SGLT-2 Inhibitors in Heart Failure and Type-2 Diabetes: Hitting Two Birds with One Stone?

Diogo Santos-Ferreira\textsuperscript{a, b}, Pedro Gonçalves-Teixeira\textsuperscript{a, b}, Ricardo Fontes-Carvalho\textsuperscript{a, b}

\textsuperscript{a}Serviço de Cardiologia, Centro Hospitalar Vila Nova de Gaia/Espinho, Porto, Portugal; \textsuperscript{b}Departamento de Cirurgia e Fisiologia, Unidade de Investigação Cardiovascular, Faculdade de Medicina da Universidade do Porto, Porto, Portugal

Keywords
Diabetes mellitus · Type 2 diabetes mellitus · Diabetic cardiomyopathies · Heart failure · Chronic heart failure · Preventive cardiology · Sodium-glucose transporter 2 inhibitors

Abstract
Type 2 diabetes mellitus (T2DM) and heart failure (HF) have a tremendous impact worldwide, markedly reducing life-expectancy and quality of life. It is now known that each disease represents a risk factor for the other. Moreover, when they are combined, the prognosis is significantly worse. Until recently, these pathologies have been managed independently. However, their treatment paradigm is rapidly changing, with recent cardiovascular outcome trials showing that sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are effective in the management of both diseases. This article explores the interactions between T2DM and HF and the concept of diabetic cardiomyopathy and summarizes recent data regarding the effects of SGLT-2i on HF hospitalization and the proposed pathophysiological mechanisms involved.

Introduction

It is estimated that 1 in every 11 adults has diabetes mellitus (DM), and the number is increasing for multiple reasons, such as ageing of the population, economic development, urbanization, and unhealthy lifestyles. Over 90\% of cases are of type 2 DM (T2DM) [1]. Although the most paradigmatic consequence of T2DM is a chronic hyperglycemic state, cardiovascular complications are responsible for most of the mortality associated with the disease [1]. More recent studies have also shown that heart failure (HF) is the second most common initial cardiovascular manifestation in T2DM patients [2], highlighting the importance of this interaction.

In 2008, the US Food and Drug Administration required that all commercialized glucose-lowering drugs demonstrate cardiovascular safety [3]. This led to the development of dozens of cardiovascular outcome clinical trials which provided significant new data to improve our understanding of the relation between T2DM and cardiovascular disease. Moreover, they showed that sodium-glucose cotransporter-2 inhibitors (SGLT-2i) and some glucagon-like peptide-1 receptor agonists could significantly reduce the risk of cardiovascular events, changing the landscape of T2DM treatment. Instead of an exclu-
sively "glucocentric approach," T2DM management should rather contemplate the use of strategies that can reduce the risk of cardiovascular (and renal) events, including these new drugs and integrated control of all cardiovascular risk factors.

This article aims to review the interaction between T2DM and HF and the concept of diabetic cardiomyopathy and to summarize recent data regarding the effects of SGLT-2i on HF hospitalization (HHF) and the proposed pathophysiological mechanisms involved.

The Interaction between T2DM and HF: the Concept of Diabetic Cardiomyopathy

Diabetic cardiomyopathy is defined as the presence of diastolic or systolic dysfunction in a patient with DM without other obvious causes of cardiomyopathy, such as coronary artery disease, hypertension, or valvular heart disease [4–6]. It is initially characterized by myocardial fibrosis and dysfunctional remodeling and associated diastolic dysfunction, followed by systolic dysfunction and, eventually, clinical HF [6].

DM represents an important risk factor for the development of HF, with a relative risk of 1.82 and 3.75 over 2 years in men and women with diabetes, respectively [7]. In fact, T2DM patients have about a 2.5 times higher risk of developing HF than nondiabetes patients, with younger patients being at the greatest risk [8]. This appears to be, at least in part, glycemic dependent because each 1% increase in glycated hemoglobin (HbA1c) is associated with an 8% increased risk of HF [9]. Additionally, in the UKPDS study, a 1% reduction of HbA1c was associated with a 16% reduction of the risk of developing HF [10]. Even in non-DM patients, for every increase of 18 mg/dL in fasting plasma glucose there is an increase of 1.23 times in HHF [11]. Interestingly, and adding more complexity to the data, subclinical changes in diastolic function are observed even before the onset of diabetes, and they are mainly associated with the state of insulin resistance [12].

