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KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV)

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Supplementary material is available online at www.kidney-international.org.

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Reference keys

NOMENCLATURE AND DESCRIPTION FOR RATING GUIDELINE RECOMMENDATIONS

Within each recommendation, the strength of the recommendation is indicated as **Level 1** or **Level 2**, and the certainty of the supporting evidence is shown as **A**, **B**, **C**, or **D**.

	Implications		
Grade	**Patients**	**Clinicians**	**Policy**
Level 1, "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

Practice points are consensus-based statements representing the expert judgment of the Work Group and are not graded. They are issued when a clinical question did not have a systematic review performed, to help readers implement the guidance from graded recommendations (e.g., frequency of monitoring, provision of standard care [such as regular clinic visits], and referral to specialist care), or to issue "good practice statements" when the alternative is considered to be absurd. Users should consider the practice point as expert guidance and use it as they see fit to inform the care of patients. Although these statements are developed based on a different methodology, they should not be seen as less important or a downgrade from graded recommendations.

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health. CKD is classified based on Cause, GFR category (G1–G5), and Albuminuria category (A1–A3), abbreviated as CGA.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min/1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				< 30 mg/g < 3 mg/mmol	30–300 mg/g 3–30 mg/mmol	> 300 mg/g > 30 mg/mmol
	G1	Normal or high	≥ 90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	< 15			

Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk; GFR, glomerular filtration rate.

CONVERSION FACTORS OF CONVENTIONAL UNITS TO SI UNITS

	Conventional unit	Conversion factor	SI unit
Albumin	g/dl	10	g/l
Creatinine	mg/dl	88.4	μmol/l
Creatinine clearance	ml/min	0.01667	ml/s
Cyclosporine	ng/ml	0.832	nmol/l
Mycophenolic acid	μg/ml	3.12	μmol/l
PCR	mg/g	0.113	mg/mmol

PCR, protein-to-creatinine ratio; SI, International System of Units.
Note: Conventional unit × conversion factor = SI unit.

RELATIONSHIP AMONG CATEGORIES FOR ALBUMINURIA AND PROTEINURIA

	Categories		
Measure	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/d)	<30	30–300	>300
PER (mg/d)	<150	150–500	>500
ACR			
(mg/mmol)	<3	3–30	>30
(mg/g)	<30	30–300	>300
PCR			
(mg/mmol)	<15	15–50	>50
(mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to positive	Positive or greater

ACR, albumin-to-creatinine ratio; AER, albumin excretion rate; PCR, protein-to-creatinine ratio; PER, protein excretion rate.
Relationships among measurement methods within a category are not exact. For example, the relationships between AER and ACR and between PER and PCR are based on the assumption that average creatinine excretion rate is ∼1.0 g/d or 10 mmol/d. The conversions are rounded for pragmatic reasons. (For an exact conversion from mg/g of creatinine to mg/mmol of creatinine, multiply by 0.113.) Creatinine excretion varies with age, sex (biological attributes), race and diet; therefore, the relationship among these categories is only approximate. The relationship between urine reagent strip results and other measures depends on the urine concentration.

Abbreviations and acronyms

AAV	antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis
ACEi	angiotensin-converting enzyme inhibitor(s)
AKI	acute kidney injury
ANCA	antineutrophil cytoplasmic antibody
ARB	angiotensin II receptor blocker
CI	confidence interval
CKD	chronic kidney disease
DAPA-CKD	Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease
DEARA	dual endothelin angiotensin receptor antagonist
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA-KIDNEY	The Study of Heart and Kidney Protection With Empagliflozin
ERT	Evidence Review Team
FDA	Food and Drug Administration
GBM	glomerular basement membrane
gd-IgA1	galactose-deficient IgA1
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IgA	immunoglobulin A
IgA-IC	immunoglobulin A–containing immune complex
IgAN	immunoglobulin A nephropathy
IgAV	immunoglobulin A vasculitis
IgAVN	immunoglobulin A vasculitis–associated nephritis
KDIGO	Kidney Disease: Improving Global Outcomes
MCD	minimal change disease
MEST-C	mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]
NEFIGAN	Targeted-release budesonide versus placebo in patients with IgA nephropathy
NefIgArd	Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy
NS	nephrotic syndrome
PCR	protein-to-creatinine ratio
PICOD	Population, Intervention, Comparator, Outcomes, and study Design
PROTECT	A Study of the Effect and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy
RAS	renin-angiotensin system
RASi	renin-angiotensin system inhibitor(s)
RCT	randomized controlled trial
RPGN	rapidly progressive glomerulonephritis
RR	risk ratio
SAE	serious adverse event
SBP	systolic blood pressure
SCr	serum creatinine
SGLT2i	sodium-glucose cotransporter-2 inhibitor(s)
SoF	summary of findings
STOP-IgAN	Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy
TEAE	treatment emergent adverse event
TESTING	Therapeutic Effects of Steroids in IgA Nephropathy Global

Notice

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINE

This Clinical Practice Guideline document is based on literature searches last conducted in April 2023 and updated in August 2024. It is designed to assist decision-making. It is not intended to define a standard of care and should not be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians consider the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Healthcare professionals using these recommendations should decide how to apply them to their own clinical practice.

SECTION II: DISCLOSURE

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise from an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived as or are actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is published in its entirety at the end of this document in the Work Group members' Disclosure section and is kept on file at KDIGO.

Foreword

Kidney International (2025) **108** (Suppl 4S), S1–S71; https://doi.org/10.1016/j.kint.2025.04.004

The mission of Kidney Disease: Improving Global Outcomes (KDIGO) is to "improve the care and outcomes of people with kidney disease worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines." Since the publication in 2008 of the very first KDIGO guideline, devoted to hepatitis C and chronic kidney disease, KDIGO has published guidelines on many distinct topics. The Clinical Practice Guideline for Glomerular Diseases was published in 2021. The guideline chapters covering lupus nephritis and antineutrophil cytoplasmic antibody–associated vasculitis were updated in 2024. The 2025 updates of the Nephrotic Syndrome in Children and the IgA Nephropathy (IgAN) and IgA-associated Vasculitis (IgAV) guidelines reflects the rapid growth of evidence in glomerular diseases in general and in nephrotic syndrome and IgAN in particular. While an updated evidence review was conducted for the chapter dedicated to minimal change disease, no new evidence was identified; therefore, the 2021 chapter is still deemed current and valid.

Frequent updates to guidelines are important as new evidence is published. But frequent updates should not come at the expense of quality. KDIGO continuously strives to maintain the highest standards of excellence and to provide healthcare providers with the most relevant, evidence-based guidance, incorporating both recent advancements and widely accepted clinical standards through a systematic process. As such, the guideline updates include a combination of both graded recommendations and practice points as put forth in the KDIGO Methods Manual. Graded recommendations are based on a systematic review of the evidence and are graded for the strength of the recommendation (Level 1 or Level 2) and certainty of the evidence (A, "high"; B, "moderate"; C, "low"; or D, "very low"). Practice points are ungraded, consensus-based statements representing the expert judgment of the Work Group. Although practice points are issued when there has not been a systematic review, most practice points aim to inform the implementation of graded recommendations; they are often provided in a graphical format. Readers should consider practice points to be expert guidance or "good practice statements" and use them as they see fit to inform the care of patients.

We are very grateful to Jürgen Floege, MD, and Brad H. Rovin, MD, FACP, FASN, for leading this important initiative, and we appreciate the continued dedication of the Work Group members, in particular the lead for this update to the IgAN and IgAV guideline, Jonathan Barratt, MBChB, PhD. Every Work Group member volunteered a considerable amount of time and expertise to the current guideline, which was informed by the independent Evidence Review Team (ERT) from the Brown University School of Public Health led by Ethan M. Balk, MD, MPH, and Craig E. Gordon, MD, MS.

To ensure transparency and rigorous public review during guideline development, the draft of the 2025 update to the IgAN and IgAV guideline was made publicly available for comment in August–September 2024, per KDIGO policy. We very much appreciate the feedback received from the scientific community, which further improved this update. All Work Group members have revised and approved the update for formal release.

In summary, we are pleased to present the KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), reflecting the most recent and up-to-date global evidence for the care of people with these conditions throughout the world. We are thrilled at the pace of scientific advancement and are exceptionally grateful to the Work Group Co-Chairs, Work Group members, the Methods Committee led by Reem A. Mustafa, MD, PhD, MPH, and other contributors to this very important KDIGO activity.

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Abstract

The Kidney Disease: Improving Global Outcomes (KDIGO) 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) represents a focused update of Chapter 2: Immunoglobulin A Nephropathy (IgAN)/ Immunoglobulin A Vasculitis (IgAV) from the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. The aim is to assist healthcare providers caring for people with IgAN or IgAV. The update takes into consideration evidence from randomized controlled trials published through April 2023 and updated in August 2024. As in 2021, this guideline provides guidance related to diagnosis, prognosis, treatment, and special situations. Based on the new evidence, this update is mostly related to the guidance relevant to IgAN. Development of this guideline followed an explicit process of evidence review and appraisal. Treatment approaches and guideline recommendations are based on systematic reviews of relevant studies, and appraisal of the certainty of the evidence and the strength of recommendations following the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach. Limitations of the evidence are discussed, and areas of future research are also presented.

Keywords: evidence-based; glomerular diseases; guideline; IgAN; IgAV; KDIGO; systematic review

CITATION

In citing this document, the following format should be used: Kidney Disease: Improving Global Outcomes (KDIGO) IgAN and IgAV Work Group. KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV). *Kidney Int.* 2025;108(4S):S1–S71.

Summary of recommendation statements and practice points

Immunoglobulin A nephropathy

1.1 Global implementation of the KDIGO 2025 IgAN Guideline

[No recommendations or practice points]

1.2 Diagnosis

Practice Point 1.2.1: **Considerations regarding the diagnosis of immunoglobulin A nephropathy (IgAN):**

- **IgAN can be diagnosed only with a kidney biopsy, as there are no validated serum or urine biomarkers for the diagnosis of IgAN.**
- **To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be considered in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and kidney biopsy is not contraindicated.**
- **Once a diagnosis of IgAN is made, assess for secondary causes.**
- **In cases of primary IgAN, determine the MEST-C (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) score according to the revised Oxford Classification.[3]**

1.3 Prognosis

Practice Point 1.3.1: **Considerations regarding the prognosis of primary IgAN:**

- **Clinical and histologic data at the time of kidney biopsy can be used for risk stratification.**
- **The International IgAN Prediction Tools are a valuable resource to quantify short-term (up to 7 years from kidney biopsy) risk of progression and inform shared decision-making with patients.**
  - **International IgAN Prediction Tool at biopsy – Adults**
  - **International IgAN Prediction Tool post-biopsy – Adults**
  - **International IgAN Prediction Tool at biopsy – Pediatrics**
  - **International IgAN Prediction Tool post-biopsy – Pediatric**
- **The International IgAN Prediction Tools incorporate clinical information at the time of kidney biopsy or at 1 or 2 years post-biopsy (Figure 1).**
- **There are no validated prognostic serum or urine biomarkers for IgAN other than estimated glomerular filtration rate (eGFR) and proteinuria.**

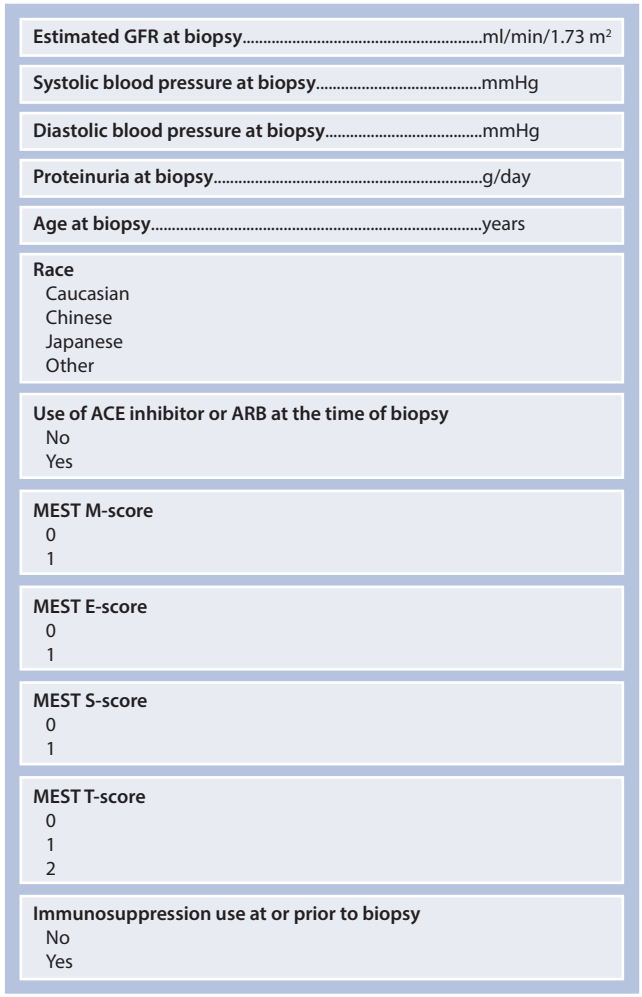

Figure 1 | Data elements included in the International Immunoglobulin A Nephropathy (IgAN) Prediction Tools. Using clinical and histologic data at the time of kidney biopsy, or up to 2 years post–kidney biopsy, users can calculate the risk of a 50% decline in eGFR or kidney failure up to 7 years from kidney biopsy in adults and children. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

Practice Point 1.3.2: The initial assessment of the patient with IgAN is shown in Figure 2.

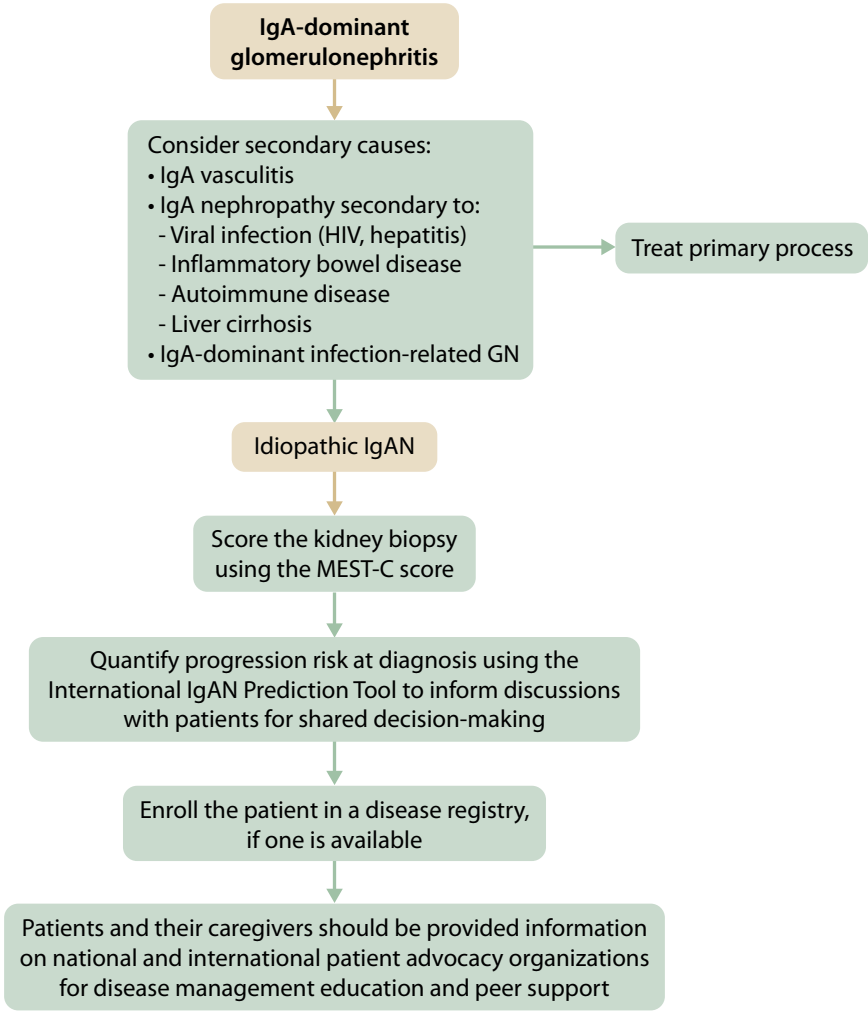

Figure 2 | Initial assessment and management of the patient with immunoglobulin A nephropathy (IgAN). GN, glomerulonephritis; HIV, human immunodeficiency virus; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

1.4 Treatment

1.4.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 1.4.1.1: Because patients with IgAN are at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent) while on or off treatment of IgAN, treatment or additional treatment should be considered in all such cases.

1.4.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 1.4.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to the physiological state (i.e., <1 ml/min/yr for most adults) for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at a minimum of <0.5 g/d (or equivalent), and ideally at <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring, this may not be possible and that multiple treatment strategies, including non-pharmacologic interventions, may be needed to achieve this.

Practice Point 1.4.2.2: Treatment of patients with IgAN who are at risk of progressive loss of kidney function and do not have a variant form (Section 1.5) of primary IgAN (Figure 3):

- **The focus of management in most patients should be to *simultaneously*:**
  - **Prevent or reduce immunoglobulin A–containing immune complex (IgA-IC) formation and IgA-IC–mediated glomerular injury (whether this requires lifelong or intermittent therapy is currently unknown)**
  - **Manage the consequences of existing IgAN-induced nephron loss (likely lifelong)**
- **Reduction or prevention of IgA-IC formation should incorporate treatments that have been proven to reduce pathogenic forms of IgA (commonly measured as galactose-deficient IgA1 [gd-IgA1]).**
- **Prevention of IgA-IC–mediated injury should incorporate treatments with proven anti-inflammatory and/or antifibrotic effects and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA-IC formation.**
- **Management of the consequences of IgAN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction (<2 g/d), smoking and vaping cessation, weight control, and endurance exercise, as appropriate**
  - **Control of blood pressure with a target of ≤120/70 mm Hg**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism, singly or in combination with a sodium-glucose cotransporter-2 inhibitor (SGLT2i)**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as per local guidelines and as necessary**
- **Enrollment in a clinical trial should always be considered for all patients with IgAN. With the increase in the number of newly approved treatments, clinical trial design will need to evolve from the current 2-year, placebo-controlled approach to remain relevant to the changing standard of care for treating IgAN.**

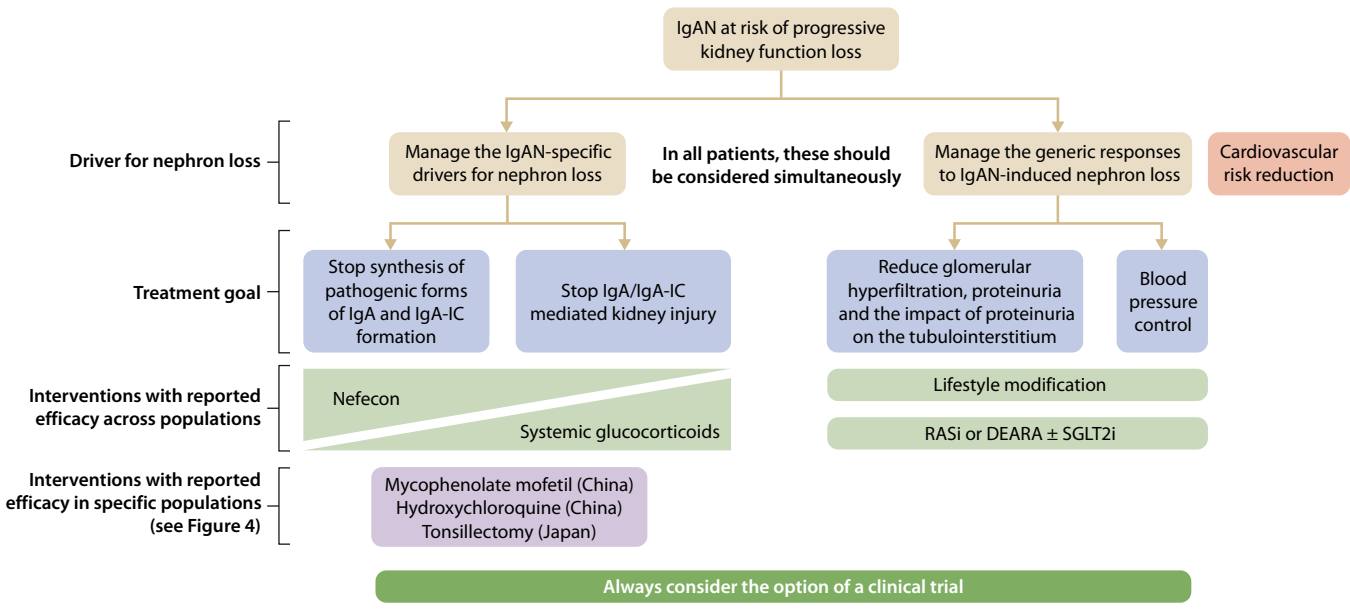

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

Practice Point 1.4.2.3: Treatment selection in IgAN:

- **The key factors to consider when making treatment choices are summarized in Tables 1 and 2.**
- **Issues related to accessibility and affordability of newly approved treatments for IgAN, alongside the requirement for continual or cyclical dosing, mean that it is unlikely that newly approved treatments will be used in resource-limited settings, where cheaper and more easily resourced drugs will be used.**
- **The International IgAN Prediction Tools have not been evaluated as a means of determining the likely impact of any particular treatment regimen and at present should not be used to decide on a specific treatment therapy.**
- **Kidney biopsy features are often used in clinical practice to help inform treatment decisions in IgAN. However, biopsies offer only a snapshot in time of a relatively small sample of tissue, and there are no data from clinical studies that show patients prospectively randomized to particular treatment regimens based on their Oxford Classification MEST-C scores have better clinical outcomes. In particular:**
  - **There is insufficient evidence to base treatment decisions solely on the presence and number of cellular/fibrocellular crescents in the kidney biopsy. Histopathologic features must be interpreted in the context of clinical features, in particular the rate of change in eGFR.**
  - **While it would seem logical that very proliferative or inflammatory lesions may be more amenable to treatment with agents targeting inflammation than lesions with sclerotic or fibrotic changes, this has not been proven in a prospective clinical trial.**
- **Due to the lack of proximate kidney biopsies in all phase 3 clinical trials in IgAN, with many patients undergoing random assignment many years after their biopsy, it is not possible to determine whether any of the new treatments for IgAN should be preferentially selected based on the Oxford Classification MEST-C score or histology in general.**
- **Dynamic assessment of patient risk over time should be performed, as decisions regarding the relative merits of different treatments may change.**

Table 1 | Factors to consider when choosing a treatment and/or treatment combinations for patients with IgAN at risk of progressive loss of kidney function

Question	Considerations
Is the clinical trial population in which the drug was tested representative of the patient being treated (Table 2)?	**Age:** In the trials of SGLT2i, patients were on average 6–8 years older than those recruited into the NefIgArd and PROTECT trials and 15–17 years older than those recruited into the STOP-IgAN and TESTING studies.
	Race: The TESTING study was almost exclusively conducted in Asian patients. STOP-IgAN was exclusively conducted in Caucasians. In the NefIgArd and PROTECT studies, Asian patients were relatively underrepresented compared with those in trials of SGLT2i and systemic glucocorticoids.
	eGFR: In the trials of SGLT2i, the average eGFR at inclusion was 12–14 ml/min per 1.73 m^2 lower than that of patients included in the NefIgArd, PROTECT, STOP-IgAN, and TESTING studies.
	Concomitant medications: In all recent studies in IgAN, patients were required to be on a stable optimized dose of RASi for 90 days prior to enrollment. An optimized maximally tolerated dose was not required in the trials of SGLT2i.
	Optimization of RAS blockade: The only trial to formally up-titrate RASi was the PROTECT trial. In the NefIgArd and TESTING studies, participants were required to be on locally physician-attested, optimized, maximally tolerated dose of RASi.
What is the labeled indication for the drug?	With the new drug approval pathway for IgAN, labeled indications may vary depending on the country and whether the drug has an accelerated approval or conditional market authorization, where assessment of efficacy has been made on the basis of proteinuria, or full approval, based on its effect on the rate of loss of kidney function.
What are the key advantages of the available treatment options?	Nefecon is the only treatment to date proven to reduce the levels of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs).
	Systemic glucocorticoids are highly effective anti-inflammatory drugs, but have no proven impact on levels of pathogenic forms of IgA or IgA-ICs at the doses recommended in this guideline.
	SGLT2i have been shown to not only reduce the rate of progressive loss of kidney function but also reduce the incidence of adverse cardiovascular events, particularly in people with diabetes. They are also generally well tolerated.
	The DEARA sparsentan is the only drug to have shown efficacy beyond the in-trial up-titrated RASi. Of note, more patients were included in the PROTECT trial than in all the trials of RASi in IgAN combined.
	RASi effectively reduce proteinuria and have extensive efficacy and safety data in CKD and cardiovascular disease.
What are the key risks of the available treatment options?	As there is some systemic absorption of budesonide, patients and healthcare providers should be aware of the possibility of some systemic glucocorticoid-related side effects with Nefecon. These are usually mild and reversible upon treatment cessation.
	When using systemic glucocorticoids, a reduced-dose protocol should be followed. Antimicrobial prophylaxis against *Pneumocystis jirovecii* and antiviral prophylaxis in hepatitis B carriers should be used, and the patient should be made aware of the risks of gastrointestinal bleeding, infection, and metabolic, cosmetic, and neuropsychiatric side effects, alongside the potential impact on bone health.
	As with all endothelin receptor antagonists, there is a significant risk of embryofetal toxicity, and women of childbearing potential must use a reliable form of contraception and undergo monthly pregnancy testing.

