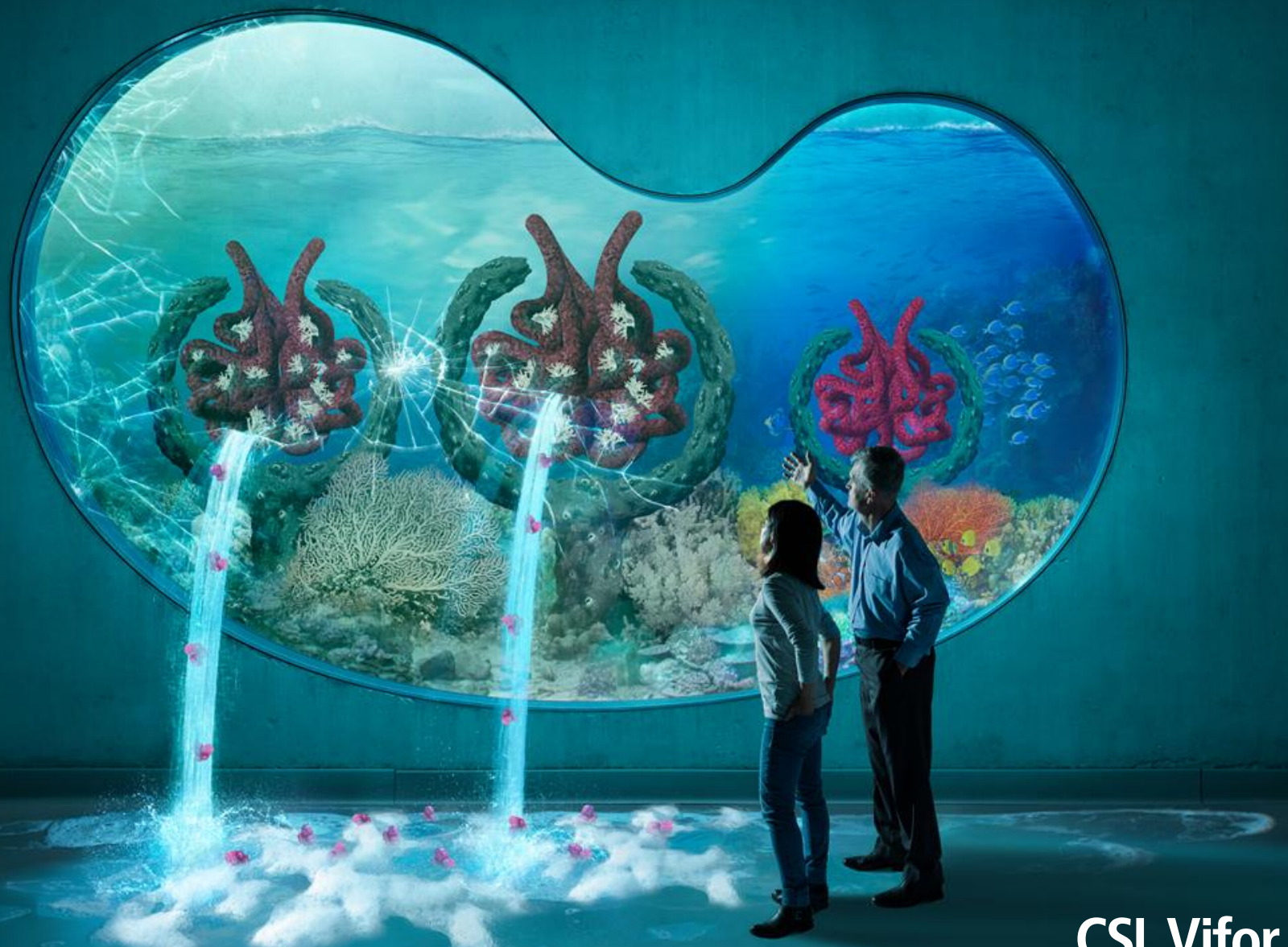
Target Proteinuria

Immunoglobulin A Nephropathy (IgAN) explained

EDUCATIONAL PRESENTATION



This presentation is intended for Healthcare Professionals (HCPs)

MED-HQ-SPT-2300020 | September 2023

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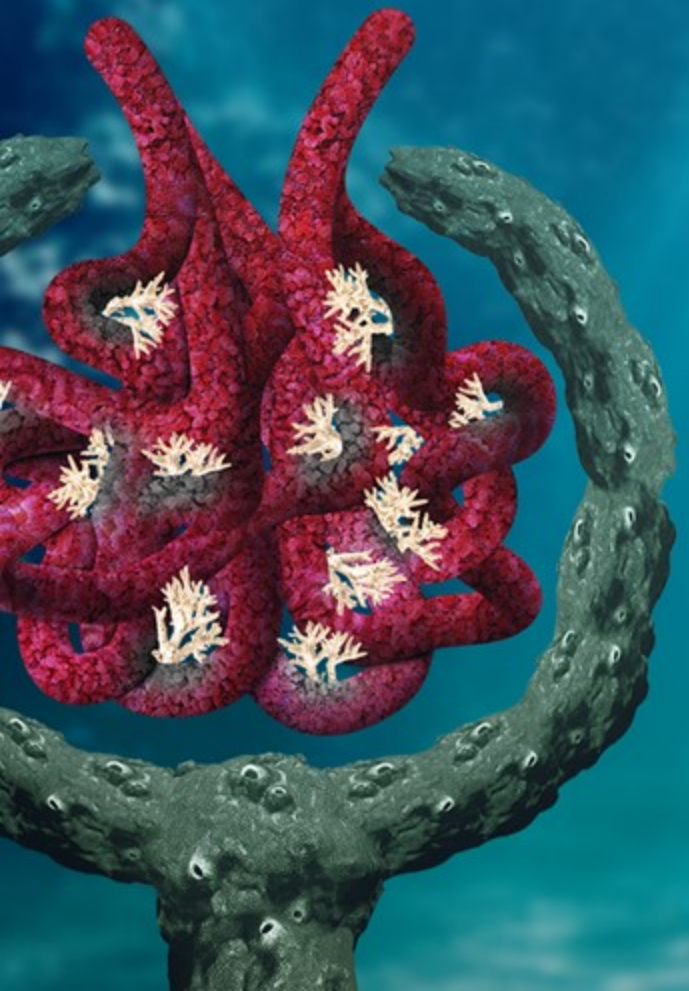
Guiding you through IgAN

- Epidemiology
- Mechanism of disease
- Disease progression
- Importance of proteinuria
- KDIGO current treatment

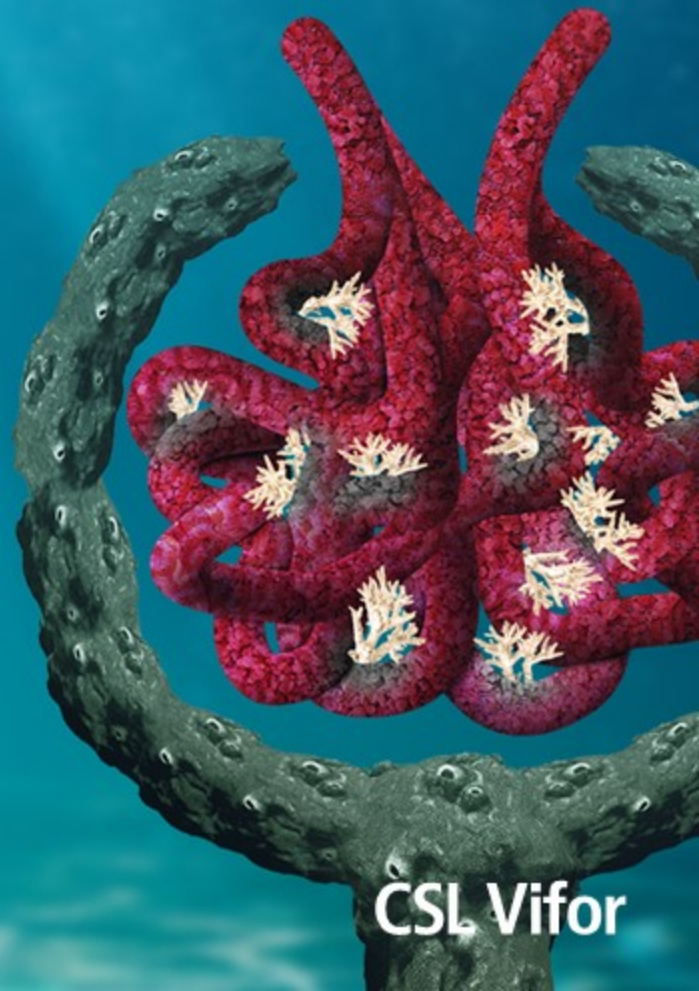
IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.

Target Proteinuria



EPIDEMIOLOGY

Immunoglobulin A Nephropathy (IgAN) explained



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IgAN IS THE MOST PREVALENT TYPE OF PRIMARY GLOMERULONEPHRITIS WORLDWIDE[1,2]

IgAN is a major global cause of kidney failure[1,2]

Globally, the incidence of biopsy-documented IgAN is up to

~2.5 per 100,000

persons per year[3]

IgAN is detected in 19–51% of kidney biopsies performed in glomerular diseases in Europe[4]

In the European Union, IgAN affects approximately 4 in 10,000 people[5]*

*The number of patients affected by IgAN is estimated and assessed on the basis of data from the EU, Iceland, Liechtenstein, Norway, and the UK. This represents a population of 519,200,000 (Eurostat)[5].

IgAN, immunoglobulin A nephropathy.

1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100:S1–276; **2.** Yeo SC, *et al. Pediatr Nephrol* 2018;33:763–77; **3.** McGrogan A, *et al. Nephrol Dial Transplant* 2011;26:414–30; **4.** Coppo R. *Kidney Dis* 2018;4:58–64; **5.** EU/3/20/2336: Orphan designation for the treatment of primary IgA nephropathy. Available at: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202336 (accessed: August 2023).

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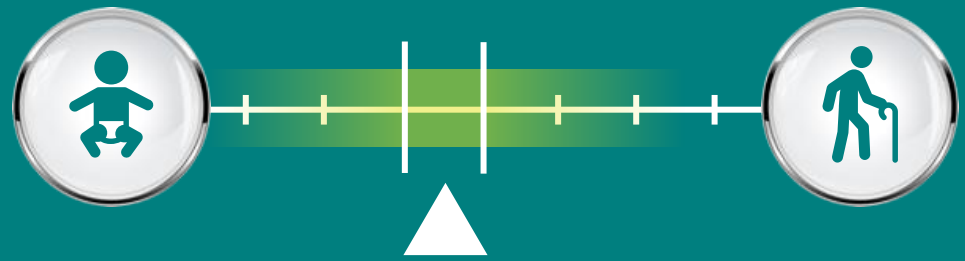
IgAN CAN AFFECT PEOPLE OF ALL AGES AND ETHNICITIES[1–5]

The prevalence of IgAN may vary by ethnicity and sex[1–5]

2:1 in Asia[6]
6:1 in Europe and the US[6]

- Most prevalent in people of East Asian descent followed by Caucasians, and it is rare in individuals of African descent[1–4]
  - Up to **13 times** less prevalent in African Americans than in Caucasians[5]
- Frequently affects **males and young adults** who are otherwise healthy and **often asymptomatic**[4–6]

Prevalence may be higher than reported due to country-level differences in biopsy techniques and policies, and varying levels of access to primary care[4,5]



Frequently detected during the **third** or **fourth decade** of life[5]

IgAN, immunoglobulin A nephropathy.

