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A Review on The Use of Dapagliflozin in Cardiovascular Diseases

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ABSTRACT

Dapagliflozin is a sodium-glucose co-transporter 2 inhibitor (SGLT2), used in decreasing the blood sugar levels in Type 2 diabetes mellitus patients by boosting urine glucose excretion, which also reduces the incidence of major adverse cardiovascular events. The drug has a higher affinity for cardio-protection and is observed to have reduced the risk of cardiovascular events in clinical trials and benefited in the prevention of cardiovascular diseases. It is recommended especially in patients with pre-existing CV conditions such as hypertension or myocardial infarction due to its higher baseline risk, but the use of drug was cautioned in patients who take pioglitazone or loop diuretics for hypertensive diabetes as it is believed to cause further volume depletion, resulting in lower eGFR. Dapagliflozin is a crucial treatment choice for a variety of individuals despite of its advised risk and regardless of patient history of cardiovascular disease, as it improves glycaemic control, body weight, and blood pressure while lowering the risk of cardiovascular mortality. This study reviews the therapeutic efficacy and the effects of dapagliflozin in diabetic patients with coexisting cardiovascular conditions and also compares several recent publications to comprise the risk and benefits of the drug in cardiovascular events and its role in the prevention of cardiovascular diseases and their complications.

Keywords: Dapagliflozin, sodium-glucose co-transporter 2 inhibitor (SGLT2), cardiovascular diseases.

INTRODUCTION

Type 2 diabetes mellitus was estimated to have been diagnosed in over 415 million individuals worldwide and is anticipated that over 640 million adults would have diabetes by 2040 due to its rising prevalence.[1] Patients with type 2 diabetes mellitus (T2DM) have a higher risk of developing cardiovascular diseases. Although the management of diabetes has traditionally been placed on achieving efficient glycaemic control, controlling other cardiovascular risk factors is crucial for enhancing patient outcomes. The drug class of sodium-glucose co-transporter 2 inhibitors (SGLT2) are used to decrease the blood sugar levels in T2DM patients by boosting urine glucose excretion, which also lowers the incidence of major adverse cardiovascular events.[2] Patients who have had a previous myocardial infarction (MI) or other major CV events may benefit even more from this class of drugs due to their higher baseline risk.[3] A novel SGLT2 inhibitor called dapagliflozin is recommended for enhancing glycaemic management (HbA1c of~5.5 mmol/mol together with diet and exercise.

Dapagliflozin is approved for use in people between the ages of 18 and 75 who do not already take pioglitazone or loop diuretics and have eGFR of less than 60 ml per minute (1.73 $m)^2$. Yet in some cases, the patients who do not fit these requirements are still given with the medication.[4] Use of dapagliflozin is a beneficial treatment option in the control of type 2 diabetes with underlying CVD due to its distinct mechanism of action and well-established efficacy and tolerability profile, however, its impact on cardiovascular and microvascular complications are still being assessed.[5]

In this review, an attempt has been made to cover the effects of dapagliflozin, its therapeutic efficacy, pharmacology and mechanism associated with the treatment of type 2 diabetes mellitus and underlying cardiovascular diseases and also discussed on the risk and benefits of the drug in cardiovascular events and its effects on comprehensive cardiovascular risk management.

PHARMACOLOGICAL ASPECT OF DAPAGLIFLOZIN

Dapagliflozin is used together with proper diet and exercise to treat type 2 diabetes. It works in the kidneys to prevent absorption of glucose (blood sugar). This helps lower the blood sugar level. Dapagliflozin does not help patients who have insulin-dependent or type 1 diabetes.

Dapagliflozin is orally administered antidiabetic drug with 91% plasma binding affinity, and has a distribution volume of about 118 litres. Adults' peak plasma concentration is estimated to reach in 1.5-2 hours of treatment.[6] And when administered at 10 mg dosing (OD), the bioavailability is found to be 78% and is not affected by any hepatic diseases.[7] It has an average plasma terminal half-life of 13 hours (10 mg dosing) and along with its metabolites, the drug is primarily eliminated by urine, and the process is delayed by renal impairment; the remaining 15% is eliminated through the faeces.[8] UGT1A9, an enzyme found in the liver and kidneys, metabolizes dapagliflozin into the major inactive metabolite 3-O-glucuronide, which is not involved in its effects on blood sugar levels.[6] Dapagliflozin also showed a slight drop in blood pressure (BP), which may be related to the drug's diuretic/natriuretic effects, which induce a reduction in circulation volume.[10]

