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Review article

The effects of Dapagliflozin in type 2 diabetes mellitus patients with complications of cardiovascular disease: a review article

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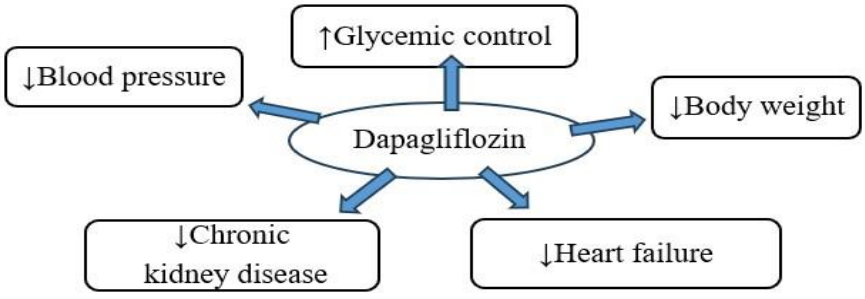
ABSTRACT

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder in which concomitant insulin resistance and beta-cell impairment lead to hyperglycemia. Cardiovascular problems are more common in T2DM but after the discovery of the dapagliflozin class of SGLT2 (Sodium-glucose co-transporter 2) inhibitor, the rate of cardiovascular disease (CVD) reduced slightly including heart failure (HF). Numerous recent clinical studies emphasized that dapagliflozin as monotherapy and combined therapy with another hypoglycemic agent help to improve glycaemic control and decrease blood pressure and body weight. In the present review, the safety and efficacy of dapagliflozin have been highlighted in patients with HFrEF(Heart failure with reduced ejection fraction), after comparison with placebo and dapagliflozin. It decreased the risk of total HF hospitalizations and cardiovascular death with a low-hypoglycaemic effect. Recurrent hospitalizations are a common problem in patients with HFrEF and it is also preventable. This review article also emphasized the comparative effects of drugs and placebo to prove the effectiveness of drugs and a further reduction in the rate of heart failure. The mild adverse effect is observed in clinical trials where urinary tract infection is most common.

Figure 1: Function of Dapagliflozin



Keywords: Type-2 Diabetes mellitus, Cardiovascular disease, Heart failure, Dapagliflozin.

INTRODUCTION

Type-2 Diabetes mellitus (T2DM) is a complex metabolic disorder. It occurs due to Insulin resistance and β-cellimpairment leading to hyperglycaemia. T2DM if left untreated may cause complications such as cardiovascular problems, myopathy, neuropathy, nephropathy, and retinopathy [1]. Due to rising obesity rates, longer life expectancies, and the westernization of lifestyles in nations that are developing, the rate of obesity is rapidly and steadily increasing, and its lasting consequences are the main contributors to

mortality, morbidity, and high healthcare expenditures [2]. Cardiovascular disease (CVD) including HF is a worldwide health problem. In most cases HF is formed due to arterial atherosclerotic disease it is a significant threat factor of T2DM for cardiovascular morbidity and mortality. Indeed, the incidence of HF is 2-4 times greater among diabetic patients than among the general population [3]. Dapagliflozin is an SGLT2 inhibitor that is effective in the treatment of T2DM and reduces the incidence of diabetes-related complications. It is a newly released class of hypoglycaemic drugs of SGLT2 inhibitors like Dapagliflozin, canagliflozin, and empagliflozin are effective in improving glycemic control. The financial burden and expense of managing heart failure with DM type-2 are reduced with the treatment of dapagliflozin [4, 5].

Epidemiology of t2dm with heart failure

CVD is responsible for around 70% and 30% of heart failure of all causes of death in patients with DM and more than 90% of patients are T2DM worldwide [6]. The prevalence of T2DM has increased by 30% worldwide. The studies have interpreted that about 333 million people in 2005 and 435 million people in 2015 have been diagnosed with T2DM [7]. The major risk factors contributing to developing T2DM with CVD include heart failure, hypertension, hyperlipidemia, smoking, sedentary lifestyle, lack of exercise, obesity, and positive family history.

Glycaemic and non-glycaemic effects of Dapagliflozin

The glycaemic and non-glycaemic effects of dapagliflozin are presented in Table 1.

