Remission of Proteinuria Improves Prognosis in IgA Nephropathy

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ABSTRACT

Proteinuria has been shown to be an adverse prognostic factor in IgA nephropathy. The benefit of achieving a partial remission of proteinuria, however, has not been well described. We studied 542 patients with biopsy-proven primary IgA nephropathy in the Toronto Glomerulonephritis Registry and found that glomerular filtration rate (GFR) declined at -0.38 ± 0.61 ml/min per 1.73 m^2/mo overall, with 30% of subjects reaching end-stage renal disease. Multivariate analysis revealed that proteinuria during follow-up was the most important predictor of the rate of GFR decline. Among the 171 patients with <1 g/d of sustained proteinuria, the rate of decline was 90% slower than the mean rate. The rate of decline increased with the amount of proteinuria, such that those with sustained proteinuria >3 g/d ($n = 121$) lost renal function 25-fold faster than those with <1 g/d. Patients who presented with ≥3 g/d who achieved a partial remission (<1 g/d) had a similar course to patients who had ≤1 g/d throughout, and fared far better than patients who never achieved remission. These results underscore the relationship between proteinuria and prognosis in IgA nephropathy and establish the importance of remission.

Primary IgA nephropathy (IgAN) is the most common form of idiopathic glomerulonephritis (GN) throughout the world and the main cause of ESRD in patients with primary glomerular disease.[1] In Toronto, nearly 40% of patients with IgAN progress to ESRD by 10 yr.[2] Variability in the literature regarding the clinical course of patients with IgAN[3–7] may be related to multiple factors, including patient biologic differences, nephrologists' practice patterns (*e.g.*, biopsy timing), and geography.[7] The ability to predict outcome in patients with IgAN remains a critical feature of patient treatment and has been a primary focus of previous studies.[2,3,5,6,8–15]

Many studies[7,16,17] have shown that proteinuria is a predictor of outcome in IgAN. Experimental evidence supports these human data by clarifying the direct deleterious effect of proteinuria on renal tissue.[18–23] In contrast to other progressive types of GN, in which it seems that only sustained nephrotic-range proteinuria (>3 to 3.5 g/d) ensures a poor prognosis, studies in IgAN[5,10,17,24,25] and have suggested that much lower levels of proteinuria adversely affect prognosis. Furthermore, although the concept of achieving "partial remission" is not commonly associated with IgAN, recent evidence in other forms of GN has determined its clinical significance and established its prognostic value.[26,27] The relevance of such a definition and its value in IgAN would be important for management of this disease.

Accordingly, we examined the effects of proteinuria at diagnosis as well as sustained exposure to

proteinuria on outcome in a large cohort of patients who had primary IgAN and were followed longitudinally in the Toronto Glomerulonephritis Registry. We also assessed the prognostic relevance of achieving partial remission as defined by achieving sustained proteinuria values <1 g/d.

RESULTS

Baseline Characteristics and Clinical Outcome

As described in Table 1, the majority (61%) of the 542 patients studied were male and of white or Asian (China, Japan, or Pacific Rim) descent. Mean initial proteinuria was 2.4 g/d, and creatinine clearance (CrCl) was 77 ml/min per 1.73 m^2. Patients were followed for 6.5 yr. By study completion, one third of patients had reached ESRD. The rate of progression as measured by slope of CrCl was -0.38 ± 0.61 ml/min per 1.73 m^2/mo (-4.56 ml/min per 1.73 m^2/yr).

