

# Focus on Microalbuminuria to Improve Cardiac and Renal Protection

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## Key Words

Microalbuminuria · Estimated glomerular filtration rate · Chronic kidney disease · Screening

## Abstract

With the recent attention to diagnose earlier stages of chronic kidney diseases (CKD), most attention focuses on screening for an impaired estimated glomerular filtration rate (eGFR), i.e. CKD stages 3–5. Less attention is given to the impact of the urinary leakage of albumin. Its presence is not taken into account in the definition of stages 3–5, but only required to diagnose stages 1 and 2. As in stages 1 and 2 CKD, eGFR is not or only modestly impaired, these stages are generally considered to have a relatively better prognosis. In this review, we will show evidence that screening for albuminuria may be of great benefit, not only as an argument to start treatment to prevent progressive renal function loss, but also to prevent cardiovascular events.

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## Introduction

Proteinuria, the loss of proteins in urine, is one of the hallmarks of patients with kidney disease. Nephrotic syndrome, i.e. the loss of >3 g protein per day, was often the presenting symptom of a patient with glomerular or interstitial renal disease. In the last decades of the 20th

century, it became clear that the amount of proteinuria was directly associated with the severity of the renal function loss in the years after the first diagnosis. Moreover, it became clear that the extent to which treatment with antihypertensive agents lowers proteinuria, in particular blockers of the renin-angiotensin system in combination with diuretics, determines the effects of these drugs to prevent progressive renal function decline. The beneficial effects of such treatments to prevent end-stage renal disease (ESRD) may partly explain the trend that the number of patients reaching ESRD due to the classical renal diseases, as glomerulonephritis and type 1 diabetes, is presently diminishing [1]. On the other hand, however, the number of patients reaching ESRD due to type 2 diabetes, hypertension and generalized atherosclerosis is constantly increasing [1]. The latter is not unexpected as these patients generally are not diagnosed with the underlying disease, or – if diagnosed – are not monitored for their kidney function.

This is in fact the major boost behind the activities of various institutions to promote campaigns to detect chronic kidney disease (CKD) in an early phase. To that purpose the KDOQI published guidelines to define and to diagnose CKD. Since then, many efforts have been undertaken to detect subjects with CKD stage 3–5, i.e., subjects with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m<sup>2</sup>. Because GFR decreases with age, and is lower in women when compared to men, this type of screening results in the detection of a group of mostly

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elderly and frequently female subjects. Clinical practice and epidemiological studies have taught us that these subjects often have a fairly stable renal function over time. As a consequence there is much controversy whether this is the optimal approach to detect subjects at risk for ESRD [2]. Surprisingly, in this respect, less attention is given to the detection of subjects with stage 1 and 2 CKD, that is, patients with signs of renal damage but with still normal or only modestly impaired eGFR. As albuminuria, compared to erythrocyturia or abnormalities on ultrasonography, is the manifestation of chronic kidney damage easiest to be measured, we hypothesize that screening for an elevated albuminuria is a better approach to detect subjects at risk for progressive CKD.

### **Microalbuminuria – The Consequence of Just Renal or of Generalized Vascular Damage?**

Though the only difference between micro- and macroalbuminuria is the amount of albumin excreted in the urine, 30–300 versus >300 mg/day, it is generally expected not to be likely that microalbuminuria is a manifestation of glomerular damage, as the proximal tubule has an extensive potential to reabsorb albumin from the glomerular ultrafiltrate. On the other hand, there is evidence that microalbuminuria may be the consequence of generalized endothelial damage, thus not limited to the renal endothelium only. This is suggested from the Steno hypothesis arguing that diabetes leads to a generalized reduction of negative charges of extracellular matrix and plasma membranes, reflecting qualitative changes in the composition of the membranes severe enough to induce changes in permeability [3]. In line with this hypothesis, the presence of albuminuria in diabetes [4] and hypertension [5] is associated with markers of endothelial dysfunction.

If then assuming that microalbuminuria is a manifestation of generalized endothelial damage, it still is difficult to imagine why loss of albumin from the glomerulus is so closely associated with the vascular prognosis, when most of the albumin is next reabsorbed in the tubule. This can in fact be explained when tubular dysfunction instead of glomerular loss is adopted as the main determinant of the level of albuminuria. There is indeed evidence to support this theory, as tubular abnormalities are present early in the course of diabetes [6] and as tubular degradation of albumin also is inhibited in diabetic nephropathy [7]. The hypothesis that microalbuminuria might be considered as a tubular defect more than as a glomerular

defect, and that microalbuminuria is related to systemic vascular prognosis more than to only renal prognosis, may point to the tubular hypoxia hypothesis as a mechanism underlying the association between microalbuminuria and both renal and vascular prognoses. Generalized endothelial damage may well impair blood flow in peritubular capillaries, which will result in tubular interstitial damage, interstitial fibrosis and impaired oxygen diffusion and the supply to tubular cells. This may impair the tubular epithelial albumin reabsorption [8].

