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REVIEW

The Role of Dapagliflozin in the Management of Heart Failure: An Update on the Emerging Evidence

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Abstract: The burden and cost of heart failure management, primarily in the form of hospitalization in the setting of decompensated heart failure, continue to be some of the biggest clinical challenges in cardiovascular medicine. In recently published randomized controlled trials, including DAPA-HF, sodium-glucose cotransporter 2 (SGLT2) inhibitor dapagliflozin was shown to reduce hospitalization from heart failure or mortality associated with cardiovascular causes, when added to existing guideline-directed medical therapy. The American College of Cardiology (ACC) released a Clinical Pathway guideline that recommends the use of dapagliflozin in clinical management of heart failure, with or without diabetes. Furthermore, the results of the DAPA-CKD trial broaden the utility of dapagliflozin as a therapeutic option in patients with advanced kidney disease. In this article, the authors explore the existing evidence on dapagliflozin in heart failure with reduced ejection fraction and highlight the need for further research on uses of dapagliflozin in the world of heart failure.

Keywords: dapagliflozin, DAPA-HF, DECLARE-TIMI, DEFINE-HF, HFrEF, DAPA-CKD

Introduction

The worldwide burden of heart failure (HF) has been estimated to be upwards of 23 million individuals. In the United States (US) alone, an estimated 6 million adults are affected by HF, with close to 1 million hospitalizations with a primary discharge diagnosis of HF annually. Approximately 50% of these cases can be attributed to HF with reduced ejection fraction (HFrEF), referring to a left ventricular ejection fraction (LVEF) of 40% or less.[1,2] Traditionally, guideline-directed medical therapy (GDMT) for HFrEF has been focused on inhibition of the renin-angiotensin-aldosterone system, neprilysin and sympathetic pathways through agents including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers (BB) and mineralocorticoid receptor antagonists (MRA).[3] More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown further reductions in heart failure hospitalization (HHF), cardiovascular (CV) events and mortality, especially for HFrEF patients. Initial SGLT2 inhibitor trials focused on improvement in glycemic control in diabetics, with CV outcomes explored only as secondary endpoints. Subsequent randomized trials of SGLT2 inhibitors (based on empagliflozin and dapagliflozin), including the EMPEROR-Reduced and DAPA-HF trials, were designed to evaluate CV outcomes and reported reductions in CV events (particularly HHF) in HFrEF (with or without diabetes).[4,5] In the light of

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these landmark trials, the American College of Cardiology (ACC) recently released the 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes, which is specific for HFrEF and calls for use of SGLT2 inhibitors (including dapagliflozin) in HFrEF with or without diabetes mellitus (DM).[6] In this review article, the authors review the evidence on dapagliflozin in HF, including existing literature and ongoing trials, and the role of this drug in the clinical management of HF.

Pharmacology of SGLT2 Inhibitors, in Particular Dapagliflozin

Sodium-glucose cotransporter 2 is responsible for reabsorption of approximately 90% of the urinary glucose in the proximal tubule of the nephron. Inhibition of SGLT2 induces glucosuria, which is more pronounced in hyperglycemic individuals owing to the higher amounts of glucose filtered into the urine. The effect of glucosuria diminishes with normalizing of blood glucose levels.[7] Among individuals with HFrEF, with or without DM, the addition of dapagliflozin has been associated with decreased rates of CV death or worsening HF, as well as all-cause mortality.[5] In addition to lowering blood glucose, SGLT2 inhibitors such as dapagliflozin also enhance natriuresis, change tissue sodium handling, lower systolic blood pressure and reduce body mass.[8,9] Early decreases in systolic blood pressure, weight and estimated glomerular filtration rate (eGFR), as well as increase in hematocrit are consistent with a diuretic action.[10] According to the established side effect profile, dapagliflozin is associated with significantly higher rates of urinary tract infections (4.3% vs 3.7%), urinary urgency, frequency, and genital mycotic infections in females (6.9% vs 1.5%) and in males (2.7% vs 0.3%).[11]

Molecular Mechanisms of Dapagliflozin

Regarding outcomes relating to CV benefit, specific mechanisms have not been fully elucidated, but several putative mechanisms have been proposed. Among these are reduction in preload and afterload (resulting in improvement in ventricular loading), improvement in myocardial metabolism and alterations of cardiac fibrosis.[9,12] SGLT2 inhibitors have been shown to inhibit the sodium proton channel (NHE) in the cardiac myocytes that eventually leads to the reduction in intracellular calcium and mitochondria-induced cellular damage that lies at the heart of myocardial remodeling.[13,14]

