

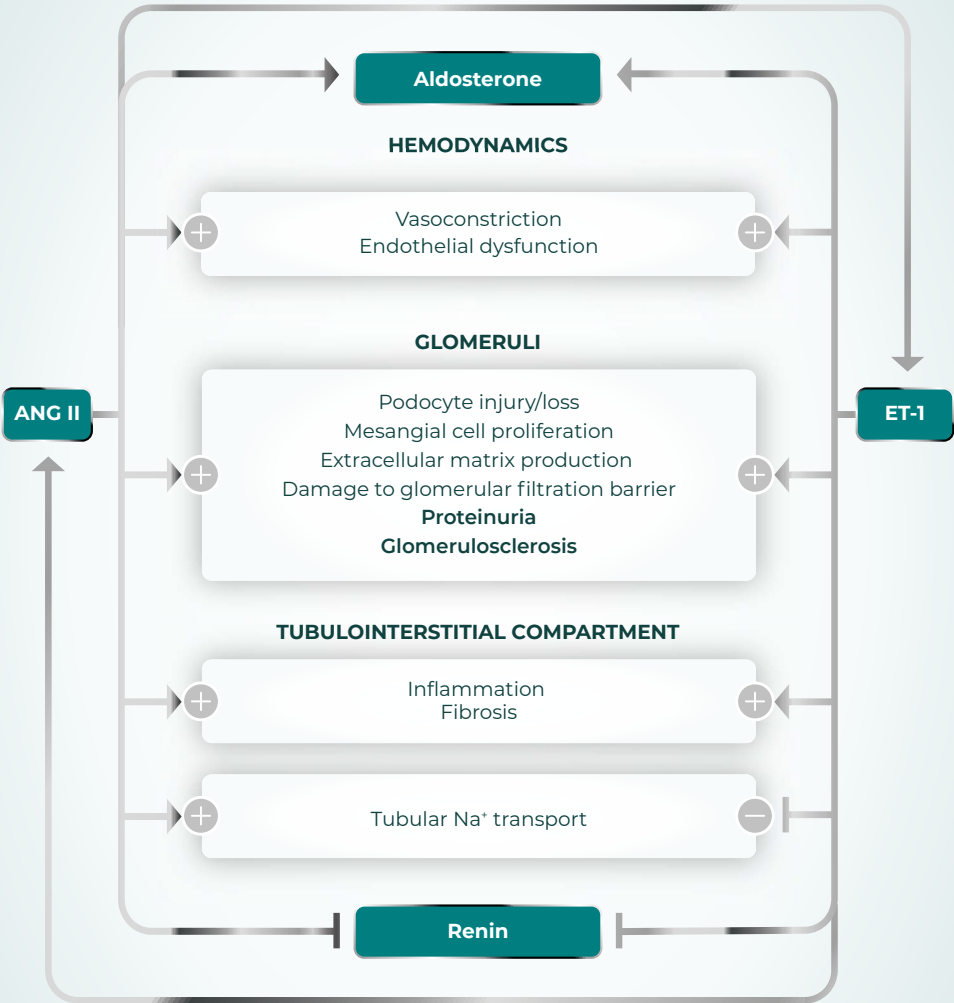
TARGET PROTEINURIA

In IgA nephropathy (IgAN)



ET-1 AND ANG II IN IgAN

ET-1 and **ANG II** both play fundamental roles in the pathophysiology of IgAN¹⁷⁻²⁰



