Review Article

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# Clinical Review on the Cardiorenal Benefit of Dapagliflozin in Type 2 Diabetes

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**Abstract:** Type 2 diabetes (T2D) is a chronic disorder with a growing prevalence. The progression and incidence of diabetes-related complications can be reduced with improved glycemic control. Dapagliflozin is a highly selectively SGLT2 inhibitor through which reabsorption of glucose into the bloodstream is diminished and promotes glucose filtration through the kidneys. The addition of dapagliflozin to therapies of metformin, glimepiride, sitagliptin, and insulin demonstrated positive reductions in HbA1c, FPG, and body weight compared with placebo. SGLT2 inhibitors have favorable cardiovascular effects predominantly in patients with type 2 diabetes and established cardiovascular disease; they have also been shown to delay kidney disease progression.

**Background:** Type 2 diabetes (T2D) is a chronic disorder with a growing prevalence.[1] India is estimated to have a prevalence of 134.3 million by 2045, which makes it the largest diabetes population. In Indians, T2D occurs earlier, progresses expeditiously. More than half the patients in India fail to achieve glycemic control and have higher rates of complication. The progression and incidence of diabetes-related complications can be reduced with improved glycemic control.[2, 3]

To effectively manage hyperglycemia in T2D, multiple agents with complementary mechanisms of action are often required. The oral antidiabetic agent's a currently available act by either increasing insulin secretion or by sensitizing tissues to insulin action. Their efficacy depends on the pancreatic β-cell function. In T2D, due to the progressive loss of β-cell function, to achieve target hemoglobin $A_{1c}$ ($HbA_{1c}$) levels, many patients require multiple agents.[4]

Patients with diabetes are at high risk for adverse outcomes from atherosclerotic cardiovascular disease, heart failure, and renal disease.[5]

SGLT2 inhibitors have favorable cardiovascular effects predominantly in patients with type 2 diabetes and established cardiovascular disease; they have also been shown to delay the progression of kidney disease.[5]

Dapagliflozin, an SGLT2 inhibitor, reduces systemic glycemic load by selectively inhibiting SGLT2 and reduces hyperglycemia independently of insulin secretion or action. With this mechanism, some of the filtered glucose passes into the urine for elimination.[4]

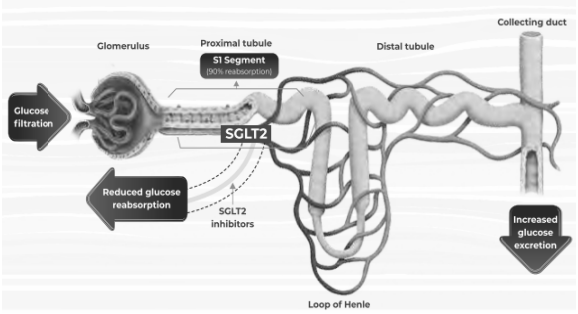


*Figure 1: Mechanism of action*

## Pharmacology

In the proximal renal tubule and the intestinal epithelium, SGLTs, a family of membrane proteins, are present, and they are responsible for the transport of glucose, amino acids, and other substances. Approximately 90% of glucose absorption occurs in the proximal convoluted tubule, and these transporters are responsible for it. [5] (Fig.1)

Dapagliflozin is a highly selectively SGLT2 inhibitor through which reabsorption of glucose into the bloodstream is diminished and promotes glucose filtration through the kidneys. Studies have examined 24 h glucose excretion in healthy subjects at doses of 20–100 mg and have resulted in urinary glucose excretion of approximately 60 g over 24 h.[6]

**Therapeutic benefits of dapagliflozin**

*a. In patients with heart failure*

SGLT 2 inhibitors were initially developed to treat type 2 diabetes. In various trials, the drugs led to a reduction in incident heart failure.

4742 patients with heart failure and reduced ejection fraction with and without type 2 diabetes the primary outcome which was the worsening of heart failure or cardiovascular death occurred in 171 of 1298 (13.2%) in the dapagliflozin group and 231 of 1307 (17.7%) in the placebo group in patients without diabetes and 215 of 1075 (20.0%) in the dapagliflozin group and 271 of 1064 (25.5%) in the placebo group in patients with diabetes.[7]

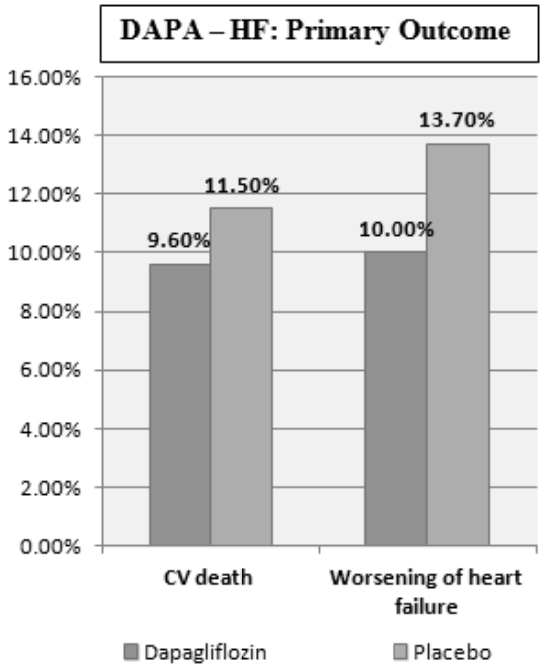


*Figure 2*

In the DEFINE – HF study, 263 patients with heart failure and reduced ejection fraction, the use of dapagliflozin over 12 weeks did not affect mean NT-proBNP but increased the proportion of patients experiencing clinically meaningful improvements in HF-related health status or natriuretic peptides.[8]

