The Importance of Proteinuria Reduction in IgA Nephropathy
Proteinuria Plays a Key Role in the Pathophysiology of IgA Nephropathy

IgA nephropathy is characterized by immune complex deposition in the mesangium that leads to glomerular injury.\textsuperscript{1,4}

As a result of glomerular injury, the glomerular filtration barrier is compromised, leading to proteinuria, hematuria, and glomerulosclerosis.\textsuperscript{1–3}

Ang II = angiotensin II; ET-1 = endothelin-1; IgA = immunoglobulin A; IgA\textsubscript{1} = immunoglobulin A subclass 1; IgG = immunoglobulin G; IL-6 = interleukin-6; TNF = tumor necrosis factor.

Proteinuria Drives Further Injury in the Tubulointerstitial Compartment

After entering the urinary space, leaked proteins and IgA1-containing immune complexes drive tubular atrophy and interstitial fibrosis1,2

The Goal of Treatment Is to Delay Progressive Decline in Kidney Function through Reduction of Proteinuria

KDIGO Clinical Practice Guideline for Glomerulonephritis

Complete remission in glomerulonephritis:
- Reduction of proteinuria to <0.3 g/24 hrs

Reduction of proteinuria in IgA nephropathy:
- Adults: <1 g/24 hrs
- Children: <0.2 g/24 hrs

Target blood pressure in patients with CKD:
- Patients with proteinuria <1 g/24 hrs:
  - SBP <120 mmHg

High risk of progression in IgA nephropathy is defined as proteinuria >0.75–1 g/24 hrs despite ≥90 days of optimized supportive care.

IgA = immunoglobulin A; KDIGO = Kidney Disease: Improving Global Outcomes; SBP = systolic blood pressure.

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The Goal of Treatment Is to Delay Progressive Decline in Kidney Function through Reduction of Proteinuria

First-line therapy for patients with IgA nephropathy includes antiproteinuric and antihypertensive treatment with ACEis or ARBs

All patients with proteinuria >0.5 g/24 hrs, irrespective of whether they have hypertension, should be treated with either an ACEi or an ARB

High risk of progression in IgA nephropathy is defined as proteinuria >0.75–1 g/24 hrs despite ≥90 days of optimized supportive care

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker.
Proteinuria Is Associated with Reduction of eGFR in Patients with IgA Nephropathy

RaDaR: a study investigating the relationship between proteinuria (measured over follow-up) and rate of kidney function loss and survival in 2439 patients with IgA nephropathy

Clinical outcomes for patients categorized by TA-PU (Population 1*)

<table>
<thead>
<tr>
<th>TA-PU</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>eGFR slope (mL/min/1.73 m²/year)</th>
<th>Survival rate (10 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.44 g/g</td>
<td>215</td>
<td>-0.0</td>
<td>7.3</td>
<td>0.78 (0.68–0.85)</td>
<td></td>
</tr>
<tr>
<td>0.44 to &lt;0.88 g/g</td>
<td>175</td>
<td>-1.1</td>
<td>5.7</td>
<td>0.69 (0.56–0.79)</td>
<td></td>
</tr>
<tr>
<td>0.88 to &lt;1.76 g/g</td>
<td>251</td>
<td>-3.8</td>
<td>5.5</td>
<td>0.40 (0.31–0.48)</td>
<td></td>
</tr>
<tr>
<td>≥1.76 g/g</td>
<td>246</td>
<td>-9.5</td>
<td>9.4</td>
<td>0.15 (0.09–0.22)</td>
<td></td>
</tr>
</tbody>
</table>

Higher grades of TA-PU were associated with accelerated reduction of eGFR

* Data shown for population 1, (n=887) a representative incident population examining TA-PU over follow-up without requirement for a baseline UPCR at diagnosis
CI = confidence interval; eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; RaDaR = Registry of Rare Kidney Diseases; SD = standard deviation; TA-PU = time-averaged proteinuria; UPCR = urinary protein-to-creatinine ratio.
Proteinuria Is Associated with Worse Kidney Survival Outcomes in Patients with IgA Nephropathy

RaDaR: a study investigating the relationship between proteinuria (measured over follow-up) and rate of kidney function loss and survival in 2439 patients with IgA nephropathy

