Microalbuminuria Reduction With Valsartan in Patients With Type 2 Diabetes Mellitus
A Blood Pressure–Independent Effect

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Background—Elevated urine albumin excretion (UAER) is a modifiable risk factor for renal and cardiovascular disease in type 2 diabetes. Blockade of the renin-angiotensin system lowers UAER, but whether this effect is independent of blood pressure (BP) reduction remains controversial. The MicroAlbuminuria Reduction With VALsartan (MARVAL) study was designed to evaluate the BP-independent effect of valsartan on UAER in type 2 diabetic patients with microalbuminuria.

Methods and Results—Three hundred thirty-two patients with type 2 diabetes and microalbuminuria, with or without hypertension, were randomly assigned to 80 mg/d valsartan or 5 mg/d amlodipine for 24 weeks. A target BP of 135/85 mm Hg was aimed for by dose-doubling followed by addition of bendrofluazide and doxazosin whenever needed. The primary end point was the percent change in UAER from baseline to 24 weeks. The UAER at 24 weeks was 56% (95% CI, 49.6 to 63.0) of baseline with valsartan and 92% (95% CI, 81.7 to 103.7) of baseline with amlodipine, a highly significant between-group effect (P<0.001). Valsartan lowered UAER similarly in both the hypertensive and normotensive subgroups. More patients reversed to normoalbuminuria with valsartan (29.9% versus 14.5%; P=0.001).

Over the study period, BP reductions were similar between the two treatments (systolic/diastolic 11.2/6.6 mm Hg for valsartan, 11.6/6.5 mm Hg for amlodipine) and at no time point was there a between-group significant difference in BP values in either the hypertensive or the normotensive subgroup.

Conclusions—For the same level of attained BP and the same degree of BP reduction, valsartan lowered UAER more effectively than amlodipine in patients with type 2 diabetes and microalbuminuria, including the subgroup with baseline normotension. This indicates a BP-independent antiproteinuric effect of valsartan. (Circulation. 2002;106:672-678.)

Key Words: diabetes mellitus • kidney • angiotensin • blood pressure • valsartan

The development of microalbuminuria in type 2 diabetes increases the risk for renal and cardiovascular disease.1,2 The incidence of end-stage renal disease in type 2 diabetes has risen in many regions of the world.4,5 There is growing evidence that reduction and normalization of proteinuria is a key treatment goal for renal protection and possibly cardioprotection.6 Inhibition of the renin-angiotensin system (RAS), either by ACE inhibitors or angiotensin II antagonists (AIIAs), prevents the development or reduces the level of proteinuria in the diabetic animal model, resulting in less renal structural damage.7,8 In type 2 diabetic patients with microalbuminuria, ACE inhibitor treatment lowers albumin excretion rate (UAER) and prevents the progression of renal disease as measured by serum creatinine.9 Selective blockade of the AT₁ receptor by AIIAs also lowers microalbuminuria in these patients to the same extent as ACE inhibition.10 Because of the blood pressure (BP)-lowering effect of blockade of the RAS, it has been difficult in all these studies to establish whether the antiproteinuric effect was specific to this type of drug or simply the results of lower BP. A reduction of proteinuria over and above that which is afforded by BP lowering would be important because it may confer added cardio renal protection.6

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The purpose of this study, therefore, was to investigate whether the effect of the highly selective AIIA, valsartan, on UAER was independent of its BP-lowering properties. To fully test this hypothesis, microalbuminuric patients with baseline arterial normotension were allowed to enter the study. The third-generation calcium channel blocker (CCB) amlodipine was chosen as a comparator in view of its similar
dosing schedule and the expectation that it would confer similar control of BP. Moreover, in patients with microalbuminuria, dihydropyridine CCBs appear to affect UAER in a pressure-dependent way.

