Review Article

SGLT-2 Inhibitors' Antiarrhythmic Benefits in Patients Undergoing Cardiac Surgery: A Systematic Review and Meta-Analysis

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Abstract

Background: Cardiac arrhythmias, particularly postoperative atrial fibrillation (POAF), are frequent and serious complications following cardiac surgery. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors have demonstrated antiarrhythmic potential, but their efficacy in the perioperative setting remains unclear. This systematic review and meta-analysis aimed to evaluate the evidence on the potential antiarrhythmic effects of SGLT-2 inhibitors in patients undergoing cardiac surgery.

Methods: A systematic search across PubMed, Scopus, Web of Science, Embase, and Cochrane was conducted to capture relevant articles on randomized controlled trials (RCTs) and observational studies comparing SGLT-2 inhibitors to placebo or standard care in adult patients undergoing cardiac surgeries. The primary outcome was the incidence of postoperative arrhythmias, focusing on POAF. The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement, and the search protocol was registered in PROSPERO, code: CRD420251117844. Comprehensive Meta-Analysis (CMA) software (version 3.0) was used for the meta-analysis.

Results: Eleven studies were included in the systematic review: five RCTs, one secondary analysis of an RCT, and five observational studies. The meta-analysis of three observational studies (n = 6,310) demonstrated that the use of SGLT-2 inhibitor was associated with a significantly lower risk of POAF (Risk Ratio [RR]: 0.79; 95% CI: 0.70–0.89; $P < 0.001$). In contrast, the meta-analysis of three RCTs (n = 282) showed a trend towards a reduction in POAF that did not reach statistical significance (RR: 0.73; 95% CI: 0.47–1.13; $P = 0.154$). The safety profile of SGLT-2 inhibitors was favorable.

Conclusion: This systematic review and meta-analysis, the first of its kind, suggests that SGLT-2 inhibitors may reduce the risk of POAF after cardiac surgery, a finding supported by the observational data. However, evidence from the RCTs is currently inconclusive. Further studies are warranted to definitively establish the antiarrhythmic role of SGLT-2 inhibitors in this context.

Keywords: SGLT-2 inhibitors, Postoperative Atrial Fibrillation, Cardiac Surgery, Antiarrhythmic Effects, Meta-analysis

1. Introduction

Cardiac arrhythmias are common complications following cardiac surgeries and represent a significant source of morbidity and mortality. Atrial fibrillation (AF) is the most frequently observed arrhythmia in these patients. It often occurs alongside other atrial tachyarrhythmias, such as atrial flutter (AFL), premature atrial complexes, and multifocal atrial tachycardia. It has been shown that AF may affect between 15% and 40% of patients during the early postoperative phase after coronary artery bypass grafting (CABG) and can reach as high as 60% in patients undergoing valve replacement combined with CABG.[1-3]

Based on the growing body of evidence linking glycemic control and AF outcomes, the 2024 European Society of Cardiology (ESC) guidelines for managing AF recommend effective glycemic control as part of a comprehensive approach to risk factor management for individuals with diabetes mellitus (DM) and AF.[4] This issue highlights the importance of glycemic control and the proper use of anti-diabetic agents in managing postoperative atrial fibrillation (POAF).

A growing body of research has emphasized the benefits of sodium-glucose cotransporter-2 (SGLT-2) inhibitors across a wide range of cardiovascular diseases (CVDs) through various interconnected molecular pathways, in addition to their effects on glycemic control and natriuresis. [5] The American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Failure Society of America (HFSA) strongly recommend the use of SGLT-2 inhibitors for patients with symptomatic chronic heart failure (CHF), regardless of their diabetes status.[6,7] The 2023 ESC guideline also recommends (class IA) administration of SGLT-2 inhibitors for patients with CHF.[8]

Furthermore, SGLT-2 inhibitors have been shown to display antiarrhythmic properties by reducing oxidative stress, improving sodium and calcium handling, influencing structural

remodeling, and electrical remodeling.[9] A post hoc analysis of the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) trial revealed that dapagliflozin significantly reduced the incidence of AF and AFL by 19% in patients with type 2 DM, regardless of any prior history of AF, atherosclerotic heart disease, or HF.[10] A meta-analysis of 38 randomized controlled trials (RCTs) involving 88,704 patients showed that SGLT-2 inhibitors could reduce the risk of atrial arrhythmia in patients with type 2 DM and/or HF or chronic kidney disease (CKD).[11] To date, a limited number of studies have assessed the potential benefits of SGLT-2 inhibitors on the incidence of arrhythmias after cardiac surgeries, and robust data in this area are still lacking.

In light of the above information, the present systematic review and meta-analysis aimed to evaluate the potential benefits of SGLT-2 inhibitors on cardiac arrhythmias in patients undergoing cardiac surgery. To our knowledge, this study represents the first systematic review and meta-analysis evaluating the antiarrhythmic effect of SGLT-2 inhibitors in cardiac surgery patients.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12] The review protocol was registered with PROSPERO (Registration ID: CRD420251117844). We registered the protocol prospectively. After evaluating the eligible studies, we found that data on the severity of arrhythmias are limited, prompting us to revise the registered protocol accordingly.

2.1. Search Strategy

To identify all pertinent literature, a comprehensive systematic search was executed across major electronic databases, including Web of Science, PubMed, Scopus, Embase, and Cochrane.

The search spanned from each database's inception up until December 26, 2025, employing a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The detailed search strategy is presented in ***Supplementary Table*** S1.

2.2.Eligibility Criteria

Studies were selected based on the following PICO (Population, Intervention, Comparator, and Outcome) framework. We included adult patients aged 18 years or older who underwent any form of cardiac surgery, encompassing CABG, valve repair or replacement, combined procedures, and transcatheter aortic valve implantation (TAVI). The intervention of interest was the administration of any SGLT-2 inhibitor (e.g., dapagliflozin, empagliflozin, etc.), regardless of its specific dose or the timing of its administration relative to the surgical procedure (i.e., preoperative, perioperative, or postoperative). Comparators were defined as either a placebo or standard medical care in the absence of SGLT-2 inhibitors. The primary outcome of interest was the incidence of POAF. The incidence of other arrhythmias, including atrial flutter, ventricular arrhythmia, premature ventricular contractions (PVCs), new-onset bundle branch blocks, and the need for pacemaker implantation, was also evaluated as secondary outcomes. We considered a broad range of study designs for inclusion, such as RCTs, prospective and retrospective observational cohort studies, and secondary analyses of larger clinical trials. Conversely, we rigorously excluded reviews, meta-analyses, individual case reports, editorials, animal or in vitro studies, any research that failed to report relevant arrhythmia outcomes, or studies where SGLT-2 inhibitors were not administered in the context of cardiac surgery.

2.3.Study Selection

Following the search, all retrieved records were imported into EndNote X20 for deduplication and subsequently screened using the Rayyan QCRI web-based platform.[13] Two

independent reviewers (A.R. and S.P.) then embarked on the initial screening phase, meticulously evaluating the titles and abstracts of the remaining unique records against our predefined eligibility criteria. Records that were deemed potentially relevant were subsequently advanced to the full-text review stage. During this crucial second screening phase, two independent reviewers (A.R. and S.P.) assessed the retrieved full-text articles for final eligibility. Any discrepancies or disagreements encountered at either the title/abstract or full-text screening stages were resolved through collaborative discussion and consensus between the two reviewers, with recourse to a third reviewer (S.K.) when necessary.

