Beyond Glucose Control: Exploring New Frontiers in Type 2 Diabetes Management

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Declaration of Interests

- Nothing to declare

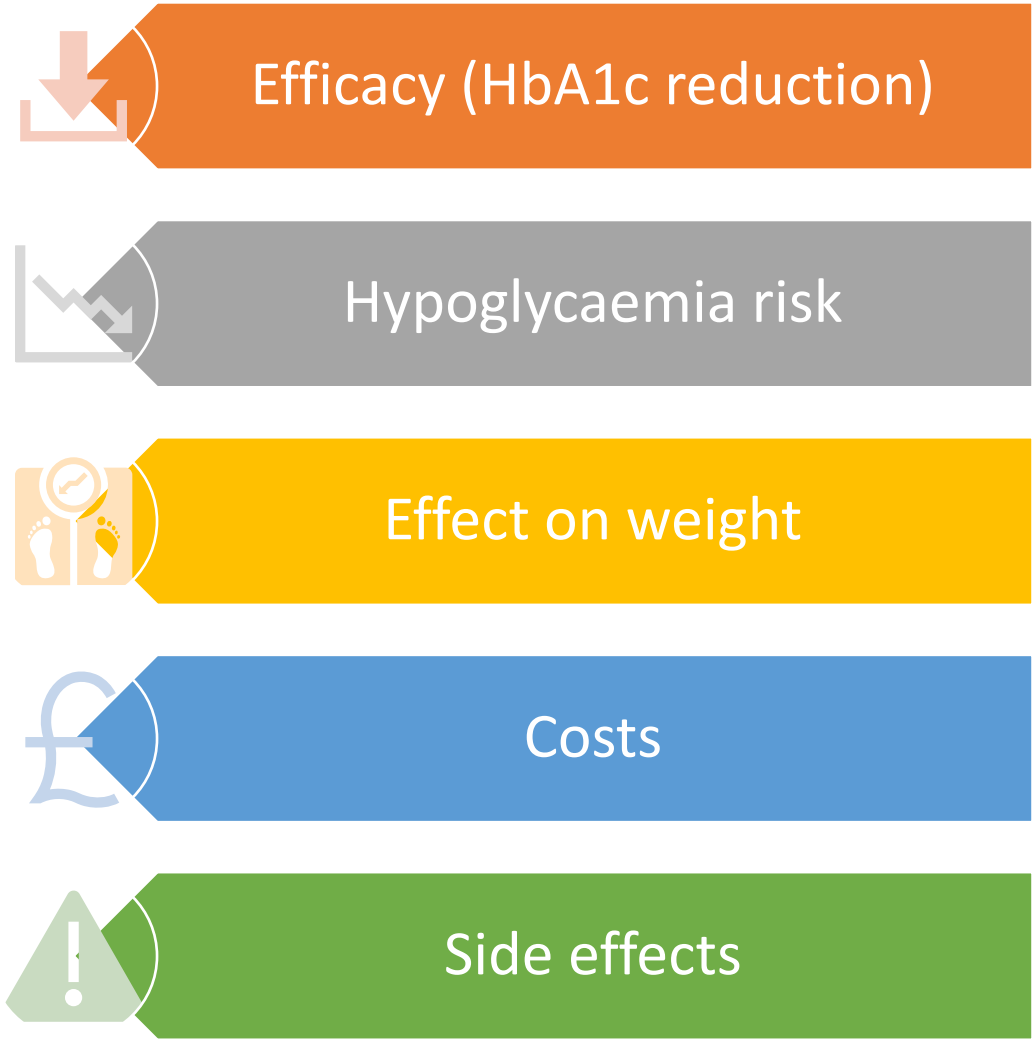
Objectives

Review the scientific evidence supporting the cardiovascular and renal benefits of SGLT2 inhibitors and GLP1-RA.

Improve understanding of the potential adverse effects linked with these new medications, enabling safer prescription practices.

Historical Perspectives

Factors affecting the choice of antihyperglycemic therapy in T2DM



- Metformin
- Sulfonylureas
- Thiazolidinediones
- DDP4-inhibitors
- Insulin
- GLP1-RA

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

N Engl J Med 2007; 356:2457-2471

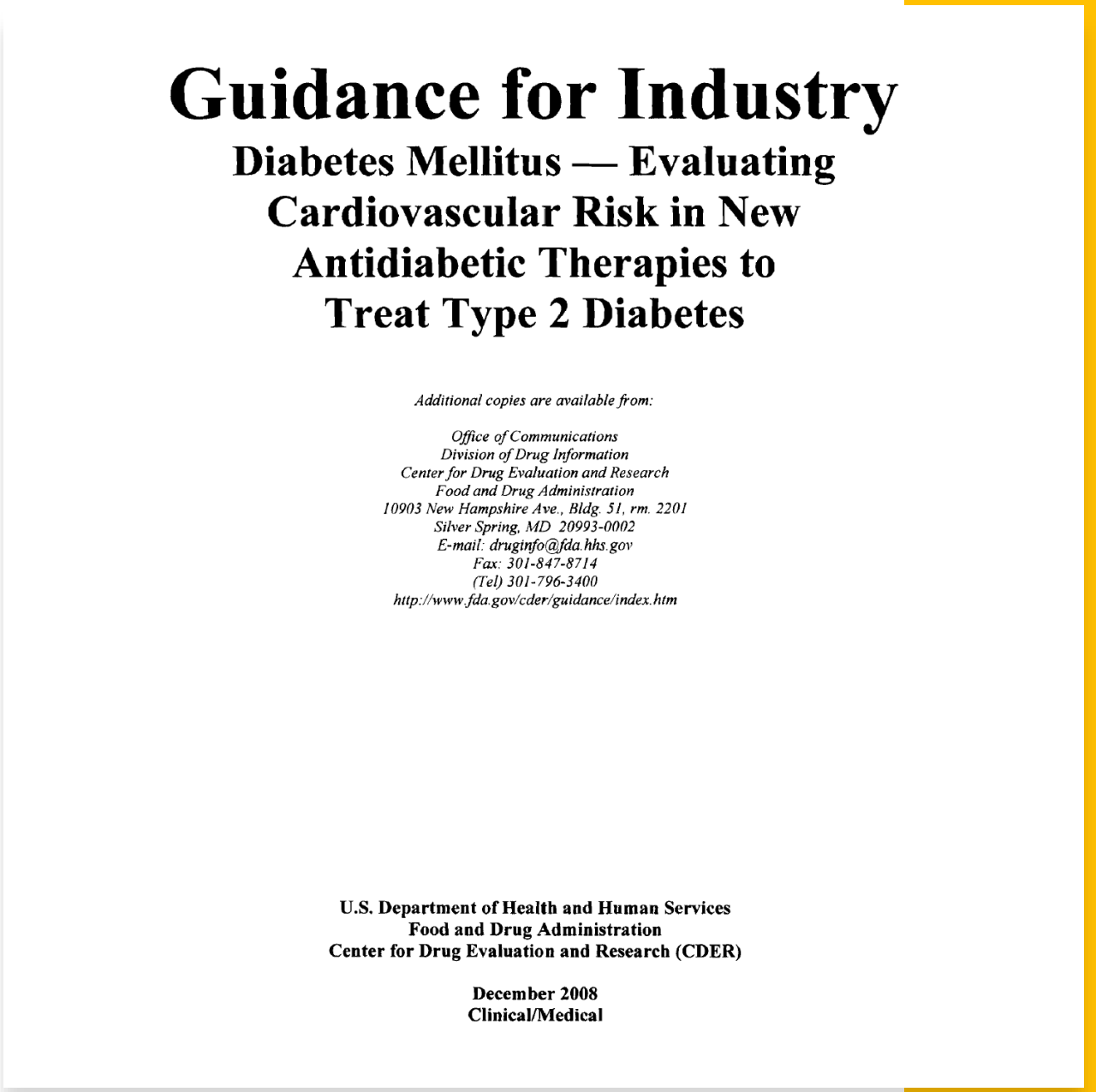
Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction (**43% increased risk**) and with an increase in the risk of death from cardiovascular causes that had borderline significance

Dec 2008

Diabetes Care 2018;41:14–31



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Additional copies are available from:

Office of Communications
Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, rm. 2201
Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
http://www.fda.gov/cder/guidance/index.htm

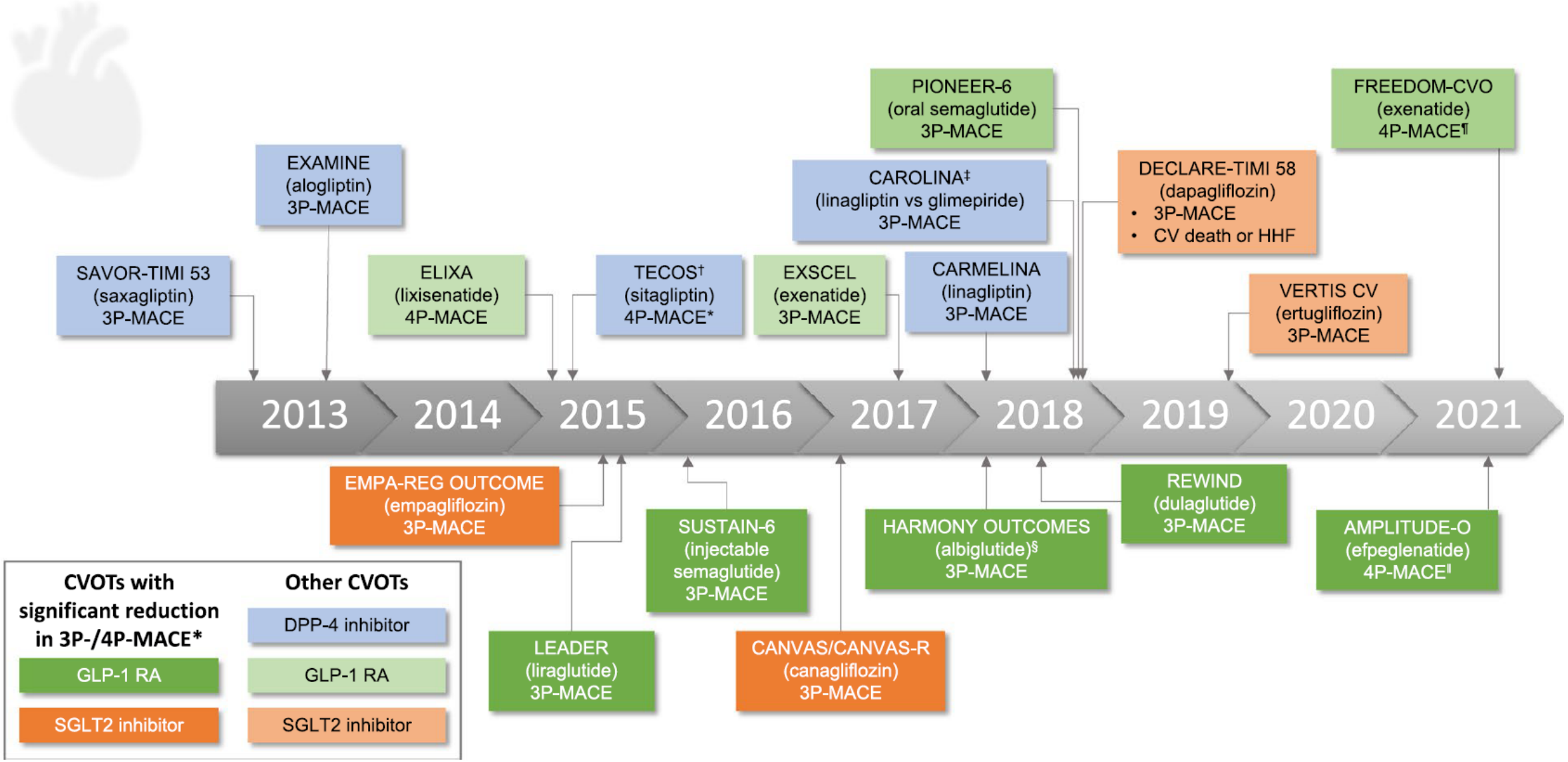
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

Design of CVOT

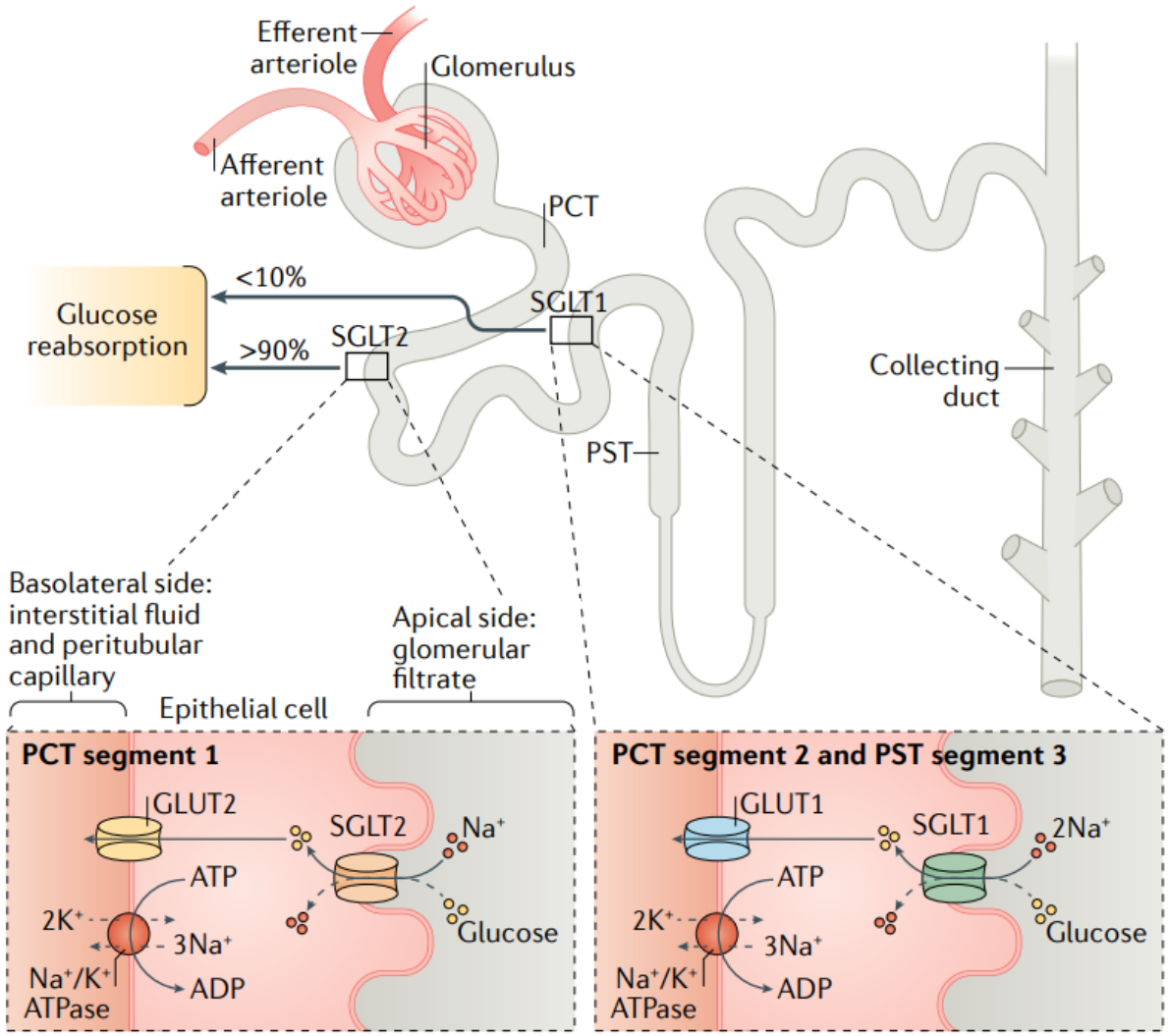
- Aim – demonstrates cardiovascular safety (no increase in CV risk compared to placebo)
- Design:
  - Patients – established CVD or have risk factors of ASCVD
  - Primary outcome – 3-point MACE (CV death, nonfatal MI, nonfatal stroke)
  - Non-inferiority study (upper limit of 2-sided confidence interval < 1.3)
  - Drug vs placebo with no major difference in characteristics between two arms

New Era of Cardiovascular Outcome Trials



Davies *et al. Cardiovascular Diabetology (2022) 21:144*

SGLT2 inhibitors



Nat Rev Cardiol **17**, 761–772 (2020)

SGLT2 inhibitors

- Canagliflozin
- Dapagliflozin
- Empagliflozin
- Ertugliflozin
- Others (not licensed by EMA/FDA) – Ipragliflozin, Luseogliflozin, Tofofliflozin, Remogliflozin

Dual SGLT1/SGLT2 inhibitor

- Sotagliflozin

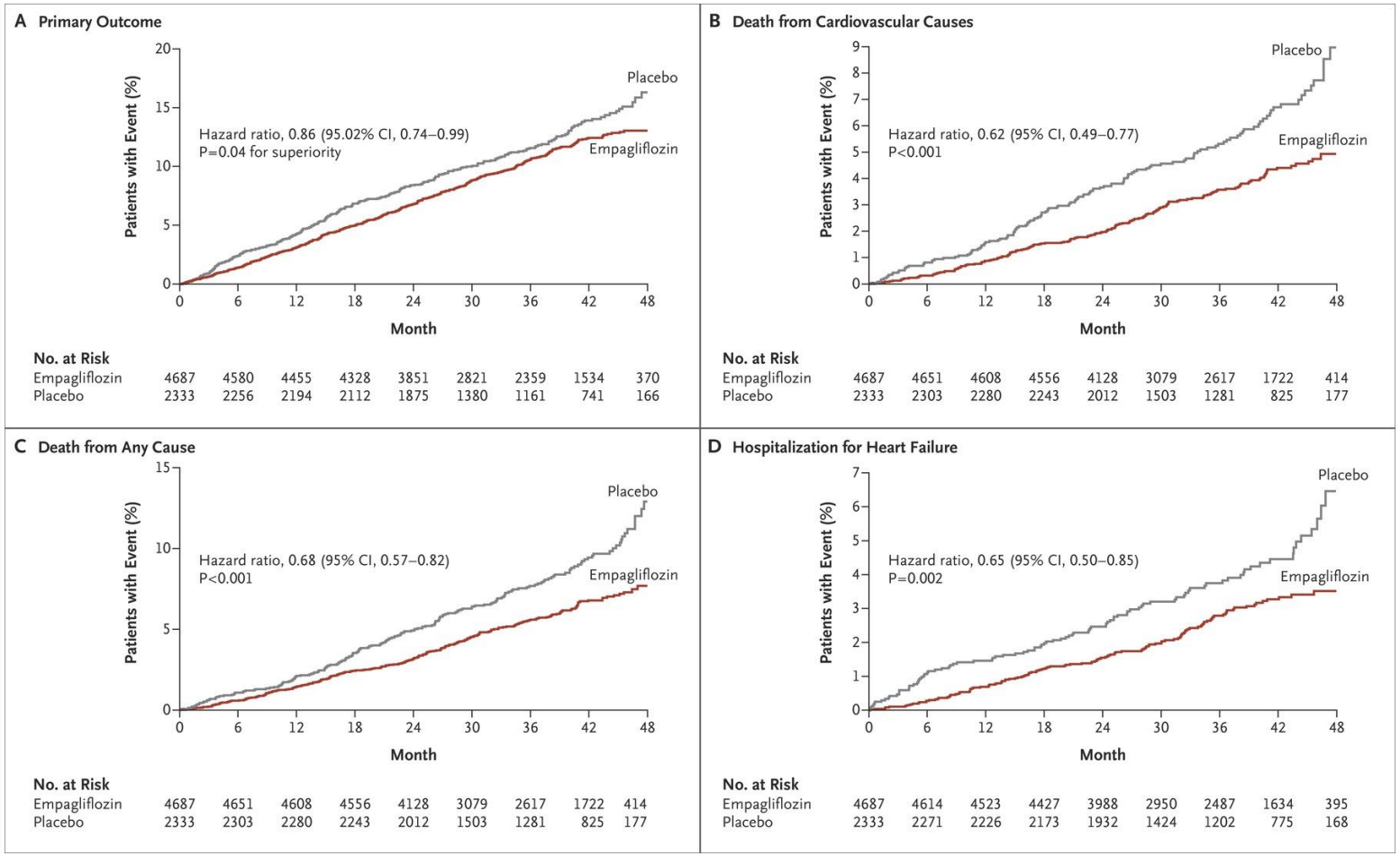
EMPA-REG Outcome

Primary

- 14% reduction in 3P-MACE
- 38% reduction in CV death
- Non-fatal stroke - NS
- Non-fatal MI – NS

Other:

- Reduce HHF
- Reduce all-cause death



N Engl J Med 2015; 373:2117-2128

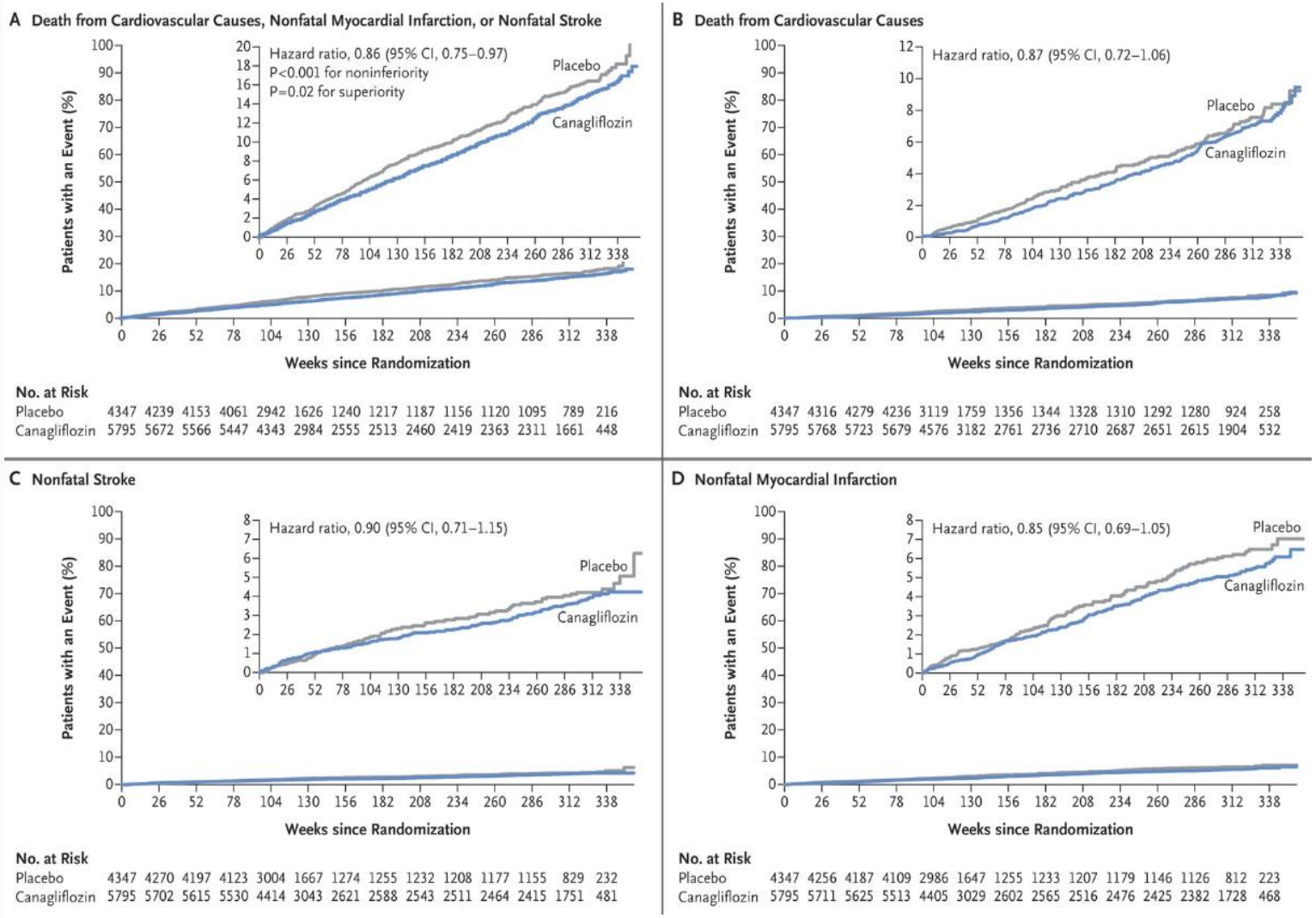
CANVAS

Primary

- 14% reduction in 3P-MACE
- CV death – NS
- Non-fatal MI – NS
- Non-fatal stroke – NS

Secondary

- Beneficial renal outcome (progression of albuminuria and composite renal outcome)
- Reduced HHF



N Engl J Med 2017; 377:644-657

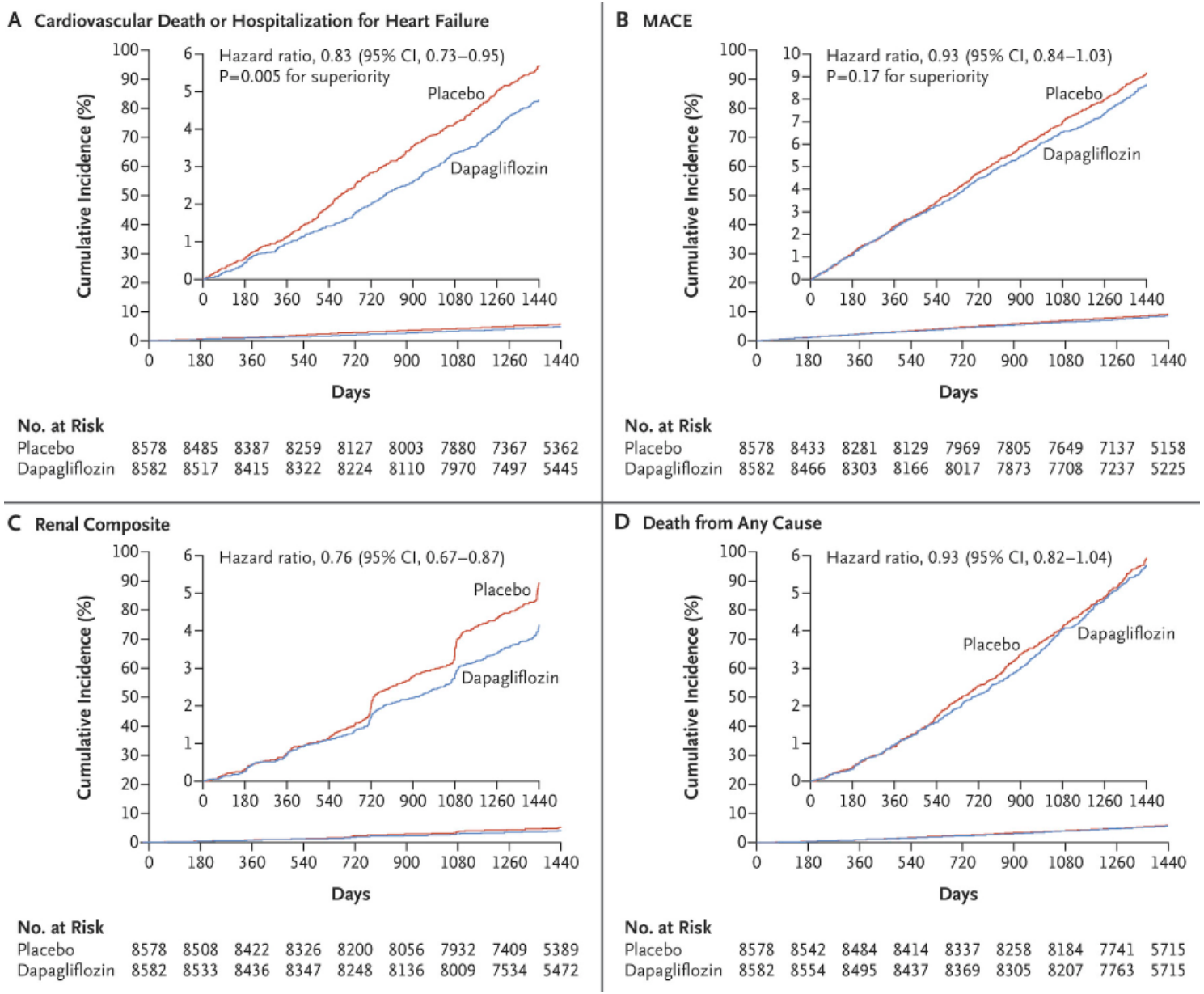
DECLARE-TIMI 58

Primary

- MACE –NS
- Composite CV death or HHF – 27% reduction (mainly driven by reduction in HHF)

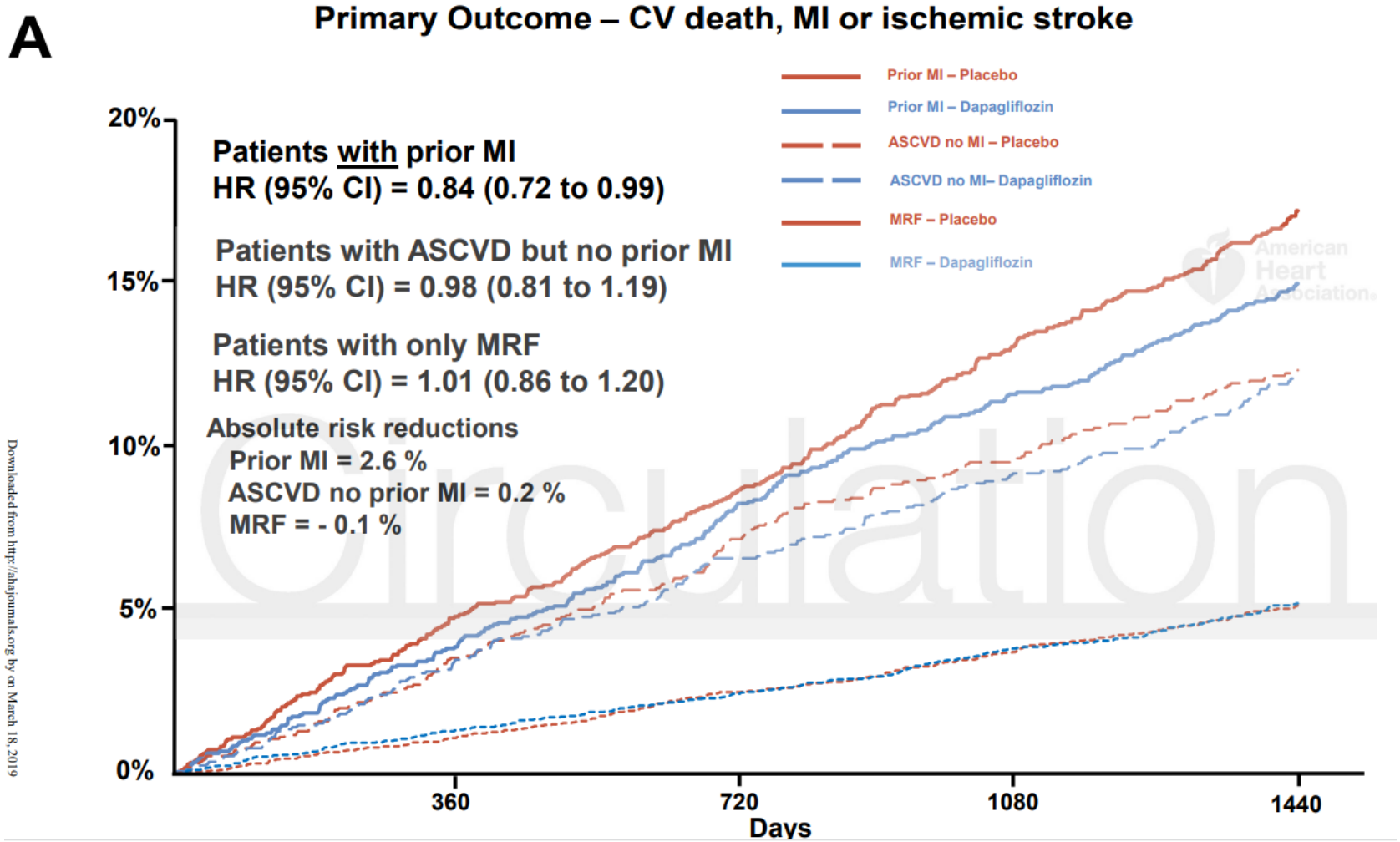
Other:

- Reduced HHF
- Renal benefit



N Engl J Med 2019; 380:347-357

Subgroup analysis of DECLARE TIMI 58

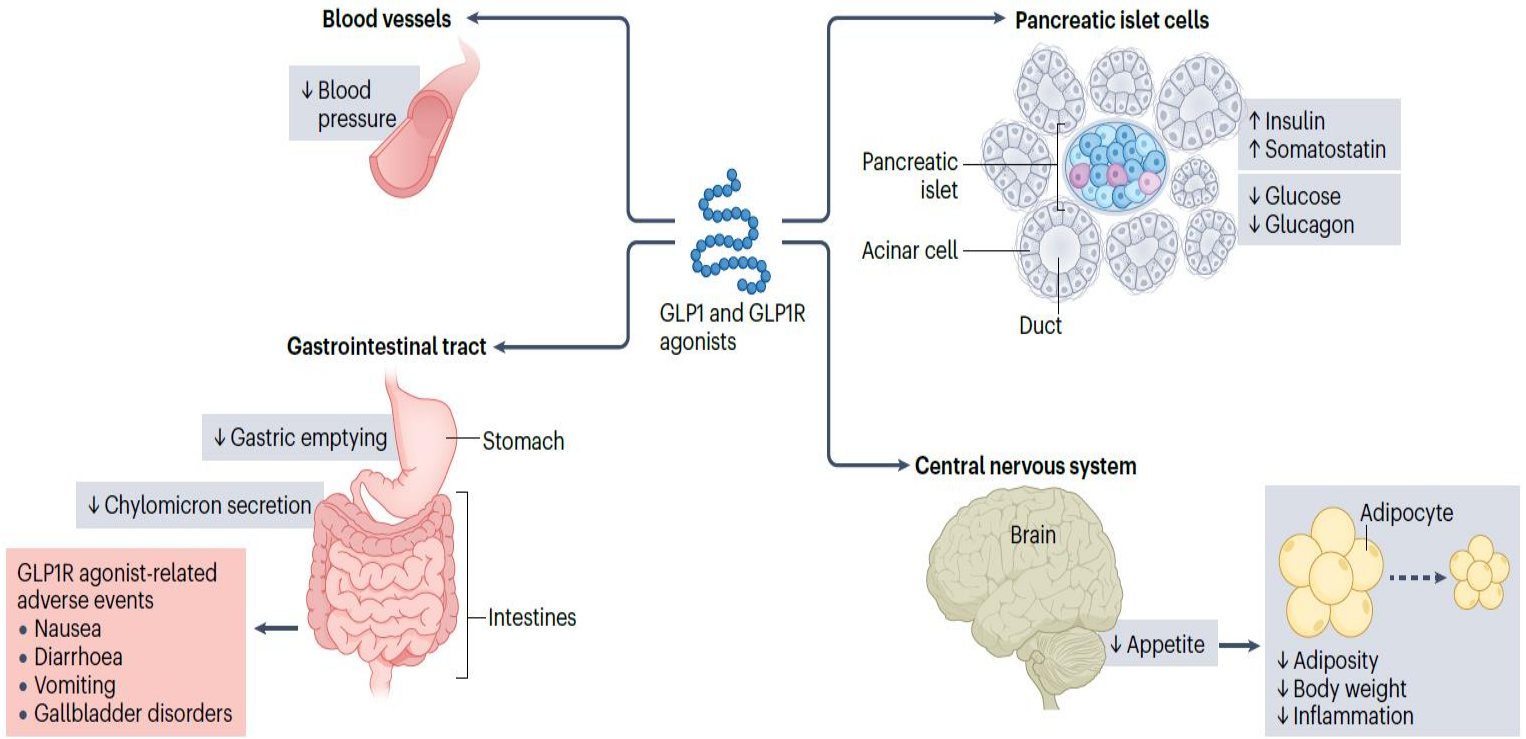


Circulation. 2019 May 28;139(22):2516-2527.

SGLT2 inhibitors - CVOT

- Trials:
  - EMPA-REG Outcome (Empagliflozin)
  - CANVAS Program(Canagliflozin)
  - DECLARE-TIMI (Dapagliflozin)
  - VERTIS CV (Ertugliflozin)
- Summary:
  - **Empagliflozin and Canagliflozin decrease atherosclerotic CV morbidity and mortality**
  - Dapagliflozin* and Ertugliflozin did not show benefit in 3P-MACE or CV death
  - In secondary outcome – SGLT2i reduced the risk of HHF and showed renal benefits

GLP1-RA



- Twice-daily Exenatide
- Once-weekly Exenatide
- Liraglutide
- Lixisenatide
- Dulaglutide
- Semaglutide (SC, oral)
- Albiglutide (withdrawn from the market)

Nat Rev Cardiol **20**, 463–474 (2023)

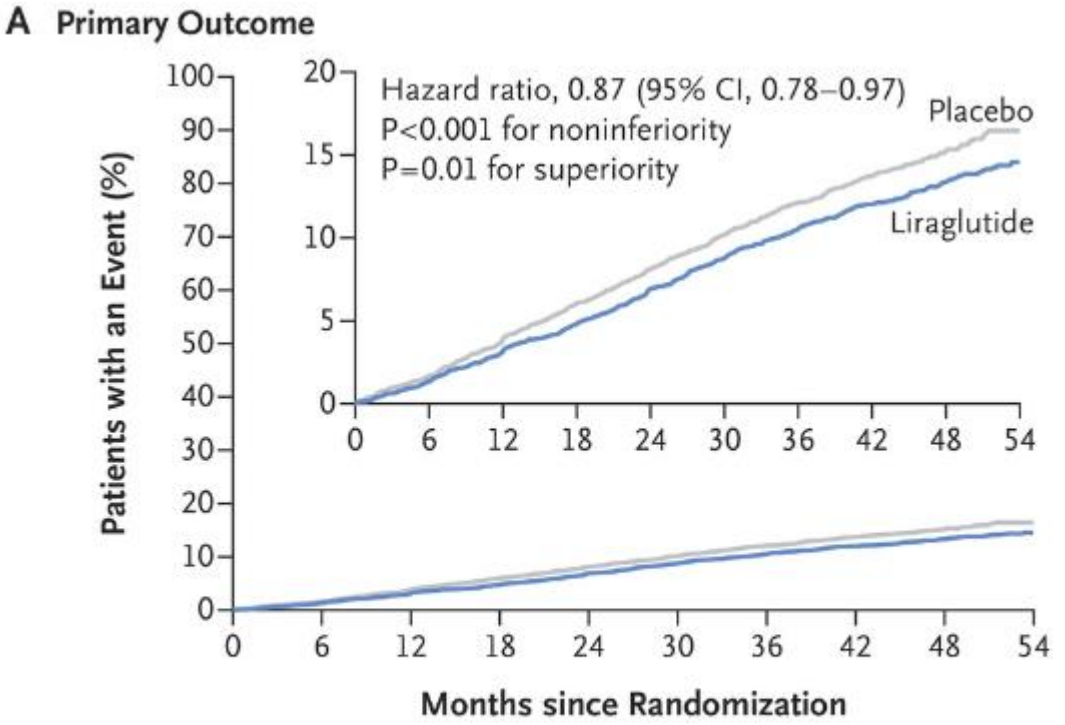
LEADER

Primary

- 13% reduction in 3P-MACE
- 22% reduction in CV death
- Non-fatal stroke - NS
- Non-fatal MI – NS

Other:

- Protective effect on albuminuria
- Reduced all-cause death (15%)