Proteinuria and the Rate of Decline of Renal Function

Clinical variables at onset of disease and during follow-up were tested for association with the slope of CrCl. Regression anal-

Table 1. Baseline characteristics and clinical outcome in 542 patients with IgAN

Characteristic	Value
Baseline	
age (yr; mean $\pm$ SD [range])	38.2 $\pm$ 13.01 (15.6 to 73.5)
gender (% male)	61
BMI (kg/m^2; mean $\pm$ SD [range])	25.9 $\pm$ 5 (16 to 43)
creatinine (μmol/L; mean $\pm$ SD [range])	129.7 $\pm$ 70.6 (50 to 731)
MAP (mmHg; mean $\pm$ SD [range])	103 $\pm$ 16 (73 to 170)
24-h urine protein (g; mean $\pm$ SD [range])	2.37 $\pm$ 2.5 (0 to 22)
CrCl (ml/min per 1.73 m^2; mean $\pm$ SD [range])	77.0 $\pm$ 33 (9 to 217)
ethnicity (%)	
white	50.4
black	2.8
Asian	23.1
other	10.0
unknown	13.7
Follow-up	
length of follow-up (mo; mean $\pm$ SD [range])	78.1 $\pm$ 59 (12 to 315)
MAP (mmHg; mean $\pm$ SD [range])	99.7 $\pm$ 10 (72 to 141)
peak proteinuria (g/24 h; mean $\pm$ SD)	3.71 $\pm$ 3.20
proteinuria (g/24 h; mean $\pm$ SD)	2.19 $\pm$ 1.94
treatment (%)	
ACEi or ARB	53
fish oil	15.1
any immunosuppression	15.7
prednisone	12.5
renal failure (%)	27.7
slope CrCl (ml/min per 1.73 m^2/mo; mean $\pm$ SD)	-0.38 ± 0.61

ysis revealed that several factors, shown in Table 2, were predictive of a faster rate of renal function decline (steeper, more negative slope).

The time-average proteinuria (TA-proteinuria; see Concise Methods section) was a critical determinant of slope by univariate and multivariate analysis ($P < 0.01$) and the most important predictor of renal function decline ($R^2 = 0.162$, $F = 104.5$, $P < 0.01$). Proteinuria at presentation was not predictive of slope by multivariate analysis.

The TA-proteinuria was also analyzed as a categorical variable, as illustrated in Table 3. When adjusted for multiple comparisons, the rate of deterioration (slope) of renal function differed significantly across the entire range of proteinuria. The greatest difference in rate of decline occurred between the ≤1 and >1 g/d TA-proteinuria. On the basis of the mean 10-yr slope, patients with ≤1 g of TA-proteinuria had stable renal function, and patients with 1 to 2 g of TA-proteinuria had a projected unadjusted loss of 40 ml/min per 1.73 m^2 by 10 yr. Trend test and nonparametric testing did not establish differences among patients with ≤1 g/d TA-proteinuria: 0 to 0.3 ($n = 36$) versus 0.3 to 0.6 ($n = 63$) versus 0.6 to 1 g/d TA-proteinuria ($n = 72$; slopes 0.00 $\pm$ 0.39, 0.02 $\pm$ 0.48, and -0.06 ± 0.48 ml/min per 1.73 m^2/mo, respectively; NS). Proteinuria categories did not overlap (i.e., patients were assigned to only one category of TA-proteinuria).

Proteinuria and Renal Survival

The TA-proteinuria was the most important predictor of renal survival, even when corrected for other parameters (multivariate hazard 1.57; 95% confidence interval 1.39 to 1.77; $P < 0.01$). The graded effect of TA-proteinuria on renal survival is illustrated in Figure 1. Having <0.3 g/d proteinuria was similar to 0.3 to 1.0 g/d, but each gram above 1 g/d (reference group) was associated with worse renal survival, with a hazard ratio of 3.5 for ESRD with 1 to 2 g/d, 5 with 2 to 3 g/d, and 10 with >3 g/d.

