Impact of SGLT2 Inhibitors in the Management of Diabetes and Heart Failure Comorbidity: A Review of Current Evidence

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ABSTRACT

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a novel class of medication for managing both type 2 diabetes mellitus and heart failure (HF), offering significant cardioprotective benefits beyond glycemic control. This study reviewed current findings on the efficacy of SGLT2 inhibitors as a therapeutic approach for managing diabetes and HF comorbidity. Based on reports from clinical trials on empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, and ertugliflozin, the review revealed that SGLT2 inhibitors demonstrated superior efficacy compared to placebo for managing HF and reducing the risk of major adverse cardiovascular events in patients with and without diabetes mellitus. However, higher incidences of adverse effects such as diarrhea, amputation, hypoglycemia, genitourinary infections, and diabetic ketoacidosis were reported in patients who received SGLT2 inhibitors. Most of the trials represent the initial studies undertaken for each of the drugs, and their findings informed regulatory approvals for HF management and reduction of cardiovascular events. While most of the studies focused on assessing the clinical outcomes, a few mechanistic studies were undertaken, which revealed that the reported cardiovascular outcomes of SGLT2 inhibitors could be due to the promotion of reverse cardiac remodeling. Furthermore, only a few of the studies compared the clinical efficacy of SGLT2 inhibitors with that of other classes of hypoglycemic agents. This review highlighted research directions that can contribute to a more comprehensive understanding of SGLT2 inhibitor safety and efficacy, ensuring optimal utilization in diverse patient populations.

Keywords: SGLT2 inhibitors, Cardioprotection, Heart failure comorbidity, Adverse effects, Cardiac remodeling

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Highlights

- Multiple studies highlighted clinical benefits of SGLT2 inhibitors in comparison to placebo in reducing the incidence of cardiovascular deaths and worsening HF.
- The clinical benefits of SGLT2 inhibitors for managing HF may be caused by the promotion of reverse cardiac remodeling.
- Treatment with SGLT2 inhibitors may cause increased risk of amputation and adverse effects such as diarrhea, hypoglycemia, genitourinary infections, and diabetic ketoacidosis.

Introduction

Diabetes mellitus, characterized by long-term dysregulation of blood glucose, is associated with clinical complications and adverse effects on some organ systems in the body. Specifically, these complications include damage to the eyes, kidneys, and nerves.[1] Diabetes mellitus is a clinical manifestation of insufficient insulin activity in the body, which may arise from low insulin secretion from defective beta cells or reduced sensitivity of insulin receptors. Although these two mechanisms may coexist in both type 1 and type 2 diabetes, depending on the severity, dysregulated insulin secretion is associated with type 1 diabetes, while reduced peripheral sensitivity to insulin is associated with type 2 diabetes.[2] Notwithstanding, both types of diabetes have high prevalences worldwide and cause substantial morbidity and mortality. Globally, approximately 828 million people were estimated to have diabetes in 2022,[3] corresponding to a prevalence of about 14% in the adult population and causing about 1.6 million deaths annually.[4] As indicated in Figure 1, in 2021, diabetes also contributed to 530,000 kidney disease-related deaths, as well as 11% of cardiovascular deaths.[4]

Poorly managed diabetes mellitus affects the heart and blood vessels, promoting the development and worsening of cardiovascular disorders, including heart failure (HF) (Figure 2). In other words, diabetes is a well-known risk factor for HF. Elendu et al.[5] described the relationship between the two conditions as "bidirectional," implying that any of the two metabolic diseases can contribute to the pathogenesis and/or worsening of the other condition (Figure 3). This relationship is associated with the shared risk factors—obesity, dyslipidemia, physical inactivity, and hypertension—between diabetes and HF.[6] Therefore, diabetes mellitus and HF often coexist in the same person. Hoek et al.[7] reported the prevalence of various types of HF in patients who have diabetes to be 6–43%. HF occurs when the pumping ability of the heart is insufficient to meet the body's circulatory requirements. This could result from structural dysfunctions in cardiac muscles, resulting from conditions such as ischemic heart disease, cardiomyopathies, hypertension, chronic obstructive pulmonary disease, and congenital heart anomalies.[8]

Originally used to treat hyperglycemia in patients with diabetes, sodium-glucose cotransporter 2 (SGLT2) inhibitors, including dapagliflozin, canagliflozin, and empagliflozin, have also been reported to reduce symptoms of HF, reduce the risk of major adverse cardiovascular events (MACE), improve renal outcomes in patients with chronic kidney disease, and improve overall quality of life.[9] The cardioprotective action of SGLT2 inhibitors was first reported in a randomized controlled trial by Zinman et al.[10] The study, which assessed the effects of empagliflozin on the cardiovascular system, reported that patients who received the drug had a reduced risk of hospitalization with HF and deaths. Subsequently, other studies have

