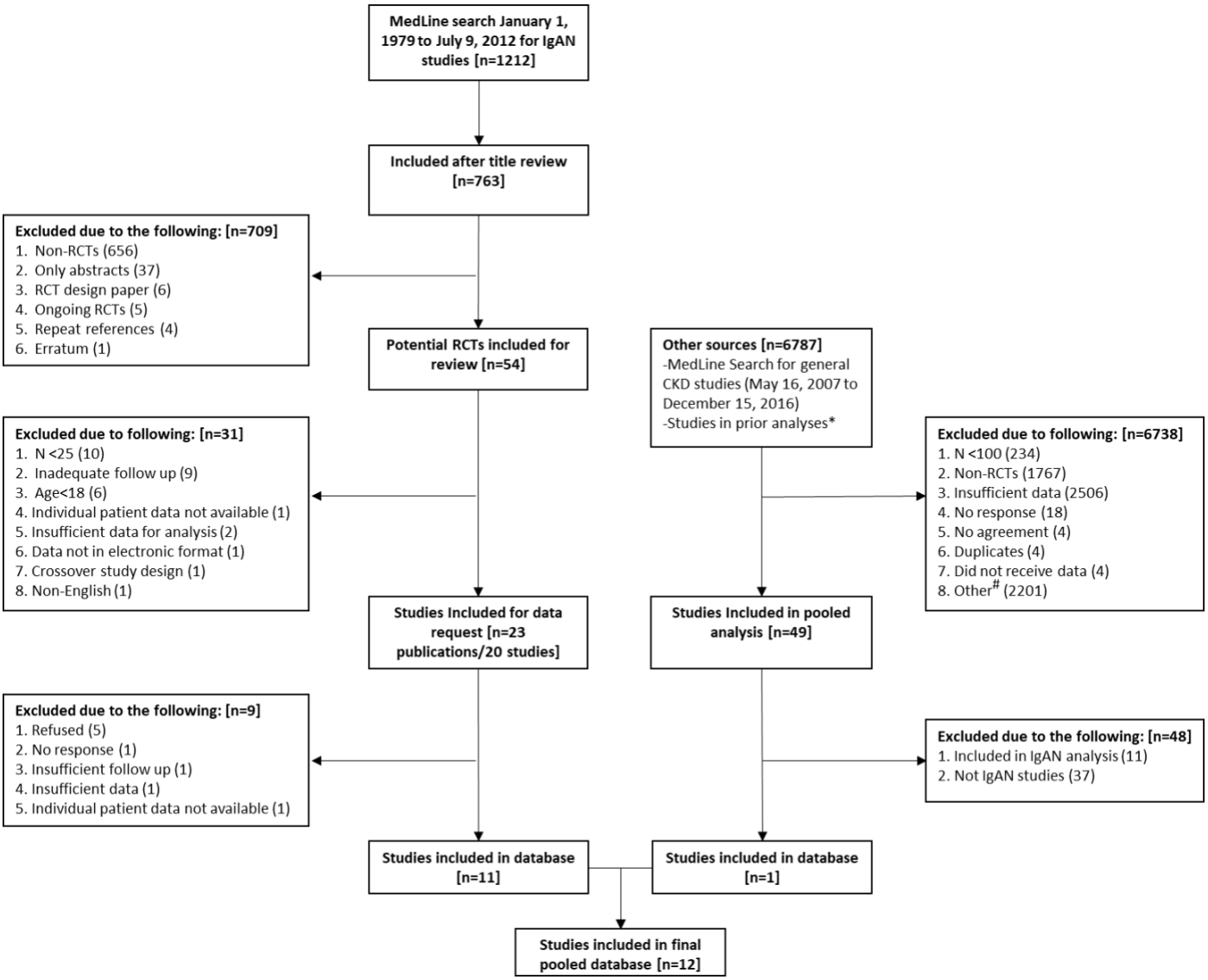
Figure S1 Flowchart of study identification process



* Ref [24]

Other reasons included no long-term kidney outcome, not studying progression of kidney disease, and not a primary investigation paper.

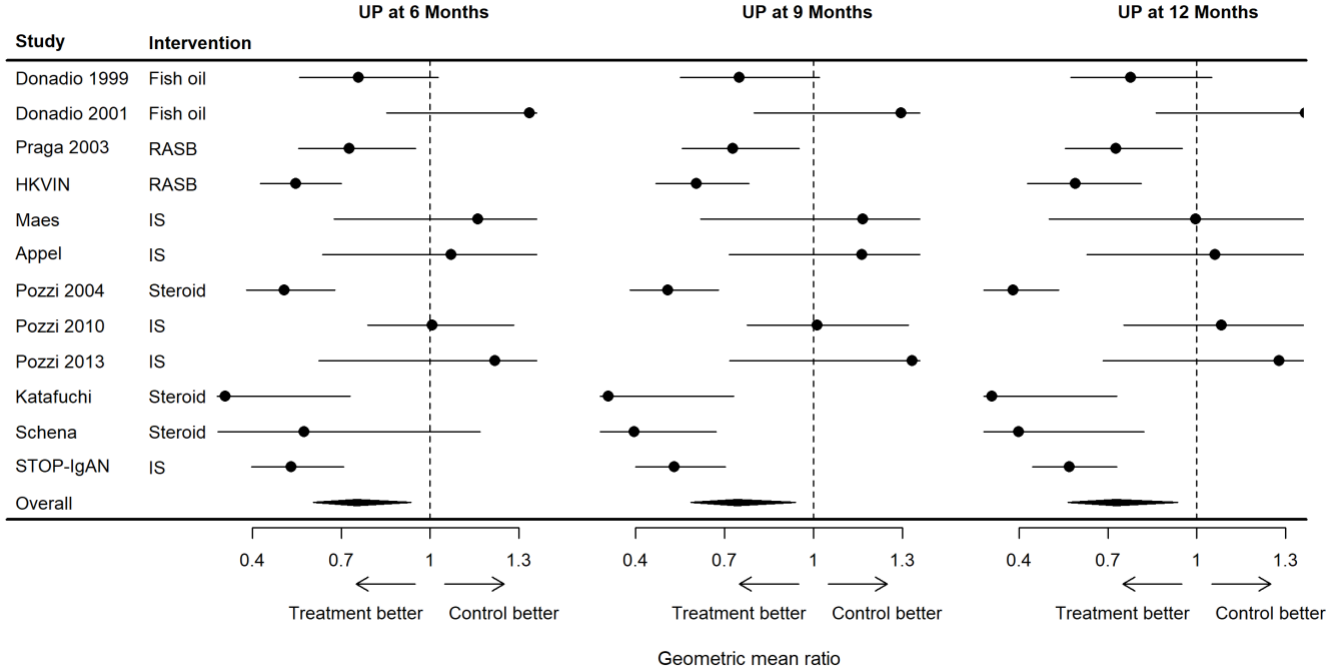
Figure S2 Assessment of bias in each study

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Donadio 1999	?	?	–	+	?	+
Donadio 2001	–	–	–	+	+	+
Praga 2003	+	+	–	+	+	+
HKVIN	+	+	+	+	+	+
Maes	?	?	–	+	+	+
Appel	+	+	+	+	+	+
Pozzi 2004	+	?	–	+	+	+
Pozzi 2010	+	?	–	+	?	+
Pozzi 2013	?	?	–	+	+	+
Katafuchi	–	?	–	–	+	+
Schena	+	+	–	+	+	+
STOP-IgAN	+	?	–	+	+	+

Key:
Green color and +, low risk of bias;
Red color and –, high risk of bias;
Yellow color and ?, unclear risk of bias.

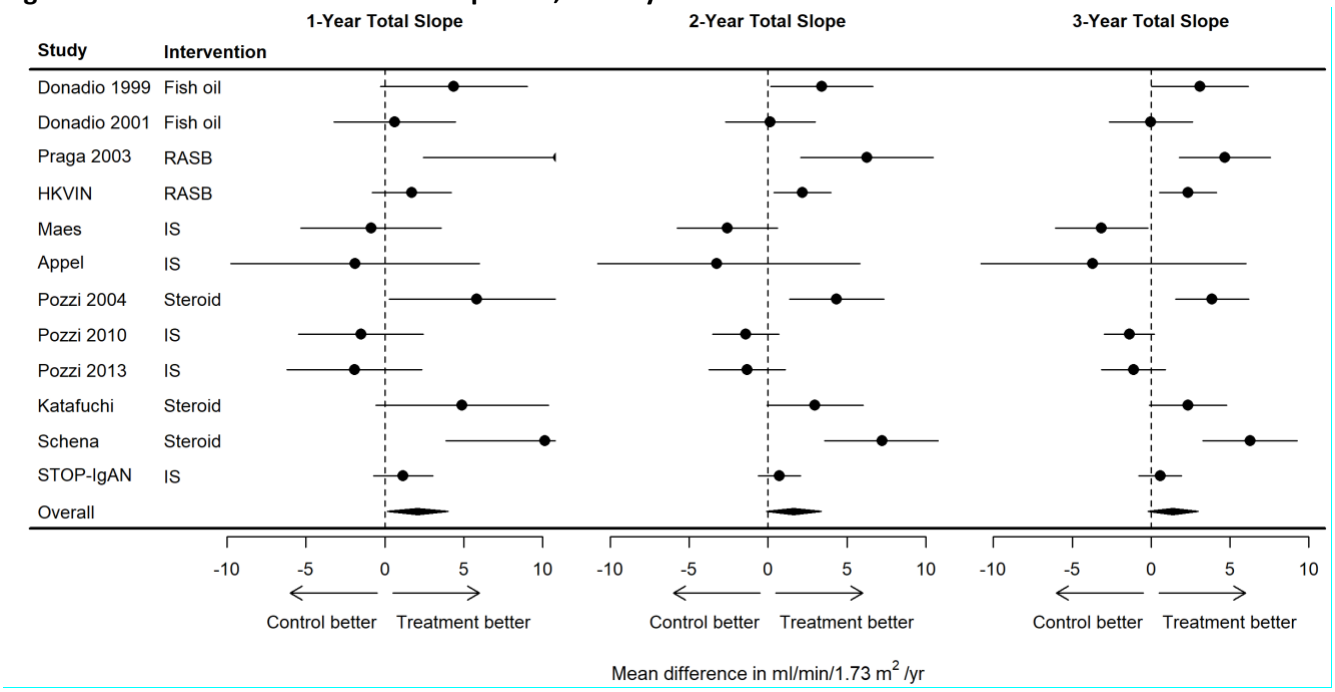
Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration. The tool includes these components: sequence generation (i.e. computer-generated random number, use of random number table or other truly random process); allocation concealment (i.e. web-based or telephone central randomization or consecutively numbered sealed opaque envelopes); blinding of participants, study personnel and outcome assessors; incomplete outcome data; selective outcome reporting. Each item of potential bias was scored as low, high or unclear based on criteria specified by the Cochrane Handbook[1].

Figure S3 Treatment effect on change in urine protein at 6, 9 and 12 months



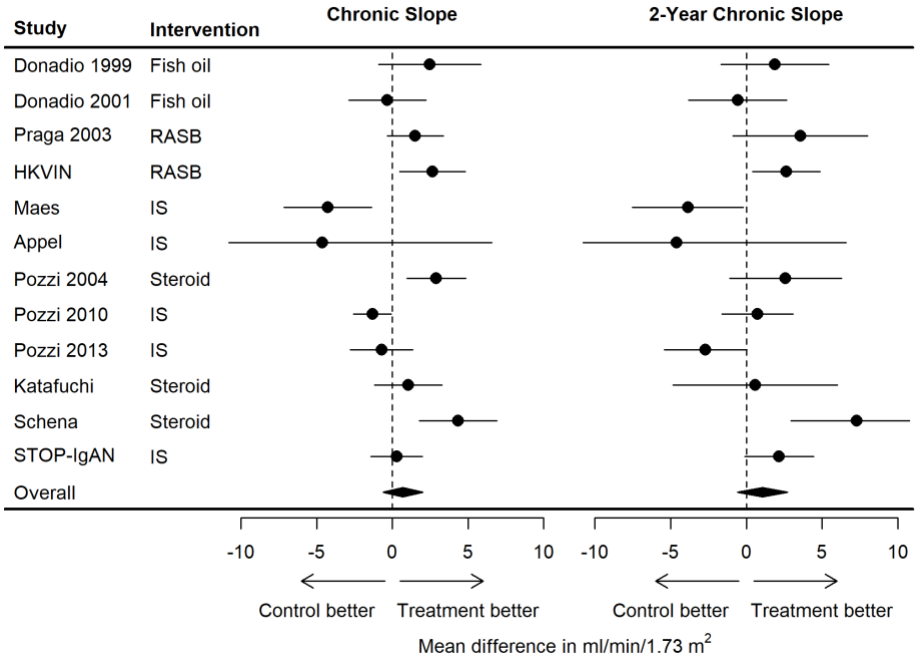
Treatment effects on urine protein are expressed as geometric mean ratios and were estimated by performing analyses of covariance within each study. The circles represent the estimated treatment effects and the horizontal line the 95% confidence intervals. UP, urine protein measured in gram/day; RASB, renin-angiotensin receptor blocker; IS, immunosuppression.

