ACCADEMIA di
ALTA FORMAZIONE CLINICA
per MEDICI del TERRITORIO

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Associazione aGLP 1 e iSGLT 2

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2 Pleiotropic effects of SGLT2is and GLP-1RAs

MoA and multifactorial effects of GLP-1RAs

Multifactorial effects of GLP-1RAs

Potential mechanisms underlying the cardiovascular benefits of GLP-1RAs include:

Reduction in HbA_{1c}
Up to 1.8% reduction in HbA_{1c}[1]

Reduction in the risk of CV events like non-fatal MI and non-fatal stroke[2]

Reduction in body weight
Up to 6.5 kg of weight loss[1]

Promote diuresis/natriuresis to improve cardiac load and lipid leves[1]

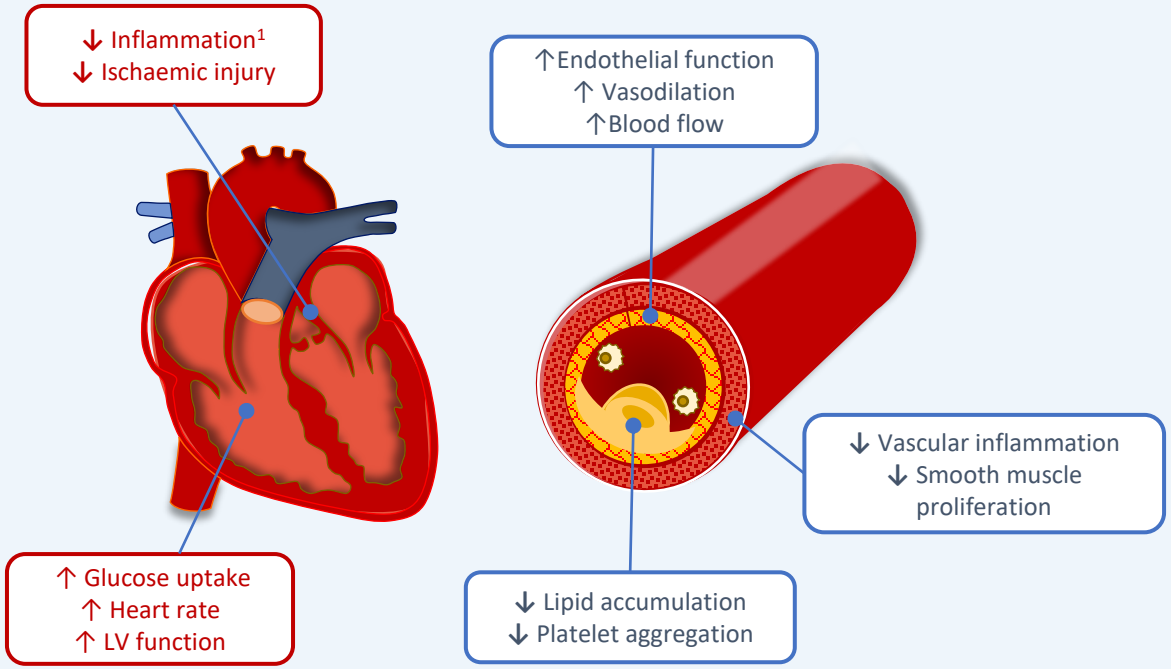
Decreases angiotensin II levels to reduce blood pressure

Enhance endothelial relaxation through:

- ↑NO production and ↓VCAM-I/ICAM-I
- ↑Vasodilation and coronary flow
- ↑Proliferation of coronary artery endothelial cells

**Significantly greater reductions in HbA1c were achieved in patients with higher starting HbA_{1c} level.*
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; MI, myocardial infarction; NO, nitric oxide; T2D, type 2 diabetes; VCAM-I/ICAM-I, vascular cell adhesion molecule 1/intracellular adhesion molecule 1.
1. Guja C and Dănciulescu Miulescu R. Ann Transl Med 2017;5:475; 2. Kristensen SL et al. Lancet Diabetes Endocrinol 2019;7:776–785.

GLP-1RAs positively impact risk of ASCVD in T2D[1]



