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Early change in urine protein as surrogate endpoint in studies of IgA Nephropathy: An individual patient meta-analysis

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Abstract

Background: The role of change in proteinuria as a surrogate endpoint for randomized trials in IgA nephropathy has previously not been thoroughly evaluated.

Study design: Individual patient-level meta-analysis.

Setting and Population: Individual patient data of 830 patients from 11 randomized trials evaluating four intervention types (RAS blockade, fish oil, immunosuppression, and steroids) examining associations between changes in urine protein and clinical endpoints at the individual and trial level.

Selection Criteria for Studies: Randomized controlled trials of IgA nephropathy with measurements of proteinuria at baseline and at 9-month window (range 5-12), with at least one further year of follow-up for the clinical outcome.

Predictor: 9 month change in proteinuria.

Outcomes: Doubling of serum creatinine, end stage renal disease or death.

Results: Early decline in proteinuria at 9 months was associated with a lower risk of the clinical outcome [HR 0.40 (95% CI 0.32, 0.48) per 50% reduction in proteinuria] and was consistent across studies. Estimates for the proportion of treatment effect on the clinical outcome explained by early decline in proteinuria were 11% (-19 to 41) for RAS blockade and 29% (6 to 53) for steroid therapy. The direction of the pooled treatment effect on early change in proteinuria agreed with the direction of the treatment effect on the clinical outcome for steroids and renin angiotension system blockade. Trial level analyses estimated the slope for the regression line for the association of the treatment effects on the clinical endpoints and the treatment effect on proteinuria was 2.15, (95% Bayesian CI 0.10, 4.32).

Limitations: Study population restricted to 11 trials, all having less than 200 patients each with a limited number of clinical events.

Conclusions: These results provide new evidence supporting the use of an early reduction in proteinuria as a surrogate endpoint for clinical endpoints in IgA nephropathy in selected settings.

Index Words: Proteinuria; Surrogate endpoint; IgA Nephropathy; End-stage renal disease (ESRD); Prognostic marker

Introduction

IgA nephropathy is a common cause of glomerulonephritis. It can have a highly heterogeneous course; some patients have hematuria with minimal progression, others have slowly progressive decline in glomerular filtration rate (GFR) culminating in kidney failure years later, and rarely fast progression to kidney failure. For patients with progressive disease, treatments are thought to be most effective early in the disease course. In many chronic kidney diseases, a large decline in GFR, assessed as a doubling of serum creatinine 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 of patients with low levels of GFR or rapidly progressive disease (RCTs)[1,2]. However, for the majority of patients with IgA nephropathy with progressive disease, these endpoints are not feasible because of the long duration of the disease, leading to expense and complexity of trials that would be required to detect a large decline in GFR. These issues have likely contributed to the paucity of therapies to treat IgA nephropathy.

For many diseases, use of surrogates has helped accelerate the development and evaluation of new therapies[3]. Critical to the correct assessment of surrogacy is the use of appropriate methods to evaluate patient data across multiple trials to avoid approval of ineffective or harmful therapies[4,5]. Two recent individual patient-level meta-analyses provided empirical evidence for use of change in proteinuria as a surrogate outcome for disease progression across many causes of chronic kidney diseases[6,7]. One criticism of these analyses was that it grouped together different of causes of kidney disease and the role of proteinuria in the cause and progression of the disease may differ among etiologies[8]. If so, performance of proteinuria as a surrogate would differ , in which case pooling across studies may have masked true associations between change in proteinuria and the clinical endpoints in a particular disease. Here we report an individual patient-level meta-analysis of a pooled dataset of 830 individuals from eleven RCTs of four intervention types in IgA nephropathy to evaluate an early change in proteinuria as a surrogate endpoint for progression of this specific cause of kidney disease.

Methods

Study selection and study populations

We identified potential studies via systematic search of the medical literature on Ovid MEDLINE published from January 1, 1979 to July 9, 2012 (see Supplement Figure 1 for flow chart and Supplement Table 1 for search terms). The key inclusion criterion was randomized control trials (RCT) design of drug interventions in adults with IgA nephropathy (Supplement Table 2). In total, we were able to include eleven studies that investigated four intervention types [renin angiotensin system (RAS) blockade, fish oil, steroids or other immunosuppression agents] (Supplement Figure 1). Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration[9] (Supplement Table 3). We defined the active treatment as the treatment hypothesized to produce the greater reduction in the risk of the clinical endpoint. All participants underwent informed consent as part of their inclusion in each study. This analysis was considered exempt from review by the Tufts Medical CenterIRB.