Table 1 Non Glycemic Mechanisms of SGLT2 Inhibitors

Renal effects	Reduction in albuminuria Reduction in tubular inflammation due to lower RAAS activation Reduction in intraglomerular pressure and tubular hypertrophy
Cardiovascular effects	Weight loss BP reduction Decrease in epicardial fat thickness - empagliflozin Reduction in the serum uric acid Favorable effect on the lipid profile Lesser surges of insulin secondary to hypoglycemia as the glycemic actions of the class are non-insulin dependent

At the level of the kidneys, in addition to glucosuria by direct inhibition of glucose reabsorption in the proximal convoluted tubules, the SGLT2 inhibitors have also been demonstrated to have anti-inflammatory activity in animal models.[15] The blockade of SGLT2 channels causes a decrease in intraglomerular pressure and subsequently decreases in glomerular filtration and tubular hypertrophy. This consequence is further amplified by afferent vasoconstriction mediated by direct action.[16] The cardioprotective and renoprotective actions of SGLT2 inhibitors are summarized in Table 1.[17]

Existing Literature on Role of Dapagliflozin in Cardiorenal Disease

In the first of the series of trials focused on the role of dapagliflozin in CV diseases, the DECLARE-TIMI 58 trial studied 17,160 patients with type 2 DM. The trial found that the use of dapagliflozin resulted in lower rates of CV death and a reduction in HHF, with the number needed to treat calculated at 111. The reduction in HHF was added in the post hoc analysis and the trial was not powered for these outcomes. The trial did not show any statistically significant difference with regards to reduction in major adverse CV events.[18] Subsequently, 263 patients with HFrEF (NYHA functional class II–III), and elevated natriuretic peptides were studied in the DEFINE-HF trial. The trial did not find any significant difference in the levels of NT-proBNP in patients receiving dapagliflozin versus placebo. However, there was an increased proportion of patients experiencing clinically meaningful

improvements in HF related health status measured in terms of the Kansas City Cardiomyopathy Questionnaire or KCCQ (number needed to treat of 7–10).[19] This trial was effective in demonstrating the safety of dapagliflozin in patients without type 2 DM. The DAPA-HF trial studied a larger group of patients with similar characteristics (4744 patients with HFrEF, NYHA class II–IV) with and without DM. The investigators of this landmark trial found a significant reduction in the primary endpoint of worsening HF or death from CV causes in the dapagliflozin group compared with the placebo group, irrespective of presence of DM. The secondary outcome of the trial included a change in KCCQ at the end of 8 months, compared with baseline, which was also found to improve with dapagliflozin.[5] When stratified according to the baseline score, exploratory analysis revealed improvement with dapagliflozin compared with placebo across the entire range of baseline KCCQ score.[20] 71% of patients in the enrolled population in the DAPA-HF trial were taking MRA and an exploratory analysis of the trial data revealed similar results in the population with MRA compared with the population without MRA (HR 0.74; 95% CI 0.63–0.87 versus HR 0.74; 95% CI 0.57–0.95, respectively, for the primary combined endpoint of HF exacerbation or CV death).[21] 10.7% of patients in the DAPA-HF cohort were on the sacubitril/valsartan combination, and were found to have similar outcomes in terms of primary endpoints of efficacy and safety with add-on of dapagliflozin, when compared with the remaining population that did not receive the sacubitril/valsartan combination, supporting the safe use of the drug in addition to GDMT.[22] The absolute risk reduction of the primary endpoint was also seen to be greatest in the subgroup that had a history of recent hospitalization (defined as within 12 months of randomization) from HF worsening (ARR 9.9%, 95% CI 3.3–16.5% compared with groups with hospitalization prior to the 12 month period of before randomization).[23] In another interesting post hoc analysis of the DAPA-HF trial, similar results in terms of efficacy and safety with dapagliflozin in ischemic and non-ischemic cardiomyopathy were noted. The incidence of objective parameters such as HHF and mortality were found to be similar in both groups (HR 0.77 [0.65–0.92] and HR 0.71 [0.58–0.87], respectively; p for interaction = 0.55) and the comparability of both the groups extended to qualitative measures such as improvement in functional status (measured using KCCQ).[24] Lastly, no difference was noted in benefits seen with the drug between men and women in the enrolled group.[24] The details of the trials are summarized in Table 2. Following the publication of the game changing DAPA-HF trials, multiple systemic analysis have confirmed dapagliflozin to be more effective than placebo in reducing HHF and CV death, in patients both with and without DM.[25–28]

In another recently published landmark trial (DAPA-CKD), the population with eGFR as low as 25 mL/min/1.73 m^2 was shown to have improved CV outcomes and HHF with dapagliflozin, compared with placebo, which expands the usability of dapagliflozin in this unique population.[29]