2.4.Data Extraction

For data extraction, two reviewers (A.R. and S.P.) independently utilized a standardized, pre-piloted data extraction form to ensure consistency and accuracy. Any discrepancies that emerged during this process were resolved through discussion or, if consensus could not be reached, by arbitration from a third reviewer (S.K.). The extracted data encompassed a wide array of information, including study identification details such as study ID, year, and country, alongside comprehensive information on study design and participant characteristics, including sample size, mean age, percentage of male participants, and the specific type of cardiac surgery performed. Detailed intervention specifics were also captured, covering the type and dose of the SGLT-2 inhibitor, the precise timing of its administration relative to surgery, and the duration of follow-up.

Crucially, comprehensive outcome data were extracted, including arrhythmia rates for both SGLT-2 and control groups, the specific types of arrhythmias reported, and details regarding the comparator groups. Information on safety and other secondary outcomes, such as mortality, intensive care unit stay, hospital length of stay, and adverse events, was also collected. Where data were presented solely in figures or graphs, careful extraction was performed using digital tools

when appropriate. For conference abstracts, data were extracted as reported, acknowledging the inherent limitations of potentially incomplete information.

2.5. Risk of Bias Assessment

The methodological quality and inherent risk of bias for each included study were rigorously and independently assessed by two reviewers (A.R. and S.P.), employing established and appropriate tools tailored to the study design. For RCTs, the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2)[14] was applied, focusing on domains such as bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

For non-randomized studies of interventions (NRSIs), Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool was utilized.[15] This tool assessed domains including bias due to confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. All disagreements in bias judgments were resolved through discussion and consensus, involving a third reviewer (S.K.) when necessary. It is important to note that due to the abstract-only nature of some publications, certain judgments regarding bias were classified as "unclear" due to insufficient reporting detail. The visualization of the data was performed using the online Risk-of-bias Visualization (robvis) tool.[16]

2.6.Assessment of Certainty of Evidence (GRADE)

The certainty of evidence for primary outcomes was assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework.[17] Evidence from RCTs starts as High certainty; evidence from observational studies starts as Low certainty. Two reviewers

independently rated certainty, considering five factors for downgrading: (1) risk of bias, (2) inconsistency, (3) indirectness, (4) imprecision, and (5) publication bias. For observational evidence, three factors could upgrade certainty: a large effect size, a dose-response gradient, or if all plausible confounding would reduce the observed effect. Final ratings (High/Moderate/Low/Very Low) are presented in a GRADE table with explanatory footnotes.

2.7.Statistical data analysis

The synthesis of the extracted data commenced with a narrative overview, providing a qualitative summary of the findings across all included studies. The Comprehensive Meta-Analysis (CMA) software version 3.0 was utilized for the meta-analysis and visualization of the results. Statistical heterogeneity between studies was assessed using I^2 statistics. A rough guide for interpreting the I^2 index based on the Cochrane Handbook for systematic reviews of interventions is as follows: 0% to 40%: not important, 30% to 60%: moderate, 50% to 90%: substantial, and 75% to 100%: considerable heterogeneity.[18] Results were reported as risk ratio (RR) with 95% Confidence Intervals (CIs). A P value < 0.05 was considered statistically significant. Despite the absence of significant statistical heterogeneity, the inherent clinical and methodological diversity of the studied variables and outcomes warranted the use of a random-effects model, which is a more conservative and appropriate approach.

3. Results

A total of 1,580 studies were obtained from the literature search. Following duplicate removal and screening of the records by their titles and abstracts, 36 unique records were entered into the eligibility assessment. Full-text review of these articles led to the final inclusion of 11 studies in the systematic review.[19-29] The PRISMA flow diagram is shown in Fig. 1.

3.1.Studies' Characteristics

The eligible studies exhibited a mix of designs, comprising RCTs, one secondary analysis of an RCT, and four observational cohort studies. Sample sizes varied substantially, ranging from small pilot studies with 55 patients to large retrospective cohorts with over 4500 patients. The patient populations predominantly consisted of middle-aged to elderly individuals (mean age ranging from 56.97 ± 7.32 years to 82.4 years in Raposeiras-Roubin et al.[25]), with a high proportion of males reported in most cohorts. Many studies focused on patients with DM or a history of HF, reflecting the main indications for SGLT-2 inhibitors. Geographically, the studies were diverse, originating from Qatar/United States, Russia, Germany, Spain, Iran, Brazil, Netherlands, India, Canada, multinational TriNetX network (18 countries**),** and multinational collaborations (Tables 1 and 2).

The types of cardiac surgery investigated primarily included CABG, performed either off-pump, valve replacement/repair, combined procedures or TAVI. One study examined cardiac surgery in general. The evaluated SGLT-2 inhibitors included dapagliflozin (10 mg) and empagliflozin (10 mg and 25 mg), with one large observational study not specifying the particular SGLT-2 inhibitor used.[29] Some initiated treatment several days preoperatively and continued into the early postoperative period, others utilized pre-existing/ongoing therapy continued until shortly before surgery, while two studies initiated dapagliflozin postoperatively and at the hospital discharge after TAVI. One study examined patients on chronic SGLT-2 inhibitor therapy at the time of TAVR.[29] Follow-up durations for arrhythmia assessment ranged from immediate in-hospital periods to 30 days post-discharge and up to one year or longer for primary cardiovascular outcomes. Comparators generally consisted of placebo or standard care without SGLT-2 inhibitor use, with some observational studies utilizing propensity-score-matched control groups. The

definition of POAF ranged from one episode of AF lasting longer than five minutes within 72 hours after surgery to any new-onset AF occurring within 5 to 30 days post-surgery. All the included studies in the meta-analysis provided scientifically accurate definitions of POAF.

3.2. Risk of bias assessment

Across RCTs, overall risk was never unequivocally low for arrhythmia outcomes (Figure S1). Of the six RCTs with arrhythmia-relevant endpoints, three had an overall judgment of some concerns. Among NRSIs, four were at overall serious risk and one was at moderate (Figure S2). Despite propensity score matching in some cohorts, residual confounding by indication and perioperative management (e.g., AF prophylaxis, surgical complexity, cardiopulmonary bypass times, atrial size, HF severity, renal function, and glycemic control) remained likely. Missing data were often inadequately reported, leading to a lack of information.

3.3.Data Synthesis

3.3.1. Impact on AF

The incidence of POAF, as the main outcome of the present meta-analysis, is the most frequently investigated arrhythmia outcome among the eligible studies. In a large multicenter retrospective cohort study, Rahhal et al. found a significant reduction in POAF within 30 days of cardiothoracic surgery (11.2% in SGLT-2 inhibitor users *vs.* 13% in non-users, aHR 0.75, *P* <0.004).[24] Similarly, a prospective observational study in diabetic CABG patients by Li et al. reported a significantly lower POAF incidence (19.6% vs. 25.7%, OR 0.686, P < 0.001) with preoperative SGLT-2 inhibitor use.[21] Kremneva et al., a smaller observational study, also found a significant association between SGLT-2 inhibitor use and a lower incidence of paroxysmal AF after CABG (an inferred ~ 5.9% vs. ~ 34.7%, p =0.019).[19] Morel et al., in a large multinational

retrospective cohort of TAVR patients with high baseline AF prevalence (>54%), reported a borderline reduction in incident AF during extended follow-up (annual rate 6.46% vs. 7.53%, HR 0.776, P = 0.06).[29]