### **Microalbuminuria – How Reliable Is Its Diagnosis?**

Albuminuria can semiquantitatively be measured using test strips. These strips are relatively cheap, but have limited sensitivity and specificity [9]. Another option is measurement of urinary albumin concentration (UAC) with a point-of-care device. This device offers the possibility to measure UAC at the doctor's office. Results can immediately be used for clinical decision-making. Test characteristics of these devices are almost similar to that of the gold standard, being a measurement of UAC by radioimmunoassay or nephelometry [10]. The most used is measurement of albumin in a spot urine sample, preferably a first morning urine void [11]. A UAC of >20 mg/l in such a simple and relatively cheap collected first morning urine void showed in a European study a sensitivity of 69% and a specificity of 96% to diagnose a 24-hour urinary albumin excretion of >30 mg/24 h in two consecutive 24-hour urine samples [12]. These data are comparable to those in an Indo-Asian population. In that study the sensitivity and specificity of a UAC were 37 and 97%, respectively, for women and 69 and 94%, respectively, for men [13]. A drawback of this approach is that there will be false positive results. Since the consequence of having a 'positive' first morning void urine sample is just the need to repeat urine collections in a more accurate fashion, we feel that the limitation of this approach is acceptable when promoting population-based screening for albuminuria.

Reluctance to implement measurement of albuminuria in population studies is also based upon questions regarding the reproducibility of the test result. It has been shown that the within-person coefficient of variation between two consecutive 24-hour UACs is 19.2%, between two albumin creatinine ratios 13.8%, and between two 24-hour albumin excretions 14.3% [14]. These figures may seem high, however, the chances that by repeat measurement subjects change class, i.e. going from normal to

microalbuminuric, or vice versa, are small [11]. Measurement of UAC in fresh urine samples is to be preferred over measurement in samples that have been stored frozen, as the receiver-operating characteristics of a UAC of fresh urine samples to predict mortality was  $0.80 \pm 0.014$ , which was significantly better compared to  $0.74 \pm 0.016$  for frozen samples ( $p = 0.006$ ) [15].

Various risk factors have been found to be associated with an elevated albuminuria (see table 1) [16]. Discussion of these associations is out of the scope of this review. As exercise and inflammation are also known to influence urinary albumin excretion, it should be realized that urine collection for albuminuria testing should be avoided after heavy exercise and whenever acute inflammatory processes are present.

Another topic that should be addressed is the reversibility in time of albuminuria. While this is well known for diabetes [17], the phenomenon is also manifest in the general population [16]. It has been shown that progression or regression of albuminuria class (0–15, 15–30, 30–300 or >300 mg/day, respectively) may both occur within a 4-year period in about 10% of the subjects. The changes in fasting glucose and in blood pressure as well as the start of antihypertensives were associated with the changes in a urinary albumin excretion class multivariate model [18], however, the role of changes in BMI in this multivariate model was marginal. In a separate analysis to study the impact of the extremes of changes in body weight, that is in subjects who lost or gained more than 10 kg over a 4-year period, changes in body weight ran parallel with changes in albuminuria, which could not fully be attributed to the impact of changes in body weight on classical cardiovascular (CV) risk factors. In contrast, the data suggested that obesity-related changes in inflammatory markers may underlie the effects of body weight changes on changes in albuminuria [19].

