Con il patrocinio di

Evento Congiunto di

Quarto Meta Open Forum

"Al CUORE del DIABETE"

Roma | 14-15 marzo 2025

Aula Brasca, Policlinico Gemelli

II Sessione
Basta con la DKD!

Semaglutide

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Disclosure

Dichiaro di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche per relazioni/moderazioni/partecipazioni a board retribuite:

- Astra-Zeneca;
- Bayer;
- Boehringer Ingelheim;
- Eli Lilly;
- Mundipharma;
- Novo Nordisk.

Dichiaro altresì il mio 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.).

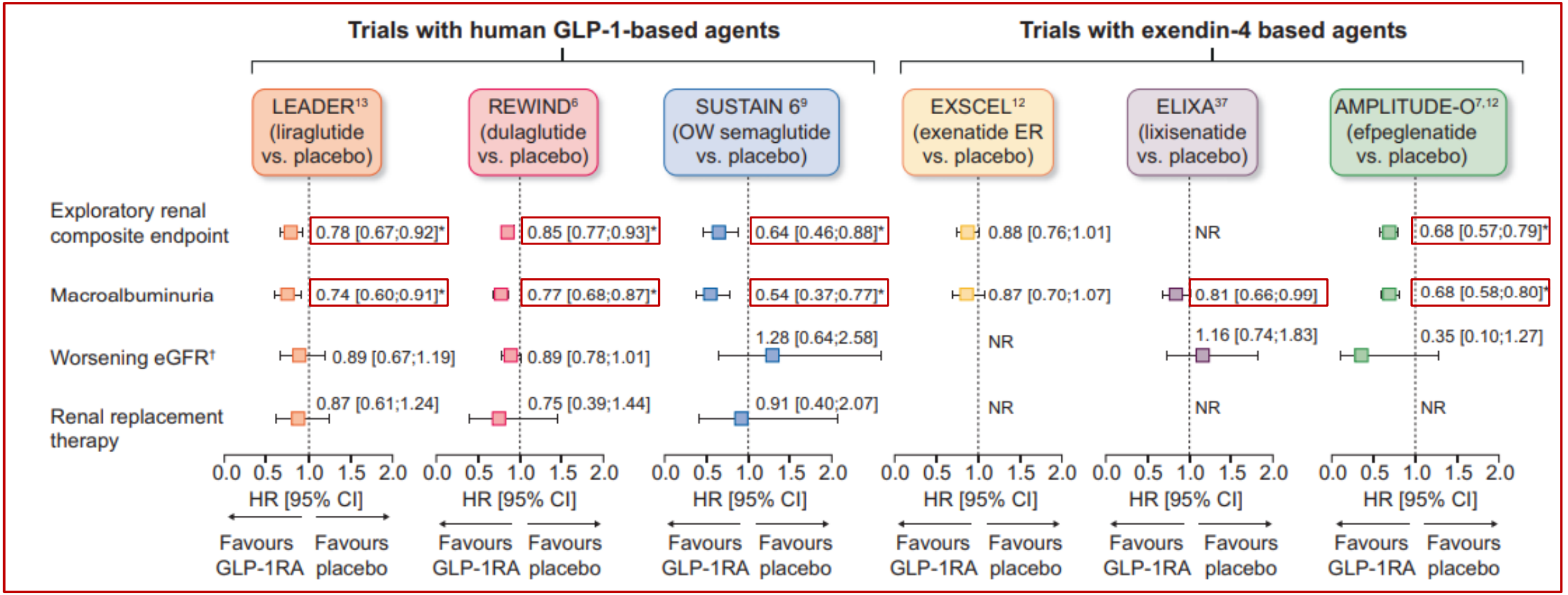
In fede

Giuseppe Pugliese

Agenda

- Renal outcomes in CV outcome trials with GLP-1 receptor agonists
- Renal outcomes in the FLOW renal outcome trial with semaglutide
- Renal outcomes in trials with dual/triple incretin receptor agonists
- Semaglutide in the treatment algorithm of diabetic kidney disease

Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

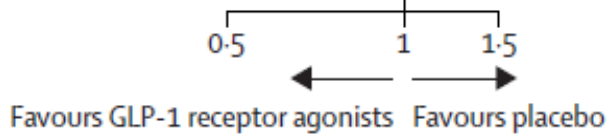


Rossing P et al. *Nephrol Dial Transplant.* 2023;38:2041–2051

Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

Meta-analysis

	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Composite kidney outcome including macroalbuminuria					
ELIXA	172/2647 (6%)	203/2639 (8%)	0·84 (0·68 to 1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67 to 0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46 to 0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76 to 1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77 to 0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57 to 0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73 to 0·87)**	**47 (37 to 77)**	**<0·0001**
Worsening of kidney function*					
ELIXA	41/3031 (1%)	35/3032 (1%)	1·16 (0·74 to 1·83)		0·513
LEADER	87/4668 (2%)	97/4672 (2%)	0·89 (0·67 to 1·19)		0·43
SUSTAIN-6	18/1648 (1%)	14/1649 (1%)	1·28 (0·64 to 2·58)		0·48
EXSCEL	246/6456 (4%)	273/6458 (4%)	0·88 (0·74 to 1·05)		0·16
REWIND	169/4949 (3%)	237/4952 (5%)	0·70 (0·57 to 0·85)		0·0004
AMPLITUDE-O	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10 to 1·27)		0·11
Subtotal (I^2=43·0%, p=0·12)			**0·86 (0·72 to 1·02)**	**241 (120 to –1694)†**	**0·089**

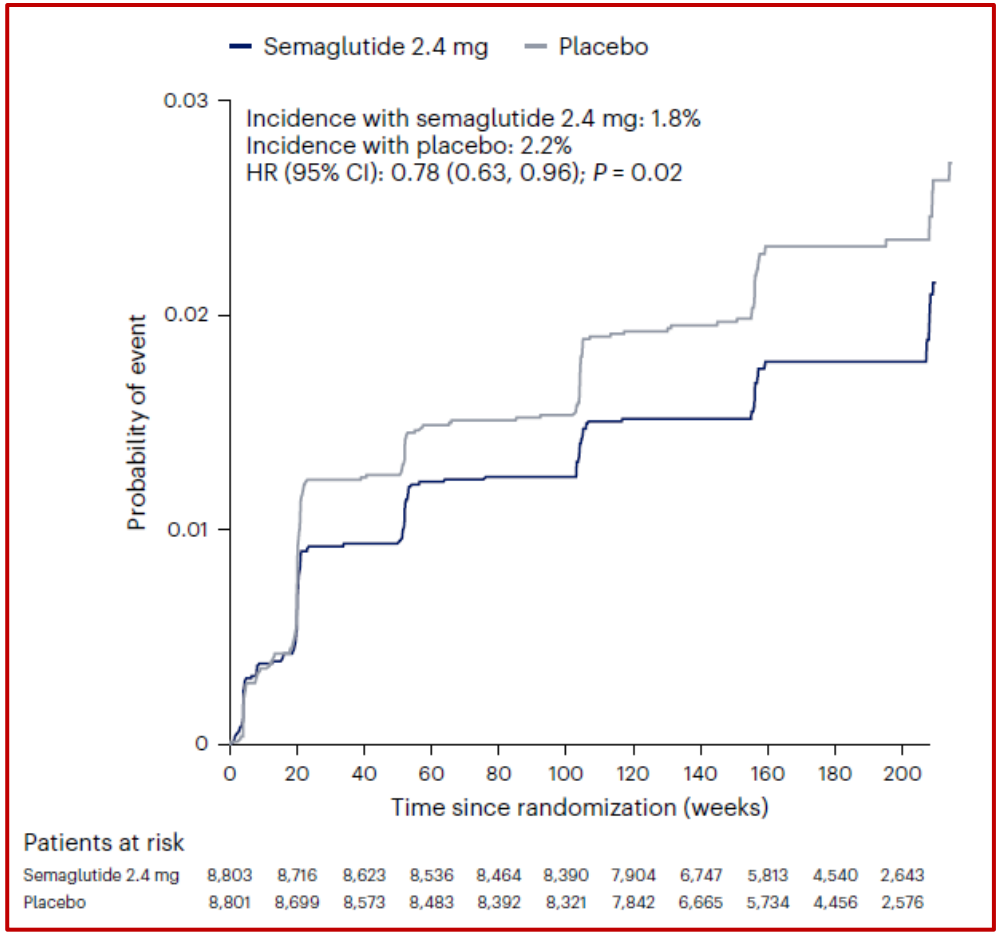


* Either doubling of serum creatinine or ≥40% decline in eGFR + renal replacement therapy or renal death (in EXSCEL)

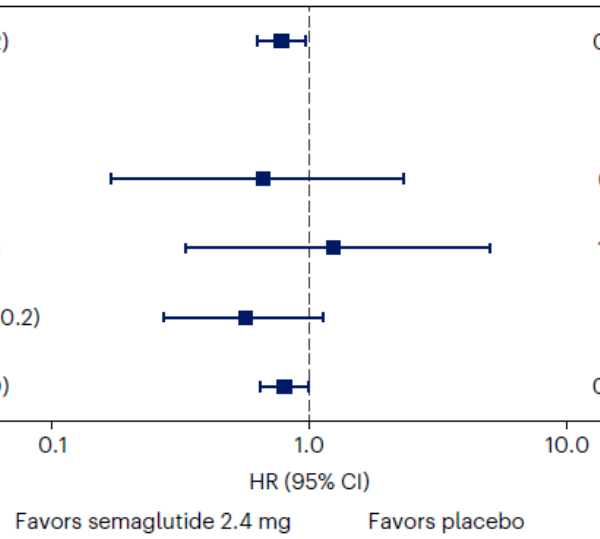
Sattar N et al. *Lancet Diabetes Endocrinol.* 2021;9:653–662

Renal outcomes in CVOTs with GLP-1 RA in people with obesity

The Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity (SELECT) trial



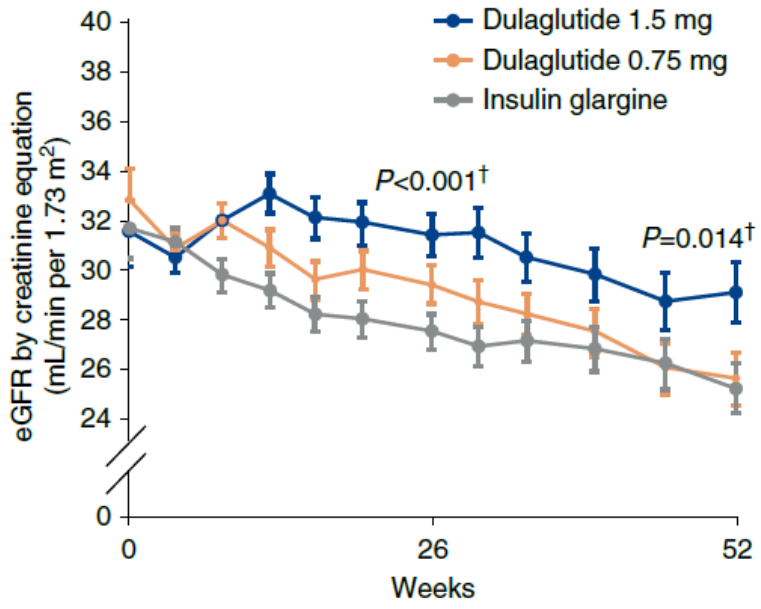
	Semaglutide 2.4 mg (*N* = 8,803), *n* (%)	Placebo (*N* = 8,801), *n* (%)	HR (95% CI); *P* value
5-component kidney composite endpoint	155 (1.8)	198 (2.2)	0.78 (0.63, 0.96); 0.02
Death due to kidney disease	0	0	N/A
Initiation of chronic kidney replacement therapy[a]	4 (0.0)	6 (0.1)	0.66 (0.17, 2.32); 0.52
Onset of persistent eGFR <15 ml min^{-1} 1.73 m^{-2}	5 (0.1)	4 (0.0)	1.24 (0.33, 5.02); 0.74
Onset of persistent ≥50% reduction in eGFR	12/8,724[b] (0.1)	21/8,742[b] (0.2)	0.57 (0.27, 1.14); 0.11
Onset of persistent macroalbuminuria	144 (1.6)	179 (2.0)	0.80 (0.64, 1.00); 0.05

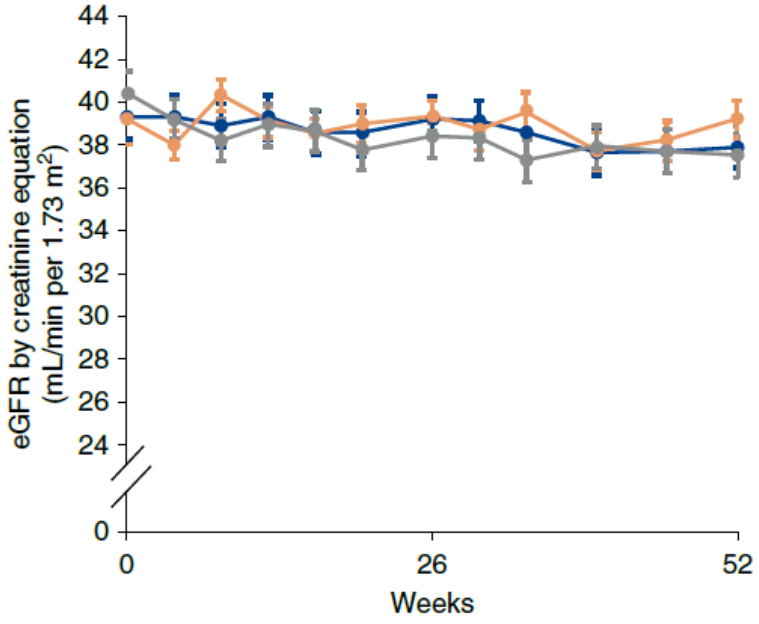


Colhoun HM et al. *Nat Med.* 2024;30:2058 – 2066

Renal outcomes in registrative trials with GLP-1 RA in people with type 2 diabetes

A Study Comparing Dulaglutide With Insulin Glargine on Glycemic Control in Participants With Type 2 Diabetes [T2D] and Moderate or Severe Chronic Kidney Disease [CKD] (AWARD-7 trial) post hoc analysis





Number of participants	Week 0	Week 26	Week 52
Dulaglutide 1.5 mg	84	71	69
Dulaglutide 0.75 mg	84	73	67
Insulin glargine	90	78	64

Number of participants	Week 0	Week 26	Week 52
Dulaglutide 1.5 mg	108	92	93
Dulaglutide 0.75 mg	106	96	93
Insulin glargine	104	98	95

Tuttle KR et al. *Kidney360.* 2020;2:254–262

Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

REWIND
Dulaglutide CV Outcomes Trial

	Dulaglutide (n=4949)		Placebo (n=4952)		Hazard ratio (95% CI)	p value
	Number of patients (%)	Incidence rate (number of events per 100 person-years)	Number of patients (%)	Incidence rate (number of events per 100 person-years)		
Main analyses of renal effect						
Composite renal outcome	848 (17·1%)	3·47	970 (19·6%)	4·07	0·85 (0·77–0·93)	0·0004
Components of composite renal outcome						
New macroalbuminuria	441 (8·9%)	1·76	561 (11·3%)	2·29	0·77 (0·68–0·87)	<0·0001
Sustained decline in eGFR of ≥30%	453 (9·2%)	1·79	500 (10·1%)	2·00	0·89 (0·78–1·01)	0·066
Chronic renal replacement therapy	16 (0·3%)	0·06	21 (0·4%)	0·08	0·75 (0·39–1·44)	0·39
Serious renal adverse event*	84 (1·7%)	0·32	93 (1·9%)	0·36	0·90 (0·67–1·20)	0·46
Sensitivity analyses of renal effect						
Sustained decline in eGFR of ≥40%	169 (3·4%)	0·66	237 (4·8%)	0·93	0·70 (0·57–0·85)	0·0004
Composite renal outcome with this decline	587 (11·9%)	2·36	751 (15·2%)	3·10	0·76 (0·68–0·84)	<0·0001
Sustained decline in eGFR of ≥50%	61 (1·2%)	0·24	108 (2·2%)	0·42	0·56 (0·41–0·76)	0·0002
Composite renal outcome with this decline	496 (10·0%)	1·99	649 (13·1%)	2·66	0·74 (0·66–0·84)	<0·0001

eGFR=estimated glomerular filtration rate. *Based on a search of the REWIND database for any reported adverse event linked to acute renal failure.