In contrast, RCTs specifically yielded less conclusive results. Zarei et al., a double-blind RCT in off-pump CABG patients, showed a numerical reduction in POAF (11.6% *vs.* 28.2%) but it did not reach statistical significance (P = 0.09).[28] In an open-label RCT in diabetic on-pump CABG patients, Pitta et al. found no significant difference in new-onset POAF (15.4% vs. 13.5%, P =0.73). [23] On the other hand, Snel et al., employing an underpowered pilot RCT, reported a trend towards reduced overall (52% vs. 73%) and de novo (20% vs. 33%) POAF, but without statistical significance.[26] In a prospective risk-matched cohort study, Taghiyev et al. observed identical AF rates (9% in both groups) within 7 days post-cardiac surgery.[27] Pandey et al. performed a secondary analysis of an RCT to note an exploratory trend towards lower POAF incidence (P-trend = 0.084) in diabetic cardiac surgery patients treated with SGLT-2 inhibitors.[22]

3.3.2. Other efficacy outcomes

Beyond POAF, data on other arrhythmia types is scarce and less consistent. Zarei et al. uniquely demonstrated a significant reduction in ventricular arrhythmias (ventricular tachycardia: 4.7% *vs.* 23.1%, P = 0.02; premature ventricular contractions: 27.9% *vs.* 66.6%, P = 0.001) with perioperative empagliflozin.[28] Raposeiras-Roubin et al. in a large TAVI trial reported no significant differences in new-onset BBB or pacemaker implantation rates between dapagliflozin and standard care.[25] Taghiyev et al. also found no statistically significant difference in new-onset LBBB/RBBB or AV/SA blocks, although numerical trends suggested lower incidence in the SGLT-2 inhibitor group for these conduction disorders. [27] Morel et al. found no significant differences in pacemaker implantation (HR 1.204, P = 0.2), AV block (HR 1.153, P = 0.36), or combined VT/VF/cardiac

arrest (HR 1.054, P = 0.55) in TAVR patients.[29] Studies indicated benefits on other cardiovascular or renal outcomes, including reduced HF exacerbation [25]), reduced AKI [23], and reduced myocardial injury markers. [21] Notably, Morel et al. demonstrated significant reductions in all-cause mortality (HR 0.828, P = 0.02) and bioprosthetic valve failure (HR 0.617, P = 0.04) in TAVR patients.[29]

3.3.3. Safety profile

No cases of DKA were reported in any of the included studies, even when the drug was continued up to or during surgery. Minor adverse events like genital/urinary infections and hypotension were sometimes numerically higher in SGLT-2 inhibitor groups[25], but generally considered tolerable.

3.4. Meta-Analysis of RCTs

The meta-analysis of three RCTs [23,26,28], which included a total of 282 patients, indicated a trend toward a reduced incidence of POAF associated with the use of SGLT-2 inhibitors. However, this trend did not reach statistical significance in the random-effect model (RR: 0.73; 95% CI: 0.47–1.13; $P = 0.154$). An assessment of inter-study heterogeneity showed a low and statistically insignificant level of variability across the trials (Cochran's Q = 2.61, $P = 0.27$; $I^2 = 23.5\%$). Detailed results and corresponding forest plots are presented in Fig. 2. Results were consistent when comparing a fixed-effect model to our primary random-effects model, demonstrating robustness to this methodological assumption (RR: 0.73; 95% CI: 0.51–1.03; P = 0.076)

3.5. Meta-Analysis of observational studies

The meta-analysis of three observational studies 21,24,27, including 6,310 patients, showed that the use of SGLT-2 inhibitors led to a statistically significant reduction in the risk of POAF in the random-effects model (RR: 0.79; 95% CI: 0.70–0.89; P < 0.001). An assessment of

inter-study heterogeneity showed no statistical heterogeneity across the studies (Cochran's Q = 0.98, P = 0.61), with an I2 value of 0.0%. This result suggests that patients treated with SGLT-2 inhibitors had a 21% lower risk of developing POAF compared to the control groups. The detailed results and corresponding forest plots are shown in Fig. 3. Results were similar when comparing a fixed-effect model to our primary random-effects model, demonstrating robustness to this methodological assumption (RR: 0.79; 95% CI: 0.70–0.89; P < 0.001).

3.6.Certainty of Evidence (GRADE Assessment)

Evidence from three RCTs involving 282 patients indicates a non-significant 27% relative reduction in the risk of POAF (RR 0.73, 95% CI 0.51–1.03). The certainty of this evidence is rated as VERY LOW due to serious risk of bias (lack of blinding) and very serious imprecision (insufficient number of patients and events), and inconsistency (variation in effect direction). In contrast, evidence from three observational studies with 6,310 patients demonstrates a significant 21% relative reduction in the risk of POAF (RR 0.79, 95% CI 0.70–0.89). The certainty of this evidence is rated as LOW because of serious risk of bias (residual confounding) and serious publication bias (discordance with null RCTs) (Table 3).

4. **Discussion**

To our knowledge, this is the first systematic review and meta-analysis evaluating the potential antiarrhythmic effects of SGLT-2 inhibitors in patients undergoing cardiac surgeries. According to the meta-analysis of observational studies, SGLT-2 inhibitors could reduce the risk of POAF after cardiac surgeries. However, the meta-analysis of RCTs did not support the hypothesis.

SGLT-2 inhibitors have revolutionized the management of a variety of CVDs and have recently emerged as a promising therapy for the management of cardiac outcomes beyond the approved use for HF.[30] It has been proposed that SGLT-2 inhibitors may provide antiarrhythmic effects by reducing cardiac hypertrophy, decreasing inflammation and apoptosis, and activating antioxidant enzymes, while also lowering biomarkers of hypoxia. Moreover, SGLT-2 inhibitors have been shown to lower uric acid levels, which is known to activate the NOD-like receptor protein 3 (NLRP3) inflammasome. SGLT-2 inhibitors also enhance magnesium reabsorption in the kidneys, which helps prevent the arrhythmogenic effects caused by hypomagnesemia. In vitro studies indicate that SGLT-2 inhibitors could inhibit the Na+/H+ exchanger, which typically promotes fibrosis and contributes to the electrical remodeling of atrial myocytes. Additionally, SGLT-2 inhibitors could enhance the phosphorylation of AMP-activated protein kinase, thereby reducing mitochondrial dysfunction and the risk of cardiac arrhythmias.[31,32]

4.1. SGLT-2 inhibitors' Effects on AF

A series of clinical trials has demonstrated the antiarrhythmic effects of SGLT-2 inhibitors in a wide range of patients with CVDs. The DECLARE-TIMI58 trial showed that dapagliflozin reduced the incidence of AF/AFL events by 19% (264 *vs*. 325 events; 7.8 *vs*. 9.6 events per 1000 patient-years; HR, 0.81 [95% CI, 0.68–0.95]; $P = 0.009$) compared to a placebo in patients with DM. This reduction occurred regardless of the patients' baseline CVD, HF, or AF status.[10] A meta-analysis involving 22 trials with a total of 52,115 patients with HF, DM, or CKD indicated that SGLT-2 inhibitors could reduce the risk of AF (RR 0.82, 95% CI 0.70–0.96) and embolic stroke (RR 0.32, 95% CI 0.12–0.85).[33] Additionally, a recent systematic review and meta-analysis of 38 RCTs involving 88,704 patients showed that SGLT-2 inhibitor therapy was associated with a lower overall risk of AF in patients with type 2 DM and/or HF or CKD.[11]

Regarding the positive impacts of SGLT-2 inhibitors on AF across a diverse patient population, our meta-analysis of observational studies indicated the promising effects of SGLT-2 inhibitors on the occurrence of POAF in individuals undergoing cardiac surgeries.

Based on the present systematic review and meta-analysis, the evidence derived from RCTs remains inconclusive for several reasons. These include the small number of eligible studies and their limited sample sizes, the failure to assess arrhythmia as the primary endpoint, inconsistencies in the administration protocols for SGLT-2 inhibitors and follow-up period, the techniques employed to detect arrhythmias, as well as the specific types and dosages of SGLT-2 inhibitors that were investigated.