CKD, chronic kidney disease; DEARA, dual endothelin angiotensin receptor antagonist; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor(s); SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

Table 2 | Baseline characteristics and key inclusion criteria for recently reported trials in IgAN and including trials with significant numbers of patients with IgAN

	DAPA-CKD		EMPA-KIDNEY	NefIgArd		PROTECT		STOP-IgAN		TESTING	
Characteristic	Dapagliflozin (n = 137)	Placebo (n = 133)	Empagliflozin (n = 817)	Nefecon (n = 182)	Placebo (n = 182)	Sparsentan (n = 202)	Irebsartan (n = 202)	Supportive care (n = 80)	Immunosuppression (n = 82)	Methylprednisolone (n = 257)	Placebo (n = 246)
Age inclusion criteria	≥18 years		≥18 years	≥18 years		≥18 years		≥18 years		≥18 years	
Age, years, mean ± SD	52.2 ± 13.1	50.1 ± 13.1	50.6 ± 12.7	Median: 43 (IQR: 36–50)	Median: 42 (IQR: 34–49)	46.6 ± 12.8	45.4 ± 12.1	45.8 ± 12.5	42.8 ± 13.1	Median: 35.6 (IQR: 29.4–46.3)	Median: 36.6 (IQR: 29.0–45.9)
Female sex, n (%)	44 (32.1)	44 (33.1)	282 (34.5)	65 (36)	59 (32)	63 (31)	59 (29)	15 (19)	19 (24)	102 (40)	96 (39)
Race, n (%)											
White	54 (39.4)	54 (40.6)	361 (44.2)	138 (76)	137 (75)	130 (64)	142 (70)	80 (100)	82 (100)	13 (5)	12 (5)
Black	0 (0)	1 (0.8)	1 (0.1)	0 (0)	0 (0)	1 (<1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	82 (59.9)	77 (57.9)	442 (54.1)	43 (24)	40 (22)	67 (33)	48 (24)	0 (0)	0 (0)	244 (95)	233 (95)
Other	1 (0.7)	1 (0.8)	13 (1.6)	1 (1)	5 (3)	4 (2)	10 (5)	0 (0)	0 (0)	0 (0)	1 (<1)
BMI, kg/m^2, mean ± SD	26.3 ± 4.2	27.6 ± 6.1	26.8 ± 5.5	N/A	N/A	N/A	N/A	28.6 ± 5.3	27.0 ± 5.0	Median: 24.2 (IQR: 21.6–26.7)	Median: 24.7 (IQR: 22.0–28.0)
Blood pressure, mm Hg, mean ± SD											
Systolic	127.7 ± 16.2	127.0 ± 13.9	131.8 ± 15.1	Median: 126 (IQR: 121–132)	Median: 124 (IQR: 117–130)	128.0 ± 14.4	129.9 ± 12.4	127 ± 8.5	124 ± 9.7	Median: 123.8 (IQR: 115.0–132.5)	Median: 125.0 (IQR: 115.5–131.0)
Diastolic	78.7 ± 11.8	79.5 ± 10.1	82.5 ± 10.4	Median: 79 (IQR: 76–84)	Median: 79 (IQR: 74–84)	81.6 ± 10.6	83.2 ± 10.6	78 ± 7.0	77 ± 7.0	Median: 80.0 (IQR: 73.5–85.0)	Median: 80.0 (IQR: 74.0–86.0)
eGFR inclusion criteria, ml/min per 1.73 m^2	25–75		≥20 to <45, or ≥45 to <90 and ACR: ≥200 mg/g [20 mg/mmol] or PCR: ≥300 mg/g [30 mg/mmol]	≥35 and ≤90		>30		30–90		≥30 and ≤120	
eGFR, ml/min per 1.73 m^2, mean ± SD	44.3 ± 12.4	43.2 ± 12.0	43.3 ± 17.5	Median: 56.14 (IQR: 45.50–70.97)	Median: 55.11 (IQR: 45.96–67.74)	56.8 ± 24.3	57.1 ± 23.6	57.4 ± 24.9	61.1 ± 29.0	Median: 56.1 (IQR: 43.2–75.0)	Median: 59.0 (IQR: 42.0–77.6)
Urinary ACR inclusion criteria, mg/g	200–5000		See eGFR criteria	N/A		N/A		N/A		N/A	
Urinary ACR, mg/g, median (Q1–Q3)	889.5 (557.5–1472.0)	902.5 (500.5–1633.0)	662 (331–1265)	990 (680–1400)	980 (660–1420)	N/A	N/A	N/A	N/A	N/A	N/A
Urinary protein excretion inclusion criteria	N/A		See eGFR criteria	>1 g/d		>1 g/d		>0.75 g/d		>1 g/d	

(*Continued on following page*)

Table 2 | (Continued) **Baseline characteristics and key inclusion criteria for recently reported trials in IgAN and including trials with significant numbers of patients with IgAN**

	DAPA-CKD		EMPA-KIDNEY	NefIgArd		PROTECT		STOP-IgAN		TESTING	
Characteristic	Dapagliflozin (n = 137)	Placebo (n = 133)	Empagliflozin (n = 817)	Nefecon (n = 182)	Placebo (n = 182)	Sparsentan (n = 202)	Irebsartan (n = 202)	Supportive care (n = 80)	Immunosuppression (n = 82)	Methylprednisolone (n = 257)	Placebo (n = 246)
Urinary protein excretion, g/24 h, median (Q1–Q3)	N/A	N/A	N/A	2.29 (1.61–3.14)	2.17 (1.53–3.39)	1.8 (1.2–2.9)	1.8 (1.3–2.6)	Mean (SD): 1.6 (0.7)	Mean (SD): 1.8 (0.8)	1.99 (1.36–3.09)	1.93 (1.38–2.88)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	58 (7.1)	16 (9)	8 (4)	N/A	N/A	0 (0)	0 (0)	7 (3)	10 (4)
Baseline medication, n (%)											
ACEi	44 (32.1)	41 (30.8)	770 (94.2)	179 (98)	179 (98)	202 (100)	202 (100)	27 (34)	40 (49)	140 (54.5)	128 (52.0)
ARB	89 (65.0)	96 (72.2)						24 (30)	12 (15)	119 (46.3)	120 (48.8)
ACEi + ARB	–	–	–	–	–	–	–	26 (32)	30 (36)		
Levels of RASi as a percentage of the maximum allowable dose at screening, n (%)											
<50%	N/A	N/A	N/A	39 (22)	34 (19)	0	0	N/A	N/A	30 (11.7)	35 (14.2)
>50%	N/A	N/A	N/A	141 (78)	145 (81)	202 (100)	202 (100)	N/A	N/A	222 (86.4)	201 (81.7)
100%	N/A	N/A	N/A	N/A	N/A	130 (64)	125 (62)	61 (76)	58 (71)	N/A	N/A
Immunosuppression	0 (0)	0 (0)	53 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; N/A, not applicable; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PCR, protein-to-creatinine ratio; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; Q1, quartile 1; Q3, quartile 3; RASi, renin-angiotensin system inhibitor; STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

1.4.3 Managing the IgAN-specific drivers of nephron loss

Recommendation 1.4.3.1: We suggest treatment with a 9-month course of Nefecon for patients who are at risk of progressive loss of kidney function with IgAN *(2B)*.

Practice Point 1.4.3.1: Factors to consider before using Nefecon in patients with IgAN:

- **A 9-month treatment course of Nefecon, a targeted-release formulation of budesonide, may not result in a sustained clinical response in terms of proteinuria reduction or eGFR stabilization.**
- **Data on the safety and efficacy of additional courses of Nefecon are awaited.**
- **Nefecon's approval status, labeled indication, and availability vary globally.**

Recommendation 1.4.3.2: In settings where Nefecon is not available, we suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis *(2B)*.

Practice Point 1.4.3.2: Reduced-dose systemic glucocorticoid regimen:

- **Methylprednisolone (or equivalent) 0.4 mg/kg/d (maximum 32 mg/d) for 2 months followed by dose tapering by 4 mg/d each month for a total of 6–9 months.**
- **The conversion of methylprednisolone to commonly used forms of systemic glucocorticoids is as follows: 1 mg of methylprednisolone equals 1.25 mg of prednisone or prednisolone.**
- **Treatment with systemic glucocorticoids should incorporate antimicrobial prophylaxis against *Pneumocystis jirovecii* and antiviral prophylaxis in hepatitis B carriers, along with gastroprotection and bone protection according to national guidelines.**

Practice Point 1.4.3.3: Factors that increase the risk of toxicity of systemic glucocorticoids:

- **eGFR <30 ml/min per 1.73 m^2**
- **Diabetes and prediabetes**
- **Obesity**
- **Latent infections (e.g., viral hepatitis and tuberculosis)**
- **Active peptic ulceration**
- **Uncontrolled psychiatric illness**
- **Osteoporosis**
- **Cataracts**

Practice Point 1.4.3.4: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated, often in small studies in restricted populations, and they failed to show a consistent benefit in IgAN (Figure 4).**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence of efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: The first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m^2) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients.[2] The second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m^2), showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side effects in the combina tion-therapy arm. The third from Guangdong (n=170, eGFR 50 ml/min/1.73 m^2), showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m^2),[5] New York (n=32, eGFR ~39 ml/min/1.73 m^2 and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m^2, MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[8]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4| Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*,[43] [2]Tang *et al.*,[44] [3]Hou *et al.*,[38] [4]Hou *et al.*[45] [5]Maes *et al.*,[46] [6]Frisch *et al*,[47] [7]Hogg *et al.*,[48] [8]Liu *et al.*[49] ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial; SC, standard of care.

Practice Point 1.4.3.5: Tonsillectomy in IgAN:

- **Tonsillectomy alone or with pulsed glucocorticoids may extend kidney survival and increase the likelihoods of partial or complete remission of hematuria and proteinuria based on multiple, mostly retrospective studies from Japan (Supplementary Table S5[50–54]).[40,50–52,54,55]**
- **Tonsillectomy alone or with pulsed glucocorticoids is recommended in the Japanese Society of Nephrology guidelines for the treatment of patients with IgAN.**
- **Tonsillectomy should not be performed as a treatment of IgAN in non-Japanese patients.**

1.4.4 Managing the responses to IgAN-induced nephron loss

Practice Point 1.4.4.1: For lifestyle and blood pressure targets for all patients with IgAN, please refer to Practice Point 1.4.2.2.

Recommendation 1.4.4.1: We recommend that all patients with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) *(1B)*.

Practice Point 1.4.4.2: Factors to consider before using an ACEi or ARB:

- **All patients with IgAN should receive an ACEi or ARB at the maximally tolerated dose, except patients with contraindications such as low blood pressure, bilateral renal artery stenosis, or hyperkalemia, especially due to advanced CKD.**
- **As ACEi or ARB do not mitigate the IgAN-specific drivers of nephron loss, their use should not preclude the concomitant introduction of therapies that target the drivers of IgAN or glomerular inflammation as stated in Section 1.4.3 for patients who will likely benefit from them.**

Recommendation 1.4.4.2: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with sparsentan *(2B)*.

Practice Point 1.4.4.3: Factors to consider before using sparsentan in patients with IgAN:

- **Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a renin-angiotensin system inhibitor (RASi), because sparsentan already combines RASi with an endothelin antagonist in a single molecule.**
- **Sparsentan's approval status, labeled indication, and availability vary globally.**

Recommendation 1.4.4.3: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with an SGLT2i *(2B)*.

Practice Point 1.4.4.4: Factors to consider before using an SGLT2i in patients with IgAN:

- **There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) or the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.**
- **Patients with IgAN included in EMPA-KIDNEY and DAPA-CKD likely had long-standing disease, based on their age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i, especially in younger patients with IgAN and relatively preserved kidney function (eGFR >60 ml/min per 1.73 m^2) (see Table 2).**

1.5 Special situations

Practice Point 1.5.1: IgAN with nephrotic syndrome:

- Rarely, patients with IgAN present with nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).
- In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling minimal change disease (MCD).
- It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.
- Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD in Chapter 5 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[15]
- Patients with nephrotic syndrome whose kidney biopsy has coexistent features of mesangioproliferative glomerulonephritis should be managed in the same way as those who are at risk of progressive loss of kidney function due to IgAN.
- Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (e.g., in obesity and uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.

Practice Point 1.5.2: IgAN with acute kidney injury (AKI):

- AKI can occur in patients with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks of cessation of the hematuria. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.
- IgAN may also present with AKI either *de novo* or during its natural history due to rapidly progressive glomerulonephritis (RPGN), often with extensive crescent formation, commonly in the absence of visible hematuria. When other causes of RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA] –associated vasculitis [AAV] and anti–glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity and common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.

Practice Point 1.5.3: IgAN with RPGN:

- Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of RPGN (e.g., AAV and anti-GBM disease) and reversible causes (e.g., drug toxicity and common pre- and post-kidney causes) have been excluded.
- A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity as well as a high proportion of glomeruli affected by crescents with areas of focal necrosis.
- The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any glomerular filtration rate (GFR) decline. If this occurs, a second kidney biopsy may be considered.
- Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and systemic glucocorticoids in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis.[87]
- Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[15]
- There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.

Practice Point 1.5.4: IgAN and pregnancy planning:

- IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counseling when appropriate.
- Preconception counseling should include a discussion on cessation of RASi, SGLT2i, sparsentan, Nefecon, and systemic glucocorticoids. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.
- In women at risk of progressive loss of kidney function, a trial of treatments to optimally address the immunopathogenesis of IgAN prior to conception may be preferable and should be discussed with patients.
- Neither SGLT2i nor sparsentan should be used while breastfeeding. Enalapril can be used if a RASi is clinically indicated.
- The evidence to date suggests that systemic glucocorticoid use in the first trimester may confer a small increase in the odds of a cleft lip with or without a cleft palate, although data are conflicting, and it is unknown to what extent the underlying maternal disease may contribute. Systemic glucocorticoid use in pregnancy does not increase the risk of preterm birth, low birth weight, or preeclampsia.
- The use of Nefecon in pregnancy is not advised; however, studies examining the use of budesonide by pregnant women with inflammatory bowel disease have not identified any harmful effects. Budesonide has a Food and Drug Administration Pregnancy Category C risk designation, so risk cannot be ruled out.

Practice Point 1.5.5: IgAN in children:

General considerations for children with IgAN

- A more extensive review of the management of IgAN in children can be found in the 2025 International Pediatric Nephrology Association clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis.[1]
- In this guideline, we define children as those aged <18 years, but it is acknowledged that postpubertal children may in some respects have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.
- Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[42]
- Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[41]

Kidney biopsy in children with IgAN

- A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, and normal C3) to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.
- In particular, a kidney biopsy should be performed promptly in children with persistent (>2–3 weeks) or recurrent hematuria and nephrotic-range proteinuria and/or reduced eGFR.[88]
- A kidney biopsy should also be performed in children with persistent or recurrent hematuria and protein-to-creatinine ratio (PCR) >500 mg/g (50 mg/mmol) in ≥2 measurements 1–2 weeks apart.
- In children with persistent or recurrent hematuria and PCR 200–500 mg/g (20–50 mg/mmol) in ≥3 measurements on clear urine 1–2 weeks apart, a kidney biopsy should be considered.
- Inflammation, mesangial cell proliferation, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[89–92]

Treatment of children with IgAN

- There is strong evidence suggesting a benefit of RAS blockade in children.[64] All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>20 mg/mmol) should receive RAS blockade, advice on moderating dietary salt intake below 3–5 g/d, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).

- **It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children and that in children, the use of immunosuppressants is more widespread, particularly the use of systemic glucocorticoids. However, randomized controlled trials and expert consensus–driven indications are lacking.**
- **Evidence derived mostly from retrospective studies suggests that treatment with systemic glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[42,89,91–97]**
- **The risk-benefit balance of glucocorticoid side effects must be considered. Systemic oral glucocorticoids are used in selected settings in children with clinical risk of progression, as evidenced by one of the following: (i) PCR 500–1000 mg/g (50–100 mg/mmol) despite 3–6 months of RASi, (ii) PCR >1000 mg/g (>100 mg/mmol) despite 4 weeks of RASi, or (iii) active MEST-C scores (≥1 of the following scores: M1, E1, S1 with podocyte lesions, and/or C1) and/or PCR consistently (i.e., persisting over 2–3 weeks in ≥2 measurements 1–2 weeks apart) >1000 mg/g (100 mg/mmol) in addition to RAS blockade.**
  - **Duration of treatment is not established, but usually 2 mg/kg/d (maximum 60 mg/m^2/d) of oral prednisone/prednisolone (or equivalent) for a maximum of 4 weeks followed by alternate-day dosing tapered over 5–6 months is given.**
  - **Further extension of the duration may be useful in some cases. Lower doses, such as those emerging from the adult Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) trial (0.4 mg/kg/d of prednisone/prednisolone [or equivalent] for 2 months, tapering over 6 months) should be considered.**
- **Regimens including intravenous methylprednisolone are also used on an individual basis in patients with higher clinical and histologic risk of progression, such as in (i) children with acute onset of IgAN and worsening of kidney function (eGFR <90 ml/min per 1.73 m^2) and/or PCR >1000 mg/g (100 mg/mmol) with active severe MEST-C scores (≥2 of the following scores: M1, E1, S1 with podocyte lesions, and/or C1) or (ii) children with crescentic forms of IgAN (C2).**
  - **In cases with C1 or C2 in the absence of any other MEST-C score >0, the level of proteinuria must be considered.[41,89,91,98]**
  - **In cases with C2, irrespective of proteinuria, treatment of rapidly progressive IgAN is suggested (see below). Dosing regimens may be as follows: 3 methylprednisolone intravenous pulses given at the dose of 15 mg/kg/d each (maximum dose 500 mg) on 3 consecutive or alternate days followed by oral prednisone/prednisolone as indicated above.**
    - **Alternatively, the intravenous pulses can be repeated 3 times at 2-month intervals, with oral prednisone/prednisolone given at 0.5 mg/kg/d for 2 months between pulse cycles for a total of 6 months.[99,100]**
- **Children with IgAN not benefiting from an adequate diet, RAS blockade, and glucocorticoids alone should, whenever possible, be enrolled in clinical trials. Another potential approach in these children is the use of immunosuppressants (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil, or rituximab) in addition to glucocorticoids.**
- **As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children).[100a]**
- **As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with systemic glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.[89,91,101]**

Follow-up of children with IgAN

- **Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2 per day) or PCR ≤200 mg/g (≤20 mg/mmol).**
- **Aim for SBP at <90th percentile for age, sex, and height.**
- **Continue to follow patients after complete remission, as they can relapse even after many years.[102] In particular, yearly monitoring of blood pressure and urinalysis for patients with a history of pediatric IgAN is necessary.**

1.6 Horizon scanning for future new drug approvals and updates to the guideline

[No recommendations or practice points]

Immunoglobulin A vasculitis

1.7 Diagnosis

Practice Point 1.7.1: Considerations for the diagnosis of immunoglobulin A vasculitis (IgAV)–associated nephritis (IgAVN):

- There are no internationally agreed upon criteria for the diagnosis of IgAV in adults.
- In children, a clinical diagnosis of IgAV can be made based on international criteria.[103–105]
- A diagnosis of IgAVN can be made only with a kidney biopsy.
- A kidney biopsy should be performed in adults with suspected IgAV if there are signs of significant end-organ tissue damage: proteinuria ≥0.5 g/d persistent for >4 weeks, kidney function impairment, or RPGN.
- Assess all adult patients with IgAV and IgAVN for secondary causes and for malignancy using age- and sex-appropriate screening tests.

1.8 Prognosis

Practice Point 1.8.1: Considerations regarding the prognosis of IgAVN:

- Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation and hypertension and mean proteinuria during follow-up as predictors of a poor kidney outcome in adults with IgAV.[106–108]
- The use of the Oxford Classification MEST-C score has recently been studied.[109] This showed that E1 lesions were strongly associated with initial improvement followed by progressive decline in kidney function in patients treated with immunosuppression.
- The International IgAN Prediction Tools[12] are not designed to determine the prognosis of IgAVN.

1.9 Treatment

1.9.1 Prevention of nephritis in IgAV

Recommendation 1.9.1.1: We recommend not using systemic glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

Practice Point 1.9.1.1: Considerations for the management of all patients with IgAVN who are at risk of progressive loss of kidney function and do not have RPGN:

- Proteinuria ≥0.5 g/d (while on or off treatment of IgAVN) identifies a patient with IgAVN at increased risk of progressive loss of kidney function.
- The goal for managing IgAVN, like IgAN, should be to ***simultaneously***:
  - Prevent or reduce IgA-IC formation, mesangial deposition, and IgA-IC–mediated glomerular injury
  - Manage the consequences of existing IgAVN-induced nephron loss
- Unlike IgAN, there are no treatments proven to prevent or reduce IgA-IC formation in IgAVN.
- Prevention of IgA-IC–mediated injury should incorporate treatments with proven anti-inflammatory effects and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA-IC formation.
  - In all patients in whom systemic glucocorticoids are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient.
  - In patients who wish to try systemic glucocorticoids, a reduced-dose regimen as described for IgAN should be employed with antimicrobial prophylaxis.
- Management of the consequences of IgAVN-induced nephron loss should include:
  - Lifestyle advice, including information on dietary sodium restriction (<2 g/d), smoking and vaping cessation, weight control, and endurance exercise, as appropriate

- Control blood pressure with a target of ≤120/70 mm Hg using a RASi as the first-choice drug intervention
- Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using RASi and SGLT2i, singly or in combination
- A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary

- Offer participation in a clinical trial if one is available.
- There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in patients with IgAVN.
- There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy.
- The International IgAN Prediction Tools cannot be used to determine the likely impact of any particular treatment regimen.
- Dynamic assessment of patient risk over time should be performed, as decisions regarding immunosuppression may change.

1.10 Special situations

Practice Point 1.10.1: IgAV with RPGN:

- The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.
- Patients agreeing to the treatment should be treated in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis.[87]
- IgAVN with RPGN, as well as other presentations of IgAVN, may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.
- There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role of the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV.[116]

1.10.1 IgAVN in children

Practice Point 1.10.1.1: In this guideline, we define children as those aged <18 years, but it is acknowledged that post-pubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.

