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CLINICAL REVIEW
Obesity and metabolic syndrome

Cardioprotective anti-hyperglycaemic medications: a review of clinical trials

Haitham M. Ahmed[1]*, Haitham Khraishah[2], and Leslie Cho[1]

[1]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Ave, Desk JB1 Cleveland, OH 44195, USA; and [2]Beth Israel Deaconess Medical Center, 330 Brookline Ave Boston, MA 02215, USA

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Despite extensive clinical efforts to achieve stricter glycaemic control over the past few decades, cardiovascular (CV) disease remains the leading cause of death among diabetic patients. Recently, sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-1-R) agonists have gained attention due to their apparent effects in reducing CV mortality. Four CV randomized controlled trials: EMPA-REG, CANVAS, LEADER, and SUSTAIN-6, found a decrease in CV events among patients with type 2 diabetes on empagliflozin, canagliflozin, liraglutide, and semaglutide, respectively. In light of this data, the US Food and Drug Administration has recently approved empagliflozin for CV mortality reduction in type 2 diabetic patients, making it the first diabetes medication approved for such an indication. The purpose of this review is to summarize the results of novel anti-hyperglycaemic medication trials, and shed light on their mode of action and cardioprotective pathways.

Keywords Diabetes mellitus • Diabetes complications • Hypoglycaemic agents • Cardiac death • Sodium-glucose transport proteins • Glucagon-like peptide-1 receptor

Introduction

By the year 2035, more than 600 million adults are expected to have diabetes.[1] Among these patients, cardiovascular (CV) events are estimated to be the leading cause of death.[2] Although several trials have established an association between tight glycaemic control and reduced microvascular complications,[3,4] the association with CV events was less clear in the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes (VADT) trials.[5–8]

Since the discovery of insulin almost a century ago, multiple generations of antihyperglycaemic medications have been introduced to the market over the years including metformin, sulfonylureas, and thiazolidinediones. While all of these agents have moderate effects on blood glucose, none have been shown to substantially and consistently lower CV events in clinical trials. Small trials comparing metformin to glipizide have shown a relative reduction in CV events,[9] but recent larger meta-analyses have shown overall data to be insufficient or of low strength.[10]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor (GLP-1-R) agonists are two different classes of anti-hyperglycaemic agents that have recently drawn interest due to the results of four randomized controlled trials (RCTs): EMPA-REG,[11] CANVAS,[12] LEADER,[13] and SUSTAIN-6[14] that have demonstrated an apparent CV benefit of empagliflozin, canagliflozin, liraglutide, and semaglutide, respectively, in patients with type 2 diabetes. While both EMPA-REG and LEADER trials showed a decrease in CV mortality among patients with type 2 diabetes, SGLT-2 inhibitors were additionally shown to significantly reduce heart failure hospitalizations in EMPA-REG and CANVAS which may provide insights into the mechanistic pathways of this drug.[11,12] In this article, we review the data regarding benefits with SGLT-2 inhibitors and GLP-1-R agonists and discuss the possible mechanistic pathways by which CV event reduction may occur.

The importance of cardiovascular safety trials in diabetes

In 2008, the US Food and Drug Administration (FDA) issued a Guidance for Industry requiring all new anti-hyperglycaemic therapies that treat type 2 diabetes to undergo pre-approval trials to rule out unacceptable CV risk using a composite endpoint of major adverse

* Corresponding author. Tel: +1 216 445 2332, Fax: +1 216 444 8856, Email: ahmedh3@ccf.org

