Microalbuminuria in Type 2 Diabetes and Hypertension

A marker, treatment target, or innocent bystander?

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Albuminuria is a well-known predictor of poor renal outcomes in patients with type 2 diabetes and in essential hypertension (1–4). Albuminuria has also been shown more recently to be a predictor of cardiovascular outcomes in these populations (5–8). There is emerging data that reduction of albuminuria leads to reduced risk of adverse renal and cardiovascular events (9–12). It has become increasingly clear that albuminuria should not only be measured in all patients with type 2 diabetes and hypertension, but also steps should be taken to suppress albuminuria to prevent future renal and cardiovascular adverse events. This review discusses the measurement of albuminuria and summarizes the current literature on the association between albuminuria and adverse cardiovascular and renal outcomes in type 2 diabetes and hypertension. It also summarizes the evidence that reduction of albuminuria leads to improvement in the risk profiles of these patients.

DEFINITION AND MEASUREMENT OF ALBUMINURIA

— Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-h urine collection (13). Overt albuminuria, macroalbuminuria, or proteinuria is defined as a urinary albumin excretion of ≥300 mg/24 h. Urinary albuminuria comprises 20–70% or urinary total protein excretion. Measuring urinary albumin excretion by dipstick without simultaneously measuring creatinine is subject to false-negative and false-positive results due to variations in urine concentration caused by hydration level (13). Although urinary dipsticks are acceptable for quick screening, other more precise measurements should be done to quantify urinary albumin excretion rates (AERs). Albuminuria can be measured in several ways (Table 1): *1*) measurement of albumin-to-creatinine ratio (ACR) in a random or first morning spot collection, *2*) 24-h urine collection with measurement of creatinine to verify adequacy of the collection, and *3*) timed (4-h or overnight) urine collections (13). Although the 24-h urine collection would overcome issues of diurnal variation in albumin excretion, it is subject to collection errors. The Kidney Disease Outcomes Quality Initiative guidelines state that ACR measurement in a first-morning spot urine collection is adequate and a timed urine collection is not necessary (14). However, because women excrete less creatinine than men and microalbuminuria is based on a fixed amount of urinary albumin excretion per day, the definitions of microalbuminuria are different in men and women when using ACRs (15).

Microalbuminuria was first defined by Mogensen (1) and others as 30–300 mg urinary albumin excretion per 24 h. However, at the time, there was not widespread use of inhibitors of the renin angiotensin system. As noted below, inhibition of the renin angiotensin system decreases urinary albumin excretion, and drugs to inhibit the renin angiotensin system are currently in wide use. A patient being treated with drugs that inhibit the renin angiotensin system, with urinary albumin excretion of 30–300 mg per 24 h, would have likely had much higher levels of AER without such drugs when Mogensen first defined microalbuminuria. Hence, most patients who have urinary albumin excretion in the microalbuminuria range currently have more advanced disease than patients in the past. In addition, microalbuminuria and albuminuria or proteinuria are part of a clinical continuum of risk and prognosis.

PREVALENCE OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION

— Reported figures concerning the prevalence of albuminuria in essential hypertension have yielded variable results due to the chosen cutoff value, patient selection, and more importantly the duration of hypertension and of prior treatment.

In a cohort of 787 patients aged 18–72 years, studied after discontinuation of antihypertensive treatment for at least 4 weeks, a prevalence of microalbuminuria (AER ≥30 mg/24 h) of 8% was observed (16). A prevalence of microalbuminuria of 6% was found in a cohort of 1,041 younger patients (aged 18–45 years) with untreated mild hypertension (140–159/90–99 mmHg) (17). Analysis of the population of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study of 8,029 subjects (aged 55–80 years) with stage II–III essential hypertension (sitting office blood pressure of 160–200/95–115 mmHg) and electrocardiographic left ventricular hypertrophy (LVH) and using a single cutoff value

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Abbreviations: ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; ARB, angiotensin receptor blocker; GFR, glomerular filtration rate; IDNT, Irbesartan Diabetic Nephropathy Trial; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; LVH, left ventricular hypertrophy; PREVEND, Prevention of Renal and Vascular End-Stage Disease; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan; SAP, systolic arterial pressure.

