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REVIEW

DAPA-HF trial: dapagliflozin evolves from a glucose-lowering agent to a therapy for heart failure

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Abstract

Heart failure (HF) continues to be a major global health problem with a notable impact in terms of morbidity and mortality and so, in consequence, with a large unmet necessity for new therapies. The inhibition of sodium–glucose cotransporter 2 (SGLT2) causes glycosuria and natriuresis, leading to reductions in hyperglycemia (antidiabetic effect), body weight, and blood pressure. In this context, outcome trials have been shown to reduce hospitalizations for HF in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors. The underlying protective cardiovascular (CV) mechanisms of these agents are complex, multifactorial, and not entirely understood as, in addition to a diuretic-like function, SGLT2 inhibitors may mitigate glycemic-related toxicity, promote ketogenesis, increase hematocrit, and exert antihypertrophic, antifibrotic, and antiremodeling properties. The DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial enrolled 4744 patients with HF and reduced ejection fraction (EF) who were receiving excellent guideline-directed treatment before the addition of dapagliflozin (a SGLT2 inhibitor) or placebo. The DAPA-HF trial clearly showed that dapagliflozin was superior to placebo at preventing CV deaths and HF events. The relative and absolute risk reductions in death and hospitalizations were consistent across subgroups including patients with and without diabetes; so, in consequence, dapagliflozin represents the first in a new class of drug for HF with reduced EF. The recently published Dapagliflozin Effects on Biomarkers, Symptoms, and Functional Status in Patients With Heart Failure With Reduced Ejection Fraction (DEFINE-HF) trial is also described in this review as well as the thought-to-be mechanisms of action of SGLT2 inhibitors beyond their known glucose-lowering effects. There is a vast, ambitious, and promising ongoing clinical investigation program with dapagliflozin and other SGLT2 inhibitors, which may result in changes to the therapeutic approach to HF in a relatively short time.

Keywords: dapagliflozin, sodium–glucose cotransporter 2 inhibitors, DAPA-HF trial, DEFINE-HF trial, heart failure.

Citation

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Introduction

Heart failure (HF) is one of the most important causes of mortality and morbidity in developed countries with an estimated prevalence of around 1–2% and reaching >10% among patients >70 years old.[1]

Despite the fact that hospitalization rates and survival of patients with HF have markedly improved in the last decades, the current mortality and morbidity rates of HF in patients receiving a guideline-directed therapy is still high. For example, in the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM HF) study, the composite of death from cardiovascular (CV) causes or hospitalization for HF (HFH; 27 months of follow-up) was 21.8% in the sacubitril/valsartan (S/V) arm.[2] This fact clearly indicates that a large unmet necessity for new therapies remains in this field.[3]

Clinical outcomes of trials showed that sodium–glucose cotransporter 2 (SGLT2) inhibitors, which are a novel class of antidiabetic agents, in addition to standard care, were associated with a consistent reduction in HFH among patients with type 2 diabetes (T2D). The primary goals of these trials were oriented to determine the effects of SGLT2 inhibitors (*versus* placebo) on major CV adverse events (CV death, nonfatal myocardial infarction, or nonfatal stroke), and besides that, it should be considered that most of the enrolled

patients did not present with HF at the time of study inclusion (10–15%).[4–6]

In this setting, empagliflozin in the EMPA-REG OUTCOME (Empagliflozin CV Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial,[4] canagliflozin in the CANVAS trial (canagliflozin CV assessment study),[5] and dapagliflozin in the DECLARE–TIMI 58 (Dapagliflozin and CV Outcomes in T2D) trial,[6] were, respectively, associated with a 35%, 33%, and 28% reduction in the relative risk of HFH.

Consequently, all the benefits of SGLT2 inhibitors in the reduction of HFH raised the question of whether these agents could be used to treat HF patients with or without T2D assuming an eventual benefit independent of the glucose-lowering action.[7]

All these points were addressed for the first time in the landmark DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial, in which the SGLT2 inhibitor, dapagliflozin, reduced the risk of HFH and CV death (*versus* placebo) in patients with HF and reduced ejection fraction (EF) regardless of the presence or absence of T2D.[8]

The aim of this review is to focus initially on the DAPA-HF study and its consequences and then to re-evaluate the possible mechanisms of action of SGLT2 inhibitors considering that DAPA-HF results do not endorse previous hypotheses in this setting.

