



Pathogenesis and Treatment of IgA Nephropathy in 2025



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Potential Conflicts of Interest

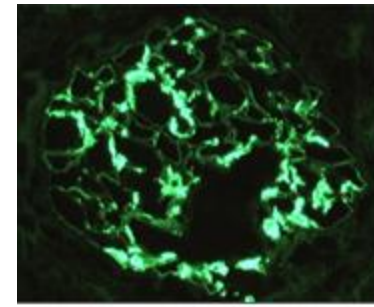
Dr. Appel has research grants through Columbia U. with Achillion-Alexion, Apellis, Calliditas, Genentech-Roche,, Sanofi-Genzyme, Traverre, Novartis.

He lectures for Aurinia and Glaxo on Lupus Nephritis, and Calliditas on Mechanisms of IgA nephropathy

He has consultantships with : Alexion-Achillion, Apellis, Aurinia, Glaxo, Calliditas, Genentech-Roche, Mallinkrodt, Up-to-Date, Sanofi-Genzyme, Novartis.

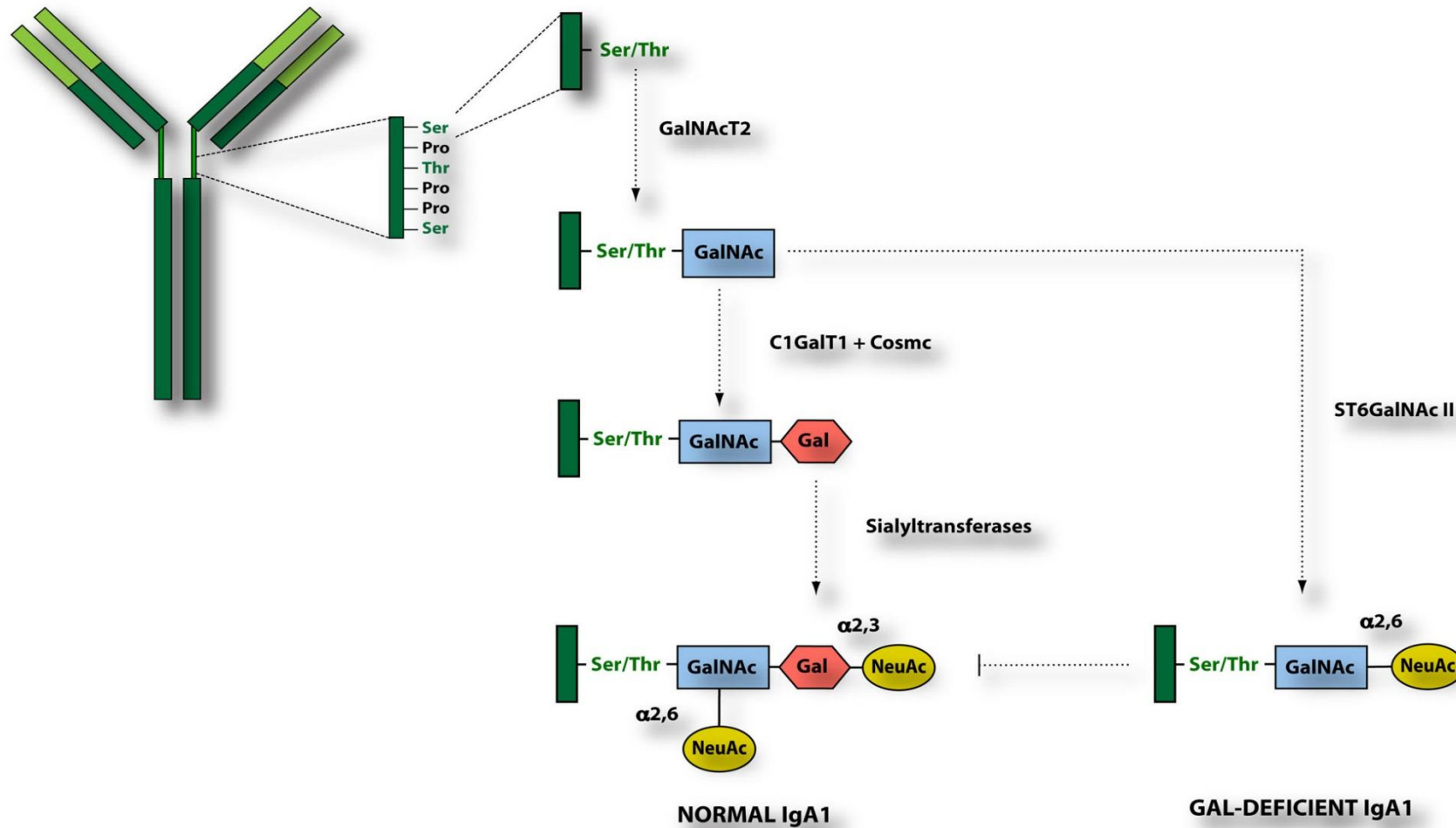
He has no major stock holdings.

IgA Nephropathy



- **Defined by IgA deposition in glomerular mesangium-dominant or co-dominant.(IgG 40-50% IgM 70-80)**
- **Presentation- Young – gross hematuria**
Adults – Proteinuria + hematuria
- **ESRD in 15-20% by 10 yrs from onset and 30-40 % by 20 yrs.**
- **Risk Factors for Progression. Predictions of Course.**
- **Treatment – Changing Views but clearly no SINGLE Path of Therapy for Everyone**
- **Must diagnose earlier and treat all elements in the pathogenesis of IgAN in 2025.**

Low O-glycosylation of IgA1 and gal deficient IgA1 formation



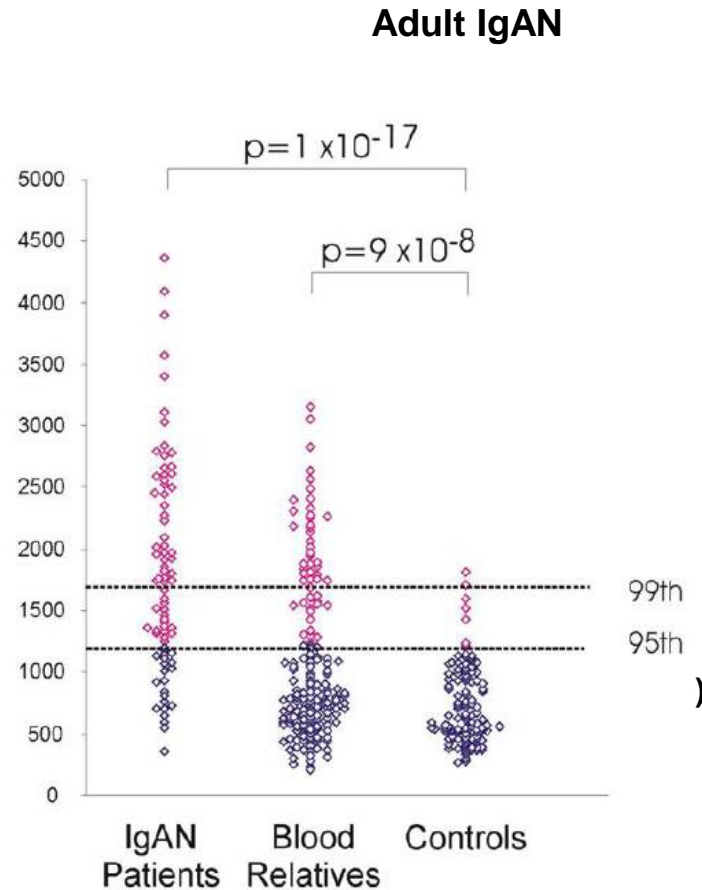
GalNAc = N-acetylgalactosamine

Gal = Galactose

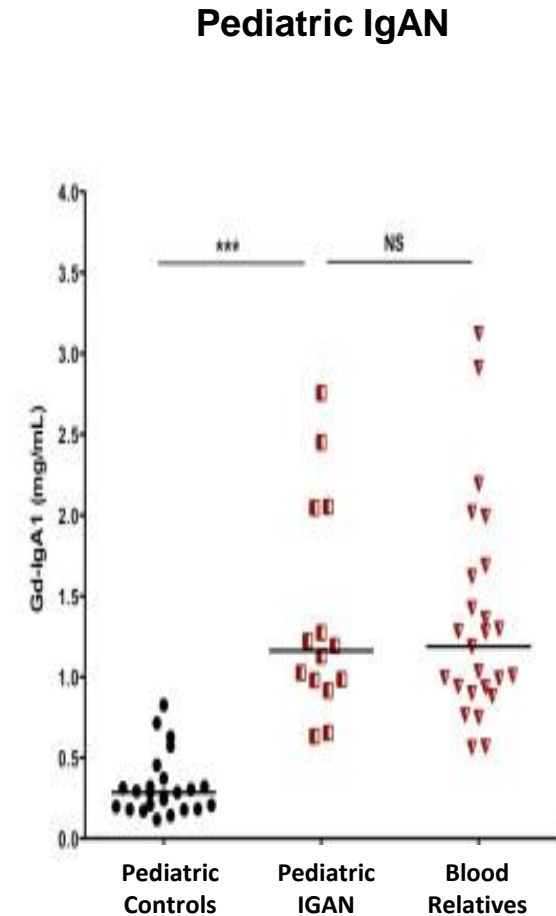
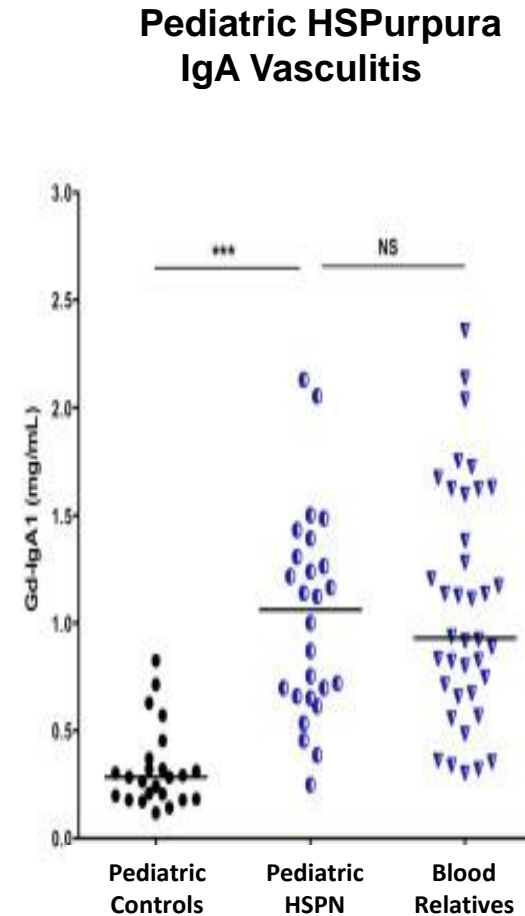
NeuAc = Sialic Acid

Kiryluk et al. *Pediatr Nephrol* (2010)

Serum Levels of Gal-deficient IgA1



A.Gharavi 2011

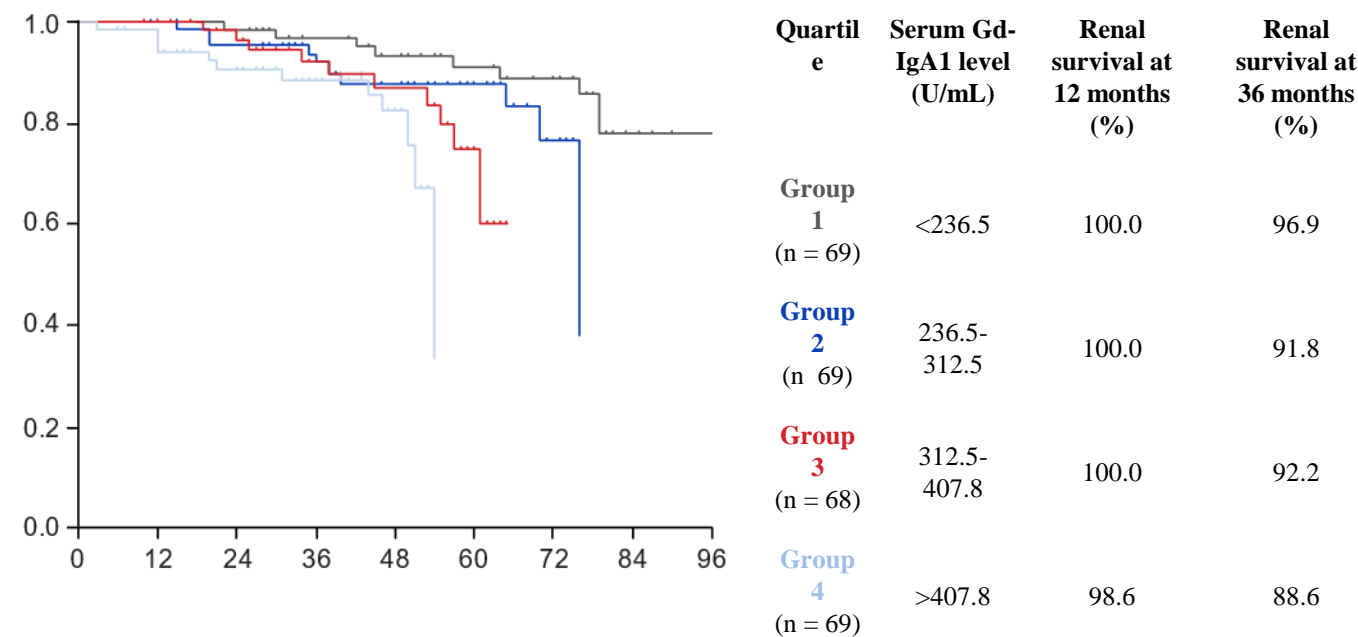
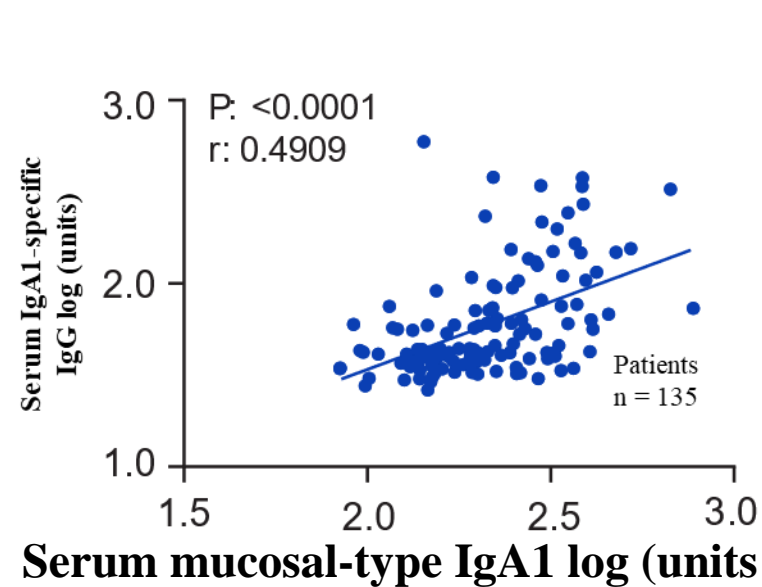


Kiryluk et al. *Kidney Int.* (2011)

Serum Levels of Mucosal-type Gd-IgA1 Are Elevated in Patients With IgA Nephropathy and Elicit an Autoimmune Response

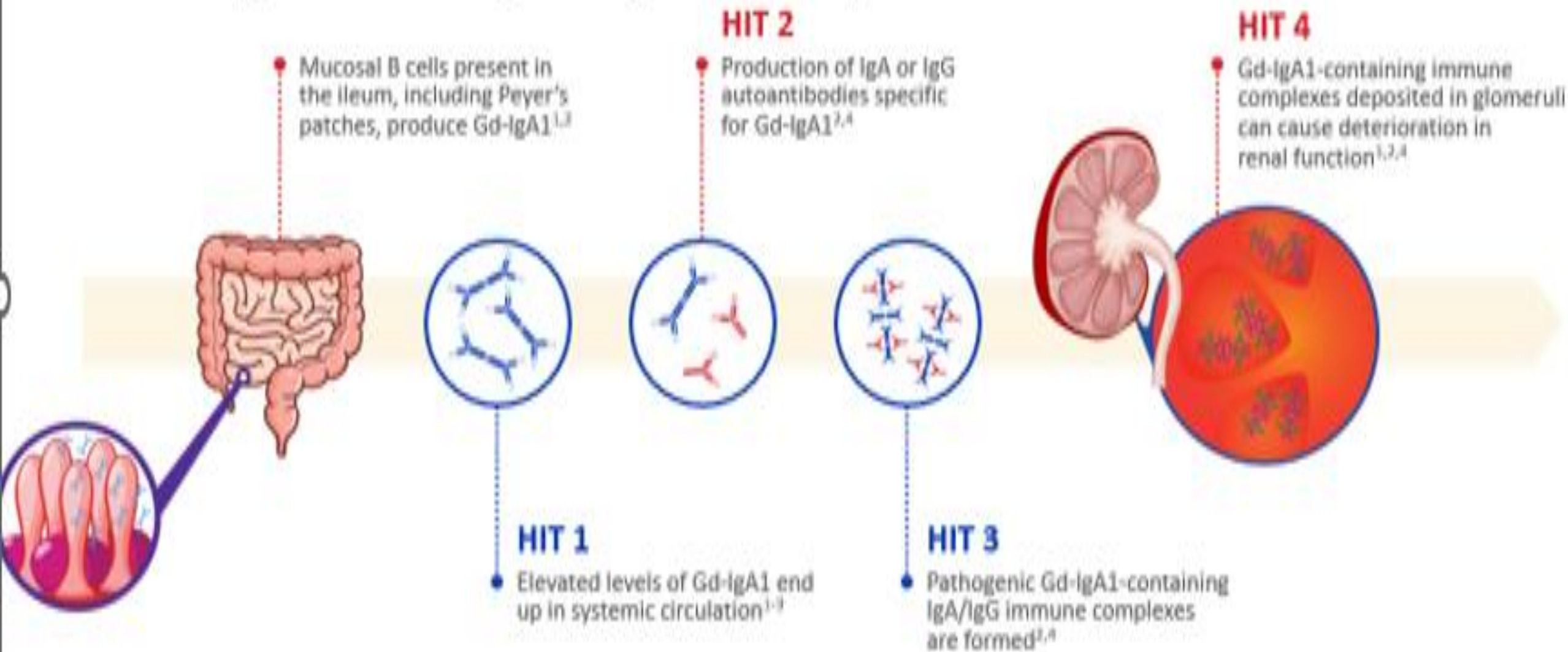
Serum IgG autoantibodies are correlated with serum Gd-IgA1 in IgA N²

