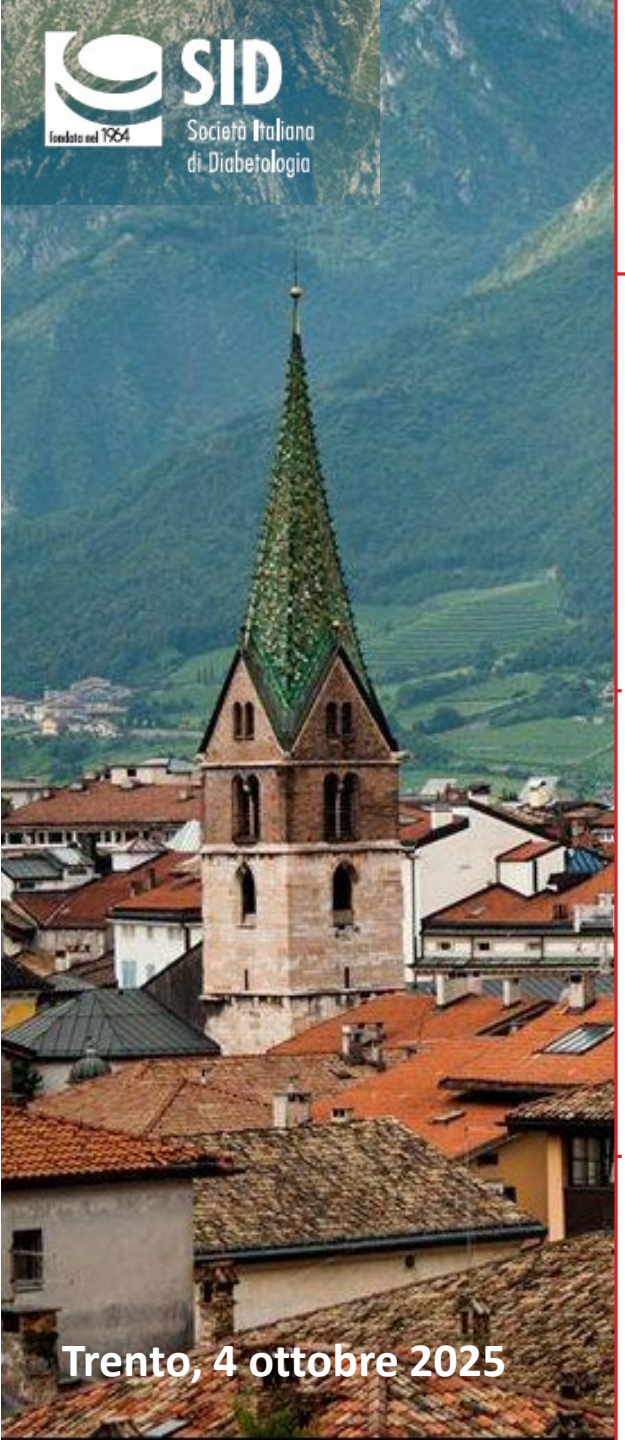


CONVEGNO SID
VENETO - TRENTINO ALTO ADIGE

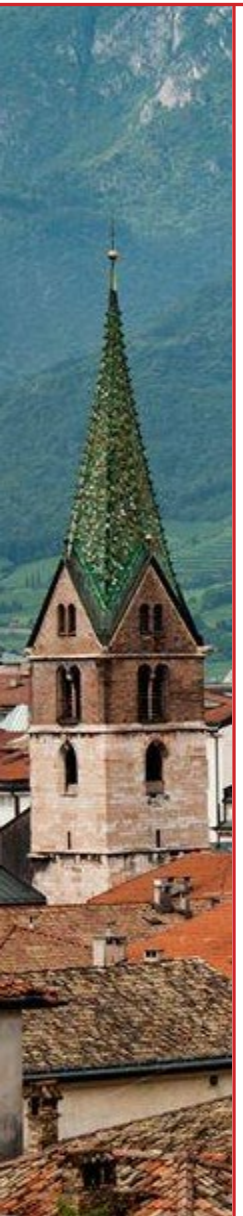
Nuove opportunità terapeutiche e impatto sugli ENDPOINT EPATICI, CARDIOVASCOLARI e RENALI nel DIABETE TIPO 2

Le opzioni terapeutiche della CKD nel diabete: come metterle in fila?

Mauro Rigato, MD, PhD

UOC Malattie Endocrine, del Ricambio e della Nutrizione
Azienda ULSS 2 della Marca Trevigiana

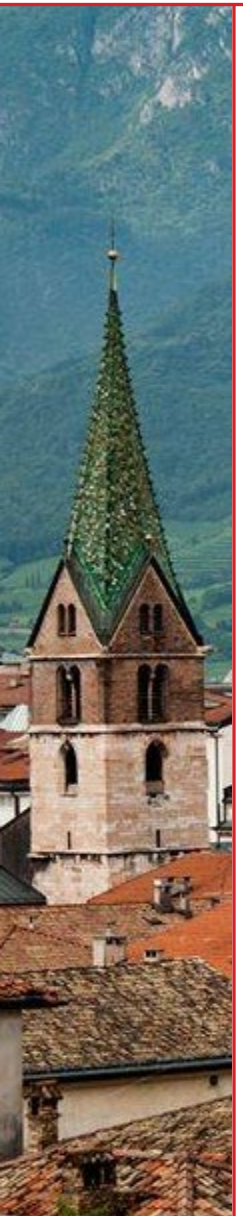
Disclosure



Il sottoscritto Rigato Mauro dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

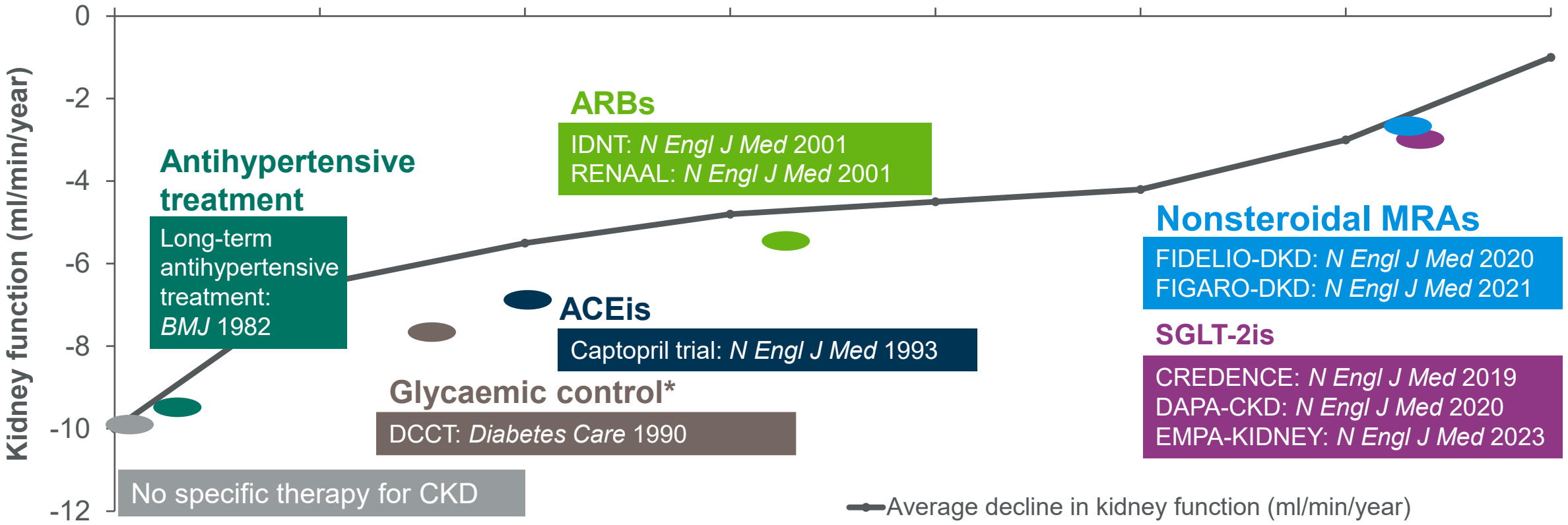
- Eli Lilly

Agenda



- Evoluzione della terapia per CKD nel DM
- Linee guida attuali
- Opzioni terapeutiche disponibili
- Approccio sequenziale o associazione simultanea?

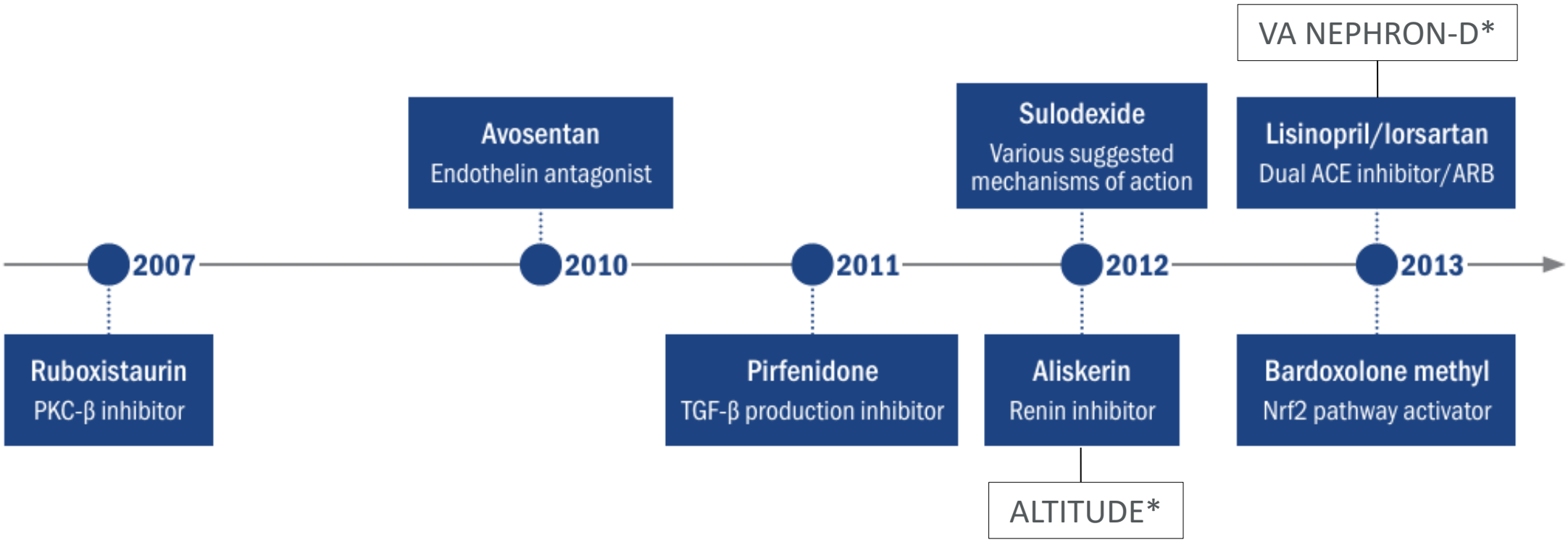
Evoluzione delle terapie in grado di ridurre la progressione della CKD e il rischio CV negli ultimi 40 anni



Recent findings on the cardiorenal benefits of finerenone and SGLT-2is have changed the therapeutic landscape for CKD and T2D

