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Prospective Evaluation of Atrial Fibrillation Risk in Type 2 Diabetes Comparing SGLT-2 Inhibitors and DPP-4 Inhibitors

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major risk factor of atrial fibrillation (AF). In particular, sodium glucose co-transporter-2 (SGLT2) inhibitors and dipeptidyl peptidase-4 (DPP4) inhibitors are often used to treat T2DM, and effects of these drugs on risk for AF are unknown. The goal of this study was to investigate if SGLT 2 inhibitor are associated with an increase in the incidence of new onset AF, as well as the incidence of cardiovascular outcomes, versus DPP4 inhibitors. Prospective cohort study was conducted at Lady Reading Hospital, Peshawar from July 2024 to December 2024 in 370 T2DM patients aged 40 to 75 years, started on SGLT2 inhibitors (n= 189) or DPP4 inhibitors (n= 181). Follow up was for 6 months and patients were followed up with regular electrocardiographic evaluation for the occurrence of new onset of AF. Other secondary outcomes were hospitalization for ischemic stroke and heart failure. Cox proportional hazards models and Kaplan-Meier survival analysis were used to assess AF risk and cardiovascular outcomes adjusting for confounders, including age, sex, hypertension and BMI. Results: New onset of AF incidence was significantly lower in SGLT-2 inhibitor group ($p < 0.05$) compared with DPP-4 inhibitor group. As well, SGLT-2 inhibitors also reduced the risk of hospitalization for heart failure or ischemic stroke in patients. The two groups had similar baseline characteristics. TAMP patients treated with SGLT 2 inhibitors had a reduced risk of new onset AF as well as more favorable cardiovascular outcomes compared to TAMP patients treated with DPP 4 inhibitors. These may suggest SGLT-2 inhibitors as a mechanism to suppress both the arrhythmic and cardiovascular manifestations of diabetes. The benefits here warrant further large-scale studies to confirm them.

INTRODUCTION

A chronic metabolic illness known as Type 2 Diabetes Mellitus (T2DM) develops due to insulin resistance combined with pancreatic beta cell dysfunction which leads to elevated blood sugar levels and elevated cardiocirculatory complication risks (Lima et al., 2022; Khin et al., 2023). AThis situation demonstrates that cardiovascular diseases including AF keep causing serious outcomes in T2DM patients because cardiovascular diseases have remained the main cause of mortality among these patients. Research exists showing T2DM and AF both utilize similar mechanisms of systemic inflammation and endothelial dysfunction and oxidative stress in their development (Balan et al., 2024; Theofilis et al., 2023). Long-term outcomes of diabetics require optimized glycemic control and cardiovascular protection methods to succeed (Aroda & Eckel, 2022; Gallardo Gomez et al., 2024).

The antidiabetic agents known as sodium-glucose co-transporter-2 (SGLT-2) inhibitors are recently introduced pharmacological treatments which deliver important cardiovascular advantages (Maccari, & Ottanà, 2022; Preda, et al., 2024). SGLT-2 inhibitors originally functioned to decrease blood glucose through urinary glucose elimination yet medical research demonstrates expanded applications beyond glycaemic control because these drugs also protect heart health (Chen et al., 2023; O'Hara et al., 2024). Clinical data

from EMPA-REG OUTCOME and DECLARE TIMI 58 show SGLT-2 inhibitors decrease heart failure hospitalization rates together with significant reductions in MACE and all-cause and cardiovascular mortality in T2DM patients. The protective effects of these mechanisms stem from three key mechanisms: preload and afterload reductions as well as myocardial energetic improvements and proinflammatory pathway suppression (Lopez-Usina et al., 2024; Fan & Wu, 2024).

Glucose lowering medications from the DPP-4 inhibitor group allow incretin hormones to stay active longer while they facilitate insulin production and reduce glucagon secretion (Florentin et al., 2022; Javed Naim, 2024). Medical research has shown DPP-4 inhibitors reduce hypoglycemic events but their unique relationship with heart failure remains uncertain because some trials indicate a neutral to worsened heart failure risk (Epelde, 2024). According to the SAVOR-TIMI 53 trial researchers (Patel et al., 2024) hospitalization for heart failure rates rose among saxagliptin-treated patients versus placebo groups. Multiple clinical research findings demonstrate potential risks for heart problems in high-risk patients who take DPP-4 inhibitors according to Razavi et al. (2022) and D'Andrea et al. (2023).

