drug classes on BP lowering, we measured urinary albumin excretion (UAE) in two groups: a group in which BP was well controlled to <130/85 mmHg, and in whom we replaced the CCB with the ARB valsartan; and a group in which the BP was over 130/85 mmHg, and in whom valsartan was added to the CCB.

Methods

Patients and Protocol

The subjects were 28 patients (average age: 60.2±15.3 [SD] years) with type 2 diabetes mellitus and a UAE in the range of 30–300 mg/g creatinine at the time of screening in two consecutive urine samples collected in the morning. Patients with poor glycemic control with an HbA_{1C} level greater than 10% were excluded. In addition, a serum creatinine concentration greater than 2 mg/dL and other renal, endocrine, cardiac, liver, gastrointestinal, or connective tissue diseases were also reasons for exclusion. BPs were determined using a sphygmomanometer with subjects seated after 5 min of rest. Two readings were taken 30 s apart and read to the nearest 2 mmHg, and the average was used for the calculations. When the average BP at two consecutive visits was well controlled to <130/85 mmHg with a CCB, we replaced the CCB with valsartan at 80 mg/day (Group B; $n=11$). On the other hand, valsartan was added at 80 mg/day to the CCB when the average BP was over 130/85 mmHg (Group A; $n=17$). The target BP was <130/85 mmHg.

The protocol was approved by the hospital review board and written informed consent was obtained from all patients. Before and at 3, 6 and 12 months after changing to or adding an ARB, fasting plasma glucose levels, HbA_{1C} values determined by high-performance liquid chromatography, serum total cholesterol, triglyceride, and high-density lipoprotein (HDL)–cholesterol levels were determined. Serum creatinine concentrations and electrolyte levels were also measured. Estimated glomerular filtration rate (eGFR) was calculated by the MDRD (Modification of Diet in Renal Disease) equation

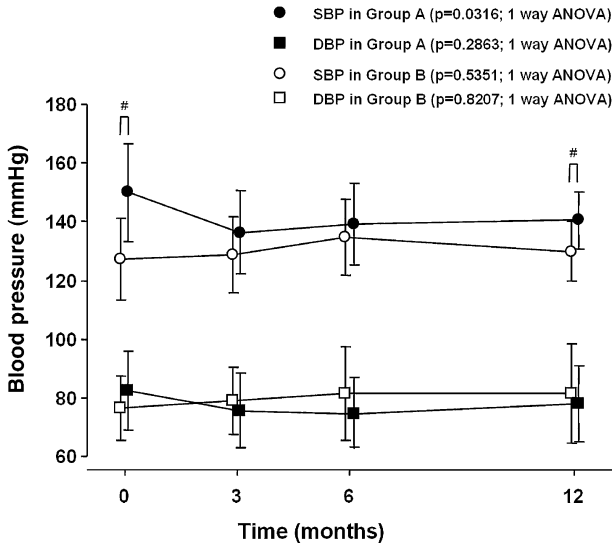

Fig. 1. *Changes in systolic (SBP) and diastolic blood pressure (DBP) throughout the study period in Group A (closed circles and squares) and Group B (open circles and open squares). In Group A, valsartan was added to a CCB, while in Group B, the CCB was changed to valsartan.* $^{\#}p < 0.05$ *vs. Group B.*

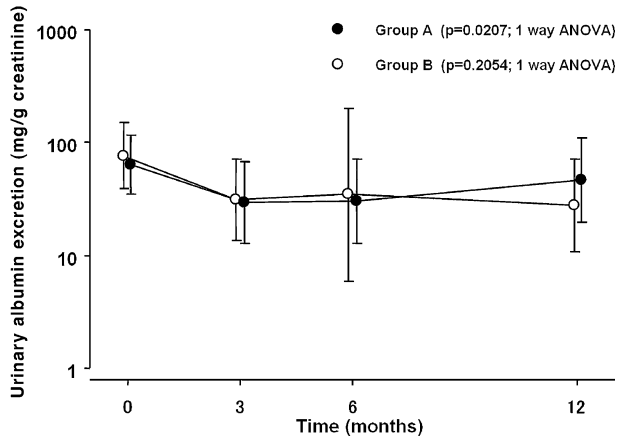

Fig. 2. *Changes in urinary albumin excretion (mg/g creatinine) throughout the study period in Group A (closed circles) and Group B (open circles). In Group A, valsartan was added to the CCB, while in Group B, the CCB was changed to valsartan. In both groups, urinary albumin excretion was significantly decreased during the course* ($p < 0.05$) *and did not differ each other.*

modified for the Japanese as follows (*10*):

$$\text{eGFR (mL/min/1.73 m}^2) = 0.881 \times 175 \times \text{serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \ (\times 0.742 \text{ if in females}).$$

Urine samples were also collected for analysis of urinary albumin concentration by a radioimmunoassay and creatinine concentration by the Jaffe colorimetric method. UAE was calculated as albumin/creatinine (mg/g creatinine).