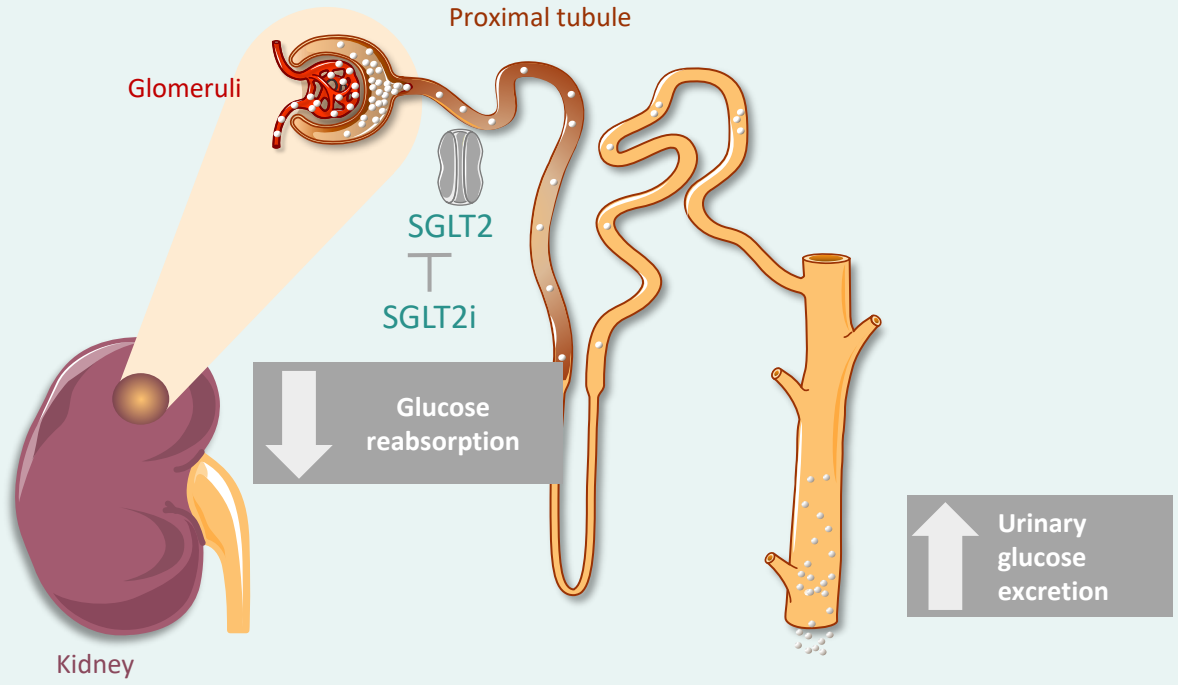
The efficacy of GLP-1RAs:[2]

- Is **independent** on the amount of **glucose** filtered through the glomeruli
- Is **dependent** on **insulin levels and sensitivity** ➔ Moderate risk of hypoglycaemia
  ➔ Can be used in combination with other agents (insulin or sulfonylureas)
- **Declines** with progressive renal impairment as glomerular filtration rates (**GFR**) decline
  ➔ Caution with low eGFR

ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; ; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.
1. Drucker D J. Cell Metab 2016;24(1):15–30; 2. Khat D.Z. & Husain M. Current Diabetes Reports 2018:1–15.

MoA and multifactorial effects of SGLT2is

SGLT2is in T2D



The efficacy of SGLT2is:[1]

- Is **dependent** on the amount of **glucose** filtered through the glomeruli
- Is **independent** of **insulin levels and sensitivity** ➔ Low risk of hypoglycaemia
  ➔ Can be used in combination with other agents
- **Declines** with progressive renal impairment as glomerular filtration rates (**GFR**) decline
  ➔ Caution with low eGFR (low eGFR can lead to low efficacy)

eGFR, estimated glomerular filtration rate; SGLT2, sodium-glucose co-transporter 2; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T2D, type 2 diabetes.
1. Misra M. J Pharm Pharmacol 2013;65(3):317–27.

Multifactorial effects of SGLT2is

Decrease ratio of insulin to glucagon, leading to increase of ketone bodies[1,2]

Up to 2.7% reduction* in HbA_{1c} when combined with other oral hypoglycaemic agents[3]

Improve cardiac energy metabolism and reducing pathological remodeling[4]

Improve oxygenation[4,5]

Increases in haemoglobin and hematocrit[1]

Promote diuresis/natriuresis, reducing blood pressure, and improving cardiac load[1,4,5]

Suppress tubular hypertrophy and regulate tubuloglomerular feedback[4,5]

Inhibit SGLT1[1,4]

Anti-inflammation, reducing oxidative stress and apoptosis, and increasing autophagy[1,4]

Increase circulating pro-angiogenic progenitor cells[4]

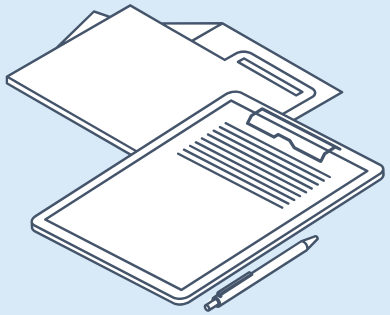
Reductions in body weight[1,5]

Up to 3 kg weight loss[3]

**Significantly greater reductions in HbA1c were achieved in patients with higher starting HbA_{1c} level.*
HbA1c, glycated haemoglobin; SGLT, sodium-glucose co-transporter; SGLT2i, sodium-glucose co-transporter 2 inhibitor.
1. Rabizadeh et al. Int J Endocrinol Metab 2019;17(2):e84353; 2. Kaneto H et al. Int J Mol Sci 2021;22(6):3062. 3. Foote C, Perkovic V and Neal B. Diab Vasc Dis Res 2012;9(2):117–23; 4. Gao Y et al. eBioMedicine 2022;83:104215; 5. Dominguez Rieg JA et al. Curr Opin Nephrol Hypertens 2022; 29(5):523–530.