Among six eligible RCTs, three were excluded from the meta-analysis because they lacked specific data on the incidence of POAF as an outcome. Moreover, in two included trials that yielded negative results, the incidence of POAF was not assessed as the primary outcome, potentially underpowering the studies to detect meaningful effects, which may have contributed to a lack of statistical significance or false negative results.[34]

The non-significant effects observed in the meta-analysis of RCTs may also relate to the SGLT-2 inhibitors' half-life of approximately 12 hours and the timing of drug discontinuation before the surgeries, which may reduce the efficacy of the drug. Notably, two RCTs included in the meta-analysis discontinued SGLT-2 inhibitors three days prior to cardiac surgery, which aligns with current guidelines recommending cessation of SGLT-2 inhibitors about three days before surgery (four days for ertugliflozin).[35]

The relatively brief follow-up period and the methodologies employed to assess AF in the RCTs may have resulted in undetected cases of AF, leading to erroneous findings and conclusions. AF can occur early in the postoperative period or as a late complication following cardiac surgery.

In a study involving over 2,000 patients participating in cardiac rehabilitation after surgery, it was found that 11% developed AF.[36] Additionally, a randomized trial with 336 cardiac surgical patients at risk for stroke demonstrated that continuous cardiac rhythm monitoring using wearable sensors significantly increased the detection rate of AF within 30 days after discharge.[37]

The antiarrhythmic effects of SGLT-2 inhibitors reported in the literature may not necessarily apply to all drugs in this class. A meta-analysis from large clinical trials investigating SGLT-2 inhibitors has shown protective effects against AF in patients with type 2 DM.[11,38] However, these findings were primarily influenced by trials that focused on dapagliflozin. In a nationwide, population-based cohort study of 37,928 patients in the Republic of Korea, the risk of developing AF was significantly lower in the dapagliflozin group compared to the empagliflozin group.[39] Notably, empagliflozin was the SGLT-2 inhibitor used in the RCTs included in our meta-analysis.

The exact dose for antiarrhythmic effects for SGLT-2 inhibitors is not clear in the literature. A systematic review and network meta-analysis involving forty-five randomized trials and 48,067 patients indicated that the renoprotective efficacy of SGLT-2 inhibitors is not influenced by increased dosages, suggesting that lower doses may be sufficient for achieving renal outcomes.[40] However, another systematic review and network meta-analysis of 51 RCTs with 23,989 participants found that the overall efficacy of SGLT-2 inhibitors on cardiometabolic outcomes is dose dependent.[41] Thus, the optimal dosage of SGLT-2 inhibitors, considering both efficacy and safety profiles, remains uncertain. As stated in the preceding sections, we observed significant variability among the eligible studies regarding the dosage of SGLT-2 inhibitors, and some studies did not specify the dosage of these medications.

4.2.Effects of SGLT-2 inhibitors in other arrhythmias

The effects of SGLT-2 inhibitors on various cardiac arrhythmias, excluding AF, have been explored in the literature. A meta-analysis of 38 RCTs involving 88,704 patients found that SGLT-2 inhibitor therapy did not reduce the risk of ventricular arrhythmias in individuals with type 2 DM, HF, or CKD.[11] Additionally, a network meta-analysis of 11 RCTs with 23,701 patients indicated that SGLT-2 inhibitors did not lower the risk of ventricular arrhythmias or conduction disorders in patients with HF.[42] Currently, information regarding the impact of SGLT-2 inhibitors on other arrhythmias following cardiac surgeries is limited and inconsistent, which complicates the possibility of conducting a meta-analysis in this area.

4.3.SGLT-2 inhibitors' safety in surgeries

The U.S. Food and Drug Administration has issued several warnings regarding the increased risk of DKA associated with the use of SGLT-2 inhibitors. It is recommended that canagliflozin, dapagliflozin, and empagliflozin be discontinued at least 3 days before scheduled surgery. Additionally, ertugliflozin should be stopped at least 4 days prior to the procedure.[35] However, recent findings suggest that this preoperative withdrawal period may be unnecessary. A cohort study involving 34,671 patients with type 2 DM undergoing emergency surgery, where adherence to current guidelines on withholding SGLT-2 inhibitors was unlikely, found no increased risk of postoperative DKA associated with the preoperative use of these medications.[43] According to our systematic review results, no cases of DKA were reported in any of the included studies, even when the drug was continued up to or during surgery.

While minor adverse events, including genital and urinary infections as well as hypotension, were numerically more prevalent in the SGLT-2 inhibitor group, they have typically been regarded as manageable and tolerable in patients undergoing cardiac surgeries.

4.4.Limitations and future directions

The present meta-analysis compiled all available clinical data on the potential antiarrhythmic effects of SGLT-2 inhibitors in cardiac surgeries. However, it is important to interpret these findings with caution due to the following limitations. First, most research has concentrated specifically on the incidence of POAF, which limits the overall applicability of the findings to other types of arrhythmias. Second, the incidence of cardiac arrhythmias has not been evaluated as a primary outcome in most studies, particularly in RCTs. As a result, important endpoints, including POAF, may not have been adequately powered. Third, the lack of adequate data resulted in the omission of specific eligible studies from the concluding meta-analysis in the systematic review. Fourth, a subgroup analysis or meta-regression could not be performed due to insufficient statistical power from the number of eligible studies. This restriction hinders the analysis of the impact of underlying disorders such as chronic obstructive pulmonary disease, CKD, DM, and HF, all of which are associated with an increased risk of arrhythmias. The influence of concurrent medications, like beta blockers, has not been considered as well. Lastly, another limitation of the study is the low certainty of the evidence itself, as graded by the GRADE framework.

It is crucial to conduct real-world studies and well-designed RCTs with larger sample sizes and longer follow-up periods to clarify the potential effects of SGLT-2 inhibitors on cardiac arrhythmias. These studies should also examine their safety profiles and the administration protocols for both prophylactic and therapeutic strategies before, during, and after cardiac surgeries. Additionally, it is important to take into account patients' clinical characteristics, including any concurrent medications and pre-existing comorbidities.

5. Conclusion

This meta-analysis shows a promising link between perioperative SGLT-2 inhibitors and reduced POAF in cardiac surgery, primarily seen in observational data. However, formal grading reveals the evidence certainty is low to very low. RCT data are inconclusive due to significant limitations in both power and study design. While observational studies suggest stronger signals, they are also subject to inherent biases that can affect the findings. Although SGLT-2 inhibitors show promise for reducing POAF, these are preliminary, hypothesis-generating results that urgently justify large, definitive randomized trials with long follow-up periods to clarify the potential antiarrhythmic effects of SGLT-2 inhibitors in patients undergoing cardiac surgery.

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Statements and Declarations

The authors declare no competing interests.

