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Impact of Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors on Cardiovascular Events in Type 2 Diabetes

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by persistent hyperglycemia and insulin resistance. **Objective:** The main objective of the study is to find the impact of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors on cardiovascular events in Type 2 diabetes. **Methodology:** This randomized control trial was conducted at Shalamar Hospital, Lahore, from 1st March to 31st August 2024. Data were collected from 195 patients. Data were collected at baseline and subsequent follow-up visits through standardized protocols. **Results:** Data were collected from 195 patients. Only 12.2% of patients in the SGLT2 inhibitor group experienced MACE, compared to 25.8% in the control group, reflecting a 52.7% relative risk reduction ($p = 0.01$). Similarly, heart failure hospitalizations were reduced to 5.1% in the SGLT2 inhibitor group compared to 15.5% in the control group, yielding a 67% relative risk reduction ($p = 0.005$). These findings highlight the significant cardiovascular protective effects of SGLT2 inhibitors. The Kaplan-Meier analysis revealed that patients in the SGLT2 inhibitor group had a significantly longer median time to the first cardiovascular event (11.5 months) compared to the control group (8.5 months), with a p-value of 0.002. **Conclusion:** It is concluded that sodium-glucose cotransporter-2 (SGLT2) inhibitors significantly reduce cardiovascular events in patients with type 2 diabetes mellitus, making them a pivotal advancement in diabetes management.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder marked by persistent hyperglycemia and insulin resistance. This condition influences glucose digestion as well as expands the endanger of a few hazardous entanglements, essentially cardiovascular infections (CVD). Cardiovascular occasions, including cardiovascular breakdown, myocardial localized necrosis, and stroke, represent a significant extent of horribleness and mortality in people with T2DM, making cardiovascular gamble the board a foundation of diabetes care [1]. Over the course of the last 10 years, the presentation of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors has changed the scene of T2DM treatment. At first planned as glucose-bringing down specialists, these medications have earned respect for their interesting skill to convey cardiovascular and renal security past glycemic control. By hindering SGLT2 proteins in the proximal renal tubules, these meds decrease glucose reabsorption, prompting expanded urinary glucose discharge [2]. This component brings down blood glucose levels as well as prompts osmotic diuresis and natriuresis, which add to their cardiovascular advantages. SGLT2 inhibitors have shown momentous commitment in lessening major unfriendly cardiovascular occasions (MACE), like myocardial dead tissue, stroke, and cardiovascular passing, in patients with T2DM [3]. Moreover, they fundamentally affect lessening hospitalization for cardiovascular breakdown, a typical and crippling condition in this populace. Clinical preliminaries,

including EMPA-REG Result, Material, and Pronounce TIMI 58, have given vigorous proof supporting the cardiovascular viability of SGLT2 inhibitors [4]. These examinations uncovered reliable advantages across different patient populaces, paying little mind to benchmark cardiovascular illness status, making SGLT2 inhibitors a flexible device in diabetes the board. Past their direct cardiovascular advantages, SGLT2 inhibitors offer different benefits, for example, weight decrease and pulse control, the two of which are basic in moderating cardiovascular disease [5]. Weight reduction is accomplished through calorie discharge because of glucosuria, while pulse decrease is worked with by natriuresis and a lessening in plasma volume. These impacts contribute synergistically to the by and large cardiovascular advantages saw with SGLT2 inhibitors. The systems basic the cardiovascular impacts of SGLT2 inhibitors are complex. As well as lessening glucose levels, these medications work on endothelial capability, decline blood vessel firmness, and decrease oxidative pressure and aggravation, which are all crucial variables in the pathogenesis of cardiovascular sicknesses [6]. Besides, SGLT2 inhibitors advance ketogenesis, giving an elective energy source to the weak heart, and diminish cardiovascular preload and afterload, accordingly reducing the weight on the heart. Regardless of these promising results, the utilization of SGLT2 inhibitors isn't without challenges [7]. Possible unfavorable impacts, including genital contaminations, volume consumption, and interesting occurrences of diabetic ketoacidosis, warrant cautious patient choice and observing. Besides, their generally significant expense might restrict openness, especially in asset obliged settings, representing an obstruction to their broad reception. As the collection of proof supporting the cardiovascular advantages of SGLT2 inhibitors keeps on developing, their part in T2DM the executives are extending [8]. Momentum rules suggest SGLT2 inhibitors for glycemic control as well as for cardiovascular gamble decrease, especially in patients with laid out cardiovascular illness or cardiovascular breakdown. This change in perspective highlights the significance of a comprehensive way to deal with diabetes care, focusing on results that stretch out past glucose control to work on in general quiet endurance and personal satisfaction [9]. SGLT2 inhibitors address a momentous progression in the treatment of T2DM, offering huge advantages for cardiovascular health. Their capacity to decrease the frequency of major cardiovascular occasions and hospitalizations for cardiovascular breakdown, joined with their great impacts on weight and pulse, positions them as a foundation of present-day diabetes treatment. Future research ought to zero in on advancing their utilization, addressing boundaries to openness, and investigating their expected in more extensive populaces, including those without diabetes, to amplify their clinical effect [10].