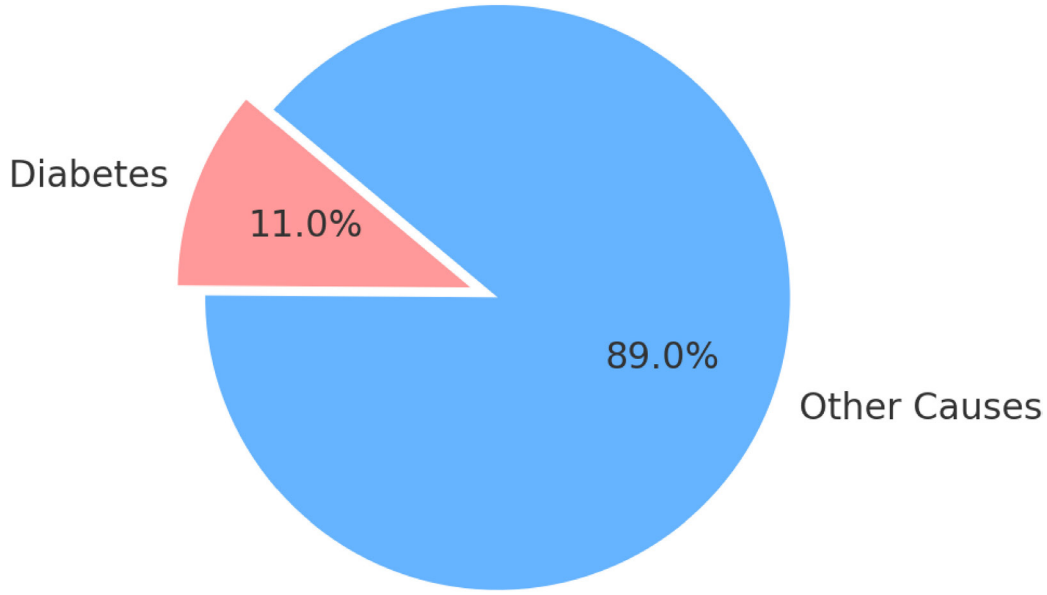

Fig 1 | Percentage of cardiovascular deaths associated with diabetes mellitus

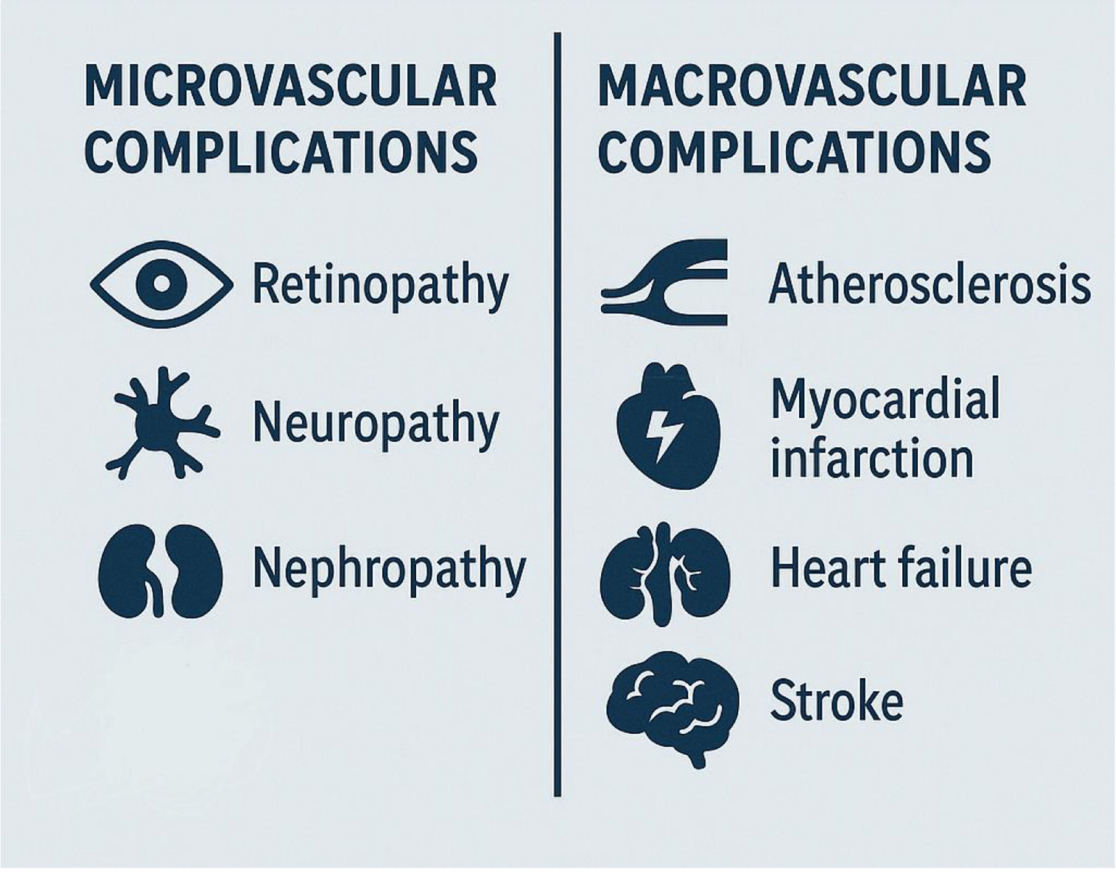

Fig 2 | Complications of diabetes mellitus

been undertaken to verify this finding and determine the benefits of SGLT2 inhibitors in the management of cardiovascular disorders. Hence, this study aimed to review available evidence in the past decade on the efficacy of SGLT2 inhibitors as a therapeutic approach for managing diabetes and HF comorbidity.

