The Expanding Role of Dapagliflozin Beyond the Glucose-lowering Effect

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have varied metabolic effects beyond increasing glycosuria. This consensus review examines the role of dapagliflozin in health promotion, particularly its benefits in patients with and without type 2 diabetes mellitus (T2DM) and in cardiorenal rehabilitation post-coronavirus disease 2019 (COVID-19). Consensus recommendations were developed by subject experts in Endocrinology and Diabetology based on the online meeting held on 27 June 2020 to review the available evidence related to the role of SGLT2 inhibitors, with a focus on cardiovascular and renal metabolic therapy. Evidence suggests that dapagliflozin has a direct role in improving clinical outcomes in patients with chronic kidney disease (CKD) or heart failure (HF). These benefits of dapagliflozin were independent of reduction in blood pressure, glycemic control and weight, and also extend to patients without diabetes. The use of dapagliflozin in metabolic syndrome was endorsed by the majority of the experts; however, this would be off-label. It was opined that the role of dapagliflozin would currently be limited to treating T2DM with a focus on preventing HF or kidney disease progression. The need for conducting multidisciplinary academic meetings to have a balanced approach regarding the use of dapagliflozin among nondiabetic patients and the need for detailed evaluation of the role of SGLT2 inhibitors in vasculometabolic and cardiorenal rehabilitation post-COVID was also suggested.

Keywords: Dapagliflozin, heart failure, kidney disease, type 2 diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the most prevalent progressive, complex and metabolic disorder that is characterized by inconsistent insulin production and utilization. Estimates indicate that approximately 573 million people aged 20 to 79 years are living with diabetes globally, which may increase to 783 million by 2045. Currently, India has around 74.2 million individuals diagnosed with diabetes, which may increase to 124.9 million by 2045.[1] Current international guidelines consider sodium-glucose cotransporter 2 (SGLT2) inhibitors as an alternative to metformin plus either sulfonylurea or dipeptidyl peptidase-4 (DPP-4) inhibitors.[2,3] SGLT2 inhibitors can be used in patients with T2DM and atherosclerotic cardiovascular disease (ASCVD) or kidney disorder or indicators of high risk, or heart failure (HF).[3]

According to the 2016 management protocols of stable coronary artery disease (SCAD) in India, oral antidiabetic agents, including SGLT2 inhibitors should be considered for diabetes management.[4] The 2020 Research Society for the Study of Diabetes in India (RSSDI) guidelines recommend SGLT2 inhibitors for patients with HF, ASCVD, diabetic kidney disease (DKD) or those who require weight reduction.[5] The South Asian Federation of Endocrine Societies (SAFES) also endorsed the use of SGLT2 inhibitors for managing various comorbid conditions associated with T2DM.[6] Dapagliflozin, a selective SGLT2 inhibitor, is suggested to improve glycemic control along with diet and exercise in T2DM. It may be preferred in patients with

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chronic kidney disease (CKD) or HF with reduced ejection fraction (HFrEF), as it has favorable renal and cardiovascular (CV) effects.[7-9]

Prior studies have proven that most adults with diabetes in India have at least one comorbid condition.[10-12] In clinic-based studies, the prevalence of coronary artery disease among patients with diabetes was ~11% to 30%, while the prevalence in community-based studies was ~9% to 15%. CKD is also an inadequately addressed complication of T2DM affecting approximately 2 in every 5 patients. According to the Chennai Urban Rural Epidemiology Study (CURES), an urban population-based study of patients with diabetes in India, overall prevalence of nephropathy and microalbuminuria was 2.2% and 26.9%, respectively.[13]

Antidiabetic medications like metformin, originally indicated for the management of T2DM, have been prescribed for the management of polycystic ovarian syndrome. Liraglutide has the potential for being used as an antiobesity drug, while gliptins are being explored for their benefits beyond endocrinology.[14] Similarly, SGLT2 inhibitors, including dapagliflozin, have a role in several metabolic activities beyond glycosuria.[15] The chronic landscape of diabetes along with a high prevalence of concurrent chronic medical conditions necessitates multifaceted approach from both patients and healthcare providers. Considering the aforementioned literature views, this study aims to present expert opinions on the role of dapagliflozin beyond diabetes care.