As a result, the prevalence of DM in patients hospitalized for HF can be as high as 44% [13].

Likewise, HF also acts as a risk factor for T2DM, as its incidence in HF studies is more than twice that in the general population [4]. The prevalence of HF in patients with T2DM is about 10–23%, i.e., 3 times higher than in nondiabetes control groups [14, 15]. One of the explanations for this is based on p53-induced adipose tissue inflammation through chronic pressure overload and insulin resistance [16].

The clinical outcomes associated with HF are considerably worse for patients with DM [6], with a median survival of 4 years [17]. Therefore, patients with a simultaneous diagnosis of T2DM and HF represent a significant subpopulation that should receive therapies proven to be effective under those conditions.

Several pathophysiological mechanisms have been implicated in the onset of diabetic cardiomyopathy (Fig. 1). Beyond hyperglycemia and its metabolic consequences (such as increased free fatty acids, formation of advanced glycation end products, cytokines, enzymatic O-GlcNAcylation of cardiomyocyte proteins, and impaired cardiac insulin metabolic signaling), other mediators have been implicated, i.e., changes in myocardial metabolism and perfusion (through microvascular dysfunction), oxidative stress, inflammation, autonomic dysfunction, the sympathetic nervous system (SNS), renin-angiotensin-aldosterone system (RAAS) activation, reduced nitric oxide bioavailability, endoplasmic reticulum stress, and increased collagen-based cardiomyocyte and extracellular matrix stiffness, resulting in cardiac remodeling, with development and progression of diabetic cardiomyopathy [5, 6, 18, 19]. In fact, the decreased cardiomyocyte function may be in part mediated by abnormal cytosolic and mitochondrial calcium handling [5]. Another common denominator between T2DM and HF appears to be stimulation of the sodium-hydrogen exchanger (NHE) in the heart and vasculature (NHE1 isofrom) and the kidneys (NH3 isofrom) by agents such as norepinephrine, angiotensin, and aldosterone – associated with HF – and insulin, glucose, and certain adipokines – increased in T2DM [20].

SGLT-2i: from Mechanisms of Action to Cardiovascular Outcome Trials

Glucose-Lowering Effects of SGLT-2i

Seven isoforms of sodium-glucose cotransporter (SGLT) have been described [21], with 2 most studied to date being SGLT-1 and SGLT-2. SGLT-1 is mainly expressed in the small intestines and in the proximal convoluted tubule of the kidneys, where it is responsible for less than 10% of filtered glucose reabsorption. SGLT-2 is also expressed in the apical membrane of the proximal convoluted tubule cells and it is responsible for about 90% of filtered glucose reabsorption, which occurs in a 1:1 stoichiometry of sodium to glucose. In T2DM, SGLT-2 can be upregulated, which intensifies and perpetuates hyperglycemia [22]. SGLT-2i represent a relatively new
class of drugs for T2DM; they were approved in the USA and Europe in 2013. Their glucose-lowering effect occurs via an insulin-independent pathway mainly through glucosuria, increasing the urinary excretion of glucose and the fractional excretion of sodium, with modest diuretic and natriuretic effects [4]. It is expected that, with their use, HbA1c will be decreased by about 0.5–1% [23–25] (IFCC: 5.5–11 mmol/mol). Several SGLT-2i, such as dapagliflozin, empagliflozin, ipragliflozin, canagliflozin, tofogliflozin, luseogliflozin, ertugliflozin, and sotagliflozin, are currently available (though some are not yet approved).

Cardiovascular Effects of SGLT-2i: Effects on Major Adverse Cardiovascular Events

Over the last years, 3 important clinical trials have been conducted regarding the cardiovascular safety and benefits of SGLT-2i [4]: the EMPA-REG OUTCOME trial (for 10 or 25 mg of empagliflozin) [26], the CANVAS Program (for 100 or 300 mg of canagliflozin) [27], and DECLARE-TIMI 58 (for 10 mg of dapagliflozin) [28], all performed on T2DM patients. Although these studies focused on different populations (as detailed in Table 1), which may account for the different findings, the combined data suggests that this new class reduces the risk of major adverse cardiovascular events (MACE) – a combined endpoint of death from cardiovascular causes, non-fatal myocardial infarction (MI), or nonfatal stroke – by 14% in patients with atherosclerotic cardiovascular disease, i.e., there were no differences statistically significant in patients with only multiple risk factors and no cardiovascular disease [29]. There was also a reduction of MI by 15%, of cardiovascular death by 20%, and of all-cause death by 17%, again, only in T2DM patients with established cardiovascular disease [29].

