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

Supplemental Methods, Tables and Figures

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Appendix 1: Abbreviations, units, and terms

AASK	African American Study of Kidney Disease and Hypertension
ABCD	Appropriate Blood Pressure Control in Diabetes trial
ACEI	angiotensin-converting enzyme inhibitor
ACR	albumin to creatinine ratio
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial
AIPRI	The Angiotensin-converting-enzyme Inhibition on Progressive Renal Insufficiency trial
Alb Protocol	albuminuria targeted protocol
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
Clinical endpoint	ESKD, doubling of serum creatinine and GFR < 15 ml/min per 1.73 m2
CI	confidence interval
CKD	chronic kidney disease
CNS	cause not specified
CSG	Collaborative Study Group
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 m2)
Glom	glomerular disease
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
HTN	hypertension
IDNT	Irbesartan Diabetic Nephropathy Trial
IgA	immunoglobulin A nephropathy
Interv	intervention
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
Mem or Mebran	membranous
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
POM model	power of the mean model
PPV	positive predictive value
RASB	renin-angiotensin system blockade
RCT	randomized controlled trial
REIN	Ramipril Efficacy In Nephropathy study
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study
ROAD	Renoprotection of Optimal Antiproteinuric Doses study
SCr	serum creatinine (mg/dL)
SD	standard deviation
SE	standard error
SHARP	Study of Heart and Renal Protection
Simva/Eze	simvastatin+ezetimibe
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial
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
AIPRI	Supported by a grant from Ciba–Geigy
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
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). Funding for the MDRD Study included the formerly named Health Care and Financing Administration (HCFA); now the Center for Medicare and Medicaid Services.
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
SHARP	Funded by Merck & Co. and Schering Plough Corporation, which merged in 2009. Additional support was provided from the Australian National Health Medical Research Council, the British Heart Foundation and the Medical Research Council.
STOP-IgAN	Supported by a grant (GFVT01044604) from the German Federal Ministry of Education and Research.
SUN-MACRO	Sponsored by Keryx Biopharmaceuticals, Inc.

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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.

At higher GFR, a trial designed to compare mean slopes of GFR decline vs. time between randomized groups may have greater statistical power than comparison of time to a GFR decline. However, acute effects are often greater at higher GFR levels, so they can in some cases pose a more serious problem at higher GFR. Design and analytic strategies proposed to overcome these limitations include evaluation of a "chronic" slope evaluated during the portion of follow-up after acute effects are expected to occur, rather than "total slope from randomization", and evaluation of reversal of acute effects following discontinuation of treatment, or both. However, there is no generally accepted method, and there is substantial controversy.

In March 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 to creatinine ratio (ACR) change and GFR slope as surrogate endpoints. Here we report on the individual patient meta-analysis of randomized control trials to provide a comprehensive assessment of the validity of using GFR slope as surrogate endpoints for trials of CKD progression using Bayesian analyses to examine the agreement

between treatment effects on GFR slope and treatment effects on the clinical endpoint to investigate how to appropriately use GFR slope as a surrogate endpoint in future randomized controlled trials (RCT).

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 the literature and developed a pooled 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. In addition, we reviewed references of published meta-analyses of RCTs including the REASSURE study.[7,8] eTable 1 lists the search terms. eTable 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 agreement and obtain access to 49 studies that had sufficient data (eFigure 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] (eFigure 1), and demonstrated that there is not likely to be differential bias on the clinical endpoint and surrogate endpoint. 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] (eTable 3). eTable 4 describes the individual treatment comparisons.

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 (BP) 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 (CNS)).

As previously described, if the study defined censoring dates were not available, we approximated a study level administrative data by using information on the length of follow-up across the participants in the study. Specifically, we computed an administrative censoring date 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 that occurred up to 1 month following administrative censoring time as often study centers do not hear about kidney failure or death

events until close out time. Patients who had events but no visits were included if event occurred before 12 months.

1.2.3 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 that occurred over the full study duration. Two studies did not have sufficient clinical endpoints and were not included in the main analyses.

1.2.4 Estimated GFR

GFR was estimated using the CKD-EPI equation 2009 creatinine equation[34]. Creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or was reduced by 5% as has previously been described[35]. eTable 4 shows which studies were calibrated.

1.2.5 GFR slope

We used a simplified linear mixed effects model based on a single slope starting at three months post randomization adjusted for baseline GFR. Under this model, the differences between the randomized groups in the mean intercepts (at 3 months follow-up), the mean slopes after 3 months, and the estimated mean changes from baseline to either 1, 2, 3 or 4 years follow-up factored by the follow-up duration from baseline represent the treatment effects on the acute, chronic, and total slopes, respectively. We accounted for between-subject variability in GFR trajectories by inclusion of random slopes and intercepts, for greater variation in individual GFR measurements at higher GFR using a power of the mean (POM) model, and for non-uniform treatment effects in which treatments slowed progression by a greater extent among patients with faster GFR decline than for patients with slower GFR decline by allowing for different between-patient slope variances in the treatment and control groups.[36] In studies in which at least 15 subjects died or reached ESRD, we accounted for informative censoring by these events by nesting the mixed model for the GFR measurements within a shared parameter model in which the risk of ESRD or death was assumed to be related to the random slopes and intercepts of the GFR part of the model.[37,38] Simplified models were used in cases where convergence could not be obtained with the full model. The full shared parameter mixed effects models were fit using the SAS (version 9.4) nonlinear mixed-effects regression procedure, NLMIXED.

1.3 Analyses

1.3.1 Trial level model for relating treatment effects on the clinical endpoint to treatment effects on GFR slope

Our analytic approach for trial-level analyses was based on the causal association framework described in Joffe and Greene (2008),[39] in which 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 have been developed by other authors, including Daniels MJ, Hughes MD (1997), Burzykowski T, Molenberghs G, Buyse M (2005), and Burzykoski T and Buyse (2006)[40-42].

The trial level analyses were performed in two stages to relate the true treatment effects on the clinical endpoint to the true treatment effects on GFR slope while accounting for error in the estimation of these effects within each trial. In the first stage, for each randomized comparison of an active treatment vs. control within each trial, separate linear regression and Cox regression analyses were performed to estimate the effects of the treatment on the GFR slope and on the clinical endpoint, respectively. Treatment effects were expressed as mean difference between the GFR slope in treatment and control groups. For the clinical endpoint, treatment effects were expressed as log transformed hazard ratios.

We choose to express GFR slope on the absolute scale (in ml/min/1.73m^2/year) instead of as a percentage change per year based on an analysis of log transformed GFR for several reasons. First, the majority of prior analyses of GFR slope in CKD RCTs have expressed slope on the absolute scale. Second, the exponents from our POM model for residual GFR variance suggested that for most studies the optimum transformation stabilizing GFR residual variance was intermediate between the untransformed and log transformed scales, and closer to untransformed. Third, we found that the trial level slope results were not substantially altered after excluding RCTs with a slow expected rate of progression. This suggests that using an absolute instead of a % difference in mean slopes is not skewing our results

To express the statistical model precisely, let i = 1, 2, …, 47 denote the 47 randomized treatment comparisons included in the analysis. 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 GFR slope 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 GFR slope 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 GFR slope 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 GFR slope in the population of trials represented by this meta-regression, σ_θ and σ_γ are the standard

deviations (SD) 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 either the chronic or total GFR slope as a surrogate endpoint if the slope of the meta-regression relating the treatment effect on the clinical endpoint to the treatment effect on the designated GFR slope endpoint differs significantly from 0, the R^2 and RMSE or the meta-regression indicates that the estimated treatment effect on the GFR slope endpoint 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 the GFR slope endpoint predicts the absence of a treatment effect on the clinical endpoint[40,41,43].

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 (expressed as a log hazard ratio) and on each GFR slope endpoint (expressed in ml/min/1.73m^2/year) 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 the GFR slope endpoints were each taken to be inverse gamma distributions with shape parameter 0.261. The scale parameter was 0.000408 for the clinical endpoint and 0.3 for the slope endpoints. The prior distribution for the clinical endpoint was selected by the investigators to assign 1/3 prior probabilities each to low treatment effect heterogeneity (which we defined as a treatment effect SDs 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 GFR slope by simulating the posterior distribution of $\alpha + \beta \times \text{True.Eff}_{slope} + \Delta_0$, where True.Eff_{slope} is the designated true treatment effect on early change in GFR slope, $\alpha + \beta \times \text{True.Eff}_{slope}$ 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 SD 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 GFR slope. 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 GFR slope 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 $\alpha + \beta \times \mathrm{True.Eff}_{slope} + \Delta_0$, but now assume that $\mathrm{True.Eff}_{slope}$ has a random distribution to reflect the uncertainty in its estimation in the new trial instead of taking $\mathrm{True.Eff}_{slope}$ to be a fixed value. Specifically, we assumed that the posterior distribution of $\mathrm{True.Eff}_{slope}$ is normally distributed with mean equal to the estimated treatment effect on GFR slope and SD given by the standard error for the estimated treatment effect on GFR slope based on the sample size. We considered SDs of 0.25, to reflect a large RCT and 0.4, corresponding to a modest-sized RCT for evaluating treatment effects on GFR slope. This posterior distribution for $\mathrm{True.Eff}_{slope}$ reflects a fully non-informative prior distribution for the treatment effect and is not influenced by the estimated distribution of treatment effects on GFR slope in the trials contributing to the meta-regression. We chose to use a fully noninformative prior for $\mathrm{True.Effslope}_{slope}$ 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 GFR slope, and not on the average treatment effect on GFR slope in the previously conducted trials.

We used a similar sampling approach from the posterior distribution of $\alpha + \beta \times \mathrm{True.Eff}_{slope} + \Delta_0$ 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 GFR slope in the new trial. These latter quantities provide estimates of the positive predictive value (PPV) 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 GFR slope. By considering the positive predictive value as a function of $\mathrm{True.Eff}_{slope}$, we determined the size of the smallest treatment effect on GFR slope that would be required to assure a positive predictive value of at least 0.975 for a benefit on the clinical endpoint.

eTable 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)

eTable 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 (ie 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 - (ESRD, 2X Scr, 40% or 30% decline)

eTable 3. Studies pooled by intervention

Study	Pooled group
Pozzi 2004[22]	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]	

eTable 4. Description of studies

Interven-tion	Disease	Study Name	Collaborators	Year	Region	Creatinine calibration required*
RASB v Control	CKD (CNS)	Kamper[44]	Anne Lise Kamper, Svend Strandgaard	1992	NA, Eur, Aus	Yes
	CKD (CNS)	Ihle/Kincaid[45]	Gavin .J. Becker, Benno Ihle, Priscilla S. Kincaid-Smith	1996	NA, Eur, Aus	Yes
	CKD (CNS)	Hou[46]	Fan Fan Hou	2006	Asia	Yes
	CKD (CNS)	Hannedouche[47]	Thierry P. Hannedouche	1994	NA, Eur, Aus	Yes
	CKD (CNS)	Brenner[48]	Barry M. Brenner	1993	NA, Eur, Aus	Yes
	CKD (CNS)	Toto[48]	Robert Toto	1993	NA, Eur, Aus	Yes
	CKD (CNS)	AIPRI[49]	Guiseppe Maschio, Francesco Locatelli	1996	NA, Eur, Aus	Yes
	CKD (CNS)	REIN[50]	Giuseppe Remuzzi, Piero Ruggenenti	1999	NA, Eur, Aus	Yes
	CKD (CNS)	Van Essen[51]	Paul E. de Jong, GG van Essen	1997	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[52]	Ronald D. Perrone, Vicente Torres, Arlene Chapman, Godela Brosnahan	2014	NA	No
	CKD (PKD)	HALT-PKD B[13]	Ronald D. Perrone, Vicente Torres, Arlene Chapman, Godela Brosnahan	2014	NA	No
	Diabetes	ADVANCE[53]	Vlado Perkovic	2008	International	Yes
	Diabetes	ALTITUDE[32]	Hans-Henrik Parving	2012	International	No
	Diabetes (CKD)	RENAAL[54]	Dick De Zeeuw, Hiddo J Lambers Heerspink ,Barry M. Brenner, William Keane	2001	International	Yes
	Diabetes (CKD)	ORIENT[55]	Enyu Imai, Fumiaki Kobayashi, Hirofumi Makino, Sadayoshi Ito	2011	Asia	Yes
	Diabetes (CKD)	IDNT[9]	Ed Lewis, Lawrence G. Hunsicker	2001	International	Yes
	Diabetes (CKD)	Lewis 1993[27]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis, John M. Lachin	1993	NA	Yes
	Glom (IgAN)	HKVIN[15]	Philip Kam-Tao Li, CB Leung, CC Szeto, KM Chow	2006	Asia	Yes
	Glom (IgAN)	Praga 2003[14]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2003	Eur	Yes
RASB v CCB	CKD (CNS)	Zucchelli[56]	Pietro Zucchelli	1992	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes
	Diabetes (CKD)	IDNT[9]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis, Lawrence G. Hunsicker	2001	International	Yes
Intensive BP	CKD (CNS)	MDRD Study B[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (CNS)	REIN 2[57]	Giuseppe Remuzzi, Piero Ruggenenti	2005	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study A[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (HTN)	AASK[10]	Tom Greene	2002	NA, Eur, Aus	Yes
	CKD (PKD)	HALT-PKD A[52]	Ronald D. Perrone, Kaleab Z. Abebe	2014	NA	No
	Diabetes	ABCD[12]	Robert W. Schrier, Raymond O. Estacio	2000	NA, Eur, Aus	Yes
Low Protein Diet	CKD (CNS)	MDRD Study A[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	CKD (CNS)	MDRD Study B[11]	Gerald J Beck, Tom Greene, John W. Kusek, Saulo Klahr	1994	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2012[24]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2012	NA, Eur, Aus	No

