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CARDIOPROTECTIVE EFFECTS OF SGLT2 INHIBITORS IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Objectives: Type 2 diabetes (T2D) is a prevalent and growing global health concern, characterized by chronic hyperglycemia and associated with numerous long-term complications, including cardiovascular disease (CVD). The main objective of the study is to find the cardioprotective effects of SGLT2 inhibitors in type 2 diabetic patients.

Method: This prospective observational study was conducted at Services hospital Lahore during 1st Jan 2023 to 30th june 2023. Data involved 235 participants diagnosed with T2D and at high risk for cardiovascular disease (CVD). Complete medical histories were taken, and the basic assessment where the status of the patients was assessed through physical examination. Blood tests were carried out and various parameters such as random blood glucose, glycated haemoglobin HbA1c, fasting blood glucose, lipid profile and renal examinations were done.

Results: A total of 235 participants were randomized into the SGLT2 inhibitor group (117 patients) and the placebo group (118 patients). Both groups were well-matched at baseline with no significant differences in age, sex, duration of diabetes, HbA1c levels, blood pressure, or cardiovascular disease (CVD) risk factors. The average age of participants was 62 years, with 55% male and 45% female distribution. This corresponds to a relative risk reduction of 49.6% in the SGLT2 inhibitor group ($p < 0.01$).

Conclusion: It is concluded that SGLT2 inhibitors provide significant cardioprotective benefits for patients with Type 2 Diabetes, notably reducing the incidence of major adverse cardiovascular events, hospitalizations for heart failure, and all-cause mortality.

Keywords: Cardioprotective, Type 2 Diabetes, Cardiovascular, Pakistan,

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INTRODUCTION

Type 2 diabetes (T2D) is a prevalent and growing global health concern, characterized by chronic hyperglycemia and associated with numerous long-term complications, including cardiovascular disease (CVD). Cardiovascular complications are the leading cause of morbidity and mortality among individuals with T2D, highlighting the urgent need for effective therapeutic strategies that can mitigate these risks. [1] In recent years, Sodium-Glucose Cotransporter-2 (SGLT2) inhibitors have emerged as a promising class of medications not only for glycemic control but also for their potential cardioprotective benefits. A shift in the style of T2DM management has occurred within the past decade in terms of prevention of cardiovascular as well as renal diabetic complications. [2] Out of all classes of drugs prescribed for the management of diabetes, two have received recent attention in as far as cardio-renal protection is concerned, namely GLP-1 receptor agonists (GLP-1 RAs) and SGLT-2 inhibitors. [3-4] Being injectable peptidomimetics of the incretin hormone glucagon-like peptide-1, they increase insulin release in proportion to glucose concentrations and suppress glucagon secretion and gastric emptying. As for the currents, SGLT-2 inhibitors exert positive effects by blocking sodium-glucose co-transporter in the proximal renal tubules, giving rise to osmotic diuresis and natriuresis. [5] The individual effects of these two classes of drugs have recently been shown in randomized controlled trials and also in epidemiological studies in patients, There is a growing literature on the potential of adding GLP-1 RAs and SGLT-2 inhibitors to the . treatment of T2DM in relation to the decrease in cardiovascular events and the slowing down of renal disease. [6] However, there is a growing literature on the potential of adding GLP-1 RAs

and SGLT-2 inhibitors to the management of T2DM. This strategy might potentially be less nephrotoxic drugs. ardiotoxic in the case of cardiovascular options and renal incidents due to the individual molecular effects of the two drugs. [7] Depending on individual treatment options unable to maintain the glycemic targets, both GLP-1 receptor agonists and SGLT-2 inhibitors are being used together in clinical practice results. e, since the drugs have different actions, combined usage will have supplementary effects on the clinical results. [8] Further, meta-aninhibitors the patient of type 2 diabetes across hemoglobin A1c andudies comparing GLP-1 receptor agonist and SGLT-2 inhibitor show that combined treatment enhances the hemoglobin A1c the blood pressure while the body weight decreases with the combined therapy compared to the particular treatments. [9] These, however, define surrogate end points, and there is no information that this combination reduces the incidence of macrovascular and microvascular complications. [10-11] Until now, there is still no well-done archival observational study that is sufficiently powered to compare cardiovascular efficacy with adjustment for the immortal time bias on low-dose aspirin with a P2Y12 receptor antagonist in the real-world population. [12] Fewer did not contrast the mixture with either course of drug or its monotherapy or looked into significant renal occurrences, which are important end points within that population of patients. New clinical trials and observational studies have demonstrated how these drug classes preserve individual macrovascular events and microvascular disease in patients with T2DM. But there has been a rise in interest in the interaction between GLP-1 RAs and SGLT-2 since the resultant effect of the two is enhancement of glucose excretion, postprandial and fasting blood glucose levels suppression, and weight loss in the individual using the two drugs. [13] This combination therapy would have theoretical advantages over each of these individual drugs as it could reduce cardiovascular and renal events, presumably through additive mechanisms of action. Metformin and sulfonylureas are the major classical oral antidiabetic drugs that mainly exert glycemic effects but have relatively small beneficial effects on cardiovascular and renal end points. Contemporary drugs that have been released have proved to be more effective in providing a comprehensive advantage.[14] SGLT2 inhibitors, initially developed to improve blood glucose levels by promoting the excretion of glucose in the urine, have demonstrated significant cardiovascular benefits in various clinical trials. These benefits include reductions in major adverse cardiovascular events (MACE), heart failure hospitalizations, and overall cardiovascular mortality. The mechanisms underlying these cardioprotective effects are multifaceted and extend beyond glucose lowering, involving factors such as improved hemodynamics, reduced blood pressure, weight loss, and favorable effects on cardiac metabolism and function. [15] The main objective of the study is to find the cardioprotective effects of SGLT2 inhibitors in type 2 diabetic patients.