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Table 1. Characteristics of Studies Investigating SGLT-2 Inhibitors in Cardiac Surgery Patients

Study Identifier	Design	Country/Region	Blinding	Randomization/Matching Method	Follow-up Duration	Total N (Analyzed)	Intervention N	Control N	Key Inclusion Criteria	Key Exclusion Criteria	Mean Age (Years) / Median	Female %	T2DM %	Primary Procedure Type	CABG % (if Mixed)	LVEF ≤ 50% (n/%)	Mean LVEF (%)	Baseline AF (n/%)	Mean/Median Risk Score (EuroSCORE II / STS)	SGLT2i Drug	SGLT2i Dosage	SGLT2i Duration & Timing	Comparator
Zarei et al. (2024) [28]	Placebo-controlled RCT	Iran	Double-blind (patients & investigators)	Permuted-block (size 4)	72 hours (post-op)	82	43	39	Adults (18-70y), elective off-pump CABG, standard care	Pacemaker, severe HF (EF<30%), CKD (GFR<20), SGLT2i use <2wks, AF hx, prior heart surgery, pregnancy/lactation	57	~48.4	~30.5	CABG	100%	~42%	NR	0 (0%) (exclusion criteria)	NR	Empagliflozin	10 mg daily	6 days (3 days pre-op, 3 days post-op); Peri-op	Placebo tablets + standard regimen
Pitta et al. (2025) [23]	Investigator-initiated, pragmatic, single-center, open-label with blinded outcome adjudication RCT	Brazil	Partial (open-label, blinded outcome adjudication)	Automated, stratified by age/eGFR, variable blocks	Up to 30 days (post-op)	145	71	74	T2DM, multivessel CAD, elective on-pump CABG	Prior SGLT2i, eGFR <30, chronic dialysis, urgent revascularization	61.9	33.1	100	CABG	100%	~29%	NR	NR	Median: EuroSCORE II 0.94 / STS 1.06	Empagliflozin	25 mg daily	Min. 3 months prior to CABG; Pre-op	Standard care
Kuchay et al. (2023) [20]	Investigator-initiated, prospective,	India	Open-label	Computer-generated (opaqu	Hospital stay (median 10 days,	250	125	125	T2D, admitted for cardiac surgery	CKD eGFR<30, insulin units <12,	Median: 61.0	12.4	100	Mixed Cardiac Surgery	NR (CABG, valve, or	42%	NR	NR	NR	Dapagliflozin	10 mg daily	Median hospital stay (10	Basal-bolus insulin alone

	open-label, treat-to-target RCT			e sealed envelopes)	max 12 days)				(CABG, valvular, mixed)	BMI<18, recurrent UTIs					combined)							days); Post-op	
Raposeiras-Roubin et al. (2025) [25]	Pragmatic, open-label with blinded outcome adjudication RCT	Spain	Partial (open-label, blinded outcome adjudication)	Secure Web-based system, stratified by DM/LVEF/eGFR	In-hospital	1222	605	617	Severe aortic stenosis, TAVI, history of HF + (renal insufficiency, DM, or LVEF ≤40%)	Contraindication to Dapagliflozin, current SGLT2i/SU, SBP<100, DBP<50, eGFR<25, chronic cystitis/recurrent UTI	82.4	49.4	43.9	TAVI	0%	~17% (LVEF ≤40%)	NR	Dapagliflozin: 250 (41.3%), Control: 274 (44.3%)	NR	Dapagliflozin	10 mg daily	1 year (post-TAVI); Post-op	Standard care
Snel et al. (2025) [26]	Open-label randomized pilot study (sub-study of MERCURI trial) RCT	The Netherlands	Open-label	Electronic, balanced-block (2, 4, or 6 blocks)	NR	55	25	30	Adults scheduled for elective CPB-assisted cardiac surgery	T1D, eGFR<30, SBP<100	66 ± 10	27	NR	Mixed Cardiac Surgery	NR (mostly valve or combined)	Majority had preserved (>50%)	NR	NR	NR	Empagliflozin	10 mg daily	3 days pre-op to 2 days post-op; Peri-op	Standard care
Taghiyev et al. (2025) [27]	Retrospective cohort with covariate adjustment	Germany	Open-label (N/A observational)	N/A (Covariate adjustment)	Up to 7 days (post-op)	66	33	33	Cardiac surgery, HF	CKD eGFR<60, ESRD, AKI stage 2/dialysis	64.1 (matched cohort)	22.5	71.5	Mixed Cardiac Surgery	72.7% (Bypass surgery)	NR	Mean: SGLT2i 41.0, Ctrl 45.9	9 (13.6%) (pre-existing)	EuroSCORE II 2.03 / STS 1.61	Dapagliflozin or Empagliflozin	NR	Current use, every 24 hours post-op; Peri-op	Other HF patients from same period (matched)
Pandey et al. (2022) [22]	Secondary observational analysis within RCT	Canada	Open-label (N/A observational)	N/A (Observational exposure)	30 days after discharge	176	176 (diabetic cohort)	N/A	DM, cardiac surgery, CHA2DS2-VASc ≥2, no pre-op AF	History of preoperative AF	NR	NR	100	Cardiac Surgery	NR	NR	NR	NR (exclusion criteria)	NR	NR	NR	Current use (duration not specified); Chroni	No glucose-lowering therapy/oral hypogl

																					c/Varied	ycemic agents/ insulin
Rahhal et al. (2025) [24]	Retrospective observational cohort with propensity matching	Qatar/ USA	Open-label (N/A observational)	N/A (Propensity matching)	30 days pre-op (Study period)	2240	1123	1117	Cardiothoracic surgery (CABG, valve replacement/repair), 2017-2023	Not explicitly detailed	62	22	NR	Mixed Cardiothoracic	~79%	NR	NR	NR	EuroSCORE II 2.03 / STS 1.61	NR	NR	Minimum 1 week pre-op; Chronic/Varied	Non-SGLT 2i users (matched)
Kremneva et al. (2023) [19]	Observational cohort	Russia	Open-label (N/A observational)	N/A (Observational)	NR (after CABG)	92	17 (SGLT 2i users)	75 (non-users)	Stable angina, CABG	Not explicitly detailed	64	21.7	35.6	CABG	100%	NR	NR	10 (10.9 %) (preprocedural AF)	NR	NR	NR	NR; Chronic/Varied	Non-SGLT 2i users
Li et al. (2024) [21]	Prospective cohort, propensity score matching	NR	Open-label (N/A observational)	N/A (Propensity score matching)	5 days (post-op)	4004	1001	3003	Adult diabetic patients without AF history, undergoing primary CABG (±valve surgery)	Patients with acute coronary syndrome or emergency surgery	NR	NR	100	CABG (±valve surgery)	NR	NR	NR	0 (0%) (exclusion criteria)	NR	NR	NR	Discontinued at least 3 days pre-op; Discontinued Pre-op	Non-SGLT 2i users
Morel et al. (2025) [29]	Retrospective cohort with propensity score matching	Multinational (TriNetX global network, 18 countries)	Open-label (N/A observational)	N/A (1:1 Propensity score matching, greedy nearest neighbor)	Mean 1.4 ± 1 years (Median 1.2, IQR 1.8)	4594	2297	2297	Adults with non-rheumatic aortic stenosis who underwent TAVR	History of endocarditis, aortocoronary bypass graft surgery, presence of prosthetic or xenogenic heart valves	76.0 ± 8.8 (SGLT2i) vs 76.1 ± 9.3 (Control)	39.7% (SGLT 2i) vs 39.9% (Control)	70.1% (SGLT 2i) vs 72.6% (Control) (after matching)	TAVR	0% (exclusion criteria)	NR (specific not reported)	51.3 ± 16.0 (SGLT2i) vs 51.9 ± 15.4 (Control)	1257 (54.7 %) (SGLT 2i) vs 1246 (54.2 %) (Control)	NR	NR (unspecified SGLT 2 inhibitor)	NR	Current use at time of TAVR; Chronic/Varied	Non-SGLT 2i users (propensity matched)

ACEi = Angiotensin-Converting Enzyme inhibitor; AF = Atrial Fibrillation; AKI = Acute Kidney Injury; ARB = Angiotensin Receptor Blocker; BMI = Body Mass Index; CABG = Coronary Artery Bypass Graft; CAD = Coronary Artery Disease; CKD = Chronic Kidney Disease; CPB = Cardiopulmonary Bypass; DBP = Diastolic Blood Pressure; DM = Diabetes Mellitus; eGFR = estimated Glomerular Filtration Rate; ESRD = End-Stage Renal Disease; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; GFR = Glomerular Filtration Rate; HF = Heart Failure; IQR = Interquartile Range; LVEF = Left Ventricular Ejection Fraction; N = Number of participants; N/A = Not Applicable; NR = Not Reported; NRCT = Non-Randomized Controlled Trial; RCT = Randomized Controlled Trial; SBP = Systolic Blood Pressure; SD = Standard Deviation; SGLT2i = Sodium-Glucose Cotransporter 2 inhibitor; STS = Society of Thoracic Surgeons (risk score); SU = Sulfonylurea; T1D = Type 1 Diabetes; T2D/T2DM = Type 2 Diabetes Mellitus; TAVI = Transcatheter Aortic Valve Implantation; UTI = Urinary Tract Infection.