Intervention	Disease	Study Name	Collaborators	Year	Region	Creatinine calibration required*
Immuno-suppression	Glom (IgAN)	Donadio 2001[58]	James Donadio, Fernando Fervenza	2001	NA, Eur, Aus	Yes
	Glom (IgAN)	Appel[21]	Gerald B. Appel, Gershon Frisch	2005	NA, Eur, Aus	Yes
	Glom (IgAN)	STOP-IgAN[59]	Jürgen Floege, Thomas Rauen, Christina Fitzner; Ralf-Dieter Hilgers	2015	Eur	No
	Glom (IgAN)	Maes[20]	Bart Maes	2004	NA, Eur, Aus	Yes
	Glom (IgAN)	Donadio 1999[60]	James Donadio, Fernando Fervenza	1999	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2010[23]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2010	NA, Eur, Aus	Yes
	Glom (IgAN)	Pozzi 2004[22]	Francesco Locatelli, Lucia Del Vecchio, Simeone Andrulli, Claudio Pozzi	2004	NA, Eur, Aus	Yes
	Glom (IgAN)	Schena[26]	Francesco Paolo Schena, Manno Carlo	2009	Eur	No
	Glom (IgAN)	Katafuchi[25]	Ritsuko Katafuchi	2003	Asia	Yes
	Glom (Lupus)	Lewis 1992[61]	Edmund Lewis, Roger A. Rodby, Richard D. Rohde, Julia B. Lewis	1992	NA, Eur, Aus	Yes
	Glom (Lupus)	Chan[29]	Tak-Mao Chan	2005	Asia	Yes
	Glom (Membran)	Ponticelli 1998[18]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1998	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1989[17]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1989	NA, Eur, Aus	Yes
	Glom (Membran)	Ponticelli 1992[19]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	1992	NA, Eur, Aus	Yes
	Glom (Membran)	Praga 2007[28]	Manuel Praga, Fernando Caravaca, Eduardo Gutierrez, Angel Sevillano	2007	Eur	Yes
	Glom (Membran)	Ponticelli 2006[16]	Claudio Ponticelli, Patrizia Passerini, Gabriella Moroni, Giuseppe Montogrino	2006	NA, Eur, Aus	Yes
Alb Protocol	CKD (CNS)	ROAD[30]	Fan Fan Hou	2007	Asia	Yes
Sulodexide	Diabetes (CKD)	SUN-MACRO[31]	Julia B. Lewis, Jamie P. Dwyer, Edmund J. Lewis	2012	International	Yes
EMPA	Diabetes	EMPA-REG OUTCOME[33]	Christoph Wanner, Maximilian von Eynatten	2010	International	Yes
Allopurinol	CKD (CNS)	Goicoechea[62]	Marian Goicoechea, Eduardo Verde, Ursula Verdalles, Jose Luño	2015	NA, Eur, Aus	Yes
GLUC	Diabetes	ADVANCE[53]	Vlado Perkovic	2008	International	Yes
Nurse Care	CKD (CNS)	MASTERPLAN[63]	Jack F.M. Wetzels, Peter J Blankestijn, Arjan D. van Zuilen, Jan van den Brand	2014	Eur	Yes
	CKD (CNS)	CanPREVENT[64]	Brendan Barret	2011	NA, Eur, Aus	No
Simva/Eze	CKD (CNS)	SHARP[65]	Martin Landray, Will Herrington, Natalie Staplin, Colin Baigent	2011	NA, Eur, Aus	No

*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.[35] NA, Eur, Aus: study conducted in North America, Europe or Australia

eTable 5. Patient characteristics by study

Intervention	Disease	Study	N	Age	Female	Black	Diabetes	eGFR	ACR
RASB v Control	CKD (CNS)	Kamper	55	49.8 (11.7)	28 (50.9)	0 (0.0)	0 (0.0)	14.8 (9.0)	654 (264, 1558)
	CKD (CNS)	Ihle/Kincaid	67	45.5 (12.8)	34 (50.7)	0 (0.0)	0 (0.0)	16.5 (6.7)	856 (449, 1766)
	CKD (CNS)	Hou	224	44.7 (15.4)	113 (50.4)	0 (0.0)	0 (0.0)	16.8 (4.4)	1012 (635, 1338)
	CKD (CNS)	Hannedouche	98	51.2 (14.1)	47 (48.0)	0 (0.0)	0 (0.0)	23.4 (7.8)	958 (359, 1916)
	CKD (CNS)	Brenner	106	46.7 (13.2)	38 (35.8)	37 (34.9)	0 (0.0)	35.4 (17.2)	747 (154, 1883)
	CKD (CNS)	Toto	122	52.4 (11.6)	44 (36.1)	74 (60.7)	0 (0.0)	37.0 (17.5)	136 (60, 585)
	CKD (CNS)	AIPRI	562	50.9 (12.5)	157 (27.9)	0 (0.0)	0 (0.0)	38.6 (11.6)	500 (78, 1473)
	CKD (CNS)	REIN	322	48.8 (13.6)	73 (22.7)	2 (0.6)	0 (0.0)	41.5 (18.8)	1646 (916, 2599)
	CKD (CNS)	Van Essen	103	50.6 (12.9)	35 (34.0)	1 (1.0)	0 (0.0)	48.1 (19.3)	299 (60, 1497)
	CKD (HTN)	AASK	876	54.6 (10.7)	339 (38.7)	876 (100.0)	0 (0.0)	48.9 (15.8)	74 (26, 364)
	CKD (PKD)	HALT-PKD B	462	48.8 (8.2)	238 (51.5)	12 (2.6)	0 (0.0)	48.2 (11.8)	30 (17, 76)
	CKD (PKD)	HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	18 (12, 33)
	Diabetes	ALTITUDE	8150	64.4 (9.7)	2572 (31.6)	267 (3.3)	8150 (100.0)	58.4 (21.2)	284 (57, 881)
	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	15 (7, 40)
	Diabetes (CKD)	RENAAL	1513	60.2 (7.4)	557 (36.8)	230 (15.2)	1513 (100.0)	41.3 (13.2)	1307 (616, 2732)
	Diabetes (CKD)	ORIENT	566	59.2 (8.1)	175 (30.9)	0 (0.0)	566 (100.0)	47.5 (12.1)	1270 (617, 2285)
	Diabetes (CKD)	IDNT	1135	58.8 (7.7)	363 (32.0)	139 (12.2)	1135 (100.0)	50.2 (19.5)	1816 (1051, 3234)
	Diabetes (CKD)	Lewis 1993	407	34.5 (7.6)	191 (46.9)	32 (7.9)	407 (100.0)	73.2 (25.3)	1111 (605, 2299)
	Glom (IgAN)	HKVIN	109	40.5 (9.5)	79 (72.5)	0 (0.0)	3 (2.8)	75.1 (29.0)	958 (629, 1560)
	Glom (IgAN)	Praga 2003	44	31.6 (11.5)	17 (38.6)	0 (0.0)	0 (0.0)	98.1 (26.5)	1018 (659, 1437)
RASB v CCB	CKD (CNS)	Zucchelli	121	55.4 (10.9)	47 (38.8)	0 (0.0)	0 (0.0)	24.9 (10.1)	599 (251, 1557)
	CKD (HTN)	AASK	652	54.4 (10.8)	255 (39.1)	652 (100.0)	0 (0.0)	48.7 (15.8)	67 (25, 343)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	127 (56, 661)
	Diabetes (CKD)	IDNT	1128	59.2 (7.5)	400 (35.5)	147 (13.0)	1128 (100.0)	50.1 (18.7)	1740 (1009, 3059)
Intensive BP	CKD (CNS)	MDRD Study B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	425 (102, 1222)
	CKD (CNS)	REIN 2	330	54.2 (14.9)	82 (24.8)	0 (0.0)	17 (5.2)	32.3 (18.1)	1429 (906, 2194)
	CKD (CNS)	MDRD Study A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	120 (33, 668)
	CKD (HTN)	AASK	1093	54.6 (10.7)	425 (38.9)	1093 (100.0)	0 (0.0)	48.7 (15.7)	70 (25, 349)
	CKD (PKD)	HALT-PKD A	542	36.6 (8.3)	270 (49.8)	13 (2.4)	0 (0.0)	91.9 (17.7)	18 (12, 33)
	Diabetes	ABCD	392	59.0 (8.2)	130 (33.2)	63 (16.1)	392 (100.0)	72.1 (18.7)	127 (56, 661)
Low Protein Diet	CKD (CNS)	MDRD Study B	255	50.8 (12.8)	104 (40.8)	13 (5.1)	13 (5.1)	20.3 (5.8)	425 (102, 1222)
	CKD (CNS)	MDRD Study A	584	52.2 (12.2)	228 (39.0)	53 (9.1)	30 (5.1)	40.7 (11.0)	120 (33, 668)
Immunosuppression	Glom (IgAN)	Pozzi 2012	46	42.0 (11.5)	9 (19.6)	0 (0.0)	0 (0.0)	27.8 (7.0)	1497 (898, 2395)
	Glom (IgAN)	Donadio 2001	72	46.3 (13.1)	13 (18.1)	2 (2.8)	0 (0.0)	40.8 (14.4)	971 (441, 1886)
	Glom (IgAN)	Appel	29	37.9 (12.3)	5 (17.2)	0 (0.0)	0 (0.0)	42.2 (26.6)	1371 (982, 1976)
	Glom (IgAN)	STOP-IgAN	151	44.2 (12.4)	34 (22.5)	0 (0.0)	0 (0.0)	59.7 (27.6)	928 (641, 1229)
	Glom (IgAN)	Maes	34	44.8 (11.3)	10 (29.4)	0 (0.0)	0 (0.0)	62.2 (18.9)	596 (353, 1599)
	Glom (IgAN)	Donadio 1999	96	38.5 (13.4)	26 (27.1)	0 (0.0)	0 (0.0)	66.1 (22.5)	1257 (719, 2066)

