REGION

Stellenwert der GLP-1-Rezeptor Agonisten

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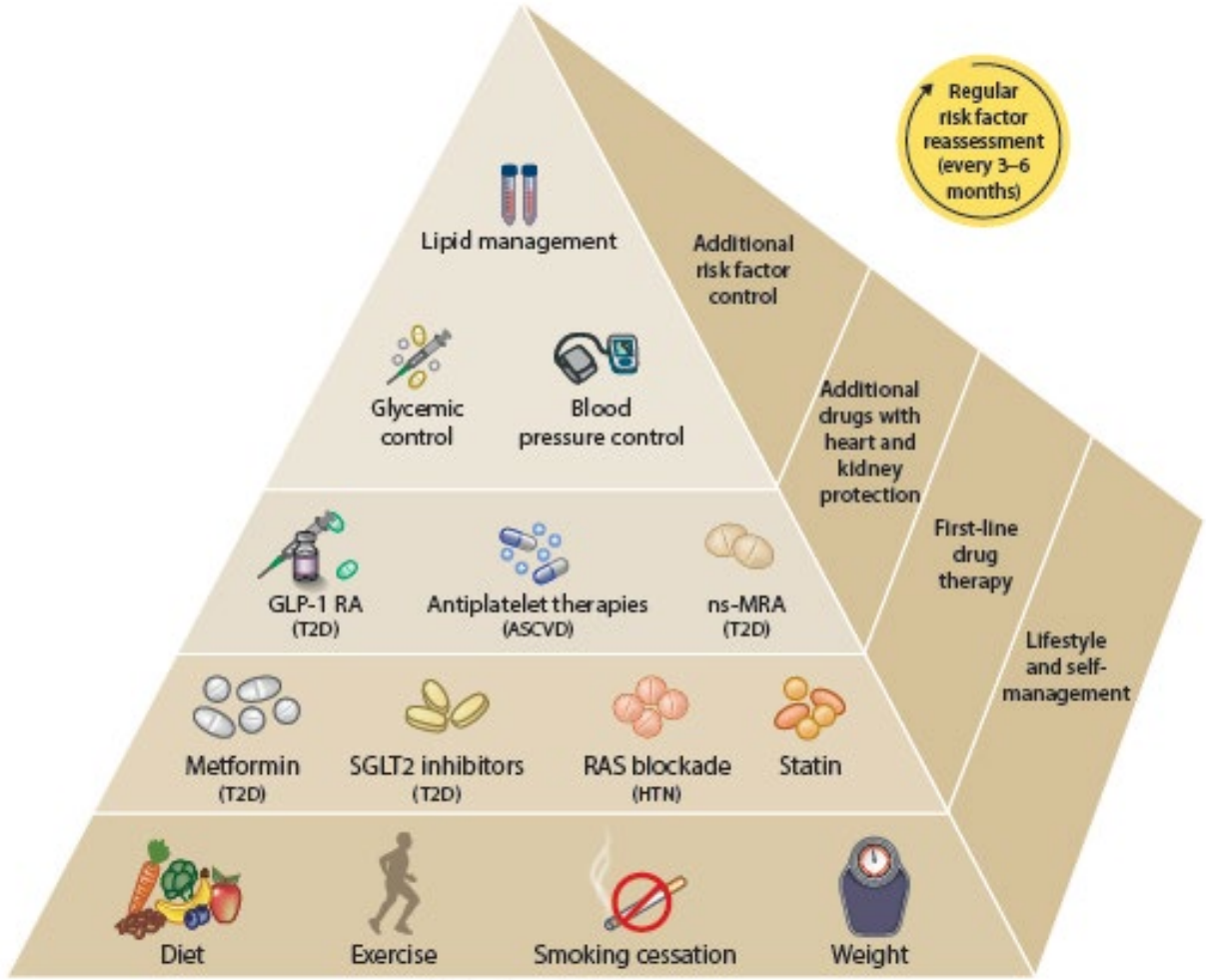
Berliner DialyseSeminar

Potential conflicts of interest declaration

The content of the following speech is the result of efforts to achieve the maximum degree of impartiality and independence.

As a speaker, I wish to point out that there are **personal connections (honoraria to institution)** to companies whose products are of interest within the context of the following speech. The companies concerned and connections are listed below:

Companies	**Connections** (Fee for activities associated with lecturing and in an advisory capacity expert reports and work as an author; fee for preparing training programmes; reimbursement for travel and accommodation costs; reimbursement of participation fees regarding training courses; patents; money from licences and royalties; fee for undertaking commissioned studies; receipt of research funds, etc.)
Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, and Novo Nordisk	Steering group, advisory boards and education All honoraria to Steno Diabetes Center Copenhagen
Astra Zeneca, Bayer Novo Nordisk	Grants to institution
Astra Zeneca, Bayer, Novo Nordisk Lexicon Pharma	Study drugs to investigator trials

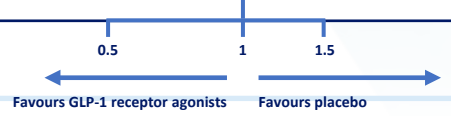


Diabetes with CKD

GLP-1 Receptor Agonists Cardiovascular Outcomes Trials in Type 2 Diabetes

- Reduce risk of major adverse CVD events.
  - Atherosclerotic events
  - CVD death
  - Decrease macroalbuminuria.
- Reduce eGFR decline from early- to late-stage CKD.
- CVD and CKD benefits and safety have been demonstrated in patients with pre-existing CKD.

	GLP-1 Receptor agonist, n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	*p* value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89-1.17)		0.78
LEADER	608 (4668 (13%)	694/4672 (15%)	0.87 (0.78-0.97)		0.01
SUSTAIN-6	108 (1648 (7%)	146/1649 (9%)	0.74 (0.58-0.95)		0.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83-1.00)		0.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68-0.90)		0.0006
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79-0.99)		0.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57-1.11)		0.17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0.73 (0.58-0.92)		0.0069
Subtotal (I^2=44.5%, p=0.082)			0.86 (0.80-0.93)	65 (45-130)	<0.0001

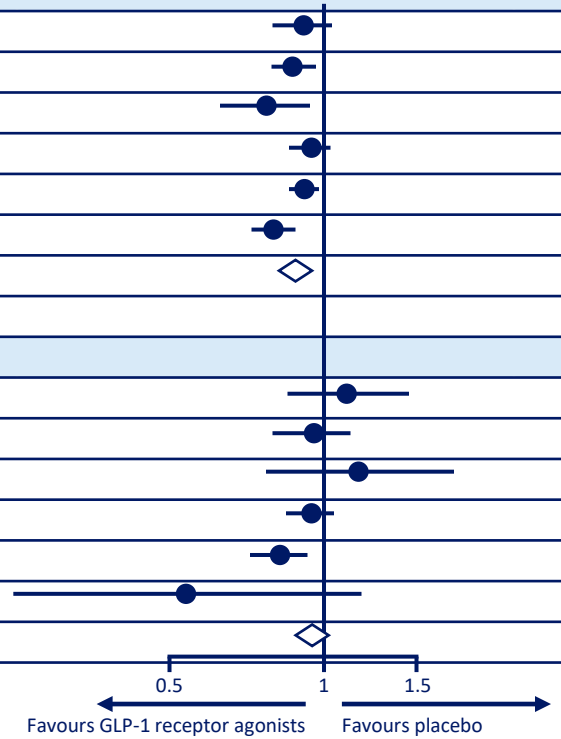


Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5

Renal outcomes from CVOTs

GLP-1 RAs show consistent renal benefit

	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 (0·68-1·02)		0·083
LEADER	268/4668 (6%)	337/4672 (7%)	0·78 (0·67-0·92)		0·003
SUSTAIN-6	62/1648 (4%)	100/1649 (6%)	0·64 (0·46-0·88)		0·005
EXSCEL	366/6256 (6%)	407/6222 (7%)	0·88 (0·76-1·01)		0·065
REWIND	848/4949 (17%)	970/4952 (20%)	0·85 (0·77-0·93)		0·0004
AMPLITUDE-O	353/2717 (13%)	250/1359 (18%)	0·68 (0·57-0·79)		<0·0001
Subtotal (I^2=47·5%, p=0·090)			**0·79 (0·73-0·87)**	**47 (37-77)**	**<0·0001**
Worsening of kidney function not including macroalbuminuria					
ELIXA†	41/3031 (1%)	35/3032 (1%)	1·16 (0·74-1·83)		0·513
LEADER§	87/4668 (2%)	97/4672 (2%)	0·89 (0·67-1·19)		0·43
SUSTAIN-6¥	18/1648 (1%)	14/1649 (1%)	1·28 (0·64-2·58)		0·48
EXSCEL£	246/6456 (4%)	273/6458 (4%)	0·88 (0·74-1·05)		0·16
REWIND#	169/4949 (3%)	237/4952 (5%)	0·70 (0·57-0·85)		0·0004
AMPLITUDE-O±	7/2717 (<1%)	7/1359 (1%)	0·35 (0·10-1·27)		0·11
Subtotal (I^2=43·0%, p=0·12)			**0·86 (0·72-1·02)**	**241 (120 to -1694)***	**0·089**



Weights are from random effect analysis. In addition to primary cardiovascular outcome results papers, data were extracted from additional sources. AMPLITUDE-O data were provided by the authors. Data on kidney outcomes were not available in Harmony outcomes and PIONEER 6. The composite kidney outcome consisted of development of macroalbuminuria, doubling of serum creatinine or at least 40% decline in eGFR, kidney replacement therapy, or death due to kidney disease; for ELIXA, data are for new-onset macroalbuminuria alone NNTs were calculated over a weighted average median follow-up of 3.4 years; Worsening of kidney function outcome was defined as: †doubling of serum creatinine; §doubling of serum creatinine; ¥doubling of serum creatinine and CrCl per MDRD <45 mL/min per 1.73m2 ; £the worsening of kidney function outcome included kidney replacement therapy, or death due to kidney disease; #≥40% worsening of eGFR; ±≥40% worsening of eGFR (≥30 days) Data on kidney outcomes were not available in Harmony outcomes and PIONEER 6.