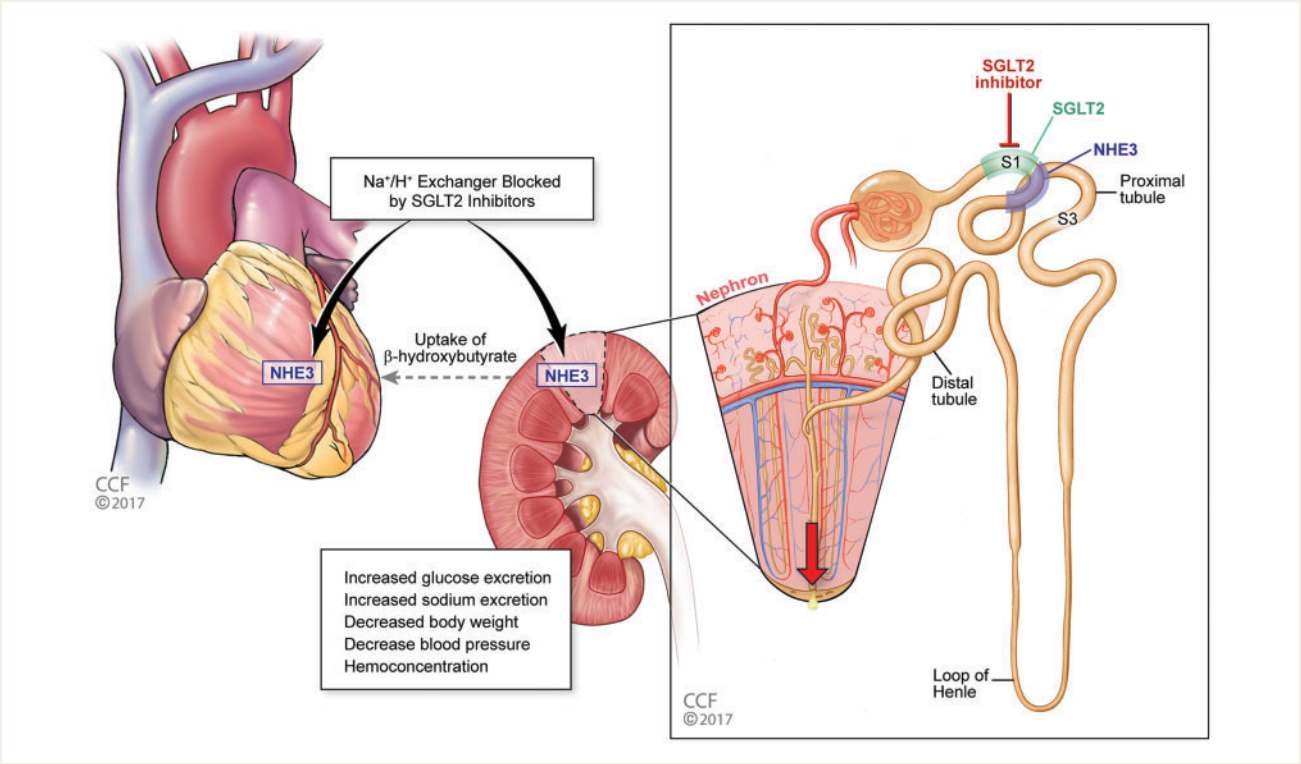

Figure 1 Sodium-glucose cotrasporter-2 (SGLT-2) inhibitor action on the kidneys and heart.

cardiovascular events (MACE). Furthermore, post-approval trials for the same composite MACE endpoints were required for continued marketing of anti-hyperglycaemic drugs.[15] These recommendations came as a consequence of multiple reports highlighting the increased risk of CV events among patients using rosiglitazone, a thiazolidinedione.[15,16] This observation came in line with already existing evidence of increased mortality with intense glycaemic control in the ACCORD trial,[8] and initial reports during the development of the peroxisome proliferator-activated receptor agonist, muraglitazar.[17] Accordingly, following the development of SGLT-2 inhibitors and GLP-1-R agonists, CV outcomes trials were also launched to evaluate the CV safety of these novel agents.

Sodium-glucose co-transporter-2 inhibitors

Sodium-glucose cotransporter-2 inhibitors are a novel class of oral anti-hyperglycaemic medications that work by increasing urinary excretion of glucose in the renal tubules (*Figure 1*).[18] The SGLT-2 receptors are predominantly found in the first segment (S1) of the kidney's proximal tubules, in contrast to SGLT-1, which is found in the small intestine brush boarder cells and to a lesser extent in the heart, and S2 and S3 of the kidney's proximal tubules.[19,20] Glucose reabsorption from the proximal tubules into the blood stream is dependent upon two sequential processes. First, SGLT actively transports glucose across the apical membrane of the epithelial cells against its concentration gradient (secondary active transport) using the energy produced by the electrochemical potential gradient of sodium ions generated by the sodium–potassium pump (primary active transport). The second step involves transporting glucose into the blood across the basolateral membrane of the proximal tubule epithelial cells by a downhill concentration gradient through facilitated diffusion using mainly GLUT-2 channels.[21]

Sodium-glucose cotransporter-2 has also been recently shown to be expressed on pancreatic alpha cells.[22] In a study by Bonner *et al.*, mRNA and protein was detected by western blots and confocal microscopy in human alpha cells. Furthermore, blocking SGLT-2 was shown to promote glucagon secretion and hepatic gluconeogenesis which suggests possible additional effects in the pancreas and liver.

There are currently three SGLT-2 inhibitors that are approved by the FDA for the treatment of type 2 diabetes: canagliflozin, dapagliflozin, and empagliflozin, with post-approval trials available only for empagliflozin and canagliflozin (*Table 1*).[24] There is an ongoing post-marketing clinical trial that is evaluating the CV outcomes of Dapagliflozin (*Table 2*).

The safety profile for these agents has been verified by several trials where it was demonstrated that these drugs, as mono- or in-combination therapy, have improved glycaemic control without an increase in risk of hypoglycaemia[29,30]; this is due to the fact that these drugs do not increase insulin secretion. Additionally, they were found to reduce blood pressure (BP), body weight, triglyceride levels (-2.77 ± 9.2 mg/dL), and increase HDL (1.08 ± 1.9 mg/dL). Adverse effects of SGLT-2 inhibitors include an increase in low-density lipoprotein (LDL) (1.09 ± 2.3 mg/dL) and total cholesterol (2.14 ± 3.7 mg/dL), an increase in the incidence of superficial mycotic genital infections without an

Table 1 Randomized controlled trials of cardiovascular disease outcomes in diabetic patients treated with glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors

	SGLT-2 inhibitors		GLP-1 receptor agonists		
Drug	**Empagliflozin**[11]	**Canagliflozin**[12]	**Liraglutide**[13]	**Semaglutide**[14]	**Lixisenatide**[23]
Study	EMPA-REG (2015)	CANVAS (2017)	LEADER (2016)	Sustain-6 (2016)	ELIXA (2015)
Size	7028	10 142	9340	3297	6068
Median follow-up (years)	3.1	2.4	2.8	2.1	2.1
Mean age (years)	63.1	63.3	64.3	64.6	60.2
Baseline HbA1C (%)	8.1	8.2	8.7	8.7	7.7
↓ HbA1C% (%)	0.49–0.58	0.56–0.61	0.34–0.45	0.7–1	0.22–0.31
Primary cardiac end-point[a]	Significant decrease (↓14%)	Significant decrease (↓14%)	Significant decrease (↓14%)	Significant decrease (26%)	No significant decrease[b]
Relevant 2 end-points	↓35% heart failure hospitalizations	↓Heart failure hospitalizations (↓33%)	↓22% cardiovascular death	↓26% expanded composite outcome[c]	No reduction in heart failure hospitalizations
	↓38% cardiovascular death		Up to 8% decrease in body weight		No reduction in cardiovascular deaths
Dose	10–25 mg qd	100–300 mg qd	0.6, 1.2, 1.8 mg/dose (subcutaneous injection)	0.5–1.0 mg/dose (subcutaneous injection)	10–20 mcg (subcutaneous injection)
Side effects	Genital infections, hypotension, diabetic ketoacidosis (rare), amputation		Gastrointestinal disturbances (nausea, vomiting, diarrhoea); pancreatitis		
Contraindication	Severe renal dysfunction (eGFR ≤ 30 mL/min)		Hx of medullary thyroid CA	Hypersensitivity reaction	Hypersensitivity reaction

CANVAS, CANagliflozin cardioVascular Assessment; CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events; EMPA-REG, Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

[a]A composite of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.

[b]A composite of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, or unstable angina hospitalization.

[c]Death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularization (coronary or peripheral), and hospitalization for unstable angina or heart failure.

Table 2 Ongoing randomized controlled trials of cardiovascular disease outcomes in diabetic patients treated with glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter-2 inhibitors

	Exenatide[25]	Dulaglutide[26]	Albiglutide[27]	Dapagliflozin[28]
Clinical trial	EXSCEL	REWIND	HARMONY	DECLARE-TIMI 58
Number of subjects	14 000	9622	3297	17 150
Key inclusion criteria	Type 2 diabetes HbA1c 6.5–10% Age > 18 years	Established vascular complications if age > 50 years OR 2 CV risk factors if age > 60 years HbA1c ≤ 9.5% Age > 50 years	Established vascular complications if age > 40 years HbA1c > 7.0% Age > 40 years	High risk for cardiovascular events Age > 40
Primary endpoint	CV death, non-fatal MI, non-fatal stroke	CV death, non-fatal MI, non-fatal stroke	CV death, non-fatal MI, non-fatal stroke	CV death, non-fatal MI, non-fatal stroke
Reporting year	2018	2018	2019	2019

CV, cardiovascular; DECLARE-TIMI 58, Dapagliflozin Effect on CardiovascuLAR Events; EXSCEL, EXenatide Study of Cardiovascular Event Lowering trial; HARMONY, study to evaluate the effect of ranolazine and dronedarone when given alone and in combination in patients with paroxysmal atrial fibrillation; MI, myocardial infarction; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes.

increase in upper urinary tract infections, and a possible increase in amputations at the level of the toe or metatarsal.[12,29–31]

Recently, the EMPA-REG OUTCOME trial evaluated the CV safety of empagliflozin.[11] In this trial, a total of 7020 patients with type 2 diabetes, body-mass index (BMI) < 45, and glomerular filtration rate (GFR) > 30 mL/min/1.73 m^2 body surface area were randomly assigned to receive either 10 or 25 mg of empagliflozin vs. placebo daily. The primary outcome was a composite of CV death, non-fatal myocardial infarction (MI), or non-fatal stroke. Results showed a significant decrease in all-cause mortality (32%), CV mortality (38%) and hospitalization from heart failure (35%) in the empagliflozin-treated groups when compared to control subjects. The absolute reduction in heart failure hospitalizations, CV mortality, and all-cause mortality, was 1.4%, 2.2%, and 2.6%, respectively over a mean duration of 3 years. There was no significant difference in the incidence of MI or stroke between the arms of the trial. Based on these results, the FDA released a statement in December 2016 approving the use of empagliflozin in type 2 diabetic patients with pre-existing cardiovascular disease (CVD) to reduce the risk of CV death.[32]

Further investigations from the EMPA-REG OUTCOME TRIAL showed persistent CVD risk reduction for patients with 'prevalent' chronic kidney disease (GFR between 30 and 60 mL/min/1.73 m^2),[33] as well as patients with heart failure and at very high risk, high risk, and low-average risk for heart failure.[34,35] Subsequently, two studies were initiated to evaluate the effects of empagliflozin on heart failure patients, regardless of diabetes status: empagliflozin outcome trial in patients with chronic heart failure with reduced ejection fraction and preserved ejection fraction, EMPEROR-Reduced,[36] and EMPEROR-Preserved,[37] respectively. The results of the two trials are expected by 2020.

