

Review

The Impact of SGLT2i Therapy on the Onset and Prognosis of Heart Failure in Patients with Type 2 Diabetes

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Abstract: The prevention of heart failure (HF) development in patients with diabetes mellitus (DM) represents one of the greatest challenges to date. Several studies have shown that targeting a very strict HbA_{1c} does not reduce cardiovascular risk in type 2 diabetes (T2D) patients, concluding that there are additional factors that contribute to the risk of HF, as well as mechanisms possibly related to the therapeutic agents used to lower glycemic values. All these findings led to the reconsideration of T2D management. SGLT₂ inhibitors (SGLT₂i), a new generation of antihyperglycemic drugs, have gained the attention of cardiologists, since they proved cardioprotective effects by reducing three-point major adverse cardiovascular events (MACE) and heart failure hospitalizations in T2D patients. The mechanisms underlying the cardiovascular protection of SGLT₂ inhibitors in T2D are complex and multifactorial, but not fully understood. This review discusses the onset and prognosis of heart failure in T2D patients treated with SGLT₂ inhibitors.

Keywords: heart failure; diabetes; SGLT₂ inhibitors; CVOT trials

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Introduction

Heart failure (HF) has marked a progressive increase over the past decades, mostly due to the increase in life expectancy of the population and the incidence of obesity and diabetes mellitus (DM). Affecting over 26 million people worldwide, HF has an incidence of almost 2% in the general population and more than 10% in the over 70 age group. Despite the treatments and devices available today, the morbidity and mortality of this clinical condition remain high. Data show that HF can be a clinical condition that is more malignant than some cancers. Thus, the 5-year survival rates from the diagnosis of HF can be more severe than those estimated in breast cancer or colorectal cancer in women over 70 years old, or in prostate or colorectal cancer in men within the same age group [1]. With a pandemic-like spread, increasing from decade to decade, DM contributes to an increasing number of HF cases, both medical conditions becoming serious public

health issues and a financial burden for all healthcare systems. Recent data indicate that approximately 44% of patients with HF that needed admission had DM, and 18% of patients that underwent transplant were patients with DM [2,3]. The coexistence of the two conditions consequently becomes one of the biggest medical challenges we presently face.

The causality relation between DM and HF has been discussed for over 40 years. The prevalence of the latter within the segment of DM patients varies between 19% and 26%, four times that of the general population segment [4–7]. The results of the Framingham Heart Study, involving 30 years of observation, are proof that DM is indeed a risk factor for HF. The discrepancies found between male and female patients are not entirely understood to this day, the risk for women being five times higher than that of individuals without DM. At the same time, men face a risk only twice as high compared to individuals without DM. Notably, this risk remains constant, regardless of the presence of high blood pressure, coronary artery disease, obesity, and dyslipidemia [8].

HF in patients with DM occurs as a result of complex alterations that occur at a systemic, myocardial, and cellular level. The structural and functional alterations could be caused by myocardial ischemia due to coronary atherosclerosis, which results from hyperglycemia and hyperinsulinemia, in the absence of significant epicardial coronary involvement. This clinical entity we nowadays call diabetic cardiopathy was first mentioned by professor Lundbaeck in 1954 and has been of great scientific interest lately [9]. Diabetic cardiomyopathy is defined by the presence of structural and functional anomalies in the absence of coronary artery disease, high blood pressure, significant valvulopathies, or alcohol consumption according to ACC/AHA/ESC definitions from 2013. During a myocardial infarction of the same size, a patient with DM has a much higher risk of developing HF compared to a patient without DM, supporting the idea that many times, overlapping situations do occur (diabetic cardiomyopathy and coronary ischemia can coexist at any given point), resulting in a more severe and accelerated contractile deterioration.

The HF classification based on ejection fraction was updated in 2016 when the European Society of Cardiology recommended three terminologies: HF with preserved ejection fraction ($EF \geq 50\%$), HF with reduced ejection fraction ($EF < 40\%$), and HF with mid-range ejection fraction ($EF 40\%–49\%$) [10]. This new classification imposes the identification of different underlying conditions by the physician, underlines demographic characteristics, and the associations between certain comorbidities, being of great importance for the prognosis of these patients. By far, the essential difference between the three categories of HF is represented by their response to treatment. For HF with reduced ejection fraction, several pharmaceutical options significantly improve general and cardiovascular mortality, as well as the number of hospital admissions. Furthermore, several designed devices such as resynchronization therapy, cardiac defibrillators, cardiac contractility modulation devices, or ventricular assist devices have proven clear benefits for these patients. Unfortunately, in the case of HF with preserved ejection fraction, studies involving angiotensin enzyme inhibitors/angiotensin receptor blockers, beta-blockers, or mineralocorticoid receptor antagonists failed to convince on the endpoints mentioned above. The sacubitril/valsartan combination shows promise in the most recent study (PARALLAX), proving to be beneficial in those with an $EF > 40\%$ [11]. Data collected from registries show that most patients with DM and HF have a preserved systolic function (75% of cases), with treating these patients becoming particularly challenging and complicated [12].