Effect of treatment allocation on renal outcomes

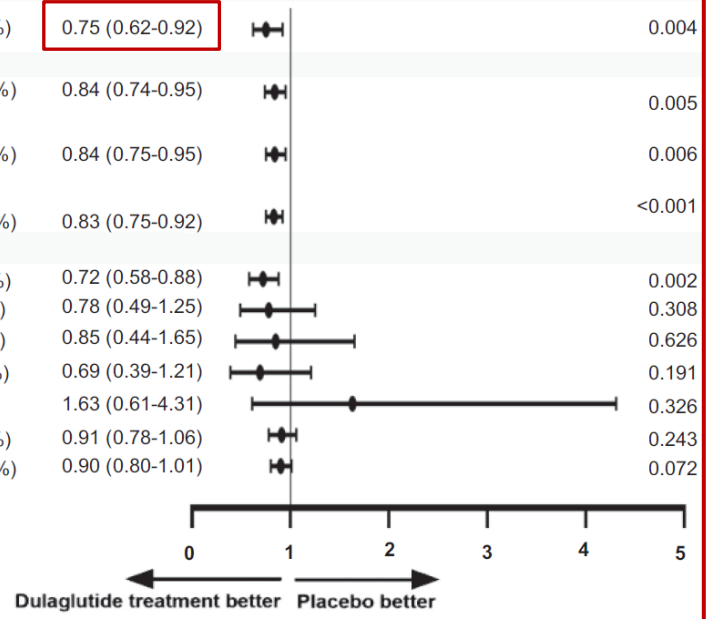
Gerstein H et al. *Lancet.* 2019;394:131–138

Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

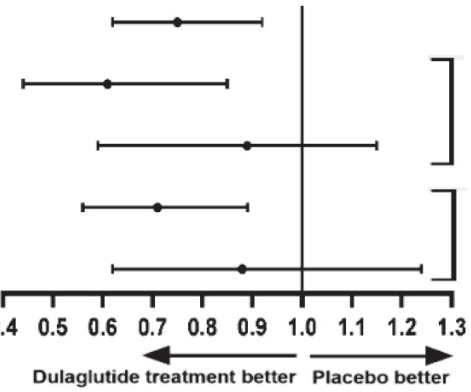
Post hoc analysis

REWIND
Dulaglutide CV Outcomes Trial

	DU 1.5 mg *n* = 4,949 [n(%)]	Placebo *n* = 4,952 [n (%)]	HR (95% CI)	*p*-value
Composite Endpoint				
Sustained eGFR decline ≥40%, ESRD, renal death	181 (3.7%)	238 (4.8%)	0.75 (0.62-0.92)	0.004
Additional Composite Outcomes				
Sustained eGFR decline ≥40%, ESRD, CV death	477 (9.6%)	565 (11.4%)	0.84 (0.74-0.95)	0.005
Sustained eGFR decline ≥40%, ESRD, renal or CV death	485 (9.8%)	570 (11.5%)	0.84 (0.75-0.95)	0.006
Sustained eGFR decline ≥40%, ESRD, all-cause death	676 (13.7%)	800 (16.2%)	0.83 (0.75-0.92)	<0.001
Composite Endpoint Components				
Sustained eGFR decline ≥40%	156 (3.2%)	214 (4.3%)	0.72 (0.58-0.88)	0.002
ESRD	31 (0.6%)	43 (0.9%)	0.78 (0.49-1.25)	0.308
Renal replacement therapy	16 (0.3%)	21 (0.4%)	0.85 (0.44-1.65)	0.626
Sustained eGFR < 15	21 (0.4%)	32 (0.5%)	0.69 (0.39-1.21)	0.191
Renal death	11 (0.2%)	7 (0.1%)	1.63 (0.61-4.31)	0.326
CV death	317 (6.4%)	346 (7.0%)	0.91 (0.78-1.06)	0.243
All-cause death	536 (10.8%)	592 (12.0%)	0.90 (0.80-1.01)	0.072

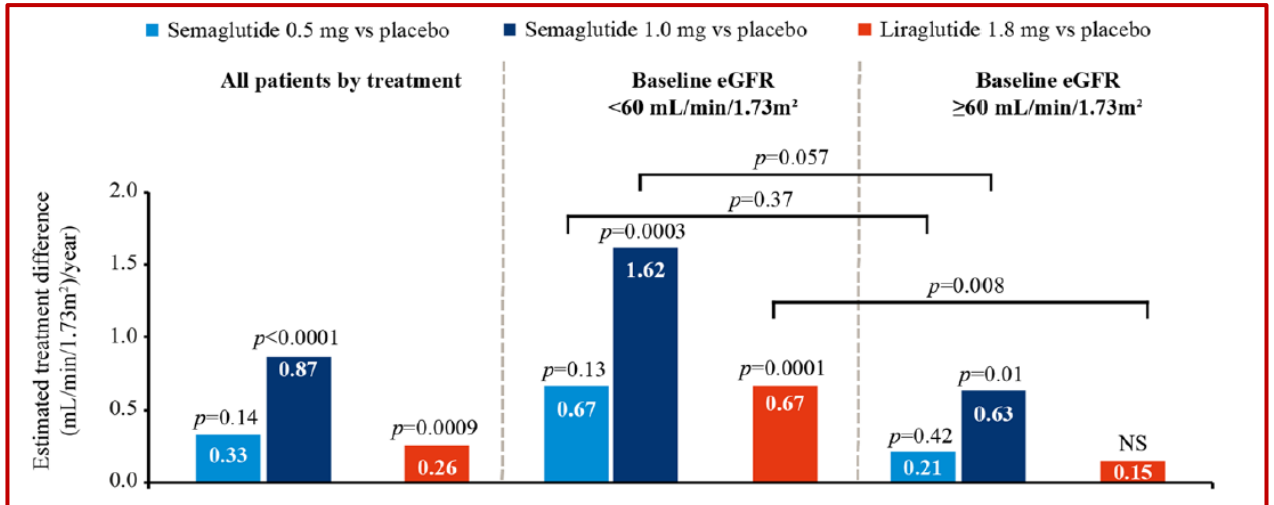


Population group	Dulaglutide 1.5 mg *n* = 4,949 [n(%)]	Placebo *n* = 4,952 [n(%)]	HR (95% CI)	Interaction *p*-value
All participants	181 (3.7%)	238 (4.8%)	0.75 (0.62-0.92)	
UACR <30 mg/g	58/2,917 (2.0%)	94/2,863 (3.3%)	0.61 (0.44-0.85)	0.077
UACR ≥30 mg/g	115/1,707 (6.7%)	129/1,760 (7.3%)	0.89 (0.69-1.15)	
eGFR ≥60 mL/min/1.73 m²	120/3,904 (3.1%)	165/3,870 (4.3%)	0.71 (0.56-0.89)	0.306
eGFR <60 mL/min/1.73 m²	60/944 (6.4%)	72/988 (7.3%)	0.88 (0.62-1.24)	



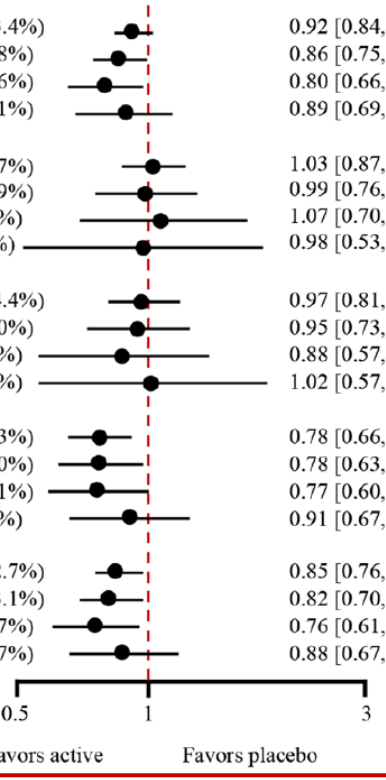
Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

Pooled analysis



Annual eGFR change (mL/min/1.73m²)/year	Estimate [95% CI]				
	SUSTAIN 6			LEADER	
	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	Liraglutide 1.8 mg	Placebo
All patients by treatment	n=825 −1.59 [−1.95, −1.23]	n=821 −1.05 [−1.41, −0.69]	n=1648 −1.92 [−2.18, −1.67]	n=4512 −1.72 [−1.84, −1.61]	n=4498 −1.98 [−2.10, −1.87]
<60 mL/min/1.73m² at baseline	n=212 −1.20 [−1.90, −0.49]	n=204 −0.25 [−0.97, 0.48]	n=427 −1.87 [−2.37, −1.36]	n=968 −1.44 [−1.68, −1.19]	n=905 −2.11 [−2.37, −1.85]
≥60 mL/min/1.73m² at baseline	n=613 −1.73 [−2.15, −1.32]	n=617 −1.31 [−1.72, −0.90]	n=1221 −1.94 [−2.24, −1.64]	n=3544 −1.80 [−1.92, −1.67]	n=3593 −1.95 [−2.08, −1.83]

Subgroup/outcome	Events/N_{Active}	Events/$N_{Placebo}$	HR [95% CI]	*p* value	*p* value for interaction
Pooled population					
30% eGFR reduction	791/6316 (12.5%)	848/6321 (13.4%)	0.92 [0.84, 1.02]	0.10	
40% eGFR reduction	378/6316 (6.0%)	432/6321 (6.8%)	0.86 [0.75, 0.99]	0.039	
50% eGFR reduction	185/6316 (2.9%)	229/6321 (3.6%)	0.80 [0.66, 0.97]	0.023	
57% eGFR reduction	121/6316 (1.9%)	135/6321 (2.1%)	0.89 [0.69, 1.13]	0.34	
Normoalbuminuria					
30% eGFR reduction	304/3842 (7.9%)	292/3807 (7.7%)	1.03 [0.87, 1.21]	0.75	0.06
40% eGFR reduction	112/3842 (2.9%)	111/3807 (2.9%)	0.99 [0.76, 1.28]	0.91	0.32
50% eGFR reduction	44/3842 (1.1%)	40/3807 (1.1%)	1.07 [0.70, 1.65]	0.75	0.43
57% eGFR reduction	21/3842 (0.5%)	21/3807 0.6%)	0.98 [0.53, 1.79]	0.94	0.94
Microalbuminuria					
30% eGFR reduction	239/1695 (14.1%)	237/1645 (14.4%)	0.97 [0.81, 1.17]	0.78	0.06
40% eGFR reduction	112/1695 (6.6%)	115/1645 (7.0%)	0.95 [0.73, 1.23]	0.69	0.32
50% eGFR reduction	39/1695 (2.3%)	43/1645 (2.6%)	0.88 [0.57, 1.36]	0.57	0.43
57% eGFR reduction	23/1695 (1.4%)	22/1645 (1.3%)	1.02 [0.57, 1.83]	0.95	0.94
Macroalbuminuria					
30% eGFR reduction	232/657 (35.3%)	301/729 (41.3%)	0.78 [0.66, 0.92]	0.004	0.06
40% eGFR reduction	147/657 (22.4%)	197/729 (27.0%)	0.78 [0.63, 0.97]	0.022	0.32
50% eGFR reduction	100/657 (15.2%)	139/729 (19.1%)	0.77 [0.60, 1.00]	0.050	0.43
57% eGFR reduction	75/657 (11.4%)	89/729 (12.2%)	0.91 [0.67, 1.24]	0.55	0.94
Micro- or macroalbuminuria					
30% eGFR reduction	471/2352 (20.0%)	538/2374 (22.7%)	0.85 [0.76, 0.97]	0.013	0.08
40% eGFR reduction	259/2352 (11.0%)	312/2374 (13.1%)	0.82 [0.70, 0.97]	0.019	0.25
50% eGFR reduction	139/2352 (5.9%)	182/2374 (7.7%)	0.76 [0.61, 0.95]	0.016	0.16
57% eGFR reduction	98/2352 (4.2%)	111/2374 (4.7%)	0.88 [0.67, 1.16]	0.37	0.76

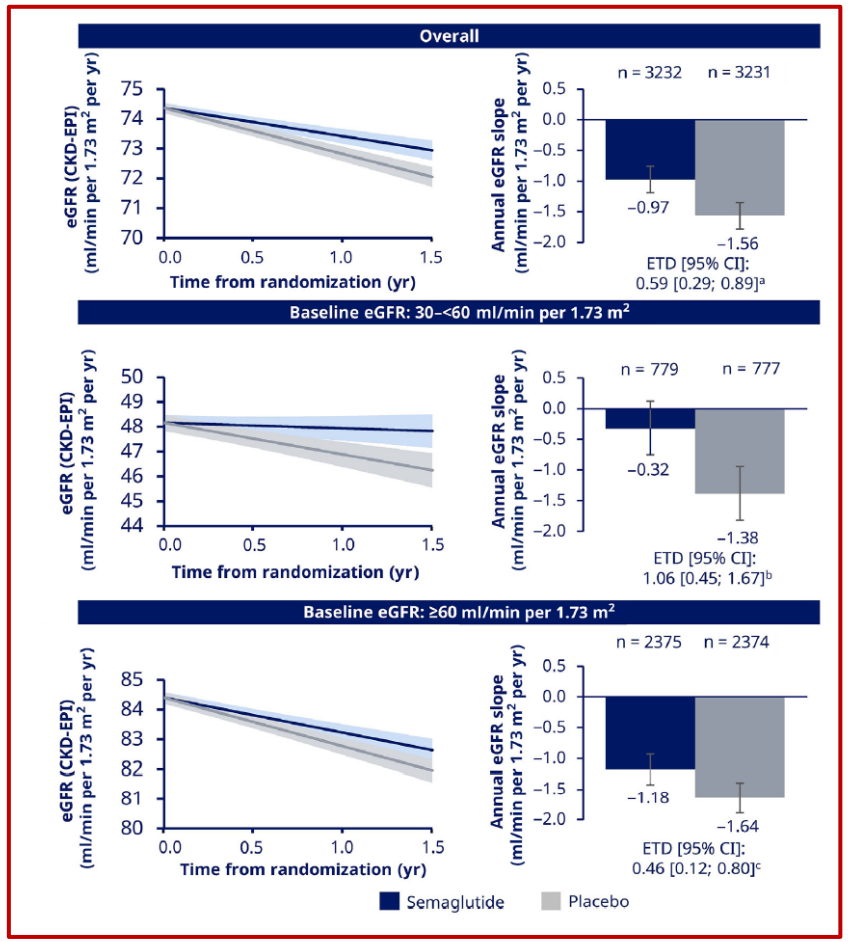


Shaman AM et al. *Circulation.* 2022;145:575–585

Renal outcomes in CVOTs with GLP-1 RAs in people with type 2 diabetes

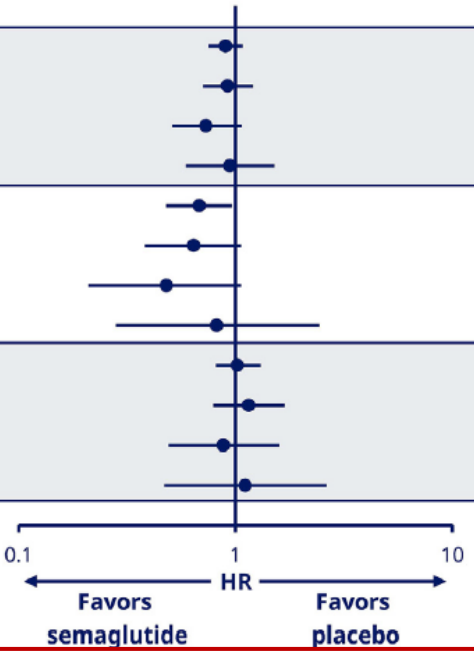
Pooled analysis

Annual eGFR change



Time to onset of persistent eGFR reductions

	eGFR reduction threshold (%)	Semaglutide (n)	Placebo (n)	HR [95% CI]	*P* value	Interaction *P* value[a]
Overall pooled population	≥30	223	244	0.90 [0.75; 1.08]	0.27	N/A
	≥40	105	113	0.92 [0.71; 1.20]	0.54	N/A
	≥50	48	65	0.73 [0.51; 1.07]	0.11	N/A
	≥57	34	36	0.94 [0.59; 1.51]	0.81	N/A
Baseline eGFR ≥30 to <60 ml/min per 1.73 m²	≥30	58	79	0.68 [0.48; 0.96]	0.03	0.05
	≥40	25	37	0.64 [0.38; 1.06]	0.08	0.07
	≥50	9	18	0.48 [0.21; 1.06]	0.07	0.22
	≥57	6	7	0.82 [0.28; 2.44]	0.72	0.66
Baseline eGFR ≥60 ml/min per 1.73 m²	≥30	136	134	1.02 [0.81; 1.30]	0.84	0.05
	≥40	57	50	1.15 [0.79; 1.68]	0.47	0.07
	≥50	21	24	0.88 [0.49; 1.59]	0.68	0.22
	≥57	11	10	1.11 [0.47; 2.63]	0.80	0.66



Tuttle KR et al. *Kidney Int.* 2023;103:772–781

Renal outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

FLOW
semaglutide | renal outcomes trial

The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease

Background

Evidence has emerged of potential kidney-protective effects of GLP-1RAs in people with T2D. FLOW is a dedicated kidney outcomes trial to assess semaglutide in a population with CKD and T2D at high risk of kidney disease progression.