Figure S4 Treatment effect on total slope at 1, 2 or 3 years



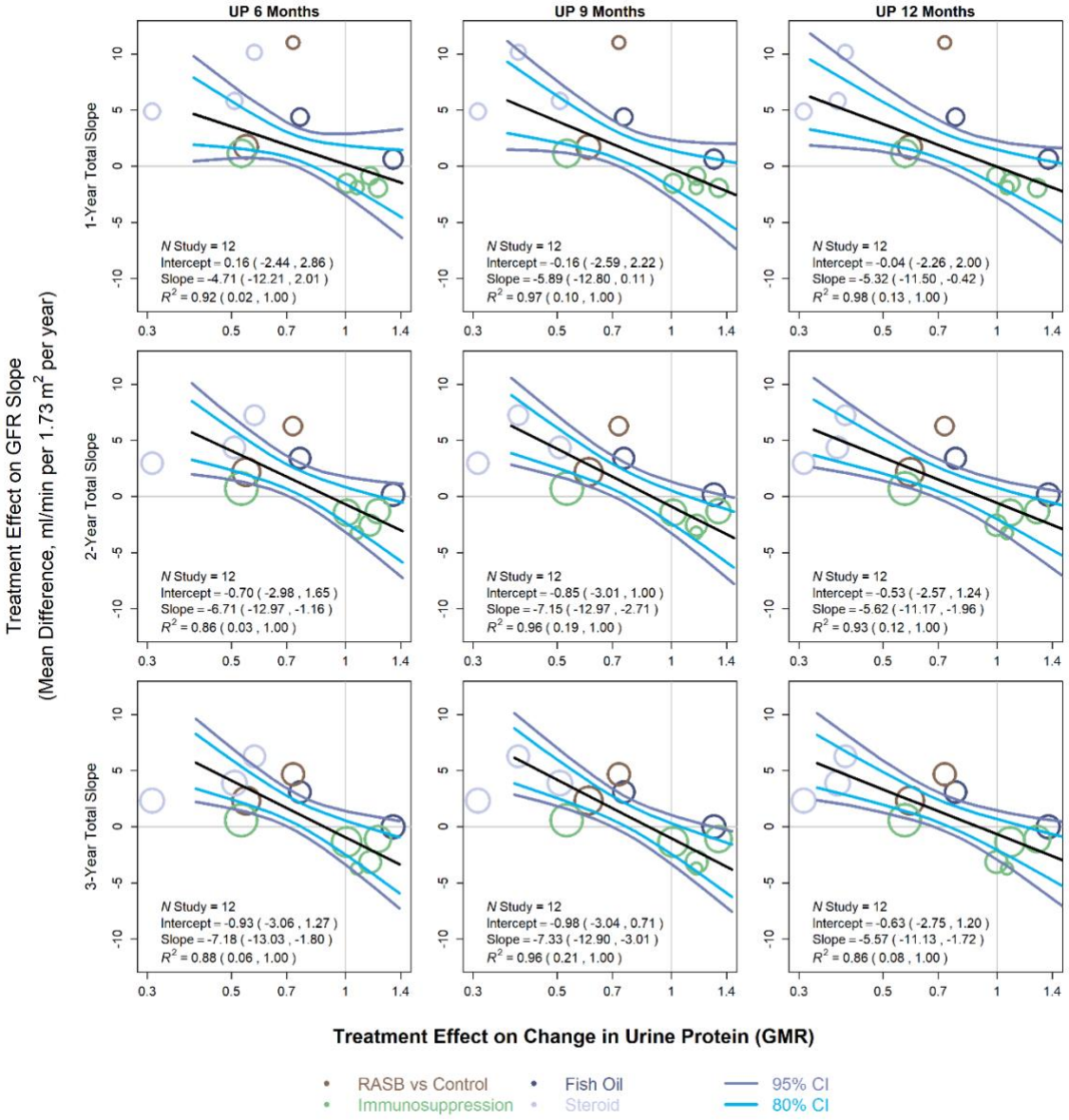
Treatment effects on slope are measured as difference in glomerular filtration rate between treatment and control arm and are expressed as ml/min/1.73m^2/year and were estimated using a shared parameter mixed effects model (see above). The circles represent the estimated treatment effects and the horizontal line the 95% confidence intervals. RASB, renin-angiotensin receptor blocker; IS, immunosuppression.

Figure S5 Treatment effect on chronic slope computed overall and at two years



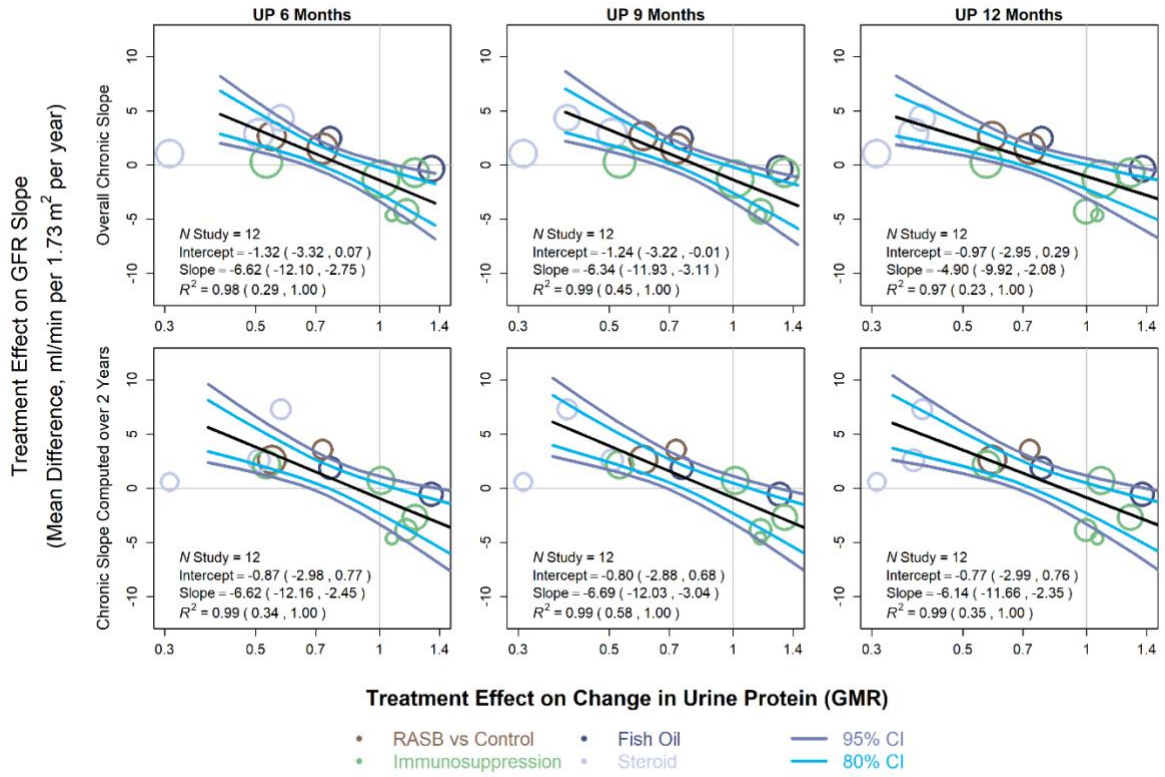
Treatment effects on slope are measured as difference in glomerular filtration rate between treatment and control arm and are expressed as ml/min/1.73m^2/year and were estimated using a shared parameter mixed effects model (see above). The circles represent the estimated treatment effects and the horizontal line the 95% confidence intervals. RASB, renin-angiotensin receptor blocker; IS, immunosuppression.

Figure S6 Trial level association of UP with total GFR slope at 1, 2 and 3 years



Shown is the relationship between estimated treatment effects on the 1, 2, and 3-year GFR slope on the vertical axis to estimated treatment effects on the change in urine protein on the horizontal axis. Treatment effects on GFR slope are expressed as mean difference in treatment and control and expressed in ml/min/1.73m^2/year. Treatment effects on urine protein are expressed as geometric mean ratios. Each circle is a separate intervention with the size of the circle proportional to the number of events. The colors of the circles indicate intervention type. The black line is the line of regression through the studies. The dark blue lines represent the 95% prediction band and the light blue lines represent the 85% prediction band computed from the model. More informed priors were used: Slope igamma(shape=0.261,scale=0.005), urine protein igamma(shape=0.261,scale=0.000408). RASB, renin angiotensin system blockers; GMR, geometric mean ratio.

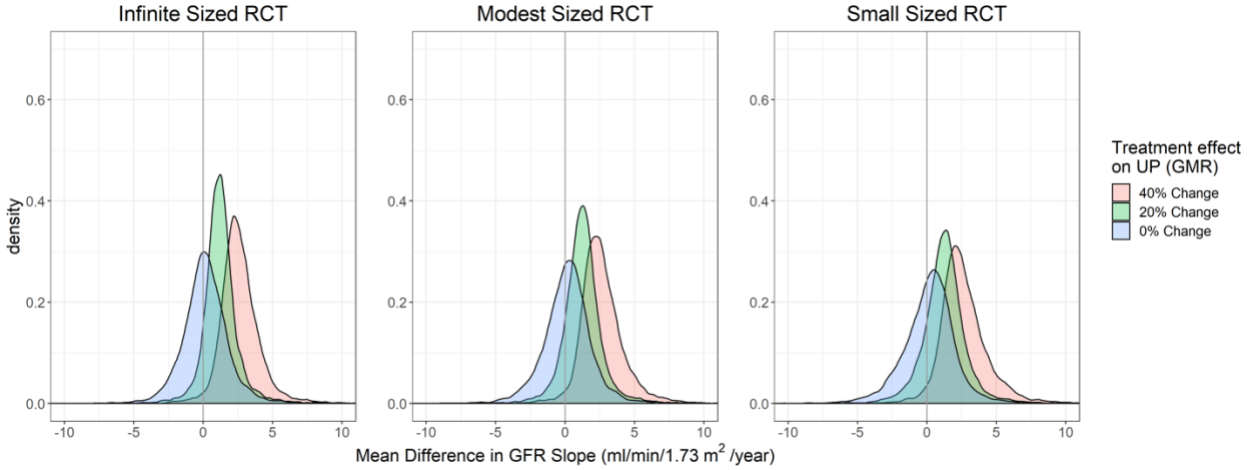
Figure S7 Trial level association of UP with overall chronic slope and 2 year chronic slope



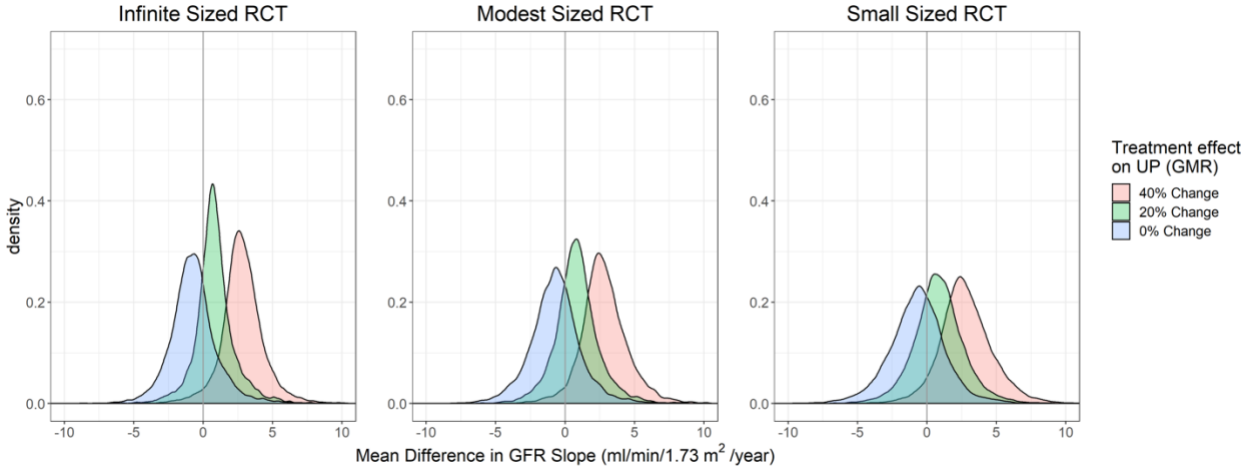
Shown is the relationship between estimated treatment effects on the chronic GFR slopes on the vertical axis to estimated treatment effects on the change in urine protein on the horizontal axis. Treatment effects on GFR slope are expressed as mean difference in treatment and control and expressed in ml/min/1.73m^2/year. Treatment effects on urine protein are expressed as geometric mean ratios. Each circle is a separate intervention with the size of the circle proportional to the number of events. The colors of the circles indicate intervention type. The black line is the line of regression through the studies. The dark blue lines represent the 95% prediction band and the light blue lines represent the 85% prediction band computed from the model. More informed priors were used: Slope igamma(shape=0.261,scale=0.005), urine protein igamma(shape=0.261,scale=0.000408). RASB, renin angiotensin system blockers; GMR, geometric mean ratio.

Figure S8 Posterior predictive probabilities for true treatment effects on total GFR slope at 1 and 2 years and 2 year chronic slope

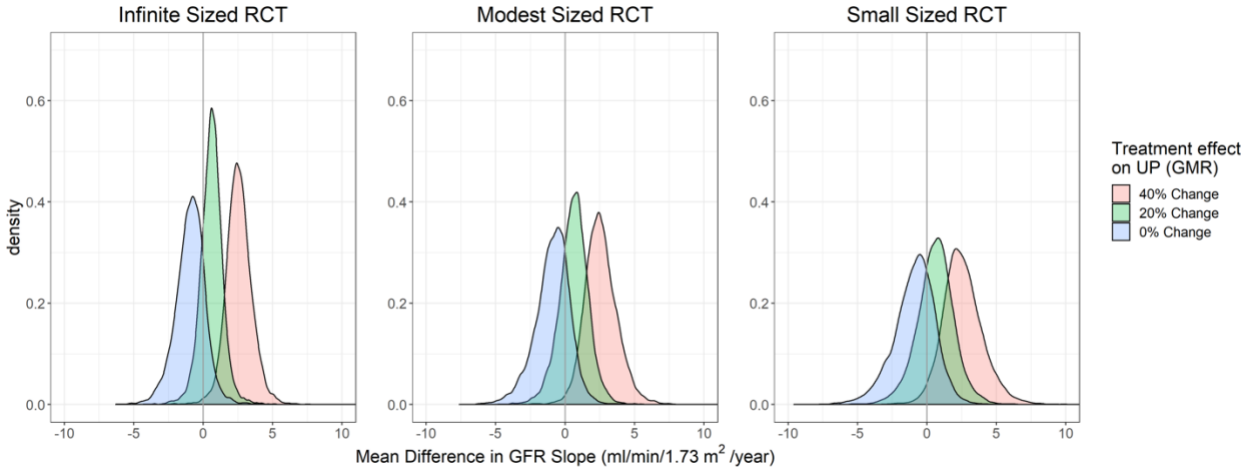
a. **Total GFR slope at 1 year**



b. **Total GFR slope at 2 years**



c. **2 year chronic slope**



UP, urine protein; GMR, geometric mean ratio. More informed priors were used: Slope igamma(shape=0.261,scale=0.005), urine protein igamma(shape=0.261,scale=0.000408).