Increased proteinuria associated with worse kidney survival and more rapid eGFR reduction

30% of patients develop KF within 10 years with 0.44 to <0.88 g/g (≈0.5−1 g/24 hrs)

~20% of patients with TA-PU <0.44 g/g (<0.5 g/24 hrs) progressed to KF within 10 years

Kaplan–Meier survival curve of time to kidney failure/death event (Population 1*)

<table>
<thead>
<tr>
<th>Total time-averaged proteinuria</th>
<th>Survival from kidney failure/death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – &lt;0.44 g/g</td>
<td>215</td>
</tr>
<tr>
<td>0.44 – &lt;0.88 g/g</td>
<td>175</td>
</tr>
<tr>
<td>0.88 – &lt;1.76 g/g</td>
<td>147</td>
</tr>
<tr>
<td>≥1.76 g/g</td>
<td>142</td>
</tr>
</tbody>
</table>

* Data shown for population 1, (n=887) a representative incident population examining TA-PU over follow-up without requirement for a baseline UPCR at diagnosis

eGFR = estimated glomerular filtration rate; IgA = immunoglobulin A; KF = kidney failure; RaDaR = Registry of Rare Kidney Diseases; TA-PU = time-averaged proteinuria; UPCR = urinary protein-to-creatinine ratio.

Proteinuria Persists in Real-World Patients with IgA Nephropathy, Despite Standard of Care

A real-world study from the IgA nephropathy DSP™; 295 nephrologists completed records for 1376 patients with IgA nephropathy *

Physician-reported signs and symptoms experienced by patients at time of survey

Despite standard-of-care therapies, proteinuria, hematuria, hypertension, and fatigue were the most commonly reported signs and symptoms experienced by patients, increasing risk of KF

* Patients were treated for a minimum of 1 week at time of survey.
DSP = disease-specific program; EU5 = France, Germany, Italy, Spain, and the United Kingdom; IgA = immunoglobulin A; KF = kidney failure.
Early Reduction in Proteinuria Can Positively Impact Kidney Function in IgA Nephropathy

An individual patient-level meta-analysis of 1037 patients with IgA nephropathy from 12 randomized trials to compare treatment effects on change in proteinuria and change in eGFR slope.

Trial-level associations between treatment effects on change in urine protein and total GFR slope at 3 years and chronic slope at 6 months:

- Treatment effects on proteinuria accurately predicted treatment effects on total slope at 3 years ($R^2 = 0.88; 95\%\, BCI = 0.06–1.00$) and on chronic slope ($R^2 = 0.98; 95\%\, BCI = 0.29–1.00$).

10% reduction in GM urine protein level was associated with a reduction of 0.72 mL/min/1.73 m$^2$ per year in mean eGFR slope (at 6 months).

**Table:**

<table>
<thead>
<tr>
<th>Treatment effect on eGFR slope (mean difference, mL/min/1.73 m$^2$/year)</th>
<th>Treatment effect on urine protein</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-year total slope</strong></td>
<td></td>
</tr>
<tr>
<td>N Study = 12</td>
<td></td>
</tr>
<tr>
<td>Intercept = −0.93 (−3.06, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Slope = −7.18 (−13.03, −1.80)</td>
<td></td>
</tr>
<tr>
<td>$R^2 = 0.98$ (0.66, 1.00)</td>
<td></td>
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<tr>
<td><strong>Chronic slope</strong></td>
<td></td>
</tr>
<tr>
<td>N Study = 12</td>
<td></td>
</tr>
<tr>
<td>Intercept = −1.32 (−3.32, 0.07)</td>
<td></td>
</tr>
<tr>
<td>Slope = −6.62 (−12.10, −2.75)</td>
<td></td>
</tr>
<tr>
<td>$R^2 = 0.98$ (0.29, 1.00)</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

- **BCI** = Bayesian credible interval; **CI** = confidence interval; **eGFR** = estimated glomerular filtration rate; **GFR** = glomerular filtration rate; **GM** = geometric mean; **IgA** = immunoglobulin A; **IST** = immunosuppressive therapy; **R$^2$** = squared correlation; **RASB** = renin-angiotensin system blockade. Inker LA, et al. Am J Kidney Dis 2021; 78:340–349.