Participants
Patients 35 to 75 years of age with type 2 diabetes mellitus and evidence of persistent microalbuminuria (median UAER of 3 nonconsecutive timed overnight urine collections in the range of 20 to 200 µg/min during a 5-week period before entry) were recruited from 31 centers in the United Kingdom. Other inclusion criteria were normal serum creatinine and BP at baseline <180/105 mm Hg. Exclusion criteria were type 1 diabetes (onset <35 years and requiring insulin within the first year), use of ACE inhibitors, AIIAs, and CCBs in the 5 weeks before random assignment; child-bearing potential for women; heart failure within the preceding 6 months requiring ACE inhibitor therapy; history of myocardial infarction, PTCA or cerebrovascular accident within the preceding 3 months; severe diabetic neuropathy; history of hypertensive or hepatic encephalopathy; and evidence of hepatic disease.

Patients could be withdrawn from the study because of intolerable adverse events (AEs), exclusion criteria, noncompliance, or protocol violations. Patients were not excluded if they failed to reach the target BP.

The study was approved by the South Thames Multicentre Research Ethics Committee and undertaken in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients gave written informed consent.

Study Design
This was a multicenter, randomized, double-blind, active control, parallel group, 24-week study of 80 mg/d valsartan versus 5 mg/d amlodipine. The study duration was based on the observation that inhibition of the RAS lowers albuminuria with full effect after 24 weeks.

At screening, CCBs (n=27), ACE inhibitors, or AIIAs (n=48) were withdrawn from patients 5 weeks before study entry and replaced with non–potassium-sparing diuretics to maintain BP control. Other antihypertensive drugs were continued during the run-in (n=14). Hypertension was defined as BP ≥140/90 mm Hg and/or antihypertensive therapy at baseline. All antihypertensive medications were withdrawn and replaced by study drug, before random assignment by a computer-generated, random allocation, concealed sequence.

The target BP was 135/85 mm Hg, based on evidence at the time of study design that these BP values slow progression of renal disease in type 2 diabetes. If adequate BP control was not achieved with study drug by week 4, the valsartan or amlodipine dose was doubled. If necessary, 2.5 mg/d bendrofluazide could be added from week 8 and doxazosin from week 12.

Patients were followed up at weeks 4, 8, 12, 18, and 24. At baseline and follow-ups, urinary albumin concentrations were measured with immunoturbidimetry centrally at Guys Hospital. Three consecutive urine collections for albumin concentration were made at baseline and 24 weeks and two collections at the other time points. The median value was used for calculation. At each time point the lowest arterial blood pressure during a 24-hour period (trough BP) was measured (Korotkoff phase I/V) by automatic oscillometry (OMRON 705CP, OMRON Healthcare) in the dominant arm, with the patient in the sitting position after at least 5 minutes of rest. Three measurements were taken 2 minutes apart, and the mean value was used for calculation. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography centrally at Pool Laboratories Ltd, UK, at baseline and 12 and 24 weeks. Full blood count, electrolytes, serum creatinine, liver function tests, and cholesterol were measured by routine biochemical methods at the local laboratory.

The primary end point was the percentage change in UAER from baseline to week 24. The secondary end point was the proportion of patients returning to normoalbuminuria status (UAER <20 µg/min as the median of the last visit measurements). At each visit, all new AEs were recorded.

Statistical Methodology
With 150 patients in each group, the study had 90% power at 5% significance (2-sided) to detect a clinically significant (15%) between-group difference in the primary end point. This sample size would also provide ~80% power to detect a 15% difference in the primary end point in the hypertensive subgroup, estimated at 70% of study population.

Efficacy analyses were carried out on the intention-to-treat population, all randomly assigned patients receiving medication and having at least 1 postdose assessment. For all variables analyzed, the end point measurement was the last post–random assignment measurement carried forward (for the primary efficacy parameter this was required for 14% and 15% in the valsartan and amlodipine groups, respectively). In addition, sensitivity analyses were carried out for the primary and secondary efficacy parameters on completers (all patients completing the study and having both baseline and end of study assessments). An additional sensitivity analysis was carried out for the primary efficacy parameter by using predicted mean imputation performed using an ordinary least squares regression (Solas version 2.0, Statistical Solutions). In all cases, the analyses gave results very similar to the intention-to-treat population and are not shown. Safety analyses were carried out on all randomly assigned patients who received study medication.

