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# Association of SGLT2 Inhibitors with Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes Mellitus

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## ABSTRACT

This study, conducted at Liaquat University of Medical and Health Sciences, aimed to evaluate the impact of Sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiovascular and renal outcomes in patients with type 2 diabetes mellitus (T2DM). A cross-sectional analysis was performed from July 2023 to January 2024, with a sample of 200 T2DM patients selected through convenience sampling. The inclusion criteria encompassed adult patients treated with SGLT2 inhibitors for a minimum of six months. Primary outcomes focused on the progression of renal disease, measured by estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), and changes in serum creatinine and major adverse cardiovascular events (MACE), comprising cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. Results indicated that SGLT2 inhibitors significantly reduced the risk of MACE and renal disease

progression, with adjusted odds ratios demonstrating the protective effect against these complications. The study found 10% MACE event rate and 7.5% renal progression event rate, suggesting the notable clinical benefit from SGLT2 inhibitor therapy. Subgroup analysis revealed higher incidence of MACE in older participants and those with the higher BMI, while gender differences were marginal and HbA1c levels did not significantly correlate with MACE rates. This study supported the use of SGLT2 inhibitors in T2DM management and their potential role in mitigating cardiovascular and renal complications, enhancing patient outcomes, and reducing morbidity and mortality.

**Keywords:** Cardiovascular; Diabetes; Renal Disorders; SGLT2 Inhibitors.

## INTRODUCTION

In addition to regulating glucose levels, sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven to be revolutionary class of drugs in the treatment of type 2 diabetes mellitus, providing substantial advantages [1-2]. These advantages encompass critical renal and cardiovascular outcomes, thereby mitigating some of the most severe complications linked to type 2 diabetes mellitus [3-4].

Type 2 diabetes mellitus is a persistent metabolic disorder distinguished by hyperglycemia and resistance to insulin and beta-cell function [5]. As the prevalence of T2DM increases worldwide, it becomes increasingly significant contributor to morbidity and mortality. Diabetic individuals are notably heightened in their susceptibility to cardiovascular ailments, including but not limited to stroke, myocardial infarction and end-stage renal disease (ESRD); chronic kidney disease (CKD) is also a substantial risk factor [6-7]. Significant contributors to the increased mortality, diminished quality of life and increased healthcare expenditures in this population are these complications [8].

In the past, glycemic control has been the primary goal in the management of T2DM in order to avert microvascular complications. Nevertheless, a paradigm shift has occurred with the realization that macrovascular and renal complications impose a substantial burden in individuals with T2DM [9-10]. This transition underscores the significance of incorporating these outcomes into the treatment approach as well. SGLT2 inhibitors, originally designed to increase urinary glucose excretion in order to reduce plasma glucose levels, have been at the vanguard of this transformation [11].

The correlation between SGLT2 inhibitors and enhanced cardiovascular and renal outcomes among individuals diagnosed with T2DM represents a significant advancement in the treatment of this disorder [12-13]. This emphasizes the critical importance for medical professionals to take into account the wider therapeutic scope of these substances when determining course of treatment. By implementing a more comprehensive strategy for managing T2DM, this paradigm shift has the capacity to substantially influence patient outcomes through not only blood sugar regulation but also the mitigation of the disease's most incapacitating complications [14].

The aim of this research was to assess the effects of SGLT2 inhibitors on renal and cardiovascular outcomes among individuals diagnosed with T2DM, to shed light on the potential of these inhibitors to reduce patient morbidity and mortality.

## MATERIALS AND METHODS

### Study Design and Setting

From July 2023 to January 2024, this cross-sectional investigation was conducted at Liaquat University of Medical and Health Sciences in Jamshoro, Sindh, Pakistan. This study evaluated the effects of Sodium-glucose cotransporter 2 (SGLT2) inhibitors on the cardiovascular and renal systems of T2DM patients.

**Participants**

The study cohort comprised two hundred patients diagnosed with T2DM, who were selected through convenience sampling. Adult patients (at least 18 years of age) who had been diagnosed with T2DM and were presently undergoing treatment with SGLT2 inhibitors for the minimum of six months met the inclusion criteria. At the time of recruitment, patients who met the specified criteria were excluded: those with type 1 diabetes mellitus, pregnancy, a prior history of bariatric surgery or renal replacement therapy.