SGLT2is and ASCVD

Evidence



A meta-analysis of
3 large trials:

- EMPAREG OUTCOME
- CANVAS Program
- DECLARE-TIMI 58

revealed an 11% reduction in MACE by using SGLT2is (effect only seen in patients with previous ASCVD)[2,3]

SGLT2is robustly **reduced cardiovascular death or hospitalisation for HF by 23%,** with similar benefits in patients with and without ASCVD[3]

Interpretation

SGLT2is modestly reduce serum glucose through glycosuria, which may be mechanistically linked with the observed reduction in ASCVD events seen with this drug class[1]

Though the beneficial effects of SGLT2is on established intermediate markers of cardiometabolic health (e.g. blood pressure, body weight) are clear, these changes are unlikely to fully explain the ASCVD benefits seen[1]

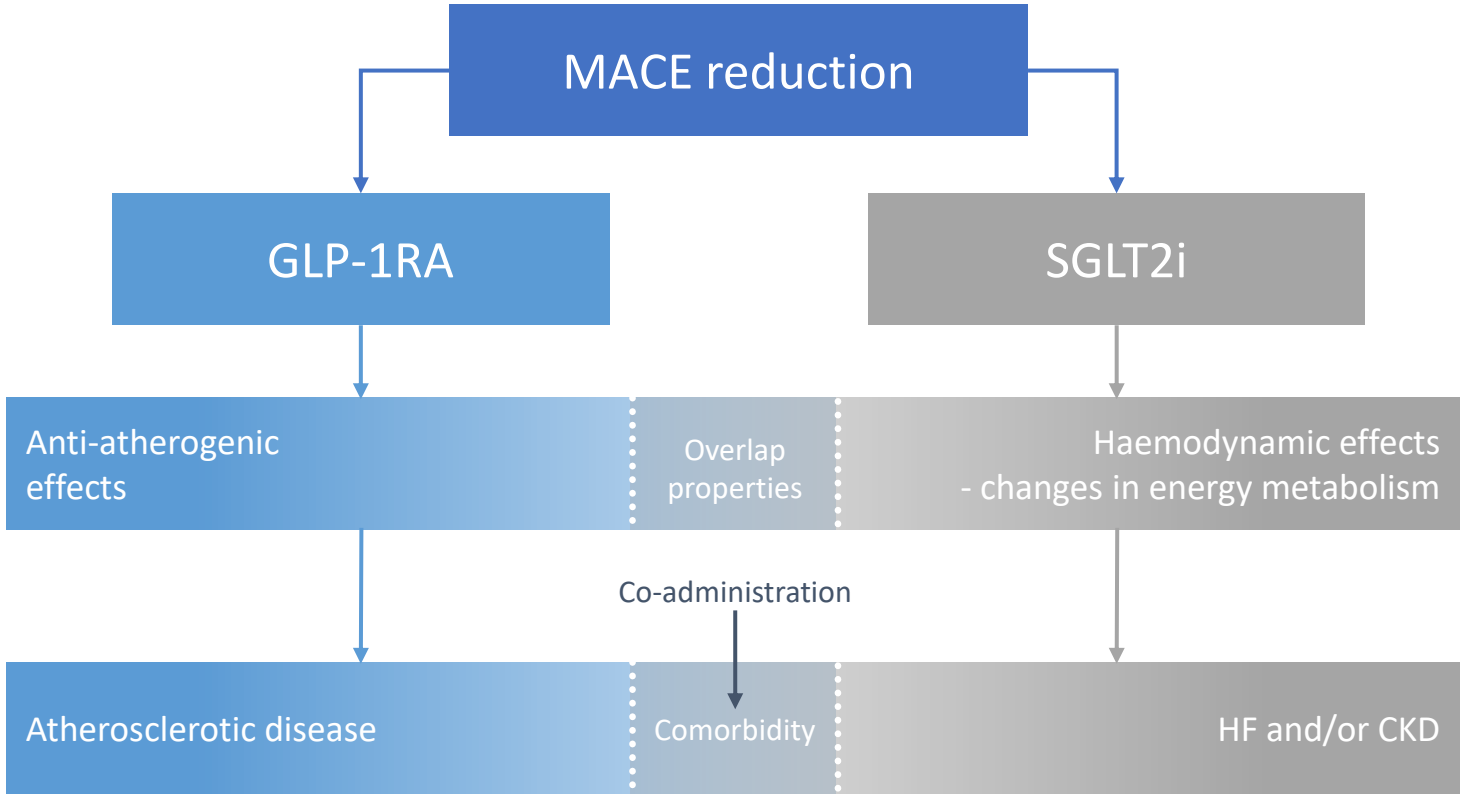
There is little evidence that SGLT2is reduce the incidence of fatal or non-fatal stroke, despite clear effects on blood pressure[1]

ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; MACE, major adverse cardiovascular event; SGLT2i, sodium-glucose co-transporter 2 inhibitor.
1. Barraclough JY et al. Cells 2021;10(10):2699. 2. Rabizadeh S et al. Int J Endocrinol Metab 2019;17(2):e84353; 3. Gao Y et al. eBioMedicine 2022;83:104215

Proposed use of SGLT2is and GLP-1RAs to target ASCVD-related endpoints

Use of GLP-1RAs and SGLT2is in CVD

A Horse, a Jockey, and a Therapeutic Dilemma: Choosing the Best Option for a Patient with Diabetes and Coronary Artery Disease



- **SGLT2is reduce CV risk primarily through haemodynamic** effects and changes in energy metabolism, making them the first choice in cases where HF or CKD predominates
- **GLP-1RAs exert powerful anti-atherogenic properties** that are the main drivers of their cardioprotection, and seem to have a **consistent benefit in the atherosclerotic components of MACE**
- Most people with diabetes and CV disease could take **advantage of the complementary effects of the two drug categories on glycaemic control, body weight, and diabetic complications**

CKD, chronic kidney disease; CV, cardiovascular; CKD, chronic kidney disease; CVD, cardiovascular disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; SGLT2i, sodium-glucose co-transporter 2 inhibitor.
Koufakis T, Liberopoulos EN and Kalliopi K. Am J Cardiovasc Drugs 2022 Jul;22(4):357-361.