N Engl J Med 2016; 375:311-322

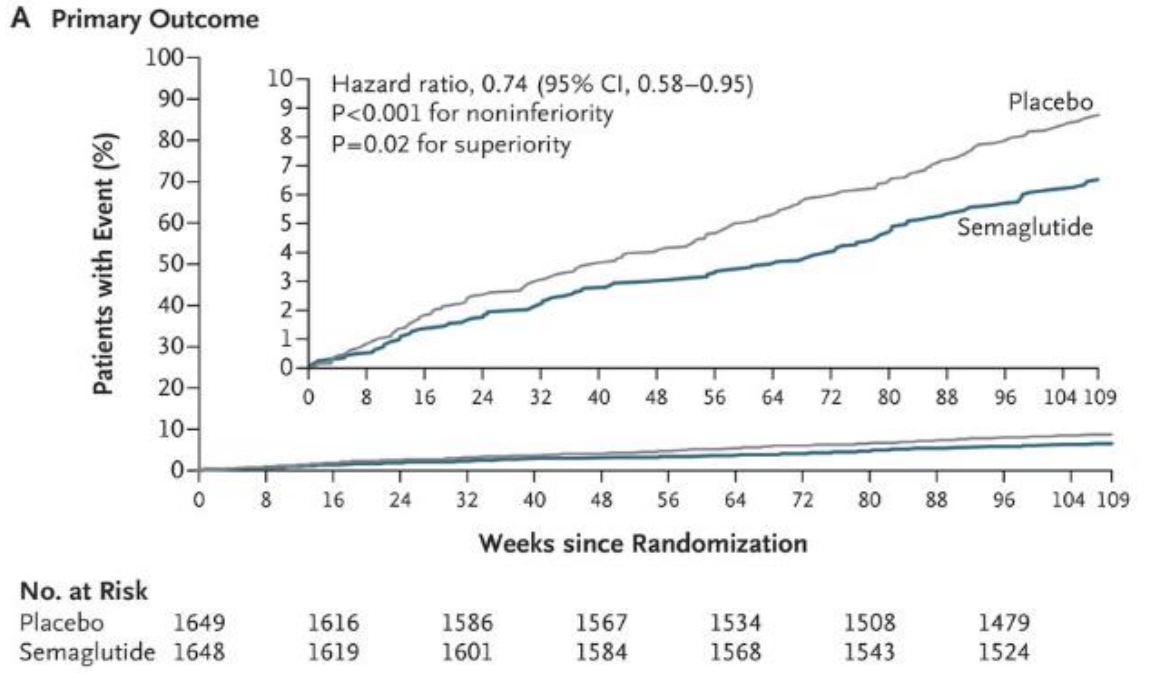
SUSTAIN-6

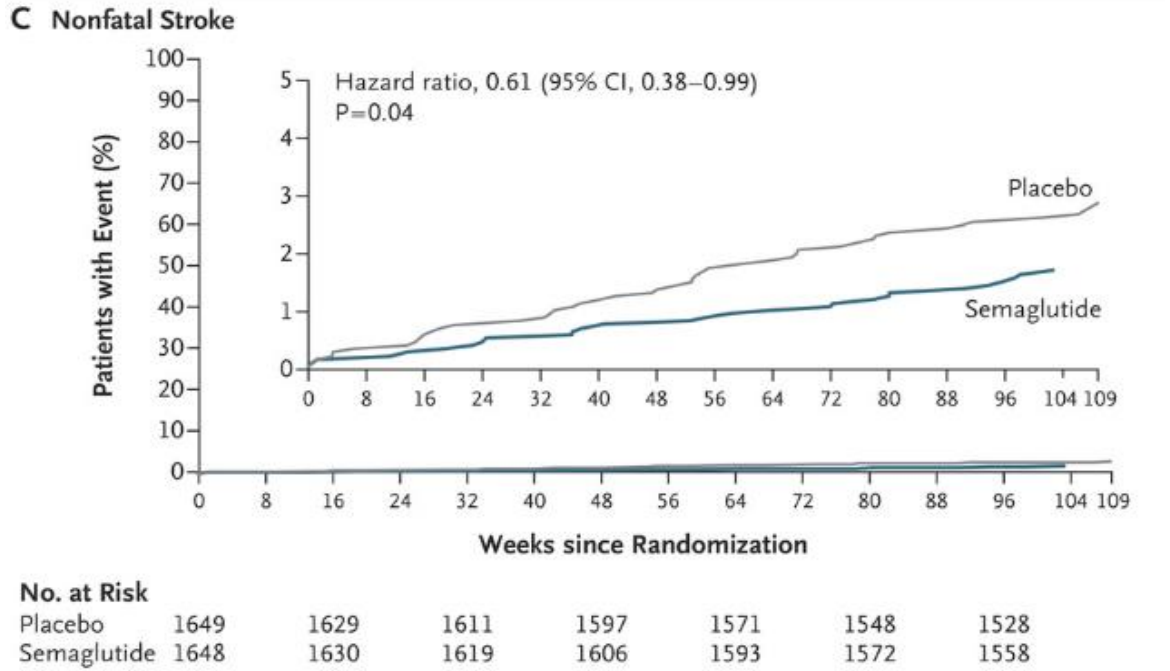
Primary

- 26% reduction in 3P-MACE
- CV death - NS
- 39% reduction of non-fatal stroke
- Non-fatal MI – NS

Other:

- Protective effect on albuminuria





N Engl J Med 2016; 375:1834-1844

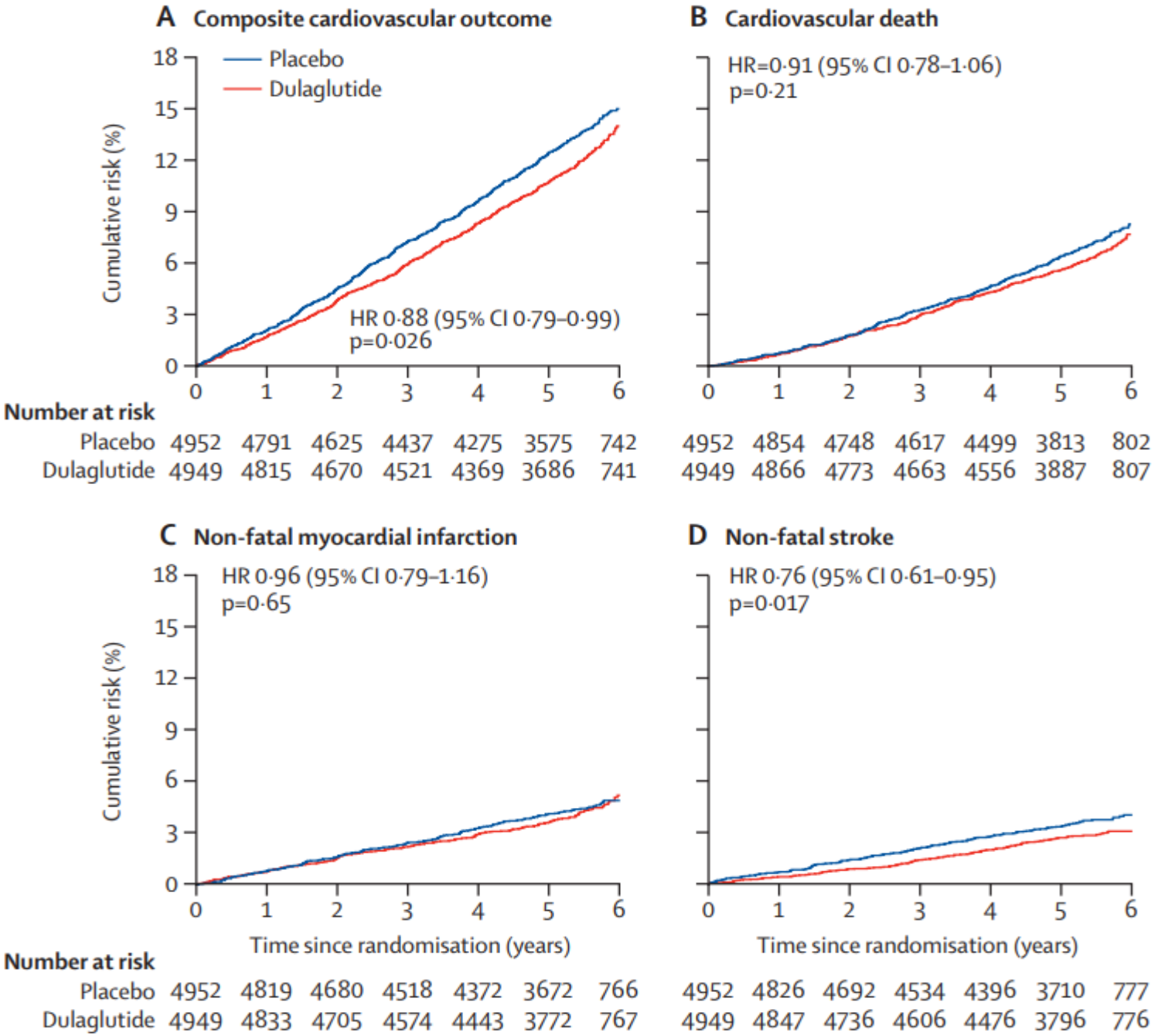
REWIND

Primary

- 12% reduction in 3P-MACE
- CV death – NS
- 24% reduction of non-fatal stroke
- Non-fatal MI – NS

Other:

- Protective effect on renal outcome



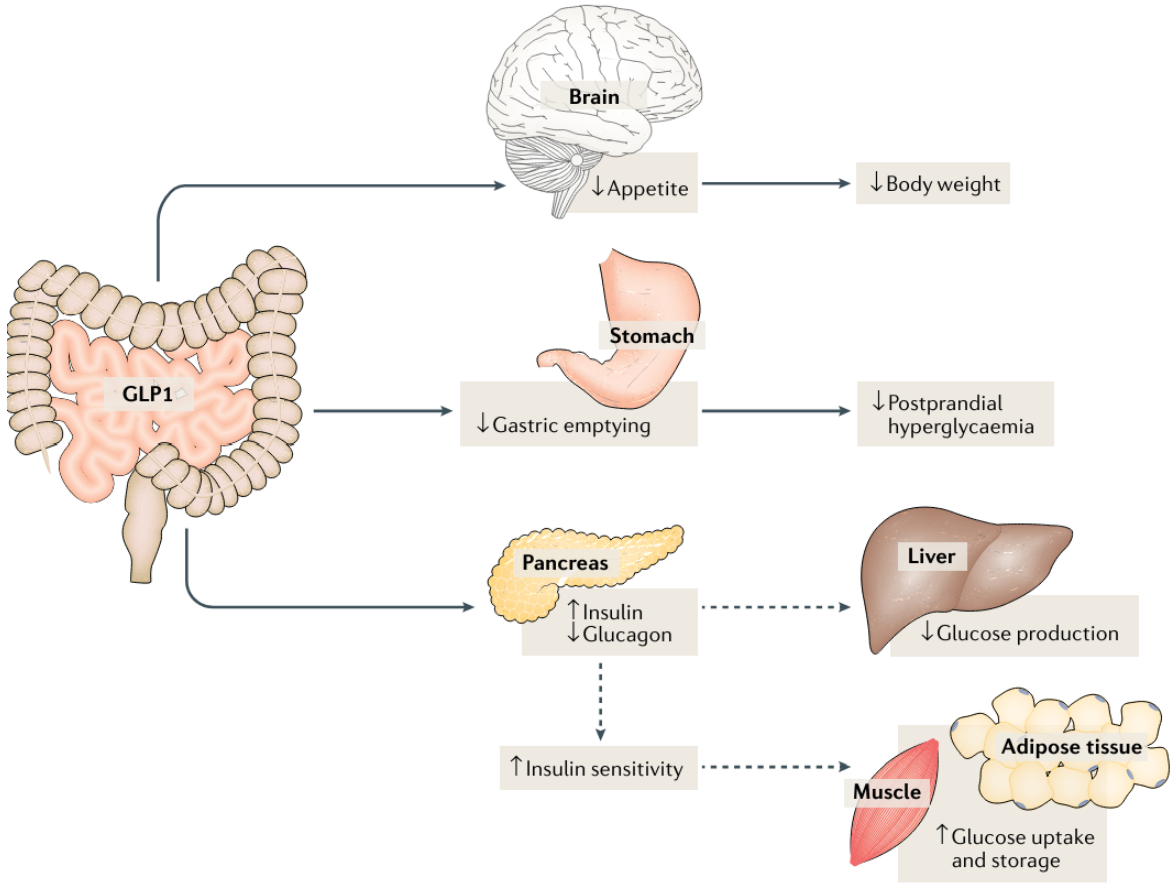
Lancet . 2019 Jul 13;394(10193):121-130.

GLP1-RA – CVOT

- Trials:
  - LEADER (Liraglutide)
  - SUSTAIN-6 (SC Semaglutide)
  - PIONEER-6 (oral Semaglutide)
  - ELIXA (Lixisenatide)
  - EXSCEL (once-weekly Exenatide)
  - HARMONY Outcomes (Albiglutide)
  - REWIND (Dulaglutide)
  - FREEDOM-CVO (Exenatide SC implants)
  - AMPLITUDE-O (efpeglenatide)
- Summary:
  - **Liraglutide, SC Semaglutide, Dulaglutide, Albiglutide* and Efpeglenatide* – reduce ASCVD outcomes**
  - Lixisenatide, once-weekly exenatide, continuous exenatide infusion and oral Semaglutide – neutral

Dipeptidyl peptidase 4 inhibitors (DDP4i)

- Inhibit DDP4 activity → prevent degradation of GLP1



- Sitagliptin
- Linagliptin
- Saxagliptin
- Alogliptin
- Vildagliptin

DDP-4 inhibitors

- Trials:
  - SAVOR-TIMI 53 (Saxagliptin)
  - EXAMINE (Alogliptin)
  - TECOS (Sitaglptin)
  - CAROLINA (Linagliptin vs glimpride)
  - CARMELINA (Linagliptin)
- Summary:
  - **DDP-4 demonstrates CV safety with no benefits**
  - Saxagliptin increases the risk of hospitalization for heart failure

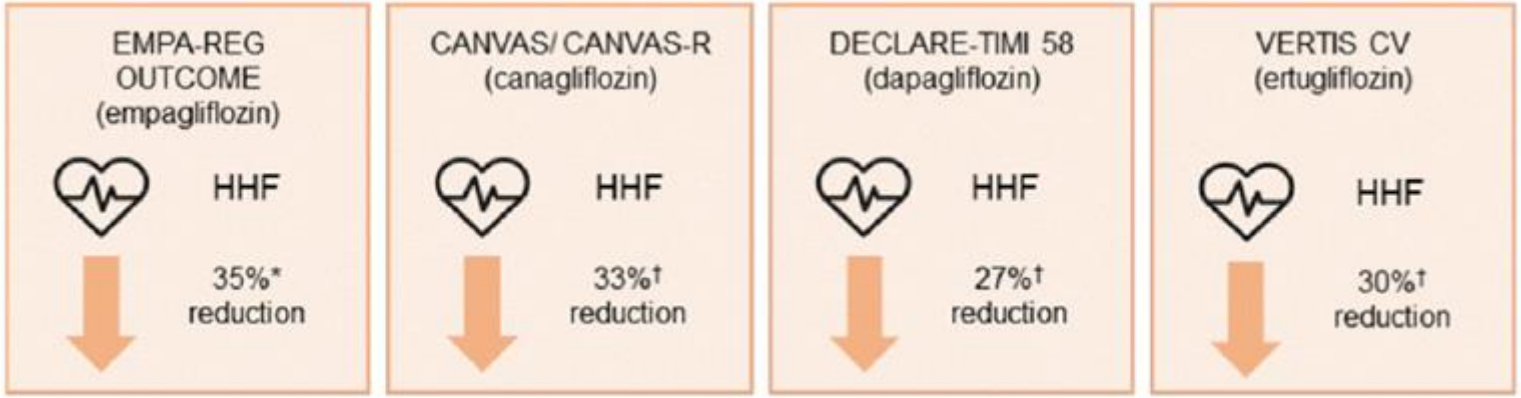
Beyond MACE

Additional HF and Renal benefits

- Initial CVOT suggested additional benefits on HF and renal outcomes.
- Therefore, dedicated HF outcome trials and renal outcome trials were conducted
- Some of these studies included patients with and without T2DM

Heart Failure

SGLT2i – Evidence from CVOT



SGLT2i reduced the risk of HHF by 30-35%

Davies *et al. Cardiovascular Diabetology (2022) 21:144*

SGLT2i – dedicated HF trials

- HFrEF (EF ≤ 40%)
  - DAPA-HF (Dapagliflozin)
  - EMPEROR-Reduced (Empagliflozin)
- HFpEF (EF > 40%)
  - EMPEROR-preserved (Empagliflozin)
  - DELIVER (Dapagliflozin)
- Worsening HF/Acute HF
  - SOLOIST-WHF (Sotagliflozin)
  - EMPULSE (Empagliflozin)
  - DICTATE-AHF (Dapagliflozin)

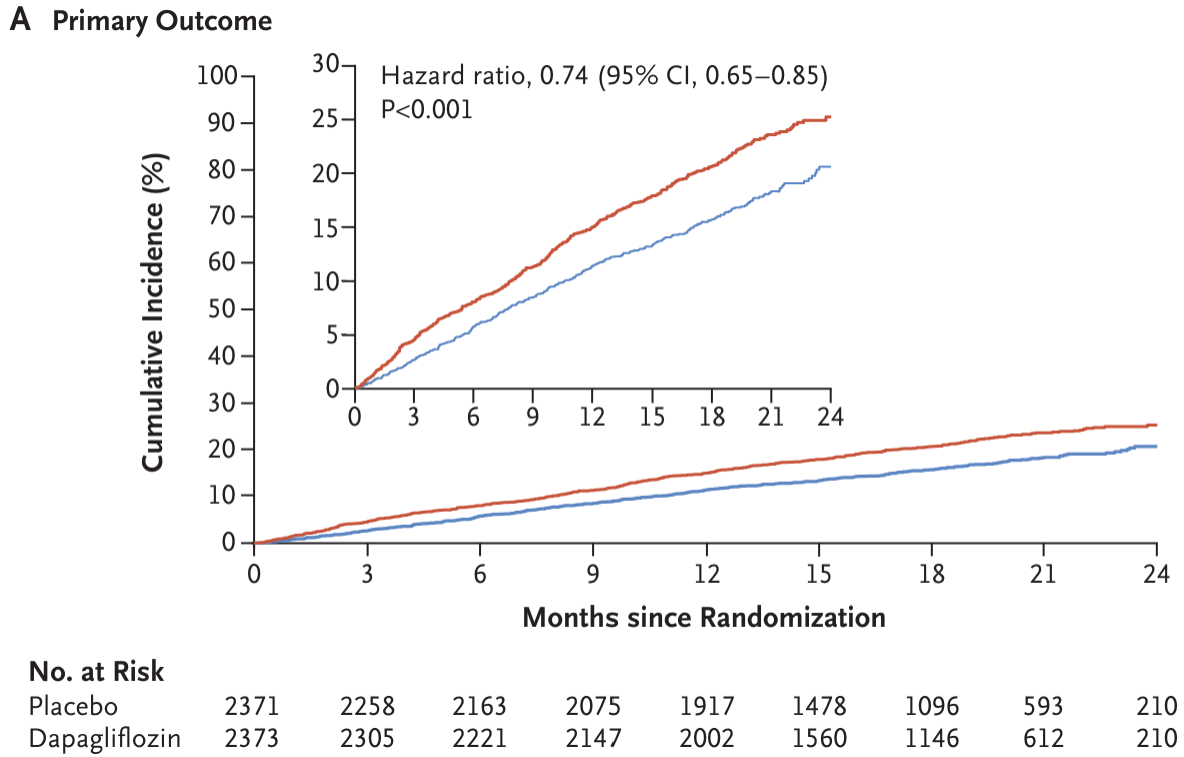
DAPA-HF

Primary outcome

- 26% reduction (NNT 21)

Secondary outcome:

- HHF– 30% reduction
- CV death – 18% reduction
- Death from any cause – 17% reduction



Composite of

- Worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or
- CV death.

N Engl J Med 2019;381:1995-2008.

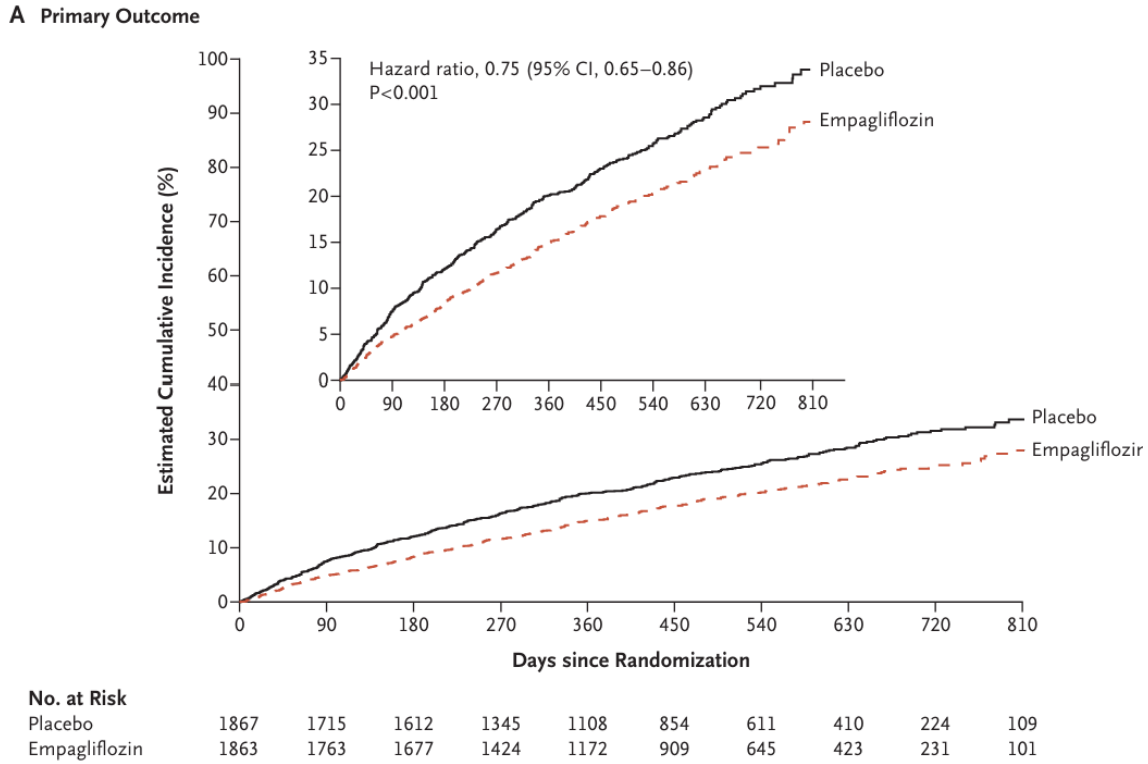
EMPEROR-Reduced

Primary outcome

- 25% reduction

Secondary outcome:

- HHF– 31% reduction
- Slower decline in eGFR
- CV death – NS



Composite of

- Hospitalization for worsening heart failure or
- CV death.