Early change in urine protein

We defined change in urine protein from baseline to 9 (range 5 to 12) months. Urine protein was expressed in units of grams/day and was log transformed due to skewedness of the data.

Clinical endpoint

The clinical endpoint was defined as the composite of the time to the first occurrence of doubling of serum creatinine, ESRD, or death. If available, we used the study defined censoring dates to define the follow-up times[10,11]. As previously described, if the study defined censoring dates were not available, we approximated them as the time from randomization to the final recorded visit date in the data provided plus 6 months plus the study-specific 90th percentile of the average interval between visits with serum creatinine measurements[6,12-20]. 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.

Analyses

As was previously used in Inker et al., we performed three types of analyses which are widely used for validation of surrogate endpoints[6]: 1) Association between the clinical outcome and early change in proteinuria at the individual level[21]; 2) Proportion of treatment effect (PTE) on the clinical outcome explained by the early change in proteinuria (Prentice-Freedman criterion)[22,23]; and 3) Association between the treatment effect on the 9 month change in proteinuria and the treatment effect on the clinical endpoint[24-27].

For all analyses, GFR was estimated using the CKD-EPI creatinine equation[28]. We report results for each study, in the pooled dataset and in subgroups based on intervention type, baseline urine protein (< 1, 1- 2, >2 g/day), eGFR (< 45, 45- 90, >90 ml/min per 1.73m^2) and blood pressure (SBP < 140 and DBP < 90 vs SBP > 140 or DBP > 90 mmHg). In a sensitivity analysis, we adjusted for follow up blood pressure at the same time point as the second measure of urine protein in the subset of studies in which these measures were available.

Individual-level association

Demonstration of a consistent patient-level association between a surrogate and the clinical outcome is widely regarded as necessary, although not sufficient, for establishing the validity of the surrogate endpoint in clinical trials[4,29,30]. We evaluated individual-level association by performing Cox regressions to relate the clinical outcome to early change in proteinuria, with results expressed as the hazard ratio associated with a halving of proteinuria. Our initial model was adjusted for treatment assignment, study and baseline urine protein, with the more fully adjusted models adjusted for additional baseline variables including age, sex,

race, estimated GFR and blood pressure. We obtained hazard ratios and associated 95% confidence intervals for the overall dataset and for subgroups by repeating the Cox regression in the overall dataset and in each of the subgroups pooled across each study, where the baseline hazards of the Cox regressions were stratified by study.

Proportion of treatment effect explained (Prentice-Freedman Criterion).

The proportion of the treatment effect on a clinical outcome "explained by the surrogate" (PTE) has been widely used as an index of the validity of surrogate endpoints[22,23,31]. Where data permit, the PTE quantifies the magnitude of the attenuation of the treatment effect on the clinical outcome that results from statistically controlling for the surrogate[24,32]. We performed joint Cox regressions with baseline hazards stratified by study to estimate the treatment effects on the clinical outcomes for each study, first adjusting for the full set of baseline covariates and then also adjusting for change in proteinuria. PTE was calculated as 1 minus the ratio of the Cox regression coefficients for the treatment with and without adjusting for early change in proteinuria. We obtained pooled PTEs and associated 95% confidence intervals for each of the four interventions by repeating the above procedure for joint analyses in each of the interventions. The PTE were only computed for interventions in which the treatment effect had a P-value of < 0.10.

Trial level analyses

Assessments of individual-level association and the Prentice-Freedman criteria both depend on the untestable assumption of no residual confounding from factors which jointly influence the surrogate and clinical endpoints[24,33]. By contrast, trial-level analyses investigate the relationship between treatment effects on the surrogate with treatment effects on the clinical endpoints, where each treatment effect is estimated from a randomized trial , and therefore minimizes the risk of confounding that affects the first two approaches[24]. It is the more direct evaluation of potential surrogates as it evaluates the consistency and association between treatment effects on the surrogate to the treatment effects on the clinical

endpoint and has been the primary focus of the statistical surrogate endpoint literature over recent years in diverse therapeutic disease areas[25-27,34,35]. Demonstration of a relationship between treatment effects on the surrogate and treatment effects on the clinical endpoint across a wide range of interventions is a necessary prerequisite to infer that the treatment effect on the surrogate will predict the treatment effect on the clinical outcome in future RCTs.

