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Mini Review

Beyond glucose control agents: Sodium-Glucose Co-transporter 2 Inhibitors in Heart failure

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Introduction

HF and T2D often coexist and the maleficent effects of this coupling prompted the US Food and Drug Administration to set hypoglycaemic drugs clinical trials, designed to rule out cardiovascular harm and promote cardioprotection in the year 2008 [1]. In the line of this strategic motivation, cardiovascular outcome trials (CVOTs) with a novel class of hypoglycaemic drugs, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, emerged and surprisingly demonstrated positive cardiovascular outcomes, mainly due to a decline in heart failure (HF) risk. The EMPAREG OUTCOME trial with empagliflozin, the CANVAS Program with canagliflozin, the DECLARE-TIMI 58 with dapagliflozin and the most recent VERTIS-CV with ertugliflozin, are the focal point and impel novel heart failure therapy strategies, as no other known CVOT has displayed such benefit on heart failure events so far [2-4]. The so far proposed cardioprotective mechanisms of SGLT2 inhibition include diuresis and natriuresis, decline in arterial blood pressure, erythropoiesis, enhanced heart energy metabolism, decline in inflammation, inhibition of the sympathetic nervous system, reduce in oxidative stress and improved endothelium function, among others [5-8]. In this review, we present a comprehensive, evidence-based thesis about the treatment with SGLT2 inhibitors (SGLT2i) in cardiovascular patients with or without T2D, their effect in HF and analyse the major published and ongoing SGLT2i trials. We also shed light upon the SGLT2i mechanisms of action and provide practical considerations about their application in HF patients, based on current recommendations.

SGLT2 Inhibitors and Heart Failure: The Clinical Trials

SGLT2i Cardiovascular Outcome Trials in T2D Patients

The EMPA-REG OUTCOME Trial

Empagliflozin is the first SGLT2i and glucose-lowering medication to receive approval for cardiovascular protection. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) trial, patients with T2D and known cardiovascular disease (CVD) who received empagliflozin presented reduced risk of 3 point MACE (a composite of death from CV causes, non-fatal MI or non-fatal stroke), as well as significant reduction in all-cause mortality, cardiovascular mortality and HF hospitalization (35% reduction compared with placebo, HR 0.65; 95% CI [0.50–0.85]; p=0.002).(2) Post hoc analysis of the trial demonstrated that the risk reduction of all cause/cardiovascular mortality and HF hospitalizations with empagliflozin was obvious in patients with and without HF, although patients with HF had higher rates of the aforementioned outcomes [9]. In addition, empagliflozin had a beneficial impact in HF route by lowering not only sudden cardiac death but also death due to pump failure events [10]. The HF patient in the EMPA-REG OUTCOME trial was defined as a patient i) with known HF from the beginning, ii) or had been hospitalised for HF or iii) or presented HF during the course of the trial.

The CANVAS Program

The Canagliflozin Cardiovascular Assessment Study (CANVAS) program, which included the CANVAS and CANVAS-R (renal) studies, assessed the use of canagliflozin in patients with T2D and i) known CVD at baseline or ii) at least two risk factors for CVD [11]. In consistency with the EMPA-REG OUTCOME trial, the CANVAS trial showed substantial improvements in HF hospitalisation rate for HF for canagliflozin versus placebo (33% reduction compared with placebo, HR 0.67; 95% CI [0.52–0.91]) [11]. The results for the CANVAS program were driven by a reduction in HF hospitalizations, but with no significant reduction in CV death was noticed.

DECLARE-TIMI 58 Trial

The Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58) trial compared dapagliflozin vs. placebo in T2D patients with either atherosclerotic CVD at baseline or multiple risk factors [4]. This trial demonstrated a significant reduction in its co-primary endpoint which was HF hospitalisation for HF and CV death (HR 0.83; 95% CI [0.73–0.95]; p=0.005), mostly due to a lower rate in HF

hospitalisation (27% reduction compared with placebo, HR 0.73; 95% CI [0.61–0.88]). Similar results were shown in dapagliflozin treatment for patients with and without HF at baseline [4]. A non-statistically significant reduction in the second primary endpoint which included CV death, MI or stroke was noticed, possibly because of the lower overall rate of CV events in this trial compared with other SGLT2i CVOTs [2,4,11].

