Med

CellPress

Review

Cardiorenal mechanisms of action of glucagon-like-peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors

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SUMMARY

Cardiovascular and renal outcome trials (CVOTs) for glucagon-like-peptide-1 receptor agonists (GLP1RA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i) highlight new options for people with and without type 2 diabetes (T2D). Drugs within these classes reduce rates of major adverse cardiovascular events (MACE), with SGLT2i simultaneously attenuating decline in kidney function. SGLT2i reduce rates of heart failure in people with and without T2D, whereas GLP1RA lower rates of myocardial infarction and stroke in people with T2D with or without preexisting cardiovascular disease. Mechanistically, SGLT2 and the GLP-1 receptor are expressed at low levels in the heart, and within some blood vessels and immune cells, implying indirect mechanisms of action for the preservation of ventricular function, and reduction of atherosclerosis. SGLT2i likely preserve renal function through the alteration of glomerular hemodynamics. These two drug classes enable organ protection and reduced mortality in people with T2D and represent promising therapies for some people without T2D.

INTRODUCTION

Traditional guidelines for the treatment of type 2 diabetes (T2D) focused on the efficacy, safety, and cost of glucose-lowering medications,[1] providing recommendations for the initiation and intensification of these medications, generally in a stepwise iterative manner. Based on the results of longitudinal analyses and randomized controlled trials,[2] early initial treatment of glycemia appears highly beneficial for the reduction in microvascular disease, and when sustained over longer periods of time, is also associated with a reduction in macrovascular disease in people with T2D.[3,4]

The approach to the assessment of the safety and approval of glucose-lowering medications was modified in 2008 by guidance from regulatory authorities mandating more extensive scrutiny of cardiovascular (CV) events in new drug development programs, both pre- and postapproval of new drug applications (NDAs) submitted for T2D. These concerns stemmed from questions about the CV safety of rosiglitazone, and were raised in an environment reflecting uncertainty about the benefits versus risk of aggressive glucose lowering in people with T2D at risk for CV disease (CVD).[5] Accordingly, companies filing NDAs for new glucose-lowering medicines were mandated to carry out clinical trials to address the safety guidelines, requirements that were generally fulfilled through dedicated CV safety trials (Figure 1).

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https://doi.org/10.1016/j.medj.2021.10.004

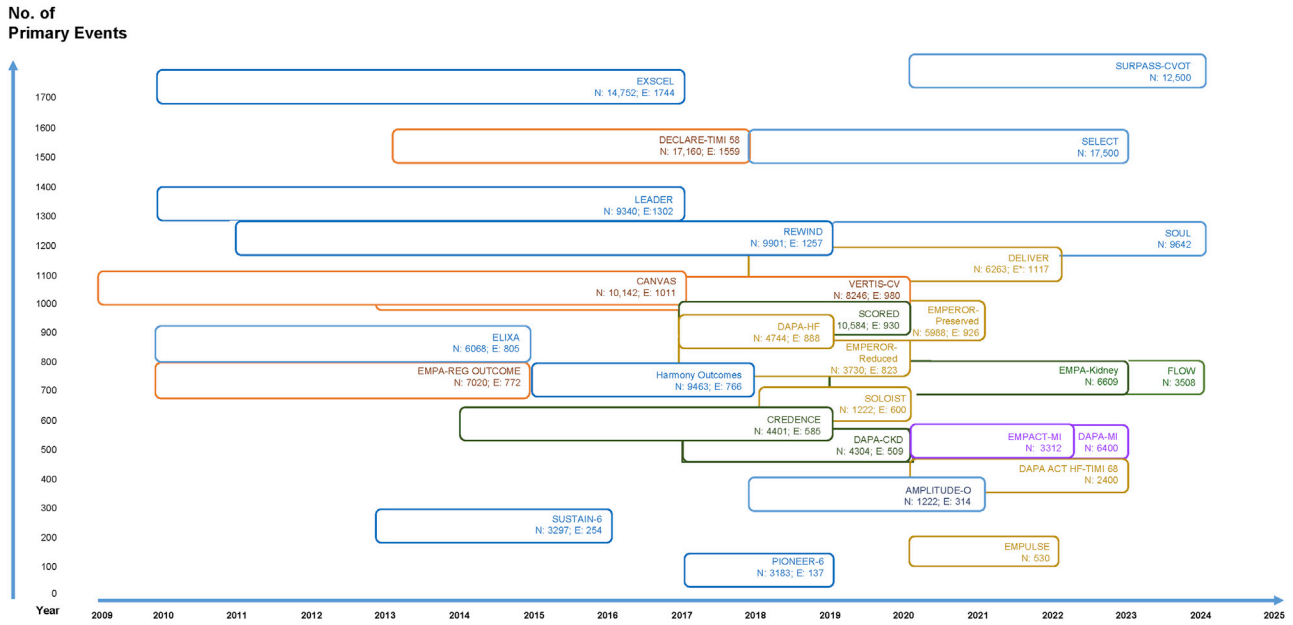

Figure 1. Timeline and characteristics of key outcome trials

The y axis presents the overall number of primary events observed in each trial, which is an indicator of study power reflected in the number of patients enrolled into the trial, length of follow-up, and the risk of the population. The x axis presents time in years. The length of the bars reflect the time (in years) from first patient enrolled to primary results publication. N, sample size; E, observed number of primary endpoints. Some ongoing trials have not reported their expected number of endpoints; their placement is therefore an estimate along the y axis. The use of different colors denotes the different drug classes and trials. GLP1R agonist CVOTs (blue), SGLT2i CVOTs (orange), GLP1RA and SGLT2i renal trials (green), SGLT2i heart failure trials (gold), and SGLT2i CVOT trials in people with previous MI (purple).

Since 2008, three new classes of medicines were approved for the treatment of T2D: the dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like-peptide-1 receptor agonists (GLP1RA), and the sodium-glucose cotransporter 2 inhibitors (SGLT2i). Several DPP-4i CV outcome trials (CVOTs) reported first, and generally demonstrated safety, but not CV benefit.[6–8] In contrast, the majority of trials studying the CV safety of the SGLT2i and GLP1RA medicines have shown a reduction in major CV events within a shorter time horizon than previously demonstrated with the older glycemic drugs.[9,10] The previously completed and ongoing landmark GLP1RA and SGLT2i outcome trials of patients with or at risk for CVD and renal disease are presented in Figure 1. Trials are organized according to chronology, from the year of first patient enrolled through to publication, sample size, and by the observed or estimated number of primary endpoints accrued, which together give a sense of the risk of the population studied. Here, we describe cardiorenal and metabolic mechanisms of action of the GLP1RA and SGLT2i with translational relevance and discuss these mechanisms and gaps in our understanding in the context of clinical trial data.

The biology of glucagon-like peptide-1 (GLP-1)

GLP-1 is co-encoded with glucagon and a series of structurally related peptide hormones in a single mammalian preproglucagon (PPG) precursor (*GCG* gene) expressed in the pancreas, intestine, and central nervous system (CNS).[11,12] GLP-1 is liberated from proglucagon by posttranslational processing predominantly in gut endocrine cells and brainstem neurons.[13] A small amount of GLP-1 is also generated in the pancreas[14]; however pancreatic GLP-1 is not known to meaningfully

contribute to circulating GLP-1[14] or GLP-1R-dependent actions outside the pancreas.[13] The metabolic actions of GLP-1 include glucose-dependent stimulation and inhibition of pancreatic insulin and glucagon secretion, respectively, as well as the inhibition of gastric emptying and reduction in appetite, leading to weight loss.[11,13] These actions are mediated by a single G protein-coupled GLP-1 receptor (GLP-1R). Metabolites of the native GLP-1 peptide generated through enzymatic cleavage may also exert metabolic and CV activity through membrane and mitochondrial signaling pathways independent of the known GLP-1R.[15] Nevertheless, the majority of structurally distinct GLP1RA used for the treatment of T2D or obesity do not result in the generation of these metabolites[11]; hence, they are not considered here further in the context of understanding how the actions of GLP1RA used clinically result in cardioprotection.