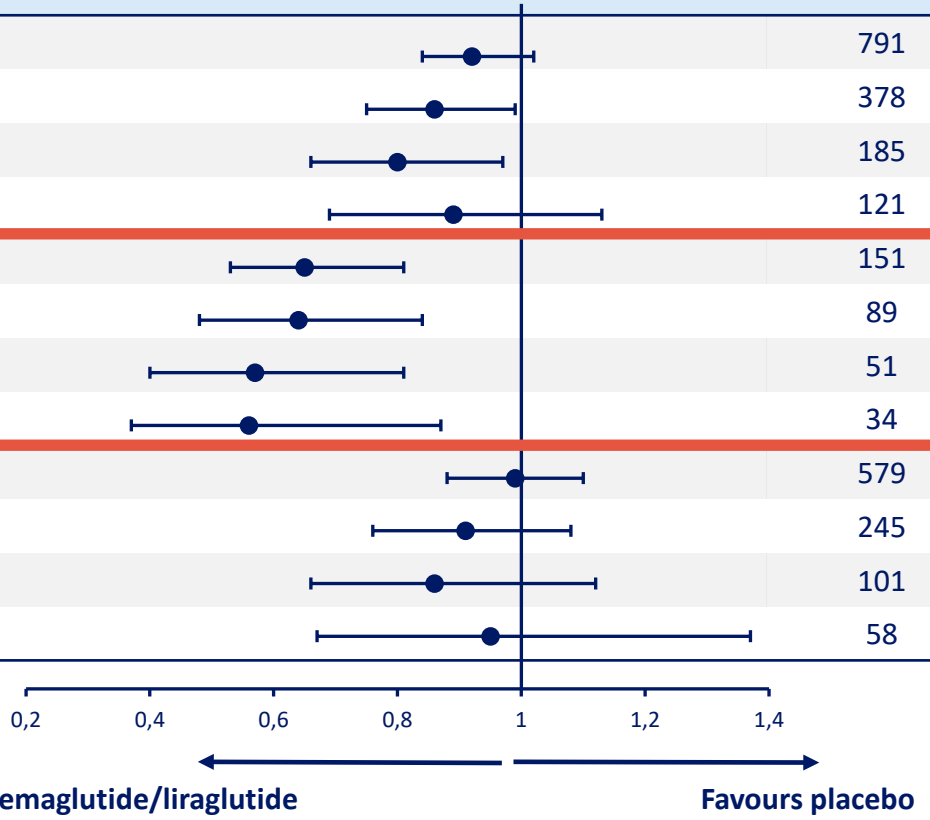
CI, confidence interval; CVOTs. cardiovascular outcome trials; GLP-1, glucagon-like peptide-1; GLP-1 RAs, GLP-1 receptor agonists; NNT, number needed-to-treat

Sattar N et al. Lancet Diabetes Endocrinol. 2021; S2213-8587(21)00203-5., doi:10.1016/S2213-8587(21)00203-5

Time to categorical eGFR reduction

Post-hoc pooled analysis of LEADER AND SUSTAIN 6

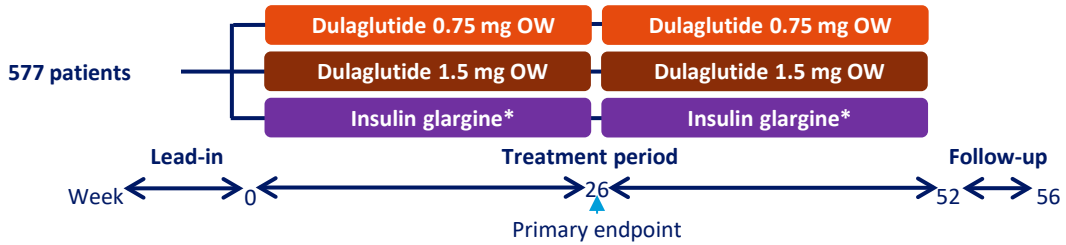
	Reduction in eGFR	Sema/lira pooled (N)	Placebo pooled (N)	HR (95% CI)	p-value
Overall pooled population	30%	791	848	0.92 (0.84; 1.02)	0.1005
	40%	378	432	0.86 (0.75; 0.99)	0.0386
	50%	185	229	0.80 (0.66; 0.97)	0.0233
	57%	121	135	0.89 (0.69; 1.13)	0.3423
eGFR ≥30 to <60 mL/min/1.73 m^2 and micro-or macroalbuminuria	30%	151	196	0.65 (0.53; 0.81)	<0.0001
	40%	89	120	0.64 (0.48; 0.84)	0.0013
	50%	51	78	0.57 (0.40; 0.81)	0.0017
	57%	34	53	0.56 (0.37; 0.87)	0.0093
eGFR ≥60 mL/min/1.73 m^2 or normoalbuminuria	30%	579	591	0.99 (0.88; 1.10)	0.7982
	40%	245	270	0.91 (0.76; 1.08)	0.2810
	50%	101	118	0.86 (0.66; 1.12)	0.2598
	57%	58	61	0.95 (0.67; 1.37)	0.7961



CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Shaman et al Circulation 2022

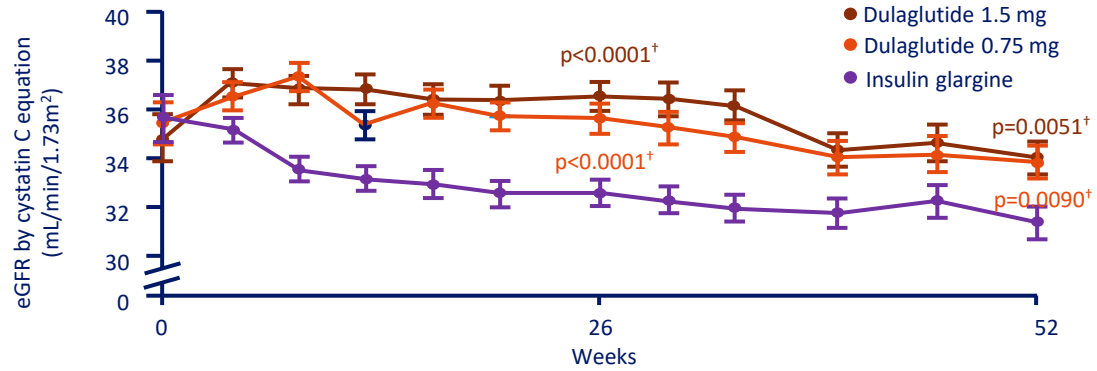
AWARD-7: Efficacy & safety of dulaglutide in DKD stage 3-4

AWARD-7
(Study design)

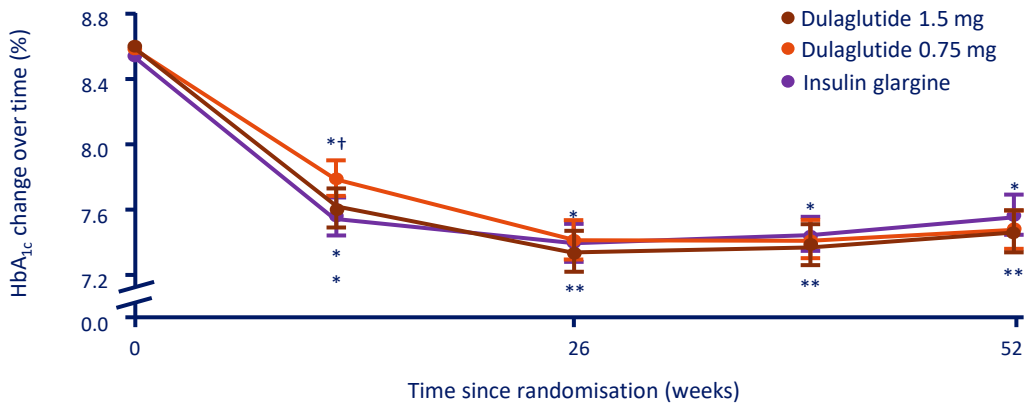


Primary objective
- To assess the efficacy and safety of dulaglutide in patients with T2D and moderate-to-severe CKD

