Change in Albuminuria as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-analysis of Treatment Effects of Randomized Trials

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Abstract

Background: There is strong biologic plausibility for change in albuminuria as a surrogate endpoint for progression of chronic kidney diseases (CKD), but empirical evidence to support its validity is lacking.

Methods: We performed a systematic review of treatment comparisons from randomized clinical trials (studies) of interventions to slow progression of CKD and requested agreement for use of the individual patient data. For each of 41 studies, that included a total of 29,979 participants (21,206 (71%) with diabetes), we estimated the treatment effects on 6-month albuminuria change and on the composite clinical endpoint of treated end stage kidney disease (ESKD)eGFR < 15 ml/min per 1.73 m^2 or doubling of serum creatinine. We used a Bayesian mixed effects analysis to relate the treatment effects on albuminuria to those on the clinical endpoint across these studies and developed a prediction model for the treatment effect on the clinical endpoint based on the treatment effect on albuminuria.

Findings: Across all studies, each 30% reduction in geometric mean albuminuria by the treatment relative to control was associated with an average 27% lower hazard for the clinical endpoint [95% Bayesian Credible Interval (BCI) 5% to 45%]; median R^2=0.47 [95% BCI 0.02 to 0.96]. The association strengthened after restricting to patients with baseline albuminuria > 30 mg/g (3.4 mg/mmol) (R^2=0.72 [95% BCI 0.05 to 0.99]). For future trials, the model predicts that treatments that reduce the geometric mean albuminuria by 30% relative to the control group will provide an average hazard ratio (HR) for the clinical endpoint of 0.68, and 95% of sufficiently large studies would have HRs between 0.47 and 0.95.

Interpretation: The results support a role for change in albuminuria as a surrogate endpoint for CKD progression, particularly in patients with higher baseline albuminuria. Results are less certain at lower levels of albuminuria.

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Research in Context

Evidence before this study

The currently established endpoints for clinical trials of progression of chronic kidney disease (CKD), are end-stage kidney disease (ESKD) and doubling of serum creatinine, which approximates a 57% decline in estimated glomerular filtration rate. There is increased interest in using alternative endpoints in clinical trials to shorten trial duration and reduce sample size. Emerging data support a strong biologic possibility for a change in albuminuria as a surrogate endpoint for CKD progression. In observational studies albuminuria has consistently been shown to be a strong predictor of ESKD in a range of patients and settings. However, two previous meta-analyses reported conflicting results with respect to the strength of the association between treatment effects on early change in albuminuria and treatment effects on ESKD. The US National Kidney Foundation, in collaboration with the US Food and Drug Administration and European Medicines Agency sponsored a workshop to evaluated candidate surrogate endpoints for clinical trials of drugs to slow kidney disease progression, particularly among participants with early stages of CKD. Search criteria: We searched PubMed from January 1, 1946, to December 15, 2016 for all English-language publications with the search terms “Chronic Kidney Disease”, “Chronic Renal Insufficiency”, “Albuminuria”, “Proteinuria”, “Randomized Controlled Trial”.

Added value of this study

Based on a joint analysis of 29,979 individuals in 41 treatment comparisons from randomized controlled trials we showed that in studies of interventions in which albuminuria has biologic plausibility as a surrogate endpoint, the treatment effect on albuminuria has significantly associated with the treatment effect on clinical endpoints. This association is stronger in populations with elevated albuminuria [albumin:creatinine ratio > 30 mg/g ((3.4 mg/mmol)]. Our model predicts that for future trials with sufficiently large sample size, treatments that reduce geometric mean albuminuria relative to the

control group to 0.7 (i.e. 30% reduction in albuminuria) would have a high likelihood to confer clinical benefit.

Implications of all the available evidence

In conjunction with all available experimental and clinical evidence, including the accompanying article of associations of change in albuminuria with subsequent outcomes in observational studies, the results of this study support a role for change in albuminuria as a surrogate endpoint for CKD progression in clinical trials particularly in patients with elevated albuminuria. Future studies are warranted to determine how albuminuria change can be best applied in designs for clinical trials of CKD progression while protecting against the risk of a false conclusion of clinical benefit.

Introduction

Chronic kidney disease (CKD) is a major global health concern with few proven effective therapies. One of the challenges in development and evaluation of therapies for CKD is that randomized controlled trials (RCTs) to assess efficacy and safety of novel therapies traditionally use end-stage kidney disease (ESKD), estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2 and doubling of serum creatinine [equivalent to a 57% decline in eGFR] as clinical endpoints.[1] These endpoints are late events in the progression of CKD. Consequently, many RCTs have been restricted to patients with later stages of CKD or faster decline in glomerular filtration rate (GFR) to obtain a sufficient number of endpoints, thereby limiting the study populations and the feasibility of conducting the trials. Moreover, appropriate intervention in earlier stages of CKD has been advocated as such treatments may be more beneficial than interventions applied in later stages.[2] Alternative endpoints are thus needed to perform RCTs in earlier stages of CKD.