Summary: Patient and clinical preferences and priorities for considering SGLTis vs GLP-1RAs

2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee

Preference or priority	Consider SGLT2i use first when patient & clinician priorities include:	Consider GLP-1RA use first when patient & clinician priorities include:
MACE prevention	+++	+++
HF prevention	+++	
Weight loss	+	+++
Renal disease progression prevention	+++	+
Mode of administration	Oral	Subcutaneous
Considerations that may prompt use of an alternate class	• Severely reduced kidney function*,† • History of prior amputation, severe peripheral arterial disease, or active diabetic foot ulcers‡ • History of recurrent genital candidiasis • History of diabetic ketoacidosis • History of fracture‡ • Patient is considering pregnancy • Patient is breast feeding	• Persistent nausea, despite appropriate dietary education and low doses • History of gastroparesis • Active gallbladder disease • History of MEN2 or medullary thyroid cancer • History of proliferative retinopathy^ • Patient is considering pregnancy • Patient is breast feeding

**eGFR <45 mL/min/1.73 m^2 is currently a caution due to a decrease in glycaemic efficacy (not due to safety), but ongoing studies are testing whether SGLT2is offer renal benefits in these patients. The FDA label for canagliflozin allows use of canagliflozin to an eGFR of 30 mL/min/1.73 m^2 specifically for patients with DKD. †Use clinical judgment when initiating an SGLT2i in a patient who will be starting or up-titrating an ACE inhibitor or ARB if the patient's renal function is impaired. ‡Caution with canagliflozin. ^Caution with semaglutide or dulaglutide.*

ACE, angiotensin-converting enzyme; ARB, angiotensin reception blocker; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiovascular event; MEN2, multiple endocrine neoplasia type 2; SGLT2, sodium-glucose cotransporter-2.

Das SR et al. J Am Coll Cardiol 2020; 76(9):1117–1145.

Summary: CAD and T2D features that may guide treatment choice

A Horse, a Jockey, and a Therapeutic Dilemma: Choosing the Best Option for a Patient with Diabetes and Coronary Artery Disease

Patient feature	GLP-1RA	SGLT2i
HF		✓
CKD		✓
Stroke	✓	
Isolated CAD	✓	
Large reductions in HbA_{1c} needed	✓	
Large reductions in body weight needed	✓	
eGFR <30 mL/min/1.73 m^2	✓	
History of frequent or severe GI complaints		✓
History of frequent or severe genital mycotic or UTIs	✓	
Family or personal history of MEN/MTC		✓
Personal history of pancreatitis (relative contraindication)		✓
Suspicion of LADA or T1D	✓	

CAD, coronary artery disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GI, gastrointestinal, GLP-1RA, glucagon-like peptide-1 receptor agonist, HbA_{1c}, glycated haemoglobin; HF, heart failure; LADA, latent autoimmune diabetes in adults; MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer; SGLT2i, sodium-glucose co-transporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; UTI, urinary tract infection.

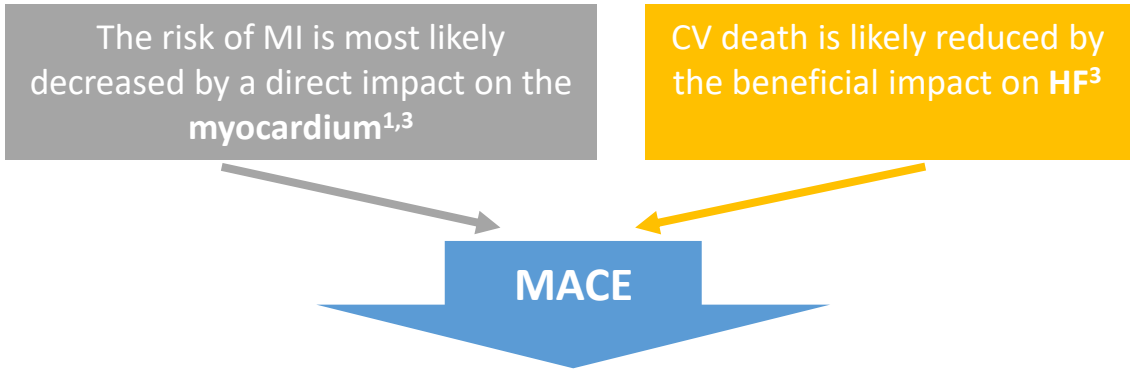
Koufakis T, Liberopoulos EN and Kalliopi K. Am J Cardiovasc Drugs 2022 Jul;22(4):357-361.