L cells as inflammation and tissue injury sensors

Enteroendocrine L cells, predominantly those located in the proximal gut, secrete GLP-1 rapidly in response to nutrient ingestion,[16] whereas the distal gut enteroendocrine cells are highly responsive to microbial metabolites and bacterial cell wall products and also function as pathogen sensors.[17,18] The administration of lipopolysaccharide rapidly increases circulating GLP-1 levels in mice and humans, as does transient intestinal ischemic injury.[18] Moreover, L cells sense multiple microbial metabolites and respond with increased secretory activity. The levels of circulating GLP-1 are increased in people with severe infection and correlate with outcomes in hospitalized critically ill people with sepsis.[19,20]

Gut L cells are also capable of sensing remote tissue injury and sterile inflammation, and respond with increased GLP-1 secretion.[21] Studies in mice, rats, and humans demonstrate that acute myocardial infarction (AMI) is associated with a rapid increase in circulating levels of GLP-1, with the magnitude of the increase correlating with the clinical outcome in human subjects. For example, GLP-1 levels were assessed at the time of admission in 918 subjects with both ST elevation MI (STEMI) and non-STEMI myocardial injury.[22] After correction for multiple comorbidities, GLP-1 levels were strong predictors of a composite outcome of non-fatal MI, non-fatal stroke, and CV death over a median follow-up period of 310 days. Notably, GLP-1 levels on admission were superior for predicting outcomes within 30 days relative to a panel of cardiac biomarkers, including high sensitivity (hs) troponin T, glomerular filtration rate, hs-C-reactive protein, and N-terminal pro-brain natriuretic peptide (NT-proBNP).[22]

Intriguingly, a single report has suggested that the increase in circulating GLP-1 evident after acute STEMI may be blunted in subjects with T2D; however, only 13 subjects with T2D were studied, and these findings await confirmation.[23] The mechanisms through which myocardial injury are communicated to L cells remain uncertain, but may include elevated levels of circulating cytokines, possibly interleukin-6 (IL-6), which increases L cell GLP-1 secretion in animals and, to a lesser extent, in humans.[19,24,25] Levels of IL-6 rise within 2 h after open heart surgery and cardiopulmonary bypass, and are associated with a subsequent 2-fold increase in circulating levels of GLP-1 ~1 h later.[26].The increase in GLP-1 levels post-MI is transient, and the clinical importance, if any, has not been established in preclinical studies.

Experimental studies of GLP-1 and cardioprotection

Animal studies demonstrate robust cardioprotective actions ensuing from the pharmacological administration of GLP-1R agonists in experimental models of CV injury, ranging from atherosclerosis to ischemic cardiac injury, hypertensive

cardiomyopathy, peripheral vascular disease, and stroke.[21,27] Remarkably, the underlying mechanisms linking activation of the GLP-1R to direct or indirect cardioprotection or the reduction of experimental vascular injury remain incompletely understood. Analysis of GLP-1R expression in the mouse or rat heart localizes the majority of cardiac *Glp1r* mRNA transcripts to the atria,[28,29] consistent with detection of *GLP1R* expression in the sinoatrial (SA) node of monkeys and humans.[30] Nevertheless, *GLP1R* mRNA transcripts in the human heart are also detectable by PCR in the ventricles.[31] Comparable levels of *GLP1R* mRNA transcripts were detected in all 4 chambers of the human heart; however, attempts to identify the precise GLP-1R$^+$ cell types by *in situ* hybridization or immunocytochemistry were inconclusive.[32]

The genetic reduction of atrial cardiomyocyte *Glp1r* expression does not attenuate the rapid cardioprotective actions of GLP-1R agonists such as liraglutide in mice with ischemic myocardial injury.[33] Whether the acute cardioprotective actions of GLP1RA demonstrated in preclinical studies are direct via cardiac GLP1Rs or indirect will require additional characterization of GLP-1R$^+$ cardiac cell types.[13] Moreover, the majority of studies interrogating mechanisms linking GLP-1 action to acute cardioprotection use young mice without established atherosclerosis; hence, their translational relevance for understanding GLP-1 action in humans with established T2D and preexisting atherosclerosis is questionable.[34] As discussed below, the time course for the reduction of major adverse CV events in CVOTs is consistent with the actions of GLP1RA to reduce atherosclerosis, rather than a rapid hemodynamic or cytoprotective process.

Localizing GLP-1R expression and function within the vasculature has been challenging.[13,35] Subsets of endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) express the GLP-1R within some vascular beds, yet the majority of ECs and VSMCs do not express the GLP-1R.[13] *Glp1r* expression was detected in murine lung ECs, the aorta, and renal blood vessels.[29,36,37] Genetic attenuation of EC *Glp1r* expression dysregulates endothelial function in mice with angiotensin II-induced hypertension, and abrogates the acute vasoprotective and blood pressure-lowering actions of liraglutide.[36] Immunoreactive GLP-1R protein has also been detected in the renal vasculature of mice, monkeys, and humans within a subset of VSMCs, predominantly in kidney arterioles, findings verified through simultaneous analysis of kidney sections using *in situ* ligand binding.[30,38] Nevertheless, the functional importance of VSMCs in the context of the CV or renal actions of GLP1RA has not yet been interrogated through the use of mouse genetics.

Heart rate (HR) and blood pressure (BP)

Acute administration of GLP1RA increases HR and BP in animals and humans, independent of changes in body weight.[39–41] Reduction in BP with chronic GLP-1R activation may be influenced by, but is often independent of, the extent of weight loss.[42] Mechanistic interpretation of these acute changes may be complicated by rapid simultaneous reductions in blood glucose, particularly in non-diabetic individuals.[43] The increases in HR and BP are not ablated by administration of L-NG-monomethyl arginine (L-NMMA), and reflect contributions from central GLP-1R-dependent augmentation of sympathetic nervous system activity in animals and humans and inhibition of vagally mediated parasympathetic circuits in rats and mice.[41,44–46] The GLP-1R-dependent activation and inhibition of sympathetic and parasympathetic nervous system activity, respectively, appears less important for the control of HR in humans and is not secondary to arterial vasodilation.[47,48] However, 12 weeks of daily liraglutide administration reduced HR variability in overweight and obese subjects with new T2D and coronary artery disease, in association with

electrocardiogram changes on Holter monitoring consistent with reduced parasympathetic activity.[49] In keeping with the importance of SA GLP-1Rs for the regulation of HR, genetic reduction in atrial *Glp1r* mRNA transcripts in mice reduces basal HR and attenuates the increase in HR pursuant to the administration of GLP-1R agonists.[33,50] The central activation of PPG-expressing neurons increases heart rate in mice; however, chemical or genetic ablation of these neurons does not affect basal heart rate or the increase in HR evident after the administration of GLP1RA.[51] Increases in HR persist in humans with T2D or obesity chronically treated with GLP1RA, whereas the increases in BP are transient. More sustained GLP-1R agonism lowers BP after several weeks in the majority of hypertensive subjects with T2D independent of weight loss, with the relative reduction in systolic BP proportional to the degree of hypertension at the start of therapy.[52–54]

Natriuresis, kidney function, and the renin angiotensin aldosterone system (RAAS)

GLP1RA rapidly increase urinary sodium excretion in preclinical studies, actions mediated through the canonical GLP-1R.[55] Acute natriuretic actions of GLP1RA are preserved in normal human volunteers and blunted in individuals with T2D or obesity.[53,56] Consistent with mechanistic data from preclinical studies, co-infusion of the GLP-1R antagonist exendin(9-39) completely blocks the natriuretic actions of GLP-1 in humans.[57] The natriuretic actions of exenatide were not abrogated by co-infusion of the nitric oxide (NO)-synthase inhibitor L-NMMA in healthy overweight male volunteers.[58] Although acute GLP-1 infusion reduced angiotensin II levels in some studies, the majority of acute or chronic experiments examining the effects of GLP1RA have not detected consistent directional changes in RAAS components such as plasma levels of renin, aldosterone, and angiotensin II. Similarly, most studies do not observe changes in natriuretic peptides or catecholamines in subjects treated with GLP1RA, with or without T2D.[53,59–61] The natriuretic actions of GLP1RA are blunted in rats with experimental heart failure (HF),[62] but whether similar findings are evident in humans with HF treated with GLP1RA has not been studied.