Intervention	Disease	Study	N	Age	Female	Black	Diabetes	eGFR	ACR
	Glom (IgAN)	Pozzi 2010	197	39.2 (12.6)	55 (27.9)	0 (0.0)	0 (0.0)	74.7 (25.5)	1198 (898, 1617)
	Glom (IgAN)	Pozzi 2004	83	38.6 (11.7)	25 (30.1)	0 (0.0)	0 (0.0)	87.2 (21.6)	1138 (838, 1437)
	Glom (IgAN)	Schena	95	33.7 (11.1)	29 (30.5)	0 (0.0)	2 (2.1)	91.3 (23.7)	982 (790, 1497)
	Glom (IgAN)	Katafuchi	81	35.6 (11.2)	48 (59.3)	0 (0.0)	0 (0.0)	98.8 (21.4)	797 (563, 1543)
	Glom (Lupus)	Lewis 1992	79	32.6 (12.0)	66 (83.5)	17 (21.5)	0 (0.0)	56.4 (36.3)	2635 (1165, 4905)
	Glom (Lupus)	Chan	61	40.1 (9.9)	51 (83.6)	0 (0.0)	2 (3.3)	70.4 (26.3)	2359 (1557, 4216)
	Glom (Membran)	Ponticelli 1998	91	49.9 (10.7)	28 (30.8)	0 (0.0)	0 (0.0)	82.5 (19.9)	3293 (2395, 5210)
	Glom (Membran)	Ponticelli 1989	75	44.4 (10.9)	15 (20.0)	0 (0.0)	0 (0.0)	87.7 (23.0)	2874 (2275, 4731)
	Glom (Membran)	Ponticelli 1992	76	46.7 (13.3)	26 (34.2)	0 (0.0)	0 (0.0)	89.0 (25.1)	3234 (2455, 4641)
	Glom (Membran)	Praga 2007	48	46.6 (12.5)	8 (16.7)	0 (0.0)	0 (0.0)	89.3 (20.2)	4338 (2640, 5828)
	Glom (Membran)	Ponticelli 2006	31	49.3 (10.5)	12 (38.7)	0 (0.0)	0 (0.0)	92.6 (22.2)	3353 (2395, 4850)
Alb Protocol	CKD (CNS)	ROAD	339	50.9 (13.7)	126 (37.2)	0 (0.0)	0 (0.0)	29.0 (13.4)	958 (641, 1599)
Sulodexide	Diabetes (CKD)	SUN-MACRO	1110	63.5 (9.3)	256 (23.1)	115 (10.4)	1110 (100.0)	33.7 (9.7)	1075 (569, 1798)
EMPA	Diabetes	EMPA-REG	6936	63.2 (8.6)	1977 (28.5)	354 (5.1)	6936 (100.0)	76.2 (19.9)	18 (7, 72)
Allopurinol	CKD (CNS)	Goicoechea	113	71.8 (8.7)	40 (35.4)	0 (0.0)	42 (37.2)	40.5 (12.4)	35 (15, 362)
GLUC	Diabetes	ADVANCE	10876	65.7 (6.4)	4611 (42.4)	37 (0.3)	10876 (100.0)	78.3 (17.3)	15 (7, 40)
Nurse Care	CKD (CNS)	MASTERPLAN	640	60.5 (12.5)	199 (31.1)	49 (7.7)	156 (24.4)	36.7 (15.4)	147 (51, 449)
	CKD (CNS)	CanPREVENT	458	65.1 (7.5)	250 (54.6)	25 (5.5)	144 (31.4)	47.6 (9.9)	72 (48, 115)
Simva/Eze	CKD (CNS)	SHARP	6245	62.9 (11.7)	2363 (37.8)	119 (1.9)	1426 (22.8)	26.2 (12.3)	206 (44, 762)
Pooled studies	Glom (IgAN)	IgAN-ACEI	153	37.9 (10.8)	96 (62.7)	0 (0.0)	3 (2.0)	81.7 (30.1)	958 (659, 1497)
	Glom (IgAN)	IgAN-MMF	63	41.6 (12.2)	15 (23.8)	0 (0.0)	0 (0.0)	53.0 (24.7)	1078 (497, 1946)
	Glom (IgAN)	IgAN-AZA	243	39.8 (12.4)	64 (26.3)	0 (0.0)	0 (0.0)	65.8 (29.5)	1198 (898, 1737)
	Glom (IgAN)	IgAN-steroid	259	35.9 (11.5)	102 (39.4)	0 (0.0)	2 (0.8)	92.3 (22.7)	1018 (726, 1497)
	Glom (Membran)	Mem-Ponticelli	273	47.4 (11.7)	81 (29.7)	0 (0.0)	0 (0.0)	86.9 (22.7)	3174 (2395, 4790)

Note: Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation) except ACR which is shown as median (25^{th}, 75^{th} percentile). 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.

eTable 6. Distribution of the maximum visit time for each person by duration

Intervention	Disease	Study Name	Median (25th, 75th) Follow up time (months)	Mean # eGFR	Mean last visit time for eGFR
RASB v Control	CKD (CNS)	Kamper	29.0 (18.1, 37.0)	4.1	24.6
	CKD (CNS)	Ihle/Kincaid	21.2 (8.2, 24.7)	8.9	15.5
	CKD (CNS)	Hou	30.9 (15.2, 37.0)	8.6	25.4
	CKD (CNS)	Hannedouche	27.4 (12.2, 38.3)	9	24.8
	CKD (CNS)	Brenner	30.2 (10.4, 36.9)	13	24.3
	CKD (CNS)	Toto	35.2 (14.9, 37.0)	13.2	27.4
	CKD (CNS)	AIPRI	36.1 (24.3, 37.0)	14.1	28.9
	CKD (CNS)	REIN	26.5 (10.4, 36.2)	9.4	24
	CKD (CNS)	Van Essen	45.0 (31.0, 49.5)	5.4	37.8
	CKD (HTN)	AASK	53.6 (41.6, 64.9)	9.5	47.1
	CKD (PKD)	HALT-PKD B	66.0 (48.0, 78.4)	10.4	58.1
	CKD (PKD)	HALT-PKD A	72.8 (61.0, 84.7)	11.3	65.1
	Diabetes	ALTITUDE	39.0 (27.2, 45.0)	10.3	28.4
	Diabetes	ADVANCE	78.1 (72.4, 78.5)	7.2	54.2
	Diabetes (CKD)	RENAAL	34.8 (24.2, 42.7)	12.3	29.9
	Diabetes (CKD)	ORIENT	30.2 (16.5, 37.2)	16.8	28.1
	Diabetes (CKD)	IDNT	30.6 (23.2, 42.2)	5.8	26.1
	Diabetes (CKD)	Lewis 1993	38.5 (33.2, 49.2)	13.5	32
	Glom (IgAN)	HKVIN	34.9 (34.8, 35.0)	10.3	24
	Glom (IgAN)	Praga 2003	76.0 (61.0, 129.5)	8.7	91.1
RASB v CCB	CKD (CNS)	Zucchelli	36.5 (16.2, 37.0)	14.5	27.5
	CKD (HTN)	AASK	53.6 (41.6, 64.5)	9.4	46.4
	Diabetes	ABCD	61.2 (48.6, 63.1)	7.8	45.7
	Diabetes (CKD)	IDNT	30.7 (22.7, 42.1)	5.8	25.9
Intensive BP	CKD (CNS)	MDRD Study B	26.8 (17.6, 39.3)	7.8	24.5
	CKD (CNS)	REIN 2	16.7 (11.2, 29.9)	9.4	14.5
	CKD (CNS)	MDRD Study A	28.0 (22.0, 35.4)	8.4	26.9
	CKD (HTN)	AASK	53.4 (41.1, 64.6)	9.5	46.6
	CKD (PKD)	HALT-PKD A	72.8 (61.0, 84.7)	11.3	65.1
	Diabetes	ABCD	61.2 (48.6, 63.1)	7.8	45.7
Low Protein Diet	CKD (CNS)	MDRD Study B	26.8 (17.6, 39.3)	7.8	24.5
	CKD (CNS)	MDRD Study A	28.0 (22.0, 35.4)	8.4	26.9
Immuno-suppresion	Glom (IgAN)	Pozzi 2012	50.3 (34.5, 63.4)	8.4	38.6
	Glom (IgAN)	Donadio 2001	26.7 (19.1, 38.4)	6.4	27.9
	Glom (IgAN)	Appel	15.3 (9.0, 27.0)	5.1	9.8
	Glom (IgAN)	STOP-IgAN	37.6 (37.1, 38.1)	4.6	34.3
	Glom (IgAN)	Maes	45.0 (33.0, 45.0)	13.1	30.4
	Glom (IgAN)	Donadio 1999	36.4 (25.8, 43.6)	5.3	20.9
	Glom (IgAN)	Pozzi 2010	72.8 (52.6, 91.2)	9.9	52.6
	Glom (IgAN)	Pozzi 2004	102.0 (66.0, 126.0)	8.8	81.8
	Glom (IgAN)	Schena	66.0 (42.0, 78.0)	7.8	45.8
	Glom (IgAN)	Katafuchi	78.0 (60.0, 90.0)	5.9	61.6
	Glom (Lupus)	Lewis 1992	22.2 (10.3, 40.6)	25.9	25.3
	Glom (Lupus)	Chan	42.0 (36.0, 72.0)	6.9	38.2
	Glom (Membran)	Ponticelli 1998	43.0 (25.0, 55.0)	5	36.7
	Glom (Membran)	Ponticelli 1989	138.0 (60.0, 138.0)	9.8	97.4

Intervention	Disease	Study Name	Median (25th, 75th) Follow up time (months)	Mean # eGFR	Mean last visit time for eGFR
	Glom (Membran)	Ponticelli 1992	25.0 (19.0, 43.0)	4.4	28.6
	Glom (Membran)	Praga 2007	24.0 (20.0, 25.0)	11.7	15.7
	Glom (Membran)	Ponticelli 2006	25.0 (16.0, 28.0)	3.7	21.1
Alb Protocol	CKD (CNS)	ROAD	46.0 (36.0, 46.0)	9.1	32.5
Sulodexide	Diabetes (CKD)	SUN-MACRO	21.0 (15.0, 27.0)	4.4	10.2
EMPA	Diabetes	EMPA-REG OUTCOME	44.0 (36.6, 53.4)	12.1	32.7
Allopurinol	CKD (CNS)	Goicoechea	66.0 (36.0, 90.0)	5.9	51.9
GLUC	Diabetes	ADVANCE	78.1 (72.4, 78.5)	7.2	54.2
Nurse care	CKD (CNS)	MASTERPLAN	68.6 (43.9, 76.5)	14	47.4
	CKD (CNS)	CanPREVENT	34.0 (26.0, 34.0)	6.2	21.3
Simva/Eze	CKD (CNS)	SHARP	47.0 (20.1, 55.8)	8.2	37.6
Pooled Studies	Glom (IgAN)	IgAN-ACEI	35.0 (34.9, 49.0)	9.8	43.3
	Glom (IgAN)	IgAN-MMF	30.3 (15.0, 45.0)	9.5	21
	Glom (IgAN)	IgAN-AZA	66.9 (47.4, 88.2)	9.6	50
	Glom (IgAN)	IgAN-steroid	78.0 (54.0, 90.0)	7.5	62.3
	Glom (Membran)	Mem-Ponticelli	37.0 (25.0, 61.0)	6	49.3

eTable 7. Slopes (95% confidence intervals) by treatment arm for each intervention

