Journal of Clinical Diabetes

Commentary Open Access

Efficacy of SGLT2 Inhibitors in Cardiovascular Risk Reduction for Diabetic Patients

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Introduction

Type 2 diabetes (T2D) is a major risk factor for cardiovascular disease (CVD), with individuals suffering from T2D experiencing significantly higher rates of heart failure, coronary artery disease, and stroke compared to the general population. The link between diabetes and CVD is well-established, and as such, managing cardiovascular risk in diabetic patients is a crucial component of diabetes care [1-3].

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a class of oral antidiabetic medications that work by inhibiting the SGLT2 protein in the proximal renal tubules. This inhibition prevents glucose reabsorption, leading to increased glucose excretion in urine, thereby lowering blood glucose levels. While initially developed for glycemic control, recent clinical trials and observational studies have demonstrated that SGLT2 inhibitors also have significant benefits for reducing cardiovascular events in patients with diabetes.

The importance of these findings cannot be overstated, as cardiovascular complications are the leading cause of morbidity and mortality in individuals with diabetes. This article aims to review the clinical evidence on the efficacy of SGLT2 inhibitors in reducing cardiovascular risk in diabetic patients, with a particular focus on their impact on heart failure, myocardial infarction, stroke, and overall cardiovascular mortality [4-6].

Description

SGLT2 inhibitors, including canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin, exert their primary effect by blocking the SGLT2 protein in the kidneys, which is responsible for the reabsorption of approximately 90% of filtered glucose back into the bloodstream. This leads to increased glucose excretion through urine, resulting in a reduction in blood glucose levels.

However, the cardiovascular benefits of SGLT2 inhibitors extend beyond their effects on glucose control. Several mechanisms are thought to contribute to the observed reduction in cardiovascular risk, including:

Diuretic effect and reduction in fluid overload

SGLT2 inhibitors have a mild diuretic effect, leading to a reduction in blood volume and a subsequent decrease in blood pressure. This diuretic action can be especially beneficial in patients with heart failure or chronic kidney disease (CKD), conditions that are common in individuals with diabetes. By reducing fluid retention, SGLT2 inhibitors help alleviate symptoms of heart failure, such as edema and shortness of breath [7].

Reduction in blood pressure

The blood pressure-lowering effects of SGLT2 inhibitors are another key contributor to their cardiovascular benefits. SGLT2 inhibitors reduce both systolic and diastolic blood pressure through their diuretic effect and direct vasodilation. This reduction in blood pressure helps lower the burden on the heart, especially in patients with hypertension or heart failure.

Improvement in cardiac metabolism

SGLT2 inhibitors have been shown to improve cardiac metabolism by increasing the availability of ketone bodies, which are a more efficient energy source for the heart than glucose. This shift in metabolism may improve myocardial function and reduce the risk of ischemia, especially in patients with heart failure. [8].

Reduction in inflammation and oxidative stress

Chronic inflammation and oxidative stress play a significant role in the development of atherosclerosis and other cardiovascular complications in diabetes. SGLT2 inhibitors have been shown to reduce markers of inflammation and oxidative stress, potentially mitigating the progression of cardiovascular disease in diabetic patients.

Renal protection

There is increasing evidence that SGLT2 inhibitors confer protective effects on the kidneys, reducing the risk of diabetic nephropathy, a common complication of diabetes that also contributes to cardiovascular risk. By preserving kidney function, SGLT2 inhibitors help prevent the development of renal failure, which is a significant contributor to cardiovascular morbidity and mortality. [9,10].

Discussion

One of the landmark studies that established the cardiovascular benefits of SGLT2 inhibitors is the EMPA-REG OUTCOME trial, which evaluated the effect of empagliflozin on cardiovascular outcomes in patients with type 2 diabetes at high cardiovascular risk. The trial included over 7,000 participants and found that empagliflozin significantly reduced the risk of major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, by 14%. More notably, empagliflozin reduced cardiovascular death by 38%, a striking result that highlighted the potential of SGLT2 inhibitors in preventing the most severe cardiovascular outcomes in diabetic patients.

