Roma
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12 • 13 dicembre 2025

SID
Società Italiana di Diabetologia

Diagnosi precoce
e trattamento efficace
della patologia
NEFRO CARDIO METABOLICA

DALLA teoria ALLA pratica

SESSIONE 4 PREVENZIONE E TERAPIA CARDIONEFROMETABOLICA

Prevenzione e terapia della nefropatia diabetica: SGLT2i, GLP-1 RA o entrambi?

Gian Paolo Fadini

Università di Padova

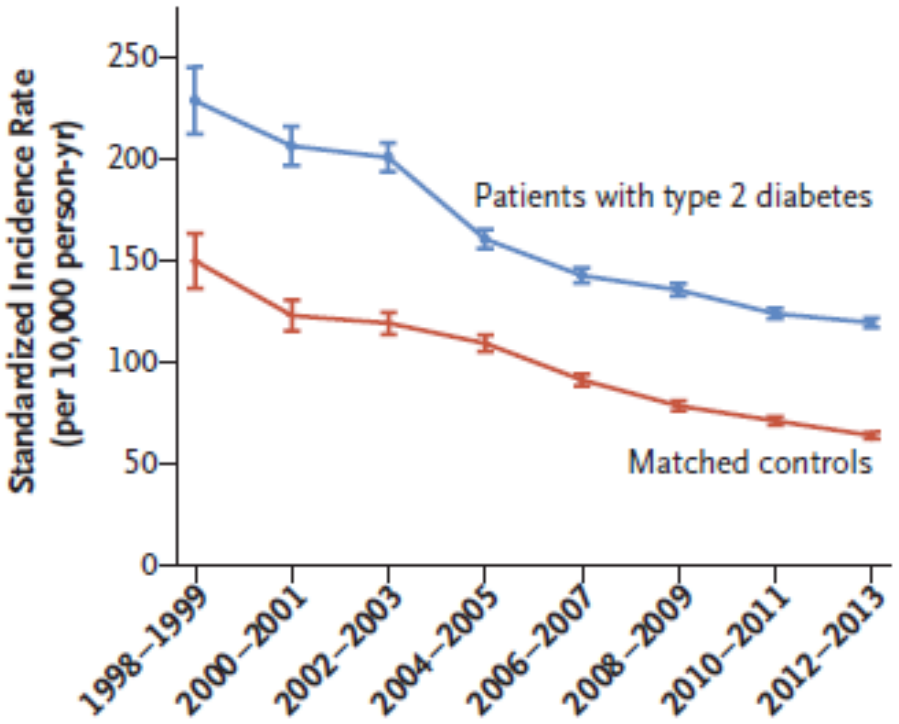
Dichiarazione di interessi

- Il Prof. GIAN PAOLO FADINI dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:
    - Astrazeneca
    - Boehringer
    - Lilly
    - Guidotti
    - Novo Nordisk
    - Sanofi

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.)

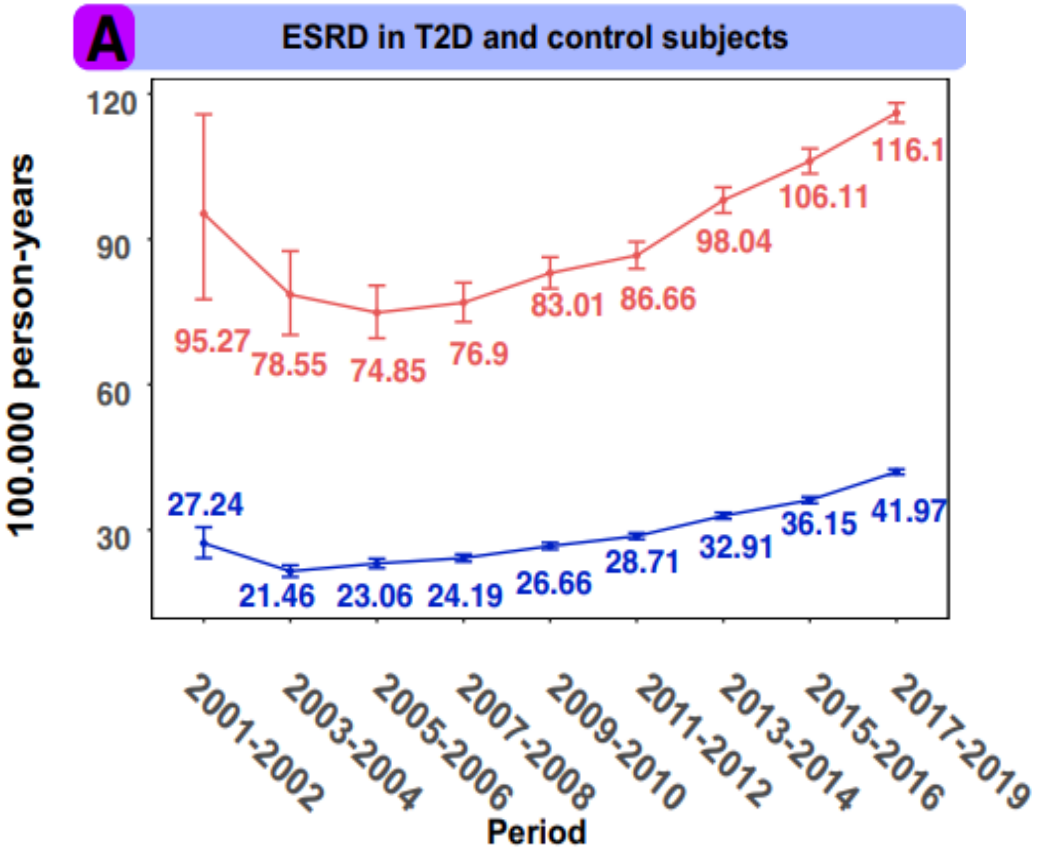
Secular trends in cardio-renal disease

Death from cardiovascular disease



Rawshani, NEJM 2017

Diabetic Kidney Disease



Halmien, Diabetes care Oct 2022

CKD primary prevention

Table 1 | **Approach to preventive strategies in CKD**

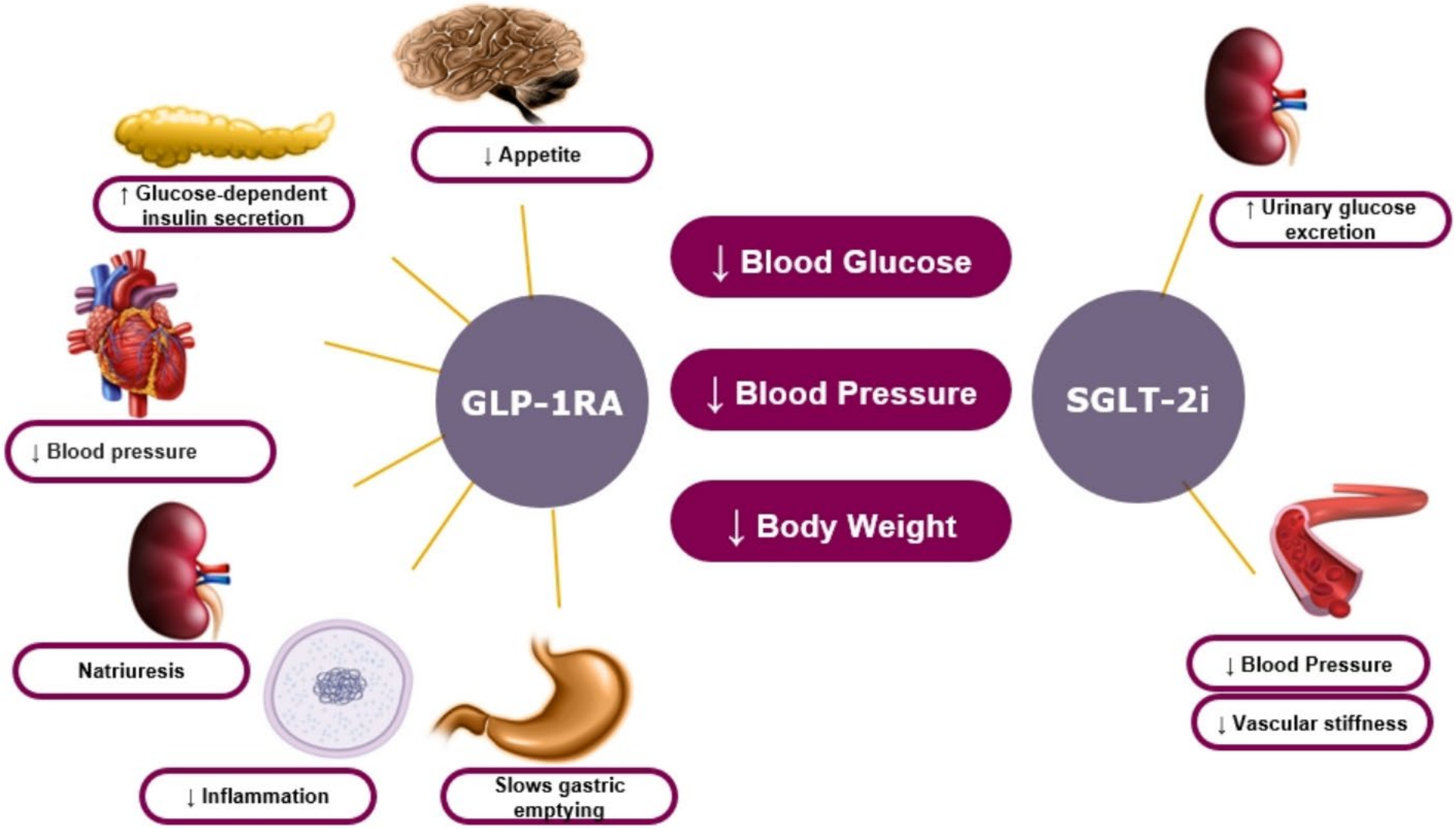
Approach	Main goal	Additional targets	Alarming signs	Risk factors to target	Interventions
Primary prevention	Avert kidney disease	Manage risk factors for kidney disease; educate on primordial prevention	Glomerular hyperfiltration	Diabetes; hypertension; obesity; solitary kidney; genetic risks; other risk factors	Support lifestyle modifications with moderate physical activity; provide dietary advice including avoidance of high sodium and excessive protein intake; prevent and manage obesity; improve glycaemic and blood pressure control; identify genetic risk factors; ensure adequate hydration
Secondary prevention	Identify early disease	Slow CKD progression; prolong kidney health	Emerging or worsening albuminuria; declining eGFR	Proteinuria; uncontrolled hypertension; poor glycaemic control; high protein intake	Manage proteinuria; encourage low-sodium and low-protein diet; encourage more plant-based sources for dietary protein; identify and offer effective pharmacotherapy; individualize therapy; identify and manage additional CKD risk factors; explore integrative and alternative approaches
Tertiary prevention	Avoid kidney failure	Delay dialysis transition; preserve the remaining kidney function	Worsening uraemic signs and symptoms	AKI events and AKI risk factors; worsening cardiac function (cardiorenal syndrome)	Manage uraemic symptoms and comorbidities; manage fluid and sodium retention; manage cardiovascular risk factors; explore novel kidney preservative and supportive therapies

