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Mechanistic insights regarding the role of SGLT2 inhibitors and GLP1 agonist drugs on cardiovascular disease in diabetes☆

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ABSTRACT

The treatment landscape for patients with established or at high risk for cardiovascular disease and type 2 diabetes mellitus has entirely changed over the past decade, with the introduction of several anti-hyperglycemic agents. Sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists are two anti-hyperglycemic classes which have been of special interest after multiple large cardiovascular disease (CVD) outcomes studies have demonstrated superiority of these agents compared to placebo for major adverse CVD events and in some cases, hospitalization for heart failure. Despite the dramatic results of these trials, only recently have we began to understand the mechanisms underlying these CVD benefits. Here we review the underlying mechanisms which have the greatest plausibility for both of these agents including the impact of ventricular loading conditions, direct effects on cardiac structure and function, myocardial energetics and sodium/hydrogen exchange for SGLT2 inhibitors, and the anti-atherosclerotic, anti-inflammatory, and modulation of endothelial function for GLP-1 agonists.

Contents

Abbreviations: AHGA, anti-hyperglycemic agents; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BP, blood pressure; Bpm, beats per minute; CAD, Coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; DPP4, dipeptidyl-peptidase-4; DPP4i, dipeptidyl-peptidase-4 inhibitor; EF, ejection fraction; FDA, Food and Drug Agency; GLP-1, glucagon-like-peptide-1; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, Heart failure; HFrEF, Heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVM, left ventricular mass; LVMi, left ventricular mass indexed; MACE, major adverse cardiovascular disease event; MI, myocardial infarction; MMP, Matrix metalloproteinases; MRI, magnetic resonance imaging; NHE, Na^+/H^+ exchanger; NO, Nitric oxide; PPAR, peroxisome proliferator-activated receptor; SA, sinoatrial; SBP, systolic blood pressure; SDF-1, stromal cell derived factor-1; SGLT2, Sodium-glucose cotransporter 2; STEMI, ST elevation myocardial infarction; T2D, type 2 diabetes mellitus; U.S., United States; VSMC, vascular smooth muscle cell.

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Introduction

The treatment options for patients with type 2 diabetes (T2D) and cardiovascular (CV) disease (CVD) has recently expanded at an unprecedented rate. The findings of significant CVD benefits with new anti-hyperglycemic agents (AHGA) such as sodium glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) agonists have dramatically changed the narrative after drugs such as the peroxisome proliferator-activated receptor (PPAR)-gamma agonists, saxagliptin and alogliptin from the class of dipeptidyl-peptidase-4 (DPP4) inhibitors showed adverse CVD outcomes. After concerns were raised about the anti-hyperglycemic agent rosiglitazone, a PPAR-gamma agonist regarding increased risk of myocardial infarction (MI), the United States (U.S.) Food and Drug Agency (FDA) issued a guidance requiring pre- and post-approval studies demonstrating CVD safety.[1–3] This resulted in multiple large cardiovascular outcomes trials in recent years that have transformed the diabetes management landscape.

Of all the AHGA agents which have been studied, SGLT2 inhibitors and GLP1-agonists standout amongst the rest as having clear, demonstrable CVD benefits (Table 1).[4–7] The EMPA-REG-OUTCOME trial which studied SGLT2 inhibitors versus placebo in patients with T2D and known atherosclerotic CVD (ASCVD) was the first to demonstrate benefit with a significant reduction in its composite primary outcome of CVD mortality, non-fatal MI or non-fatal stroke.[4] Furthermore, it showed a significant reduction in all-cause mortality, CVD mortality and a significant reduction in hospitalization for heart failure (HF).[4]

Table 1
Summary of large cardiovascular outcomes trials for SGLT2-inhibitors.