Item S1: Protocol

Dataset development

Datasets and analytical groups

We identified potential studies via systematic search of the medical literature on Ovid MEDLINE published from January 1, 1979 to July 9, 2012. We repeated the systematic search for studies published prior to December 15, 2016. Table S1 lists the search terms. Table S2 lists all of the inclusion criteria. For the overall goal of evaluating endpoints for CKD progression trials, 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.

We were able to identify, obtain agreement, and obtain access to 12 studies that had sufficient data (Figure S1). Risks of bias for each study included were assessed using the risk-of-bias tool of the Cochrane collaboration[1] (Figure S2), and demonstrated that there is not likely to be differential bias on the clinical endpoint and surrogate endpoint. Table S3 describes the individual treatment comparisons.

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, fish oil, steroids, and other immunosuppressive therapy.

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.[2-10] 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.

Early change in UP

We defined change in UP from baseline to 6 (range 2.5 to 14), 9 (2.5 to 14) and 12 (2.5 to 19) months, taking the value closest to the target month. For the primary analysis, we used change at 6 months to be consistent with our recent paper evaluating associations between treatment effects on changes in urine protein to those on the clinical endpoint in CKD. Change at 9 months was defined differently for comparison to our prior paper evaluating associations between treatment effects on changes in urine protein to those on the clinical endpoint in IgAN.[11] Urine protein was expressed in units of grams/day (g/day) and was log transformed due to skewedness of the data. For each study we used an analysis of covariance to estimate the treatment effect on the follow-up log transformed urine protein measurement after adjustment for the log transformed baseline urine protein.

Mixed effects model for 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.[12,13] This model can be expressed as:

$Y_{ij} = \left(\beta_0 + BGFR_i\beta_{0,BGFR}\right) + \left(t_{ij}\beta_1 + BGFR_i t_{ij}\beta_{1,BGFR}\right) + Z_i\beta_{0T} + Z_i t_{ij}\,\beta_{1T} + b_{0i} + t_{ij}\,b_{1i} + \varepsilon_{ij}$

$S_i \sim Weibull\,(\alpha_0 + \log(BGFR_i)\,\alpha_1 + Z_i\alpha_2 + \lambda_0 b_{i0} + \lambda_1 b_{i1}, \tau)$

$\varepsilon_{ij} \sim Normal\left(0, \sigma^2\left(\mu_{ij}^2\right)^{\theta}\right)$, where μ_{ij} is the subjects subject's expected mean GFR at time j.

where

$Y_{ij} =$ i^{th} subject's eGFR measurement at time t_{ij} where all the t_{ij} are ≥ 3 months follow-up,

$t_{ij} =$ time of the i^{th} subject's j^{th} GFR measurement measured in months,

$S_i =$ time of ESRD or Death for the i^{th} subject,

$Z_i =$ randomized treatment group for the i^{th} subject, with $Z_i = 0$ and $Z_i = 1$ indicating the control and treatment groups, respectively,

$BGFR_i =$ Centered baseline GFR for the i^{th} subject.

In this mixed effects model, b_{i0} and b_{i1} are random effects that account for variation in the GFR trajectories between patients within the two treatment groups conditional on baseline GFR. We assume that b_{0i} and b_{1i} are bivariate normal with mean 0 and unstructured covariance matrix $\begin{bmatrix}\sigma_0^2 & \sigma_{01}\\ \sigma_{01} & \sigma_{01}^2\end{bmatrix}$ for subjects in the control group, and with mean 0 and covariance matrix $\begin{bmatrix}\sigma_0^2 & (1+\kappa)\sigma_{01}\\ (1+\kappa)\sigma_{01} & (1+\kappa)^2\sigma_{01}^2\end{bmatrix}$ for subjects in the active treatment group. The mixed effects model's fixed effect parameters are β_0, $\beta_{0,BGFR}, \beta_1, \beta_{1,BGFR}, \beta_{0T}, \beta_{1T}, \alpha_0, \alpha_1, \alpha_2, \lambda_0, \lambda_1, \tau, \sigma,\ \theta$ and κ. Here, $\beta_0, \beta_{0,BGFR}, \beta_1, \beta_{1,BGFR}$ determine the mean GFR trajectories in the control group and their dependence on baseline GFR, the parameters β_{0T} and β_{1T} determine the treatment effects on the mean acute and chronic slopes, $\alpha_0, \alpha_1, \alpha_2, \lambda_0$, λ_1, and τ govern the distribution of the ESRD or death times and their relationship with baseline GFR, the randomized treatment, and the patients' underlying GFR trajectories. The inclusion of the term $\lambda_0 b_{i0} + \lambda_1 b_{i1}$ allows the ESRD or death times to depend on the underlying GFR trajectories to account for potential informative censoring of GFR follow-up by ESRD or death [14,15]. The parameters σ and θ determine the variability of the GFR residuals about their underlying linear trajectories, where θ allows for greater variation in individual GFR measurements at higher GFR based on a power of the mean (POM) model. Finally, the parameter κ allows for non-uniform treatment effects in which some treatments may slow progression by a greater extent for 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.[13]

Under this model, the differences between the randomized groups in the mean intercepts, 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. This simplified model allows for any pattern of GFR change between the baseline and 3-month assessments. To support model convergence, the ESRD or death times S_i were included only for studies in which at least 15 subjects died or reached ESKD. Simplified models were also used in several additional 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.

For all GFR models, we estimated the treatment effects as the difference in mean slopes between the treatment arms, in units of mL/min/1.73m^2/year.

Trial level analysis

Background

The trial level analysis has been a primary focus of the recent statistical literature for the assessment of the validity of surrogate endpoints.[16-20] Our analytic approach is based on the causal association framework described in Joffe and Greene (2008),[21] 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).[16,17,20,22]

We note that the trial level analyses are fundamentally distinct from so-called individual level analyses that characterize the epidemiologic association of a potential surrogate endpoint with a clinical endpoint. Individual level analyses address the utility of a potential surrogate for predicting a future clinical outcome in individual patients. However, it is well known that the presence of even quite strong individual level association is not a sufficient condition for establishing the validity of a potential surrogate for use an outcome in randomized trials. In particular, there are highly publicized examples in which the effects of treatments on a potential surrogate have failed to predict the effects of the same treatments on the desired clinical endpoint, even though the individual-level association between the potential surrogate and the clinical endpoint was quite strong.[23]

In contrast to individual level association, where the units of analysis are individual patients, the units of analysis for the trial-level analyses presented in this manuscript are full randomized trials. Rather than addressing association in individuals, trial level analyses directly address the question of whether *treatment effects* on the surrogate accurately predict *treatments effects* on the clinical endpoint across different randomized trials. This is the question that addresses whether a potential surrogate endpoint can be substituted for the clinical endpoint to reliably evaluate the clinical effects of treatments in randomized trials.

Caveats from treating slope as the clinical endpoint

While both 6-month change in urine protein and GFR slope are surrogate endpoints, GFR slope evaluate over the full follow-up period is much more proximal to the clinical endpoint of ESRD (or of the composite of ESRD or a 50% or 57% GFR decline) than is the 6-month change in urine protein. This is true because ESRD, as well as a 50% or 57% GFR decline, are either fully or partially mathematically related to the GFR level, as ESRD generally occurs within a relatively narrow GFR range of 7 to 15 ml/min/1.73m^2. This has been born out in previous trial level analyses across a broad collection of randomized trials in CKD patients, where the median posterior R^2 related the treatment effects on the

established clinical endpoint of doubling serum creatinine or ESRD to the treatment effects on the chronic and 3-year total slope were 0.96 (95% credible interval 0.63-1.00) and 0.97 (0.78-1.00), respectively, compared to 0.47 (0.02 – 0.96) for initial change in log transformed albumin to creatinine ratio.[12,24] In addition, change in GFR is the definition of CKD progression and can be considered an intermediate endpoint. Hence, the trial level analyses of this paper can be viewed as assessing the agreement of treatment effects on 6-month change in urine protein excretion with an endpoint that is biologically proximal to and empirically well-aligned with the clinical endpoint, although not the clinical endpoint itself.

Brief description of the analyses

As in our past work, to determine the meta-regression line for the association between the treatment effects on a clinical and a surrogate endpoint, we applied a Bayesian mixed effects model to relate the true treatment effects on the clinical endpoint to the true treatment effects on the surrogate endpoint while discounting the additional variation due to random sampling error that resulted from the limited sample sizes of the studies. The Bayesian meta-regression also incorporates the correlation between the deviations of the estimated vs. the true treatment effects for the two endpoints. Consideration of this correction is important, correlations in random sampling error can lead to nonzero correlation between the estimated treatment effects on the two endpoints even in the absence of any true treatment effects on either endpoint in any study.[25] We obtained estimates of the correlation between the treatment effects on the clinical and surrogate outcome within each study by robust sandwich estimators. We also provide 95% and 80% pointwise credible confidence band around the regression line to express the precision with which the meta-regression line is estimated and 95% and 80% prediction intervals to express the expected variation in the true treatment effects on the clinical endpoint given the true treatment effect on the surrogate endpoint in a newly conducted trial.

Detailed description of the trial level model for relating treatment effects on GFR slope to treatment effects on urine protein

For the trial level analyses of this manuscript GFR slope plays the role of the clinical, or established, endpoint and urine protein serves as the surrogate endpoint. We characterized GFR slope as the chronic slope and as the 1-, 2- or 3-year total slope in separate analyses. The trial level analyses were performed in two stages to relate the true treatment effects on GFR slope to the true treatment effects on urine protein while accounting for error in the estimation of these effects within each trial. In the first stage, for each trial, separate mixed effects models and analyses of covariance were performed to estimate the effects of the treatment on the GFR slope and on urine protein as described above. Treatment effects of GFR slope were expressed as mean difference between the GFR slope in treatment and control groups. Treatment effects on urine protein were expressed as the log transformed geometric mean ratio of the change in urine protein between the two groups.

To express the statistical model precisely, let i = 1, 2, …, 12 denote the 12 randomized treatment comparisons included in the analysis. The index i refers to the i^{th}trial. We let θi and γi denote the true treatment effects on GFR slope and on log urine protein, respectively, 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 slope endpoint and δ_i is the standard error of the estimated treatment effect on log urine protein in the i^{th}trial, and r_i is the

correlation between the estimated treatment effects. We estimated used estimating equations to provide robust sandwich estimates of 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 an approximate 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 urine protein 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 GFR slope and on log urine protein 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 $=(\sigma_\theta^2 - R^2\sigma_\theta^2)^{1/2}$.

The trial-level analysis indicates a significant association between the treatment effects on the change in urine protein and those on the GFR slope under the following conditions: (1) The slope of the meta-regression relating the treatment effect on the slope to the treatment effect on urine protein differs significantly from 0; (2) the R^2 and RMSE of the meta-regression indicate that the estimated treatment effect on the change in urine protein endpoint can reliably predict the treatment effect on GFR slope; and (3)the intercept of the meta-regression line is close to 0, indicating that the absence of a treatment effect on the urine protein predicts the absence of a treatment effect on the slope.[16,17,20]

Prior sets	Prior on the treatment effect on GFR slope	Prior on the treatment effect on the change in urine protein
Less informed	igamma(shape=0.001,scale=0.001)	igamma(shape=0.001,scale=0.001)
More informed	igamma(shape=0.261,scale=0.005)	igamma(shape=0.261,scale=0.000408)

We fit the second stage model using the SAS procedure MCMC to implement Bayesian Monte-Carlo Markov Chain (MCMC) sampling. We used 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. For the slope of the meta-regression we used a prior with a mean of 0 and a uniform distribution with limits of -14 to 14 ml/min/1.73m^2/year per 1 unit change in the treatment effect on log urine protein. The interval from -14 to 14 ml/min/1.73m^2/year was selected to include all plausible meta-regression slopes, and was used to improve the convergence of the model without actually impacting statistical inferences. We used nearly flat prior distributions with means of 0 and variances of 10,000 for the mean treatment effect on urine protein and on the meta-regression intercept. The table above shows the two priors we used for the variances of the treatment effects on slope and on urine protein. Both are diffuse priors based on the inverse gamma distribution. The inverse gamma with shape

and scale both equal to 0.001 has been widely used as a diffuse prior for variances in the literature. The alternative priors with shape equal to 0.261 and scale equal to either 0.005 (for GFR slope) or 0.000408 (for urine protein) were selected by the investigators to assign prior probabilities of 1/3 each to small, moderate, and high levels of variability in treatment effects between studies. For urine protein, small, moderate and large treatment variability in treatment effects was defined as a standard deviation on the log scale of ≤ 0.05, 0.05-0.20, and > 0.20, respectively. For GFR slope, small, moderate and large treatment variability in treatment effects was defined as a standard deviation of ≤ 0.175, 0.175-0.70, and > 0.70, respectively.

