Protecting your kidneys in t2D: how to keep the nephrologist unemployed

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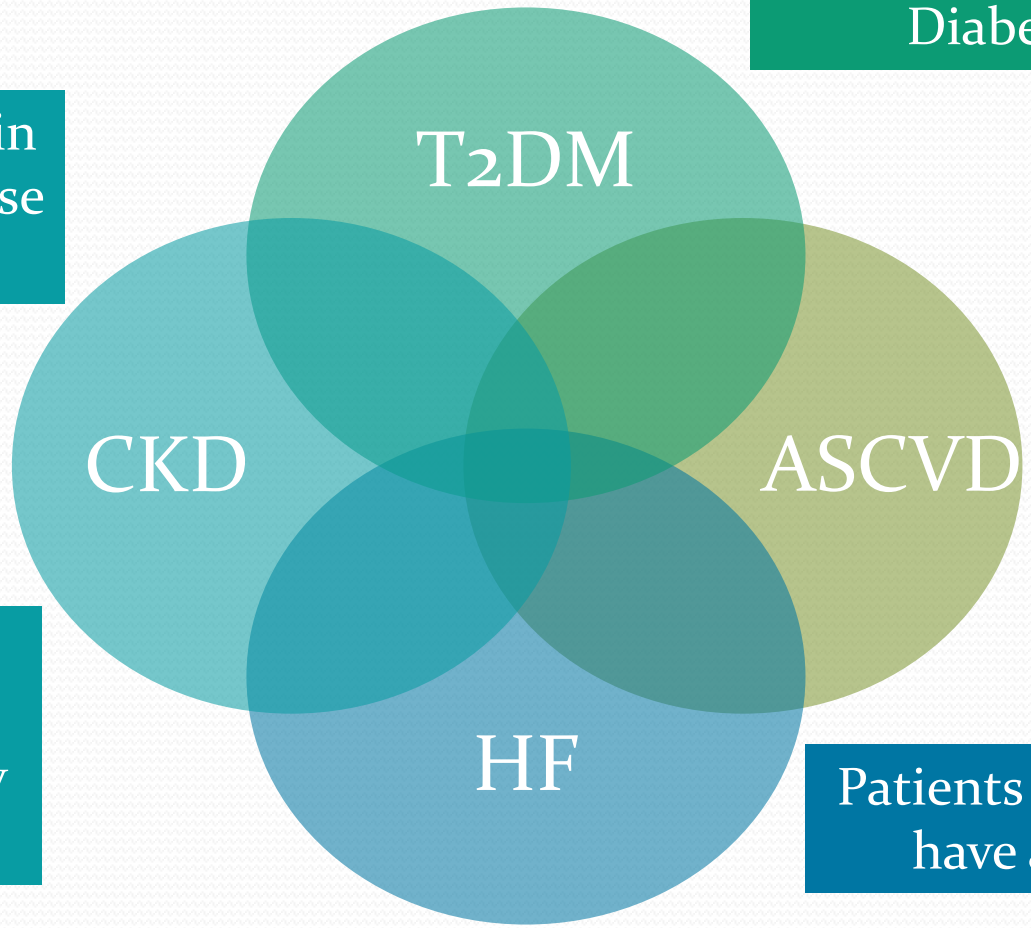
Diabetes and Cardiorenal Risk

More than 34 million Americans have diabetes – 95% of whom have Type 2 Diabetes Mellitus (T2DM).

Diabetes and CVD are the main causes of chronic kidney disease (CKD).



Adults with T2DM are twice as likely to have heart disease, a stroke, or heart failure.

The presence of diabetes and CVD in adults with CKD increases the risk of morbidity and mortality.

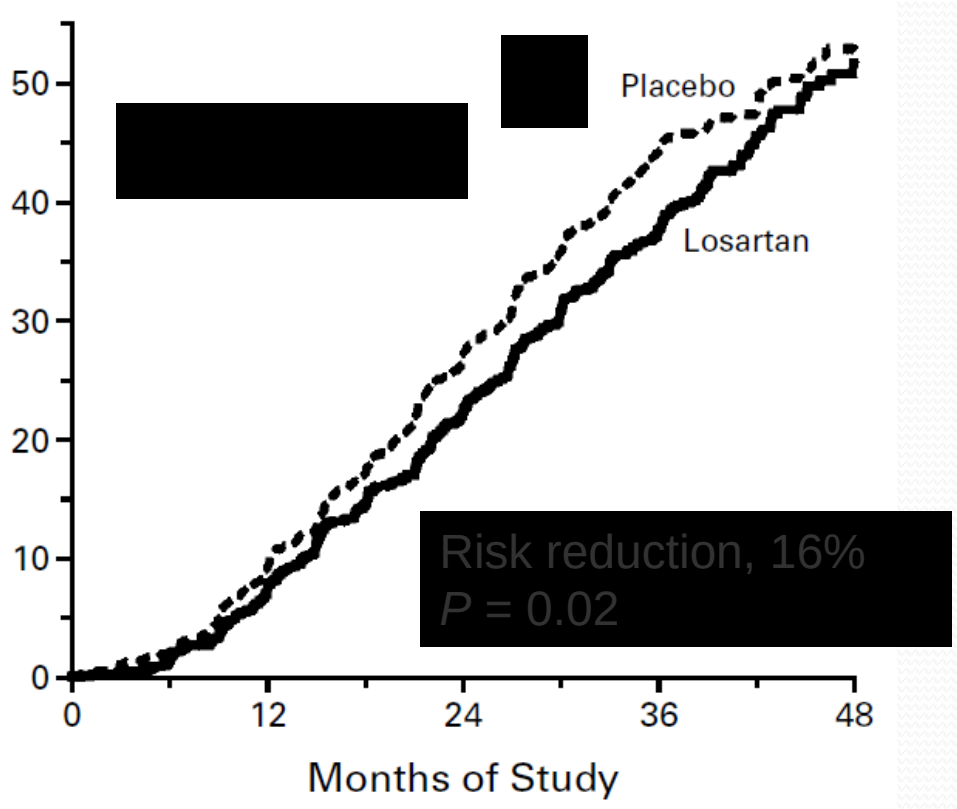
Patients with diabetes and heart failure have a 50% 5-year mortality rate.

CDC. Type 2 Diabetes [Internet]. Center for Disease Control [cited 2020 Sep 20]. Available from: https://www.cdc.gov/diabetes/basics/type2.html
National Institute of Diabetes and Digestive and Kidney Diseases. Kidney Disease Statistics for the United States [Internet]. NIH [cited 20 Sep 2020]. Available from: https://www.niddk.nih.gov/health-information/health-statistics/kidney-disease

Proven Renoprotection in T2DM: RENAAL & IDNT

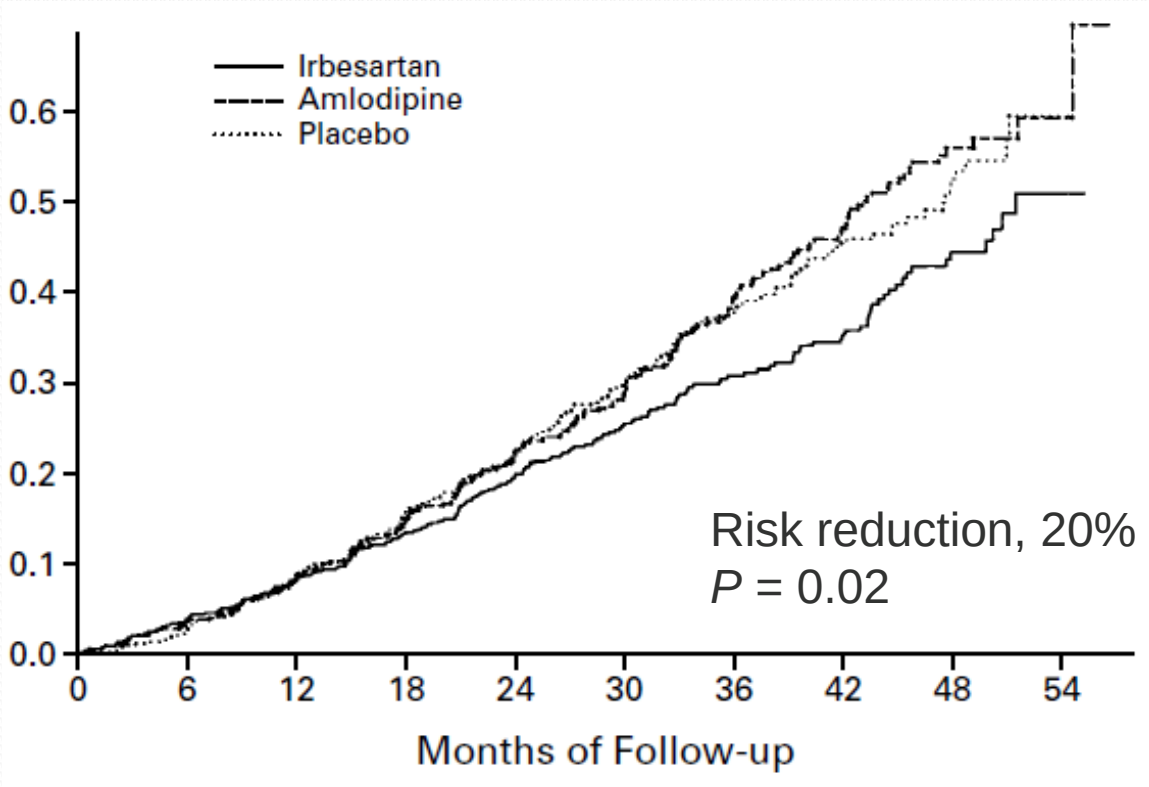
Doubling of serum creatinine, ESKD, or death

RENAAL



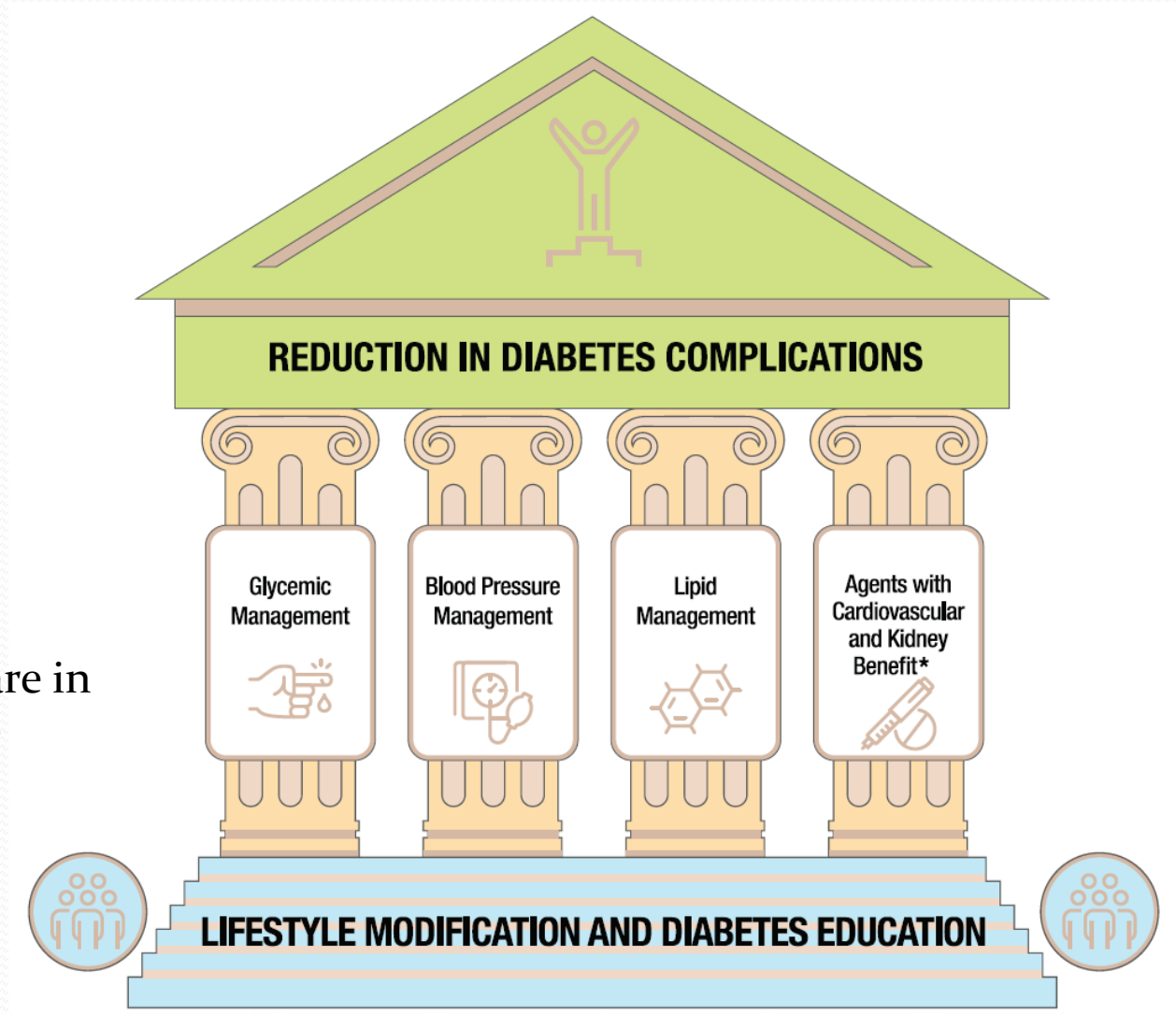
Brenner et al. *N Engl J Med*. 2001; 345:861-869.

IDNT



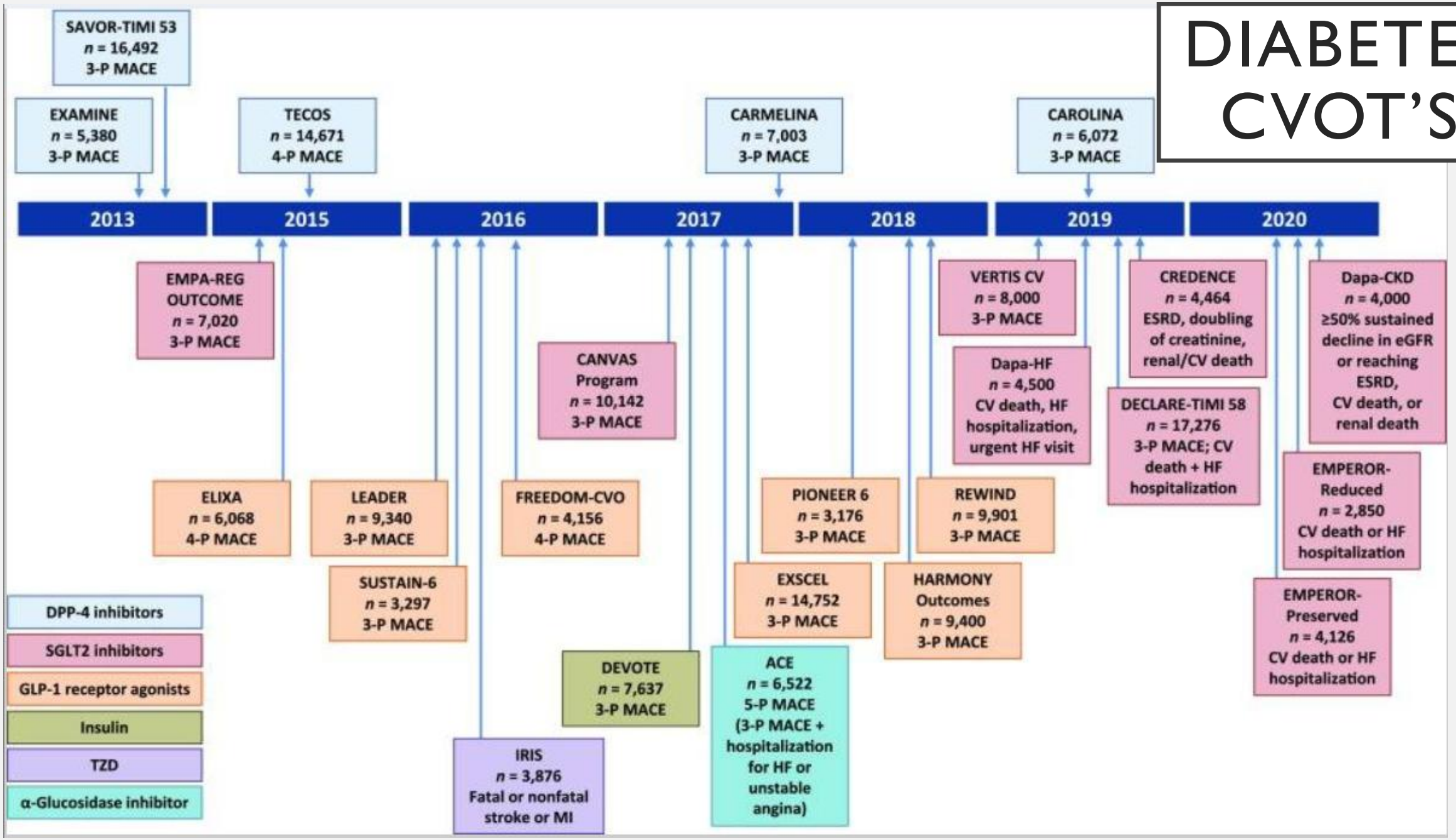
Lewis et al. *N Eng J Med*. 2001; 345:851-860.

Multifactorial approach to reduction in risk of diabetes complications



ADA. Standards of Medical Care in Diabetes – 2022. Diabetes Care 2022;45(Suppl. 1):S144–S174.

DIABETES CVOT'S



Cefalu WT et al. Cardiovascular Outcomes Trials in Type 2 Diabetes: Where Do We Go From Here? Reflections From a Diabetes Care Editors' Expert Forum. Diabetes Care 2018;41:14–31.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

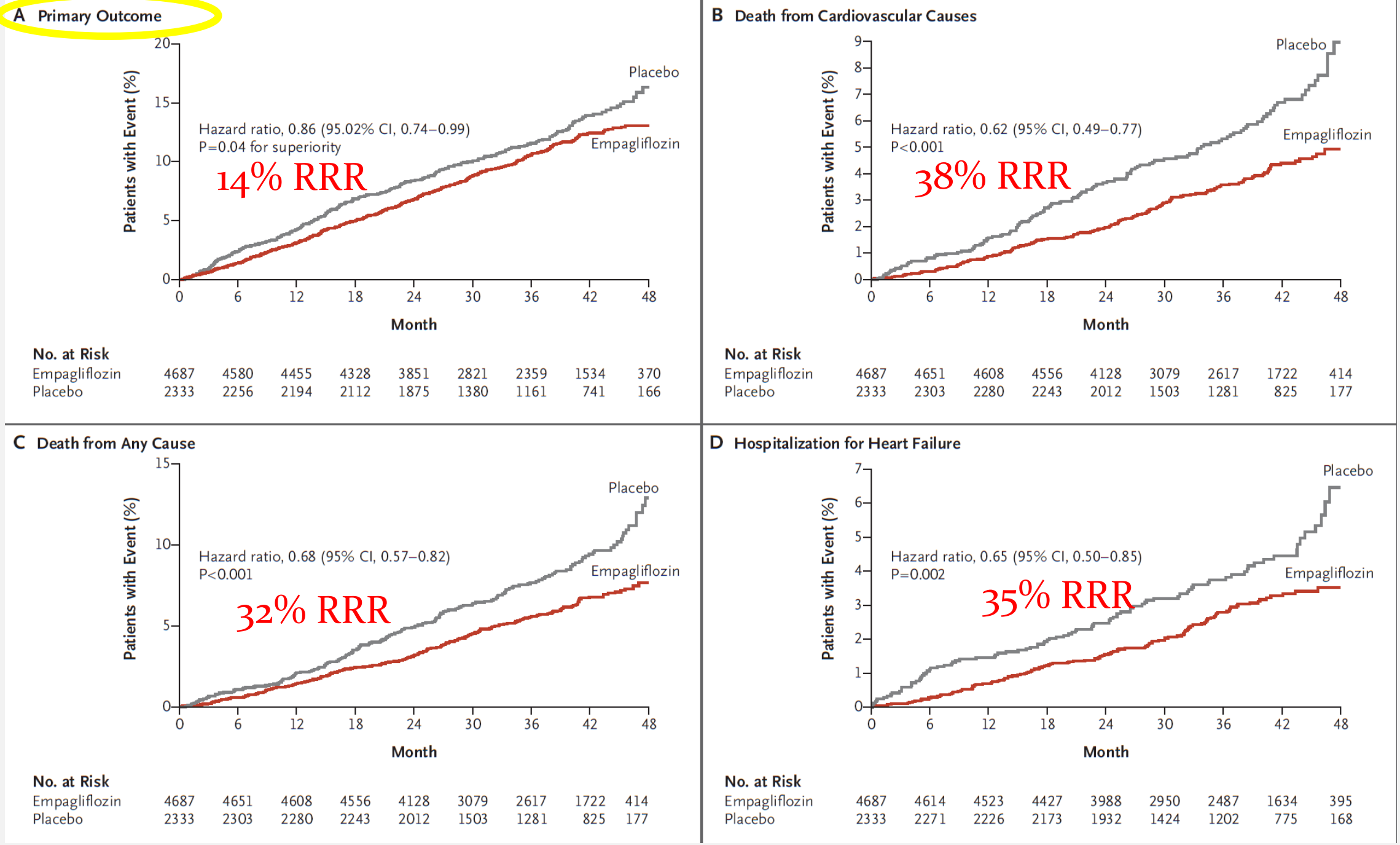
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

7,020 people with T2DM, 100% with established CVD

Empa 10 or 25 mg vs placebo (all +SOC); Median observation time of 3.1 years

Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke (3-pt MACE)

Zinman B et al. N Engl J Med. 2015;373(22):2117-28.



Zinman B et al. N Engl J Med. 2015;373(22):2117-28.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

9,340 people with T2DM at high risk of MACE

Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke: 13% reduction

Secondary Endpoint: 22% reduction of CV mortality
15% decrease in overall mortality