Name of clinical trial	Description	Key inclusion criteria	Major findings
EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)	Double-blind, placebo controlled RCT (phase 3) of Empagliflozin 10 mg or 25 mg daily vs. placebo. *N* = 7020	≥18 years old, type 2 DM with established cardiovascular disease, BMI < 45, GFR > 30	**3-point MACE**: 10.5% in Empa vs. 12.1% in placebo group (HR 0.86, 95% CI 0.74 to 0.99, P = 0.04 for superiority). **Cardiovascular death**: 3.7% in Empa vs. 5.9% in placebo group (HR 0.62, 95% CI 0.49 to 0.77, *P* < 0.001) **All-cause mortality**: 5.7% in Empa vs. 8.3% in placebo group (HR 0.68, 95% CI 0.57 to 0.82, P < 0.001) **Hospitalization for HF**: 2.7% in Empa vs. 4.1% in placebo group (HR 0.65, 95% CI 0.50 to 0.85, *P* = 0.002)
CANVAS Program (Canagliflozin Cardiovascular Assessment Study)	Combination of 2 sister (CANVAS + CANVAS-R) double-blind placebo-controlled RCTs (phase 3) of Canagliflozin 100 mg or 300 mg daily vs. placebo *N* = 10,142	≥30 years old, type 2 DM with symptomatic ASCVD or ≥ 50 years old, with ≥2 cardiac RF, eGFR>30	**3-point MACE** (no. of participants per 1000 patient-years): 26.9 in Cana vs. 31.5 in placebo group (HR 0.86 95%CI 0.75 to 0.97, *P* = 0.02 for superiority). Cardiovascular death and all-cause mortality: P=NS **Hospitalization for HF**: 5.5 in Cana vs. 8.7 in placebo group (HR 0.67 95%CI 0.52 to 0.87), P=NS based on pre-specified hypothesis testing sequence
DECLARE-TIMI-58 (Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes)	Double-blind, placebo- controlled RCT (phase 3) of dapagliflozin 10 mg vs. placebo *N* = 17,276	≥40 years old, type 2 DM, multiple risk factors for ASCVD or established ASCVD. Patients with multiple risk factors were men ≥55 or women ≥60 with ≥1 traditional cardiac risk factor	**3-point MACE:** 8.8% in Dapa vs. 9.4% in placebo group (HR 0.93, 95% CI 0.84 to 1.03, *P* = 0.17 for superiority) **Cardiovascular death or hospitalization for heart failure:** 4.9% in Dapa vs. 5.8% in placebo group (HR 0.83, 95% CI 0.73 to 0.95, *P* = 0.005) **Hospitalization for HF**: 2.5% in Dapa vs. 3.3% in placebo group (HR 0.73, 95% CI 0.61 to 0.88)
CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial	Double-blind, placebo-controlled RCT (phase 3) of canagliflozin 100 mg vs. placebo *N* = 4401	≥30 years old, type 2 DM, CKD with GFR (CKD-EPI) 30 to <90 ml per 1.73m^2 of BSA and albuminuria with urine ACR >300 to 5000	**Primary composite outcome** (ESRD, doubling of serum creatinine level from baseline, or death from renal or CV cause – no. of participants per 1000 patient-years): 43.2 in Cana vs. 61.2 in placebo group (HR 0.70, 95% CI 0.59 to 0.82, *P* = 0.00001)

Data presented that was statistically robust or met endpoint of trials.

The reduction in CVD mortality was thought to be driven by reduction in HF hospitalizations. The CANVAS program later using the same composite primary outcome demonstrated superiority of another SGLT2 inhibitor, canagliflozin, versus placebo in patients with T2D and high CVD risk.[5] The CVD benefits of SGLT2 inhibitors was confirmed as a true class effect with the results from the DECLARE-TIMI-58 study which demonstrated superiority of dapagliflozin vs. placebo in its composite primary outcome of CVD death or hospitalization for HF.[6] The statistical superiority of this primary outcome was shown to be primarily driven by hospitalization for HF.[6]

Five large CVD outcome studies using GLP1 agonists in patients with T2D and either established or elevated risk for CVD have been reported (Table 2).[8–12] The ELIXA trial, using lixisenatide in patients with T2D and a recent acute coronary event, and the EXSCEL trial using exenatide in patients with T2D with or without previous CVD events both demonstrated CVD safety, but not superior cardiovascular efficacy as compared to placebo.[8,11] Conversely, the SUSTAIN-6 trial showed superiority for semaglutide vs. placebo for their composite primary outcome (first occurrence of death from CVD causes, nonfatal MI or nonfatal stroke) in patients with T2D and either established CVD, chronic HF or high risk

Table 2
Summary of large cardiovascular outcomes trials for GLP-1 agonists.