Table 1-Glycaemic and non-glycaemic effects of dapagliflozin [8]

Diabetic effect	Reduce HbA1cby 0.8% (9 mmol/mol) and 1.5% (16 mmol/mol) after 6 and 12-months treatment with Dapagliflozin.
Cardiovascular effects	Dapagliflozin reduces body weight, blood pressure, epicardial fat thickness, serum uric acid, and lipid profiles.

Clinical efficacy and adverse effects of Dapagliflozin

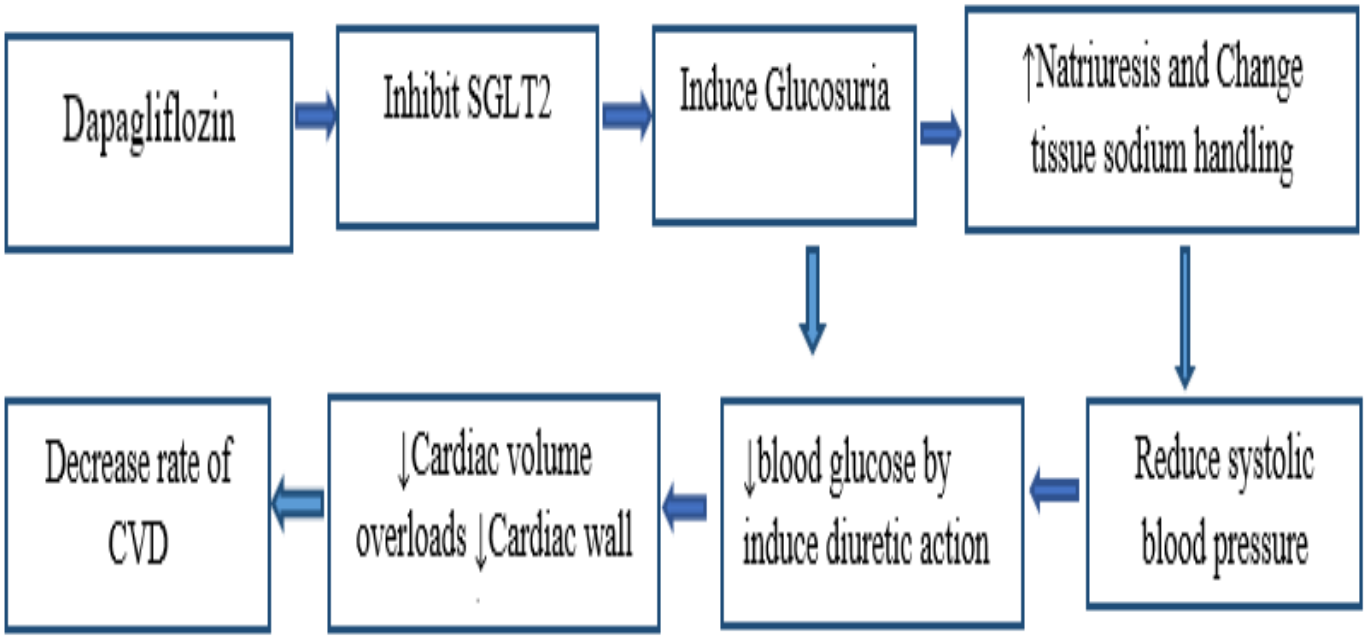
Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor that is used for the treatment of T2DM with heart failure. The safety and clinical benefits of dapagliflozin have been claimed at 5-10 mg per day dosing for T2DM with HF [9]. The important adverse effect caused by dapagliflozin are nasopharyngitis, urinary tract infection, back pain, increased urination, and male genital mycotic infections [10].

Pharmacokinetic and pharmacodynamic aspects of Dapagliflozin

Uridine-glucuronosyl transferases-1A9 metabolize dapagliflozin in the liver and kidney. Then dapagliflozin gets converted into its metabolite dapagliflozin 3-O-glucuronide (D3OG).

The plasma half-life of dapagliflozin is 13 hours (10 mg dosing). The liver and the kidney make a considerable metabolic contribution that leads to greater systemic exposure and decreased renal function. Dapagliflozin and metabolites are excreted through urine [11]. Dapagliflozin increases dose-dependent glycosuria and diuresis action averaging 375ml/day [12, 13]. SGLT2 inhibitors increase natriuresis, change tissue sodium level, and body mass, and also help in lowering systolic blood pressure (SBP). Urinary uric acid excretion is enhanced by dapagliflozin [14]. For this action, dapagliflozin has been associated with a decreased incidence of cardiovascular mortality or deteriorating HF [15].