Practice Point 1.10.1.2: A more extensive review of the management of IgAVN in children can be found in the 2025 International Pediatric Nephrology Association clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis.[1]

Briefly:

- The majority of children who will develop nephritis do so within 3 months of presentation. Urinary monitoring is necessary at the onset of vasculitis and then at least monthly for ≥6 months from the initial presentation of systemic disease.
- A kidney biopsy should be promptly performed in children with nephrotic-range proteinuria or impaired kidney function (GFR <90 ml/min per 1.73 m^2).
- In children with IgAV and PCR 1000–2000 mg/g (100–200 mg/mmol) for 2–4 weeks or PCR 200–500 mg/g (20–50 mg/mmol) for >4 weeks, a kidney biopsy should be considered.
- In children with confirmed IgAVN, a pediatric nephrologist should be consulted.
- In children with IgAVN and persistent proteinuria for >3 months, ACEi or ARB treatment should be considered.
- There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV and no evidence of kidney involvement or with isolated microhematuria.[117,118]

- **Oral prednisone/prednisolone for 3–6 months or pulsed intravenous methylprednisolone should be considered in children with IgAVN and nephrotic-range proteinuria (PCR >2000 mg/g or 200 mg/mmol) or RPGN and histologic risk of progression (International Study of Kidney Disease in Children [ISKDC] criteria ≥II).**
- **Other immunosuppressive agents in addition to glucocorticoids (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil, or rituximab) should be considered in the following indications: to reduce the glucocorticoid dose and/or if the PCR is >2000 mg/g (200 mg/mmol) and/or if there is insufficient response to glucocorticoids.**
- **Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.**
- **Monitoring children with IgAVN with the evaluation of urinalysis, eGFR, and blood pressure should be considered for ≥5 years after the initial episode. Lifelong monitoring, individualized according to the severity and response to treatment, appears prudent for children who received therapy for their IgAVN.**

Immunoglobulin A nephropathy

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common pattern of primary glomerular disease worldwide and remains a leading cause of chronic kidney disease (CKD) and kidney failure. Although IgAN is characterized by a single histopathologic criterion of predominant or codominant IgA deposits on kidney biopsy, it is now well recognized that this "disease" exhibits marked heterogeneity in its clinical and pathologic features. There is good evidence that the epidemiology, clinical presentation, disease progression, and long-term outcomes of IgAN differ across ethnic populations around the world. IgAN is most prevalent and more likely to cause kidney failure in people of East Asian descent, followed by people of European descent, and is relatively rare in people of African descent. It is unclear whether these observations are due to differences in pathogenesis and/or the contribution of varying genetic and environmental influences.

At the time of diagnosis, the majority of patients will have already suffered significant nephron loss, with an estimated glomerular filtration rate (eGFR) on average between 50 and 60 ml/min per 1.73 m^2. As the average age at diagnosis is between 30–40 years, and typical life expectancy in countries with a high prevalence of IgAN is 70–80 years, there needs to be an immediate focus on the introduction of therapies to preserve all remaining nephrons if kidney failure is to be avoided in the lifetime of the patient.

For the first time, it is now possible to simultaneously target the 2 fundamental drivers of continued nephron loss in IgAN. The first driver comprises the IgAN-specific pathogenic pathways leading to production of pathogenic forms of IgA, the formation of IgA-containing immune complexes (IgA-ICs), glomerular IgA-IC accumulation, and consequent activation of proinflammatory and profibrotic pathways within the kidneys. As with all forms of progressive kidney disease, the second driver comprises the multifaceted intrarenal responses to IgAN-induced nephron loss, including the development of glomerular hypertension/hyperfiltration, the tubulointerstitial response to persistent proteinuria, and the initiation and/or worsening of systemic hypertension.

As most people already have established CKD at the time of diagnosis, a dual approach will most commonly be needed to slow or prevent continued nephron loss. Since the Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, a number of new drugs have been approved in various countries for the treatment of both CKD and IgAN, and over the next 5 years, there are likely to be further drug approvals, offering nephrologists a number of new opportunities to slow or stop the loss of kidney function in IgAN. To be included in this guideline, the data describing clinical trial outcomes must have been published in a peer-reviewed journal, with data publicly available for evaluation at the time of guideline writing.

This guideline makes treatment recommendations for adults with IgAN and provides practice points on how to apply these recommendations to children aged 1–18 years. A more comprehensive review of the management of children with IgAN (and IgA vasculitis) has been produced by the International Pediatric Nephrology Association.[1] Where possible, we have highlighted possible racial differences in response to particular treatment regimens.

IgA vasculitis (Henoch-Schönlein purpura) is discussed later in this guideline.

1.1 Global implementation of the KDIGO 2025 IgAN Guideline

At the time of finalizing this guideline update, a number of new therapies for treating both CKD and IgAN had been approved in a limited number of countries, and these have been included in this guideline update. However, the Work Group acknowledges that cost or limited approval status of these therapies in many resource-poor countries that have a high prevalence of IgAN will mean that many nephrologists will be unable to fully implement the updated KDIGO guideline in their clinical practice.

According to a recent, global survey of nephrologists from low- and middle-resource settings, where >75% of the world's population lives, and where CKD is most prevalent (primarily in Asia, South America, and Africa), <30% of sites enrolled patients with IgAN in clinical trials, and systemic glucocorticoids, which are affordable and widely available, were the most common treatment for patients with IgAN and persistent proteinuria.[2] In Latin America and the Caribbean, only 5 of 33 nations (15%) have sites conducting IgAN clinical trials, highlighting the poor representation of these populations in clinical trial reports. In Asia, only China, Japan, Hong Kong, South Korea, Taiwan, and a small number of Southeast Asian countries have participants in IgAN clinical trials, with poor representation from the Middle East and South Asia, particularly India. IgAN is a highly heterogeneous disease, and a lack of clinical trial data from a large proportion of countries with higher prevalences of IgAN than most resource-rich countries poses challenges for translating the current clinical trial data to a large proportion of the world's at-risk population.

The reasons for lack of clinical trial activity in many resource-limited settings are multifaceted and include a shortage of trained staff and infrastructure, skepticism about the value of clinical trials, and administrative and regulatory barriers. A particular and pressing challenge in many resource-limited settings, including those with patients who participated in clinical trials in IgAN, is that once a clinical trial has completed, sponsors may not prioritize pursuing drug approval or marketing in these regions. This is becoming a

significant disincentive to many investigators from resource-limited settings who question the ethics of exposing patients to therapies that have unknown safety profiles and may not be available or affordable after trial completion.

The guideline Work Group acknowledges the many difficulties faced by low- and middle-resource settings in managing CKD in general and IgAN in particular, including possible lack of access to or interpretation of a kidney biopsy. The global implementation of this guideline will vary from region to region due to differences in drug availability or affordability or healthcare infrastructure. Lack of access to newly approved medications is also a challenge for patients in more traditionally high-resource settings where there is no universal access to subsidized medication funding. The costs may also be prohibitive within socialized healthcare systems struggling to balance the rising costs of managing chronic diseases.

The kidney community must work with healthcare providers, governments, and drug developers to ensure that clinical trials in IgAN are conducted in representative at-risk populations globally and that there is a commitment to make these potentially transformative drugs available to the global population of patients with IgAN.

1.2 Diagnosis

Practice Point 1.2.1: Considerations regarding the diagnosis of immunoglobulin A nephropathy (IgAN):

- **IgAN can be diagnosed only with a kidney biopsy, as there are no validated serum or urine biomarkers for the diagnosis of IgAN.**
- **To ensure an early diagnosis and prompt treatment of IgAN, a kidney biopsy should be considered in all adults with proteinuria ≥0.5 g/d (or equivalent) in whom IgAN is a possible diagnosis and kidney biopsy is not contraindicated.**
- **Once a diagnosis of IgAN is made, assess for secondary causes.**
- **In cases of primary IgAN, determine the MEST-C (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]) score according to the revised Oxford Classification.[3]**

1.3 Prognosis

Several prognostic scores have been developed to assist in predicting kidney outcomes in IgAN. Earlier scoring systems included a variety of pathologic classification schemas in cohorts with uniform racial and geographic origin.[4–9] More recently, the standardized MEST-C histologic score defined by the revised Oxford Classification has been incorporated into the development of prognostic scoring systems[10] and machine learning used to select predictive variables.[11] The largest study to date, with more than 4000 subjects, including sizeable training and validation populations, was used to develop a prognostic score in a multinational and multiracial cohort.[12] The initial prediction tool calculates the risk of a 50% decline in eGFR or progression to kidney failure up to 5 years from kidney biopsy in adults. It incorporates the MEST-C histologic scores and clinical variables measured at the time of kidney biopsy. The prediction tool has been updated for use in children and has also been expanded for use 1 or 2 years after kidney biopsy.[13,14] These tools are available as online calculators to assist in discussions with patients regarding possible outcomes. At present, the tools cannot be used to make inferences about treatment. However, it is envisioned that these tools could be used to aid clinical trial design and analysis in the future. Variables included in the prediction tools are listed in Figure 1.

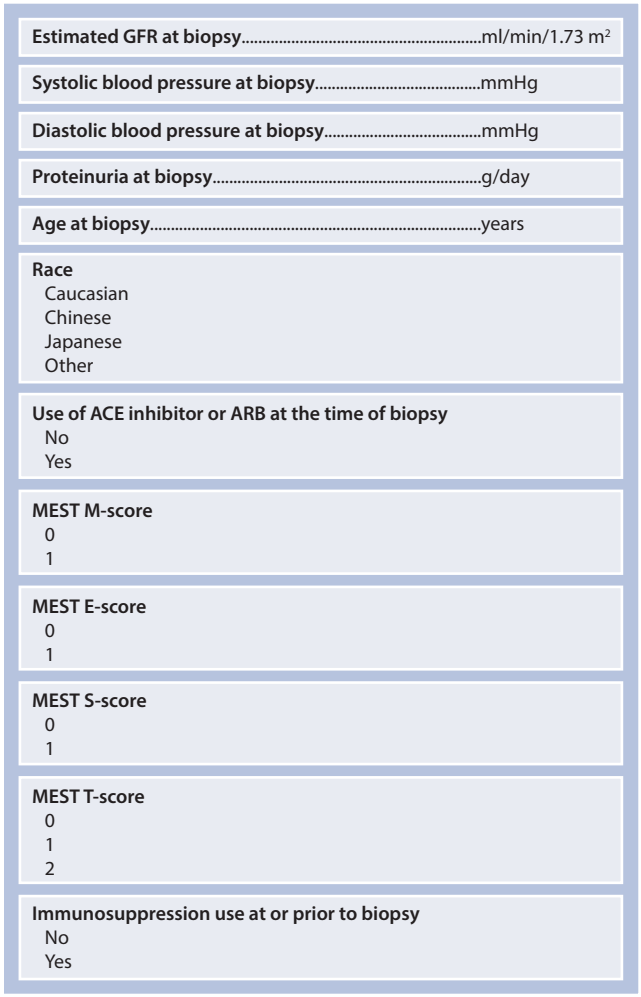

Figure 1 | Data elements included in the International Immunoglobulin A Nephropathy (IgAN) Prediction Tools. Using clinical and histologic data at the time of kidney biopsy, or up to 2 years post–kidney biopsy, users can calculate the risk of a 50% decline in eGFR or kidney failure up to 7 years from kidney biopsy in adults and children. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; MEST, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), and interstitial fibrosis/tubular atrophy (T).

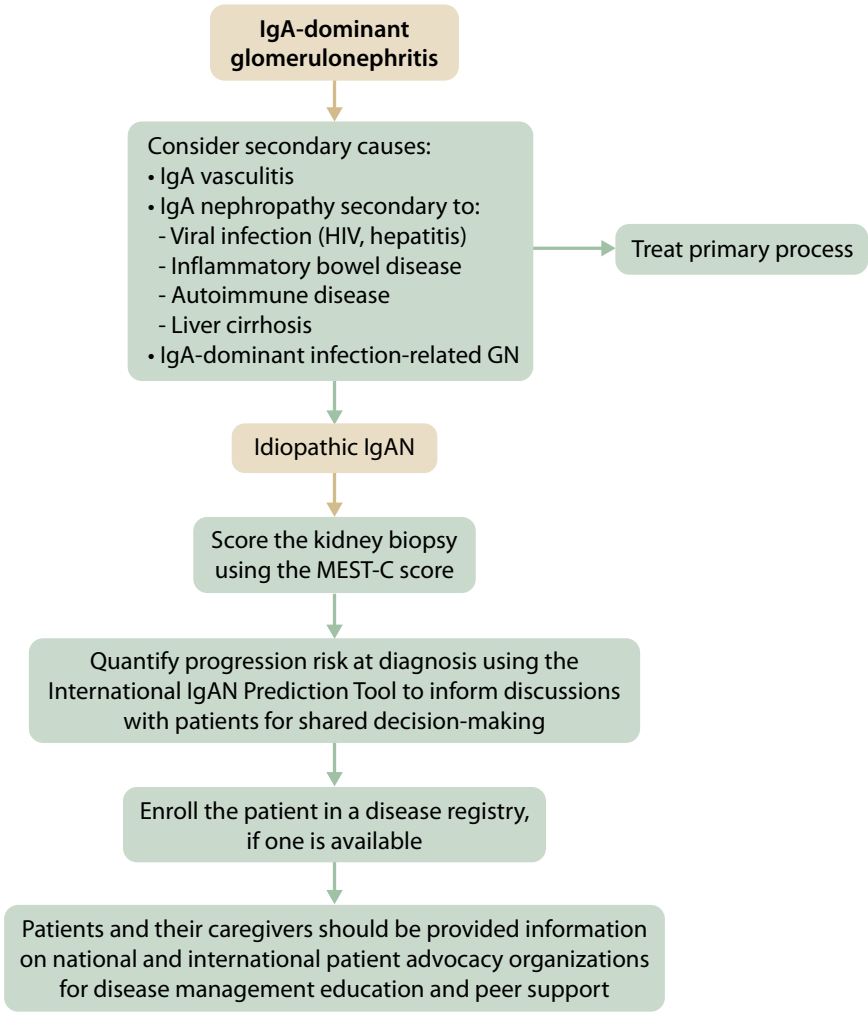

Figure 2 | Initial assessment and management of the patient with immunoglobulin A nephropathy (IgAN). GN, glomerulonephritis; HIV, human immunodeficiency virus; MEST-C, mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S), interstitial fibrosis/tubular atrophy (T), and crescents (C).

Practice Point 1.3.1: Considerations regarding the prognosis of primary IgAN:

- **Clinical and histologic data at the time of kidney biopsy can be used for risk stratification.**
- **The International IgAN Prediction Tools are a valuable resource to quantify short-term (up to 7 years from kidney biopsy) risk of progression and inform shared decision-making with patients.**
  - **International IgAN Prediction Tool at biopsy – Adults**
  - **International IgAN Prediction Tool post-biopsy – Adults**
  - **International IgAN Prediction Tool at biopsy – Pediatrics**
  - **International IgAN Prediction Tool post-biopsy – Pediatric**
- **The International IgAN Prediction Tools incorporate clinical information at the time of kidney biopsy or at 1 or 2 years post-biopsy (Figure 1).**
- **There are no validated prognostic serum or urine biomarkers for IgAN other than estimated glomerular filtration rate (eGFR) and proteinuria.**

Practice Point 1.3.2: The initial assessment of the patient with IgAN is shown in Figure 2.

1.4 Treatment

With the development and recent approval of new therapies for treating IgAN, there has been a fundamental shift in the focus for treating this immune complex–mediated glomerular disease since the publication of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[15] The development of drugs that can target the production of pathogenic forms of IgA and reduce IgA-IC formation means that it is now possible to simultaneously target the 2 fundamental drivers of continued nephron loss in IgAN: (i) IgA-IC–mediated glomerular injury and (ii) the responses in the kidney to IgAN-induced nephron loss. In most countries, a diagnosis of IgAN is made late in the natural history of the disease. Therefore, at the time of presentation, it is essential that both these drivers of continued nephron loss are considered when treatment decisions are being made. In countries with active population-wide urinalysis screening programs (e.g., Japan, South Korea, and Taiwan), identification of patients typically

occurs much earlier in the natural history of the disease where the focus for treatment is likely to be on limiting IgA-IC–mediated glomerular injury rather than on the responses in the kidney to IgAN-induced nephron loss, which have yet to become established.

1.4.1 Defining patients with IgAN at risk of progressive loss of kidney function requiring treatment

Practice Point 1.4.1.1: Because patients with IgAN are at risk of progressive loss of kidney function if they have proteinuria ≥0.5 g/d (or equivalent) while on or off treatment of IgAN, treatment or additional treatment should be considered in all such cases.

The International IgAN Prediction Tools are a valuable resource to quantify short-term (up to 7 years) risk of progression and inform shared decision-making with patients, but they have been validated only for use within the first 2 years of a kidney biopsy. Furthermore, there are no data on what threshold of the short-term risk of kidney disease progression would justify commencement of particular interventions. It is important to realize that even a low risk of kidney failure at 5 years may translate into a very high risk at ≥15 years.[16]

The traditional indicator for identifying patients with IgAN at risk of kidney disease progression requiring treatment throughout most of the natural history of the disease has been the presence of sustained proteinuria. Typically, a threshold of proteinuria of ≥1 g/d has been used to define an increased risk of kidney disease progression[17]; however, there are multiple studies supporting a lower threshold of proteinuria (≥0.5 g/d) as being a biomarker of increased risk of kidney disease progression in IgAN.[16,18,19]

In a study of 1155 Chinese patients, the 10-, 15-, and 20-year cumulative kidney survival rates, calculated using the Kaplan-Meier method, were 83%, 74%, and 64%, respectively, and patients with time-averaged proteinuria <0.5 g/d had higher kidney survival rates relative to those with time-averaged proteinuria 0.5–1.0 g/d (who had a 9.1-fold increased risk of developing kidney failure during follow-up; $P < 0.001$) or those with time-averaged proteinuria >1.0 g/d (who had a 46.5-fold increased risk; $P < 0.001$).[19] A study of the UK National Registry of Rare Kidney Diseases IgAN cohort (2299 adults and 140 children) reported that 30% of patients with time-averaged proteinuria of 0.5–<1.0 g/d and ∼20% of patients with time-averaged proteinuria <0.5 g/d developed kidney failure within 10 years of diagnosis.[16] These data are supported by the European Validation Study of the Oxford Classification of IgA Nephropathy (VALIGA), that included 1147 adults and children with IgAN from 13 European countries, in which there was a significant increase in the risk of a 50% decrease in eGFR and/or kidney failure with increasing time-averaged proteinuria: <0.5 g/d versus 0.5–0.9 g/d ($P < 0.001$); 0.5–0.9 g/d versus 1.0–1.4 g/d ($P = 0.001$); and 1.0–1.4 g/d versus 1.5–1.9 g/d ($P = 0.04$).[18]

These findings, together with the consideration that the average age at diagnosis is between 30–40 years and typical life expectancy in countries with a high prevalence of IgAN is 70–80 years, suggest that a persistent urine protein excretion of ≥0.5 g/d (whether on or off treatment of IgAN) indicates that a person with IgAN is at a significant lifetime risk of progressive loss of kidney function and, ultimately, kidney failure.

It is important to make a distinction between the increased risk of progression relevant in clinical practice (i.e., proteinuria ≥0.5 g/d), in the context of lifetime risk of kidney failure, and the "high risk" of progression (e.g., proteinuria ≥1.0 g/d while on renin-angiotensin system inhibitors [RASi]), typically required for inclusion into clinical trials that are looking for changes in rates of deterioration in kidney function over a short time period (e.g., 2 years) in a relatively small number of study participants. A consequence of conducting short clinical studies is that many people at increased risk of progressive loss of kidney function with IgAN are excluded from clinical trials.

IgAN can be diagnosed only with a kidney biopsy, and a diagnosis of IgAN is required to justify the use of the newly approved therapies as well as those that are likely to be approved in the coming years. Therefore, the threshold to perform a kidney biopsy in an adult with IgAN and signs of end-organ tissue damage (proteinuria, with or without non-visible hematuria, low eGFR, and/or systemic hypertension) should coincide with the proteinuria threshold of ≥0.5 g/d, which delineates a person with IgAN as being at risk of progressive loss of kidney function.

1.4.2 Defining a treatment goal in patients with IgAN at risk of progressive loss of kidney function

Practice Point 1.4.2.1: The treatment goal in patients with IgAN at risk of progressive loss of kidney function is to reduce the rate of loss of kidney function to the physiological state (i.e., <1 ml/min/yr for most adults) for the rest of the patient's life. The only validated early biomarker to help guide clinical decision-making is urine protein excretion, which should be maintained at a minimum of <0.5 g/d (or equivalent), and ideally at <0.3 g/d (or equivalent), accepting that in some patients with extensive kidney scarring, this may not be possible and that multiple treatment strategies, including nonpharmacologic interventions, may be needed to achieve this.

Currently the only validated short-term, modifiable biomarker that informs the future risk of kidney function decline is proteinuria. Regardless of the nature of the intervention, reduction in proteinuria in observational studies has independently been associated with improved kidney outcomes.[20] An individual patient-level meta-analysis of available data from randomized controlled trials (RCTs) has demonstrated an association between treatment effects on proteinuria and treatment effects on kidney survival (composite endpoint of time to doubling of serum creatinine [SCr], kidney failure, or death),[21] thereby

establishing reduction in proteinuria as a reasonably likely surrogate endpoint for a treatment's effect on progression to kidney failure in IgAN.[21]

Increases in proteinuria may be driven both by IgAN-specific immune-mediated drivers of nephron loss and the responses in viable nephrons to IgAN-induced nephron loss (and be positively affected by interventions in both these areas) and by irreversible glomerular scarring and the loss of the protein resorptive capacity of the nephron due to tubular loss (which will not be affected by therapeutic interventions).[22] As such, it is not possible to use proteinuria in isolation to determine which therapeutic approach is required in an individual patient.