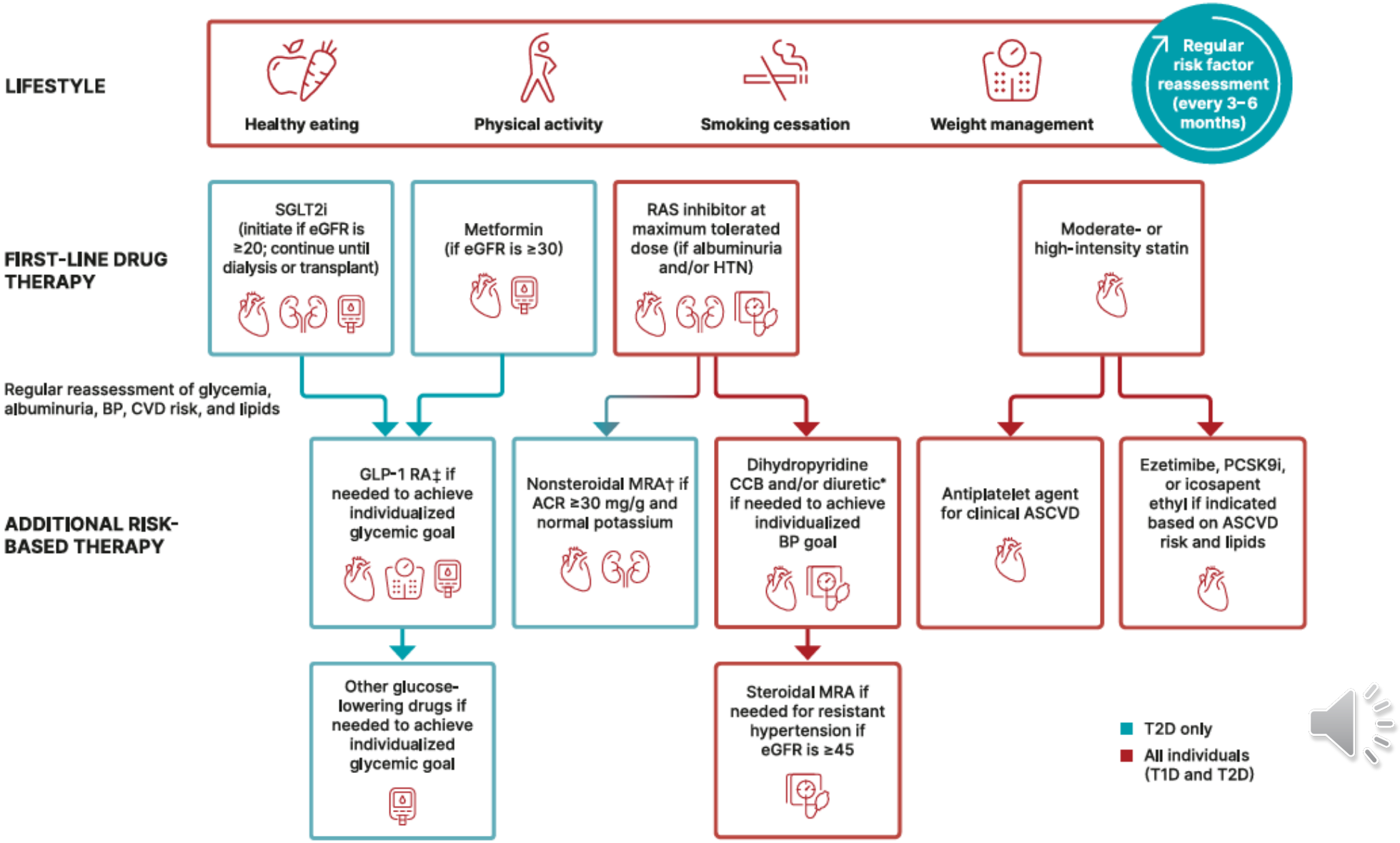
Naaman SC & Bakris GL. In: Chronic Kidney Disease and Type 2 Diabetes. American Diabetes Association; 2021. p28–32

Insuccessi terapeutici

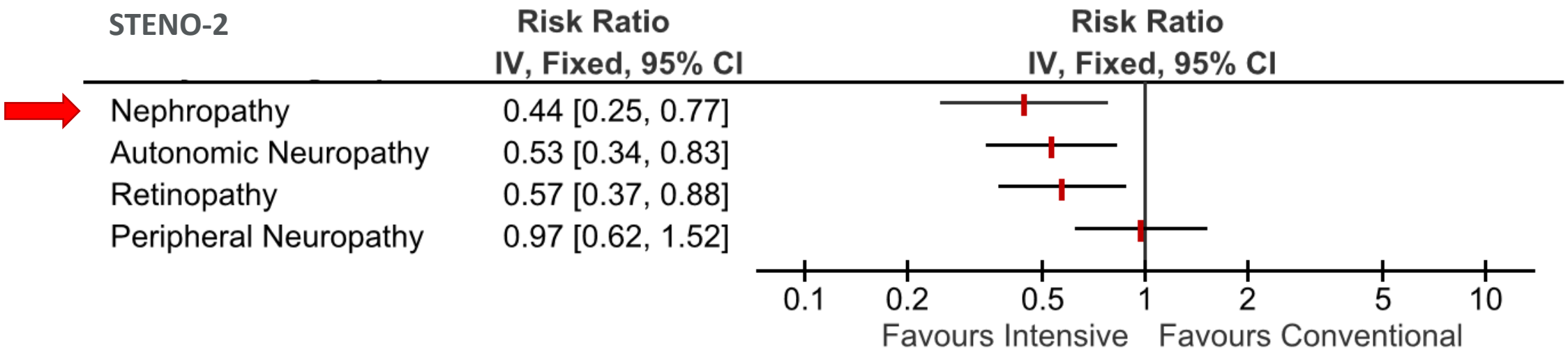


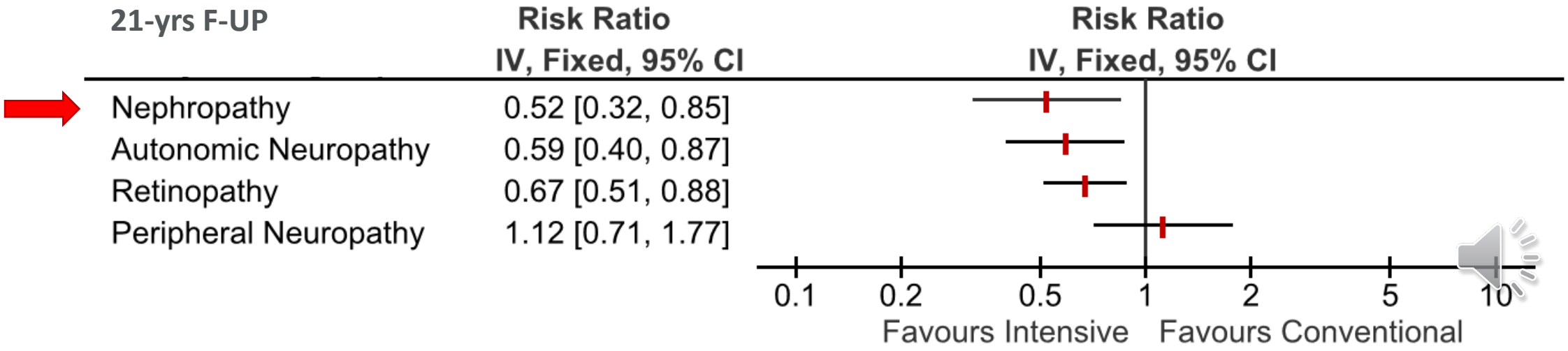
*iperpotassiemia, ipotensione, AKI

Linee guida (KDIGO 2022, ADA 2025)



Approccio multi-fattoriale





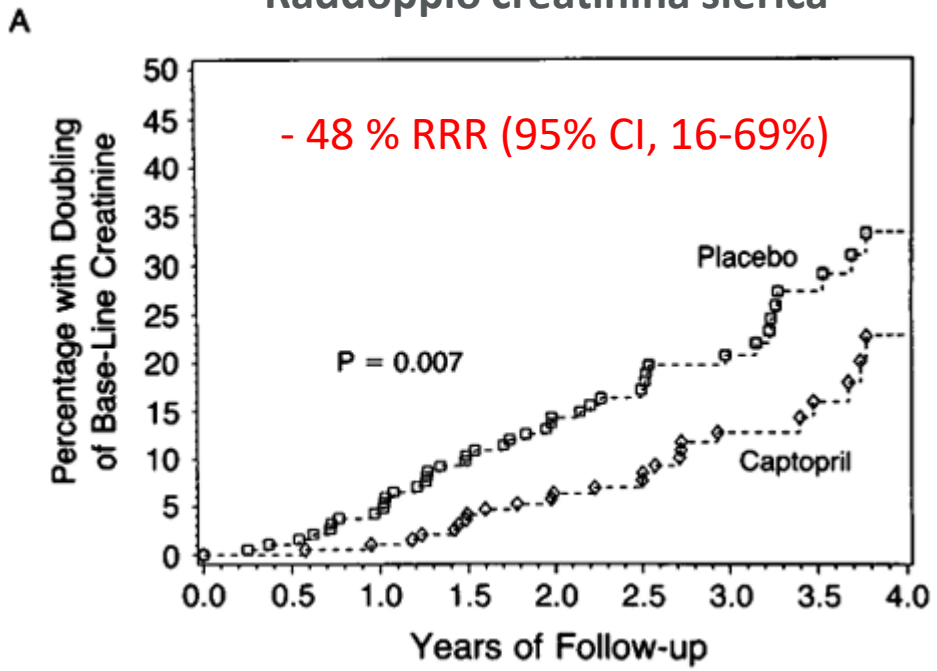
ACE-Inibitori

THE NEW ENGLAND JOURNAL OF MEDICINE Nov. 11, 1993

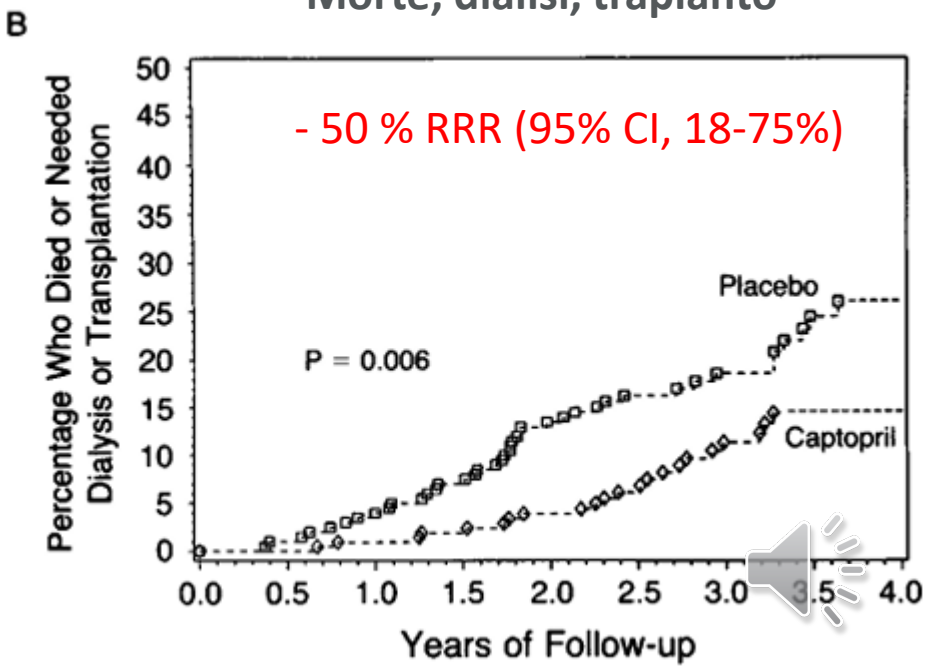
THE EFFECT OF ANGIOTENSIN-CONVERTING–ENZYME INHIBITION ON DIABETIC NEPHROPATHY

EDMUND J. LEWIS, M.D., LAWRENCE G. HUNSICKER, M.D., RAYMOND P. BAIN, PH.D., AND RICHARD D. ROHDE, B.S., FOR THE COLLABORATIVE STUDY GROUP*

