FUTURE CARDIOLOGY
2025, VOL. 21, NO. 3, 177–190
https://doi.org/10.1080/14796678.2025.2464449

Taylor & Francis
Taylor & Francis Group

META-ANALYSIS

The effect of sodium-glucose co-transporter 2 inhibitors on clinical outcomes after acute myocardial infarction: a systematic review and meta-analysis of randomized controlled trials

Ubaid Khan[a], Ahmed Mazen Amin[b], Amira Mohamed Taha[c], Yehya Khlidj[d], Majd M. AlBarakat[e], Mariam Elewidi[f], Mohamed Abuelazm[f], Mustafa Turkmani [g,h], Basel Abdelazeem[i] and Rida Laeeq[i]

[a]Division of Cardiology, University of Maryland School of Medicine, Baltimore, MD, USA; [b]Faculty of Medicine, Mansoura University, Mansoura, Egypt; [c]Faculty of Medicine, Fayoum University, Fayoum, Egypt; [d]Faculty of Medicine, University of Algiers, Algiers, Algeria; [e]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan; [f]Faculty of Medicine, Tanta University, Tanta, Egypt; [g]Faculty of Medicine, Michigan State University, East Lansing, MI, USA; [h]Department of Internal Medicine, McLaren Health Care, Oakland, MI, USA; [i]Department of Cardiology, West Virginia University Morgantown, West Virginia, USA

ABSTRACT

Introduction: Sodium-glucose cotransporter 2 inhibitors (SGLT2is) reduce cardiovascular events, especially in diabetic patients. However, the cardioprotective effects of early SGLT2i administration following acute myocardial infarction (AMI) remain unclear.
Objective: This study aims to investigate the impact of SGLT2is on clinical outcomes in patients post-AMI.
Methods: A comprehensive search was conducted in PubMed, CENTRAL, WOS, Scopus, and EMBASE up to April 2024. Risk ratio (RR) was used for dichotomous outcomes and mean difference (MD) for continuous outcomes, with 95% confidence intervals (CI).
Results: Seven studies with 11,407 patients were included. SGLT2is did not significantly reduce the incidence of major adverse cardiovascular events (MACE) (RR = 0.94, 95% CI [0.68, 1.29], $p = 0.69$), all-cause mortality (RR = 1.01, 95% CI [0.84, 1.21], $p = 0.93$), or stroke (RR = 0.61, 95% CI [0.29,1.28], $p = 0.19$). However, SGLT2is significantly reduced the risk of heart failure (RR = 0.76, 95% CI [0.63, 0.91], $p < 0.01$) and improved left ventricular ejection fraction (MD = 1.86, 95% CI [1.58, 2.14], $p < 0.01$).
Conclusion: In post-AMI patients, SGLT2is do not significantly affect MACE or mortality but are associated with reduced heart failure risk and improved ejection fraction.
Protocol registration: PROSPERO identifier number: CRD42024506806.

PLAIN LANGUAGE SUMMARY

SGLT2is represent a class of antidiabetic medication that can reduce the risk of developing cardiovascular events in diabetic patients. Nevertheless, it is unclear if they can reproduce these cardioprotective effects in patients who have had AMI. The present meta-analysis aimed to answer that question by reviewing data from seven studies with a total of 11,407 post-AMI patients who received standard care either with SGLT2is or without SGLT2is. The findings showed that the SGLT2is group did not have a lower risk of major adverse cardiovascular events, all-cause mortality, and stroke as compared to the control group. However, treatment with SGLT2is had more notable positive effects manifesting as a decrease in the risk of heart failure and an improvement in cardiac function. These results suggest that SGLT2is although have limited benefit in post-AMI patients, can still provide statistically significant protection against heart failure and cardiac dysfunction.

