Targeting Albumin Excretion Rate in the Treatment of the Hypertensive Diabetic Patient with Renal Disease

Michael J. Krimholtz,* Janaka Karalliedde,* Stephen Thomas,* Rudy Bilous,† and Giancarlo Viberti*

*Unit for Metabolic Medicine, Department of Diabetes Endocrinology and Internal Medicine, GKT School of Medicine, Kings College London, Guys Hospital, London, United Kingdom; and †Department of Diabetes and Endocrinology, James Cook University Hospital, Middlesbrough, United Kingdom

Combination of an angiotensin-converting enzyme inhibitor (ACEI) with an angiotensin II receptor blocker is advocated as a treatment option in diabetic patients with nephropathy and residual albuminuria while on antihypertensive therapy. Abrogation of albuminuria is a key treatment goal to prevent disease progression. The assumption is that albuminuria reduction is the result of more complete blockade of the renin angiotensin system; thus, the ACEI-angiotensin II receptor blocker combination would have a greater albuminuria-lowering effect than the combination of an ACEI with a calcium channel blocker such as amlodipine, which causes similar reductions in BP but does not affect the renin angiotensin system. Twenty-eight patients who had type 1 diabetes and known diabetic renal disease and had a persistently elevated albumin creatinine ratio (ACR) > 10 mg/mmol despite office BP recordings ≤140/80 mmHg on maximal recommended dose of the ACEI lisinopril were studied. Patients were allocated to receive either candesartan (16 mg/d) or amlodipine (10 mg/d) in addition to preexisting ACEI inhibition and followed for 24 wk in a randomized, double-blind, parallel-group trial. By week 24, ACR fell by 56% with candesartan and 54% with amlodipine (P < 0.01 versus baseline for both) with no significant difference between groups. Mean arterial BP fell between 3 and 6 mmHg similarly in both groups. In neither group was a significant correlation found between the change in ACR and the change in BP. Candesartan and amlodipine lowered ACR and BP by a similar degree. The fall in ACR was disproportionate to the fall of systemic BP and independent of it. The mechanism of the reduction in albuminuria seen with these agents in combination with an ACEI remains to be elucidated.


Microalbuminuria is a marker of renal disease in individuals both with and without diabetes and predicts cardiovascular disease (CVD) and early mortality (1–4). Although the terms normoalbuminuria, microalbuminuria, and macroalbuminuria (clinical albuminuria) describe different categories of albumin excretion rate (AER), it is important to recognize that the relationship between albumin excretion and cardio renal risk is part of a continuum (1,3). There is a dose–response relationship between the degree of albuminuria and renal and cardiovascular risk that seems to rise at AER between 8 and 10 μg/min, well below the level currently considered the upper boundary of the normal range of AER (1). Elevated rates of urinary albumin excretion predict target organ damage, notably renal disease, but are also related to left ventricular dysfunction, stroke, and myocardial infarction.

The rates of progression of microalbuminuria to macroalbuminuria in recent times are approximately 45 to 50%, with 25 to 30% of patients remaining microalbuminuric over a 10-yr period. The regression rates to normoalbuminuria therefore are higher than described in previous decades (5–7). This changing natural history of microalbuminuria is a result of a number of factors that include improved glycemic control, more intensive treatment of hypertension, the use of inhibitors of the renin angiotensin system (RAS), the radical change in smoking habits, and effective treatment of hyperlipidemia with new lipid-lowering agents.

Treatment of BP with angiotensin-converting enzyme inhibitors (ACEI) and the angiotensin II receptor blocker (ARB) class of antihypertensive drugs has become a cornerstone in the management of microalbuminuria as well as of the more advanced stages of clinical albuminuria in both patients with type 1 and type 2 diabetes (8,9). There is also evidence that use of ACEI may benefit patients who have diabetes and microalbuminuria in terms of CVD protection (10). A number of studies indicate that ARB achieve greater protein-lowering effects than other antihypertensive drugs for equivalent BP reductions (11–13). Whether these renal and cardioprotective effects result directly from lowering of albumin excretion is still a matter of debate. Nevertheless, in recent clinical trials, proteinuria reduction per se has been found to be associated with delayed rate of progression of renal disease and with lower CVD events, with the degree of early albuminuria reduction giving an indication on subsequent long-term degree of organ protection (10,12,13). Thus, correction of microalbuminuria/macroalbuminuria becomes a key therapeutic goal.