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 28, 2016 VOL. 375 NO. 4

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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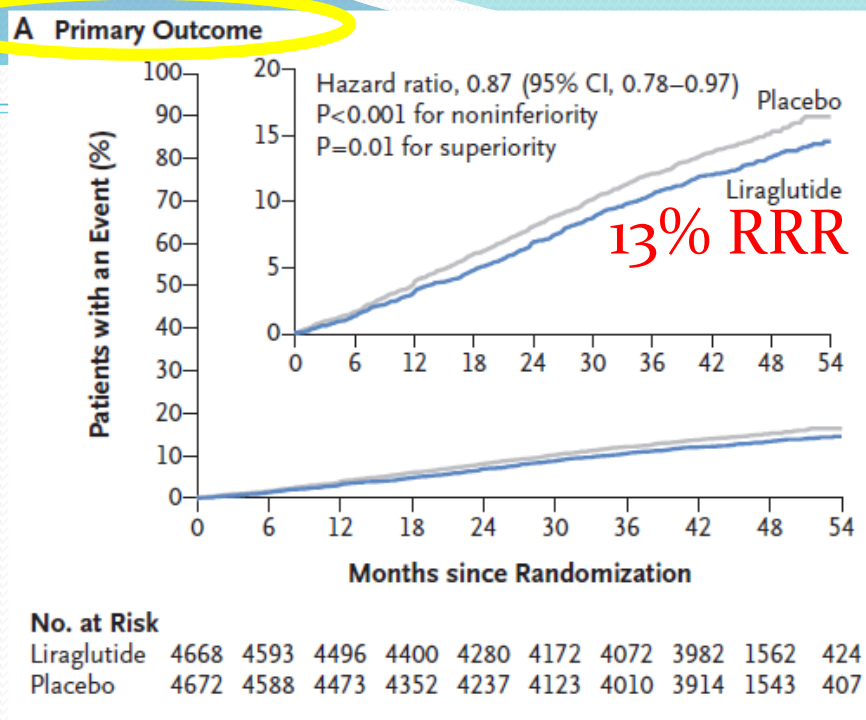
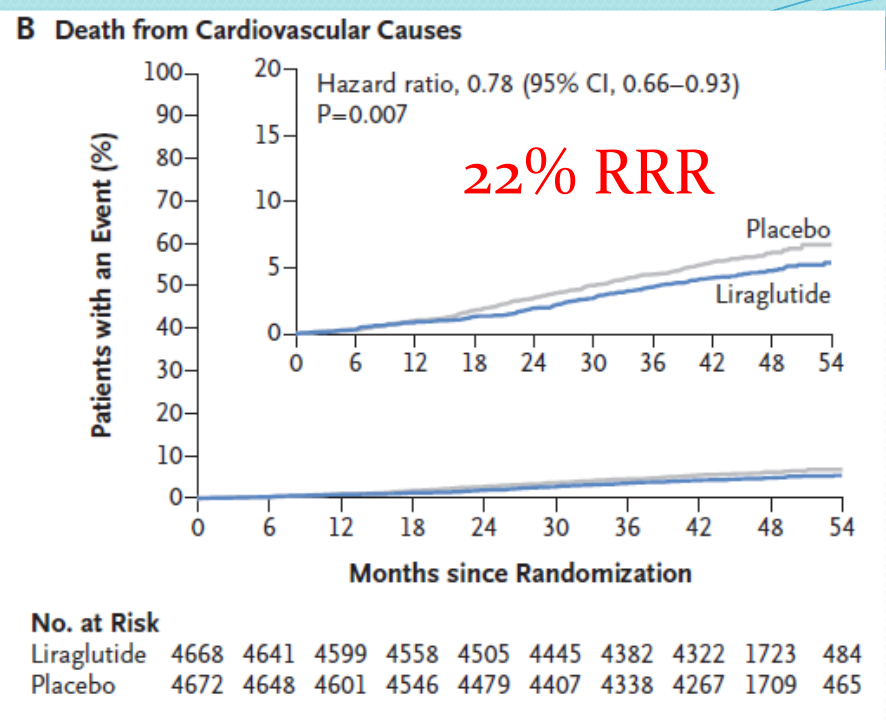
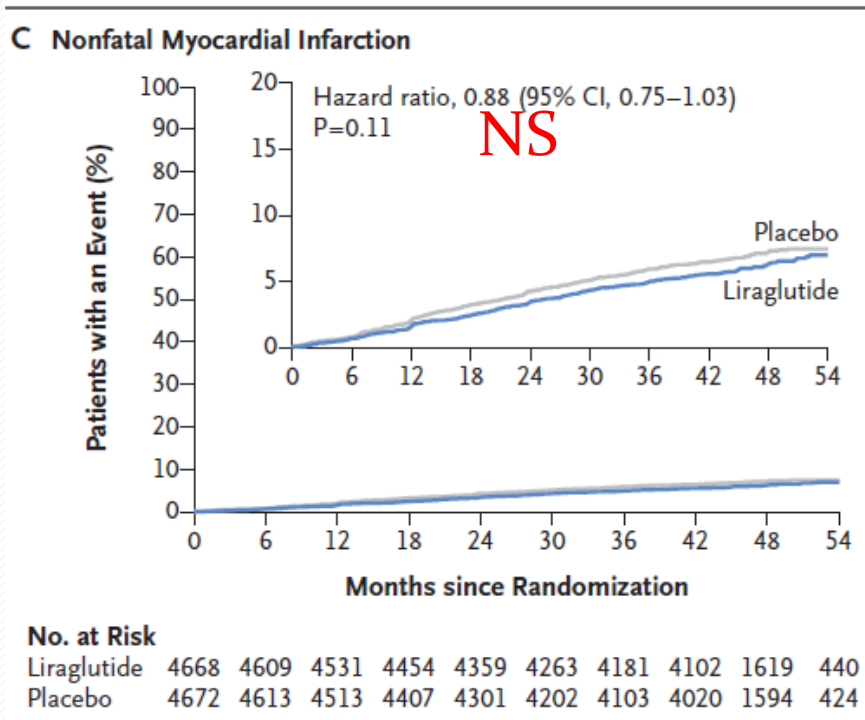
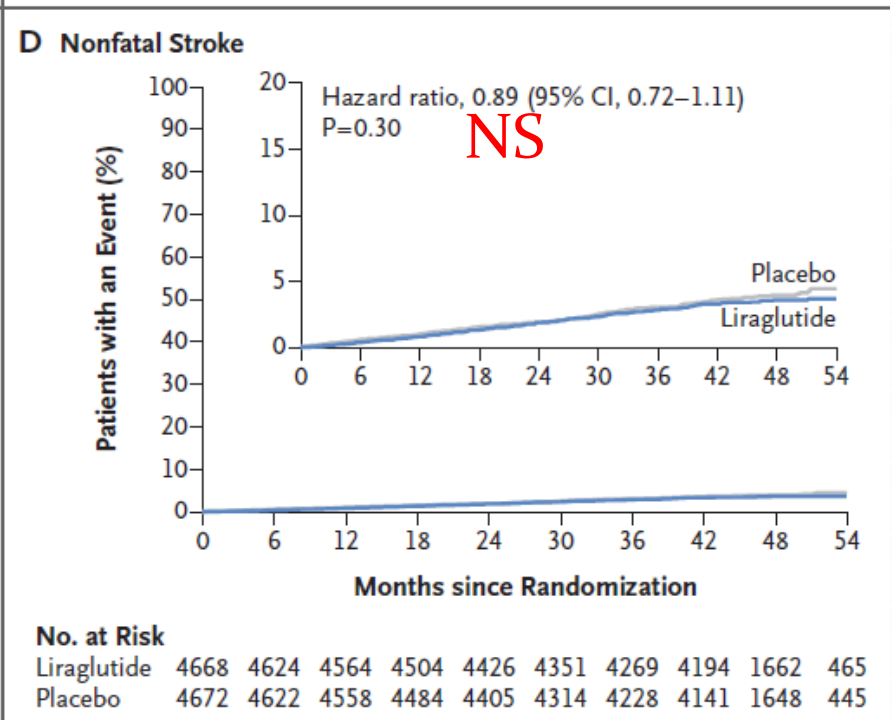
9,340 patients with T2DM at high risk of MACE (81% with CVD)
Liraglutide 1.8 mg; Median 3.8 yrs f/u
Primary Endpoint: Composite of CV death, non-fatal MI and non-fatal stroke









Marso SP et al. N Engl J Med. 2016 Jul 28;375:311-22.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sept 16, 2016.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

26% reduction of MACE

ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

METHODS

We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

From the Research Medical Center, Kansas City, MO (S.P.M.); School of Medicine, Swansea University, Swansea, United Kingdom (S.C.B.); Department of Medicine and Aging Science and Center of Excellence on Aging and Translational Medicine, G. d'Annunzio University, Chieti-Pescara, Italy (A.C.); CPClin Research Center/Hospital Israelita Albert Einstein, São Paulo (F.G.E.); Hospital Universitario Quirón Salud Madrid, Facultad de Ciencias de la Salud, Universidad Europea de Madrid, Madrid (E.J.); Li Ka Shing Knowledge Institute and Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.), and the University of Manitoba, Winnipeg (V.W.) —

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3,297 patients with T2DM at high risk of MACE (83% with CVD and/or CKD)
Semaglutide 0.5 or 1 mg; Median 2.1 yrs f/u
Primary Endpoint: 3-point MACE

ABSTRACT

BACKGROUND

Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

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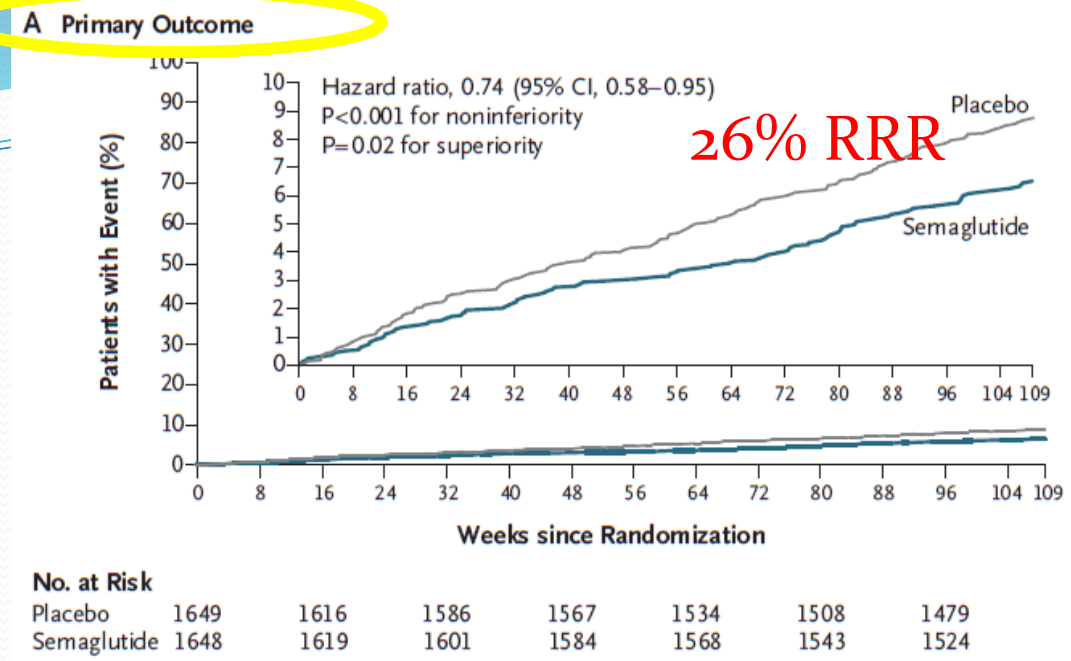
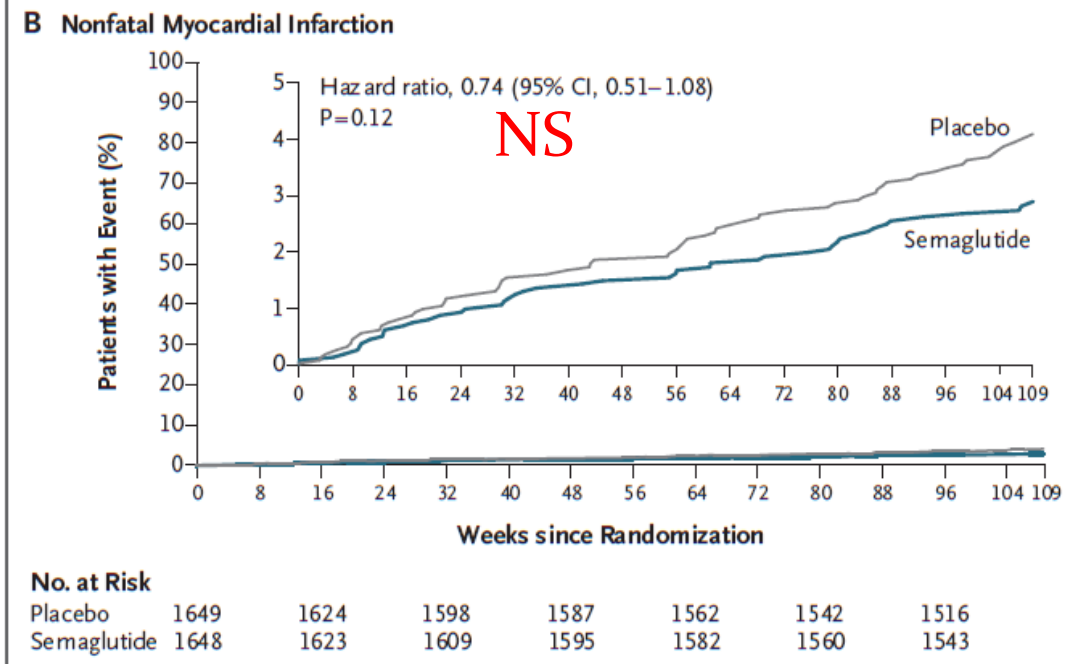
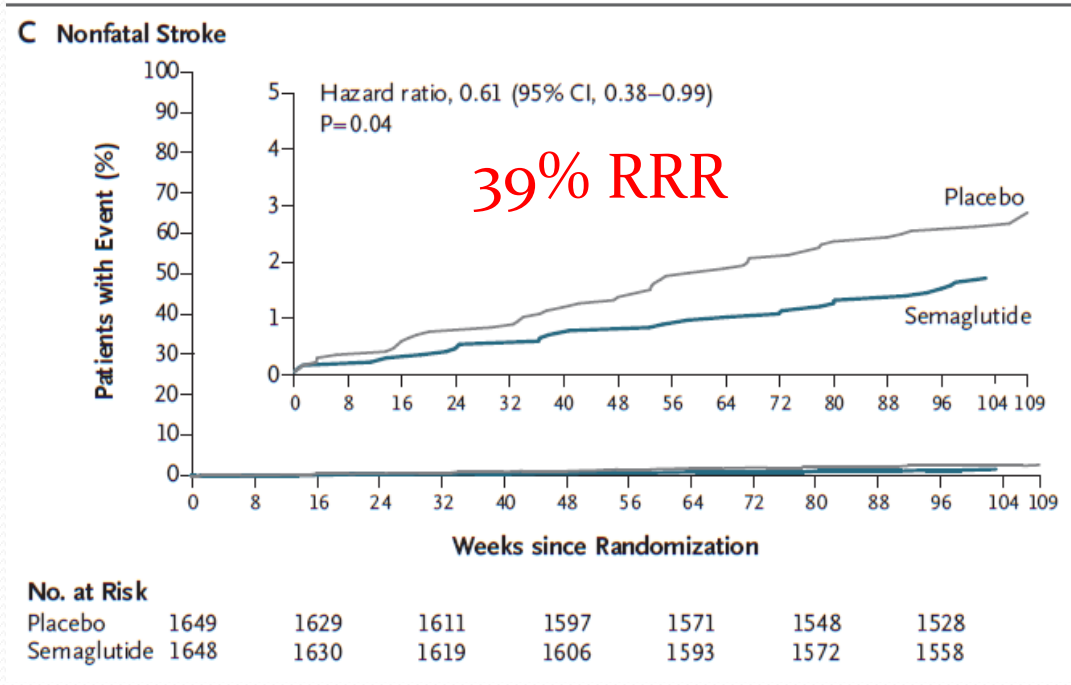
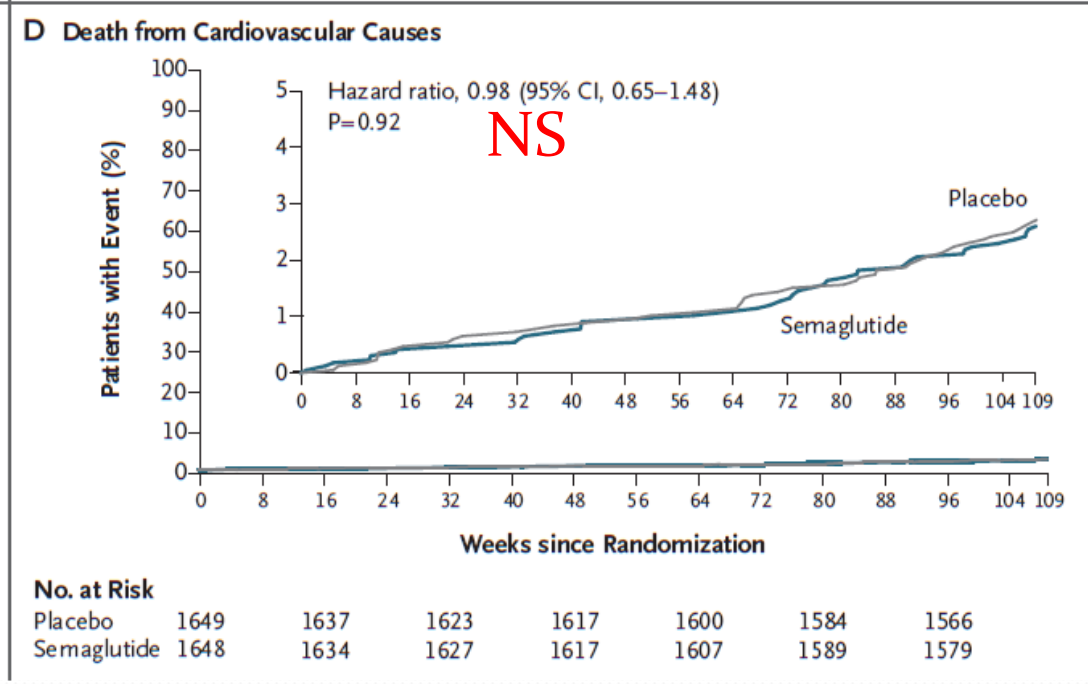








Marso SP. N Engl J Med. 2016; 375: 311-22.

Renal Protection

CV Outcomes

	MACE HR (95% CI)	CV Death HR (95% CI)	HHF HR (95% CI)
EMPA-REG OUTCOME[a]	**0.86** (0.74, 0.99)	**0.62** (0.49, 0.77)	**0.65** (0.50, 0.85)
CANVAS Program[b]	**0.86** (0.75, 0.97)	**0.87** (0.72, 1.06)	**0.67** (0.52, 0.87)
DECLARE-TIMI 58[c]	**0.93** (0.84, 1.03)	**0.98** (0.82, 1.17)	**0.73** (0.61, 0.88)
VERTIS CV[d]	**0.97*** (0.85, 1.11)	**0.92**† (0.77, 1.11)	**0.70** (0.54, 0.90)

*Full analysis set, 95.6% CI for MACE. †Intention-to-treat analysis set, 95.8% CI.

a. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. McGuire DK. Presented at the EASD Virtual Meeting, 2020.

Kidney Composite Outcomes

- Generally consistent definitions: sustained ≥ 40% decline in eGFR, ESKD or renal death

		HR (95% CI)
EMPA-REG OUTCOME[a] (post-hoc exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.55** (0.41, 0.73)
CANVAS Program[b] (prespecified exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60** (0.47, 0.77)
DECLARE-TIMI 58[c] (prespecified secondary)	Sustained ≥ 40% decrease in eGFR to < 60 mL/min/1.73 m^2 and/or end-stage renal disease and/or renal death	**0.53** (0.43, 0.66)
VERTIS CV[d]* (prespecified exploratory)	Sustained ≥ 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.66** (0.50, 0.88)

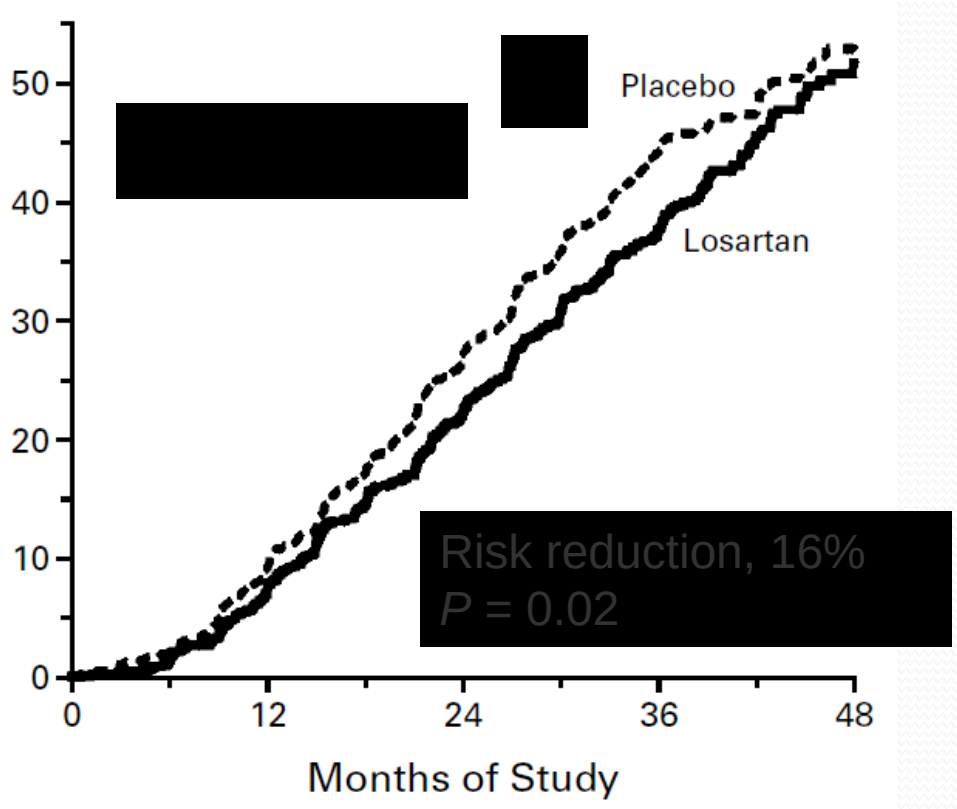
*Intention-to-treat analysis set, 95.0% CI.

a. Perkovic V, et al. *Nephrol Dial Transplant.*2019;1–9; b. Neal B, et al. *N Engl J Med*. 2017;377:644-657; c. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357; d. Cherney D. Presented at the EASD Virtual Meeting, 2020.

Proven Renoprotection in T2DM: RENAAL & IDNT

Doubling of serum creatinine, ESKD, or death

RENAAL



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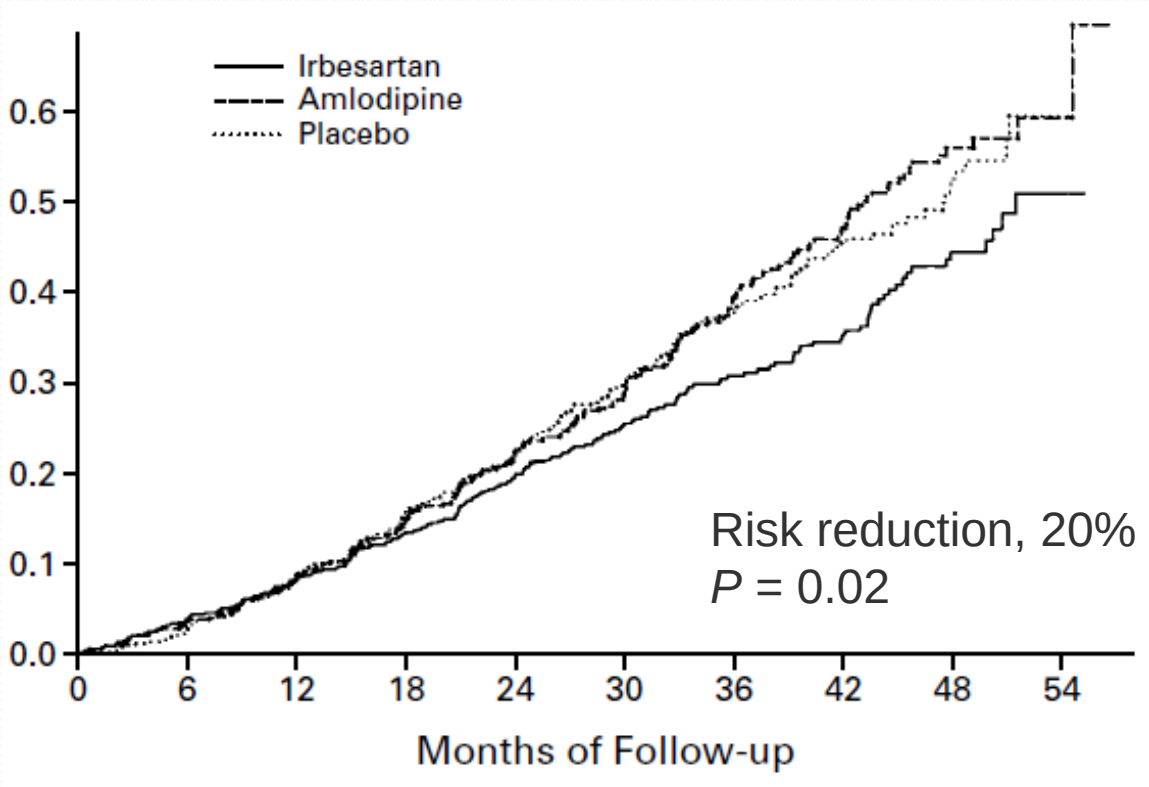


Lewis et al. *N Eng J Med*. 2001; 345:851-860.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 13, 2019 VOL. 380 NO. 24

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

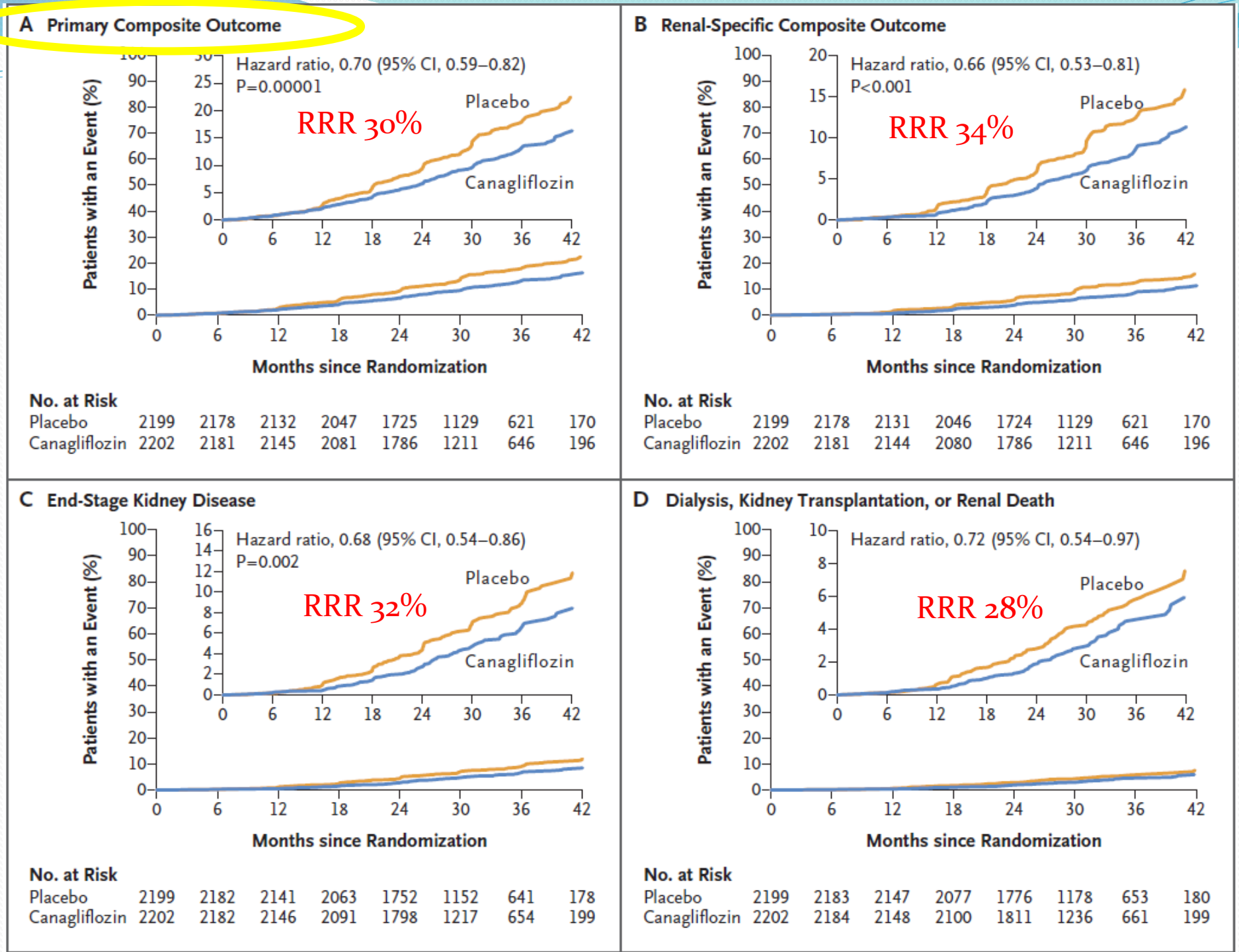
V. Perkovic, M.J. Jardine, B. Neal, S. Bompoint, H.J.L. Heerspink, D.M. Charytan, R. Edwards, R. Agarwal, G. Bakris, S. Bull, C.P. Cannon, G. Capuano, P.-L. Chu, D. de Zeeuw, T. Greene, A. Levin, C. Pollock, D.C. Wheeler, Y. Yavin, H. Zhang, B. Zinman, G. Meininger, B.M. Brenner, and K.W. Mahaffey, for the CREDENCE Trial Investigators*

4401 patients with T2DM, eGFR 30-90 ml/min with macro albuminuria (300-5000 mg/g)
Cana 100 mg mg; receiving SOC therapy, Median 2.6 yrs f/u
Primary Endpoint: composite of ESRD, a doubling of the SCr level, or renal or CV death

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South



Perkovik V et al. N Engl J Med, 2019;380:2295-306.