We analyzed the course of patients whose initial proteinuria was >1 g/d and fell below this level during follow-up. Patients were divided into groups on the basis of their peak proteinuria: 1 to 2, 2 to 3, and >3 g/d. As illustrated in Figure 2, all patients whose proteinuria reached a "partial remission" of <1 g/d, regardless of the starting point, had a similar, favorable survival (log rank NS) and rate of progression (-0.2 ± 0.47, -0.14 ± 0.63, and -0.16 ± 0.37 ml/min per 1.73 m^2/mo respectively; NS). In comparison, the outcome of "nonremitters" (i.e., those who did not achieve <1 g/d) was markedly worse than remitters, with a far more rapid rate of renal decline (-0.76 ± 0.59 versus -0.13 ± 0.41 ml/min per 1.73 m^2/mo respectively; $P < 0.01$). Patients who achieved complete remission of proteinuria (sustained level of <0.3 g/d with preserved CrCl) did not have a different rate of renal function decline than patients who achieved partial remission to <1 g/d (-0.17 ± 0.47 versus -0.13 ± 0.41 ml/min per 1.73 m^2/mo, respectively; NS).

The course of patients whose initial proteinuria was <1 g/d but subsequently rose was also analyzed. Change in proteinuria was calculated by subtracting the final from the initial value. Patients

Table 2. Factors at presentation and during follow-up influencing decline in renal function (slope in ml/min per 1.73 m²/mo) by univariate and multivariate regression[a]

Parameter	Univariate		Multivariate	
	Mean/Standardized β	P	Mean/Standardized β	P
Presentation				
ln(24 h Upro)[b]	−0.145/−0.258	<0.01	–	NS
MAP	−0.005/−0.145	<0.01	–	NS
Follow-up				
ln(24 h Upro)[b]	−0.258/−0.403	<0.01	−0.302/−0.493	<0.01
MAP	−0.020/−0.337	<0.01	−0.013/−0.231	<0.01
BP med	−0.088/−0.105	0.02	–	NS
ACEi/ARB[c]	0.227/0.092	0.03	0.077/0.124	0.02

[a]Upro, urine protein excretion; BP med, average number of BP medications during follow-up.
[b]Urine protein results were log transformed.
[c]ACEi/ARB exposure was measured as a continuous TA value and analyzed in quartiles of medication exposure (see Concise Methods section).

Table 3. Outcome based on categorical grouping of TA 24-h urine protein excretion during follow-up[a]

Group (n)	TA-Proteinuria (g/24 h)	Slope (ml/min per 1.73 m²/mo; Mean ± SD)	Renal Failure Risk (Hazard [95% CI])
1 (171)	0 to 1	−0.030 ± 0.46	Reference
2 (145)	1 to 2	−0.326 ± 0.53	3.48 (1.8 to 6.7)
3 (105)	2 to 3	−0.516 ± 0.66	5.17 (2.6 to 10.0)
4 (121)	>3	−0.719 ± 0.61	9.89 (5.3 to 18.4)

[a]CI, confidence interval.

were then grouped into three categories according to their quantitative increase in proteinuria: 1 to 2 g/d (group 1), 2 to 3 g/d (group 2), and >3 g/d (group 3). As illustrated in Figure 3, the opposite of the improvements seen with lowering proteinuria were observed: The greater the rise in proteinuria, the worse the renal survival (log rank $P = 0.004$ by trend test) and rate of renal function decline ($F = 3.8$, $P = 0.025$). *Post hoc* analysis revealed that although the rate of renal function decline of patients in group 1 was similar to that of group 2 (−0.23 ± 0.41 *versus* −0.12 ± 0.79 ml/min per 1.73 m²/mo; NS), patients in group 3 had a significantly more rapid rate of renal function decline than patients in either group 2 (−0.51 ± 0.55 *versus* −0.12 ± 0.79 ml/min per 1.73 m²/mo; $P = 0.02$) or group 1 (−0.51 ± 0.55 *versus* −0.23 ± 0.41 ml/min per 1.73 m²/mo; $P = 0.03$). In terms of renal survival, 20 of the patients who presented with "low risk" proteinuria levels of <1 g/d had a subsequent rise in proteinuria and actually progressed to ESRD. These 20 patients had a lower CrCl at presentation (58 *versus* 81.4 ml/min per 1.73 m²; $P < 0.05$) and a higher TA mean arterial pressure (TA-MAP; 101 *versus* 96 mmHg; $P < 0.05$).

