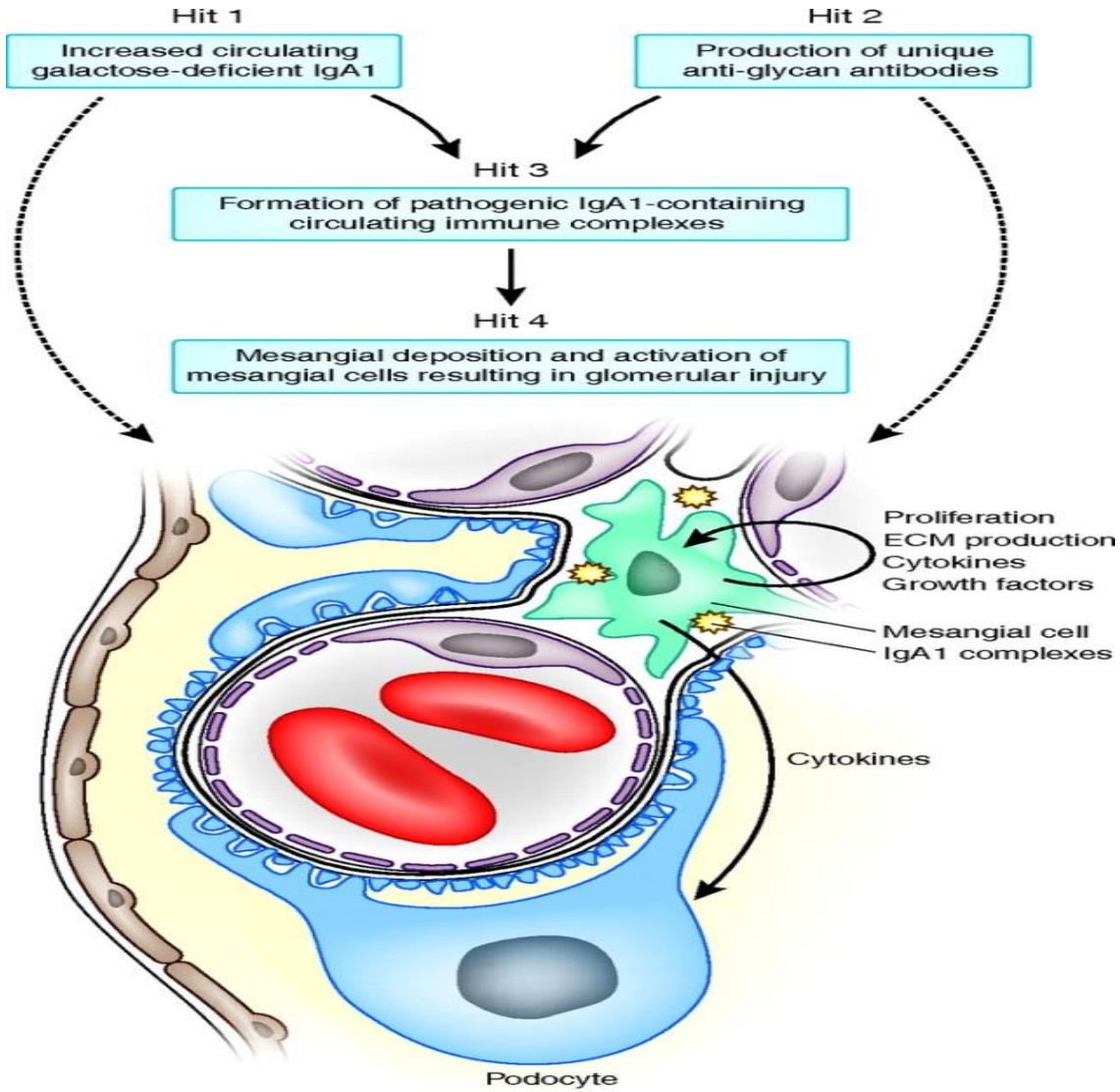
Treatment of IgA Nephropathy

Manuel Praga

Departamento de Medicina, Universidad Complutense Madrid

Proposed pathways involved in the pathogenesis of IgAN: multi-hit mechanism.



Suzuki H et al. JASN 2011;22:1795-1803

IgAN. Clinical Presentations

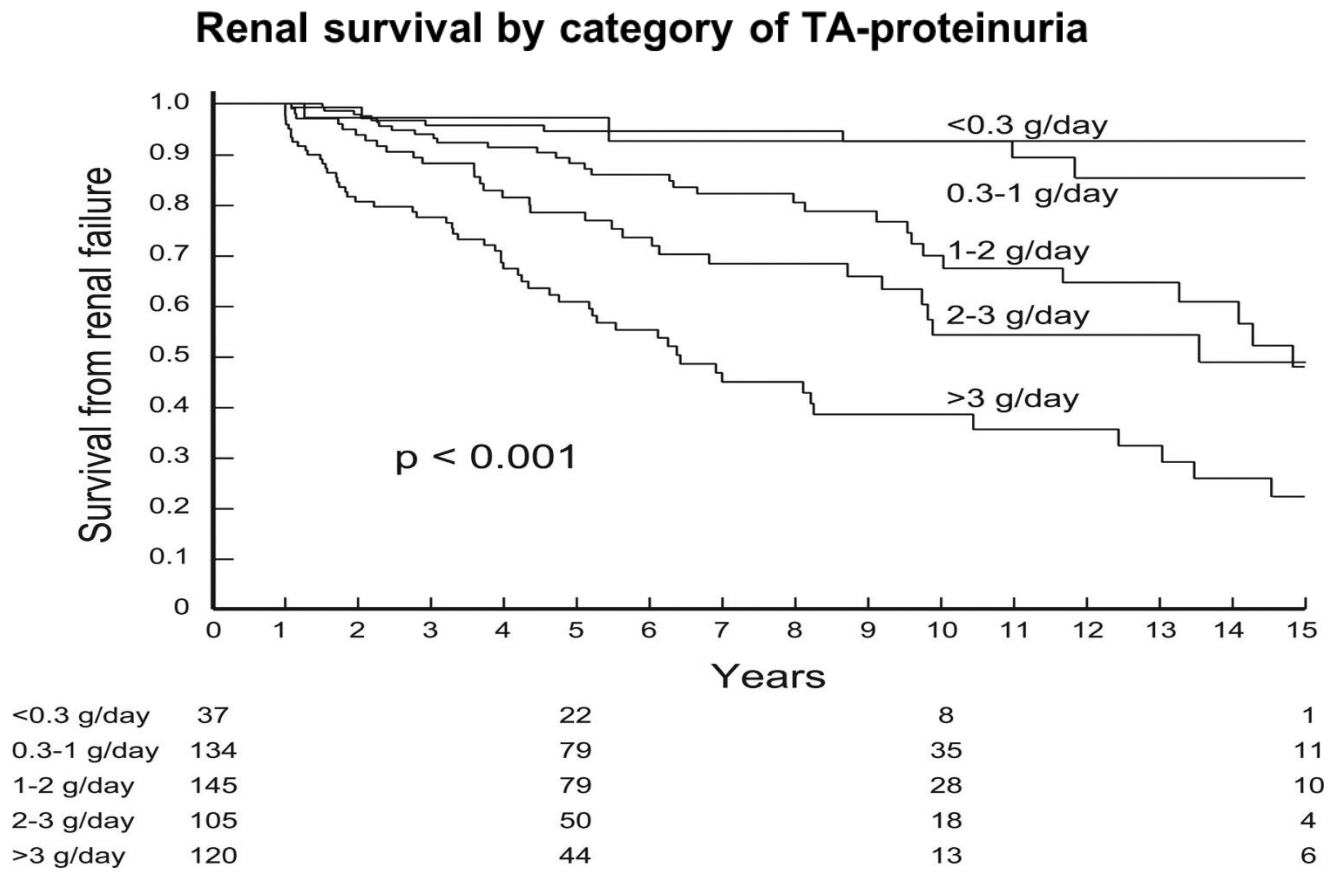
Most Frequent Presentation:

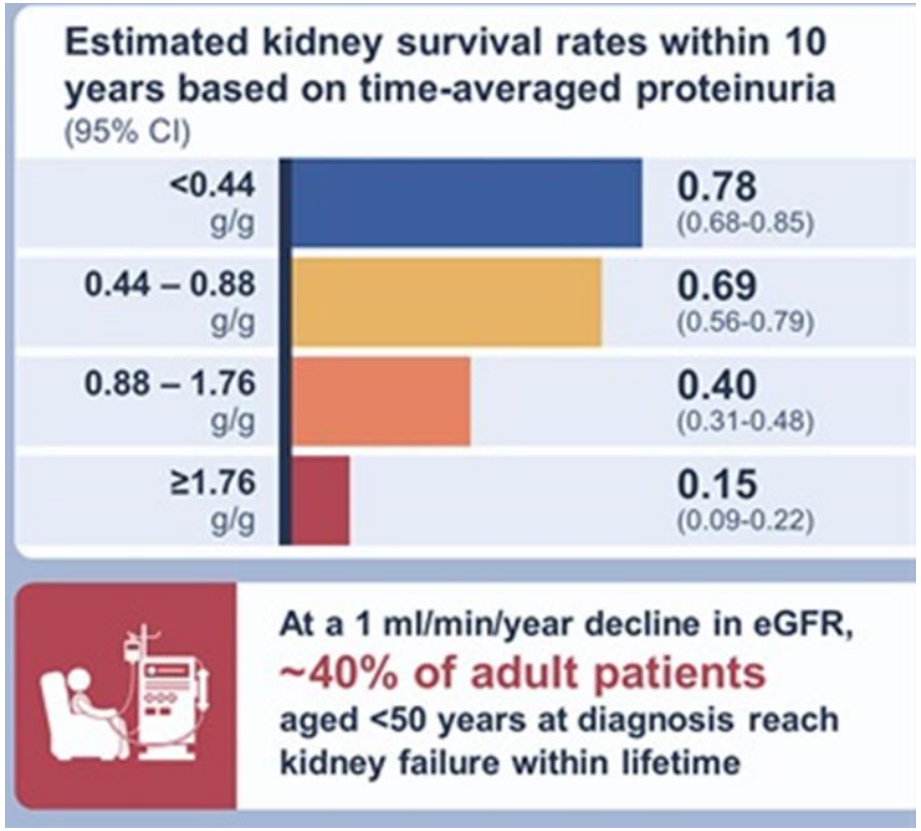
Microscopic hematuria+proteinuria with or without episodes of gross hematuria (usually coincidental with respiratory infections)