Substantial preclinical data identify a renoprotective role for GLP1RA in experimental kidney disease, associated with reduced renal inflammation and structural and functional preservation of kidney function.[37,63,64] These findings are difficult to reconcile mechanistically with localization of the GLP-1R in the kidney within a small subset of arterial VSMCs.[30] GLP1RA consistently reduce rates of albumin excretion, predominantly macroalbuminuria in CVOTs, in a baseline population at low risk of progression to chronic kidney disease (CKD); however, rates of dialysis and kidney transplantation are not different in people randomized to GLP1RA.[65,66] Acute administration of GLP1RA to people with overweight and T2D had little effect on renal hemodynamics, including glomerular filtration rate (GFR).[67] Whether long-term administration of these agents reduces the slope of estimated GFR (eGFR) decline in subpopulations of individuals with T2D has not been carefully studied,[65] and larger dedicated renal outcome trials are under way to test the hypothesis that longer durations of therapy with GLP1RA may be clinically renoprotective. Mechanistically, the putative role(s) of the renal vascular GLP-1R or GLP-1Rs outside the kidney in mediating the increase in urine sodium or the reduction in experimental kidney inflammation[37,63] evident in preclinical studies with GLP1RA requires further investigation.

Atherosclerosis and dyslipidemia

GLP1RA have little effect on fasting lipid levels beyond reductions associated with reduced food intake and weight loss. Nevertheless, gain and loss of function studies

in mice demonstrate that GLP-1R signaling is critical for postprandial secretion of ApoB48-containing triglycerides.[68] Preclinical studies in high-fat diet-fed and ob/ob mice demonstrated that 10 days of liraglutide administration reduced hepatic *Pcsk9* and induced *Ldlr*/LDLR expression.[69] Acute intraduodenal administration of exenatide suppressed the appearance and production rate of triglyceride-rich lipoprotein apolipoprotein B-48 in humans, consistent with a role for GLP-1R signaling to control enterocyte lipoprotein secretion.[70] The suppression of postprandial triglycerides is independent of gastric emptying or insulin secretion in mice and humans, remains intact in people with or without T2D or obesity, and is not diminished with sustained GLP-1R agonism.[71,72] The underlying mechanisms reflect the reduction in chylomicron secretion; however, enhanced clearance of ApoB48 lipoproteins has also been demonstrated.[68,69,70,73]

Attenuation of postprandial ApoB48 production was observed in people with T2D treated with liraglutide 1.2 mg daily for 6 months, in association with increased fractional clearance of ApoB48 assessed through kinetic studies using stable isotopic enrichment.[73] Notably, liraglutide also reduced HbA1c and body weight, confounding mechanistic interpretation of the data. Separate studies with liraglutide administration for 6 months to 10 people with T2D (baseline HbA1c 9.6%, mean body mass index [BMI] 36.6 kg/m^2) revealed increased rates of catabolism of low-density lipoprotein (LDL)- and very-low-density lipoprotein (VLDL)-associated ApoB100 and decreased circulating levels of PCSK9, in people with 4 kg of weight loss and a reduction in mean HbA1c to 7.1%.[69] Consistent with these findings, tracer kinetic studies in 8 men with obesity and T2D revealed that treatment with once-daily lixisenatide for 4 weeks had a minimal impact on chylomicron production, yet increased the clearance of triglyceride-rich chylomicrons.[74]

The relative contributions of distinct cell types linking GLP-1R signaling to the control of lipoprotein secretion or catabolism have not been conclusively identified, as the GLP-1R is not detected within enterocytes, hepatocytes, or renal epithelium.[13,75,76] Although GLP1RA have been proposed to activate neural mechanisms indirectly regulating hepatic and intestinal lipoprotein secretion,[77,78] genetic reduction in *Glp1r* expression in the CNS, enteric, or autonomic nervous system in mice did not diminish the acute actions of GLP1RA to inhibit nutrient-stimulated triglyceride secretion.[79] Hence, the cellular sites of GLP-1R expression that communicate inhibitory signals to enterocytes enabling reduction of chylomicron secretion require additional interrogation.

GLP1RA attenuate the development of plaque formation and experimental atherosclerosis in genetically sensitized *Ldlr*$^{-/-}$ and *Apoe*$^{-/-}$ mice.[10,80] Liraglutide and semaglutide downregulated genes associated with inflammatory processes in major blood vessels from mice with atherosclerosis, independent of changes in body weight. However, it is difficult to localize GLP-1R expression within many arteries or in macrophages.[75,80] Whether and how GLP1RA reduce macrophage activation and plaque formation in blood vessels, perhaps through indirect neural mechanisms that contribute to restraining vascular inflammation and reduction of atherosclerosis, is under investigation.

Within the immune system, the predominant site of GLP-1R expression is the intestinal intraepithelial lymphocyte (IEL).[81,82] Low levels of *Glp1r* mRNA transcripts are detected within other immune cell populations[83]; however, their functional importance for GLP-1R-dependent control of inflammation and atherosclerosis has not been established. Acute and chronic administration of GLP1RA lowers biomarkers

of circulating and tissue inflammation in animals and in some but not all human studies.[81,84–87] How this is accomplished, independent of weight loss or improvements in metabolic control, is not clear, as the GLP-1R is not expressed in hepatocytes, adipocytes, myocytes, or the majority of circulating or tissue-resident immune cells.[13] The possibility that the IEL or neuronal GLP-1Rs communicate anti-inflammatory signals to distal organs requires genetic targeting of these GLP-1R populations in preclinical studies.

Platelets and coagulation

The actions of GLP1RA to directly inhibit platelet activation and aggregation and reduce clot formation have been inconsistent, detected in some but not all studies.[88,89] Moreover, functional expression of the canonical GLP-1R has not been reproducibly demonstrated on human platelets.[90,91] Native GLP-1, GLP-1(9-36), and liraglutide inhibited platelet aggregation *ex vivo* in donor platelets obtained from normocholesterolemic but not hypercholesterolemic human subjects, and the treatment of hypercholesterolemic subjects with simvastatin reduced plasma lipid levels and decreased platelet aggregation, yet it did not restore platelet responsivity to GLP1RA.[92] In contrast, GLP-1 reduced experimental thrombus formation in a perfused human blood flow system *ex vivo*, but it failed to inhibit platelet aggregation in static platelets studied *ex vivo*.[91] Although experimental thrombus formation was greater in recipients of GLP-1R-deficient bone marrow,[88] platelet aggregation was not different in platelets from *Glp1r*$^{-/-}$ versus *Glp1r*$^{+/+}$ mice.[91] Hence, the available data support a possible indirect role for GLP1RA in the regulation of experimental platelet aggregation.

AMI

Animal studies have demonstrated the cardioprotective benefits of GLP1RA given at the time of experimental ischemia.[27,93] Therapy with native GLP-1, exenatide, or liraglutide has been initiated in people with or without T2D at the time of AMI and revascularization, with the period of administration ranging from several hours to 28 days. The results have been mixed, with several studies showing no clinical difference in the extent of infarction or related clinical outcomes.[94–96] Some studies show modest improvements in ejection fraction (EF) and reductions in infarct size and area at risk; however, the magnitude of these changes have been small and the clinical relevance remains uncertain.[97] Despite considerable clinical investigation, there is little compelling evidence to support a clinically meaningful benefit of using GLP1RA in people with AMI.[98,99] Although no safety concerns have been noted, and circulating levels of pro-inflammatory biomarkers have trended lower in people with AMI treated with GLP1RA, there is little evidence that GLP1RA meaningfully preserve ventricular function or decrease hospitalization or rates of complications after MI.

The disappointing studies of GLP1RA in AMI stand in contrast to the reduction in rates of the composite outcome of non-fatal MI, stroke, and CV death in CVOTs in people with T2D treated with long-acting GLP1RA.[100–106] Notwithstanding the limitations of making conclusions based on analysis of secondary endpoints, it is intriguing to note that GLP1RA such as albiglutide exert a predominant effect to reduce rates of MI relative to stroke when administered as therapy for T2D.[103] The GLP-1R may be expressed in a small subset of coronary artery vascular smooth muscle cells or ECs; however, the majority of blood vessels and cardiomyocytes in the heart do not express the GLP-1R.[13,29,32,107] Acute infusion of native GLP-1 produces coronary artery microvascular dilation and increased blood flow in stable subjects

without acute ischemia[107]; however, studies with degradation-resistant GLP1RA have not consistently detected similar changes in coronary blood flow.