### Microalbuminuria – A Marker of CV Events

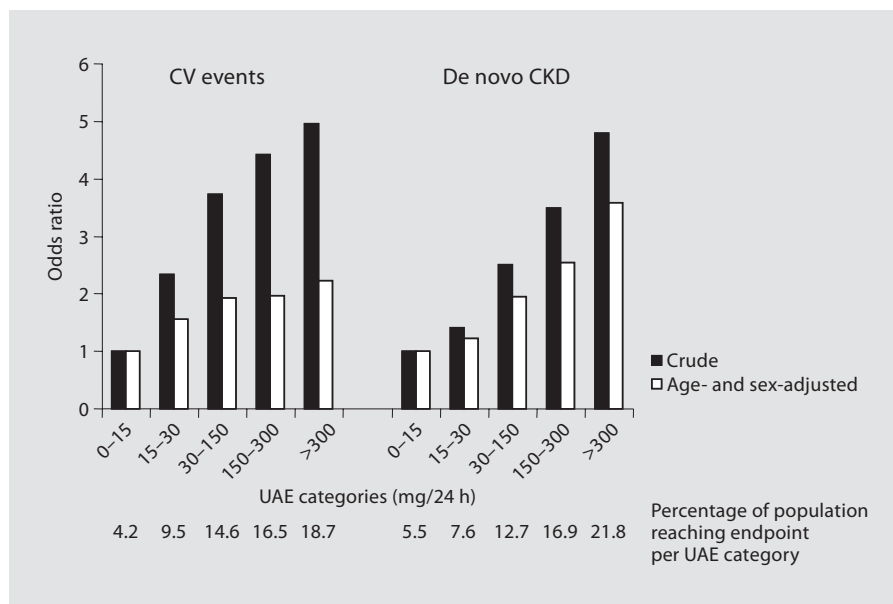
The first evidence of a worse CV prognosis of subjects with microalbuminuria was derived from data in patients with type 1 and type 2 diabetes. Shortly thereafter similar data were published for the presence of microalbuminuria in hypertension [20], in the elderly [21] and in the general population [22]. The increased vascular risk seems comparable for both cardiac and cerebrovascular events [20]. Interestingly, the level of eGFR has also been found associated with an increased risk for CV events [23]. As many patients with stage 3 CKD have microalbuminuria, it is of importance to study to what extent in those subjects the increased CV risk is related to either the lower eGFR or the increased albuminuria. Both in a cohort of subjects with preexisting coronary heart disease [24] as in a general population cohort [25] the risk for CV events was not increased in subjects with stage 3 CKD without albuminuria as compared to subjects with normal renal function and without albuminuria, while the risk was clearly elevated in stage 3 CKD subjects with increased urinary albumin loss. Moreover, in patients with stage 1 and 2 CKD, thus those with (nearly) normal eGFR but with increased albuminuria, the risk was also elevated as compared to those without CKD [24, 25]. In a recent publication of the PREVEND cohort, it was shown that the increased CV risk in subjects with stage 3 CKD without albuminuria is not elevated compared to the subjects without CKD after age and sex adjustment. On the other hand, the CV risk for subjects with albuminuria is equally increased in stages 1, 2 and 3, thus independent of the level of eGFR [26].

**Table 1.** Risk factors associated with elevated albuminuria

Non-modifiable	Modifiable	
	well documented	likely
Race/ethnicity	diabetes	hyperlipidemia
Male gender	hypertension	high salt (and protein) diet
Older age	obesity	oral contraceptives
Low birth weight	smoking	hormone replacement therapy

Although microalbuminuria is independent from other known CV risk factors associated with CV prognosis, there is debate whether microalbuminuria (and other new biomarkers as C-reactive protein, B-type natriuretic peptide, etc.) add to conventional risk scores to predict CV events. Some studies suggest that the new biomarkers add only little to the conventional ones [27], whereas other studies found a significant added value [28, 29]. These studies take into account the overall population. The more important question is whether assessment of albuminuria adds in subjects with an intermediate risk profile in the classical risk scores, in whom it is not clear that treatment should be instituted or not. To that purpose we studied the CV event rate (both fatal and non-fatal) in subjects with a SCORE function [30] of 5–10%. In that group the subjects with microalbuminuria had a 33% CV event rate in 10 years compared to 14% in the subjects with normoalbuminuria. These data make it clear that

**Fig. 1.** The percentage of the population (values at the bottom) and the odds ratio (bars) for developing de novo CV events (left) and de novo CKD (right) after 6 years of follow-up in relation to baseline urinary albumin excretion (UAE). Data are derived from the PREVEND cohort of 8,592 subjects from the general population. De novo CKD is defined as GFR <60 ml/min/1.73 m<sup>2</sup> [derived from 34].



knowledge on albuminuria status is indeed helpful to guide clinical decision-making.

If microalbuminuria is associated with a greater CV risk, the question is whether lowering of albuminuria is associated with a better CV prognosis. This has already been shown in subjects with macroalbuminuria. However, it was recently shown that lowering of albuminuria with an ACE inhibitor in subjects with an elevated albuminuria (15–300 mg/day) was also associated with fewer CV events, especially in subjects with an albumin loss in the range of 50–300 mg/day [31].