Figure 2: Mechanism of action of dapagliflozin at pharmacokinetic and pharmacodynamic Level



Recommendations for the use of Dapagliflozinin T2DM with HF

Dapagliflozin-HF trial illustrated the advantages of SGLT2 inhibitors (specific Dapagliflozin) in the treatment of established HF by demonstrating that it not only significantly decreased the risk of CV mortality. However, HFrEF (Heart failure with reduced ejection fraction) patient symptoms were also improved the command clinical pathway in HF tips presently suggests Dapagliflozin 10 mg once a day to lessen the risk of HF hospitalization in individuals with DM and existing cardiovascular disease, as well as to lessen the risk of hospitalization and cardiovascular death in population with HFrEF. Therefore, this drug is used not only for glycaemic control but also for cardiac problems. Contraindications for dapagliflozin include hypersensitivity, pregnancy, breastfeeding, End-Stage Renal Disease (ESRD), and dialysis [16].A recent clinical trial conducted by the association for heart failure in the European Society of Cardiology (ESC) recommended using SGLT2 inhibitors in HF. Researchers also emphasized the use of dapagliflozin in preventing hospitalization of HF patients with T2DM. For individuals with symptomatic HFrEF, dapagliflozin is advised to reduce the risk of HHF (hospitalization heart failure) and CV death who are currently on GDMT (Guide-line directed medical therapy) [17, 18].

Therapeutic efficacy of Dapagliflozin

Dapagliflozin, as monotherapy has been demonstrated its efficacy for improving glycemia, reducing blood pressure, and body weight in a huge number of patients with T2DM, including the patients with high baseline HbA1c (≥9%) and elderly (aged ≥65 years) [19]. Dapagliflozin 10 mg once daily, reduced systolic blood pressure (SBP). This drug is more effective with a calcium-channel blocker, β blocker, or another antihypertensive drug than a thiazide diuretic. This medication is used in patients who have received a calcium channel blocker as an additional antihypertensive medication, and it is used less frequently with thiazide diuretics [20].

Dapagliflozin 10 mg once daily dosing had been used as monotherapy in two studies conducted in 2014 and 2015 as randomized, double-blind, multicentre, phase 3 trials improved glycemia and reduced SBP and body weight. In both studies, HbA1c was found low after adding dapagliflozin in the treatment line than placebo at week 24. Dapagliflozin reduced HbA1c by 0.8% (9 mmol/mol) in patients with cardiovascular disease after 12 weeks of therapy compared to placebo (0.1%, 2 mmol/mol). Body weight reduction was found more prominent among dapagliflozin treated group than the placebo group [21]. Further extension of these studies noticed the therapeutic benefits of dapagliflozin after 52 weeks of therapy [22]. A significantly ($p < 0.005$) greater proportion of patients in the dapagliflozin than placebo groups in both studies achieved a target HbA1c of < 7% at week 24 (19 vs. 13%). These studies found that the effectiveness of dapagliflozin was sustained through the second extension of 52 weeks (total 104 weeks of therapy). In a joint analysis of five phases, phase 2–3 clinical trials of ≤ 52 weeks duration, patients with T2DM with HF experienced clinically significant decreases in HbA1c (placebo-adjusted mean change - 0.55% and baseline 8.2%), SBP (2.1 mmHg; baseline 134 mmHg) and bodyweight (2.7 kg, baseline 97 kg), with 10 mg monotherapy of dapagliflozin [23].

Recent trials on Dapagliflozin in heart failure

A comparative study conducted by New York Heart Association (NYHA) among 1000 CV patients who had been administered placebo and dapagliflozin identified cardiac death as a first event (placebo vs dapagliflozin: 176 vs149) followed by HF hospitalization (placebo vs dapagliflozin: 307 vs 229), CV death (placebo vs dapagliflozin: 97 vs 78) and HF hospitalization as a subsequent event (placebo vs dapagliflozin: 162 vs 111). The researcher concluded from the above study that Dapagliflozin was more effective than a placebo. In a multivariable model, highly probable to have recurrent hospitalization for cardiovascular death or heart failure. When compared to those in class II, those in NYHA elegance III/IV substantially have greater chances of having a subsequent HF hospitalization if they had type 2 diabetes mellitus as opposed to those who did not. In longer duration, patients with HF have a greater chance of having frequent HF hospitalization than those with a duration of <1 year. Increased heart rate and higher N-terminal pro-B-type natriuretic peptide were significant predictors for a greater probability of cardiovascular mortality or repeat HF hospitalization [24].