HF

Functional improvement in ventricular function in animals or people with ventricular dysfunction or HF has been observed following the infusion of native GLP-1[108,109] or degradation-resistant GLP1RA.[86,110] GLP-1 may improve HF indirectly by reducing BP, enhancing vasodilation, and shifting myocardial fuel utilization to a more favorable energetic state. Nevertheless, ventricular *Glp1r* expression is very low in mice, rats, and humans.[13,28,32] It seems likely that the beneficial cardiac actions of GLP1RA are indirect or mediated through the vasculature.[111] Although within individual CVOTs, evaluation of the efficacy of GLP1RA on HF has been underpowered and inconclusive, in a meta-analysis of all GLP1RA CVOTs, the risk of hospitalization for HF was reduced by 9% predominantly in subjects with no HF at baseline.[112]

Albiglutide was studied in people with class II or III HF and reduced EF. No meaningful benefit was observed in functional outcomes, myocardial glucose, or oxygen utilization, or echocardiographic parameters of cardiac function after 12 weeks.[113] CVOTs assessing the safety of GLP1RA included substantial (10%–18%) proportions of individuals with class I and class II HF; no safety signal nor any unique benefit was detected in this subset of trial participants.[100–102,104–106] Analysis of a real-world cohort of 1,499,650 patients and 29,741 subsequent hospitalizations for HF in Canada, the United Kingdom, and the United States did not reveal any increased risk associated with the use of GLP1RA.[114]

The effect of the LIraglutide on Left VEntricular Function (LIVE) trial assessed liraglutide 1.8 mg once daily for 24 weeks in stable individuals (89% men) with HF with reduced EF (HFrEF), namely an EF <45%, the majority with New York Heart Association (NYHA) functional class I or II status. Baseline EF was 33.7% and 35.4% in volunteers randomized to liraglutide versus placebo, respectively. Of 241 enrolled subjects, ~30% of had T2D, the majority treated with metformin.[115] The EF, NYHA functional class, and levels of NT-proBNP were not different between groups at the end of the trial; however, perfomance in the walking test was greater in people treated with liraglutide and BP trended lower; however, HR increased by 7 beats per minute and serious cardiac adverse events (AEs), including atrial fibrillation and ventricular tachycardia, were more common with liraglutide (10% versus 3%) treatment.[115]

The Functional Impact of GLP-1 for HF Treatment (FIGHT) trial examined the effects of liraglutide in people with HFrEF and a recent (within 2 weeks of enrollment) hospitalization for HF, predominantly reflecting the presence of ischemic heart disease.[116] Notably, 59% of subjects had T2D and >85% of study enrollees had been hospitalized for HF at least once before the most recent hospitalization required for trial eligibility.[116] NYHA classifications were 29%, 63%, and 5%, for class II, II, and IV HF, respectively. No difference in the primary composite endpoint encompassing time to death, or re-hospitalization for HF, and time-averaged change from baseline to 180 days in NT-proBNP was detected between groups.

Some evidence from animal and human studies, including experiments carried out with native GLP-1, suggests that GLP-1R agonism may improve substrate utilization in the failing heart. Twelve weeks of albiglutide administration improved peak oxygen uptake but had no effect on EF or myocardial glucose utilization in non-diabetic subjects with NYHA class II or class III HF.[113] Analysis of a subset of individuals

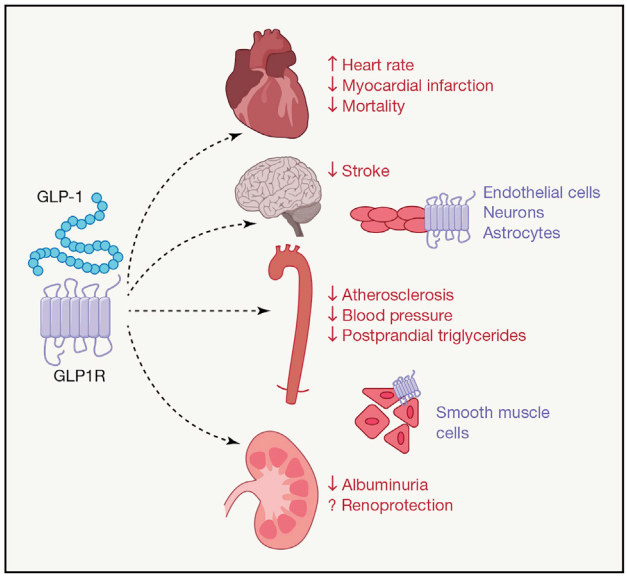

Figure 2. Mechanisms of GLP-1 action in the cardiorenal system
GLP1R, glucagon-like peptide-1 receptor.

without T2D treated with liraglutide 1.8 mg daily or placebo for 26 weeks in the LIVE trial revealed no changes in myocardial glucose uptake, myocardial blood flow (MBF), or MBF reserve, despite the reduction in body weight and HbA1c in liraglutide-treated subjects.[117] Post hoc analysis of biomarkers in the LIVE trial (EF <45%) revealed that subjects with T2D randomized to liraglutide exhibited a 27% and 25% reduction in levels of mid-regional pro-atrial natriuretic peptide (MR-proANP) and NT-proBNP, respectively, despite no accompanying evidence for clinical benefit.[118] Liraglutide increased HR in subjects in the LIVE trial in sinus rhythm (SR), but not in those without SR; however, these increases in HR were not correlated with the development of AEs.[118]

Stroke

The GLP-1R is widely distributed within the CNS, and gain and loss of function preclinical studies demonstrate a role for the GLP-1R in neuroprotection.[13,119,120] Whether the neuroprotective actions of GLP1RA are direct on neuronal or astrocyte populations, or they reflect activities on atherosclerosis, blood vessels, platelets, or inflammation, remains uncertain.[13] In some human CVOTs, GLP1RA reduced the rates of ischemic but not hemorrhagic stroke,[101,106,121] actions evident in people with or without a history of stroke.[121] Post hoc analysis of people treated with dulaglutide in the dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND) trial revealed a reduction in the composite endpoint of non-fatal stroke or all-cause mortality, as well as a decrease in disabling stroke.[121]

Future directions

The mechanisms linking GLP1RA to cardioprotection are not understood (Figure 2). The use of GLP1RA in CVOTs may be associated with reduced rates of severe hypoglycemia, due in part to their glucose-dependent mechanisms of action, coupled with greater use of insulin and sulfonylureas in control subjects. Although severe hypoglycemia is associated with increased rates of major adverse cardiovascular events (MACEs) in several CVOTs, its contribution to the overall rates of MACE is

generally low (1%–3%), and GLP1RA such as liraglutide reduced the rates of MACE in people with and without a history of severe hypoglycemia.[122]

The cardioprotective actions of GLP1RA in people with T2D have been associated with observations of reduced rates of cognitive impairment in CVOTs, ascertained through serial standardized assessment of cognitive function[123] or via spontaneous reporting of diagnoses of neurodegenerative disorders. The improvement in cognitive function may be detected within 12 weeks, independent of changes in cardiometabolic risk factors, and associated with increased brain activation approximated through measurements of oxyhemoglobin concentrations.[124] Oral semaglutide is being studied in an investigational Phase III program in people at risk for developing Alzheimer's disease. The preponderance of outcome data for GLP1RA reflects their use in people with T2D. Hence, the forthcoming results of the Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) trial examining the CV safety of semaglutide in people with obesity and established CVD without diabetes are of great interest.[125] Based on the above mechanisms and promising data from CVOTs with GLP1RA, including Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER), Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), REWIND, and others, these therapies reduce albuminuria progression and may prevent significant eGFR loss. Accordingly, the ongoing FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial (NCT03819153) is designed to assess the impact of semaglutide on cardiorenal risk in patients with established diabetic kidney disease (DKD) (Figure 1).

