Review Article

Exploring the Efficacy of Sotagliflozin on Heart and Kidney Health in Diabetic Patients: A Comprehensive Meta-Analysis

Greeshma S. S. Nayudu[1], Binit M. Benny[1], Grace Thomas[1], Maria A. Khan[1], Roopa S. Basutkar[2]

[1]Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, The Nilgiris, Tamil Nadu,
[2]Department of Pharmacy Practice, Nitte (Deemed to be University), NGSM Institute of Pharmaceutical Sciences (NGSMIPS), Mangalore, Karnataka, India

Abstract

Evidence for reducing cardiovascular and renal events with sotagliflozin is uncertain among type 2 diabetes mellitus (T2DM) patients. To gather more evidence, this meta-analysis assesses the beneficial effects of sotagliflozin, a dual sodium–glucose cotransporter 1 and 2 inhibitor, in reducing the cardiovascular and renal events in diabetic patients with or without chronic kidney disease (CKD). Scopus, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed were the databases used to search. The studies published from January 1, 2018, to January 30, 2022, were considered. The eligibility of studies was assessed independently. The data were collected in a modified Cochrane data extraction form. The included studies' quality was assessed with the Cochrane risk-of-bias tool. The quality of evidence for renal and cardiovascular outcomes was evaluated using GRADEpro software. The number of events of urgent visits to the hospital and requiring hospitalization was reduced (RR: 0.73; 95% CI: 0.69, 0.78; *P* value <0.00001). The mortality rate because of cardiovascular events was decreased with sotagliflozin (RR: 0.73; 95% CI: 0.67, 0.80; *P* value <0.00001). Patients taking sotagliflozin had a drastic decline in the number of deaths due to stroke and non-fatal myocardial infarction. Yet, there is no difference between the groups in terms of changes in mortality due to other causes or the glomerular filtration rate (GFR). Sotagliflozin demonstrated effectiveness in reducing the mortality rate related to heart failure and cardiovascular events when the dose was increased from 200 mg to 400 mg. Despite this, evidence is still needed to prove the renal protective action.

Keywords: Heart failure, renal disorders, sodium–glucose cotransporter 2 inhibitor, sotagliflozin, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that is a public concern globally.[1,2] A total of 642 million people will have diabetes mellitus (DM) by the end of 2040.[1,3] As per the 2015 Global Burden of Disease and Injuries, diabetes is the third global risk factor associated with disability-adjusted life years (DALYs).[3,4] Complications linked to diabetes will incur a cost of 90000 dollars toward the medical expenses per individual per year.[3,5-7]

Registry data indicate that about 25% to 40% of patients with diabetes have heart failure condition.[8,9] Diabetic patients end up having cardiovascular complications approximately 14.6 years ahead of those without diabetes.[3] Kidney failure is seen in roughly 25% of diabetic patients, and 10% of such cases result in fatalities.[1,3] Even with the utilization of antihyperglycemic, which has kidney-preserving properties in diabetic patients, there is an annual 9% increase in end-stage renal disease (ESRD).[5]

During the last few years, a new class of antidiabetic medications has emerged, including glucagon-like peptide receptor agonists (GLP-1RAs), dipeptidyl peptidase 4 inhibitors (DPP-4Is), and sodium/glucose cotransporter 2 inhibitors (SGLT-2Is). All the drugs are available starting in the years 2005, 2006, and 2013, respectively. These antidiabetic medications have been shown to have cardiovascular and renal protective properties. However, these newer-class antidiabetic medications are chosen as a second line of medications toward the management of atherosclerosis, cardiac insufficiency, and renal impairment in patients with diabetes.

Address for correspondence: Dr. Roopa S. Basutkar, Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Paneer, Deralakatte, Mangaluru, Karnataka - 575 018, India.
E-mail: roopasatyanarayan@gmail.com

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Until recently, metformin is the drug of choice with beneficial effects on cardiovascular outcomes in T2DM, along with a well-established safety profile and affordability,[4] whereas the recent class of antidiabetic medications such as DPP-4Is and GLP-1RAs reduces glycemic index and partially addresses the prevention of cardiovascular disease (CVD) risk.[10] The SGLT-2I class of antidiabetic medications, approved in 2013, reduces cardiac injury by regulating sympathetic tone and metabolism. SGLT-2Is also decrease the incidence of ESRD or requiring dialysis and lessen the glomerular filtration rate (GFR).[11,12] Currently approved SGLT-2I includes ertugliflozin, empagliflozin, dapagliflozin, canagliflozin, and sotagliflozin.[13-15] There is a need for more conclusive data to establish the reno and cardio-protective actions of the SGLT-2Is, despite many meta-analyses that have been published on SGLT-2Is.[16-19] The first drug approved, which has a dual inhibitor of SGLT-1 and SGLT-2, is sotagliflozin.[11] Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) and Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED), both trials provide support for the efficacy of sotagliflozin in addressing the reduced cardiovascular events and protective actions post-worsening heart failure among the patients with renal complications in diabetic patients.[20] The aim of this review was to appraise the beneficial impacts and safety outcomes of sotagliflozin from the large-scale randomized placebo-controlled studies among T2DM patients at risk of CVD with or without chronic kidney disease (CKD).

Methods

Preferred Reporting Items reported this meta-analysis for Systematic Reviews and Meta-Analyses (PRISMA) was used. The type of studies included in this meta-analysis are double-blinded randomized placebo-controlled trials (RCTs). CRD42022314906 is the International Prospective Register of Systematic Reviews registration number and is registered prospectively.