The relation between HF and DM is full of interferences, presenting many pathophysiological similarities. The incidence of DM among patients with HF is higher than in the general population, correlating with the insulin resistance found in these patients. The main predictors of the development of DM in patients with HF are: increased BMI, increased abdominal girth, smoking, an increase in HbA1c values, a history of high

blood pressure, the duration of HF, the severity of the NYHA functional class, and the prolonged use of loop diuretics [13,14].

The prevention of HF development in patients with DM represents one of the greatest challenges to date. Increased levels of HbA_{1c} are associated with an increased risk of HF [15].

The results of some important clinical trials (Table 1) come as proof that a strict glycaemic control to mimic normal values does not decrease the patient's cardiovascular risk to that of a person without DM. Although in the endpoints of these studies, HF was not encountered, post hoc analysis has shown that intensive glycaemic control did not reduce the HF risk, nor the number of hospital admissions for this condition [16].

Table 1. Evidence of clinical trials with cardiovascular outcomes.

Clinical Trial	Results
UKPDS ^a	A reduction in HbA _{1c} by 1% reduces the risk for HF by 16% [17]
ADVANCE ^b	HbA _{1c} reduction to levels around 6.5% did not prove to induce an additional reduction in macrovascular complications, nor did it increase mortality within the strict glycaemic control group [16]

^a The UK Prospective Diabetes Study; ^b Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation.

It has become apparent that there are additional factors that contribute to the risk of HF, as well as mechanisms possibly related to the therapeutic agents used to lower glycaemic values. This idea led to the conclusion that treatments used in patients with DM should not be solely chosen with glucose values in mind. Direct or indirect mechanisms have been identified by which antihyperglycaemic agents may intervene in myocardial remodeling and injury regardless of their blood glucose-lowering effect. The first line of treatment for the patient that has DM and HF, or an increased risk of HF, should consist of a medication that decreases the risk of HF or that will not sustain the progression of HF. At the same time, it was suggested that the HbA_{1c} targets should be individualized according to the severity of the HF and the patient's comorbidities.

Patients with HF and DM have a more severe prognosis than those with HF without DM. The association of these two clinical conditions increases cardiovascular mortality, including that caused by worsening heart failure by 50–90% regardless of the ejection fraction, and the number of hospitalizations by 50% [18–20].

We are looking optimistically to new therapeutic drugs, such as the sacubitril/valsartan combination, and therefore, we can extend the optimism to SGLT2 inhibitors, which provide consistent proof that will undoubtedly change the treatment algorithm of patients with HF and DM.

Cardiovascular Outcome Trials and Mechanisms of Action of SGLT2 Inhibitors

Although the association of DM and cardiovascular disease (CVD) was already well known, it was only in 2008 that the U.S. Food and Drug Administration (FDA) issued guidance to the pharmaceutical industry for the development of antihyperglycaemic drugs for type 2 DM (T2D). This decision was followed by the European Medicines Agency (EMA), requiring that all these agents should undergo a rigorous assessment of CV safety through large-scale cardiovascular outcome trials (CVOTs) [21,22]. Therefore, authorities considered CV death, non-fatal stroke, or non-fatal myocardial infarction as a three-point major adverse CV event (3P-MACE) in the CVOTs for antidiabetic drugs [23].