High Levels of Gd-IgA1 Are Associated With Poor Disease Outcomes

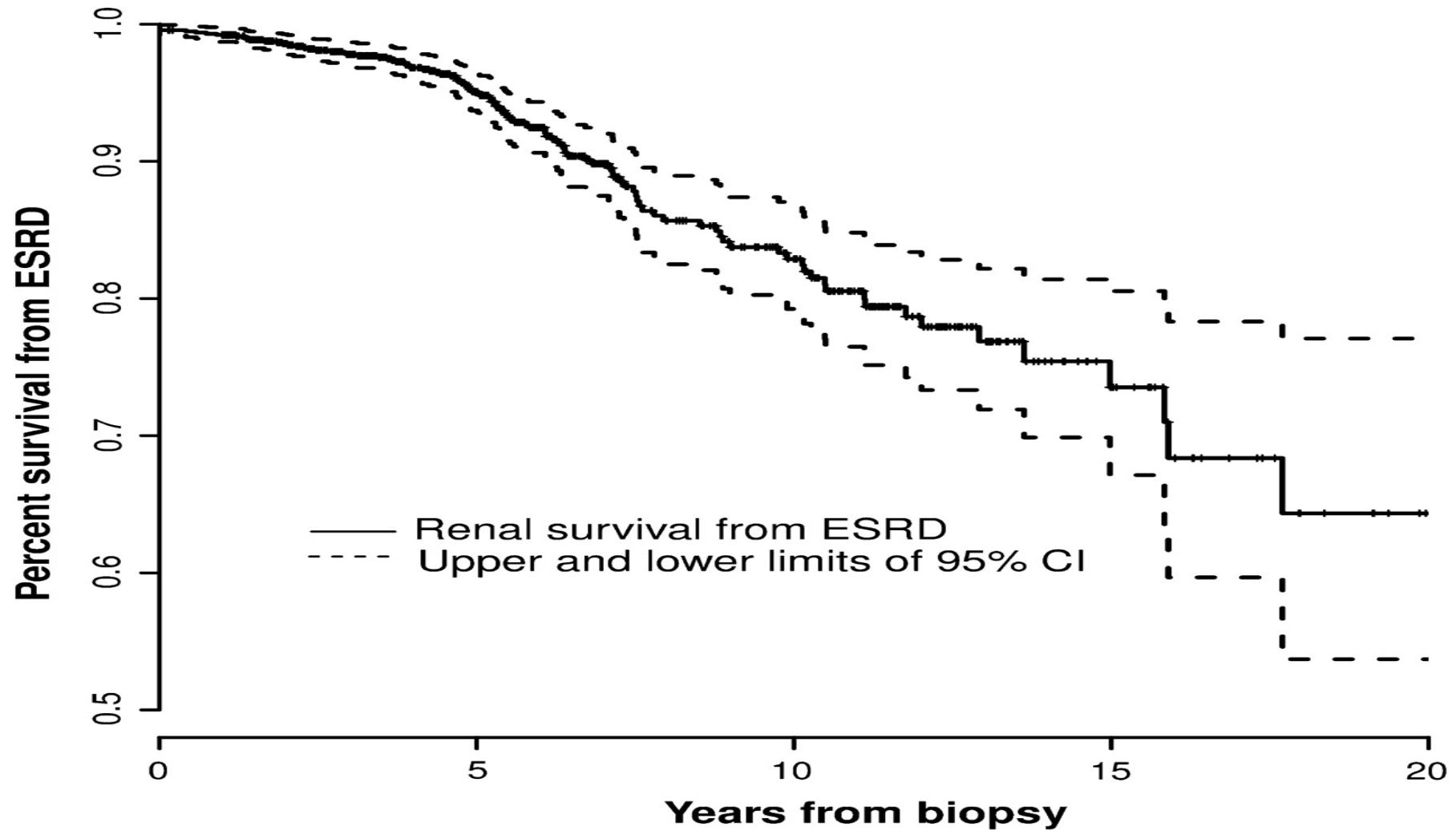


1. Zhao N, et al. *Kidney Int.* 2012;82(7):790-796 ; 2. Placzek WJ, et al. *PLoS One.* 2018;13(1):e0190967

"4-Hit" Hypothesis: A Widely Accepted Model for Understanding the Pathogenesis of IgA Nephropathy



Long-term Renal Survival in 1126 IGAN Patients



Le W, Liang SS, Hu YL,... Liu ZH Nephrol. Dial. Transplant 2011

Risk Stratification in IgA Nephropathy

Clinical Features

Proteinuria

GFR

Hypertension

Kidney Biopsy – MESTC

CoMorbidity

Evaluating a New International Risk-Prediction Tool in IgA Nephropathy

JAMA Intern Med. 2019;179(7):942-952

Sean J. Barbour, MD, MSc; Rosanna Coppo, MD, FERA; Hong Zhang, MD, PhD; Zhi-Hong Liu, MD; Yusuke Suzuki, MD, PhD; Keiichi Matsuzaki, MD, PhD; Ritsuko Katafuchi, MD, PhD; Lee Er, MSc; Gabriela Espino-Hernandez, MSc; S. Joseph Kim, MD, PhD; Heather N. Reich, MD, PhD; John Feehally, FRCP; Daniel C. Cattran, MD, FRCPC; for the International IgA Nephropathy Network

AT&T LTE 10:12 AM 100%

< International IgAN Pr... ☆ ☰ ↗

Questions

Estimated GFR at biopsy 30 ml/min/1.73m² >

Systolic blood pressure at biopsy 190 mmHg >

Diastolic blood pressure at biopsy 90 mmHg >

Proteinuria at biopsy 6.9 g/day >

Age at biopsy 54 Years >

Race Caucasian >

Use of ACE inhibitor or ARB at the time of biopsy Yes >

MEST M-score 1 >

MEST E-score 1 >

MEST S-score 0 >

AT&T LTE 10:12 AM 100%

< International IgAN Pr... ☆ ☰ ↗

MEST S-score 0 >

MEST T-score 1 >

Immunosuppression use at or prior to biopsy No >

At how many months after renal biopsy would you like to determine risk of renal progression? 48 Months >

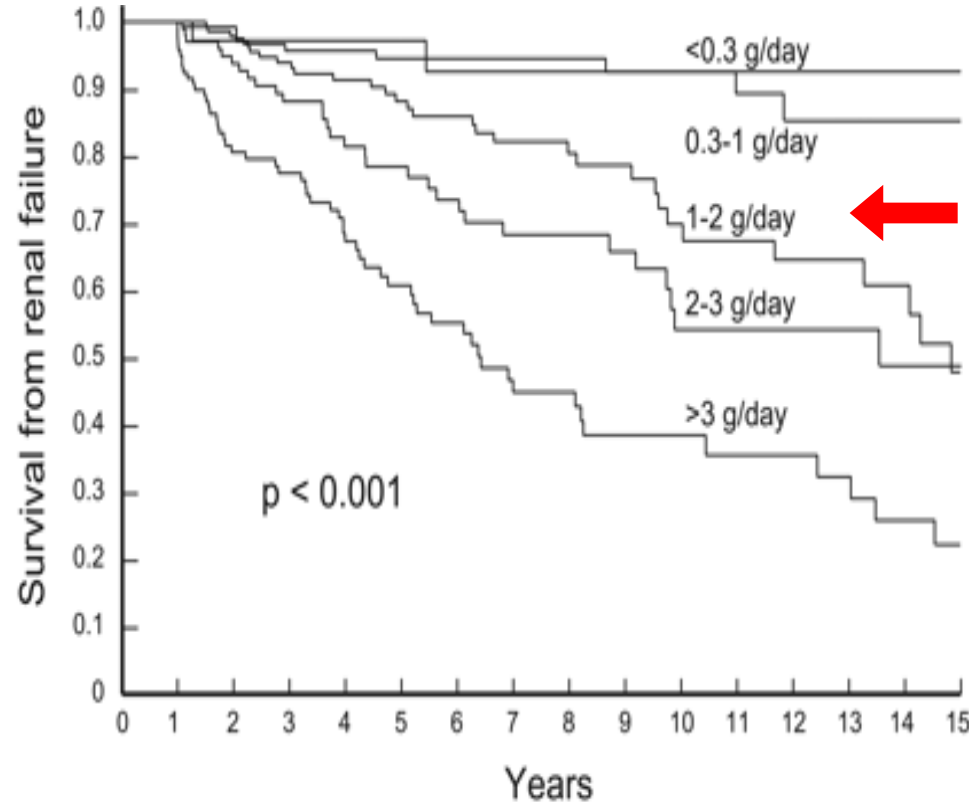
Results

Risk of Progression

The risk of a 50% decline in estimated GFR or progression to end-stage renal disease 4.0 years after renal biopsy is 56.66%

Reduction of Proteinuria Improves Prognosis in IgAN

- 542 pts with IgAN from Toronto registry
- Followed for 78 mos
- GFR declined at -4.5 ml/min/1.73 m²/yr
- 30% reached ESRD



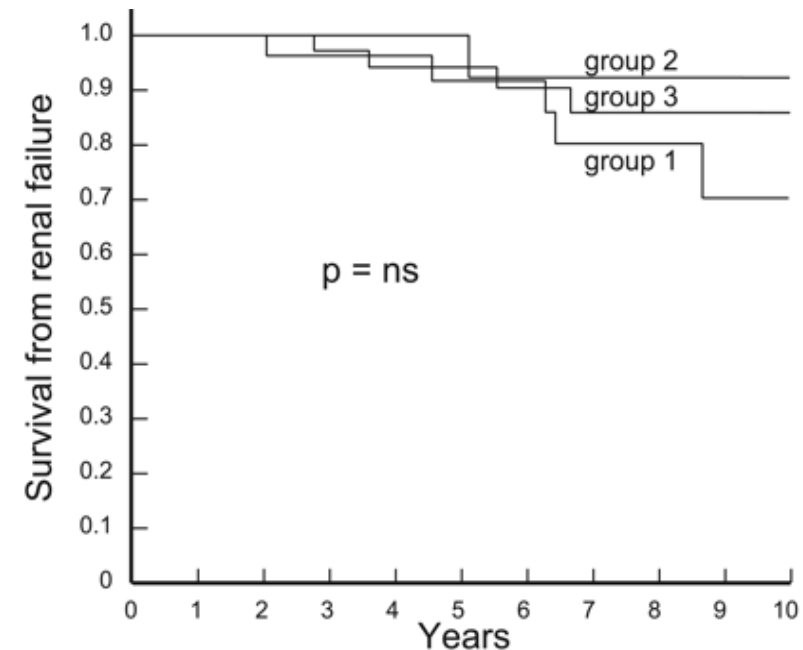
Regardless of peak proteinuria, attaining partial remission (<1 g/d)

leads to similarly good outcomes.

Group 1: 1-2 g/d peak proteinuria

Group 2: 2-3 g/d peak proteinuria

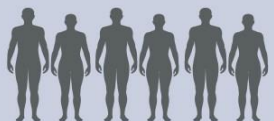
Group 3: >3 g/d peak proteinuria



CKD progression, kidney failure, and mortality among US patients with IgA nephropathy

We evaluated kidney outcomes among a racially, ethnically, and socioeconomically diverse IgAN population in the USA.

Methods



655 adults with primary IgAN
(31% Asian/Pacific Islander, 3% Black,
40% Hispanic/Latino, 24% White)
2000–2022



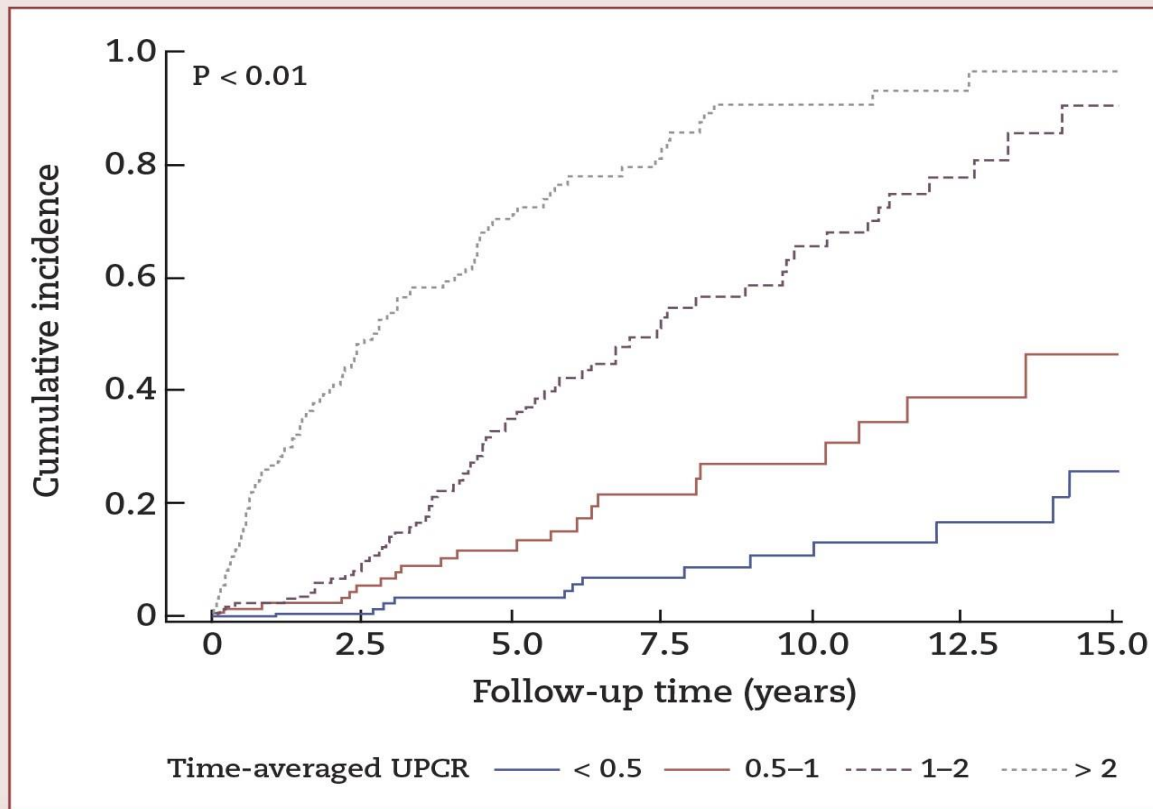
Composite endpoint
1. $\geq 50\%$ eGFR decline
2. Kidney failure
or 3. Mortality



234 (36%)
**reached composite
kidney endpoint**

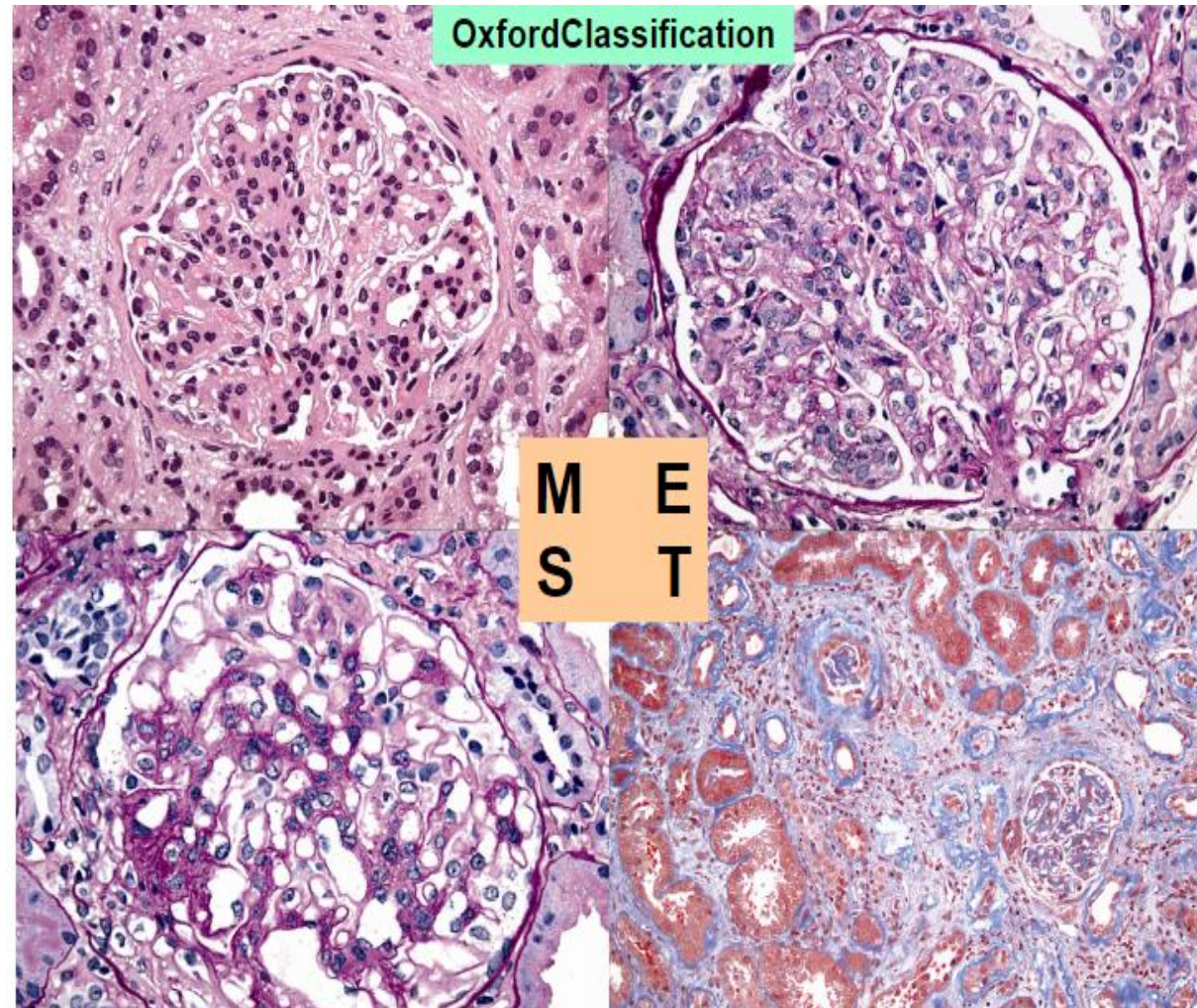
Incidence rate
79.4 events
per 1000 patient-years
(95% CI 69.6, 90.7)

Results



MESTC-Oxford Classification

- **Mesangial hypercellularity**
0 = <50%;
1 = >50% glomeruli involved
 - **Endocapillary proliferation**
0 = Absent 1 = Present
 - **Segmental glomerulosclerosis**
0 = Absent 1 = Present
 - **Tubulo-Interstitial fibrosis**
0 = <25%
1 = 25-50%
2 = >50%
- Crescents**
C0 – absent
C1-0-24%
C2 = or > 25%