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Robert D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

4304 patients **with CKD** (eGFR 25-75 ml/min and urinary Alb:Cr 200-5000 mg/g)
On stable renal protection therapy; Dapa 10 mg; Median 2.4 yrs f/u; 2/3's with T2DM
Primary Endpoint: composite of a sustained decline in the eGFR of at least 50%, ESRD, or death from renal or cardiovascular causes

ABSTRACT

BACKGROUND

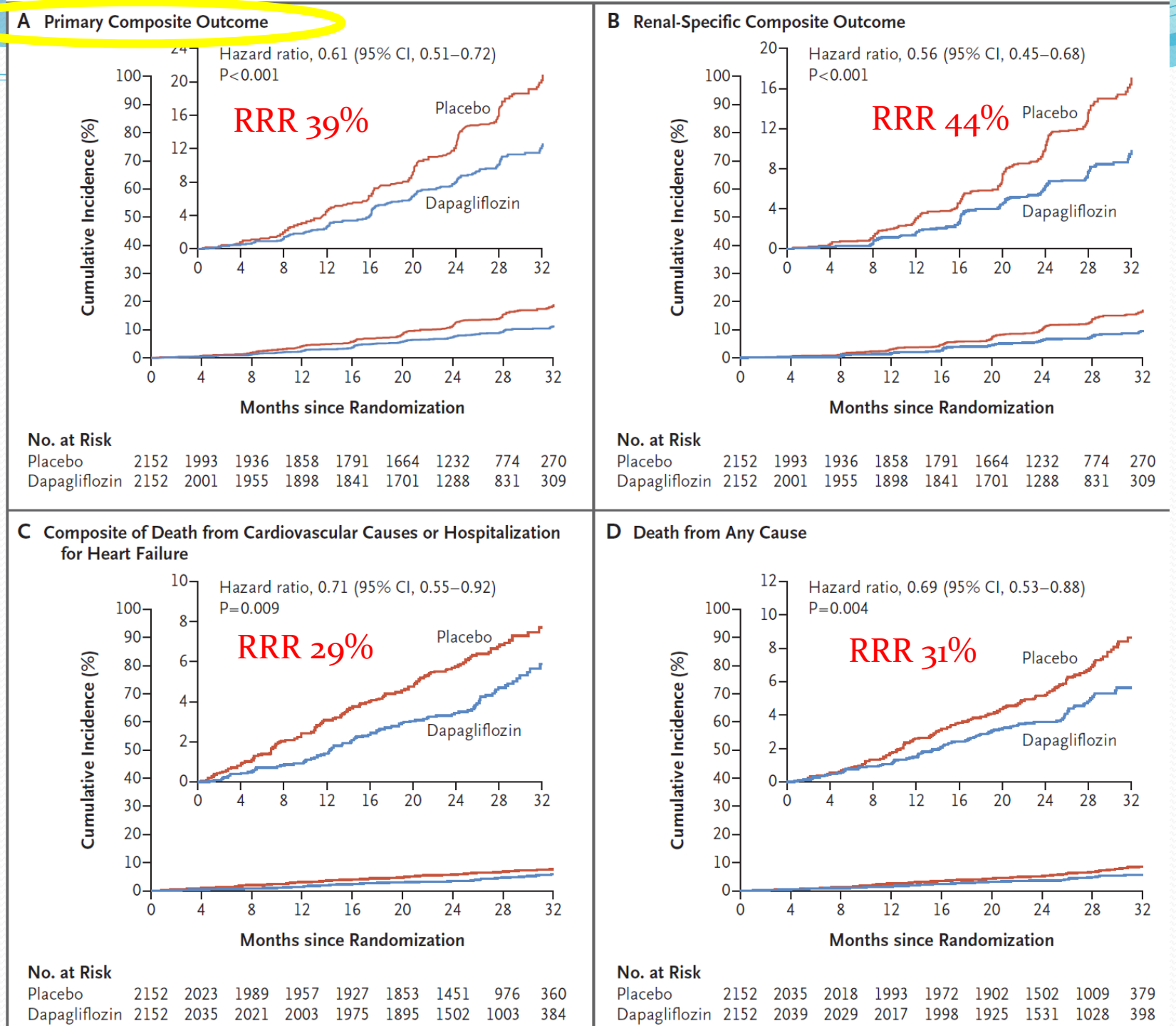
Patients with chronic kidney disease have a high risk of adverse kidney and cardiovascular outcomes. The effect of dapagliflozin in patients with chronic kidney disease, with or without type 2 diabetes, is not known.

METHODS

We randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m^2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo. The primary outcome was a composite of a sustained decline in

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Heerspink at the Department of Clinical Pharmacy and Pharmacology, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, the Netherlands, or at h.j.lambers.heerspink@umcg.nl.

*A complete list of DAPA-CKD committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.



Heerspink HJL et al. NEJM 2020;
DOI: 10.1056/NEJMoa2024816

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

Heerspink HJL et al. NEJM 2020;
DOI: 10.1056/NEJMoa2024816

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

ABSTRACT

BACKGROUND

The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

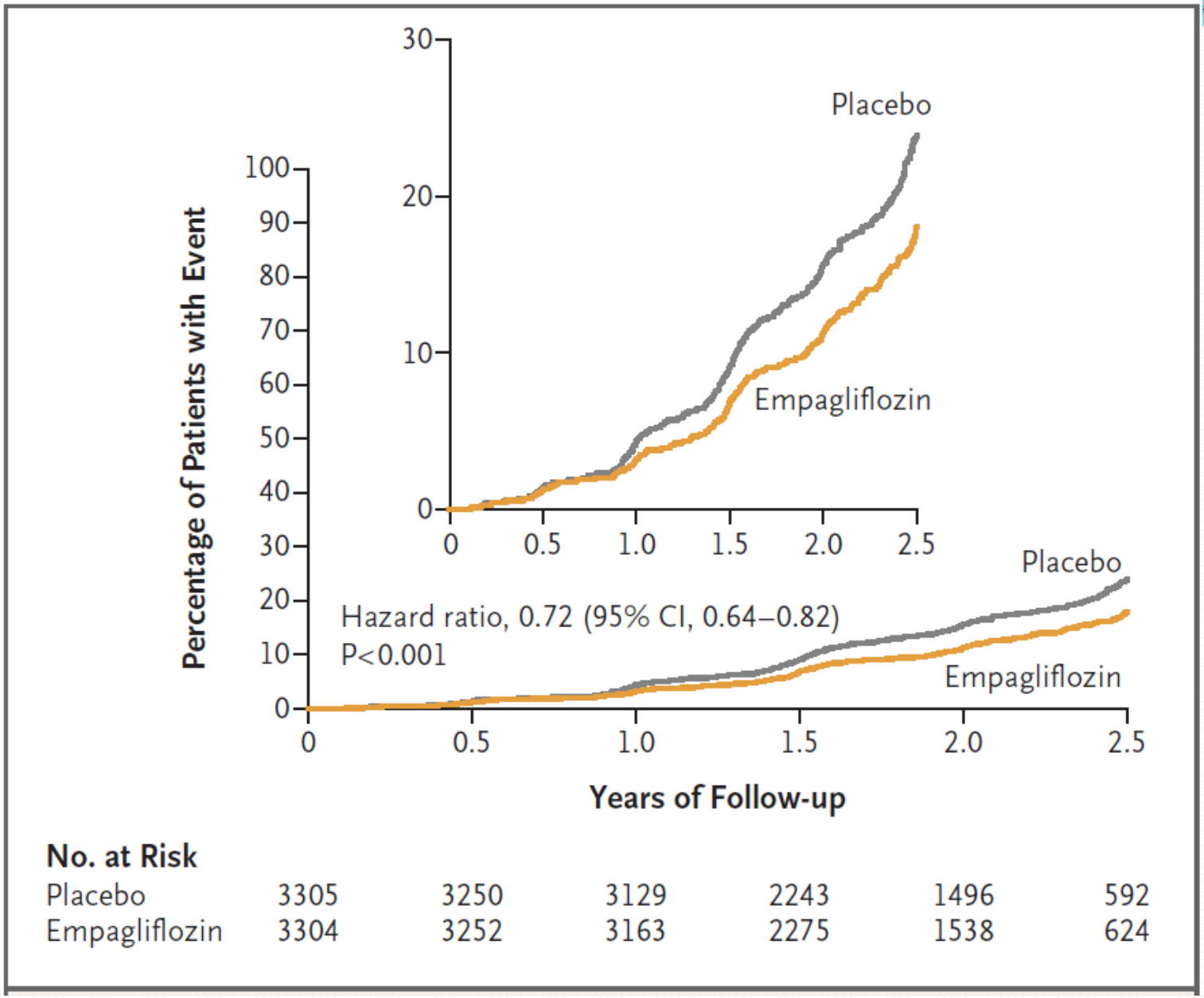
METHODS

We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m^2 of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per

The members of the writing committee (W.G. Herrington, N. Staplin, C. Wanner, J.B. Green, S.J. Hauske, J.R. Emberson, D. Preiss, P. Judge, K.J. Mayne, S.Y.A. Ng, E. Sammons, D. Zhu, M. Hill, W. Stevens, K. Wallendszus, S. Brenner, A.K. Cheung, Z.-H. Liu, J. Li, L.S. Hooi, W. Liu, T. Kadowaki, M. Nangaku, A. Levin, D. Cherney, A.P. Maggioni, R. Pontremoli, R. Deo, S. Goto, X. Rossello, K.R. Tuttle, D. Steubl, M. Petrini, D. Massey, J. Eilbracht, M.

N Engl J Med 2023;388:117-27.

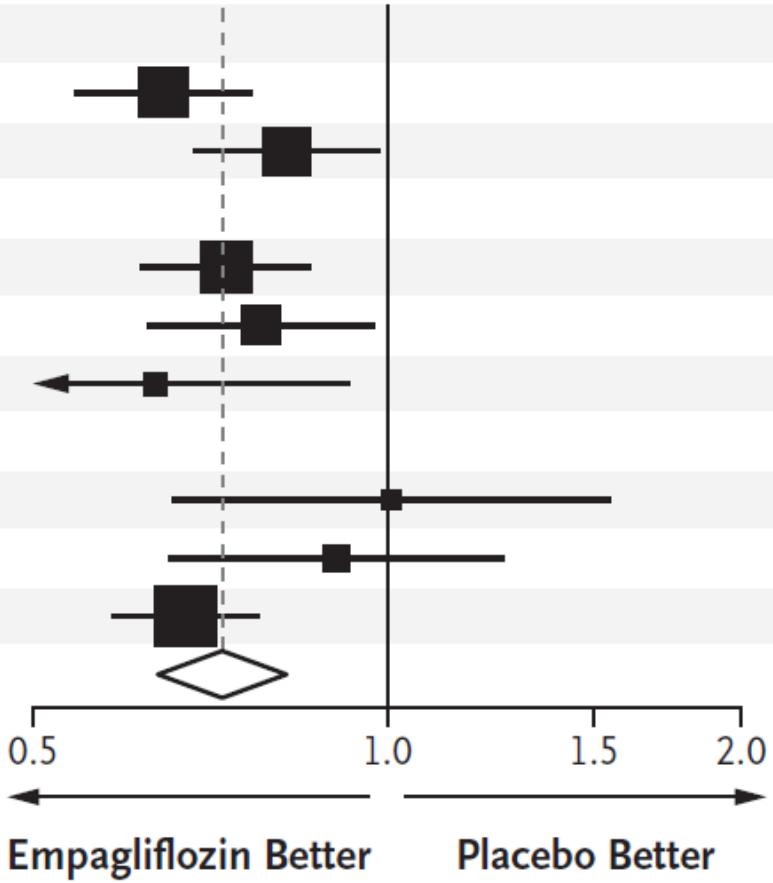
Progression of Kidney Disease or Death from CV Causes



N Engl J Med 2023;388:117-27.

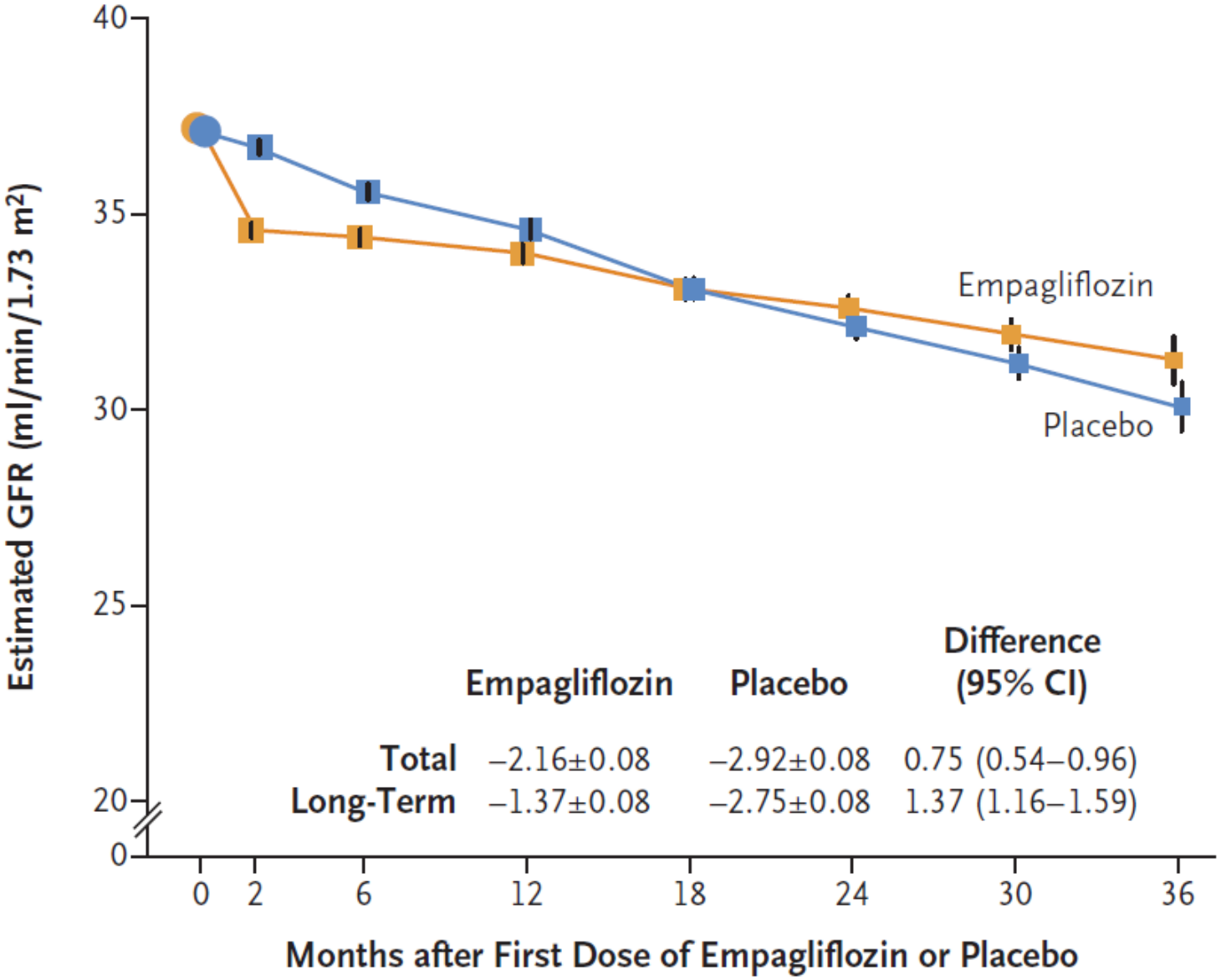
Subgroups

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



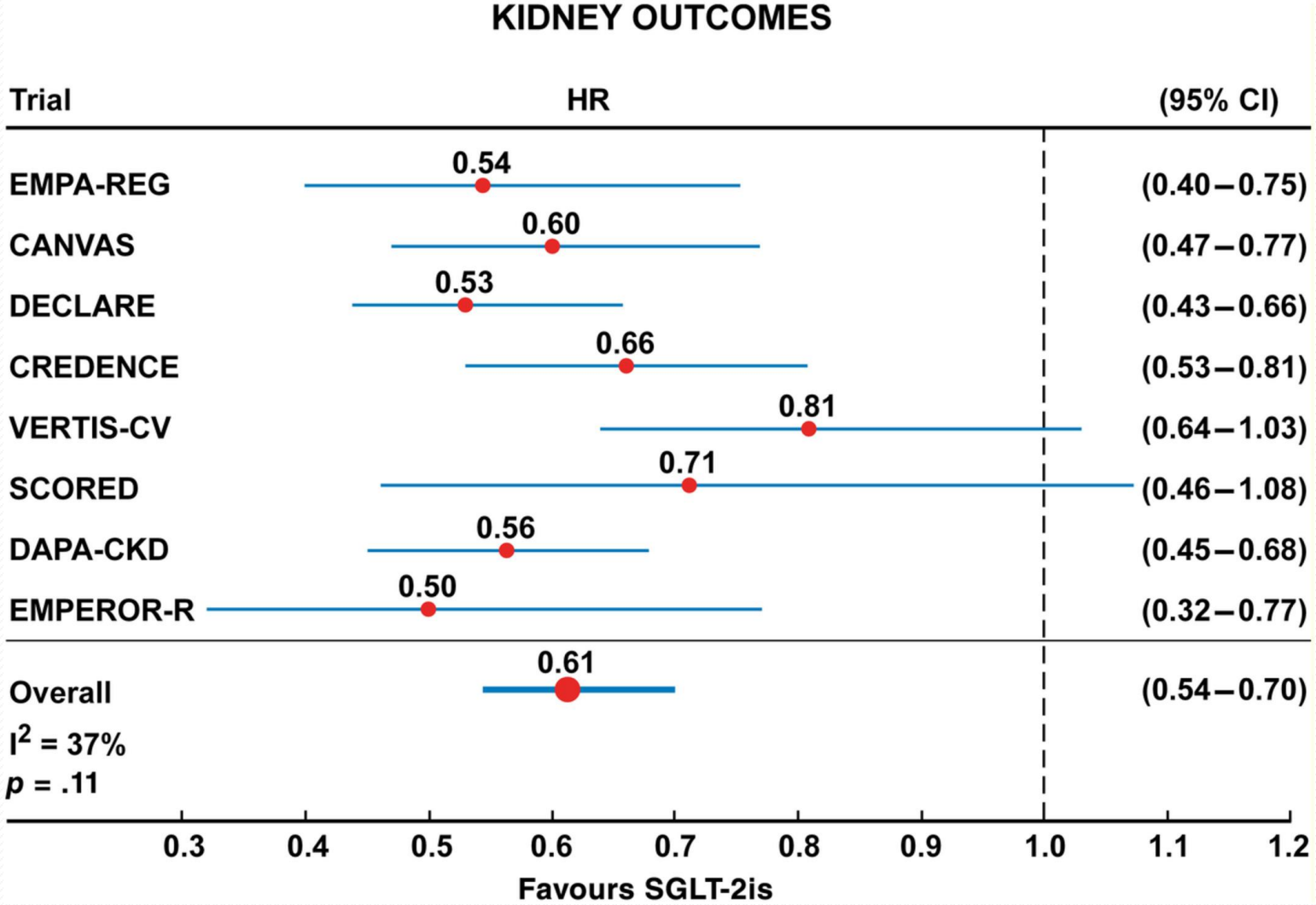
N Engl J Med 2023;388:117-27.

Change from Baseline in the Estimated GFR



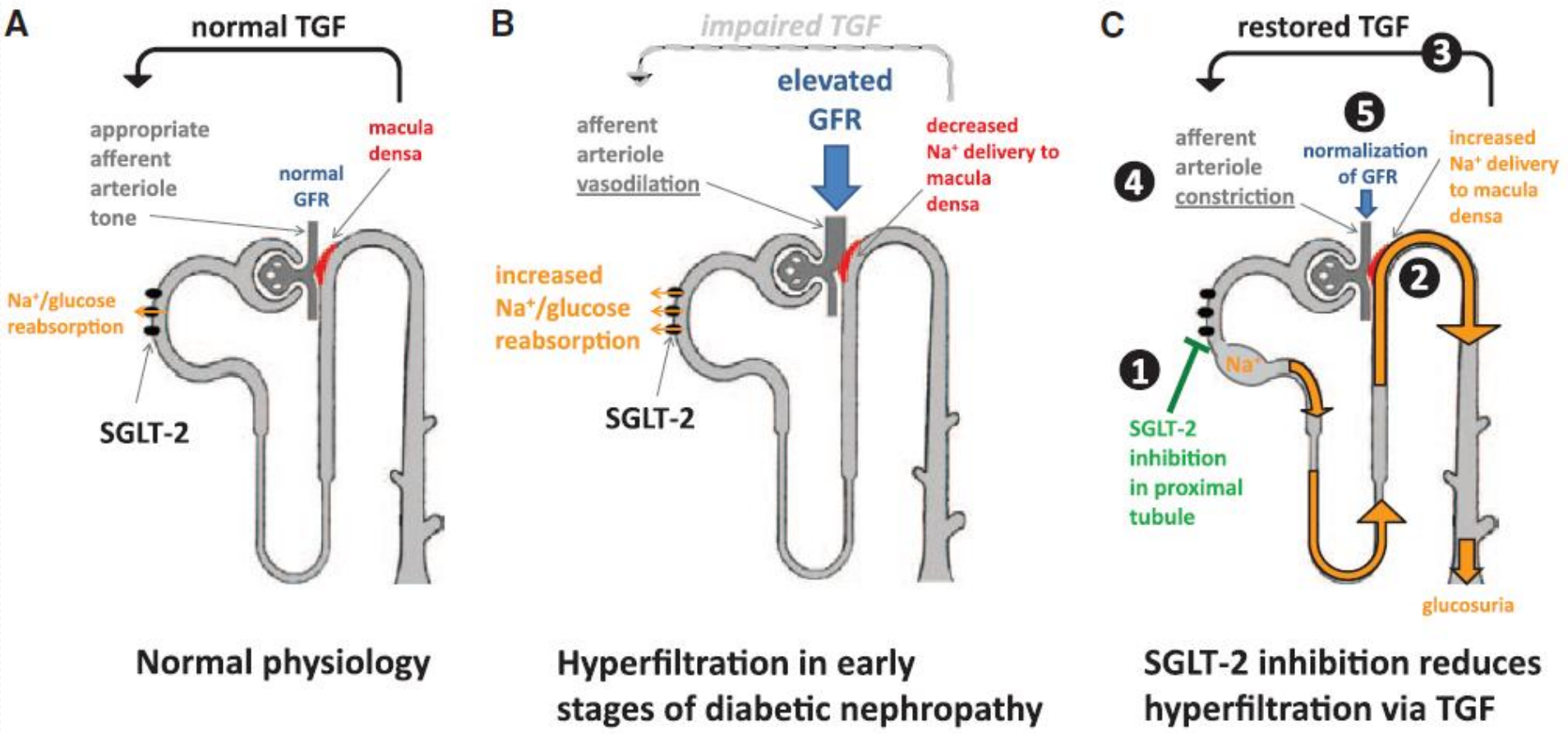
N Engl J Med 2023;388:117-27.

Effect of SGLTs on Renal Endpoints



Giugliano et al. Diabetes Obesity Metabolism 2021; Om-line 12 March

Postulated SGLT2i tubuloglomerular feedback (TGF) mechanisms



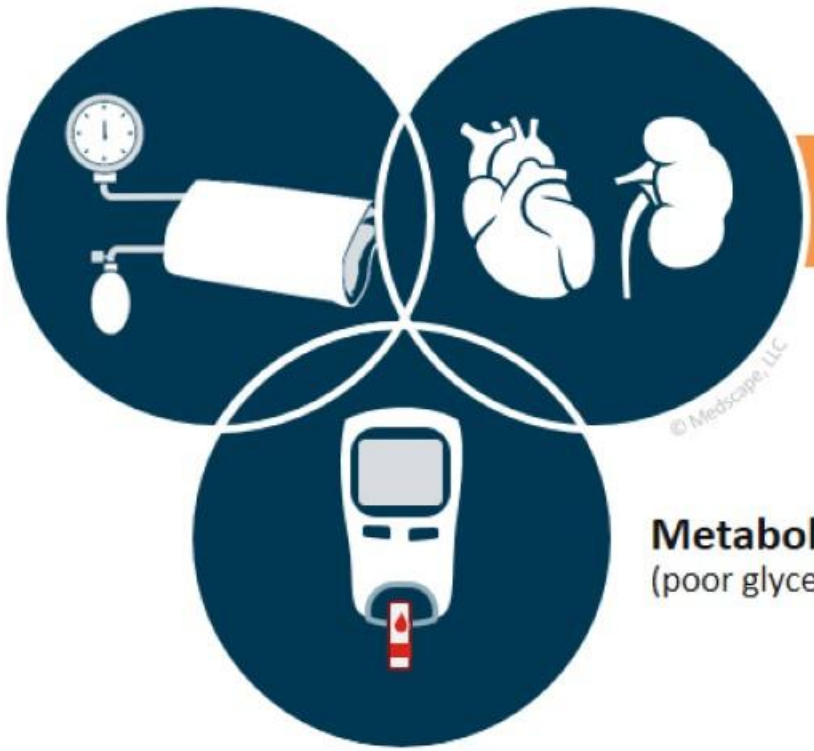
Cherney DZI et al. Circulation. 2014;129:587-97.