Methods

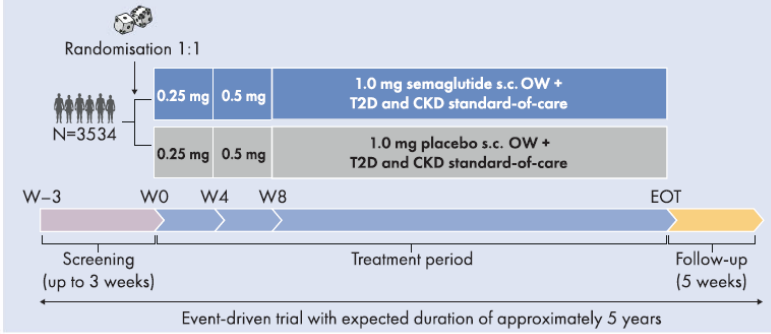
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

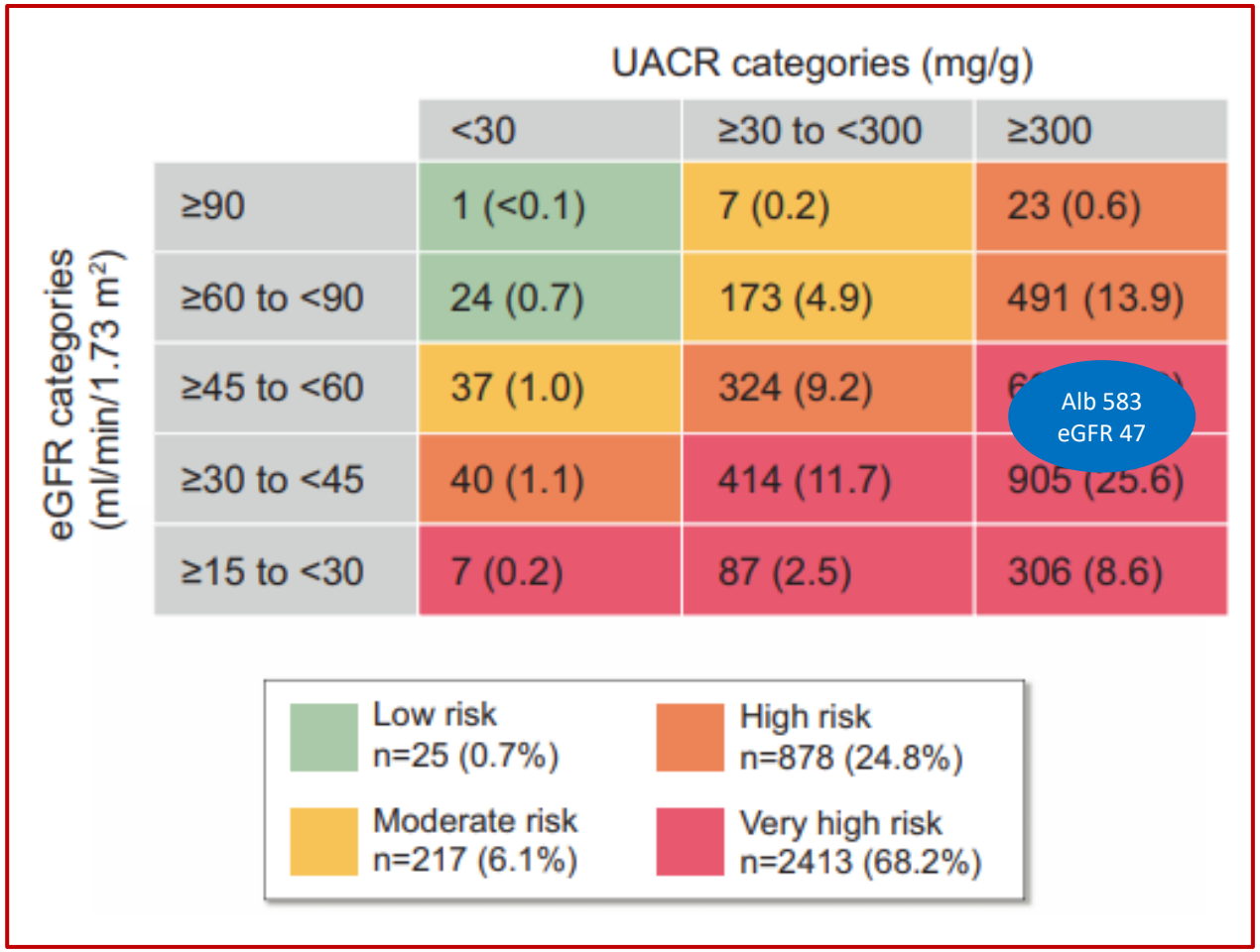
CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Conclusion

FLOW will evaluate the effect of semaglutide on kidney outcomes in participants with CKD and T2D, and is expected to complete in late 2024.

ERA NDT NEPHROLOGY DIALYSIS TRANSPLANTATION

Rossing, P., et al. NDT (2023)
@NDTSocial

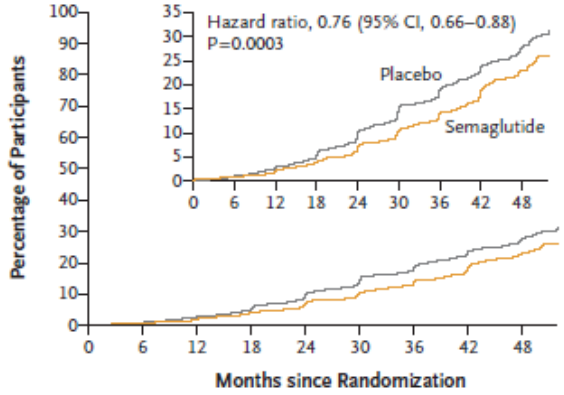


Rossing P et al. *Nephrol Dial Transplant.* 2023;38:2041–2051

Renal outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

FLOW
semaglutide | renal outcomes trial

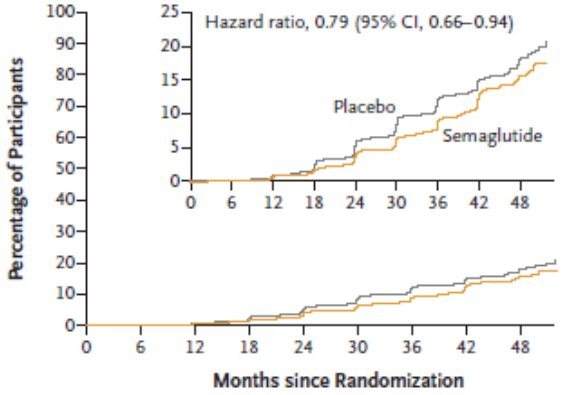
A First Major Kidney Disease Event



No. at Risk

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

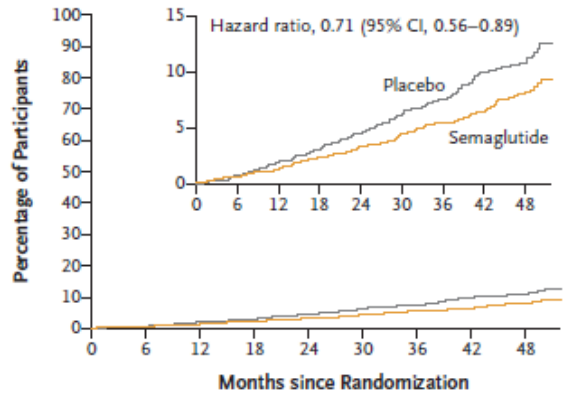
B First Kidney-Specific Component Event



No. at Risk

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

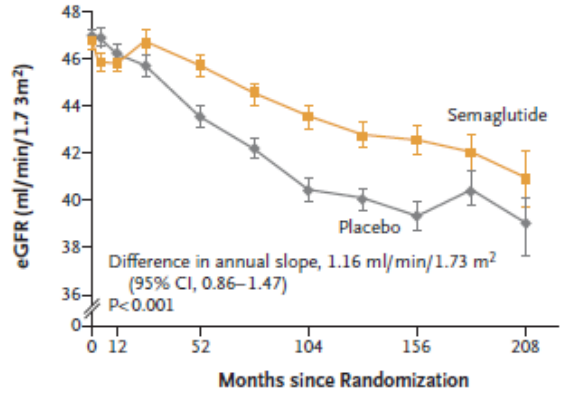
C Death from Cardiovascular Causes



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
Semaglutide	1767	1739	1703	1665	1627	1583	1234	838	460

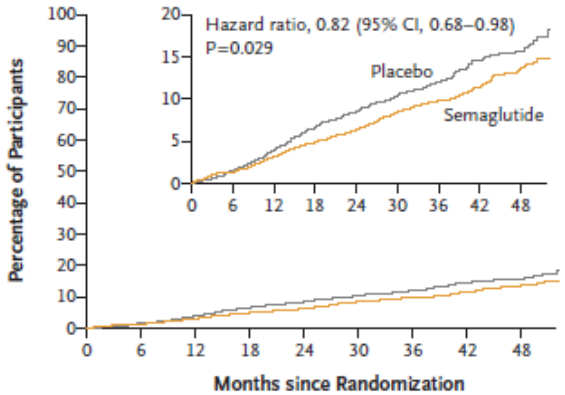
D Total eGFR Slope



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

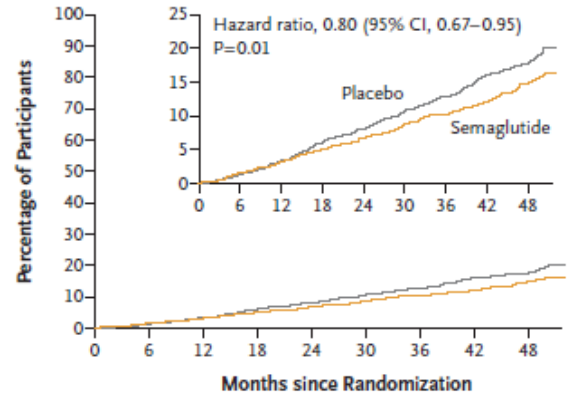
E First Major Cardiovascular Event



No. at Risk

Placebo	1766	1721	1663	1583	1535	1478	1133	731	418
Semaglutide	1767	1725	1672	1622	1575	1515	1176	793	430

F Death from Any Cause



No. at Risk

Placebo	1766	1737	1697	1641	1601	1544	1185	772	437
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Perkovic V et al. *N Engl J Med.* 2024;391:109–121

Renal outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

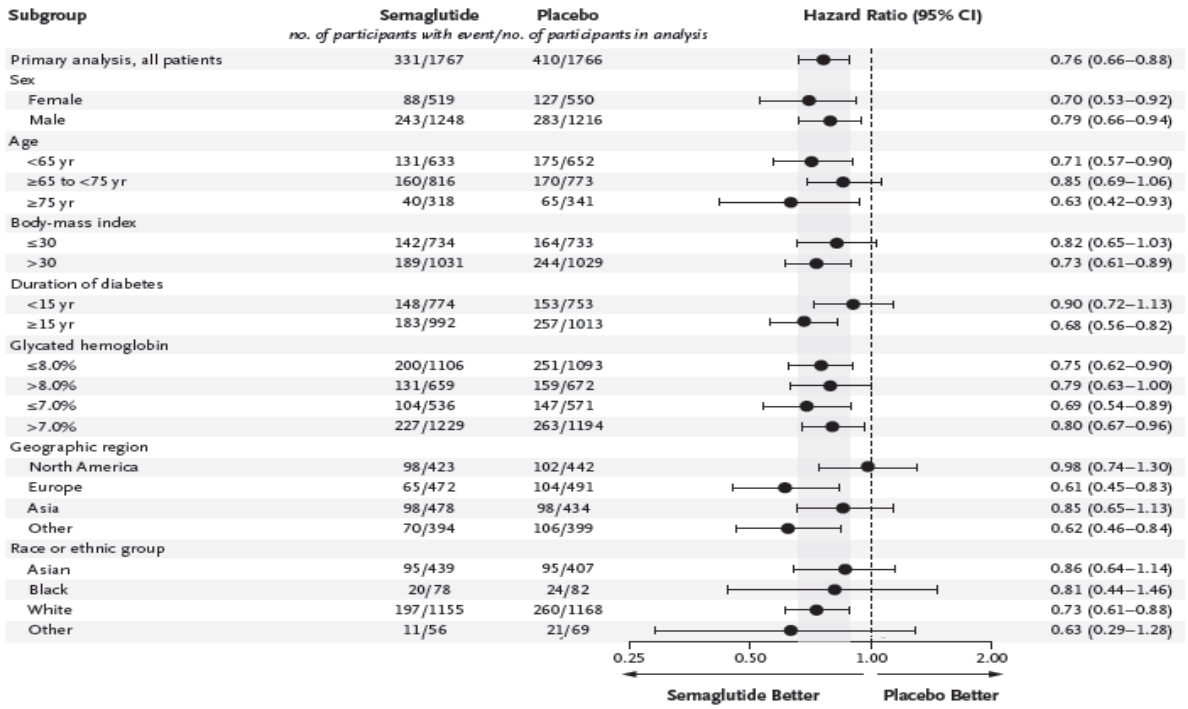
FLOW
semaglutide | renal outcomes trial

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01
Supportive secondary outcomes					
Ratio of urinary albumin-to-creatinine ratio at week 104 to urinary albumin-to-creatinine ratio at baseline	0.60	0.88	0.68 (0.62 to 0.75)‡	—	—
Mean change in body weight from baseline to week 104 — kg	−5.55	−1.45	—	−4.10 (−4.56 to −3.65)	—
Mean change in glycated hemoglobin level from baseline to week 104 — percentage points	−0.87	−0.06	—	−0.81 (−0.90 to −0.72)	—
Mean change in systolic blood pressure from baseline to week 104 — mm Hg	−3.79	−1.55	—	−2.23 (−3.33 to −1.13)	—
Mean change in diastolic blood pressure from baseline to week 104 — mm Hg	−0.23	−1.01	—	0.78 (0.16 to 1.41)	—
Mean change in eGFR from baseline to week 12 — ml/min/1.73 m²	−1.07	−1.05	—	−0.03 (−0.56 to 0.51)	—
Mean annual rate of change in eGFR from week 12 to end of trial — ml/min/1.73 m²	−2.36	−3.30	—	0.94 (0.62 to 1.26)	—
Mean change in eGFR by the cystatin C equation from baseline to week 104 — ml/min/1.73 m²	−2.01	−5.41	—	3.39 (2.63 to 4.15)	—

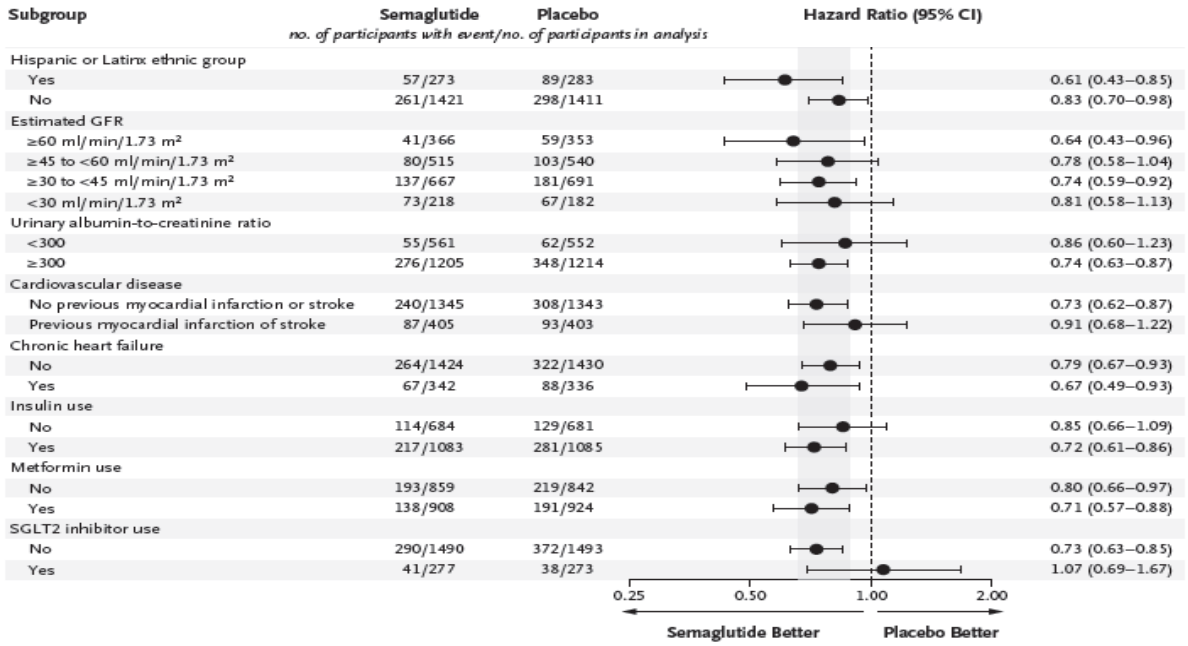
Perkovic V et al. *N Engl J Med.* 2024;391:109–121