Group level	Subgroup	N studies	N patients	Total 1y	Total 2y	Total 3y	Total 4y	Chronic
Overall	Treated	47	31520	-2.77 (-3.57, -1.97)	-2.89 (-3.46, -2.32)	-2.94 (-3.45, -2.43)	-2.96 (-3.45, -2.47)	-3.03 (-3.49, -2.57)
	Control		29100	-3.34 (-4.11, -2.56)	-3.45 (-4.04, -2.86)	-3.49 (-4.04, -2.93)	-3.50 (-4.04, -2.96)	-3.55 (-4.07, -3.02)
RASB v Control	Treated	19	13153	-4.05 (-5.17, -2.94)	-3.71 (-4.57, -2.86)	-3.60 (-4.39, -2.81)	-3.54 (-4.30, -2.77)	-3.37 (-4.09, -2.65)
	Control		13186	-4.48 (-5.68, -3.28)	-4.31 (-5.31, -3.31)	-4.25 (-5.19, -3.30)	-4.22 (-5.14, -3.29)	-4.12 (-5.00, -3.24)
RASB v CCB	Treated	4	1261	-3.21 (-6.64, 0.22)	-3.09 (-5.34, -0.84)	-3.05 (-4.95, -1.14)	-3.03 (-4.77, -1.28)	-2.96 (-4.33, -1.60)
	Control		1032	-2.29 (-6.25, 1.68)	-2.83 (-5.38, -0.29)	-3.02 (-5.20, -0.83)	-3.11 (-5.15, -1.07)	-3.39 (-5.22, -1.55)
Intensive BP	Treated	6	1594	-3.31 (-4.55, -2.08)	-3.46 (-4.82, -2.11)	-3.50 (-5.07, -1.93)	-3.53 (-5.23, -1.82)	-3.62 (-5.81, -1.44)
	Control		1602	-2.53 (-4.20, -0.86)	-3.29 (-4.91, -1.67)	-3.53 (-5.26, -1.81)	-3.66 (-5.45, -1.86)	-4.04 (-6.12, -1.95)
Low Protein Diet	Treated	2	417	-3.04 (-3.84, -2.25)	-3.14 (-3.76, -2.52)	-3.21 (-4.03, -2.40)	-3.26 (-4.24, -2.27)	-3.38 (-4.88, -1.89)
	Control		422	-4.86 (-5.42, -4.29)	-4.22 (-4.66, -3.77)	-4.02 (-4.54, -3.50)	-3.93 (-4.56, -3.30)	-3.65 (-4.60, -2.71)
Immunosuppression	Treated	8	609	1.01 (-2.37, 4.38)	-1.02 (-2.38, 0.34)	-1.46 (-2.41, -0.50)	-1.68 (-2.53, -0.82)	-2.50 (-3.34, -1.65)
	Control		627	-1.40 (-4.39, 1.60)	-2.32 (-3.86, -0.78)	-2.54 (-3.85, -1.23)	-2.63 (-3.87, -1.39)	-2.88 (-4.04, -1.71)
Alb Protocol	Treated	1	168	-3.50 (-4.55, -2.46)	-3.07 (-3.88, -2.26)	-2.93 (-3.67, -2.18)	-2.85 (-3.57, -2.14)	-2.64 (-3.29, -1.99)
	Control		171	-3.88 (-4.68, -3.07)	-3.51 (-4.15, -2.86)	-3.38 (-3.98, -2.78)	-3.32 (-3.90, -2.74)	-3.13 (-3.67, -2.60)
Sulodexide	Treated	1	539	-4.12 (-5.06, -3.18)	-4.23 (-5.15, -3.31)	-4.27 (-5.21, -3.32)	-4.28 (-5.25, -3.31)	-4.34 (-5.39, -3.29)
	Control		571	-3.92 (-4.60, -3.24)	-4.06 (-4.74, -3.39)	-4.11 (-4.81, -3.41)	-4.13 (-4.85, -3.42)	-4.20 (-4.98, -3.43)
EMPA	Treated	1	4615	-2.36 (-2.78, -1.95)	-1.41 (-1.64, -1.17)	-1.09 (-1.29, -0.88)	-0.93 (-1.13, -0.73)	-0.45 (-0.68, -0.22)
	Control		2321	-2.12 (-2.46, -1.78)	-2.14 (-2.34, -1.94)	-2.14 (-2.32, -1.97)	-2.15 (-2.32, -1.97)	-2.15 (-2.35, -1.96)
Allopurinol	Treated	1	57	0.94 (-2.00, 3.88)	-0.41 (-2.03, 1.22)	-0.86 (-2.14, 0.42)	-1.08 (-2.23, 0.07)	-1.76 (-2.82, -0.70)
	Control		56	-3.75 (-5.90, -1.61)	-3.13 (-4.34, -1.91)	-2.92 (-3.89, -1.94)	-2.81 (-3.70, -1.93)	-2.50 (-3.32, -1.68)
GLUC	Treated	1	5436	-2.49 (-2.88, -2.11)	-1.91 (-2.10, -1.71)	-1.71 (-1.86, -1.57)	-1.62 (-1.75, -1.49)	-1.32 (-1.45, -1.19)
	Control		5440	-2.44 (-2.71, -2.17)	-1.84 (-1.98, -1.70)	-1.63 (-1.74, -1.53)	-1.53 (-1.63, -1.44)	-1.23 (-1.33, -1.13)
Nurse Care	Treated	2	555	-1.41 (-2.25, -0.58)	-1.64 (-2.06, -1.21)	-1.73 (-2.28, -1.18)	-1.81 (-2.55, -1.07)	-2.01 (-3.30, -0.73)
	Control		543	-1.94 (-2.41, -1.46)	-2.10 (-2.58, -1.62)	-2.16 (-2.73, -1.59)	-2.19 (-2.80, -1.58)	-2.26 (-2.99, -1.53)
Simva/Eze	Treated	1	3116	-1.27 (-1.58, -0.97)	-1.66 (-1.86, -1.46)	-1.79 (-1.97, -1.61)	-1.85 (-2.02, -1.68)	-2.04 (-2.21, -1.87)
	Control		3129	-1.69 (-1.90, -1.47)	-1.95 (-2.10, -1.81)	-2.04 (-2.17, -1.91)	-2.08 (-2.21, -1.96)	-2.22 (-2.34, -2.09)
Diabetes	Treated	12	22844	-4.97 (-6.47, -3.48)	-4.16 (-5.44, -2.88)	-3.90 (-5.13, -2.66)	-3.76 (-4.98, -2.55)	-3.37 (-4.57, -2.18)
	Control		20637	-4.48 (-6.08, -2.88)	-4.23 (-5.65, -2.80)	-4.15 (-5.54, -2.76)	-4.11 (-5.48, -2.73)	-3.99 (-5.33, -2.64)
Glomerular	Treated	9	686	0.32 (-2.90, 3.54)	-1.43 (-2.95, 0.09)	-1.88 (-3.05, -0.72)	-2.09 (-3.12, -1.05)	-2.66 (-3.46, -1.87)
	Control		703	-2.24 (-5.51, 1.03)	-2.91 (-4.80, -1.01)	-3.09 (-4.68, -1.50)	-3.16 (-4.64, -1.68)	-3.31 (-4.59, -2.03)
Other CKD	Treated	26	7990	-2.58 (-3.18, -1.98)	-2.71 (-3.19, -2.24)	-2.74 (-3.17, -2.30)	-2.75 (-3.17, -2.32)	-2.79 (-3.20, -2.39)
	Control		7760	-3.01 (-3.80, -2.22)	-3.21 (-3.80, -2.63)	-3.27 (-3.82, -2.72)	-3.29 (-3.83, -2.76)	-3.38 (-3.93, -2.84)

Values are based on single studies under Alb Protocol, Allopurinol, EMPA, GLUC, Simva/Eze, Sulodexide; values for the rest are based on group of studies under each level

eTable 8. Treatment effects by intervention

Group	N studies	N patients	Total				Chronic
			1	2	3	4	
Overall	47	60620	0.32 (-0.15, 0.78)	0.42 (0.12, 0.73)	0.45 (0.19, 0.72)	0.47 (0.23, 0.71)	0.53 (0.32, 0.74)
RASB v Control	19	26339	0.29 (-0.39, 0.97)	0.48 (0.02, 0.94)	0.53 (0.14, 0.93)	0.56 (0.19, 0.92)	0.62 (0.34, 0.90)
RASB v CCB	4	2293	-1.04 (-2.16, 0.08)	-0.19 (-0.71, 0.33)	0.10 (-0.34, 0.53)	0.21 (-0.24, 0.67)	0.57 (-0.16, 1.30)
Intensive BP	6	3196	-0.78 (-2.01, 0.45)	-0.25 (-1.02, 0.51)	-0.05 (-0.68, 0.57)	0.05 (-0.49, 0.60)	0.42 (0.11, 0.73)
Low Protein Diet	2	839	1.82 (1.02, 2.61)	1.07 (0.45, 1.69)	0.82 (0.23, 1.42)	0.70 (0.11, 1.29)	0.32 (-0.29, 0.92)
Immunosuppression	8	1236	2.45 (0.05, 4.86)	1.41 (-0.56, 3.38)	1.03 (-0.81, 2.87)	0.84 (-0.95, 2.62)	0.25 (-1.39, 1.88)
Alb protocol	1	339	0.38 (-0.67, 1.42)	0.44 (-0.37, 1.24)	0.46 (-0.29, 1.20)	0.47 (-0.25, 1.18)	0.50 (-0.15, 1.14)
Sulodexide	1	1110	-0.20 (-1.14, 0.74)	-0.17 (-1.09, 0.75)	-0.16 (-1.11, 0.79)	-0.15 (-1.12, 0.82)	-0.14 (-1.19, 0.92)
EMPA	1	6936	-0.24 (-0.65, 0.17)	0.73 (0.50, 0.97)	1.06 (0.85, 1.26)	1.22 (1.02, 1.42)	1.70 (1.48, 1.93)
Allopurinol	1	113	4.70 (1.76, 7.64)	2.72 (1.09, 4.35)	2.06 (0.78, 3.34)	1.73 (0.58, 2.88)	0.74 (-0.32, 1.80)
GLUC	1	10876	-0.05 (-0.44, 0.33)	-0.07 (-0.27, 0.12)	-0.08 (-0.23, 0.07)	-0.08 (-0.21, 0.05)	-0.09 (-0.22, 0.04)
Nurse Care	2	1098	0.60 (-0.50, 1.70)	0.41 (-0.01, 0.84)	0.40 (0.02, 0.78)	0.40 (0.03, 0.77)	0.41 (-0.04, 0.86)
Simva/Eze	1	6245	0.41 (0.11, 0.72)	0.29 (0.09, 0.49)	0.25 (0.07, 0.43)	0.23 (0.06, 0.41)	0.17 (0.00, 0.35)
Diabetes	12	43481	-0.60 (-1.21, 0.00)	-0.03 (-0.43, 0.37)	0.17 (-0.20, 0.53)	0.26 (-0.10, 0.62)	0.57 (0.19, 0.95)
Glomerular	9	1389	2.70 (0.54, 4.85)	1.68 (-0.10, 3.47)	1.32 (-0.36, 3.00)	1.13 (-0.50, 2.76)	0.56 (-0.96, 2.08)
Other CKD	26	15750	0.40 (-0.15, 0.95)	0.42 (0.09, 0.75)	0.42 (0.16, 0.69)	0.43 (0.19, 0.66)	0.47 (0.27, 0.66)

Values are based on single studies under Alb Protocol, Allopurinol, EMPA, GLUC, Simva/Eze, Sulodexide; values for the rest are based on group of studies under each level

eTable 9 Endpoints used by study

Intervention	Disease	Study	N	Individual Endpoints, N(%)			Composite Endpoint, N (%)	
				ESKD	Doubling SCr	GFR < 15	Clinical endpoint	FU clinical endpoint, median (25^{th},75^{th})
RASB v Control	CKD (CNS)	Kamper	55	21 (38.2)	9 (16.4)	0 (0.0)	23 (41.8)	29.0 (18.1, 37.0)
	CKD (CNS)	Ihle/Kincaid	67	15 (22.4)	11 (16.4)	2 (3.0)	23 (34.3)	21.2 (8.2, 24.7)
	CKD (CNS)	Hou	224	83 (37.1)	47 (21.0)	5 (2.2)	111 (49.6)	30.9 (15.2, 37.0)
	CKD (CNS)	Hannedouche	98	26 (26.5)	25 (25.5)	14 (14.3)	37 (37.8)	27.4 (12.2, 38.3)
	CKD (CNS)	Brenner	106	15 (14.2)	13 (12.3)	8 (7.5)	24 (22.6)	30.2 (10.4, 36.9)
	CKD (CNS)	Toto	122	10 (8.2)	14 (11.5)	8 (6.6)	23 (18.9)	35.2 (14.9, 37.0)
	CKD (CNS)	AIPRI	562	2 (0.4)	77 (13.7)	51 (9.1)	88 (15.7)	36.1 (24.3, 37.0)
	CKD (CNS)	REIN	322	58 (18.0)	40 (12.4)	34 (10.6)	76 (23.6)	26.5 (10.4, 36.2)
	CKD (CNS)	Van Essen	103	7 (6.8)	10 (9.7)	4 (3.9)	10 (9.7)	45.0 (31.0, 49.5)
	CKD (HTN)	AASK	876	130 (14.8)	96 (11.0)	73 (8.3)	171 (19.5)	53.6 (41.6, 64.9)
	CKD (PKD)	HALT-PKD B	462	72 (15.6)	62 (13.4)	33 (7.1)	125 (27.1)	66.0 (48.0, 78.4)
	CKD (PKD)	HALT-PKD A	542	1 (0.2)	27 (5.0)	1 (0.2)	27 (5.0)	72.8 (61.0, 84.7)
	Diabetes	ALTITUDE	8150	218 (2.7)	427 (5.2)	280 (3.4)	528 (6.5)	39.0 (27.2, 45.0)
	Diabetes	ADVANCE	10876	25 (0.2)	125 (1.1)	43 (0.4)	142 (1.3)	78.1 (72.4, 78.5)
	Diabetes (CKD)	RENAAL	1513	338 (22.3)	360 (23.8)	105 (6.9)	488 (32.3)	34.8 (24.2, 42.7)
	Diabetes (CKD)	ORIENT	566	101 (17.8)	168 (29.7)	105 (18.6)	201 (35.5)	30.2 (16.5, 37.2)
	Diabetes (CKD)	IDNT	1135	131 (11.5)	231 (20.4)	72 (6.3)	284 (25.0)	30.6 (23.2, 42.2)
	Diabetes (CKD)	Lewis 1993	407	35 (8.6)	65 (16.0)	33 (8.1)	69 (17.0)	38.5 (33.2, 49.2)
RASB v CCB	CKD (CNS)	Zucchelli	121	21 (17.4)	22 (18.2)	10 (8.3)	32 (26.4)	36.5 (16.2, 37.0)
	CKD (HTN)	AASK	652	104 (16.0)	67 (10.3)	49 (7.5)	127 (19.5)	53.6 (41.6, 64.5)
	Diabetes	ABCD	392	0 (0.0)	22 (5.6)	5 (1.3)	22 (5.6)	61.2 (48.6, 63.1)
	Diabetes (CKD)	IDNT	1128	132 (11.7)	240 (21.3)	79 (7.0)	310 (27.5)	30.7 (22.7, 42.1)
Intensive BP	CKD (CNS)	MDRD Study B	255	134 (52.5)	63 (24.7)	16 (6.3)	146 (57.3)	26.8 (17.6, 39.3)
	CKD (CNS)	REIN 2	330	71 (21.5)	30 (9.1)	26 (7.9)	84 (25.5)	16.7 (11.2, 29.9)
	CKD (CNS)	MDRD Study A	584	43 (7.4)	74 (12.7)	45 (7.7)	93 (15.9)	28.0 (22.0, 35.4)
	CKD (HTN)	AASK	1093	174 (15.9)	120 (11.0)	90 (8.2)	222 (20.3)	53.4 (41.1, 64.6)
	CKD (PKD)	HALT-PKD A	542	1 (0.2)	27 (5.0)	1 (0.2)	27 (5.0)	72.8 (61.0, 84.7)
	Diabetes	ABCD	392	0 (0.0)	22 (5.6)	5 (1.3)	22 (5.6)	61.2 (48.6, 63.1)
Low Protein Diet	CKD (CNS)	MDRD Study B	255	134 (52.5)	63 (24.7)	16 (6.3)	146 (57.3)	26.8 (17.6, 39.3)
	CKD (CNS)	MDRD Study A	584	43 (7.4)	74 (12.7)	45 (7.7)	93 (15.9)	28.0 (22.0, 35.4)
Immuno-suppression	Glom (IgAN)	Donadio 2001	72	18 (25.0)	8 (11.1)	5 (6.9)	19 (26.4)	26.7 (19.1, 38.4)
	Glom (IgAN)	STOP-IgAN	151	7 (4.6)	6 (4.0)	5 (3.3)	13 (8.6)	37.6 (37.1, 38.1)
	Glom (IgAN)	Donadio 1999	96	16 (16.7)	3 (3.1)	3 (3.1)	17 (17.7)	36.4 (25.8, 43.6)
	Glom (Lupus)	Lewis 1992	79	15 (19.0)	9 (11.4)	8 (10.1)	17 (21.5)	22.2 (10.3, 40.6)