1. Jennette JC, *et al. Kidney Int* 1985;29:944–50; **2.** Korbet SM, *et al. Am J Kidney Dis* 1996;27:647–51; **3.** Kiryluk K, *et al. PLoS Genetics* 2012;8:e1002765; **4.** Yeo SC, *et al. Nephrology* 2019;24:885–95; **5.** Nair R, *et al. Kidney Int* 2006;69:1455–58; **6.** Deng W, *et al. BMC Nephrol* 2018;19:31.

SEVERAL FACTORS INFLUENCE A PATIENTS' SUSCEPTIBILITY TO IgAN

Genetic factors[1–4]

- Serum galactose-deficient IgA_1 levels have a high heritability
- Genetic factors may influence the presentation of antibodies to galactose-deficient IgA_1
- Genetic and epigenetic factors may influence the immune response to infectious and dietary antigens

Environmental[1,2]

- Mucosal exposure to infectious antigens may increase circulating galactose-deficient IgA_1 and circulating antibodies directed against this abnormal IgA_1 as well as disease progression

Lifestyle factors[1,3,4]

- Mucosal exposure to dietary antigens may increase circulating galactose-deficient IgA_1 and circulating antibodies directed against this abnormal IgA_1
- Increased salt intake, obesity, hypertension, diabetes, and lipid disorders can contribute to disease progression

IgAN, immunoglobulin A nephropathy.

1. Suzuki H, *et al. J Am Soc Nephrol* 2011;22:1795–803; **2**. Maiguma M, *et al. PLoS One* 2014;9:e90558; **3**. Coppo R. *Nephrol Dial Transplant* 2015;30:360–6; **4**. Yuzawa Y, *et al. Clin Exp Nephrol* 2016;20:511–35.

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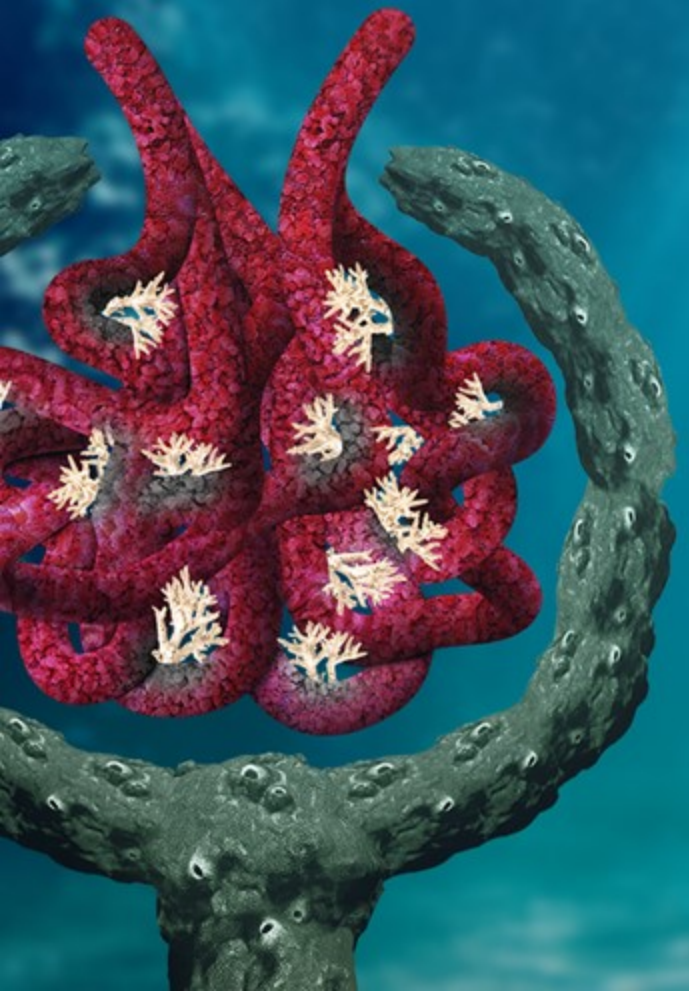
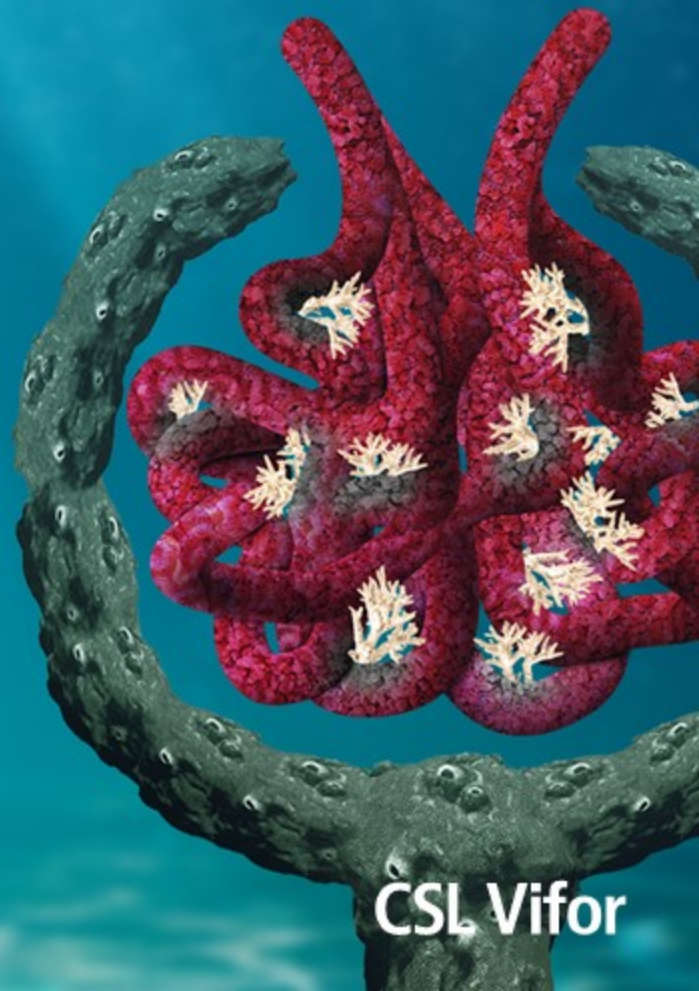
MECHANISM OF DISEASE

Immunoglobulin A Nephropathy (IgAN) explained





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GLOMERULAR DEPOSITION OF IMMUNE COMPLEXES CONTAINING GALACTOSE-DEFICIENT IgA_1 (Gd-IgA_1) IS A KEY FEATURE LEADING TO KIDNEY DAMAGE[1]

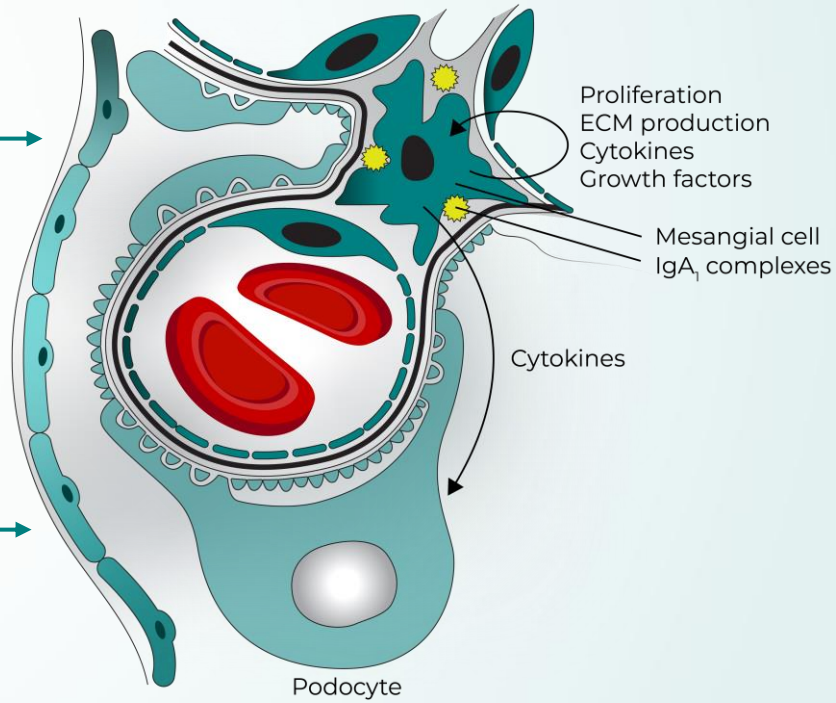
THERE ARE 4 HITS INVOLVED IN THE PATHOGENESIS OF IgAN:

Hit 1:
Aberrant glycosylation of IgA_1 results in the increase of Gd-IgA_1 circulation

Hit 2:
Production of anti–glycan antibodies that recognize Gd-IgA_1

Hit 3:
Formation of pathogenic IgA_1 -containing circulating immune complexes

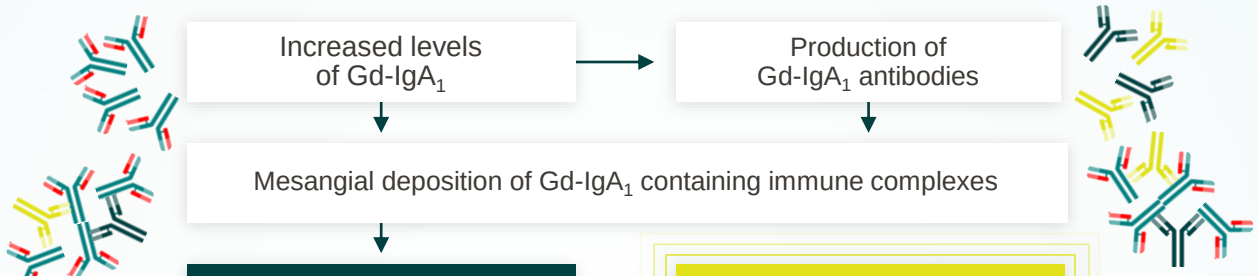
Hit 4:
Mesangial deposition and activation of mesangial cells resulting in glomerular injury



ECM, extracellular matrix; Gd-IgA_1, galactose-deficient IgA_1; IgA, immunoglobulin A; IgA_1, immunoglobulin A subclass 1.

