# SGLT-2 Inhibitors After Acute Coronary Syndrome: A Preventive Approach for Heart Failure-Related Complications: A Meta-Analysis

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Sodium–glucose cotransporter-2 (SGLT-2) inhibitors have proven to be highly effective in the treatment of heart failure (HF), but their role in preventing stroke, cardiac death, or worsening heart failure events in patient's postacute coronary syndrome remains unclear. This meta-analysis evaluates whether SGLT-2 inhibitors improve cardiovascular outcomes in this setting. A comprehensive search of PubMed, Embase, and the Cochrane database was conducted for studies published up to December 2024, identifying 10 studies, 7 randomized controlled trials (RCTs), and 3 cohort studies, which compared the use of SGLT-2 inhibitors initiated after ACS versus placebo in patients hospitalized for acute coronary syndrome with at least 1 additional risk factor for heart failure hospitalization or adverse cardiovascular outcomes. Following PRISMA guidelines, the meta-analysis (PROSPERO registration: CRD42024543392) included data from 15,114 patients (6826 receiving SGLT-2 inhibitors and 8288 receiving placebo). SGLT-2 inhibitors significantly reduced the risk of first HF hospitalization (RR = 0.78, 95% CI, 0.66–0.92, $P = 0.003$) and stroke (RR = 0.56, 95% CI, 0.35–0.90, $P = 0.02$), with low heterogeneity ($I^2 = 0\%$). A significant reduction in cardiac death was also observed (RR = 0.84, 95% CI, 0.74–0.96, $P = 0.0009$), though this was driven mainly by observational studies. No significant effect was found for all-cause mortality. Subgroup analyses showed that empagliflozin significantly reduced HF hospitalization risk, while dapagliflozin did not. These findings suggest that the use of SGLT-2 inhibitors as part of postacute coronary syndrome management lowers the risk of heart failure hospitalization, cardiac death, and stroke.

**Keywords:** heart failure, acute coronary syndrome, sodium–glucose cotransporter-2 inhibitors, cardiac death, stroke

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This analysis relied on previously published data at the study level, so ethical approval was not necessary.

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## INTRODUCTION

Heart failure (HF) is characterized by structural or functional impairments that compromise the ventricle's ability to fill adequately with or eject blood, resulting in inadequate circulation. It is a common and severe complication after acute coronary syndrome (ACS).[1,2]

The incidence of HF varies by ACS subtype, with reported 1-year cumulative HF rates of 23.4% in patients with ST-segment elevation myocardial infarction (STEMI) and 25.4% in those with non-ST-elevation myocardial infarction (NSTEMI), compared with 16% in patients with unstable angina.[3] Despite advancements in ACS management, the risk of developing HF and its complications after ACS remains high[4,5] with several risk factors contributing to its development, including advanced age, prior myocardial infarction (MI), hypertension, and diminished renal function, among others.[6,7]

The development of this condition also increased significant morbidity of other conditions, as evidenced by increased hospitalization rates and poor prognosis in patients who experienced stroke.[8,9] For this reason, treatment strategies that modify or delay the progression of HF are essential.



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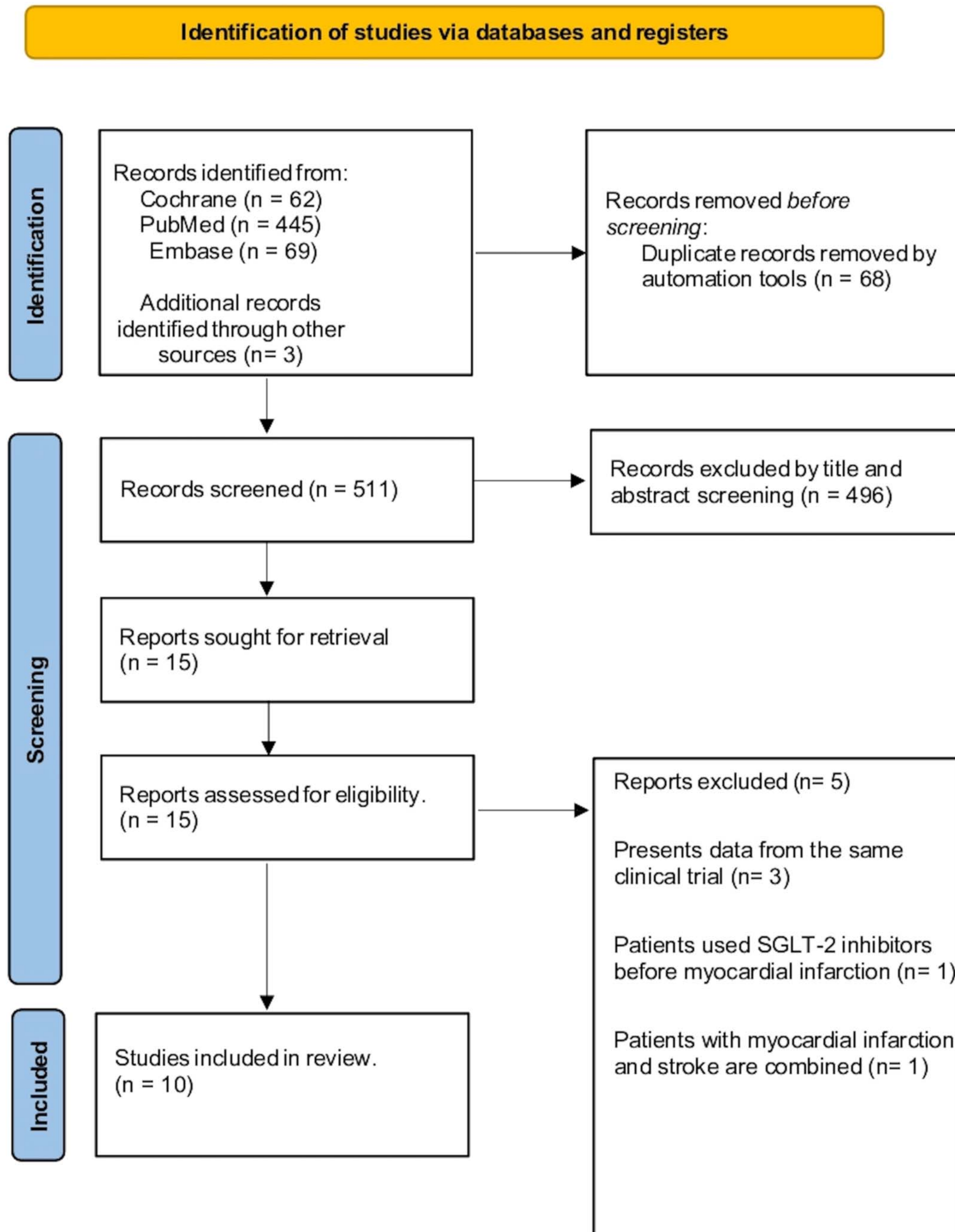


**FIGURE 1.** PRISMA flow diagram.

One such pharmacologic approach is the sodium–glucose cotransporter-2 (SGLT-2) inhibitors, which have demonstrated cardioprotective benefits in patients with various cardiometabolic conditions.[10]

However, the specific role of SGLT-2 inhibitors in preventing HF and its associated complications after ACS, regardless of the presence of type 2 diabetes, remains insufficiently explored.