SGLT₂ inhibitors were introduced in the management of T₂D in 2013 and showed cardioprotective effects by reducing the three-point MACE, as shown in the latest clinical trials (Table 2). SGLT₂ inhibitors are a new generation of antihyperglycemic drugs that lower blood sugar by causing an approximate daily 70 g urinary glucose excretion with a consecutive increase in diuresis by 200–300 mL, independent of beta-cell function, with a decrease in HbA_{1c} up to 0.5–1.5% [24]. Usually, the kidneys filter glucose from the blood, which is then reabsorbed back into the bloodstream. Proteins that perform glucose reabsorption are called sodium-glucose transporter proteins. SGLT₂ inhibitors block some of the proteins, a process that allows the kidneys to lower blood glucose levels and eliminate excess glucose from the blood through the urine [25]. In addition, by removing glucose from the body, SGLT₂ inhibitors have a beneficial weight loss effect (triggered by a loss of about 280 kilocalories daily) and glucose-induced osmotic diuresis [26]. However, this class of drugs has specific side effects, such as an increased risk of genital and urinary tract infections and, in rare cases, diabetic ketoacidosis at lower glycemic values than usually expected [23,27–29].

The first SGLT₂ inhibitor that proved CV benefits in a large CVOT was empagliflozin. In EMPA-REG OUTCOME, a large number of patients with T₂D and established CVD were enrolled (coronary, peripheral, or cerebrovascular disease), who were randomly assigned to be treated with 10 or 25 mg of empagliflozin or placebo. After a median 3.1 years follow-up, empagliflozin showed not only a reduction in 3P-MACE by 14% compared to the placebo but also a significant reduction of 38% in cardiovascular mortality, of 32% in all-cause mortality, respectively, and of 35% in hospitalization for heart failure [30]. Additionally, data from the EMPA-REG OUTCOME suggested that changes in plasma volume were the most crucial factor in reducing the risk of cardiovascular death with empagliflozin compared to the placebo [31].

Similar benefits were shown by another SGLT₂ inhibitor, canagliflozin, in the CANVAS Program, which included two major clinical trials, CANVAS and CANVAS-Renal. A total of 66% of patients with T₂D included in the CANVAS trial also had CVD, unlike the previously mentioned study where more than 99% of patients had cardiovascular disease. Included patients were aged ≥ 30 years, with a HbA_{1c} $\geq 7\%$ and less than 10.5% and history of symptomatic atherosclerotic CVD, or aged over 50 years with more than two CV risk factors (SBP > 140 mmHg, eGFR > 30 mL/min/1.73 m²). This CVOT demonstrated that canagliflozin reduces 3P-MACE, but has no significant effect on the reduction in all-cause mortality between the two groups (HR: 0.86; 95% CI: 0.75–0.97; $p < 0.001$ for non-inferiority and $p = 0.02$ for superiority) [23].

Similar to the previously mentioned studies, the DECLARE-TIMI 58 trial has proven that dapagliflozin significantly reduced mortality due to CV causes and reduced the rates of hospitalization due to heart failure (HR: 0.98; 95% CI: 0.83–0.95; $p = 0.005$). However, the study has shown no significant effects on the 3P-MACE outcome in the DAPA group. The study included a larger number of T₂D patients, among which 41% had established atherosclerotic CVD (ASCVD), while the others had multiple risk factors for ASCVD, which were randomized to receive either 10 mg dapagliflozin or placebo, for a median follow-up of 4.2 years [32].

All of these findings led to a paradigm shift in T₂D treatment. Through their unique mechanism of action, independent of the beta-cellular function of the pancreas, SGLT₂ inhibitors have proven cardiorenal protection. The previously mentioned reduction in hospitalizations for heart failure observed in studies with cardiorenal targets in patients with T₂D was due to the effect of SGLT₂i producing osmotic diuresis and natriuresis, and as a consequence, decreasing in preload and pulmonary congestion, as well as in systemic edema [33]. A notable effect mediated by these molecules is the inhibition of the NHE1 antiporter, which determines the reduction in sodium and calcium levels at the cytoplasmic level and increases calcium levels at the mitochondrial level [34–36]. SGLT₂ inhibitors reduce cardiac overload by lowering blood pressure

without increasing heart rate, even in patients with low glomerular filtration rate, suggesting that they decrease the action of the sympathetic nervous system in heart failure [37,38]. Besides, studies have shown that SGLT2i improves the mechanical efficiency of the myocardium by producing ketone bodies, namely beta-hydroxybutyrate, which is preferentially oxidized by the heart [39]. Another mechanism underlying the cardiorenal protection of SGLT2 inhibitors is erythrocytosis by stimulating renal erythropoietin secretion. Through this mechanism, SGLT2 inhibitors attenuate metabolic stress in renal cells and inhibit the sympathetic nervous system response [40]. It should not be overlooked that they reduce inflammation and improve mitochondrial function [41,42].