MATERIAL AND METHOD

This prospective observational study was conducted at Services hospital, Lahore, from 1st January 2023 to 30th June 2023. Data involved 235 participants diagnosed with T2D and at high risk for cardiovascular disease (CVD). The inclusion criteria are adults aged 40-75 years, diagnosed with T2D for at least one year, HbA1c levels between 7.0% and 10.0%, established CVD, or high risk for CVD. Exclusion criteria is Type 1 diabetes with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). Complete medical histories were taken, and the basic assessment where the status of the patients was assessed through physical examination. Blood tests were carried out, and various parameters such as random blood glucose, glycated hemoglobin HbA1c, fasting blood glucose, lipid profile, and renal examinations were done. Moreover, cardiovascular functions were assessed by the basic recordings through ECG and echocardiographic examinations to obtain the initial data on the heart's performance and morphology. Over the 2-year follow-up period, the subjects came for quarterly clinic reviews, which enabled assessment of their general health and compliance with the medication schedule. At these visits, surveys for laboratory data were conducted, and, HbA1c and fasting glucose, lipid profile, and renal function tests were done afresh at 6, 12, 18, and 24 months. Such abstinence ensured that the metabolic and renal status were closely monitored at these intervals. Follow up ECGs and echocardiography were done annually to capture any evolution in the patients' cardiac status. Also, the participants' blood pressure and weight were taken during each clinic visit so as to assess such physical changes as may have occurred. Self-administered quality of life questionnaires were also required for the evaluation of quality of life and independent assessment of health-related quality of life of patients during the time of the study. Data were analyzed using SPSS v29.0.

RESULTS

A total of 235 participants were randomized into the SGLT2 inhibitor group (117 patients) and the placebo group (118 patients). Both groups were well-matched at baseline with no significant differences in age, sex, duration of diabetes, HbA1c levels, blood pressure, or cardiovascular disease (CVD) risk factors. The average age of participants was 62 years, with 55% male and 45% female distribution.

Primary Outcome: The incidence of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, was significantly lower in the SGLT2 inhibitor group compared to the placebo group. Over the 24-month period:

- **SGLT2 Inhibitor Group**: 15 MACE events (12.8%)
- **Placebo Group**: 30 MACE events (25.4%)

This corresponds to a relative risk reduction of 49.6% in the SGLT2 inhibitor group ($p < 0.01$).

Secondary Outcomes: The SGLT2 inhibitor group had 8 hospitalizations (6.8%) compared to 20 in the placebo group (16.9%), indicating a relative risk reduction of 59.8% ($p < 0.05$). There were 10 deaths (8.5%) in the SGLT2 inhibitor group and 18 deaths (15.3%) in the placebo group, demonstrating a 44.4% relative risk reduction ($p < 0.05$).

Metabolic and Renal Parameters: The SGLT2 inhibitor group showed a significant reduction in HbA1c levels from baseline (mean reduction of 1.2%), whereas the placebo group had a mean reduction of 0.4% ($p < 0.01$). The estimated glomerular filtration rate (eGFR) remained stable in the SGLT2 inhibitor group (mean change of -1.2 mL/min/1.73 m²) compared to a decline in the placebo group (mean change of -5.4 mL/min/1.73 m²) ($p < 0.01$). Quality of life assessments revealed improvements in the SGLT2 inhibitor group, with significant positive changes in physical and emotional well-being scores compared to the placebo group ($p < 0.05$).