We used the Gelman Rubin statistic to assess convergence of the MCMC procedures.[26] This diagnostic evaluates the consistency of results using different starting values for the MCMC chains. We used three chains. We used a cutpoint of greater than 1.05 for the upper bound of the Gelman Rubin statistic, which indicates large difference between multiple Markov chains indicating nonconvergence. We then evaluated whether the Markov chains were of sufficient length by ensuring the effective sample size was > 400.[27]

Prediction intervals and positive predictive value

We obtained 95% pointwise prediction intervals for the treatment effect on the slope given a particular value for the true treatment effect on change in log UP by simulating the posterior distribution of $\alpha + \beta \times \mathrm{True.Eff}_{UP} + \Delta_0$, where $\mathrm{True.Eff}_{UP}$ is the designated true treatment effect on early change in log UP, $\alpha + \beta \times \mathrm{True.Eff}_{UP}$ represents the associated predicted mean true treatment effect on the GFR slope 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 GFR slope across different trials with the same treatment effect on early change log UP. 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 GFR slope about the regression line for different trials.

The prediction results from the model can be thought as if they were applied to a study of infinite sample size. However, actual studies have finite sample sizes. As such, 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 UP 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 vs when it is small. 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 $\alpha + \beta \times \mathrm{True.Eff}_{UP} + \Delta_0$, but now assume that $\mathrm{True.Eff}_{UP}$ has a random distribution to reflect the uncertainty in its estimation in the new trial instead of taking $\mathrm{True.Eff}_{UP}$ to be a fixed value. Specifically, we assumed that the posterior distribution of $\mathrm{True.Eff}_{UP}$ is normally distributed with mean equal to the estimated treatment effect on early change in log UP and standard deviation given by the standard error for the estimated treatment effect on log UP based on the sample size. We considered study of size 100 (SE of 0.15) and 250 (SE 0.09) which assumes a standard deviation of 0.75 for change in log urine protein.

We used a similar sampling approach from the posterior distribution of $\alpha + \beta \times \mathrm{True.Eff}_{UP} + \Delta_0$ to estimate the probability that the GFR slope would be > 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 GFR slope given designated values for the true or observed treatment effects on early change in urine protein. By considering the positive predictive value as a function of $\mathrm{True}.\mathrm{Eff}_{\mathrm{UP}}$, we determined the size of the smallest treatment effect on log urine protein that would be required to assure a positive predictive value of at least 0.975, 0.95 and 0.9 for a benefit on the GFR slope.

Item S2: Study funding sources

Study name	Funding
Appel	This study was supported in part by Roche Pharmaceuticals and the Glomerular Center at Columbia University as an investigator-initiated study the NKF of NY/NJ under the Fred C. Trump Fellowship, a KUFA fellowship and the Kidney Foundation of Canada (G.F.).
Donadio 2001	Supported by research grants from Pronova Biocare a.s. (Oslo, Norway) and Mayo Foundation (Rochester, MN)
HKVIN	Supported by Novartis Pharmaceuticals (Hong Kong) Ltd by providing the study medication and placebo
Maes	The study medication was kindly provided by Hoffmann-LaRoche, Basel, Switzerland
Pozzi 2004	The authors did not receive any financial support
Pozzi 2010	The authors did not receive any financial support
Pozzi 2013	The authors did not receive any financial support
Praga 2003	The authors did not receive any financial support
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.
Other support	The research reported in this publication was supported (in part or in full) by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1TR002538. The project was also supported by the National Center for Advancing Translational Sciences, National Institutes of Health, award number UL1TR002544. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Item S3: Abbreviations, units, and terms

BCI	Bayesian credible interval
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease- Epidemiology Collaboration
EMA	European Medicines Association
ESKD	End-stage kidney disease
F/U	Follow-up time (months)
FDA	Food and Drug Administration
GFR	Glomerular filtration rate(mL/min/1.73 m^2)
GMR	Geometric mean ratio
HKVIN	Hong Kong study using Valsartan in IgA Nephropathy
HR	Hazard ratio
I^2	Study heterogeneity
IgAN	Immunoglobulin A nephropathy
IS	Immunosuppression
MCMC	Monte-Carlo Markov Chain
N	Sample size
NKF	National Kidney Foundation
NLMIXED	Nonlinear mixed-effects regression procedure
POM	Power of mean
PPV	Positive predictive value
R^2	Coefficient of determination
RASB	Renin-angiotensin system blockade
RCT	Randomized controlled trial
RMSE	Root mean squared error
S_{cr}	Serum creatinine (mg/dL)
SD	Standard deviation
SE	Standard error
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy trial
UP	Urine protein (gram/day)

Table S1 Search terms for systematic review

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)

Table S2 Inclusion criteria for studies in systematic review

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 mL/min/1.73 m^2
8. First follow up albuminuria/proteinuria or Scr latest at 12 months
9. Number of events as defined by ESKD, doubling of S_{cr}, 40% or 30% eGFR decline: At least 10

Table S3 Study characteristics and inclusion criteria

Study name	Year	N	Region	Intervention	Control	Duration of Intervention	Age	Scr/GFR	Urine protein
Donadio 1999 [28]	1999	106	US	Fish oil	Placebo	104 (2)	NR	NR	NR
Donadio 2001 [29]	2001	73	US	High dose fish oil	Low dose fish oil	Min. 104 (2)	≥18	S_{cr} 1.5-4.9	NR
Praga 2003[30]	2003	44	Spain	Enalapril	Conventional therapy[#]	156 (3)	>18	S_{cr} ≤1.5	≥0.5
HKVIN[2]	2006	109	Hong Kong	Valsartan	Placebo	104 (2)	≥18	S_{cr} <2.8	>1
Maes[5]	2004	34	Belgium	Mycophenolate mofetil	Placebo	156 (3)	≥18	IC 20-70	>1
Appel[31]	2005	32	US	Mycophenolate mofetil	Placebo+conventional	52 (1)	18-75	CrCl ≤ 80	≥1
Pozzi 2004[6,32,33]	2004 1999 2001	86	Italy	Steroids (MP + predni.) + conventional	Conventional therapy	26 (.5)	15–69	S_{cr} ≤1.5	1–3.5
Pozzi 2010[7]	2010	207		Steroids (MP + predni.) + AZA	Steroids only	26 (.5)	NR	S_{cr} ≤2.0	≥1
Pozzi 2013[8]	2012	46				52 (1)	15–69	S_{cr} >2.0	≥1
Katafuchi[9]	2003	90	Japan	Prednisol. + dipyridamole	Dipyridamole	104 (2)	<60	S_{cr} ≤1.5	NR
Schena[10]	2009	95	Italy	Predni. + ramipril	Ramipril	26 (0.5)	16-70	eGFR>50	≥1
STOP-IGAN[34]	2015	162	Germany	Conventional+ (MP+prednisol.)* or (CPA+AZA+prednisol.)^	Conventional only	6 months* Or 3 years^	18-70	eGFR<90	>0.75

Age represented in years. Duration of intervention is in weeks (years). eGFR and inulin clearance reported in mL/min/1.73 m^2. CrCl, creatinine clearance in mL/min; UP, Urine protein in g/day; min., minimum; MP, methylprednisolone; predni., prednisone; AZA, azathioprine; prednisol., prednisolone; CPA, cyclophosphamide; IC, inulin clearance. [#]Except angiotensin converting enzyme inhibitor; *For eGFR≥60 mL/min/1.73 m^2; ^For eGFR 30 - 59 mL/min/1.73 m^2;

Table S4 Patient characteristics, by study, for analysis of change in urine protein

Study	Intervention	N	Age (SD)	Female (%)	eGFR (SD)	UP (IQR)	FU (IQR)
6 months							
Donadio 1999	Fish oil	91	38.8 (13.4)	23 (25.3)	65.8 (21.7)	1.9 (1.2, 3.4)	37.1 (26.4, 44.9)
Donadio 2001	Fish oil	66	46.4 (13.4)	10 (15.2)	41.8 (14.1)	1.6 (0.7, 2.6)	28.2 (25.1, 38.5)
Praga 2003	RASB	44	31.6 (11.5)	17 (38.6)	98.1 (26.5)	1.7 (1.1, 2.4)	76.0 (61.0, 129.5)
HKVIN	RASB	107	40.1 (9.1)	77 (72.0)	75.6 (29.1)	1.6 (1.1, 2.6)	34.9 (34.8, 35.1)
Maes	IS	34	44.8 (11.3)	10 (29.4)	62.2 (18.9)	1.0 (0.6, 2.7)	45.0 (33.0, 45.0)
Appel	IS	20	37.6 (13.3)	2 (10.0)	47.4 (29.2)	2.3 (1.6, 3.0)	25.8 (15.1, 28.8)
Pozzi 2004	Steroid	83	38.6 (11.7)	25 (30.1)	87.2 (21.6)	1.9 (1.4, 2.4)	102.0 (66.0, 126.0)
Pozzi 2010	IS	190	39.3 (12.7)	55 (28.9)	74.0 (25.0)	2.0 (1.5, 2.7)	72.7 (52.6, 90.3)
Pozzi 2013	IS	44	42.1 (11.6)	8 (18.2)	27.9 (7.1)	2.5 (1.5, 3.9)	50.3 (35.2, 62.9)
Katafuchi	Steroid	74	36.2 (11.4)	44 (59.5)	98.5 (21.8)	1.3 (0.9, 2.6)	78.0 (60.0, 90.0)
Schena	Steroid	95	33.7 (11.1)	29 (30.5)	91.3 (23.7)	1.6 (1.3, 2.5)	66.0 (42.0, 78.0)
STOP-IgAN	IS	142	44.5 (12.3)	32 (22.5)	59.5 (27.3)	1.6 (1.1, 2.1)	37.6 (37.2, 38.0)
9 months							
Donadio 1999	Fish oil	91	38.8 (13.4)	23 (25.3)	65.8 (21.7)	1.9 (1.2, 3.4)	37.1 (26.4, 44.9)
Donadio 2001	Fish oil	66	46.4 (13.4)	10 (15.2)	41.8 (14.1)	1.6 (0.7, 2.6)	28.2 (25.1, 38.5)
Praga 2003	RASB	44	31.6 (11.5)	17 (38.6)	98.1 (26.5)	1.7 (1.1, 2.4)	76.0 (61.0, 129.5)
HKVIN	RASB	107	40.1 (9.1)	77 (72.0)	75.6 (29.1)	1.6 (1.1, 2.6)	34.9 (34.8, 35.1)
Maes	IS	34	44.8 (11.3)	10 (29.4)	62.2 (18.9)	1.0 (0.6, 2.7)	45.0 (33.0, 45.0)
Appel	IS	20	37.6 (13.3)	2 (10.0)	47.4 (29.2)	2.3 (1.6, 3.0)	25.8 (15.1, 28.8)
Pozzi 2004	Steroid	83	38.6 (11.7)	25 (30.1)	87.2 (21.6)	1.9 (1.4, 2.4)	102.0 (66.0, 126.0)
Pozzi 2010	IS	190	39.3 (12.7)	55 (28.9)	74.0 (25.0)	2.0 (1.5, 2.7)	72.7 (52.6, 90.3)
Pozzi 2013	IS	44	42.1 (11.6)	8 (18.2)	27.9 (7.1)	2.5 (1.5, 3.9)	50.3 (35.2, 62.9)
Katafuchi	Steroid	74	36.2 (11.4)	44 (59.5)	98.5 (21.8)	1.3 (0.9, 2.6)	78.0 (60.0, 90.0)
Schena	Steroid	95	33.7 (11.1)	29 (30.5)	91.3 (23.7)	1.6 (1.3, 2.5)	66.0 (42.0, 78.0)
STOP-IgAN	IS	142	44.5 (12.3)	32 (22.5)	59.5 (27.3)	1.6 (1.1, 2.1)	37.6 (37.2, 38.0)
12 months							
Donadio 1999	Fish oil	91	38.8 (13.4)	23 (25.3)	65.8 (21.7)	1.9 (1.2, 3.4)	37.1 (26.4, 44.9)
Donadio 2001	Fish oil	67	46.2 (13.4)	11 (16.4)	41.7 (14.0)	1.6 (0.7, 2.6)	29.0 (25.1, 38.5)
Praga 2003	RASB	44	31.6 (11.5)	17 (38.6)	98.1 (26.5)	1.7 (1.1, 2.4)	76.0 (61.0, 129.5)
HKVIN	RASB	107	40.1 (9.1)	77 (72.0)	75.6 (29.1)	1.6 (1.1, 2.6)	34.9 (34.8, 35.1)
Maes	IS	34	44.8 (11.3)	10 (29.4)	62.2 (18.9)	1.0 (0.6, 2.7)	45.0 (33.0, 45.0)
Appel	IS	20	37.6 (13.3)	2 (10.0)	47.4 (29.2)	2.3 (1.6, 3.0)	25.8 (15.1, 28.8)
Pozzi 2004	Steroid	83	38.6 (11.7)	25 (30.1)	87.2 (21.6)	1.9 (1.4, 2.4)	102.0 (66.0, 126.0)
Pozzi 2010	IS	192	39.3 (12.7)	55 (28.6)	74.0 (25.0)	2.0 (1.5, 2.7)	72.5 (52.2, 89.8)
Pozzi 2013	IS	44	42.1 (11.6)	8 (18.2)	27.9 (7.1)	2.5 (1.5, 3.9)	50.3 (35.2, 62.9)
Katafuchi	Steroid	74	36.2 (11.4)	44 (59.5)	98.5 (21.8)	1.3 (0.9, 2.6)	78.0 (60.0, 90.0)
Schena	Steroid	95	33.7 (11.1)	29 (30.5)	91.3 (23.7)	1.6 (1.3, 2.5)	66.0 (42.0, 78.0)
STOP-IgAN	IS	143	44.6 (12.4)	33 (23.1)	59.4 (27.2)	1.6 (1.1, 2.1)	37.6 (37.2, 38.0)

Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation) or median (interquartile range represented as 25th and 75th percentile). UP, Urine protein in g/day; FU, follow-up; RASB, renin-angiotensin system blockade; IS, immunosuppression.