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Table 1—*Measurement of albuminuria*

	Normal	Microalbuminuria	Macroalbuminuria	Advantages	Disadvantages
Dipstick for Protein	−	−	+	Convenience	Dependent on level of hydration
24-h protein (mg)	<150	<500	≥500	Overcomes problem of diurnal variation in excretion	Subject to collection errors
24-hour albumin (mg)	<30	30–300	>300	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Timed collection (μg/min)	<20	20–200	>200	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Spot collection (μg albumin/mg creatinine)	<30	30–300	>300	Convenience Not dependent on hydration level Most reproducible	Ratios vary based on sex

for AER in men and women (≥3.5 mg/mmol creatinine corresponding to 30 mg/24 h) revealed a prevalence of microalbuminuria of 26%. Before inclusion, treatment was discontinued for 2–4 weeks; this may have increased the prevalence of microalbuminuria (18). Of interest, it was recently shown that 70% of patients with electrocardiographic LVH included in the LIFE study have echocardiographic LVH (left ventricular mass index ≥104 in women and ≥116 g/m^2 in men) (19).

In a subgroup of 376 never-treated individuals aged ≥40 years from our personal cohort of essential hypertensive patients, analysis of the prevalence of target organ damage (LVH defined as left ventricular mass index ≥110 in women and ≥125 g/m^2 in men and microalbuminuria defined as AER ≥30 mg/24 h) showed that 27% had LVH alone and 6% had microalbuminuria alone, whereas both abnormalities were present in 10% of patients and 57% were free of target organ damage. Overall, the presence of microalbuminuria was found in 16%, whereas LVH was found in 37% of the population. In addition, 21% of patients with LVH were classified as microalbuminuric, whereas 59% of patients with microalbuminuria had LVH, thus suggesting that microalbuminuria is a good predictor of the presence of LVH. Of interest, male patients were more frequently affected by the combination of LVH and microalbuminuria than women (15 vs. 4% in the population aged ≥40 years). The group of patients with both LVH and microalbuminuria had the highest arterial pressure level, a larger proportion of smokers, and a longer duration of hypertension than patients with only one isolated target organ damage. Importantly, urinary sodium excretion taken as an index of dietary sodium intake was markedly higher than in the other groups.

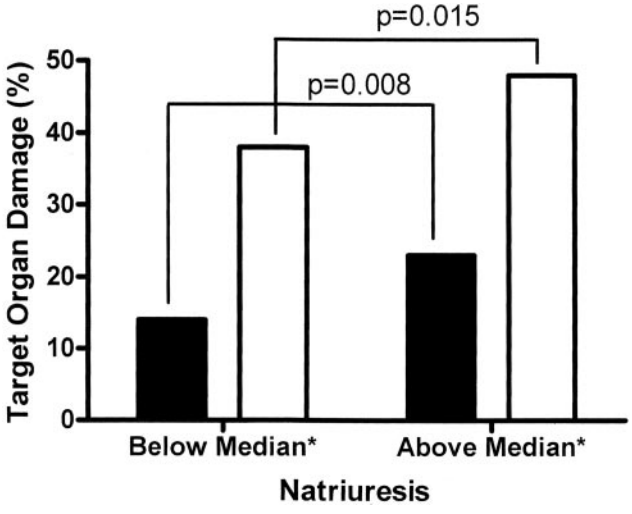

Figure 1—*Prevalence of microalbuminuria (MA) (■) (≥20 μg/min) or LVH (□) (≥125 in men and 110 g/m^2 in women) in a cohort of 376 patients with never-treated essential hypertension aged ≥40 years.*