Primary prevention is to avert emergence of de novo chronic kidney disease (CKD), secondary prevention aims to identify CKD as early as possible and tertiary prevention strives to avoid end-stage kidney disease, also known as kidney failure. AKI, acute kidney injury; eGFR, estimated glomerular filtration rate.

NATURE REVIEWS NEPHROLOGY, 16(3); 2020

Razionale fisiopatologico

dell'associazione SGLT2i + GLP-1RA



Ele Ferrannini. «Pathophysiological basis of SGLT2i/GLP-1 RA combination», presented at EASD 2016

- ✓ **SGLT2i e GLP-1RA agiscono sui principali fattori di rischio dello sviluppo di malattia renale cronica**

What is missing?

with

SGLT2i alone

we miss…

- Better A1c control
- Better weight control
- Anti-inflammatory effect
- Anti-atherosclerotic effect

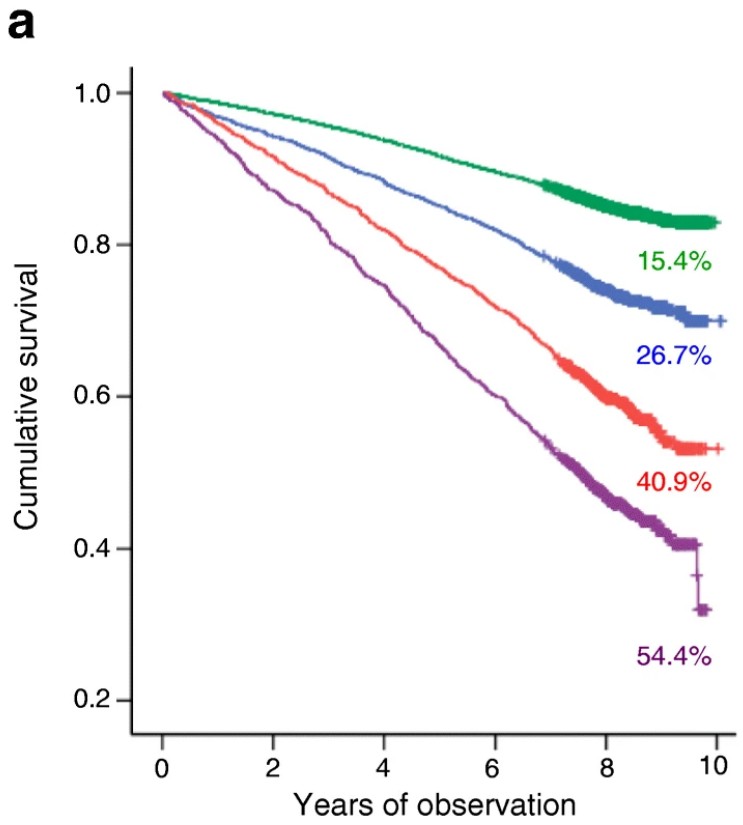
with

GLP-1RA alone

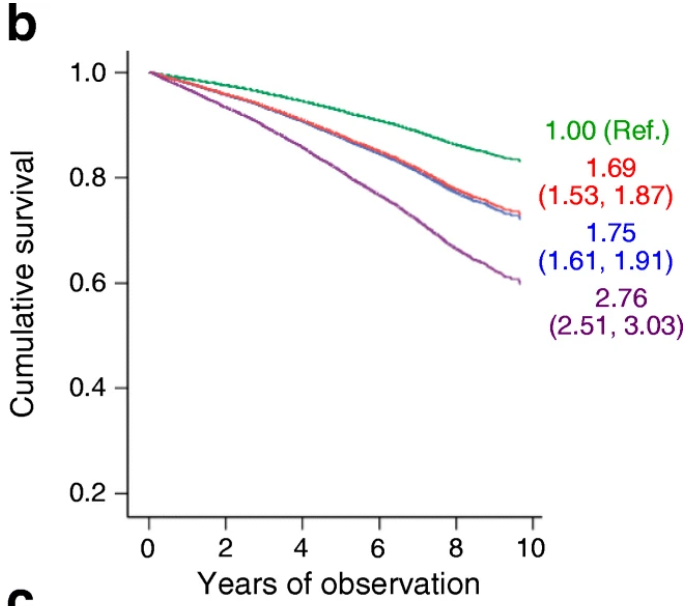
we miss…

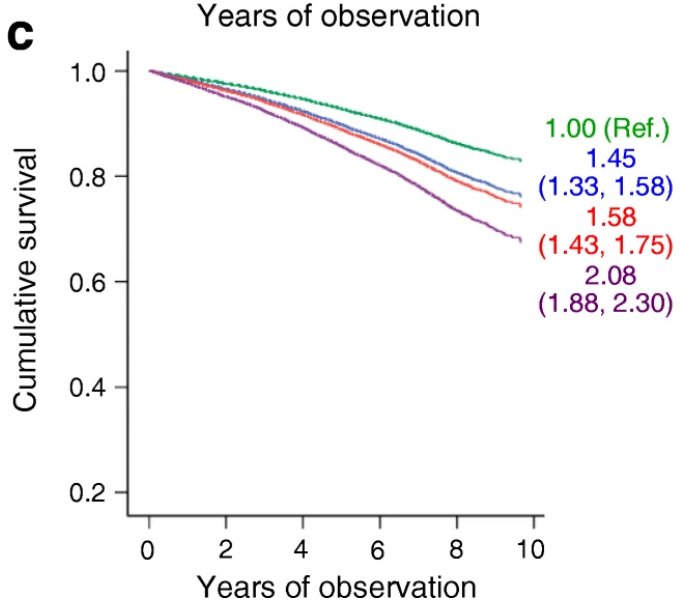
- Stronger eGFR preservation
- Effect independent of A1c / BW
- Hemodynamic effect
- Synergy on albuminuria reduction