METHODS

An advisory board comprising 9 regional endocrinologists/diabetes specialists from different parts of India was formed to review the role of SGLT2 inhibitors with a focus on CV and renal metabolic therapy. An online meeting of the advisory board was held on 27 June 2020 to arrive at conclusions regarding the benefits and drawbacks of SGLT2 inhibitors based on the existing knowledge and clinical experience. Recommendations were formulated based on the opinions and agreement of the majority post-discussion on the following:

- Role of dapagliflozin in health promotion
- Role of dapagliflozin in patients with and without T2DM
- Cardiorenal rehabilitation post-COVID.

Based on the agreed statements, supporting data was extracted from multiple databases including PubMed/Medline, Embase, Cochrane and Google Scholar. The criteria for consensus were set to statements with ≥80% agreement among experts. The experts' statements on each of these topics were recorded and are presented in this article.

ROLE OF DAPAGLIFLOZIN IN HEALTH PROMOTION

Dapagliflozin, when added to conventional antidiabetic agents, is associated with improvement in hemoglobin A1c (HbA1c) by 0.50%, weight loss of 2 kg, systolic/diastolic blood pressure (SBP/DBP) by 4/2 mmHg, fasting plasma glucose (FPG) by 18 mg/dL and body mass index by 1.1%, over 6 to 13 months.[16,17] Growing evidence suggests that SGLT2 inhibitors have several benefits beyond glycemic control.[18] They have a myriad of metabolic and hemodynamic effects, such as increasing glucagon levels and hematocrit production, while promoting lipolysis, hepatic fatty acid oxidation and ketone production.[19-21] Further, SGLT2 inhibition can trigger a fasting-like physiological environment.[21] Inhibition of SGLT2 directly activates AMP-activated protein kinase (AMPK) and also causes inhibition of mammalian target of rapamycin (mTOR) in the kidneys with beneficial effects on autophagy, mitofusion, mitofission and endoplasmic reticulum stress.[20] Inhibition of SGLT2 also decreases the progression of diabetic nephropathy by activating AMPK in mesangial cells, which causes a decrease in inflammatory mediators.[22] Notably, SGLT2 inhibitors may also influence several physiological functions that can improve HF outcomes. The decreased glucose absorption by tubular cells improves the interstitial hypoxia and promotes erythropoiesis in patients with diabetes.

This leads to an increase in both hemoglobin and hematocrit and a decrease in the afferent renal neural activity. Subsequently, SGLT2 inhibition has effects on the downregulation of sympathetic activity and reduces the effect on preload and afterload of the heart.[23] By improving cardiac energy metabolism through an indirect increase in ketone oxidation, SGLT2 inhibition may provide an additional source of energy for the failing heart. Moreover, SGLT2 inhibition may increase glucose oxidation in the heart. These factors may improve the overall heart functioning.[24]

PLEIOTROPIC EFFECTS OF SGLT2 INHIBITORS

Weight Loss

Weight loss associated with dapagliflozin has been mainly attributed to reduction in visceral fat. A recent meta-analysis of randomized controlled trials (RCTs) reported that SGLT2 inhibitors, including dapagliflozin

(2.5-10 mg/d), as an add-on to metformin were associated with significant reduction in body weight vs. non-SGLT2 inhibitors at 52 weeks. Significant reduction was also noted in both visceral and subcutaneous adipose tissue, along with lean mass.[25] Similarly, reduction in weight by approximately 1.5 to 3 kg with dapagliflozin alone and up to 5 kg reduction in weight with dapagliflozin and sulfonylurea combination therapy was also reported.[26]

