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Change in albuminuria as a surrogate endpoint

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Purpose of review
Chronic kidney disease is a global health problem with few effective therapies available that slow the progression to end-stage renal disease. The established clinical endpoints for renal trials; doubling of serum creatinine or end-stage renal disease, are late manifestations of CKD. This leads to large trials enrolling preferably patients with advanced stages of CKD. The use of valid surrogate biomarkers that substitute a clinical endpoint (surrogate endpoints), can lead to trials of shorter duration that can be performed at earlier stages of CKD. Change in albuminuria has been proposed as surrogate endpoint in CKD. Yet, although albuminuria is a strong risk factor for CKD progression, there is persistent uncertainty about its validity to substitute clinical endpoints.

Recent findings
New observational studies have demonstrated robust associations between changes in albuminuria and risk of end-stage renal disease. In addition, a meta-analysis of observational studies confirmed the strong association between change in albuminuria and end-stage renal disease. Another meta-analysis of clinical trials showed moderately strong associations between treatment effects on albuminuria and treatment effects on clinical endpoints. These new data support a role for change in albuminuria as surrogate endpoint for clinical trials of progression of CKD.

Summary
There is increasing evidence that change in albuminuria is a valid surrogate endpoint for CKD. Implementing albuminuria as surrogate requires proper understanding of the settings in which the surrogate works well.

Keywords
albuminuria, chronic kidney disease, clinical trial, end-stage renal disease, surrogate endpoint, urinary–albumin–creatinine ratio

INTRODUCTION

Chronic kidney disease (CKD) is a global and common health problem associated with significant morbidity and mortality [1]. Prevalence figures from the United States show that approximately 15% of the population is diagnosed with CKD [2]. Data from Europe indicate that the prevalence ranges between 3.3 and 17.3% in various general population cohorts, depending on, among others, prevalence of comorbidities and survey characteristics [3]. CKD is associated with a significant health burden, and medical resources [2]. Despite the high prevalence and burden of the disease, the number of proven effective therapies for patients with CKD is low. Novel therapies to prevent or slow the progression of CKD are thus highly desired.

Randomized controlled trials to test new interventions for CKD commonly use end-stage renal disease (ESRD) as clinical endpoint. However, ESRD is a late event in the progression of CKD. Accordingly, clinical trials to test new treatments for CKD require a large sample size and long follow-up in order that sufficient endpoints will occur to appropriately assess the drug's efficacy [4]. This hampers the feasibility of clinical trials in CKD.

Surrogate endpoints are laboratory markers that can be used in clinical trials as endpoints to substitute for a clinical endpoint. There is increased interest in using surrogate endpoints in clinical trials as they can be used in early stages of drug development to select promising drugs for future trials. In later

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KEY POINTS

- There is an increasing body of evidence that change in albuminuria is a valid surrogate endpoint in clinical trials testing renoprotection in CKD.
- Additional research on change in albuminuria as a surrogate endpoint in different specific populations is necessary to more precisely define the optimal use of albuminuria in clinical trial design.
- Albuminuria shows considerable day-to-day variation that needs to be taken into account when using change in albuminuria as a surrogate endpoint, for example, by collecting multiple urine samples at baseline and during follow-up.
- Novel approaches for clinical trial design should be explored (i.e. enrichment designs or adaptive designs) to optimally use change in albuminuria as surrogate endpoint.

stages of drug development, the use of surrogate endpoints, when accepted as valid, can shorten trial duration and reduce sample size.

Change in albuminuria has been proposed as a surrogate endpoint in CKD [5,6]. Changes in albuminuria occur earlier in the course of disease than changes in estimated glomerular filtration rate (eGFR) and it is a strong risk factor for the progression of CKD [7–9]. However, there is persistent uncertainty whether change in albuminuria can reliably reflect a drug's efficacy to slow renal function decline or delay ESRD.