Raddoppio creatinina sierica

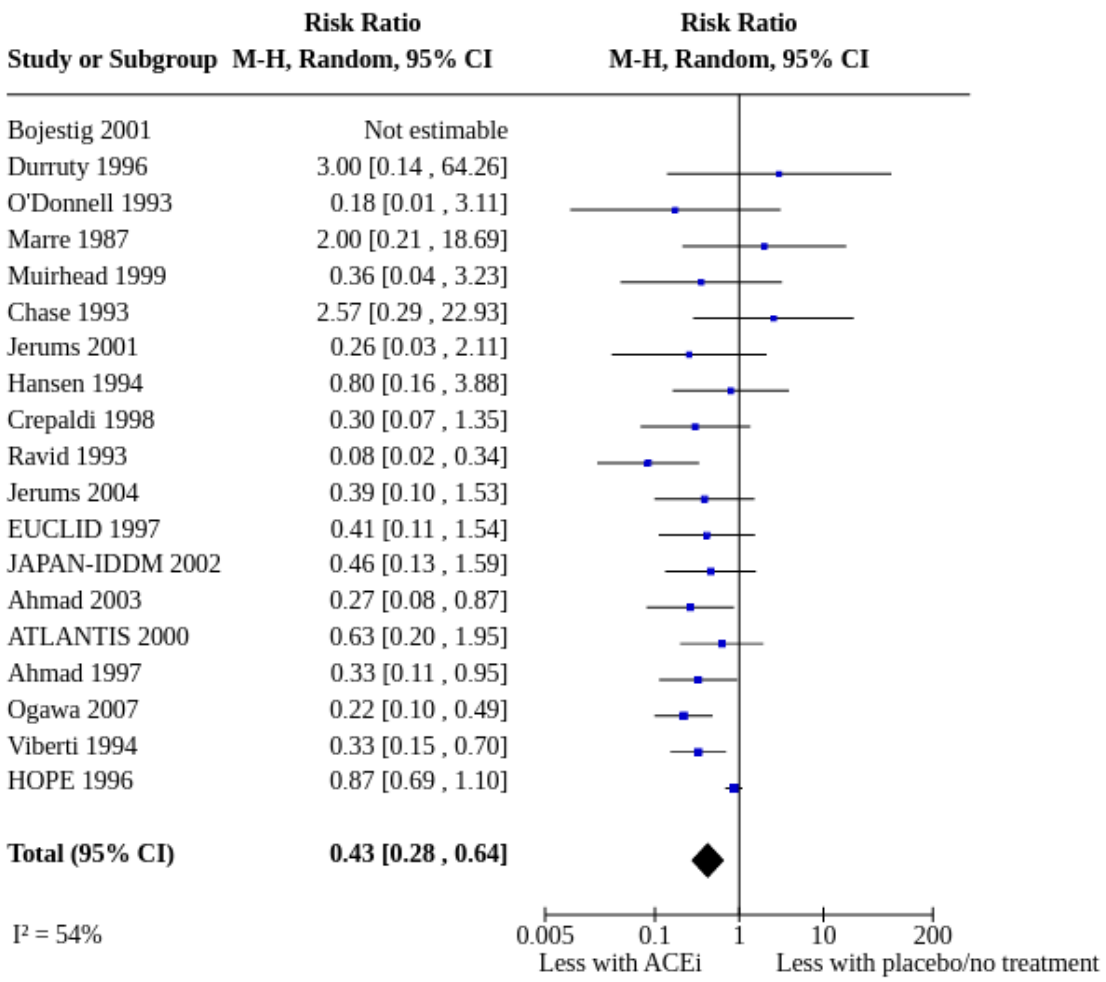


Morte, dialisi, trapianto

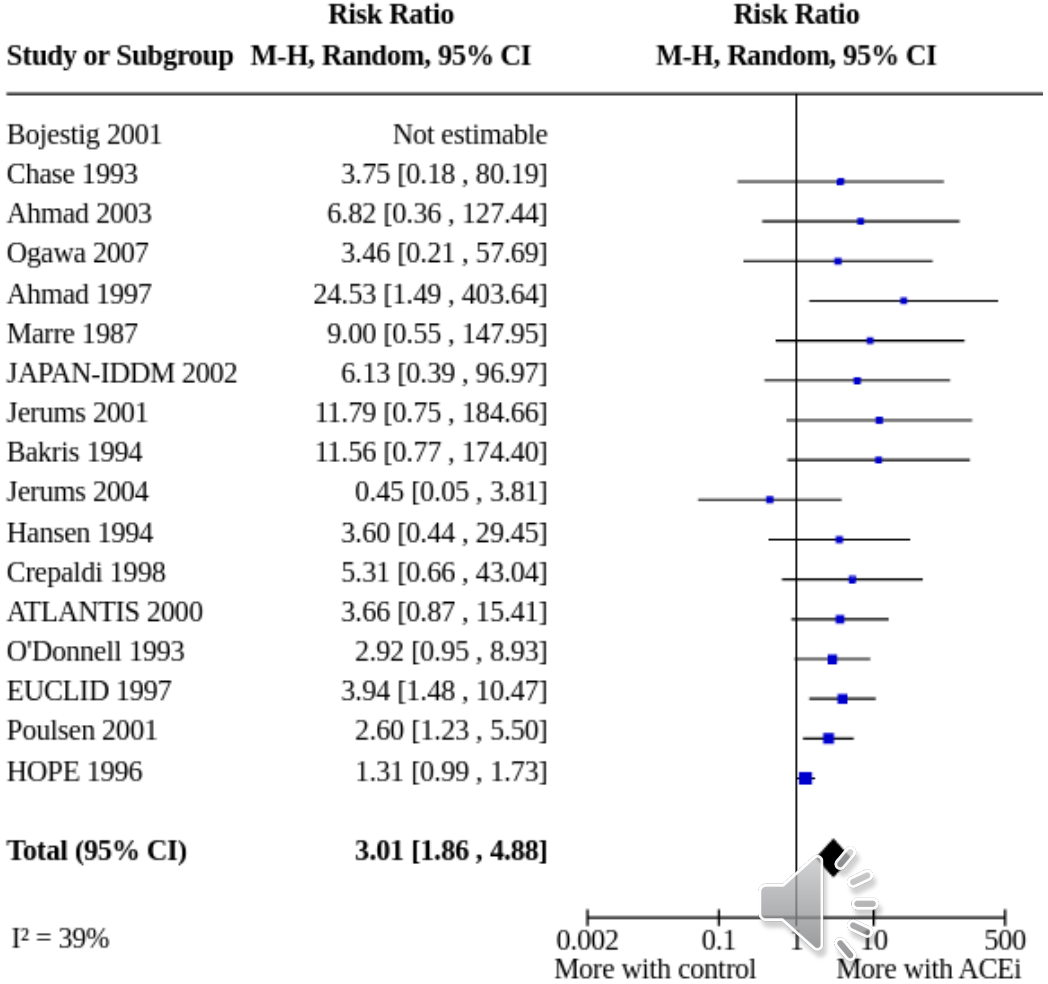


ACE-Inibitori

MICRO-TO MACROALBUMINURIA



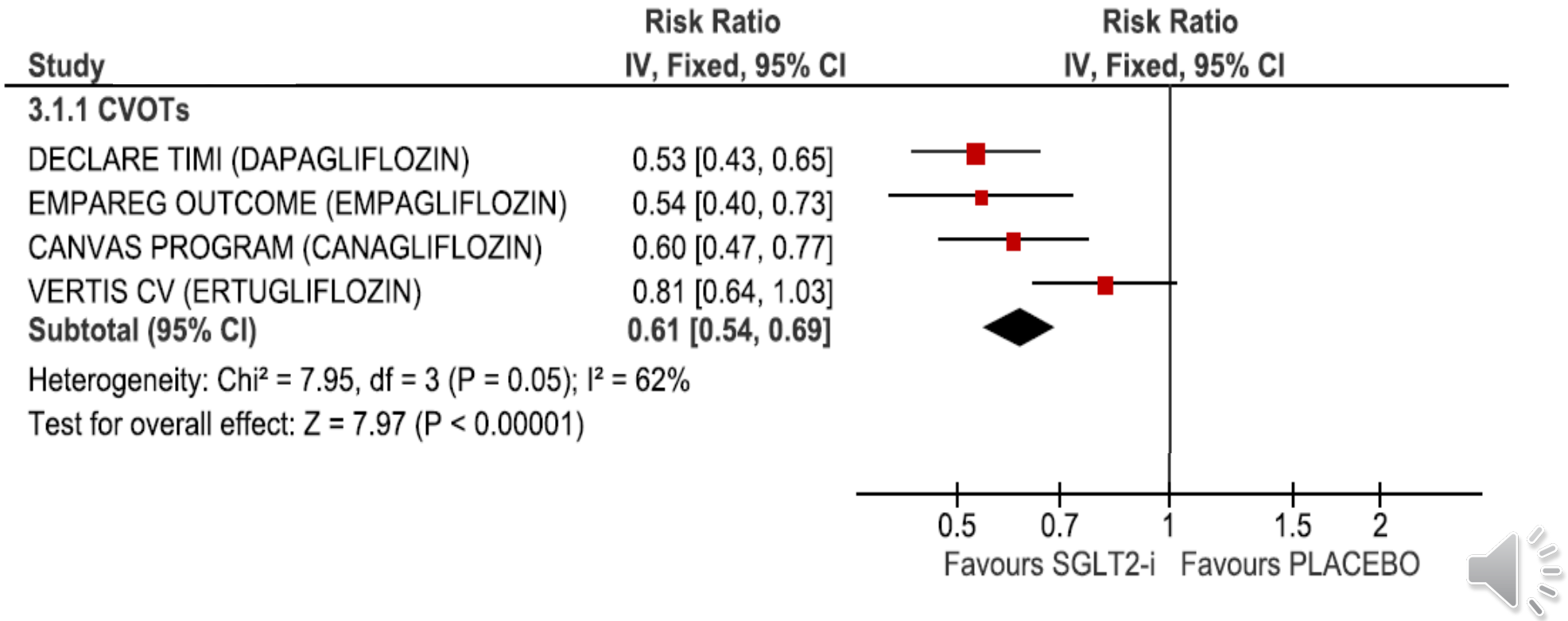
MICRO-TO NORMOALBUMINURIA



Natale et al. Cochrane Database Syst Rev. 2024 Apr 29;4(4):CD006257

SGLT-2 inibitori

Renal secondary outcomes of CVOT



SGLT-2 inibitori

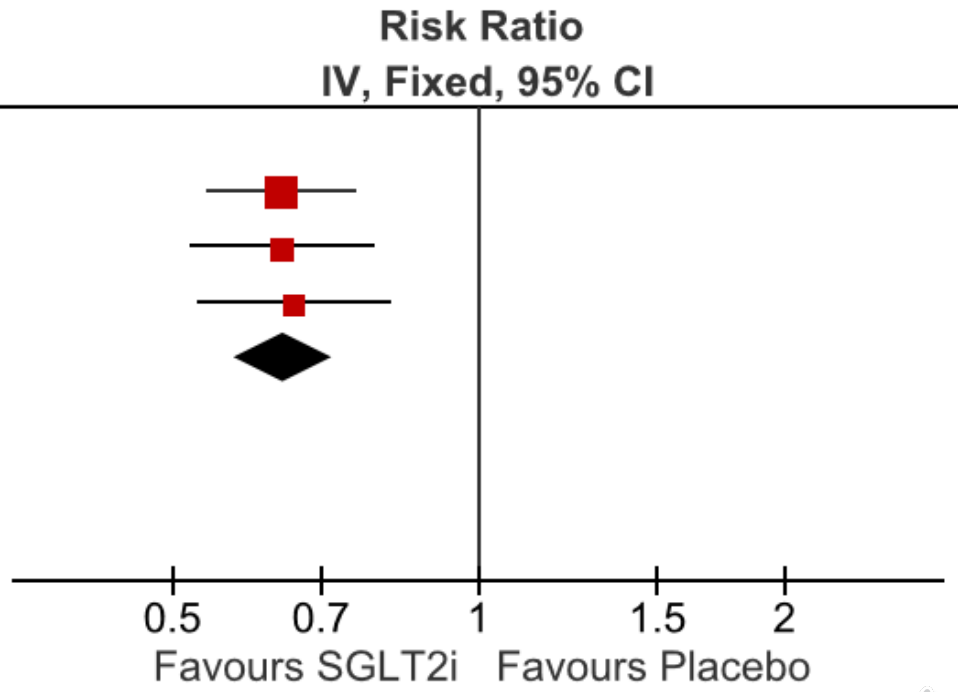
Background
Ace-I or ARBs
85-100%

Renal Outcomes Trials

Study or Subgroup	Risk Ratio IV, Fixed, 95% CI
1.1.1 CKD progression	
EMPA-KIDNEY	0.64 [0.54, 0.76]
DAPA-CKD	0.64 [0.52, 0.79]
CREDENCE	0.66 [0.53, 0.82]
Subtotal (95% CI)	**0.65 [0.58, 0.72]**