The presence of albuminuria worsens all outcomes

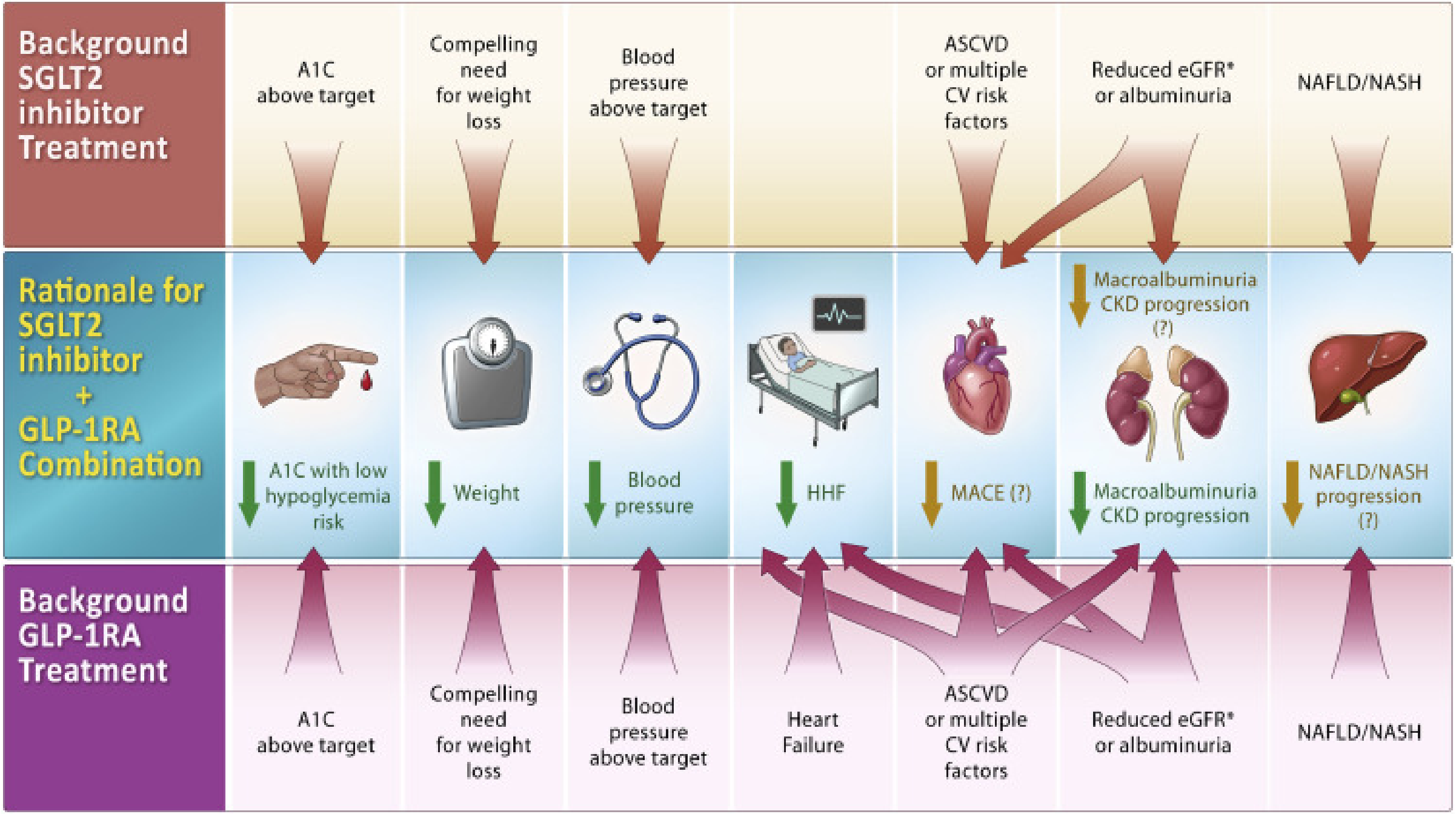


No. at risk						
All	15,656	14,926	14,110	13,179	8243	3
$Alb^-/eGFR^-$	9984	9707	9362	8949	5761	0
$Alb^+/eGFR^-$	2966	2795	2619	2430	1535	1
$Alb^-/eGFR^+$	1476	1352	1210	1060	558	2
$Alb^+/eGFR^+$	1230	1072	919	740	389	0





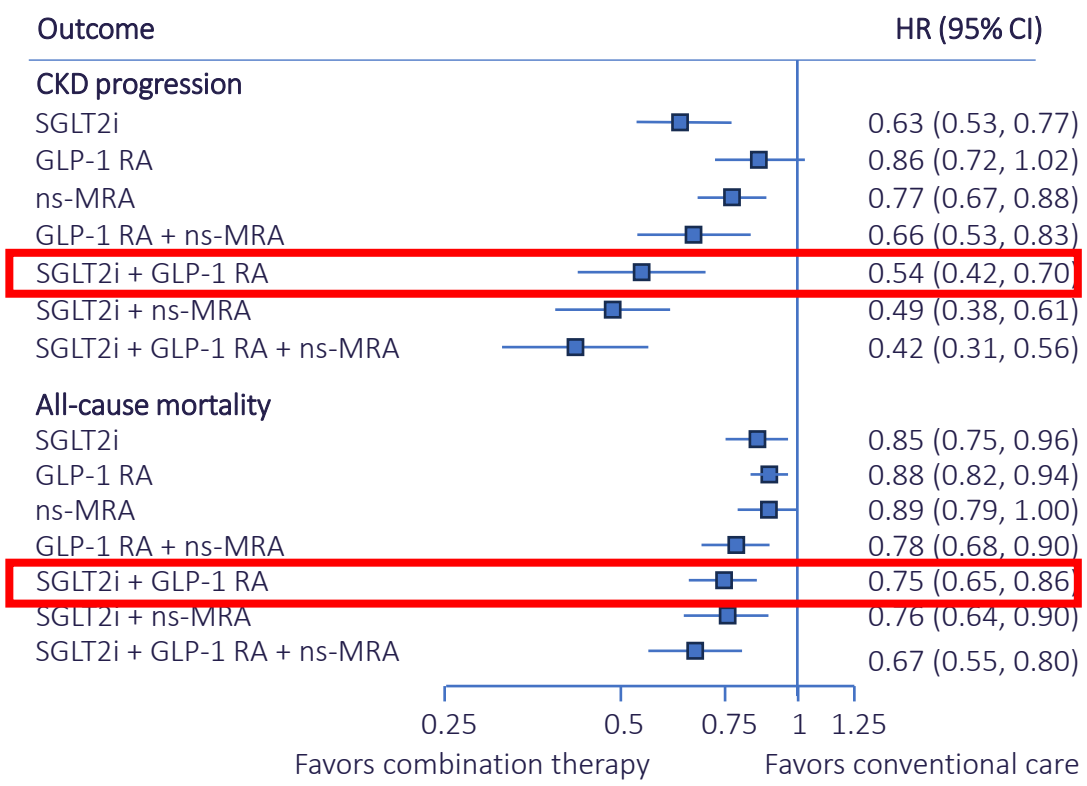
Diabetologia Volume 61, pages 2277–2289, (2018)
Hong Kong Diabetes Biobank Study Group, AJKD 2022

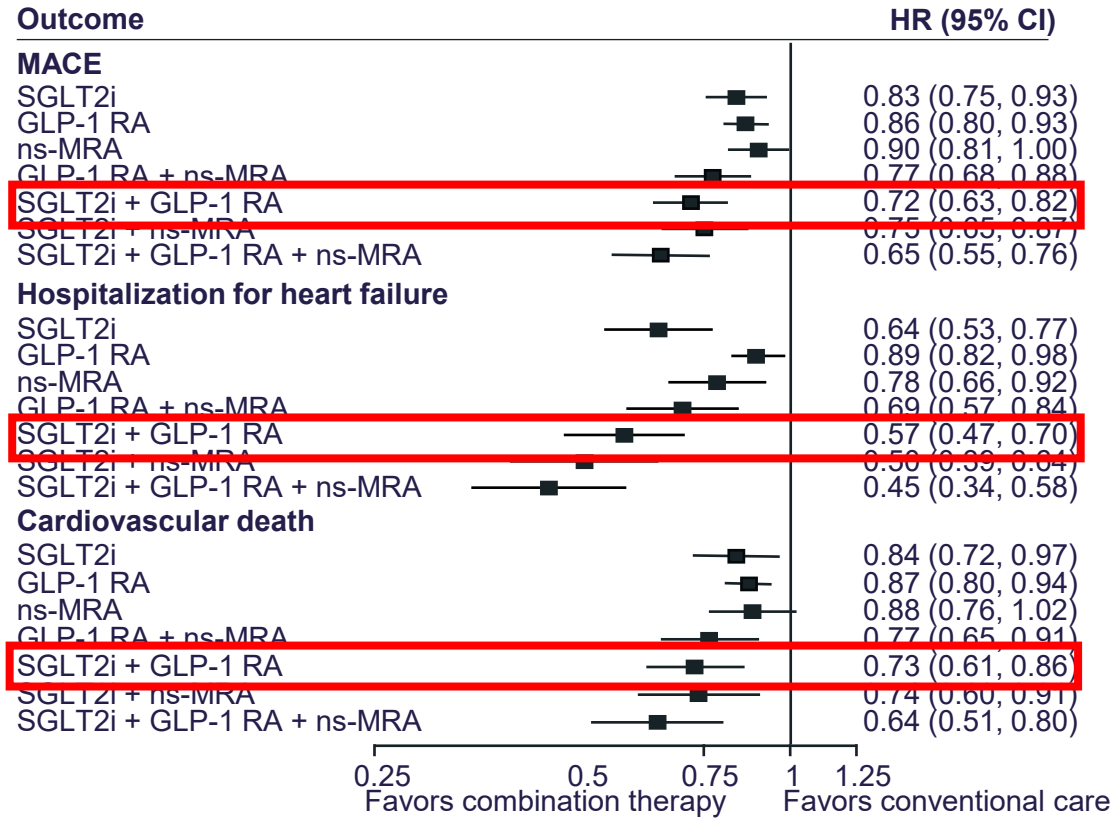


Doldenberg et al. Can J Diabetes 2021

Effects of combination therapies

Combination treatment was projected to offer improved cardiorenal benefits over conventional treatment[a,b]





Following treatment with an SGLT2i, a GLP-1 RA may offer a suitable additional treatment option

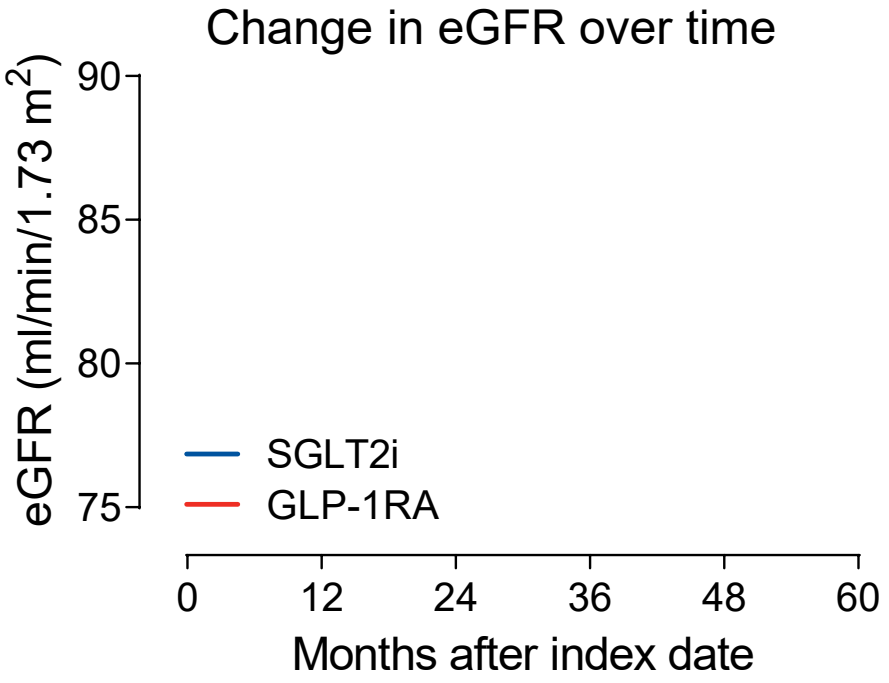
Neuen BL, et al. *Circulation* 2024;149:450–462

