

Systematic Review

Effect of SGLT2 Inhibitors on Post-PCI Outcomes after Acute Myocardial Infarction in Diabetic Patients: A Systematic Review and Meta-Analysis

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Submitted: 20 November 2023 Revised: 20 February 2024 Accepted: 7 March 2024 Published: 17 April 2024

Abstract

Background: Acute myocardial infarction (AMI) is related with poor outcomes in patients with diabetes mellitus (DM). Whether diabetic patients with AMI undergoing percutaneous coronary intervention (PCI) benefit from sodium–glucose cotransporter 2 inhibitors (SGLT2i) in terms of cardiovascular mortality, myocardial damage, and left ventricular function is unclear. **Methods:** Through a comprehensive search in PubMed, EMBASE, and Web of science databases from January 2018 to September 2023, randomized controlled trials were performed to compare SGLT2i with other oral antidiabetic medications in diabetic patients with AMI undergoing PCI. Cardiovascular mortality constituted the primary outcome. Secondary outcomes were high-sensitivity troponin I (hs-TnI) levels, left ventricular ejection fraction (LVEF), and contrast-induced acute kidney injury (CI-AKI). **Results:** SGLT2i significantly reduced cardiovascular mortality risk versus other antidiabetic agents (hazard ratio (HR): 0.35, 95% confidence interval (CI): 0.21–0.58, $p < 0.0001$). SGLT2i also lowered hs-TnI levels across all time points (mean difference: -293 ng/L, $p < 0.001$). After adjustment for publication bias, this difference was no longer significant. However, peak hs-TnI levels remained significantly lower with SGLT2i (mean difference: -3836 ng/L, $p < 0.001$). Finally, SGLT2i improved LVEF versus comparators, with a mean difference of -5.00% (95% CI: -6.69 to -3.31 , $p < 0.001$) at hospital discharge. SGLT2i was also associated with 60% lower odds of CI-AKI (odds ratio (OR): 0.40, 95% CI: 0.22–0.75, $p = 0.004$). **Conclusions:** Compared with other antidiabetic medications, SGLT2i may lower cardiovascular mortality, infarct size, and prevent left ventricle (LV) systolic dysfunction in diabetic patients with AMI undergoing PCI. The use of SGLT2i in this high-risk group is supported by these findings.

Keywords

sodium–glucose cotransporter 2 inhibitor; acute myocardial infarction; percutaneous coronary intervention; high-sensitivity troponin I; left ventricular ejection fraction; contrast-induced acute kidney injury

Introduction

Cardiovascular disease continues to be the primary cause of illness and death in those with diabetes mellitus (DM) [1]. Acute myocardial infarction (AMI) is a major complication of DM and portends a poor prognosis, especially when complicated by left ventricular systolic dysfunction [2]. For diabetic patients presenting with AMI, timely revascularization with percutaneous coronary intervention (PCI) is the recommended treatment strategy [3]. However, optimal medical therapy after PCI is also crucial for reducing adverse cardiovascular outcomes and improving survival.

Sodium–glucose cotransporter 2 inhibitor (SGLT2i) is a novel class of oral antidiabetic agents that reduce cardiovascular events and mortality across a broad range of patients with DM [4–6]. Multiple large randomized trials, including EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, and DAPA-HF, have demonstrated the cardioprotective effects of SGLT2i [7]. The mechanisms underlying the benefits of SGLT2i are multifactorial and may involve improvement in myocardial metabolism, reduction in necrosis and fibrosis, decreased inflammation and oxidative stress, and other favorable metabolic effects [8–10].

Despite the growing evidence for SGLT2i in chronic DM management, data on their use during the acute phase of AMI are limited. A few small randomized studies have evaluated SGLT2i as an adjunct to standard therapy in diabetic patients presenting with AMI undergoing PCI. By contrast, the effect of SGLT2i on cardiovascular mortality, infarct size, left ventricular function, and other important outcomes in this cohort is unknown.

Consequently, to understand further the cardiovascular advantages of SGLT2i over other antidiabetic drugs in diabetic patients with AMI undergoing PCI, we conducted a systematic review and meta-analysis. The outcomes of interest were cardiovascular mortality, myocardial injury assessed by high-sensitivity troponin I (hs-TnI), and left ventricular ejection fraction (LVEF).

Methods

The checklist of PRISMA were completed (**Supplementary Material**).

Literature Search Strategy

We conducted a comprehensive search of the PubMed, EMBASE, and Web of Science databases from January 2018 to September 2023 to identify pertinent studies.

We used the following keywords in our search: “SGLT2 inhibitor” OR “sodium-glucose co-transporter 2 inhibitor” OR specific drug names, such as “canagliflozin” combined with “acute myocardial infarction” OR “myocardial infarction” and “percutaneous coronary intervention” OR “PCI”. There were no linguistic limitations. For further records, we manually examined clinical trial registries and the reference lists of the included papers.