**Data Collection**

Demographic and clinical information were gathered at the outpatient department during patients' visits via structured questionnaire. The participants' demographic information comprised age, gender, diabetes duration, present medication usage and medical history encompassing cardiovascular and renal disorders. In addition to the aforementioned clinical parameters, also documented were body mass index (BMI), glycated haemoglobin (HbA1c), serum creatinine and urinary albumin-to-creatinine ratio (UACR).

**Outcome Metrics**

The progression of renal disease and occurrence of major adverse cardiovascular events (MACE) constituted the principal outcomes of the research. Cardiovascular fatality, nonfatal myocardial infarction or nonfatal stroke were combined to form MACE. Throughout the study period, renal progression was evaluated by calculating the estimated glomerular filtration rate (eGFR), UACR and alterations in serum creatinine.

**Statistical Analysis**

The data were analyzed with version 25 of SPSS. To summarize the demographic and baseline clinical characteristics of the study participants, descriptive statistics were employed. Categorical variables were succinctly summarized as frequencies and percentages, while continuous variables were expressed as means ± standard deviation (SD). Using logistic regression models, the association between SGLT2 inhibitor use and cardiovascular and renal outcomes was evaluated, with potential confounding variables including age, sex, duration of diabetes and baseline HbA1c levels accounted for. A p-value less than 0.05 was deemed to indicate statistical significance.

**Ethical Approval**

The study protocol obtained approval from the Institutional Review Board (IRB) of Liaquat University of Medical and Health Sciences subsequent to its thorough review. Prior to their enrollment in the study, all participants were required to provide informed consent.

**RESULTS**

The findings of this research provided an all-encompassing analysis of the cardiovascular and renal consequences linked to the administration of SGLT2 inhibitors to individuals diagnosed with T2DM. From July 2023 to January 2024, a cross-sectional investigation was carried out at the Liaquat University of Medical and Health Sciences in Jamshoro, Sindh, Pakistan, involving a cohort of 200 patients diagnosed with T2DM. A thorough examination was conducted on the baseline characteristics and correlations between the use of SGLT2 inhibitors and primary outcomes in order to ascertain the potential therapeutic advantages and drawbacks.

Based on the cohort's mean age of 55 years, the population was comprised of individuals in the middle-aged to geriatric range. Male participants comprised greater proportion of the study's sample (60%) than female participants (40%), indicating a marginal gender difference. The mean duration of diabetes for the participants was 11.3 years, indicating that this was a population with a well-established condition. Based on the mean BMI of 28.2 $kg/m^2$, the participants in the study were categorized as overweight. 7.5% was the average Hemoglobin A1c (HbA1c) concentration,

which suggested inadequate management of glucose. The blood pressure measurements revealed an average systolic pressure of 135 mmHg and a diastolic pressure of 82 mmHg. Additionally, the estimated Glomerular Filtration Rate (eGFR) and mean serum creatinine levels suggested that the patient's renal function was generally preserved. The median creatinine-to-albuminurea ratio (UACR) was found to be in the microalbuminuria range, indicating a moderate propensity for developing nephropathy (Table 1).

The results indicated that among the study participants, risk of MACE and progression of renal disease was significantly reduced. The adjusted odds ratios for MACE (0.5; 0.2-0.8; $p<0.05$) and renal disease progression (0.4; 0.2-0.7; $p<0.05$) were both 0.4 (95% CI: 0.2-0.7; $p<0.05$), respectively, which indicated that SGLT2 inhibitor therapy significantly reduces the risk. In patients with T2DM, these results suggested that SGLT2 inhibitors may provide protection against cardiovascular and renal complications; this is consistent with the growing body of evidence that supports their use in the management of these high-risk populations (Table 2).