Changes from baseline in UAER, BP, HbA1c level, and serum creatinine was assessed with the use of ANOCOVA models (including terms for treatment, center, and treatment by center interactions) to adjust for any baseline differences. Baseline UAER was also included as a covariate for the primary analysis of UAER. Because of its skewed distribution, UAER raw data were log-transformed for calculation and expressed as the ratio from baseline. Summary statistics for UAER are provided as geometric mean with 95% CI. An additional analysis for UAER included baseline hypertensive status in the model. To further investigate whether changes in BP might explain the differences in UAER between treatments, an exploratory general linear model was carried out including center and treatment as factors and change in BP as a covariate. Model assumptions of normality and constant variance were both upheld. Treatment differences in blood pressure at each visit were analyzed by ANOVA, allowing for...
TABLE 1. Demographic and Clinical Features of Type 2 Diabetic Patients With Microalbuminuria Receiving Either Valsartan or Amlodipine

<table>
<thead>
<tr>
<th>Subject</th>
<th>Valsartan (n=169)</th>
<th>Amlodipine (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n (%)</td>
<td>139 (82.2)/30 (17.8)</td>
<td>126 (77.3)/37 (22.7)</td>
</tr>
<tr>
<td>Mean age, y (range)</td>
<td>59 (36–75)</td>
<td>57 (35–75)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.9 (5.95)</td>
<td>30.7 (5.58)</td>
</tr>
<tr>
<td>UAER, μg/min,* geometric mean (IQR)</td>
<td>57.9 (33–102.3)</td>
<td>55.4 (34.3–84.6)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>107 (63.3)</td>
<td>109 (66.8)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>147.3 (17.83)</td>
<td>148.3 (17.6)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>85.4 (8.79)</td>
<td>85.7 (9.8)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.1 (0.5)</td>
<td>4.3 (0.5)</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>97.3 (19)</td>
<td>93.3 (17.8)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise stated.
*Baseline UAER was available in 167 and 161 patients only in the valsartan and amlodipine groups, respectively.

the effects of center and treatment and are shown for the whole group as well as the hypertensive and normotensive subgroups.

The proportion of patients returning to normoalbuminuria was analyzed with the use of Fisher’s exact test. For safety evaluation and binary efficacy parameters, between-treatment differences (valsartan minus amlodipine) together with exact binomial 95% CI are shown.

All analyses were performed with the use of version 6.12 of the SAS statistical package (version 4.0). All hypothesis tests were 2-tailed, with α=0.05.

Results

Patients were recruited between March 1998 and December 1999. Of 683 patients screened, a total of 332 were randomly assigned (valsartan 169, amlodipine 163). Main reasons for withdrawal were AEs (valsartan 8, amlodipine 7), protocol violations (valsartan 7, amlodipine 5), withdrawn consent (valsartan 4, amlodipine 4), and others (valsartan 4, amlodipine 2).

The demographic and clinical characteristics of the two treatment groups were comparable at baseline (Table 1). The majority of patients were white (88% valsartan and 85% amlodipine) and approximately 10% were Asian. Baseline UAER values were similar in the two groups, as was trough systolic (SBP) and diastolic BP (DBP). Five patients in the valsartan group had baseline UAER below (n=2) or above (n=3) the microalbuminuria range.