THERAPEUTIC EFFICACY OF DAPAGLIFLOZIN

Type 2 diabetes mellitus possess a significant risk of increased morbidity and mortality related to cardiovascular events. In terms of novel methods for reducing cardiovascular diseases and heart failures in T2DM patients, the outcomes of using dapagliflozin are found to be favourable.[9] The drug has shown to be effective in improving glycaemic blood pressure control in diabetic patients with additional cardiovascular disease or the risk for cardiovascular events, even in individuals with high baseline HbA1c (9%).[10] When combined with routine background medication, dapagliflozin 10 mg once daily showed improved glycemic control, decreased body weight, and lowered systolic blood pressure in two phase-3 studies in patients with poorly managed type 2 diabetes (HbA1c 7-10.5% across the studies) with pre-existing cardiovascular disease and hypertension.[11] According to the study conducted by *Komoroski B et al.,* Dapagliflozin apparently showed clinically significant changes in glycaemic parameters and dose-dependent elevations in glycosuria in T2DM patients with cardiovascular diseases.[12]

In a large multinational study conducted by *Kosiborod M et al.,* the efficacy found with SGLT inhibitors in a randomized trial may represent a class effect relevant to a large population of patients with type 2 diabetes mellitus in everyday practice. Treatment with SGLT-2 inhibitor was associated with a decreased risk of heart failure and cardiovascular mortality compared to other glucose-lowering medications.[13] The multinational observational analysis

conducted by *Birkeland K I et al.,* concluded that the use of SGLT inhibitors was linked to lower rates of cardiovascular disease and mortality in a population of patients with type 2 diabetes and a wide range of cardiovascular risk factors.[29] More than 85% of participants in the EMPA-REG OUTCOME and CANVAS CVOT study, testing the SGLT2 inhibitor, did not demonstrate cardiovascular symptoms at the start of the study. However, SGLT2 inhibitors showed a clinically and statistically significant reduction in hospitalization related to cardiovascular events compared to placebo.[15]

BENEFITS OF USING DAPAGLIFLOZIN IN PATIENTS WITH ADDITIONAL CVD

In large-scale clinical trials of persons with type 2 diabetes and other established cardiovascular disease or several cardiovascular risk factors, sodium-glucose cotransporter-2 inhibitors have shown exceptional cardio-renal benefits.[14,37] Administration of SGLT2 inhibitor such as dapagliflozin was found to reduce CVD mortality and serious adverse CVD events compared to other glucose-lowering medications.[23] Dapagliflozin is also benefited by its association with reducing in weight and blood pressure. In patients with established or high-risk atherosclerotic cardiovascular disease, SGLT2 has positive effects on the heart and kidneys.[15,36] The ability of the drug to reduce atherogenic small dense LDL particle levels might extend long-term cardiovascular protection.[6] On the lipid profile, dapagliflozin is found to have positive effects, benefiting in patients who are obese and possesses high risk for developing atherosclerosis.

Dapagliflozin significantly decreased triglycerides by 18 mg/dL in T2DM patients, while LDL-C was either unaffected or slightly increased.[20] Sodium-glucose cotransporter-2 (SGLT2) inhibitors are known to lower blood glucose levels, blood pressure, and weight in patients with type 2 diabetes.[18] To lower blood glucose levels without raising insulin dosages, weight gain, or hypoglycaemia, SGLT2 inhibitors can be added to insulin regimens. In a meta-analysis conducted by *Min SH et al.,* an advantage in terms of body weight and no rise in the rates of hypoglycemia were related to the SGLT2 inhibitor-insulin combination.[20] The above-mentioned ability of the drug in turn may help in cardiovascular conditions by preventing atherosclerosis.[38]

It has been shown that SGLT2 inhibitors cause a significant drop in systolic blood pressure and a smaller drop in diastolic blood pressure without any distinctions amongst the drugs in this class including dapagliflozin.[26,37] The SGLT2 inhibitors considerably decreased both systolic and diastolic blood pressure when compared to placebo and active controls in the study conducted by *Baker WL et al.,* which could be due to osmotic diuresis.[28] Another possibility for dapagliflozin's potential cardio-protective action is that it directly benefits ventricular myocytes by a secondary reduction in intracellular and mitochondrial calcium.[9,30]