The EMPA-REG OUTCOME trial also demonstrated a significant reduction in heart failure hospitalizations (35%) and a 32% reduction in the risk of death from any cause. These findings were consistent across

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Received: 3-Oct-2024, Manuscript No: jcds-25-159841, **Editor assigned:** 10- Oct -2024 PreQC No: jcds-25-159841 (PQ), **Reviewed:** 17-Oct -2024, QC No: jcds-25-159841, **Revised:** 23-Oct -2024, Manuscript No: jcds-25-159841 (R), **Published:** 30-Oct -2024, DOI: 10.4172/jcds.1000254

Citation: Till B (2024) Efficacy of SGLT2 Inhibitors in Cardiovascular Risk Reduction for Diabetic Patients. J Clin Diabetes 8: 254.

various subgroups, including those with established cardiovascular disease and those with no prior history of heart disease.

The CANVAS program

The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) is another large clinical trial that investigated the cardiovascular effects of canagliflozin in patients with type 2 diabetes. The CANVAS Program included over 10,000 participants and showed that canagliflozin reduced the risk of MACE by 14% and lowered the risk of cardiovascular death by 20%. The trial also found that canagliflozin significantly reduced the risk of heart failure hospitalizations by 33%, reinforcing the cardiovascular protective effects of SGLT2 inhibitors.

However, the CANVAS Program also raised some concerns regarding the increased risk of lower-limb amputations in patients treated with canagliflozin, a potential side effect that requires further investigation. Despite this, the cardiovascular benefits observed in the trial far outweighed the risks, leading to the widespread adoption of SGLT2 inhibitors in clinical practice.

The DAPA-HF trial

The DAPA-HF trial investigated the effect of dapagliflozin in patients with heart failure and reduced ejection fraction (HFrEF), regardless of whether they had diabetes. The trial included over 4,700 participants and demonstrated that dapagliflozin significantly reduced the risk of cardiovascular death or worsening heart failure by 26%. The benefits of dapagliflozin were consistent in both diabetic and non-diabetic patients, highlighting the potential of SGLT2 inhibitors to improve outcomes in heart failure, a common complication of both diabetes and cardiovascular disease.

The DECLARE-TIMI 58 trial

The DECLARE-TIMI 58 trial evaluated the cardiovascular effects of dapagliflozin in a large cohort of patients with type 2 diabetes and a high risk of cardiovascular events. While the trial did not show a significant reduction in the primary endpoint (MACE), it did demonstrate a significant reduction in the risk of heart failure hospitalizations and cardiovascular death, particularly in patients with a history of heart failure. This study further supports the role of SGLT2 inhibitors in reducing heart failure risk in diabetic patients.

Conclusion

The growing body of evidence supporting the cardiovascular benefits of SGLT2 inhibitors has fundamentally changed the way we approach cardiovascular risk management in patients with diabetes. These drugs, originally developed for glycemic control, have proven to be effective in reducing major cardiovascular events, including heart failure hospitalizations, myocardial infarctions, strokes, and cardiovascular mortality.

SGLT2 inhibitors work through multiple mechanisms, including diuresis, blood pressure reduction, and improved cardiac metabolism, making them uniquely effective in managing both diabetes and its associated cardiovascular complications. Landmark trials, such as EMPA-REG OUTCOME, CANVAS, DAPA-HF, and DECLARE-TIMI 58, have provided strong evidence of their benefits in reducing cardiovascular risk, leading to their inclusion in clinical guidelines as part of the standard treatment for high-risk diabetic patients.

Despite their promising cardiovascular benefits, SGLT2 inhibitors are not without potential risks, including urinary tract infections, dehydration, and the aforementioned risk of amputations with certain agents like canagliflozin. As such, careful patient selection and monitoring are essential.

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