Original Article

Impact of Renin-Angiotensin System Inhibition on Microalbuminuria in Type 2 Diabetes: A Post Hoc Analysis of the Shiga Microalbuminuria Reduction Trial (SMART)

The Shiga Microalbuminuria Reduction Trial (SMART) Group*

The Shiga Microalbuminuria Reduction Trial (SMART) showed the advantage of ARB over CCB beyond the blood pressure (BP)–lowering effect in reducing microalbuminuria. To further assess the impact of BP control or renin-angiotensin system inhibition on microalbuminuria, the SMART patients were re-analyzed. Hypertensive patients with type 2 diabetes and microalbuminuria were randomly assigned to valsartan or amlodipine treatment groups for 24 weeks. Target blood pressure was set at <130/80 mmHg. Changes in the urinary albumin creatinine ratio (ACR) from baseline were assessed in the valsartan monotherapy (VM) group (*n*=33), the amlodipine monotherapy (AM) group (*n*=36), the concomitant valsartan and angiotensin-converting enzyme inhibitor group (VA) (*n*=33), and the concomitant amlodipine and angiotensin-converting enzyme inhibitor (AA) group (*n*=38). At the end of the study, mean BP was not different among the four treatment groups. The changes in ACR from baseline to the end of the treatment period in VM, AM, VA, and AA were −36%, +30%, −26%, and +8%, respectively. The dissociation between the anti-albuminuric and anti-hypertensive effects of valsartan or amlodipine was observed in the respective monotherapy groups. In the AA group, however, a significant positive relationship was found between the changes in ACR and those in systolic BP. In conclusion, RAS inhibitors may be necessary in order for calcium channel blockers to have an effect on microalbuminuria. Therefore, RAS inhibitors are first-line drugs for hypertensive patients with type 2 diabetes and microalbuminuria. (*Hypertens Res* 2008; 31: 1171–1176)

***Key Words*: diabetic nephropathy, microalbuminuria, renin-angiotensin system, blood pressure**

Introduction

There is accumulating evidence that treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) can reduce microalbuminuria in patients with type 2 diabetes (*1–3*). Based on these findings, the reduction of blood pressure (BP) to less than 130/80 mmHg by the use of renin-angiotensin system (RAS)–blocking drugs has been recommended for diabetic patients with hypertension (*4–6*). However, no controlled studies have yet compared the therapeutic effects of an RAS-blocking drug with those of another antihypertensive agent that does not interfere with an RAS target of BP <130/80 mmHg. Therefore, we compared the effect of valsartan, an ARB, on microalbuminuria with that of amlodipine, a calcium channel blocker (CCB), in type 2 hypertensive diabetic patients, at a target BP of less than 130/80 mmHg, and confirmed that valsartan is more effective than amlodipine in reducing microalbuminuria (the Shiga Microalbuminuria Reduction Trial; SMART (*7*)). The SMART also clearly showed the advantages of ARB over CCB, beyond the BP-lowering effect, in

*Details of the SMART Group are shown in Appendix.

Clinical trial reg. no.: NCT00202618, clinicaltrials.gov.

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Table 1. Baseline Characteristics of the Patients

	Monotherapy		Concomitant with ACE inhibitors	
	Valsartan (n=34)	Amlodipine (n=36)	Valsartan (n=34)	Amlodipine (n=38)
Age (years)	61±8	62±10	62±9	60±9
Sex (male/female)	23/11	24/12	24/10	24/14
Current smokers	13 (38)	13 (36)	12 (35)	11 (29)
BMI (kg/m^2)	25.0±3.3	25.4±4.2	24.7±3.8	24.3±3.5
Systolic BP (mmHg)	151±12	145±11	145±14	152±11*
Diastolic BP (mmHg)	83±7	80±9	82±11	81±11
ACR (μg/mg)	93 (71–115)	96 (67–119)	95 (71–118)	97 (71–115)
Serum creatinine (mg/dL)	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Serum potassium	4.2±0.4	4.3±0.4	4.4±0.4	4.3±0.4
Total cholesterol (mg/dL)	188±32	190±30	191±36	190±34
HbA1c (%)	7.3±1.1	7.5±1.2	7.1±1.1	7.2±1.1

