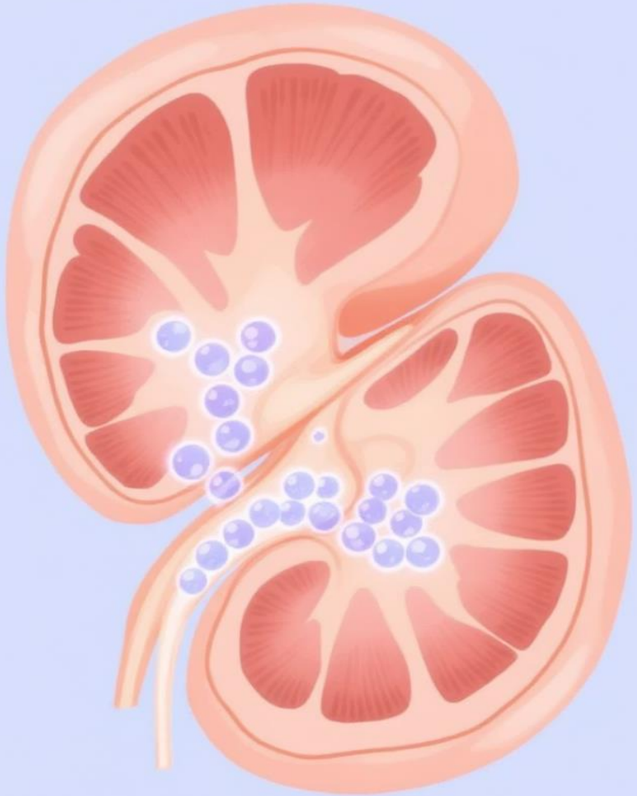
بسم الله الرحمن الرحيم

SGLT2 Inhibitors In Glomerular Disease: Clinical Trials And Mechanisms



Iranian Society of Nephrology

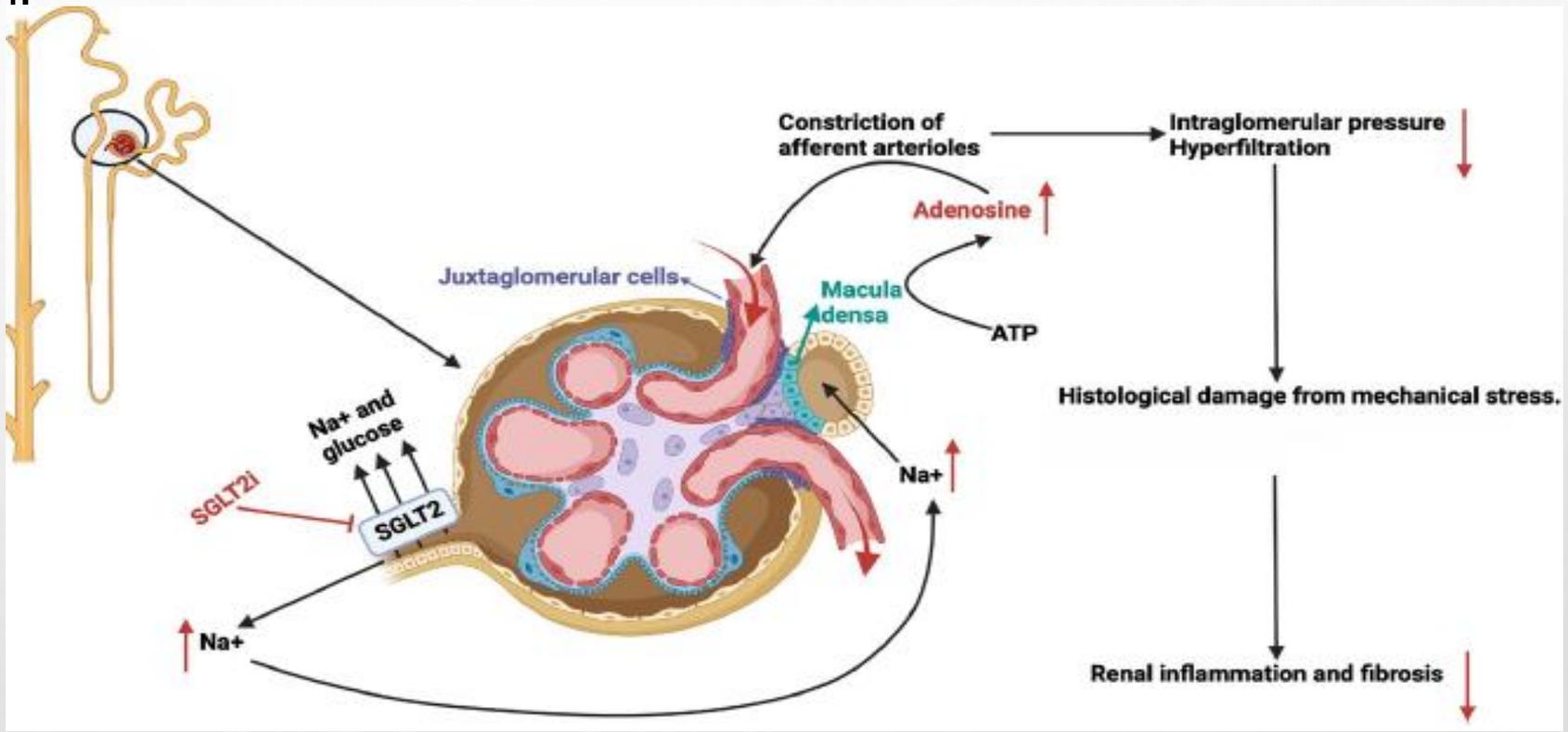
- Neda Najafi M.D
- Assistant Professor Of Nephrology
- Hasheminejad Kidney Center

- 5/22/2025

Introduction

- sodium-glucose cotransporter-2 (SGLT2) inhibitor ...reduces glucose reabsorption in the PCT of the kidney …enhancing urinary glucose excretion.…involves tubuloglomerular feedback (TGF)

  Tubular flow and composition modulate arteriolar vascular tone and thus the glomerular filtration.