There are emerging data suggesting that the kidney function protection associated with proteinuria reduction delivered by drugs that act through a predominant glomerular hemodynamic effect may be different than protection by drugs that act through the reduction of IgA-IC formation.[23–26] Suppressing proteinuria solely through a hemodynamic effect is likely to diminish the ability of proteinuria to reflect ongoing IgA-IC–mediated glomerular injury. This may explain why patients in global cohorts with proteinuria <0.5 g/d, most of whom were on RASi, remained at increased risk of kidney failure.[18,19]

Practice Point 1.4.2.2: Treatment of patients with IgAN who are at risk of progressive loss of kidney function and do not have a variant form (Section 1.5) of primary IgAN (Figure 3):

- **The focus of management in most patients should be to *simultaneously*:**
  - **Prevent or reduce immunoglobulin A–containing immune complex (IgA-IC) formation and IgA-IC–mediated glomerular injury (whether this requires lifelong or intermittent therapy is currently unknown)**
  - **Manage the consequences of existing IgAN-induced nephron loss (likely lifelong)**
- **Reduction or prevention of IgA-IC formation should incorporate treatments that have been proven to reduce pathogenic forms of IgA (commonly measured as galactose-deficient IgA1 [gd-IgA1]).**
- **Prevention of IgA-IC–mediated injury should incorporate treatments with proven anti-inflammatory and/or antifibrotic effects and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA-IC formation.**
- **Management of the consequences of IgAN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction (<2 g/d), smoking and vaping cessation, weight control, and endurance exercise, as appropriate**
  - **Control of blood pressure with a target of ≤120/70 mm Hg**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using renin-angiotensin system (RAS) blockade or dual endothelin angiotensin receptor antagonism, singly or in combination with a sodium-glucose cotransporter-2 inhibitor (SGLT2i)**

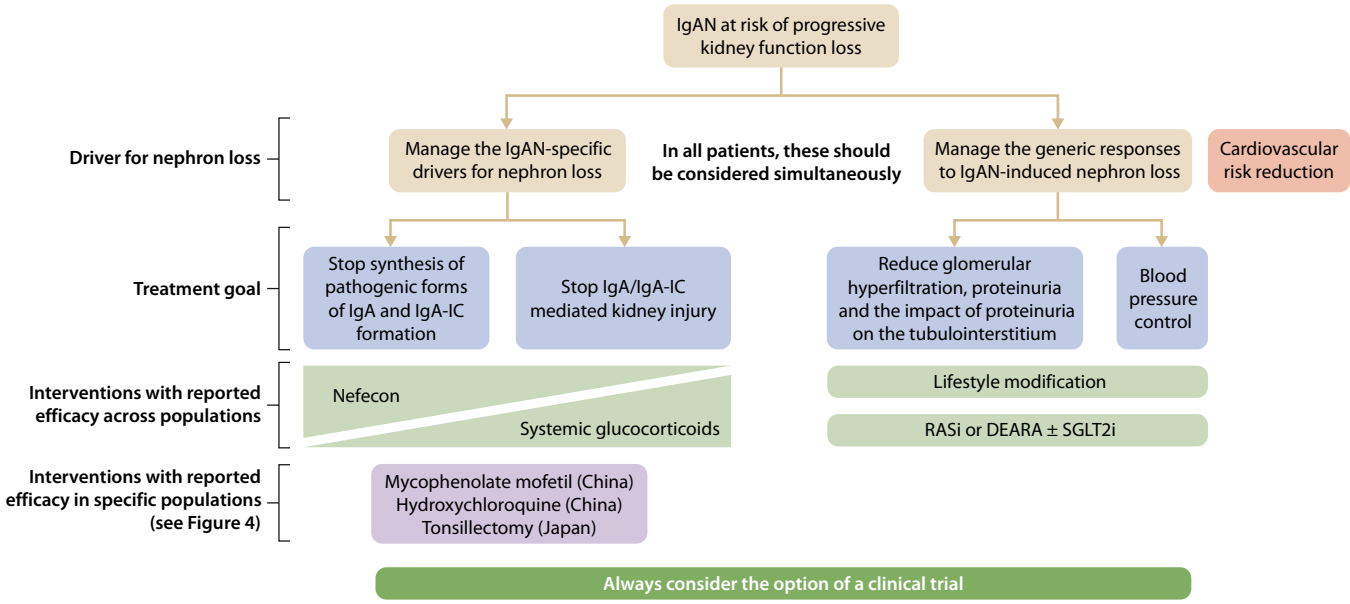

Figure 3 | Treatment targets in immunoglobulin A nephropathy (IgAN) and the positioning of drugs included in this guideline. Reflecting current understanding, Nefecon is shown as having a predominant effect on the production of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs), with an undetermined direct effect of systemically absorbed budesonide on the kidneys. Systemic glucocorticoids have a well-documented anti-inflammatory effect within the kidneys and an undetermined direct effect on the production of pathogenic forms of IgA and IgA-ICs. Strategies to manage the generic response to IgAN-induced nephron loss may also include the use of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors in selected patients. DEARA, dual endothelin angiotensin receptor antagonist; RASi, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

- A thorough cardiovascular risk assessment and commencement of appropriate interventions, as per local guidelines and as necessary
- Enrollment in a clinical trial should always be considered for all patients with IgAN. With the increase in the number of newly approved treatments, clinical trial design will need to evolve from the current 2-year, placebo-controlled approach to remain relevant to the changing standard of care for treating IgAN.

Practice Point 1.4.2.3: Treatment selection in IgAN:

- The key factors to consider when making treatment choices are summarized in Tables 1 and 2.
- Issues related to accessibility and affordability of newly approved treatments for IgAN, alongside the requirement for continual or cyclical dosing, mean that it is unlikely that newly approved treatments will be used in resource-limited settings, where cheaper and more easily resourced drugs will be used.
- The International IgAN Prediction Tools have not been evaluated as a means of determining the likely impact of any particular treatment regimen and at present should not be used to decide on a specific treatment therapy.
- Kidney biopsy features are often used in clinical practice to help inform treatment decisions in IgAN. However, biopsies offer only a snapshot in time of a relatively small sample of tissue, and there are no data from clinical studies that show patients prospectively randomized to particular treatment regimens based on their Oxford Classification MEST-C scores have better clinical outcomes. In particular:
  - There is insufficient evidence to base treatment decisions solely on the presence and number of cellular/fibrocellular crescents in the kidney biopsy. Histopathologic features must be interpreted in the context of clinical features, in particular the rate of change in eGFR.
  - While it would seem logical that very proliferative or inflammatory lesions may be more amenable to treatment with agents targeting inflammation than lesions with sclerotic or fibrotic changes, this has not been proven in a prospective clinical trial.
- Due to the lack of proximate kidney biopsies in all phase 3 clinical trials in IgAN, with many patients undergoing random assignment many years after their biopsy, it is not possible to determine whether any of the new treatments for IgAN should be preferentially selected based on the Oxford Classification MEST-C score or histology in general.
- Dynamic assessment of patient risk over time should be performed, as decisions regarding the relative merits of different treatments may change.

Table 1 | Factors to consider when choosing a treatment and/or treatment combinations for patients with IgAN at risk of progressive loss of kidney function

Question	Considerations
Is the clinical trial population in which the drug was tested representative of the patient being treated (Table 2)?	**Age:** In the trials of SGLT2i, patients were on average 6–8 years older than those recruited into the NefIgArd and PROTECT trials and 15–17 years older than those recruited into the STOP-IgAN and TESTING studies.
	Race: The TESTING study was almost exclusively conducted in Asian patients. STOP-IgAN was exclusively conducted in Caucasians. In the NefIgArd and PROTECT studies, Asian patients were relatively underrepresented compared with those in trials of SGLT2i and systemic glucocorticoids.
	eGFR: In the trials of SGLT2i, the average eGFR at inclusion was 12–14 ml/min per 1.73 m^2 lower than that of patients included in the NefIgArd, PROTECT, STOP-IgAN, and TESTING studies.
	Concomitant medications: In all recent studies in IgAN, patients were required to be on a stable optimized dose of RASi for 90 days prior to enrollment. An optimized maximally tolerated dose was not required in the trials of SGLT2i.
	Optimization of RAS blockade: The only trial to formally up-titrate RASi was the PROTECT trial. In the NefIgArd and TESTING studies, participants were required to be on locally physician-attested, optimized, maximally tolerated dose of RASi.
What is the labeled indication for the drug?	With the new drug approval pathway for IgAN, labeled indications may vary depending on the country and whether the drug has an accelerated approval or conditional market authorization, where assessment of efficacy has been made on the basis of proteinuria, or full approval, based on its effect on the rate of loss of kidney function.
What are the key advantages of the available treatment options?	Nefecon is the only treatment to date proven to reduce the levels of pathogenic forms of IgA and IgA-containing immune complexes (IgA-ICs).
	Systemic glucocorticoids are highly effective anti-inflammatory drugs, but have no proven impact on levels of pathogenic forms of IgA or IgA-ICs at the doses recommended in this guideline.
	SGLT2i have been shown to not only reduce the rate of progressive loss of kidney function but also reduce the incidence of adverse cardiovascular events, particularly in people with diabetes. They are also generally well tolerated.
	The DEARA sparsentan is the only drug to have shown efficacy beyond the in-trial up-titrated RASi. Of note, more patients were included in the PROTECT trial than in all the trials of RASi in IgAN combined.
	RASi effectively reduce proteinuria and have extensive efficacy and safety data in CKD and cardiovascular disease.
What are the key risks of the available treatment options?	As there is some systemic absorption of budesonide, patients and healthcare providers should be aware of the possibility of some systemic glucocorticoid-related side effects with Nefecon. These are usually mild and reversible upon treatment cessation.
	When using systemic glucocorticoids, a reduced-dose protocol should be followed. Antimicrobial prophylaxis against *Pneumocystis jirovecii* and antiviral prophylaxis in hepatitis B carriers should be used, and the patient should be made aware of the risks of gastrointestinal bleeding, infection, and metabolic, cosmetic, and neuropsychiatric side effects, alongside the potential impact on bone health.
	As with all endothelin receptor antagonists, there is a significant risk of embryofetal toxicity, and women of childbearing potential must use a reliable form of contraception and undergo monthly pregnancy testing.

CKD, chronic kidney disease; DEARA, dual endothelin angiotensin receptor antagonist; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; NefIgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; RAS, renin-angiotensin system; RASi, renin-angiotensin system inhibitor(s); SGLT2i, sodium-glucose cotransporter-2 inhibitor(s); STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

Table 2| Baseline characteristics and key inclusion criteria for recently reported trials in IgAN and including trials with significant numbers of patients with IgAN

	DAPA-CKD		EMPA-KIDNEY	NefIgArd		PROTECT		STOP-IgAN		TESTING	
Characteristic	**Dapagliflozin (n = 137)**	**Placebo (n = 133)**	**Empagliflozin (n = 817)**	**Nefecon (n = 182)**	**Placebo (n = 182)**	**Sparsentan (n = 202)**	**Irebsartan (n = 202)**	**Supportive care (n = 80)**	**Immunosuppression (n = 82)**	**Methylprednisolone (n = 257)**	**Placebo (n = 246)**
Age inclusion criteria	≥18 years		≥18 years	≥18 years		≥18 years		≥18 years		≥18 years	
Age, years, mean ± SD	52.2 ± 13.1	50.1 ± 13.1	50.6 ± 12.7	Median: 43 (IQR: 36–50)	Median: 42 (IQR: 34–49)	46.6 ± 12.8	45.4 ± 12.1	45.8 ± 12.5	42.8 ± 13.1	Median: 35.6 (IQR: 29.4–46.3)	Median: 36.6 (IQR: 29.0–45.9)
Female sex, n (%)	44 (32.1)	44 (33.1)	282 (34.5)	65 (36)	59 (32)	63 (31)	59 (29)	15 (19)	19 (24)	102 (40)	96 (39)
Race, n (%)											
White	54 (39.4)	54 (40.6)	361 (44.2)	138 (76)	137 (75)	130 (64)	142 (70)	80 (100)	82 (100)	13 (5)	12 (5)
Black	0 (0)	1 (0.8)	1 (0.1)	0 (0)	0 (0)	1 (<1)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Asian	82 (59.9)	77 (57.9)	442 (54.1)	43 (24)	40 (22)	67 (33)	48 (24)	0 (0)	0 (0)	244 (95)	233 (95)
Other	1 (0.7)	1 (0.8)	13 (1.6)	1 (1)	5 (3)	4 (2)	10 (5)	0 (0)	0 (0)	0 (0)	1 (<1)
BMI, kg/m^2, mean ± SD	26.3 ± 4.2	27.6 ± 6.1	26.8 ± 5.5	N/A	N/A	N/A	N/A	28.6 ± 5.3	27.0 ± 5.0	Median: 24.2 (IQR: 21.6–26.7)	Median: 24.7 (IQR: 22.0–28.0)
Blood pressure, mm Hg, mean ± SD											
Systolic	127.7 ± 16.2	127.0 ± 13.9	131.8 ± 15.1	Median: 126 (IQR: 121–132)	Median: 124 (IQR: 117–130)	128.0 ± 14.4	129.9 ± 12.4	127 ± 8.5	124 ± 9.7	Median: 123.8 (IQR: 115.0–132.5)	Median: 125.0 (IQR: 115.5–131.0)
Diastolic	78.7 ± 11.8	79.5 ± 10.1	82.5 ± 10.4	Median: 79 (IQR: 76–84)	Median: 79 (IQR: 74–84)	81.6 ± 10.6	83.2 ± 10.6	78 ± 7.0	77 ± 7.0	Median: 80.0 (IQR: 73.5–85.0)	Median: 80.0 (IQR: 74.0–86.0)
eGFR inclusion criteria, ml/min per 1.73 m^2	25–75		≥20 to <45, or ≥45 to <90 and ACR: ≥200 mg/g [20 mg/mmol] or PCR: ≥300 mg/g [30 mg/mmol]	≥35 and ≤90		>30		30–90		≥30 and ≤120	
eGFR, ml/min per 1.73 m^2, mean ± SD	44.3 ± 12.4	43.2 ± 12.0	43.3 ± 17.5	Median: 56.14 (IQR: 45.50–70.97)	Median: 55.11 (IQR: 45.96–67.74)	56.8 ± 24.3	57.1 ± 23.6	57.4 ± 24.9	61.1 ± 29.0	Median: 56.1 (IQR: 43.2–75.0)	Median: 59.0 (IQR: 42.0–77.6)
Urinary ACR inclusion criteria, mg/g	200–5000		See eGFR criteria	N/A		N/A		N/A		N/A	
Urinary ACR, mg/g, median (Q1–Q3)	889.5 (557.5–1472.0)	902.5 (500.5–1633.0)	662 (331–1265)	990 (680–1400)	980 (660–1420)	N/A	N/A	N/A	N/A	N/A	N/A
Urinary protein excretion inclusion criteria	N/A		See eGFR criteria	>1 g/d		>1 g/d		>0.75 g/d		>1 g/d	

(*Continued on following page*)

Table 2 | (Continued) **Baseline characteristics and key inclusion criteria for recently reported trials in IgAN and including trials with significant numbers of patients with IgAN**

	DAPA-CKD		EMPA-KIDNEY	NeflgArd		PROTECT		STOP-IgAN		TESTING	
Characteristic	Dapagliflozin (n = 137)	Placebo (n = 133)	Empagliflozin (n = 817)	Nefecon (n = 182)	Placebo (n = 182)	Sparsentan (n = 202)	Irebsartan (n = 202)	Supportive care (n = 80)	Immunosuppression (n = 82)	Methylprednisolone (n = 257)	Placebo (n = 246)
Urinary protein excretion, g/24 h, median (Q1–Q3)	N/A	N/A	N/A	2.29 (1.61–3.14)	2.17 (1.53–3.39)	1.8 (1.2–2.9)	1.8 (1.3–2.6)	Mean (SD): 1.6 (0.7)	Mean (SD): 1.8 (0.8)	1.99 (1.36–3.09)	1.93 (1.38–2.88)
Type 2 diabetes diagnosis, n (%)	24 (17.5)	14 (10.5)	58 (7.1)	16 (9)	8 (4)	N/A	N/A	0 (0)	0 (0)	7 (3)	10 (4)
Baseline medication, n (%)											
ACEi	44 (32.1)	41 (30.8)	770 (94.2)	179 (98)	179 (98)	202 (100)	202 (100)	27 (34)	40 (49)	140 (54.5)	128 (52.0)
ARB	89 (65.0)	96 (72.2)						24 (30)	12 (15)	119 (46.3)	120 (48.8)
ACEi + ARB	–	–	–	–	–	–	–	26 (32)	30 (36)		
Levels of RASi as a percentage of the maximum allowable dose at screening, n (%)											
<50%	N/A	N/A	N/A	39 (22)	34 (19)	0	0	N/A	N/A	30 (11.7)	35 (14.2)
>50%	N/A	N/A	N/A	141 (78)	145 (81)	202 (100)	202 (100)	N/A	N/A	222 (86.4)	201 (81.7)
100%	N/A	N/A	N/A	N/A	N/A	130 (64)	125 (62)	61 (76)	58 (71)	N/A	N/A
Immunosuppression	0 (0)	0 (0)	53 (6.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ACEi, angiotensin-converting enzyme inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; DAPA-CKD, Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; EMPA-KIDNEY, The Study of Heart and Kidney Protection With Empagliflozin; IgAN, immunoglobulin A nephropathy; IQR, interquartile range; N/A, not applicable; NeflgArd, Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy; PCR, protein-to-creatinine ratio; PROTECT, A Study of the Effect and Safety of Sparsentan in the Treatment of Patients With IgA Nephropathy; Q1, quartile 1; Q3, quartile 3; RASi, renin-angiotensin system inhibitor; STOP-IgAN, Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy; TESTING, Therapeutic Effects of Steroids in IgA Nephropathy Global.

1.4.3 Managing the IgAN-specific drivers of nephron loss

The key initiators of nephron loss in IgAN are as follows: (i) production of pathogenic forms of IgA and formation of IgA-ICs; mesangial deposition of these immune complexes and triggering of (ii) inflammatory and (iii) profibrotic responses within the glomerulus. Ultimately, blocking the production of pathogenic IgA would be expected to switch off all downstream pathogenic pathways. However, this is likely to take time and, by the time of presentation, patients may already have significant glomerular inflammation and fibrosis evident in their kidney biopsy.

Recommendation 1.4.3.1: We suggest treatment with a 9-month course of Nefecon for patients who are at risk of progressive loss of kidney function with IgAN *(2B)*.

Practice Point 1.4.3.1: Factors to consider before using Nefecon in patients with IgAN:

- **A 9-month treatment course of Nefecon, a targeted-release formulation of budesonide, may not result in a sustained clinical response in terms of proteinuria reduction or eGFR stabilization.**
- **Data on the safety and efficacy of additional courses of Nefecon are awaited.**
- **Nefecon's approval status, labeled indication, and availability vary globally.**

Nefecon, which localizes release of budesonide to the terminal ileum, is designed to suppress mucosal IgA synthesis by the gut-associated lymphoid tissue and thereby reduce serum levels of pathogenic IgA1 and IgA-IC formations. A single phase 3 RCT of Nefecon in IgAN has been conducted, the Efficacy and Safety of Nefecon in Patients With Primary IgA Nephropathy (NefIgArd) study. Based on the achievement of the primary efficacy endpoint, statistically significant reduction in proteinuria at 9 months of treatment compared with placebo, Nefecon received accelerated U.S. Food and Drug Administration (FDA) approval for use in IgAN in 2021 and conditional market authorization by the European Medicines Agency (EMA) in 2022. The 2-year analysis, including 15 months of follow-up, demonstrated a lower rate of eGFR decline with Nefecon compared with placebo, and Nefecon received full approval by the FDA in 2023. Since then, Nefecon has received approval or is being evaluated for approval in several other countries. Rates of adverse events were low and generally mild to moderate in severity with Nefecon and reversible following cessation of Nefecon, as expected for a locally acting budesonide product.

Key information

Balance of benefits and harms. *Benefits.* In the NefIgArd study, 364 adult patients with IgAN, eGFR 35−90 ml/min per 1.73 m^2, and persistent proteinuria (urine protein-to-creatinine ratio [PCR] ≥0.8 g/g [80 mg/mmol] or proteinuria ≥1 g/24 h), despite physician-attested, optimized RASi use, were randomized (1:1) to receive 16 mg/d of Nefecon or placebo for 9 months, followed by a 15-month observational follow-up period off study drug. Treatment with a 9-month course of Nefecon resulted in a 27% reduction in proteinuria at 9 months compared with placebo on the background of RASi.[27] This was consistent with the proteinuria reduction observed in the phase 2b Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN) trial.[28] Over the 2 years of the NefIgArd study, a 9-month course of Nefecon resulted in statistically significant treatment benefit in kidney function for Nefecon versus placebo (difference: 5.05 ml/min per 1.73 m^2; 95% confidence interval [CI]: 3.24–7.38 ml/min per 1.73 m^2; P <0.0001), with a time-weighted average change of –2.47 ml/min per 1.73 m^2 (95% CI: –3.88 to –1.02 ml/min per 1.73 m^2) reported with Nefecon and –7.52 ml/min per 1.73 m^2 (95% CI: –8.83 to –6.18 ml/min per 1.73 m^2) reported with placebo.[24] After 2 years, the change in eGFR from baseline was –6.11 ml/min per 1.73 m^2 (95% CI: –8.04 to –4.11 ml/min per 1.73 m^2) in the Nefecon group compared with –12.00 ml/min per 1.73 m^2 (95% CI: –13.76 to –10.15 ml/min per 1.73 m^2) in the placebo group. These changes corresponded to a difference in the 2-year total eGFR slope of 2.95 ml/min per 1.73 m^2 per year (95% CI: 1.67–4.58 m^2 per year; P <0.0001) in favor of Nefecon. The time from randomization to confirmed 30% eGFR reduction or kidney failure was significantly delayed with Nefecon versus placebo (hazard ratio: 0.45; 95% CI: 0.26−0.75; P = 0.0014); 12% of patients in the Nefecon group and 21% of patients in the placebo group had a confirmed event.

Harms. During the 9-month treatment period, treatment-emergent serious adverse events (SAEs) were reported in 10% of patients in the Nefecon group and 5% of patients in the placebo group. The most commonly reported treatment-emergent adverse events (TEAEs) during treatment with Nefecon were peripheral edema (17% vs. 4%), hypertension (12% vs. 3%), muscle spasms (12% vs. 4%), acne (11% vs. 1%), and headache (10% vs. 8%). Discontinuations due to TEAEs occurred in 9% of patients in the Nefecon group and 2% of patients in the placebo group. During the 15-month observational follow-up period, the incidence of TEAEs and treatment-emergent SAEs was similar between the groups, and the frequencies of the most commonly reported TEAEs were similar in both treatment groups. Four participants who were prediabetic at baseline and received Nefecon progressed to overt diabetes during the 9-month treatment period.[24]

Certainty of evidence. Moderate certainty of evidence supports the benefits of Nefecon treatment in patients with IgAN, when used together with physician-attested, optimized maximally tolerated RASi (Supplementary Table S4). Two trials—NEFIGAN and NefIgArd—compared Nefecon with placebo for 9 months, during which all patients received physician-attested, optimized maximally tolerated RASi.[24,28] These studies had consistent findings among 480 patients in total. The 2 studies provided high certainty of evidence that

treatment with Nefecon slows eGFR loss (mean difference: 5.4 ml/min per 1.73 m^2) and has a substantial impact on lowering proteinuria (mean difference: 29%) over the 9-months. One of the trials provided moderate certainty of evidence for prevention of eGFR loss, including prevention of kidney failure or eGFR reduction by ≥30%, in addition to reduced proteinuria.[28]

Due to small numbers of events and thus serious imprecision, there is low certainty of evidence that Nefecon may make little or no difference in the risk of severe infections or upper respiratory tract infections.

Values and preferences. The Work Group judged that the majority of patients would place a high value on a treatment that reduces proteinuria, slows the loss of kidney function, and is generally well-tolerated. Healthcare providers should, however, advise patients of the potential adverse events associated with systemic absorption of budesonide before commencing Nefecon.

Resource use and costs. At the time of writing, Nefecon has been approved for use in a limited number of countries that have a high prevalence of IgAN. Furthermore, the cost of Nefecon means it is unlikely to be commonly used in resource-limited settings, and therefore global adoption of this recommendation is likely to be highly variable. Other, less-expensive formulations of budesonide have not been rigorously tested in an RCT setting and therefore cannot be recommended for the treatment of IgAN.

Considerations for implementation. Treatment with Nefecon requires no specific monitoring; however, due to the potential for limited systemic absorption of budesonide, healthcare providers should be aware of the potential for some systemic glucocorticoid-related adverse events. These are commonly mild and reversible on cessation of Nefecon. In people with prediabetes, changes in glycemic control may occur; therefore, during Nefecon treatment, more intensive blood glucose monitoring may be justified. Latent infection (e.g., viral hepatitis and tuberculosis) should be ruled out. An increase in proteinuria and a decline in eGFR were observed on stopping Nefecon treatment. Treatment options include a repeated 9-month cycle or a lower-dose Nefecon maintenance regimen, but to date there are no data on the extended use of Nefecon. Alternatively, patients may benefit from other IgAN treatments or entry into a clinical trial.

Rationale

There is a large body of research evidence supporting a pathogenic link between mucosa-associated lymphoid tissue, and in particular gut-associated lymphoid tissue, and generation of pathogenic forms of IgA and immune complex formation in IgAN.[29]

Both the NEFIGAN and NefIgArd clinical trials showed that 9-month treatment with Nefecon in addition to RASi resulted in a significant reduction in proteinuria, and the NefIgArd trial showed that this proteinuria reduction was associated with an eGFR benefit at 2 years. In a study examining biomarker changes in the NEFIGAN study, 16 mg/d of Nefecon was shown to result in significant reductions in pathogenic forms of IgA (measured as gd-IgA1) and IgA-ICs, alongside a pattern of changes in serum cytokines, chemokines, and markers of lymphocyte activation, consistent with an effect on the intestinal immune network for IgA production.[30]

The beneficial effect on pathogenic forms of IgA and IgA-ICs, urine protein excretion, and the rate of eGFR decline means that Nefecon may modulate the early steps of IgAN pathogenesis. In addition, the adverse effects of Nefecon were generally mild and reversible in the NefIgArd study and consistent with some systemic absorption of budesonide. The implications of this systemic absorption on the modulation of IgAN, and in particular a systemic anti-inflammatory action, are not clear at this time. The Work Group believes that the potential impact of Nefecon early in the immunopathogenesis of IgAN provides a reasonable rationale to consider Nefecon use in the majority of people with IgAN at risk of progressive loss of kidney function. Interrupting disease immunopathogenesis is a goal in managing all immune-mediated glomerular diseases, including IgAN.