- ✓ SGLT2i e GLP-1RA agiscono sui principali fattori di rischio dello sviluppo di malattia renale cronica

- ✓ **La combinazione SGLT2i + GLP-1RA promette una maggiore protezione renale rispetto alle singole terapie, anche grazie a meccanismi sinergici**

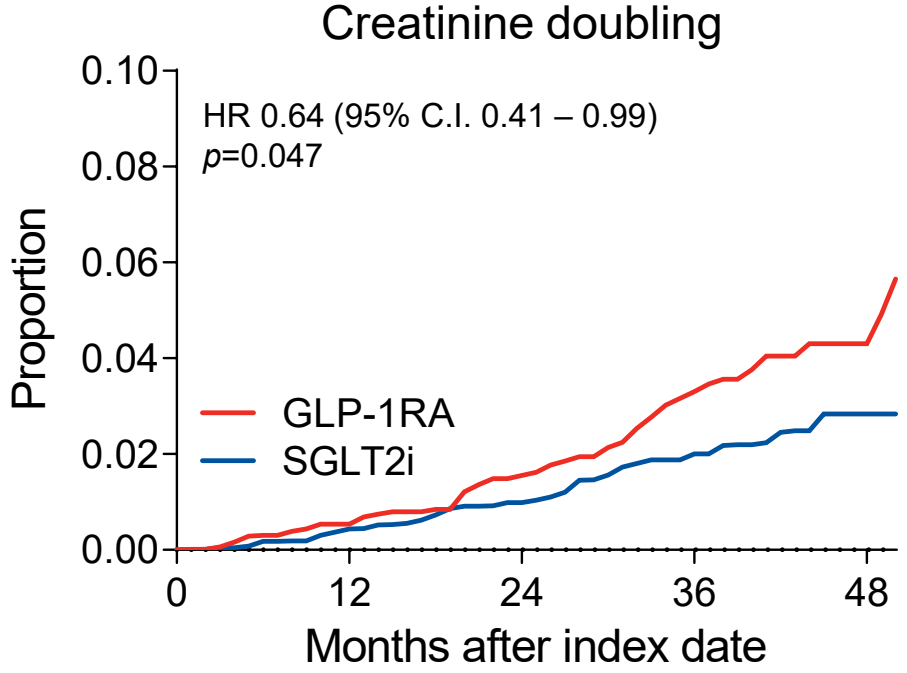
SGLT2i vs GLP-1RA

5701 new users of SGLT2i: dapa (52.8%), empa (38.6%), cana (8.5%)
5701 new users of GLP-1RA: dula (52.3%), lira (30.8%), exe (10.7%), sema (3.8%)



	4182	1867	1352	867	971	621*
GLP-	4155	1842	1211	754	849	572*

*54



	4182	2821	1646	704	100
LP-	4155	2542	1416	643	161

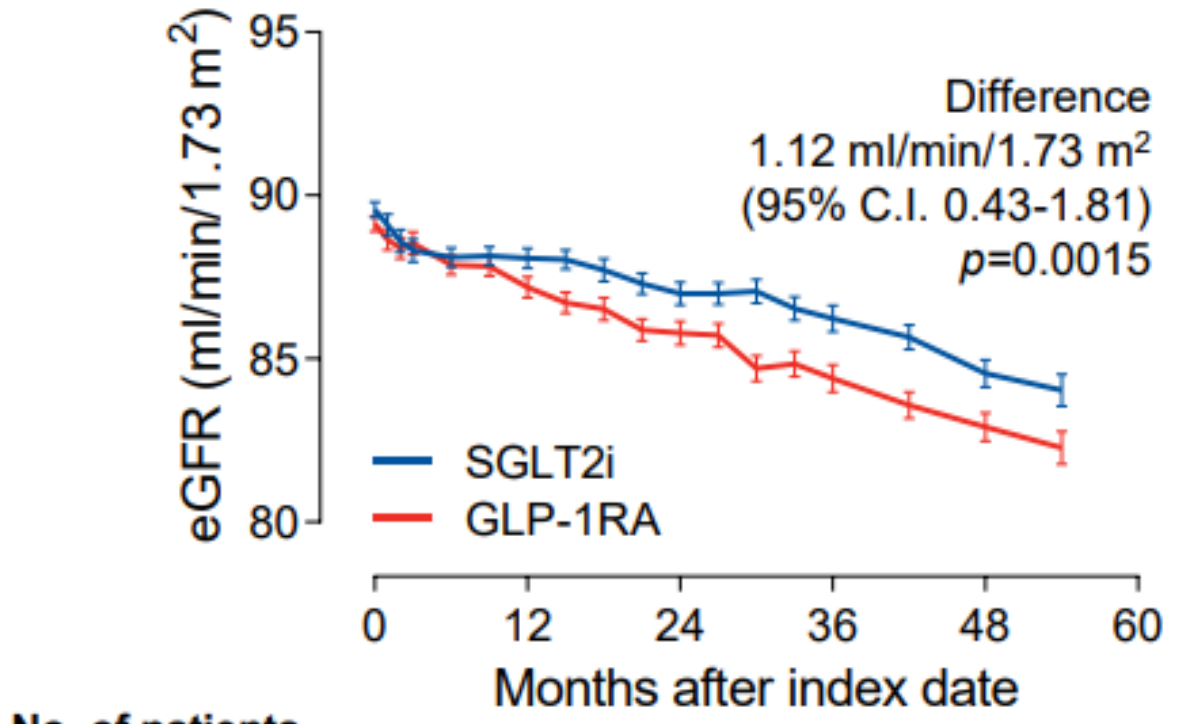
DARWIN-Renal

SGLT2i *vs* GLP-1RA

Primary prevention

4430 pts / group
Age 60
Baseline eGFR 90 ml/min

0% eGFR <60 ml/min
0% UACR >30 mg/g



No. of patients						
SGLT2i	3078	1395	1032	665	750	482*
GLP-1RA	3009	1394	915	585	676	464*

*54 months

Diabetologia. 2024 Nov;67(11):2585-2597.