Mechanisms of Action in Non-Diabetic Kidney Disease

Tubuloglomerular Feedback

Afferent arteriolar vasoconstriction via adenosine

Podocyte Protection

Reduced podocyte shedding and cytoskeleton preservation

Anti-inflammatory Effects

Decreased NF-κB activation and inflammatory signaling

Anti-fibrotic Effects

Reduced interstitial fibrosis and glomerulosclerosis

SGLT2 inhibitors may also mitigate the transition of renal monocytes to inflammatory M1 macrophages that contribute to fibrosis.

In the 5/6 nephrectomy rat model, empagliflozin ameliorated glomerular hypertrophy and fibrosis as effectively as renin-angiotensin system inhibition. Higher urinary adenosine levels correlated with preserved kidney function and reduced fibrosis.

Gilda M. Portalatin, et al. Sodium glucose co-transporter 2 inhibitors (SGLT2i) for pediatric kidney disease: the future is near. frontiersin.org

DAPA-CKD Trial: Design and Key Findings

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D.,

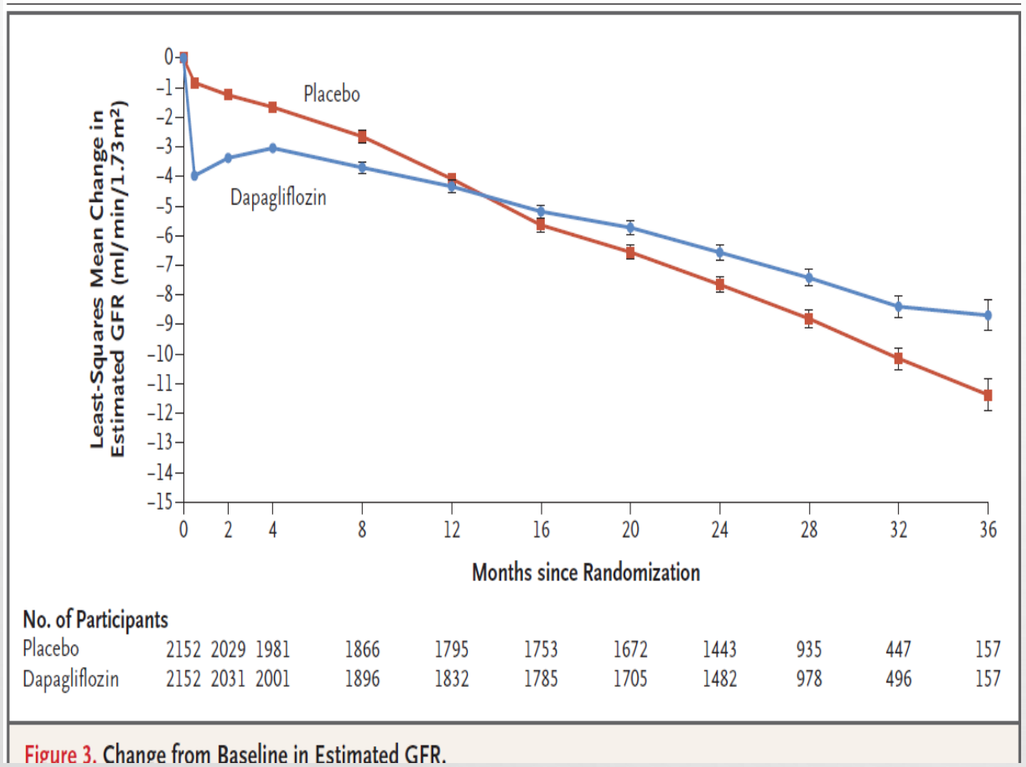


Figure 3. Change from Baseline in Estimated GFR.

Study Population

4,304 participants with eGFR 25-75 ml/min/1.73m^2 and UACR 200-5000 mg/g

exclusion criteria :type 1 diabetes, ADPKD, lupus nephritis, antineutrophil cytoplasmic antibody–associated vasculitis. immunotherapy for kidney disease within 6 months before enrollment

Duration and Follow-up: Median follow-up of 2.4 years. Regular visits at 2 weeks, 2, 4, and 8 months, then every 4 months.

Primary Outcome

Composite of sustained eGFR decline ≥50%, end-stage kidney disease, or death from renal or cardiovascular causes

Key Results

Significantly lower risk of primary outcome with dapagliflozin vs. placebo; similar effects in participants with and without type 2 diabetes

This article was published on September 24, 2020, at NEJM.org.

SGLT2 Inhibitors in IgA Nephropathy

270

IgAN Patients

Number of IgAN patients enrolled in DAPA-CKD trial

75%

Risk Reduction

Reduction in composite renal endpoint with dapagliflozin (HR 0.24)

