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LETTER

# SGLT2 Inhibitors in Cardiovascular Medicine: Panacea or Pandora's Box?

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## Abstract

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are antidiabetic agents that effectively lower blood glucose levels in patients with Type 2 Diabetes Mellitus (T2DM). Beyond their glycemic control properties, SGLT2 inhibitors have demonstrated significant cardiovascular benefits, including reductions in major adverse cardiovascular events. However, the limitations of the pivotal trials investigating these outcomes have not been fully explored. This letter aims to critically assess the major randomized clinical trials that evaluated the cardiovascular effects of SGLT2 inhibitors, highlighting both their strengths and limitations.

**Key words: SGLT2 inhibitors; heart failure; cardiovascular events; diabetes mellitus; myocardial infarction**

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i) function by specifically targeting and inhibiting the SGLT2 protein, which is crucial for the reabsorption of glucose in the proximal renal tubule. Under physiological conditions, SGLT2 is responsible for the reabsorption of approximately 90% of the glucose filtered by the kidneys, thereby returning it to the systemic circulation. By obstructing this transporter, SGLT2i impede glucose reabsorption, thereby enhancing the urinary excretion of glucose and consequently reducing plasma glucose levels. The pharmacological agents classified as SGLT2i include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin.

SGLT2i were initially developed for the management of Type 2 Diabetes Mellitus (T2DM) owing to their glycosuric properties. However, cardiovascular outcome trials conducted in patients with T2DM revealed an unanticipated and significant reduction in hospitalizations for heart failure (HF) associated with these agents (Cowie and Fisher, 2020). Subsequent studies conducted in patients with cardiomyopathies or high cardiovascular risk have confirmed the cardiovascular benefits of SGLT2i, as shown in Table 1. Despite these observations, the extent of the cardiovascular benefits provided by this class of drugs remains a subject of debate. This article aims to present a critical analysis of the key aspects of these cardiovascular effects.

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**Table 1. Summary of cardiovascular outcome trials with SGLT2i.**

| Study | Publication year | Recruitment period | Number of patients | Comparison groups | Follow-up | Inclusion criteria | Primary endpoint result | Cardiovascular or all-cause death result |
|---|---|---|---|---|---|---|---|---|
| EMPA-REG OUTCOME | 2015 | 2010–2013 | 7020 | Empagliflozin vs. Placebo | 3.1 years | T2DM with high CV risk | MACE: HR 0.86 (0.74–0.99) | HR 0.62 (0.49–0.77) |
| DECLARE-TIMI 58 | 2019 | 2013–2015 | 17,160 | Dapagliflozin vs. Placebo | 4.2 years | T2DM with or without ASCVD | MACE: HR 0.93 (0.84–1.03) | HR 0.98 (0.82–1.17) |
| CANVAS | 2017 | 2009–2015 | 10,142 | Canagliflozin vs. Placebo | 2.4 years | T2DM with high CV risk | MACE: HR 0.86 (0.75–0.97) | HR 0.87 (0.72–1.06) |
| DAPA-HF | 2019 | 2017–2018 | 4744 | Dapagliflozin vs. Placebo | 18.2 months | HFrEF with or without T2DM | CV death or HF hospitalization: HR 0.74 (0.65–0.85) | HR 0.82 (0.69–0.98) |
| EMPEROR-Reduced | 2020 | 2017–2019 | 3730 | Empagliflozin vs. Placebo | 16 months | HFrEF with or without T2DM | CV death or HF hospitalization: HR 0.75 (0.65–0.86) | HR 0.92 (0.75–1.12) |
| EMPA-RESPONSE-AHF | 2017 | 2014–2015 | 80 | Empagliflozin vs. Placebo | 60 days | AHF | NT–proBNP reduction (–30%) | HR 0.59 (0.41–0.85) |
| EMPULSE | 2022 | 2020–2021 | 530 | Empagliflozin vs. Placebo | 90 days | AHF | Composite of death, HF events, or symptoms: HR 0.67 (0.50–0.89) | HR 0.73 (0.51–1.04) |
| SOLOIST-WHF | 2020 | 2017–2020 | 1222 | Sotagliflozin vs. Placebo | 9 months | Worsening HF | Composite CV death, HF hospitalization: HR 0.67 (0.52–0.85) | HR 0.84 (0.64–1.11) |
| SCORED | 2021 | 2017–2020 | 10,582 | Sotagliflozin vs. Placebo | 9 months | CKD and T2DM | CV death or HF hospitalization: HR 0.74 (0.63–0.88) | HR 0.73 (0.60–0.89) |