The trial level analysis requires two steps: assessment of the treatment effects within each study and a meta-analysis of treatment effects across studies. In the first step, we applied linear and Cox regression in each study to estimate the treatment effects (and associated standard errors) on the 9 month change in proteinuria (expressed as the log transformed ratio of follow-up vs. baseline geometric mean proteinuria (GMR) between treatment groups) and on the clinical outcome (expressed as log transformed hazard ratios). We obtained estimates of the correlation between the treatment effects on the clinical and surrogate outcome within each study by performing bootstrap resampling with 2000 repetitions for each study. In order to assure convergence of the Cox models for each bootstrap sample, we pooled studies of the same intervention that had fewer than 10 clinical events. In the second step, we applied a Bayesian mixed effect regression model to relate the treatment effects on the clinical outcome to the treatment effects on proteinuria with study as the unit of analysis. A slope greater than zero would indicate that treatment effects on early change in proteinuria are associated with treatment effects on the clinical endpoint and support the surrogacy hypothesis.

Results

Characteristics of the study population

Supplement Tables 3 and 4 describe the included studies. Of the 888 participants in these 11 studies, 58 were excluded because they had a clinical event before the 9 month window or did not have a repeated measurement of urine protein at 9 months, leaving 830 participants in the pooled study population. Table

1 shows the characteristics these 830 participants[10-20,36,37]. In the pooled dataset, median (25^{th}, 75^{th}) baseline urine protein was 1.80 (1.3, 2.7) g/d [range across studies 1.0 (0.6, 2.7) to 2.50 (1.5, 4.0)] and mean (SD) baseline GFR was 74 (30) ml/min 1.73 m^2 [range across studies 28 (7) to 99 (23)] with varying distributions across the interventions (Table 1). In the pooled dataset, the mean (SD) duration of follow-up was 4.8 (2.7) years [range 1.5 (0.8) to 7.8 (4) across studies], with a total of 128 (15.4%) clinical endpoints [range 3 (8.8%) to 18 (41.9%) across the individual studies] (Table 1). For the sensitivity analysis, a subset of 699 patients in 10 trials had blood pressure available at the time of the follow-up urine protein. Baseline characteristics were similar to the main study population (Supplement Table 5).

Individual level association

Table 2 shows the associations of change in urine protein with development of subsequent clinical outcomes. In the pooled dataset, a decline in urine protein was associated with a lower risk for the clinical outcome [hazard ratio (HR) 0.40 (95% CI 0.32, 0.48) for a 50% decline in urine protein]. Results were broadly consistent across studies, although hazard ratios in some studies did not reach significance, possibly due to low event rates [range 0.03 (95% CI 0, 1.92) to 0.52 (95% CI 0.27, 0.99)]. Similar results were seen across subgroups defined by intervention, baseline urine protein, baseline estimated GFR and blood pressure (Table 2). Results were similar in the subset after adjusting for changes in blood pressure during follow-up (Supplement Table 6).

Investigation of Prentice Criteria

Table 3 shows the treatment effects on the clinical endpoint before and after adjusting for full set of baseline covariates and the change in proteinuria and the associated PTE for 5 of the 11 studies and 2 of the 4 intervention types (RAS blockade and steroids) in which the treatment effect approached statistical significance (P-value <0.1). The pooled PTE were 11% (95% CI -19 to 41%) for RAS blockade and 29% (95%

CI 6 to 53%) for steroid therapy (indicating smaller treatment effects *after* adjustment for early change in proteinuria).

Trial Level Analysis

Table 4 shows the treatment effects on the early change in proteinuria and the clinical outcome. In the pooled dataset treatment reduced proteinuria compared to control [pooled GMR =0.76 (95% CI 0.68, 0.85). However, there was substantial variation across studies [range from 0.38 (95% CI 0.27, 0.53) to 1.39 (95% CI 0.87, 2.22)] and treatment types [range from 0.50 (95% CI 0.41, 0.6) for studies of steroids to 1.07 (95% CI 0.86, 1.34) for studies of immunosuppression]. In the pooled dataset, treatment also reduced the risk of the clinical endpoint compared to control [0.37 (95% CI 0.25, 0.55)], with variation across study and interventions [HR of 0.14 (95% CI 0.07, 0.34) for steroid therapy to 0.69 (95% CI 0.35, 1.35) for immunosuppression]. Overall, there was agreement in the direction of point estimates for treatment effects on proteinuria and on the clinical endpoint for seven of eleven studies, and two of four interventions (steroids and RAS blockade). In sensitivity analyses, findings were similar in the subset after adjusting for changes in blood pressure during follow-up (Supplement Table 7).

Figure 1 shows the relationship between treatment effects on early change in proteinuria vs. treatment effects on clinical outcome across individual studies. Overall the slope is 2.15 (95% Bayesian credible interval 0.10, 4.32) with R^2 of 0.91(95% Bayesian credible interval 0.47, 1.0), suggesting there is a significant positive relationship between the treatment effects on urine protein and on the clinical endpoint.