Evidence related to potential effects of SGLT2is and GLP-1RAs on atherosclerosis-related outcomes

SGLT2is are associated with reduced MI and HF risks, not with direct anti-atherogenic effects

Current evidence supports that SGLT2is can **reduce the risk of MI**[1,3], while **the risks of unstable angina, stroke, TIA, arterial revascularisation, and PAD seem to be unaffected by SGLT2is**[1]

This suggests that effects are restricted to the heart (pump) and not ASCVD (pipe)[3]



EMPA-REG OUTCOME study

A direct anti-atherogenic effect is **unlikely** to explain the benefit of empaglifozin because of:

- Lack of beneficial effect of empagliflozin on nonfatal stroke and nonfatal MI[2]
- Absence of reduction in unstable angina[2]
- Rapid onset of decrease in CV mortality and hospitalisation for heart failure[2]

The significant reduction in CV death was possibly due to a **reduction in hHF**[3]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HF, heart failure; hHF, hypertensive heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD; peripheral artery disease; SGLT2i, sodium-glucose co-transporter 2 inhibitors; TIA, transient ischaemic attack.

1. Pahud de Mortanges A et al. Front Pharmacol 2021;5:751214; 2. DeFronzo RA. Diabetes Obes Metab. 2017; 19(10):1353-1362; 3. Sinha B and Ghosal S. Diabetes Ther 2019; 10:891–899.

GLP-1RA benefits on atherosclerosis and peripheral artery disease (PAD) in people with T2D

Post hoc analysis of LEADER showed that treatment with liraglutide in patients with T2D and a high risk of CV events did not increase the risk of DFU events and was associated with a **significantly lower risk of DFU-related amputations** compared with placebo[1]

HR (95% CI): 0.55 (0.36, 0.84), p=0.006

Because the absolute risk was higher in patients with T2D and PAD, **liraglutide and semaglutide treatments were associated with numerically higher absolute risk reductions for primary outcome in patients with PAD vs without[2]**:

- LEADER (absolute risk reduction of 4.1% points; HR (95% CI): 0.77 (0.58,1.01), p = 0.06
- SUSTAIN 6 (absolute risk reduction of 4.6% points; HR (95% CI): 0.61 (0.33, 1.13), p = 0.11

GLP-1RAs were found to lower the risk of major adverse limb events by reducing the rate of amputations needed
(see next two slides)

CI, confidence interval; CV, cardiovascular; DFU, diabetes-related foot ulcer; GLP-1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; PAD, peripheral artery disease; T2D, type 2 diabetes.
1. Dhatariya K et al. Diabetes Care 2018;41:2229–35; 2. Verma S et al. Diabetes Obes Metab 2022;24(7):1288–1299.

GLP-1RAs vs SGLT2i: MALE in people with diabetes

Study overview

Study design
- Retrospective cohort study
- Data source: Taiwan – National Payer Research Database

Inclusion criteria
- Diagnosed with T2D
- Started on GLP-1RA or SGLT2i between 1 May 2016 and 31 December 2019

Propensity score matching
4:1 ratio (SGLT2i:GLP-1RA)

Primary endpoint
Major adverse limb events (MALE), defined as the composite of:
- Newly diagnosed critical limb ischaemia (CLI)*
- Percutaneous transluminal angioplasty (PTA) or peripheral bypass (revascularisation due to PAD)
- Non-traumatic amputation

Secondary endpoint
3-point MACE
(CV death, non-fatal MI, non-fatal ischaemic stroke)

Other endpoints
- Total mortality
- Hospitalisation due to HF

**CLI was defined as persistent limb, foot or digit pain at rest or threatened tissue loss due to ischaemia (i.e., Fontaine classification III or IV ischaemia).*
CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; SGLT2i, sodium-glucose co-transporter 2 inhibitors.
Lin DS et al. Diabetologia 2022; 65(12):2032–2043.

Major adverse cardiovascular and limb events in people with diabetes treated with GLP-1RAs vs SGLT2is

Study Overview

N=37,925

- Diagnosed with T2D
- Started on GLP-1RA or SGLT2i between 1 May 2016 and 31 December 2019

Propensity score matching (4:1 ratio)

- GLP-1RA (N=20,288)
- SGLT2i (N=81,152)

Mean follow-up 1.96 years

Study design

- Retrospective cohort study
- Data source: Taiwan – National Payer Research Database

Outcomes

Major adverse limb events

HR 0.80

95% CI (0.67-0.96)

Critical limb ischemia

HR 0.83

95% CI (0.68-1.02)

Major adverse cardiovascular events

HR 0.93 95% CI (0.84-1.02)

All-cause mortality

HR 0.90 95% CI (0.80-1.00)

The incidence of MALE was significantly lower in the GLP-1RA group than in the SGLT2i group

The risk of newly diagnosed CLI was numerically lower in the GLP-1RA

**CLI was defined as persistent limb, foot or digit pain at rest or threatened tissue loss due to ischaemia (i.e., Fontaine classification III or IV ischaemia).*

CV, cardiovascular; CLI, critical limb ischemia; GLP-1RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiac events; MALE, major adverse limb event; MI, myocardial infarction; PAD, peripheral artery disease; SGLT2i, sodium-glucose co-transporter 2 inhibitors.

Lin DS et al. Diabetologia 2022; 65(12):2032–2043.