**Table 1. Continued.**

| Study | Publication year | Recruitment period | Number of patients | Comparison groups | Follow-up | Inclusion criteria | Primary endpoint result | Cardiovascular or all-cause death result |
|---|---|---|---|---|---|---|---|---|
| DAPA-MI | 2024 | 2020–2023 | 4017 | Dapagliflozin vs. Standard of care | 24 months | MI within the preceding 7 days | Death, HF hospitalization, MI, atrial fibrillation/flutter, T2DM, NYHA class, and weight decrease: win ratio 1.34 (1.20–1.50) | HR 0.81 (0.45–1.16) |
| EMPACT-MI | 2024 | 2020–2023 | 6522 | Empagliflozin vs. Standard of care | 17.9 months | Post-MI patients | MI recurrence or HF hospitalization: HR 0.90 (0.76–1.06) | HR 0.96 (0.78–1.19) |

SGLT2i, Sodium-glucose cotransporter 2 inhibitors; AHF, Acute Heart Failure; ASCVD, Atherosclerotic cardiovascular disease; CANVAS, Canagliflozin Cardiovascular Assessment Study; CKD, Chronic Kidney Disease; CV, Cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DAPA-MI, Dapagliflozin in Patients with Myocardial Infarction; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPACT-MI, Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients with Acute Myocardial Infarction; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPA-RESPONSE-AHF, Effects of Empagliflozin on Clinical Outcomes in Patients with Acute Decompensated Heart Failure; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPULSE, Empagliflozin in Patients Hospitalized with Acute Heart Failure which has been stabilized; HF, heart failure; HFrEF, Heart failure with reduced ejection fraction; HR, hazard ratio; MACE, Major adverse cardiovascular events; MI, Myocardial Infarction; NYHA, New York Heart Association; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure; T2DM, Type 2 Diabetes Mellitus.

The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) was groundbreaking in demonstrating the cardiovascular benefits of empagliflozin (Zinman et al, 2015). Empagliflozin was associated with a reduction in cardiovascular mortality, non-fatal Myocardial Infarction (MI), or non-fatal stroke (10.5% vs. 12.1%; hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.74 to 0.99; $p$ = 0.04; number needed to treat [NNT] = 62.5). The 95% CI for NNT from the EMPA-REG OUTCOME trial was 31 to 10,000, indicating significant imprecision in the effect of empagliflozin in this studied population. Moreover, 67% of patients who were adjudicated as cardiovascular death in the placebo group and 72% of patients adjudicated for the same outcome in the empagliflozin group had sudden death or other cardiovascular death (which includes only fatal cases that were not assessable due to a lack of information and were presumed to be cardiovascular deaths as per conventional definition), with the latter definition accounting for approximately 40% of deaths in each group, which, if they had occurred for non-cardiovascular reasons, could influence the results. Acute MI had a low annual incidence (1.77%, including silent MI) even in a population considered at high cardiovascular risk. There was no difference between the groups regarding Myocardial Infarction or hospitalization for unstable angina (the latter considered a secondary outcome). Although we did not find data on ventricular function in the study population and events related to heart failure were not part of the primary or secondary outcomes, a significant reduction in hospitalization for heart failure was found in the group that received empagliflozin (HR 0.65, 95% CI 0.50 to 0.85). However, as ventricular function in the population was not used as an inclusion or exclusion criterion, we do not know if there was a discrepancy between the groups, that is, more patients with heart failure may have been randomized to the placebo group, with a greater probability of having a higher rate of hospitalization for this condition.

