

Albuminuria: A Target for Treatment of Type 2 Diabetic Nephropathy

Dick de Zeeuw, MD, PhD

Summary: Both renal and cardiovascular morbidity and mortality is increased markedly in patients with type 2 diabetes. Besides the classic risk factors and markers such as glucose, blood pressure, blood lipid profile, and lifestyle (smoking, overweight), novel risk markers are identified, among them urine albumin excretion. Levels of urinary albumin excretion greater than normal are observed frequently in patients with type 2 diabetes. Moderately increased levels of albuminuria, so-called *microalbuminuria*, are predictive both for progressive renal function loss to diabetic nephropathy, and for cardiovascular morbidity and mortality: the higher the albuminuria level, the more chance of renal and cardiovascular complications. More advanced levels of albuminuria (overt albuminuria) are observed in patients in the diabetic nephropathy state. In this condition, renal and cardiovascular risk are extremely high, and again one may observe that the level of albumin excretion is predictive of renal and cardiovascular outcome. Several drug strategies decrease the level of urinary albumin excretion in type 2 diabetic patients. Data on using drugs that intervene in the renin-angiotensin-aldosterone-system (RAAS) are the most extensive and conclusive. RAAS intervention is a very effective strategy to decrease the amount of albumin in the urine, independent from the blood pressure decreasing characteristics of the treatment. RAAS intervention is associated with long-term renal and cardiovascular protection. Importantly, the degree of short-term albuminuria decrease is associated with the degree of renal and cardiovascular protection: the more albuminuria reduction, the more protection. The protective predictive power of the albuminuria effect of RAAS intervention is not related to (or dissociated from) the blood pressure decreasing effect of these drugs. The protective effect of RAAS intervention is present at normoalbuminuric, microalbuminuric, and overt albuminuria levels. This makes albuminuria a target for therapy in type 2 diabetes. New drug strategies that decrease or prevent albuminuria without affecting other risk factors currently are being tested, and not only will add to underscoring the need to treat albuminuria as a separate target, but also will assist in reducing the enormous residual risk burden of individual diabetic patients.

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Patients with diabetes are prone to all kinds of complications; renal and cardiovascular (CV) complications are the most common and carry the most morbidity and mortality.^{1,2} Controlling risk factors such as glucose metabolism, blood pressure, blood lipid profile, and lifestyle (such as overweight and smoking)

has been instrumental in reducing the renal and CV risk. However, the residual risk is still devastating. The challenge for the future is to find drug strategies that add to the current armamentarium. In addition, we need to find biomarkers or surrogate end points that help us in the short-term identification of potentially renal/CV-protective drugs, and subsequent monitoring of protective effects. This article delineates urine albumin leakage or albuminuria as such a clinical tool: increased urine albumin excretion is an indication for increased renal and CV risk in the diabetic population,

Department of Clinical Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands.

Address reprint requests to Dick de Zeeuw, MD, PhD, Department of Clinical Pharmacology, University Medical Center Groningen, Ant Deusinglaan 1, 9713 AV Groningen, The Netherlands. E-mail: d.de.zeeuw@med.umcg.nl
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Table 1. Threshold Levels for Abnormalities in Urinary Albumin According to the Kidney Disease: Improving Global Outcomes (KDIGO) Consensus

24-Hour Urine Collection Albumin Excretion Rate, mg/d	Albumin Concentration, mg/L	Spot Morning Urine Sample Albumin-to- Creatinine Ratio*		Terms
		mg/mmol	mg/g	
<30	<20	<3	<30	Normal
		M <2.0	M <20	
		F <30	F <3.0	
3–300	20–200	3–30	30–300	Microalbuminuria†
		M 2.0–20	M 20–200	
		F 3.0–30	F 30–300	
>300	>200	>30	>300	Macroalbuminuria†
		M >20	M >200	
		F >30	F >300	

Abbreviations: M, male; F, female.