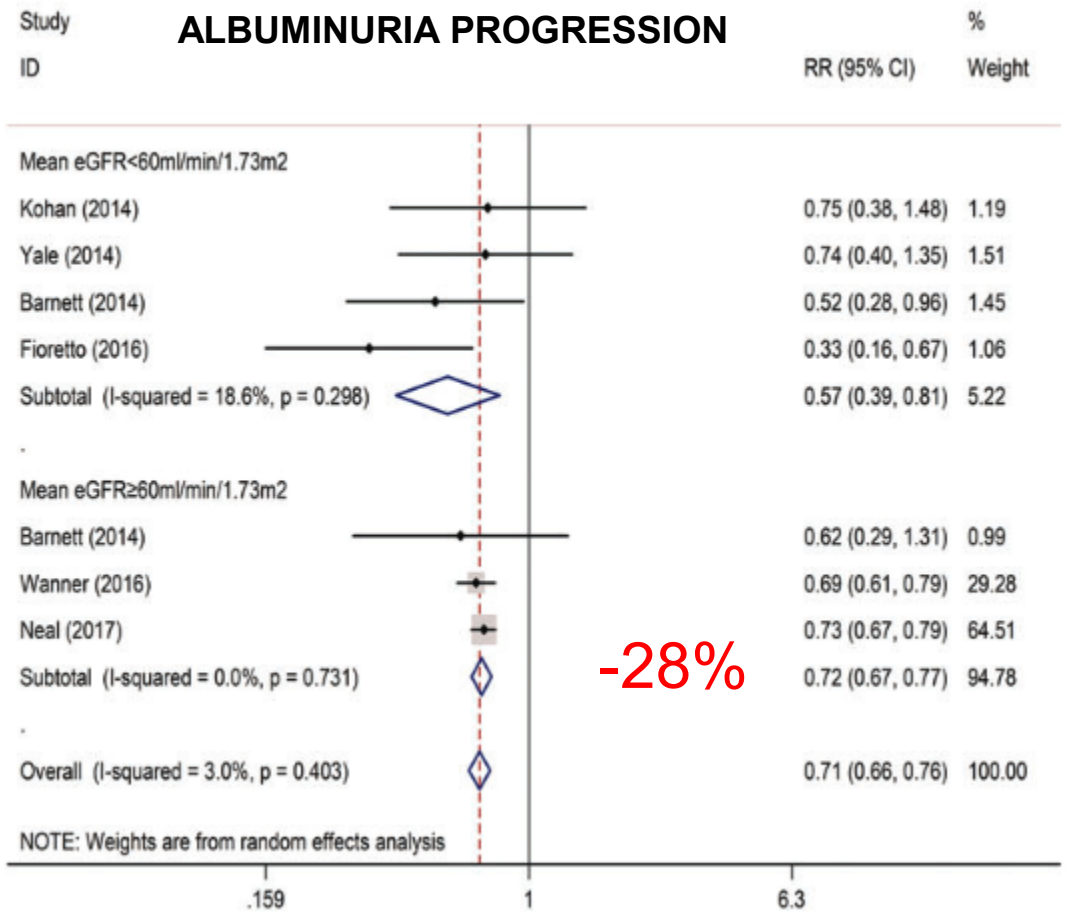
Heterogeneity: Chi² = 0.06, df = 2 (P = 0.97); I² = 0%

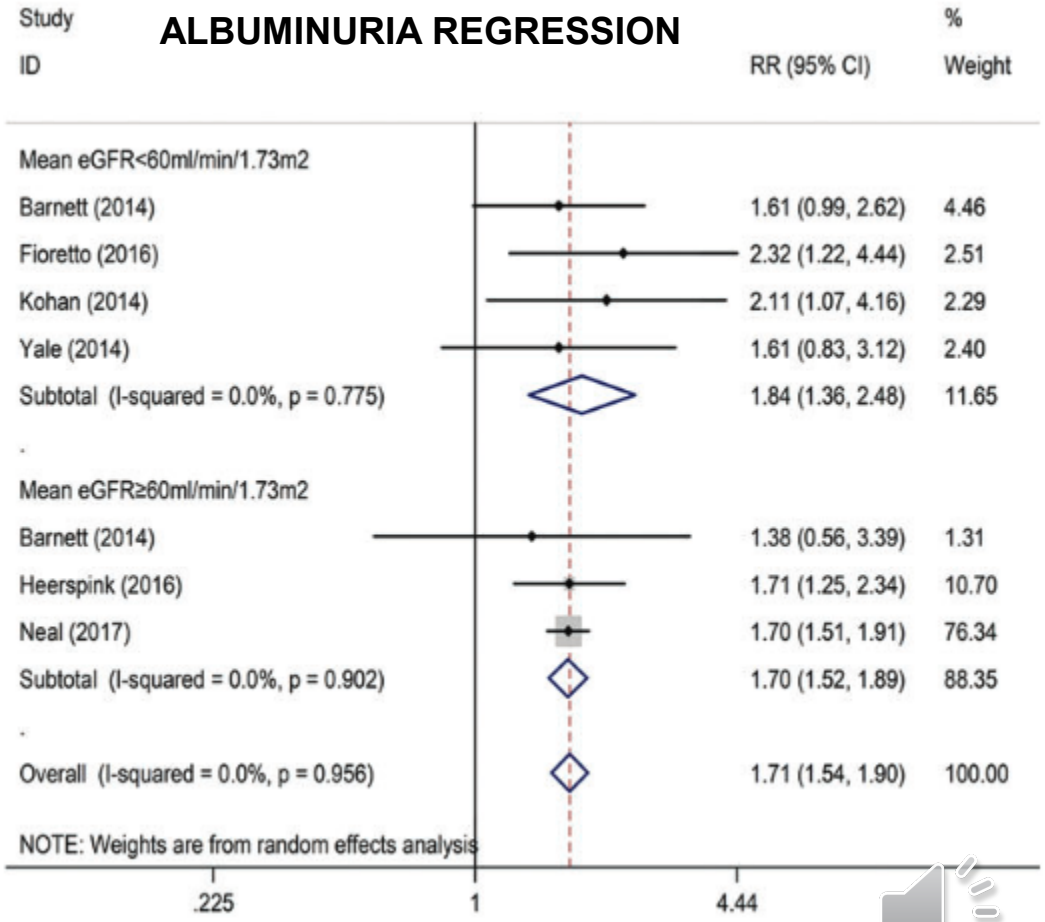
Test for overall effect: Z = 7.62 (P < 0.00001)



CREDENCE: ESRD (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes
DAPA-CKD: sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes
EMPA-KIDNEY: progression of kidney disease (defined as ESRD, a sustained decrease in eGFR to <10 ml per minute per 1.73 m2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

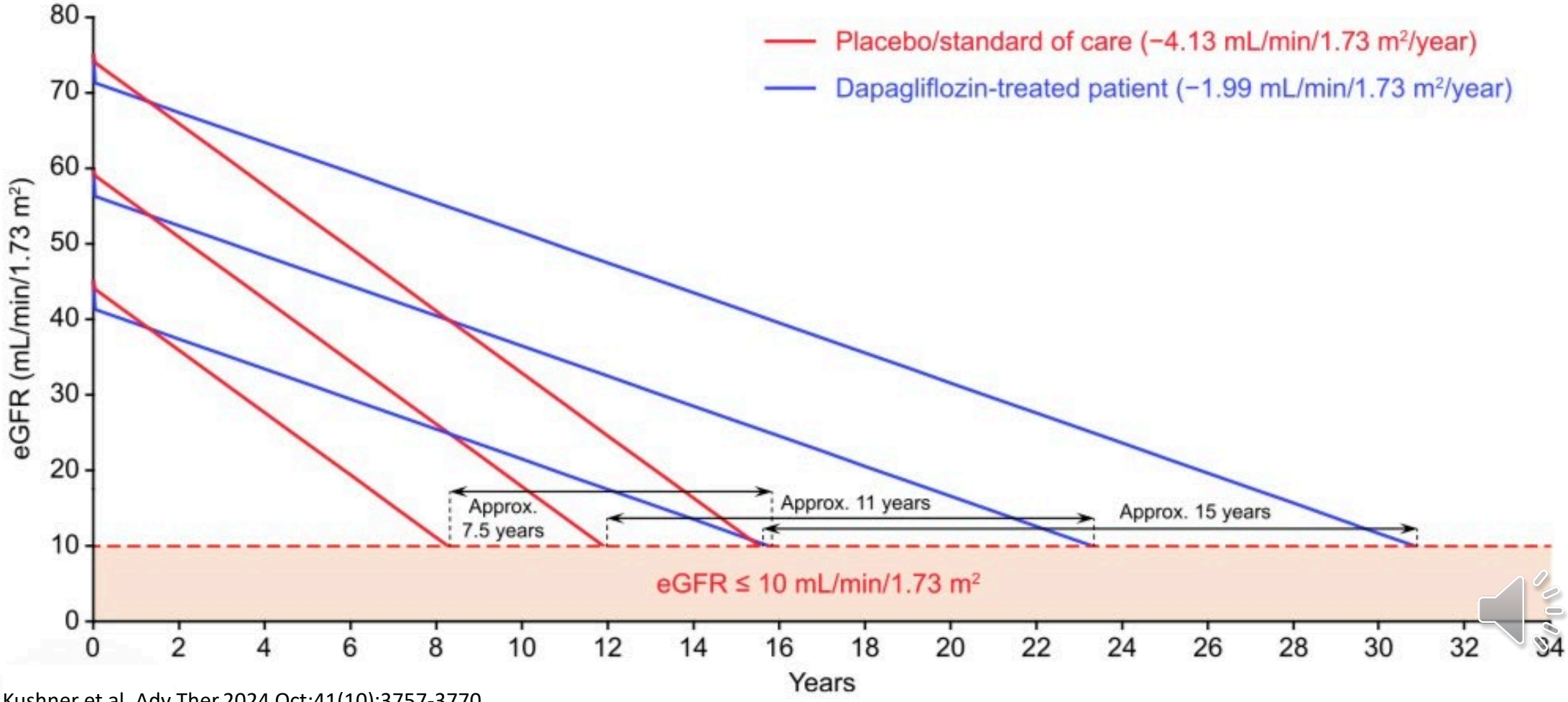
SGLT-2 inibitori: UACR





SGLT2 inibitori

L'IMPORTANZA DELL'INTERVENTO PRECOCE CON GLIFLOZINE



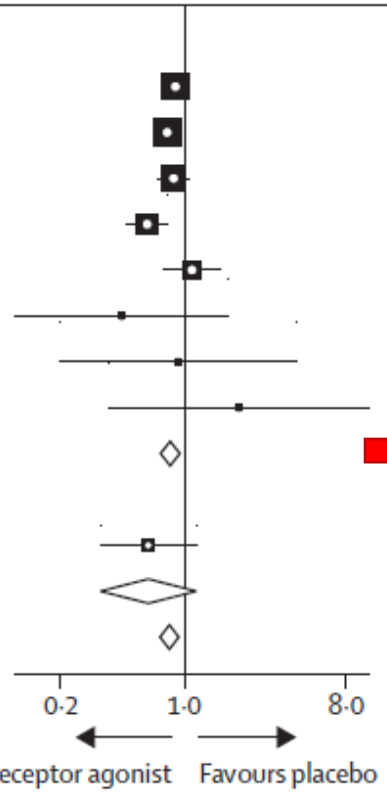
Kushner et al. Adv Ther.2024 Oct;41(10):3757-3770

