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

Supplemental Methods, Tables and Figures

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Appendix 1: Abbreviations, Units, and Terms

2xSCR	doubling of serum creatinine
AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes trial
ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin/creatinine ratio (mg/g)
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AIPRI	ACE Inhibition in Progressive Renal Insufficiency
ALB	albuminuria targeted protocol
Alb Pathway	intervention whose mechanism is theorized to operate through effect on albuminuria
ALLO	allopurinol
Alternative clinical endpoint	ESKD, 40% GFR decline and GFR < 15 ml/min per 1.73 m2
ALTITUDE	Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints
Aus	Australia
AZA	azathioprine
BP	blood pressure
CanPREVENT	Canadian Prevention of Renal and Cardiovascular Endpoints Trial
CI	confidence interval
CKD	chronic kidney disease
CSG	Collaborative Study Group
Clinical endpoint	ESKD, doubling of serum creatinine and GFR < 15 ml/min per 1.73 m^2
DIET	low protein diet
EMA	European Medicines Association
EMPA	Empagliflozin
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (referred to as EMPA-REG here on in)
ESKD	end-stage kidney disease
Est	estimate
Eur	Europe
F/U	follow-up time (months)
FDA	Food and Drug Administration
GFR	glomerular filtration rate(mL/min/1.73 m^2)
GLUC	intensive glucose
GMR	geometric mean ratio
HALT-PKD	Halt Progression of Polycystic Kidney Disease study
HKVIN	Hong Kong study using Valsartan in IgA Nephropathy
HR	hazard ratio
I^2	study heterogeneity
IDNT	Irbesartan Diabetic Nephropathy Trial
IgA	immunoglobulin A nephropathy
IS	immunosuppresion
MASTERPLAN	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners study
MDRD Study	Modification of Diet in Renal Disease study
MMF	mycophenolate mofetil
N	sample size
NA	North America
NKF	National Kidney Foundation
ORIENT	Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial

RASB	renin-angiotensin system blockade
RCT	randomized control trial
REIN 1	Ramipril Efficacy In Nephropathy study 1
REIN 2	Ramipril Efficacy In Nephropathy study 2
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
ROAD	Renoprotection of Optimal Antiproteinuric Doses study
RvC	RASB v CCB
SCr	serum creatinine (mg/dL)
SE	standard error
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial
SUL	sulodexide
SUN-MACRO	Sulodexide Macroalbuminuria trial

Appendix 2: Study Funding Sources

Study Name	Funding
AASK	Supported by grants to each clinical center and the coordinating center from the National Institute of Diabetes and Digestive and Kidney Diseases. In addition, AASK was supported by the Office of Research in Minority Health (now the National Center on Minority Health and Health Disparities, NCMHD) and the following institutional grants from the National Institutes of Health: M01 RR-00080, M01 RR-00071, M0100032, P20-RR11145, M01 RR00827, M01 RR00052, 2P20 RR11104, RR029887, and DK 2818-02. King Pharmaceuticals provided monetary support and antihypertensive medications to each clinical center. Pfizer Inc, AstraZeneca Pharmaceuticals, Glaxo Smith Kline, Forest Laboratories, Pharmacia and Upjohn also donated antihypertensive medications.
ABCD	Supported by Bayer and the National Institute of Diabetes, Digestive, and Kidney Diseases (DK50298-02)
ADVANCE	ADVANCE was funded by grants from Servier and the National Health and Medical Research Council of Australia
ALTITUDE	Supported by Novartis
Appel	This study was supported in part by Roche Pharmaceuticals and the Glomerular Center at Columbia University as an investigator-initiated study (J.L. and G.A.), the NKF of NY/NJ under the Fred C. Trump Fellowship (J.L.), a KUFA fellowship (J.R.) and the Kidney Foundation of Canada (G.F.).
Brenner	Supported by Merck & Co.
CanPREVENT	Supported by the Memorial University of Newfoundland
Chan	Supported by the Wai Hung Charity Foundation and the Lee Wing Tat Renal Research Fund
Donadio 2001	Supported by research grants from Pronova Biocare a.s. (Oslo, Norway) and Mayo Foundation (Rochester, MN)
EMPA-REG OUTCOME	Supported by Boehringer Ingelheim (BI) and Eli Lilly
Goicoechea	Supported by REDINREN RD016/0019 FEDER funds
HALT-PKD	Supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK62410 to Dr. Torres, DK62408 to Dr. Chapman, DK62402 to Dr. Schrier, DK082230 to Dr. Moore, DK62411 to Dr. Perrone, and DK62401 to Washington University at St. Louis) and the National Center for Research Resources General Clinical Research Centers (RR000039 to Emory University, RR000585 to the Mayo Clinic, RR000054 to Tufts Medical Center, RR000051 to the University of Colorado, RR023940 to the University of Kansas Medical Center, and RR001032 to Beth Israel Deaconess Medical Center), National Center for Advancing Translational Sciences Clinical and Translational Science Awards (RR025008 and TR000454 to Emory University, RR024150 and TR00135 to the Mayo Clinic, RR025752 and TR001064 to Tufts University, RR025780 and TR001082 to the University of Colorado, RR025758 and TR001102 to Beth Israel Deaconess Medical Center, RR033179 and TR000001 to the University of Kansas Medical Center, and RR024989 and TR000439 to Cleveland Clinic), by funding from the Zell Family Foundation (to the University of Colorado), and by a grant from the PKD Foundation.
Hannedouche	Supported by Merck Sharp & Dohme
HKVIN	Supported by Novartis Pharmaceuticals (Hong Kong) Ltd by providing the study medication and placebo
Hou	Supported by a National Nature and Sciences Grant for Major Projects (30330300) and a People's Liberation Army Grant for Major Clinical Research (to Dr. Hou) and in part by Novartis
IDNT	Supported by the Bristol-Myers Squibb Institute for Medical Research and Sanofi–Synthelabo
Ihle/Kincaid	Supported in part by Merck & Co, Inc, West Point, PA
Kamper	Supported by Merck Sharp & Dohme
Lewis 1992	Supported by grants (R01-AM-27769 and R01-AM-27770) from the Public Health Service

Lewis 1993	Supported by grants from the Public Health Service (5 R01-DK 39908, 5 R01-DK 39826, MO1-RR00030, MO1-RR00034, MO1-RR00036, MO1-RR00051, MO1-RR00058, MO1-RR00059, and MO1-RR00425) and by the Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, N.J.).
Maes	The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland
Maschio	Supported by a grant from Ciba–Geigy
MASTERPLAN	Supported by the Dutch Kidney Foundation, grant number PV-01, and the Netherlands Heart Foundation, grant number 2003B261. Unrestricted grants were providedby Amgen, Genzyme, Pfizer and Sanofi-Aventis
MDRD Study	Supported by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK UO1 DK35073 and K23 DK67303, K23 DK02904)
ORIENT	Supported by a research grant from Daiichi Sankyo
Ponticelli 1989	Supported in part by a grant (82.01308.04) from the Consiglio Nazionale delle Ricerche.
Ponticelli 1998	Supported in part by a grant from Ospedabc Maggiore di Milano
Ponticelli 2006	This was a spontaneous clinical trial sponsored by the grant “Project Glomerulonephritis”
Pozzi 2004	The authors did not receive any financial support
Pozzi 2010	The authors did not receive any financial support
Pozzi 2012	The authors did not receive any financial support
Praga 2007	This study was partially supported by Astellas
REIN	Supported in part by a grant from Aventis Pharma SA, Antony, France.
REIN 2	REIN2 was an independent, academic study, where Aventis Pharma SA, Antony (France) and SIMESA SpA (Italy) only provided study medication (ramipril and felodipine, respectively).
RENAAL	Supported by Merck & Co.
ROAD	Supported by a National Nature and Sciences Grant for Major Projects (30330300), a People's Liberation Army Grant for Major Clinical Research (2000), and National 11th Five-Years Plan Foundation (to F.F.H.)
Schena	Supported in part by a grant of University of Bari
STOP-IgAN	Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.
SUN-MACRO	Sponsored by Keryx Biopharmaceuticals
Toto	By grant RO1 DK53869A from the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (Dr. Levey); grant RO1 HS 10064 from the Agency for Healthcare Research and Quality (Dr. Schmid); a grant from Dialysis Clinic, Inc., Paul Teschan Research Fund 1097-5 (Dr. Jafar); New England Medical Center St. Elizabeth’s Hospital Clinical Research Fellowship, Boston, Massachusetts (Dr. Jafar); and an unrestricted grant from Merck Research Laboratories, West Point, Pennsylvania (Dr. Levey).
Van Essen	Supported by Merck Sharp & Dohme, Haarlem, The Netherlands

Protocol

1.1 Background and rationale

Chronic kidney disease (CKD) is a significant global public health problem, but the progression of CKD is often slow and there are few specific symptoms until the stage of kidney failure has been reached. There is general agreement that biomarkers will be needed to approve new drugs to slow the progression of kidney disease. The two most widely studied biomarkers are glomerular filtration rate (GFR) and albuminuria - maximizing the information on both is desired.

The National Kidney Foundation (NKF) in collaboration with the Food and Drug Administration (FDA) held a Scientific Workshop in December 2012, "GFR Decline as an End Point in Clinical Trials in CKD". The results of the analyses performed for the workshop showed strong relationships between change in eGFR and kidney failure and mortality in observational studies and based on analyses from past clinical trials and simulations proposed that a 30 or 40% decline in GFR would be an acceptable alternative endpoint in clinical trials in some circumstances[1-5] Application of this endpoint is limited at higher baseline GFR and for agents that cause an "acute effect" on GFR. As such, these alternative endpoints are less applicable in drug development for drugs targeted at earlier stages of kidney disease and for many drugs with potential hemodynamic effects. Strategies to overcome these limitations include assessing changes in albuminuria (or proteinuria) as an earlier marker of kidney disease progression, alternative approaches to assessing GFR decline, and combinations of both strategies.

On March 15-16 2018, the NKF, in collaboration with the 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. The Workshop was chaired by Andrew S Levey MD and Ron Gansevoort MD and was supported by the planning committee and operations committee. Planning and operations committee members consisted of Andrew Levey (Chair), Ron Gansevoort, Josef Coresh, Dick de Zeeuw, Kai-Uwe Eckardt, Hrefna Gudmundsdottir, Adeera Levin, Romaldas Maciulaitis, Tom Manley, Vlado Perkovic, Kimberly Smith, Norman Stockbridge, Aliza Thompson, Thorsten Vetter, Kerry Willis, and Luxia Zhang. Prior to the workshop, the protocol was reviewed by the planning committee, analytical committee and stakeholder advisory group and was available at https://www.kidney.org/CKDEndpoints.

For this workshop, analyses were performed to support the validity of albumin-creatinine ratio (ACR) change and GFR slope as surrogate endpoints. Here we report on the individual patient meta-analysis of randomized control trials (RCTs) to provide a comprehensive assessment of the validity of using early changes in albuminuria as surrogate endpoints for trials of CKD progression using Bayesian analyses to examine the agreement between treatment effects on early changes in albuminuria and treatment effects on the clinical endpoint to investigate how to appropriately use albuminuria as a surrogate endpoint in future RCTs.

1.2 Dataset development

1.2.1 Datasets and analytical groups

For our prior work investigating surrogate endpoints, we had performed a systematic search of Ovid Medline from January 1, 1946 to May 15, 2007 and developed a pooled database[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. In addition, we reviewed references of published meta-analyses of RCTs including the REASSURE study[7,8]. sTables 1 lists the search terms. sTable 2 lists all of the inclusion criteria. Our goal was to include all studies where there was sufficient progression of kidney failure for analyses and to include studies of rarer diseases. We therefore varied the number of events required for inclusion based on disease state. For studies of glomerular disease, we required 10 events whereas for studies of other kinds of CKD, we required 30 events as well as 500 person years of follow-up and for studies of high risk populations, we required 30 events and 1000 person years of follow-up.

We were able to identify, obtain initial agreement and obtain access to 61 studies (sFigure 2). We were not able to obtain data or data was not sufficient in 12 studies leading to a total of 49 studies. Risks of bias for each study included were assessed using the risk-of-bias tool of the Cochrane collaboration[7] (sFigure 1). For trials that evaluated more than one intervention, we included a separate group for each independent treatment comparison, such that some participants were included in more than one analytical comparison. [9-13] We then pooled small studies that had less than 100 participants if the disease and intervention was the same[14-26] (sTable 3). sTable 4 describes the individual treatment comparisons.

For the primary analysis, 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)[27-29] leading to a total of 43 treatment comparisons (referred to here on in as studies). The decisions were based on current understanding of the interventions and after discussion with the Scientific Workshop Planning Committee prior to the analyses.

1.2.2 Data management

For each study, we defined the active treatment as the treatment hypothesized to produce the greater reduction in the risk of the clinical endpoint. We categorized the studies by intervention type: renin angiotensin system blockade (RASB) vs. control, RASB vs. calcium channel blocker (CCB), intensive blood pressure control, low protein diet; immunosuppressive therapy (including steroid, azathioprine, tacrolimus, fish oil, plasmapheresis). We categorized disease as diabetes (studies of people with diabetes not restricted to CKD, and studies of diabetic kidney disease), glomerular disease and other CKD (other causes or cause not specified).

As previously described, if the study defined censoring dates were not available we approximated them as the time from randomization to the final recorded visit date in the data provided plus 6 months plus the study-specific 90th percentile of the average interval between visits with serum creatinine measurements. [15-17,20,22-33] The purpose of adding 6 months to the estimated right censoring date is to retain a higher proportion of clinical outcome events which occurred following the patient's final study visit. We included events event time occurred prior to 1 month following administrative censoring time. Patients who had events but no visits were included if event occurred before 12 months.

1.2.3 Urine protein or albumin measures and computation of change

sTable 4 shows the urine protein or albumin measures used in each study. We converted each to the urine albumin to creatinine ratio using the validated conversion factor[34]. If studies had more than one measure of urine protein or albumin, we used the method was most commonly used within that study. To compute the change in albuminuria, we log transformed the original values and computed the change from baseline to follow-up using the measure closest to 6 (2.5-14) or 12 months (2.5 to 19). Note that since the main predictor in the analysis was percentage change the urine protein measure at an individual patient level within each study, the different methods of albuminuria quantification were not critical for the purpose of analysis.

1.2.4 Estimated GFR

GFR was estimated using the CKD-EPI equation 2009 creatinine equation.[35] Creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or was reduced by 5% as has previously been described.[36] sTable 4 shows which studies were calibrated. The CKD-EPI equation uses Black vs. nonBlack as a key demographic variable and thus race was defined in this paper in the paper.

1.2.5 Reference Test: Clinical Endpoints

We defined clinical endpoints as treated kidney failure [end-stage kidney disease (ESKD), defined as initiation of treatment with dialysis or transplantation], untreated kidney failure, defined as GFR < 15 ml/min/1.73 m^2 in those with GFR > 25 ml/min per 1.73m^2 at baseline or doubling of serum creatinine (EGS) that occurred over the full study duration. Two studies did not have sufficient clinical endpoints and were not included in the main analyses;

thus in sensitivity analyses, we used ESKD, GFR < 15 and time to 40% decline (EG40). For both GFR < 15 and 40% decline, we used only those that were confirmed by an eGFR determination at the next visit as the clinical endpoint. If the endpoint occurred at the last visit, we considered it as confirmed.