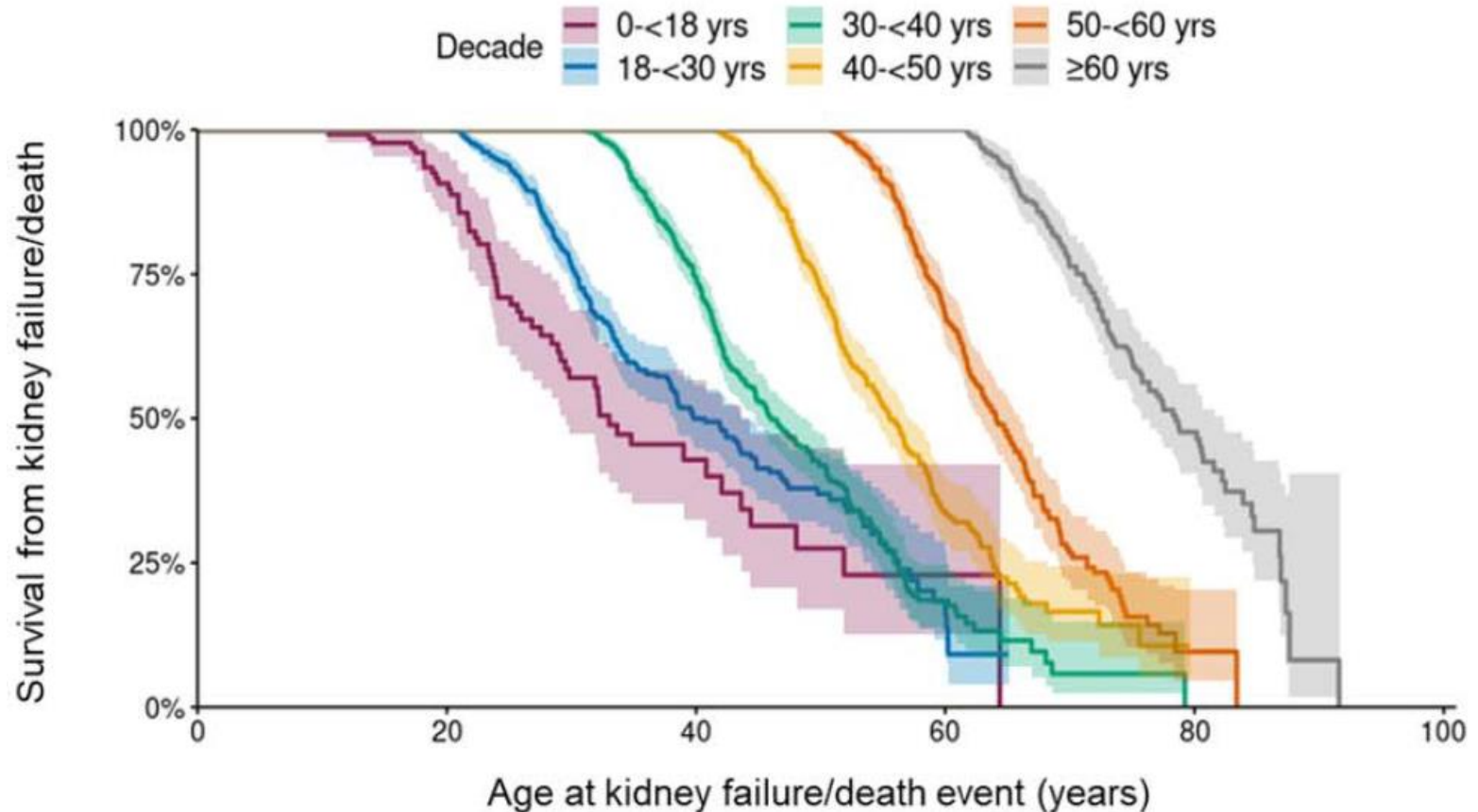


UK Registry Data: Most Patients With IgA Nephropathy Progressed to Kidney Failure Within 10 to 15 Years of Diagnosis

RaDaR IgA nephropathy cohort¹

- Retrospective study (n=2299 adults; n=140 children)
- Biopsy-proven IgA nephropathy plus proteinuria >0.5 g/day or eGFR <60 mL/min/1.73 m² at any time in their disease history

- **50% of patients reached kidney failure* or died during the study (median follow: 5.9 years)**
- **Median (95% CI) kidney survival: 11.4 (10.5-12.5) years**
- **Mean (SD) age at kidney failure/death*: 48 (15) years**



Patients With Low Proteinuria Levels Can Progress to Kidney Failure

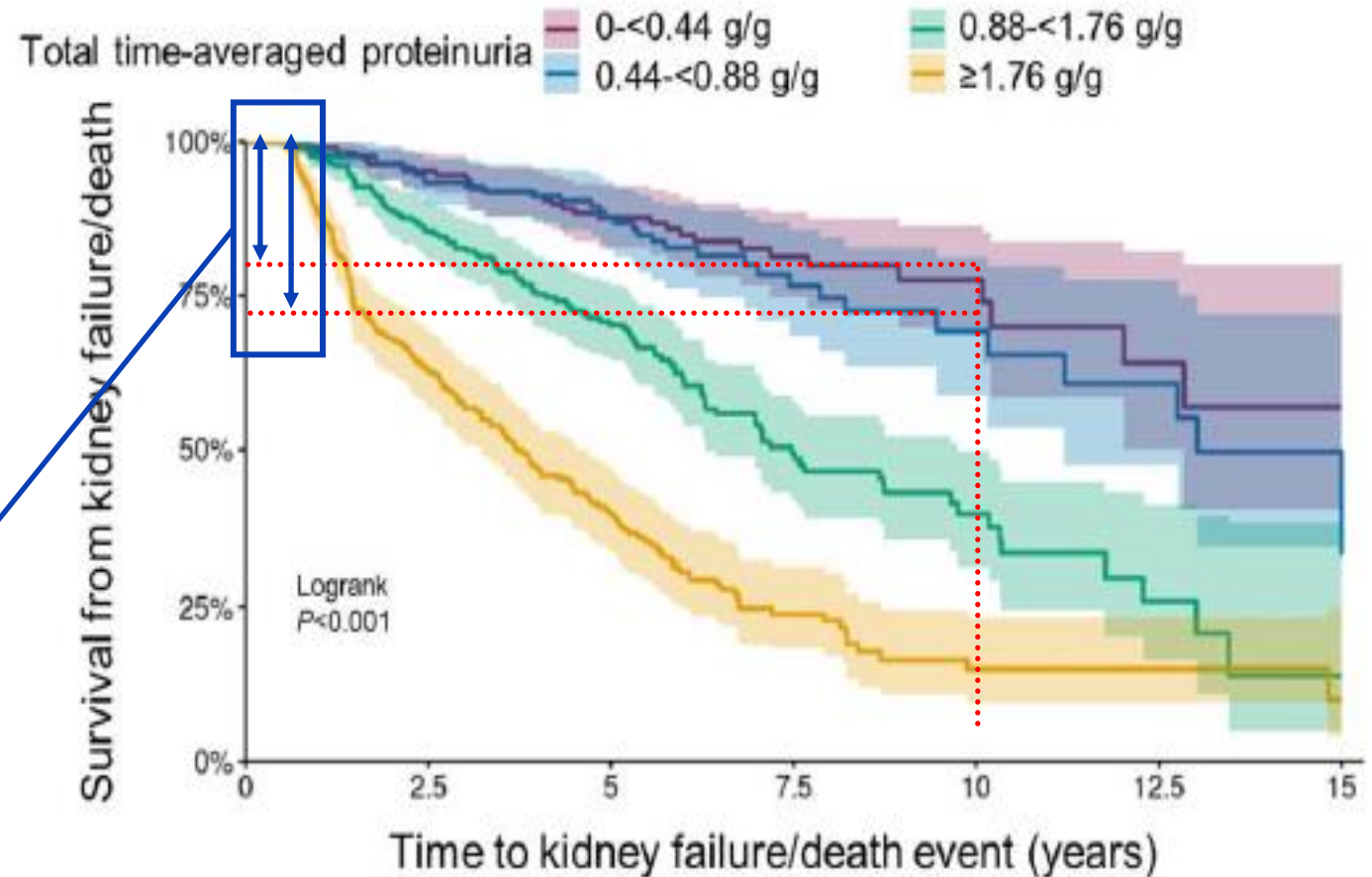
RaDaR IgA nephropathy cohort (2299 adults and 140 children) – proteinuria findings¹

Time-averaged proteinuria was significantly associated with worse kidney survival (and more rapid eGFR loss)

However, the 10-year risk of kidney failure/death was also relatively high in patients typically perceived to be “low-risk”:

~30% of patients with time-averaged
UPCR 0.44-<0.88 g/g

~20% of patients with time-averaged
UPCR <0.44 g/g

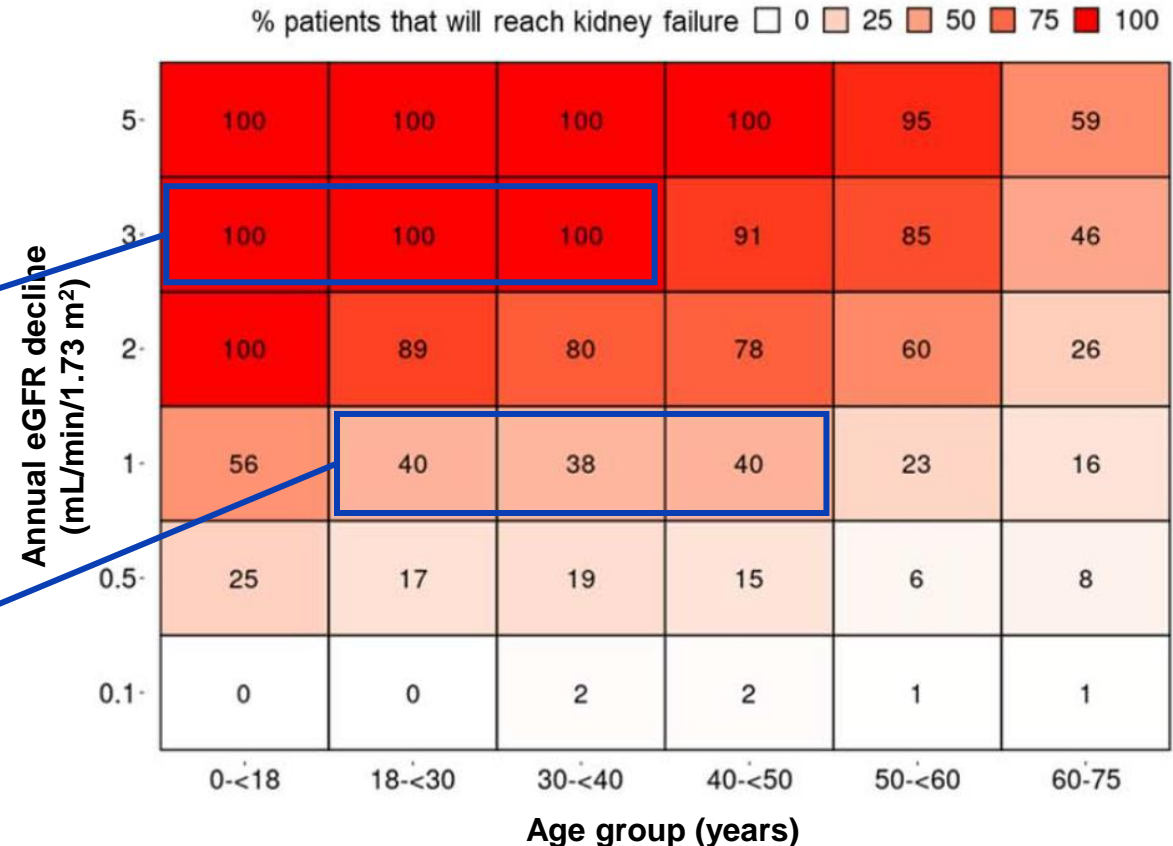


A Faster Rate of eGFR Decline in IgA Nephropathy = A Shorter Time to Kidney Failure

RaDaR (UK registry) IgA nephropathy cohort (2299 adults and 140 children)¹

eGFR decline of 3 mL/min/1.73 m²/year = 100% of patients <40 years old at diagnosis reaching kidney failure within expected lifetime

eGFR decline of 1 mL/min/1.73 m²/year of ~40% of adult patients <50 years old at diagnosis reaching kidney failure within expected lifetime

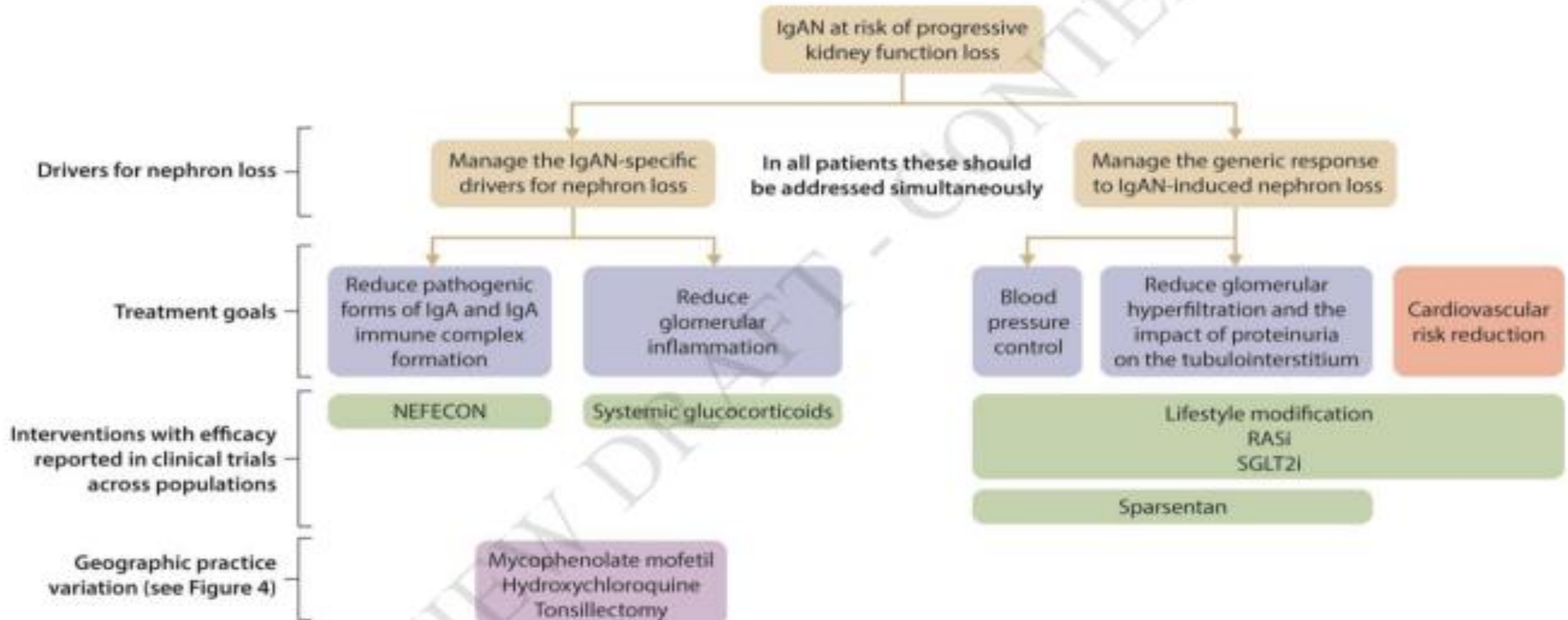


Pitcher D, Braddon F, Hendry B... Barratt J. CJASN 18:1-12, 2023

| Kidney Function Loss in Control Pts with Optimized Supportive Care In IgAN Trials | | | | | | |
|---|--|--|--|---|---|---|
| Baseline characteristics | Manno et al. ¹ (Active control [ramipril]) | TESTING ² (Placebo + RAS inhibition) | STOP-IgAN 10-year results ^{3,4} (RAS inhibition) | PROTECT ⁵ (Active control [irbesartan]) | DAPA-CKD ⁶ (Placebo + RAS inhibition) | NeflgArd ⁷ (Placebo + RAS inhibition) |
| N in PBO ARM | 49 | 246 | 80 | 202 | 133 | 182 |
| Age, years* | 35 (11) | 37 (29-46) | 45 (12) [†] | 45 (12) | 50 (13) | 42 (34-49) |
| Systolic blood pressure, mmHg* | 123 (8) | 125 (116-131) | 126 (10) [†] | 130 (12) | 127 (14) | 124 (117-130) |
| Diastolic blood pressure, mmHg* | 82 (7) | 80 (74-86) | 78 (8) [†] | 83 (11) | 80 (10) | 79 (74-84) |
| Median proteinuria, g/24 h (IQR) | 1.5 (1.4-2.3) | 1.9 (1.4-2.9) | 1.7 (0.8) [†] | 1.8 (1.3-2.6) | N/A | 2.2 (1.5-3.4) |
| eGFR, mL/min/1.73 m ² * | 98 (28) | 59 (42-78) | 59 (27) [†] | 57 (24) | 43 (12) | 55 (46-68) |
| Median time since IgAN diagnosis, years (IQR) | ≤1 year before randomization | 0.4 (0.3-1.2) | N/A | 4.0 (1.0-10.0) | N/A | 2.6 (0.6-6.5) |
| Total eGFR slope, mL/min/1.73 m ² per year [§] | −6.2 | −5.0 | −2.7 | −3.9 | −4.7 | −5.4 |

KDIGO 2024 “Proposed “ Guidelines – Final Version as yet unpublished

- **Dynamic assessment of patient risk over time should be performed, as decisions regarding the relative merits of different treatments may change.**



Current and Future developments in IgA Nephropathy therapy

For Glomerular Inflammation steroids and MMF work

TR Budesonide – FDA approved

Sparsentan – FDA Approved -combined ETA antagonist + ARB

Dapagliflozin and Empagliflozin – FDA approved for CKD

Iptacopan – FDA accelerated FDA approval

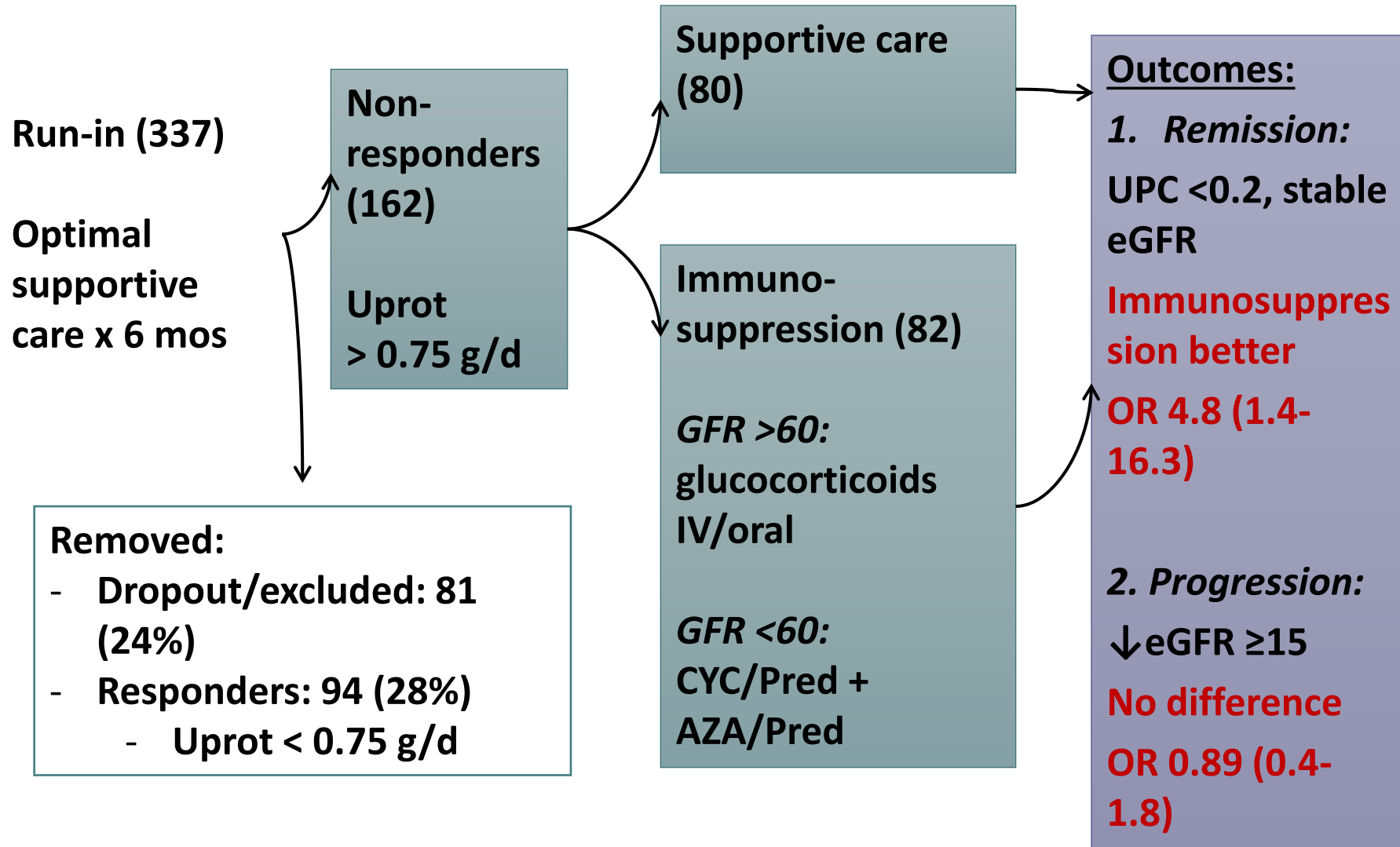
Atrasentan - FDA accelerated FDA approval