Unmet Need

Addressing the 3 Drivers of CKD Progression in T2D

3 Drivers of CKD Progression in T2D

Hemodynamic
(elevated blood pressure and/
or intraglomerular pressure)



Metabolic
(poor glycemic control)

Inflammation and fibrosis

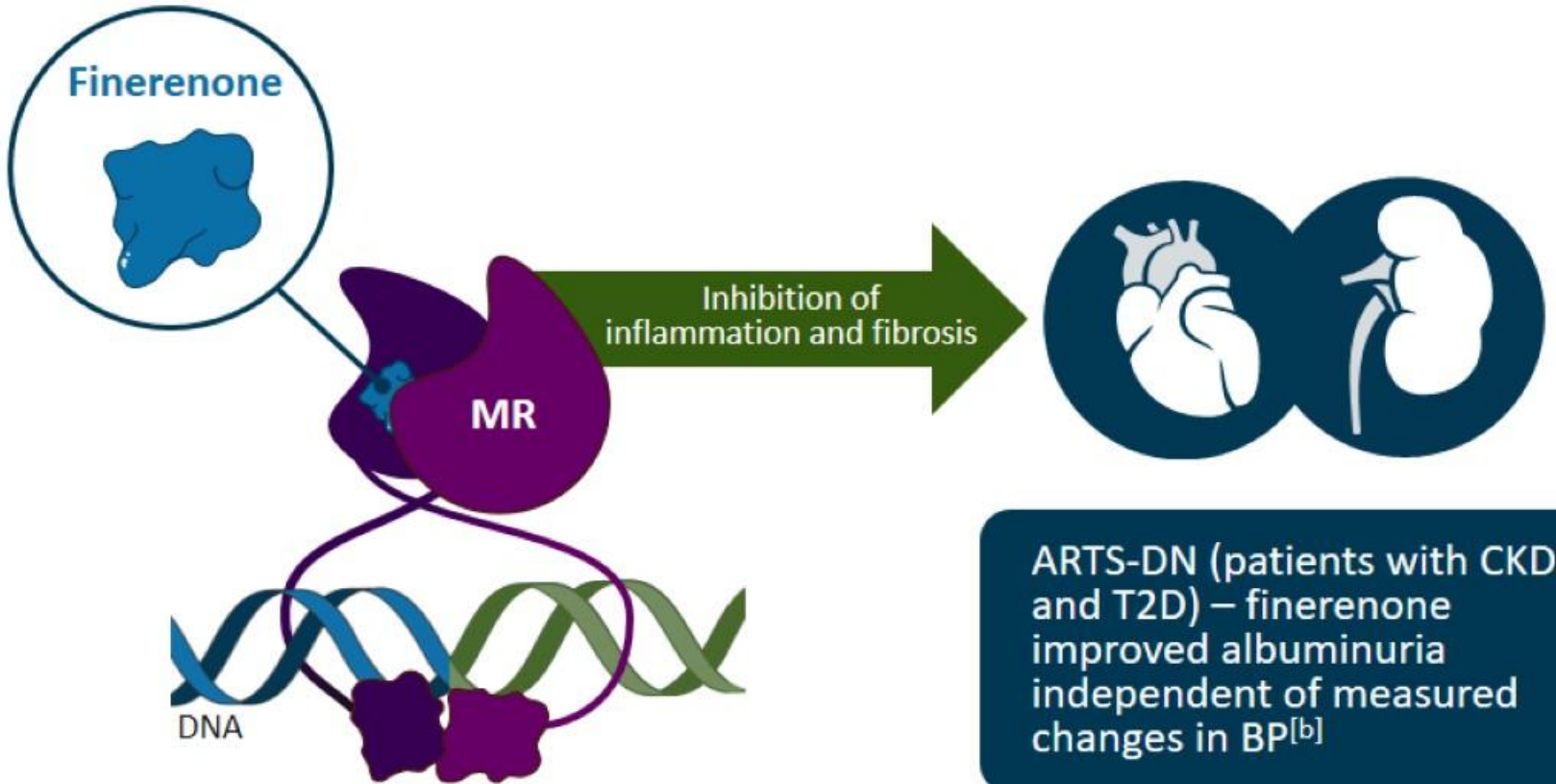
Not specifically targeted by existing treatments[a,d]

*Composite of doubling of serum creatinine, ESKD, or death.

a. Alicic RZ, et al. *Clin J Am Soc Nephrol*. 2017;12:2032-2045; b. Mora-Fernández C, et al. *J Physiol*. 2014;18:3997-4012; c. Bauersachs J, et al. *Hypertension*. 2015;65:257-263; d. Alicic RZ, et al. *Adv Chronic Kidney Dis*. 2018;25:181-191.

The Rationale for a Mineralocorticoid Receptor Antagonist to Treat CKD in T2D

Finerenone is a novel, selective, non-steroidal MRA that inhibits inflammation and fibrosis and protects against progressive kidney and CV dysfunction in preclinical models[a]



ARTS-DN (patients with CKD and T2D) – finerenone improved albuminuria independent of measured changes in BP[b]

Hypothesis: MR antagonism with finerenone slows CKD progression and reduces CV morbidity and mortality in patients with advanced CKD and T2D[c]

a. Agarwal R, et al. *Eur Heart J*. 2020;ehaa736; 2. Bakris GL, et al. *JAMA*. 2015;314:884-894; c. Bakris GL, et al. *Am J Nephrol*. 2019;50:333-344.

Finerenone (Kerendia)

- Anti-mineralocorticoid agent approved 7/9/21 for slowing the progression of chronic kidney disease in type 2 diabetes patients.
- Indicated to reduce the risk of sustained eGFR decline, ESKD, CV death, non-fatal MI, and hospitalization for heart failure in patients with T2DM CKD.
- FIDELIO-DKD, a phase III trial of over 5,600 participants with type 2 diabetes. 17.8% of patients on finerenone experienced a primary outcome event -- **kidney failure, a sustained decrease of at least 40% in eGFR from baseline, or death from renal causes** -- versus 21.1% of those assigned to placebo (HR 0.82, 95% CI 0.73-0.93, P=0.001).

FIDELIO-DKD Eligibility Criteria

Key inclusion criteria

- Aged ≥ 18 years with CKD and T2D
- Pretreated with optimized therapy, including an ACEi or ARB at a max tolerated dose for ≥ 4 weeks
- Serum potassium ≤ 4.8 mmol/L
- Diabetic retinopathy for patients with A2 albuminuria

Key exclusion criteria

- HFrEF with NYHA class II to IV
- HbA_{1c} > 12%
- Uncontrolled arterial hypertension*

Albuminuria categories (mg albumin/g creatinine)

GFR categories (mL/min/1.73 m²)		A1 Normal to mildly elevated	A2 Moderately elevated	A3 Severely elevated
		0 to 29	30 to 299	≥ 300 to 4999
G1	> 90			
G2	60-89			
G3a	45-59			
G3b	30-44			
G4	15-29			
G5	< 15			

*Mean sitting SBP ≥ 170 mm Hg or mean sitting DBP ≥ 110 mm Hg at the run-in visit or mean sitting SBP ≥ 160 mm Hg or mean sitting DBP ≥ 100 mm Hg at the screening visit.

Bakris GL, et al. *N Eng J Med*. 2020. [Epub ahead of print]; Bakris GL, et al. *Am J Nephrol*. 2019;50:333-344.

FIDELIO-DKD Study Design

13,911 patients enrolled

5734 patients randomized

2.6 years' median follow-up

Run-in (4–16 weeks) → **Screening** → **R**

- **Finerenone 10 or 20 mg od*** → **Post-treatment follow-up**
- **Placebo** → **Post-treatment follow-up**

Hierarchical endpoints

1. Kidney composite

Time to kidney failure, sustained ≥40% decrease in eGFR from baseline, or renal death

2. CV composite

Time to CV death, non-fatal MI, non-fatal stroke or hospitalization for HF

3. + 4.

Death from any cause

Hospitalization for any cause

5. + 6.

Change in UACR

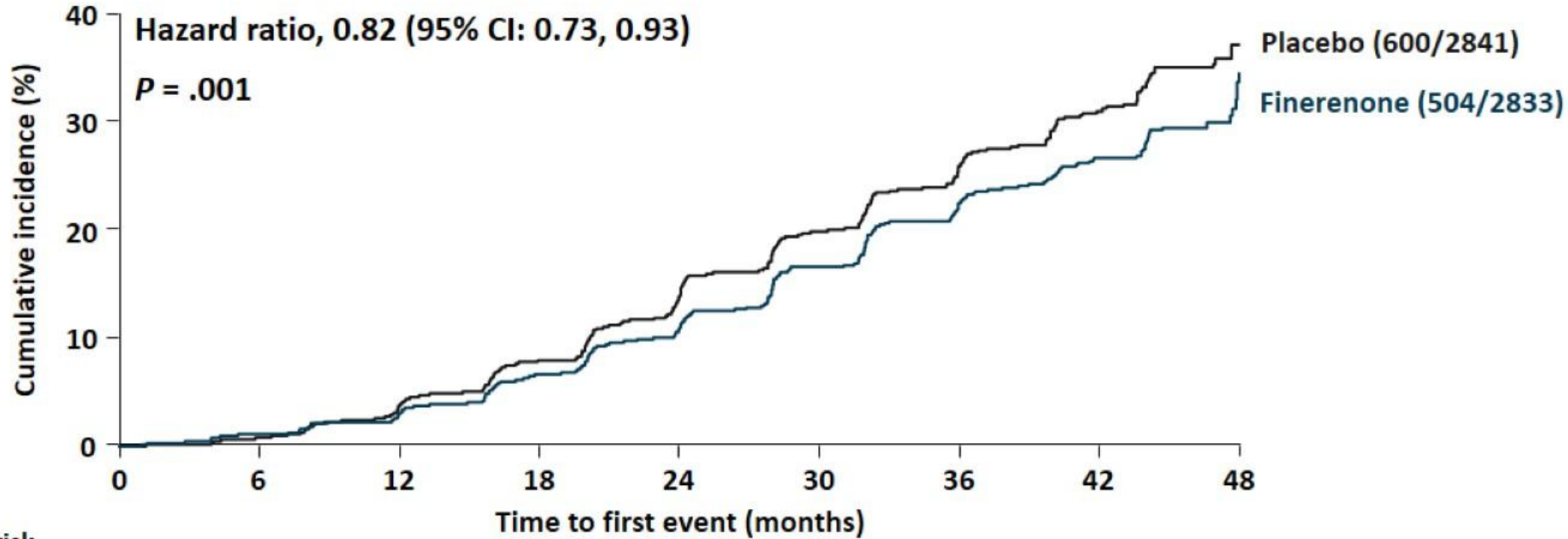
Second kidney composite

*10 mg if screening eGFR < 60 mL/min/1.73 m^2; 20 mg if ≥ 60 mL/min/1.73 m^2;uptitration encouraged from month 1 if serum potassium ≤ 4.8 mEq/L and eGFR stable.

Bakris GL, et al. *N Eng J Med.* 2020. [Epub ahead of print]; Bakris GL, et al. *Am J Nephrol*. 2019;50:333-344.

FIDELIO-DKD (Finerenone) Primary Endpoint

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



No. at risk					
Finerenone	2833	2607	1808	787	83
Placebo	2841	2586	1758	792	82

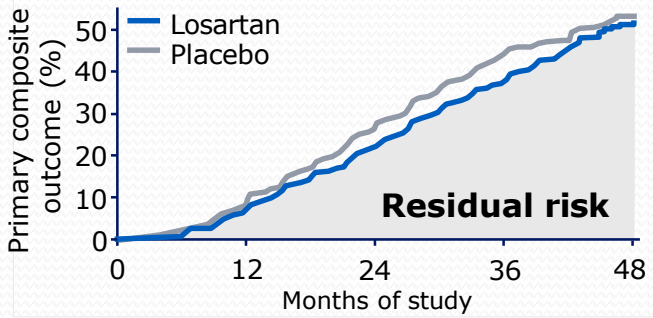
*End-stage kidney disease or an eGFR < 15 mL/min/1.73 m2.

Bakris GL, et al. *N Eng J Med.* 2020. [Epub ahead of print]

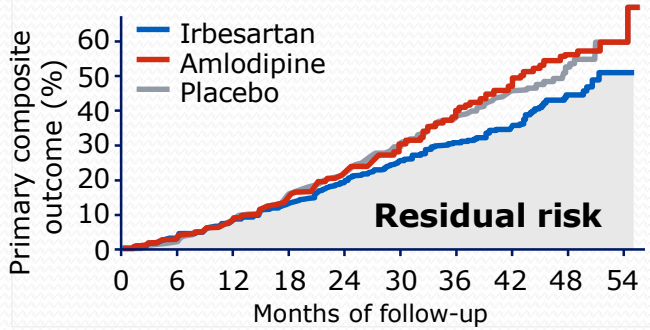
Residual risk despite available treatment options

RAS inhibitors

RENAAL[1]

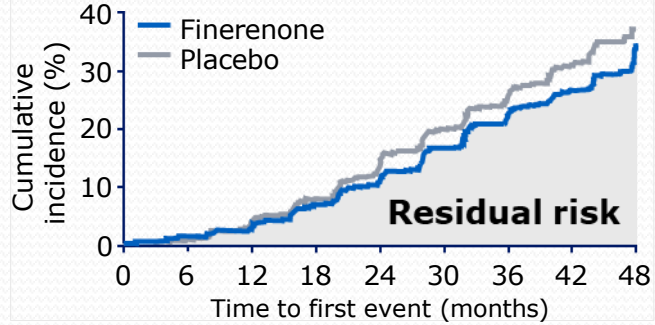


IDNT[2]



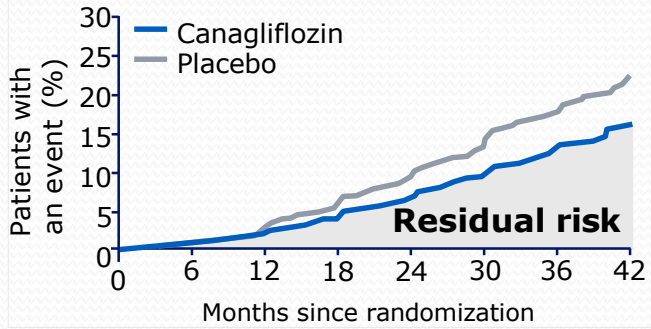
Non-steroidal MRAs

FIDELIO-DKD[3]

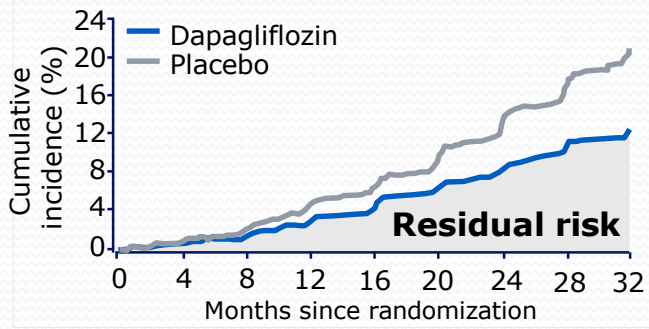


SGLT2 inhibitors

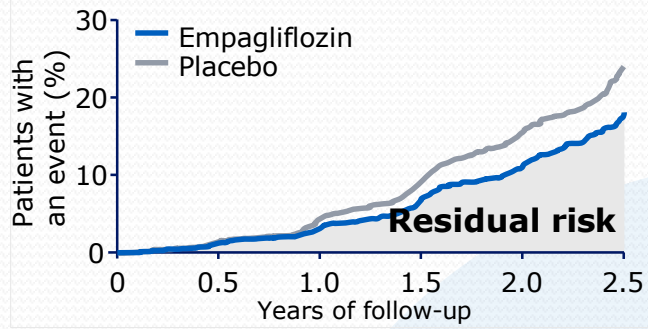
CREDENCE[4]



DAPA-CKD[5]



EMPA-KIDNEY[6]



MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2.

1. Brenner BM et al. *N Engl J Med* 2001;345:861–869; 2. Lewis EJ et al. *N Engl J Med* 2001;345:851–860; 3. Bakris GL et al. *N Engl J Med* 2020;383:2219–2229; 4. Perkovic V et al. *N Engl J Med* 2019;380:2295–2306; 5. Heerspink HJL et al. *N Engl J Med* 2020;383:1436–1446; 6. The EMPA-KIDNEY Collaborative Group. *N Engl J Med* 2023;388:117–127.

FLOW semaglutide | kidney outcomes trial

Despite improvements in kidney-related outcomes with available treatment, the risk of kidney failure, and CVD in people with CKD and T2D remains high[1,2]

GLP-1RAs in CVOTs, including semaglutide, have suggested possible positive effects on kidney-related outcomes in people with T2D[3]

FLOW
semaglutide | renal outcomes trial

FLOW is the **first dedicated kidney outcomes trial with a GLP-1RA** to evaluate kidney and CV outcomes and mortality with once-weekly semaglutide in people with T2D and CKD[4]

CKD, chronic kidney disease; CVOT, cardiovascular outcomes trial; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.

1. Perkovic V et al. *N Engl J Med* 2019;380:2295–2306; 2. Heerspink HJL et al. *N Engl J Med* 2020;383:1436–1446;
3. Rossing P et al. *Cardiovasc Diabetol* 2023;22:220; 4. Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051.

FLOW
semaglutide | renal outcomes trial

Effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes: a meta-analysis of randomised controlled trials

Sunil V Badve, Anika Bilal, Matthew M Y Lee, Naveed Sattar, Hertzel C Gerstein, Christian T Ruff, John J V McMurray, Peter Rossing, George Bakris, Kenneth W Mahaffey, Johannes F E Mann, Helen M Colhoun, Katherine R Tuttle, Richard E Pratley, Vlado Perkovic

Summary

Background GLP-1 receptor agonists reduce the risk of major adverse cardiovascular events (MACE) and can also have kidney benefits. However, whether GLP-1 receptor agonists improve clinically important kidney outcomes remains uncertain. We aimed to comprehensively assess the effects of GLP-1 receptor agonists on kidney and cardiovascular disease outcomes by performing a meta-analysis of randomised controlled trials.

Methods For this meta-analysis, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials that included at least 500 participants with type 2 diabetes, compared a GLP-1 receptor agonist with placebo with at least 12 months of follow-up, and reported a primary clinical kidney or cardiovascular outcome, from database inception to March 26, 2024. Post hoc, we included the SELECT trial (NCT03574597), which enrolled participants with cardiovascular disease and a BMI of 27 kg/m² or more without diabetes. Study-level summary data were extracted independently by two authors for inclusion in this random-effects analysis. The main kidney outcome was a composite outcome, consisting of kidney failure (kidney replacement therapy or a persistent estimated glomerular filtration rate [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. The main cardiovascular outcome was MACE, consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. This study is registered with PROSPERO, CRD42024528864.

Lancet Diabetes Endocrinol 2024

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See Online/Comment
https://doi.org/10.1016/S2213-8587(24)00315-2

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Study Overview

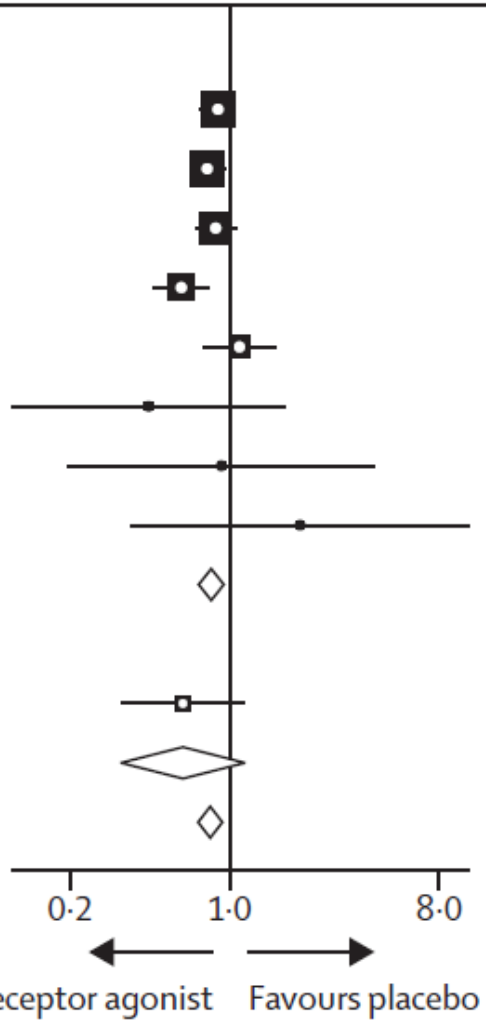
- Meta-analysis of 11 GLP-1 RA clinical trials
- Inclusion Criteria
  - Included at least 500 participants with type 2 diabetes,
  - Compared a GLP-1 receptor agonist with placebo with at least 12 months of follow-up
  - Reported a primary clinical kidney or cardiovascular outcome.
- Primary Study Outcomes
  - Renal: composite of kidney failure (kidney replacement therapy or a persistent estimated glomerular filtration rate [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.
  - Cardiovascular: MACE, consisting of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Badve SV et al. Lancet Diabetes Endocrinol Nov 25, 2024.
https://doi.org/10.1016/S2213-8587(24)00271-7

A Composite 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



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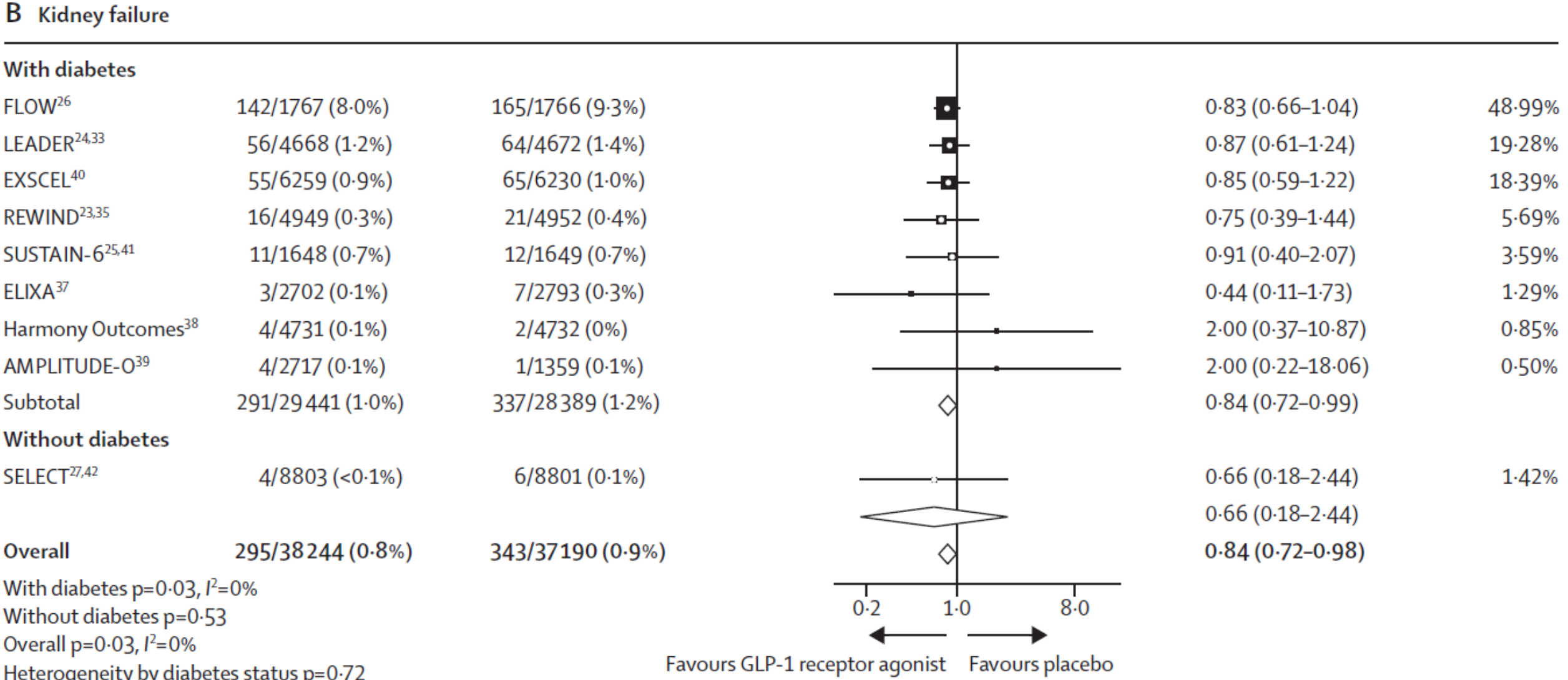