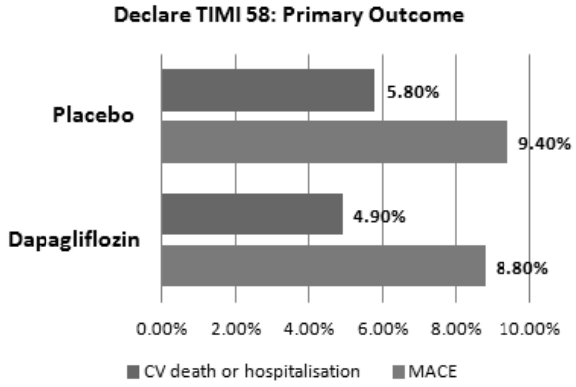


*Figure 3*

In the DAPA-HF trial, the primary outcome being worsening heart failure or cardiovascular death occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and in 502 of 2371 patients (21.2%) in the placebo group. The risk of worsening heart failure or death from cardiovascular causes regardless of the presence or absence of diabetes was lower among those who received dapagliflozin than among those who received placebo.[9] (Fig.2)

The DECLARE–TIMI 58 trial evaluated T2D patients who had or were at risk for atherosclerotic cardiovascular disease. They were treated with dapagliflozin, which resulted in a lower rate of cardiovascular death or hospitalization for heart failure.[10] (Fig.3)

*b. In patients, chronic kidney disease*

Patients with chronic kidney disease were randomized to either placebo or 10g of dapagliflozin. The primary outcome in the DAPA-CKD trial was a decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes. The primary outcome event occurred in 197 of 2152 participants

(9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group. The study concluded that End-stage kidney disease or death from renal or cardiovascular causes is significantly lower with dapagliflozin than with placebo.[11] (Fig.4)

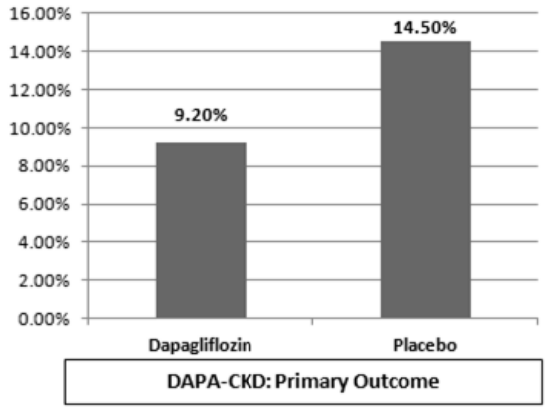


*Figure 4*

In a study done by Dekkers et al., in patients with type 2 diabetes and Stages 3b–4 CKD, the mean eGFR changed by −3.6 mL/min/1.73 $m^2$ for 5mg dapagliflozin and −3.8 mL/min/1.73 $m^2$ for 10 mg dapagliflozin at four weeks. The difference between dapagliflozin compared with placebo in UACR was −49.7%. [12]

In The DERIVE Study, 321 patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A) were included. The patients in the dapagliflozin group had a greater decrease of eGFR compared to placebo.[13]

**Cardio renal benefit**

In the DAPA-HF study, Patients who have HFrEF with or without type 2 diabetes and an estimated glomerular filtration rate (eGFR), ≥30mL/min/1.73 $m^{2,}$ were enrolled. Dapagliflozin had a lesser Rate of decline in eGFR −1.09mL/min/1.73 $m^2$ versus placebo −2.85 mL/min/1.73 $m^2$.[14]

In the DECLARE- TIMI trial, the authors identified a 46% reduction in a sustained decline in eGFR by at least 40% to less than 60 mL/min per 1·73 $m^2$ in the dapagliflozin group. The risk of end-stage renal disease or renal death was lower in the dapagliflozin group than in the placebo group. Both the cardiorenal and renal-specific composite outcomes were improved with dapagliflozin versus placebo across various prespecified subgroups.[15]

**Dapagliflozin in the Indian scenario**

IN the FOREFRONT study, 1941 patients completed the study. In this study, the largest mean decrease in HbA1c was in patients with baseline HbA1c >10% at month three and the maximum weight loss in patients with BMI >30 kg/$m^2$.[2]

**The safety profile of Dapagliflozin**

Dapagliflozin is generally well tolerated. Pooled data from 2b/3 clinical trial for a duration of 24 to 208 weeks reported the treatment-emergent adverse events, the most common ones being nasopharyngitis (5 vs. 6% with placebo), diarrhea (3 vs. 4%), headache (3 vs. 4%), upper respiratory tract infections (3 vs. 4%), urinary tract infection (UTIs; 4 vs. 3%) and back pain (4 vs. 2%).[16]

Genital infections were more frequent with dapagliflozin than in the placebo group (5.5% vs. 0.6%); women were twice more likely to experience genital infection than in men in both the treatment groups.[16]

| **Clinical Perspectives of dapagliflozin in the treatment of T2D** |
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| 1. Good Glycemic Control |
| 2. Reduces the risk of hHF, CV death, and all-cause Mortality |
| 3. Reduces the risk of kidney failure, CV deaths, and hHF In CKD patients |
| 4. Low risk of Hypoglycemia |

In conclusion, in view of its well-established efficacy and tolerability profile and its unique mechanism of action independent of the pancreatic beta cells, dapagliflozin is a

useful therapeutic option for patients at different stages of type 2 diabetes mellitus. Dapagliflozin has also found itself beneficial in patients with advanced stages of the disease with a significantly compromised β-cell function who are already receiving one or more OADs. Landmark studies have shown that dapagliflozin exerts beneficial effects in the management of heart failure and diabetic kidney disease. Thus, Dapagliflozin is an important addition to the therapeutic armamentarium for managing patients with T2DM with cardio-renal benefits.

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