Objective

The main objective of the study is to find the impact of Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors on cardiovascular events in Type 2 diabetes.

METHODOLOGY

This randomized control trial was conducted at Shalamar Hospital, Lahore, from 1st March to 31st August 2024. Data were collected from 195 patients.

Inclusion Criteria

Individuals aged 40–75 years with a confirmed diagnosis of T2DM for at least one year. Patients were required to have either established cardiovascular disease or a high risk of cardiovascular events based on clinical history and risk factors such as hypertension, hyperlipidemia, or obesity.

Exclusion Criteria

It included individuals with Type 1 diabetes, severe renal impairment (eGFR < 30 mL/min/1.73 m^2), recurrent diabetic ketoacidosis, or active infections.

Data Collection

Data were collected at baseline and at subsequent follow-up visits through standardized protocols. The participants were divided into two groups.
Group I: SGLT2 inhibitor group
Group II: Control Group

Group I consisted of 98 patients who received a daily dose of an SGLT2 inhibitor such as empagliflozin, dapagliflozin, or canagliflozin in addition to their standard diabetes care. The remaining 97 patients formed the control group, continuing their usual diabetes treatment regimen without the inclusion of SGLT2 inhibitors. The intervention lasted for 12 months, during which participants attended follow-up visits every three months to monitor their progress and record outcomes. The primary outcomes measured in this study included the reduction in MACE, specifically cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Hospitalizations for heart failure were also evaluated as a key measure of cardiovascular health. Data included HbA1c levels for glycemic control, blood pressure measurements, body weight, and BMI. Renal function was monitored using serum creatinine and eGFR values. Any cardiovascular events, hospitalizations, or adverse effects were documented during follow-ups.

Statistical Analysis

Data were analyzed using SPSS v26. Continuous variables, such as HbA1c and blood pressure, were expressed as mean ± standard deviation (SD) and compared between groups using t-tests. Categorical variables, such as the occurrence of MACE, were

analyzed using chi-square tests. A significance threshold of $p < 0.05$ was established for all analyses.

RESULTS

Data were collected from 195 patients. Only 12.2% of patients in the SGLT2 inhibitor group experienced MACE, compared to 25.8% in the control group, reflecting a 52.7% relative risk reduction ($p = 0.01$). Similarly, heart failure hospitalizations were reduced to 5.1% in the SGLT2 inhibitor group compared to 15.5% in the control group, yielding a 67% relative risk reduction ($p = 0.005$). These findings highlight the significant cardiovascular protective effects of SGLT2 inhibitors.

