Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-analysis

Lesley A Inker, MD MS[1], Hiddo Lambers-Heerspink, PharmD[2], Hocine Tighiouart, MS[3,4], Juhi Chaudhari, MPH[1], Shiyuan Miao, MS[1], Ulysses Diva, PhD[5], Alex Mercer, PhD[6], Gerald B Appel, MD[7], James V Donadio, MD[8], Jürgen Floege, MD[9], Philip K T Li, MD[10], Bart D Maes, MD, PhD[11], Francesco Locatelli, MD[12], Manuel Praga, MD PhD[13], Francesco P Schena, MD[14], Andrew S Levey, MD[1], Tom Greene, PhD[15]

[1.]Division of Nephrology, Tufts Medical Center, Boston, Massachusetts [2.]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands [3.]The Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts [4.]Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts [5.]Biometrics, Travere Therapeutics, Inc., San Diego, California, USA [6.]Clinical Drug Development, JAMCO Pharma Consulting AB, Stockholm, Sweden [7.]Division of Nephrology, Columbia University Medical Center and the New York Presbyterian Hospital, New York, New York [8.]Emeritus Staff, Mayo Clinic, Rochester, Minnesota [9.]Division of Nephrology and Immunology, RWTH Aachen University, Aachen, Germany [10.]Division of Nephrology, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong [11.]AZ Delta, Roeselare, Belgium [12.]Department of Nephrology and Dialysis, Alessandro Manzoni Hospital, Lecco, Italy [13.]Instituto de Investigación Hospital Universitario 12 de Octubre, i+12, Complutense University, Madrid, Spain [14.]Renal, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy [15.]Departments of Population Health Sciences and Internal Medicine, University of Utah, Salt Lake City, Utah

Abstract

Rationale & Objective : An early change in proteinuria is considered a reasonably likely surrogate endpoint in IgA nephropathy (IgAN), and can be used as basis for accelerated approval of therapies with verification in a post-marketing confirmatory trial. GFR slope is a recently

Corresponding author Lesley A Inker, Division of Nephrology, Tufts Medical Center, Boston, MA 02111, linker@tuftsmedicalcenter.org, 617-636-2569.

validated surrogate endpoint for CKD progression and may be considered as the endpoint used for verification. We undertook a meta-analysis of clinical trials in IgAN to compare treatment effects on change in proteinuria to change in eGFR slope.

Study design: Individual patient-level meta-analysis.

Setting and Study Populations: Individual data of 1037 patients from 12 randomized trials.

Selection Criteria for Studies: Randomized trials of IgAN with proteinuria measurements at baseline and 6-months (range 2.5–14) and at least one further year of follow-up for the clinical outcome.

Analytical Approach: For each trial we estimated the treatment effects on proteinuria and on the eGFR slope, computed as either the total slope starting at baseline or the chronic slope starting 3-months after randomization. We used a Bayesian mixed effects analysis to relate the treatment effects on proteinuria to effects on GFR slope across these studies and developed a prediction model for the treatment effect on the GFR slope based on the effect on proteinuria.

Results: Across all studies, treatment effects on proteinuria accurately predicted treatment effects on the total slope at 3 years (median R^2=0.88 [95% Bayesian credible Interval (BCI) 0.06–1] and on the chronic slope (R^2 0.98 [95% BCI 0.29–1]). For future trials, an observed treatment effect of approximately 30% reduction in proteinuria would confer probabilities of at least 90% for nonzero treatment benefits on the total and chronic slope of eGFR. We obtained similar results for proteinuria at 9 and 12 months and total slope at 2 years.

Limitations: Study population restricted to 12 trials of small sample size, leading to wide BCIs. There was heterogeneity among trials with respect to study design and interventions.

Conclusions: These results provide new evidence supporting that early reduction in proteinuria can be used as a surrogate endpoint for studies of CKD progression in IgAN.

Plain language summary

Drug regulatory agencies allow change in urine protein to be used as endpoints for trials in IgA nephropathy (IgAN), as part of accelerated approval of treatments, as long as there is confirmation of the treatment benefit following approval in post-marketing trials. We performed an individual patient meta-analysis including data from 1037 patients across 12 trials to assess how treatment effects on the change in proteinuria predicts the treatment effects on the change in eGFR, a surrogate outcome that has recently been validated. We found that treatment effects on urine protein accurately predicted treatment effects on the total GFR slope at 3 years and on chronic GFR slope. These results provide new evidence supporting that a change in proteinuria can be used as a surrogate endpoint in treatment trials of progression of IgAN.