Efficacy

There was a statistically significant decrease in UAER with valsartan compared with amlodipine (P<0.001; 95% CI for ratio, 0.539, 0.729). Valsartan, in contrast to amlodipine, lowered UAER progressively over time to a nadir at 24 weeks (Table 2 and Figure 1A). The UAER at 24 weeks with valsartan was 56% (95% CI, 49.6 to 63.0) of baseline, equivalent to a 44% reduction. The UAER for amlodipine at week 24 was 92% (95% CI, 81.7 to 103.7) of baseline, a reduction of only 8%. The treatment effect was highly significant (P<0.001; 95% CI for ratio, 0.520, 0.710). When baseline hypertensive status was entered into the model, there was no change to the outcome of the analysis.

Subgroup analyses for patients who were hypertensive or normotensive at entry produced a similar pattern of results for change in UAER (hypertensive subgroup: P<0.001, 95% CI for ratio, 0.482, 0.737; normotensive subgroup: P<0.001, 95% CI for ratio, 0.486, 0.772). The time course of these changes is shown in Figure 1, B and C.

The mean reductions in trough BP from baseline to week 24 were similar in both treatment groups (SBP: valsartan, −11.2 mm Hg; amlodipine, −11.6 mm Hg, between-treatment adjusted mean change: −1.1 mm Hg, 95% CI,

TABLE 2. Urine Albumin Excretion Rate at Baseline and During Follow-Up in Type 2 Diabetic Patients With Microalbuminuria Allocated to Valsartan or Amlodipine

<table>
<thead>
<tr>
<th>No. for</th>
<th>UAER* μg/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Valsartan</td>
</tr>
<tr>
<td>Baseline 167</td>
<td>57.9 (33.0–102.3)</td>
</tr>
<tr>
<td>Baseline (−) 163</td>
<td>57.2 (33.0–102.3)</td>
</tr>
<tr>
<td>Week 4 155</td>
<td>49.4 (30.1–91.6)</td>
</tr>
<tr>
<td>Week 8 155</td>
<td>44.7 (24.9–83.5)</td>
</tr>
<tr>
<td>Week 12 149</td>
<td>41.6 (25.1–69.9)</td>
</tr>
<tr>
<td>Week 18 144</td>
<td>36.3 (21.4–64.8)</td>
</tr>
<tr>
<td>Week 24 142</td>
<td>32.3 (18.1–59.7)</td>
</tr>
<tr>
<td>Week 24 (LOCF) 163</td>
<td>33.7 (18.8–60.3)</td>
</tr>
</tbody>
</table>

*Values are geometric mean (interquartile range). Baseline UAER was available in 167 and 161 patients and end-of-study UAER in 142 and 136 patients only in the valsartan and amlodipine groups, respectively. Baseline (−) represents the baseline results for patients with week 24 (LOCF) data. Week 24 (LOCF) represents the week 24 results after last observation carried forward imputation.
DBP: valsartan, $-5.1$, $3.0$, $P=0.610$; DBP: amlodipine, $-6.6$ mm Hg, between-treatment adjusted mean change, $-1.2$ mm Hg, $95\%$ CI, $-3.3$, $1.0$, $P=0.296$). The time courses of the BP changes were similar in the two treatment groups for all patients as well as the hypertensive and normotensive subgroups (Figure 2, A through C). Table 3 shows the actual systolic and diastolic BP values attained at each time point during the study in the two treatment groups. Data are given for the whole group and the subgroups with baseline arterial hypertension or normotension. At no time

Figure 1. Percentage of baseline UAER in type 2 diabetic patients with microalbuminuria allocated to valsartan (●) or amlodipine (●). Error bars indicate 95% CI. Probability values indicate between-group differences in baseline to 24-week change. A, Whole population; B, subset of patients with hypertension at study entry; C, subset of patients with normotension at study entry.

Figure 2. Mean systolic and diastolic blood pressure in type 2 diabetic patients with microalbuminuria allocated to valsartan (●) or amlodipine (●). Error bars indicate standard deviation. A, Whole population; B, subset of patients with hypertension at study entry; C, subset of patients with normotension at study entry.
point was there a significant difference in either systolic or diastolic BP between the valsartan and the amlodipine group. This was true for both the normotensive as well as the hypertensive subgroup.