GLP1RA have also shown promise as neuroprotective agents, and oral semaglutide is being studied in 2 Phase III trials of early Alzheimer's disease. The mechanisms underlying the neuroprotective actions of GLP-1 are likely multifactorial and include direct cytoprotective actions on neurons, and likely indirect benefits arising through reduction of inflammation.[10,119] Two exploratory trials have also demonstrated therapeutic benefit in people with Parkinson's disease treated with exenatide twice daily or exenatide once weekly,[126,127] benefits that persisted for several months following drug discontinuation.

SGLT2 inhibition, use as an anti-hyperglycemic agent, and clinical endpoints

SGLT2i were originally developed and used as a glucose-lowering therapy in people with T2D.[128] Anti-hyperglycemic efficacy with SGLT2i is achieved through an increase in urine glucose excretion, leading to HbA1c lowering of between 0.6% and 0.9% in people with preserved kidney function.[129] In addition, body weight is reduced by 2–3 kg, and blood pressure is lowered by 3–5 mmHg systolic and 1–2 mmHg diastolic, with preserved BP lowering in people with CKD.[129,130] Beyond this favorable metabolic and CV profile, CVOTs with SGLT2i have demonstrated consistent reductions in CV and kidney endpoints across patients with a wide range of baseline atherosclerotic CVD (ASCVD), HF, and CKD risk (Figure 1).[131–134] Although similar physiological effects with SGLT2i occur in people with type 1 diabetes (T1D) compared to those with T2D,[135,136] this review is focused primarily on those with T2D, non-diabetic CKD, and non-diabetic HF.

Among CVOTs with SGLT2i, the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) and Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS-CV) trials were completed in patients with established ASCVD, while those in the Canagliflozin

Cardiovascular Assessment Study (CANVAS) Program included patients with a predominance of established ASCVD at baseline in approximately two-thirds of participants.[131,133,134] At the other end of the spectrum, the Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial included the lowest risk cohort, only 40% of whom had established ASCVD at baseline.[132] In addition, the mean eGFR was ~10 mL/min/1.73 m^2 higher in this trial compared to EMPA-REG OUTCOME, the CANVAS Program, and VERTIS-CV. In the Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial, patients at high CV risk with kidney function impairment (eGFR 20–60 mL/min/1.73 m^2) were included.[137] Across these CVOTs, CV death was reduced only in EMPA-REG OUTCOME, while MACE was reduced in EMPA-REG OUTCOME,[131] CANVAS,[133] and SCORED.[137]. However, the risk of hospitalization for HF (HHF) was reduced in all of the trials, regardless of baseline risk.[138] Differences in benefits across these trials may reflect the era of the trial, differences in background use of other therapies, or heterogeneity in the cohorts recruited into these trials.[138,139] Reductions in HHF have also been demonstrated in dedicated HF trials in patients with and without T2D as well as individuals with and without reduced EF.[140–143] Benefits in people with HF have been reported across different levels of CKD risk, including those with more advanced CKD.[140,141,144]

Beyond the reduction of HHF, SGLT2i prevent kidney disease progression.[138,145,146] In CVOTs, kidney composite endpoints, especially when decline in eGFR is defined using a sustained ≥40% eGFR loss, were reduced by >30% with no significant heterogeneity across different trials.[147] Of note, in VERTIS-CV, the hazard ratio for the key secondary kidney composite endpoint involving a double of serum creatinine (equivalent to ≥57% decline in eGFR) did not reach significance. This may reflect (1) the composite endpoint not mandating the eGFR decline is sustained; (2) the level of decline of ≥57%, which was a much more severe level of progression not typical of DKD over a relatively brief period of time captured in a clinical trial in patients included on the basis of CVD; and (3) the lower overall risk of the cohort, making it additionally challenging to show benefits within the time frame of the trial.[148,149] Nevertheless, when the more conventional sustained ≥40% eGFR loss definition was used, the benefits of ertugliflozin aligned closely with effects seen in other trials with these agents. Furthermore, dedicated kidney protection trials such as Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) and A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease (DAPA-CKD) have demonstrated reductions in the risk of CKD progression in patients with albuminuria, with the latter trial also showing benefits in people with non-diabetic CKD.[150–152] Therefore, based on both dedicated HF and kidney disease trials, SGLT2i reduce cardiorenal risk in those with and without diabetes (Figure 3).

Mechanisms for protection against kidney disease

Hemodynamics

Based on evidence generated in people without diabetes in the DAPA-CKD trial, the understanding of how SGLT2i exert kidney protection has continued to move away from a "glucocentric" focus.[153–156] Before DAPA-CKD, it was known that kidney benefits are likely glucose independent and do not appear to be associated with renal SGLT2 mRNA expression.[157] The concept of glucose-independent kidney benefits was predicated on several clinical observations such as renal hemodynamic mechanisms, including changes in GFR and albuminuria reductions

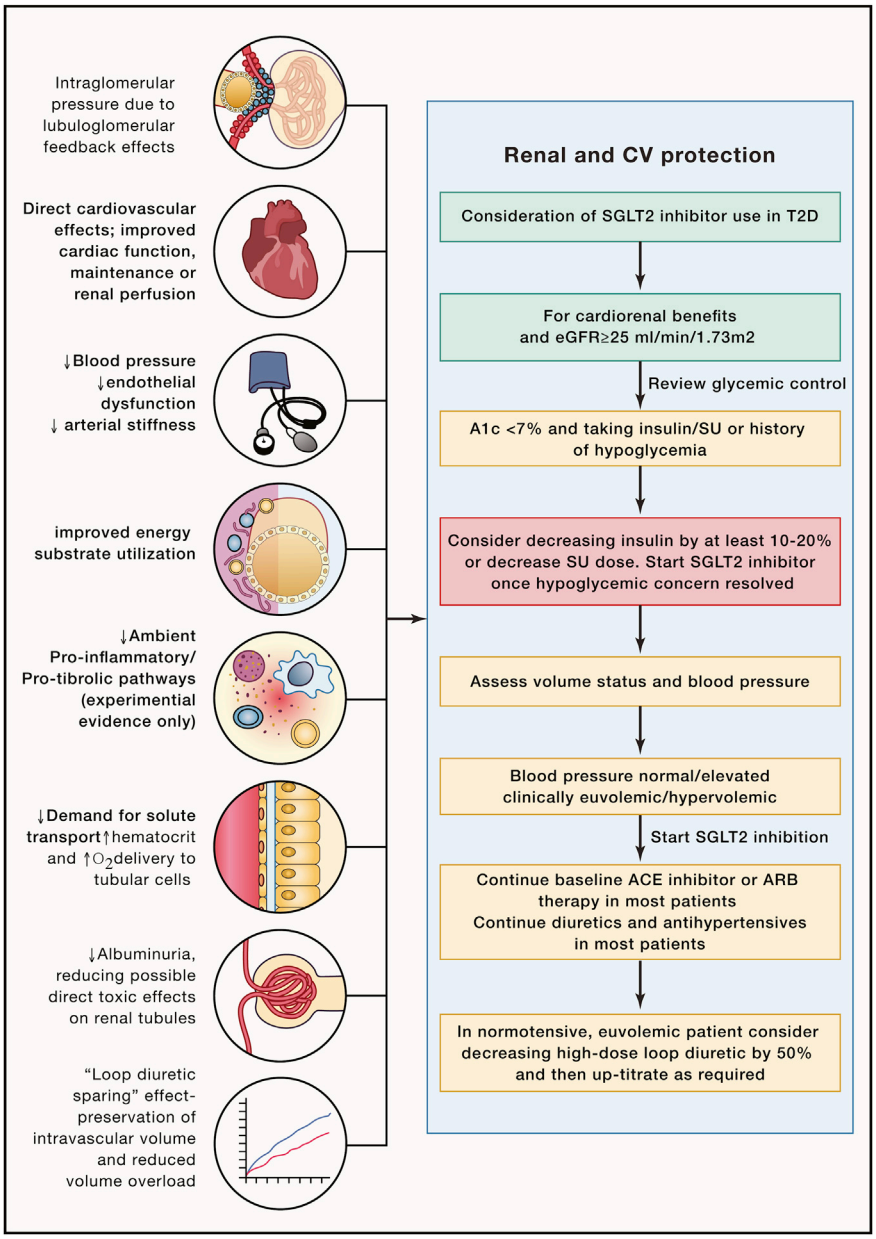

Figure 3. Cardiorenal protection and possible mechanisms associated with SGLT2 inhibition

occurring regardless of kidney function at baseline, with those with low GFR.[158] Since glucosuria and glucose lowering attenuates with the loss of kidney function, kidney benefits are unrelated to glycemic improvements. Moreover, beneficial effects on albuminuria and kidney function have been reported with SGLT2i studies that used an active control such as sulfonylurea agents, which achieved similar glycemic efficacy.[159] Analyses from EMPA-REG OUTCOME and CREDENCE have examined the interaction between SGLT2 inhibition and kidney composite endpoints and have demonstrated that kidney benefits are statistically independent of both HbA1c at baseline and changes over time.[160,161] Similarly, mediation analyses have not demonstrated a statistical relationship between HbA1c and kidney outcomes.[162]