As per the outcome of the clinical trial DAPA-HF (Dapagliflozin in heart failure) was the complex of intensifying HF or cardiovascular death (HF hospitalization). The day of death's hospitalization was not included in this analysis. We looked at the outcomes of repeated heart failure of HF (HF urgent visits in hospitalization) as well as cardiovascular death. The trial's first result was this composite analysis of the time-to-first incident. However, this analysis looked at all instances of worsening HF (for example, the initial and subsequent episodes). According to Lin Wei Yang Ying's (LWYY) model, From 15 February 2017 to 17 August 2018, a total of 4744 patients were randomly selected to receive either dapagliflozin or a Placebo at 410 healthcare centers in 20 countries. 809 HF hospitalizations with 548 individuals were recorded in total. Most inpatients were hospitalized once or twice during a median follow-up of 18.2 months (1st to 3rd quarter, 14.2 to 21.5 months). 7 hospitalizations were the maximum number. Hospitalizations were more prevalent in the placebo group (318 admissions out of 469 patients) than in the dapagliflozin group (230 hospitals out of 340

patients). There were 500 cardiovascular deaths (227 in the dapagliflozin group and 273 in the placebo group) and 105 deaths from non-cardiovascular disease (49 in the dapagliflozin and 56 in the placebo group) [25].

Dapagliflozin reduces total HF hospitalizations and cardiovascular death

The percentage of overall (first and recurrent) HF hospitalizations and cardiovascular fatality was yearly 21.6 % of placebo group patients and yearly 16.3% of the dapagliflozin group patients. The rate ratio between dapagliflozin versus placebo from the LWYY was 0.75 (95% CI, 0.65–0.88), p=0.0002, which was the same as the hazard ratio determined by time to first event analysis for heart failure hospitalization or cardiovascular mortality suggesting no attenuation of the effectiveness of dapagliflozin over recurrent events [26].

A randomized, multinational, double-blind, placebo-controlled, phase 3 trial was organized by the DECLARE-TIMI 58 (funded by Astra Zeneca). Phase 3 trial was conducted to monitor the consequences of dapagliflozin in patients of T2DM with HF or numerous risk factors atherosclerotic CVD [27]. During the phase 3 trial, 17160 patients participated in the run-in phase out of 25698 patients recruited by the clinical trial group. This randomized study included 6974 patients (40.6%) affected with atherosclerotic CVD and 10186 (59.4%) patients affected with numerous risk factors for atherosclerotic CVD. Patients were followed for an average time of 4.2 years. The patient's group was divided into sub-groups (Table 2)

Table 2: Efficacy outcomes of the Dapagliflozin-treated group and placebo group [28].

Sub-group	Dapagliflozin N=8582	Rate/1000 patients/year	Placebo N=8578	Rate/1000 patients/year
Cardiovascular death or hospitalization for heart failure	417	12.2	496	14.7
Hospitalization for heart failure	212	6.2	286	8.5
Myocardial infarction	393	11.7	441	13.2
Death from a cardiovascular cause	245	7.0	249	7.1
major adverse cardiovascular events (MACE)	756	22.6	803	24.2

CONCLUSION

Dapagliflozin is a very effective and less expensive drug in the population with HFrEF. It decreasedabout a placebo, and the risk of total HF hospitalization (recurrent and first) and cardiovascular death was higher. Recurrent hospitalizations are very common among patients with HFrEF that can be prevented. The initial evidence shows the use of dapagliflozin as an add-on therapy for patients with HFrEF reduces the incidence of CV endpoints such as cardiac death. Patients with HFpEF (heart failure with preserved ejection fraction) who took dapagliflozin reported a marked improvement in their clinical signs and functional limitations within 12 weeks of therapy which have been found consistent across all key subgroups including T2DM with CVD. Dapagliflozin is well tolerated by patients whose ejection fraction is above and below the normal value (50-75%).

Author's contribution

Study conception and design: SD. Data collection: SD, FJ, DD. Analysis of all reviews: DKU, DD. Draft manuscript preparation: SD, DD, FJ.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this review article.

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