Keywords

GFR slope; Urine protein; Surrogate endpoint; IgA Nephropathy; End-stage renal disease (ESRD)

Introduction

IgA nephropathy (IgAN) is rare, but the most common cause of glomerulonephritis, with few proven therapies. Trials early in the disease course are challenging to undertake because of low event rate for clinical endpoints, generally defined as kidney failure (treated end stage kidney disease (ESKD) or glomerular filtration rate (GFR) < 15 mL/min/1.73 m^2) or doubling of serum creatinine (S_{cr}). In many chronic kidney diseases (CKD), a large decline in GFR, assessed as a doubling of S_{cr} from baseline, and more recently 30 or 40% decline in GFR, has often been used as a surrogate endpoint for kidney failure in randomized clinical trials (RCTs) of patients with low levels of GFR or rapidly progressive disease RCTs.[1–3] In a rare disease such as IgAN, these endpoints may not be feasible because of the long duration of the disease, leading to large expense and complexity of trials that would be required to detect treatment effects on a large decline in GFR. In addition, the goal of most therapeutic strategies is to treat the disease early, prior to development of irreversible changes. These issues have likely contributed to the paucity of therapies. Recent evidence supports early changes in urine protein as a reasonably likely surrogate in IgAN.[4,5]

In the US, reasonably likely surrogate endpoints can be used as a basis for accelerated approval of therapies intended to treat serious or life-threating conditions, such as IgAN.[6,7] The clinical benefit of products approved under this program would need to be verified in a post-marketing confirmatory trial.[8] Recent empirical data demonstrated the validity of GFR slope as a surrogate endpoint for clinical benefit in general CKD progression studies.[9–13] For IgAN, the slope of GFR decline would be a more viable endpoint for verification in post-marketing confirmatory trials given the low likelihood of sufficient clinical events. Here we report an individual patient-level meta-analysis of a pooled dataset of 1037 individuals from twelve RCTs in IgAN to evaluate the association of treatment effects on early change in urine protein compared to treatment effects on GFR slope. These data would be valuable for design of confirmatory trials.

Methods

Study selection and study populations

We identified studies through systematic searches of the medical literature on Ovid MedLine published from January 1, 1979 to December 15, 2016, as previously described[10,14] (Item S3, Tables S1–S2, Figures S1–S2). Twelve studies were included that investigated four intervention types [renin angiotensin system blockade (RASB), fish oil, steroids, or other immunosuppression agents] (Table S3).[15–28] Participants provided informed consent at inclusion in each study. This analysis was considered exempt from review by the Tufts Medical Center Institutional Review Board.

Early change in urine protein

We defined change in urine protein 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 the recent publication evaluating associations between treatment effects on changes in urine protein to those on the clinical endpoint.[14]

Urine protein was in units of grams/day (g/day) and was log transformed due to skewness of the data.

GFR slope

GFR was estimated using the CKD-EPI 2009 creatinine equation.[29] Creatinine was standardized to isotope dilution mass spectroscopy traceable reference methods using direct comparison or was reduced by 5%.[10] As we have previously described, we used a simplified linear mixed effects model based on a single slope starting at 3 months post randomization adjusted for baseline GFR with the model accounting for various sources of variation in GFR slopes between and within subjects and treatment arms.[10,30] The slope was estimated for all participants in each study. For studies with greater than 15 dialysis or death events, we used a shared parameter model to account for informative censoring due to dialysis or death.[16–18,22] 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, or 3 years follow-up factored by the follow-up duration represented the treatment effects on the acute, chronic, and total slopes, respectively. To recreate a more realistic trial scenario, in sensitivity analysis, we also present the results for the chronic slope computed over a two-year period which we defined as last visit by 27 months (referred to as 2 year chronic slope).

Analyses

Objective—Our first goal was to evaluate the association of the treatment effects on the change in urine protein with treatment effects on GFR slope. Our second goal was to use these results to describe the probabilities of treatment benefit on GFR slope associated with varying treatment effects on urine protein for application to future studies. The supplement includes a more detailed description of the methods.

Trial level analysis—The trial level analysis requires two steps: intent-to-treat estimation of the treatment effects on both endpoints within each RCT, followed by a meta-regression to relate the treatment effects on the two endpoints of interest across RCTs.[2,5,10,31] In the first step, treatment effects on change in urine protein were estimated by performing analyses of covariance within each study, with log urine protein change as the endpoint adjusting for treatment and log baseline urine protein. Treatment effects on urine protein were expressed as geometric mean ratios (GMR). Treatment effects on GFR slope were estimated using a shared parametric mixed effects model as described above and were expressed as mean differences in the GFR slopes between the treatment vs control groups, in units of ml/min/1.73m^2/year.

In the second step, a Bayesian mixed effects meta-regression related the estimated treatment effects on one endpoint to the estimated treatment effects on the second endpoint with study as the unit of analysis (details in supplement). The model relates the treatment effects on the two endpoints after accounting for random errors in the estimated effects in each RCT. The meta-regression supports strong association between the two endpoints if 1) the slope of the meta-regression line is statistically significant as defined by Bayesian credible intervals (BCI) that do not cross 0, with a large magnitude, 2) the intercept is close to 0, implying

absence of an average effect on the GFR slope when the treatment does not affect urine protein, 3) the R^2 is high, so that treatment effects on urine protein account for most of the variation in treatment effects on the GFR slope, and 4) the root mean square error (RMSE) is low, assuring low variation in the GFR slope given a fixed treatment effect on urine protein. We also used separate random effects meta-analyses to summarize the distributions of the treatment effects on each endpoint across the 12 RCTs.