FACTORS INFLUENCING THE RELATIONSHIP BETWEEN ARTERIAL PRESSURE AND ALBUMINURIA

— It is generally accepted that arterial pressure, mainly systolic arterial pressure (SAP) and to a lesser extent pulse pressure, is a major determinant of albuminuria. The slope of the relationship between albuminuria and SAP is steeper in men than in women. In fact, albuminuria remains almost unaltered with SAP within the normotensive range (<140 mmHg). In contrast, the response of the left ventricle to SAP is linear within the whole range of SAP (20). Some factors were shown to influence this relationship such as oral contraception in nonmenopausal women (21) and impaired glucose tolerance or diabetes. In 2002, du Cailar et al. (22) assessed the influence of sodium intake (estimated by two consecutive determinations of 24-h natriuresis) on the relationship between SAP and target organs (i.e., left ventricular mass index and AER) in a large cohort of 839 normotensive and never-treated hypertensive subjects aged 15–70 years. It was observed that increasing dietary sodium was associated with an increasingly steeper slope of the relationship of SAP versus AER or left ventricular mass index. As shown in Fig. 1, the prevalence of LVH or microalbuminuria was higher in hypertensive patients aged ≥40 years with a natriuresis above a median of 147 mmol/24 h than in patients with natriuresis below the median. This was the first evidence in favor of a modulating influence of dietary sodium on blood pressure–associated target organ lesions.

In addition to SAP, obesity as well as insulin resistance and smoking were shown to be associated with a level of AER inappropriately high for the SAP status

(23). The influence of obesity and insulin resistance suggests that albuminuria may be linked to the presence of the metabolic syndrome. It was reported that in patients with the metabolic syndrome defined according to the Adult Treatment Panel III report, the prevalence of LVH and microalbuminuria was higher in patients with the metabolic syndrome than in patients without (30 vs. 24% for LVH and 11 vs. 8% for microalbuminuria) (24). A similar prevalence of target organ damage was found in a larger population; in fact, the prevalence of microalbuminuria increased with the number of components of the metabolic syndrome (from 3% in subjects without any abnormality to 9.8% in subjects with three abnormalities and 22.1% in subjects with five abnormalities) (25).

C-reactive protein is a sensitive marker of subclinical inflammation that was shown to be a good predictor of cardiovascular outcomes. In a cross-sectional study conducted in the large Groningen cohort, Stuveling et al. (26) observed that increasing C-reactive protein values from 0.2 to 10 mg/l resulted in a remarkable steepening of the slope of the relationship of albuminuria versus mean arterial pressure, with a potentiating effect of C-reactive protein that became significant for mean arterial pressures >90 mmHg.

With regard to plasma homocysteine as a predictor of clinical vascular disease, it was shown that this parameter was correlated with arterial stiffness assessed by the pulse wave velocity in hypertensive subjects with a mean age of 58 years (27). Nevertheless, the highest level of homocysteine was associated with the lowest level of glomerular filtration rate. Taking into account the fact that plasma homocysteine concentration is closely related to renal function (28), the significance of plasma homocysteine should be considered with great caution.

ALBUMINURIA AND TREATMENT OF HYPERTENSION

— In the Treatment of Mild Hypertension Study (TOMS) conducted in patients with mild hypertension (diastolic blood pressure 85–99 mmHg), it was reported that the use of enalapril over 12 months afforded a larger decrease in albuminuria despite a similar achieved blood pressure decrease when compared with acebutolol, amlodipine, chlortalidone, and doxazosin (29). In the population of the LIFE study, administration for 4.8 years of losartan (an angiotensin II receptor antagonist)- or atenolol (a β-blocker)-based treatment to a target blood pressure of 140/90 mmHg was associated with a more marked decrease in AER with losartan (−33 vs. −25% at the 1-year follow-up) (12). As in most studies on the long-term effect of treatment on target organ damage, the numbers as well as the characteristics of patients in whom no improvement in LVH or AER occurred were not disclosed. Efforts should be devoted to the issue of resistance of target organ damage despite adequate control of blood pressure. In a study conducted in 187 normoalbuminuric patients aged <50 years, with previously untreated hypertension and followed up for 2.7 years on various antihypertensive regimens including ACE inhibitors, Redon et al. (30) observed progression from normo- to microalbuminuria (AER ≥30 mg/24 h) in 11% of patients and less frequently in subjects treated with ACE inhibitors. Moreover, a tendency to a higher BMI, less reduction in blood pressure, and an increase in blood glucose and uric acid was found in "albuminuria progressors." Analysis of the influence of obesity, insulin resistance, or the metabolic syndrome and more importantly sodium intake could be of great value in the search for causes of resistance of target organ damage despite satisfactory control of blood pressure.