There is strong biological plausibility for a change in albuminuria as a surrogate endpoint for CKD progression in RCTs, and clinicians consider an early reduction in albuminuria as indicative of a favorable response to treatment.[3-6] Albuminuria is a sensitive marker of kidney disease progression in early stages of CKD and appears to be a cause of CKD progression in some disease.[3-5] In observational studies increased albuminuria has consistently been shown to be a strong correlate and predictor of ESKD.[7-12] However, there is persistent uncertainty regarding the empirical evidence that treatment effects on change in albuminuria can be used to reliably predict treatment effects on the clinical endpoint.[13,14]

On March 15-16 2018, the National Kidney Foundation (NKF), in collaboration with the Food and Drug Administration (FDA) and European Medicines Agency (EMA), sponsored a scientific workshop “Change

in Albuminuria and GFR as Endpoints for Clinical Trials in Early Stages of Chronic Kidney Disease" to evaluate surrogate endpoints for trials of kidney disease progression and improve understanding of change in albuminuria and GFR as measures of kidney disease progression. Here we report on the results of an individual patient Bayesian meta-analysis of 41 treatment comparisons from RCTs including 29,979 participants to examine the agreement between treatment effects on early changes in albuminuria and treatment effects on the clinical endpoint and to inform the use of albuminuria as a surrogate endpoint in future RCTs. In the companion paper, we report on the results of an observational analysis of 28 cohorts including 693,816 individuals to examine the association between change in albuminuria to ESKD risk. Together these papers provide a comprehensive assessment of the validity of using early changes in albuminuria as surrogate endpoints for trials of CKD progression.

Methods

Datasets and analytical groups

For our prior work investigating surrogate endpoints, we had performed a systematic search of the Medline database from January 1 1946 to May 15 2007.[2,6] To update this dataset for the current analysis, we repeated our systematic search beginning May 16 2007 when the initial search had been completed and ending in December 15, 2016 (see sTable 1 lists the search terms). Key inclusion criteria were quantifiable measurements of albuminuria or proteinuria at baseline and within 12 months of follow-up and information on ESKD incidence (sTable 2 shows complete list of study inclusion criteria). Additional details are available in the protocol found in the Supplement. Risks of bias for each RCT were assessed using the risk-of-bias tool of the Cochrane collaboration (sFigure 1).[15] For RCTs that evaluated more than one intervention, we included a separate randomized treatment comparisons for each independent treatment vs control comparison reported, such that some participants were included in more than one analytical unit. We pooled RCTs with fewer than 100 participants that evaluated the

same disease and intervention (sTable 3 and sFigure 2). Based on a priori discussion with the Workshop planning committee, we excluded three studies with interventions in which change in albuminuria was not thought to have biologic plausibility as a surrogate endpoint (nurse coordinated management and allopurinol, sTable4) leading to a total of 43 treatment comparisons (referred to here on in as studies). Tufts Medical Center Institutional Review Board approved this study. Informed consent was not required for this analysis but was obtained for each individual RCT.

Change in albuminuria

The measures of albuminuria varied across studies, with most measuring protein excretion rate (PER) (sTable 4). Because recent guidelines recommend use of albumin to creatinine ratio (ACR), we express all measures to ACR using a commonly used conversion: ACR mg/g (mg/mmol) = 0.6 * PER mg/day.[16] For further reporting of methods and results, we utilize the term ACR. An early change was quantified as the change in log-transformed ACR from baseline to the measurement closest to 6 months (within 2.5 and 14 months) or 12 months (within 2.5 to 19 months).

Clinical Endpoints

The clinical endpoint was defined as a composite of ESKD (initiation of chronic treatment with dialysis or kidney transplantation), or eGFR < 15 ml/min/1.73 m^2, or doubling of serum creatinine sustained at the subsequent visit. Of the 43 studies, 41 had sufficient endpoints for estimation of treatment effects on clinical endpoint and were used for the primary analysis. In a sensitivity analyses, we used an alternative clinical endpoint, defined as ESKD, eGFR < 15 ml/min/1.73 m^2 and time to 40% eGFR decline, and used all 43 studies.

Statistical analyses

Objectives. Our first goal was to evaluate the validity of albuminuria change as a surrogate endpoint for CKD progression by modeling the association between treatment effects on ACR change and treatment effects on the clinical endpoint across the studies. Our second goal was to use these results to inform the application of ACR change as a surrogate endpoint in future RCTs by estimating the probability of clinical benefit associated with a range of treatment effects on ACR change.

Trial level analysis. The trial level analysis requires two steps: intent-to-treat estimation of the treatment effects on the surrogate and clinical endpoints within each study and a meta-regression to relate the treatment effects on the surrogate and clinical endpoints across studies. In the first step, treatment effects on ACR change were estimated by performing analyses of covariance within each study, with log ACR change as the endpoint adjusting for treatment and log baseline ACR. Treatment effects on ACR were expressed as geometric mean ratios (GMR). Treatment effects on the clinical endpoint were estimated by Cox proportional hazard regressions to estimate hazard ratios for the treatment in each study. In the second step, a Bayesian mixed effects meta-regression related the estimated treatment effects on the clinical endpoint to the estimated treatment effects on ACR change with study as the unit of analysis (details in supplement). The model relates the treatment effects on the two endpoints after accounting for random errors in the estimated effects in each RCT. The meta-regression supports validity of ACR change as a surrogate endpoint if 1) the slope of the meta-regression line is statistically significant with a large magnitude, 2) the intercept is close to 0, implying absence of an average effect on the clinical endpoint when the treatment does not affect ACR, 3) the R^2 is high, so that treatment effects on ACR account for most of the variation in treatment effects on the clinical endpoint, and 4) the root mean square error (RMSE) is low, assuring low variation in the clinical endpoint given a fixed treatment effect on ACR. We used the designations of low, moderate and strong trial level association as defined by $R^2 < 0.49$, 0.49-0.72, and ≥ 0.72, respectively.[17]

Positive predictive value. We used positive predictive values (PPV) to describe the uncertainty in predicting the treatment effect on the clinical endpoint. From the trial level meta-regression, we computed 95% Bayesian prediction intervals and estimated the probabilities of clinical benefit (defined as HR < 1) for an infinite, large or modest sized RCT. A large RCT was defined as one in which the treatment effect on ACR can be estimated to within a standard error (SE) of 0.05, corresponding to a total sample size (N) of about 1090. A modest RCT was defined as having SE of 0.12 (N roughly 190). We computed the threshold associated with the smallest observed treatment effect on ACR that would assure a high probability of benefit of the treatment on the clinical endpoint, defined as a PPV of 97.5%.

