

Proteinuria and its association with disease progression in IgA nephropathy: Analysis of the UK National RaDaR IgA nephropathy cohort

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CONCLUSIONS

Elevated proteinuria over time is significantly associated with rapid loss of eGFR and greater risk of progression to KF/death in IgAN

Although TA-PU below 100 mg/mmol (~1 g/day) is strongly associated with lower risk of KF/death, 25% of patients in this treated, monitored group reached KF/death within 10 years

DISCLOSURES

DP has nothing to disclose; FB, BH is an employee and stockholder of Travere Therapeutics, Inc.; AM received consultancy fees from Travere Therapeutics, Inc.; KO, MAS received consultancy fees from Travere Therapeutics, Inc. and Purespring Therapeutics; RS has nothing to disclose; NT, KW is an employee and stockholder of Travere Therapeutics, Inc.; JB received consultancy fees from Travere Therapeutics, Inc.; DPG received consultancy fees from Travere Therapeutics, Inc.

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RaDaR

RareRenal
Information on rare kidney diseases

UKKA
UK Kidney Association
Rare Renal

TRAVERE
THERAPEUTICS

RESULTS

Characteristics at diagnosis and clinical outcomes

The cohort included 923 patients (68% male and 96% adult) with a median age at diagnosis of 41.7 years (Table 1)

Among patients with available data, the median urinary protein-creatinine ratio (PCR) at diagnosis was 172 mg/mmol (1.5 g/g) and median estimated glomerular filtration rate (eGFR) was 50 mL/min/1.73 m² (Table 1)

Median duration of follow-up was 4.5 years and 38% of patients progressed to kidney failure (KF)/death during follow-up (Table 1)

Mean eGFR slope was -3.6 mL/min/1.73 m²/year (Table 1)

Elevated time-averaged proteinuria is associated with kidney failure/death

Time to KF/death was significantly shorter with higher levels of time-averaged proteinuria (TA-PU) (Figure 1)

Approx. 1 in 4 patients with time-averaged proteinuria (TA-PU) <100 mg/mmol (<0.88 g/g; approximately <1 g/day) progressed to KF/death within 10 years (Figure 1)

TA-PU 100-200 mg/mmol (0.88-1.76 g/g; approximately 1.0-2.0 g/day) was associated with an almost 3-fold increase in risk of KF/death compared with TA-PU <100 mg/mmol (Table 2)

The risk of KF/death was increased almost 5-fold at TA-PU 200-300 mg/mmol (1.76-2.64 g/g; approximately 2.0-3.0 g/day) compared with TA-PU <100 mg/mmol (Table 2)

TA-PU ≥300 mg/mmol (≥2.64 g/g; ≥3.0 g/day) was associated with a 9-fold increase in the risk of KF/death compared with TA-PU <100 mg/mmol (Table 2)

Elevated time-averaged proteinuria is associated with more rapid loss of eGFR

Higher grades of TA-PU were associated with a higher rate of eGFR loss (p<0.001) (Table 2)

The rate of eGFR loss escalated from an eGFR slope of -0.35 mL/min/1.73 m²/year for TA-PU <100 mg/mmol to -12.41 mL/min/1.73 m²/year with TA-PU ≥300 mg/mmol (Table 2)

Table 1. Characteristics at diagnosis and clinical outcomes

	N	%
Age (years)	923	100
Median (IQR)	41.7 (30.3-53.3)	
Pediatric	36	4
Sex	923	100
Female	294	32
Male	629	68
PCR at baseline, n (%)	515	56
mg/mmol	Median (IQR)	172 (73-356)
g/g	Median (IQR)	1.5 (0.6-3.1)
eGFR at baseline, n (%)	565	61
Median, mL/min/1.73 m ²	49.8	
IQR	33.0-78.2	
Duration of follow-up, n (%)	923	100
Median, years	4.5	
IQR	2.5-6.8	
KF or death event, n (%)	923	100
Yes	355	38
No	568	62
eGFR slope, n (%)	856	93
Mean, mL/min/1.73 m ² /year	-3.6	
SD	9.4	