1.3 Analyses

1.3.1 Trial Level Model Relating Treatment Effects on the Clinical Endpoint to Treatment Effects on the Early Change in Albumin to Creatinine Ratio (ACR)

Our analytic approach for trial-level analyses followed the causal association framework described in Joffe and Greene (2008).[37] In this framework, the validity of surrogate endpoints is evaluated based on the relationship between the average causal effect of the treatment on the surrogate endpoint and the average causal effect of the treatment on the clinical endpoint across a population of randomized trials which are viewed as similar to a new randomized trial in which conclusions concerning clinical benefit are to be based on the surrogate endpoint. This approach takes advantage of the fact that the average causal effects on the surrogate and clinical endpoints can be estimated with little bias within each randomized trial by applying intent-to-treat analyses. The approach is closely related to frameworks for trial-level analyses which has been developed by other authors, including Daniels MJ, Hughes MD (1997), Burzykowski T, Molenberghs G, Buyse M (2005), and Burzykoski T and Buyse (2006)[38-40].

We performed the trial level analyses in two stages to relate the true treatment effects on the clinical endpoint to the true treatment effects on early change in log ACR while accounting for error in the estimation of these effects within each trial. In the first stage, we performed separate linear regression and Cox regression analyses to estimate the effects of the treatment on the early change in log ACR and on the clinical endpoint for each randomized comparison of an active treatment vs. control in each trial. For ACR, treatment effects were expressed as log transformed geometric mean ratios between the early follow-up ACRs between the treatment and control groups. For the clinical endpoint, treatment effects were expressed as log transformed hazard ratios. To express the statistical model precisely, let $i = 1, 2, \ldots, 41$ denote the 41 treatment comparisons performed across the contributing clinical trials. For simplicity, as most trials included a single treatment comparison, we abuse the notation slightly and write that the index i refers to the i^{th}trial. We let θ_i and γ_i denote the true treatment effects on the clinical endpoint and on change in log ACR in the i^{th} trial, and use $\hat{\theta}_i$ and $\hat{\gamma}_i$ to indicate the estimated effects obtained as described above. The Stage 1 model relates the estimated and true treatment effects in the i^{th}trial by:

$$\begin{bmatrix}\hat{\theta}_i \\ \hat{\gamma}_i\end{bmatrix} = \text{Normal}\left(\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix}, \begin{bmatrix}\sigma_i^2 & r_i\sigma_i\delta_i \\ r_i\sigma_i\delta_i & \delta_i^2\end{bmatrix}\right).$$

Here, σ_i is the standard error of the estimated treatment effect on the clinical endpoint and δ_i is the standard error of the estimated treatment effect on change in log ACR in the i^{th}trial, and r_i is the correlation between the estimated treatment effects. We used bootstrap resampling to estimate the standard errors σ_i and δ_i as well as the correlations r_i. The notation Normal() indicates that the estimated treatment effects are assumed to follow a bivariate normal distribution given the true treatment effects within each trial; this assumption is satisfied to a high degree of accuracy due to the central limit theorem.

The second stage models the variation in the true treatment effects on change in log ACR and on the clinical endpoint across the trials. The stage 2 model is expressed as:

$$\begin{bmatrix}\theta_i \\ \gamma_i\end{bmatrix} = \text{Normal}\left(\begin{bmatrix}\mu_\theta \\ \mu_\gamma\end{bmatrix}, \begin{bmatrix}\sigma_\theta^2 & R\sigma_\theta\sigma_\gamma \\ R\sigma_\theta\sigma_\gamma & \sigma_\gamma^2\end{bmatrix}\right),$$

where μ_θ and μ_γ are respectively the means of the true treatment effects on the clinical endpoint and on change in log ACR in the population of trials represented by the meta-regression, σ_θ and σ_γ are the standard deviations of the true treatment effects across the population of trials, and R is the correlation between the true treatment effects on the two endpoints.

Based on this 2-stage model, the slope and intercept of the meta-regression line predicting the true treatment effect on the clinical endpoint from the true treatment effect on the surrogate endpoint are given by $\beta = R\sigma_\theta/\sigma_\gamma$ and $\alpha = \mu_\theta - \beta\mu_\gamma$, respectively, and the root mean square error that defines the uncertainty in the treatment effect on the clinical endpoint given a particular treatment effect on the surrogate endpoint is RMSE $=(\sigma_\theta^2 - R\sigma_\theta^2/\sigma_\gamma^2)^{1/2}$.

The trial-level analysis will support ACR as a surrogate endpoint if the slope of the meta-regression differs significantly from 0, the R^2 and RMSE or the meta-regression indicates that the estimated treatment effect on log ACR can reliably predict the treatment effect on the clinical endpoint, and the intercept of the meta-regression line is close to 0, indicating that the absence of a treatment effect on log ACR predicts the absence of a treatment effect on the clinical endpoint[38,39,41].

We fit the second stage model using Bayesian Monte-Carlo Markov Chain sampling, using diffuse prior distributions for the model parameters that we selected so that the final results would depend primarily on the data with little influence of the prior distributions. The priors for the mean treatment effects on the clinical endpoint and on log ACR were taken to be normal distributions each with mean 0 and variance 10,000; the priors for the variances of the treatment effects on the clinical endpoint and on change in log ACR were each taken to be inverse gamma distributions with shape parameter 0.261 and scale parameter 0.000408. This prior distribution was selected by the investigators to assign 1/3 prior probabilities each to low treatment effect heterogeneity (which we defined as a treatment effect standard deviation (SD) on the log scale ≤ 0.05), medium treatment effect heterogeneity (defined as a treatment effect SD on the log scale between 0.05 and 0.20), and high treatment effect heterogeneity (defined as a treatment effect SD on the log scale > 0.20). We checked that the prior distributions had only a small influence on the results by verifying that the results of each analysis were similar under a corresponding Frequentist analysis that did not require explicit representation of prior distributions.

1.3.2 Prediction Intervals and Positive Predictive Value

We obtained 95% pointwise prediction intervals for the treatment effect on the clinical endpoint given a particular value for the true treatment effect on change in log ACR by simulating the posterior distribution of $\alpha + \beta \times \text{True.Eff}_{ACR} + \Delta_0$, where True.Eff_{ACR} is the designated true treatment effect on early change in log ACR, $\alpha + \beta \times \text{True.Eff}_{ACR}$ represents the associated predicted mean true treatment effect on the clinical endpoint based on the meta-regression from the 2-stage model, and Δ_0 is normally distributed with mean 0 and standard deviation given by the RMSE from the meta-regression. Here Δ_0 represents the variation in the treatment effects on the clinical endpoint across different trials with the same treatment effect on early change log ACR. This prediction interval accounts for uncertainty in the estimation of α, β, and RMSE that define the meta-regression, as well as uncertainty due to variation in the treatment effects on the clinical endpoint about the regression line for different trials.

When the trial level meta-regression is applied to a newly conducted randomized trial, there is an additional source of uncertainty that results from imprecision in the estimation of the treatment effect on early change in ACR in the new trial. This added uncertainty depends on the sample size, and is smaller when the sample size for the new trial is large. We obtained 95% prediction intervals for the treatment effect in a new trial that take into account this uncertainty by again sampling from the posterior distribution of $\alpha + \beta \times \text{True.Eff}_{ACR} + \Delta_0$, but now assume that True.Eff_{ACR} has a random distribution to reflect the uncertainty in its estimation in the new trial instead of taking True.Eff_{ACR} to be a fixed value. Specifically, we assumed that the posterior distribution of True.Eff_{ACR} is normally distributed with mean equal to the estimated treatment effect on early change in log ACR and standard deviation given by the standard error for the estimated treatment effect on log ACR based on the sample size. We considered standard errors of 0.05, to reflect a large RCT and 0.12, corresponding to a modest-sized RCT for evaluating treatment effects on early change in log ACR. This posterior distribution for True.Eff_{ACR} reflects a fully non-informative prior distribution for the treatment effect and is not influenced by the estimated distribution of treatment effects on early change in log ACR in the trials contributing to the meta-regression. We chose to use a fully noninformative prior for True.Eff_{ACR} so that our estimation of the treatment effect in the new trial would depend only on the relationship between the treatment effects on the clinical endpoint and on early change in log ACR, and not on the average treatment effect on early change in log ACR in the previously conducted trials.

We used a similar sampling approach from the posterior distribution of $\alpha + \beta \times \text{True.Eff}_{ACR} + \Delta_0$ to estimate the probability that the treatment effect in the new trial would fall below 0 (corresponding to a treatment benefit) given either the true or the estimated treatment effects on early change in log ACR in the new trial. These latter quantities provide estimates of the positive predictive value for demonstrating a benefit of the treatment on the clinical endpoint given designated values for the true or observed treatment effects on early change in log ACR. By considering the positive predictive value as a function of True.Eff_{ACR}, we determined the size of the smallest treatment effect on early change in log ACR that would be required to assure a positive predictive value of at least 0.975 for a benefit on the clinical endpoint.

Tables and Figures

sTable 1. Search terms

Database: Ovid MEDLINE(R)
Search Strategy:

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1 kidney disease$.mp. (112999)
2 chronic renal insufficiency.mp. (4302)
3 chronic kidney disease.mp. (21120)
4 renal disease.mp. (41875)
5 IgA nephropathy.mp. (4903)
6 lupus nephritis.mp. (6931)
7 diabetic nephropathy.mp. (12605)
8 glomerular disease.mp. (2168)
9 polycystic kidney disease.mp. (5535)
10 focal sclerosis.mp. (118)
11 membranous nephropathy.mp. (2402)
12 CKD.mp. (12820)
13 Hypertension/ and (renal or kidney).mp. (36281)
14 albuminuria.mp. (15383)
15 proteinuria.mp. (38350)
16 or/1-15 (222355)
17 randomized controlled trial.pt. (403784)
18 controlled clinical trial.pt. (89947)
19 randomized controlled trials/ (100110)
20 Random Allocation/ (85054)
21 Double-blind Method/ (132413)
22 Single-Blind Method/ (21138)
23 clinical trial.pt. (495584)
24 Clinical Trials.mp. or exp Clinical Trial/ (939562)
25 (clinic$ adj25 trial$).tw. (271601)
26 ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. (129554)
27 placebo$.tw. (159277)
28 Placebos/ (32953)
29 random$.tw. (710194)
30 trial$.tw. (636501)
31 (latin adj square).tw. (3512)
32 or/17-31 (1577197)
33 16 and 32 (23308)
34 limit 33 to (guideline or meta analysis or practice guideline or "review") (5907)
35 33 not 34 (17401)
36 limit 35 to comment and (letter or editorial).pt. (187)
37 limit 35 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or news or newspaper article or patient education handout or periodical index) (501)
38 35 not (36 or 37) (16778)
39 limit 38 to animals/ (2192)
40 38 not 39 (14586)
41 limit 40 to humans (14553)

42 limit 40 to English language (13398)
43 limit 42 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (11047)
44 limit 43 to yr="2007 -Current" (5299)
45 remove duplicates from 44 (5257)

sTable 2. Study inclusion criteria

1. RCT
2. Articles published in English
3. Human subjects
4. Adults
5. Follow up > 12 months after first follow up measurement of UP or GFR
6. Quantifiable albuminuria/proteinuria (i.e. not dipstick)
7. GFR > 15
8. First follow up albuminuria/proteinuria or Scr latest at 12 months
9. Number of events (differ by disease)*
   a. Glomerular disease : >10 events
   b. Kidney disease DM, HTN, PKD, nonspecified or other: follow-up > 500 person years and > 30 events*
   c. High risk population (diabetes, HTN, CVD, heart failure not selected for having kidney disease): follow-up > 1000 person years and > 30 events*

*Events - (ESKD, 2X Scr, 40% or 30% decline)

sTable 3. Studies pooled by intervention

Study	Pooled group
Pozzi 2004[22]	IgA-Steroid
Katafuchi[25]	
Schena[26]	
Praga 2003[14]	IgA-ACEI
HKVIN[15]	
Maes[20]	IgA-MMF
Appel[21]	
Pozzi 2010[23]	IgA-AZA
Pozzi 2012[24]	
Ponticelli 1989[17]	Mem-Ponticelli
Ponticelli 1992[19]	
Ponticelli 1998[18]	
Ponticelli 2006[16]	

sTable 4. Description of studies

Interven-tion	Disease	Study Name	Collaborators	Year	Region	Used in Alb Subset[#]	Urine measurement used (other available)	Creatinine calibration required*
RASB v Control	CKD (CNS)	Kamper[42]	Anne Lise Kamper, Svend Strandgaard	1992	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Ihle/Kincaid[43]	Gavin .J. Becker, Benno Ihle, Priscilla S. Kincaid-Smith	1996	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Hou[44]	Fan Fan Hou	2006	Asia	Yes	PER	Yes
	CKD (CNS)	Hannedouche[45]	Imitiaz Jehan, Nish Chaturvedi, Neil Poulter, Thierry P. Hannedouche	1994	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Brenner[46]	Barry M. Brenner	1993	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Toto[47]	Robert Toto	1993	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Maschio[48]	Guiseppe Maschio, Francesco Locatelli	1996	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	REIN[49]	Giuseppe Remuzzi, Piero Ruggenenti	1999	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	Van Essen[50]	Paul E. de Jong, GG van Essen	1997	NA, Eur, Aus	Yes	PER	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes	PER	Yes
	CKD (PKD)	HALT-PKD A[51]	Ronald D. Perrone, Kaleab Z. Abebe	2014	NA	Yes	AER	No
	CKD (PKD)	HALT-PKD B[13]	Ronald D. Perrone, Kaleab Z. Abebe	2014	NA	Yes	AER	No
	Diabetes	ALTITUDE[32]	Hans-Henrik Parving	2012	International	Yes	SACR	No
	Diabetes (CKD)	RENAAL[52]	Dick De Zeeuw, Hiddo J Lambers Heerspink ,Barry M. Brenner, William Keane	2001	International	Yes	PER (SAER)	Yes
	Diabetes (CKD)	ORIENT[53]	Enyu Imai, Fumiaki Kobayashi, Hirofumi Makino, Sadayoshi Ito	2011	Asia	Yes	SPCR	Yes
	Diabetes (CKD)	IDNT[9]	Edmund Lewis, Lawrence G. Hunsicker	2001	International	Yes	PER (AER)	Yes
	Diabetes (CKD)	Lewis 1993[27]	Julia B. Lewis, Jamie Dwyer, Edmund Lewis, John M. Lachin	1993	NA	Yes	PER (AER)	Yes
	Glom (IgAN)	HKVIN[15]	Philip Kam-Tao Li, CB Leung, CC Szeto, KM Chow	2006	Asia	Yes	PER	Yes
	Glom (IgAN)	Praga 2003[14]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2003	Eur	Yes	PER	Yes
RASB v CCB	CKD (CNS)	Zucchelli[54]	Pietro Zucchelli	1992	NA, Eur, Aus	Yes	PER	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes	PER	Yes
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes	AER	Yes
	Diabetes (CKD)	IDNT[9]	Edmund Lewis, Lawrence G. Hunsicker	2001	International	Yes	PER (AER)	Yes
Intensive BP	CKD (CNS)	MDRD Study B[11]	Gerald J. Beck, Tom Greene, John Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	REIN 2[55]	Giuseppe Remuzzi, Piero Ruggenenti	2005	NA, Eur, Aus	Yes	PER	Yes
	CKD (CNS)	MDRD Study A[11]	Gerald J. Beck, Tom Greene, John Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes	PER	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes	PER	Yes
	CKD (PKD)	HALT-PKD A[51]	Ronald D. Perrone, Kaleab Z. Abebe	2014	NA	Yes	AER	No
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes	AER	Yes
Low Protein Diet	CKD (CNS)	MDRD Study A[11]	Gerald J. Beck, Tom Greene, John Kusek, Saulo Klahr	1994	NA, Eur, Aus	No	PER	Yes
	CKD (CNS)	MDRD Study B[11]	Gerald J. Beck, Tom Greene, John Kusek, Saulo Klahr	1994	NA, Eur, Aus	No	PER	Yes
Immuno-suppresion	Glom (IgAN)	Pozzi 2012[24]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2012	NA, Eur, Aus	Yes	PER	No
	Glom (IgAN)	Donadio 2001[56]	James Donadio, Fernando Fervenza	2001	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	Appel[21]	Gerald B. Appel, Gershon Frisch	2005	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	STOP-IgAN[57]	Jürgen Floege, Thomas Rauen, Christina Fitzner; Ralf-Dieter Hilgers	2015	Eur	Yes	PER	No
	Glom (IgAN)	Maes[20]	Bart Maes	2004	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	Donadio 1999[58]	James Donadio, Fernando Fervenza	1999	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	Pozzi 2010[23]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2010	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	Pozzi 2004[22]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2004	NA, Eur, Aus	Yes	PER	Yes
	Glom (IgAN)	Schena[26]	Francesco Paolo Schena, Manno Carlo	2009	Eur	Yes	PER	No

