Influence of microalbuminuria in achieving blood pressure goals
Irena Duka and George Bakris

Introduction
Microalbuminuria is increasingly recognized as an independent risk factor for cardiovascular morbidity and mortality in individuals with and without diabetes [1,2]. It occurs in 30% of middle-aged individuals with type 1 and type 2 diabetes and in 10–15% of individuals without diabetes [3].

Microalbuminuria is defined by the current National Kidney Foundation as a urinary excretion rate of albumin between 20 and 200 μg/min (30–300 mg/day) [4]. There are several ways of measuring microalbuminuria, as shown in Table 1. Although 24-h collections were the traditional way, a quick and accurate way of measuring albuminuria is an albumin to creatinine ratio on a spot collection of morning urine in the fasting state. Because the test for microalbuminuria is inexpensive, quick and easy to obtain and has significant prognostic value, screening for microalbuminuria has been suggested to assess risk for cardiovascular and renal disease not only in diabetes but also in the general population [5].

Several pathogenic mechanisms have been proposed as to how microalbuminuria may contribute to the pathogenesis of cardiovascular disease (CVD). The current proposed mechanisms involve local injury to the vascular smooth muscle and endothelial cells through vessel shear stress, and subsequent changes in nitric oxide and increase in a variety of cytokines that culminate in cell proliferation and increases in vascular permeability [6,7] (Fig. 1).

Prevalence of microalbuminuria in primary hypertension
The prevalence of microalbuminuria in essential hypertension varies from 5 to 37% in patients without diabetes.
but with essential hypertension [8–10]. This high variation relates to different factors such as the assay used, duration of blood pressure control, low-density lipoprotein (LDL) levels, increased body mass index, insulin resistance, endothelial dysfunction, smoking and age.

A large study of 11,343 hypertensive patients without diabetes demonstrated that microalbuminuria was present in 32% of men and 28% of women and increased with age and with the severity of hypertension [11].

Patients with microalbuminuria show higher blood pressure levels than patients with normal albumin excretion. Several studies have shown a significant correlation between office blood pressure and urinary albumin excretion [12–14]. In the Magic study, albuminuria was related to both diastolic and mean blood pressure [15]. Continuous blood pressure monitoring has shown better correlation with urinary albumin excretion than occasional office blood pressure readings. These studies have demonstrated a significant correlation between daytime diastolic blood pressure and urinary albumin excretion [16] and 24-h systolic and diastolic blood pressure values and urinary albumin excretion [17].

Microalbuminuric subjects have shown several abnormalities in the circadian blood pressure profile such as higher 24-h mean levels, lower day to night ratio (non-dippers) and higher variability of pressure readings. Bianchi et al. [18] observed a blunted or absent nocturnal dipping of blood pressure in hypertensive patients with microalbuminuria compared with those with normal urinary albumin excretion.

Figure 1 Endothelial permeability defect from injury to the endothelium is triggered by increases in microvascular pressure, which cause atherosclerotic changes

Table 1 Classification of abnormal urinary albumin excretion

<table>
<thead>
<tr>
<th>24-h urine albumin (mg/24 h)</th>
<th>Overnight urine albumin (µg/min)</th>
<th>Albumin (mg/l)</th>
<th>Gender</th>
<th>Albumin/creatinine ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;15</td>
<td>&lt;10</td>
<td>M</td>
<td>&lt;1.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>&lt;1.75</td>
</tr>
<tr>
<td>High normal</td>
<td>15 to &lt;30</td>
<td>10 to &lt;20</td>
<td>M</td>
<td>1.25 to &lt;2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>1.75 to &lt;3.5</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30 to &lt;300</td>
<td>20 to &lt;200</td>
<td>M</td>
<td>2.5 to &lt;3.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F</td>
<td>3.5 to &lt;3.5</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300</td>
<td>&gt;200</td>
<td>M</td>
<td>&gt;25</td>
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<tr>
<td></td>
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<td>F</td>
<td>&gt;35</td>
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</tbody>
</table>


Figure 1 Endothelial permeability defect from injury to the endothelium is triggered by increases in microvascular pressure, which cause atherosclerotic changes.
excretion and with normotensive participants. Twenty-four of 63 hypertensive subjects failed to decrease the blood pressure (at least 10/5 mmHg) during nighttime and were defined as non-dippers, the remainder were defined as dippers. Urinary albumin excretion in non-dippers was significantly higher than in dippers and normal subjects (Fig. 2). Other studies have also confirmed this correlation of a reduced nocturnal dipping and urinary albumin excretion in subjects with essential hypertension [19] and type 1 or 2 diabetes [20,21].