Eligibility criteria

Inclusion criteria

Patients of both genders, aged ≥18 years.

The studies included patients who had the risk of CVD and with or without CKD among T2DM (HbA1C ≥ 7).

Patients with estimated GFR (eGFR) of 25 to 60 ml/minute/body surface area of 1.73 m^2.

Exclusion criteria

The studies involved patients with hypertension and type 1 diabetes mellitus.

Patients who are treated with antidiabetic medications for a period of 12 weeks are found to be not stable with their blood sugar levels before enrollment.

Patients with planned surgery for coronary artery disease treatment.

Patients discovered with lower limb complications (infection, osteomyelitis, skin ulcer, and gangrene) and requiring treatment at the stage of randomization.

Types of interventions

- Intervention group: the sotagliflozin starting dose of 200 mg, later adjusted to 400 mg, and well-tolerated, and received medication from 9 to 16 months.
- Control group: unknown placebo.

Outcome measures

Primary outcome measures

1. Emergency visit to the hospital and requiring hospitalization due to cardiac failure.
2. Cardiovascular deaths.

Secondary outcome measures

1. Death resulting from other causes.
2. Death due to non-fatal stroke and non-fatal myocardial infarction.
3. Changes in eGFR from baselines to study conclusion.

Electronic search

GSS, BMB, GT, and MAK performed the search independently during the period January to March 2022 using keywords such as "Placebo, Chronic Renal Failure, Kidney Insufficiency, Stroke, Myocardial Failure, Diabetes Mellitus, Non-Insulin Dependent diabetes, Myocardial infraction, Cardiac Failure, Heart Decompensation, Heart Failure, Empagliflozin, Ertugliflozin, Canagliflozin, Dapagliflozin, and Decreased Mortality, Hospitalization Reduction, Mortality, Death, Sotagliflozin" with Title/Abstract, Medical Subject Headings (MeSH) terms. The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Scopus, and Google Scholar were databases used for searching the most relevant studies published between January 1, 2018, and January 30, 2022. A manual search was performed. We also explored looking into ongoing studies listed in the Clinical Trials Registry of India. All the retrieved studies were imported in Zotero, converted into "ris" format, and pooled into Rayyan. The papers published only in the English language were included in this review.

Data collection and analysis

GSS, BMB, GT, and MAK assessed all the studies independently and confirmed the eligible studies in Rayyan. The following details were extracted in the modified data extraction form of Cochrane CENTRAL: methods, details of the intervention, control, duration of the treatment, participants' details, outcome measures, the unit of measurement, general information and registration number of study ID, and randomization details. All the published studies included in the review have reported the outcomes in the form of occurrence of events, which is categorical data. RSB reviewed the retrieved data for completion and resolved any discrepancies.

Quality of studies' assessment

The reviewers (GT, GSS, MAK, and BMB) individually assessed the quality of the studies using the risk-of-bias tool for the domains: performance bias, selection bias, detection bias, reporting bias, attrition bias, and other biases, and were classified as "high, low, and unclear" with proper explanation and judgment. RSB resolved the discrepancy involving the judgment of bias found in the study. The risk-of-bias plot is created according to the judgment [Figure 2]. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) technique was used to grade the quality of evidence on the effect size of the treatment received by both groups using the GRADEpro software. A summary of the finding table is created, grading the certainty of the evidence as low to high.

The meta-analysis was conducted using the guidelines outlined in the Cochrane Handbook for Systematic Reviews to perform the analysis on the quantitative data of primary and secondary outcomes to assess the beneficial effects of sotagliflozin in T2DM patients to reduce cardiovascular risk among patients with T2DM with or without CKD. The ReviewManager 5.4.1 software was used to compute the analysis to obtain the risk ratio and a forest plot. All the data extracted were reported as the number of events in the included studies in the categorical data format. When the heterogeneity (I^2) fell below 50%, the fixed-effect model was applied. For values between 50% and 90% denoting substantial heterogeneity, the random-effect model was chosen. Sensitivity analysis is planned to be performed when the heterogeneity is more than 50%. To know about the publication bias, the funnel plot was used to determine.

Results

Search results

A total of 122 studies were found during the entire search, and 110 studies need to be excluded as these studies did not mention the cardiorenal outcomes. This led to 18 studies, and nine were removed as duplicates. Of nine studies, five could not be considered due to the unavailability of the data. The remaining four studies' full-text articles were reviewed, and the quantitative data were available to perform the analysis, as illustrated in Figure 1.

Characteristics of studies

RCTs were included in this review, which had outcomes mentioning the reduction of cardiovascular and renal outcomes among T2DM patients. The details of the adverse drug reactions that occurred during the study period with sotagliflozin and placebo are mentioned in the discussion. Table 1 mentions the details of the characteristics of the included studies in this review.

Risk-of-bias assessment

All the studies demonstrated a low risk associated with random sequence generation. As the included studies were double-blinded, the risk of blinding the study participants was low. The selective reporting for all the outcomes was low as all the included studies had performed the analysis on outcome data. The registration details of all the studies were available. The risk assessment of the studies is presented in Table 2 and Figure 2.