However, the studies and evidence did not stop here. In June 2020, at the 80th Scientific Sessions of the American Diabetes Association, the results of another CVOT were revealed, those of the VERTIS-CV trial (eValuation of ERtugliflozin efficacy and Safety CardioVascular outcomes trial) with the SGLT2i ertugliflozin. The primary study aim was to demonstrate the non-inferiority of ertugliflozin versus placebo on major adverse CV events, a composite of CV death, non-fatal myocardial infarction (MI), and non-fatal stroke, while the secondary objectives were to demonstrate the superiority of ertugliflozin versus placebo regarding the composite outcome of CV death or hospitalization for HF, CV death, and the first event of renal death, dialysis/transplant, or doubling of serum creatinine from baseline. Moreover, all of the enrolled patients were over 40 years old with T2D and established atherosclerotic cardiovascular disease (ASCVD) involving the coronary, cerebrovascular, and/or peripheral arterial systems [43].

The results have shown that the primary objective of the non-inferiority of ertugliflozin versus placebo on major adverse CV events was met (HR 0.97, 95% CI 0.85–1.11, $p < 0.001$ for non-inferiority), demonstrating the CV safety of this SGLT2i. The secondary endpoints that were aiming for superiority regarding the composite of CV death/hospitalization for HF (HR 0.88, 95% CI 0.75–1.03, $p = 0.11$ for superiority), CV death (HR 0.92, 95% CI 0.77–1.11, $p = 0.39$), and the renal composite (HR 0.81, 95% CI 0.63–1.04, $p = 0.08$) did not show statistical significance. However, another prespecified endpoint, the effect of ertugliflozin versus placebo regarding hospitalization for heart failure, has proven the statistically significant superiority of ertugliflozin (HR 0.90, 95% CI 0.54–0.90, $p = 0.006$), results that prove consistent effects across the class of SGLT2i [44].

The latest agent in the class, sotagliflozin, is the first dual sodium-glucose co-transporter-2 and 1 inhibitor, meaning that its mechanisms involve not only the urinary excretion of glucose, similarly to other drugs, but also the intestinal absorption of glucose, with effects on postprandial glycemic levels. The inhibition of both SGLT2 and SGLT1 would also lead to an increased glycosuric effect—the SGLT2 is responsible for the reabsorption of approximately 90% of the filtered glucose, with the remaining being reabsorbed by the SGLT1 that presumably presents a compensatory action with the inhibition of the former [45]. Moreover, SGLT1 is reported to be highly expressed in both human autopsied hearts and murine perfused hearts [46,47]. These findings alongside a study that analyzed the effects of loss-of-function mutations in the SGLT1 gene that has shown a decrease in the incidence of DM, of HF, and even of mortality suggest long-term protective effects of this new agent on cardiometabolic outcomes [48].

However, the phase 3 study that is evaluating the effects of sotagliflozin—SCORED (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk)—is still ongoing, with an estimated completion date of January 2022. Its primary objectives are to demonstrate that when compared to placebo in patients with T2D, CV risk factors, and moderately impaired renal function, sotagliflozin does not increase the risk of CV events, including death

from CVD, non-fatal heart attack, and non-fatal stroke and that it reduces the risk of death from CV disease or hospitalization for heart failure [49].

Table 2. Cardiovascular outcome trials of SGLT2 inhibitors in type 2 diabetes (T2D) patients.

Clinical Trial	SGLT2i	Characteristics	Results
EMPA-REG OUTCOME	Empagliflozin	Established CVD	Reduction in 3P-MACE, CV mortality, all-cause mortality, and HFH [30]
CANVAS	Canagliflozin	66% of included patients had CVD	Reduction in 3P-MACE, but no significant effect in all-cause mortality [23]
DECLARE-TIMI 58	Dapagliflozin	41% of included patients had ASCVD	Reduction in CV mortality and in HFH rates, no significant effects on the 3P-MACE outcome [32]
VERTIS-CV	Ertugliflozin	Established ASCVD	Non-inferiority on major adverse CV events (CV death, non-fatal myocardial infarction, and non-fatal stroke) [43]
SCORED	Sotagliflozin	CV risk factors and moderately impaired renal function	Estimated completion date of January 2022 [49]