Anti - APRIL inhibitors (Sibeprenlimab , ZigaKibart)

Anti BAFF/anti April inhibitors (Atacicept, telitacicept, Povetacicept)

STOP-IgAN: Supportive care vs. Immunosuppression

Rauen T et al. NEJM 2015;373:2225-2236



STOP-IgAN, 10-Year Follow-up

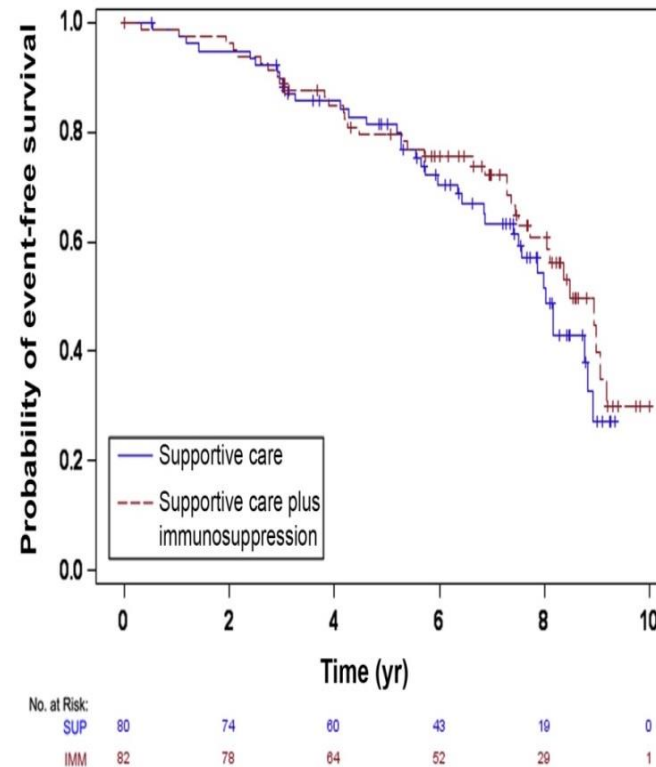
Follow-up:

- 92% of original cohort
- Median **7.4 y** (IQR 5.7-8.3y)

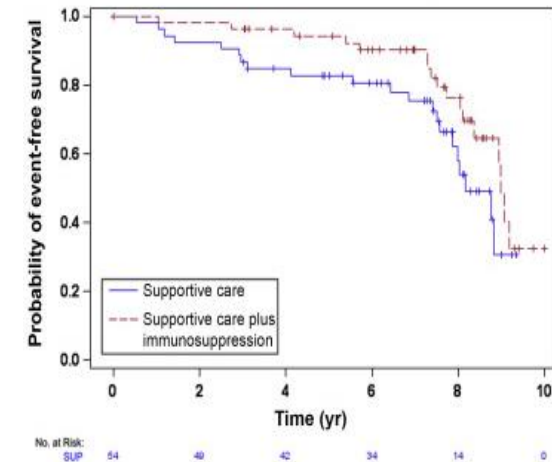
Outcome: *Death, ESKD, or ↓40% GFR*

- 36/72 in supportive care
- 35/77 in IS group
- HR 1.20 (95%CI 0.75 -1.92)

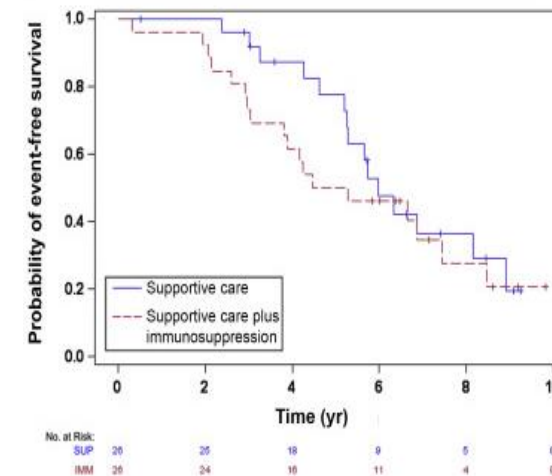
a Entire STOP-IgAN cohort




b Patients with baseline GFR ≥ 60 ml/min per 1.73 m^2



c Patients with baseline GFR < 60 ml/min per 1.73 m^2



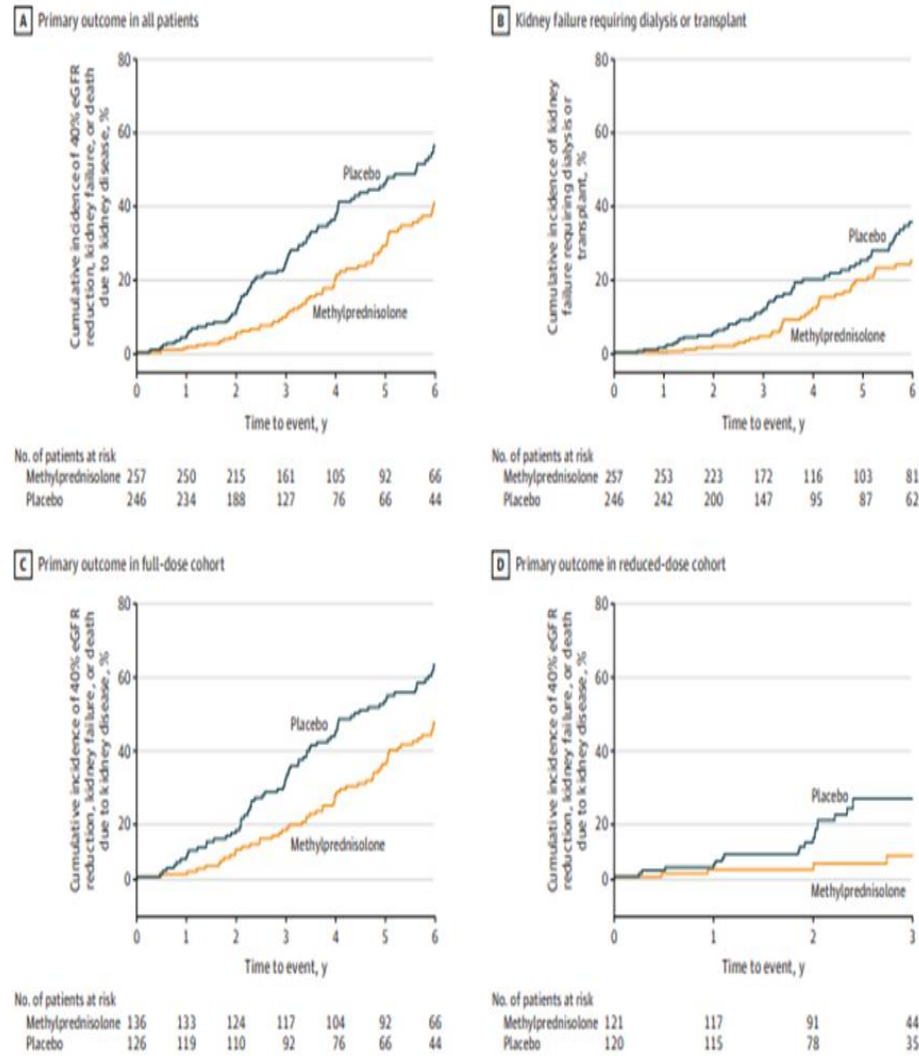
TESTING Reduced-Dose (ASN KW 2021)

| | Full Dose (n=262) | Reduced Dose (n=241) |
|---|---|--|
| Regimen | <ul style="list-style-type: none"> MP 0.6-0.8 mg/kg/d (max 48 mg) x2mo Tapering 8 mg/mo over additional 4-6mo | <ul style="list-style-type: none"> MP 0.4 mg/kg/d (24-32 mg) x2mo Tapering 4 mg/mo over additional 4-6mo antibiotic prophylaxis x12 wks |
| Follow-up | 5.7 yr | 2.5 yr |
| Primary composite outcome | 0.58 (95%CI 0.41-0.81) | 0.27 (95%CI 0.11-0.65) |
| Serious Adverse Events | 30 vs 5 in placebo | 7 vs 3 in placebo |
| <ul style="list-style-type: none"> <i>Hospitalized infection</i> | <ul style="list-style-type: none"> 11 vs 1 ($p=0.006$) | <ul style="list-style-type: none"> 5 vs 2 ($p=0.45$)  |
| <ul style="list-style-type: none"> <i>Death</i> | <ul style="list-style-type: none"> 3 vs 0 | <ul style="list-style-type: none"> 1 vs 0 |

Effect of Oral Methylprednisolone on Decline in Kidney Function/Kidney Failure in IgA N - TESTING STUDY

LV J, Wong MG, Hladunewich M, et al JAMA 327: 188-1898,2022

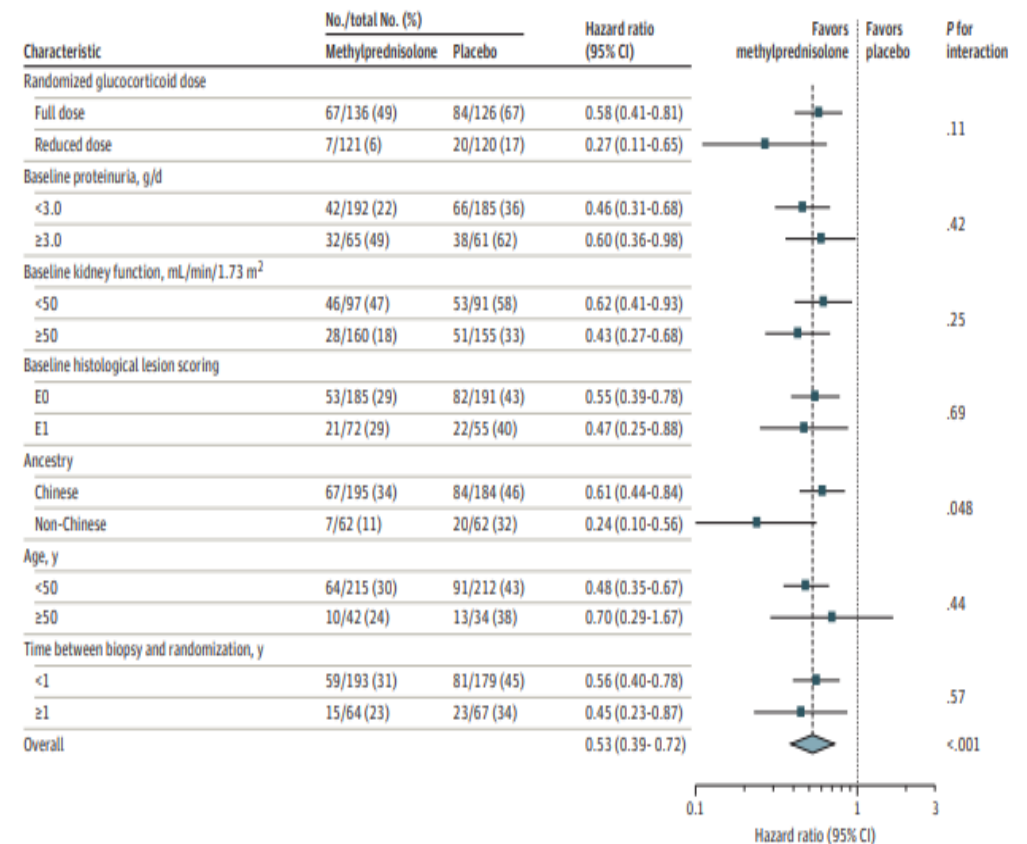
Figure 2. Time From Randomization to First Outcome in a Study of the Effect of Oral Methylprednisolone on Kidney Function Decline in Patients With IgA Nephropathy



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

Original Investigation Research

Figure 3. Primary Outcome in a Study of the Effect of Oral Methylprednisolone on Kidney Function Decline in Patients With IgA Nephropathy



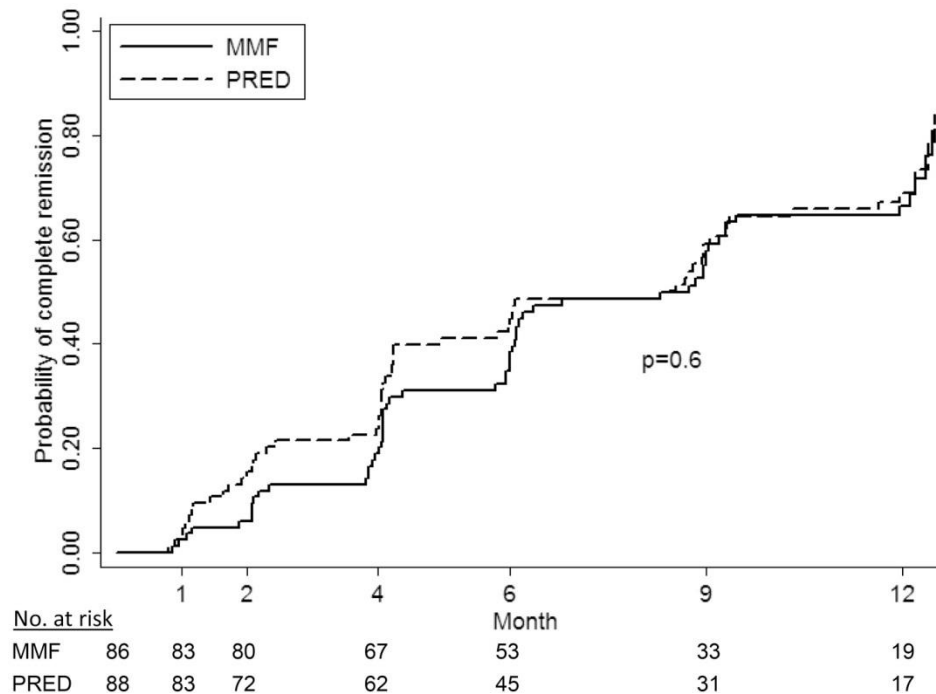
Mycophenolate in IgAN

| | Frisch G et al. Neph Dial Tran, 2005 | Hogg R et al., AJKD, 2015 | Maes BD et al. Kidney Int, 2004 | Tang SC et al. Kidney Int, 2010 |
|--------------------------|---|--|---|--|
| N | 32 | 52 | 34 | 40 |
| Ethnicity | Mixed/NYC | US/Canada | Belgian | Chinese |
| MMF dose | 2 g/d x 1 yr | 25-36 mg/kg/d x1yr | 2 g/d x 3 yrs | 1.5-2.0 g/d x 6 mo |
| eGFR (ml/min) | 39 (MDRD) | 100.6 ± 42.8 (CrCl, Schwartz or C-G) | 71 (Inulin) | 72 (CrCl) |
| Proteinuria | 2.7 g/d | 1.48 ± 0.74 g/g | 1.6 g/d | 1.8 g/d |
| SBP (mmHg) | 134 | 129 | 128 | 121 |
| ACEi/ARB | all | all | all | all |
| Followup | 59-75 wks | 54% completed 12mo MMF; only 33% completed 1yr post-Rx followup | 3 yrs | 6 yrs |
| Outcome | 50% rise Cr at 2 y: - MMF 5/17 (29%) - Placebo 2/15 (13%) - P= 0.4 | No differences in: -Mean proteinuria change at 12/24 mo -CrCl at 12/24 mo | No differences in: - 25% loss inulin clr. - 50% rise sCr - Rate of delta-GFR | ESRD rate at 6 yrs: - MMF 2/20 (10%) - Control 9/20 (45%) - P = 0.015 |
| Conclusion | NEGATIVE | NEGATIVE | NEGATIVE | POSITIVE |

Mycophenolate + Low-dose Prednisone vs. Full-dose Prednisone

Response at 12 months ($P = 0.7$):

- 82% in MMF
- 85% in PRED



| | MMF | PRED | P |
|------------|-----|------|--------|
| Any AE | 78% | 77% | 0.9 |
| SAE | 6% | 7% | 0.9 |
| Cushings | 18% | 48% | <0.001 |
| Diabetes | 1% | 14% | 0.002 |
| Infections | 31% | 23% | 0.2 |

BP ~120/75, but....

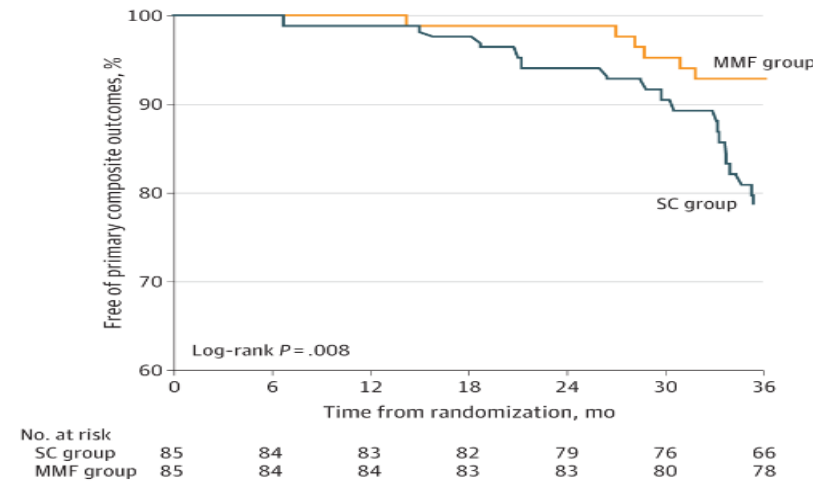
Only ~24% got RAS blockade

MAIN Trial : Effectiveness of Mycophenolate Mofetil Among Patients With Progressive IgA Nephropathy: A Randomized Clinical Trial

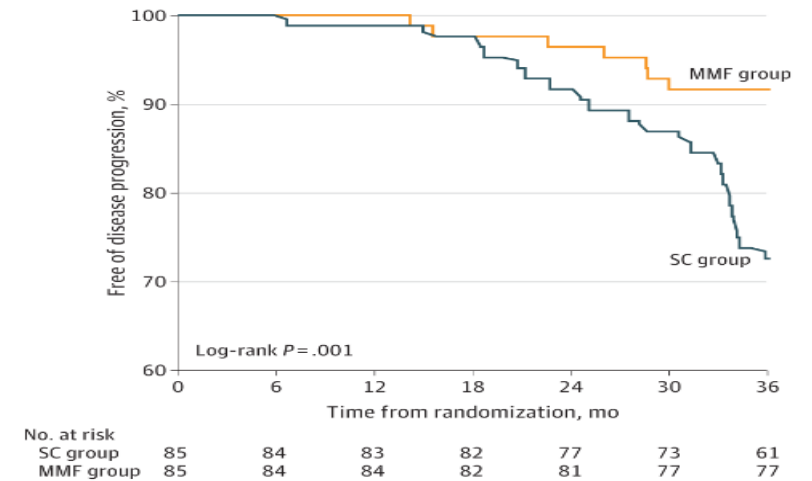
JAMA Network Open. 2023;6(2):e2254054. Feb 6,2023

- MMF 1.5 g/d x 12 months + 0.75-1.0 g for at least 6 months
- vs placebo
- N=170