Intervention	Disease	Study	N	Individual Endpoints, N(%)			Composite Endpoint, N (%)	
				ESKD	Doubling SCr	GFR < 15	Clinical endpoint	FU clinical endpoint, median (25^{th},75^{th})
Alb protocol	CKD (CNS)	ROAD	339	58 (17.1)	65 (19.2)	17 (5.0)	85 (25.1)	46.0 (36.0, 46.0)
Sulodexide	Diabetes (CKD)	SUN-MACRO	1110	21 (1.9)	26 (2.3)	38 (3.4)	64 (5.8)	21.0 (15.0, 27.0)
EMPA	Diabetes	EMPA-REG OUTCOME	6936	26 (0.4)	138 (2.0)	25 (0.4)	159 (2.3)	44.0 (36.6, 53.4)
Allopurinol	CKD (CNS)	Goicoechea	113	17 (15.0)	29 (25.7)	22 (19.5)	30 (26.5)	66.0 (36.0, 90.0)
GLUC	Diabetes	ADVANCE	10876	25 (0.2)	125 (1.1)	43 (0.4)	142 (1.3)	78.1 (72.4, 78.5)
Nurse Care	CKD (CNS)	MASTERPLAN	640	121 (18.9)	133 (20.8)	50 (7.8)	171 (26.7)	68.6 (43.9, 76.5)
	CKD (CNS)	CanPREVENT	458	3 (0.7)	6 (1.3)	4 (0.9)	8 (1.7)	34.0 (26.0, 34.0)
Simva/Eze	CKD (CNS)	SHARP	6245	2126 (34.0)	787 (12.6)	491 (7.9)	2494 (39.9)	47.0 (20.1, 55.8)
Pooled Studies	Glom (IgAN)	IgAN-ACEI	153	18 (11.8)	12 (7.8)	7 (4.6)	23 (15.0)	35.0 (34.9, 49.0)
	Glom (IgAN)	IgAN-MMF	63	9 (14.3)	2 (3.2)	4 (6.3)	9 (14.3)	30.3 (15.0, 45.0)
	Glom (IgAN)	IgAN-AZA	243	24 (9.9)	21 (8.6)	13 (5.3)	29 (11.9)	66.9 (47.4, 88.2)
	Glom (IgAN)	IgAN-steroid	259	20 (7.7)	30 (11.6)	18 (6.9)	30 (11.6)	78.0 (54.0, 90.0)
	Glom (Membran)	Mem-Ponticelli	273	14 (5.1)	31 (11.4)	18 (6.6)	31 (11.4)	37.0 (25.0, 61.0)

N, number of participants; ESKD, end-stage kidney disease; Scr, serum creatinine; FU, follow-up

Values are based on single studies under Alb Protocol, Allopurinol, EMPA, GLUC, Simva/Eze, Sulodexide; values for the rest are based on group of studies under each level

eTable 10. Trial level analysis for GFR slope overall and by different duration

	N Studies (N Interv)	N patients (N events)	Slope	Intercept	R^2	RMSE
1 year	47 (12)	60620 (7115)	-0.13 (-0.21, -0.05)	-0.24 (-0.32, -0.15)	0.50 (0.10, 0.80)	0.18 (0.11, 0.29)
2 year	47 (12)	60620 (7115)	-0.30 (-0.42, -0.19)	-0.14 (-0.22, -0.06)	0.83 (0.48, 0.97)	0.12 (0.06, 0.21)
3 year	47 (12)	60620 (7115)	-0.42 (-0.55, -0.30)	-0.05 (-0.14, 0.02)	0.97 (0.78, 1.00)	0.06 (0.02, 0.14)
4 year	47 (12)	60620 (7115)	-0.48 (-0.61, -0.35)	-0.01 (-0.09, 0.06)	0.99 (0.88, 1.00)	0.04 (0.01, 0.11)
Chronic	47 (12)	60620 (7115)	-0.46 (-0.62, -0.29)	0.02 (-0.09, 0.12)	0.96 (0.63, 1.00)	0.06 (0.01, 0.16)

Clinical endpoint: Dialysis (or transplant), GFR < 15 or doubling of serum creatinine; Interv. Intervention

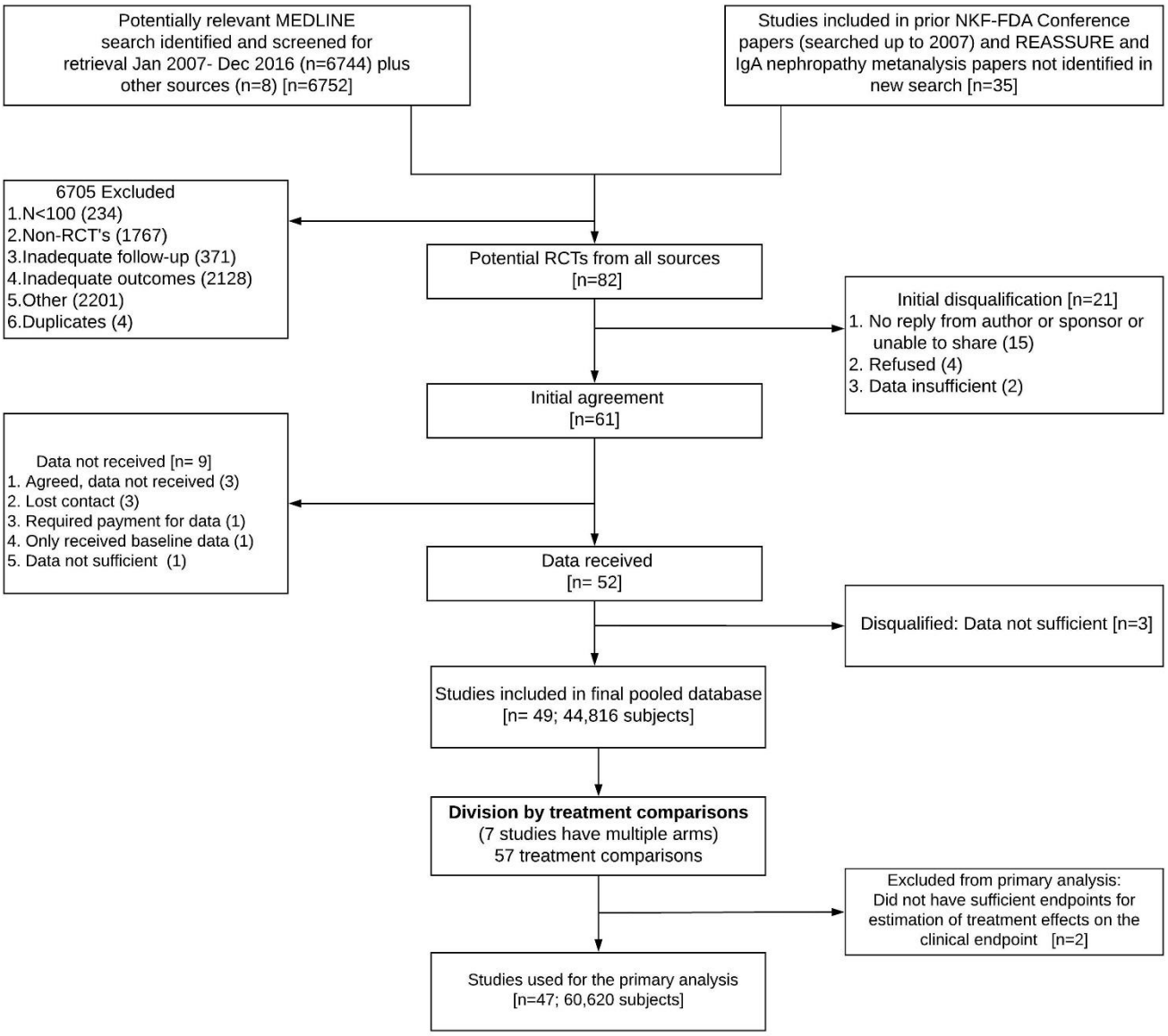
eTable 11. Summary of trial level analyses for GFR slope by subgroup