A subgroup analysis of DECLARE-TIMI 58 concluded that, in patients with a prior MI, dapagliflozin reduced the relative risk of MACE by 16%, with a number-needed-to-treat (NNT) of 39 over 4 years, without having an effect on patients without a prior MACE. There was a risk reduction of recurrent MI, and it was more pronounced in type 2 MI. The relative risk reductions in cardiovascular

![Fig. 1. Mechanisms mediating HF in T2DM patients. FFA, free fatty acids; AGEs, advanced glycation end products.](image)
Cardiovascular Effects of SGLT-2i: HF Hospitalization

The most impressive results of SGLT-2i trials were a consistent reduction of 37% in the risk of HHF, independently of the presence of a history of atherosclerotic cardiovascular disease or multiple risk factors alone or even of preexisting HF or not (i.e., as both primary and as secondary prevention) [29, 31]. The reduction in the risk of HHF is evident immediately by the first month after initiating SGLT-2i, and it persists throughout the trials’ duration [31]. As is known, repeated HHF is a strong predictor of mortality [32] and preventing the former may lower the latter. In fact, a recent meta-analysis showed a combined reduction of HHF/cardiovascular death of 23% [29]. Additional data suggests that these agents might halve the post-acute HHF and mortality in the vulnerable phase [33].

The effects of SGLT-2i according to the subtype of HF remain to be established. An interesting subgroup analysis of DECLARE-TIMI 58 compared patients with a known reduced ejection fraction (EF; <45%) (HF with a reduced EF; HFrEF) with subjects with a history of HF without a known EF reduction. Dapagliflozin was able to lower HHF both in the HFrEF group (HR = 0.64) and in the non-HFrEF group (HR = 0.76) [34], which is particularly interesting because there are no specific therapies approved for HF with a preserved EF. This hypothesis is being specifically evaluated in several on-going clinical trials.

The first evidence that SGLT-2i should be used as HF drugs, rather than merely as glucose-lowering agents, was recently shown in DAPA-HF. This trial studied the effect of dapagliflozin (10 mg) versus placebo in patients with HF and a reduced EF (below 40%), including 58% of non-T2DM patients. There was a 26% reduction in the primary composite endpoint of worsening HF and cardiovascular death (NNT = 21), with a 30% reduction in HHF and a reduction in total mortality. Notably, this benefit was observed independently of the presence of T2DM. The effect was most significant among NYHA class II patients versus class III/IV patients. Its use was safe, even in non-T2DM patients [35].

The benefits of SGLT-2i in HHF have been also demonstrated outside of the clinical trial environment, using data from an unselected population from clinical settings, as detailed in Table 2. For example, the first interim analysis from the EMPRISE study [36] showed a 50% re-