Name of clinical trial	Description	Key inclusion criteria	Major findings
ELIXA (The Evaluation of Lixisenatide in Acute Coronary Syndrome) trial	Double-blind, placebo controlled RCT (phase 3) of lixisenatide 10μg to 20μg daily vs. volume matched placebo $N = 6068$	≥30 years old, type 2 DM and had an ACS within 180 days of screening	Primary outcome – time to event analysis of first occurrence of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina: 13.4% in lixisenatide vs. 13.2% in placebo group (HR 1.02, 95% CI 0.80 to 1.17, P < 0.001 for non-inferiority, $P = 0.81$ for superiority) **Hospitalization for HF**: 4.0% in lixisenatide vs. 4.2% in placebo group (HR 0.96, 95% CI 0.75 to 1.23, $P = 0.75$)
LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial	Double-blind, placebo controlled RCT (phase 3) of liraglutide 1.8 mg or maximum tolerated dose vs. matching placebo once daily in addition to standard care $N = 9340$	≥50 years old, type 2 DM with at least one cardiovascular co-existing condition or ≥ 60 with at least one cardiovascular risk factor	Primary outcome – time to event analysis of first occurrence of CV death, nonfatal MI, nonfatal stroke: 13% in liraglutide vs. 14.9% in placebo group (HR 0.87, 95% CI 0.78 to 0.97, $P = 0.01$ for superiority) **Cardiovascular death**: 4.7% in liraglutide vs. 6.0% in placebo group (HR 0.78, 95% CI 0.66 to 0.93, $P = 0.007$) **All-cause mortality**: 8.2% in liraglutide vs. 9.6% in placebo group (HR 0.85, 95% CI 0.74 to 0.97, $P = 0.02$) **Hospitalization for HF**: 4.7% in liraglutide vs. 5.3% in placebo group (HR 0.87, 95% CI 0.73 to 1.05, $P = 0.14$)
SUSTAIN-6 (The pre-approval Trial to Evaluate Cardiovascular and other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)	Double-blind, placebo- controlled RCT (phase 3) of semaglutide 0.5 or 1.0 mg vs. matched placebo once weekly $N = 3297$	≥50 years old, type 2 DM with established cardiovascular disease, chronic heart failure or chronic kidney disease, or age ≥ 60 with at least one cardiovascular risk factor	**Primary outcome – first occurrence of CV death, nonfatal MI, nonfatal stroke:** 6.6% in semaglutide vs. 8.9% in placebo group (HR 0.74, 95% CI 0.58 to 0.95, P = 0.02 for superiority) **Nonfatal Stroke:** 1.6% in semaglutide vs. 2.7% in placebo group (HR 0.61, 95% CI 0.39 to 0.99, $P = 0.04$) **Hospitalization for HF**: 3.6% in semaglutide vs. 3.3% in placebo group (HR 1.11, 95% CI 0.77 to 1.61, $P = 0.57$)
EXSCEL (Exenatide Study of Cardiovascular Event Lowering)	Double-blind, placebo-controlled RCT (phase 3) of exenatide 2 mg or matching placebo once weekly $N = 14,752$ (10,782, 73% with previous CV disease)	Adults with type 2 DM. Designed such that 70% had previous cardiovascular events and 30% had no prior history of cardiovascular events	**Primary outcome – first occurrence of CV death, nonfatal MI, nonfatal stroke:** 11.4% in exenatide vs. 12.2% in placebo group (HR 0.91, 95% CI 0.83 to 1.00, $P = 0.06$ for superiority) **Hospitalization for HF:** 3.0% in exenatide vs. 3.1% in placebo group (HR 0.94, 95% CI 0.78 to 1.13)
Harmony Outcomes (Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease)	Double-blind, placebo-controlled RCT (phase 3) of albiglutide 30-50 mg vs. matched volume placebo once weekly $N = 9463$	≥40 years old, type 2 DM and established coronary, cerebrovascular or peripheral arterial disease with HbA1c >7.0%	**Primary outcome – first occurrence of CV death, nonfatal MI, nonfatal stroke:** 7% in albiglutide vs. 9% in placebo group (HR 0.78, 95% CI 0.68 to 0.90, $P = 0.0006$ for superiority) **Fatal or nonfatal MI:** 4% in albiglutide vs. 5% in placebo group (HR 0.75, 95% CI 0.61 to 0.90, $P = 0.003$) **Composite of CV death and hospital admission for heart failure:** 4% in albiglutide vs. 5% in placebo group (HR 0.85, 95% CI 0.70 to 1.04, $P = 0.113$)

Data presented that was statistically robust or met endpoint of trials.

for CVD.[10] It is important to note however that SUSTAIN-6 was not powered for superiority but rather designed as a non-inferiority trial for CVD outcomes, and thus the superiority analysis was not prespecified. Nonetheless, a higher event rate than initially estimated in addition to the treatment effect of semaglutide supported the superiority analysis, which was found to be largely driven by a significant reduction in nonfatal stroke with semaglutide. In addition, the LEADER trial investigating liraglutide vs. placebo in patients with T2D and high CVD risk definitively showed CVD benefit.[9] The primary outcome was similar to SUSTAIN-6 with a time to event analysis of the first occurrence of CVD death, nonfatal MI and nonfatal stroke. Using hierarchical testing, the investigators demonstrated non-inferiority, and then superiority of liraglutide vs. placebo for its primary outcome. Finally, in 2018 the results of the Harmony Outcomes study demonstrated that a once weekly GLP1 agonist, albiglutide, was superior to placebo for the composite primary outcome of the first occurrence of CVD death, MI or stroke in patients with T2D and established CVD.[12]

Furthermore, a meta-analysis of these trials with the exception of the Harmony Outcomes study showed a 10% relative risk reduction in the three-point major adverse CVD event (MACE) primary outcome (CVD death, non-fatal MI, non-fatal stroke), a 13% risk reduction in CVD mortality and a 12% risk reduction in all-cause mortality, confirming the beneficial effect of GLP1 agonists on CVD outcomes.[13]

Despite these dramatic findings, insight into the mechanisms which drive the CVD outcomes seen in these large clinical trials has only recently become available, with a tremendous amount of research still ongoing to resolve considerable knowledge gaps. Here we provide a summary of the currently explored mechanisms by which SGLT2 inhibitors and GLP1 agonists modulate the CV system in T2D patients. Discussion about other AHGA, such as dipeptidyl-peptidase 4 inhibitors (DPP4i), and their impact on CVD outcomes is beyond the scope of this article.

Type 2 diabetes and cardiovascular disease

T2D is a well-known independent risk factor for macrovascular disease, including coronary, cerebrovascular and peripheral vascular disease. Dating back to the Framingham study in 1979, T2D was noted to have a twofold to threefold increased risk of clinical ASCVD.[14,15] Diabetes results in hyperglycemia, increased free fatty acid oxidation, and insulin resistance, all which increase oxidative stress. Hyperglycemia decreases endothelial derived nitric oxide (NO) leading to impaired endothelial relaxation. Furthermore, hyperglycemia can increase the production of oxygen free radical species which in turn causes endothelial dysfunction. Platelet function is also adversely affected by T2D; glycoproteins Ib, IIb and IIIa are increased which augment von Willebrand factor and platelet-fibrin interaction. Thus, there is a predisposition for platelet activation and aggregation with risk of thrombosis and associated plaque rupture.[16]