Mechanisms of Action of SGLT2 Inhibitors

Sodium-glucose cotransporters (SGLTs) are transmembrane proteins that facilitate the transport of sodium and glucose in the same direction, earning them the name "symporters." SGLTs are mainly classified into SGLT1 and SGLT2, both of which facilitate the reabsorption of

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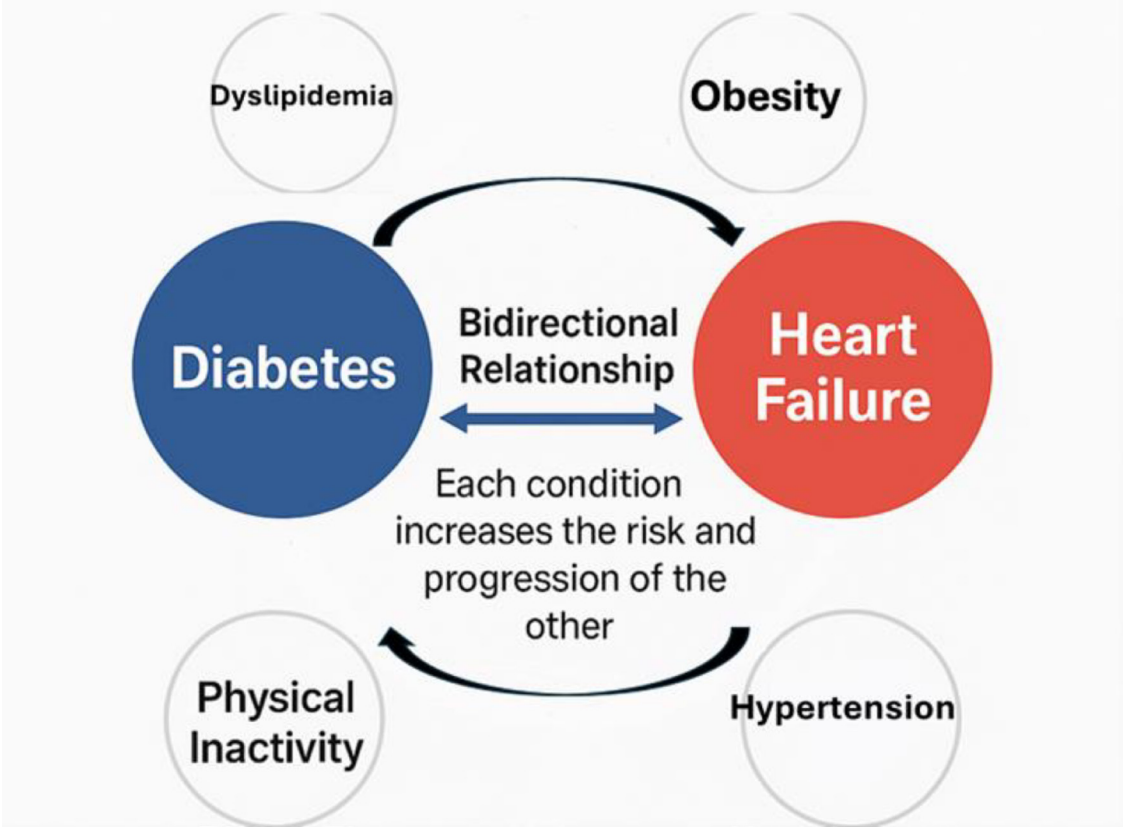

Fig 3 | Bidirectional relationship between diabetes mellitus and HF

glucose. However, SGLT2 is the most expressed subtype in the kidney, while SGLT1 is found in the gut, skeletal muscle, brain, etc.[11] To conserve energy in the body, SGLTs, located primarily in the proximal tubules, aid the reabsorption of filtered glucose back into the circulation.[12] This process is promoted by the Na-K-ATPase pump. Due to its high expression in the kidney and its high capacity for reabsorption, SGLT2 is primarily responsible for reabsorbing most of the glucose filtered by the kidney. The degree of reabsorption is determined by variations in serum glucose levels.

In the management of diabetes mellitus, SGLT2 inhibitors block the reabsorption of glucose in renal tissue, thereby promoting the elimination of excess glucose through the urine (glucosuria) and reducing the serum glucose level.[13] This mechanism, while beneficial, also predisposes patients on this class of medication to genitourinary tract infections.[14] Over time, SGLT2 inhibitors cause a reduction in levels of glycated hemoglobin and increased sensitivity to insulin.

