eGFR and proteinuria as surrogate endpoints for GLOMERULAR DISEASE clinical trials

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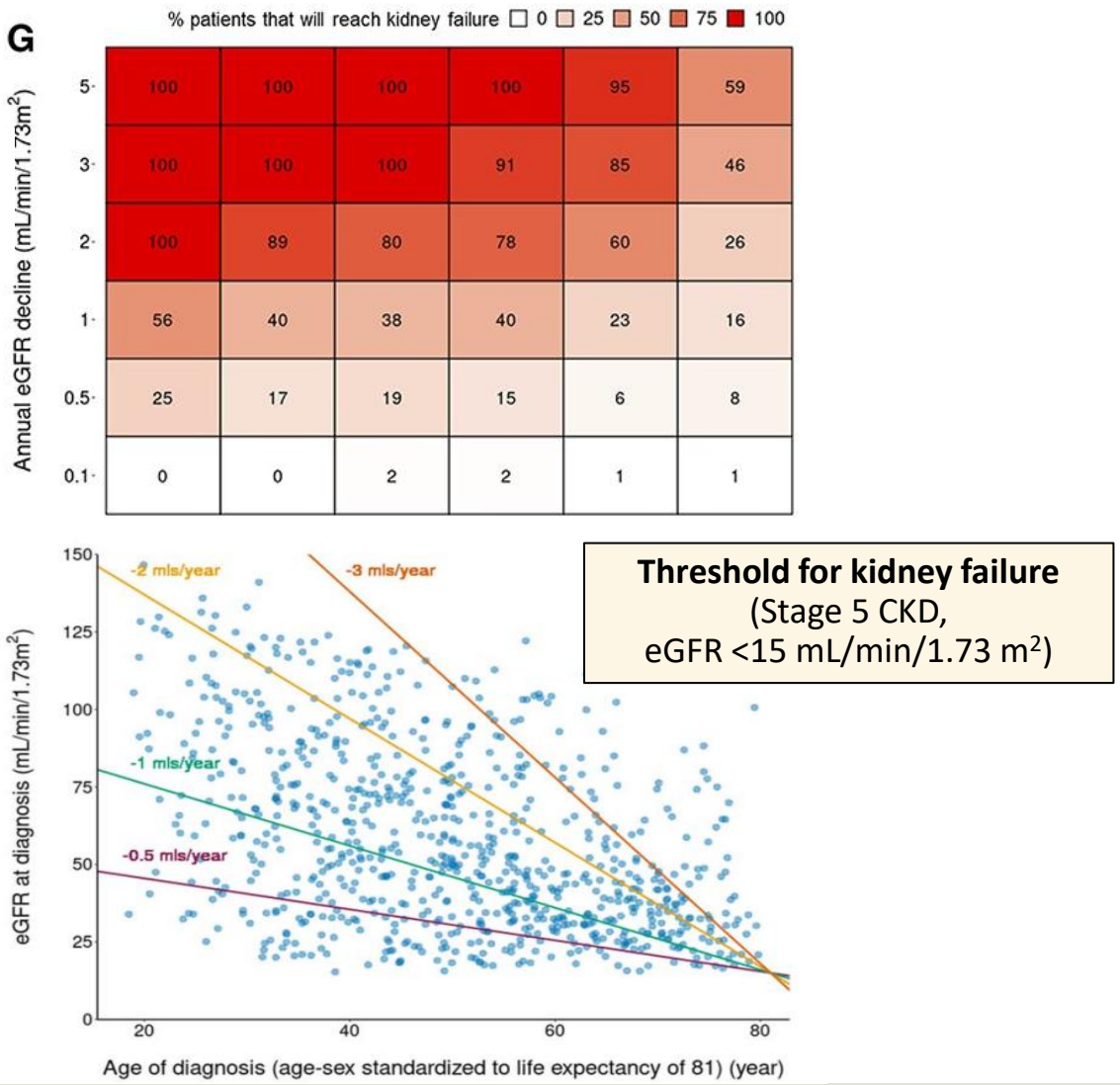
Disclosures

- Investigative support- FDA, NIH, UMichigan, UPenn, Biogen, Vera, Novartis, Alexion, Roche, Travere. Beigene, Calliditas

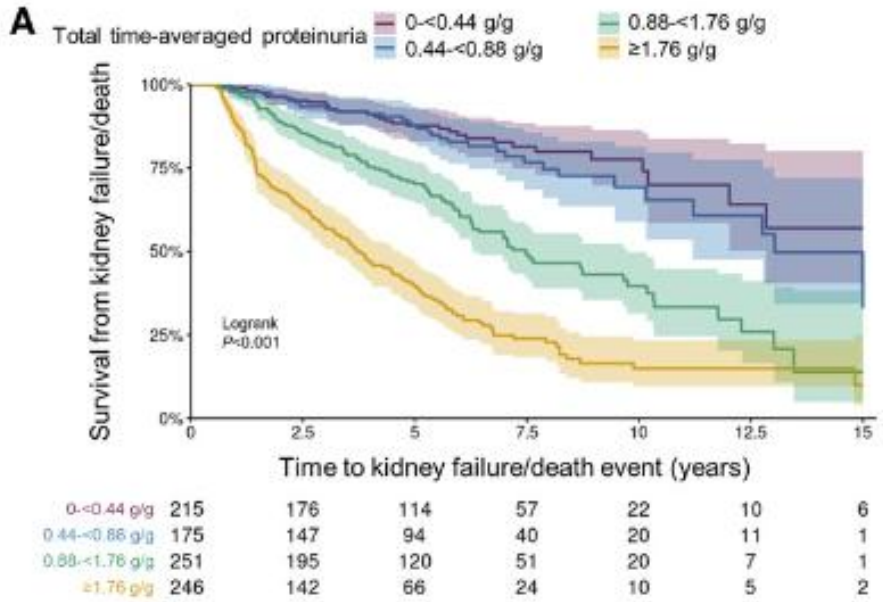
- Consulting services- Alexion, Amgen, Beigene, Biogen, Calliditas, Dimerix, Takeda, Vertex, Vera, Travere, BIohaven

Most IgAN patients are at risk of progression to kidney failure in their lifetime - by eGFR, eGFR slope and proteinuria



Threshold for kidney failure
(Stage 5 CKD,
eGFR <15 mL/min/1.73 m²)

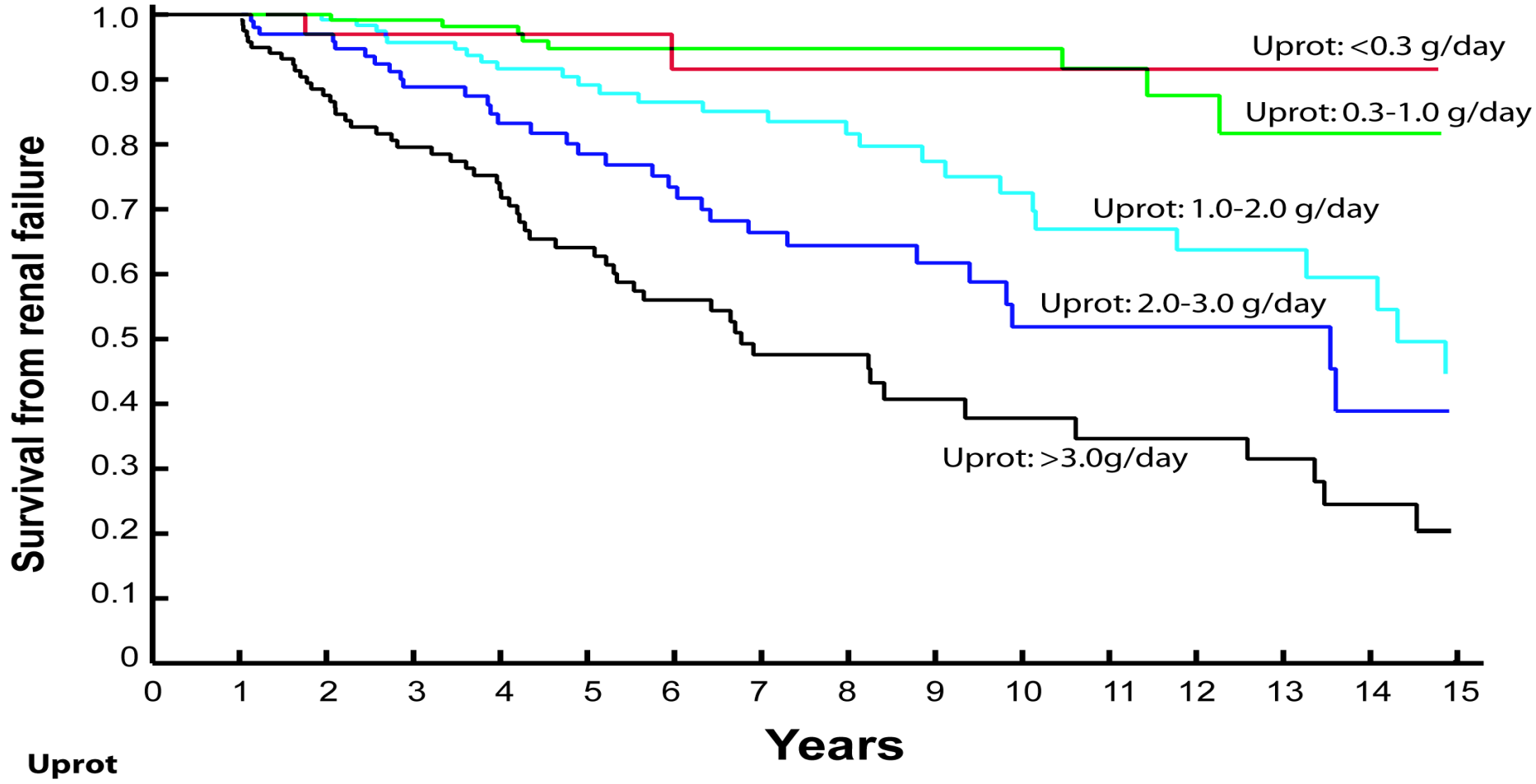
Even "low-risk" proteinuria levels (<0.88 g/g), patients still face a 20%-30% risk of progressing to kidney failure within 10 years