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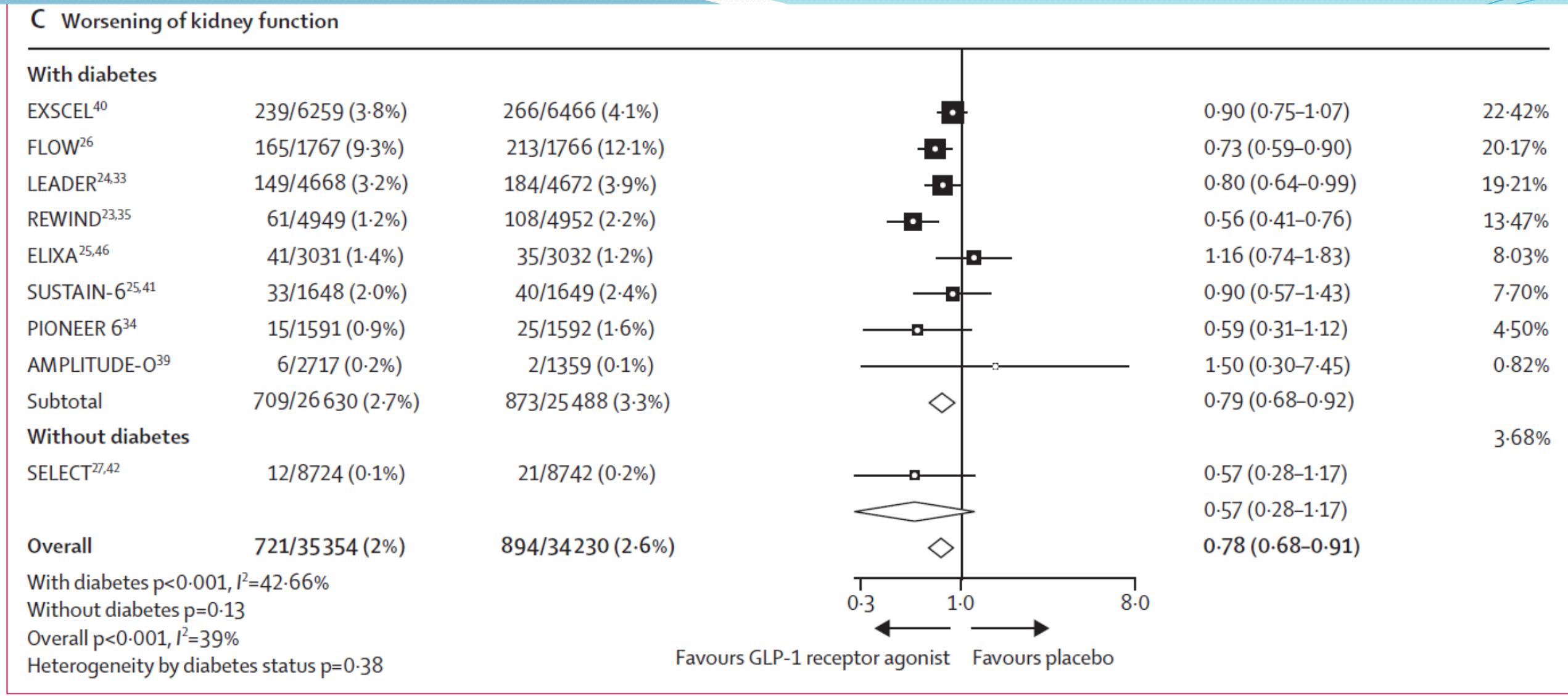

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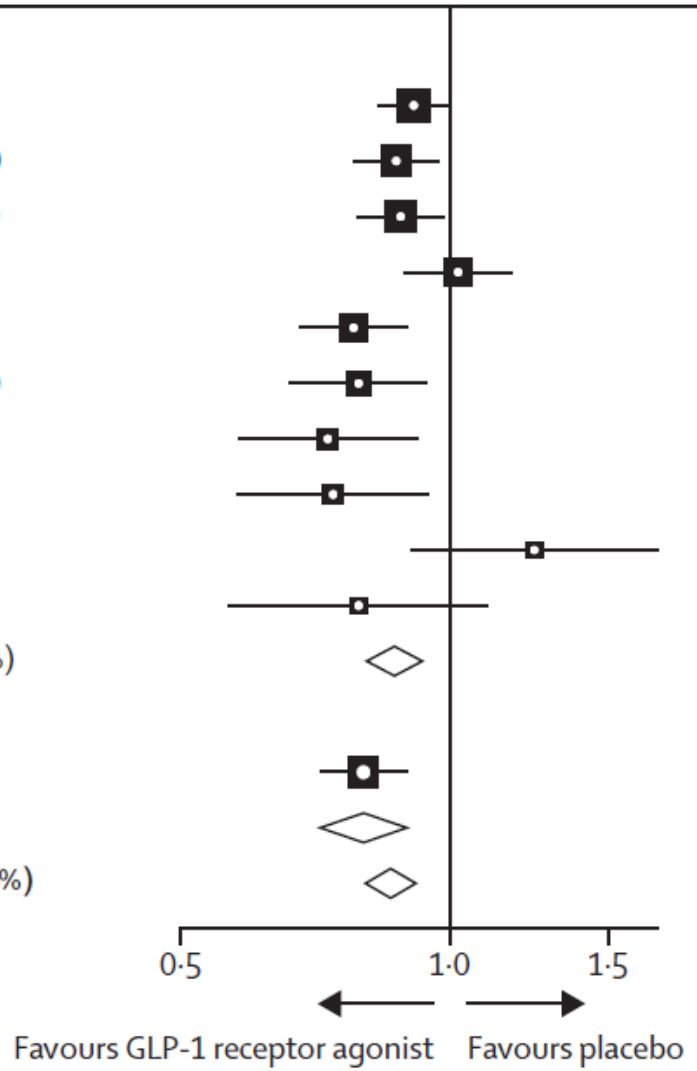
https://doi.org/10.1016/S2213-8587(24)00271-7

A Major adverse cardiovascular events

	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	Weight (%)
With diabetes				
EXSCEL[40]	839/7356 (11·4%)	905/7396 (12·2%)	0·91 (0·83–1·00)	14·51%
LEADER[24,33]	608/4668 (13·0%)	694/4672 (14·9%)	0·87 (0·78–0·97)	13·06
REWIND[23,35]	594/4949 (12·0%)	663/4952 (13·4%)	0·88 (0·79–0·99)	12·72%
ELIXA[37]	400/3034 (13·2%)	392/3034 (12·9%)	1·02 (0·89–1·17)	10·76%
Harmony Outcomes[38]	338/4731 (7·1%)	428/4732 (9·0%)	0·78 (0·68–0·90)	10·51%
FLOW [26]	212/1767 (12·0%)	254/1766 (14·4%)	0·79 (0·66–0·94)	8·13%
AMPLITUDE-O[39]	189/2717 (7·0%)	125/1359 (9·2%)	0·73 (0·58–0·92)	5·70%
SUSTAIN-6[25,41]	108/1648 (6·6%)	146/1649 (8·9%)	0·74 (0·58–0·95)	5·16%
FREEDOM-CVO[36]	85/2075 (4·1%)	69/2081 (3·3%)	1·24 (0·90–1·70)	3·45%
PIONEER 6[34]	61/1591 (3·8%)	76/1592 (4·8%)	0·79 (0·57–1·10)	3·19%
Subtotal	3434/34536 (9·9%)	3752/33233 (11·3%)	0·87 (0·81–0·93)	
Without diabetes				
SELECT[27,42]	569/8803 (6·5%)	701/8801 (8%)	0·80 (0·72–0·89)	12·83%
			0·80 (0·72–0·89)	
Overall	**4003/43339 (9·2%)**	**4453/42034 (10·6%)**	**0·86 (0·80–0·92)**	

With diabetes p<0·001, I^2=49·75%
Without diabetes p<0·001
Overall p<0·001, I^2=48·9%
Heterogeneity by diabetes status p=0·24



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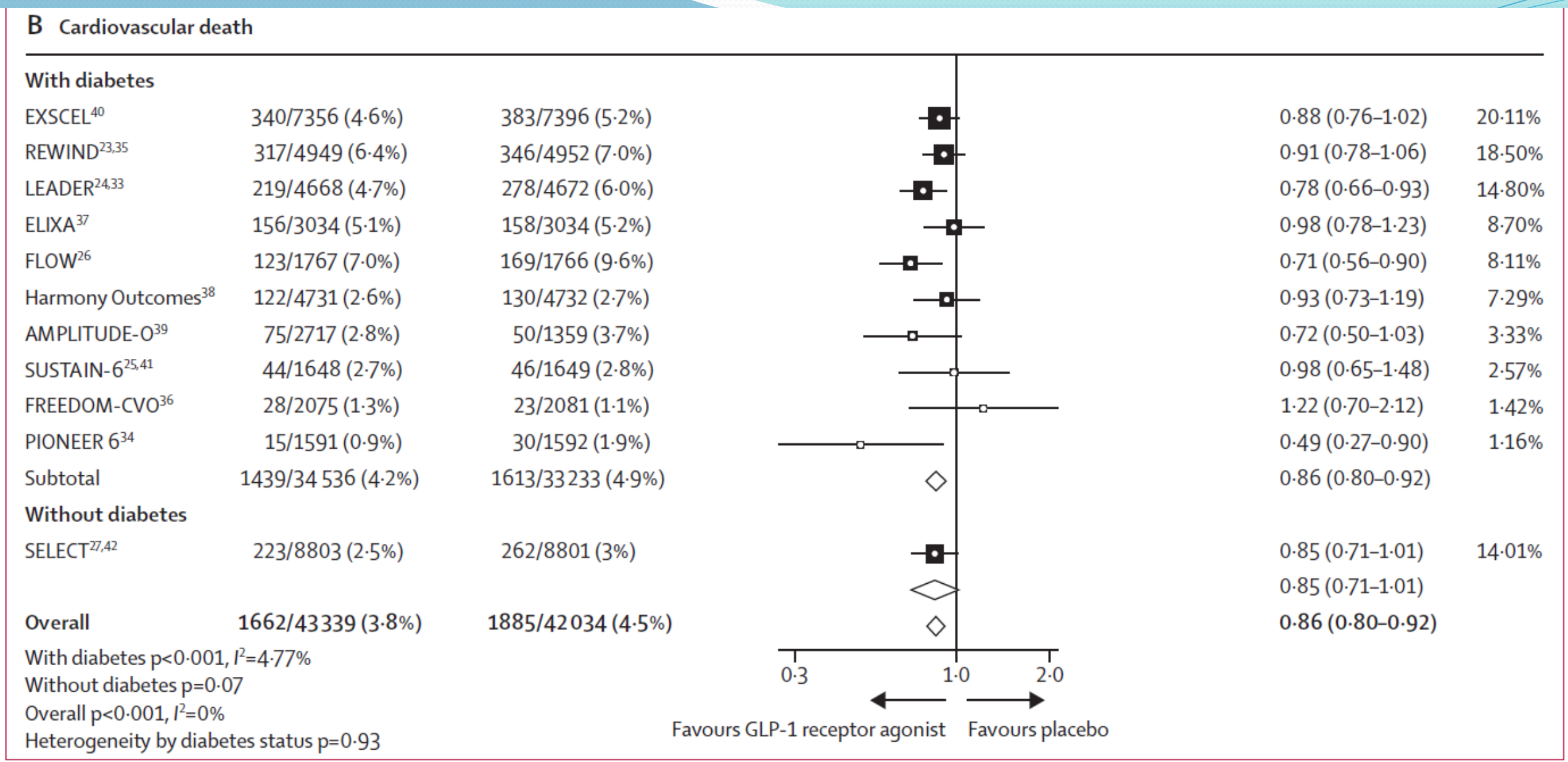

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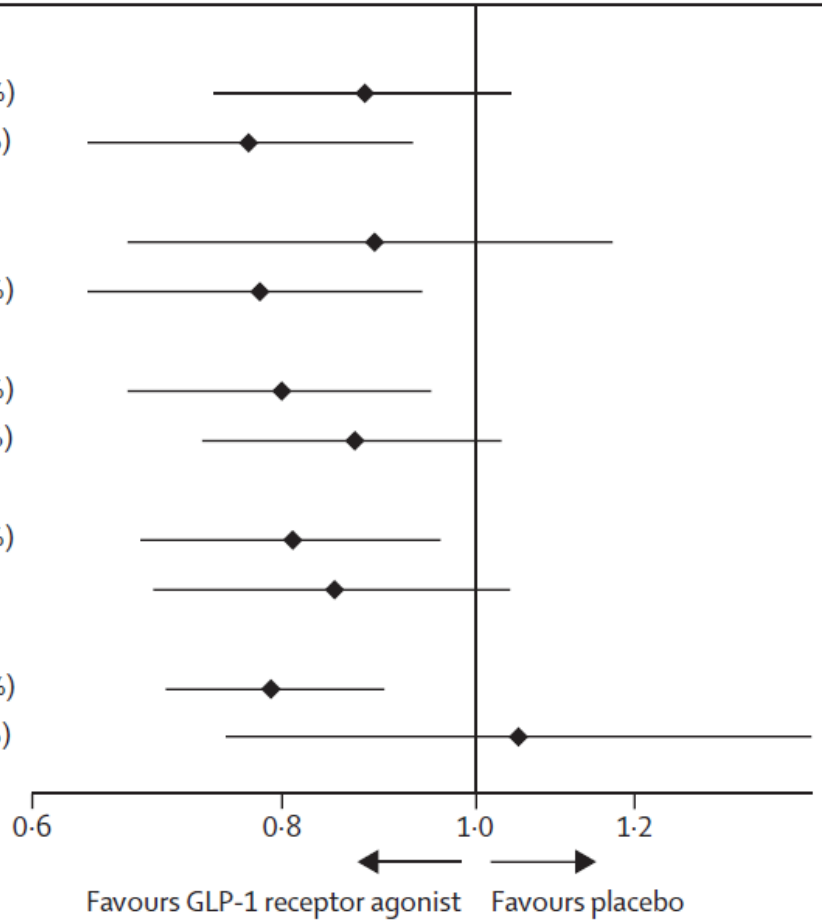
https://doi.org/10.1016/S2213-8587(24)00271-7

A Composite kidney outcome

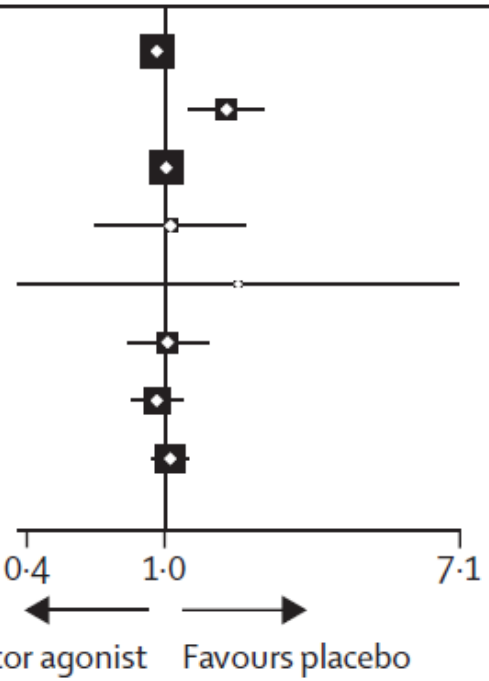
	Trials (n)	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	I^2 (%)	$p_{interaction}$
Participants with cardiovascular disease						
≥80%	6	275/25 269 (1·1%)	308/24 006 (1·3%)	0·88 (0·74–1·04)	0%	0·30
<80%	3	548/12 975 (4·2%)	669/13 184 (5·1%)	0·77 (0·64–0·93)	60·7%	
Participants with chronic kidney disease						
≥25%	3	285/6132 (4·6%)	320/4774 (6·7%)	0·89 (0·67–1·17)	37·8%	0·45
<25%	6	538/32 112 (1·7%)	657/32 416 (2·0%)	0·78 (0·64–0·94)	41·4%	
Type of GLP-1 receptor agonist						
Human GLP-1	6	565/26 566 (2·1%)	694/26 572 (2·6%)	0·80 (0·67–0·95)	42·9%	0·48
Exendin-4	3	258/11 678 (2·2%)	283/10 618 (2·7%)	0·87 (0·73–1·03)	0%	
Frequency of administration						
Once per week	7	636/30 874 (2·1%)	758/29 725 (2·6%)	0·81 (0·68–0·96)	42·7%	0·71
Once per day	2	187/7370 (2·5%)	219/7465 (2·9%)	0·85 (0·69–1·04)	0%	
Duration of follow-up						
≥3 years	5	749/26 446 (2·8%)	908/26 657 (3·4%)	0·79 (0·70–0·90)	30·4%	0·13
<3 years	4	74/11 798 (0·6%)	69/10 533 (0·7%)	1·05 (0·75–1·47)	0%	



Badve SV et al. Lancet Diabetes Endocrinol Nov 25, 2024.
https://doi.org/10.1016/S2213-8587(24)00271-7

Pooled estimates for adverse events

	Trials (n)	GLP-1 receptor agonist (n/N [%])	Placebo (n/N [%])	Hazard ratio (95% CI)	I^2 (%)
Total serious adverse events	9	11286/35644 (31·7%)	11731/35680 (32·9%)	0·95 (0·90–1·01)	88·5%
Discontinuation due to adverse event	9	4494/35329 (12·7%)	3127/33996 (9·2%)	1·51 (1·18–1·94)	96·3%
Cancers	10	1884/41235 (4·6%)	1838/39910 (4·6%)	1·01 (0·95–1·07)	0%
Pancreatic cancer	9	63/32739 (0·2%)	56/31413 (0·2%)	1·04 (0·63–1·71)	30·5%
Medullary thyroid cancer	8	4/30665 (<0·1%)	2/29343 (<0·01%)	1·63 (0·38–7·03)	0%
Acute pancreatitis	11	138/43309 (0·3%)	104/41980 (0·3%)	1·02 (0·78–1·33)	10·8%
Severe hypoglycaemia	11	943/43309 (2·5%)	949/41980 (2·3%)	0·95 (0·80–1·12)	57·4%
Retinopathy	10	1107/34506 (3·2%)	1059/33196 (3·2%)	1·04 (0·92–1·18)	39·9%



Badve SV et al. Lancet Diabetes Endocrinol Nov 25, 2024.
https://doi.org/10.1016/S2213-8587(24)00271-7

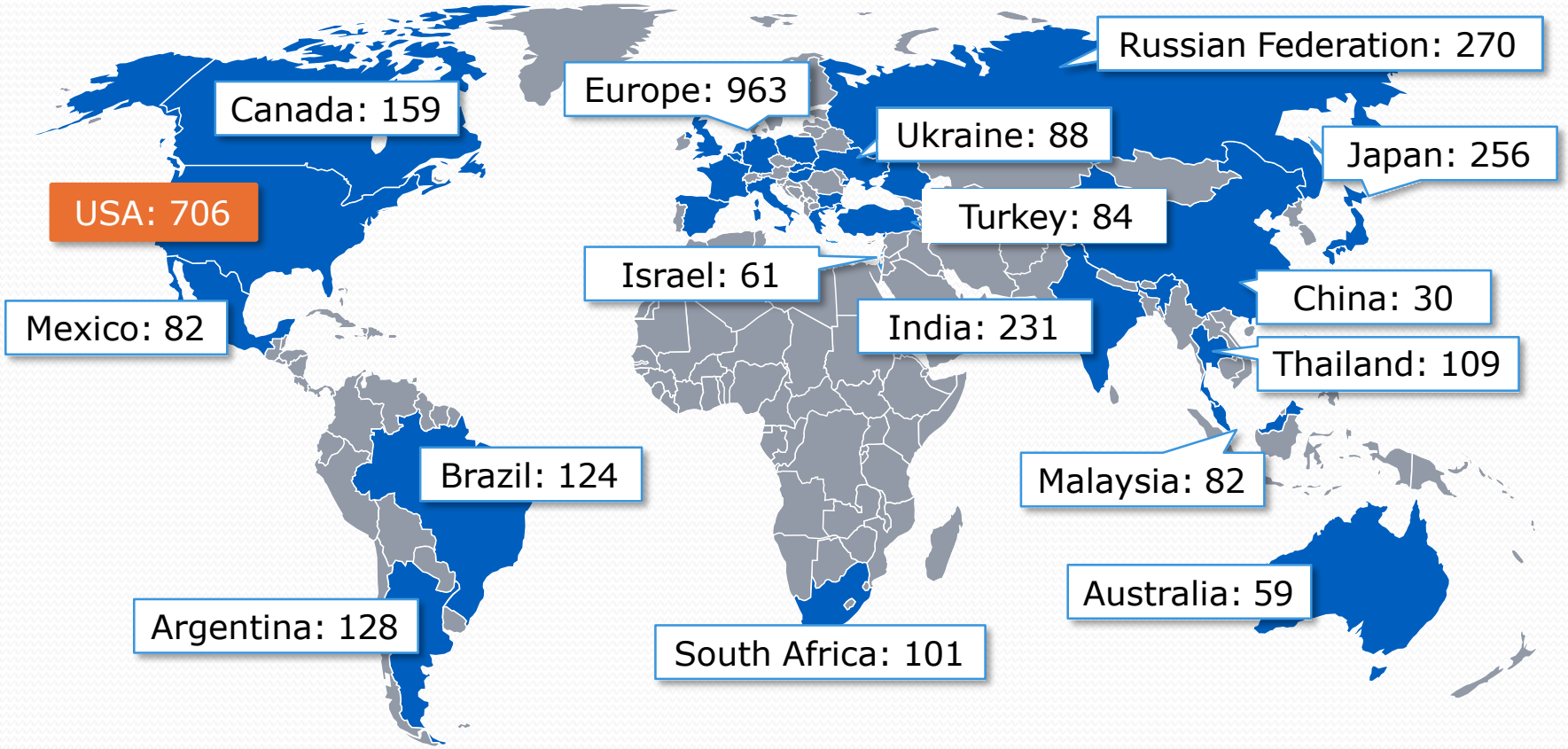
Study Conclusions

- GLP-1 receptor agonists significantly reduced the risk of kidney outcomes, major adverse cardiovascular events, and all-cause death, without increasing the risk of serious adverse events such as hypoglycemia and acute pancreatitis.
- Study findings support the use of GLP-1 receptor agonists to improve cardiovascular, kidney, metabolic, and mortality outcomes among eligible individuals.

Badve SV et al. Lancet Diabetes Endocrinol Nov 25, 2024.
https://doi.org/10.1016/S2213-8587(24)00271-7

The First Dedicated Kidney Outcome Trial with a GLP-1 Receptor Agonist—Once-Weekly Semaglutide and the FLOW Trial Results

A global kidney outcomes trial



3.4
years' median follow-up

28
countries

387
sites

3533
participants

Numbers in diagram represent number of participants.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Trial design

A multinational, randomized controlled clinical trial

Key eligibility criteria

- Adults with T2D, HbA_{1c} ≤10%
- RAS inhibitor
- eGFR ≥50 and ≤75 mL/min/1.73 m^2 and UACR >300 and <5000 mg/g
  OR
  eGFR ≥25 and <50 mL/min/1.73 m^2 and UACR >100 and <5000 mg/g

N=3533

R
1:1

Once-weekly s.c. **semaglutide** 1 mg + standard of care

Placebo + standard of care

Event-driven treatment period
(≥854 first primary outcome events)

Early trial cessation was recommended at a pre-specified **interim** analysis for efficacy at **~570 events**

Follow-up

eGFR was calculated using the CKD-EPI formula.

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; R, randomization; RAS, renin–angiotensin–aldosterone system; s.c., subcutaneous; T2D, type 2 diabetes; UACR, urinary albumin:creatinine ratio.

Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Primary outcome

Time to first occurrence of major kidney outcomes consisting of:

- Onset of persistent ≥50% reduction in eGFR compared with baseline
- Kidney failure:
  - Onset of persistent eGFR <15 mL/min/1.73 m^2
  - Initiation of chronic kidney replacement therapy (dialysis or kidney transplantation)
- Kidney death
- CV death

Confirmatory secondary outcomes

- Annual rate of change in eGFR (total eGFR slope)
- Time to first occurrence of a composite MACE outcome consisting of CV death, non-fatal MI, or non-fatal stroke
- Time to occurrence of all-cause death

Other supportive secondary outcomes

- Time to occurrence of each of the individual components of the primary composite outcome, and of the confirmatory secondary MACE outcome
- Time to first occurrence of composite of acute limb ischemia hospitalization or chronic limb ischemia hospitalization
- Change in eGFR, UACR, body weight, HbA_{1c}, BP

Primary and secondary outcomes other than eGFR assessments derived from the central laboratory were adjudicated in a blinded fashion by an Event Adjudication Committee

eGFR was calculated using the CKD-EPI formula. CV death includes undetermined cause of death.
BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; MACE, major adverse cardiovascular event; MI, myocardial infarction; UACR, urinary albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

FLOW
semaglutide | kidney outcomes trial

Hierarchical testing strategy

Superiority if two-sided p value <0.0322†

Primary outcome

Composite kidney outcome

Total eGFR slope

MACE (CV death, non-fatal MI, or non-fatal stroke)

All-cause death

Confirmatory secondary outcome

eGFR was calculated using the CKD-EPI formula. CV death includes undetermined cause of death.
†Limit determined by the Lan–DeMets alpha spending function, approximating the O'Brien-Fleming stopping boundaries accounting for the group sequential design (interim analysis).
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

FLOW semaglutide | kidney outcomes trial

Demographics

	Semaglutide (n=1767)	Placebo (n=1766)
Age, mean (SD), years	66.6 (9.0)	66.7 (9.0)
Sex, n (%)		
Female	519 (29.4)	550 (31.1)
Region, n (%)		
Asia	478 (27.1)	434 (24.6)
Europe	472 (26.7)	491 (27.8)
North America	423 (23.9)	442 (25.0)
Other	394 (22.3)	399 (22.6)

	Semaglutide (n=1767)	Placebo (n=1766)
Race, n (%)		
White	1155 (65.4)	1168 (66.1)
Asian	439 (24.8)	407 (23.0)
Black or African American	78 (4.4)	82 (4.6)
Other†	95 (5.4)	109 (6.2)
Ethnicity, n (%)		
Hispanic or Latino	273 (15.4)	283 (16.0)
Not Hispanic or Latino	1421 (80.4)	1411 (79.9)
Not reported	73 (4.1)	72 (4.1)

†Includes participants whose race was reported as "American Indian or Alaska Native", "Native Hawaiian or Other Pacific Islander", or "Not reported".
SD, standard deviation.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

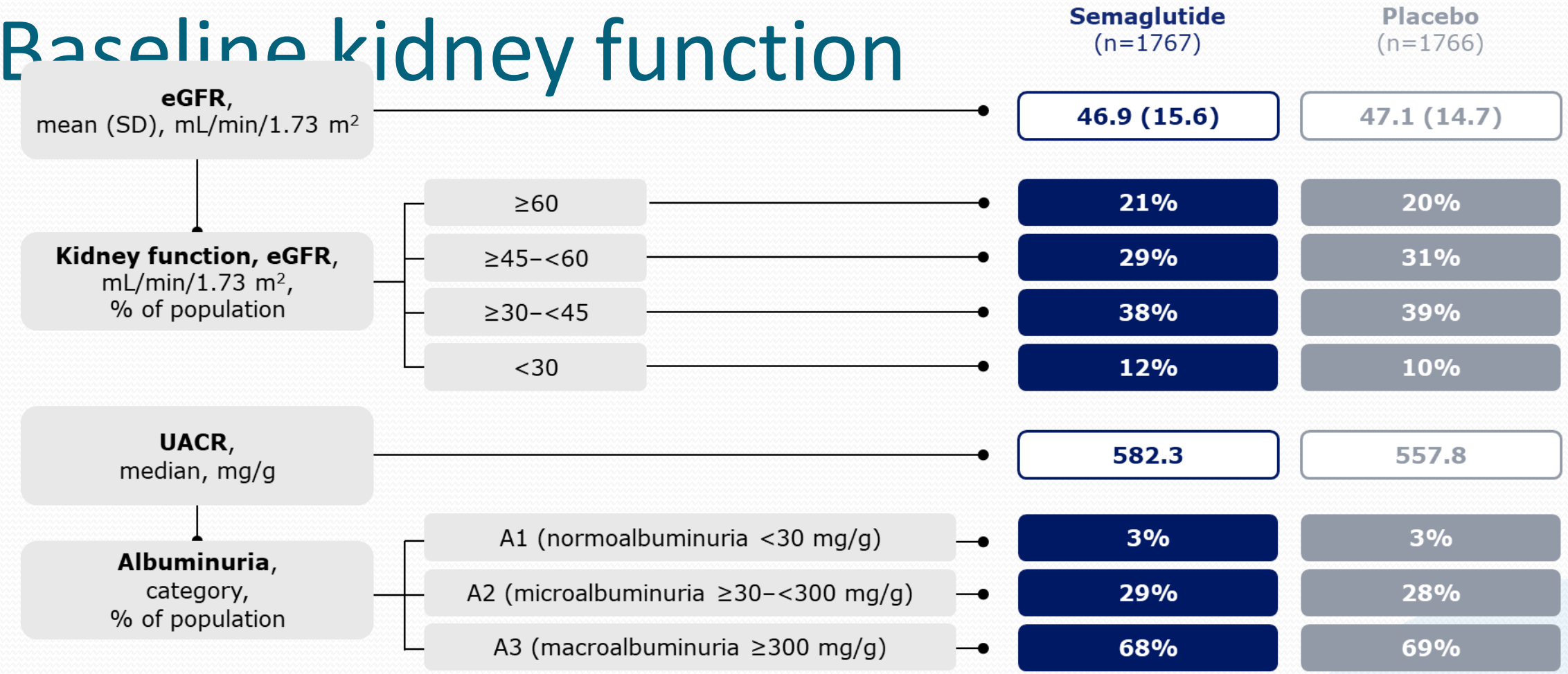
Baseline characteristics

	Semaglutide (n=1767)	Placebo (n=1766)
HbA_{1c}, mean (SD), %	7.8 (1.3)	7.8 (1.3)
BMI, mean (SD), kg/m^2	31.9 (6.1)	32.0 (6.5)
Body weight, mean (SD), kg	89.5 (19.8)	89.8 (21.2)
Systolic BP, mean (SD), mmHg	138.9 (16.1)	138.4 (15.4)
Diastolic BP, mean (SD), mmHg	76.8 (10.0)	76.1 (10.0)

	Semaglutide (n=1767)	Placebo (n=1766)
Diabetes duration, years, n (%)		
<15	774 (43.8)	753 (42.6)
≥15	992 (56.1)	1,013 (57.4)
Prior MI or stroke, n (%)	405 (22.9)	403 (22.8)
Chronic HF, n (%)	342 (19.4)	336 (19.0)
Tobacco use,† n (%)		
Current smoker	223 (12.6)	206 (11.7)
Never smoked	883 (50.0)	864 (48.9)
Previous smoker	661 (37.4)	696 (39.4)

†Smoking is defined as smoking at least one cigarette or equivalent daily.
BMI, body mass index; BP, blood pressure; HbA_{1c}, glycated hemoglobin; HF, heart failure; MI, myocardial infarction; SD, standard deviation.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Baseline kidney function



For eGFR, baseline assessment was defined as the mean of the two assessments from the randomization visit and the screening visit. Albuminuria categories are based on UACR, and baseline assessment was defined as the mean of the two assessments from the randomization visit. If only one of the assessments for either UACR or eGFR is available, this is used as the baseline assessment. The kidney function categories are based on the eGFR as per CKD-EPI.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; SD, standard deviation; UACR, urinary albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

FLOW
semaglutide | kidney outcomes trial

Baseline kidney function

Key kidney function eligibility criteria

eGFR ≥50 and ≤75 mL/min/1.73 m² and UACR >300 and <5000 mg/g

OR

eGFR ≥25 and <50 mL/min/1.73 m² and UACR >100 and <5000 mg/g

KDIGO risk categories among FLOW participants, n (%)

eGFR categories (mL/min/1.73 m²)	UACR categories (mg/g) <30	≥30–<300	≥300
≥90	1 (<0.1)	7 (0.2)	23 (0.6)
≥60–<90	24 (0.7)	173 (4.9)	491 (13.9)
≥45–<60	37 (1.0)	324 (9.2)	694 (19.6)
≥30–<45	40 (1.1)	414 (11.7)	905 (25.6)
≥15–<30	7 (0.2)	87 (2.5)	306 (8.6)

Low risk (n=25) Moderate risk (n=217) High risk (n=878) Very high risk (n=2413)

eGFR was calculated using the CKD-EPI formula.
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urinary albumin:creatinine ratio.
Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051.

Baseline kidney function

KDIGO risk categories among FLOW participants, n (%)

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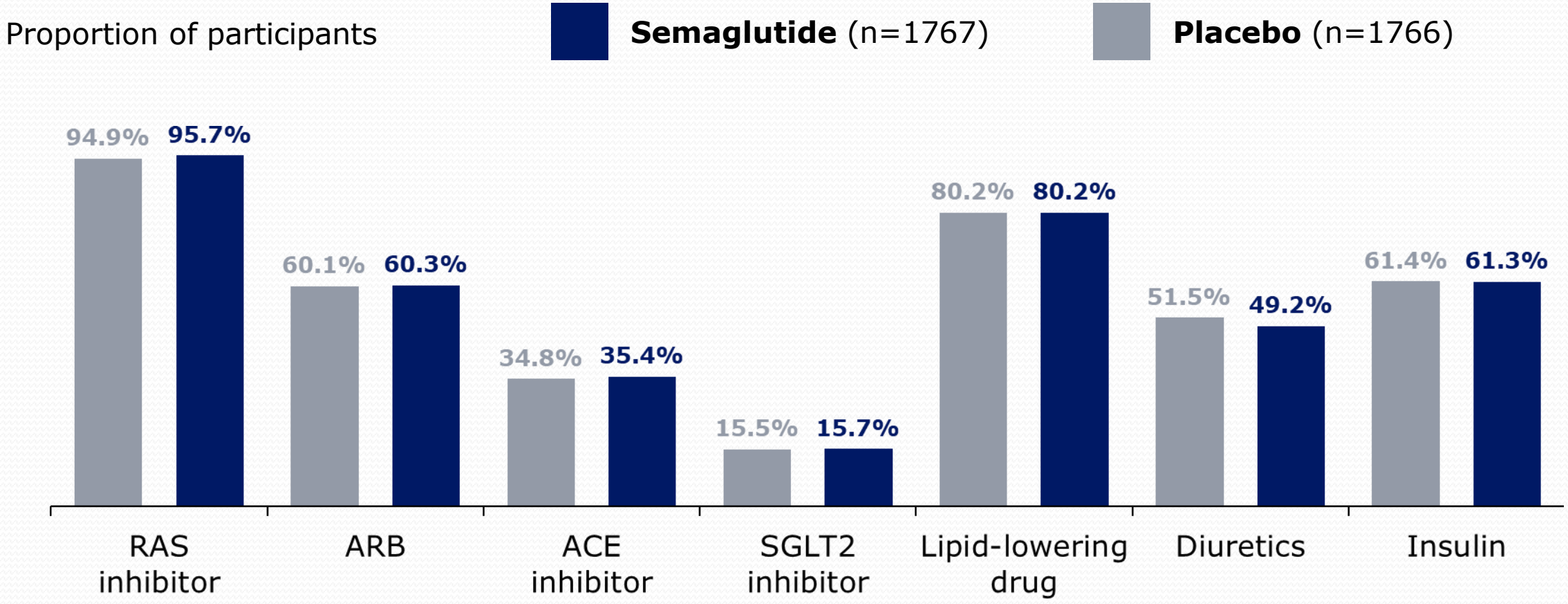
Low risk (n=25)
Moderate risk (n=217)
High risk (n=878)
Very high risk (n=2413)

93%

were at high or very high risk

eGFR was calculated using the CKD-EPI formula.
CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; UACR, urinary albumin:creatinine ratio.
Rossing P et al. *Nephrol Dial Transplant* 2023;38:2041–2051.

Baseline medication use



ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2.

Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

AEs leading to permanent treatment discontinuation

	Semaglutide (n=1767)		Placebo (n=1766)	
	n	%	n	%
All	**233**	**13.2**	**211**	**11.9**
Gastrointestinal disorders	79	4.5	20	1.1
Infections and infestations	28	1.6	22	1.2
Neoplasms[†]	25	1.4	20	1.1
Kidney and urinary disorders	21	1.2	34	1.9
Nervous system disorders	14	0.8	20	1.1
Investigations	12	0.7	14	0.8
Metabolism and nutrition disorders	11	0.6	12	0.7
Cardiac disorders	9	0.5	21	1.2
Eye disorders	7	0.4	5	0.3
General disorders and administration site reactions	6	0.3	6	0.3
Respiratory, thoracic, and mediastinal disorders	4	0.2	6	0.3
Hepatobiliary disorders	4	0.2	4	0.2

Full analysis set. Data from the in-trial period. All permanent treatment discontinuations up until the end of treatment visit are included.
[†]Includes benign, malignant, and unspecified neoplasms, cysts, and polyps.
AE, adverse event.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

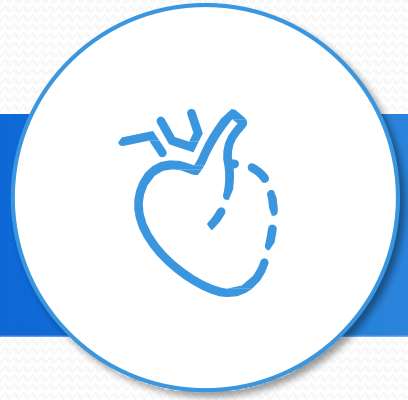
FLOW
semaglutide | kidney outcomes trial

FLOW enrolled a **diverse group** of participants with CKD and T2D

Substantial **T2D burden**

48% with HbA_{1c} ≥7.5%

57% had T2D for ≥15 years



High **comorbidity burden**

42% with prior MI or stroke, or heart failure

Significant **CKD burden**

93% at high/very high risk of CKD progression

SAEs were reported in fewer participants in the semaglutide group (49.6%) versus the placebo group (53.8%)

CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; MI, myocardial infarction; T2D, type 2 diabetes.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Kidney outcomes

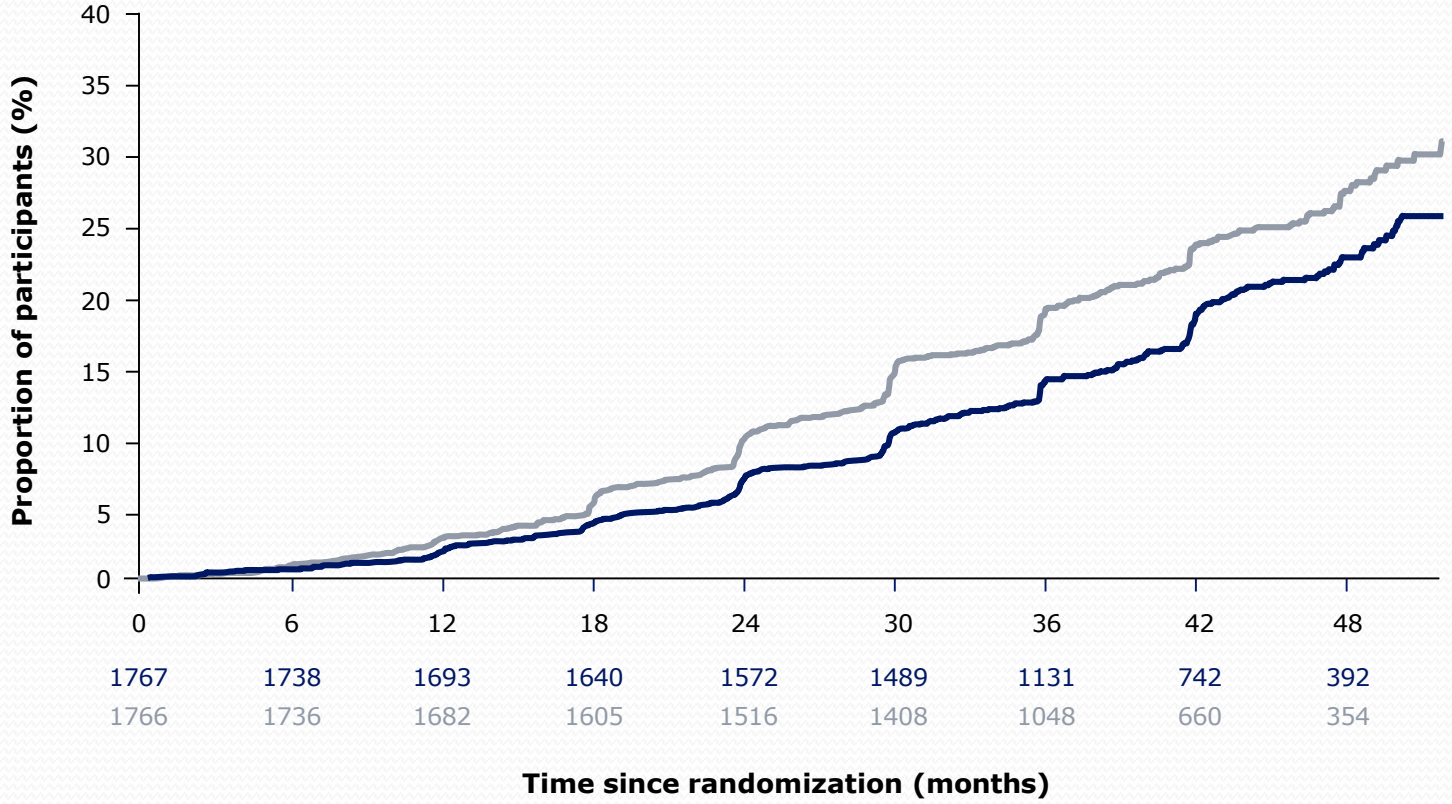
Overall mortality

CV outcomes

CV, cardiovascular.

Composite kidney outcome

Primary outcome



Placebo 23.2%
(410/1766)

Semaglutide 18.7%
(331/1767)

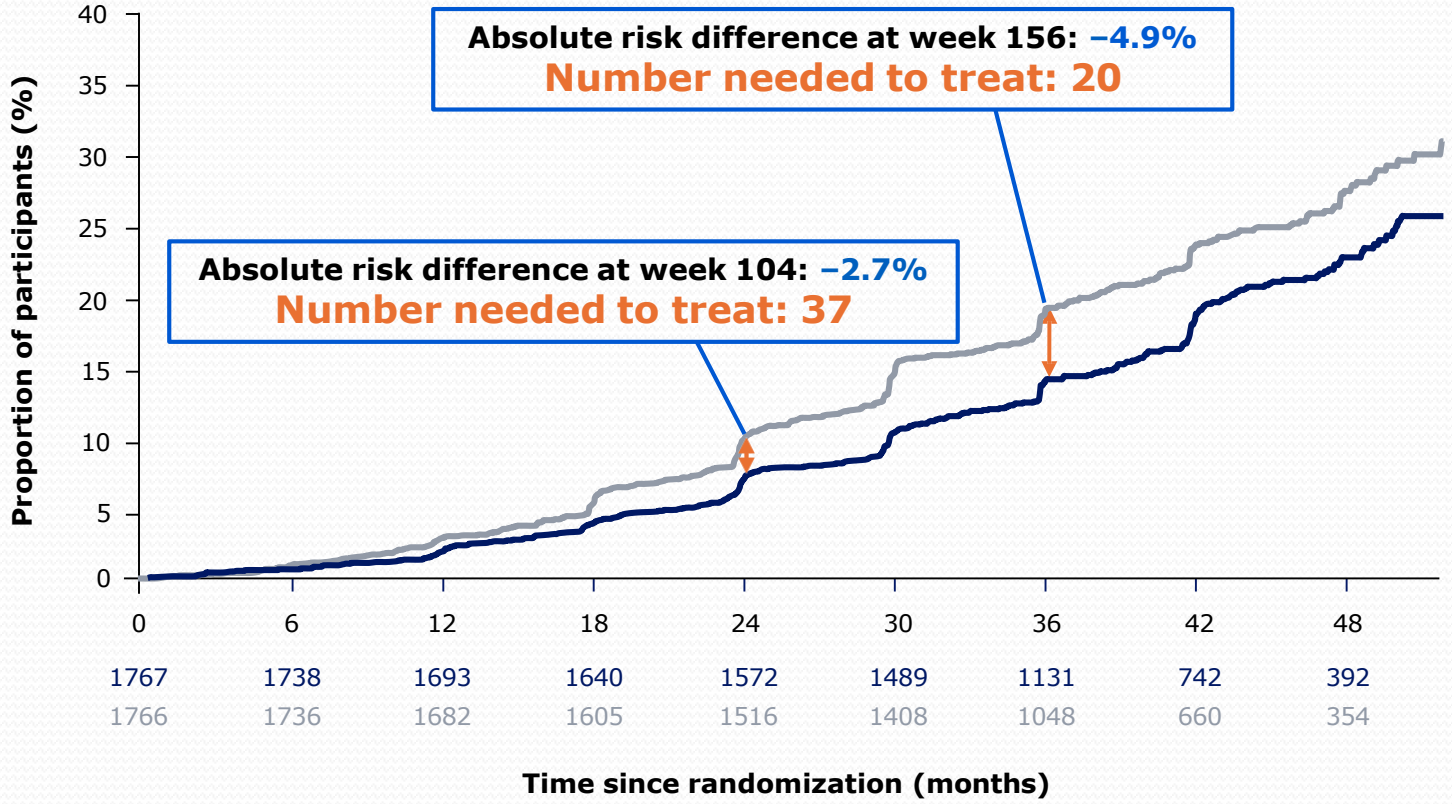
HR 0.76 (95% CI 0.66, 0.88)
p=0.0003

Full analysis set. Data from the in-trial period. Numbers shown in the lower panels represent the number of participants at risk.
Event rates: 5.8 and 7.5 per 100 patient-years of follow-up for participants receiving semaglutide and placebo, respectively.
CI, confidence interval; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Superiority if two-sided
p value <0.0322

Composite kidney outcome

Primary outcome



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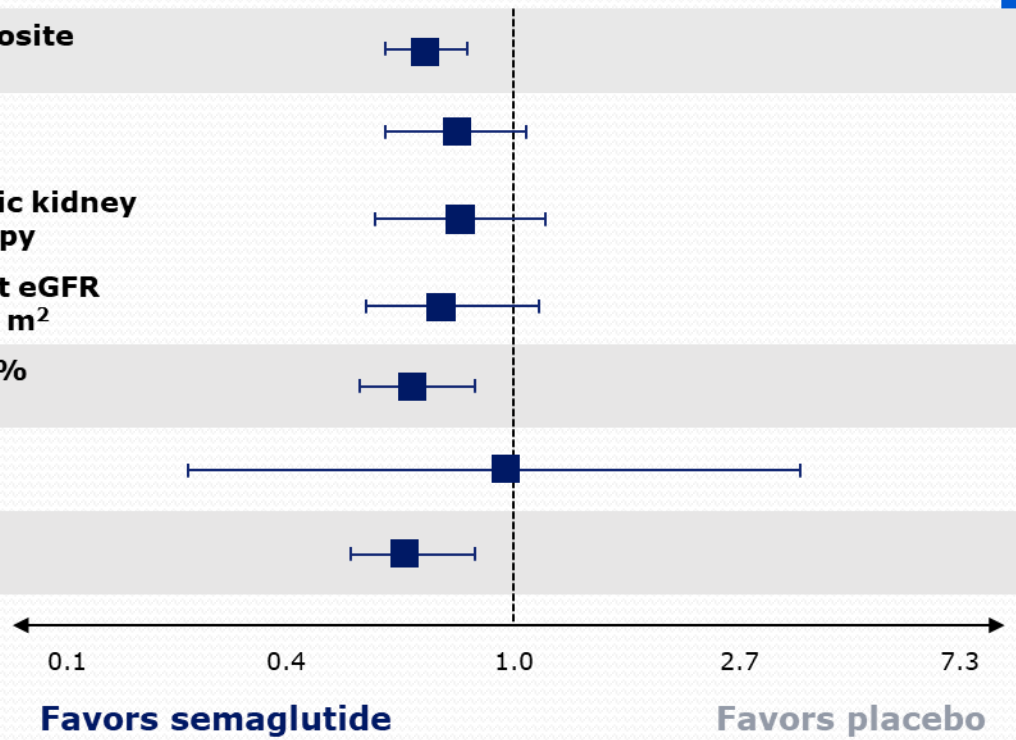
Superiority if two-sided
p value <0.0322

Composite kidney outcome

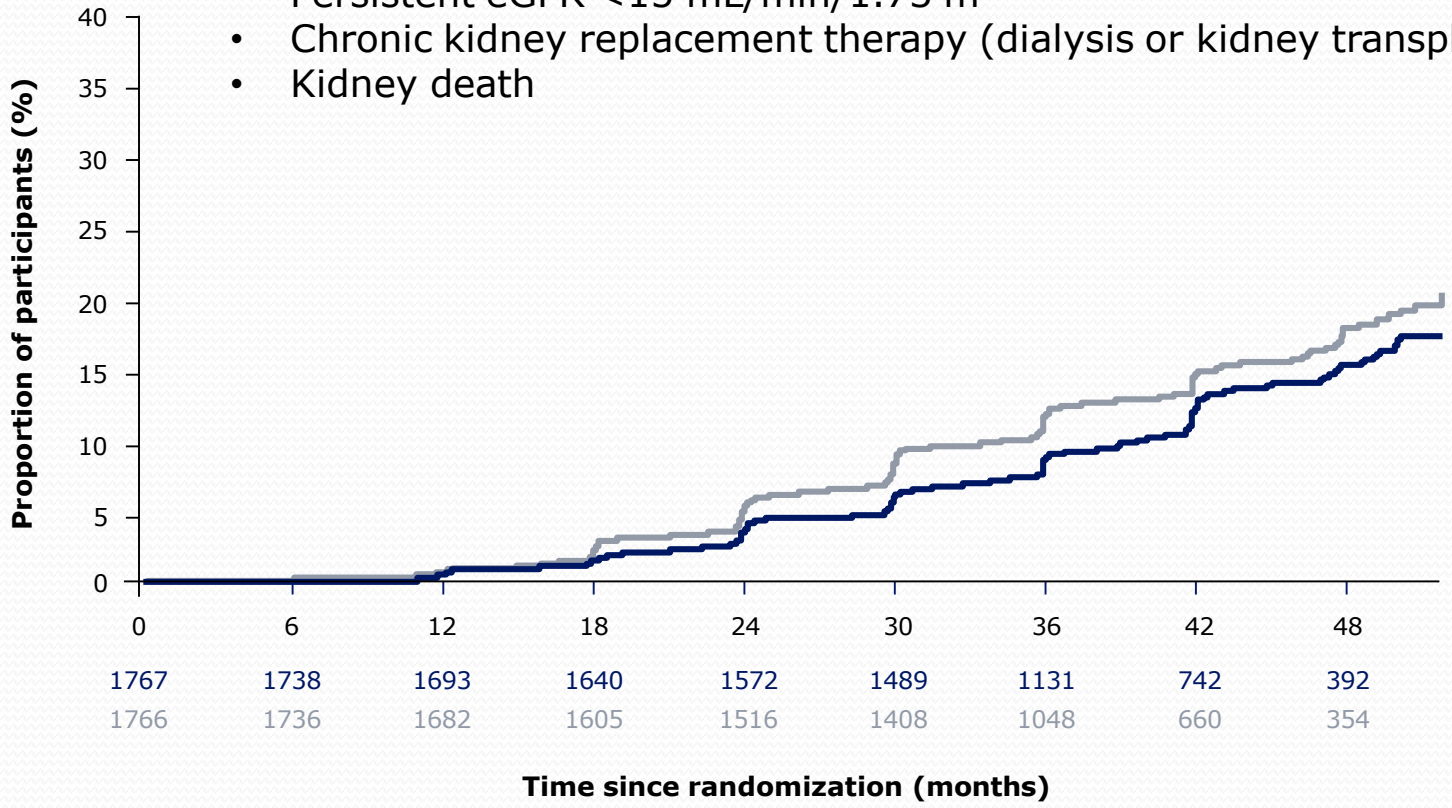


	HR (95% CI)	Semaglutide, n/N	Placebo, n/N
Primary outcome: Composite kidney outcome	**0.76** (0.66, 0.88)	331/1767	410/1766
Kidney failure[†]	**0.83** (0.66, 1.03)	142/1767	165/1766
Initiation of chronic kidney replacement therapy	**0.84** (0.63, 1.12)	87/1767	100/1766
Onset of persistent eGFR <15 mL/min/1.73 m²	**0.80** (0.61, 1.06)	92/1767	110/1766
Onset of persistent ≥50% reduction in eGFR	**0.73** (0.59, 0.89)	165/1767	213/1766
Kidney death	**0.97** (0.27, 3.49)	5/1767	5/1766
CV death	**0.71** (0.56, 0.89)	123/1767	169/1766

