

IgA Nephropathy:

Current Perspectives & Future Outcomes

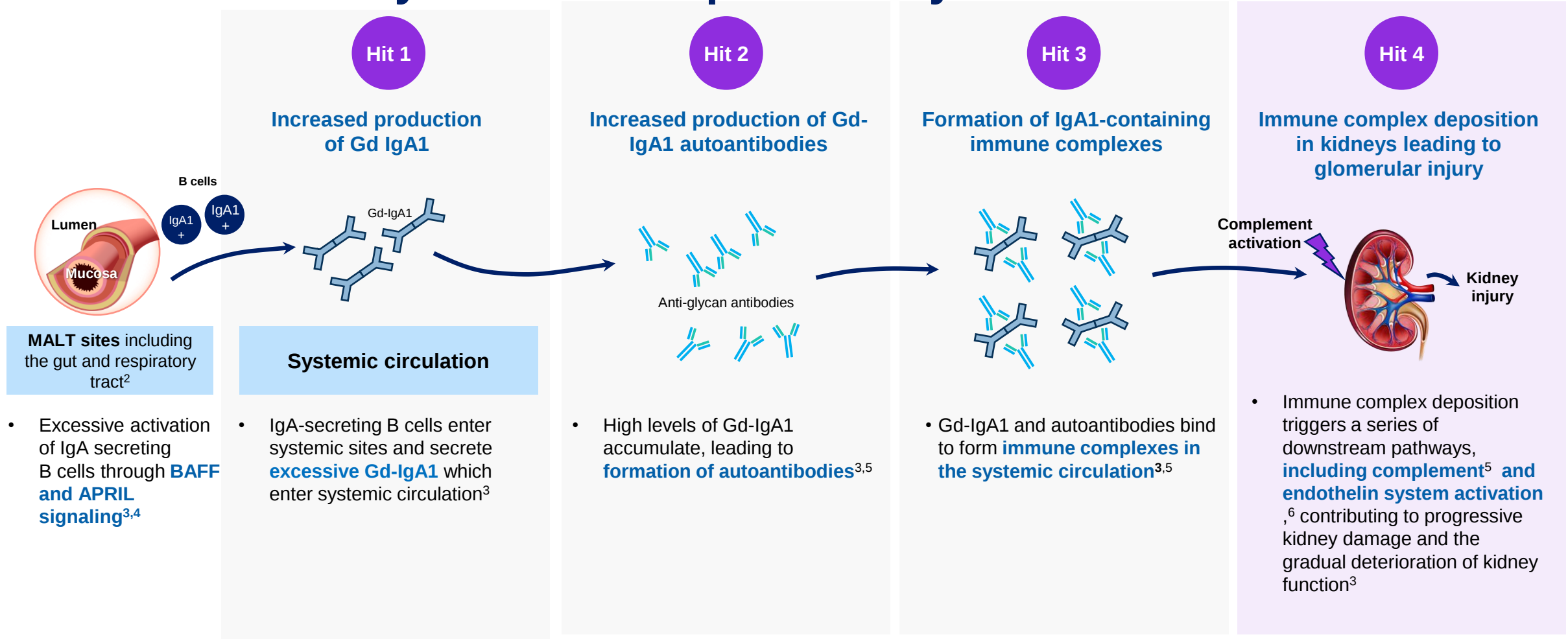
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IgAN Pathophysiology is driven by 4 “Hits” with Hit-4 activating the Endothelin System & Complement System Activation



Gd, galactose-deficient; IgA, immunoglobulin A.

1. Knoppova B, et al. *J Clin Med*. 2021;10:4501; 2. Gesualdo L, et al. *Semin Immunopathol* 2021;43:657–668; 3. Boyd JK, et al. *Kidney Int* 2012;81:833–43; 4. Yeo SC & Barratt J. *Clin Kidney J*. 2023;16(Suppl 2):ii9–ii18; 5. Rizk DV, et al. *Front Immunol* 2019;10:504; 3. 6. Kohan DE, et al. *Kidney Int Rep*. 2023;8:2198–2210; Tecklenborg J, et al. *Clin Exp Immunol* 2018;192:142–150.

Prognosis



Various clinical and histological factors impact disease prognosis

Clinical factors

Poor prognosis¹⁻²

- Increasing age
- Duration of preceding symptoms
- Severity of proteinuria
- Hypertension
- Decreased/decreasing eGFR
- Increased body mass index

Good prognosis

- Recurrent macroscopic hematuria

No impact on prognosis

- Gender
- Serum IgA level

Histological factors³⁻⁵

Poor prognosis

- Tubular atrophy
- Interstitial fibrosis
- Vascular wall thickening
- Capillary wall IgA deposits
- Crescents
- Glomerular sclerosis

No impact on prognosis

- Intensity of IgA deposits

Table adapted and updated from Barratt J, et al. 2005¹

eGFR, estimated glomerular filtration rate; IgA; immunoglobulin A; IgAN, immunoglobulin A nephropathy

1. Barratt J, et al. *J Am Soc Nephrol*. 2005;16:2088–97; 2. Rodrigues J, et al. *Clin J Am Soc Nephrol*. 2017;2:691–701. 3. Markowitz G. *Nat Rev Nephrol*. 2017;13:385–86; 4. Haas M, et al. *J Am Soc Nephrol*. 2017;2:691–701; 5. Trimarchi H, et al. *Kidney Int*. 2017;91:1014–21.