GLP-1 RA

COMPOSITE OF KIDNEY OUTCOME*

	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	Weight (%)
With diabetes				
EXSCEL[40]	246/6459 (3·8%)	273/6466 (4·2%)	0·88 (0·74–1·05)	25·22%
FLOW[26]	218/1767 (12·3%)	260/1766 (14·7%)	0·79 (0·66–0·94)	24·94%
LEADER[24,33]	184/4668 (3·9%)	212/4672 (4·5%)	0·86 (0·70–1·05)	21·36%
REWIND[23,35]	84/4949 (1·7%)	136/4952 (2·7%)	0·61 (0·46–0·80)	14·08%
SUSTAIN-6[25,41]	58/1648 (3·5%)	57/1649 (3·5%)	1·09 (0·75–1·58)	8·94%
ELIXA[37]	3/2702 (0·1%)	7/2793 (0·3%)	0·44 (0·11–1·73)	0·77%
AMPLITUDE-O[39]	9/2717 (0·3%)	3/1359 (0·2%)	0·91 (0·20–4·19)	0·62%
Harmony Outcomes[38]	4/4731 (0·1%)	2/4732 (<0·1%)	2·00 (0·37–10·87)	0·51%
Subtotal	806/29 441 (2·7%)	950/28 389 (3·3%)	0·82 (0·73–0·93)	
Without diabetes				
SELECT[27,42]	17/8803 (0·2%)	27/8801 (0·3%)	0·62 (0·33–1·15)	3·56%
			0·62 (0·33–1·15)	
Overall	**823/38 244 (2·2%)**	**977/37 190 (2·6%)**	**0·81 (0·72–0·92)**	

With diabetes p<0·001, I^2=26·41%
Without diabetes p=0·13
Overall p<0·001, I^2=23·11%
Heterogeneity by diabetes status p=0·38



*Composite of: kidney failure (kidney replacement therapy or a persistent eGFR <15 mL/min per 1·73 m²), a sustained reduction in eGFR by at least 50% or the nearest equivalent, or death from kidney failure.

Badve et al. Lancet Diabetes Endocrinol. 2025 Jan;13(1):15-28

Semaglutide: FLOW study

T2DM (n=3533) with **CKD**

- eGFR 50-75 ml/min and ACR > 300 e <5000 mg/g, or
- eGFR 25-50 ml and ACR > 100 e < 5000 mg/g

Randomization

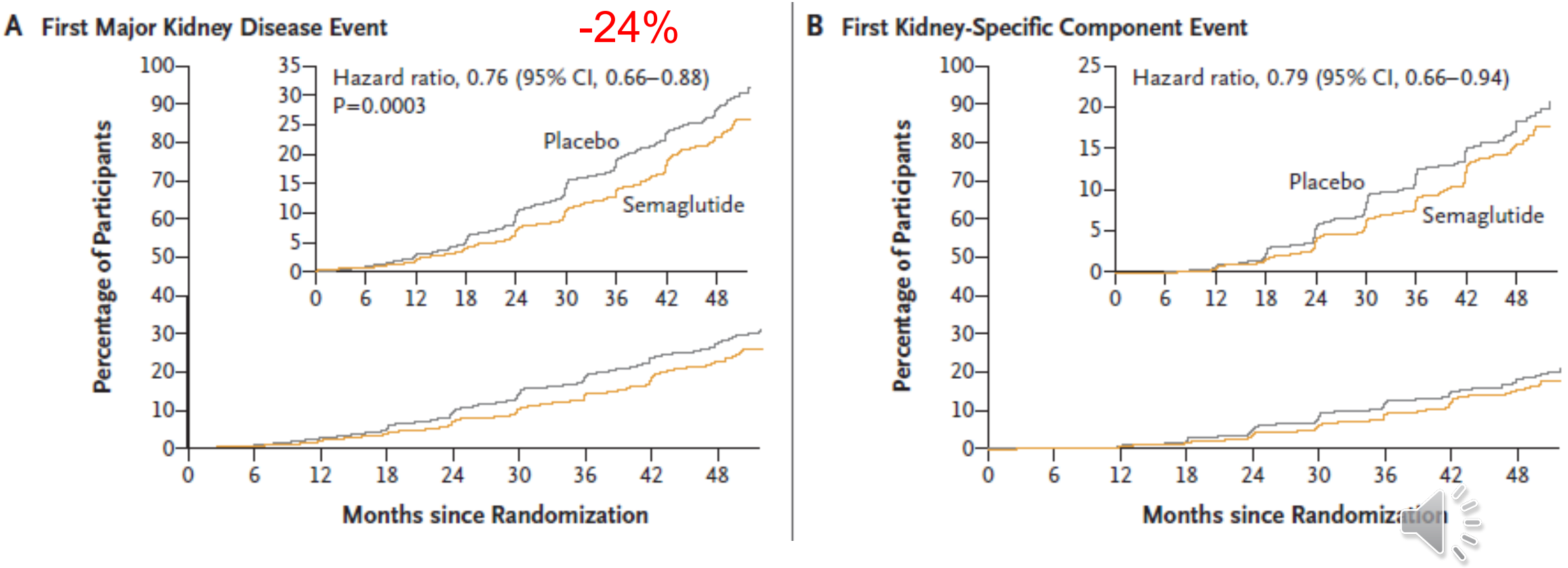
- Semaglutide s.c. 1 mg/week, or
- Placebo

Primary Outcome: First major kidney disease event

Composite of the onset of kidney failure (dialysis, transplantation, or an eGFR of <15 ml per minute per 1.73 m2), at least a 50% reduction in the eGFR from baseline, or death from kidney-related or cardiovascular causes.

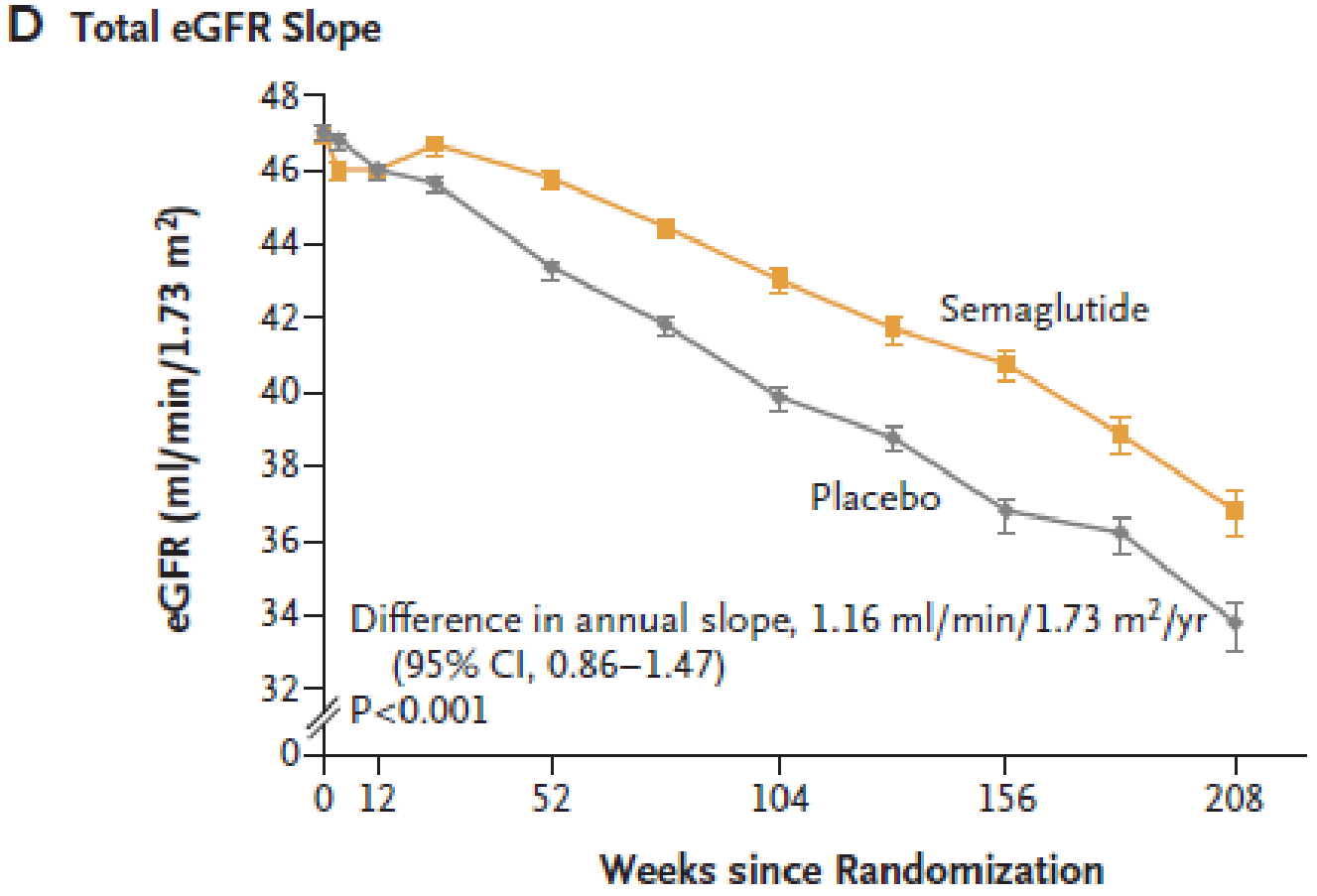
FLOW study

95% on Ace-I or ARB
15% on SGLT-2i



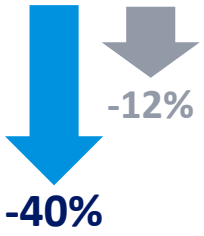
Perkovic et al. N Engl J Med. 2024 Jul 11;391(2):109-121.

FLOW study: eGFR decline



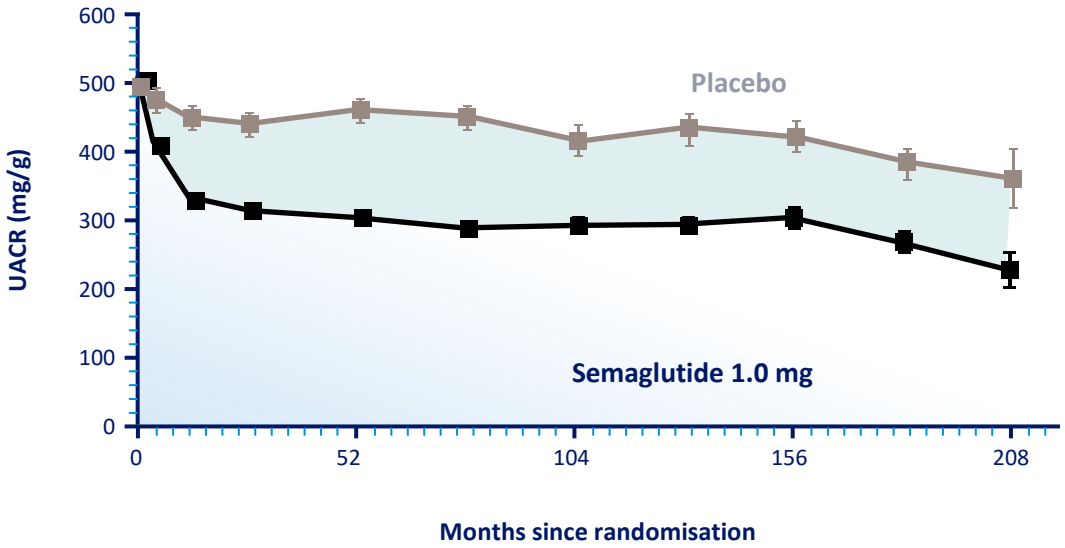
Perkovic et al. N Engl J Med. 2024 Jul 11;391(2):109-121.