The results of these CVOTs have led to changes in international guidelines. Whereas in 2017, SGLT2i were considered one of the multiple options for dual antihyperglycemic therapy in association with metformin, in 2018, the ADA guidelines included the recommendation of associating with metformin as a second-line therapy, an agent proven to reduce major adverse CV events and CV mortality [50]; meanwhile, in the month of October of the same year, the Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) added a different algorithm for the approach of T2D based on the individualization of antihyperglycemic treatment. The recommended first-line therapy in this consensus is still represented by metformin alongside lifestyle changes; however, the second-line agent is chosen taking into consideration the presence or absence of ASCVD or chronic kidney disease (CKD), in their presence the predominating condition such as ASCVD or HF/CKD and in their absence the major goal, be it to minimize hypoglycemia, to minimize weight gain or the promotion of weight loss, and, lastly, the reduction in costs. SGLT2i are one of the two recommendations for second-line treatment in ASCVD and one of the options for the second-line drug in all patients without ASCVD or CKD, with the only exception for situations when cost is a major issue for the management of the patient. However, SGLT2i are the definite preferred option for second-line treatment in patients with established ASCVD or CKD if the HF or the CKD predominates [51].

The 2019 update of this Consensus and the 2020 recommendations of the American Diabetes Association emphasized even more the importance of new classes of antidiabetic drugs, the SGLT2i and the GLP-1 receptor agonists. The documents mention that high-risk patients (not only those with established ASCVD or CKD) should be treated with a GLP-1 RA or an SGLT2i to reduce MACE, hospitalization for HF, cardiovascular death, and the progression of CKD and that their use should be considered independently of the baseline HbA1c or of the HbA1c target. Furthermore, it is specified that SGLT2i—with a preference for empagliflozin, canagliflozin, and dapagliflozin—are recommended in T2D patients with HF, particularly those with HFrEF, to reduce hospitalization for HF, MACE, and CVD death as well as in patients with T2D and CKD [52,53]. Moreover, the 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD also mention that SGLT2i, namely empagliflozin, canagliflozin, or dapagliflozin, are recommended to lower the risk of HF hospitalization and to reduce the progression of CKD and even suggest using an SGLT2i or a GLP-1 RA as monotherapy in drug-naïve patients with

T2D and ASCVD or high/very high CV risk in order to reduce CV events (empagliflozin, canagliflozin, or dapagliflozin) and to reduce the risk of death in patients with T2D and CVD (empagliflozin) [20].

Heart Failure Trials with SGLT2 Inhibitors

The consistent and statistically significant results from the aforementioned CVOTs regarding reductions in the hospitalization for heart failure and the ongoing research about the mechanisms of the SGLT2i have led to continuously increasing interest about the possible beneficial effects of these agents in patients with heart failure, with or without DM.

The first trial to investigate these effects, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) included patients at least 18 years old with an ejection fraction of 40% or less, with New York Heart Association (NYHA) class II-IV symptoms and with NT-proBNP of 600 pg/mL or more (if hospitalized for HF within the last 12 months, 400 pg/mL or more, and if they also had atrial fibrillation or flutter or 900 pg/mL or more). The primary outcome of this trial was a composite of worsening HF—either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for HF—or death from CV causes, while the key secondary outcome was a composite of hospitalization for heart failure or CV death. Of all the patients in each trial group, 42% had a history of T2D and an additional 3% received a new diagnosis of DM. The results have shown that dapagliflozin reduced the risk of the composite of death from CV causes, hospitalization for HF, or an urgent visit resulting in intravenous therapy for HF (HR 0.74, 95% CI 0.65–0.85, $p < 0.001$). Furthermore, each of the three components of the composite outcome was less common in the dapagliflozin group, while the use of this agent resulted in a clinical improvement of heart failure as measured on the Kansas City Cardiomyopathy Questionnaire. It is of paramount importance that these beneficial effects have been demonstrated both in patients with and without T2D, findings that once again suggest that the impact of SGLT2i lies far beyond the glucose-lowering effects [54].

Moreover, the New Onset Diabetes Sub-study has shown that dapagliflozin reduced the incidence of T2D by 32%, results mainly driven by participants with prediabetes, and, thus, is the first SGLT2i trial to show a potential diabetes prevention effect, although further studies are needed for a better understanding of this discovery [55]. Regarding the concerns about potential adverse events, these were proven to be infrequent and to occur with a similar incidence in both arms, including volume depletion, renal dysfunction, fractures, amputations, major hypoglycemia, ketoacidosis, or Fournier's gangrene [56].