Table S5 Follow-up time, mean number of GFR measurements and average max eGFR visit time

Intervention	Study Name	Overall			Truncated at 2 years	
		Median (25^{th}, 75^{th}) Follow up time	Mean # eGFR over study duration (SD)	Max eGFR visit time (SD)	Mean # eGFR over study duration (SD)	Max eGFR visit time (SD)
Fish oil	Donadio 1999	36.4 (25.8, 43.6)	5.3 (1.4)	20.9 (7.6)	5.2 (1.4)	20.7 (7.5)
Fish oil	Donadio 2001	26.7 (19.1, 38.4)	6.4 (2.4)	27.9 (14.0)	5.2 (1.4)	20.5 (7.4)
RASB	Praga 2003	76.0 (61.0, 129.5)	8.7 (4.0)	91.1 (46.8)	3.0 (0.0)	24.0 (0.0)
RASB	HKVIN	34.9 (34.8, 35.0)	10.3 (2.0)	24.0 (6.1)	10.2 (1.9)	23.6 (5.3)
IS	Maes	45.0 (33.0, 45.0)	13.1 (2.9)	30.4 (8.6)	11.2 (1.9)	24.7 (5.6)
IS	Appel	15.3 (9.0, 27.0)	5.1 (3.4)	9.8 (8.0)	5.1 (3.4)	9.8 (8.0)
Steroid	Pozzi 2004	102.0 (66.0, 126.0)	8.8 (3.1)	81.8 (37.3)	3.9 (0.2)	23.3 (2.9)
IS	Pozzi 2010	72.8 (52.6, 91.2)	9.9 (4.8)	52.6 (24.3)	7.0 (3.4)	20.4 (6.3)
IS	Pozzi 2013	50.3 (34.5, 63.4)	8.4 (4.5)	38.6 (19.4)	6.0 (2.9)	20.9 (6.8)
Steroid	Katafuchi	78.0 (60.0, 90.0)	5.9 (2.0)	61.6 (23.8)	2.9 (0.4)	22.5 (4.8)
Steroid	Schena	66.0 (42.0, 78.0)	7.8 (1.6)	45.8 (18.0)	5.8 (0.6)	22.3 (4.6)
IS	STOP-IgAN	37.6 (37.1, 38.1)	4.6 (0.8)	34.3 (7.9)	3.7 (0.7)	22.2 (5.8)

#, number; follow-up and visit times are represented as months; RASB, renin-angiotensin system blockade; IS, immunosuppression; SD, standard deviation.

Table S6 Change in urine protein by treatment arm and treatment effect, at 6, 9 and 12 months.

Study name	Study name	Control		Treatment		Treatment effect estimate (95% CI)
		N	Change in urine protein Median (25th, 75th)	N	Change in urine protein Median (25th, 75th)	
6 months						
Donadio 1999	Fish oil	45	0.86 (0.50, 1.42)	46	0.67 (0.42, 1.23)	0.76 (0.56, 1.03)
Donadio 2001	Fish oil	35	0.68 (0.40, 1.23)	31	0.91 (0.48, 1.50)	1.34 (0.85, 2.09)
Praga 2003	RASB	21	1.14 (0.93, 1.53)	23	0.80 (0.57, 1.20)	0.73 (0.56, 0.95)
HKVIN	RASB	54	1.05 (0.68, 1.65)	53	0.59 (0.41, 1.00)	0.55 (0.43, 0.70)
Maes	IS	13	0.76 (0.71, 1.04)	21	0.86 (0.67, 1.40)	1.16 (0.68, 2.00)
Appel	IS	11	0.83 (0.53, 1.11)	9	0.87 (0.59, 1.25)	1.07 (0.64, 1.80)
Pozzi 2004	Steroid	42	0.88 (0.63, 1.29)	41	0.43 (0.33, 0.65)	0.51 (0.38, 0.68)
Pozzi 2010	IS	97	0.39 (0.24, 0.65)	93	0.37 (0.24, 0.68)	1.01 (0.79, 1.28)
Pozzi 2013	IS	26	0.39 (0.27, 0.70)	18	0.39 (0.28, 0.93)	1.22 (0.62, 2.38)
Katafuchi	Steroid	39	0.56 (0.43, 1.24)	35	0.24 (0.24, 0.89)	0.31 (0.13, 0.73)
Schena	Steroid	49	0.53 (0.50, 0.92)	46	0.30 (0.28, 0.65)	0.58 (0.28, 1.17)
STOP-IgAN	IS	76	0.75 (0.52, 1.21)	66	0.40 (0.23, 0.87)	0.53 (0.40, 0.71)
Overall		508	0.65 (0.43, 1.18)	482	0.47 (0.32, 0.91)	0.75 (0.61, 0.94)
9 months						
Donadio 1999	Fish oil	45	0.86 (0.50, 1.51)	46	0.66 (0.42, 1.20)	0.75 (0.55, 1.02)
Donadio 2001	Fish oil	35	0.66 (0.30, 1.23)	31	0.85 (0.46, 1.50)	1.30 (0.80, 2.10)
Praga 2003	RASB	21	1.14 (0.93, 1.53)	23	0.80 (0.57, 1.20)	0.73 (0.56, 0.95)
HKVIN	RASB	54	0.93 (0.57, 1.39)	53	0.57 (0.34, 0.86)	0.60 (0.47, 0.78)
Maes	IS	13	0.61 (0.27, 1.04)	21	0.74 (0.64, 1.11)	1.17 (0.62, 2.20)
Appel	IS	11	0.76 (0.49, 1.11)	9	0.87 (0.78, 1.11)	1.16 (0.72, 1.89)
Pozzi 2004	Steroid	42	0.88 (0.63, 1.29)	41	0.43 (0.33, 0.65)	0.51 (0.38, 0.68)
Pozzi 2010	IS	97	0.33 (0.19, 0.55)	93	0.32 (0.17, 0.65)	1.01 (0.78, 1.32)
Pozzi 2013	IS	26	0.35 (0.19, 0.80)	18	0.42 (0.28, 0.85)	1.33 (0.72, 2.48)
Katafuchi	Steroid	39	0.56 (0.43, 1.24)	35	0.24 (0.24, 0.89)	0.31 (0.13, 0.73)
Schena	Steroid	49	0.66 (0.48, 0.91)	46	0.26 (0.20, 0.58)	0.39 (0.23, 0.67)
STOP-IgAN	IS	76	0.76 (0.54, 1.28)	66	0.41 (0.24, 0.87)	0.53 (0.40, 0.70)
Overall		508	0.63 (0.40, 1.15)	482	0.44 (0.27, 0.89)	0.74 (0.59, 0.94)
12 months						
Donadio 1999	Fish oil	45	0.81 (0.58, 1.36)	46	0.64 (0.40, 1.00)	0.78 (0.57, 1.05)
Donadio 2001	Fish oil	35	0.67 (0.39, 1.21)	32	0.91 (0.68, 1.54)	1.37 (0.86, 2.17)
Praga 2003	RASB	21	1.14 (0.93, 1.53)	23	0.80 (0.57, 1.20)	0.73 (0.56, 0.95)
HKVIN	RASB	54	0.82 (0.53, 1.56)	53	0.50 (0.30, 0.88)	0.59 (0.43, 0.81)
Maes	IS	13	0.70 (0.58, 1.29)	21	0.72 (0.49, 1.35)	1.00 (0.50, 1.98)
Appel	IS	11	0.90 (0.62, 1.10)	9	0.95 (0.83, 1.09)	1.06 (0.63, 1.79)
Pozzi 2004	Steroid	42	0.85 (0.50, 1.29)	41	0.31 (0.21, 0.53)	0.38 (0.27, 0.53)
Pozzi 2010	IS	98	0.28 (0.15, 0.69)	94	0.29 (0.17, 0.51)	1.08 (0.75, 1.56)
Pozzi 2013	IS	26	0.30 (0.19, 0.55)	18	0.34 (0.19, 0.59)	1.28 (0.68, 2.39)
Katafuchi	Steroid	39	0.56 (0.43, 1.24)	35	0.24 (0.24, 0.89)	0.31 (0.13, 0.73)
Schena	Steroid	49	0.52 (0.33, 0.84)	46	0.21 (0.17, 0.58)	0.40 (0.19, 0.82)
STOP-IgAN	IS	76	0.73 (0.49, 1.26)	67	0.41 (0.23, 0.78)	0.57 (0.45, 0.73)
Overall		509	0.58 (0.37, 1.13)	485	0.41 (0.24, 0.83)	0.73 (0.56, 0.94)

Treatment effect is expressed as geometric mean ratio, and was adjusted for baseline urine protein

Table S7 Total GFR slope by treatment arm and treatment effect at 1, 2 and 3 years.

Study name	One year slopes			Two year slopes			Three year slopes		
	Control estimate (SE)	Treatment estimate (SE)	Treatment effect estimate (95% CI)	Control estimate (SE)	Treatment estimate (SE)	Treatment effect estimate (95% CI)	Control estimate (SE)	Treatment estimate (SE)	Treatment effect estimate (95% CI)
Donadio 1999	-4.56 (1.84)	-0.19 (1.52)	4.37 (-0.30, 9.03)	-4.62 (1.37)	-1.20 (0.94)	3.42 (0.18, 6.66)	-4.64 (1.32)	-1.53 (0.86)	3.10 (0.03, 6.18)
Donadio 2001	-4.13 (1.34)	-3.52 (1.44)	0.61 (-3.24, 4.46)	-3.95 (0.98)	-3.81 (1.09)	0.14 (-2.71, 3.00)	-3.89 (0.91)	-3.90 (1.02)	-0.01 (-2.66, 2.64)
Praga 2003	-11.70 (3.13)	-0.69 (3.07)	11.01 (2.43, 19.59)	-7.94 (1.56)	-1.68 (1.48)	6.26 (2.05, 10.47)	-6.69 (1.10)	-2.01 (0.98)	4.68 (1.79, 7.57)
HKVIN	-8.26 (0.92)	-6.56 (0.88)	1.70 (-0.80, 4.21)	-7.74 (0.70)	-5.56 (0.60)	2.18 (0.36, 4.00)	-7.56 (0.70)	-5.23 (0.60)	2.34 (0.52, 4.15)
Maes	-0.98 (1.61)	-1.86 (1.58)	-0.88 (-5.33, 3.56)	-0.08 (1.02)	-2.65 (1.24)	-2.57 (-5.76, 0.61)	0.22 (0.90)	-2.91 (1.18)	-3.14 (-6.08, -0.19)
Appel	-7.70 (1.52)	-9.60 (3.73)	-1.89 (-9.77, 5.98)	-6.23 (1.41)	-9.49 (4.44)	-3.26 (-12.35, 5.84)	-5.74 (1.55)	-9.46 (4.73)	-3.71 (-13.44, 6.01)
Pozzi 2004	-6.05 (2.03)	-0.24 (1.96)	5.82 (0.29, 11.35)	-5.42 (1.18)	-1.06 (0.96)	4.36 (1.37, 7.34)	-5.21 (0.99)	-1.34 (0.65)	3.87 (1.55, 6.19)
Pozzi 2010	2.90 (1.39)	1.38 (1.44)	-1.52 (-5.48, 2.44)	0.90 (0.72)	-0.51 (0.79)	-1.42 (-3.53, 0.70)	0.24 (0.53)	-1.14 (0.61)	-1.38 (-2.98, 0.22)
Pozzi 2013	2.09 (1.37)	0.16 (1.69)	-1.93 (-6.22, 2.36)	-0.27 (0.77)	-1.59 (0.96)	-1.32 (-3.74, 1.10)	-1.05 (0.65)	-2.17 (0.81)	-1.12 (-3.15, 0.91)
Katafuchi	1.00 (1.92)	5.89 (2.01)	4.90 (-0.59, 10.38)	-0.53 (1.07)	2.45 (1.12)	2.98 (-0.07, 6.03)	-1.04 (0.86)	1.30 (0.90)	2.34 (-0.12, 4.79)
Schena	-7.87 (2.26)	2.25 (2.27)	10.13 (3.85, 16.40)	-6.76 (1.43)	0.47 (1.20)	7.24 (3.58, 10.89)	-6.39 (1.25)	-0.12 (0.88)	6.27 (3.28, 9.26)
STOP-IgAN	-1.65 (0.65)	-0.48 (0.71)	1.16 (-0.72, 3.05)	-1.62 (0.44)	-0.90 (0.52)	0.72 (-0.62, 2.06)	-1.61 (0.44)	-1.03 (0.53)	0.58 (-0.78, 1.94)
Overall	-3.68 (1.28)	-0.97 (1.04)	2.09 (0.17, 4.01)	-3.57 (0.94)	-1.65 (0.66)	1.64 (-0.09, 3.37)	-3.51 (0.83)	-1.91 (0.54)	1.39 (-0.21, 2.99)

Treatment effect is difference in GFR slope between treatment and control arms expressed in mL/min/1.73 m^2 per year. SE, standard error; CI, confidence interval.

