Come trattare la DKD (SGLT2i, Finerenone e/o altro?)

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Il sottoscritto prof. Luca De Nicola dichiara di aver non ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche.

Nephroprotection by SGLT2i: Universal efficacy

JAMA | Original Investigation

SGLT2 Inhibitors and Kidney Outcomes by Glomerular Filtration Rate and Albuminuria

A Meta-Analysis

- 70 361 participants (mean age, 64.8 years; 35.0% females) from 10 randomized trials, 75% with DM

Figure 1. Effects of SGLT2 Inhibitors on CKD Progression According to Baseline eGFR

Baseline estimated GFR, mL/min/1.73 m^2	No. of participants/total No. (%) SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)
All participants			
≥60	271/23 164 (1.2)	369/19 951 (1.8)	0.61 (0.52-0.71)
45 to <60	164/6255 (2.6)	273/5902 (4.6)	0.57 (0.47-0.70)
30 to <45	274/5561 (4.9)	389/5323 (7.3)	0.64 (0.54-0.75)
<30	241/1928 (12.5)	333/1966 (16.9)	0.71 (0.60-0.83)
Overall	950/36 911 (2.6)	1364/33 146 (4.1)	0.62 (0.57-0.68)
Trend by baseline estimated GFR: *P* = .16			
Participants with diabetes			
≥60	246/19 861 (1.2)	335/16 665 (2.0)	0.59 (0.50-0.70)
45 to <60	137/4355 (3.1)	226/4004 (5.6)	0.57 (0.46-0.71)
30 to <45	213/3586 (5.9)	306/3368 (9.1)	0.62 (0.52-0.74)
<30	139/1122 (12.4)	199/1105 (18.0)	0.66 (0.53-0.82)
Overall	735/28 940 (2.5)	1066/25 165 (4.2)	0.60 (0.55-0.66)
Trend by baseline estimated GFR: *P* = .39			
Participants without diabetes			
≥60	25/3303 (0.8)	34/3286 (1.0)	0.75 (0.45-1.28)
45 to <60	27/1900 (1.4)	47/1898 (2.5)	0.59 (0.37-0.96)
30 to <45	61/1975 (3.1)	83/1955 (4.2)	0.71 (0.51-0.99)
<30	102/788 (12.9)	134/837 (16.0)	0.78 (0.60-1.01)
Overall	215/7971 (2.7)	298/7981 (3.7)	0. 70 (0.59-0.84)
Trend by baseline estimated GFR: *P* = .57			

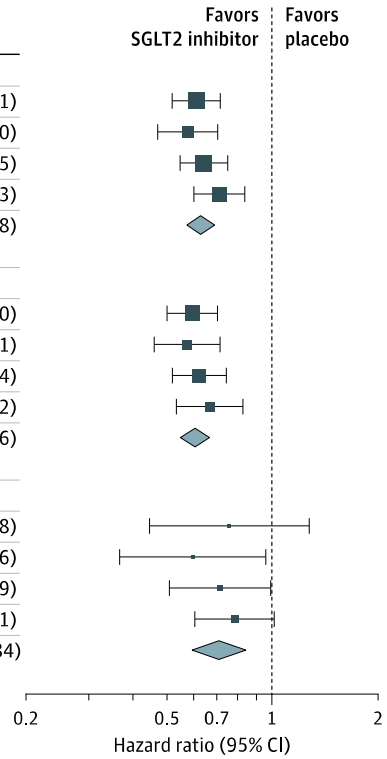
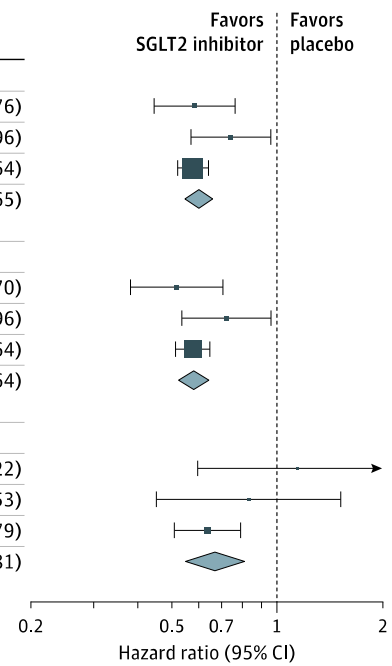


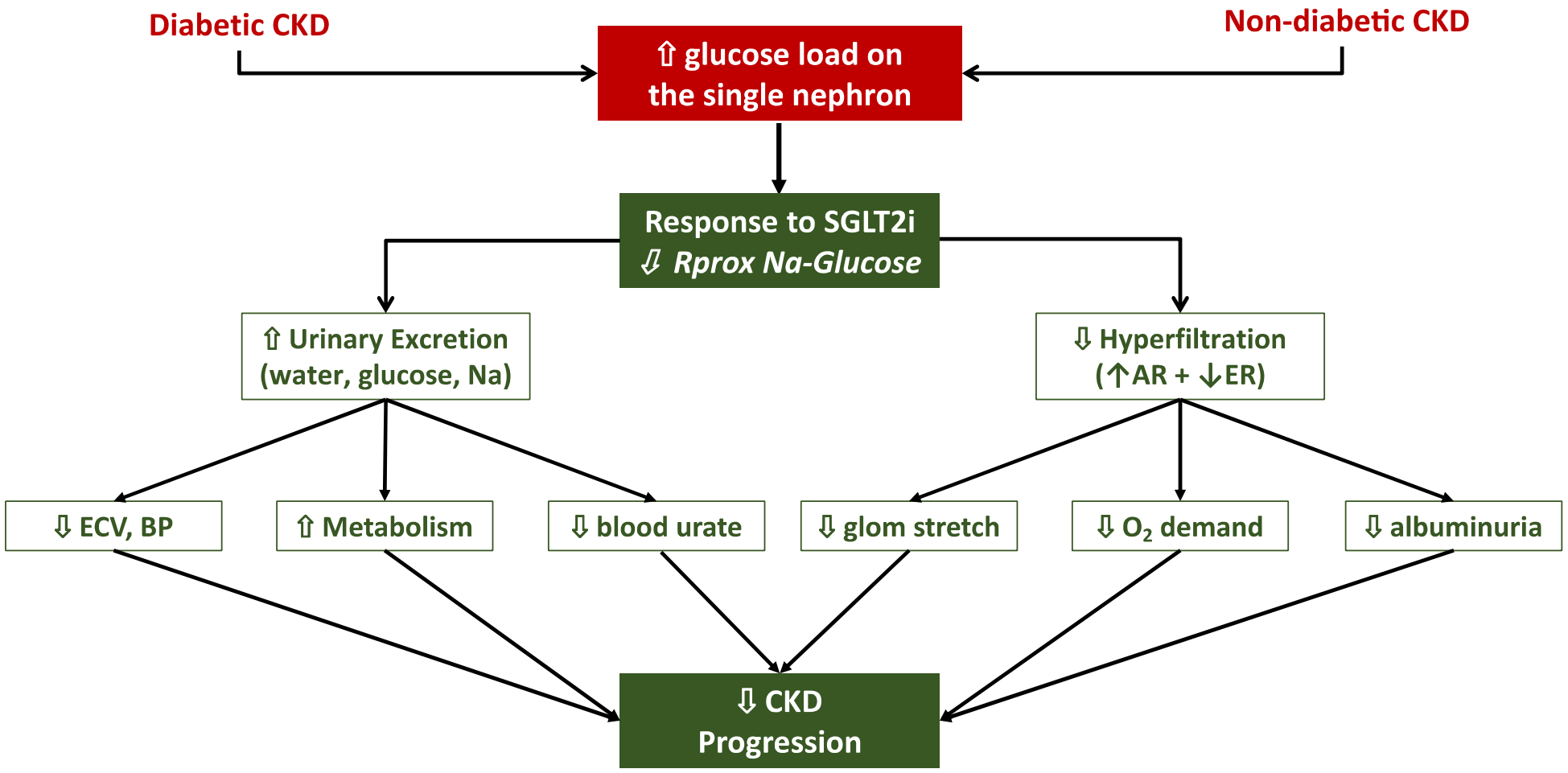
Figure 2. Effects of SGLT2 Inhibitors on CKD Progression According to Baseline UACR