*Threshold levels for albumin-to-creatinine ratios vary among guidelines. Threshold levels shown here are close to the various recommendations, but rounded to figures that are close to the threshold levels given in mg/d and mg/L.

†Terms are used commonly but should be avoided because they are misleading (see text).

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and, more importantly, short-term reduction of urine albumin excretion using specific drugs heralds long-term renal and CV protection.

DEFINITION OF NORMAL ALBUMINURIA

The established consensus is that in physiologic conditions no, or small, amounts of albumin are detected in the urine. If the amount of urine albumin exceeds 30 mg/d and is less than 300 mg/d it is called *microalbuminuria*, and if it is greater than 300 mg/d it is called *macroalbuminuria* or *overt albuminuria* (Table 1).³

The earlier-described cut-off levels are derived from studies that defined the urine albumin levels in normal individuals. However, there are reasons to redefine the normal urine albumin range. It recently has become clear that the pathology associated with increases in urine albumin levels is not restricted to microalbuminuria or overt albuminuria, but is also apparent at levels of less than 30 mg/d.^{4,6} In fact, the risk associated with albuminuria appears to be a continuum at all levels of albuminuria. In addition, one could question whether an albuminuria that is decreased by several current therapies still can be categorized by the same classes as before.

Thus, microalbuminuria may need to be redefined based on the cut-off levels. In addition, the term *microalbuminuria* is misleading because we are not dealing with small (micro) albumin molecules (as the term appears to define), but with mild increases in the amount of urine albumin. The latter would be defined better by *hyperalbuminuria*. Hyperalbuminuria then could be categorized, if needed, as mild, moderate, and severe. This also would help to eliminate misleading terms such as *microalbuminuria*, *macroalbuminuria*, or *overt albuminuria*. A recent review by Ruggenenti and Remuzzi⁷ addressed this issue of definitions.

WHAT DO WE MEASURE

As stated previously, the glomerular filter is designed to retain macromolecules within the vascular compartment. In case of a defective filter, several macromolecules may be found in the urine. Indeed, in case of excess albumin leakage, increased amounts of other proteins also are found in the urine. Interestingly, there are interprofessional differences in what to measure in the urine. Many nephrologists are trained to measure the total urinary protein excretion. Commonly, the main component of

this total protein is albumin (>50%). Doctors dealing with diabetic patients mostly use techniques that measure the albumin level in the urine. It is hard to define today which plasma protein is the one that should be measured in the urine. Urinary proteins are measured to assess kidney dysfunction (damage) and vascular function (damage), and are used as tools to predict renal and cardiovascular risk. It could be that the molecule of interest is albumin, however, it also could be that another plasma protein (cofiltered with albumin) is better related to the renal and CV damage or its prediction.⁸ Until otherwise concluded, urine albumin level is the best measure for diagnostic purposes.

Another ongoing debate is which technique we should use to measure the albumin level in the urine. Most common laboratory techniques use antibodies that bind to the albumin molecule (or its fragments), and subsequently detect the amount of formed complexes. Recently, a new approach was introduced that detects the albumin molecule more directly. Plasma is separated using high-pressure liquid chromatography, and subsequently the albumin peak is quantified. This technique appears to detect markedly more albumin in the urine of some individuals compared with the classic method.^{9,10} It is suggested that this high-pressure liquid chromatography technique enhances the sensitivity for CV or renal risk.⁹ However, prospective trials still are pending.

HOW DO WE MEASURE

To diagnose substances in the urine, the urine needs to be collected. Traditional collection covers a 24-hour period (24-h collection). This forces the patient to carry urine collection containers. Other collection strategies involve spot urine samples (the patient produces a urine portion at any time of the day) or first morning void (the patient collects the first urine passed after waking). In case of a 24-hour collection, one can calculate the amount of albumin excretion per time. This allows standardized monitoring between patients and within a patient. The problem with urine portion collection techniques is that they cannot be linked to time, and therefore lack within-patient and in-

terpatient standardization. This problem can be overcome by using the urine creatinine excretion as a reference. Creatinine is excreted in the urine with relative constancy over time. The albumin/creatinine ratio thus introduces a relative constant measure. One of the disadvantages is that the amount of creatinine may differ between individuals depending on their muscle mass. The definition of normal levels for the different collection techniques and for creatinine correction are shown in Table 1.