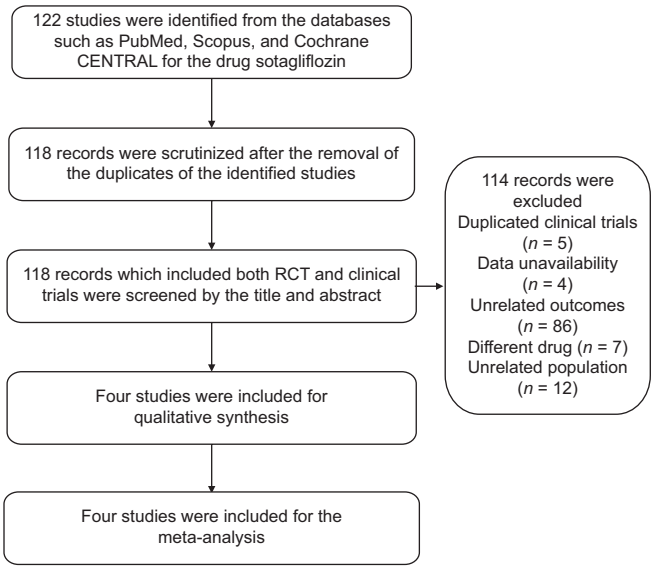

Figure 1: Flow diagram of the included studies in the review

Outcome measures

Primary outcome

Urgent hospital visits and requiring hospitalization due to heart failure

The details of the outcome were mentioned in all four studies; 905 patients with T2DM received sotagliflozin 200 mg, and the dose was increased to 400 mg subsequently. One thousand two hundred forty-three enrolled participants received a placebo. When the meta-analysis was performed, it was found that the study participants who received sotagliflozin had a reduced risk of getting hospitalized for heart failure (RR: 0.73; 95% CI: 0.69, 0.78; *P* value <0.00001). The heterogeneity among the included studies was on the higher side ($\chi^2 = 17.10$; $I^2 = 82\%$; $P = <0.0007$), and the sensitivity analysis was performed by removing the outcome details of the study by Szarek *et al*.[24] The heterogeneity was 0%. The analysis of this outcome is shown in Figure 3.

Death due to cardiovascular causes

Three of the included studies mentioned the number of deaths that occurred due to CVD. Two hundred seven study participants received sotagliflozin, and 233 received placebo. The participants who received sotagliflozin had reduced events of death due to CVD when compared to the patients who received placebo, and there was a considerable difference between the groups (RR: 0.73; 95% CI: 0.67, 0.80; *P* value <0.00001). There is no variation between the studies is more ($\chi^2 = 0.89$; $I^2 = 0\%$; $P = 0.35$). The details of the analysis are shown in Figure 4.

Table 1: Characteristic table of the included studies

Author, year	Study country	Study sample	Study design	Enrolled period	Population	Age	Gender	Interventions	Co-morbidities	Outcomes measured
Bhatt *et al.* 2020[21]	Multicenter—Eastern Europe, Western Europe, Latin America, North America, rest of the world	10,584	Phase 3, randomized, double-blind, placebo-controlled trial	Not mentioned	Adult patients with T2DM	Median age (IQR)—years 69 (63–74)	Females—44.9%, and males—55.1%	Intervention group: Sotagliflozin (200 mg once daily, with an increase to 400 mg once daily if unacceptable side effects did not occur) Control group: Placebo	CKD, and additional cardiovascular risk	Primary outcome measures: 1. Reduction of the number of hospitalization or urgent visit hospital due to heart failure in T2DM 2. Mortality due to cardiovascular diseases in T2DM patients with altered GFR. Secondary outcome measure: 1. Mortality due to other medical conditions 2. Mortality due to non-fatal myocardial infarction and non-fatal stroke 3. Improvement in GFR
Bhatt *et al.* 2021[22]	Multicenter—Eastern Europe, Western Europe, Latin America, North America, rest of the world	1222	Phase 3, double-blind, randomized, placebo-controlled trial	June 15, 2018, and the last on March 20, 2020.	Adult patients with T2DM	Median age (IQR)—years 70 (64–76)	Females—33.7%, and males—66.3%	Intervention group: 200 mg of sotagliflozin once daily (with a dose increase to 400 mg, depending on side effects) Control group: Placebo	Heart failure	Primary Outcome measures: 1. Reduction of the number of hospitalization or urgent visit hospital due to heart failure in T2DM 2. Mortality due to cardiovascular diseases in T2DM patients with altered GFR. Secondary outcome measure: 1. Mortality due to other medical conditions 2. Mortality due to non-fatal myocardial infarction and non-fatal stroke
Cherney *et al.* 2020[23]	92 centers in 15 countries in North and South America, Europe, and Asia	277	Phase 3, multicenter, randomized, double-blind, placebo-controlled study	August 2017 and December 2019	T2DM an HbA1c between ≥7% and <11%, and an eGFR between ≥15 and <30 mL/min/1.73 m^2	Age, years—67.3 (9.6)	Males: 48%, and females: 52%	Intervention group: Sotagliflozin 200 mg or sotagliflozin 400 mg once daily Control group: Placebo	Hypertension, renal failure, and heart failure	Primary outcome measures: 1. Reduction of the number of hospitalization or urgent visit hospital due to heart failure in T2DM 2. Mortality due to cardiovascular diseases in T2DM patients with altered GFR. Secondary outcome measures: 1. Mortality due to non-fatal myocardial infarction and non-fatal stroke. 2. Improvement in GFR

Contd...

Table 1: Contd..