Moreover, the Framingham study observed that the impact of T2D on HF was actually greater than that for coronary heart disease.[14] Numerous reports since the Framingham study have shown the strong association between T2D and HF.[17] In a study of 65,619 patients with T2D treated with insulin in a U.S claims database, the incident rate of hospitalization for HF during the 6-year period of study was 243 per 10,000 patients.[18] To provide perspective, the incident rate of hospitalization for MI was only 97 per 10,000 patients.[18] Although the correlation between T2D and HF is well established, T2D as a direct causal factor for HF has been less certain.[19] Yet, large CV societies, such as the American Heart Association and European Society of Cardiology, have devised definitions for the entity of “diabetic cardiomyopathy” which focuses on ventricular dysfunction in the absence of ASCVD and hypertension.[20] Diabetic cardiomyopathy manifests as left ventricular (LV) hypertrophy and fibrosis, leading to decreased LV compliance (stiffness), impaired diastolic filling and eventually systolic dysfunction.[20] Similar to the impact of diabetes on the development of endothelial dysfunction and coronary atherosclerosis, the pathogenesis of HF in T2D patients also implicates free fatty acid oxidation, reactive oxygen species and impaired calcium handling in addition to neurohormonal changes in the renin-angiotensin-aldosterone system and autonomic dysfunction.[20] Understanding the pathogenesis of CVD in T2D patients can help clarify the mechanisms involved in improved CVD outcomes with the use of SGLT2 inhibitors and GLP1 agonists.

SGLT2 inhibitors: mechanisms modulating the CV system

Despite the profound CV impacts of SGLT2 inhibitors, the high capacity low affinity SGLT2 receptors are located in the proximal convoluted tubules of the kidney rather than in cardiomyocytes.[21,22] Inhibition of these SGLT2 receptors prevents reabsorption of filtered glucose at the proximal convoluted tubule and leads to insulin-independent glycosuria. The use of SGLT2 inhibitors in patients with T2D results in an average loss of 1 to 3 kg of body weight, a reduction of approximately 1% in HbA1c, a 3 to 6 mmHg reduction in systolic blood pressure (BP; SBP) and a 0 to 2 mmHg drop in diastolic BP.[4–6,21,22] Moreover, the weight loss associated with SGLT2 inhibitors is not merely a reflection of fluid loss but rather is associated with a significant loss of adipose tissue mass, demonstrated using bioimpedance spectroscopy.[23] However, analyses have demonstrated that even when adjusting for BP, lipid status and HbA1c over time, the reductions in HF hospitalization and CVD death were preserved.[24,25]

It is also important to note the heterogeneous effects of SGLT2 inhibitors in primary and secondary prevention populations for CVD outcomes. In a systematic review and meta-analysis of SGLT2 inhibitors from the three largest CVD outcomes trials of SGLT2 inhibitors, including EMPA-REG-OUTCOME, CANVAS and DECLARE TIMI-58 studies, it was shown that a reduction in ASCVD events were limited to patients with established ASCVD.[26] Whereas the benefit of SGLT2 inhibitors in reducing hospitalization for HF or progression of renal disease was apparent even in primary prevention populations without a history of established HF or pre-existing ASCVD.[17,26]

Currently there are a number of potential hypothesis under investigation regarding the underlying mechanisms thought to significantly impact CVD outcomes.[22,27,28] Here we will focus on the most plausible and accepted mechanisms of CV benefit, including osmotic diuresis and natriuresis and its impact on LV loading conditions, cardiac metabolism and bioenergetics, and the impact of SGLT2 inhibitors on the myocardial sodium/hydrogen ion exchanger.

Impact on ventricular loading conditions

Optimal cardiac function relies upon intricate balances in the preload and afterload of the ventricle. Sufficient preload is required to maintain cardiac output. However, in HF with volume overload, the cardiomyocytes are unable to stretch any further to augment forward systolic flow and maintain cardiac output.[29] These principles illustrated by the Frank-Starling curve suggest that reducing the volume overload, i.e. preload, through diuresis may help to put the patient on a more optimal part of the Starling-Curve to optimize cardiac function. SGLT2 inhibitors support these principles through both osmotic diuresis and natriuresis.

The mechanism of osmotic diuresis in SGLT2 inhibitors is directly linked to how the drug promotes reduction in plasma glucose levels and improved glucose homeostasis. By blocking the SGLT2 receptors in the proximal convoluted tubule, SGLT2 inhibitors prevent reabsorption of glucose. Glucose which is now forced to remain in the tubule draws water across the osmotic gradient, and leads to electrolyte free water diuresis in addition to glycosuria.[30] In addition to this osmotic diuresis, SGLT2 inhibitors promote natriuresis.[31] Typically, 60–70% of sodium filtered by the glomerulus is reabsorbed by the proximal convoluted tubule.[32] SGLT2 receptors are responsible for approximately 5% of the sodium reabsorption at the proximal convoluted tubule, and

under conditions of chronic hyperglycemia, SGLT2 capacity is increased and thus contributes even more to sodium reabsorption.[22] Normally, inhibition of sodium reabsorption at the level of the proximal convoluted tubule would lead to increased reabsorption of sodium in the loop of Henle. However, due to the osmotic effect of increased glucose and sodium in the tubule, the tubular fluid has a lower concentration of sodium and chloride, which effectively inhibits the Na-K-2Cl cotransporter involved in reabsorption of sodium in the loop of Henle.[33] The natriuretic effect of SGLT2 inhibitors is further supported by studies demonstrating decreased plasma volume and total body sodium content.[34] In a mediation analysis of the EMPA-REG-OUTCOME trial, Inzucchi et al., sought to determine the underlying mechanism behind empagliflozin's reduction in CVD death. They found that changes in hematocrit of all the variables explored had the largest impact on the hazard ratio for cardiovascular death.[35] Empagliflozin significantly increased hematocrit, which could be a surrogate marker for a decrease in plasma volume. Thus, through osmotic diuresis and natriuresis, SGLT2 inhibitors are able to have favorable impacts on preload and LV filling pressures for patients with heart failure.