A number of strategies have been introduced recently to
maximize proteinuria reduction. Combination therapies of ACEI and diuretic or ACEI and ARB have obtained greater proteinuria-lowering effects in patients with diabetes compared with maximal dose of ACEI or ARB (14–16). This was usually obtained concomitant to a further reduction in BP (14–16). It is worth considering in this context that the dose–response curves of ACEI and ARB in lowering BP and proteinuria differ. At higher drug dosage, proteinuria may be further reduced in the face of unchanged BP. This notwithstanding, a significant number of patients with diabetic nephropathy have persistent elevated AER despite treatment with recommended doses of ACEI and good BP control (17). Although this residual proteinuria may still be due to ACEI under dosing, “ACEI escape,” the generation of angiotensin II by ACE-independent pathways may also be implicated (18,19). Residual proteinuria indicates continued renal dysfunction and high risk for disease progression. The optimal management strategy to abrogate this residual proteinuria in patients with type 1 diabetes remains unclear. Dual blockade of the RAS, with the combination of ACEI and ARB, further reduces BP and albuminuria in type 1 and type 2 diabetes and in nondiabetic renal disease has been shown to reduce the primary end points of doubling of serum creatinine or development of end-stage renal failure (15,16,20–24).

Information on patients who have diabetes and have achieved good BP control on ACEI but still have an abnormal excretion of albumin is limited and confined to short-term studies that are placebo (rather than comparator) controlled and have included patients with unsatisfactory BP control (15,16,24). For assessing the potential additional benefit for protein lowering in combination treatment with ACEI, an active control study of the addition of an ARB versus another antihypertensive agent that does not interfere with the RAS but has similar BP lowering potency is needed. We therefore conducted a 24-wk double-blind, parallel-group study in which patients who had diabetes and albumin creatinine ratio (ACR) >10 mg/mmol despite taking the maximum recommended dose of the ACEI lisinopril and who had persistent clinic BP recordings ≤140/80 mmHg were randomized to receive either the ARB candesartan or the calcium channel blocker (CCB) amlodipine.

**Materials and Methods**

**Patients**

Twenty-eight patients with type 1 diabetes were recruited from the diabetes clinics of Guys’ & St. Thomas’ and St. Helier hospitals. All patients were receiving insulin injections since diagnosis and had developed diabetic nephropathy with a documented history of albuminuria, arterial hypertension, and diabetic retinopathy but no other kidney or urinary tract disease or heart failure. Patients were on chronic treatment with the maximum dose of ACEI, which for at least 4 wk before randomization was uniformed to lisinopril 20 mg/d, which is the maximum recommended dose by the British National Formulary for the treatment of diabetic kidney disease. All patients were on a diabetic diet with no further restriction of dietary sodium or protein intake.

To qualify for entry into the study, patients had to have residual proteinuria, with an ACR >10 mg/mmol on their maximum ACEI treatment and after lisinopril just before randomization documented by at least two of three timed overnight urine collections. In addition, their office BP had to be persistently (≥6 mo) ≤140/80 mmHg, hemoglobin A1c (HbA1c) had to be <10%, and serum creatinine had to be <150 μmol/L.

Exclusion criteria were inability to understand patient information, alcohol or medicine abuse, age <18 yr, potassium ≥5.5 mmol/L, pregnancy, and mean arterial pressure (MAP) <60 mmHg. Written informed consent was obtained from all patients after full explanation of the study procedures.

