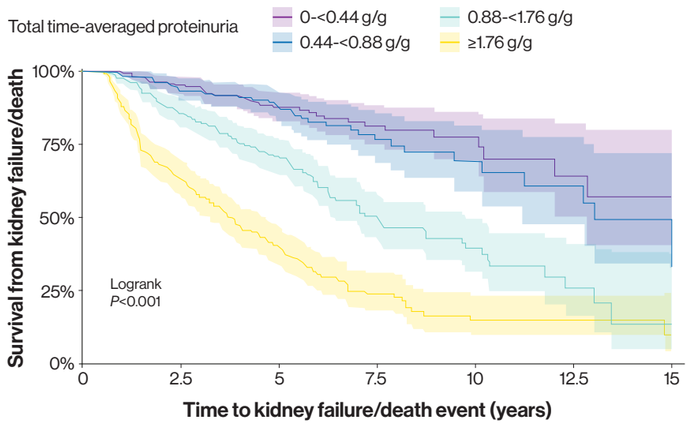
Kaplan-Meier Survival Curves of Time to Kidney Failure/Death Event on the Basis of Total Follow-Up Time-Averaged Proteinuria in a UK Retrospective Cohort [3]



0-<0.44 g/g	215	176	114	57	22	10	6
0.44-<0.88 g/g	175	147	94	40	20	11	1
0.88-<1.76 g/g	251	195	120	51	20	7	1
≥1.76 g/g	246	142	66	24	10	5	2

Permission granted by Pitcher D et al.[3]

- Data from retrospective cohort of 2299 adults and 140 children with IgAN in the UK National Registry of Rare Kidney Diseases (RaDaR)
- Patients enrolled had a biopsy-proven diagnosis of IgAN plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m² at any time in the history of their disease
- Analyses of kidney survival were conducted using Kaplan-Meier and Cox regression
- Availability of patient medication and blood pressure data was a limiting factor in this study
- 0.88 g/g is approximately equivalent to 1 g/day

KDIGO recommends assessing proteinuria as a prognostic biomarker and to monitor treatment outcomes[2,3]

KDIGO 2021 guidelines state that proteinuria **reduction to <1 g/d is a reasonable treatment target**. Guidelines are evolving with emerging information regarding disease state and treatment modalities[2,3]

Patients with proteinuria are at increased risk for developing kidney failure[3]

References: 1. Rizk DV et al. *Front Immunol*. 2019;10:504. **2.** Lai KN et al. *Nat Rev Dis Primers*. 2016;2:16001. **3.** Pitcher D et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738. **4.** Kwon CS et al. *J Health Econ Outcomes Res*. 2021;8(2):36-45. **5.** Lafayette RA, Kelepouris E. *Am J Nephrol*. 2018;47(suppl 1):43-52. **6.** Penfold RS et al. *Int J Nephrol Renovasc Dis*. 2018;11:137-148. **7.** Xie J et al. *PLoS One*. 2012;7(6):e38904. **8.** Inker LA et al. *Am J Kidney Dis*. 2016;68(3):392-401. **9.** Thompson A et al. *Clin J Am Soc Nephrol*. 2019;14(3):469-481. **10.** Reich HN et al. Toronto Glomerulonephritis Registry. *J Am Soc Nephrol*. 2007;18(12):3177-3183. **11.** Makhammajanov Z et al. *Nephrol Dial Transplant*. 2024;39(4):589-599. **12.** Suzuki H et al. *J Am Soc Nephrol*. 2011;22(10):1795-1803. **13.** Maillard N et al. *J Am Soc Nephrol*. 2015;26(7):1503-1512. **14.** Barratt J et al. *Kidney Int*. 2023;104(2):254-264. **15.** Kohan D et al. *Kidney Int Rep*. 2023;8(11):2198-2210. **16.** Ruggenenti P et al. *J Am Soc Nephrol*. 2012;23(12):1917-1928. **17.** Nakayama M et al. *Kidney Int Rep*. 2022;7(12):2726-2729. **18.** Stefan G et al. *Kidney Int Rep*. 2024;9(2):356-369. **19.** Thurman JM et al. *Clin J Am Soc Nephrol*. 2016;11(10):1856-1866. **20.** Huang Z et al. *Cytokine*. 2008;42(2):222-233. **21.** Huang G et al. *Biochem Biophys Rep*. 2022:33:101417. **22.** Zhuang Y et al. *J Biol Chem*. 2014;289(36):25101-25111. **23.** KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100(4S):S1-S276.