This systematic review with meta-analysis aims to consolidate the existing evidence regarding the role of SGLT-2 inhibitors in reducing HF risk and its complications post-ACS.

## METHODS

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All procedures adhered to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3).[11] The


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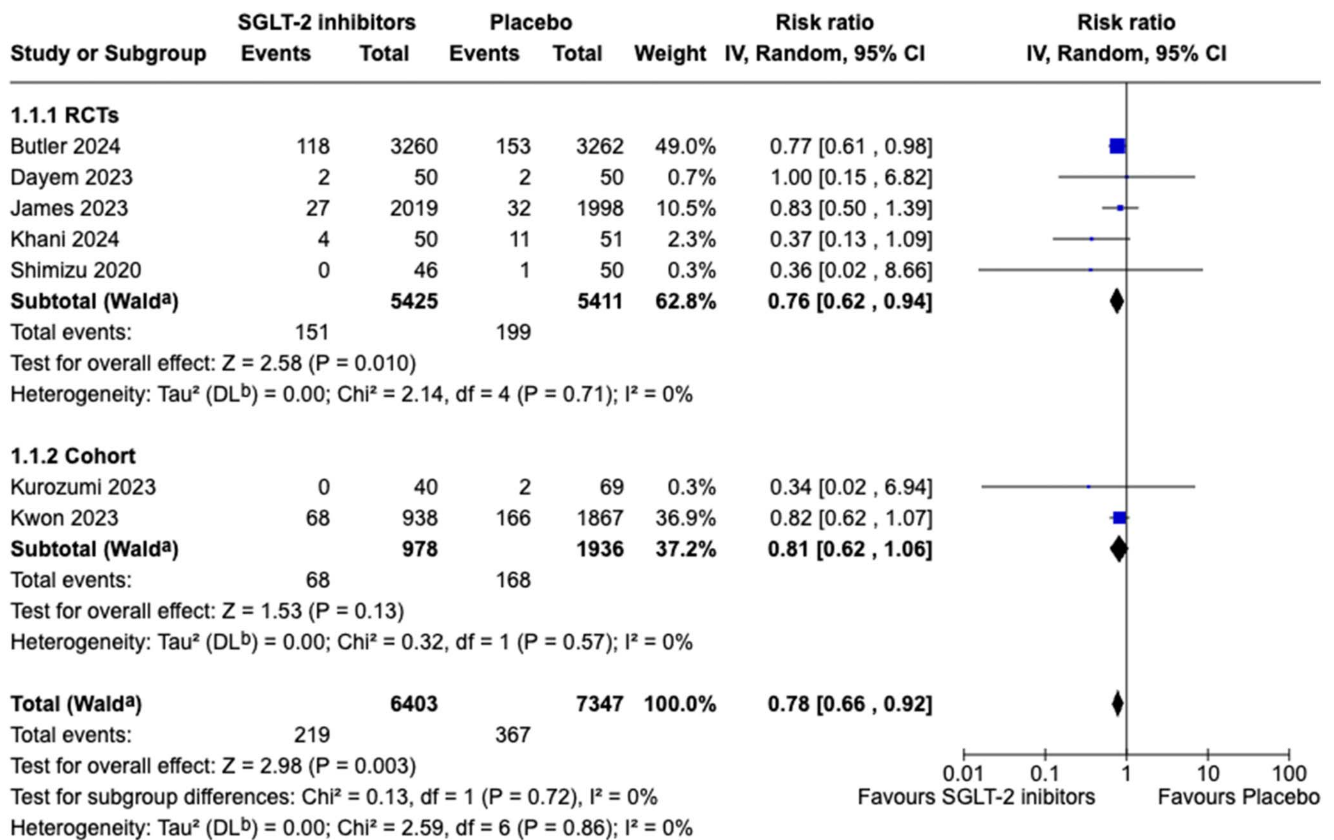


**FIGURE 2.** FH-HF. RRs for first hospitalization due to heart failure across 7 studies (5 RCTs and 2 cohort studies). A total of 219 events occurred in the SGLT-2 inhibitor group and 368 events in the placebo group. Pooled RRs for both subgroups and the overall effect shown as diamonds. Included studies: Butler 2024, Dayem 2023, James 2023, Khani 2024, Shimizu 2020 (RCTs), and Kurozumi 2023, Kwon 2023 (cohorts).

meta-analysis protocol was registered in PROSPERO on May 16, 2024, under ID: CRD42024543392.

## Data sources and search strategy

A systematic search was conducted in PubMed, Embase, and the Cochrane Library from their inception to June 2024. Considering the time of the first search, we conducted an exploratory search in December 2024 to identify new relevant clinical controlled trials. The search used keywords such as "heart failure," "empagliflozin," "SGLT-2 inhibitors," "myocardial infarction," "dapagliflozin," "hospitalization," "acute coronary syndrome," "cardiovascular death," and "stroke," using Boolean operators (AND, OR).

## Study selection

After removing duplicates using Zotero, 2 independent reviewers (K.V.J.-A. and S.E.C.-H.) screened the titles and abstracts. Full-text reviews were conducted for articles that met the inclusion criteria. Discrepancies were resolved by consensus with a third reviewer (M.P.-V.). In addition, the references of included studies were manually reviewed to identify additional eligible studies.

We included studies that met the following criteria: patients hospitalized with ACS who received standard treatment plus first-time administration of SGLT-2 inhibitors (eg, dapagliflozin, empagliflozin) compared with standard therapy plus placebo. Eligible studies comprised original research, including randomized controlled trials (RCTs) and observational studies.

Studies were excluded if they involved patients with prior use of SGLT-2 inhibitors, which was corroborated exhaustively through the revision of the exclusion criteria reported in the selected studies. Case–control studies, cross-sectional studies, systematic reviews, meta-analyses, case reports, basic science research, conference abstracts, and letters to the editor were also excluded. The search was restricted to studies published in English and Spanish.

