International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 04 Issue 06 June 2024

Page No: 1093-1096

DOI: https://doi.org/10.47191/ijmscrs/v4-i06-19, Impact Factor: 7.949

Cardioprotective Effects of SGLT2 Inhibitors in Diabetic Patients with Cardiovascular Disease

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ABSTRACT

Type 2 diabetes is a chronic and multifactorial disease associated with a twofold increase in the incidence of numerous cardiovascular and renal diseases, which are a significant health limitation for patients with diabetes. Throughout the years, cardiovascular diseases have marked a significant health burden in these patients. Many studies have shown that Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce cardiovascular mortality in patients with diabetes mellitus, by inhibiting cardiomyocyte apoptosis. Patients with diabetes are at a higher mortality risk after their first event of myocardial infarction than those without diabetes. The keystone in the therapy of diabetic patients is significantly linked to the prevention of cardiovascular events.

The high prevalence of cardiovascular and renal disease in patients with diabetes, as well as suboptimal glycemic controls and the significance of cardiovascular and renal risk reduction in type 2 diabetes, suggest that SGLT2 inhibitors have a significant clinical advantage, enhancing not just a better glycemic control, but improving cardiovascular and renal outcomes.

ARTICLE DETAILS

Published On:
12 June 2024

Available on:
https://ijmscr.org/

INTRODUCTION

Tabla 1. SGLT2 (4, 5, 8)

SGLT2 Inhibitor	Brand Name	Cardiovascular Benefits	Key Clinical Trials	Additional Benefits
Empagliflozin	Jardiance	Reduced risk of cardiovascular death, reduced hospitalization for heart failure (HF).	EMPA-REG OUTCOME	Improved kidney outcomes, weight loss, reduced HbA1c
Canagliflozin	Invokana	Reduced risk of major adverse cardiovascular events (MACE), reduced hospitalization for HF.	CANVAS, CANVAS-R, CREDENCE	Reduced progression of kidney disease, weight loss

Dapagliflozin	Farxiga	Reduced risk of cardiovascular death or worsening HF, reduced hospitalization for HF.	DECLARE-TIMI 58, DAPA-HF, DAPA-CKD	Improved kidney outcomes, weight loss, reduced HbA1c
Ertugliflozin	Steglatro	Non-inferiority for major adverse cardiovascular events (MACE) compared to placebo, reduced hospitalization for HF.	VERTIS CV	Improved kidney outcomes, weight loss
Sotagliflozin	Zynquista (not widely available)	Reduced risk of cardiovascular death and hospitalization for HF.	SCORED, SOLOIST-WHF	Dual SGLT1 and SGLT2 inhibition, potential GI benefits

Type 2 diabetes is associated with a twofold increase in the incidence of numerous cardiovascular and renal diseases, which are a significant health limitation for patients with diabetes. Throughout the years, cardiovascular diseases have marked a significant health burden in these patients. Diabetics are at a higher mortality risk after their first event of myocardial infarction than those without diabetes. The keystone in the therapy of diabetic patients is significantly linked to the prevention of cardiovascular events.[1].

In Iran, a study conducted at a university-affiliated clinic, examined the impact of antidiabetic medications; metformin, glibenclamide/metformin, insulin, and insulin/metformin, on blood pressure and pulse pressure. The results of the study did not indicate any significant differences between the anti-hyperglycemic drugs used. Regrettably, there is a lack of nationally representative data on the mortality of diabetes patients who are receiving treatment with various oral antidiabetic medications. The treatment with glyburide was found to be correlated with all-cause mortality and cardiovascular mortality in a relatively large sample at a diabetes center [2, 3].

SGLT2 (sodium-glucose cotransporter type 2) inhibitors are novel glucose-lowering compounds that have the potential to enhance renal outcomes and decrease the risk of major adverse cardiovascular events (MACE). The role of SGLT2 inhibitors as renal and cardioprotector was uncertain, however, in 2022 a study conducted in China demonstrated that these improved cardiac function by inhibiting the Na+/H+ exchanger 1 (NHE1) in the cardiomyocyte. SGLT2 inhibitors decrease an excessive response of autophagia through the NHE1. Diabetes is also linked to an elevated risk of adverse renal events, rendering diabetic kidney disease the primary cause of end-stage renal disease. Cardiovascular outcomes are likely to be influenced by renal events [4, 8].

The cardiovascular outcomes of SGLT2 inhibitors have been the subject of optimistic recent trials. In the EMPA-REG OUTCOME study, 7020 participants with type 2 diabetes and a history of cardiovascular disease (CVD) were divided into two groups to receive either empagliflozin or a placebo in addition to their standard treatment. The three-point MACE, which includes cardiovascular mortality, non-fatal MI, and non-fatal stroke, was associated with a relative risk reduction of approximately 14% with empagliflozin. The DECLARE-TIMI 58 study published a randomized controlled trial with dapagliflozin, which demonstrated a substantial decrease in primary composite cardiovascular endpoints (MACE) in patients treated with SGLT2 inhibitors compared to placebo, and the CANVAS program included data from two trials [5].

A meta-analysis of 57 published trials, which included 33385 patients and six regulatory submissions (37525 patients), and data for seven different SGLT2 inhibitors, demonstrated a substantial decrease in primary composite cardiovascular endpoints (MACE) in patients treated with SGLT2 inhibitors compared to placebo. A 20% decrease in MACE was observed with SGLT2 inhibitors in a recent meta-analysis conducted by Zhang et al. in 2018 [4, 6].