Predicting clinical benefit in future trials—From the trial level meta-regression, we computed 95% and 80% Bayesian credible prediction intervals and estimated the probabilities of treatment benefit on GFR slope (defined by a difference in slope > 0) for an infinite, modest or small sized RCT. Under the meta-regression model for an infinite sized RCT, a treatment effect has a 95% or 80% probability of falling within the prediction interval, a 2.5% and 10% probability of exceeding the upper limit, and a 2.5% and 10% probability or falling below the lower limit, respectively. A modest RCT was defined as having a sample size of 250 (SE 0.09) and a small RCT was defined as having a sample size of 100 (SE 0.15), assuming a standard deviation of 0.75 for change in log urine protein. We computed the threshold associated with the smallest observed treatment effect on a change in urine protein that provides a positive predictive value (PPV) of 97.5%, 95% and 90% for treatment benefit on the GFR slope.

Analyses were performed using SAS version 9.4M6 (SAS Institute, Cary, NC) and R 4.0.1 (R Project for Statistical Computing www.r-project.org.[32]

Results

Table 1 and Tables S4 and S5 summarize aggregate characteristics of the included studies. Of the 12 studies, two tested RAS blockade,[15,16] 3 tested steroids,[23–27] 2 tested fish oil,[17,18] 2 tested MMF,[19,20] and 2 others tested azathioprine.[21,22] STOP-IgAN contained two interventions, each at different levels of GFR. At higher GFR the intervention was steroids whereas at lower levels of GFR, the intervention was cyclophosphamide followed by azathioprine as well as steroids. Across the trials, the mean age of the study participants ranged from 32 to 46 years and the proportion of women ranged from 10% (2/20) to 72% (77/107). Average baseline eGFR and urine protein were 71 (standard deviation (SD) 30) ml/min/1.73 m^2 and 1.8 (25th, 75th percentile: 1.2, 2.6) g/day, respectively, in the pooled dataset.

Over a 6 month (25th, 75th percentiles, 5.9, 6.9 months) period, the overall percent mean change in urine protein in the control and treatment arms was 35% reduction (25th, 75th percentiles 57% reduction, 18% increase) and 53% reduction (25th, 75th percentile, 68% reduction, 9% reduction), respectively, resulting in a treatment effect corresponding to a GMR of 0.75 [95th confidence intervals (CI) 0.61, 0.94)] which corresponds approximately to a 25% relative reduction in urine protein due to the treatment (95% CI: 39% reduction, 6% reduction); Figure 1, left panel; Table S6). Similar results were seen with the 9 or 12 month change in urine protein (Table S6; Figure S3).

For most studies, the mean total GFR slope at 1, 2, and 3 years and chronic GFR slope was less steep (less negative) in the treatment arm compared to the control arm (Tables S7–S8; Figure S4–S5). The pooled mean total slope at 3 years was –3.51 (SE 0.83) ml/min/1.73 m^2/year in the control arm and –1.91 (SE 0.54) ml/min/1.73m^2/year in the treatment arm. The mean treatment effect on the total slope at 3 years (1.39 (95% CI –0.21, 2.99) ml/min/1.73 m^2/year) was stronger than on the chronic slope (0.70 (95% CI –0.62, 2.02)) ml/min/1.73m^2/year) with variation by study (Figure 1).

There appeared to be strong agreement between the treatment effects on the change in urine protein to treatment effects on total slope at 3 years (Figure 2; Table S9a; Figure S6). For change in urine protein at 6 months, the slope of the meta-regression line was –7.18 (95% BCI –13.03 to –1.80). A slope of –7.18 would imply that each additional 10% reduction in geometric mean urine protein by the treatment is associated with an additional 0.72 ml/min/1.73m^2/year reduction in mean slope by the treatment. The intercept of the regression line was –0.93 (95% BCI –3.06 to 1.27) indicating that there is no evidence that treatments with no effect on the change in urine protein at 6 months have a nonzero average effect on the total slope at 3 years. The median posterior estimate for R^2 was 0.88 (95% BCI 0.06 to 1.00; 80% BCI 0.30, 1.00). Results were similar for total slope at 2 years (R^2 0.86, 95% BCI 0.03 to 1.0; 80% BCI 0.24 to 1.0). Higher R^2 values were estimated for the chronic slope (R^2 0.98, 95% BCI 0.29, 1.00; 80% BCI 0.68, 1). For total slope at 1 year, there was a nonsignificant association between the two treatment effects (Table S9a and Figure S6). Results were similar for chronic slope estimate over the entire study duration and over two years (Table S9a and Figure S7). Results were similar for change in urine protein at 9 and 12 months (Tables S9b and S9c, Table S10, and Figures S6 and S7).