Interven-tion	Disease	Study Name	Collaborators	Year	Region	Used in Alb Subset[#]	Urine measurement used (other available)	Creatinine calibration required*
	Glom (IgAN)	Katafuchi[25]	Ritsuko Katafuchi	2003	Asia	Yes	PER	Yes
	Glom (Lupus)	Lewis 1992[59]	Edmund Lewis, Roger A. Rodby, Richard D. Rohde, Julia B. Lewis	1992	NA, Eur, Aus	Yes	PER	Yes
	Glom (Lupus)	Chan[29]	Tak-Mao Chan	2005	Asia	Yes	PER	Yes
	Glom (Membran)	Ponticelli 1998[18]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1998	NA, Eur, Aus	Yes	PER	Yes
	Glom (Membran)	Ponticelli 1989[17]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1989	NA, Eur, Aus	Yes	PER	Yes
	Glom (Membran)	Ponticelli 1992[19]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1992	NA, Eur, Aus	Yes	PER	Yes
	Glom (Membran)	Praga 2007[28]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2007	Eur	Yes	PER	Yes
	Glom (Membran)	Ponticelli 2006[16]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	2006	NA, Eur, Aus	Yes	PER	Yes
Nurse Care	CKD (CNS)	MASTERPLAN[60]	Jack F.M. Wetzels, Peter J Blankestijn, Arjan D. van Zuilen, Jan van den Brand	2014	Eur	No	PCR (ACR)	Yes
	CKD (CNS)	CanPREVENT[61]	Brendan Barret	2011	NA, Eur, Aus	No	PER (AER)	No
Alb Protocol	CKD (CNS)	ROAD[30]	Fan Fan Hou	2007	Asia	Yes	PER	Yes
Sulodexide	Diabetes (CKD)	SUN-MACRO[31]	Julia B. Lewis, Jamie Dwyer, Edmund Lewis	2012	International	Yes	PER (AER)	Yes
EMPA	Diabetes	EMPA-REG[33]	Christoph Wanner, Maximilian von Eynatten	2010	International	Yes	SACR	Yes
Allopurinol	CKD (CNS)	Goicoechea[62]	Marian Goicoechea, Eduardo Verde, Ursula Verdalles, Jose Luño	2015	NA, Eur, Aus	No	AER	Yes

*If calibration required, creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or were reduced by 5% as has previously been described.[36]

[#]Alb subset refers to the subset of studies restricted to interventions whose mechanisms are hypothesized to affect albuminuria and were used for the primary analysis

Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified.

CKD, chronic kidney disease; Glom, glomerular disease; HTN, hypertension; IgAN immunoglobulin A nephropathy; PKD, polycystic kidney disease

sTable 5: Clinical characteristics of the population stratified by disease etiology in females and males

Disease	N studies	N	Age mean (SD)	Black N (%)	Diabetes N (%)	eGFR mean (SD)	ACR median ($25,75^{th}$)	Clinical Endpoints N (%)
Female								
Overall	41	10008	57.1 (13.1)	1608 (16.1)	6590 (65.8)	56.7 (26.8)	239 (26, 1142)	1486 (14.8)
Diabetes	10	6544	61.8 (10.5)	601 (9.2)	6544 (100.0)	59.9 (25.0)	306 (24, 1315)	805 (12.3)
Glomerular	9	469	39.2 (12.1)	13 (2.8)	3 (0.6)	75.0 (30.9)	1347 (808, 2356)	49 (10.4)
Other CKD	22	2995	49.7 (12.7)	994 (33.2)	43 (1.4)	46.9 (26.6)	72 (24, 587)	632 (21.1)
Male								
Overall	41	20087	58.8 (12.3)	2300 (11.5)	14650 (72.9)	58.9 (24.1)	286 (32, 1130)	2473 (12.3)
Diabetes	10	14592	62.4 (9.6)	738 (5.1)	14592 (100)	62.1 (22.5)	257 (27, 1051)	1301 (8.9)
Glomerular	9	860	41.6 (13.2)	5 (0.6)	2 (0.2)	73.7 (29.1)	1266 (838, 2335)	125 (14.5)
Other CKD	22	4635	50.4 (12.9)	1557 (33.6)	56 (1.2)	46.3 (22.9)	198 (36, 1018)	1047 (22.6)

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.

sTable 6. Patient characteristics, by study for analyses that used 6 month change in albuminuria

Intervention	Disease	Study	N	Age	Female	Black	Diabetes	eGFR	ACR
RASB v	CKD (CNS)	Kamper	53	49.6 (11.9)	26 (49.1)	0 (0.0)	0 (0.0)	15.2	635 (264, 1558)
Control	CKD (CNS)	Ihle/Kincaid	61	45.0 (13.0)	32 (52.5)	0 (0.0)	0 (0.0)	16.6	784 (449, 1527)
	CKD (CNS)	Hou	223	44.7 (15.5)	112 (50.2)	0 (0.0)	0 (0.0)	16.8	1012 (629, 1341)
	CKD (CNS)	Hannedouche	77	50.8 (14.5)	38 (49.4)	0 (0.0)	0 (0.0)	23.7	719 (299, 1796)
	CKD (CNS)	Brenner	92	47.5 (13.2)	32 (34.8)	33 (35.9)	0 (0.0)	37	653 (143, 1467)
	CKD (CNS)	Toto	109	53.0 (11.5)	39 (35.8)	65 (59.6)	0 (0.0)	37.5	129 (60, 498)
	CKD (CNS)	Maschio	523	50.8 (12.7)	146 (27.9)	0 (0.0)	0 (0.0)	38.9	509 (78, 1497)
	CKD (CNS)	REIN	272	48.4 (13.4)	64 (23.5)	1 (0.4)	0 (0.0)	42.3	1517 (874, 2424)
	CKD (CNS)	Van Essen	95	50.1 (12.9)	34 (35.8)	1 (1.1)	0 (0.0)	47.9	299 (60, 1497)
	CKD (HTN)	AASK	737	55.3 (10.3)	279 (37.9)	737 (100.0)	0 (0.0)	49.2	72 (26, 299)
	CKD (PKD)	HALT-PKD B	436	48.9 (8.2)	222 (50.9)	10 (2.3)	0 (0.0)	48.3	30 (17, 74)
	CKD (PKD)	HALT-PKD A	505	36.9 (8.3)	248 (49.1)	12 (2.4)	0 (0.0)	91.2	18 (12, 33)
	Diabetes	ALTITUDE	8084	64.4 (9.7)	2546 (31.5)	267 (3.3)	8084 (100.0)	58.4	284 (57, 883)
	Diabetes (CKD)	RENAAL	1461	60.1 (7.4)	540 (37.0)	221 (15.1)	1461 (100.0)	41.2	1299 (616, 2732)
	Diabetes (CKD)	ORIENT	554	59.2 (8.1)	172 (31.0)	0 (0.0)	554 (100.0)	47.6	1264 (612, 2291)
	Diabetes (CKD)	IDNT	1065	58.8 (7.6)	336 (31.5)	129 (12.1)	1065 (100.0)	50.4	1772 (1035, 3144)
	Diabetes (CKD)	Lewis 1993	394	34.4 (7.5)	189 (48.0)	29 (7.4)	394 (100.0)	73.1	1121 (605, 2289)
	Glom (IgAN)	HKVIN	107	40.1 (9.1)	77 (72.0)	0 (0.0)	3 (2.8)	75.6	946 (629, 1560)
	Glom (IgAN)	Praga 2003	44	31.6 (11.5)	17 (38.6)	0 (0.0)	0 (0.0)	98.1	1018 (659, 1437)
RASB v CCB	CKD (CNS)	Zucchelli	110	55.8 (11.0)	41 (37.3)	0 (0.0)	0 (0.0)	25.2	596 (239, 1617)
	CKD (HTN)	AASK	554	54.5 (10.7)	207 (37.4)	554 (100.0)	0 (0.0)	49	65 (24, 277)
	Diabetes	ABCD	329	59.2 (8.2)	102 (31.0)	51 (15.5)	329 (100.0)	73	121 (56, 550)
	Diabetes (CKD)	IDNT	1055	59.1 (7.5)	372 (35.3)	135 (12.8)	1055 (100.0)	50.2	1723 (999, 3055)
Intensive BP	CKD (CNS)	MDRD Study B	251	50.9 (12.8)	102 (40.6)	13 (5.2)	13 (5.2)	20.3	419 (102, 1210)
	CKD (CNS)	REIN 2	289	53.9 (14.8)	68 (23.5)	0 (0.0)	15 (5.2)	32.6	1429 (896, 2168)
	CKD (CNS)	MDRD Study A	571	52.2 (12.2)	219 (38.4)	50 (8.8)	29 (5.1)	40.8	120 (30, 665)
	CKD (HTN)	AASK	929	55.0 (10.5)	353 (38.0)	929 (100.0)	0 (0.0)	49	66 (25, 294)
	CKD (PKD)	HALT-PKD A	505	36.9 (8.3)	248 (49.1)	12 (2.4)	0 (0.0)	91.2	18 (12, 33)
	Diabetes	ABCD	329	59.2 (8.2)	102 (31.0)	51 (15.5)	329 (100.0)	73	121 (56, 550)
Low Protein	CKD (CNS)	MDRD Study B	251	50.9 (12.8)	102 (40.6)	13 (5.2)	13 (5.2)	20.3	419 (102, 1210)
Diet	CKD (CNS)	MDRD Study A	571	52.2 (12.2)	219 (38.4)	50 (8.8)	29 (5.1)	40.8	120 (30, 665)
Immuno-	Glom (IgAN)	Pozzi 2012	44	42.1 (11.6)	8 (18.2)	0 (0.0)	0 (0.0)	27.9	1467 (898, 2305)
suppression	Glom (IgAN)	Donadio 2001	66	46.4 (13.4)	10 (15.2)	2 (3.0)	0 (0.0)	41.8	934 (420, 1538)
	Glom (IgAN)	Appel	20	37.6 (13.3)	2 (10.0)	0 (0.0)	0 (0.0)	47.4	1365 (958, 1778)
	Glom (IgAN)	STOP-IgAN	142	44.5 (12.3)	32 (22.5)	0 (0.0)	0 (0.0)	59.5	931 (646, 1246)
	Glom (IgAN)	Maes	34	44.8 (11.3)	10 (29.4)	0 (0.0)	0 (0.0)	62.2	596 (353, 1599)
	Glom (IgAN)	Donadio 1999	91	38.8 (13.4)	23 (25.3)	0 (0.0)	0 (0.0)	65.8	1138 (719, 2036)

Intervention	Disease	Study	N	Age	Female	Black	Diabetes	eGFR	ACR
	Glom (IgAN)	Pozzi 2010	190	39.3 (12.7)	55 (28.9)	0 (0.0)	0 (0.0)	74	1198 (898, 1617)
	Glom (IgAN)	Pozzi 2004	83	38.6 (11.7)	25 (30.1)	0 (0.0)	0 (0.0)	87.2	1138 (838, 1437)
	Glom (IgAN)	Schena	95	33.7 (11.1)	29 (30.5)	0 (0.0)	2 (2.1)	91.3	982 (790, 1497)
	Glom (IgAN)	Katafuchi	74	36.2 (11.4)	44 (59.5)	0 (0.0)	0 (0.0)	98.5	785 (532, 1543)
	Glom (Lupus)	Lewis 1992	70	31.6 (11.7)	58 (82.9)	16 (22.9)	0 (0.0)	59.9	2665 (1385, 4898)
	Glom (Lupus)	Chan	51	40.2 (9.5)	43 (84.3)	0 (0.0)	2 (3.9)	71.4	2275 (1557, 3898)
	Glom (Membran)	Ponticelli 1998	86	49.7 (10.9)	25 (29.1)	0 (0.0)	0 (0.0)	82.7	3593 (2575, 5389)
	Glom (Membran)	Ponticelli 1989	73	44.3 (11.0)	14 (19.2)	0 (0.0)	0 (0.0)	87.6	2994 (2275, 4731)
	Glom (Membran)	Ponticelli 1992	75	46.9 (13.3)	26 (34.7)	0 (0.0)	0 (0.0)	88.5	3293 (2455, 4790)
	Glom (Membran)	Praga 2007	48	46.6 (12.5)	8 (16.7)	0 (0.0)	0 (0.0)	89.3	4338 (2640, 5828)
	Glom (Membran)	Ponticelli 2006	31	49.3 (10.5)	12 (38.7)	0 (0.0)	0 (0.0)	92.6	3353 (2395, 4850)
Nurse Care	CKD (CNS)	MASTERPLAN	419	60.6 (12.2)	124 (29.6)	32 (7.6)	109 (26.0)	37.1	144 (46, 478)
	CKD (CNS)	CanPREVENT	407	65.1 (7.5)	222 (54.5)	22 (5.4)	131 (32.2)	47.8	72 (48, 115)
Alb Protocol	CKD (CNS)	ROAD	338	50.8 (13.7)	126 (37.3)	0 (0.0)	0 (0.0)	29.1	958 (641, 1599)
Sulodexide	Diabetes (CKD)	SUN-MACRO	1028	63.4 (9.3)	237 (23.1)	109 (10.6)	1028 (100.0)	33.7	1074 (569, 1819)
EMPA	Diabetes	EMPA-REG	6803	63.1 (8.6)	1931 (28.4)	343 (5.0)	6803 (100.0)	76.2	18 (6, 72)
Allopurinol	CKD (CNS)	Goicoechea	89	71.4 (8.6)	32 (36.0)	0 (0.0)	34 (38.2)	41.1	30 (15, 529)
Pooled	Glom (IgAN)	IgAN_steroid	252	36.0 (11.5)	98 (38.9)	0 (0.0)	2 (0.8)	92.1	1018 (734, 1497)
Studies	Glom (IgAN)	IgAN_MMF	54	42.1 (12.5)	12 (22.2)	0 (0.0)	0 (0.0)	56.7	991 (449, 1719)
	Glom (IgAN)	IgAN-ACEI	151	37.6 (10.5)	94 (62.3)	0 (0.0)	3 (2.0)	82.1	958 (647, 1497)
	Glom (IgAN)	IgAN-AZA	234	39.8 (12.5)	63 (26.9)	0 (0.0)	0 (0.0)	65.3	1198 (898, 1737)
	Glom (Membran)	Mem-Pont	265	47.3 (11.8)	77 (29.1)	0 (0.0)	0 (0.0)	86.9	3293 (2395, 4850)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation).
The number of participants refers to those included in the GFR analysis. Participants with missing data on age, race, sex, serum creatinine, urine albumin were excluded
Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified. CKD, chronic kidney disease; Glom, glomerular disease; Membran, membranous nephropathy; HTN, hypertension; IgAN immunoglobulin A nephropathy; PKD, polycystic 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.