Subgroup and sensitivity analyses. We performed the trial level analysis for the primary analytical dataset overall and by subgroups defined by baseline ACR (< or ≥ 30 mg/g or 3.4 mg/mmol), eGFR (< or ≥ 60 ml/min/1.73m^2), disease (diabetes and diabetic kidney disease, glomerular diseases, or other or unspecified causes of CKD) and interventions. Because of differences in the ranges of treatment effects, accuracy in predicting the treatment effects on the clinical endpoint is best compared between subgroups using the RMSE. In sensitivity analyses, we repeated the analyses in the full data set (i.e. not restricted to studies where ACR change is hypothesized to have biological plausibility as a surrogate), using ACR change at 12 months, alternative clinical endpoint, and using a clinical endpoint that also includes death), and excluding the EMPA-REG OUTCOME study, which was identified as a key outlier[18] or the Hou study, which had unusually small variability in the serum creatinine measurements used to define the clinical endpoint.[19]

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R 3.16.1 (R Project for Statistical Computing www.r-project.org.[20]

Results

Table 1 and sTable 5 summarize aggregate characteristics of the included studies stratified by disease overall and stratified by sex. The characteristics of each individual study are reported in sTable 6. The mean age of the study participants ranged from 12 to 68 years and the proportion of men ranged from 16% (8/51) to 90% (18/20). Average baseline eGFR and ACR were 58 (standard deviation 25) ml/min/1.73 m^2 and 258 (25^{th}- 75^{th} percentiles 30, 1114) mg/g, respectively, in the pooled dataset and ranged from 47 to 74 ml/min/1.73m^2 and 126 to 1311 mg/g, respectively, across the disease groups, respectively.

Over a 6 month (25^{th}- 75^{th} percentiles 6, 6.4) period, the overall GMR in ACR in the control and treatment arms was 16% (95% confidence intervals (CI) 8-24) and 34% (95% CI 27-40), respectively, resulting in a 22% reduction in ACR due to the treatment (geometric mean ratio 0.78 (CI 0.74-0.82); Figure 1, left panel, sTable 7), with larger effects at baseline ACR levels greater or less than 30 mg/g (3.4 mg/mmol) (GMR 0.76 (95% CI 0.72-0.81) vs 0.92 (95% CI 0.89-0.96). Similar results were seen for subgroups defined by age, sex, race, baseline eGFR, and cause of disease, or when the 12 month change in ACR was analyzed (sFigures 3a, 3b and 4).

Over a median follow-up of 3.4 years, 3939 patients reached the composite clinical endpoint (sTable 8). Across all interventions, the active treatment led to reduction in risk for the clinical endpoint (HR 0.73 (95% CI 0.67, 0.81), with similar results across subgroups; Figure 1, right panel, sFigure 5 and sTable 7). Results were consistent in sensitivity analysis using the alternative clinical endpoint (sFigure 6).

Results of the trial level analysis (association between the treatment effects on ACR change to those of the clinical endpoint) are shown in Figure 2, left panel and sTable 9. The slope on the log scale was 0.89

(95% BCI 0.13 to 1.70) which indicates that every 30% greater treatment effect on the geometric mean ACR was associated with an average 27% lower hazard for the clinical endpoint [95% BCI 5% to 45%]. The intercept of the regression line was -0.07 (95% BCI -0.29 to 0.14) indicating that at 0% reduction in ACR, there was a low probability of having a large treatment effect on the clinical endpoint. The median estimates for R^2 and RMSE were 0.47 (95% BCI 0.02 to 0.96) and 0.14 (95% BCI 0.03 to 0.27), respectively. Reflecting the wide Bayesian confidence interval of the R^2, the trial level association has Bayesian probabilities of 53%, 28%, and 19% of falling into low, moderate, or high ranges for the strength of a surrogate endpoint. The association strengthened when the analyses were restricted to the subgroup of patients with baseline ACR $\geq$ 30 mg/g (3.4 mg/mmol) [R^2=0.72 (95% BCI 0.05 to 0.99)] (Figure 2, right panel and sTable 9), with Bayesian probabilities of 27%, 24%, and 49% that R^2 falls in the low, moderate, and high ranges.

No clear evidence of significant differences in RMSE for the trial level associations was found in among subgroups stratified by eGFR or cause of disease, but credible intervals were wide (Table 2 and sTable 9). Results were consistent when RAAS intervention versus control treatments were analyzed separately [median R^2=0.64 (95% BCI 0.0 to 0.99)]. . Results were also similar for treatment effects on ACR at 12 months rather than 6 months (sFigure 7 and sTable 10), for the alternative clinical endpoint (sFigures 8 and sTable 11-12), when death was included as part of the composite with the clinical endpoint (sTable 13), and were slightly weaker when all studies were analyzed instead of restricting to the interventions hypothesized to have a biological effect on albuminuria (sFigures 9 and sTable 14). Excluding EMPA-REG OUTCOME from the overall analysis strengthened the results (R^2 increased from 0.47 (95% BCI 0.02 to 0.96) to 0.72 (95% BCI 0.08 to 0.99)). However, this effect was not present when restricting to subgroup of participants with baseline ACR > 30 mg/g (3.4 mg/mmol) [R^2 0.72 (BCI 0.05 to 0.99) with inclusion of EMPA-REG OUTCOME and 0.68 (95% BCI 0.04 to 0.99) after exclusion; sTable 9-12]. Results were

consistent excluding the Hou study [R^2 0.47(95% BCI 0.02 to 0.96) with inclusion of Hou and 0.42 (95% BCI 0.01 to 0.95) after exclusion of the Hou study].