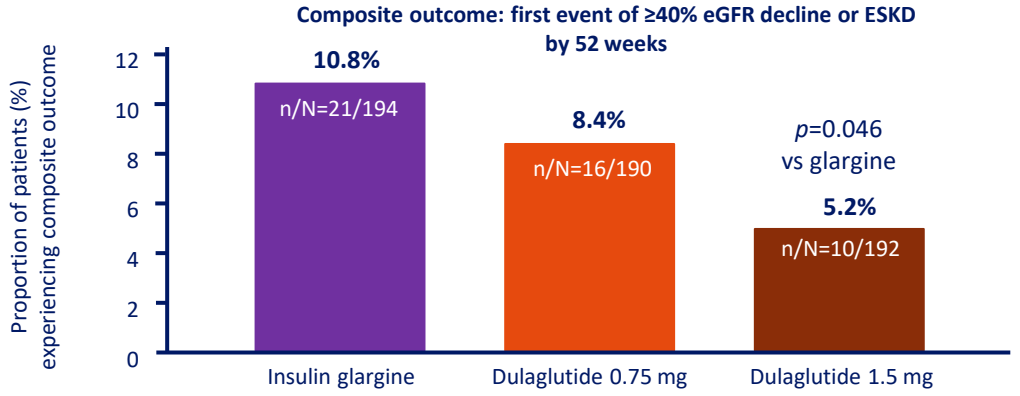
Less decline in eGFR with dulaglutide



Dulaglutide non-inferior to insulin glargine for change in HbA_{1c}



≥40% eGFR decline or ESKD with dulaglutide vs insulin glargine



**Subcutaneous injection to be given at bedtime per sliding scale; †eGFR ≥15 to <60 mL/min/1.73m²;‡Versus insulin glargine*
BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stange kidney disease; HbA_{1C}, glycosylated hemoglobin; OW, once weekly
Tuttle KR et al. Lancet Diabetes Endocrinol 2018; 6(8):605–617; Tuttle KR et al. ASN Kidney Week; October 25, 2018

FLOW trial design: Kidney outcomes trial in T2D

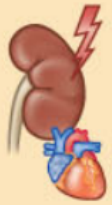
FLOW
semaglutide | kidney outcomes trial

Methods

Participants:

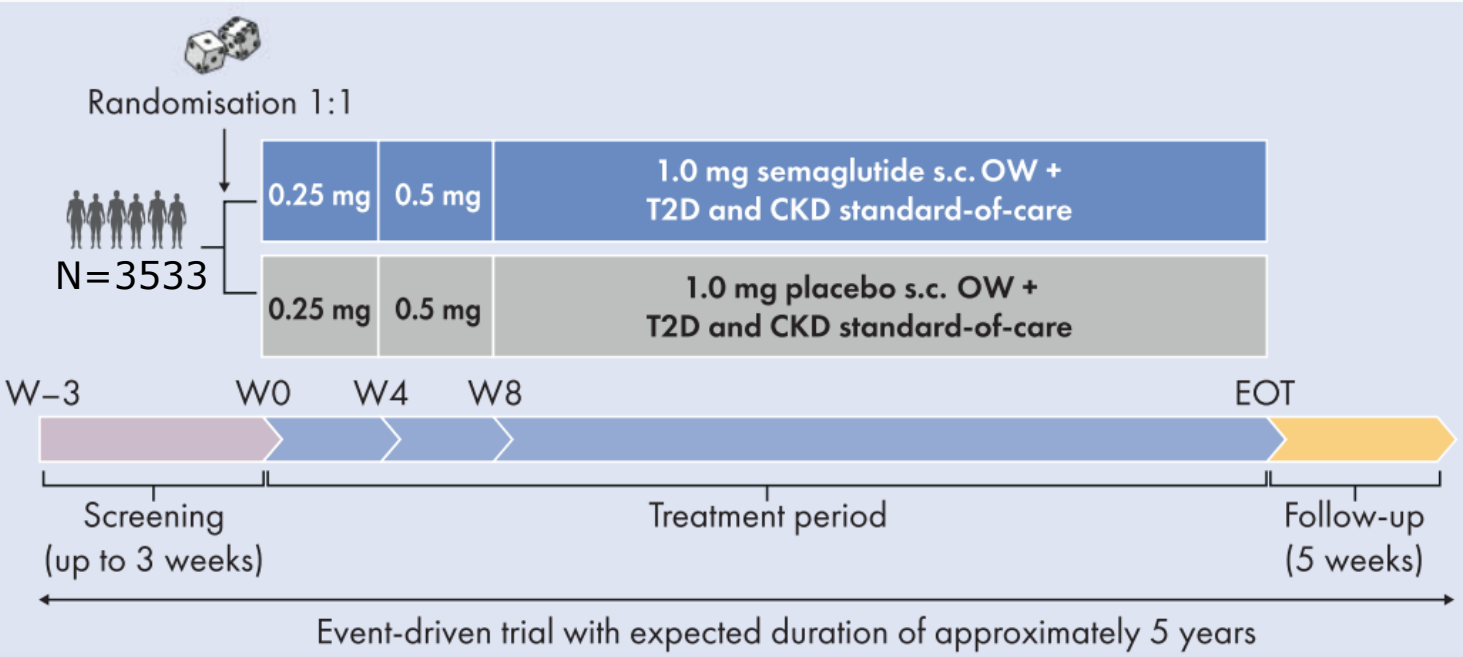
- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m^2 and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m^2 and UACR >100 to <5000 mg/g

Composite primary endpoint:



Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m^2 or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes

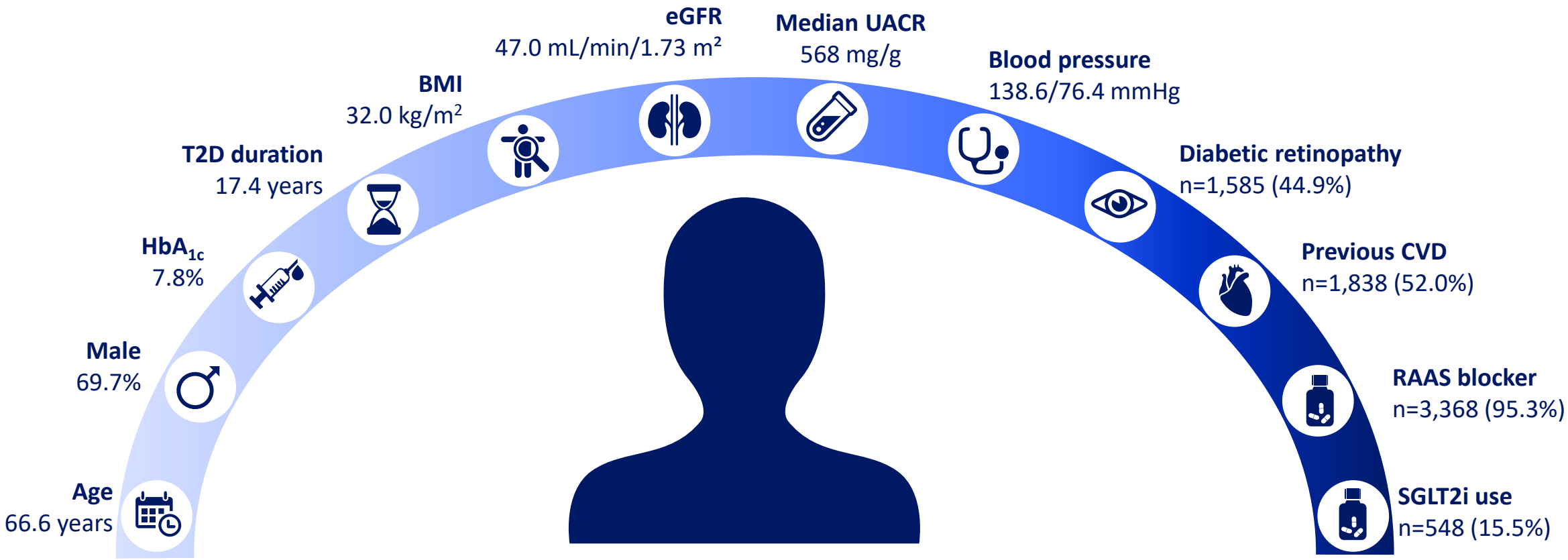


CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; OW, once-weekly; s.c., subcutaneous; T2D, type 2 diabetes; UACR, urine albumin:creatinine ratio; W, week.

Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051; Novo Nordisk. 5 March 2024. https://www.novonordisk.com/content/nncorp/global/en/news-and-media/news-and-ir-materials/news-details.html?id=167028 (accessed May 2024).