ALBUMINURIA AND RENAL OUTCOMES IN ESSENTIAL HYPERTENSION

— In population studies, no correlation between albuminuria and glomerular filtration rate (GFR) has been detected. In the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study conducted in nondiabetic residents of the city of Groningen (the Netherlands), it was observed that GFR estimated by 24-h creatinine clearance tended to be elevated in subjects with high-normal AER (15–30 mg/day), whereas macroalbuminuria was independently associated with a reduction in creatinine clearance below values expected for age and sex (4). In the Gubbio study conducted in a sample of an Italian community of 1,632 subjects aged 45–64 years, no relationship between increasing AER and the prevalence of "low" creatinine clearance (<60 ml/min) was found (31).

In the PREVEND cohort and within a follow-up period of 4 years, an incidence of de novo development of renal insufficiency (creatinine clearance <60 ml/min per 1.73 m^2) of 4.2% was observed. Although age as well as serum cholesterol and glucose were higher, whereas baseline renal function was lower in this group of the population, multivariate analysis showed that baseline AER was a good predictor of the risk of developing impaired renal function (32). In a group of 486 aborigines (10.5% with type 2 diabetes at inclusion), Hoy et al. (33) reported on a close correlation between baseline albuminuria (range ACR <1.1 in 30% to >100 mg/mmol in 6.2% of the population) and the decline in GFR estimated by the Cockroft and Gault equation within a follow-up period of 1–6 years. In fact, the annual decrease in GFR was almost negligible in normoalbuminuric people, but increased to 2.2 and 11.6 $ml \cdot min^{-1} \cdot year^{-1}$ in micro- and macroalbuminuric subjects, respectively.

In patients with essential hypertension, no difference in GFR was detected between normo- and microalbuminuric individuals, and no alteration in intrarenal hemodynamics, including an increase in the filtration fraction that would be suggestive of elevated intra-glomerular pressure, was detected. Of interest, the renal vasodilatory response to acute administration of the ACE inhibitor captopril was significantly blunted in microalbuminuric subjects, despite a similar level of circulating renin. This suggested that microalbuminuria may be a marker of early intra-renal vascular dysfunction (34). In a minority of patients, hyperfiltration relative to a theoretical age-related value may be observed and associated with a slightly higher level of albuminuria (35). Whether microalbuminuria or hyperfiltration is a precursor of further renal alterations, as already reported in type 1 diabetes, remains to be documented.

In cross-sectional studies, age is strongly inversely correlated with GFR, and glomerular filtration progressively decreases during aging at a rate of ~0.5 to 1 $ml \cdot min^{-1} \cdot year^{-1}$. Several factors were identified as accelerators of the age-related decline in GFR. In a recent study conducted in 195 normotensive subjects and 645 patients with never-treated hypertension, it was observed that the existence of hypertension and more precisely concentric LVH was associated with a marked acceleration of the age-related decline in GFR (36). Other cross-sectional studies have shown that the slope of the relationship age versus GFR is steeper in

Table 2—*Morbidity mortality studies and albuminuria in nondiabetic patients*

	Age range (years)	Population characteristics	Follow-up duration (years)	Outcome	Cutoff value of albuminuria
Copenhagen (43)	30–70	HT in 10–15%	5	CHD	>4.8 μg/min (0.64 mg/mmol)
Monica (42)	30–70	Blood pressure <150/90 mmHg	10	CHD	>0.65 mg/mmol (5.1 μg/min)
Hunt (44)	>20	Nondiabetic subjects	4.4	All-cause death	>0.76 mg/mmol (6 μg/min)
Life (41)	55–80	Electrocardiogram LVH	4.8	Cardiovascular death, first myocardial infarction, stroke	>1.28 mg/mmol (10 μg/min)
Hunt (45)	>20	Treated HT	4.3	All-cause death	>1.7 mg/mmol (13.3 μg/min)
Hoorn (46)	50–75	Peripheral arterial disease	5	Cardiovascular death	>2 mg/mmol (16 μg/min)
Utrecht (47)	52–67	Postmenopausal	20	Cardiovascular death	>2.4 mg/mmol (18 μg/min)

CHD, coronary heart disease; HT, hypertension.

patients with impaired glucose tolerance or diabetes discovered during an oral glucose tolerance test (37).