Blood Pressure Reduction

With the combined effects of osmotic diuresis, natriuresis and reduction in arterial stiffness, SGLT2 inhibitors may reduce blood pressure (BP) in patients with T2DM and diabetic nephropathy.[27-30] In a recent meta-analysis, the pooled estimate (22 RCTs on treatment with dapagliflozin) of the weighted mean difference of dapagliflozin on SBP and DBP was −2.59 mmHg (95% confidence interval [CI] −2.70 to −2.49) and −1.09 mmHg (95% CI −1.18 to −1.01), respectively.[28] Another study reported that dapagliflozin decreased SBP by 3.6 mmHg and DBP by 2.0 mmHg in patients with T2DM. Post-dapagliflozin treatment, treatment-naive patients with T2DM with inadequate glycemic control with diet and exercise had the highest reductions in SBP.[29]

Lipid Management

Dapagliflozin has been associated with an increase in total cholesterol by 2.5%, high-density lipoprotein cholesterol (HDL-C) by 3.3%, low-density lipoprotein cholesterol (LDL-C) by 3.9% and a reduction in triglyceride levels by 2.0%.[26] Dapagliflozin as an add-on to metformin and/or sulfonylurea significantly increased HDL-C and LDL-C vs. DPP-4 inhibitors (linagliptin, gemigliptin) add-on therapy.[31]

Outcomes in Cardiovascular and Renal Disease

In a pooled analysis of five trials (up to 52 weeks duration) including patients with T2DM and HF, dapagliflozin 10 mg monotherapy or add-on therapy produced a clinically meaningful reduction from baseline in HbA1c (placebo-adjusted mean change: 0.55%), weight (−2.7 kg) and SBP (−2.1 mmHg) over 52 weeks.[32] In a post hoc analysis of phase 2/3 clinical trials, dapagliflozin was found to reduce weight and BP with improvement in glycemic control among patients with T2DM and renal impairment.[33] Similarly, findings from RCTs support the benefits of dapagliflozin 10 mg in improving glycemic control and weight loss and lowering BP among patients with T2DM with mild or moderate renal insufficiency.[34,35]

ROLE OF DAPAGLIFLOZIN IN PATIENTS WITH AND WITHOUT T2DM

Several RCTs have determined the effects of dapagliflozin on CV and renal outcomes, which are discussed below.

The Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial evaluated the safety of dapagliflozin in over 17,000 patients with ASCVD or risk factors (including ~40% without cardiovascular disease [CVD]). Significant benefits were reported at median follow-up of 4.2 years. Treatment with dapagliflozin significantly reduced CV death or hospitalization for heart failure (HHF) compared to placebo (4.9% vs. 5.8%; hazard ratio [HR] 0.83; 95% CI, 0.73-0.95; p = 0.005). This finding was mainly driven by a reduction in HHF (HR 0.73; 95% CI, 0.61-0.88). Further, dapagliflozin was noninferior to placebo for major adverse cardiovascular events (MACE; p < 0.001 for noninferiority). The incidence of the composite of ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2, new end-stage renal disease (ESRD), or death from renal or CV causes was also in favor of dapagliflozin versus placebo (HR 0.53 95% CI 0.43-0.66). Dapagliflozin did not increase the incidence of stroke, amputations or fractures compared to placebo. However, a higher rate of diabetic ketoacidosis (excess rate <1% per year) and genital infections compared to placebo were reported.[9]

The DECLARE-TIMI 58 study also analyzed (prespecified subgroup analysis) the clinical benefits of dapagliflozin in patients with T2DM and prior myocardial infarction (MI). Dapagliflozin significantly reduced MACE in patients with a prior history of MI (HR 0.84, 95% CI 0.72-0.99) vs. those without a prior history of MI (HR 1.00, 95% CI 0.88-1.13). However, HHF and CV death did not differ irrespective of prior MI status.[36] In another subgroup analysis, Kato et al assessed the outcomes of dapagliflozin according to baseline HF status. It defined HFrEF as ejection fraction <45%. Dapagliflozin greatly reduced CV death or HHF in patients with HFrEF (HR 0.62, 95% CI 0.45-0.86), but not in patients with HF without known reduced EF (HR 0.88, 95% CI 0.66-1.17 and HR 0.88, 95% CI 0.74-1.03, respectively). Dapagliflozin did not increase the incidence of diabetic ketoacidosis and amputation. The overall safety profile was comparable to placebo.[37] In a real-world study of patients who met DECLARE-TIMI 58 inclusion criteria (n = 28,408), 21% lower risk of CV mortality or HHF (HR 0.79, 95% CI 0.69-0.92) were noted with dapagliflozin therapy compared to

other glucose-lowering drugs (OGLDs) without any significant association with MACE (HR 0.90, 95% CI 0.79-1.03).[38]

