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Paradigm shift in heart failure treatment: are cardiologists ready to use gliflozins?

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Abstract

Despite recent advances in chronic heart failure (HF) therapy, the prognosis of HF patients remains poor, with high rates of HF rehospitalizations and death in the early months after discharge. This emphasizes the need for incorporating novel HF drugs, beyond the current approach (that of modulating the neurohumoral response). Recently, new antidiabetic oral medications (sodium-glucose cotransporter 2 inhibitors (SGLT2i)) have been shown to improve prognosis in diabetic patients with previous cardiovascular (CV) events or high CV risk profile. Data from DAPA-HF study showed that dapaglifozin is associated with a significant reduction in mortality and HF hospitalization as compared with placebo regardless of diabetes status. Recently, results from EMPEROR-Reduced HF trial were consistent with DAPA-HF trial findings, showing significant beneficial effect associated with empagliflozin use in a high-risk HF population with markedly reduced ejection fraction. Results from the HF with preserved ejection fraction trials using these same agents are eagerly awaited. This review summarizes the evidence for the use of gliflozins in HF treatment.

Keywords Chronic heart failure · Diabetes mellitus · Gliflozin · Empagliflozin · Dapagliflozin · Canagliflozin · Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

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Introduction

Heart failure (HF) is one of the major public health problems and causes of high rates of morbidity and mortality worldwide. Type 2 diabetes mellitus (T2DM) is a highly prevalent disease with more than 400 million people affected [1]. The relative risk of incident HF and/or idiopathic cardiomyopathy is higher in patients with diabetes compared with those without diabetes [2–6]. Moreover, impaired glucose regulation is associated with a high risk of development of HF [7, 8].

Reducing mortality and hospitalizations is the most important clinical endpoint in HF patients, and the risk of these events is markedly increased in HF patients with concomitant diabetes: the higher mortality risk attributable to diabetes is applicable to both HF with preserved ejection fraction (HFpEF) and with reduced ejection fraction (HFrEF), as well as to ischemic and non-ischemic cardiomyopathy.

The pathophysiologic mechanisms connecting T2DM and HF are complex and cannot be explained by the sharing of some CV risk factors alone such as hypertension and coronary artery disease (CAD). Direct toxic effects of hyperglycaemia, effects of renin–angiotensin–aldosterone system (RAAS) activation, mitochondrial dysfunction, and metabolic derangements in cardiac myocytes, for example, are some of the mechanisms that play key roles in the development of HF in diabetic patients [9–11].

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2i), also called gliflozins, are a new class of blood glucose lowering medications that block renal glucose reabsorption in the proximal tubule, leading to increased urinary sodium and glucose excretion. The aim of this review is to introduce this new class of antidiabetic drugs, describe preclinical and clinical evidence in support of their use, and emphasize their role in the treatment of HF by providing practical advice for their use by non-diabetologists.

Mechanism of action

The proximal renal tubule absorbs most of the filtered glucose which is about 180 g/day. This is achieved by utilizing active Na^+ absorption through basolateral Na^+/K^+ ATPase pumps in the epithelial tubular cells that generate an electrochemical gradient favouring glucose to enter the cell using the sodium-glucose cotransporter1 (SGLT) and SGLT2 when the Na^+ concentration in the glomerular filtrate is higher versus lower Na^+ concentration in the epithelial cells [12]. SGLT2 is a high-capacity, low-affinity transporter that is expressed almost exclusively in the initial portion of the proximal tubule [13], which accounts for 90% of the reabsorbed glucose. Residual glucose is reabsorbed by SLGT1, a low-capacity, high-affinity transporter, at the end of the proximal tubule. Patients with T2DM express a significantly higher number of SGLT2s in the proximal tubule as compared with healthy individuals [14]. Consequently, glucose reabsorption from the glomerular filtrate is greatly increased in T2DM patients. The glucose resorption capacity from the blood reaches its maximum when the blood glucose levels exceed 200 mg/dl, at which point it would be excreted in urine to prevent extreme hyperglycemia. Inhibition of SGLT2 lowers this threshold [15]. In patients with T2DM in treatment with SGLT2i, lower incidence of hypoglycaemia was noted, because SGLT2i leave the metabolic counter regulation intact. In fact, SGLT2i increase plasma glucagon concentrations and gluconeogenesis in patients with T2DM [16]. Furthermore, SGLT2 inhibition enhances lipolysis and shifts substrate utilisation from carbohydrates to lipids [17], contributing to a reduction in fat mass and body weight [18]. This physiological response to excessive renal glucose excretion may prevent hypoglycaemia. Since SGLT2i utilize glomerular filtration rate, its glucose lowering ability declines when the eGFR falls < 45 ml/min/1.73 m^2. In addition, in patients without hyperglycemia, it has been observed that the glycosuria with SGLT2i is reduced, resulting in lower risk of hypoglycemia (Table 1) [25].

Pleiotropic effects

The use of SGLT2i is associated with many favourable effects such as reduction of preload (diuretic effects [19]) and afterload (blood pressure (BP) [20], arterial stiffness [21], improvement of mitochondrial efficiency [22], delay of decline in eGFR, delay of microalbuminuria and macroalbuminuria, weight loss [23], reduction in epicardial adipose tissue [24], improvement in glycaemia, and reduction in uric acid [25]. Considering those effects and numerous

Table 1 SGLT2 inhibitors in T2DM and CVD according the ESC recommendations

Recommendations	Class	Level
SGLT2 inhibitors		
Empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with T2DM and CVD, or at very high/high CV risk, to reduce CV events	I	A
Empagliflozin is recommended in patients with T2DM and CVD to reduce CV events	I	B

hypotheses has been formulated to justify the cardioprotective effects of gliflozins:

1. The diuretic hypothesis [26]: increase natriuresis and act as diuretics leading to a reduction in preload and myocardial stretch);
2. The blood pressure lowering hypothesis [27]: decrease blood pressure and afterload;
3. The 'thrifty substrate' hypothesis [28]: favor the production of ketones, which can act as a 'superfuel' in the cardiac and renal tissue;
4. The metabolic hypothesis [29]: improve/change metabolic variables;
5. The anti-inflammatory hypothesis: cause many anti-inflammatory effects [30];
6. The RAAS hypothesis [31]: through the angiotensin II type II receptors in the context of simultaneous RAAS blockade may lead to vasodilation and positive inotropic effects;
7. The sodium hypothesis [32]: directly decrease the activity of the Na+-H+exchanger in myocardial cells leading to restoration of mitochondrial calcium handling in cardiomyocytes;
8. The SGLT1 inhibition hypothesis [33] (some SGLT2 inhibitors also exhibit SGLT1 inhibitory action possibly resulting in an attenuation of oxidative stress in the ischemic myocardium).