sTable 7: Meta-analysis of treatment effects on change in albuminuria, on the clinical endpoint and the alternative clinical endpoint

Group	Subgroup	Treatment effect on change in albuminuria (6 months)		Treatment effect on change in clinical endpoint		Treatment effect on change in alternative clinical endpoint	
		GMR (95%CI)	I^2 (%)	HR (95% CI)	I^2 (%)	HR (95% CI)	I^2 (%)
Overall		0.78 (0.74, 0.82)	84	0.74 (0.67, 0.82)	47	0.77 (0.70, 0.84)	55
Age	< 60	0.77 (0.72, 0.81)	75	0.72 (0.63, 0.81)	50	0.76 (0.70, 0.84)	39
	≥ 60	0.79 (0.70, 0.88)	91	0.82 (0.73, 0.92)	5	0.85 (0.75, 0.96)	34
Sex	Men	0.78 (0.73, 0.83)	82	0.73 (0.65, 0.82)	37	0.76 (0.68, 0.84)	46
	Women	0.79 (0.75, 0.84)	49	0.75 (0.65, 0.87)	31	0.80 (0.71, 0.91)	37
Race	Black	0.78 (0.69, 0.87)	57	0.84 (0.72, 0.97)	0	0.90 (0.79, 1.02)	0
	Non-Black	0.79 (0.75, 0.83)	80	0.72 (0.64, 0.81)	47	0.75 (0.68, 0.83)	56
GFR	< 60	0.79 (0.74, 0.83)	75	0.76 (0.69, 0.84)	38	0.77 (0.70, 0.84)	45
	≥ 60	0.77 (0.72, 0.83)	59	0.69 (0.54, 0.88)	37	0.85 (0.71, 1.00)	37
ACR	< 30	0.92 (0.88, 0.96)	0	0.80 (0.53, 1.21)	36	0.89 (0.63, 1.26)	60
	≥ 30	0.76 (0.72, 0.81)	82	0.74 (0.67, 0.81)	39	0.76 (0.70, 0.83)	45
Disease	Diabetes	0.80 (0.74, 0.85)	86	0.77 (0.64, 0.92)	69	0.85 (0.73, 0.98)	73
	Glomerular	0.74 (0.61, 0.90)	72	0.49 (0.30, 0.80)	48	0.57 (0.38, 0.85)	49
	Other CKD	0.79 (0.73, 0.85)	77	0.76 (0.67, 0.85)	29	0.76 (0.68, 0.84)	35
Intervention	RASB vs Control	0.76 (0.70, 0.83)	84	0.77 (0.66, 0.90)	59	0.79 (0.68, 0.91)	71
	RASB vs CCB	0.72 (0.56, 0.92)	86	0.66 (0.55, 0.79)	0	0.81 (0.69, 0.94)	0
	Intensive BP	0.84 (0.77, 0.91)	49	0.87 (0.74, 1.04)	0	0.87 (0.75, 1.00)	0
	Low Protein Diet	0.80 (0.67, 0.96)	55	0.80 (0.62, 1.04)	0	0.68 (0.52, 0.89)	19
	Immunosuppression	0.76 (0.62, 0.94)	71	0.50 (0.29, 0.86)	54	0.61 (0.40, 0.93)	48
	Alb Target Protocol	0.75 (0.66, 0.85)	0	0.47 (0.30, 0.74)	0	0.73 (0.52, 1.02)	0
	Sulodexide	0.96 (0.89, 1.03)	0	0.81 (0.50, 1.34)	0	0.96 (0.66, 1.39)	0
	Empagliflozin	0.83 (0.79, 0.88)	0	0.51 (0.37, 0.70)	0	0.56 (0.44, 0.72)	0

Race was defined as Black vs non Black for use in categorization of race in computing eGFR using the CKD-EPI creatinine equation.

sTable 8. Endpoints used, by study

Intervention	Disease	Study	N	Individual Endpoints, N (%)				Composite Endpoints, N (%)			
				ESKD	Doubling SCr	GFR < 15	40% GFR decline	Clinical endpoint*	FU clinical endpoint*	Alternative Clinical endpoint	FU alternative endpoint*
RASB v Control	CKD (CNS)	Kamper	53	19 (35.8)	9 (17.0)	0 (0.0)	19 (35.8)	21 (39.6)	29 (20, 37)	26 (49.1)	25 (17, 37)
	CKD (CNS)	Ihle/Kincaid	61	13 (21.3)	11 (18.0)	2 (3.3)	28 (45.9)	21 (34.4)	22 (9, 25)	32 (52.5)	19 (9, 24)
	CKD (CNS)	Hou	223	82 (36.8)	46 (20.6)	5 (2.2)	154 (69.1)	110 (49.3)	32 (15, 37)	162 (72.6)	21 (12, 33)
	CKD (CNS)	Hannedouche	77	22 (28.6)	22 (28.6)	14 (18.2)	39 (50.6)	32 (41.6)	32 (18, 38)	43 (55.8)	27 (15, 38)
	CKD (CNS)	Brenner	92	12 (13.0)	13 (14.1)	7 (7.6)	29 (31.5)	20 (21.7)	34 (15, 37)	30 (32.6)	32 (14, 37)
	CKD (CNS)	Toto	109	10 (9.2)	13 (11.9)	8 (7.3)	19 (17.4)	22 (20.2)	36 (20, 37)	26 (23.9)	36 (20, 37)
	CKD (CNS)	Maschio	523	2 (0.4)	75 (14.3)	49 (9.4)	131 (25.0)	85 (16.3)	36 (26, 37)	132 (25.2)	36 (24, 37)
	CKD (CNS)	REIN	272	56 (20.6)	40 (14.7)	34 (12.5)	89 (32.7)	74 (27.2)	29 (17, 39)	101 (37.1)	27 (16, 37)
	CKD (CNS)	Van Essen	95	7 (7.4)	10 (10.5)	4 (4.2)	14 (14.7)	10 (10.5)	47 (36, 50)	14 (14.7)	45 (32, 50)
	CKD (HTN)	AASK	737	107 (14.5)	80 (10.9)	62 (8.4)	171 (23.2)	138 (18.7)	55 (43, 66)	195 (26.5)	54 (41, 65)
	CKD (PKD)	HALT-PKD B	436	70 (16.1)	62 (14.2)	33 (7.6)	259 (59.4)	123 (28.2)	66 (51, 79)	270 (61.9)	60 (42, 73)
	CKD (PKD)	HALT-PKD A	505	1 (0.2)	27 (5.3)	1 (0.2)	81 (16.0)	27 (5.3)	73 (62, 85)	83 (16.4)	73 (61, 85)
	Diabetes	ALTITUDE	8084	216 (2.7)	427 (5.3)	278 (3.4)	1223 (15.1)	526 (6.5)	39 (29, 45)	1253 (15.5)	36 (27, 45)
	Diabetes (CKD)	RENAAL	1461	333 (22.8)	359 (24.6)	105 (7.2)	268 (18.3)	482 (33.0)	35 (25, 43)	460 (31.5)	36 (27, 44)
	Diabetes (CKD)	ORIENT	554	99 (17.9)	168 (30.3)	104 (18.8)	283 (51.1)	196 (35.4)	31 (17, 38)	302 (54.5)	24 (13, 36)
	Diabetes (CKD)	IDNT	1065	125 (11.7)	227 (21.3)	72 (6.8)	352 (33.1)	275 (25.8)	31 (24, 43)	414 (38.9)	30 (23, 40)
	Diabetes (CKD)	Lewis 1993	394	35 (8.9)	65 (16.5)	33 (8.4)	92 (23.4)	69 (17.5)	40 (34, 49)	93 (23.6)	37 (28, 49)
	Glom (IgAN)	HKVIN	107	3 (2.8)	6 (5.6)	6 (5.6)	12 (11.2)	8 (7.5)	35 (35, 35)	13 (12.1)	35 (35, 35)
	Glom (IgAN)	Praga 2003	44	15 (34.1)	6 (13.6)	1 (2.3)	14 (31.8)	15 (34.1)	76 (61, 130)	18 (40.9)	73 (55, 102)
RASB v CCB	CKD (CNS)	Zucchelli	110	21 (19.1)	22 (20.0)	10 (9.1)	37 (33.6)	32 (29.1)	37 (21, 37)	38 (34.5)	34 (19, 37)
	CKD (HTN)	AASK	554	90 (16.2)	58 (10.5)	41 (7.4)	117 (21.1)	107 (19.3)	55 (43, 65)	140 (25.3)	54 (42, 65)
	Diabetes	ABCD	329	0 (0.0)	19 (5.8)	4 (1.2)	39 (11.9)	19 (5.8)	61 (60, 63)	40 (12.2)	61 (54, 63)
	Diabetes (CKD)	IDNT	1055	123 (11.7)	235 (22.3)	79 (7.5)	349 (33.1)	298 (28.2)	31 (24, 42)	414 (39.2)	30 (22, 40)
Intensive BP	CKD (CNS)	MDRD Study B	251	131 (52.2)	63 (25.1)	16 (6.4)	110 (43.8)	143 (57.0)	27 (18, 39)	148 (59.0)	25 (16, 38)
	CKD (CNS)	REIN 2	289	61 (21.1)	30 (10.4)	26 (9.0)	72 (24.9)	73 (25.3)	19 (13, 33)	93 (32.2)	17 (13, 28)
	CKD (CNS)	MDRD Study A	571	41 (7.2)	74 (13.0)	45 (7.9)	120 (21.0)	91 (15.9)	28 (22, 35)	125 (21.9)	27 (21, 35)
	CKD (HTN)	AASK	929	147 (15.8)	103 (11.1)	77 (8.3)	216 (23.3)	184 (19.8)	55 (43, 65)	250 (26.9)	54 (41, 65)
	CKD (PKD)	HALT-PKD A	505	1 (0.2)	27 (5.3)	1 (0.2)	81 (16.0)	27 (5.3)	73 (62, 85)	83 (16.4)	73 (61, 85)
	Diabetes	ABCD	329	0 (0.0)	19 (5.8)	4 (1.2)	39 (11.9)	19 (5.8)	61 (60, 63)	40 (12.2)	61 (54, 63)
Low Protein Diet	CKD (CNS)	MDRD Study B	251	131 (52.2)	63 (25.1)	16 (6.4)	110 (43.8)	143 (57.0)	27 (18, 39)	148 (59.0)	25 (16, 38)
	CKD (CNS)	MDRD Study A	571	41 (7.2)	74 (13.0)	45 (7.9)	120 (21.0)	91 (15.9)	28 (22, 35)	125 (21.9)	27 (21, 35)
Immuno-suppression	Glom (IgAN)	Pozzi 2012	44	15 (34.1)	7 (15.9)	7 (15.9)	16 (36.4)	15 (34.1)	50 (35, 63)	19 (43.2)	49 (35, 62)
	Glom (IgAN)	Donadio 2001	66	15 (22.7)	8 (12.1)	5 (7.6)	16 (24.2)	16 (24.2)	28 (25, 38)	23 (34.8)	27 (23, 38)
	Glom (IgAN)	Appel	20	4 (20.0)	0 (0.0)	2 (10.0)	5 (25.0)	4 (20.0)	26 (15, 29)	5 (25.0)	24 (13, 29)
	Glom (IgAN)	STOP-IgAN	142	7 (4.9)	6 (4.2)	5 (3.5)	16 (11.3)	13 (9.2)	38 (37, 38)	20 (14.1)	38 (37, 38)
	Glom (IgAN)	Maes	34	2 (5.9)	2 (5.9)	2 (5.9)	4 (11.8)	2 (5.9)	45 (33, 45)	4 (11.8)	45 (33, 45)
	Glom (IgAN)	Donadio 1999	91	15 (16.5)	2 (2.2)	2 (2.2)	8 (8.8)	16 (17.6)	37 (26, 45)	18 (19.8)	37 (26, 44)
	Glom (IgAN)	Pozzi 2010	190	9 (4.7)	14 (7.4)	6 (3.2)	20 (10.5)	14 (7.4)	73 (53, 90)	20 (10.5)	69 (52, 89)
	Glom (IgAN)	Pozzi 2004	83	7 (8.4)	13 (15.7)	8 (9.6)	23 (27.7)	13 (15.7)	102 (66, 126)	23 (27.7)	90 (54, 120)
	Glom (IgAN)	Schena	95	8 (8.4)	10 (10.5)	5 (5.3)	19 (20.0)	10 (10.5)	66 (42, 78)	19 (20.0)	66 (36, 78)
	Glom (IgAN)	Katafuchi	74	4 (5.4)	5 (6.8)	4 (5.4)	7 (9.5)	5 (6.8)	78 (60, 90)	7 (9.5)	78 (54, 90)
	Glom (Lupus)	Lewis 1992	70	10 (14.3)	6 (8.6)	6 (8.6)	15 (21.4)	12 (17.1)	25 (14, 42)	16 (22.9)	25 (14, 42)

Intervention	Disease	Study	N	Individual Endpoints, N (%)				Composite Endpoints, N (%)			
				ESKD	Doubling SCr	GFR < 15	40% GFR decline	Clinical endpoint*	FU clinical endpoint*	Alternative Clinical endpoint	FU alternative endpoint*
	Glom (Lupus)	Chan	51	1 (2.0)	0 (0.0)	1 (2.0)	4 (7.8)	1 (2.0)	54 (36, 72)	4 (7.8)	42 (36, 72)
	Glom (Membran)	Ponticelli 1998	86	2 (2.3)	3 (3.5)	3 (3.5)	3 (3.5)	3 (3.5)	43 (31, 55)	3 (3.5)	43 (25, 55)
	Glom (Membran)	Ponticelli 1989	73	10 (13.7)	19 (26.0)	12 (16.4)	25 (34.2)	19 (26.0)	138 (60, 138)	25 (34.2)	108 (48, 138)
	Glom (Membran)	Ponticelli 1992	75	2 (2.7)	8 (10.7)	2 (2.7)	11 (14.7)	8 (10.7)	25 (19, 43)	11 (14.7)	31 (19, 43)
	Glom (Membran)	Praga 2007	48	0 (0.0)	3 (6.3)	0 (0.0)	4 (8.3)	3 (6.3)	24 (20, 25)	4 (8.3)	24 (19, 25)
	Glom (Membran)	Ponticelli 2006	31	0 (0.0)	1 (3.2)	1 (3.2)	1 (3.2)	1 (3.2)	25 (16, 28)	1 (3.2)	25 (16, 28)
Alb Protocol	CKD (CNS)	ROAD	338	57 (16.9)	65 (19.2)	17 (5.0)	141 (41.7)	84 (24.9)	46 (46, 46)	141 (41.7)	46 (28, 46)
Sulodexide	Diabetes (CKD)	SUN-MACRO	1028	20 (1.9)	26 (2.5)	38 (3.7)	97 (9.4)	63 (6.1)	21 (15, 27)	112 (10.9)	21 (15, 27)
EMPA	Diabetes	EMPA-REG	6803	24 (0.4)	136 (2.0)	25 (0.4)	260 (3.8)	156 (2.3)	45 (37, 53)	273 (4.0)	44 (37, 53)
Pooled	Glom (IgAN)	IgAN_steroid	252	19 (7.5)	28 (11.1)	17 (6.7)	49 (19.4)	28 (11.1)	78 (54, 90)	49 (19.4)	78 (48, 90)
Studies	Glom (IgAN)	IgAN_MMF	54	6 (11.1)	2 (3.7)	4 (7.4)	9 (16.7)	6 (11.1)	33 (25, 45)	9 (16.7)	33 (23, 45)
	Glom (IgAN)	IgAN-ACEI	151	18 (11.9)	12 (7.9)	7 (4.6)	26 (17.2)	23 (15.2)	35 (35, 54)	31 (20.5)	35 (35, 43)
	Glom (IgAN)	IgAN-AZA	234	24 (10.3)	21 (9.0)	13 (5.6)	36 (15.4)	29 (12.4)	67 (47, 86)	39 (16.7)	65 (45, 86)
	Glom (Membran)	Mem-Pont	265	14 (5.3)	31 (11.7)	18 (6.8)	40 (15.1)	31 (11.7)	37 (25, 61)	40 (15.1)	37 (25, 61)

Other CKD refers to causes of CKD other than glomerular disease or diabetes or cause not specified.