Table 1

Reduction in Major Adverse Cardiovascular Events (MACE) and Heart Failure Hospitalizations

Outcome	SGLT2 Inhibitor Group (n=98)	Control Group (n=97)	Relative Risk Reduction (%)	p-Value
Patients with MACE	12 (12.2%)	25 (25.8%)	52.7%	0.01
Heart failure hospitalizations	5 (5.1%)	15 (15.5%)	67.0%	0.005

HbA1c levels decreased from 8.5% to 7.3% in the SGLT2 inhibitor group compared to a smaller reduction from 8.6% to 8.1% in the control group ($p = 0.001$). Body weight decreased by 3.5 kg in the SGLT2 inhibitor group compared to 0.8 kg in the control group ($p = 0.004$). Systolic and diastolic blood pressure reductions were more pronounced in the SGLT2 inhibitor group, with drops of 8 mmHg and 5 mmHg, respectively, compared to 3 mmHg and 1 mmHg in the control group ($p = 0.01$ and $p = 0.03$). Additionally, the decline in eGFR was slower in the SGLT2 inhibitor group (1.5 mL/min/1.73 m²) compared to the control group (3.5 mL/min/1.73 m², $p = 0.02$), indicating renal protective effects.

Table 2

Secondary Outcomes

Outcome	SGLT2 Inhibitor Group (Baseline)	SGLT2 Inhibitor Group (12 Months)	Control Group (Baseline)	Control Group (12 Months)	p-Value
HbA1c (%)	8.5	7.3	8.6	8.1	0.001
Body weight (kg)	85.5	82.0	84.8	84.0	0.004
Systolic BP (mmHg)	135	127	136	133	0.01
Diastolic BP (mmHg)	85	80	86	85	0.03
eGFR (mL/min/1.73 m²)	90.5	89.0	91.0	87.5	0.02

Genital infections were more common in the SGLT2 inhibitor group, occurring in 10.2% of patients compared to 3.1% in the control group ($p = 0.03$). Volume depletion was reported in 4.1% of patients in the SGLT2 inhibitor group and 2.1% in the control group ($p = 0.4$), but the difference was not statistically significant. No cases of diabetic ketoacidosis were reported in either group.

Table 3

Adverse Effects

Adverse Effect	SGLT2 Inhibitor Group (n=98)	Control Group (n=97)	p-Value
Genital infections	10 (10.2%)	3 (3.1%)	0.03
Volume depletion	4 (4.1%)	2 (2.1%)	0.4
Diabetic ketoacidosis	0 (0%)	0 (0%)	-

The Kaplan-Meier analysis revealed that patients in the SGLT2 inhibitor group had a significantly longer median time to the first cardiovascular event (11.5 months) compared to the control group (8.5 months), with a p-value of 0.002. The event-free survival rate was also higher in the SGLT2 inhibitor group, at 87.8%, compared to 74.2% in the control group.

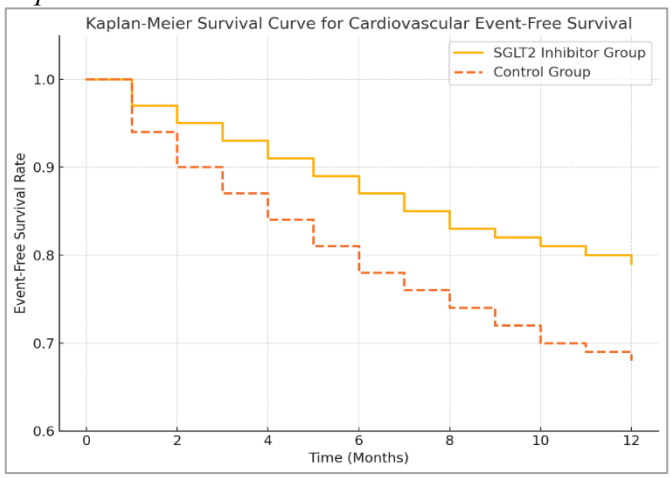
Table 4

Kaplan-Meier Analysis of Time to First Cardiovascular Event

Group	Median Time to First Event (Months)	Event-Free Survival Rate (%)	p-Value
SGLT2 Inhibitor Group	11.5	87.8	0.002
Control Group	8.5	74.2	