Of note, it has been widely demonstrated that SGLT2i have diuretic and natriuretic effect (combining properties of proximal tubule diuretics and osmotic diuretics) [34]. Because SGLT2 reabsorbs sodium along with glucose, use of SGLT2i increase urinary sodium excretion and reduce plasma volume, resulting in haematocrit increase and blood pressure lowering as reported in the EMPA-REG Outcome study [35] and the Canvas program [36, 37]. The SGLT2i reno-protective effect is also demonstrated by the reduction of albuminuria and macroalbuminuria; these could be explained by increased sodium delivery at the macula densa and subsequent activation of tubuloglomerular feedback, which increases afferent arteriolar tone and may reduce intraglomerular pressure [38].

Additionally, as compared with classical diuretics, SGLT2i may have differential effects on interstitial and intravascular compartment, as recently proposed. In this regard, findings from healthy volunteers showed that dapaglifozin is associated with a reduction in sodium and interstitial fluid with negligible change in blood volume as opposed to loop diuretic bumetanide, which showed greater reductions in intravascular volume; dapaglifozin administration induce greater electrolyte-free water clearance, and greater fluid clearance from the interstitial fluid space than from the circulation via peripheral sequestration of osmotically inactive sodium. This may also limit the deleterious effects of reflex neurohumoral stimulation that usually occurs in response to intravascular volume depletion with traditional diuretics.

Other, recently, demonstrated that beneficial effects of SGLT2i are directly or indirectly related to a hemodynamic effect due to SGLT2 influence on RAAS system include the improvement in left atrial dilatation, attenuated intracardiac fibrosis, improved dp/dt of left ventricle [39]. SGLT2i produce mild but meaningful reductions in BP [40]-36 and a strict BP control in patients with diabetes is associated with reductions in cardiovascular and renal risk.

Preclinical evidences in heart failure

In several preclinical models of T2DM, SGLT2i improved endothelial function and arterial stiffness [37], decreased oxidative stress [37], exerted anti-inflammatory effects [37], ameliorated cardiac fibrosis [37], and improved LV systolic [37] and diastolic function [37]. Dapagliflozin may be able to prevent and reduce cardiac fibrosis after MI, also in non diabetic patients, by activating the STAT3 signalling pathway promoting M2 macrophage activation and, consequently, reducing the myofibroblast infiltration and collagen accumulation [35]. Empagliflozin improved cardiac function and reduced myocardial fibrosis in non-diabetic rats with HFrEF after a large MI [36]. These effects are probably related to Empagliflozin action on metabolism of cardiac cells. It may be able to reduce mitochondrial DNA damage and oxidative stress, stimulating mitochondrial biogenesis and increasing ATP levels [37]. In a rabbit model, Empagliflozin exerted a direct effect on cardiomyocytes, inhibiting the Na^+/K^+ exchanger, with a reduction of Na^+ and Ca^{++} intracellular concentrations and an increase of mitochondrial Ca^{++} [38]. Empagliflozin influences the activity of Ca^{++}/calmodulin-dependent Kinase II in myocytes that is overexpressed in HF ventricle [38], it ameliorates adverse cardiac remodelling and HF by influencing the switches of myocardial fuel utilization away from glucose toward ketone bodies, free fatty acid, and branched-chain amino acid; improving myocardial energetics; enhancing left ventricular (LV) systolic function; and ameliorating LV reverse remodelling [39]. On the basis of this pathophysiological background, the clinical usefulness of SGLT2i has been evaluated in humans with HF with or without DM.

Gliflozin in diabetic patients: clinical trials results

Four gliflozins have been approved by the US Food and Drug Administration (FDA) for glycaemic control in T2DM. The EMPA-REG OUTCOME trial [40] was the first long-term

CV safety trial performed in 7020 patients with a long duration of T2DM (57% > 10 years), at high CV risk (CV disease in 99%), who were randomized to empaglifozin 10 or 25 mg once daily or placebo, in addition to standard of care. The primary major adverse CV events (MACE) endpoint (CV death, non-fatal myocardial infarction, or non-fatal stroke) was reduced by 14% in the treatment-group compared with the placebo-group. This reduction was driven mainly by a highly significant (38%) reduction in CV death. In a secondary analysis, empagliflozin was associated with a 35% reduction in HF hospitalization. The reduction of overall mortality was 32%. Empagliflozin reduced the endpoint of "new onset or worsening nephropathy" as well [40].

The CANVAS Program integrated data from two trials [41, 42] involving a total of 10,142 patients with T2DM (glycated haemoglobin level ≥ 7.0% and ≤ 10.5%) and eGFR ≥ 30 ml/min/1.73 m^2, in secondary (66%) and primary prevention (34%) of CV disease, canagliflozin significantly reduced the primary endpoint by 14% and HF hospitalization by 33%, but the effects on CV death and overall death, non-fatal myocardial infarction, and non-fatal stroke were not significant. The comparison among participants with and without a history of CV disease showed a significant benefit in secondary prevention.

The DECLARE-TIMI 58 trial [43] examined the effect of 10 mg dapagliflozin o.d. vs. placebo in 6971 patients with DM and CV disease, and 10,189 patients with DM and multiple CV risk factors, who were followed for a median of 4.2 years. In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE but did result in a lower rate of the composite endpoint of CV death or hospitalization for HF. This was driven by a lower rate of hospitalization for HF. Also, renal endpoints (40% decreases in eGFR to 60 ml/min/m^2 and ESRD or renal death) were significantly reduced by 47%.

A meta-analysis of the three trials including 34,322 patients suggested consistent benefits on reducing the composite of HF hospitalization or CV death, as well as on the progression of kidney disease, regardless of existing atherosclerotic CV disease or a history of HF [44].