CKD, chronic kidney disease; Glom, glomerular disease; Membran, membranous nephropathy; HTN, hypertension; IgAN immunoglobulin A nephropathy; PKD, polycystic kidney disease.

*FU, follow-up time expressed in median months (25^{th}, 75^{th} percentile)

sTable 9. Trial level analyses for change in albuminuria at 6 months by the clinical endpoint for studies whose interventions has biologic plausibility as a surrogate endpoint

Group	Subgroup	N patients (N events)	Studies/ Interv	Slope	Intercept	R^2	RMSE
All							
Overall		29979 (3935)	41 (8)	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	17387 (3329)	39 (8)	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	12348 (598)	23 (6)	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*	7401 (180)	10 (5)	-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	22544 (3749)	41 (8)	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	21102 (2103)	10 (5)	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	1352 (174)	9 (2)	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	7552 (1658)	22 (5)	0.73 (-0.16, 1.76)	-0.10 (-0.34, 0.17)	0.75 (0.01, 0.99)	0.05 (0.01, 0.22)
Intervention	RASB vs Control	14892 (2254)	18 (1)	1.18 (-0.19, 2.67)	0.07 (-0.33, 0.46)	0.64 (0.00, 0.99)	0.11 (0.02, 0.33)
	RASB v CCB	2048 (456)	4 (1)	-0.21 (-16.21, 14.39)	-0.49 (-5.98, 4.50)	0.78 (0.00, 1.00)	0.06 (0.01, 0.49)
	Immunosuppression	1174 (151)	8 (1)	1.71 (0.12, 5.11)	-0.16 (-0.76, 0.84)	0.98 (0.09, 1.00)	0.07 (0.01, 0.66)
Disease where ACR > 30	Diabetes	15532 (2030)	10 (5)	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	1324 (174)	9 (2)	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	5688 (1545)	22 (5)	0.53 (-0.38, 1.53)	-0.15 (-0.42, 0.14)	0.65 (0.00, 0.99)	0.05 (0.01, 0.21)
Excluding EMPA-REG OUTCOME							
Overall		23176 (3779)	40 (7)	0.99 (0.29, 1.75)	-0.02 (-0.22, 0.19)	0.72 (0.08, 0.99)	0.09 (0.02, 0.23)
GFR	< 60	15866 (3265)	38 (7)	0.87 (0.02, 1.79)	-0.03 (-0.27, 0.21)	0.62 (0.01, 0.99)	0.09 (0.02, 0.24)
	≥ 60	7066 (506)	22 (5)	2.80 (0.64, 6.83)	0.40 (-0.16, 1.33)	0.98 (0.32, 1.00)	0.05 (0.01, 0.29)
ACR	< 30	3314 (128)	9 (4)	-1.47 (-35.12, 32.69)	-0.13 (-3.28, 3.05)	0.91 (0.01, 1.00)	0.06 (0.01, 0.43)
	≥ 30	19828 (3645)	40 (7)	0.85 (0.17, 1.62)	-0.05 (-0.26, 0.17)	0.68 (0.04, 0.99)	0.09 (0.02, 0.23)
Disease	Diabetes	14299 (1947)	9 (4)	0.95 (-0.97, 2.60)	0.04 (-0.47, 0.46)	0.57 (0.00, 0.99)	0.09 (0.02, 0.35)
	Glomerular	1325 (174)	9 (2)	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	7552 (1658)	22 (5)	0.73 (-0.16, 1.76)	-0.10 (-0.34, 0.17)	0.75 (0.01, 0.99)	0.05 (0.01, 0.22)

*Event rate < 5%. Estimates unreliable

sTable 10. Trial level analyses for change in albuminuria at 12 months by the clinical endpoint for studies whose interventions has biologic plausibility as a surrogate endpoint

Group	Subgroup	N patients (N events)	Studies/Interv	Slope	Intercept	R^2	RMSE
All							
Overall		30095 (3959)	41 (8)	0.85 (0.11, 1.66)	-0.04 (-0.29, 0.20)	0.47 (0.02, 0.95)	0.15 (0.03, 0.27)
GFR	< 60	17476 (3351)	39 (8)	0.94 (-0.11, 2.12)	0.02 (-0.32, 0.37)	0.57 (0.00, 0.99)	0.09 (0.02, 0.25)
	≥ 60	12375 (600)	23 (6)	1.30 (0.03, 2.68)	-0.02 (-0.42, 0.41)	0.82 (0.04, 1.00)	0.12 (0.02, 0.45)
ACR	< 30*	7426 (180)	10 (5)	-11.32 (-50.87, 36.68)	-1.14 (-4.40, 2.25)	0.97 (0.03, 1.00)	0.07 (0.01, 0.57)
	≥ 30	22635 (3773)	41 (8)	1.00 (0.29, 1.79)	0.04 (-0.21, 0.30)	0.80 (0.10, 0.99)	0.08 (0.02, 0.21)
Disease	Diabetes	21136 (2106)	10 (5)	-0.10 (-2.13, 1.78)	-0.29 (-0.89, 0.27)	0.11 (0.00, 0.73)	0.21 (0.06, 0.49)
	Glomerular	1329 (174)	9 (2)	1.11 (0.10, 2.43)	-0.26 (-0.80, 0.34)	0.97 (0.08, 1.00)	0.07 (0.02, 0.59)
	Other CKD	7630 (1679)	22 (5)	1.09 (0.08, 2.57)	0.03 (-0.27, 0.46)	0.86 (0.05, 0.99)	0.05 (0.01, 0.20)
Intervention	RASB vs Control	14935 (2262)	18 (1)	1.49 (-0.01, 3.37)	0.21 (-0.28, 0.78)	0.71 (0.01, 0.99)	0.11 (0.02, 0.34)
	RASB v CCB	2076 (464)	4 (1)	-0.79 (-33.82, 30.90)	-0.75 (-15.04, 12.81)	0.87 (0.01, 1.00)	0.05 (0.01, 0.48)
	Immunosuppression	1178 (151)	8 (1)	1.08 (0.03, 2.41)	-0.27 (-0.86, 0.32)	0.97 (0.05, 1.00)	0.07 (0.01, 0.74)
Disease where ACR > 30	Diabetes	15560 (2033)	10 (5)	0.81 (-0.95, 2.32)	0.02 (-0.56, 0.49)	0.50 (0.00, 0.99)	0.10 (0.02, 0.36)
	Glomerular	1328 (174)	9 (2)	1.13 (0.09, 2.58)	-0.26 (-0.81, 0.37)	0.97 (0.08, 1.00)	0.07 (0.01, 0.59)
	Other CKD	5747 (1566)	22 (5)	1.12 (-1.29, 6.31)	0.07 (-0.74, 1.74)	0.82 (0.01, 0.99)	0.05 (0.01, 0.20)
Excluding EMPA-REG OUTCOME							
Overall		23288 (3803)	40 (7)	1.00 (0.32, 1.74)	0.03 (-0.19, 0.26)	0.78 (0.11, 0.99)	0.09 (0.02, 0.22)
GFR	< 60	15954 (3287)	38 (7)	0.93 (-0.13, 2.07)	0.02 (-0.33, 0.36)	0.55 (0.00, 0.99)	0.10 (0.02, 0.26)
	≥ 60	7090 (508)	22 (5)	1.70 (0.58, 3.15)	0.21 (-0.17, 0.66)	0.98 (0.52, 1.00)	0.05 (0.01, 0.25)
ACR	< 30	3337 (128)	9 (4)	-1.68 (-35.81, 30.83)	-0.13 (-3.36, 2.97)	0.92 (0.01, 1.00)	0.06 (0.01, 0.42)
	≥ 30	19917 (3669)	40 (7)	0.97 (0.26, 1.75)	0.03 (-0.21, 0.29)	0.81 (0.09, 0.99)	0.08 (0.02, 0.22)
Disease	Diabetes	14329 (1950)	9 (4)	0.69 (-1.19, 2.17)	0.01 (-0.58, 0.46)	0.46 (0.00, 0.99)	0.10 (0.02, 0.38)
	Glomerular	1329 (174)	9 (2)	1.11 (0.10, 2.43)	-0.26 (-0.80, 0.34)	0.97 (0.08, 1.00)	0.07 (0.02, 0.59)
	Other CKD	7630 (1679)	22 (5)	1.09 (0.08, 2.57)	0.03 (-0.27, 0.46)	0.86 (0.05, 0.99)	0.05 (0.01, 0.20)

*Event rate < 5%. Estimates unreliable

sTable 11. Trial level analyses for change in albuminuria at 6 months by the alternative clinical endpoint for studies whose interventions has biologic plausibility as a surrogate endpoint

Group	Subgroup	N patients (N events)	Studies/Interv	Slope	Intercept	R^2	RMSE
All							
Overall		30078 (6059)	43 (8)	0.76 (0.04, 1.57)	-0.07 (-0.27, 0.14)	0.30 (0.01, 0.73)	0.55 (0.03, 0.86)
GFR	< 60	17402 (4687)	40 (8)	0.66 (-0.21, 1.66)	-0.10 (-0.34, 0.17)	0.25 (0.00, 0.88)	0.50 (-0.16, 0.94)
	≥ 60	12477 (1355)	27 (7)	0.33 (-11.09, 3.55)	-0.07 (-2.48, 0.65)	0.30 (0.00, 0.99)	0.18 (-0.99, 0.97)
ACR	< 30	7408 (457)	11 (5)	-14.39 (-52.86, 43.98)	-1.31 (-4.79, 3.35)	0.97 (0.02, 1.00)	-0.97 (-1.00, 1.00)
	≥ 30	22643 (5596)	43 (8)	0.87 (0.21, 1.61)	-0.02 (-0.22, 0.20)	0.57 (0.04, 0.97)	0.75 (0.19, 0.99)
Disease	Diabetes	21102 (3401)	10 (5)	0.78 (-1.13, 2.55)	0.03 (-0.46, 0.46)	0.20 (0.00, 0.89)	0.41 (-0.46, 0.94)
	Glomerular	1424 (253)	11 (2)	1.62 (0.31, 4.19)	-0.06 (-0.57, 0.75)	0.97 (0.16, 1.00)	0.99 (0.34, 1.00)
	Other CKD	7552 (2405)	22 (5)	0.31 (-0.54, 1.18)	-0.20 (-0.42, 0.03)	0.30 (0.00, 0.96)	0.47 (-0.79, 0.98)
Intervention	RASB vs Control	14892 (3667)	18 (1)	1.48 (-0.04, 3.04)	0.16 (-0.27, 0.57)	0.59 (0.01, 0.99)	0.77 (-0.03, 1.00)
	RASB v CCB	2048 (632)	4 (1)	-0.33 (-27.14, 23.87)	-0.34 (-9.41, 7.99)	0.79 (0.00, 1.00)	-0.46 (-1.00, 1.00)
	Immunosuppression	1273 (222)	10 (1)	1.47 (0.04, 5.76)	-0.07 (-0.60, 1.07)	0.97 (0.07, 1.00)	0.98 (0.03, 1.00)
Disease where ACR > 30	Diabetes	15532 (3199)	10 (5)	1.43 (0.37, 2.46)	0.23 (-0.06, 0.49)	0.93 (0.13, 1.00)	0.04 (0.01, 0.18)
	Glomerular	1423 (253)	11 (2)	1.67 (0.34, 4.30)	-0.05 (-0.56, 0.82)	0.98 (0.15, 1.00)	0.06 (0.01, 0.45)
	Other CKD	5688 (2144)	22 (5)	0.23 (-0.56, 1.01)	-0.24 (-0.48, -0.01)	0.41 (0.00, 0.97)	0.05 (0.01, 0.19)
Excluding EMPA-REG OUTCOME							
Overall		23275 (5786)	42 (7)	0.84 (0.16, 1.58)	-0.03 (-0.23, 0.17)	0.43 (0.02, 0.88)	0.66 (0.13, 0.94)
GFR	< 60	15881 (4581)	39 (7)	0.63 (-0.21, 1.59)	-0.09 (-0.33, 0.16)	0.26 (0.00, 0.87)	0.51 (-0.16, 0.93)
	≥ 60	7195 (1188)	26 (6)	1.21 (-1.23, 4.53)	0.23 (-0.34, 0.99)	0.87 (0.01, 1.00)	0.93 (-0.84, 1.00)
ACR	< 30	3321 (362)	10 (4)	-6.48 (-42.86, 36.45)	-0.43 (-4.01, 3.54)	0.96 (0.02, 1.00)	-0.91 (-1.00, 1.00)
	≥ 30	19927 (5418)	42 (7)	0.82 (0.16, 1.55)	-0.02 (-0.22, 0.19)	0.56 (0.03, 0.97)	0.75 (0.16, 0.99)
Disease	Diabetes	14299 (3128)	9 (4)	1.34 (0.29, 2.37)	0.24 (-0.05, 0.48)	0.91 (0.09, 0.99)	0.96 (0.24, 1.00)
	Glomerular	1424 (253)	11 (2)	1.62 (0.31, 4.19)	-0.06 (-0.57, 0.75)	0.97 (0.16, 1.00)	0.99 (0.34, 1.00)
	Other CKD	7552 (2405)	22 (5)	0.31 (-0.54, 1.18)	-0.20 (-0.42, 0.03)	0.30 (0.00, 0.96)	0.47 (-0.79, 0.98)

*Event rate < 5%. Estimates unreliable

sTable 12. Trial level analysis for change in albuminuria at 12 months for the alternative clinical endpoint for studies whose interventions has biologic plausibility as a surrogate endpoint