Table 2. Outcomes of Studies Investigating SGLT-2 Inhibitors in Cardiac Surgery Patients

Study Identifier	Arrhythmia	SGLT2i Group (E/N)	Control Group (E/N)	Reported Effect (RR/OR/HR)	95% CI	p-value	New-onset BBB (E/N)	Pacemaker Implantation (E/N)	New-onset AV Block (E/N)	Ventricular Tachycardia (E/N)	Premature Ventricular Contractions (E/N)	Atrial Tachycardia (E/N)	Premature Atrial Contraction (E/N)	Ketoacidosis (E/N)	Hypoglycemia (E/N)	AKI (E/N)	Other severe AEs (E/N)
Zarei et al. (2024) [28]	POAF: one episode of AF lasting longer than five minutes within 72 hours after surgery	5/43	11/39	N/A	N/A	0.09	LBBB: 1/43, RBBB: 5/43 (Empagliflozin) vs. LBBB: 0/39, RBBB: 7/39 (Placebo)	N/A	4/43 (AV Block Degree 1) (Empagliflozin) vs. 3/39 (Placebo)	2/43 (Empagliflozin) vs. 9/39 (Placebo)	12/43 (Empagliflozin) vs. 26/39 (Placebo)	2/43 (Empagliflozin) vs. 5/39 (Placebo)	5/43 (Empagliflozin) vs. 8/39 (Placebo)	N/A	N/A	N/A(main outcome was AF)	N/A
Pitta et al. (2025) [23]	POAF: postoperative atrial fibrillation during hospitalization up to 30 days	11/71	10/74	RR: 1.15	0.52 – 2.53	0.73	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/145 (overall)	N/A	16/71 (Empagliflozin) vs. 29/74 (Control)	All-cause mortality: 0/71 (Empagliflozin) vs. 3/74 (Control)
Kuchay et al. (2023) [20]	Cardiac arrhythmia requiring medical treatment	7/125	7/125	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/250 (overall)	BG >70: 12/125 (Dapagliflozin) / 9/125 (Insulin)	9/125 (Dapagliflozin) / 16/125 (Insulin)	Total complications: 27/125 (Dapagliflozin) vs. 31/125 (Insulin)
Raposeiras-Roubin et al. (2025) [25]	N/A	N/A	N/A	N/A	N/A	N/A	151/471 (Dapagliflozin) / 146/448 (Control)	105/544 (Dapagliflozin) vs. 103/543 (Control)	N/A	N/A	N/A	N/A	N/A	0/1222 (overall)	N/A	N/A	Genital infection: 11/605 (Dapa) vs. 3/617 (Control); Hypotension: 40/605 (Dapagliflozin) vs. 22/617 (Control)

Study Identifier	Arrhythmia	SGLT2i Group (E/N)	Control Group (E/N)	Reported Effect (RR/OR/HR)	95% CI	p-value	New-onset BBB (E/N)	Pacemaker Implantation (E/N)	New-onset AV Block (E/N)	Ventricular Tachycardia (E/N)	Premature Ventricular Contractions (E/N)	Atrial Tachycardia (E/N)	Premature Atrial Contraction (E/N)	Ketoacidosis (E/N)	Hypoglycemia (E/N)	AKI (E/N)	Other severe AEs (E/N)
Snel et al. (2025) [26]	POAF: Postoperative AF in patients with no known history of AF	13/25 (for all POAF); 5/25 (for de novo)	22/30 (for all POAF); 10/30 (for de novo)	N/A	N/A	0.101 for all POAF; 0.269 for de novo	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Taghiyev et al. (2025) [27]	POAF: New-onset AF after cardiac surgery (maximum of 7 days)	3/33	3/33	N/A(MD for eGFR)	N/A	1	5/33 (LBBB or RBBB)	0/33	0/33 (AV-/SA-Block Grade II)	N/A	N/A	N/A	N/A	N/A	N/A	KDIGO: 8/33 (SGLT2i) vs. 12/33 (Control)	Need for assist devices: 4/33
Pandey et al. (2022) [22]	Cumulative AF/AFL ≥6 min	~8/~176 (estimated)	~14/~176 (estimated)	Log-rank p-trend=0.084	N/A	0.084 (trend)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rahhal et al. (2025) [24]	POAF: Confirmed AF after surgery (up to 30 days)	126/1123 (derived from %)	145/1117 (derived from %)	aHR 0.75	0.61 – 0.91	0.004	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/2240 (overall)	N/A	N/A(main outcome was AF)	N/A
Kremneva et al. (2023) [19]	Paroxysmal AF	~1/~17 (derived from %, N est.%)	~26/~75 (derived from %, N est.)	N/A	N/A	0.019	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	16.3% (overall)	Intraoperative MI and cardiac death: higher in Paroxysmal AF group

Study Identifier	Arrhythmia	SGLT2i Group (E/N)	Control Group (E/N)	Reported Effect (RR/OR/HR)	95% CI	p-value	New-onset BBB (E/N)	Pacemaker Implantation (E/N)	New-onset AV Block (E/N)	Ventricular Tachycardia (E/N)	Premature Ventricular Contractions (E/N)	Atrial Tachycardia (E/N)	Premature Atrial Contraction (E/N)	Ketoacidosis (E/N)	Hypoglycemia (E/N)	AKI (E/N)	Other severe AEs (E/N)
Li et al. (2024) [21]	POAF: Incidence of POAF within 5 days post-surgery in those wothout history of AF	196/1001 (19.6%)	771/3003 (25.7%)	OR: 0.686	0.592-0.794	<0.001	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/4004 (No DKA events)	N/A	13/1001 (SGLT2i)vs. 129/3003 (Control)	In-hospital death: 21/4004 (0.5%), Stroke: 8/4004 (0.2%), Peri-op MI: 81/4004 (2.0%), Reoperation: 97/4004 (2.4%)
Morel et al. (2025) [29]	Incident AF (new diagnoses during follow-up)	90/2297	140/2297	HR: 0.776	0.595–1.011	0.06	N/A	97/2297 (SGLT2i) vs 97/2297 (Control); HR: 1.204 (0.908–1.597), p=0.2	80/2297 (SGLT2i) vs 85/2297 (Control); HR: 1.153 (0.848–1.566), p=0.36	VT/VF/ Cardiac arrest combined: 252/2297 (SGLT2i) vs 274/2297 (Control); HR: 1.054 (0.888–1.251), p=0.55	N/A	N/A	N/A	NR	NR	ESKD: 29/2297 (SGLT2i) vs 34/2297 (Control); HR: 1.087 (0.660–1.788), p=0.74	Death: 250/2297 (SGLT2i) vs 370/2297 (Control); HR: 0.828 (0.705–0.973), p=0.02; Bioprosthetic valve failure: 27/2297 (SGLT2i) vs 51/2297 (Control); HR: 0.617 (0.387–0.985), p=0.04; Acute MI: 62/2297 vs 81/2297; Ischemic stroke/thromboembolism: 95/2297 vs 105/2297; Major bleeding: 444/2297 vs 550/2297