«Atypical presentations»

-AKI accompanying episodes of macroscopic hematuria

- ***Malignant hypertension/Thrombotic microangiopathy lesions in kidney biopsy***
- ***Crescentic IgAN (>50% glomeruli with crescents)***
- ***Complete nephrotic syndrome***





Remission of proteinuria improves prognosis in IgA nephropathy

Heather N Reich et al

J Am Soc Nephrol 2007;18:3177-3183

Pitcher D at el. Long-Term Outcomes in IgA Nephropathy. Clin J Am Soc Nephrol 2023; 18(6):727-738

Remission of Hematuria Improves Renal Survival in IgA Nephropathy

Angel M. Sevillano,* Eduardo Gutiérrez,* Claudia Yuste,* Teresa Cavero,* Evangelina Mérida,* Paola Rodríguez,* Ana García,* Enrique Morales,* Cristina Fernández,† Miguel Angel Martínez,‡ Juan Antonio Moreno,§ and Manuel Praga*‖

Cohort of 112 biopsy-proven IgAN, regularly monitored with urine sediment examination

Two groups according with the mean value of hematuria (erythrocytesxhpf) during follow-up (Time-averaged hematuria: TA-H):

-Persistent Hematuria (TA-H >5 hxhpf)

-Negative or minimal Hematuria (TA-H <5 hxhpf)

Patients were also divided according to the magnitude of Time-averaged proteinuria (TA-P):

-TA-P <0.75 g/d

-TA-P >0.75 g/d

JASN 2017;28:3089-3099

Remission of hematuria improves renal survival in IgAN

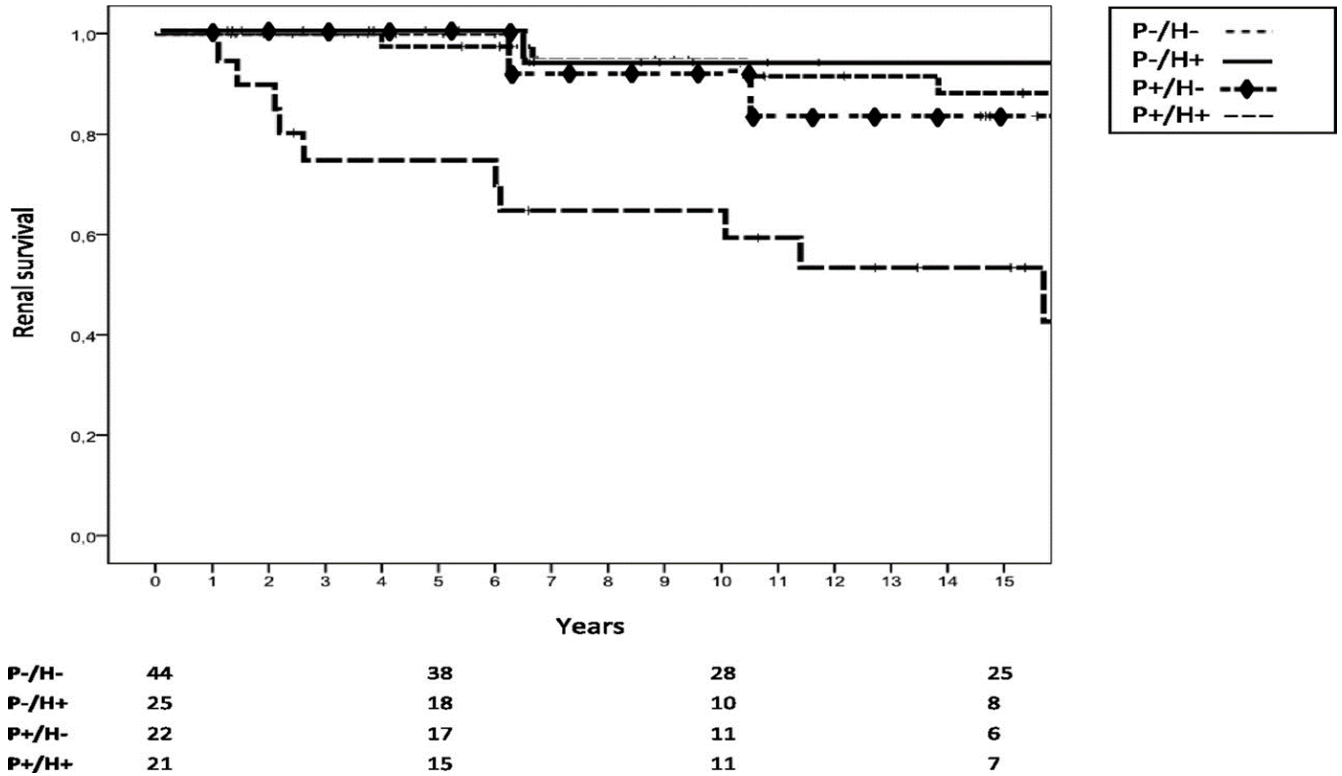


Table 5. Rate of renal function decline before and after hematuria disappearance

Variable	Before Hematuria Disappearance	After Hematuria Disappearance	*P* Value
Rate of renal function decline, ml/min per 1.73 m^2 per yr[a]	−6.45±14.66	−0.18±2.56	0.001
Follow-up, mo	5.98±5.92[b]	10.71±9.5[c]	0.003

Table 1. Association between patient characteristics and hematuria at baseline

Baseline variables	Hematuria at baseline[a]			
	Absent ($n=28$)	Present ($n=97$)	P-value	Total
Histology, *n* (%)				
M (1 versus 0)	18 (64.3)	84 (86.6)	**0.007**	102 (81.6)
E (1 versus 0)	0 (0.0)	30 (30.9)	**0.001**	30 (24.0)
S (1 versus 0)	20 (71.4)	62 (63.9)	0.46	82 (65.6)
T (≥1 versus 0)	13 (46.4)	32 (33.0)	0.19	45 (36.0)
C (≥1 versus 0)	3 (10.7)	31 (32.0)	**0.026**	34 (27.2)

The association of microhematuria with mesangial hypercellularity, endocapillary hypercellularity, crescent score and renal outcomes in immunoglobulin A nephropathy

Shane A. Bobart [1,*], Mariam P. Alexander [2,*], Khaled Shawwa [1], Lisa E. Vaughan [3], Ranine Ghamrawi [1], Sanjeev Sethi [2], Lynn Cornell [2], Richard J. Glassock [4], Fernando C. Fervenza [1] and Ladan Zand [1]

Table 2. Estimates for rate of eGFR change per year by median degree of hematuria throughout follow-up

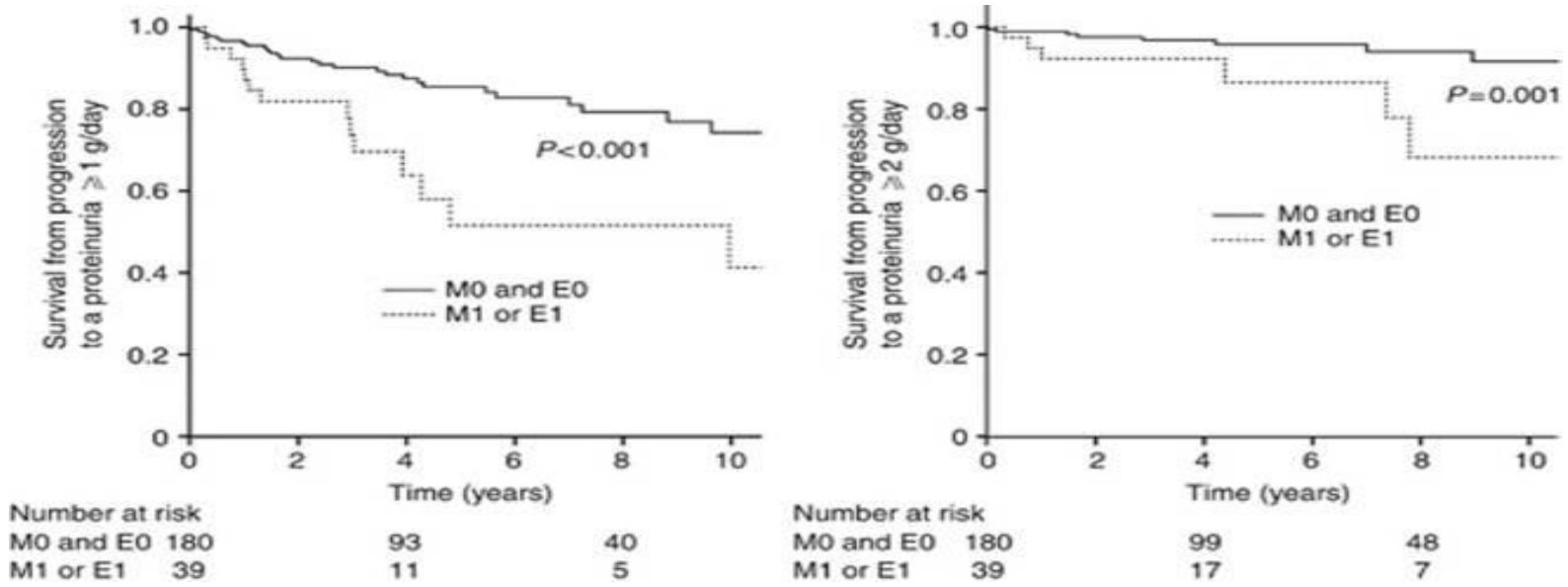
Median degree of hematuria throughout follow-up[a]	eGFR decline rate (SE)[b]
0	5.80 (2.05)
1 to ≤3	2.10 (1.44)
3–10	−1.60 (1.14)
11–20	−5.30 (1.38)
21–30	−9.00 (1.96)
31–40	−12.70 (2.67)
41–50	−16.40 (3.43)
51–100	−20.10 (4.22)
>100	−23.80 (5.01)