Based on the findings of EMPA-REG OUTCOME, investigators from The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) evaluated the effect of dapagliflozin compared with placebo and added hospitalization for heart failure to the already known Major adverse cardiovascular events (MACE) in the primary composite outcome (Wiviott et al, 2019). Once again, there was no statistically significant difference in cardiovascular events such as non-fatal MI or stroke. The reduction in cardiovascular death or hospitalization for HF was 17% (HR 0.83, 95% CI 0.73 to 0.95).

The benefits of SGLT2i have been considered a class effect. However, despite no head-to-head comparisons, less than impressive results have been found when evaluating other medications in the class. The Canagliflozin Cardiovascular Assessment Study (CANVAS) trial showed a lower rate of cardiovascular mortality, MI, or stroke (26.9 vs. 31.5 per 1000 patient-years; HR 0.86; 95% CI 0.75 to 0.97, NNT 52.6) with canagliflozin in patients with T2DM (Neal et al, 2017). The 95% CI for NNT from the CANVAS trial was 31 to 160, again indicating the imprecision in estimating the effect of the SGLT2i, in this case, canagliflozin. In this study, there was no discrimination of cardiovascular deaths. It is worth noting the increase in the incidence of non-traumatic amputation in patients using canagliflozin versus

placebo, 6.3% vs. 3.3%, respectively (HR 1.97, 95% CI 1.41 to 2.75), whose mechanisms are still unclear.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) and the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial evaluated the role of SGLT2i in patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF), renewing enthusiasm for this class of medications. In the DAPA-HF trial, dapagliflozin reduced the composite primary outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or cardiovascular death (16.3% vs. 21.2%; HR 0.74; 95% CI 0.65 to 0.85; $p < 0.001$; NNT 20.4) (McMurray et al, 2019), while EMPEROR-Reduced showed that empagliflozin reduced the composite primary outcome of cardiovascular death or hospitalization for worsening HF (19.4% vs. 24.7%; HR 0.75; 95% CI 0.65 to 0.86; $p < 0.001$; NNT 19) (Packer et al, 2020). The 95% CI for NNT in the DAPA-HF and EMPEROR-Reduced trials were 14 to 37 and 12.6 to 37, respectively, indicating that both medications have good precision of effect in the respective populations studied. However, SGLT2i was not superior to placebo in reducing cardiovascular mortality in the EMPEROR-Reduced trial. Amid the comparison of subgroups, the post-hoc analysis did not find homogeneity between groups. However, trends in confidence intervals pointed to greater benefit among elderly, less symptomatic patients (New York Heart Association [NYHA] II) with reduced LVEF and previous HF hospitalizations.

In patients with acute decompensated heart failure (HF), the study The Effects of Empagliflozin on Clinical Outcomes in Patients with Acute Decompensated Heart Failure (EMPA-RESPONSE-AHF) study demonstrated that empagliflozin was associated with a reduction in a composite endpoint of worsening HF, rehospitalization for HF, or death within 60 days (Damman et al, 2020). However, several limitations of this study should be noted: (1) a small sample size; (2) a relatively short follow-up period; and (3) no significant reduction in mortality or in the combined outcome of death or HF readmission within 60 days.

The Empagliflozin in Patients Hospitalized with Acute Heart Failure which has been stabilized (EMPULSE) and the Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trials evaluated the effects of empagliflozin and sotagliflozin, respectively, in patients with acute HF (Bhatt et al, 2021a; Biegus et al, 2023). In the EMPULSE trial, empagliflozin versus placebo was associated with significant clinical benefit (composite of death from any cause, number of HF events and time to first HF event, or improvement in quality-of-life score) at 90 days, although the risk of cardiovascular death was not significantly reduced with empagliflozin (Biegus et al, 2023). The SOLOIST-WHF trial showed a reduction in the composite primary outcome of cardiovascular deaths or hospitalizations and urgent visits for HF with sotagliflozin (HR 0.67; 95% CI 0.52 to 0.85; $p < 0.001$; NNT 3.9, with a 95% CI for NNT of 3.3 to 4.9) (Bhatt et al, 2021a). However, early discontinuation of the study affected its statistical power and may have overestimated the clinical benefits of sotagliflozin. Bassler et al (2010) showed that truncated randomized controlled

