ET-1 AND ANG II IN IgAN

ET-1 and **ANG II** both play fundamental roles in the pathophysiology of IgAN[17–20]

Aldosterone

HEMODYNAMICS

Vasoconstriction
Endothelial dysfunction

GLOMERULI

Podocyte injury/loss
Mesangial cell proliferation
Extracellular matrix production
Damage to glomerular filtration barrier
Proteinuria
Glomerulosclerosis

TUBULOINTERSTITIAL COMPARTMENT

Inflammation
Fibrosis

Tubular Na⁺ transport

Renin

ANG II

ET-1
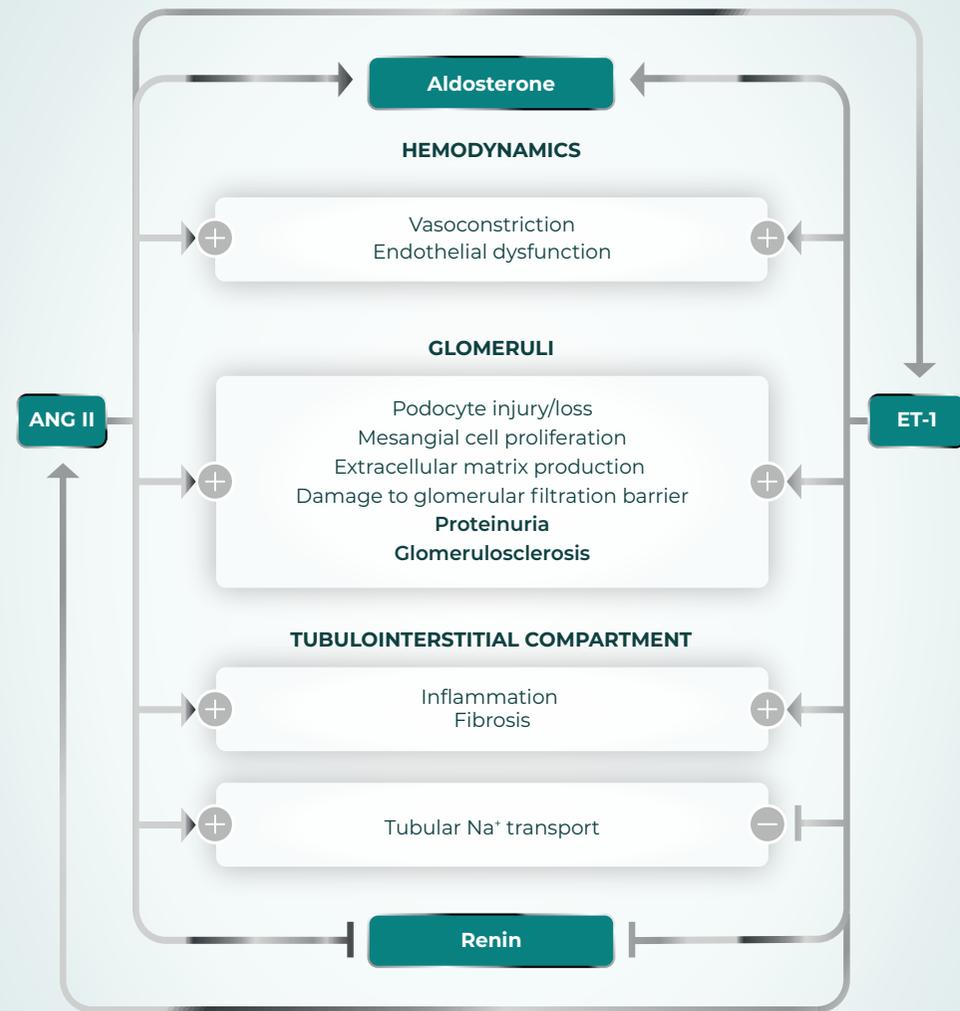
Adapted from Komers R, Plotkin H. 2016[17]

The combined effect of ET-1 and ANG II contribute to disease progression in IgAN[17]

TARGET PROTEINURIA
In IgA nephropathy (IgAN)

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*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 baseline[16]

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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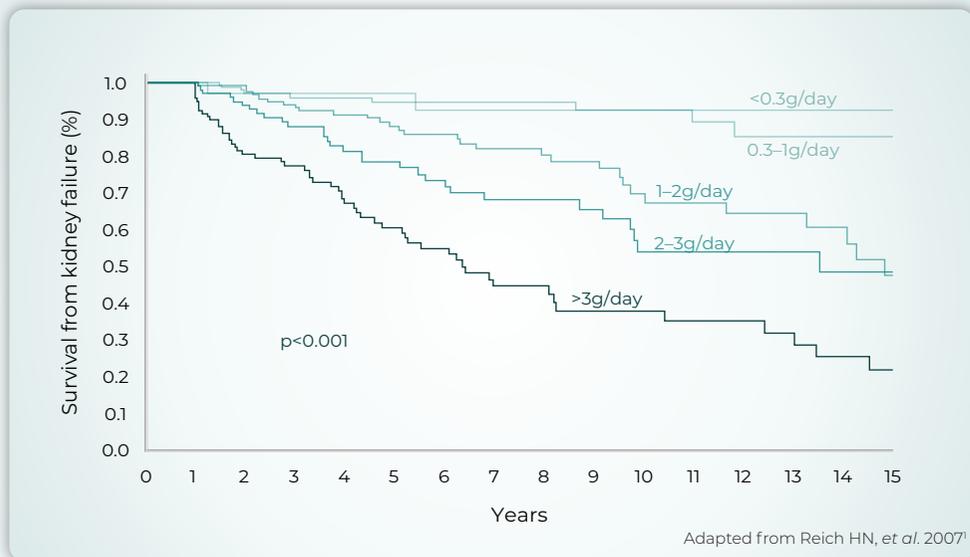
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This leaflet is intended for Healthcare Professionals (HCPs)