Proteinuria—a key prognostic biomarker **for patients with IgA nephropathy**

IgA nephropathy is a heterogeneous, progressive autoimmune disease characterized by glomerular injury, inflammation, and scarring, leading to chronic kidney disease[1-6]

It contributes significantly to the global burden of CKD and kidney failure[1-6]

Up to 50% of patients with IgA nephropathy progress to kidney failure* within 10 to 20 years of diagnosis[3,4,7]

In a retrospective study of patients with IgA nephropathy in the UK, data suggest that high-risk patients (ie, with total time-averaged proteinuria >0.88 g/g) **progress more quickly** to kidney failure[3]

However, even patients with **less severe proteinuria may still experience progression**[3,10]

Persistent proteinuria (>1 g/day) is the strongest predictor of disease progression in IgA nephropathy[8,9]

~30% of patients with time-averaged proteinuria of 0.44-0.88 g/g will experience kidney failure within 10 years of diagnosis[3]

*Defined by the need for renal replacement therapy (dialysis or transplantation).

CKD, chronic kidney disease; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 10/24 FA-11241365

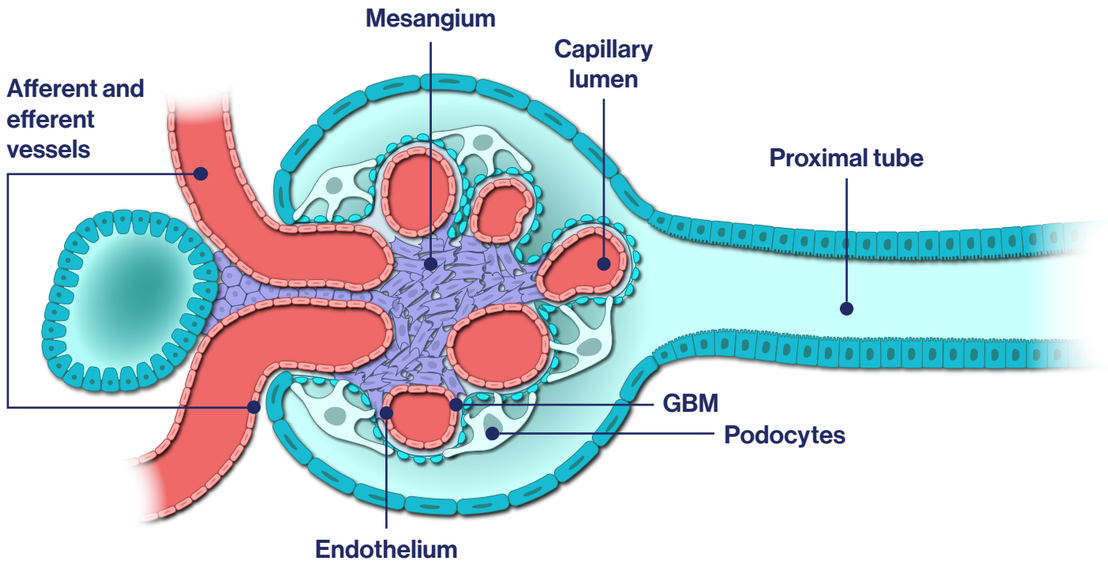
Proteinuria is a consequence of glomerular damage, **but it can also be a cause of tubular damage and progression of kidney disease through several mechanisms**[11]

Preclinical disease models

Immune complexes with Gd-IgA1 can induce cultured mesangial cells to proliferate and secrete extracellular matrix, which can then alter glomerular permeability[12]

Damage to the glomerular filtration barrier and podocyte injury can occur via:

- Complement activation[1,13,14]
- Increased proinflammatory cytokines[12,14]
- ET_A receptor activation[15]
- Podocyte dysfunction[16]



IC deposition in the mesangium leads to glomerular damage and proteinuria

High levels of proteinuria may induce inflammation in the proximal tubule

Permission granted by Thurman JM et al.[19]

Urinary proteins in patients with nephrotic syndrome induce inflammatory and cytotoxic responses in tubular epithelial cells in vitro, and this is thought to contribute to interstitial fibrosis[20]

Proteinuria may activate tubular inflammation via:

- Increased ER stress and ROS in proximal tubule epithelial cells[11]
- NLRP3 inflammasome activation[21,22]
- ET_A receptor activation[15]
- Complement activation[11,14]

Clinical observations

- High Gd-IgA1 deposition in the mesangium is associated with the presence of inflammatory lesions (E1, C1) and increased proteinuria[17]
- A systematic literature review of 34 studies found that tissue staining for C3 and C4 is associated with higher MEST-C scores[18]
- Strong ET_A receptor staining in the tubule and glomerulus is linked to proteinuria[15]
- NLRP3 is upregulated in patients with chronic kidney disease and proteinuria[21,22]

C3, complement 3; C4, complement 4; ER, endoplasmic reticulum; ET_A, endothelin A; GBM, glomerular basement membrane; Gd-IgA1, galactose-deficient immunoglobulin A1; IC, immune complex; MEST-C, mesangial(M) and endocapillary hypercellularity(E), segemental sclerosis(S), interstitial fibrosis/tubular atrophy(T), and crescents(C); NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species.