UK National Registry of Rare Kidney Disease (RaDaR) Long-Term Outcomes in the IgA Nephropathy Cohort

Summary

Background

- The UK Registry of Rare Kidney Diseases (RaDaR) includes a cohort of patients with biopsy-proven IgA nephropathy, comprised of 2299 adults and 140 children[1]
- KDIGO guidelines note that a decrease in proteinuria to <1.0 g/day is a treatment target for patients at high risk for progressive CKD[2]
- The RaDaR study examined lifetime kidney failure risk and burden associated with IgA nephropathy, and predictive value of proteinuria and eGFR slope in long-term outcomes[1]

Study Data

- In the analysis of the 2439 patients of the IgAN cohort of RaDaR, almost all patients were at risk of progression to KF within their expected lifetime unless a rate of eGFR loss ≤1 mL/min/1.73 m^2/year was maintained[1]
- In adult patients, CKD stage at baseline was the strongest predictor of 10-year kidney survival and eGFR slope[1]
- Regardless of age group, most patients progressed to KF within 10-15 years[1]
- Higher TA-PU was significantly associated with worse kidney survival and more rapid decline in eGFR[1]

Background

IgA Nephropathy Disease State

IgA nephropathy is the most common primary glomerulonephritis and major cause of kidney failure and CKD worldwide.[1] Management involves supportive care in order to slow the rate of disease progression, through control of blood pressure, inhibition of the RAS, and modification of lifestyle factors such as weight reduction and dietary changes.[2]

The RaDaR Study

The IgA Nephropathy Rare Disease Group (RaDaR-IgAN) is a subset of RaDaR, a National UK Kidney Association initiative collecting data from patients with rare kidney diseases in the UK. Adult and pediatric patients with biopsy-proven primary IgA nephropathy have been enrolled since 2013. The RaDaR-IgAN cohort study investigated the association between proteinuria and progression of kidney function loss and kidney survival, as measured by eGFR.[3] In this retrospective study, characteristics and outcomes of patients with IgA nephropathy were analyzed to assess burden of disease progression by age at diagnosis, magnitude of change in proteinuria, and rate of eGFR decline. The study also described associations between key disease factors, including baseline proteinuria and TA-PU, rate of eGFR loss, kidney survival, and value of short-term changes in proteinuria and eGFR slope.[1]

Study Population

Patients with biopsy-proven IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m^2 at any point in their disease were eligible for enrollment. Cases of secondary IgA nephropathy were excluded. Adult patient subpopulations were created based on UPCR measurements, which were available at diagnosis for 23% of patients. Population 1 was a representative incident population to examine TA-PU without necessity of baseline UPCR at diagnosis. Population 2 was also representative of incident cases, and Population 3 represented prevalent cases; both groups allowed assessment of baseline proteinuria and TA-PU. Population 4 is a prevalent population representative of patients in a typical phase 3 RCT.[1] Population details are presented in **Table 1**.[4]

Table 1. Description of Populations 1-4

	Population 1	Population 2	Population 3	Population 4
Surrogate for	Incident population	Incident population	Prevalent population	Prevalent clinical trial population
Baseline Date	Diagnosis	Diagnosis	First UPCR value more than 6 months after diagnosis	First UPCR value >0.88 g/g*, more than 6 months after diagnosis
Inclusion Criteria	1. UPCR value in first 2 years of follow-up 2. Additional UPCR value if follow-up >3 years	1. UPCR value in first 2 years of follow-up 2. Additional UPCR value if follow-up >3 years 3. UPCR value in window 6 months before baseline to 1 month after baseline	1. UPCR value at least 6 months after diagnosis 2. UPCR value at least 6 months after baseline 3. Additional UPCR value if follow-up >3 years	1. UPCR value >880 at least 6 months after diagnosis 2. eGFR >30 mL/min/1.73 m^2 at baseline 3. UPCR value at least 6 months after baseline 4. Additional UPCR value if follow-up >3 years

*0.88 g/g=100 mg/mmol (~1 g/day).

Definitions

KF was defined as first occurrence of either long-term KRT, confirmed eGFR <15 mL/min/1.73 m^2, or CKD stage 5. Kidney survival was the absence of either KF or death. Annualized eGFR slopes were calculated for total follow-up and 6-30 months post-baseline. UPCR values were presented in g/g; UACR values were converted to UPCR (UPCR=UACR/0.7). For comparison with other studies, UPCR 0.88 g/g (100 mg/mmol) was considered comparable to protein excretion of 1.0 g/day. TA-PU was defined as time-weighted averages for UPCR.[1]

Study Data

Patient Characteristics, Outcomes, and KF Risk

The IgAN cohort of RaDaR included 2299 adult and 140 pediatric patients. Median kidney survival time was 11.4 years, and most patients reached KF or died within 10-15 years. Mean age at time of KF or death was 48 years. Patient characteristics are presented in **Table 2**.[1]