**Design**

This was a randomized, double-blind, parallel-group, controlled study that compared the effects of candesartan versus amlodipine added to preexisting ACEI treatment on albuminuria and BP. Eligible patients were allocated by an outside observer in random blocks of eight to ensure a balanced distribution between treatment groups, either to candesartan 8 mg/d or amlodipine 5 mg/d, which, after 4 wk, was forced uptitrated to candesartan 16 mg/d and amlodipine 10 mg/d until the end of the study at 24 wk. After the screening phase, assessments were made at the following time points: baseline, 4 wk, 12 wk, and 24 wk.

At baseline and weeks 4 and 24, the following measurements were taken: BP was taken using a 24-h ambulatory BP monitor (Spacelabs, Redmond, WA). Venous blood was sampled for serum electrolytes, creatinine, hemoglobin measurements (Cobas Mira analyser; Roche, Montclair, NJ), and HbA1c by HPLC (CLC 330; Primus, Kansas City, MO), and urine was collected on three timed overnight nonconsecutive samples for calculation of ACR (Imunoturbidimetry Cobas Mira analyser) (25,26). GFR was calculated using the Cockroft-Gault formula (27).

Discontinuation criteria during study were inability to tolerate study medication, rise in serum potassium to >5.5 mmol/L, or a rise in serum creatinine >150 μmol/L. The study protocol was in accordance with the Helsinki declaration and was approved by the local ethics committees of each participating center.

**Statistical Analyses**

Data were assessed on an intention-to-treat basis with results carried forward for patients who did not complete the study but who had at least one measurement after baseline. The primary outcome measure was change in ACR. The secondary outcome measure was change in BP. Differences within and between groups were tested using paired or unpaired parametric tests as appropriate, and adjustments for baseline differences were made using one-way analysis of covariance.

ACR values were log-transformed before analysis because of their positively skewed distribution, and the geometric mean was used for calculations. Correlation analysis was carried out by the least-squares method. Data were analyzed using the Stat Plus for Microsoft Windows (Berk Carey, Pacific Grove, CA) and SPSS 10.0 (Chicago, IL) software packages. Power calculation was based on a pilot study that indicated that two groups...
of at least 12 subjects would be required to have an 80% chance to detect a 20% between-group difference in the change of ACR at the 5% significance level.

Results

Of the 28 patients enrolled, 26 were suitable for analysis. Twenty-three patients completed the full 24-wk study. Two patients in the amlodipine group and one from the candesartan group were withdrawn after the 4-wk time point because of side effects (edema and flushing for amlodipine and serum potassium >5.5 for candesartan). Two patients dropped out before week 4 and were not assessable.

Baseline characteristics of the two treatment groups are shown in Table 1. Patients in the two treatment groups had similar gender distribution, age, and duration of disease. Their baseline BP, HbA1c, ACR, and renal function were also comparable.

Effects of Treatment

Effects on Albuminuria

There was a highly significant fall in ACR from baseline to week 4 (geometric mean [interquartile range]: amlodipine 25.7 [13.0 to 39.1] to 14.0 mg/mmol [6.5 to 29.31 mg/mmol]; candesartan 32.3 [12.2 to 89.8] to 18.7 mg/mmol [12.6 to 32.1 mg/mmol]) and further to week 24 (amlodipine 10.6 mg/mmol [5.0 to 34 mg/mmol]; candesartan baseline to 15.0 mg/mmol [6.6 to 31.0 mg/mmol]; P < 0.01 for both groups at both time points). ACR fell by 56% (P < 0.01) with candesartan and by 53% (P < 0.01) with amlodipine by week 24 (Figure 1). There was no significant difference in the magnitude of the fall between treatment groups, and this remained so after adjustment for baseline differences. One patient in the amlodipine group and two in the candesartan group achieved normoalbuminuria as defined by ACR <3 mg/mmol.

