

Early Change in Urine Protein as a Surrogate End Point in Studies of IgA Nephropathy: An Individual-Patient Meta-analysis

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Background: The role of change in proteinuria as a surrogate end point for randomized trials in immunoglobulin A nephropathy (IgAN) has previously not been thoroughly evaluated.

Study Design: Individual patient-level meta-analysis.

Setting & Population: Individual-patient data for 830 patients from 11 randomized trials evaluating 4 intervention types (renin-angiotensin system [RAS] blockade, fish oil, immunosuppression, and steroids) examining associations between changes in urine protein and clinical end points at the individual and trial levels.

Selection Criteria for Studies: Randomized controlled trials of IgAN with measurements of proteinuria at baseline and a median of 9 (range, 5-12) months follow-up, with at least 1 further year of follow-up for the clinical outcome.

Predictor: 9-month change in proteinuria.

Outcome: Doubling of serum creatinine level, end-stage renal disease, or death.

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

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

Conclusions: Results of this analysis offer novel evidence supporting the use of an early reduction in proteinuria as a surrogate end point for clinical end points in IgAN in selected settings.

Am J Kidney Dis. ■(■):■-■. © 2016 by the National Kidney Foundation, Inc.

INDEX WORDS: Proteinuria; urine protein; surrogate endpoint; IgA nephropathy (IgAN); end-stage renal disease (ESRD); prognostic marker; clinical end point; disease progression; kidney disease; glomerulonephritis; meta-analysis.

Immunoglobulin A nephropathy (IgAN) 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

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Received October 20, 2015. Accepted in revised form February 12, 2016.

Because 2 authors of this article are editors for AJKD, the peer-review and decision-making processes were handled entirely by an Associate Editor (Stephen Seliger, MD, MS) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Information for Authors & Journal Policies.

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0272-6386

<http://dx.doi.org/10.1053/j.ajkd.2016.02.042>

most effective early in the disease course. In many chronic kidney diseases (CKDs), a large decline in GFR, assessed as doubling of serum creatinine level from baseline and more recently 30% or 40% decline in GFR, has often been used as a surrogate end point for kidney failure in randomized clinical trials of patients with low GFRs or rapidly progressive disease.^{1,2} However, for the majority of patients with IgAN with progressive disease, these end points 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 IgAN.

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 the use of change in proteinuria as a surrogate outcome for disease progression across many causes of CKDs.^{6,7} One criticism of these analyses was that they grouped together different causes of kidney disease, and the role of proteinuria in the cause and progression of the disease may differ among causes.⁸ If so, the performance of proteinuria as a surrogate would differ, in which case pooling across studies may have masked true associations between change in proteinuria and clinical end points in a particular disease. We report an individual patient-level meta-analysis of a pooled data set of 830 individuals from 11 randomized controlled trials of 4 intervention types in IgAN to evaluate an early change in proteinuria as a surrogate end point for progression of this specific cause of kidney disease.

METHODS

Study Selection and Study Populations

We identified potential studies by a systematic search of the medical literature on Ovid MEDLINE published from January 1, 1979, to July 9, 2012 (see Fig S1 for flow chart and Table S1 for search terms, provided as online supplementary material). The key inclusion criterion was randomized controlled trial design of drug interventions in adults with IgAN (Table S2). In total, we were able to include 11 studies that investigated 4 intervention types (renin-angiotensin system [RAS] blockade, fish oil, steroids, or other immunosuppression agents; Fig S1). Risks of bias for each study were assessed using the risk-of-bias tool of the Cochrane collaboration⁹ (Table S3). We defined the active treatment as the treatment hypothesized to produce the greater reduction in risk for the clinical end point. All participants gave informed consent as part of their 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 excretion from baseline to a median of 9 (range, 5-12) months. Urine protein was expressed in

units of grams per day and was log transformed due to skewedness of the data.

Clinical End Point

The clinical end point was defined as the composite of time to the first occurrence of doubling of serum creatinine level, end-stage renal disease, or death. If available, we used the study-defined censoring dates to define follow-up times.^{10,11} As previously described, if study-defined censoring dates were not available, we approximated them as 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 that occurred following the patient's final study visit.