Data are the mean±SD, geometric mean (95% CI) or number of patients (%). ACE, angiotensin-converting enzyme; BMI, body mass index; BP, blood pressure; ACR, urinary albumin-to-creatinine ratio; CI, confidence intereval. *$p<0.05$ *vs*. amlodipine monotherapy.

reducing microalbuminuria. However, at the beginning of the SMART, 80 of 150 patients (53%) were receiving antihypertensive agents, and 72 of those were receiving ACE inhibitors during the study period. A recent study involving nondiabetic renal disease demonstrated the superior effect of a dual blockade of the RAS by an ACE inhibitor paired with an ARB in comparison to a single blockade of the RAS with only an ACE inhibitor or an ARB (*8*). In type 2 diabetes, the dual blockade of the RAS is also reported to provide superior renal protection to that of a single blockade (*9*). Therefore, patients who received an ACE inhibitor may have affected the results of the SMART. In addition, although multiple studies have demonstrated the effectiveness of RAS, no controlled studies have yet compared the efficacy of ARB monotherapy with that of CCB monotherapy for diabetic patients at a target BP <130/80 mmHg. Therefore, to assess whether or not ARB has a greater effect on the reduction of microalbuminuria than CCB as a first-line therapy in type 2 diabetes more clearly than in the previous report, the SMART patients treated with valsartan or amlodipine monotherapy were re-analyzed in the present study. In addition, the SMART patients who received an ACE inhibitor during the study period were evaluated to examine the advantages of concomitant therapy with an ACE inhibitor plus valsartan or amlodipine in type 2 diabetes.

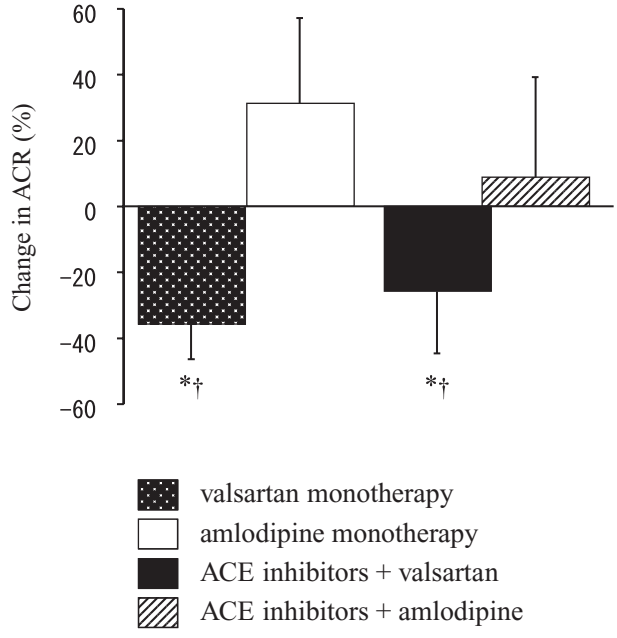

Fig. 1. *The changes in ACR from baseline. Mean±95% CI. *$p<0.01$ vs. amlodipine monotherapy, †$p<0.01$ vs. ACEI inhibitors+amlodipine. ACR, urinary albumin-to-creatinine ratio; ACE, angiotensin-converting enzyme.*

Methods

The SMART was a 24-week prospective, multi-center, randomized, open-label active-control study of valsartan *vs*. amlodipine using a two-arm parallel treatment group (*7*). The details regarding the exclusion and inclusion criteria and the study design are described in the main study article (*7*). The trial was monitored by a safety board that operated independently from the SMART group. 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. All patients had at least a 5-year history of type 2 diabetes and persistent microalbuminuria, which was defined as a urinary albumin creatinine ratio (ACR) of 30–299 μg/mg on average in first-voided urine samples for 3 consecutive days during the 4-week screening period. The patients were randomly assigned to receive either 5 mg of amlodipine once daily or 80 mg of valsartan once daily. Urinary albumin excretion in the first morning urine was mea-

Table 2. Remission and Regression of Microalbuminuria

	Monotherapy		Concomitant with ACE inhibitors	
	Valsartan (n=34)	Amlodipine (n=36)	Valsartan (n=34)	Amlodipine (n=38)
Remission	12 (35)	3 (8)	9 (26)	8 (21)
Regrresion	10 (29)	1 (3)	13 (38)	9 (24)

Data indicate the number of patients (%). ACE, angiotensin-converting enzyme.