The VERTIS CV trial

In the most recent Evaluation of Ertugliflozin efficacy and Safety Cardiovascular outcomes trial (VERTIS-CV), the fourth to be released SGLT2i was compared to placebo in T2D patients with CVD [12]. After a follow-up of 3.5 years, 5499 out of 8246 randomised patients who received ertugliflozin did not present increase in terms of MACE defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke [12]. In contrast to the other SGLT2i CVOTs, in the VERTIS CV trial, the rate of CV death or HF hospitalization (the first key secondary composite outcome) did not differ significantly between the compared groups. While the participants characteristics in the trial were similar to the other SGLT2i CVOTs, there is not an obvious explanation for the noninferiority conducted by the statistical analysis [12]. Advances in terms of secondary prevention medication in the recent years following the previous CVOTs may had an effect on VERTIS CV. Another possible reason is a variation in the SGLT2 class effect, as ertugliflozin presents higher selectivity to SGLT2 compared to SGLT1 [13].

Metanalyses and Real-World Data

In the so far published metanalyses, SGLT2i have demonstrated a broad class effect in reducing HF hospitalisations in patients with or without baseline CVD and but also in preserving renal function [14,15]. Despite the encouraging results of the aforementioned trials, a semantic disparity is noticed in rates of CV death. Excluding patients with risk factors, in patients with established CVD, empagliflozin was the only agent in class that reduced significantly all-cause and CV mortality [9,15]. In addition, the EMPAREG-OUTCOME had a more lenient inclusion protocol in terms of renal function, allowing patients with lower estimated glomerular filtration rate (eGFR) to participate. Patients with eGFR < 60 mL/min had a notable portion of 25.9% in EMPA-REG, while that percentage was 20.1% and 7.4% in the CANVAS and DECLARE-TIMI 58 trial accordingly [4, 9, 11, 16].

Metanalyses have shown that the SGLT2i class effect of risk reduction in terms of HF hospitalisation is consistent among a wide spectrum of renal function and it is profound in patients with greater renal dysfunction [15]. The most recent Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial included patients with T2D and nephropathy described as an eGFR of 30 to < 90 mL/min and albuminuria [17]. At baseline, over 50% of the participants had established CVD and 14.8% suffered from HF. During a median follow-up of 2.62 years, this trial demonstrated a considerable reduction in terms of a composite of HF hospitalisation and CV death (HR 0.69; 95% CI [0.57–0.83]; p<0.001) and HF hospitalisation (HR 0.61; 95% CI [0.47–0.80]; p<0.001) for patients who received canagliflozin instead of placebo [17].

In real world setting, CV outcomes and HF reduction risk associated with the use of SGLT2i have been evaluated in the CVD-REAL and EMPRISE studies.(18-20) The CVD-REAL study had access in six countries registries and compared initiation of SGLT2i vs other glucose-lowering drugs, in 309,056 T2D patients with or without CVD. SGLT2i demonstrated beneficial effect by reducing HF hospitalisations (HR 0.61, 95% CI 0.51–0.73, p < 0.001); all-cause mortality (HR 0.49, 95% CI 0.41–0.57, p < 0.001), and a composite of HF hospitalisation or all-cause death (HR 0.54, 95% CI 0.48–0.60, p < 0.001) [18, 20].

The EMPRISE study is currently in progress and evaluates the safety and efficacy of newly started empagliflozin or sitagliptin in 232,000 US T2D patients in standard care setting [19]. About 32,000 paired patients, with or without CVD, who received empagliflozin have shown a 50% rick reduction in HF hospitalisations (HR 0.50, 95% CI 0.28–0.91, p = NA), after 5 months of follow-up [16,19]. The fourth SGLT2i, ertugliflozin, is expected soon to be released and results of its CVOT metanalyses and real-world data are underway [12, 21].

SGLT2i Trials in HFrEF Patients with or without T2D

DAPA-HF is the first SGLT2i CVOT to evaluate Dapagliflozin as HF treatment in HFrEF patients with or without T2D [22]. Dapagliflozin in DAPA-HF was compared to placebo in a multicentre Phase III trial participating 4,744 patients with NYHA class II, III or IV HF and LVEF equal or less than 40%. Inclusion criteria consisted of i) NT-proBNP equal or more than 600 pg/ml or ii) 400 pg/ml if they had a HF hospitalisation within a year or iii) 900 pg/ml if they suffered from atrial fibrillation or atrial flutter on inclusion ECG. Patients randomised were on optimal HF guideline-oriented medication, including an ACEi, an ARB, or sacubitril–valsartan plus a beta-blocker, unless contraindicated and received dapagliflozin 10 mg once daily or placebo. There were no substantial differences in initial therapies between the two groups· 45% of the participants suffered from T2D and 55% did not [22].