Author, year	Study country	Study sample	Study design	Enrolled period	Population	Age	Gender	Interventions	Co-morbidities	Outcomes measured
Szarek *et al.* 2021[24]	306 sites in 32 countries	1222	Randomized, double-blind, placebo-controlled trial.	-	Patients with T2DM.	Median age (IQR), years—70 (64–76)	Females—33.8%, and males—66.2%	Intervention group: 200 mg of sotagliflozin once daily (with a possible dose increase to 400 mg) Control group: Matching placebo	Reduced or preserved ejection fraction who were recently hospitalized for worsening heart failure	Primary outcome measures: 1. Reduction of the number of hospitalization or urgent visit hospital due to heart failure in T2DM Secondary outcome measure: 1. Mortality due to other medical conditions

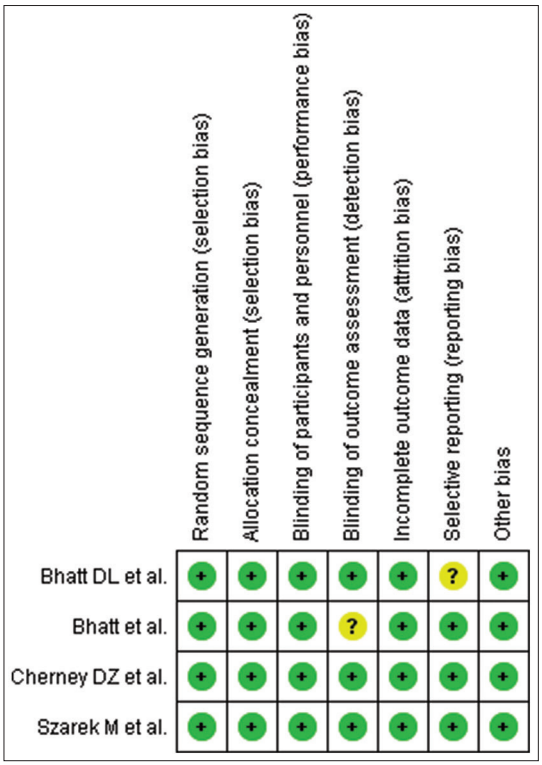

Figure 2: Risk-of-bias assessment of the included study

Secondary outcomes

Other causes of death

Three hundred seventy-five study participants received sotagliflozin, and 398 received placebo. Only three studies included in this review mentioned the details of other causes of death. In the two included studies, it was observed that there was a decrease in the number of event deaths due to other causes and in one of the included studies, the deaths due to other causes were similar in both groups. When the pooled analysis was performed, it was noticed that there was no change in the number of deaths due to other causes between the groups. Thus, it can be concluded that sotagliflozin will not prevent deaths due to other causes except for CVD conditions (RR: 0.95; 95% CI: 0.83, 1.08; *P* value = 0.42). There is not much variation between the included studies ($\chi^2 = 1.17$; $I^2 = 0\%$; $P = 0.56$). The analysis is shown in Figure S1.

Deaths due to non-fatal stroke and non-fatal myocardial infarction

In the pooled analysis, three studies were included. Seven hundred ninety-one study participants received sotagliflozin, and 1074 were given placebo. Deaths due to non-fatal stroke and non-fatal infarction were less among the high-risk cardiovascular patients who were on sotagliflozin, and there was an evident difference between the groups (RR: 0.74; 95% CI: 0.68, 0.80; *P* value <0.00001). Zero percent was the heterogeneity between studies ($\chi^2 = 0.42$; $I^2 = 0\%$; $P = 0.81$). Figure S2 depicts the analysis of this outcome.

Table 2: Risk-of-bias table

Bhatt *et al*. (2021)[22]		
Methods	Phase 3, randomized, double-blind, placebo-controlled trial	
Participants	Patients were eligible for enrollment in the study if they were 18 to 85 years of age and had been hospitalized because of the presence of signs and symptoms of heart failure and received treatment with intravenous diuretic therapy. Patients were also required to have received a previous diagnosis of T2DM before the index admission or to have laboratory evidence to support a diagnosis of T2DM during the index admission.	
Intervention	200 mg of sotagliflozin once daily (with a dose increase to 400 mg, depending on side effects) or placebo.	
Outcome	Sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure than placebo.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Randomization was conducted using interactive response technology.
Allocation concealment (selection bias)	Low risk	Stratification was conducted with respect to left ventricular ejection fraction less than 50% or greater than or equal to 50% or based geographical regions.
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded, both physicians and patient were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	The blinding of the outcome assessor was not mentioned.
Incomplete outcome data (attrition bias)	Low risk	Data of all the participants who have undergone randomization were included for analysis
Selective reporting (reporting bias)	Low risk	All outcomes' measures were analyzed and reported
Other biases	Low risk	No
Bhatt *et al*. (2020)[21]		
Methods	This was a phase 3, randomized, double-blind, placebo-controlled trial	
Participants	Persons 18 years of age or older with T2DM with a glycated hemoglobin level of 7% or higher, CKD (eGFR, 25 to 60 ml per minute per 1.73 m^2 of body surface area), and additional cardiovascular risk factors were enrolled.	
Intervention	Sotagliflozin (200 mg once daily, with an increase to 400 mg once daily if unacceptable side effects did not occur) with placebo	
Outcome	Sotagliflozin resulted in a lower risk of the composite of deaths from cardiovascular causes, hospitalizations for heart failure, and urgent visits for heart failure than placebo but was associated with adverse events.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to the groups in the ratio of 1:1.
Allocation concealment (selection bias)	Low risk	Stratification was conducted with respect to left ventricular ejection fraction less than or equal to 40% documented within the past year or hospitalization for heart failure during the previous 2 years and geographical regions.
Blinding of participants and personnel (performance bias)	Low risk	Double-blinded study. Both the physician and patient were blinded.
Blinding of outcome assessment (detection bias)	Unclear risk	The blinding of the outcome assessor was not mentioned.
Incomplete outcome data (attrition bias)	Low risk	All the participants randomized were analyzed in the study group
Selective reporting (reporting bias)	Low risk	All the mentioned primary and secondary outcomes were assessed
Other biases	Low risk	No
Cherney *et al*. (2021)[23]		
Methods	Phase 3, multicenter, randomized, double-blind, placebo-controlled study.	
Participants	Eligible patients were ≥18 years of age with diagnosed T2DM, an HbA1c between ≥7% and <11%, and an eGFR between ≥15 and <30 mL/min/1.73 m^2.	
Intervention	Treatment with placebo or sotagliflozin 200 mg, or sotagliflozin 400 mg, administered as two tablets once a day before breakfast.	
Outcome	Results with sotagliflozin at 52 weeks were encouraging in terms of sustained glycemic control, less rescue therapy for hyperglycemia, and a favorable safety profile. Renal function remained stable over time.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to the groups in the ratio of 1:1:1.