### Table 1. Outcomes of randomized control trials studying SGLT-2i

<table>
<thead>
<tr>
<th></th>
<th>EMPA-REG OUTCOME (empagliflozin at 10 or 25 mg)</th>
<th>CANVAS Program (canagliflozin at 100 or 300 mg)</th>
<th>DECLARE-TIMI 58 (dapagliflozin at 10 mg)</th>
<th>CREENCE Trial (canagliflozin at 100 mg)</th>
<th>DAPA-HF Trial (dapagliflozin at 10 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>7,020</td>
<td>10,142</td>
<td>17,160</td>
<td>4,401</td>
<td>4,744</td>
</tr>
<tr>
<td>Age, years</td>
<td>63</td>
<td>63</td>
<td>64</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Males, %</td>
<td>72</td>
<td>72</td>
<td>63</td>
<td>63</td>
<td>76</td>
</tr>
<tr>
<td>White race, %</td>
<td>72</td>
<td>72</td>
<td>80</td>
<td>67</td>
<td>70</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.1</td>
<td>8.2</td>
<td>8.3</td>
<td>8.3</td>
<td>na</td>
</tr>
<tr>
<td>T2DM, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>T2DM duration, years</td>
<td>57% &gt;10</td>
<td>13.5</td>
<td>11.8</td>
<td>15.8</td>
<td>na</td>
</tr>
<tr>
<td>BMI</td>
<td>30.6</td>
<td>32</td>
<td>32</td>
<td>31.3</td>
<td>28.2</td>
</tr>
<tr>
<td>BP control</td>
<td>61% &lt;140/90</td>
<td>137/78</td>
<td>SBP 135</td>
<td>140/78</td>
<td>SBP 122</td>
</tr>
<tr>
<td>e-GFR, mL/min/1.73 m²</td>
<td>74, exc. &lt;30</td>
<td>77, exc. &lt;30</td>
<td>85, exc. &lt;60</td>
<td>56, exc. 30–90</td>
<td>66, exc. &lt;30</td>
</tr>
<tr>
<td>Urine A/C ratio, mg/g</td>
<td>59% &lt;30</td>
<td>70% &lt;30</td>
<td>na</td>
<td>927, inc. 300–5,000</td>
<td>na</td>
</tr>
<tr>
<td>Previous CVD, %</td>
<td>100</td>
<td>66</td>
<td>41</td>
<td>50</td>
<td>56(ischemic HF)</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td>3.1</td>
<td>2.4 (mean)</td>
<td>4.2</td>
<td>2.62</td>
<td>1.5</td>
</tr>
<tr>
<td>MACE Death</td>
<td>0.86 (0.74–0.99)</td>
<td>0.86 (0.75–0.97)</td>
<td>0.93 (0.84–1.03)</td>
<td>0.80 (0.67–0.95)</td>
<td>na</td>
</tr>
<tr>
<td>Any cause</td>
<td>0.68 (0.57–0.82)</td>
<td>0.87 (0.74–1.01)</td>
<td>0.93 (0.82–1.04)</td>
<td>0.83 (0.68–1.02)</td>
<td>0.83 (0.71–0.97)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.62 (0.49–0.77)</td>
<td>0.87 (0.72–1.06)</td>
<td>0.98 (0.82–1.17)</td>
<td>0.78 (0.61–1.00)</td>
<td>0.82 (0.69–0.98)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.65 (0.50–0.85)</td>
<td>0.67 (0.52–0.87)</td>
<td>0.73 (0.61–0.88)</td>
<td>0.61 (0.47–0.80)</td>
<td>0.70 (0.59–0.83)</td>
</tr>
<tr>
<td>Renal outcomes</td>
<td>na</td>
<td>0.60 (0.47–0.77)</td>
<td>0.76 (0.67–0.87)</td>
<td>0.70 (0.59–0.82)</td>
<td>0.71 (0.44–1.16)</td>
</tr>
</tbody>
</table>

Values are presented as hazard ratio (95% confidence interval) unless otherwise stated. SBP, systolic blood pressure; A/C, albumin/creatinine; CVD, cardiovascular disease; inc., included; exc., excluded; na, not available.
duction of HF discharge diagnosis in patients who initiated empagliflozin (10 or 25 mg) versus sitagliptin (a dipeptidyl peptidase-4 inhibitor) in T2DM patients with or without a history of cardiovascular disease at baseline. Also, CVD-REAL analyzed data from medical claims, primary care/hospital records, and national registries from the USA and Europe and confirmed that the initiation of SGLT-2i versus other glucose-lowering drugs was associated with a lower rate of HHF (HR = 0.61) and all-cause death (HR = 0.49). The majority of the patients did not have established cardiovascular disease, suggesting that these benefits in cardiovascular outcomes may be applicable also in primary prevention, which was confirmed by other analyses [37, 38]. A subanalysis demonstrated that there also seems to be a modest reduction of MI (HR = 0.85) and stroke (HR = 0.83) [39]. CVD-REAL Nordic was only applied to Denmark, Norway, and Sweden and it found that SGLT-2i initiation was associated with a decreased risk of cardiovascular mortality (HR = 0.53) and all-cause mortality (HR = 0.51), MACE (HR = 0.78), and HHF (HR = 0.70), without significant differences regarding nonfatal MI, nonfatal stroke, or atrial fibrillation. There was also a decreased risk of severe hypoglycemia (HR = 0.76). The effects were evident irrespectively of existing cardiovascular disease [40]. The CVD-REAL 2 study confirmed, in a community-based population outside the USA and Europe, again through claims, medical records, and national registries, that initiation of an SGLT-2i versus other glucose-lowering drugs was associated with a lower risk of death (HR = 0.51), HF (HR = 0.64), MI (HR = 0.81), and stroke (HR = 0.68), which was consistent across countries and patient subgroups and irrespective of previous cardiovascular disease [41]. In both studies, the benefits seemed to be class related.