The results of VERTIS-CV trial [45] indicated that ertugliflozin is superior to placebo for reducing CV events in patients with T2DM and established CVD (23.7% patients with history of HF). Ertugliflozin significantly reduced HF hospitalization. The benefit was consistent regardless of ertugliflozin dose, history of HF, and systolic function. Total and recurrent HF events were also reduced in the ertugliflozin arm.

Clinical evidences in heart failure trials

The effects of empagliflozin were analysed in EMPEROR-Reduced [46] in HFrEF patients with and without T2DM. In this study were enrolled ≈3600 patients with LVEF ≤ 40% and patients were randomized to placebo or empagliflozin 10 mg daily, on top of recommended HF treatment: primary endpoint was the time-to-first event analysis of the combined risk of CV death and hospitalization for HF. These trials also evaluated the effects of empagliflozin on renal function, CV death, all-cause mortality, and recurrent hospitalization events. The results from EMPEROR-Reduced trial showed that in patients with HFrEF, the empagliflozin group had a lower risk of CV death or hospitalization for HF as compared to the placebo group, regardless of the presence or absence of diabetes [47]

In a randomized, double-blind, placebo-controlled study in patients with acute decompensated HF (EMPA-RESPONSE-AHF study) [48], no difference was observed in dyspnoea, diuretic response, length of hospital stay, or change in NT-proBNP between empagliflozin and placebo. However, a reduction of the combined endpoint of in-hospital worsening HF, rehospitalization for HF, or death at 60 days was observed in the empagliflozin group as compared to placebo. Empagliflozin treatment was safe, well tolerated, and without adverse effects on blood pressure or renal function in patients with acute decompensated HF [48].

Results from DAPA-HF trial [49] demonstrated a significant reduction in CV death, HF hospitalization, and worsening HF or CV death [41] in patients treated with dapagliflozin compared with the placebo group, in both diabetics and nondiabetics. Dapagliflozin was added to recommend HFrEF therapy [50] and demonstrated incremental efficacy and safety in HFrEF patients with and without diabetes. Dapagliflozin did not strengthen the actions of diuretics in DAPA-HF [51], and its benefit was similar in patients with or without ischemic cardiomyopathy or in patients who were and who were not taking sacubitril/valsartan [52]. Dapagliflozin improved symptoms, physical function, and quality of life in patients with HFrEF [53]. In a recent post hoc analysis [54], the benefit of dapagliflozin remained consistent regardless of background HF therapy. The benefit and safety of dapagliflozin were consistent across the range of SBP [55] and across the diuretic subgroups [56] examined. Left ventricular EF did not modify the beneficial effect of dapagliflozin in patients with and without diabetes in DAPA-HF [55]. In the DEFINE-HF [57] in HFrEF patients (EF ≤ 40%, NYHA class II-III, eGFR ≥ 30 mL/min/1.73 m^2, and elevated natriuretic peptides (NP)), treatment with dapagliflozin over 12 weeks increase the amount of patients (also without T2DM) with improvements in HF-related health status.

DAPA HF and EMPEROR reduced studied the same target population, patients with HFrEF (EF < 40%), and elevated NT proBNP concentration, with or without DM, but the EMPEROR reduced included preferentially patients with advanced HFrEF; therefore, the two populations were overlapping and complementary. The characteristics of the analysed populations in EMPEROR reduced are illustrated in Table 2 [46, 47].

The primary outcome was the same for DAPA HF and EMPEROR reduced, and it was a composite outcome of cardiovascular death or HF. In each trial, the SGLT2 inhibitors reduced significantly the risk of this outcome, but the benefit was driven mainly by the reduction in HF; the effects of these drugs on cardiovascular death were modest, particularly in the EMPEROR. This difference in cardiovascular death could be related to the higher percentage of patients with advanced HFrEF, but also to a shorter follow-up (16 vs 18 months) and to a higher percent of patients that discontinued therapy in EMPEROR. However, Zannad et al. [58] have shown in a recent meta-analysis of these two trial that empaglifozin and dapaglifozin reduced all cause and cardiovascular death and HF without heterogeneity between the two trials [59].

Tables 3 and 4 go through trials using gliflozins specifically in HF populations.

Safety of gliflozins

The safety of gliflozins has been under scrutiny given the reporting of worrisome side effects such as lower limb amputation, fractures, and genital/urinary infections linked to increased glycosuria. Increased rates of infections of male or female genitalia (and less so for urinary infections) were consistently observed for all three mentioned gliflozins.

Although in the CANVAS Program [42] canagliflozin was associated with higher rates of fractures (15.4 vs. 11.9 participants with fracture per 1000 patient-years; hazard ratio, 1.26; 95% CI, 1.04 to 1.52), there was significant heterogeneity between CANVAS and CANVAS-R results [41, 42]; also, in the CREDENCE trial [59], fracture rates were similar between the canagliflozin and the placebo groups. A similar risk was reported in the CANVAS program for lower limb amputation; no difference as compared to placebo was found neither in CREDENCE trial [59] nor in the analysis of a large real-world meta-analysis of 4 databases (OBSERVE-4D) [60]. Such risk was not documented for both dapaglifozin and empagliflozin.

VERTIS (eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes) trial [61] evaluating a fourth SGLT2 drug—ertugliflozin—showed a similar pattern of adverse effects with more urinary tract infections (12.1% vs. 10.2%; $p<0.05$).

Some patients will experience a decline in eGFR following the initiation of gliflozins. This has been an area of concern, limiting prescription. DAPA-CKD [62] assessed renal events in a broad range of patients with CKD (including patients with a low baseline eGFR between 25 and 30 mL/min per 1.73 m^2) with and without DM treated with dapagliflozin. It demonstrated the reduction of risk of kidney failure, and prolonged survival in people with CKD, with or without T2DM, independently of the presence of concomitant CV disease.

Actual approach to prescription to SGLT2i

Gliflozins are effective in reducing CV events independent of their effects on blood glucose, and cardiologists should be very familiar with how to use them, in order to incorporate these drugs into the HF therapeutic armamentarium [63]. The FDA has broadened the labelling of empagliflozin and canagliflozin specifically for use to lower CV risk in patients with T2DM and established CVD. Despite the potential benefits of SGLT2i in reducing adverse clinical events, SGLT2i is under prescribed for eligible patients [63]; furthermore, patients treated versus those not treated with an SGLT2i were more likely to be younger and men, and less likely to have prevalent CAD and HF. In the year after addition of the CV indication for empagliflozin, endocrinologists contribute to the highest proportion of prescriptions (45.4%), while cardiologists only to 4.5% of annual prescriptions [64]. The top 3 barriers for cardiology providers were lack of knowledge about these medications, concerns of introducing confusion into diabetes care, and discomfort of prescribing diabetes medications.