Study Selection

To find possibly qualifying studies, two reviewers independently went through the titles and abstracts of the data they had retrieved. We included randomized controlled trials (RCTs) to compare SGLT2 inhibitor (SGLT2i) therapy with other oral antidiabetic (OAD) agents in adult diabetic patients with AMI undergoing PCI. Studies were excluded if they were non-RCTs, had a sample size of <50 patients, or did not report sufficient data for extraction. Any disagreements were resolved through discussion.

Data Extraction

The extracted data comprised various aspects of the studies, including patient characteristics (sample size, mean age, duration of SGLT2i exposure, author, year, country, and design), intervention and comparison details, and outcome measures. Outcomes of interest were cardiovascular mortality, hs-TnI levels at various timepoints, and LVEF.

Estimation of Sample Mean and Standard Deviation

The approach suggested by Wan *et al.* [11] was employed to estimate the sample mean and standard deviation using the sample size, median, range, and/or interquartile range as inputs. This method operated under the condition that the data adhered to a normal distribution and em-

ployed distinct formulas in accordance with the information at hand. Comparing SGLT2i users and nonusers, we utilized this method to analyze nine studies that reported the median, minimum, maximum, and sample size of hs-TnI levels in diabetic patients with AMI undergoing PCI.

We used the formula in the study of Wan *et al.* [11] to calculate the mean and standard deviation of each group in each study: $\text{Mean} = m + (q_3 - q_1) \times f(n)$, where m is the median, q_3 is the upper quartile, q_1 is the lower quartile, and $f(n)$ is a function of sample size.

Quality Assessment

The methodological quality of the included RCTs was assessed by two reviewers in an independent manner, employing the Cochrane risk of bias instrument. This instrument assesses various sources of bias, including but not limited to random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Each domain’s risk of bias was categorized as low, unclear, or high [12].

Statistical Analysis

We conducted random effects model meta-analyses to collect the hazard ratios (HRs) for cardiovascular mortality and mean differences (MDs) for hs-TnI levels and LVEF between SGLT2i and non-SGLT2i groups. The I^2 statistic and chi-square test were applied to evaluate heterogeneity among studies. Potential publication bias was evaluated through Egger’s and Begg’s tests. Trim-and-fill analysis was conducted to mitigate the influence of publication bias. Subgroup analyses were conducted on the basis of the type of Cox regression model for cardiovascular mortality and on the basis of the timing of biomarker measurements. All statistical analyses were conducted utilizing the “meta” utility in R [13]. The median and quartiles were used to estimate the mean and standard deviation.

Results

Study Selection and Characteristics

From January 2018 to September 2023, we applied the following keywords to a systematic search of the PubMed, EMBASE, and Web of Science databases: “SGLT2 inhibitor” OR “sodium-glucose co-transporter 2 inhibitor” OR “canagliflozin” OR “dapagliflozin” OR “empagliflozin” OR “ertugliflozin” AND “acute myocardial infarction” OR “AMI” OR “myocardial infarction” OR “MI” AND “percutaneous coronary intervention” OR “PCI”. We also searched for additional records from other sources, such as reference lists of relevant articles and clinical trial registries. Fig. 1 depicts the process flow diagram for the literature search and selection.

Table 1. Baseline characteristics of trials evaluating SGLT2i in AMI patients undergoing PCI.

Study Name	Region	Study Design	Intervention	Patients number	Median age	Mean time of exposure to SGLT2i therapy	Study Quality
Paolisso <i>et al.</i> , 2023a [14]	Italy	RCT	SGLT2i & OAD	646	70	7.3 ± 3.0 months	Good
Paolisso <i>et al.</i> , 2023b [15]	Italy	RCT	SGLT2i & OAD	646	70	7.3 ± 3.0 months	Good
Paolisso <i>et al.</i> , 2022 [16]	Italy	RCT	SGLT2i & OAD	583	71	7.3 ± 3.1 months	Good
Marfella <i>et al.</i> , 2023 [17]	Italy	RCT	SGLT2i & OAD	377	66.2	18.0 ± 7.0 months	Good

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; RCTs, randomized controlled trials; SGLT2i, sodium–glucose cotransporter 2 inhibitors; OAD, oral antidiabetic.

A total of 43 full-text publications were found for eligibility evaluation after duplicates were eliminated and titles and abstracts were screened. Of these, 35 articles were excluded for the following reasons: reviews/meta-analyses ($n = 8$), not a randomized controlled trial (RCT) ($n = 12$), sample size <50 ($n = 0$), and insufficient data ($n = 15$). Finally, we included four RCTs in our systematic review and meta-analysis, involving a total of 2646 patients with AMI undergoing PCI, who were treated with SGLT2i or other OAD agents. Table 1 (Ref. [14–17]) shows a summary of the baseline features of the studies that were included.

Evaluate the Effect of SGLT2i on Cardiovascular Death in AMI Patients Undergoing PCI

With an HR of 0.35 (95% confidence interval (CI): 0.21–0.58, $p < 0.0001$), the overall meta-analysis demonstrated that SGLT2i users had a considerably lower risk of cardiovascular death than non-SGLT2i users. No heterogeneity was found among the studies, with an I^2 value of 0% and a Q statistic of 0.86 ($p = 0.8343$). A forest plot and a funnel plot representing the overall meta-analysis are presented in Fig. 2A,B, respectively.