It is important to note that classic diuretics such as thiazides and loop diuretics, such as furosemide have not been shown to have CVD outcome benefits. This is potentially due to the observation that SGLT2 inhibitors promote a greater decrease in interstitial fluid relative to blood volume.[30] This may have significant benefits in reducing neurohormonal activation via the renin-angiotensin-aldosterone system which act to increase fluid and sodium retention, vasoconstriction and accordingly decrease peripheral and renal perfusion.[30]

SGLT2 inhibitors also have an important role in modulation of afterload through reduction in arterial stiffness in addition to the previously described reduction in BP. Afterload is comprised from resistance at the level of the arterioles in addition to the pulsatile load generated by increased arterial stiffness.[36] Increased afterload is also indicative of increased myocardial oxygen demand, which is associated with CVD morbidity and mortality.[37] Using surrogates for arterial stiffness such as the ambulatory arterial stiffness index and pulse pressure, a large post-hoc analysis of phase III trials in which patients with T2D received empagliflozin demonstrated that empagliflozin was associated with not only decreased BP, but also favorable effects on markers of arterial stiffness and vascular resistance.[37] These findings were further supported by a pilot study designed to explore the systemic and renal vascular effects of dapagliflozin.[38] In this study, measures of vascular and endothelial dysfunction such as differences in aortic pulse wave velocity, brachial flow mediated dilation and shear rates were found to be statistically significant in the dapagliflozin group versus hydrochlorothiazide, suggesting that SGLT2 inhibitors specifically improve systemic vascular function.[38]

Direct impact on cardiac structure and function

There is emerging evidence that independent of the impact of SGLT2 inhibitors on LV loading conditions, there may be benefits directly on cardiac remodeling. The EMPA-Heart trial (NCT: NCT02998970) which studied patients with T2D and established coronary artery disease demonstrated a reduction in LV mass (LVM) indexed (LVMi) to body surface area in patients treated with empagliflozin versus placebo for 6 months.[39] This was thought to be in part due to a reduction in wall stress, a concept explained best by the Laplace relationship whereby in order to produce a given intraventricular pressure for a given ventricular radius, cardiomyocytes are required to generate stress.[40] Hypertrophy is an expected response to reduce wall stress. Thus, by empagliflozin's ability to reduce wall stress, it may have reduced LVMi.

Improving myocardial energetics and metabolism

Given the continuous nature of cardiac contractility to sustain life, the metabolic demands of cardiomyocytes are exceptionally high, cycling 6 kg of ATP daily.[41] In order to be sustainable, the heart is able to use several different metabolic substrates to maintain its ATP demands including fatty acids, glucose, ketone bodies and amino acids.[42] The relative shift in metabolism of any one of these substrates can depend on fed versus fasted state, substrate availability, increase in cardiac workload or pathological processes. In pathologic states such as heart failure, though glucose metabolism is more efficient and improves myocardial oxygen demand, it is unable to keep up with the high ATP demand and thus leads to poor contractile reserve and depressed myocardial function. Interestingly, in patients with T2D with increased fatty acid levels and reduced glucose oxidation secondary to insulin resistance, there is increased reliance on fatty acid metabolism which is less efficient, increases myocardial oxygen demand, generates free oxygen radical species inducing oxidative stress and can be lipotoxic.[42] As such, metabolic substrate flexibility is essential for the heart, and relative metabolism of each individual substrate needs to be kept in balance for optimal myocardial function.

Ketone bodies represent an alternative energy source. The benefit of preferential ketone metabolism was demonstrated in a recent crossover study of 3-hydroxybutyrate versus placebo in humans with chronic HF with reduced ejection fraction (EF;HFrEF). These data demonstrated beneficial hemodynamic effects with ketone infusion versus placebo with regards to increased stroke volume, cardiac output and LVEF in a dose responsive fashion.[43]

SGLT2 inhibitors are known to create an increase in ketone bodies, namely beta-hydroxybutyrate, through multiple possible avenues including a “starvation” effect by depleting the body of glucose through the kidneys, raising glucagon levels, and reduction in excretion of ketone bodies via the kidney.[42,44] In a non-diabetic animal model of MI, pigs were randomized to empagliflozin versus placebo.[45] After evaluation with cardiac magnetic resonance imaging (MRI) and echocardiography, myocardial fuel metabolism was noted to be shifted to ketone body oxidation with improved LV systolic function. However, another study using an animal model of T2D demonstrated that empagliflozin increased overall ATP production via glucose and fatty acid oxidation with no change in rate of ketone oxidation.[44] Precise data regarding SGLT2 inhibitors and their effect on myocardial energetics are currently lacking but it is very likely that modulation of myocardial energetic plays a role in the CV benefit derived from SGLT2 inhibitors.

