nature REVIEWS
CARDIOLOGY

Effects of new antidiabetic drugs on cardiovascular health

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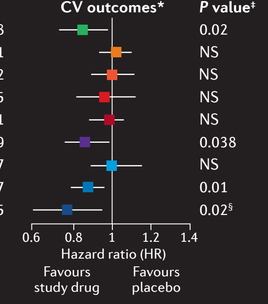
Reducing the risk of cardiovascular disease remains a major target in people with type 2 diabetes mellitus. While the effect of strict glycaemic control on the risk of cardiovascular disease remains a matter of debate[1], more emphasis has been placed on the safety and potential cardiovascular protection of new glucose-lowering agents. Results of the PROactive trial[2] of pioglitazone were inconclusive for the primary cardiovascular end point, although prespecified secondary end points showed cardiovascular protection. Studies of the insulin analogue glargine[3] and the DPP4 inhibitors saxagliptin[4], alogliptin[5], and sitagliptin[6] showed overall cardiovascular safety, but not superiority for cardiovascular outcomes compared with placebo. By contrast, SGLT2 inhibitors and GLP1-receptor agonists have demonstrated not only cardiovascular safety, but also cardiovascular benefits. The EMPA-REG OUTCOME trial[7] of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes and prior cardiovascular disease was the first to show a significant reduction in cardiovascular death, all-cause mortality, and hospitalization for heart failure. A study of the GLP1-receptor agonist lixisenatide in patients with type 2 diabetes and recent ACS showed safety, but did not show any cardiovascular benefit[8]. However, the LEADER[9] and SUSTAIN-6 trials[10] showed that the GLP1-receptor agonists liraglutide and semaglutide have cardiovascular benefits that might prove to be of clinical importance in the management of type 2 diabetes.

Cardiovascular outcome trials of glucose-lowering agents

Study	Glucose-lowering drug	HR	95% CI	*P* value‡
PROactive[2]	Pioglitazone	0.84	0.72–0.98	0.02
ORIGIN[3]	Insulin glargine	1.02	0.94–1.11	NS
SAVOR-TIMI 53[4]	Saxagliptin	1.00	0.89–1.12	NS
EXAMINE[5]	Alogliptin	0.96	0.80–1.15	NS
TECOS[6]	Sitagliptin	0.99	0.89–1.11	NS
EMPA-REG[7]	Empagliflozin	0.86	0.74–0.99	0.038
ELIXA[8]	Lixisenatide	1.02	0.89–1.17	NS
LEADER[9]	Liraglutide	0.87	0.78–0.97	0.01
SUSTAIN-6[10]	Semaglutide	0.74	0.58–0.95	0.02§



*Main secondary end point (composite of all-cause death, nonfatal MI, and nonfatal stroke) shown for PROactive; primary end point shown for all other trials (definition specified in the table below).
‡Study drug vs placebo in addition to standard therapy.
§Testing for superiority for the primary outcome was not prespecified or adjusted for multiplicity.

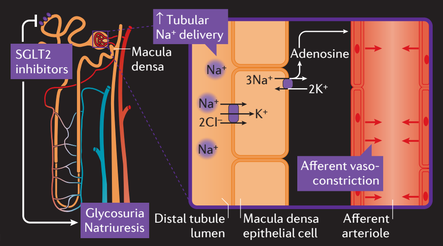
Agent	Clinical trial	Patients (*n*)	Patient characteristics	Follow-up (years)	Primary end point
Glitazones					
Pioglitazone	PROactive[2]	5,328	T2DM with history of CV event	2.8*	Composite of all-cause mortality, nonfatal MI, stroke, ACS, revascularization, amputation
Insulin analogues					
Glargine	ORIGIN[3]	12,537	IFG, IGT, T2DM, and CV risk factors	6.2‡	Composite of CV death, nonfatal MI, nonfatal stroke
DPP4 inhibitors					
Saxagliptin	SAVOR-TIMI 53[4]	16,492	T2DM with history of CV event or CV risk factors	2.1‡	Composite of CV death, nonfatal MI, nonfatal stroke
Alogliptin	EXAMINE[5]	5,380	T2DM with ACS within 15–90 days before randomization	1.5‡	Composite of CV death, nonfatal MI, nonfatal stroke
Sitagliptin	TECOS[6]	14,671	T2DM with history of CV event	3.0‡	Composite of CV death, nonfatal MI, nonfatal stroke, unstable angina
SGLT2 inhibitors					
Empagliflozin	EMPA-REG OUTCOME[7]	7,020	T2DM with history of CV event	3.1‡	Composite of CV death, nonfatal MI, nonfatal stroke
GLP1-receptor agonists					
Lixisenatide	ELIXA[8]	6,068	T2DM with ACS within 180 days before screening	2.1‡	Composite of CV death, nonfatal MI, nonfatal stroke, unstable angina
Liraglutide	LEADER[9]	9,340	T2DM, aged ≥50 years with history of CV event, or aged ≥60 years with ≥1 CV risk factor	3.8‡	Composite of CV death, nonfatal MI, nonfatal stroke
Semaglutide	SUSTAIN-6[10]	3,297	T2DM, aged ≥50 years with history of CV event, or aged ≥60 years with ≥1 CV risk factor	2.1‡	Composite of CV death, nonfatal MI, nonfatal stroke