The increase in proteinuria and decline in eGFR observed in the NefIgArd trial after cessation of Nefecon suggest that IgAN, like most other immune-mediated glomerular diseases, may likely need longer-term immunomodulation. Whether this means repeated courses of treatment with a specific agent or maintenance treatment, which is often used in other glomerular diseases, remains to be clarified for IgAN.

Recommendation 1.4.3.2: In settings where Nefecon is not available, we suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis *(2B)*.

Practice Point 1.4.3.2: Reduced-dose systemic glucocorticoid regimen:

- **Methylprednisolone (or equivalent) 0.4 mg/kg/d (maximum 32 mg/d) for 2 months followed by dose tapering by 4 mg/d each month for a total of 6–9 months.**
- **The conversion of methylprednisolone to commonly used forms of systemic glucocorticoids is as follows: 1 mg of methylprednisolone equals 1.25 mg of prednisone or prednisolone.**
- **Treatment with systemic glucocorticoids should incorporate antimicrobial prophylaxis against *Pneumocystis jirovecii* and antiviral prophylaxis in hepatitis B carriers, along with gastroprotection and bone protection according to national guidelines.**

Practice Point 1.4.3.3: Factors that increase the risk of toxicity of systemic glucocorticoids:

- **eGFR <30 ml/min per 1.73 m^2**
- **Diabetes and prediabetes**
- **Obesity**
- **Latent infections (e.g., viral hepatitis and tuberculosis)**

- **Active peptic ulceration**
- **Uncontrolled psychiatric illness**
- **Osteoporosis**
- **Cataracts.**

The largest available RCT of systemic glucocorticoids is the Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) study. The 503 participants in this study included patients at high risk of disease progression. Subjects had an average level of proteinuria of 2.46 g/d at randomization, despite optimized supportive care and a mean eGFR of 61.5 ml/min per 1.73 m^2, and 95% were of Asian descent. The full dose of methylprednisolone used in the initial TESTING study protocol was associated with an unacceptable risk of harms, particularly infections. The study had to be paused; a lower dose of methylprednisolone combined with antimicrobial prophylaxis was employed for the remainder of the study. About half of the study participants received the standard full-dose regimen; most of the remainder received a reduced-dose regimen. The reduced dose of methylprednisolone was associated with a significant reduction in the frequency of a 40% eGFR decline, kidney failure, or death due to kidney disease compared with placebo. SAEs were less frequent with reduced-dose methylprednisolone and antimicrobial prophylaxis, with a reduced frequency of infections requiring hospitalization; however, 1 patient died of infection.

Key information

Balance of benefits and harms. *Benefits.* Participants on the reduced-dose methylprednisolone regimen in the TESTING study experienced a significant reduction in the frequency of the composite primary outcome (40% eGFR decline, kidney failure, or death due to kidney disease) compared with those who received placebo (7/121 events vs. 22/120 events; hazard ratio: 0.24; 95% CI: 0.10–0.58; $P = 0.002$).[31] Overall, the mean annual eGFR slope was –0.7 ml/min per 1.73 m^2 per year in the reduced-dose methylprednisolone arm and –3.0 ml/min per 1.73 m^2 per year in the placebo arm (mean difference: 2.3 ml/min per 1.73 m^2 per year; 95% CI: 0.0–4.6 ml/min per 1.73 m^2 per year; $P = 0.05$). The mean between-group difference in total eGFR slope over 3 years calculated using a linear spline model was 2.9 ml/min per 1.73 m^2 per year; 95% CI: 0.6–5.2 ml/min per 1.73 m^2 per year; $P = 0.01$). The mean difference in the reduction in proteinuria and in eGFR from baseline between the 2 groups was –1.15 g/d and 7.9 ml/min per 1.73 m^2 ($P < 0.001$), respectively, at 12 months. Proteinuria and eGFR benefits were lost over time after methylprednisolone was stopped. These data are in contrast to a lack of benefit of systemic glucocorticoids (methylprednisolone, administered intravenously at a dose of 1 g/d for 3 days at the start of months 1, 3, and 5; and prednisolone, administered orally at a dose of 0.5 mg/kg/48 h on the other days) seen in the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy (STOP-IgAN) study in terms of the time to first occurrence of the same composite outcome used in the TESTING study after a median follow-up of 7.4 years (interquartile range: 5.7–8.3 years).[32,33] Two other small studies, published in 2009, included a total of 160 patients; both evaluated an angiotensin-converting enzyme inhibitor (ACEi) with or without prednisone.[34,35] Each of these studies found that individuals treated with prednisone had lower risks of kidney disease progression.

Harms. The TESTING study protocol was revised once it became evident that the use of a higher dose of methylprednisolone (0.6–0.8 mg/kg/d for 2 months, maximum 48 mg/d, tapering by 8 mg/d each month for a total treatment period of 6–8 months) was associated with an unacceptable risk of harm.[36] The number of patients with at least 1 SAE was greater with methylprednisolone versus placebo (11% vs. 3%), mostly due to an excess of hospitalizations (10% vs. 3%) and serious infections (7% vs. 1%).[36] The excess of patients with at least 1 SAE was primarily observed with the full-dose methylprednisolone regimen (16% methylprednisolone vs. 3% placebo) rather than the reduced-dose regimen (5% methylprednisolone vs. 3% placebo). Four SAEs were fatal, all of which were in the methylprednisolone group (1.6%) and infection-related, including 3 in the full-dose protocol (2.2%) and 1 in the reduced-dose protocol (0.8%). In the 3 years of the STOP-IgAN study, more patients in the systemic glucocorticoid group than in the supportive care group had severe infections, impaired glucose tolerance, and a weight gain of >5 kg in the first year of treatment.[32,37]

Certainty of evidence. Moderate certainty of evidence supports the benefits of systemic glucocorticoid therapy, although with low certainty risk of infections (Supplementary Table S6[31–37]). Four trials evaluated various systemic glucocorticoid regimens in patients with IgAN (excluding studies of Nefecon).[33–37] The largest of these, TESTING ($n = 503$), was conducted in a mostly Chinese population (75%, with an additional 19% from South and Southeast Asia). The earlier studies were conducted in more racially diverse populations. Across studies, there was moderate certainty of evidence that systemic glucocorticoid therapy reduces kidney failure (risk ratio [RR]: 0.42; 95% CI: 0.17–1.03; 4 studies), ≥50% loss of glomerular filtration rate (GFR) (RR: 0.62; 95% CI: 0.45–0.84; TESTING study), and doubling of SCr (RR: 0.22; 95% CI: 0.07–0.76; 2 studies), together with high certainty of evidence that systemic glucocorticoid plus supportive therapy reduces annual GFR loss (mean difference: 5.4 ml/min per 1.73 m^2 per year; 95% CI: 2.3–8.6 ml/min per 1.73 m^2 per year; 2 studies). Due to few events and thus serious imprecision, there is very low certainty of evidence regarding the effect of systemic glucocorticoids on all-cause mortality (over an average of about 2.5 years). There is low certainty of evidence that systemic glucocorticoids may increase complete remission (RR: 1.78; 95% CI: 1.09–2.89; with serious inconsistency across 4 trials). There is low certainty of evidence that (reduced-dose) glucocorticoids may increase infections based on the TESTING study (RR: 2.31; 95% CI: 0.61–8.74).

Values and preferences. The Work Group judged that the majority of patients would place a high value on a treatment that reduces proteinuria, slows the loss of kidney function, and is generally well-tolerated. The recommended reduced-dose systemic glucocorticoid regimen combined with appropriate antimicrobial prophylaxis reduced the rates of infection and hospitalization compared with higher-dose regimens in TESTING; however, there was an infection-related death despite these measures. The Work Group notes that the frequent metabolic, cosmetic, and neuropsychiatric complications of systemic glucocorticoid use were not reported in the TESTING study but have been reported in other studies of systemic glucocorticoids in IgAN.[32,37,38] The Work Group felt that these well-known side effects may be reflected in patient preference for therapies other than systemic glucocorticoids if available and accessible. Healthcare providers must engage in a thorough discussion of risks and benefits of systemic glucocorticoids and consider individual patient characteristics that may place them at higher risk of toxicity (see Practice Point 1.4.3.3). Healthcare providers should advise patients that it is likely that repeated cycles of systemic glucocorticoids may be required to maintain disease remission, as an increase in proteinuria and decline in eGFR were observed upon stopping methylprednisolone in the TESTING study.

Resource use and costs. Systemically acting glucocorticoids are included in the World Health Organization Model List of Essential Medicines (2019[39]) and are generally readily accessible and inexpensive in all countries where there is a high prevalence of IgAN. Consequently, their use is likely to be higher in resource-limited settings where access to newly approved therapies is likely to be limited.

Considerations for implementation. Healthcare providers should provide an individualized assessment of patient risk of progression and risk of treatment-emergent toxicity with systemic glucocorticoids. Healthcare providers may choose not to consider systemic glucocorticoids as a treatment option in patients having particular clinical characteristics placing them at higher risk of treatment-emergent toxicity (see Practice Point 1.4.3.3), especially if there are other options readily available and accessible. Healthcare providers should consider that, similar to Nefecon, there was an increase in proteinuria and a decline in eGFR after methylprednisolone was stopped in the TESTING study. The increase in proteinuria and decline in eGFR observed after cessation of methylprednisolone suggest that IgAN, like most other immune-mediated glomerular diseases, may likely need longer-term immunomodulation. Whether this means repeated courses of treatment with a specific agent or maintenance treatment as used in other glomerular diseases remains to be clarified for IgAN. Repeated courses of systemic glucocorticoids, even at the reduced dose used in TESTING, will put patients at risk of long-term complications from systemic steroid exposure, such as bone disease and metabolic syndrome, in addition to the acute metabolic, cosmetic, and neuropsychiatric side effects.

Rationale

An initial series of small, placebo-controlled RCTs supported greater reduction in proteinuria with systemic glucocorticoids compared with supportive therapy alone, with or without the uniform use of RASi.[40–42] However, the confidence in estimates of efficacy and toxicity for these studies is low due to small sample size. While the STOP-IgAN study, conducted in White Europeans, failed to show a benefit of systemic glucocorticoids (or combination immunosuppression) on GFR endpoints,[32,33] the larger TESTING study, conducted in an almost exclusively Asian population, did show a significant reduction in the frequency of the composite primary kidney outcome (40% eGFR reduction, kidney failure, or death due to kidney disease) with methylprednisolone.[31] The baseline characteristics of patients included in the 2 trials are different (see Table 2), and this may account for the differences in the rates of eGFR loss from baseline during the trial periods in the 2 studies and the reported efficacies of systemic glucocorticoids.

Although the data from TESTING showed a convincing short-term benefit of systemic glucocorticoids in IgAN, several factors contributed to the Work Group recommendation that Nefecon be considered a first choice for IgAN treatment. An important concern was the lack of population diversity in TESTING and discrepancies with other trials of systemic glucocorticoids in IgAN. Furthermore, while there is little doubt that systemic glucocorticoids are effective anti-inflammatory agents, their effectiveness in modulating the early steps in the immunopathogenesis of IgAN remains to be determined. The Work Group believes that reducing levels of pathogenic forms of IgA and IgA-IC is a desirable goal for an IgAN treatment. Finally, the well-described multiple acute and chronic side effects of systemic glucocorticoids was felt to be something most patients would like to avoid, if possible.

The Work Group does, however, acknowledge that in many parts of the world, systemic glucocorticoids may be the only available option for most patients.

Practice Point 1.4.3.4: Other pharmacologic therapies evaluated in IgAN:

- **Multiple agents have been evaluated, often in small studies in restricted populations, and they failed to show a consistent benefit in IgAN (Figure 4).**

Agent	Suggested usage	Remarks
Antiplatelet agents	Not recommended	No evidence of efficacy
Anticoagulants	Not recommended	No evidence of efficacy
Azathioprine	Not recommended	No evidence of efficacy as monotherapy or when combined with glucocorticoids
Cyclophosphamide	Not recommended	Unless in the setting of rapidly progressive IgAN
Calcineurin inhibitors	Not recommended	No evidence of efficacy
Rituximab	Not recommended	No evidence of efficacy
Fish oil	Not recommended	Patients who wish to take fish oil should be advised of the dose and formulation used in the published clinical trials that reported efficacy.
Mycophenolate mofetil (MMF)	**Chinese patients** In those patients in whom glucocorticoids are being considered MMF may be used as a glucocorticoid-sparing agent	Three RCTs have been conducted in China: The first from Hong Kong (n=40, eGFR ~51 ml/min/1.73 m^2) showed a significant reduction in time-averaged proteinuria after MMF (1.5 to 2.0 g/day for 6 months) was added to SC in patients with proteinuria >1 g/d.[1] An extended 6-year follow-up showed a lesser slope of eGFR decline and lower probability of reaching kidney failure in MMF-treated patients.[2] The second from around Jiangsu (n=176, eGFR >90 ml/min/1.73 m^2), showed that MMF with low-dose glucocorticoids (0.4–0.6 mg/kg/d prednisone) for 6 months was non-inferior to standard-dose glucocorticoids (0.8–1.0 mg/kg/d) for the treatment of incident IgAN presenting with proliferative histologic lesions (E or C lesions with or without necrosis) on kidney biopsy and proteinuria >1.0 g/d.[3] There were significantly fewer glucocorticoid-related side effects in the combina tion-therapy arm. The third from Guangdong (n=170, eGFR 50 ml/min/1.73 m^2), showed that MMF (initially, 1.5 g/d for 12 months, maintained at 0.75–1.0 g/d for at least 6 months) and SC reduced the frequency of the primary composite outcome (doubling of serum creatinine, kidney failure, or death due to kidney or cardiovascular causes, aHR 0.23; 95% CI, 0.09–0.63) and CKD progression (aHR 0.23; 95% CI, 0.1–0.57) compared to SC alone.[4] MMF was well tolerated in all the 3 trials.
	Non-Chinese patients There is insufficient evidence to support the use of MMF	In three smaller RCTs of MMF in non-Chinese patients there was no evidence for efficacy of MMF monotherapy: these were from Belgium (n=34, inulin clearance ~71 ml/min/1.73 m^2),[5] New York (n=32, eGFR ~39 ml/min/1.73 m^2 and required glomerulosclerosis or tubulointerstitial atrophy and fibrosis on kidney biopsy reflecting relatively advanced CKD already)[6] and US/Canada (n=44, eGFR >90 ml/min/1.73 m^2, MMF versus omega-3 fatty acid).[7]
Hydroxychloroquine	**Chinese patients** In those patients who remain at high risk of progression in spite of optimized supportive care	In a small, short-term RCT conducted in China, hydroxychloroquine introduced to patients with proteinuria of 0.75–3.5 g/d despite optimized ACEi/ARB reduced proteinuria by 48% versus 10% in the placebo group at 6 months.[8]
	Non-Chinese patients There is insufficient evidence to support the use in those patients	Hydroxychloroquine has not been evaluated in non-Chinese patients.

Figure 4| Other pharmacologic therapies evaluated in immunoglobulin A nephropathy (IgAN). [1]Tang *et al.*,[43] [2]Tang *et al.*,[44] [3]Hou *et al.*,[38] [4]Hou *et al.*[45] [5]Maes *et al.*,[46] [6]Frisch *et al*,[47] [7]Hogg *et al.*,[48] [8]Liu *et al.*[49] ACEi, angiotensin-converting enzyme inhibitor; aHR, adjusted hazard ratio; ARB, angiotensin II receptor blocker; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial; SC, standard of care.

Practice Point 1.4.3.5: Tonsillectomy in IgAN:

- **Tonsillectomy alone or with pulsed glucocorticoids may extend kidney survival and increase the likelihoods of partial or complete remission of hematuria and proteinuria based on multiple, mostly retrospective studies from Japan (Supplementary Table S5[50–54]).[40,50–52,54,55]**
- **Tonsillectomy alone or with pulsed glucocorticoids is recommended in the Japanese Society of Nephrology guidelines for the treatment of patients with IgAN.**
- **Tonsillectomy should not be performed as a treatment of IgAN in non-Japanese patients.**

1.4.4 Managing the responses to IgAN-induced nephron loss

Progressive and significant nephron loss from any cause leads to the initiation and propagation of a characteristic pattern of initially adaptive but ultimately maladaptive responses within the remaining nephrons, which accelerates further nephron loss.[56] In addition, proteinuria that develops as a consequence of glomerular injury potentiates further nephron loss through direct activation of, and ultimately damage to, tubular epithelial cells by promoting tubulointerstitial inflammation and fibrosis.[57] These processes are compounded by an increased risk of systemic hypertension, and collectively these responses result in a significantly increased risk of cardiovascular disease.[58]

Practice Point 1.4.4.1: For lifestyle and blood pressure targets for all patients with IgAN, please refer to Practice Point 1.4.2.2.

Recommendation 1.4.4.1: We recommend that all patients with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) *(1B)*.

Practice Point 1.4.4.2: Factors to consider before using an ACEi or ARB:

- **All patients with IgAN should receive an ACEi or ARB at the maximally tolerated dose, except patients with contraindications such as low blood pressure, bilateral renal artery stenosis, or hyperkalemia, especially due to advanced CKD.**
- **As ACEi or ARB do not mitigate the IgAN-specific drivers of nephron loss, their use should not preclude the concomitant introduction of therapies that target the drivers of IgAN or glomerular inflammation as stated in Section 1.4.3 for patients who will likely benefit from them.**

This recommendation is based on an extensive body of evidence in proteinuric CKD, showing that treatment with RASi reduces the risk of progression to kidney failure. Data specifically in IgAN, while not extensive, are consistent with these observations. In the judgment of the Work Group, a Level 1 recommendation is warranted because of the consistency of the benefits for RASi across the spectrum of kidney diseases, the generally low risk of harm for RASi, and the lack of rationale for a different recommendation for IgAN specifically.

Key information

Balance of benefits and harms. *Benefits.* Epidemiologic studies of large IgAN cohorts in North America, Asia, and Europe consistently identify sustained increases in proteinuria as an independent risk factor for progression in IgAN.[17–19] Retrospective data from large registries show that people with IgAN treated with an ACEi have a lower rate of annual loss of kidney function than similar patients not treated with ACEi or angiotensin II receptor blocker (ARB).[17] A meta-analysis of 8 trials involving 866 patients with CKD evaluated the antiproteinuric effect of ARB in people who were normotensive with proteinuria. Compared with a control group, the use of an ARB was associated with a significant reduction in urine protein excretion in patients either with diabetes and moderately increased albuminuria or without diabetes and nephropathy with overt proteinuria. This effect was consistently seen in both Western and Asian populations.[59] Included in this meta-analysis was a small study in IgAN that included 32 people who were normotensive, aged 18–54 years, with proteinuria (1–3 g/d) and normal kidney function (creatinine clearance >80 ml/min) and who were randomly divided into 4 treatment groups: verapamil 120 mg/d, trandolapril 2 mg/d, candesartan cilexetil 8 mg/d, and placebo.[60] The antiproteinuric response in the trandolapril and candesartan cilexetil groups were similar (–38% vs. –40%) and significantly greater than that of verapamil (P <0.01). An RCT of 44 people with IgAN demonstrated a benefit of an ACEi (enalapril) on progressive kidney disease (better kidney survival and reduced proteinuria) compared with equivalent blood pressure control with alternative antihypertensive medications (nifedipine, amlodipine, atenolol, diuretics, and doxazosin).[17] An RCT of 109 Asian patients with IgAN showed greater proteinuria reduction and less kidney deterioration with an ARB (valsartan) compared with placebo.[61] In an individual participant-level meta-analysis of data for 830 patients from 11 RCTs, a reduction in proteinuria was associated with a lower risk of doubling of SCr, kidney failure, or death in IgAN, and this was consistent across studies.[20] This effect was independent of the presence or absence of hypertension. Reducing proteinuria also reduces cardiovascular risk in general populations with CKD.[62,63]

Harms. There is no evidence that the harms (e.g., angioedema, orthostatic hypotension, and adverse drug reactions) are different for people with IgAN compared with those experienced by people with other forms of CKD, and there is some evidence that they are similar. In normotensive people, RASi should be initiated cautiously, and we outline a potential approach in the section on *Considerations for implementation*.

Certainty of evidence. Moderate certainty of evidence supports the benefits of reduction in proteinuria with RASi for slowing of kidney disease progression in patients with IgAN. There is high-certainty evidence to support the benefits of

reduction in proteinuria for slowing of kidney disease progression in all populations with CKD.[81] The Work Group believes that there is no *a priori* reason to suspect that the larger body of evidence is not generalizable to people with IgAN. Limited data specific to patients with IgAN provide low certainty of evidence of clinical effects of RASi and low-to-moderate certainty of evidence on improvements in intermediate outcomes (Supplementary Table S7[53,60,61,64]). One study provided low certainty of evidence of no effect of RASi on kidney failure or doubling of SCr in patients with IgAN, but with a very imprecise estimate due to a small number of events (RR: 0.25; 95% CI: 0.03–2.21).[61] Another small study provided low certainty of evidence of no effect on complete remission of proteinuria, again with imprecision (RR: 5.29; 95% CI: 0.27–102.49).[64] However, 3 studies provided moderate certainty of evidence that RASi leads to decreases proteinuria (mean difference: −0.73 g/24 h; 95% CI: −1.06 to −0.39 g/24 h) and low certainty of evidence that RASi may contribute to maintaining creatinine clearance, with imprecision (mean difference: 7.0 ml/min; 95% CI: −0.6 to 14.5 ml/min).[60,61,64]

Values and preferences. The Work Group judged that most patients would place a higher value on the potential benefits of antiproteinuric treatment than on the potential harms associated with treatment. However, younger patients with low or normal blood pressure may place a lower value on the potential benefits of RASi due to the risk of orthostatic hypotension.

Resource use and costs. According to the World Health Organization Global Health Observatory data repository, ACEi are widely, but not uniformly, available in areas with high IgAN prevalence.[65] It is important to note, however, that in some countries, the use of RASi in patients who are normotensive but have proteinuria is widely implemented but not always supported by health insurers.

Considerations for implementation. When commencing RASi in patients who are normotensive, it is imperative that patients are started on low-dose therapy and that dose escalation is controlled, with the aim for the patient to be treated with the maximally tolerated dose of either ACEi or ARB to achieve the maximal benefit to proteinuria level while minimizing side effects, in particular orthostatic hypotension. The maximally tolerated dose will often be less than the recommended maximal dose. There are no RCT data available on the efficacy or safety of dual blockade with an ACEi and ARB in IgAN. A *post hoc* analysis of the STOP-IgAN study demonstrated no additional benefit with dual blockade.[66]

Rationale

The bulk of the evidence reviewed suggests that the use of RASi to control blood pressure and proteinuria in patients with proteinuric CKD provides benefits for long-term kidney survival.[67–75] Although there are fewer trials specifically in patients with IgAN, there is general support for the value of RASi in IgAN. While 2 trials suggest no benefit of RASi for patients with IgAN in terms of kidney failure, doubling of SCr, or complete remission based on low-certainty evidence,[61,64] these studies, along with an additional study,[60] provide moderate-certainty evidence that RASi leads to decreased proteinuria in patients with IgAN. Also relevant to the use of RASi in patients with IgAN for whom any of the new drugs may be considered is that all the IgAN trials required adding novel therapies to a background of RASi. Whether novel therapies need to always be used with RASi remains an open question that is important given that this combination of therapies currently forms the basis of regulatory approvals.

