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Reduction of microalbuminuria in patients with type 2 diabetes mellitus: the Shiga Microalbuminuria Reduction Trial (SMART)

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Although the reduction of blood pressure (BP) to less than 130/80 mmHg using rennin-angiotensin system (RAS) blocking drugs has been recommended for diabetic patients with hypertension (1,2), there have been no controlled studies comparing the therapeutic effects of the RAS blocker with another antihypertensive agent targeting the target BP level. Therefore, the objective of this study was to assess the effect of an ARB, valsartan, on microalbuminuria in comparison to that of a calcium channel blocker (CCB), amlodipine, in patients with the targeting BP level of less than 130/80 mmHg.

Research Design and Methods

From December 2003 through March 2006, we recruited Japanese type 2 diabetic patients who had at least a 5-year history of diabetes and persistent microalbuminuria (urinary albumin creatinine ratio (ACR) of 30 to 299 μg/mg creatinine on the average of first-voided urine samples for three consecutive days)(3,4) . The other inclusion criterion was a baseline BP ≧140/90 mmHg and ≦180/110 in the patients who were not taking antihypertensive agents and ≧130/80 mmHg and ≦180/110 in the patients taking antihypertensive agents. The exclusion criteria were type I diabetes, a baseline serum creatinine > 133 mmol/l, a baseline serum potassium > 5.6 mmol/l, kidney or renal disease other than diabetic nephropathy, cardiovascular accidents within the preceding 6 months, severe peripheral vascular disease, congestive heart failure, pregnancy and childbearing potential. At the beginning of the screening period, CCBs or ARBs were withdrawn from patients if they had already been administered to the patient. Other antihypertensive medications were maintained at the same dosage throughout the study. The patients were randomly assigned to receive either 80 mg of valsartan once daily or 5 mg of amlodipine once daily. The target BP was <130/80 mmHg. If adequate BP control was not achieved with the initial dose of the study drug by week 4 of the intervention period, the valsartan or amlodipine dose was doubled. If necessary, additional antihypertensive drugs (except ACE inhibitors) could be added after week 8 of the intervention period. ACR was measured at the central laboratory (Medic Lab.) using the first morning urine samples. The study was approved by the Ethics Committee of Shiga University of Medical Science and was undertaken in accordance with the Declaration of Helsinki Principles. Written informed consent was obtained from all patients.

Analyses were performed with the last observation carried forward method. Differences between the study groups in BP and the percentage change in the ACR were analyzed by applying the two-way analysis of variance repeated measurement model.

Results

Three-hundred forty-one patients were enrolled for screening and 153 patients were randomly assigned to the valsartan group or the amlodipine group. Three patients were excluded from efficacy analyses due to the lost of their follow-up. In summary, we analyzed a total of 150 patients (mean age 62 years, male/female 51/99). The baseline characteristics (age, gender, history of cardiovascular diseases, total cholesterol, HDL, HbA1c and smoking) of the two groups were similar. At baseline, 72 patients (34 of 73 in the valsartan group, 38 of 77 in the amlodipine group) were treated with ACE inhibitors for at least 3 months. The frequency of antihypertensive drug usage was not different between the two groups. The glycated hemoglobin levels at the end of follow-up period of the two treatment groups were similar (7.2±1.1 % vs. 7.5±1.3 % respectively). Over the study period, the reductions in blood pressure were also similar between the two treatment groups (Fig 1a). The percentage of the patients who achieved the target SBP was 50.7% in the valsartan group and 48.1% in the amlodipine group.

At the end of study, the changes in the ACR from baseline was 68% in the valsartan group and 118% in the amlodipine group ($p<0.001$) (Fig. 1b). The frequency of patients who achieved remission (shift of the ACR from microalbuminuria to normoalbuminuria) or regression (50% reduction in the ACR from baseline) of microalbuminuria(5-7) was significantly higher in the valsartan group than in the amlodipine group (remission 23% vs. 11%, $p = 0.011$, regression 34% vs. 16%, $p=0.008$). In patients who were also treated with ACE inhibitors, the ACR in the valsartan group was significantly reduced than that in the amlodipine group (valsartan group -26%, amlodipine group +8%, $p=0.04$). Figure 1c shows the changes of in the ACR in relation to the SBP (controlled group: <130 mmHg, uncontrolled group: ≧ 130 mmHg) and the treatments. In the valsartan group, there was a progressive reduction in the ACR (controlled group: -40%, uncontrolled group: -23%) and no significant difference was found regarding the change in the ACR between the two subgroups. However, in the amlodipine group, the changes in the ACR were different between the two subgroups (controlled group: - 11%, uncontrolled group: + 40%, $p<0.001$). The changes in the ACR were also different between the paired valsartan and amlodipine subgroups.