Experimental and human mechanistic studies have reported other pathways that are closely linked with kidney protection in response to SGLT2 inhibition (Figure 3), especially those related to natriuresis.[163–165] The natriuresis induced by SGLT2 inhibition is physiologically important in animals and humans and associated with reduced glomerular pressure after even a single dose.[166] A reduction in glomerular hypertension also occurs with SGLT2i, which likely reflects tubuloglomerular feedback (TGF), although other mediators may also be involved.[167,168] In brief, by inducing a proximal natriuresis, sodium chloride delivery is increased to the macula densa, which is a salt-sensing structure located between the afferent and efferent arterioles. This increase in sodium chloride delivery leads to the increased metabolism of adenosine triphosphate to reabsorb these electrolytes, resulting in the generation of adenosine. Once generated, adenosine acts as a vasoconstrictor at the glomerular inflow afferent arteriole, leading to a decline in glomerular blood flow and glomerular pressure, thereby attenuating the intraglomerular hypertensive state that is characteristic of diabetes, especially in early disease when hyperfiltration is common. Notably, human mechanistic studies demonstrate a decline in hyperfiltration in young people with T1D, in conjunction with an increase in urine adenosine excretion, decreases in kidney hyperperfusion, and an increase in renal vascular resistance, all in keeping with afferent vasoconstriction.[135,169]

In animal models of T1D, studies using *in vivo* microscopy demonstrated that the afferent arteriole constricts acutely after 2 h, leading to reduced single nephron GFR.[170] While reductions in glomerular pressure were previously demonstrated, the direct visualization of afferent constriction highlights the intriguing concept that the afferent hemodynamic effects of SGLT2i may be complementary to the efferent vasodilatory action of RAS inhibitors.[171,172] Moreover, in the experimental work by Kidokoro et al.,[170] the investigators were able to abolish the afferent vasoconstrictive effect of SGLT2 inhibition with the use of pharmacological adenosine receptor antagonism, demonstrating for the first time that SGLT2i signaling is adenosine dependent.

While the GFR "dip" with SGLT2 inhibition occurs in people with and without diabetes,[173] whether this afferent adenosine-mediated mechanism is as central in people with T2D, those with established CKD, and those with non-diabetic CKD is less clear and merits further investigation.[174] Regardless of the mechanism, however, the magnitude of the eGFR dip is similar across the use of different vasoactive medications (RAS inhibitors, diuretics), and is linked with long-term eGFR preservation, perhaps due to an underlying reduction in glomerular hypertension.[175,176] The lack of safety concern around this initial eGFR dip has led to more streamlined guidance for initiating these therapies in practice, without routine monitoring of blood work in most patients.[177,178]

Hypoxia-related pathways

In addition to hemodynamic-related pathways, SGLT2 inhibition may activate renoprotective mechanisms by improving kidney oxygenation (Figure 3). Diabetes and CKD are associated with renal hypoxia and ischemia, leading to inflammation, fibrosis, and decline in kidney function.[179] The basis for hypoxia is multifactorial and includes increased energy requirements due to glomerular hyperfiltration, tubular growth, and increased transporter (including SGLT1 and SGLT2) activity. In addition, diabetes is associated with impaired energy delivery and utilization on the basis of vascular ischemia, mitochondrial dysfunction, and switches to use of energy-inefficient fuel substrates. These processes have been described in detail elsewhere and lead to oxidative cell injury and death, as well as the activation

of pro-inflammatory pathways, matrix remodeling and capillary rarefaction.[180] Blockade of SGLTs can improve kidney oxygenation through several pathways, including attenuation of hyperfiltration, which reduces kidney workload and improves renal tubular oxygenation, at least in the renal cortex of diabetic rats.[181–183] Improved renal tubular oxygen tension on the basis of declines in hypoxia-induced factor 1α (HIF-1α) with SGLT2 inhibition reflects alleviation of tissue hypoxia leading to attenuated fibrosis. In addition to improved oxygenation, kidney protection may arise from favorable changes in the metabolome in response to SGLT2 inhibition, reflected by a reduction in tricarboxylic acid metabolite accumulation, effects that are linked with less oxidative stress and albuminuria lowering.[184]

Less is known about the effects of SGLT2 inhibition on human kidney oxygenation. In cultured human epithelial cells, SGLT2 inhibition attenuates hypoxia-induced HIF-1α expression and expression of genes linked with tissue fibrosis.[185] *In vivo*, in healthy humans with no evidence of CKD, SGLT2i do not affect blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI)-derived measures of cortical or medullary hypoxia.[186]

Similar trials involving kidney oxygenation in people with diabetes and/or CKD are under way but have not been reported. Studies involving individuals with hyperfiltration and diabetes are needed to answer this question, since this is the clinical setting with the most potential to demonstrate whether SGLT2i-mediated improvements in tissue oxygenation would produce meaningful clinical benefit.

In addition to intrarenal mechanisms leading to improved renal parenchymal oxygenation, it is important to recognize potential contributions from systemic factors that preserve kidney perfusion and energy balance. SGLT2i reduce the risk of HHF, and in doing so, lead to the maintenance of adequate end-organ perfusion, including the kidney. This may be achieved physiologically through several pathways, including a reduction in loop diuretic doses and avoidance of volume depletion.[187] Empagliflozin also optimizes left ventricular (LV) filling pressure, leading to improvements in Starling forces, cardiac contractility, and forward flow.[188]

Beyond these preload-related factors, SGLT2i reduce blood pressure and arterial stiffness, effects that are linked to decreases in afterload, which could improve subendocardial blood flow and cardiac function, thereby increasing forward flow and kidney perfusion.[177,189] A final "systemic" factor that may augment renal oxygenation is an increase in oxygen-carrying capacity based on elevations in hematocrit in response to SGLT2 inhibition. Whether the increase in hematocrit associated with SGLT2 inhibition promotes an improvement in target-organ perfusion remains controversial, since long-term increases in hematocrit are most closely linked with hemoconcentration, rather than with an increase in erythropoiesis.[163] Nevertheless, based on close associations between higher hematocrit and improved CV prognosis, the relationship between oxygen-carrying capacity and kidney physiology and CKD progression merits further investigation.[190]

Inflammation

Activation of pro-inflammatory factors is a common final pathway for CKD progression in many conditions, including DKD and also various causes of non-diabetic CKD.[191] Renal inflammation is multifactorial and can occur secondary to high intraglomerular pressure resulting in glomerular wall tension and shear stress; inflammation may also arise secondary to metabolic stress and neurohormonal activation. SGLT2 inhibition suppresses levels of inflammatory cytokines in animals, including

monocyte chemoattractant protein-1 (MCP-1), IL-6, IL-1β, and tumor necrosis factor α (TNF- α).[192] SGLT2i also suppress the injurious effects of advanced glycation end products (AGEs) and AMP-activated kinase dysfunction on pro-fibrotic pathways that are activated by hyperglycemia.[193–196] Importantly, the impact of SGLT2 inhibition on pro-inflammatory and pro-fibrotic pathways is additive to the effect of RAS inhibition in experimental models.[197,198] The impact of SGLT2 inhibition on glomerular pressure, albuminuria lowering, and renal neurohormones (Figure 3) may also contribute to anti-inflammatory effects of these therapies.[193,199–201]