A second post-approval CV outcome trial (see *Table 1*) was also recently published for canagliflozin (CANVAS).[12] In that trial, a total of 10 142 patients with type 2 diabetes and high CV risk were randomized to canagliflozin vs. placebo and followed for a mean of 188 weeks. The primary outcome was the same composite outcome of CV death, non-fatal MI, or non-fatal stroke as in EMPA-REG. The mean age of participants was 63 years and the mean duration of diabetes was 14 years. Results showed that canagliflozin decreased the rate of the primary outcome from 31.5 to 26.9 participants per 1000 patient-years [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.75–0.97]. There was not a statistically significant reduction in the individual components of the primary outcome or all-cause death, although the point estimates of effect suggested benefit. Similar to EMPA-REG, there was a lower risk of hospitalization for heart failure, as well as a slower progression of albuminuria and a composite of renal outcomes (HR 0.60, 95% CI 0.47–0.77) although on the basis of the pre-specified hypothesis testing sequence these cannot be viewed as significant.

Since the publication of the initial RCTs, studies of real-world practice have shown reductions in CVD events, heart failure hospitalizations, and mortality across over 150 000 diabetic patients taking SGLT-2 inhibitors in the USA and Europe.[38,39] As real-world prescriptions continue to rise, data will further inform clinical practice in diabetes and CVD preventive care.

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists and dipeptidylpeptidase-4 (DPP-4) inhibitors are two classes of anti-hyperglycaemic medications that were developed based on the incretin pathway (*Figure 2*). Glucagon-like peptide-1 is secreted by a form of enteroendocrine cells that are mainly found in the ileum and colon, called L-cells, in response to food ingestion indicating that this action is independent of food interaction with L-cells and is controlled by neuronal and other poorly understood mechanisms.[40–42]

The GLP-1-R is expressed in a wide range of organs including the pancreas, stomach, intestines, heart, lung, kidney, skin, and central nervous system.[40] Upon the release of GLP-1 from the enteroendocrine cells, it is rapidly inactivated by DDP-4, a ubiquitous protease, giving it a half-life of only 1–2 min. Glucagon-like peptide-1 increases

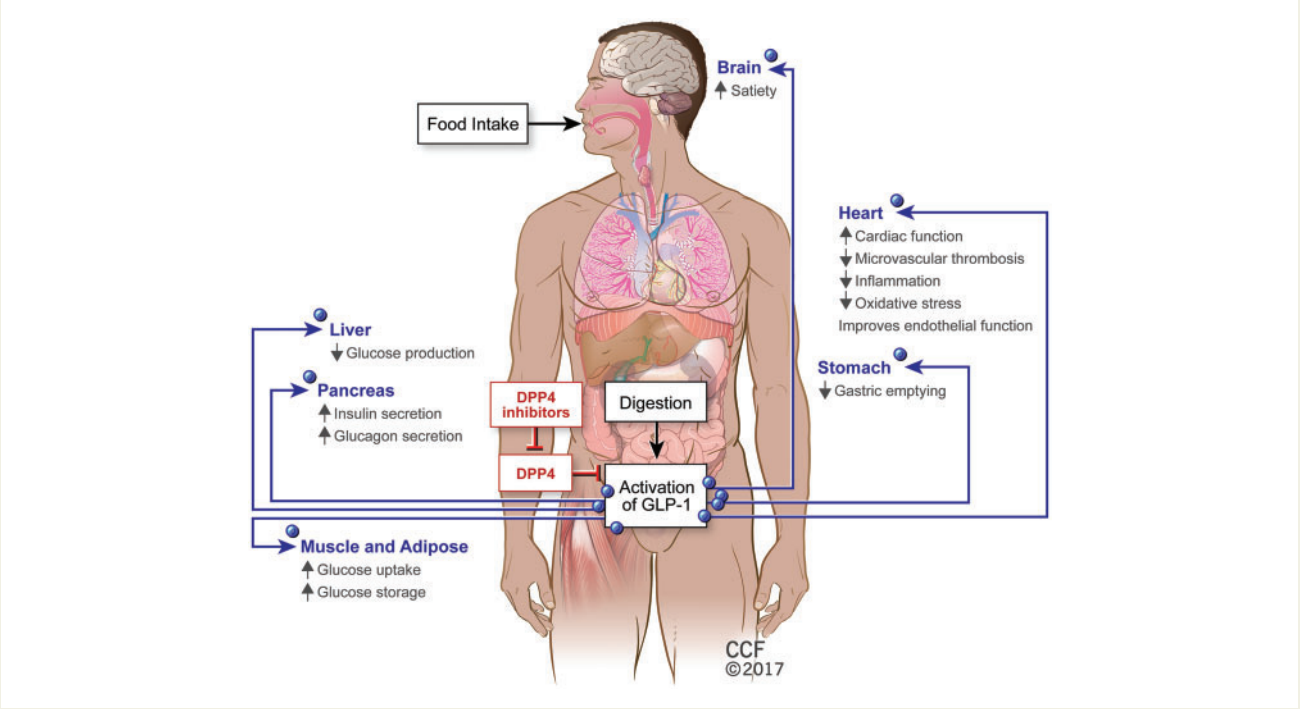

Figure 2 Glucagon-like peptide-1 receptor (GLP-1-R) agonist actions across various organ systems.