Dapagliflozin 10 mg od demonstrated a significant reduction in HF deterioration (aka HF hospitalisation or urgent HF visit) and CV death (HR 0.74, 95% CI 0.65–0.85, p = 0.001), both in T2D patients (HR 0.75, 95% CI 0.63–0.90, p = NA) and T2D-free patients (HR 0.73, 95% CI 0.60–0.88, p=NA) [22]. Primary and recurrent HF hospitalisations were significantly lower for the ones receiving dapagliflozin compared to placebo [23]. In DAPA HF, when on dapagliflozin, the number of patients needed to treat (NNT) in order to prevent a primary event was 21 (95% CI 15–38). A non-significant 29% reduction in terms of worsening renal function, was also noticed in the dapagliflozin group (HR 0.71; 95% CI [0.44–1.16]). A post hoc analysis revealed that patients receiving sacubitril/valsartan at baseline, despite representing a

mere 10% of the trial participants, had the same added benefit of SGLT2i therapy and the beneficial effect is consistent regardless of background HF therapy [24].

In The Empagliflozin Compared With Placebo On Exercise Ability and Heart Failure Symptoms in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPERIAL-Reduced) study 312 HFrEF patients with or without T2D were evaluated in terms of exercise capacity via a 6 minute walk test and patient-reported HF outcomes [25]. Empagliflozin was well tolerated and approved for safety but results for the primary outcome were neutral [25].

In the EMPEROR-Reduced Phase III trial, 3,730 patients with HF NYHA class II, III or IV and LVEF equal or less than 40%, received either empagliflozin 10 mg od or placebo [26]. Like DAPA HF, patients randomised were already on optimal HF guideline-oriented medication. Inclusion NT-proBNP level criteria were in concordance with LVEF at initation of the trial: ≥600 pg/ml for patients with LVEF ≤30%, ≥1,000 pg/ml for LVEF 31–35%, ≥2,500 pg/ml for LVEF 36–<40% and when in AF the NT-proBNP inclusion threshold was doubled. Patients with eGFR less than 20 ml/min/1.73m2 or in dialysis were excluded from the trial [26]. Again, like DAPA HF, there were no substantial differences in initial therapies between the two groups· 49.5% of the participants suffered from T2D.

After a median follow-up of 16 months, the primary outcome (combined risk of CV death and HF hospitalisation) was addressed in 361 of 1,863 patients (19.4%) in the empagliflozin group and in 462 of 1,867 patients (24.7%) in the placebo group (HR 0.75; 95% CI [0.65–0.86]; p<0.001), mainly because of reduced rates of HF hospitalisation in the empagliflozin arm (HR 0.70; 95% CI [0.58–0.85]; p<0.001) [27]. Empagliflozin-treated patients had a lower risk of serious renal events and demonstrated a significant reduction in the rate of renal disease progression, as measured by eGFR slope over time (–0.55 versus –2.28 ml/min/1.73m^2 per year; absolute difference 1.73 ml/min/1.73m^2 per year; 95% CI [1.10–2.37]; p<0.001).(27) On the other hand, empagliflozin did not affect CV and all-cause death rates (HR 0.92; 95% CI [0.75–1.12] and HR 0.92; 95% CI [0.77–1.10] accordingly) [2, 26, 27]. The beneficial effect of empagliflozin was observed throughout the range of renal function, regardless of RAAS inhibition and ARNI administration, in patients with or without T2D [27].

SGLT2i Trials in HFpEF Patients

The first SGLT2i trial dedicated in HFpEF patients, but restricted in 312 participants, was the Empagliflozin Compared With Placebo on Exercise Ability and Heart Failure Symptoms, In Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPERIAL-Preserved) trial [25]. It evaluated the effect of empagliflozin administration on exercise capacity but after 12 weeks no significant difference was shown between the empagliflozin and placebo groups in terms of 6-minute walk test or KCCQ total symptom scores [25].

Among the heterogeneous groups of HF patients with preserved ejection fraction, two major SGLT2i CVOTs are underway. In the soon to be completed Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR-Preserved; NCT03057951) trial, 5,988 HFpEF patients with or without T2D will be randomised to receive empagliflozin or placebo [28]. In the same route, the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER; NCT03619213) trial will evaluate administration of dapagliflozin or placebo as add-on to standard therapy in 6,100 HFpEF patients with or without T2D [29].

Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction (DETERMINE-Preserved; NCT03877224) is a another randomised controlled trial to evaluate the effect of dapagliflozin on exercise capacity and QoL in 504 HFpEF patients. The SOLOIST trial with the SGLT1/SGLT2 inhibitor sotagliflozin, which was early terminated due to financial issues, included both HFpEF and HFrEF patients and could add valuable information provided sufficient data were collected [23]. The HFpEF phenotype, albeit common in real world setting, is not often represent in trials and hard to evaluate. A CANVAS program derived, post-hoc analysis of a HFpEF subgroup demonstrated reduction in rates of hospitalisation and death events (HR 0.83; 95% CI [0.55–1.25]), but because of the limited HFpEF sample it could not reach statistical significance [30]. Likewise, a DECLARE_TIMI 58 study derived, post-hoc analysis of a HFpEF subgroup demonstrated reduction in HF hospitalisations (HR 0.74; 95% CI [0.48–1.14]) but because only 4.7% of the participants were HFpEF patients, these results should be taken with a grain of salt [31].

SGLT2i Mechanisms of Cardiovascular Protection

Despite the intriguing trial results, the SGLT2i mechanisms of CV protection are not totally understood and some parts remain covered in mystery. SGLT2i inhibitors have demonstrated a broad effect in the cardio–renal axis, affecting many systems, regardless of glycaemic control. The SGLT2 channel, located in the proximal kidney tubule, is responsible for the majority of glucose reabsorption [6,7]. SGLT2i promote glycosuria and natriuresis by restraining glucose and Na+ reabsorption. Through improvement in blood glucose and HbA1c levels, arterial blood pressure lowering and body weight loss, they seem to protect against CVD and HF [6,32]. Along with glycosuria and natriuresis, SGLT2i inhibitors push for uricosuria [33,34]. Although impressive, these effects of SGLT2i do not explain thoroughly the outcomes observed in CVOTs compared to placebo, shifting the SGLT2i beneficial impact beyond glycaemic or blood pressure control.

SGLT2 inhibitors retain intravascular volume and reduce interstitial volume, in contradistinction to diuretics. By reducing preload and afterload, they boost improvement in endothelial function, arterial elasticity and an overall upturn in hemodynamic parameters [6]. Incoming data imply that SGLT2i prevent electrolyte

disturbances, neurohormonal activation and renal function deterioration caused commonly by diuretics [35, 36]. Along with volume contraction, SGLT2i promote haemoconcentration, probably due to intrinsic renal processes, such as increased erythropoietin (EPO) production and restoration of the tubulointerstitial oxygenation [5]. The failing myocardium in HF patients suffers from underutilisation of glucose and fatty acids, thus creating an accumulation of metabolic products. SGLT2i increase the oxidation of ketone bodies, by enhanced lipid mobilization caused by glycosuria, lowered plasma glucose and insulin levels, along with an upraise in plasma glucagon [37]. This so called "thrifty substrate" hypothesis, suggests that SGLT2i improve the heart's energetic and metabolic function by producing and consuming ketone bodies who are more energy-efficient than fatty acids [38].

Another proposed mechanism of SLGT2i related cardio-renal protection, implies inhibition of the Na+/H+ exchangers in the heart and kidney [6,39]. Cardiac and renal Na+/H+ exchange inhibition reduces cytoplasmic Na+ and Ca2+, which in cardiomyocytes, translates to an upturn in contractility and mitochondrial function [6, 40]. Preliminary in-vitro studies have also described the positive effect of SGLT2i on cytokine production, adipokine expression and epicardial adipose tissue mass [6,40]. SGLT2i reduce the maximum renal transport capacity for glucose reabsorption leading to a lower cut-off for glycosuria (60–90 g/day). Because of the insulin-independent mechanism to lower blood glucose, patients receiving SGLT2is are at a limited risk of hypoglycemia [41,42]. Thus, in the three large prospective CVOTs, hypoglycemia was at similar rates in the SGLT2i and in the placebo groups [2, 4, 11]. Several studies with Empagliflozin or Dapagliflozin are now conducted, investigating the effect of SGLT2i on cardiac metabolic and energetic function and their results will lead us to a better comprehension of the SGLT2i actions and mechanism of cardioprotection [43-45].