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

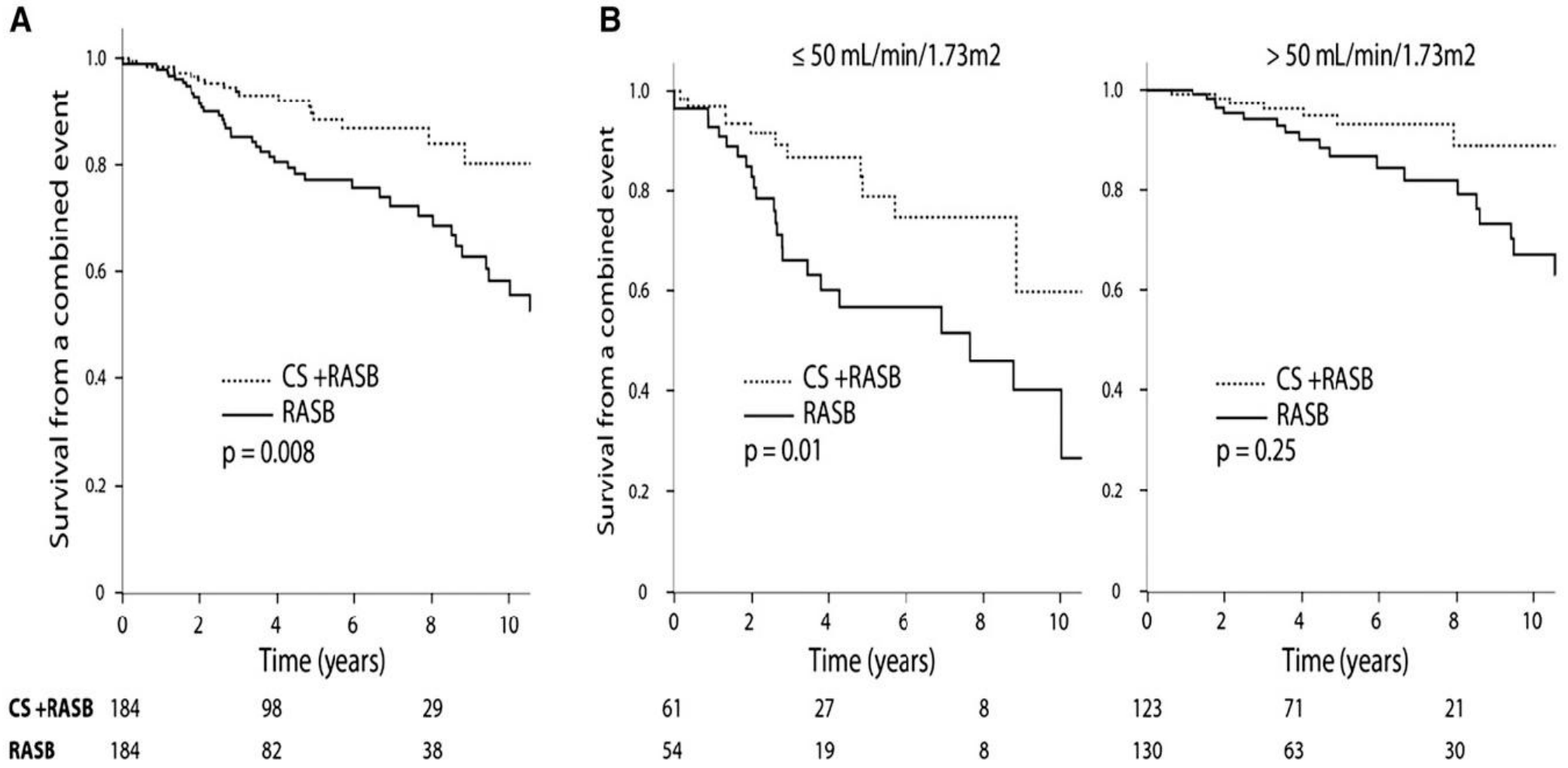
Pitcher D, et al. Clin J Am Soc Nephrol. 2023; 18:727–738 doi: 10.2215/CJN.0000000000000135

Proteinuria over time determines outcome



Reich, H et al.JASN 18:3177, 2007

Example of classic outcomes- Composite kidney outcome

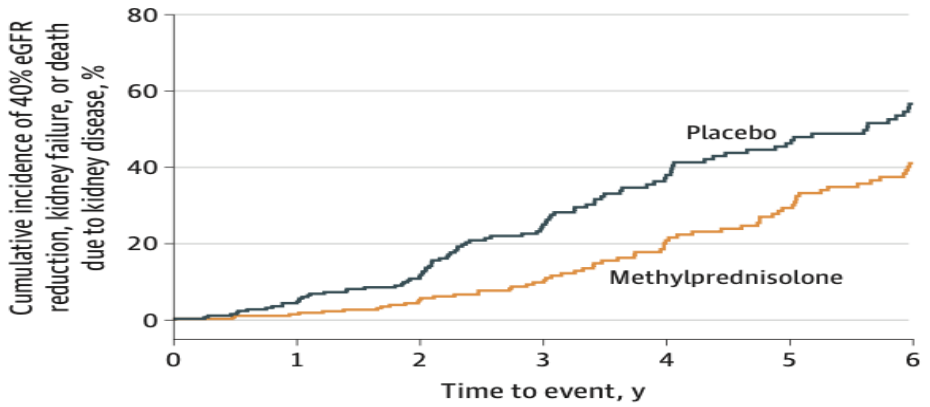


JASN 2015 in press. Tesar et al, VALIGA study.

Figure 2. Response to CS and RASB compared with RASB alone in propensity-matched individuals. (A) Entire propensity-matched cohort. (B) Stratified by initial eGFR. *P* values obtained using time-dependent Cox regression.

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

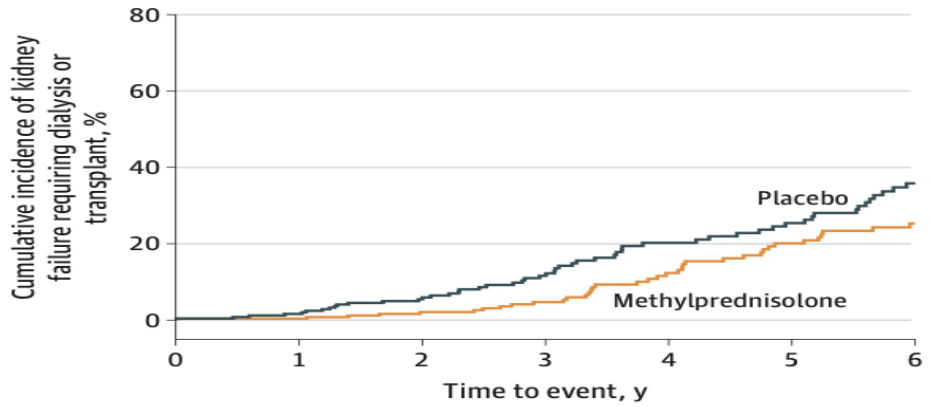
A Primary outcome in all patients



No. of patients at risk

Methylprednisolone	257	250	215	161	105	92	66
Placebo	246	234	188	127	76	66	44

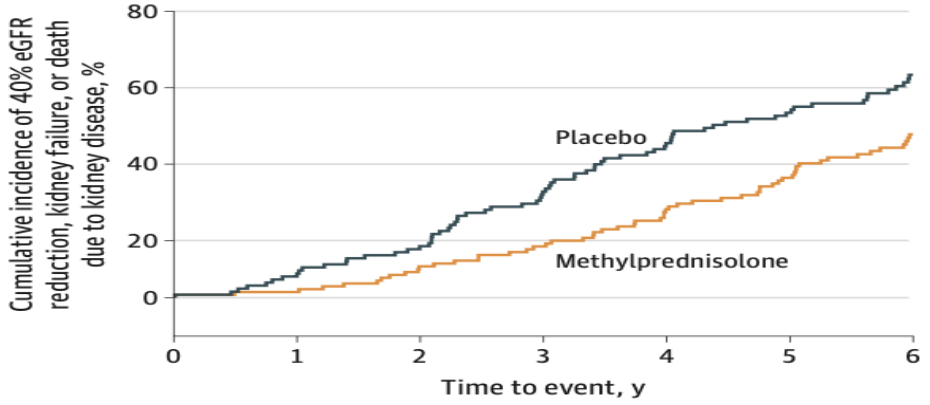
B Kidney failure requiring dialysis or transplant