In normotensive patients there were small decreases in BP with both treatments (valsartan: SBP/DBP, −2.8/−2.7 mm Hg; amlodipine, −1.9/−1.1 mm Hg) and no significant between-treatment differences (DBP, \( P = 0.246 \); SBP, \( P = 0.329 \)). True equivalence of BP reduction was thus obtained between the two antihypertensive regimens, and this applied irrespective of normotensive or hypertensive status. The results of the analysis to assess whether changes in BP might explain the differences in UAER between treatments showed both change in DBP and SBP were statistically significant covariates (\( P = 0.03 \) and \( < 0.001 \), respectively). However, the treatment effect remained significant (\( P < 0.001 \)) in both models, indicating that the observed changes in UAER were independent of differences in BP reduction. The proportion of patients achieving target BP was similar in the two groups (valsartan, 53%; amlodipine, 45%) and not significantly different (\( P = 0.196 \); difference 8.3%; 95% CI, −3.7%, 20.1%). In the valsartan group, 55% received bendroflumiazide and 28% doxazosin; the proportions in the amlodipine group were 50% and 29%, respectively.

The secondary end point analysis showed a significantly greater percentage of patients returning to normoalbuminuria status by week 24 with valsartan (29.9%; \( n = 49 \)) than with amlodipine (14.5%; \( n = 23 \)) (between-treatment difference, 15.4%; 95% CI, 5.6, 25.8; \( P < 0.001 \)).

There was no significant difference in mean change in absolute values of HbA1c from baseline to week 24 between valsartan (0.04%) and amlodipine (0.16%) (\( P = 0.427 \); 95% CI, −0.34, 0.15). HbA1c remained stable and did not differ throughout the study with either treatment (Table 4). Eighty-five percent of patients received oral hypoglycemic agents in both treatment groups. Insulin was used by the remainder.

Total cholesterol, serum potassium, and serum creatinine were similar at baseline between the two groups and did not change significantly during follow-up.

Safety
Treatment was well tolerated in both groups, but ankle edema occurred less frequently with valsartan (1.2% versus 7.4%; difference, −6.2%; 95% CI, −12.9%, −0.4%, \( P = 0.006 \)). There were no deaths related to study medication. There were 9 serious AEs with valsartan and 10 with amlodipine, of which 2 were suspected to be study drug-related. Both events resolved within 6 days.

Discussion
This study demonstrates that UAER was significantly reduced by valsartan in type 2 diabetic patients with microalbuminuria. Amlodipine had no significant effects on UAER over the time period of this trial. Valsartan also induced regression to normoalbuminuria in a significantly greater proportion of patients than amlodipine. Importantly, BP was reduced to a nearly identical extent by both drugs. Specific analysis of the relation between changes in BP and UAER confirmed that the differences in UAER reduction between treatment groups were not related to differences in BP reduction. This conclusion is strengthened further by the observation that in the normotensive subgroup valsartan but not amlodipine significantly lowered UAER despite similar minimal and nonsignificant changes in arterial pressure. We believe the results to be of importance because they suggest that blockade of the AT1 receptor might be used to prevent progression of albuminuria in the absence of arterial hypertension. Even in the subgroup that achieved BP targets, the between-treatment group differences in the reduction of UAER persisted (data not shown). These results strongly support the notion that the albuminuria-lowering effects of valsartan are in addition to and, to a large extent, divorced from its antihypertensive action.