KDIGO Guideline recommends using the International Risk Prediction Tool to predict risk of IgAN progression for each patient

The tool uses patient information to calculate the risk of a 50% decline in eGFR or kidney failure over a specified period of time¹⁻³



- eGFR at biopsy (mL/min/1.73m²)
- Proteinuria at biopsy (g/day)
- MEST-C scores at biopsy



- Systolic BP at biopsy (mmHg)
- Diastolic BP at biopsy (mmHg)



- Age at biopsy (years)
- Race



- Use of ACEi/ARB at the time of biopsy (yes/no)
- Immunosuppression use at, or prior to, biopsy (yes/no)

Patients then commence optimized supportive care
(BP management, maximally tolerated ACEi/ARB, lifestyle modification, address cardiovascular risk)



[Click Here to Access the International Risk Prediction Tool](#)

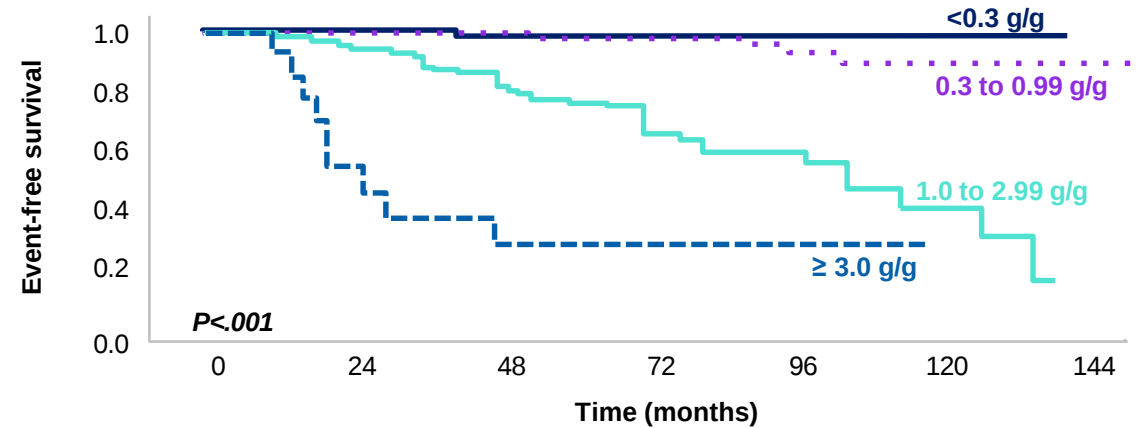
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; MEST-C, mesangial [M] and endocapillary [E] hypercellularity, segmental glomerulosclerosis [S], tubular atrophy/interstitial fibrosis [T], crescents [C].

KDIGO. Kidney Int. 2021;100(4S):S1-S276.

KDIGO Guideline defines high-risk patients as those with proteinuria $> 0.75\text{--}1$ g/day despite 3 months of optimized supportive care*¹

- Time-averaged proteinuria is the strongest clinical predictor of kidney function decline in IgAN.¹⁻⁴
- Proteinuria >1 g/day is associated with a 9.4-fold increased risk of kidney failure compared to patients with proteinuria <1 g/day⁴
- There are no validated prognostic serum or urine biomarkers for IgAN other than eGFR and proteinuria¹

Time-averaged proteinuria as a clinical predictor for IgAN kidney function decline³



No. patient							
< 0.3 g/g	130	126	107	72	41	20	5
0.3 to 0.99 g/g	226	220	196	134	61	25	8
1.0 to 2.99 g/g	130	127	113	80	42	13	4
≥ 3.0 g/g	14	13	6	3	1	-	-

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes.

*Optimized supportive care includes BP management, maximally tolerated dose of ACEi/ARB, lifestyle modification, and addressing cardiovascular risk reduction

1.KDIGO. *Kidney Int.* 2021;100(4S):S1-S276; 2. Lai KN, et al. *Nat Rev Dis Primers.* 2016;2:16001; 3. Nam KH, et al. *PLoS One* 2014;9:e101935; 4. Cattran DC, et al. *Kidney Int Rep.* 2023; 8:2515–28

Emerging evidence supports proteinuria of **< 1g/day** being associated with high rates of kidney failure progression within 10 years

Materials and Methods	Results	Estimated kidney survival rates within 10 years based on time averaged proteinuria by UPCR (95% CI)	
- Large retrospective cohort study - UK national registry of Rare kidney diseases (RaDaR) 2,299 adults and 140 children with biopsy-proven IgAN - Proteinuria > 0.5g/day or eGFR <60ml/min	Median kidney survival 11.4 years (95% CI 10.5-12.5)	<0.44 g/g	0.78 (0.68-0.85)
	Time-averaged proteinuria significantly associated with worse kidney survival and more rapid eGFR loss	0.44 – 0.88 g/g	0.69 (0.56-0.79)
	30% patients with UPCR of <0.88 g/g and 20% patients with UPCR <0.44 developed kidney failure within 10 years	0.88 – 1.76 g/g	0.40 (0.31-0.48)
		≥1.76g/g	0.15 (0.09-0.22)

Patients traditionally regarded as being “low risk”, with UPCR <0.88 g/g also had high rates of kidney failure within 10 years

Note: UPCR of 0.88 g/g (100 mg/mmol) considered comparable with protein excretion of 1 g/day.

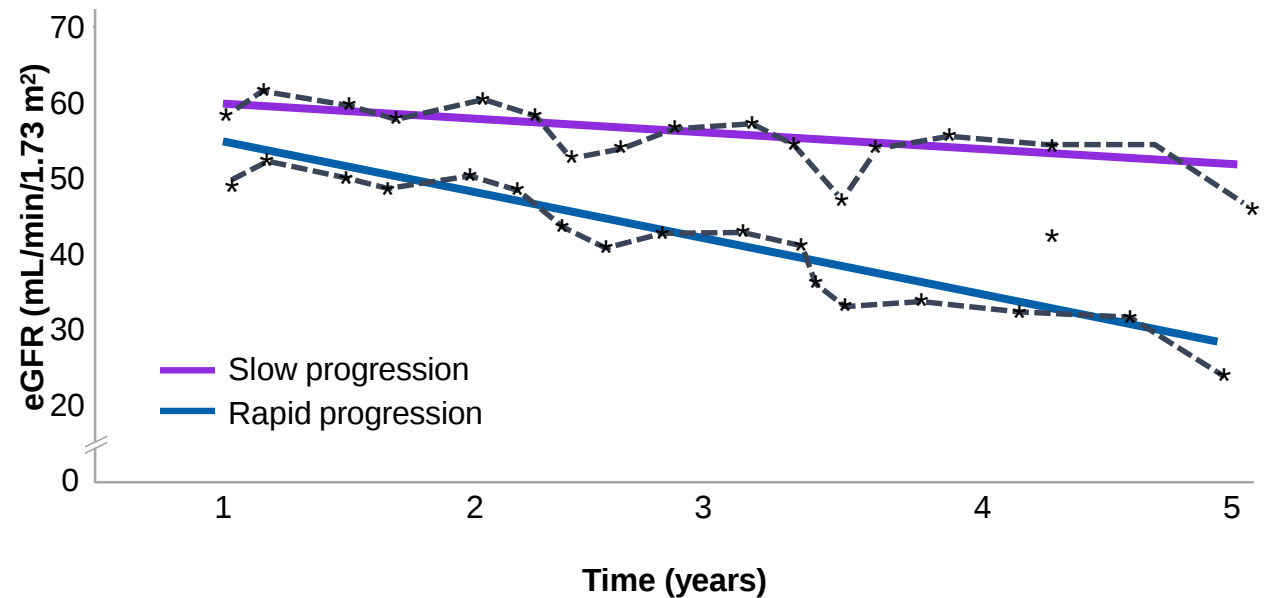
CI, confidence interval; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy. David P et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738.