Baseline UACR, mg/g	No. of participants/total No. (%) SGLT2 inhibitor	Placebo	Hazard ratio (95% CI)
All participants			
<30	94/15 973 (0.6)	125/13 595 (0.9)	0.58 (0.44-0.76)
30 to 300	109/7583 (1.4)	128/6519 (2.0)	0.74 (0.57-0.96)
>300	637/7575 (8.4)	999/7275 (13.7)	0.57 (0.52-0.64)
Overall	843/31 407 (2.7)	1252/27 644 (4.5)	0.60 (0.55-0.65)
Trend by baseline UACR: *P* = .49			
Participants with diabetes			
<30	73/13 984 (0.5)	108/11 645 (0.9)	0.52 (0.38-0.70)
30 to 300	89/6365 (1.4)	103/5309 (1.9)	0.72 (0.53-0.96)
>300	503/5849 (8.6)	786/5497 (14.3)	0.57 (0.51-0.64)
Overall	668/26 464 (2.5)	997/22 696 (4.4)	0.58 (0.52-0.64)
Trend by baseline UACR: *P* = .96			
Participants without diabetes			
<30	21/1988 (1.1)	17/1950 (0.9)	1.15 (0.59-2.22)
30 to 300	20/1218 (1.6)	25/1210 (2.1)	0.83 (0.45-1.53)
>300	134/1726 (7.8)	213/1778 (12.0)	0.63 (0.51-0.79)
Overall	175/4943 (3.5)	255/4948 (5.2)	0.66 (0.55-0.81)
Trend by baseline UACR: *P* = .07			



Neuen BL et al. JAMA 2025

Nephroprotection by SGLT2i: Expanded View on Mechanisms



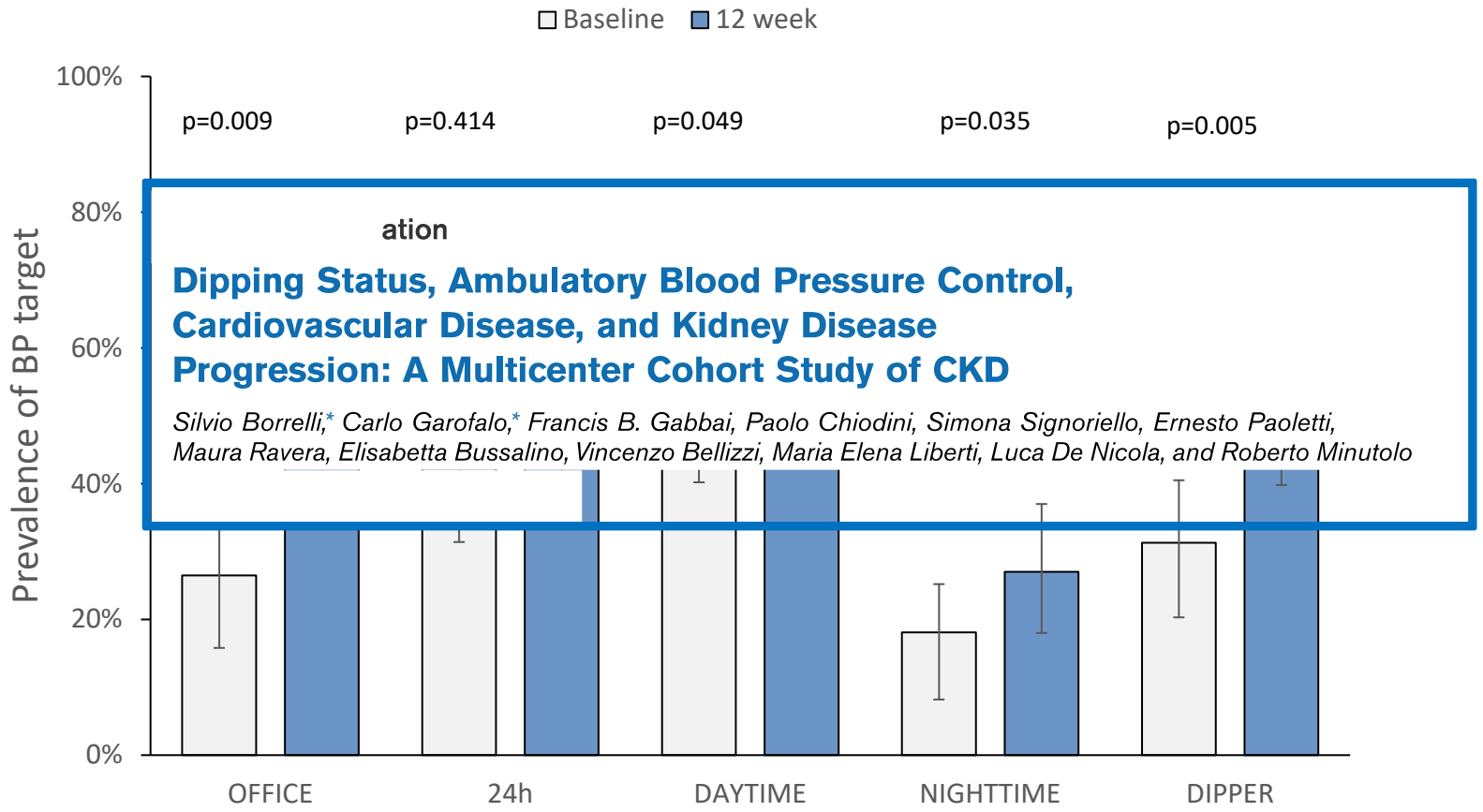
De Nicola, et al. J Nephrol 2025

Nephroprotection by SGLT2i: role of nighttime BP

- Multicentric prospective study in DKD under nephrology care in 83 patients from 11 italian renal clinics: age 67±13 years, 73% males, DM2 60%, CVD 44%, eGFR 43.5 ±17.4 ml/min/1.73 m2 , Ualb 180 mg/24h (severe albuminuria 70.1%)
- Baseline and follow-up ABP after 12±2 weeks of DAPA

AHA GOALS for ABPM:

- ✓ daytime SBP < 130
- ✓ nighttime SBP < 110
- ✓ nighttime/daytime SBP < 0.9



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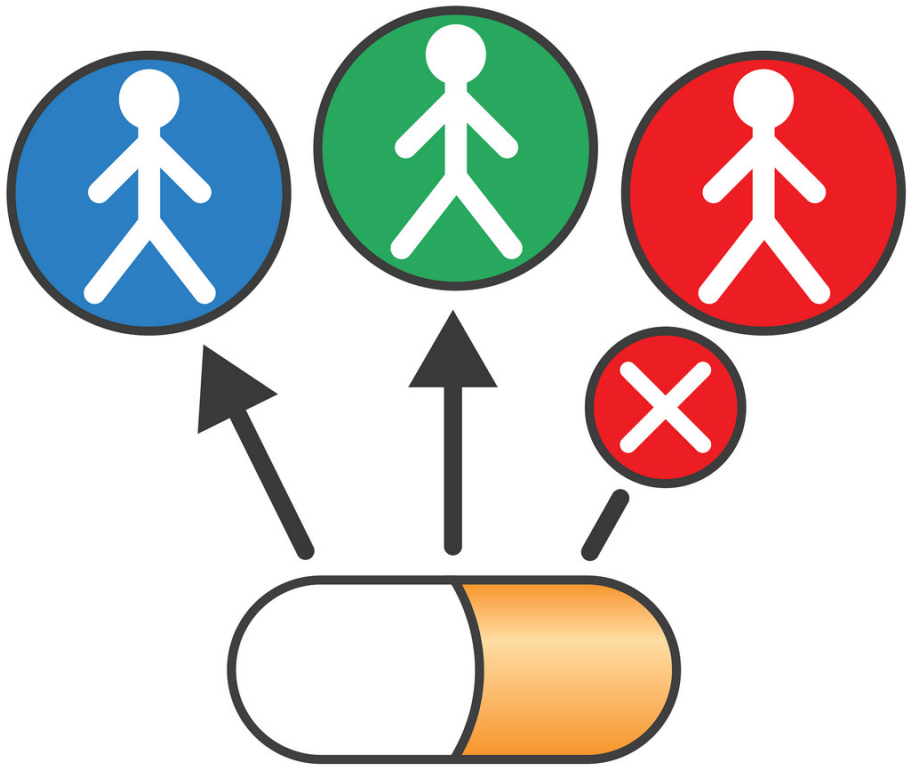
Dipping Status, Ambulatory Blood Pressure Control, Cardiovascular Disease, and Kidney Disease Progression: A Multicenter Cohort Study of CKD