The American Diabetes Association and European Association for the Study of Diabetes consensus guidance [65] provided strong support for upfront CV risk assessment and consideration of SGLT2 inhibitors as second-line therapies. Metformin is still preferred as backbone therapy given clinician familiarity, low cost, and widespread availability.

In current HF guidelines, SGLT2i are the first class of glucose-lowering therapy to prevent HF (in clinical trials and real-world studies) in patients with T2DM with or without established CV disease and with or without baseline HF [66].

The European Society of Cardiology (ESC) guidelines [67] strongly recommend to stratify CV risk in all patients with T2DM who are antihyperglycemic drug naïve or on metformin monotherapy and to start SGLT2i in patients with high or very high risk, irrespective of glycated haemoglobin; in particular, empagliflozin, canagliflozin, or dapagliflozin should be used in patients with T2DM and CV disease, or at very high/high CV risk to reduce CV events and empagliflozin in patients with T2DM and CV disease to reduce the risk of death.

It is necessary to suggest that cardiologists perform routine measurement of HbA1c in all patients with established CV disease in order to use a glucose-lowering drug that improves glycaemia and CV outcome [68].

A few rules may help cardiologists to prescribe SGLT2i. The former cardiologists should consider thiazide or loop diuretic dose reduction at the time of SGLT2i initiation to

Table 2 Comparison of the EMPEROR-reduced and DAPA HF populations

	EMPEROR reduced		DAPA-HF	
	Empaglifozin	Placebo	Dapaglifozin	Placebo
Number of patients	1863	1867	2373	2371
Age, years*	67.2	66.5	66.2	66. 5
Female sex (%)	437 (23.5)	456 (24.4)	23.8	23.0
BMI*	28.0	27.8	28.2	28.1
Race, *n* (%)				
White	1325 (71.1)	1304 (69.8)	1662 (70.0)	1671 (70.5)
Black	123 (6.6)	134 (7.2)	122 (5.1)	104 (4.4)
Asian	337 (18.1)	335 (17.9)	552 (23.3)	564 (23.8)
Other	78 (4.2)	94 (5.0)	37 (1.6)	32 (1.3)
Region n. (%)				
North America	212 (11.4)	213 (11.4)	335 (14.1)	342 (14.4)
South America	641 (34.4)	645 (34.5)	401 (16.9)	416 (17.5)
Europe	676 (36.3)	677 (36.3)	1094 (46.1)	1060 (44.7)
Asia Pacific	248 (13.3)	245 (13.1)	543 (22.9)	553 (23.3)
NHYA class, *n* (%)				
II	1399 (75.1)	1401 (75.0)	1606 (67.7)	1597 (67.4)
III	455 (24.4)	455 (24.4)	747 (31. 5)	751 (31.7)
IV	9 (0.5)	11 (0.6)	20 (0.8)	23 (1.0)
Heart rate, beats/min*	71.0	71.5	71.5	71.5
Systolic blood pressure, mmHg *	122.6	121.4	122.0	121.6
Left ventricular ejection fraction*	27.7	27.2	31.2	30.9
Median NT pro BNP (IQR), pg/ml	1887	1926	1428	1446
Cause of heart failure, *n* (%)				
Ischemic	983 (52.8)	946 (50.7)	1316(55.5)	1358 (57.3)
Non ischemic	880 (47.2)	921 (49.3)	857 (36.1)	830 (35.0)
Medical history, *n* (%)				
Hospitalization for heart failure in < 12 mo	577 (31.0)	574 (30.7)	1124 (47.4)	1127 (47.5)
Atrial fibrillation	664 (35.6)	705 (37.8)	916 (38.6)	902(38.0)
Diabetes mellitus	927 (49.8)	929 (49.8)	993 (41.8)	990 (38.0)
Estimated GFR				
Mean value, ml/min/1.73 m^2	61. 8	62.2	66.0	65.5

Table 2 (continued)

	EMPEROR reduced		DAPA-HF	
	Empaglifozin	Placebo	Dapaglifozin	Placebo
Rate < 60 ml/min/1.73 m^2, *n* (%)	893 (48.0)	906 (48.6)	962 (40.6)	964 (40.7)
Device therapy, *n* (%)				
Implantable cardioverter-defibrillator	578 (31.0)	593 (31.8)	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy	220 (11.8)	222 (11.9)	190 (8.0)	164 (6.9)
Heart failure medication, *n* (%)				
ACE inhibitor or ARB	1314 (70.5)	1286 (68.9)	2007 (84.5)	1961 (82.8)
Sacubitril Valsartan	340 (18.3)	387 (20.7)	250 (10.5)	258 (10.9)
Beta blockers	1765 (94.7)	1768 (94.7)	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)	1696 (71.59	1674 (70.6)
Clinical outcomes, *n* % Hazard or rate ratio or difference (95% CI)				
Primary composite outcome**	361 (19.4) 0.75 (0.65–0.86) $p < 0.001$	462 (24.7)	386 (16.3) 0.75 (0.65–0.85) $p < 0.001$	502 (21.2)
Hospitalization for heart failure	246 (13.2) 0.69 (0.59–0.81)	342 (18.3)	237 (10) 0.70 (0.59–0.83)	326 (13.7)
Cardiovascular death	187 (10.0) 0.92 (0.75–1.12)	202 (10.8)	227 (9.6) 0.82 (0.69–0.98)	273(11.5)
Death from any cause	249 (13.4) 0.92 (0.77–1.10)	266 (14.2)	276 (11.6) 0.83 (0.71–0.97)	329(13.9)
Laboratory and other measures (changes from baseline)***				
Glycated haemoglobin %	−0.28 ± 1.14	−0.12 ± 0.03	−0.21 ± 1.14	−0.04 ± 1.29

Table 2 (continued)