Renal outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

FLOW
semaglutide | renal outcomes trial



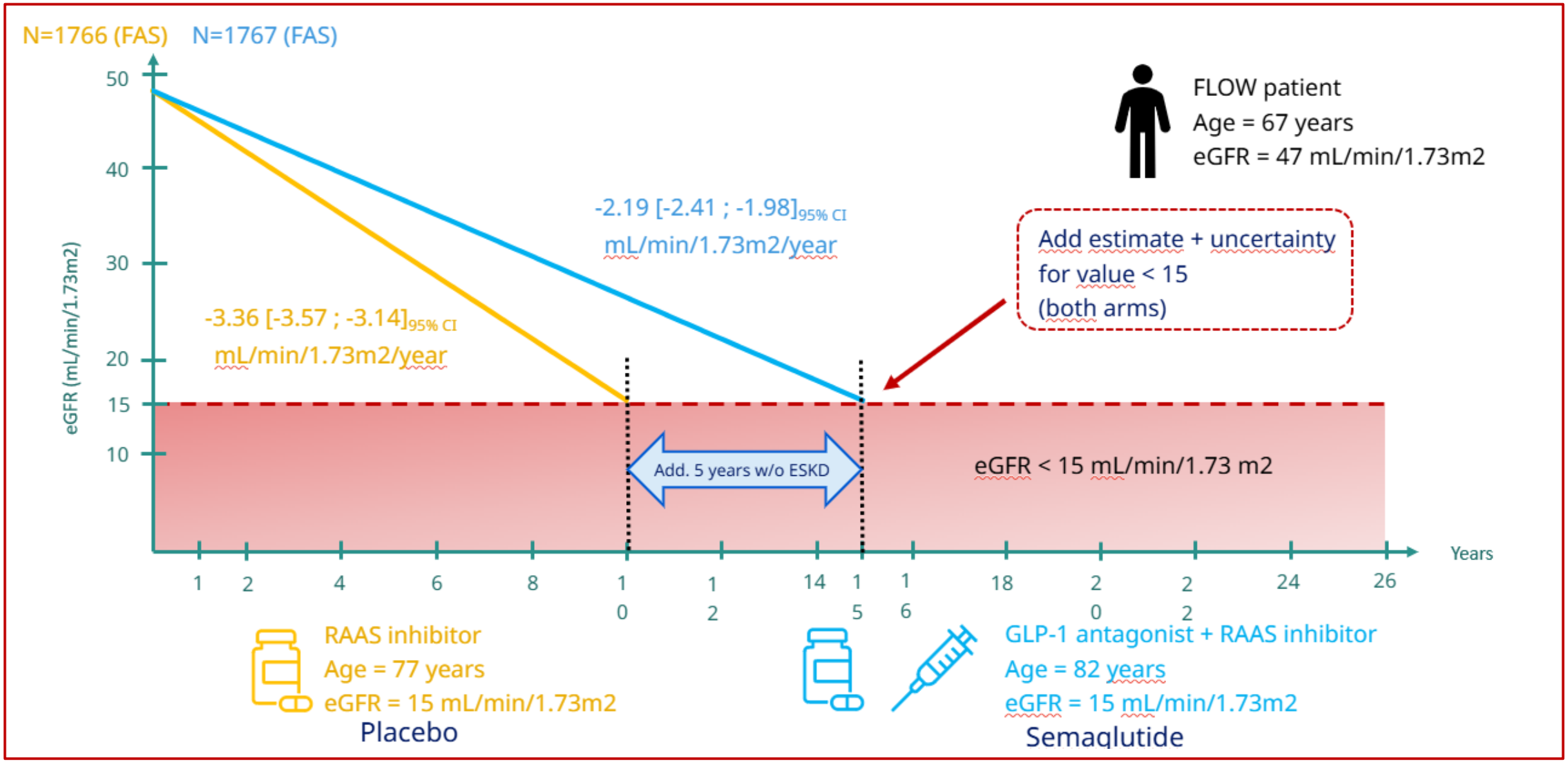
Subgroup	Semaglutide	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/no. of participants in analysis		
Primary analysis, all patients	331/1767	410/1766	0.76 (0.66–0.88)
Sex			
Female	88/519	127/550	0.70 (0.53–0.92)
Male	243/1248	283/1216	0.79 (0.66–0.94)
Age			
<65 yr	131/633	175/652	0.71 (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			
North America	98/423	102/442	0.98 (0.74–1.30)
Europe	65/472	104/491	0.61 (0.45–0.83)
Asia	98/478	98/434	0.85 (0.65–1.13)
Other	70/394	106/399	0.62 (0.46–0.84)
Race or ethnic group			
Asian	95/439	95/407	0.86 (0.64–1.14)
Black	20/78	24/82	0.81 (0.44–1.46)
White	197/1155	260/1168	0.73 (0.61–0.88)
Other	11/56	21/69	0.63 (0.29–1.28)



Subgroup	Semaglutide	Placebo	Hazard Ratio (95% CI)
	no. of participants with event/no. of participants in analysis		
Hispanic or Latinx ethnic group			
Yes	57/273	89/283	0.61 (0.43–0.85)
No	261/1421	298/1411	0.83 (0.70–0.98)
Estimated GFR			
≥60 ml/min/1.73 m²	41/366	59/353	0.64 (0.43–0.96)
≥45 to <60 ml/min/1.73 m²	80/515	103/540	0.78 (0.58–1.04)
≥30 to <45 ml/min/1.73 m²	137/667	181/691	0.74 (0.59–0.92)
<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)

Perkovic V et al. *N Engl J Med.* 2024;391:109–121

Long-term renal protection with semaglutide in people with type 2 diabetes and CKD



CV outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

FLOW
semaglutide | renal outcomes trial

Participants and treatment

- Adults with T2D and CKD
- Subcutaneous semaglutide 1 mg or placebo weekly (R 1:1)

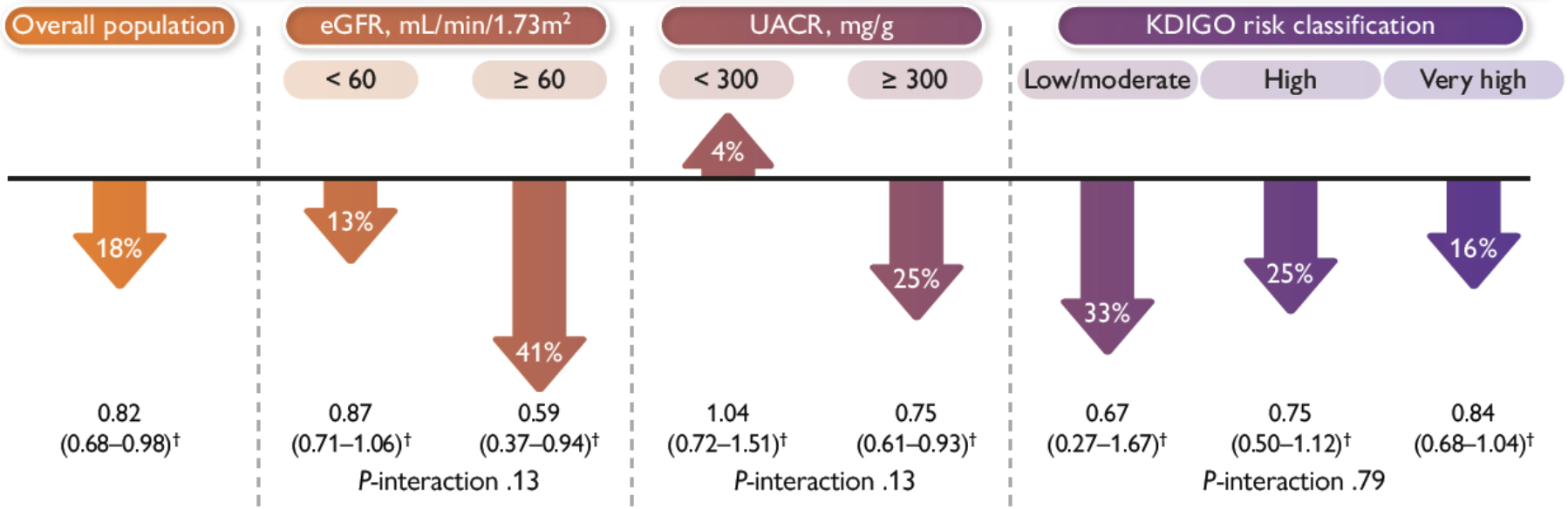
Main outcomes

- Composite major CV events outcome (CV death, non-fatal MI, non-fatal stroke)
- Death from any cause

CKD severity

eGFR	< 60mL/min/1.73m² or ≥ 60mL/min/1.73m²
UACR	< 300mg/g or ≥ 300mg/g
KDIGO risk*	1/2 (low/moderate), 3 (high), or 4 (very high)

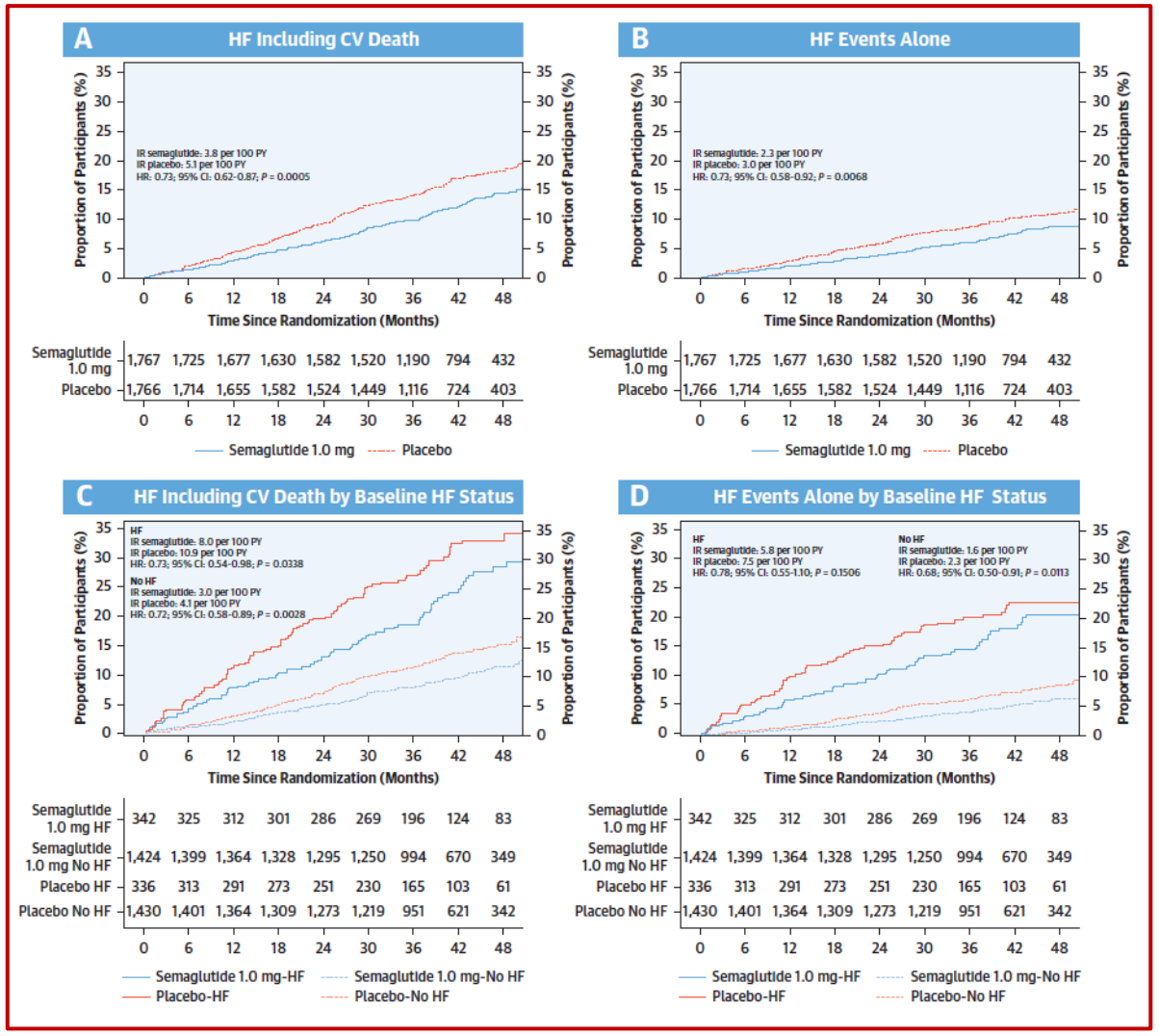
Effect of semaglutide versus placebo on the composite of CV death, non-fatal MI, and non-fatal stroke by baseline CKD status

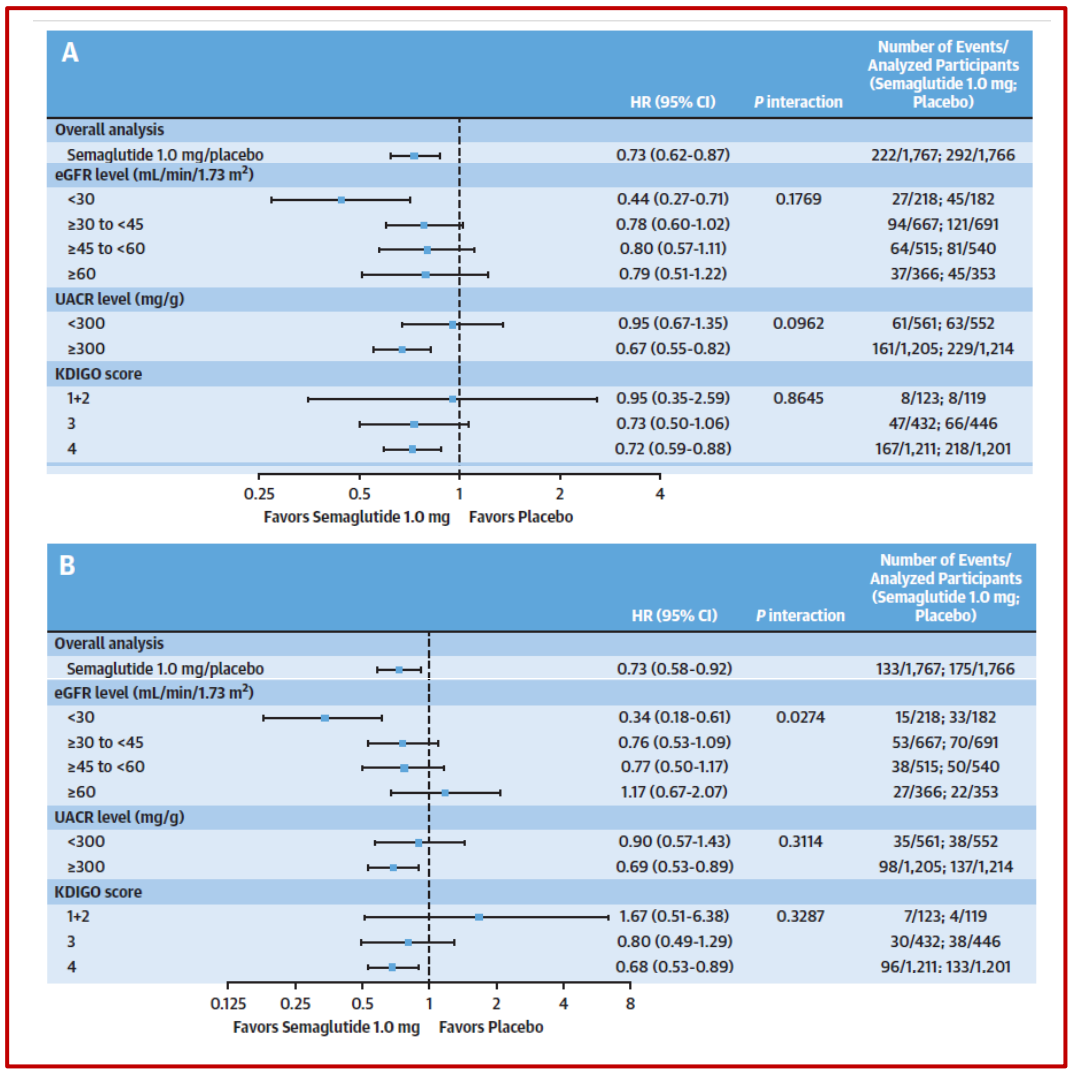


Mahaffey KW et al. *Heart J.* 2024 Aug 30

CV outcomes in the FLOW ROT with semaglutide in people with type 2 diabetes and CKD