FLOW study: UACR



Greater reduction in UACR in the semaglutide group for a between-group difference of 32% (95% CI: [0.62; 0.75])[1†]

OW s.c. semaglutide 1.0 mg versus placebo in addition to SoC at Week 104

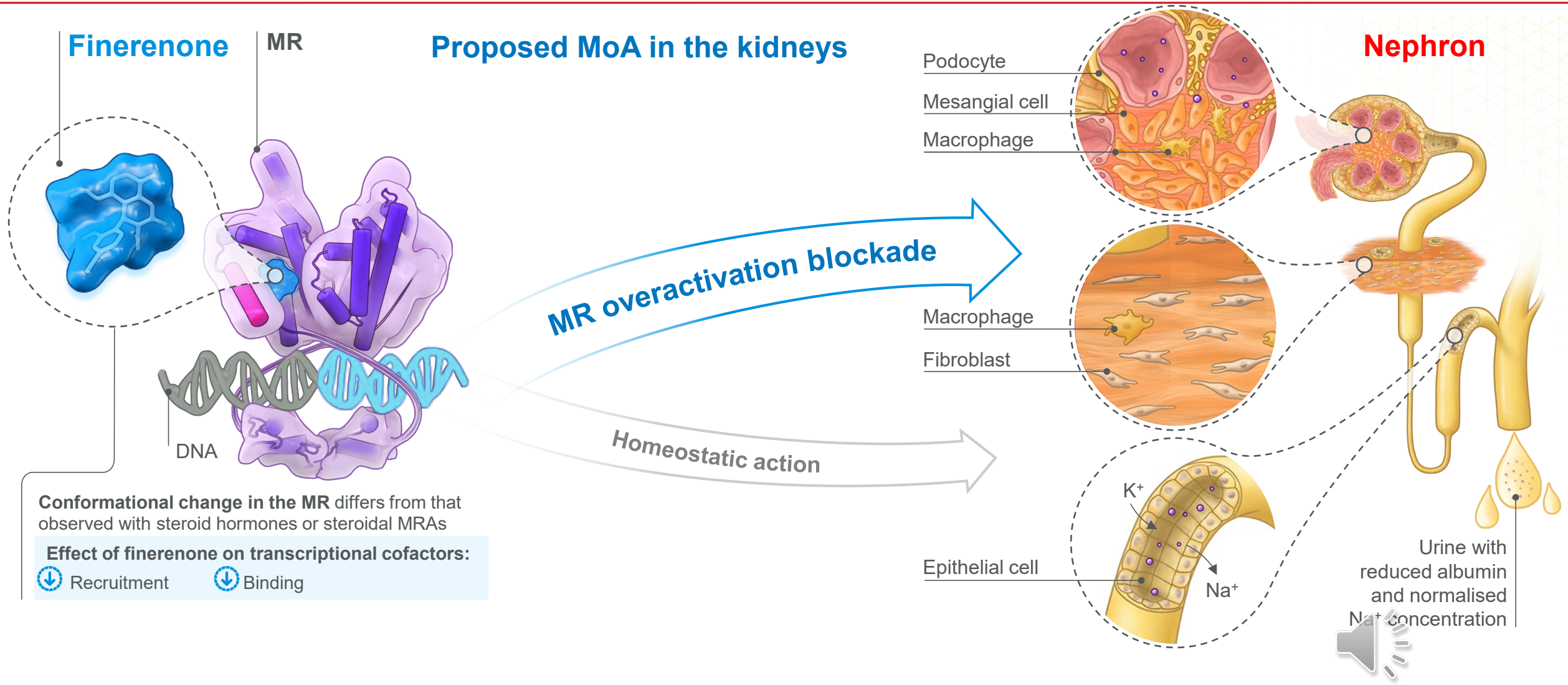


**Full analysis set. Data from the in-trial period. †Error bars are +/- standard error of the mean. Mean estimates are from an ANCOVA with treatment and use of SGLT-2 inhibitor (yes/no) at baseline as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and includes baseline value as a covariate and use of SGLT-2 inhibitor (yes/no) at baseline as a fixed factor and was fitted to all subjects with a measurement regardless of treatment status at Week 104. The fitted model was used to impute values for subjects with missing data at Week 104. The ratio to baseline and the corresponding baseline value were log-transformed prior to analysis. The complete datasets were analysed and the results combined using Rubin's Rules. Mean estimates were adjusted according to observed baseline distribution. The geometric mean at baseline for subjects contributing to the analysis was 494.84 mg/g.*

CI, confidence interval; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; OW, once weekly; s.c., subcutaneous; SGLT-2, sodium/glucose cotransporter 2; SoC, standard of care; UACR, urine albumin-creatine ratio; T2D, type 2 diabetes.

1. Perkovic V, et al. Published online 6 May, 2024. N Engl J Med. DOI: 10.1056/NEJMoa2403347.

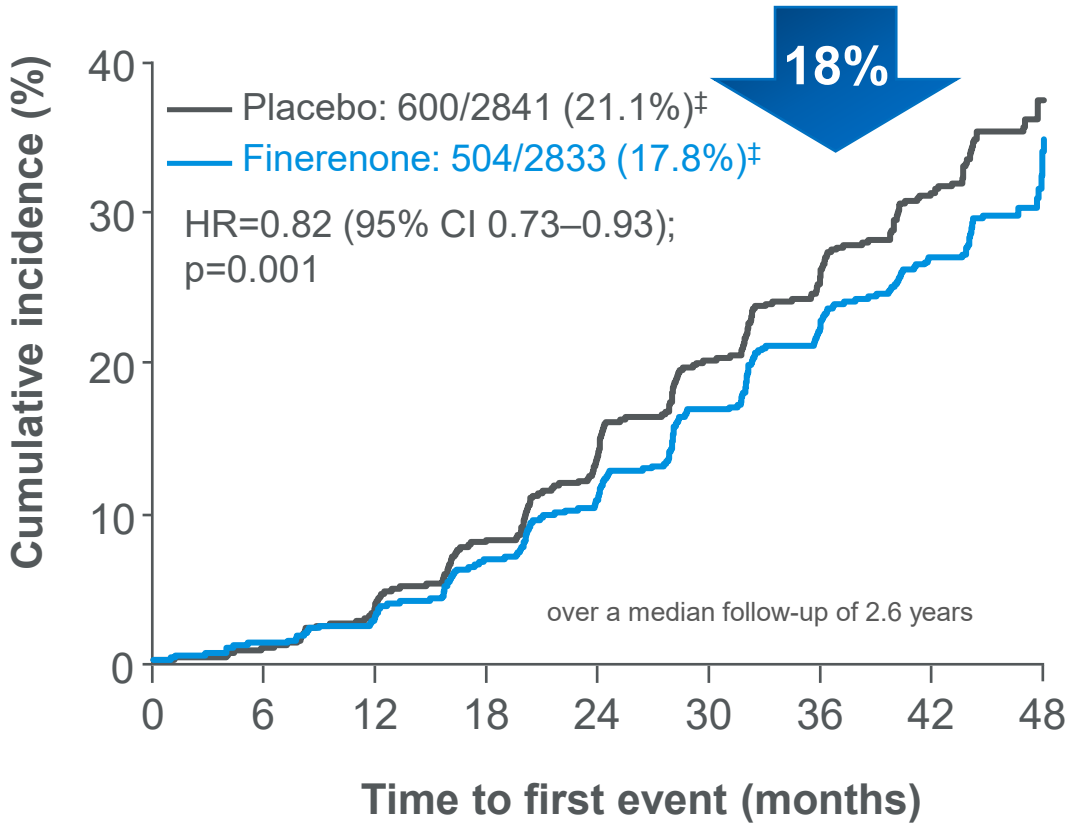
Finerenone: a novel, selective, nonsteroidal MRA



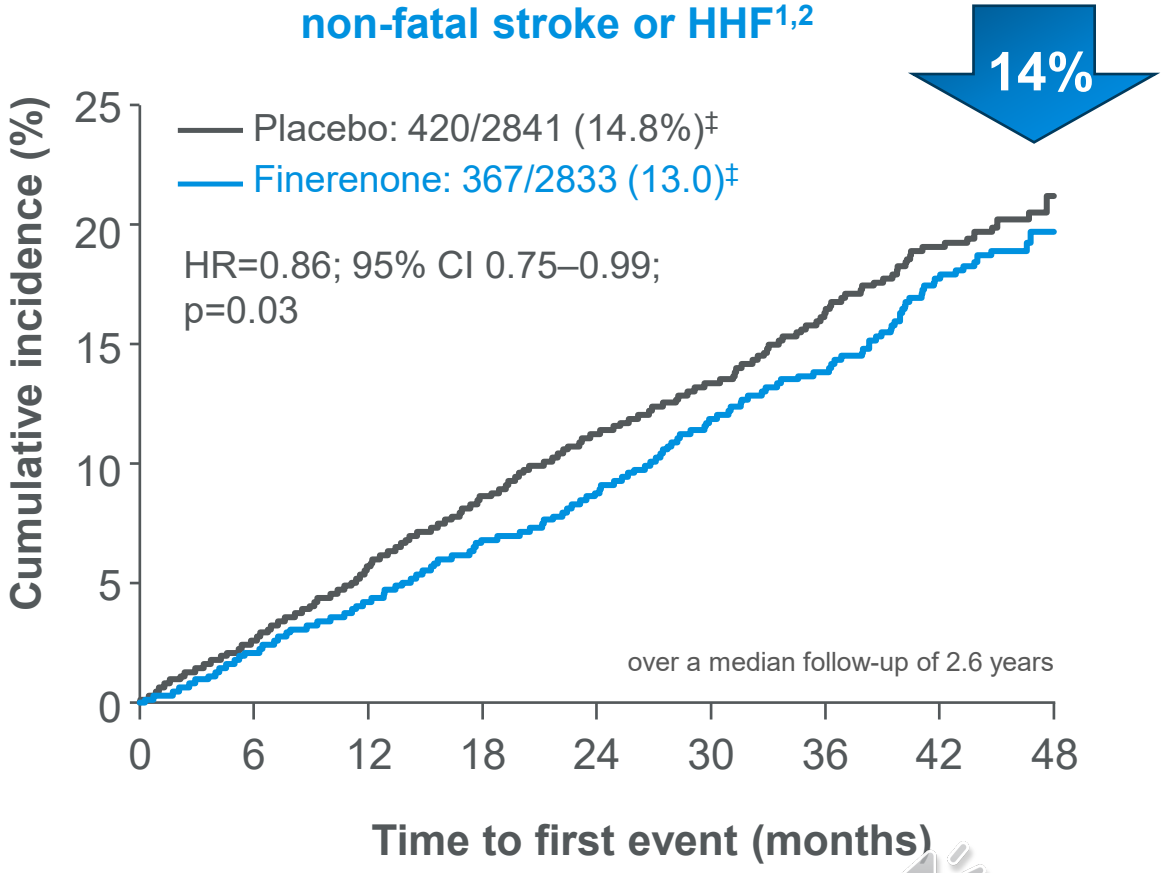
1. Kintscher U, *et al. Br J Pharmacol* 2021; doi:10.1111/bph.15747; 2. Agarwal R, *et al. Eur Heart J* 2021;42:152–162; 3. Amazit L, *et al. J Biol Chem* 2015;290:21876–21889;
4. Agarwal R, *et al. Nephrol Dial Transplant* 2020;37:1014–1023

FIDELIO-DKD

Kidney failure*, sustained ≥40% decrease in eGFR from baseline, or renal death#1



Time to CV death, non-fatal MI, non-fatal stroke or HHF1,2



*ESKD or an eGFR <15 mL/min/1.73 m^2; †Events were classified as renal death if: (1) the patient died; (2) KRT had not been initiated despite being clinically indicated; and (3) there was no other likely cause of death; ‡Number of patients with an event over a median of 2.6 years of follow-up.