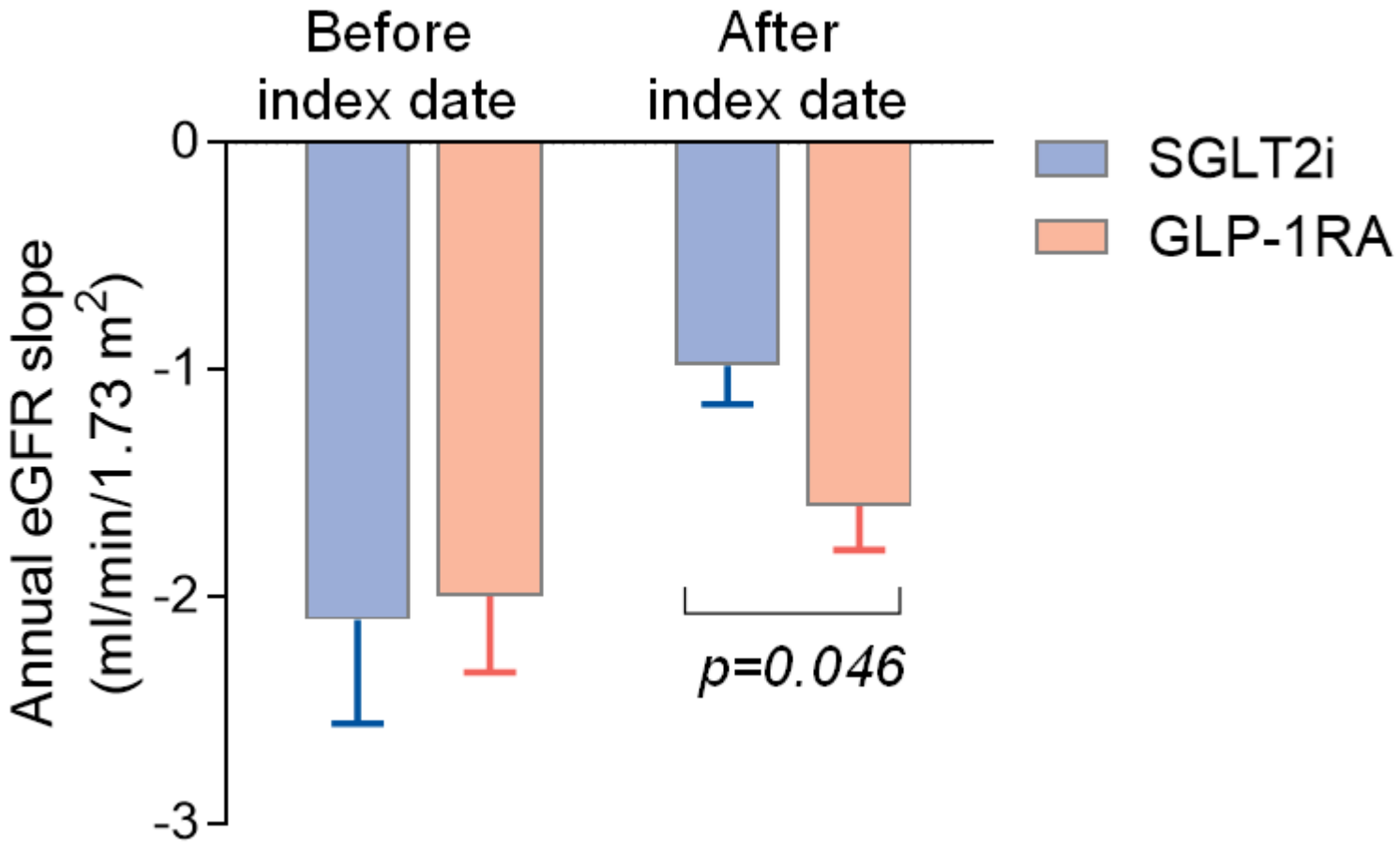
DARWIN-Renal

SGLT2i *vs* GLP-1RA

Secondary prevention

1226 pts / group
Age 63
Baseline eGFR 74 ml/min

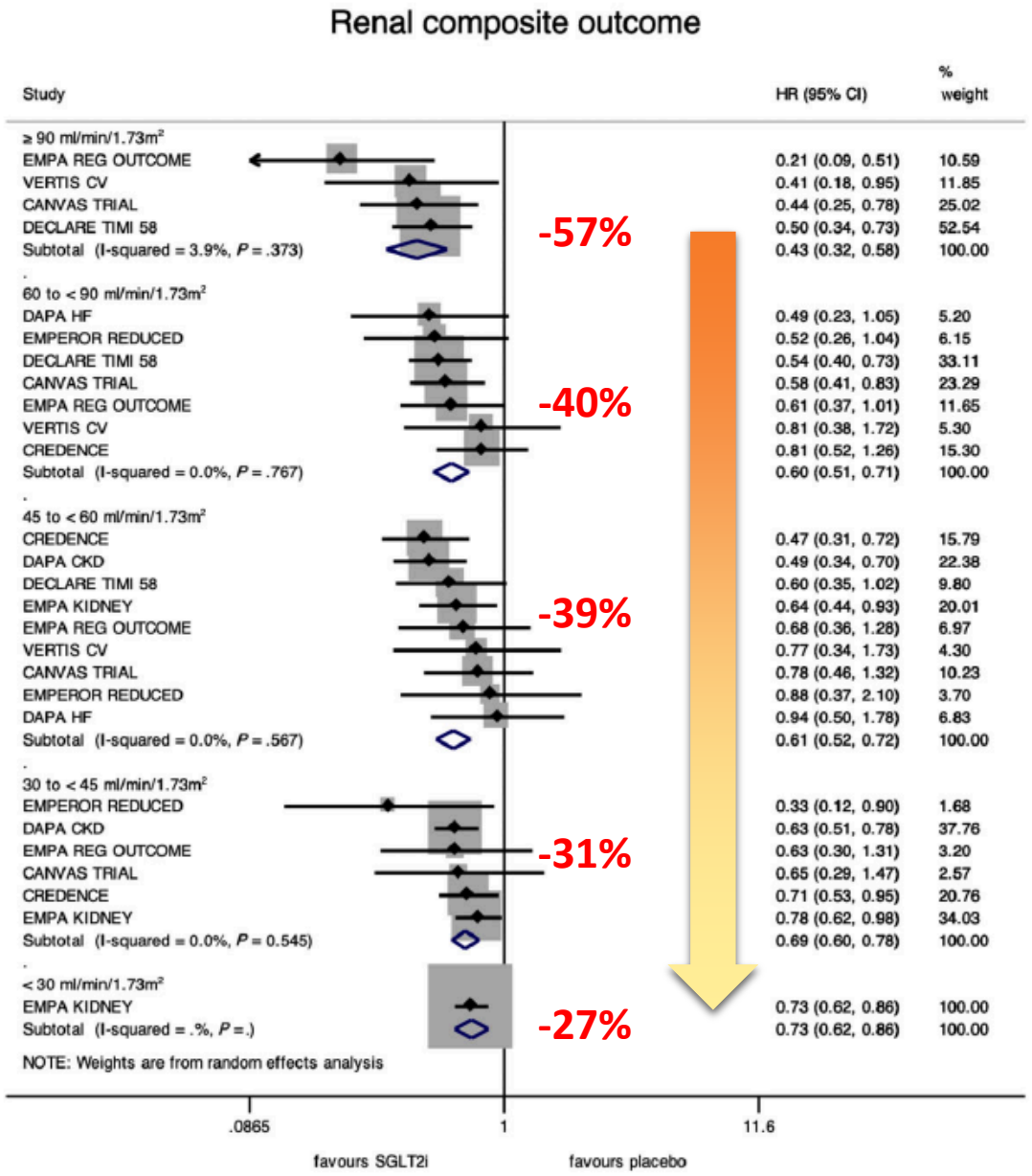
38% eGFR <60 ml/min
71% UACR >30 mg/g



Fadini et al. Diabetes Obes Metab . 2025 Sep;27(9):5182-5191.

SGLT2i:
risk of adverse kidney outcomes by baseline eGFR

Kidney protection is well consolidated i
different populations and in those with ver
low renal risk



Diabetes Obes Metab. 2023 May;25(5):1341-1350

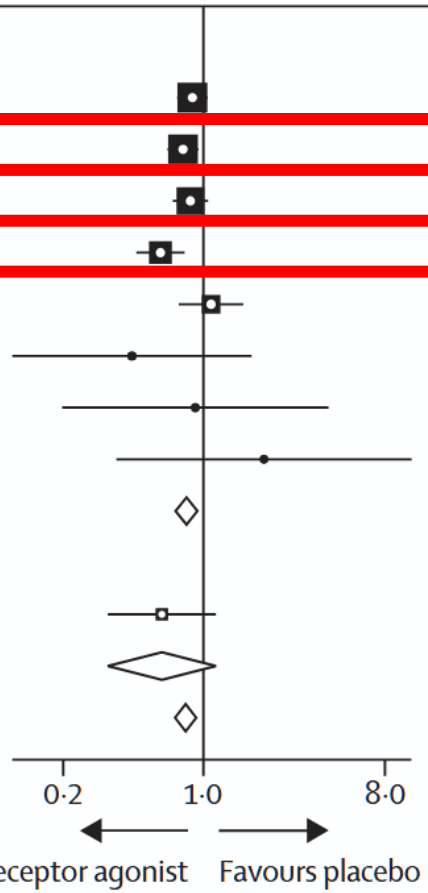
Effects of GLP-1RA on kidney and cardiovascular disease outcomes

A meta-analysis of randomised controlled trials

Composite kidney outcome excluding albuminuria

	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)
With diabetes			
EXSCEL[40]	246/6459 (3·8%)	273/6466 (4·2%)	0·88 (0·74–1·05)
2nd prev FLOW[26]	218/1767 (12·3%)	260/1766 (14·7%)	0·79 (0·66–0·94)
LEADER[24,33]	184/4668 (3·9%)	212/4672 (4·5%)	0·86 (0·70–1·05)
1st prev REWIND[23,35]	84/4949 (1·7%)	136/4952 (2·7%)	0·61 (0·46–0·80)
SUSTAIN-6[25,41]	58/1648 (3·5%)	57/1649 (3·5%)	1·09 (0·75–1·58)
ELIXA[37]	3/2702 (0·1%)	7/2793 (0·3%)	0·44 (0·11–1·73)
AMPLITUDE-O[39]	9/2717 (0·3%)	3/1359 (0·2%)	0·91 (0·20–4·19)
Harmony Outcomes[38]	4/4731 (0·1%)	2/4732 (<0·1%)	2·00 (0·37–10·87)
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)
			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



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

Kidney protection with semaglutie

FLOW trial (semaglutide in albuminuric DKD)

Population

Type 2 DM and CKD:
GFR 50-75 ml/min +
ACR 300-5000 mg/g
or
GFR 25-<50 ml/min +
ACR 100-5000 mg/g

Median follow-up,
3.4 years

	Major kidney disease events	Death from any causes	Adverse event leading to discontinuation
Major kidney disease events- kidney failure, ≥50% reduction in GFR, death from CV or kidney-related causes			
Placebo n = 1766	7.5 events per 100 patient-years	279(15.8%)	211(11.9%)
	HR 0.76 (95% CI, 0.66-0.88)	HR 0.80 (95% CI, 0.67-0.95)	
Semaglutide n = 1767	5.8 events per 100 patient-years	227(12.8%)	233(13.2%)