Silvio Borrelli, Carlo Garofalo,* Francis B. Gabbai, Paolo Chiodini, Simona Signoriello, Ernesto Paoletti, Maura Ravera, Elisabetta Bussalino, Vincenzo Bellizzi, Maria Elena Liberti, Luca De Nicola, and Roberto Minutolo*

Borrelli...De Nicola, CKJ 2024

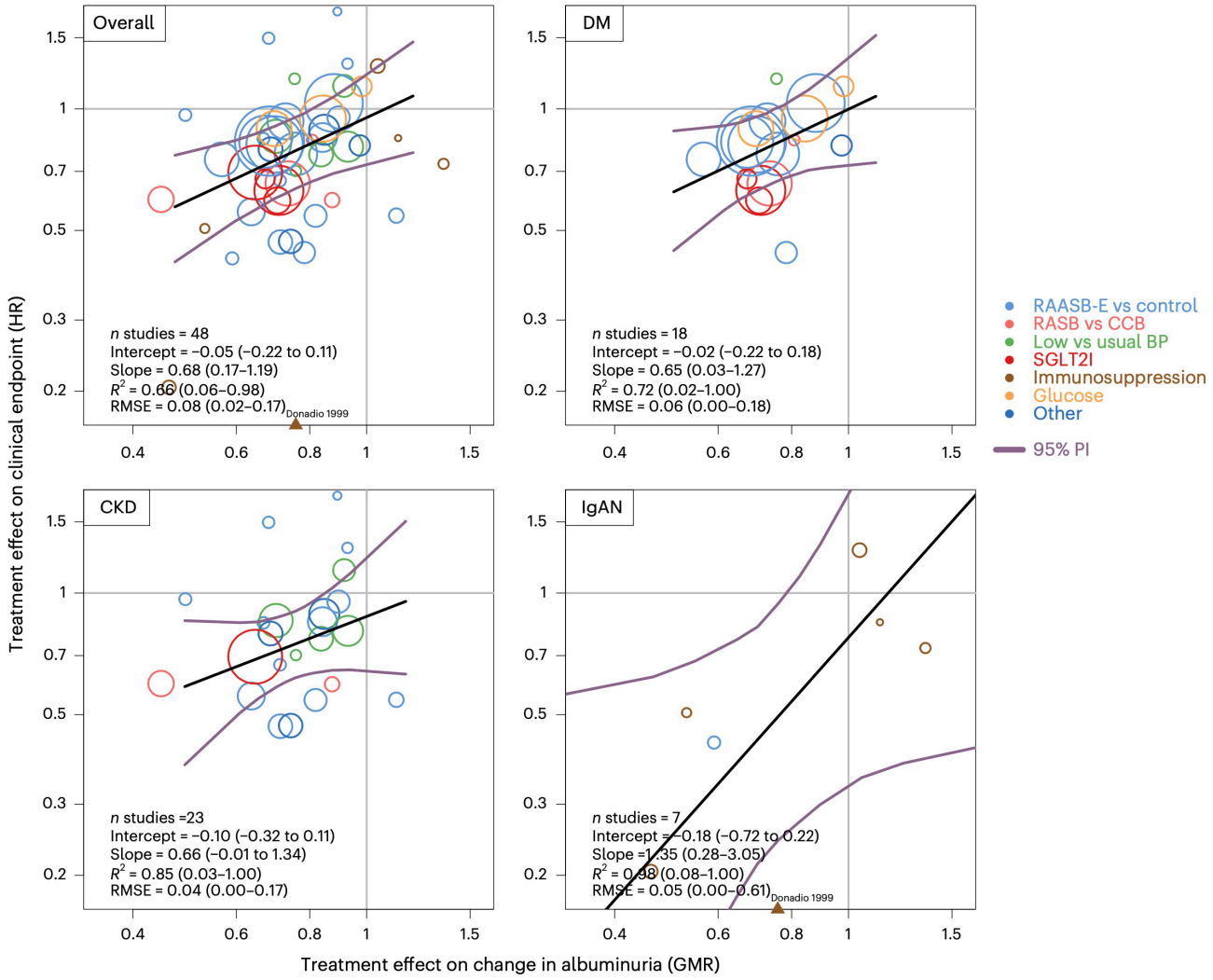
Personalized Medicine

"same drug not for all"



Proxy of long-term efficacy on CKD progression ?

6-month change in albuminuria predicts future renal endpoint (kidney failure or doubling of sCreat)
in individual participant data analysis of 48 RCTs including 85,681 patients under traditional and innovative drugs



Renal risk reduction explained by the average treatment effect on 6-month UACR:

70%

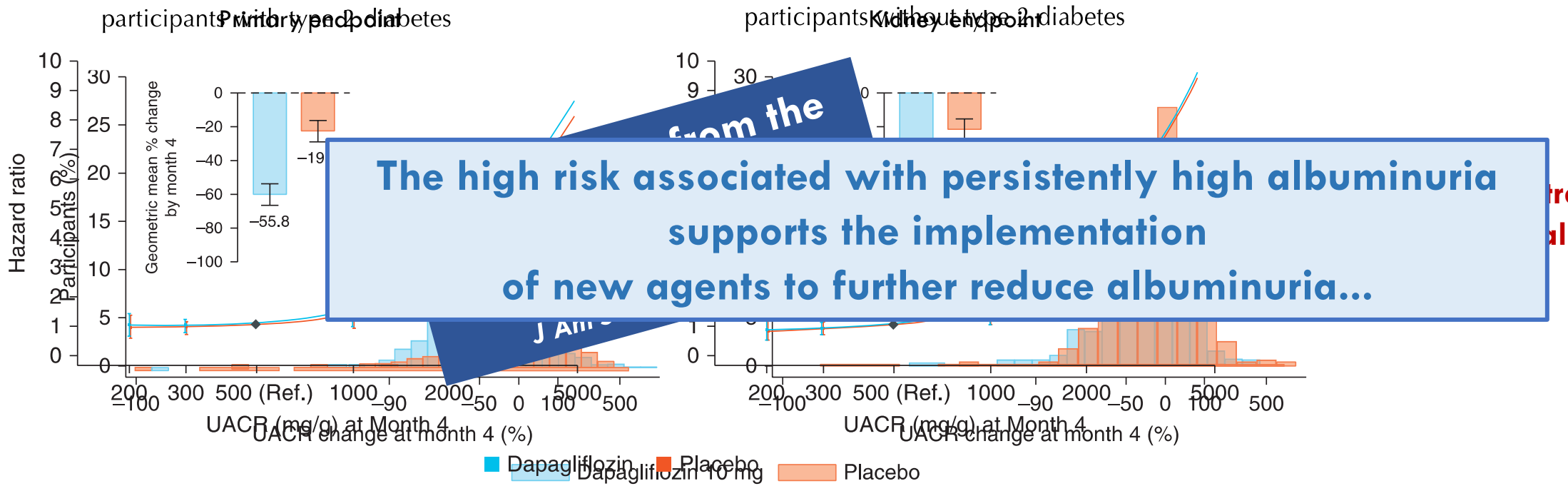
Change in albuminuria to have a high confidence that the drug will exert clinical benefit:

25%

Heerspink HJL, et al. Nature Medicine 6 Nov 2025

Residual Renal Risk with RASI and SGLT2I

Residual albuminuria at moth 4 predicted renal risk, similar in dapa and placebo arm



The high risk associated with persistently high albuminuria supports the implementation of new agents to further reduce albuminuria...