Although a recent longitudinal study confirmed that the decline in GFR found in hypertensive subjects left untreated for 6 years is accentuated compared with a normotensive group (−1.22 vs. 0.12 ml/min using 99m-Tc-DTPA urinary clearance) (38), only a few studies have assessed the evolution of renal function during long-term antihypertensive treatment in individuals with normal renal function. In a retrospective study conducted in 141 patients (38% with microalbuminuria defined as 30–300 mg/day), it was shown that within the 7 years of follow-up, the decrease in 24-h creatinine clearance amounted to 12.1 in microalbuminuria vs. 7.7 ml/min in normoalbuminuric patients, and no influence of the type of antihypertensive regimen (containing or not containing an ACE inhibitor) was detected (39). Within a follow-up period of 14 years, a decrease in GFR, estimated by inulin clearance, of ~19 ml/min was found in a small group of 23 hypertensive subjects adequately controlled by antihypertensive therapy (40). No relationship between baseline albuminuria and the yearly decline in GFR was reported in most studies (38,40). Of interest, the most important determinant of the GFR progression was the baseline level of blood pressure.

ALBUMINURIA AND CARDIOVASCULAR OUTCOMES IN ESSENTIAL HYPERTENSION

— In the last few years, several studies have pointed out the role of microalbuminuria as a predictor of cardiovascular morbidity (8,41,42) and mortality (8,43–46). The characteristics of some of these important prospective studies are shown in Table 2. It clearly appears that threshold values of microalbuminuria that increase risk are consistently lower than the usually accepted cutoff points for microalbuminuria criteria. In studies performed in people aged >40 years, the risk of increased cardiovascular mortality was significant above ACR values of 1.28 (8) to 2 mg/mmol (45), which corresponds to AER of 10–16 μg/min in timed urine collections. In contrast, in two studies conducted in populations aged 30–70 years (41,42) with ischemic heart disease as the primary end point, the threshold of ACR was 0.65 mg/mmol creatinine, roughly corresponding to AER of 5–6 μg/min. The hypothesis that microalbuminuria may reflect generalized atherosclerosis was tested in the 5-year follow-up period of the Hoorn study (45) conducted in 50- to 75-year-old subjects. It was observed that both microalbuminuria (ACR >2 mg/mmol) and peripheral arterial disease (assessed by the ankle-brachial index) were associated with a fourfold increase in cardiovascular mortality, which was more marked in hypertensive subjects than in normotensive subjects; however, it was concluded that microalbuminuria affected mortality through a mechanism different from extensive atherosclerosis.

ALBUMINURIA AND RENAL OUTCOMES IN TYPE 2 DIABETES

— There have been several studies examining the relationship between microalbuminuria and renal outcomes in type 2 diabetes. Mogensen (1) studied the predictive value of microalbuminuria in patients with type 2 diabetes. It was predictive of the development of overt proteinuria as well as mortality. Patients with type 2 diabetes and albumin concentrations of 30–140 μg/ml at baseline were more likely to develop clinically detectable proteinuria (>400 μg/ml) after 9 years of average follow-up than patients with baseline urinary albumin concentrations <30 μg/ml. These findings were supported by Berrut et al. (2), who examined patients with type 2 diabetes and hypertension. The GFR of patients with microalbuminuria declined more than the GFR of patients with normoalbuminuria over the average 22 months of follow-up ($P < 0.01$).