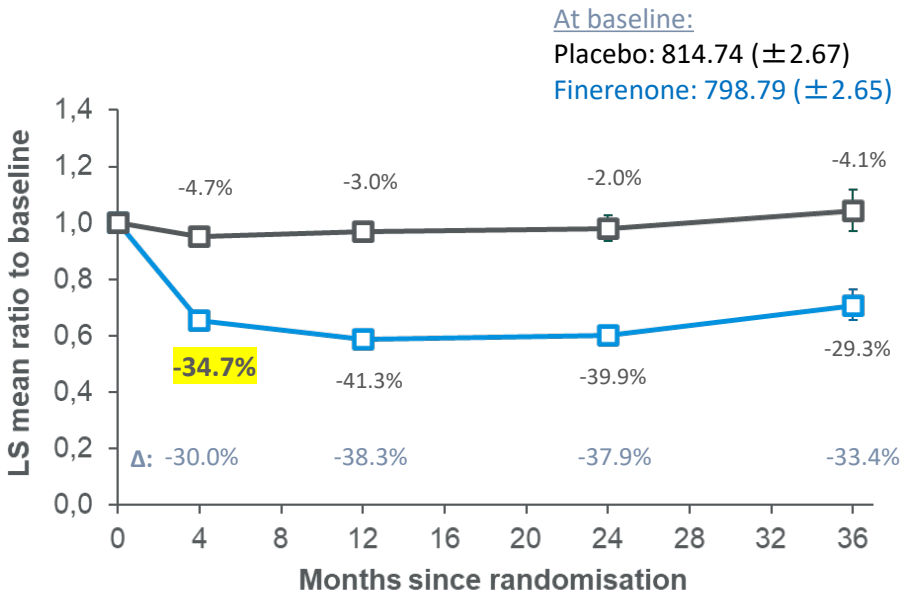
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HHF, hospitalization for heart failure; HR, hazard ratio; KRT, kidney replacement therapy; MI, myocardial infarction.

1. Bakris GL, et al. *N Engl J Med.* 2020;383:2219–2229; 2. Bakris GL, et al. *N Engl J Med.* 2020;383:2219–2229 (supplement).

FIDELIO-DKD

Finerenone reduces UACR starting from 4th months and worsening of eGFR overtime

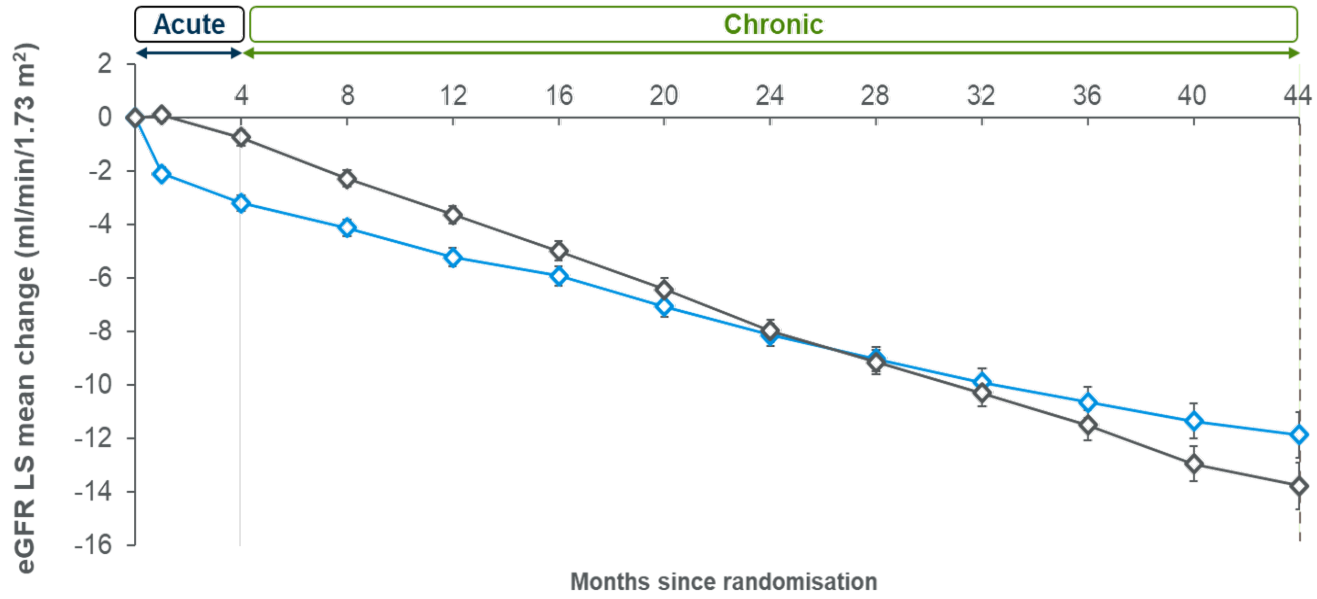
UACR



No. of patients				
Finerenone 2831	2582	1841	856
Placebo 2840	2598	1825	834

Ratio of least-squares mean change from baseline [Finerenone vs placebo]= **0.69; 95% CI 0.66–0.71**

eGFR



Finerenone	2799	2722	2613	1870	867	336
Placebo	2800	2720	2611	1846	844	339

At baseline:
Placebo: 44.3 (±12.6)
Finerenone: 44.4 (± 12.6)

→

Acute eGRF change:
Placebo: -0.73 (-1.03 to -0.44)
Finerenone: -3.18 (-3.44 to -2.91)

Chronic analysed eGRF change:
Placebo: -3.97 (-4.27 to -3.66)
Finerenone: -2.66 (-2.96 to -2.36)

Bakris et al., N Engl J Med 2020; doi: 10.1056/NEJMoa2025845

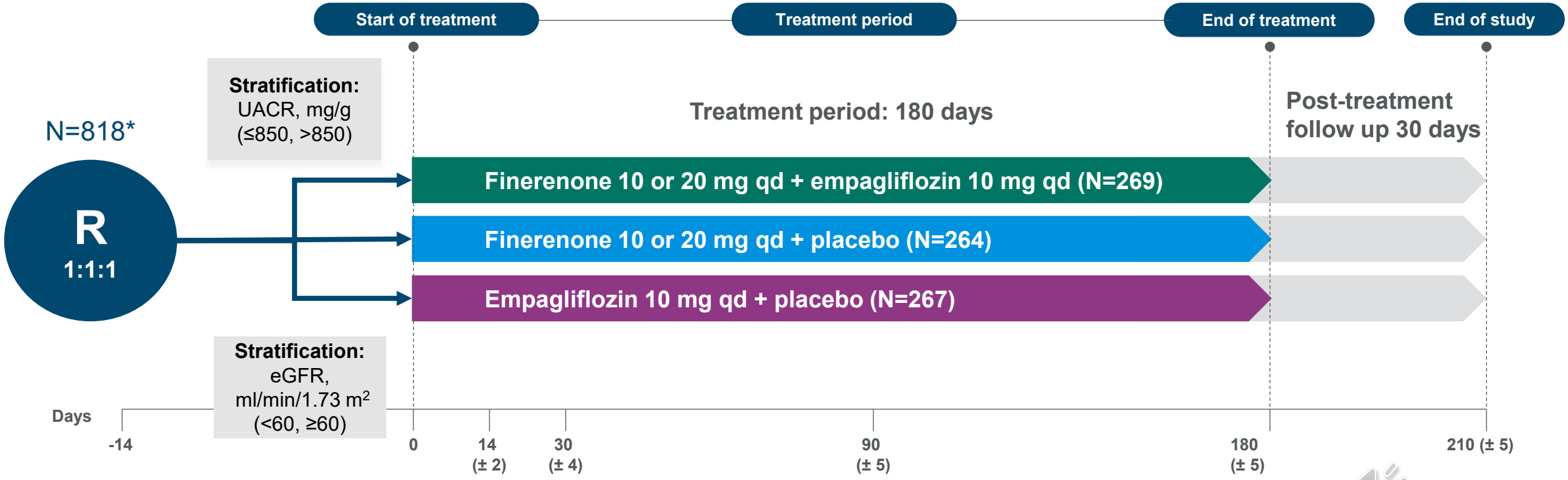
Finerenone: indicazioni AIFA

Pazienti adulti con DMT2 e malattia renale cronica (stadio 3 e 4 con albuminuria), in trattamento con ACEi/ARB alla massima dose tollerata e che presentino una delle seguenti condizioni:

1. Controindicazione o intolleranza agli inibitori SGLT2
2. Comprovata evidenza di persistente albuminuria e/o rapido declino funzionale renale (perdita di eGFR ≥3 mL/min/anno), nonostante il trattamento con inibitori SGLT2

CONFIDENCE TRIAL

Participants enrolled from 185 sites across multiple countries/regions: Belgium, Canada, Denmark, France, Germany, India, Israel, Italy, Japan, Republic of Korea, the Netherlands, Spain, Taiwan, and the USA



*Four participants underwent randomization twice in error and 14 participants from one site were excluded owing to historic violations of Good Clinical Practice guidelines not related to this study, and their data were not included. Therefore, 800 participants were included in the full analysis set for the efficacy analyses.[3]
eGFR, estimated glomerular filtration rate; qd, once daily; R, randomization; UACR, urine albumin-creatinine ratio.
1. Green JB, et al. *Nephrol Dial Transplant*. 2023;38:894–90. This figure is reproduced from Green JB, et al. under the terms of the Creative Commons Attribution-Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/); 2. NCT05254002. Available at: https://clinicaltrials.gov/study/NCT05254002; 3. Agarwal R, et al. *N Engl J Med*. 2025; doi:10.1056/NEJMoa2410659.

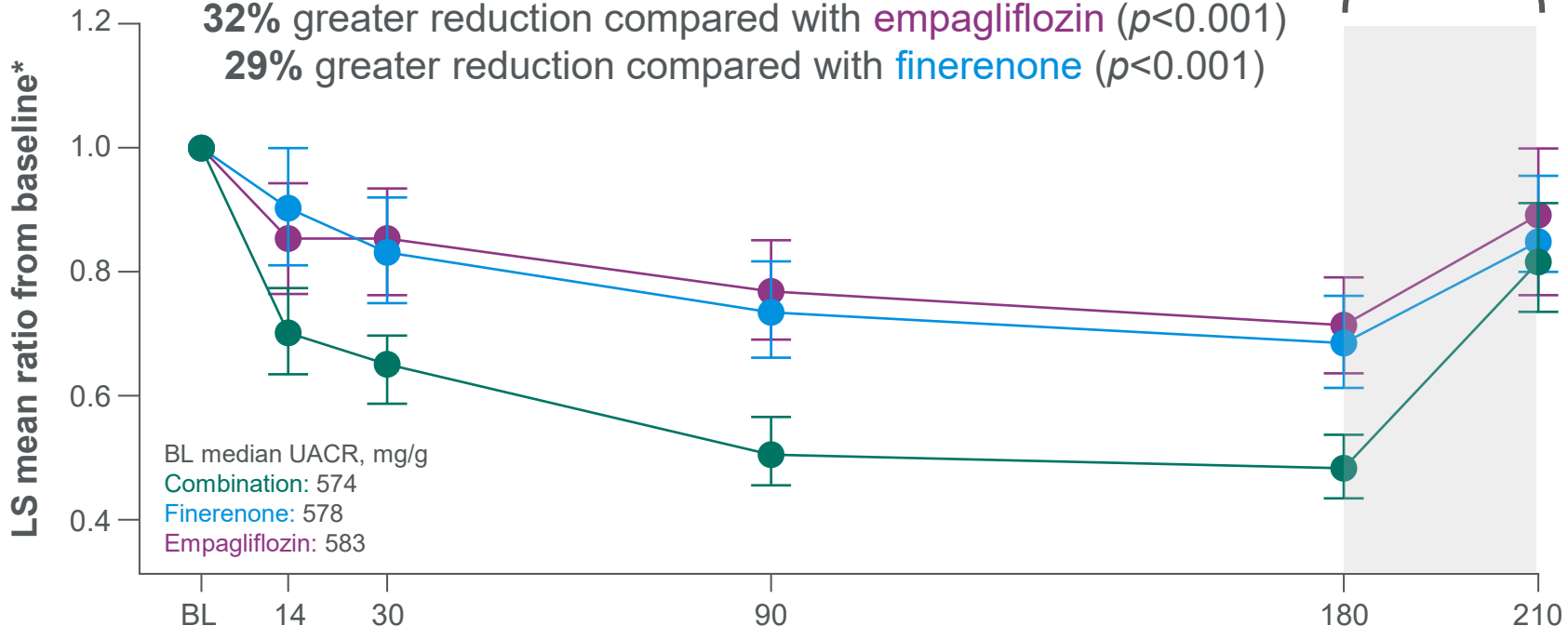
CONFIDENCE

Simultaneous initiation of finerenone and an SGLT-2i led to an additive reduction in UACR of up to 52% in T2DM with CKD

Primary endpoint:
UACR reduction with combination therapy at Day 180

32% greater reduction compared with empagliflozin ($p<0.001$)
29% greater reduction compared with finerenone ($p<0.001$)

30 days off-treatment



Patients, n						
Combination	265	248	253	248	240	238
Finerenone	258	247	248	237	236	227
Empagliflozin	261	254	252	246	238	232

LS mean ratio (95% CI)
0.68 (0.59–0.79)
0.71 (0.61–0.82)

A UACR reduction from baseline of **greater than 30%** was seen **within 14 days** of initiating combination therapy

*LS means (95% CI) for the ratio to baseline of UACR under "missing at random" in the full analysis set.
BL, baseline; CI, confidence interval; CKD, chronic kidney disease; LS, least-squares; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio.
Agarwal R, et al. *N Engl J Med.* 2025; doi:10.1056/NEJMoa2410659.

