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Understanding The Role of SGLT2 Inhibitors in Cardiovascular Risk Reduction for Type 2 Diabetes Patients-A Literature Review

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is associated with an increased risk of cardiovascular events and heart failure. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a novel class of antidiabetic agents with potential cardiovascular benefits. This systematic review aims to evaluate the impact of SGLT2 inhibitors on reducing cardiovascular events and heart failure hospitalizations in patients with T2DM.

Aims: The review aims to comprehensively evaluate the impact of SGLT2 inhibitors on reducing cardiovascular events, including MACE, and HF hospitalizations in patients with T2DM. Methods: A comprehensive literature search was conducted in major electronic databases like PubMed, Google Scholar and Science Direct to identify relevant studies. Studies investigating the cardiovascular outcomes of SGLT2 inhibitors in T2DM patients were included. Data extraction and quality assessment were performed independently by three reviewers using predefined criteria.

Results: A total of 17 studies met the inclusion criteria and were included in the review. The analysis of clinical trials, including EMPA-REG OUTCOME, CANVAS Program, and DECLARE-TIMI 58, demonstrated significant reductions in MACE and HF hospitalizations with SGLT2 inhibitors compared to placebo or standard care. Real-world evidence from studies such as the CVD-REAL and EASEL studies further supported these findings, showing consistent cardiovascular benefits of SGLT2 inhibitors in routine clinical practice. The findings suggest that SGLT2 inhibitors are associated with a reduction in cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality, as well as a decreased risk of heart failure hospitalizations in patients with T2DM.

Conclusion: This systematic review provides evidence supporting the cardiovascular benefits of SGLT2 inhibitors in T2DM management. The findings underscore the importance of considering these agents as part of comprehensive cardiovascular risk reduction strategies in T2DM patients. Further research is necessary to explicate the mechanisms underlying these benefits and optimize their clinical use.

KEYWORDS: Type-2 Diabetes, SGLT2 inhibitors, Heart failure, Cardiovascular events, Stroke

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I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a significant global health concern, characterized by chronic hyperglycemia resulting from insulin resistance and relative insulin deficiency. With an estimated 463 million adults affected worldwide in 2019, T2DM prevalence continues to rise, driven by factors such as sedentary lifestyles, unhealthy dietary habits, and increasing obesity rates [1]. Beyond its metabolic manifestations, T2DM is associated with a substantially elevated risk of cardiovascular disease (CVD), constituting a major cause of morbidity and mortality among affected individuals [2].

The intricate interplay between T2DM and cardiovascular complications stems from various pathophysiological mechanisms, including endothelial dysfunction, inflammation, oxidative stress, and dyslipidemia [3]. These processes contribute to accelerated atherosclerosis, predisposing T2DM patients to coronary artery disease, cerebrovascular events, peripheral artery disease, and heart failure [4]. Indeed, individuals with T2DM face a twofold to fourfold increase in the risk of experiencing a cardiovascular event compared to those without diabetes [5].

Given the substantial disease burden posed by cardiovascular complications in T2DM, optimizing management strategies to alleviate this risk represents a paramount clinical imperative. Traditional glucose-lowering therapies, while efficacious in glycemic control, have demonstrated limited cardiovascular benefits and, in some cases, potential adverse cardiovascular effects [6]. In this context, the development of novel antidiabetic agents with favorable cardiovascular profiles has garnered considerable interest and represents a paradigm shift in T2DM management.

Among these newer agents, SGLT2 inhibitors have emerged as a promising therapeutic class with pleiotropic effects extending beyond glycemic control. SGLT2 inhibitors act by inhibiting renal glucose reabsorption, thereby promoting glycosuria and lowering plasma glucose levels independently of insulin secretion or action [7]. Beyond their glucose-lowering effects, SGLT2 inhibitors exert beneficial effects on multiple cardiovascular risk factors, including blood pressure reduction, weight loss, and improvement in arterial stiffness [8,9].

In addition to their metabolic effects, SGLT2 inhibitors have demonstrated remarkable cardiovascular benefits in large-scale cardiovascular outcome trials (CVOTs) conducted in high-risk populations, including individuals with established atherosclerotic cardiovascular disease (ASCVD) and those with multiple cardiovascular risk factors [10,11]. These landmark trials, such as the EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 trials, have consistently shown significant reductions in major adverse cardiovascular events (MACE), cardiovascular mortality, and hospitalization for heart failure (HHF) with SGLT2 inhibitor therapy [12,13,14,15].