FLOW
semaglutide | renal outcomes trial





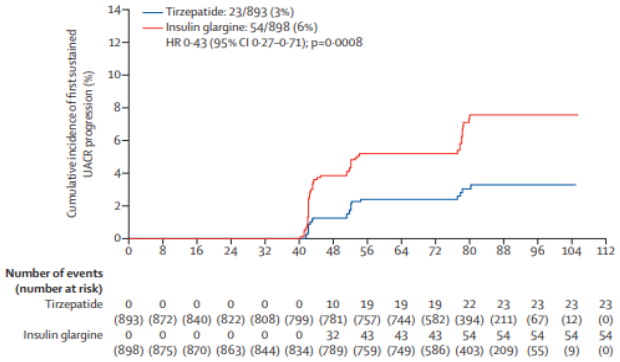
Pratley RE et al. *J Am Coll Cardiol.* 2024;84:1615–1628

Renal outcomes in trial with dual GLP-1 and GIP agonist in people with type 2 diabetes

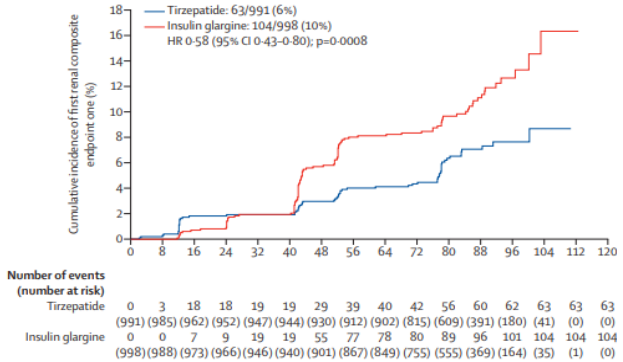
SURPASS-4

Efficacy and Safety of Tirzepatide Once Weekly Versus Insulin Glargine in Patients with Type 2 Diabetes and Increased Cardiovascular Risk

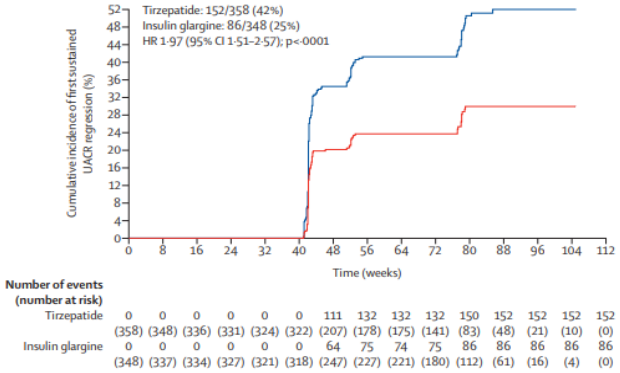
Time to first sustained UACR progression



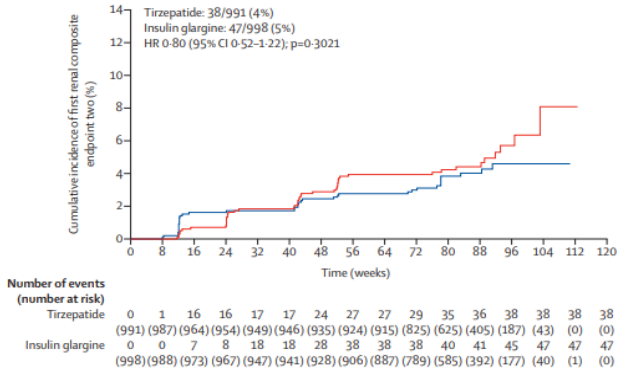
Time to first occurrence of renal composite endpoint with macroalb



Time to first sustained UACR regression



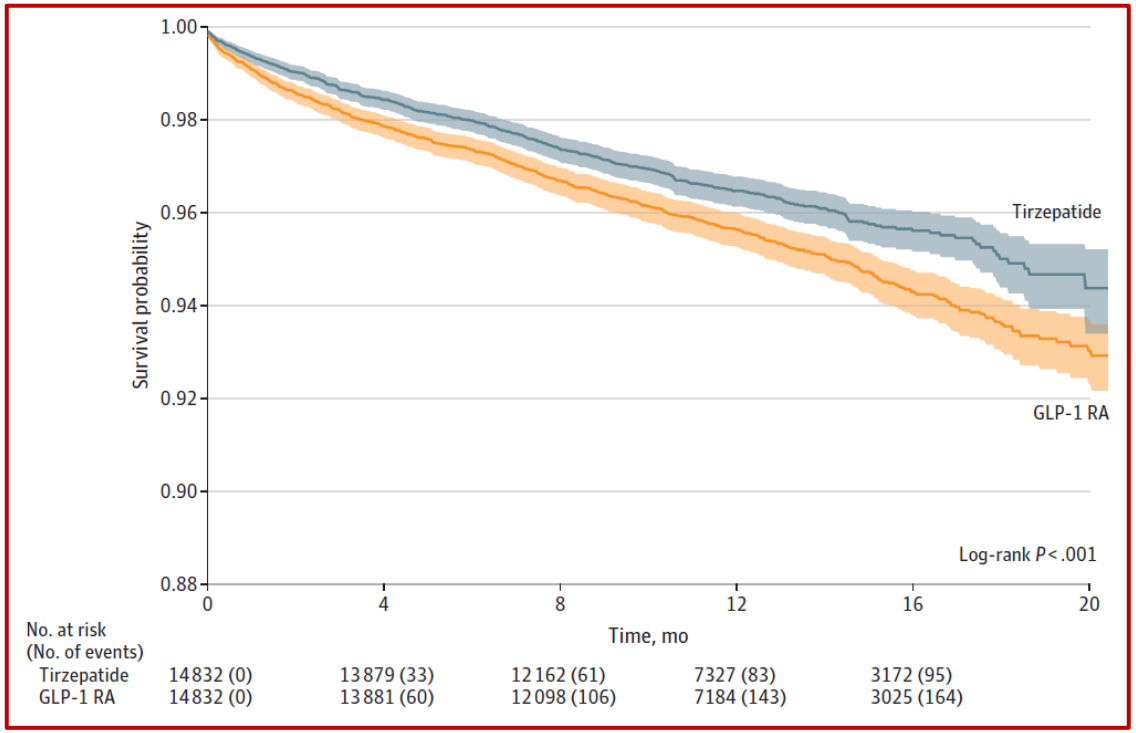
Time to first occurrence of renal composite endpoint without macroalb



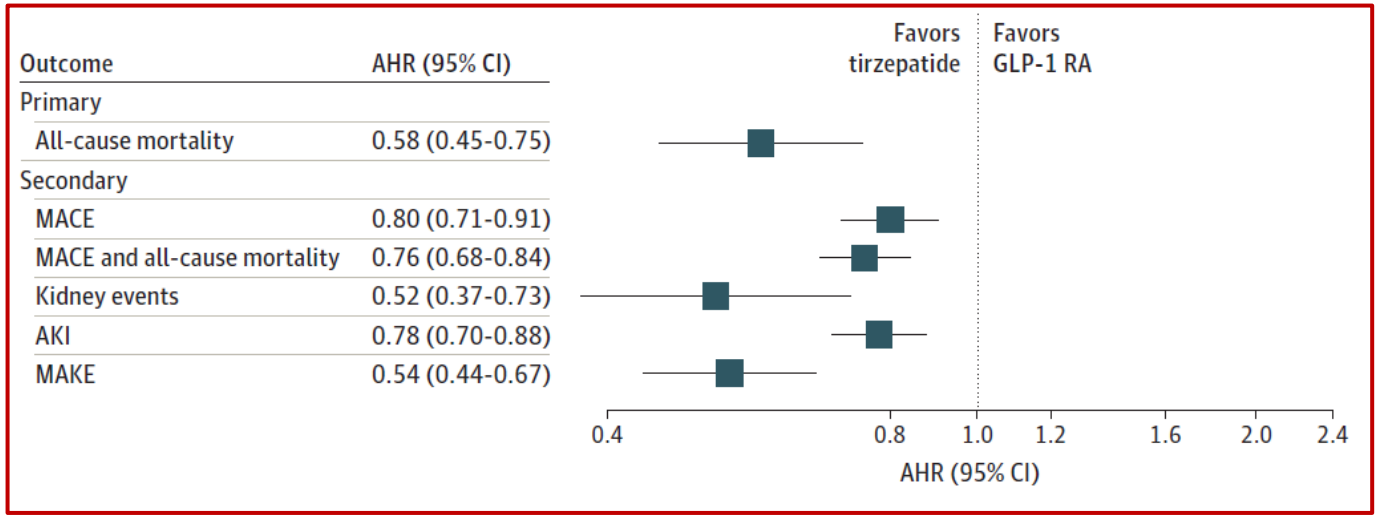
Heerspink HJL et al. *Lancet Diabetes Endocrinol.* 2022;10:774–785

Cardio-renal outcomes with dual vs single incretin agonists in people with type 2 diabetes

Retrospective cohort study using the US Collaborative Network of TriNetX data



Outcome	No. of patients with outcome		AHR (95% CI)	*P* value	E-value (E-value for the upper limit of CI)
	Tirzepatide (n = 14 832)	GLP-1 RA (n = 14 832)			
Primary outcome					
All-cause mortality	95	166	0.58 (0.45-0.75)[a]	<.001[b]	2.82 (1.99)
Secondary outcomes					
MACEs	472	589	0.80 (0.71-0.91)[a]	<.001[b]	1.79 (1.44)
MACE and all-cause mortality	543	721	0.76 (0.68-0.84)[a]	<.001[b]	1.98 (1.65)
Kidney events	53	102	0.52 (0.37-0.73)[a]	<.001[b]	3.24 (2.09)
Acute kidney injury	506	652	0.78 (0.70-0.88)[a]	<.001[b]	1.87 (1.53)
MAKEs	129	241	0.54 (0.44-0.67)[a]	<.001[b]	3.11 (2.35)

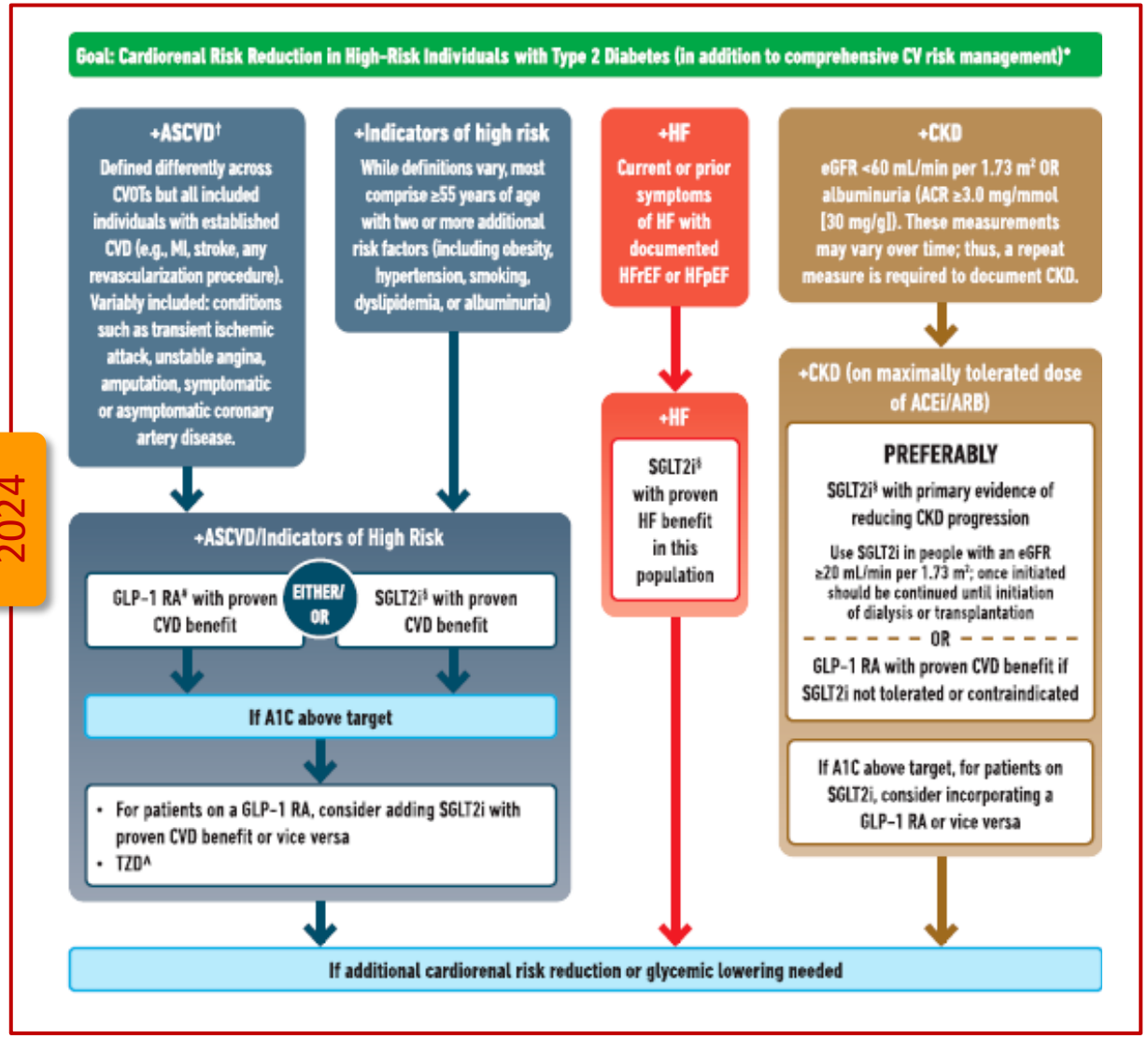


Chuang M-H et al. *JAMA Network Open.* 2024;7:e2427258

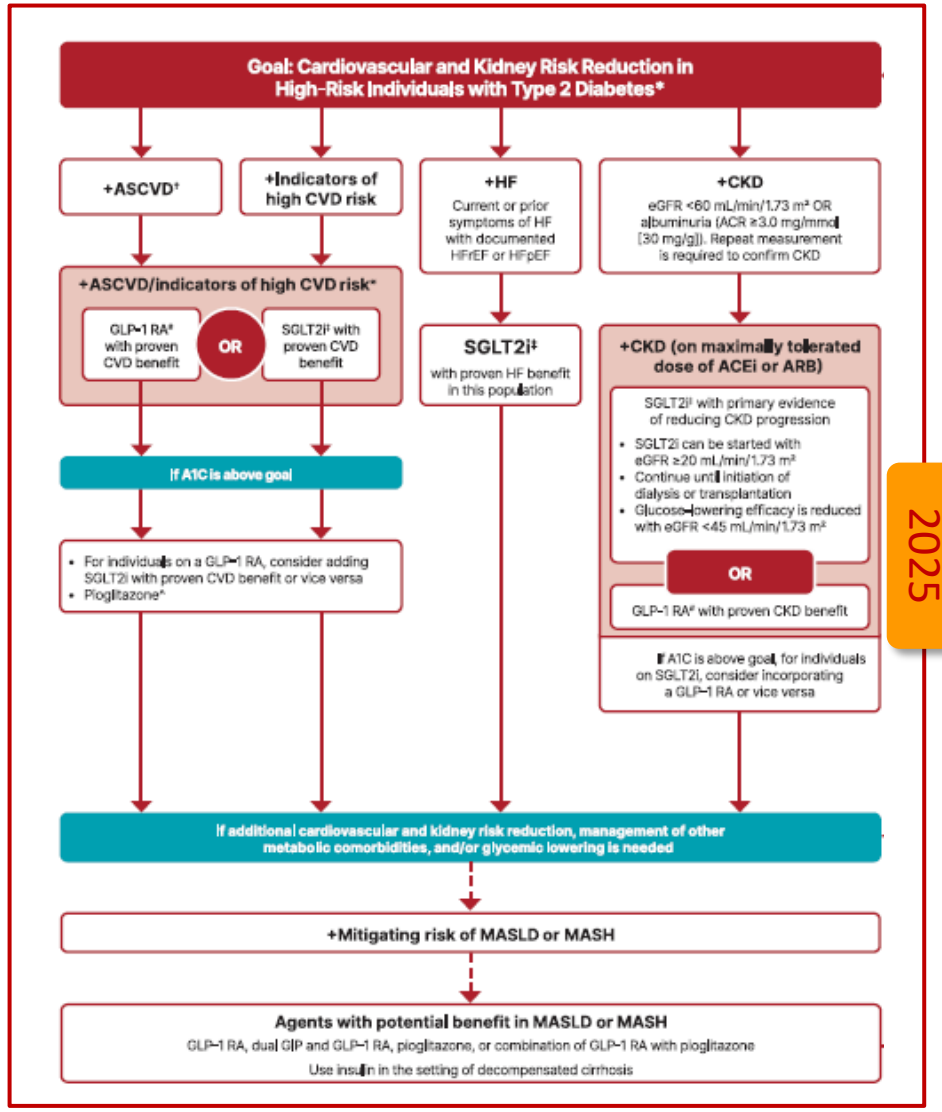
Guidelines for the management of hyperglycemia in people with type 2 diabetes