Effect of different antihypertensive drugs on microalbuminuria
Microalbuminuria is an early marker of CVD risk in all patients regardless of whether or not they have other comorbidities such as diabetes or nephropathy. Therefore its reduction may result in greater cardiovascular and renal protection. Although good glycemic control and protein restriction have an effect on renal function that is independent of blood pressure, studies have shown that achieving target blood pressure is critical in preserving renal function in diabetes. In the United Kingdom Prospective Diabetes Study, blood pressure control resulted in greater reduction in stroke, all diabetes endpoints and microvascular complications than did tight glucose control [22]. These results showed that achieving a blood pressure of less than 130/80 mmHg in subjects with proteinuria and diabetes and kidney disease is the most effective way to preserve kidney function and reduce cardiovascular events [23].

Investigators have carried out a lot of studies to see the effect of antihypertensive drugs on urinary albumin excretion and have shown that different classes of antihypertensive drugs have different effects on urinary albumin excretion. In patients with severe hypertension, reduction of blood pressure results in decreased urinary albumin excretion [24].

Angiotensin-converting enzyme inhibitors
Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce urinary albumin excretion more effectively than any other antihypertensive drugs, so one of these agents should be part of the regimen in controlling blood pressure in people who have microalbuminuria. Several investigators have confirmed that ACE inhibitors reduce urinary albumin excretion in patients with essential hypertension [25–27]. The greater antiproteinuric action of ACE inhibitors has been attributed to selective vasodilation of the glomerular efferent arterioles and to a decrease in intraglomerular hydrostatic pressure but a direct effect of these drugs on glomerular basement membrane permselectivity cannot be ruled out. The final result is the prevention of glomerulosclerosis that is independent of blood pressure and glucose control. These conclusions are supported by studies in normotensive patients with type 2 diabetes in whom ACE inhibitors decreased the rate of progression to overt proteinuria (42% versus 12% in the group that received ACE inhibitors) [28]. Also, administration of an ACE inhibitor to normotensive patients with type 1 diabetes patients with microalbuminuria decreased both albumin excretion and, at 2 years, progression to overt diabetic nephropathy when compared with patients treated with placebo [29].

The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) demonstrated that therapy with the ACE inhibitor trandolapril alone or in combination with a nondihydropyridine calcium channel blocker verapamil reduced the onset of microalbuminuria in hypertensive patients with type 2 diabetes with normal urinary albumin excretion [30].

The Heart Outcomes Prevention Evaluation (HOPE) study showed that the reduction in microalbuminuria (20% lower urinary albumin excretion rate) with the ACE inhibitor ramipril improved cardiovascular outcomes (21% reduction in primary outcome, myocardial infarction, stroke or cardiovascular death) [31].

The antiproteinuric action of ACE inhibitors is potentiated by dietary salt restriction and reduced by high salt intake and appears to be greater in patients with greater levels of plasma renin activity [32].

Angiotensin receptor blockers
More data are currently available on the efficacy of angiotensin receptor blockers (ARBs) in patients with
nephropathy due to type 2 diabetes. Two major trials have demonstrated a clear benefit in terms of renoprotection with ARBs in patients with nephropathy due to type 2 diabetes. None of these trials compared ARBs with ACE inhibitors in patients with diabetes.

In the Irbesartan Diabetic Nephropathy Trial (IDNT), 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomly assigned to irbesartan (300 mg/day), amlodipine (10 mg/day), or placebo [33]. At 2.6 years, irbesartan showed a 37% lower risk for doubling of the plasma creatinine.

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, 1513 patients with type 2 diabetes and nephropathy were randomly assigned to losartan (50 titrating up to 100 mg once daily) or placebo, both in addition to conventional antihypertensive therapy (but not ACE inhibitors) [34]. Compared with placebo, losartan reduced the incidence of a doubling of the plasma creatinine by 25% and end-stage renal disease by 28%; the mean follow-up was 3.4 years. These benefits were again not associated with differences in blood pressure levels between the groups, therefore the investigators concluded that renoprotection from the ARB was related to its antiproteinuric effect and not to achieved blood pressure.