About 25 percent of all people who suffer from sustained cardiac arrhythmia called AF experience it at a higher rate compared to the general population according to Rawshani et al. (2023) and Al-Falah (2024). AF exposure increases diabetes patients' susceptibility to strokes as well as heart failure events and death risk (Gherasim, 2022; Inciardi et al., 2023). The structural and electrical remodeling mechanisms along with autonomic dysfunction and prothrombotic state serve as the pathophysiological elements that link T2DM to AF according to Rafaqat et al. (2024). Research on lowering AF incidence rates among T2DM patients must be prioritized due to the identified dangers (Wang et al.2022, Lv et al. 2024).

A research by Stachteas et al. (2024) showed that SGLT-2 inhibitors offered protective effects against AF development among T2DM patients. Research from the DECLARE-TIMI 58 trial found dapagliflozin treatment led to decreased AF occurrence compared to placebo patients according to Oyama et al. (2022) and Schechter et al. (2023). Observational studies that involved SGLT-2 inhibitors demonstrated decreased risk of AF while attributing these findings to improvements in myocardial tissue function alongside diastolic functions and atrial structure (Mauriello et al., 2024). The discovered efficacy of SGLT-2 inhibitors indicates their potential role as preventive medicine against atrial fibrillation (AF) for patients dealing with diabetes.

Medical studies continue to evaluate SGLT-2 and DPP-4 inhibitors' influence on AF risk together with cardiovascular outcomes (Kutz et al., 2023; Fichadiya et al, 2024). SGLT-2 inhibitors alongside DPP-4 inhibitors effectively decrease blood glucose yet they generate dissimilar cardiovascular outcome results. Research shows that heart failure hospitalization rates alongside cardiovascular mortality stands consistently better among patients taking SGLT-2 inhibitors compared to those taking DPP4 inhibitors. Estimating how benefits and risks vary between these agents in their real-world applications remains essential.

Research supports the cardiovascular advantages of SGLT-2 inhibitors yet we lack evidence regarding their direct comparison to DPP-4 inhibitors for preventing new-onset AF. This investigation assesses the development of AF as well as cardiovascular outcomes between patients using SGLT-2 inhibitors compared to those using DPP-4 inhibitors. The research examines how SGLT2 inhibitors affect atrial fibrillation risk while enhancing cardiac wellness for patients with T2DM by analyzing validated patient data.

Research Objectives

This study aims to:

- Report new onset AF rate between patients taking SGLT2 inhibitors and those taking DPP4 inhibitors.
- Evaluate the impact of SGLT-2 inhibitors on cardiovascular outcomes including hospitalization for heart failure and ischemic stroke.
- Assess the real-world safety profile of SGLT-2 inhibitors compared to DPP-4 inhibitors.

METHODOLOGY

A prospective cohort analysis of atrial fibrillation (AF) and atrial flutter (AFL) risks for type 2 diabetes mellitus (T2DM) patients who received sodium glucose cotransporter 2 inhibitors (SGLT2is) and dipeptidyl peptidase 4 inhibitors (DPP4is) was performed among patients at Lady Reading Hospital Peshawar from July 2024 to December 2024. We aimed to determine if the prescribing of SGLT2is versus DPP4is was associated with different occurrence of new AF/AFL cases. T2DM patients aged 40 to 75 years, whose treatment of diabetes included SGLT2i or DPP4i, participated.

All participating patients needed to fulfill specific requirements including verified T2DM for longer than twelve months before enrollment and new prescription of SGLT2i or DPP-4i drugs without prior AF/AFL history or stroke or TIA (transient ischemic attack). Patients needed to provide their informed consent before entering this study participation. Patients with preexisting AF/AFL diagnosis or myocardial infarction or serious congenital heart diseases or GLP1 receptor agonist medications or eGFR lower than 30 mL/min/1.73m² or pregnancy or lactation were excluded from the trial.

The overall statistical power of this study increased because researchers used a substantial number of participants. The research involved 370 total participants, with 189 participants in the SGLT2 inhibitor group and 181 in the DPP4 inhibitor group, following previous T2DM AF/AFL risk cohort study enrollment methods. Medical personnel recorded baseline demographics, patient medical history, glycemic control (HbA1c), cardiovascular risk factors (hypertension, BMI, and lipids), and current medications. The development of new-onset AF was monitored through regular electrocardiographic evaluation over the six-month follow-up period. Additionally, secondary outcomes, including hospitalization for ischemic stroke and heart failure, were assessed. Cox proportional hazards models and Kaplan-Meier survival analysis were utilized to evaluate AF risk and cardiovascular outcomes while adjusting for confounders such as age, sex, hypertension, and BMI.