Role of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker

Because this is not a therapeutic trial, the direct role of specific interventions cannot be accurately assessed. It was observed that the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) lowered the rate of decline of renal function, even when adjusted for other clinical parameters. A greater proportion of patients who achieved partial remission of proteinuria were treated with ACEi/ARB, compared with patients who did not (66 *versus* 52%; $\chi^2 = 12.7$, $P < 0.01$). The beneficial effects of ACEi/ARB may have been

related to effects on both proteinuria and BP; however, use of other antihypertensive agents did not influence loss of renal function by multivariate analysis. The use of ACEi/ARB and GFR at the start of these medications were significant determinants of renal survival by univariate analysis ($P < 0.01$), however not multivariate analysis. The majority (86%) receiving ACEi/ARB were treated with ACEi alone, and there were insufficient patient numbers to analyze relative differences in ACEi *versus* ARB *versus* combination therapy.

Other Determinants of Outcome

Multivariate analysis revealed that only TA-proteinuria, TA-MAP, and quartile of exposure to ACEi/ARB were predictors of renal function decline (see Table 2) and were also predictive of
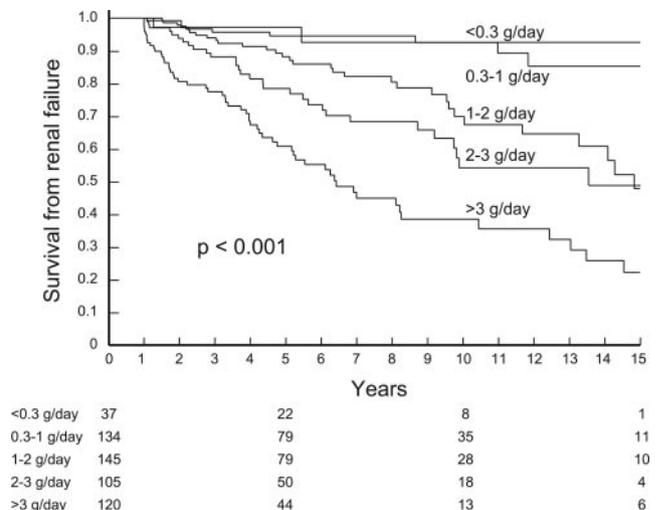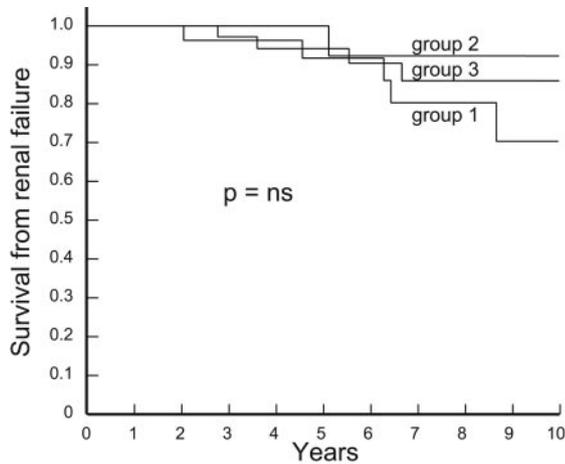

Figure 1. Renal survival by category of TA-proteinuria.