	EMPEROR reduced		DAPA-HF	
	Empaglifozin	Placebo	Dapaglifozin	Placebo
Hematocrit	1.98 ± 0.10	− 0.38 ± 0.10	2.31 ± 3.90	− 0.19 ± 3.81
NT proBNP pg/ml	− 244 ± (− 890 to 260)	− 141 (− 784 to 585)	196 ± 2387	101 ± 2944
Weight, kg	− 0.73 ± 0.13	0.08 ± 0.13	− 0.88 ± 3.86	0.10 ± 4.09
Systolic blood pressure, mmHg	− 2.4 ± 0.4	1.7 ± 0.4	− 1.92 ± 14.92	− 0.38 ± 15.27

ACE angiotensin converting enzyme, *ARB* angiotensin receptor blockers, *ARNI* angiotensin receptor neprilysin inhibitor, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *EMPEROR* empaglifozin outcome trial in patients with chronic heart failure, *DAPA HF* dapaglifozin and prevention of adverse outcomes in heart failure, *NHYA* New York Heart Association, *NT proBNP* N terminal pro B type natriuretic peptide

*Mean values. **The primary outcome for EMPEROR reduced was a composite outcome of cardiovascular death or hospitalization for heart failure; the primary outcome of DAPA HF was a composite outcome of worsening heart failure (hospitalization or an urgent visit resulting in intravenous therapy for heart failure) or dead from cardiovascular causes. ***Changes from baseline at month 8 and from baseline to 52 weeks for EMPEROR reduced

avoid excessive diuresis and volume depletion (SGLT2i may induce osmotic diuresis via glucosuria); the following suggestions should be given to patients: genital/perineal hygiene (increased risk of genital infections due to their effect of increased urinary glucose excretion), regular foot exams (increased risk of amputation), avoid excessive alcohol. During multidisciplinary follow-up, serial assessment of renal function, body weight, blood pressure, and symptoms (including symptoms of diabetic ketoacidosis) are needed. In patients with a history of frequent hypoglycemia, recommended medication adjustments include a 50% reduction in sulfonylurea dose and a 20% reduction in basal insulin dose at the time of SGLT2i initiation. If the patient is taking a DPP4i, the prescribing physician may decide to discontinue that medication before starting the SGLT2i [68–70].

Paradigm shift in HF treatment

RAAS inhibition, beta-blockade, and angiotensin receptor blockers/neprilysin inhibitors (ARNI) reduce hospitalization and mortality risk in patients with HFrEF; however, despite these results, HF patients still have an increased risk for morbidity and mortality and, furthermore, these drugs often predispose hypotension, renal dysfunction, and electrolyte abnormalities. In recent times, we are witnessing an important turning point in the treatment of HF; in fact, after a long time, the interest of cardiologists is shifting from contrasting the sympathetic system to research new and different targets. In order to improve the development of drug for HF, the researchers have to develop the "right" drugs, starting from the "right" targets. Thanks to gliflozins we are able to begin to know the "Dark Side" of HF beyond neurohormonal system (new mechanisms and new targets for drugs in HF). The encouraging results obtained by gliflozins in diabetic patients in terms of prevention of HF events and in HF patients regardless the presence of diabetes, as in DAPA-HF trial [71], lead us to imagine a possible role of gliflozin in the treatment of HFrEF. Because dapagliflozin was similarly efficacious and safe in patients who were and who were not taking sacubitril/valsartan in the DAPA-HF trial [52], the use of both agents together could further low morbidity and mortality in patients with HFrEF.

Trials with gliflozins as treatment in HFpEF are still ongoing (Table 5). In the next future, there may be some changes in clinical approach of HF, the management of HF will become even more multidisciplinary, the diabetologists will be new allies in the battle against HF, and likely, we could suggest a diabetologic consultation already in early phase of HF (NYHA class II) according to baseline characteristics of DAPA-HF [71].

The cardiologist and the other specialists treating patients with HF may have no difficulties in adopting this class of drugs. SGLT2i use is not accompanied by hypotension, bradycardia,

Table 3 Clinical pharmacology of sodium-glucose co-transporter-2 inhibitors

	Empagliflozin	Canagliflozin	Dapagliflozin	Ertuglifozin
Selectivity SGLT-2/SGLT-1	≃2700-fold	≃260-fold	≃1200-fold	≃2200-fold
Dose range	10–25 mg once daily	100–300 mg once daily	5–10 mg once daily	5–15 mg once daily
Oral bioavailability (%)	> 60	65	78	70–90%
T_{max}	1.5 h	1–2 h	1 h	1 h
Half-life	12.4 h	10.6 ± 2.13 h (100 mg) 13.1 ± 3.28 h (300 mg)	12.9 h	16 h
Biotransformation	Extensively metabolized by glucuronidation (UGT2B7, UGT1A3, UGT1A8, and UGT1A9), and to a lesser extent, oxidation to six inactive metabolites	Extensively metabolized by O-glucuronidation (UGT1A9 and UGT2B4) to two major inactive metabolites	Extensive O-glucuronidation (UGT1A9) to inactive conjugates (primarily dapagliflozin 3-O- glucuronide)	Extensive O-glucuronidation (UGT1A9 and UGT2B7) to inactive conjugates (ertugliflozin-2-O-β-glucuronide-M5a; ertugliflozin-3-O-β-glucuronide-M5c) CYP-mediated (oxidative) metabolism is minimal (12%)
Elimination pathway	96% of drug is excreted; 54% of drug in urine (50% is parent drug); 42% of drug in faeces (most of drug is parent drug)	84.7% of drug is excreted; 51.7% of drug in faeces (41.5% parent drug); 33% of drug in urine (< 1% parent drug)	96% of drug is excreted; 75% of drug in urine (primarily eliminated via urinary excretion, < 2% as parent drug); 21% of drug in faeces (15% as parent drug)	91.2% of drug is excreted; 50.2% of drug in urine (1.5% as parent drug); 40.9% of drug in faeces (33.8% as parent drug)
Dose modifications	Dose adjustment in patients with creatinine clearance < 60 ml/min Contraindicated or to be stopped in patients with creatinine Clearance < 45 ml/min/1.73 m^2 No adjustment in hepatic failure	Should not be initiated in patients with eGFR < 60 ml/min/1.73 m^2 Dose limited to 100 mg once daily if eGFR falls to < 60 but > 45 ml/min/1.73 m^2 Stopped in patients with eGFR < 45 ml/min/1.73 m2	Should not be initiated in patients with eGFR < 60 ml/mt/1.73 m^2 No dose adjustment in patients with eGFR > 60 ml/min/1.73 m^2	Should not be initiated in patients with eGFR < 60 ml/mt/1.73 m^2 Contraindicated if eGFR < 30 mL/min/1.73 m^2 No dose adjustment in patients with eGFR > 60 ml/min/1.73 m^2

eGFR estimated glomerular filtration rate, *UGT* uridine diphosphate-glucuronosyltransferase.