Even though efficacy related data support the addition of dapagliflozin to GDMT in HFrEF, the practical use may be limited by the additional cost of the drug. In a study based out of the United Kingdom by McEwan et al., the treatment with dapagliflozin was noted to reduce the lifetime cost by £2552 in patients with type II DM for major adverse CV events.[30] Similar favorable cost-benefit ratios were seen in studies based on Australian and Thai healthcare systems.[31,32] In a study performed on data extrapolated to the American healthcare system, it was found that the addition of dapagliflozin to GDMT was beneficial in terms of long term cost-benefit ratios, possibly in both diabetic and non-diabetic populations.[33]

Ongoing Trials on Dapagliflozin in Heart Failure

In an interesting analysis performed by Maltês et al. aimed at evaluating the generalizability of the results of the DAPA-HF trial, it was noted that the limiting factors to widespread use of dapagliflozin remained the lack of literature regarding efficacy in patients with advanced chronic kidney disease (CKD), defined as eGFR <25 mL/min/1.73 m^2, and LVEF >40%.[34] Thus, the ongoing trials are focused on bridging this gap. In addition to evaluating the role of dapagliflozin in these patients with advanced CKD and HF with preserved ejection fraction (HFpEF), there is also ongoing research focusing on patients with acute decompensated HF. The DICTATE-HF trial is currently recruiting patients presenting to the hospital with decompensated HF requiring intravenous diuretics to evaluate the change in the weight seen with the addition of dapagliflozin to standard diuretic regimen. The inclusion criteria include patients across all ejection fractions but with established DM (NCT04298229). There are two major trials focused on HFpEF that are currently

Table 2 Summary of Major Clinical Trials on Dapagliflozin in Heart Failure

Trial Name (Year of Publication)	Sample Size, Trial Design and Follow-Up Period	Sample Population	Primary & Secondary Outcomes	Results
DAPA-HF (2019)[5]	4744 Randomized, double-blind, placebo-controlled Phase 3 trial Median follow up 18.2 months	Adults, ≥18 years Symptomatic HFrEF (NYHA class II–IV), LVEF≤40%, elevated NT-proBNP, eGFR ≥30 mL/min/1.73 m^2 (CKD-EPI formula) on GDMT	**Primary outcome:** Composite of worsening heart failure or death from cardiovascular causes. **Secondary Outcome:** Composite of hospitalization for heart failure or cardiovascular death.	Primary outcome and secondary outcomes were significantly lower in the dapagliflozin group compared with placebo (HR 0.74; 95% CI 0.65–0.85; P<0.001 and HR 0.75; 95% CI, 0.65–0.85; P<0.001, respectively for primary and secondary outcomes)
DECLARE-TIMI 58 (2019)[12]	17,190 Randomized, double-blind, multinational, placebo-controlled, phase 3 trial. Median follow up 4.2 years	Male or female 40 years of age or older with type 2 diabetes, and a creatinine clearance of 60 mL or more per minute.	**Primary safety outcome** was MACE (defined as cardiovascular death, myocardial infarction, or ischemic stroke). **Two Primary efficacy outcomes** were MACE and a composite of cardiovascular death or hospitalization for heart failure **Secondary efficacy outcomes:** Renal composite outcome, defined as a sustained decrease of 40% or more in estimated glomerular filtration rate, new end-stage renal disease, or death from renal or cardiovascular cause. Death from any cause	Dapagliflozin met with primary safety efficacy outcome (upper boundary of the 95% CI, <1.3; P<0.001 for noninferiority). It did not result in a lower rate of MACE than placebo (8.8% and 9.4% in the two groups, respectively; hazard ratio, 0.93; 95% CI, 0.84–1.03; P = 0.17); It did however, result in a lower rate of cardiovascular death or hospitalization for heart failure than placebo (4.9% vs 5.8%; hazard ratio, 0.83; 95% CI, 0.73–0.95; P = 0.005). There was no statistically significant difference between the groups with regards to the secondary efficacy outcomes.
DEFINE- HF (2019)[13]	263 Randomized, double-blind, placebo controlled, investigator-initiated multi-center trial Follow up 12 weeks	Adult ambulatory patients with or without T2DM, established HF for at least 16 weeks and NYHA II–III HF	**Primary end points:** Average of 6- and 12-week mean NT-proBNP. Composite of the proportion of patients that achieved a meaningful improvement in health status (≥5-point increase in average of 6- and 12-week KCCQ-OS) or NT-proBNP (≥20% decrease in average of 6- and 12-week NT-proBNP). **Secondary end points** included proportion of patients with meaningful change in KCCQ, and NT-proBNP at each time point, mean BNP and proportion of patients with meaningful change in BNP, functional status based on 6-minute walk test, change in weight, systolic blood pressure and HbA1c	There was no statistically significant difference in the dual primary outcome between patients treated with dapagliflozin versus placebo [NT pro-BNP 1133 pg/dL (95% CI, 1036–1238) vs 1191 pg/dL (95% CI 1089–1304), adjusted ratio 0.95; 95% CI 0.84–1.08, P = 0.43]; the second dual primary outcome was statistically significant with a greater proportion of patients treated with dapagliflozin with clinically meaningful improvement compared with placebo (61.5% vs 50.4%, adjusted OR 1.8, 95% CI 1.03–3.06, nominal P value = 0.039). Among the binary secondary end points the statistically significant ones were KCCQ OS increase ≥ 5 points at 6 weeks, KCCQ CS increase ≥ 5 points at 12 weeks, NT pro-BNP decrease ≥20% at 12 weeks, BNP decrease ≥20% at 12 weeks. Among the continuous secondary end points the mean adjusted BNP at 12 weeks, mean adjusted KCCQ OS at 12 weeks, mean adjusted KCCQ CS at 12 weeks, mean adjusted HbA1c at 6 weeks were statistically significant