Full analysis set. Data from the in-trial period. CV death includes undetermined cause of death.
[†]Data on file. Kidney failure was a three-component composite outcome consisting of initiation of chronic replacement therapy (dialysis or kidney transplantation), onset of persistent eGFR <15 mL/min/1.73 m², and kidney death.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Four-component composite kidney outcome (excluding CV death)

- Persistent ≥50% reduction in eGFR
- Persistent eGFR <15 mL/min/1.73 m²
- Chronic kidney replacement therapy (dialysis or kidney transplantation)
- Kidney death



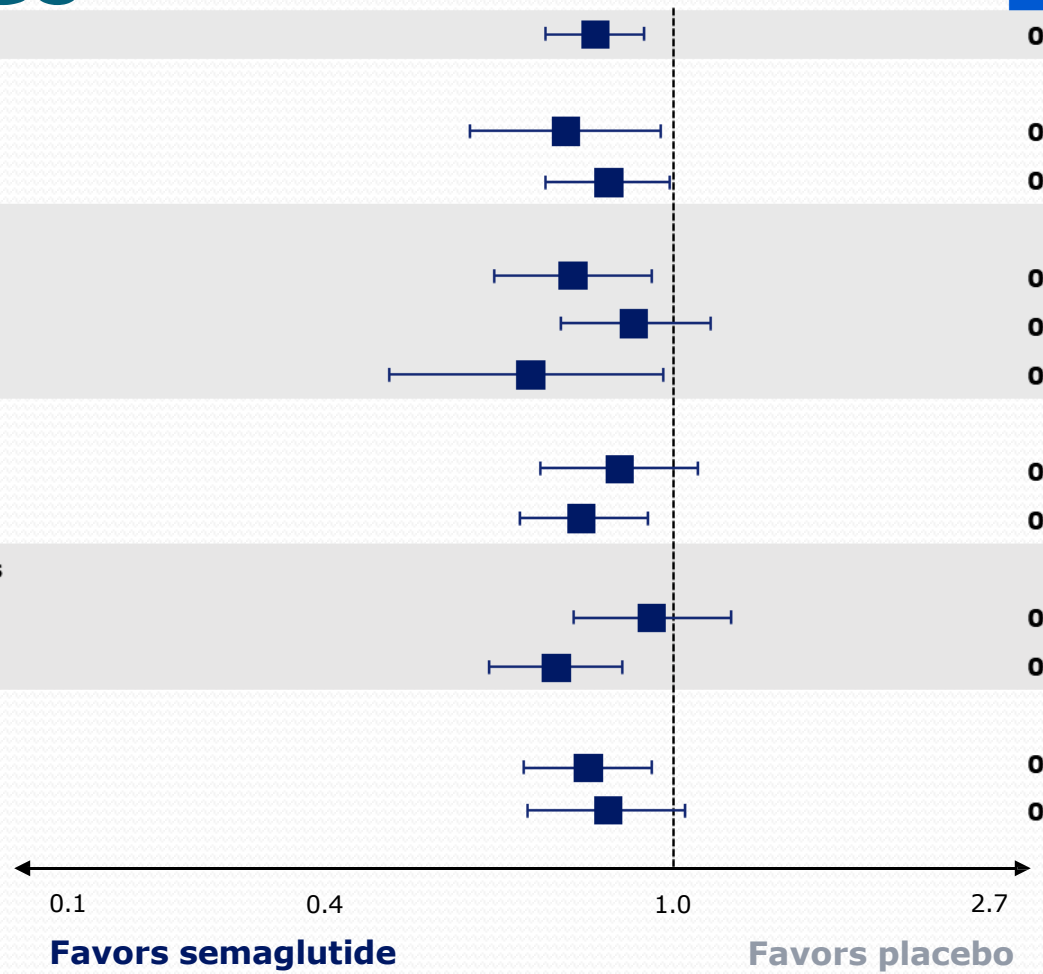
Placebo 14.7%
(260/1766)

Semaglutide 12.3%
(218/1767)

HR 0.79 (95% CI 0.66, 0.94)

Full analysis set. Data from the in-trial period. Four-component composite kidney outcome included onset of persistent ≥50% reduction in eGFR compared with baseline, onset of persistent eGFR <15 mL/min/1.73 m², initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), or kidney death.
Numbers shown in the lower panels represent the number of participants at risk.
CI, confidence interval; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

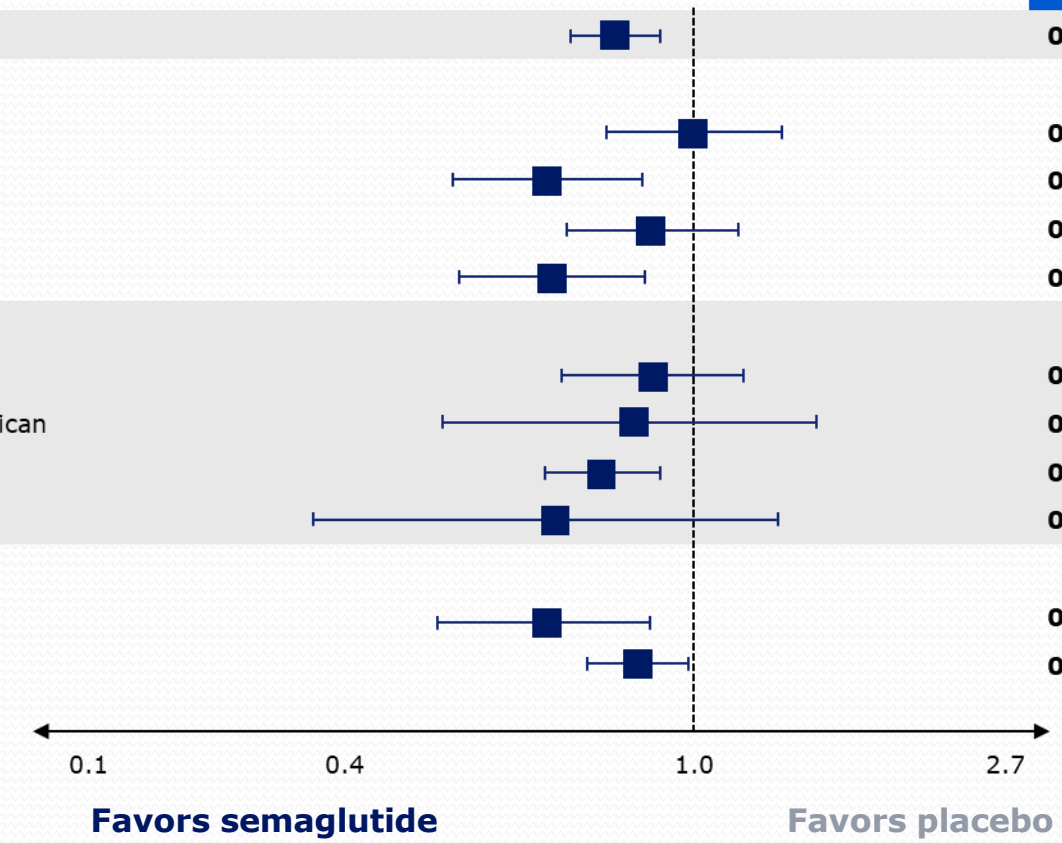
Composite kidney outcome: Subgroup analyses



	HR (95% CI)	p heterogeneity	Semaglutide, n/N	Placebo, n/N
Primary analysis	**0.76** (0.66, 0.88)		331/1767	410/1766
Sex				
Female	**0.70** (0.53, 0.92)	0.46	88/519	127/550
Male	**0.79** (0.66, 0.94)		243/1248	283/1216
Age, years				
<65	**0.71** (0.57, 0.90)	0.33	131/633	175/652
≥65–<75	**0.85** (0.69, 1.06)		160/816	170/773
≥75	**0.63** (0.42, 0.93)		40/318	65/341
BMI, kg/m²				
≤30	**0.82** (0.65, 1.03)	0.46	142/734	164/733
>30	**0.73** (0.61, 0.89)		189/1031	244/1029
Diabetes duration, years				
<15	**0.90** (0.72, 1.13)	0.06	148/774	153/733
≥15	**0.68** (0.56, 0.82)		183/992	257/1013
HbA_{1c}, %				
≤8.0	**0.75** (0.62, 0.90)	0.68	200/1106	251/1093
>8.0	**0.79** (0.63, 1.00)		131/659	159/672

Full analysis set. Data from the in-trial period.
BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated hemoglobin; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

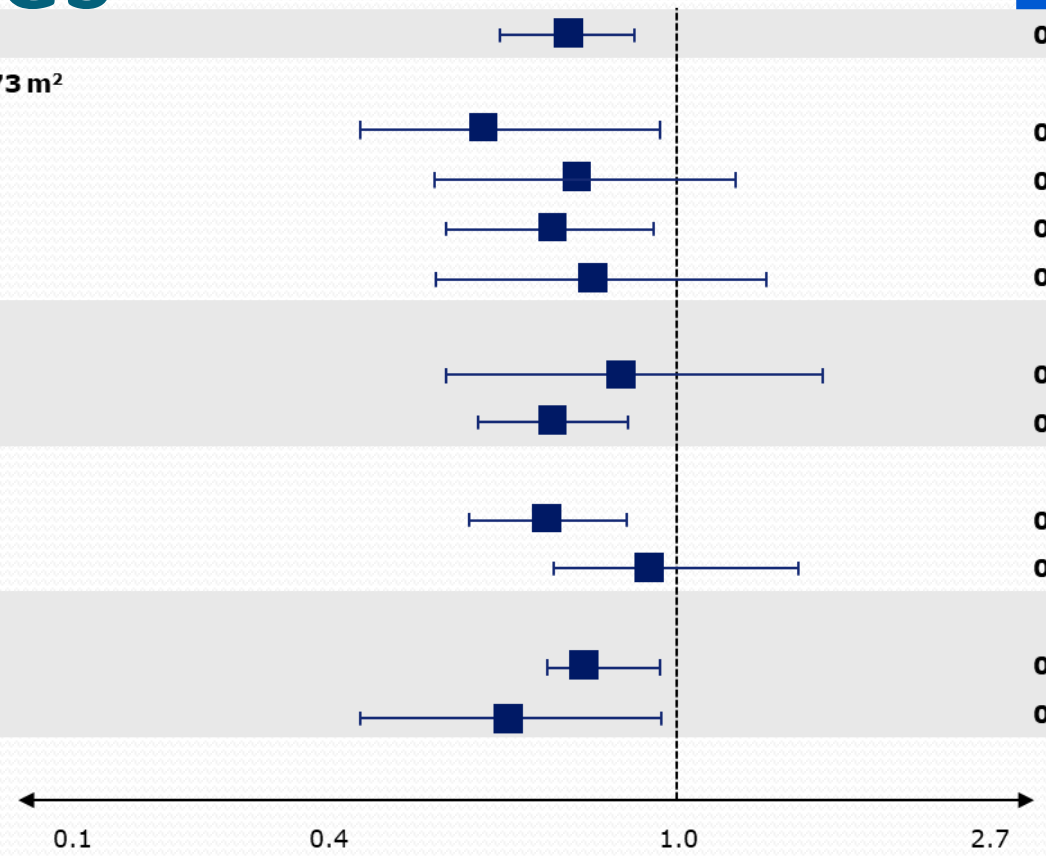
Composite kidney outcome: Subgroup analyses



	HR (95% CI)	p heterogeneity	Semaglutide, n/N	Placebo, n/N
Primary analysis	**0.76** (0.66, 0.88)		331/1767	410/1766
Region				
North America	**0.98** (0.74, 1.30)	0.052	98/423	102/442
Europe	**0.61** (0.45, 0.83)		65/472	104/491
Asia	**0.85** (0.65, 1.13)		98/478	98/434
Other	**0.62** (0.46, 0.84)		70/394	106/399
Race				
Asian	**0.86** (0.64, 1.14)	0.78	95/439	95/407
Black or African American	**0.81** (0.44, 1.46)		20/78	24/82
White	**0.73** (0.61, 0.88)		197/1155	260/1168
Other	**0.63** (0.29, 1.28)		11/56	21/69
Ethnicity				
Hispanic/Latino	**0.61** (0.43, 0.85)	0.10	57/273	89/283
Not Hispanic/Latino	**0.83** (0.70, 0.98)		261/1421	298/1411

Full analysis set. Data from the in-trial period.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Composite kidney outcome: Subgroup analyses

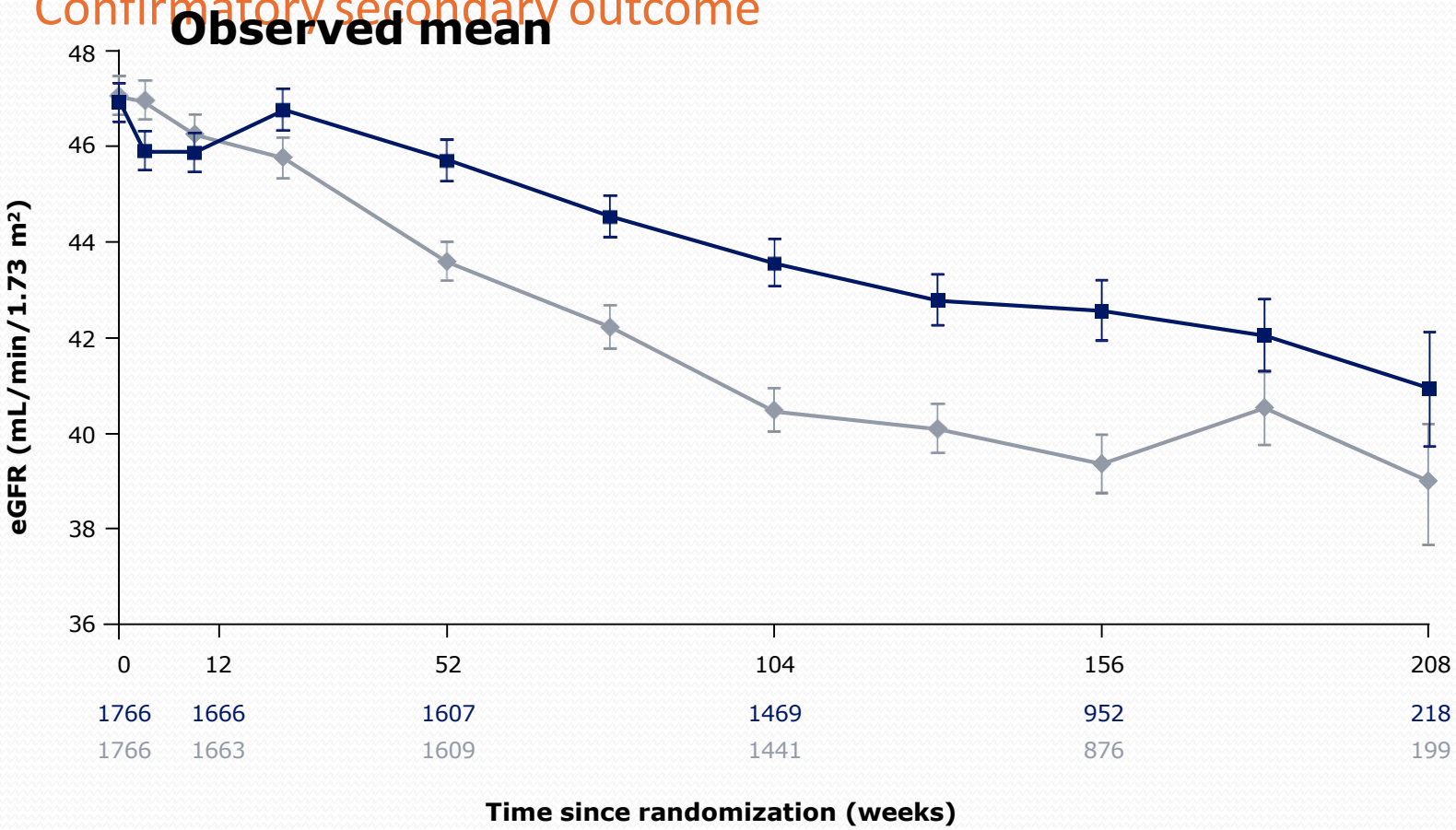


	HR (95% CI)	p heterogeneity	Semaglutide n/N	Placebo, n/N
Primary analysis	**0.76** (0.66, 0.88)		331/1767	410/1766
eGFR level, mL/min/1.73 m²				
≥60	**0.64** (0.43, 0.96)	0.83	98/366	59/353
≥45–<60	**0.78** (0.58, 1.04)		80/515	103/540
≥30–<45	**0.74** (0.59, 0.92)		137/667	181/691
<30	**0.81** (0.58, 1.13)		73/218	67/182
UACR level, mg/g				
<300	**0.86** (0.60, 1.23)	0.47	55/561	62/552
≥300	**0.74** (0.63, 0.87)		276/1205	348/1215
CVD				
No prior MI or stroke	**0.73** (0.62, 0.87)	0.20	240/1345	308/1343
Prior MI or stroke	**0.91** (0.68, 1.22)		87/405	93/403
Heart failure				
No	**0.79** (0.67, 0.93)	0.40	264/1424	322/1430
Yes	**0.67** (0.49, 0.93)		67/342	88/336

Full analysis set. Data from the in-trial period.
CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; UACR, urine albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Total eGFR slope

Confirmatory secondary outcome



Annual rate of change:

Semaglutide −2.19

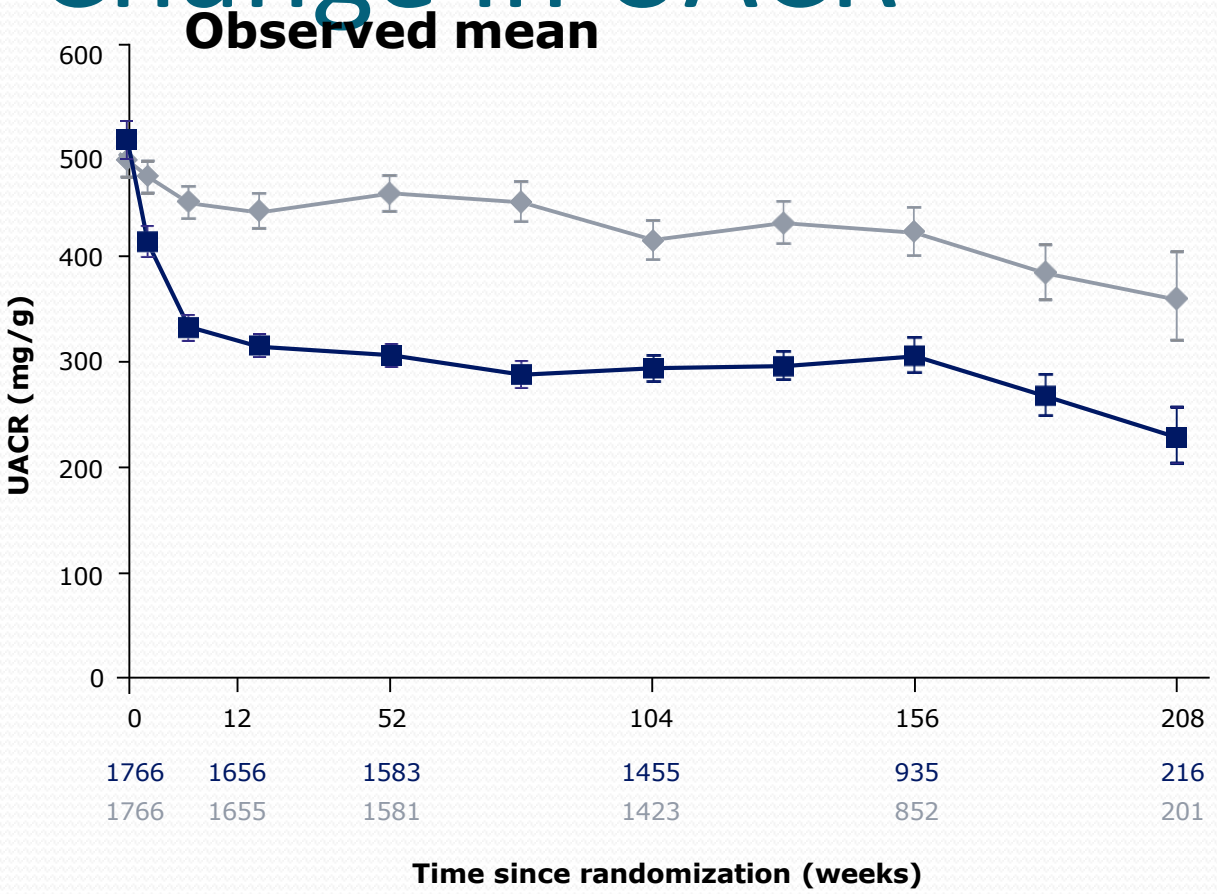
Placebo −3.36

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

Full analysis set. Data from the in-trial period. Error bars indicate ± the standard error. Numbers shown in the lower panels represent the number of participants.
CI, confidence interval; eGFR, estimated glomerular filtration rate.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Superiority if two-sided
p value <0.0322

Change in UACR



Ratio to baseline at week 104:

Placebo 0.88

Semaglutide 0.60

Estimated treatment ratio
0.68 (95% CI 0.62, 0.75)

Full analysis set. Data from the in-trial period. Error bars indicate ± the standard error. Numbers shown in the lower panels represent the number of participants.
CI, confidence interval; UACR, urine albumin:creatinine ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

FLOW
semaglutide | kidney outcomes trial

24% lower risk of the composite primary outcome

Consistent risk reductions for kidney disease components of the primary outcome

Consistent risk reductions across pre-specified participant subgroups

Slower reduction of kidney function by a mean eGFR of 1.16 mL/min/1.73 m^2/year

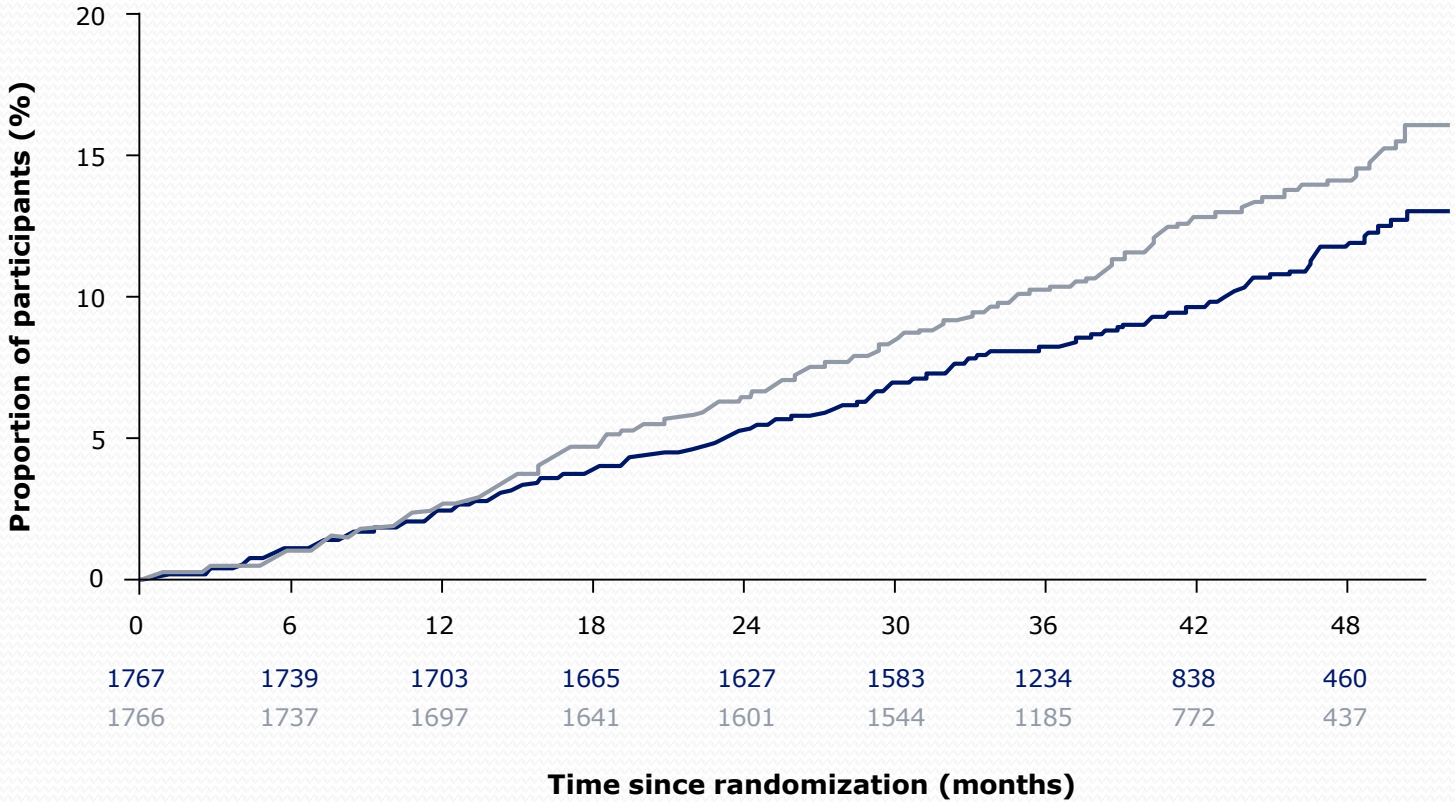
Over 3 years, 20 people would need to be treated to prevent one primary outcome

eGFR, estimated glomerular filtration rate.

Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

All-cause death

Confirmatory secondary outcome



Placebo 15.8%
(279/1766)

Semaglutide 12.8%
(227/1767)

HR 0.80 (95% CI 0.67, 0.95)
p=0.010

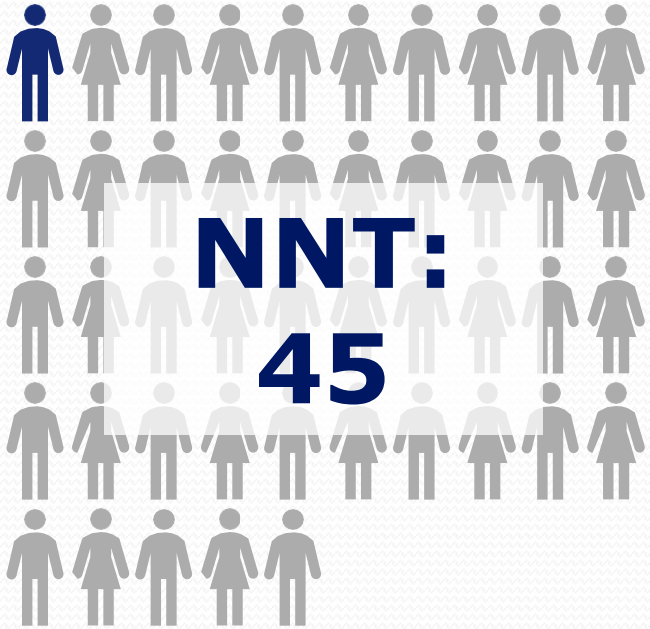
Numbers shown in the lower panel represent the number of participants at risk.
CI, confidence interval; HR, hazard ratio.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Superiority if two-sided
p value <0.0322

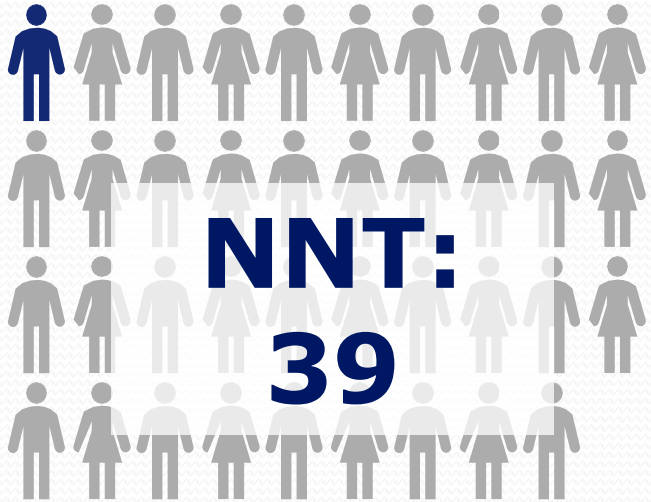
Benefits of semaglutide over 3 years

To prevent one primary outcome:†

To prevent one MACE:‡

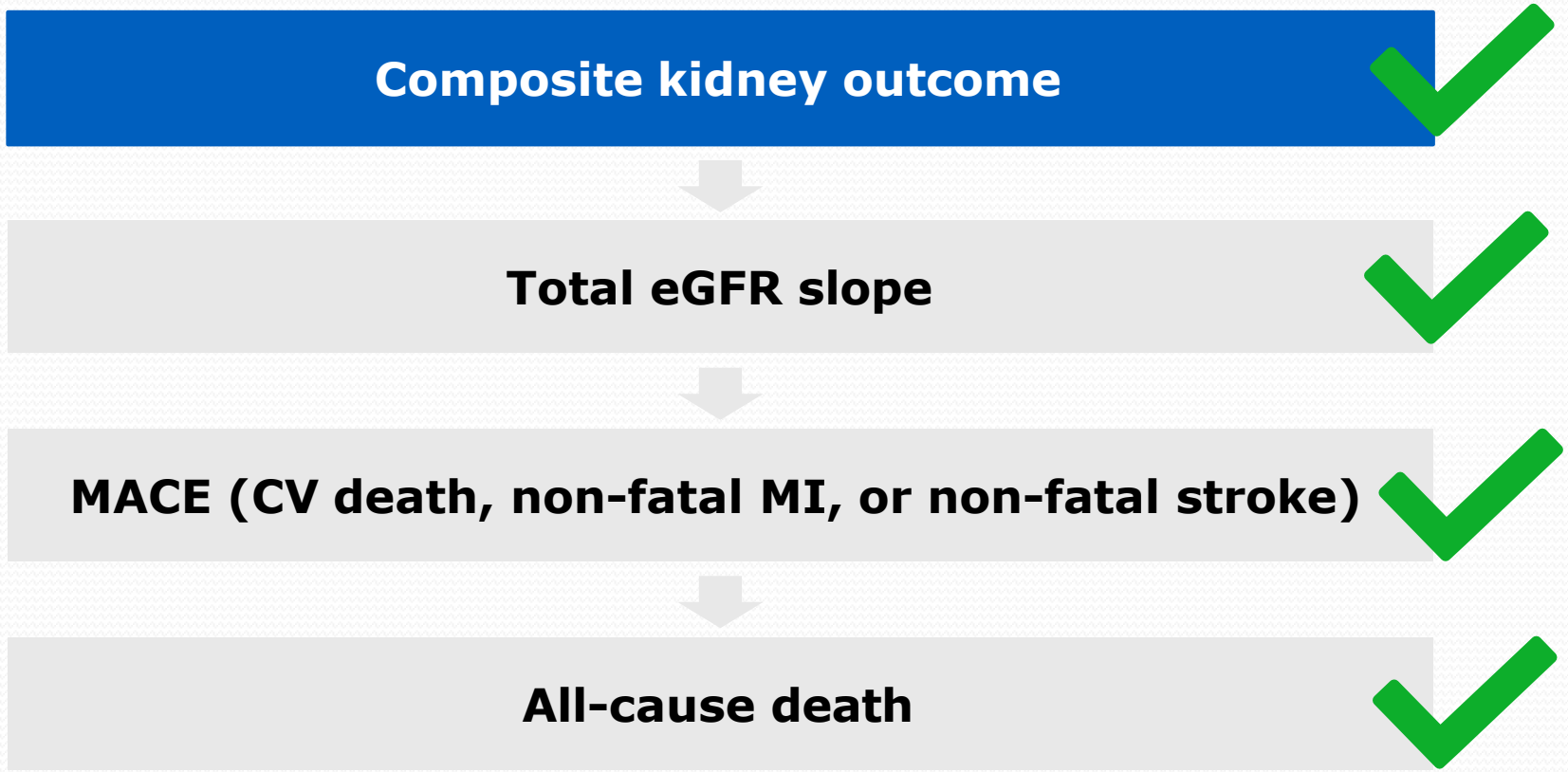


To prevent one death due to any cause:



†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; doi: 10.1056/NEJMoa2403347.

Hierarchical testing strategy



eGFR was calculated using the CKD-EPI formula. CV death includes undetermined cause of death.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.

Primary and confirmatory secondary outcomes

First composite kidney event HR: 0.76 [0.66; 0.88]$_{95\%\ CI}$	✓	24% RRR
Annual rate of change in eGFR (total slope) ETD: 1.16 [0.86; 1.47]$_{95\%\ CI}$	✓	ETD 1.16 ml/min/1.73m^2/year
MACE HR: 0.82 [0.68; 0.98]$_{95\%\ CI}$	✓	18% RRR
All-cause-death HR: 0.80 [0.67; 0.95]$_{95\%\ CI}$	✓	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; MACE, major adverse cardiovascular event; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration. Perkovic V, et al. N Engl J Med. 2024: DOI: 10.1056/NEJMoa2403347

FLOW
semaglutide | kidney outcomes trial

Semaglutide reduced the risk of major kidney outcomes, MACE, and death in people with T2D and CKD irrespective of baseline SGLT2 inhibitor use

found for kidney, CV and mortality outcomes

CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; SGLT2i, sodium–glucose cotransporter-2 inhibitor; T2D type 2 diabetes; UACR, urine albumin:creatinine ratio.
Mann JFE et al. *Nat Med* 2024; doi: 10.1038/s41591-024-03133-0.

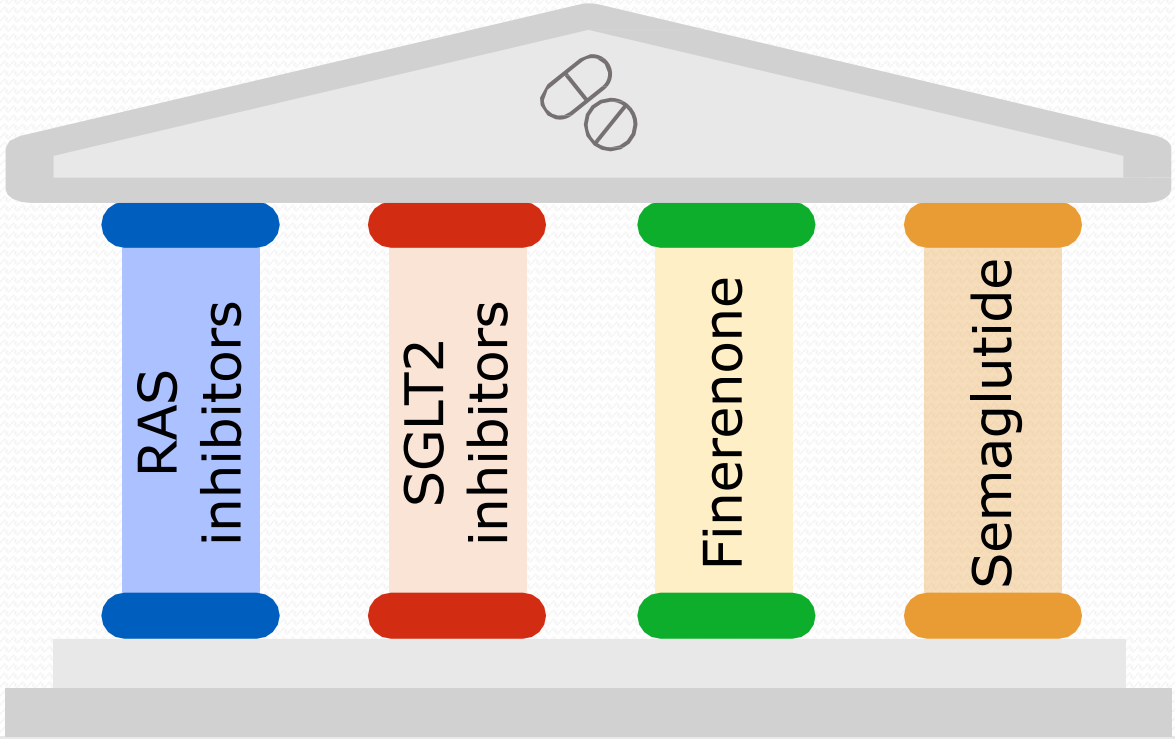
A pillared approach is recommended to treat CKD and diabetes

RAS inhibitors

- Decrease efferent arteriole tone
- Decrease hyperfiltration
- Decrease endothelial dysfunction
- Decrease cardiac remodeling

SGLT2 inhibitors

- Increase afferent artieriole tone
- Improve tubuloglomerular feedback
- Decrease hyperfiltration
- Decrease proteinuria
- Decrease oxidative stress
- Increase anti-inflammatory and anti-fibrotic effects



Finerenone

- Decreases inflammation
- Decreases fibrosis
- Decreases endothelial dysfunction
- Decreases tissue remodeling
- Decreases proteinuria

Semaglutide

- Decrease weight
- Decrease dyslipidemia
- Decrease oxidative stress
- Decrease endothelial dysfunction

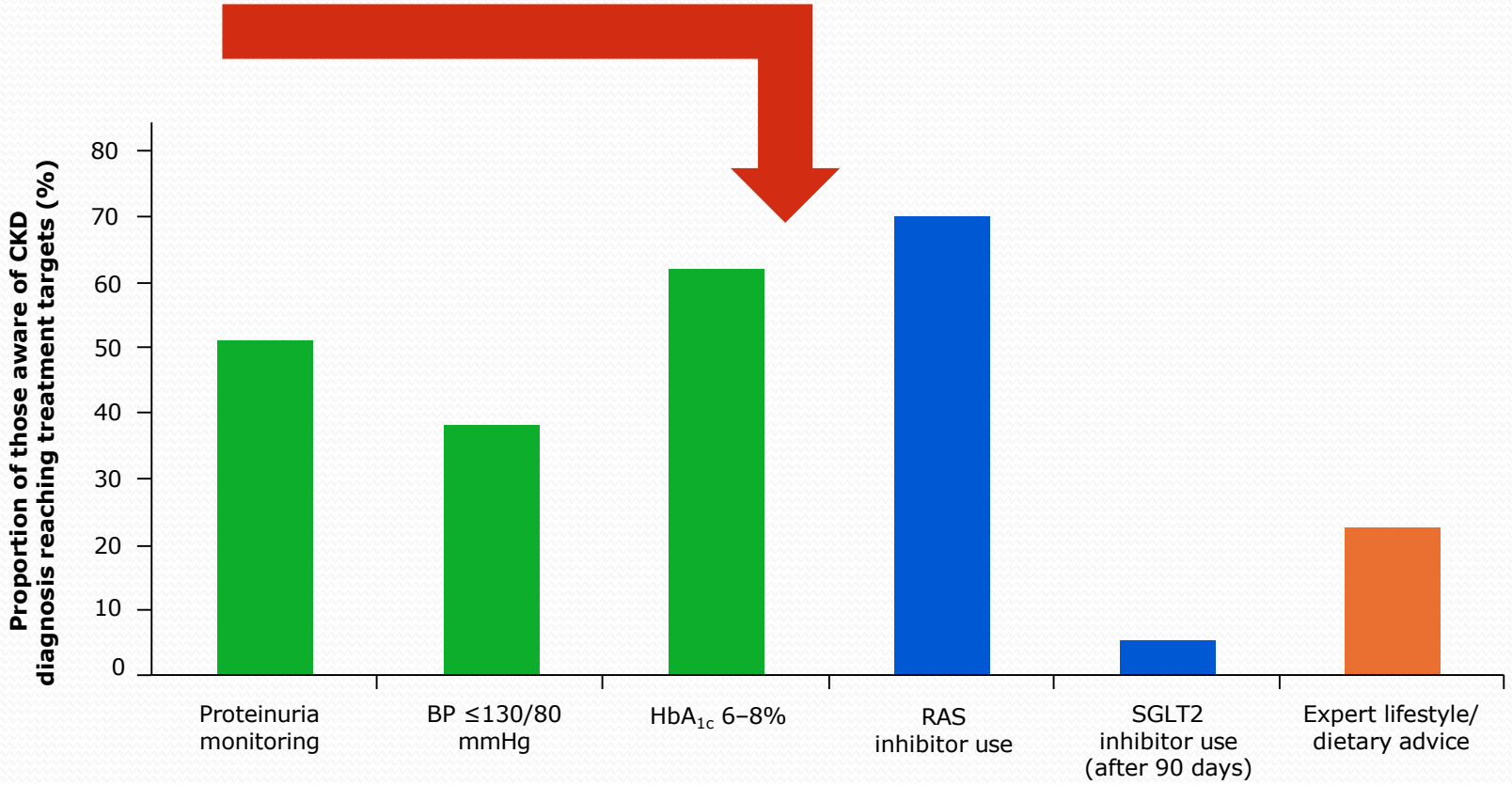
CKD, chronic kidney disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

Naaman SC, Bakris GL. *Diabetes Care* 2023;46:1574–1586.

Most people with CKD are unaware of their condition

7–20%

Aware of CKD



BP, blood pressure; CKD, chronic kidney disease; HbA_{1c}, glycated hemoglobin; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2.
Luyckx VA et al. *Kidney Int* 2024;105:406–417.

Semaglutide saves kidneys, hearts, and lives

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, and death in people with T2D and CKD

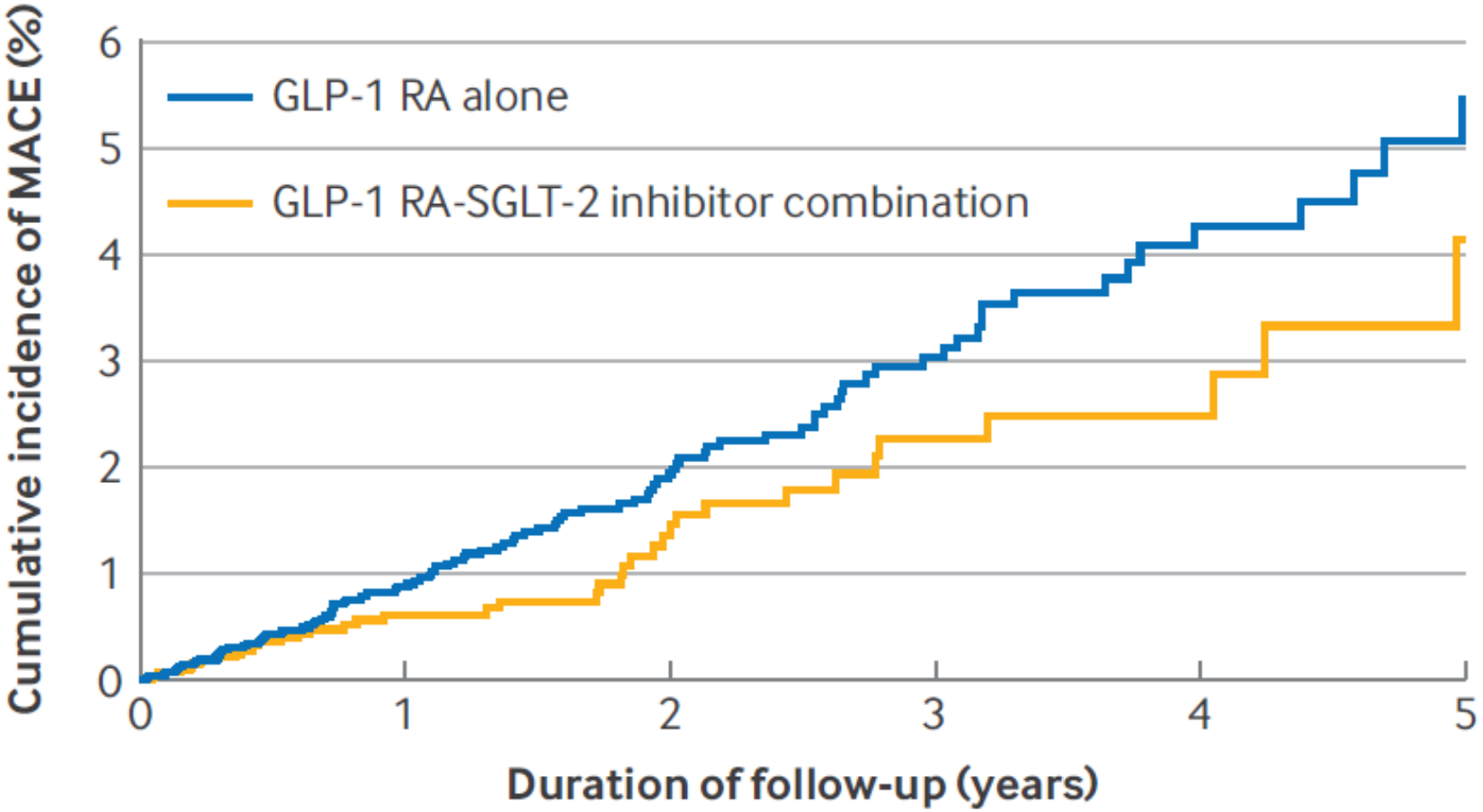
The four pillars of therapy are now a RAS inhibitor, an SGLT2 inhibitor, a non-steroidal MRA, and semaglutide

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; MACE, major adverse cardiovascular event; MRA, mineralocorticoid receptor antagonist; RAS, renin–angiotensin–aldosterone system; SGLT2, sodium–glucose cotransporter-2; T2D, type 2 diabetes.

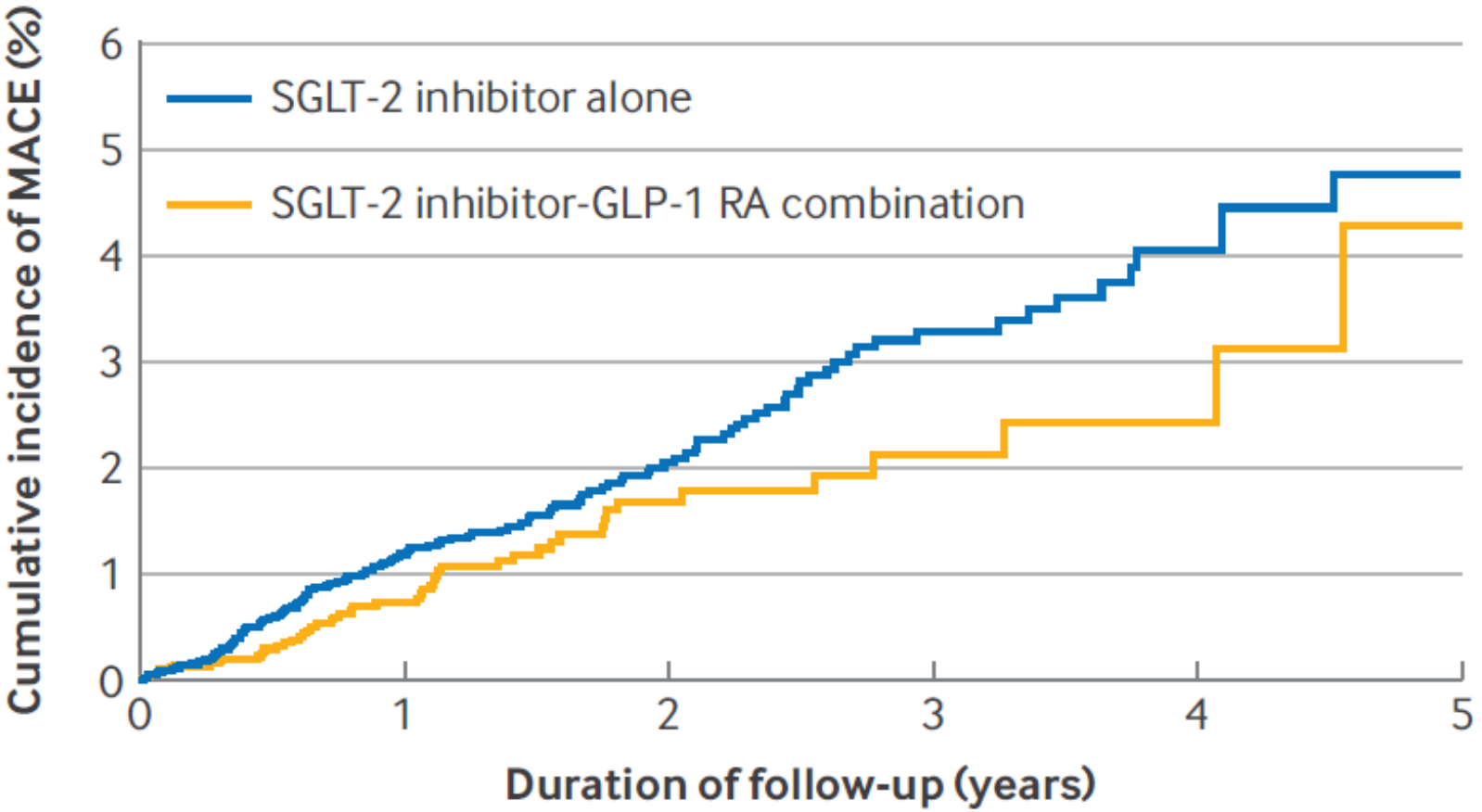
de Boer IH et al. *Diabetes Care* 2022;45:3075–3090; Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. *Kidney Int* 2022;102:S1–S127; Perkovic V et al. *N Engl J Med* 2024; doi: 10.1056/NEJMoa2403347.



No at risk

GLP-1 RA alone					
6696	3798	1996	1072	532	242
GLP-1 RA-SGLT-2 inhibitor combination					
6696	1986	1000	519	259	114

Simms-Williams N et al. BMJ; 2024;385:e078242 .



No at risk

SGLT-2 inhibitor alone					
8942	4732	2347	1146	514	176
SGLT-2 inhibitor-GLP-1 RA combination					
8942	2556	1035	428	157	48

Simms-Williams N et al. BMJ; 2024;385:e078242 .

Protecting your kidneys in t2D: how to keep the nephrologist unemployed

Robert S. Busch, MD, FACE
Attending Physician
Director of Clinical Research
Albany Medical Center Division of Community Endocrinology
Albany, NY

The dynamic duo: GLP-1 Receptor Agonists and SGLT2 Inhibitors

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Albany Medical center Division of community Endocrinology

Director of research