Table 2. Outcomes of SGLT-2i observational studies

<table>
<thead>
<tr>
<th></th>
<th>EMPRISE (empagliflozin vs. sitagliptin)</th>
<th>CVD-REAL (SGLT-2i vs. other GLD)</th>
<th>CVD-REAL NORDIC (SGLT-2i vs. other GLD)</th>
<th>CVD-REAL 2 (SGLT-2i vs. other GLD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>32,886</td>
<td>309,056</td>
<td>91,320</td>
<td>470,128</td>
</tr>
<tr>
<td>Age, years</td>
<td>59</td>
<td>57</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>Males, %</td>
<td>54</td>
<td>56</td>
<td>60</td>
<td>55</td>
</tr>
<tr>
<td>Previous CVD, %</td>
<td>25</td>
<td>13</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Death (any cause)na</td>
<td>0.49 (0.41–0.57)</td>
<td>0.51 (0.45–0.58)</td>
<td>0.51 (0.37–0.70)</td>
<td>0.64 (0.50–0.82)</td>
</tr>
<tr>
<td>HHF</td>
<td>0.51 (0.39–0.68)</td>
<td>0.61 (0.51–0.73)</td>
<td>0.70 (0.61–0.81)</td>
<td>0.64 (0.50–0.82)</td>
</tr>
</tbody>
</table>

Values are presented as hazard ratio (95% confidence interval) unless otherwise stated. GLD, glucose-lowering drugs; na, not available.

Although the SGLT-2i effects on kidney function are not a subject for this review, briefly, the CREDEENCE trial (canagliflozin at 100 mg) showed, in patients with T2DM stage 2–3 chronic kidney disease with albuminuria, a statistically significant 30% reduction in a composite outcome of end-stage kidney disease, doubling serum creatinine levels, or death from renal or cardiovascular causes. Moreover, HHF was significantly reduced by 39% [42]. Similar benefits were also shown in the subanalysis of the EMPAREG-OUTCOME, CANVAS Program, and DECLARE-TIMI 58 trials. In conclusion, these data demonstrate that the benefits of SGLT-2i go beyond the metabolic and cardiovascular territories and delay the decline in renal function.

Benefits of SGLT-2i: A Class Effect?

The joint analyses of all these studies suggest that most of the cardiovascular benefits of SGLT-2i reflect a class effect. However, we cannot rule out that they may vary with the drug used. Investigation has shown that dapagliflozin (and ipragliflozin) may be categorized as long-acting SGLT-2i, in contrast to empagliflozin and canagliflozin (besides tofogliflozin and luseogliflozin), as they have an intermediate action [43]. Long-acting SGLT-2i may be more potent, with better glucose control throughout the day and a lower plasma insulin variability, also improving glucose tolerance in T2DM mice and demonstrating a trend towards superiority regarding diabetes-related complications [44, 45]. Regarding selectivity for SGLT-2, empagliflozin is the most selective of the 3, followed by dapagliflozin, with canagliflozin being the least selective [46–48]. Note that SGLT-2i with low SGLT-2/SGLT-1 selectivity elevate the level of circulating glucagon-like peptide-1 [49], which may contribute to a pleiotropic effect.
Possible Mechanisms Responsible for SGLT-2i Effects on Cardiovascular Outcomes

There are several pathophysiological pathways that can mediate the cardiovascular and renal benefits of SGLT-2 inhibition. Although SGLT-2i have a clear glucose-lowering effect, their impact on cardiovascular and renal outcomes is not mediated by the reduction in HbA1c. Importantly, the recent DAPA-HF trial confirmed that the benefits were also observed in the non-T2DM population [35].