eGFR is an important prognostic biomarker for IgAN¹

Rapid eGFR decline is defined as a **sustained decrease in eGFR of >5 mL/min/1.73 m²/y²**

Variability in eGFR is associated with kidney failure, CV events, and death and could therefore be an indicator of reduced kidney function/resilience²

eGFR slopes for slow vs rapid progression of CKD³



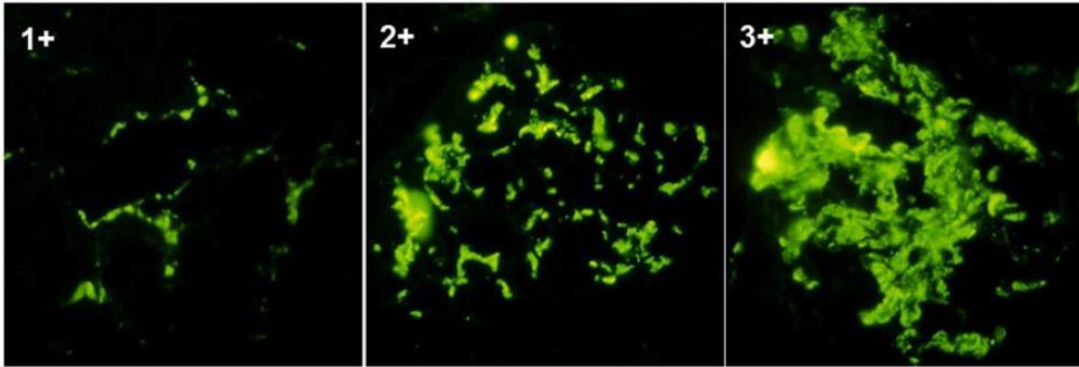
*Data shown are hypothetical values based on common patient presentations.

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy.

1. KDIGO. *Kidney Int* 2021;100:S1–S276; 2. Hirst J, et al. *Br J Gen Pract* 2022, 72(717): e261–e268; 3. Johnson RJ and Rodriguez-Iturbe B. *Nat Rev Nephrol* 2018;14:411–412.

Degree of C3 deposition correlates with kidney injury and morphological lesions

IF staining of mesangial C3 deposition¹



C3 deposition intensity is assessed via immunofluorescence staining of kidney biopsy

Intensity of C3 deposition correlates with more severe pathological lesions and higher MEST-C scores in the Oxford classification³⁻⁵

C3 deposition intensity is associated with various histopathological features²⁻⁵

- Globally sclerosed glomeruli
- Mesangial hypercellularity
- Thickening of Bowman's capsule
- Increased total crescent formation
- Interstitial fibrosis
- Interstitial inflammatory cell infiltration

AP, alternative pathway; C3, complement 3; IF, immunofluorescence; IgAN, immunoglobulin A nephropathy; MEST-C, mesangial [M] and endocapillary [E] hypercellularity, segmental glomerulosclerosis [S], tubular atrophy/interstitial fibrosis [T], cellular/fibrocellular crescents [C].

1. Medjeral-Thomas NR, et al. *Adv Chronic Kidney Dis.* 2020;27(2):111-119. 2. Markowitz G. *Nat Rev Nephrol.* 2017;13:385-386. 3. Roberts ISD. *Nat Rev Nephrol.* 2014;10(8):445-455. 4. Trimarchi H, et al. *Kidney Int.* 2017;91(5):1014-1021. 5. KDIGO. *Kidney Int.* 2021;100(4S):S1-S276.

Glomerular C3 deposition has been proposed to be an independent risk factor for prognosis in IgAN



821 Chinese adult patients with IgAN (biopsy verified)

⊖ C3 negative (n = 156)

⊕ C3 positive (n = 665)

C3^{low}^a (n = 180)

C3^{high}^b (n = 485)



Kidney composite endpoint: Kidney failure,^c 50% reduction in eGFR, kidney transplantation, or death from kidney failure

C3 deposition at the time of kidney biopsy is likely an independent risk factor for IgAN severity and progression¹

	Model 1	Model 2	Model 3
HR	1.822	1.851	1.732
95% CI	1.077, 3.084	1.104, 3.104	1.015, 2.955
P value	.025 ^d	.019 ^d	.044 ^d

Model 1: Sex, age, hemoglobin, uric acid, albumin, serum creatinine, 24-h urinary total protein, C3 deposition