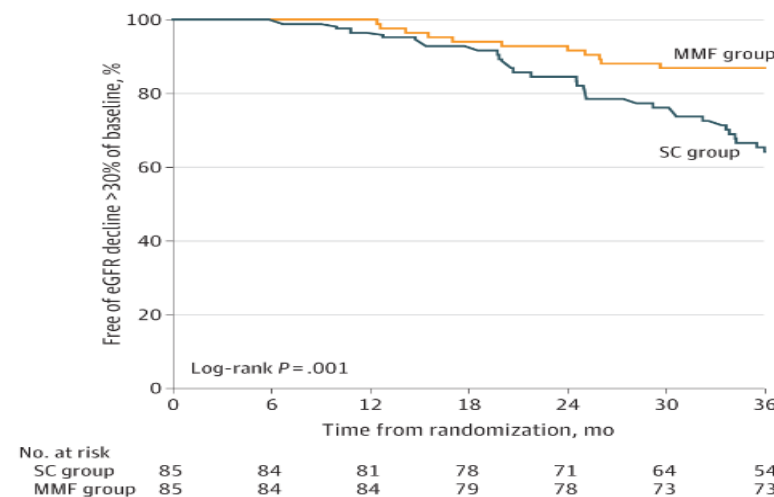
A Composite end point



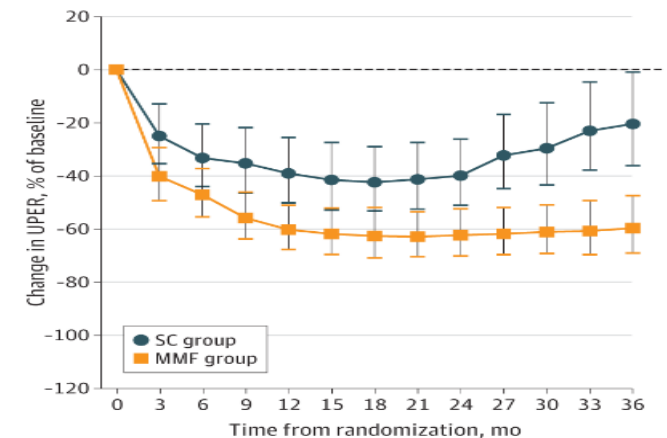
B Disease progression



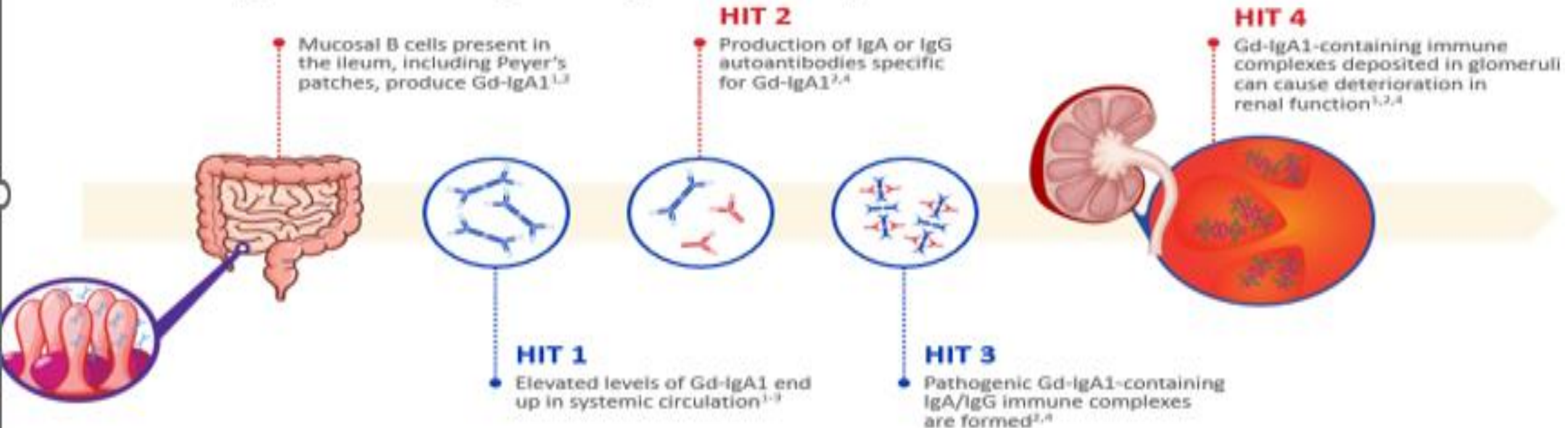
C eGFR decline



D Change in UPER



"4-Hit" Hypothesis: A Widely Accepted Model for Understanding the Pathogenesis of IgA Nephropathy



Block autoimmune mech of IgAN

Block formation of Gd IgA1
Block IgA1 immune Complexes

Block nonspecific - CGN

ACE inhib/ARBs
SGLT2inhibs
Sparsentan

Block Glom inflammation /scarring

Steroids, MMF, other immune meds

Current and Future developments in IgA Nephropathy therapy

For Glomerular Inflammation steroids and MMF work

TR Budesonide – FDA approved

Sparsentin – FDA Approved -combined ETA antagonist + ARB

Dapagliflozin – FDA approved for CKD

Iptacopan – FDA accelerated FDA approval

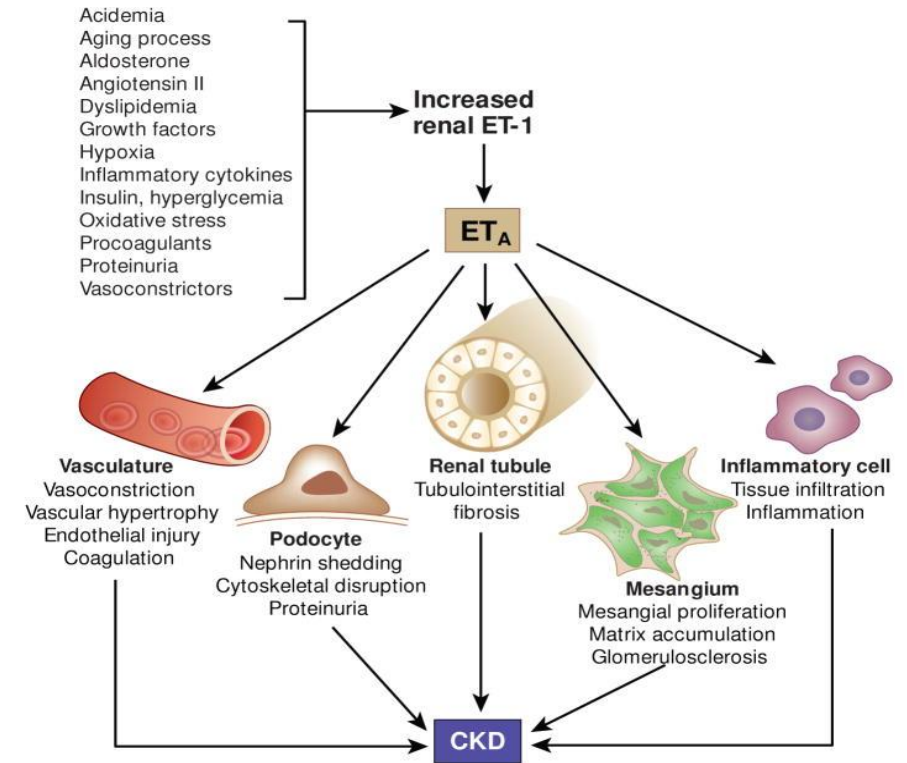
Atrasentan - FDA accelerated FDA approval

Anti - APRIL inhibitors (Sibeprenlimab , Zigakibart)

Anti BAFF/anti April inhibitors (Atacicept, telitacicept, Povetacicept)

The Endothelial System Is Upregulated in IgAN

- ET-1 is a potent vasoconstrictor
 - promotes tubular cell death, fibrosis and scar formation
- ET_AR activation causes glomerular injury via podocyte damage
 - Results in damage to the glomerular basement membrane and proteinuria



ET-1, endothelin-1; ET_AR, endothelin A receptor; GBM,.
Suzuki H et al. *J Am Soc Nephrol*. 2011;22:1795–1803.
Lancet 402:2077 2023

Efficacy and Safety of Sparsentan vs Irbesartan in IgA nephropathy

(Protect Study 2 yr blinded Phase 3 Trial Lancet 402:2077 2023

- N=404 randomized
- 29% Asian
- Age at IgAN dx = ~40y
- Age at enrollment = 46y
- UPE = 1.8 g/d
- eGFR = 57 ml/min/1.73m²

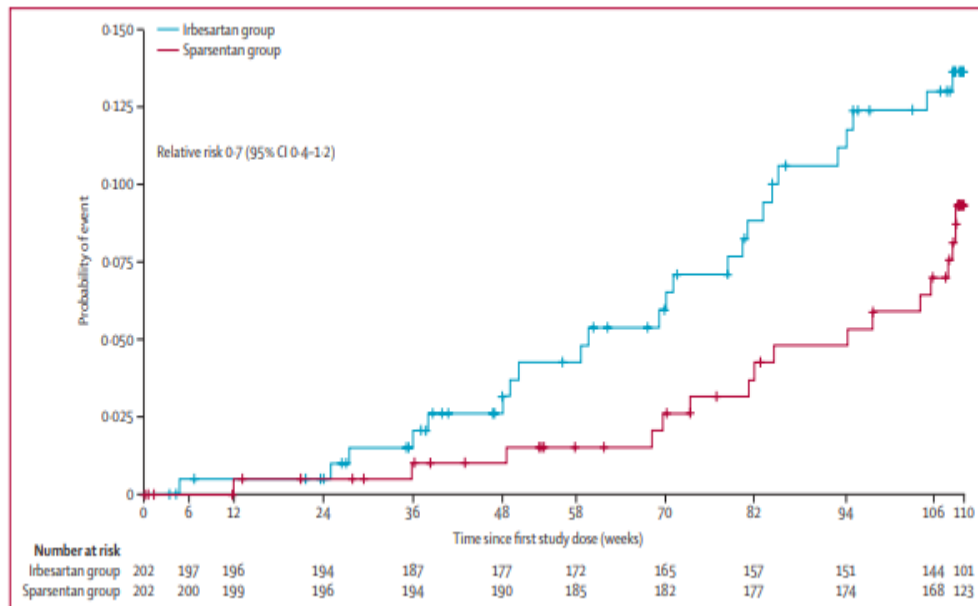
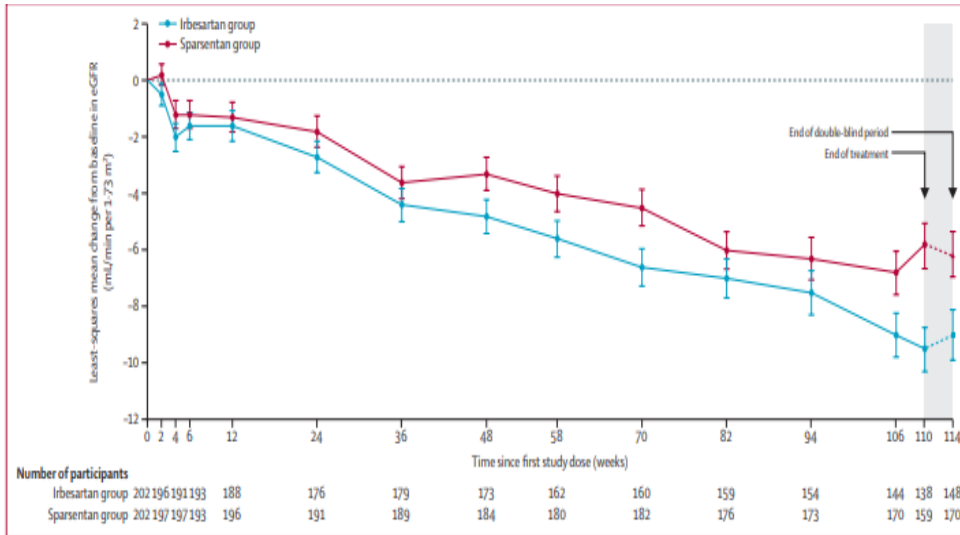


Figure 4: Time to reach the composite kidney failure endpoint of confirmed 40% eGFR reduction, end-stage kidney disease, or all-cause mortality

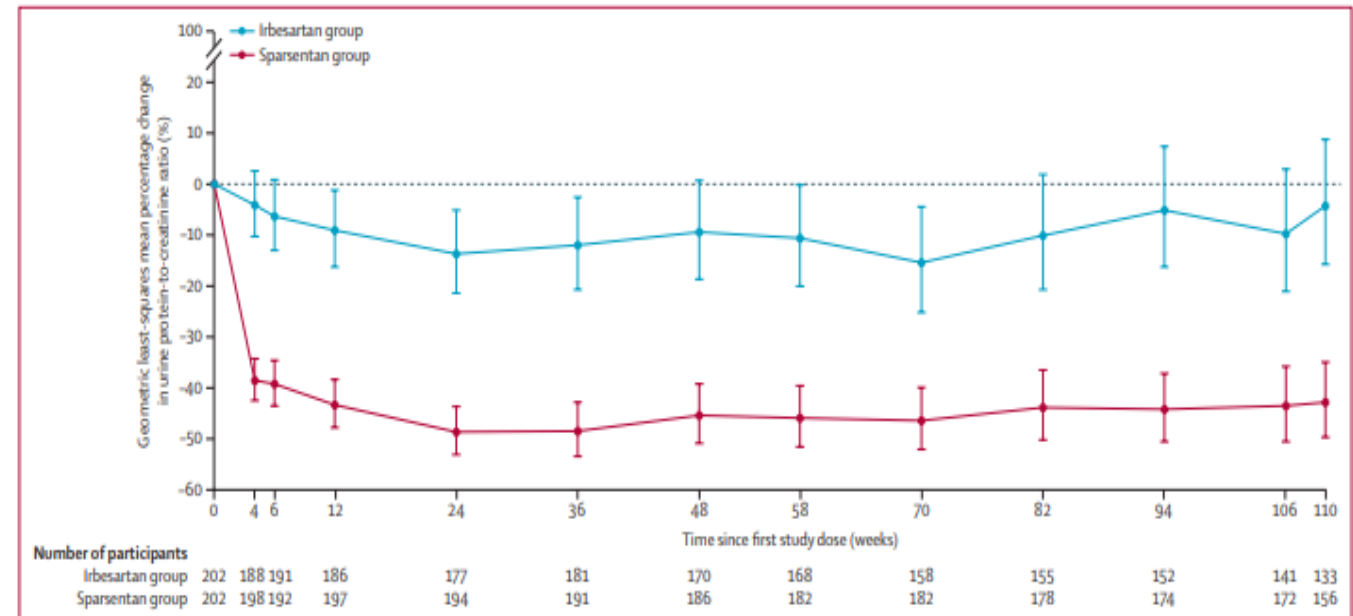
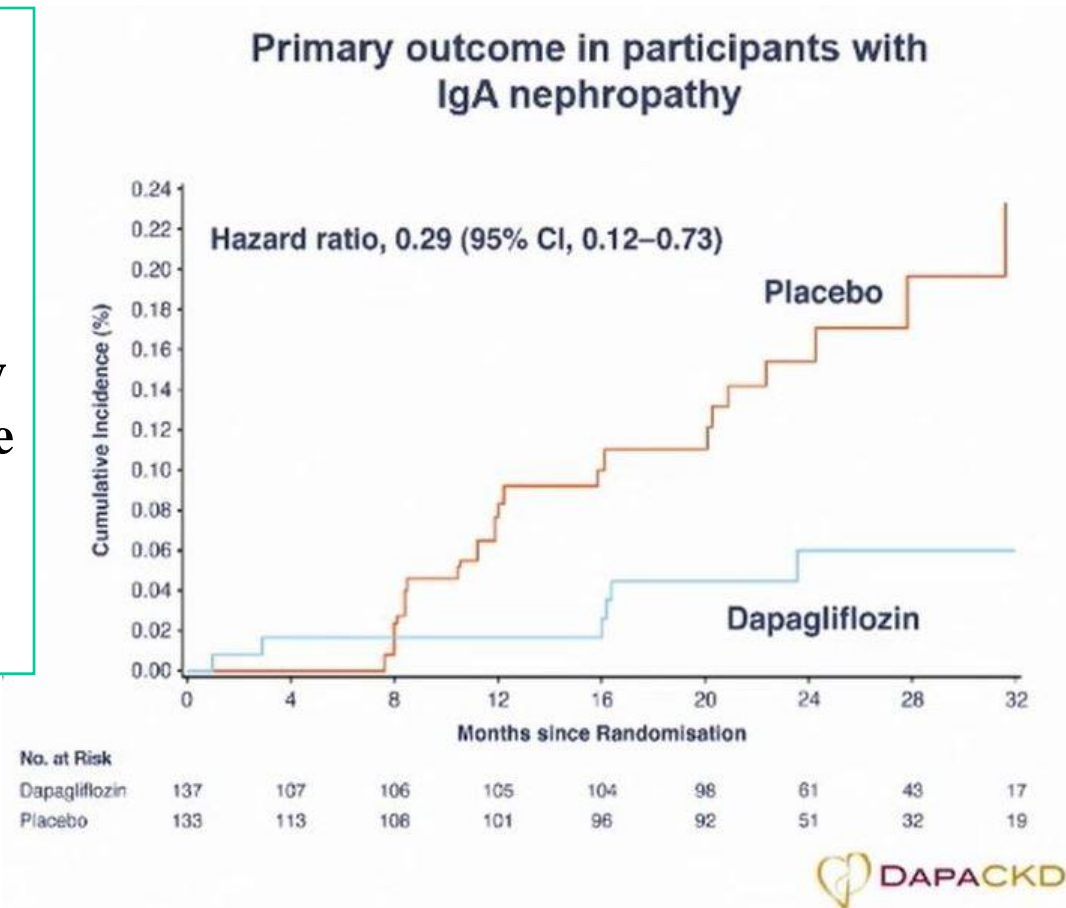


Figure 5: Geometric least-squares mean percentage change from baseline in the urine protein-to-creatinine ratio at each visit up to week 110

SGLT2 Inhibition

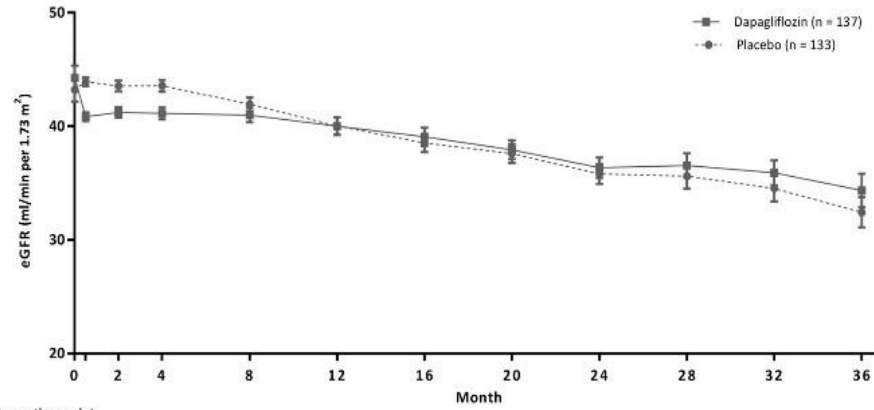
DAPA-CKD, NEJM, Oct 2020

- Randomized N=4304
- 16% (~700) had GN
- 270 with IgAN
- *Excluded:*
 - immune-mediated kidney disease thought to require immunosuppression
 - any immunosuppression within past 6 months



Wheeler DC et al.; DAPA-CKD Trial Committees and Investigators. *Lancet Diabetes Endocrinol.* 2021 Jan;9(1):22-31