## Risk of bias assessment

The quality of observational cohort studies was assessed using the Risk of Bias in Non-Randomized Studies

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**Table 1.** Summary of included studies.

| Author & year | Journal | Country | Study design | Population size (included) | Compared interventions | Mean follow-up | Key findings |
|---|---|---|---|---|---|---|---|
| Butler et al[21] 2024 | NEJM | International | Randomized controlled trial | 6522 | SGLT-2i versus non-SGLT-2i | 17.9 mo | The primary end point event, which was the first hospitalization for heart failure or death from any cause, occurred in 8.2% of the empagliflozin group and 9.1% of the placebo group (HR 0.90; CI, 0.76–1.06; $P$=0.21).<br>Death from cardiovascular causes occurred in 4.0% in the empagliflozin group and 4.0% in the placebo group (HR 1.03; CI 0.81–1.31). The time to death from cardiovascular causes and the time to the first hospitalization for heart failure or death from cardiovascular causes were similar between the 2 groups |
| James et al[22] 2023 | NEJM | International | Randomized controlled trial | 4017 | SGLT-2i versus non-SGLT-2i | 1 yr | The outcomes obtained in this hierarchical composite study had a greater result in favor of those patients undergoing the study with dapagliflozin than with placebo, with a 95% confidence interval of 1.20–1.50; $P<0.001$<br>Another win ratio was adopted because of a change in analysis due to low accumulation of events, the time to death plus hospitalization for heart failure obtained 50/2019 (2.5%) patients with dapagliflozin and 52/1998 (2.6%) placebo patients (risk ratio, 0.95%; 95% CI, 0.64 to 1.40).<br>Other cardiovascular events had low rates and the differences obtained between the groups did not reach nominal statistical significance. |
| von Lewinski et al[23] 2022 | European Heart Journal | Austria | Randomized controlled trial | 476 | SGLT-2i versus non-SGLT-2i | 26 wk | Mean NT-proBNP levels decreased in both groups during the study, but the reduction was significantly greater in the empagliflozin group than in the placebo group, becoming apparent by 12 weeks ($P$=0.021).<br>The left-ventricular ejection fraction increased by an absolute 1.5% (95% CI 0.2%–2.9%; $P$=0.029) more in the empagliflozin group than in the placebo group.<br>Serious adverse event rates were similar between the empagliflozin and placebo groups. A total of 72 serious adverse events occurred, with 63 participants hospitalized. Of these, 7 participants were hospitalized for heart failure (3 in the empagliflozin group and 4 in the placebo group). There were 3 deaths during the study, all in the empagliflozin group. |
| Adel et al[25] 2022 | Saudi Medical Journal | Iran | Randomized controlled trial | 93 | SGLT-2i versus non-SGLT-2i | 6 mo | Weight change was significantly greater in the experimental group ($P$=0.001). During the 6-month follow-up, the empagliflozin group lost an average of 2 kg of weight, while the placebo group did not have any weight loss. The fasting blood sugar levels post-treatment were significantly lower in the experimental group ($P$=0.048).<br>There was no significant difference between the 2 groups during the 6-month follow-up in terms of cardiovascular death |


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**Table 1.** (*Continued*) Summary of included studies.

| Author & year | Journal | Country | Study design | Population size (included) | Compared interventions | Mean follow-up | Key findings |
|---|---|---|---|---|---|---|---|
| | | | | | | | (*P*=0.598), hospitalization due to unstable angina (*P*=0.433), and coronary revascularization (*P*=0.312) after treatment. In addition, there were no occurrences of nonfatal MI, TIA, stroke, hospitalization due to heart failure, or all-cause mortality in either group. |
| Shimizu et al[26] 2022 | Cardiovascular Diabetology | Japan | Randomized controlled trial | 96 | SGLT-2i versus non-SGLT-2i | 24 wk | A significant improvement in HRT was observed exclusively in the empagliflozin group (*P* = 0.01). However, when comparing HRV and HRT between groups, no notable differences were found between the empagliflozin and placebo groups. In contrast, the empagliflozin group demonstrated significant reductions in body weight, systolic blood pressure, and uric acid levels compared with the placebo group. Furthermore, no adverse events were reported in the empagliflozin group. |
| Dayem et al[24] 2023 | International Journal of Cardiology | Egypt | Randomized controlled trial | 100 | SGLT-2i versus non-SGLT-2i | 12 wk | A significant drop in NT-proBNP levels by 10.17% and decreased LV mass index by 7.07% was observed in the study group in comparison with the control group. |
| Khani et al[27] 2024 | American Journal of Cardiovascular Drugs | Iran | Randomized controlled trial | 101 | SGLT-2i versus non-SGLT-2i | 6 mo | LV ejection fraction 40 days after percutaneous coronary intervention was higher in the intervention group than in the placebo group [43.2% (5.8%) versus 39.2% (6.7%); *P* = 0.002].<br>They did not observe any significant difference in the mean level of cTnI at each time point analyzed between the 2 groups. |
| Kwon et al[18] 2023 | Journal of the American Heart Association | South Korea | Retrospective cohort study | 2814 | SGLT-2i versus non-SGLT-2i | 5 yrs | The lower risk of the primary end point was associated with the early use of SGLT-2 inhibitors compared with no use of SGLT-2 inhibitors, where it was possible to observe a 95% CI, 0.54–0.87; *P*= 0.002.<br>All-cause of death had an incidence significantly lower in the SGLT-2 inhibitors group compared with the no use of SGLT-2 inhibitors group (3.7% vs. 6.6%; adjusted HR, 0.55 [95% CI, 0.37–0.80] *P* =0.002).<br>Those patients treated with SGLT-2 inhibitors had a lower cumulative hospitalization rate for HF (7.4% vs. 9.8%; adjusted HR, 0.74 [95% CI,0.56–0.98]; *P* = 0.03).<br>Patients treated with SGLT-2 inhibitor had a lower rate of secondary end point, unlike those without SGLT-2 inhibitor (9.1% vs. 11.6%, adjusted HR, 0.77 [95% CI, 0.60–0.99]; *P*= 0.04).<br>Were observed in term of incidence of nonfatal MI no statistical differences of (4.8% in the SGLT-2 inhibitor group vs. 4.9% in the no use of SGLT-2 inhibitor group; adjusted HR 0.97[95%CI 0.68–1.40]; *P*= 0.01), nonfatal ischemic stroke (1.5% in the SGLT-2 inhibitors group vs. |