Table S8 Chronic GFR slope by treatment arm and treatment effect

Study name	N	Overall chronic slope			2-year chronic slope		
		Control estimate (SE)	Treatment estimate (SE)	Treatment effect estimate (95% CI)	Control estimate (SE)	Treatment estimate (SE)	Treatment effect estimate (95% CI)
Donadio 1999	96	-4.68 (1.42)	-2.20 (1.01)	2.47 (-0.90, 5.84)	-4.26 (1.50)	-2.37 (1.05)	1.88 (-1.67, 5.44)
Donadio 2001	72	-3.77 (0.90)	-4.10 (0.98)	-0.32 (-2.89, 2.24)	-3.33 (1.15)	-3.91 (1.19)	-0.58 (-3.81, 2.66)
Praga 2003	44	-4.18 (0.80)	-2.67 (0.52)	1.52 (-0.33, 3.37)	-7.44 (1.68)	-3.88 (1.59)	3.56 (-0.90, 8.01)
HKVIN	109	-7.22 (0.84)	-4.56 (0.74)	2.66 (0.48, 4.83)	-7.40 (0.84)	-4.76 (0.77)	2.64 (0.41, 4.87)
Maes	34	0.82 (0.86)	-3.44 (1.17)	-4.26 (-7.16, -1.37)	0.15 (1.37)	-3.71 (1.23)	-3.86 (-7.53, -0.19)
Appel	29	-4.76 (1.99)	-9.38 (5.38)	-4.62 (-15.82, 6.58)	-4.76 (1.99)	-9.38 (5.38)	-4.62 (-15.82, 6.58)
Pozzi 2004	83	-4.78 (0.94)	-1.89 (0.34)	2.90 (0.95, 4.85)	-6.02 (1.44)	-3.43 (1.21)	2.59 (-1.11, 6.28)
Pozzi 2010	197	-1.09 (0.38)	-2.40 (0.51)	-1.31 (-2.56, -0.06)	-2.08 (0.87)	-1.34 (0.82)	0.74 (-1.61, 3.09)
Pozzi 2013	46	-2.63 (0.66)	-3.34 (0.83)	-0.71 (-2.78, 1.36)	-2.28 (0.85)	-4.97 (1.09)	-2.70 (-5.44, 0.04)
Katafuchi	81	-2.06 (0.78)	-1.00 (0.83)	1.06 (-1.18, 3.30)	3.90 (1.86)	4.48 (2.03)	0.59 (-4.84, 6.02)
Schena	95	-5.65 (1.19)	-1.31 (0.55)	4.34 (1.78, 6.91)	-8.38 (1.78)	-1.09 (1.34)	7.29 (2.93, 11.65)
STOP-IgAN	151	-1.59 (0.56)	-1.31 (0.66)	0.29 (-1.41, 1.98)	-1.85 (0.80)	0.31 (0.85)	2.16 (-0.12, 4.44)
Overall	1037	-3.33 (0.66)	-2.48 (0.34)	0.70 (-0.62, 2.02)	-3.63 (0.96)	-2.53 (0.71)	1.06 (-0.60, 2.72)

Treatment effect is difference in GFR slope between treatment and control arms expressed in mL/min/1.73 m^2 per year. SE, standard error; CI, confidence interval.

Table S9 Trial level associations between treatment effect on change in urine protein and treatment effect on GFR slope

a. Treatment effect on urine protein at 6 months

GFR slope	Slope			Intercept			R^2			RMSE		
	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
More informed priors												
Total slope at 3y	-7.18	(-13.03, -1.80)	(-11.12, -3.91)	-0.93	(-3.06, 1.27)	(-2.31, 0.36)	0.88	(0.06, 1.00)	(0.30, 1.00)	0.78	(0.06, 2.77)	(0.10, 2.05)
Total slope at 2y	-6.71	(-12.97, -1.16)	(-10.91, -3.34)	-0.70	(-2.98, 1.65)	(-2.14, 0.70)	0.86	(0.03, 1.00)	(0.24, 1.00)	0.81	(0.06, 3.01)	(0.11, 2.21)
Total slope at 1y	-4.71	(-12.21, 2.01)	(-9.56, -0.67)	0.16	(-2.44, 2.86)	(-1.47, 1.76)	0.92	(0.02, 1.00)	(0.20, 1.00)	0.30	(0.05, 3.00)	(0.08, 1.82)
Chronic slope	-6.62	(-12.10, -2.75)	(-9.94, -4.19)	-1.32	(-3.32, 0.07)	(-2.51, -0.43)	0.98	(0.29, 1.00)	(0.68, 1.00)	0.24	(0.05, 1.66)	(0.08, 1.05)
Chronic slope truncated at 2y	-6.62	(-12.16, -2.45)	(-10.04, -3.99)	-0.87	(-2.98, 0.77)	(-2.13, 0.18)	0.99	(0.34, 1.00)	(0.76, 1.00)	0.21	(0.05, 1.71)	(0.07, 0.94)
Less informed priors												
Total slope at 3y	-6.61	(-12.68, -1.13)	(-10.52, -3.38)	-0.75	(-3.01, 1.52)	(-2.15, 0.62)	0.75	(0.03, 1.00)	(0.20, 1.00)	1.19	(0.05, 3.18)	(0.12, 2.39)
Total slope at 2y	-6.38	(-12.49, -0.61)	(-10.38, -3.03)	-0.53	(-2.85, 1.88)	(-1.98, 0.91)	0.73	(0.02, 1.00)	(0.17, 1.00)	1.25	(0.04, 3.51)	(0.12, 2.61)
Total slope at 1y	-4.88	(-12.14, 1.43)	(-9.38, -1.05)	0.20	(-2.33, 2.83)	(-1.41, 1.80)	0.82	(0.01, 1.00)	(0.14, 1.00)	0.64	(0.04, 3.78)	(0.07, 2.54)
Chronic slope	-6.36	(-11.82, -2.48)	(-9.67, -3.98)	-1.26	(-3.22, 0.22)	(-2.42, -0.36)	0.98	(0.20, 1.00)	(0.57, 1.00)	0.30	(0.03, 2.00)	(0.05, 1.31)
Chronic slope truncated at 2y	-6.56	(-11.87, -2.18)	(-9.78, -3.87)	-0.84	(-2.91, 0.87)	(-2.11, 0.25)	0.98	(0.18, 1.00)	(0.62, 1.00)	0.27	(0.03, 2.23)	(0.05, 1.34)

Y, years; BCI, Bayesian credible interval.

More informed priors: Treatment effect on GFR slope igamma(shape=0.261,scale=0.005), and on urine protein igamma(shape=0.261,scale=0.000408); Less informed priors: Treatment effect no GFR slope igamma(shape=0.001,scale=0.001), and treatment effect on urine protein igamma(shape=0.001,scale=0.001)

b. Treatment effect on urine protein at 9 months

GFR slope	Slope			Intercept			R^2			RMSE		
	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
More informed priors												
Total slope at 3y	-7.33	(-12.90, -3.01)	(-11.02, -4.53)	-0.98	(-3.04, 0.71)	(-2.27, 0.09)	0.96	(0.21, 1.00)	(0.53, 1.00)	0.47	(0.06, 2.27)	(0.09, 1.62)
Total slope at 2y	-7.15	(-12.97, -2.71)	(-11.06, -4.20)	-0.85	(-3.01, 1.00)	(-2.19, 0.30)	0.96	(0.19, 1.00)	(0.52, 1.00)	0.44	(0.06, 2.44)	(0.09, 1.69)
Total slope at 1y	-5.89	(-12.80, 0.11)	(-10.45, -2.26)	-0.16	(-2.59, 2.22)	(-1.70, 1.26)	0.97	(0.10, 1.00)	(0.50, 1.00)	0.27	(0.05, 2.37)	(0.08, 1.39)
Chronic slope	-6.34	(-11.93, -3.11)	(-9.66, -4.11)	-1.24	(-3.22, -0.01)	(-2.40, -0.41)	0.99	(0.45, 1.00)	(0.77, 1.00)	0.22	(0.05, 1.47)	(0.07, 0.90)
Chronic slope truncated at 2y	-6.69	(-12.03, -3.04)	(-9.95, -4.29)	-0.80	(-2.88, 0.68)	(-2.07, 0.19)	0.99	(0.58, 1.00)	(0.85, 1.00)	0.20	(0.05, 1.43)	(0.07, 0.80)
Less informed priors												
Total slope at 3y	-6.88	(-12.54, -2.35)	(-10.57, -4.00)	-0.84	(-2.93, 1.01)	(-2.15, 0.33)	0.89	(0.12, 1.00)	(0.40, 1.00)	0.83	(0.04, 2.70)	(0.08, 1.97)
Total slope at 2y	-6.82	(-12.68, -2.25)	(-10.57, -3.94)	-0.70	(-2.86, 1.25)	(-2.06, 0.48)	0.89	(0.12, 1.00)	(0.40, 1.00)	0.82	(0.04, 2.86)	(0.09, 2.07)
Total slope at 1y	-5.87	(-12.55, -0.44)	(-10.30, -2.41)	-0.09	(-2.51, 2.24)	(-1.62, 1.27)	0.94	(0.08, 1.00)	(0.39, 1.00)	0.43	(0.03, 3.01)	(0.06, 1.98)
Chronic slope	-6.12	(-11.54, -2.67)	(-9.29, -3.87)	-1.16	(-3.13, 0.17)	(-2.30, -0.31)	0.98	(0.30, 1.00)	(0.66, 1.00)	0.28	(0.03, 1.83)	(0.05, 1.14)
Chronic slope truncated at 2y	-6.60	(-11.91, -2.95)	(-9.77, -4.23)	-0.78	(-2.80, 0.73)	(-2.02, 0.22)	0.99	(0.45, 1.00)	(0.79, 1.00)	0.24	(0.03, 1.82)	(0.05, 1.09)

Y, years; BCI, credible interval.

More informed priors: Treatment effect on GFR slope igamma(shape=0.261,scale=0.005), and on urine protein igamma(shape=0.261,scale=0.000408); Less informed priors: Treatment effect no GFR slope igamma(shape=0.001,scale=0.001), and treatment effect on urine protein igamma(shape=0.001,scale=0.001)

c. Treatment effect on urine protein at 12 months

GFR slope	Slope			Intercept			R^2			RMSE		
	Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
More informed priors												
Total slope at 3y	-5.57	(-11.13, -1.72)	(-8.65, -3.31)	-0.63	(-2.75, 1.20)	(-1.82, 0.41)	0.86	(0.08, 1.00)	(0.33, 1.00)	0.84	(0.06, 2.73)	(0.11, 2.01)
Total slope at 2y	-5.62	(-11.17, -1.96)	(-8.81, -3.37)	-0.53	(-2.57, 1.24)	(-1.72, 0.51)	0.93	(0.12, 1.00)	(0.41, 1.00)	0.57	(0.06, 2.67)	(0.09, 1.88)
Total slope at 1y	-5.32	(-11.50, -0.42)	(-9.05, -2.29)	-0.04	(-2.26, 2.00)	(-1.39, 1.22)	0.98	(0.13, 1.00)	(0.58, 1.00)	0.25	(0.05, 2.40)	(0.08, 1.34)
Chronic slope	-4.90	(-9.92, -2.08)	(-7.55, -3.10)	-0.97	(-2.95, 0.29)	(-2.03, -0.19)	0.97	(0.23, 1.00)	(0.58, 1.00)	0.29	(0.05, 1.83)	(0.08, 1.18)
Chronic slope truncated at 2y	-6.14	(-11.66, -2.35)	(-9.28, -3.70)	-0.77	(-2.99, 0.76)	(-2.10, 0.22)	0.99	(0.35, 1.00)	(0.76, 1.00)	0.21	(0.05, 1.79)	(0.07, 1.03)
Less informed priors												
Total slope at 3y	-5.32	(-10.55, -1.31)	(-8.28, -2.98)	-0.50	(-2.53, 1.41)	(-1.68, 0.61)	0.76	(0.05, 1.00)	(0.25, 0.99)	1.19	(0.05, 3.01)	(0.17, 2.30)
Total slope at 2y	-5.45	(-10.93, -1.49)	(-8.54, -3.13)	-0.41	(-2.46, 1.59)	(-1.59, 0.73)	0.82	(0.07, 1.00)	(0.30, 1.00)	1.02	(0.05, 3.13)	(0.12, 2.31)
Total slope at 1y	-5.34	(-11.45, -0.43)	(-8.98, -2.26)	0.00	(-2.23, 2.16)	(-1.37, 1.32)	0.96	(0.07, 1.00)	(0.43, 1.00)	0.38	(0.03, 3.04)	(0.06, 1.92)
Chronic slope	-4.75	(-9.31, -1.65)	(-7.18, -2.89)	-0.90	(-2.71, 0.48)	(-1.92, -0.07)	0.93	(0.11, 1.00)	(0.44, 1.00)	0.47	(0.03, 2.20)	(0.07, 1.51)
Chronic slope truncated at 2y	-6.04	(-11.34, -2.00)	(-9.10, -3.63)	-0.73	(-2.87, 0.88)	(-1.99, 0.29)	0.99	(0.24, 1.00)	(0.66, 1.00)	0.26	(0.03, 2.18)	(0.05, 1.34)

Y, years; BCI, credible interval.