SGLT2i in Clinical Practice

After the phenomenal results of the DAPA-HF and EMPEROR-Reduced trials, SGLT2i are now candidates for joining the big three (ACEIs/ARBs, MRAs and beta blockers) as disease modifying agents in HFrEF patients. Empagliflozin was the first of its class to enter the 2016 ESC HF guidelines: "Empagliflozin should be considered in patients with T2D in order to prevent or delay the onset of HF" with a IIa class of recommendation and level of evidence B [46]. After 3 years, in the 2019 ESC guidelines for diabetes and CV protection all three SGLT2i (canagliflozin, dapagliflozin or empagliflozin) were included and were recommended for T2D patients with established CVD or at high/very high rick for CVD with an Ia class of recommendation [47]. Canagliflozin, dapagliflozin and empagliflozin were recommended for T2D patients to lower the risk of HF hospitalisation, again with an Ia class of recommendation [47].

In a 2019 position paper, joined by ESC/HFA, empagliflozin canagliflozin and dapagliflozin gained approval as recommended therapies in T2D patients and high CV risk for the prevention of HF hospitalisations, after demonstrating a substantial reduction in the risk of hospitalisation for HF across the spectrum of CV risk and regardless of a history of HF [48]. Also, in a most recent update by ESC/HFA, SLT2i ertugliflozin gained the class recommendation for preventing HF hospitalization in T2D patients and established CV disease or at high CV risk [49]. The DAPA HF and EMPEROR REDUCED positive results on CV and all-cause death, along with the significant reduction noticed in HF hospitalisations, elevated dagliflozin and empagliflozin as the preferred SGLT2i in symptomatic HFrEF patients and administration should be pursued regardless of the presence of T2DM [49] (Table 1).

Table 1: Major sodium-glucose co-transporter 2 inhibitors cardiovascular outcome trials.

SGLT2 inhibitors trials	Empagliflozin	Canagliflozin	Dapagliflozin	Ertugliflozin
Patients with T2D and CVD	EMPA-REG OUTCOME *benefit in* • HHF • CV death • All cause death • 3 point MACE • Renal events			VERTIS CV *benefit in* • HHF • Renal events
Patients with T2D and CVD or CV risk		CANVAS program *benefit in* • HHF • 3 point MACE • Renal events	DECLARE-TIMI 58 *benefit in* • HHF • Renal events	
Patients with T2D and CKD		CREDENCE *benefit in* • HHF • Renal events		
Patients with HFrEF +/- T2D	EMPEROR-Reduced *benefit in* • HHF • Renal events		DAPA-HF *benefit in* • HHF • CV death • All cause death	
Patients with HFpEF +/- T2D	EMPEROR-Preserved *currently in progress*		DELIVER *currently in progress*	

Abbreviations: SGLT2: sodium-glucose co-transporter 2, T2D: type 2 diabetes, CVD: cardiovascular disease, CV: cardiovascular, CKD: chronic kidney disease, HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction.

SGLT2i are associated with a minimal risk of drug-drug interactions and can be combined with all other glucose control agents [50]. On the other hand, due to their unique pharmacological profile and possible adverse effects, an individual benefit-risk evaluation must be taken before initiation [51]. Adverse events in patients receiving SGLT2i, such as urinary and genital infections, are not to be neglected, but can be correlated with predisposing conditions, such as volume depletion and euglycemic diabetic ketoacidosis [52]. Frail elderly patients who are prone to dehydration and orthostatic hypotension should be treated with caution. Other side effects, such as bone fractures and lower limb amputations are unexpected and remain poorly understood [53, 54]. Still, results regarding the aforementioned side effects are highly heterogeneous and real-world data seem to be reassuring [55] (Figure 1 and 2).