Adapted from Komers R, Plotkin H. 2016⁷

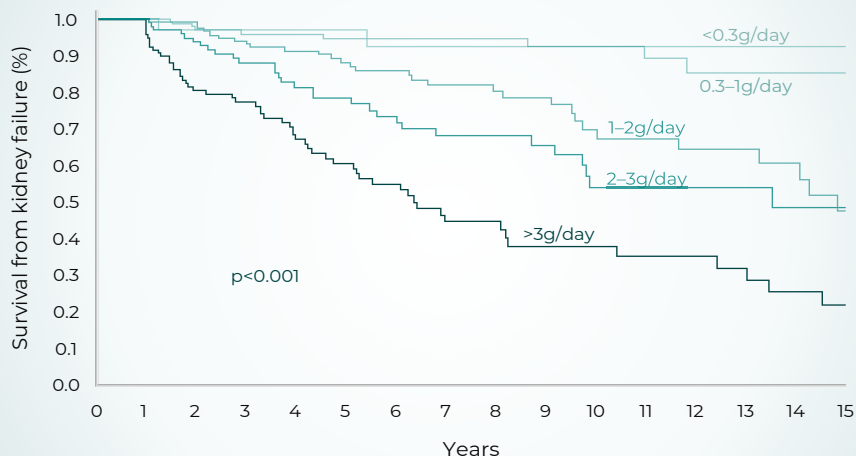
The combined effect of ET-1 and ANG II contribute to disease progression in IgAN¹⁷

PROTEINURIA

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

Increased proteinuria is associated with faster progression to kidney failure¹²

In patients with biopsy-confirmed IgAN (n=542), proteinuria levels over time were the strongest modifiable predictor of the rate of kidney function decline*



Adapted from Reich HN, et al. 2007¹

Proteinuria is not only a marker for kidney disease, it also plays a critical role in **accelerating disease progression** to end stage kidney disease (ESKD) through various pathways^{3,4}



Tubular chemokine expression and complement activation^{3,4}



Activated endothelin-1 (ET-1) and angiotensin II (ANG II)^{3,4}



Cycle of inflammation and response leading to podocyte damage and fibrosis³

To slow progression to kidney failure
TARGET PROTEINURIA

IgAN EXPLAINED

Prevalence and presentation

IgAN is the most common type of glomerulonephritis worldwide, and has a variable clinical presentation and progression to ESKD⁵⁻⁸



In Europe, IgAN is detected in **19–51%** of kidney biopsies performed in glomerular diseases⁷

Patients may be asymptomatic or present with symptoms such as:⁸⁻¹⁰

- Proteinuria
- Macrohematuria
- Renal insufficiency
- Hypertension
- Edema
- Acute kidney injury

Pathophysiology

IgAN is characterized by glomerular deposition of immune complexes containing galactose-deficient IgA₁ that lead to kidney damage^{8,11-13}

There are 4 processes or '**Hits**' involved in the pathogenesis of IgAN:¹³

Hit 1

Aberrant glycosylation of IgA₁ results in the increase of galactose-deficient IgA₁ circulation¹³

Hit 2

Production of anti-glycan antibodies that recognize galactose-deficient IgA₁¹³

Hit 3

Formation of pathogenic IgA₁-containing circulating complexes¹³

Hit 4

Mesangial deposition and activation of mesangial cells resulting in glomerular injury¹³

IgAN EXPLAINED

Patients with IgAN are at an increased risk of death and kidney failure:^{9,11,14,15}



Progression to ESKD¹¹



Death or kidney failure¹⁴

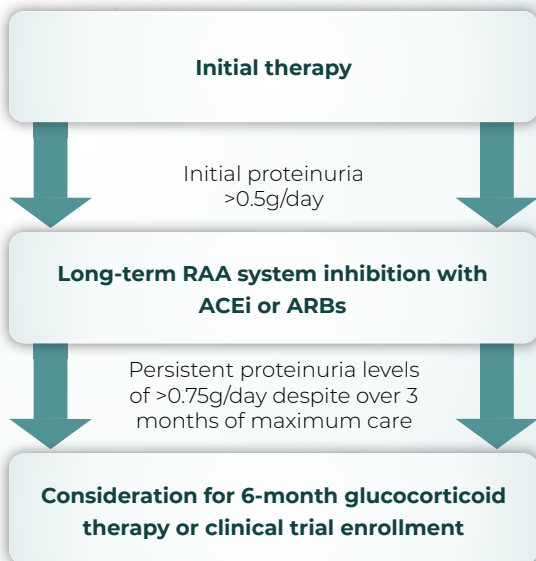
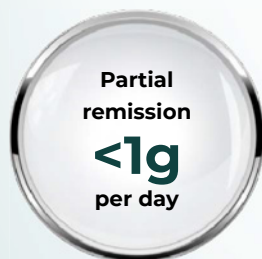