Contd...

Table 2: Contd...

Cherney *et al*. (2021)[23]		
Bias	**Author's judgment**	**Support for judgment**
Allocation concealment (selection bias)	Low risk	1:1:1 stratification was conducted
Blinding of participants and personnel (performance bias)	High risk	Double-blinded study. Both physicians and patients were blinded.
Blinding of outcome assessment (detection bias)	Low risk	Laboratory values, including fasting plasma glucose (FPG), HbA1c, and urinary glucose excretion (UGE) were determined by a central laboratory and masked to study sites and patients from randomization until study end
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis was conducted.
Selective reporting (reporting bias)	Low risk	All the mentioned primary and secondary outcomes were assessed
Other biases	Low risk	No
Szarek *et al*. (2021)[24]		
Methods	Randomized, double-blind, placebo-controlled trial	
Participants	Patients with T2DM and reduced or preserved ejection fraction who were recently hospitalized for worsening heart failure.	
Intervention	200 mg of sotagliflozin once daily (with a possible dose increase to 400 mg) or matching placebo.	
Outcome	Sotagliflozin also reduced the incidence of total hospitalizations primarily through a decrease in recurrent hospitalizations among a minority of patients.	
Bias	**Author's judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The patients were randomly assigned to the groups in the ratio of 1:1.
Allocation concealment (selection bias)	Low risk	Stratification was conducted with respect to left ventricular ejection fraction less than 50% or greater than or equal to 50% or based geographical regions
Blinding of participants and personnel (performance bias)	Low risk	Randomization was double-blinded; the patients, investigators, and other parties involved in the study were masked to the true treatment assignments.
Blinding of outcome assessment (detection bias)	Low risk	The outcome assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	All analyses were conducted according to intention to treat, including all patients and events from randomization to the common study end date
Selective reporting (reporting bias)	Low risk	All the mentioned primary and secondary outcomes were assessed
Other biases	Low risk	No

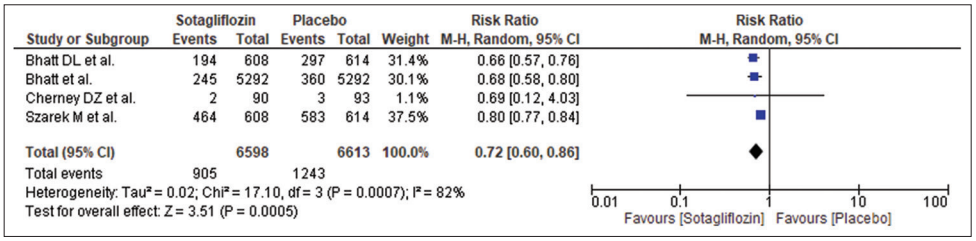

Figure 3: Forest plot showing the effect of sotagliflozin in the reduction of the number of hospitalization or urgent visit hospital due to heart failure in T2DM patients with altered GFR

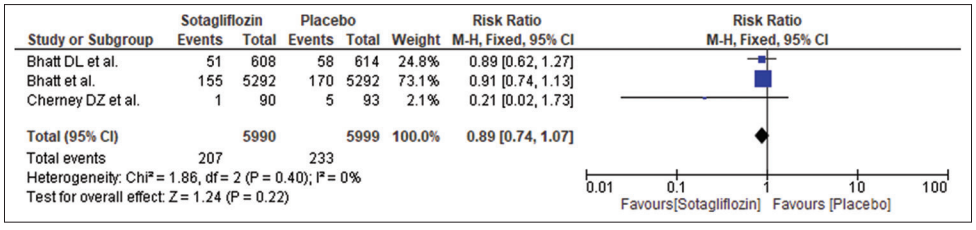

Figure 4: Forest plot showing the effect of sotagliflozin on mortality due to cardiovascular diseases in T2DM patients with altered GFR

Change in eGFR

The pooled analysis included two studies: 50 participants received sotagliflozin, and 63 received placebo. In each of the included studies among the high-risk CV patients, it was found that there was a change in eGFR or the same who were on sotagliflozin but the pooled analysis shows no significant difference between the patients who received sotagliflozin and placebo (RR: 0.80; 95% CI: 0.56, 1.15; *P* value = 0.23). There was 34% variation between the included studies (χ^2 = 1.53; I^2 = 34%; *P* = 0.22). The analysis is mentioned in Figure S3.