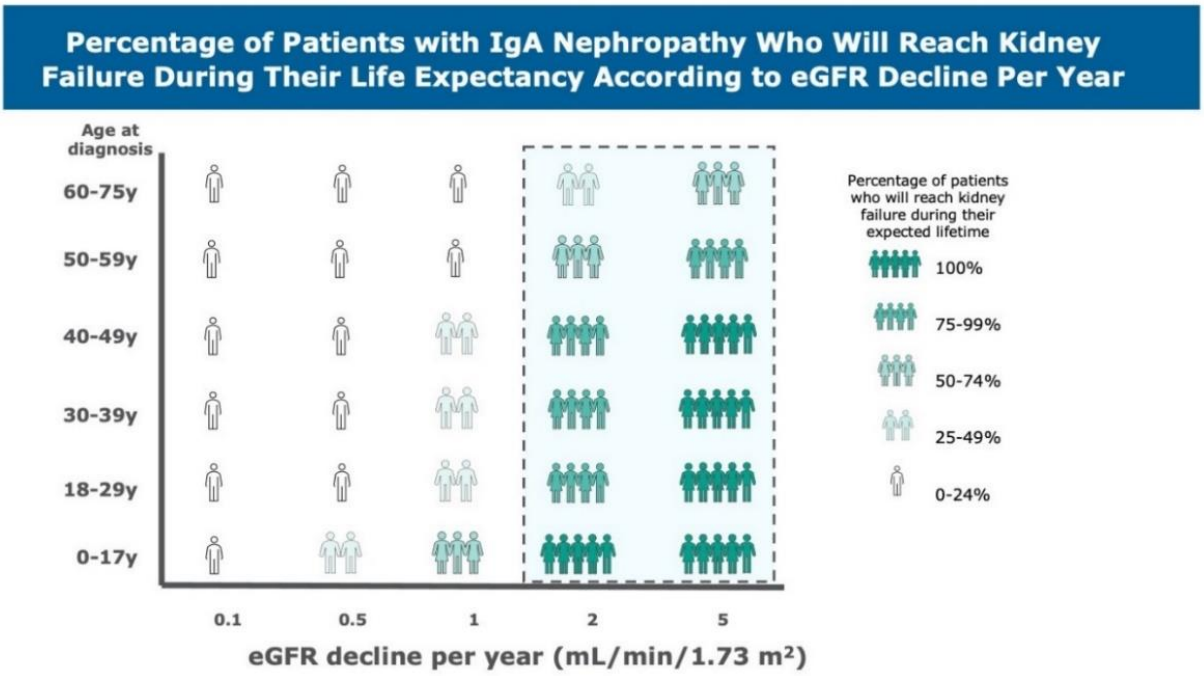
Table 2. Demographic and Clinical Characteristics at Diagnosis, and Clinical Outcomes During Follow-up (Full-Analysis Population)