(*Continued*)

Table 2 (Continued).

Trial Name (Year of Publication)	Sample Size, Trial Design and Follow-Up Period	Sample Population	Primary & Secondary Outcomes	Results
IDDIA (2020)[26]	60 Randomized, double-blind, placebo-controlled trial Follow up 24 weeks	Patients with T2DM and HbA1c of 7.0% to 10.0% accompanied by LV diastolic dysfunction at least grade 1 (relaxation abnormality) on resting echocardiography	**Primary end point:** Change is LV diastolic reserve at 24 weeks from baseline as assessed by diastolic stress echocardiography **Secondary end points:** Changes at 24 weeks in LV diastolic parameters at rest and during exercise, LV mass index, and left atrial volume index	The patients in dapagliflozin group had significantly improved DR25W (0.88 ±1.24 cm/s versus −0.52±1.53 cm/s; P = 0.001) and DR50W (0.59±1.47 cm/s versus −0.58±1.63 cm/s; P = 0.035) compared with those in the placebo group at 24 weeks.

Abbreviations: DAPA-HF, Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; DECLARE-TIMI 58, Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes; DEFINE-HF, Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure With Reduced Ejection Fraction; IDDIA, Randomized, Controlled Trial to Evaluate the Effect of Dapagliflozin on Left Ventricular Diastolic Function in Patients With Type 2 Diabetes Mellitus; HFrEF, Heart failure with reduced ejection fraction; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GDMT, guideline-directed medical therapy; MACE, major adverse cardiovascular events; T2DM, Type 2 Diabetes Mellitus; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; HbA1c, Glycated hemoglobin; KCCQ CS, Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; BNP, B-type natriuretic peptide; LV, left ventricular; DR25W, Diastolic reserve at 25 Watts; DR50W, Diastolic reserve at 50 Watts.

ongoing – the DETERMINE-Preserved trial (NCT03877224) and the DELIVER trial (NCT03619213) that will help shed light on the role of the drug in this largely under-treated patient population. In the light of a very recent press release indicating beneficial effects of empagliflozin in HFpEF patients, the likelihood of similar results with dapagliflozin is higher due to significant overlap in the mechanism of both the drugs (NCT03057951).

Furthermore, there are numerous trials that are aimed at providing a mechanistic explanation for the benefit seen with dapagliflozin in terms of cardiac remodeling and change in biomarkers. Cardiac remodeling measured with parameters such as left atrial anatomy, functionality and left ventricular distensibility (on echocardiography) and myocardial perfusion reserve index (on cardiac magnetic resonance imaging) is one way of understanding these mechanisms. The REFORM trial studied the left ventricular end systolic volume on cardiac magnetic resonance imaging (MRI) as an endpoint in HF patients with DM treated with dapagliflozin. Unfortunately, at the end of the follow-up period of 1 year, no significant difference was noted.[35] In another MRI-based study, treatment with dapagliflozin showed a significant reduction in left ventricular mass after 12 months, compared with the placebo group.[36] In a small study in Japan, it was shown that treatment with dapagliflozin significantly improved mitral inflow E and mitral annular e' velocities (E/e') after 6 months in diabetics with established HF.[37] The IDDIA trial further showed improvement in left ventricular diastolic dysfunction (assessed on diastolic stress echocardiography) in type II diabetics with LVEF >50%.[38] With only small-scale studies evaluating the mechanism of remodeling, our understanding remains limited and further research is required in this area. The ongoing STADIA trial is also recruiting patients with HFpEF to study the change in left ventricular stiffness measured as extracellular volume change (on cardiac magnetic resonance) and changes in E/e'/LV end-diastolic volume index (on echocardiography).[39]