Safety

In the amlodipine group, one experienced a cerebral hemorrhage, one reported angina pectoris, and one had leg edema. No correlation between these events and the test drug was proven by the safety board. There were no deaths related to the study medication. No significant changes were observed in the serum creatinine and potassium levels in either group.

Conclusions

A recent meta-analysis showed that the benefit of RAS inhibitors on renal outcome most likely resulted from a blood pressure effect (8). They emphasized that the lack of advantage of RAS inhibitors over other antihypertensive drugs beyond lowering BP in preventing diabetic nephropathy. In this open-label randomized study, the reductions in BP were similar between the valsartan group and the amlodipine group. However, valsartan was more effective than amlodipine for reducing microalbuminuria. In addition, the reduction of the ACR was significantly greater in the valsartan group with uncontrolled SBP than that in the amlodipine group with controlled SBP. These findings showed that the anti-protenuric effect of valsartan may be independent of its effect on BP. We conclude that ARBs can therefore be a first-line drug for the patients with type 2 diabetes and microalbuminuria.

Appendix SMART group.

Safety board;

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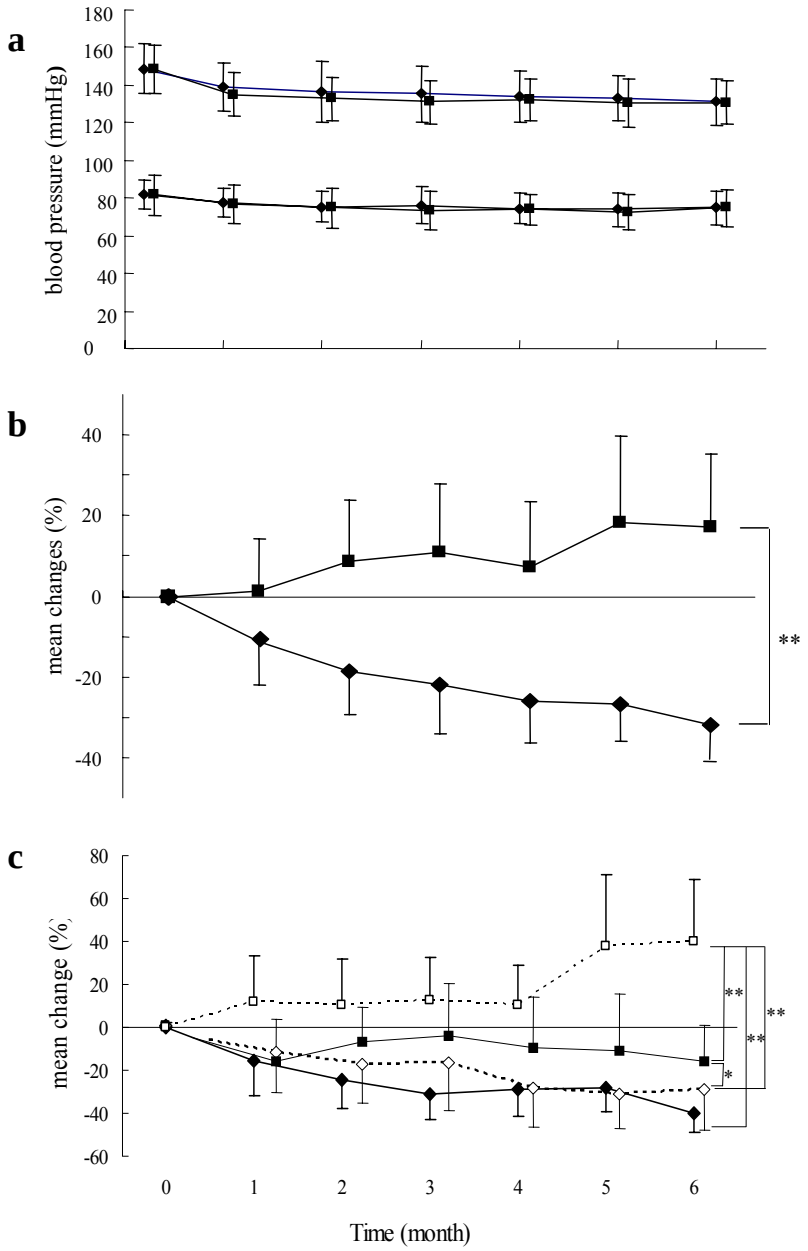

Figure 1

The time courses the changes in the BP (a, mean±SD) and ACR (b, mean±95% CI) in patients administrated with valsartan (◆) or amlodipine (■). c) The time course the changes in ACR subset of patients with controlled BP (end point SBP <130 mmHg) treated with valsartan (◆) or amlodipine (■) and a subset of patients with uncontrolled BP (end point SBP ≧130 mmHg) treated with valsartan (◇) or amlodipine (□)

* $p<0.005$ and ** $p<0.001$ between the groups.