Most doctors use a central laboratory facility for albumin measurement. This is determined mainly by the fact that precise and accurate measurement of albumin requires advanced and dedicated equipment. However, small desktop point-of-care machines were introduced recently that can measure urine albumin with the same accuracy and precision as central laboratory machines (see Florvall et al¹¹ for an example). This is an important clinical development, comparable with what happened with blood pressure measurement techniques. This will allow patient care to be much more direct at the patient bedside. Doctors and even patients can monitor their risk (based on albuminuria) more easily and doctors can determine therapeutic actions without delay.

ALBUMINURIA AND RENAL RISK

Microalbuminuria

In patients with diabetes, an increased level of urine albumin heralds an ominous sign for the development of diabetic nephropathy. In type 1 diabetes, Mogensen¹² identified a level of albuminuria above which 80% of the patients progress to diabetic nephropathy in 10 years, whereas the subjects with levels that are less than this microalbuminuric threshold do not progress. A similar phenomenon was established in type 2 diabetes. Patients with microalbuminuria have an increased risk for both losing kidney function (glomerular filtration rate loss) and progression to overt albuminuria.¹³⁻¹⁶

The threshold of an increased albumin excretion that is associated with renal risk is not absolute. High normal levels of albuminuria are associated with more renal risk than low nor-

mal levels. Verhave et al⁶ showed in a general population that high normal levels of albuminuria are associated with renal risk compared with low normal levels. In addition, Ruggenti et al,¹⁷ recently showed in a large hypertensive type 2 diabetic cohort that patients with normal albuminuria levels are at risk to progress to microalbuminuria, which can be reduced by intervention.

The current guidelines indicate that we should use the microalbuminuric range of albumin excretion as the renal risk marker in type 2 diabetes. However, we appear to be dealing with albuminuria as a continuous renal risk parameter. Future risk assessment in type 2 diabetes may involve either lower cut-off levels for the definition of microalbuminuria, or better implementation of the albuminuria level in the total renal risk engine, including levels of albumin and other renal risk factors.

Overt Albuminuria

The chance of developing end-stage renal disease is enhanced drastically if a patient with type 2 diabetes has levels of albumin excretion greater than the microalbuminuric range (>300 mg/d). The relation between proteinuria and renal damage was found long ago, both in experimental and clinical settings. Remuzzi and Bertani¹⁸ proposed a mechanism in 1990, and this was updated recently,¹⁹ suggesting that there is a direct detrimental effect of leaked albumin in the kidney. Since then, many clinical studies have looked at the role of overt albuminuria as a risk marker for renal progressive function loss. In nondiabetic patients, Ruggenti et al²⁰ clearly showed that proteinuria is an important clinical contributor to renal outcome. The most recent data for type 2 diabetes come from 2 recent large intervention trials.^{21,22} Keane et al²³ clearly showed that albuminuria is the most important predictor of renal risk out of all currently known renal risk factors in a type 2 diabetic population that is well treated according to the guidelines. Keane et al² recently published a renal risk score for such patients, in which albuminuria is next to hemoglobin, serum creatinine, and serum albumin, the factors dictating renal outcome. Atkins et al²⁴ showed that proteinuria is indeed an impor-

tant predictor of renal outcome, irrespective of systemic blood pressure.

The cumulative data over the past decades show that albuminuria has a definite role in causing progressive renal damage.