The results from DAPA-HF regarding the favorable impact of dapagliflozin on the Kansas City Cardiomyopathy Questionnaire score are similar to those from the DEFINE-HF Trial (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction). The latter, a trial that included patients with HF and LVEF of 40% or less, NYHA class II-III, eGFR of 30 mL/min/1.73 m² or higher, and elevated natriuretic peptides (NT-proBNP of 400 pg/mL or higher or BNP of 100 pg/mL or higher) has also suggested that a greater proportion of patients treated with dapagliflozin for 12 weeks had a clinically meaningful improvement of 5 or more points in the Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Summary Score or at least a 20% reduction in NT-proBNP as compared with the placebo. Furthermore, these beneficial effects were consistent within subgroups of patients with or without T2D. However, the DEFINE-HF Trial has not shown between-group differences in patients treated with dapagliflozin versus placebo regarding the average 6- and 12-week adjusted mean NT-proBNP, although the proportion of patients with a 20% or higher decrease in NT-proBNP and BNP at the end of the treatment period, two secondary outcome measures, were higher in patients treated with dapagliflozin, and, thus, further studies are needed to establish the mechanisms behind these findings [57].

The DEFINE-HF Trial is just one of the several studies included in the series named DAPAMECH whose goal is to continue to advance the understanding of the underlying science behind the CV and renal effects of dapagliflozin, including the mechanisms that make SGLT2i “smart diuretics” [58,59]. The series also includes, among others, the ongoing PRESERVED-HF trial (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure) that will complement the data from DAPA-HF with results about the changes from baseline in NTproBNP and other HF-related measurements in patients with HFpEF.

This August (2020), the results from the EMPEROR-Reduced Trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction) were published and presented in the ESC Congress. The study included patients of at least 18 years in age with chronic HF and a NYHA functional class of II-IV, with a LVEF of 40% or less, with a HF hospitalization within 12 months if the EF was higher than 30%, or with NT-proBNP levels of 600 pg/mL or higher if EF was $\leq 30\%$, of 1000 pg/mL or higher if the EF was 31–35%, or of 2500 pg/mL or higher if the EF $> 35\%$ (with doubled thresholds if concomitant atrial fibrillation was present). The primary outcome was a composite of cardiovascular death or hospitalization for heart failure analyzed as the time to the first event, while the secondary endpoints were represented by the total (first and recurrent) heart failure hospitalizations and by the slope of decline in glomerular filtration rate over time. It is important to notice that half of the enrolled patients—similar to the DAPA-HF trial—had DM.

The results have shown that empagliflozin reduced the risk of the composite of death from CV causes or hospitalization for heart failure (HR 0.75, 95% CI 0.65–0.86, $p < 0.001$). The two prespecified secondary outcomes were also favorably influenced, while all of these benefits were seen in patients with or without diabetes mellitus or, even more clearly than in DAPA-HF, in those treated with sacubitril/valsartan and in those without this combination. Furthermore, similar to the DAPA-HF trial, the treatment with empagliflozin improved the scores measured on the KCCQ. The potential difference in CV mortality noticed between the DAPA-HF trial (HR 0.82, 95% CI 0.69–0.98) and the EMPEROR-Reduced trial (HR 0.92, 95% CI 0.75–1.12) could be explained by an array of different reasons—including the heterogeneity of drugs and the increased severity of HF in the latter—however, a head-to-head comparison would be needed for an appropriate conclusion [60–62]. Further results about the effects of empagliflozin on heart failure are going to be published after the termination of several ongoing trials, including EMPEROR-Preserved that will complement the data from EMPEROR-Reduced with information about the time to the first event of adjudicated CV death or HFH in patients with HFpEF [63].

The heart failure clinical trials with SGLT2i are presented in Table 3.

Therefore, in 2020, the European Society of Cardiology and the Heart Failure Association published a position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. This document summarizes the relevant clinical trial evidence concerning the SGLT2i, GLP-1 RA and DPP-4i. Furthermore, it mentions that the significant reduction in cardiovascular mortality and HF events in patients with HFrEF, with or without T2D, that has been shown in DAPA-HF (the only HF trial completed at that time) together with the ongoing clinical trials (including EMPEROR-Reduced at that moment) would lead to determining whether SGLT2i could be used for the treatment of HF, with or without reduced LVEF and whether their beneficial CV effects could be extended to HF patients without T2D [20]. Moreover, in May 2020, the U.S. Food and Drug Administration approved dapagliflozin for adults with HF with reduced ejection fraction and NYHA functional class II-IV to reduce the risk of CV death and hospitalization for HF [64,65].