Statistics

For demographics and characteristics expressed as means±SD, differences between the two groups were analyzed by the Kruskal-Wallis test, χ^2 test for association, or analysis of variance. Analysis was performed on an intention-to-treat basis, and the effects of treatments on the change from baseline in body weight, BP, UAE, fasting plasma glucose, HbA_{1C} and serum lipid levels were determined by analysis of variance. Before the analysis, the skewed distribution of UAE was normalized by log-transformation.

Results

Table 1 shows the baseline characteristics of the two groups. There were no significant differences in the age, fasting plasma glucose, HbA_{1C}, total cholesterol, triglyceride or HDL-cholesterol levels between the two groups. Baseline UAE, serum creatinine and eGFR levels were also not different between the two groups, although the systolic blood pressure (SBP) was significantly higher in Group A (150/83 *vs*. 127/77 mmHg).

Figure 1 shows changes in BP throughout the study period. The addition of ARB in Group A significantly lowered the BP from 150±16.7/83±13.4 to 141±9.6/78±13.0 mmHg at 12 months ($p<0.0316$ for the SBP). The values of SBP at 3 and 6 months after the initiation of the study tended to be higher in Group A than in Group B. At 12 months, SBP was significantly higher in Group A than in Group B (141±9.6 *vs*. 130±10.2 mmHg, $p=0.0104$). The DBP was not significantly different between the two groups throughout the study period. The changes in UAE during the study are illustrated in Fig. 2. UAE was significantly decreased in both groups: from 76.7±51.4 to 68.3±69.5 mg/g creatinine in Group A ($p=0.0102$) and from 93.9±62.8 to 38.0±27.7 mg/g creatinine in Group B ($p=0.0405$). In other words, the UAE in Groups A and B was decreased to 89% and 41% of the basal value, respectively, and the amount of decrease was not significantly different between the groups

As shown in Table 1, the fasting plasma glucose levels (mg/dL) did not differ significantly between groups (147±38.7 in Group A *vs*. 156±38.5 in Group B), and the HbA_{1C} levels (%) also did not show a significant difference between the groups (7.4±1.6 in Group A *vs*. 7.4±1.7 in Group B). Serum lipid levels were also not altered throughout the study period in either group. Serum creatinine (mg/dL) and eGFR levels (mL/min/1.73 m^2) were not altered significantly in each group (0.66±0.21 and 113±35.2 in Group A *vs*. 0.73±0.24 and 100±23.9 in Group B, respectively).

Discussion

The present study confirmed the findings in previous studies that ARBs decrease UAE in microalbuminuric patients with type 2 diabetes mellitus. Of interest is the observation that, when an ARB alone was given in place of the CCB in patients whose BP was well controlled (<130/85 mmHg), the UAE was further lowered from 93.9±62.8 to 38.0±27.7 mg/g creatinine. BP was not changed throughout the study in this group, and the final BP was 130/82 mmHg, indicating UAE-lowering effect of valsartan, which might be a class effect of ARB based on previous many studies. This effect of ARBs might be due to their blockade of the renin-angiotensin system, which dilates the efferent glomerular arteries, and thereby improves the glomerular capillary hypertension (*9*). In addition, ARBs may contribute to the decrease in UAE by altering the expression of the genes encoding nephrin or other proteins, and thereby creating structural changes in the glomerular basement membranes and/or podocytes (*11*, *12*).