ALBUMINURIA AND CV RISK

Microalbuminuria

To establish the relation between albuminuria and CV risk one needs a large population or patient studies with relatively long-term follow-up periods. Few, if any, studies have looked at an isolated unselected type 2 diabetic population prospectively for a relation between CV risk and microalbuminuria. However, there are several large randomized clinical trial studies such as heart outcomes prevention evaluation (HOPE) that have type 2 diabetic patients among the recruited subjects.²⁵ Such studies have shown that the presence of type 2 diabetes itself is a cardiovascular risk factor, and that microalbuminuria is a major cardiovascular risk factor. More dedicated studies directly associate microalbuminuria to CV outcome. In 1984, Mogensen²⁶ described the relation between microalbuminuria and mortality in type 2 diabetes. Marshall²⁷ described the CV mortality risk as about 4 times higher in microalbuminuric compared with normoalbuminuric type 2 diabetes. Yuyun et al²⁸ described the relative CV risk within a type 2 diabetes microalbuminuria cohort and clearly showed that even within the microalbuminuria range there is increasing CV risk (Fig. 1). Sukhija et al²⁹ showed that microalbuminuria clearly differentiated the cardiovascular risk within type 2 diabetic patients, increasing the chance of coronary artery disease considerably. Mykkanen et al³⁰ showed that microalbuminuria is associated with cerebrovascular problems. Keech et al³¹ found that even within the normoalbuminuric range one finds an increased risk for vascular morbidity in type 2 diabetic patients. Finally, a meta-analysis found that microalbuminuria doubles the cardiovascular morbidity and mortality in type 2 diabetes after adjusting for traditional risk factors.³²

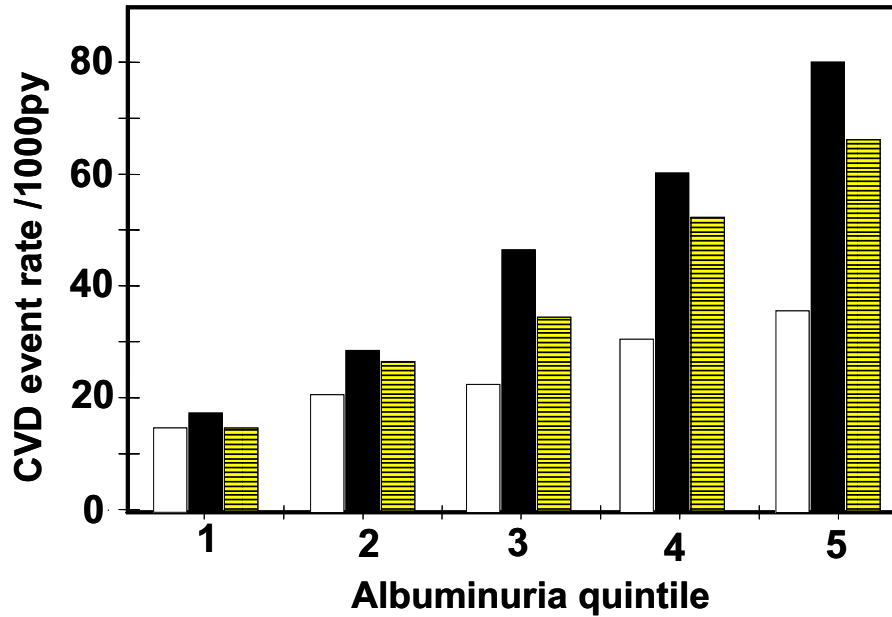


Figure 1. Baseline albuminuria in quintiles is associated with cardiac events in diabetes with albuminuria levels greater than 30 mg/d. □, type 1 diabetes (n = 161); ■, type 2 diabetes (n = 266); ▨, total. Modified and reprinted with permission from Yuyun et al.²⁸

Overt Albuminuria

The relation between higher quantities of albumin or protein in the urine and cardiovascular disease already was established by the Framingham data published in 1984.³³ The exact reason for this relation remains unknown to date. Clearly, also in type 2 diabetic patients, who already have an increased risk for CV disease, the role of overt albuminuria as a CV risk predictor is important. This again was established in 2 recent large type 2 diabetic trials of nephropathy patients.^{21,22} Both trials showed that there is a relation between baseline proteinuria or albuminuria and CV outcome as measured by composite end points.^{34,35}