Taken together these data support the notion that ACE inhibitors and ARBs have similar effect in the outcomes. Generally ARBs are tolerated better than ACE inhibitors because of their lower side effects (cough, angioedema, hyperkalemia).

If a patient continues to have microalbuminuria despite the treatment with an ACE inhibitor or an ARB, several options are available. Combination of high doses of an ACE inhibitor with an ARB lead to an additional 18–20% reduction in protein excretion that is not explainable by further blood pressure reduction [35,36**]. In the Can-desartan and Lisinopril Microalbuminuria (CALM) study, low doses of two different renin–angiotensin system (RAS) blockers, an ACE inhibitor and an ARB, in hypertensive type patients with type 2 diabetes who had microalbuminuria was more effective in reducing albuminuria than either agent used as monotherapy [37]. In this study, however, blood pressure was also significantly lowered.

**Calcium channel blockers**

Dihydropriyamide calcium channel blockers, unlike non-dihydropyrimidine calcium channel blockers, do not have significant antiproteinuric action despite effective blood pressure reduction. Only diltiazem and verapamil appear to be consistently effective in lowering protein excretion in patients with diabetes [38]; furthermore, the antiproteinuric effects of verapamil and an ACE inhibitor are additive. In one study of patients with type 2 diabetes, lisinopril or verapamil alone lowered protein excretion from 5.8 to 2.7 g/day [39]. In comparison, using roughly one-half the dose of both drugs (mean of 16 mg of lisinopril and 187 mg of sustained-release verapamil) had a much greater antiproteinuric effect: 6.8 down to 1.7 g/day. The low-dose combination regimen was also associated with fewer drug-induced side effects (such as constipation with verapamil and dizziness with lisinopril). A similar antiproteinuric advantage has been demonstrated with combination therapy with verapamil and trandolapril [40].

In humans, antiproteinuric effects with diltiazem may also be due to improved glomerular size permselectivity [41]. These drugs were excluded in the captopril–diabetes trial noted above; as a result, their efficacy in the preservation of renal function in relation to ACE inhibitors has not yet been evaluated in humans.

**Beta-blockers**

Beta-blockers have shown a variable response: the fall in protein excretion is generally less than that induced by an ACE inhibitor or ARB. The cardioselective β-blockers such as metoprolol and atenolol are known to delay the progression of renal disease to a lesser degree than RAS blockers. But the newer vasodilating β-blockers such as carvedilol and nebivolol have different effects on renal hemodynamics and function because of their greater adjunctive α1-blocking activity [42].

A large scale randomized clinical trial, the Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, compared carvedilol and metoprolol added to a treatment regimen containing a RAS antagonist on changes in albuminuria in 1235 patients with diabetes with established hypertension. After 5 months of maintenance therapy, blood pressure was decreased to the same extent in both groups, but the carvedilol group showed a greater reduction in microalbuminuria (−16.2% Δ, P = 0.003). Of those patients with trace protein loss (<30 mg/g at baseline), 47% fewer carvedilol-treated patients progressed to microalbuminuria than those receiving metoprolol (Fig. 3) [43,44]. These results were not explained by differences in blood pressure. Also they were not explained by the α-blocking blood pressure-lowering properties of carvedilol because most of the studies of α-blockade performed in people with diabetes failed to show a reduction in albuminuria [45]. One possible explanation for the carvedilol effect on prevention of microalbuminuria can be attributed to its antioxidant effect that may reduce vascular injury and permeability.
Carvedilol may delay development of microalbuminuria by a dual action: inhibiting inflammatory processes and lowering blood pressure [46].

This is an important finding, as any additional intervention to lower albuminuria is very important, especially in the cases in which the RAS blockade has not reached the desired goal in patients with advanced stages of diabetic nephropathy, despite achieving the blood pressure target.

Diuretics

Although diuretics have shown a reduction in blood pressure, they generally have not been shown to have an antiproteinuric effect [38,39]. Combination of thiazide diuretics with agents that block the RAS are used in 60 and 90% of patients in studies of hypertension treatment in diabetic kidney disease [47,48] and are more effective than either type of treatment alone for lowering blood pressure and achieving the target blood pressure of less than 130/80 mmHg.