No. of patients at risk

Methylprednisolone	257	253	223	172	116	103	81
Placebo	246	242	200	147	95	87	62

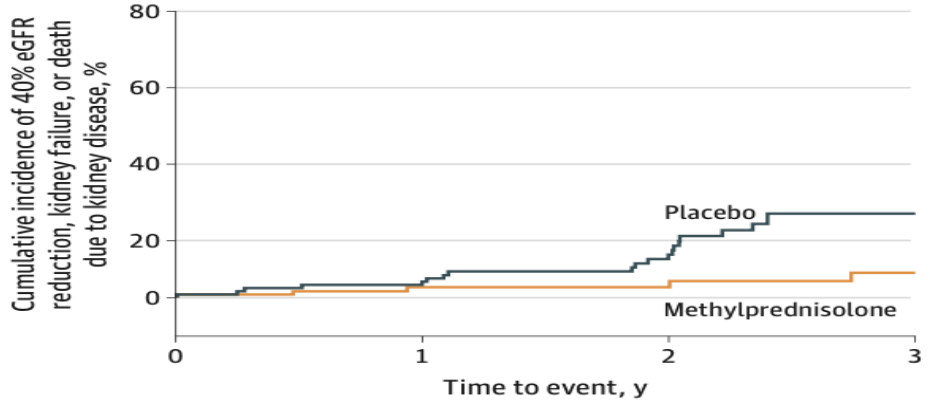
C Primary outcome in full-dose cohort



No. of patients at risk

Methylprednisolone	136	133	124	117	104	92	66
Placebo	126	119	110	92	76	66	44

D Primary outcome in reduced-dose cohort



No. of patients at risk

Methylprednisolone	121	117	91	44
Placebo	120	115	78	35

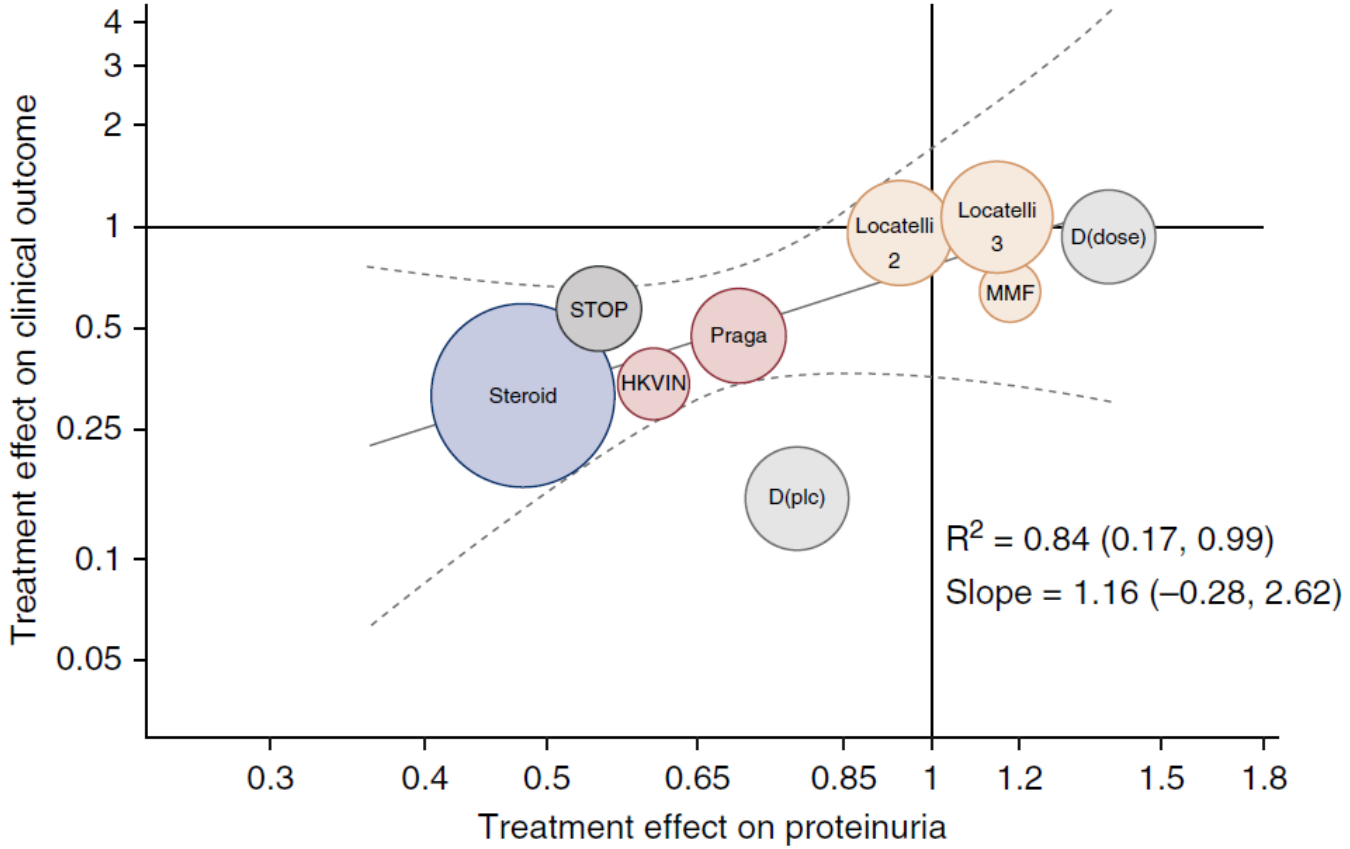
Component outcome of 40% eGFR reduction is shown in eFigure 4 in

least 1 dose of methylprednisolone or placebo. Analyses were censored at the

Lv. TESTING trial. JAMA

Meta-analyses of Clinical Trials Show Association between Treatment Effects on Change in Proteinuria and Treatment Effects on Clinical Endpoints* in IgAN Patients

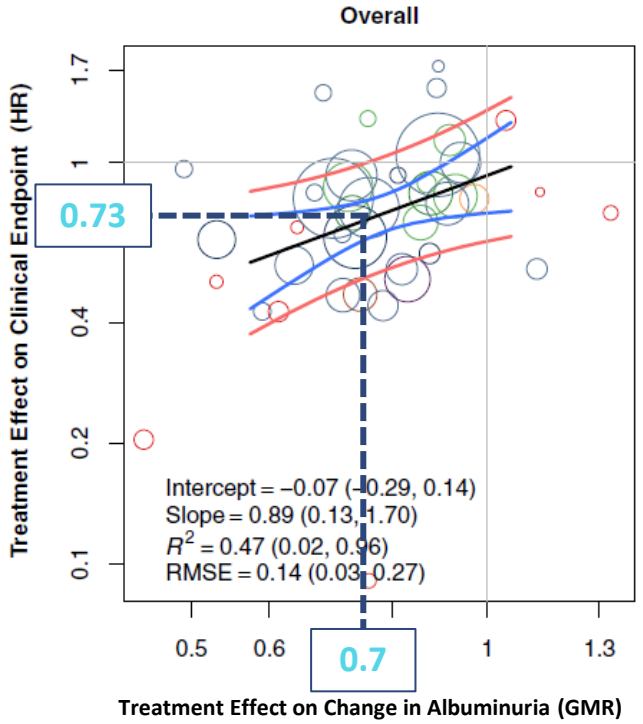
Relationship between the Treatment Effect on the Change in Proteinuria from Baseline to ~9 Months† and the Treatment Effect on Clinical Endpoints*



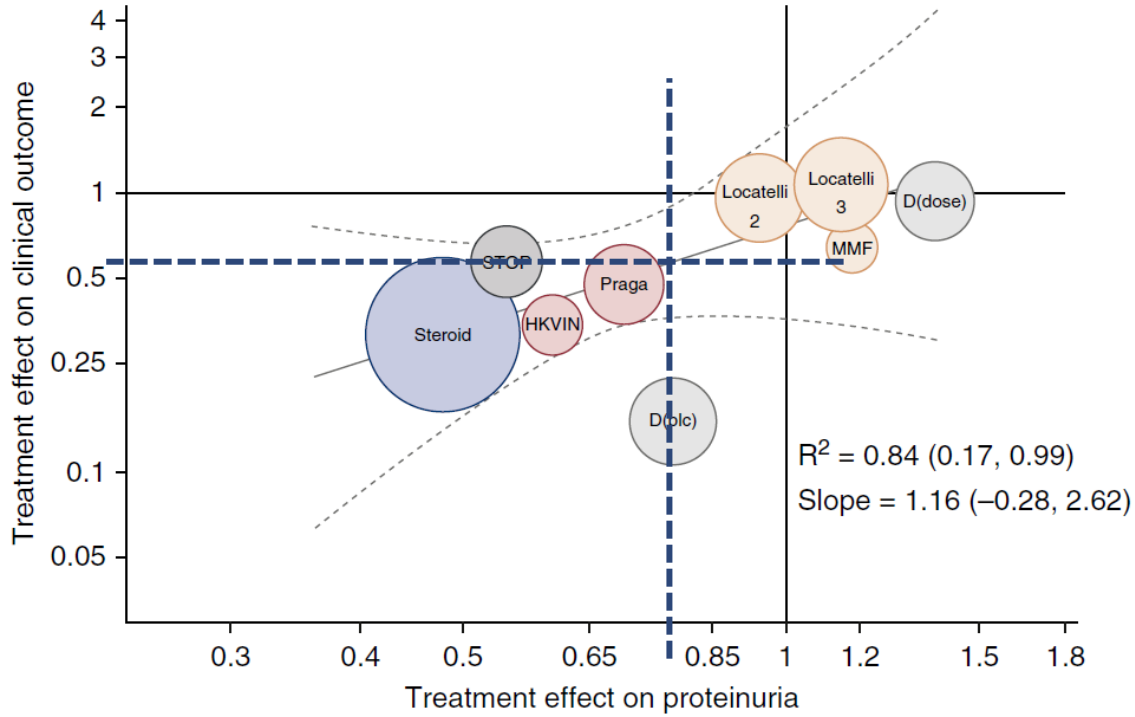
* Clinical endpoints defined as the composite of the time to the first occurrence of a doubling of serum creatinine level, end-stage renal disease, or death;
† Measurements could be made between 7 and 12 months. R^2 = squared correlation.
Image reproduced with permission: Thompson A, *et al. Clin J Am Soc Nephrol* 2019; **14:**469–481.