N Engl J Med 2020;383:1413-24

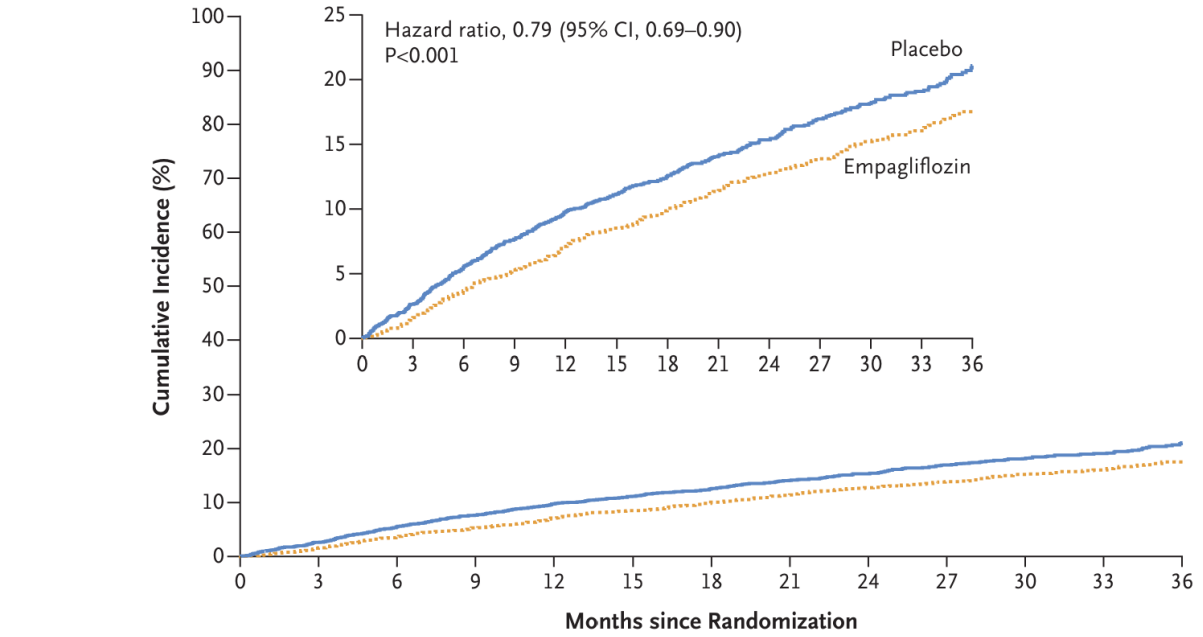
EMPEROR-Preserved

Primary outcome

- 21% reduction

Secondary outcome:

- HHF– 29% reduction
- Slower decline in eGFR
- CV death – NS



No. at Risk													
Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

Composite of

- Hospitalization for heart failure or
- CV death.

N Engl J Med 2021;385:1451-61

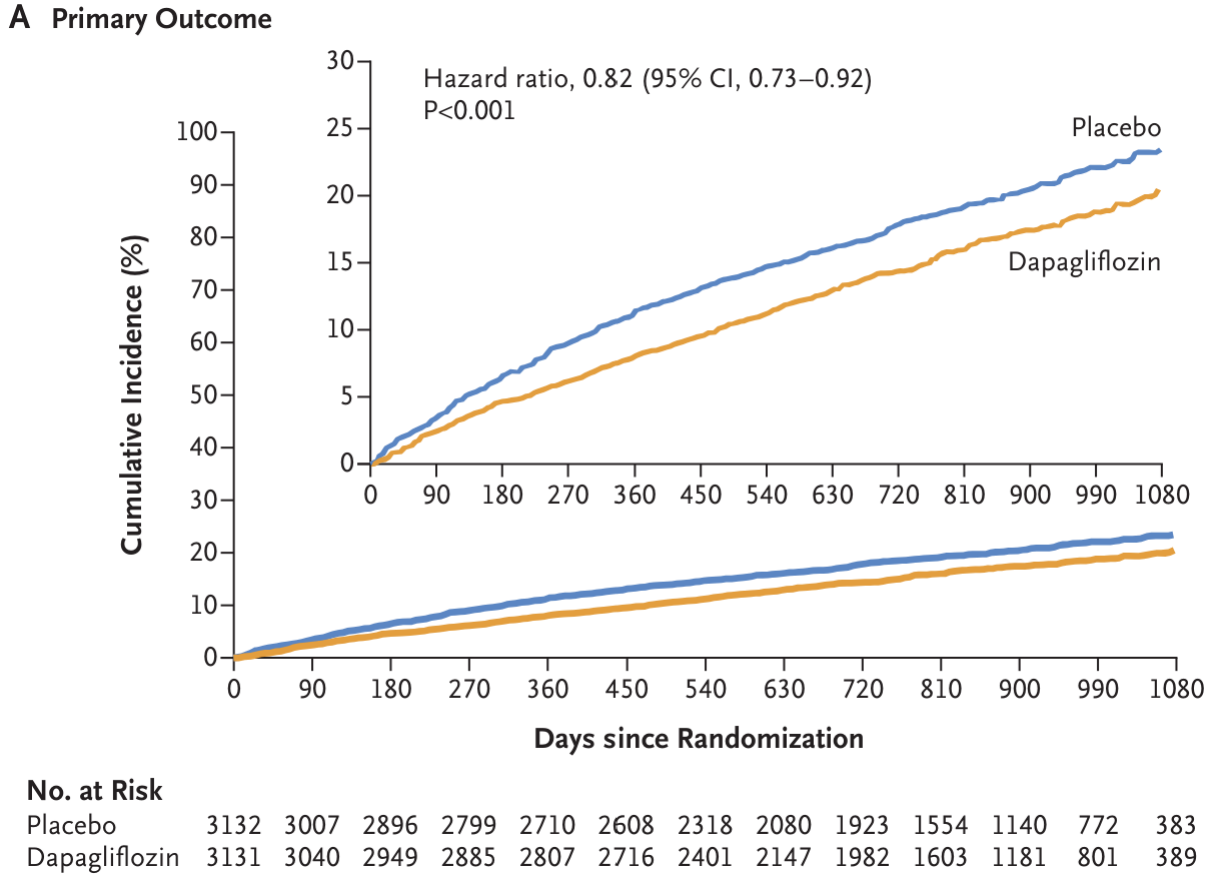
DELIVER

Primary outcome

- 18% reduction

Secondary outcome:

- WHF – 21 % reduction
- CV death – NS



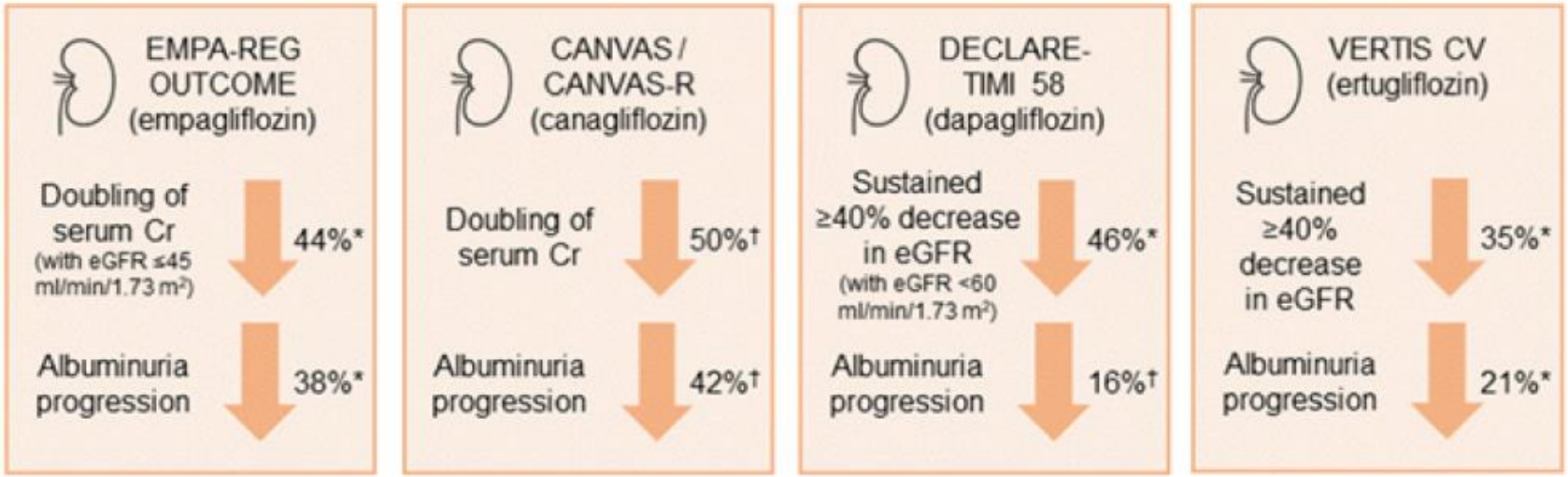
Composite of

- Worsening heart failure (an unplanned hospitalization for heart failure or an urgent visit for heart failure) or
- CV death

N Engl J Med 2022;387:1089-1098

Renal outcome

SGLT2 inhibitors – Renal outcome in CVOT



*$p < 0.05$. †Exploratory analysis

Davies *et al. Cardiovascular Diabetology (2022) 21:144*

SGLT2 inhibitors – Dedicated Renal Trials

	CREDENCE (2.6 y)	DAPA-CKD (2.4 y)	EMPA-Kidney (2 y)
	Canagliflozin vs Placebo	Dapagliflozin vs Placebo	Empagliflozin vs Placebo
Diabetes	100%	67.6%	46%
HF	15%	11%	NR
CV disease	50%	37%	26%
Mean eGFR	56	43	37
eGFR range	30-90	25-75 (14% had eGFR <30)	20-90 (30% had eGFR < 30)
Median UACR mg/g	923	965	331

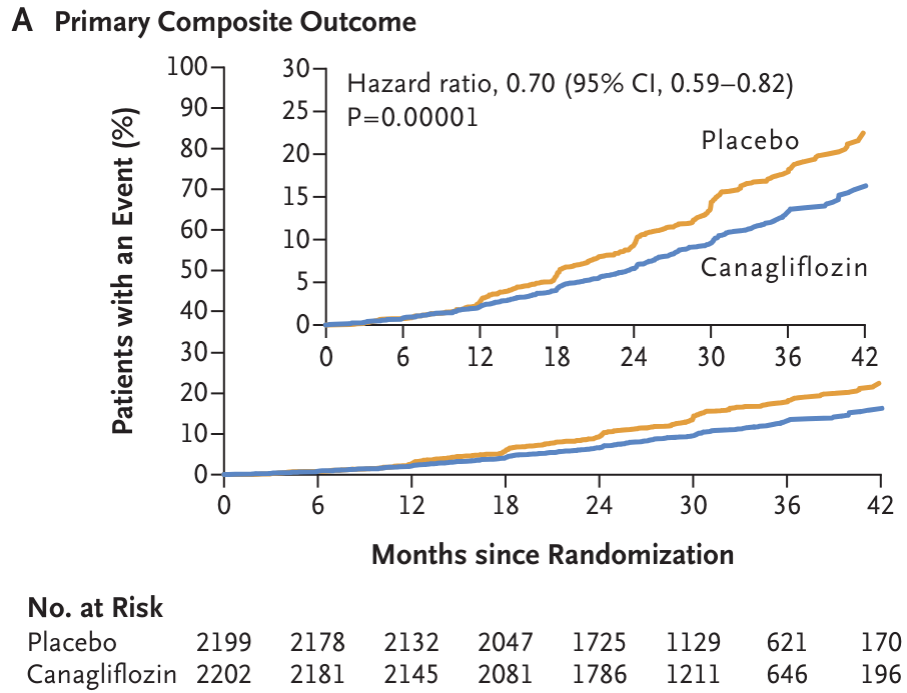
CREDENCE

Primary composite outcome

- 30% reduction (NNT 22)

Secondary outcome:

- Renal-specific composite outcome – 34% reduction
- ESKD – 32% reduction
- CV death/MI/Stroke – 20% reduction
- HHF – 39% reduction



Composite of

- End-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min) **or**
- Doubling of the serum creatinine level from baseline **or**
- Death from renal or cardiovascular causes

N Engl J Med 2019;380:2295-306.

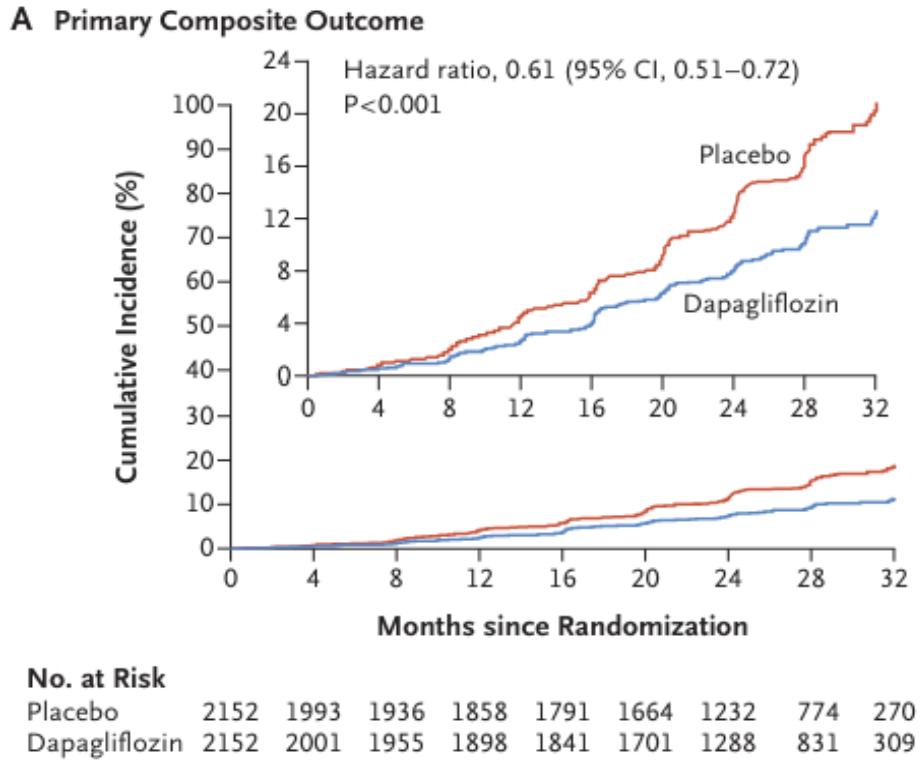
DAPA-CKD

Primary composite outcome

- 39% reduction (NNT 19)

Secondary outcome:

- Renal-specific composite outcome – 44% reduction
- CV death or HHF – 29 % reduction
- Death from any cause – 31% reduction



Composite of

- Sustained decline in the estimated GFR of at least 50%,
- End-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml/min), or
- Death from renal or cardiovascular causes.

N Engl J Med 2020;383:1436-46

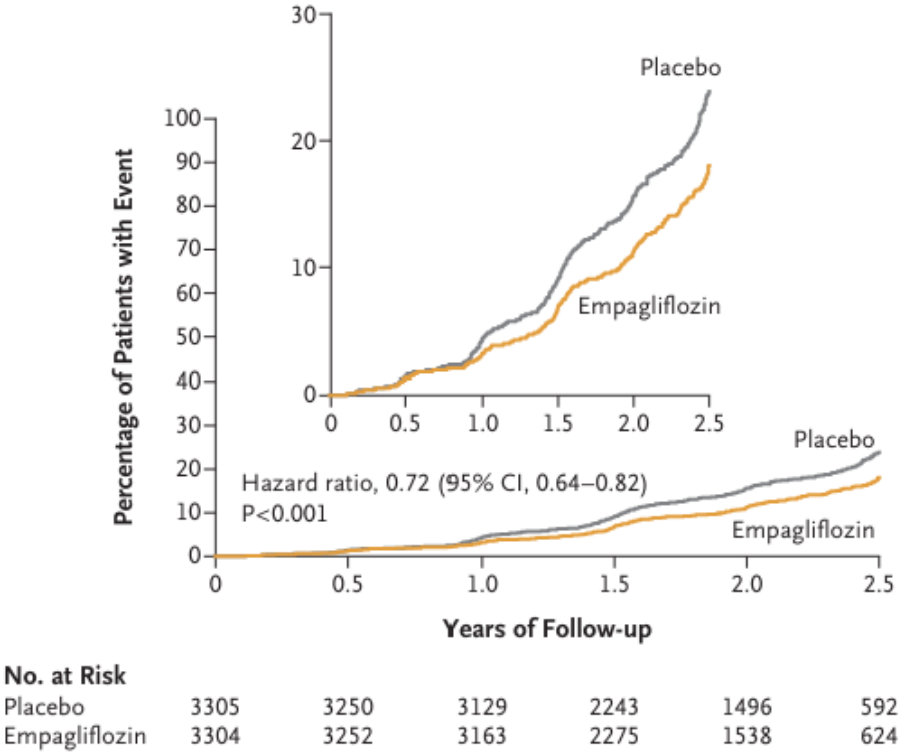
EMPA-KIDNEY

Primary composite outcome

- 28% reduction (NNT 27)

Secondary outcome:

- Hospitalization from any cause – 14% reduction
- CV death or HHF – NS
- Death from any cause – NS

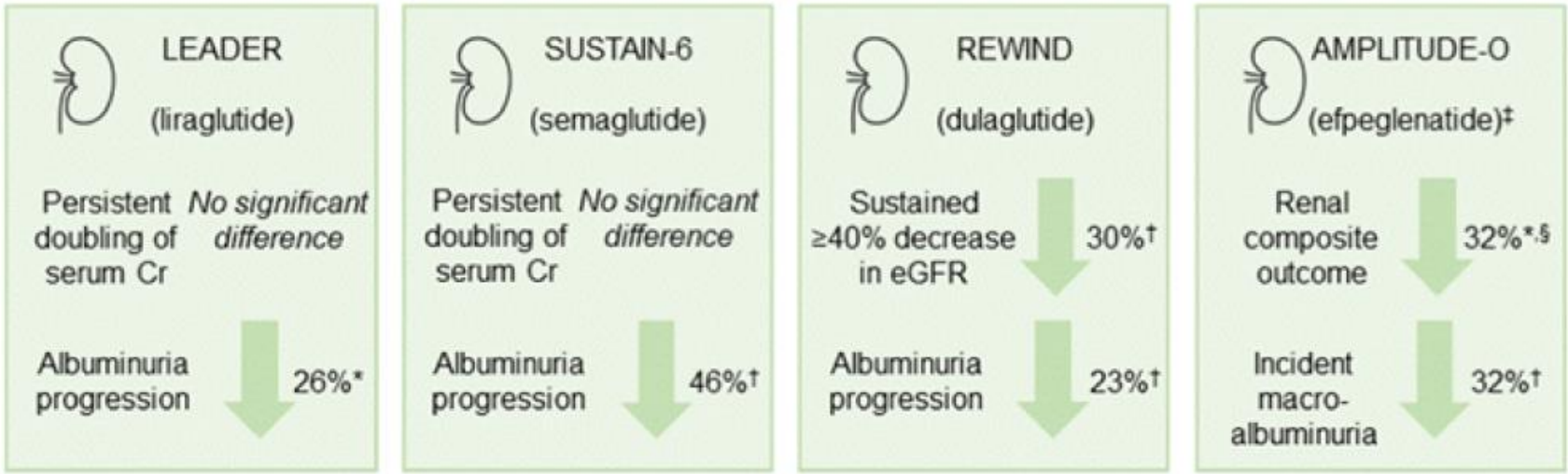


Composite of

- Progression of kidney disease – defined as ESKD (dialysis or transplant), decrease of GFR of <10 ml/min, decrease in the eGFR of ≥ 40% or death from renal causes **or**
- Death from cardiovascular causes