We used Egger’s test and Begg’s test to evaluate the publication bias. The random effects model served as the foundation for both tests. Egger’s test used a linear regression methodology to quantify the asymmetry of the funnel plot, while Begg’s test used a rank correlation approach. The results of both tests showed no significant publication bias, with a t statistic of 0.74 ($p = 0.5352$) for Egger’s test (Fig. 2C) and a z statistic of 0.68 ($p = 0.4969$) for Begg’s test (Fig. 2D). We also performed a Baujat analysis to identify the most influential studies. Results showed that none of them had a high contribution to heterogeneity or low contribution to precision, indicating that they were all consistent and reliable. In Fig. 2E, a Baujat diagram of the meta-analysis is displayed.

We also performed a subgroup analysis according to the Cox regression model used in each study, dividing the studies into two groups: univariate and multivariate. The results showed that the HR between SGLT2i users and non-SGLT2i users was 0.33 (95% CI: 0.12–0.90, $p = 0.031$) in the univariate group and 0.36 (95% CI: 0.20–0.65, $p < 0.0001$) in the multivariate group, both in the random ef-

fects model. No statistically significant difference existed among the subgroups, with a Q statistic of 0.02 ($p = 0.8871$). In Fig. 2F, a forest diagram of the subgroup meta-analysis is displayed.

The findings indicated that SGLT2i may exert a positive influence on cardiovascular mortality in diabetic patients with AMI undergoing PCI, compared with other oral antidiabetic agents alone. This effect was robust and consistent across different types of Cox regression models and was not affected by publication bias.

Meta-Analysis of SGLT2i on hs-TnI Levels in AMI Patients Undergoing PCI

To examine the effects of SGLT2i against non-SGLT2i on the levels of hs-TnI in diabetic patients with AMI undergoing PCI, we conducted a meta-analysis of nine trials. The hs-TnI levels were measured at four time points: before PCI (I), 3–6 hours after PCI (II), 24 hours after PCI (III), and peak value during hospitalization (peak). Prior to its decline, the hs-TnI peak was thought to be the greatest value. The overall MD between SGLT2i users and non-SGLT2i users was 2931.7 ng/L (95% CI: 2066.7–3796.7, $p < 0.001$) in the random effects model, indicating that SGLT2i users had significantly lower hs-TnI levels than non-SGLT2i users across all time points. The studies exhibited significant heterogeneity, with an I^2 value of 100% and a Q statistic of 6780.07 ($p < 0.001$). Fig. 3A displays a forest plot of the comprehensive meta-analysis.

Egger’s test and Begg’s test were employed to evaluate the publication bias of the meta-analysis. Both tests were based on the random effects model. Egger’s test employed a linear regression methodology to quantify the asymmetry of the funnel plot, while Begg’s test used a rank correlation approach. The results of Egger’s test showed a significant publication bias ($t = 12.73$, $p < 0.001$) (Fig. 3B); by contrast, Begg’s test showed non-significance ($z = 1.25$, $p = 0.21$) (Fig. 3C).

We implemented the trim-and-fill technique to rectify the publication bias detected by Egger’s test. This method imputed five missing datasets on the left side of the funnel plot, assuming a symmetric distribution of effect sizes. The adjusted MD between SGLT2i users and non-SGLT2i users was 801.5 ng/L (95% CI: –61.8 to 1664.8, $p = 0.07$) in the