treated patients albuminuria by

van Mil (DAPA-CKD trial), cJASN Dec 2024

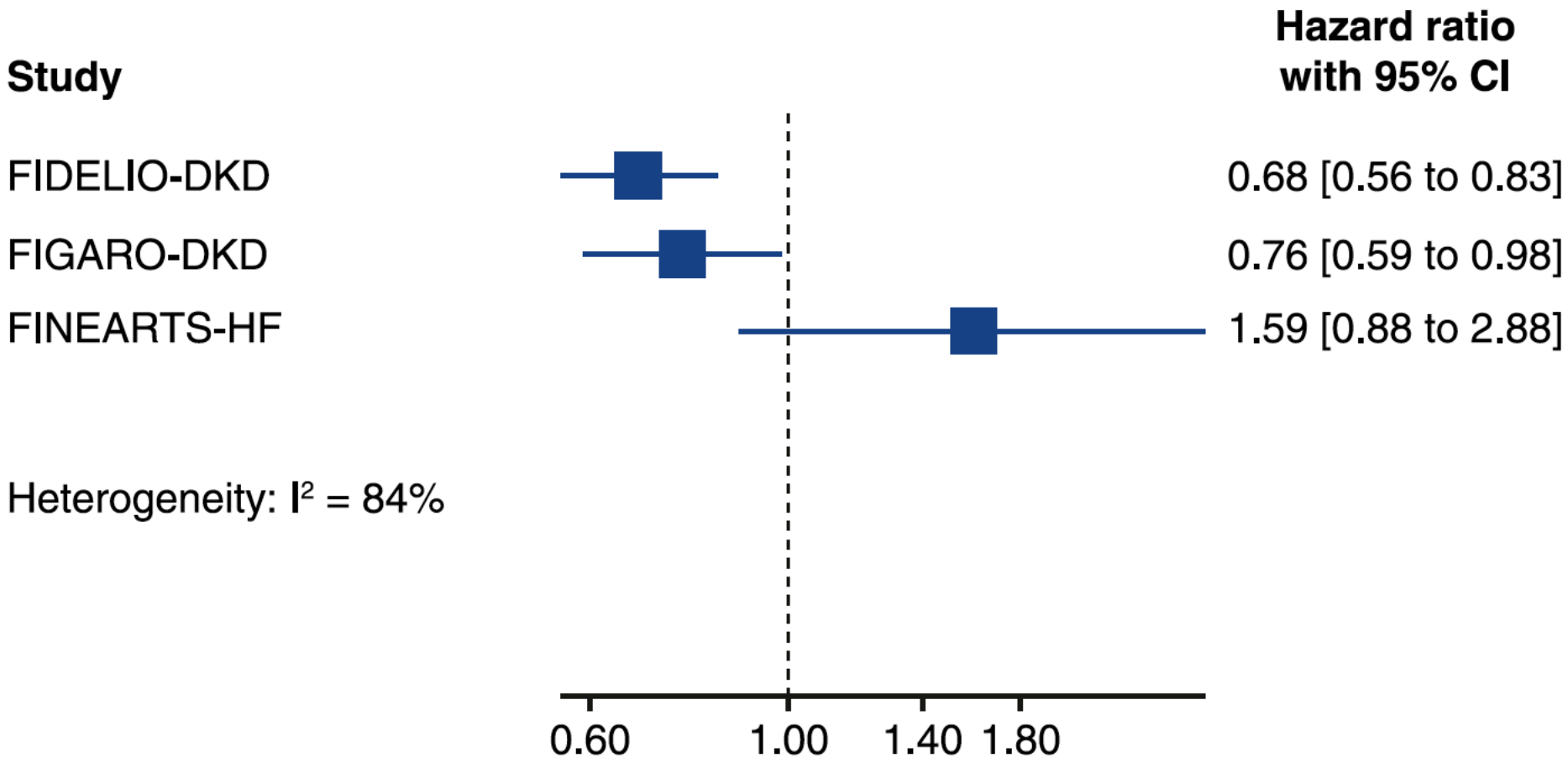
Finerenone

- pooled analysis of FIDELIO, FIGARO, FINE-HEART
- 14,180 patients with DKD. median follow-up of 3.0 years

Outcomes	Finerenone (n=7094)		Placebo (n=7086)		Finerenone versus Placebo
	# With Event (%)	Incidence Rate (per 1000 py)	# With Event (%)	Incidence Rate (per 1000 py)	HR (95% CI)
Cardiovascular events[a]					
Cardiovascular death or heart failure hospitalization	576 (8)	27.9	694 (10)	33.9	0.83 (0.75 to 0.93)
Cardiovascular death	242 (3)	11.4	288 (4)	13.6	0.84 (0.71 to 1.00)
Heart failure hospitalization	383 (5)	18.6	475 (7)	23.2	0.81 (0.71 to 0.93)
Major adverse cardiovascular events	916 (13)	45.6	1017 (14)	51.2	0.90 (0.82 to 0.99)
New-onset atrial fibrillation	227 (4)[b]	12.3	273 (4)[b]	14.8	0.83 (0.70 to 0.99)
Cardiovascular events[c]					
Cardiovascular death or heart failure hospitalization	723 (10)	35.0	844 (12)	41.2	0.86 (0.78 to 0.95)
Cardiovascular death	409 (6)	19.3	467 (7)	22.1	0.88 (0.77 to 1.00)
Major adverse cardiovascular events	1039 (15)	51.8	1159 (16)	58.3	0.90 (0.82 to 0.97)
Kidney outcomes					
Composite kidney outcome (eGFR ≥50%)[d]	514 (7)	26.7	645 (9)	33.7	0.79 (0.70 to 0.88)
Composite kidney outcome (eGFR ≥57%)[e]	373 (5)	19.2	477 (7)	24.7	0.78 (0.69 to 0.89)
All-cause morbidity and mortality					
All-cause death	688 (10)	32.4	757 (11)	35.8	0.91 (0.82 to 1.01)
All-cause hospitalization	3165 (45)	201.4	3260 (46)	209.4	0.97 (0.92 to 1.01)
All-cause death or all-cause hospitalization	3300 (47)	209.9	3426 (48)	220.1	0.96 (0.91 to 1.00)