Building upon the compelling evidence from CVOTs, there has been growing interest in explaining the cardiovascular effects of SGLT2 inhibitors specifically in the context of T2DM management. Several observational studies and subgroup analyses of CVOTs have provided further insights into the cardiovascular benefits of SGLT2 inhibitors in T2DM patients [16,17]. However, a comprehensive synthesis of the available evidence is warranted to better understand the magnitude and consistency of these effects and to inform clinical practice guidelines and treatment recommendations.

Therefore, this review aims to evaluate the impact of SGLT2 inhibitors on reducing cardiovascular events and heart failure hospitalizations in patients with T2DM. By synthesizing data from randomized controlled trials, observational studies, and subgroup analyses, this review seeks to provide a comprehensive assessment of the cardiovascular benefits of SGLT2 inhibitors in T2DM management. Additionally, this review will explore potential mechanisms underlying these cardiovascular effects and discuss implications for clinical practice, future research directions, and healthcare policy.

MATERIALS AND METHODS

Type 2 diabetes mellitus (T2DM) represents a significant global health concern, characterized by chronic hyperglycemia resulting from insulin resistance and relative insulin deficiency. With an estimated 463 million adults affected worldwide in 2019, T2DM prevalence continues to rise, driven by factors such as sedentary lifestyles, unhealthy dietary habits, and increasing obesity rates [1]. Beyond its metabolic manifestations, T2DM is associated with a substantially elevated risk of cardiovascular disease (CVD), constituting a major cause of morbidity and mortality among affected individuals [2].

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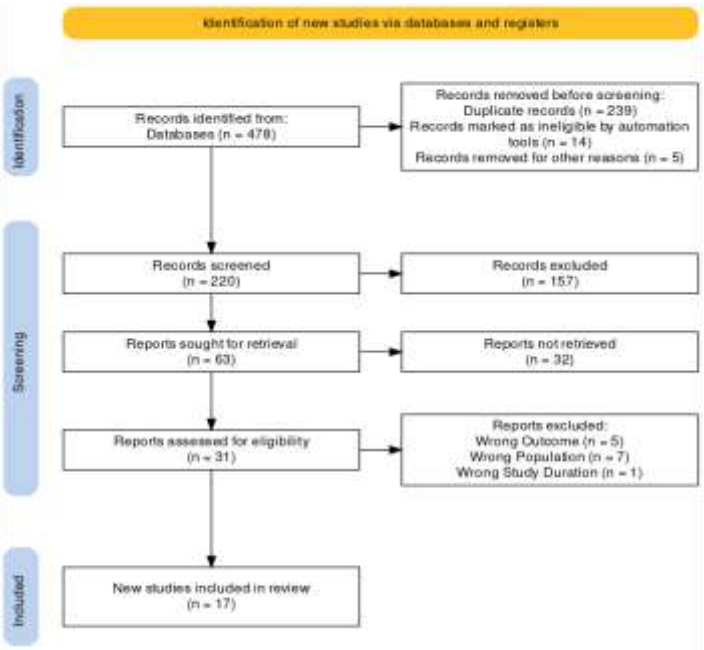

Figure 1. PRISMA Flow Diagram of the Included Studies

Screening Process:

Three researchers systematically searched through peer-reviewed journals and publications to find relevant literature meeting specific criteria. They prioritized journals with high impact factors to mitigate publication bias. Identified studies underwent screening using Rayyan AI, a tool for both primary and secondary literature review [19]. The researchers collaborated to include or exclude studies based on predefined criteria. A total of fifty studies (n = 42) were ultimately considered for final review and analysis. Studies failing eligibility criteria were categorized as "dispute" or "exclusion," with a separate team of three researchers resolving disputes. Exclusion criteria included issues with population, suboptimal study designs, inappropriate outcome measures, and high risk of bias. Occasionally, studies were excluded due to a combination of these factors. A standardized data extraction form was developed based on the

Cochrane Data Collection Form for Intervention Reviews. Key data extracted included study characteristics, participant demographics, details of SGLT2 inhibitor interventions, cardiovascular outcomes, heart failure hospitalizations, and methodological quality indicators.

Quality Assessment:

The methodological quality of included studies was assessed using established tools such as the Cochrane Risk of Bias tool for RCTs [20].