26%

UACR Reduction

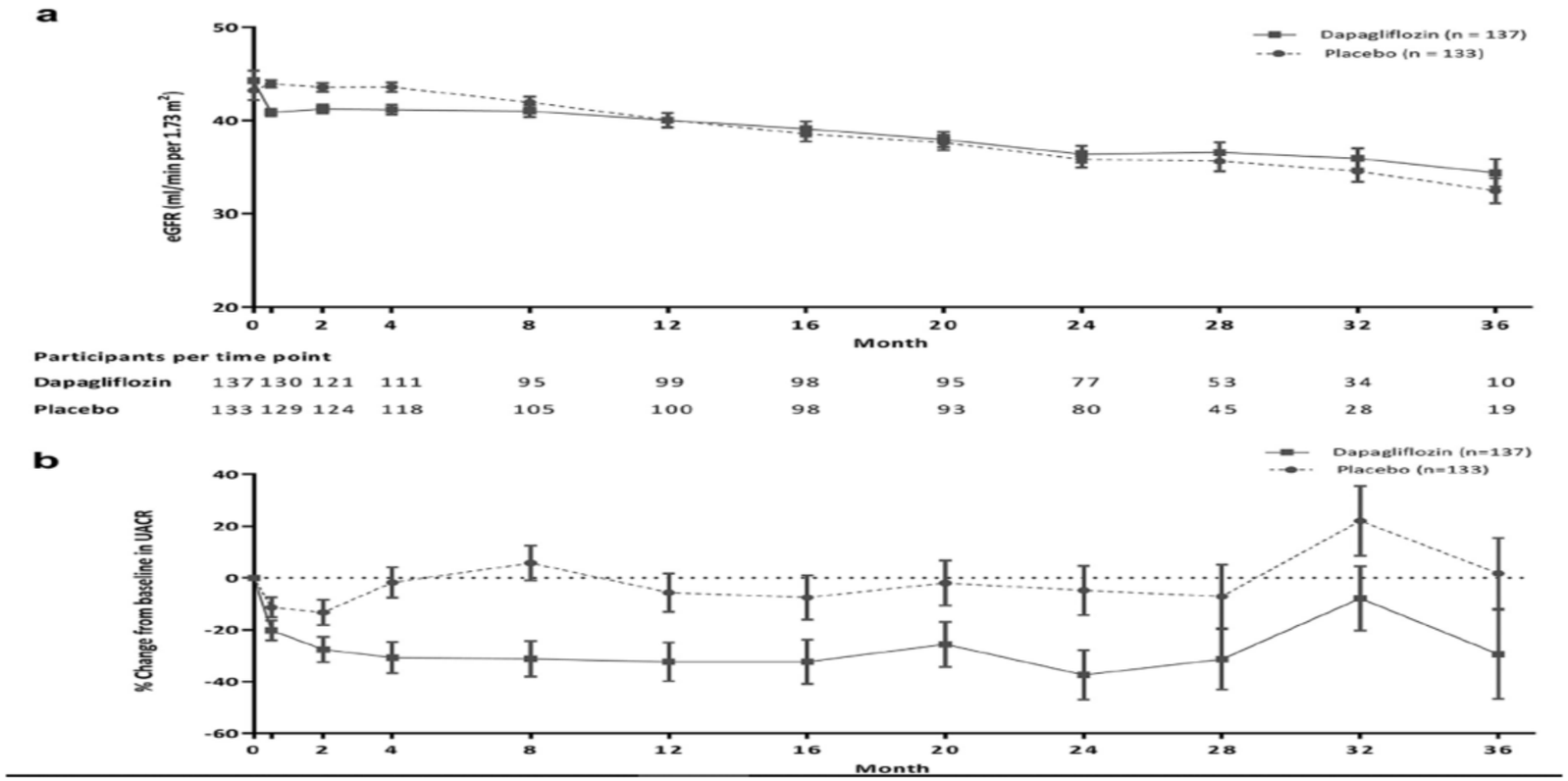
Relative reduction in urinary albumin-to-creatinine ratio with dapagliflozin

- ✓ Primary end point: HR, 0.29 (95% CI, 0.12–0.73)
- ✓ Mean rates of eGFR decline with dapagliflozin and placebo were -3.5 and -4.7 mL/1.73m2/min/year, respectively.
- ✓ 5 participants (4%) in the dapagliflozin group and 16 (12%) in the placebo group developed ESKD during the trial (HR, 0.30 [95% CI, 0.11–0.83]; P0.014;
- ✓ The incidence of the primary composite outcome was 3.5-fold higher in participants with baseline eGFR < 45 ml/min per 1.73 m2 or UACR > 1000 mg/g.
- ✓ In these high-risk subgroups, the HR for the primary composite outcome was 0.41 (95% CI, 0.15–1.14) and 0.27 (95% CI, 0.09–0.82)
- ✓ the effects of dapagliflozin …pronounced starting at month 8,

(immediate hemodynamic effects ,cellular and metabolic effects)

DC Wheeler et al. Dapagliflozin in IgA nephropathy. Kidney International (2021) 100, 215–224
Georg iga2.

SGLT2 Inhibitors in IgA Nephropathy



Changes over time in (a) eGFR) trajectory, (b) UACR

DC Wheeler et al.: Dapagliflozin in IgA nephropathy, Kidney International (2021) 100, 215–224

SGLT2 Inhibitors in FSGS/ DAPA

-DAPACKD …..104 participants with FSGS .

-kidney composite outcome: HR 0.67 (0.19– 2.44)

-The annual rate of eGFR decline was also slower in the dapagliflozin (by 2 mL/min/1.73m2per year compared with placebo (95% CI 0.6–3.5)).

-At Week 2, mean change from baseline in UACR was −26.1% in the dapagliflozin group and −9.9% in the placebo group.

-This reduction in UACR persisted through to Month 12, although after 12 months UACR levels were similar between the two groups;

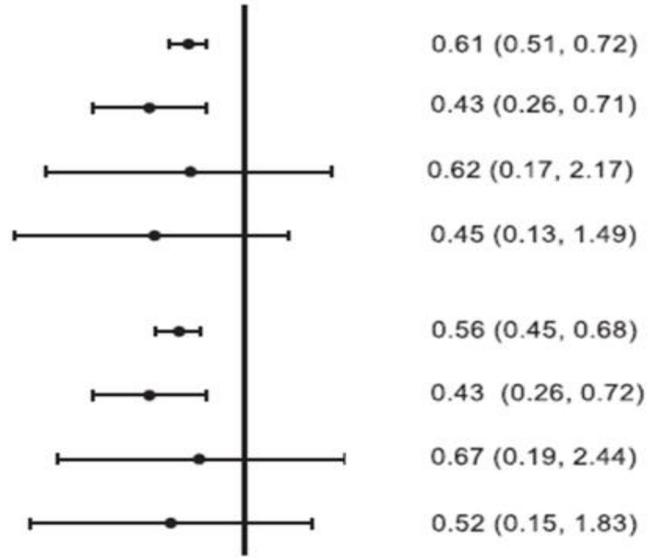
caveat: primary form, or genetic, and secondary causes? (excluded immunosuppressive therapies within 6 months prior to enrollment),