In this review, we will summarize the recent literature on the association between changes in albuminuria and subsequent risk for ESRD and review the requirements for implementation of change in albuminuria as surrogate endpoint. We will first discuss the association between changes in albuminuria and renal endpoints in large observational studies. Observational studies have the advantage to study a large population with a long follow-up time enabling more accurate assessment of associations than clinical trials. In the second part of this article, we will review the association between changes in albuminuria and renal endpoints in clinical trials. Clinical trials offer the advantage to assess the association between treatment effects on albuminuria and treatment effect on clinical outcomes, which cannot be done in observational studies. We finally summarize the evidence and make recommendations for future research.

CHANGE IN ALBUMINURIA IN OBSERVATIONAL STUDIES

Albuminuria has long been recognized as an important marker predicting the risk of progression of renal disease. Already in the 19th century, Hermann Senator demonstrated the presence of proteins in the urine of otherwise healthy individuals and hypothesized that these urinary proteins predicted a higher risk of mortality [10]. Nowadays, with the more sensitive albumin assays, it has been unambiguously demonstrated that increased urinary albumin excretion is a strong predictor of ESRD, cardiovascular disease and mortality in various populations [11–14]. Although the association between albuminuria and outcome has been studied in multiple populations, until recently, there were only few observational studies that investigated how changes in albuminuria over time associate with CKD progression and cardiovascular disease.

In the last years, several large observational cohort studies investigated the association between change in albuminuria and long-term progression of kidney disease to ESRD. Two large cohorts found a linear association between changes in albuminuria and risk of ESRD [15▪] and incident CKD [16]. In an observational study of 31 732 participants of the SCREAM project, it was shown that a four-fold increase in albuminuria over 2 years was associated with a hazard ratio of 3.08 [95% confidence interval (CI) 2.59–3.67] for the risk of ESRD [15▪]. Similar results were seen in a large cohort of United States veterans involving 56 946 participants with an eGFR of at least 60 ml/min/1.73 m^2 where a more than two-fold increase in albuminuria was associated with a hazard ratio of 1.29 (95% CI 1.21–1.38) for developing a sustained eGFR of less than 60 ml/min/1.73 m^2 [16].

Uncertainty about the association between change in albuminuria and renal outcome was one of the reasons to organize a workshop sponsored by the US National Kidney Foundation (NKF), in collaboration with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). The aim of this meeting was to obtain a better understanding of the validity and utility of change in albuminuria and change in eGFR as surrogate endpoints for clinical trials in CKD [17]. In preparation for this workshop, a meta-analysis of observational studies was performed to provide more definitive evidence about the relationship between changes in albuminuria and subsequent risk of ESRD [18▪▪].

This meta-analysis of observational studies included data from 675 904 individuals from 28 cohorts in the Chronic Kidney Disease Prognosis Consortium (CKD-PC). Eighty percent of these participants had diabetes. Change in albuminuria or proteinuria during a 2-year baseline period was strongly associated with the long-term risk for ESRD, and an increase in albuminuria or proteinuria increased the adjusted hazard ratio for ESRD almost