Dapagliflozin in Guidelines

The DAPA-HF trial illustrated the benefits of SGLT2 inhibitors (specifically dapagliflozin) in treating established HF, by showing that dapagliflozin not only significantly reduced the risk of worsening HF or the risk of CV death, but also improved the symptoms of HF in 4744 patients with HFrEF.[5] The ACC Clinical Pathway in HF guidelines currently recommend dapagliflozin 10 mg daily, for reducing the risk of HF hospitalizations in adults with DM and established CV disease (or having multiple risk factors), and for reducing the risk of hospitalizations and CV death in patients with HFrEF.[6] The use of the medication is not recommended for glycemic control in patients with eGFR <45 mL/min/1.73 m^2. Other contraindications include hypersensitivity, pregnancy/breastfeeding, need for dialysis, and end stage renal disease.[6]

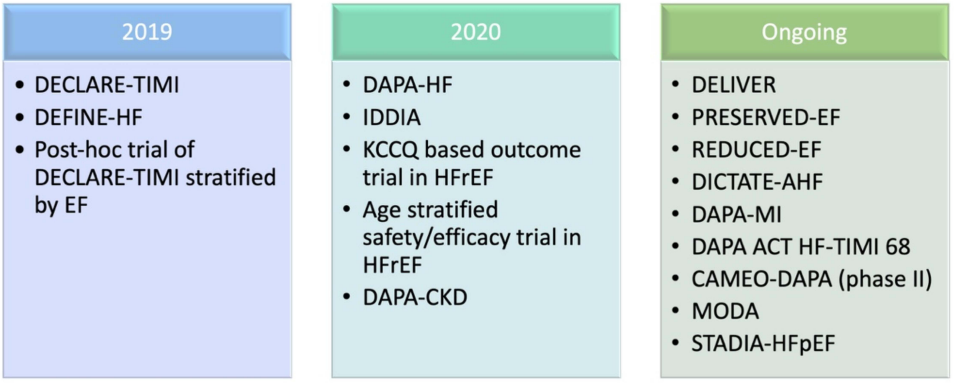

Figure 1 Chronology of key trials evaluating dapagliflozin.
Abbreviations: EF, ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; HFrEF, heart failure with reduced ejection fraction.

In October 2020, the Heart Failure Association of the European Society of Cardiology (ESC) released updated recommendations for the utilization of SGLT2 inhibitors in HF patients, based on the new clinical trial evidence. Dapagliflozin is recommended for prevention of HHF in patients with DM and established CV disease or at high risk for CV disease (similar to the ACC guidelines).[40,41] The use of dapagliflozin is also recommended for reducing the combined risk of HHF and CV death in symptomatic HFrEF patients, already receiving GDMT, regardless of the presence of DM.[40,41]

Conclusion

Dapagliflozin is the latest addition to the toolbox of therapies used to manage HF and has garnered substantial interest in the last year and a half, as represented in Figure 1. The initial evidence supporting use of dapagliflozin as an add-on therapy for patients with HFrEF to significantly reduce the incidence of CV endpoints such as CV death and HHF was extrapolated from trials based on evaluation of the drug for primary treatment of DM. However, in recent times, the drug has been studied in dedicated HF clinical trials to reveal clinically significant utility as an add-on to GDMT in patients with HFrEF, irrespective of DM status. Another huge step forward is the result of the DAPA-CKD trial that prove the safety of dapagliflozin in patients with eGFR as low as 25 mL/min/1.73 m^2, enabling clinicians to target a population that cannot be managed with traditional therapy. Initial data also indicate cost-related benefits of adding dapagliflozin to GDMT, when compared with the overall cost of HF management including hospitalization. Professional societies such as ACC and ESC endorse the addition of dapagliflozin in patients with an established diagnosis of HFrEF (with or without DM) to prevent HHF and reduce CV mortality. The ACC Clinical Pathway in HF also recommends the use of the drug in patients with DM at risk for CV disease. This article is the first article that we know of that summarizes the current and ongoing evidence on use of dapagliflozin. The exact indication of the drug is yet to be established as newer evidence will possibly expand its use in HFpEF and acutely decompensated HF, which were outside the scope of this article.

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