REDUCING ALBUMINURIA REDUCES RISK

Renal Outcome

It is well known that several different therapeutic interventions may decrease albumin excretion in the urine considerably. Among these measures are drugs that intervene in the renin-angiotensin-aldosterone system (RAAS). These measures may decrease albumin excretion on average by about 50%.³⁶ The intriguing phenomenon can be observed that drugs (or strat-

egies) that decrease urine albumin excretion are in most cases also associated with renal protection. More importantly, the more a drug reduces the albumin in a certain individual patient in the short term, the more the kidney is protected in the long term.^{37,38} This finding has been confirmed in many large diabetic and non-diabetic intervention trials that followed such as the Captopril Collaborative Study Group trial, the ramipril efficacy nephropathy (REIN) trial, the reduction in endpoints in patients with non-insulin-dependent diabetes mellitus with the angiotensin II antagonist losartan (RENAAL), and the irbesartan in diabetic nephropathy trial (IDNT). These trials showed that renoprotective therapy was associated with a reduction of albuminuria (proteinuria), with more or less similar blood pressures as the comparator group.^{21,22,39,40} Some of these trials and their post hoc analyses clearly showed that the degree of reduction of albuminuria (or proteinuria) conferred by the drug given was associated with the follow-up renal outcome: the more the drug initially decreased the urinary albumin/protein excretion, the more the patients were protected (Fig. 2).^{24,41} These data were observed not only in overt albuminuria,