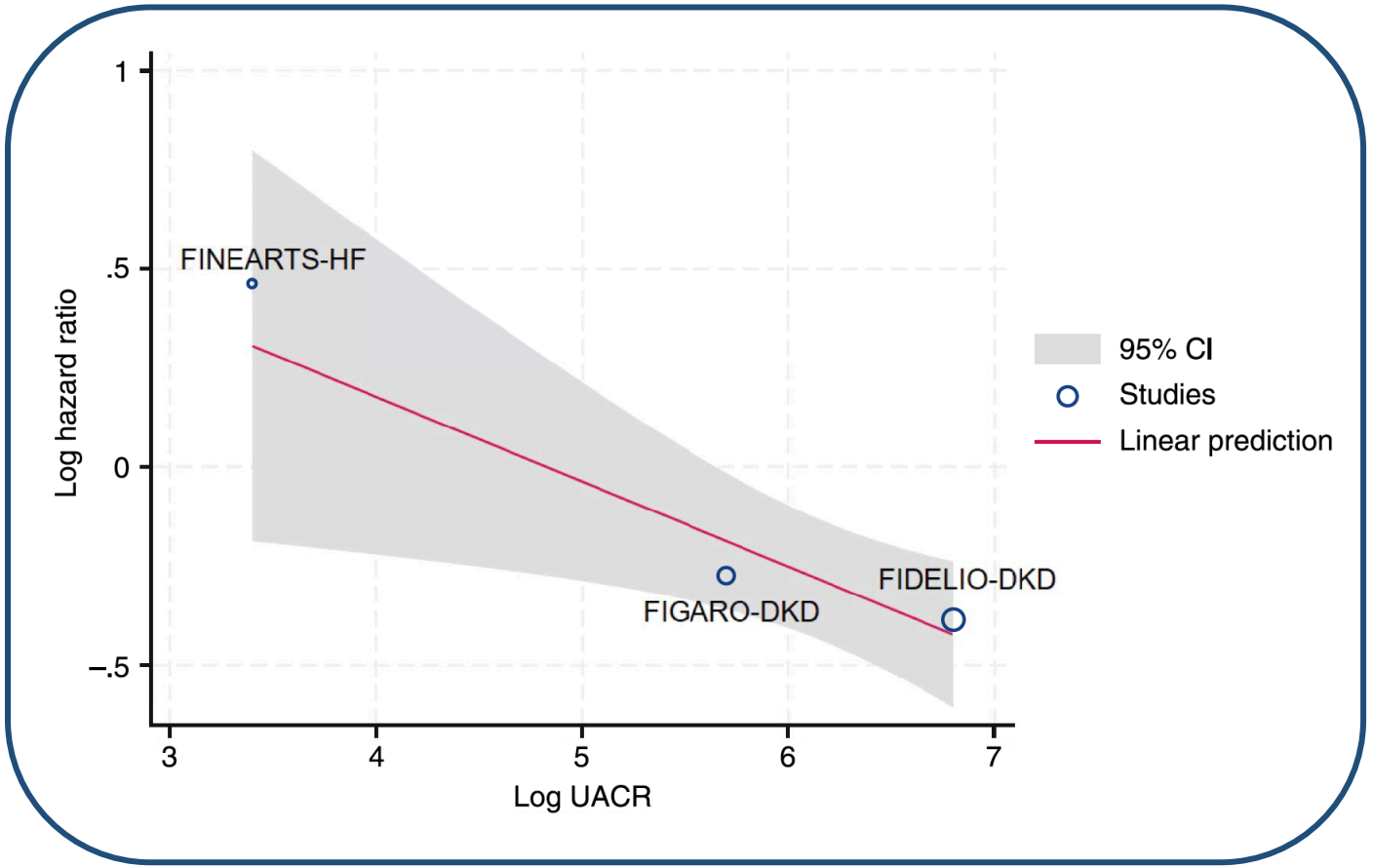
Ostrominski JW et al. JASN 2025

Albuminuria is the Main Determinant of Kidney Benefits with Finerenone



Ferreira et al., JASN 2026

Albuminuria is the Main Determinant of Kidney Benefits with Finerenone

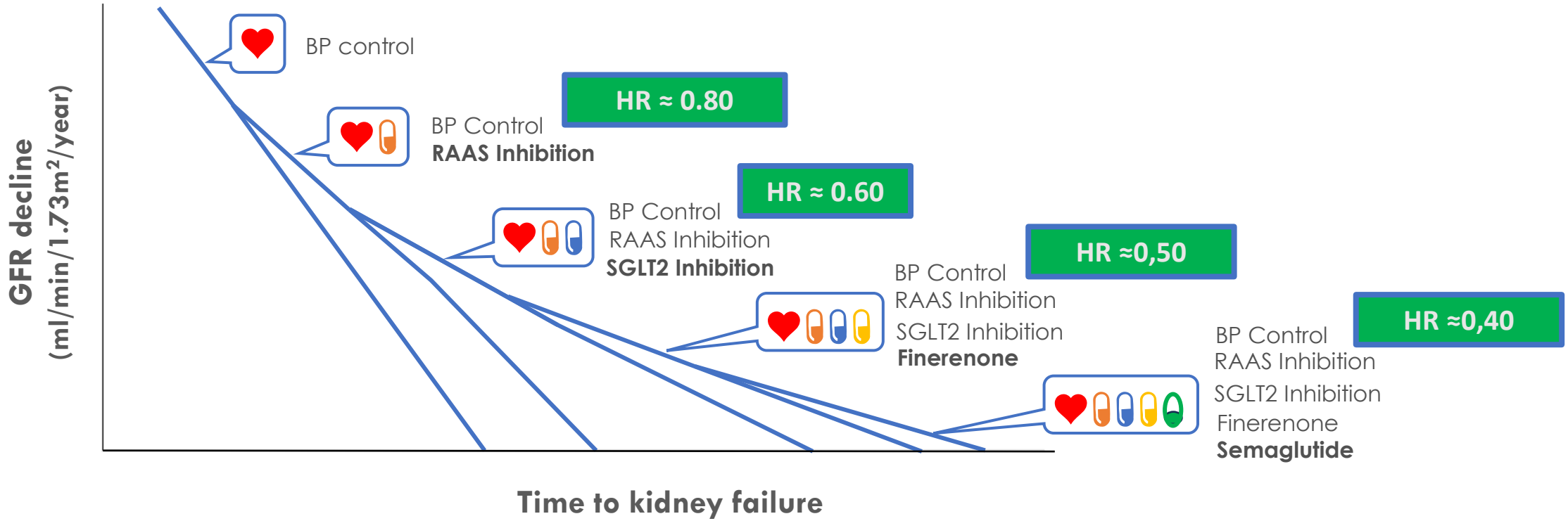


HYPOTHESIS

Albuminuria marker of MR overactivation by aldosterone in the kidneys ➜ Nephroprotection by nsMRA

Ferreira et al., JASN 2026

Incremental Benefits by Incremental Treatment on eGFR Decline in Patients with DKD and Albuminuria



Modified from Neuen et al. Circulation 2024

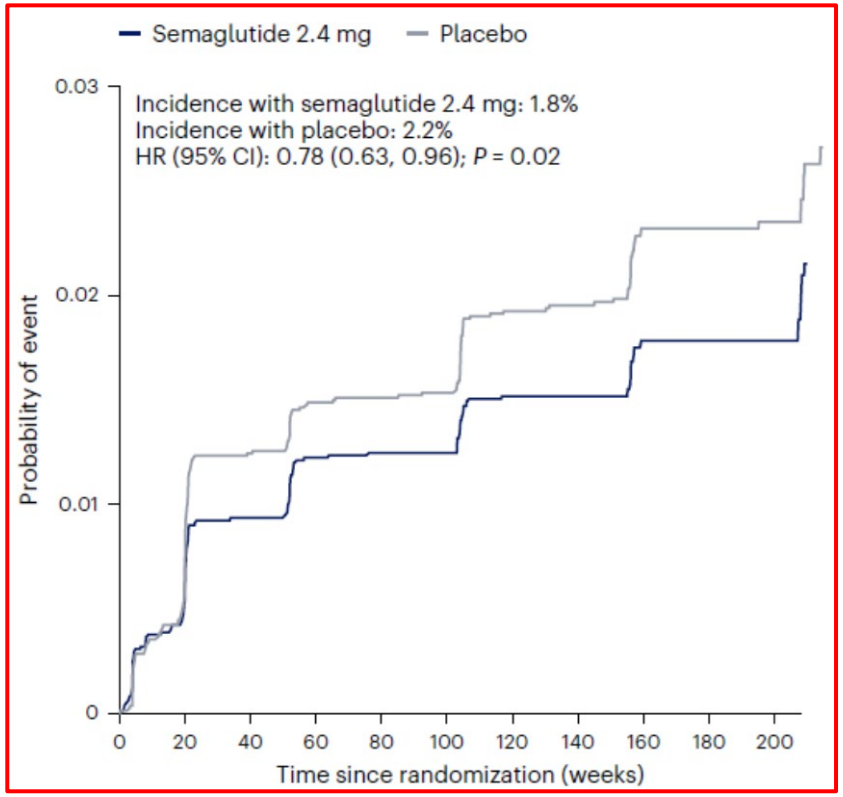
nature medicine

The favourable effect of GLP1-RA on body weight mediates (in part) nephroprotection

Long-term kidney outcomes of semaglutide in obesity and cardiovascular disease in the SELECT trial