Analyses

As was previously used in Inker et al,⁶ we performed 3 types of analyses that are widely used for validation of surrogate end points: (1) association between the clinical outcome and early change in proteinuria at the individual level,²¹ (2) proportion of treatment effect 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 end point.²⁴⁻²⁷

For all analyses, GFR was estimated using the CKD-EPI (CKD Epidemiology Collaboration) creatinine equation.²⁸ We report results for each study, in the pooled data set and in subgroups based on intervention type, baseline urine protein excretion (<1, 1-2, and >2 g/d), estimated GFR (eGFR; <45, 45-90, and >90 mL/min/1.73 m²), and blood pressure (systolic blood pressure < 140 and diastolic blood pressure < 90 mm Hg vs systolic blood pressure ≥140 or diastolic blood pressure ≥ 90 mm Hg). In a sensitivity analysis, we adjusted for follow-up blood pressure at the same time point as the second measurement of urine protein excretion in the subset of studies in which these measurements 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 end point 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 (HR) associated with a halving of proteinuria. Our initial model was adjusted for treatment assignment, study, and baseline urine protein excretion, with the more fully adjusted models adjusted for additional baseline variables including age, sex, race, eGFR, and blood pressure. We obtained HRs and associated 95% confidence intervals (CIs) for the overall data set and for subgroups by repeating the Cox regression in the overall data set and in each of the subgroups pooled across each study, in which baseline hazards of 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" (proportion of treatment effect) has been widely used as an index of the validity of surrogate end points.^{22,23,31} When data permit, the proportion of treatment effect 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 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. The proportion of treatment effect 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 proportions of treatment effect and associated 95% CIs for each of the 4 interventions by repeating the mentioned procedure for joint analyses in each of the interventions. Proportions of treatment effect were only computed for interventions in which the treatment effect had $P < 0.10$.

Trial-Level Analyses

Assessments of individual-level association and Prentice-Freedman criteria both depend on the untestable assumption of no residual confounding from factors that jointly influence the surrogate and clinical end points.^{24,33} By contrast, trial-level analyses investigate the relationship between treatment effects on the surrogate with treatment effects on the clinical end points, for which each treatment effect is estimated from a randomized trial and therefore minimizes the risk for confounding that affects the first 2 approaches.²⁴ It is the more direct evaluation of potential surrogates because it evaluates the consistency and association between treatment effects on the surrogate to treatment effects on the clinical end point and has been the primary focus of the statistical surrogate end point 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 end point 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 randomized controlled trials.

Trial-level analysis requires 2 steps: assessment of 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 treatment effects (and associated standard errors) on 9-month change in proteinuria (expressed as the log-transformed ratio of follow-up vs baseline geometric mean proteinuria between treatment groups) and on the clinical outcome (expressed as log-transformed HRs). We obtained estimates of the correlation between treatment effects on the clinical and surrogate outcomes within each study by performing bootstrap resampling with 2,000 repetitions for each study. In order to ensure 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 treatment effects on the clinical outcome to 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 end point and support the surrogacy hypothesis.

RESULTS

Characteristics of Study Population

Tables S4 and S5 describe the included studies. Of 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 repeat measurement of urine protein at 9 months, leaving 830 participants in the pooled study population. Table 1 shows the characteristics of these 830 participants.^{10-20,36,37} In the pooled data set, median baseline urine protein excretion was 1.80 (interquartile range [IQR], 1.3-2.7) g/d (range across studies, 1.0 [IQR, 0.6-2.7] to 2.50

[IQR, 1.5-4.0] g/d) and mean baseline eGFR was 74 ± 30 (standard deviation) mL/min/1.73 m² (range across studies, 28 ± 7 to 99 ± 23 mL/min/1.73 m²) with varying distributions across the interventions (Table 1). In the pooled data set, mean follow-up was 4.8 ± 2.7 (range across studies, 1.5 ± 0.8 to 7.8 ± 4) years, with a total of 128 (15.4%) clinical end points (range across individual studies, 3 [9%] to 18 [42%]; Table 1). For the sensitivity analysis, a subset of 699 patients in 10 trials had blood pressure information available at the time of the follow-up urine protein measurement. Baseline characteristics were similar to the main study population (Table S6).