For application of ACR as a surrogate endpoint in future RCTs, Table 3 shows the predicted hazard ratios and 95% prediction intervals for the treatment effects on the clinical endpoint as well as the corresponding PPVs across range of magnitudes of ACR treatment effects overall and for participants with baseline ACR > 30 mg/g (3.4 mg/mmol). For a study of infinite or large sample size, treatments that reduce the geometric mean albuminuria to 30% vs. the control group will provide an average HR for the clinical endpoint of 0.68, with 95% of such trials having HRs between 0.47 and 0.95. A treatment effect of 25% reduction in ACR would be required to provide 97.5% confidence of a clinical benefit, with a 31% reduction required for modest sized trials. If participants were restricted to baseline ACR > 30 mg/g (3.4 mg/mmol), a 20% reduction would be required for studies of infinite or large sample size and 27% reduction for modest sized trials. Similar results are seen for changes in albuminuria at 12 months (sTable 15).

Discussion

Use of surrogate endpoints in clinical trials of CKD progression could decrease the number of participants, shorten the duration of follow up required to achieve statistical power to assess the efficacy of new interventions, and evaluate interventions earlier in the disease course. There is strong biologic plausibility for consideration of change in albuminuria as a candidate surrogate endpoint.[3-5] The current report provides a comprehensive evaluation of change in albuminuria as a surrogate endpoint based on a joint analysis of 29,979 individuals in 41 studies. We found that in studies of interventions in which albuminuria has biologic plausibility as a surrogate endpoint, the treatment effect on albuminuria

had moderately strong associations with treatment effect on clinical endpoints. The association was stronger for participants with baseline ACR > 30 mg/g (3.4 mg/mmol), whereas there was no evidence for differing effects by level of GFR or other subgroups. We provide thresholds for minimum effects on change in albuminuria that provide high confidence for significant treatment effects on the clinical endpoint, providing guidance as how to implement ACR change in future RCTs. The companion meta-analysis of observational studies examined the association between changes in ACR with subsequent ESKD incidence in more than 1 million individuals , demonstrated that after adjustment for measurement error a 30% reduction in albuminuria assessed over a 2 years period was associated with a hazard risk reduction of 22% (95% CI 8% - 34%) for ESKD. The similarity between the results from this report and ours provides reassurance about the robustness of the data and utility of changes in albuminuria to predict clinical prognosis.[21] Together these results support the use of early change in albuminuria as surrogate endpoint in RCTs.[10-14,22]

Previous meta-analyses reported conflicting results about the validity of change in albuminuria as a surrogate endpoint.[14,22,23] The first large meta-analysis involving 9088 participants of 37 trials showed no clear association between early changes in albuminuria and the clinical endpoint, but had insufficient variation in treatment effects and/or statistical power to adequately address the question.[13] A second meta-analysis involved larger clinical trials and reported a strong association between treatment effects on early and late changes in albuminuria and ESKD, which was consistent across drug classes and patient characteristics. However, that study did not account for correlation among the sampling errors in the treatment effects.[4] A more recent meta-analysis also failed to show a significant association but was limited by an insufficient number of studies, an insufficient range of interventions, and lack of harmonization of the endpoints.[23,24] The different conclusions from these prior meta-analyses likely result from differences in inclusion of trials and analytical methodology and precluded definitive

conclusion regarding validity of change in albuminuria as a surrogate endpoint. The current analysis is an advance to these prior analyses. It is the largest evaluation of this topic to date with the most diverse inclusion of trials, which is necessary for a robust trial level analysis. The Bayesian analyses also allowed us to articulate thresholds for treatment effect on change in albuminuria that are sufficiently large to result in high confidence that the treatment effect on the clinical endpoint would also be significant. Similar analyses, using less formal analyses with fewer trials, have been used to establish blood pressure and plasma cholesterol as surrogates for cardiovascular endpoints.[25-27]

The stronger association between treatment effects on change in albuminuria and on the clinical endpoint in subgroups with higher baseline albuminuria is consistent with the hypothesis that the mechanism of the beneficial effect of interventions is by lowering albuminuria and implies that future RCTs that use change in albuminuria as an endpoint should be restricted to participants with some degree of albuminuria. Indeed, one study, EMPA-REG OUTCOME, appeared to be an outlier only because its average level of albuminuria was substantially lower than most other included studies.[18] Similarly, the stronger associations when we restricted the analyses to interventions where albuminuria change has biologic plausibility as surrogate endpoint suggests that albuminuria cannot be used independently of the hypothesized mechanism of the effect of the intervention on albuminuria. We did not have sufficient power to be able to make definitive conclusions for or against differences in trial level associations by level of GFR and CKD etiology. Nevertheless, in the absence of an a priori hypothesis that results would differ among these groups, together with the similarity of the results for treatment effects on albuminuria and on the clinical endpoint by level of GFR and disease, our interpretation is that these results provide support for use of albuminuria as surrogate endpoint across the range of GFR and disease.