Abbreviations: eGFR, estimated glomerular filtration rate; KF, kidney failure; IQR, interquartile range; SD, standard deviation
Note: PCR of 1 mg/mmol is equivalent to 0.0088 g/g

Figure 1. Kaplan Meier survival curves for patients categorized by TA-PU

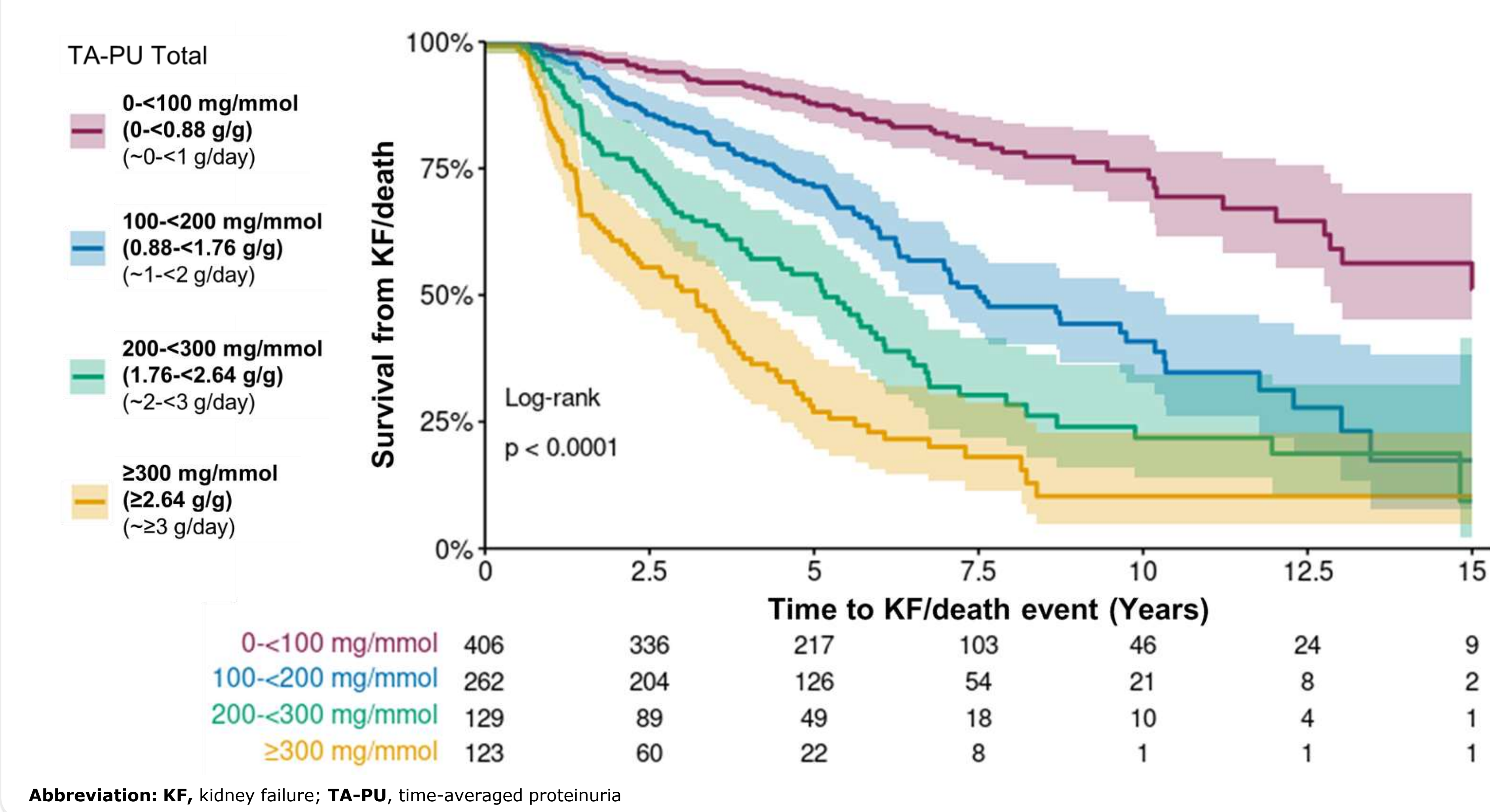


Table 2. Clinical outcomes for patients categorized by TA-PU

TA-PU	eGFR slope (mL/min/1.73 m ² /year)			KF/death risk		
	N	Mean	SD	N	HR	95% CI
<100 mg/mmol	385	-0.35	7.15	405	Ref	Ref
100 to <200 mg/mmol	247	-3.32	10.09	264	2.83	2.09-3.82
200 to <300 mg/mmol	113	-6.67	5.73	128	4.82	3.49-6.66
≥300 mg/mmol	111	-12.41	11.28	126	9.00	6.56-12.34

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KF, kidney failure; Ref, reference; SD, standard deviation; TA-PU, time-averaged proteinuria
Note: PCR of 100 mg/mmol (0.88 g/g) is approximately equivalent to 24-hour urinary protein excretion of 1.0 g/day

INTRODUCTION

Primary IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide and a major cause of kidney failure (KF)^{1,2}

Rate of progression to KF varies widely and can span over decades³

Time-averaged proteinuria (TA-PU) over long-term follow-up is an important predictor of disease progression and KF risk in patients with IgAN^{3,4}

Objective

To investigate the relationship between proteinuria (PU) measured over follow-up (TA-PU) and rate of kidney function loss and kidney survival in UK IgAN patients within the UK National Registry of Rare Kidney Diseases (RaDaR)

METHODS

Data Source

This study uses data from the RaDaR database

Since 2013, patients with biopsy-proven IgAN and estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or PU ≥0.5 g/day have been enrolled into (RaDaR) IgAN Cohort

RaDaR contains data on IgAN patients from 87 kidney units across the UK, with automated collection of retrospective and prospective laboratory data

Definitions and Clinical Measures

Diagnosis was the earliest of either primary kidney diagnosis date or date of biopsy recorded in RaDaR

eGFR calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula⁵ (adults) and the modified Schwartz formula⁶ (pediatric)