Category	Overall	Adult	Pediatric
Age at Diagnosis, n (%)	2439 (100)	2299 (100)	140 (100)
Mean, yrs (SD)	41 (15)	42 (14)	13 (5)
Median, yrs (Q1, Q3)	40 (29, 51)	41 (31, 52)	14 (10, 17)
Sex, n (%)	2439 (100)	2299 (100)	140 (100)
Female	716 (29)	674 (29)	42 (30)
Male	1723 (71)	1625 (71)	98 (70)
Ethnicity, n (%)	2439 (100)	2299 (100)	140 (100)
Asian	228 (9)	221 (10)	7 (5)
Black	32 (1)	32 (1)	0 (0)
Mixed	14 (1)	12 (1)	2 (1)
Others	36 (1)	36 (2)	0 (0)
White	1885 (77)	1768 (77)	117 (84)
Not stated/missing	244 (10)	230 (10)	14 (10)
BMI at Diagnosis, n (%)	328 (13)	313 (14)	15 (11)
Mean, (SD)	28 (8.5)	29 (8.3)	20 (7.9)
Median, (Q1, Q3)	28 (24.1, 31.5)	28 (24.2, 31.6)	21 (16.2, 24.6)
Systolic BP at Diagnosis, n (%)	299 (12)	287 (12)	12 (9)
Mean, (SD)	138 (24)	139 (24)	118 (16)
Median, (Q1, Q3)	137 (124, 152)	138 (125, 153)	113 (108, 127)
UPCR at Diagnosis, n (%)	545 (22)	526 (23)	19 (14)
Mean, g/g[a] (SD)	2.42 (3.57)	2.41 (2.72)	2.75 (2.78)
Median, g/g (Q1, Q3)	1.51 (0.64, 3.13)	1.51 (0.66, 3.09)	2.10 (0.42, 4.04)
Nephrotic range proteinuria (>2.64 g/g)	169 (7)	161 (7)	8 (6)
eGFR at Diagnosis, n (%)	896 (37)	880 (38)	16 (11)
Mean, mL/min per 1.73 m^2 (SD)	55 (29)	55 (29)	78 (33)
Median, mL/min per 1.73 m^2 (Q1, Q3)	48 (32, 75)	48 (32, 75)	76 (53, 108)
CKD Stage at Diagnosis, n (%)	896 (37)	880 (38)	16 (11)
Stage 1	141 (16)	136 (15)	5 (31)
Stage 2	197 (22)	191 (22)	6 (38)
Stage 3	366 (41)	361 (41)	5 (31)
Stage 4	178 (20)	178 (20)	0 (0)
Stage 5	14 (2)	14 (2)	0 (0)
Length of Follow-up, n (%)	2439 (100)	2299 (100)	140 (100)
Mean, yrs (SD)	8.0 (7.3)	7.7 (6.7)	13.4 (12.4)
Median, yrs (Q1, Q3)	5.9 (3.0, 10.5)	5.8 (2.9, 10.1)	8.2 (5.3, 17.0)
Kidney Failure or Death Event, n (%)	2439 (100)	2299 (100)	140 (100)
Yes	1210 (50)	1156 (50)	54 (39)
No	1229 (50)	1143 (50)	86 (61)
First Event, n (%)	1210 (50)	1156 (50)	54 (39)
Death	21 (2)	21 (2)	0 (0)
Dialysis	298 (25)	277 (24)	21 (39)
Transplant	95 (8)	86 (7)	9 (17)
eGFR <15 mL/min per 1.73 m^2	796 (66)	772 (67)	24 (44)
Time to First Event, n (%)	1210 (50)	1156 (50)	54 (39)
Mean, yrs (SD)	6.9 (7.1)	6.6 (6.6)	13.6 (12.3)
Median, yrs (Q1, Q3)	4.5 (1.9, 9.6)	4.3 (1.8, 9.3)	10.2 (6.1, 16.1)
Age at First Event, n (%)	1210 (50)	1156 (50)	54 (39)
Mean, yrs (SD)	48 (15)	49 (14)	27 (10)
Median, yrs (Q1, Q3)	48 (37, 58)	49 (38, 59)	24 (21, 32)
Survival Rate, Estimate (95% CI)	2439 (100)	2299 (100)	140 (100)
5-year	0.72 (0.70 to 0.74)	0.71 (0.69 to 0.73)	0.91 (0.85 to 0.95)
10-year	0.54 (0.51 to 0.56)	0.52 (0.50 to 0.55)	0.76 (0.66 to 0.83)
15-year	0.40 (0.37 to 0.43)	0.38 (0.36 to 0.41)	0.62 (0.52 to 0.72)
20-year	0.29 (0.27 to 0.32)	0.28 (0.25 to 0.31)	0.52 (0.41 to 0.62)
Quartile Survival Estimate, yr (95% CI)	2439 (100)	2299 (100)	140 (100)
75%	4.2 (3.9 to 4.7)	4.0 (3.7 to 4.4)	10.9 (7.3 to 12.4)
50%	11.4 (10.5 to 12.5)	10.8 (10.0 to 12.0)	21.6 (15.9 to NE)
25%	24.3 (21.8 to 25.8)	22.9 (19.6 to 25.5)	NE (NE to NE)
eGFR Slope, Total, n (%)	1863 (76)	1795 (78)	68 (49)
Mean, mL/min per 1.73 m^2/yr (SD)	−3.6 (8.2)	−3.7 (7.4)	−2.2 (19.6)
Median, mL/min per 1.73 m^2/yr (Q1, Q3)	−2.4 (−5.7, −0.6)	−2.4 (−5.6, −0.6)	−3.6 (−8.3, −0.9)

[a]0.0088 g/g = 1 mg/mmol.

Among adult patients, baseline CKD stage was the strongest predictor of 10-year kidney survival and eGFR slope. In long-term follow up (median 5.9 years), based on eGFR and age at diagnosis, almost all patients were at risk of progressing to KF within their expected lifetime unless a rate of eGFR loss ≤1 mL/min/1.73 m^2/year was maintained. In patients <40 years of age at time of diagnosis, a sustained decline in eGFR of 3 mL/min/1.73 m^2/year would result in 100% of patients reaching KF within their expected lifetime (**Figure 1**). A decline as low as 1 mL/min/1.73 m^2/year would still lead to ~40% of patients <50 years old at diagnosis reaching KF in their expected lifetime.[1]