*Mean. ‡Median.

Potential mechanisms for the cardiovascular benefit of different glucose-lowering agents

Cardio–renal protection

Glomerular filtration rate and intraglomerular pressure are maintained by modulation of the afferent arteriole via Na^+ delivery from the proximal to the distal tubule and the macula densa, where adenosine release leads to afferent arteriole vasoconstriction (i.e. tubuloglomerular feedback; TGF). In diabetes, higher glucose and Na^+ reabsorption in the proximal tubule via increased SGLT2 activity reduces Na^+ delivery to the distal tubule and the macula densa, impairing TGF. Lower adenosine release leads to afferent arteriole vasodilatation, hyperfiltration, and increased intraglomerular pressure. SGLT2 inhibition blocks Na^+ reabsorption, increasing Na^+ delivery to the distal tubule and restoring TGF, with normalization of afferent arteriole tone and reduction of intraglomerular pressure[11]. Higher oxygen supply to the kidney via increased haematocrit, and higher energy supply via increased β-hydroxybutyrate availability might also contribute to renal protection. Improved renal function and reduced albuminuria can contribute to lowering blood pressure, reducing arterial stiffness and hence cardiac afterload, and improving Na^+/water homeostasis and circulating volume, improving cardiac haemodynamics[11].



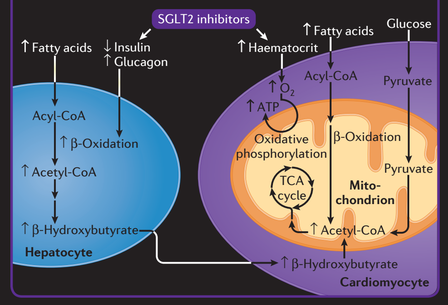
Reduced volaemia

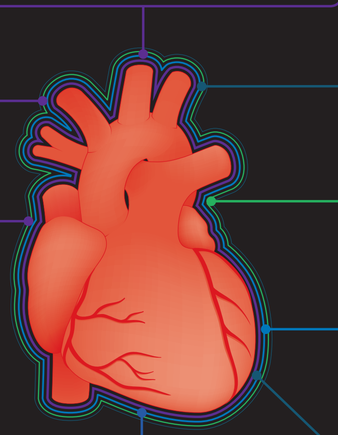
SGLT2 inhibitors increase urinary glucose excretion, which is associated with higher osmotic diuresis and reduction of circulating volume.

Concomitant increase in erythropoietin release can further increase haematocrit and oxygen supply to the heart[12].

Metabolic shift

SGLT2 inhibitors increase glucagon and decrease insulin concentration in plasma, which in turn increase fatty acid oxidation and ketone production (β-hydroxybutyrate) in the liver. In the mitochondria of cardiomyocytes, β-hydroxybutyrate is converted to acetyl-CoA, which enters the TCA cycle for oxidative phosphorylation. β-Hydroxybutyrate has been shown to be a more efficient energy substrate for the heart than glucose or fatty acids owing to a more efficient oxidation of the mitochondrial coenzyme Q couple and an increase in the free energy of ATP hydrolysis[12].





Reduced inflammation

Type 2 diabetes mellitus is associated with increased oxidative stress and low-grade inflammation as a result of insulin resistance, hyperglycaemia, hyperlipidaemia, obesity, central adiposity, NAFLD, and NASH. Inflammation can worsen insulin sensitivity and β-cell function (see figure), as well as contribute to risk of CV disease.

Antidiabetic agents improving one or more of these conditions might reduce oxidative stress and inflammation. Pioglitazone and GLP1-receptor agonists might exert a direct anti-inflammatory effect.

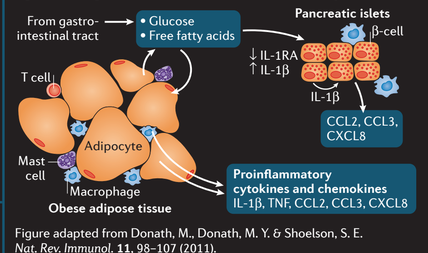


Figure adapted from Donath, M., Donath, M. Y. & Shoelson, S. E. *Nat. Rev. Immunol.* **11**, 98–107 (2011).