Some studies have reported that CCBs did not show a renoprotective effect despite exerting a hypotensive action comparable to that of other drug classes. In the IDNT trial, amlodipine was not as effective as an ARB at decreasing the incidence of serum creatinine doubling, end-stage renal disease and death (*7*). Amlodipine was also reported to be less effective than valsartan in decreasing microalbuminuria in normotensive and hypertensive diabetics (*8*). However, some studies have demonstrated that non-dihydropyridine and dihydropyridine CCBs diminish macro- and microalbuminuria (*13*, *14*). Almost all of the L-type dihydropyridine CCBs may dilate the afferent glomerular artery and increase the intraglomerular capillary pressure. However, if a systemic BP decrease is great enough for lowering the intraglomerular capillary pressure, CCBs may play a renoprotective role. Thus, there may exist clear differences between CCBs and ARBs in terms of the renoprotective effects in diabetics with proteinuria or microalbuminuria.

In patients whose BP was not well controlled, *i.e.*, over 130/85 mmHg, the addition of an ARB to the CCB decreased UAE further, along with a decrease in BP from 150/83 to 141/78 mmHg ($p<0.0316$ for SBP). It has been well established that BP is sometimes resistant to hypotensive agents in diabetics. In our previous survey 5 years ago, only 11.4% of diabetic hypertensives had a BP of less than 130/85 mmHg after administration of 1.52 hypotensive agents on average (*15*). Many recent guidelines, including those of the Japanese Society of Hypertension, have recommended that BP be lowered to less than 130/80 mmHg in diabetics (*16*). In our present study, 11 of 28 diabetics had a BP less than 130/85 mmHg at the initial screening. In the remaining 17 diabetics, an ARB was thus added to the CCB. Although achieved BP, *i.e.* 141/78 mmHg, was not enough, far higher than the current target BP (<130/80 mmHg), a combination therapy of ARB with CCB may be a very beneficial tool to lower not only BP but also UAE furthermore as demonstrated in the present study. In fact, combination therapy of ACEIs and CCBs has been demonstrated to be effective especially to decrease proteinuria, possibly due to a protection against renal injury (*17*, *18*). Combination therapy of CCBs with ARBs has also been reported to be beneficial in preserving cardiac and vascular morphology in animal models (*19*, *20*). The mechanisms proposed to explain the beneficial effect of CCBs are antioxidant activity on vascular endothelial cells and antiproliferative action in vascular smooth muscle cells (*21*, *22*) in addition to BP lowering.

Recently, tight BP control using ACEIs and ARBs has been elucidated to reduce proteinuria to microalbuminuria and microalbuminuria to normoalbuminuria. The concept of remission and regression has received much attention. When proteinuria is more than 1 g/day, it is recommended that the target BP be less than 125/75 mmHg based on the results of the Multiple Risk Factor Intervention Trial (MRFIT) and Modification of Diet in Renal Disease (MDRD) (*23*, *24*). However, these trials did not include a large number of diabetic patients, who accounted for only 1.5% to 3% of the subjects. However, UKPDS (United Kingdom Prospective Diabetes Study) (*25*), which was conducted on newly diagnosed type 2 diabetics, recently demonstrated that tight BP control with captopril or atenolol (final average BP: 147/82 mmHg) reduced the risk of diabetic nephropathy, reducing UAE of more than 50 mg/L by 29% and of more than 300 mg/L by 39% at 6 years after the initiation of the study as compared to less tight control (final average BP: 154/87 mmHg). The Captopril Collaborative Study (*26*) demonstrated that intensive BP control (mean arterial BP to 92 mmHg or less) with ramipril with or without other hypotensive medications lowered urinary protein excretion to 535 mg/day in comparison with 1,723 mg/day in the less tight BP control group (mean arterial BP to 100 to 107 mmHg), supporting the target BP of 125/75 mmHg or less. Factors associated with remission of microalbuminuria were recently reported to be renin-angiotensin system–blocking drugs, lower HbA_{1C} (<6.95%) and SBP (<129 mmHg) (*27*). The Kashiwa Study in Japan very recently demonstrated that development and progression were low and regression was high with an SBP of 120 mmHg, if HbA_{1C} was maintained at 6.5% (*28*).

These results suggest that combination therapy with an ARB and a CCB is very effective in lowering BP and UAE when BP is not well controlled, while, even in patients with a sufficient BP control of <130/85 mmHg, treatment with an ARB singly results in a further, significant decrease in UAE without a further decrease in BP, indicating that this ARB has a renoprotective action independent of any change in BP. We conclude that diabetic patients with microalbuminuria should be treated with ARBs irrespective of whether or not their BP is well controlled.

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