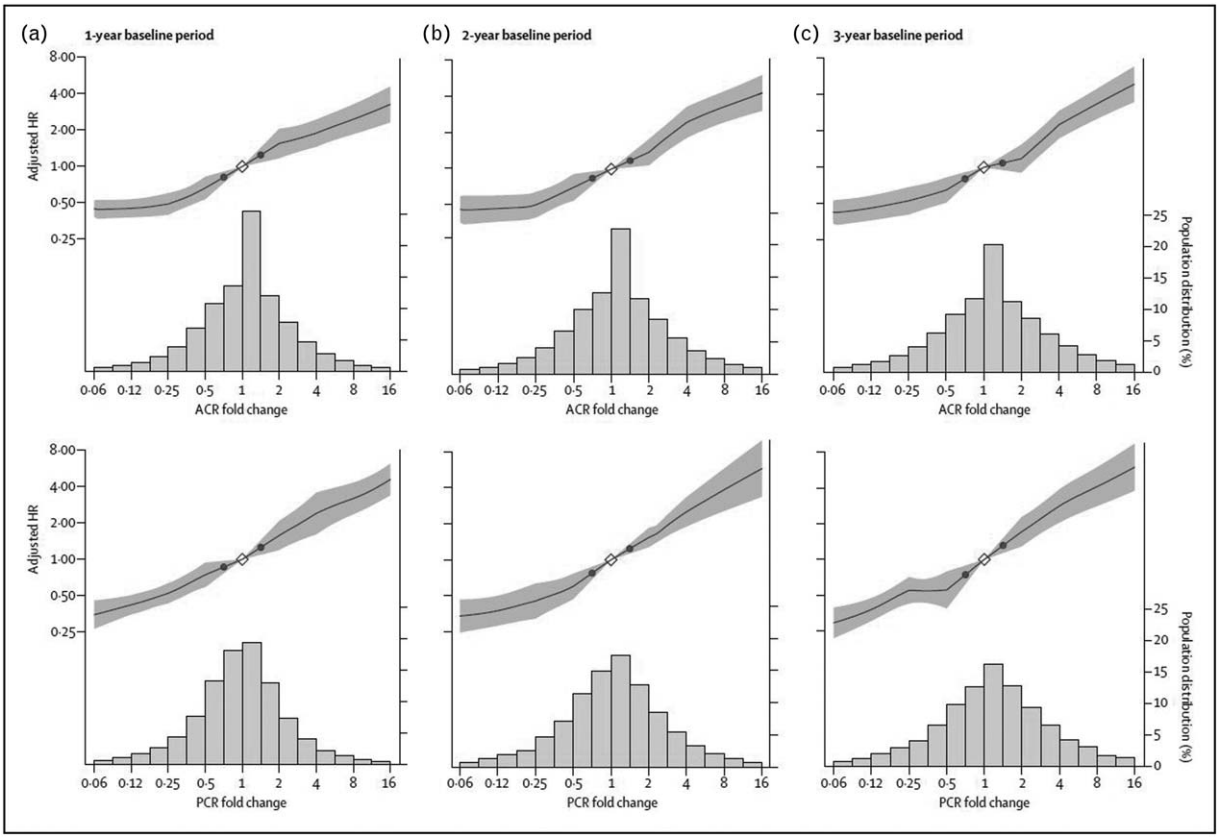

FIGURE 1. Adjusted hazard ratio for end-stage renal disease and population distribution of change in albuminuria measured by ACR and PCR over 1-year (a), 2-year (the base case scenario) (b), and 3-year (c) baseline periods in the meta-analysis of observational studies. ACR, urine albumin-to-creatinine ratio; PCR, urine protein-to-creatinine ratio. Reproduced from Coresh *et al.* [18▪▪].

linearly (Fig. 1). A reduction in albuminuria of 30% during the 2-year baseline period was associated with a hazard ratio for ESRD of 0.83 (95% CI 0.74–0.94). One of the challenges is that albuminuria can show considerable day-to-day variability [19,20], which has to be taken into account when analyzing the association between change in albuminuria and outcomes. A recent study showed a stronger association with change in albuminuria when correcting for random measurement error and variability in albuminuria [21▪]. To address this random day-to-day variation in albuminuria, the meta-analysis was corrected for regression dilution. After considering the variability in albuminuria, the association between albuminuria change and renal outcomes appeared to be stronger: 0.78 (95% CI 0.66–0.92) [18▪▪]. When instead of a 2-year baseline period, a 1-year or 3-year period was used to assess change in albuminuria, essentially similar results were obtained (Fig. 1). Risk associations were moreover fairly consistent across cohorts and subgroups (i.e., eGFR, diabetes, and sex), but the association was somewhat stronger among participants with higher baseline albuminuria (*P* for interaction <0.0001) [18▪▪].