For future trials, an observed treatment effect of a 30% reduction in urine protein at 6 months confers probabilities of approximately 90% for nonzero treatment benefit on total GFR slope at 3 and 2 years and on the chronic GFR slope (Table 2 and Table S10). Predicted treatment effects on GFR slope are stronger at higher magnitude of treatment effect on urine protein (Figure 3, Table 2, Figure S8, Tables S10 and S11). For example, for future modest sized trials, the model predicts that a treatment effect of change in urine protein of 30% would predict a treatment effect on total GFR slope at 3 years of 1.62 (95% BCI –1.59, 4.91; 80% BCI –0.06, 3.48), whereas treatment effect of 40% would predict treatment effect of 2.73 (95% BCI –0.63, 6.15; 80% BCI 0.94, 4.79) (Table 2 and Table S10). Similar results were observed for changes in urine protein at 9 and 12 months (Tables S10 and S11; Figure S8).

Discussion

Valid surrogate endpoints may improve the efficiency of clinical trials, particularly for clinical trials of chronic kidney disease in which progression to clinical endpoints can be slow. For studies of IgAN, use of surrogate endpoints also allows for evaluation of interventions early in the disease course prior to kidney scarring and irreversible changes when interventions might have additional value. There is sound biological and empirical basis for the hypothesis that an early change in urine protein is a valid surrogate endpoint for progression of IgAN. First, pathological data shows that the degree of urine protein

correlates with greater evidence of disease.[33–35] Second, baseline levels of urine protein are prognostic for long-term disease progression,[36–43] and attenuation of urine protein after steroid therapy is associated with improved prognosis.[44,45] Third, we have previously provided trial level analyses that demonstrate that early changes in urine protein are a moderately strong surrogate relative to the clinical endpoint across a broad collection of kidney diseases, including IgAN.[5,14] A recent paper by the Kidney Health Initiative supports "the use of proteinuria reduction as a reasonably likely surrogate endpoint in future trials studying IgAN…. when accompanied by verification of the clinical benefits in a postmarketing confirmatory trial".[8] Drug development programs for treatments in IgAN using change in GFR are underway.[46–48] The current report provides evidence useful for the design of such studies in IgAN.

Using the trial level approach, we found that across 12 studies of multiple interventions, there is a positive relationship between the treatment effects on urine protein and on GFR slope. The Bayesian credible intervals that did not cross 0. This suggests that observed treatment effects on the early changes in urine protein can inform investigators and sponsors on the longer-term treatment effects on GFR slope. The Bayesian credible intervals for the key parameters of our trial level meta-regression analysis are wide. This uncertainty leads to uncertainty in the Bayesian credible prediction intervals for the treatment effects on slope that can be expected for different observed treatment effects on urine protein in future trials. For example, our model would predict that even a treatment effect of 0.8 (20% reduction) on the change in urine protein the predicted treatment effect on GFR slope would have confidence intervals that cross 0. These limitations in precision lead to for the requirement for large thresholds for the treatment effects on the change in urine protein to demonstrate a high probability of benefit on slope. The imprecision is the result of the limited number of studies, all with small samples sizes, rather than an inherent limitation of urine protein as an endpoint in IgAN. Future analyses relating treatment effects on change in urine protein to treatment effects on GFR slope in the overall set of CKD studies, are expected to achieve higher level of precision.

Previously, we demonstrated that treatment effects on GFR slope have very strong associations with treatment effects on the clinical endpoint in 49 studies evaluating treatments for CKD progression, providing evidence for its validation.[10,11] These associations are substantially stronger than that observed for treatment effects on change in albuminuria to the clinical endpoint in CKD,[14] consistent with the biological nature of GFR decline as an intermediate endpoint along the path to kidney failure. The FDA has stated that they have "accepted GFR slope as an endpoint and basis for full approval of therapies for rare chronic kidney diseases", and the EMA stated that GFR slope "offers promising potential for a surrogate endpoint in the confirmatory phase of a specific clinical program"[13]. This supplements the FDA's prior acceptance of confirmed 40% and 30% decline in GFR as a basis for drug approval of therapies intended to treat common and rare chronic kidney diseases, respectively.[12] Thus the results presented here together with our prior work evaluating treatment effects on urine protein and on GFR slope to clinical endpoints, suggest at least two potential uses for urine protein as a surrogate endpoint in IgAN studies.[10] First, treatment effects on early change in urine protein can be used in early phase studies for proof-of-concept or dose finding, both of which may accommodate some

degree of uncertainty. Second, change in urine protein can be used for initial regulatory approval followed by a confirmatory trial that uses mean difference in GFR slope as the endpoint. This can be performed as two separate trials or as part of an adaptive clinical trial design. In such a design, the treatment effect on early change in proteinuria at an interim analysis can be used to estimate conditional power for treatment effects on GFR slope, as an intermediate endpoint for the clinical endpoint. In this setting, treatment effects on both change in urine protein and on GFR slope could also be used in combination to jointly predict treatment effect on the clinical endpoint should the patients be followed sufficiently. The ultimate decision as to how urine protein is integrated into a trial design or drug development program rests with the sponsor and regulatory body and would be influenced by multiple factors, including but not limited to the intervention and population being studied. These data support these discussions.

