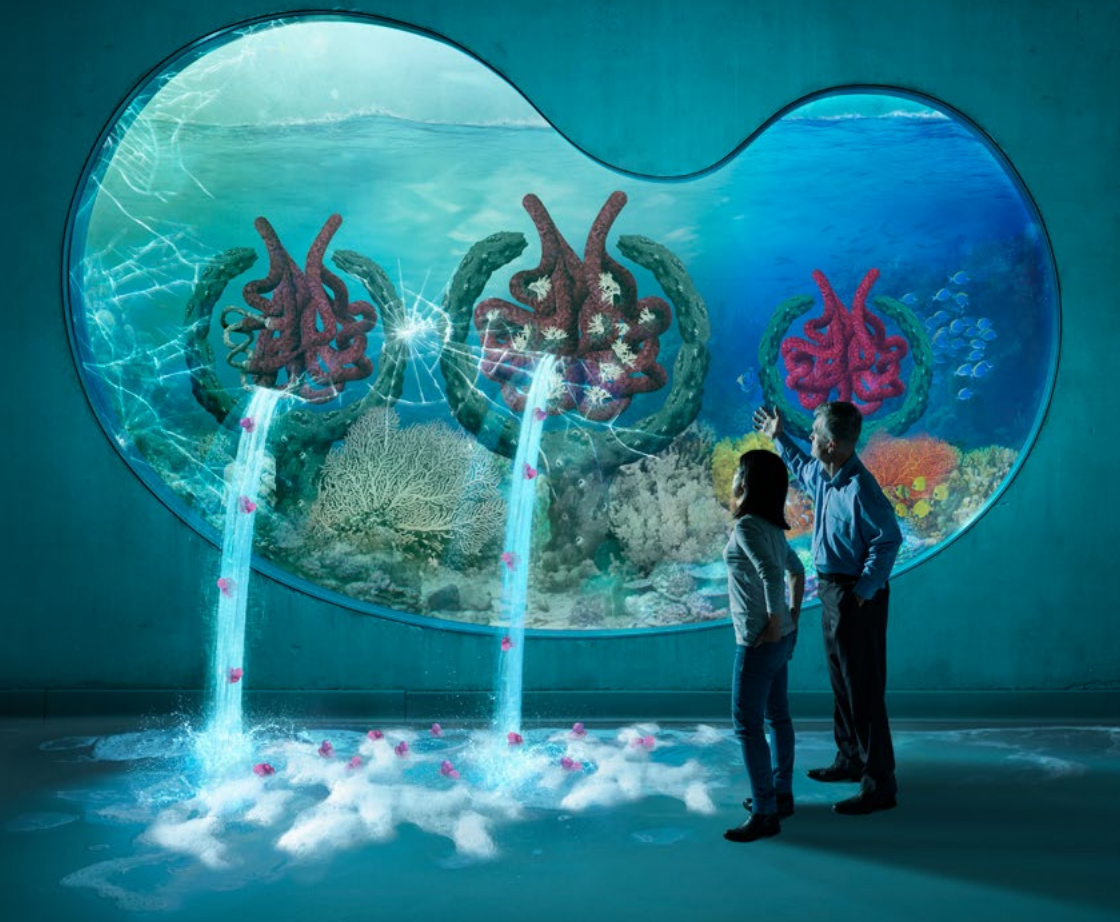
TARGET **PROTEINURIA**

In IgA nephropathy (IgAN)

Target Proteinuria



This material is intended for Healthcare Professionals

CSL

IgAN EXPLAINED

Prevalence and presentation

IgAN is the most common type of glomerulonephritis worldwide, and has a variable clinical presentation and progression to end-stage kidney disease (ESKD)[1–4]

In Europe, IgAN is detected in **19–51%** of kidney biopsies performed in glomerular diseases[3]

IgAN is asymptomatic for many patients, but some may present with signs and symptoms such as:[4–6]

- Proteinuria
- Macro- or microhematuria
- Renal insufficiency
- Hypertension
- Edema
- Acute kidney injury

IgAN can only be diagnosed with a kidney biopsy, but the majority of patients are diagnosed by chance late in the disease course with significant proteinuria and impaired eGFR.[1,7] Almost 2/3 patients have CKD stage ≥3 at diagnosis.[8,9]

Pathophysiology

There are 4 processes or **'Hits'** proposed to be involved in the pathogenesis of IgAN:[10]

Hit 1
Aberrant glycosylation of IgA_1 results in the increase of galactose-deficient IgA_1 circulation[10]

Hit 2
Production of anti-glycan antibodies that recognize galactose-deficient IgA_1[10]

Hit 3
Formation of pathogenic IgA_1-containing circulating complexes[10]

Hit 4
Mesangial deposition and activation of mesangial cells resulting in glomerular injury[10]