Group 1	29					18				6
Group 2	21					13				2
Group 3	39					26				10

Figure 2. Impact of reduction of proteinuria on renal survival. Patients attaining partial remission (<1 g/d), regardless of peak proteinuria, had a similar favorable outcome (NS). Group 1, 1 to 2 g/d peak proteinuria; group 2, 2 to 3 g/d peak proteinuria; group 3, >3 g/d peak proteinuria.

renal survival by multivariate Cox regression analysis. The complex nature of the interaction between MAP and proteinuria is illustrated in Figure 4; patients with the highest quartile of TA-MAP also had high levels of proteinuria and the greatest rate of loss of renal function; however, TA-proteinuria was still the most important predictor of outcome, independent of BP. Neither body mass index (BMI; continuous variable) nor high BMI (>27) was a predictor of slope by univariate analysis. As a continuous
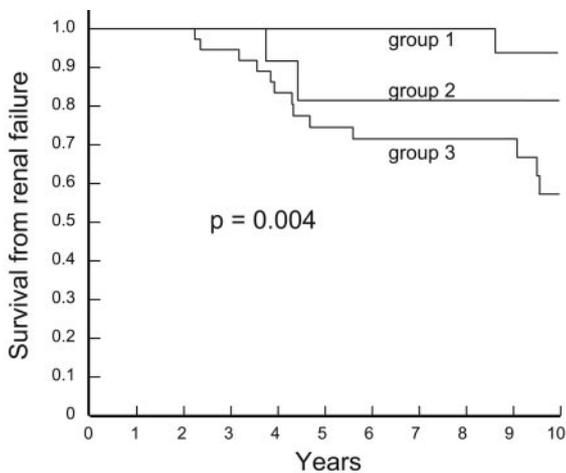
Group 1	37					27				11
Group 2	16					8				2
Group 3	37					25				11

Figure 3. Renal survival in patients with ≤1 g/d proteinuria at presentation differed significantly on the basis of increase in proteinuria from baseline. Group 1, 1 to 2 g/d increase; group 2, 2 to 3 g/d increase; group 3, >3 g/d increase in proteinuria from baseline. *P* = 0.004 by trend test.

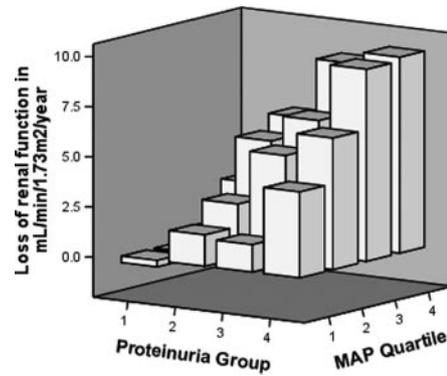**Figure 4.** Relationship between TA-proteinuria group, quartile of MAP, and loss of CrCl. Group 1, TA-proteinuria <1 g/24 h; group 2, 1 to 2 g/24 h; group 3, 2 to 3 g/24 h; group 4, >3 g/24 h.

variable, BMI related to renal survival only by univariate (not multivariate) Cox regression, which may have been driven by a higher risk for ESRD in patients with BMI >29 (hazard ratio 2.1; 95% confidence interval 1.2 to 3.6). No other factor (initial renal function, smoking, gender, ethnicity, fish oil, or immunotherapy) was predictive of the rate of loss of kidney function.

DISCUSSION

The purpose of this study was to quantify the value of proteinuria reduction on outcome in patients with IgAN. We also sought to determine whether by defining partial remission and by assessing the impact of change in proteinuria on outcome we could confirm the importance of the definition by quantifying its value in relationship to both rate of disease progression and renal survival.

Although proteinuria is a known risk factor for progression of IgAN,[2–6,8,9,14,28] important questions regarding its role in the prognosis of IgAN remain. First, timing of measurement requires clarification; proteinuria at diagnosis often is not a predictor of outcome by multivariate analysis,[2,17] whereas proteinuria at 1 yr or later may better indicate prognosis.[2] Second, although many studies suggest that patients with ≤1 g/d at presentation have a favorable prognosis,[5,29] this observation is not uniform,[10] and it is not known whether patients who achieve this target from higher values have the same prognosis as patients who present with and maintain low-level proteinuria. Finally, the importance of defining partial remission in proteinuria was established recently for other forms of GN[26,27]; it has not been confirmed or quantified in IgAN and would represent important information for clinicians.