One of the central mechanisms leading to kidney injury and DKD progression involves high levels of oxidative and endoplasmic reticulum stress, in part due to impaired autophagy, a mechanism that usually clears the cytoplasm of dysfunctional organelles. A role for SGLT2i has also been reported in the context of impaired renal autophagy, associated with reduction in the extent of impaired mitochondrial oxygen consumption, reduced inflammation, decreased expression of HIF-1, and improved energy metabolism.[185,202,203] Another major pathway that likely contributes to the suppression of tubular injury, inflammation, and fibrosis involves increased renal generation of ketones. Ketone bodies inhibit the mechanistic target of rapamycin complex 1 (mTORC1), which enhances kidney fibrosis.[204,205] SGLT2 inhibition has increased ketone levels and prevented kidney injury in diabetic mice through an mTORC1-dependent mechanism.[205]

SGLT2 inhibition also reduces biomarkers of inflammation and fibrosis, including IL-6, TNF receptor-1, and fibronectin, in human studies.[191,199] The urinary excretion of kidney injury molecule (KIM)-1 was reduced in people treated with dapagliflozin[199] or empagliflozin,[206] suggesting a decline in tubular injury. Beyond prevention of CKD progression over time, hypoxia-inflammation benefits with SGLT2 inhibition may also protect against ischemia-perfusion injury in animal models.[207,208] Consistent with data from animal studies,[207] the risk of acute kidney injury with SGLT2 inhibition is lower in CVOTs and in real-world evidence studies.[163,209,210]

The mechanisms responsible for protection against CKD protection with SGLT2 inhibitors are summarized in Figure 3. The clinical benefits of these therapies have been demonstrated across clinical trials in people with diverse etiologies of CKD. Accordingly, clinical practice guidelines and approved indications for SGLT2i recommend the use of these therapies in populations of patients who were included in the clinical trials described above.[211–213] Ongoing trials are evaluating the use of SGLT2i in novel subgroups of patients such as in kidney transplant recipients (e.g., NCT04965935),[211] in which there is a large unmet need for new cardiorenal protective therapies.[214] In addition, the Study of Heart and Kidney Protection With Empagliflozin (EMPA-KIDNEY) trial is evaluating the effect of empagliflozin in those with low GFR and also normoalbuminuria and microalbuminuria who were not enrolled into RAS inhibitor or dedicated SGLT2i renal trials.[212,213]

CV protection and SGLT2 inhibition

As with renal protection, CV benefits in patients treated with SGLT2i are disproportionate to the degree of glycemic control, weight loss, and blood pressure lowering achieved with this class of therapy.[9,190] Furthermore, the very early emergence of a treatment benefit on reducing incident or recurrent HHF and CV death argues that the mechanism must at least in part affect CV physiology acutely.[215] In contrast, effects on the metabolic milieu or atherosclerotic plaque, although potentially contributory and beneficial long term, are not likely responsible for the consistently

observed early CV benefit among patients with and without HF at baseline, including those without diabetes.

Studies of SGLT2 inhibition in patients with T2D and stable ischemic heart disease or LV hypertrophy have demonstrated a reduction in LV mass and reverse myocardial remodeling over a short duration of time.[216,217] Similarly, SGLT2 inhibition may prevent or reduce adverse cardiac remodeling in patients with HFrEF,[218–221] although there has been inconsistency in the results.[222] Preclinical studies have shown that SGLT2 inhibition can preserve or improve systolic and diastolic function in HF.[220,223,224] No unifying mechanism has been established; however, a number of hypotheses are under investigation.

One prevailing mechanism focuses on whether the sodium excretion from SGLT2 inhibition results in a natriuresis and osmotic diuresis leading to sustained reduction in plasma volume without a depletion in intravascular volume or an adverse activation of the sympathetic nervous system.[225] Among 20 patient volunteers with T2D and chronic HF with reduced LV systolic function, empagliflozin therapy modestly (0.4%) increased the fractional excretion of sodium ($FENa^+$) compared with placebo, without concomitant loop diuretic therapy.[225] When studied in conjunction with bumetanide, there was a synergistic effect on the fractional excretion of Na^+, which increased 1.7%. The natriuretic effect of empagliflozin persisted out to 14 days, with a resultant reduction in plasma volume and total body water. However, in contrast to loop and thiazide diuretics, natriuresis with empagliflozin was not associated with off-target electrolyte wasting, renal dysfunction, and neurohormonal activation. Whether the natriuretic effect is transient or persistent remains unclear with divergent findings to date.[226,227]

These observations have been called the "smart natriuresis" hypothesis since this favorable diuretic profile may offer a significant advantage in the management of volume status in patients with or at risk of HF by reducing preload and myocardial stretch. Nevertheless, this hypothesis has yet to be convincingly demonstrated in clinical outcome studies via a reduction in circulating natriuretic peptides, surrogate markers of myocardial overload typically responsive to natriuresis and associated with improved outcomes.[228] For instance, although canagliflozin modestly reduced circulating levels of NT-proBNP (11%) at 1 and 6 years of follow-up in the CANVAS trial, mediation analysis suggested that the reduction in NT-proBNP explained only a small proportion of the benefit of canagliflozin on HHF events in the trial.[229] In the Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) and Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure (DEFINE-HF) studies, treatment of patients with (1) acute decompensated HF with empagliflozin and (2) stable HF with reduced EF with dapagliflozin did not result in significant differences in NT-proBNP levels. despite a reduction in HF outcomes at 60 days in the former study and improvement in HF quality of health status in the latter study.[230,231]

Another theory that has emerged to explain HHF benefits is that SGLT2 inhibition directly affects cardiomyocyte cytosolic sodium and mitochondrial calcium handling, resulting in protection by early amelioration of cardiac injury and reduction of hypertrophy.[232] One mechanism may be via cross-inhibition of the upregulated sodium-hydrogen exchanger (NHE) receptor in the presence of myocardial stress and injury.[233] Activation of the NHE in the heart and vasculature (NHE1 isoform) and the kidneys (NHE3 isoform) contributes to the pathophysiology of HF with cardiac hypertrophy, injury, and fibrosis in part via mediation of aldosterone,

angiotensin II, and norepinephrine.[233] Specifically, the increased expression of NHE1 results in increased cytosolic sodium (Na^+) and calcium ion (Ca^{2+}) concentrations but reduced mitochondrial Ca^{2+} and ATP generation. Although SGLT2 has traditionally not been thought to be expressed in the heart.[234] SGLT2 inhibition can inhibit the cardiac NHE1 receptor via a shared binding site affinity.[235,236] The inhibition of cardiac NHE1 reduces cytosolic Na^+ and Ca^{2+} levels and increases mitochondrial Ca^{2+} levels, resulting in improved mitochondrial respiration, increase in ATP production, and consequently improved cardiomyocyte viability and coronary vasodilation.[236] Furthermore, improved contractile function and reduced risk of arrhythmia may also be mediated via cross-inhibition of Ca^{2+}/calmodulin-dependent kinase II activity,[232] and the late component of the cardiac sodium channel current (late-I_{Na}),[237] resulting in improved Ca^{2+} handing. Synergistically, SGLT2 inhibition also reduces cardiac inflammation via blunting activation of the nucleotide-binding domain-like receptor protein 3 (NLRP3) inflammasome in a Ca^{2+}-dependent manner, which may also contribute to its beneficial cardiac effects.[237,238] Interestingly, SGLT2 is transiently expressed in the heart tissue of non-diabetic mice with AMI.[221] Treatment with empagliflozin reduced the infarct size within 3 days of MI. SGLT2 localized to the infarct zone, was detectable within 1 day, and peaked within 3 days post-MI in the controls, but there was a slower onset and reduced overall appearance of SGLT2 in mice treated with empagliflozin.[221] Thus, through NHE inhibition, possibly leading to transiently expressed SGLT2 in the injured heart or other calcium-handling mediated mechanisms, there appears to be increasing recognition of potential direct cardioprotective effects from SGLT2 inhibition. Accordingly, 3 ongoing trials, EMPACT-MI (A Streamlined, Multicenter, Randomized, Parallel Group, Double-Blind Placebo-Controlled Superiority Trial to Evaluate the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction, NCT04509674), EMMY (Impact of Empagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute Myocardial Infarction; NCT03087773), and DAPA-MI (Dapagliflozin Effects on Cardiovascular Events in Patients With an Acute Heart Attack; NCT04564742), are designed to assess the cardioprotective effects of SGLT2i in patients with recent acute myocardial infarction with or without T2D (Figure 1).