The requirement for changes in albuminuria of approximately 20-30% or large sample sizes might appear to be excessively severe and not obtainable in many settings. However, these thresholds increase probability of a significant treatment effect on the clinical endpoint, essentially making albuminuria a stronger surrogate. In addition, use of change in albuminuria as a surrogate endpoint shortens the time frame of the trial which can lead to more efficient and likely less expensive designs. It can be expected that increasing the number of albuminuria measurements would increase precision of the treatment effect,[28] and decrease the required threshold for albuminuria change when the sample size is modest. In our view, these results are particularly useful for diabetic kidney disease with higher albuminuria levels at baseline. There is a high prevalence, and a high risk associated with the disease, with few therapies available, and therefore an unmet clinical need. In addition, we see that these results are complementary with ongoing work to define clinical endpoints for RCTs in glomerular diseases with nephrotic syndrome or IgA nephropathy.[29,30] We do not suggest that the current results should replace these initiatives. Indeed, the large sample size to reliably assess treatment effects on albuminuria would not be possible in rare diseases. Nevertheless, investigators designing studies in rare disease could still use the PPV results presented here but apply less stringent criteria for a minimal treatment effect on ACR change. These results may also be applicable to RCTs evaluating interventions in patients with CKD of other or unspecified cause in whom absolute risk is high (for example, the subgroup with higher baseline levels of albuminuria). Critically, shorter trials based on changes in albuminuria would require additional longer-term evaluation for safety.

There are several limitations to these analyses. First, although we used an unbiased systematic review and we were able to obtain the largest number of RCTs used in any evaluation of a surrogate endpoint in CKD, the number of studies with available data was limited and some declined to participate. This led to some imprecision in the estimates of the trial level associations, particularly within subgroups, and

insufficient power to adequately determine differences in the results by CKD etiology, race, ethnicity or geographic areas. In particular, the proportion of women among the participants was lower than men, and while our results provide no evidence that the trial-level association differs between men and women, our analyses did not have sufficient power to rule out such a difference. We did not have consistent categorization of race and ethnic groups among the studies to enable a finer categorization. Second, we only included clinical endpoints that occurred during the course of the trial. As such, disagreement between the surrogate and clinical endpoint may arise from insufficient follow-up to capture the longer-term treatment effect on the clinical endpoint. Third, the observed heterogeneity in treatment effects across trials reflects not only biological differences between treatments but also heterogeneity in clinical trial design and procedures between trials thereby diluting the strength of the true association. Fourth, the reported prediction intervals and PPV at different magnitudes of treatment effects on ACR reflect not only the implications of varying treatment effects on ACR, but also the specific results in the previously conducted studies which showed an average beneficial effect on the clinical endpoint. As a result, achieving a treatment effect on ACR large enough to provide a high PPV does not necessarily guarantee a low risk of a false conclusion of clinical benefit for an ineffective treatment. Additional work is required to determine how albuminuria can be applied in clinical trial design to protect against risk of false positive conclusion under the null hypothesis of no clinical benefit. Fifth, the majority of studies tested renin angiotensin system blockers (RASB). The strength of the association was similar in trials comparing RASB versus control treatment compared to the overall population, but there was insufficient data to analyse other interventions separately.

When interpreted in conjunction with experimental evidence and observational studies on the association of change in ACR with CKD progression, particularly our companion paper, the results of our trial-level analyses support a role for early change in albuminuria as a surrogate endpoint for CKD

progression in clinical trials, particularly in trials with entry criteria that restrict enrollment to patients with higher baseline albuminuria. The use as surrogate endpoint is not unlimited; it does not appear to be possible to infer clinical benefit for interventions that produce relatively modest reductions in albuminuria under 20% to 30%. Future research is needed to elucidate how albuminuria can be optimally applied in the design of CKD clinical trials while protecting against the risk of a false conclusion of clinical benefit.

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Contributors:

HJLH, LAI, TG, JC, ASL and RTG conceived of the study concept and design. The CKD-EPI investigators/collaborators listed below acquired the data. HT, ALS, TG and LAI analyzed the data. All authors took part in the interpretation of the data. HJHL and LAI drafted the manuscript, and all authors provided critical revisions of the manuscript for important intellectual content. All collaborators shared data and were given the opportunity to comment on the manuscript. LAI, TG, HJH and ASL obtained funding for CKD-EPI and individual cohort and collaborator support is listed in appendix 2 in the Supplement.

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References

1. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *American Journal of Kidney Diseases* 2014; **64**(6): 821-35.
2. Schievink B, Kropelin T, Mulder S, et al. Early renin-angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes. *Diabetes, obesity & metabolism* 2016; **18**(1): 64-71.
3. Burton C, Harris KP. The role of proteinuria in the progression of chronic renal failure. *Am J Kidney Dis* 1996; **27**(6): 765-75.
4. Abbate M, Zoja C, Remuzzi G. How does proteinuria cause progressive renal damage? *J Am Soc Nephrol* 2006; **17**(11): 2974-84.
5. Tryggvason K, Pettersson E. Causes and consequences of proteinuria: the kidney filtration barrier and progressive renal failure. *J of Internal Medicine* 2003; **254**: 216-24.
6. Ruggenenti P, Perticucci E, Cravedi P, et al. Role of remission clinics in the longitudinal treatment of CKD. *J Am Soc Nephrol* 2008; **19**(6): 1213-24.
7. Carrero JJ, Grams ME, Sang Y, et al. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. *Kidney international* 2017; **91**(1): 244-51.
8. Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G. Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). *Kidney international* 1998; **53**(5): 1209-16.
9. Heerspink HJ, Ninomiya T, Persson F, et al. Is a reduction in albuminuria associated with renal and cardiovascular protection? A post hoc analysis of the ALTITUDE trial. *Diabetes, obesity & metabolism* 2016; **18**(2): 169-77.
10. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. *Kidney international* 2004; **65**(6): 2309-20.
11. Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. *Archives of internal medicine* 2005; **165**(8): 947-53.
12. Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. *Am J Kidney Dis* 2005; **45**(2): 281-7.
13. Inker LA, Mondal H, Greene T, et al. Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis. *Am J Kidney Dis* 2016.
14. Lambers-Heerspink HJ, Kropelin TF, Hoekman J, de Zeeuw D. Drug-Induced Reduction in Albuminuria Is Associated with Subsequent Renoprotection: A Meta-Analysis. *J Am Soc Nephrol* 2015; **26**(8): 2055-64.
15. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration; 2011.
16. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl* 2013; **3**(1): 1-150.
17. Prasad V, Kim C, Burotto M, Vandross A. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. *JAMA internal medicine* 2015; **175**(8): 1389-98.
18. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine* 2015; **373**(22): 2117-28.
19. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *The New England journal of medicine* 2006; **354**(2): 131-40.

20. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 2010; **36**(3): 1-48.
21. Coresh J, Heerspink HLJ, Sang Y, al e. Change in albuminuria and subsequent risk of end-stage kidney disease: A consortium meta-analysis. Manuscript submitted to Lancet Diabetes and Endocrinology (THELANCETDE-D-18-00583); 2018.
22. Inker LA, Levey AS, Pandya K, Stoycheff N, Okparavero A, Greene T. Early Change in Proteinuria as a Surrogate End Point for Kidney Disease Progression: An Individual Patient Meta-analysis. *Am J Kidney Dis* 2014; **64**(1): 74-85.
23. Palmer SC, Ruospo M, Teixeira-Pinto A, Craig JC, Macaskill P, Strippoli GFM. The Validity of Drug Effects on Proteinuria, Albuminuria, Serum Creatinine, and Estimated GFR as Surrogate End Points for ESKD: A Systematic Review. *Am J Kidney Dis* 2018.
24. Inker LA, Heerspink HJ. Evaluation of surrogate end points for progression to ESKD: necessary and challenging. *Am J Kidney Dis* 2018; **72**(6): 771-3.
25. Turnbull F, Neal B, Pfeffer M, et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. *Journal of hypertension* 2007; **25**(5): 951-8.
26. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**(9493): 1267-78.
27. Lassere MN, Johnson KR, Schiff M, Rees D. Is blood pressure reduction a valid surrogate endpoint for stroke prevention? An analysis incorporating a systematic review of randomised controlled trials, a by-trial weighted errors-in-variables regression, the surrogate threshold effect (STE) and the Biomarker-Surrogacy (BioSurrogate) Evaluation Schema (BSES). *BMC medical research methodology* 2012; **12**: 27.
28. Kropelin TF, de Zeeuw D, Andress DL, et al. Number and frequency of albuminuria measurements in clinical trials in diabetic nephropathy. *Clinical journal of the American Society of Nephrology : CJASN* 2015; **10**(3): 410-6.
29. Nachman P, Thompson A. Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy. 2017. https://www.asn-online.org/khi/project.aspx?ID=58 (accessed 6/15/18 2018).
30. Thompson A, Cattran DC, Blank M, Nachman PH. Complete and Partial Remission as Surrogate End Points in Membranous Nephropathy. *J Am Soc Nephrol* 2015; **26**(12): 2930-7.

Figure legends

Figure 1: Treatment effect on 6-month change in albuminuria and on the clinical endpoint in the overall population and subgroups

Shown are treatment effects on 6 month change in albuminuria (left) and treatment effects on clinical endpoint (right). Treatment effect on albuminuria is expressed at geometric mean ratio of ACR. To convert to percentage ACR reduction (1-GMR)*-100. Clinical endpoint is defined as treated kidney failure, doubling of creatinine or eGFR < 15 ml/min/1.73m^2. Treatment effect on the clinical endpoint is expressed as hazard ratio. In SI units, ACR < 30 mg/g is equivalent to 3.4 mg/mmol. There was not a significant difference for both treatment effect on albuminuria and treatment effect on the clinical endpoint by disease and intervention. The circles represent the estimated treatment effects and the horizontal line its 95% confidence interval. Data for all studies is shown in sFigure 3a and 4a. ACR was log transformed in each analysis. Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified. GFR, glomerular filtration rate; ACR, albumin to creatinine ratio; RAS, renin angiotensin system blockers; CCB, calcium channel blocker; BP, blood pressure; Alb, albuminuria; CKD, chronic kidney disease. Race was defined as Black vs non Black for use in categorization of race in computing eGFR using the CKD-EPI creatinine equation.

Figure 2: Trial level analyses for the association between treatment effects on change in albuminuria and treatment effects on the clinical endpoint

Left panel: Overall pooled population of studies where albuminuria is hypothesized to be a surrogate endpoint. **Right panel:** Participants in those studies with baseline urine ACR of > 30 mg/g (3.4 mg/mmol). Shown is the relationship between estimated treatment effects on the clinical endpoint on the vertical axis to estimated treatment effects on the 6 month change in albuminuria on the horizontal axis. Treatment effects on the clinical endpoint are expressed as hazard ratios and treatment effects on change in albuminuria are expressed as geometric mean ratios of ACR. ACR was log transformed. To convert to percentage ACR reduction (1-GMR)*-100. Clinical endpoint is defined as treated kidney failure, doubling of creatinine or eGFR < 15 ml/min/1.73m^2. The colors indicate intervention type. Each circle is a separate intervention with the size of the circle proportional to the number of events. The black line is the line of regression through the studies. The blue line is the confidence band. The pink lines are the prediction bands computed from the model. RAS, renin angiotensin system blockers; CCB, calcium channel blocker; BP, blood pressure; Alb, albuminuria.