Nephrol Dial Transplant (2021) 36: 840–847

Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments

MEST-C score

- *Mesangial proliferation*
- *Endocapillary hypercellularity*
- *Segmental glomerulosclerosis*
- *Tubulointerstitial fibrosis*
- *Crescents*



Kidney Int, 2014; 86:828

IgAN Management

Non-Immunosuppressive drugs

(+ conservative antiproteinuric/renoprotective measures: smoking, obesity, physical activity, salt restriction)

***-RAS blockers** (ACEI; ARBs)*

***-Antiproteinuric diuretics** (antialdosteronics; thiazides; chortalidone; amiloride)*

-SGLT2i

-Sparsentan

-Endothelin antagonists

(Atrasentan and others; ongoing trials)

Immunosuppressive/pathogenically-targeted drugs

-Corticosteroids

-MMF

-Targeted-released budesonide

Ongoing trials with positive preliminary results

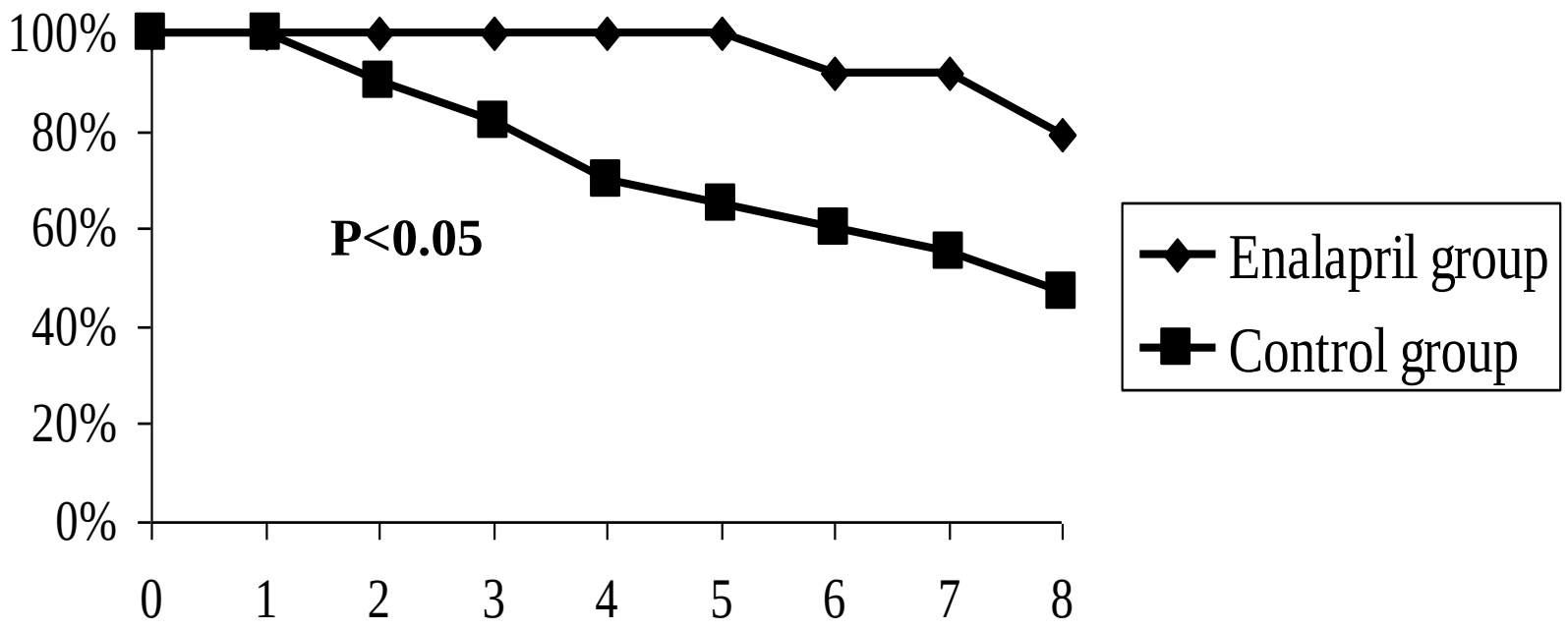
-Anti-April drugs

-Complement blockers (Iptacopan, Avacopan, Eculizumab, Cemdisiran)

Treatment of IgA nephropathy with ACE inhibitors
A randomized and controlled trial

44 IgAN patients
SCr < 1.5 mg/dl
Proteinuria > 0.5 g/24 h,

Renal survival
(50% increase in SCr)



Praga M et al
J Am Soc Nephrol 2003; 14:1578-1583

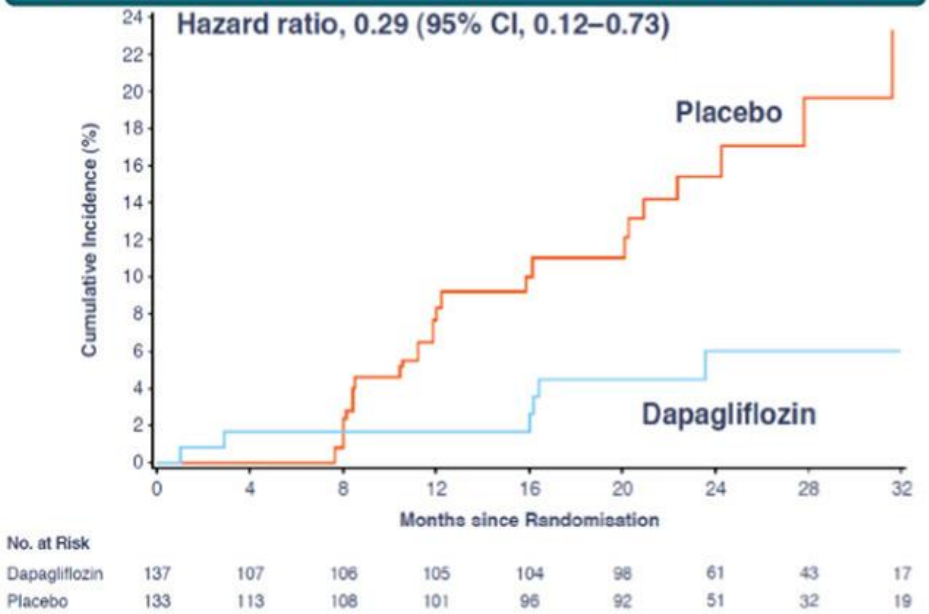
A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy.

DAPA-CKD population:

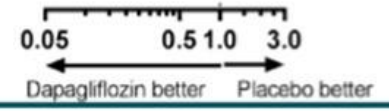
- eGFR 25-75 mL/min/1.73m^2
- UACR 200-5000 mg/g
- Receiving a stable, maximally tolerable ACEi/ARB dose
- With and without type 2 diabetes

⇨ **270 participants with IgA nephropathy** ⇨ **254 participants with biopsy-confirmed IgA nephropathy**

Composite primary endpoint in patients with IgA nephropathy (n=270)



	Hazard Ratio (95%CI)	P Value
Composite primary endpoint (≥50% eGFR decline/ESKD/CV or kidney death)		
Patients with IgA nephropathy	0.29 (0.12, 0.73)	0.005
Patients with biopsy-confirmed IgA nephropathy	0.28 (0.11, 0.72)	0.005
Composite of kidney endpoint (≥50% eGFR decline/ESKD/kidney death)		
Patients with IgA nephropathy	0.24 (0.09, 0.65)	0.002
Patients with biopsy-confirmed IgA nephropathy	0.23 (0.09, 0.63)	0.002



IgA, immunoglobulin A; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; ESKD, end-stage kidney disease

CONCLUSION:

In patients with IgA nephropathy, when added to ACEi/ARB therapy, dapagliflozin significantly and substantially reduced the risk of CKD progression