It is also interesting to observe that the positive cardiovascular outcomes were not dose dependent. For example, the reduction in the risk of cardiovascular death after initiating empagliflozin was not affected by dosing, baseline HbA1c, or its change throughout the trial [14, 50]. Additionally, though the glucose-lowering effect of SGLT-2i is reduced in patients with chronic kidney disease, the cardiovascular and renal benefits persist in patients with different kidney functions, even with estimated glomerular filtration rates of 30–60 mL/min/1.73m² [51]. This observation suggests that the mechanisms involved in glycemic control and cardiovascular risk reduction are dissociated and/or follow a different dose-response curve [52].

The Hemodynamic Effect of SGLT-2i and the “Smart Diuresis” Hypothesis

Several trials have shown that the reduction in HHF is seen almost immediately after starting SGLT-2i, i.e., after just 1 month, which supports the concept that these benefits reflect an improvement in the hemodynamic state. It is believed that SGLT-2i can ameliorate ventricular loading conditions thanks to a preload reduction due to its diuretic and natriuretic effects [52]. In fact, changes in markers of plasma volume (such as increasing hematocrit and hemoglobin) are key mediators in the reduction of cardiovascular death [53].

Some authors have postulated the concept of smart diuresis. It seems that SGLT-2i, unlike loop diuretics, lead to a greater electrolyte-free water clearance, with more fluid clearance from the interstitial fluid space than from circulation and a lower impact on blood volume, arterial filling, and organ perfusion. In fact, though both blood and interstitial fluid volumes are increased in HF, there is a relative arterial underfilling due to a low cardiac output, so it may be more relevant to reduce the interstitial volume than the blood volume [54]. Another important difference from conventional diuretics is that SGLT-2i can lower uric acid serum levels instead of raising them, without altering potassium homeostasis or impairing glucose tolerance [55, 56].

Furthermore, it is known that SGLT-2i reduce blood pressure (BP), i.e., about 4/1.6 mm Hg [57] – and alter vascular function, with improvement of endothelial function and aortic stiffness indices [52]. In fact, diuresis is not the only mechanism involved in BP reduction, because this effect is sustained, unlike the increased urinary output, which is temporary and returns to pretreatment levels after 12 weeks [19, 58]. This lower BP is not followed by an increase in heart rate, unlike vasodilators – suggesting that the SNS is not activated and may even be inhibited [56]. Chronic activation of the SNS has been identified in HF [59] – a higher activation and, consequently, a higher heart rate are associated with an increased risk of microvascular and cardiovascular complications and even death [60, 61]. The use of luseogliflozin is able to reduce the heart rate; the higher the pre-treatment rate is, the greater its fall is [62, 63].

The Metabolic Effect: Changing the Heart Metabolic Substrate

Another important pathway likely involved in cardiovascular benefits of SGLT-2i is their impact on cardiac metabolism by improving myocardial energetics and substrate efficiency. It is known that this class–drug promotes an increase in ATP production with higher rates of fatty acids and glucose oxidation [64] and ketogenesis. Increasing β-hydroxybutyrate has been associated with multiple cardiovascular benefits [19, 52, 55, 65]. Moreover, SGLT-2i may promote branched–chain amino acid degradation, which is impaired in HF [66].

Other Possible Mechanisms

Hyperglycemia induces reactive oxygen species production through activation of NOX. This signaling occurs via SMIT1 (an isoform of SGLT) which senses hyperglycemia through SGLT-1. Therefore, the use of SGLT-2i – especially those less selective for SGLT-2 with partial inhibition of SGLT-1 – may be responsible for the lower oxidative stress in the myocardium [21, 67]. Regarding cardiac fibrosis, it is curious that these drugs may exert antifibrotic effects, with decreased myocardial oxidative stress [52, 68]. There may also be a reduction in left ventricular (LV) mass index [69]. In prediabetes ob/ob−/−mice, empagliflozin improved coronary microvascular function and contractile performance, as well as liver function, steatosis, glycemic status, and lipid profile, with increased nitric oxide production [70]. A study using ipragliflozin showed its ability to prevent LV hypertrophy.
and fibrosis in nonDM SD/obese rats with spontaneous development of cardiomyopathy, without affecting plasma glucose levels, which strengthens the possibility of its use in nonDM patients [71].