In HF, the mechanisms of action of SGLT2 inhibitors are thought to be multifaceted, but they are yet to be fully elucidated. Similar to actions in diabetes mellitus, SGLT2 inhibitors also block sodium reabsorption and thereby promote natriuresis. This results in reduced salt and water retention, leading to a decrease in blood pressure.[15] Other cardioprotective mechanisms of SGLT2 inhibitors include the promotion of weight loss, amelioration of inflammation, reduction in the risk of atrial fibrillation, as well as improvement in cardiac structure and function.[16] Furthermore, SGLT2 inhibitors also promote renoprotection by reducing albuminuria, promoting urinary elimination of uric acid, and reducing renal fibrosis.[17]

Methods

Search Strategy

A comprehensive literature search was conducted across PubMed, Embase, Scopus, and the Cochrane Library, focusing on studies published in the last 10 years (May 1, 2015 to April 30, 2025). The search aimed to gather a broad range of evidence on the role of SGLT2 inhibitors in the management of concurrent type 2 diabetes mellitus and HF. Both Medical Subject Headings and free-text terms were used, including "SGLT2 inhibitors," "dapagliflozin," "empagliflozin," "canagliflozin," "ertugliflozin," "sotagliflozin," "type 2 diabetes," "heart failure," "HFrEF," "HFpEF," "cardiovascular outcomes," and "renal function." Boolean operators such as AND, OR, and NOT were used to combine search terms and refine results. Search results were supplemented by manually reviewing the reference lists of relevant review articles.

Study Selection

Priority was given to high-quality randomized controlled trials and large-scale observational studies. Only studies published in English and focusing on human subjects were included. Exclusion criteria included preclinical or animal studies, editorials without primary data, and case reports. Articles that lacked

outcome data related to either cardiovascular or renal endpoints were also excluded. Additionally, duplicate publications and abstracts without full-text availability were removed from consideration.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines.[18]

Quality Assessment

A formal risk of bias appraisal was not conducted because this review employed a narrative design rather than a systematic or meta-analytic approach. Narrative reviews are typically descriptive and exploratory, aiming to provide a broad overview of the existing literature rather than synthesizing findings through standardized methods. Unlike systematic reviews, which focus on specific research questions, narrative reviews often include diverse study types with varying methodologies, making the application of standardized risk of bias tools inappropriate. Nonetheless, care was taken to ensure that included studies were relevant, clearly reported, and contributed meaningfully to the aims of the review.

Results

A total of 269 reports were retrieved and assessed for eligibility following the initial screening, as indicated in the PRISMA flow diagram (Figure 4). These reports were evaluated based on the predefined inclusion and exclusion criteria. During the eligibility assessment, 246 reports were excluded due to various reasons: 96 were excluded because their publication date fell outside the specified time frame; 102 were excluded because they were not published in English; and 48 were excluded based on study design, including non-original studies, reviews, and editorials. After applying all exclusion criteria, a total of 23 articles[10,19–40] were deemed eligible and included in the final synthesis.

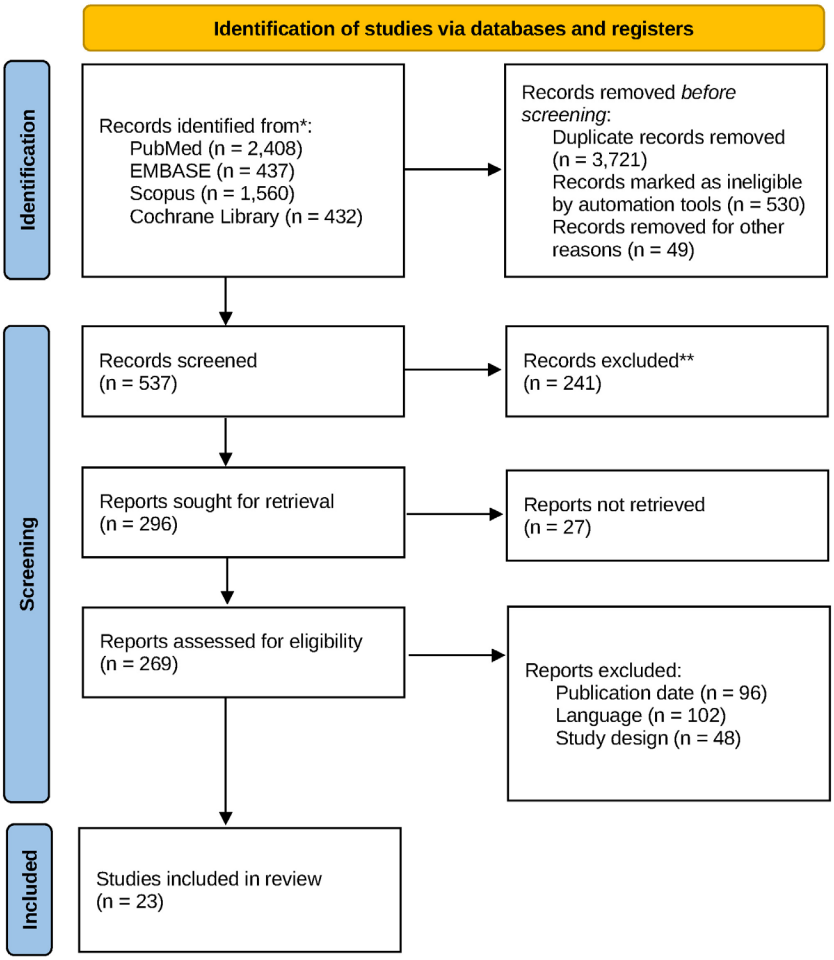

Fig 4 | PRISMA flow diagram. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)