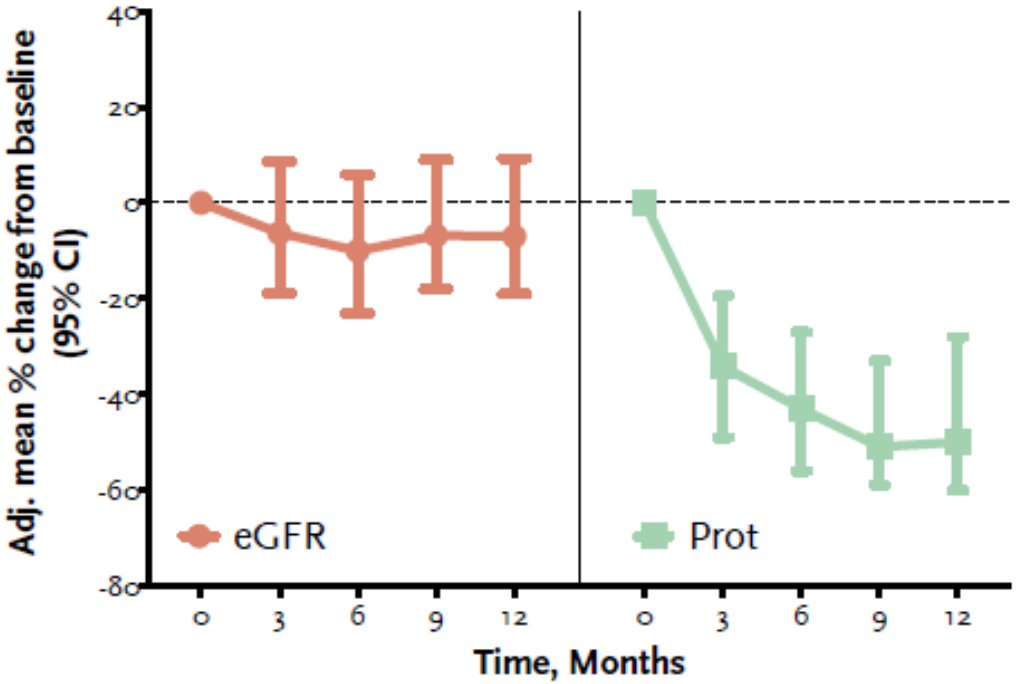
kidney INTERNATIONAL ISN

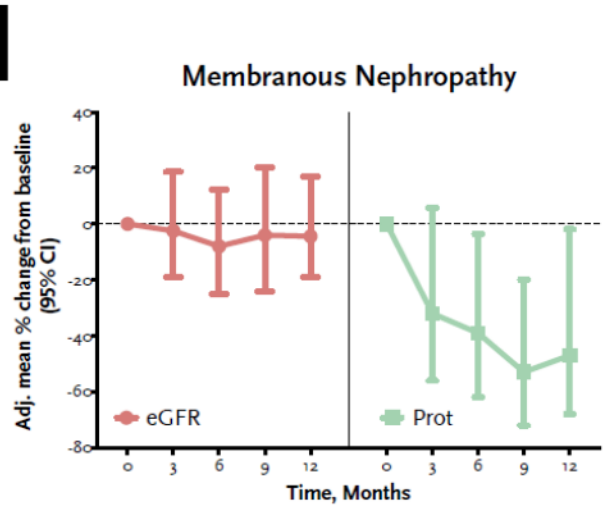
Wheeler et al, 2021

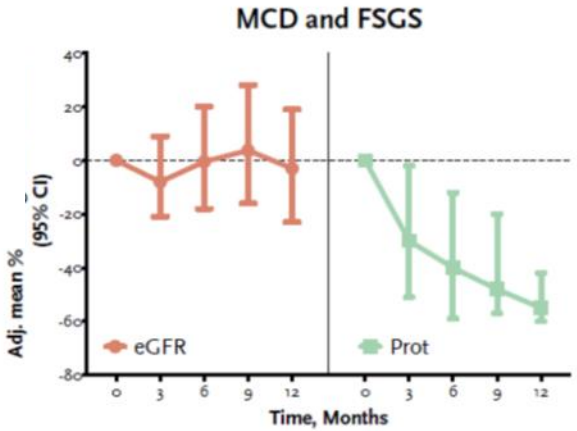
Nephrol Dial Transplant, 2024, 39, 328–340
https://doi.org/10.1093/ndt/gfad175
Advance access publication date: 7 August 2023

Sodium-glucose cotransporter 2 inhibition in primary and secondary glomerulonephritis

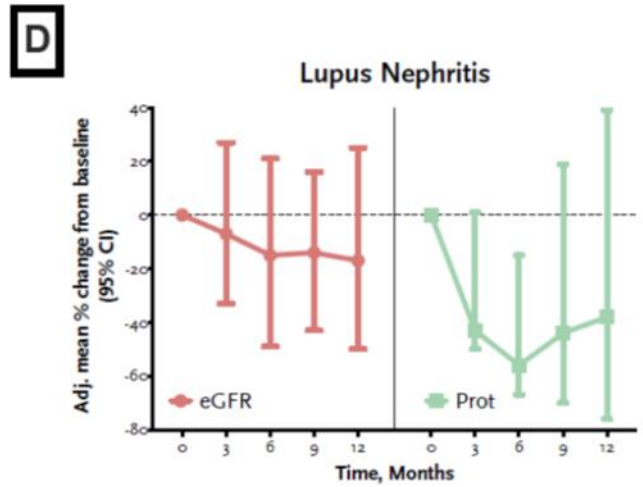
IgAN=192







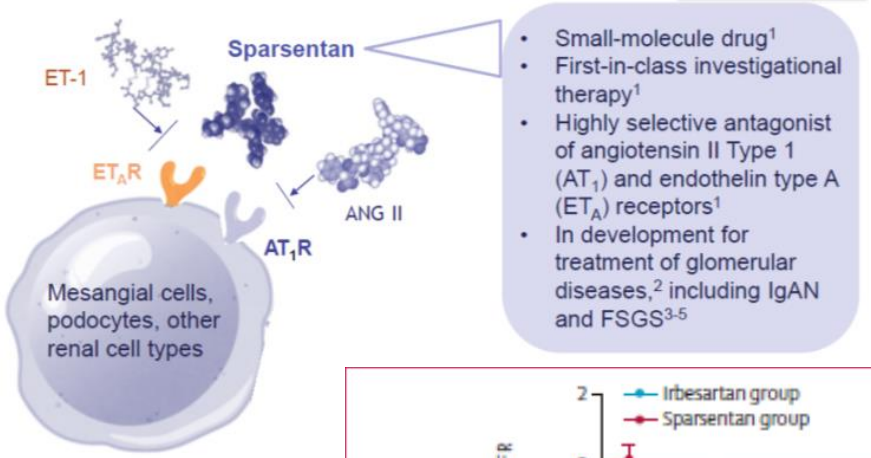
Number of Patients 104 104 70 43 25



Caravaca-Fontán F et al. NDT 2024

Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial

Brad H Rovin, Jonathan Barratt*, Hiddo J L Heerspink, Charles E Alpers, Stewart Bieler, Dong-Wan Chae, Ulysses A Diva, Jürgen Floege, Loreto Gesualdo, Jula K Inrig, Donald E Kohan, Radko Komers, Laura Ann Kooienga, Richard Lafayette, Bart Maes, Robert Małecki, Alex Mercer, Irene L Noronha, SeWon Oh, Chen Au Peh, Manuel Praga, Priscila Preciado, Jai Radhakrishnan, Michelle N Rheault, William E Rote, Sydney C W Tang, Vladimir Tesar, Howard Trachtman, Hernán Trimarchi, James A Tumlin, Muh Geot Wong, Vlado Perkovic, on behalf of the DUPRO steering committee and PROTECT Investigators†*



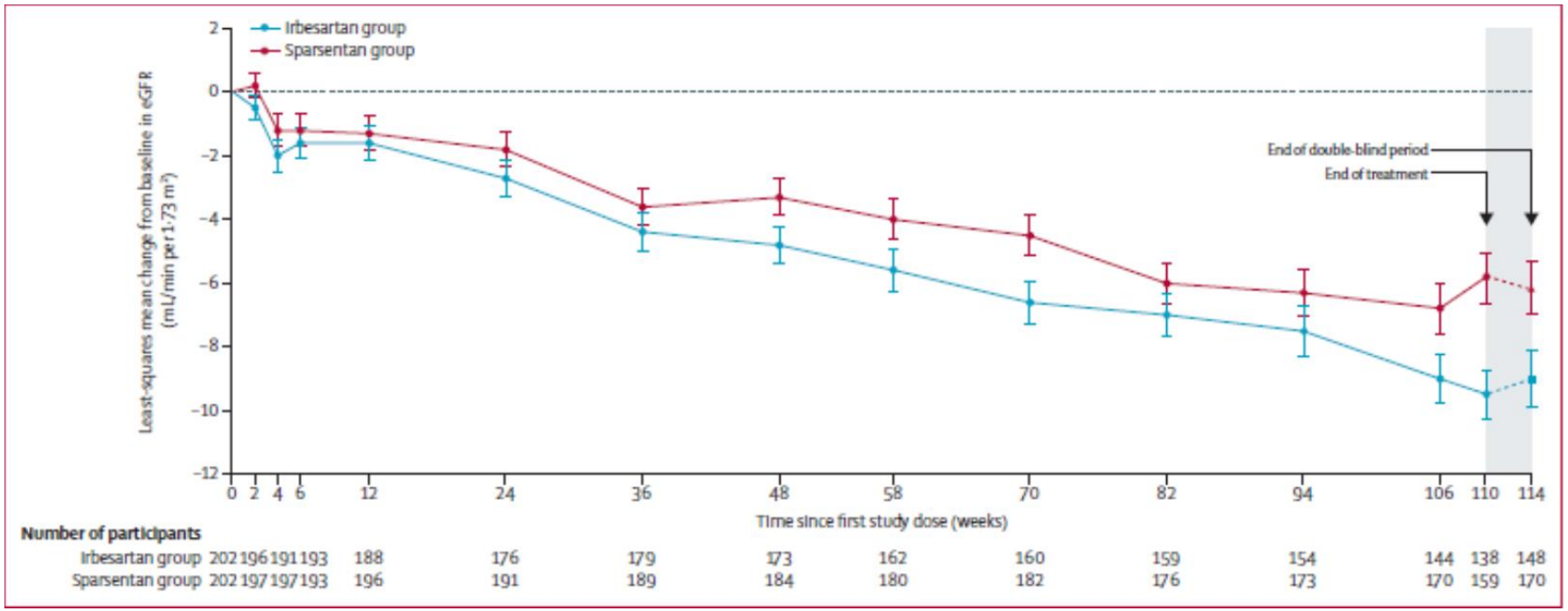
- Small-molecule drug[1]
- First-in-class investigational therapy[1]
- Highly selective antagonist of angiotensin II Type 1 (AT_1) and endothelin type A (ET_A) receptors[1]
- In development for treatment of glomerular diseases,[2] including IgAN and FSGS[3-5]

	Sparsentan group (n=202)	Irbesartan group (n=202)
Urine protein-to-creatinine ratio, g/g	−42·8% (−49·8 to −35·0)	−4·4% (−15·8 to 8·7)
Urine protein excretion, g per day	−46·9% (−53·4 to −39·5)	−5·9% (−17·9 to 7·9)
Urine albumin-to-creatinine ratio, g/g	−56·0% (−62·1 to −49·1)	−17·3% (−29·1 to −3·5)
Urine albumin excretion, g per day	−58·8% (−64·7 to −52·0)	−17·9% (−30·1 to −3·6)

Data are geometric least-squares mean (95% CI) change in proteinuria from baseline to week 110 unless otherwise stated.