Model 2: Oxford classification, C3 deposition

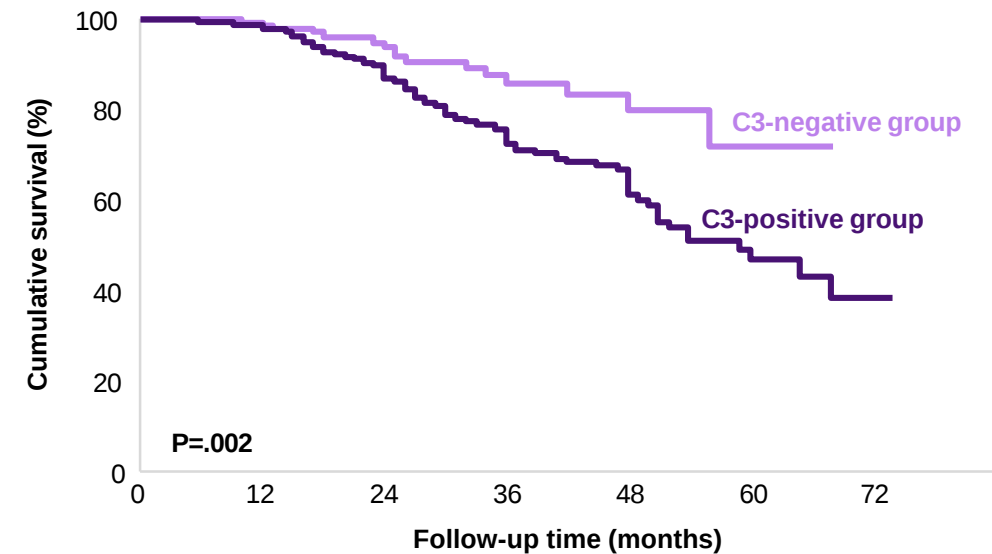
Model 3: Model 1, Oxford classification, treatment, C3 deposition

^aC3 staining intensity grade < 2+; ^bC3 staining intensity grade ≥ 2+; ^cKidney failure was defined as eGFR < 15 mL/min/1.73 m² or dialysis therapy; ^dP < .05 was considered statistically significant.

AP, alternative pathway; C3, complement 3; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IgAN, immunoglobulin A nephropathy.

Xie M, et al. *J Nephrol.* 2023;36:495-505.

Prognosis was significantly worse in patients with IgAN with C3 deposition compared to those without



No. at risk							
C3 positive	665	658	335	147	81	24	5
C3 negative	156	155	99	49	24	5	0

Current Treatment Approach and Unmet Need

Today's Treatment Guidelines
Focus on Supportive Care,
Highlighting the Unmet Need for
Innovative Treatments



KDIGO clinical practice guidelines recommend optimized supportive care for patients diagnosed with IgAN*

Optimized supportive care is the primary focus of management

- BP management
 - Involves initial lifestyle modification followed by medication for persistent hypertension (SBP goal: <120 mmHg)
- Maximally tolerated ACEi/ARB
 - If **proteinuria is >0.5 g/24 h**, initial therapy with either an ACEi or an ARB is recommended, irrespective of whether the patient has hypertension
- Lifestyle modification
 - Dietary sodium restriction
 - Smoking cessation
 - Weight control
 - Exercise
- Assess CV risk and begin appropriate interventions as necessary

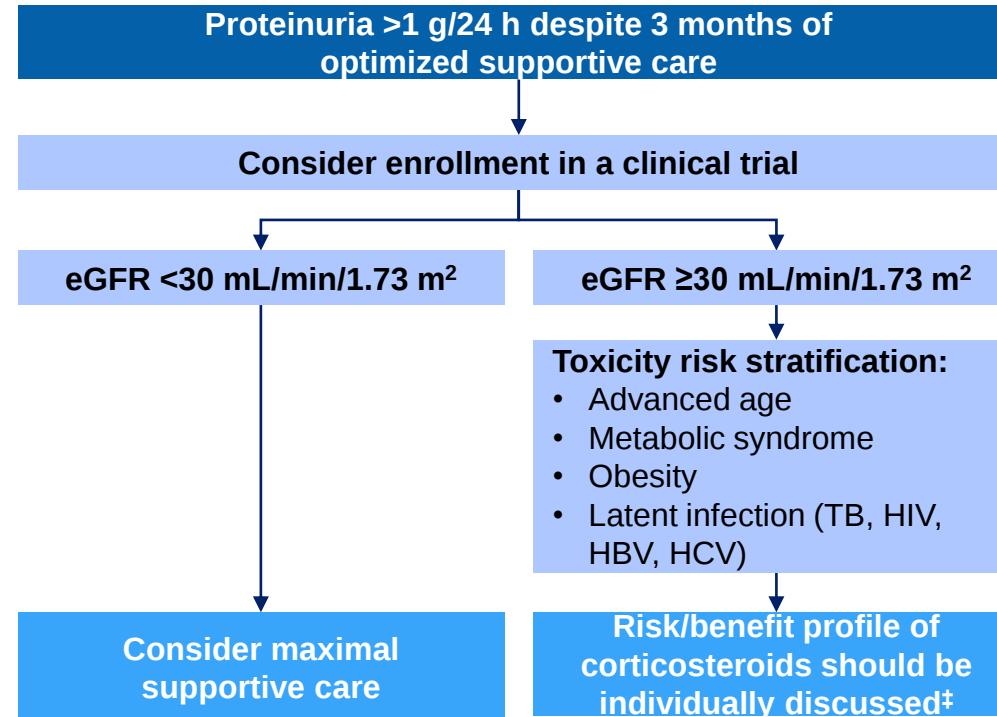
Watch out for KDIGO update in 2024: Empagliflozin/Dapagliflozin (SGLT2i) are indicated for the treatment of CKD and recommended in the KDIGO CKD guideline. *Supportive care* in the upcoming KDIGO Glomerular Disease guideline update in late 2024 might evolve to include additional treatment options such as SGLT2is.

*Excludes variant forms of IgAN who require specific immediate treatment: IgA deposition with minimal change disease; IgAN with acute kidney injury and IgAN with rapidly progressive glomerulonephritis. ACEi, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; BP, blood pressure; CV, cardiovascular; IgAN, immunoglobulin A nephropathy; SBP, systolic blood pressure
KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100(4S):S1–S276.