Role in myocardial Na^+/H^+ exchange 1

Myocardial intracellular sodium plays a significant role in regulation of calcium cycling and in turn modulates contractility, oxidative states and the potential for arrhythmias. In HF states, myocyte intracellular sodium is increased which augments sarcoplasmic reticulum calcium levels through calcium influx via the Na^+/Ca^{2+} exchanger; this should work to improve cardiac contractility and improve cardiac dysfunction.[46] However, elevations in intracellular sodium and calcium promote arrhythmia and induce oxidative stress by reducing mitochondrial calcium levels via activation of the mitochondrial Na^+/Ca^{2+} exchanger.[22,46] In fact, increased myocardial sodium and calcium levels are potentially early drivers of CVD death and HF.[22,47] Interestingly, the intracellular concentration of Na^+ is also elevated in diabetic hearts, thus making patients with diabetic cardiomyopathy especially susceptible to the deleterious effects of elevated intracellular sodium.[46]

The SGLT2 inhibitor empagliflozin has recently been shown to lower intracellular Na^+ and Ca^{2+} while increasing mitochondrial Ca^{2+} concentrations via inhibition of the Na^+/H^+ exchanger (NHE) in isolated rabbit and rat ventricular cardiomyocytes.[48] NHE inhibition and increase in intracellular Na^+ by SGLT2 inhibitors was shown to be a true class effect in a study including dapagliflozin and canagliflozin in mouse cardiomyocytes.[49] Furthermore, Uthman et al. performed molecular docking studies which demonstrated direct inhibition of the cardiomyocyte expressed NHE-1 isoform with SGLT2 inhibitors.[49] As SGLT2 receptors are not expressed in the heart, the mechanism of the direct

cardiac effects has remained unclear, and thus far have been thought to be indirect and potentially mainly via the kidney, where SGLT2 receptors are expressed. This finding of direct inhibition of cardiac NHE-1 by SGLT2 inhibitors may potentially explain these effects. This is further supported by numerous experimental studies showing the attenuation of cardiac remodeling and heart failure with NHE-1 inhibition, although it is important to note that larger trials of NHE-1 inhibitors such as ESCAMI (Evaluation of the Safety and Cardioprotective effects of eniporide in Acute Myocardial Infarction), GUARDIAN (GUARD During Ischemia Against Necrosis) and the EXPEDITION (sodium hydrogen Exchange inhibition to Prevent coronary Events in acute cardiac conDITION) did not show positive results.[50]

GLP1 agonists: mechanisms modulating the CV system

GLP-1 is an entero-endocrine derived peptide which acts on the GLP-1 receptor, a G-protein-coupled receptor, that is widely distributed throughout the body including pancreatic islet cells, central and peripheral nervous systems, cardiac, renal and lung tissue.[51] GLP-1 is a well-known "incretin" hormone which is released from the gut in a glucose dependent fashion. In response to increased levels of GLP-1, the pancreatic islet cells release insulin and thus act to regulate glucose concentrations, in addition to gut motility, lipid metabolism, and body weight.[51] GLP-1 has been shown to modulate the CV system and demonstrate benefits on BP, endothelial function, decrease atherosclerosis and myocardial ischemia, and inflammation.[52] Interestingly, two classes of drugs which increase GLP-1 levels, including GLP-1 agonists and DPP4 inhibitors did not demonstrate the same levels of CV efficacy in large outcome studies. As mentioned previously, GLP-1 agonists have been shown to have increased CV efficacy with regards to CVD death, non-fatal MI and stroke, whereas large CVD outcome studies of DPP4i have demonstrated the potential for increased hospitalization for HF.[53–55] A potential explanation for the difference in CV efficacy between the GLP-1 agonists and DPP4i is that DPP4i also potentiate additional peptides, including stromal cell-derived factor-1 (SDF-1) which can have adverse CV effects such as cardiac inflammation, fibrosis, adverse remodeling and increased risk for HF.[56] This lends further support to GLP-1 specifically being essential in the positive CVD outcomes seen in large clinical trials. It is however important to note that even amongst the different GLP-1 agonists there have been differences in observed CVD outcomes. Possible explanations for these observed differences are the difference in molecular structure of these drugs and differences in duration of action. Notably, the drugs with greater half-lives/duration of action such as liraglutide (11–15 h) and semaglutide (7 days) demonstrated greater superiority in CVD outcomes trials.[57]

In contrast to SGLT2-inhibitors, in large CVD outcomes trials, GLP-1 agonists demonstrated cardiovascular safety and/or superiority in atherosclerotic MACE outcomes, but not for HF. Moreover, in the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) study, whereby patients with established HF with an LVEF of 40% or less with a recent hospitalization for HF were randomized to liraglutide versus placebo, there was a trend towards harm with liraglutide therapy with regards to time to death (HR 1.10, 95% CI, 0.57 to 2.14 $P = 0.78$) and composite of time to death and hospitalization for HF (HR 1.30, 95% CI, 0.92 to 1.83 $P = 0.14$).[58] Moreover, in pre-specified sub-group analyses, the trend towards harm was even more pronounced in patients with established T2D, (HR 1.54, 95%CI, 0.97 to 2.46, $P = 0.07$).[58]

Here we will focus on a few of the main mechanisms of GLP-1 agonists thought to exert positive effects on CVD outcomes, including the impact of GLP-1 agonists on traditional risk factors for CVD, anti-atherosclerotic and inflammatory effects, and improved endothelial function.