sured at the central laboratory. To achieve a treatment goal of <130/80 mmHg, patients were followed up every 4 weeks for 24 weeks. If adequate BP control was not achieved with the initial dose of the study drug by week 4 of the intervention period, the dose was doubled. If necessary, additional antihypertensive drugs (except ACE inhibitors) were added after week 8 of the intervention period. Patients received standard diabetes care throughout the study. Patients were followed up every 4 weeks for 24 weeks. BP was measured using a mercury sphygmomanometer after the patients had remained seated for at least 5 min. Three measurements were taken 1 min apart, and the average of the last two measurements was used for analysis. Urinary albumin excretion was measured at the central laboratory (Medic Lab, Shiga, Japan) by an immunoturbidimetry assay (Hitachi 7070E; Hitachi High Technologies, Tokyo, Japan) using the first morning urine samples.

At baseline, 70 patients (34 in the valsartan group and 36 in the amlodipine group) of the 150 SMART patients were treated without antihypertensive agents. None of the 70 patients received any antihypertensive agents other than the protocol drugs. All of the remaining 80 patients received antihypertensive agents at baseline, including 72 (34 in the valsartan group and 38 in the amlodipine group) who received ACE inhibitors. The ACE inhibitors were maintained at the same dosage throughout the study. Four different antihypertensive regimens were compared (valsartan monotherapy [VM], amlodipine monotherapy [AM], concomitant valsartan and ACE inhibitor [VA], concomitant amlodipine and ACE inhibitor [AA]) on the following outcomes: the change in ACR from baseline to the end of the study; the remission of microalbuminuria, which was defined as a shift of the ACR from microalbuminuria to normoalbuminuria (ACR<30 μg/mg creatinine) at the end of study; and the regression of microalbuminuria, which was defined as a 50% reduction in the ACR from baseline to the end of the study. All adverse events, medications, and patient compliance information were also recorded.

Statistical Analysis

Analyses were performed with the last-observation-carried-forward method. The results are expressed as means±SD. The groups were compared by analysis of variance (ANOVA) with subsequent Scheffe's test for continuous variables or by the χ^2 test as appropriate. A p-value of less than 0.05 was considered statistically significant. All analyses were performed using a commercially available program, JMP version 5.1 for Windows (SAS Institute, Cary, USA).

Results

The baseline characteristics of the patients are listed in Table 1. In AA, the baseline systolic BP (SBP) was significantly higher in the AM group than in the other groups. The mean DBPs were not different among the four groups. The mean daily dosages of valsartan were 99±34 mg for the monotherapy group and 108±39 mg for the concomitant therapy group, and the mean daily dosages of amlodipine were 5.4±1.4 mg for the monotherapy group and 6.1±2.1 mg for the concomitant therapy group. Among the 72 patients receiving ACE inhibitors, 30 received imidapril (mean 5 mg/d), 21 received enarapril (mean 5 mg/d), 18 received trandolapril (1 mg/d), 2 received temocapril (2 mg/d), and 1 received lisinopril (5 mg/d). The dosages of the drugs were those commonly used in Japan, and there was no substantial difference between the two treatment arms.

At the end of the study, the mean BP values were not different among the four groups (VM: 131/74±11/6 mmHg; AM: 132/771±1/10 mmHg; VA: 132/75±13/8 mmHg; AA: 132/74±11/9 mmHg). The mean glycated hemoglobin levels at the end of the study were also similar among the four groups (VM: 7.3±1.2%; AM: 7.4±1.3 mmHg; VC: 7.4±1.3 mmHg; AC group: 7.5±1.3 mmHg). The changes in the ACR from baseline in VM, AM, VA, and AA were −36%, +30%, −26%, and +8%, respectively (Fig. 1). Not only in the monotherapy group but also in the concomitant therapy group, the changes in the ACR from baseline were significantly different between the valsartan arm and the amlodipine arm. In addition, the percentages of patients who achieved remission or regression of microalbuminuria were lower in AM than in the other groups (Table 2).

Next, the impact of SBP reduction on microalbuminuria was examined in the treatment regimens, since the baseline SBPs differed among the four treatment groups. Figure 2 shows the relationship between changes in ACR and SBP from baseline to the end of the study. In the patients with monotherapy, there was no significant correlation in either group (Fig. 2A and B). However, in the AA group, a significant correlation was found between the changes in ACR and SBP (Fig. 2D).