The average FLOW patient

FLOW baseline characteristics (N=3,534)



All values are mean unless otherwise stated
BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; RAAS, renin-angiotensin-aldosterone system; SGLT2i, sodium-glucose co-transporter-2 inhibitor; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio
Rossing P et al. Nephrol Dial Transplant 2023;38:2041–2051

CKD stage and corresponding risk category can guide management

FLOW semaglutide | kidney outcomes trial

Albuminuria categories
Description and range

CKD is classified based on: Cause GFR (G) Albuminuria (A)			A1	A2	A3
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
G1	Normal or high	≥90			
G2	Mildly decreased	60–89			
G3a	Mildly to moderately decreased	45–59			
G3b	Moderately to severely decreased	30–44			
G4	Severely decreased	15–29			
G5	Kidney failure	<15			

GFR categories (mL/min/1.73 m²)
Description and range

Low risk*
Moderately increased risk
High risk
Very high risk

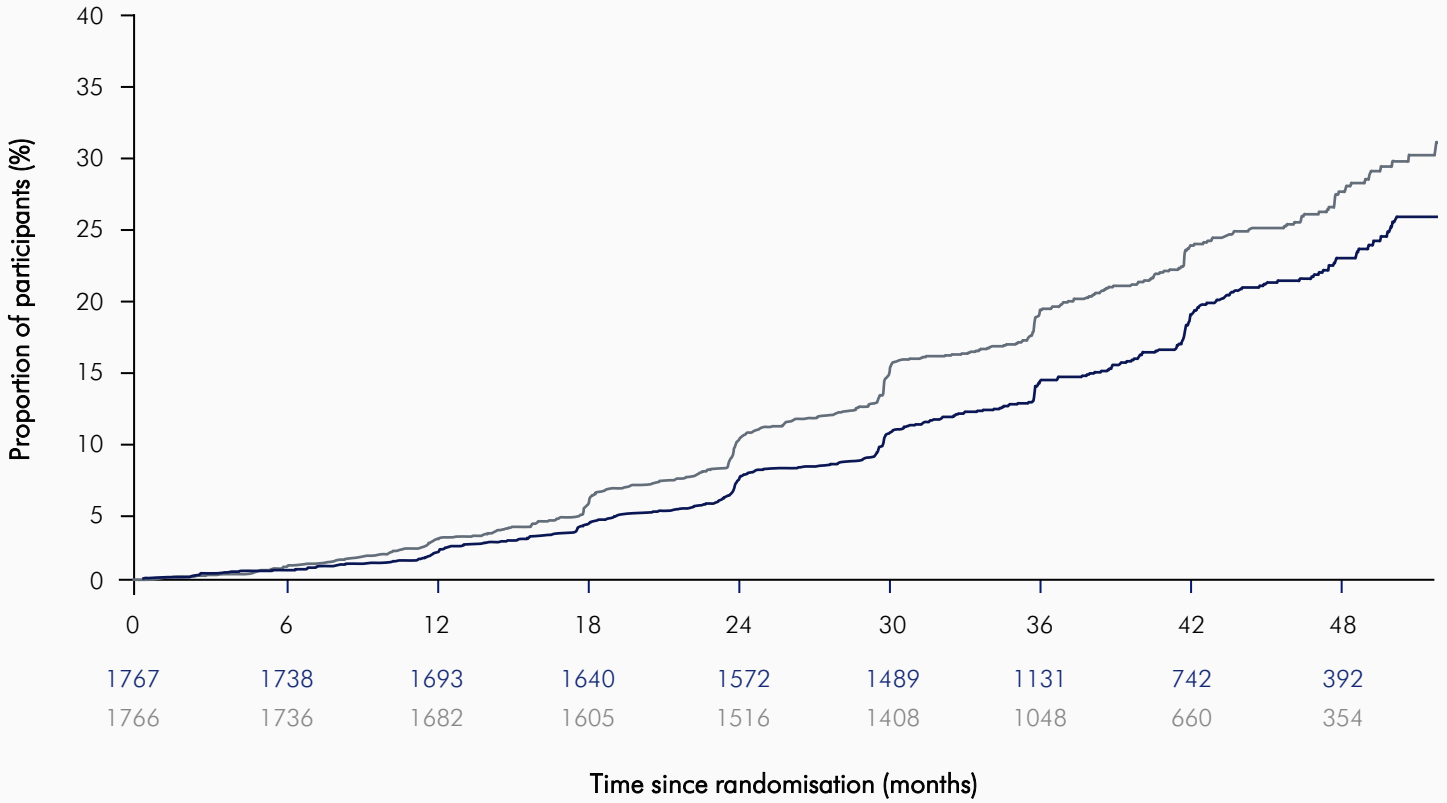
93%
were at high or very high risk

Risks:
- Loss of kidney function
- Kidney failure
- CVD events

Increased risk

Numbers in the boxes are a guide to the frequency of screening or monitoring (number of times per year). Green reflects no evidence of CKD by estimated GFR or albuminuria, with screening indicated once per year.
For monitoring of prevalent CKD, suggested monitoring varies from once per year (yellow) to four times or more per year (i.e. every 1–3 months [deep red]) according to risks of CKD progression and CKD complications.
These are general parameters only, based on expert opinion, and underlying comorbid conditions and disease state must be taken into account, as well as the likelihood of impacting a change in management for any individual patient.
*If no other markers of kidney disease, no CKD.
CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.
de Boer IH et al. *Diabetes Care* 2022;45:3075–3090; Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2022;102:S1–S127; Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051.

Primary Kidney Disease Outcome



Placebo 23.2%
(410/1766)

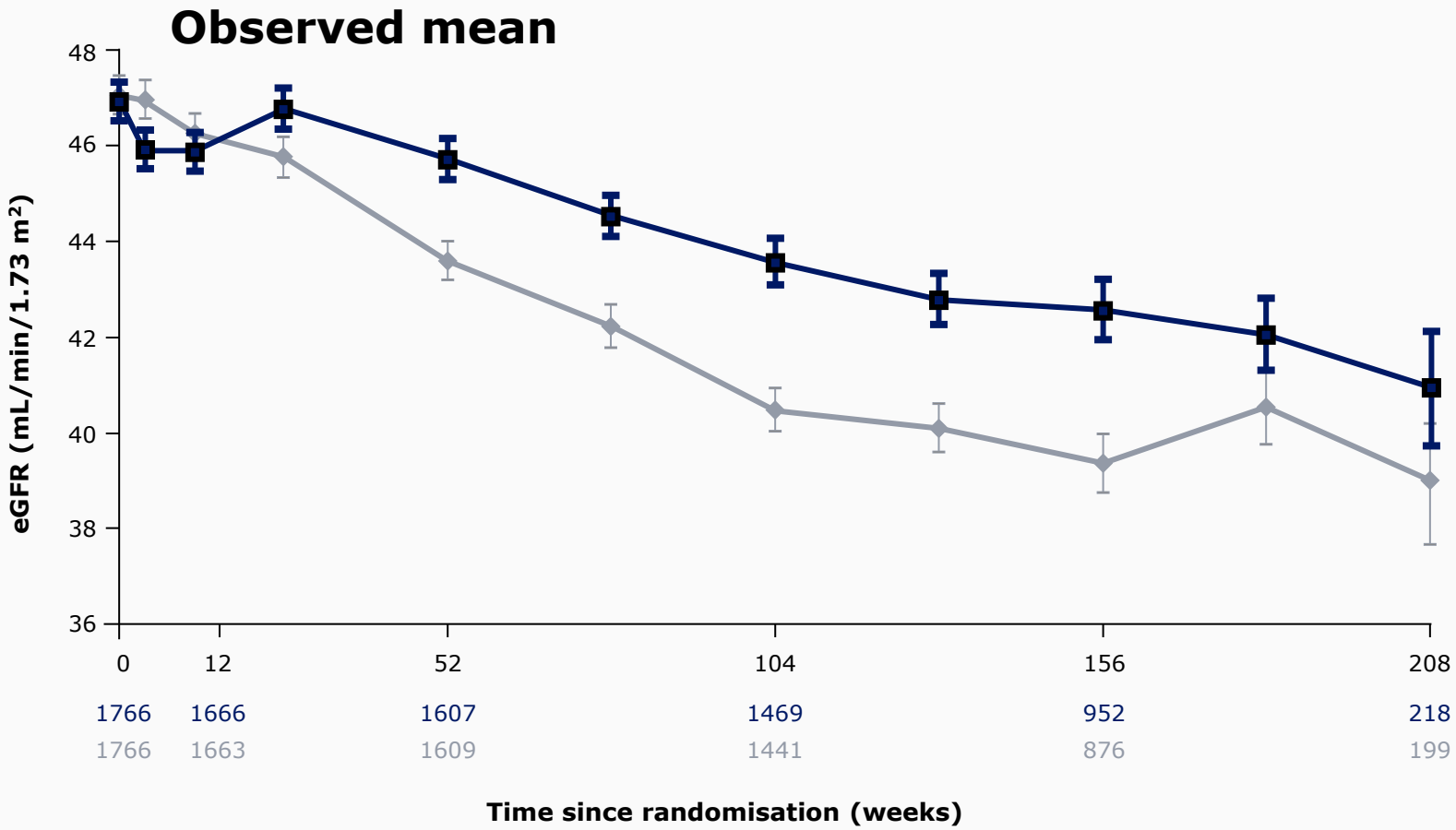
Semaglutide 18.7%
(331/1767)

HR 0.76 (95% CI 0.66, 0.88)
p=0.0001

Perkovic V, Tuttle KR, Rossing P *et al. N Engl J Med* 2024;391:109–121

Superiority if two-sided p value <0.0322

Total eGFR Slope



Annual rate of change:

Semaglutide −2.19

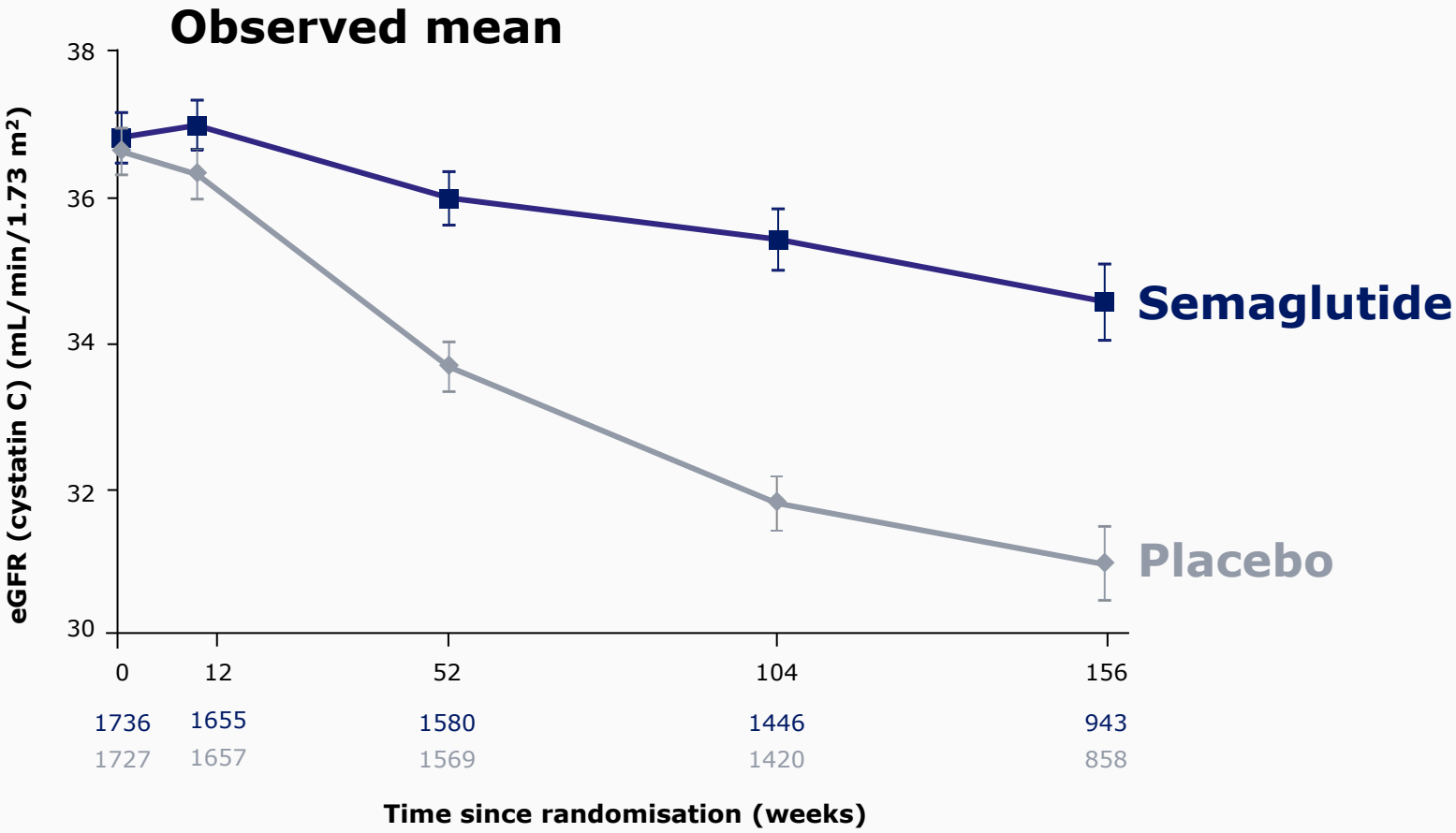
Placebo −3.36

eGFR slope:
1.16 mL/min/1.73 m²/year
(95% CI 0.86, 1.47)
p<0.001

Perkovic V, Tuttle KR, Rossing P *et al. N Engl J Med* 2024;391:109–121

Superiority if two-sided
p value <0.0322

Change in eGFR



Calculated by cystatin C
ETD at **week 104**
3.39 mL/min/1.73 m²
(95% CI 2.63, 4.15)

Calculated by serum creatinine
ETD at **week 104**
3.30 mL/min/1.73 m²
(95% CI 2.43, 4.17)

Perkovic V, Tuttle KR, Rossing P *et al. N Engl J Med* 2024;391:109–121

Primary and confirmatory secondary outcomes

FLOW semaglutide | kidney outcomes trial

First composite kidney event
HR 0.76
(95% CI 0.66, 0.88)

Annual rate of change in eGFR (total slope)
ETD 1.16
(95% CI 0.86, 1.47)

MACE
HR 0.82
(95% CI 0.68, 0.98)

All-cause death
HR 0.80
(95% CI 0.67, 0.95)

24% RRR

ETD 1.16 mL/min/1.73 m²/year

18% RRR

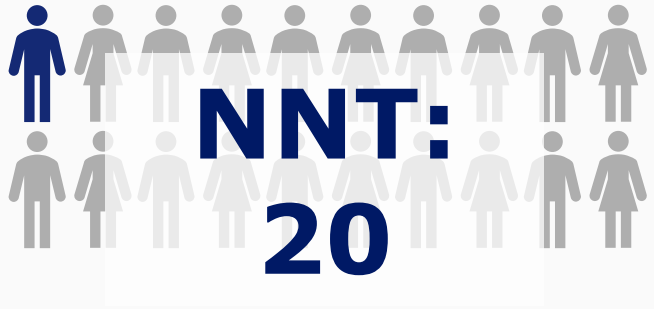
20% RRR

The p value limit was determined by the Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries accounting for the group sequential design (interim analysis). eGFR was calculated using the CKD-EPI formula.
CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ETD, estimated treatment difference; HR, hazard ratio; MACE, major adverse cardiovascular event; RRR, relative risk reduction.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

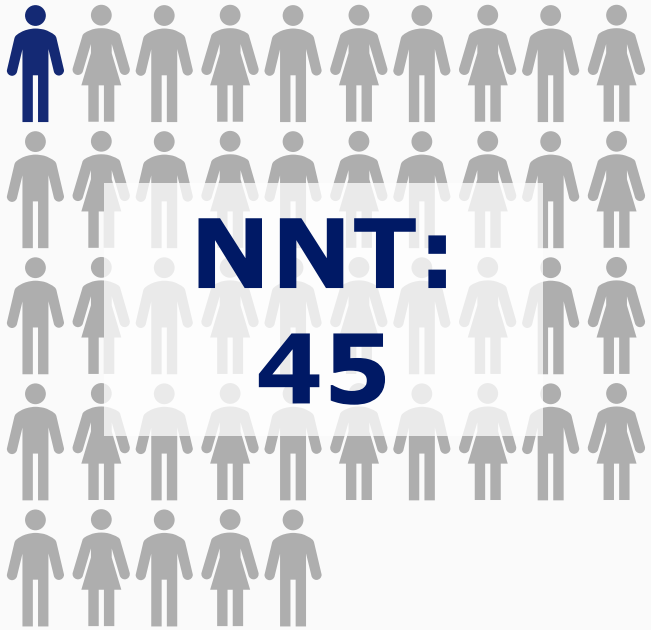
Benefits of semaglutide over 3 years

FLOW
semaglutide | kidney outcomes trial

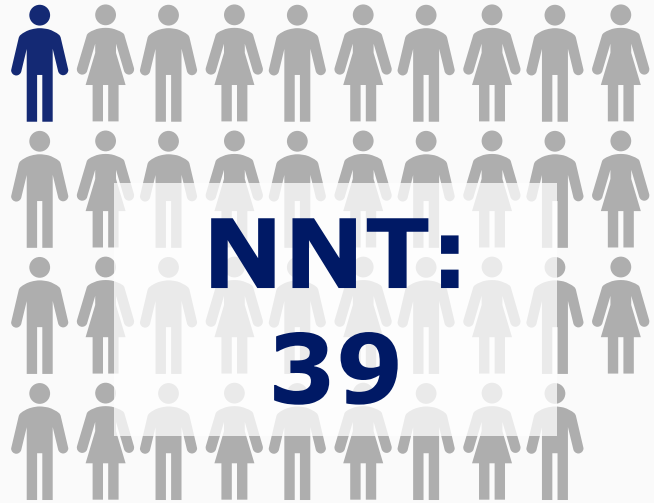
To prevent one primary outcome:†



To prevent one MACE:‡



To prevent one death due to any cause:



†Onset of persistent ≥50% reduction in eGFR compared with baseline, onset of persistent eGFR <15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy dialysis, or kidney transplantation, kidney death or CV death; ‡Non-fatal MI, non-fatal stroke or CV death. CV death includes undetermined cause of death.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat.
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

MoA by which GLP-1 RAs may provide a kidney benefit

Not well understood, but likely involves a combination of direct and indirect effects

Indirect effects:

- Improved glycaemic control
- Reduction in blood pressure
- Weight loss

Direct effects:

- Natriuresis
- Haemodynamic effects
- Endothelial function
- Anti-inflammatory and reduced oxidative stress
- Inhibition of RAAS