Table 3. Heart failure trials with SGLT2 inhibitors.

Clinical Trial	SGLT2i	Characteristics	Results
DAPA-HF	Dapagliflozin	42% patients with T2D, 3% received a new diagnosis of DM	Reduced the risk of the composite of CV death, HFH both in patients with and without T2D [55]
DEFINE-HF	Dapagliflozin	Patients with HF and LVEF \leq 40%, NYHA class II-III, eGFR \geq 30 mL/min/1.73 m ² or higher and elevated natriuretic peptides	A clinically meaningful improvement of 5 or more points in the KCCQ Overall Summary Score or at least a 20% reduction in NT-proBNP as compared with placebo [58]
EMPEROR-Reduced	Empagliflozin	Chronic HF and a NYHA of II-IV, with a LVEF \leq 40%, 50% of the enrolled patients had DM	Reduced the risk of the composite of CV death or HFH, regardless of sacubitril/valsartan therapy, in patients with or without DM [61–63]

Therefore, with the recent findings from the EMPEROR-Reduced trial, extremely consistent with the results from DAPA-HF and at the same time complementing them (patients lower LVEF and higher NT-proBNP in EMPEROR-Reduced versus DAPA-HF), it is no surprise that SGLT2i are considered as a potential new standard of care for patients with heart failure with reduced ejection fraction, with or without T2D [61,65]. Furthermore, due to the fact that the three drug classes that were proven to reduce mortality in patients with HFrEF beyond conventional therapy consisting of ACE inhibitors or ARBs and beta-blockers, namely SGLT2i, mineralocorticoid receptor antagonists, and the association of angiotensin receptor antagonist and neprilysin inhibitors that have been studied with different background therapies, a cross-trial analysis from 2020 estimated lifetime gains in event-free survival and overall survival with comprehensive therapy versus conventional therapy. The results support the combination use of an ARNI, a beta-blocker, MRA, and SGLT2i as a new therapeutic standard, with an estimation of 2.7 additional years (for an 80-year-old) to 8.8 additional years (for a 55-year-old) free from CV death or first hospital admission for heart failure and 1.4 additional years (for an 80-year-old) to 6.3 additional years (for a 55-year-old) of survival in comprehensive disease-modifying pharmacological therapy versus conventional therapy [66].

It is expected that these results will lead to changes in current guidelines regarding the management of patients with HFrEF—the Canadian Cardiovascular Society and the Canadian Heart Failure Society have already recommended the use of SGLT2i in patients with mild or moderate heart failure who have an EF of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization for HF and cardiovascular mortality [67,68]—and that the ongoing studies about the effects of SGLT2i on HFpEF will fill the gaps of knowledge and will lead to a shift of paradigm in diabetology and cardiology.

Conclusions

At this point, after revealing the results of the latest clinical trials with SGLT2 inhibitors, the approach for the patient with CVD, HF, and reduced EF, with or without DM, needs to be reconsidered. SGLT2 inhibitors should be added to currently recommended treatments in patients with or without T2D, with HF, in line with the current evidence base and guidelines.

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Abbreviations

ACC	American College of Cardiology
ADA	American Diabetes Association
AHA	American Heart Association
ARNI	Angiotensin receptor-neprilysin inhibitor
ASCVD	Atherosclerotic cardiovascular disease
CI	Confidence interval
CKD	Chronic Kidney Disease
CV	Cardiovascular
CVOT	Cardiovascular outcome trials
DM	Diabetes mellitus
DPP-4i	Dipeptidyl peptidase-4 inhibitors
EASD	European Association for the Study of Diabetes
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GLP-1 RA	Glucagon-like peptide-1 receptor agonists
HbA _{1c}	Hemoglobin A _{1c}
HF	Heart Failure
HFpEF	Heart failure with preserved ejection fraction
HF _r EF	Heart failure with reduced ejection fraction
HFH	Heart Failure Hospitalization
HR	Hazard ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	Left ventricle ejection fraction
MACE	Major adverse cardiovascular events
MR	Modified release
MRA	Mineralocorticoid receptor antagonists
NHE 1	Sodium–hydrogen antiporter 1
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA	New York Heart Association
SGLT2i	Sodium-Glucose co-transporter-2 inhibitors
T ₂ D	Type 2 diabetes

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