insulin secretion by pancreatic β cells and inhibits glucagon secretion by α cells. It has to be noted that GLP-1-insulin-secretory effect is glucose dependent i.e. GLP-1 has no effect on insulin secretion when glucose levels are approximately ≤81 mg/dL.[40]

Currently, there are six FDA-approved GLP-1-R agonists for the treatment of type 2 diabetes. Three of these agents are short-acting (half-life < 24 h): exenitide, liraglutide, and lixisenatide; and three are long-acting (half-life > 24 h/weekly injections): long-acting exenitide, dulaglutide, and albiglutide. Additionally, there is semaglutide, a long-acting GLP-1-R agonist that has not been approved yet by the FDA for the treatment of type 2 diabetes. In addition to their benefits in reducing HbA1c, GLP-1-R agonists have additional favourable metabolic effects in reducing body weight, LDL, hypoglycaemia events, and BP.[43]

Major side effects of GLP-1 agonists include gastrointestinal disturbances and injection site pruritus.[44] Glucagon-like peptide-1 receptor agonists should be avoided in patients with a history of medullary thyroid carcinoma or family history of multiple endocrine neoplasia 2A and 2B as animal studies have shown that liraglutide can cause thyroid C-cell hyperplasia[45]; however, this finding was not noted in human clinical trials or follow-up studies.[46] Moreover, GLP-1-R agonists are not recommended in patients with a history of pancreatitis based on post-marketing surveillance after the approval of exenitide, and hence, the FDA issued a cautionary letter in 2008.[47] However, several retrospective studies and a meta-analysis of 41-trials with a total of 14 972 subjects did not find an association between GLP-1-R agonist use and pancreatitis.[48,49]

There are currently three available CV outcome trials for GLP-1-R agonists (see *Table 1*): Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)[23] and Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)[13]; and one pre-marketing safety trial: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.[14] There are three additional ongoing trials that are investigating the CV outcomes of exenitide, dulaglutide, and albiglutide (*Table 2*).

The ELIXA trial evaluated the CV outcomes of lixisenatide in type 2 diabetic patients.[23] ELIXA included patients >30 with type 2 diabetes and who had had an acute coronary syndrome within 180 days of screening. A total of 6068 patients with a mean age of 60 years and an estimated GFR > 30 mL/min/1.73 m^2 body surface area were randomly assigned to either 10 μg of subcutaneous lixisenatide per day or volume-matched placebo. The patients were followed for a median of 25 months. The primary outcome of the study was a composite of CV death, non-fatal MI, or non-fatal stroke. The trial did not reveal any CV benefit of lixisenatide over the standard treatment including heart failure hospitalizations.

The LEADER trial assessed the CV outcomes of liraglutide among type 2 diabetics with high CV risk by randomizing them to receive either 1.8 mg (or maximum tolerated dose) of liraglutide or placebo.[13] The trial followed 9340 subjects with a mean age of 64 years for a median of 3.8 years. The primary outcome was a composite of CV death, non-fatal MI, or non-fatal stroke. Results demonstrated a reduction in the primary composite outcome in patients on liraglutide when compared to standard therapy (HR 0.87; 95% CI 0.78–0.97; $P < 0.01$ for superiority). Also, death from CV causes (HR 0.78; 95% CI 0.66–0.93; $P = 0.007$) and any cause (HR 0.85; 95% CI 0.74–0.97; $P = 0.02$) was less likely to occur in the liraglutide group. Although not statistically significant, the rates of non-fatal MI, non-fatal stroke, and heart failure hospitalizations were lower in the liraglutide group.

Although not yet approved for clinical use in patients with type 2 diabetes, semaglutide appears to be safe in terms of its CV profile.[14] SUSTAIN-6 evaluated the CV outcomes of semaglutide by randomizing diabetic patients with pre-existing CV risks to receive either 0.5 mg or 1.0 mg of subcutaneous semaglutide weekly or standard therapy. SUSTAIN-6 included 2735 patients and followed them for a median of 2.1 years.[14] The primary outcome was a composite of CV death, non-fatal MI, or non-fatal stroke. The trial revealed a reduction in the primary outcome in the semaglutide treated-patients when compared to placebo (HR 0.74; 95% CI 0.58–0.95; $P < 0.02$ for superiority). This observation was driven mainly by a significant reduction in non-fatal stroke (HR 0.61; 95% CI 0.38–0.99; $P = 0.04$). However, there was no significant decrease in cardiovascular deaths between both arms of the trial.

Trial comparisons

The groundbreaking results of the EMPA-REG, CANVAS, LEADER, and SUSTAIN-6 trials will likely change the way that clinicians treat type 2 diabetes moving forward. However, several points are important to note. First, the EMPA-REG and CANVAS trials showed significant reduction in composite cardiovascular events as well as heart failure hospitalizations, while the LEADER trial showed only a reduction in cardiovascular mortality without a significant change in heart failure hospitalizations. The difference in impact of both drugs on heart failure hospitalizations, MI, and stroke risk may reflect the differences in mechanistic pathways of these therapies.