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**Table 1.** (*Continued*) Summary of included studies.

| Author & year | Journal | Country | Study design | Population size (included) | Compared interventions | Mean follow-up | Key findings |
|---|---|---|---|---|---|---|---|
| | | | | | | | 2.5% in the no use of SGLT-2 inhibitors; adjusted HR, 0.61[95% CI, 0.33–1.10]; $P$= 0.10) |
| Zhu et al[20] 2022 | Cardiovascular Diabetology | China | Retrospective cohort study | 786 | SGLT-2i versus non-SGLT-2i | 23 mo | Patients undergoing DAPA-free revealed a cumulative incidence of MACE (log-rank test, $P$= 0.009), heart failure ($P$=0.003), nonfatal MI ($P$=0.005), and URR ($P$=0.031).<br>Patients with DAPA had a reduced risk of MACE (hazard ratio = 0.170, 95% CI= 0.078–0.373, $P < 0.001$.<br>Significant protection against MACE can be observed in those who underwent DAPA. |
| Kurozumi et al[19] 2023 | AHA/ASA Journals Circulation | Japan | Retrospective cohort study | 109 | SGLT-2i versus. non-SGLT-2i | 6 mo | A retrospective study with ACS and T2DM showed that SGLT-2 inhibitors significantly improved unstable plaque characteristics.<br>Optical coherence tomography revealed thicker fibrous caps and reduced lipid arcs in patients treated with SGLT-2i<br>Patients receiving SGLT-2i had a lower incidence of major adverse cardiovascular events (MACEs) and reduced rates of revascularization after 1 year. |

DAPA, dapagliflozin; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; NEJM, The New England Journal of Medicine; URR: urea reduction ratio.

of Interventions (ROBINS-I) tool.[12] Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (ROB 2) tool.[13] All assessments were performed independently by 2 reviewers, with conflicts resolved through consensus.

## Data extraction

Data extraction was performed using standardized Excel forms. The collected information included study identifiers such as author, year of publication, journal, and study design type. Baseline population characteristics, including sex, age, and comorbidities, were also extracted. In addition, the type and dosage of SGLT-2 inhibitors used were recorded when available. Finally, data related to the primary and secondary outcomes were collected. Two reviewers performed data extraction independently, with any discrepancies resolved by a third reviewer.

The primary outcome established for this meta-analysis included (1) first hospitalization for heart failure (FH-HF), defined as the first hospital admission for HF after ACS[1,2]; (2) cardiac death, defined as cardiac arrest occurring within 1 hour of onset of symptoms[14]; (3) stroke, defined as an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction.[14,15] Secondary outcomes included (1) myocardial infarction, established according to the fourth universal definition[14–16]; (2) all-cause mortality, defined as mortality from any cause using the standardized definition for evaluation of heart failure therapies[17]; (3) first hospitalization for heart failure or all-cause mortality: a combined outcome including FH-HF or mortality.

All outcomes were assessed as dichotomous categorical variables, which were reported in percentages. We calculated the risk ratio (RR) with its corresponding 95% confidence interval (95% CI).

## Analytic approach

The statistical analysis was performed on all outcome measures extracted from the included studies. Given the combination of randomized controlled trials and observational studies in our meta-analysis, we selected risk ratios (RR) with 95% confidence intervals as our primary effect measure to ensure consistent interpretation across different study designs.

Although RCTs and cohort studies differ in methodological characteristics, both were included to provide a comprehensive evaluation of the evidence. RCTs provide high internal validity, and cohort studies contribute external validity by reflecting real-world clinical settings.

To address anticipated variations in study populations and protocols, we used a random-effects model using the DerSimonian–Laird estimator, which provides more conservative estimates when heterogeneity is present. In addition, for all primary outcomes, we conducted a stratified analysis based on study design to enhance the interpretability of our findings.

Heterogeneity was assessed using the $I^2$ statistic with values interpreted as follows: <25% (low), 26%–50% (moderate), 51%–75% (significant), and >75% (high). Statistical


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**Table 2.** Baseline characteristics of the included studies' populations.

| Reference | Group | N | Age (year), mean | STEMI (%) | NSTEMI (%) | Unstable angina (%) | Previous MI (%) | Stroke | Hypertension | DM2 |
|---|---|---|---|---|---|---|---|---|---|---|
| Randomized controlled trial studies | | | | | | | | | | |
| Butler et al[21] 2024 | EMPA | 3260 | 63.6 | 2444 (75.0) | 814 (25.0) | — | 388 (11.9) | — | 2262 (69.4) | 1046 (32.1) |
| | Placebo | 3262 | 63.7 | 2401 (73.6) | 861 (26.4) | — | 459 (14.1) | — | 2276 (69.8) | 1035 (31.7) |
| Stefan James et al[22] 2023 | DAPA | 2019 | 63 | 1465 (72.6) | 544 (26.9) | — | 178 (8.8) | 46 (2.3) | — | — |
| | Placebo | 1998 | 62.8 | 1428 (71.5) | 562 (28.1) | — | 189 (9.5) | 50 (2.5) | — | — |
| Lewinski et al[23] 2022 | EMPA | 237 | 57 | — | — | — | 14 (5.9) | 5 (2.1) | 92 (39.0) | 33 (14) |
| | Placebo | 239 | 57 | — | — | — | 9 (3.8) | 1 (0.4) | 107 (45.0) | 30 (13) |
| Adel et al[25] 2022 | EMPA | 45 | 55 | 27 (60.0) | 2 (4.4) | 16 (35.6) | — | 1 (2.2) | 26 (57.8) | — |
| | Placebo | 48 | 57 | 23 (50.0) | 4 (8.3) | 21 (43.8) | — | 2 (4.2) | 32 (66.7) | — |
| Shimizu et al[26] 2022 | EMPA | 46 | 63.9 | — | — | — | — | — | 38 (82.6) | 46 (100) |
| | Placebo | 50 | 64.6 | — | | — | — | — | 39 (78) | 50 (100) |
| Dayem et al[24] 2023 | DAPA | 50 | 55.2 | 50 (50.0) | — | — | — | 0 (0.0) | 32 (64.0) | — |
| | Placebo | 50 | 56.7 | 50 (50.0) | — | — | — | 0 (0.0) | 29 (58.0) | — |
| Khani et al[27] 2024 | EMPA | 50 | 59.2 | 50 (49.5) | — | — | — | 0 (0.0) | 24.0 (48.0) | — |
| | Placebo | 51 | 61.6 | 51 (50.5) | — | — | — | 0 (0.0) | 22.0 (43.0) | — |
| Retrospective cohort studies | | | | | | | | | | |
| Osung Kwon et al[18] 2023 | SGLT-2i | 938 | 56.4 | 550 (58.6) | 739 (39.4) | — | — | 54 (5.8) | 699 (74.5) | — |
| | Placebo | 1876 | 57.6 | 1137 (60.6) | 739 (39.4) | — | — | 111 (5.9) | 1398 (74.5) | — |
| Yi Zhu et al[20] 2022 | DAPA | 141 | 60.6 | 99 (70.2) | — | — | — | 8 (5.7) | 104 (73.8) | 96 (68.1) |
| | Placebo | 645 | 62.5 | 396 (61.4) | — | — | — | 40 (6.2) | 393 (60.9) | 96 (14.9) |
| Kurozumi et al[19] 2024 | SGLT-2i | 40 | 65.4 | 29 (72.5%) | 6 (15.0) | 5 (12.5) | — | — | 29 (72.5) | 40 (100.0) |
| | Placebo | 69 | 73.8 | 41 (59.4%) | 17 (24.6) | 11 (15.9) | — | — | 54 (78.3) | 69 (100.0) |