Figure 1. Progression to Kidney Failure Based on eGFR at Diagnosis



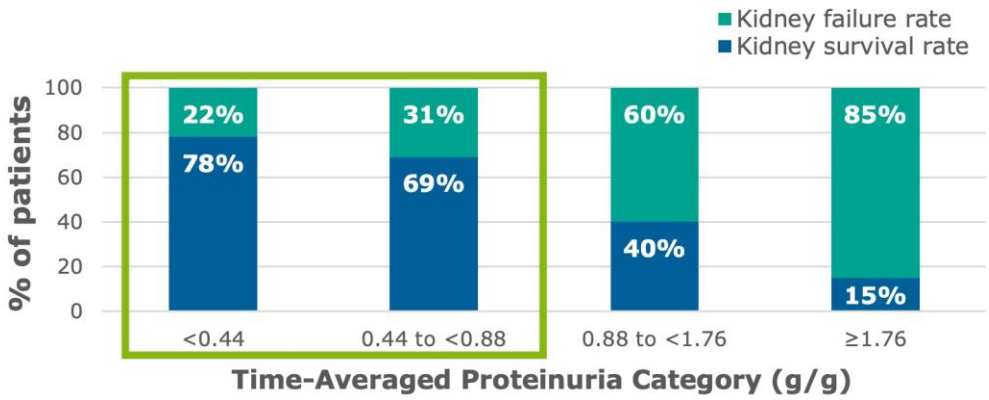
Adapted from Pitcher D et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. doi: 10.2215/CJN.0000000000000135

Association of Proteinuria and Kidney Failure

Study Population 1

TA-PU over total follow-up time was analyzed in Population 1. Higher TA-PU was significantly associated with worse kidney survival and faster eGFR loss. Kidney survival rate for patients with TA-PU <0.44g/g and mean eGFR slope of −0.0 mL/min/1.73 m^2/year was 78%. Kidney survival became less probable with increases in TA-PU and eGFR decline. Among patients with TA-PU $\geq$1.76 g/g and mean eGFR slope of −9.5 mL/min/1.73 m^2/year, kidney survival was only 15% (**Figure 2**).[1]

Figure 2. 10-Year Kidney Survival and Failure Rate in Population 1



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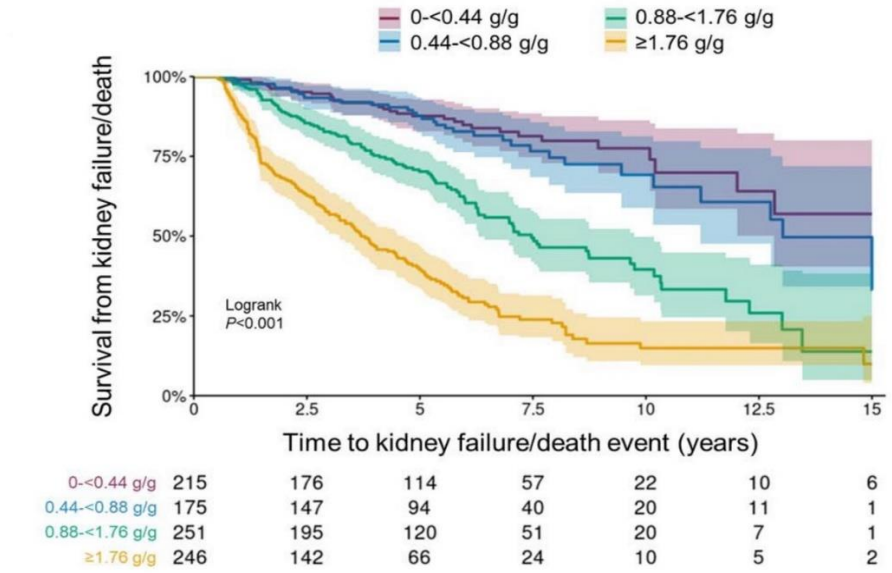
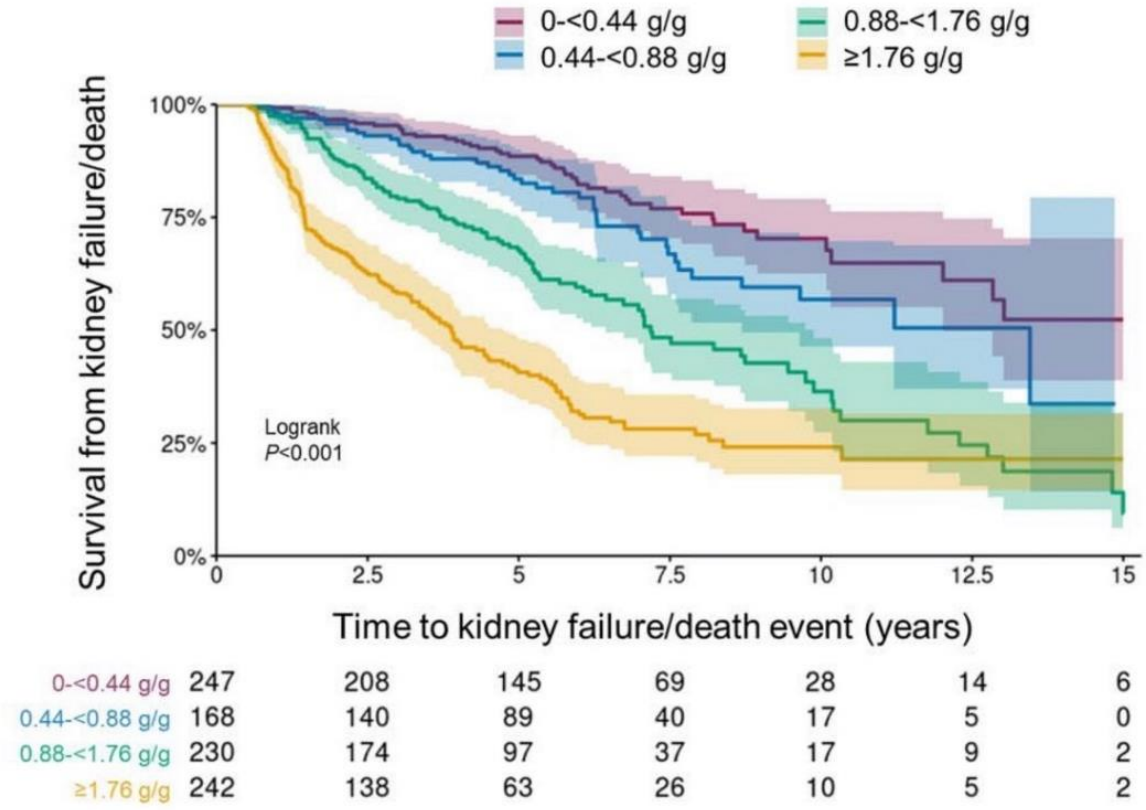
Patients with TA-PU >0.88 g/g were at higher risk of progressing to KF or death faster than patients with TA-PU <0.88 g/g. Kidney survival probability decreased by almost 50% over 15 years among patients with TA-PU 0.44 to <0.88 g/g (**Figure 3**). At total follow up, the study found that 30% of patients with TA-PU 0.44 to <0.88 g/g and ~20% of patients with TA-PU <0.44 g/g developed KF within 10 years. Similar results were found in TA-PU calculated over 0-24 months (**Figure 4**).[1]