…..secondary FSGS

Dapagliflozin in focal segmental glomerulosclerosis. D. C.Wheeler *et al*

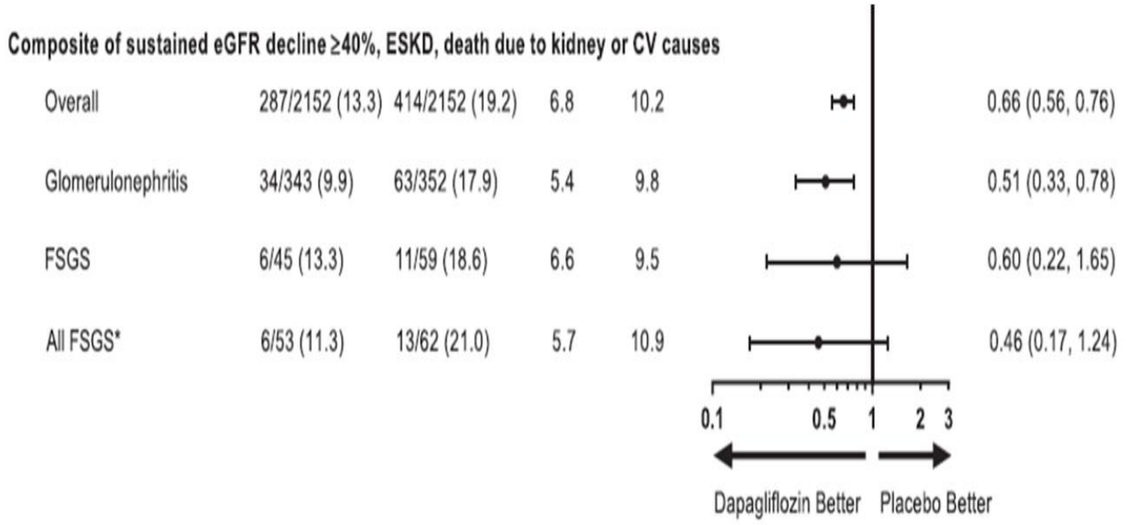
-Primary composite outcome, sustained ≥50% decline in eGFR, onset of ESKD, or death from a kidney or cardiovascular cause;
-kidney-specific composite outcome, sustained ≥50% decline in eGFR, onset of ESKD or death from a kidney cause.

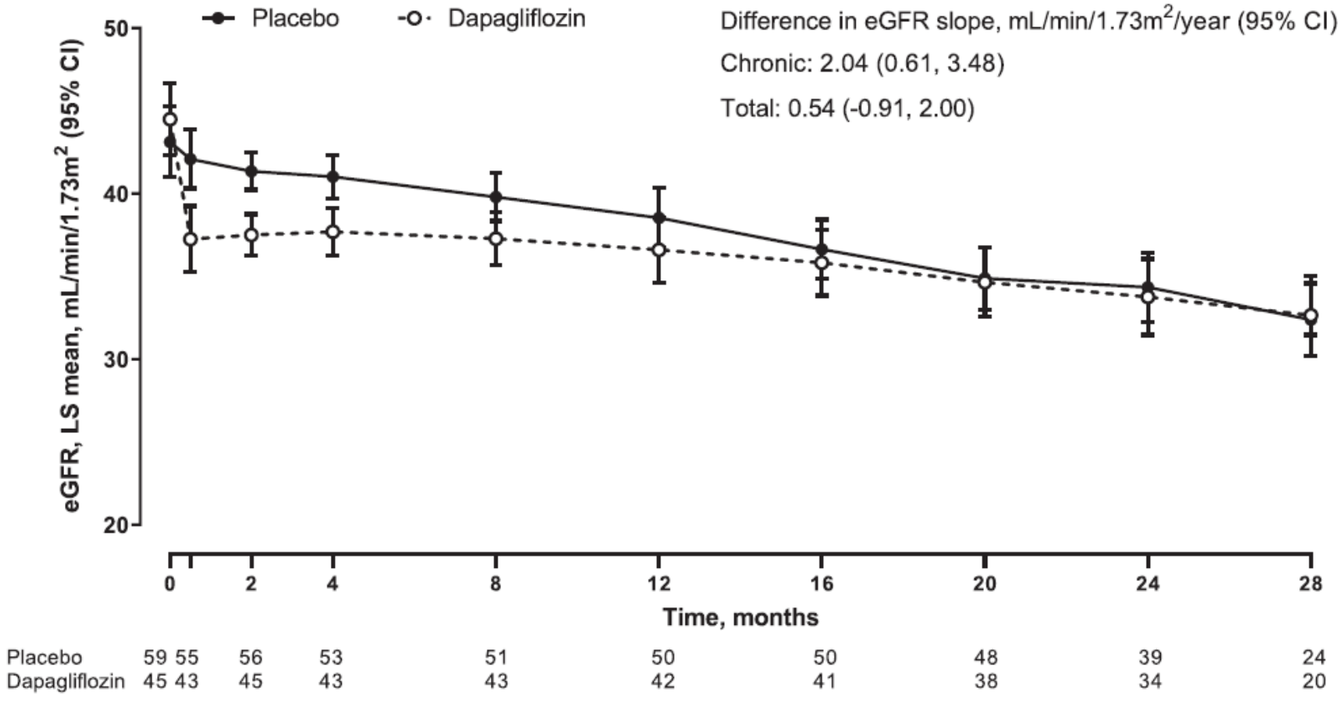
	Dapagliflozin	Placebo	Dapagliflozin	Placebo	Hazard ratio (95% CI)
	n/N (%)		*Events/100 patient-years*		
Primary composite endpoint					
Overall	197/2152 (9.2)	312/2152 (14.5)	4.6	7.5	0.61 (0.51, 0.72)
Glomerulonephritis	22/343 (6.4)	49/352 (13.9)	3.4	7.5	0.43 (0.26, 0.71)
FSGS	4/45 (8.9)	7/59 (11.9)	4.3	5.8	0.62 (0.17, 2.17)
All FSGS*	4/53 (7.5)	9/62 (14.5)	3.7	7.3	0.45 (0.13, 1.49)
Kidney composite endpoint					
Overall	142/2152 (6.6)	243/2152 (11.3)	3.3	5.8	0.56 (0.45, 0.68)
Glomerulonephritis	21/343 (6.1)	46/352 (13.1)	3.3	7.0	0.43 (0.26, 0.72)
FSGS	4/45 (8.9)	6/59 (10.2)	4.3	5.0	0.67 (0.19, 2.44)
All FSGS*	4/53 (7.5)	7/62 (11.3)	3.7	5.7	0.52 (0.15, 1.83)



Forest plot for the primary composite endpoint, kidney-disease specific composite endpoint

Dapagliflozin in focal segmental glomerulosclerosis. D. C.Wheeler *et al*.