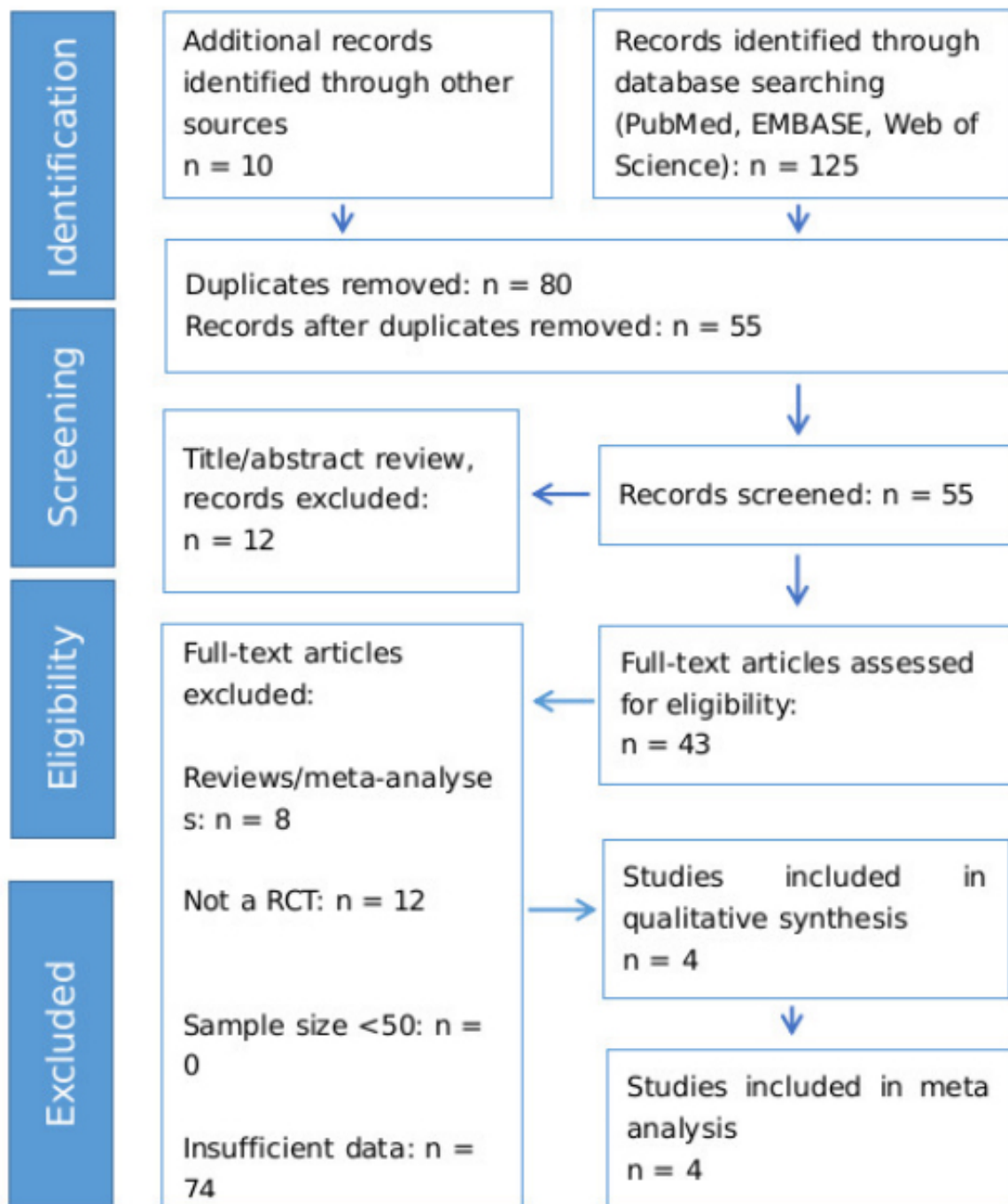


Fig. 1. Prisma diagram.

random effects model, which was not statistically significant. This result suggested that the publication bias might have inflated the effect size of SGLT2i on hs-TnI levels. A funnel plot of the trim-and-fill method is shown in Fig. 3D.

We also performed a subgroup analysis based on the time point of hs-TnI measurement, dividing the studies into two groups: nonpeak (I, II, III) and peak. The results showed that the MD between SGLT2i users and non-SGLT2i users was 2474.5 ng/L (95% CI: 1570.8–3378.1, $p < 0.001$) in the non-peak group and 3836.4 ng/L (95%

CI: 2792.5–4880.4, $p < 0.001$) in the peak group, both in the random effects model. The heterogeneity within each subgroup was still high, with I^2 values of 100% and 99%, respectively. Fig. 3E displays a forest plot of the subgroup meta-analysis.

Evaluate the Effect of SGLT2i on LVEF in Diabetic Patients with AMI Undergoing PCI

The overall meta-analysis showed that SGLT2i users had significantly higher LVEF than non-SGLT2i users