We have confirmed that in IgAN, proteinuria exposure over time (TA-proteinuria) is the strongest predictor of the rate of renal function decline. The relationship between TA-proteinuria and outcome is dramatically altered down to levels as low as 1 g/d, which is in marked contrast to the other progressive types of primary nephropathy, including membranous GN and FSGS. A quantitative estimate of the impact of proteinuria

has been determined: Each incremental gram per day above 1 is associated with a 10- to 25-fold more rapid rate of renal function decline and similar differences in renal survival. Although we could not determine a difference in outcome below 1 g/d, this may reflect inadequate statistical power because the benefit is likely continuous; however, even if power were improved, the clinical relevance of improved slope below this level will be minor given the overall slow rate of decline observed in the patients with <1 g/d TA-proteinuria.

Patients who reached <1 g/d proteinuria regardless of their starting point, whether "partial remission" was reached spontaneously or with intervention, had an excellent prognosis, similar to patients whose proteinuria never exceeded 1 g/d. This is strong support for using this partial remission definition as a goal for clinicians and provides new insights regarding the value of proteinuria reduction as a therapeutic target. Although previously recognized as important, the magnitude of the effect of proteinuria reduction on progression and renal survival has not been described in IgAN. By determining the quantitative value of partial remission, intensive therapy targeting significantly lower levels of proteinuria than in the other primary glomerulopathies is justified. Providing this information to the patient—that is, the substantial value of small reductions in proteinuria—should also aid compliance in these largely asymptomatic individuals.

This study was not a therapeutic trial and not designed to assess the benefit of therapeutic interventions in the course of IgAN. The most important conclusion derived is that the reduction of proteinuria by whatever means (medication, MAP reduction) is of great clinical benefit. The use of ACEi/ARB was the only intervention associated with a slower rate of renal function decline and prolonged renal survival, in keeping with both published randomized, controlled trials and retrospective reviews demonstrating the renoprotective effect of renin-angiotensin-aldosterone system blockade.[30–39] These beneficial effects may reflect both hemodynamic and nonhemodynamic antiproteinuric effects of ACEi/ARB[24,35,40–42] or alterations in glomerular permselectivity[43]; however, this study was not designed to determine causality or mechanism. Similarly, although MAP was an important determinant of outcome and patients with the highest quartile of MAP had the highest levels of proteinuria, this is not necessarily a causal relationship.

The results of this study may not be generalizable to other populations. We previously demonstrated differences across geographic regions of the world in patients with IgAN.[7] Although the majority of the difference was due to practice patterns, we could not explain all of the regional differences. In addition, because of the dominant effect of protein reduction on outcome, the effects of interventions and clinical parameters (fish oil, BMI) may have been obscured. Finally, this study was not designed to assess the role of renal biopsy findings in predicting outcome. Our aim was to measure factors during the course of disease that relate to outcome (e.g., TA-proteinuria), as opposed to implications of cross-sectional factors, such as biopsy grade at the time of diagnosis. As demonstrated in our previous study[2] of a large cohort of patients

with IgAN, although biopsy findings are clinically important, we do not believe that the findings at the time of biopsy provide additional information that is not captured by time-dependent variables. Although many studies have found a relationship between sclerosis/fibrosis and outcome, these studies did not include sequential measurements of MAP/proteinuria over time[5,44,45] or had shorter follow-up.[3] Indeed, a relationship between biopsy class and final follow-up data has been noted[15]; however, the value of adding the pathologic information to repeated sequential clinical measurements over time has not been demonstrated.