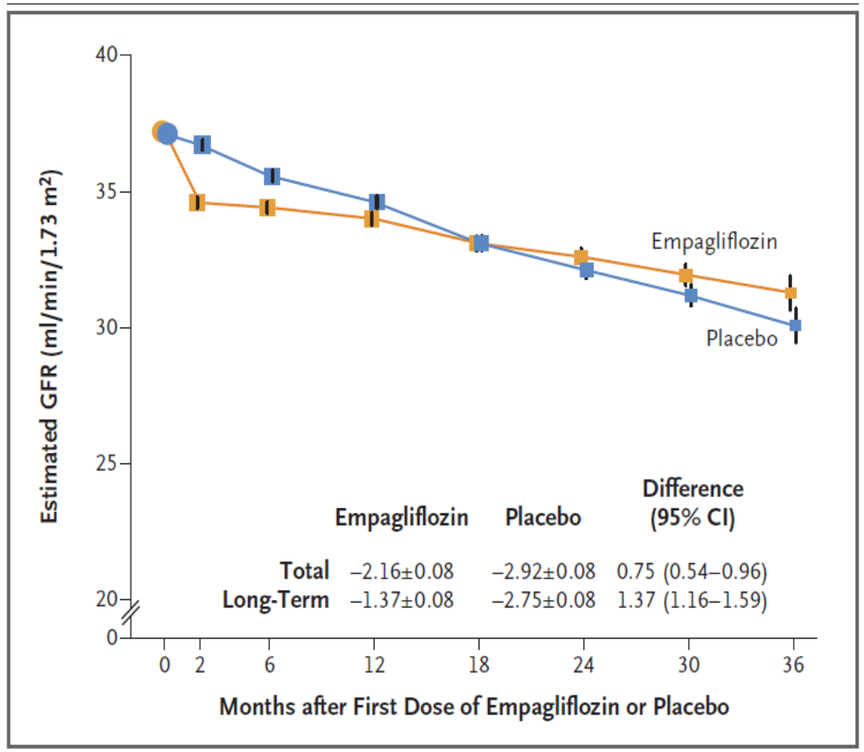
Dapagliflozin in focal segmental glomerulosclerosis. D. C.Wheeler *et al*.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*



Study population: eGFR 20 - 45 ml/min. 45 – 90mL/min. UACR > 200 Mg/gr.

primary outcome: ESKD, decrease in eGFR to <10 ml/min/1.73 m^2, sustained decrease in eGFR of ≥40% from baseline, death from renal causes or cardiovascular causes.

Results: 6609 patients. median of 2.0 years of follow-up,

primary outcome in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (HR, 0.72; 95% CI, 0.64 to 0.82; P<0.001).

patients with or without diabetes and across subgroups defined according to eGFR ranges.

Glomerular disease: 853 EMPA, 816 placebo.

817 with IgAN ,

195 FSGS,

96 MGN,

(lupus nephritis, granulomatosis with polyangiitis, microscopic polyangiitis and MPGN).

Total" from randomization to the final follow-up visit.
"Long-Term" from 2 months after the first dose of empagliflozin or placebo to the final follow-up visit

This article was published on November 2022, at NEJM.org. W.G. Herrington, N. Staplin, C. Wanner,. et al.

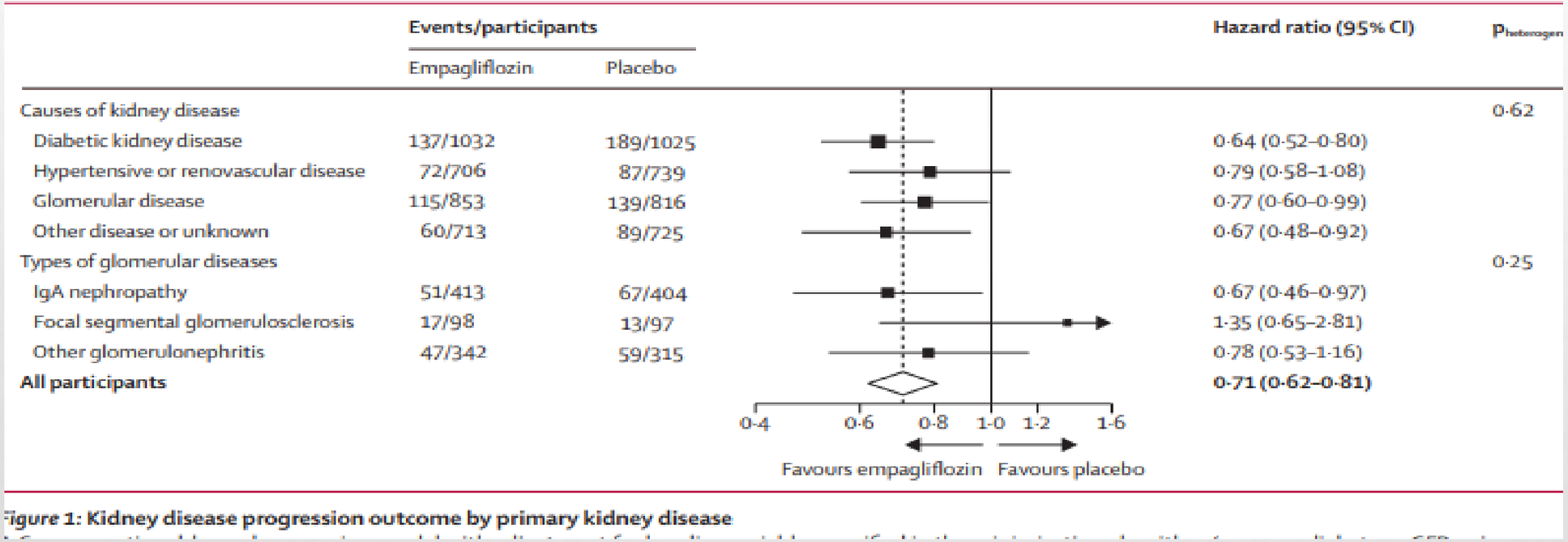
EMPA-KIDNEY/ GN

FSGS: Secondary analysis of EMPA-KIDNEY /FSGS: N = 195 …..

NO decrease the kidney progression outcome (ESKD or ≥40% GFR decrease). HR 1.35 (0.65–2.81) (placebo over empagliflozin).
Analyses of GFR slope for FSGS patients in EMPA-KIDNEY did appear to favor empagliflozin slightly over placebo,

IgA: Secondary analysis of the EMPA-KIDNEY/IgAN: N=870…

IgAN patients. kidney progression outcome was reduced in those IgAN patients receiving empagliflozin [Hazard ratio 0.67 (95% CI: 0.46–0.97)].