1. Suzuki H, *et al. J Am Soc Nephrol* 2011;22:1795–803.

Gd–IgA$_1$ CONTAINING IMMUNE COMPLEXES CAN LEAD TO PROTEINURIA, PROGRESSIVE LOSS OF GLOMERULAR FILTRATION RATE (GFR) AND KIDNEY FAILURE[1–5]



Increased levels of Gd-IgA$_1$

Production of Gd-IgA$_1$ antibodies

Mesangial deposition of Gd-IgA$_1$ containing immune complexes

Mesangial cell activation

Mediators including **ET-1 & Ang II**

Inflammation
Mesangial cell proliferation
Podocyte injury/loss
Increased glomerular pressure

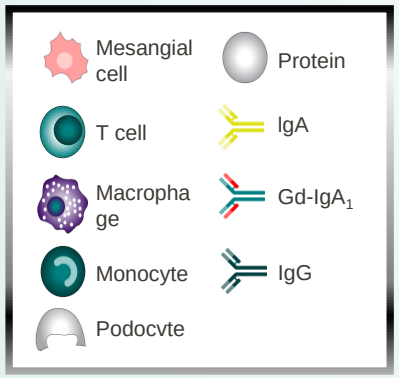
Glomerulosclerosis and compromised glomerular filtration barrier

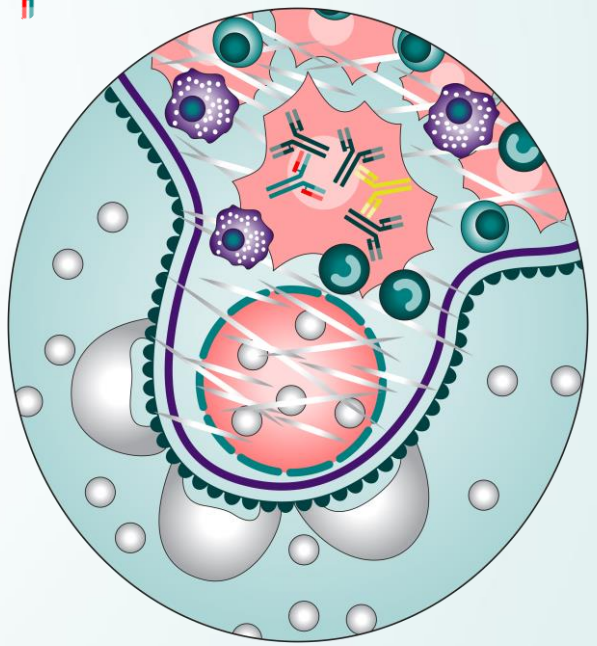
Proteinuria and hematuria

Tubulointerstitial inflammation and fibrosis

CKD

Proteinuria drives further disease progression





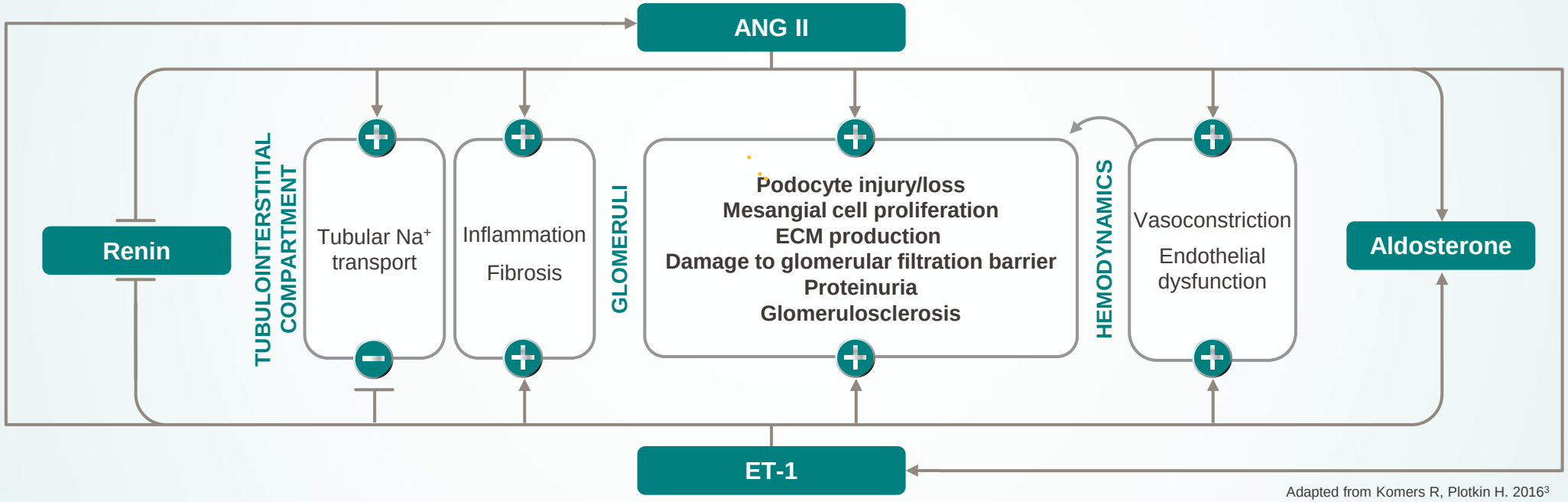
Ang II, angiotensin II; CKD, chronic kidney disease; ET-1, endothelin-1; Gd-IgA$_1$, galactose-deficient IgA$_1$; GFR, glomerular filtration rate; IgA, immunoglobulin A; IgA$_1$, immunoglobulin A subclass 1; IgG, immunoglobulin G.

1. Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R877–84; **2.** Lai K, *et al. Nat Rev Dis Primers* 2016;2:16001; **3.** Raina R, *et al. Kidney Dis* 2020;6:22–34; **4.** Wyatt RJ, Julian BA. *N Engl J Med* 2013;368:2402–14; **5.** Sharma S, Smyth B. *Kidney Blood Press Res* 2021;46:411−20.

Target Proteinuria

ET-1 AND ANG II ACT IN TANDEM TO AMPLIFY DAMAGE THROUGH MULTIPLE PATHOPHYSIOLOGIC PROCESSES

Pathophysiologic actions of ET-1 and ANG II in the kidney



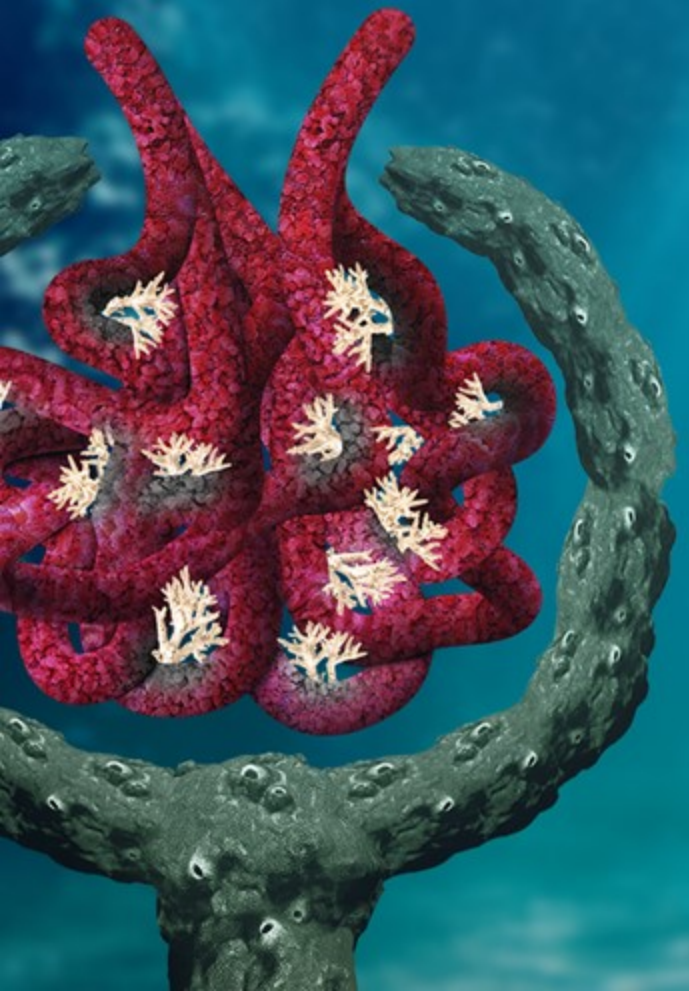
Adapted from Komers R, Plotkin H. 2016[3]

ET-1 and ANG II act in tandem to amplify the inflammatory cytokine response and potentiate glomerular dysfunction, tubulointerstitial injury, and vascular dysfunction, worsening proteinuria and resulting in a progressive decline in kidney function[1–3]

ANG II, angiotensin II; ECM, extracellular matrix; ET-1, endothelin-1.

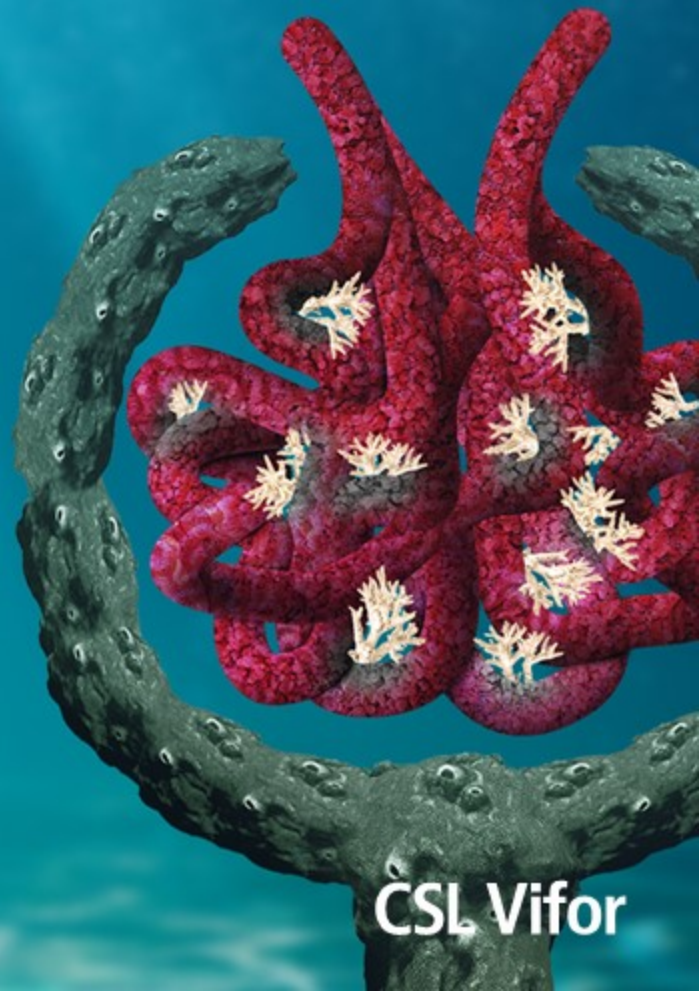
1. Siragy H, Carey R. *Am J Nephrol* 2010;31:541–50; **2.** Ruiz-Ortega M, *et al. Nat Rev Nephrol* 2020;16:269–88. **3.** Komers R, Plotkin H. *Am J Physiol Regul Integr Comp Physiol.* 2016;310:R877–84.