Empagliflozin

EMPA-REG OUTCOME and EMPULSE Trials

Diabetes mellitus is a well-known risk factor for cardiovascular disorders; this prompted the evaluation of the beneficial effects of empagliflozin on cardiovascular outcomes in the EMPA-REG OUTCOME trial.[10] The study became the first clinical trial to demonstrate that SGLT2 inhibitors significantly reduce the risk of cardiovascular disease and cardiovascular-related deaths in patients with diabetes. Subsequently, empagliflozin has been evaluated for the management of acute HF,[19] HF with reduced ejection fraction (HFrEF),[20] as well as HF with preserved ejection fraction (HFpEF).[21] In the EMPULSE trial, a multinational study in which patients with a new diagnosis of HF and those with decompensated chronic HF were randomized to receive a 10 mg daily dose of empagliflozin or placebo.[19] In addition to significantly higher clinical benefits reported in those who receive empagliflozin, reduced incidences of adverse events were also reported for this patient cohort.

EMPEROR-Reduced and EMPEROR-Preserved Trials

The EMPEROR-Reduced trial[20] assessed the cardiovascular outcomes of empagliflozin in patients with ≤40% ejection fraction, regardless of the presence of diabetes mellitus. With a median follow-up of 16 months, the patients who received 10 mg daily dose of empagliflozin, in addition to their standard clinical care, had lower incidence of death or hospitalization due to worsening symptoms (19.4%) compared to those who received standard clinical care and placebo (24.7%; hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.65–0.86; $p < 0.001$). However, genital tract infection, a well-known side effects of SGLT2 inhibitors, were reported more frequently in patients who received empagliflozin. Likewise, based on findings from the EMPEROR-Preserved trial, empagliflozin caused a significant reduction in symptom worsening and hospitalization in patients with preserved ejection function compared to placebo.[21] Further studies have reported that these favorable findings could be attributed to an improvement in left ventricular function and reverse remodeling, as indicated in EMPA-TROPISM[22] and SUGAR-DM-HF[23] trials.

Dapagliflozin

The DECLARE–TIMI trial was undertaken to determine the cardiovascular outcomes in patients with diabetes mellitus who also had atherosclerosis or were at a high risk for the disease.[24] The main study outcomes were

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MACE and death/hospitalization for HF, while the follow-up duration was 4.2 years. The study recorded no reduction in the incidence of MACE in the dapagliflozin group compared to the control; however, a lower incidence of death/hospitalization for HF was reported in those who received dapagliflozin (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73–0.95; p = 0.005). Reduced incidence of cardiovascular death or hospitalization due to worsening symptoms has also been confirmed individually in patients with reduced ejection fraction and in those with preserved ejection fraction in DAPA-HF[25] and DELIVER[26] trials, respectively. The DICTATE-AHF trial reported decongestion benefits associated with the use of dapagliflozin in guideline-directed medical therapy for acute HF, including enhanced diuresis and reduced need for loop diuretics.[27]

In addition to cardiovascular outcomes of dapagliflozin in patients with HF, dapagliflozin has also been assessed for its impact on patient-reported symptoms and patients' physical abilities.[28,29] The studies utilized data collection tools such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) and 6-minute walk distance (6MWD); these tools are used to assess the health status and functional capacity of patients with HF. In patients with preserved ejection fraction, Nassif et al.[28] reported that dapagliflozin increased KCCQ scores in patients who received the drug for 12 weeks in both clinical summary score (68.6 vs. 62.8; p = 0.001) and overall summary score (68.9 vs. 64.5; p = 0.009) domains; this was associated with reduction of symptoms and physical limitations. Likewise, the 6MWD was higher in patients who received dapagliflozin (262 m vs. 242 m; p = 0.007).

In contrast, McMurray et al.[29] recently reported that dapagliflozin did not demonstrate superiority over placebo in improving KCCQ scores or 6MWD in patients with preserved ejection fraction who received the drug for 16 weeks. The study further reported that dapagliflozin only improved the total symptom score domain of KCCQ in patients with reduced ejection fraction, while the physical limitation domain of KCCQ and 6MWD were comparable between the treatment and control groups. This could be because dapagliflozin's initial benefits in HF are more closely associated with symptom relief rather than immediate improvements in physical function or exercise capacity. Additionally, the lack of objectivity of the assessment tools may also introduce bias in the reported findings.