DAPA, dapagliflozin; DM2, type 2 diabetes mellitus; EMPA, empagliflozin; NSTEMI, non-ST-elevation myocardial infarction; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.

significance was set at $P < 0.05$. Forest plots were generated using RevMan v.5.4.1.

## RESULTS

A total of 10 studies, including 3 observational studies[18–20] and 7 RCTs,[21–27] were included in the meta-analysis. Figure 1 shows the study selection process in the PRISMA flow diagram. In total, 15,114 patients were included, with 6826 receiving SGLT-2 inhibitors and 8288 assigned to placebo. Table 1 presents a summary of patient demographics and baseline characteristics, and Table 2 outlines the characteristics of the individual studies.

### First hospitalization due to heart failure

The pooled evidence demonstrated a significant reduction in the risk of FH-HF with SGLT-2 inhibitors (RR = 0.78, 95% CI, 0.66–0.92, $P = 0.003$), with low heterogeneity across the studies ($I^2 = 0\%$). This was also observed in the analysis of RCTs (RR = 0.76, 95% CI, 0.62–0.93, $P = 0.0009$, $I^2 = 0\%$); however, among the observational studies, a similar but nonsignificant trend was observed (RR = 0.81, 95% CI, 0.62–1.06, $P = 0.13$, $I^2 = 0\%$). These findings are presented in Figure 2. In a subgroup analysis, the use of empagliflozin showed a significant risk reduction (RR = 0.74, 95% CI, 0.59–0.94, $P = 0.01$, $I^2 = 0\%$), whereas dapagliflozin did not demonstrate a statistically significant effect (RR = 0.84, 95% CI, 0.52–1.38, $P = 0.50$, $I^2 = 0\%$). Findings are shown in **Supplemental Digital Content 1**, **Figures 1 and 2**, http://links.lww.com/AJT/A237.

### Cardiac death

A significant decrease in the risk of cardiac death in the SGLT-2 inhibitors group was observed in the overall analysis (RR = 0.84, 95% CI, 0.74–0.96, $P = 0.0009$, $I^2 = 0\%$). RCT analysis showed a favorable tendency for the SGLT-2 inhibitors but without reaching statistical significance (RR = 0.89, 95% CI, 0.76–1.05, $P = 0.17$, $I^2 = 0\%$); in contrast, observational studies demonstrated a significant reduction in the risk (RR = 0.73, 95% CI, 0.58–0.92, $P = 0.009$, $I^2 = 0\%$). These findings are shown in Figure 3. A nonsignificant trend for risk reduction was observed in an exploratory subgroup analysis of empagliflozin (RR = 0.89, 95% CI, 0.76–1.05, $P = 0.17$, $I^2 = 0\%$). No RCTs reporting this outcome evaluated dapagliflozin specifically. Findings are shown in **Supplemental Digital Content 1**, **Figure 3**, http://links.lww.com/AJT/A237.

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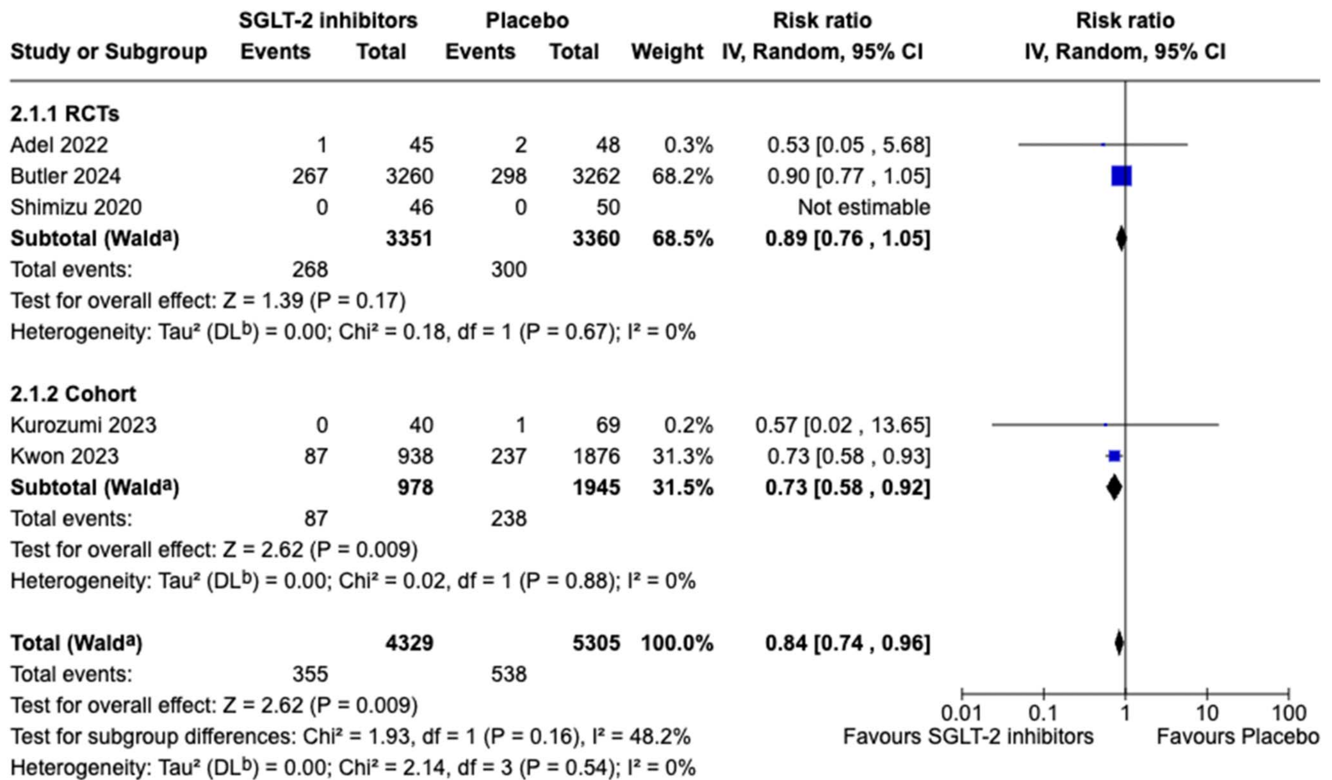