Target Proteinuria



DISEASE PROGRESSION

Immunoglobulin A Nephropathy (IgAN) explained



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THE INTERNATIONAL IgAN PREDICTION TOOL CAN HELP IDENTIFY PATIENTS AT HIGH RISK OF RAPID DISEASE PROGRESSION

RISK PREDICTION TOOL

The International IgAN Prediction Tool, recommended by the KDIGO Guidelines, incorporates clinical and histologic data to provide a prognosis at the time of biopsy to help identify patients who are at a high risk of rapid disease progression and require urgent care to protect kidney function[1–4]

The Risk Prediction Tool identifies factors that contribute to disease progression, including **proteinuria**

DATA ELEMENTS INCLUDED IN THE INTERNATIONAL IgAN PREDICTION TOOL

Estimated GFR at biopsy.....ml/min/1.73 m^2

Systolic blood pressure at biopsy.....mm Hg

Diastolic blood pressure at biopsy.....mm Hg

Proteinuria at biopsy.....g/day

Age at biopsy.....years

Race
- Caucasian
- Chinese
- Japanese
- Other

Use of ACE inhibitor or ARB at the time of biopsy
- No
- Yes

MEST M-score
- 0
- 1

MEST E-score
- 0
- 1

MEST S-score
- 0
- 1

MEST T-score
- 0
- 1
- 2

Immunosuppression use at or prior to biopsy
- No
- Yes

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; MEST, mesangial hypercellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy.

1. Zhang J, *et al. Clin J Am Soc Nephrol* 2020;15:1112–20; **2.** Barbour SJ, *et al. JAMA Intern Med* 2019;179:942–52; **3**. QxMD. International IgAN Prediction Tool. Available at: https://qxmd.com/calculate/calculator_499/international-IgAN-prediction-tool (accessed May 2023); **4**. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100(4S):S1–276.

Target Proteinuria

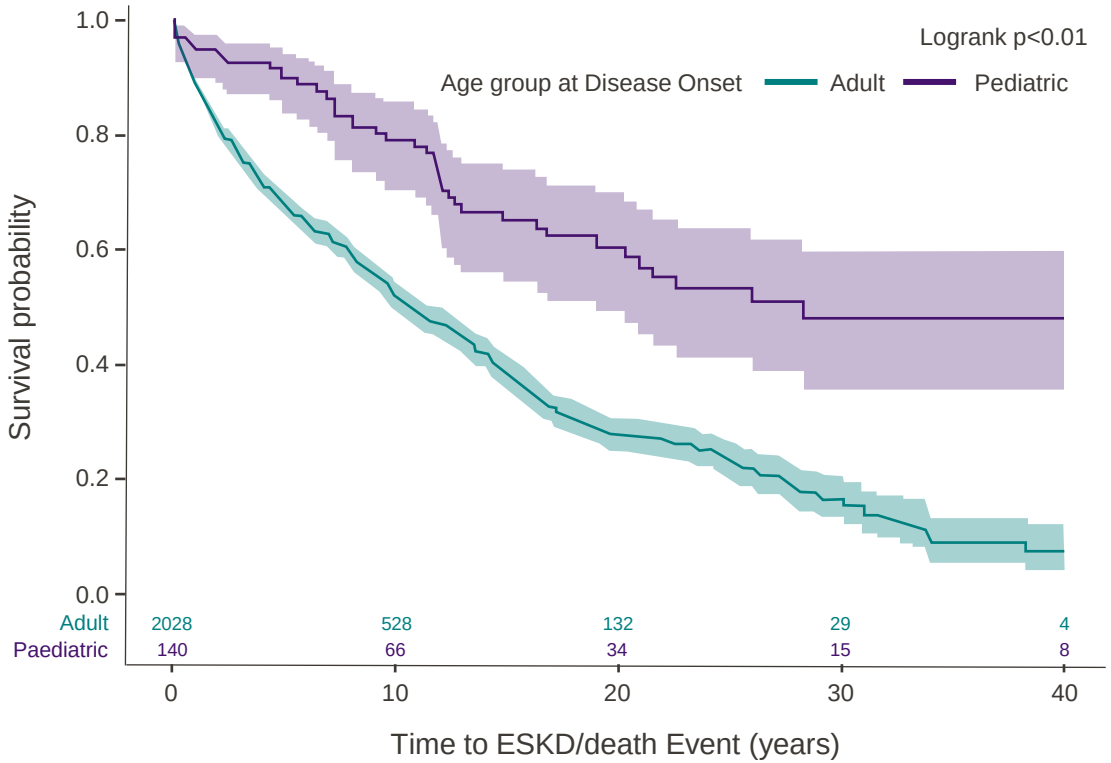
ADULT AND PEDIATRIC PATIENTS WITH IgAN HAVE AN INCREASED RISK OF PROGRESSIVE KIDNEY DISEASE[1]

STUDY TYPE AND OBJECTIVE

- UK-based study of biopsy-verified patients with IgAN (N=2168)
- **Objective:** Describe the natural history of IgAN in adult and pediatric patients with a focus on time from diagnosis to ESKD

KEY RESULTS

- Median UP/C at onset of 1.52g/g with ~27% of patients having nephrotic range proteinuria
- Pediatric and adult patients showed a 50% kidney survival probability of 28 and 11years, respectively
- Over a median follow-up of 9.5years, 34% of pediatric and 51% of adult patients progressed to ESKD



Adapted from Barratt J, *et al*. 2021

ESKD, end-stage kidney disease; IgAN, immunoglobulin A nephropathy; UP/C, urinary protein-to-creatinine ratio.

1. Barratt J, *et al.* ASN 2021; poster presentation (PO1577).

Target Proteinuria

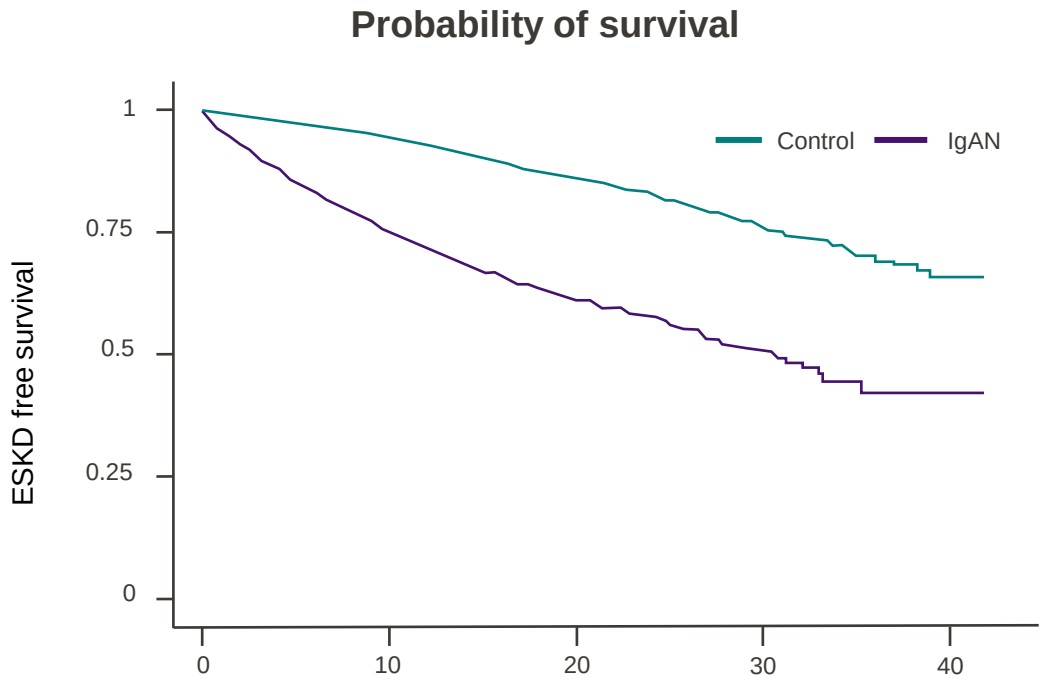
PATIENTS WITH IgAN HAVE AN INCREASED RISK OF KIDNEY FAILURE OR DEATH[1]

STUDY TYPE AND OBJECTIVE

- Swedish population-based cohort study (1974–2011) (N=3622)
- **Objective:** Examine overall and cause-specific mortality as well as the risk of ESKD against matched controls*

KEY RESULTS

- Patients with IgAN had a 53% increased risk of all-cause mortality compared with matched controls
- This corresponded to a 6-year reduction in median life expectancy



Controls	18041 (0)	11262 (831)	4621 (690)	949 (300)	25 (34)
IgAN	3622 (0)	1796 (789)	656 (243)	133 (67)	3 (9)

Adapted from Jarrick *et al*. 2019

*Matched for age, sex, calendar year, and country of residence at the time of kidney biopsy.
ESKD, end-stage kidney disease; ESRD, end-stage renal disease; IgAN, immunoglobulin A nephropathy.
1. Jarrick S, *et al. J Am Soc Nephrol* 2019;30:866–76.

Target Proteinuria

LONG-TERM OUTCOMES IN IgA NEPHROPATHY: THE RADAR* STUDY[1]

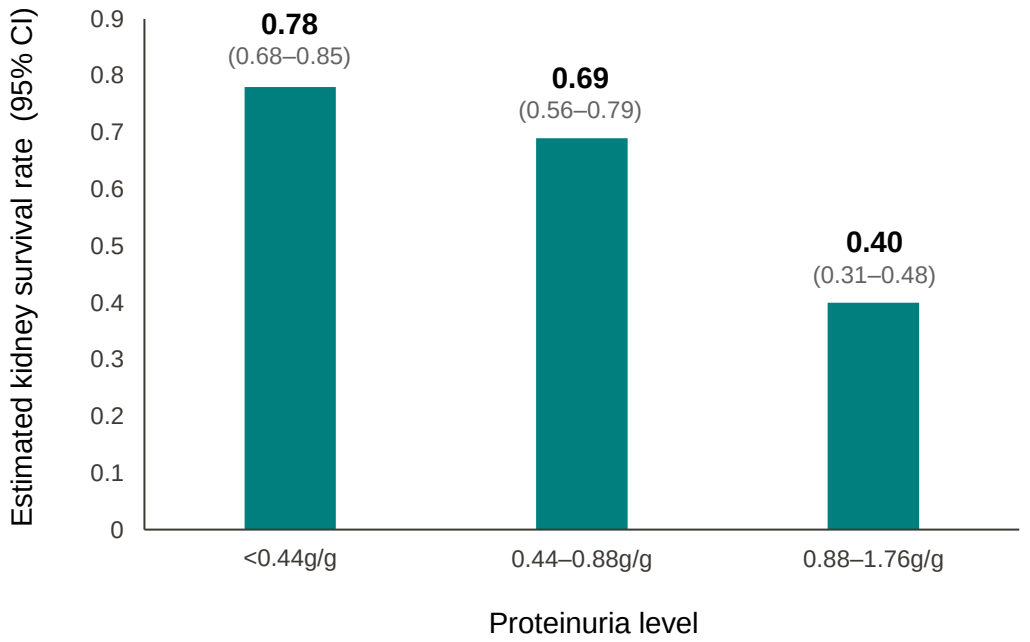
STUDY TYPE AND OBJECTIVE

- UK population-based retrospective cohort study (2013-2022) (N=2439)
- **Objective:** Examine the relationship between proteinuria, eGFR slope, and long-term risk of kidney failure in patients with IgAN

KEY RESULTS

- Median age at diagnosis was 40 and the median age of kidney failure/death was 48
- Median kidney survival time of 11.4years
- 30% of patients with time-averaged proteinuria of 0.44 to <0.88g/g and approximately 20% of patients with time-averaged proteinuria <0.44g/g developed kidney failure within 10years

Estimated kidney survival rates within 10 years based on time average proteinuria



Adapted from Pitcher *et al*. 2023

*UK Registry of Rare Kidney Diseases.
eGFR, estimated glomerular filatration rate; IgAN, immunoglobulin A nephropathy.
1. Pitcher D, *et al. Clin J Am Soc Nephro* 2023;18:727–38.