	Events/participants		Hazard ratio (95% CI)	$p_{heterogen}$
	Empagliflozin	Placebo		
Causes of kidney disease				0·62
Diabetic kidney disease	137/1032	189/1025	0·64 (0·52–0·80)	
Hypertensive or renovascular disease	72/706	87/739	0·79 (0·58–1·08)	
Glomerular disease	115/853	139/816	0·77 (0·60–0·99)	
Other disease or unknown	60/713	89/725	0·67 (0·48–0·92)	
Types of glomerular diseases				0·25
IgA nephropathy	51/413	67/404	0·67 (0·46–0·97)	
Focal segmental glomerulosclerosis	17/98	13/97	1·35 (0·65–2·81)	
Other glomerulonephritis	47/342	59/315	0·78 (0·53–1·16)	
All participants			**0·71 (0·62–0·81)**	

Figure 1: **Kidney disease progression outcome by primary kidney disease**

E.-K.C. Group. Impact of primary kidney disease on the effects of empagliflozin in patients with chronic kidney disease: secondary analyses of the EMPA-KIDNEY trial. Lancet Diabetes Endocrinol. (2024)

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

Fernando Caravaca-Fontán[1], Kate Stevens[2], Maite Padrón[3], Ana Huerta[4], Marco Montomoli[5], Juan Villa[6],

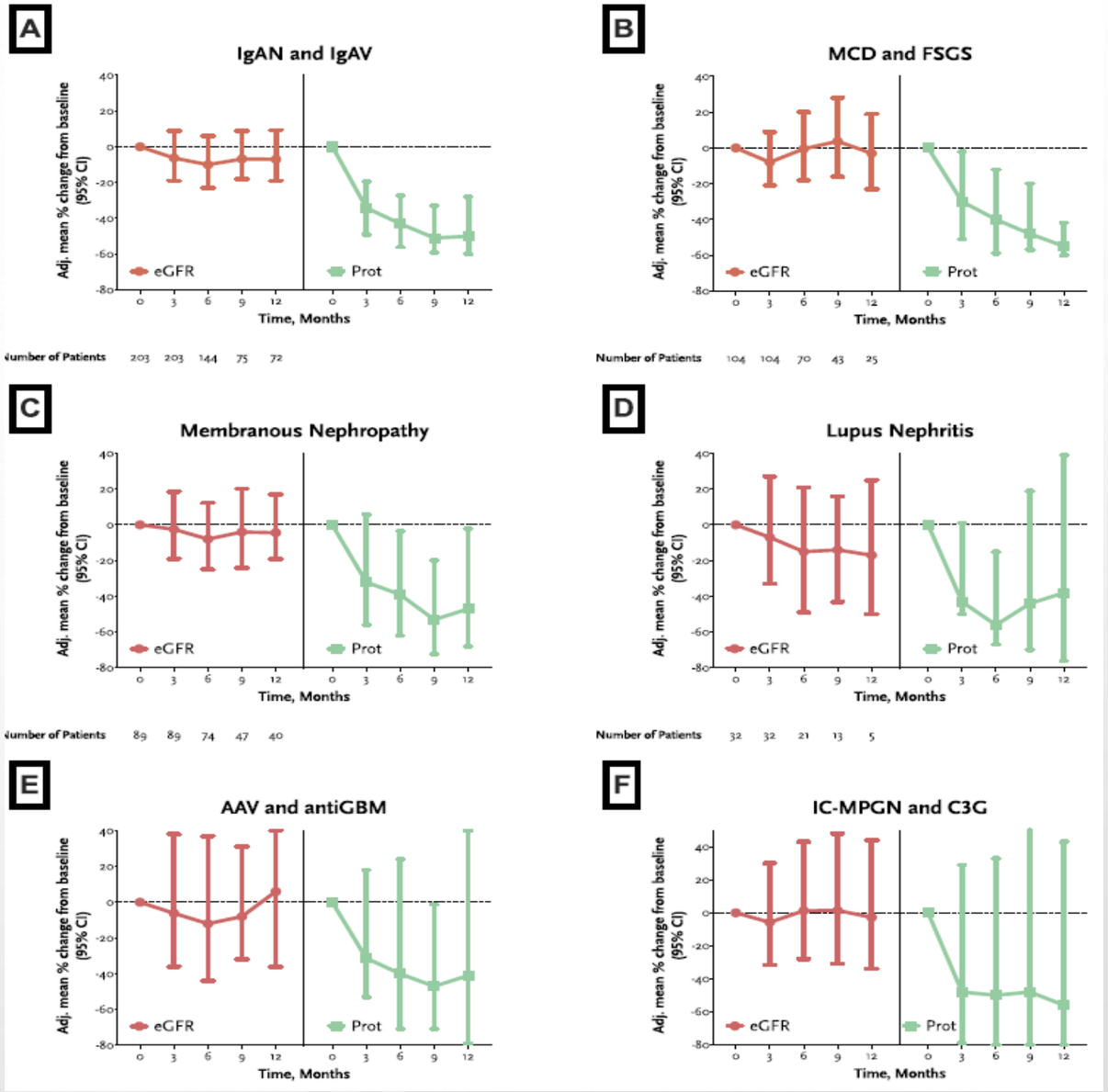
- ✓ retrospective, observational, international cohort study.
- ✓ 493 biopsy-proven glomerular diseases.
- ✓ Proteinuria from baseline changed by –35%, –41%, –45% and –48% at 3, 6, 9 and 12 months after SGLT2i initiation,
- ✓ eGFR changed by –6%, –3%, –8% and –10.5% at 3, 6, 9 and 12 months, respectively.

IgA: 203 patients with IgAN or IgAV who showed a 50% decrease in proteinuria after 12 months of SGLT2i treatment.