Treatment options recommended by KDIGO today are limited and participation in a clinical trial should be considered

Not applicable to:

- IgA vasculitis
- IgAN secondary to
 - Viral infection (HIV, hepatitis)
 - Inflammatory bowel disease
 - Autoimmune disease
 - Cirrhosis
 - IgA-dominant post-infectious glomerulonephritis
- Variant forms of IgA[†]
 - IgA deposition with minimal change in disease
 - IgAN with acute kidney injury
 - IgAN with a rapidly progressive glomerulonephritis



Specific populations:

- Japanese – consider tonsillectomy
- Chinese – consider mycophenolate mofetil (MMF) as a corticosteroid-sparing agent

Current 2021 KDIGO guideline does not recommend:

- SGLT2i for IgAN (in the absence of diabetes)
- Nefecon (targeted-release budesonide) or sparsentan

Watch out for KDIGO update in 2024:

Supportive care in the upcoming guideline update might evolve to include recommendation for SGLT2is and, is likely to include guidance on newly approved treatments; sparsentan and nefecon ^{2,3}

*High risk of progressive CKD is defined as proteinuria >0.75–1 g/24 h despite ≥90 days of optimized supportive care. [†]Refer to the guidelines for guidance on treatment for these patients. [‡]the TESTING study showed early evidence of efficacy in patients who had marked proteinuria (2.4 g/day average) at the expense of treatment associated mortality and morbidity.

eGFR; estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis c virus; HIV, human immunodeficiency virus; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease Improving Global Outcomes; TB, tuberculosis.

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100(4S):S1–S276.

1 <https://ir.travere.com/news-releases/news-release-details/travere-therapeutics-announces-fda-accelerated-approval>; 2 <https://www.calliditas.se/en/calliditas-therapeutics-announces-full-fda-approval-of-tarpeyo-the-only-fda-approved-treatment-for-iga-nephropathy-to-significantly-reduce-the-loss-of-kidney-function/>; 3 <https://www.calliditas.se/en/european-commission-approves-kinpeygo-for-adults-with-primary-iga-nephropathy/>

Benefit/risk of corticosteroids (CS) should be carefully assessed be used with caution/avoided in certain populations

Corticosteroids

- Patients at **high risk of progressive CKD** despite ≥ 90 days of optimized supportive care are considered for a **6-month course of corticosteroid therapy**
- Corticosteroids should be used with **extreme caution** or **avoided** in patients with
 - eGFR < 30 mL/min/1.73 m^{2*}
 - Diabetes
 - Obesity (BMI > 30 kg/m²)[†]
 - Latent infections (eg, viral hepatitis, TB)
 - Secondary disease (eg, cirrhosis)
 - Active peptic ulceration
 - Uncontrolled psychiatric illness
 - Severe osteoporosis

Other pharmacologic therapies

- The following therapies are **not recommended**:
 - Antiplatelet agents
 - Anticoagulants
 - Azathioprine
 - Cyclophosphamide
 - Calcineurin inhibitors
 - Rituximab
 - Fish oil
- **Mycophenolate mofetil (MMF)**:
 - In **Chinese patients only** as a steroid-sparing agent
- **Hydroxychloroquine**:
 - In **Chinese patients** who remain at high risk of progression despite optimized supportive care

*The TESTING) study included patients with eGFR 20–30 mL/min/1.73 m², but only 26 patients in total had this range of kidney function. Prespecified subgroup analyses for signals of efficacy and toxicity were underpowered and did not distinguish patients with eGFR < 30 mL/min/1.73 m²; [†]High BMI in TESTING was not specifically considered an exclusion, but the mean BMI was < 24 kg/m²

BMI, body mass index; CKD, chronic kidney disease; CS, corticosteroids; eGFR, estimated glomerular filtration rate; TB, tuberculosis.

KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney Int* 2021;100(4S):S1–S276.

There is an unmet need for a more targeted treatment approach in IgA nephropathy

The heterogeneity in risk of progression poses a significant challenge in the management of IgAN¹



International IgAN Risk Prediction Tool was developed to improve risk prediction for individual patients but cannot be used to guide treatment decisions^{2,3}

- Proteinuria is used to define patients remaining at high risk despite optimized supportive care²
- More specific guidance is needed to further characterize risk of progression, disease severity, and response to treatment and potentially guide treatment decisions in the future²

Current treatment options are not targeted, have limited efficacy, and often come with significant, long-term, life-altering side effects; therefore, KDIGO in 2021 recommended that patients are included in clinical trials³⁻⁷

There is a need for a **more tailored approach** to the treatment of IgAN patients at risk of progression to kidney failure, with effective, well-tolerated, targeted therapies that:⁴

- Help to slow or prevent progression to kidney failure⁸
- Improve quality of life⁹

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

1. Penfold RS, et al. *Int J Nephrol Renovasc Dis* 2018;11:137–148; 2. KDIGO. *Kidney Int* 2021;100:S1–S276; 3. Barbour SJ, et al. *JAMA Intern Med* 2019;179:942–952; ; 4. Reich HN, et al. *J Am Soc Nephrol* 2007;18:3177–3183; 5. Rauen T, et al. *Kidney Int* 2020;98:1044–1052; 6. Wong MG, et al. *Am J Nephrol* 2021;51:827–836; 7. Perkovic V. TESTING presentation at ASN Kidney Week 2021; 8. Xie J, et al. *PLoS One* 2012;7:e38904; 9. National Kidney Foundation. Voice of the Patient 2020.

Future Treatment Approach

Multiple New Entrants to the IgAN
Treatment Landscape Providing
Increasing Choice to Physicians