CHANGE IN ALBUMINURIA IN CLINICAL TRIALS

The observational studies on change in albuminuria and subsequent renal endpoints suggest that when lowering albuminuria with a pharmacological intervention the risk for renal events decreases. Indeed, several small-scale studies that investigated various interventions (pharmacological and dietary) have shown a decrease in albuminuria and slowing of the progression of renal disease [22,23]. Analyses of these studies have also shown that the early change in albuminuria within the study was associated with the rate of kidney function decline thereafter further supporting a causal association and a potential role for early change in albuminuria as surrogate endpoint [24,25].

This observation was subsequently confirmed in larger scale clinical trials in patients with type 2 diabetes (RENAAL [26], IDNT [27], ALTITUDE [28]), in patients with nondiabetic kidney disease (AASK [29], REIN [30]) and more recently also in children with CKD (ESCAPE [31]). A summary of these studies and their main results are shown in Table 1.

Table 1. Post hoc analyses from randomized clinical trials that reported an association between change in albuminuria and renal outcomes

Study	Number of patients	Patient population	Albuminuria measurement	Clinical outcome	Strength of the association between albuminuria change and clinical outcomes
RENAAL [26]	1513	Type 2 diabetes and chronic kidney disease	First-morning void urine sample at baseline and 6 months	Doubling of serum creatinine, ESRD or death	At least 30% reduction in albuminuira compared with reference group of no change (<0%) was associated with a hazard ratio of 0.46 ($P < 0.0001$)
IDNT [27]	1312	Type 2 diabetes and chronic kidney disease	24-h urinary protein excretion at baseline and at 12 months	Doubling of baseline serum creatinine, serum creatinine level of 6.0 mg/dl (530 μmol/l) or ESRD	Each halving of proteinuria was associated with a hazard ratio 0.44 (95% CI 0.40–0.49)
ALTITUDE [28]	8561	Type 2 diabetes and chronic kidney disease or cardiovascular disease	Three consecutive first morning void urines at baseline and at 6 months	Composite renal and a composite cardiovascular endpoint	More than 30% reduction in albuminuria, compared with an albuminuria increase (0–30%), was associated with a hazard ratio of 0.38 (95% CI 0.30–0.49) for the renal endpoint and a hazard ratio of 0.75 (95% CI 0.65–0.87) for the cardiovascular endpoint
AASK [29]	810	Afro-Americans with hypertensive nephrosclerosis	Urine protein-to-creatinine ratio at baseline and 6 months	Mean GFR slope and ESRD	A doubling in albuminuria was associated with a 0.63 (SD 0.10) ml/min/1.73 m^2/year greater decline in GFR and a relative risk for ESRD of 2.11 (95% CI 1.89–2.36)
REIN [30]	273	Nondiabetic chronic kidney disease	24-h urinary protein excretion rates. Two consecutive measurements at baseline and one measurement at 3 months	GFR decline	Patients with a reduction in proteinuria had a slower GFR decline (-0.28 ± 0.04 ml/min/1.73 m^2/month) compared with patients who did not have a short-term reduction in proteinuria (-0.53 ± 0.07 ml/min/1.73 m^2/month)
ESCAPE [31]	280	Children with chronic kidney disease	24-h urine sample or random sample at baseline and at the first visit after full dose of ramipril (within 6 months after start of the study)	Sustained 50% reduction of eGFR or progression to ESRD	More than 60% reduction in proteinuria, compared with a reference group of less than 30% reduction, was associated with a hazard ratio of 0.42 (95% CI 0.22–0.79)

(e)GFR, (estimated) glomerular filtration rate; CI, confidence interval; ESRD, end-stage renal disease; SD, standard deviation.