Meta-analyses of Clinical Trials Show Association between Treatment Effects on Change in Albuminuria or Proteinuria and Treatment Effects on Clinical Endpoints*

Overall CKD Population[1,2]
Surrogate Endpoint: Change in Albuminuria



Patients with IgAN[3]
Surrogate Endpoint: Change in Proteinuria



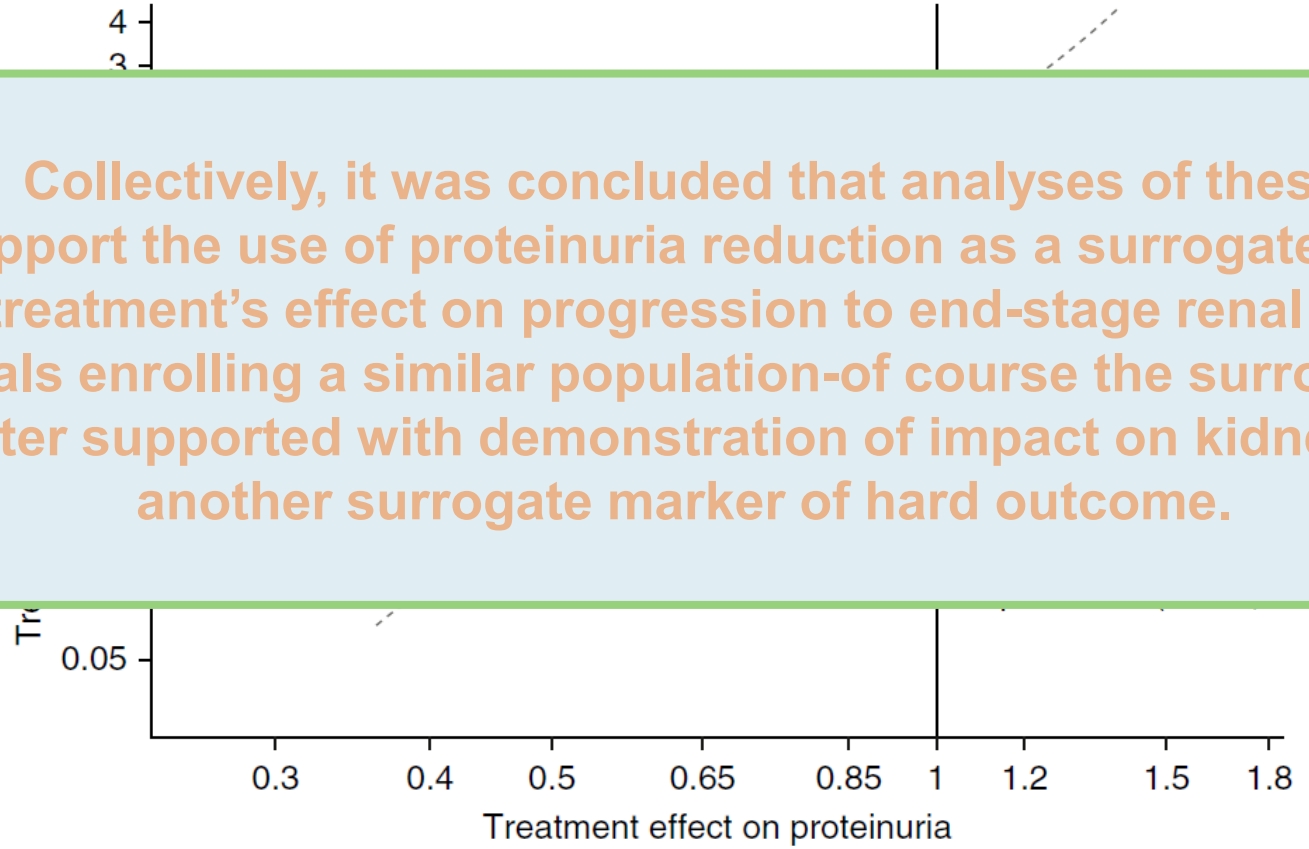
Trend observed between treatment effect on **early change in albuminuria** and treatment effect on clinical endpoint in patients with **CKD is similar** when evaluating the impact of **proteinuria reduction** by treatment in patients with **IgAN**

* Clinical endpoints defined as the composite of the time to the first occurrence of a doubling of serum creatinine level, end-stage renal disease, or death.
GMR = geometric mean ratio; HR = hazard ratio; RMSE = root mean square errors.

1. Levey AS, *et al*. *Am J Kidney Dis* 2019; **75:**84–104; 2. Heerspink HJL, *et al. Lancet Diabetes Endocrinol* 2019; **7:**128–139; 3. Thompson A, *et al. Clin J Am Soc Nephrol* 2019; **14:**469–481;
Images reproduced with permission from Heerspink HJL, *et al. Lancet Diabetes Endocrinol* 2019; **7:**128–139, and Thompson A, *et al. Clin J Am Soc Nephrol* 2019; **14:**469–481.

Proteinuria Could Be Used as a Basis for Accelerated Approval of New IgAN Therapies

Relationship between the Treatment Effect on the Change in Proteinuria from Baseline to ~9 Months† and the Treatment Effect on Clinical Endpoints*

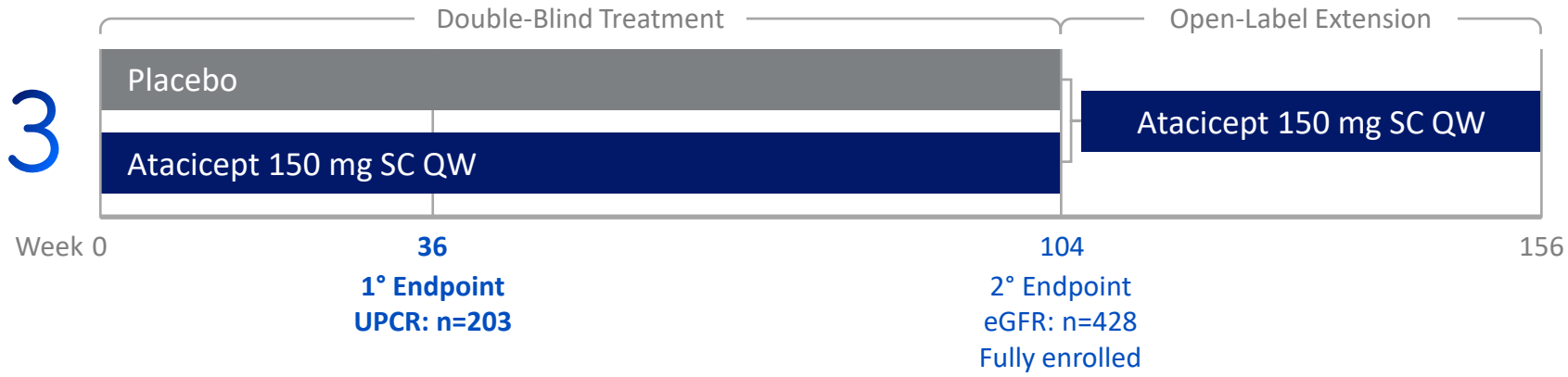


Collectively, it was concluded that analyses of these data support the use of proteinuria reduction as a surrogate endpoint for a treatment's effect on progression to end-stage renal disease in future trials enrolling a similar population-of course the surrogate endpoint has to be later supported with demonstration of impact on kidney function as another surrogate marker of hard outcome.

* Clinical endpoints defined as the composite of the time to the first occurrence of a doubling of serum creatinine level, end-stage renal disease, or death;
† Measurements could be made between 7 and 12 months.
Thompson A, *et al. Clin J Am Soc Nephrol* 2019; **14:**469–481.

ORIGIN Phase 3 Study Design

Multinational, randomized, placebo-controlled trial of atacicept, self-administered at home via weekly 1-mL SC injection



Key Inclusion Criteria

- Patients ≥18 years old with biopsy-proven IgAN and high risk of disease progression
- Stable and optimized RASi for ≥12 weeks, use of SGLT2i allowed
- UPCR-24h ≥1.0 g/g or UP ≥1.0 g per 24h
- eGFR ≥30 mL/min/1.73m^2
- Blood pressure ≤150/90 mmHg

Key Endpoints

- Primary efficacy: UPCR-24h at week 36 to support potential accelerated approval
- Key secondary: eGFR change up to week 104
- Safety

- Similar trial design, patient profile, and worldwide sites as ORIGIN 2b
- At home self-administered SC formulation and dose studied in ORIGIN 2b

RASi, renin angiotensin system inhibitor.

Table 3. Independent contribution of GFR decline slope to CKD progression in patients with IgAN
•Multivariate Cox regression analyses are performed

	HR (95% CI)	***P*-value**
eGFR slope mL/min/1.73 m^2 per year	0.89 (0.84-0.94)	<.001
Time-averaged uPCR	1.82 (0.83-3.98)	.133
M score (1 vs 0)	1.87 (0.47-7.46)	.376
T score (1 vs 0)	5.37 (1.84-15.69)	.002
Baseline eGFR	0.96 (0.94-0.99)	.002
Systolic BP	1.01 (0.98-1.04)	.647
Sex	0.31 (0.08-1.24)	.097
Smoking	3.58 (1.13-11.28)	.030

Lee et al 2018, EJCI. https://doi.org/10.1111/eci.12936

GFR slope as a Surrogate End Point for Kidney Disease Progression in Clinical Trials: A Meta-analysis of Treatment Effects of Randomized Controlled Trials

METHODS

Bayesian individual patient meta-analysis

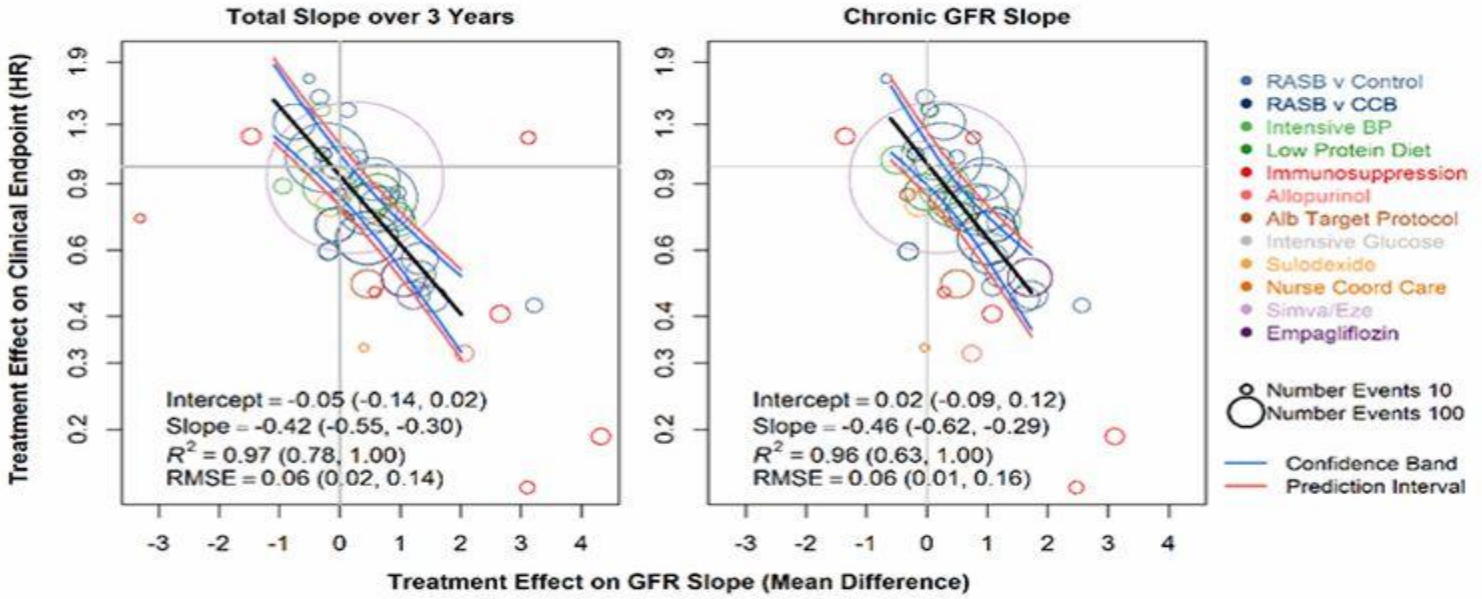
47 studies
60620 participants

Treatment effects on GFR slope: difference in GFR slope between the randomized groups.