In summary, sustained proteinuria >1 g/d was the strongest predictor of the rate of progression of renal disease and the development of renal failure in IgAN. We demonstrated that with each sustained gram-per-day increment of proteinuria above 1, fold differences in progression rate and renal survival were observed. More important, patients who were able to achieve and sustain reduction in proteinuria to <1 g/d had an excellent prognosis regardless of the level of initial proteinuria. This study quantifies the impact of proteinuria reduction in IgAN and the clinical relevance of defining partial remission in this disease as a valuable prognostic indicator for both the clinician and the patient.

CONCISE METHODS

Patient Selection

As described previously,[26,27,46] the Toronto Glomerulonephritis Registry was started in 1974 and includes all biopsy-proven cases of GN from the greater Toronto area. Patient information is documented from first clinical presentation and collected on a periodic prospective basis by registrars.

All patients who had biopsy-proven IgAN and were enrolled in the Toronto Glomerulonephritis Registry were considered ($n = 1373$) and were excluded only when clinical data were incomplete (37 lacked proteinuria data, 18 lacked weight data), they were younger than 16 yr at presentation ($n = 54$), they had <12 mo of follow-up ($n = 713$), or they had a secondary cause of IgA deposition ($n = 9$). A total of 542 patients were included.

Gender, ethnicity, age, and BMI were recorded at the time of first assessment suggestive of GN. Weight; BP; exposure to medications; and laboratory parameters recorded, including creatinine, albumin, urinalysis results, and 24-h urine protein and creatinine excretion, were collected prospectively.

Definitions

CrCl was estimated using the Cockroft-Gault method adjusted for body surface area.[47,48] The GFR was also estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation,[49] and the results of the analysis were the same in terms of relative importance of predictors in determining outcome. Start of follow-up was defined as the first assessment suggestive of renal disease. A CrCl <15 ml/min per 1.73 m^2, initiation of dialysis, or transplantation defined ESRD. MAP was defined as the diastolic pressure (in mmHg) plus one third of the pulse pressure. For each patient, an average MAP was

determined for each 6-mo block during follow-up; the average of every 6-mo period's MAP is represented by the TA-MAP. Proteinuria was measured by 24-h urine protein collection. In a similar manner to MAP, the TA-proteinuria represents an average of the mean of every 6-mo period's proteinuria measurements.

The rate of renal function decline is expressed as the slope of CrCl, which was obtained by fitting a straight line through the calculated CrCl using linear regression and the principal of least squares. This was plotted and visually examined for each patient. Periods of reversible acute renal failure (a rapid reduction and recovery in CrCl of ≥40% within a 1-mo time frame) were removed from the calculation.

Statistical Analyses
Data were analyzed using Microsoft Excel (Redmond, WA) and SPSS software (SPSS, Chicago, IL). Normally distributed variables are expressed as means ± SD and compared using t test or ANOVA as required. Nonparametric variables are expressed as median and range and compared using either Mann-Whitney U or Kruskal-Wallis test. Categorical variables were compared using a χ^2 test. All P values were two-tailed; $P < 0.05$ was considered statistically significant. Univariate followed by multivariate linear regression was used to determine independent predictors of slope. Clinically relevant parameters or variables significantly associated with slope by univariate analysis were included in the multivariate models. Because proteinuria distribution was skewed (at presentation and time averaged), log-transformed values were used in the regression analysis, and similar results in terms of the significance of proteinuria were obtained with non-transformed data (data not shown). Multivariate regression models were assessed by stepwise and block entry of variables. Renal survival times were calculated from the first clinical assessment suggestive of renal disease to last follow-up. The relationship between parameters and renal survival was assessed using Cox regression.

Exposure to ACEi or ARB was considered as both a dichotomous variable and a continuous TA measurement of ACEi/ARB exposure. This variable had a skewed distribution and was considered in quartiles of exposure to ACEi/ARB for multivariate regression. For assessment of the role of ACEi/ARB on survival, these factors were considered as time-dependent variables for Cox regression analysis to account for time of initiation as well as residual GFR at that moment.

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