GLP-1RA benefits on atherosclerosis and coronary artery disease (CAD) in people with T2D

GLP-1 is proposed to be a marker of incidence, clinical course, and recurrence of CAD and related to the text and severity of atherosclerosis and myocardial ischemia[1]

- Two small studies show that some GLP-1RAs are associated with a significant reduction in CIMT thickness[2,3]
- A correlation analyses showed that CIMT was positively associated with LDL cholesterol[3]
- The use of GLP-1RAs for patients with T2D and CAD may reduce the CV risk and improve lipid profile by lowering the level of small dense LDL[4]

CAD, coronary artery disease; CV, cardiovascular; CIMT, carotid intima-media thickness test; GLP-1RA, GLP-1, glucagon-like peptide-1 receptor agonist; LDL, low-density lipoprotein; T2D, type 2 diabetes.

1. Jonik S et al. Biology (Basel) 2022;11(2):288; 2. Rizzo M et al. Cardiovasc Diabetol 2014;13:49; 3. Zhang J et al. Cardiovasc Diabetol 2020;19:48; 4. Anholm C et al. Atherosclerosis 2019;288:60–66.

Comparing evidence of anti-inflammatory effects between GLP-1RAs and SGLT2is

Though evidence suggests that both GLP-1RAs and SGLT2is exhibit anti-inflammatory effects, there is **greater evidence that supports the proposed MoA of GLP-1RAs on inflammation** than SGLT2is[1–3]

	GLP-1RAs	SGLT2is
Proposed primary MoA	• Suppress M1 macrophage secretion of many inflammatory cytokines (IFN-γ, IL-17, IL-2, TNF-α, IL-6, IL-1β)[1] • Induce M2 macrophage secretion of IL-10	• **Inhibit endothelial dysfunction** to reduce expression of circulating inflammatory molecules (IL-6, IL-12, IL-1β, TNF-α) and LDL-oxidation • **Attenuate macrophage** infiltration, M1 polarisation and foam cell formation • **Induce M2 macrophage polarisation**
Evidence supporting MoA	Inhibitory effects on inflammatory pathways from pre-clinical studies have been **confirmed** in both in vivo studies and clinical trials[1] GLP-1 receptors are **expressed** in vasculature, myocardium and immune cells (T and B lymphocytes, macrophages, iNKT cells, eosinophils, neutrophils)[1]	Molecular mechanisms are still **unclear** despite observations of an anti-inflammatory effect[2] SGLT2 receptors are primarily localised in the kidney and **have not been found in vasculature, myocardium, macrophages, nor endothelial cells**[2,3]

GLP-1RA, glucagon-like peptide-1 receptor agonist; IL, interleukin; iNKT cell, invariant natural killer T cell; MoA, mechanism of action; SGLT2i, sodium-glucose co-transporter 2 inhibitors; TNF-a, tumor necrosis factor-a.

1. Bendotti G et al. Pharmcol Res 2022;182:106320; 2. Scisciola L et al. Front Cardiovasc Med 2022;9:1008922; 3. DeFronzo RA. Diabetes Obes Metab 2017; 19(10):1353-1362.

GLP-1RAs vs SGLT2is ASCVD-related outcomes

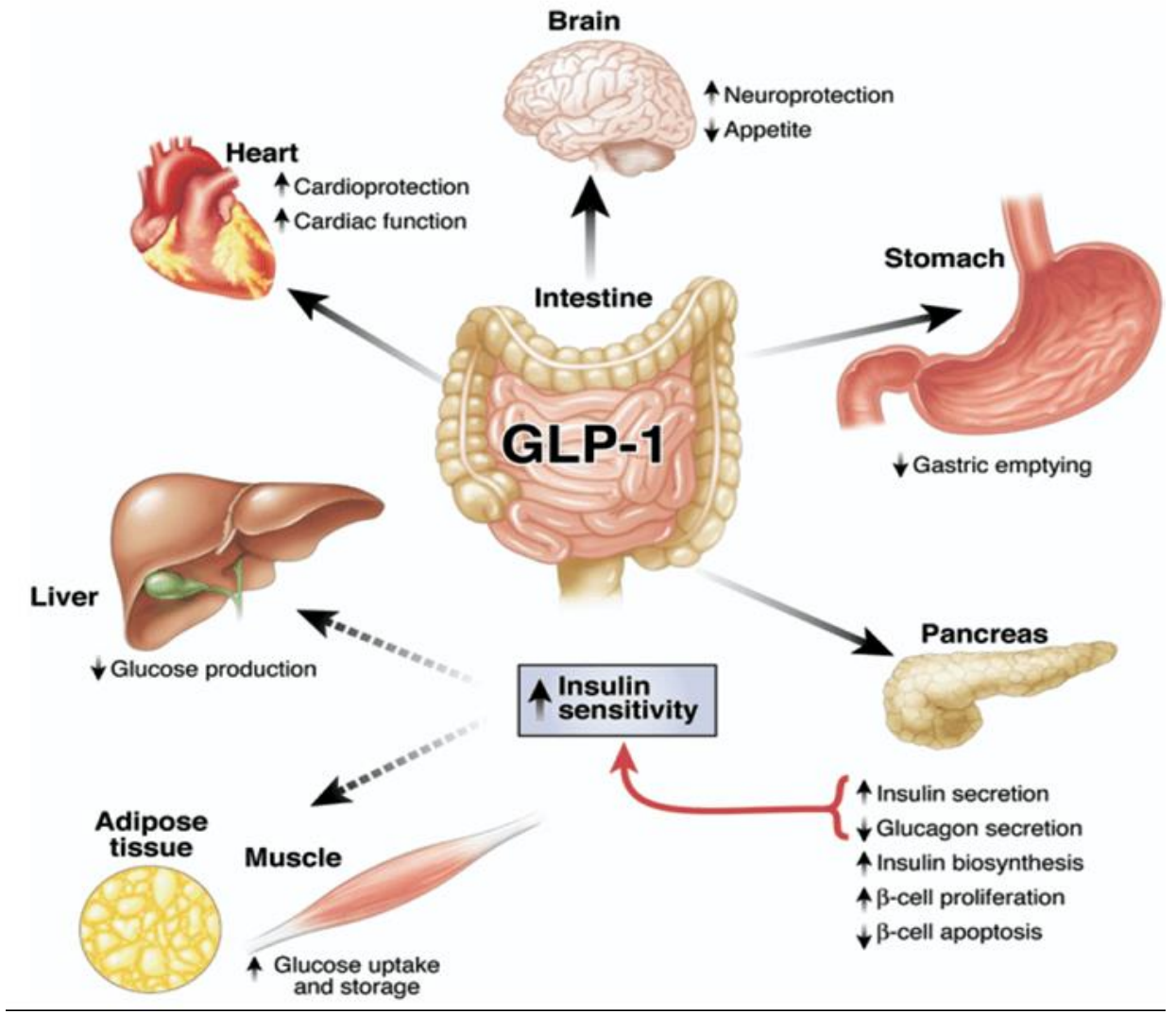
Summary of data from meta-analyses of CVOTs