Table 1: Clinical characteristics of the population stratified by disease etiology

Disease	N Studies	N	Age mean (SD)	Female N (%)	Black N (%)	Diabetes N (%)	eGFR mean (SD)	ACR median (25,75th)	Clinical Endpoints N (%)	Interventions
Overall	41	29979	58.2 (12.6)	9951 (33.2)	3833 (12.8)	21206 (70.7)	58.2 (25.0)	272 (30, 1134)	3935 (13.1)	
Diabetes	10	21102	62.2 (9.9)	6527 (30.9)	1335 (6.3)	21102 (100.0)	61.4 (23.3)	270 (26, 1126)	2103 (10.0)	RASB v CCB Low v Usual BP RASB vs Control Sulodexide Empagliflozin
Glomerular disease	9	1325	40.8 (12.9)	467 (35.2)	18 (1.4)	5 (0.4)	74.2 (29.7)	1311 (838, 2335)	174 (13.1)	Immunosuppression RASB vs Control
Other CKD	22	7552	50.1 (12.9)	2957 (39.2)	2480 (32.8)	99 (1.3)	46.6 (24.5)	126 (30, 838)	1658 (22.0)	RASB vs Control RASB v CCB Low v Usual BP Albuminuria Targeted Protocol Low v Usual Diet

Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified. Clinical end point defined as the composite of chronic dialysis or kidney transplantation, eGFR<15 ml/min/1.73m^2 or confirmed doubling of serum creatinine. CKD, chronic kidney disease; ACR, albumin to creatinine ratio; Age is measured in years. FU time in months; RASB, renin angiotensin system blockers; CCB, calcium channel blocker; BP, blood pressure. Race was defined as Black vs non Black for use in categorization of race in computing eGFR using the CKD-EPI creatinine equation.

Table 2: Trial level analysis by subgroups

Group	Subgroup	Studies /Interv.	N patients (N events)	Slope	Intercept	R^2	RMSE
All							
Overall		41 (8)	29979 (3935)	0.89 (0.13, 1.70)	-0.07 (-0.29, 0.14)	0.47 (0.02, 0.96)	0.14 (0.03, 0.27)
GFR	< 60	39 (8)	17387 (3329)	0.89 (0.04, 1.83)	-0.03 (-0.27, 0.22)	0.62 (0.01, 0.99)	0.09 (0.02, 0.23)
	≥ 60	23 (6)	12348 (598)	2.15 (-1.49, 7.52)	0.13 (-0.71, 1.23)	0.77 (0.01, 1.00)	0.14 (0.02, 0.50)
ACR	< 30*	10 (5)	7401 (180)	-9.86 (-53.39, 45.19)	-1.07 (-5.01, 3.39)	0.96 (0.02, 1.00)	0.07 (0.01, 0.60)
	≥ 30	41 (8)	22544 (3749)	0.91 (0.19, 1.67)	-0.04 (-0.26, 0.18)	0.72 (0.05, 0.99)	0.09 (0.02, 0.22)
Disease	Diabetes	10 (5)	21102 (2103)	0.41 (-2.10, 2.67)	-0.16 (-0.78, 0.39)	0.13 (0.00, 0.86)	0.20 (0.04, 0.47)
	Glomerular	9 (2)	1352 (174)	1.63 (0.19, 3.95)	-0.16 (-0.77, 0.68)	0.98 (0.11, 1.00)	0.06 (0.01, 0.57)
	Other CKD	22 (5)	7552 (1658)	0.73 (-0.16, 1.76)	-0.10 (-0.34, 0.17)	0.75 (0.01, 0.99)	0.05 (0.01, 0.22)
ACR > 30							
	Diabetes	10 (5)	15532 (2030)	1.10 (-0.76, 2.72)	0.06 (-0.45, 0.48)	0.63 (0.00, 0.99)	0.08 (0.02, 0.32)
	Glomerular	9 (2)	1324 (174)	1.63 (0.12, 3.91)	-0.16 (-0.78, 0.65)	0.98 (0.11, 1.00)	0.06 (0.01, 0.56)
	Other CKD	22 (5)	5688 (1545)	0.53 (-0.38, 1.53)	-0.15 (-0.42, 0.14)	0.65 (0.00, 0.99)	0.05 (0.01, 0.21)

Units of GFR are ml/min per 1.72 m^2. Units of ACR are mg/g. Interv, number of distinct types of intervention, GFR, glomerular filtration rate. ACR, albumin to creatinine ratio. RMSE, root mean square error. Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified. In SI units, ACR cutpoints are 3.4 mg/mmol)

Results for slope, intercept, R^2 and RMSE are presented as median and 2.5 to 97.5 Bayesian credible intervals

*Event rate < 5%. Estimates unreliable

Table 3: Application of albuminuria as Surrogate Endpoint in New RCT: Predicted Treatment effect on clinical endpoint and Positive Predictive Value