### TABLE 4. Mean (SD) Glycated Hemoglobin, HbA1c, %, at Baseline and During Follow-Up in Type 2 Diabetic Patients With Microalbuminuria Allocated to Valsartan or Amlodipine

<table>
<thead>
<tr>
<th>Time</th>
<th>Valsartan</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>8.7 (1.4)</td>
<td>8.7 (1.6)</td>
</tr>
<tr>
<td>Week 12</td>
<td>8.8 (1.3)</td>
<td>8.7 (1.4)</td>
</tr>
<tr>
<td>Week 24</td>
<td>8.7 (1.3)</td>
<td>8.9 (1.5)</td>
</tr>
</tbody>
</table>
Our data add new information to previous studies suggesting that lowering of BP in diabetic patients by ACE inhibition or AT₁ receptor antagonism results in greater reduction of albuminuria than that obtained with other antihypertensive agents. In virtually all these trials, however, the reduction in BP obtained by ACE inhibitor or AIIA was greater than that of the comparator group, and this confounded interpretation. Our findings leave little doubt that AT₁ receptor antagonism affects albuminuria also by mechanisms separate from systemic BP changes. These may involve distinct renal effects relating to microcirculation changes, glomerular capillary wall permeability properties, and tissue remodeling. Angiotensin II receptor blockade also prevents the loss of nephrin in the glomeruli of the diabetic animal, and recent data suggest that AIIAs may reduce levels of TGF-β in type 2 diabetic patients with microalbuminuria.

There are possible alternative interpretations of our results. Amlodipine per se, independent of its BP effect, could promote albuminuria, as suggested for other CCBs. If this was the case, one could still argue that because of the properties of the comparator, the effect of valsartan on proteinuria was entirely attributable to BP lowering. This interpretation, however, is unlikely. Several publications suggest that CCBs lower UAER through a systemic BP dependent mechanism, especially at BP reductions of the magnitude achieved in this study, though their effects may be delayed. There is no consistent evidence that dihydropyridine CCBs have an independent proteinuria-enhancing action. Thus, our conclusion that the prompt and profound effect of valsartan on UAER was independent of its antihypertensive effect.

Sixty-five percent of the whole group was found to be hypertensive at entry into the study. The observation that valsartan reduced microalbuminuria by >40% both in the hypertensive and particularly the normotensive subgroups is very important. Microalbuminuria in this patient population is an independent risk factor for both renal disease and cardiovascular disease. Our study was short-term and cannot establish whether the correction of microalbuminuria by valsartan will be translated into clinical benefit. Several studies, however, in patients with more advanced proteinuria, with and without diabetes, have shown a clear relation between proteinuria reduction and slowing of renal disease progression. Moreover, it is the type 2 diabetic subgroup with microalbuminuria that appears to benefit most from ACE inhibition in terms of cardioprotection. A recent trial in type 2 diabetic patients with microalbuminuria, all of whom had hypertension, has shown that 300 mg/d (but not 150 mg/d) irbesartan significantly reduced UAER by 46% and lowered the risk of progression to persistent albuminuria by 70% over a 2-year period, compared with conventional antihypertensive therapy that excluded ACE inhibitors and dihydropyridine CCBs. These results were obtained in the face of similar average reductions in DBP, but mean SBP, throughout the trial, was highly significantly lower by ≈3 mm Hg in the 300 mg/d irbesartan group compared with placebo. This further underscores the importance of our findings in the normotensive subgroup in which the administration of valsartan was BP neutral but highly effective in lowering UAER.

Two other trials in type 2 diabetic patients with overt nephropathy have also recently shown a renoprotective effect of angiotensin receptor antagonism with losartan and irbesartan that appears largely though not entirely independent of BP reduction, underscoring the therapeutic relevance of other mechanisms of action, of which proteinuria lowering is likely to be an important one, of this class of compounds.

In conclusion, valsartan significantly reduces microalbuminuria in type 2 diabetic patients, an effect that appears to be independent of its BP-lowering action.

Acknowledgments

This study was supported by a grant from Novartis Pharmaceuticals UK Ltd, Frimley, UK, which did not have access to unblinded information. We thank Dr G. McInnes for constructive suggestions in the design of the study and Tony Munsman from SQN for statistical analysis.

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References
678 Circulation August 6, 2002


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_Circulation_. 2002;106:672-678; originally published online July 15, 2002;
doi: 10.1161/01.CIR.0000024416.33113.0A
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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