AEs = adverse events; AF=atrial fibrillation; AFL= atrial flutter; aHR = adjusted Hazard Ratio; AKI = acute kidney injury; AV = atrioventricular; BBB = bundle branch block; BG = blood glucose; CI = confidence interval; DKA = diabetic ketoacidosis; E/N = events per the number of participants; eGFR = estimated glomerular filtration rate; freq/dur/intery = frequency/duration/interventionary details; HR = hazard ratio; KDIGO = kidney disease: improving global outcomes; LBBB = left bundle branch block; MD = mead difference; MI = myocardial infarction; N/A = not available/applicable; OR = odds ratio; pAF = paroxysmal atrial fibrillation; POAF = postoperative atrial fibrillation; peri-op = perioperative; Post-op = postoperative; RBBB = right bundle branch block; RR = relative risk; SGLT2i = sodium-glucose cotransporter-2 inhibitor

Table 3. GRADE assessment

Type	No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	SGLT2i	Control	95% CI		Certainty Assessment
RCT	3	Randomized trials	serious [1]	serious [2]	not serious	very serious [3]	none [4]	29/139 (20.9%)	43/143 (30.1%)	RR: 0.73; 95% CI: 0.51–1.03; p = 0.076		VERY LOW *(⊕○○○)*
NRSI	3	Observational studies (cohorts with propensity score matching)		serious [5]	not serious	not serious	not serious	very serious [6]	325/2,157 (15.1%)	920/4,153 (22.2%)	RR: 0.79; 95% CI: 0.70–0.89; p < 0.001	LOW [7] *(⊕⊕○○)*

*[1] **Risk of bias (serious, -1).** Two of three RCTs were open-label without blinding of participants, providers, or outcome assessors. Small sample sizes (55-145 patients) increase risk of selection and performance bias. AF assessment methods not standardized across trials. Different SGLT2i doses (empagliflozin 10 mg vs. 25 mg) and treatment durations used.[2] **Inconsistency (serious, -1).** Direction of effect varied across studies: Zarei et al. favored SGLT2i (11.6% vs. 28.2%), Pitta et al. favored control (15.5% vs. 13.5%, RR 1.15), Snel et al. favored SGLT2i (52% vs. 73%). Extreme heterogeneity in baseline POAF rates: control groups 13.5-73%, intervention groups 11.6-52%. Statistical heterogeneity I^2 = 43.07%. All studies non-significant despite different directions. Population heterogeneity in diabetes status and surgical procedures. [3] **Imprecision (very serious, -2).** Total sample only 282 patients with 72 POAF events. Confidence intervals cross line of no effect and include important benefit and harm. Optimal Information Size not met: required ~1,200 patients for 80% power, achieved only 282 (23% of required). Each study severely underpowered for POAF. [4] **Publication bias.** Not downgraded (already very low certainty). However, publication bias suspected as small null studies may be unpublished and Snel et al. reported POAF as secondary outcome only. [5] **Risk of bias (serious, -1).** Confounding by indication: patients on SGLT2i may differ systematically. Selection bias despite PSM: Rahhal et al. (retrospective, immortal time bias requiring ≥7 days SGLT2i), Li et al. (survivor bias requiring ≥3 months SGLT2i), Taghiyev et al. (small n=66, extensive baseline imbalances). PSM only adjusts measured confounders; important unmeasured confounders include frailty, inflammation, genetic susceptibility, intraoperative factors. Measurement bias: Rahhal used ICD codes (may miss paroxysmal AF), Taghiyev et al. unclear ascertainment with small events (3 vs. 3). [6] **Publication bias (very serious, -1).** Critical discordance with RCTs: all large observational studies show significant benefit while all RCTs show non-significant results, strongly suggesting selective publication. Rahhal et al. published as congress abstract only. Negative observational analyses likely unpublished (file drawer effect). Pattern highly suspicious for publication bias. [7] **Upgraded for large effect (+1).** Rahhal et al.: aHR 0.75 (25% RRR), Li et al.: OR 0.686 (31% RRR). Pooled estimate RR <0.8 meets GRADE "large effect" criteria. However, upgrade tempered by concerns that effect may be entirely due to confounding. Taghiyev et al. showed null result (RR=1.0), suggesting heterogeneity. **GRADE certainty definitions:** High (⊕⊕⊕⊕): very confident true effect lies close to estimate; Moderate (⊕⊕⊕○): moderately confident, true effect likely close to estimate; Low (⊕⊕○○): limited confidence, true effect may be substantially different; Very low (⊕○○○): very little confidence, true effect likely substantially different. **Abbreviations:** AF, atrial fibrillation; CABG, coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio; OR, odds ratio; POAF, postoperative atrial fibrillation; PSM, propensity score matching; NRSI, non-randomised studies of interventions; RCT, randomized controlled trial; RR, relative risk; SGLT2i, sodium-glucose cotransporter-2 inhibitors.*

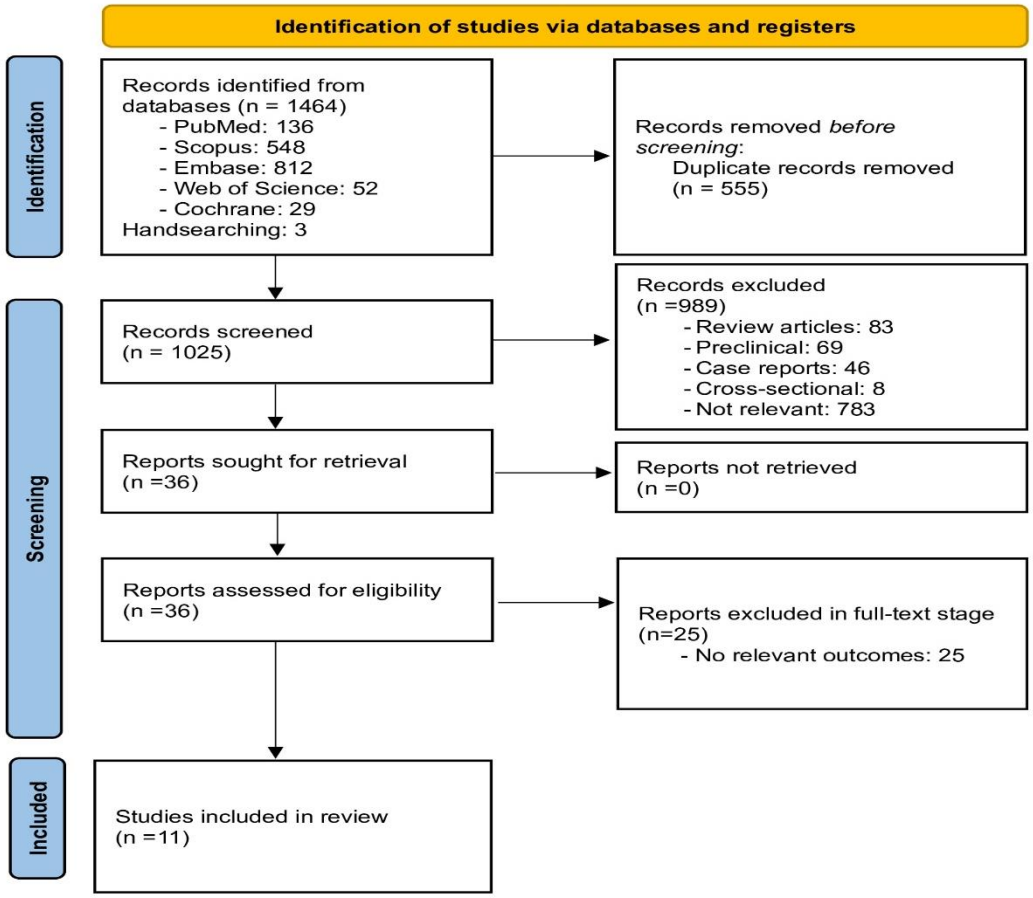

Figure 1. Study selection flow diagram. Preferred reporting items for systematic reviews and metaanalyses (PRISMA).