Table 3: **Change in proteinuria**

Lancet 2023; 402: 2077–90



Management of IgAN

Non-Immunosuppressive drugs

(+ conservative antiproteinuric/renoprotective measures: smoking, obesity, physical activity, salt restriction)

-RAAS blockers

-SGLT2i

-Sparsentan

-Endothelin antagonists

Immunosuppressive/pathogenically-targeted drugs

-Corticosteroids

-MMF

-Targeted-released budesonide

Ongoing trials with positive preliminary results

-Anti-April drugs

-Complement blockers (Iptacopan)

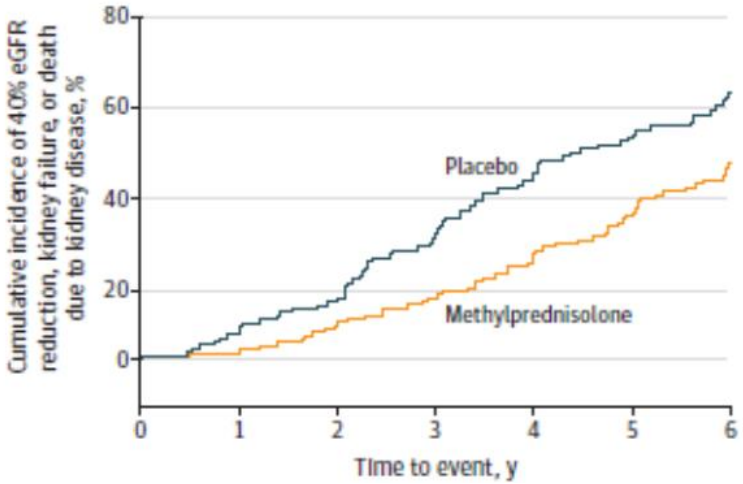
JAMA | Original Investigation

Effect of Oral Methylprednisolone on Decline in Kidney Function or Kidney Failure in Patients With IgA Nephropathy

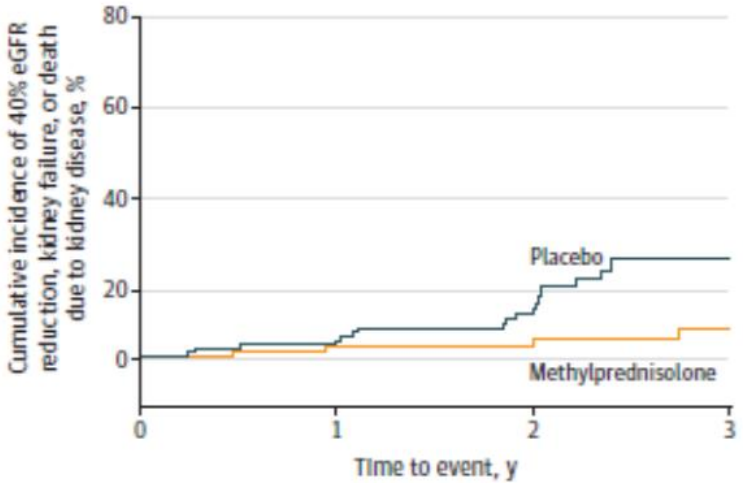
The TESTING Randomized Clinical Trial

INTERVENTIONS Participants were randomized in a 1:1 ratio to receive oral methylprednisolone (initially 0.6-0.8 mg/kg/d, maximum 48 mg/d, weaning by 8 mg/d/mo; n = 136) or placebo (n = 126). After 262 participants were randomized, an excess of serious infections was identified, leading to dose reduction (0.4 mg/kg/d, maximum 32 mg/d, weaning by 4 mg/d/mo) and addition of antibiotic prophylaxis for pneumocystis pneumonia for subsequent participants (121 in the oral methylprednisolone group and 120 in the placebo group).

C Primary outcome in full-dose cohort



D Primary outcome in reduced-dose cohort



JAMA. 2022;327(19):1888-1898.

AJKD
Original Investigation

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

176 patients with IgAN
Active proliferative lesions in renal biopsy
Proteinuria > 1 g/24H
eGFR > 30 mL/min/1.73 m2

Intervention:

-MMF 1.5 g/d for 6 m + Prednisone 0.4-0.6 mg/kg/d for 2 m, tapered for other 4 m

OR

-Prednisone 0.8-1 mg/Kg/d for 2 m, tapered for other 4 m

***Outcome*: Complete remission,**
defined by Proteinuria <0.3 g/d and stable serum creatinine

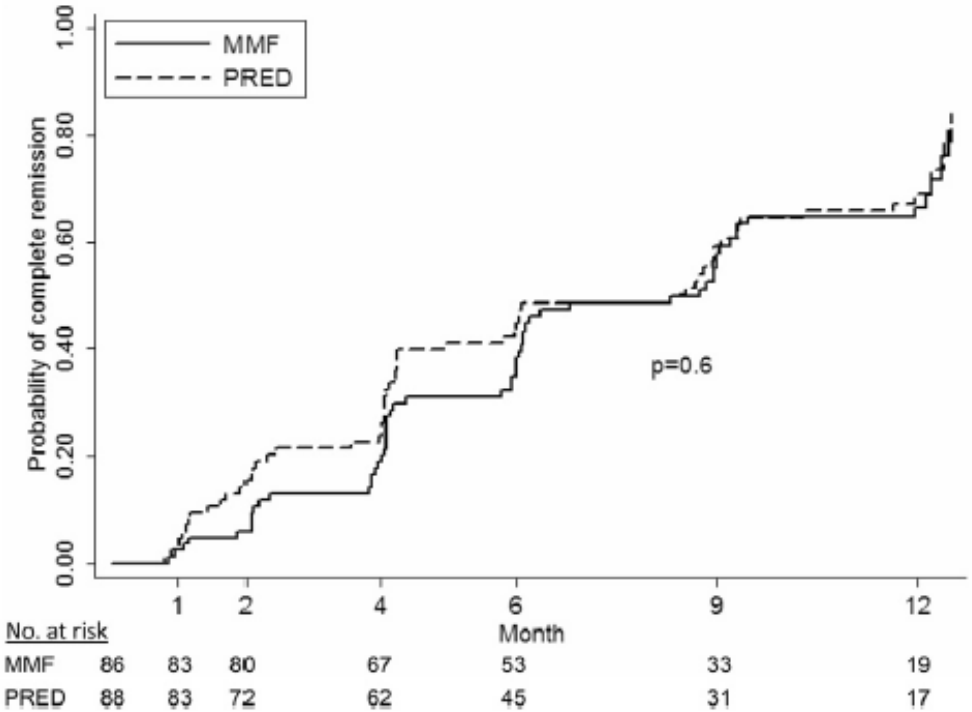


Figure 2. Kaplan-Meier analysis for the probability of complete remission. Abbreviations: MMF, mycophenolate mofetil; PRED, prednisone.

Significantly less side effects
in the MMF+ low Prednisone arm

Original Investigation | Nephrology

Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy

A Randomized Clinical Trial

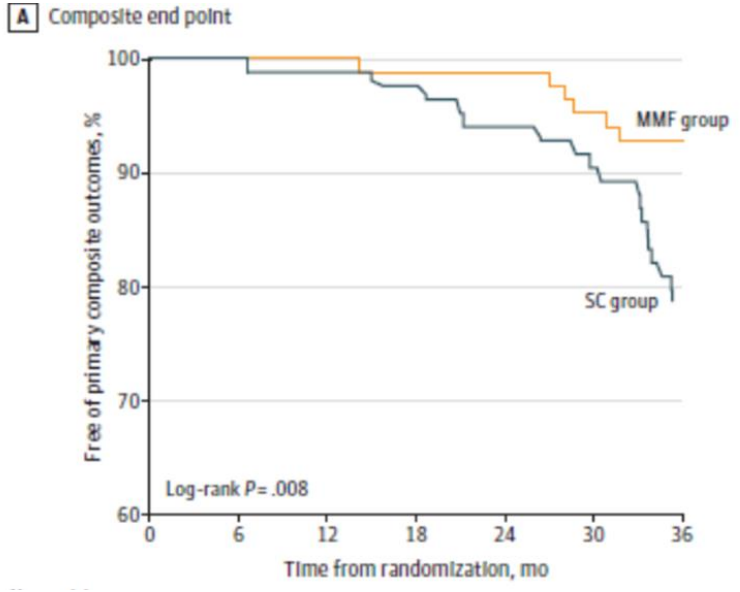
<u>170 patients randomized to:</u>

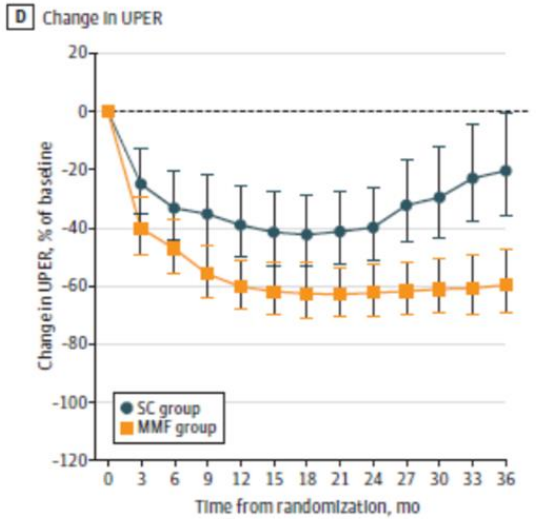
-MMF 1.5 g/d for 12 m,
0.75-1.0 g for at least 6 months
plus SOC

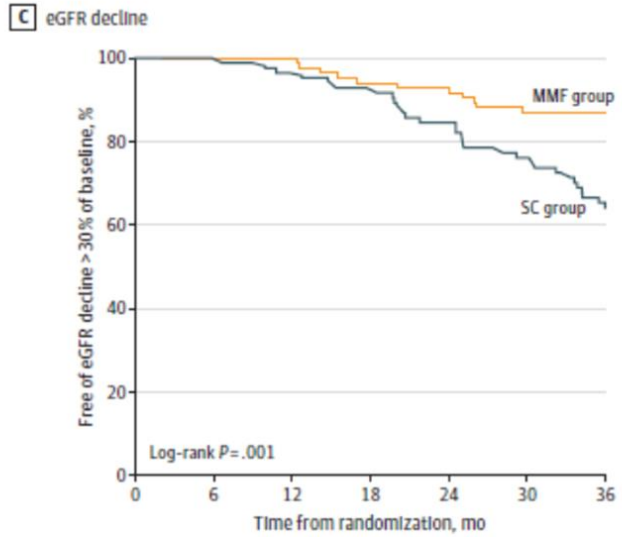
<u>OR</u>

-SOC alone

Outcomes:
-Composite of doubling of SCr, ESKD or death
-Progression of CKD:
eGFR decrease >30% if baseline eGFR>60
« >50% « <60