DAPA-HF trial

DAPA-HF enrolled 4744 HF patients with or without T2D, reduced EF (≤40%), *New York Heart Association* (NYHA) functional class II–IV, and an elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration, who were randomly assigned to dapagliflozin at a dose of 10 mg once daily (n: 2373) or matching placebo (n: 2371) with a median follow-up of 18.2 months.[8] Main baseline general characteristics included the following: mean age was 66±11, 23% were women, ischemic etiology was present in 56%, 68% were in NYHA II, mean left ventricular ejection fraction was 31±7%, median NT-proBNP was 1428 pg/mL, and 38% had atrial fibrillation. Contemporary HF therapies were similar in both groups, including a renin–angiotensin system inhibitor in 94%, a beta-blocker in 96%, and a mineralocorticoid receptor antagonist (MRA) in 71% (S/V 11%).

At screening, 42% (n: 1983) of patients in each group had T2D, and an additional 3% (n: 154) of subjects in each group received a new diagnosis of diabetes; subjects with type 1 diabetes or exhibiting a severe renal disease were excluded.

Main baseline general characteristics of T2D patients (*versus* not diabetic) were[9]:

1. bigger median body mass index and more presence of obese subjects
2. higher proportion of ischemic etiology, including myocardial infarction, and coronary revascularization procedures
3. worse distribution of NYHA class and higher NT-proBNP values (LVEF was similar in both groups)
4. lower mean estimated glomerular filtration rate (eGFR) and more patients with hypertension, eGFR < 60 mL/min/1.73 m^2, and anemia.

The primary endpoint (a composite of death from CV causes or worsening HF, which was defined as an unplanned hospitalization or an urgent visit requiring intravenous therapy for HF) was reduced in the dapagliflozin group by a significant 26% (16.3 *versus* 21.2%; hazard ratio [HR] 0.74; 95% confidence interval [CI]: 0.65–0.85; $p<0.001$). Each component of the composite outcome was significantly decreased by dapagliflozin: 30% reduction in worsening HF (10.0 *versus* 13.7%; HR 0.70; 95% CI: 0.59–0.83; $p<0.00004$) and 18% reduction in CV mortality (9.6 *versus* 11.5%; HR 0.82; 95% CI: 0.69–0.98; $p=0.029$). The secondary outcome of HFH or death from CV causes was lower in the dapagliflozin group (16.1 *versus* 20.9%; HR 0.75; 95% CI: 0.65–0.85; $p<0.001$) with fewer total and recurrent events (567 *versus* 742; HR 0.75; 95% CI: 0.65–0.88; $p<0.001$). Death from any cause also affected fewer patients in the dapagliflozin group (11.6 *versus* 13.9%; HR 0.83; 95% CI: 0.71–0.97). Finally, more patients in the dapagliflozin arm had a ≥5-point improvement in the clinical summary of the Kansas City Cardiomyopathy Questionnaire (KCCQ) score (58.3 *versus* 50.9% odds ratio 1.15, 95% CI: 1.08–1.23; $p<0.001$), and fewer had a significant deterioration (25.3 *versus* 32.9% odds ratio 0.84, 95% CI: 0.78–0.90; $p<0.001$).

A subgroup analysis indicated that the benefits were consistent regardless of diabetes status at baseline (presence or absence: HR 0.75; 95% CI: 0.63–0.90 *versus* HR 0.73; 95% CI: 0.60–0.88) and the etiology of HF (ischemic *versus* nonischemic: HR 0.77; 95% CI: 0.65–0.92 *versus* HR 0.71; 95% CI: 0.58–0.87). In addition, the primary outcome was consistent regarding other subgroups such as age (above or below 65 years), sex, race, body mass index (above or below 30 kg/m^2), geographic region, left ventricular EF (above or below median), NT-proBNP (above or below median), and the eGFR (above or below 60 mL/min).

Conversely, the benefit was greater among patients in NYHA functional class II (68%) than those in class III or IV (HR 0.63; 95% CI: 0.52–0.75 versus HR 0.90; 95% CI: 0.74–1.09); however, this observed benefit may not be 'real' because of the disparity in patient numbers between the groups. It was also inconsistent when other markers of severity were analyzed (LVEF, NT-proBNP, worse renal function, etc.).