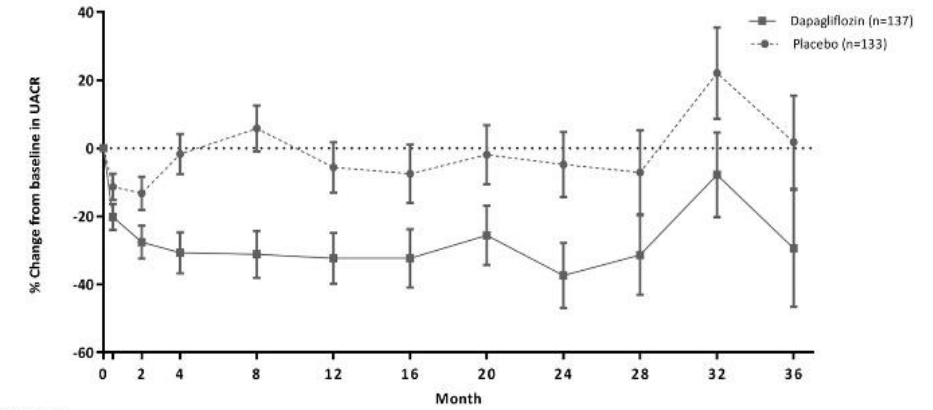
a



Participants per time point

| | | | | | | | | | | | | |
|---------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| Dapagliflozin | 137 | 130 | 121 | 111 | 95 | 99 | 98 | 95 | 77 | 53 | 34 | 10 |
| Placebo | 133 | 129 | 124 | 118 | 105 | 100 | 98 | 93 | 80 | 45 | 28 | 19 |

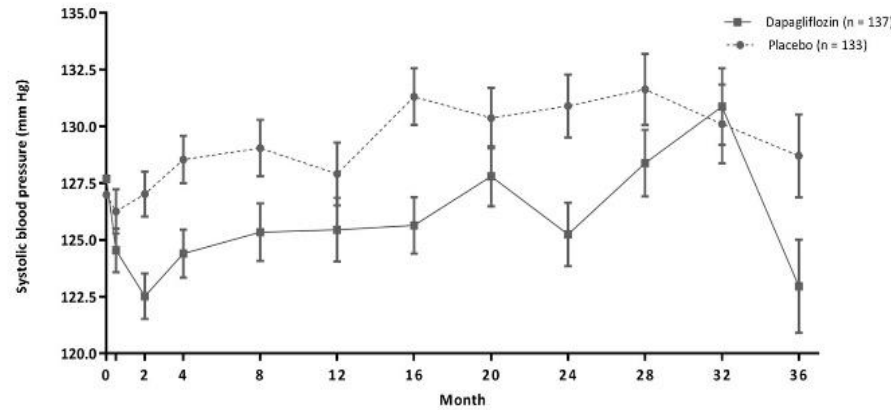
b



Participants per time point

| | | | | | | | | | | | | |
|---------------|-----|-----|-----|-----|-----|-----|----|----|----|----|----|----|
| Dapagliflozin | 137 | 130 | 121 | 111 | 95 | 99 | 98 | 95 | 77 | 53 | 34 | 10 |
| Placebo | 133 | 129 | 124 | 118 | 105 | 100 | 98 | 93 | 80 | 45 | 28 | 19 |

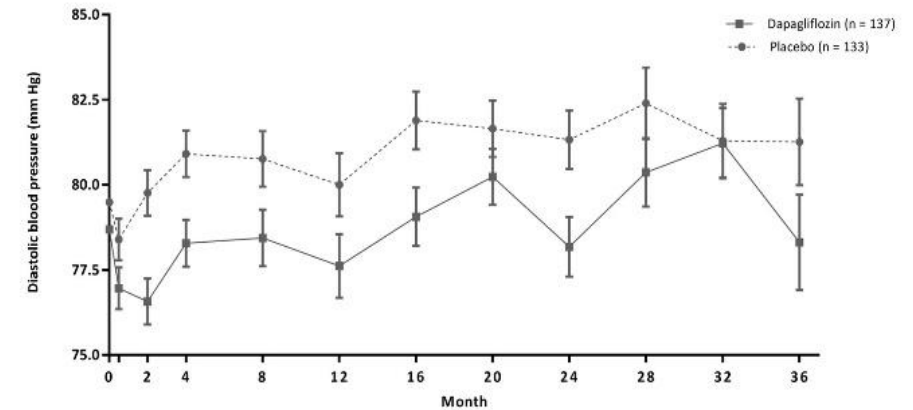
c



Participants per time point

| | | | | | | | | | | | | |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Dapagliflozin | 137 | 131 | 122 | 122 | 105 | 103 | 103 | 102 | 86 | 59 | 39 | 14 |
| Placebo | 133 | 129 | 128 | 126 | 110 | 106 | 105 | 100 | 90 | 51 | 35 | 21 |

d



Participants per time point

| | | | | | | | | | | | | |
|---------------|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Dapagliflozin | 137 | 131 | 122 | 122 | 105 | 103 | 103 | 102 | 86 | 59 | 39 | 14 |
| Placebo | 133 | 129 | 128 | 126 | 110 | 106 | 105 | 100 | 90 | 51 | 35 | 21 |

Table 2 | Safety

| Characteristic | Dapagliflozin (n = 137) | Placebo (n = 133) |
|---|----------------------------|----------------------|
| Adverse events leading to discontinuation of study drug | 6 (4.4) | 7 (5.3) |
| Serious adverse events ^a | 22 (16.1) | 34 (25.6) |

Values are n (%).

^aIncluding death.

DAPA-CKD and IgAN

Wheeler et al., Kidney International, April 17 2021

Meta-analysis of Large Trials of SGLT2 inhibitors in Diabetics and Non-Diabetics Lancet 11/19/2022

- Included 13 trials with 90,413 pts Double blind, PBO controlled, adults, >500 pts /group
- End points progression of kidney disease, ESKD, AKI, Cvasc Death, CHF Hosp, keto acidosis . lower limb amputations.

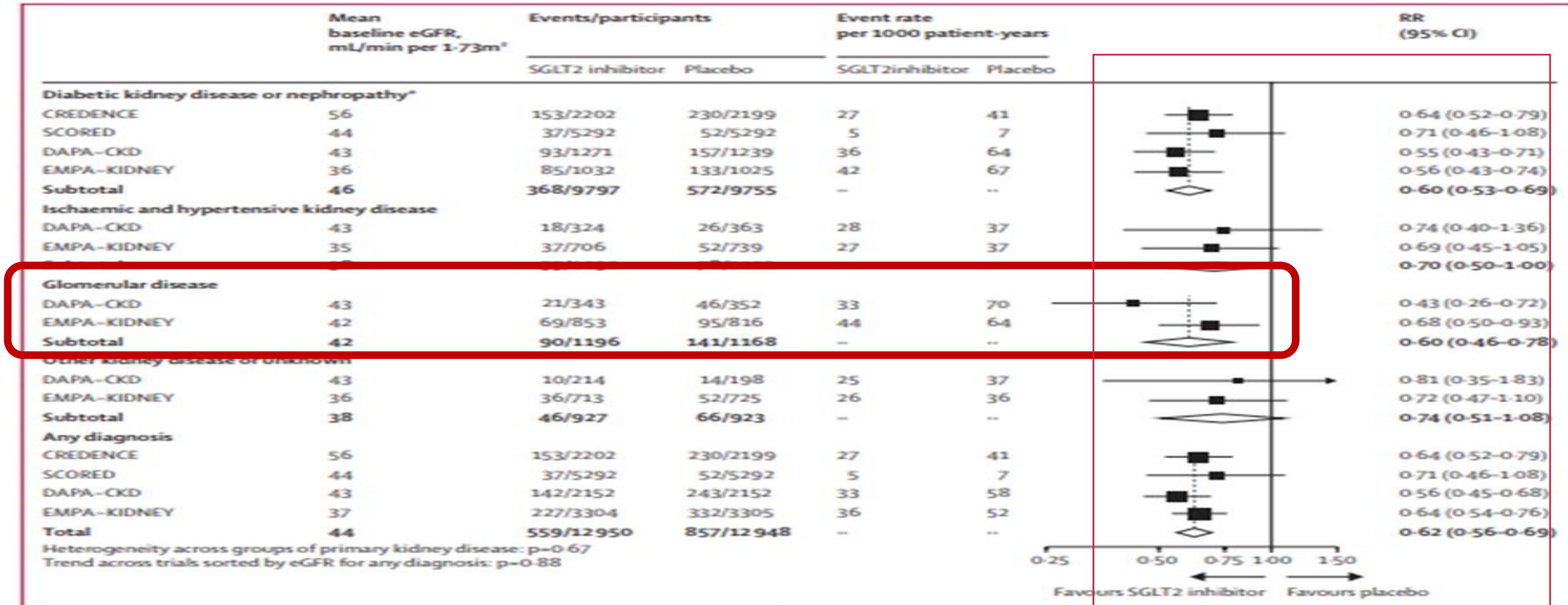
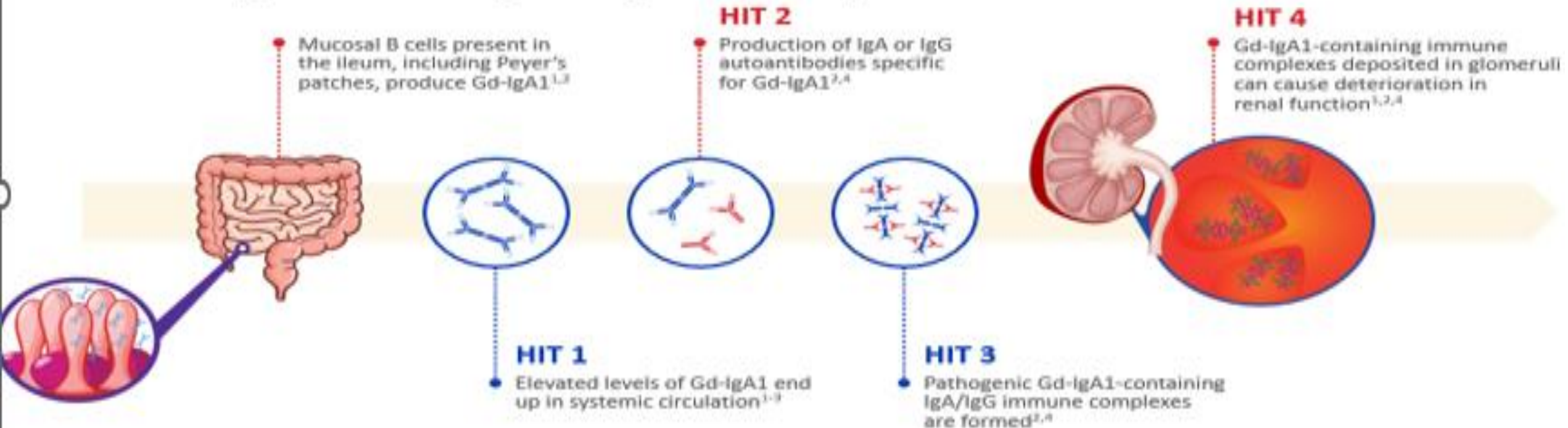


Figure 2: Effect of sodium glucose co-transporter-2 inhibition on kidney disease progression by presumed primary kidney disease (chronic kidney disease

"4-Hit" Hypothesis: A Widely Accepted Model for Understanding the Pathogenesis of IgA Nephropathy



Block autoimmune mech of IgAN

Block formation of Gd IgA1
Block IgA1 immune Complexes

Block nonspecific - CGN

ACE inhib/ARBs
SGLT2inhibs
Sparsentan

Block Glom inflammation /scarring

Steroids, MMF, other immune meds

Efficacy and Safety of TR Budesonide in Primary IgA N (NefigArd)

Lafayette R, Kristensen J, Stone A et al. The Lancet 402: 859-870, 2023

364 Pts w IgAN , eGFR 35-90cc/min Uprot/Ucreat >0.8g/g
or Uprot >1 g/D

16 TR budesonide for 9 mo vs PBO All Optimized support.

Most common side effects edema (17%), HBP(12%) acne 11%

No increase infections, 7 DM all pre-DM or prior DM

No deaths

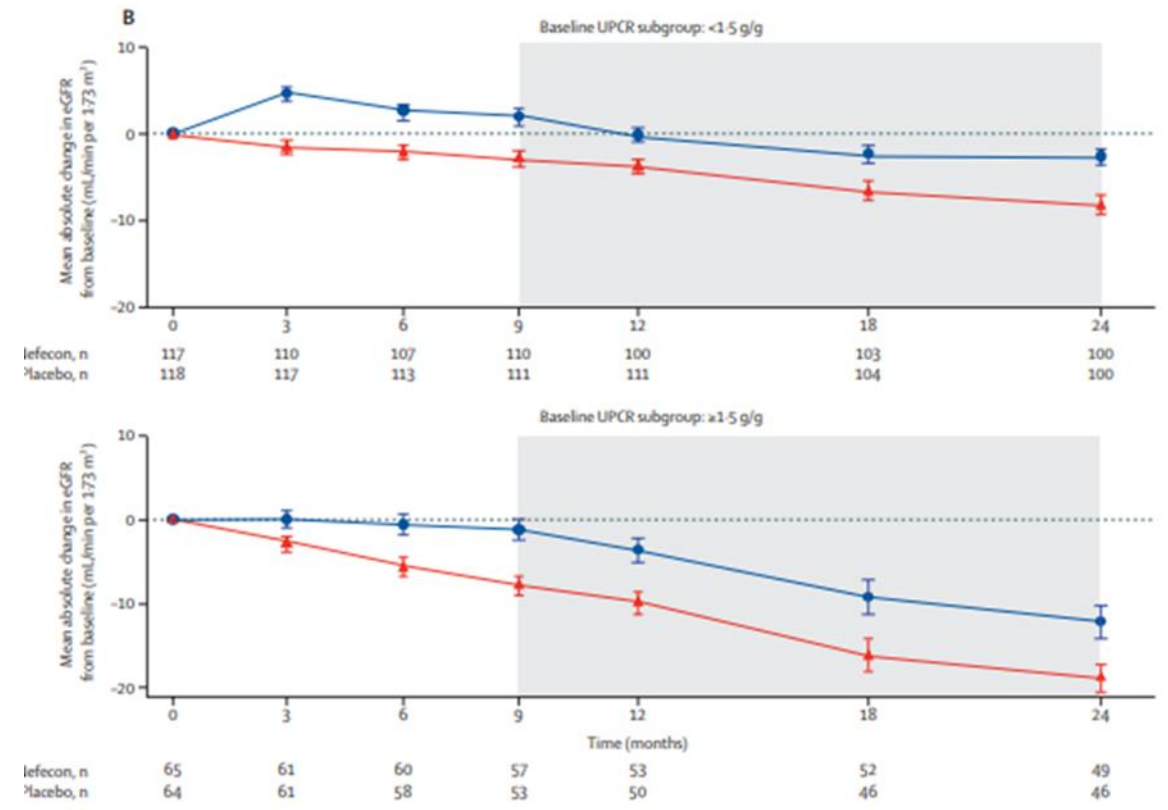
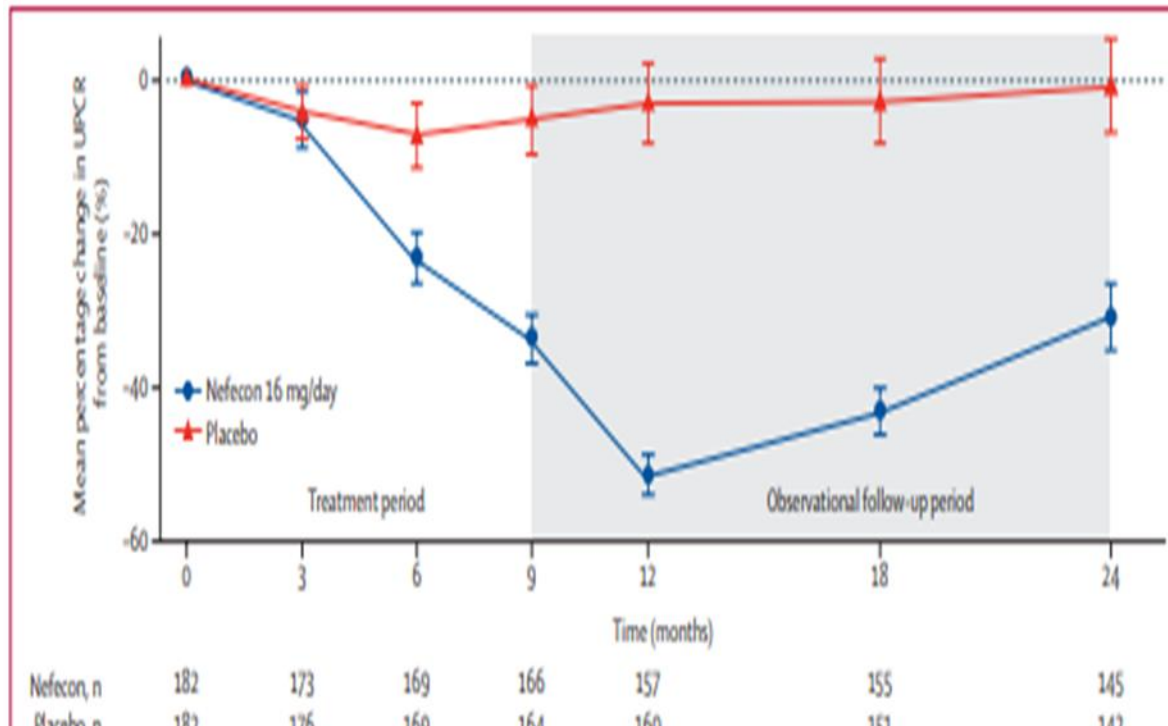


Figure 1: Mean absolute change in eGFR from baseline to 24 months (full analysis set)

Targeted-release budesonide modifies key pathogenic biomarkers in immunoglobulin A nephropathy: insights from the NEFIGAN trial

Kidney int. 2024 105:381-388

David Wimbury^{1,8}, Masahiro Muto^{2,8}, Jasraj S. Bhachu¹, Katrin Scionti¹, Jeremy Brown¹, Karen Molyneux³, Claudia Seikrit³, Dita Maixnerová⁴, Laura Pérez-Alós⁵, Peter Garred⁵, Jürgen Floege³, Vladimír Tesar⁴, Bengt Fellstrom^{6,8}, Rosanna Coppo⁷ and Jonathan Barratt¹

¹Mayer IgA Nephropathy Laboratories, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK; ²Department of Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan; ³Division of Nephrology and Clinical Immunology, Rheinisch-Westfälische Technische Hochschule Aachen University, Aachen, Germany; ⁴Department of Nephrology, 1st Faculty of Medicine, General University Hospital, Charles University, Prague, Czech Republic; ⁵Laboratory of Molecular Medicine, Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark; ⁶Department of Medical Sciences, Uppsala University, Uppsala University Hospital, Uppsala, Sweden; and ⁷Fondazione Ricerca Molinette, Regina Margherita Hospital, Turin, Italy

Kidney International (2024) 105, 381–388; <https://doi.org/10.1016/j.kint.2023.11.003>

KEYWORDS: chronic kidney disease; complement; cytokines; glomerulus; IgA nephropathy; proteinuria

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Nefecon is the first approved treatment for patients with immunoglobulin A nephropathy (IgAN) at high risk of progression to kidney failure (accelerated approval by US Food and Drug Administration; conditional approval by European Medicines Agency).^{1–3} Nefecon delivers budesonide, in a targeted formulation, to the gut-associated