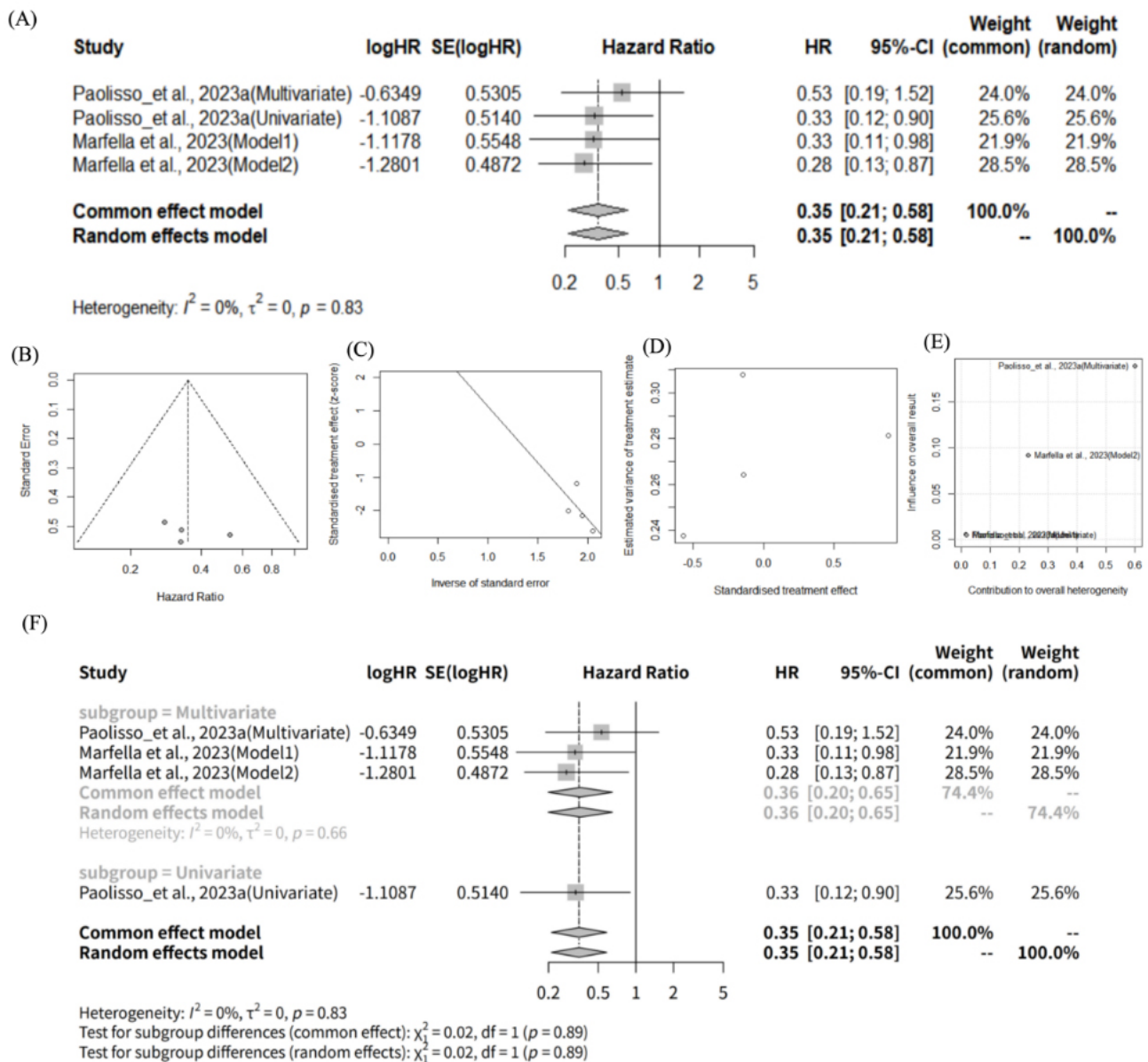


Fig. 2. Evaluate the effect of SGLT2i on cardiovascular death. (A) Meta-analysis of forest maps. (B) Funnel plot of the meta-analysis. (C) Egger's test for publication bias. (D) Begg's test for publication bias. (E) Baujat plot of the meta-analysis. (F) Forest plot of the subgroup meta-analysis.

across all time points and subgroups, with an MD of -2.39% (95% CI: -4.12 to -0.67 , $p = 0.007$). The investigations exhibited a significant level of variation, the I^2 value was 64% , and Q statistic was 13.92 ($p = 0.02$). Fig. 4A displays a forest plot of the overall meta-analysis.

Egger's test and Begg's test were used to evaluate the presence of publication bias. The results of Egger's test showed no significant publication bias ($t = -0.05$, $p = 0.96$) (Fig. 4B), and Begg's test also showed no significance ($z = -0.56$, $p = 0.57$) (Fig. 4C). A funnel plot of the trim-and-fill method is shown in Fig. 4D.

We also performed a subgroup analysis based on the time point of the LVEF measurement, dividing the studies into two groups: hospital admission and hospital discharge.

The results showed that the MD between SGLT2i users and non-SGLT2i users was -1.08% (95% CI: -2.28 to 0.13 , $p = 0.08$) at hospital admission and -5.00% (95% CI: -6.69 to -3.31 , $p < 0.001$) at hospital discharge, both in the random effects model. The heterogeneity within each subgroup was low, with I^2 values of 0% and 0% , respectively. Fig. 4E displays a forest plot of the subgroup meta-analysis.

The findings indicate that SGLT2i may exert a positive influence on LVEF in diabetic patients with AMI undergoing PCI, especially at hospital discharge, compared with other oral antidiabetic agents alone.