American Diabetes Association (ADA) Standards of Care

2024



2025



ADA. *Diabetes Care.* 2024;47(Suppl. 1):S158–S178

ADA. *Diabetes Care.* 2025;48(Suppl. 1):S181–S206

Domanda 1

Nei pazienti con diabete di tipo 2 e CKD, i GLP-1 RAs determinano una riduzione dell'endpoint composito renale senza macroalbuminuria:

A. Simile a quella di SGLT-2 inibitori e MRA non steroidei

B. Inferiore a quella di SGLT-2 inibitori e MRA non steroidei

C. Inferiore a quella di SGLT-2 inibitori e superiore a quella di MRA non steroidei

D. Inferiore a quella di SGLT-2 inibitori e simile a quella di MRA non steroidei

Renal outcomes in ROTs with SGLT-2 inhibitors and GLP-1 RAs

Trial	(1) CREDENCE	(2) DAPACKD	(3) EMPA-KIDNEY	(4) FIDELIO-DKD[1]	(5) FLOW
Drug	Canagliflozin	Dapagliflozin	Empagliflozin	Finerenone	Semaglutide
Participants, n	4,401	4,304	6,609	5,734	3,533
Follow-up, years	2.6	2.4	2.0	2.6	3.4
GFR impairment, %	60.0	89.5	>80	88.8	79.6
Albuminuria (macro), %	99.3 (87.9)	~100 (>80)	79.9 (51.7)	99.5 (87.2)	97.1 (68.2)
Doubling of serum creatinine	0.60 (0.48–0.76)	NA	NA	NA	NA
eGFR reduction	NA	0.53 (0.42–0.67)*	0.70 (0.61–0.81)†	0.81 (0.72–0.92)†	0.73 (0.59–0.89)*
ESRD / need for RRT	0.68 (0.54–0.86)	0.64 (0.50–0.82)	0.67 (0.52–0.85)	0.86 (0.67–1.10	0.84 (0.63–1.12)
Renal death	NA	NA	0.90 (0.22–3.66)	NA	0.97 (0.27–3.49)
Cardiovascular death	0.78 (0.61–1.00)	0.81 (0.58–1.12)	0.84 (0.60–1.19)	0.86 (0.68–1.08)	0.71 (0.56–0.89)
Composite cardiorenal outcome	0.70 (0.59–0.82)	0.61 (0.51–0.72)	0.72 0.64–0.82)	NA	0.76 (0.66–0.88)
Composite kidney outcome	0.66 (0.53–0.81)	0.56 (0.45–0.68)	NA	0.82 (0.73–0.93)	0.79 (0.66–0.94)

* ≥50% eGFR reduction; † ≥40% eGFR reduction

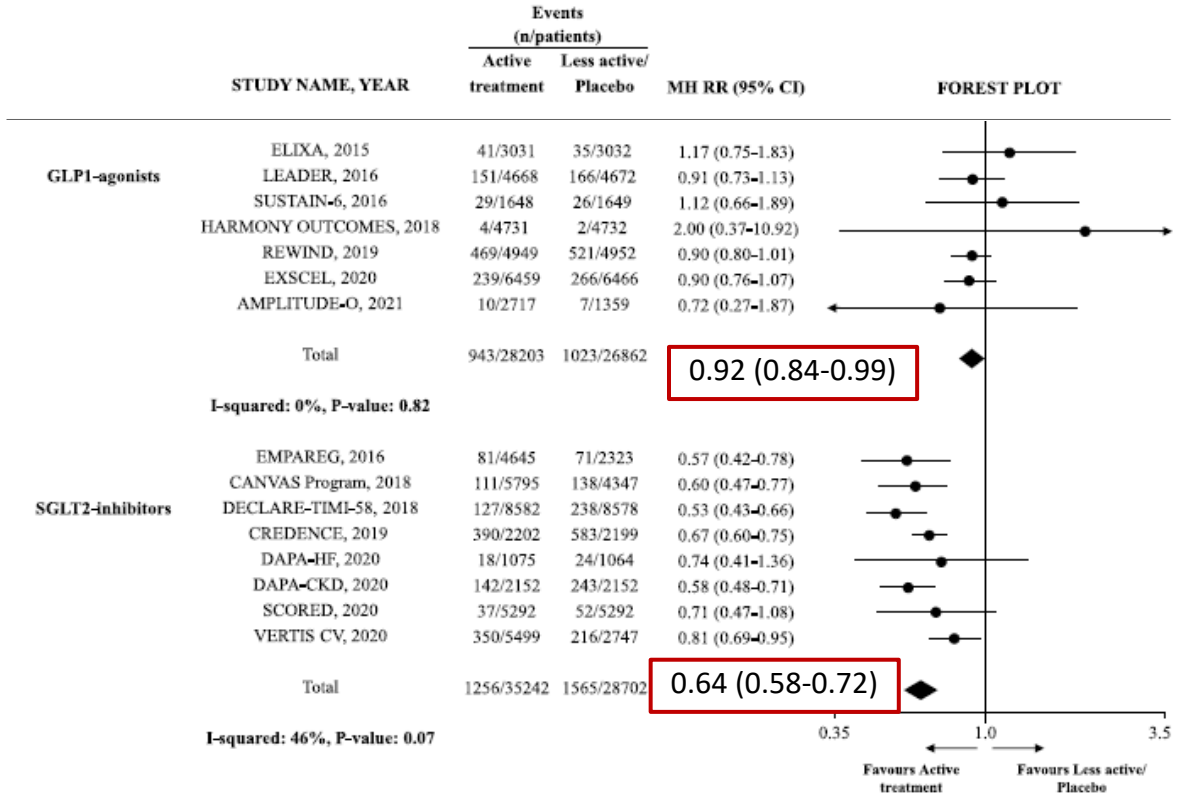
1. Perkovic V et al. *N Engl J Med.* 2019;80:2295–2306; 2. Heerspink HJL et al. *N Engl J Med.* 2020;383:1436–1446; 3. EMPA–KIDNEY Collaborative Group. *N Engl J Med.* 2020;383:1436–1446; 4. Bakris GL et al. *N Engl J Med.* 2020;383:2219–2229; 5. Perkovic V et al. *N Engl J Med.* 2024;391:109–121

Renal outcomes in trials with GLP-1 RAs vs SGLT-2 inhibitors

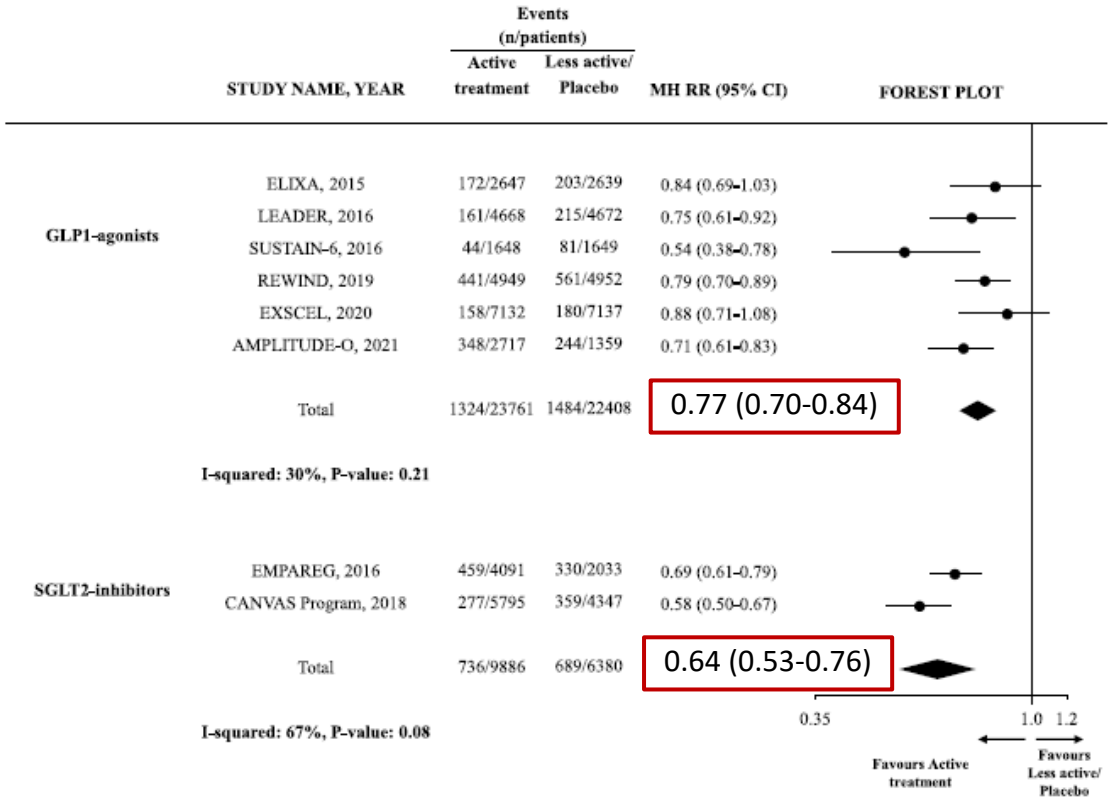
Meta-analysis

Worsening of kidney function

(doubling of serum creatinine or ≥30% GFR reduction 30%, renal death, ESRD, renal dialysis or renal transplantation)



Incident macroalbuminuria



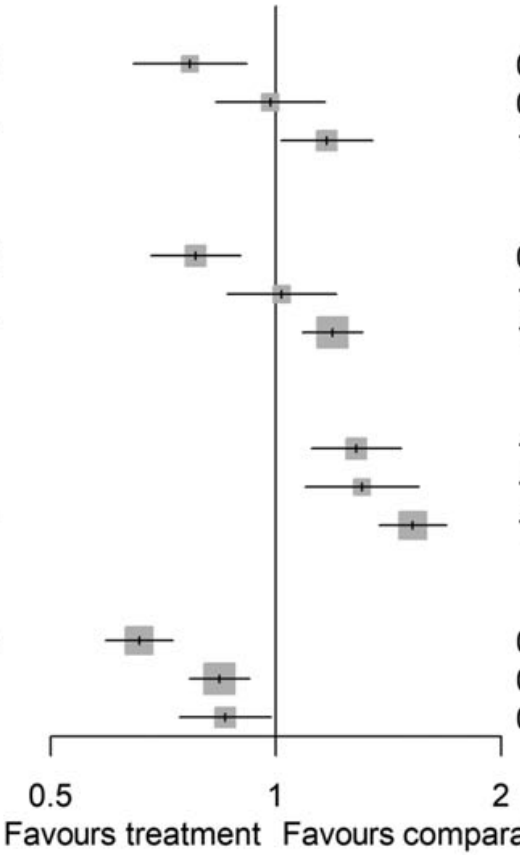
Chalmoukou K et al. *Eur J Intern Med.* 2022;97:78–85

Renal outcomes in trials with GLP-1 RAs vs SGLT-2 inhibitors vs nonsteroidal MRAs

Network meta-analysis

Composite renal outcome: doubling of serum creatinine or ≥40% GFR reduction, ESRD or renal death

Comparison	Direct comparisons	Number of events	Number of participants	RR	95% CI	*P* score
Other vs. 'GLP-1RA'						
SGLT-2i	0	657	15 315	0.77	[0.64; 0.91]	1.00
nsMRA	0	854	6519	0.98	[0.83; 1.16]	0.53
Placebo	4	2279	24 237	1.17	[1.02; 1.35]	0.01
Other vs. 'nsMRA'						
SGLT-2i	0	657	15 315	0.78	[0.68; 0.90]	1.00
GLP-1RA	0	365	3894	1.02	[0.86; 1.20]	0.47
Placebo	2	2279	24 237	1.19	[1.08; 1.30]	0.01
Other vs. 'SGLT-2i'						
nsMRA	0	854	6519	1.28	[1.11; 1.47]	0.53
GLP-1RA	0	365	3894	1.30	[1.09; 1.55]	0.47
Placebo	12	2279	24 237	1.52	[1.37; 1.69]	0.01
Other vs. 'placebo'						
SGLT-2i	12	657	15 315	0.66	[0.59; 0.73]	1.00
nsMRA	2	854	6519	0.84	[0.77; 0.92]	0.53
GLP-1RA	4	365	3894	0.86	[0.74; 0.99]	0.47