Recommendation 1.4.4.2: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with sparsentan *(2B)*.

Practice Point 1.4.4.3: Factors to consider before using sparsentan in patients with IgAN:

- **Sparsentan is a dual endothelin angiotensin receptor antagonist (DEARA) and should not be prescribed together with a renin-angiotensin system inhibitor (RASi), because sparsentan already combines RASi with an endothelin antagonist in a single molecule.**
- **Sparsentan's approval status, labeled indication, and availability vary globally.**

This recommendation is based on a single global, randomized, double-blind, and active comparator clinical trial undertaken in 406 patients with IgAN at risk of progressive loss of kidney function, despite physician-attested, optimized maximally tolerated RASi, where the effect of sparsentan 400 mg on proteinuria and eGFR slope was compared with that of irbesartan 300 mg over 2 years. Based on the primary efficacy endpoint of a reduction in proteinuria at 9 months of treatment compared with irbesartan, sparsentan received accelerated FDA approval for use in IgAN in 2023 and conditional market authorization by the EMA in 2024. The full 2-year study demonstrated that treatment with sparsentan led to a lower rate of eGFR decline compared with irbesartan.

Key information

Balance of benefits and harms. *Benefits.* The PROTECT trial (A Study of the Effect and Safety of Sparsentan in the Treatment of Patients with IgA Nephropathy)[26,76] enrolled 406 patients (Table 2) with biopsy-proven primary IgAN, proteinuria ≥1.0 g/d despite physician-attested, optimized maximally tolerated RASi (with all participants required to be on at least half-maximal RASi dose) for at least 12 weeks, an eGFR of ≥30 ml/min per 1.73 m^2, and controlled blood pressure.[26,76] The study was designed to evaluate the efficacy and safety of sparsentan 400 mg once daily versus irbesartan 300 mg once daily to determine whether sparsentan led to greater reductions in proteinuria and risk of CKD progression. At week 36, the reduction in PCR was statistically significantly greater in the sparsentan group (–49.8%) than in the irbesartan group (–15.1%) (least-squares mean ratio: 0.59; 95% CI: 0.51–0.69; P <0.0001). At week 110, the change in

PCR from baseline was −42.8% (95% CI: −49.8% to −35.0%) with sparsentan versus −4.4% (95% CI: 15.8%–8.7%) with irbesartan (geometric least-squares mean ratio: 0.60; 95% CI: 0.50–0.72). Sparsentan treatment also led to a lower decline in eGFR compared with irbesartan (–5.8 ml/min per 1.73 m^2 per 110 weeks vs. –9.5 ml/min per 1.73 m^2 per 110 weeks). The 2-year chronic eGFR slope (weeks 6–110) was −2.7 ml/min per 1.73 m^2 per year (95% CI: −3.4 to −2.1 ml/min per 1.73 m^2 per year) with sparsentan, which was statistically significantly lower than that with irbesartan (−3.8 ml/min per 1.73 m^2 per year; 95% CI: −4.6 to −3.1 ml/min per 1.73 m^2 per year) (difference: 1.1 ml/min per 1.73 m^2 per year; 95% CI: 0.1–2.1 ml/min per 1.73 m^2 per year; $P = 0.037$). The 2-year total eGFR slope (day 1–week 110) was −2.9 ml/min per 1.73 m^2 per year (95% CI: −3.6 to −2.2 ml/min per 1.73 m^2 per year) with sparsentan and −3.9 ml/min per 1.73 m^2 per year (95% CI: −4.6 to −3.1 ml/min per 1.73 m^2 per year) with irbesartan (difference: 1.0 ml/min per 1.73 m^2 per year; 95% CI: −0.03 to 1.94 ml/min per 1.73 m^2 per year; $P = 0.058$). Fewer sparsentan-treated patients reached the composite kidney failure endpoint (40% eGFR reduction, kidney failure, or all-cause mortality) compared with irbesartan.

Harms. In the PROTECT trial, TEAEs were reported in 93% of patients in the sparsentan group and 88% of patients in the irbesartan group. TEAEs that occurred more frequently with sparsentan than irbesartan (≥5 percentage points) included dizziness (15% vs. 6%) and hypotension (13% vs. 4%). Serious TEAEs were reported in 37% of patients in the sparsentan group and 35% of patients in the irbesartan group, and TEAEs led to treatment discontinuation in 10% and 9% of patients, respectively. Peripheral edema and use of diuretics were similar in both groups, with no increases in body weight. Regarding liver function, 2% of sparsentan-treated patients had an alanine aminotransferase or aspartate aminotransferase elevation of ≥3 times the upper limit of normal, versus 3% of irbesartan-treated patients. No cases of drug-induced liver injury occurred in either group.

Certainty of evidence. In people with IgAN, there is moderate-certainty evidence, derived from a single phase 3 trial, regarding the effect of sparsentan, compared with the ARB irbesartan (Supplementary Table S9[26,76]). Due to small numbers of events, there is only very low certainty of evidence (very imprecise estimates) for the effect of sparsentan on all-cause mortality and kidney failure. However, there is moderate certainty of evidence that sparsentan greatly increases the likelihood of complete remission (RR: 2.70; 95% CI: 1.74–4.17); the certainty of evidence was downgraded because only a single study has been reported. There is also moderate certainty of evidence that sparsentan leads to reductions in proteinuria (mean difference: −40%; 95% CI: −50% to −28%), but, due to imprecision, low certainty of evidence that sparsentan results in annual reduction of GFR loss (mean difference: 1.0; 95% CI: −0.03 to 1.94). There is also low certainty of evidence that sparsentan may not have different risks of adverse events than irbesartan (RR: 1.06; 95% CI: 0.81–1.37); the certainty of evidence was downgraded for indirectness since coronavirus disease 2019 infections were included among adverse events, likely biasing any estimate of treatment-related adverse events toward the null.

Values and preferences. The Work Group judged that most patients would place a high value on a treatment that reduces proteinuria, slows the loss of kidney function, and is generally well-tolerated. Healthcare providers should, however, advise female patients of the increased risk of fetal toxicity and the need for contraception, where appropriate, and regular pregnancy testing.

Resource use and costs. In 2024, sparsentan was approved for use in a limited number of countries having a high prevalence of IgAN. This, combined with the cost of sparsentan and the fact that it is a lifelong therapy, means its use may be limited in resource-limited settings.

Considerations for implementation. In the United States, the FDA mandates a Risk Evaluation and Mitigation Strategy requiring all patients treated with sparsentan to have transaminases and bilirubin measured before initiating treatment and monthly for the first 12 months and then every 3 months during treatment. This is not a requirement in Europe. In addition, pregnancy testing is required before the initiation of treatment, during treatment, and 1 month after discontinuation of treatment. People who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for 1 month after discontinuation of treatment with sparsentan.

Rationale

In IgAN, the endothelin system is activated, inducing pathophysiological responses that augment those associated with the activation of the RAS.[77] Both systems mediate kidney injury through mechanisms including changes in glomerular hemodynamics, inflammation, and fibrosis. In this context, endothelin receptor antagonism combined with RASi has been shown in numerous preclinical models, including a mouse model of IgAN, and human studies to lead to reductions in proteinuria and the rate of kidney disease progression.[78,79]

In the PROTECT trial, treatment with sparsentan resulted in a greater sustained reduction in proteinuria than an ARB alone.[26,76] Two different measures of eGFR change were reported, and these were dictated by different regulatory agencies. Chronic eGFR slope (i.e., rate of eGFR change over weeks 6–110, requested by the EMA) and total eGFR slope over the full double-blind treatment period (i.e., day 1–week 110, requested by the FDA) were reported for the PROTECT trial. There remains considerable debate over which measure is the most appropriate, particularly for drugs that have an acute negative effect on eGFR that opposes their chronic beneficial effects, as seen with RASi, sodium-glucose cotransporter-2 inhibitor (SGLT2i), and sparsentan. In a meta-regression analysis of individual participant data from 66 RCTs, total slope was more strongly and precisely associated with a doubling of SCr, eGFR <15 ml/min per 1.73 m^2, or kidney failure with replacement therapy.[80] However, in

simulations, when an acute negative effect was present, chronic slope had a higher statistical power to detect an effect than total slope. This may explain why in the PROTECT trial there was a significant difference in chronic, but not total, eGFR slope with sparsentan.

The PROTECT trial required all patients to have persistent proteinuria, despite first taking optimized maximally tolerated RASi. The observed greater proteinuria reduction and eGFR preservation with combined dual blockade of the renin-angiotensin and endothelin systems via a DEARA suggest that this approach may be an appropriate first-line approach to manage the responses of IgAN-induced nephron loss in contrast to the RASi-first approach.

Recommendation 1.4.4.3: We suggest that patients who are at risk of progressive loss of kidney function with IgAN be treated with an SGLT2i *(2B)*.

Practice Point 1.4.4.4: Factors to consider before using an SGLT2i in patients with IgAN:

- **There was no requirement for patients with IgAN to be on an optimized maximally tolerated dose of RASi for a minimum of 3 months for inclusion in the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) or the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial.**
- **Patients with IgAN included in EMPA-KIDNEY and DAPA-CKD likely had long-standing disease, based on their age and eGFR at randomization; therefore, there is uncertainty over the value of SGLT2i, especially in younger patients with IgAN and relatively preserved kidney function (eGFR >60 ml/min per 1.73 m^2) (see Table 2).**

This recommendation is based on an extensive body of evidence in the general population with CKD and is consistent in principle with the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[81] *While there are SGLT2i data specifically in IgAN, these data were not generated in a population with IgAN comparable to patients included in current phase 3 IgAN-focused clinical trials and were generated in a generally older patient population with more advanced CKD, in which there was a less strict requirement for adherence to optimized maximally tolerated RASi.*

Key information

Balance of benefits and harms. *Benefits.* For the general population with CKD, benefits of SGLT2i include a reduction in the risk of kidney disease progression and a reduction in the risk of acute kidney injury (AKI).[81] In a collaborative meta-analysis of people with CKD, SGLT2i use was also shown to result in reduced risk of the composite of cardiovascular death or hospitalization for heart failure by 23%, although there were limited numbers of cardiovascular events in people with CKD without diabetes.[82,83] In the EMPA-KIDNEY[83,84] and DAPA-CKD[85] trials, use of an SGLT2i was associated with a lower rate of loss of kidney function in people with IgAN. Patients in both these trials, however, were generally older, had more advanced CKD, and had a less strict requirement for optimized maximally tolerated RASi than those who are typically recruited into IgAN clinical trials (Table 2).

Harms. SGLT2i are generally well-tolerated. There is no risk of hypoglycemia; however, there is an increased risk of infections, particularly of mycotic genital infections (in men and women).

Certainty of evidence. High certainty of evidence supports the benefits of SGLT2is in the general population with CKD, as summarized in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.[81] Data specific to the treatment of IgAN are limited to patients with IgAN included in the EMPA-KIDNEY and DAPA-CKD trials, who were likely to have had long-standing disease based on the age at randomization, with more advanced CKD, and for whom adherence to optimized maximally tolerated RASi was uncertain (Table 2).[83,86] For patients with IgAN, there is overall moderate certainty of evidence based on indirectness of the high-certainty evidence from the general population with CKD and moderate-certainty evidence specific to patients with IgAN (Supplementary Table S8). Reported data from the 2 SGLT2i trials provide moderate certainty of evidence of reduction in risk of kidney disease progression (defined as halving of eGFR, sustained low eGFR, kidney failure, or death due to kidney failure) and high certainty of evidence of lower annual GFR loss (mean difference: 1.7 ml/min per 1.73 m^2 per year; 95% CI: 1.1–2.3 ml/min per 1.73 m^2 per year). A single trial of dapagliflozin provides moderate certainty of evidence for reduced likelihood of kidney failure (RR: 0.30; 95% CI: 0.11–0.80) and proteinuria (mean difference: −26%; 95% CI: −37% to −14%).[86] Low certainty evidence of fewer adverse events with dapagliflozin than with placebo (RR: 0.63; 95% CI: 0.39–1.02) was due to imprecision.

Values and preferences. The Work Group judged that the majority of patients with IgAN with an indication for an SGLT2i would choose to receive an SGLT2i for their proven benefits on the risk of CKD progression, AKI, and a range of cardiovascular outcomes, alongside their generally good safety profile. Healthcare providers should, however, advise patients of the increased risk of infections, particularly of mycotic genital infections.

Resource use and costs. There is significant global variability in the affordability of SGLT2i, particularly in resource-limited settings with a high prevalence of IgAN. The availability of generic SGLT2i is likely to improve accessibility and affordability over the coming years.

Considerations for implementation. Commencement of an SGLT2i can be associated with a reversible dip in eGFR, but there is no associated risk of either AKI or hyperkalemia.

Rationale

There is a very clear rationale for the use of SGLT2i in CKD with and without diabetes based on data from large trials of individual SGLT2i and from meta-analyses of such trials. The use of SGLT2i is more difficult to generalize to patients with IgAN given the differences in age and kidney function between trial populations discussed above. In light of this, the Work Group felt that SGLT2i should be considered for people with IgAN and proteinuria ≥0.5 g/d, in distinction to the recommendations in the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[81] for kidney disease with and without diabetes. SGLT2i should not be used as a replacement for disease-modifying therapies in IgAN, and for patients with eGFR >60 ml/min per 1.73 m^2, not using an SGLT2i may be appropriate in the absence of other risk factors such as diabetes and cardiovascular disease.

1.5 Special situations

Practice Point 1.5.1: IgAN with nephrotic syndrome:

- **Rarely, patients with IgAN present with nephrotic syndrome (including edema and both hypoalbuminemia and nephrotic-range proteinuria >3.5 g/d).**
- **In these cases, mesangial IgA deposition can be associated with light and electron microscopy features otherwise consistent with a podocytopathy resembling minimal change disease (MCD).**
- **It is unclear whether this is a specific podocytopathic variant of IgAN or the existence of MCD in a patient with IgAN.**
- **Patients with a kidney biopsy demonstrating mesangial IgA deposition and light and electron microscopy features otherwise consistent with MCD should be treated in accordance with the guidelines for MCD in Chapter 5 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[15]**
- **Patients with nephrotic syndrome whose kidney biopsy has coexistent features of mesangioproliferative glomerulonephritis should be managed in the same way as those who are at risk of progressive loss of kidney function due to IgAN.**
- **Nephrotic-range proteinuria without nephrotic syndrome may also be seen in IgAN, and this commonly reflects coexistent secondary focal segmental glomerulosclerosis (e.g., in obesity and uncontrolled hypertension) or development of extensive glomerulosclerosis and tubulointerstitial fibrosis.**

Practice Point 1.5.2: IgAN with acute kidney injury (AKI):

- **AKI can occur in patients with IgAN in the context of severe visible hematuria, commonly in association with an upper respiratory tract infection. A repeat kidney biopsy should be considered in patients who fail to show improvement in kidney function within 2 weeks of cessation of the hematuria. Immediate management of AKI with visible hematuria should focus on supportive care for AKI.**
- **IgAN may also present with AKI either *de novo* or during its natural history due to rapidly progressive glomerulonephritis (RPGN), often with extensive crescent formation, commonly in the absence of visible hematuria. When other causes of RPGN (e.g., antineutrophil cytoplasmic antibody [ANCA]–associated vasculitis [AAV] and anti–glomerular basement membrane [GBM] disease) and reversible causes (e.g., drug toxicity and common pre- and post-kidney causes) have been excluded, a kidney biopsy should be performed as soon as possible.**

Practice Point 1.5.3: IgAN with RPGN:

- **Rapidly progressive IgAN is defined as a ≥50% decline in eGFR over ≤3 months, where other causes of RPGN (e.g., AAV and anti-GBM disease) and reversible causes (e.g., drug toxicity and common pre- and post-kidney causes) have been excluded.**
- **A kidney biopsy is essential in these cases and will commonly demonstrate mesangial and endocapillary hypercellularity as well as a high proportion of glomeruli affected by crescents with areas of focal necrosis.**
- **The presence of crescents in a kidney biopsy in the absence of a concomitant change in serum creatinine does not constitute rapidly progressive IgAN; however, these patients require close follow-up to ensure prompt detection of any glomerular filtration rate (GFR) decline. If this occurs, a second kidney biopsy may be considered.**
- **Patients with rapidly progressive IgAN should be offered treatment with cyclophosphamide and systemic glucocorticoids in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis.[87]**
- **Prophylactic measures that should accompany immunosuppression are discussed in Chapter 1 of the KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases.[15]**
- **There is insufficient evidence to support the use of rituximab for the treatment of rapidly progressive IgAN.**

Practice Point 1.5.4: IgAN and pregnancy planning:

- **IgAN is a disease predominantly of young adults, and all women of childbearing potential should be offered preconception counseling when appropriate.**
- **Preconception counseling should include a discussion on cessation of RASi, SGLT2i, sparsentan, Nefecon, and systemic glucocorticoids. Blood pressure control should be optimized with alternative antihypertensive medications prior to conception.**
- **In women at risk of progressive loss of kidney function, a trial of treatments to optimally address the immunopathogenesis of IgAN prior to conception may be preferable and should be discussed with patients.**
- **Neither SGLT2i nor sparsentan should be used while breastfeeding. Enalapril can be used if a RASi is clinically indicated.**

- The evidence to date suggests that systemic glucocorticoid use in the first trimester may confer a small increase in the odds of a cleft lip with or without a cleft palate, although data are conflicting, and it is unknown to what extent the underlying maternal disease may contribute. Systemic glucocorticoid use in pregnancy does not increase the risk of preterm birth, low birth weight, or preeclampsia.
- The use of Nefecon in pregnancy is not advised; however, studies examining the use of budesonide by pregnant women with inflammatory bowel disease have not identified any harmful effects. Budesonide has a Food and Drug Administration Pregnancy Category C risk designation, so risk cannot be ruled out.

Practice Point 1.5.5: IgAN in children:

General considerations for children with IgAN

- A more extensive review of the management of IgAN in children can be found in the 2025 International Pediatric Nephrology Association clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis.[1]
- In this guideline, we define children as those aged <18 years, but it is acknowledged that postpubertal children may in some respects have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.
- Visible hematuria is more frequent in children than in adults, and this may account for earlier diagnosis in children.[42]
- Children generally have higher eGFR, lower urine protein excretion, and more hematuria than adults at diagnosis.[41]

Kidney biopsy in children with IgAN

- A kidney biopsy is usually performed at presentation of symptoms (hematuria, proteinuria, and normal C3) to confirm the diagnosis (and rule out other diagnoses) and assess the degree of inflammation/presence of necrosis.
- In particular, a kidney biopsy should be performed promptly in children with persistent (>2–3 weeks) or recurrent hematuria and nephrotic-range proteinuria and/or reduced eGFR.[88]
- A kidney biopsy should also be performed in children with persistent or recurrent hematuria and protein-to-creatinine ratio (PCR) >500 mg/g (50 mg/mmol) in ≥2 measurements 1–2 weeks apart.
- In children with persistent or recurrent hematuria and PCR 200–500 mg/g (20–50 mg/mmol) in ≥3 measurements on clear urine 1–2 weeks apart, a kidney biopsy should be considered.
- Inflammation, mesangial cell proliferation, and endocapillary hypercellularity tend to be more prevalent in kidney biopsies of IgAN in children than in those of adults.[89–92]

Treatment of children with IgAN

- There is strong evidence suggesting a benefit of RAS blockade in children.[64] All children with IgAN and proteinuria >200 mg/d or PCR >200 mg/g (>20 mg/mmol) should receive RAS blockade, advice on moderating dietary salt intake below 3–5 g/d, and optimal lifestyle and blood pressure control (systolic blood pressure [SBP] <90th percentile for age, sex, and height).
- It is widely acknowledged that treatment of IgAN with immunosuppression differs between adults and children and that in children, the use of immunosuppressants is more widespread, particularly the use of systemic glucocorticoids. However, randomized controlled trials and expert consensus–driven indications are lacking.
- Evidence derived mostly from retrospective studies suggests that treatment with systemic glucocorticoids (plus second-line immunosuppression) leads to improved kidney survival.[42,89,91–97]
- The risk-benefit balance of glucocorticoid side effects must be considered. Systemic oral glucocorticoids are used in selected settings in children with clinical risk of progression, as evidenced by one of the following: (i) PCR 500–1000 mg/g (50–100 mg/mmol) despite 3–6 months of RASi, (ii) PCR >1000 mg/g (>100 mg/mmol) despite 4 weeks of RASi, or (iii) active MEST-C scores (≥1 of the following scores: M1, E1, S1 with podocyte lesions, and/or C1) and/or PCR consistently (i.e., persisting over 2–3 weeks in ≥2 measurements 1–2 weeks apart) >1000 mg/g (100 mg/mmol) in addition to RAS blockade.
  - Duration of treatment is not established, but usually 2 mg/kg/d (maximum 60 mg/m^2/d) of oral prednisone/prednisolone (or equivalent) for a maximum of 4 weeks followed by alternate-day dosing tapered over 5–6 months is given.
  - Further extension of the duration may be useful in some cases. Lower doses, such as those emerging from the adult Therapeutic Effects of Steroids in IgA Nephropathy Global (TESTING) trial (0.4 mg/kg/d of prednisone/prednisolone [or equivalent] for 2 months, tapering over 6 months) should be considered.
- Regimens including intravenous methylprednisolone are also used on an individual basis in patients with higher clinical and histologic risk of progression, such as in (i) children with acute onset of IgAN and worsening of kidney function (eGFR <90 ml/min per 1.73 m^2) and/or PCR >1000 mg/g (100 mg/mmol) with active severe MEST-C scores (≥2 of the following scores: M1, E1, S1 with podocyte lesions, and/or C1) or (ii) children with crescentic forms of IgAN (C2).
  - In cases with C1 or C2 in the absence of any other MEST-C score >0, the level of proteinuria must be considered.[41,89,91,98]

- **In cases with C2, irrespective of proteinuria, treatment of rapidly progressive IgAN is suggested (see below). Dosing regimens may be as follows: 3 methylprednisolone intravenous pulses given at the dose of 15 mg/kg/d each (maximum dose 500 mg) on 3 consecutive or alternate days followed by oral prednisone/prednisolone as indicated above.**
  - **Alternatively, the intravenous pulses can be repeated 3 times at 2-month intervals, with oral prednisone/prednisolone given at 0.5 mg/kg/d for 2 months between pulse cycles for a total of 6 months.**[99,100]
- **Children with IgAN not benefiting from an adequate diet, RAS blockade, and glucocorticoids alone should, whenever possible, be enrolled in clinical trials. Another potential approach in these children is the use of immunosuppressants (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil, or rituximab) in addition to glucocorticoids.**
- **As for adults, IgAN with MCD may be found, and it should be treated as steroid-sensitive nephrotic syndrome (KDIGO 2025 Clinical Practice Guideline for the Management of Nephrotic Syndrome in Children).**[100a]
- **As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with systemic glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.**[89,91,101]

Follow-up of children with IgAN

- **Aim for proteinuria ≤200 mg/d (≤400 mg/1.73 m^2 per day) or PCR ≤200 mg/g (≤20 mg/mmol).**
- **Aim for SBP at <90th percentile for age, sex, and height.**
- **Continue to follow patients after complete remission, as they can relapse even after many years.**[102] **In particular, yearly monitoring of blood pressure and urinalysis for patients with a history of pediatric IgAN is necessary.**

1.6 Horizon scanning for future new drug approvals and updates to the guideline

A number of new therapeutic approaches are being tested in clinical trials in IgAN, supported by a greater understanding of the IgAN pathogenesis, including factors promoting generation of pathogenic forms of IgA, the process of immune complex formation, and the importance of processes such as complement activation in glomerular inflammation. In parallel, there have been significant advances in targeting pathways that are activated following cumulative nephron loss. A number of drugs initially evaluated in diabetic kidney disease are now being evaluated in CKD without diabetes. As we have seen in trials of SGLT2i, it is likely that a significant proportion of these patients will have IgAN. Equally exciting, we are beginning to see trials of drug combinations, mirroring what we are likely to utilize in clinical practice.