Treatment effects on the clinical endpoint: confirmed doubling of serum creatinine, GFR < 15 mL/min per 1.73 m^2 or end stage kidney disease.

OUTCOME

Trial level analyses for the association between treatment effects on GFR slope and treatment effects on the clinical endpoint

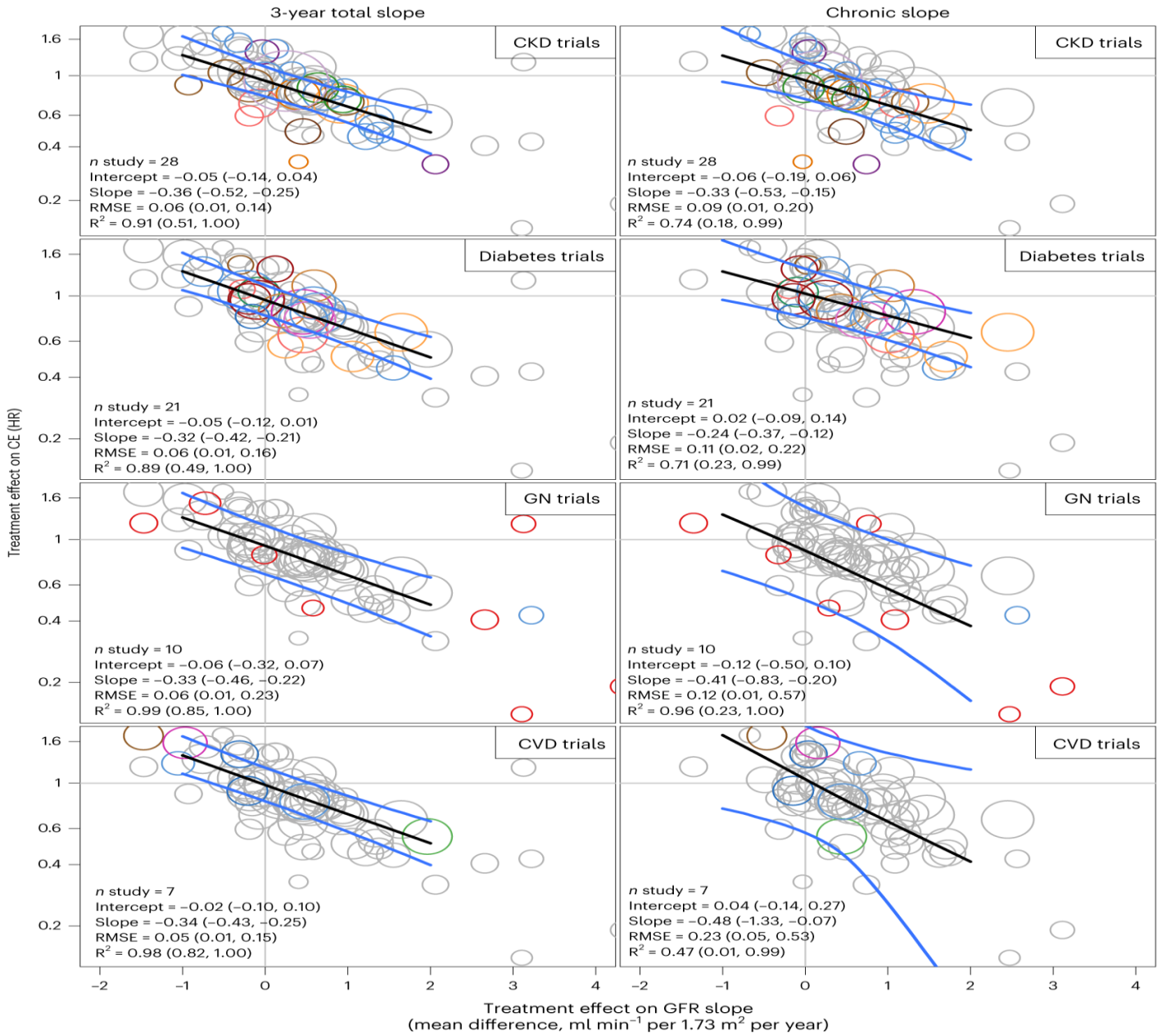


CONCLUSION

The strong association of treatment effects on GFR slope with treatment effects on the clinical endpoint suggests **GFR slope can play a useful role as a surrogate endpoint in CKD RCTs.**

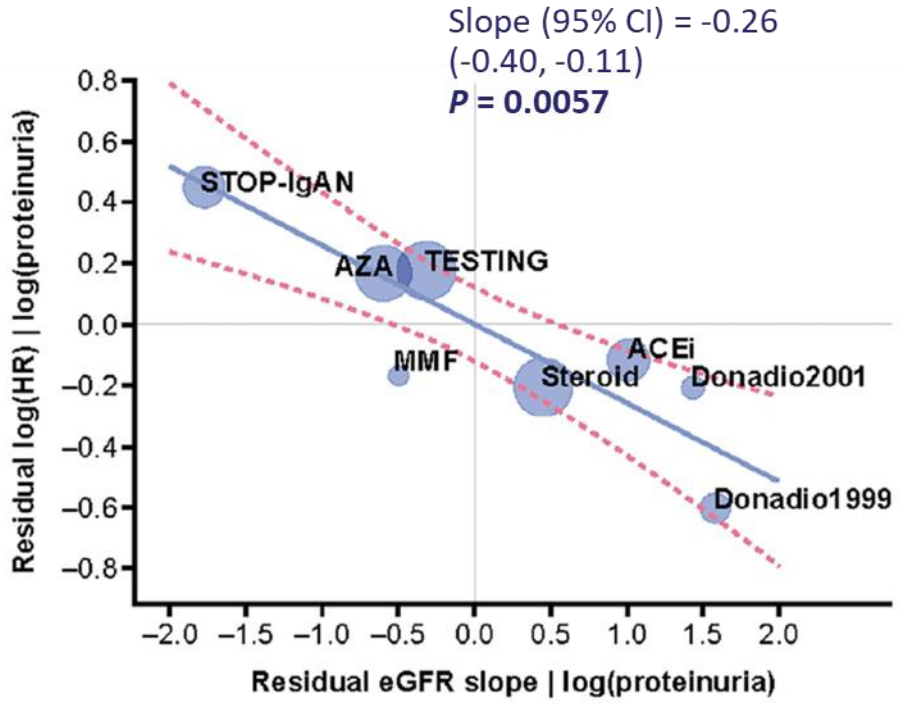
doi: 10.1681/ASN.2019010007.

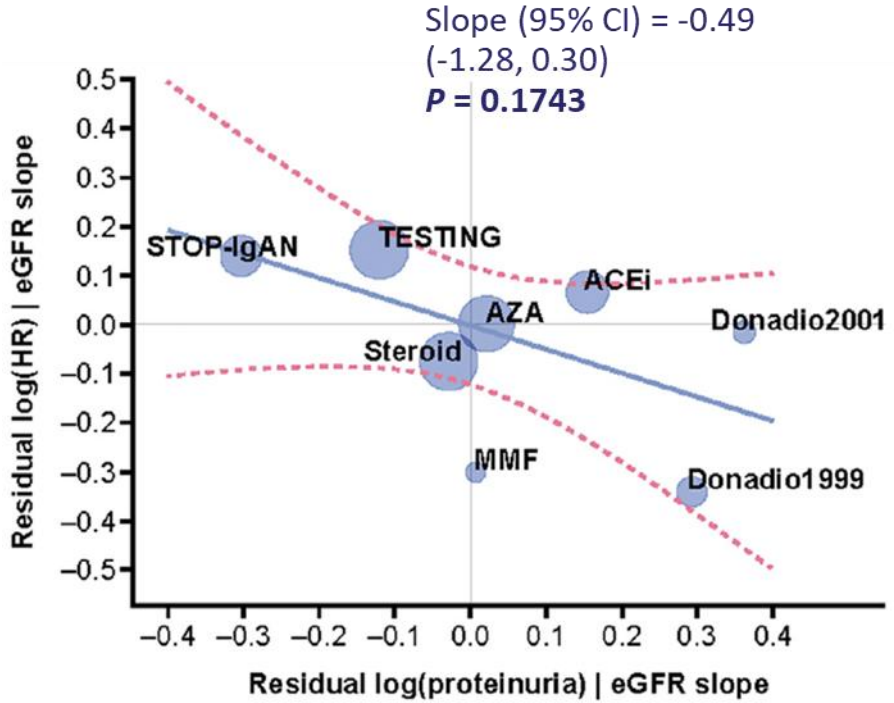
JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY



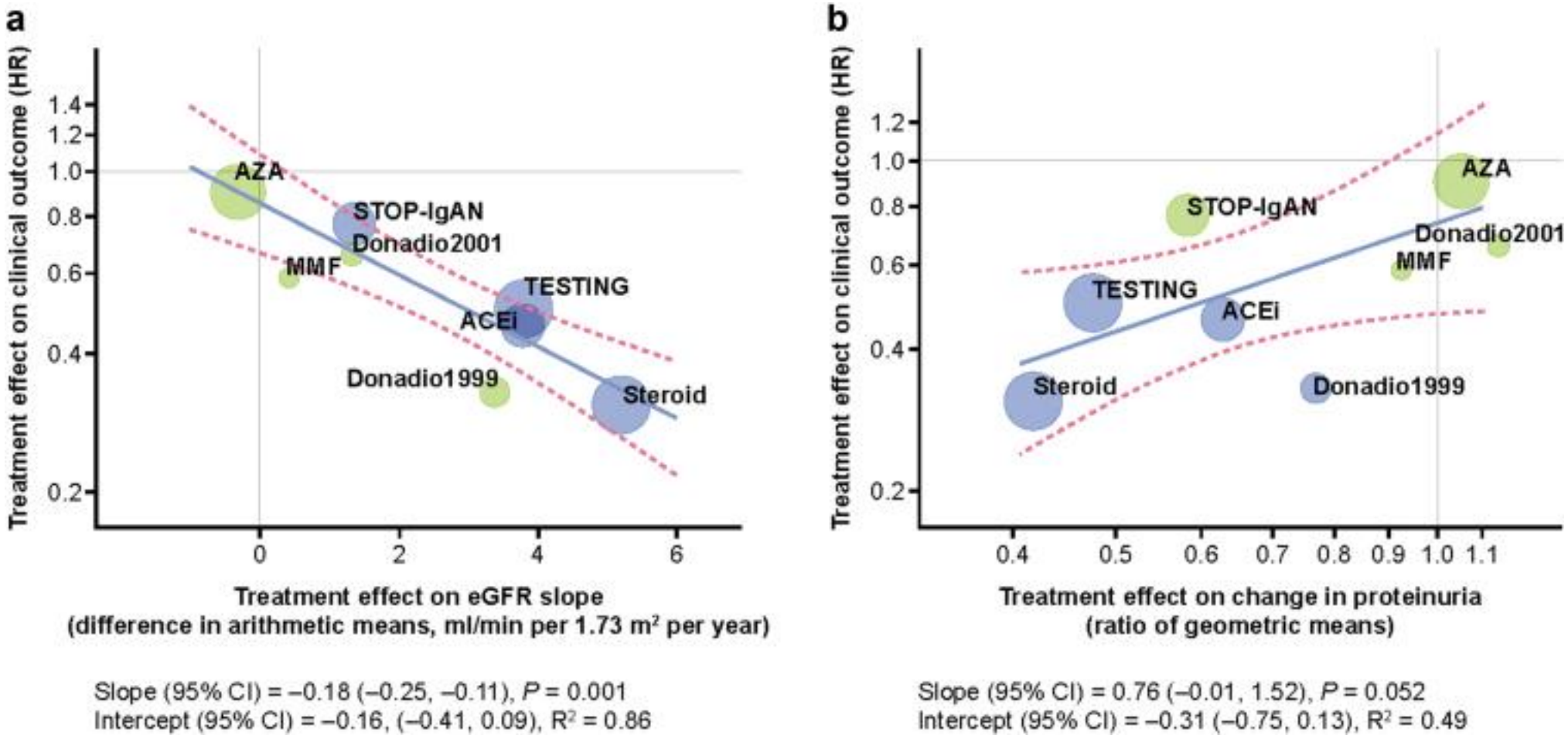
Nat Med **29**,
1867–1876 (2023)

Treatment effect on 1-year eGFR slope, but not proteinuria, is an independent predictor of clinical outcome in IgAN





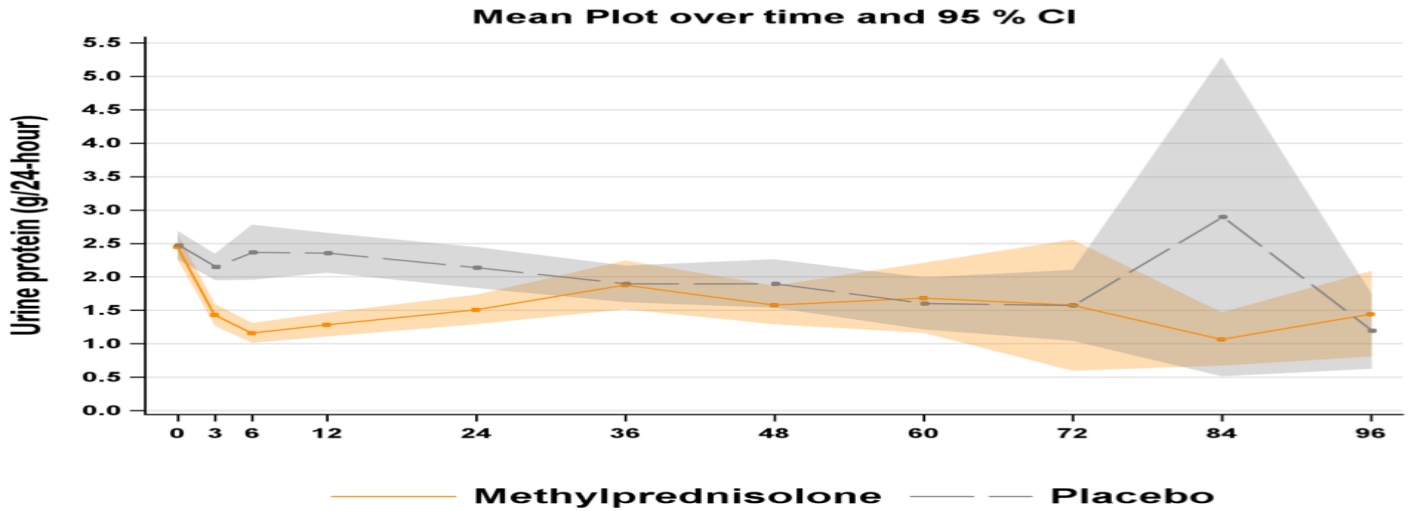
GFR alone is the most predictive- 1 year?



Lafayette et al, Kidney Int Rep. 2022 Sep 29;7(12):2730-2733

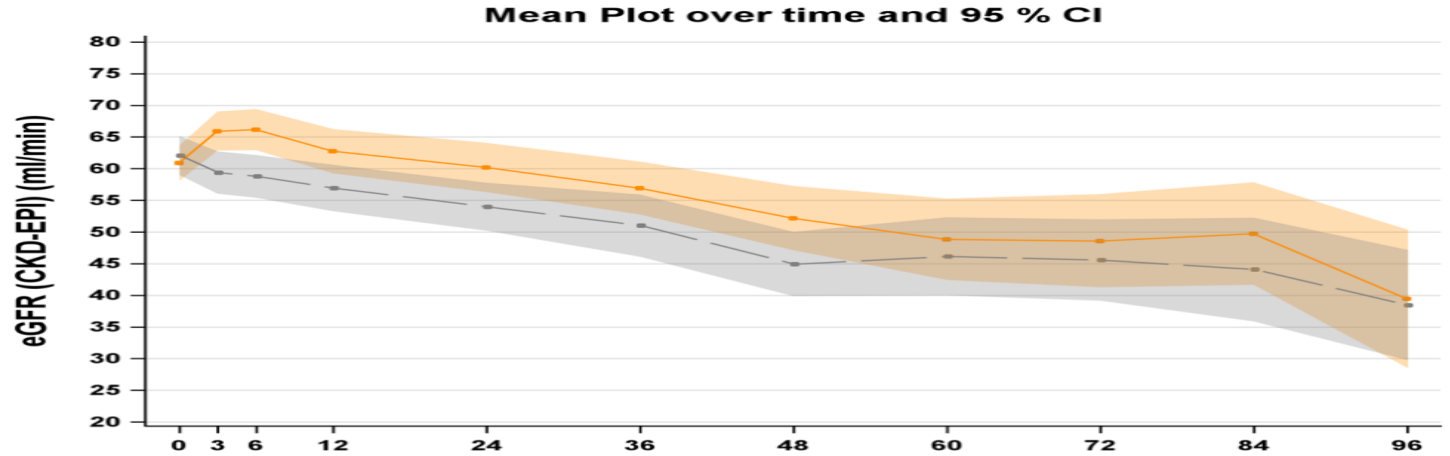
TESTING proteinuria, EGFR trends

A) Mean 24 hour protein excretion by randomized group over time



mber of patients :										
thylprednisolone	257	227	213	178	132	86	54	16	13	11
cebo	246	217	200	159	98	71	48	14	10	15

B) Mean eGFR over time

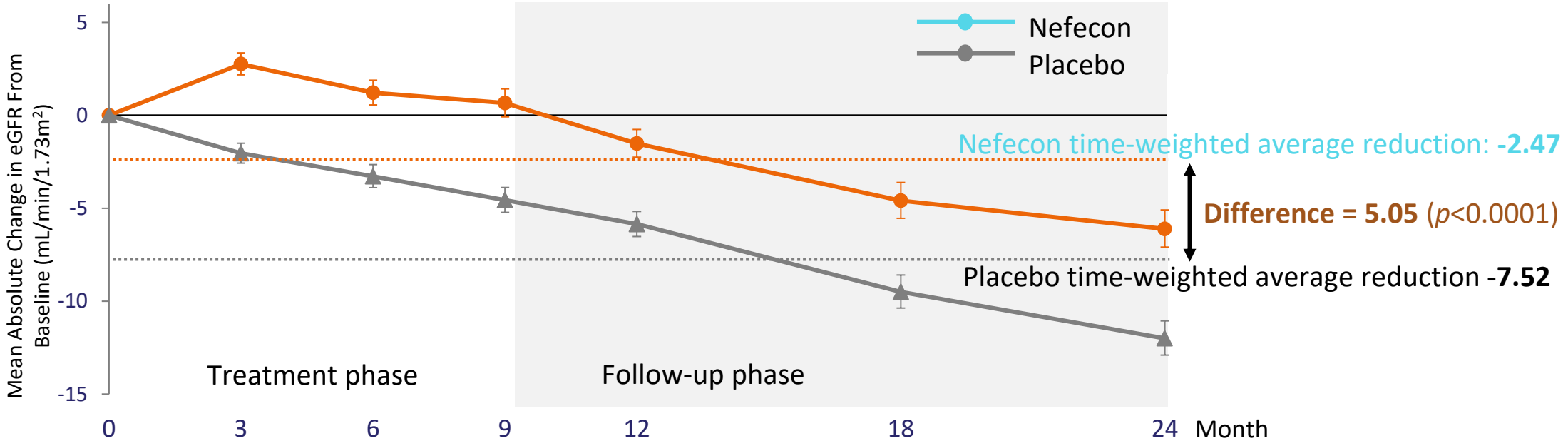


mber of patients :										
thylprednisolone	257	232	218	200	155	104	71	66	45	22
cebo	246	225	209	185	123	90	59	59	30	24