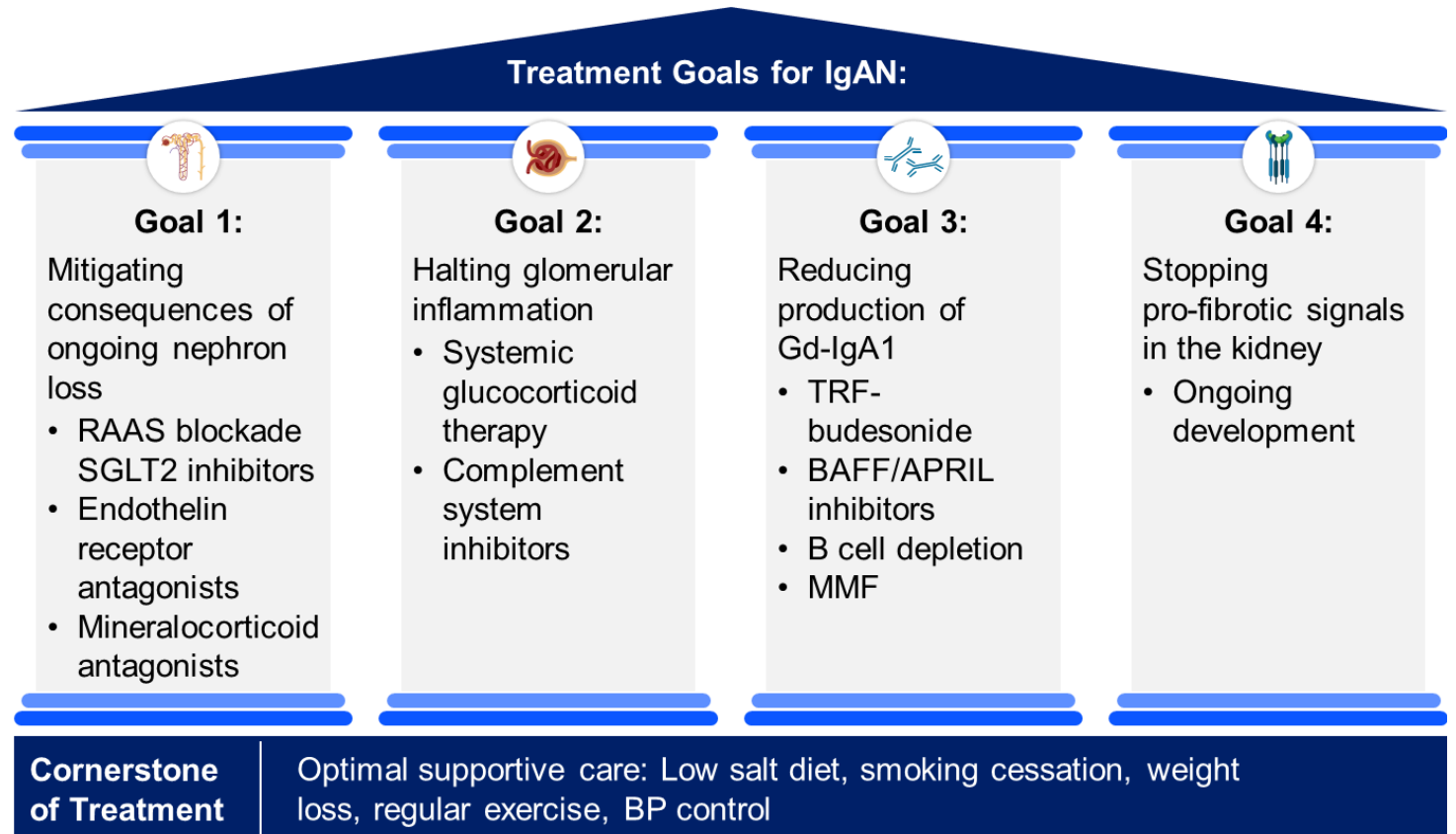


Due to the heterogenous pathophysiology of IgAN a comprehensive approach that addresses various components of pathophysiology is seen as necessary by Nephrologists ...

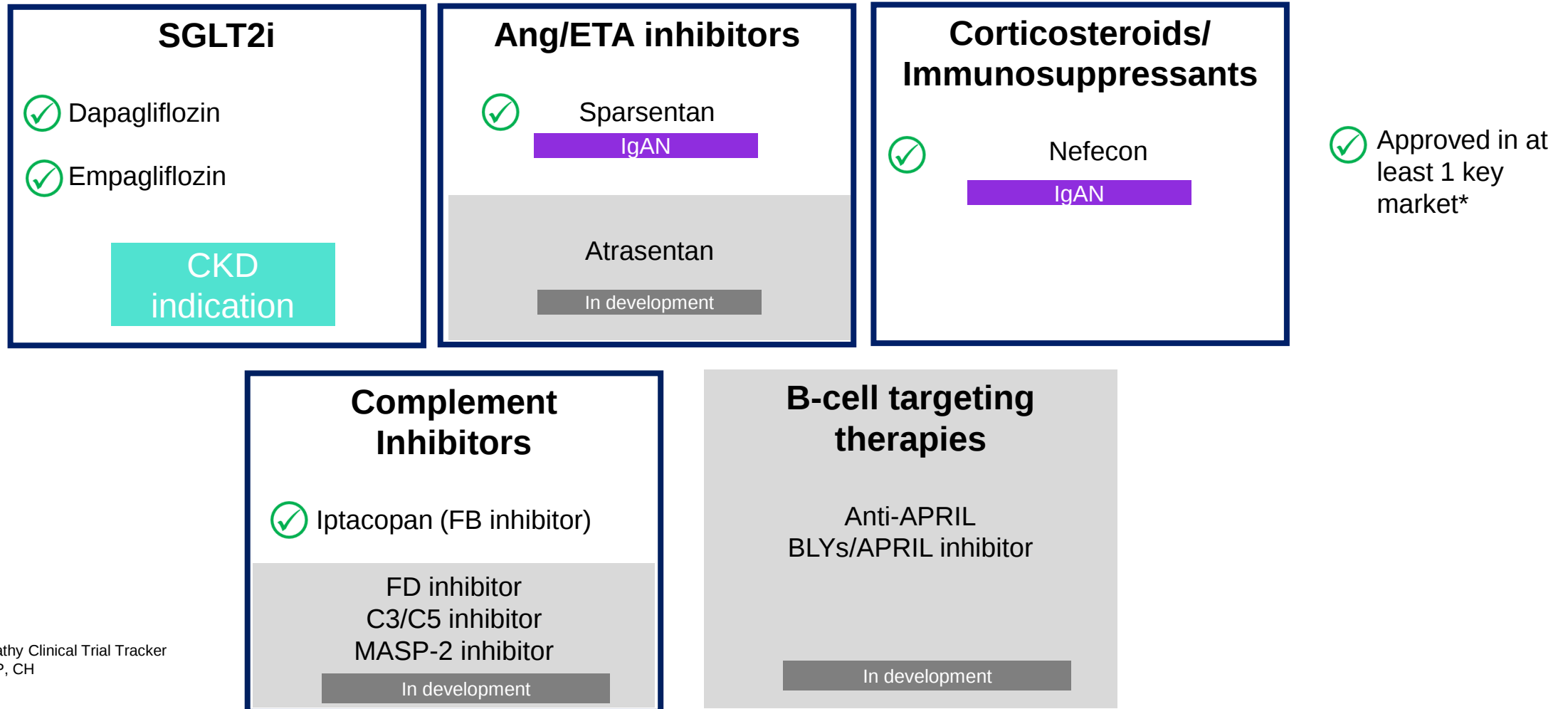
- Evolving treatment landscape will provide **increasing choice** for treating physicians and guidance to inform treatment decisions is needed
- Increasingly important to understand disease pathogenesis
- Treatments will in future be **addressing different parts of the disease** pathogenesis