Surro-gate	Group	N Studies (N Interv)	N patients (N events)	Slope	Intercept	R^2	RMSE
1 year	Overall	47 (12)	60620 (7115)	-0.13 (-0.21, -0.05)	-0.24 (-0.32, -0.15)	0.50 (0.10, 0.80)	0.18 (0.11, 0.29)
	GFR < 60	34 (10)	28633 (6375)	-0.05 (-0.17, 0.07)	-0.22 (-0.32, -0.14)	0.11 (0.00, 0.61)	0.14 (0.06, 0.24)
	GFR ≥ 60	13 (6)	31987 (740)	-0.20 (-0.31, -0.10)	-0.31 (-0.53, -0.08)	0.90 (0.36, 1.00)	0.20 (0.02, 0.51)
	ACR < 30	6 (4)	30234 (622)	-0.12 (-0.42, 0.23)	-0.18 (-0.68, 0.40)	0.31 (0.00, 0.98)	0.29 (0.04, 0.87)
	ACR ≥ 30	41 (10)	30386 (6493)	-0.12 (-0.23, -0.01)	-0.24 (-0.34, -0.15)	0.37 (0.01, 0.78)	0.17 (0.09, 0.28)
	Diabetes	12 (6)	43481 (2431)	-0.23 (-0.42, -0.02)	-0.30 (-0.50, -0.11)	0.65 (0.02, 0.99)	0.16 (0.03, 0.37)
	Glomerular	9 (2)	1389 (188)	-0.27 (-1.08, 0.04)	0.04 (-0.76, 1.79)	0.99 (0.17, 1.00)	0.06 (0.01, 0.52)
	Other CKD	26 (8)	15750 (4496)	-0.04 (-0.16, 0.09)	-0.24 (-0.36, -0.12)	0.16 (0.00, 0.77)	0.14 (0.04, 0.29)
2 year	Overall	47 (12)	60620 (7115)	-0.30 (-0.42, -0.19)	-0.14 (-0.22, -0.06)	0.83 (0.48, 0.97)	0.12 (0.06, 0.21)
	GFR < 60	34 (10)	28633 (6375)	-0.20 (-0.43, 0.03)	-0.15 (-0.26, -0.05)	0.43 (0.00, 0.90)	0.11 (0.04, 0.21)
	GFR ≥ 60	13 (6)	31987 (740)	-0.34 (-0.48, -0.22)	-0.19 (-0.35, -0.01)	0.99 (0.77, 1.00)	0.06 (0.01, 0.30)
	ACR < 30	6 (4)	30234 (622)	-0.39 (-0.67, -0.04)	-0.17 (-0.40, 0.07)	0.95 (0.05, 1.00)	0.08 (0.02, 0.48)
	ACR ≥ 30	41 (10)	30386 (6493)	-0.29 (-0.45, -0.14)	-0.14 (-0.25, -0.04)	0.77 (0.28, 0.96)	0.12 (0.05, 0.22)
	Diabetes	12 (6)	43481 (2431)	-0.45 (-0.66, -0.24)	-0.16 (-0.27, -0.06)	0.97 (0.50, 1.00)	0.06 (0.01, 0.21)
	Glomerular	9 (2)	1389 (188)	-0.27 (-0.51, -0.07)	-0.19 (-0.60, 0.28)	0.99 (0.27, 1.00)	0.06 (0.01, 0.49)
	Other CKD	26 (8)	15750 (4496)	-0.18 (-0.39, 0.06)	-0.17 (-0.30, -0.05)	0.50 (0.01, 0.93)	0.12 (0.03, 0.24)
3 year	Overall	47 (12)	60620 (7115)	-0.42 (-0.55, -0.30)	-0.05 (-0.14, 0.02)	0.97 (0.78, 1.00)	0.06 (0.02, 0.14)
	GFR < 60	34 (10)	28633 (6375)	-0.39 (-0.62, -0.13)	-0.06 (-0.18, 0.05)	0.86 (0.18, 0.99)	0.06 (0.02, 0.16)
	GFR ≥ 60	13 (6)	31987 (740)	-0.41 (-0.57, -0.28)	-0.10 (-0.26, 0.06)	1.00 (0.87, 1.00)	0.05 (0.01, 0.22)
	ACR < 30	6 (4)	30234 (622)	-0.50 (-0.77, -0.20)	-0.07 (-0.26, 0.10)	0.98 (0.38, 1.00)	0.05 (0.01, 0.31)
	ACR ≥ 30	41 (10)	30386 (6493)	-0.41 (-0.57, -0.26)	-0.06 (-0.16, 0.04)	0.95 (0.63, 1.00)	0.07 (0.02, 0.16)
	Diabetes	12 (6)	43481 (2431)	-0.52 (-0.73, -0.32)	-0.05 (-0.15, 0.05)	0.98 (0.72, 1.00)	0.04 (0.01, 0.16)
	Glomerular	9 (2)	1389 (188)	-0.29 (-0.50, -0.09)	-0.26 (-0.62, 0.10)	0.99 (0.33, 1.00)	0.06 (0.01, 0.47)
	Other CKD	26 (8)	15750 (4496)	-0.35 (-0.59, -0.09)	-0.08 (-0.22, 0.05)	0.87 (0.16, 0.99)	0.07 (0.02, 0.18)
4 year	Overall	47 (12)	60620 (7115)	-0.48 (-0.61, -0.35)	-0.01 (-0.09, 0.06)	0.99 (0.88, 1.00)	0.04 (0.01, 0.11)
	GFR < 60	34 (10)	28633 (6375)	-0.48 (-0.71, -0.23)	-0.01 (-0.13, 0.10)	0.95 (0.47, 1.00)	0.04 (0.01, 0.12)
	GFR ≥ 60	13 (6)	31987 (740)	-0.45 (-0.62, -0.30)	-0.05 (-0.22, 0.12)	1.00 (0.89, 1.00)	0.04 (0.01, 0.20)
	ACR < 30	6 (4)	30234 (622)	-0.53 (-0.80, -0.26)	-0.01 (-0.18, 0.16)	0.99 (0.57, 1.00)	0.05 (0.01, 0.25)
	ACR ≥ 30	41 (10)	30386 (6493)	-0.47 (-0.63, -0.31)	-0.02 (-0.12, 0.07)	0.98 (0.78, 1.00)	0.04 (0.01, 0.13)
	Diabetes	12 (6)	43481 (2431)	-0.53 (-0.75, -0.33)	0.01 (-0.10, 0.12)	0.98 (0.73, 1.00)	0.04 (0.01, 0.16)
	Glomerular	9 (2)	1389 (188)	-0.29 (-0.49, -0.09)	-0.30 (-0.65, 0.05)	0.99 (0.35, 1.00)	0.06 (0.01, 0.45)
	Other CKD	26 (8)	15750 (4496)	-0.45 (-0.69, -0.20)	-0.03 (-0.16, 0.09)	0.95 (0.44, 1.00)	0.05 (0.01, 0.14)
Chronic	Overall	47 (12)	60620 (7115)	-0.46 (-0.62, -0.29)	0.02 (-0.09, 0.12)	0.96 (0.63, 1.00)	0.06 (0.01, 0.16)
	GFR < 60	34 (10)	28633 (6375)	-0.42 (-0.74, -0.11)	0.00 (-0.18, 0.15)	0.89 (0.13, 0.99)	0.06 (0.01, 0.16)
	GFR ≥ 60	13 (6)	31987 (740)	-0.50 (-0.71, -0.32)	0.10 (-0.13, 0.31)	0.99 (0.70, 1.00)	0.06 (0.01, 0.31)
	ACR < 30	6 (4)	30234 (622)	-0.48 (-0.77, -0.21)	0.16 (-0.06, 0.41)	0.98 (0.34, 1.00)	0.06 (0.01, 0.34)
	ACR ≥ 30	41 (10)	30386 (6493)	-0.45 (-0.71, -0.21)	0.00 (-0.16, 0.14)	0.94 (0.39, 1.00)	0.06 (0.02, 0.18)
	Diabetes	12 (6)	43481 (2431)	-0.48 (-0.69, -0.28)	0.15 (-0.01, 0.31)	0.98 (0.62, 1.00)	0.04 (0.01, 0.18)
	Glomerular	9 (2)	1389 (188)	-0.33 (-0.63, -0.09)	-0.42 (-0.78, -0.06)	0.99 (0.35, 1.00)	0.06 (0.01, 0.46)
	Other CKD	26 (8)	15750 (4496)	-0.49 (-0.82, -0.22)	-0.01 (-0.15, 0.14)	0.96 (0.48, 1.00)	0.04 (0.01, 0.13)

eFigure 1. Evaluation of bias

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Kamper	+	+	-	+	?	+
Ihle/Kincaid	?	?	+	+	+	+
Hou	+	+	+	+	+	+
Hannedouche	+	?	-	+	?	+
Brenner	+	?	+	+	-	+
Toto	?	?	?	?	+	+
AIPRI	?	?	+	+	+	+
REIN	?	?	+	+	+	+
Van Essen	?	?	+	+	+	+
AASK	?	?	+	+	+	+
HALT-PKD B	+	?	+	+	+	+
HALT-PKD A	+	+	+	+	+	+
ALTITUDE	+	+	+	+	+	+
ADVANCE	+	+	+	+	+	+
RENAAL	+	+	+	+	+	+
ORIENT	?	?	+	+	?	+
IDNT	+	?	+	+	+	+
Lewis 1993	+	?	+	+	+	+
HKVIN	+	+	+	+	+	+
Praga 2003	+	+	-	+	+	+
Zucchelli	?	?	?	+	+	+
ABCD	?	?	+	+	+	+
MDRD Study	+	+	-	+	?	+
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	+	?	+	+	+	+
Goicoechea	+	?	-	+	+	+
MASTERPLAN	+	?	-	-	?	+
CanPREVENT	-	+	-	+	?	+
SHARP	+	+	+	+	+	+

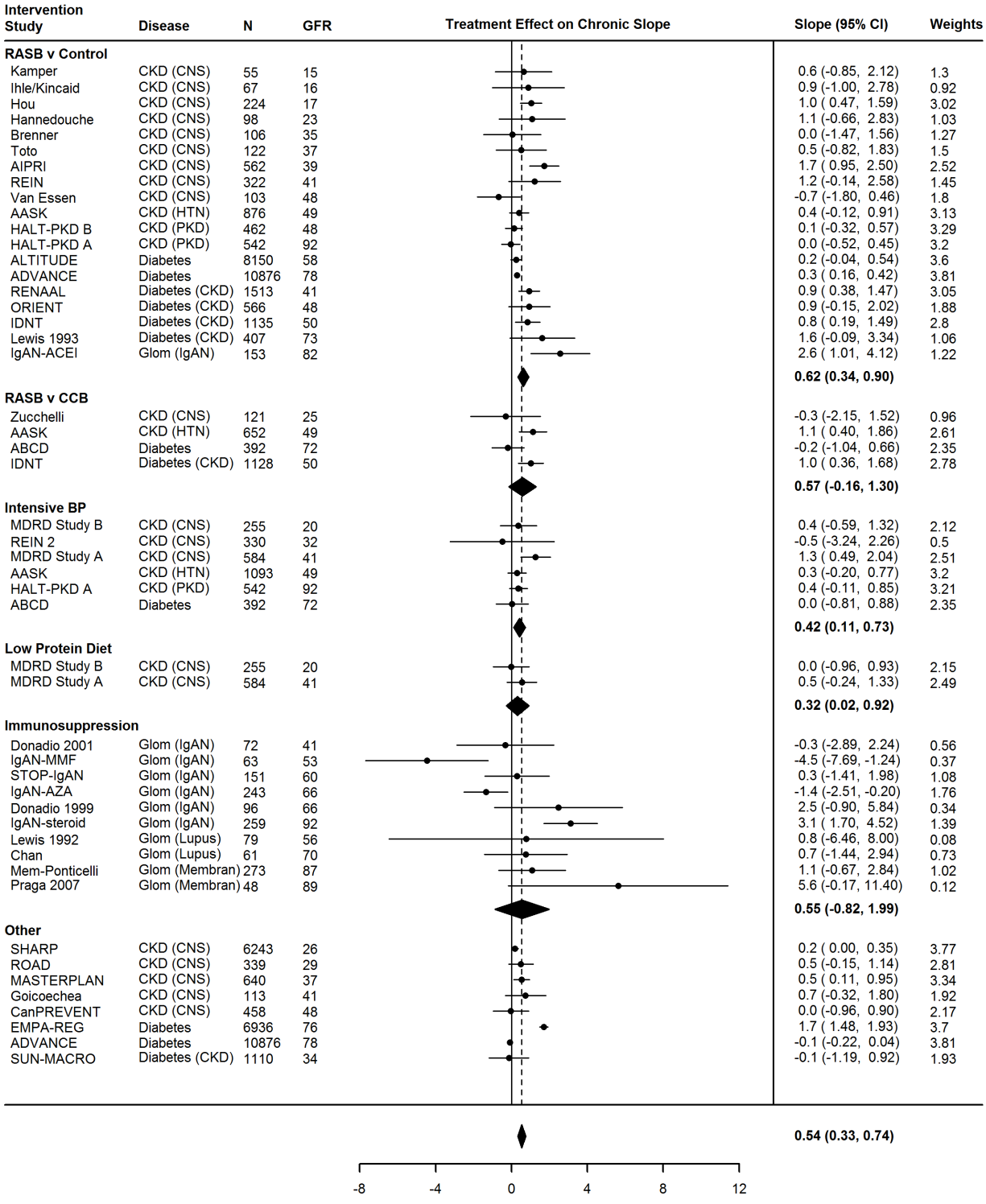
eFigure 2. Flowchart



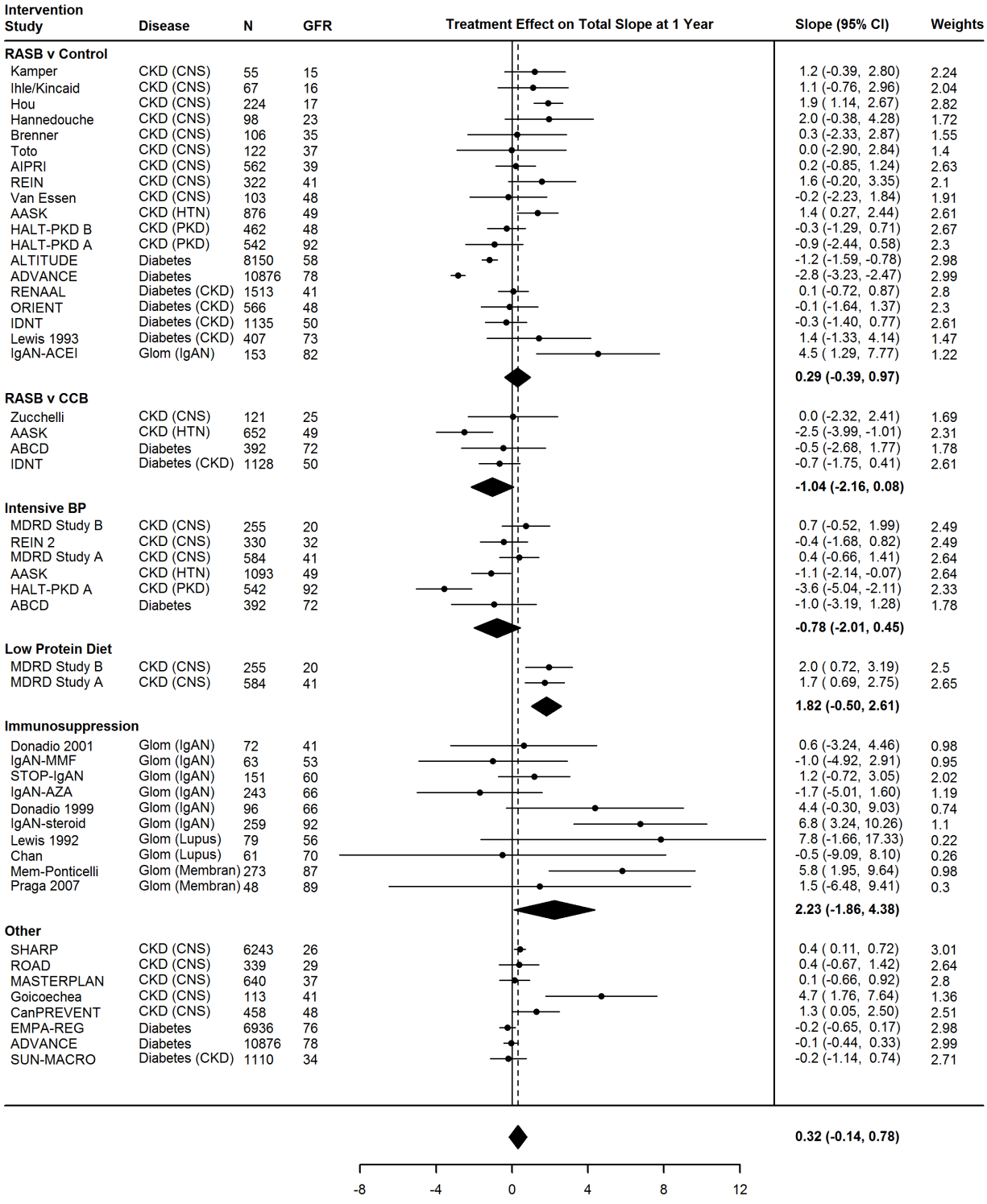
Legend for eFigures 3a-3e. Treatment effect on GFR slope

GFR refers to baseline level of GFR in each study and units are ml/min per 1.73 m^2. Treatment effects on slope are difference in GFR between treatment and control arm and are expressed as ml/min per 1.73 m^2/year. The figures display a total of 49 studies, including the two studies that were excluded from primary analysis due to insufficient number of clinical endpoints (Chan[29] and Praga 2007[28]). Dashed vertical line represents the overall slope. Solid vertical line represents no effect.