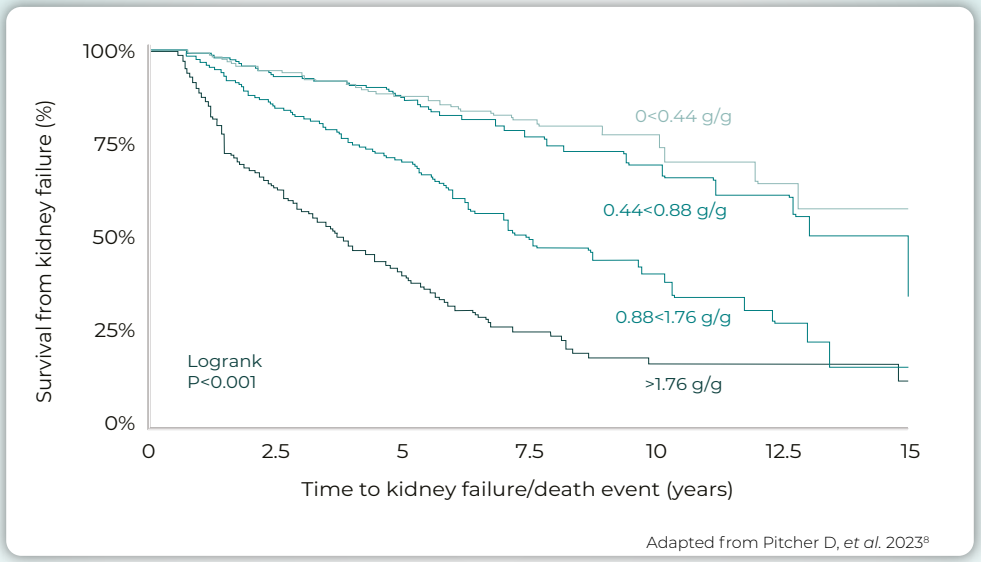
Adapted from Suzuki H, *et al*. 2011[10]

PROTEINURIA

and its importance as a predictor and driver of disease progression in IgAN

Increased proteinuria is associated with faster progression to kidney failure[8,11]

Time-averaged proteinuria strongly predicts IgAN progression; even patients traditionally regarded as being low risk, with proteinuria <0.88 g/g had substantial kidney failure risk as seen in the RaDaR IgAN cohort, underscoring the need for earlier disease management[8]*



Adapted from Pitcher D, *et al.* 2023[8]

Proteinuria is not only a marker for kidney disease, it also plays a critical role in **accelerating disease progression** to ESKD through various pathways[12,13]

Tubular chemokine expression and complement activation[12]

Activated endothelin 1 (ET-1) and angiotensin II (ANG II)[12]

Cycle of inflammation and response leading to podocyte damage and fibrosis[12]

To slow progression to kidney failure

TARGET PROTEINURIA

2025 KDIGO RECOMMENDATIONS FOR IgAN[1]

In 2025, KDIGO released their updated recommendations for the management of IgAN[1]

IgAN can only be diagnosed with a kidney biopsy[1]

There are no validated serum or urine biomarkers for the diagnosis of IgAN[1]

A kidney biopsy should be considered in all adults with proteinuria ≥0.5 g/day (or equivalent) in whom IgAN is a possible diagnosis and kidney biopsy is not contraindicated[1]

Patients are considered at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/day while on or off treatment for IgAN[1]

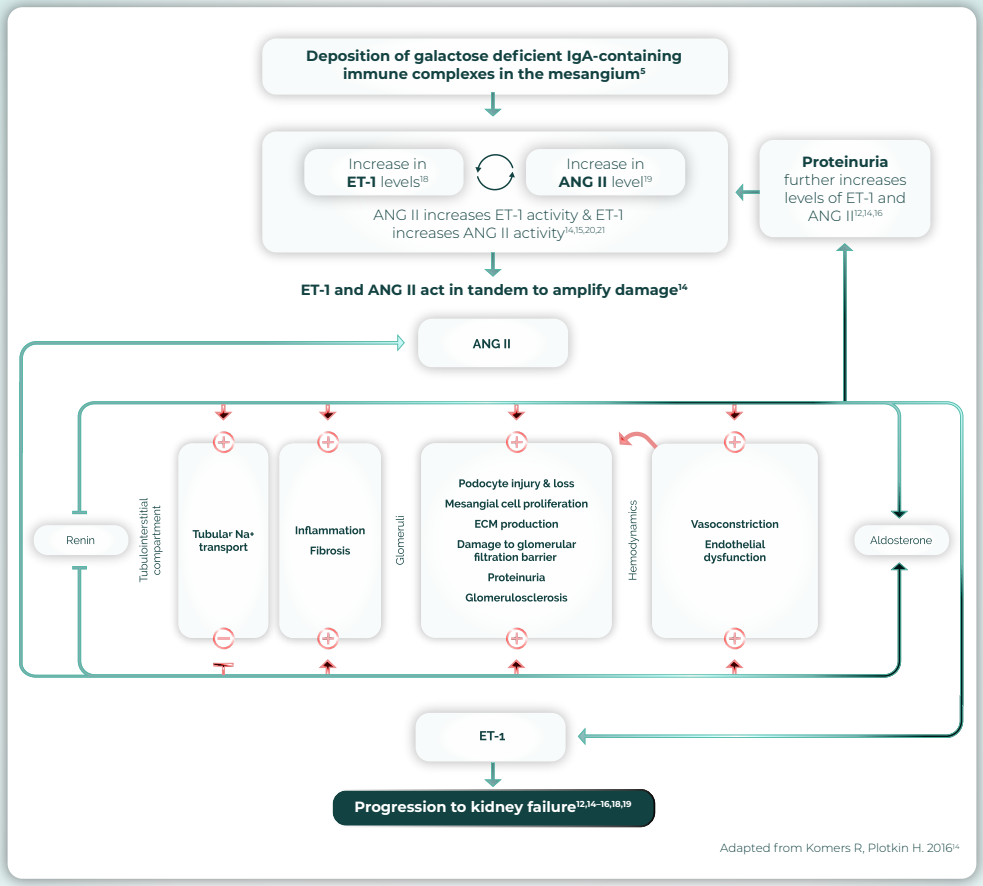
Treatment goals in patients with IgAN at risk of progressive loss of kidney function:[1]