Canagliflozin

CANVAS Program

The CANVAS program was designed to provide scientific evidence for the cardiovascular safety of canagliflozin in diabetic patients.[30] With fewer incidences of cardiovascular deaths, nonfatal myocardial infarction, and nonfatal stroke in the treatment group, the study not only provided the required evidence for the Food and Drug Administration (FDA) approval of the drug but also revealed that the drug conferred a lower risk of cardiovascular events in patients. However, there was a higher risk of amputation in the treatment group compared to the placebo group; this was a new finding in terms of the side effect profile of canagliflozin. The cardiovascular outcomes of canagliflozin have also been assessed with respect to the cardiovascular outcomes of other classes of antidiabetic medications, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sulfonylureas.[31] The study recorded lower incidences of the primary outcomes, which included worsening HF and a composite of worsening acute myocardial infarction, ischemic stroke, or hemorrhagic stroke. For worsening HF, the study reported an HR of 0.70 (95% CI, 0.54–0.92) relative to dipeptidyl peptidase-4 inhibitors, 0.61 (0.47–0.78) relative to glucagon-like peptide-1 receptor agonists, and 0.51 (0.38–0.67) relative to sulfonylureas.[31]

CREDENCE Trial

Another notable trial that evaluated the cardiovascular activity of canagliflozin was the CREDENCE trial.[32] Although the study was designed primarily to assess renal events associated with canagliflozin in diabetic patients, cardiovascular endpoints were evaluated as secondary endpoints in the study. The study reported that canagliflozin reduced the risk of the composite of cardiovascular death, myocardial infarction, and stroke (HR, 0.80; 95% CI, 0.67–0.95; p = 0.01) as well as the risk of HF (HR, 0.61; 95% CI, 0.47–0.80; p < 0.001). However, contrary to the report of the higher incidence of amputation in the treatment group in the CANVAS trial, the CREDENCE trial[32] demonstrated comparable incidences of amputation in the treatment and control groups. These findings were corroborated by a post hoc analysis of the trial, which had a longer follow-up.[33] Kuo et al.[34] undertook a mechanistic study to explain the reported cardioprotective effects of canagliflozin and reported that canagliflozin improved hemodynamic parameters such as glycated hemoglobin and systolic blood pressure. Similar to the EMPA-TROPISM[22] and SUGAR-DM-HF[23] trials, the study also revealed that canagliflozin promoted reverse cardiac remodeling.

Sotagliflozin

The SCORED[35] and SOLOIST-WHF[36] trials are the major clinical trials conducted to ascertain the utility of sotagliflozin in the management of HF, among other cardiovascular complications. The SCORED trial recruited patients with diabetes who also had chronic kidney disease, while the SOLOIST-WHF trial involved patients with diabetes mellitus who were hospitalized for HF. Both trials reported significantly lower incidences of cardiovascular deaths and worsening HF in patients who received sotagliflozin compared to those who received a placebo. The SCORED trial reported that the clinical benefits of sotagliflozin were associated with higher incidences of adverse effects, including gastrointestinal disturbance, genital fungal infections, and diabetes ketoacidosis; likewise, the SOLOIST-WHF reported higher incidences of diarrhea and hypoglycemia. It is important to note that sotagliflozin inhibits both SGLT1 and SGLT2, which may explain the reported risks of adverse effects.[37] Notwithstanding,

Table 1 | Use of SGLT2 inhibitors in HF and diabetes comorbidity

SGLT2 Inhibitor	Dose	HF Phenotype	Diabetes Status	eGFR Cut-Off (ml/min/1.73 m2)	Benefit	Notable Adverse Effects	Clinical Trial
Empagliflozin	10 mg daily	Acute HF	With or without	20	Reduced all-cause death and HF events. Improved quality of life	Acute renal failure, UTI, and hepatic injury	EMPULSE[19]
	10 mg daily	HFrEF EF ≤40%	With or without	20	Lower risk of cardiovascular death or hospitalization for HF	Uncomplicated genital tract infection	EMPEROR-Reduced[20] SUGAR-DM-HF[23] EMPA-TROPISM[22]
	10 mg daily	HFpEF EF ≥40%	With or without	20	Lower risk of cardiovascular death or hospitalization for HF	Hypotension and uncomplicated genital and urinary tract infection	EMPEROR-Preserved[21]
Dapagliflozin	10 mg daily	HFrEF EF ≤40%	With or without	30	Reduced risk of worsening HF or death from cardiovascular causes	Volume depletion, renal dysfunction, and hypoglycemia	DAPA-HF[25]
	10 mg daily	HFpEF EF ≥45%	With or without	20	Improved patient-reported symptoms, physical limitations, and exercise function	Volume depletion and acute kidney injury	PRESERVED-HF[28] DELIVER[26]
Canagliflozin	100 mg	All	With or without	30	Rapid clinical improvement in symptoms. Low risk of cardiovascular events	-	CANVAS[30] CREDENCE[32]
Sotagliflozin	200 mg daily	All	Type 2 diabetes	30	Low risk of cardiovascular deaths and hospitalizations for HF	Diarrhea, hypoglycemia, hypotension, genital mycotic infections, volume depletion, diabetic ketoacidosis, and kidney injury	SOLOIST-WHF[36] SCORED[35]
Ertugliflozin	5 mg or 15 mg	Not reported	Type 2 diabetes mellitus	30	No clinical significance compared to placebo	Genital mycotic infections, amputation, and diabetic ketoacidosis	VERTIS CV[39]

SGLT2, Sodium-glucose cotransporter 2; HF, Heart failure; eGFR, Estimated glomerular filtration rate; UTI, Urinary tract infection; HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction.