Modulation of traditional risk factors for CVD

GLP-1 agonists have been shown to cause significant reduction in SBP, body weight, glycosylated hemoglobin (HbA1c), and lipid status, all which are traditional risk factors for CVD. In reviewing the ELIXA, LEADER, SUSTAIN-6 and EXSCEL CVD outcomes trials of GLP-1 agonists in T2D patients, SBP was noted to be between 0.8 and 2.6 mmHg less than the placebo group, a measure that was statistically significant in all four of these trials.[8–12,57] The largest BP difference was seen in SUSTAIN-6, with a mean reduction of 2.6 mmHg in SBP ($P = 0.001$).[10]

The mean reduction in body weight was between 0.7 kg and 4.3 kg, $P < 0.001$ in all four trials. Again, semaglutide in the SUSTAIN-6 trial had the greatest weight reduction at 4.3 kg for the 1.0 mg dose, and 2.9 kg for the 0.5 mg dose. The reduction in body weight in T2D patients was further replicated in non-diabetes patients using GLP-1 agonists.[59] The mechanism for weight loss by GLP-1 agonists is thought to center around increased satiety through modulation of the gastrointestinal and neurological systems.[59] The SCALE-Obesity trial tested liraglutide 3 mg daily versus placebo in non-diabetic patients with a body mass index (BMI) >30, or BMI >27 if they had untreated dyslipidemia or hypertension.[60] Patients were followed for 56 weeks. By the end of the trial, patients in the liraglutide group lost 5.6 kg more weight than those treated with placebo, $P < 0.001$. The superior weight loss with liraglutide as compared with placebo was preserved in patients with pre-diabetes versus those without pre-diabetes, although liraglutide treatment did show improved beta cell function with greater insulin sensitivity and delayed onset of T2D.

Furthermore, a study which conducted both a pair-wise and network meta-analysis of GLP-1 agonists found that GLP-1 agonists are associated with significant reductions in low-density lipoprotein cholesterol (LDL-C) as compared with placebo, and insulin. Certain GLP-1 agonists, such as liragluitde and exenatide, were also associated with a reduction in total cholesterol and triglyceride levels, although improvement in high-density lipoprotein cholesterol (HDL—C) was not seen.[61] These results have been demonstrated in a number of studies of GLP-1 agonists. Importantly, there is strong evidence for the association of improved CVD outcomes with reductions in LDL-C in T2D patients.[62,63] Given the LDL-C reduction combined with reductions in BP, body weight, and improved glycemic control, it is clear that modulation of these traditional CVD risk factors must be at least partly responsible for the CVD benefits seen with use of GLP-1 agonists. However, the magnitude of effect on these traditional CVD risk factors overall is modest, especially with regards to BP. The lowering of SBP for example is considerably less than demonstrated by SGLT2 inhibitors. Accordingly, alternative effects of GLP-1 agonists on the CV system are likely to contribute to the CVD benefits observed with this class of anti-hyperglycemic agents.

GLP-1 agonists: anti-atherosclerotic and anti-inflammatory effects

The large CVD outcome trials for GLP-1 agonists have demonstrated cardiac benefits which appear to be mostly related to atherosclerosis mediated events: MI and cerebrovascular events.[64] The development and progression of atherosclerosis is biologically complex, but at the basic level involves an impetus for inflammation due to endothelial injury caused by traditional CVD risk factors, such as smoking, high blood pressure and/or high lipid states. Expression of vascular adhesion molecules in addition to pro-inflammatory cytokines signal for recruitment of leukocytes and other inflammatory white cells, which are then deposited into the vessel wall. Macrophages, another inflammatory cell, digest the lipids deposited in the wall and form foam cells, and further stimulate vascular endothelial and smooth muscle cells. This inflammation propagates due to a cascade of pro-inflammatory signaling, ultimately leading to intimal fibrosis, and formation of dense extracellular matrix.[65] Matrix metalloproteinases (MMPs) are at least partly implicated in this process.[66] Interestingly, in several human and animal

pre-clinical studies, the use of native GLP-1 and GLP-1 receptor agonists both independently reduced inflammatory markers.[67] In one study of atherosclerosis prone mice (Apoe knockout mice), Burgmaier and colleagues noted reduced plaque macrophage and MMP-9 accumulation, enhanced plaque stability and reduced plaque lesion area in mice who were treated with 12 weeks of GLP-1.[68] In addition, the peptide Angiotensin II (Ang II), promotes atherosclerosis via vascular smooth cell (VSMC) proliferation and migration. In a study using cultured rat aorta VSMCs, pre-treatment with a GLP-1 agonist significantly reduced VSMC proliferation and migration via inhibition of ERK1/2 and JNK signaling pathways.[69] Moreover, in a hyperglycemic mouse model of cerebral ischemia, a GLP-1 agonist was shown to reduce cerebral infarct size via inhibition of MMP-9.[70] In small human studies of patients with ST elevation MI (STEMI), the use of GLP-1 agonists has shown a reduction in infarct size measured by cardiac MRI.[71,72] Taken together, these studies further support the anti-atherosclerotic and anti-inflammatory mechanism of GLP-1 agonists and provide insight into the CVD benefits demonstrated in large CVD outcome trials such as the LEADER study.