CSL Vifor

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

Increased proteinuria is associated with faster progression to kidney failure[1,2]

In patients with biopsy-confirmed IgAN (n=542), proteinuria levels over time were the strongest modifiable predictor of the rate of kidney function decline[1]*

Survival from kidney failure (%) vs Years
- <0.3g/day
- 0.3–1g/day
- 1–2g/day
- 2–3g/day
- >3g/day
- p<0.001

Adapted from Reich HN, et al. 2007[1]

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 fibrosis[3]

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 ESKD[5–8]
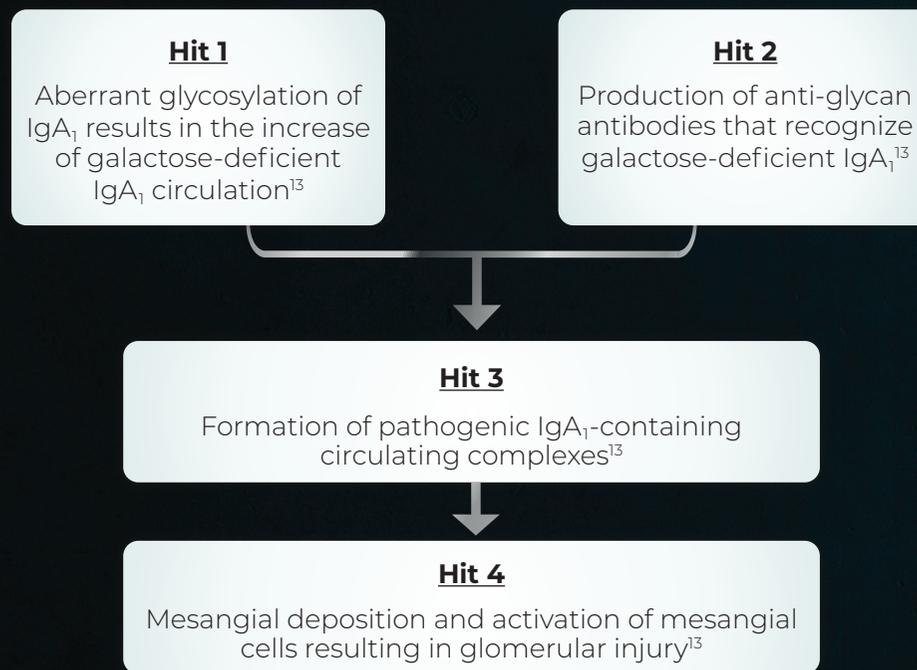
In Europe, IgAN is detected in **19–51%** of kidney biopsies performed in glomerular diseases[7]

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 IgA_1 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 IgA_1 results in the increase of galactose-deficient IgA_1 circulation[13]

Hit 2
Production of anti-glycan antibodies that recognize galactose-deficient IgA_1[13]

Hit 3
Formation of pathogenic IgA_1-containing circulating complexes[13]

Hit 4
Mesangial deposition and activation of mesangial cells resulting in glomerular injury[13]

Adapted from Suzuki H, et al. 2011[13]

IgAN EXPLAINED

Patients with IgAN are at an increased risk of death and kidney failure:[9,11,14,15]
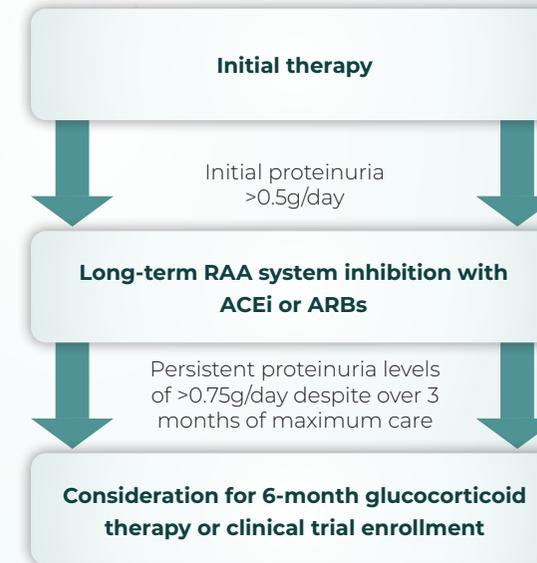
- Progression to ESKD[11]
- Death or kidney failure[14]
- As well as a profound decrease in QoL[9,15]

KDIGO treatment goals

The KDIGO guidelines outline current proteinuria targets for IgAN[5]

Full remission
<0.3g per day

Partial remission
<1g per day

Current treatment recommendations according to KDIGO:[5]

Initial therapy

Initial proteinuria >0.5g/day

Long-term RAA system inhibition with ACEi or ARBs

Persistent proteinuria levels of >0.75g/day despite over 3 months of maximum care

Consideration for 6-month glucocorticoid therapy or clinical trial enrollment

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