There have also been several larger trials that have shown the association between albuminuria and renal outcomes in patients with type 2 diabetes (Table 3). The Irbesartan Diabetic Nephropathy Trial (IDNT) examined 1,715 patients with hypertension, type 2 diabetes, and proteinuria. Patients enrolled in IDNT had urinary protein excretion of at least 900 mg/24 h and serum creatinine concentration between 1.0 and 3.0 mg/dl in women and 1.2 and 3.0 mg/dl in men at baseline (10). The risk for the development of end-stage renal disease or doubling of serum creatinine during the average 4 years of follow-up doubled for each doubling of baseline proteinuria level (hazard ratio [HR] 2.04, 95% CI 1.87–2.22) (47). Similarly, the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study followed 1,513 patients with type 2 diabetes and nephropathy (9). Nephropathy was defined as a urinary ACR ≥300 mg/g with a serum creatinine level of 1.3–3.0 mg/dl. The presence of albuminuria was associated with an adjusted HR of 6.2 (95% CI 4.4–8.7; $P < 0.001$) for the outcome of

Table 3—*Albuminuria and renal outcomes in type 2 diabetes*

	Number of patients	Study population	Mean follow-up	Intervention	Renal risk with albuminuria
IDNT (5,10,47)	1,715	Type 2 diabetes, hypertension	4 years	Irbesartan, amlodipine, or placebo	• HR 2.04; 95% CI 1.87–2.22 • Each 50% decrease in proteinuria in the first 12 months: reduction in renal risk (HR 0.44; 95% CI 0.40–0.49
RENAAL (3,7,9,48)	1,513	Type 2 diabetes	3.4 years	Losartan (50 mg or 100 mg) vs. placebo	• HR 6.2; 95% CI 4.4–8.7 • Each 50% decrease in albuminuria in the first 6 months: reduction in risk for end-stage renal disease of 45%
MARVAL (49)	332	Type 2 diabetes	6 months	Valsartan vs. amlodipine	• Urinary AER at 24 weeks was 56% (95% CI 49.6–63.0) of baseline with valsartan and 92% (95% CI 81.7–103.7) of baseline with amlodipine
IRMA-2 (11)	590	Type 2 diabetes, hypertension	2 years	Irbesartan (150 mg or 300 mg) vs. placebo	• HR for progression to overt nephropathy: in the 150 mg group: HR 0.56, 95% CI 0.31–0.99; in the 300 mg group: 0.32, 95% CI 0.15–0.65)

doubling of serum creatinine or end-stage renal disease (3).

Multiple datasets have demonstrated that microalbuminuria is a potent risk factor for the development of progressive kidney disease. It portends the future development of overt proteinuria, doubling of serum creatinine, end-stage renal disease, and mortality. Because of this relationship, the association between reduction of albuminuria and renal outcomes was examined.

TREATMENT OF ALBUMINURIA AND RENAL OUTCOMES IN TYPE 2 DIABETES

— Several studies have shown that reduction of albuminuria by inhibition of the renin-angiotensin-aldosterone system is associated with the preservation of renal function. RENAAL was a randomized double-masked study of patients with type 2 diabetes and nephropathy comparing losartan (50–100 mg once daily) with placebo, both taken in addition to conventional antihypertensive treatment (9). In patients randomized to losartan, proteinuria declined by 35% compared with placebo. Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction 25%; $P = 0.006$) and end-stage renal disease (risk reduction 28%; $P = 0.002$). Each 50% decrease in albuminuria in the first 6 months was associated with a reduction in risk for end-stage renal disease of 45% (48). The decrease in albuminuria associated with losartan therapy was an important predictor of preservation of renal function.

Similarly, the IDNT trial compared the effects of irbesartan, amlodipine, and placebo in 1,715 hypertensive patients with type 2 diabetes and nephropathy (10). The risk of doubling the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P = 0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P < 0.001$). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23% lower than that in both other groups. For each halving of proteinuria level between baseline and 12 months, with treatment, the risk for doubling of baseline serum creatinine level or the development of end-stage renal disease was reduced by more than half (HR 0.44, 95% CI 0.40–0.49) (47).

The Microalbuminuria Reduction with Valsartan (MARVAL) trial administered 80 mg/day valsartan or 5 mg/day amlodipine to 332 patients with type 2 diabetes and microalbuminuria (49). The urinary albumin excretion rate at 24 weeks was 56% (95% CI 49.6–63.0) of baseline with valsartan and 92% (95% CI 81.7–103.7) of baseline with amlodipine. Blood pressure reductions were similar between the two treatments.