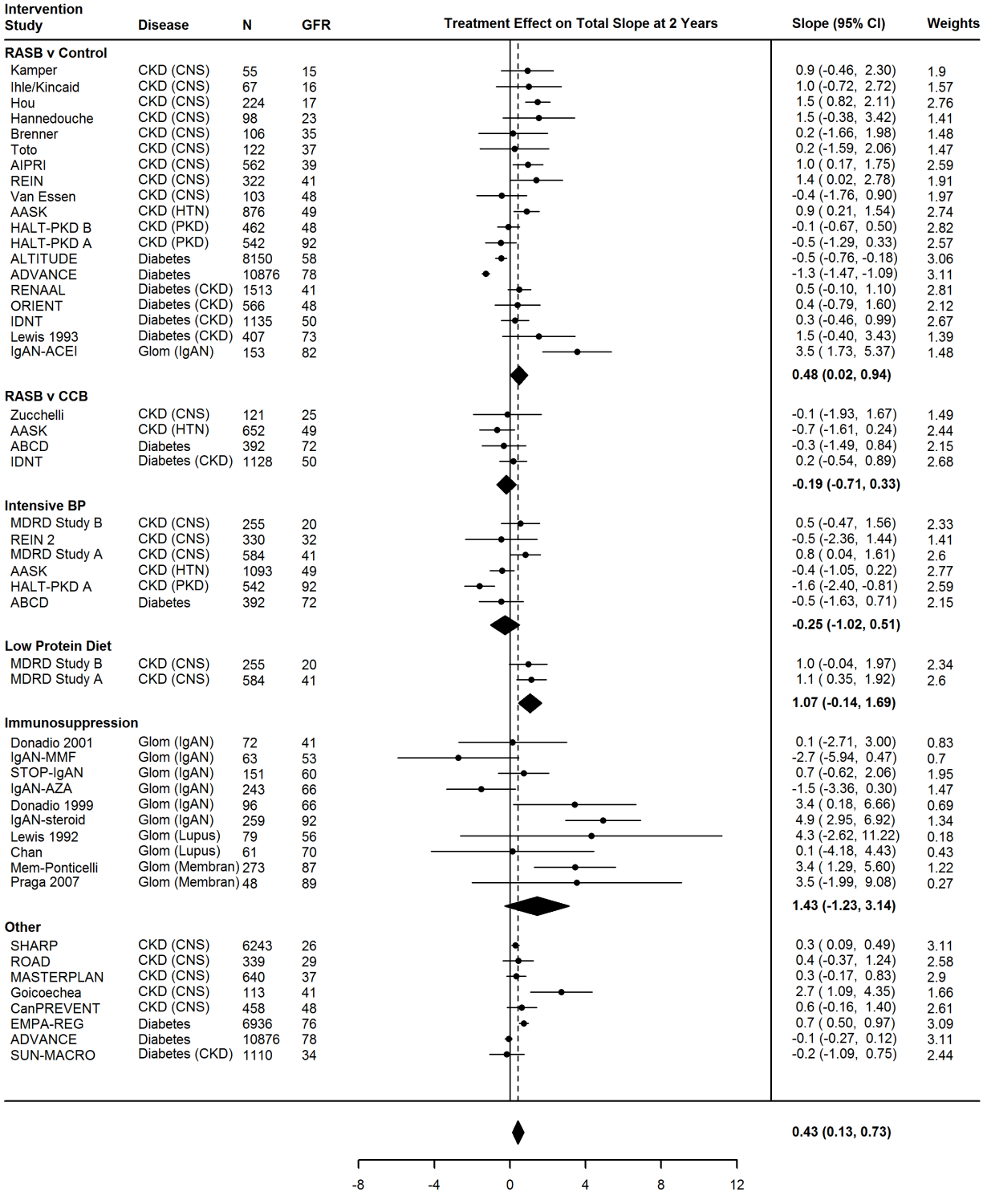
eFigure 3a. Chronic slope



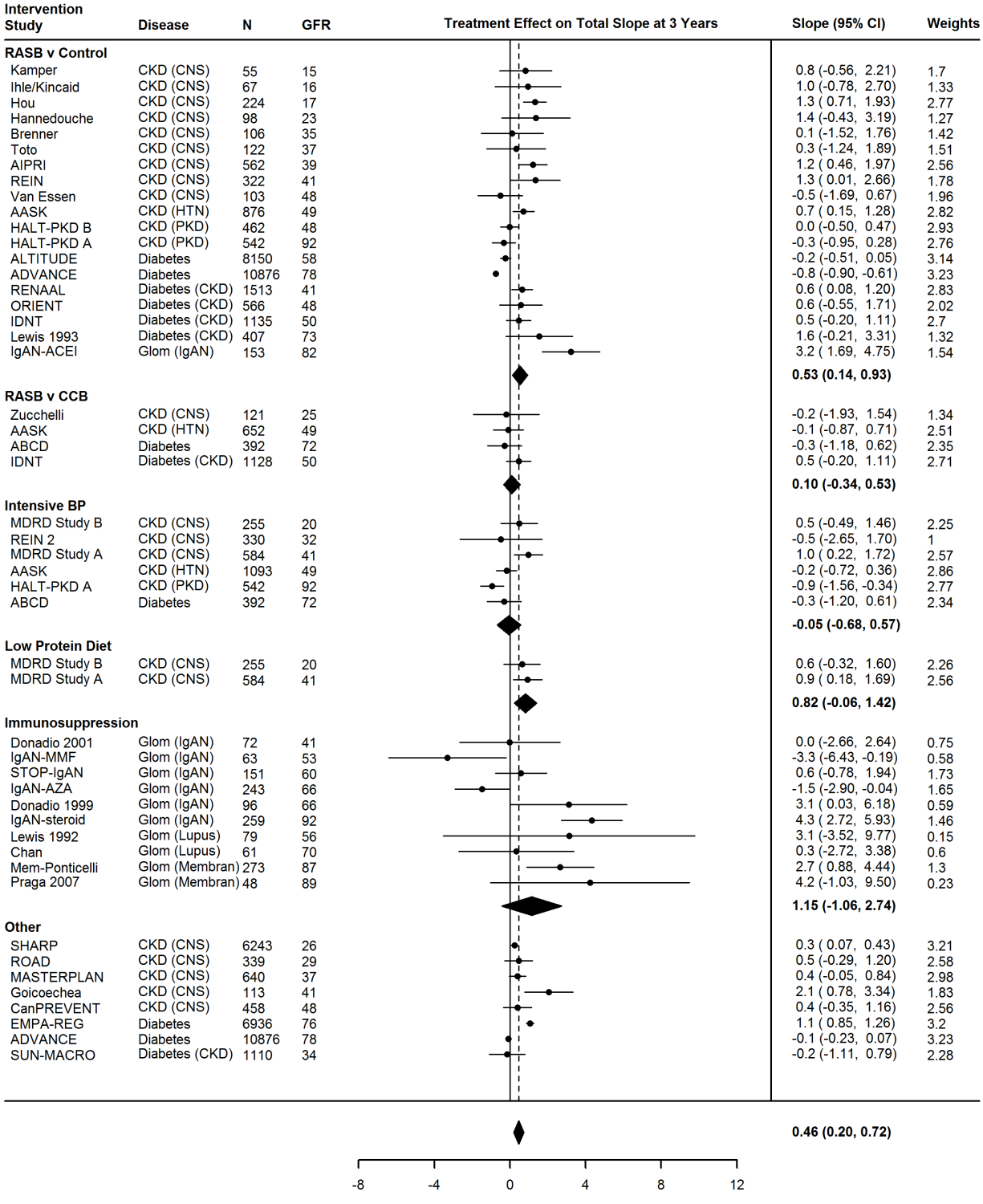
eFigure 3b. Total slope at 1 year



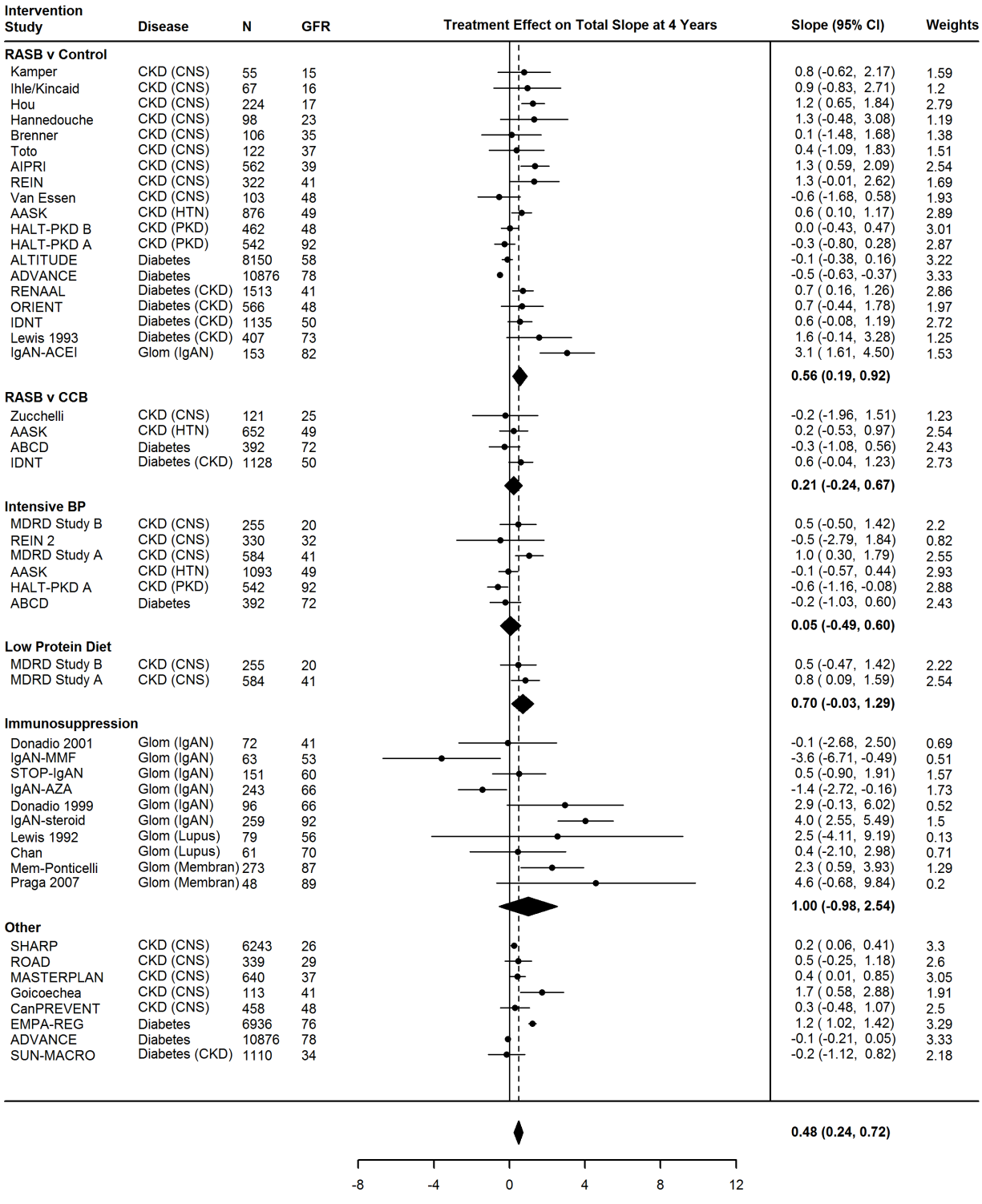
eFigure 3c. Total slope at 2 years



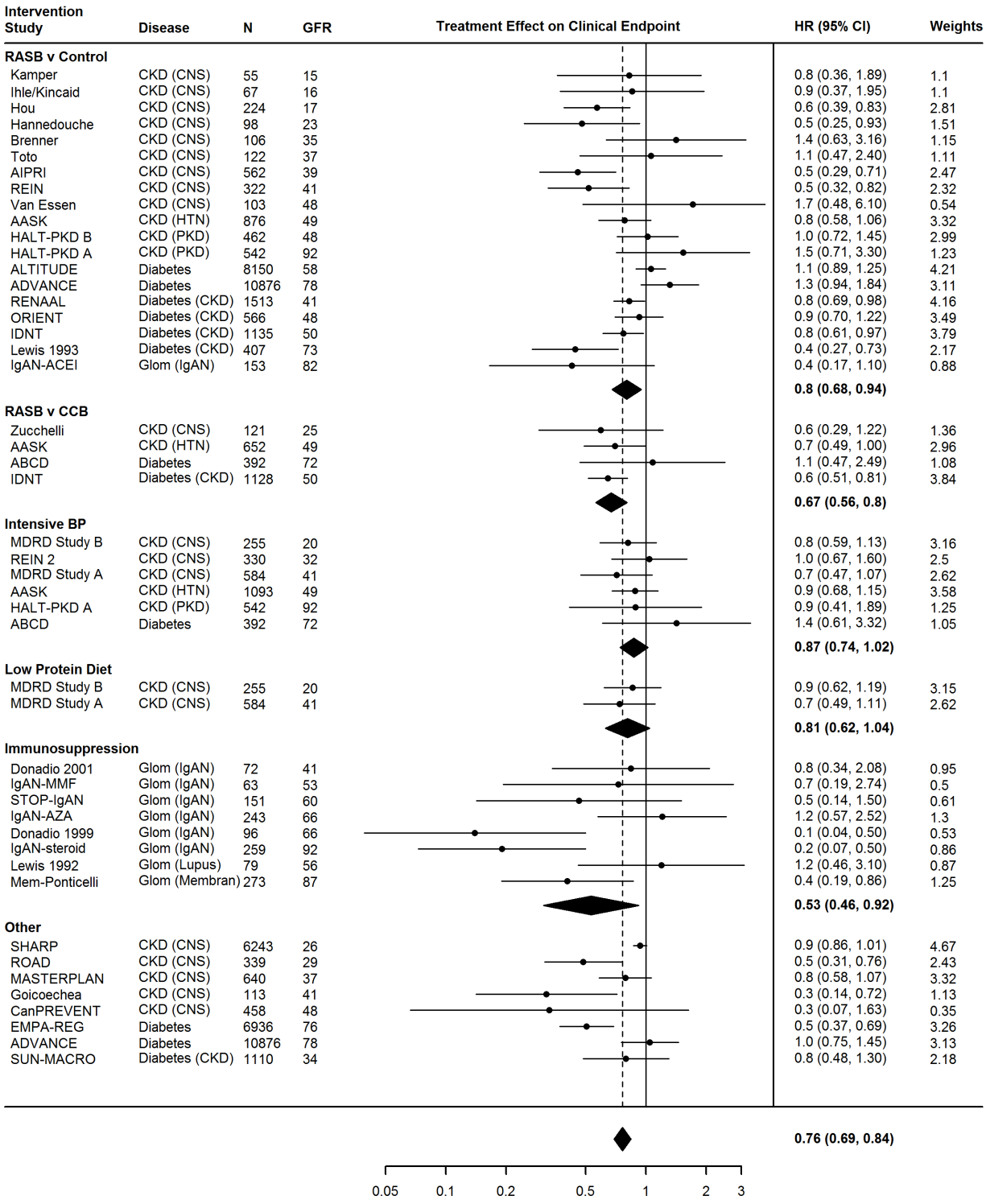
eFigure 3d. Total slope at 3 years



eFigure 3e. Total slope at 4 years



eFigure 4. Forest plot for clinical endpoint

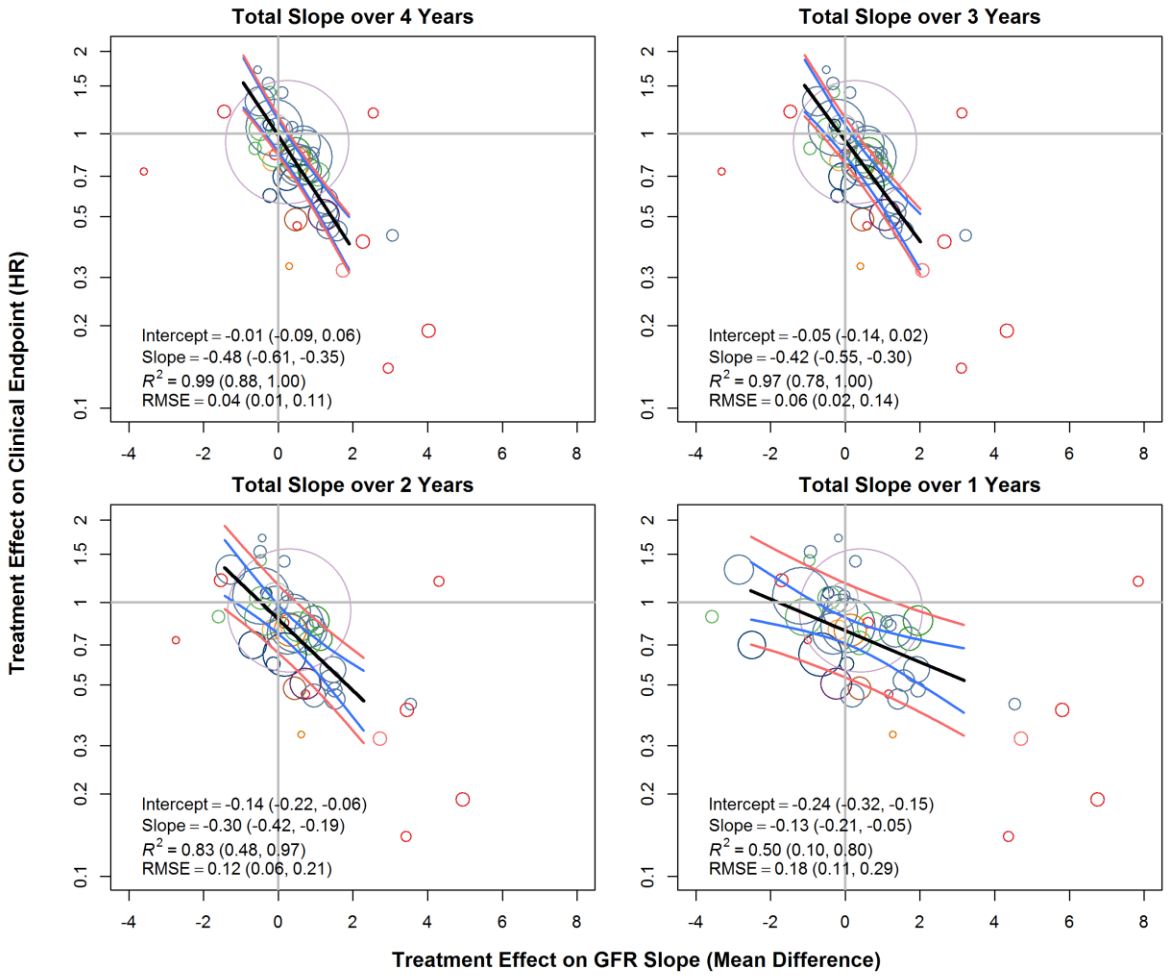


Dashed vertical line represents the overall hazard ratio (HR). Solid vertical line represents no effect.

Legend for eFigures 5-6

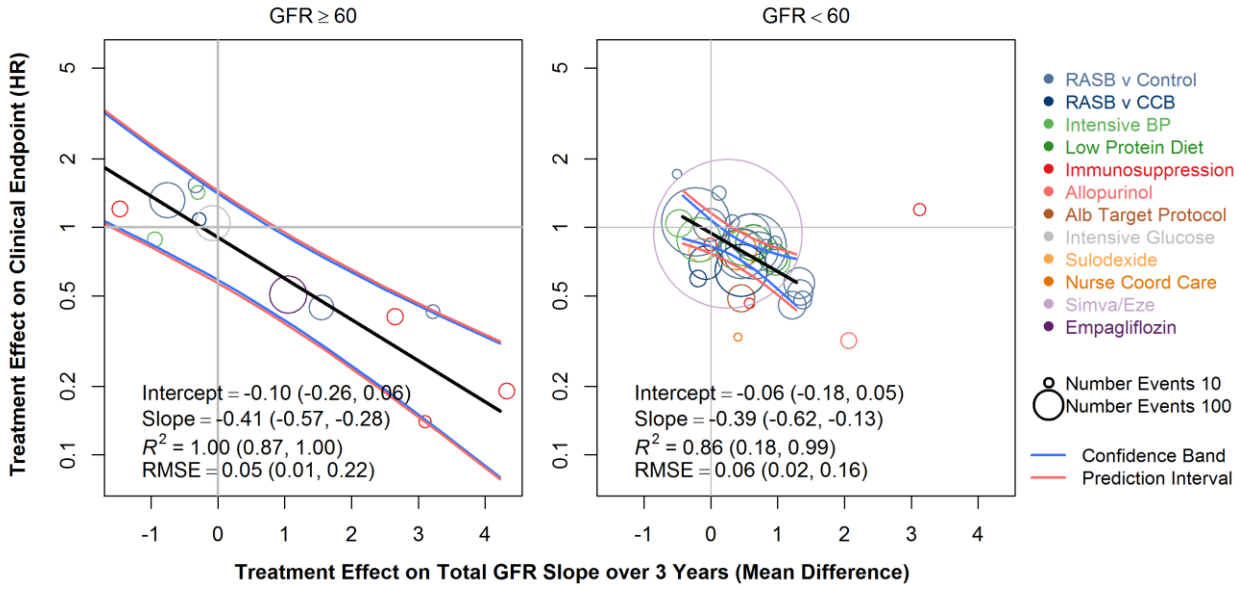
Shown is the relationship between estimated treatment effects on the clinical endpoint or alternative clinical endpoint on the vertical axis to estimated treatment effects on the GFR slope (on the horizontal axis). Treatment effects on GFR slope are