Group	Subgroup	N patients (N events)	Studies/Interv	Slope	Intercept	R^2	RMSE
All							
Overall		30194 (6090)	43 (8)	0.76 (0.11, 1.46)	-0.03 (-0.24, 0.18)	0.34 (0.01, 0.75)	0.17 (0.10, 0.27)
GFR	< 60	17491 (4715)	40 (8)	0.79 (-0.20, 2.05)	-0.03 (-0.34, 0.36)	0.27 (0.00, 0.94)	0.14 (0.04, 0.25)
	≥ 60	12504 (1358)	27 (7)	0.50 (-0.64, 1.54)	-0.01 (-0.36, 0.31)	0.29 (0.00, 0.96)	0.18 (0.02, 0.39)
ACR	< 30	7433 (457)	11 (5)	-11.09 (-42.74, 22.15)	-1.07 (-3.88, 1.48)	0.97 (0.03, 1.00)	0.08 (0.02, 0.57)
	≥ 30	22734 (5627)	43 (8)	1.00 (0.35, 1.78)	0.08 (-0.16, 0.34)	0.70 (0.12, 0.99)	0.10 (0.02, 0.20)
Disease	Diabetes	21136 (3406)	10 (5)	0.23 (-1.43, 1.78)	-0.10 (-0.59, 0.36)	0.10 (0.00, 0.69)	0.19 (0.08, 0.40)
	Glomerular	1428 (253)	11 (2)	1.03 (0.20, 2.17)	-0.17 (-0.61, 0.32)	0.97 (0.14, 1.00)	0.06 (0.01, 0.48)
	Other CKD	7630 (2431)	22 (5)	0.69 (-0.23, 1.95)	-0.08 (-0.35, 0.29)	0.58 (0.00, 0.98)	0.07 (0.02, 0.23)
Intervention	RASB vs Control	14935 (3676)	18 (1)	1.88 (0.24, 3.86)	0.34 (-0.19, 0.93)	0.72 (0.02, 0.99)	0.12 (0.02, 0.31)
	RASB v CCB	2076 (643)	4 (1)	-0.91 (-36.22, 31.05)	-0.61 (-15.70, 12.97)	0.87 (0.01, 1.00)	0.06 (0.01, 0.47)
	Immunosuppression	1277 (222)	10 (1)	0.96 (0.16, 1.97)	-0.14 (-0.56, 0.34)	0.97 (0.13, 1.00)	0.06 (0.01, 0.49)
Disease where ACR > 30	Diabetes	15560 (3204)	10 (5)	1.17 (-0.01, 2.23)	0.22 (-0.16, 0.54)	0.86 (0.02, 0.99)	0.06 (0.01, 0.22)
	Glomerular	1427 (253)	11 (2)	1.05 (0.20, 2.26)	-0.17 (-0.60, 0.34)	0.97 (0.11, 1.00)	0.06 (0.01, 0.50)
	Other CKD	5747 (2170)	22 (5)	0.72 (-1.48, 5.51)	-0.06 (-0.79, 1.52)	0.70 (0.01, 0.99)	0.05 (0.01, 0.18)
Excluding EMPA-REG OUTCOME							
Overall		23387 (5817)	42 (7)	0.88 (0.25, 1.59)	0.03 (-0.18, 0.26)	0.51 (0.05, 0.90)	0.14 (0.06, 0.24)
GFR	< 60	15969 (4609)	39 (7)	0.80 (-0.20, 1.98)	-0.02 (-0.33, 0.36)	0.31 (0.00, 0.95)	0.14 (0.03, 0.24)
	≥ 60	7219 (1191)	26 (6)	0.79 (-0.04, 1.72)	0.17 (-0.12, 0.46)	0.91 (0.04, 1.00)	0.05 (0.01, 0.23)
ACR	< 30	3344 (362)	10 (4)	-2.66 (-31.87, 24.66)	-0.16 (-3.39, 2.76)	0.95 (0.02, 1.00)	0.07 (0.01, 0.52)
	≥ 30	20016 (5449)	42 (7)	0.96 (0.33, 1.68)	0.07 (-0.16, 0.31)	0.71 (0.12, 0.99)	0.10 (0.02, 0.20)
	Diabetes	14329 (3133)	9 (4)	1.10 (-0.07, 2.09)	0.24 (-0.15, 0.53)	0.87 (0.02, 0.99)	0.05 (0.01, 0.21)
Disease	Glomerular	1428 (253)	11 (2)	1.03 (0.20, 2.17)	-0.17 (-0.61, 0.32)	0.97 (0.14, 1.00)	0.06 (0.01, 0.48)
	Other CKD	7630 (2431)	22 (5)	0.69 (-0.23, 1.95)	-0.08 (-0.35, 0.29)	0.58 (0.00, 0.98)	0.07 (0.02, 0.23)

sTable 13. Trial level analysis for change in albuminuria at 6 months for the clinical endpoint with and without death for studies whose interventions has biologic plausibility as a surrogate endpoint

Event	N patients (N events)	N studies (N interv)	Beta	Intercept	R^2	RMSE
Overall						
Clinical Endpoint	29979 (3935)	41 (8)	0.89 (0.13, 1.70)	-0.07 (-0.29, 0.14)	0.47 (0.02, 0.96)	0.14 (0.03, 0.27)
Clinical Endpoint + death	29979 (5483)	41 (8)	0.85 (0.11, 1.68)	-0.07 (-0.27, 0.15)	0.39 (0.01, 0.81)	0.16 (0.08, 0.27)
ACR > 30 mg/g						
Clinical Endpoint	22544 (3749)	41 (8)	0.91 (0.19, 1.67)	-0.04 (-0.26, 0.18)	0.72 (0.05, 0.99)	0.09 (0.02, 0.22)
Clinical Endpoint + death	22544 (4957)	41 (8)	0.90 (0.18, 1.65)	-0.03 (-0.25, 0.18)	0.53 (0.03, 0.95)	0.13 (0.04, 0.25)

sTable 14. Trial level analysis for change in albuminuria at 6 months for the clinical endpoint for all studies

Group	Subgroup	N patients (N events)	Studies/Interv	Slope	Intercept	R^2	RMSE
Overall		30894 (4084)	44 (10)	0.78 (0.00, 1.58)	-0.11 (-0.32, 0.10)	0.39 (0.01, 0.93)	0.15 (0.04, 0.27)
GFR	< 60	18221 (3474)	42 (10)	0.75 (-0.14, 1.66)	-0.07 (-0.32, 0.17)	0.49 (0.00, 0.98)	0.10 (0.02, 0.25)
	≥ 60	12348 (598)	23 (6)	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*	7520 (195)	12 (7)	-8.90 (-47.29, 42.32)	-0.99 (-4.40, 3.09)	0.96 (0.02, 1.00)	0.07 (0.01, 0.55)
	≥ 30	23307 (3883)	44 (10)	0.82 (0.09, 1.57)	-0.07 (-0.29, 0.14)	0.62 (0.02, 0.99)	0.10 (0.02, 0.24)
Disease	Diabetes	21102 (2103)	10 (5)	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	1325 (174)	9 (2)	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	8467 (1807)	25 (7)	0.59 (-0.32, 1.54)	-0.15 (-0.38, 0.10)	0.68 (0.01, 0.99)	0.05 (0.01, 0.22)
Intervention	RASB vs Control	14892 (2254)	18 (1)	1.18 (-0.19, 2.67)	0.07 (-0.33, 0.46)	0.64 (0.00, 0.99)	0.11 (0.02, 0.33)
	RASB v CCB	2048 (456)	4 (1)	-0.21 (-16.21, 14.39)	-0.49 (-5.98, 4.50)	0.78 (0.00, 1.00)	0.06 (0.01, 0.49)
	Immunosuppression	1174 (151)	8 (1)	1.71 (0.12, 5.11)	-0.16 (-0.76, 0.84)	0.98 (0.09, 1.00)	0.07 (0.01, 0.66)
	Diabetes	15532 (2030)	10 (5)	1.10 (-0.76, 2.72)	0.06 (-0.45, 0.48)	0.63 (0.00, 0.99)	0.08 (0.02, 0.32)
ACR > 30	Glomerular	1324 (174)	9 (2)	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	5688 (1545)	22 (5)	0.53 (-0.38, 1.53)	-0.15 (-0.42, 0.14)	0.65 (0.00, 0.99)	0.05 (0.01, 0.21)

sTable 15: Application of albuminuria as Surrogate Endpoint in New RCT: Predicted Treatment effect on clinical endpoint and Positive Predictive Value for change in albuminuria at 12 months

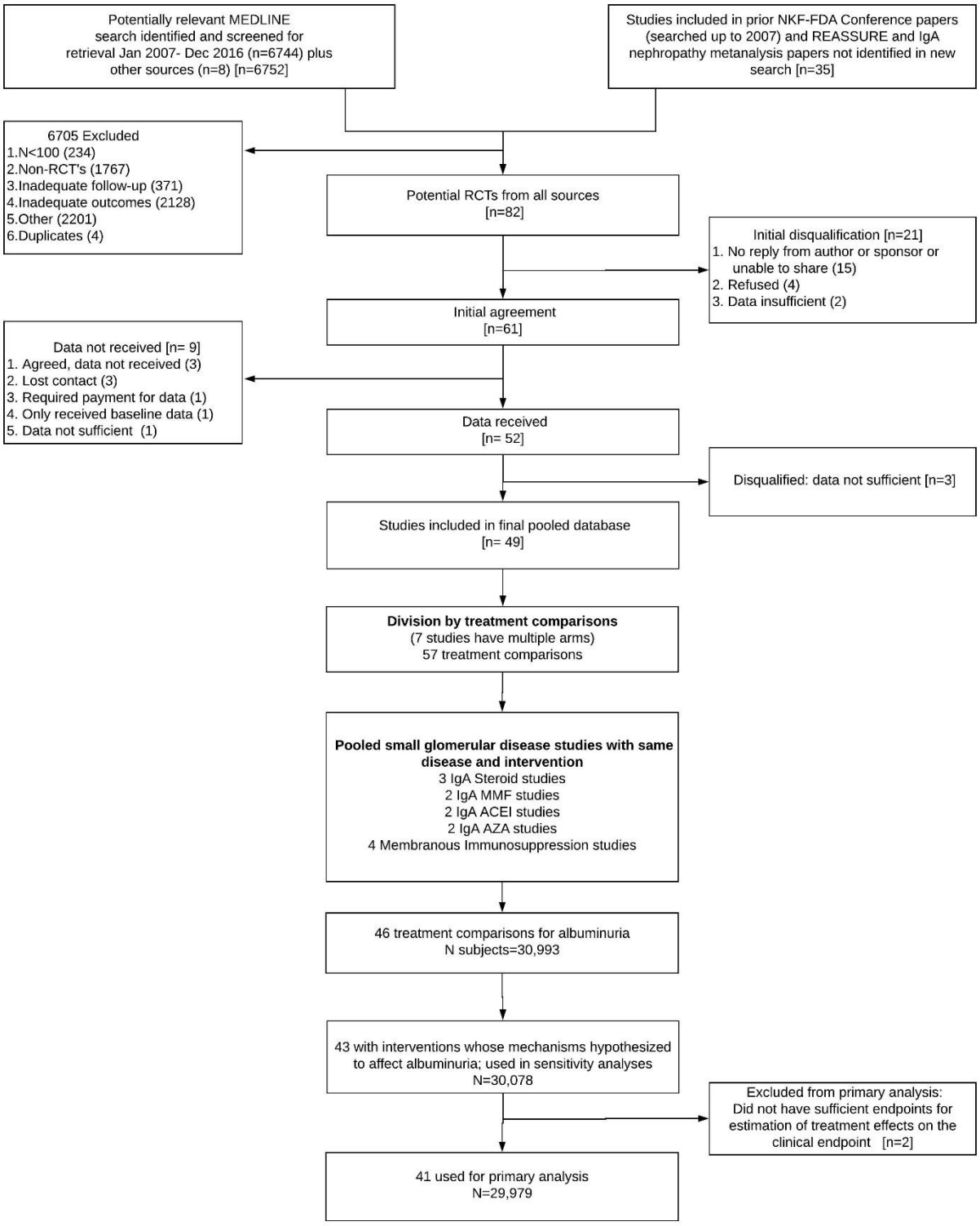
Observed Treatment effect on change in ACR	Infinite sample size in new RCT		Large New RCT		Modest New RCT	
	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV	Median HR and 95% Prediction Interval	PPV
Overall						
0.5	0.53 (0.33, 0.82)	1.00	0.53 (0.32, 0.83)	1.00	0.54 (0.31, 0.84)	0.99
0.6	0.62 (0.42, 0.90)	0.99	0.62 (0.41, 0.90)	0.99	0.63 (0.39, 0.93)	0.99
0.7	0.71 (0.49, 0.99)	0.98	0.71 (0.49, 1.00)	0.98	0.71 (0.46, 1.05)	0.96
0.8	0.79 (0.55, 1.11)	0.93	0.79 (0.55, 1.12)	0.92	0.79 (0.52, 1.20)	0.89
0.9	0.88 (0.60, 1.25)	0.80	0.87 (0.59, 1.27)	0.79	0.87 (0.57, 1.37)	0.76
1.0	0.96 (0.63, 1.42)	0.60	0.96 (0.63, 1.45)	0.60	0.95 (0.61, 1.56)	0.60
Threshold to assure PPV ≥ 97.5%	0.71		0.70		0.66	
ACR > 30 mg/g						
0.5	0.52 (0.36, 0.74)	1.00	0.52 (0.35, 0.74)	1.00	0.53 (0.31, 0.76)	1.00
0.6	0.62 (0.47, 0.81)	1.00	0.63 (0.45, 0.82)	1.00	0.63 (0.41, 0.87)	1.00
0.7	0.73 (0.56, 0.91)	0.99	0.73 (0.55, 0.92)	0.99	0.73 (0.50, 1.01)	0.97
0.8	0.84 (0.64, 1.04)	0.96	0.83 (0.63, 1.07)	0.94	0.83 (0.59, 1.19)	0.87
0.9	0.94 (0.69, 1.21)	0.69	0.94 (0.68, 1.25)	0.69	0.93 (0.65, 1.40)	0.66
1.0	1.05 (0.74, 1.43)	0.38	1.04 (0.73, 1.47)	0.40	1.03 (0.71, 1.63)	0.44
Threshold to assure PPV ≥ 97.5%	0.77		0.76		0.69	

ACR, albumin to creatinine ratio. 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.

sFigure 1. Bias assessment for included studies

	Random sequence generation	Allocation concealment	Blinding of participants	Blinded outcome assessment	Incomplete outcome data	Selective reporting
Kamper	+	+	-	+	?	+
Ihle/Kincaid	?	?	+	+	+	+
Hou	+	+	+	+	+	+
Hannedouche	+	?	-	+	?	+
Brenner	+	?	+	+	-	+
Toto	?	?	?	?	+	+
Maschio	?	?	+	+	+	+
REIN	?	?	+	+	+	+
Van Essen	?	?	+	+	+	+
AASK	?	?	+	+	+	+
HALT-PKD B	+	?	+	+	+	+
HALT-PKD A	+	+	+	+	+	+
ALTITUDE	+	+	+	+	+	+
RENAAL	+	+	+	+	+	+
IDNT	+	?	+	+	+	+
Lewis 1993	+	?	+	+	+	+
HKVIN	+	+	+	+	+	+
Praga 2003	+	+	-	+	+	+
Zucchelli	?	?	?	+	+	+
ABCD	?	?	+	+	+	+
REIN 2	+	+	-	-	+	+
Pozzi 2012	?	?	-	+	+	+
Donadio 2001	-	-	-	+	+	+
Appel	+	+	+	+	+	+
STOP-IgAN	+	?	-	+	+	+
Maes	?	?	-	+	+	+
Donadio 1999	?	?	-	+	?	+
Pozzi 2010	+	?	-	+	?	+
Pozzi 2004	+	?	-	+	+	+
Schena	+	+	-	+	+	+
Katafuchi	-	?	-	-	+	+
Lewis 1992	+	+	?	?	+	+
Chan	+	?	-	+	+	+
Ponticelli 1998	+	?	-	+	+	+
Ponticelli 1989	+	+	-	+	+	+
Ponticelli 1992	?	?	?	+	+	+
Praga 2007	+	+	-	+	+	+
Ponticelli 2006	+	+	?	?	+	+
ROAD	+	+	-	+	+	+
SUN-MACRO	+	?	+	+	+	+
EMPA-REG OUTCOME	+	?	+	+	+	+