Effects on BP

Both amlodipine 10 mg and candesartan 16 mg reduced 24-h MAP by a similar degree when combined with ACEI. The fall in BP seen with amlodipine occurred mainly in the first 4 wk of the study, whereas the BP fall seen with candesartan occurred later. Both groups induced a significant reduction in BP by week 24 (P = 0.028 for amlodipine, P = 0.03 for candesartan). Attained 24-h MAP at 24 wk was 96 mmHg in the amlodipine group and 94 mmHg in the candesartan group (Figure 2A). A similar pattern was seen with both systolic and diastolic 24-h BP. Although the fall in MAP was numerically greater in the amlodipine group, there was no statistically significant difference in BP fall between the two groups after adjusting for baseline differences. There was a slight nonsignificant reduction in HbA1c during the study that was similar in the two groups (Figure 2B).

There was no statistically significant change in GFR in either group during the study, with no group difference. Calculated GFR increased numerically by 2 ml/min in the amlodipine group and fell by 6 ml/min in the candesartan group by week 24. Plasma potassium levels remained stable during the study, with no significant difference between the groups. In neither group was a significant correlation found between the fall in ACR and the fall in MAP over the 24 wk. Furthermore, there was no significant between-group difference in the fall in ACR per unit fall in MAP.

Discussion

This study demonstrated that in patients who have type 1 diabetes with diabetic nephropathy and residual albuminuria despite maximum recommended dose of an ACEI and good BP control, the addition of either candesartan or amlodipine caused a further significant reduction in albuminuria. The antialbuminuric effect of the two agents was similar. BP was reduced further and, after adjusting for baseline differences, similarly by both treatments, but this did not seem to explain the reduction in albuminuria. That combination therapy of ACEI and amlodipine reduced albuminuria to a similar extent as ACEI plus ARB is of interest and intriguing. The rationale for using combination treatment of ACEI with ARB in patients who show insufficient antiproteinuric response to ACEI is that the addition of an ARB may provide a more complete blocking of the RAS, by neutralizing the effects of angiotensin II produced by ACE-independent pathways and/or prevent a possible ACEI escape (18,19).

Table 1. Baseline demographic and clinical features of patients who have type 1 diabetes with diabetic nephropathy and residual albuminuria on maximal ACEI treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Amlodipine (n = 14)</th>
<th>Candesartan (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>9/5</td>
<td>6/6</td>
<td>0.77</td>
</tr>
<tr>
<td>Mean age, yr (range)</td>
<td>47 (33–61)</td>
<td>47 (30–70)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean duration of diabetes, yr (range)</td>
<td>30 (14–46)</td>
<td>31 (20–61)</td>
<td>0.77</td>
</tr>
<tr>
<td>Geometric mean (interquartile range) ACR, mg/mmol</td>
<td>25.7 (13–39.1)</td>
<td>32.3 (12.2–89.8)</td>
<td>0.44</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>103 ± 9</td>
<td>96 ± 13</td>
<td>0.10</td>
</tr>
<tr>
<td>Serum potassium, mmol/L</td>
<td>4.5 ± 0.4</td>
<td>4.6 ± 0.4</td>
<td>0.33</td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>90.1 ± 41.4</td>
<td>94.1 ± 23.9</td>
<td>0.76</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>8.9 ± 1.5</td>
<td>9.7 ± 1.7</td>
<td>0.3</td>
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</tbody>
</table>