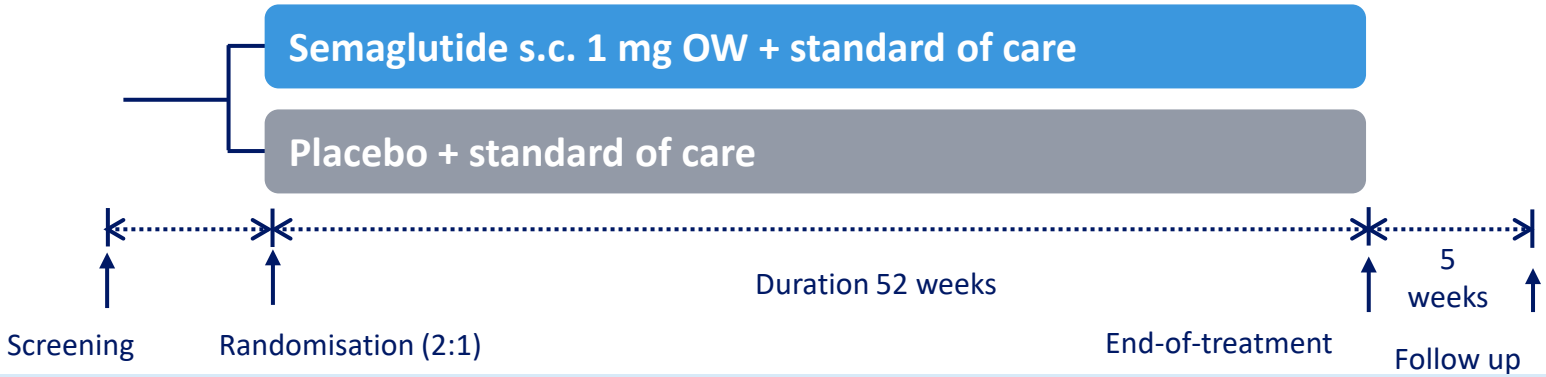
GLP-1 RAs, glucagon-like peptide-1 receptor agonists; MoA, mechanism of action; RAAS, renin-angiotensin-aldosterone system.
Muskiet MHA et al. Nat Rev Nephrol 2017; 13(10):605-628.

REMODEL - Renal mode of action with semaglutide

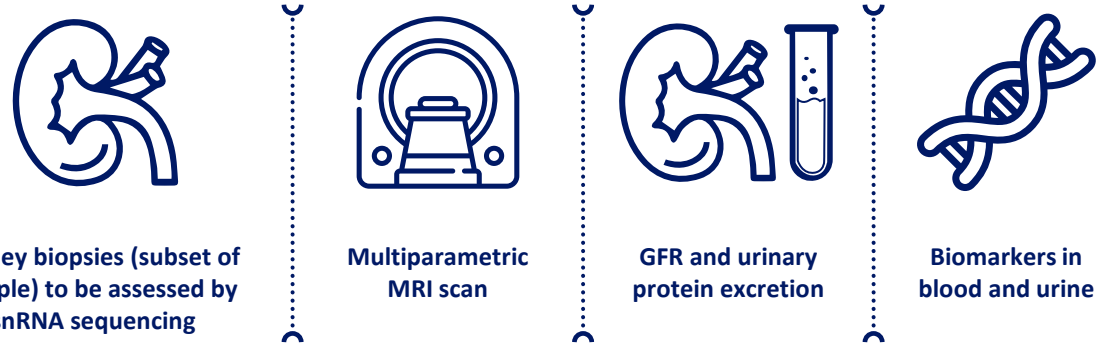
Mechanistic renal mode of action with OW semaglutide

105 people

- T2D, HbA_{1c} ≤9%
- RAAS blocker treatment
- eGFR ≥40 to ≤75 ml/min/1.73m^2
- UACR ≥20 to <5000 mg/g
- Capped SGLT-2i use

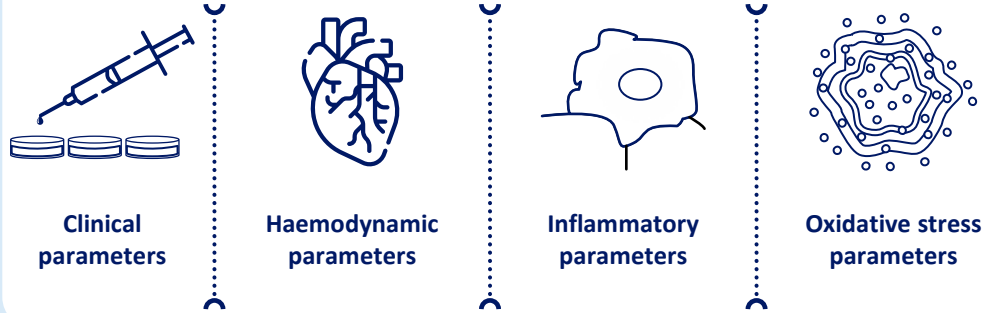


Key methods



Key endpoints

Change in:

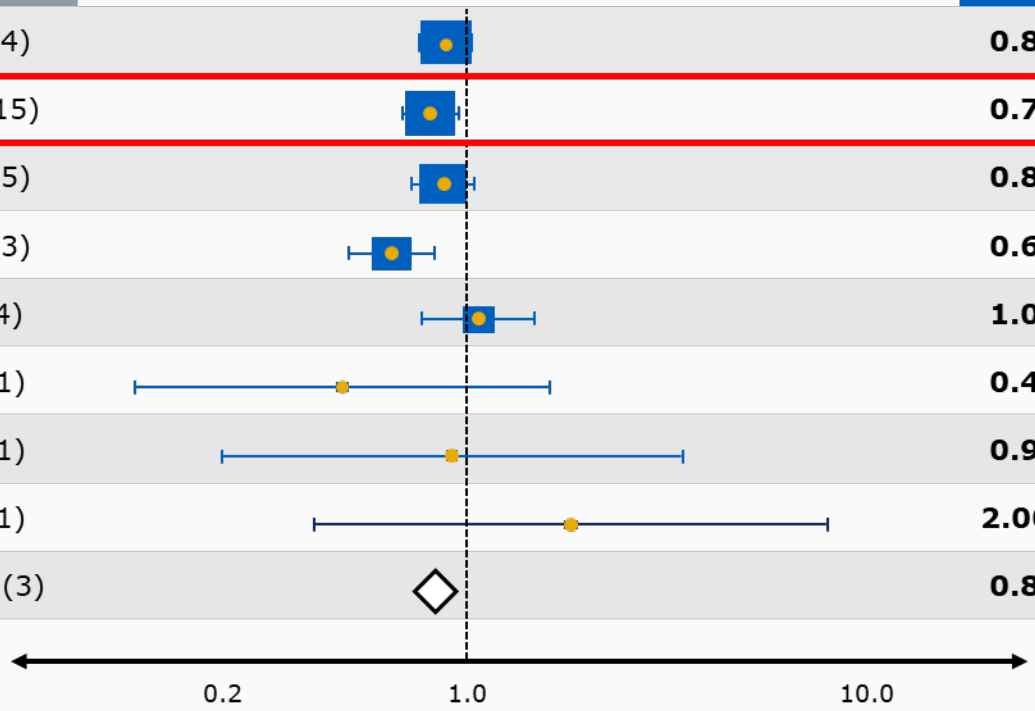


eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated haemoglobin; OW, once weekly; MRI, Magnetic resonance imaging; RAAS, renin-angiotensin-aldosterone system; s.c., subcutaneous ; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; snRNA, small nuclear ribonucleic acid; T2D, type 2 diabetes; UACR, urine albumin:creatinine ratio.

Data on file. https://clinicaltrials.gov/ct2/show/NCT04865770

Composite kidney outcome

Study	GLP-1RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	Weight, %
EXSCEL	246/6459 (4)	273/6466 (4)	**0.88** (0.74, 1.05)	25.97
FLOW	218/1767 (12)	260/1766 (15)	**0.79** (0.66, 0.94)	25.69
LEADER	184/4668 (4)	212/4672 (5)	**0.86** (0.70, 1.05)	22.13
REWIND	84/4949 (2)	136/4952 (3)	**0.61** (0.46, 0.80)	14.75
SUSTAIN-6	58/1648 (4)	57/1649 (4)	**1.09** (0.75, 1.58)	9.43
ELIXA	3/2702 (<1)	7/2793 (<1)	**0.44** (0.11, 1.73)	0.82
AMPLITUDE-O	9/2717 (<1)	3/1359 (<1)	**0.91** (0.20, 4.19)	0.66
Harmony Outcomes	4/4731 (<1)	2/4732 (<1)	**2.00** (0.37, 10.87)	0.54
Overall	806/29,441 (3)	950/28,389 (3)	**0.82** (0.73, 0.93)	