The CVD-REAL study is the largest real-world comparative effectiveness study that evaluated a range of CV outcomes in patients with T2DM at high CV risk initiated on SGLT2 inhibitors vs. OGLDs. A total of 1,54,528 patients were grouped in each treatment group after propensity matching. Canagliflozin followed by dapagliflozin accounted for more drug exposure with 53% and 42%, respectively. Significant reduction of HHF (pooled HR, 0.61; 95% CI, 0.51-0.73; p < 0.001) and all-cause death (pooled HR, 0.49; 95% CI, 0.41-0.57; p < 0.001) were observed in the SGLT2 inhibitors group vs. the OGLDs group.[39] The CVD-REAL 2 study was conducted across 6 countries in the Middle East, Asia Pacific and North American regions. A total of 2,35,064 episodes of treatment were grouped in each treatment group after propensity matching (~27% had CVD). Of all SGLT inhibitors, dapagliflozin accounted for 75% of drug exposure time. The SGLT2 inhibitors were associated with a significant reduction in the risk of mortality (HR: 0.51, 95% CI 0.37-0.70; p < 0.001), HHF (HR 0.64; 95% CI 0.50-0.82; p < 0.001), mortality or HHF (HR 0.60, 95% CI 0.47-0.76; p < 0.001), stroke (HR 0.68; 95% CI 0.55-0.84; p < 0.001) and MI (HR 0.81; 95% CI 0.74-0.88; p < 0.001) compared to OGLDs.[40] The CVD-REAL 3 study conducted across five countries (Israel, Italy, Japan, Taiwan and the UK) included patients with measurements of eGFR within 3 months before and after initiation of SGLT2 inhibitor or OGLDs. After propensity matching, a total of 35,561 episodes of treatment were grouped in each of the treatment groups. In the SGLT2 inhibitor cohort, dapagliflozin and empagliflozin accounted for 58% and 34% of drug exposure time, respectively. The baseline mean HbA1c was 8.71%, and mean eGFR was 90.7 mL/min/1.73 m^2. The between-group difference in the rate of eGFR decline was 1.53 mL/min/1.73m^2 per year favoring SGLT2 inhibitors over OGLDs (p < 0.0001). The decline in eGFR across eGFR and HbA1c subgroups was similar and consistent, regardless of CVD or concomitant treatments with antihypertensives (p < 0.0001 in favor of SGLT2 inhibition in all subpopulations). Further, SGLT2 inhibitors were associated with a lower risk for ESRD alone compared to OGLDs (HR 0.33, 95% CI 0.16-0.68; p = 0.0024).[41]

The Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure (DAPA-HF) trial evaluated the safety and efficacy of dapagliflozin in patients with HF with reduced LVEF (defined as LVEF ≤40%) regardless of T2DM status (n = 4,744). The primary endpoint (a composite of death from CV causes or worsening HF) was significantly reduced in the dapagliflozin group vs. the placebo group (16.3% vs. 21.2%; HR 0.74; 95% CI 0.65-0.85; p < 0.001). Dapagliflozin was also associated with significant reduction in the individual components of the primary endpoints: worsening HF (10.0 vs. 13.7%; HR 0.70; 95% CI: 0.59-0.83) and CV mortality (9.6 vs. 11.5%; HR 0.82; 95% CI: 0.69-0.98; p = 0.029). These CV improvements were also seen in patients with diabetes (n = 215/1,075 in the dapagliflozin group and n = 271/1,064 in placebo group) as well as patients without diabetes (n = 171/1,298 and 231/1,307); with no difference between the groups (HR 0.75 (95% CI 0.63-0.90) in diabetes and HR 0.73 (95% CI 0.60-0.88) in no diabetes). The incidence of HHF or CV mortality in the dapagliflozin group was lower compared to the placebo group (16.1 vs. 20.9%; HR 0.75; 95% CI: 0.65-0.85; p < 0.001). The total first and recurrent events with dapagliflozin was 567 (340 HHF and 227 CV mortality) compared to 742 events with placebo (469 HHF and 273 CV mortality; HR 0.75; 95% CI: 0.65-0.88; p < 0.001). Further, the incidence of death from any cause was low with dapagliflozin vs. placebo (11.6 vs. 13.9%; HR 0.83; 95% CI: 0.71-0.97).[8] Physical function, symptom burden and quality of life in patients with HFrEF were also improved with dapagliflozin. The proportion of patients with ≥5-point improvement in the clinical summary of the Kansas City Cardiomyopathy Questionnaire (KCCQ) score was higher with dapagliflozin compared to placebo (58.3% vs. 50.9%; odds ratio [OR] 1.15, 95% CI: 1.08-1.23; p < 0.001), while significant deterioration was noted in a smaller proportion compared to placebo (25.3% vs. 32.9%; OR 0.84, 95% CI: 0.78-0.90; p < 0.001).[42] Hypoglycemia, volume depletion and renal dysfunction were the most frequent adverse events noted and were similar between the dapagliflozin and placebo arms.[8]

In an exploratory analysis of DAPA-HF patients without diabetes at baseline (n = 2,605), 6.0% of patients developed T2DM during the trial, of which 95.5% of patients had prediabetes at randomization (HbA1c 5.7-6.4%). The rate of new-onset diabetes was 4.9% with dapagliflozin compared to 7.1% with placebo, indicating a 32% reduction in risk with dapagliflozin.[43]

The DELIGHT trial was a prospective, double-blind, placebo-controlled randomized trial that assessed the effects of dapagliflozin alone or in combination with saxagliptin in patients with T2DM who were already on treatment with other glucose-lowering drugs and had moderate-to-severe CKD (n = 461). Dapagliflozin significantly reduced albuminuria by 21% (baseline

eGFR of ~50 mL/min/1.73 m^2 and a mean urine albumin-to-creatinine ratio [UACR] of ~27 mg/g) and by 38% with the combination of saxagliptin, 24 weeks post-treatment. The HbA1c reduction was three times higher with combination therapy compared to dapagliflozin monotherapy (58% vs. 16%). After adjusting for concomitant changes in HbA1c, SBP, eGFR and uric acid, dapagliflozin reduced albuminuria by 15% and by 31% with the combination therapy indicating that there was no influence of these covariates on the albuminuria-lowering effect. While minor hypoglycemia was more common with the dapagliflozin and saxagliptin combination, major hypoglycemia did not vary across the groups. Further, volume depletion and impaired kidney function related adverse events were common with the dapagliflozin and saxagliptin combination but did not differ between dapagliflozin alone and placebo groups.[44]

DAPA-CKD is a randomized double-blind trial that assessed the safety and efficacy of dapagliflozin in reducing renal events in CKD 2-4 stage patients (n = 4,304) The primary composite endpoint was the worsening of renal function, defined as a composite of an eGFR decline of at least 50%, onset of end-stage kidney disease, and death from a CV or renal cause. Overall, 197/2,152 primary endpoint events occurred with dapagliflozin, compared to 312/2,152 events with placebo (HR 0.61; 95% CI: 0.51-0.72; $p < 0.001$). The benefits of dapagliflozin were consistent regardless of T2DM status. Dapagliflozin also reduced worsening renal function or death due to kidney failure (HR 0.56; 95% CI: 0.45-0.68; $p < 0.001$); HHF or CV death (HR 0.71; 95% CI: 0.55-0.92; $p = 0.009$) and all-cause mortality (HR 0.69; 95% CI: 0.53-0.88; $p = 0.004$).[45]

Table 1 presents the expert opinions on the beneficial role of dapagliflozin concerning cardiac and renal outcomes.