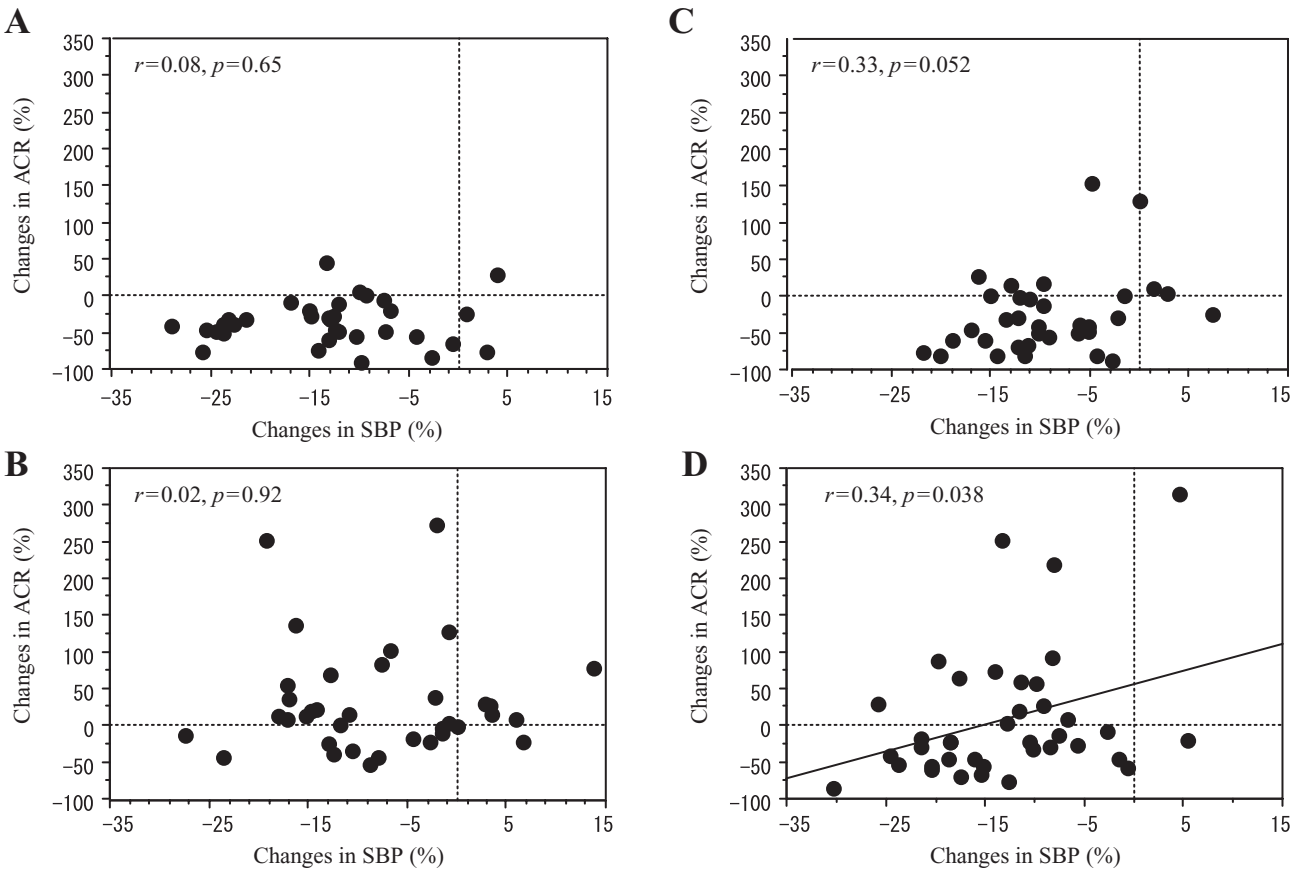

Fig. 2. *Relationship between the changes in ACR and SBP from baseline. A: Monotherapy with valsartan. B: Monotherapy with amlodipine. C: Combination therapy with ACE inhibitor and valsartan. D: Combination therapy with ACE inhibitor and amlodipine. SBP, systolic blood pressure; ACR, urinary albumin-to-creatinine ratio; ACE, angiotensin-converting enzyme.*

Safety

Although treatment was well tolerated in all groups, in the amlodipine group one patient experienced a cerebral hemorrhage and one had leg edema. No correlation between these events and the test drug was proven by the safety board, which operated independently from the SMART group. There were no deaths related to the study medication. In addition, no significant changes were observed in the serum creatinine and potassium levels in any of the groups.