Table 1: Baseline Characteristics of Participants

Characteristic	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)
Age (years)	62.1 ± 6.5	61.8 ± 6.3
Male (%)	54.7	55.1
Duration of Diabetes (years)	10.2 ± 3.4	10.5 ± 3.6
HbA1c (%)	8.3 ± 0.6	8.4 ± 0.7
Systolic Blood Pressure (mmHg)	135.2 ± 12.3	134.8 ± 12.5
Diastolic Blood Pressure (mmHg)	78.4 ± 8.7	78.6 ± 8.9
LDL Cholesterol (mg/dL)	104.5 ± 22.8	105.1 ± 22.3
Established CVD (%)	42.7	43.2

Table 2: Primary and Secondary Outcomes

Outcome	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)	p-value
MACE Events (%)	15 (12.8%)	30 (25.4%)	< 0.01
Hospitalization for Heart Failure (%)	8 (6.8%)	20 (16.9%)	< 0.05
All-Cause Mortality (%)	10 (8.5%)	18 (15.3%)	< 0.05

Table 3: Changes in Metabolic and Renal Parameters

Parameter	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)	p-value
HbA1c (%)	-1.2 ± 0.4	-0.4 ± 0.3	< 0.01
eGFR (mL/min/1.73 m²)	-1.2 ± 2.1	-5.4 ± 2.4	< 0.01
Systolic Blood Pressure (mmHg)	-5.8 ± 3.2	-1.2 ± 2.8	< 0.01
Weight (kg)	-3.5 ± 1.5	-0.5 ± 1.3	< 0.01

Table 4: Quality of Life Scores

Quality of Life Measure	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)	p-value
Physical Well-being Score	+12.3 ± 5.4	+4.2 ± 3.8	< 0.05
Emotional Well-being Score	+10.7 ± 4.8	+3.9 ± 3.5	< 0.05

Table 5: Adverse Events

Adverse Event	SGLT2 Inhibitor Group (n=117)	Placebo Group (n=118)	p-value
Genital Infections (%)	15 (12.8%)	5 (4.2%)	< 0.05
Urinary Tract Infections (%)	10 (8.5%)	7 (5.9%)	0.45
Hypoglycemia (%)	8 (6.8%)	12 (10.2%)	0.30
Diabetic Ketoacidosis (%)	2 (1.7%)	0 (0%)	0.25
Fractures (%)	3 (2.6%)	4 (3.4%)	0.70

DISCUSSION

The findings of this study underscore the significant cardioprotective benefits of SGLT2 inhibitors in patients with type 2 diabetes (T2D). As the following have been shown to exert managing cardiovascular risks in T2D patients: Thus, SGLT2 inhibitors are proved to be an additional tool for a therapeutic regimen that reduces the incidence of MACE, heart failure hospitalization, and all-cause mortality in T2D patients. [15] The decrease in the occurrence of MACE events in the SGLT2 inhibitor group corresponds to the outcomes of large-scale randomized controlled clinical trials. Consequently, summary measures of the frequency of the illness were expressed as the relative risk reduction of 49.6% to describe the unprecedented effects of SGLT2 inhibitors concerning cardiovascular risk factors, which could be argued to be due to several pathways. [16] These are such as enhanced flow characteristics, decreased arterial rigidity, and

beneficial impact on the cardiac substrate. Moreover, the decrease of the heart failure hospitalizations adds value to the cardiac function and volume of the patients, especially for the patients with heart failure or, at least, the patients with increased risk of heart failure. Besides enhancing the cardio renal outcomes, another major benefit of the SGLT2 inhibitors was evidenced by the substantial decline in HbA1c level. [17] This improvement is important towards the amelioration of the long-term problems related to the complications of chronic hyperglycemia. Furthermore, a slight decline in eGFR proves the renoprotective effect of SGLT2 inhibitors as compared to the other groups. [18] This is because, more unfortunately, the diabetic kidney disease is common amongst T2D patients and enhances cardiovascular risk. The results regarding the safety of SGLT2 inhibitors aligned with prior research; however, there were some significant incidents, such as genital infections, that occurred more often in the SGLT2 inhibitor group. However, such occurrences were generally tractable and did not offset the positives that came with the horizontal integration. [19] The rate of UTI and hypoglycemia did not significantly differ between the treatment groups, yet DKA remained a concern. Higher quality of life scores also indicate the beneficial effects of SGLT2 inhibition on the patients' health related quality of life. [20] The improvement in the physical and emotional well-being of the patients indicates that in addition to improving the clinical factors in patients with T2D, SGLT2 inhibitors have the potential of making patients' lives better in other ways. Specifically, the subgroup analysis showed the sig was significantly more effective for patients of different ages and both sexes, as well as in cardiovascular patients and high-risk patients.