KF was defined as the first occurrence of either chronic kidney replacement therapy, a confirmed eGFR <15 mL/min/1.73 m², or KF/CKD stage 5 recorded in RaDaR

TA-PU was defined as the time-weighted averages for urinary protein-creatinine ratio (PCR), calculated from the area under the curve of serial measurements divided by the length of follow-up

Eligibility Criteria

Patients were included if they had a biopsy date recorded in RaDaR and PU measurements in follow-up (within 2 years from diagnosis and ≥2 values if follow-up >3 years)

Patients were excluded if they had a KF event (CKD stage 5 or kidney replacement therapy [KRT]) or death within 6 months from diagnosis or prior to first PU value

Statistical Analyses

TA-PU and rate of eGFR loss (eGFR slope) were calculated over the full duration of follow-up or until KF or death. A linear mixed model was used to estimate each patient's intercept and slope of eGFR

Kaplan-Meier estimates for kidney survival, from diagnosis to KF/death, were calculated for each TA-PU group. The log-rank test was used for differences between pairwise and all groups

Association of TA-PU and survival from KF/death evaluated using Cox regression

DISCUSSION

Adults represent >90% of the cohort with a median baseline age of 41.7 years reflecting a disease with onset at a stage when patients should have a long life-expectancy remaining

Higher grades of TA-PU are significantly associated with shorter time to KF/death and increased KF/death risk

Higher grades of TA-PU are also significantly associated with more rapid loss of eGFR

Proteinuria <1 g/day is commonly perceived as defining patients at low risk, however, in this cohort, approx. 1 in 4 patients progressed to KF/death within 10 years, despite a TA-PU of <100 mg/mmol (approximately <1 g/day)

Limitations

The inclusion criteria for RaDaR-IgAN leads to enrollment of patients with progressive disease who represent a high risk IgAN population

Reporting of proteinuria and eGFR data at disease onset is incomplete and may not be representative of the full cohort, however data are likely to be missing at random with limited bias