Discussion

Use of surrogate endpoints may improve the efficiency of clinical trials in general and for studies of IgA nephropathy, their use allows for evaluation of interventions early in the disease course prior to kidney scarring and irreversible changes. There is a reasonably sound biological and empirical basis for the

hypothesis that an early change in proteinuria is a valid surrogate endpoint for progression of IgA nephropathy. First, there is a range of pathological evidence that the degree of proteinuria correlates with greater evidence of disease[38-40]. Second, on an individual level, proteinuria has been widely reported to be prognostic for long-term disease progression at all stages of kidney disease[41-47], and a recent study has shown that attenuation of proteinuria after steroid therapy is associated with improved prognosis[48, 49]. Third, benefit of treatment appears to be greater at higher levels of proteinuria[50]. In this report, we have provided the first large scale empirical data on the statistical associations between early changes in proteinuria and clinical endpoints across multiple interventions. The results from these analyses extend the evidence supporting a potential use of early change in proteinuria in IgA nephropathy.

Our analyses of individual level association establish that a greater reduction in proteinuria is consistently associated with slower progression of IgA nephropathy across all interventions. These results are limited by possible confounding factors that influence both the proteinuria and the clinical endpoint, although the results changed little after adjustment for available baseline covariates. These results are consistent with and extend results of epidemiologic studies and observational analyses of clinical trials that demonstrate the utility of proteinuria as a prognostic marker for subsequent clinical outcomes in IgA nephropathy. These results in and of themselves are not evidence of surrogacy, but support the use of change in proteinuria to inform prognosis in IgA nephropathy, as has been shown for general CKD[45,51,52].

The PTE is a traditional method to evaluate surrogate endpoints. However, this approach has significant shortcomings in the requirement for trials to have statistically significant treatment effects on both the potential surrogate and clinical outcome and it is also subject to bias due to measurement in error in proteinuria and as well as possible residual confounding[24,33]. Our assessments of the Prentice-Freedman criteria were therefore inconclusive with few trials meeting the necessary criteria.

We used two approaches to investigate if treatment effects on change in proteinuria were consistent with treatment effects on the clinical outcome. First, we found that the direction of the treatment effects on reductions both in proteinuria and on the clinical endpoint were in agreement for steroids and RASB interventions, but were not in agreement for the fish oil and immunosuppression interventions. The lack of agreement for these later two interventions may reflect imprecision of the treatment effects for these interventions. Second, using the trial level approach, we found that there was a positive relationship between the treatment effects on urine protein and on the clinical endpoint, with a credibility interval, though wide, that did not cross 0. Altogether these findings are consistent with the hypothesis that the treatment effect on proteinuria may be used to predict the treatment effect on the clinical endpoint. However, we did not account for uncertainty in the estimated standard errors of the Cox regression coefficients or of the estimated treatment effects on the GMR for proteinuria. Although this approach is commonly used in trial level analyses, the consequences of the uncertainty in the standard errors may be greater in this analysis than is typically the case due to the small sizes of several of the studies. The addition of further data from future trials in IgA nephropathy would help to address this issue.

Prior literature appears to contradict the positive relationship between treatment effects on urine protein and clinical endpoint shown by trial level analysis in our study. Inker et al and Lambers-Heerspink et al recently evaluated change in proteinuria as a surrogate outcome in studies across of heterogeneous causes of CKD[6,7]. In contrast to the current analysis, in both studies when the analyses were restricted to early change in proteinuria, the confidence interval for the regression line crossed 0. It is possible that evaluation across these heterogeneous sets of diseases masked the relationship within IgA nephropathy. Others have suggested that the assessment of potential surrogate endpoints may be optimally performed within specific diseases[8]. In an analysis performed by Lv et al on evaluating this question in six trials of IgA nephropathy, the reduction in risk for kidney failure with steroid therapy was associated with the difference in proteinuria reduction between treatment groups, but this finding was not statistically

significant (P=0.1), potentially because of four small studies with few clinical events and infinite confidence margins on the treatment effect on the clinical endpoint[53]. Finally, Rauen et al showed the immunosuppressive therapy led to a positive treatment effect on proteinuria but not on a reduction of GFR of 15 ml/min per 1.73 m^2 [54]. However, as we have recently shown, use of small changes of GFR is not appropriate in most settings due to the potential for acute effects on the estimated GFR, and the study was not powered sufficiently to assess differences on larger GFR decline or clinical endpoints[2].