Individual-Level Association

Table 2 shows associations of change in urine protein excretion with the development of subsequent clinical outcomes. In the pooled data set, a decline in urine protein excretion was associated with lower risk for the clinical outcome (HR for a 50% decline in urine protein excretion, 0.40; 95% CI, 0.32-0.48). Results were broadly consistent across studies, although HRs 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 eGFR, and blood pressure (Table 2). Results were similar in the subset after adjusting for changes in blood pressure during follow-up (Table S7).

Investigation of Prentice-Freedman Criteria

Table 3 shows treatment effects on the clinical end point before and after adjusting for full set of baseline covariates and change in proteinuria and the associated proportion of treatment effect 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 ($P < 0.10$). Pooled proportions of treatment effect 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 treatment effects on early change in proteinuria and the clinical outcome. In the pooled data set, treatment reduced proteinuria compared to control (pooled geometric mean ratio, 0.76; 95% CI, 0.68-0.85). However, there was substantial variation across studies (range, 0.38 [95% CI, 0.27-0.53] to 1.39 [95% CI, 0.87-2.22]) and treatment types (range, 0.50 [95% CI, 0.41-0.60] for studies of steroids to 1.07 [95% CI, 0.86-1.34] for studies of immunosuppression). In the pooled data set, treatment also reduced the risk for the clinical end point compared to

Table 1. Characteristics of Study and Study Groups

Study Group and Code	N ^a	Female, %	Age, y	Urine Protein, g/d ^b	eGFR, mL/min/1.73 m ²	No. of Events					Follow-up, y
						ESRD	Doubling Scr	Deaths	Composite		
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 (0)	8 (7.6)		2.75 ± 0.60
A2	44	39	31.6 ± 11.5	1.70 [1.1-2.4]	98.1 ± 26.5	15 (34)	6 (14)	0 (0)	15 (34)		7.84 ± 3.95
Fish oil											
B1	66	16	46.4 ± 13.4	1.56 [0.7-2.6]	41.8 ± 14.1	10 (15)	10 (15)	0 (0)	14 (21)		2.35 ± 1.09
B2	89	26	38.8 ± 13.6	2.00 [1.2-3.4]	66.4 ± 21.6	15 (17)	1 (1)	2 (2)	16 (18)		3.00 ± 1.08
Immunosuppression											
C1	34	29	44.8 ± 11.3	1.00 [0.6-2.7]	62.2 ± 18.9	2 (6)	2 (6)	1 (3)	3 (9)		3.20 ± 0.86
C2	18	11	38.2 ± 13.9	2.28 [1.5-2.9]	49.1 ± 30.0	3 (17)	0 (0)	0 (0)	3 (17)		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	19	42.0 ± 11.7	2.50 [1.5-4.0]	28.0 ± 7.1	18 (42)	9 (21)	0 (0)	18 (42)		4.29 ± 1.68
Steroids											
D1	83	30	38.6 ± 11.7	1.90 [1.4-2.4]	87.2 ± 21.6	7 (8)	14 (17)	0 (0)	14 (17)		7.93 ± 3.26
D2	94	31	33.8 ± 11.1	1.66 [1.4-2.5]	91.2 ± 23.8	8 (9)	15 (16)	0 (0)	15 (16)		4.44 ± 1.93
D3	70	60	36.4 ± 11.5	1.36 [1.0-2.6]	98.5 ± 22.3	4 (6)	5 (7)	0 (0)	5 (7)		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 (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	1.70 [1.3-2.5]	91.8 ± 23.0	19 (7.8)	34 (13.8)	0 (0)	34 (13.8)		6.15 ± 2.88

Note: 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 RAS blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Table S4 for the study name for each study code and Table S5 for description of the studies. Unless otherwise indicated, values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations: eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RAS, renin-angiotensin system; Scr, serum creatinine.

^aSample size.

^bAll except one study measured urine protein excretion using 24-hour urine collections, and this study estimated it using urine protein-creatinine ratio in spot urine samples.

control (HR, 0.37; 95% CI, 0.25-0.55), with variation across study and interventions (HRs 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 end point for 7 of 11 studies and 2 of 4 interventions (steroids and RAS blockade). In sensitivity analyses, findings were similar in the subset after adjusting for changes in blood pressure during follow-up (Table S8).

Figure 1 shows the relationship between treatment effects on early change in proteinuria versus 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 treatment effects on urine protein excretion and on the clinical end point.