GLP-1 agonists and endothelial function

As stated previously, endothelial dysfunction is an important factor in the pathophysiology of cardiac diseases especially in the setting of type 2 diabetes. Moreover, endothelial dysfunction is strongly associated with insulin resistance and T2D.[73] Augmenting GLP-1 has been shown to ameliorate endothelial dysfunction, and thus is an important potential mechanism of how GLP-1 agonists may prevent atherosclerotic related CVD morbidity.[67] In a cross-over study of 12 T2D patients with stable coronary artery disease (CAD) and 10 healthy normal controls with normal endothelial function, the use of recombinant GLP-1 infusion demonstrated improved endothelial function versus saline infusion using flow-mediated vasodilation of the brachial artery as a surrogate marker.[73] In another study, exenatide improved postprandial endothelial function in T2D patients compared to placebo as assessed by measurement of digital hyperemia.[74] Conversely, several studies failed to show that GLP-1 agonists or recombinant GLP-1 improved endothelial function in both diabetic and non-diabetic patients.[67,75] A randomized cross-over study of liraglutide in patients with T2D, in which patients received liraglutide versus no treatment for 10 weeks with a 2-week washout period demonstrated no impact on coronary microcirculation as assessed by transthoracic Doppler flow echocardiography during a dipyridamole induced stress.[76] Furthermore, although studies have shown ex-vivo evidence of GLP-1 receptor expression in endothelial cell lines, there remains a paucity of conclusive data to demonstrate in-vivo expression of the GLP-1 receptor in both human vascular smooth muscle cells and endothelial cells.[67] Accordingly, it is still unclear whether the beneficial CV effects of GLP-1 agonists are mediated by improvement in endothelial function.

GLP-1 agonists and effects on heart rate (HR)

In human cardiac tissue, GLP-1 receptors have been localized to all four chambers, including the sinoatrial (SA) node.[77] GLP-1 agonists have been shown to cause an increase in HR.[78] This is of particular interest as it has been shown that elevation in HR is an independent risk factor for CVD.[79,80] Furthermore, HF in particular is associated with an imbalance in autonomic function, higher sympathetic activity, lower vagal activity, with a resultant higher resting HR.[20] A meta-analysis of GLP-1 agonists and their effects on HR show a single time point increase in HR of 1–4 beats per minute (bpm).[81] However, when examining more closely and differentiating between short and long acting GLP-1 agonists using 24-hour continuous monitoring, it has been shown that long-acting GLP-1 agonists increase HR in the range of.

6–10 bpm while short-acting agents increase HR approximately 3–4 bpm.[82] Moreover, the short-acting GLP-1 agonists' effect on HR was transient, and present only shortly after the injection. An additional study using Holter monitors and power spectrum analysis in patients given GLP-1 agonists demonstrated that both direct sinoatrial node stimulation and relative sympathetic enhancements were responsible for the increase in HR.[83]

In the previously discussed FIGHT Trial looking at liraglutide vs. placebo in patients with pre-existing HF, there was no statistically significant difference in HR with treatment ($P = 0.33$) that could be used to explain the trend towards harm.[58] However, the HR data was based on single time point assessments and did not include more robust measurements of HR, such as with 24-h Holter monitoring. The currently available evidence does not suggest clinically apparent harm with the increase in HR seen with these agents, although emerging evidence will be helpful to better characterize the importance of the increase in HR observed with GLP-1 agonists, especially longer-acting formulations.

Combination therapy with SGLT2 inhibitors and GLP-1 agonists

The CV benefits seen with both SGLT2 inhibitors and GLP-1 agonists make the prospect of combination therapy with these agents particularly enticing in patients with T2D. Thus far however the benefits of additive therapy remain largely unknown in addition to potential adverse effects.[84] The DURATION-8 study, looking at exenatide plus dapagliflozin versus exenatide alone versus dapagaliflozin alone, and the AWARD-10 study, evaluating dulaglutide as add-on therapy to patients taking SGLT2-inhibitors both demonstrate improvement in glycemic control and on CVD risk factors.[85,86] However, larger CVD outcome studies with SGLT2 inhibitor and GLP-1 agonist combination therapy are yet to be completed to provide strong evidence for their combined use in patients at this point in time.

Conclusion: clinical outlook of T2D and CVD

The future has never been brighter with regards to the treatment landscape for patients with T2D and established or at high risk for CVD. The addition of SGLT2 inhibitors and GLP-1 agonists to the armamentarium of glucose lowering therapies has transformed the management of T2D patients, and allows the prized goal of personalized medicine to become one step closer to fruition. The vast number of large randomized controlled CVD outcome trials that have demonstrated not only non-inferiority, but CV superiority of SGLT2 inhibitors and select GLP-1 agonists (liraglutide, semaglutide and albiglutide) in T2D patients with CVD or CVD risk factors provides confidence in the use of these drugs, with relatively minimal side effects. The mechanisms of CV benefit of these drugs is beginning to become clearer over time, but significant amounts of translational research are ongoing, and will further clarify and support the use of these drugs in a more elegant, and personalized fashion for the benefit of our patients.

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