- Reduce the **rate of loss of kidney function** to the physiological state (<1 mL/min/year) for the rest of the patient's life
- Urine protein excretion should be maintained at **<0.5 g/day** or ideally **<0.3 g/day†**

Even proteinuria <0.5 g/day cannot be considered benign[8]

ET-1 AND ANG II IN IgAN

ET-1 and **ANG II** both play fundamental roles in the pathophysiology of IgAN[14–17]



Adapted from Komers R, Plotkin H. 2016[14]

The combined effect of ET-1 and ANG II contribute to disease progression in IgAN[14]

References, footnotes and abbreviations

1. Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group. Kidney Int. 2025;108(4S):S1–S71. **2.** McGrogan A, *et al. Nephrol Dial Transplant.* 2011;26:414–30. **3.** Coppo R. *Kidney Dis.* 2018;4:58–64. **4.** Wyatt R, Julian B. *N Engl J Med.* 2013;368:2402–14. **5.** Lai KN, *et al. Nat Rev Dis Primers.* 2016;2:16001. **6.** Penfold RS, *et al. Int J Nephrol Renovasc Dis.* 2018;11:137–48. **7.** Barratt J, *et al. Front Med.* 2024;11:1461879. **8.** Pitcher D, *et al. Clin J Am Soc Nephrol.* 2023;18(6):727–38. **9.** Caster D, *et al. Kidney Int Reports.* 2023;8:1792–800. **10.** Suzuki H, *et al. J Am Soc Nephrol.* 2011;22:1795–1803. **11.** Reich HN, *et al. J Am Soc Nephrol.* 2007;18:3177–83. **12.** Sharma S,Smyth B. *Kidney Blood Press Res.* 2021;46:411–20. **13.** Eddy A. *Nephrol Dial Transplant.* 2004;19:277–81. **14.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–84. **15.** Kohan DE, Barton M. *Kidney Int.* 2014;86:896–904. **16.** Raina R, *et al. Kidney Dis.* 2020;6:22–34. **17.** Siragy H, Carey R. *Am J Nephrol.* 2010;31:541–50. **18.** Lehrke I, *et al. J Am Soc Nephrol.* 2001;12(11):2321–9. **19.** Chan L, *et al. J Am Soc Nephrol.* 2005;16(8):2306–17. **20.** Benigni A, *et al. Pediatr Nephrol.* 2021;36(4):763–75. **21.** Lin YJ, *et al. Biochem Biophy Res Commun.* 2014;451:263–9.

*RaDaR is a UK based rare kidney disease registry, with an IgAN cohort of 2,439 patients, 2,299 adults and 140 children, forming the study population of this analysis. Patients eligible for enrolment had biopsy-proven IgAN, with proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m^2 at any time in the history of their disease[8]

†In some patients with extensive kidney scarring this may not be possible and multiple treatment strategies are likely to be needed to achieve this[1]

ANG II, angiotensin II; **eGFR**, estimated glomerular filtration rate; **ECM**, extracellular matrix; **ESKD**, end-stage kidney disease; **ET-1**, endothelin 1; **IgA**, immunoglobulin A; **IgA_1**, immunoglobulin A subclass 1; **IgA-IC**, immunoglobulin A containing immune complexes; **IgAN**, immunoglobulin A nephropathy; **KDIGO**, Kidney Disease: Improving Global Outcomes; **Na^+**, sodium; **RaDaR**, UK National Registry of Rare Kidney Diseases; **UK**, United Kingdom

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