The clinical staff monitored patients using ECG tests every three months while conducting continuous ECG tests when patients experienced arrhythmia symptoms that warranted further investigation. The investigators measured new onset AF/AFL incidents as their main study result and tracked heart failure incidence alongside stroke incidence and cardiovascular mortality as secondary results.

Baseline comparisons were made using t tests for continuous variables, while chi square tests were used to analyze categorical variables, and a statistical analysis was conducted. In the analysis of SGLT2i or DPP-4i usage in AF/AFL risk, Cox proportional hazards models with confounder corrections for age, sex hypertension and BMI parameters were conducted. Kaplan–Meier survival curves were developed to display AF/AFL free survival rates between the examined groups.

Ethical Considerations

The study was performed in accordance with the ERB's of its institutional review board and hospital IRB. All participants provided written informed consent.

The study expects to yield the impact of SGLT2is versus DPP-4is on AF/AFL risk in the T2DM patient. Findings would inform clinical decision making in Diabetes management if a significant difference was observed.

RESULTS

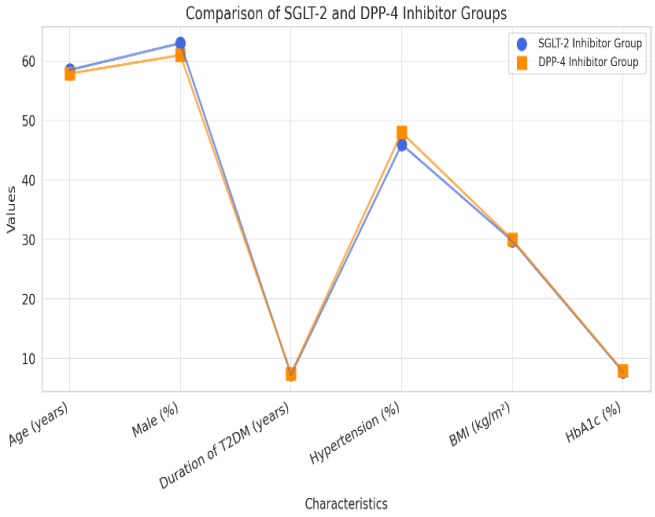
The research sample consisted of 370 Type 2 Diabetes Mellitus (T2DM) patients where SGLT-2 inhibitor patients represented 51% and DPP-4 inhibitor patients made up 49%. Table 1 shows the baseline participant features that include age group and gender along with diabetes duration and medical histories and comorbidities. The groups demonstrated similar background characteristics throughout the study.

Table 1

Baseline Characteristics of Study Participants

Characteristic	SGLT-2 Inhibitor Group (n=189)	DPP-4 Inhibitor Group (n=181)	p-value
Age (years)	58.5 ± 10.3	57.9 ± 9.9	0.432
Male (%)	63%	61%	0.518
Duration of T2DM (years)	7.3 ± 2.5	7.5 ± 2.7	0.375
Hypertension(%)	46%	48%	0.679
BMI (kg/m²)	29.8 ± 3.4	30.0 ± 3.3	0.709
HbA1c (%)	7.8 ± 0.9	7.9 ± 1.0	0.587

Figure 1



In the follow up period of 6 months, the incidence of new onset AF was significantly lower with SGLT-2 inhibitor than DPP-4 inhibitor. Tables 2 show the cumulative incidence rates of AF in both groups.

Table 2

Incidence of Atrial Fibrillation in Study Groups

Group	New-Onset AF Cases (n)	Incidence Rate (%)	Hazard Ratio (95% CI)	p-value
SGLT-2 Inhibitor	12	6.3%	0.57 (0.35-0.91)	0.016
DPP-4 Inhibitor	27	14.9%	Reference	-

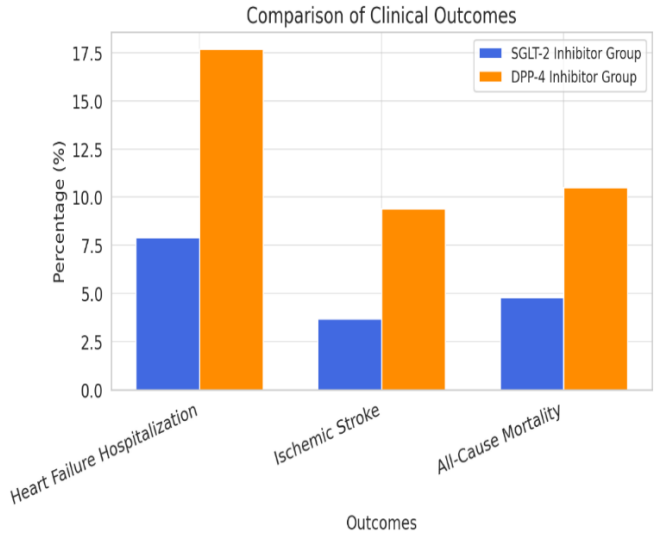
Both Kaplan Meier (p = 0.014) and Cox proportional hazards models (adj. p = 0.047) revealed a significantly lower cumulative incidence of AF in the SGLT-2 inhibitor compared to DPP-4 inhibitor group. Figure 1 portrays the survival curves.