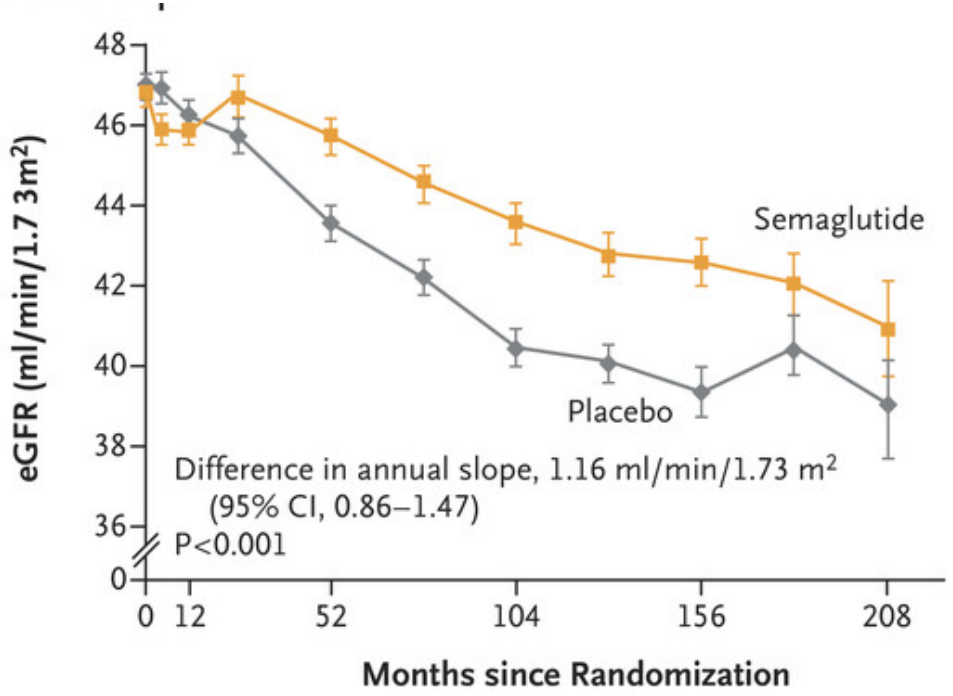
HR= Hazard ratio

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

The NEW ENGLAND JOURNAL of MEDICINE

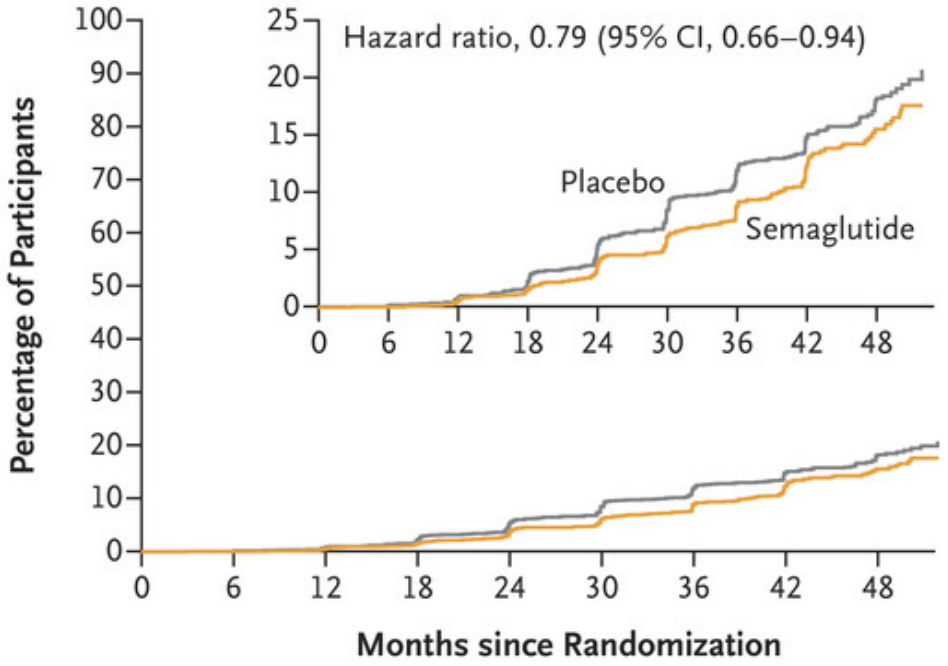
ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes



No. at Risk

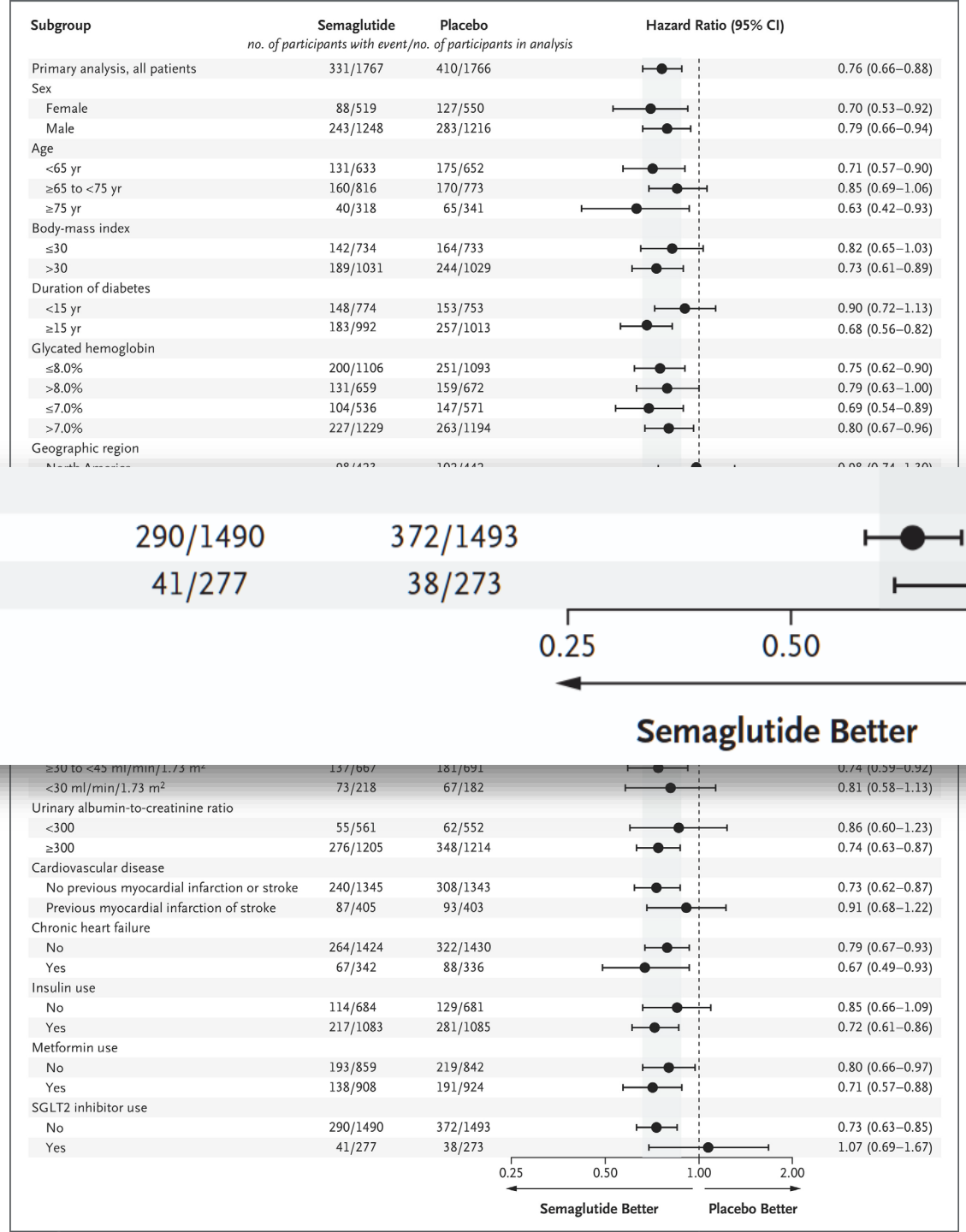
Placebo	1766	1663	1573	1609	1490	1441	1284	876	609	199
Semaglutide	1766	1665	1590	1606	1521	1468	1345	952	651	218



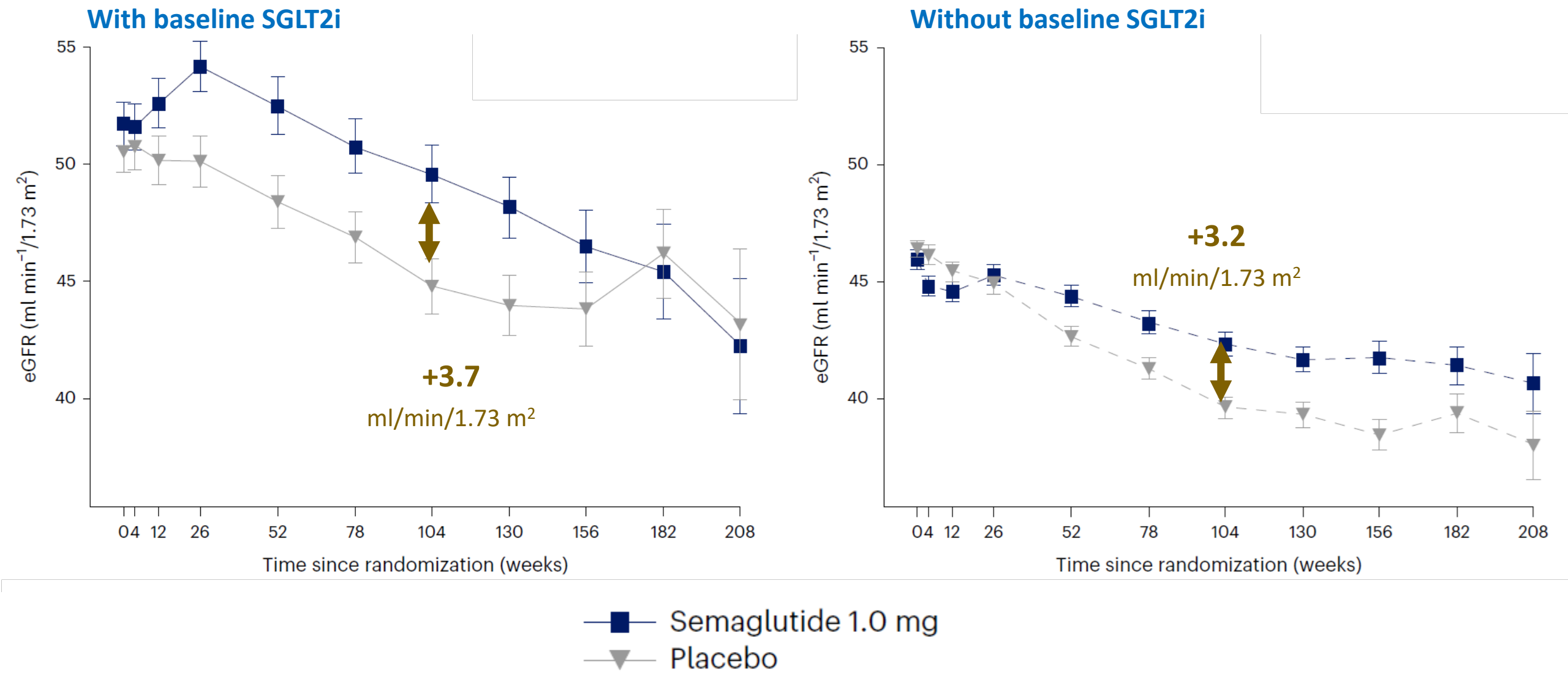
No. at Risk

Placebo	1766	1736	1682	1605	1516	1408	1048	660	354
Semaglutide	1767	1738	1693	1640	1572	1489	1131	742	392

Perkovic V et al. Tuttle KR, Rossing P, Mahaffey KW, Mann JFE, Bakris G, Baeres FMM, Idorn T, Bosch-Traberg H, Lausvig NL, Pratley R; FLOW Trial Committees and Investigators. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. N Engl J Med. 2024 May 24.