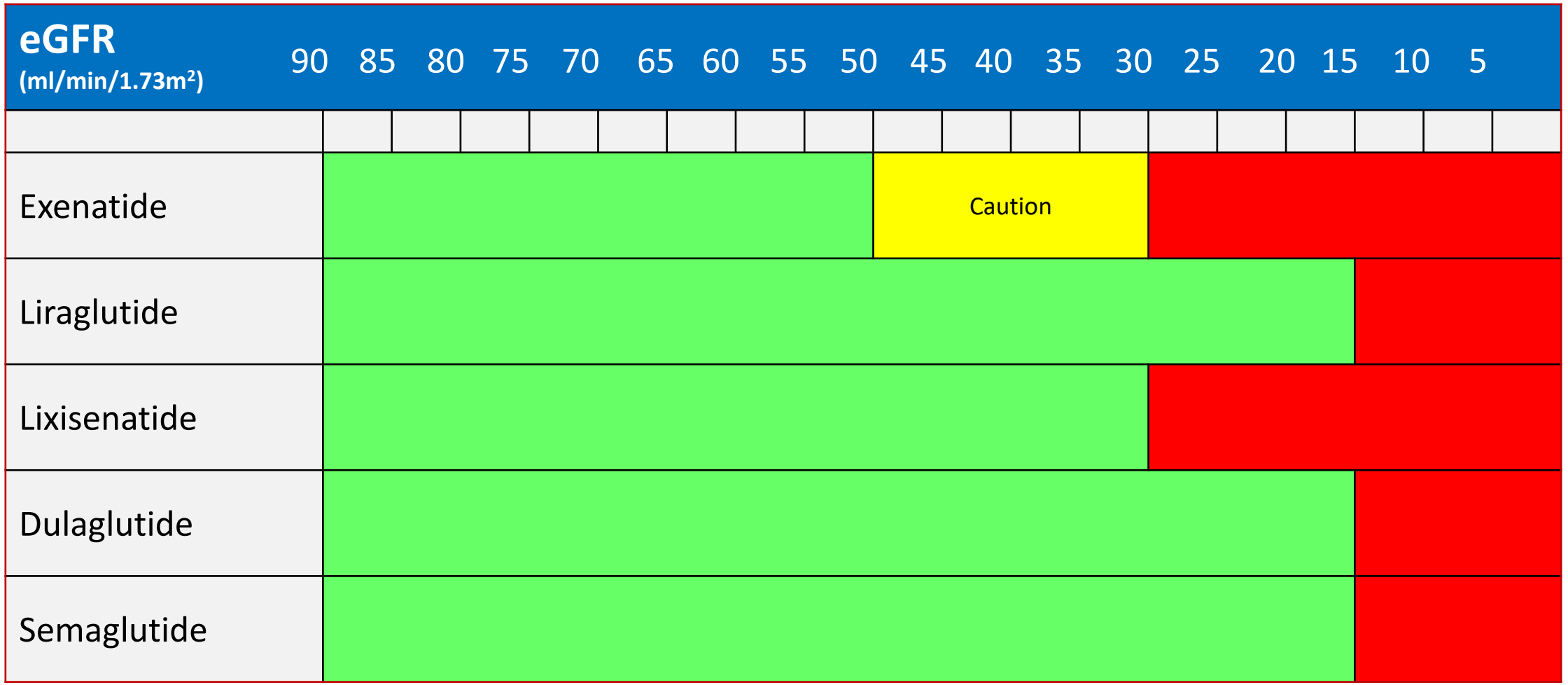


Test of heterogeneity: $tau^2 = 0$; $I^2 = 0\%$; $P = .792$

Nguyen BN et al. *Diabetes Obes Metab.* 2023;25:1614–1623

Use of GLP-1 RAs according to renal function

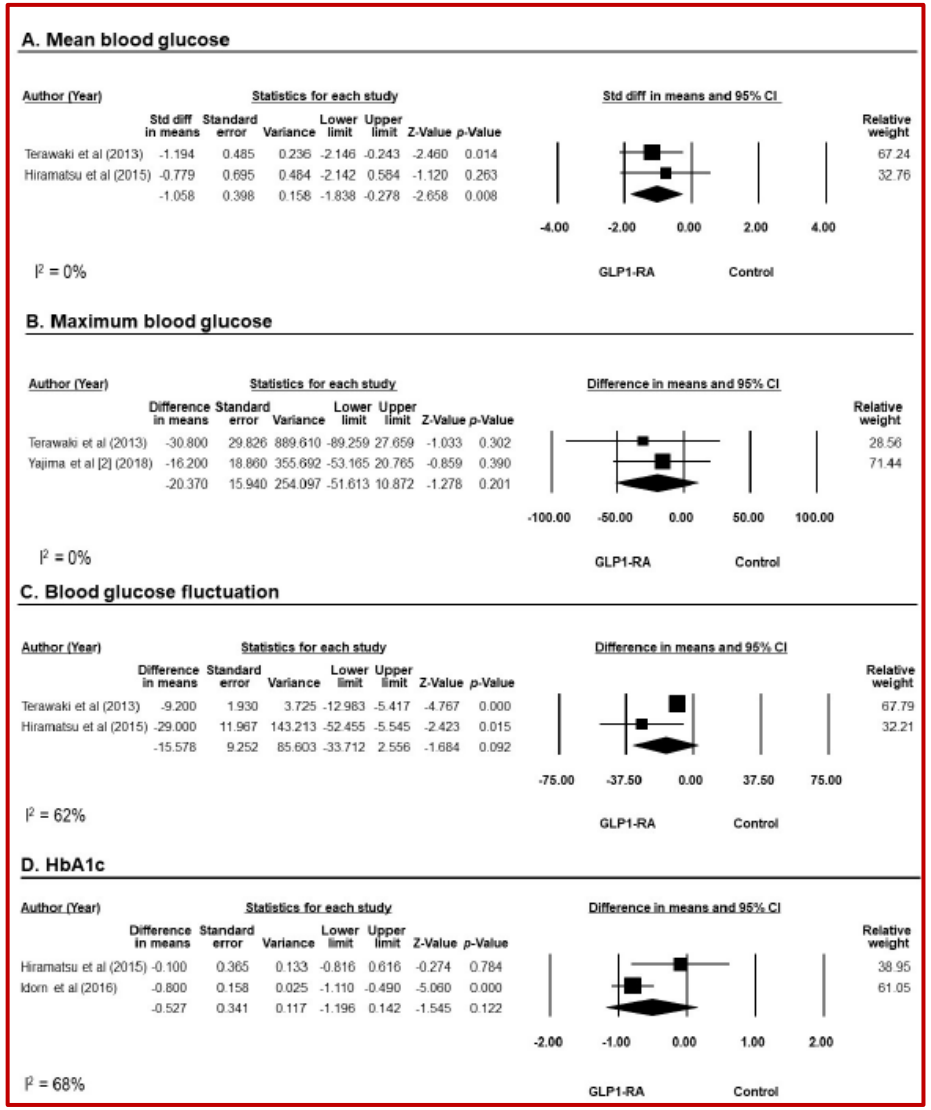
Joint position statement of the Italian Diabetes Society and the Italian Society of Nephrology



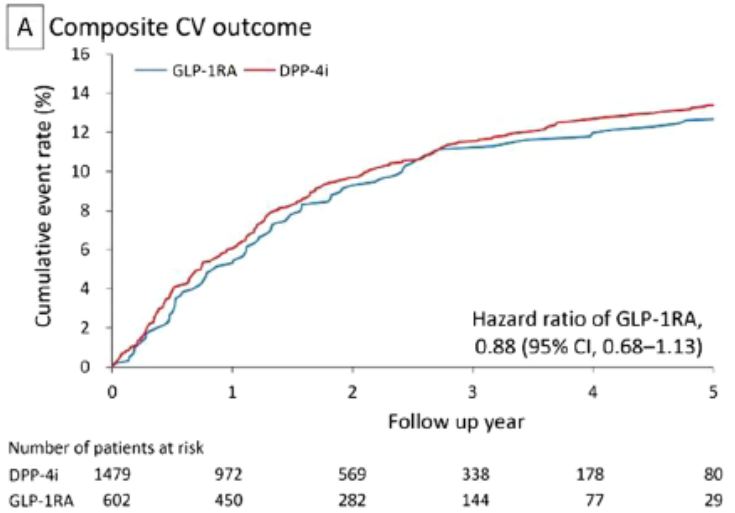
Pugliese G et al. *Nutr Metab Cardiovasc Dis.* 2019;29:1127–1150

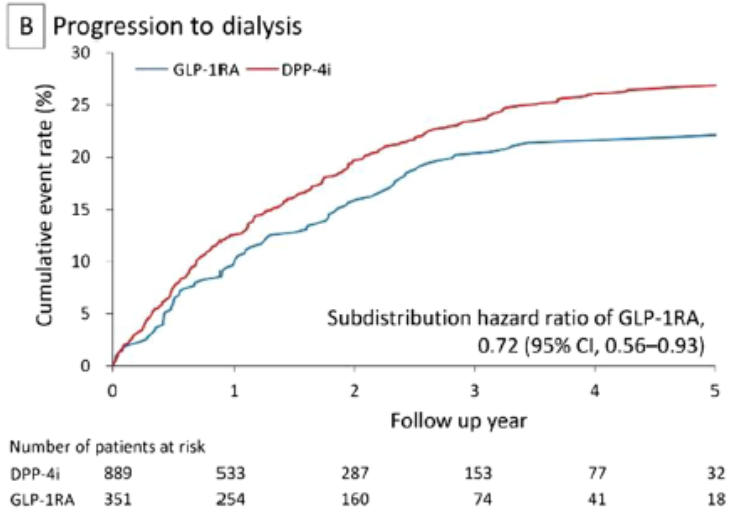
Use of GLP-1 RAs in advanced CKD

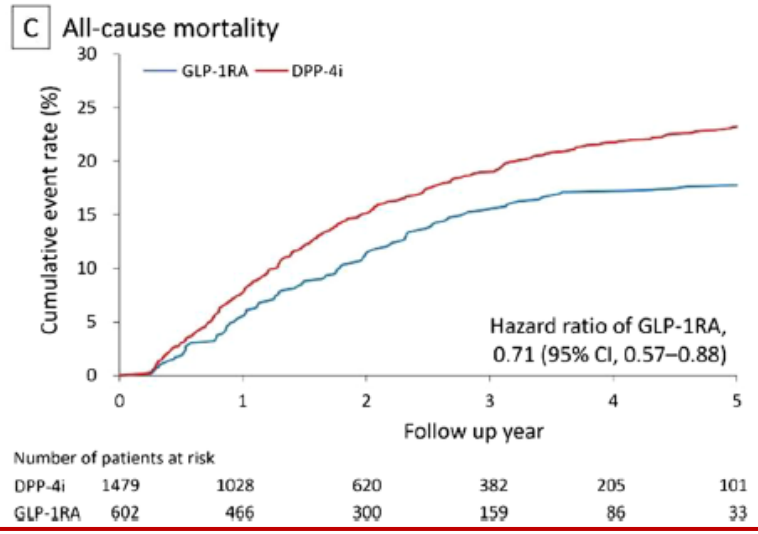
Meta-analysis

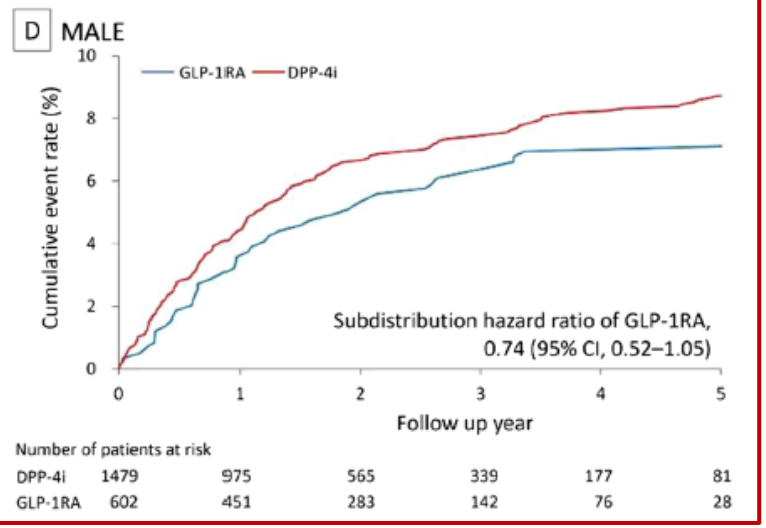


Prospective cohort study using the Chang Gung Research Database





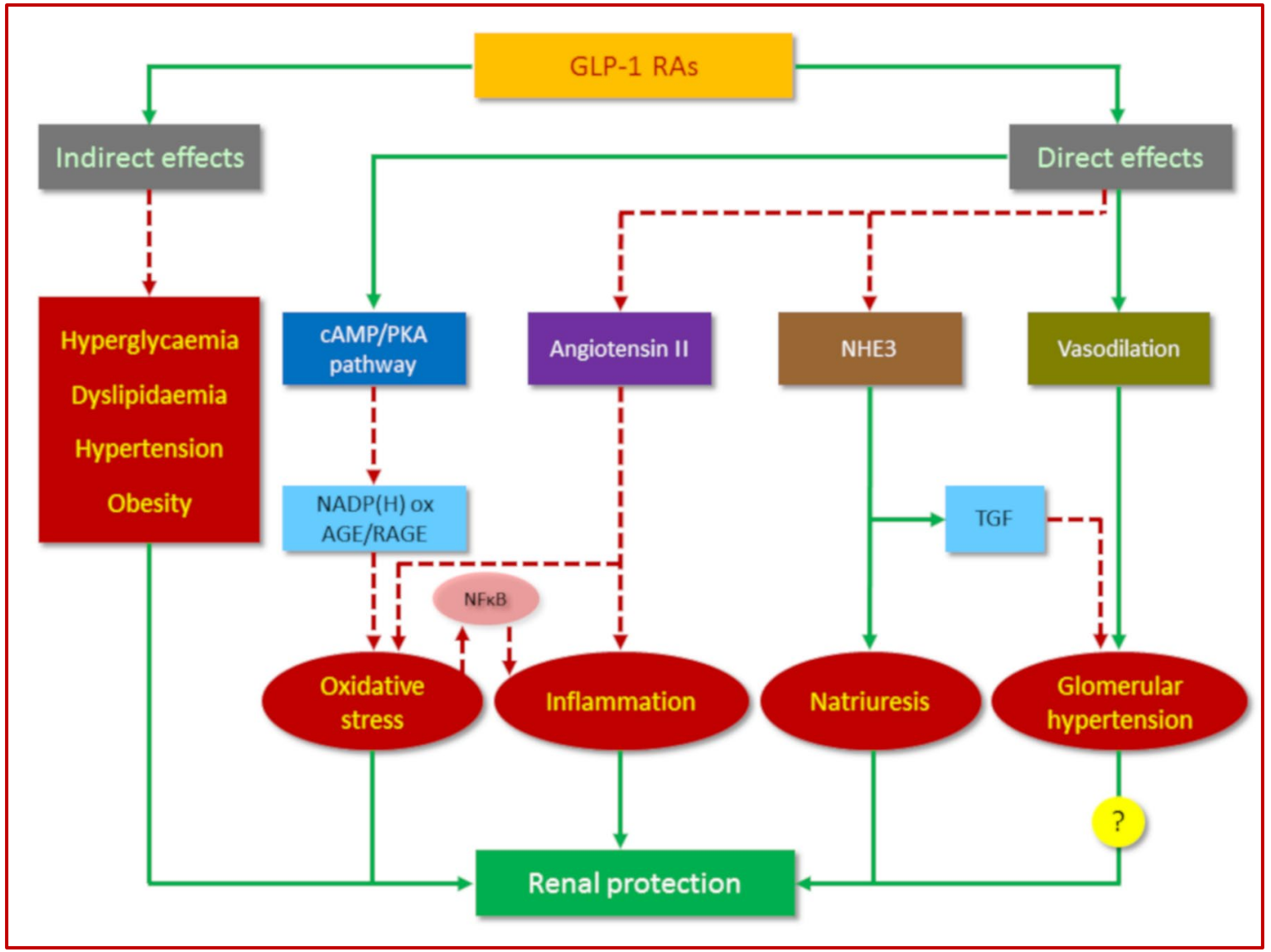




Krisanapan P et al. *Diseases.* 2024;12:14

Lin Y et al. Cardiovascular Diabetol. 2023;22:60

Mechanisms underlying renal protection by GLP-1 RAs



Vitale M et al. *Curr Opin Pharmacol.* 2020;54:91–101

Domanda 2

Qual è risultato essere il principale determinante della protezione cardiorenale con GLP-1 RAs in analisi di mediazione?

A. Calo ponderale

B. Riduzione di HbA_{1c}

C. Incremento della natriuresi

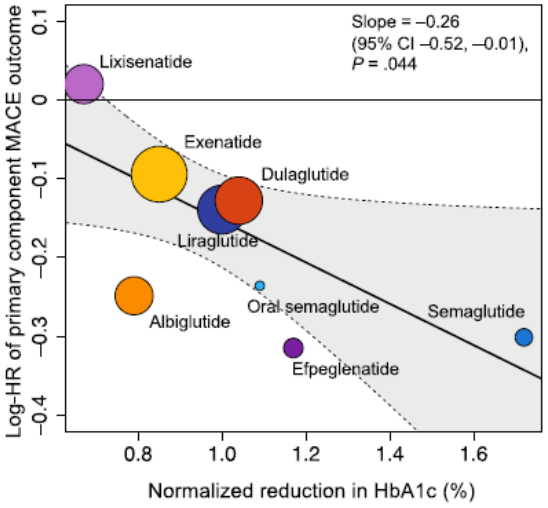
D. Attenuazione dell'infiammazione

Determinants of cardiorenal protection by GLP-1 RAs

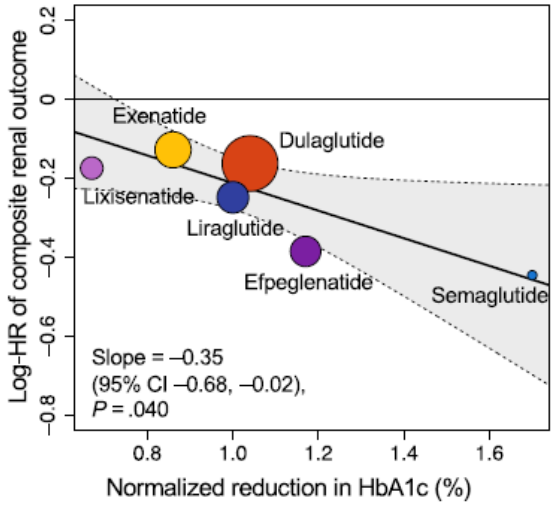
Meta-regression analysis

HbA_{1c} reduction

Primary composite CV outcome (MACE: CV death, stroke, and myocardial infarction)

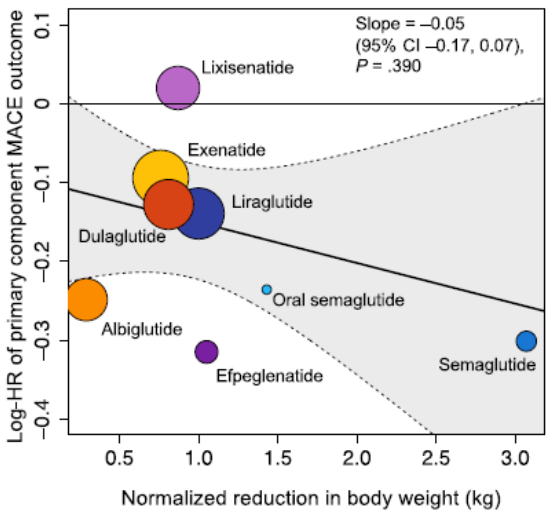


Secondary composite renal outcome (including macroalbuminuria and worsening eGFR))