Discussion

In the present post hoc analysis of the SMART, valsartan was shown to be superior to amlodipine monotherapy in reducing microalbuminuria and inducing remission or regression of albuminuria in type 2 diabetes patients. Preventing the development and progression of diabetic nephropathy has been a major focus of diabetes care, not only for renal but also for cardiovascular protection (*10–12*). Microalbuminuria has also been repeatedly shown to be associated with an increased incidence of cardiovascular diseases in both diabetic and non-diabetic subjects (*13*, *14*). In addition, a recent study found that a reduction of microalbuminuria in type 2 diabetes was related to a reduced risk of future renal and cardiovascular events (*15*). These results indicate that the reduction of microalbuminuria is a therapeutic target in order to decrease not only nephropathy but also cardiovascular complications. Therefore, valsartan was expected to provide more beneficial effects than amlodipine as a first-line therapy for type 2 diabetes patients.

Dissociation between the anti-albuminuric and antihypertensive effects of valsartan or amlodipine was observed in the respective monotherapy groups, VM and AM. This finding has been clearly established is previous studies (*16*). In addition, RAS blocking agents decreased urinary albumin excretion independent of BP changes in type 2 diabetes patients (*3*, *17*, *18*). These findings indicate that valsartan's renoprotective effects cannot simply be explained by its BP-lowering effect. On the other hand, amlodipine monotherapy was associated with an increased albuminuria level (AM group). However, in the patients who received concomitant therapy with

amlodipine and ACE inhibitor (AA group), changes in ACR were significantly related with those in SBP. Likewise, in the VA group changes in ACR tended to correlate with changes in SBP. These results also indicate the possibility that, when an ACE inhibitor is administered, greater anti-albuminuric action is associated with a greater reduction in BP in type 2 diabetes. Therefore, the administration of RAS blocking agents is necessary in the treatment of type 2 diabetes patients with hypertension and microalbuminuria.

The renoprotective effects of various dihydropyridine CCBs are inconsistent. These inconsistencies may be due to the different specificities for the calcium channels among dihydropyridine CCBs, such as L, N, T, P/Q, and R. L-type Ca channels were expressed in the afferent glomerular arterioles but not in the afferent glomerular arterioles (*19*, *20*). This distribution of L-type Ca channels may explain why the L-type CCB preferentially dilates the afferent arterioles and increases urinary albumin excretion. Altough amlodipine, an L-type dihydropyridine CCB, failed to reduce albuminuria with monotherapy in the present study, other types dihydropyridine CCBs have been shown to suppress renal injury in both diabetic and nondiabetic patients (*21–23*). Therefore, other types of CCBs, such as L and N, may show different results. In addition, the post hoc analysis was related to a study that was not primarily designed to investigate the effects of concomitant therapy with ACE inhibitors and ARB on microalbuminuria. Therefore, an additional limitation of our study is that the type and dosage of ACE inhibitors have not yet been well controlled. Recently, the uptitration of ARB and ACE inhibitors against proteinuria was found to further improve the renal outcome in patients with both proteinuria and renal insufficiency (*24*). Since the ACE inhibitor dosage was not titrated in the present study, we could not compare the anti-albuminuric effect among the ACE inhibitor monotherapy group, the ARB monotherapy group, and the group receiving both an ACE inhibitor and ARB.

In conclusion, ACR reduction was significantly greater in the valsartan monotherapy group than in the amlodipine monotherapy group in type 2 diabetic patients. The present post hoc study clearly showed that ARB is an effective first-line drug for hypertensive patients with type 2 diabetes and microalbuminuria.

Appendix

Shiga Microalbuminuria Reduction Trial (SMART) Group

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RETRACTION

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The authors have indicated to the journal that this paper should be withdrawn in response to the interim report on the Shiga Microalbuminuria Reduction Trial (SMART), and in consequence of the retraction of the main report from the same trial.[1] After careful consideration, *Hypertension Research* editorial committee formally retracts this paper with agreement of the authors.

1 The Shiga Microalbuminuria Reduction Trial (SMART) Group. Reduction of microalbuminuria in patients with type 2 diabetes: The Shiga Microalbuminuria Reduction Trial (SMART). *Diabetes Care* 2007; **30**: 1581–1583.