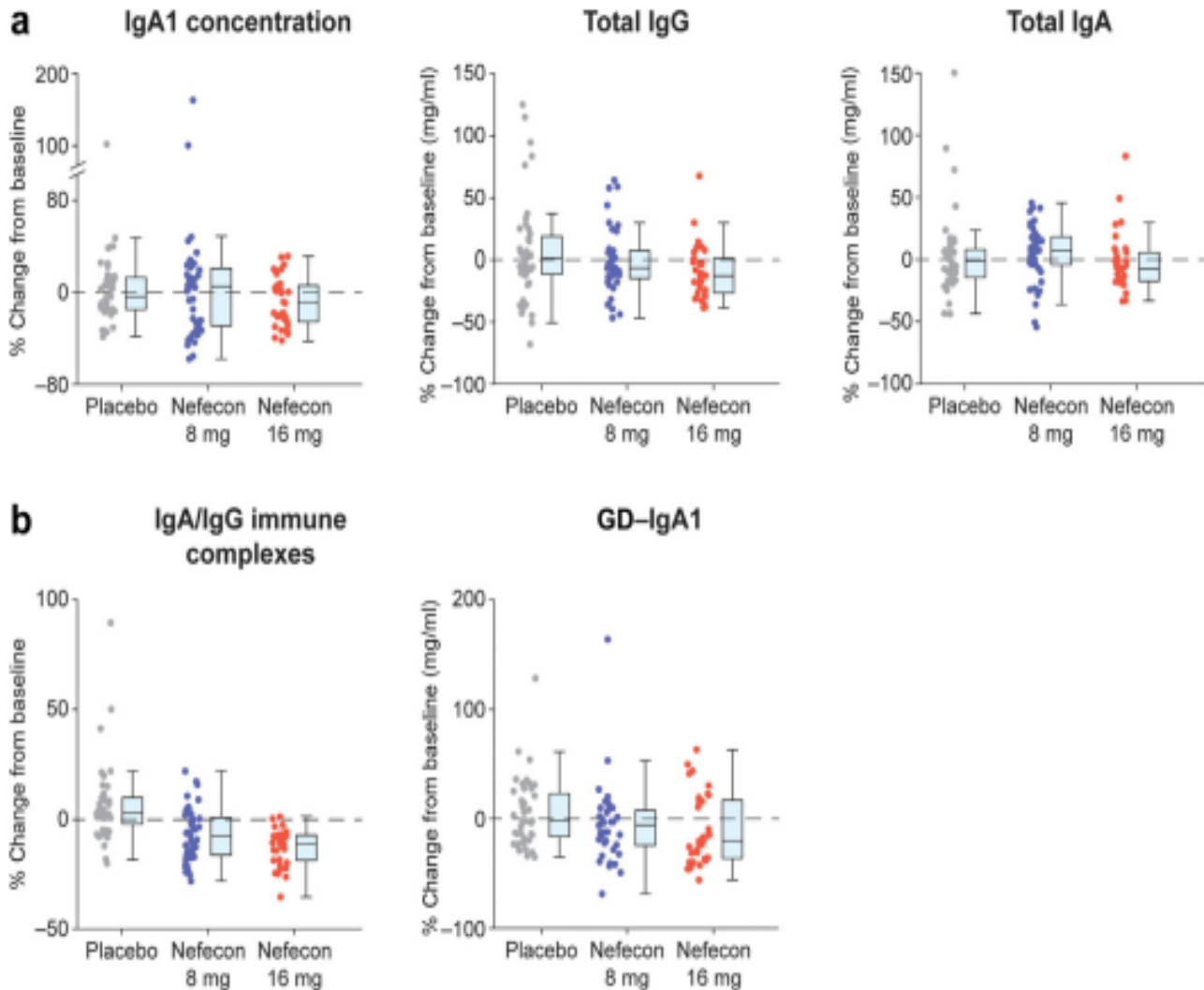


Figure 1 | Change from baseline by treatment group in biomarkers demonstrating the disease-modifying effect of Nefecon at 9 months. (a) IgA1 concentration ($p = 0.0656$), total IgG ($p = 0.2491$), total IgA ($p = 0.3955$). (b) IgA/IgG immune complexes ($p < 0.0001$).

Current and Future developments in IgA Nephropathy therapy

For Glomerular Inflammation steroids and MMF work

TR Budesonide – FDA approved

Sparsentin – FDA Approved -combined ETA antagonist + ARB

Dapagliflozin – FDA approved for CKD

Iptacopan – FDA accelerated FDA approval

Atrasentan - FDA accelerated FDA approval

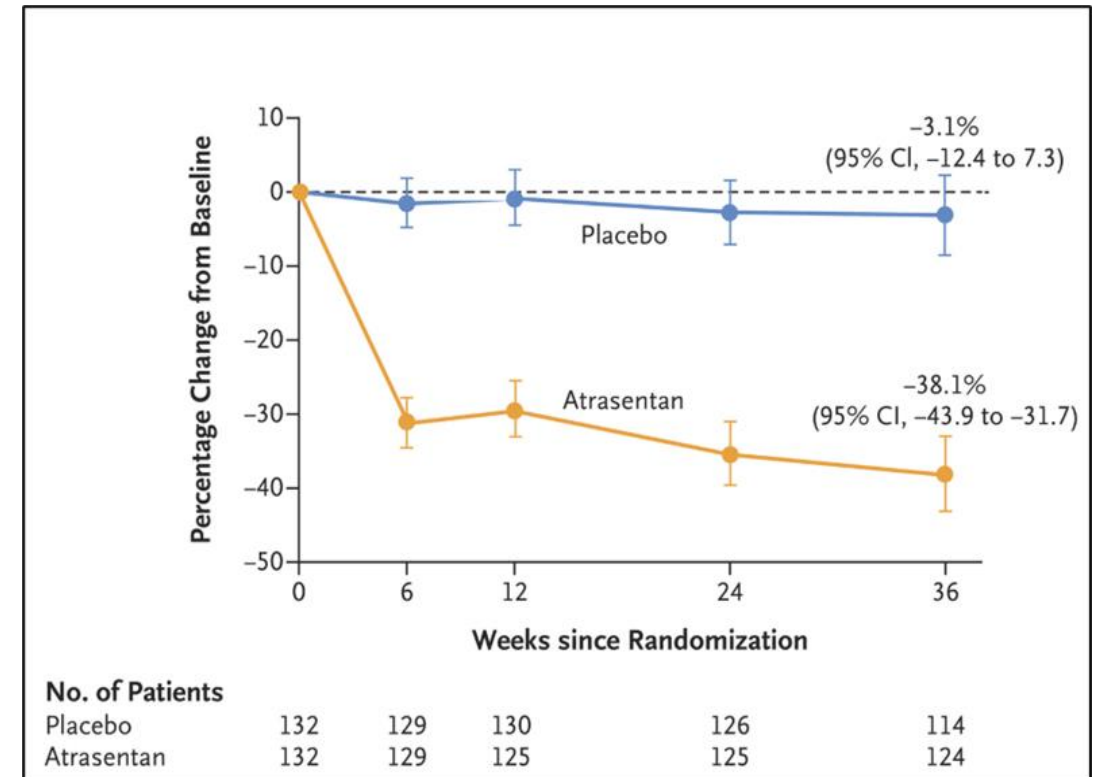
Anti - APRIL inhibitors (Sibeprenlimab , Zigakibart)

Anti BAFF/anti April inhibitors (Atacicept, telitacicept, Povetacicept)

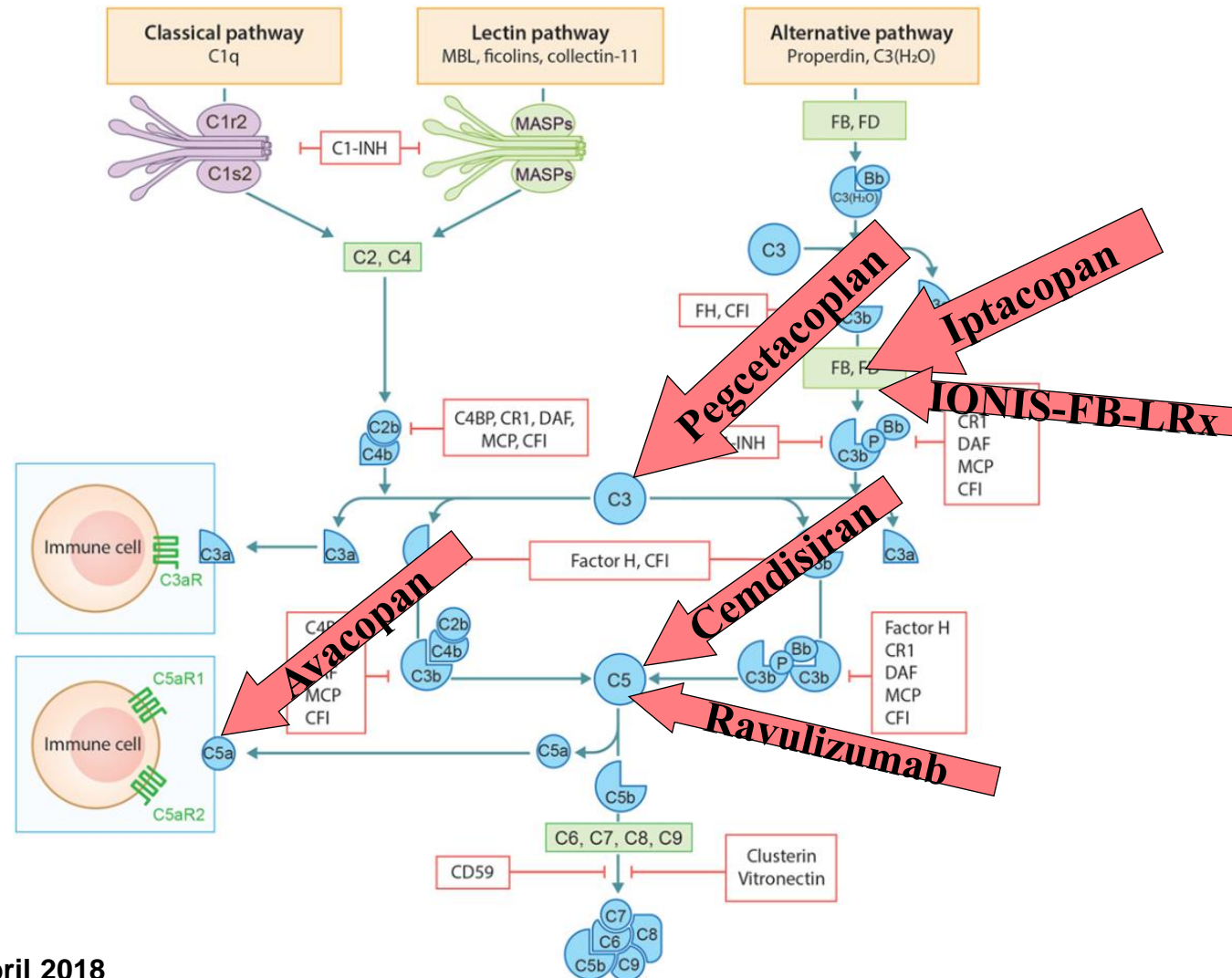
ALIGN Trial: Atrasentan vs Placebo in Patients with IgAN

- 264 IgAN Pts
- eGFR ≥ 30 ml/min
- UPCR ≥ 1 g/g
- Max tolerated ACE inhib/ ARB for ≥ 12 weeks

**Atrasentan reduced proteinuria at 36 mo
vs PBO**



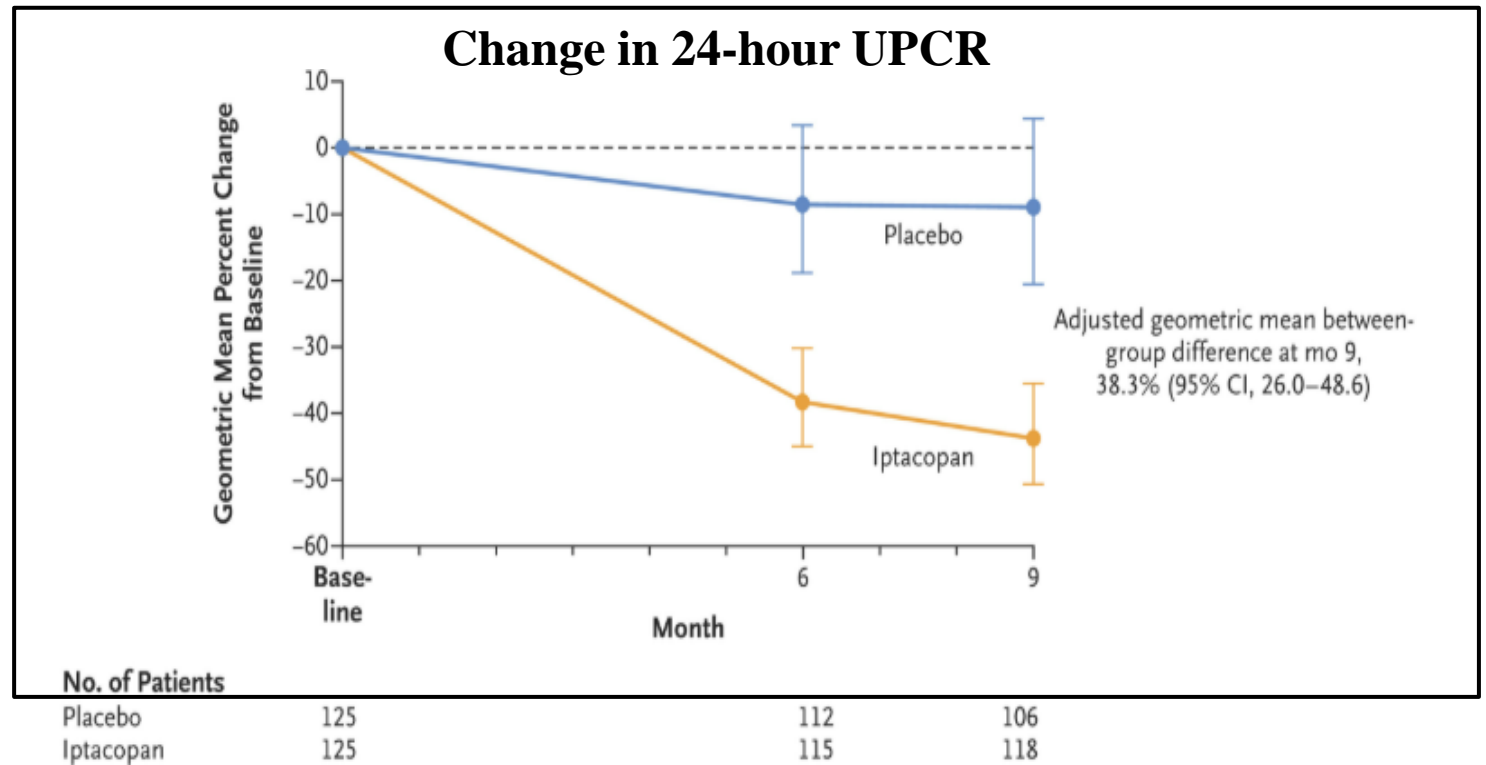
Experimental complement therapies for IgAN



Phase 3 APPLAUSE-IgAN: Iptacopan vs Placebo in Patients with IgAN

Study Patients

- Biopsy-proven IgAN
- eGFR ≥ 30 ml/min
- UPCR ≥ 1 g/g
- Stable dose of ACE inhibitor or ARB for ≥ 90 days w or w/o SGLT2inhibitor
- 200mg PO daily
- End point 2 yrs eGFR slope vs PBO

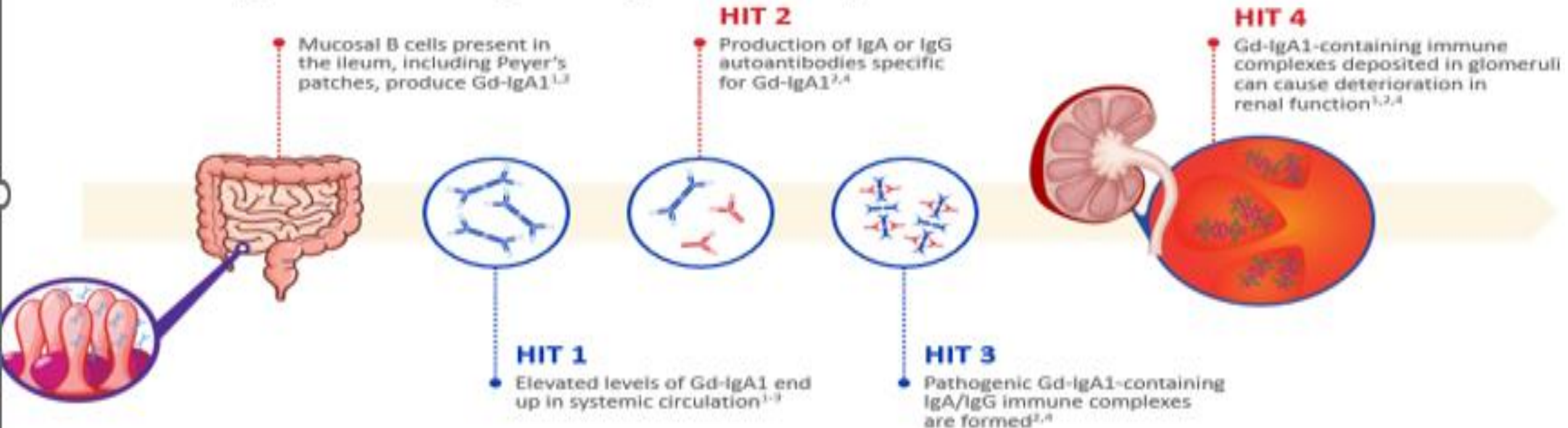


Iptacopan reduced proteinuria at 9 months by 38.3% compared to placebo

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; UPCR, urinary protein-to-creatinine ratio.

Perkovic V et al. *New Engl J Med*. 2025;392(6):531-543.

"4-Hit" Hypothesis: A Widely Accepted Model for Understanding the Pathogenesis of IgA Nephropathy



Block autoimmune mech of IgAN

Block formation of Gd IgA1
Block IgA1 immune Complexes

Block nonspecific - CGN

ACE inhib/ARBs
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Block Glom inflammation /scarring

Steroids, MMF, other immune meds

Current and Future developments in IgA Nephropathy therapy

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Atrasentan - FDA accelerated FDA approval

Anti - APRIL inhibitors (Sibeprenlimab , Zigakibart)

Anti BAFF/anti April inhibitors (Atacicept, telitacicept, Povetacicept)

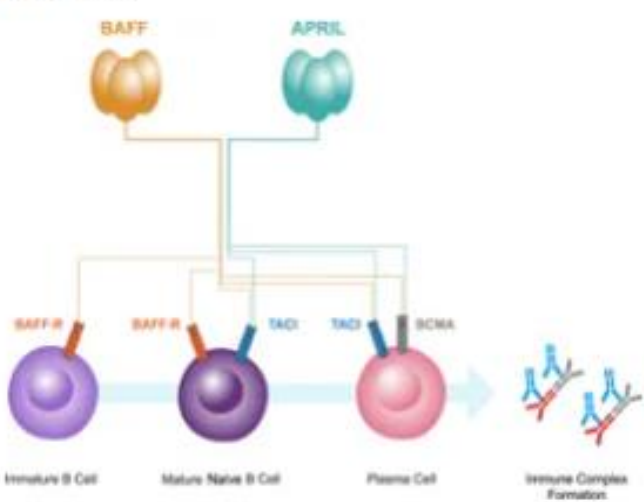
Emerging Agents: Blockers of APRIL and BAF/BLyS

A Proliferation Inducing Ligand and and B Cell Activating Factor are cytokines that bind to key receptors on B cells and plasma cells.