Figure 3. Time to Kidney Failure/Death Using Total Follow-Up TA-PU in Population 1



0.44 g/g = 50 mg/mmol; 0.88 g/g = 100 mg/mmol; 1.76 g/g = 200 mg/mmol.

Figure 4. Time to Kidney Failure/Death Using 0-24–Month TA-PU in Population 1



0.44 g/g = 50 mg/mmol; 0.88 g/g = 100 mg/mmol; 1.76 g/g = 200 mg/mmol.

Although KDIGO guidelines state that a decrease in proteinuria to <1.0 g/day is a reasonable target for treatment, the study found that many patients with TA-PU levels typically believed to be low-risk for CKD progression had poor long-term outcomes.[1,2]

Study Populations 2 and 3

Populations 2 and 3 were defined as incident and prevalent populations, respectively. Data from these groups evaluated the relationship between TA-PU and clinical outcomes in patients typically considered to be low or high risk for CKD progression, based on baseline UPCR values (<0.88 g/g vs ≥0.88 g/g). In Population 3, higher TA-PU was associated with lower probability of kidney survival at 5, 10, and 15 years of follow-up in patients with baseline UPCR ≥0.88 g/g. The association of poorer kidney survival with higher TA-PU was also demonstrated in patients with baseline TA-PU <0.88 g/g. These findings support the predictive value of proteinuria even at levels considered to be low risk for disease progression. Newly diagnosed patients in Population 2 experienced a similar association between proteinuria and long-term clinical outcomes.[1]

Population 4: Clinical Outcomes

Study Population 4 included patients who were representative of those in RCTs and not believed to be high risk for disease progression[1]:

- Age ≥18 years
- Baseline UPCR ≥0.88 g/g
- eGFR ≥30 mL/min/1.73 m^2

Evaluation of this population described associations between changes in proteinuria and near- and long-term rate of eGFR loss and kidney survival. Data were analyzed over 6 to 12 months (representative of interim analysis) and 6 to 24 months (representing full-term study duration). In both analyses, higher TA-PU was linked to greater eGFR loss and risk of KF (**Figure 5**). The 6-to-24-month analysis showed greater separation of outcomes (**Figure 6**); however, the 6-to-12-month assessment showed similar findings, suggesting predictive value of interim results.[1]