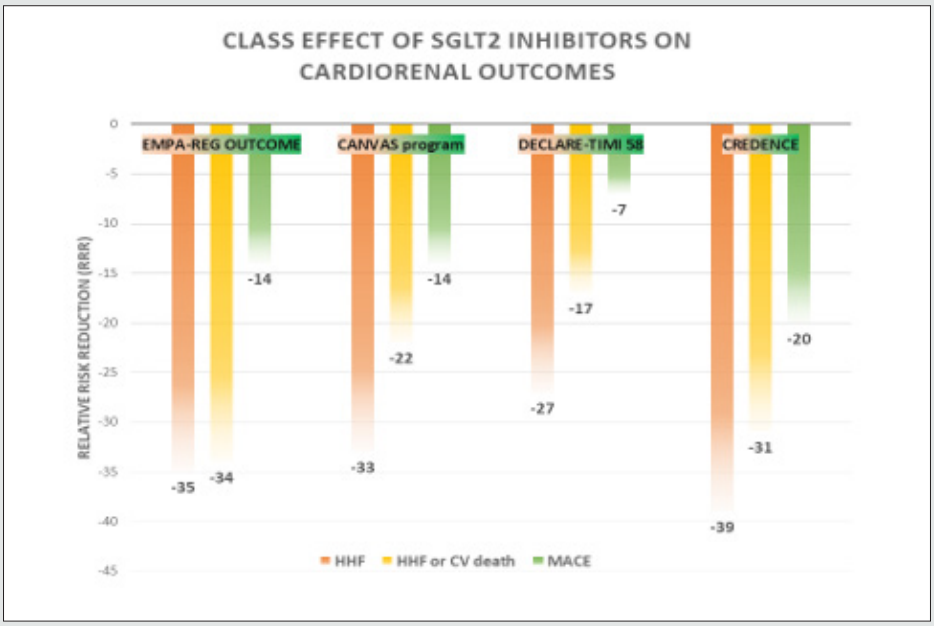

Figure 1: Class effect of Sodium-Glucose Co-transporter 2 inhibitors on cardiorenal outcomes. H
HF: hospitalization for heart failure, CV: cardiovascular, MACE: major adverse cardiovascular events.

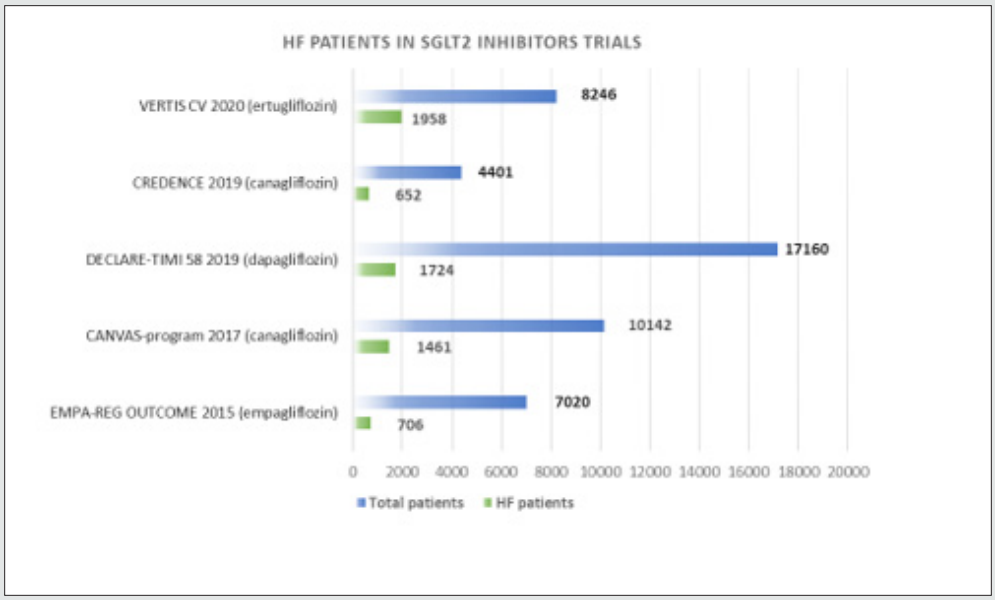

Figure 2: Participation of heart failure patients in Sodium-Glucose Co-transporter 2 inhibitors in cardiovascular outcome trials.
HF: heart failure, SGLT2: Sodium-Glucose Co-transporter 2.

Conclusion

Despite advances in drug and device-therapy n HF patients, there is still an unmet need for disease-modifying agents. SGLT2i have shown to offer cardiac and renal protection for HF (mostly HFrEF) patients, but also to reduce the risk for HF occurrence, regardless of glycaemic control, in patients with or without T2D. Addition of dapagliflozin and empagliflozin in the conventional recommended ACEi/ARB, MRA and beta-blocker algorithm is beneficial at any point during HFrEF course. The SGLT2i underlying mechanisms of action, although still under investigation, provide cardiac and renal benefit in many ways, complementary or collectively. Along with pending trials' results, further trials are required to fully understand the SGLT2i pharmacokinetics, but also to determine whether these results can be applied in HFpEF patients, where no other known therapy has shown improved outcomes.

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