A third postulated mechanism is that SGLT2 inhibition induces a physiologic adaptive response in increased free fatty acid and ketone levels from a whole-body shift in fuel metabolism away from glucose oxidation and toward fat oxidation in the presence of continuous glucosuria (a perceived pseudo-starvation state).[239–241] Animal models and biospecimen data from clinical trial participants show a rapid onset and sustained duration in the shift in fuel metabolism with SGLT2 inhibition, which is postulated to result in improved cardiomyocyte energetics and early improvement in cardiovascular outcomes.[242,243] For example, in a non-diabetic pig model of ischemic cardiomyopathy, Santos-Gallego et al.[244] showed that empagliflozin rapidly and profoundly modulated cardiac metabolism with reduced glucose oxidation and increased use of ketone bodies, fatty acids, and branched-chain amino acids, resulting in improved myocardial efficacy and cardiac ATP content and a parallel improvement in LV mass, size, and function. Nevertheless, it remains unclear whether a more efficient fuel supply in the heart is the cause or a consequence of improved cardiac function.

Beyond improvement in blood pressure and weight, reduction in arterial stiffness and oxidative stress with SGLT2i therapy has been associated with improvements in LV filling pressures, myocardial pressure handling, and cardiac contractility.[245,246] For example, in isolated perfused heart experiments and molecular

docking analyses of pressure-overloaded non-diabetic mice models, empagliflozin was found to directly bind cardiac glucose transporters, which resulted in rebalanced coupling between glycolysis and oxidative phosphorylation and regulation of the activation of adenosine monophosphate-activated protein kinase mTORC1 pathway to attenuate adverse cardiac remodeling and the progression of HF.[247]

Further indirect effects of improved myocardial oxygen delivery via increased erythropoietin production and hematocrit concentration as described above have been raised as another potential contributor to improved myocardial tissue oxygen delivery and reduced LV mass.[248–250]

Finally, preclinical and translational experiments suggest that SGLT2i treatment has the potential to prevent or stabilize atherosclerotic plaque. Postulated mechanisms include reduction in circulating inflammatory factors, modulating lipid profiles and inhibition of the RAAS,[251,252] inhibition of platelet activation via reduction in plasminogen activator inhibitor (PAI)-1,[253] modulation of endothelial function via increased production of NO and endothelial NO synthases (eNOS),[254] reduction in foam cell formation and macrophage activation through a number of intermediary signaling pathways,[255] reduction in oxidative stress via reduction in reactive oxygen species (ROS) formation and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits,[256] reduction in VSMC proliferation and migration via hemeoxygenase (HO)-1 augmentation,[257] and prevention of autophagy via augmentation of AMP-activated protein kinase and sirtuin (SIRT)-1.[258] Nevertheless, further research is needed in this field to elucidate whether the atheroprotective effects of SGLT2i are independent of simply lowering glucose and lipid levels. Moreover, such atherosclerotic plaque-stabilizing mechanisms may contribute longer term to CV risk reduction, but are not typically expected to translate short term (i.e., within weeks to months) into improved clinical outcomes. The very early and marked HF protective effect of SGLT2i in clinical trials suggests that anti-atherosclerotic effects are not the predominant mechanism of early CV protection, including a modest reduction in the risk of MI across the totality of outcome data. However, as patients are studied with SGLT2i earlier following an AMI, and with extended follow-up of outpatients treated long term with SGLT2i, these effects may become more appreciable.

In summary, although a unifying mechanism remains elusive, treatment with SGLT2 inhibition has demonstrated consistent reductions in incident and recurrent HF, and to a lesser degree, cardiovascular mortality.[9,138,259] Clinical practice guidelines recommend SGLT2i therapy in patients with diabetes at high cardiovascular risk or with existing atherosclerosis.[260] Furthermore, SGLT2i therapy is strongly recommended in patients with HF with reduced LV systolic function irrespective of the presence or absence of T2D.[261–263] Given the recent results showing a promising reduction in risk in patients with HF and preserved EF with empagliflozin, as well as recent decompensated HF across the spectrum of EF with sotagliflozin, it is likely that this class of therapy will soon be the standard of care across among all patients with HF, irrespective of EF.[263] Similarly, further ongoing trials investigating the benefit of SGLT2i in patients with HF and preserved EF[264] and acute decompensated HF[265] will presumably emphasize that these benefits are a class effect of SGLT2i. Next on the horizon are trials testing the efficacy and safety of SGLT2i in patients early following AMI[266,267] with or without T2D. As their benefit across the spectrum of patients with CVD continues to expand, this class of therapy is coming of age as the next-generation cardioprotective therapy to the cardiologist, much as RAAS inhibition did in the 1990s.

Conclusions

There is great interest in the combined use of GLP1RA and SGLT2i in people with T2D at risk of developing cardiovascular events. Although 15%–20% of people enrolled in the efpeglenatide cardiovascular outcome trial were treated with both a SGLT2i and the GLP1RA efpeglenatide,[106] larger, longer studies in different patient populations will be needed to ascertain the unique cardioprotective potential of this combination.

The cardioprotective actions of SGLT2i and GLP1RA have not been extensively studied in people with T1D. Although some SGLT2i are approved for the treatment of T1D in Europe, GLP1RA are not licensed anywhere for the therapy of T1D. Given the risks of developing CKD, HF, and ASCVD in people with T1D, it seems prudent to reconsider the need for studies of these agents in people with T1D at heightened risk of developing cardiorenal complications. The development of SGLT2i and GLP1RA holds great potential for reducing the burden of CV and renal complications in people with and without T2D, which may be achieved through enhanced multispecialty collaboration involving diabetologists, cardiologists, and nephrologists dedicated to reducing the complications of chronic cardiometabolic disorders.

ACKNOWLEDGMENTS

This work was supported in part by CIHR grant 154321, a Banting and Best Diabetes Centre-Novo Nordisk Chair in Incretin Biology, and the Sinai Health Novo Nordisk Fund in regulatory peptides (all to D.J.D.). D.Z.I.C. is supported by a Department of Medicine, University of Toronto Merit Award and receives support from the CIHR, Diabetes Canada, and the Heart and Stroke Richard Lewar Centre of Excellence. J.A.U. is supported by a Department of Medicine, University of Toronto Merit Award and receives support from the Ontario Ministry of Colleges and Universities Early Researcher Award (ER15-11-037), CIHR, the Heart and Stroke Foundation of Canada, the Women's College Research Institute, the Department of Medicine, Women's College Hospital, and the Peter Munk Cardiac Centre, Toronto General Hospital.

DECLARATION OF INTERESTS

D.J.D. has served as a consultant or speaker for Eli Lilly, Forkhead, Kallyope, Merck, Novo Nordisk, and Pfizer. Basic science studies in the Drucker lab are supported in part by grants from Novo Nordisk and Pfizer. DJD holds non-exercised stock options in Kallyope. D.Z.I.C. has received consulting fees, speaking honoraria, or both, from Bristol-Myers Squibb, Novo Nordisk, Mitsubishis-Tanabe, MAZE, Janssen, Bayer, Boehringer Ingelheim-Eli Lilly, AstraZeneca, Merck, Prometic, and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli Lilly, Sanofi, AstraZeneca, Novo Nordisk, and Merck. J.A.U. has served as a consultant or speaker for AstraZeneca, Bayer, Boehringer Ingelheim-Lilly, Janssen, Merck, Novartis, and Sanofi and receives research grants to his institution from Amgen, Bayer, Boehringer Ingelheim-Lilly, and Janssen.

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