Figure 5. Rate of eGFR Decline From 6 to 24 Months According to TA-PU in Population 4

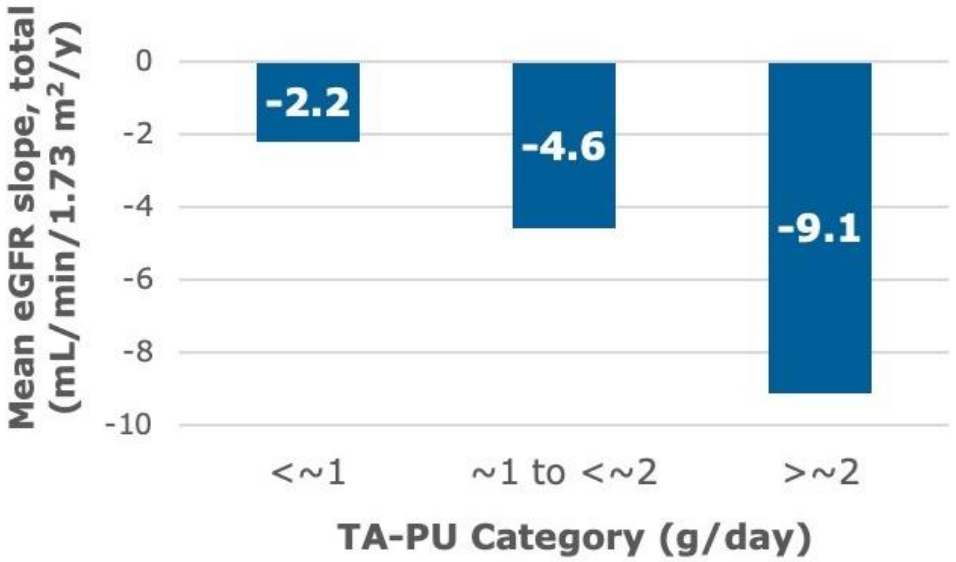


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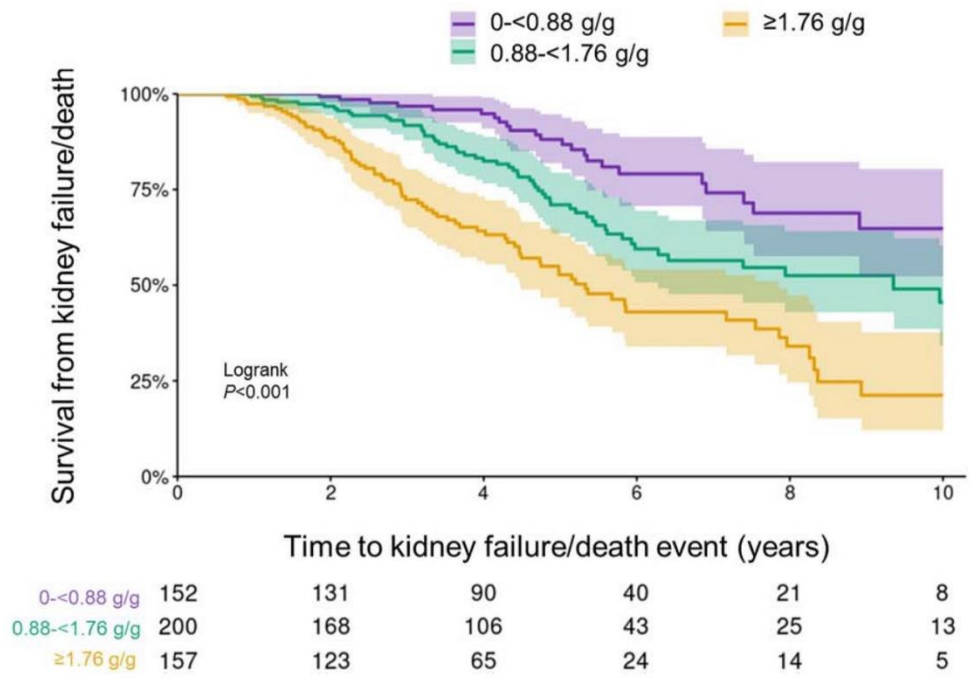
Figure 6. Time to Kidney Failure/Death Using 6-24–Month TA-PU in Population 4