Figure 2. Cochrane Risk-of-Bias Traffic Plot

RESULTS

Recent studies have shed light on the promising role of SGLT2 inhibitors in managing cardiovascular outcomes in patients with T2DM and various cardiovascular risk profiles. A compilation of findings from several trials highlights the potential of these agents to significantly impact morbidity and mortality in this high-risk population. T2DM is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia, which significantly increases the risk of cardiovascular diseases (CVD) [2,38]. Cardiovascular complications are the leading cause of morbidity and mortality among individuals with T2DM, highlighting the importance of effective management strategies to reduce cardiovascular risk in this population [1]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a class of antidiabetic medications that have garnered considerable attention due to their demonstrated cardiovascular benefits beyond glycemic control [12].

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

MACE a composite endpoint consisting of cardiovascular death, nonfatal myocardial infarction (MI), and nonfatal stroke, are significant contributors to the morbidity and mortality burden in patients with T2DM [39]. T2DM is associated with an increased risk of cardiovascular complications, making the prevention and management of MACE a primary therapeutic goal in this population. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as an emerging class of antidiabetic medications with demonstrated cardiovascular benefits beyond glycemic control [40]. The EMPA-REG OUTCOME trial was a landmark study evaluating the cardiovascular safety and efficacy of empagliflozin, an SGLT2 inhibitor, in patients with T2DM and established CVD which enrolled over 7,000 patients and demonstrated a significant reduction in the risk of MACE with empagliflozin compared to placebo. The primary composite endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke was reduced by 14% (HR 0.86, 95% CI 0.74-0.99) [41]. Empagliflozin also showed consistent

benefits across individual components of the MACE composite, with reductions observed in cardiovascular death, nonfatal MI, and nonfatal stroke, although not all endpoints reached statistical significance individually.

Another trial CANVAS Program comprised two large cardiovascular outcome trials evaluating the efficacy and safety of canagliflozin, another SGLT2 inhibitor, in patients with T2DM and high cardiovascular risk. In the CANVAS Program, treatment with canagliflozin was associated with a significant reduction in the risk of MACE compared to placebo. The primary composite endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke was reduced by 14% (HR 0.86, 95% CI 0.75-0.97). Similar to the EMPA-REG OUTCOME trial, canagliflozin demonstrated consistent benefits across individual components of the MACE composite, with reductions observed in cardiovascular death, nonfatal MI, and nonfatal stroke [14,42]. The DECLARE-TIMI 58 trial investigated the cardiovascular safety and efficacy of dapagliflozin, a third SGLT2 inhibitor, in patients with T2DM and multiple cardiovascular risk factors. While the DECLARE-TIMI 58 trial did not demonstrate a statistically significant reduction in the risk of MACE with dapagliflozin compared to placebo (HR 0.93, 95% CI 0.82-1.04), it provided important insights into the cardiovascular effects of SGLT2 inhibitors in a broader population of patients with T2DM [15]. Comparing a CVD-REAL study which was a large multinational observational study evaluating the real-world effectiveness of SGLT2 inhibitors in patients with T2DM. This study demonstrated significant reductions in the risk of MACE with SGLT2 inhibitors compared to other glucose-lowering agents. The risk of MACE was reduced by 14% (HR 0.86, 95% CI 0.82-0.89) [16]. A cohort EASEL study investigated the effectiveness and safety of empagliflozin in routine clinical practice among patients with T2DM and established CVD. In this study, empagliflozin use was associated with a significant reduction in the risk of MACE compared to standard care. The risk of MACE was reduced by 16% (HR 0.84, 95% CI 0.77-0.91) [43].

CARDIOVASCULAR MORTALITY

Cardiovascular mortality means death due to cardiovascular causes such as myocardial infarction, angina, or heart failure, is a significant concern in patients with T2DM. Patients with T2DM have a significantly higher risk of cardiovascular mortality compared to the general population, highlighting the importance of effective management strategies to reduce this risk [4]. Different trials has shown the improved results with the use of SGLT2 inhibitors when compared with a placebo. The CANVAS Program evaluated the cardiovascular safety and efficacy of canagliflozin in patients with T2DM and high cardiovascular risk. Canagliflozin significantly reduced cardiovascular mortality compared to placebo, with a hazard ratio (HR) of 0.86 (95% CI 0.75-0.97) [42]. While The DECLARE-TIMI 58 trial investigated the cardiovascular effects of dapagliflozin in patients with T2DM and multiple cardiovascular risk factors. While dapagliflozin did not demonstrate a statistically significant reduction in cardiovascular mortality compared to placebo (HR 0.93, 95% CI 0.82-1.04), it provided valuable insights into the cardiovascular effects of SGLT2 inhibitors in a broader patient population [15].