Second, before constructing an assumption about the SUSTAIN-6 trial, the following points should be taken into consideration: semaglutide has not yet been approved for clinical use, and the SUSTAIN-6 trial is mainly a safety trial that was powered to prove non-inferiority with a relatively small sample size and short follow-up, compared to post-marketing trials with larger sample sizes and follow-up, so we have to wait for post-marketing trials to make definitive conclusions.

Third, class-specific generalizations cannot be made on anti-hyperglycaemic drugs of the same category. The ELIXA trial showed a neutral effect of lixisenatide in terms of cardiovascular benefit, while liraglutide showed a decrease in CVD mortality. Nevertheless, it has to be noted that ELIXA trial included patients with recent acute coronary syndrome, who are somewhat younger, had broader range HbA1c levels on entry and shorter duration of diabetes than the LEADER trial, which excluded patients with acute coronary syndrome in the preceding 90 days. Additionally, the LEADER trial followed patients for a longer duration when compared to ELIXA (3.8 years vs. 2 years). However, ELIXA showed no trend in decreasing cardiovascular events during the 2 years of follow-up.

Similarly, the EMPA-REG trial showed CVD mortality reduction with empagliflozin, but a meta-analysis on pooled clinical trials[30] failed to show similar cardiovascular mortality with other SGLT-2 inhibitors. In CANVAS, there was a trend toward reduced risk of cardiovascular death but the difference was not statistically significant (HR 0.87, 95% CI 0.72–1.06). Hence, we have to wait for the results of the larger DECLARE-TIMI 58 trial in order to make a meaningful conclusion on the cardiovascular profile of this class of anti-hyperglycaemic drugs. Also, unlike the EMPA-REG and CANVAS trials, DECLARE-TIMI will contain a larger cohort of primary prevention patients which is an important group to better understand.

Sodium-glucose cotransporter-2 inhibitors: mechanistic pathways in cardiovascular disease event reduction

Sodium-glucose cotransporter-2 inhibitors and blood pressure

Although SGLT-2 inhibitors were found to cause a significant reduction in both systolic and diastolic BP[50–52] primarily through their diuretic effect,[53] the actual absolute BP lowering effect of empagliflozin in EMPA-REG and CANVAS was minimal (approximately 4 mmHg difference in systolic BP).[11,12] Another recent RCT (HOPE-3) showed no difference in MACE with more significant systolic BP reduction of 6 mmHg.[54] Therefore, it is questionable whether this degree of BP reduction or the diuretic effect of empagliflozin alone is enough to explain the CVD reduction that was seen in EMPA-REG.

Sodium-glucose cotransporter-2 inhibitors and metabolic profile

The key for the metabolic effects observed with SGLT-2 inhibitors can be attributed to their glucosuric mechanism of action.[55] Inhibiting SGLT-2 receptors in the kidneys leads to urinary excretion of glucose, resulting in better glycaemic control, negative energy balance leading to weight loss, and hence better insulin sensitivity. This negative energy balance would direct the cardiac myocytes toward using ketone bodies, a more efficient energy source.[56]

Recent meta-analyses show that SGLT-2 inhibitors significantly reduced haemoglobin A1C (HbA1c) levels by 0.5–0.7% over a follow-up period between 52 and 89 weeks.[30,57] In addition to lowering HbA1C, SGLT-2 inhibitors regulate post-prandial hyperglycaemia and improve insulin sensitivity.[55,58] Despite this glycaemic effect, it is unlikely that this is the mechanism alone by which the EMPA-REG trial reduced CVD mortality since several earlier trials have demonstrated that tight glycaemic control was not associated with a reduction in macrovascular complications.[59]

Sodium-glucose cotransporter-2 inhibitors have also been found to decrease body weight by 2–3 kg independent of its diuretic action.[11,12,29,30,60] This is because of the aforementioned negative glucose balance, shifting body energy metabolism to fat oxidation and lipolysis while decreasing glucose oxidation and utilization.[61]

High uric acid levels have also been linked to CVD events along with hypertension, diabetes and other metabolic diseases.[62] A reduction in uric acid levels among diabetic patients on SGLT-2 inhibitors has been observed in several trials;[63,64] however, the exact mechanism of action by which this occurred is not yet fully understood.

Sodium-glucose cotransporter-2 inhibitors and chronic kidney disease

Diabetes mellitus is the leading cause of end-stage renal disease worldwide with approximately 20% of diabetic patients eventually developing chronic diabetic nephropathy.[65] Glomerular hyperfiltration, which

may be attributed to failure to constrict the afferent arteriole, is the earliest change in a diabetic kidney; and has been linked to the increased risk of developing diabetic nephropathy.[66] As the GFR increases, the proximal tubule reabsorption of the hyperfiltrate increases via tubular glomerulotubular balance.[65] This increase in proximal tubular reabsorption leads to a decrease in the delivery of solutes to the macula densa by approximately 30%, which leads to a further increase in GFR via tubuloglomerular feedback.[65] This eventually leads to hypertrophy and hyperplasia of the proximal tubules through the activation of various growth factors. In the light of the aforementioned tubular hypothesis of diabetic nephropathy, SGLT-2 inhibitors tend to break this vicious cycle through increasing the solute delivery to the macula densa, and hence, decreasing GFR. Moreover, SGLT-2 inhibitors tend to decrease transport work across the proximal tubules, thus decreasing kidney oxygen requirements.[55] Additionally, SGLT-2 inhibitors may protect the kidneys through their effects on lowering BP and controlling hyperglycaemia.[29–31,50]