expressed as mean difference in treatment – control and expressed in ml/min/1.73 m^2. Clinical endpoint is defined as treated kidney failure, doubling of creatinine or GFR < 15 ml/min/1.73 m^2. Treatment effect on the clinical endpoint is expressed as hazard ratio. 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. RASB, renin angiotensin system blockers; CCB, calcium channel blocker; BP, blood pressure; Alb, albuminuria.

eFigure 5.Trial level analyses for the association between treatment effects on total GFR slope by varying duration and treatment effect on the clinical endpoint

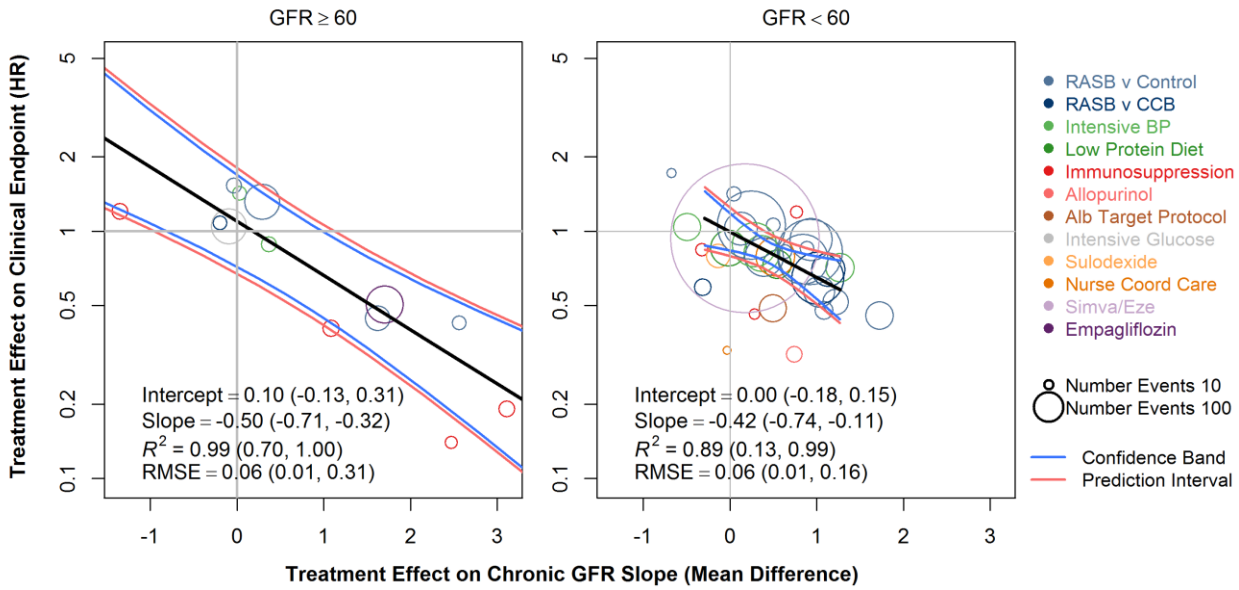


eFigure 6. Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint by level of eGFR

eFigure 6a. Total GFR slope over 3 Years



eFigure 6b. Chronic GFR slope



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