ARTICLE HISTORY
Received 21 October 2024
Accepted 5 February 2025

KEYWORDS
SGLT2i; myocardial infarction; cardiac remodeling; heart failure; mortality

1. Introduction

Acute myocardial infarction (AMI), a critical and often life-threatening cardiac emergency, mainly occurs due to the disruption of weak coronary plaques leading to full or partial blockages in the coronary arteries with subsequent myocardial ischemia or necrosis. Even with current treatment advancements, individuals who have experienced AMI face a higher likelihood of future fatal and nonfatal cardiovascular complications [1].

Sodium-glucose cotransporter 2 inhibitors (SGLT2is) could provide cardioprotection through metabolic and anti-inflammatory processes and alter myocardial signal transduction. Notably, the favorable cardiovascular outcomes found in cardiovascular outcome trials (CVOTs) occur within weeks of treatment beginning and are unaffected by glycemic status.

SGLT2is have been demonstrated to lower hospitalizations for heart failure and total mortality, including cardiovascular deaths, in patients with chronic heart failure with reduced ejection fraction (HFrEF) [2]. These advantages extend to starting SGLT2i treatment after an acute heart failure episode. Diabetes is an established risk factor for coronary artery disease; hence, the safety of SGLT2is, particularly for individuals with type 2 diabetes mellitus (T2DM) and AMI, should be

CONTACT Mustafa Turkmani turkman5@msu.edu Faculty of Medicine, Michigan State University, East Lansing, MI 48824, USA
Supplemental data for this article can be accessed online at https://doi.org/10.1080/14796678.2025.2464449

Article highlights

- Early use of SGLT2is post-AMI does not significantly reduce major adverse cardiovascular events (MACE).
- Early use of SGLT2is post-AMI does not significantly reduce all-cause mortality.
- SGLT2is are associated with a significantly reduced risk of heart failure in post-AMI patients.
- Left ventricular ejection fraction improved significantly with SGLT2is post-AMI.
- SGLT2is may offer targeted benefits in heart failure prevention and cardiac function improvement after AMI.
- No significant impact was observed on stroke risk with SGLT2i use post-AMI.
- Further research is needed to determine the cardioprotective effects of SGLT2 inhibitors in the early post-acute myocardial infarction phase.
- This paper supports SGLT2is as a promising adjunctive therapy for heart failure prevention in post-AMI care.

carefully considered. SGLT2is therapy may cause an asymptomatic increase in blood ketone levels; however, most patients can tolerate this small increase. Ketone levels rise as a metabolic response to glucose depletion and can provide an efficient energy supply and cardio-protection during metabolic stress, particularly in diabetes and heart failure patients [3]. SGLT2is have been shown in cardiovascular trials to minimize the risk of incident HF hospitalization in people with T2DM who have or are at high risk of cardiovascular disease [4].

Dapagliflozin, in particular, has demonstrated a significant reduction in MACE relative risk by 16% in diabetic individuals with prior MI [5]. Furthermore, SGLT2is have been shown to lower the risk of death and hospitalization in individuals with chronic HF, regardless of diabetes or ejection fraction maintenance. However, these studies frequently excluded patients who just had an MI, raising the question of whether the use of SGLT2is may help AMI survivors.

This meta-analysis hypothesizes that SGLT2 inhibitors enhance clinical outcomes in post-AMI patients, regardless of diabetes status, by lowering heart failure events and improving left ventricular ejection fraction (LVEF). The primary objectives are major adverse cardiovascular events (MACE) and cardiac death.

2. Methodology

2.1. Protocol registration

The present systematic review and meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [6] and the Cochrane Handbook of Systematic Reviews and Meta-Analysis [7]. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024506806.

2.2. Data sources & search strategy

Until October 2023, a comprehensive search was systematically conducted across five databases (PubMed, CENTRAL, WOS, SCOPUS, EMBASE) by the UK without imposing any search restrictions. On 5 April 2024, we conducted a manual searching update using PubMed. Detailed information about the search strategy is available in (Table S1).