DISCUSSION

Use of surrogate end points may improve the efficiency of clinical trials in general, and for studies of

IgAN, 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 early change in proteinuria is a valid surrogate end point for progression of IgAN. First, there is a range of pathologic evidence that 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, the 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 for statistical associations between early changes in proteinuria and clinical end points across multiple interventions. Results from these analyses extend the evidence supporting a potential use of early change in proteinuria in IgAN.

Table 2. Association of Change in Urine Protein at 9 Months on Clinical End Points

	N ^a	No. of Events	Adj for Baseline Urine Protein		Fully Adj ^b	
			HR (95% CI)	P	HR (95% CI)	P
Study code						
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						
RAS blockade	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
Immunosuppression	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 g/d	88	5	0.22 (0.05-0.91)	0.04		
1-2 g/d	368	35	0.43 (0.29-0.64)	<0.001	0.46 (0.32-0.68)	<0.001
>2 g/d	374	88	0.38 (0.29-0.50)	<0.001	0.39 (0.29-0.51)	<0.001
eGFR categories						
<45 mL/min/1.73 m ²	154	45	0.44 (0.31-0.61)	<0.001	0.46 (0.32-0.65)	<0.001
45-90 mL/min/1.73 m ²	422	66	0.33 (0.24-0.46)	<0.001	0.34 (0.25-0.48)	<0.001
>90 mL/min/1.73 m ²	254	17	0.42 (0.24-0.75)	0.003	0.47 (0.25-0.89)	0.02
BP categories						
SBP < 140 and DBP < 90 mm Hg	534	75	0.42 (0.32-0.55)	<0.001	0.40 (0.31-0.53)	<0.001
SBP ≥ 140 or DBP ≥ 90 mm Hg	296	53	0.35 (0.25-0.49)	<0.001	0.40 (0.28-0.55)	<0.001

Note: 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 RAS blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See [Table S4](#) for the study name for each study code and [Table S5](#) for the description of the studies. Blank cells indicate that the model did not converge.

Abbreviations: Adj, adjusted; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RAS, renin-angiotensin system; SBP, systolic blood pressure.

^aSample size.

^bFully adjusted models include treatment assignment, study, baseline urine protein excretion, age, sex, race, eGFR, and BP. HRs are reported for 50% decline in urine protein excretion.

Our analyses of individual-level association establish that a greater reduction in proteinuria is consistently associated with slower progression of IgAN across all interventions. These results are limited by possible confounding factors that influence both proteinuria and the clinical end point, although 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 IgAN. These results in and of themselves are not evidence of surrogacy, but support the use of change in proteinuria to inform prognosis in IgAN, as has been shown for general CKD.^{45,51,52}

Proportion of treatment effect is a traditional method to evaluate surrogate end points. 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 error in proteinuria and possible residual confounding.^{24,33} Our assessments of Prentice-Freedman criteria were therefore inconclusive, with few trials meeting the necessary criteria.

We used 2 approaches to investigate whether treatment effects on change in proteinuria were consistent with treatment effects on the clinical outcome. First, we found that the direction of treatment effects on reductions both in proteinuria and on the clinical end point were in agreement for steroid and RAS blockade

Table 3. Treatment Effect on the Composite End Point, With and Without Adjustment for Change in Urine Protein and Proportion of Treatment Effect, Adjusted for Prentice-Freedman Covariates

	No. of Patients (No. of Events)	Not Adj for Change in Urine Protein			Adj for Change in Urine Protein			PTE ^a (95% CI)
		PE	HR (95% CI)	P	PE	HR (95% CI)	P	
Study code								
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 to 28)
B2	89 (16)	-1.19	0.30 (0.08-1.13)	0.08	-0.68	0.50 (0.14-1.80)	0.2	43 (-24 to 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 to 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 to 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 to 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 to 31)
Treatment type								
RAS blockade	150 (23)	-1.42	0.24 (0.08-0.74)	0.01	-1.27	0.28 (0.08-1.01)	0.05	11 (-19 to 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 to 53)

Note: 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 RAS blockade versus control, B is fish oil, C is immunosuppression, and D is steroids. See Table S4 for the study name for each study code and Table S5 for the description of the studies.