Colhoun H et al. Nature Medicine 2024

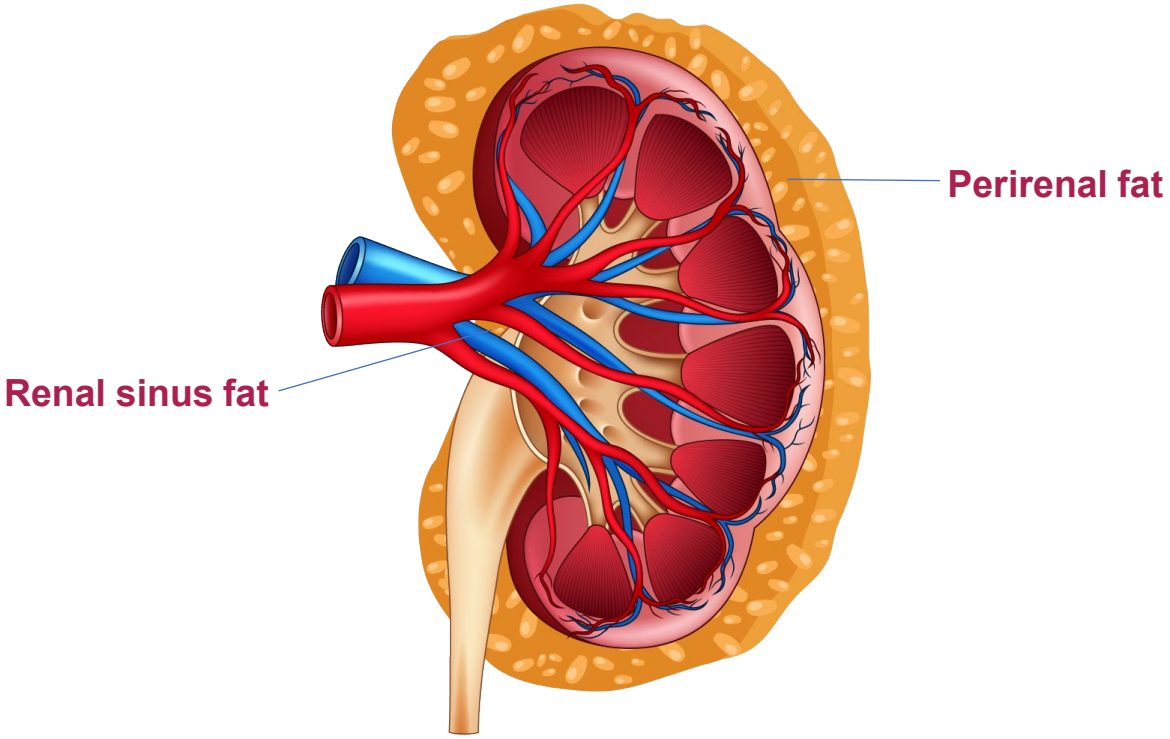
- 17,604 patients
- Overweight or obesity (BMI ≥27 kg/m^2)
- Age ≥45 years and established CVD
- No prior history of diabetes (HbA1c <6.5%)
- Semaglutide 2.4 mg OW vs placebo

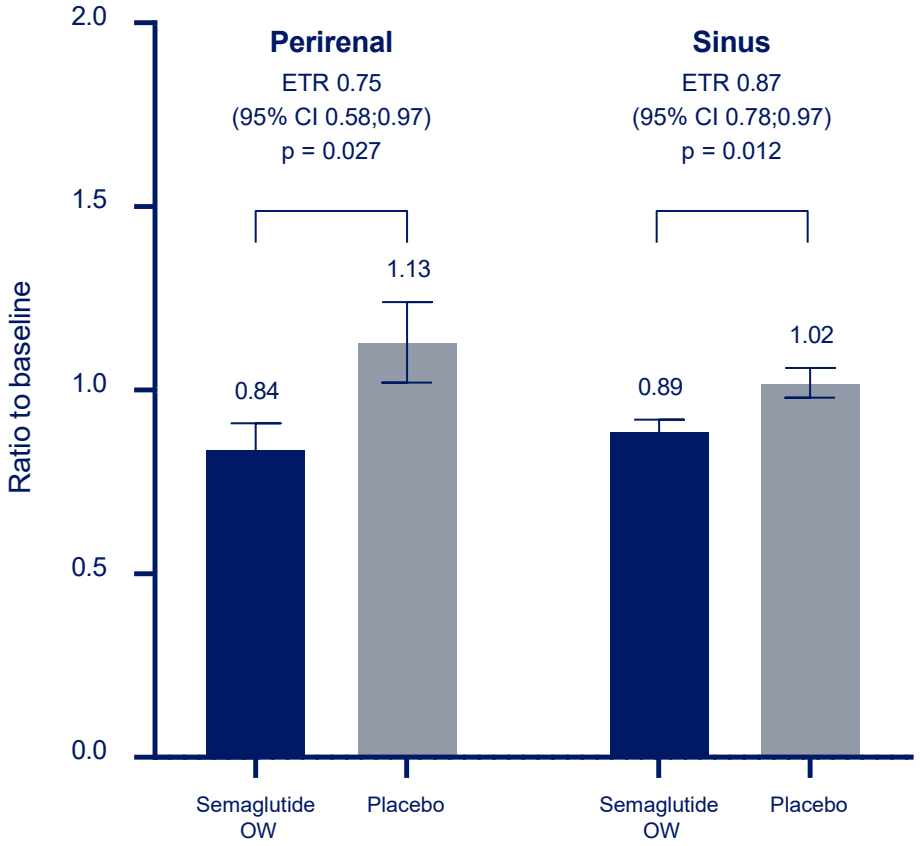


Outcome	Semaglutide 2.4 mg (*N*=8,803)	Placebo (*N*=8,801)	ETD (95% CI); *P* value
Change in eGFR at week 104, mL min^{-1} 1.73 m^{-2}	−0.86	−1.61	0.75 (0.43, 1.06); *P*<0.001
By baseline eGFR			
<60 ml min^{-1} m^{-2}	5.28	3.09	2.19 (1.00, 3.38); *P*<0.001
≥60 ml min^{-1} m^{-2}	−1.62	−2.20	0.57 (0.26, 0.89); *P*<0.001
Total eGFR slope, ml min^{-1} m^{-2} per year	−0.78	−1.17	0.39 (0.30, 0.48); *P*<0.001
Chronic eGFR slope, ml min^{-1} m^{-2} per year	−0.98	−1.28	0.29 (0.18, 0.40); *P*<0.001
Acute eGFR slope, ml min^{-1} m^{-2} per year	−2.41	−1.08	−1.33 (−2.68, 0.02); *P*=0.05

5-component kidney composite endpoint:
death from kidney causes, initiation of chronic RRT,
onset of eGFR<15, eGFR decline ≥50% or onset of UACR ≥ 300 mg/g

REMODEL: Semaglutide significantly reduces kidney fat





Perirenal fat volume decreased by 25%
Sinus fat volume decreased by 13%

Tuttle KR, et al. American Society of Nephrology Kidney Week, Nov 2025

The FUTURE...Tailored Treatment

ZENITH High Proteinuria

Phase III, randomised, multicentre, double-blind study to evaluate the efficacy, safety, and tolerability of **Zibotentan/Dapagliflozin compared to Dapagliflozin alone** in CKD with high proteinuria

Primary Objective

To determine whether zibotentan + dapagliflozin is superior to dapagliflozin alone to slow eGFR decline

Primary Endpoint

Change in eGFR from baseline to Month 24

Estimated Enrollment

1500 are being enrolled

FINESSE

Randomized, open-label, cross-over, multicentre trial in patients with HbA1c ≥5.7%, eGFR 25-90, UACR 100-3500 mg/g, under RASI and/or SGTL2-I to evaluate ACR after 6 wks of **Finerenone, oral Semagutide and combination**

Primary Objective

To determine whether finerenone + semaglutide further lowers albuminuria at a population level