There was also a reliable benefit of dapagliflozin among patients taking S/V (11%) and those not taking it (HR 0.75; 95% CI: 0.50–1.13 *versus* HR 0.74; 95% CI: 0.65–0.86), showing that dapagliflozin added to S/V exerts a complementary beneficial effect.

With regard to safety issues, 111 patients (4.7%) in the dapagliflozin group and 116 (4.9%) in the placebo arm withdrew due to an adverse event ($p=0.79$). The considered adverse events of interest were infrequent and occurred with

a similar incidence in both arms (dapagliflozin *versus* placebo), including volume depletion (7.5 *versus* 6.8%), renal dysfunction (6.5 *versus* 7.2%, fractures (2.1 *versus* 2.1%), amputations (0.5 *versus* 0.5%), major hypoglycemia (0.2 *versus* 0.2%), ketoacidosis (three cases on dapagliflozin), and Fournier´s gangrene (one case on placebo).

Other adverse effects such as urinary tract infections or genital infections were not routinely collected in DAPA-HF as extensive safety information was obtained from the previous DECLARE–TIMI 58 trial.[6] In summary, there was no remarkable surplus of any adverse event in the dapagliflozin arm compared to placebo in DAPA-HF. Reported limitations of the DAPA-HF study included a reduced participation of Black patients (~5%), very elderly subjects (mean age 66±11), subjects on S/V at baseline(~11%), or patients in NYHA functional class IV (~1%).

Dapagliflozin was effective in 55% of subjects (with or without T2D) with an estimated number needed to treat of 21 to prevent one primary endpoint during 18 months of treatment; the authors concluded that among patients with HF and reduced EF, the risk of worsening HF and death from CV causes was lower in those receiving dapagliflozin compared to placebo, regardless of the presence or absence of diabetes.[8]

Prospects after DAPA-HF trial

The DAPA-HF trial represents an impressive innovation in the therapeutic field of HF with reduced EF as its results imply that an SGLT2 inhibitor may be added as a fourth type of agent to its standard treatment, thus making dapagliflozin a first-in-class medication. In this scenario, there are some important points to highlight or comment on:

1. The composite outcome of HFH, urgent HF visit, or death from CV causes was significantly reduced by dapagliflozin, which is an agent initially developed and approved for the treatment of T2D as a glucose-lowering agent.
2. Dapagliflozin showed a similar clinical impact regardless of the presence or absence of T2D, meaning that diabetes had no impact on HF benefit with dapagliflozin, and these findings were independent of different variables including the patient's body mass index and glycated hemoglobin level.
3. Considering its glucose-lowering effect, dapagliflozin proved to be very safe as the incidence of major hypoglycemia was exceptional; however, there was a significant change (baseline to 8 months) of glycated hemoglobin (−0.21±1.14% dapagliflozin *versus* 0.04±1.29% placebo; $p<0.001$).
4. Patients with diabetes are at an augmented risk of urinary tract infections and genital infections, and this risk is considered to be increased by SGLT2 inhibitor utilization.[10] The incidence of these adverse events (previously mentioned) was not tracked or reported in DAPA-HF and are based on the adverse events analysis of the DECLARE–TIMI 58 trial. In this trial that only included T2D patients (dapagliflozin n=8574 *versus* placebo n=8569), urinary tract infections reported as serious adverse events were rare and balanced in both arms (dapagliflozin 1.5% *versus* placebo 1.6%), while genital infections leading to discontinuation were more infrequent (dapagliflozin 0.9% *versus* placebo 0.1%).[6] Therefore, and taking into account these very low rates in diabetic patients, it would be reasonable to expect even lower numbers in patients without diabetes.
5. DAPA-HF had the largest population of HF patients with reduced EF treated with an MRA at baseline (71%). According to McMurray and colleagues, this fact reflects a trend of increased clinical use, especially in patients with certain renal dysfunction, which had already been seen in other studies.[9]
6. A large proportion of patients in the DAPA-HF trial were on diuretics at baseline (93%), and dapagliflozin addition was followed (baseline to 8 months) only by a modest (but significant) fall in NT-proBNP level (−196±2387 pg/mL dapagliflozin *versus* 101±2994 pg/mL placebo; $p<0.001$). This fact reinforces the idea that its beneficial effects are not solely driven by natriuresis/diuresis enhancement.
7. A relatively small proportion of patients included in DAPA-HF were on S/V at baseline (11%), but this figure was enough to show a consistent benefit with the addition of dapagliflozin. This fact is really important since this "complementary" positive effect surely indicates dapagliflozin's future use in therapy, considering that S/V is currently the last therapeutic option in the HF field.
8. Taking into account this last point, dapagliflozin probably will fit in the HF American guidelines receiving a class I recommendation ('strong') with the level of evidence being B-R ('moderate quality') because it is based on a single study (class I and level of evidence B for European guidelines). In consequence and in my opinion, dapagliflozin will be recommended to further reduce morbidity and mortality in patients with chronic symptomatic HF, reduced EF, and NYHA class II to IV. It signifies that dapagliflozin should be included in the standard therapy as an additive agent despite optimal treatment with S/V, a beta-blocker, and an MRA.
9. The benefit observed with dapagliflozin in the DAPA-HF trial confirms the 28% reduction in HFH that was observed in the DECLARE-TIMI 58 trial.[6] This is most probably an SGLT2 inhibitor class effect, taking into account similar impacts documented with empagliflozin in the EMPA-REG trial[4] and with canagliflozin in the CANVAS study.[5]