Abbreviations: Adj, adjusted; CI, confidence interval; HR, hazard ratio; PE, parameter estimate; PTE, proportion of treatment effect; RAS, renin-angiotensin system.

^aPTE = $(1 - \alpha/\beta)\%$ where α is the PE for treatment effect under the model without change in urine protein excretion and β is the PE for treatment effect under the model with change in urine protein excretion. Models are adjusted for baseline urine protein excretion, estimated glomerular filtration rate, race, age, and sex. PTE is traditionally computed for studies with significant treatment effect on the clinical end point 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 ($P < 0.10$).

interventions, but were not in agreement for the fish oil and immunosuppression interventions. The lack of agreement for these latter 2 interventions may reflect imprecision of treatment effects for these interventions. Second, using the trial-level approach, we found that there was a positive relationship between treatment effects on urine protein excretion and the clinical end point, with a credibility interval, though wide, that did not cross zero. 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 end point. 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 geometric mean ratio for proteinuria. Although this approach is commonly used in trial-level analyses, the consequences of the uncertainty in 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 IgAN would help address this issue.

Prior literature appears to contradict the positive relationship between treatment effects on urine protein excretion and the clinical end point shown by trial-level analysis in our study. Inker et al⁶ and Lambers-Heerspink et al⁷ recently evaluated change in proteinuria as a surrogate outcome in studies across heterogeneous causes of CKD. In contrast to the current analysis, in both studies, when analyses were restricted to early change in proteinuria, the CI for the regression line crossed zero. It is possible that evaluation across

these heterogeneous sets of diseases masked the relationship within IgAN. Others have suggested that assessment of potential surrogate end points may be optimally performed within specific diseases.⁸ In an analysis performed by Lv et al⁵³ evaluating this question in 6 trials of IgAN, the decrease in risk for kidney failure with steroid therapy was associated with the difference in proteinuria reduction between treatment groups. However, this finding was not statistically significant ($P = 0.1$), potentially because of 4 small studies with few clinical events and infinite confidence margins on the treatment effect on the clinical end point. Finally, Rauven et al⁵⁴ showed that immunosuppressive therapy led to a positive treatment effect on proteinuria but not on a reduction in GFR of 15 mL/min/1.73 m². However, as we have recently shown, use of small changes in GFR is not appropriate in most settings due to the potential for acute effects on eGFR, and the study was not powered sufficiently to assess differences on larger GFR decline or clinical end points.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 3 standard approaches for validating surrogate end points in the statistical and medical literatures. Results from these analyses extend the evidence supporting the use of proteinuria in some settings. There are also limitations. First, all the studies included had follow-up less than 10 years, whereas for most patients with IgAN, it is a slowly progressive indolent disease and studies with

Table 4. Treatment Effect on Change in Urine Protein, Adjusted for Baseline Urine Protein

	N ^a	Treatment Effect on Proteinuria		Treatment Effect on Clinical End Points	
		GMR (95% CI)	P	HR (95% CI)	P
Study code					
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					
RAS blockade	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
Immunosuppression	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 g/d	66	0.90 (0.64-1.36)	0.7	1.47 (0.16-13.65)	0.7
1-2 g/d	368	0.68 (0.57-0.80)	<0.001	0.22 (0.09-0.54)	0.001
>2 g/d	374	0.80 (0.67-0.95)	0.01	0.40 (0.25-0.64)	<0.001
eGFR categories					
<45 mL/min/1.73 m ²	154	0.96 (0.71-1.29)	0.8	0.66 (0.35-1.24)	0.3
45-90 mL/min/1.73 m ²	422	0.81 (0.69-0.96)	0.01	0.30 (0.17-0.53)	<0.001
>90 mL/min/1.73 m ²	254	0.59 (0.49-0.72)	<0.001	0.07 (0.01-0.56)	0.01
BP categories					
SBP < 140 and DBP < 90 mm Hg	534	0.72 (0.62-0.83)	<0.001	0.33 (0.19-0.56)	<0.001
SBP ≥ 140 or DBP ≥ 90 mm Hg	296	0.83 (0.68-1.02)	0.08	0.42 (0.23-0.76)	0.004

Note: Each study is referred to by an alphanumeric code. Each letter refers to treatment comparisons, and each number refers to the individual studies: A, RAS blockade versus control; B, fish oil; C, immunosuppression; D, steroids. See Table S4 for the study name for each study code and Table S5 for the description of the studies.