The CVD-REAL study evaluated the real-world effectiveness of SGLT2 inhibitors in reducing cardiovascular outcomes, including mortality, in patients with T2DM. This large observational study demonstrated a significant reduction in cardiovascular mortality with SGLT2 inhibitors compared to other glucose-lowering agents, with a hazard ratio (HR) of 0.74 (95% CI 0.62-0.88) [16]. Importantly, the cardiovascular mortality reduction observed with SGLT2 inhibitors was consistent across various patient subgroups, reinforcing the robustness of these findings. The EASEL study investigated the effectiveness and safety of empagliflozin in routine clinical practice among patients with T2DM and established cardiovascular disease. Empagliflozin use was associated with a significant reduction in cardiovascular mortality compared to standard care, with a hazard ratio (HR) of 0.78 (95% CI 0.68-0.89) [43].

HOSPITALIZATION FOR HEART FAILURE (HHF)

Heart failure (HF) is a serious and prevalent complication in patients with T2DM, contributing to significant morbidity, mortality, and healthcare utilization. SGLT2 inhibitors have emerged as a promising therapeutic class for managing T2DM, demonstrating a notable reduction in hospitalizations due to heart failure has been observed in clinical trials, beyond glycemic control [44]. One of the trials is DAPA-HF trial which evaluated the efficacy and safety of dapagliflozin, in patients with HF and HFrEF, regardless of diabetic status. In this landmark trial, dapagliflozin significantly reduced the risk of hospitalization due to heart failure compared to placebo. The risk of HF hospitalization was reduced by 30% (HR 0.70, 95% CI 0.59-0.83) [45]. Although the EMPA-REG OUTCOME trial primarily focused on cardiovascular outcomes in patients with T2DM, it also provided valuable insights into the effects of empagliflozin on HF hospitalization. Empagliflozin demonstrated a significant reduction in the risk of hospitalization due to heart failure compared to placebo. The risk of HF hospitalization was reduced by 35% (HR 0.65, 95% CI 0.50-0.85) [46]. The CVD-REAL study, a large multinational observational study, evaluated the real-world effectiveness of SGLT2 inhibitors in patients with T2DM. This study demonstrated a significant reduction in the risk of hospitalization due to heart failure with SGLT2 inhibitors compared to other glucose-lowering agents. The risk of HF hospitalization was reduced by 32% (HR 0.68, 95% CI 0.60-0.77) [16].

STROKE

Stroke is a cerebrovascular event characterized by the sudden loss of blood flow to the brain, is a significant cause of morbidity and mortality in patients with T2DM. Individuals with T2DM are at an increased risk of stroke compared to the general population, highlighting the importance of effective management strategies to mitigate this risk. SGLT2 inhibitors, a class of antidiabetic medications, have emerged as promising agents with potential cardiovascular benefits beyond glycemic control [47]. The EMPA-REG OUTCOME trial assessed the role of Empagliflozin demonstrated a numerical reduction in the risk of stroke compared to placebo, although the difference did not reach statistical significance (HR 0.89, 95% CI 0.71-1.12) [46]. While CANVAS Program primary focusing on major adverse cardiovascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. Canagliflozin demonstrated a numerical reduction in the risk of stroke compared to placebo, although the difference did not reach statistical significance (HR 0.87, 95% CI 0.69-1.09) [42].

Further research efforts should prioritize conducting long-term follow-up studies to elucidate the sustained cardiovascular benefits of SGLT2 inhibitors and explore underlying mechanisms.