Target Proteinuria

IgAN PROFOUNDLY IMPACTS PATIENTS' QUALITY OF LIFE

The **wellbeing of patients** with progressive IgAN is **significantly affected,** with **pain and fatigue** commonly reported[1] alongside depression and anxiety[2]

- **Fear of uncertainty and complications with therapies** leaves patients feeling anxious and depressed[2]

QoL is seriously affected in patients who **progress to kidney failure:**

- **Physical symptoms** include fatigue*, sexual dysfunction, weakness, insomnia, anorexia, dysgeusia, nausea, muscle cramps, pruritus, bone pain and fractures, visual disturbances, and neuropathy[2,3]
- **Mental symptoms** include depression, anxiety, and cognitive dysfunction[2,3]

*Defined as extreme and persistent tiredness, weakness, or exhaustion.
IgAN, immunoglobulin A nephropathy; QoL, quality of life.
1. Kwon CS, *et al. J Health Econ Outcomes Res* 2021;8:36–45; **2**. Lai KN, *et al. Nat Rev Dis Primers* 2016;2:16001; **3.** Artom M, *et al. Kidney Int* 2014;86:497–505.

Target Proteinuria

FATIGUE COMMONLY OCCURS IN PATIENTS WITH IgAN AND IS ASSOCIATED WITH POOR OUTCOMES[1]

STUDY TYPE AND OBJECTIVE

- Systematic literature review of Embase, MEDLINE, Cochrane, and EconLit, and relevant congresses*
- **Objective:** Analyze published evidence on epidemiology, burden, and current treatment patterns in IgAN

KEY RESULTS

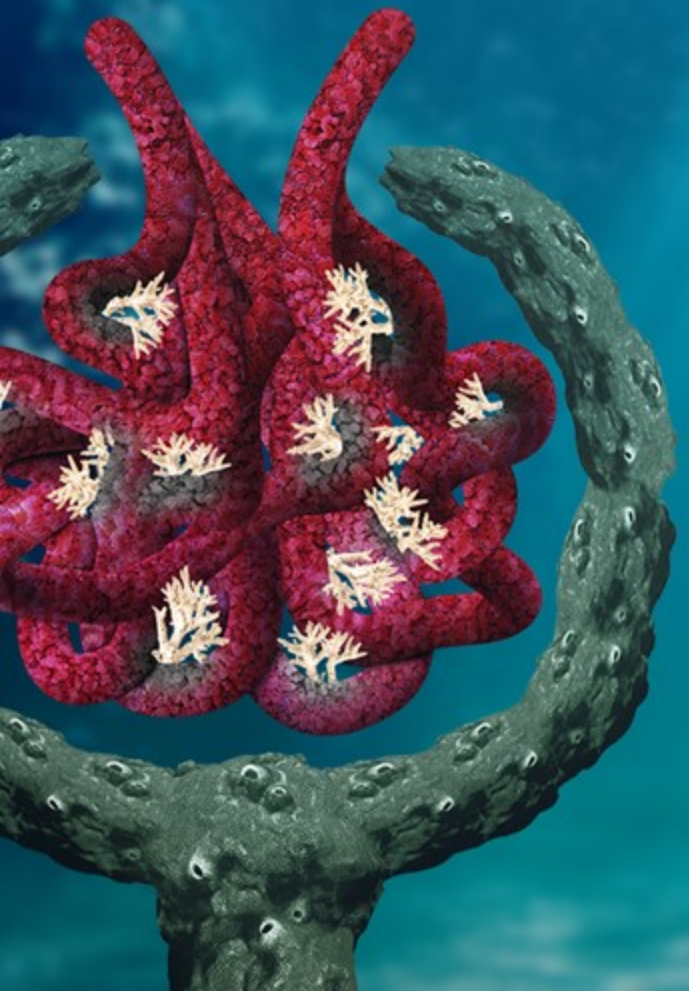
- Across 8 studies reporting HRQOL, pain and fatigue were the most reported symptoms

Impact of pain and fatigue on patients with IgAN

- **Pain and fatigue** were the most common symptoms associated with an impact on physical activity.
- Patients and caregivers reported **emotional distress from lack of counseling** or detailed information on IgAN.
- Patients were impacted by **anxiety, depression, fear of progression to kidney failure**, the requirement for dialysis or transplantation, and the risk of IgAN recurrence post transplant

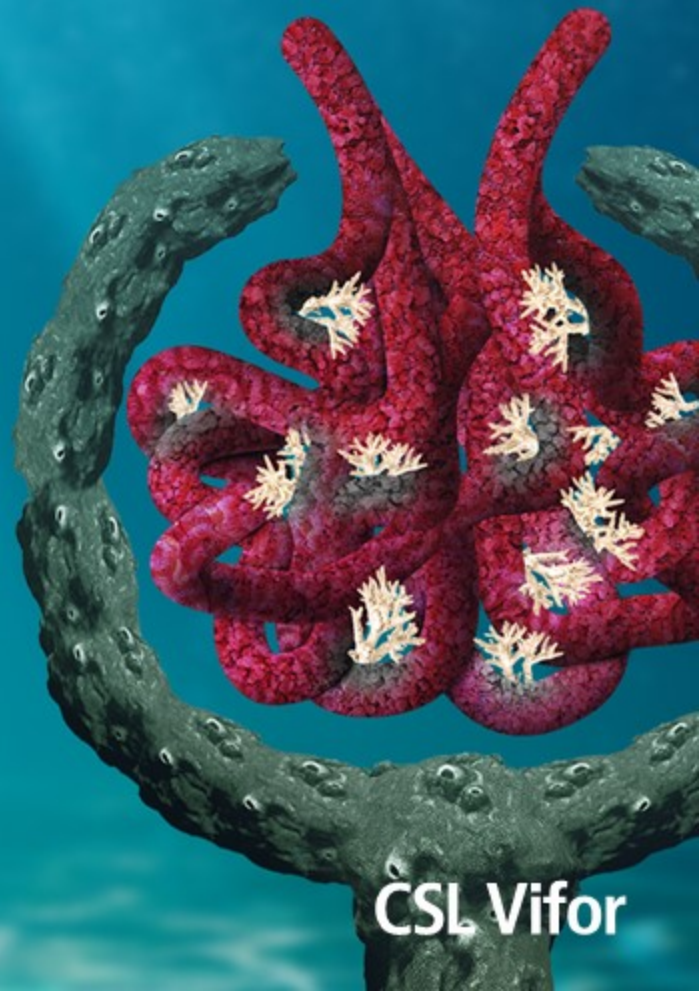
*Searches conducted between January 2010 and June 2020 and 2017 to 2020, respectively.
HRQOL, health-related quality of life; IgA, immunoglobulin A nephropathy.
1. Kwon CS, *et al. J Health Econ Outcomes Res* 2021; 8:36–45.

Target Proteinuria



IMPORTANCE OF PROTEINURIA

Immunoglobulin A Nephropathy (IgAN) explained



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PROTEINURIA-ACTIVATED MECHANISMS DRIVE PROGRESSIVE KIDNEY DISEASE

PROTEINURIA

↓

Excessive protein absorption in the proximal tubule[1,2]

↓

Protein overload of tubular epithelial cells and **spreading of injury**[1]

↓

Tubular cell apoptosis, monocyte infiltration, and interstitial accumulation of extracellular matrix[1]

↓

Proximal tubular cell activation, **interstitial inflammation,** and disturbed expression of proteins are associated with **fibrosis**[1,3,4]

Apoptosis increased in tubular cells

- Albuminuria induced apoptosis *in vitro*[5]
- Proteinuria correlated with number of apoptotic tubular cells in pediatric biopsy specimens[6]

Interstitial inflammation induced

- Driver of interstitial inflammation upregulated in *in vitro* model of proteinuria in kidney failure[7]

1. Abbate M, *et al. J* Am *Soc Nephrol* 2006;17:2974–84; **2.** Christensen EI, Birn H. *Am J Physiol Renal Physiol* 2001;280:F562–73; **3.** Solic I, *et al. Int J Molecular Sci* 2021;22:3500; **4.** Cravedi P, Remuzzi G. *Br J Clin Pharmacol* 2013;76:516–23; **5.** Erkan E, *et al. Am J Physiol Renal Physiol* 2001;280:F1107–14; **6.** Erkan E, *et al. J Am Soc Nephrol* 2005;16:398–407; **7.** Wang Y, *et al. J Am Soc Nephrol* 1997;8:1537–45.

Target Proteinuria

PROTEINURIA IS A BIOMARKER OF GLOMERULAR DISEASE SEVERITY[1]

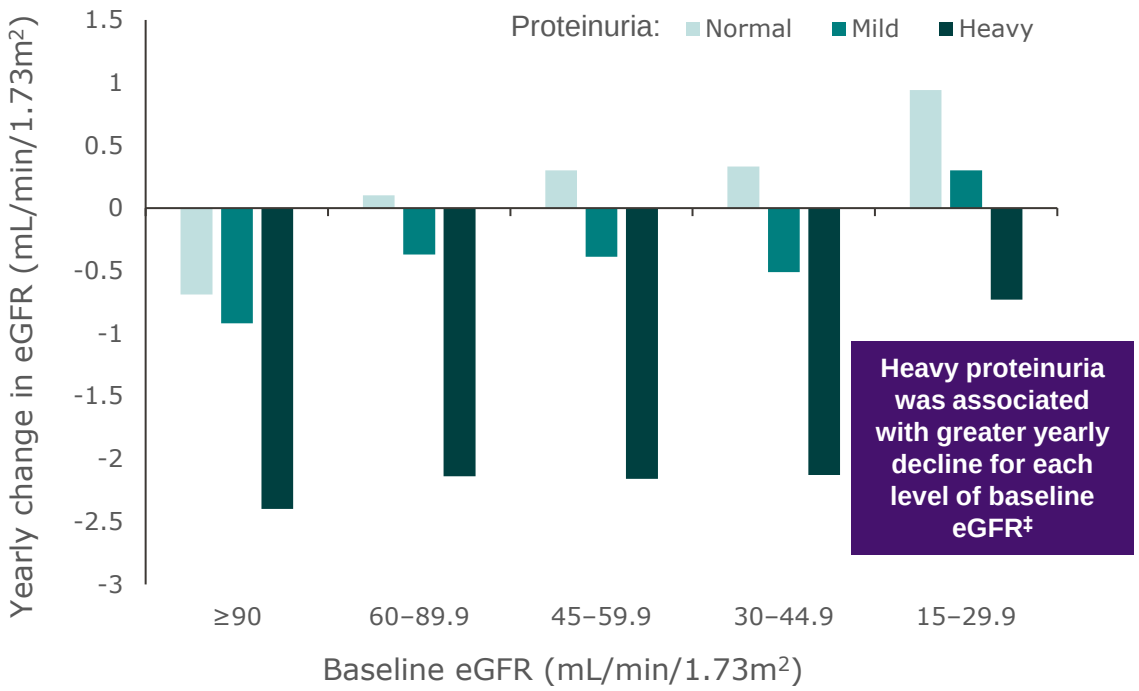
STUDY TYPE AND OBJECTIVE

- **Study**: Analysis* of a cohort of adults receiving routine kidney disease care in a Canadian province (N=638,150)
- **Objective:** Determine the association between baseline proteinuria and yearly decline in kidney function

KEY RESULTS

- Proteinuria of increasing severity was associated with a greater decline in eGFR, irrespective of baseline eGFR

Rate of change in eGFR by proteinuria categories†



Adapted from Turin CT, *et al.* 2013

*Covariates: age, sex, socioeconomic status, kidney function, proteinuria, and comorbid conditions. †Rate of change shown in men. ‡Normal: urine dipstick negative or ACR <30mg/g; mild: urine dipstick trace 1+ or ACR 30–300mg/g; heavy: urine dipstick reading 2+ or ACR >300mg/g. eGFR ≥90, 60–89.9, 45–59.9, 30–44.9, and 15–29.9mL/min/1.73m².
ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate.