Table 3 summarizes phase 3 trials currently underway that are specifically in IgAN, with the hope that there will be at least 8 new drugs approved for the treatment of IgAN in the

Table 3 | Phase 3 clinical trials open in 2025 evaluating new treatments for IgAN

Drug targets	Drug	Target	Clinical trial Registration number	Status as of July 2024
Drugs targeting the production of pathogenic forms of IgAN	Sibeprenlimab (VIS649)	APRIL	VISIONARY NCT05248646	In follow-up
	Zigakibart (BION-1301)	APRIL	BEYOND NCT05852938	Recruiting
	Atacicept	APRIL/BAFF	ORIGIN3 NCT04716231	Recruiting
	Telitacicept	APRIL/BAFF	NCT05799287	In follow-up
	Povetacicept	APRIL/BAFF	RAINIER NCT06564142	Recruiting
Drugs targeting IgA-containing immune complex–mediated inflammation	Iptacopan (LNP023)	Complement alternative pathway factor B	APPLAUSE-IgAN NCT04578834	In follow-up
	Sefaxersen (RO7434656)	Complement alternative pathway factor B	IMAGINATION NCT05797610	Recruiting
	Ravulizumab	Complement terminal pathway C5	I CAN NCT06291376	Recruiting
Drugs targeting the generic downstream consequences of IgAN-induced nephron loss	Atrasentan	Endothelin A receptor	ALIGN NCT04573478	In follow-up

ALIGN, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Atrasentan in Patients With IgA Nephropathy at Risk of Progressive Loss of Renal Function; APPLAUSE-IgAN, A Multi-center, Randomized, Double-blind, Placebo-controlled, Parallel Group, Phase III Study to Evaluate the Efficacy and Safety of LNP023 in Primary IgA Nephropathy Patients; APRIL, a proliferation-inducing ligand; BAFF, B cell–activating factor of the tumor necrosis factor family; BEYOND, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of BION-1301 in Adults With IgA Nephropathy; I CAN, A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Participants With Proliferative Lupus Nephritis or Immunoglobulin A Nephropathy; IgAN, immunoglobulin A nephropathy; IMAGINATION, A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of RO7434656, an Antisense Inhibitor of Complement Factor B, in Patients With Primary IgA Nephropathy at High Risk of Progression; ORIGIN3, A Phase 2b/3, Multi-part, Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With IgA Nephropathy (IgAN); RAINIER, A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Povetacicept in Adults With Immunoglobulin A Nephropathy; VISIONARY, A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects With Immunoglobulin A Nephropathy.

next 4–5 years that target novel pathways in IgAN, including B cell modulation and complement activation. Similarly, there are likely to be new additions to the treatment of nondiabetic CKD that will need to be reviewed as part of the management of the responses to IgAN-induced nephron loss. It is therefore likely that this guideline will require frequent updating for the foreseeable future.

Research recommendations

The following areas are of high priority for future research to improve the treatment and outcomes of patients with IgAN:

- **Risk stratification:** This is important for both patient evaluation and design of clinical trials. The International IgAN Prediction Tool should be:
  - Validated in additional racial populations not included in the original cohorts
  - Further developed to enable prediction of progression risk serially during follow-up
  - Evaluated in relation to specific treatment responses
  - Evaluated in populations with optimized CKD therapy (RASi, SGLT2i, and sparsentan)
  - Evaluated to guide clinicians in understanding what percentage ranges define low, moderate, high, or very high risk of progression in line with other risk calculators.
- **Biomarker discovery and validation:** Identification and validation of serum, plasma, urine, and/or kidney biomarkers to inform:
  - Prognosis
  - Treatment selection, particularly around the need for anti-inflammatory therapy
  - Monitoring response to treatment.
- **A better understanding of disease heterogeneity:** Incorporating studies of fundamental biology and continuing transcontinental collaborative research to identify genetic, sex-specific (biological attributes), and environmental factors influencing disease phenotype across races.
- **Developing a clearer understanding of the mechanisms of action of treatments being studied in IgAN:**
  - Do RASi, SGLT2i, endothelin receptor antagonism, Nefecon, B cell–activating factor of the tumor necrosis factor family, or proliferation-inducing ligand inhibition have direct anti-inflammatory and antifibrotic effects in the kidney?
  - Do systemic glucocorticoids at the dose recommended for the treatment of IgAN modulate production of pathogenic forms of IgA and immune complexes?
  - Does complement inhibition have effects outside the glomerulus in terms of modulating tubulointerstitial inflammation and scarring?
- **Developing clearer distinctions for what constitutes glomerular inflammation requiring specific anti-inflammatory treatment:** Global studies should be undertaken to determine the glomerular lesions (presence and extent) that necessitate adding an anti-inflammatory treatment to a therapy that suppresses production of pathogenic forms of IgA and immune complexes.
- **Clinical trial design in IgAN:** The establishment of using earlier surrogate biomarkers of disease progression as a pathway to regulatory approval of novel therapies in IgAN has led to the rapid expansion of industry-sponsored studies targeting novel pathways to prevent progressive loss of kidney function in IgAN. These include ongoing phase 3 studies of agents targeting pathways regulating IgA production and activity of the alternate complement pathway (Table 3). Data from completed phase 3/4 clinical trials from emerging approved therapies now challenge the ability to execute placebo-controlled trials in this disease. As new treatments come to market, patients in lengthy placebo-controlled studies with perceived inadequate treatment response are at risk of receiving off-protocol agents, potentially contaminating the treatment arms in a disproportionate manner. Thought must now be given to the use of an active comparator arm consisting of a therapy with proven efficacy. This will undoubtedly make future clinical trials more complex and emphasizes the need to identify even earlier surrogate biomarkers of an intervention's long-erm benefit on kidney function decline; this, in turn, would allow a reduction in the duration of clinical studies, thereby reducing the time patients are exposed to novel agents compared to current standard-of-care treatments. Thought must also be given to treating people with IgAN currently excluded from major trials (e.g., those with proteinuria <1 g/d or those with baseline eGFR <30 ml/min per 1.73 m^2).
- Finally, none of the available IgAN therapies are curative. Further research is required to establish the optimal combinations, sequencing, and duration of treatments for delivering maximal efficacy and minimal toxicity.

Immunoglobulin A vasculitis

IgA vasculitis (IgAV), formerly Henoch-Schönlein purpura, is a form of vasculitis marked by IgA deposition within the blood vessels of affected tissues. IgAV commonly affects the small blood vessels of the skin, joints, intestines, and kidneys. Rarely, it can affect the lungs and central nervous system. It is the most common form of vasculitis in children. When IgAV occurs in children aged <16 years, it is often self-limiting. Adults may have more severe and relapsing disease. Kidney involvement in IgAV is histopathologically indistinguishable from that seen in the kidney-limited disease IgAN. This guideline outlines management guidance for adults with IgAV-associated nephritis (IgAVN) and provides a practice point for children aged 1–18 years. A more extensive review of the management of IgAVN in children can be found in the 2025 International Pediatric Nephrology Association clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis.[1]

The evidence base in IgAVN is extremely limited. This guideline, therefore, relies heavily on extrapolating data from IgAN studies to IgAVN studies, although there is still no clear understanding of how these diseases are related. We make no specific recommendations on how to treat extrarenal organ involvement, in particular gastrointestinal vasculitis and pulmonary hemorrhage, which can be life-threatening and require immunosuppressive therapy independent of any kidney involvement.

1.7 Diagnosis

Practice Point 1.7.1: Considerations for the diagnosis of immunoglobulin A vasculitis (IgAV)–associated nephritis (IgAVN):

- **There are no internationally agreed upon criteria for the diagnosis of IgAV in adults.**
- **In children, a clinical diagnosis of IgAV can be made based on international criteria.[103–105]**
- **A diagnosis of IgAVN can be made only with a kidney biopsy.**
- **A kidney biopsy should be performed in adults with suspected IgAV if there are signs of significant end-organ tissue damage: proteinuria ≥0.5 g/d persistent for >4 weeks, kidney function impairment, or RPGN.**
- **Assess all adult patients with IgAV and IgAVN for secondary causes and for malignancy using age- and sex-appropriate screening tests.**

1.8 Prognosis

Practice Point 1.8.1: Considerations regarding the prognosis of IgAVN:

- **Retrospective data from a limited number of small registries have identified uncontrolled hypertension and the amount of proteinuria at presentation and hypertension and mean proteinuria during follow-up as predictors of a poor kidney outcome in adults with IgAV.[106–108]**
- **The use of the Oxford Classification MEST-C score has recently been studied.[109] This showed that E1 lesions were strongly associated with initial improvement followed by progressive decline in kidney function in patients treated with immunosuppression.**
- **The International IgAN Prediction Tools[12] are not designed to determine the prognosis of IgAVN.**

1.9 Treatment

1.9.1 Prevention of nephritis in IgAV

Recommendation 1.9.1.1: We recommend not using systemic glucocorticoids to prevent nephritis in patients with isolated extrarenal IgAV *(1B)*.

This recommendation puts a high value on the moderate-certainty evidence demonstrating the risks of systemic glucocorticoid use with no added benefit in preventing nephritis in IgAV.

Key information

Balance of benefits and harms. There are no RCT data on the effectiveness of strategies to prevent IgAVN in adults with IgAV. There is, however, a significant body of evidence in children that prophylactic use of systemic glucocorticoids in extrarenal IgAV does not reduce the incidence of kidney involvement. In an RCT of 352 children with IgAV, early treatment with prednisolone did not reduce the prevalence of proteinuria 12 months after disease onset.[110] This finding was also observed in 171 children showing that early use of prednisolone did not prevent the development of nephritis.[111] A meta-analysis of 5 RCTs in which 789 children were examined for the effects of short-duration systemic glucocorticoids (2–4 weeks) at presentation on preventing persistent nephritis at 6 and 12 months after presentation concluded that such treatment had no preventive effect on the onset of persistent nephritis.[112]

Certainty of evidence. There is moderate-certainty evidence from 5 RCTs of prednisone versus placebo or supportive therapy in patients with IgAV (Supplementary Table S10[110–115]). The studies did not report on the critical and important outcomes of mortality, kidney failure, or ≥50% GFR loss, but had moderate certainty of evidence that prednisone did not significantly reduce the development of kidney disease any time after treatment (RR: 0.74; 95% CI: 0.42–1.32) or alter the presence of continuing kidney disease at 6 months (RR: 0.51; 95% CI: 0.24–1.11). There was also low certainty of evidence that prednisone did not affect the risk of continuing

kidney disease at 12 months (RR: 1.06; 95% CI: 0.38–2.91) or development of severe kidney disease at about 4 years (RR: 1.58; 95% CI: 0.42–6.0). The certainty of evidence was downgraded due to methodological concerns in the trials (inadequate allocation concealment and lack of blinding) and imprecision.

Values and preferences. The Work Group judged that most patients would place a high value on the potential toxicity of this drug and the lack of any clear benefit.

Resource use and costs. None.

Considerations for implementation. None.

Rationale

The lack of benefit and the well-documented risks associated with systemic glucocorticoids meant the Work Group could not support their use in preventing nephritis in IgAV.

Practice Point 1.9.1.1: Considerations for the management of all patients with IgAVN who are at risk of progressive loss of kidney function and do not have RPGN:

- **Proteinuria ≥0.5 g/d (while on or off treatment of IgAVN) identifies a patient with IgAVN at increased risk of progressive loss of kidney function.**
- **The goal for managing IgAVN, like IgAN, should be to *simultaneously*:**
  - **Prevent or reduce IgA-IC formation, mesangial deposition, and IgA-IC–mediated glomerular injury**
  - **Manage the consequences of existing IgAVN-induced nephron loss**
- **Unlike IgAN, there are no treatments proven to prevent or reduce IgA-IC formation in IgAVN.**
- **Prevention of IgA-IC–mediated injury should incorporate treatments with proven anti-inflammatory effects and ideally should be used in combination with, and not as a replacement for, treatments that prevent or reduce IgA-IC formation.**
  - **In all patients in whom systemic glucocorticoids are being considered, a detailed discussion of the risks and benefits of each drug should be undertaken with the patient.**
  - **In patients who wish to try systemic glucocorticoids, a reduced-dose regimen as described for IgAN should be employed with antimicrobial prophylaxis.**
- **Management of the consequences of IgAVN-induced nephron loss should include:**
  - **Lifestyle advice, including information on dietary sodium restriction (<2 g/d), smoking and vaping cessation, weight control, and endurance exercise, as appropriate**
  - **Control blood pressure with a target of ≤120/70 mm Hg using a RASi as the first-choice drug intervention**
  - **Measures to reduce glomerular hyperfiltration and the impact of proteinuria on the tubulointerstitium, using RASi and SGLT2i, singly or in combination**
  - **A thorough cardiovascular risk assessment and commencement of appropriate interventions, as necessary.**
- **Offer participation in a clinical trial if one is available.**
- **There is insufficient evidence to support the use of the Oxford Classification MEST-C score in determining which drug should be commenced in patients with IgAVN.**
- **There is insufficient evidence to base treatment decisions on the presence and number of crescents in the kidney biopsy.**
- **The International IgAN Prediction Tools cannot be used to determine the likely impact of any particular treatment regimen.**
- **Dynamic assessment of patient risk over time should be performed, as decisions regarding immunosuppression may change.**

1.10 Special situations

Practice Point 1.10.1: IgAV with RPGN:

- **The potential risks and benefits of immunosuppression should be evaluated at the individual patient level and discussed with the patient.**
- **Patients agreeing to the treatment should be treated in accordance with the KDIGO 2024 Clinical Practice Guideline for the Management of Antineutrophil Cytoplasmic Antibody (ANCA)–Associated Vasculitis.[87]**
- **IgAVN with RPGN, as well as other presentations of IgAVN, may be associated with significant extrarenal involvement (pulmonary, gastrointestinal, and skin), which may dictate alternative immunosuppressive strategies.**
- **There are insufficient data to determine the efficacy of plasma exchange in IgAVN with RPGN. However, uncontrolled case series describe the potential role of the addition of plasma exchange to glucocorticoid therapy to accelerate recovery in patients with life- or organ-threatening extrarenal complications of IgAV.[116]**

1.10.1 IgAVN in children

Practice Point 1.10.1.1: In this guideline, we define children as those aged <18 years, but it is acknowledged that postpubertal children in some respects may have a similar course and response to treatment as adults with IgAN. However, there are insufficient data currently to recommend that they be managed as adults with IgAN.

Practice Point 1.10.1.2: A more extensive review of the management of IgAVN in children can be found in the 2025 International Pediatric Nephrology Association clinical practice recommendations for the diagnosis and management of children with IgA nephropathy and IgA vasculitis nephritis.[1]

Briefly:

- **The majority of children who will develop nephritis do so within 3 months of presentation. Urinary monitoring is necessary at the onset of vasculitis and then at least monthly for ≥6 months from the initial presentation of systemic disease.**
- **A kidney biopsy should be promptly performed in children with nephrotic-range proteinuria or impaired kidney function (GFR <90 ml/min per 1.73 m^2).**
- **In children with IgAV and PCR 1000–2000 mg/g (100–200 mg/mmol) for 2–4 weeks or PCR 200–500 mg/g (20–50 mg/mmol) for >4 weeks, a kidney biopsy should be considered.**
- **In children with confirmed IgAVN, a pediatric nephrologist should be consulted.**
- **In children with IgAVN and persistent proteinuria for >3 months, ACEi or ARB treatment should be considered.**
- **There are no data supporting the use of glucocorticoids to prevent nephritis in children with IgAV and no evidence of kidney involvement or with isolated microhematuria.**[117,118]
- **Oral prednisone/prednisolone for 3–6 months or pulsed intravenous methylprednisolone should be considered in children with IgAVN and nephrotic-range proteinuria (PCR >2000 mg/g or 200 mg/mmol) or RPGN and histologic risk of progression (International Study of Kidney Disease in Children [ISKDC] criteria ≥II).**
- **Other immunosuppressive agents in addition to glucocorticoids (e.g., calcineurin inhibitors, cyclophosphamide, mizoribine where available, mycophenolate mofetil, or rituximab) should be considered in the following indications: to reduce the glucocorticoid dose and/or if the PCR is >2000 mg/g (200 mg/mmol) and/or if there is insufficient response to glucocorticoids.**
- **Children with IgAVN with nephrotic syndrome and/or rapidly deteriorating kidney function are treated in the same way as those with rapidly progressive IgAN.**
- **Monitoring children with IgAVN with the evaluation of urinalysis, eGFR, and blood pressure should be considered for ≥5 years after the initial episode. Lifelong monitoring, individualized according to the severity and response to treatment, appears prudent for children who received therapy for their IgAVN.**

Research recommendations

- Unlike IgAN, there are currently few clinical trials of novel therapies in IgAVN. It is recommended that those agents currently being evaluated in patients with IgAN should also be tested for safety and efficacy in IgAVN in adults and children.
- In light of preliminary observational data[119,120] suggesting a potential benefit with rituximab, we recommend a dedicated prospective RCT of rituximab in IgAV.
- Better understanding of the natural history and pathogenesis of IgAVN is warranted, as is identification of factors predictive of future kidney function decline in IgAVN, which may be possible by utilizing large national registries and biorepositories in North America, the United Kingdom, and Europe.

Methods for guideline development

Aim

This guideline is an update of Chapter 2: Immunoglobulin A Nephropathy (IgAN)/Immunoglobulin A Vasculitis (IgAV) from the KDIGO Clinical Practice Guideline for the Management of Glomerular Diseases published in 2021.[15] Based on the recently published evidence in the field, it was decided that a guideline update was required.

The objective of this project was to update the evidence-based clinical practice guideline for the management of IgAN and IgAV. The guideline development methods are described below.

Overview of the process

This guideline adhered to international best practices for guideline development (Appendix B: Supplementary Tables S2 and S3).[121] This guideline has been developed and reported in accordance with the Appraisal of Guidelines for Research and Evaluation II reporting checklist.[122] The processes undertaken for the development of the KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV) are described as follows.

- Appointing Work Group members and the Evidence Review Team (ERT)
- Finalizing guideline development methodology
- Defining scope of the guideline
- Implementing literature search strategies to update the evidence base for the guideline
- Selecting studies according to predefined inclusion criteria
- Conducting data extraction and critical appraisal of the literature
- Updating evidence synthesis and meta-analysis to include newly identified studies
- Updating the certainty of the evidence for each outcome across studies
- Grading the strength of the recommendation based on the certainty of the evidence and other considerations
- Convening a public review in August–September 2024
- Amending the guideline based on the external review feedback, and updating the literature search
- Finalizing and publishing the guideline.

Commissioning of the Work Group and ERT. The KDIGO Co-Chairs appointed the Work Group Co-Chairs, who then assembled the Work Group, to include content experts in adult nephrology, epidemiology, pathology, and public health. The Work Group was responsible for writing the recommendations, practice points, and underlying rationale, as well as grading the strength of each recommendation.

For the 2025 update, the Brown University School of Public Health Center for Evidence Synthesis in Health was contracted to update the systematic evidence review and provide expertise in guideline development methodology. The Brown ERT consisted of a senior physician-methodologist who led the ERT for the KDIGO 2012 Clinical Practice Guideline for Glomerulonephritis, an adult nephrologist, and a librarian-methodologist, all with expertise in evidence synthesis and guideline development, including for KDIGO guidelines. Cochrane Kidney and Transplant was contracted to conduct systematic evidence review and provide expertise in guideline development methodology for the 2021 guideline.

Defining the scope and topics and formulating key clinical questions. Due to resourcing and the probability of practice-changing studies, clinical questions on the effectiveness and safety of interventions included in the guideline update were limited to RCTs to avoid bias by design. Guideline topics and clinical questions focusing on nonrandomized studies were not included in the guideline update (Appendix A: Supplementary Table S1). The guideline Work Group, with assistance from the ERT, determined the overall scope of the guideline. A preliminary list of topics and key clinical questions was informed by the previous KDIGO guideline.[15] Clinical questions adhered to the Population, Intervention, Comparator, Outcomes, and study Design (PICOD) format (a list of critical and important outcomes was compiled after voting by the Work Group [Table 4]). Clinical questions were mapped to existing Cochrane Kidney and Transplant systematic reviews. These systematic reviews were updated accordingly. For clinical questions that did not map to any Cochrane Kidney and Transplant systematic reviews, *de novo* systematic reviews were undertaken. The previous guideline was reviewed to ensure that all identified studies were included in the evidence review.[15] Details of the PICOD questions and associated Cochrane Kidney and Transplant systematic reviews are provided in Table 5.[123–125] All evidence reviews were conducted in accordance with the *Cochrane Handbook*,[126] and guideline development adhered to the standards of GRADE (Grading of Recommendations Assessment, Development and Evaluation).[127]

Table 4 | Hierarchy of outcomes

Hierarchy	Outcomes
Critical outcomes	• All-cause mortality
	• Kidney failure
	• ≥50% loss of GFR
	• Infection
	• Glucocorticoid-related adverse events
	• Malignancy
Important outcomes	• Complete remission/relapse
	• Annual GFR loss (minimum 3-year follow-up)

GFR, glomerular filtration rate.
The critical and important outcomes were voted on by the Work Group using an adapted Delphi process (1–9 Likert scale). Critical outcomes were rated 7–9 and important outcomes were rated 4–6 on the 9-point scale.

Table 5 | Clinical questions and systematic review topics in PICOD format

PICOD criteria	IgAN or IgAV
Clinical question	**In patients with biopsy-proven IgAN, what nonimmunosuppressive agents, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Nonimmunosuppressive agents or treatments: Sparsentan, sodium-glucose cotransporter-2 inhibitors, fish oil, anticoagulants or antiplatelets, antioxidants, tonsillectomy, statins, allopurinol, etc. Exclude: traditional Chinese medicine, complementary and alternative medicine, and diets
Comparator	No treatment, placebo, standard of care, or other nonimmunosuppressive agents or treatments
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2025 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Reid SM, Cawthon PM, Craig JC, et al. Non-immunosuppressive treatment for treating IgA nephropathy [review]. *Cochrane Database Syst Rev.* 2011;16:CD003962[53]
SoF tables	Supplementary Tables S5, S7–S9, and S38–S56
Clinical question	**In patients with biopsy-proven IgAN, what immunosuppressive agents, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAN
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, standard of care, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2025 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Natale P, Palmer SC, Ruospo M, et al. Immunosuppressive agents for treating IgA nephropathy [review]. *Cochrane Database Syst Rev.* 2020;3:CD003965[128]
SoF tables	Supplementary Tables S4, S6, and S11–S37
Clinical question	**In patients with biopsy-proven IgAV (Henoch-Schönlein purpura), what immunosuppressive agents, compared with no treatment, placebo, or standard of care, improve efficacy outcomes and reduce adverse effects?**
Population	Patients with IgAV with nephritis
Intervention	Immunosuppressive therapy
Comparator	No treatment, placebo, standard of care, or other immunosuppressive therapies
Outcomes	Outcomes listed in Table 4
Study design	2021 Guideline: RCTs and observational studies 2025 Guideline: RCTs published in peer-reviewed journals (or meta-analysis based on RCTs)
Cochrane systematic review	Hahn D, Hodson EM, Willis NS, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein purpura (HSP) [review]. *Cochrane Database Syst Rev.* 2015;2015:CD005128[112]
SoF tables	Supplementary Tables S10 and S57–S65

IgAN, immunoglobulin A nephropathy; IgAV, immunoglobulin A vasculitis; PICOD, Population, Intervention, Comparator, Outcomes, and study Design; RCT, randomized controlled trial; SoF, summary of findings.