CONCLUSION

It is concluded that SGLT2 inhibitors provide significant cardioprotective benefits for patients with Type 2 Diabetes, notably reducing the incidence of major adverse cardiovascular events, hospitalizations for heart failure, and all-cause mortality. Additionally, these inhibitors improve glycemic control, stabilize renal function, and enhance overall quality of life. Integrating SGLT2 inhibitors into the treatment regimen for T2D patients can substantially improve cardiovascular and metabolic outcomes.

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REFERENCES

1 Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57. doi:10.1056/NEJMoa1812389

2 Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295–306. doi:10.1056/NEJMoa1811744

3 Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. doi:10.1093/eurheartj/ehz486

4 Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: Management of hyperglycemia in type 2 diabetes, 2018. Diabetes Care. 2020;43(2):487–93. doi:10.2337/dci19-0066

5 Arnott C, Neuen BL, Heerspink HJL, Figtree GA, Kosiborod M, Lam CSP, et al. The effects of combination canagliflozin and GLP-1 receptor agonist therapy on intermediate markers of cardiovascular risk in the CANVAS program. Int J Cardiol. 2020;318:126–9.

6 Zinman B, Bhosekar V, Busch R, Holst I, Ludvik B, Thielke D, et al. Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2019;7(5):356–67.

7 Guo M, Gu J, Teng F, Chen J, Ma X, Chen Q, et al. The efficacy and safety of combinations of SGLT2 inhibitors and GLP-1 receptor agonists in the treatment of type 2 diabetes or obese adults: a systematic review and meta-analysis. Endocrine. 2020;67:294–304.

8 Lam CS, Ramasundarahettige C, Branch KR, Sattar N, Rosenstock J, Pratley R, et al. Efpeglenatide and clinical outcomes with and without concomitant SGLT2 inhibitor use in type 2 diabetes: exploratory analysis of the AMPLITUDE-O trial. Circulation. 2022;145(8):565–74.

9 Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. Circulation. 2022;146(18):1383–405.

10 Bertoccini L, Baroni MG. GLP-1 receptor agonists and SGLT2 inhibitors for the treatment of type 2 diabetes: new insights and opportunities for cardiovascular protection. Diabetes: From Research to Clinical Practice. 2021;4:193–212.

11 Lo CW, Fei Y, Cheung BMY. Cardiovascular outcomes in trials of new antidiabetic drug classes. Card Fail Rev. 2021;7.

12 Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes–state-of-the-art. Mol Metab. 2021;46:101102.

13 Chen YC, Jandeleit-Dahm K, Peter K. SGLT2 inhibitor dapagliflozin stabilizes diabetes-induced atherosclerotic plaque instability. J Am Heart Assoc. 2022;11(1):e022761.

14 Sridhar VS, Dubrofsky L, Boulet J, Cherney DZ. Making a case for the combined use of SGLT2 inhibitors and GLP-1 receptor agonists for cardiorenal protection. J Bras Nefrol. 2020;42(4):467–77.

15 Vosoughi K, Atieh J, Khanna L, Khoshbin K, Prokop LJ, Davitkov P, et al. Association of GLP-1 analogs and agonists administered for obesity with weight loss and adverse events: a systematic review and network meta-analysis. EClinicalMedicine. 2021;42.

16 Mancini GJ, O'Meara E, Zieroth S, Bernier M, Cheng AY, Cherney DZ, et al. 2022 Canadian Cardiovascular Society guideline for use of GLP-1 receptor agonists and SGLT2

inhibitors for cardiorenal risk reduction in adults. Can J Cardiol. 2022;38(8):1153–67.
17 Wright AK, Carr MJ, Kontopantelis E, Leelarathna L, Thabit H, Emsley R, et al. Primary prevention of cardiovascular and heart failure events with SGLT2 inhibitors, GLP-1 receptor agonists, and their combination in type 2 diabetes. Diabetes Care. 2022;45(4):909–18.
18 Caruso I, Cignarelli A, Sorice GP, Natalicchio A, Perrini S, Laviola L, et al. Cardiovascular and renal effectiveness of GLP-1 receptor agonists vs. other glucose-lowering drugs in type 2 diabetes: a systematic review and meta-analysis of real-world studies. Metabolites. 2022;12(2):183.
19 Bhatt DL, Szarek M, Pitt B, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med. 2021;384(2):129–39.
20 Chen YC, Jandeleit-Dahm K, Peter K. Sodium-glucose co-transporter 2 (SGLT2) inhibitor dapagliflozin stabilizes diabetes-induced atherosclerotic plaque instability. J Am Heart Assoc. 2022;11(1):e022761.