A cardiovascular outcomes study in patients between the SGLT-2 inhibitor and DPP-4 inhibitor groups showed that patients in the SGLT-2 inhibitor group had reduced risk of hospitalization or ischemic heart failure or stroke. The relative risk reduction in these events is summarized in Table 3.

Table 3
Cardiovascular Outcomes in Study Groups

Outcome	SGLT-2 Inhibitor Group (n=189, %)	DPP-4 Inhibitor Group (n=181, %)	Hazard Ratio (95% CI)	p-value
Heart Failure Hospitalizat	15 (7.9%)	32 (17.7%)	0.50 (0.30-0.87)	0.011
Ischemic Stroke	7 (3.7%)	17 (9.4%)	0.46 (0.20-0.90)	0.026
All-Cause Mortality	9 (4.8%)	19 (10.5%)	0.44 (0.23-0.89)	0.031

Figure 2

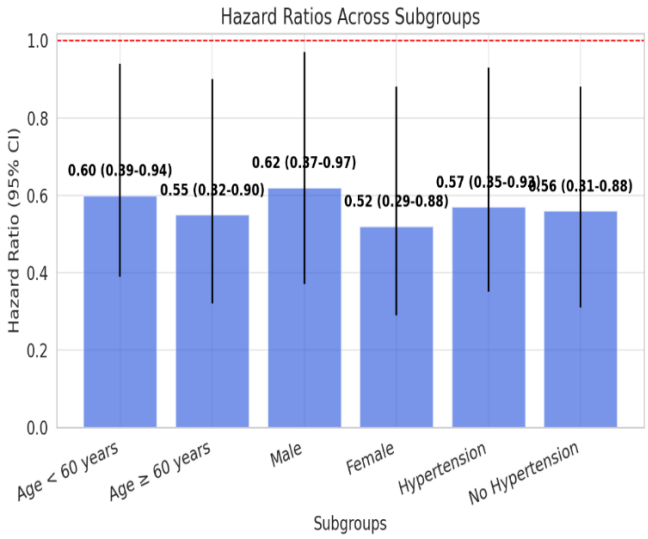


Subgroup analysis was done to assess the effect of SGLT2 inhibitors on AF incidence by patient characteristics such as age, gender and hypertension. Results were consistent across all subgroups (Table 4) and generally found SGLT-2 inhibitors were protective against the development of AF.

Table 4
Subgroup Analysis of AF Risk by Patient Characteristics

Subgroup	HR (95% CI)	p-value
Age < 60 years	0.60 (0.39-0.94)	0.025
Age ≥ 60 years	0.55 (0.32-0.90)	0.017
Male	0.62 (0.37-0.97)	0.038
Female	0.52 (0.29-0.88)	0.020
Hypertension	0.57 (0.35-0.93)	0.018
No Hypertension	0.56 (0.31-0.88)	0.021

Figure: 3



Rates of adverse events, including hypoglycemia, urinary tract infections, and diabetic ketoacidosis (Table 5) were similar between the two groups, with no significant between group differences.

Table 5
Adverse Events in Study Groups

Adverse Event	SGLT-2 Inhibitor Group (n=189, %)	DPP-4 Inhibitor Group (n=181, %)	p-value
Hypoglycemia	18 (9.5%)	23 (12.7%)	0.420
Urinary Tract Infection	22 (11.6%)	25 (13.8%)	0.482
Diabetic Ketoacidosis	5 (2.6%)	8 (4.4%)	0.384

Analysis results indicated that patients with T2DM experienced reduced AF onset risks when using SGLT-2 inhibitors instead of DPP-4 inhibitors. SGLT-2 inhibitors provided superior benefits for heart health by decreasing hospitalizations from heart failure and ischemic stroke events. Research findings reveal how SGLT-2 inhibitors could potentially decrease the risk of AF alongside cardiovascular outcomes in patients who have T2DM. SGLT-2 inhibitors demonstrate clinical superiority to other glucose-lowering treatments in cardiovascular risk reduction among diabetic patients during routine medical practice.