Proposal to guide treatment choice by Treatment Goal for IgAN¹:



The IgAN treatment landscape is evolving quickly with approval of the first targeted treatments for IgAN



IgA Nephropathy Clinical Trial Tracker
*US, GER, JP, CH

The alternative pathway (AP) is one of three pathways of the complement system^{1,2}

The complement system plays a key role in immunosurveillance and tissue homeostasis¹

INITIATION

Each pathway has a **different triggering mechanism** but **ends** with the **same sequence and effects**^{1,3}

- The CP is triggered by the binding of IgG or IgM to antigens to form an immune complex
- The LP is triggered by binding of mannose-binding lectin to the polysaccharide on the surface of pathogenic bacteria
- The AP is constitutively active at a low level (tick-over)

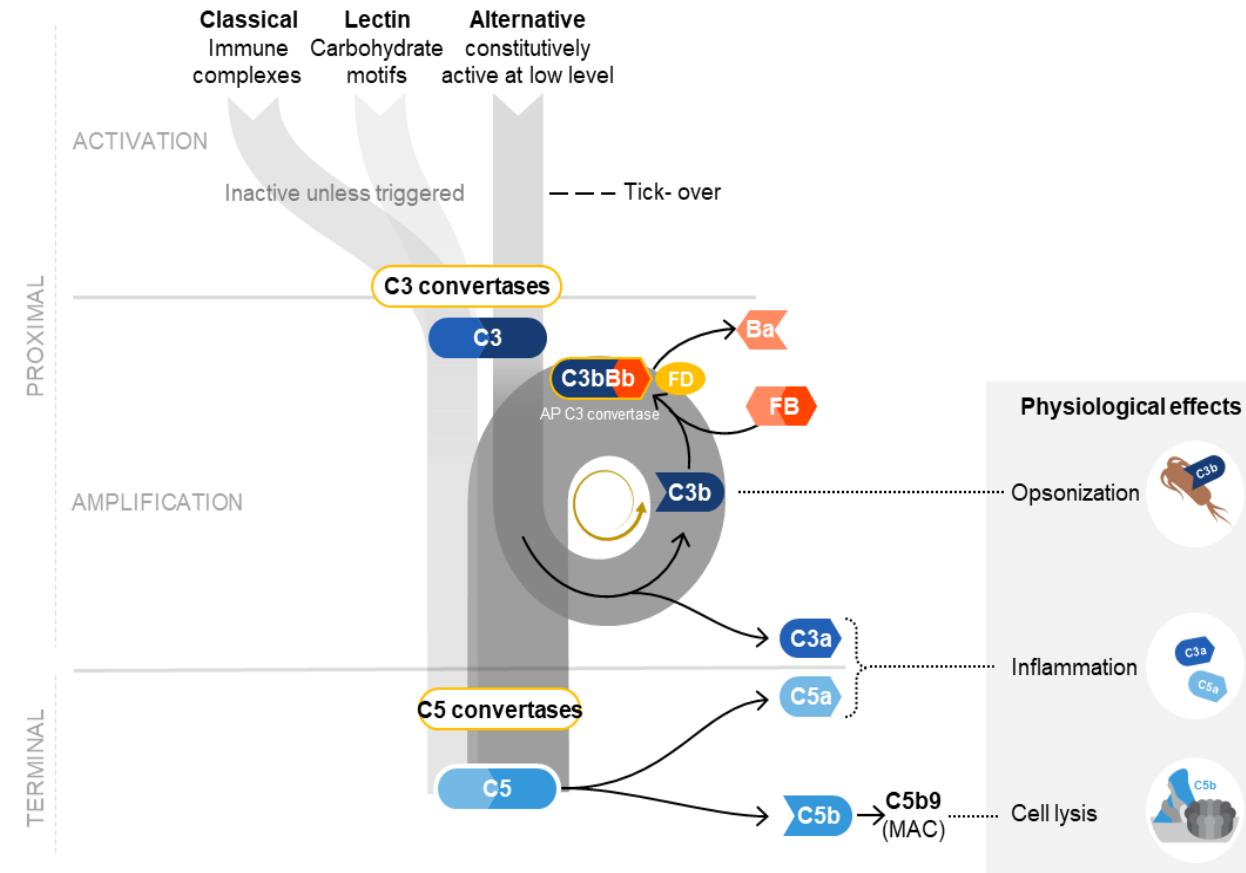
AMPLIFICATION

The AP amplifies signals from the LP and CP through the amplification loop. For example, the AP contributes more than 80% of the terminal complement activity during pathogen recognition^{4,5}

EFFECTORS

Effectors of the complement system are¹:

- **C3b** (opsonization, phagocytosis)
- Anaphylatoxins **C3a** and **C5a** (inflammation and chemotaxis)
- MAC **C5b9** (cell lysis)



AP, alternative pathway; C, complement; CP, classical pathway; Ig, immunoglobulin; IgAN, immunoglobulin A nephropathy; LP, lectin pathway; MAC, membrane attack complex.

1. Rizk DV, et al. *Front Immunol.* 2019;10:504; 2. Schubart A, et al. *Proc Natl Acad Sci.* 2019;116:7926–7931; 3. Bomback AS, et al. *Kidney Int Rep.* 2016;1:148–155; 4. Pandian SRK, et al. *Biotech.* 2020;10:479.