GLP-1RAs		SGLT2is
⬇13% risk of CV death[1]	⬇14% risk of 3-point MACE[2]	⬇11% risk of 3-point MACE[3]
⬇10% risk of HHF[1]	⬇17% risk of non-fatal stroke[2]	⬇17% risk of CV death[3]
⬇17% composite renal outcomes[1]	⬇10% risk of MI[2]	⬇30% risk of HHF[3]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; HHF, hospitalisation for heart failure; MI, myocardial infarction; SGLT2, sodium–glucose cotransporter-2.

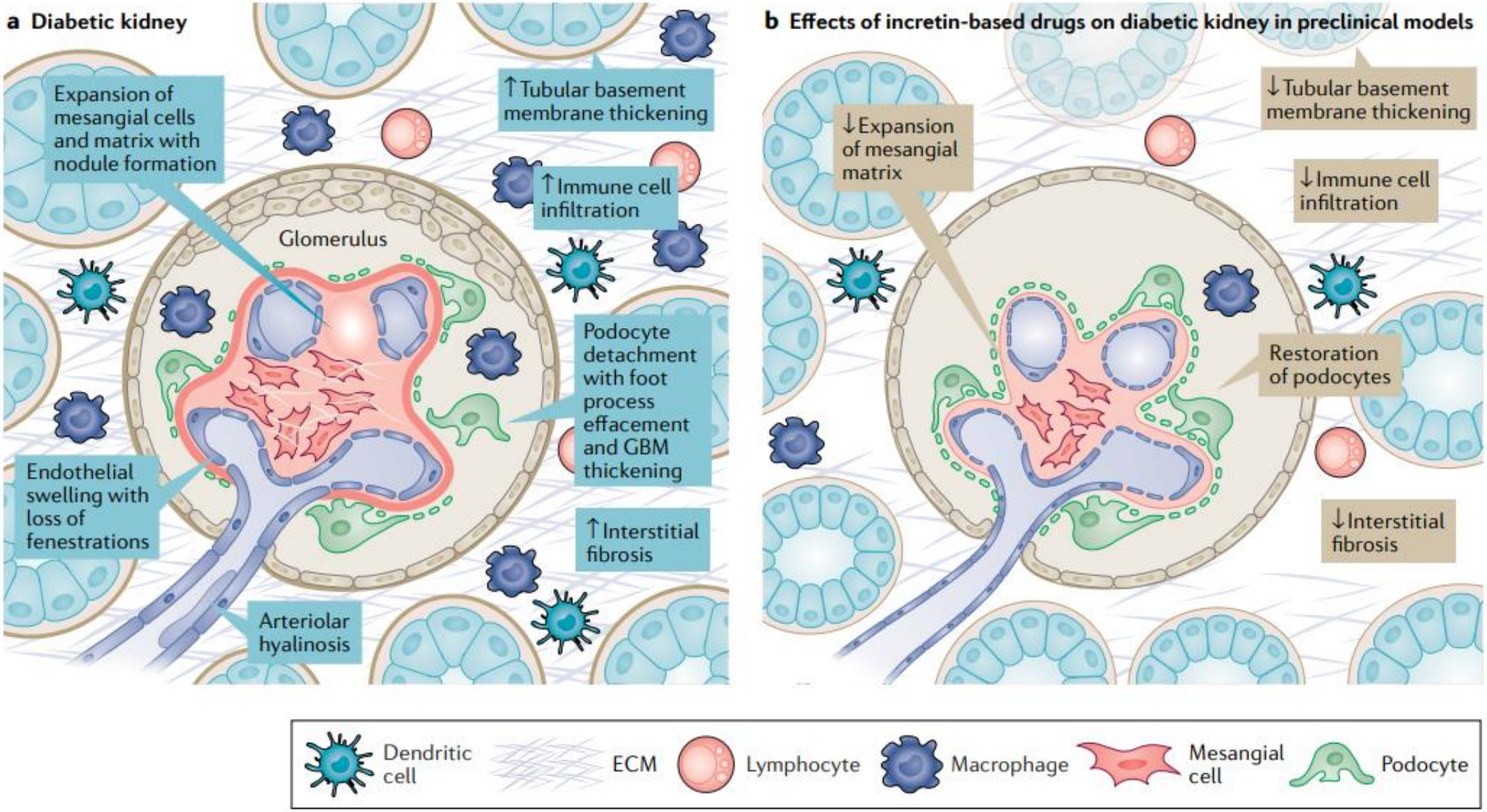
1. Giugliano D et al. Cardiovasc Diabetol 2021;189:1–11; 2. Sattar N et al. Lancet Diabetes Endocrinol. 2021;9(10):653–662; 3. McGuire DK et al. JAMA Cardiol 2021;6(2):148–158.