As well as a profound decrease in QoL^{9,15}

KDIGO treatment goals

The KDIGO guidelines outline current proteinuria targets for IgAN⁵

Current treatment recommendations according to KDIGO:⁵



With current KDIGO treatment recommendations, **63%** of patients **do not reach the treatment targets** of proteinuria remission^{5,16†}

There is a high clinical unmet need for disease course modifying treatments that preserve kidney function for patients with IgAN

References

1. Reich HN, et al. *J Am Soc Nephrol*. 2007;18:3177–83. 2. Cattiran D, et al. *Nephrol Dial Transplant*. 2008;23:2247–53. 3. Sharma S, Smyth B. *Kidney Blood Press Res*. 2021;46:411–20. 4. Eddy A. *Nephrol Dial Transplant*. 2004;19: 277–81. 5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int*. 2021;100:S1–S276. 6. McGrogan A, et al. *Nephrol Dial Transplant*. 2011;26:414–30. 7. Coppo R. *Kidney Dis*. 2018;4:58–64. 8. Wyatt R, Julian B. *N Engl J Med*. 2013;368:2402–14. 9. Lai KN, et al. *Nat Rev Dis Primers*. 2016;2:16001. 10. Penfold RS, et al. *Int J Nephrol Renovasc Dis*. 2018;11:137–48. 11. Barratt J, et al. ASN. 2021; poster presentation (PO1577). 12. Boyd JK, et al. *Kidney Int*. 2012;81:833–43. 13. Suzuki H, et al. *J Am Soc Nephrol*. 2011;22:1795–1803. 14. Jarrick S, et al. *J Am Soc Nephrol*. 2019;30:866–76. 15. Kwon CS, et al. *J Health Econ Outcomes Res*. 2021;8:36–45. 16. Bagchi S, et al. *Kidney Int Rep*. 2021;6(6):1661–8. 17. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol*. 2016;310:R877–84. 18. Kohan DE, Barton M. *Kidney Int*. 2014;86:896–904. 19. Raina R, et al. *Kidney Dis*. 2020;6:22–34. 20. Siragy H, Carey R. *Am J Nephrol*. 2010;31:541–50.

*Data from a cohort of 542 patients with primary IgAN who were followed longitudinally in the Toronto Glomerulonephritis Registry. Time-average proteinuria (TA-proteinuria) was the most important predictor of kidney function decline ($R^2=0.162$, $F=104.5$, $P<0.01$)¹

[†]In 96 patients with IgAN receiving supportive therapy with ACEi/ARBs, 35 (36.5%) achieved either partial remission or complete remission at 3 months. Complete remission is defined as proteinuria <0.5g/day, partial remission was defined as proteinuria <1g/day with at least a 50% decline from baseline¹⁶

ACEi, angiotensin-converting enzyme inhibitor; **ANG II**, angiotensin II; **ARB**, angiotensin II receptor blocker; **ECM**, extracellular matrix; **ESKD**, end-stage kidney disease; **ET-1**, endothelin-1; **HCP**, health care professional; **IgA**, immunoglobulin A; **IgA₁**, IgA subclass 1; **IgAN**, IgA nephropathy; **KDIGO**, Kidney Disease: Improving Global Outcomes; **Na⁺**, sodium; **QoL**, quality of life; **RAA**, renin-angiotensin-aldosterone; **TA**, time-average

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