Data are mean (SD) unless otherwise stated. ACEI, angiotensin-converting enzyme inhibitor; ACR, albumin creatinine ratio; MAP, mean arterial pressure; HbA1c, hemoglobin A1c.
The finding that the addition of amlodipine, a CCB with no effect on the RAS, achieved the same antiproteinuric effect suggests that modulation of albuminuria can occur through different pathways. We cannot provide a ready explanation for the similarity of effect but are in a position to exclude certain potential candidates. Attained systemic BP levels during treatment were similar between groups; moreover, changes in BP did not correlate with changes in albumin/creatinine ratios. Also, GFR remained stable and comparable between groups after 24 wk. This does not exclude, however, that intraglomerular pressure may have been affected by treatment. One would expect CCB and ARB to act at different sites of the glomerular circulation, with amlodipine affecting the afferent arteriole tone and candesartan acting predominantly on the efferent arteriole. Whatever the mechanism of action, the resultant proteinuria-lowering effect seems the same. Of interest is that the improvement in sieving coefficient seen in patients who have diabetes and receive ACEI or ARB is not further ameliorated by combination therapy of these two drugs (28). Differences in glycemic control also cannot account for the result that amlodipine was as effective as candesartan in reducing proteinuria further. Thus, the BP-independent weaker antiproteinuric effect of amlodipine versus ARB that has been reported in monotherapy studies in patients who have type 2 diabetes with microalbuminuria and macroalbuminuria does not seem to apply when this drug is used in combination with ACEI treatment (11,13). A number of other studies have compared the antiproteinuric effect of ACEI and CCB as monotherapy with diverse results. CCB (either dihydro- or nondihydropyridine) and ACEI were found to lower AER and BP to the same extent and in a correlative manner in patients who have type 2 diabetes with microalbuminuria and hypertension (29,30). Progression of albuminuria was also impaired similarly by nisoldipine and enalapril in type 2 diabetes, the effect being explained entirely by their antihypertensive action (30).

Figure 1. Candesartan and amlodipine reduce albumin creatinine ratio (ACR) by a similar degree in patients who have type 1 diabetes with diabetic nephropathy and residual albuminuria and were on maximal angiotensin-converting enzyme inhibitor (ACEI) treatment and randomized to either amlodipine or candesartan.

Figure 2. Mean arterial pressure (MAP) and hemoglobin A1c (HbA1c) change in patients who have type 1 diabetes with diabetic nephropathy and residual albuminuria and were on maximal ACEI treatment and randomized to either amlodipine or candesartan.
In type 1 diabetes with overt nephropathy, lisinopril lowered AER significantly more compared with nisoldipine in a 4-yr controlled trial, although the effect on disease progression as measured by preservation of GFR was similar between treatments (31). In a 3-yr randomized trial of nonhypertensive patients who had type 1 diabetes with nephropathy, enalapril and nifedipine retard were neutral in lowering AER, but in this study, enalapril may have been underdosed (32). In patients who have type 1 diabetes and microalbuminuria with either normal or elevated BP, both ACEI and dihydropyridine CCB as monotherapy tended either to prevent progression of albuminuria or to lower AER to the same extent, but results were not always consistent among studies and the albumin-lowering effect was explained by BP reduction in some (33) but not in other cases (34).

Multiple therapy studies in type 2 diabetes have suggested that treatment with combined CCB and ACEI therapy has a greater renal protective effect than individual monotherapy despite similar degrees of BP lowering (35,36). A 12-wk Japanese study compared the combination of ACEI (temocapril) and ARB (candesartan) versus ARB (candesartan) and CCB (amlodipine) in patients who had type 2 diabetes with nephropathy and hypertension. The combination of ACEI and ARB reduced proteinuria more effectively, but CCB were underdosed. Both combinations of drugs lowered BP to a similar degree. However, the combination of CCB and ARB seemed to be safer with lower incidence of raised serum potassium and worsening of anemia (37). Some authors favor combination therapy of ACEI with CCB for diabetic renal protection in view of the need to attain required BP targets with a multiple antihypertensive drug treatment regimen in these patients (38).

Our study strongly supports the view that once good control of BP is obtained with maximal ACEI, further reduction of residual proteinuria is obtained equally by the addition of either an ARB or a CCB. This effect seems independent of BP changes. Although the mechanisms of these effects as well as the long-term impact on renal function preservation remains to be established, current therapeutic decisions for maximizing albuminuria-lowering effects in a multiple drug regimen ought to be made after a careful risk/benefit assessment.

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