1. Turin CT, *et al. J Am Soc Nephrol* 2013;24:1661–7.

Target Proteinuria

INCREASING PROTEINURIA ACCELERATES KIDNEY FUNCTION DECLINE[1]

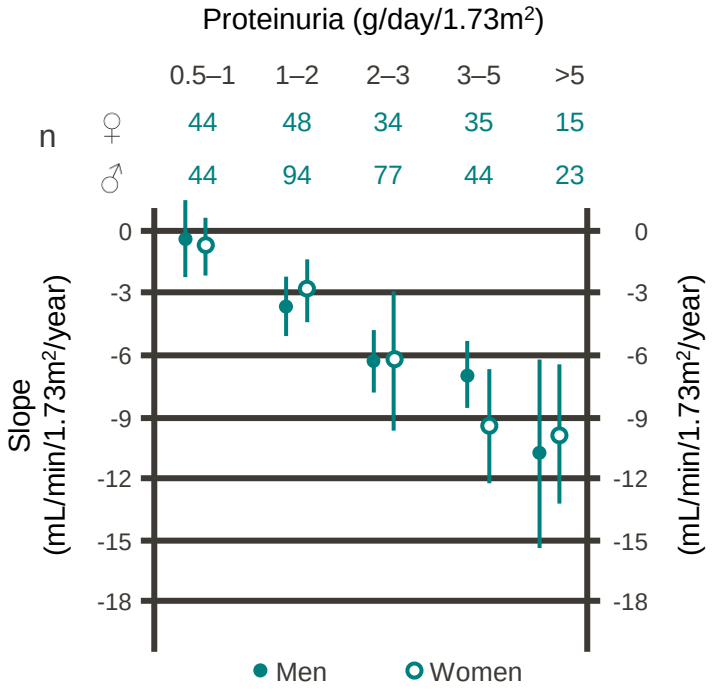
STUDY TYPE AND OBJECTIVE

- Analysis of 542 patients* from the Toronto Glomerulonephritis Registry between 1974 and 2005
- **Objective:** Evaluate the interaction between proteinuria and decline in kidney function in male and females with glomerular disease

KEY RESULTS

- Kidney function decline is accelerated with increasing levels of proteinuria in patients with IgAN

Interaction between proteinuria and rate of kidney function decline



Adapted from Cattran D, *et al.* 2008

*With biopsy-proven IgAN.
IgA, immunoglobulinin A nephropathy.
1. Cattran D, *et al. Nephrol Dial Transplant* 2008;23:2247–53.

Target Proteinuria

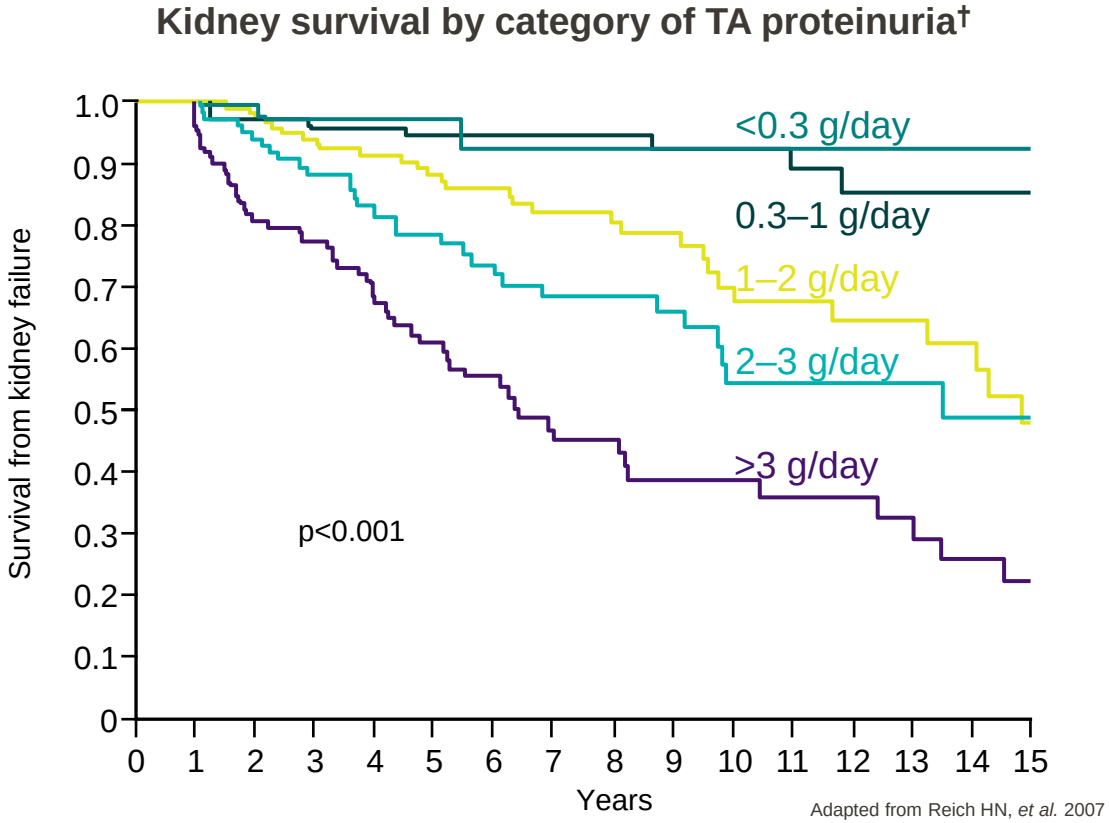
SUSTAINED PROTEINURIA IS THE STRONGEST PREDICTOR OF DISEASE PROGRESSION[1]

STUDY TYPE AND OBJECTIVE

- Analysis of eligible* patients with biopsy-proven IgAN (N=542)
- **Objective:** Examine the effects of sustained exposure to proteinuria on outcome

KEY RESULTS

- Sustained proteinuria of >1g/day was the strongest predictor of the rate of progression of kidney disease and the development of kidney failure
- Each incremental gram per day **above 1g** is associated with a **10- to 25-fold** more rapid rate of **decline in kidney function**‡



*Of 1373 patients in the Toronto Glomerulonephritis Registry, 542 patients met the elibility criterta; patients had to have proteinuria data, weight data, be at least 16 years of age, have more than 12 months follow upand were excluded if they had a secondary cause of IgA deposition; †TA proteinuria represents an average of the mean of every 6-month period's proteinuria measurements, with 6.5 years follow up; ‡Similar differences were observed for kidney survival.
IgA, immunoglobulin A nephropathy; TA, time averaged.

1. Reich HN, *et al. J Am Soc Nephrol* 2007;18:3177–83.

Target Proteinuria

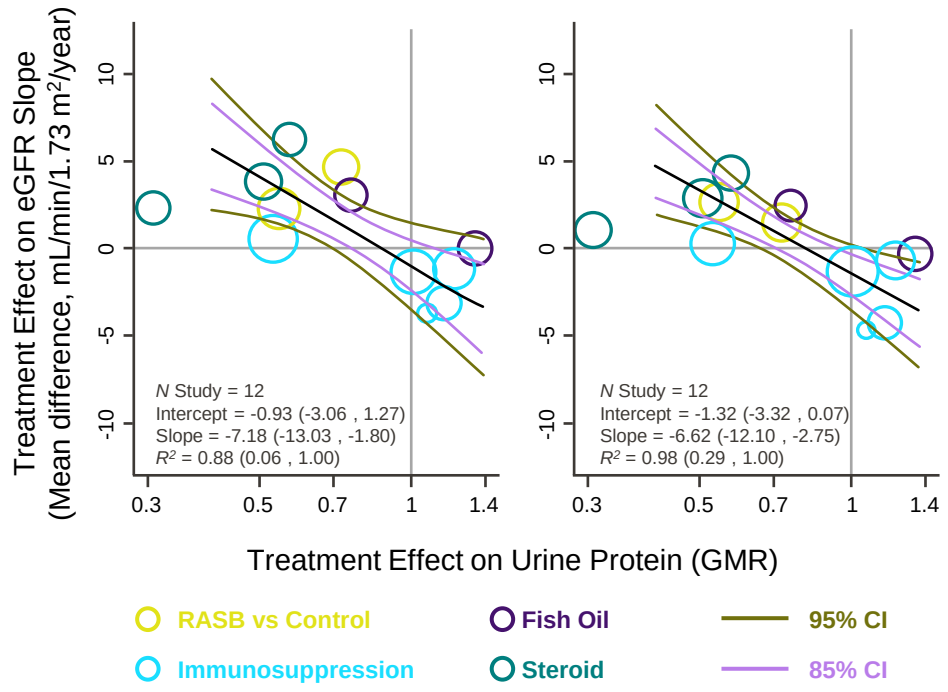
EARLY REDUCTION IN PROTEINURIA CAN IMPROVE DISEASE OUTCOMES IN IgAN[1]

STUDY TYPE AND OBJECTIVE

- Individual patient-level meta-analysis of 1037 patients with IgAN across 12 RCTs
- **Objective:** Evaluate the treatment effect on change in proteinuria and eGFR slope

KEY RESULTS

- For every **10% reduction** in geometric mean urine protein level by treatment there was an associated **0.72mL/min/1.73m²** per year reduction in mean eGFR slope



Adapted from Inker LA, *et al.* 2021

eGFR, estimated GFR; GFR, glomerular filtration rate; IgAN, immunoglobulin A nephropathy; RASB, renin-angiotensin system blockade; RCT, randomized clinical trials.