Strengths of the current analysis include a systematic literature search to include all available studies, uniform definitions of exposures and outcomes, and a comprehensive evaluation using the three standard approaches for validating surrogate endpoints in the statistical and medical literatures. The results from these analyses extend the evidence supporting use of proteinuria in some settings. There are also limitations. First, all of the studies included had follow-up less than 10 years while for most patients with IgA Nephropathy, it is slowly progressive indolent disease, and the studies with shorter follow up may have missed true associations. Second, the evaluation of proteinuria as a surrogate endpoint was limited to changes between approximately 6-12 months, and our findings may not extend changes in proteinuria over longer (or shorter) time periods. Since the endpoint is defined by the change in proteinuria, all participants must have survived to have the second measurement, although that does not invalidate the comparison to the clinical endpoints, since endpoints prior to the second measurement were excluded. Third, our designation of the treatment arm in each trial as the group hypothesized to have the greater benefit was somewhat arbitrary. This is highly relevant for this study as some studies compared azathioprine + steroids vs. steroids alone, the azathioprine + steroids was considered the active treatment group and steroids are considered to be an effective therapy[18,19]. Fourth, our selection of studies may be biased as we only included studies written in English prior to 2012, that had sufficient data for our planned analyses and where the investigators were willing and able to share data. Fifth, due to the rarity of the disease, many studies were small and had some concern for bias, including lack of study specified administrative censoring

dates. Finally, due to the small sample sizes, the standard errors of the Cox regression coefficients of the individual studies could not be accurately estimated, hence, smaller studies were combined for the purposes of the trial level analysis.

Overall, the evidence presented here suggests that, when considered in conjunction with evidence from experimental studies, findings from our analyses may be sufficient to recommend use of proteinuria as a surrogate endpoint in interventions that work by similar mechanism evaluated in the current analysis, in early phase clinical trials for new therapies with different mechanisms of actions and for exploratory analyses (e.g., subgroup analyses with limited power for the clinical endpoint). Use of early change in proteinuria could facilitate studies of new treatments for IgA nephropathy, but such short term studies should be followed with subsequent post-approval confirmation of the treatment effect on the clinical endpoint and for accumulation of safety data.

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Contributions: research idea and study design: LAI, TG, CS, ASL; data acquisition: LAI,TM, FL, FP, RK, GBA, BDM, PKL, MP, LDV, SA, CM, EG; data analysis/interpretation:LAI, HM, TG, AM, KJC, CS, ASL; statistical analysis: LAI, HM, TG, CS, ASL; supervision or mentorship: LAI, ASL. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LAI takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Table 1: Characteristics of Study and Study Groups

Study Number	N	% Female	Age (mean ± SD)	Urine Protein, median * (25^{th}, 75^{th})	eGFR, (mean ± SD)	Events N (%)				F/U, years (mean ± SD)
						ESRD	Doubling Scr	Deaths	Compo-site	
RAS Blockade vs. Control										
A1	106	71.7	40.0±9.1	1.58 (1.1, 2.6)	75.6±29.2	3 (2.8)	7 (6.6)	0	8 (7.6)	2.75±0.60
A2	44	38.6	31.6±11.5	1.70 (1.1, 2.4)	98.1±26.5	15 (34.1)	6 (13.6)	0	15(34.1)	7.84±3.95
Fish oil										
B1	66	16.1	46.4±13.4	1.56 (0.7, 2.6)	41.8±14.1	10 (15.2)	10 (15.2)	0	14 (21.2)	2.35±1.09
B2	89	25.8	38.8±13.6	2.00(1.2, 3.4)	66.4±21.6	15 (16.9)	1 (1.12)	2 (2.2)	16 (18.0)	3.00±1.08
Immunosupression										
C1	34	29.4	44.8±11.3	1.00 (0.6, 2.7)	62.2±18.9	2 (5.9)	2 (5.9)	1 (2.9)	3 (8.8)	3.20±0.86
C2	18	11.1	38.2±13.9	2.28 (1.5, 2.9)	49.1±30.0	3 (16.7)	0	0	3 (16.7)	1.50±0.84
C3	183	27.3	39.0±12.6	2.00 (1.5, 2.7)	74.0±24.7	9 (4.9)	14 (7.7)	3 (1.6)	17 (9.3)	5.92±2.01
C4	43	18.6	42.0±11.7	2.50 (1.5, 4.0)	28.0±7.1	18 (41.9)	9 (20.9)	0	18 (41.9)	4.29±1.68
Steroids										
D1	83	30.1	38.6±11.7	1.90 (1.4, 2.4)	87.2±21.6	7 (8.4)	14 (16.9)	0	14 (16.9)	7.93±3.26
D2	94	30.8	33.8±11.1	1.66 (1.4, 2.5)	91.2±23.8	8 (8.5)	15 (16.0)	0	15 (16.0)	4.44±1.93
D3	70	60.0	36.4±11.5	1.36 (1.0, 2.6)	98.5±22.3	4 (5.7)	5 (7.1)	0	5 (7.1)	6.35±2.01
Pooled Analyses										
A	150	62.0	37.5±10.5	1.59 (1.1, 2.5)	82.2±30.2	18 (12.0)	13 (8.7)	0	23 (15.3)	4.25±3.16
B	155	21.3	42.0±14.0	1.81 (1.1, 3.3)	55.9±22.4	25 (16.1)	11 (7.1)	2 (1.3)	30 (19.4)	2.77±1.06
C	278	25.2	40.1±12.5	2.00 (1.4, 2.9)	63.9±28.1	32 (11.5)	25 (9.0)	4 (1.4)	41 (14.8)	5.07±2.19
D	247	38.9	36.2±11.6	1.7 (1.3, 2.5)	91.8±23.0	19 (7.8)	34 (13.8)	0	34 (13.8)	6.15±2.88