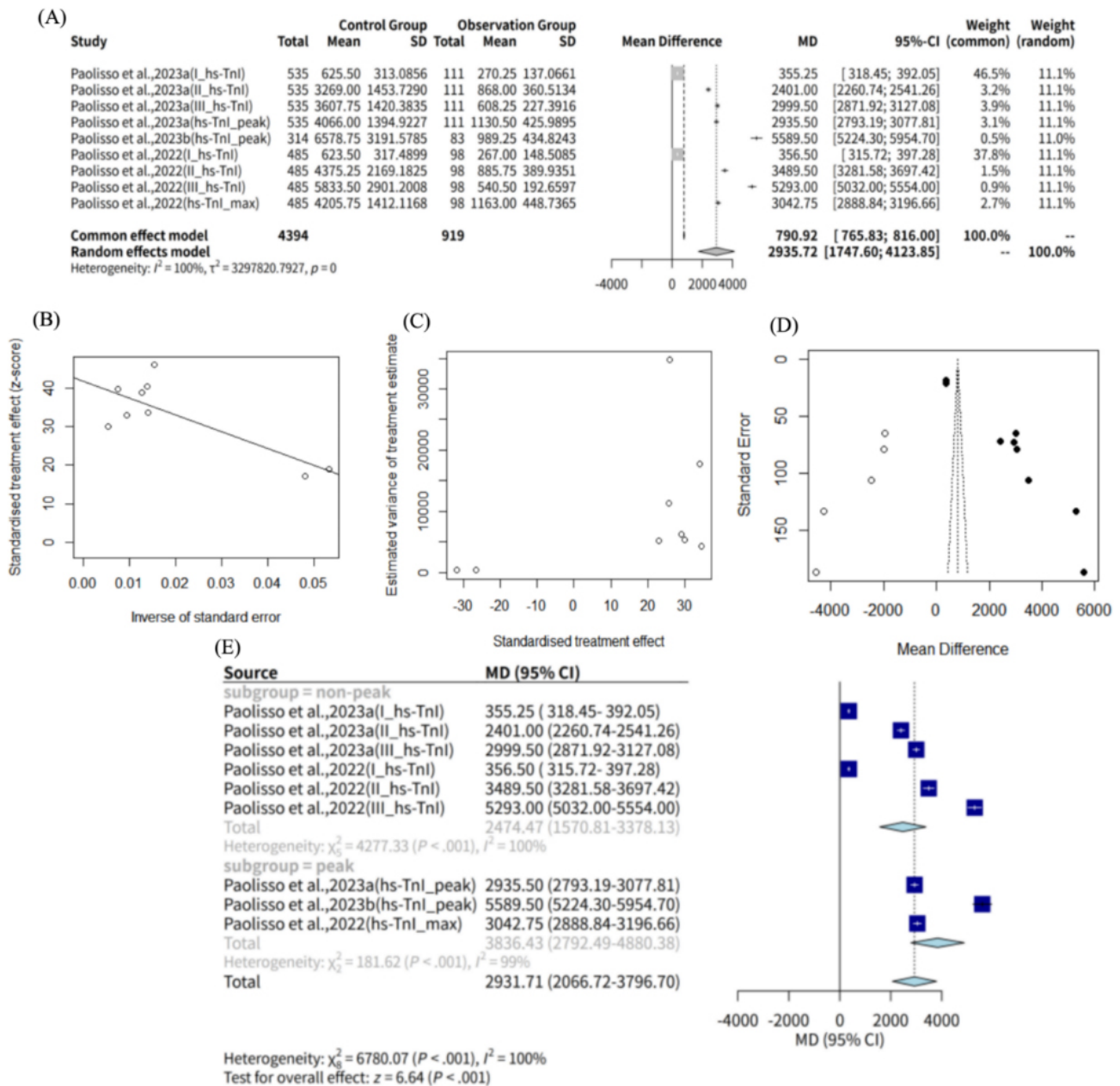


Fig. 3. Meta-analysis of SGLT2i on hs-TnI levels. (A) Meta-analysis of forest maps. (B) Egger's test for publication bias. (C) Begg's test for publication bias. (D) Funnel plot of overall meta-analysis. (E) Forest plot of the subgroup meta-analysis. hs-TnI, high-sensitivity troponin I.

Association between SGLT2i Use and CI-AKI Risk

The odds ratio (OR) of the common effect model for developing contrast-induced acute kidney injury (CI-AKI) in patients treated with SGLT2i compared with those not treated was 0.4070 (95% CI: 0.2209–0.7497). The z-score was -2.88 , and the p -value was 0.0039, indicating a statistically significant association. By contrast, the OR in the random effects model was 0.4286 (95% CI: 0.2314–0.7936), with a z-score of -2.70 and a p -value of 0.0070, also indicating a significant association (Fig. 5A).

Minimal variability was observed among the included studies, with an I^2 statistic of 0.0%, suggesting no significant heterogeneity. The Q-test for heterogeneity yielded a p -value of 0.4598, further supporting the absence of substantial heterogeneity. The funnel plot (Fig. 5B) illustrated that the data points were distributed symmetrically, suggesting that publication bias is improbable.

The plot covered a range from 0.1007 to 1.7662 on the x-axis and from 0.7418 to 0.0000 on the y-axis, with no evidence of data asymmetry.