1. Inker LA, *et al. Am J Kidney Dis* 2021; 78:340–9.

Target Proteinuria

PROTEINURIA REDUCTION MAY PREDICT TREATMENT EFFECT ON DELAYING KIDNEY FUNCTION DECLINE[1]

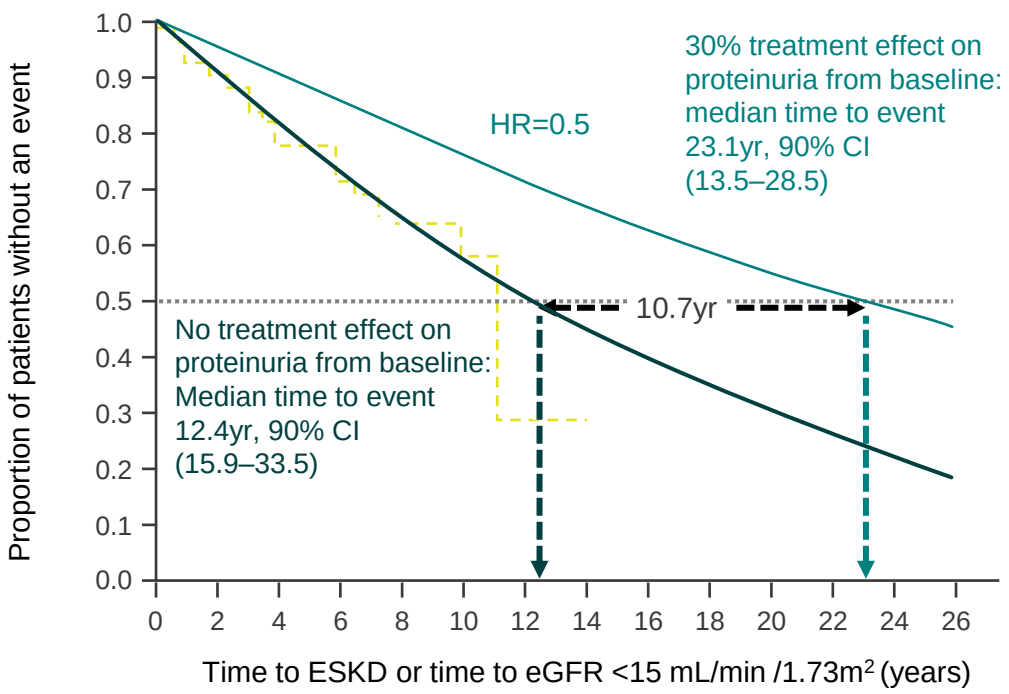
STUDY TYPE AND OBJECTIVE

- Modeling study of n=81 patients with IgAN and proteinuria ≥1.0g/day (or UP/C ≥1.0g/g) and an eGFR ≥30mL/min/1.73 m^2 at the initiation of RAS blockade from the Leicester University Hospital's cohort
- **Objective:** Estimate the delay in time to ESKD* conferred by the hypothesized treatment effect on proteinuria

KEY RESULTS

- 30% reduction in proteinuria at 9 months conferred a 50% lower risk of ESKD, extending the median time to ESKD by 10.7 years

Time to ESKD in patients with IgAN*



Adapted from Carroll KJ, *et al.* 2021

*ESKD defined as eGFR <15 mL/min, initiation of dialysis or transplantation.
eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; IgAN, immunoglobulin A nephropathy; RAS, renin-angiotensin system

1. Carroll KJ, *et al*. ERA-EDTA Congress 2021; oral presentation (MO246).

Target Proteinuria

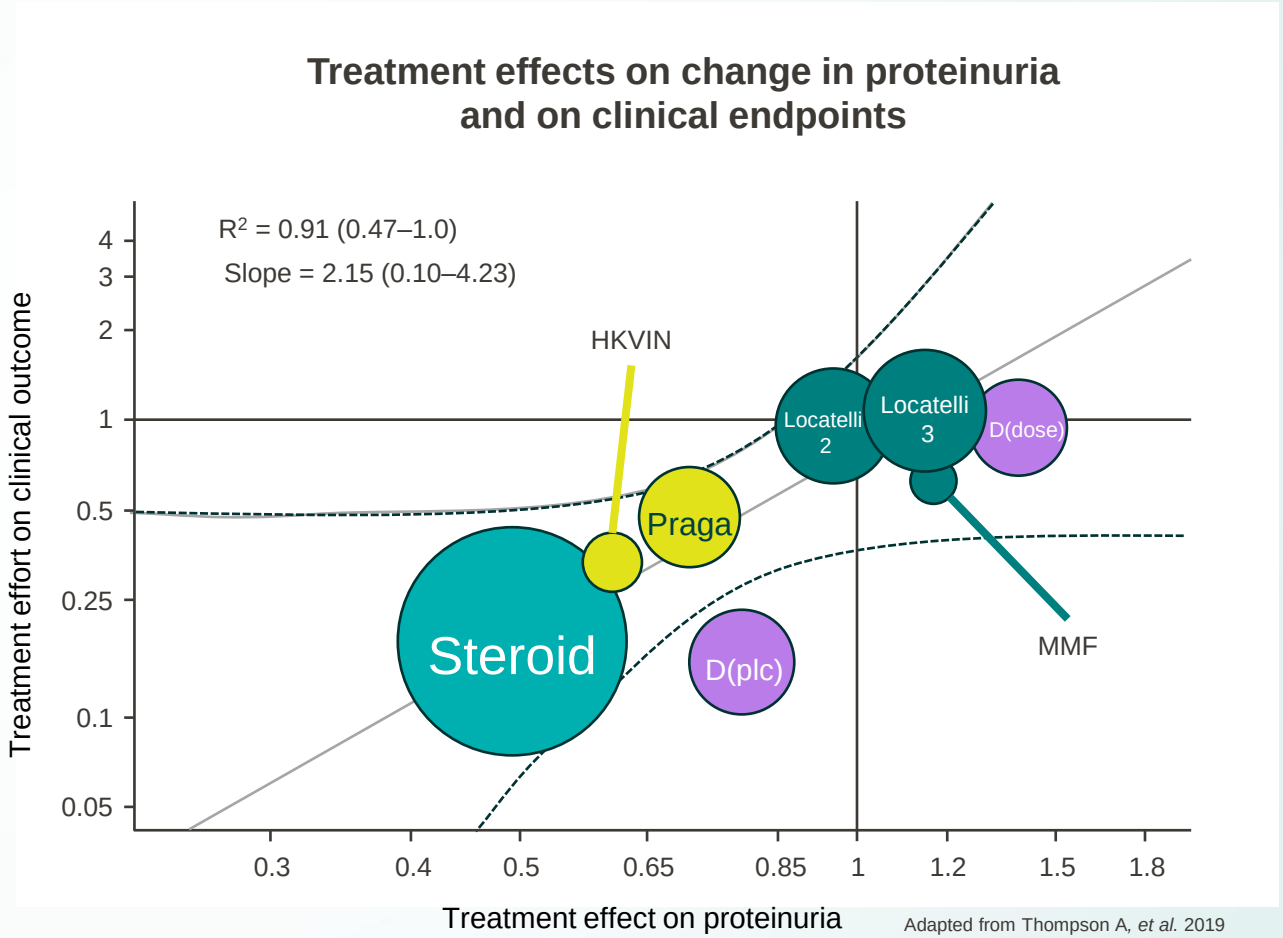
TREATMENT–INDUCED REDUCTION IN PROTEINURIA IS ASSOCIATED WITH IMPROVED KIDNEY OUTCOMES[1]

STUDY TYPE AND OBJECTIVE

- Meta-analysis of 13 controlled trials
- **Objective:** To identify surrogate end points serving as reliable predictors of a treatment's effect on long-term kidney outcomes*

KEY RESULTS

- Association between treatment effect on proteinuria and effect on doubling of serum creatinine or ESKD (R^2=0.91 [0.47–1.0]†)
- An R^2 of 0.91 indicates that for a given treatment effect on urine-protein excretion, the clinical outcome is expected to be double the treatment effect on urine-protein excretion‡



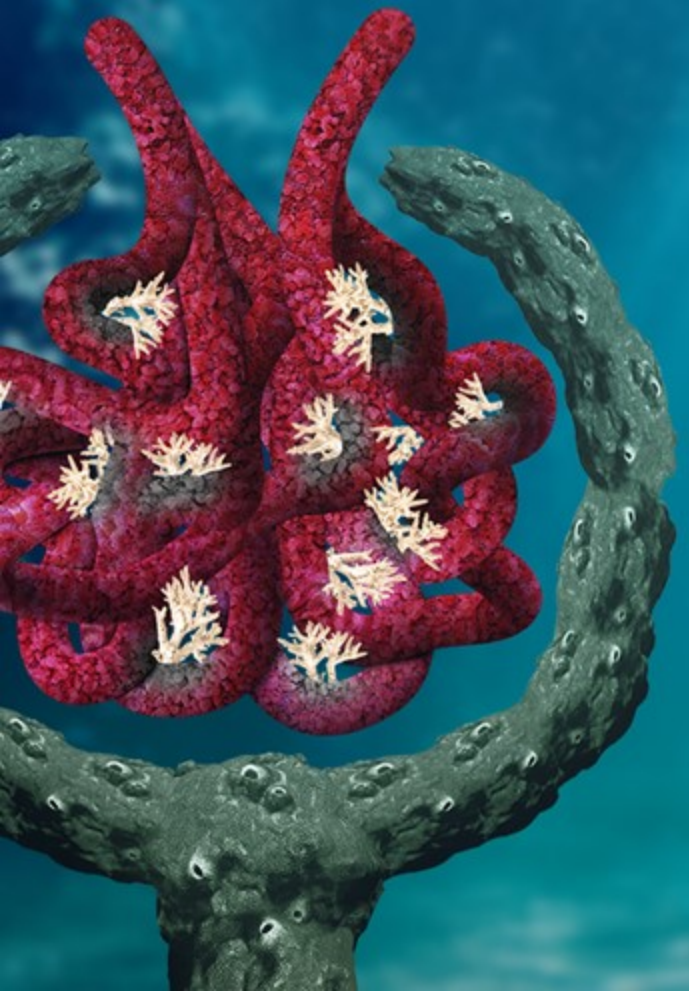
Adapted from Thompson A, *et al.* 2019

*Clinical endpoints defined as the composite of the time to the first occurrence of a doubling of serum creatinine level, ESKD, or death. †Measurements could be made between 7 and 12 months. ‡When the respective treatment effects are expressed on the log hazard ratio and log geometric mean scales.
ESKD, end-stage kidney disease; R^2, squared correlation.