FSGS: 56% of primary FSGS patients (N = 32)

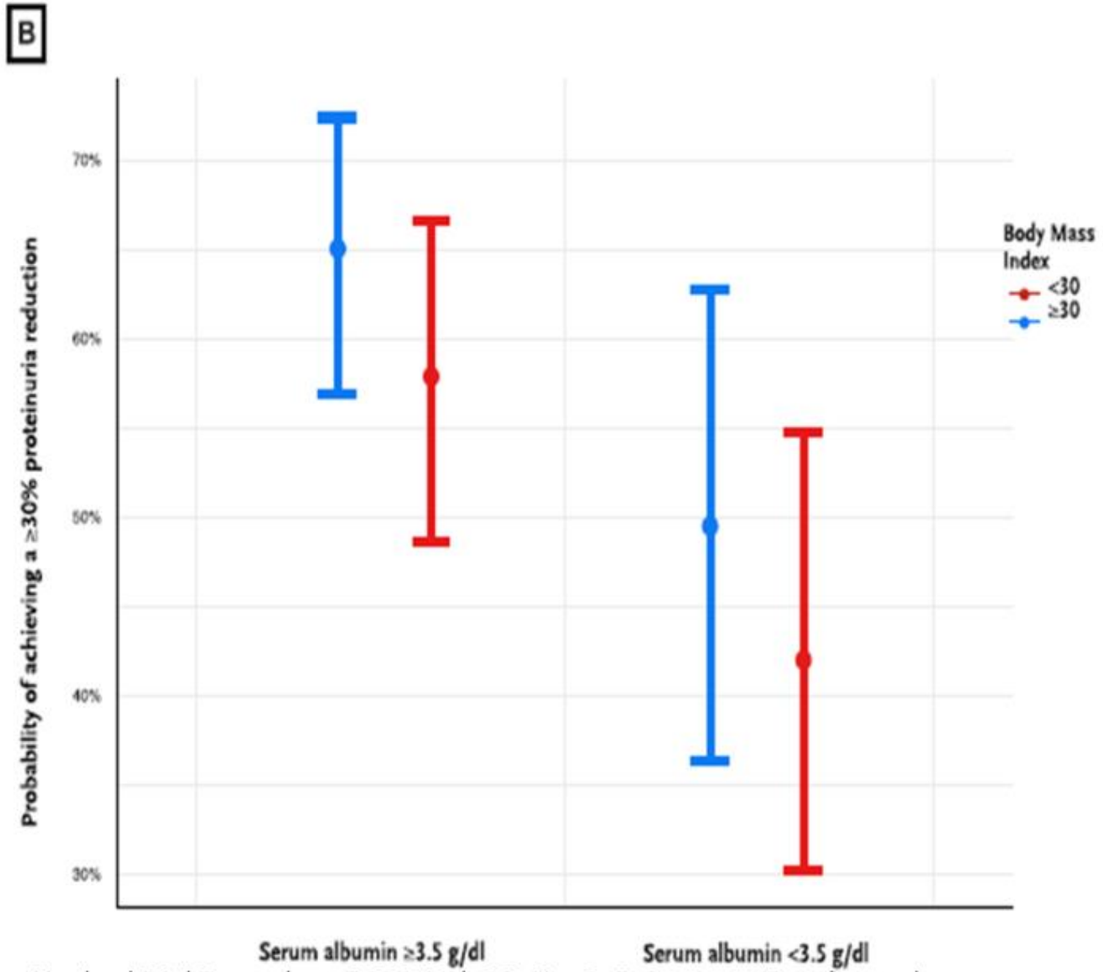
and 83% of secondary FSGS (N = 58)

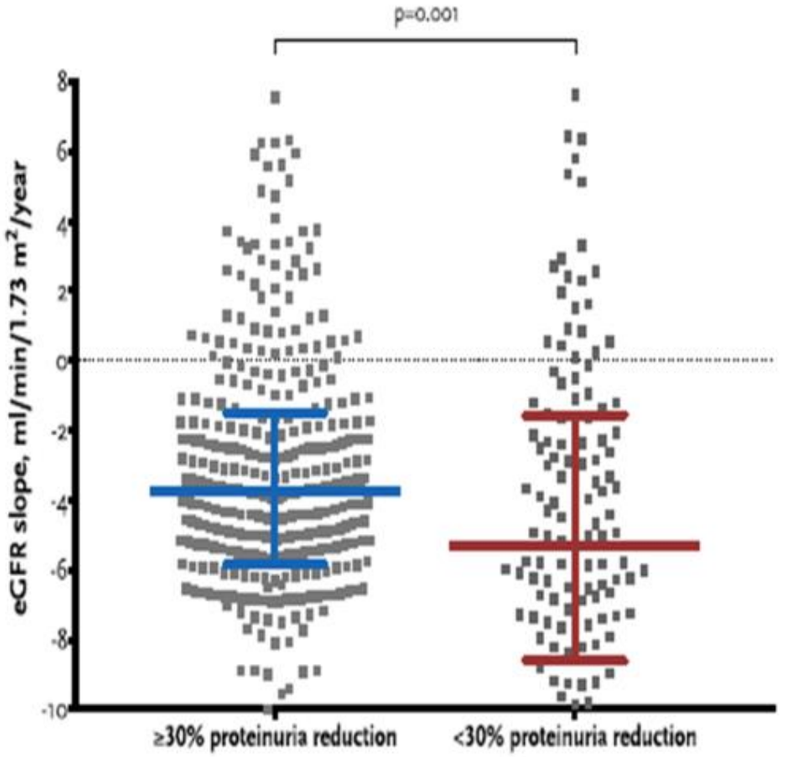
showed a ≥30% reduction in proteinuria



Nephrol Dial Transplant, 2024, Vol. 39, No. 2. F. Caravaca-Fontán *et al.*

-Patients with higher BMI and Higher serum albumin… higher probability of achieving a >30% proteinuria reduction.
-Who achieved a >30% proteinuria reduction … have a slower eGFR decline over time.