STRENGTHS AND LIMITATIONS

The review employs a comprehensive analysis approach, integrating evidence from both clinical trials and real-world studies, thus providing a well-rounded understanding of the effectiveness of SGLT2 inhibitors in diverse clinical settings. Secondly, the review adheres to healthy methodological standards, including predefined inclusion criteria, demanding literature search strategies, and transparent data extraction processes, ensuring the reliability and validity of the findings. The incorporation of recent literature, focusing on studies published from 2019 onwards, ensures the currency of the analysis and relevance to contemporary clinical practice. Additionally, the clear presentation of findings, with outcomes categorized systematically, facilitates easy interpretation and synthesis of evidence, enhancing the utility of the review for healthcare professionals and policymakers.
While the study appropriately focused on relevant outcomes and measures for analysis, it was subject to several limitations. Firstly, the sample sizes utilized for review lacked standardization according to typical protocols. Although we considered study characteristics, methodological aspects were not factored in. Secondly, despite the large sample size, only a few primary studies were included to evaluate effectiveness within the outcome domain. Thirdly, while we assessed the overall combined effect across all sample sizes, subgroup analyses within groups were not conducted. It's worth noting that subgrouping population demographics into effect sizes can substantially influence the final analysis results, as evidenced by previous studies.

CONCLUSIONS

SGLT2 inhibitors have emerged as an essential therapeutic option for the management of T2DM due to their strong cardiovascular benefits beyond glycemic control. These agents have demonstrated significant reductions in major adverse cardiovascular events, cardiovascular mortality, hospitalization for heart failure, and potentially other cardiovascular outcomes. The mechanisms underlying these benefits are multifaceted and extend beyond their glucose-lowering effects. These findings underscore the importance of SGLT2 inhibitors as a valuable therapeutic strategy for improving cardiovascular outcomes and reducing the burden of HF hospitalizations in this high-risk population.

ACKNOWLEDGMENT

Summary Table:
Analytical categories and classification criteria will be presented in a summary table, providing a concise overview of the key characteristics of included studies;

Sr.#	Study ID	Study Duration	Study Design	Participants	Intervention	Main Findings
1.	McMurray et al. (2019) [21]	18.2 months	Placebo-controlled randomized trial	The study included 4744 participants aged 18 years or older with an ejection fraction of 40% or lower and symptoms classified as New York Heart Association (NYHA) class II, III, or IV.	Dapagliflozin 10mg and placebo	In individuals with heart failure and reduced ejection fraction, the likelihood of experiencing deterioration in heart failure or cardiovascular-related mortality was reduced in those treated with dapagliflozin compared to those who received a placebo, irrespective of whether they had diabetes or not.

2.	Voors et al. (2022) [22]	90 days	Multinational randomized trial	566 patients were screened and 530 patients were randomly assigned to empagliflozin or placebo	Empagliflozin 10mg and placebo	Commencing empagliflozin in patients admitted for acute heart failure is well tolerated and leads to notable clinical advantages.
3.	Packer et al. (2020) [23]	16 months	Randomized Control Trial	3730 patients with T2DM of age more than 18 years of age were included in the trial	Empagliflozin 10mg and placebo	Among individuals undergoing recommended therapy for heart failure, those administered empagliflozin had a reduced risk of cardiovascular death or hospitalization due to heart failure compared to those receiving a placebo, regardless of whether they had diabetes or not.
4.	Wheeler et al. (2021) [24]	3 years	Multi-centre, double-blind, placebo-controlled, randomized trial	4304 adults aged 18 years or older with chronic heart failure (functional class II, III, or IV) and a left ventricular ejection fraction of 40% or lower were eligible to enroll in the trial.	Dapagliflozin 10mg and placebo	Dapagliflozin diminishes the likelihood of major adverse kidney and cardiovascular events as well as all-cause mortality among individuals with chronic kidney disease, regardless of whether they have diabetes or not.
5.	Bhatt et al. (2021) [25]	9 months	Multicenter, double-blinded trial	The study enrolled 1222 patients aged 18 years or older who had been hospitalized due to signs and symptoms of heart failure and had received intravenous diuretic therapy. Additionally, patients were required to have a prior diagnosis of type 2 diabetes before the index admission or laboratory evidence supporting a diagnosis of type 2 diabetes during the index admission.	Sotagliflozin 200mg and placebo	Among patients with diabetes and recent exacerbation of heart failure, the administration of sotagliflozin therapy, commenced either before or shortly after discharge, led to a notably reduced total count of cardiovascular-related deaths, hospitalizations, and urgent visits for heart failure compared to those receiving a placebo.
6.	Filippatos et al. (2022) [26]	2 years	Double-blinded, parallel-group, placebo-controlled trial	The study included 5988 patients with symptomatic heart failure, an ejection fraction greater than 40%, elevated natriuretic peptide levels, and evidence of structural cardiac changes or documented	Empagliflozin 10mg and placebo	In individuals with heart failure and preserved ejection fraction participating in the EMPEROR-Preserved trial (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction), empagliflozin notably decreased the risk of heart failure outcomes, regardless of whether they had