**FIGURE 3.** Cardiac death. RRs for cardiac death across 5 studies (RCTs and cohort studies), 355 events in the SGLT-2 inhibitor group and 538 in the placebo group, across a combined population of 9634 participants. A diamond summarizes the pooled RR using random-effects model. Studies included Adel 2022, Butler 2024, Shimizu 2020 (RCTs), and Kurozumi 2023, Kwon 2023 (cohort).

## Stroke

Our main analysis showed a statistically significant reduction in stroke risk with SGLT-2 inhibitors compared with placebo (RR = 0.56, 95% CI, 0.35–0.90, $P$ = 0.02, $I^2$ = 0%). Observational studies demonstrated a significant reduction in risk (RR = 0.56, 95% CI, 0.31–1.00, $P$ = 0.05, $I^2$ = 0%), whereas only one controlled trial reported this outcome, and did not show a significant difference (RR = 0.58, 95% CI, 0.27–1.27, $P$ = 0.17). Findings are shown in Figure 4.

## All-cause mortality

The combined analysis showed no significant difference between SGLT-2 inhibitors and placebo (RR = 0.86, 95% CI, 0.62–1.20, $P$ = 0.38, $I^2$ = 42%; Figure 5).Although a significant risk reduction was observed among the observational studies (RR = 0.58, 95% CI, 0.40–0.83, $P$ = 0.003, $I^2$ = 0%), no significant difference was observed in the RCT analysis. Findings are shown in Figure 5. In the empagliflozin subgroup analysis, no difference was found when compared with placebo (RR = 1.07, 95% CI, 0.75–1.54, $P$ = 0.69, $I^2$ = 39%). These findings are presented in the **Supplemental Digital Content 1**, **Figure 4**, http://links.lww.com/AJT/A237.

## DISCUSSION

This meta-analysis demonstrated that incorporating SGLT-2 inhibitors into post-ACS management is associated with reductions in the risk of first hospitalization due to HF, and cardiovascular death, as well as a reduction of stroke risk. However, it is important to note that these benefits did not translate into a statistically significant reduction in mortality (Figure 5).

We confirmed that SGLT-2 inhibitors significantly reduce the risk of FH-HF compared with placebo, particularly in randomized controlled trials. Although observational studies did not show a significant reduction in FH-HF risk, the overall analysis confirmed a significant benefit. These findings align with the cardiovascular outcomes from the DAPA-MI trial,[22] which found that dapagliflozin improved cardiometabolic outcomes and reduced new-onset HF in patients with acute MI and impaired left ventricular function. Similarly, the EMPACT-MI[21] reported a significant reduction


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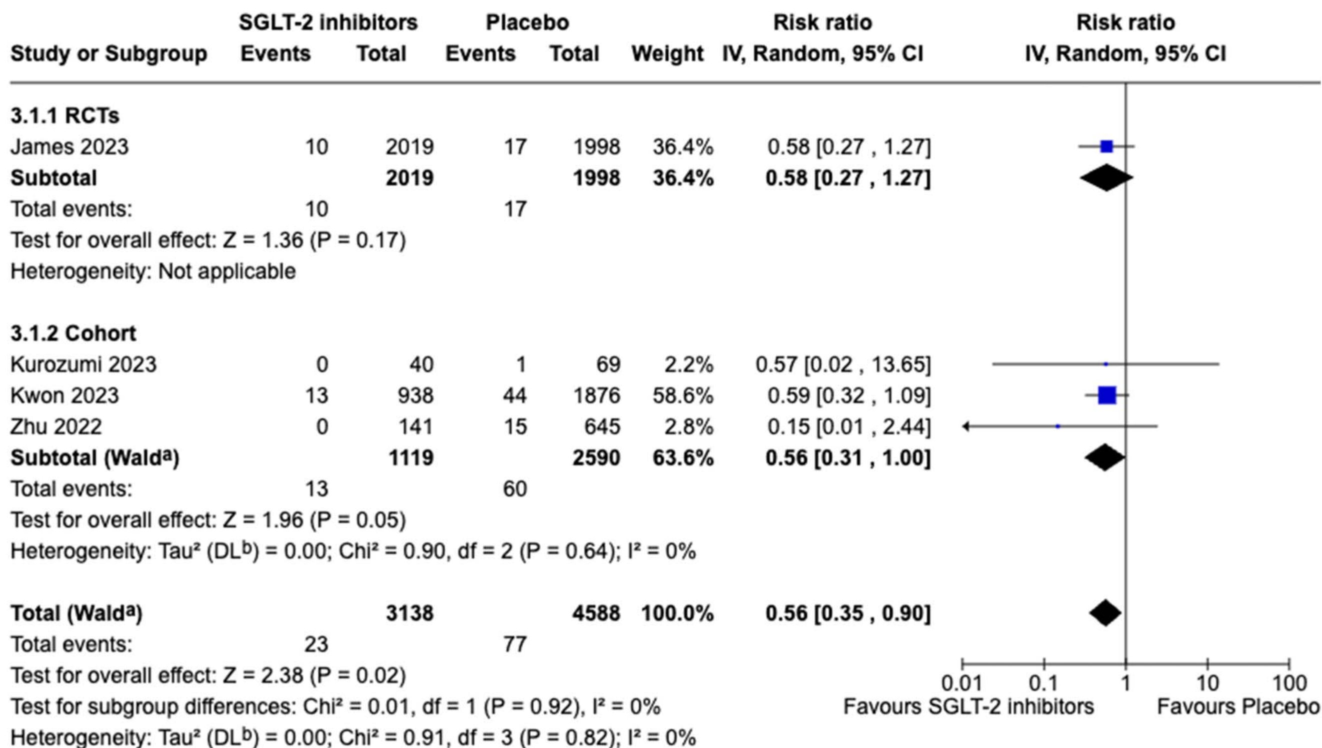