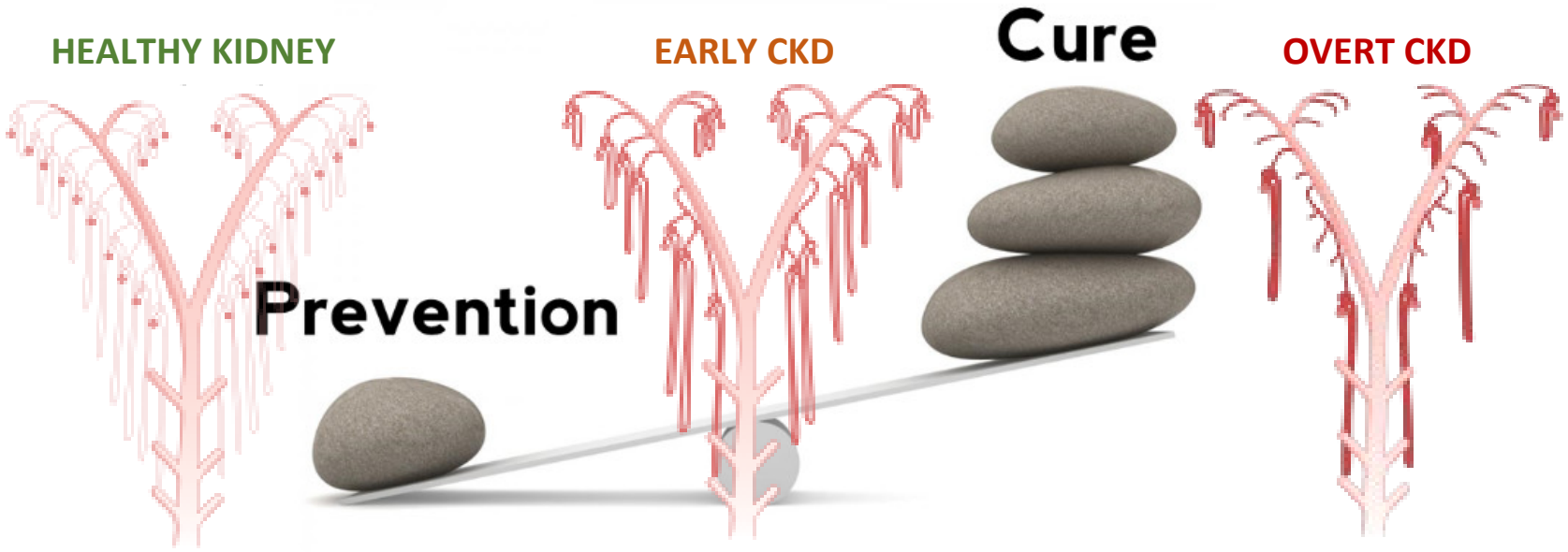
Primary Endpoint

% change of EACR from baseline to wk 6

Estimated Enrollment

36 are being enrolled

...meanwhile... the Early the Better



THERAPEUTIC TARGET

⇧

Greater Effectiveness of Nephroprotective Interventions

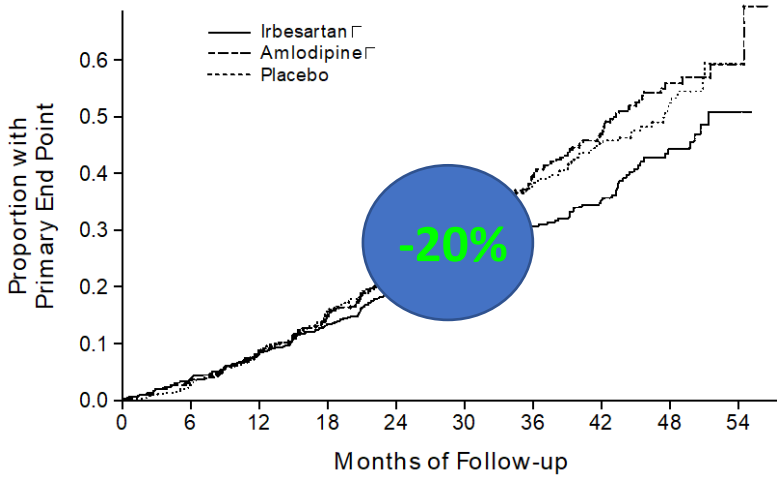
Nephroprotection by anti-RAS is higher at early stages of CKD

The New England
Journal of Medicine

VOLUME 345 SEPTEMBER 20, 2001 NUMBER 12

RENOPROTECTIVE EFFECT OF THE ANGIOTENSIN-RECEPTOR ANTAGONIST IRBESARTAN IN PATIENTS WITH NEPHROPATHY DUE TO TYPE 2 DIABETES

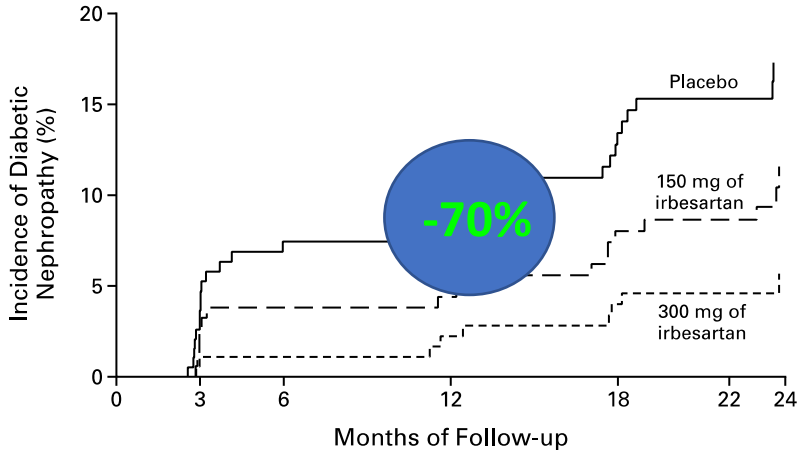
EDMUND J. LEWIS



sCreat 1.7 mg/dL, Ualb 1.9 g/24h

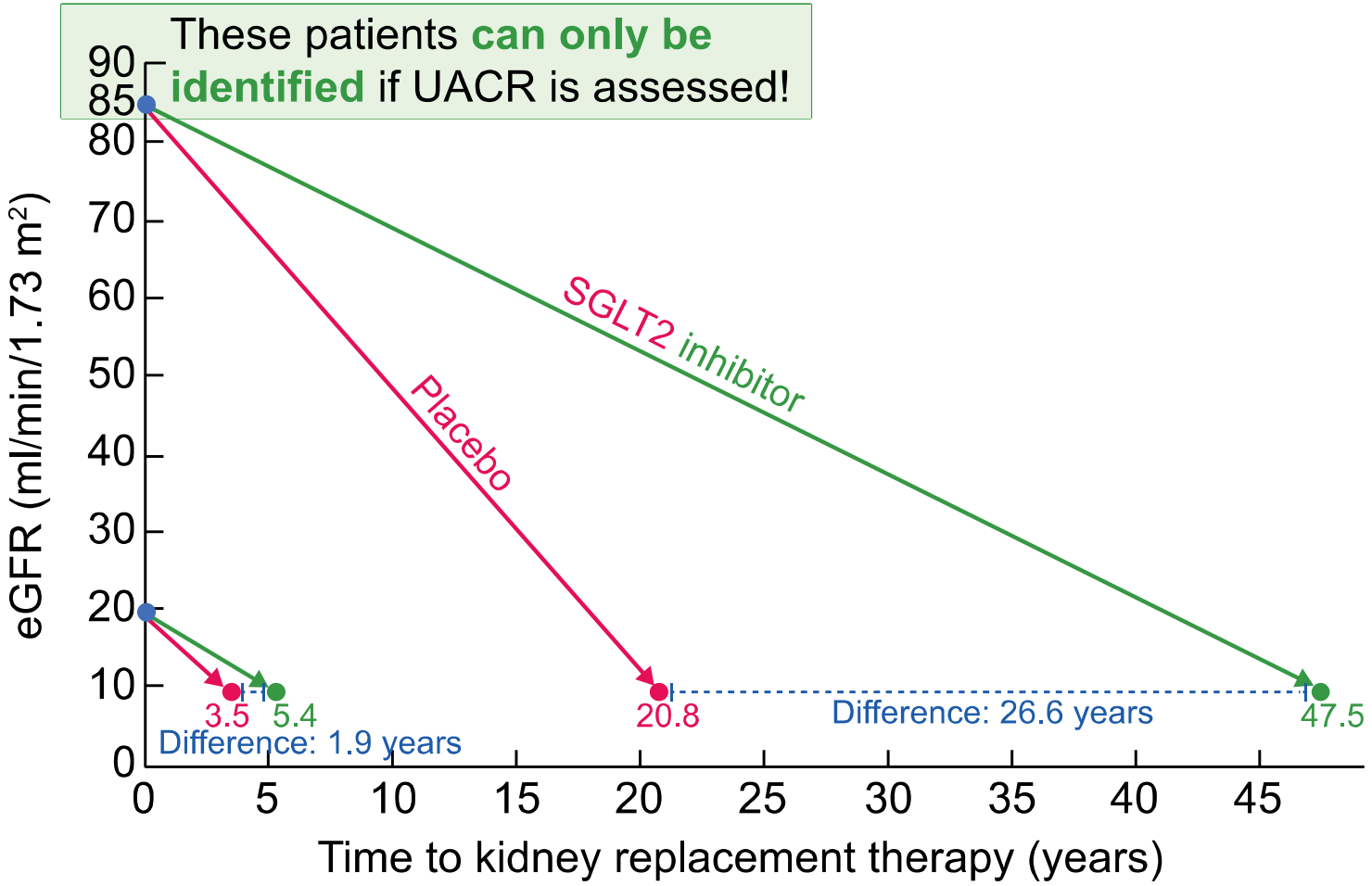
THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