PROPOSED MECHANISM FOR CARDIOPROTECTIVE EFFECT OF DAPAGLIFLOZIN

There are several mechanisms that propose the cardio protective property of dapagliflozin. This includes the blood pressure-lowering effect that can be caused due to reduced sodium and glucose reabsorption in the proximal renal tubules resulting in lower blood pressure.[11,25] The possible osmotic diuresis, natriuresis, and arterial stiffness reduces plasma volume that in turn reduce blood pressure.[25] The reduction of uric acid and improvement of insulin sensitivity in addition to other metabolic effects, and the constriction of afferent renal arterioles was caused by the increase in sodium transport to the macula densa caused by SGLT2 inhibition, which decrease intraglomerular pressure.[27]

The reduction of atherogenic small dense LDL particle level results in the prevention of atherosclerosis which indirectly act as a cardioprotective.[18] Dapagliflozin has also been proposed as having a potential cardioprotective mechanism through a direct beneficial effect on ventricular myocytes through a decrease in myocardial intracellular Na+ concentrations via inhibition of the myocardial Na+/H+ exchanger flux, which then results in a secondary reduction in intracellular and mitochondrial calcium.[,26,30]

DAPAGLIFLOZIN-ANTIHYPERTENISVE COMBINATION: POSSIBLE RISK FOR CARDIOVASCULAR EVENTS

The treatment approach for type 2 diabetes in patients with underlying cardiovascular diseases requires control of glycaemia and careful consideration of cardiovascular risk factor management with the goal of reducing complications and maintaining the quality of life in the context of comprehensive cardiovascular risk management.[17]

In contrast to their benefits, dapagliflozin found to make modest changes in serum lipids, particularly in the study conducted by *Wu JH et al.,* an increase in total cholesterol and enhanced high-density lipoprotein cholesterol (HDL-C) by 2.2 mg/dL, as well as decreases in triglycerides are seen.[18] This class of drug, when used in combination with diuretics and/or ACE inhibitors and angiotensin receptor blockers, caution should be exercised because SGLT2 inhibitors have been linked to an increased risk of acute renal injury, dehydration, and orthostatic hypotension, which can worsen the underlying cardiovascular condition. [16,34]

In patients using a long-term combination of SGLT2 inhibitors and loop diuretics, regular monitoring of volume-depletion adverse events is warranted in the study conducted by *Rahhal A et al*., particularly at a daily dose of diuretics with an equivalent dose greater than 40 mg.[19]

STUDIES SUPPORTING THE CARDIOVASCULAR BENEFITS OF DAPAGLIFLOZIN OVER RISKS

Recent studies state that the combination of SGLT2 inhibitors with diuretics may not significantly deplete volume.[19] This claim is verified in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) study conducted by *McMurray JJ et al.,* where the group of patients prescribed with dapagliflozin (16.3%) experienced the primary composite outcome of hospitalisation or death from cardiovascular causes comparatively lesser than the placebo group (21.2%)[21] and the study conducted by *Wu JH et al.,* produced data that provides compelling and beneficial evidence for anticipating benefits from the use of SGLT2 inhibitors in those with type 2 diabetes who are at high risk of cardiovascular events.[18] Based on the volume depletion results of SGLT2 inhibitors used in diabetes mellitus obtained from the study conducted by *Jackson AM et al*., the volume depletion may not be a clinically significant adverse outcome when SGLT2 inhibitors are used alone. Especially given that a subgroup analysis of the DAPA-HF trial assessed the use of dapagliflozin among patients with cardiovascular disease, showed that the volume depletion events were significantly less common with dapagliflozin compared to placebo.[22]

According to the study conducted by *Wiviott SD et al.,* treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo, but it did result in a decreased rate of cardiovascular death in patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease.[1] And a study conducted by *Birkeland KI et al.,* showed that the use of SGLT2 inhibitors was associated with lower rates of cardiovascular disease and mortality in patients with type 2 diabetes and a wide range of cardiovascular risk factors.[29] Dapagliflozin has a unique mechanism of action, a well-proven efficacy and tolerance

profile, and is a safe treatment for type 2 diabetes in terms of cardiovascular outcomes.[31,33]

CONCLUSION

Dapagliflozin is found to be promising in the management of type 2 diabetes mellitus with underlying cardiovascular diseases. The available evidences support the dapagliflozin-induced cardioprotection and nephroprotection but the potential mechanism needs to be further investigated and clarified. We have highlighted some of the key determinants that could account for the significant cardiovascular advantages of SGLT2 inhibitors.

Dapagliflozin is an effective treatment for type 2 diabetes and is safe in terms of cardiovascular outcomes due to its distinct mode of action along with its established efficacy and tolerance profile. Although cardiovascular-related risk factors were observed in a combination therapy involving dapagliflozin, the treatment option can be considered with caution as the benefits overweigh their potential risk.

Declaration by Authors

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