Assessment of publication bias

An asymmetrical funnel plot is seen concerning the outcome of death because of CV cause. There is a need for more studies to be conducted in the future to overcome the publication bias. Figures S4-S8 mention the details of the funnel plots for all the included outcomes.

Assessment of quality of evidence

The strength and recommendation of the evidence generated was assessed using the GRADEpro software. We found the evidence rating was moderate and high for the cardiovascular and renal outcomes, and these findings are presented in Table 3.

Discussion

Four RCTs were included in the pooled analysis. We found that the patients on sotagliflozin experienced a reduction in cardiovascular events. Still, there was no reduction in the number of deaths because of other causes compared to placebo. There is a need to conduct more studies to know the effects of sotagliflozin on renal outcomes as the drug is showing a very minimal effect on eGFR, and there is no difference between the groups. The findings from SOLOIST-WHF show a 33% reduction in CVD outcomes in patients who received sotagliflozin.[21,22] Szarek *et al*.[24] conducted a study wherein 3% of patients on sotagliflozin were found to be alive and were discharged from the hospital without any complications.

Li *et al*.[25] conducted a meta-analysis in patients with stage 3 and 4 renal impairment, and T2DM patients who received the SGLT-2I class of medications found to have reduced CV events. In the research study conducted by Bhattarai *et al*.,[26] there was a 33% reduction in cardiovascular events among the patients who received SGLT-2I. The primary outcomes of these two pooled analyses were similar to the findings mentioned by Lo KB *et al*., wherein the hospitalization for heart failure (HHF) was less among the patients who received SGLT-2I.[25-27]

Among the SGLT-2I, empagliflozin and ertugliflozin are similar in terms of selectivity. At the same time, dapagliflozin and canagliflozin have the least selectivity among the four drugs. The reduction of the risk of death due to cardiovascular events was less with empagliflozin; these results were similar in this meta-analysis.[17] Among the SGLT-2I, dapagliflozin and canagliflozin show a reduction in the occurrence of kidney disease in patients with stage 4. These findings were similar to the meta-analysis conducted by McGuire *et al*.[17] There is a requirement to conduct more studies to understand further the effects of sotagliflozin in reducing the progression of kidney disorders.

In the meta-analysis conducted by Li N *et al*.,[25] liraglutide, a GLP-1, reduces the serum creatinine levels and the ratio of urine albumin-to-creatinine ratio [UACR] to urinary albumin excretion rate [UAER] among T2DM patients, regardless of the nephropathy stage. The medications albiglutide and liraglutide were compared with other identical medications in reducing the major adverse cardiac event (MACE) among T2DM patients; however, none had a significant impact.

The safety endpoints were consistent across all included studies in this review. In the study performed by Bhatt *et al*.,[22] the discontinuation of medications due to serious adverse events was 3% for sotagliflozin and 2.8% for the placebo group. The most common adverse events reported during the study period were renal or urinary and renal disorders, hypotension, diarrhea, urinary tract infections, and genital mycotic infections. These adverse events' incidence was high among the patients who were on placebo except for renal or urinary disorders, urinary tract infection, and hypoglycemia, where the incidence of adverse effects was high for those who were on sotagliflozin. The same author conducted another study. In this study, diarrhea, genital mycotic infection, reduction in eGFR, ketoacidosis, and depletion of volume were the adverse events experienced by the patients who received sotagliflozin.[21] In the research conducted by Cherney *et al*.,[23] the overall occurrence of adverse events was 82.8% in patients administered a placebo. For those who received 200 mg of sotagliflozin, the adverse events reported were 86.2%, and for those who received 400 mg of sotagliflozin, 81.1% of the patients had adverse events. About 1.1%, 21.1%, and 1.1% had treatment-related severe adverse effects who received sotagliflozin 400 and 200 mg and placebo, respectively. About 13.3%, 10.6%, and 2.9% experienced adverse events that permanently led to discontinuation of treatment with sotagliflozin 400 and 200 mg and placebo, respectively. About 13.8% of the patients had renal effects and had received sotagliflozin.[28]

Avgerinos *et al*.[29] have conducted a systematic review and meta-analysis to assess the efficacy of sotagliflozin on glycemic control, that is, change in HbA1c from baseline, reduction in blood pressure levels, weight, and 15 safety outcomes, which is different from the objectives our meta-analysis. The meta-analysis by Avgerinos *et al*.[29] did not mention the efficiency of sotagliflozin on renal outcomes. Our meta-analysis indicates a reduction in the cardiovascular outcomes of the patient with altered eGFR and T2DM differing from the objectives of the meta-analysis conducted by Avgerinos *et al*.[29] Thus, the cardiorenal outcome findings of our meta-analysis are not comparable with the meta-analysis conducted by Avgerinos *et al*.[29]

This review demonstrates notable strength due to the inclusion of studies with a substantially larger sample size