Treatment effects on urine protein appeared to be more strongly associated with treatment effects on the chronic slope than on the total slope. In general, variation between effects on the total and chronic slope likely reflects the presence of acute or immediate effects that differ from the longer-term effects. It is possible that a stronger trial level association would also be observed between treatment effects on urine protein and on the total slope in trials investigating treatments without an acute effect. We have previously shown that use of chronic slope is one method to reduce the impact of the acute effect, and these results are consistent with that observation.[10,11] For future trials, the decision about use of total vs chronic slope as the primary endpoint would rely on multiple considerations such as the drug's mechanism of action, knowledge about acute effects and prior knowledge about the drug in similar or other populations. There has been reluctance to use the chronic slope as a sole primary endpoint because the chronic slope is computed from a post-baseline time point, after the GFR has already been modified by the treatment. In certain scenarios this incurs a risk of bias due to attenuation of the acute effect or early discontinuation of the study medication.[49] Future work should guide us on how to minimize bias with endpoints which are designed to estimate and minimize the impact of the acute effect similarly to the chronic slope. Possibilities include employing off-treatment GFR measurements and application of different pre-randomization baseline measurements for the treatment and control arms following introduction of the treatment in a run-in phase, as seen in the recent studies evaluating tolvaptan in polycystic kidney disease.[50] For some treatments, it may be appropriate to evaluate both slope endpoints as part of the totality of evidence in a drug development program.

Strengths of the current analysis include a systematic literature search to include all available published English language studies, uniform definitions of exposures and outcomes across studies, and a robust trial level analysis. There are also limitations. First, due to the rarity of the disease, the analysis is underpowered to estimate the associations given the small number of studies, all of which had small sample size. Second, our designation of the treatment arm in each trial as the group hypothesized to have the greater benefit was somewhat arbitrary. Since in the studies that compared azathioprine and steroids vs. steroids alone, the azathioprine + steroids was considered the active treatment group and steroids are considered effective, this could have biased the results.[21,22] Third, we only included studies written in English that had sufficient data for our analyses and where the investigators were

able to share data. Fourth, the evaluation of urine protein as a surrogate endpoint was limited to changes between approximately 6–12 months, and our findings may not extend changes in urine protein over longer (or shorter) time periods. However, our intention is to evaluate early changes in urine protein as if trials are longer, then GFR slope generally becomes more informative. Since the endpoint is defined by the change in urine protein, all participants must have survived to have the second measurement. Finally, IgAN is heterogeneous, and treated with heterogeneous treatments and these results apply to populations selected for inclusions and for treatments evaluated in the current analysis.