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

GLP1-RA and renal outcome



*p < 0.05. †Exploratory analysis

Davies *et al. Cardiovascular Diabetology (2022) 21:144*

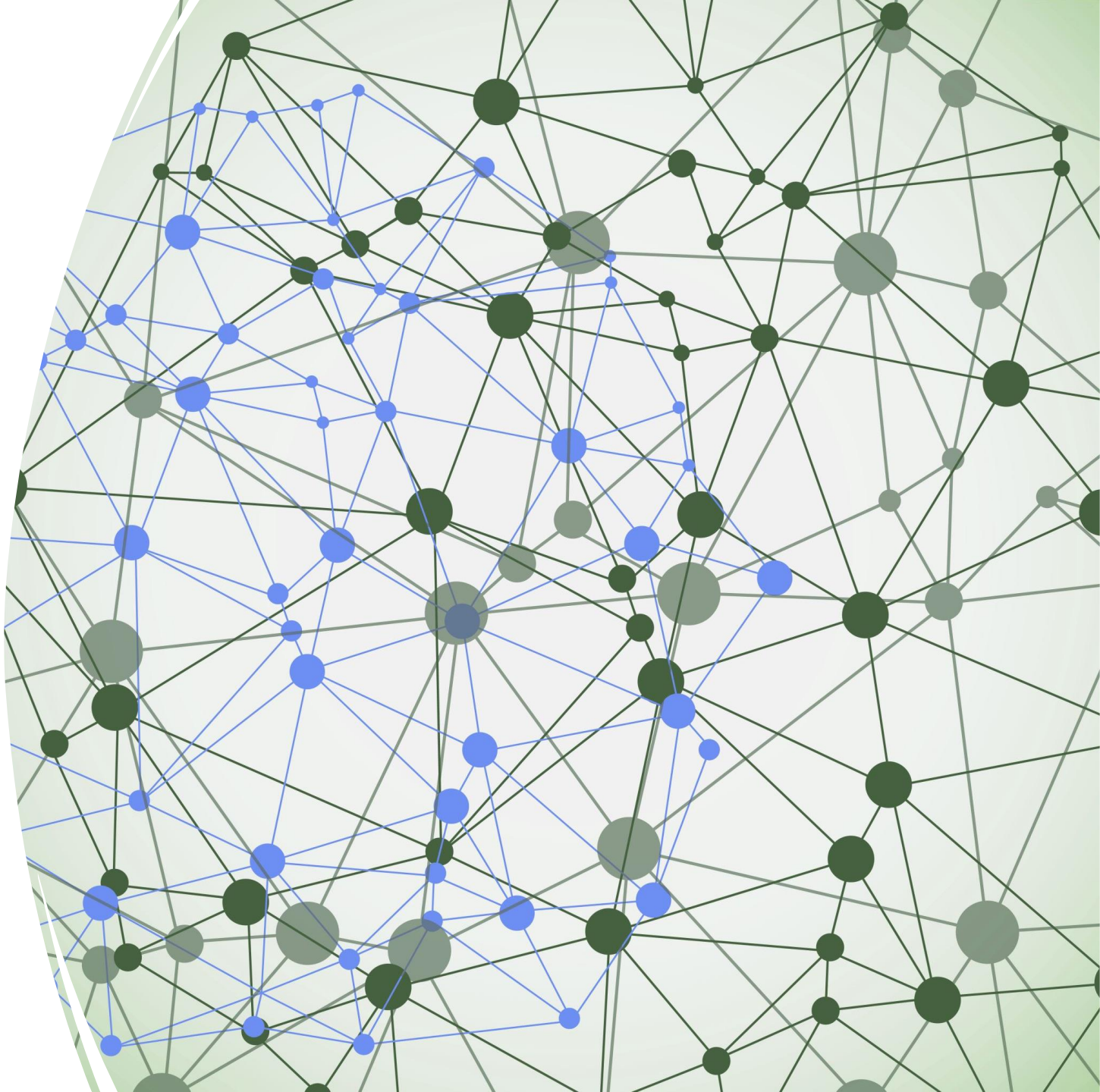
FLOW Trial

- Semaglutide in T2DM with CKD
  - eGFR 50-75 + UACR 300-5000 mg/g or
  - eGFR 25-50 + UACR 100-5000 mg/g
- Primary outcome – composite of kidney failure, ≥ 50% reduction in eGFR, Death from kidney failure, CV death.
- Stopped early based on interim analysis demonstrating efficacy
- A/W full publication – ADA 2024

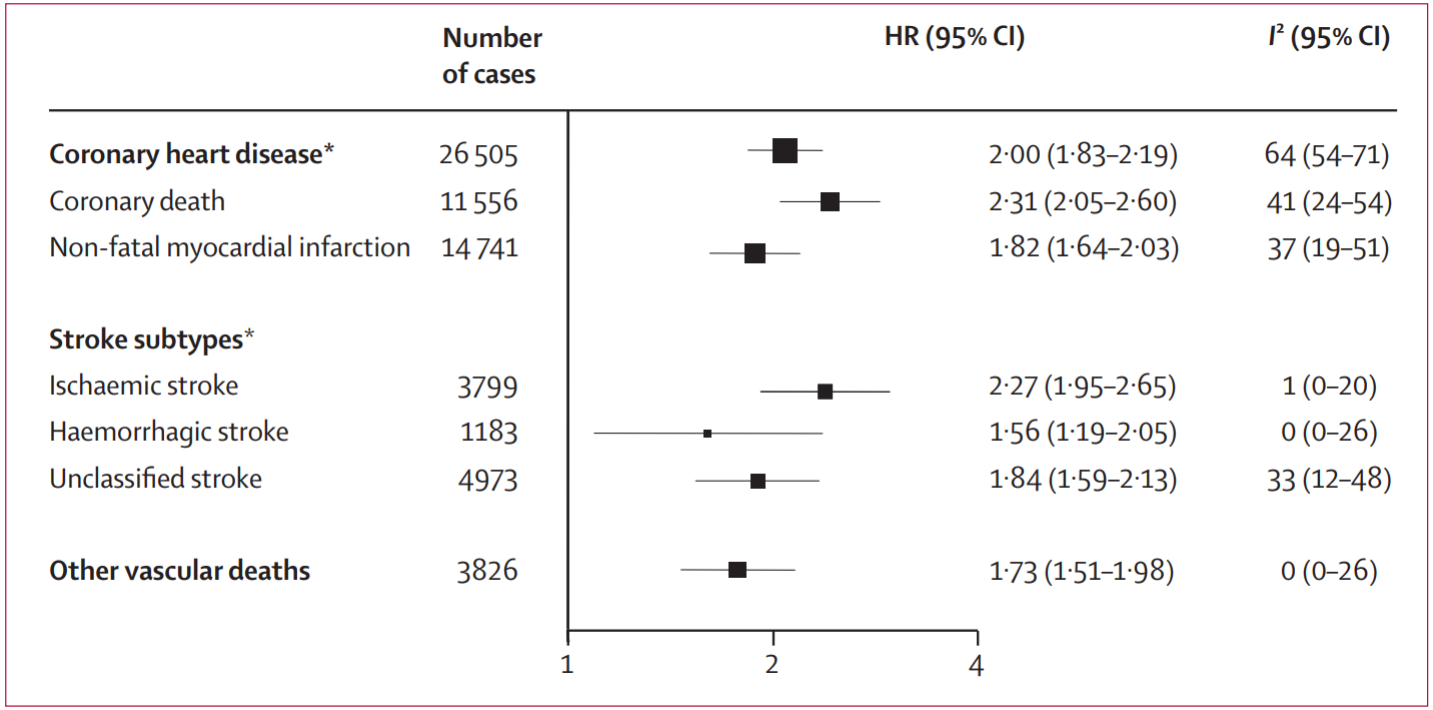
Eur Heart J Cardiovasc Pharmacother 2024; 10 (1): 7–9

Paradigm Shift in T2DM Management

Impact of CVOT



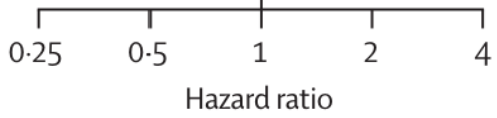
CV risk associated with diabetes



2x fold excess risk of CHD, stroke and CV mortality independently from other conventional risk factors compared to people without diabetes

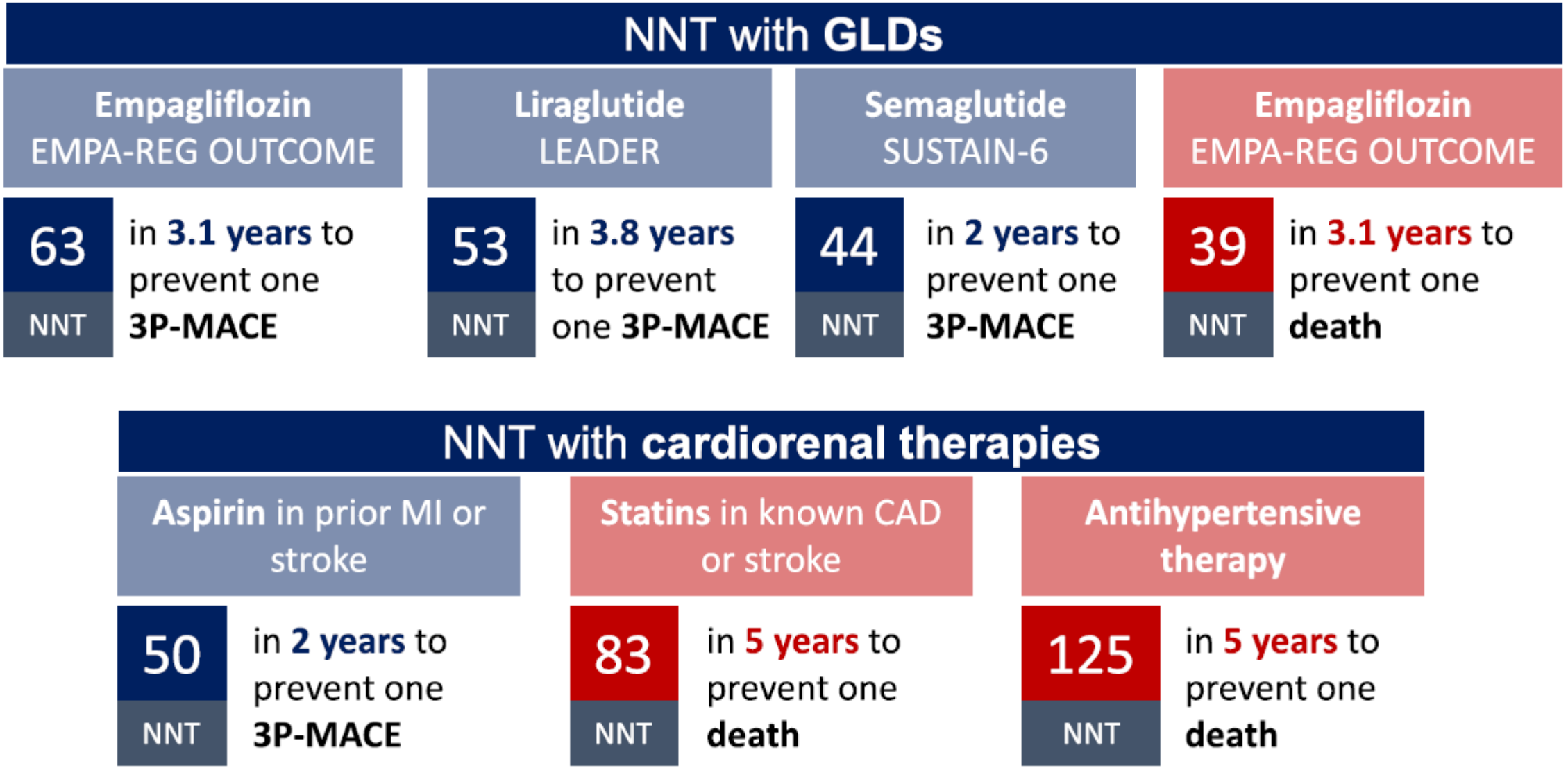
Lancet. 2010;375(9733):2215.

Initial presentation of cardiovascular disease	Number of events		Hazard ratio (95% CI)	p value
	No diabetes	Type 2 diabetes		
Stable angina	12 232	728	1·62 (1·49–1·77)	<0·0001
Unstable angina	5286	245	1·53 (1·32–1·76)	<0·0001
Non-fatal myocardial infarction	15 191	706	1·54 (1·42–1·67)	<0·0001
Unheralded coronary death	5101	255	1·43 (1·23–1·65)	<0·0001
Heart failure	13 072	866	1·56 (1·45–1·69)	<0·0001
Arrhythmia or sudden cardiac death	3218	100	0·95 (0·76–1·19)	0·65
Transient ischaemic attack	10 990	513	1·45 (1·31–1·60)	<0·0001
Ischaemic stroke	5643	316	1·72 (1·52–1·95)	<0·0001
Subarachnoid haemorrhage	1260	11	0·48 (0·26–0·89)	0·020
Intracerebral haemorrhage	2265	84	1·28 (1·02–1·62)	0·035
Peripheral arterial disease	10 074	992	2·98 (2·76–3·22)	<0·0001
Abdominal aortic aneurysm	3051	62	0·46 (0·35–0·59)	<0·0001



cohort study in 1·9 million people (98·2% without diabetes, 1.8% with T2DM)

Lancet Diabetes Endocrinol 2015; 3: 105–13



Davies *et al. Cardiovascular Diabetology (2022) 21:144*

Effect of CVOT on Diabetes Guidelines

The current guidelines signify a significant shift in the management approach for individuals with T2DM

Previous guidelines primarily emphasized the management of hyperglycemia, as indicated by HbA1c levels.

Current guidelines broaden their scope to encompass the management of cardiorenal risk aiming to reduce CV-related deaths and hospitalizations in patients with T2DM.

NICE 2022

How to choose first-line medicines

NICE National Institute for Health and Care Excellence

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or a sulfonylurea and review when blood glucose control has been achieved.

First-line treatment — Assess HbA1c, cardiovascular risk and kidney function

For information on using SGLT2 inhibitors for people with type 2 diabetes and chronic kidney disease see the section on diabetic kidney disease in the guideline.

Not at high CVD risk

Offer
- Metformin

Or if GI disturbance
- Metformin MR

Chronic heart failure or established atherosclerotic CVD

Offer
- Metformin

or if GI disturbance
- Metformin MR

and as soon as metfomin tolerability is confirmed, offer
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

High risk of CVD
QRISK2 of 10% or higher or elevated lifetime risk

Offer
- Metformin

or if GI disturbance
- Metformin MR

and as soon as metfomin tolerability is confirmed, consider
- SGLT2 inhibitor ('flozin') with proven cardiovascular benefit

Start metformin alone to assess tolerability before adding an SGLT2 inhibitor

Consider
- DPP-4 inhibitor ('gliptin') or
- Pioglitazone or
- Sulfonylurea

An SGLT2 inhibitor ('flozin') for some people:
- TA 390 Canagliflozin
- TA 390 Dapagliflozin
- TA 390 Empagliflozin
- TA 572 Ertugliflozin

If metformin contraindicated

Offer
- SGLT2 inhibitor alone

If metformin contraindicated

Consider
- SGLT2 inhibitor alone

If metformin contraindicated

NICE technology appraisals recommend SGLT2 inhibitors as monotherapy options in people:
- who cannot have metformin
- for whom diet and exercise alone do not provide adequate glycaemic control.

The SGLT2 inhibitors are recommended only if a dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and a sulfonylurea or pioglitazone is not appropriate.

In February 2022, using ertugliflozin to reduce cardiovascular risk when blood glucose is well controlled was off label. See NICE's information on prescribing medicines.

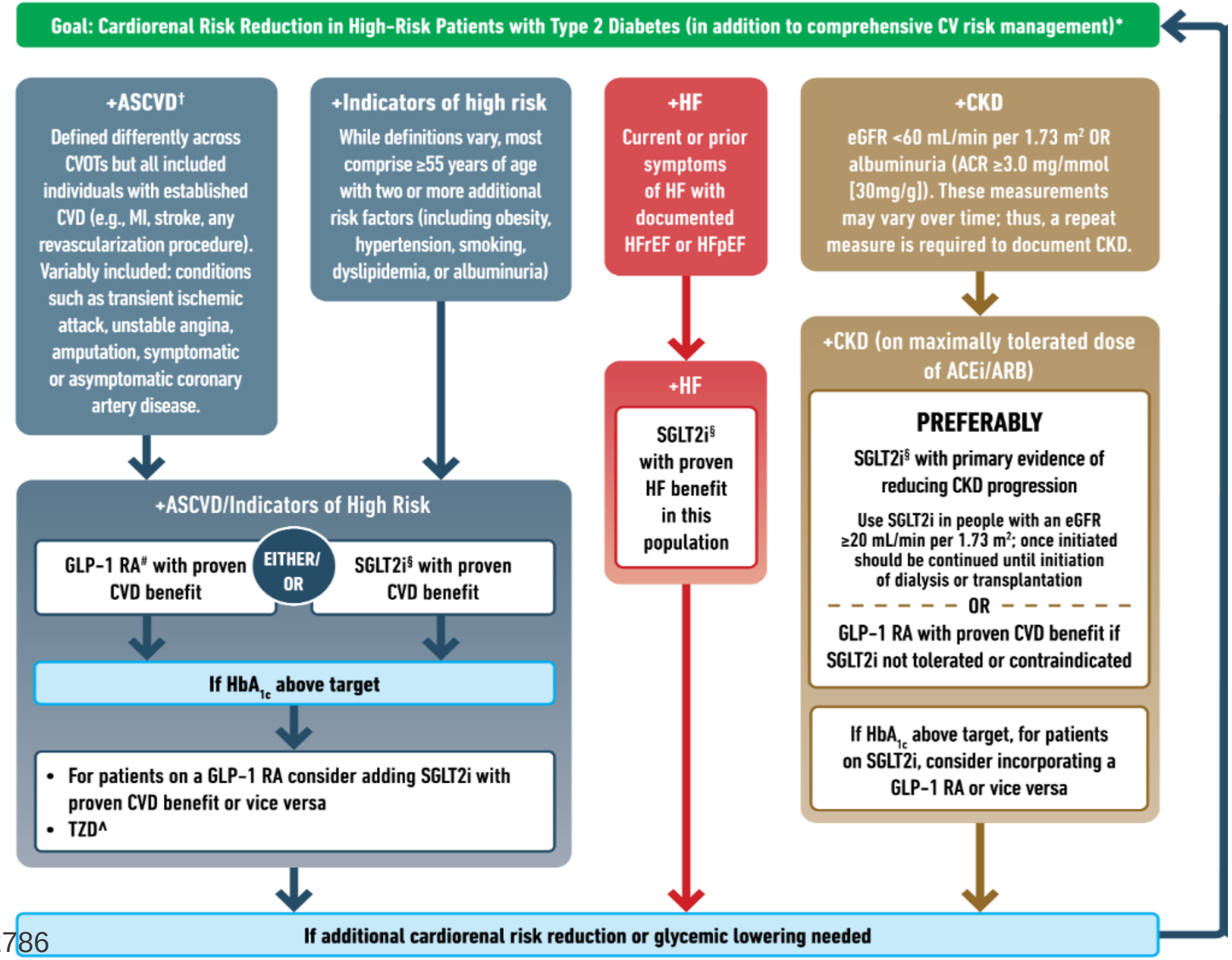
Person's HbA1c not controlled below individually agreed threshold, or the person develops CVD or a high risk of CVD

See treatment options if further interventions are needed

Established atherosclerotic CVD includes coronary heart disease, acute coronary syndrome, previous myocardial infarction, stable angina, prior coronary or other revascularisation, cerebrovascular disease (ischaemic stroke and transient ischaemic attack) and peripheral arterial disease.

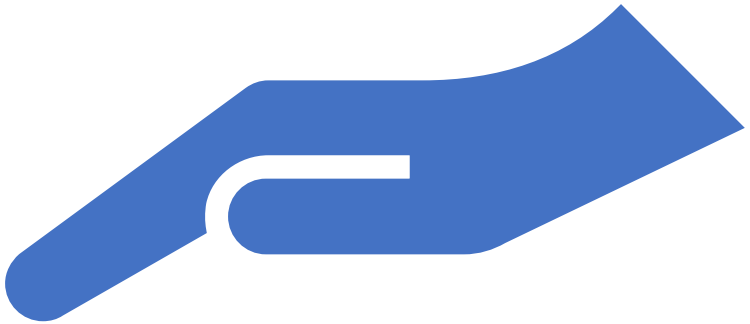
Published date: February 2022. Last updated: August 2022. This is a summary of the advice in the NICE guideline on type 2 diabetes in adults: management.