Observed Treatment effect on change in ACR	Infinite sample size in new RCT		Large New RCT		Modest New RCT	
	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV
Overall						
0.5	0.50 (0.30, 0.80)	1.00	0.50 (0.30, 0.80)	1.00	0.51 (0.28, 0.82)	1.00
0.6	0.59 (0.39, 0.86)	0.99	0.59 (0.39, 0.87)	0.99	0.60 (0.36, 0.90)	0.99
0.7	0.68 (0.47, 0.95)	0.98	0.68 (0.46, 0.96)	0.98	0.68 (0.44, 1.01)	0.97
0.8	0.77 (0.53, 1.06)	0.96	0.76 (0.53, 1.07)	0.95	0.76 (0.50, 1.14)	0.92
0.9	0.85 (0.59, 1.19)	0.86	0.85 (0.58, 1.21)	0.84	0.84 (0.56, 1.30)	0.81
1.0	0.93 (0.63, 1.35)	0.66	0.93 (0.62, 1.37)	0.66	0.92 (0.60, 1.48)	0.65
Threshold to assure PPV ≥ 97.5%	**0.75**		**0.74**		**0.69**	
ACR > 30 mg/g						
0.5	0.51 (0.34, 0.76)	1.00	0.52 (0.33, 0.76)	1.00	0.52 (0.32, 0.77)	1.00
0.6	0.61 (0.44, 0.81)	1.00	0.61 (0.43, 0.81)	1.00	0.61 (0.41, 0.84)	1.00
0.7	0.70 (0.53, 0.89)	0.99	0.70 (0.52, 0.89)	0.99	0.70 (0.49, 0.96)	0.98
0.8	0.79 (0.60, 0.99)	0.98	0.79 (0.59, 1.02)	0.97	0.79 (0.56, 1.10)	0.93
0.9	0.88 (0.65, 1.13)	0.87	0.88 (0.64, 1.16)	0.85	0.87 (0.62, 1.26)	0.80
1.0	0.97 (0.69, 1.30)	0.60	0.96 (0.69, 1.34)	0.61	0.95 (0.66, 1.45)	0.60
Threshold to assure PPV ≥ 97.5%	**0.80**		**0.79**		**0.73**	

ACR, albumin to creatinine ratio. Change in albuminuria expressed over 6 months. Treatment effect on ACR is expressed at geometric mean ratio. To convert to percentage ACR reduction (1-GMR)*-100. Treatment effect on Clinical Endpoint is expressed as hazard ratio. A modest trial was defined as one that results in treatment effect of albuminuria with SE of 0.12, minimal detectable GMR of 0.675 and approximate sample size of 190, and large trial was defined as one with SE of 0.05, minimal detectable GMR of 0.849 and approximate sample size of 1090.

Figure 1: **Treatment effect on change in albuminuria at 6 months and on clinical endpoints in the overall population and subgroups.**

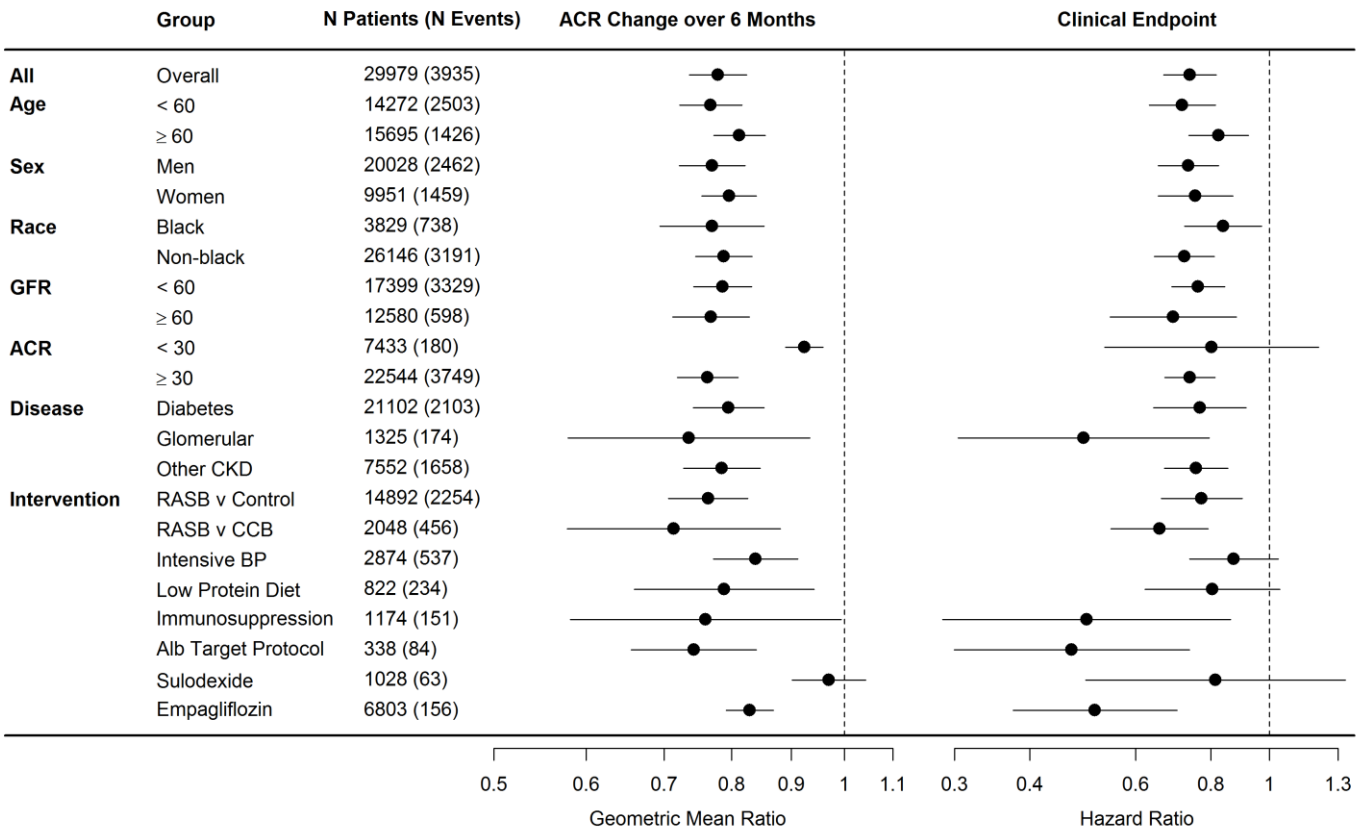

Figure 2: Trial level analyses for the association between treatment effects on change in albuminuria and treatment effects on the clinical endpoint