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Treatment-Induced Proteinuria Changes in Patients with IgA Nephropathy Were Associated with Improved Kidney Outcomes

A meta-analysis of 13 controlled trials to identify surrogate endpoints as predictors of a treatment’s effect on long-term kidney outcomes*

Association between treatment effect on proteinuria and a composite time to doubling of serum creatinine, ESKD, or death ($R^2=0.91; 95\% \text{ BCI}=0.47–1.00\dagger$)

An $R^2$ of 0.91 indicates that for a given treatment effect on proteinuria, the treatment effect on the clinical outcome is expected to be double the treatment effect on proteinuria‡

* Clinical endpoints defined as the composite of the time to 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.

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A modeling study of 81 patients with IgA nephropathy and proteinuria ≥1.0 g/24 hrs to estimate the delay in time to ESKD* conferred by the hypothesized treatment effect on proteinuria

30% reduction in proteinuria was associated with:

- **50%** lower risk of ESKD
- Increased median time to ESKD of **10.7 years**
- Increased **5-year ESKD-free survival rate**

*ESKD defined as eGFR <15 mL/min/1.73 m², initiation of dialysis, or transplantation. CI = confidence interval; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HR = hazard ratio; IgA = immunoglobulin A. Carroll KJ, et al. ERA-EDTA 2021; oral presentation (abstract MO246).
The Magnitude and Duration of Proteinuria Reduction Impacts Long-Term Clinical Endpoints in IgA Nephropathy

A retrospective, multi-ethnic cohort of adult patients (N=1864) with biopsy-proven IgA nephropathy were studied to evaluate the association between duration of proteinuria remission* and the subsequent risk of disease progression.

Each 3-month interval of sustained proteinuria remission up to ~4 years was associated with an additional 9% reduction in the risk of disease progression (HR=0.91; 95% CI=0.89–0.93).

Thereafter, each additional 3 months in remission was associated with a smaller, non-significant risk reduction (HR=0.99; 95% CI=0.96–1.03).

* Proteinuria remission was defined as ≥25% reduction in proteinuria from the peak value after biopsy and an absolute reduction in proteinuria to <1 g/24 hrs; † Smoothed plot of the HR (grey line) and associated 95% CI (shaded area) (grey dotted line is reference) for the risk of the primary outcome associated with the cumulative duration of remission. CI = confidence interval; ESKD = end-stage kidney disease; GFR = glomerular filtration rate; HR = hazard ratio; IgA = immunoglobulin A. Canney M, et al. J Am Soc Nephrol 2021; 32:436–447. Reprinted with permission from Wolters Kluwer Health, Inc. Canney M et al, Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy, Journal of the American Society of Nephrology, 32, 436–447, https://journals.lww.com/jasn/pages/articleviewer.aspx?year=2021&issue=02000&article=00018&type=Fulltext.
Proteinuria Is a Major Component of Risk Stratification in Patients with IgA Nephropathy

The International IgAN Prediction Tool is recommended by the KDIGO Guidelines\(^1\) and utilizes clinical and histologic data to provide a prognosis at the time of biopsy\(^2,3\).

2.2 Prognosis
Practice Point 2.2.1: Considerations for the prognostication of primary IgA nephropathy:

- Clinical and histologic data at the time of biopsy can be used to risk stratify patients.
- The International IgAN Prediction Tool is a valuable resource to quantify risk of progression and inform shared decision-making with patients.
  - Calculated by QxMD
- The International IgAN Prediction Tool incorporates clinical information at the time of biopsy and cannot be used to determine the likely impact of any particular treatment regimen.
- **There are no validated prognostic serum or urine biomarkers for IgA nephropathy other than eGFR and proteinuria.**

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IgA = immunoglobulin A; KDIGO = Kidney Disease: Improving Global Outcomes; MEST = mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

The goal of therapy in IgA nephropathy is to delay progressive decline in kidney function through the reduction of proteinuria and blood pressure.

First-line therapy is antiproteinuric and antihypertensive treatment with ACEis or ARBs as recommended by the KDIGO Guidelines.

Proteinuria is the single strongest and modifiable prognostic factor and is associated with decreased kidney survival and death.

Treatment-induced reductions in proteinuria are strongly associated with improved kidney function and lower risk of kidney failure and death.