Although the consistency of results of the clinical trial analyses support the validity of albuminuria as a surrogate endpoint, it should be noted that the analyses were conducted post hoc and were not based on randomized comparisons. It could, therefore, be possible that the low risk of kidney disease progression among patients with a reduction in albuminuria was caused by factors unrelated to the albuminuria-lowering effect of the intervention. To overcome this bias, a meta-analysis of randomized controlled clinical trials is needed to correlate the placebo-controlled effect of the intervention on the early change in albuminuria with the placebo-controlled treatment effect on a clinical kidney outcome. Two such meta-analyses were conducted in the last years with conflicting results, however. The study by Inker *et al.* [32] did not provide enough evidence to support the validity of change in proteinuria as surrogate endpoint. In contrast, the other meta-analysis published around the same time reported an association between short-term changes in albuminuria and a long-term renoprotective effect [33]. The difference in results of these meta-analyses may be explained by differences in the inclusion of clinical trials and differences in methodological approach to study the association of the treatment effect on albuminuria and on clinical outcomes [32,33]. In addition that their results were conflicting, the generalizability of the results was questioned because of the limited number of interventions and patient subgroups [34,35].

To overcome these limitations, a novel meta-analysis of randomized controlled trials was performed by the authors of the two previous, conflicting meta-analyses [36▪▪]. In this new analysis, they aimed to include all past randomized controlled trials and analyze the data according a predefined, robust, and consistent methodological approach. In addition, it was a priori decided that results were to be studied across several interventions and patient subgroups. A total of 41 clinical trials with 29 979 participants were included in this novel meta-analysis. A significant association was shown between change in albuminuria and the treatment effect on ESRD ($R^2 = 0.47$; Fig. 2a). Results were consistent across interventions and patient subgroups. However, the association strengthened when the analysis was restricted to only patients with higher baseline albuminuria (UACR >30 mg/g, $R^2 = 0.72$), indicating that for using albuminuria in surrogate