DEFINE-HF study

Both the DAPA-HF and DEFINE-HF trials were published at the same time; yet, the DEFINE-HF study focused on the effects of dapagliflozin on symptoms, functional status, and biomarkers in patients with HF.[11]

The DEFINE-HF trial included 263 patients (62% diabetics) with established HF and reduced EF (≤40%), NYHA class II (66%) or III (34%), eGFR <30 mL/min per 1.73 m^2, and elevated natriuretic

peptides. Patients were randomized to dapagliflozin 10 mg/d (n: 131) or placebo (n: 132) for 12 weeks. The primary outcomes were (1) the average of mean NT-proBNP at 6 and 12 weeks and (2) a composite of the proportion of patients with a ≥5 point increase in HF health status on the KCCQ overall score or at least a 20% decrease in NT-proBNP.[10]

At both 6 and 12 weeks, there was no significant difference between groups in the biomarker dual primary outcome (dapagliflozin 1133 pg/dl [95% CI: 1036–1238] *versus* placebo 1191 pg/dl [95% CI: 1089–1304], p=0.43). However, at 12 weeks, the dapagliflozin group did better in both components of the second outcome (61.5 *versus* 50.4%; odds ratio 1.8; 95% CI: 1.03–3.06; p=0.039), which was to linked to both a higher magnitude of patients with a ≥5 point increase in the KCCQ overall score (42.9 *versus* 32.5%, odds ratio [OR]: 1.73; 95% CI: 0.98–3.05) and a ≥20% reduction in NT-proBNP (44.0 *versus* 29.4%, OR: 1.9; 95% CI: 1.1–3.3). Results were similar in patients with or without diabetes and among other studied subgroups.

The fact that dapagliflozin did not significantly reduce dual primary outcome (mean adjusted NT-proBNP), while it improved the second primary outcome could probably be explained by the fact that the DEFINE-HF trial did not have sufficient power to find a difference on the first endpoint. In any case, a larger proportion of patients had a clinically meaningful ≥20% reduction in NT-proBNP levels at the end of the study accompanied by improvement of symptoms, physical limitations, and quality of life (irrespective of diabetes status). Strengths of the DEFINE-HF trial include that a substantial proportion of patients were African-American (40%) and that a third of patients were taking S/V (33%). Limitations of the DEFINE-HF trial include the lack of data on the outcomes of hospitalization and mortality and the short duration of follow-up.[11] Most likely, the results of this study together with those of DAPA-HF reinforce the idea that diuresis/natriuresis promoted by SGLT2 inhibitors is not particularly potent. There seems to be, in any case, an inadequate correlation between the beneficial effects of SGLT2 inhibitors on the morbidity and mortality of patients with HF observed in the DAPA-HF trial, with only an apparently modest diuretic/natriuretic effect.