trials (RCTs) are associated with greater effect sizes than RCTs not stopped early. Additionally, the study showed that sotagliflozin was not associated with a reduction in cardiovascular death (HR 0.84, 95% CI 0.58 to 1.22). In the combined analysis of the Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) (Bhatt et al, 2021c) and SOLOIST-WHF trials, the benefits were preserved regardless of baseline LVEF (including patients with HF with preserved LVEF) and previous history of HF (Bhatt et al, 2021b). However, sotagliflozin was associated with increased occurrences of diarrhea (6.9% vs. 4.1%; $p = 0.032$) and severe hypoglycemia (1.5% vs. 0.3%; $p = 0.037$).

Meta-analyses of RCTs have consistently demonstrated the benefit of SGLT2i in reducing the composite outcome of cardiovascular death or hospitalization for heart failure in patients with heart failure, with the primary driver of this benefit being a significant reduction in hospitalizations for heart failure (Albalushi and Rashid Nadeem, 2023; Arnott et al, 2020; Jaiswal et al, 2023; McGuire et al, 2021; Usman et al, 2024; Vaduganathan et al, 2022; Zannad et al, 2020; Zelniker et al, 2019). However, moderate to high heterogeneity is often observed in the outcome of cardiovascular mortality, likely influenced by differences in study population characteristics, comorbidities, concomitant medication use, and variability in trial protocols. The efficacy of SGLT2i in reducing cardiovascular mortality appears to vary significantly depending on the type of heart failure, with clear benefits in heart failure with reduced ejection fraction (HFrEF), while results in heart failure with preserved ejection fraction (HFpEF) are more modest and primarily limited to reducing hospitalizations. Furthermore, many meta-analyses include mixed populations, such as those with T2DM or chronic kidney disease, which can dilute the interpretation of the heart failure-specific outcomes. The lack of a significant reduction in cardiovascular mortality in HFpEF, coupled with variability in study designs and follow-up durations, highlights the need for further research, particularly in targeted subgroups. Despite these limitations, the robust evidence supporting SGLT2i' ability to reduce heart failure hospitalizations underscores their importance in the therapeutic landscape, though more precise conclusions on mortality benefits remain elusive in certain populations.

In the scenario of patients with Myocardial Infarction, two recent clinical trials evaluated the effects of SGLT2i. The Dapagliflozin in Patients With Myocardial Infarction (DAPA-MI) study did not show significant benefits of dapagliflozin on the composite of cardiovascular death or hospitalization for heart failure compared with placebo (HR 0.95, 95% CI 0.64 to 1.40) (James et al, 2024). In the Effect of Empagliflozin on Hospitalization for Heart Failure and Mortality in Patients With Acute Myocardial Infarction (EMPACT-MI) study, empagliflozin did not provide a reduction in the composite outcome of a first hospitalization for HF or all-cause death when compared with placebo (HR 0.90, 95% CI 0.76 to 1.06) (Butler et al, 2024).

It is important to note that there are significant limitations in the RCTs evaluating the cardiovascular effects of SGLT2i. These limitations include: (1) a lack of uniformity in the outcomes studied; (2) the need for more long-term research to

fully understand the cardiovascular effects; (3) issues related to sample size; and (4) variability in the study populations, which may impact the generalizability of the results.