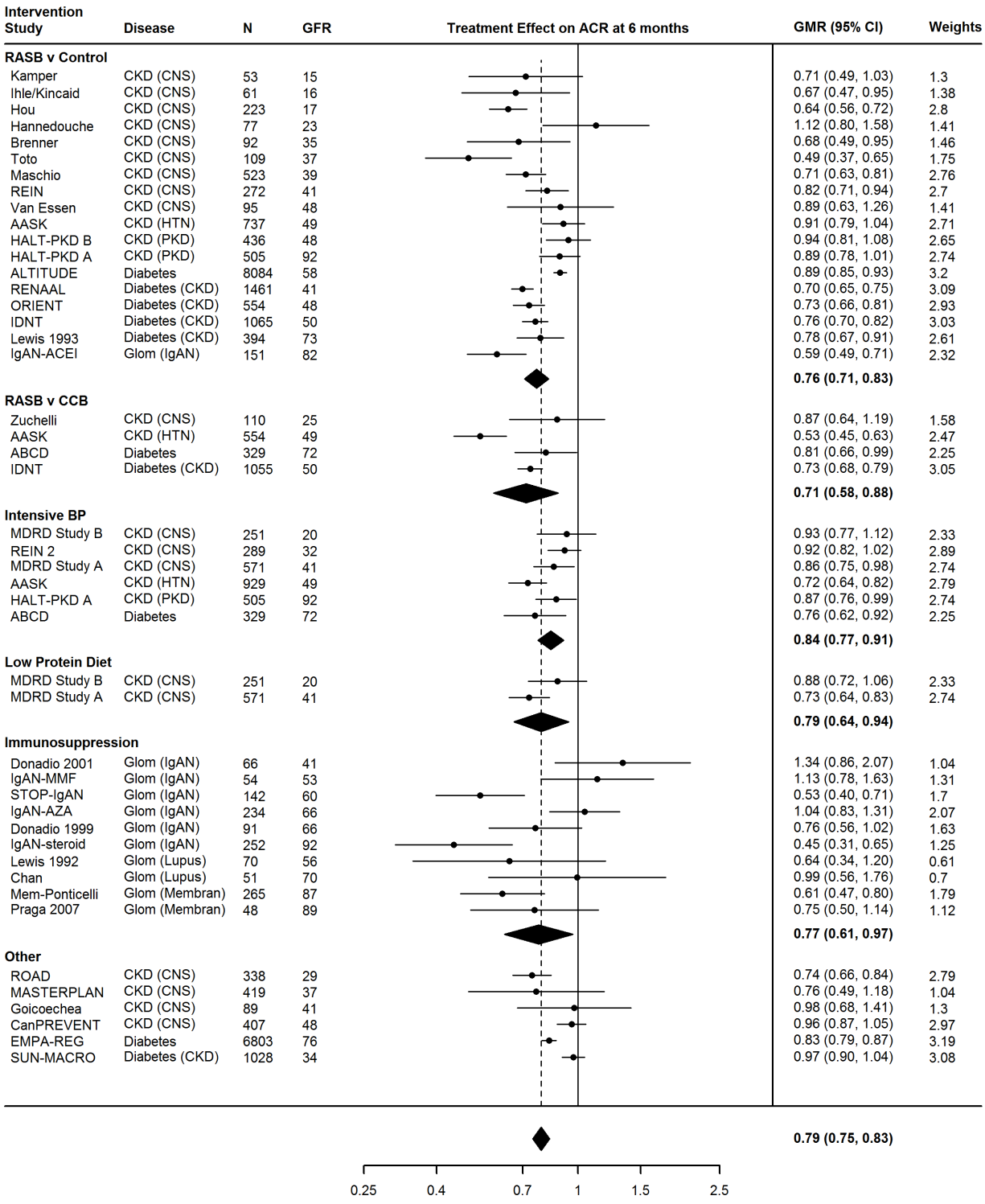
sFigure 2. Flow chart



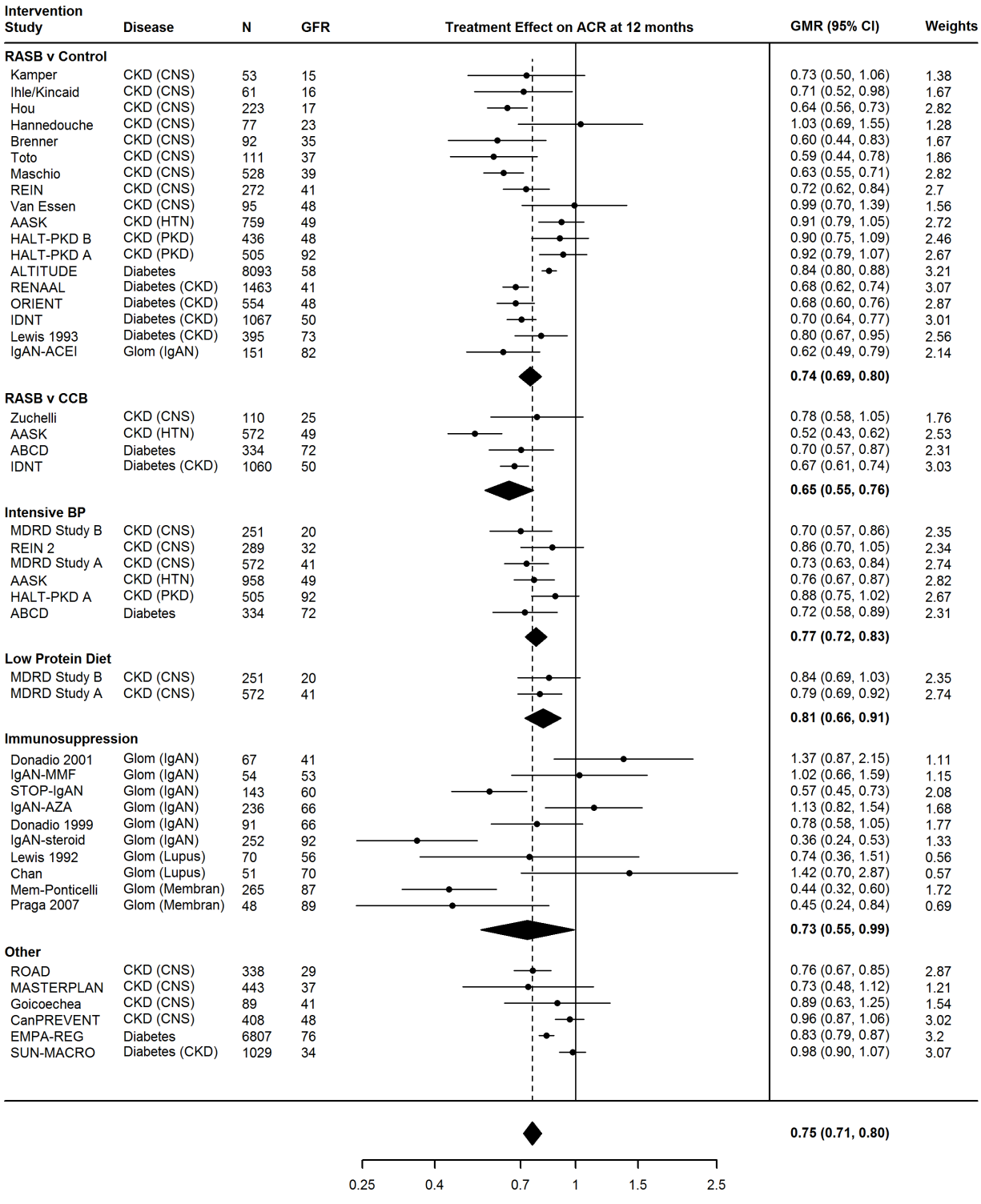
Clinical end point defined as the composite of chronic dialysis or kidney transplantation, eGFR<15 ml/min/1.73m^2 or confirmed doubling of serum creatinine. In a sensitivity analyses, we used ESKD, eGFR < 15 ml/min/1.73 m^2 and time to 40% eGFR decline as an alternative clinical endpoint and used all 43 studies.

sFigure 3. Forest plot for treatment effect on change in albuminuria

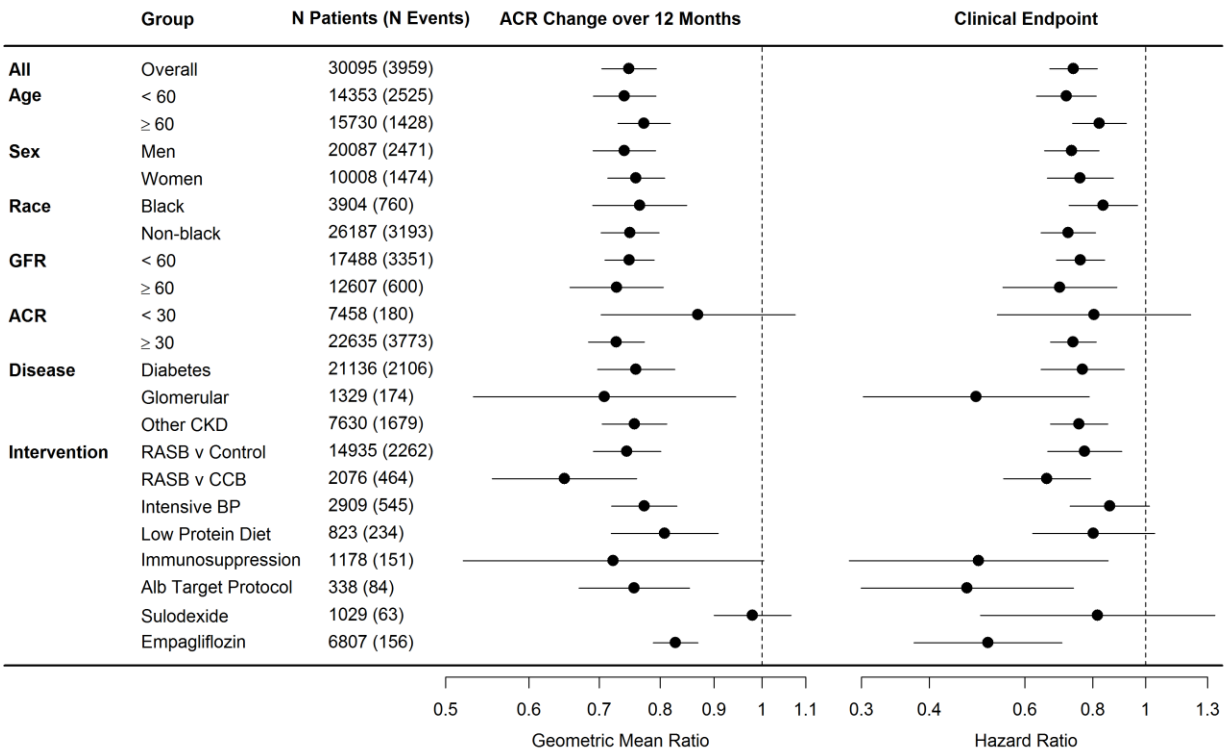
sFigure 3a. 6 months



sFigure 3b. 12 months



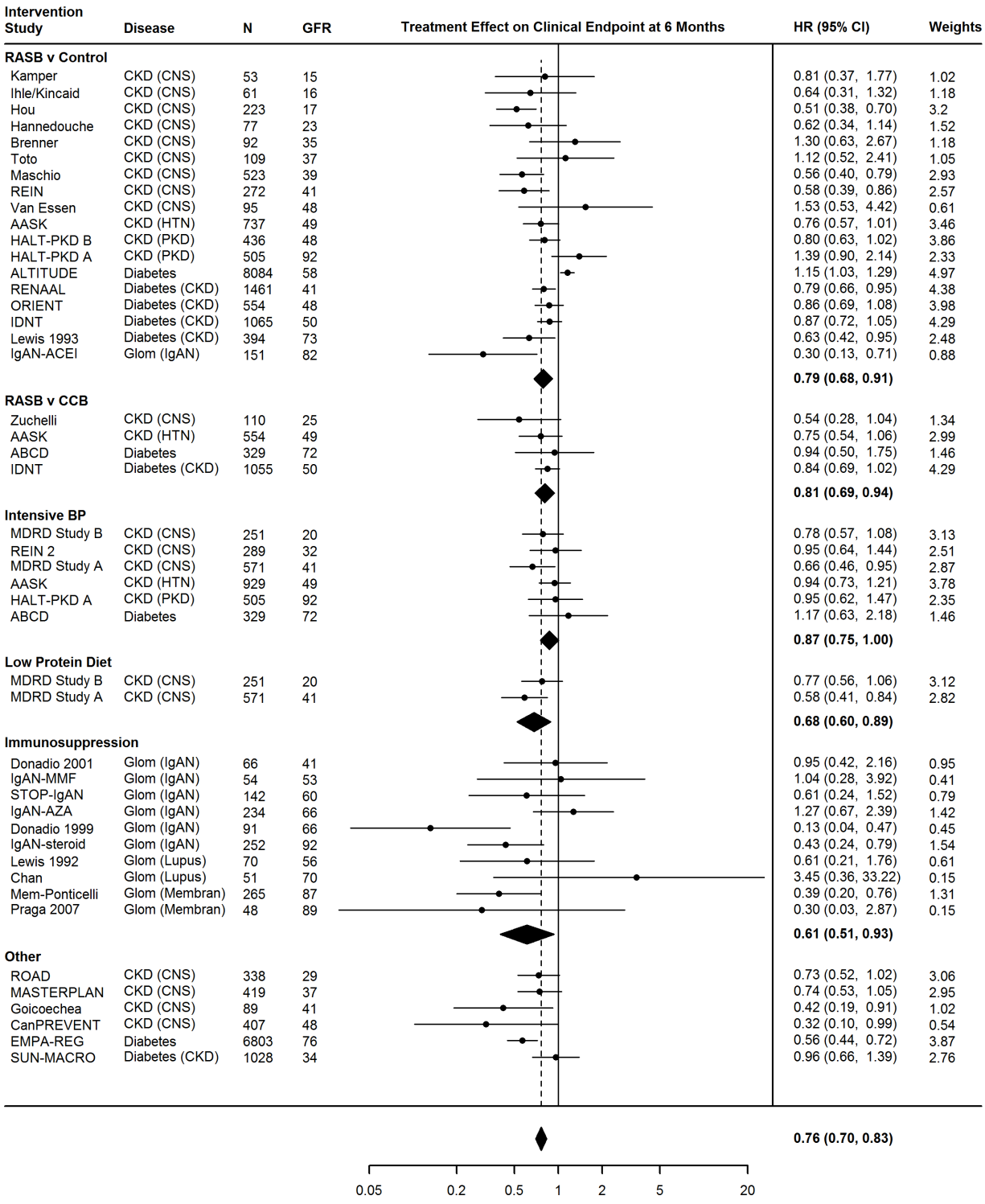
sFigure 4. Meta-analysis of change in albuminuria and clinical endpoint at 12 months by subgroups