1. Thompson A, *et al. Clin J Am Soc Nephrol* 2019;14:469–81.

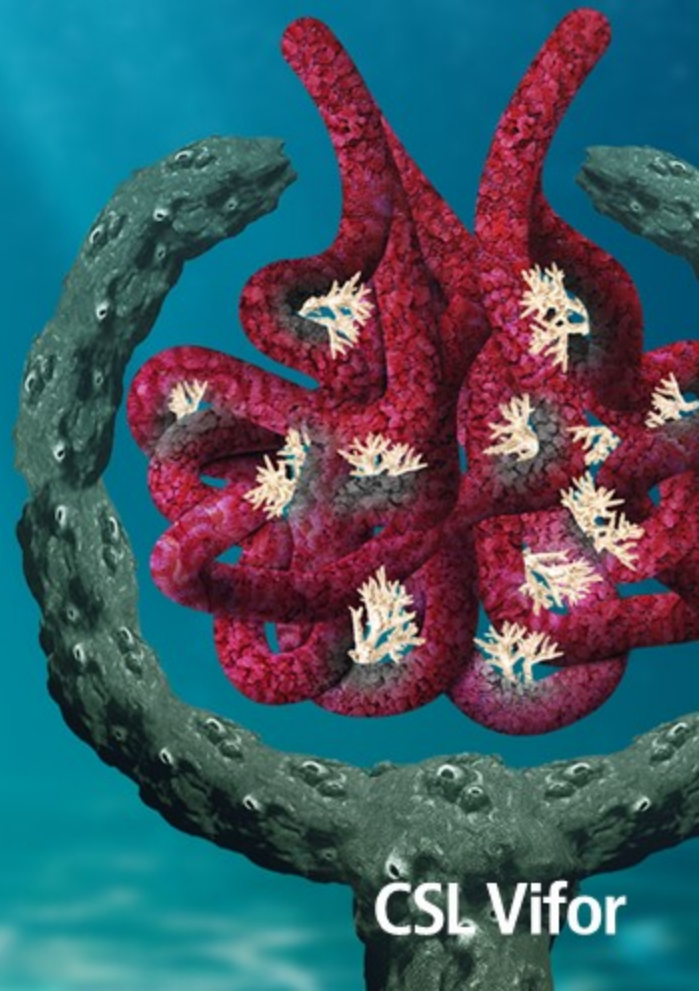
Target Proteinuria

Target Proteinuria



KDIGO CURRENT TREATMENT

Immunoglobulin A Nephropathy (IgAN) explained



CSL Vifor

KDIGO RECOMMEND PROTEINURIA LEVELS <1G/DAY TO PRESERVE KIDNEY FUNCTION

In IgAN, the KDIGO guidelines define proteinuria targets:[1]

Full remission
<0.3g
per day

Partial remission
<1g
per day

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULAR DISEASES

- A **target of treatment** is to **reduce proteinuria to <1g/day**[1], and for adults with high BP and CKD to be treated to a target systolic blood pressure of <120mmHg[2]
- The KDIGO Guideline defines high risk of progression in IgAN as proteinuria >0.75–1g/day despite at least 90 days of optimized supportive care[1]

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

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100(4S):S1–276; **2**. Cheung A, *et al*. *Kid Int* 2021;99:559–69.

KDIGO RECOMMEND REDUCING PROTEINURIA AND BP TO PRESERVE KIDNEY FUNCTION IN PATIENTS WITH IgAN[1]

CURRENT TREATMENT OPTIONS:

- First-line therapy includes **antiproteinuric** and **antihypertensive treatment** with ACEi or ARB
- All patients with **proteinuria >0.5g/day**, irrespective of whether they have hypertension, should be **treated with either an ACEi or ARB***
- Patients with **persistent proteinuria >1g/day** (despite at least 3 months of optimized supportive care)
  and eGFR ≥30mL/min/1.73m^2 should be considered for a 6-month course of **glucocorticoid therapy**.
  The important risk of treatment-emergent toxicity must be discussed with patients

*Included as recommendation 1B within the KDIGO guidelines.
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.
1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int*. 2021;100(4S):S1–276.

KDIGO RECOMMEND MANAGEMENT OF PATIENTS WITH IgAN WHO REMAIN AT HIGH RISK OF PROGRESSION[1]*

Proteinuria >1g/day despite 3 months of optimized supportive care:
- BP management
- Maximally tolerated dose of ACEi/ARB
- Lifestyle modification
- Address cardiovascular risk

Consider enrollment in a clinical trial **or**

Not applicable to variant forms of IgA:
- IgA deposition with minimal change disease
- IgAN with acute kidney injury
- IgAN with a rapidly progressive glomerulonephritis

Not applicable to:
- IgA vasculitis
- IgAN secondary to:
  - Viral (HIV, hepatitis)
  - Inflammatory bowel disease
  - Autoimmune disease
  - Cirrhosis
- IgA-dominant post-infectious GN

Specific populations:
- Japanese – consider tonsillectomy
- Chinese – consider mycophenolate mofetil as a corticosteroid-sparing agent

Patients who remain at a high risk of progression* should be offered a 6-month course of glucocorticoid therapy with corticosteroids

eGFR <30mL/min/1.73m^2

Consider maximal supportive care

eGFR ≥30mL/min/1.73m^2

Toxicity risk stratification:
- Advanced age
- eGFR <50mL/min/1.73m^2
- Metabolic syndrome
- Morbid obesity
- Latent infection (TB, HIV, HCV, HBV)

Risk/benefit profile of glucocorticoids should be individually discussed

Adapted from KDIGO 2021

*Defined as proteinuria >0.75–1g/day despite 3 months of optimized supportive care.

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; TB, tuberculosis.

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100(4S):S1–276.

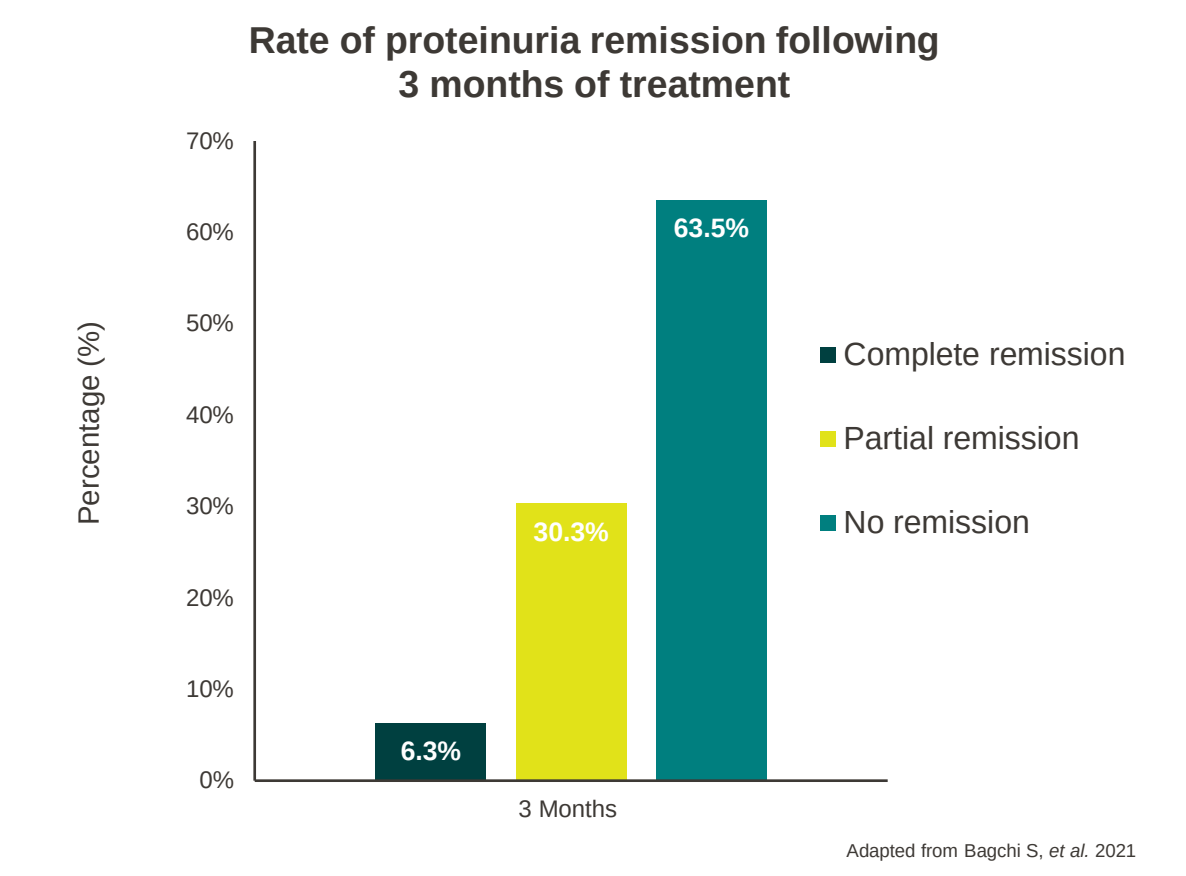
DESPITE CURRENT THERAPIES, MANY PATIENTS REMAIN AT HIGH RISK OF DISEASE PROGRESSION[1]

STUDY TYPE AND OBJECTIVE

- Prospective study of patients with IgAN* (N=96)
- **Objective:** To investigate the effect of ACEi/ARB on progression to kidney disease

KEY RESULTS

- Partial remission† of proteinuria was seen in 29 patients (30.2%) after 3 months of treatment
- 63.5% of patients treated with an ACEi or ARB did not achieve remission after 3 months of treatment



Adapted from Bagchi S, *et al.* 2021

*With biopsy-proven IgAN and urinary protein ≥1g/day.
†Partial remission of proteinuria was defined as <1g/day and ≥50% decrease from baseline with stable kidney function (≤25% reduction in eGFR).
ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IgAN, Immunoglobulin A nephropathy.
1. Bagchi S, *et al. Kidney Int Rep* 2021;6:1661–8.

THERE IS A HIGH UNMET NEED FOR DISEASE–MODIFYING TREATMENTS THAT PRESERVE KIDNEY FUNCTION

CONSIDERATIONS FOR CURRENTLY AVAILABLE TREATMENT OPTIONS

- With **current standard of care therapies**, more than half of patients **remain above the target proteinuria level** of >0.75–1g/day and are at **high risk of disease progression**[1–3]
- Data supporting the recommendation of ACEi/ARB are of low to moderate quality, and studies specific to IgAN are limited[1]
- The use of RAS blockade with ACEi/ARB and immunosuppression versus RAS blockade alone is still debated[4,5]
- **Immunosuppressive therapy** should be avoided in certain patients and carries a **significant risk of toxicity**[1,6] or increased risk of mortality[7]
- The use of high-dose steroids and other immunosuppressants was associated with an increased risk of infections in patients with IgAN[6,8]

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; IgA, immunoglobulin A nephropathy; RAS, renin-angiotensin system; SoC, standard of care.

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100(4S):S1–276; **2.** Woo KT, *et al. Kidney Int* 2000;58:2485–91; **3**. Bagchi S, *et al. Kidney Int Rep* 2021;6:1661–8; **4.** Campbell KN. *Kidney360* 2021;29:1084–6; **5**. Rauen T, *et al. Kidney Int* 2020;98:1044–52; **6**. Rauen T, *et al. J Am Soc Nephrol* 2018;29:317–25; **7**. Jarrick S, *et al. J Am Soc Nephrol* 2019;30:866–76; **8**. Lv J, *et al. JAMA* 2017;318:432–42.

- IgAN, the **most common glomerulonephritis worldwide**, is characterized by glomerular deposition of immune complexes containing Gd-IgA$_1$ that **lead to kidney damage**
- In IgAN, **reducing proteinuria** is associated with a **slower rate of disease progression** and **improved kidney survival**
- KDIGO guidelines recommend **reducing proteinuria to <1g/day** in order to reduce the risk of renal events and **improve kidney survival**
- There remains a **high unmet clinical need in IgAN therapy**; a significant proportion of patients remain at an increased risk of progression despite maximal supportive care

Gd-IgA$_1$, galactose-deficient immunoglobulin A subclass 1; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.