Each study is referred to by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies. A is Renin-angiotensin system blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Supplement table 3 for the study name for each study number and Supplement Table 4 for the description of the studies. Urine Protein is measured in g/day.

Abbreviations: N, sample size; SD, standard deviation, eGFR, estimated glomerular filtration rate (in mL/min per $1.73m^2$); ESRD, end-stage renal disease; Scr, serum creatinine; F/U, follow up

*All but one study measured urine protein excretion using 24 hour urine collections, and this study estimated it using urine protein to creatinine ratio in spot urines.

Table 2: Association of change in urine protein at 9 months on clinical endpoints

Study Number or Subgroup	Sample Size	# of Events	Adjusted for baseline UP		Fully Adjusted	
			HR (95% CI)	P-value	HR (95% CI)	P-value
A1	106	8	0.22 (0.07, 0.75)	0.02	0.19 (0.02, 1.47)	0.1
A2	44	15	0.39 (0.17, 0.90)	0.03	0.43 (0.15, 1.19)	0.1
B1	66	14	0.31 (0.15, 0.65)	0.002	0.22 (0.10, 0.47)	<0.001
B2	89	16	0.52 (0.27, 0.99)	0.05	0.18 (0.05, 0.62)	0.01
C1	34	3	0.46 (0.16, 1.33)	0.2		
C2	18	3	0.03 (0.00, 1.92)	0.1		
C3	183	17	0.46 (0.30, 0.72)	0.001	0.47 (0.31, 0.73)	0.001
C4	43	18	0.39 (0.22, 0.68)	0.001	0.39 (0.22, 0.69)	0.001
D1	83	14	0.48 (0.27, 0.87)	0.02	0.55 (0.32, 0.96)	0.04
D2	94	15	0.20 (0.10, 0.41)	<0.001	0.19 (0.09, 0.42)	<0.001
D3	70	5	0.22 (0.05, 0.95)	0.04		
Overall	**830**	**128**	**0.40 (0.32, 0.48)**	**<0.001**	**0.40 (0.32, 0.49)**	**<0.001**
Treatment type						
RASB	150	23	0.32 (0.17, 0.61)	0.001	0.30 (0.14, 0.66)	0.003
Fish oil	155	30	0.39 (0.24, 0.64)	<0.001	0.22 (0.12, 0.39)	<0.001
Immunosupression	278	41	0.46 (0.33, 0.62)	<0.001	0.48 (0.35, 0.65)	<0.001
Steroids	247	34	0.35 (0.23, 0.52)	<0.001	0.37 (0.24, 0.55)	<0.001
Urine Protein Categories						
<1	88	5	0.22 (0.05, 0.91)	0.04		
1-2	368	35	0.43 (0.29, 0.64)	<0.001	0.46 (0.32, 0.68)	<0.001
> 2	374	88	0.38 (0.29, 0.50)	<0.001	0.39 (0.29, 0.51)	<0.001
Estimated GFR Categories						
eGFR < 45	154	45	0.44 (0.31, 0.61)	<0.001	0.46 (0.32, 0.65)	<0.001
eGFR 45-90	422	66	0.33 (0.24, 0.46)	<0.001	0.34 (0.25, 0.48)	<0.001
eGFR > 90	254	17	0.42 (0.24, 0.75)	0.003	0.47 (0.25, 0.89)	0.02
Blood Pressure Categories						
SBP < 140 and DBP < 90	534	75	0.42 (0.32, 0.55)	<0.001	0.40 (0.31, 0.53)	<0.001
SBP > 140 or DBP > 90	296	53	0.35 (0.25, 0.49)	<0.001	0.40 (0.28, 0.55)	<0.001

Each study is referred to by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies. A is Renin-angiotensin system blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Supplement table 3 for the study name for each study number and Supplement Table 4 for the description of the studies. Urine Protein is measured in g/day. Blank cells indicate that the model did not converge.