Lv, TESTING trial, JAMA

NefIgArd Primary Endpoint of Time-Weighted Average eGFR Change Over 2 Years Was Met With Statistical Significance in Favor of Nefecon

Mean eGFR Over 24 Months – Absolute Change[a]



eGFR, mean absolute change from baseline (ml/min/1.73 m²):							Time-weighted average
Nefecon	2.76	1.22	0.66	-1.52	-4.59	-6.11	**-2.47**
Placebo	-2.04	-3.28	-4.56	-5.85	-9.5	-12	**-7.52**
Difference	**4.8**	**4.49**	**5.21**	**4.33**	**4.9**	**5.89**	**5.05**

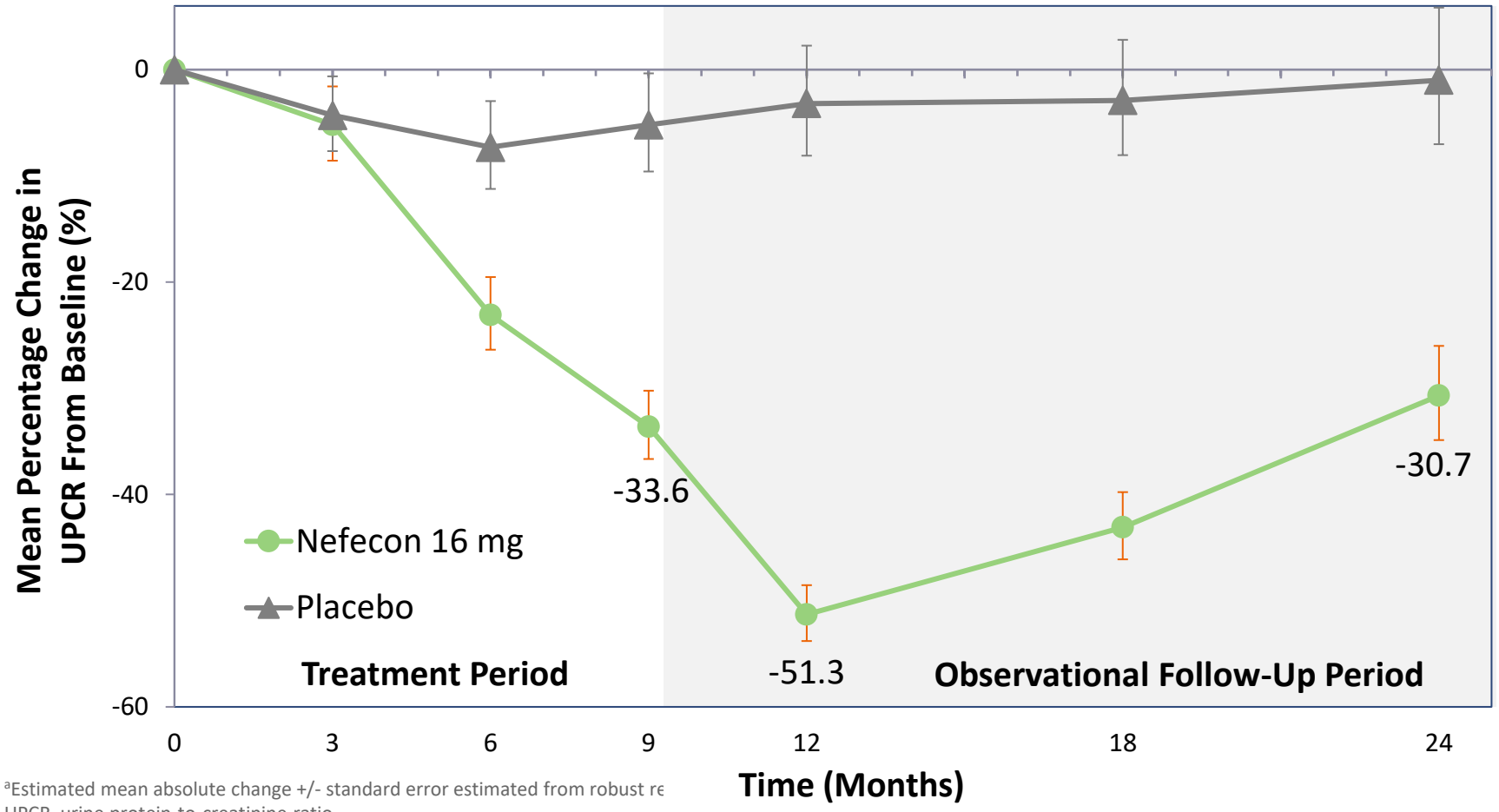
[a]Estimated mean absolute change +/- standard error estimated from robust regression analysis.

eGFR, estimated glomerular filtration rate.

Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

Reduction in Proteinuria With Nefecon Was Durable

Mean Percent Change in UPCR (g/g) From Baseline to 24 Months[a]



[a]Estimated mean absolute change +/- standard error estimated from robust re
UPCR, urine protein-to-creatinine ratio.

Lafayette R, et al. *Lancet*. 2023;402(10405):859-870.

- Durable treatment effect was observed with Nefecon – the >30% reduction in UPCR from baseline at 9 months was maintained through the entire 15-month observational follow-up period while off treatment
- UPCR continues to improve for a further 3 months after Nefecon was

	Sparsentan group (n=202)	Irbesartan group (n=202)	Geometric least-squares mean ratio (95% CI)
Urine protein-to-creatinine ratio, g/g	−42·8% (−49·8 to −35·0)	−4·4% (−15·8 to 8·7)	0·60 (0·50 to 0·72); 40% reduction
Urine protein excretion, g per day	−46·9% (−53·4 to −39·5)	−5·9% (−17·9 to 7·9)	0·56 (0·47 to 0·68); 44% reduction
Urine albumin-to-creatinine ratio, g/g	−56·0% (−62·1 to −49·1)	−17·3% (−29·1 to −3·5)	0·53 (0·43 to 0·66); 47% reduction
Urine albumin excretion, g per day	−58·8% (−64·7 to −52·0)	−17·9% (−30·1 to −3·6)	0·50 (0·40 to 0·63); 50% reduction

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

Table 3: **Change in proteinuria**

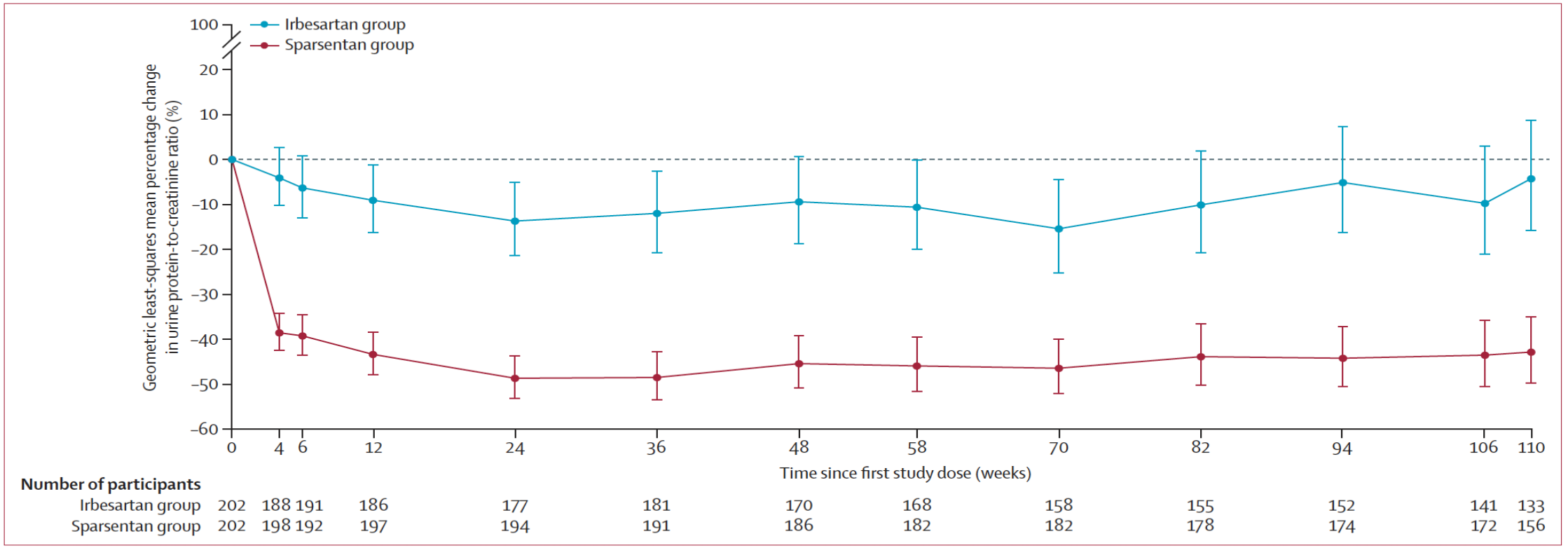


Figure 5: **Geometric least-squares mean percentage change from baseline in the urine protein-to-creatinine ratio at each visit up to week 110**

Error bars indicate 95% CIs

Rovin, 2024, Lancet

	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	−2·7 (−3·4 to −2·1)	−3·8 (−4·6 to −3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	−2·9 (−3·6 to −2·2)	−3·9 (−4·6 to −3·1)	1·0 (−0·03 to 1·94)	0·058
Other secondary efficacy endpoint*				
Absolute change from baseline to week 110, mL/min per 1·73 m²	−5·8 (−7·4 to −4·2)	−9·5 (−11·2 to −7·9)	3·7 (1·5 to 6·0)	..
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	−6·1 (−7·7 to −4·5)	−9·0 (−10·7 to −7·2)	2·9 (0·5 to 5·3)	..