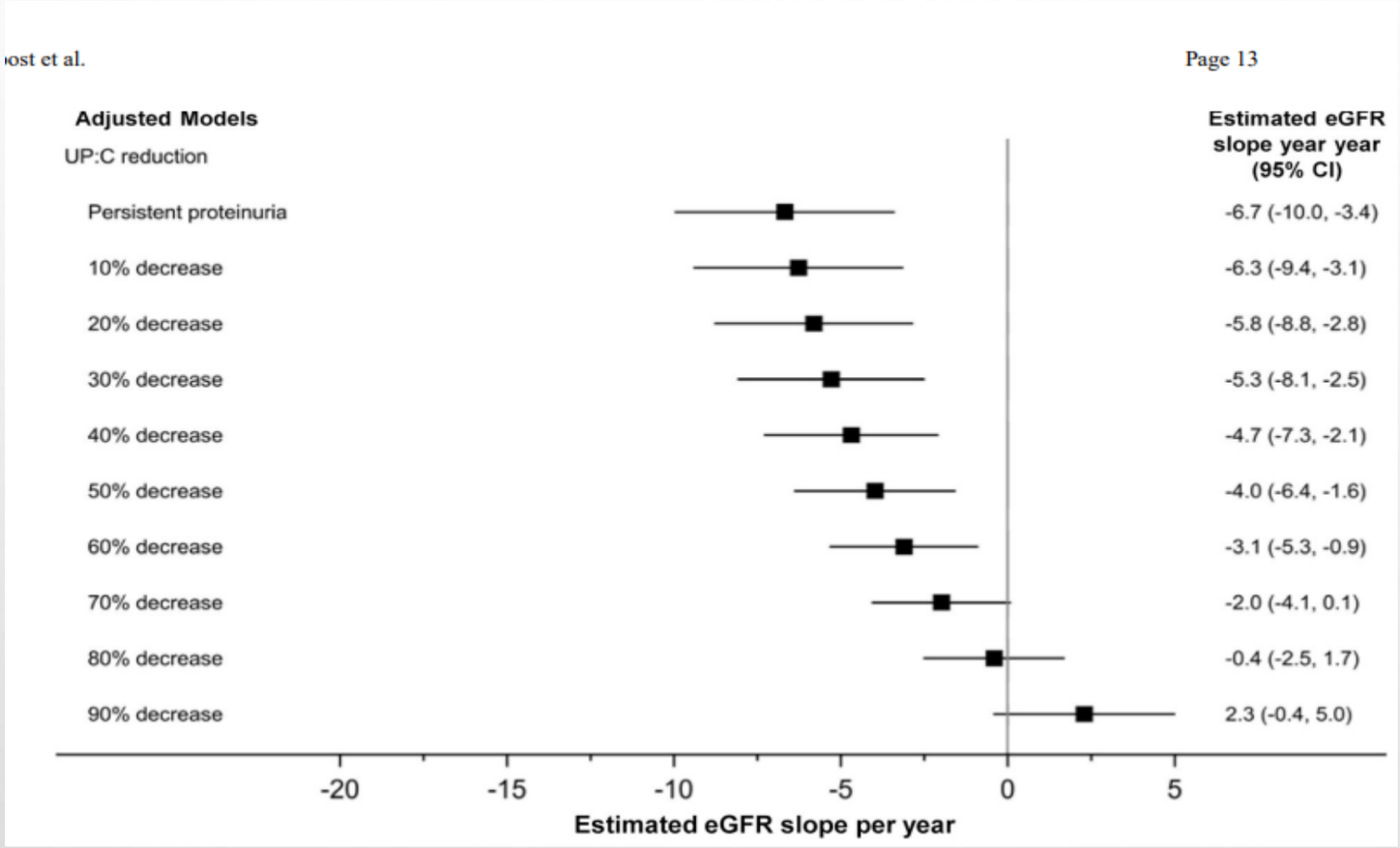




Nephrol Dial Transplant, 2024, Vol. 39, No. 2. F. Caravaca-Fontán *et al*.

Change in albuminuria and eGFR slope

1 log unit reduction in UACR over 26 weeks was associated with an increase in eGFR of 3.9 mL/min/1.73m2/year.
continuous measure without a requirement to achieve a minimal absolute threshold.



Troost JP, *et al.* Proteinuria reduction and kidney survival in focal segmental glomerulosclerosis. *Am J Kidney Dis* 2021

Efficacy in Other Glomerular Diseases

Obesity-Related Glomerulopathy

Ameliorates metabolic derangements; increases adiponectin; decreases leptin, TNF-alpha and IL-6

General Glomerulonephritis

Observational data shows 35-48% proteinuria reduction at 3-12 months

Alport Syndrome

Reduced UACR from 1,797 to 1,197 mg/g after 1-3 months in 112 patients and remained after 9–15 months.

Lupus Nephritis

Limited data; patients were excluded from large SGLT2i trials

Portalatin GM, Hong-McAtee I, Burgner AM, Gould ER, Hunley TE. Sodium glucose co-transporter 2 inhibitors (SGLT2i) for pediatric kidney disease: the future is near. *Front Pediatr*. 2025

Monitoring and Expected Changes

Initiation

Baseline labs; patient education on hydration and expected changes

4-8 Weeks

Basic metabolic panel; expect 3-6 mL/min/1.73m² eGFR drop; up to 25-30% creatinine rise acceptable

12 Weeks

Some "recovery" of eGFR often observed; continued monitoring

Long-term

Regular follow-up; favorable change in eGFR slope over time despite initial drop

When initiating SGLT2 inhibitors, clinicians should anticipate an initial drop in eGFR similar to that seen with ACEi/ARB therapy. This hemodynamic effect typically manifests as a 3-6 mL/min/1.73m² reduction in eGFR or up to a 25-30% rise in serum creatinine.

Patients should be monitored with basic metabolic panels at 4-8 weeks after initiation, with some eGFR recovery often observed by week 12. Greater changes may require volume assessment and hydration counseling. Despite this initial dip, the long-term eGFR slope is favorable compared to untreated disease progression.

Clinical Implications and Future Directions

IgA Nephropathy

Strong evidence supports SGLT2i use, with dramatic risk reduction (HR 0.24-0.67) across trials. Consider as standard therapy alongside ACEi/ARB for proteinuric IgAN.

FSGS

Mixed results with initial proteinuria reduction but questionable long-term benefit. May be more effective in secondary FSGS (56-83% showed ≥30% proteinuria reduction in observational data).

Other Glomerular Diseases

Promising observational data for Alport syndrome and obesity-related glomerulopathy. Limited evidence for lupus nephritis. Higher BMI may predict better response.

Research Needs

Longer follow-up needed for FSGS; studies in excluded populations like lupus nephritis; better understanding of mechanisms beyond hemodynamic effects.

SGLT2 inhibitors represent a significant advance in kidney disease management, particularly for IgA nephropathy where evidence is strongest. For FSGS, the initial promise of proteinuria reduction may not translate to long-term benefit, with conflicting results between trials. Patient selection may be key, with BMI and albumin levels potentially predicting response.

Future research should focus on longer follow-up periods, excluded populations, and deeper understanding of disease-specific mechanisms to optimize treatment selection and timing.


Thank you