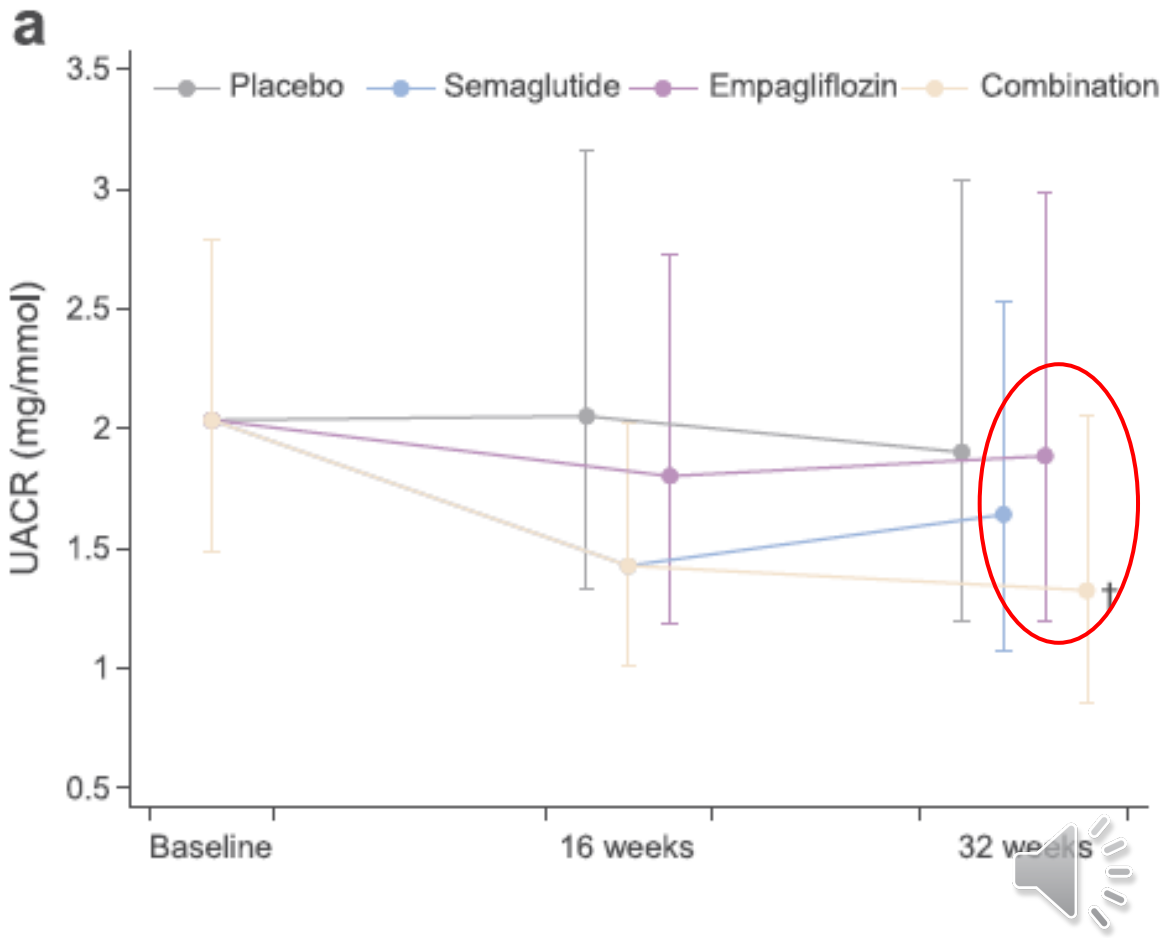
Sema+Empa vs singole molecole

- **120 pz con DMT2**
- **Alto rischio CV**

Randomizzati a:
- Semaglutide: open label
- Empagliflozin: double blind
- Combination Sema+Empa
- Placebo

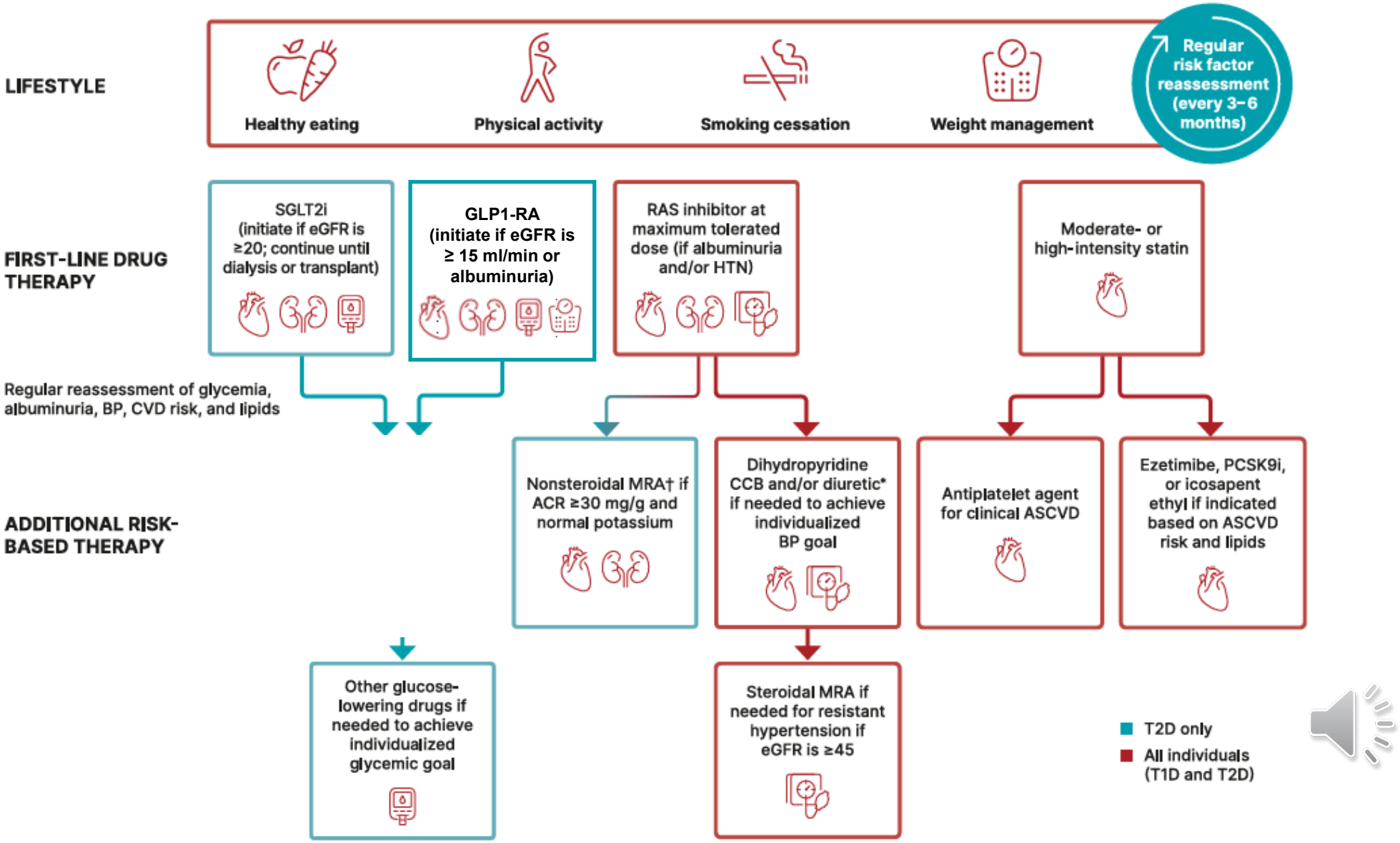
Primary outcomes
- Change in kidney oxigenation
- Change in arterial stiffness

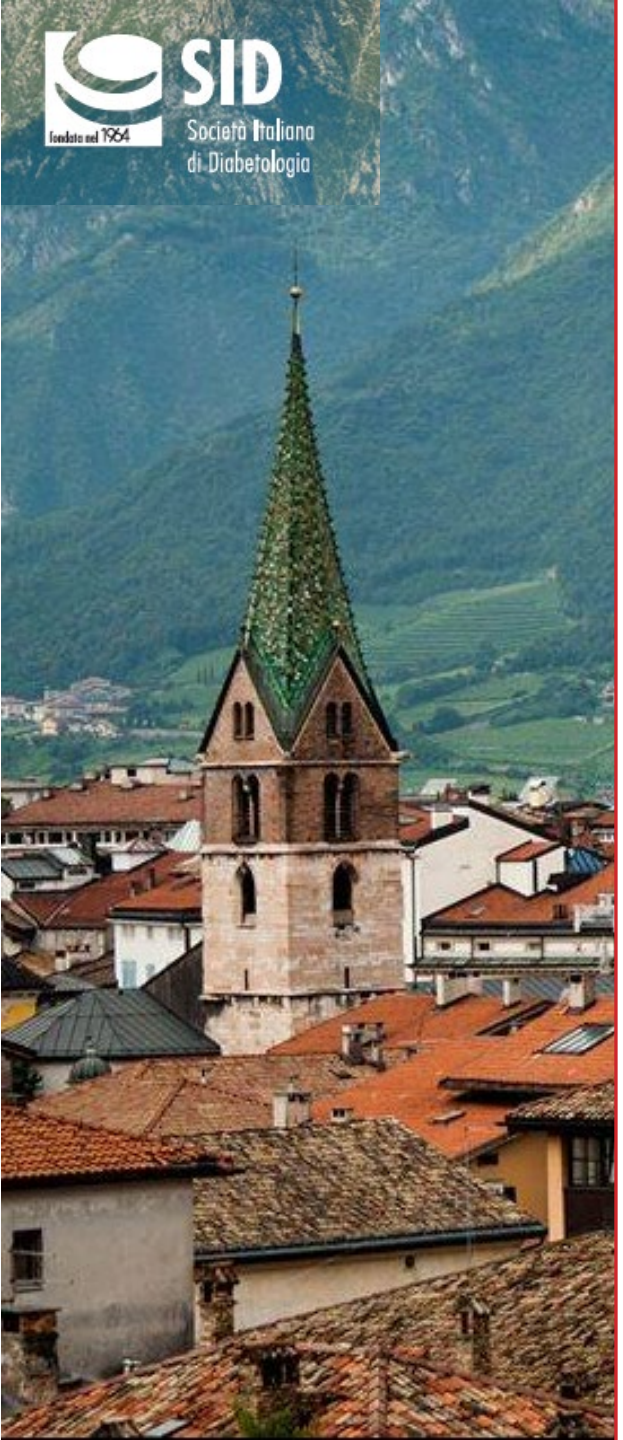
Secondary outcomes
- UACR
- eGFR



Gullaksen et al. Diabetologia. 2023 May;66(5):813-825.

Come metterle in fila?





Grazie!