More informed priors: Treatment effect on GFR slope igamma(shape=0.261,scale=0.005), and on urine protein igamma(shape=0.261,scale=0.000408); Less informed priors: Treatment effect no GFR slope igamma(shape=0.001,scale=0.001), and treatment effect on urine protein igamma(shape=0.001,scale=0.001)

Table S10 Predicted GFR slope for future trials

a. Treatment effect on urine protein at 6 months

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
Total slope at 3 years										
0.5	Predicted slope	4.10	0.34, 7.46	2.07, 6.17	4.07	0.24, 8.01	1.92, 6.46	4.01	0.05, 8.53	1.69, 6.75
	PPV of GFR slope > 0		0.98			0.98			0.98	
0.6	Predicted slope	2.77	-0.49, 5.73	1.15, 4.43	2.73	-0.63, 6.15	0.94, 4.79	2.70	-0.86, 6.69	0.60, 5.07
	PPV of GFR slope > 0		0.96			0.96			0.94	
0.7	Predicted slope	1.61	-1.26, 4.61	0.23, 3.16	1.62	-1.59, 4.91	-0.06, 3.48	1.62	-1.96, 5.35	-0.47, 3.81
	PPV of GFR slope > 0		0.92			0.89			0.85	
0.8	Predicted slope	0.61	-2.13, 3.77	-0.73, 2.23	0.66	-2.51, 4.00	-1.07, 2.48	0.68	-2.98, 4.30	-1.49, 2.80
	PPV of GFR slope > 0		0.75			0.70			0.67	
0.9	Predicted slope	-0.27	-3.01, 3.21	-1.74, 1.52	-0.19	-3.46, 3.37	-2.07, 1.72	-0.13	-4.05, 3.56	-2.46, 2.00
	PPV of GFR slope > 0		0.40			0.44			0.46	
1	Predicted slope	-1.04	-3.94, 2.69	-2.72, 0.92	-0.95	-4.43, 2.82	-3.01, 1.10	-0.89	-5.07, 2.95	-3.42, 1.35
	PPV of GFR slope > 0		0.21			0.25			0.30	
Total slope at 2 years										
0.5	Predicted slope	4.01	0.24, 7.77	2.01, 6.26	3.94	0.16, 8.25	1.91, 6.53	3.90	-0.01, 8.66	1.62, 6.82
	PPV of GFR slope > 0		0.98			0.98			0.97	
0.6	Predicted slope	2.75	-0.48, 6.19	1.14, 4.61	2.70	-0.54, 6.51	0.95, 4.90	2.68	-0.89, 6.93	0.62, 5.25
	PPV of GFR slope > 0		0.96			0.96			0.95	
0.7	Predicted slope	1.66	-1.26, 5.08	0.25, 3.38	1.67	-1.39, 5.38	-0.02, 3.68	1.67	-1.84, 5.70	-0.36, 4.04
	PPV of GFR slope > 0		0.92			0.90			0.86	
0.8	Predicted slope	0.74	-2.19, 4.22	-0.68, 2.51	0.79	-2.41, 4.44	-1.03, 2.76	0.81	-2.92, 4.78	-1.34, 3.04
	PPV of GFR slope > 0		0.78			0.73			0.70	
0.9	Predicted slope	-0.07	-3.11, 3.66	-1.67, 1.87	0.00	-3.44, 3.81	-1.95, 2.04	0.04	-3.93, 4.11	-2.28, 2.29
	PPV of GFR slope > 0		0.48			0.50			0.51	
1	Predicted slope	-0.77	-4.04, 3.26	-2.65, 1.33	-0.71	-4.44, 3.35	-2.89, 1.47	-0.65	-4.98, 3.59	-3.20, 1.71

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
	PPV of GFR slope > 0		0.28			0.32			0.35	
Total slope at 1 year										
0.5	Predicted slope	3.35	0.10, 7.69	1.47, 5.87	3.32	0.05, 8.20	1.44, 6.01	3.25	0.03, 8.36	1.35, 6.18
	PPV of GFR slope > 0		0.98			0.98			0.98	
0.6	Predicted slope	2.49	0.05, 6.05	1.16, 4.29	2.47	-0.05, 6.41	1.08, 4.51	2.42	-0.29, 6.72	0.90, 4.75
	PPV of GFR slope > 0		0.98			0.97			0.97	
0.7	Predicted slope	1.79	-0.45, 4.95	0.70, 3.18	1.79	-0.63, 5.20	0.53, 3.41	1.78	-1.08, 5.46	0.27, 3.69
	PPV of GFR slope > 0		0.96			0.95			0.93	
0.8	Predicted slope	1.18	-1.23, 4.21	-0.02, 2.59	1.23	-1.54, 4.45	-0.25, 2.73	1.25	-2.01, 4.69	-0.55, 2.95
	PPV of GFR slope > 0		0.90			0.87			0.83	
0.9	Predicted slope	0.63	-2.18, 3.86	-0.88, 2.24	0.70	-2.51, 3.97	-1.10, 2.34	0.76	-2.94, 4.14	-1.35, 2.48
	PPV of GFR slope > 0		0.72			0.71			0.70	
1	Predicted slope	0.12	-3.14, 3.70	-1.78, 2.04	0.20	-3.47, 3.76	-1.90, 2.11	0.28	-3.96, 3.93	-2.17, 2.20
	PPV of GFR slope > 0		0.54			0.56			0.57	
Chronic slope										
0.5	Predicted slope	3.27	1.08, 5.83	2.01, 4.84	3.25	0.91, 6.36	1.80, 5.13	3.19	0.56, 6.96	1.54, 5.42
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.06	0.26, 3.92	1.13, 3.16	2.04	-0.01, 4.56	0.83, 3.55	1.99	-0.47, 5.18	0.47, 3.92
	PPV of GFR slope > 0		0.98			0.97			0.95	
0.7	Predicted slope	1.03	-0.56, 2.60	0.25, 1.87	1.03	-1.03, 3.16	-0.14, 2.31	1.02	-1.57, 3.82	-0.57, 2.71
	PPV of GFR slope > 0		0.94			0.88			0.81	
0.8	Predicted slope	0.13	-1.46, 1.74	-0.72, 0.95	0.16	-2.05, 2.18	-1.11, 1.36	0.17	-2.62, 2.73	-1.54, 1.72
	PPV of GFR slope > 0		0.58			0.57			0.56	
0.9	Predicted slope	-0.66	-2.49, 1.13	-1.72, 0.27	-0.61	-3.13, 1.39	-2.04, 0.61	-0.59	-3.70, 1.91	-2.45, 0.96
	PPV of GFR slope > 0		0.17			0.26			0.31	
1	Predicted slope	-1.35	-3.58, 0.69	-2.67, -0.28	-1.30	-4.11, 0.86	-2.93, -0.01	-1.27	-4.69, 1.28	-3.31, 0.33
	PPV of GFR slope > 0		0.06			0.10			0.15	

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
Chronic slope truncated at 2 years										
0.5	Predicted slope	3.75	1.44, 6.36	2.36, 5.39	3.72	1.30, 6.95	2.17, 5.64	3.66	0.99, 7.55	1.92, 5.95
	PPV of GFR slope > 0		1.00			1.00			0.99	
0.6	Predicted slope	2.53	0.74, 4.50	1.47, 3.73	2.50	0.45, 5.08	1.22, 4.08	2.46	0.00, 5.70	0.92, 4.42
	PPV of GFR slope > 0		0.99			0.99			0.98	
0.7	Predicted slope	1.50	-0.06, 3.19	0.59, 2.45	1.49	-0.52, 3.72	0.27, 2.83	1.47	-1.12, 4.37	-0.08, 3.18
	PPV of GFR slope > 0		0.97			0.94			0.89	
0.8	Predicted slope	0.61	-1.06, 2.23	-0.36, 1.52	0.65	-1.59, 2.68	-0.70, 1.87	0.65	-2.22, 3.30	-1.06, 2.22
	PPV of GFR slope > 0		0.80			0.74			0.70	
0.9	Predicted slope	-0.17	-2.16, 1.62	-1.34, 0.83	-0.12	-2.69, 1.93	-1.63, 1.12	-0.09	-3.26, 2.45	-2.00, 1.45
	PPV of GFR slope > 0		0.42			0.46			0.47	
1	Predicted slope	-0.87	-3.23, 1.15	-2.27, 0.29	-0.80	-3.71, 1.38	-2.52, 0.54	-0.77	-4.26, 1.79	-2.89, 0.83
	PPV of GFR slope > 0		0.17			0.22			0.27	

UP, urine protein; RCT, randomized controlled trial; N, sample size; BCI, Bayesian credible interval; PPV, positive predictive value; GFR, glomerular filtration rate. Treatment effect on change in urine protein is expressed as geometric mean ratio. This can be converted to percent reduction in urine protein by 1-GMR *100

b. Treatment effect on urine protein at 9 months

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
Total slope at 3 years										
0.5	Predicted slope	4.13	1.15, 7.01	2.46, 5.95	4.09	1.01, 7.67	2.28, 6.26	4.04	0.69, 8.26	1.95, 6.58
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.77	0.26, 5.18	1.48, 4.15	2.75	0.01, 5.82	1.19, 4.56	2.73	-0.48, 6.36	0.83, 4.95
	PPV of GFR slope > 0		0.98			0.98			0.96	
0.7	Predicted slope	1.61	-0.63, 3.99	0.53, 2.78	1.61	-1.04, 4.38	0.14, 3.21	1.61	-1.60, 4.96	-0.29, 3.63
	PPV of GFR slope > 0		0.95			0.91			0.87	
0.8	Predicted slope	0.60	-1.54, 3.07	-0.52, 1.78	0.64	-2.07, 3.34	-0.89, 2.16	0.65	-2.69, 3.88	-1.33, 2.58
	PPV of GFR slope > 0		0.78			0.72			0.68	
0.9	Predicted slope	-0.29	-2.52, 2.35	-1.56, 1.03	-0.22	-3.13, 2.63	-1.90, 1.32	-0.20	-3.80, 3.03	-2.31, 1.70
	PPV of GFR slope > 0		0.37			0.42			0.45	
1	Predicted slope	-1.07	-3.54, 1.83	-2.57, 0.43	-0.98	-4.18, 2.02	-2.88, 0.65	-0.98	-4.82, 2.32	-3.24, 1.01
	PPV of GFR slope > 0		0.16			0.21			0.26	
Total slope at 2 years										
0.5	Predicted slope	4.16	1.24, 7.26	2.47, 6.15	4.09	1.13, 7.91	2.33, 6.38	4.04	0.79, 8.5	2.02, 6.74
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.82	0.30, 5.48	1.54, 4.35	2.77	0.16, 6.06	1.29, 4.71	2.76	-0.31, 6.61	0.90, 5.08
	PPV of GFR slope > 0		0.98			0.98			0.96	
0.7	Predicted slope	1.69	-0.61, 4.22	0.59, 2.97	1.67	-0.89, 4.64	0.23, 3.40	1.68	-1.47, 5.24	-0.18, 3.76
	PPV of GFR slope > 0		0.95			0.92			0.88	
0.8	Predicted slope	0.71	-1.52, 3.37	-0.43, 1.97	0.74	-2.04, 3.66	-0.84, 2.35	0.76	-2.64, 4.16	-1.23, 2.72
	PPV of GFR slope > 0		0.81			0.75			0.71	
0.9	Predicted slope	-0.15	-2.53, 2.74	-1.49, 1.23	-0.09	-3.17, 2.94	-1.86, 1.53	-0.06	-3.78, 3.34	-2.23, 1.87
	PPV of GFR slope > 0		0.43			0.47			0.48	
1	Predicted slope	-0.91	-3.55, 2.24	-2.52, 0.64	-0.84	-4.22, 2.37	-2.84, 0.88	-0.78	-4.82, 2.74	-3.20, 1.20
	PPV of GFR slope > 0		0.20			0.25			0.30	

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
Total slope at 1 year										
0.5	Predicted slope	3.86	1.00, 7.53	2.08, 6.17	3.80	0.89, 8.06	1.98, 6.35	3.75	0.77, 8.55	1.83, 6.62
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.79	0.60, 5.68	1.50, 4.44	2.74	0.42, 6.22	1.33, 4.73	2.70	0.09, 6.68	1.12, 5.00
	PPV of GFR slope > 0		0.99			0.99			0.98	
0.7	Predicted slope	1.89	-0.03, 4.41	0.83, 3.15	1.88	-0.34, 4.81	0.57, 3.47	1.89	-0.88, 5.28	0.29, 3.80
	PPV of GFR slope > 0		0.97			0.96			0.93	
0.8	Predicted slope	1.12	-0.91, 3.55	-0.02, 2.34	1.17	-1.40, 3.86	-0.33, 2.61	1.20	-2.01, 4.22	-0.61, 2.89
	PPV of GFR slope > 0		0.9			0.85			0.82	
0.9	Predicted slope	0.43	-1.98, 3.09	-0.96, 1.84	0.50	-2.51, 3.19	-1.25, 2.01	0.56	-3.05, 3.49	-1.52, 2.24
	PPV of GFR slope > 0		0.66			0.66			0.65	
1	Predicted slope	-0.19	-3.07, 2.87	-1.91, 1.47	-0.11	-3.57, 2.93	-2.16, 1.60	-0.04	-4.09, 3.04	-2.40, 1.80
	PPV of GFR slope > 0		0.44			0.46			0.49	
Chronic slope										
0.5	Predicted slope	3.18	1.29, 5.60	2.00, 4.67	3.15	1.06, 6.16	1.81, 4.90	3.11	0.68, 6.75	1.54, 5.21
	PPV of GFR slope > 0		1.00			0.99			0.99	
0.6	Predicted slope	2.01	0.44, 3.76	1.12, 3.04	1.99	0.15, 4.39	0.85, 3.37	1.97	-0.36, 4.98	0.52, 3.73
	PPV of GFR slope > 0		0.99			0.98			0.96	
0.7	Predicted slope	1.03	-0.38, 2.43	0.27, 1.80	1.02	-0.86, 3.06	-0.10, 2.19	1.01	-1.47, 3.60	-0.47, 2.58
	PPV of GFR slope > 0		0.95			0.88			0.82	
0.8	Predicted slope	0.16	-1.37, 1.53	-0.68, 0.89	0.18	-1.90, 2.03	-1.04, 1.28	0.18	-2.56, 2.57	-1.41, 1.64
	PPV of GFR slope > 0		0.61			0.58			0.57	
0.9	Predicted slope	-0.59	-2.44, 0.90	-1.64, 0.22	-0.55	-2.95, 1.26	-1.96, 0.56	-0.55	-3.55, 1.76	-2.30, 0.89
	PPV of GFR slope > 0		0.18			0.26			0.32	
1	Predicted slope	-1.26	-3.49, 0.41	-2.59, -0.32	-1.21	-3.96, 0.67	-2.83, -0.02	-1.20	-4.54, 1.12	-3.13, 0.25
	PPV of GFR slope > 0		0.05			0.09			0.15	