**FIGURE 4.** Stroke. RRs for stroke across 5 studies (3 RCTs and 2 cohort studies). A total of 23 stroke events occurred in the SGLT-2 inhibitor group and 77 in the placebo group (n = 7726; 3138 SGLT-2 inhibitors; 4588 placebo). Pooled subgroup and overall RRs, calculated using random-effects models, are shown as diamonds. Studies included James 2023 (RCT), Kurozumi 2023, Kwon 2023, Zhu 2022 (cohorts).

in the individual outcome of FH-HF; however, it did not show differences in the composite end point of FH-HF and mortality. In addition, Zhu et al[20] highlighted that dapagliflozin reduced the risk of major adverse cardiovascular events (MACE) in this special population, with special benefits observed in older patients and those with concomitant diabetes. This evidence suggests that SGLT-2 inhibitors are consistently effective in reducing HF-related outcomes, particularly in controlled trial settings, where stricter patient selection and adherence to protocols may enhance treatment effects.

Regarding cardiovascular death, we observed a significant overall reduction in risk with the use of SGLT-2 inhibitors. However, although cohort studies demonstrated a clear benefit, randomized controlled trials only showed a nonsignificant trend toward risk reduction, as illustrated by the EMPACT-MI trial,[21] which did not show differences. Given the absence of a definitive benefit in RCTs, these findings should be interpreted with caution.

Concerning stroke outcomes, studies such as those by Kurozumi et al,[19] Kwon et al[18] and Zhu et al[20] observed a reduced stroke incidence in the SGLT-2 inhibitors group. Our meta-analysis identified a statistically significant reduction in stroke risk when combining data from both RCTs and observational studies. However, because this result is based on only 4 studies, it should be considered an exploratory finding and interpreted with caution. Further dedicated RCTs are warranted to confirm this potential benefit.

Important to note that no statistical significance was found regarding all-cause mortality, a result consistent across major controlled trials such as EMPACT-MI[21] or DAPA-MI.[22] In contrast, Kwon et al[18] reported a mortality benefit in their cohort study. This lack of benefit may reflect the complex interplay of conditions of cardiometabolic risk factors in patients with ACS and contribute to increased mortality through chronic complications such as nephropathy. This finding highlights an important limitation that warrants further investigation.

On a molecule-specific exploratory analysis, empagliflozin[21,26,27] was associated with a significant risk reduction in FH-HF, whereas dapagliflozin was not,[22,24] possibly because of the small number of available studies. Only empagliflozin could be evaluated for cardiovascular death and all-cause mortality, with no significant differences observed.[21,25,26] Stroke outcome could not be stratified by molecule because of insufficient data. These findings should

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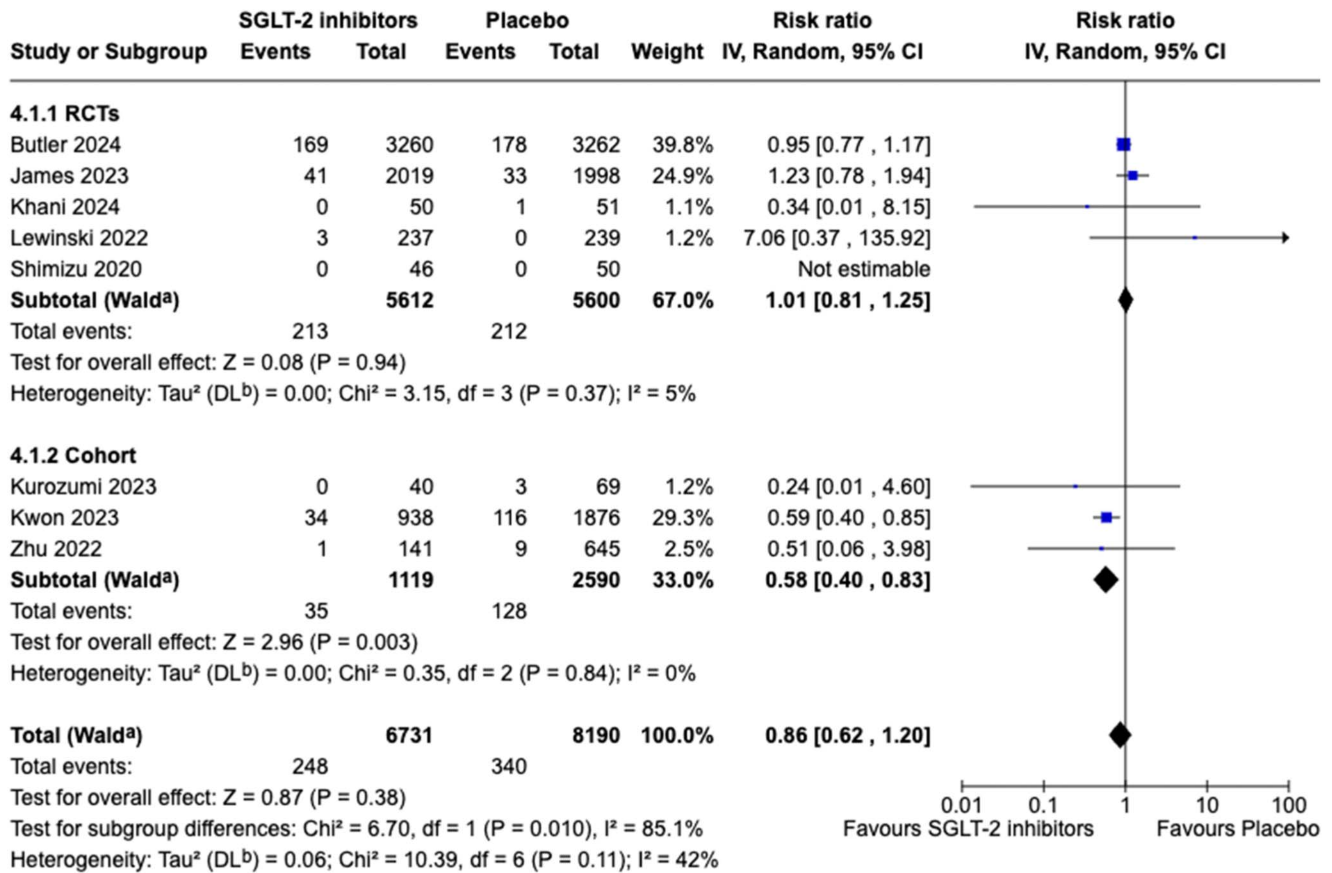


**FIGURE 5.** All-cause mortality. RRs for all-cause mortality across 8 studies (5 RCTs and 3 cohort studies). A total of 248 events occurred in the SGLT-2 inhibitor group and 340 in the placebo group, across 14,041 participants (6731 and 8,190, respectively). Diamonds represent pooled effect estimates for each subgroup and the overall analysis. Contributing studies include Butler 2024, James 2023, Khani 2024, Lewinski 2022, Shimizu 2020 (RCTs), and Kurozumi 2023, Kwon 2023, Zhu 2022 (cohorts).

be interpreted with caution, because the subgroup analyses were limited because of insufficient data. Nonetheless, they underscore the need for future research aimed at elucidating potential differences among individual SGLT-2 inhibitors in the context of ACS.