5. Medjeral-Thomas NR, et al. *Adv Chronic Kidney Dis.* 2020;27(2):111-119.

Activation of the kidney ET system drives CKD Progression via the ET_A receptor

- Acidemia
- Ageing
- Aldosterone
- Angiotensin II
- Dyslipidemia

- Growth factors
- Proteinuria
- Oxidative stress

- Vasoconstrictors
- Proteinuria
- Oxidative stress

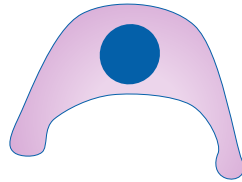
Increased Renal ET-1

ET_A



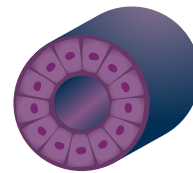
Vasculature

Vasoconstriction
Vascular hypertrophy
Endothelial injury
Coagulation



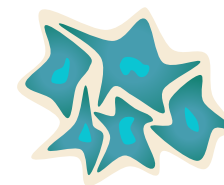
Podocyte

Nephrin shedding
Cytoskeletal disruption
Proteinuria



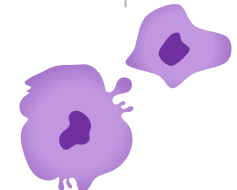
Renal tubule

Tubulointerstitial fibrosis



Mesangium

Mesangial proliferation
Matrix accumulation
Glomerulosclerosis



Inflammatory cell

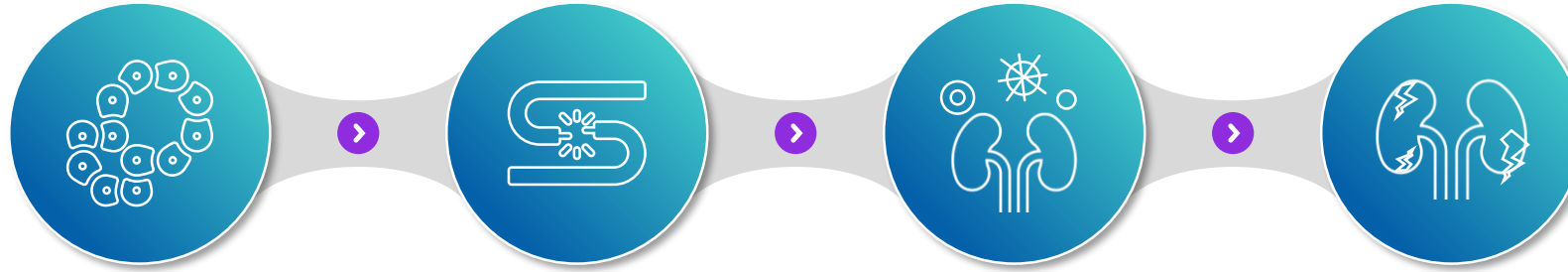
Tissue infiltration
Inflammation

CKD

Figure adapted with permission from Kohan et al. 2014

CKD, chronic kidney disease; ET, endothelin; ET-1, endothelin-1; ET_A, endothelin A.
Kohan DE, et al. *Kidney Int.* 2014;86(5):896-904.

ET_A receptor activation drives IgAN progression via multiple mechanisms

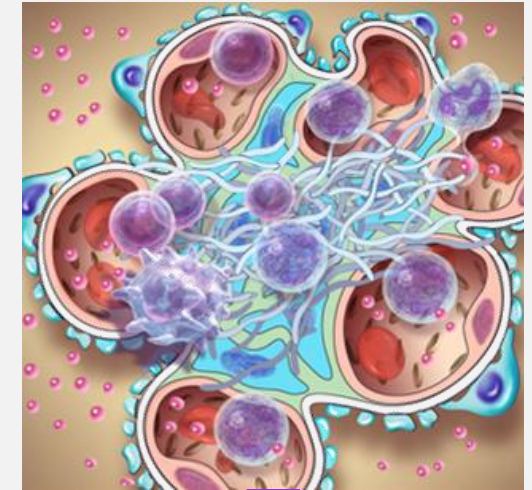


Kidney ET-1 levels elevated in patients with IgAN, with expression of **ET-1 positively correlated with proteinuria**¹⁻³

Activation of the ET system in kidney tissues drives CKD via the **ET_A receptor**^{2,3}

Activation of ET_A drives proteinuria, renal cell injury, and mesangial cell activation, along with promoting kidney inflammation, and fibrosis^{1,3,4}

Occurrence of renal injury, fibrosis and progression to CKD (hallmark characteristics of IgAN)^{1,3}



Hit 4
ET_A receptor activation

- **Blockade of the ET_A receptor with Endothelin A antagonists represent a potential approach to treat patients with IgAN who are at high risk of progression (Hit 4)**

See notes for additional details

CKD, chronic kidney disease; ET, endothelin; ET-1, endothelin-1; ET_A, endothelin A; IgAN, IgA nephropathy.

1. Lehrke I, et al. *J Am Soc Nephrol*. 2001;12(11):2321-29; 2. Zanatta CM, et al. *Ren. Fail.* 2012(34):308-15; 3. Kohan DE, et al. *Kidney Int. Rep.* 2023;8:2198-2210; 4. Tycová I, et al. *Physiol Res*. 2018;67(1):93-105.

Summary

- **IgAN is the most common primary glomerulonephritis globally**, contributing significantly to the global patient burden of CKD and kidney failure^{1–4}; **30% of IgAN patients** with proteinuria >1g/day **progress to kidney failure within 10 years** of diagnosis⁶
- **KDIGO guidelines define high-risk patients as those with proteinuria >0.75–1 g/day despite ≥3 months of optimized supportive care**⁷. Evidence is currently emerging that patients with **proteinuria <1g/day** still have a **significant life-time risk** of progressing to kidney failure⁵

Summary

- IgAN has a **heterogeneous** clinical presentation requiring an **individualized treatment approach**; **proteinuria, persistent microscopic haematuria, rate of eGFR loss** and **MEST-C score** guide treatment decisions^{7–9}
- **A rapidly evolving treatment landscape** with approval of several treatments for IgAN on the horizon will provide physicians and patients with more options and a need to revise current treatment algorithms

Thank You

