Research Article

Cardiometabolic Effectiveness and Safety of SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus at High Cardiovascular Risk: A Prospective Observational Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is associated with substantial cardiovascular and renal morbidity. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as an important therapeutic class because their effects extend beyond glycemic control to include reductions in body weight, blood pressure, cardiovascular events, heart-failure outcomes and progression of chronic kidney disease.

Objective: To evaluate the cardiometabolic effectiveness and safety of SGLT2 inhibitors among adults with T2DM and cardiovascular risk factors in routine clinical practice.

Materials and Methods: This prospective observational study will include adults aged ≥18 years with established T2DM, at least one cardiovascular risk factor and a prescription for an SGLT2 inhibitor as part of routine clinical care. Participants will be evaluated at baseline, 12 weeks and 24 weeks. The primary outcome will be change in glycated hemoglobin (HbA1c) from baseline to 24 weeks. Secondary outcomes will include fasting blood glucose, postprandial blood glucose, body weight, body mass index, systolic and diastolic blood pressure, lipid profile, serum creatinine, estimated glomerular filtration rate, treatment persistence and adverse drug reactions.

Results: Patient-level study results are pending completion of recruitment, follow-up and statistical analysis. Results will be reported as changes in glycemic, anthropometric, cardiovascular, lipid and renal parameters and as frequencies of adverse drug reactions.

Conclusion: This prospective observational study is designed to provide real-world evidence regarding the effectiveness and safety of SGLT2 inhibitors among patients with T2DM at increased cardiovascular risk. The results may help characterize their clinical pharmacology and pharmacovigilance profile in a tertiary-care medical-college setting.

Keywords: SGLT2 inhibitors; type 2 diabetes mellitus; cardiovascular risk; HbA1c; renal function; pharmacovigilance; cardiometabolic outcomes.

Introduction

Type 2 diabetes mellitus is one of the major chronic metabolic disorders contributing to cardiovascular disease, heart failure, chronic kidney disease and premature mortality. Traditionally, treatment of diabetes focused predominantly on achieving glycemic targets. However, contemporary management increasingly emphasizes comprehensive cardiovascular and renal risk reduction in addition to lowering plasma glucose. Patients with diabetes frequently have accompanying hypertension, dyslipidemia, obesity, chronic kidney disease and established atherosclerotic cardiovascular disease, creating a substantial cumulative cardiometabolic burden.

Sodium-glucose cotransporter-2 inhibitors represent a relatively novel class of glucose-lowering agents with a mechanism independent of pancreatic insulin secretion. These drugs inhibit SGLT2 in the proximal renal tubule, thereby reducing glucose reabsorption and increasing urinary glucose excretion. The consequent glycosuria contributes to improved glycemic control and modest reductions in body weight. Osmotic diuresis and natriuresis may also contribute to reductions in arterial blood pressure. The uploaded study framework therefore considers not only HbA1c but also weight, BMI, blood pressure, lipid profile and renal parameters as important treatment outcomes.

Evidence supporting SGLT2 inhibitors has expanded substantially following large cardiovascular and renal outcome trials. The EMPA-REG OUTCOME trial demonstrated cardiovascular benefits of empagliflozin among patients with T2DM and established cardiovascular disease. Subsequent studies including CANVAS, CREDENCE and DECLARE-TIMI 58 extended the evidence base for canagliflozin and dapagliflozin. Trials such as DAPA-CKD and EMPA-KIDNEY further demonstrated important kidney-protective effects in populations with chronic kidney disease.

Zinman et al. reported that empagliflozin significantly improved cardiovascular outcomes in high-risk patients with T2DM.[2] Neal et al. similarly demonstrated cardiovascular and renal benefits associated with canagliflozin in the CANVAS program.[3] In patients with diabetic nephropathy, Perkovic et al. demonstrated significant renoprotective effects with canagliflozin in the CREDENCE

trial.[4] Wiviott et al., in DECLARE-TIMI 58, further established the cardiovascular safety and heart-failure benefits of dapagliflozin.[5]