The use of angiotensin receptor blockers (ARBs) is clearly beneficial in reducing proteinuria, and this is associated with improving renal outcomes. In addition, increasing the dose of ARB has been found to have greater renoprotection, independent of blood pressure control. The Irbestartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study, which compared 150 and 300 mg irbesartan daily to placebo in 590 hypertensive patients with type 2 diabetes and microalbuminuria found the hazard ratio for progressing to overt nephropathy (urinary albumin excretion rate in an overnight specimen >200 μg/min and at least 30% higher than the baseline rate on at least two consecutive visits) was 0.56 in the 150 mg group (95% CI 0.31–0.99) and 0.32 in the 300 mg group (95% CI 0.15–0.65) (11). This was after adjustment for the baseline level of microalbuminuria and the blood pressure achieved during the study. Given the improvement in outcomes with higher doses of ARBs, there is now interest in whether doses beyond the current recommended dosage levels may provide increased RAAS blockade and therefore greater renoprotection. Irbesartan, 600 or 900 mg/day, compared to the current maximal daily dosage of 300 mg/day was given to 52 hypertensive type 2 diabetic patients with microalbu-

minuria also treated with other antihypertensive medications (50). Irbesartan, 900 mg/day, caused an additional 15% decrease in microalbuminuria compared with 300 mg/day irbesartan ($P = 0.02$). In addition to increasing the dose of ACE inhibitors or ARBs, other potential ways to increase the inhibition of the rennin angiotensin system include combining ACE inhibitors and ARBs, adding an aldosterone inhibitor, or adding a renin inhibitor.

ALBUMINURIA AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES

— A strong association has been reported between microalbuminuria and cardiovascular outcomes in patients with type 2 diabetes. An analysis of 3,498 patients with diabetes and 5,545 patients without diabetes in the Heart Outcomes Prevention Evaluation (HOPE) study found that microalbuminuria increased the adjusted relative risk (RR) of major cardiovascular events (RR 1.83, 95% CI 1.64–2.05) (6). Participants with diabetes had a RR of 1.97 (95% CI 1.68–2.31) and those without diabetes had an RR of 1.61 (95% CI 1.36–1.90).

The IDNT study, described above, also reported that albuminuria was an independent risk factor for cardiovascular events (5). The study defined a cardiovascular composite end point consisting of cardiovascular death, nonfatal myocardial infarction, hospitalization for heart failure, stroke, amputation, and coronary and peripheral revascularization. The ACR was associated with an increased risk of this cardiovascular composite end point (RR 1.29 per natural log unit, 95% CI 1.13–1.48). Data from the RENAAL study also demonstrated that the presence of albuminuria was associated with increased cardiovascular events (7). Cardiovascular events were defined as a composite of myocardial infarction, stroke, first hospitalization for heart failure or unstable angina, coronary or peripheral revascularization, or cardiovascular death. It was found that patients with a high baseline ACR (≥3 g/g) had a 1.92-fold higher risk (95% CI 1.54–2.38) for the cardiovascular end point and a 2.70-fold higher risk (95% CI 1.94–3.75) for heart failure compared with patients with low baseline levels of ACR (<1.5 g/g).

Furthermore, Gimeno-Orna et al. (51) classified 436 type 2 diabetic patients into one of four groups based on if they had baseline cardiovascular disease or microalbuminuria. Patients with no baseline cardiovascular disease, but microalbuminuria, had an increased RR for incident cardiovascular disease (RR 2.8, 95% CI 1.7–4.6) compared with patients with no baseline cardiovascular disease and normoalbuminuria. In addition, patients with no baseline cardiovascular disease and microalbuminuria had the same risk for a subsequent cardiovascular event as patients who had a previous cardiovascular event documented at baseline. Microalbuminuria was as potent a risk factor for cardiovascular events as a previous history of actual cardiovascular disease.