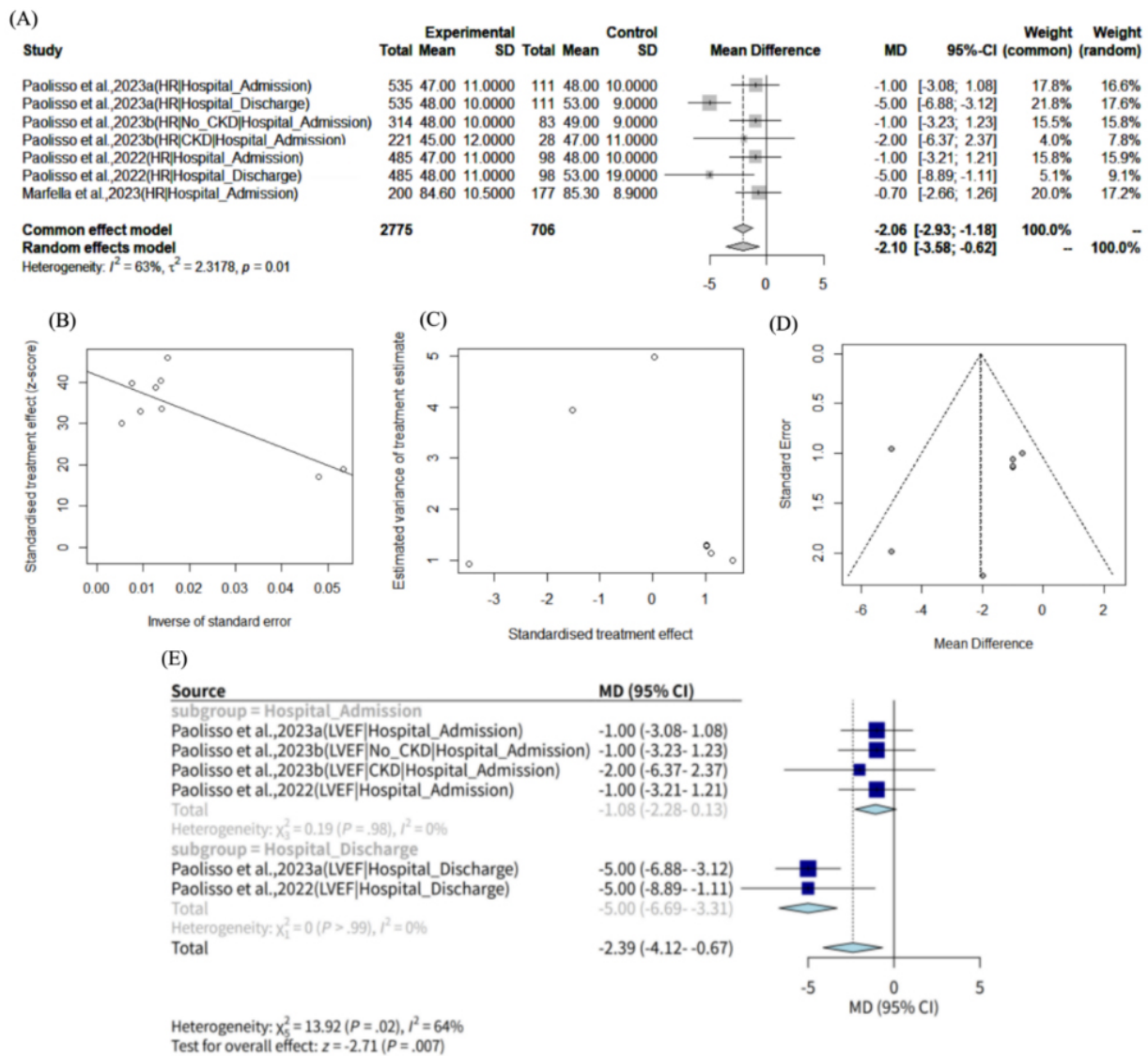


Fig. 4. Evaluate the effect of SGLT2i on LVEF. (A) Meta-analysis of forest maps. (B) Egger's test for publication bias. (C) Begg's test for publication bias. (D) Funnel plot of overall meta-analysis. (E) Forest plot of the subgroup meta-analysis. LVEF, left ventricular ejection fraction.

According to this meta-analysis, we observed a strong statistical correlation, indicating that the use of SGLT2i is linked to a reduced incidence of CI-AKI in patients with AMI who are undergoing PCI. The findings suggest that SGLT2i usage is associated with a reduced risk of CI-AKI in this patient population, emphasizing the potential renal protective effects of SGLT2i.

Discussion

This systematic review and meta-analysis found that compared with other oral antidiabetic agents, SGLT2i therapy was associated with a substantially lower risk of cardiovascular mortality in diabetic patients with AMI undergoing PCI.

The HR for cardiovascular death was 0.35 (95% CI: 0.21–0.58, $p < 0.0001$), suggesting a 65% reduction in cardiovascular mortality with SGLT2i treatment. This cardiovascular benefit was consistent across studies [18] and was not affected by the type of statistical model used.

Several mechanisms may explain the cardioprotective effects of SGLT2i. SGLT2i has been shown to reduce oxidative stress, improve myocardial energetics, decrease inflammation, and attenuate cardiac fibrosis and remodeling in animal models of ischemic heart disease [19–21]. A study by Lee *et al.* [10] has demonstrated that empagliflozin preserves mitochondrial structure and function in a mouse model of AMI. The findings of our meta-analysis offer empirical support for the notion that corroborates the experimental data on the protective mechanisms of SGLT2i against ischemic myocardial injury.