Overall, the evidence presented here, when considered in conjunction with prior studies, supports the use of urine protein as an initial surrogate endpoint followed by GFR slope for subsequent confirmatory studies and accumulation of safety data, or as parts of early phase studies. This presents a pathway for drug development that could facilitate studies for new treatments for IgAN.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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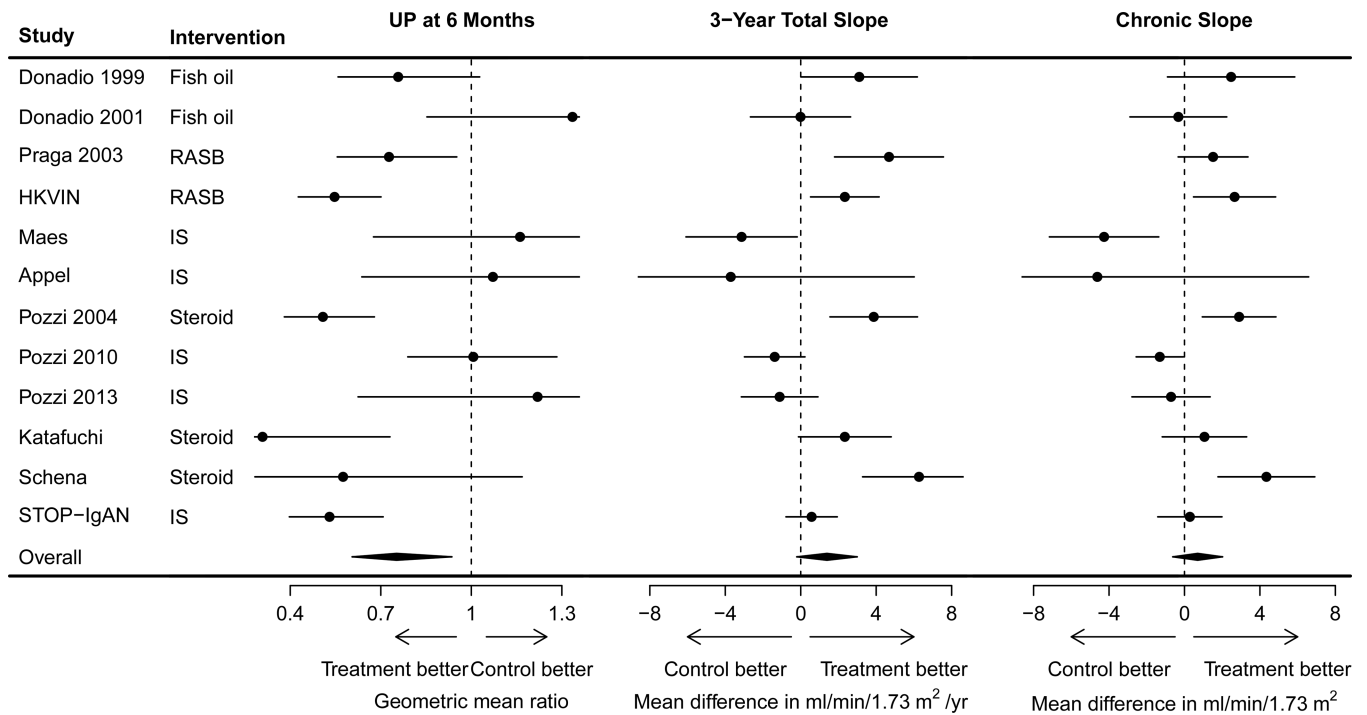
Figure 1: Treatment effect on change in urine protein at 6 months, on 3-year total GFR slope, and on chronic slope