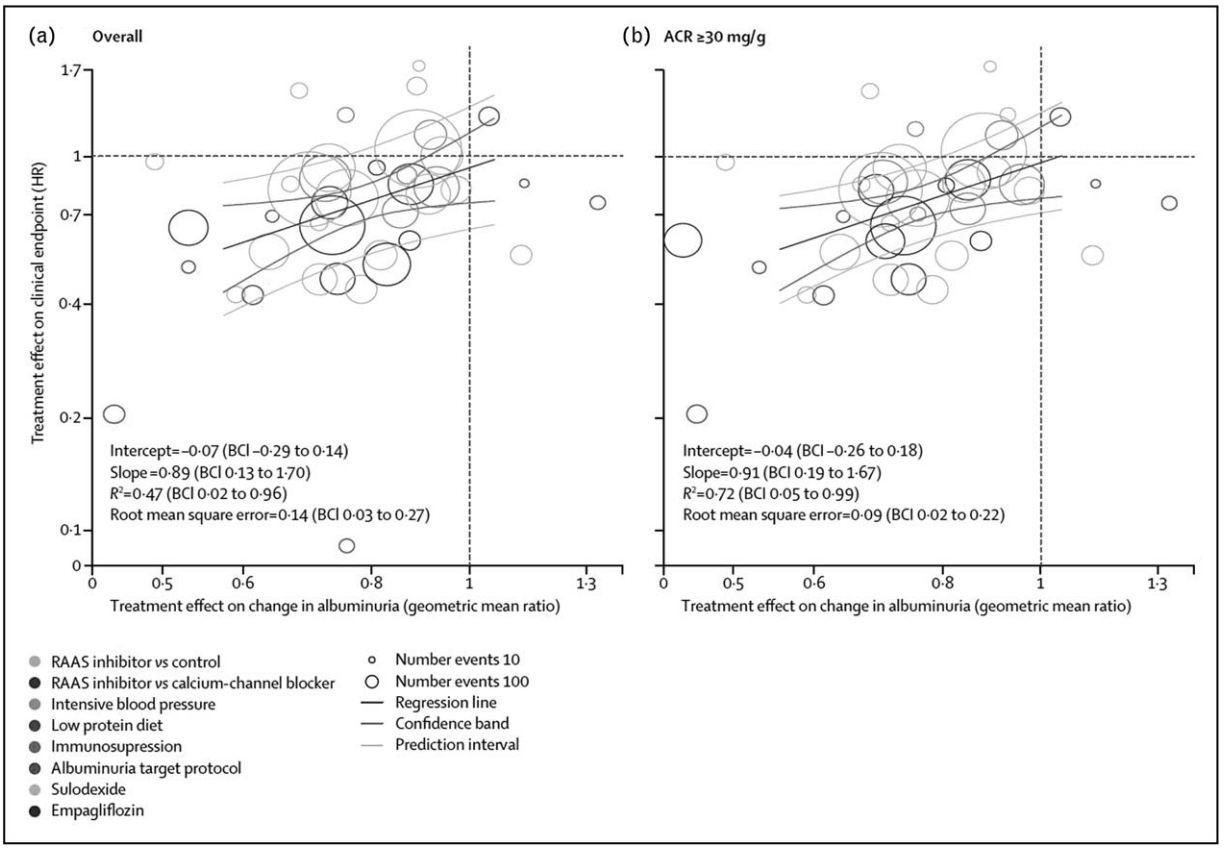

FIGURE 2. Trial-level analyses for the association between treatment effects on change in albuminuria and treatment effects on the clinical endpoint for the pooled population (a) and for participants who had baseline ACR of more than 30 mg/g (b) in the meta-analysis of randomized clinical trials. ACR, urine albumin-to-creatinine ratio. Reproduced from Heerspink *et al.* [36▪▪].

clinical trials, these trials should use a minimal albuminuria level as entry criterion (Fig. 2b) [36▪▪]. The trial-level analysis also enabled calculation of the minimal effect size for lowering albuminuria with a drug to have high confidence that this drug will also decrease the risk of ESRD, the so called positive predictive value. It turned out that a 20–30% reduction in albuminuria is necessary to achieve clinical benefit. Such an effect size has been observed in clinical trials with interventions that indeed slow the progression of renal disease, such as ACE-inhibitors, angiotensin 2 receptor blockers and sodium glucose co-transporter inhibitors [26,30,37].

SYNTHESIS OF THE AVAILABLE EVIDENCE AND RESEARCH RECOMMENDATIONS

Taken together, the results of this meta-analysis of clinical trials and the aforementioned meta-analysis of observational studies support a role for change in albuminuria as surrogate endpoint [18▪▪,36▪▪]. Their results are applicable to various kidney diseases, such as diabetic kidney disease, but also nondiabetic kidney disease. The 20–30% reduction in albuminuria required to have a high confidence that the intervention will also demonstrate clinical benefit can be used as criterion to select the promising interventions from phase 2 studies to be tested in larger scale phase 3 clinical trials. There is also a potential role for albuminuria to facilitate phase 3 clinical trials. Albuminuria could be used as a surrogate endpoint for conditional approval in phase 3 trials with confirmation of long-term efficacy and safety in subsequent outcome trials. Another option could be that in case of proven short-term albuminuria-lowering efficacy, the subsequent phase 3 clinical outcome trials can be designed less stringent, for example, by adopting a one-sided instead of two-sided testing strategy and relaxing the alpha level from 0.01, which is required for marketing approval for a single pivotal trial, to 0.05. However, these approaches require further discussion and require regulatory approval.

Albuminuria could also be a useful surrogate in glomerular diseases. The prevalence of glomerular diseases is lower than of diabetic kidney disease, which makes it even more challenging to perform large clinical outcome trials. For example, IgA nephropathy is a serious condition for which there are few ongoing clinical studies and proven effective therapies. A kidney health initiative project recently performed a critical appraisal of literature to assess the validity of albuminuria change for clinical trials in IgA nephropathy and concluded, in line with the conclusions of the meta-analyses, that the data support a role for albuminuria as a valid surrogate endpoint [38▪].