ADA/ EASD 2022



Diabetes Care 2022;45(11):2753–2786

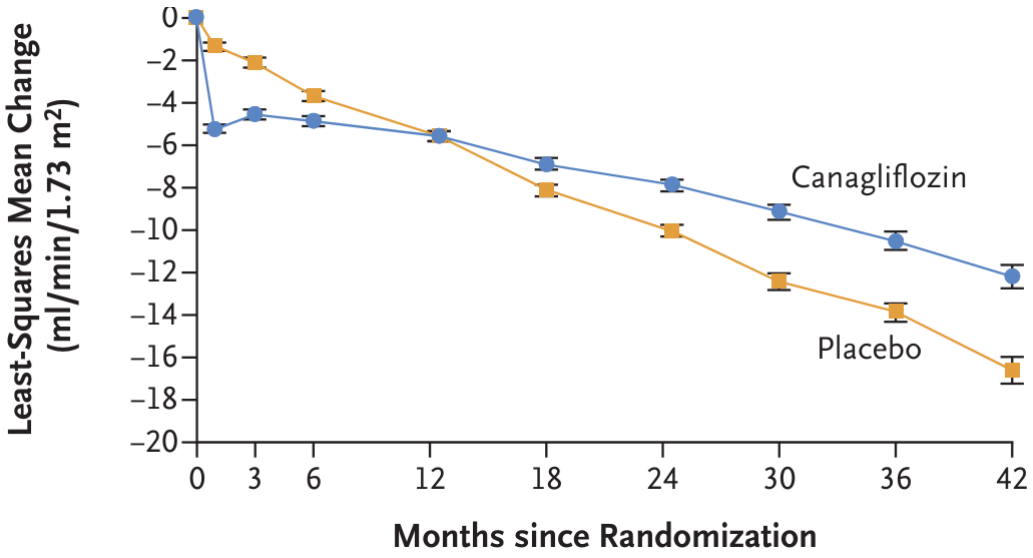
Safety

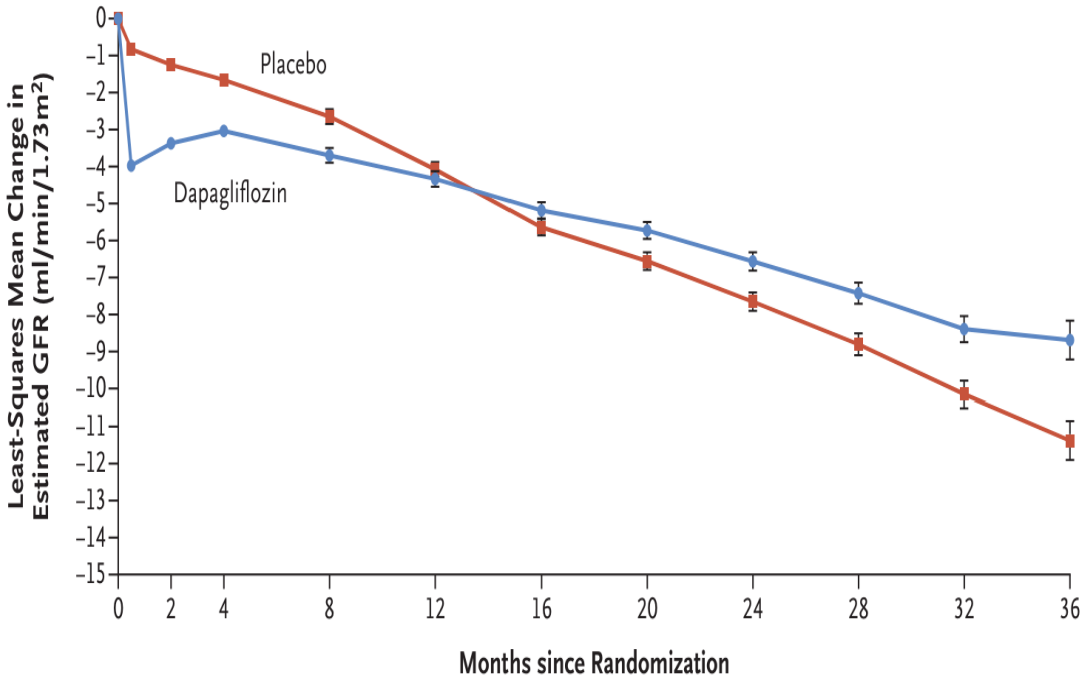


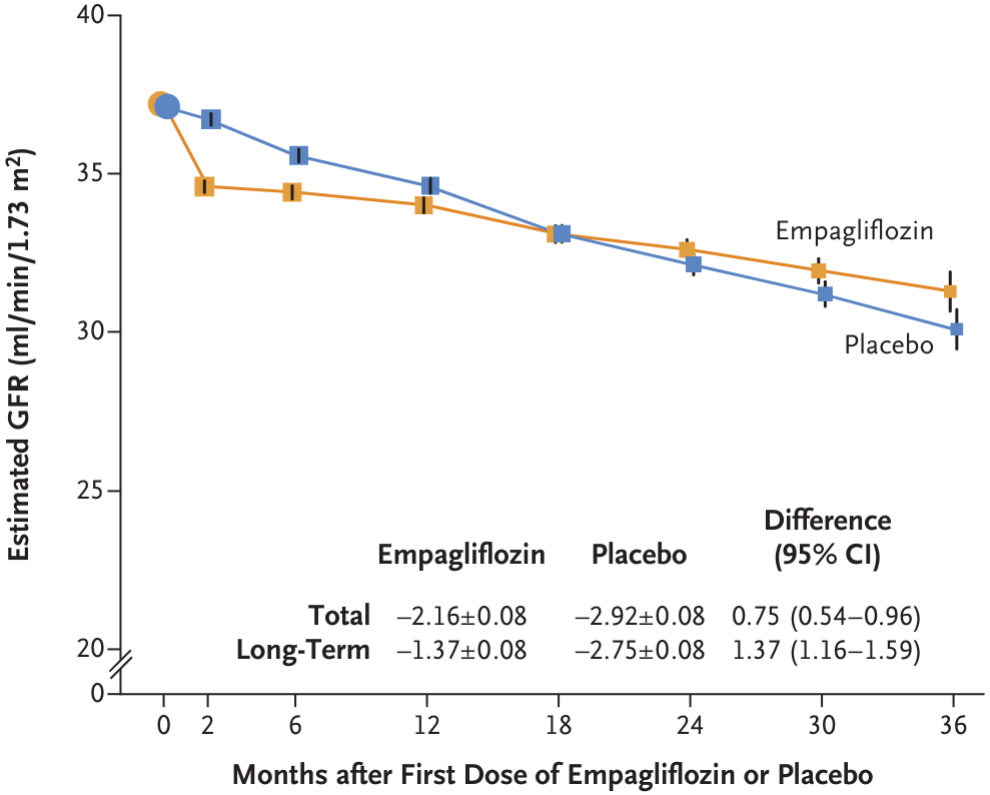
SGLT2 inhibitors – side effects

- **Mycotic genital infection** – common, more in women (e.g. ~10% of women develops vulvovaginal candidiasis) but usually mild and treatable
- **Hypotension/volume depletion -** esp. in elderly, concomitant ACE inhibitors/ARBs/diuretics.
- **DKA** – SGLT2i increases risk of DKA (can be euglycaemic) – 2-fold increase compared to other antihyperglycaemic agents, incidence is 0.1-0.6% in RCTs
- **? Amputations (toes and midfoot)** – with canagliflozin* (MHRA/EMA warning)
- **UTI and Fournier's gangrene** (FDA/MHRA warning)
- **No strong evidence** – AKI, fractures

Effect of SGLT2i on eGFR

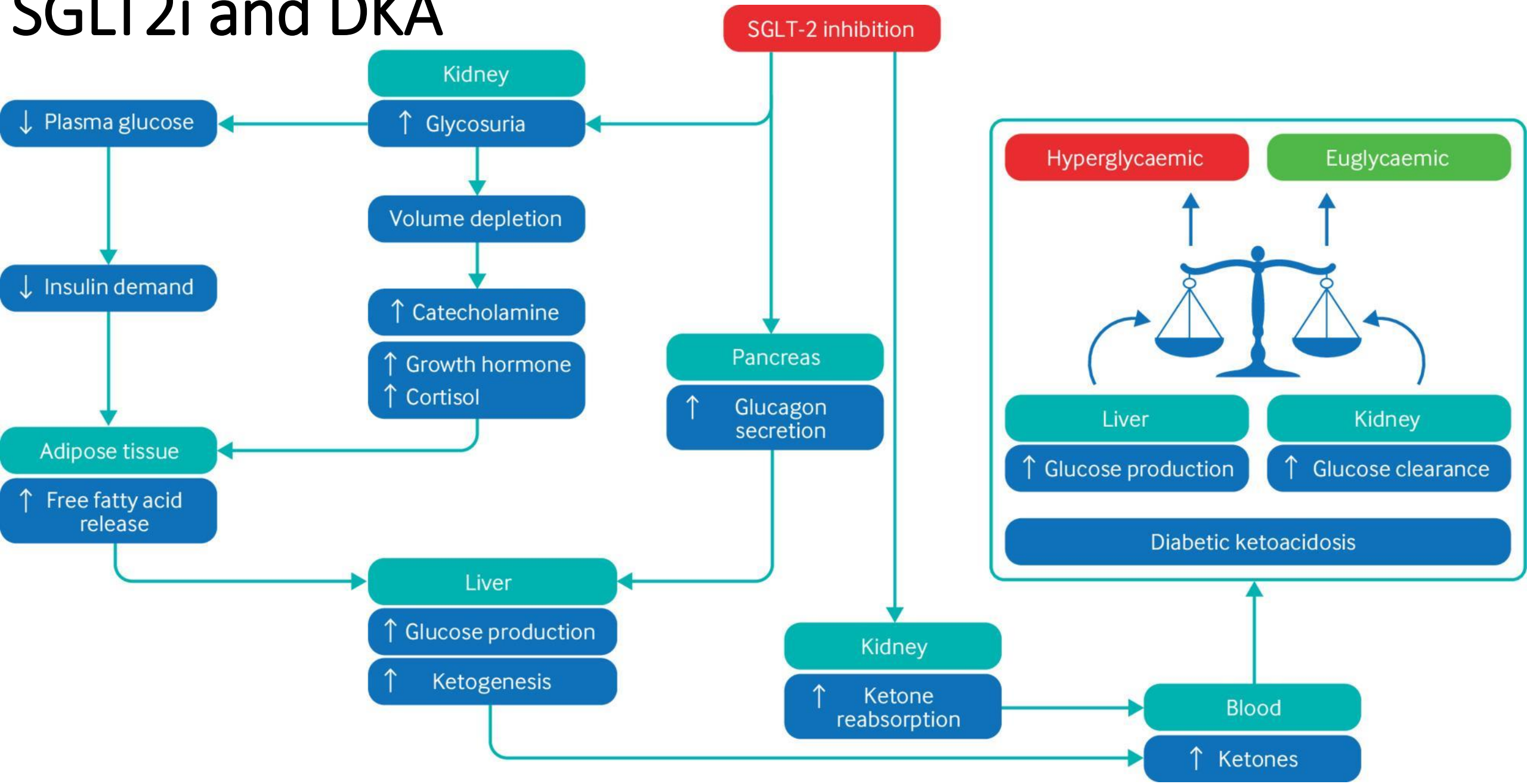






N Engl J Med 2019;380:2295-306
N Engl J Med 2020;383:1436-46
N Engl J Med 2023;388:117-27.

SGLT2i and DKA



BMJ 2020;371:m4147

Avoid DKA with SGLT2i – Patient selection

- **Avoid**
  - T1DM
  - Unwell person (acute infection/sepsis)
  - Planned surgery/procedure (at least one day before surgery)
  - Patient with previous DKA (unless a clear cause was identified)
  - Excess alcohol intake
- **Caution**
  - VLCD or ketogenic diet (delay starting SGLT2i until the diet change)
  - People with cognitive impairment (may interfere with adequate understanding of sick day rules)
  - Very high HbA1c (>86 mmol/mol) or symptomatic hyperglycaemia

Diabetes Ther . 2024 ;15(5):1099-1124.
Guideline for Perioperative Care for People with Diabetes Mellitus Undergoing Elective and Emergency Surgery, 2022

Avoid DKA with SGLT2i – Patient education

- **Symptoms of DKA**

  Nausea, vomiting, abdominal pain, difficulty breathing (Kusmmaul breathing), sweet smelling (pear-drop) breath

- **Sick day rules (Give written information)**
  - Stop the SGLT2i if the patient is
    1. Acute dehydrating illness (e.g. diarrhoea or vomiting) or unable to eat/drink normally.
    2. Fever/infection – seek medical advice if seriously unwell
    3. Admission for elective surgery or procedure requiring fasting – omit SGLT2i one day before surgery/procedure.
  - SGLT2i can be restarted **ONLY** after the patient starts to eat and drink normally for 24 hour and no longer acutely unwell.

GLP1-RA – side effects

- GI – nausea, vomiting and diarrhea
  - Common but tend to improve over time
  - Gradual up-titration is important
  - Educate the patient on the difference between satiety (positive) and nausea (negative)
- Gallstones and cholecystitis
- No evidence
  - Acute Pancreatitis
  - Medullary thyroid cancer
  - Worsening of retinopathy (rapid glycaemic control does!)

Prescribing

Which SGLT2-i should I use in T2DM?

Comorbidities	Best agent
None (SGLT2i used for glycaemic control)	Any
Heart failure	Dapagliflozin or Empagliflozin
ASCVD	Empagliflozin or Canagliflozin
CKD	Canagliflozin, Dapagliflozin or Empagliflozin

SGLT2 inhibitors used for Glycaemic control

	Daily Dose (once daily)
Canagliflozin	eGFR ≥ 60 – initiate at 100 mg and titrate to 300 mg if needed eGFR < 60 – 100 mg eGFR < 45 – low glycaemic efficacy
Dapagliflozin	eGFR ≥ 45 – 10 mg eGFR < 45 – low glycaemic efficacy
Empagliflozin	eGFR ≥ 60 – initiate at 10 mg and titrate to 25 mg if needed eGFR 30- 60 – 10 mg once daily. eGFR < 45 – low glycaemic efficacy

SGLT2 inhibitors for CKD/HF

	Indication	Daily Dose (once daily)
Canagliflozin	DKD in T2DM	eGFR ≥ 30 – initiate or continue 100 mg eGFR < 30 – Do not initiate. Continue 100 mg if uACR ≥ 30 mg/mmol (can be continued to dialysis or renal transplantation)
Dapagliflozin	CKD – eGFR 25-75 ml/min + either T2DM or uACR ≥ 22.6 mg/mmol Symptomatic chronic heart failure (HFrEF and HFpEF) in adults with or without diabetes	eGFR ≥ 15 – initiate or continue 10 mg eGFR < 15 – do not initiate but can be continued
Empagliflozin	CKD – eGFR 20-45 ml/min or eGFR 45-90 ml/min + either T2DM or uACR ≥ 22.6 mg/mmol Symptomatic chronic heart failure (HFrEF and HFpEF) in patients with or without diabetes	eGFR ≥ 20 – initiate or continue 10 mg eGFR < 20 – do not initiate but can be continued

GLP1-RA and GLP1/GIP-RA

GLP1-RA	Brand name (route)	Frequency	Dose (mg)	Titration schedule
Liraglutide	Victoza (SC)	Daily	0.6 → 1.2 → 1.8	Weekly
SC Semaglutide	Ozempic (SC)	Weekly	0.25 → 0.5 → 1	4-weekly
Oral Semaglutide	Rybelsus (oral)	Daily	3 → 7 → 14	Monthly
Dulaglutide	Trulicity (SC)	Weekly	0.75 → 1.5 → 3.0 → 4.5	4-weekly
Tirzepatide	Mounjaro (SC)	Weekly	2.5 → 5 → 7.5 → 10 →12.5 →15.0	4-weekly

Avoid in End-stage renal disease (eGFR < 15 ml/min) – limited experience

Effect on HbA1c reduction Tirzepatide > Semaglutide > Dulaglutide and Liraglutide
Effect on weight reduction Tirzepatide > Semaglutide > Liraglutide > Dulaglutide

Home message (1)

SGLT2 inhibitors have shown effectiveness in reducing major adverse cardiovascular events (MACE), hospitalization for heart failure (HHF), and improving kidney outcomes

GLP1-RA demonstrate a reduction in MACE, particularly noteworthy in lowering stroke incidence, while emerging evidence suggests renal benefits. However, significant benefits in heart failure have not been observed.

Even if HbA1c is within target range, SGLT2 inhibitors should still be prescribed for their cardiorenal benefits, if indicated.

Home Message (2)

It's essential for all physicians to proactively consider prescribing these medications or liaising with primary care to ensure their prescription.

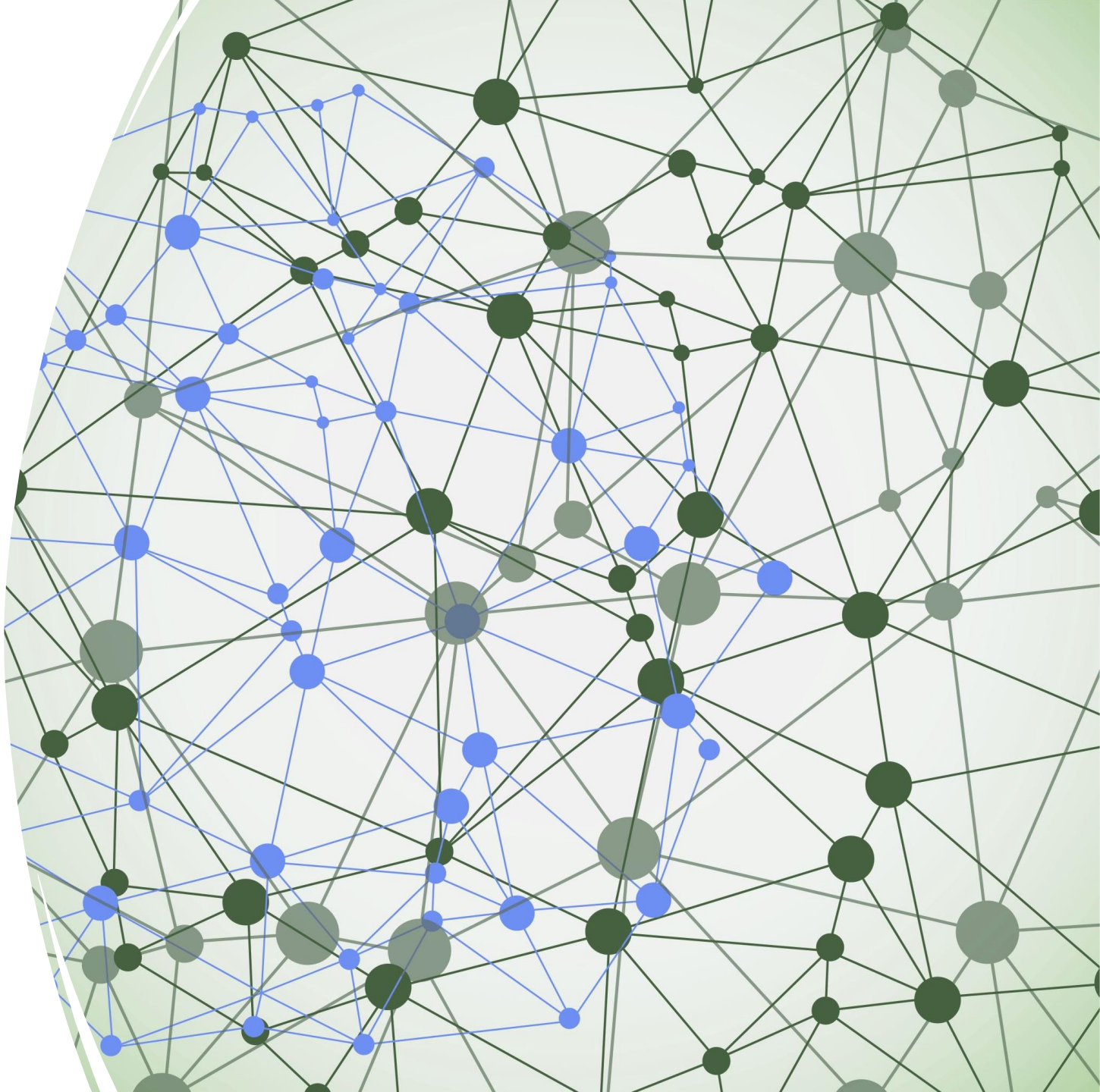
It's crucial to inform patients about the risk of DKA with SGLT2i and provide written guidance on sick day rules.

SGLT2i should be temporarily withheld during acute illness admissions.