Literature searches and article selection. For the KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), updated literature searches were conducted in MEDLINE (via PubMed), Embase, and the Cochrane Central Register of Controlled Trials (Appendix A: Supplementary Table S1). The searches were restricted to records entered into the databases since January 1, 2020. This was done to provide a 6-month overlap with the prior searches. The searches were conducted on April 19, 2023, and updated on August 22, 2024. These search updates included terms for IgAN, IgAV, nephrotic syndrome (NS), and minimal change disease (MCD) (which all underwent concurrent updates).

The titles and abstracts resulting from the searches were screened by the 3 members of the ERT who independently assessed retrieved abstracts, and for accepted abstracts, the full text, to determine which studies satisfied the inclusion criteria. Disagreement about inclusion was resolved by discussion among the 3 members of the ERT.

For the KDIGO 2021 guideline, a total of 25,925 citations were screened. Of those, 479 RCTs and 102 observational studies were included in the evidence review for all glomerular diseases. For the current update, a total of 4621 citations were screened (for IgAN/IgAV, NS, and MCD) (Figure 5). From those, we found 27 new eligible articles on IgAN, representing 21 new RCTs.

Data extraction. For the KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), data extraction was performed by 1 member of the Brown ERT and confirmed by the 2 other members of the ERT. The Brown ERT extracted data into the forms designed by the Cochrane ERT. The Cochrane ERT designed data extraction forms to capture data on study design, study participant characteristics, intervention and comparator characteristics,

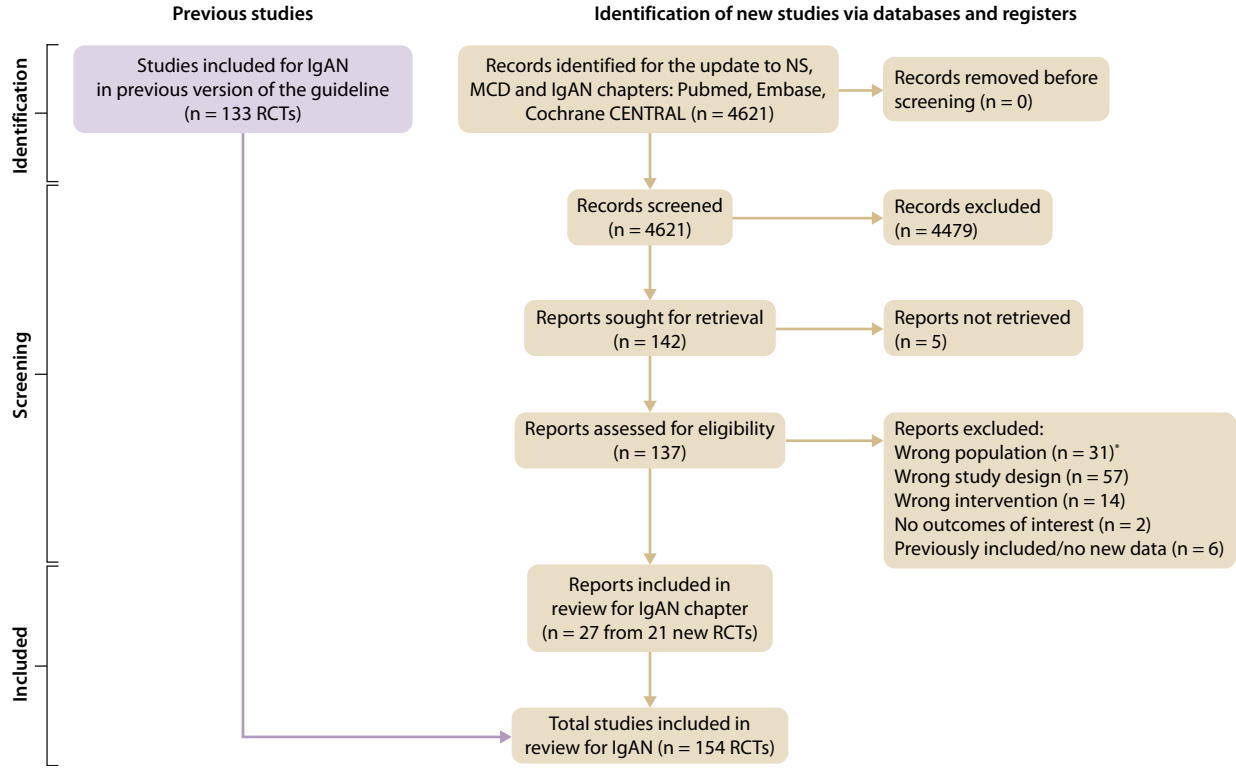

Figure 5 | Search yield and study flow diagram. *Includes 19 studies identified for guideline updates relevant to minimal change disease (MCD) and nephrotic syndrome (NS) in children. IgAN, immunoglobulin A nephropathy; RCT, randomized controlled trial.

and critical and important outcomes. Any differences in extraction between members of the ERT were resolved through discussion. A third reviewer was included if consensus could not be achieved.

Critical appraisal of studies. The update included only RCTs. For these studies, the Cochrane risk of bias tool was used to assess individual study limitations based on the following items[129]:

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at risk of bias?

All critical appraisal was conducted independently by 2 members of the ERT, with disagreements regarding the risk of bias adjudications resolved by consultation with a third review author.

Evidence synthesis and meta-analysis. *Measures of treatment effect.* The dichotomous outcome (all-cause mortality, kidney failure, ≥50% loss of GFR, infection, malignancy, adverse events, and complete remission/relapse) results were expressed as an RR with a 95% CI. The continuous scale outcome, annual GFR loss, was evaluated as a mean difference with a 95% CI.

Data synthesis. Data were pooled using the Mantel-Haenszel random effects model for dichotomous outcomes and the inverse variance random effects model for continuous outcomes. The random effects model was chosen because it provides a conservative estimate of effect in the presence of known and unknown heterogeneity.[126]

Assessment of heterogeneity. Heterogeneity was assessed by visual inspection of forest plots of standardized mean effect sizes, and of RRs, and by the I^2 statistic, which measures the proportion of the total variation in the estimates of treatment effect that was due to heterogeneity beyond chance. We used conventions of interpretation as defined by Higgins *et al.*[130]

Assessment of publication bias. To assess publication bias, we used funnel plots of the log odds ratio (effect vs. standard error of the effect size) when a sufficient number of studies were available (i.e., >10 studies).[126] Other reasons for the asymmetry of funnel plots were considered.

Subgroup analysis and investigation of heterogeneity. Subgroup analysis was undertaken to explore whether there were clinical differences among the studies that may have systematically influenced the differences that were observed in the critical and important outcomes. However, subgroup analyses are hypothesis-forming rather than hypothesis-testing and should be interpreted with caution. The following subgroups were considered: baseline kidney function (GFR, proteinuria,

Table 6 | Classification for the grade of the certainty of the evidence

Grade	Certainty of evidence	Meaning
A	High	We are confident that the true effect is close to the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of the effect is very uncertain, and often it will be far from the true effect.

presence of albuminuria, and presence of macroscopic hematuria), histopathologic class of disease, primary versus secondary forms of disease, sex (biological attributes), and adult versus pediatric. The test of subgroup differences used the I^2 statistic and a *P* value of 0.10 (noting that this is a weak test).[126]

Sensitivity analysis. The following sensitivity analyses were considered:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis, taking account of the risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry vs. other), and country in which the study was conducted.

However, the available data were insufficient to determine the influence of these factors on the effect size of critical and important outcomes.

Grading the certainty of the evidence and the strength of the guideline recommendation. *Grading the certainty of the evidence for each outcome across studies.* The overall certainty of the evidence related to each critical and important outcome was assessed using the GRADE approach,[127,131] which assesses the certainty of the evidence for each outcome. For all outcomes, the data were from RCTs; thus, the initial grade of the certainty of the evidence is considered to be high. The certainty of the evidence is lowered in the event of study limitations; important inconsistencies in results across studies; indirectness of the results, including uncertainty about the population, intervention, and outcomes measured in trials and their applicability to the clinical question of interest; imprecision in the evidence review results; and concerns about publication bias. For imprecision, we considered the width of the 95% CI, such that for the RR, if the 95% CI extended beyond both 0.5 and 2.0, the evidence was considered very imprecise. We also considered sparse data (i.e., only 1 study) to be imprecise.[131] The final grade of the certainty of the evidence for an outcome could be high, moderate, low, or very low (Table 6). For further details on the GRADE approach for grading the certainty of the evidence, see Table 7.

Summary of findings (SoF) tables. The SoF tables were developed to include a description of the population, intervention, and comparator. In addition, the SoF tables included results from the data synthesis as relative and absolute effect estimates. The grading of the certainty of the evidence for each critical and important outcome is also provided in the SoF tables. For the 2025 update, the SoF tables were updated or created manually. The SoF tables are available in Data Supplement: Appendices C and D.

Developing the recommendations. For the KDIGO 2025 Clinical Practice Guideline, the existing recommendations were reviewed and revised, as necessary, and new recommendations were drafted by the Work Group and Co-Chairs. Recommendations were revised in a multistep process by

Table 7 | GRADE system for grading the certainty of evidence

Study design	Step 1—starting grade for the certainty of evidence	Step 2—lower the grade	Step 3—raise the grade for observational studies
RCT	High	Study limitations: −1, serious −2, very serious	Strength of association: +1, large effect size (e.g., <0.5 or >2) +2, very large effect size (e.g., <0.2 or >5)
	Moderate	Inconsistency: −1, serious −2, very serious	Evidence of a dose-response gradient
Observational	Low	Indirectness: −1, serious −2, very serious	All plausible confounding would reduce the demonstrated effect
	Very low	Imprecision: −1, serious −2, very serious −3, extremely serious	
		Publication bias: −1, strongly suspected	

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial.

Table 8 | KDIGO nomenclature and description for grading recommendations

Grade	Implications		
	Patients	Clinicians	Policy
Level 1, "We recommend"	Most people in your situation would want the recommended course of action, and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2, "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

KDIGO, Kidney Disease: Improving Global Outcomes.

email and teleconferences. The Brown ERT participated in these discussions to ensure consistency with the evidence base and to provide additional feedback.

The final draft was sent for external public review, and reviewers provided open-ended responses. Based on the external stakeholder feedback, the draft was further revised by the Work Group. All Work Group members provided feedback on the initial and final drafts of the guideline statements and text and approved the final version of the guideline. The ERT also provided a descriptive summary of the certainty of the evidence in support of the recommendations.

Grading the strength of the recommendations. The strength of the recommendation is graded as Level 1, "We recommend" or Level 2, "We suggest" (Table 8). The strength of the recommendation was determined by the balance of benefits and harms across all critical and important outcomes, the grading of the overall certainty of the evidence, patient values and preferences, resource use and costs, and considerations for implementation (Table 9).

Balance of benefits and harms. The Work Group and ERT determined the anticipated net health benefit on the basis of expected benefits and harms across all critical and important outcomes from the underlying evidence review.

Overall certainty of evidence. The overall certainty of the evidence was based on the certainty of the evidence for all critical and important outcomes, taking into account the relative importance of each outcome to the population of interest. The overall certainty of the evidence was graded as A, B, C, or D (Table 6).

Patient values and preferences. No patients or caregivers participated in the Work Group. The Work Group, from their experience in managing patients with glomerular diseases and their understanding of the best available scientific literature, made judgments on the values and preferences of patients. Formal qualitative evidence synthesis on patient priorities and preferences was undertaken by the Cochrane ERT for the 2021 update, but there was limited evidence available to inform the formulation of guideline recommendations.

Resource use and costs. Healthcare and non-healthcare resources, including all inputs in the treatment management pathway,[132] were considered in grading the strength of the recommendation. The following resources were considered: direct healthcare costs; non-healthcare resources, such as transportation and social services; informal caregiver resources (e.g., time from the family and caregivers); and changes in productivity. Economic evaluations, including cost-effectiveness analysis, were not conducted for any of the guideline topics.

Practice points

In addition to graded recommendations, KDIGO guidelines now include "practice points" to help clinicians better evaluate and implement the guidance from the expert Work Group. Practice points are consensus statements about a specific aspect of care, and they supplement recommendations for which a larger quantity of evidence was identified. Although systematic reviews are not performed for clinical questions underlying practice points, they are often crafted to help readers implement the guidance from graded recommendation. Practice points represent the expert judgment of the guideline Work Group, but they may also be based on limited evidence. For example, practice points were provided

Table 9 | Determinants of the strength of a recommendation

Factor	Comment
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the more likely a Level 1 recommendation is provided. The narrower the gradient, the more likely a Level 2 recommendation is warranted.
Certainty of evidence	The higher the certainty of evidence, the more likely a Level 1 recommendation is warranted. However, there are exceptions for which low or very low certainty of evidence will warrant a Level 1 recommendation.
Values and preferences	The more variability in values and preferences, or the more uncertainty in values and preferences, the more likely a Level 2 recommendation is warranted. Values and preferences were obtained from the literature, when possible, or were assessed by the judgment of the Work Group when robust evidence was not identified.
Resource use and costs	The higher the costs of an intervention—that is, the more resources consumed—the less likely a Level 1 recommendation is warranted.

on monitoring, factors for consideration in treating patients with IgAN/IgAV, dosing adjustments, and use of therapies in specific subgroup populations. Practice points are sometimes formatted as a table, a figure, or an algorithm to make them easier to use in clinical practice.

Format for guideline recommendations

Each guideline recommendation provides an assessment of the strength of the recommendation (Level 1 or Level 2) and the certainty of the evidence (A, B, C, D). The recommendation statements are followed by Key information (Balance of benefits and harms, Certainty of the evidence, Values and preferences, Resource use and costs, and Considerations for implementation), and Rationale. Each recommendation is linked to relevant SoF tables. An underlying rationale may support a practice point.

Limitations of the guideline development process

The evidence review prioritized RCTs as the primary source of evidence. Therefore, the reviews were not exhaustive, as specialty or regional databases were not searched and manual searching of journals was not performed for these reviews. In the development of this guideline, no scoping exercise with patients nor formal qualitative evidence synthesis examining patient experiences and priorities were undertaken. As noted, although resource implications were considered in the formulation of recommendations, formal economic evaluations were not undertaken for all topics.

Biographic and disclosure information

Jürgen Floege, MD (Work Group Co-Chair), trained at the Hannover Medical School, Hannover, Germany; the Albert Einstein College of Medicine, Bronx, New York; and the University of Washington, Seattle, Washington, USA. He was Head of the Division of Nephrology and Immunology at the University of Aachen, Aachen, Germany, from 1999 to July 31, 2023. Thereafter, he was awarded the position of Senior Professor at the RWTH Aachen University Medical School.

Professor Floege is a former executive council member of the International Society of Nephrology, the European Renal Association (ERA), and Kidney Disease: Improving Global Outcomes (KDIGO). He is a Distinguished Fellow of ERA and recipient of the 2018 ERA Award for Outstanding Clinical Contributions to Nephrology. Together with Professors Richard Johnson and Marcello A. Tonelli, he edits the best-selling textbook *Comprehensive Clinical Nephrology*. Until 2017, he served as Associate Editor of *Nephrology Dialysis Transplantation*. He has been Associate Editor of *Kidney International* since January 2018 and Editor-in-Chief of *Clinical Kidney Journal* since September 2023.

His research interests encompass both basic research (i.e., studies underlying progression of kidney disease in particular kidney fibrosis) and clinical research on immune-mediated kidney disease, in particular IgA nephropathy, as well as chronic kidney disease-mineral and bone disorders and cardiovascular disease in patients with uremia.

JF reports receiving consultancy fees and/or speaker honoraria from AstraZeneca, Biogen, Boehringer Ingelheim, CSL, Novartis, Otsuka, Roche, STADA, Travere, Vera Therapeutics, Vertex, and Vifor and serving on data safety monitoring boards of Novo Nordisk and Visterra.

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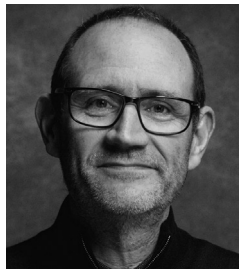
BHR reports receiving consultancy fees from Alexion, Artiva, AstraZeneca, Aurinia, BioCryst, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Calliditas, Exagen, Genentech/Roche, Gilead, GlaxoSmithKline, Kezar Life Sciences, Kyverna, Lilly, Novartis, Otsuka, Travere, Vera Therapeutics, and Vertex and grant/research support from Biogen, Lupus Research Alliance*, and the National Institutes of Health.**
**Monies paid to institution*



Jonathan Barratt, MBChB, PhD, is the Mayer Professor of Renal Medicine in the Department of Cardiovascular Sciences at the University of Leicester, Leicester, UK. His research focuses on a bench-to-bedside approach to better understanding the pathogenesis of IgA nephropathy, a common global cause of kidney failure. Dr. Barratt is the IgA Nephropathy Rare Disease Group lead for the UK National Registry of Rare Kidney Diseases and Convener of the International IgA Nephropathy Network. He works closely with pharmaceutical companies interested in new treatments for IgA nephropathy and is the chief investigator for several international phase 2 and 3 randomized controlled trials in IgA nephropathy. He was a member of the Work Group of the Food and Drug Administration and American Society of Nephrology's Kidney Health Initiative project "Identifying Surrogate Endpoints for Clinical Trials in IgA Nephropathy."

JB reports receiving grants or contracts from Alexion, Argenx, Calliditas, Chinook, Galapagos, GlaxoSmithKline, Novartis, Omeros, Travere, and Visterra and consultancy fees from Alexion, Alnylam, Argenx, Astellas, BioCryst, Calliditas, Chinook, Dimerix, Galapagos, Novartis, Omeros, Travere, Vera Therapeutics, and Visterra.

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His major research interests include the role of complement activation in glomerular disease and the use of histologic features in human kidney biopsies to predict outcomes and treatment responses. He has conducted international collaborative studies to develop consensus classifications for

lupus glomerulonephritis, IgA nephropathy, and C3 glomerulopathy. He is a past president of the Renal Pathology Society and has contributed to more than 370 peer-reviewed publications.

HTC reports receiving consultancy fees from Novartis, Q32 Bio, Sobi, and Purespring.

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Upon returning to Brazil, Dr. Noronha played a key role in developing kidney, kidney-pancreas, and islet transplantation programs, with a particular emphasis on diabetic kidney disease. She leads a research laboratory focused on the immune, cellular, and molecular mechanisms involved in the progression of kidney disease and development of cell therapies. She also heads the Glomerular Diseases Unit at the University Hospital and coordinated the first Brazilian Registry on Glomerular Diseases through the Brazilian Society of Nephrology.

Dr. Noronha is the principal investigator in numerous clinical trials and, as Coordinator of the Clinical Research Center at the University Hospital, she has worked diligently to establish and strengthen clinical research in her region. From 2021 to 2024, she served as a member of the Kidney Disease: Improving Global Outcomes (KDIGO) Executive Committee.

ILN reports receiving consultancy fees from AstraZeneca; grant/research support from George Clinical–Dimerix, George Clinical–Travere, Roche*, and Vertex*; speaker honoraria from AstraZeneca and Bayer; and travel support from AstraZeneca, Chinook, and Novartis.*

**Monies paid to institution.*

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HNR reports receiving consultancy fees or clinical trial support from Alexion, Biogen, Calliditas, Novartis, Otsuka, Travere, and Vera Therapeutics. She supervises the University Health Network Glomerulonephritis (UHN GN) Fellowships supported by the Louise Fast Foundation and Otsuka.

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**Monies paid to institution.*

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Dr. Trimarchi is a former council member of the Glomerular Diseases Committee of the Buenos Aires Nephrology Association and of the Argentine Society of Nephrology. He has been a member of many scientific committees of the Argentine Congress of Nephrology for the past 15 years. He is a member of the Steering Committee of the International IgA Nephropathy Network, a member of the International Society of Nephrology (ISN) Continuing Medical Education (CME) Program Committee (since 2020), a member of the ISN Latin America Regional Board (since 2021), and Editor-in-Chief of the *Journal of the Argentinian Society of Nephrology* (*Nefrología Argentina*). He is also a Fellow of the American Society of Nephrology and of the American College of Physicians and an active member of the ISN and of the International Society of Transplantation. Dr. Trimarchi received his PhD degree in 2010 for research on the endothelium in chronic hemodialysis and he has been awarded the Miatello Prize of the Argentine Society of Nephrology in 2003, 2013, and 2015 and the Lanari Prize of the Argentine Society of Nephrology in 2016; he was also the recipient of yearly Hospital Británico de Buenos Aires Clinical Research Award consecutively from 2007 to 2012. He was also awarded the Facultad de Medicina Prize from the Universidad de Buenos Aires in 2013 for his research on endothelium and homocysteine in chronic kidney disease. Professor Trimarchi also serves on the editorial boards of many nephrology and transplantation journals and has written numerous book chapters on endothelium, hypertension, glomerulonephritis, and transplantation. He is the lead editor of the book *Glomerular Diseases* published in 2017, the first of its kind in Spanish.

Dr. Trimarchi is also involved in many clinical research protocols related to glomerular diseases, in which he participates as a member of the advisory board, knowledge leader, or national coordinator. Finally, he is Professor of Medicine at the Universidad Católica Argentina and Director of the

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**Monies paid to institution.*

KDIGO Chairs

Michel Jadoul, MD, chaired the Division of Nephrology of the Cliniques universitaires Saint-Luc for 20 years (2003–2023) and is now a young emeritus full clinical professor at UCLouvain, both in Brussels, Belgium. His clinical activities still include follow-up of patients with chronic kidney disease (CKD) undergoing hemodialysis.

His research interests encompass various complications of hemodialysis, including hepatitis C, cardiovascular complications after kidney transplantation, various causes of drug nephrotoxicity, and the epidemiology of CKD in sub-Saharan Africa.

Professor Jadoul has (co-)authored more than 360 scientific papers, most of them published in major nephrology journals. He is an associate editor of *Nephrology Dialysis Transplantation*. In 2008, he received the International Distinguished Medal of the National Kidney Foundation and was a member of the European Renal Association Council (2013–2016). Professor Jadoul co-chaired the development of the 2008, 2018, and 2022 versions of the Kidney Disease: Improving Global Outcomes (KDIGO) Hepatitis C Virus in Chronic Kidney Disease Guideline and is a KDIGO Co-Chair since January 1, 2019.

MJ reports receiving consultancy fees from Astellas, AstraZeneca, Bayer*, and Boehringer Ingelheim*; speaker honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Menarini, and STADA-Eurogenerics; funding for expert testimony from STADA-Eurogenerics*; travel support from AstraZeneca and Boehringer Ingelheim*; and serving as an advisory board member of Boehringer Ingelheim, CSL Vifor, and Novo Nordisk.*
**Monies paid to institution.*

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MEG reports receiving grants or contracts from the National Institutes of Health and National Kidney Foundation (NKF)*; speaker honoraria from the University of Washington; and travel support from ASN, KDIGO, and NKF and serving as an advisory board member of Kidney Research Institute, Optimal Aging Institute, and United States Renal Disease System.*
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Methods Chair

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MAT declared no competing interests.

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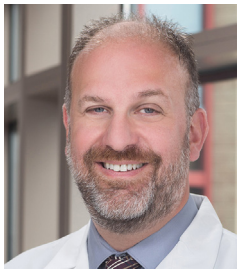
EMB reports receiving grants or contracts from the Agency for Healthcare Research and Quality, the American Society of Hematology*, and KDIGO* and consultancy fees from the Centers for Disease Control and Prevention and the Society of Gynecologic Surgeons.*

**Monies paid to institution.*



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Dr. Gordon provided methodological expertise to the Work Group during the guideline development process and assisted in the collection, evaluation, grading, and synthesis of evidence for the guideline as well as providing guidance to the Work Group members in the areas of topic refinement, key question formulation, data extraction, study assessment, evidence grading, and recommendation formulation. His primary research and clinical interests are in the management of hepatitis C virus in patients with chronic kidney disease, polycystic kidney disease, and thrombotic microangiopathies as well as evidence-based medicine and systematic review related to other areas of nephrology.

CEG reports receiving consultancy fees from Alexion, Calliditas, and Novartis and speaker honoraria from Alexion and Novartis.

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GPA declared no competing interests.

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