The benefits of SGLT2 inhibition are not restricted to glycemic control. DAPA-CKD demonstrated that dapagliflozin reduced adverse kidney and cardiovascular outcomes in patients with chronic kidney disease.[6] Similarly, EMPA-KIDNEY demonstrated beneficial renal outcomes with empagliflozin across a broad spectrum of chronic kidney disease.[7] Meta-analytic evidence has further supported cardiovascular and renal benefits across the drug class.[8]

Despite robust randomized controlled trial evidence, real-world and prospective observational studies continue to be important. Clinical trials often enroll carefully selected patients under standardized conditions, whereas routine clinical practice involves greater heterogeneity in demographic characteristics, comorbidity, adherence, concomitant medication use and follow-up. Observational studies can therefore provide complementary information on effectiveness, persistence with treatment, changes in routinely measured laboratory variables and adverse drug reactions.

The present study was consequently planned to prospectively assess glycemic control, cardiometabolic parameters, renal function, treatment persistence and adverse drug reactions among adults with T2DM and cardiovascular risk factors receiving SGLT2 inhibitor therapy in routine clinical practice.

Materials And Methods

This study is designed as a prospective observational study to be conducted by the Department of Pharmacology in collaboration with the Department of Medicine/Diabetology at a tertiary-care medical college hospital. The overall study duration is expected to be approximately 12–18 months, including recruitment, 24-week follow-up and statistical analysis.

Study Population

Adult patients with established T2DM and at least one cardiovascular risk factor who receive an SGLT2 inhibitor as part of routine clinical care will be eligible. The decision to prescribe the drug, choice of individual SGLT2 inhibitor and dosage will remain entirely with the treating clinician because treatment allocation is not determined by the study protocol.

Potential SGLT2 inhibitors may include dapagliflozin, empagliflozin, canagliflozin and ertugliflozin, depending on local availability and prescribing patterns.

Inclusion Criteria

Participants will be eligible if they are ≥18 years of age, have an established diagnosis of T2DM, have been prescribed an SGLT2 inhibitor, and possess at least one cardiovascular risk factor including hypertension, dyslipidemia, overweight/obesity, established cardiovascular disease, chronic kidney disease or current smoking. Written informed consent will be mandatory.

Exclusion Criteria

Patients with type 1 diabetes mellitus, pregnancy or lactation, an acute medical emergency requiring immediate hospitalization at enrollment, a known contraindication to the prescribed SGLT2 inhibitor or inability/unwillingness to complete follow-up will be excluded.

Follow-Up Schedule

Participants will be evaluated at three predefined time points.

At baseline**,** demographic and clinical information, duration of diabetes, concomitant medications, HbA1c, fasting and postprandial blood glucose, body weight, BMI, blood pressure, lipid profile and renal function will be documented.

At 12 weeks**,** HbA1c, fasting/postprandial glucose, weight, BMI, blood pressure and renal function will be reassessed along with adverse events and treatment persistence.

At 24 weeks**,** HbA1c, fasting/postprandial glucose, anthropometric parameters, blood pressure, lipid profile and renal function will again be measured. Adverse drug reactions, discontinuation and treatment persistence will also be documented.

Outcome Measures

The **primary outcome** will be the change in HbA1c between baseline and 24 weeks.

Secondary outcomes will include changes in fasting and postprandial glucose, body weight, BMI, systolic blood pressure, diastolic blood pressure, total cholesterol, LDL-C, HDL-C, triglycerides, serum creatinine and eGFR. Treatment continuation, discontinuation and adverse drug reactions will also be evaluated.

Safety and Pharmacovigilance

All adverse events occurring during follow-up will be documented. Suspected adverse drug reactions may be categorized according to the WHO-UMC causality assessment system. Particular attention will be given to genital mycotic infection, urinary tract infection, volume depletion or hypotension, hypoglycemia when SGLT2 inhibitors are combined with insulin or insulin secretagogues and rare events such as euglycemic diabetic ketoacidosis.

Sample Size

The source protocol proposes a provisional recruitment target of approximately 120–125 participants**,** while appropriately noting that the final sample size should be obtained from a formal calculation based on expected HbA1c change, standard deviation, alpha error, statistical power and anticipated loss to follow-up.

Statistical Analysis

Data will be analyzed using appropriate statistical software. Continuous variables will be reported as mean±standard deviation for normally distributed data or median with interquartile range for skewed data. Categorical variables will be presented as frequencies and percentages.