Multifactorial benefits of GLP-1RA



Drucker 2019

Effetti dei GLP1RA sul danno renale della DKD



Alicic RZ et al. Nat Rev Nephrol 2020 Nov 20

Three mechanisms may drive the effect of GLP-1 on natriuresis (1/2)[1,2]

1. Inhibition of the **tubular sodium-hydrogen exchanger isoform 3 (NHE3)**
2. Inhibitory effects on the **renin-angiotensin-aldosterone system (RAAS)**
3. Indirect effects via **neuronal pathways**

Natriuresis and diuresis

GLP-1, glucagon-like peptide-1

1. Muskiet MHA et al. *Nat Rev Nephrol* 2017;13:605–628; 2. Skov J. *Rev Endocr Metab Disord* 2014;15:197–207;

Potential renoprotective effect of GLP1 RA

Indirect effects

CKD, chronic kidney disease; CV, cardiovascular; CVOT, cardiovascular outcomes trial; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes
1. Zoungas S et al. *Lancet Diabetes Endocrinol* 2017;5:431–437; 2. de Galan BE et al. *J Am Soc Nephrol* 2009;20:883–892; 3. Adler AL et al. *BMJ* 2000;321:412–419; 4. Bolignano D and Zoccali C. *Nephrol Dial Transplant* 2013;28 Suppl 4:iv82-98; 5. Marso SP et al. *N Engl J Med* 2016;375:311–322; 6. Marso SP et al. *N Engl J Med* 2016;375:1834–1844; 7. Mann JFE et al. *N Engl J Med* 2017;377:839–848

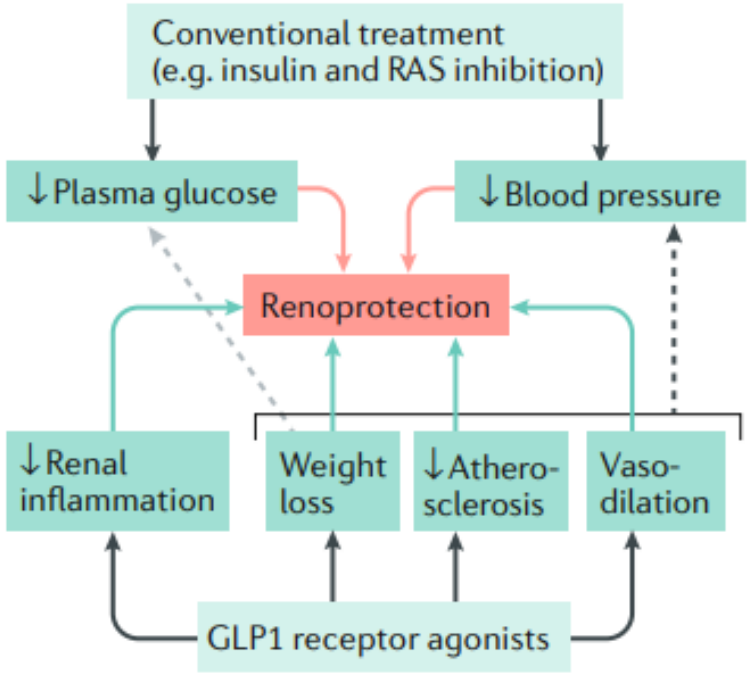


Fig. 1 | **Potential renoprotective effects of GLP1 receptor agonists.** The renoprotective effects of glucagon-like peptide 1 (GLP1) receptor agonists and of conventional treatments for type 2 diabetes mellitus are additive. GLP1 receptor agonists can reduce blood pressure and plasma glucose directly (not shown), as well as indirectly (dashed arrows) via effects on body weight, atherosclerosis and the renal vasculature. RAS, renin–angiotensin system.

Sorensen et al, nature Reviews | NePhroLoGy, 2018