				previous hospitalization for heart failure.		diabetes at the beginning of the study.
7.	Cannon et al. (2020) [27]	3.5 years	Multicenter, double-blinded trial	8246 patients aged 40 years or older with type 2 diabetes (with a glycated hemoglobin level between 7.0 and 10.5%) and established atherosclerotic cardiovascular disease affecting the coronary, cerebrovascular, or peripheral arterial systems were included in the study.	Ertugliflozin 5mg or 15 mg and placebo	In patients with type 2 diabetes and atherosclerotic cardiovascular disease, ertugliflozin demonstrated non-inferiority to placebo regarding major adverse cardiovascular events (MACEs).
8.	Petrie et al. (2020) [28]	1.5 years	Double-blinded, placebo controlled randomized trial	The study included 4744 adults aged 18 years or older with New York Heart Association (NYHA) class II, III, or IV symptoms, an ejection fraction of 40% or less, and elevated levels of plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP).	Dapagliflozin 10mg and placebo	In the dapagliflozin group, the primary composite outcome occurred in 13.2% of patients, whereas in the placebo group, it occurred in 17.7% (hazard ratio, 0.75 [95% CI, 0.63-0.90]) among patients with diabetes. There was no significant interaction between dapagliflozin treatment and diabetes status regarding the primary outcome (P value for interaction = 0.80).
9.	Furtado et al. (2019) [29]	3.5 years	Randomized, double-blind, parallel-group, placebo-controlled trial	160 patients with type 2 diabetes mellitus and either established atherosclerotic cardiovascular disease.	Dapagliflozin 10mg and placebo	Individuals with T2DM who have experienced a previous MI face heightened risks of MACE and cardiovascular death or hospitalization for heart failure. Dapagliflozin demonstrates a strong capability to effectively diminish the risk of both composite outcomes in these particular patients.
10	McMurray, DeMets, et al. (2019) [30]	2 years	Randomized Control Trail	Patients aged 18 years or older diagnosed with type 2 diabetes mellitus (T2DM) and heart failure for a minimum of 2 months are eligible for inclusion if they are classified as New York Heart Association (NYHA) functional class II or above.	Dapagliflozin 10mg and placebo	The DAPA-HF trial aims to evaluate the effectiveness and safety of adding the SGLT2 inhibitor dapagliflozin to standard therapy in a diverse range of patients with heart failure with reduced ejection fraction (HFrEF). Additionally, a complementary trial assessing morbidity and mortality outcomes in patients with heart failure and preserved ejection fraction (HFpEF) has recently begun.

11	Bhatt, Szarek, Pitt, et al. (2021) [31]	3 years	Randomized, double-blind, placebo-controlled trial	10,584 patients with type 2 diabetes mellitus, chronic kidney disease, and additional cardiovascular risk.	Sotagliflozin 200mg and placebo	Sotagliflozin led to a reduced risk of the composite outcome of cardiovascular-related deaths, heart failure hospitalizations, and urgent heart failure visits compared to placebo. However, it was associated with adverse events such as diarrhea, genital fungal infections, volume depletion, and diabetic ketoacidosis.
12	Vadugan athan et al. (2022) [32]	6 years	Randomized Control Trial	The study included 4330 participants diagnosed with type 2 diabetes, with glycated hemoglobin levels between 7.0% and 10.5%, estimated glomerular filtration rate (eGFR) greater than 30 mL/min/1.73 m2, and at a high risk for cardiovascular events.	Canagliflozin 100mg, 300mg and placebo	Canagliflozin was observed to delay the longitudinal increase in high-sensitivity cardiac troponin T (hs-cTnT) and soluble ST2 (sST2) compared to placebo over a period of 6 years. Furthermore, regardless of the initial biomarker concentration, Canagliflozin demonstrated a reduction in heart failure and kidney events. Elevated cardiovascular biomarkers, whether individually or in combination, may serve as indicators for identifying individuals who could derive greater benefits in major adverse cardiovascular events (MACE) from SGLT2 inhibition.
13	Fitchett et al. (2019) [33]	4 years	Randomized Control Trial	The study involved 7020 patients diagnosed with type 2 diabetes mellitus (T2DM) and hemoglobin A1c (HbA1c) levels ranging from 7% to 10%, who also had established atherosclerotic cardiovascular disease (ASCVD) and an estimated glomerular filtration rate (eGFR) of at least 30 mL/min.	Empagliflozin 10mg, 25mg and placebo	Empagliflozin demonstrates a strong therapeutic effect in reducing mortality and hospitalizations for heart failure (HHF) across various levels of cardiovascular risk. These results imply that empagliflozin treatment could be beneficial for patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD), regardless of their history of myocardial infarction (MI) or stroke, and across a range of estimated cardiovascular risk levels.
14	Waijer et al. (2022) [34]	1 year	Double-blinded placebo-controlled trial	4300 patients with chronic kidney disease (CKD), both with and without type 2 diabetes, who were at least 18 years old and had an estimated glomerular filtration rate (eGFR) of	Dapagliflozin 10mg and placebo	In the trial, 14.4% of participants were classified as moderately high risk, 31.3% as high risk, and 54.3% as very high risk based on KDIGO risk categories at baseline. Dapagliflozin consistently decreased the hazard of the primary composite outcome