Changes between baseline and follow-up may be evaluated using the paired Student's t-test or Wilcoxon signed-rank test depending on data distribution. Since assessments are planned at baseline, 12 weeks and 24 weeks, repeated-measures ANOVA or a suitable linear mixed-effects model may be used. Categorical variables may be compared using the chi-square test or Fisher's exact test.

Multivariable analyses may adjust for age, sex, baseline HbA1c, duration of diabetes, baseline renal function, established cardiovascular disease and concomitant glucose-lowering therapy. A two-sided P value <0.05 will be considered statistically significant.

Ethical Considerations

Institutional Ethics Committee approval should be obtained before recruitment. Written informed consent will be obtained from each participant, and confidentiality will be protected using coded study identifiers. Since this is an observational study, research participation will not alter clinically indicated treatment decisions.

Results

Table 1. Baseline demographic and clinical characteristics — hypothetical values

Characteristic	Study population (n=120)
Age, years	56.8 ± 9.4
Male, n (%)	72 (60.0%)
Female, n (%)	48 (40.0%)
Duration of diabetes, years	8.6 ± 5.1
Hypertension, n (%)	79 (65.8%)
Dyslipidemia, n (%)	68 (56.7%)
Overweight/obesity, n (%)	74 (61.7%)
Established CVD, n (%)	31 (25.8%)
Chronic kidney disease, n (%)	24 (20.0%)
Current smoking, n (%)	19 (15.8%)
Baseline HbA1c (%)	8.42 ± 1.12
Baseline eGFR (mL/min/1.73 m²)	78.6 ± 18.3

Table 2. Changes in glycemic parameters — hypothetical values

Parameter	Baseline	12 weeks	24 weeks	P value
HbA1c (%)	8.42 ± 1.12	7.78 ± 0.98	7.31 ± 0.91	<0.001
FBS (mg/dL)	168.5 ± 35.8	146.7 ± 29.6	132.4 ± 25.8	<0.001
PPBS (mg/dL)	246.8 ± 54.3	209.5 ± 44.7	187.6 ± 39.2	<0.001

The mean HbA1c decreased by approximately 1.11 percentage points over 24 weeks, while fasting and postprandial glucose also showed progressive reductions.

Table 3. Changes in weight, BMI and blood pressure — hypothetical values

Parameter	Baseline	12 weeks	24 weeks	P value
Weight (kg)	78.4 ± 11.2	76.9 ± 10.9	75.6 ± 10.7	<0.001
BMI (kg/m²)	29.1 ± 3.8	28.5 ± 3.7	28.0 ± 3.6	<0.001
SBP (mmHg)	138.7 ± 14.6	133.4 ± 12.8	130.8 ± 11.9	<0.001
DBP (mmHg)	84.6 ± 8.3	81.8 ± 7.6	80.2 ± 7.2	<0.001

Body weight decreased by about 2.8 kg and BMI by around 1.1 kg/m² over the 24-week follow-up. Both systolic and diastolic blood pressure also declined significantly.

Table 4. Lipid profile and renal function — hypothetical values

Parameter	Baseline	24 weeks	P value
Total cholesterol (mg/dL)	191.6 ± 38.5	181.4 ± 34.7	0.002
LDL-C (mg/dL)	112.8 ± 31.6	104.3 ± 28.9	0.004
HDL-C (mg/dL)	42.6 ± 8.7	44.1 ± 8.5	0.021
Triglycerides (mg/dL)	184.7 ± 65.4	164.9 ± 56.1	0.001
Serum creatinine (mg/dL)	1.06 ± 0.29	1.08 ± 0.30	0.184
eGFR (mL/min/1.73 m²)	78.6 ± 18.3	77.9 ± 18.1	0.421

The hypothetical data suggest modest improvement in lipid parameters, while renal function remains essentially stable over 24 weeks.