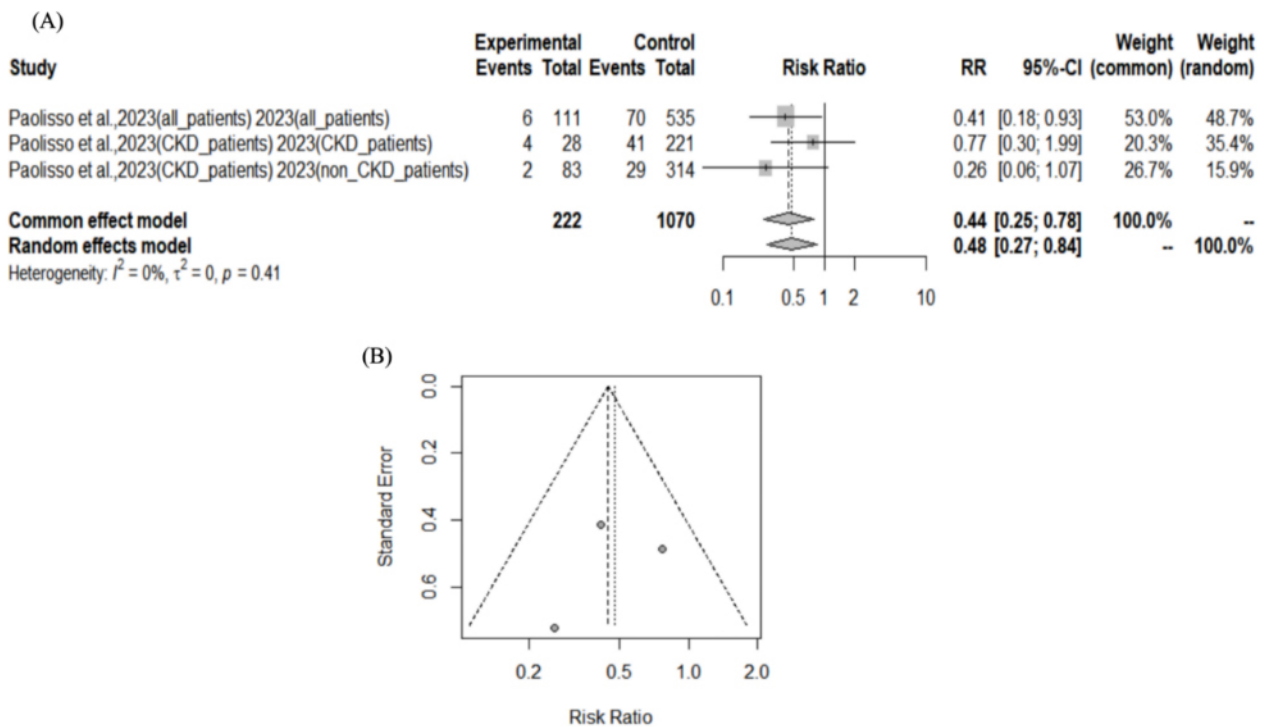


Fig. 5. Association between SGLT2i use and CI-AKI risk. (A) Meta-analysis of forest maps. (B) Funnel plot of the meta-analysis. CI-AKI, contrast-induced acute kidney injury.

We also found that SGLT2i therapy significantly lowered hs-TnI levels across all timepoints in AMI patients undergoing PCI. However, the results were heterogeneous across studies, and the effect size appeared to be inflated by publication bias. After adjusting for this bias, the difference in hs-TnI levels was no longer statistically significant. Nevertheless, the peak hs-TnI levels still showed a significant 3836 ng/L reduction with SGLT2i treatment compared with other antidiabetic medications. Given that peak hs-TnI closely correlates with infarct size, these data indicate that SGLT2i may reduce myocardial infarct size in the setting of AMI and PCI.

Finally, our meta-analysis demonstrated that SGLT2i therapy led to significant improvements in LVEF, especially at hospital discharge. The mean difference in LVEF between SGLT2i users and non-SGLT2i users was -5.00% (95% CI: -6.69 to -3.31 , $p < 0.001$) at discharge. Multiple mechanisms likely underlie the benefits of SGLT2i on cardiac function, including decreased inflammation and fibrosis, reduced ischemia/reperfusion injury, and modulation of cellular energetics [22,23]. Clinical trials have also shown that SGLT2i prevents the deterioration of LVEF in heart failure patients [24]. Our study extends these findings to the setting of AMI treated with PCI.

Limitations

Our research has some limitations. First, our research is based on published research, but some studies have not been published yet due to sample size or negative conclusions. Therefore, the studies that we included have the risk of publication bias and high heterogeneity of some variables (hs-TnI). Second, RCTs of SGLT2i in diabetic patients with AMI undergoing PCI are few, thus limiting the extrapolation of this study. Third, the RCTs included in this study were conducted in Italy. The use of SGLT2i in Italy may be different from that in Asia or China, and the universality of SGLT2i must be further verified. Finally, the studies we included lack long-term follow-up data, especially for heart failure outcomes, which require long follow-up to observe the long-term efficacy.

Conclusions

This meta-analysis of RCTs indicates that SGLT2i therapy reduces cardiovascular mortality, infarct size, and LVEF decline in diabetic patients with AMI undergoing PCI. The cardiovascular protective effects may be mediated through improvements in myocardial energetics, inflammation, fibrosis, and remodeling. Our results provide evidence in favor of incorporating SGLT2i into the standard of care for diabetic patients who have undergone revascularization and AMI procedures.

Availability of Data and Materials

Data to support the findings of this study are available on reasonable request from the corresponding author.

Author Contributions

XL and WW performed the research. XX provided help and advice on the experiments. XL, WW and XX contributed to the analysis and interpretation of the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.59958/hf.7021>.

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