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GMR, geometric mean ratio, HR, hazard ratio; RAS, renin-angiotensin system; SBP, systolic blood pressure.

^aSample size.

shorter follow-up may have missed true associations. Second, the evaluation of proteinuria as a surrogate end point was limited to changes between approximately 6 and 12 months, and our findings may not extend changes in proteinuria over longer (or shorter) periods. Because the end point is defined by change in proteinuria, all participants must have survived to have the second measurement, although that does not invalidate the comparison to the clinical end points because end points 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 because some studies compared azathioprine plus steroids versus steroids alone; azathioprine plus 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 because we only included studies written in English prior to 2012 that had sufficient data for our planned analyses and for which 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 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 the use of proteinuria as a surrogate end point in interventions that work by a

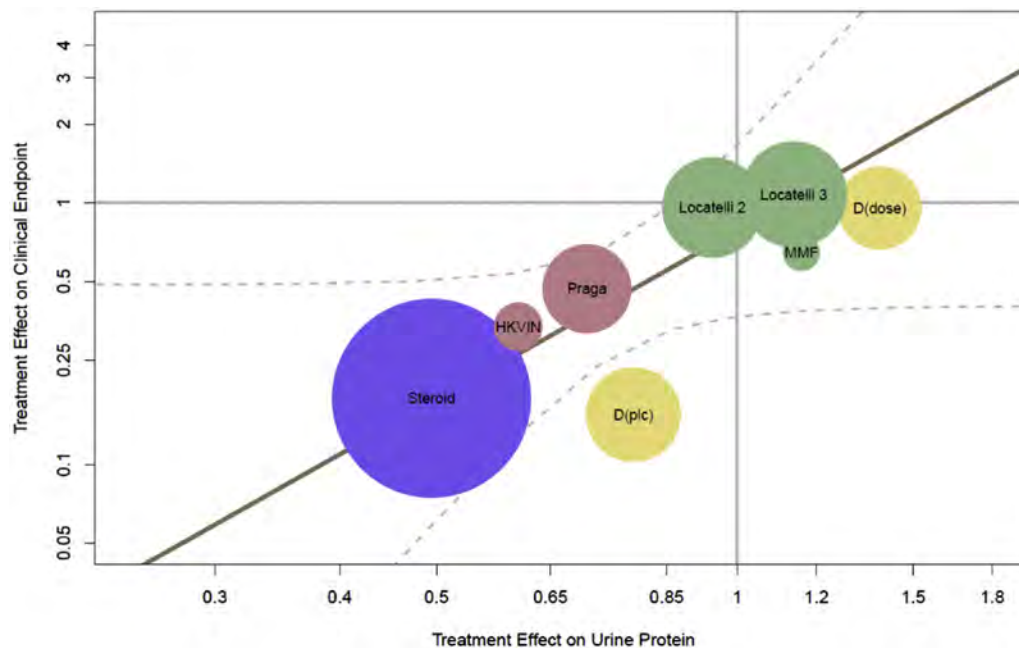


Figure 1. Trial-level assessment of the validity of proteinuria as a surrogate end point. Dots are the observed treatment effects on the clinical outcome (vertical axis) and change in urine protein (horizontal axis) for each study or study group. Colors indicate intervention. Red, renin-angiotensin system blockade; yellow, fish oil; green, immunosuppression; purple, steroids. Treatment effects on the clinical outcome are expressed as hazard ratios. Treatment effect on urine protein was computed as change in log urine protein (follow-up – baseline) in the treatment versus control groups. The treatment effect estimate was exponentiated to obtain the geometric mean ratio of the change in urine protein for the treatment versus 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 change in urine protein. Gray lines indicate the confidence band around the regression line. Overall, the slope is 2.15 with a 95% Bayesian credible interval range from 0.10 to 4.32 with R^2 of 0.91, 95% Bayesian credible interval range from 0.47 to 1.0, indicating that for a given treatment effect on urine protein excretion, the treatment effect on the clinical outcome is expected to be double the treatment effect on urine protein excretion when the respective treatment effects are expressed on the log hazard ratio and log geometric mean scales. The Bayesian credible interval around the slope was wide but did not cross zero, suggesting there is a significant positive relationship between treatment effects on urine protein and on the clinical end point. Abbreviations: AZA, azathioprine; D(dose), Donadio (dose); D(plc), Donadio (placelco); HKVIN, Hong Kong Study Using Valsartan in IgA Nephropathy; MMF, mycophenolic mofetil.