Regardless of the specific type of kidney disease, it is important that future clinical trials enroll participants at risk of progressive CKD in whom the new intervention can reverse or delay the course of disease progression. Some trials failed to show a reduction in renal events despite the drug decreased albuminuria [39]. These trials predominantly enrolled patients with (very) low levels of albuminuria, that consequently are at low risk of disease progression [40]. Albuminuria should not be applied as endpoint in such trials, but only in clinical trials enrolling patients with elevated albuminuria at risk of progressive CKD. Other examples demonstrating that a treatment effect on albuminuria does not predict a treatment effect on a clinical outcome can be explained by the fact that the reduction in albuminuria is too small to afford renal protection [28], or that a trial is terminated early, so that the statistical power to detect a treatment effect on the clinical endpoint is limited leading to an inconclusive result [41]. Thus, there are plausible explanations why in some trials the treatment effect on albuminuria did not predict clinical benefit.

Importantly, when albuminuria is applied in future clinical trials, the day-to-day variation should be adequately taken into account when determining treatment effects on albuminuria. Prior studies showed that collecting multiple urine samples across multiple study visits are needed to more precisely determine the effect size of the intervention on albuminuria [42].

There are no prospective clinical trials that target albuminuria to prevent ESRD, and such trials are highly needed. The recently published SONAR trial comes closest [43▪]. In this trial, all patients received 6-week open label treatment (enrichment) with the endothelin antagonist atrasentan. After 6 weeks, patients were randomized to continue atrasentan or to switch to placebo. Randomization was stratified by the albuminuria reduction observed during the enrichment period and two cohorts were created: the responder and nonresponder population. Response was defined by an at least 30% reduction in albuminuria from baseline. Responder patients showed a ~50% reduction in albuminuria from baseline and nonresponders only ~8%. During the double-blind trial, atrasentan compared with placebo reduced the risk of the renal endpoint by 35% (95% CI 0.49–0.88; $P = 0.0047$) in the responders and 25% (95% CI 0.55–1.03; $P = 0.079$) in the nonresponders. This effect was not anticipated based on the reduction in albuminuria in the two groups defined during the enrichment procedure. The explanation for the unexpected high benefit for

renal endpoint in the albuminuria nonresponders is unknown and requires further study. It is possible that responders and nonresponders were insufficiently separated because of random variations in albuminuria, but it could also be that that atrasentan confers renoprotection through mechanisms other than albuminuria lowering [43▪].

As a final comment, although establishing drug efficacy is important, safety is at least equally important. Accurate safety assessments are optimally performed in large-scale clinical trials of long duration. Some use this as argument against adopting change in albuminuria as valid surrogate for regulatory purposes. However, one may consider to perform the safety assessment for some drugs with an expected good safety profile in postapproval studies combined with registry-based real-world practice studies.

CONCLUSION AND FUTURE PERSPECTIVES

In the last years, an emerging body of evidence supports change in albuminuria as a valid surrogate endpoint in clinical trials of CKD progression for interventions of which reducing albuminuria is the hypothesized mechanism of action to slow progression of CKD. We caution for universally applying albuminuria in any clinical trial. Applying albuminuria as surrogate requires proper understanding of the conditions in which the surrogate is likely to perform well taking into account the specific study population, and mechanisms of action of the drug. Additional research assessing the performance of change in albuminuria in specific populations (e.g. diabetic kidney disease, IgA nephropathy, focal segmental glomerulosclerosis) is welcome to more precisely define the conditions to change in albuminuria as surrogate endpoint.

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Conflicts of interest

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This is the first clinical trial that uses change in albuminuria prospectively in an enrichment design. After a 6-week open-label period with the study drug (atrasentan), patients were randomized to placebo or atrasentan. Randomization was stratified by the change in albuminuria during open-label atrasentan treatment.