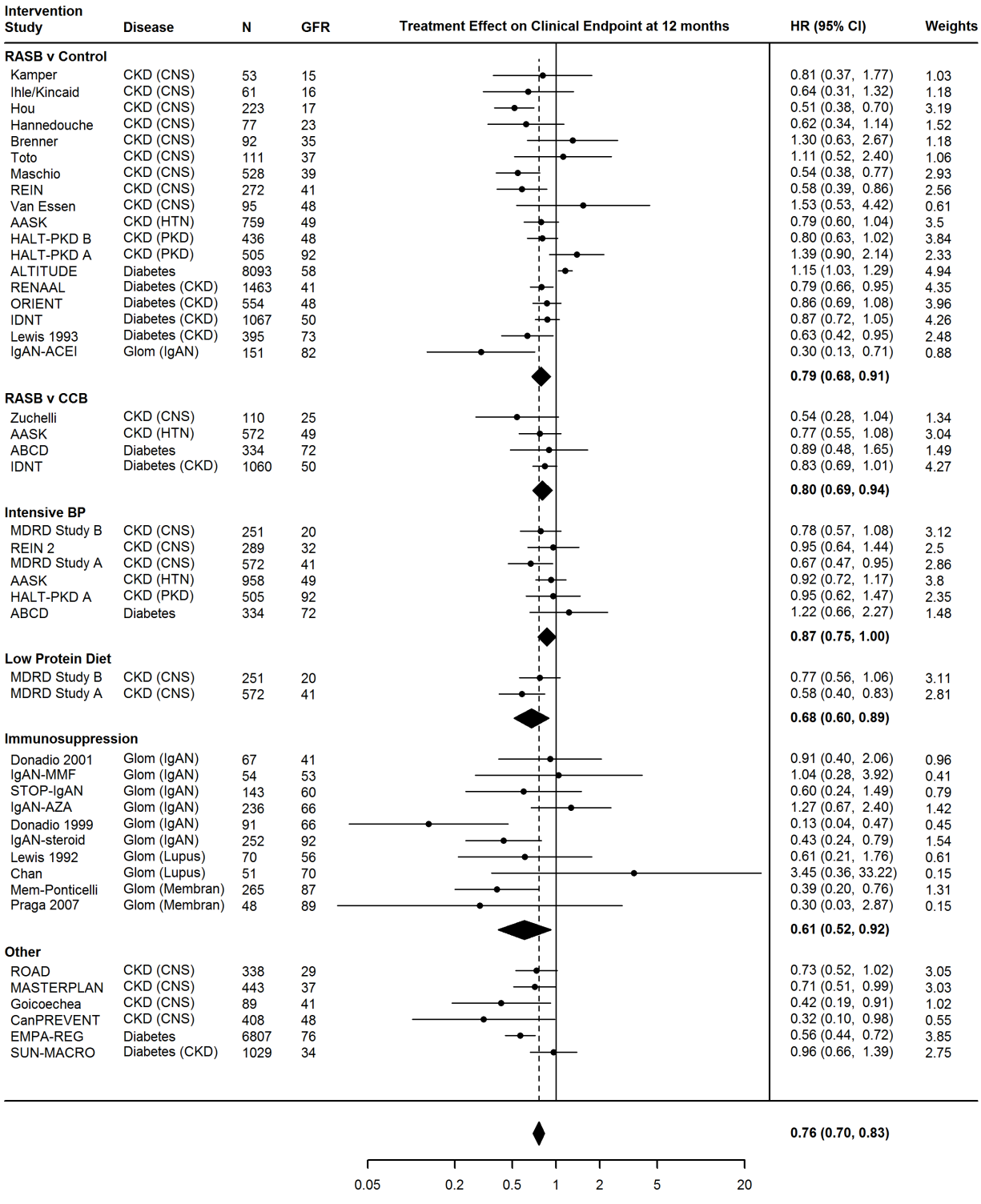
Shown are treatment effects on 12 month change in albuminuria (left) and treatment effects on clinical endpoint (right). Treatment effect on albuminuria is expressed at geometric mean ratio of ACR. To convert to percentage ACR reduction (1-GMR)*-100. Clinical endpoint is defined as treated kidney failure, 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.

sFigure 5. Forest plot for treatment effect on change in clinical endpoint

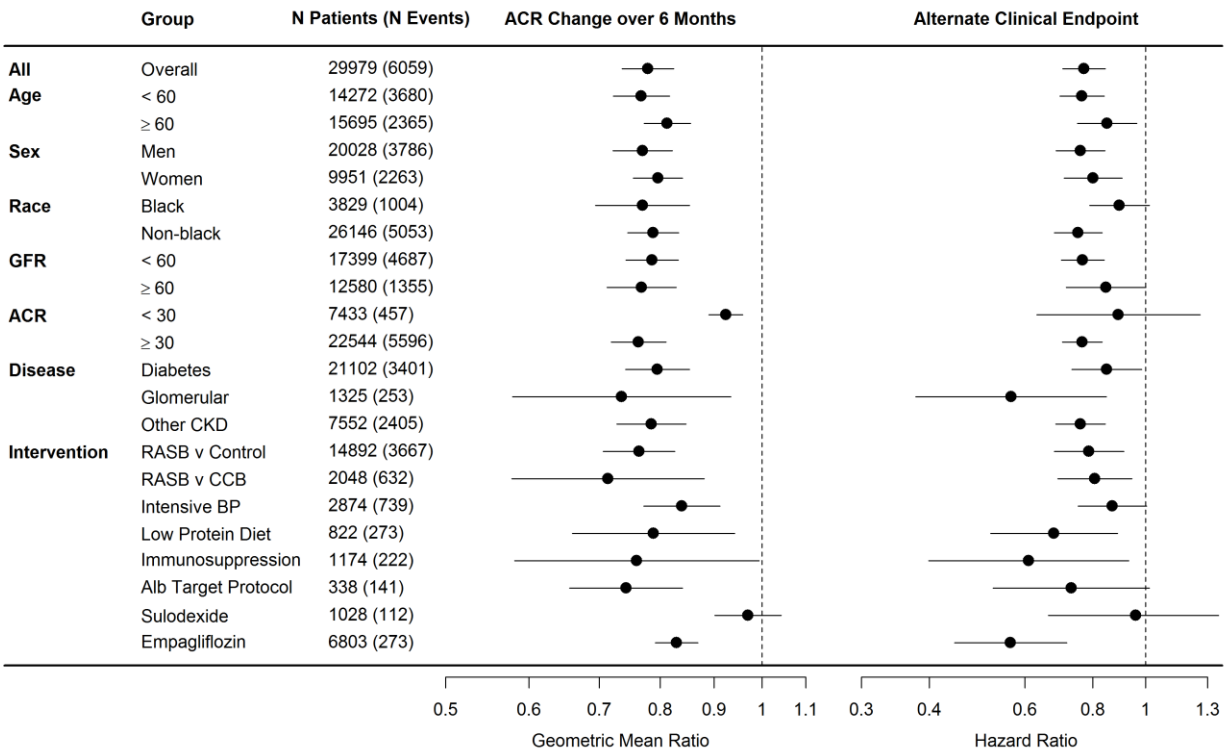
sFigure 5a. 6 months



sFigure 5b. 12 months



sFigure 6. Treatment effect on the alternative clinical endpoint

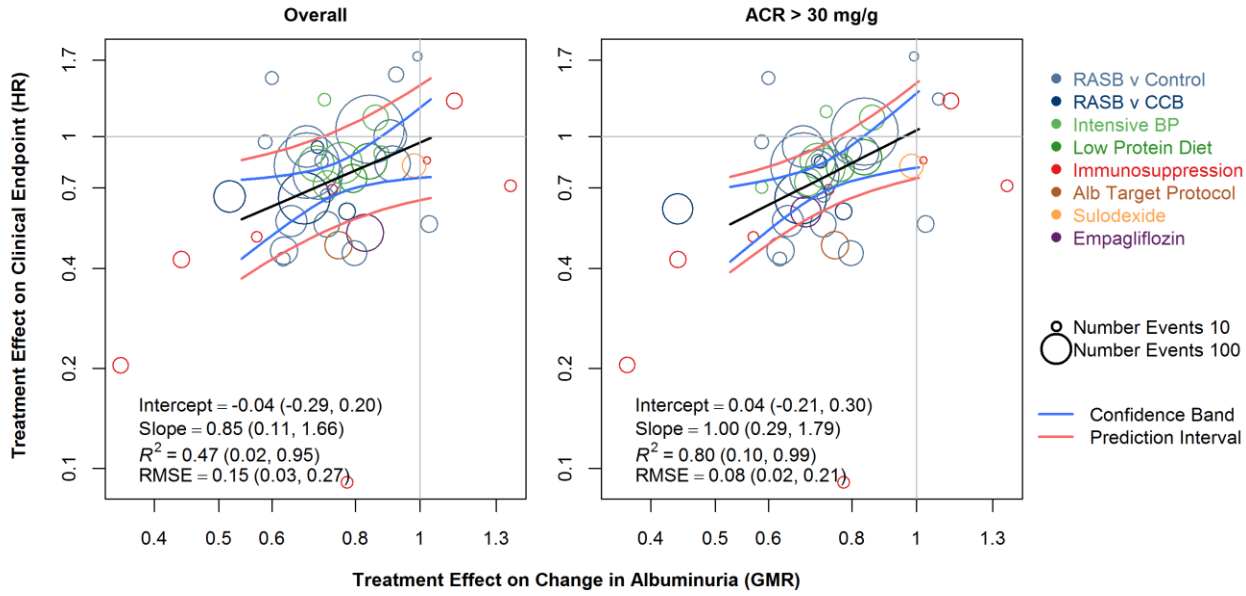


Shown are treatment effects on 6 month change in albuminuria (left) and treatment effects on alternative clinical endpoint (right). Treatment effect on albuminuria is expressed at geometric mean ratio of ACR. To convert to percentage ACR reduction (1-GMR)*-100. Alternative clinical endpoint is defined as treated kidney failure, 40% decline in GFR or eGFR < 15 ml/min/1.73m^2. Treatment effect on the alternative 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 alternative 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 5a. 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.

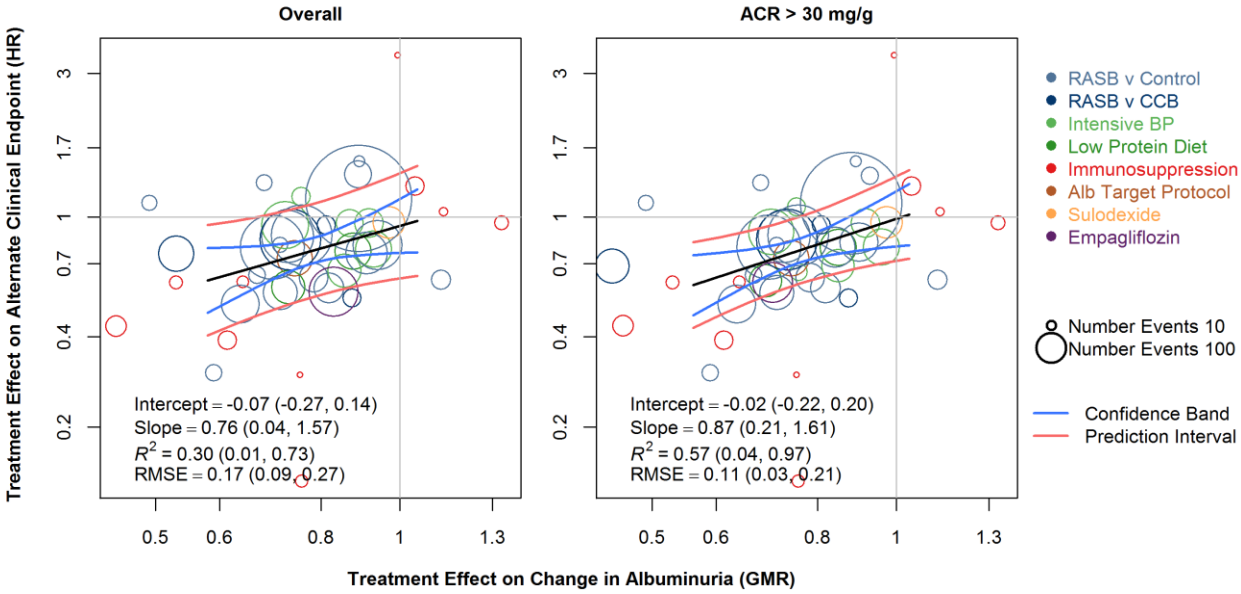
Legend for sFigures 7-9

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 or the alternative clinical endpoint on the vertical axis to estimated treatment effects on the 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. Alternative clinical endpoint is defined as treated kidney failure, 40% decline in GFR 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.

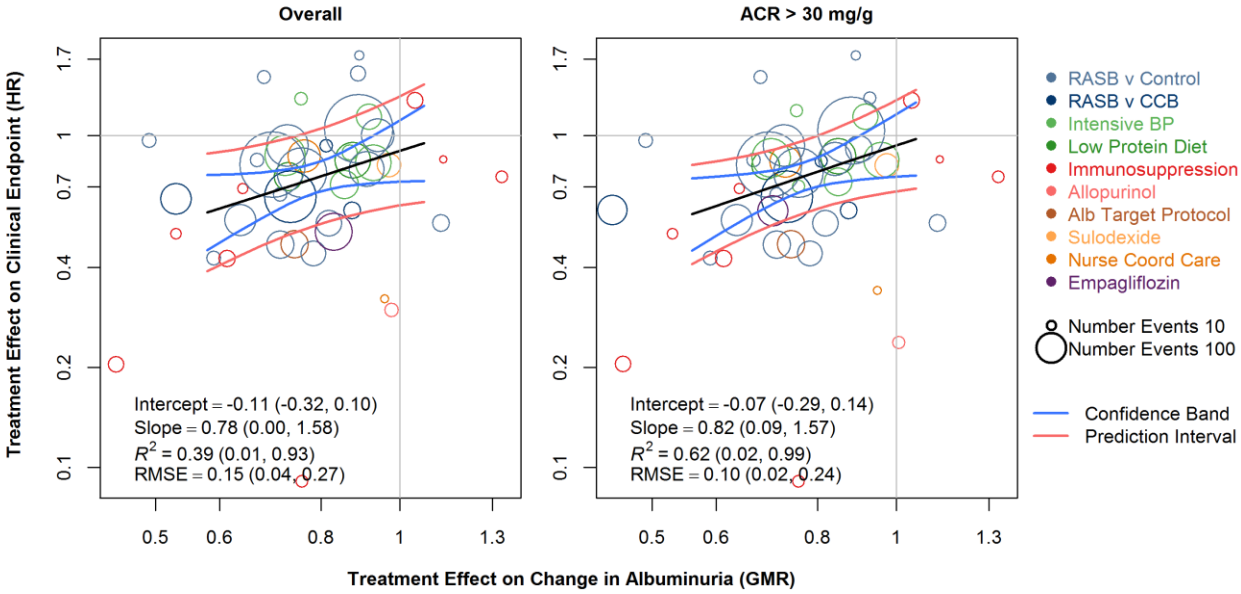
sFigure 7. Trial level analyses for the association between treatment effects on change in albuminuria at 12 months and treatment effects on the clinical endpoint, for studies whose interventions has biologic plausibility as a surrogate endpoint



sFigure 8. Trial level analyses for the association between treatment effects on change in albuminuria at 6 months and treatment effects on the alternative clinical endpoint, for studies whose interventions has biologic plausibility as a surrogate endpoint



sFigure 9. Trial level analyses for the association between treatment effects on change in albuminuria at 6 months and treatment effects in the clinical endpoint, all studies



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