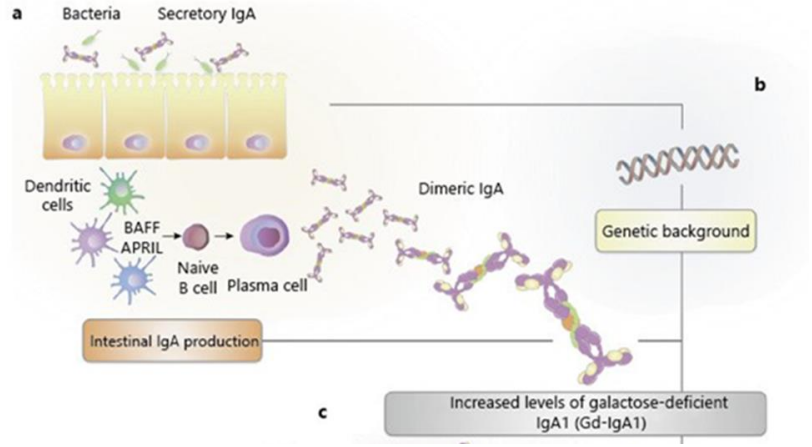




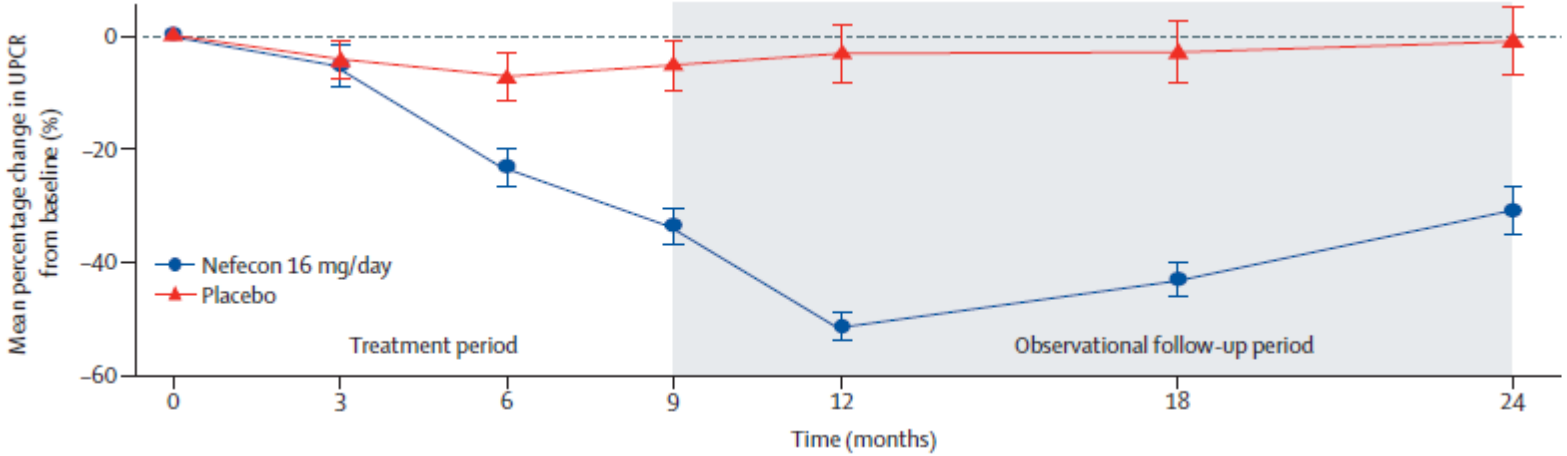
Hou, JAMA Netw Open. 2023 Feb 1;6(2):e2254054

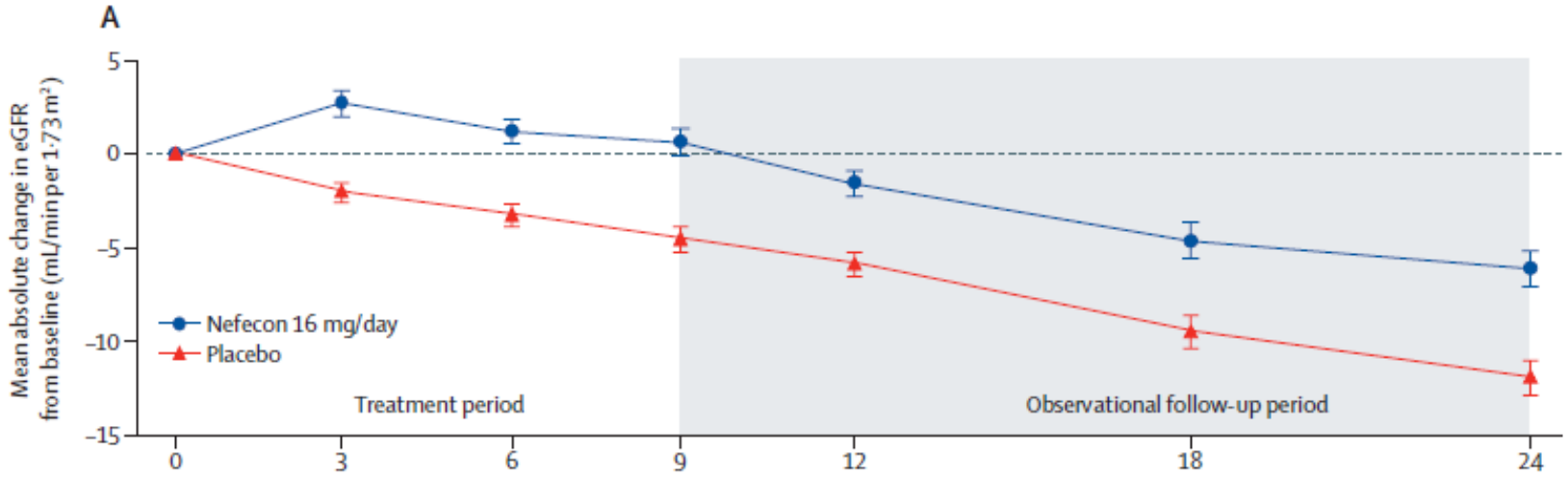
Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial

Richard Lafayette, Jens Kristensen, Andrew Stone, Jürgen Floege, Vladimir Tesař, Hernán Trimarchi, Hong Zhang, Necmi Eren, Alexander Paliege, Heather N Reich, Brad H Rovin, Jonathan Barratt, on behalf of the NefIgArd trial investigators



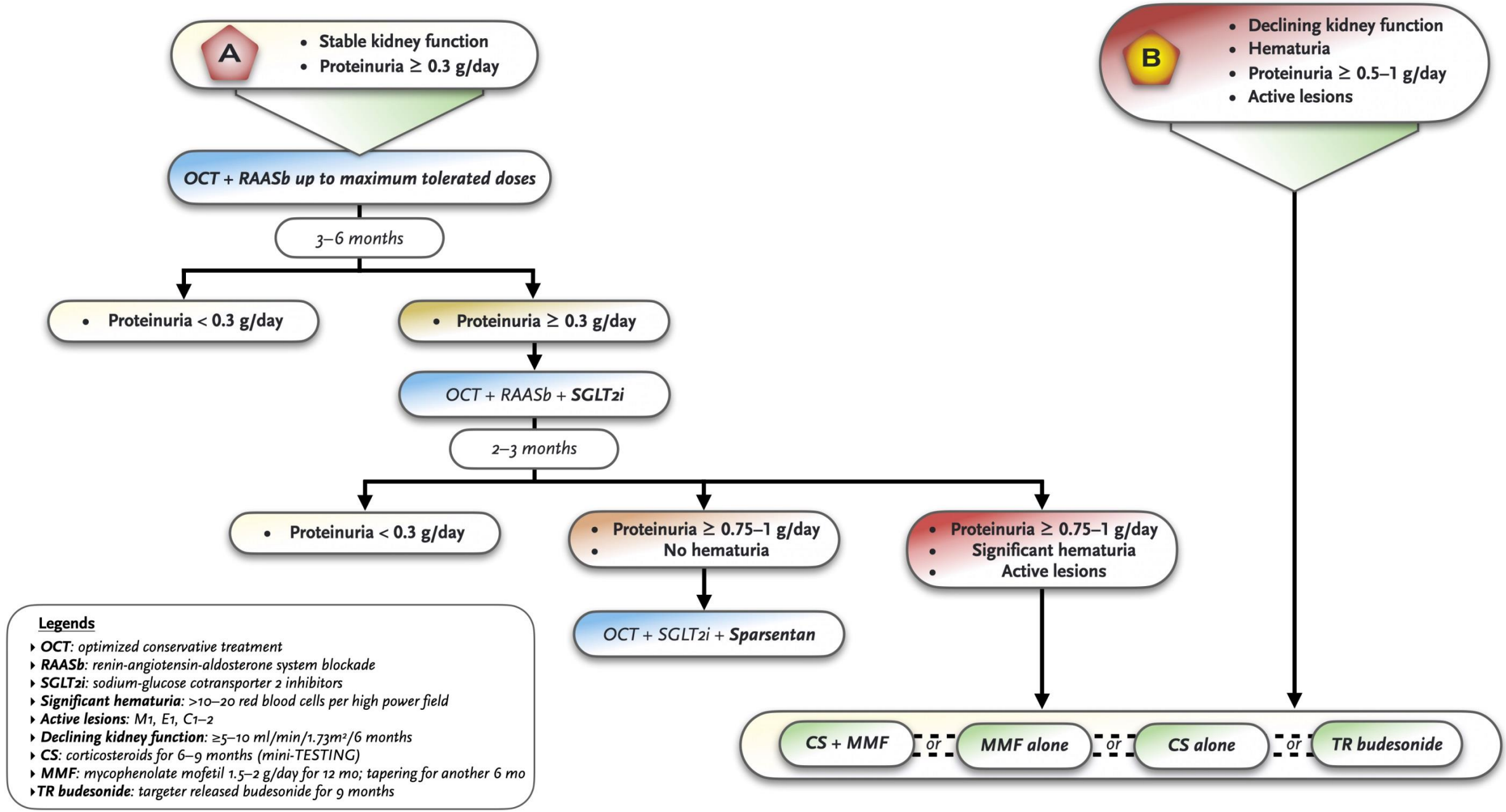
Increased production of Gd-IgA1 in the distal intestine (ileum)