Subgroup
Semaglutide
Placebo
Hazard Ratio (95% CI)
no. of participants with event/no. of participants in analysis
Primary analysis, all patients 331/1767 410/1766 0.76 (0.66–0.88)
Sex
Female 88/519 127/550 0.70 (0.53–0.92)
Male 243/1248 283/1216 0.79 (0.66–0.94)
Age
<65 yr 131/633 175/652 0.71 (0.57–0.90)
≥65 to <75 yr 160/816 170/773 0.85 (0.69–1.06)
≥75 yr 40/318 65/341 0.63 (0.42–0.93)
Body-mass index
≤30 142/734 164/733 0.82 (0.65–1.03)
>30 189/1031 244/1029 0.73 (0.61–0.89)
Duration of diabetes
<15 yr 148/774 153/753 0.90 (0.72–1.13)
≥15 yr 183/992 257/1013 0.68 (0.56–0.82)
Glycated hemoglobin
≤8.0% 200/1106 251/1093 0.75 (0.62–0.90)
>8.0% 131/659 159/672 0.79 (0.63–1.00)
≤7.0% 104/536 147/571 0.69 (0.54–0.89)
>7.0% 227/1229 263/1194 0.80 (0.67–0.96)
Geographic region
<30 ml/min/1.73 m²
73/218
67/182
0.81 (0.58–1.13)
Urinary albumin-to-creatinine ratio
<300 55/561 62/552 0.86 (0.60–1.23)
≥300 276/1205 348/1214 0.74 (0.63–0.87)
Cardiovascular disease
No previous myocardial infarction or stroke 240/1345 308/1343 0.73 (0.62–0.87)
Previous myocardial infarction of stroke 87/405 93/403 0.91 (0.68–1.22)
Chronic heart failure
No 264/1424 322/1430 0.79 (0.67–0.93)
Yes 67/342 88/336 0.67 (0.49–0.93)
Insulin use
No 114/684 129/681 0.85 (0.66–1.09)
Yes 217/1083 281/1085 0.72 (0.61–0.86)
Metformin use
No 193/859 219/842 0.80 (0.66–0.97)
Yes 138/908 191/924 0.71 (0.57–0.88)
SGLT2 inhibitor use
No 290/1490 372/1493 0.73 (0.63–0.85)
Yes 41/277 38/273 1.07 (0.69–1.67)
0.25
0.50
1.00
2.00
Semaglutide Better
Placebo Better

Change in eGFR with semaglutide vs placebo w/wo SGLT2i



Mann JFE, et al. Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial. Nat Med. 2024 Oct;30(10):2849-2856.

In the Semaglutide Cardiovascular Outcomes Trial (SOUL), Oral Semaglutide Did Not Significantly Reduce Major Kidney Outcomes but Moderately Slowed eGFR Decline Compared With Placebo

Design

Randomized, double-blind, parallel-group trial comparing oral semaglutide with placebo

Participants

People aged ≥50 years with type 2 diabetes and evidence of atherosclerotic cardiovascular disease and/or chronic kidney disease

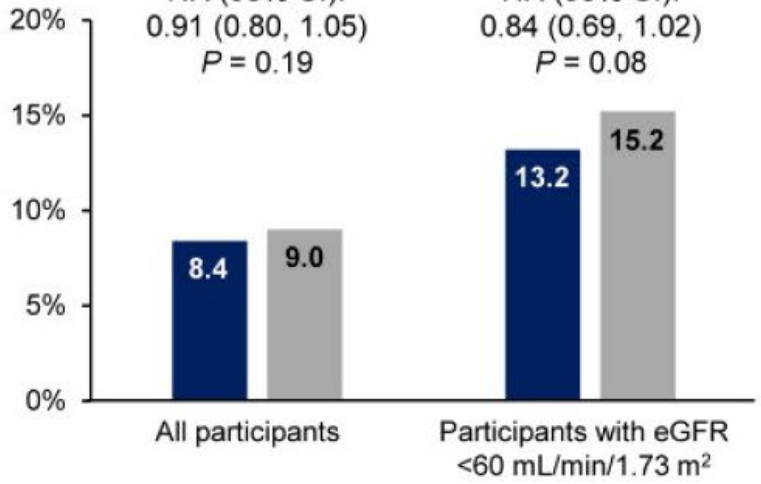
Randomized participants:
9,650

Mean follow-up:
47.5 months

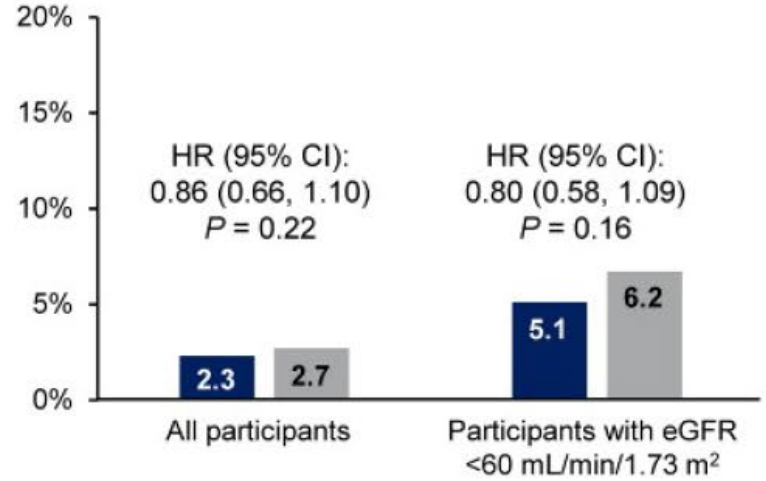
eGFR at baseline:
Mean: 73.8 mL/min/1.73 m²
<60 mL/min/1.73 m² subgroup:
2,816 (29.2%) participants

Results

Occurrence of the 5-point kidney composite outcome*



Occurrence of the 4-point kidney composite outcome†



Oral semaglutide group Placebo group

Mean annual decrease in eGFR

−1.67 mL/min/1.73 m²

−2.06 mL/min/1.73 m²

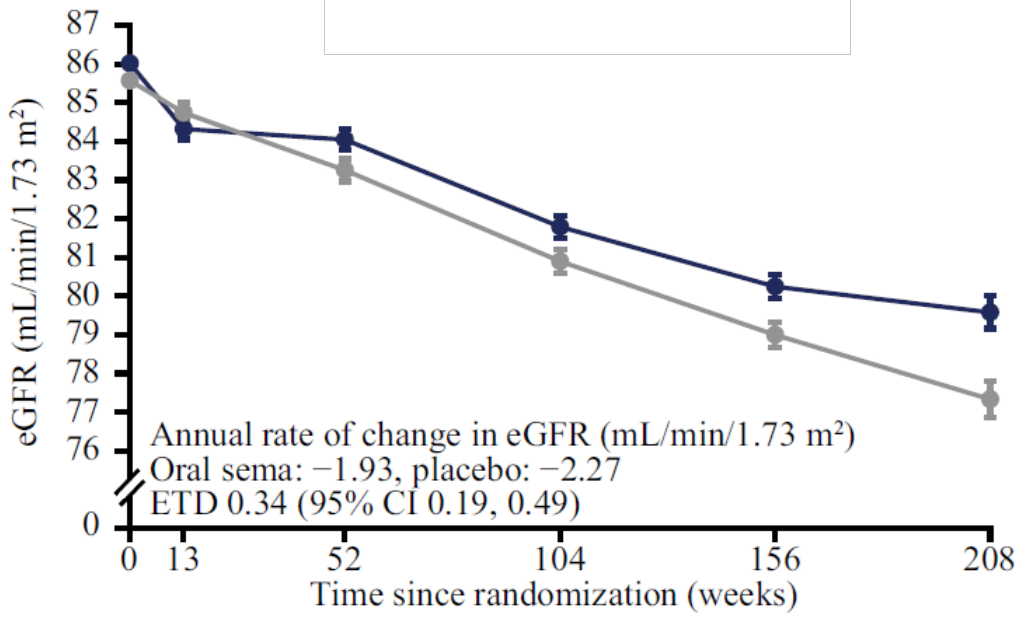
ETD (95% CI): 0.40 (0.27, 0.53)
P < 0.0001

Serious adverse events

*Persistent ≥50% reduction in eGFR from baseline, persistent eGFR <15 mL/min/1.73 m², initiation of chronic kidney replacement therapy, or death from kidney-related or CV causes. †As the 5-point composite, excluding death from CV causes.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HR, hazard ratio.