HANS-HENRIK PARVING



sCreat 1.0 mg/dL, Ualb 55 μg/min

Nephroprotection by anti-RAS is higher at early stages of CKD

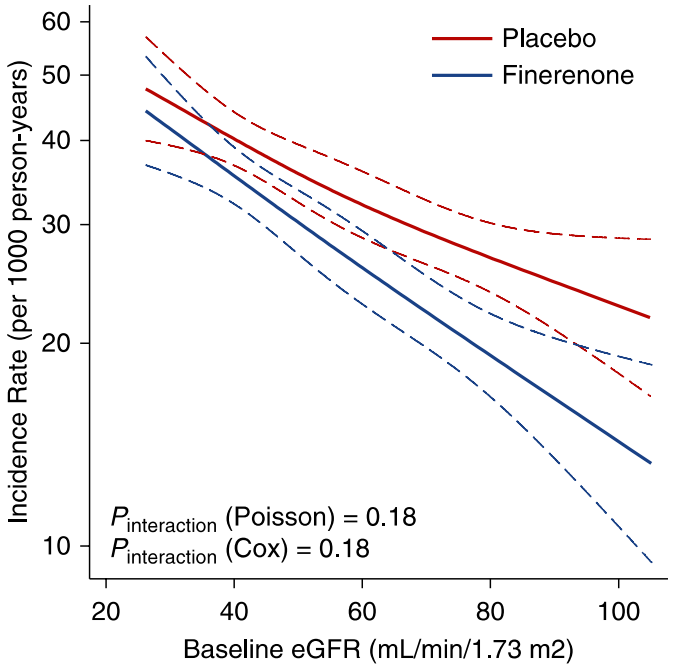


Ortiz A, et al. Evolving strategies for early diagnosis, proactive prevention and treatment of CKD. NDT 2025

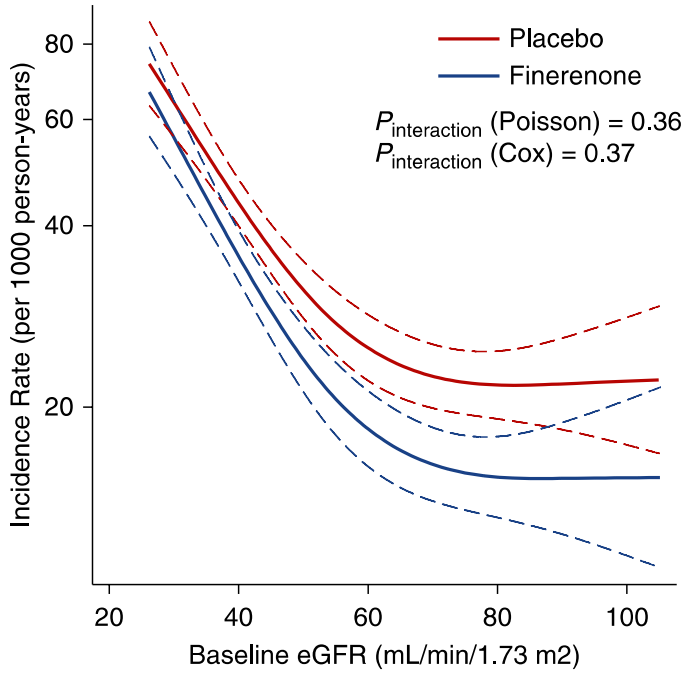
Nephroprotection by Finerenone is higher (NS) at early stages of CKD

- pooled analysis of FIDELIO, FIGARO, FINE-HEART
- 14,180 patients with DKD. median follow-up of 3.0 years

Treatment effects by eGFR of finerenone vs placebo CV death or HF hospitalization



Treatment effects by eGFR of finerenone vs placebo composite kidney outcome

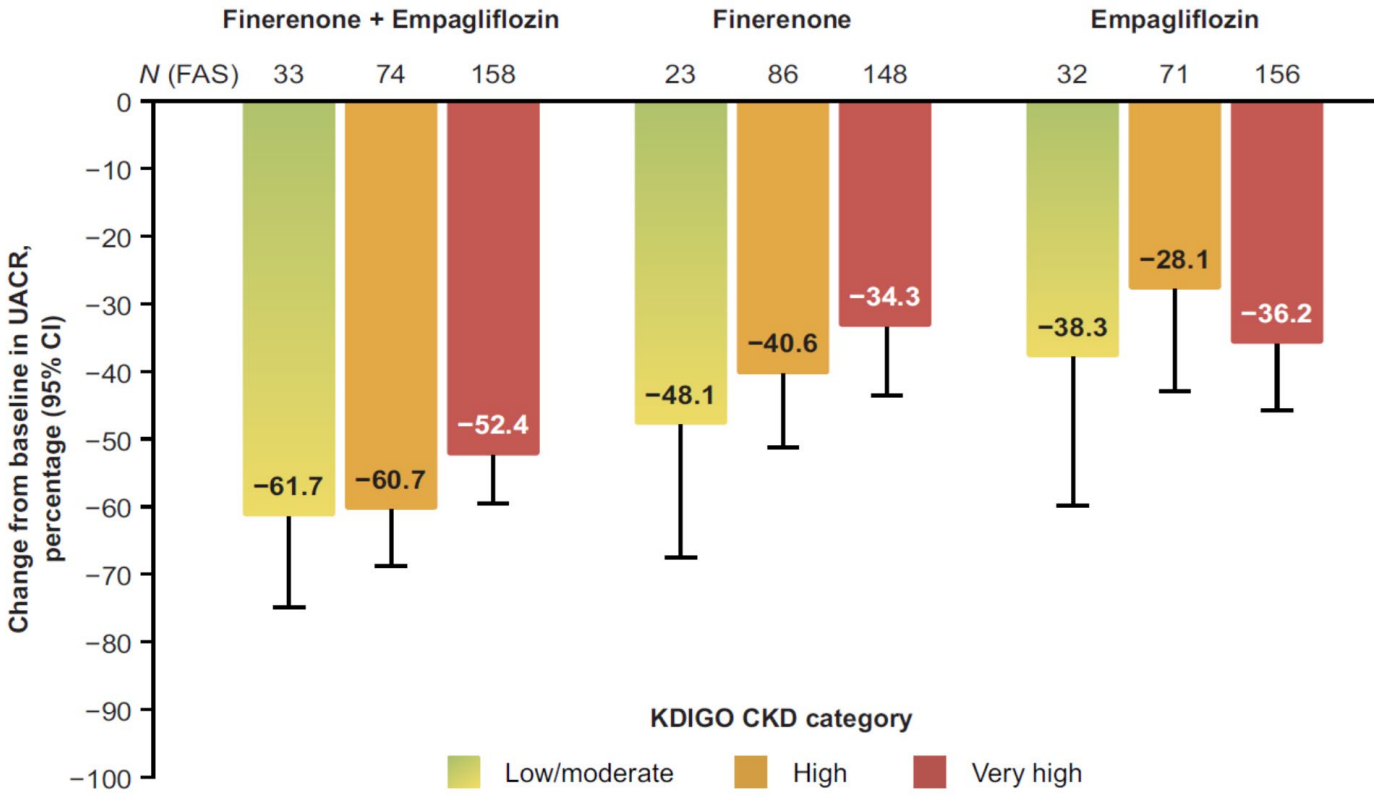


Ostrominski JW et al. JASN 2025

Nephroprotection by Finerenone is higher (NS) at early stages of CKD

Simultaneous initiation of finerenone and empagliflozin across the spectrum of kidney risk in the CONFIDENCE trial

RCT to compare combination of finerenone and empagliflozin with each single drug on ACR decline at 6 months in 800 patients with DKD (eGFR, 30-90 ml/min/1.73 m2 and ACR 100-5000 mg/g).



Nephrol Dial Transplant, 2025, **0**, 1–10
https://doi.org/10.1093/ndt/gfaf160

The U.S.A. Approach to Win the War against DKD

- ✓ **U**se albuminuria testing to timely identify, treat and monitor high-risk patients
- ✓ **S**GLT2-i as soon as possible
- ✓ **A**dd soon finerenone and/or semaglutide (to be preferred in high BMI) if albuminuria is still high