Table 1. Expert Opinion

- There is emerging evidence about the role of dapagliflozin in prediabetes, especially in the space of cardiac and kidney disease, irrespective of diabetes status. In this context, the majority of the experts agreed to the use of dapagliflozin in patients with metabolic syndrome irrespective of diabetes status. However, it was highlighted that this treatment would be considered off-label. The experts opined that data on mechanistic aspects of dapagliflozin in CV and renal metabolic therapy would provide deeper insights into the role of dapagliflozin concerning cardiac and renal outcomes.
- With emerging data on HFrEF and data in CKD, it is evident that dapagliflozin is entering the nondiabetes arena. For now, the role of endocrinologists will largely remain in the space of T2DM with a focus on preventing HF and CKD. However, in nondiabetic patients, the experience of endocrinologists should be used, so that the product is utilized optimally by other specialists. Risk assessment tools are useful in identifying patients at risk of HF and for decision-making, in assigning specific treatment of diabetes control and prevention and or management of risk factors with SGLT inhibitors. The cardiac benefits can probably be attributed to the hematocrit mechanism. The experts suggested the need for publication and multidisciplinary academic meetings involving the endocrinologists and cardiologists' communities to have a balanced view of different specialists.

CARDIORENAL REHABILITATION POST-COVID

Since its outbreak in late 2019, there has been a rapid spread of the novel coronavirus disease (COVID-19) globally.[46] The healthcare system has been severely burdened by COVID-19, especially due to the absence of an approved therapeutic protocol.[47] Despite organ support, mortality is significantly high in patients receiving advanced respiratory support or dialysis or kidney transplant (65% and 78%, respectively). Further, a prospective observational study revealed that the involvement of cardiac complications and ongoing MI in patients post-COVID recovery was independent of severity and overall course of the acute illness, pre-existing conditions and the time from the original diagnosis.[48] Since SGLT2 inhibitors have shown cardio- and renal protection among diabetes and patients without diabetes, they may offer organ support in high-risk patients. The prospective beneficial mechanisms of SGLT2 include: 1) improving ventricular load by diuresis or natriuresis; 2) improving cardiac energy metabolism and 3) reducing the risk of kidney disease progression. Further preclinical data suggest benefits on the pulmonary system as well.[49] Expert opinion on role

Table 2. Expert Opinion

As known, survivors of severe acute respiratory syndrome (SARS) and other pandemics have several complications related to the cardiopulmonary, vasculometabolic and neuropsychiatric systems. In this context, there is a need for a publication on vasculometabolic and cardiorenal rehabilitation post-COVID, to evaluate the role of SGLT2 inhibitors.
Most complications related to post-respiratory infection are largely confined to the pulmonary system, and it would be interesting to know the role dapagliflozin/SGLT2 inhibitors play in preventing pulmonary complications. The ongoing DARE-19 (Dapagliflozin in Respiratory Failure in Patients With COVID-19) trial may provide valuable insights in this regard.[50]

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of dapagliflozin concerning cardiorenal rehabilitation post-COVID-19 is presented in Table 2.

CONCLUSION

In summary, there exist robust data supporting the beneficial role of dapagliflozin concerning cardiac and renal outcomes. Further, dapagliflozin was found to reduce HHF or CV death by 23% and reduce the risk of kidney disease progression by 45% independent of baseline ASCVD or history of HF.[51] Dapagliflozin substantially reduced the risk of ESRD or acute kidney injury, dialysis, transplantation or death due to kidney disease by ~30%. Renal protection was consistent across all eGFR and baseline albuminuria values.[52] Thus, the role of dapagliflozin in cardio- and nephroprotection potentially extends beyond T2DM patients.

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Contribution Details

All authors have contributed equally towards the conception and design of the study, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content and for final approval of the version to be submitted.

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Key Messages: Dapagliflozin, a SGLT-inhibitor, has been shown to improve HbA1c reduction in patients with major comorbidities associated with T2DM and is expected to become a preferred drug in T2DM. Recent studies have shown that dapagliflozin also significantly reduces cardiovascular events and delays kidney disease progression irrespective of diabetes. Dapagliflozin is emerging as a choice in these populations.

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