The data regarding myocardial infarction (MI) in patients who are administered SGLT2 inhibitors is inconsistent. In the EMPA-REG OUTCOME trial, there was no significant reduction in MI among patients with type 2 diabetes who were treated with empagliflozin 10 or 25 mg compared to a placebo. The CANVAS trial did not result in a substantial decrease in MI, as evidenced by two sub-studies that utilized the CVD-REAL Nordic database [4, 6].

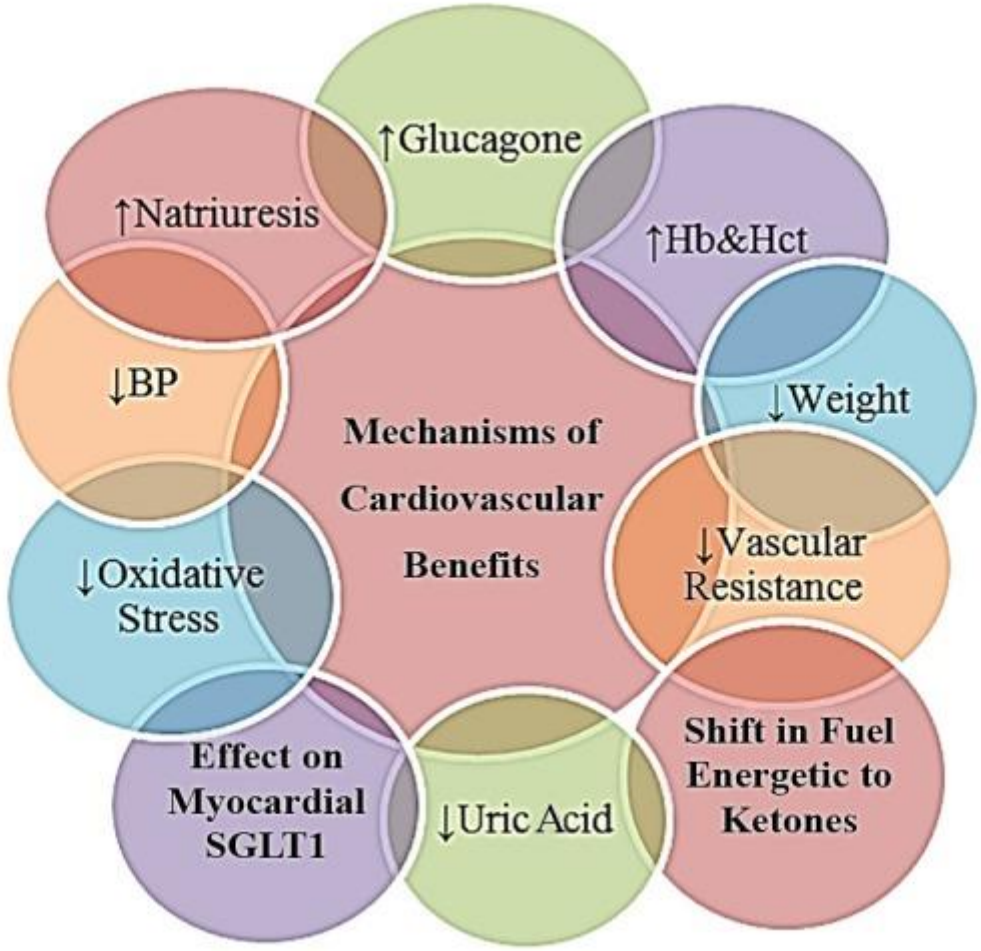
The aforementioned consolidates the efficacy of empagliflozin 10 or 25 mg in the treatment of stroke in patients with type 2 diabetes. The EMPA-REG OUTCOME trial did not demonstrate a substantial reduction in stroke incidence among patients who were administered empagliflozin in comparison to placebo. Similar to two CVD-REAL Nordic investigations, the CANVAS trial did not demonstrate any reduction in stroke. The DECLARE-TIMI study demonstrated that there was no significant difference between the dapagliflozin group and the placebo group in the incidence of ischemic stroke. The CVDREAL study demonstrated that the initiation of SGLT2 inhibitors in patients with diabetes resulted in a reduced incidence of stroke [7].

The EMPA-REG OUTCOME trial demonstrated a 38% relative risk reduction in the cardiovascular mortality rate among patients with type 2 diabetes who were treated with SGLT2 inhibitors (26). The observational CVD-REAL Nordic study, which compared SGLT2 inhibitors with other antidiabetic agents, yielded a comparable result (HR: 0.53; 95% CI: 0.40 - 0.71; $P < 0.001$). Additionally, certain meta-analyses indicated a decreased cardiovascular mortality in patients who were administered SGLT2 inhibitors [5].

A recent hypothesis posits that SGLT2 inhibitors may enhance myocardial work efficiency by modifying the fuel metabolism from free fatty acids to ketones. Another

hypothesis posits that the decrease in cardiovascular mortality associated with empagliflozin may be attributable to an immediate impact on cardiomyocytes, improving the myocardial function and mitigating rhythm disturbances [8].

Table 2. Mechanisms of CV diseases (1)



CONCLUSION

Type 2 diabetes represents a significant risk for cardiovascular and renal diseases, which pose considerable health limitations for patients. The high prevalence of these complications underscores the importance of effective management strategies. SGLT2 inhibitors have demonstrated important benefits, reducing cardiovascular mortality and improving cardiovascular and renal outcomes in diabetic patients. These benefits are achieved through different mechanisms by inhibiting cardiomyocyte apoptosis and modulating metabolic pathways. Despite the diverse results on specific outcomes like myocardial infarction and stroke, the overall evidence endorses the use of SGLT2 inhibitors to improve the patient's health and reduce diabetes-related complications. As such, these inhibitors represent the keystone management of type 2 diabetes, providing significant clinical advantages [9].

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