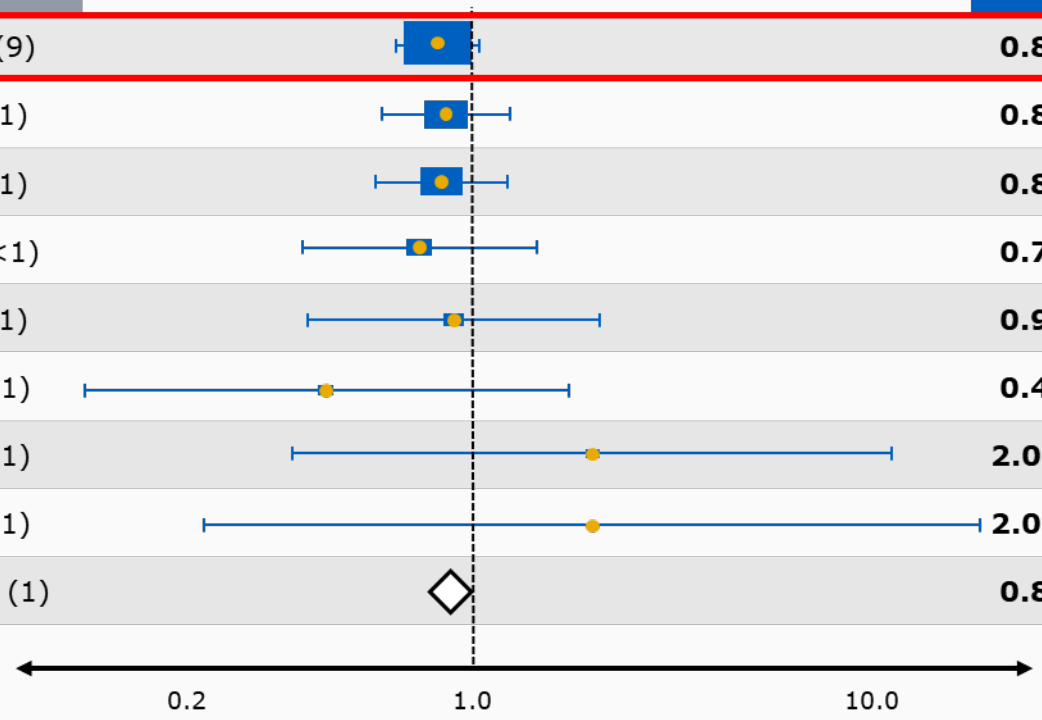


Heterogeneity: I^2 = 26%

Definitions of composite kidney outcome:
FLOW, LEADER, REWIND, SUSTAIN-6, AMPLITUDE-O: Persistent ≥50% reduction in eGFR, persistent eGFR <15 mL/min/1.73 m^2, initiation of kidney replacement therapy or kidney death.
EXSCEL: Persistent ≥40% reduction in eGFR, persistent eGFR <15 mL/min/1.73 m^2, initiation of kidney replacement therapy or kidney death.
ELIXA, Harmony Outcomes: Kidney replacement therapy.
CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio.
Badve S et al. Lancet DE 2024

Kidney failure

Study	GLP-1RA, n/N (%)	Placebo, n/N (%)	HR (95% CI)	Weight, %
FLOW	142/1767 (8)	165/1766 (9)	**0.83** (0.66, 1.04)	49.70
LEADER	56/4668 (1)	64/4672 (1)	**0.87** (0.61, 1.24)	19.56
EXSCEL	55/6259 (1)	65/6230 (1)	**0.85** (0.59, 1.22)	18.65
REWIND	16/4949 (<1)	21/4952 (<1)	**0.75** (0.39, 1.44)	5.77
SUSTAIN-6	11/1648 (1)	12/1649 (1)	**0.91** (0.40, 2.07)	3.64
ELIXA	3/2702 (<1)	7/2793 (<1)	**0.44** (0.11, 1.73)	1.31
Harmony Outcomes	4/4731 (<1)	2/4732 (<1)	**2.00** (0.37, 10.87)	0.86
AMPLITUDE-O	4/2717 (<1)	1/1359 (<1)	**2.00** (0.22, 18.06)	0.51
Overall	291/29,441 (1%)	337/28,389 (1)	**0.84** (0.72, 0.99)	



Heterogeneity: I^2 = 0%

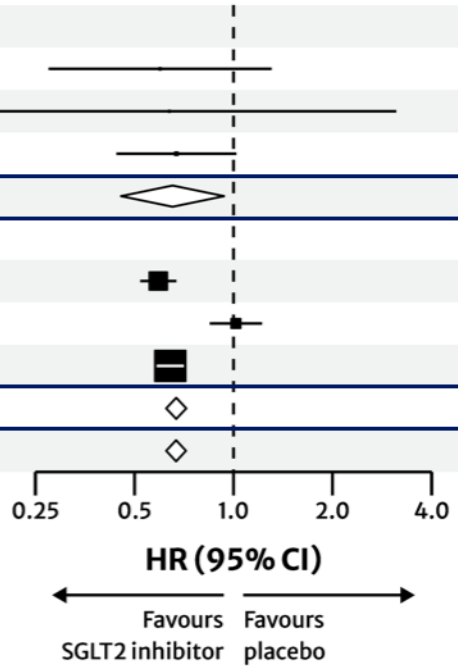
Definitions of kidney failure:
FLOW, LEADER, REWIND, SUSTAIN-6, AMPLITUDE-O: Persistent eGFR <15 mL/min/1.73 m^2, or initiation of kidney replacement therapy.
EXSCEL, ELIXA, Harmony Outcomes: Kidney replacement therapy.
CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio.
Badve S et al. Lancet DE 2024

Consistent benefit of SGLT2i on CKD progression by baseline GLP-1RA use

(40% decline in eGFR, kidney failure or death due to kidney failure)

FLOW
semaglutide | kidney outcomes trial

	Events/patients (%)		Event rate per 100 patient years		HR (95% CI)
	SGLT2 inhibitor	Placebo	SGLT2 inhibitor	Placebo	
Baseline use of GLP-1 RA **2,984**					
High atherosclerotic cardiovascular risk trials	14/936 (1·5)	17/693 (2·5)	0·4	1·0	0·60 (0·27 to 1·31)
Stable heart failure trials	3/47 (6·4)	3/33 (9·1)	2·2	4·7	0·64 (0·13 to 3·12)
Chronic kidney disease trials	40/635 (6·3)	53/640 (8·3)	3·2	4·5	0·67 (0·44 to 1·02)
Subtotal (I-squared = 0·0%, p = 0·64)	57/1618 (3·5)	73/1366 (5·3)	1·6	2·9	0·65 (0·46 to 0·94)
No baseline use of GLP-1 RA **70,122**					
High atherosclerotic cardiovascular risk trials	469/23585 (2·0)	526/17302 (3·0)	0·6	1·3	0·59 (0·52 to 0·67)
Stable heart failure trials	235/4781 (4·9)	231/4798 (4·8)	2·9	3·1	1·02 (0·85 to 1·22)
Chronic kidney disease trials	688/9839 (7·0)	1015/9817 (10·3)	3·7	5·6	0·64 (0·58 to 0·71)
Subtotal (I-squared = 70·4%, p<0.001)	1392/38205 (3·6)	1772/31917 (5·6)	1·7	2·9	0·67 (0·62 to 0·72)
Total **73,106**	1449/39823 (3·6)	1845/33283 (5·5)	1·7	2·9	0·67 (0·62 to 0·72)
Heterogeneity by use of GLP-1 RA: p = 0·81					



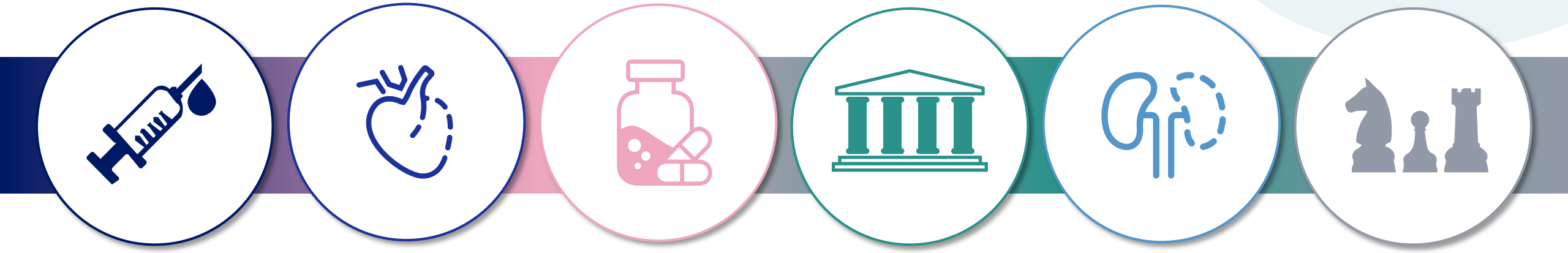
CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Apperloo EM et al. Lancet Diabetes Endocrinol. 2024;12:545-557.
https://www.smart-c.net/wp-content/uploads/2024/05/SMART-C_GLP-1RA_ERA_presentation.pdf.