Microalbuminuria may also be a risk factor for more severe or advanced cardiovascular disease as well. The 330 patients who underwent coronary angiography were divided into groups based on the presence or absence of diabetes and the presence or absence of microalbuminuria (52). Diabetic patients with microalbuminuria had a higher prevalence of three-vessel coronary artery disease compared with those without microalbuminuria (75 vs. 42%). This relationship was also seen in those patients studied without diabetes and with or without microalbuminuria (39 vs. 20%).

Multiple lines of evidence demonstrate a strong association between the presence of microalbuminuria and the risk of adverse cardiovascular events. Evidence suggests that as the amount of urinary albumin excretion increases along the continuum from microalbuminuria to albuminuria and proteinuria, the risk of adverse cardiovascular events increases. Although this has been primarily studied in the diabetic population, evidence supports the presence of albuminuria as a potent risk factor for adverse cardiovascular events in the nondiabetic population as well. Data from the Framingham study showed that in 1,568 nonhypertensive participants without diabetes, urinary albumin excretion less than the microalbuminuria threshold predicted the development of cardiovascular disease (53). In the PREVEND study, urinary albumin was measured in 6,669 nondiabetic participants, and microalbuminuria was associated with cardiovascular disease (54). Indeed some studies have suggested that the presence of microalbuminuria increases the relative risk of an adverse cardiovascular event similarly to the presence of hypercholesterolemia (55). The presence of microalbuminuria may need to be viewed in the same light as other risk factors such as blood pressure, cholesterol, and blood glucose.

TREATMENT OF ALBUMINURIA AND CARDIOVASCULAR OUTCOMES

— In the PREVEND Intervention Trial (PREVEND IT), patients with albuminuria treated with fosinopril experienced a significant decrease in urinary albumin excretion (26%) and a trend toward a decrease in cardiovascular events (40%) (56). In the LIFE study, patients with a urinary ACR greater than the median value at baseline (1.21 mg/mmol), but who were able to decrease their ACR to less than the median value at 1 year (0.67 mg/mmol), had a reduced risk for cardiovascular mortality, stroke, and myocardial infarction compared with patients who were not able to decrease their ACR (12). This suggests that there may be a cardiovascular benefit to reducing albuminuria in patients with essential hypertension but also in type 2 diabetes. Future trials are needed in patients with type 2 diabetes to explore the relationship between reduction in albuminuria and improvement in cardiovascular events.

CONCLUSIONS

— The presence of albuminuria is a powerful predictor of renal and cardiovascular risk in patients with type 2 diabetes and hypertension. In addition, multiple studies have shown that decreasing the level of albuminuria reduces the risk of adverse renal and cardiovascular outcomes. The pathophysiology is not definitively known, but is hypothesized to be related to endothelial dysfunction, inflammation, or possibly abnormalities in the renin-angiotensin-aldosterone system.

Albuminuria is therefore an important risk factor to measure in patients at risk. The American Diabetes Association recommends that patients with type 2 diabetes be tested for albuminuria at the time of initial diabetes diagnosis and yearly thereafter (13). Initiation of ACE inhibitor or ARB therapy should be considered in patients with microalbuminuria or overt proteinuria. The level of albuminuria should be followed up during treatment, and doses of the ACE inhibitor or ARB should be titrated upward to maximize the beneficial effect on albuminuria. It is possible that the combination of ACE inhibitors and ARBs may provide additional benefit over ACE inhibitors or ARBs alone (57). In addition to

ACE inhibitors and ARBs, adequate blood pressure control is an important mainstay of treatment. If blood pressure is still elevated after maximal ACE inhibitor and/or ARB therapy, additional anti-hypertension medications should be added to maintain the blood pressure at <125/75 mmHg. Finally, additional agents such as statins, renin inhibitors, and glycosaminoglycans may provide additional albuminuria reduction and are actively being studied (58).

In summary, albuminuria is associated with adverse renal and cardiovascular outcomes, and decreasing albuminuria with ACE inhibitor or ARB therapy, blood pressure lowering, and/or other agents can lead to improved outcomes. Physicians should measure urinary albumin excretion in patients with type 2 diabetes and hypertension routinely and be as aggressive in treating this modifiable risk factor as they do blood pressure, cholesterol, or blood glucose.

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