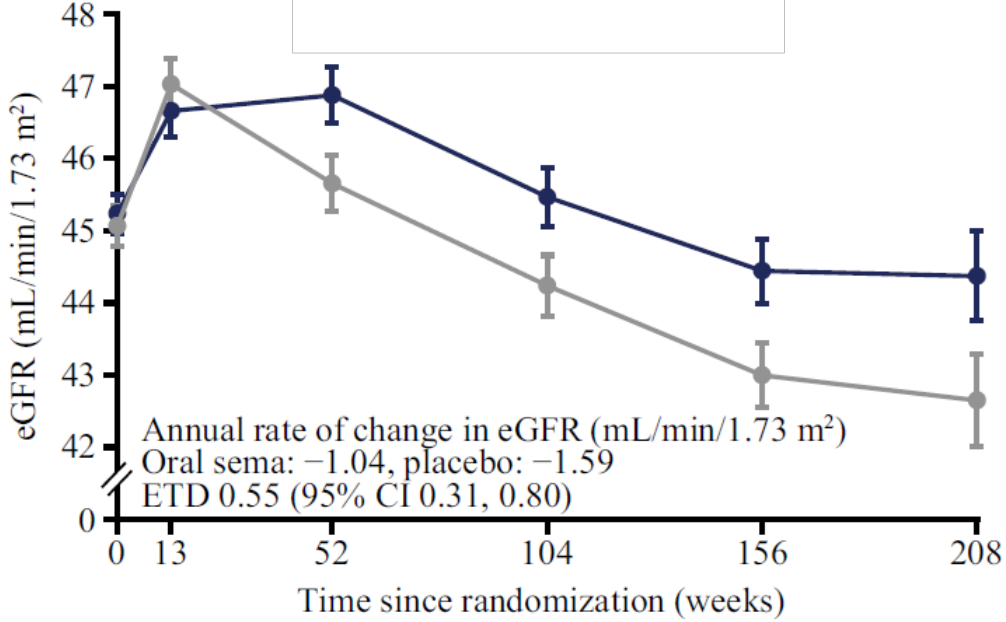
In the Semaglutide Cardiovascular Outcomes Trial (SOUL), Oral Semaglutide Did Not Significantly Reduce Major Kidney Outcomes but Moderately Slowed eGFR Decline Compared With Placebo

With eGFR >60



Oral sema	3,376	3,207	3,132	2,966	2,863	1,594
Placebo	3,375	3,198	3,118	2,935	2,785	1,532

With eGFR <60



Oral sema	1,405	1,337	1,263	1,193	1,100	555
Placebo	1,411	1,311	1,258	1,146	1,043	522

American Diabetes Association. | Publications

LIFESTYLE

Healthy eating | Physical activity | Smoking cessation | Weight management

Regular risk factor reassessment (every 3–6 months)

FIRST-LINE DRUG THERAPY

- SGLT2i (initiate if eGFR is ≥20; continue until dialysis or transplant)
- Metformin (if eGFR is ≥30)
- RAS inhibitor at maximum tolerated dose (if albuminuria and/or HTN)
- Semaglutide can be used as another first-line agent
- Moderate- or high-intensity statin

Regular reassessment of glycemia, albuminuria, BP, CVD risk, and lipids

ADDITIONAL RISK-BASED THERAPY

- GLP-1 RA‡ if needed to achieve individualized glycemic goal
  - Other glucose-lowering drugs if needed to achieve individualized glycemic goal
- Nonsteroidal MRA† if ACR ≥30 mg/g and normal potassium
- Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP goal
  - Steroidal MRA if needed for resistant hypertension if eGFR is ≥45
- Antiplatelet agent for clinical ASCVD
- Ezetimibe, PCSK9i, or icosapent ethyl if indicated based on ASCVD risk and lipids

T2D only

All individuals (T1D and T2D)

- ✓ SGLT2i e GLP-1RA agiscono sui principali fattori di rischio dello sviluppo di malattia renale cronica
- ✓ La combinazione SGLT2i + GLP-1RA promette una maggiore protezione renale rispetto alle singole terapie, anche grazie a meccanismi sinergici
- ✓ **Le evidenze dei trials supportano l'uso di SGLT2i in prevenzione primaria e secondaria e di GLP-1RA soprattutto in prevenzione secondaria e add-on**

- ✓ SGLT2i e GLP-1RA agiscono sui principali fattori di rischio dello sviluppo di malattia renale cronica
- ✓ La combinazione SGLT2i + GLP-1RA promette una maggiore protezione renale rispetto alle singole terapie, anche grazie a meccanismi sinergici
- ✓ Le evidenze dei trials supportano l'uso di SGLT2i in prevenzione primaria e secondaria e di GLP-1RA soprattutto in prevenzione secondaria ed add-on
- ✓ **Non esistono evidenze derivanti dai trials clinici a supporto di una maggiore protezione renale con la combinazione.**

Diabetologia
https://doi.org/10.1007/s00125-025-06565-6

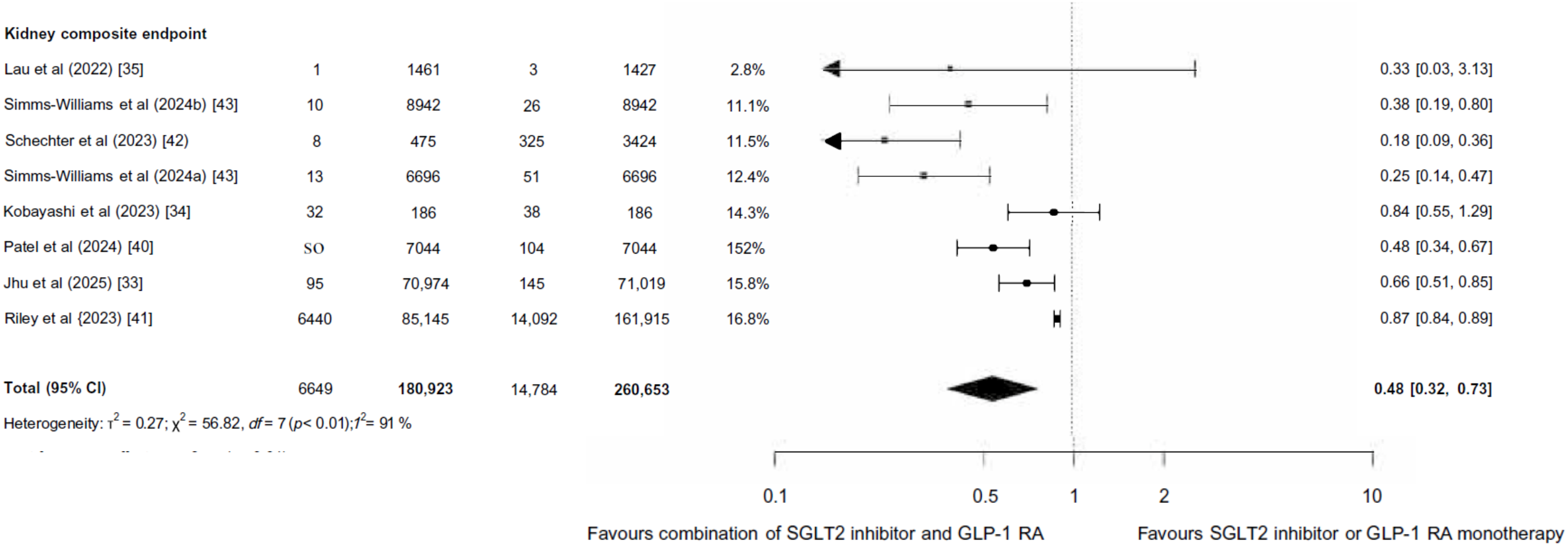
ARTICLE

Effectiveness and safety of combining SGLT2 inhibitors and GLP-1 receptor agonists in individuals with type 2 diabetes: a systematic review and meta-analysis of cohort studies

Julia M. T. Colombijn[1,2] · Jan F. de Leijer[3] · Frank L. J. Visseren[3] · Marianne C. Verhaar[1] · Daniël H. van Raalte[4] · Naveed Sattar[5] · Robin W. M. Vernooij[1,2] · Thomas T. van Sloten[3]

Effects of SGLT2i + GLP-1RA combination on kidney endpoints

M-A of observational studies



Diabetologia. 2025 Oct 21. doi: 10.1007/s00125-025-06565-6.

Effects of SGLT2i + GLP-1RA combination on kidney endpoints

M-A of observational studies

GRADE of evidence

Outcome	No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Certainty (GRADE)
			Monotherapy	Combination therapy	
MACE	364,369 (9)	0.56 (0.43, 0.71)	54 / 1000	30 / 1000 (23, 38)	⨁⨁⨀⨀[a,b]
All-cause mortality	542,989 (10)	0.50 (0.40, 0.63)	38 / 1000	19 / 1000 (1, 24)	⨁⨁⨀⨀[a,b]
Cardiovascular mortality	31,692 (2)	0.26 (0.16, 0.43)	5 / 1000	1 / 1000 (1, 2)	⨁⨁⨀⨀[a,c]
Kidney composite endpoint	299,583 (6)	0.48 (0.32, 0.73)	77 / 1000	35 / 1000 (22, 56)	⨁⨀⨀⨀[a,b,d]
Hospitalisation for heart failure	43,246 (5)	0.67 (0.64, 0.71)	101 / 1000	68 / 1000 (65, 72)	⨁⨁⨁⨀[a]
Myocardial infarction	508,018 (6)	0.62 (0.48, 0.80)	22 / 1000	14 / 1000 (11, 18)	⨁⨁⨀⨀[a,b]
Stroke	509,116 (6)	0.65 (0.49, 0.86)	23 / 1000	15 / 1000 (11, 20)	⨁⨁⨀⨀[a,b]

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- ✓ SGLT2i e GLP-1RA agiscono sui principali fattori di rischio dello sviluppo di malattia renale cronica
- ✓ La combinazione SGLT2i + GLP-1RA promette una maggiore protezione renale rispetto alle singole terapie, anche grazie a meccanismi sinergici
- ✓ Le evidenze dei trials supportano l'uso di SGLT2i in prevenzione primaria e secondaria e di GLP-1RA soprattutto in prevenzione secondaria ed add-on
- ✓ Non esistono evidenze derivanti dai trials clinici a supporto di una maggiore protezione renale con la combinazione
- ✓ **Gli studi osservazionali, con basso livello di evidenza, supportano la maggiore efficacia della combinazione su tutti gli outcomes cardio-renali**