similar mechanism evaluated in the current analysis, in early-phase clinical trials for new therapies with different mechanisms of actions and for exploratory analyses (eg, subgroup analyses with limited power for the clinical end point). Use of early change in proteinuria could facilitate studies of new treatments for IgAN, but such short-term studies should be followed with subsequent postapproval confirmation of the treatment effect on the clinical end point and for accumulation of safety data.

ACKNOWLEDGEMENTS

The authors thank Neal Shah and Aghogho Okparavero for assistance with abstracting.

Support: The analyses described here were funded by a research grant to Tufts Medical Center by Pharmalink AB. A variety of sources supported enrollment and data collection including laboratory measurements and analyses of the contributing studies to this meta-analysis. These include REDinREN (RD012/0021) and Instituto de Salud Carlos III (10/02668, 13/02502, and ICI 14/00350). The funders of this study participated in the study design, writing the report, and the decision to submit the report for publication, but did not have a role in analysis or interpretation of the data.

Financial Disclosure: Dr Inker reports receiving research grants to Tufts Medical Center from the National Institutes of Health (NIH), National Kidney Foundation (NKF), Pharmalink, Gilead Sciences, and Otsuka. Dr Greene reports receiving a research grant to University of Utah from Pharmalink and is a consultant for Keryx Biopharmaceuticals, Jansen Pharmaceuticals, Pfizer, and GenKyoTex SA. Dr Locatelli was a member of an advisory board of Akebia, Amgen, Astellas, AZ Pharma, Fresenius Medical Care, GSK, Keryx, Pharmalink AB, and Pharmacosmos. Dr Appel reports receiving research grants from Regulus, BM Squibb, and Genentech, as well as lecture fees for Genentech and Takeda and consultantships with Alexion, Genentech, Mallinkrodt, Pfizer, Merck, Roche, Bristol-Myers Squibb, Up-to-Date, Amgen, Genzyme-Sanofi, Novartis, Teva, Takeda, EMD Serono, Boehringer Ingelheim, and Regulus. Dr Maes reports serving in a strategic advisory role to Pharmalink. Dr Praga reports receiving fees for lectures and advisory boards for Alexion, Abbvie, Otsuka, Pharmalink, Astellas, Novartis, and Fresenius. Dr Del Vecchio was a member of an advisory board of Astellas. Dr Mercer reports employment at Pharmalink during the conduct of the study. Dr Carroll is a consultant to Pharmalink. Dr Levey reports funding to Tufts Medical Center for research and contracts with the NIH, NKF, Amgen, Pharmalink, and Gilead Sciences. Dr Schmid reports funding to Brown University for research and contracts with the NIH and the Agency for Healthcare Research and Quality, as well as a consulting agreement with Pfizer. The other authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: LAI, TG, AM, CHS, ASL; data acquisition: LAI, TM, FL, FPS, RK, GBA, BDM, PKL, MP, LDV, SA, CM, EG; data analysis/interpretation: LAI, HM, TG, AM, KJC, CHS, ASL; statistical analysis: LAI, HM, TG, CHS, 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 have been explained.

Peer Review: Evaluated by 3 external peer reviewers, a statistician, and an Acting Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Literature search terms.

Table S2: Inclusion criteria for eligible randomized controlled clinical trials.

Table S3: Bias of included studies.

Table S4: List of study names and study numbers, collaborators and references.

Table S5: Study characteristics.

Table S6: Clinical characteristics of subset of participants with BP at 9-mo F/U.

Table S7: Association of change in urine protein at 9 mo on clinical outcome—adjusted baseline covariates, in subset with BP at same visit as urine protein in F/U.

Table S8: Treatment effect on change in urine protein, adjusted for baseline covariates, and then for change in BP in subset of patients who have BP at same visit as urine protein in F/U.

Figure S1: Flowchart of study identification process.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2016.02.042>) is available at www.ajkd.org

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