### Microalbuminuria – A Marker of Progressive Renal Function Loss

Although it is widely accepted that albuminuria in the ranges of macroalbuminuria and nephrotic range proteinuria is the best predictor for progressive loss of renal function in subjects with known kidney disease, less data are available that document the association between microalbuminuria and progressive renal function loss. It has, however, recently been shown that microalbuminuria also predicts the de novo development of a stage 3 or worse CKD [32]. As it takes many years to progress to ESRD in subjects without known kidney disease, the impact of microalbuminuria as a predictor for progressive renal function loss can be better judged by calculating the eGFR slope over time. Brantsma et al. [26] recently showed

that the eGFR slope over time is more negative in subjects with microalbuminuria compared to those without microalbuminuria, independent of the baseline level of eGFR. Moreover, similarly as with respect to future CV events, it has been shown that the risk to develop ESRD is only marginally (2.4-fold) increased in stage 3 CKD subjects without albuminuria, while it was 12-fold increased in subjects with a GFR of 60–90 ml/min but with albuminuria, and 33-fold increased in stage 3 CKD subjects with albuminuria [33]. These data indicate that in stages 1–3 the level of albuminuria has more impact than the level of eGFR per se. If thus the level of albuminuria predicts both future CV and renal events, it is of interest to compare the impact of albuminuria regarding these various endpoints. This has been done in figure 1, showing the association of the level of albuminuria with the odds to develop a CV event and a renal event (defined as de novo development of an eGFR <60 ml/min/1.73 m<sup>2</sup>). The data show that the odds increase comparably for both endpoints [34]. The impact of the various stages of CKD for reaching both endpoints is also clear from figure 2. It shows the incidence rates (on a log scale) per CKD stage for both CV endpoints and renal endpoints (now defined as the need to start renal replacement therapy). The data show that the incidence of both endpoints in stage 1 or 2 CKD is about comparably elevated as in stage 3 CKD compared to subjects without CKD. The figure moreover shows that, while in the first three stages the risk to develop a CV event is much higher than to develop

a renal event, the reverse is true in stages 4 and 5. However, the risk to develop a renal event rises more steeply than the risk to develop a CV event already in the early stages, thus in the subjects with microalbuminuria [35]. This once more argues that screening for microalbuminuria is not only of relevance to identify subjects at risk for cardiovascular disease (CVD), but also to identify those at risk for ESRD!

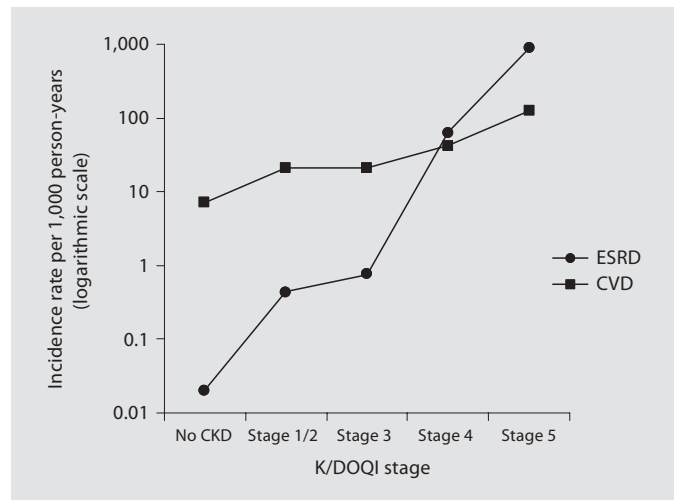
If albuminuria is associated with an increased risk for progressive renal disease, it again is of importance to study whether treatment with an ACE inhibitor will prevent microalbuminuric subjects to progress to macroalbuminuria. Thus far, this has only been studied in type 2 diabetic subjects with microalbuminuria. An ACE inhibitor prevented in these subjects the progression of micro to macroalbuminuria [36].

### Screening for Microalbuminuria: How Could It Be Organized and What Is the Benefit?

In case screening for albuminuria is to be implemented, should we consider the option to screen every subject in a certain age range for the presence of microalbuminuria, or to screen on albuminuria and eGFR in specific subsets of the population, such as those with known or expected increased risk?

With respect to the first option, a general population screen on the presence of an elevated albuminuria, most studies that have been published on this issue used the classical proteinuria dipstick test [33, 37, 38]. This test of course has the disadvantage that it is only semiquantitatively measured, and moreover has a relatively low sensitivity and specificity. Another approach was chosen in the pre-selection phase of the PREVEND study. We invited all inhabitants of the city of Groningen aged 28–75 ( $n = 85,421$ ) to fill out a short questionnaire on the presence of CV risk factors and to collect a sample of a first morning urine void in a plastic tube. Both were sent to the central laboratory of our hospital by post. Altogether 40,856 subjects (48% of the invitees) responded [39]. Macroalbuminuria was diagnosed in 0.7% of these subjects and microalbuminuria in 7.2%.