Lancet 2023; 402: 859–70

IgAN Treatment Algorithm



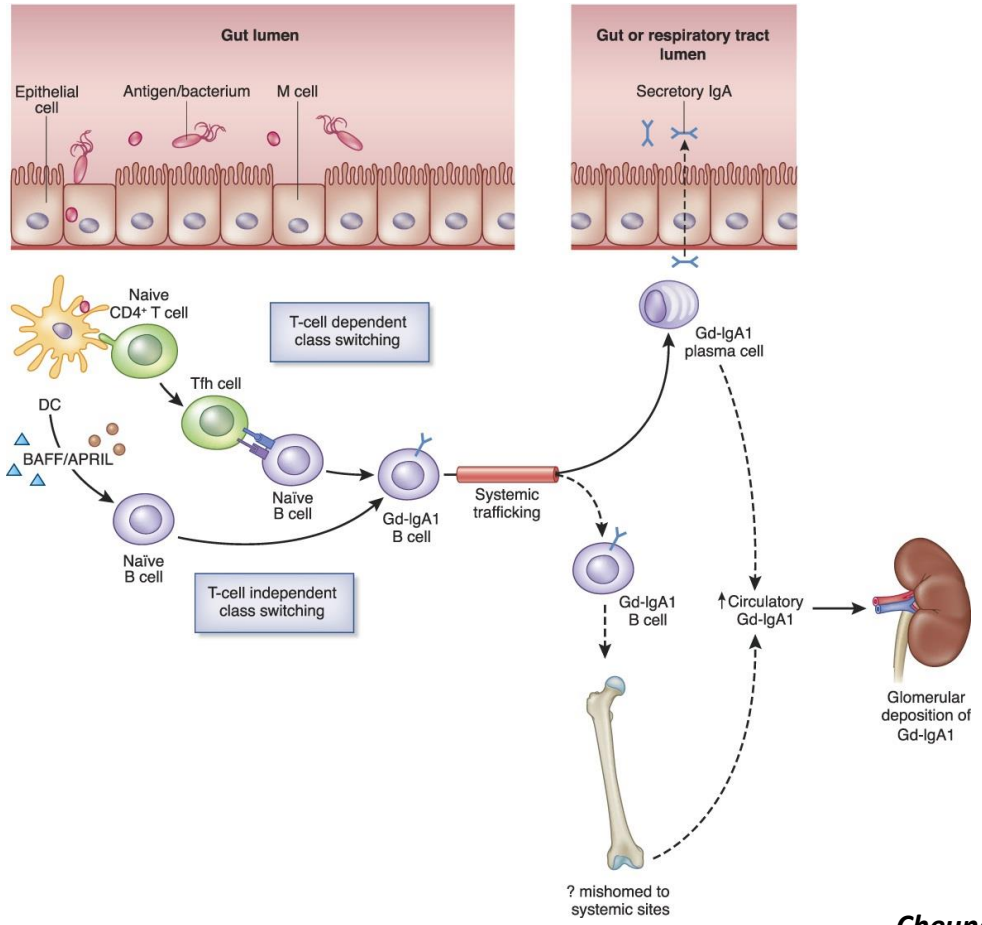
Legends

- ***OCT***: *optimized conservative treatment*
- ***RAASb***: *renin-angiotensin-aldosterone system blockade*
- ***SGLT2i***: *sodium-glucose cotransporter 2 inhibitors*
- ***Significant hematuria***: *>10–20 red blood cells per high power field*
- ***Active lesions***: *M1, E1, C1–2*
- ***Declining kidney function***: *≥5–10 ml/min/1.73m²/6 months*
- ***CS***: *corticosteroids for 6–9 months (mini-TESTING)*
- ***MMF***: *mycophenolate mofetil 1.5–2 g/day for 12 mo; tapering for another 6 mo*
- ***TR budesonide***: *targeter released budesonide for 9 months*

Refractory IgAN?

APRIL/BAFF:
- Siberprenlimab
- Bion-1301
- Atacicept
- Telitacicept
- Belimumab

Targeting APRIL in the Treatment of IgA Nephropathy



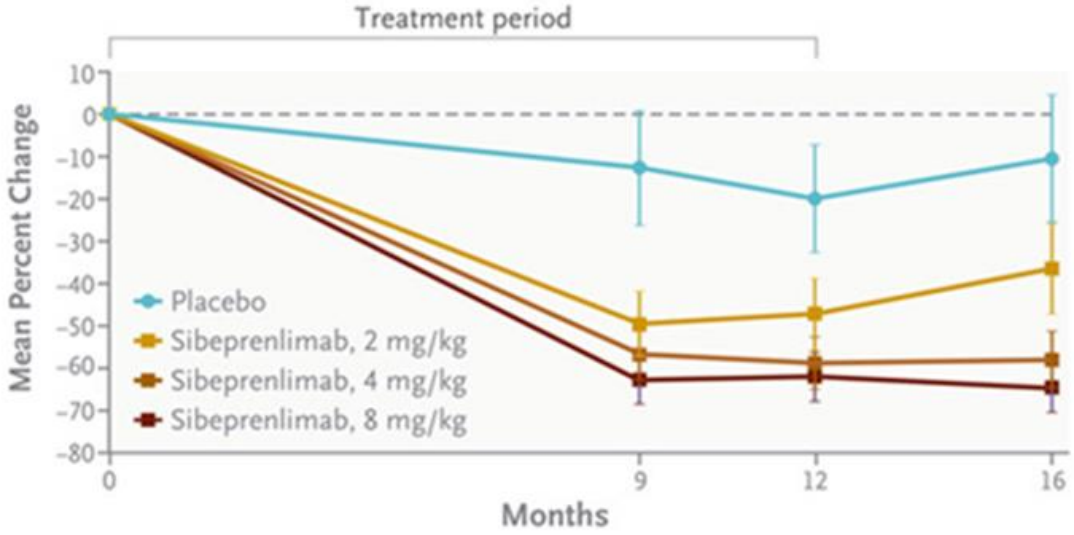
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mathur M et al. DOI: 10.1056/NEJMoa2305635

Change in 24-Hr Urinary Protein-to-Creatinine Ratio



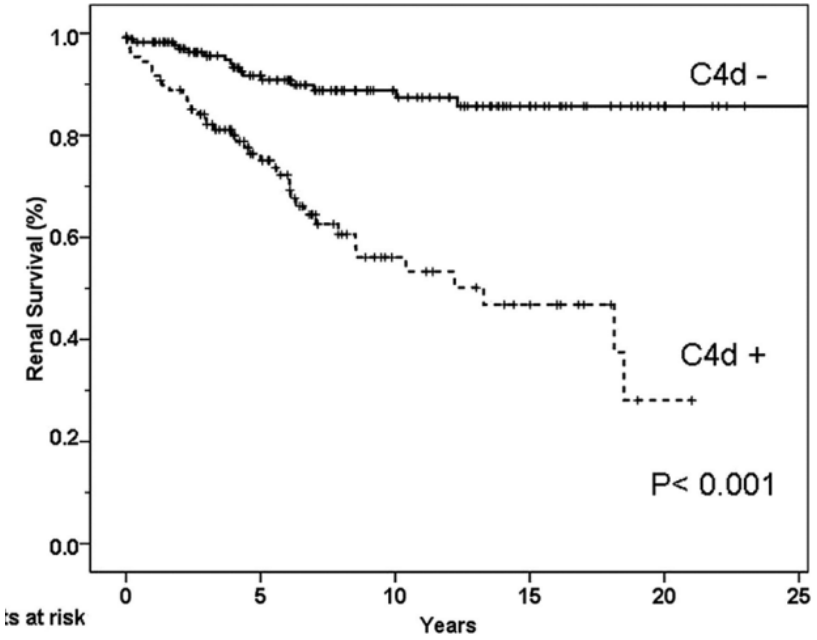
CONCLUSIONS

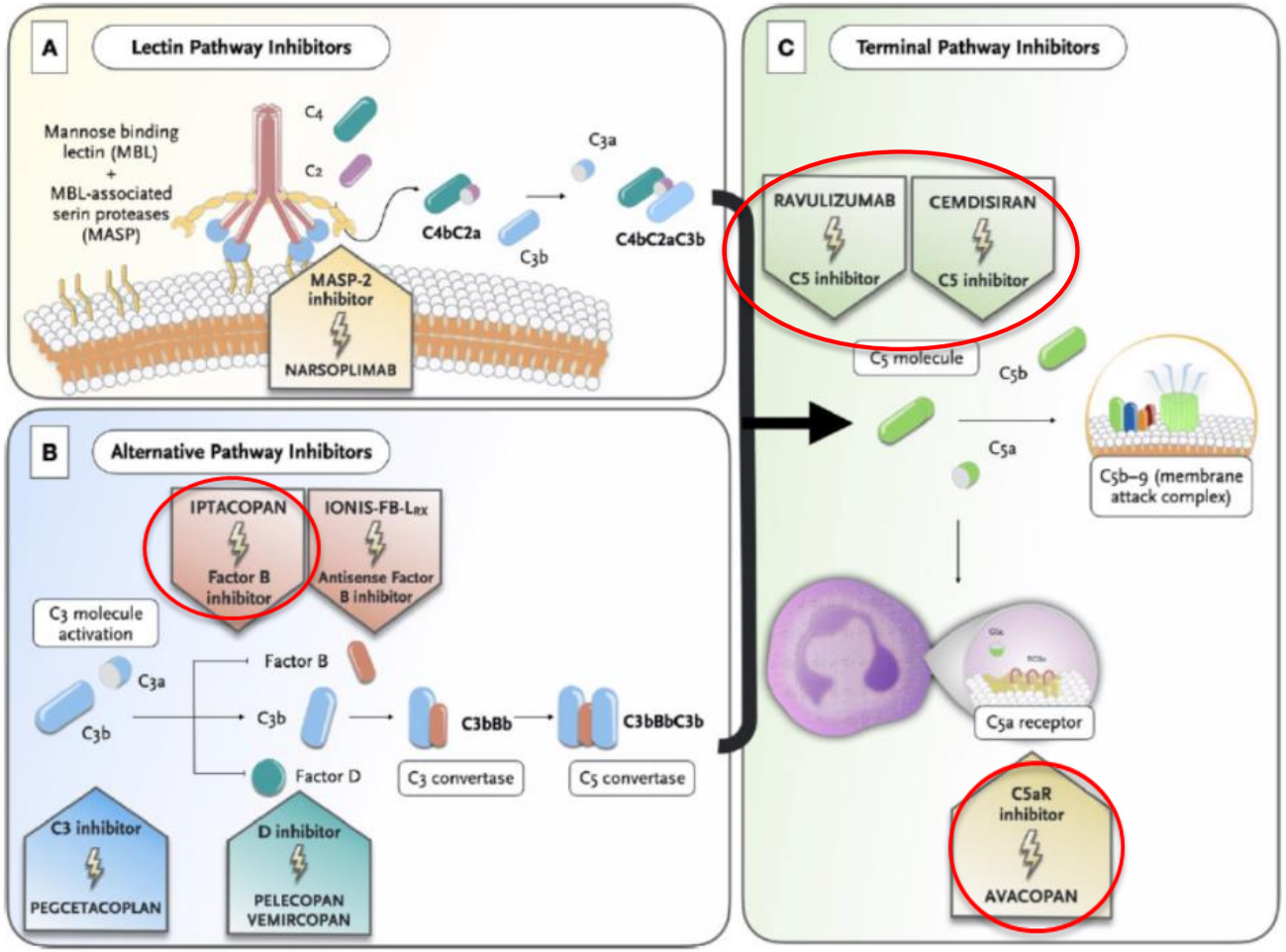
Among patients with IgA nephropathy at high risk for disease progression, 12 months of treatment with sibeprenlimab resulted in a significantly greater reduction in proteinuria than placebo.