Table 3: Summary of finding

Comparison of sotagliflozin with placebo for the reduction in risk for cardiovascular events in T2DM patients				
Patient or population: T2DM patients Intervention: sotagliflozin (200 mg and titrated to 400 mg) Comparison: placebo				
Outcomes	**Anticipated absolute effects* (95% CI)**		**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with placebo	**Risk with sotagliflozin group**		
Death from cardiovascular cause	39 per 1,000	35 per 1,000 (29 to 42)	11989 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Hospitalization and urgent visit for heart failure	188 per 1,000	135 per 1,000 (113 to 162)	13211 (4 RCTs)	⊕⊕⊕◯ Moderate[a]
Deaths from cardiovascular causes—non-fatal myocardial infarctions and non-fatal strokes	179 per 1,000	132 per 1,000 (122 to 143)	11987 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure—total no. of events	150 per 1,000	-6 per 1,000 (-7 to -4)	11806 (2 RCTs)	⊕⊕⊕◯ Moderate[a]
Deaths from any cause	61 per 1,000	58 per 1,000 (51 to 66)	13028 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
First occurrence of a sustained decrease of ≥50% in the eGFR from baseline for ≥30 days, long-term dialysis, renal transplantation, or sustained eGFR of	12 per 1,000	9 per 1,000 (7 to 13)	10767 (2 RCTs)	⊕⊕⊕⊕ High
*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect Explanations a. None of the included studies mentioned details of the content of the placebo.				

of 13211 participants. The robustness of the findings of this review is enhanced by the fact that the included studies were predominantly multicentric trials, suggesting that the results of the review may be widely applicable and generalizable. The findings of the pooled analysis can be reliable as the strength of evidence lies between moderate and high. All the primary outcomes were statistically significant and confirmed that sotagliflozin has substantial beneficial effects in lowering cardiovascular events among T2DM patients with or without CKD and altered eGFR. The limitation includes that none of the included studies mentioned the details of the contents of the placebo used. One of the studies included in the pooled analysis was prematurely terminated due to a lack of funds and the need to recruit the required sample size to complete the study, which might impact the overall findings of this meta-analysis. The data on the creatinine ratio, serum creatinine levels, and albumin were not available in the included studies of this review, and this had constraints in evaluating the effects of sotagliflozin on a decrease in the progression of renal disorders.

Conclusion

Sotagliflozin 200 mg and then increased to 400 mg had shown to have substantial beneficial effects in reducing urgent visits to the hospital and requiring hospitalization because of heart failure. Also, there was a decrease in the rate of mortality due to heart failure. Nonetheless, a statistically significant difference was not observed between the groups concerning improving the eGFR and reducing the rate of deaths attributed to other causes. Thus, there is a need to conduct larger RCTs to evaluate the role of sotagliflozin in reducing renal outcomes in T2DM with CVD risk. The findings of this meta-analysis are generalizable as all the studies included are conducted in different geographical regions.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Files

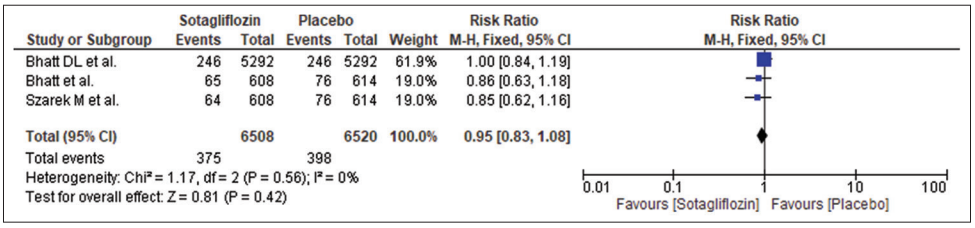

Figure S1: Forest plot showing the effect of Sotagliflozin on mortality due to other medical conditions in type-2 Diabetes Mellitus Patient with altered GFR

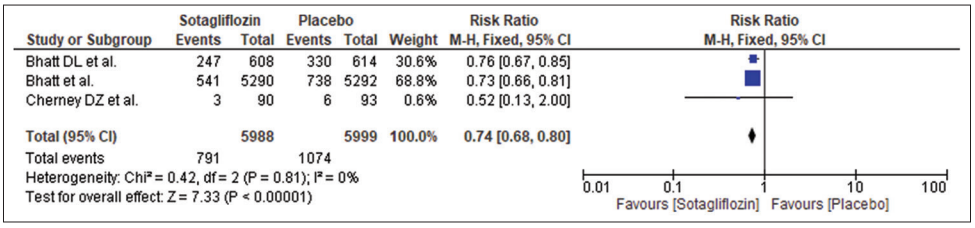

Figure S2: Forest plot showing the effect of Sotagliflozin on mortality due to non-fatal myocardial infarction and non-fatal stroke in type-2 Diabetes Mellitus Patient with altered GFR

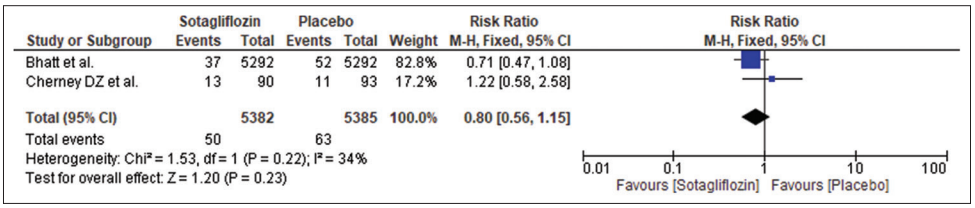

Figure S3: Forest plot showing improvement in Glomerular Filtration Rate in type-2 Diabetes Mellitus Patient with altered GFR, who received Sotagliflozin