Of course the percentage of subjects with micro- or macroalbuminuria will be much higher when the screening is limited to subjects with a known or an expected increased risk. Although many guidelines advocate screening for albuminuria in subjects known to have diabetes, in subjects known to have hypertension or in subjects over a certain age (e.g. 55 years), it is unfortunately



**Fig. 2.** Incidence of ESRD and CVD events according to baseline CKD stage. Data are derived from the PREVEND study [35].

not yet daily routine for many doctors. Preventive nephrology will already gain a lot when subjects who had a prior CV event or who are known to have diabetes and/or hypertension will indeed be screened for albuminuria and eGFR. Depending on the local situation with respect to the prevalence of diabetes and hypertension and of the age group addressed (those >55 or >60 years), this may yield information on evidence of CKD in 30–60% of the population. However, we should realize that many subjects unknowingly have diabetes and hypertension [40]. We recently showed that a population screening using a pre-selection of subjects with an UAC >10 mg/l in a first morning urine void is more discriminating than screening the subjects with a prior CV event and with known diabetes and/or hypertension, and/or age >55 years. The first approach detects better the patients with CKD who are not yet on treatment and who experience more CV events in the future and who also experience more eGFR decline in the future, too [41].

Of course, screening programs to detect CKD will only be implemented if they have been proven cost-effective. In this respect, the study of Boulware et al. [42] in the USA is of interest. They showed that screening for dipstick-positive proteinuria in a general practitioner setting is not cost-effective to prevent ESRD. Cost-effectiveness was only reached when screening was limited to high-risk subgroups such as hypertensives and elderly. Another approach was used in the PREVEND study. All subjects were invited to deliver a first morning urine void

to a central laboratory for quantitative measurement of UAC. Only the subjects with an elevated UAC were then invited for a visit to screen for CV risk factors and for signs of CKD and CVD, and those with an elevated albuminuria were treated with an ACE inhibitor. That screening and treatment program was proven to be cost-effective when it was calculated to prevent CV events [43]. These two studies show that cost-effectiveness can in a few years only be reached when it is expressed in terms of CV prevention, while the prevention of ESRD will become manifest only after a much longer time period. Second, these studies show that pre-selection of the population will increase effectiveness.

## Conclusion

In our opinion the medical society should, when discussing possibilities for screening and prevention, not only pay attention to estimating GFR in individuals, but focus more on assessing their albuminuria status. Recent

studies have shown that higher levels of albuminuria predict the occurrence of renal function loss and CV events, and that moderately impaired renal function (K/DOQI stage 3 CKD) is no such risk factor when albuminuria is absent. Besides being a valuable risk predictor in individual subjects that present themselves at a doctor's office, albuminuria can also be used to organize CKD screening. The population at large, or certain high-risk subgroups, could be asked to collect a urine sample and to send this sample to a central laboratory for assessment of albuminuria. Those with elevated levels will be asked to collect additional urine samples for confirmation. If abnormal albuminuria is confirmed, subjects will be invited to a screening facility where the presence of other CV risk factors will be assessed. When present, these risk factors should be treated, given the CV and renal risk entailed by higher levels of albuminuria. Using such a screening approach, albuminuria measurement will thus be the starting point to obtain someone's health ABCDE, being the acronym for Albuminuria, Blood pressure, Cholesterol, Diabetes and Estimated GFR.

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## Editorial Comment

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The minireview by De Jong and Gansevoort on albuminuria is a timely and excellent appraisal, by two leading world authorities in the field, of the issues relating to the diagnosis and prognostic values of albuminuria. Over the last decade, it has become increasingly recognised that albuminuria is commonly detected in the general population. A number of factors may contribute to that high prevalence (around 7% in the PREVEND study) including ageing of the population and the rising prevalence of obesity and the metabolic syndrome. However, it is also important to recognise that microalbuminuria is often associated with a number of acute and chronic inflammatory conditions and that it can be reversible with control of the underlying inflammatory process. Caution therefore should be exerted in labelling individuals as

suffering from CKD on the sole basis of transient or reversible microalbuminuria. This may have overinflated the prevalence of 'CKD'. Albuminuria is also associated with diffuse vascular pathology and endothelial dysfunction. This may explain its rise with age and the fact that albuminuria is increasingly recognised as a useful, additional, cardiovascular prognostic marker. By contrast, the evidence for microalbuminuria as an independent CKD prognostic marker is far from established. Also, a marker cannot claim to predict a disease as well as feature in its definition! Treating a marker also cannot cure the underlying disease unless it is a causative factor. This remains to be established for albuminuria.