SMART-C

Semaglutide saves kidneys, hearts, and lives

Novo Nordisk®
FLOW
semaglutide | kidney outcomes trial



CKD in people with T2D remains common and deadly

Highly effective therapies are now available to reduce risks of kidney failure, CV events, and death

FLOW has established that semaglutide prevents major kidney outcomes, MACE, HF events, and death in people with T2D and CKD

The four pillars of therapy are now a RAS inhibitor, an SGLT2 inhibitor, a non-steroidal MRA, and semaglutide

Low CKD awareness, detection and access to care are major barriers to receiving kidney, heart, and life-saving therapies

Effective strategies for therapeutic implementation are urgently needed to improve clinical outcomes in T2D and CKD

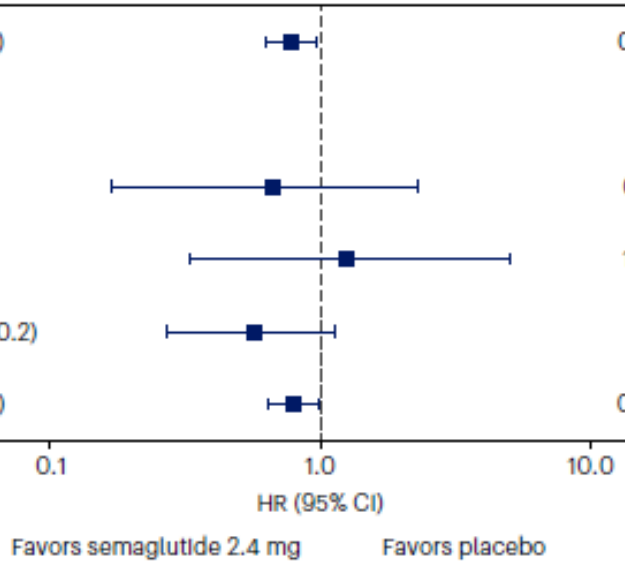
CKD, chronic kidney disease; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

de Boer IH et al. *Diabetes Care* 2022;45:3075–3090; Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2022;102:S1–S127;
Perkovic V et al. *N Engl J Med* 2024;391:109–121.

Long-term kidney outcomes of semaglutide (2.4 mg) in obesity and cardiovascular disease in the SELECT trial

https://doi.org/10.1038/s41591-024-03

	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



H Colhoun et al Nature Med 2024

nature medicine

Article

https://doi.org/10.1038/s41591-024-03327-6

Semaglutide in patients with overweight or obesity and chronic kidney disease without diabetes: a randomized double-blind placebo-controlled clinical trial

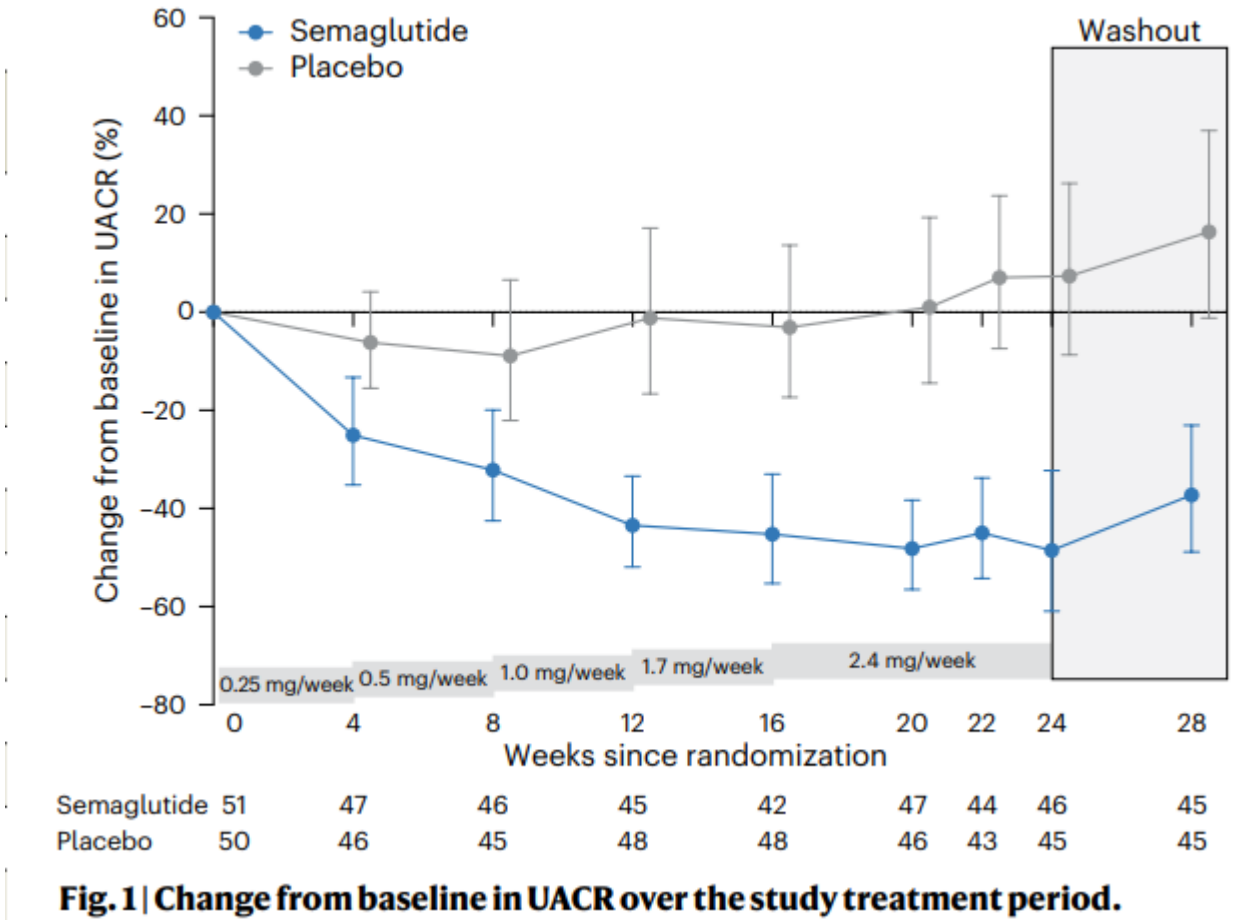


Fig. 1 | Change from baseline in UACR over the study treatment period.

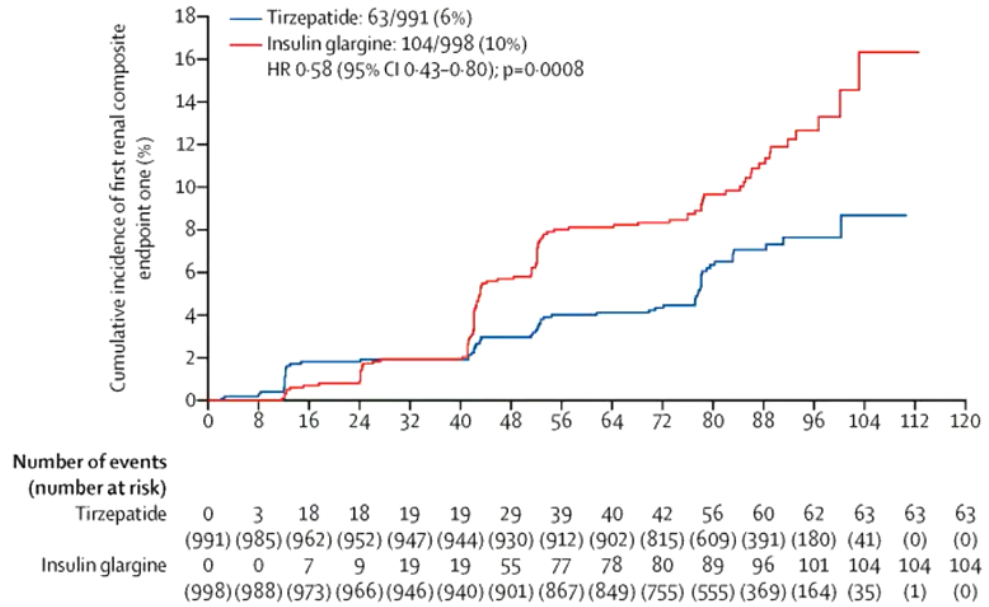
E Apperloo Nat Medicine 2024

SURPASS-4 TRIAL

Tirzepatide Reduces Risk of Composite Kidney Disease Endpoint

SURPASS-4

Incidence of Composite Kidney Disease Endpoint



Consistent effects in SGLT2 inhibitor and ACE inhibitor/ARB subgroups

Component	Treatment	N (%)	HR (95%CI)
eGFR decline ≥40% from baseline	TZP	38 (3.8%)	0.87 (0.56,1.33)
	iGLAR	45 (4.5%)	
Renal death	TZP	0	-
	iGLAR	0	
Progression to ESKD	TZP	0	-
	iGLAR	5 (0.5%)	
New onset macroalbuminuria[a]	TZP	25 (2.5%)	**0.41 (0.26,0.66)***
	iGLAR	61 (6.1%)	

Heerspink HJL *et al. Lancet Diab Endocrinol* 2022;10:774-78

Conclusions

- CKD in people with T2D remains common and deadly
- CVOTs demonstrated GLP1 RAs reduce MACE, and maybe slow progression of CKD in T2D with CKD
- The first kidney study with a GLP1 RA: FLOW demonstrated that semaglutide prevents major kidney outcomes, MACE, HF events, and death in people with T2D and CKD
- The four pillars of therapy are now a RAS inhibitor, an SGLT2 inhibitor, a non-steroidal MRA, and GLP1 RA