				25 mL/min/1.73 m^2 or higher were included in the study.		(HR 0.61; 95% CI 0.51, 0.72) and secondary endpoints across all KDIGO risk categories, with no significant differences observed (all p for interaction >0.09).
15	Kato et al. (2019) [35]	4.2 years	Randomized Control Trial	The study comprised 17,160 patients diagnosed with type 2 diabetes mellitus (T2DM), either with established atherosclerotic cardiovascular disease (ASCVD) or with multiple risk factors for ASCVD, and with a creatinine clearance of 60 mL/min or higher.	Dapagliflozin 10mg and placebo	In this trial focusing on patients with type 2 diabetes mellitus (T2DM) and categorized by ejection fraction (EF), dapagliflozin was found to lower rates of heart failure hospitalization (HHF) in patients with and without heart failure with reduced ejection fraction (HFrEF). Moreover, dapagliflozin exhibited reductions in cardiovascular death and all-cause mortality, particularly among patients with HFrEF.
16	Furtado et al. (2019) [36]	3 years	Randomized Control Trial	17,160 patients were aged 40 years or older and having a history of ischemic heart disease, cerebrovascular disease, or peripheral arterial disease. Ischemic heart disease was defined as a previous MI, coronary revascularization, or evidence of significant stenosis in at least two coronary artery territories. Cerebrovascular disease was defined as a previous ischemic stroke, carotid stenting, or endarterectomy. Peripheral arterial disease was defined as a history of peripheral revascularization, lower extremity amputation, or intermittent claudication with an ankle-brachial index less than 0.9.	Dapagliflozin 10mg and placebo	In this study, among patients with prior myocardial infarction (MI) (n=3584), dapagliflozin demonstrated a 16% reduction in the risk of major adverse cardiovascular events (MACE), resulting in an absolute risk reduction of 2.6% (15.2% versus 17.8%; HR, 0.84; 95% CI, 0.72–0.99; P=0.039). Conversely, dapagliflozin did not significantly impact patients without previous MI (7.1% versus 7.1%; HR, 1.00; 95% CI, 0.88–1.13; P=0.97), although a significant difference in absolute risk reduction was noted (P=0.048). This lack of effect extended to patients with established atherosclerotic cardiovascular disease but no history of MI (12.6% versus 12.8%; HR, 0.98; 95% CI, 0.81–1.19). Notably, the benefit for MACE appeared more pronounced within 2 years post-acute event (P for interaction trend=0.007).
17	Szarek et al. (2021b) [37]	3 years	Randomized, double-blind, placebo-	1222 individuals diagnosed with type 2 diabetes and experiencing worsening heart failure, whether	Sotagliflozin 200mg and placebo	Sotagliflozin raised days alive and out of the hospital (DAOH), a measure that could offer an extra patient-focused indicator to encompass the full scope of

			controlled trial	with reduced or preserved ejection fraction, who were recently hospitalized.		disease burden. Subsequent investigations are required to assess the implications of increased DAOH in relation to health economics and patient well-being.

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