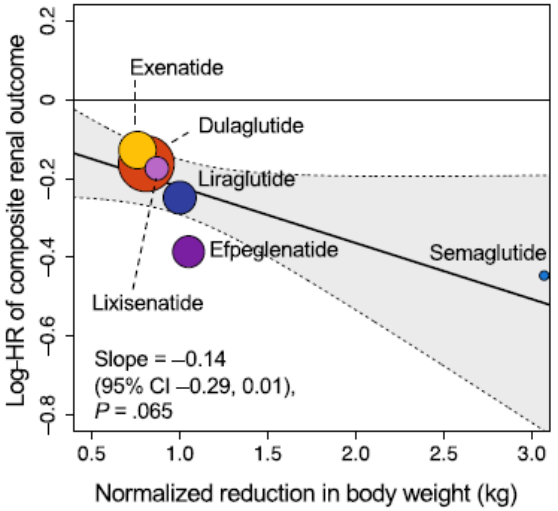


Body weight reduction

Primary composite CV outcome (MACE: CV death, stroke, and myocardial infarction)



Secondary composite renal outcome (including macroalbuminuria and worsening eGFR))



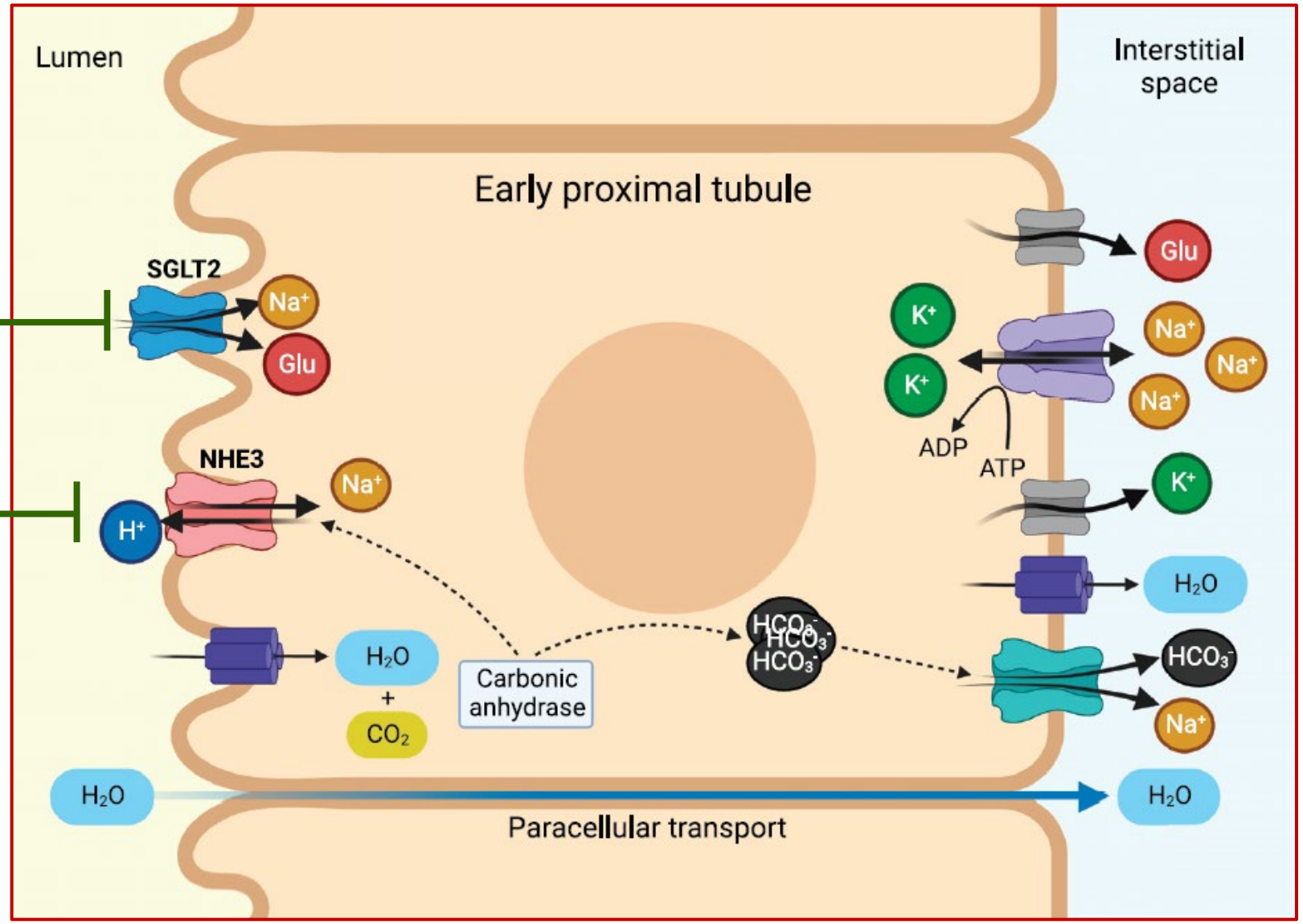
ELIXA · LEADER® Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results · SUSTAIN™ Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes · EXSCEL · REWIND® Trulicity CV Outcomes Trial · AMPLITUDE-O Efpeglenatide Cardiovascular Outcomes · PIONEER Peptide Innovation for Early Diabetes Treatment

Yoshiji S et al. *Diabetes Obes Metab.* 2022;24:1029–1037

Mechanisms of reduction of hyperfiltraion by GLP-1RAs vs SGLT-2 inhibitors

SGLT-2 Is

GLP-1 RAs
SGLT-2 Is



→ Altered sodium homeostasis

→ Reduced extracellular fluid volume

→ Restoration of tubulo-glomerular feedback

Domanda 3

I GLP-1 RA hanno un effetto di riduzione sull'iperfiltrazione?

A. Si, attraverso l'inibizione di NHE3

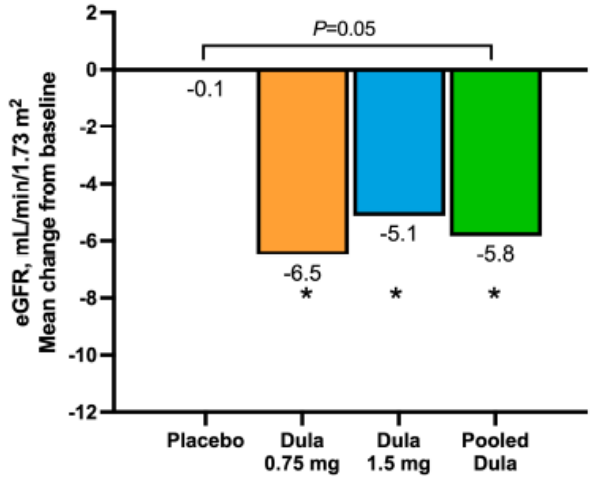
B. Si, attraverso l'inibizione del RAS

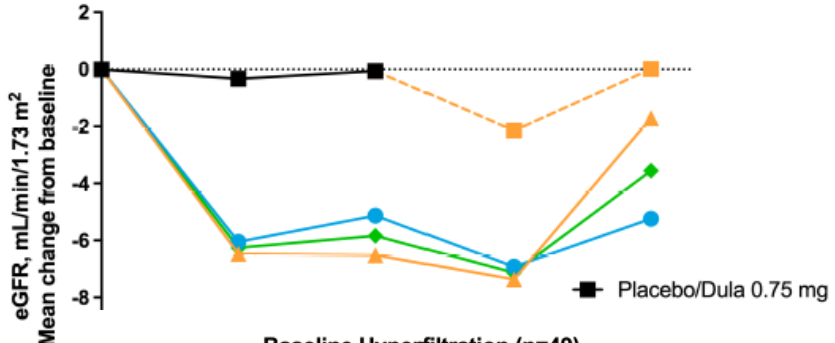
C. No, sono neutri

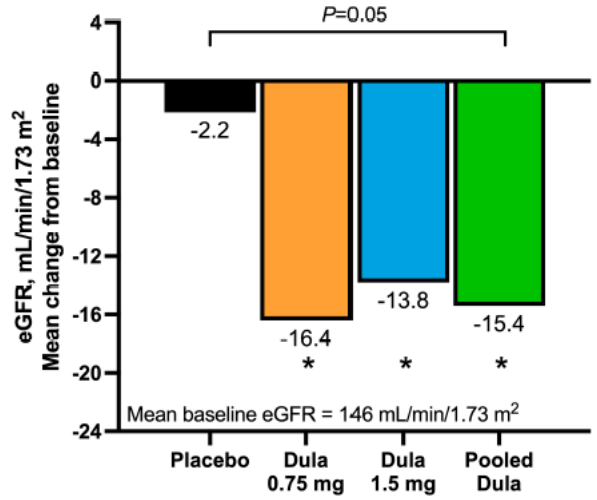
D. No, l'aumentano

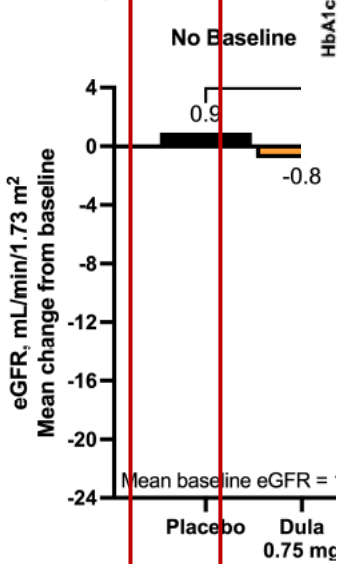
Effect on hyperfiltration of GLP-1 RAs

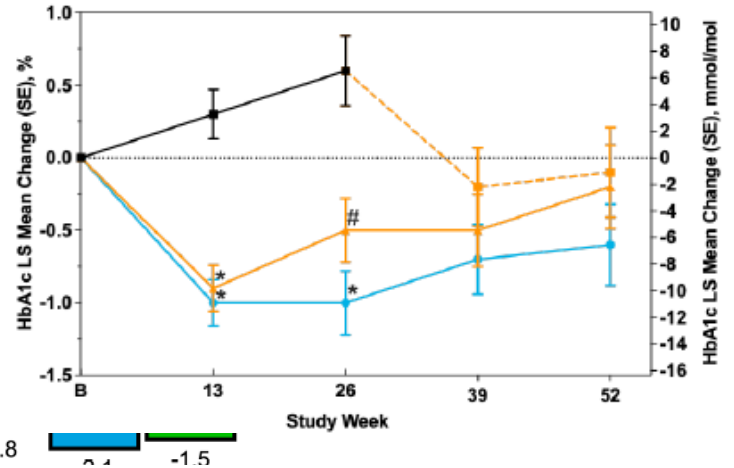
Post hoc analysis of the AWARD-PEDS Study

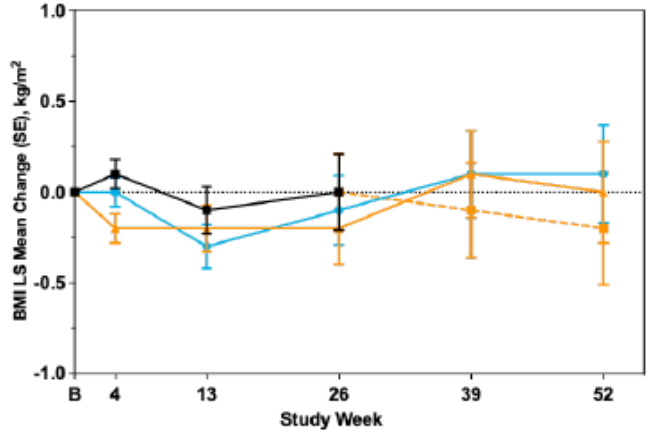






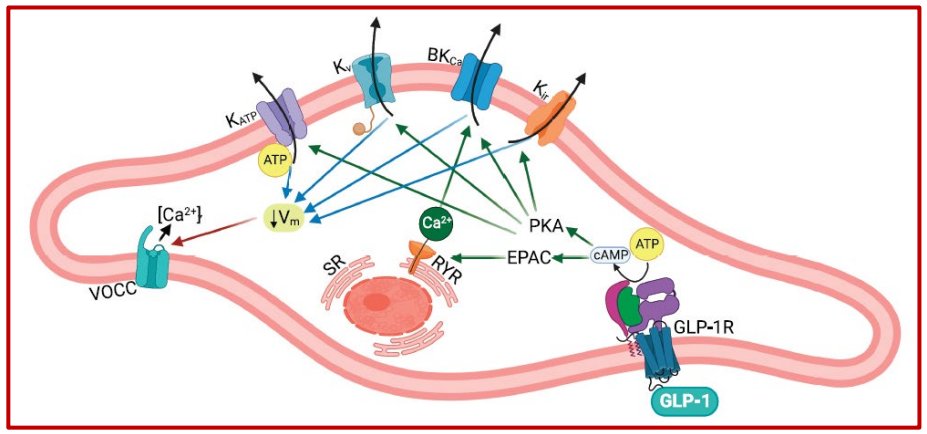


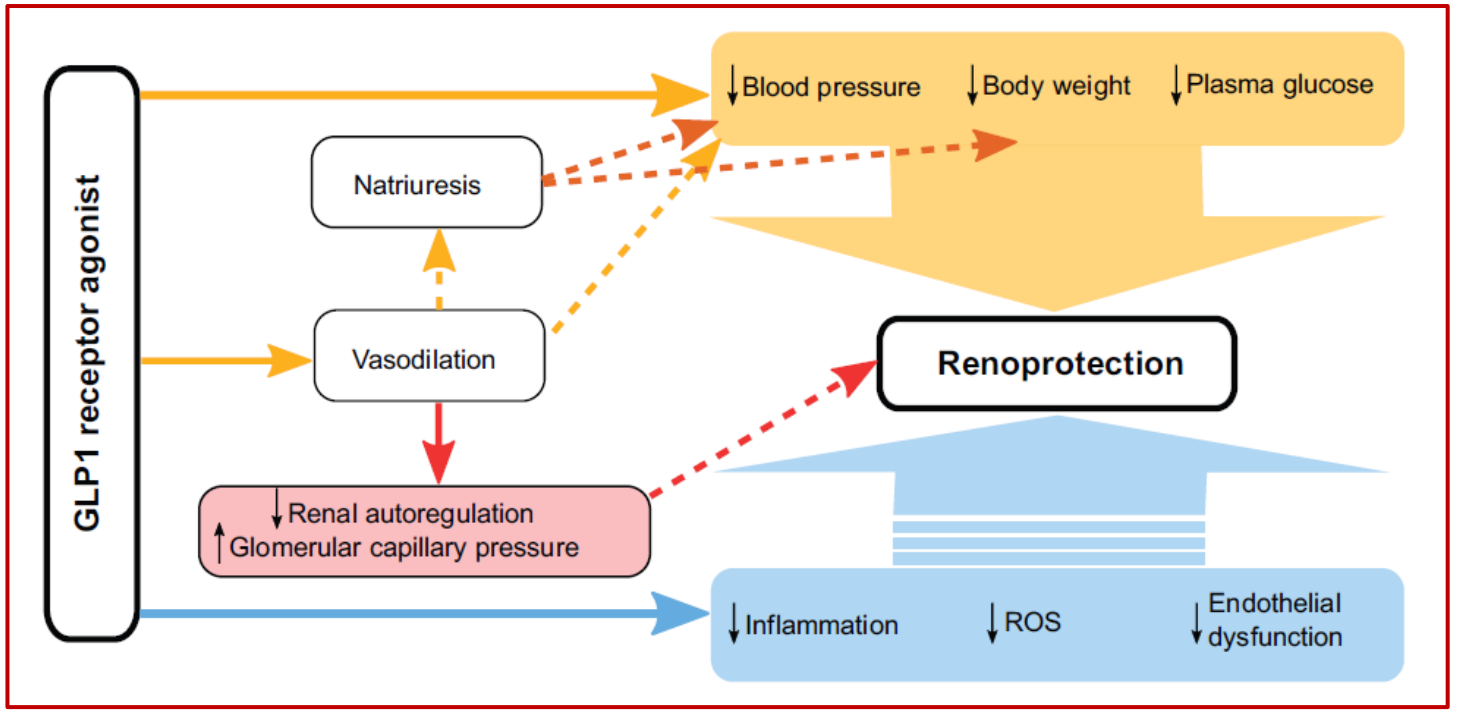




Bjornstad P et al. *Diabetes Care*. 2024;47:1617–1621

No effect on hyperfiltration of GLP-1 RAs





Lee B et al. *Am J Physiol Cell Physiol.* 2023;325:C243–C256

Conclusions

- Renal outcomes in CV outcome trials with GLP-1 receptor agonists
- Renal outcomes in the FLOW renal outcome trial with semaglutide
- Renal outcomes in trials with dual/triple incretin receptor agonists
- Semaglutide in the treatment algorithm of diabetic kidney disease