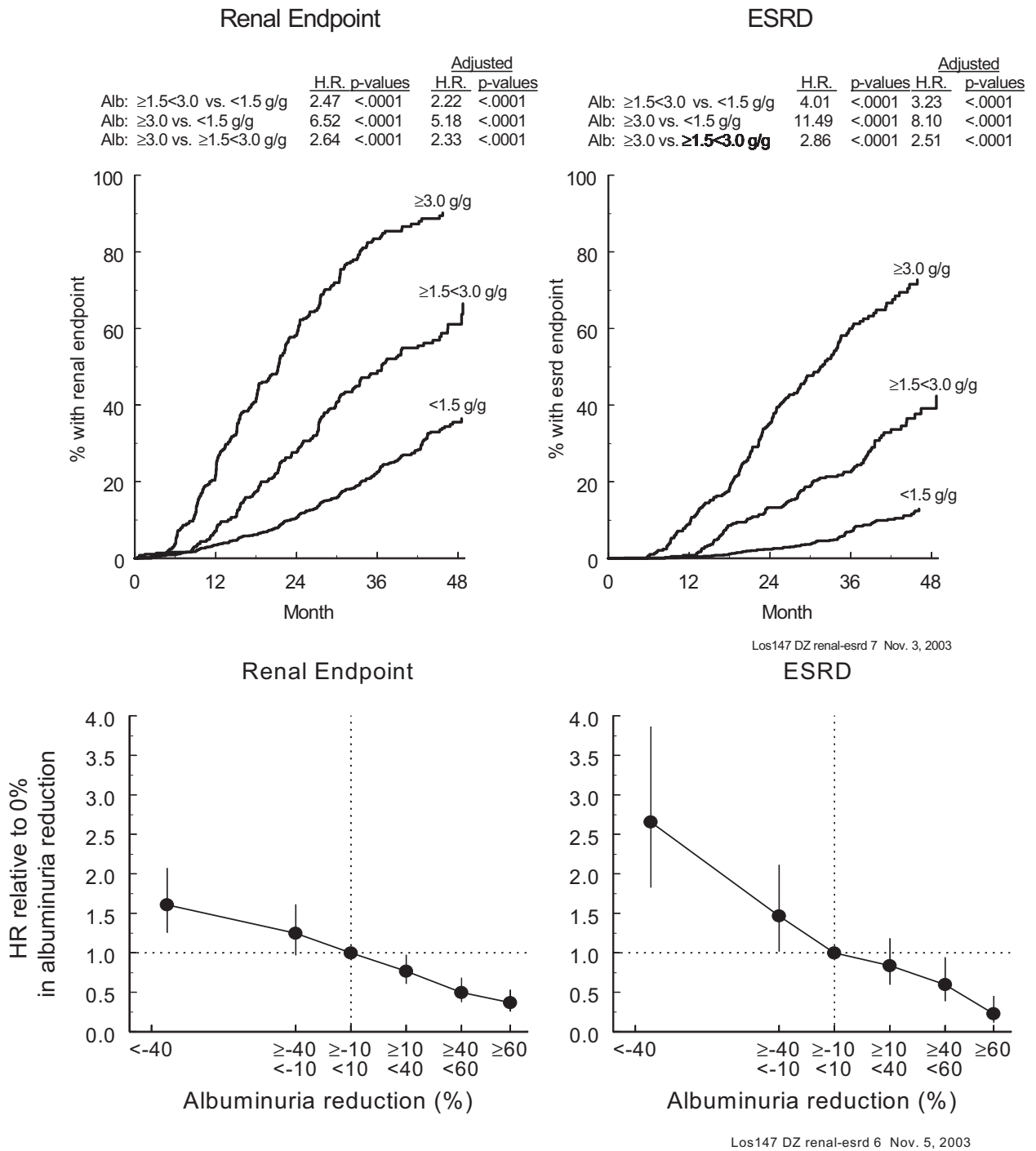


Figure 2. Data from the RENAAL trial in type 2 diabetic patients with nephropathy. Top panels show the event rate of renal end points stratified by baseline albuminuria. The lower panels show changes in the albuminuria level (baseline compared with month 6) versus the hazard ratio of the renal end point. Reprinted with permission from de Zeeuw et al.⁴¹

but also in microalbuminuric ranges, as shown in the irbesartan microalbuminuria type 2 (IRMA-2) trial in which the decrease in albuminuria was associated with renal protection.^{42,43}

The drugs most frequently associated with renal protection and albuminuria reduction are drugs that intervene in the RAAS. Because these drugs not only decrease the albuminuria but

also the systemic blood pressure, and because decreasing the systemic blood pressure also is associated with renal protection, one may wonder whether a reduction of albuminuria is related directly to renal outcome improvement. Recent data from the RENAAL trial gave the impression that indeed one should consider albuminuria reduction as a target by itself, independent from the blood pressure reduction. Eijkelkamp et al⁴⁴ found that those individuals who respond to RAAS intervention with no change or even an increase in blood pressure, still may be protected from end-stage renal disease in case one achieves a reduction in albuminuria.

Cardiovascular Outcome

There are several studies that clearly have shown that intervention in the RAAS leads to cardiovascular protection in type 2 diabetic patients.^{25,45} The question, however, is whether this protection is associated with the decrease in albuminuria that is likely to occur in these trials.

No prospective data are available on microalbuminuria in specific type 2 diabetic cohorts. However, Ibsen et al⁴⁶ showed in the losartan intervention for endpoint reduction in hypertension (LIFE) study (of which a major part was type 2 diabetes) that the short-term degree of decrease in baseline (micro)albuminuria by the instituted treatment was indeed associated with the long-term CV morbidity and mortality. The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-it) study showed that in normotensive, nondiabetic individuals with microalbuminuria, angiotensin converting enzyme (ACE) inhibition in the short term decreases albuminuria by about 30%, which is associated in the long term with CV protection.⁴⁷

In overt albuminuria, a post hoc analysis of the RENAAL study in overt albuminuric type 2 patients showed that the degree of the albuminuria decrease over the first 6 months of therapy is predictive of the CV outcome, such that the more one decreases albuminuria the better the prognosis.³⁴ Again, the effect of RAAS intervention on albuminuria may indeed be indepen-

dent from the blood pressure effect, as is the long-term associated CV outcome.⁴⁴

FUTURE AND NEW DRUG STRATEGIES

Albuminuria is clearly an important risk marker for both renal and CV morbidity and mortality in type 2 diabetic patients. Drugs that decrease blood pressure and intervene in the RAAS and decrease albuminuria do afford renal and CV protection for those patients. However, the residual risk in well-controlled trials with optimal care is still very high. Interestingly, the residual risk of these patients is related to the residual albuminuria. In other words, the future improvement of patient care in type 2 diabetes appears also to depend on, next to improvement of blood pressure control, the further reduction of albuminuria/proteinuria.