Cheung CJASN 2024; Mathur NEJM 2024

Refractory IgAN?

Targeting complement in IgA nephropathy





Caravaca-Fontan CKJ 2024; Espinosa, CJASN 2014

IgAN. Clinical Presentations

Most Frequent Presentation:

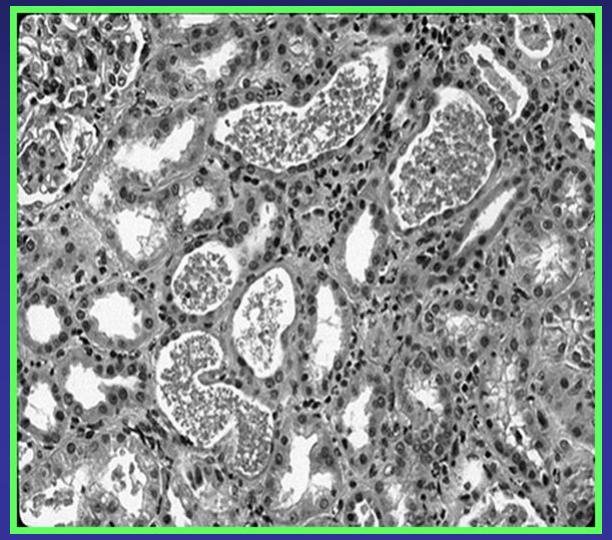
Microscopic hematuria+proteinuria with or without episodes of gross hematuria (usually coincidental with respiratory infections)

«Atypical presentations»

- ***AKI accompanying episodes of macroscopic hematuria***
- ***Malignant hypertension/Thrombotic microangiopathy lesions in kidney biopsy***
- ***Crescentic IgAN (>50% glomeruli with crescents): No RCT: Corticosteroids, Cyclophosphamide… (KDIGO 2021)***
- ***Complete nephrotic syndrome: Treatment similar to that Minimal change disease***

Acute worsening of renal function during episodes of macroscopic hematuria in IgA nephropathy

Manuel Praga, Victor Gutierrez-Millet, José J. Navas, Luis M. Ruilope, José M. Morales, José M. Alcazar, Ignacio Bello, and José L. Rodicio

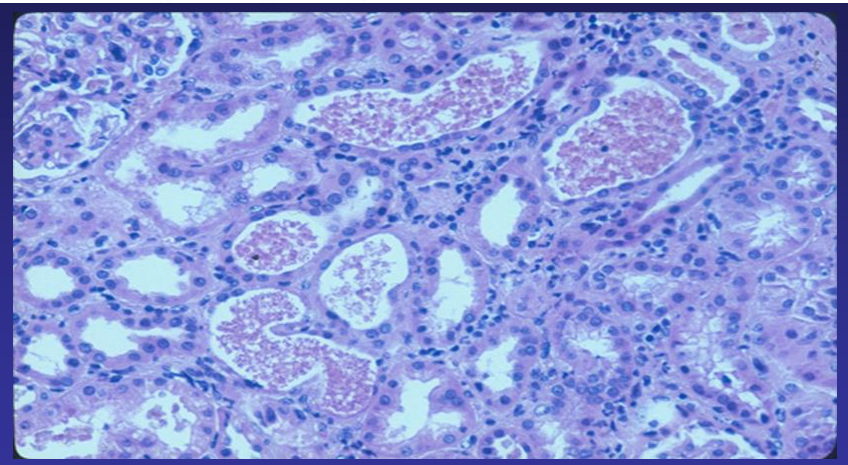


Complete recovery of renal function *in every patient 1-2 months after the onset of gross hematuriama necrosis.*

Mean age: 24 yr

Praga M et al. Kidney Int 28: 69-74, 1985

Factors That Determine an Incomplete Recovery of Renal Function in Macrohematuria-Induced Acute Renal Failure of IgA Nephropathy



25% of the patients did not recover their baseline renal function

Mean age 46.5 yr

Factors associated with an incomplete recovery:

- Age > 50 yr
- Duration of gross hematuria > 10 d
- Baseline renal function
- Severity of tubular necrosis

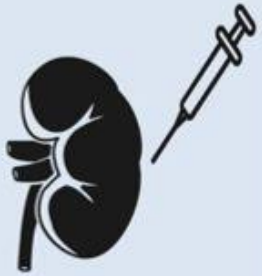
Gutiérrez E. et al. Clin J Am Soc Nephrol 2007; 2, 51-57

What is the presentation and outcomes of IgA nephropathy among older adults in Spain?

CJASN
Clinical Journal of American Society of Nephrology

Cohort

151 Patients **IgA**



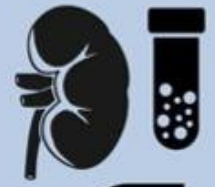
65 years or older

1990-2015 in Spain

Common Clinical Presentations

Hematuria and/or proteinuria

55%



Acute Kidney Injury (AKI)

40%

87% Hematuria-related AKI (Anticoagulation in 34%)

13% Crescentic IgA

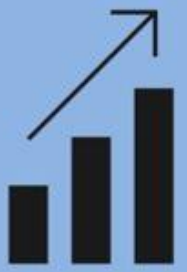
Primary Outcome: ESKD or Death

1 year	2 years	5 years
26%	48%	74%

What happened over time?

1990-1995

6 IgA Cases



2011-2015

62 IgA Cases

Conclusions The diagnosis of IgA nephropathy among older adults in Spain has progressively increased in recent years. Prognosis was poor.

Angel M. Sevillano, Monserrat Diaz, Fernando Caravaca-Fontán, Clara Barrios, et al. ***IgA Nephropathy in Elderly Patients. CJASN doi: 10.2215/CJN.***13251118. **Visual Abstract by Pablo Garcia, MD**

Thrombotic microangiopathy in patients with malignant hypertension

Cavero T et al, NDT 2023; 38(5):1217-1226

199 patients with malignant hypertension of different etiologies

Primary HTN	44%
Glomerulonephritis	16%
Primary aHUS	13%
Reno-vascular HTN	9%
Drugs	7%
Autoimmune diseases	5%
Endocrine HTN	5%

Glomerular diseases: 33 (16.6)
IgAN: 23 (11.6)
Diabetic nephropathy: 4 (2)
FSGS: 2 (1)
IC-MPGN: 1 (0.5)

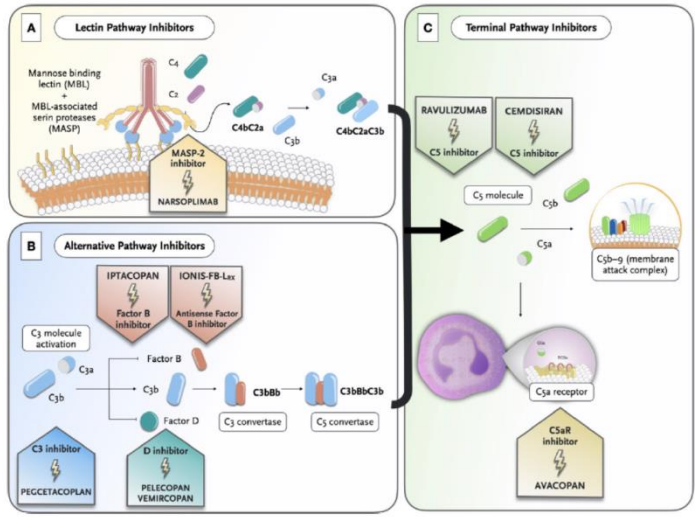


Table 1: Summary of studies addressing TMA lesions in IgAN patients, and the reported outcomes.

Reference	N	TMA (%)	Hypertension in patients with TMA (%)	Malignant hypertension in patients with TMA (%)	ESKD in patients with TMA (%)
Neves *et al.* [46]	118	18	100		71[a]
Zhang *et al.* [48]	1683	26			28[b]
El Karoui *et al.* [45]	128	53	71	26	48[c]
Chua *et al.* [53]	128	18	77	8	49[d]
Faria *et al.* [52]	126	29			
Chang *et al.* [50]	435	2.3	100	60	60[e]
Cai *et al.* [49]	944	20	67	10	39[f]

Caravaca-Fontan F et al. Clin Kidney J 2023

Conclusions

- Treatment decisions should be based on the amount of Proteinuria, the presence/amount of Hematuria, the evolution of renal function (eGFR) and histologic lesions (MEST-C score)

- Differentiate Antiproteinuric/non-inmmunosuppressive treatments:

  RAAS blockers, SGLT2i, endothelin blockers

  from Immunosuppressive/pathogenically targeted drugs

  Corticosteroids, MMF, TR-budesonide, anti-APRIL/BAFF drugs, complement blockers

- Immunosuppressive/pathogenically targeted drugs for patients with proteinuria >0.75-1 g/d, hematuria, active lesions, declining eGFR

!! ευχαριστώ !!