The renal-protective effect of SGLT-2 inhibitors has been confirmed by several studies. Empagliflozin has been shown to reduce GFR in type 1[67] and type 2[68] diabetic patients. Moreover, the EMPA-REG trial showed in *post hoc* analysis that empagliflozin reduced the worsening of chronic kidney disease (CKD), defined as progression to macroalbuminaemia, doubling of plasma creatinine, initiation of renal replacement therapy or death from renal causes, when compared to standard care.[11] Heerspink *et al.*[69] have demonstrated that canagliflozin reduced GFR decline and albumin: creatinine ratio in diabetic patients, independent of SGLT-2 glycaemic effects. In CANVAS, canagliflozin reduced the progression of albuminuria by 27%, and the composite outcome of a sustained reduction in GFR, need for renal replacement therapy, or death from renal causes by 40%.[12]

Novel pathways

A recent preliminary small study on human subjects found that adding a daily dose of 10 mg of empagliflozin to standard therapy in type 2 diabetic patients with established CV disease decreased left ventricular mass and improved diastolic function.[70] Another emerging pathway is the interaction between SGLT-2 receptors and the Na^+–H^+ exchanger (NHE). It has been shown that SGLT-2 and NHE3 co-localize and interact with each other in the kidney's proximal tubules, and that the inhibition of SGLT-2 leads to a subsequent inhibition of NH3.[71] Renal NH3 activity has been shown to be increased in heart failure rat models, and it may be responsible, at least in part, for diuretic resistance seen in heart failure patients.[72] Inhibition of NH3 increases proton absorption and might be responsible for euglycaemic diabetic ketoacidosis seen in patients on SGLT-2 inhibitors.[73] Upregulation of cardiac NHE has been implicated in the pathophysiology of heart failure in rat models.[74] Although SGLT-2 receptors are not present in cardiac tissues, empagliflozin was shown to directly inhibit NHE in rabbit myocytes, hence increasing mitochondrial calcium concentration and decreasing intracytoplasmic calcium concentration and protecting myocytes against calcium toxicity that is implicated in heart failure.[75]

In light of the profound reduction in heart failure hospitalizations with empagliflozin in EMPA-REG, Ferrannini and DeFronzo[76] have hypothesized another novel pathway. They posit that under persistent conditions of mild ketosis, as may be the case with SGLT-2 inhibition, β-hydroxybutyrate may be taken up by the heart and oxidized in preference to fatty acids. This improves oxygen consumption at the mitochondrial level, which along with haemoconcentration may synergistically enhance oxygen release to the tissues. Further investigation is needed to determine whether metabolic substrate shift plays a role in the cardioprotective pathways of these drugs.

Inflammation is another possible pathway since it is considered to be an independent risk factor for coronary heart disease,[77] and since many inflammatory diseases (e.g. rheumatoid arthritis, psoriasis, and lupus) are associated with increased cardiovascular event rates.[78] Anti-inflammatory effects may not be shared by classical antidiabetic drugs such as metformin, and thereby may explain the beneficial profile of SGLT-2 inhibitors in CVD event reduction.

Indeed, substantial anti-inflammatory, antioxidant, and vasculoprotective actions of empagliflozin were shown in a type 1 diabetic rat model.[79] Potential pleiotropic effects in cultured endothelial cells and epigenetic effects of empagliflozin treatment of ZDF rats were also recently reported.[80] Similarly, use of the SGLT-2 inhibitor, ipragliflozin, was shown to reduce inflammatory markers, namely interleukin 6, tumour necrosis factor-α, C-reactive protein, and monocyte chemotactic protein-1, in streptozotocin-nicotinamide-induced type 2 diabetic mice.[81]

Decreased oxidative stress and inflammatory mediators following a cardiovascular event can improve cardiac functional recovery and decrease mortality; however, no human studies to-date have looked at the anti-oxidative properties of SGLT-2 inhibitors.[81] Kusaka *et al.*[82] found that empagliflozin improved cardiac remodelling, independent of its effect on BP, and ameliorated cardiac oxidative stress; however, the exact mechanism by which this effect occurred is not yet fully understood. We have to await the ongoing EmDia trial[83] which also contains a sub-study on oxidative stress parameters, and a second study[84] which will focus on modulation of oxidative DNA damage by empagliflozin in type 2 diabetic patients for further insight. Further research is needed to better elucidate the mechanistic pathways by which SGLT-2 inhibitors may protect the heart.

Glucagon-like peptide-1 receptor agonists: mechanistic pathways in cardiovascular disease event reduction

Glucagon-like peptide-1 receptor agonists and blood pressure

Earlier RCTs conducted on DPP-4 inhibitors did not find a significant reduction in CVD events when compared to standard therapy as per the SAVOR-TIMI 53,[85] EXAMINE,[86] and TECOS[87] trials. This suggests that liraglutide may possess some novel characteristics that work independently of endogenous incretin pathways. Although the SUSTAIN-6 trial showed a significant reduction in the incidence of stroke, and a non-significant decrease in the incidence of MI; the literature is lacking explorative studies for this effect, as semaglutide has not been approved yet for clinical use.