Several strategies for further albuminuria reduction are available, such as combination therapies in addition to renin-angiotensin-aldosterone system intervention (RAASi). The addition of a diuretic and/or low-sodium diet to enhance the antialbuminuric response to angiotensin-converting enzyme inhibition (ACEi) or angiotensin-II receptor blocker (ARB) also is important.⁴⁸ In addition, one should look at increasing the dose of the renin-angiotensin-aldosterone system intervention (RAASi) for optimal antialbuminuric treatment.^{49,50} Interesting results have been obtained recently by new drugs such as Sulodexide (Keryx Biopharmaceuticals, New York, NY), which appears to decrease albuminuria in addition to ACEi both in microalbuminuric and overt albuminuria.⁵¹ In addition, interesting drugs to decrease albuminuria further are being tested such as statins, vitamin D,⁵² and endothelin antagonist.

Most importantly, it will be necessary to test whether this addition of drugs not only decreases albuminuria further, but also will further protect the patient with type 2 diabetes against renal and CV problems. No hard end point evidence is available yet, but several trials are ongoing or need to be started (Table 2).

Next to optimization of intervention strategies with respect to mild, moderate, or severe increases in albuminuria as a renal or CV risk marker in type 2 diabetes, perhaps we should target our efforts to prevention instead of inter-

Table 2. Inventory of Ongoing Clinical Trials in Type 2 Diabetes, Testing the Hypothesis Whether Further Reduction of Albuminuria in Addition to RAAS Intervention Will Offer Further Renal and/or Cardiovascular Protection

Drug Added to ACEi or ARB	Acronym/Status	Hard End Point	Target Organs
ACEi and ARB combination	No trials		
Aldosterone-antagonists	No trials		
Glucosaminoglycans	SUN, ongoing		Renal
Endothelin antagonist	ASCEND, ongoing	Yes	Renal
Renin inhibitor	ALTITUDE, starting	Yes	CV and renal
Vitamin D analogues	VITAL, starting	No (GFR decrease)	Renal
Statins	PLANET, ongoing	No (GFR decrease)	Renal
Statins	SHARP, ongoing	Yes	CV and renal

Abbreviations: SUN, sulodexide nephropathy trial; ASCEND, study of cardiovascular events in diabetes; ALTITUDE, aliskiren trial in type 2 diabetes using cardio-renal disease endpoints; VITAL, elective vitamin D receptor activator (Paricalcitol) for albuminuria lowering study; GFR, glomerular filtration rate; PLANET, prospective evaluation of proteinuria and renal function in diabetic patients with progressive renal disease; SHARP, study of heart and renal protection.

vention. Palmer et al⁵³ showed that treating the microalbuminuric type 2 diabetic patient appears to be more cost effective than treating the patient with established nephropathy. Even more importantly, Ruggenti et al¹⁷ recently stated that the use of RAAS intervention in normoalbuminuric type 2 diabetic patients may indeed protect them against the development of microalbuminuria.

CONCLUSIONS

Type 2 diabetic patients run a very high risk for renal and CV complications. Albuminuria is a good predictor for both renal and CV risk in this population: the more albuminuria, the more renal and/or CV risk. Strategies that reduce albuminuria are associated with renal and CV protection: the more short-term albuminuria reduction the more renal and CV protection. Albuminuria is close to becoming a separate target for treatment. Currently ongoing clinical trials targeting albuminuria itself (without affecting other risk factors) will provide the urgently needed final proof. Next to improvement of intervention strategies, the prevention of microalbuminuria development may be an important strategy for the future.

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