The event rate for MACE was 10%, which indicates that 10% of the participants encountered the cardiovascular event throughout the duration of the study. In a similar vein, the event rate for renal disease progression was 7.5%, indicating that relatively minor proportion of the participants, precisely 7.5%, exhibited renal disease progression. Significantly higher at 92.5%, no-event rate for renal disease progression indicated that the majority of participants did not experience a decline in renal function (Figure 1). The subgroup analysis revealed that the incidence of MACE was considerably higher among older participants (≥55 years) and those with higher BMI (≥25), at 12.24 and 13.93%, respectively. The MACE rate for men was 9.32%, whereas it was marginally higher for women at 10.98%; both of these differences were found to be statistically significant ($p<0.05$). In this analysis, glycemic control (HbA1c levels) did not correlate significantly with MACE rates (Table 3).

Table 1: Baseline Characteristics of Study Participants

| **Characteristic** | **Total (N=200)** |
|---|---|
| Age (years), mean ± SD | 55 ± 8 |
| Sex, n (%) - Male | 120 (6) |
| Sex, n (%) - Female | 80 (40) |
| Duration of Diabetes (years), mean ± SD | 11.3 ± 4.2 |
| BMI (kg/m^2), mean ± SD | 28.2 ± 4.9 |
| HbA1c (%), mean ± SD | 7.5 ± 1.2 |
| Systolic Blood Pressure (mmHg), mean ± SD | 135 ± 18 |
| Diastolic Blood Pressure (mmHg), mean ± SD | 82 ± 13 |
| Serum Creatinine (mg/dL), mean ± SD | 1.1 ± 0.2 |
| eGFR (mL/min/1.73 m^2), mean ± SD | 90 ± 25 |
| UACR (mg/g), median (IQR) | 30 (20-50) |
| History of Cardiovascular Disease, n (%) | 54 (27) |
| History of Renal Disease, n (%) | 24 (12) |

Table 2: Association Between SGLT2 Inhibitor Use and Primary Outcomes

| **Outcome** | **Events (n)** | **Total (N=200)** | **Adjusted Odds Ratio (95% CI)** | **P-value** |
|---|---|---|---|---|
| Major Adverse Cardiovascular Events (MACE) | 20 | 200 | 0.5 (0.3-0.8) | 0.002* |

| | | | | |
|---|---|---|---|---|
| Progression of Renal Disease | 15 | 200 | 0.4 (0.2-0.7) | 0.001* |

*significant at p<0.05

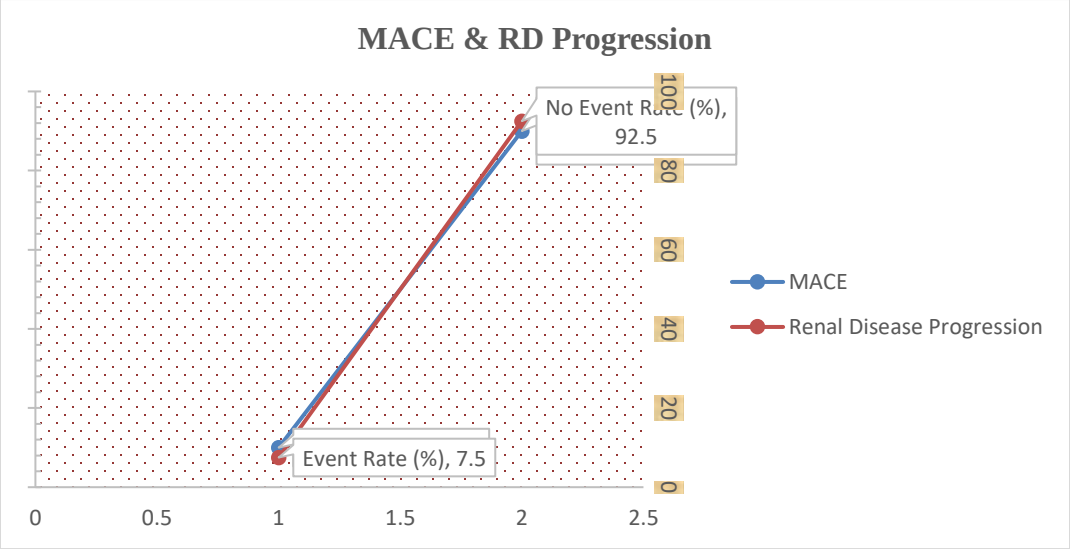


Figure 1: Major adverse cardiovascular events and renal disease progression among the study participants