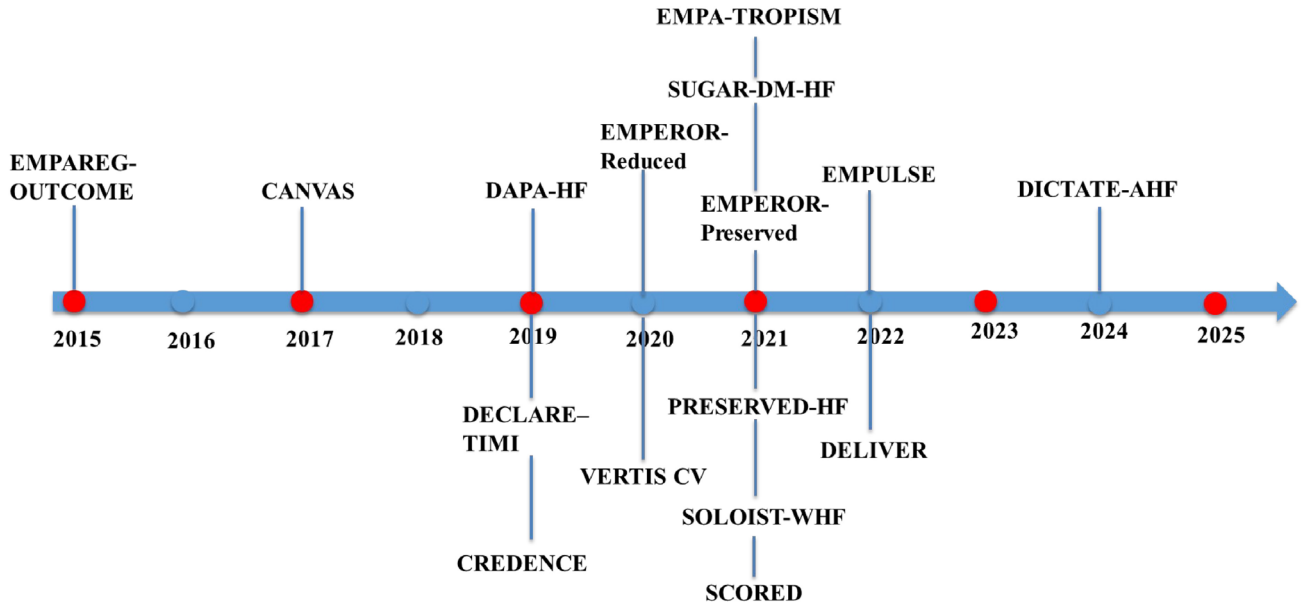

Fig 5 | Chronological timeline of major clinical trials evaluating SGLTs

findings from these studies, alongside scientific evidence from similar studies, aided the FDA approval of the drug for the management of HF in patients regardless of the presence of diabetes mellitus.[38]

Ertugliflozin

Despite limited scientific evidence, previous studies have proven the noninferiority of ertugliflozin compared to placebo in reducing the incidence of MACE in patients with type 2 diabetes.[39,40] The VERTIS CV trial enrolled patients with type 2 diabetes and atherosclerotic cardiovascular disease, and 5 mg or 15 mg of ertugliflozin was administered daily to the treatment group.[39] After a follow-up of more than 3 years, the study reported less incidence of cardiovascular deaths in the treatment group (8.1% vs. 9.1%; HR, 0.88; 95.8% CI, 0.75–1.03; p = 0.11); the reported findings did not reach statistical significance, necessitating the need for further studies in this field. However, a systematic review pooled findings regarding the cardiovascular outcomes of ertugliflozin from six studies and a cumulative sample size of 8,246 participants.[40]

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The study reported that, compared to placebo, ertugliflozin reduced exacerbations of HF (HR, 0.53; 95% CI, 0.33–0.84; $p < 0.01$) and hospitalizations due to HF (HR, 0.70; 95% CI, 0.54–0.90; $p < 0.05$).

Table 1 highlights a clinical decision matrix to guide the use of SGLT2 inhibitors in patients with coexisting HF and diabetes mellitus. Furthermore, Figure 5 presents the timeline of 16 pivotal clinical trials that have investigated the efficacy and safety of SGLT2 inhibitors in the management of type 2 diabetes mellitus and HF.

Discussion

Current Practice Guidelines

Current guidelines from the American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society of America (HFSA), and European Society of Cardiology endorse the dual use of SGLT2 inhibitors, particularly dapagliflozin and empagliflozin, for patients with and without diabetes who have HF. The benefits of SGLT2 inhibitors are seen across all stages of HF, including HF with reduced ejection fraction and HF with preserved ejection fraction.[41] The AHA/ACC/HFSA guidelines classify SGLT2 inhibitors as a Class 1 recommendation for chronic, stable HF with reduced ejection fraction and a Class 2A recommendation for HF with reduced ejection fraction and HF with preserved ejection fraction.[15] In addition to cardiovascular benefits, these drugs slow the progression of chronic kidney disease, making them a preferred choice for patients with diabetes and kidney impairment.[42] However, baseline renal function tests, as well as regular and careful monitoring, are recommended before initiating therapy to mitigate potential adverse effects.