Treatment effects on urine protein are expressed as geometric mean ratios and were estimated by performing analyses of covariance within each study. Treatment effects on slope are 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. The circles represent the estimated treatment effects and the horizontal line the 95% confidence intervals. UP, urine protein measured in gram/day.
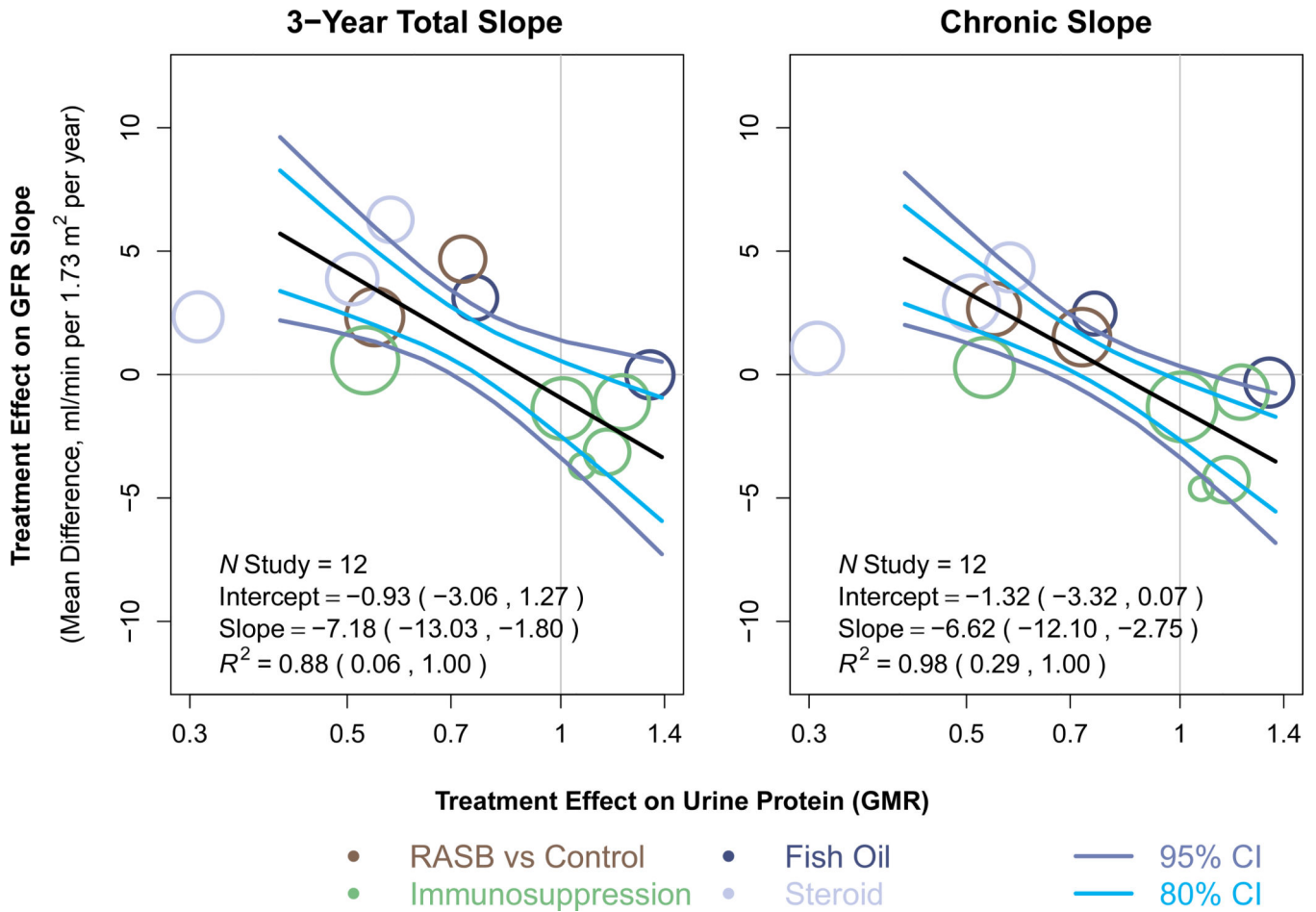
Figure 2. Trial level associations between treatment effects on change in urine protein and treatment effects on total GFR slope at 3 years and chronic slope, for urine protein at 6 months
Shown is the relationship between estimated treatment effects on the 3-year GFR slope on the vertical axis to estimated 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% confidence band and the light blue lines represent the 80% confidence band computed from the model. RASB, renin angiotensin system blockers; GMR, geometric mean ratio.
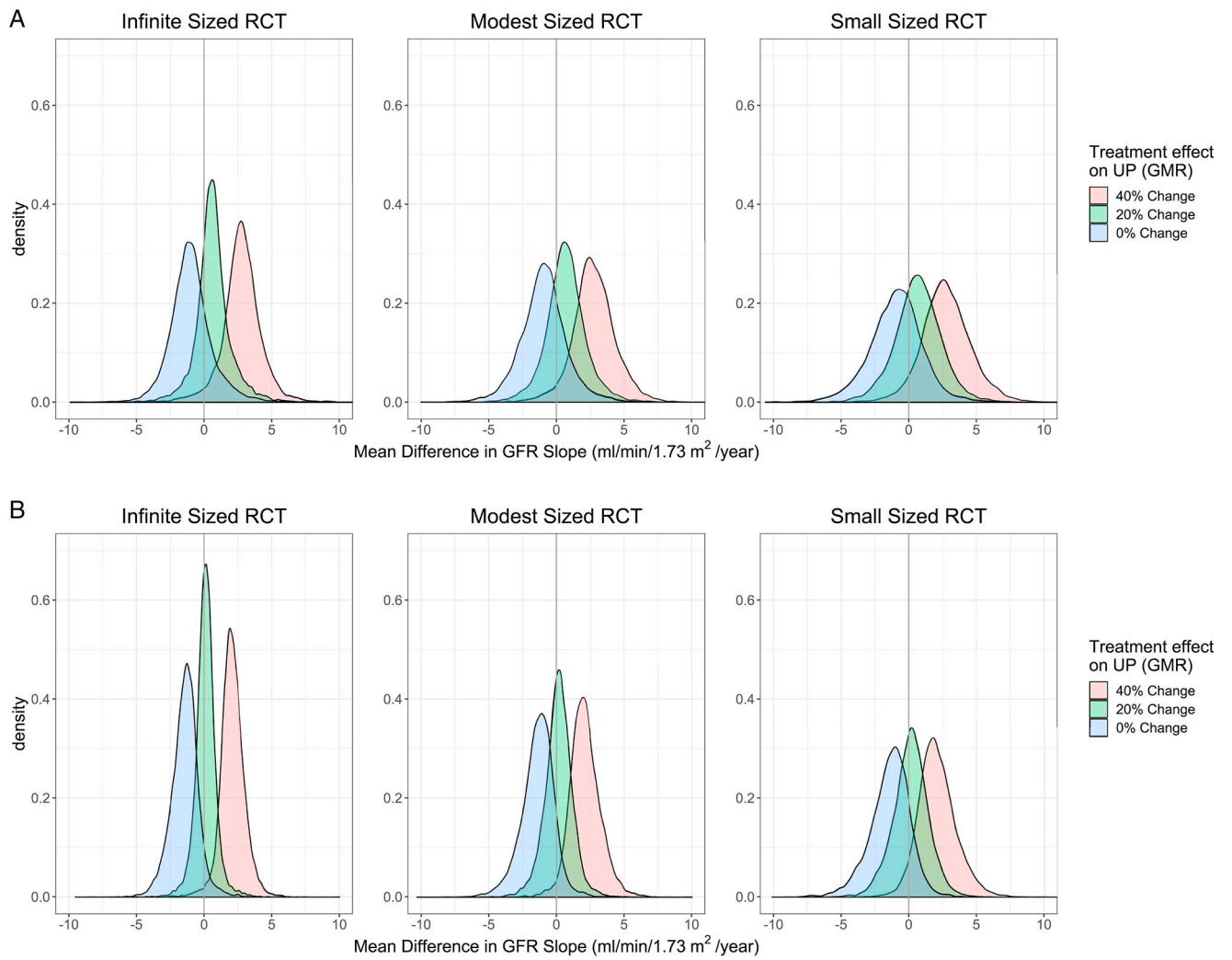
Figure 3. Posterior predictive probabilities of true treatment effect on GFR Slope at 3 years and chronic slope given true treatment effect on change in urine protein