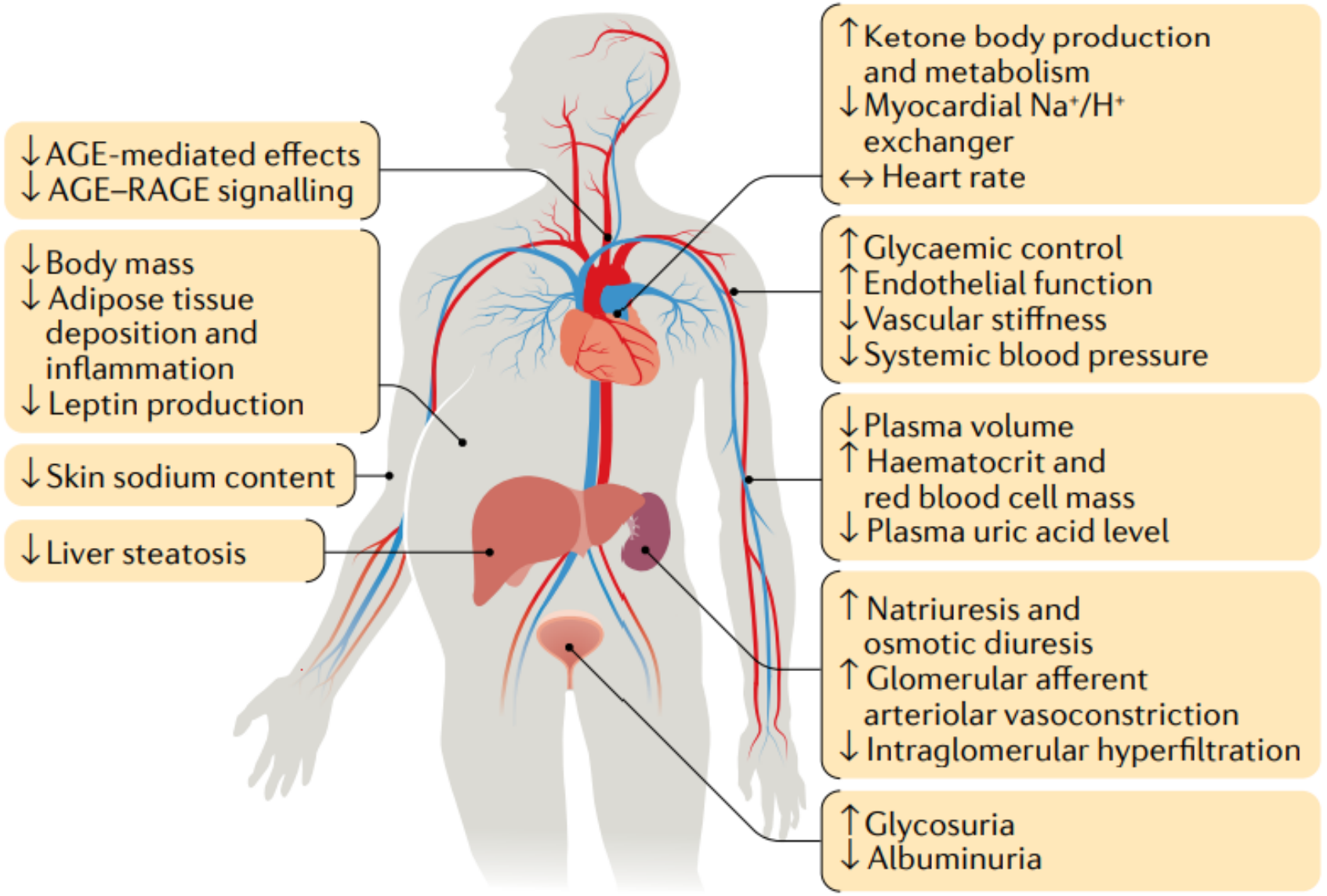
Thank You

Ahmed.Hanafy@nhs.net

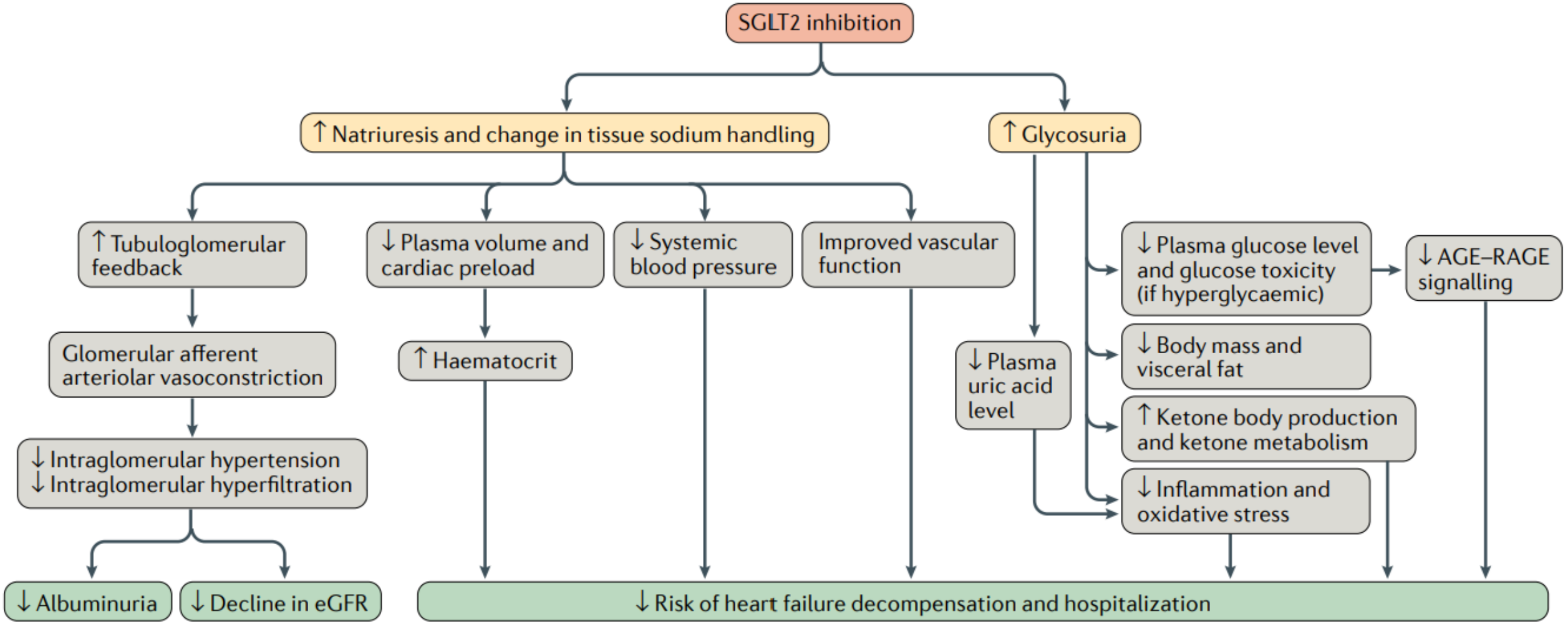
Mechanism of benefits



Mechanisms of Cardiorenal benefits of SGLT2i



Nat Rev Cardiol **17**, 761–772 (2020)



Nat Rev Cardiol **17**, 761–772 (2020)

Mechanism of CV benefits of GLP-1RA

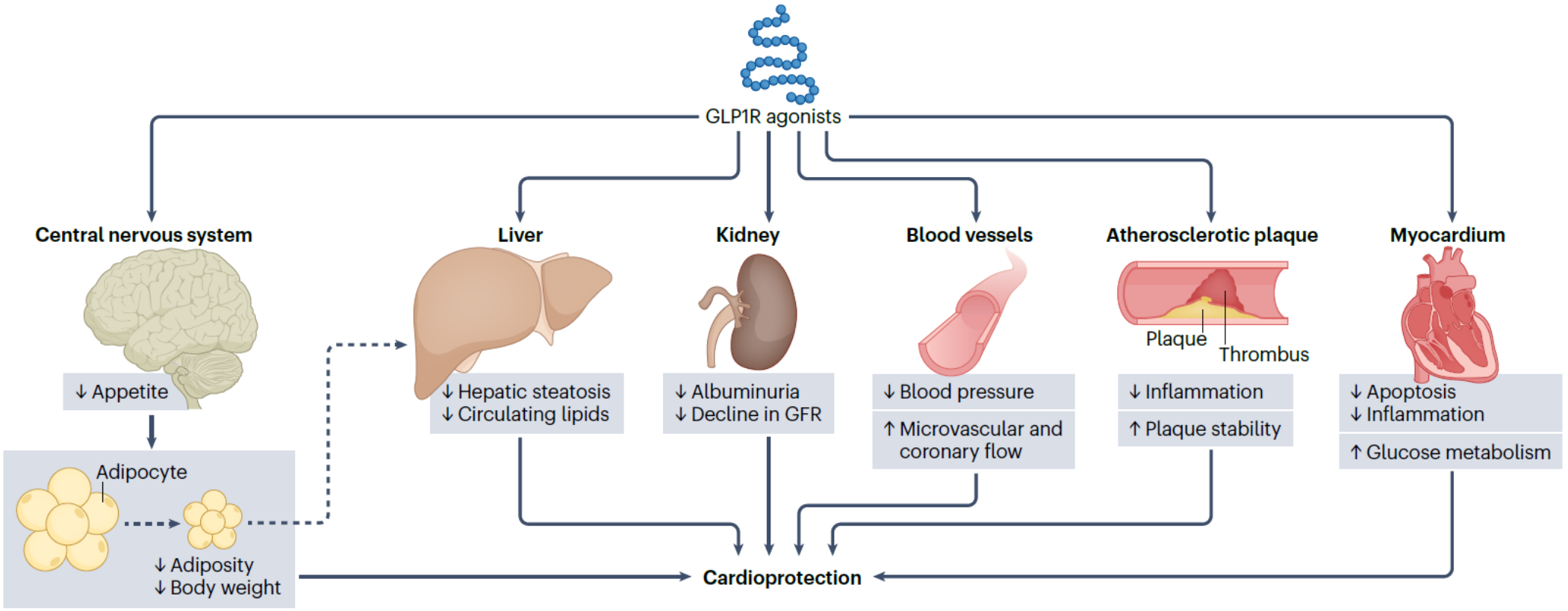
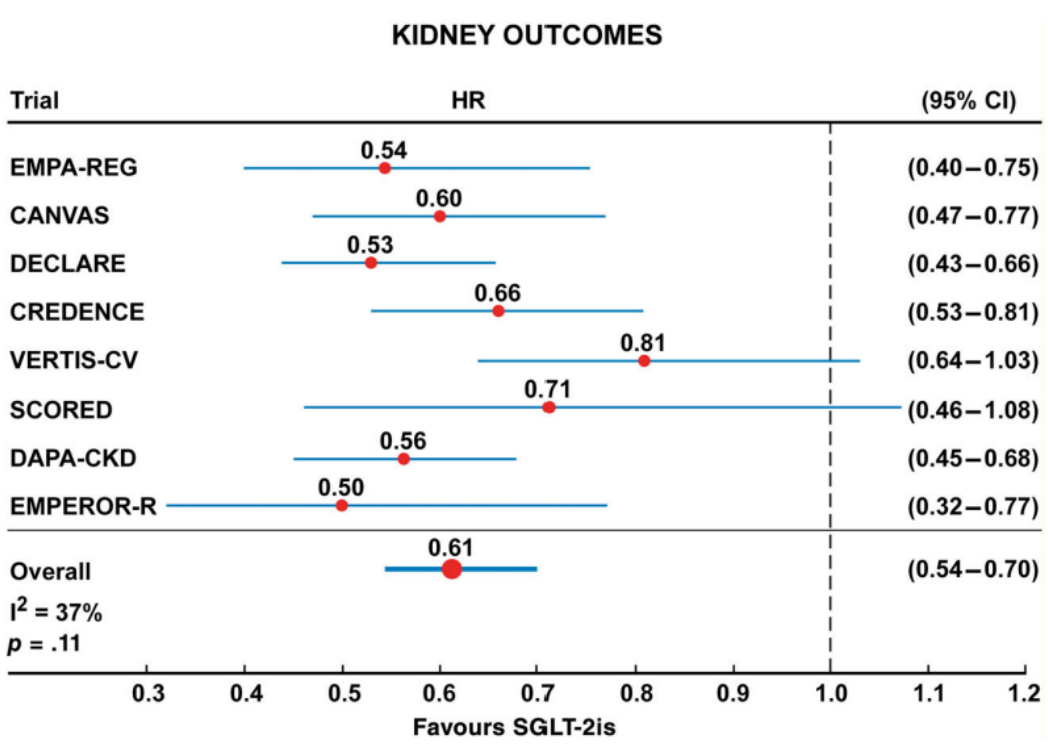
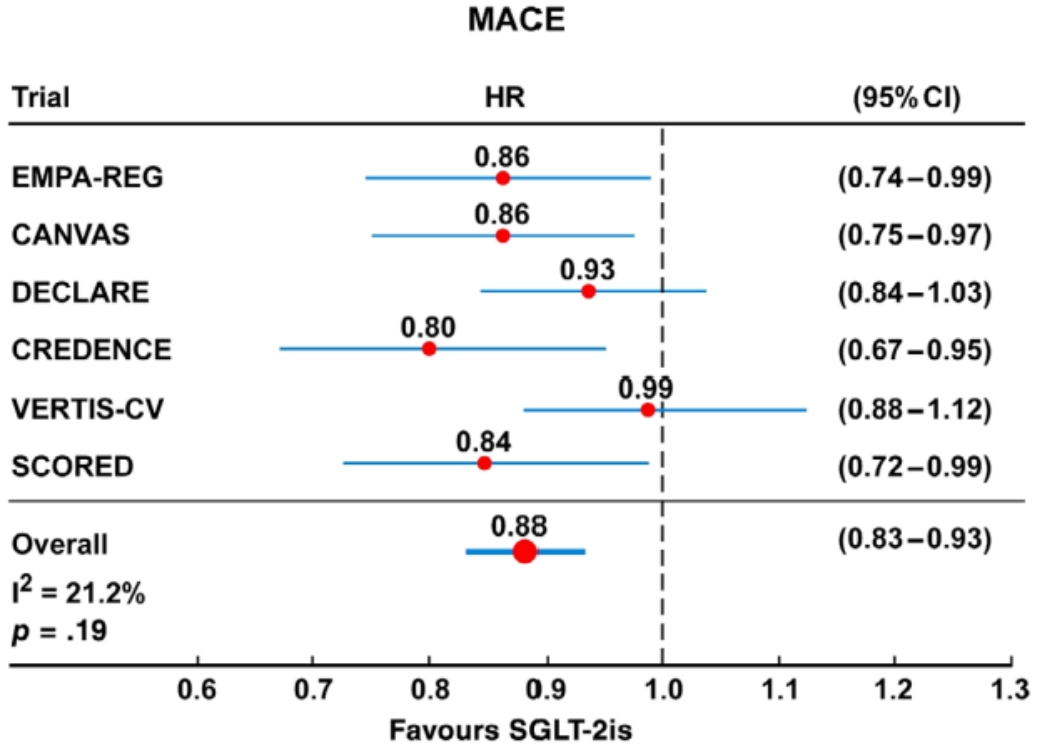


Fig. 3 | Direct and indirect actions of GLP1R agonist-mediated cardioprotection. Glucagon-like peptide 1 receptor (GLP1R) agonists might improve cardiovascular outcomes by acting on the central nervous system to reduce appetite and body weight, while indirectly improving circulating lipid profiles via a reduction in hepatic steatosis. GLP1R agonists might also have direct and indirect effects on blood vessels to improve blood flow and reduce atherosclerosis, on the kidney to preserve renal function, and on the heart to help to prevent myocardial infarction or limit infarct size. GFR, glomerular filtration rate.

Nat Rev Cardiol **20**, 463–474 (2023)

Evidence from Meta-analysis of CVOT

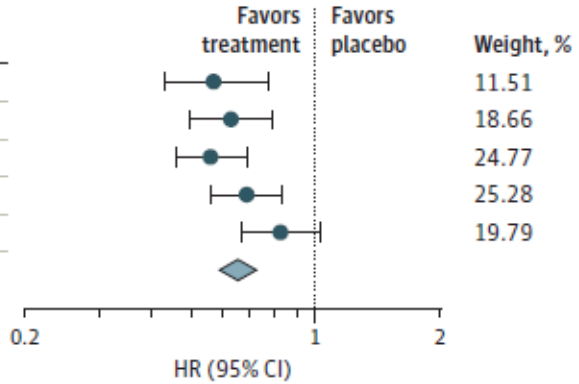




Diabetes Obes Metab. 2021;1–5.

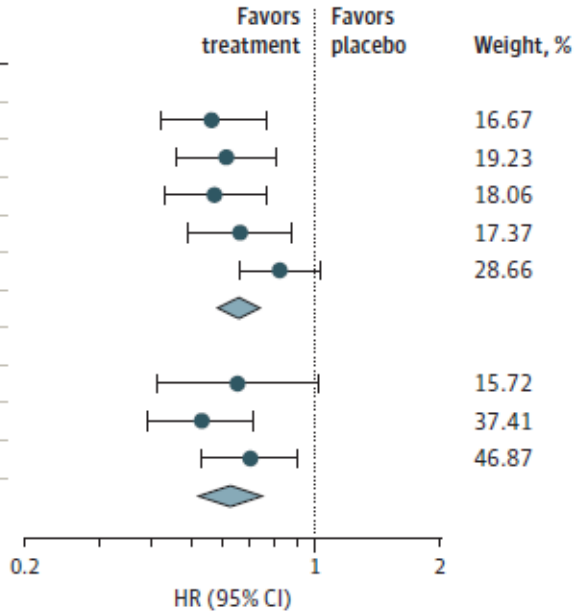
A Overall kidney outcomes

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/5795	5.5	NA/4347	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	127/8582	3.7	238/8578	7.0	0.53 (0.43-0.66)
CREDENCE	153/2202	27.0	224/2199	40.4	0.66 (0.53-0.81)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 7.96; *df* = 4; *P* = .09; I^2 = 49.7%)					0.62 (0.56-0.70)



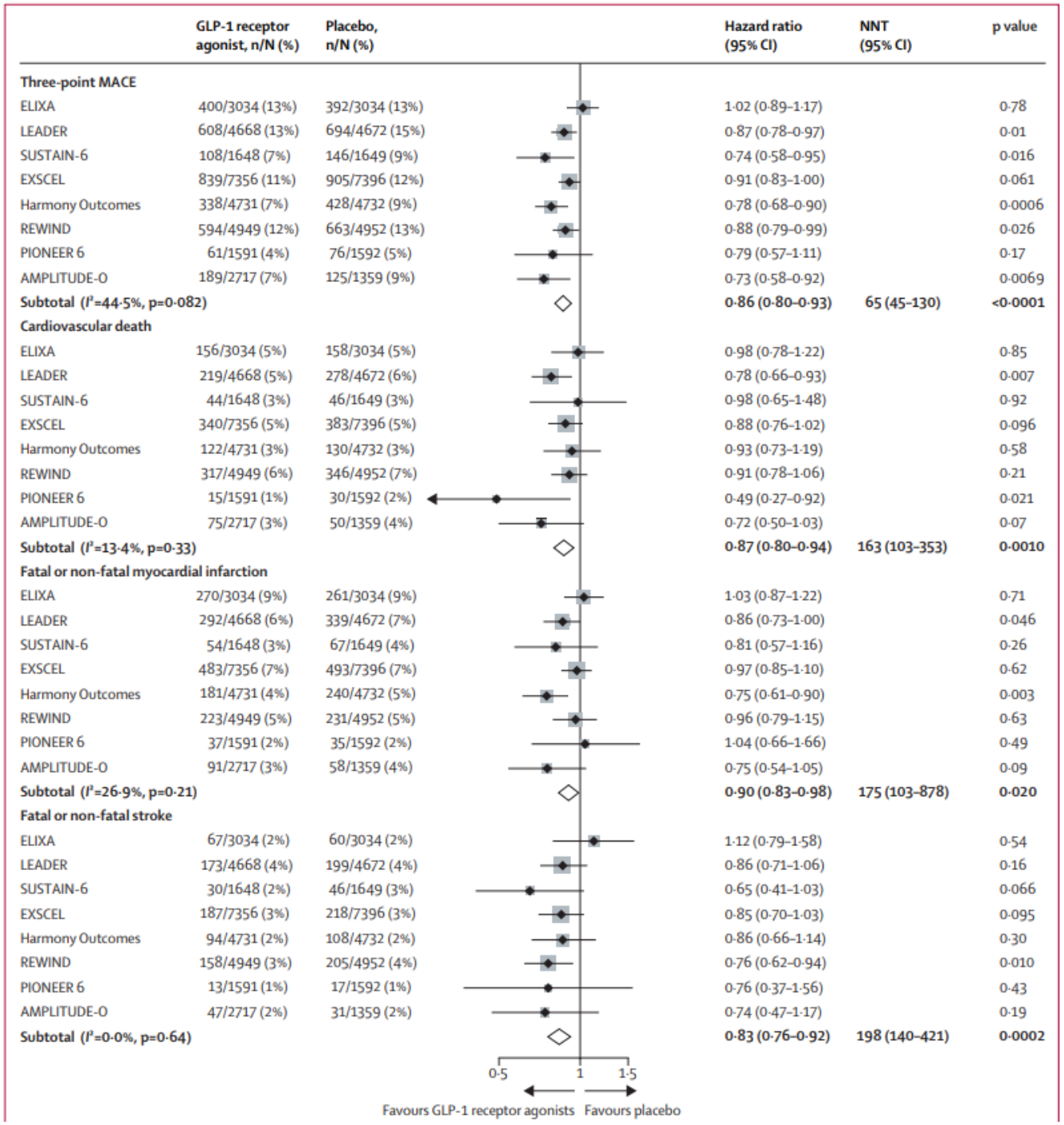
B Kidney outcomes by ASCVD status

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
Patients with ASCVD					
EMPA-REG OUTCOME	81/4645	6.3	71/2323	11.5	0.54 (0.40-0.75)
CANVAS program	NA/3756	6.4	NA/2900	10.5	0.59 (0.44-0.79)
DECLARE-TIMI 58	65/3474	4.7	118/3500	8.6	0.55 (0.41-0.75)
CREDENCE	69/1113	24.1	102/1107	36.5	0.64 (0.47-0.87)
VERTIS CV	175/5499	9.3	108/2747	11.5	0.81 (0.64-1.03)
Fixed-effects model (Q = 6.09; *df* = 4; *P* = .19; I^2 = 34.4%)					0.64 (0.56-0.72)
Patients without ASCVD					
CANVAS program	NA/2039	4.1	NA/1447	6.6	0.63 (0.39-1.02)
DECLARE-TIMI 58	62/5108	3.0	120/5078	5.9	0.51 (0.37-0.69)
CREDENCE	84/1089	29.9	122/1092	44.3	0.68 (0.51-0.89)
Fixed-effects model (Q = 1.86; *df* = 2; *P* = .40; I^2 = 0.0%)					0.60 (0.50-0.73)