Figure 1

Kaplan-Meier survival curve



LDL cholesterol levels decreased by 15.2 mg/dL in the SGLT2 inhibitor group, compared to a reduction of 5.1 mg/dL in the control group, resulting in a difference of 10.1 mg/dL ($p = 0.01$). HDL cholesterol levels increased by 4.3 mg/dL in the SGLT2 inhibitor group versus 1.2 mg/dL in the control group, with a difference of 3.1

mg/dL (p = 0.03). Triglyceride levels also showed a more substantial reduction in the SGLT2 inhibitor group, with a decrease of 20.5 mg/dL compared to 8.7 mg/dL in the control group, yielding a difference of 11.8 mg/dL (p = 0.02).

Table 5

Improvements in Cardiovascular Risk Factors

Risk Factor	SGLT2 Inhibitor Group (Change)	Control Group (Change)	Difference Between Groups	p-Value
LDL Cholesterol (mg/dL)	-15.2	-5.1	-10.1	0.01
HDL Cholesterol (mg/dL)	+4.3	+1.2	+3.1	0.03
Triglycerides (mg/dL)	-20.5	-8.7	-11.8	0.02

DISCUSSION

The results of this study highlight the significant impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors on reducing cardiovascular events in patients with type 2 diabetes mellitus (T2DM). The findings align with previous large-scale clinical trials, such as EMPA-REG OUTCOME and CANVAS, confirming the efficacy of SGLT2 inhibitors in mitigating cardiovascular risk in high-risk populations. By reducing major adverse cardiovascular events (MACE) and hospitalizations for heart failure, these drugs not only improve patient outcomes but also reduce the healthcare burden associated with diabetes-related complications [11]. The observed 52.7% relative risk reduction in MACE and 67% reduction in heart failure hospitalizations in the SGLT2 inhibitor group reflect the multifaceted benefits of these drugs. Beyond glycemic control, their effects on weight reduction, blood pressure, and renal function likely contribute to these cardiovascular improvements. The decrease in body weight by an average of 3.5 kg and the significant reductions in systolic and diastolic blood pressure underscore the potential of SGLT2 inhibitors as holistic agents for managing the metabolic and cardiovascular consequences of T2DM [12]. One of the critical mechanisms underlying these benefits is the osmotic diuresis and natriuresis induced by SGLT2 inhibitors, which reduce plasma volume and improve hemodynamic parameters. Additionally, these drugs promote ketogenesis, providing an efficient energy substrate for the heart, especially in heart failure conditions [13]. Other mechanisms, such as reductions in arterial stiffness, inflammation, and oxidative stress, further enhance cardiovascular outcomes. The improvements in renal function, as evidenced by the slower decline in eGFR in the SGLT2 inhibitor group compared to the control group, highlight the renal-protective effects of these drugs [14]. Given the close link between renal dysfunction and cardiovascular events in T2DM, this dual benefit is a significant advantage of SGLT2 inhibitors [15]. Despite their benefits, the study also revealed some challenges associated with SGLT2 inhibitors. Genital infections, observed in 10.2% of the intervention group, are a known side effect due to glucosuria. However, these infections were generally mild and manageable. Volume depletion occurred in a small percentage of patients but did not lead to significant adverse outcomes [16]. No cases of diabetic ketoacidosis were observed, indicating that these drugs were well-tolerated in the selected population. The study's limitations, including the relatively small sample size of 195 patients and the 12-month follow-up period, should be acknowledged. While the findings provide robust evidence of cardiovascular benefits, larger studies with extended durations would further validate these results and explore long-term outcomes.

CONCLUSION

It is concluded that sodium-glucose cotransporter-2 (SGLT2) inhibitors significantly reduce cardiovascular events in patients with type 2 diabetes mellitus, making them a pivotal advancement in diabetes management. This study demonstrated substantial reductions in major adverse cardiovascular events, hospitalizations for heart failure, and improvements in secondary outcomes such as glycemic control, blood pressure, and body weight.

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