As with SGLT-2 inhibitors, GLP-1-R agonists cause reduction in systolic BP[88] independent of weight loss. However, this reduction in BP is not enough to explain the CVD event reduction observed in

the LEADER trial as liraglutide led to minimal reduction in systolic BP (1.2 mmHg).[13] The mechanism underlying BP reduction is not well understood and may involve natriuresis, vasodilation through vascular smooth muscle GLP-1-R, and/or other neurohormonal pathways.[88] Moreover, chronic GLP-1-R activation leads to an increase in heart rate through poorly defined mechanisms.[13,23,88]

The different outcomes of gliptin trials as compared to the LEADER trial are indeed puzzling. Dipeptidylpeptidase-4 inhibitors have been observed to affect more adverse pathways than GLP-1-R analogues, possibly because DPP-4 has many other substrates besides GLP-1. DPP4 has been shown to interact with a number of ligands including adenine deaminase, kidney NHE3, caveolin-1, thromboxane A2 receptor, fibronectin, and CXCR4, to name a few.[89,90] Binding to these ligands may play a role in immune regulation and T-cell activation.[90]

Several animal studies have shown that DPP-4 inhibitors (e.g. linagliptin) have some preserved beneficial effects in GLP-1-R knockout mice, whereas liraglutide is devoid of protective effect.[91,92] DPP-4 inhibitors also have different vasodilator potency in isolated vessel segments. Therefore, the question is whether all gliptins should have been investigated by outcome trials with the assumption, as was seen for empagliflozin vs. canagliflozin and liraglutide vs. lixisenatide, that not all gliptins are the same.

Glucagon-like peptide-1 receptor agonists and metabolic profile

High-dose liraglutide (up to 3.0 mg) is the only GLP-1-R agonist that has been approved by the FDA for weight reduction purposes in overweight subjects with or without diabetes. This endorsement came as a result of the SCALE trial that demonstrated a significant reduction in body weight among the liraglutide group (4.0 kg independent of lifestyle modifications).[93] Moreover, liraglutide was found to cause significant reductions in total blood cholesterol, LDL, and HDL.[94] It was also shown that liraglutide improves glycaemic parameters such as HbA1C, and fasting blood glucose, and reduces hypoglycaemic events.[13,95]

Novel pathways

Glucagon-like peptide-1 receptor agonists were found to exhibit anti-inflammatory and anti-oxidant properties in multiple studies including in the settings of hypoglycaemia,[96] psoriasis, obesity, diabetes,[97] non-alcoholic steatohepatitis,[98] end-stage renal disease,[99] and sepsis.[90,100] Several small RCTs looked at the cardioprotective properties of GLP-1-R analogues and showed that the administration of exenitide in patients with MI treated with percutaneous intervention decreased infarct size on cardiac imaging.[101,102] Similarly, liraglutide therapy in patients with MI was associated with a significant decrease in troponin T levels and an improvement in left ventricular ejection fraction after infarction.[103] However, liraglutide did not improve mortality, time to re-hospitalization, or ejection fraction in patients with advanced heart failure when compared to standard therapy in the small ($N = 300$ patients) Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) Trial.[104]

Other possible mechanistic pathways that may be involved in CVD event reduction include the effect of GLP-1-R agonists on vascular endothelium and platelet aggregation.[105] In endotoxemic mice, GLP-1-R activation with linagliptin and liraglutide was shown to attenuate microvascular thrombosis, nitro-oxidative stress, and platelet activation.[90,106] Data from these pre-clinical studies show that these mechanisms may be cAMP/PKA dependent. Further research is needed to better understand the pathways by which these agents may reduce CVD events.

Conclusion

Four groundbreaking RCTs have found significant CVD risk reduction in diabetic patients treated with empagliflozin, canagliflozin, liraglutide, and semaglutide. The results of these trials are unique since prior studies investigating the use of diuretics or tight glycaemic control in diabetic patients have failed to show a decrease in cardiovascular mortality. When prescribing these agents, the CVD benefit must be weighed against the risks seen in clinical trials including risks of genital infections, toe/metatarsal amputations, and gastrointestinal disturbances. The ideal patient is one that has (i) type II diabetes, (ii) a history of prior MI, coronary revascularization, stroke, cerebrovascular disease, or peripheral artery disease, and (iii) a GFR > 30 mL/min/1.73 m^2. Patients without prior CVD, but with estimated 10-year risk >10% should also be considered.

To determine whether the cardiovascular benefit observed in these trials is class- or drug-specific, we have to wait for the results of cardiovascular outcome trials being currently conducted. Thus far, pre-clinical and clinical studies have shown several novel mechanisms whereby GLP-1-analogues may reduce microvascular thrombosis, inflammation, oxidative stress, and platelet activation. Sodium-glucose cotransporter-2 inhibitors additionally reduce BP, improve cardiac remodelling, and ameliorate cardiac oxidative stress. There is also emerging data that its impact on the Na^+–H^+ exchanger may be an important pathway in heart failure. More extensive animal and human studies are needed to help further understand the mechanistic pathways by which SGLT-2 inhibitors and GLP-1-R agonists incur cardiovascular benefit.

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