Table 4 Comparison of EMPA-REG OUTCOME, CANVAS program, DECLARE-TIMI 58, and VERTIS CV studies

	EMPA-REG OUTCOME (Empagliflozin)	CANVAS program (Canagliflozin)	DECLARE-TIMI 58 (Dapagliflozin)	VERTIS CV(Ertuglifozin)
No. patients	7028 (placebo $N=2333$)	10,142 (placebo $N=4347$)	17,160 (placebo $N=8578$)	8246 (placebo $N=2747$)
Tested dose (s)	10 or 25 mg once daily	100 or 300 mg once daily	10 mg once daily	5 or 15 mg once daily
Study design	1:1:1 ratio (10 mg, 25 mg, placebo) with 2 weeks single-blind placebo run-in period	1:1:1 ratio (100 mg, 300 mg, placebo) with 2 weeks single-blind placebo run-in period	1:1 ratio (10 mg, placebo) with 4–8 weeks single-blind placebo run-in period	1:1:1 ratio (5 mg, 15 mg, placebo)
Median study duration	3.1 years	~2.41 years (126.1 weeks)	4.2 years	3.5 years
Duration of diabetes	≤1 year: 2.7%; > 1 to 5 years: 15.2% > 5 to 10 years: 25.1% > 10 years: 57.0%	At least 10 years; average duration = 13.5 years	Median duration ~ 11 years	Average duration = 13 years
eGFR entry criteria	eGFR ≥ 30 ml/min/1.73 m^2 (MDRD)	eGFR ≥ 30 ml/min/1.73 m^2	eGFR ≥ 60 ml/min/1.73 m^2 (Cockroft-Gault equation)	eGFR ≥ 30 ml/min/1.73 m^2 (MDRD)
Primary prevention	No	35% of patients (≥ 50-year-old)	59% of patients (men ≥ 55-year-old, women ≥ 55-year-old)	No
Secondary prevention	Yes (≥ 18-year-old)	65% of patients (≥ 30-year-old)	41% of patients (≥ 40-year-old)	Yes (≥ 40 year-old)
Types of patients	All patients with established CVD: previous MI/unstable angina, known CAD, previous stroke (ischemic or hemorrhagic), occlusive peripheral artery disease	Secondary Prevention: patients with established CVD (previous MI/unstable angina/ CABG/ PCI, peripheral revascularization; symptomatic with documented hemodynamically significant carotid or peripheral vascular disease or amputation secondary to vascular disease). Primary Prevention: patients with CV risk factors: diabetes duration ≥ 10 years, SBP > 140 mmHg on ≥ 1 medication, current smoker, micro- or macroalbuminuria, or HDL-C < 39 mg/dl	Secondary prevention: established CVD (ischemic heart disease, cerebrovascular disease, peripheral artery disease). Primary prevention: age + ≥ 1 additional risk factors ((LDL-C > 130 mg/dl, on lipid lowering therapy. BP > 140/90 mm/Hg, on anti-hypertensive therapy, current tobacco use)	Secondary prevention: patients with established CVD (previous MI/ CABG/PCI; history of ischemic stroke, history of carotid revascularization; peripheral arterial disease (angiographically documented peripheral vascular disease, resting ABI of < 0.85 plus symptoms of claudication; amputation, peripheral bypass, or peripheral angioplasty of the extremities prior to the Screening visit
Primary endpoint (s)	CV death, nonfatal MI, or nonfatal stroke	CV death, nonfatal MI, or nonfatal stroke	a) CV death, MI, or ischemic stroke (MACE); b) CV death or HF hospitalization	MACE (CV death, nonfatal MI, nonfatal stroke)
Results				
Primary endpoint (s)	0.86 (0.74–0.99), $P=0.04$	0.86 (0.75–0.97), $P=0.02$	(a) 0.93 (0.84–1.03), $P=0.17$ (MACE) (b) 0.83 (0.73 − 0.95), $P=0.005$	0.97 (0.85–1.11)
All-cause death	0.68 (0.57–0.82), $P<0.001$	0.87 (0.74–1.01)	0.93 (0.82 − 1.04)	-

Table 4 (continued)

	EMPA-REG OUTCOME (Empagliflozin)	CANVAS program (Canagliflozin)	DECLARE-TIMI 58 (Dapagliflozin)	VERTIS CV(Ertuglifozin)
CV death	0.62 (0.49–0.77), $P<0.001$	0.87 (0.72–1.06)	0.98 (0.82 – 1.17)	0.92 (0.77–1.11)
HF hospitalization	0.65 (0.50–0.85), $P=0.002$	0.67 (0.52–0.87)	0.73 (0.61 – 0.88)	0.70 (0.54–0.90)
CV death or HF hospitalization	0.66 (0.55–0.79), $P<0.001$	0.78 (0.67–0.91)	- (see primary endpoint)	0.88 (0.75–1.03)
*Composite renal endpoint	0.54 (0.40–0.75), $P<0.001$	0.60 (0.47–0.77)	0.76 (0.67–0.87)	0.81 (0.63–1.04)

CVD cardiovascular disease, *CAD* coronary artery disease, *MDRD* Modification of Diet in Renal Disease criteria, *CV* cardiovascular, *MI* myocardial infarction, *MACE* major adverse cardiovascular events, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoproteincholesterol, *SBP* systolic blood pressure, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *ABI* ankle/brachial-index.

*Composite renal endpoint definitions across studies: (a) EMPAREG: Doubling of serum creatinine level accompanied by eGFR of ≤ 45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease; (b) CANVAS: sustained 40% reduction in eGFR, the need for renal-replacement therapy, or death from renal causes; (c) DECLARE-TIMI: sustained decrease of 40% or more in eGFR by calculated by means of the Chronic Kidney Disease Epidemiology Collaboration equation to less than 60 ml per minute per 1.73 m^2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes; (d)VERTIS CV: Renal death, renal replacement therapy, doubling of serum creatinine.

or hyperkalaemia, which are often the side effects of currently recommended HF medications. Furthermore, no titration of the drug is necessary. The cardiologists will learn side effects and contraindications of gliflozins (for example, increased risk of genital infections, increased risk of amputation) easily.