These Cytokines play key roles in the maturation, activation, and survival of B cells.

All are implicated in the pathogenesis of IgAN
New agents against these targets function to reduce the production of pathogenic Gd IgA and immune complexes

Figure 2



| MoA | Drugs |
|--------------------------------|-----------------------------|
| APRIL mAbs | Sibeprenlimab Zigakibart |
| Dual APRIL and BAFF inhibitors | Atacicept Telitacicept |
| Dual APRIL and BLyS antagonist | Povetacicept |

Emerging Agents: APRIL, BAFF/BLyS

APRIL, BAFF/BLyS

- Play key roles in the maturation, activation, and survival of B cells
- All are implicated in the pathogenesis of IgAN
- Agents against these targets function to reduce the production of pathogenic Gd IgA and immune complexes

| MoA | Drugs |
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| APRIL mAbs | Sibeprenlimab Zigakibart |
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| Dual APRIL and BLyS antagonist | Povetacicept |

RESEARCH SUMMARY

A Phase 2 Trial of Sibeprenlimab in Patients with IgA Nephropathy

Mathur M et al. DOI: 10.1056/NEJMoa2305635

CLINICAL PROBLEM

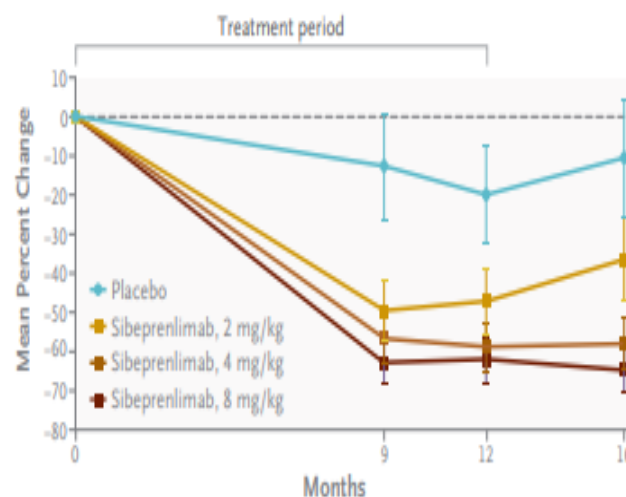
Among patients with IgA nephropathy, kidney failure develops in $\geq 30\%$ within 20 to 30 years, despite the receipt of optimized standard care. A critical step in the pathogenesis of IgA nephropathy is the production of galactose-deficient IgA1 and resulting autoantibody release. Sibeprenlimab is a humanized IgG2 monoclonal antibody that binds to and neutralizes a proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor α superfamily that regulates IgA production.

CLINICAL TRIAL

Design: A phase 2, multicenter, double-blind, randomized, placebo-controlled, multiple-dose trial examined the efficacy and safety of sibeprenlimab in adults with IgA nephropathy at high risk for disease progression.

Intervention: 155 patients were assigned to receive intravenous sibeprenlimab at a dose of 2, 4, or 8 mg per kilogram of body weight or placebo once monthly for 12 months. The primary end point was the change from baseline to month 12 in the log-transformed 24-hour urinary protein-to-creatinine ratio.

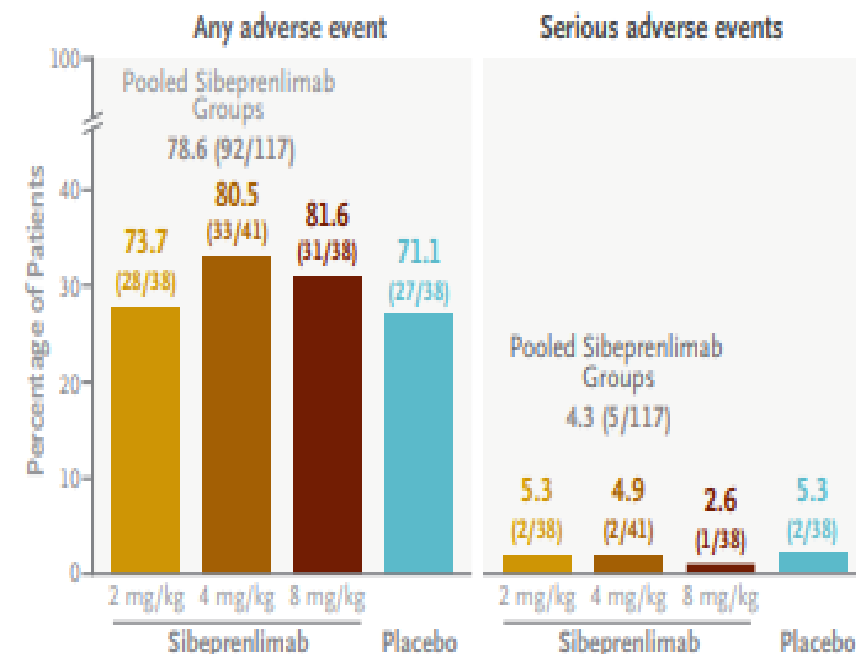
Change in 24-Hr Urinary Protein-to-Creatinine Ratio



Geometric Mean Percent Reduction in 24-Hr Urinary Protein-to-Creatinine Ratio

| End Point | Sibeprenlimab 2 mg/kg (N=38) | Sibeprenlimab 4 mg/kg (N=41) | Sibeprenlimab 8 mg/kg (N=38) | Placebo (N=38) |
|-----------|------------------------------|------------------------------|------------------------------|----------------|
| Month 9 | 49.6±7.7 | 56.7±6.2 | 62.8±5.5 | 12.7±13.4 |
| Month 12 | 47.2±8.2 | 58.8±6.1 | 62.0±5.7 | 20.0±12.6 |
| Month 16 | 36.5±10.6 | 58.0±6.6 | 64.6±5.7 | 10.6±15.0 |

Adverse Events



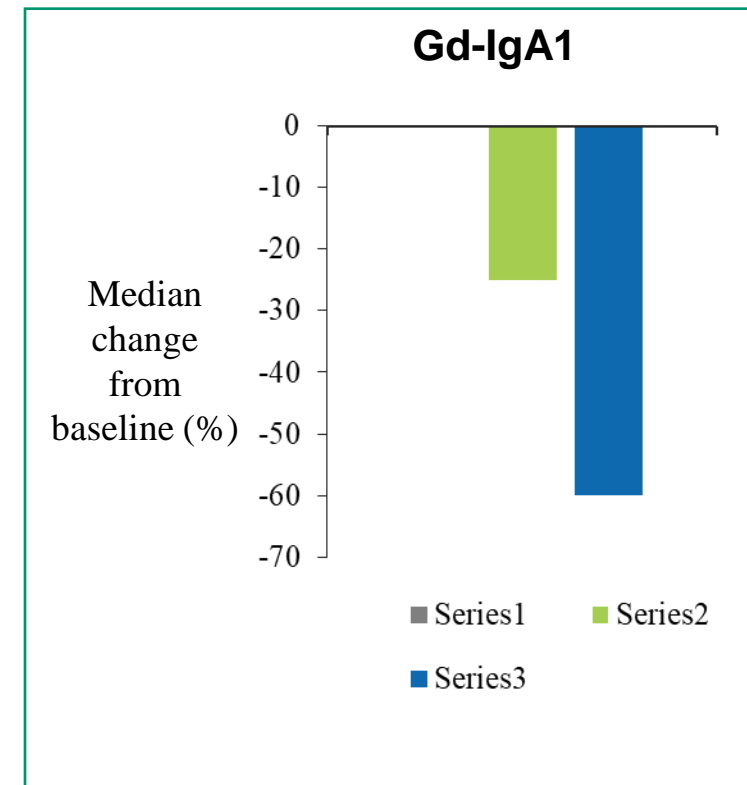
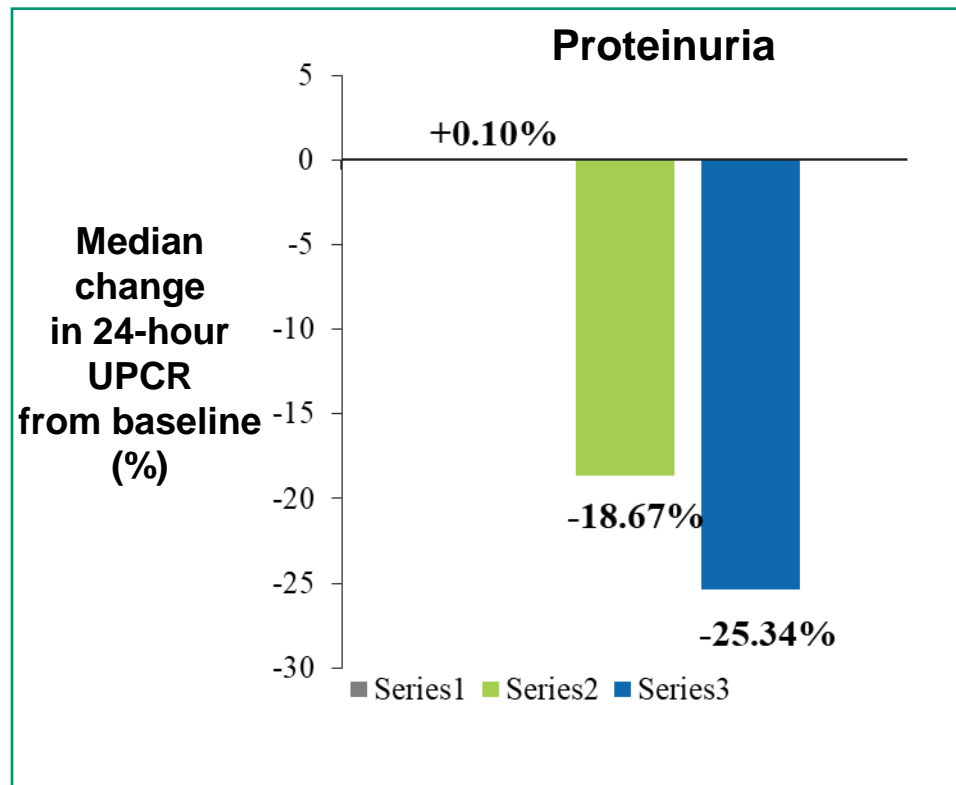
CONCLUSIONS

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.

Atacicept in IgAN Pts w Persistent Proteinuria: Phase II JANUS Study

Human TACI-IgG1 fusion protein

- Binds to BLyS/BAFF and APRIL and inhibits B cell activation and Ig production
- Associated with decreased serum Ig levels in clinical studies with MS, RA and SLE pts
 - Atacicept 75 mg vs 25 mg vs. placebo, 24 wks treatment
 - Randomized N=16

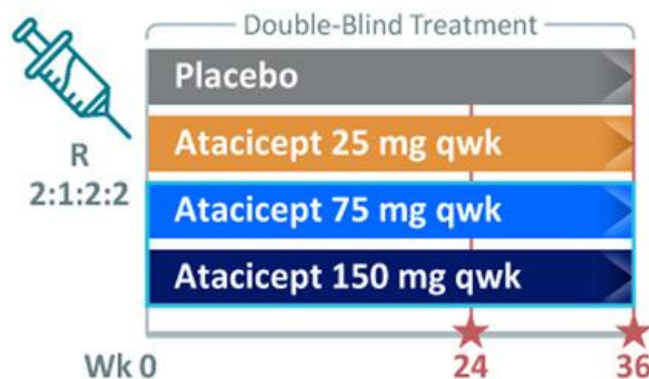


A Phase 2b, randomized double-blind, placebo-controlled, clinical trial of atacicept for treatment of IgA nephropathy

kidney
INTERNATIONAL



Methods and population

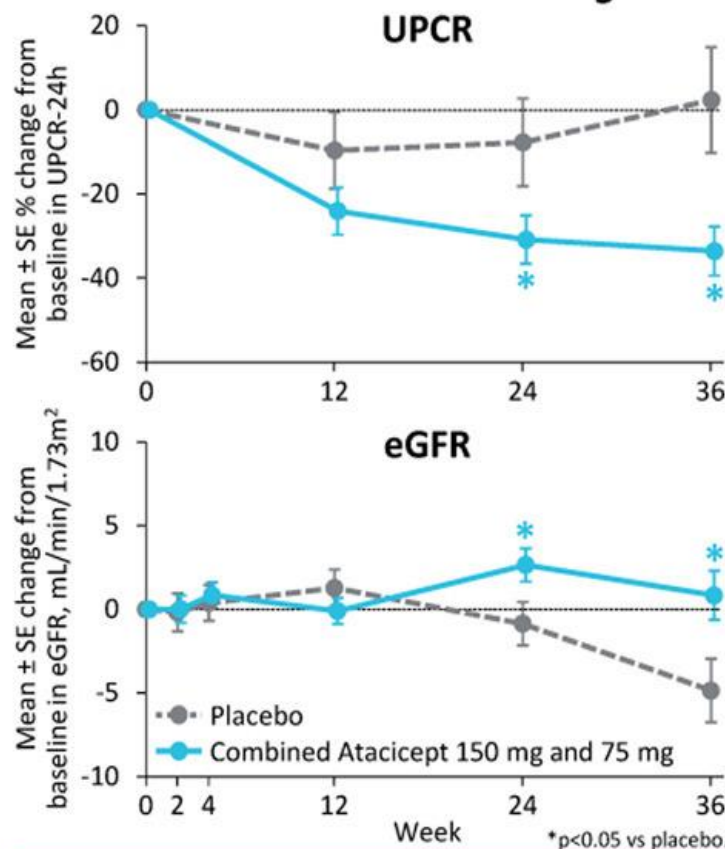


- 116 adults from 13 countries
- Biopsy-proven IgAN within 10 years prior to screening
- ≥ 12 weeks on maximally tolerated, stable dose of RAASi
- SGLT2i use was allowed

Key baseline characteristics

- Mean UPCR-24h **1.6 g/g**
- Mean eGFR **63 mL/min/1.73m²**

Outcomes with combined 75 mg and 150 mg group vs placebo



1° endpoint met at 24 weeks:
UPCR reduction **$\Delta 25\%$**
p=0.037



Key 2° endpoints at 36 weeks

UPCR reduction **$\Delta 35\%$**
p=0.004



eGFR difference **11%** **5.7**
p=0.022 mL/min/1.73m²



Gd-IgA1 reduction **$\Delta 60\%$**
p<0.0001



Safety profile of all atacicept doses similar to placebo

Lafayette et al, 2024

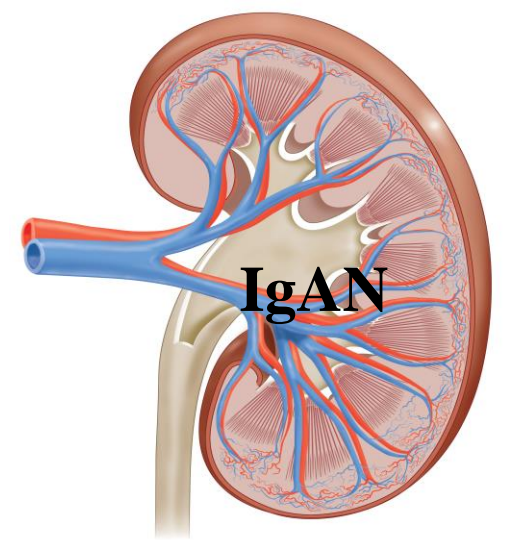
Lafayette R, Barbour S., Israni R et al
Kidney Int. 105:1306-1315, 2024

Kidney International 2024 105:1306-1315 DOI: 10.1016/j.kint.2024.03.010
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CONCLUSION

Treatment with atacicept, a dual BAFF/APRIL inhibitor, in addition to current standard of care, resulted in clinically and statistically significant UPCR reductions at weeks 24 and 36 and eGFR stabilization at week 36, supporting a pivotal phase 3 trial

KDIGO 2024 IgA N Draft Guidelines – Some Major Points



Biopsy early - recommended if proteinuria ≥ 0.5 g/d

Risk of progressive loss of kidney function if proteinuria ≥ 0.5 g/d on or off treatment. Treatment/additional treatment should be started in all pts.

Focus on simultaneously:

- Preventing or reducing IgA immune complex formation and immune complex-mediated glomerular injury and**
- Managing consequences of existing IgAN-induced nephron loss**
- Optimize BP control, adopt healthy lifestyles and utilize therapeutics with beneficial hemodynamic effects**

How do I treat IgAN in 2025?

Risk-stratify patient Proteinuria, GFR, Oxford Class, Comorbidities

Supportive care for All Patients

1. **Lifestyle:** diet, smoking, weight, etc.
2. **BP control:** KDIGO: SBP <120-130

Therapy directed at general progression of CKD for all Patients who tolerate

RAAS inhibition: ACE or ARB, consider +MRB

SGLT2 inhibitors for many

Sparsentan - ? Atrasentan

Agents directed at glomerular inflammation And/ OR production of Gd IgA-1 or IgA immune complexes

- **Glucocorticoids:** evidence supports renal effects, low dose similar efficacy less toxicity
- **MMF** controversial, Other immunosuppression lack of evidence -Weigh risks and benefits carefully in each patient.
- **TR Budesonide** – FDA approved , protein reduction and improved GFR
decreases in Gd IgA and IgA immune complexes
- **Iptacopan**

Watch for new data and approval of BAFF/APRIL blockers and complement blockers



WE PROMISE TO BE A THIRSTY KID
ONLY IN RIVERS VALLEY

**BONELESS
CHUCK
ROASTS**

\$1.37
LB.

WE'LL TAKE ALL YOURS
RED RIVER VALLEY

**RED
POTATOES**

5 TO 10 LBS.
BUY ONE GET ONE
FREE

Numbers
Go
Play
Win

WE GUARANTEE WHITE OR YELLOW
TO THE MAX
**IGA
CHEESE
SINGLES**

10 TO 120 LBS.
ONE GET ONE
FREE



KDIGO 2024 DRAFT Guidelines: Available treatments

2.3 Treatment

Recommendation 2.3.3.1.1: We suggest treatment with a 9-month course of nefecon for patients who are at risk of progressive kidney function loss with IgAN (2B).^{a,b}

Recommendation 2.3.1.2.1: In settings where nefecon is not available, we suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a limited course of a reduced-dose systemic glucocorticoid regimen combined with antimicrobial prophylaxis after a thorough toxicity risk assessment (2B).^{a,b}

Recommendation 2.3.4.1: We recommend all patients who are at risk of progressive kidney function loss with IgAN be treated with an optimized maximally tolerated dose of either an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (1B).^{a,b}

Recommendation 2.3.4.2: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with a sodium-glucose cotransporter-2 inhibitor (SGLT2i) (2B).^{a,b}

Recommendation 2.3.4.3: We suggest that patients who are at risk of progressive kidney function loss with IgAN be treated with sparsentan (2B).^{a,b}

^aStrength of recommendation: Level 1, recommended; Level 2, suggested. ^bCertainty of evidence: B, moderate.

IgAN, immunoglobulin A nephropathy.

Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO 2024 clinical practice guideline for the management of immunoglobulin A nephropathy (IgAN) and immunoglobulin A vasculitis (IgAV); public review draft, August 2024. Accessed October 21, 2024.

<https://kdigo.org/wp-content/uploads/2024/08/KDIGO-2024-IgAN-IgAV-Guideline-Public-Review-Draft.pdf>