Among diuretics, aldosterone antagonists appear to reduce proteinuria when used alone [49], and to have an additive effect on proteinuria when used in combination with an ACE inhibitor or an ARB in both type 1 and type 2 diabetes [50,51]. These effects of spironolactone were illustrated in a double-blind trial of 59 patients with type 2 diabetes already on an ACE inhibitor or ARB who were randomly assigned to spironolactone or placebo [52]. The urine albumin-to-creatinine ratio decreased by 40% in the spironolactone group, with no change in the control group. Further blood pressure reduction may partially explain the beneficial effect, although an anti-inflammatory mechanism has also been proposed [53].

The efficacy and safety of eplerenone, a selective aldosterone blocker has also been examined in a randomized trial of 268 patients with type 2 diabetes already treated with an ACE inhibitor [53]. Compared with placebo, eplerenone therapy at a dose of 50 or 100 mg/day was associated with a significant reduction in urinary albumin excretion (40–50% versus <10%). This study concluded that eplerenone in combination with an ACE inhibitor provides an additive antiproteinuric effect, with the rate of hyperkalemia being similar to placebo. In clinical practice, this combination should be used with caution in patients with reduced glomerular filtration rate. Patients should be instructed for dietary potassium restriction and avoidance of NSAIDs and COX-2 inhibitors, and probably should be prescribed concomitant kaliuretic diuretic therapy. The risk of hyperkalemia may possibly be lower with an ARB.

Conclusion

Microalbuminuria is a marker of CVD risk in all patients regardless of whether they have diabetes or nephropathy. Recent advances have made possible a better understanding of the epidemiology, pathophysiology and clinical significance of microalbuminuria in patients with diabetes and hypertension and in the general population. Screening patients with diabetes, hypertension and CVD risk factors for microalbuminuria is easy and inexpensive but often overlooked in clinical practice. Screening for microalbuminuria, however, can help identify people at risk of diabetic nephropathy and CVD, so an early and aggressive treatment can be started. The routine measurement of microalbuminuria should be done in all diabetic and hypertensive patients who also have metabolic syndrome. Such an approach, however, is
not recommended in all patients who have essential hypertension.

Blood pressure reduction toward the guideline recommended goal helps prevent the development of albuminuria, especially when RAS blockers such as ACE inhibitors or ARBs are used. Aldosterone antagonists and dihydropyridine calcium channel blockers reduce albumin excretion. Beta-blockers with α-blocking properties such as carvedilol have also been shown to reduce microalbuminuria independent of blood pressure-lowering effect. Patients with microalbuminuria also need to be treated for specific conditions, including hyperglycemia, dyslipidemia and hypertension.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
**• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 542).


2 Hermans MM, Henry R, Dekker JM, et al. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoon Study. J Am Soc Nephrol 2007; 18:1942–1952. This study investigated the association of impaired renal function expressed as lower glomerular filtration rate (GFR) or greater urinary albumin excretion with arterial stiffness. In individuals with mild renal insufficiency, both a lower GFR and a greater albumin excretion, even below levels that are considered to reflect microalbuminuria, are independently associated with greater arterial stiffness. Moreover, these associations were mutually independent. These findings may explain, in part, why eGFR and microalbuminuria are associated with greater risk for CVD and suggest that amelioration of arterial stiffness could be a target of intervention.

3 Rossi MC, Niculucci A, Pellegrini F, et al. Identifying patients with type 2 diabetes at high risk of microalbuminuria: results of the DEDAND (Developing Education on Microalbuminuria for Awareness of reNal and cardiovascular risk in Diabetes) Study. Nephrol Dial Transplant 2008; 23:1278–1284. This study evaluated to what extent the presence of risk factors and their interactions increased the likelihood of microalbuminuria (MAU) among individuals with type 2 diabetes. The likelihood of MAU is strongly related to the interaction between diabetes severity, smoking habits and several components of the metabolic syndrome. In particular, abdominal obesity, elevated blood pressure levels and low HDL cholesterol levels substantially increase the risk of MAU.


This study was designed to establish the effect of ARBs versus placebo and alternative treatments, and the effect of combined treatment with ARBs and ACE inhibitors, on proteinuria. The conclusions were that the ARBs reduce proteinuria, independent of the degree of proteinuria and of underlying disease. The magnitude of effect is similar regardless of whether the comparator is placebo or calcium-channel blocker. Reduction in proteinuria from ARBs and ACE inhibitors is similar, but their combination is more effective than either drug alone.