Panel A shows the posterior predictive probabilities for total GFR Slope at 3 years and panel B shows posterior predictive probabilities for the chronic slope; UP, urine protein; GMR, geometric mean ratio, RCT, randomized controlled trial, GFR, glomerular filtration rate.

Table 1.

Patient characteristics, by study, for analysis of change in urine protein at 6 months

Study	Intervention	N	Age (SD)	Female (%)	eGFR (SD)	UP (IQR)	FU (IQR)
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)
Overall		990	39.7 (12.5)	332 (33.5)	71.9 (29.8)	1.8 (1.2, 2.6)	42.6 (34.9, 78.0)

Values for categorical variables are given as number (percentage); values for continuous variables, as mean (standard deviation) or median (interquartile range represented as difference between 25th and 75th percentile). N, sample size; GFR, glomerular filtration rate; UP, urine protein in g/day; FU, follow-up in months; RASB, renin-angiotensin system blockade; IS, immunosuppression.

Table 2:

Application of change in urine protein to predict GFR slope in new RCTs: predicted treatment effect on c inical endpoint and positive predictive values, for 6 months sample_

GFR Slope	Observed Treatment effect on change in UP	Infinite sized RCT		Modest sized RCT (N=250)		Small sized RCT (N=100)	
		Median Treatment effect on GFR slope and 95% Prediction Interval	PPV	Median Treatment effect on GFR slope and 95% Prediction Interval	PPV	Median Treatment effect on GFR slope and 95% Prediction Interval	PPV
Total slope over 3 years	0.5	4.10 (0.34, 7.46)	0.98	4.07 (0.24, 8.01)	0.98	4.01 (0.05, 8.53)	0.98
	0.6	2.77 (−0.49, 5.73)	0.96	2.73 (−0.63, 6.15)	0.96	2.70 (−0.86, 6.69)	0.94
	0.7	1.61 (−1.26, 4.61)	0.92	1.62 (−1.59, 4.91)	0.89	1.62 (−1.96, 5.35)	0.85
	0.8	0.61 (−2.13, 3.77)	0.75	0.66 (−2.51, 4.00)	0.70	0.68 (−2.98, 4.30)	0.67
	Threshold for treatment effect on UP to assure PPV 95% (90%)	0.64 (0.72)		0.62 (0.69)		0.58 (0.66)	
Chronic slope	0.5	3.27 (1.08, 5.83)	0.99	3.25 (0.91, 6.36)	0.99	3.19 (0.56, 6.96)	0.99
	0.6	2.06 (0.26, 3.92)	0.98	2.04 (−0.01, 4.56)	0.97	1.99 (−0.47, 5.18)	0.95
	0.7	1.03 (−0.56, 2.60)	0.94	1.03 (−1.03, 3.16)	0.88	1.02 (−1.57, 3.82)	0.81
	0.8	0.13 (−1.46, 1.74)	0.58	0.16 (−2.05, 2.18)	0.57	0.17 (−2.62, 2.73)	0.56
	Threshold for treatment effect on UP to assure PPV 95% (90%)	0.69 (0.73)		0.64 (0.68)		0.60 (0.65)	

UP, urine protein; PPV, positive predictive value.

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. Treatment effect on GFR slope is expressed as mean difference between treatment arms. Prediction intervals are Bayesian credible intervals. PPV is defined as the probability that the treatment reduces the magnitude of the mean GFR slope by any amount which is greater than 0. The thresholds for the treatment effect on UP, is the change in UP required to assure PPV for a GFR slope > 0 of greater or equal to 95% (90%) modest RCT was defined as having a sample size of 250 (SE 0.09) and a small RCT was defined as having a sample size of 150 (SE 0.09), assuming a standard deviation of 0.75 for change in log urine protein. eTable10 includes the 80% Bayesian credible intervals for the predicted treatment effect on the GFR slope along with the 95% credible intervals shown here. eTable11 includes the threshold for treatment effect on UP to assure PPV 97.5%, along with the 95% and 90% as shown here.