Improved lipid profile

Owing to improved insulin sensitivity and increased LPL mass and apolipoprotein C-III inhibition[13].

Blood-pressure reduction

- Liraglutide and semaglutide increase urinary sodium excretion.
- Empagliflozin increases urinary sodium and glucose excretion and osmotic diuresis. Other potential mechanisms, such as angiotensin and/or aldosterone withdrawal, reduction of sympathetic nervous system activity, increased haemoglobin with increased nitrosohaemoglobin effects, might also have a role.

Decrease in body weight

SGLT2 inhibitors (empagliflozin)

Brain
↑ Energy intake (might compensate body weight loss)

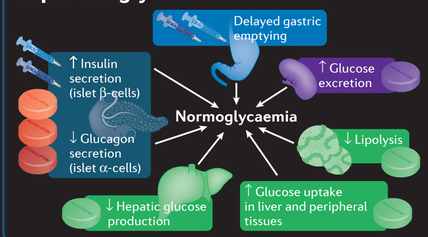
Kidney
↑ Glucose excretion and calorie loss

Adipose tissue
↑ Lipolysis

GLP1-receptor agonists (liraglutide and semaglutide)

Brain
↓ Appetite
↑ Satiety

Improved glycaemic control



Therapeutic potential

Potential therapeutic effects of the glucose-lowering drugs with some evidence of cardiovascular benefit.

	Insulin	Metformin	Pioglitazone	DPP4 inhibitors	Empagliflozin	Liraglutide	Semaglutide
All-cause death	↔	↓	↔	↔	↓↓	↓	↔
Blood pressure	↔/↑	↔	↓	↓	↓↓	↓	↓
Body weight	↑↑	↓	↑↑	↔	↓	↓↓	↓↓
Bone fractures	ND	↔	↑	↔	↔	↔	↔
CV death	↔	↓	↔	↔	↓↓	↓	↔
CV outcomes*	↔	–	↓	↔/↓	↓	↓	↓
Fluid retention	↑	↔	↑	↔	↓	↔	↔
Glucose lowering	↑↑↑	↑	↑↑	↑	↑	↑↑	↑↑↑
HDL cholesterol	↔/↓	↔	↑	↔	↑	↔	↔
Heart failure	↔/↑	↔	↑	↔‡ ↑§ ↑↑¶	↓↓	↔	↔
Insulin sensitivity	↔	↑	↑↑	↔	↑	↑	↑
LDL cholesterol	↔	↔/↓	↔	↔/↓	↑	↓	↓
Myocardial infarction	↔	↓	↓	↔	↔	↔	↔
Renal disease progression	↔	↔/↓	↓	↔↓	↓	↓	↓
Stroke	↔	↓	↓↓	↔	↔	↔	↓

Grading has been derived from refs 2–10, 14–16. ↓, decrease; ↑, increase; ↔, no change; ND, no data. *Composite of CV death, nonfatal MI, and nonfatal stroke. ‡Sitagliptin (TECOS trial[6]). §Alogliptin (EXAMINE trial[5]). ¶Saxagliptin (SAVOR-TIMI 53 trial[4]). Adapted from Schernthaner, G. & Schernthaner, G. H. *Herz* **41**, 208–216 (2016) under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Future directions

The identification of glucose-lowering drugs that improve cardiovascular outcomes is likely to change the treatment paradigm for patients with type 2 diabetes mellitus at high risk of cardiovascular disease[17]. Although the mechanism(s) by which SGLT2 inhibitors and GLP1-receptor agonists improve cardiovascular outcomes remain uncertain, the cardiovascular benefit is unlikely to be mediated by glucose reduction. Ongoing and planned mechanistic studies of these agents might help to identify the exact mechanisms of action and to assess the potential beneficial effects in other patient populations. Moreover, additional outcome studies of these agents in different populations will assess potential cardiovascular benefits, even in those individuals without cardiovascular disease and/or diabetes.

Abbreviations

ACS, acute coronary syndrome; CCL2, CC-chemokine ligand 2; CCL3, CC-chemokine ligand 3; CV, cardiovascular; CXCL8, CXC-chemokine ligand 8; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IL-1β, interleukin-1β; IL-1RA, IL-1 receptor antagonist; LPL, lipoprotein lipase; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NS, not significant; SGLT2, sodium–glucose cotransporter 2; T2DM, type 2 diabetes mellitus; TCA, tricarboxylic acid; TNF, tumour necrosis factor.

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