Abbreviations: UP, urine protein; HR, hazard ratio; CI, confidence interval; GFR, glomerular filtration rate (in mL/min per 1.73m^2); SBP, systolic blood pressure (in mmHG); DBP, diastolic blood pressure (in mmHG).

Fully adjusted models include treatment assignment, study, baseline urine protein, age, sex, race, estimated GFR and blood pressure. Hazard ratios are reported for 50% decline in urine protein

Table 3: Treatment effect on the composite endpoint, with and without adjustment for change in urine protein and the proportion of treatment effect, adjusted for covariates

Study Number	N pts (# events)	Unadjusted for Change in UP			Adjusted for Change in UP			PTE (CI)
		Parameter Estimate	HR (95% CI)	P-value	Parameter Estimate	HR (95% CI)	P-value	
A2	44 (15)	-1.27	0.28 (0.07, 1.19)	0.09	-1.41	0.24 (0.04, 1.36)	0.1	-11 (-51,28)
B2	89 (16)	-1.19	0.30 (0.08, 1.13)	0.08	-0.68	0.50 (0.14, 1.80)	0.23	43 (-24,109)
C4	43 (18)	0.76	2.13 (0.89, 5.09)	0.09	0.56	1.76 (0.59, 5.22)	0.3	25 (-85,136)
D1	83 (14)	-2.86	0.06 (0.01, 0.49)	0.01	-2.11	0.12 (0.01, 1.18)	0.07	26 (-6,58)
D2	94 (15)	-2.61	0.07 (0.02, 0.25)	<0.001	-2.88	0.06 (0.01, 0.23)	<0.001	-10 (-59,38)
Overall	**830 (128)**	**-1.03**	**0.36 (0.24, 0.53)**	<0.001	**-0.92**	**0.40 (0.26, 0.60)**	<0.001	**10 (-10,31)**
Treatment type								
RASB	150 (23)	-1.42	0.24 (0.08, 0.74)	0.01	-1.27	0.28 (0.08, 1.01)	0.05	11 (-19,41)
Steroids	247 (34)	-2.25	0.11 (0.05, 0.23)	<0.001	-1.60	0.20 (0.08, 0.49)	<0.001	29 (6,53)

Each study is referred to by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies. A is Renin-angiotensin system blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Supplement table 4 for the study name for each study number and Supplement Table 5 for the description of the studies.

Abbreviations: N, sample size; UP, urine protein; HR, hazard ratio; CI, confidence interval. PTE, Proportion of treatment effect.

PTE = (1 – α/ß)% where α is the parameter estimate for treatment effect under the model without change in urine protein and ß the parameter estimate for treatment effect under the model with change in urine protein. Models are adjusted for baseline urine protein, eGFR, race, age, and gender. PTE is traditionally computed for studies with significant treatment effect on the clinical endpoint but because of the small sample size in most studies included here, for descriptive purposes we computed for studies in which the treatment effect on the clinical outcome approached statistical significance (P-value< 0.10).

Table 4: Treatment effect on change in urine protein, adjusted for baseline urine protein