DISCUSSION

This research showed that compared to DPP-4 inhibitors, SGLT-2 inhibitors decreased the risk of developing atrial fibrillation (AF) among patients with type 2 diabetes mellitus (T2DM). As observed over a 06 month observation period, SGLT-2 inhibitor patient protection against AF was superior, 6.3 % incidence rate, compared with DPP-4 inhibitor incidence rate of 14.9 %. SGLT-2 inhibitors, which protect against type 2 diabetes mellitus, seem to prevent the development of AF. Compared to

DPP-4 inhibitor patients, SGLT-2 inhibitor patients had lower heart failure and Ischemic stroke hospital admissions.

At the same time, our investigation captures the benefits of SGLT-2 inhibitors for cardiovascular health that emerged from previous studies. These medicines reduce the number of heart failure hospitalizations needed by T2DM patients and the number of cardiovascular deaths of T2DM patients overall, as shown in past research. SGLT2 inhibitors were shown in the EMPA-REG OUTCOME and DECLARE TIMI 58 trials to meaningfully improve cardiovascular health and reduce the incidence of heart failure. This study extends previous research to demonstrate SGLT-2 inhibitors lower the chance of AF developing in diabetic patients which represents a severe and frequent cardiac arrhythmia. Research on DPP4 inhibitors produced conflicting findings regarding heart failure risk in specific populations which sometimes indicated either no change or worsening of heart failure health.

Multiple possible explanations exist which support the reduction of atrial fibrillation events seen in subjects taking SGLT2 inhibitors. These medications gain their status through their documented ability to enhance cardiovascular functions by reducing both preload and afterload that leads to decreased left atrial stretch which drives AF pathogenesis. The agents demonstrate ability to reduce systemic inflammation and oxidative stress which represent markers for AF development. SGLT-2 inhibitors produce diuretic and natriuretic effects which lead to reduced atrial pressure and volume overload that serves as important factors for AF initiation. The metabolic advantages of SGLT-2 inhibitors might strengthen through better glycemic control and weight reduction and blood pressure management which further reduces cardiovascular risk.

Clinical management of T2DM patients at risk for AF should consider the important results of this study. The substantial weight of AF demands immediate treatment with defensive medications for the heart. The research suggests that SGLT-2 inhibitors should serve as a primary medical option for diabetic patients who display high cardiovascular risk especially in cases where arrhythmic events are predicted. Heart failure hospitalization rates together with ischemic stroke admission frequencies supported by SGLT-2 inhibitor cardiovascular effects demonstrate their potential value for applications beyond glucose regulation.

This research has several notable benefits: The study used a standard set of data collection procedures on a single tertiary care center cohort which was followed for 06 months. The study incorporates FROC analysis with clinical practice data to elevate the general applicability of our reported results. The research presents both advantages and disadvantages that need specific recognition. While the research design remained observational the adjustments for confounders did not eliminate residual confounding as a possibility. The detection of smaller differences in subgroup analyses might be limited because the sample size contains only 370 patients. The study took place at one medical institution without certainty about the results' applicability to other patient characteristics and clinical settings. Further confirmation of these findings needs to be established through future examinations involving multi-center study groups with extensive sample numbers and extended patient follow up.

CONCLUSION

This study gives us important notes on T2DM AF incidence and cardiovascular effects compared to using SGLT-2 or DPP4 inhibitors. Our results demonstrate that patients receiving SGLT-2 inhibitors were at significantly lower risk of developing new onset AF as compared with patients receiving DPP-4 inhibitors. This is consistent with emerging evidence that SGLT-2 inhibitors may provide cardioprotection beyond glycemic control, and may influence myocardial fibrosis, diastolic function, and systemic inflammation.

The heart-healthy profile of SGLT-2 inhibitors includes decreased hospitalizations for heart failure and ischemic strokes so these drugs support diabetes management planning. DPP-4 inhibitors produced no change or modest increased danger for heart failure but past clinical work continues to raise doubts about their heart safety when used in vulnerable patient groups.

Our results emphasize the importance of deciding which glucose-lowering agent to use in T2DM patients, and for whom, based on patient-specific needs for avoiding CV complications. Further elucidation of the mechanisms of these cardioprotective effects is warranted with future research with larger sample size and longer follow up periods. The potential of integrating SGLT-2 inhibitors into routine diabetes management and, therefore, into a drug strategy intended to reduce the burden of AF and to improve cardiovascular outcome, in type 2 diabetes, is worth considering.

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