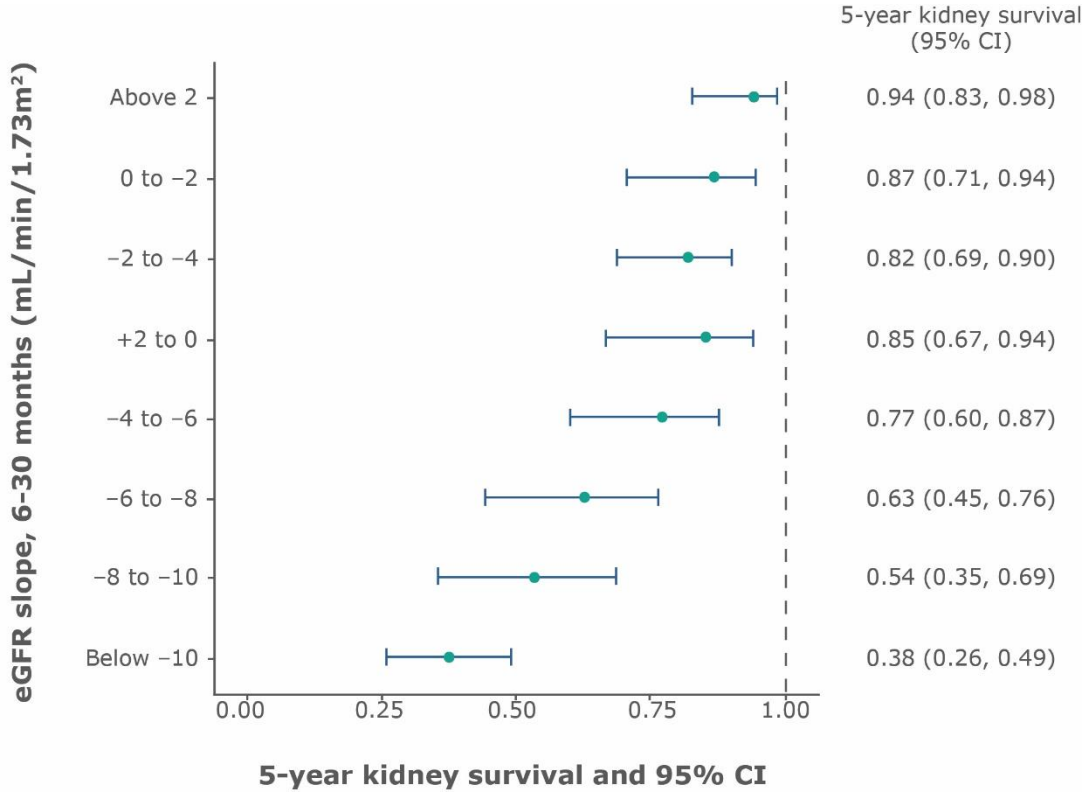


0.44 g/g = 50 mg/mmol; 0.88 g/g = 100 mg/mmol; 1.76 g/g = 200 mg/mmol.

Median kidney survival time was significantly lower at ≥1.76 g/g in both time windows compared with lower TA-PU (log-rank *P*<0.0001). In the 6-to-12-month analysis, 40% and 50% reductions in TA-PU were estimated to slow the rate of eGFR loss over 6 to 30 months, from 5.5 mL/min/1.73 m^2/year to 4.5 and 3.7 mL/min/1.73 m^2/year, respectively. These findings were repeated in the 6-24–month analysis.[1]

Additionally, a HR (95% CI) for KF/death of 0.89 (0.87 to 0.92) was associated with each 10% decrease in proteinuria from baseline. Increased eGFR loss measured over 6 to 30 months resulted in lower 5-year kidney survival rates. Patients with an eGFR slope of 0-2 mL/min/1.73 m^2/year had a 5-year kidney survival (95% CI) of 0.87 (0.71 to 0.94), whereas patients with a slope of 8-10 mL/min/1.73 m^2/year showed a HR (95% CI) of 0.54 (0.35 to 0.69) (**Figure 7**).[1]

Figure 7. 6-30–Month eGFR Slope vs 5-Year Kidney Survival Rate



eGFR and TA-PU in Progression to CKD

Additional analyses of the IgAN cohort of RaDaR examined disease progression in early vs later stages of disease utilizing degree of proteinuria and eGFR decline before and after patients reached CKD stage 3B, defined as an eGFR of 30-44 mL/min/1.73 m^2.[5,6] Analysis of eGFR values from baseline (first UPCR value ≥6 months after diagnosis) until initiation of KRT or end of follow-up was used to define each patient's Time 0 as the estimated date eGFR value passed 45 mL/min/1.73 m^2. To be included in the analysis, patients were required to have ≥3 eGFR and ≥2 UPCR values before and after Time 0. Longitudinal proteinuria was assessed as TA-PU.[5]