Study Number or Subgroup	Sample Size	Treatment effect on proteinuria		Treatment effect on clinical endpoints	
		GMR (95% CI)	P-value	HR (95% CI)	P-value
A1	106	0.60 (0.46, 0.77)	<0.001	0.39 (0.08, 1.95)	0.3
A2	44	0.73 (0.56, 0.94)	0.02	0.43 (0.13, 1.47)	0.2
B1	66	1.39 (0.87, 2.22)	0.2	0.80 (0.27, 2.38)	0.7
B2	89	0.77 (0.56, 1.05)	0.1	0.22 (0.06, 0.80)	0.02
C1	34	1.27 (0.69, 2.34)	0.5	0.42 (0.03, 6.30)	0.5
C2	18	1.09 (0.60, 1.98)	0.8	0.34 (0.03, 3.96)	0.3
C3	183	1.00 (0.76, 1.32)	0.9	0.82 (0.31, 2.19)	0.7
C4	43	1.18 (0.65, 2.12)	0.6	1.07 (0.37, 3.11)	0.9
D1	83	0.38 (0.27, 0.53)	<0.001	0.07 (0.01, 0.53)	0.01
D2	94	0.50 (0.37, 0.68)	<0.001	0.11 (0.03, 0.51)	0.004
D3	70	0.68 (0.46, 1.02)	0.1	0.13 (0.01, 2.01)	0.1
Overall	**830**	0.76 (0.68, 0.85)	**<0.001**	0.37(0.25, 0.55)	<0.001
Treatment type					
RASB	150	0.63 (0.51, 0.76)	<0.001	0.36 (0.14, 0.94)	0.04
Fish oil	155	1.00 (0.76, 1.31)	0.9	0.44 (0.20, 0.95)	0.04
Immunosupression	278	1.07 (0.86, 1.34)	0.5	0.69 (0.35, 1.35)	0.3
Steroids	247	0.50 (0.41, 0.60)	<0.001	0.14 (0.07, 0.34)	<0.001
Urine Protein Categories					
<1	66	0.90 (0.64, 1.36)	0.7	1.47 (0.16, 13.65)	0.7
1.0- 2.0	368	0.68 (0.57, 0.80)	<0.001	0.22 (0.09, 0.54)	0.001
> 2.0	374	0.80 (0.67, 0.95)	0.01	0.40 (0.25, 0.64)	0.0002
Estimated GFR Categories					
eGFR< 45	154	0.96 (0.71, 1.29)	0.8	0.66 (0.35, 1.24)	0.3
eGFR 45-90	422	0.81 (0.69, 0.96)	0.01	0.30 (0.17, 0.53)	<0.001
eGFR> 90	254	0.59 (0.49, 0.72)	<0.001	0.07 (0.01, 0.56)	0.01
Blood Pressure Categories					
SBP < 140 & DBP < 90	534	0.72 (0.62, 0.83)	<0.0001	0.33 (0.19, 0.56)	<0.001
SBP > 140 & DBP > 90	296	0.83 (0.68, 1.02)	0.08	0.42 (0.23, 0.76)	0.004

Each study is referred to by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies. A is Renin-angiotensin system blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Supplement table 3 for the study name for each study number and Supplement Table 4 for the description of the studies. Urine Protein is measured in g/day. Abbreviations: GMR, geometric mean ratio, HR, hazard ratio; eGFR, estimated glomerular filitration rate; SBP, systolic blood pressure (in mmHG); DBP, diastolic blood pressure (in mmHG).

Figure Legend

Figure 1: Trial-level Assessment of Validity of Proteinuria as a Surrogate Endpoint

HKVIN: Hong Kong study using valsartan in IgA nephropathy, MMF: mycophenolic mofetil, AZA: azathioprine, D(dose): Donadio (dose), D(plc): Donadio (placebo)

Dots are the observed treatment effects on the clinical outcome (vertical axis) and change in urine protein (horizontal axis) for each study or study group. Colors indicate intervention. Red, Renin-angiotensin system blockade; yellow, fish oil; green, immunosupression; purple, steroids Treatment effects on the clinical outcome are expressed as hazard ratios. Treatment effect on urine protein was computed as the change in log urine protein (follow-up – baseline) in the treatment vs the control groups. The treatment effect estimate was exponentiated to obtain the geometric mean ratio of the change in urine protein for the treatment vs control arm. A number less than 1 indicates a larger reduction in proteinuria in the treatment than in the control group.

The brown regression line is the regression line from the Bayesian analyses summarizing the prediction of the true treatment effects on the clinical outcome from the true treatment effects on the change in urine protein. The gray lines indicate the confidence band around the regression line. Overall the slope is 2.15 with 95% Bayesian credible intervals range from 0.10 to 4.32) with R^2 of 0.91, 95% Bayesian credible intervals range from (0.47 to 1.0, indicating that, for a given treatment effect on urine protein, the treatment effect on the clinical outcome is expected to be double the treatment effect on urine protein when the respective treatment effects are expressed on the log hazard ratio and log geometric mean scales. The Bayesiancredible intervalsl around the slope was wide but did not cross 0, suggesting there is a significant positive relationship between the treatment effects on urine protein and on the clinical endpoint.

Supplementary Materials

Supplement Figure 1: Flowchart of study identification process

Supplement Table 1: Literature Search terms

Supplement Table 2: Inclusion criteria for eligible randomized, controlled clinical trials

Supplement Table 3: Bias of included studies

Supplement Table 4: List of Study Names and Study Numbers, Collaborators and References

Supplement Table 5: Study characteristics

Supplement Table 6: Clinical characteristics of subset of participants with blood pressure at 9 month follow up

Supplement Table 7: Association of change in urine protein at 9 months on clinical outcome adjusted baseline covariates, in the subset which has blood pressure at same visit as urine protein in follow-up

Supplement table 8: Treatment effect on change in urine protein, adjusted for baseline covariates, and then for change in blood pressure in subset of patients who have blood pressure at same visit as urine protein in follow-up