Future research and future possible use

Ongoing clinical trials aim to evaluate the impact of gliflozins on circulatory hemodynamics (filling pressures, cardiac output—such as the EMBRACE trial) or LV structure and function (as assessed by echocardiography or cardiac magnetic resonance imaging). In order to determine whether empagliflozin improves cardiac function in non-diabetic HF patients, EMPA-TROPISM clinical trial [71], a randomized, double-blind, placebo-controlled, will enrol 80 HFrEF patients. The changes in LV end-diastolic volume, change in peak VO2, and change in LV mass, in LVEF, in left atrium volumes, in RV function and volumes, in interstitial myocardial fibrosis, and in epicardial adipose tissue, will be evaluated.

The Empire HF trial [72] (a randomized, double-blinded, placebo-controlled, including patients with HFrEF) will clarify the effects and mechanisms of empagliflozin in HFrEF patients with and without T2DM.

Table 5 Active clinical trials recruiting or not, using gliflozins in HFpEF

Trial name	Trial design: population and primary objective	ClinicalTrials.gov Identifier:
EMBRACE-HF	• HFr/pEF (ischemic or non-ischemic aetiology) who already have a CardioMEMs device; • assess hemodynamic parameters (pulmonary artery diastolic pressure)	NCT03030222
EMPEROR-Preserved	• Chronic HFpEF • Time to first event of adjudicated CV death or adjudicated HHF	NCT03057951
PRESERVED-HF	• Chronic HFpEF • Change from baseline in NTproBNP at 6 and 12 weeks	NCT03030235
DELIVER	• Chronic HFpEF • CV death and HF events	NCT03619213
DETERMINE- Preserved	• HFpEF • Change from baseline in 6 min walking distance	NCT03877224
Effect of dapagliflozin plus low dose pioglitazone on hospitalization rate in patients with HF and HFpEF	• HFpEF and T2DM • Time to first hospitalization for HF	NCT03794518

HF heart failure, *EF* ejection fraction, *HFpEF* HF with preserved ejection fraction, *EMBRACE-HF* Empagliflozin Impact on Hemodynamics in Patients With Heart Failure, *EMPEROR* Preserved EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, *PRESERVED-HF* Dapagliflozin in PRESERVED Ejection Fraction Heart Failure, *DELIVER* Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure, *DETERMINE* Preserved Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients With Heart Failure With Preserved Ejection Fraction, Effect of dapagliflozin plus low dose pioglitazone on hospitalization rate in patients with HF and HFpEF

Table 6 Active clinical trials recruiting or not, using empagliflozin in HF

Trial name	Trial design: population and primary objective	ClinicalTrials.gov Identifier:
EMBRACE-HF	• HFr/pEF (ischemic or non-ischemic aetiology) who already have a CardioMEMs device; • Assess hemodynamic parameters (pulmonary artery diastolic pressure)	NCT03030222
EMPA Acute Heart Failure	• Acute HF • Assess change in cardiac output	NCT03554200
EMPA-TROPISM	• HF NYHA II and III, EF < 50% • End-systolic volume (ESV) is the volume of blood in a ventricle at the end of contraction of the left ventricle (LV)	NCT 03,485,222
EMPAG-HF	• Acute decompensated HF • Total urinary output (UOP) as measured by daily volume summed up over 5 days	NCT04049045
EMPA-VISION	• Chronic HF • Change from baseline to week 12 in PCr/ATP ratio in the resting state measured by 31P MRS	NCT03332212
ELSI	• Chronic HF • Assess changes in total and tissue sodium content	NCT03128529
EMPEROR-Preserved	• Chronic HFpEF • Time to first event of adjudicated CV death or adjudicated HHF	NCT03057951
ERA-HF	• Chronic HF • PVCs percentage of all beats in a pre-specified period captured on ICD or CRTD/P device	NCT03271879
SUGAR	• HFrEF • Left ventricular end-systolic volume index measured by cardiac magnetic resonance imaging as mL/m2	NCT03485092
EMMY	• AHF and AMI • change of NT-proBNP levels to week 26	NCT03087773
A Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure	• de Novo or Decompensated Chronic HF • time to death, number of heart failure events (HFEs), time to first HFE, change in KCCQ-CSS from baseline after 90 days	NCT04157751

CV cardiovascular, *HF* heart failure, *EF* ejection fraction, *HFrEF HF* with reduced EF, *HFpEF* HF with preserved EF, *AMI* acute myocardial infarction, *EMBRACE-HF* Empagliflozin Impact on Hemodynamics in Patients With Heart Failure, *ELSI* Analysing the Effect of Empagliflozin on Reduction of Tissue Sodium Content in Patients With Chronic Heart Failure, *EMPAG-HF* Effects of Empagliflozin on Diuresis and Renal Function in Patients With Acute Decompensated Heart Failure, *EMPEROR*- Preserved EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction, *EMPA-VISION* A Randomised, Double-blind, Placebo-controlled, Mechanistic Cardiac Magnetic Resonance Study to Investigate the Effects of Empagliflozin Treatment on Cardiac Physiology and Metabolism in Patients With Heart Failure, *ERA-HF* Empagliflozin Versus Placebo on the Rate of Arrhythmic Events in Heart Failure Patients, *SUGAR* Studies of Empagliflozin and Its Cardiovascular, Renal and Metabolic Effects, *EMMY* Impact of EMpagliflozin on Cardiac Function and Biomarkers of Heart Failure in Patients With Acute MYocardial Infarction, *EMPA-TROPISM* Are the "Cardiac Benefits" of Empagliflozin Independent of Its Hypoglycemic Activity? (ATRU-4)

SGLT2 inhibitors have the potential to change the paradigm in HF with/without T2DM patients, and evidence is most eagerly expected for acute HF setting. The known diuretic effect and other unknown effects could also be of significant value in acute HF. There is evidence that urinary output could be increased with empagliflozin [72], which could potentially be of benefit in hospitalized HF patients and/or for overcoming diuretic resistance. Empagliflozin is associated with a lower risk of post-acute HF rehospitalization and mortality [73]. The ability of empagliflozin and dapagliflozin to lower HF hospitalizations following acute myocardial infarction will be further explored in the EMMY trial [74] and in the DAPA-MI trial respectively (which was recently announced by the sponsoring company: https://www.astrazeneca.com/media-centre/press-releases/2020/farxiga-granted-fast-track-designation-in-the-us-for-heart-failure-following-acute-myocardial-infarction-leveraging-an-innovative-registry-based-trial-design.html).