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: **Change in eGFR**

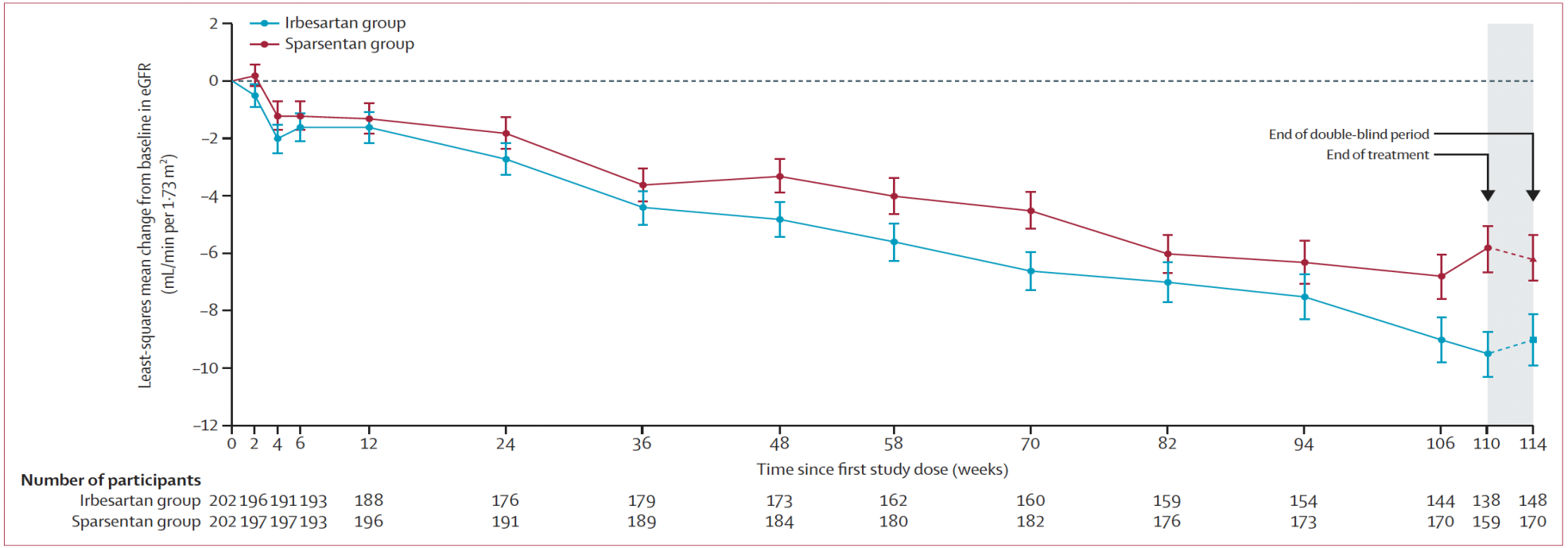


Figure 2: **eGFR by visit up to week 114**

Rovin, 2024, Lancet

Possible alternate study designs

- 9-12 month efficacy (eGFR) and safety compared to virtual placebo control, 2 year safety extension
- 9-12 month efficacy and safety compared to real placebo control, extension with modeled results from placebo group +/- virtual group
- 2 year efficacy and safety compared to active standard of care (but how to provide to global population).
- ? Length add on therapy to active treatment for supplemental benefits to eGFR and proteinuria without safety issues.

Identifying Outcomes Important to Patients with Glomerular Disease and Their Caregivers

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Due to the number of contributing authors, the affiliations are listed at the end of this article.

Which outcomes matter to patients with glomerular disease and their caregivers?

CJASN
Clinical Journal of American Society of Nephrology

Methods and cohort

Australia
Hong Kong
United Kingdom
United States

101 Patients with glomerular disease

33 Caregivers

Aged 19-85
51% female

16 focus groups
58 outcomes identified

Outcomes scored
Between 0 and 1

Emerging themes

- Constraining day-to-day experience
- Impaired agency and control over health
- Threats to future health and family

Highest ranking outcomes and scores (0-1)

0.42 Kidney function	0.29 Mortality	0.22 Dialysis/ transplant requirement
0.18 Life participation	0.17 Fatigue	0.13 Anxiety
0.12 Family impact	0.12 Infection and immunity	0.11 Ability to work
0.11 Blood pressure		

Conclusions Patients with glomerular disease and their caregivers highly prioritize kidney health and survival, but also life participation, fatigue, anxiety and family impact.

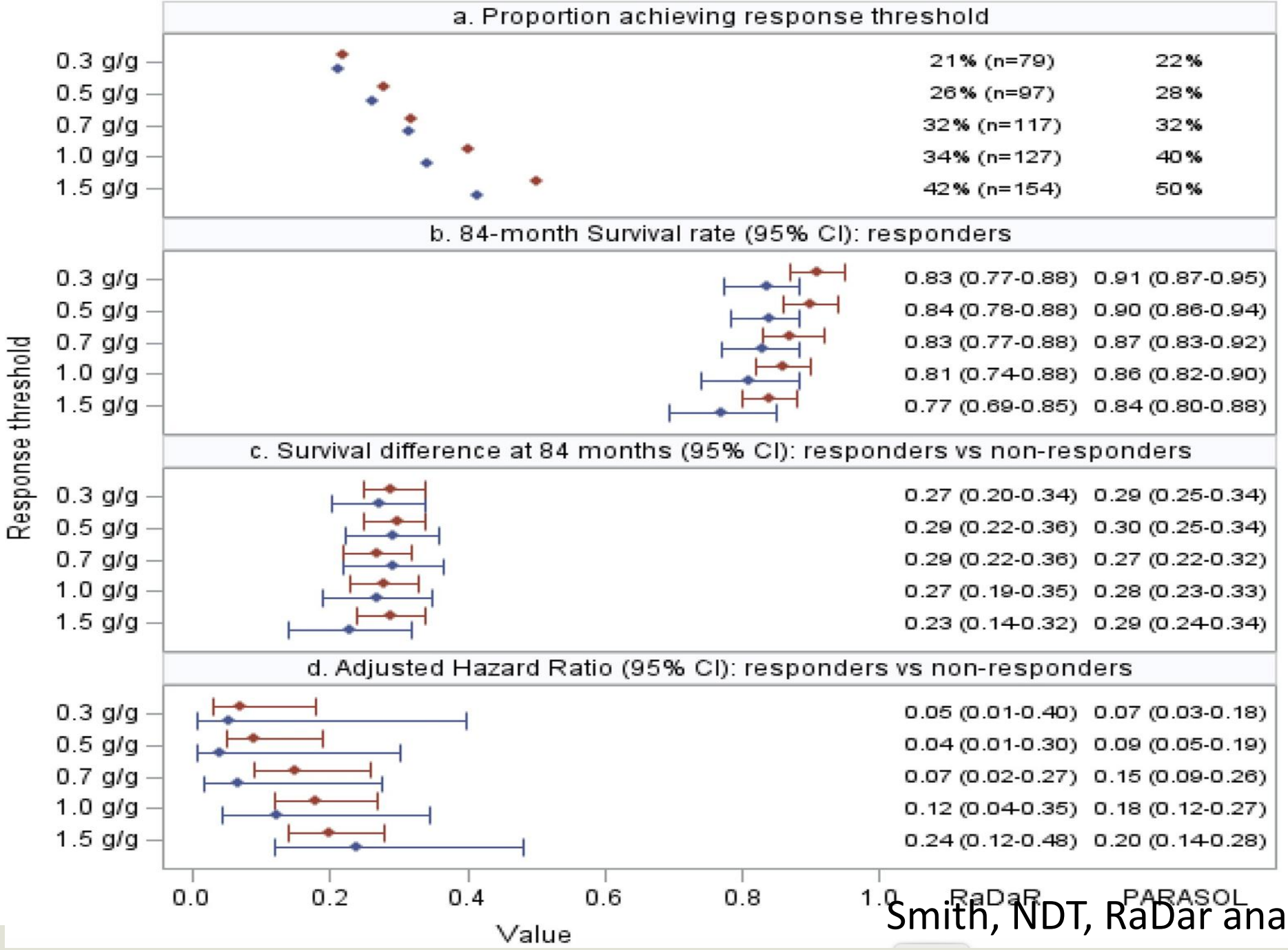
Simon Carter, Talia Gutman, Charlotte Logeman, Dan Cattran, et al. ***Identifying Outcomes Important to Patients with Glomerular Disease and Their Caregivers.*** CJASN doi: 10.2215/CJN.13101019. **Visual Abstract by Michelle Lim, MBChB, MRCP**

MEMBRANOUS NEPHROPATHY

- TRADITIONAL 2 year endpoint of COMPLETE REMISSION vs. ACTIVE COMPARATOR
- What about partial remission, change in proteinuria?
- What about GFR?
- What about biomarkers, PLA2R, etc.

FSGS

- Traditional approval not granted to any drug
- Studies tried to use 2 year eGFR
- After failed study, PARASOL project suggested TOO much variability to power eGFR endpoints with less than many hundreds of patients
- Proteinuria reduction < 1500 mg/d validated in large cohort as strong predictor of major reduction in endpoints
- Agency suggeste trials focus on one year differences in achieving < 700 mg/d
- Allows for robust study of FSGS (with ongoing concerns of primary vs genetic vs others)
- DUPLEX study (sparsentan) awaits review



Smith, NDT, RaDar analysis of Parasol, 2025

C3G

- Extremely rare disease
- Modest support for reduced proteinuria making differences in hard outcomes
- Trials focused on short term changes in proteinuria, monitored eGFR and included approach to pre and post biopsy
- 6 month proteinuria reductions, sustained in open label allowed for full approval for iptacopan and pegcetocoplan.
- Supported by eGFR stability or improvement, supported by reduction in glomerular inflammation and C3 staining.

SUMMARY

- Studies of GD will benefit from validated outcomes
- Reasonable surrogate outcome may well be proteinuria for early approval, but is GFR change better (how long?)
- ? If biopsy outcomes, other biomarkers will ever be tested/validated
- PRO also of value, but often not tested
- GFR slope could prove to be even more impactful in some diseases, but uncertain how many years of data are needed, *stuck with proteinuria for now*.
- Hard outcomes in context (freedom from ESKD, death)