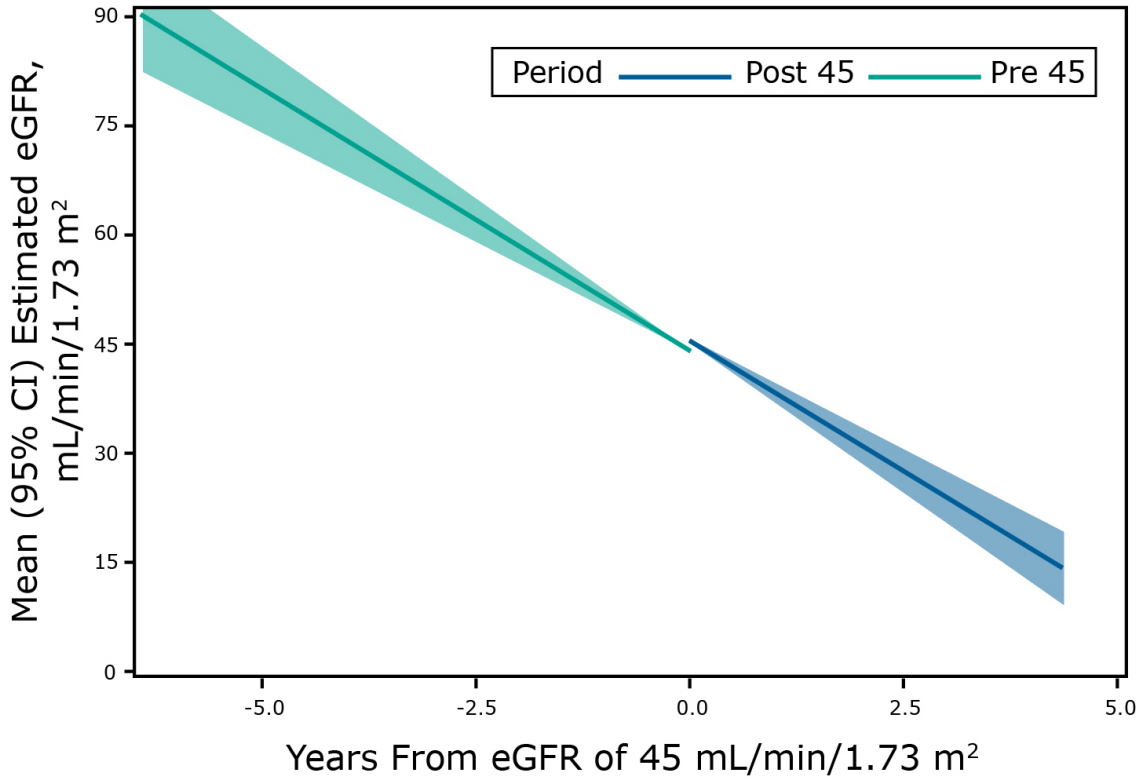
Mean eGFR decline was found to be rapid and similar for early (pre-eGFR 45 mL/min/1.73 m^2) and late (post-eGFR 45 mL/min/1.73 m^2) stages of CKD. This result was consistent when adjusting for age and sex. Median TA-PU was 41% greater in patients once past eGFR 45 mL/min/1.73 m^2 compared to measures before this point (**Table 3; Figure 8**).[5]

Table 3. Mean TA-PU and eGFR Slopes Pre- and Post-eGFR 45 mL/min/1.73 m^2

Mean Annualized eGFR Slopes (n=184)	Early CKD Stage*	Late CKD Stage†	Difference (95% CI) After Threshold
Mean annualized slope (95% CI)			
Unadjusted	-7.2 (-8.4, -6.0)	-7.0 (-8.2, -5.8)	0.13 (-0.19, 0.45)
Age-sex adjusted	-7.2 (-8.4, -6.0)	-7.0 (-8.2, -5.8)	0.14 (-0.18, 0.46)
TA-PU (n=195)	**Early CKD Stage***	**Late CKD Stage†**	**Difference, Geometric Mean (95% CI)**
Median, g/g (IQR)	1.11 (0.64, 1.89)	1.57 (0.95, 2.67)	0.42 (0.08, 0.76)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; TA-PU, time-averaged proteinuria.
*Prior to eGFR threshold of 45 mL/min/1.73 m2.
†After eGFR threshold of 45 mL/min/1.73 m2.

Figure 8. Mean eGFR Slopes Pre- and Post-eGFR 45 mL/min/1.73 m^2



The comparability in eGFR slopes across stages suggests that slope measurements in early disease may be used to estimate future eGFR loss. Differences observed in TA-PU despite comparable eGFR slopes may suggest that patients with stable rates of eGFR loss experience increasing damage to the glomerular filtration barrier.[5]

Abbreviations

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; KF, kidney failure; KRT, kidney replacement therapy; Q, quartile; RaDaR, UK National Registry of Rare Kidney Diseases; RAS, renin-angiotensin system; RCT, randomized controlled trial; SD, standard deviation; TA-PU, time-averaged proteinuria; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio; UK, United Kingdom.

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