Another question is whether SGLT2i have an additive effect on top of angiotensin–neprilysin inhibitors, as the rate of use for this class in the already published studies was rather low (no more than 10% in DAPA-HF). The effect on vulnerable populations (including the very elderly and the black) is also less known.

HFpEF is another area of profound interest, lacking any specific therapies; this is being currently investigated in

Table 7 Active clinical trials recruiting or not using dapagliflozin in HF

Trial name	Trial design: population and primary objective	ClinicalTrials.gov Identifier:
PRESERVED-HF	• Chronic HFpEF • Change from baseline in NTproBNP at 6 and 12 weeks	NCT03030235
DEFINE-HF	• Chronic HFrEF • Proportion of patients with a ≥ 5pts increase in KCCQ	NCT02653482
Dapagliflozin HF Readmission	• Acute decompensated HD • Composite number of hospital admissions, emergency department visits, urgent clinic visits for Heart Failure (HF) and death after admission	NCT04249778
DELIVER	• Chronic HFpEF • CV death and HF events	NCT03619213
DETERMINE- Reduced	• HFrEF • Change from baseline in 6 min walking distance	NCT03877237
DETERMINE- Preserved	• HFpEF • Change from baseline in 6 min walking distance	NCT03877224
DICTATE-AHF	• Acute decompensated HF • Cumulative change in weight (kilograms)	NCT04298229
DAPA-VO2	• HFrEF • Changes in VO2 at baseline, 30 and 90 days	NCT04197635
DAPA-Shuttle1	• HF NYHA class I-II • Change in urinary osmolyte concentration	NCT04080518 [42]
REFORM	• HF NYHA class II-III and T2DM • Change in LV end systolic volume or end diastolic volume	NCT02397421
SGLTi	• HFrEF • Change in myocardial perfusion reserve index	NCT04200586
Effect of dapagliflozin plus low dose pioglitazone on hospitalization rate in patients with HF and HFpEF	• HFpEF nad T2DM • Time to first hospitalization for HF	NCT03794518

HF heart failure, *EF* ejection fraction, *HFrEF* HF with reduced ejection fraction, *HFpEF* HF with preserved ejection fraction, *VO2* peak oxygen consumption, *PRESERVED-HF* Dapagliflozin in PRESERVED Ejection Fraction Heart Failure, *DEFINE-HF* Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure, *DELIVER* Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure, *DETERMINE*- Reduced/Preserved Dapagliflozin Effect on Exercise Capacity Using a 6-min Walk Test in Patients With Heart Failure With Reduced/Preserved Ejection Fraction, *DICTATE-AHF* Efficacy and Safety of Dapagliflozin in Acute Heart Failure, *DAPA-VO2* Short-term Effects of Dapagliflozin on Peak VO2 in HFrEF, *DAPA-Shuttle1* Hepato-renal Regulation of Water Conservation in Heart Failure Patients With SGLT-2 Inhibitor Treatment, *REFORM* Safety and Effectiveness of SGLT-2 Inhibitors in Patients With Heart Failure and Diabetes, *SGLTi* The Effects of SGLTi on Diabetic Cardiomyopathy

several trials, including the EMPEROR-preserved, whose results are expected in 2021. The ongoing DELIVER study [75] is evaluating the use of dapagliflozin specifically in this population as well.

Among the ongoing studies with dapagliflozin, the DAPPER [76] is an exploratory multicenter, randomized, open-labelled study, designed to evaluate whether dapagliflozin decreases albuminuria in T2DM patients with CHF and exerts cardioprotective effects.

Tables 6, 7, and 8 go through ongoing trials using gliflozins specifically in HF populations.

Table 8 Active clinical trials recruiting or not using Canagliflozin in HF

Trial name	Trial design: population and primary objective	ClinicalTrials.gov Identifier:
CHIEF-HF	• Chronic HFp/rEF • Change from baseline in KCCQ-TSS	NCT04252287
Treatment of Diabetes in Patients With Systolic Heart Failure	• Chronic HFrEF and T2DM poorly controlled • Change in VO2 at 12 weeks	NCT02920918

HF heart failure, *EF* ejection fraction, *HFrEF* HF with reduced ejection fraction, *HFpEF* HF with preserved ejection fraction, *VO2* peak oxygen consumption, *KCCQ-TSS* Kansas City Cardiomyopathy Questionnaire, *CHIEF-HF* A Study on Impact of Canagliflozin on Health Status, Quality of Life, and Functional Status in Heart Failure

Conclusions

HF is a highly debilitating condition affecting millions of individuals worldwide, with a high rate of rehospitalization and death and a poor prognosis. Several studies highlighted the important role of gliflozins, a new class of blood glucose lowering drugs, on cardiac remodelling, through improvements of both systolic and diastolic function, with positive effects on renal function and cardiovascular death, even in non-diabetic individuals. There are encouraging data on the beneficial effect of this class of drugs, in both HFrEF and HFpEF patients, with low incidence of adverse effects, so that routinely introducing these drugs in daily clinical practice is increasingly considered. However, we have to wait for the results of the ongoing studies, in order to better understand what patients, what dosages, and what associated drug classes could ensure best results.

Abbreviations Ca^{2+}: Calcium; CI: Confidence interval; FDA: US Food and Drug Administration; GFR: Glomerular filtration rate; GLP: Glucagon-like peptide; HF: Heart failure; HR: Hazard ratio; Na^{+}: Sodium; NHE: Sodium/hydrogen exchanger; RAAS: Renin–angiotensin–aldosterone system; SGLT: Sodium-glucose co-transporter; SGLT2i: Sodium-glucose co-transporter 2 inhibitor; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus

Declarations

Conflicts of interest The authors declare no competing interests.

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