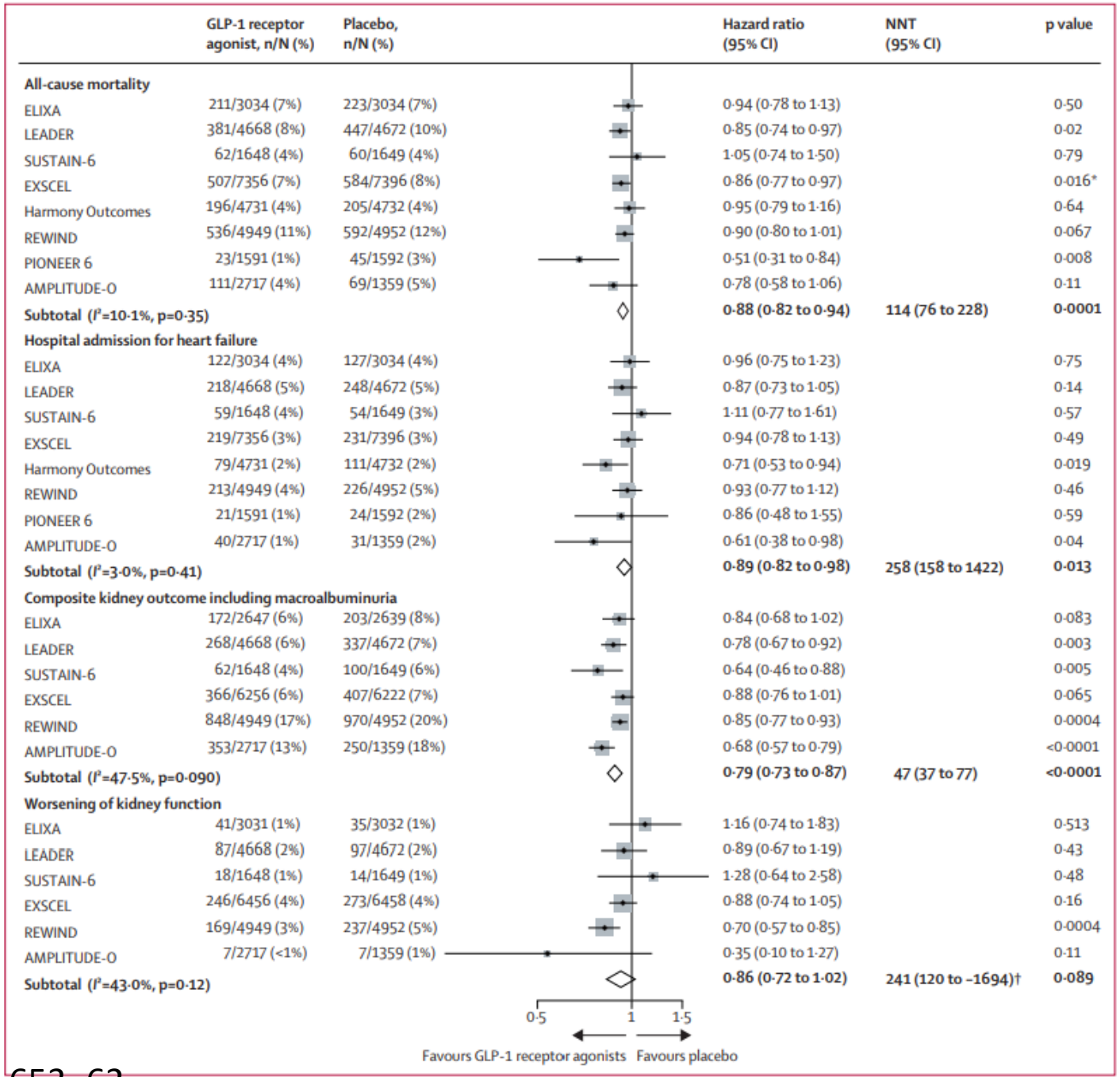
JAMA Cardiol. 2021;6(2):148-158

GLP1-RA reduces 3P-MACE and all its component with major effect on reducing stroke followed by CV death and MI



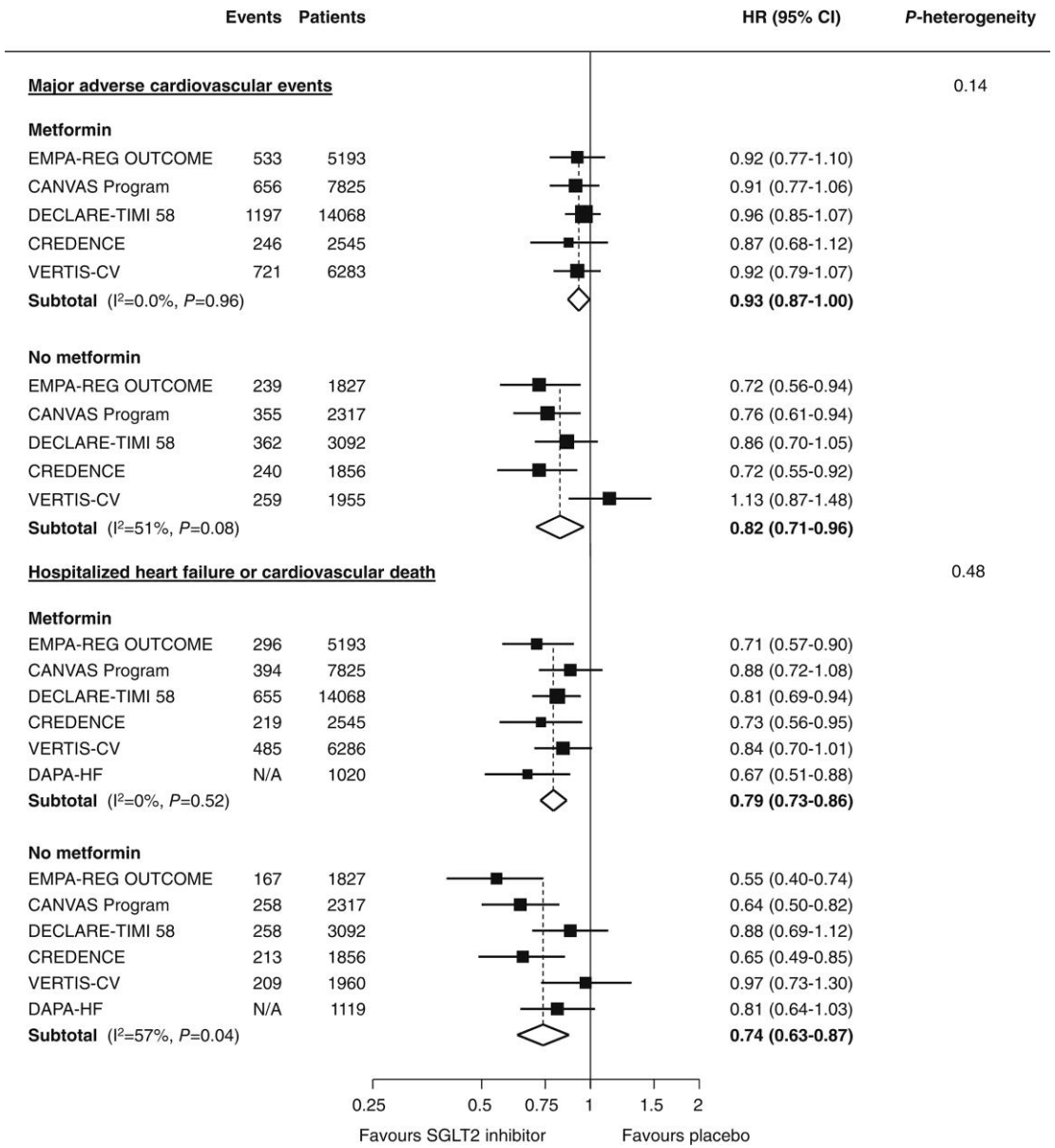
	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)	0·87 (0·78–0·97)		0·01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0·74 (0·58–0·95)		0·016
EXSCEL	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**
Cardiovascular death					
ELIXA	156/3034 (5%)	158/3034 (5%)	0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)	0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)	0·91 (0·78–1·06)		0·21
PIONEER 6	15/1591 (1%)	30/1592 (2%)	0·49 (0·27–0·92)		0·021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0·72 (0·50–1·03)		0·07
Subtotal (I^2=13·4%, p=0·33)			**0·87 (0·80–0·94)**	**163 (103–353)**	**0·0010**
Fatal or non-fatal myocardial infarction					
ELIXA	270/3034 (9%)	261/3034 (9%)	1·03 (0·87–1·22)		0·71
LEADER	292/4668 (6%)	339/4672 (7%)	0·86 (0·73–1·00)		0·046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0·81 (0·57–1·16)		0·26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0·97 (0·85–1·10)		0·62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0·75 (0·61–0·90)		0·003
REWIND	223/4949 (5%)	231/4952 (5%)	0·96 (0·79–1·15)		0·63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1·04 (0·66–1·66)		0·49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0·75 (0·54–1·05)		0·09
Subtotal (I^2=26·9%, p=0·21)			**0·90 (0·83–0·98)**	**175 (103–878)**	**0·020**
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1·12 (0·79–1·58)		0·54
LEADER	173/4668 (4%)	199/4672 (4%)	0·86 (0·71–1·06)		0·16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0·65 (0·41–1·03)		0·066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0·85 (0·70–1·03)		0·095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0·86 (0·66–1·14)		0·30
REWIND	158/4949 (3%)	205/4952 (4%)	0·76 (0·62–0·94)		0·010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0·76 (0·37–1·56)		0·43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0·74 (0·47–1·17)		0·19
Subtotal (I^2=0·0%, p=0·64)			**0·83 (0·76–0·92)**	**198 (140–421)**	**0·0002**

Lancet Diabetes Endocrinol 2021 9: 653–62

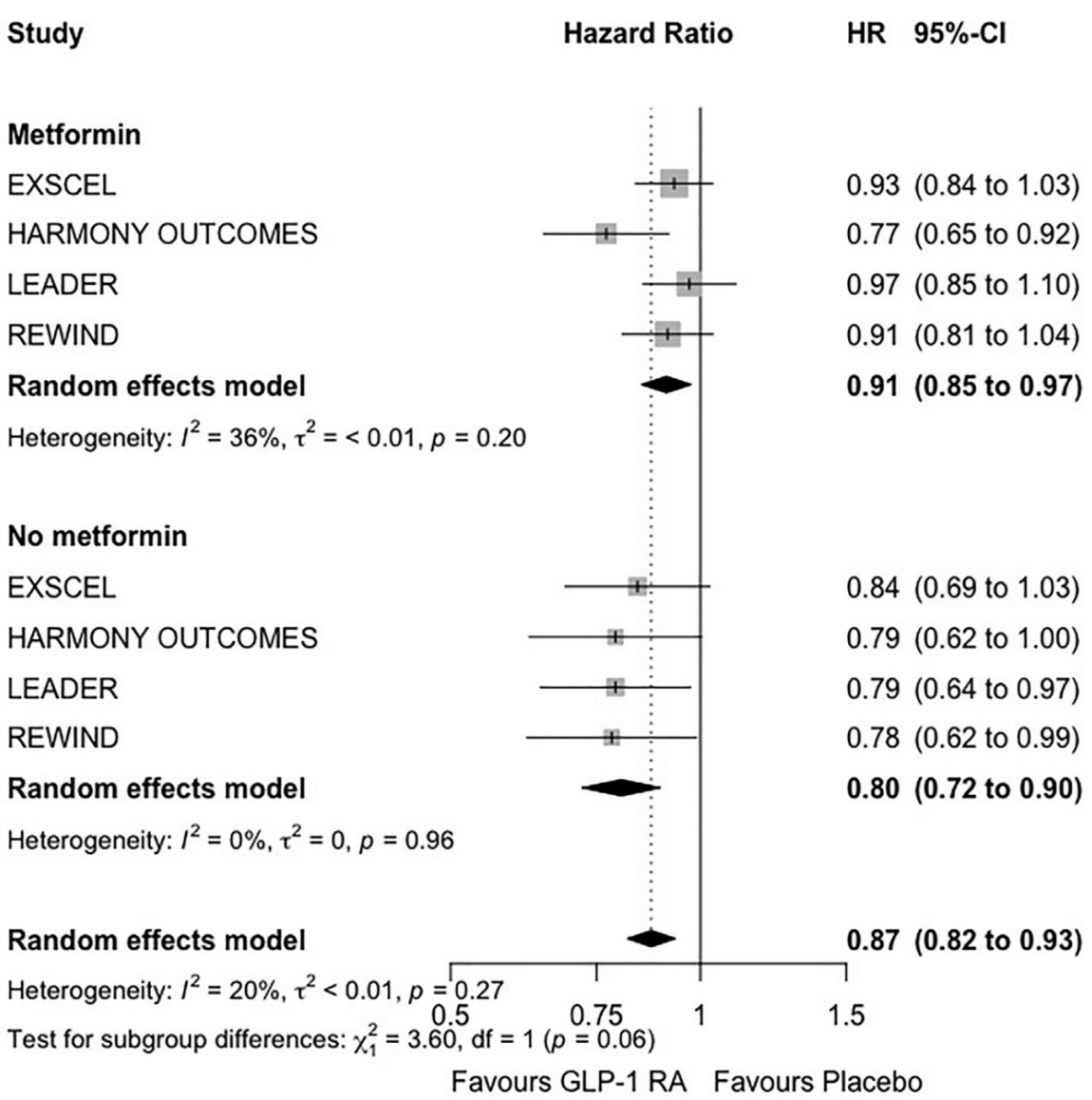


Lancet Diabetes Endocrinol 2021 9: 653–62

Does CV benefits depend on the use of metformin?

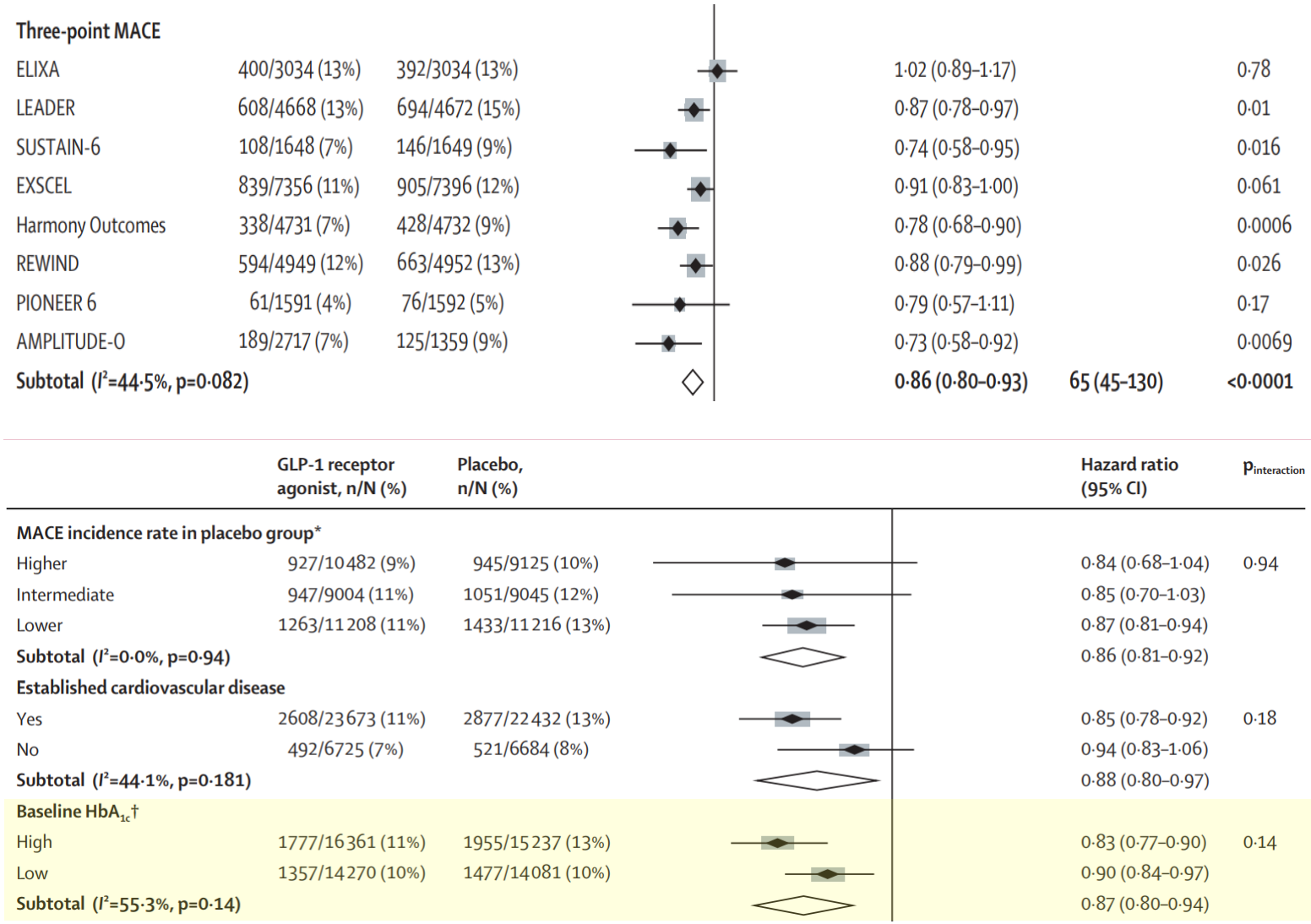


Diab Obes Metab 2021;23:382-390



Diabetes Res Clin Pract. 2021;177:108921

Does CV benefits depend on baseline HbA1c?



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	GLP-1 receptor agonist, n/N (%)	Placebo, n/N (%)	Hazard ratio (95% CI)	$p_{interaction}$
MACE incidence rate in placebo group*				
Higher	927/10 482 (9%)	945/9125 (10%)	0·84 (0·68–1·04)	0·94
Intermediate	947/9004 (11%)	1051/9045 (12%)	0·85 (0·70–1·03)	
Lower	1263/11 208 (11%)	1433/11 216 (13%)	0·87 (0·81–0·94)	
Subtotal (I^2=0·0%, p=0·94)			0·86 (0·81–0·92)	
Established cardiovascular disease				
Yes	2608/23 673 (11%)	2877/22 432 (13%)	0·85 (0·78–0·92)	0·18
No	492/6725 (7%)	521/6684 (8%)	0·94 (0·83–1·06)	
Subtotal (I^2=44·1%, p=0·181)			0·88 (0·80–0·97)	
Baseline HbA_{1c}†				
High	1777/16 361 (11%)	1955/15 237 (13%)	0·83 (0·77–0·90)	0·14
Low	1357/14 270 (10%)	1477/14 081 (10%)	0·90 (0·84–0·97)	
Subtotal (I^2=55·3%, p=0·14)			0·87 (0·80–0·94)	

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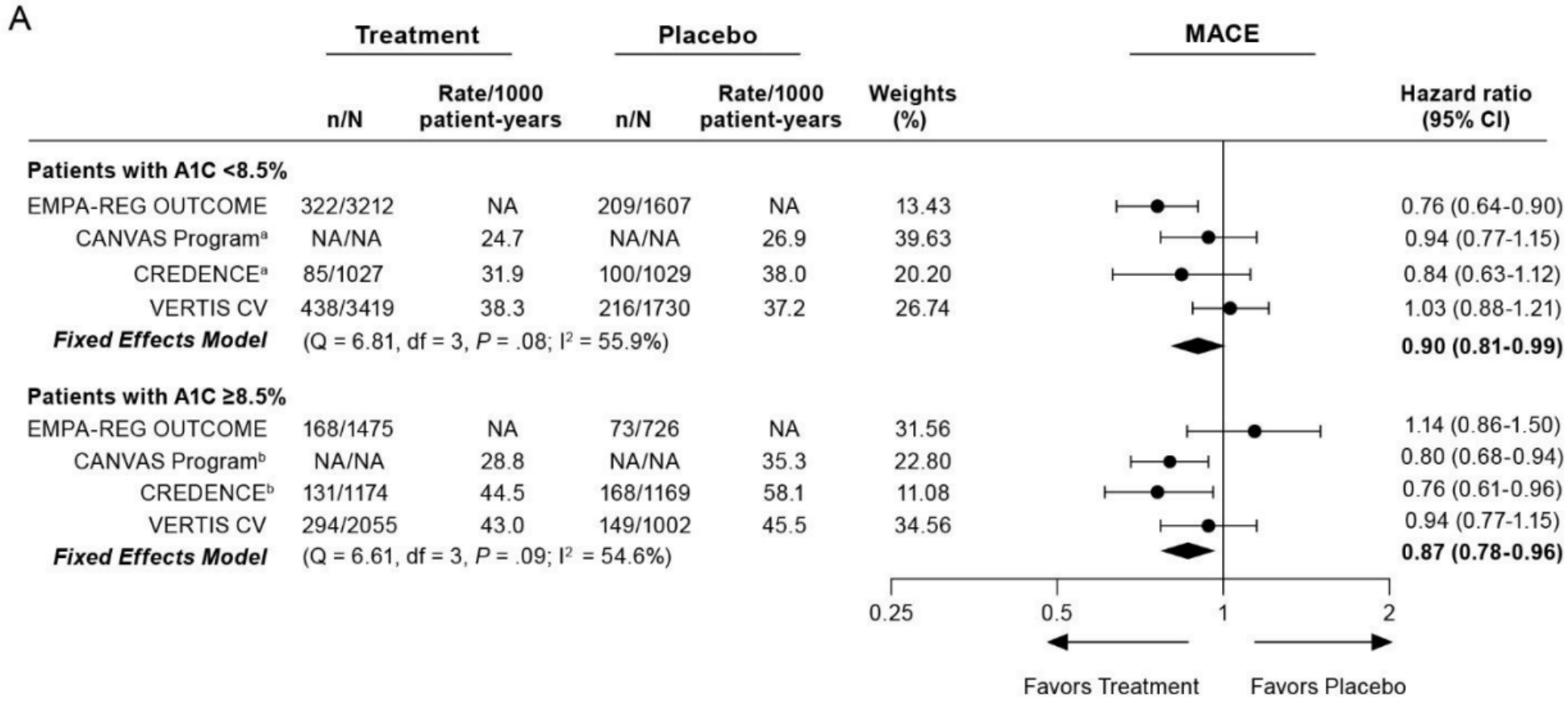
Does CV benefits depend on baseline HbA1c?



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