SGLT2 inhibitors: beyond glucose-lowering effects

Under normal conditions, about 180 g of glucose is filtered daily by the glomerular mass, most of which is reabsorbed by the proximal tubule promoted by an active glucose transportation mediated by SGLT2 proteins, which are selectively expressed in the segments S1 and S2 of the proximal convoluted tubule.[12]

SGLT2s are low-affinity and high-capacity glucose cotransporters, which are responsible for around 90% of filtered glucose reabsorption (160–180 mg/d).[12] The normal threshold for glucose reabsorption correlates with a serum glucose concentration of 180 mg/dL, but in T2D, hyperglycemia increases this threshold with the subsequent upregulation of SGLT2 expression, which ultimately ends up exacerbating hyperglycemia.[13]

In T2D patients, selective inhibition of SGLT2 proteins via SGLT2 inhibitors reduces this threshold by inducing glycosuria and consequently decreasing hyperglycemia (insulin-independent mechanism). In addition, prevention of urinary reabsorption of glucose lowers glycated hemoglobin and is accompanied by a reduction of body weight and blood pressure.[12,13]

As well as its antidiabetic impact, SGLT2 inhibition has a simultaneous diuretic and natriuretic effect as glucose is coupled with sodium and chloride when reabsorption is suppressed from the proximal tubules into the blood flow.[14]

By decreasing proximal tubular sodium and chloride uptake, SGLT2 inhibitors promote a significant reduction of the whole sodium reabsorption mechanism in the loop of Henle with secondary plasma volume contraction without triggering the sympathetic nervous system.[14,15] In essence, the diuretic and natriuretic effects caused by SGLT2 inhibitors are considered to be initially produced by osmotic diuresis acting on the proximal tubules but then (and more importantly) by lowering sodium reuptake in the loop of Henle when inhibiting the sodium–hydrogen exchanger (resembling loops diuretics).[14,15]

This diuretic action was clinically considered to be supported by the fact that SGLT2 inhibition allows for a reduction of the dose of furosemide in HF patients without a negative effect[16] or, on the other hand, to enhance diuresis when SGLT2 inhibitors are added to furosemide.[17]

Taking these facts into account, the benefit of SGLT2 inhibition in HF was considered to be secondary to an increased free water clearance, interstitial fluid removal, and reduction of congestion and preload.[18] However, the results of the DAPA-HF trial do not support this hypothesis as >90% of the patients in the trial were on diuretic therapy, and dapagliflozin addition did not potentiate an important decrease in plasmatic levels of NT-proBNP (only 10–15%) as theoretically it should have been enhanced (natriuretic action).[8]

Multiple other mechanisms have been proposed to explain the benefits of SGLT2 inhibition in HF; for example, SGLT2 inhibitors are considered to optimize myocardium energy supply by changing a source based on fat and glucose oxidation (inefficient in the diabetic heart) by a more effective one taken from ketone bodies that have intrinsic inotropic and chronotropic effects[19] Basically, ketogenesis induction is strongly promoted by SGLT2 inhibitors in T2D patients but very weakly in subjects without diabetes,[20] which means that this mechanism is again not supported by the DAPA-HF results where clinical benefits affected both kinds of patients.[8]

In another setting, it is well known that erythropoietin levels increase in T2D patients after initiation of an SGLT2 inhibitor, reaching a plateau in 2–4 weeks with the subsequent

augmentation of reticulocyte count, hemoglobin level, and hematocrit.[21] Therefore, it was proposed that SGLT2 inhibitors could favor oxygenation of the failing ischemic heart by enhancing the synthesis of erythropoietin (improving tubulointerstitial hypoxia) and thus, increasing the red cell mass.[22] Once more, this hypothesis in not sustained by DAPA-HF as the benefit observed with dapagliflozin was present in patients with and without ischemic cardiomyopathy.[8]

Other several additional proposed mechanisms of action of SGLT2 inhibition in HF are covered in a recent review by Carolyn Lam and collaborators, including, among others, reduction of cardiac remodeling (injury, hypertrophy, and fibrosis) by a direct inhibition of the myocardial sodium–hydrogen exchanger, afterload diminution by lowering arterial pressure and stiffness, improvement of diastolic function and left ventricular mass reduction secondary to remodeling attenuation, and enhancement of endothelial dysfunction.[23]