Another proposed explanation is an interaction between the use of SGLT-2i and RAAS; as SGLT-2i promote volume contraction, there is an activation of RAAS through a negative feedback loop. Because there is a significant number of subjects under RAAS inhibitors in SGLT-2i trials (i.e., angiotensin-converting enzyme inhibitors or angiotensin-receptor antagonists), the combined effect of SGLT-2i and RAAS inhibitors may favor cardioprotective pathways of RAAS, with an increased production of angiotensin 1–7 and activation of both Mas and type 2 angiotensin receptor [72], with global vasodilatation, anti-inflammatory, and positive inotropic effects [67].

As mentioned above, there seems to be a link between T2DM and HF, through stimulation of NHE1 and NH3. It is curious that, though SGLT-2 is not expressed in the heart, SGLT-2i can block cardiac NH1 (which is upregulated both in HF and in T2DM [20]), resulting in attenuation of higher cytosolic Na+ and Ca2+ concentrations and restored mitochondrial [Ca2+] [67]. They also block the renal isoform (NH3), further enhancing natriuresis [19, 20, 52].

Although there is a weight reduction with these therapies through caloric loss with glycosuria of about 200 kcal/day [19], it seems not to be the main mechanism for the cardiovascular benefits seen as they were evident too soon after the initiation of SGLT-2i. In addition, there is a small increase in glucagon, which may have an inotropic effect and assist with appetite control [55]. They may also reduce the levels of leptin and increase adiponectin, with a reduction of epicardial fat [19, 52].

**Mechanisms of Renal Protection**

As glucose absorption in the tubular cell depends on the sodium gradient (which is maintained through the activity of the basal ATP-dependent Na+/K+ pump), it is argued that, in DM, the greater glucose concentration in the filtered fluid demands a higher absorption, with a consequent greater ATP and oxygen consumption, resulting in a relative local hypoxia, which may be at least partially relieved by SGLT-2i administration [63, 73, 74]. This may account for some of the renal, and even cardiovascular, benefits of this drug class.

Some experimental studies have proven that SGLT-2i exert a consistent anti-inflammatory and antifibrotic effect, which has been best described in the kidney, with attenuation of infiltration of inflammatory cells (i.e., pro-inflammatory macrophages), accumulation of extracellular matrix, oxidative stress, and expression of some inflammatory markers, such as MCP-1, osteopontin, RANK-TES, IL-6, p65, ICAM-1, PAI-1, TGF-β, CTGF, TLR4, NFKB, AP-1 binding, collagen IV expression, CCL2, CD14, TIMP2, and Nox-4 [75–82].

Another explanation is based on the fact that natriuresis stimulates the tubuloglomerular feedback, resulting in vasoconstriction of the afferent arteriole, reducing intraglomerular hypertension and preserving kidney function [52]. As there is an important relationship between HF and kidney dysfunction, SGLT-2i may break this vicious circle [19].

**Conclusion**

**Clinical Perspectives**

The cardiovascular outcome trials with SGLT-2i have changed our understanding of the association between T2DM and cardiovascular disease. More importantly, these data are changing the paradigm of T2DM management, as reflected in the recent 2019 ESC Diabetes Guidelines [83], which focus on the importance of using agents with a demonstrated reduction in cardiovascular events instead of the classic glucocentric approach.

SGLT-2i started as a new class of oral glucose-lowering drugs of only moderate efficacy in the reduction of HbA1c that were also capable of inducing weight loss and BP reduction without a significant risk of hypoglycemia. The recent cardiovascular outcome trials have shown that they not only markedly lower the risk of HF across the cardiovascular continuum while providing renal “protection,” but they also reduce the risk of cardiovascular events in patients with atherosclerotic disease.

Recently, with demonstration of their benefits also in patients with HF with a reduced EF, irrespectively of the presence of T2DM, a new era has started. These drugs should be viewed not only as oral antidiabetic pills but also as agents that provide cardiovascular protection. The time has come to see SGLT-2i hitting 2 birds (T2DM and HF) with a single stone.

**Statement of Ethics**

As this is a review article, no human or animal experiments were conducted by the authors.
References