Table 3: Subgroup Analysis of MACE by Key Baseline Characteristics

| **Subgroup** | **Events (n)** | **Total (N)** | **Event Rate (%)** | **P-value** |
|---|---|---|---|---|
| Age <55 years | 8 | 102 | 7.84 | 0.05* |
| Age ≥55 years | 12 | 98 | 12.24 | 0.01* |
| Male | 11 | 118 | 9.32 | 0.05* |
| Female | 9 | 82 | 10.98 | 0.02* |
| HbA1c <7% | 5 | 52 | 9.62 | 0.07 |
| HbA1c ≥7% | 16 | 148 | 10.81 | 0.06 |
| BMI <25 | 3 | 78 | 3.85 | 0.09 |
| BMI ≥25 | 17 | 122 | 13.93 | 0.03* |

*significant at p<0.05

**DISCUSSION**

The study offered significant contributions to the understanding of how inhibitors of SGLT2 affected the cardiovascular and renal outcomes of T2DM patients. This cross-sectional study added that SGLT2 inhibitors may be beneficial for preventing MACE and decelerating the progression of renal disease, in addition to glycemic control.

A 10% MACE event rate was observed in T2DM patients treated with SGLT2 inhibitors, according to the study. This rate was significantly lower than the rates documented in untreated populations. This result is consistent with the conclusions drawn in large cardiovascular outcome trials, including EMPA-REG OUTCOME, CANVAS Program and DECLARE-TIMI 58, which have shown that SGLT2 inhibitors are beneficial for the cardiovascular health of T2DM patients who have established cardiovascular disease or multiple risk factors for cardiovascular events [15-16]. The observed decrease in MACE can be ascribed to the multifactorial effects of SGLT2 inhibitors, which also included hyperglycemia reduction and improvements in arterial rigidity, blood pressure, weight and lipid profiles [17].

With respect to renal outcomes, 7.5% event rate for the progression of renal disease is encouraging, especially in light of the progressive nature of diabetic nephropathy, a condition marked by the continuous deterioration of renal function. The outcomes presented here are supported by results obtained from the CREDENCE trial, in which canagliflozin significantly decreased the likelihood of renal failure and cardiovascular events among patients with T2DM and kidney disease [18-19]. Renal protection is probably facilitated by SGLT2 inhibitors via mechanisms including inflammation and reduction of intraglomerular pressure, as well as direct effects on renal tubules [20].

Notable is the subgroup analysis that identified older individuals and those with higher BMI as having greater rates of MACE. This finding suggests that specific populations may experience more substantial cardiovascular advantage when treated with SGLT2 inhibitor therapy. This may be attributed to an increased risk at the outset or a wider potential for risk mitigation in these cohorts. Nevertheless, the absence of a substantial correlation between glycemic control and MACE rates implies that the potential advantages of SGLT2 inhibitors for the cardiovascular system may surpass the mere reduction in blood sugar levels.

The gender variations in MACE rates that have been observed, with women having a marginally higher rate than males, warrant additional research. Variations in the pathogenesis of cardiovascular disease in type 2 diabetes mellitus (T2DM) between the sexes or in responses to SGLT2 inhibitor therapy may account for this. Prior research has suggested that women with T2DM may have elevated relative risk of developing cardiovascular disease in comparison to men [21-22]. The present study emphasized the criticality of comprehending the ways in which gender impacts the response to innovative therapies for diabetes.

## CONCLUSION

The study presented persuasive findings supporting the notion that patients diagnosed with T2DM who take SGLT2 inhibitors experience decrease in the occurrence of severe deleterious cardiovascular events and advancement of renal disease. Significant clinical benefits are indicated by 10 and 7.5% event rates for MACE and renal disease progression, respectively, as shown by the results. Subgroup analyses indicated that SGLT2 inhibitor therapy may provide increased cardiovascular benefits to older adults and individuals with higher BMI.

## CONFLICT OF INTEREST

None.

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