In this setting, inhibition of the myocardial sodium–hydrogen exchanger deserves particular attention; as previously mentioned, sodium tubular reuptake is markedly reduced by SGLT2 inhibitors by blocking the renal sodium–hydrogen exchanger.[17] This fact is relevant as the activity of the renal sodium–hydrogen exchanger (NHE3 isoform) is strongly augmented in HF patients, and it is considered to be responsible for diuretics and endogenous peptides refractoriness.[24,25] Furthermore, the myocardial sodium–hydrogen exchanger (NHE1 isoform) activity is also exacerbated in T2D and HF with a consequent rise in intracellular sodium concentration. This induces a secondary increase of intracellular calcium, which is a potent stimulus for myocyte hypertrophy, fibrosis, and injury. Inhibition of NHE1 in experimental models of HF reduces myocardial necrosis and infarct size and decreases the development of cardiac remodeling and systolic dysfunction.[26,27] Therefore, the favorable action of SGLT2 inhibitors in HF patients (renal and cardiac effects) could be considered to be mainly mediated by inhibiting the sodium–hydrogen exchanger rather than its effect on glucose reabsorption.[7] As a consequence, it could be hypothesized that by promoting diuresis and natriuresis, these agents relieve congestion and improve symptoms of HF, as well as attenuating the progressive deterioration of the failing heart by optimizing its intrinsic metabolism and reducing the remodeling process. According to Packer, SGLT2 inhibitors would ultimately improve the viability of the failing myocardium by reducing injury and myocyte necrosis.[28]

Several mechanisms (hemodynamic, metabolic, hormonal, and direct cardiac or renal effects) have been proposed to explain the observed benefits of SGLT2 inhibitors in HF and many of them are still not completely understood. Therefore, it means that the biological action of SGLT2 inhibitors may be mediated by multiple and different ways.

Conclusions

Regardless of its mechanism of action, dapagliflozin has started the journey of using SGLT2 inhibitors in HF beyond the presence of diabetes or not and, in this scenario, there are several ongoing trials with dapagliflozin and other SGLT2 inhibitors (Table 1). In the case of HF and reduced EF, empagliflozin is being studied in the EMPEROR-Reduced trial (NCT03057977) and sotagliflozin in the SOLOIST-WHF trial (NCT03521934); the first study includes patients with and without T2D whereas the second includes only patients with diabetes. In this context, the EMPEROR-Reduced trial will provide very valuable complementary information as it was designed to recruit patients with more severe HF than those

Table 1. SGLT2 inhibitors: main ongoing clinical studies.

Trial number*	Focus	Brief title / agent
NCT03057977	HFrEF	EMPEROR-Reduced: safety and efficacy of empagliflozin *versus* placebo on top of guideline-directed medical therapy / empagliflozin
NCT03521934	HFrEF	SOLOIST-WHF: cardiovascular events in patients with type 2 diabetes post worsening heart failure / sotagliflozin
NCT03877237	HFrEF	DETERMINE-reduced: effect on exercise capacity using a 6-minute walk test in patients with heart failure with reduced ejection fraction / dapagliflozin
NCT03057951	HFpEF	EMPEROR-Preserved: outcome trial in patients with chronic heart failure and preserved ejection fraction / empagliflozin
NCT03619213	HFpEF	DELIVER: evaluation to improve the lives of patients with preserved ejection fraction heart failure / dapagliflozin
NCT03877224	HFpEF	DETERMINE-preserved: effect on exercise capacity using a 6-minute walk test in patients with heart failure with preserved ejection fraction / dapagliflozin

*Trial number: according to ClinicalTrials.gov identifier.

HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction.

included in DAPA-HF (lower left ventricular EF and higher levels of NT-proBNP).

Regarding HF and preserved EF, the ongoing studies are the EMPEROR-preserved trial (NCT03057951) with empagliflozin, the DELIVER trial (NCT03619213) and the DETERMINE-preserved trial (NCT038 77224), the latter two both with dapagliflozin. All three trials are of real transcendental importance, considering the current lack of proven clinical benefits in this heterogeneous clinical setting especially after the recent disappointing results for S/V in the PARAGON-HF trial.[29]

In patients with HF and reduced EF with or without T2D, the DAPA-HF trial showed statistically significant benefits in terms of morbidity and mortality reduction when the SGLT2 inhibitor dapagliflozin was added to a guideline-directed therapy. This marks a dramatic evolution of this particular agent (feasibly extensible to others) from being initially a glucose-lowering medication to becoming an effective HF therapy. As previously mentioned, there is an extensive and ambitious research program in progress that allows us to predict that SGLT2 inhibitors have arrived to reach a privileged position in the treatment of HF.

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