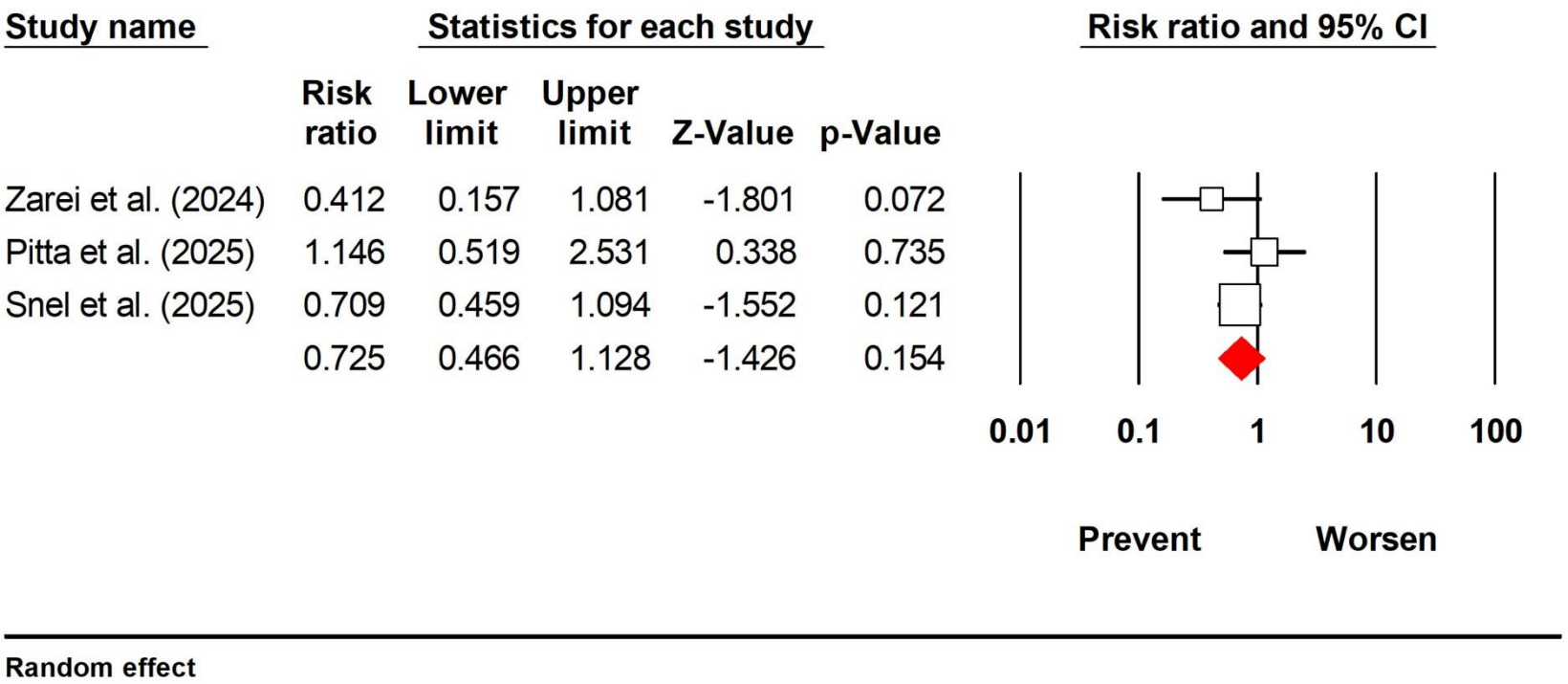

Figure 2. Meta-analysis results of the included RCT studies.

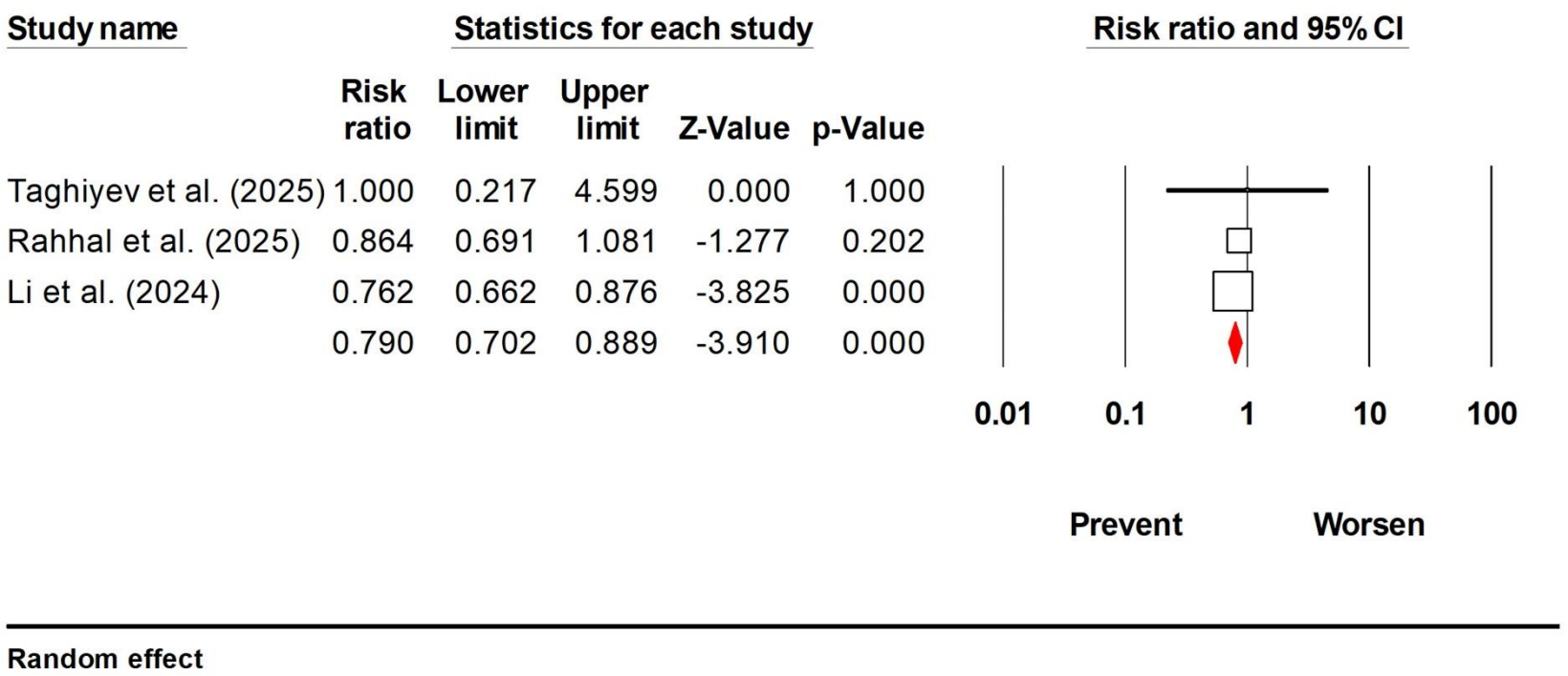

Figure 3. Meta-analysis results of the included NRSI studies.