Despite their clinical benefits, warnings about adverse events have been documented. Ueda et al (2018) showed that SGLT2i, compared with Glucagon-Like Peptide-1 (GLP1) receptor agonists, were associated with an increased risk of lower limb amputation (2.7 vs. 1.1 events per 1000 person-years; HR 2.32, 95% CI 1.37 to 3.91) and diabetic ketoacidosis (DKA) (1.3 vs. 0.6 events per 1000 person-years; HR 2.14, 95% CI 1.01 to 4.52). Furthermore, recent trials have shown that with increasing doses of SGLT2i, a greater reduction in A1C, more weight loss, and a higher risk of DKA are observed (Dandona et al, 2018; Lin et al, 2021; Rosenstock et al, 2018). Recently, Tukker et al (2023) reported a case of SGLT2i-related polycythemia in a patient with chronic HF, emphasizing the need for monitoring hemoglobin and hematocrit in these patients.

Although the prescription of SGLT2i has become routine in several cardiovascular settings, their undeniable benefits, to date, are primarily observed in the treatment of HF among populations included in the trials—mainly symptomatic (NYHA I or II) elderly white men. Patients at risk of HF, such as those with a history of MI or multiple comorbidities, including T2DM, have not demonstrated significant benefit from early SGLT2i prescription. Currently, there is a lack of data on the effectiveness of SGLT2i in preventing HF or in providing additional benefit as part of the standard of care for other cardiovascular diseases.

Pragmatic clinical trials have shown that SGLT2i are beneficial in patients with HF. However, these studies have not demonstrated a possible metabolic effect of SGLT2i (assessed through the reduction in MI, or stroke rates) but only documented a beneficial diuretic effect (through the reduction of hospitalization for HF). As is known, gliflozins, in addition to promoting the reabsorption of glucose in the renal tubules, are responsible for the reabsorption of sodium, with an effect similar to loop diuretics. Therefore, SGLT2i increase diuresis, promoting control of the symptoms of HF. So, what studies have shown is just the diuretic effect of SGLT2i in patients with HF? No subanalysis of these clinical trials will be able to adequately answer this question, and the only way to test this hypothesis is through the comparison of SGLT2i with a control group that provides more diuresis, without offering the possible metabolic effects of gliflozins.

Unfortunately, pragmatic clinical trials are not scientific panaceas, and neither are gliflozins expected to be (Pawson, 2019). The primary requirement for scientific research is the construction of a robust body of evidence through multiple methodologies. Once a scientific discovery is made and Pandora's box is opened, it cannot be closed. While there may still be hope at the bottom of this box, it does not come in the form of a cure-all.

It is crucial to recognize the limitations inherent in these studies. While the existing evidence regarding the cardiovascular effects of SGLT2i is promising, it is not without its constraints. The study populations may not fully capture the diversity of the general population, and the duration of these studies may be inadequate for a thorough assessment of long-term effects. Furthermore, variability in outcomes

across different clinical trials necessitates additional investigation. Therefore, despite the observed benefits, more comprehensive and robust evidence is required to definitively establish the cardiovascular effects of these medications.

## Key Points

- Inconsistent Cardiovascular Benefits: While some studies, such as EMPA-REG OUTCOME and DECLARE-TIMI 58, suggest that SGLT2i may reduce hospitalizations for heart failure and improve certain cardiovascular outcomes, the magnitude of these effects remains unclear.
- Variable Outcomes in Heart Failure Studies: Trials such as DAPA-HF and EMPEROR-Reduced demonstrate reductions in the composite outcome of hospitalizations and cardiovascular mortality in patients with heart failure, yet there is no evidence that these medications decrease cardiovascular mortality, thereby limiting a comprehensive understanding of their clinical impact.
- Limitations in Clinical Trials: The lack of uniformity in the outcomes studied, limited sample sizes, and variability in study populations complicate the generalization of results and indicate a need for additional research to confirm the cardiovascular benefits of SGLT2i.
- Need for More Robust Studies: The current evidence on the cardiovascular effects of SGLT2i is promising but insufficient to conclusively establish their benefits and risks, highlighting the need for more rigorous studies to fully understand their role and safety in various clinical contexts.

## Availability of Data and Materials

All the data of this study are included in this article.

## Author Contributions

SdATF, ACRdA, LLHdO, PRS and TLS conceived and coordinated the manuscript. PRS and TLS prepared the draft of the manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

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## Conflict of Interest

The authors declare no conflict of interest.

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