Adverse Effects

Reported adverse effects of SGLT2 inhibitors include increased urination, hypoglycemia, genitourinary infections, diabetic ketoacidosis, and acute kidney injury. These events occur in approximately 70–80% of individuals, with the most frequently reported adverse events of empagliflozin being urinary tract infections (62.1 events/1,000 person-years), followed by genital mycotic infections (58.0 events/1,000 person-years).[43] Additionally, patients have reported experiences of hypotension, as well as acute changes in creatinine concentrations, particularly older individuals or those on diuretics.[44] Certain rare but severe complications have also been identified, including bone fractures and necrotizing fasciitis of the perineum, commonly known as Fournier's gangrene.[45,46] A study conducted by Ueda et al.,[47] utilizing nationwide registries across two countries, investigated serious adverse events associated with SGLT2 inhibitors. Their findings indicated an elevated risk of lower limb amputation and diabetic ketoacidosis, but not bone fractures, suggesting potential limitations in observational research methods for identifying rare adverse events associated with the drug. These discrepancies highlight the inherent uncertainty of effect estimates regarding serious adverse events linked to SGLT2 inhibitors. Additionally, current clinical trials designed to assess these rare adverse events have been constrained by small sample sizes and the selective nature of the study populations, limiting their applicability to broader clinical practice.

Future Directions

Despite their shared mechanism of action, individual SGLT2 inhibitors exhibit distinct pharmacokinetic properties that may influence the occurrence of adverse events. For instance, canagliflozin has demonstrated a higher risk of lower limb amputations,[48] whereas empagliflozin is linked with strong cardiovascular benefits but requires monitoring for ketoacidosis.[49] Understanding these variations can have significant implications for practice, enabling clinicians to tailor treatment based on patient-specific risk factors. To refine patient selection criteria and improve therapeutic outcomes, future research should focus on identifying predictive biomarkers for renal response to SGLT2 inhibitors. This approach would enhance personalized medicine strategies, allowing clinicians to optimize drug selection and dosing based on patient-specific physiological markers.

As highlighted by von Lewinski et al.[50] in the EMMY trial, empagliflozin was shown to significantly reduce serum N-terminal pro-B-type natriuretic peptide levels over 26 weeks when compared with placebo among post–percutaneous coronary intervention patients. However, further randomized controlled trials evaluating empagliflozin and dapagliflozin are needed to assess their potential effects on patient mortality and hospitalization rates in populations with acute myocardial infarction and HF. Furthermore, emerging research suggests that SGLT2 inhibitors may exert anti-inflammatory and antioxidative effects, potentially reducing the risk of atherosclerosis and coronary artery disease.[51] However, their influence on cardiac metabolism, ion homeostasis, and neuroprotection remains poorly understood, necessitating further investigation into their possible role in arrhythmia prevention and stroke mitigation. Similarly, future clinical trials should explore the efficacy of initiating SGLT2 inhibitors in early-stage chronic kidney disease to delay disease progression among both diabetic and nondiabetic patients. These research directions can contribute to a more comprehensive understanding of SGLT2 inhibitor safety and efficacy, ensuring optimal utilization in diverse patient populations.

Limitations

This review employed a narrative design, which, while suitable for synthesizing a broad body of evidence, inherently lacks the systematic rigor required for minimizing selection bias. As such, the selection and interpretation of trials may reflect subjective bias. While the narrative approach allows for greater flexibility in exploring diverse and complex literature, it does not support the application of standardized risk of bias tools or the conduct of a formal quantitative synthesis. As a result, the findings presented are based on thematic and conceptual interpretations rather than on pooled

statistical evidence, which may affect the strength and generalizability of the conclusions. Furthermore, the review is potentially affected by publication bias, as clinical trials with null or negative outcomes are less likely to be published or cited, skewing the overall assessment of efficacy. Moreover, many of the cited trials underrepresented low-income and socioeconomically disadvantaged populations. Additionally, the review included only studies published in English, which introduces the possibility of language bias. Excluding non-English literature may have resulted in the omission of relevant studies, particularly from regions where significant work on the topic may be published in other languages. This could limit the comprehensiveness and global applicability of the findings. This restricts the external validity and generalizability of findings to global populations.

Conclusions

Initially designed to lower blood glucose levels by preventing renal glucose reabsorption, these agents have also demonstrated efficacy in reducing cardiovascular mortality and hospitalizations related to HF. This study reported findings from clinical trials aiming to assess the cardiovascular outcomes of five SGLT2 inhibitors—empagliflozin, dapagliflozin, canagliflozin, sotagliflozin, and ertugliflozin. Multiple studies highlighted clinical benefits of SGLT2 inhibitors in comparison to placebo in the management of HF and the reduction of MACE. However, these benefits were also accompanied by a high incidence of adverse effects. The clinical benefits were also evaluated with assessment tools such as KCCQ and 6MWD, but the lack of objectivity of these tools may have contributed to the inconsistent findings.

Given the increasing use of SGLT2 inhibitors in cardiovascular disease management, additional research is required to elucidate their long-term safety profile. These include investigating the risk of Fournier's gangrene, bone fractures, diabetic ketoacidosis, euglycemic diabetic ketoacidosis, lower limb amputations, as well as potential hepatotoxicity. Comparative studies evaluating different agents within this drug class, including canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, are also necessary.

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