Table 5. Adverse drug reactions — hypothetical values

Adverse event	n	%
Genital mycotic infection	9	7.5
Urinary tract infection	6	5.0
Volume depletion/hypotension	5	4.2
Hypoglycemia	4	3.3
Euglycemic ketoacidosis	0	0
Drug discontinuation due to ADR	5	4.2
Other minor adverse events	3	2.5

Discussion

The present prospective observational study is intended to evaluate the effectiveness and tolerability of SGLT2 inhibitors in patients with T2DM and cardiovascular risk factors under real-world clinical conditions. Interpretation of the completed study should begin with the change in HbA1c because this represents the prespecified primary outcome. Subsequently, changes in body weight, BMI, blood pressure, lipid parameters, renal function and treatment persistence should be considered.

SGLT2 inhibitors lower plasma glucose by increasing urinary glucose excretion through inhibition of renal glucose reabsorption. Their glycemic effect is accompanied by caloric loss, which may contribute to modest body-weight reduction. The osmotic diuretic and natriuretic effects of these agents can also contribute to modest reductions in systolic and diastolic blood pressure. These effects make the class particularly relevant among patients with T2DM and coexisting cardiometabolic risk factors.

The cardiovascular significance of SGLT2 inhibition was strongly supported by EMPA-REG OUTCOME. Zinman et al.[2] demonstrated clinically important cardiovascular benefits with empagliflozin in patients with established cardiovascular disease. The CANVAS program subsequently demonstrated reductions in cardiovascular and renal events associated with canagliflozin.[3]

The renal benefits of SGLT2 inhibitors have also become increasingly important. CREDENCE demonstrated that canagliflozin reduced adverse renal outcomes in patients with T2DM and nephropathy.[4] DAPA-CKD subsequently established the kidney-protective benefits of dapagliflozin in chronic kidney disease,[6] while EMPA-KIDNEY demonstrated benefits of empagliflozin across a broader population with CKD.[7]

The findings of DECLARE-TIMI 58 also supported the role of dapagliflozin in cardiovascular risk management, particularly regarding heart-failure outcomes.[5] Meta-analyses incorporating several outcome trials suggest that SGLT2 inhibitors have broadly consistent cardiovascular and kidney benefits despite differences between individual drugs and patient populations.[8]

The eventual findings of the present study should nevertheless be interpreted cautiously. Any reduction in HbA1c, body weight or blood pressure observed during a 24-week observational period should not be interpreted as direct evidence of reduced myocardial infarction, stroke, cardiovascular mortality or hospitalization for heart failure. The study was not designed or powered to evaluate such clinical outcomes.

Similarly, changes in glycemic and metabolic parameters may partly reflect concomitant antihyperglycemic therapy, antihypertensive drugs, lipid-lowering therapy, changes in diet, physical activity or variations in treatment adherence. Multivariable statistical adjustment may reduce confounding but cannot eliminate it entirely in an observational design.

Safety findings will form an important part of the study. Genital mycotic infections and symptoms related to osmotic diuresis or volume depletion are clinically relevant adverse effects. Hypoglycemia is generally uncommon with SGLT2 inhibitor monotherapy but can become clinically important when the drugs are combined with insulin or insulin secretagogues. Euglycemic diabetic ketoacidosis is uncommon but potentially serious and therefore requires appropriate clinical awareness and pharmacovigilance.

A major strength of this study is its prospective real-world design, which permits systematic collection of metabolic measurements, renal parameters and adverse-event information. It may therefore complement randomized controlled trial evidence by describing the use of SGLT2 inhibitors in patients encountered in routine tertiary-care practice.

Limitations

The single-center design may restrict the generalizability of findings. The observational nature of the study prevents definitive causal inference, and concomitant antidiabetic and cardiovascular medications may confound measured metabolic outcomes. A 24-week follow-up period is also insufficient for reliable evaluation of major adverse cardiovascular events or cardiovascular mortality. Adherence may not be measured perfectly, and loss to follow-up could introduce attrition bias.

Conclusion

SGLT2 inhibitors constitute an important component of contemporary treatment of T2DM, particularly among patients with cardiovascular and kidney risk. The present prospective observational study will evaluate changes in HbA1c, glycemic indices, body weight, BMI, blood pressure, lipid profile, renal function, treatment persistence and adverse drug reactions over a 24-week period.

The final conclusions regarding effectiveness and safety should be based exclusively on the prospectively collected and statistically analyzed study data. Once those results are available, the manuscript can provide clinically useful real-world evidence regarding SGLT2 inhibitor therapy in patients with T2DM at increased cardiovascular risk.

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