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
Chronic slope truncated at 2 years										
0.5	Predicted slope	3.84	1.77, 6.40	2.54, 5.37	3.82	1.60, 6.95	2.35, 5.67	3.76	1.19, 7.55	2.08, 6.01
	PPV of GFR slope > 0		1.00			1.00			1.00	
0.6	Predicted slope	2.61	0.99, 4.49	1.62, 3.73	2.58	0.63, 5.09	1.35, 4.10	2.56	0.07, 5.81	1.02, 4.46
	PPV of GFR slope > 0		1.00			0.99			0.98	
0.7	Predicted slope	1.57	0.08, 3.11	0.70, 2.49	1.58	-0.46, 3.73	0.36, 2.87	1.57	-1.09, 4.38	0.00, 3.24
	PPV of GFR slope > 0		0.98			0.95			0.90	
0.8	Predicted slope	0.67	-0.96, 2.13	-0.27, 1.55	0.71	-1.54, 2.69	-0.60, 1.91	0.71	-2.22, 3.29	-0.96, 2.27
	PPV of GFR slope > 0		0.83			0.77			0.72	
0.9	Predicted slope	-0.12	-2.06, 1.47	-1.24, 0.85	-0.07	-2.65, 1.89	-1.54, 1.15	-0.05	-3.24, 2.40	-1.89, 1.50
	PPV of GFR slope > 0		0.44			0.47			0.49	
1	Predicted slope	-0.82	-3.15, 0.97	-2.20, 0.30	-0.76	-3.65, 1.26	-2.44, 0.55	-0.73	-4.26, 1.69	-2.76, 0.86
	PPV of GFR slope > 0		0.17			0.23			0.28	

UP, urine protein; RCT, randomized controlled trial; N, sample size; BCI, Bayesian credible interval; PPV, positive predictive value; GFR, glomerular filtration rate. Treatment effect on change in urine protein is expressed as geometric mean ratio. This can be converted to percent reduction in urine protein by 1-GMR *100

c. Treatment effect on urine protein at 12 months

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	95% BCI	80% BCI	Median	95% BCI	80% BCI	Median	95% BCI	80% BCI
Total slope at 3 years										
0.5	Predicted slope	3.28	0.13, 6.61	1.66, 5.16	3.27	0.04, 6.95	1.55, 5.35	3.24	-0.14, 7.30	1.36, 5.55
	PPV of GFR slope > 0		0.98			0.98			0.97	
0.6	Predicted slope	2.24	-0.65, 5.27	0.85, 3.86	2.24	-0.72, 5.48	0.69, 4.07	2.21	-0.97, 5.89	0.45, 4.32
	PPV of GFR slope > 0		0.96			0.95			0.94	
0.7	Predicted slope	1.34	-1.34, 4.35	0.06, 2.87	1.37	-1.51, 4.49	-0.17, 3.08	1.35	-1.79, 4.83	-0.44, 3.35
	PPV of GFR slope > 0		0.90			0.88			0.84	
0.8	Predicted slope	0.56	-2.13, 3.69	-0.78, 2.14	0.61	-2.32, 3.77	-1.00, 2.35	0.61	-2.66, 4.05	-1.27, 2.57
	PPV of GFR slope > 0		0.74			0.70			0.68	
0.9	Predicted slope	-0.10	-2.84, 3.19	-1.59, 1.56	-0.05	-3.14, 3.27	-1.79, 1.72	-0.04	-3.49, 3.48	-2.06, 1.93
	PPV of GFR slope > 0		0.45			0.48			0.49	
1	Predicted slope	-0.69	-3.65, 2.79	-2.39, 1.07	-0.64	-4.00, 2.87	-2.55, 1.21	-0.62	-4.40, 3.04	-2.81, 1.40
	PPV of GFR slope > 0		0.27			0.30			0.34	
Total slope at 2 years										
0.5	Predicted slope	3.39	0.67, 6.88	1.91, 5.36	3.38	0.60, 7.22	1.77, 5.56	3.34	0.33, 7.58	1.58, 5.74
	PPV of GFR slope > 0		0.99			0.99			0.98	
0.6	Predicted slope	2.34	-0.16, 5.51	1.11, 3.95	2.34	-0.29, 5.78	0.91, 4.19	2.31	-0.53, 6.13	0.66, 4.44
	PPV of GFR slope > 0		0.97			0.97			0.96	
0.7	Predicted slope	1.44	-0.98, 4.53	0.32, 2.91	1.46	-1.10, 4.72	0.08, 3.15	1.47	-1.48, 5.00	-0.22, 3.41
	PPV of GFR slope > 0		0.93			0.91			0.88	
0.8	Predicted slope	0.67	-1.81, 3.85	-0.49, 2.14	0.71	-1.96, 3.96	-0.74, 2.36	0.74	-2.44, 4.22	-1.04, 2.59
	PPV of GFR slope > 0		0.80			0.75			0.72	
0.9	Predicted slope	0.01	-2.63, 3.31	-1.32, 1.56	0.05	-2.85, 3.36	-1.55, 1.72	0.07	-3.35, 3.54	-1.84, 1.93
	PPV of GFR slope > 0		0.50			0.52			0.53	
1	Predicted slope	-0.58	-3.49, 2.86	-2.14, 1.04	-0.53	-3.77, 2.95	-2.33, 1.19	-0.51	-4.21, 3.05	-2.60, 1.37
	PPV of GFR slope > 0		0.28			0.32			0.36	

Observed treatment effect on change in UP		Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
		Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
Total slope at 1 year										
0.5	Predicted slope	3.60	1.07, 7.22	2.06, 5.66	3.58	0.99, 7.59	1.96, 5.80	3.52	0.84, 7.92	1.82, 6.03
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.63	0.65, 5.52	1.46, 4.18	2.60	0.48, 5.91	1.31, 4.39	2.57	0.16, 6.25	1.10, 4.66
	PPV of GFR slope > 0		0.99			0.99			0.98	
0.7	Predicted slope	1.83	0.01, 4.38	0.80, 3.06	1.83	-0.30, 4.70	0.59, 3.31	1.83	-0.75, 5.02	0.32, 3.59
	PPV of GFR slope > 0		0.98			0.96			0.94	
0.8	Predicted slope	1.13	-0.82, 3.54	0.03, 2.29	1.16	-1.20, 3.72	-0.21, 2.51	1.19	-1.71, 4.13	-0.47, 2.77
	PPV of GFR slope > 0		0.90			0.86			0.83	
0.9	Predicted slope	0.51	-1.72, 3.00	-0.82, 1.80	0.55	-2.13, 3.18	-1.03, 1.96	0.60	-2.69, 3.38	-1.26, 2.17
	PPV of GFR slope > 0		0.70			0.69			0.67	
1	Predicted slope	-0.05	-2.67, 2.64	-1.61, 1.43	0.01	-3.09, 2.77	-1.84, 1.56	0.06	-3.59, 2.88	-1.99, 1.74
	PPV of GFR slope > 0		0.48			0.50			0.52	
Chronic slope										
0.5	Predicted slope	2.45	0.46, 4.88	1.40, 3.79	2.43	0.37, 5.22	1.25, 3.96	2.42	0.19, 5.56	1.03, 4.21
	PPV of GFR slope > 0		0.99			0.98			0.98	
0.6	Predicted slope	1.54	-0.19, 3.44	0.70, 2.54	1.53	-0.35, 3.81	0.49, 2.82	1.52	-0.66, 4.24	0.22, 3.03
	PPV of GFR slope > 0		0.97			0.96			0.93	
0.7	Predicted slope	0.77	-0.82, 2.54	-0.01, 1.61	0.76	-1.08, 2.80	-0.26, 1.90	0.78	-1.49, 3.20	-0.54, 2.14
	PPV of GFR slope > 0		0.90			0.84			0.79	
0.8	Predicted slope	0.10	-1.59, 1.87	-0.78, 0.93	0.13	-1.90, 2.08	-1.02, 1.21	0.14	-2.36, 2.42	-1.28, 1.44
	PPV of GFR slope > 0		0.57			0.56			0.56	
0.9	Predicted slope	-0.49	-2.49, 1.38	-1.55, 0.43	-0.45	-2.74, 1.54	-1.72, 0.66	-0.43	-3.20, 1.80	-1.98, 0.87
	PPV of GFR slope > 0		0.23			0.29			0.34	
1	Predicted slope	-1.00	-3.34, 1.00	-2.23, 0.02	-0.97	-3.58, 1.12	-2.40, 0.21	-0.94	-4.03, 1.33	-2.65, 0.40
	PPV of GFR slope > 0		0.10			0.14			0.18	

Observed treatment effect on change in UP		**Infinite sized RCT**			**Modest sized RCT (N=250)**			**Small sized RCT (N=100)**		
		Median	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**	**Median**	**95% BCI**	**80% BCI**
Chronic slope truncated at 2 years										
0.5	Predicted slope	3.48	1.22, 6.07	2.14, 5.02	3.46	1.05, 6.54	1.97, 5.26	3.41	0.81, 7.04	1.72, 5.55
	PPV of GFR slope > 0		0.99			0.99			0.99	
0.6	Predicted slope	2.34	0.49, 4.32	1.31, 3.48	2.32	0.20, 4.84	1.08, 3.78	2.29	-0.21, 5.38	0.76, 4.13
	PPV of GFR slope > 0		0.99			0.98			0.97	
0.7	Predicted slope	1.38	-0.34, 3.09	0.46, 2.32	1.39	-0.72, 3.57	0.16, 2.65	1.38	-1.25, 4.14	-0.18, 3.00
	PPV of GFR slope > 0		0.96			0.92			0.87	
0.8	Predicted slope	0.56	-1.25, 2.25	-0.45, 1.49	0.59	-1.66, 2.67	-0.76, 1.79	0.61	-2.32, 3.16	-1.09, 2.13
	PPV of GFR slope > 0		0.78			0.73			0.69	
0.9	Predicted slope	-0.16	-2.26, 1.66	-1.37, 0.87	-0.11	-2.66, 1.95	-1.66, 1.12	-0.09	-3.36, 2.39	-1.97, 1.42
	PPV of GFR slope > 0		0.42			0.45			0.47	
1	Predicted slope	-0.80	-3.26, 1.21	-2.26, 0.36	-0.75	-3.65, 1.41	-2.50, 0.57	-0.71	-4.27, 1.75	-2.76, 0.84
	PPV of GFR slope > 0		0.19			0.24			0.29	

UP, urine protein; RCT, randomized controlled trial; N, sample size; BCI, Bayesian credible interval; PPV, positive predictive value; GFR, glomerular filtration rate. Treatment effect on change in urine protein is expressed as geometric mean ratio. This can be converted to percent reduction in urine protein by 1-GMR *100

Table S11 Threshold for treatment effect on urine protein change to assure PPV above range of target

a. Treatment effect on urine protein at 6 months

GFR Slope	Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
	97.5%	95%	90%	97.5%	95%	90%	97.5%	95%	90%
Total 3y	0.54	0.64	0.72	0.52	0.62	0.69	0.50	0.58	0.66
Total 2y	0.53	0.65	0.73	0.52	0.62	0.70	NA	0.59	0.66
Total 1y	0.62	0.73	0.80	0.56	0.70	0.77	0.51	0.65	0.73
Chronic	0.63	0.69	0.73	0.60	0.64	0.68	0.56	0.60	0.65
2y Chronic	0.69	0.73	0.76	0.64	0.69	0.73	0.60	0.64	0.69

b. Treatment effect on urine protein at 9 months

GFR Slope	Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
	97.5%	95%	90%	97.5%	95%	90%	97.5%	95%	90%
Total 3y	0.63	0.70	0.75	0.60	0.66	0.71	0.56	0.62	0.67
Total 2y	0.63	0.70	0.76	0.61	0.67	0.72	0.58	0.63	0.68
Total 1y	0.70	0.75	0.80	0.66	0.71	0.77	0.61	0.67	0.73
Chronic	0.65	0.70	0.73	0.61	0.65	0.69	0.57	0.61	0.65
2y Chronic	0.71	0.74	0.77	0.66	0.69	0.73	0.61	0.65	0.70

c. Treatment effect on urine protein at 12 months

GFR Slope	Infinite sized RCT			Modest sized RCT (N=250)			Small sized RCT (N=100)		
	97.5%	95%	90%	97.5%	95%	90%	97.5%	95%	90%
Total 3y	0.51	0.61	0.71	0.50	0.60	0.68	NA	0.57	0.65
Total 2y	0.58	0.67	0.74	0.56	0.64	0.71	0.54	0.61	0.68
Total 1y	0.70	0.76	0.80	0.66	0.71	0.77	0.62	0.68	0.74
Chronic	0.57	0.65	0.70	0.56	0.61	0.66	0.52	0.58	0.63
2y Chronic	0.66	0.71	0.75	0.63	0.67	0.72	0.58	0.63	0.68

RCT, randomized controlled trial; Y, years; N, sample size; UP, urine protein. Treatment effect on change in urine protein is expressed as geometric mean ratio. This can be converted to percent reduction in urine protein by 1-GMR *100

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