Our meta-analysis is unique for various reasons. For instance, it evaluates a cohort where SGLT-2 was initiated after ACS, and not beforehand, a limitation present in prior studies.[28] Therefore, a more robust assessment of the cardioprotective effects of SGLT-2 was able to be conducted. In addition, this study also assessed the reduction in stroke, an outcome not systematically explored in prior analyses.[28,29] Finally, our meta-analysis included studies conducted in diverse populations, which, compared with prior focused studies, increases the generalizability of our findings.[28–30]

## Limitations

We acknowledge that our study has multiple limitations. First, the differences in quality and type of included studies. The inclusion of observational studies introduces an inherent risk of bias and confounding. All 3 observational studies included were rated as having a moderate risk of bias primarily because of their retrospective design, which limited the ability to define groups at the start of the intervention and introduced potential confounding. In the case of RCTs, three studies showed some concerns, mainly because of missing outcome data and outcome data and measurement inconsistencies, while 4 were assessed as low risk of bias. Despite these limitations, the overall consistency in the direction of effect across study types supports the reliability of the conclusions, though the magnitude of benefit should be interpreted with caution. Comprehensive details of the risk of bias assessments are presented in Figure 6.

Second, the heterogeneity in follow-up periods across the studies limits a consistent evaluation of long-term outcomes. However, most of the included studies have at least 1 year of follow-up.


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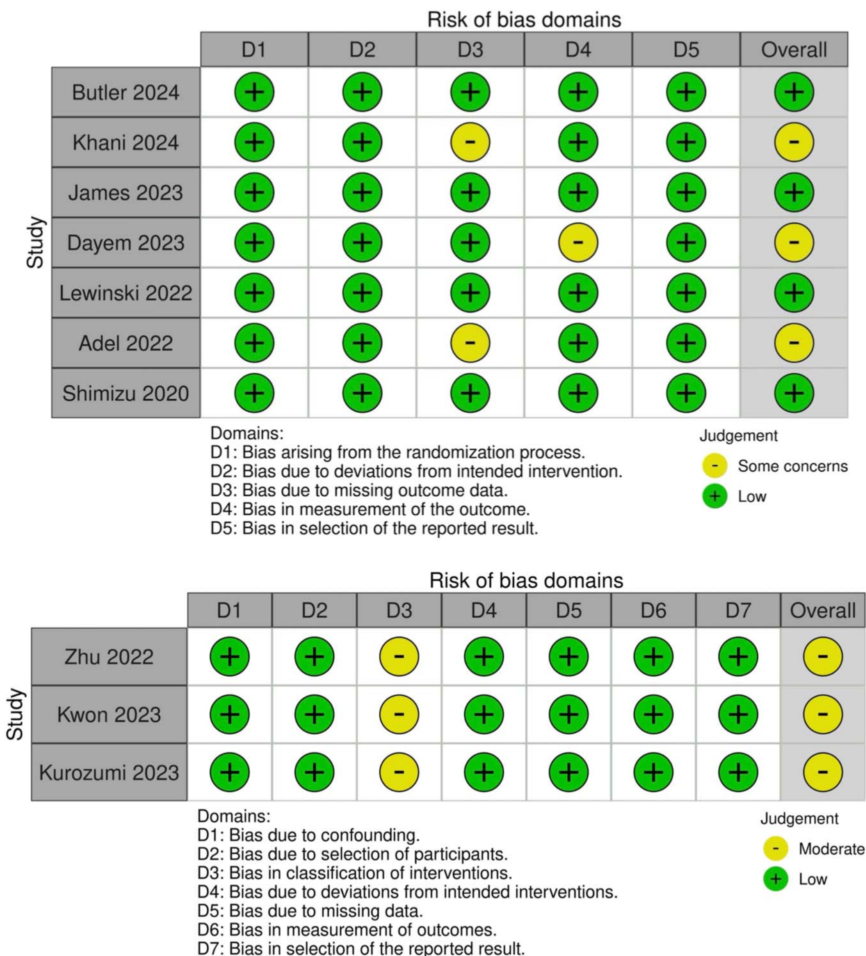


**FIGURE 6.** Risk of bias.

Third, subgroup analysis based on diabetes status, subtype of ACS, and left ventricular ejection could not be performed because of the lack of stratified data in the original reports. Further research is needed to evaluate differences in treatment response among these groups of patients.

Despite these limitations, our findings highlight the potential of SGLT-2 inhibitors to prevent HF post-ACS by improving cardiac function and reducing adverse cardiac remodeling.

## CONCLUSIONS

This meta-analysis provides robust evidence that SGLT-2 inhibitors significantly improve cardiovascular outcomes when initiated after acute coronary syndrome. The treatment was associated with a reduction in first heart failure hospitalization, a lower risk of cardiac death, and a particularly striking reduction in stroke incidence. In addition, improvements in cardiac function markers such as NT-proBNP and left ventricular ejection fraction suggest that these drugs could enhance cardiac recovery and mitigate long-term cardiovascular risks. These findings collectively demonstrate meaningful clinical benefits across multiple cardiovascular end points.

The consistent results seen in both randomized controlled trials and observational studies strengthen the case for incorporating SGLT-2 inhibitors into standard post-ACS care, particularly for patients with or at risk for heart failure. Their established safety profile and multiple potential mechanisms of action make them a valuable addition to secondary prevention strategies. Nevertheless, the absence of a confirmed mortality benefit and the exploratory nature of the stroke risk reduction highlight the importance of further studies to establish their role more definitely across all major cardiovascular outcomes, while exploring optimal timing of initiation, durability of benefits, differences in the molecules, and efficacy in specific patient subgroups to further refine their role in clinical practice.

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