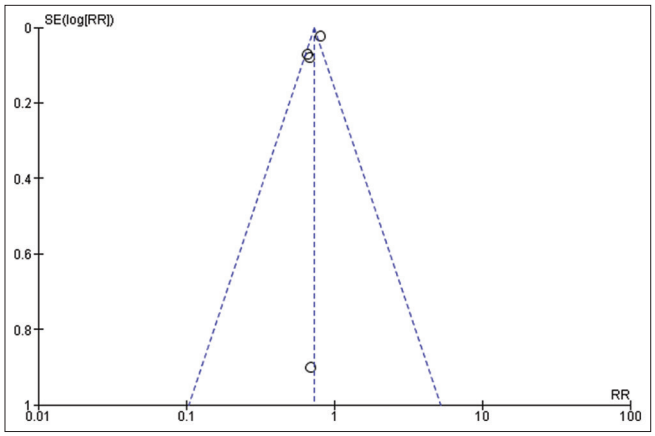

Figure S4: Funnel plot showing the effect of Sotagliflozin in the reduction of the number of hospitalization or urgent visit to the hospital due to Heart failure in type-2 Diabetes Mellitus patients with altered GFR

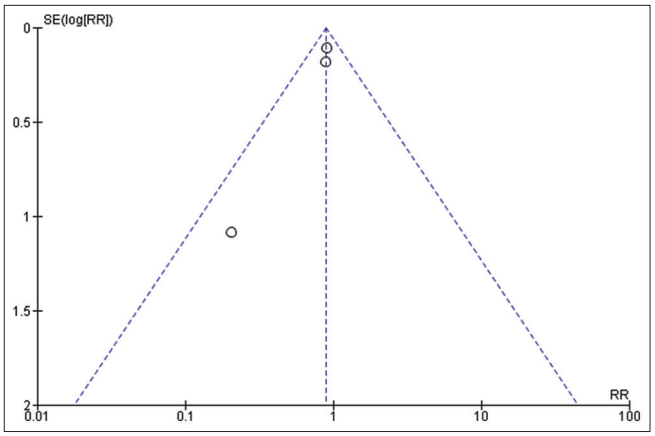

Figure S5: Funnel plot showing the effect of Sotagliflozin on mortality due to cardio-vascular diseases in type-2 Diabetes Mellitus Patient with altered GFR

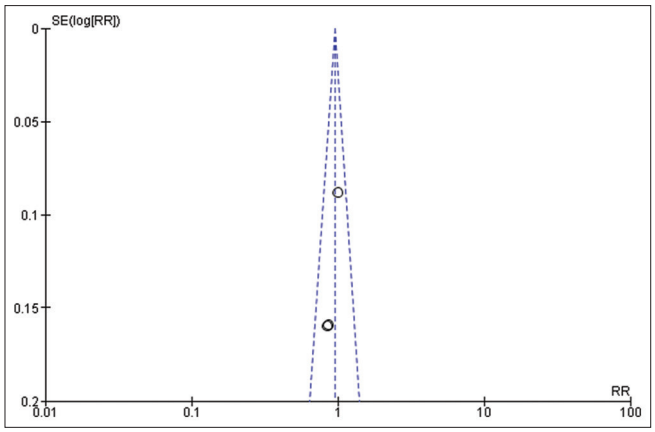

Figure S6: Funnel plot showing the effect of Sotagliflozin on mortality due to other medical conditions in type-2 Diabetes Mellitus Patient with altered GFR

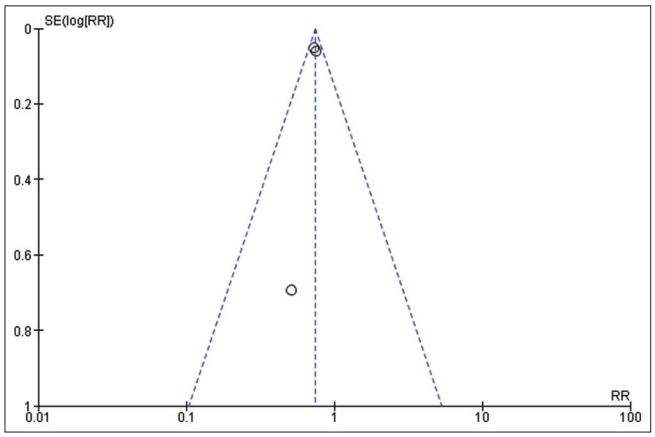

Figure S7: Funnel plot showing the effect of Sotagliflozin on mortality due to non-fatal myocardial infarction and non-fatal stroke in type-2 Diabetes Mellitus Patient with altered GFR

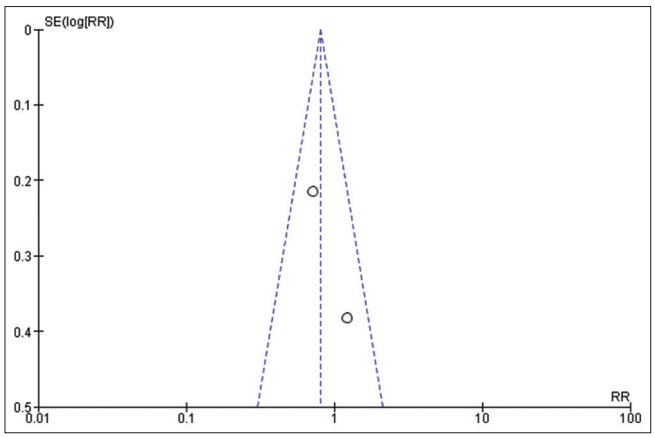

Figure S8: Funnel plot showing improvement in Glomerular Filtration Rate in type-2 Diabetes Mellitus Patient with altered GFR, who received Sotagliflozin