2.3. Eligibility criteria

The inclusion criteria for the selected studies were established using the PICO framework. Patients diagnosed with MI, regardless of their diabetic status, comprised the population (P). Intervention (I) encompassed various SGLT2is, while comparison (C) involved control groups receiving either a placebo. Primary outcomes (O) of interest included MACE & cardiac death. Our secondary outcomes are changes in left ventricular ejection fraction (LVEF), stroke, heart failure, recurrent myocardial infarction (RE-MI), NT-proBNP levels, body weight, all-cause mortality, glycosylated hemoglobin (HbA1C) levels, and estimated glomerular filtration rate (eGFR).

2.4. Study selection

After eliminating duplicates, three reviewers (AMA, ME, MMA) independently screened the titles and abstracts of the gathered studies using the Covidence online software. Following this initial screening, the same three reviewers conducted a full-text assessment based on the predefined eligibility criteria. Any discrepancies or conflicts that arose during the screening process were resolved through discussion among the reviewers.

2.5. Data extraction

UK and AMA formulated an extraction sheet to gather data on various aspects: summary characteristics such as study design, number of centers, blinding status, country, total participants, intervention and control details, main inclusion criteria, follow-up duration, and primary outcome measures. Baseline characteristics, including the number of patients in each group, age, gender, systolic and diastolic blood pressure, HbA1C levels, heart rate, eGFR, smoking status, baseline treatments, and comorbidities, were also included. The main hypothesis of this systematic review and meta-analysis is that the use of SGLT2 inhibitors in post-AMI patients, regardless of diabetic status, will lead to improved clinical outcomes, particularly by reducing heart failure events and improving left ventricular ejection fraction (LVEF). The primary endpoints of this study are the incidence of major adverse cardiovascular events (MACE) and cardiac death. Secondary endpoints include changes in all-cause mortality, heart failure events, recurrent myocardial infarction (RE-MI), stroke, as well as changes in LVEF, NT-proBNP levels, HbA1c levels, body weight, and eGFR. This study specifically aims to investigate the effect of SGLT2 inhibitors on these outcomes in patients with or without diabetes mellitus (DM) who have been treated after AMI. These endpoints are defined and measured consistently across the included studies to provide a comprehensive evaluation of the cardioprotective effects of SGLT2 inhibitors post-AMI. Data extraction was carried out independently by the three reviewers (MMA, ME, and AMA), with any discrepancies resolved through discussion.

2.6. Risk of bias and certainty of evidence

Four reviewers (MA, MA, AMA, ME) independently assessed the quality of the studies included in the research using the Cochrane ROB2 tool for RCTs [8]. The domains of the studies that were evaluated included the risk of bias resulting from the randomization process, the risk of bias due to deviation from the intended intervention, the risk of bias due to missing outcome data, the risk of bias in measuring the outcome, and the risk of bias in selecting the reported results. To investigate the certainty of evidence, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [9,10] recommendations were followed considering inconsistency, imprecision, indirectness, publication bias, and risk of bias. An evaluation was carried out for each outcome, and the decisions were justified and documented. Any discrepancies were settled through discussion.

2.7. Statistical analysis

R software version 4.3.1 was used for statistical analysis. For dichotomous outcomes, the Risk ratio (RR) was used, while for continuous outcomes, the mean difference (MD) was used, both with a 95% confidence interval (CI) using the random-effects model when there was a significant heterogeneity (I^2 > 50%) and the common-effect model when heterogeneity was not significant (I^2 < 50%). Heterogeneity was assessed using chi-square and I-square tests. The chi-square test shows the presence of heterogeneity, and the I-square test shows the degree of heterogeneity [6]. We conducted a sensitivity analysis in the case of high heterogeneity by omitting one study in each scenario to investigate the source of heterogeneity.

3. Results

3.1. Search results and study selection

A total of 3,842 results were incorporated from five databases into Covidence. One thousand eight hundred eleven were duplicates and removed by Covidence, leaving 2,031 records to be screened. Out of these, 1,988 records were found to be irrelevant and excluded in title and abstract screening. This left 43 studies for full-text screening, and 7 were found eligible for data extraction (Figure 1).

3.2. Characteristics of included studies

The final analysis included seven randomized controlled trials [11–17] with 11,407 participants. Comprehensive details of the

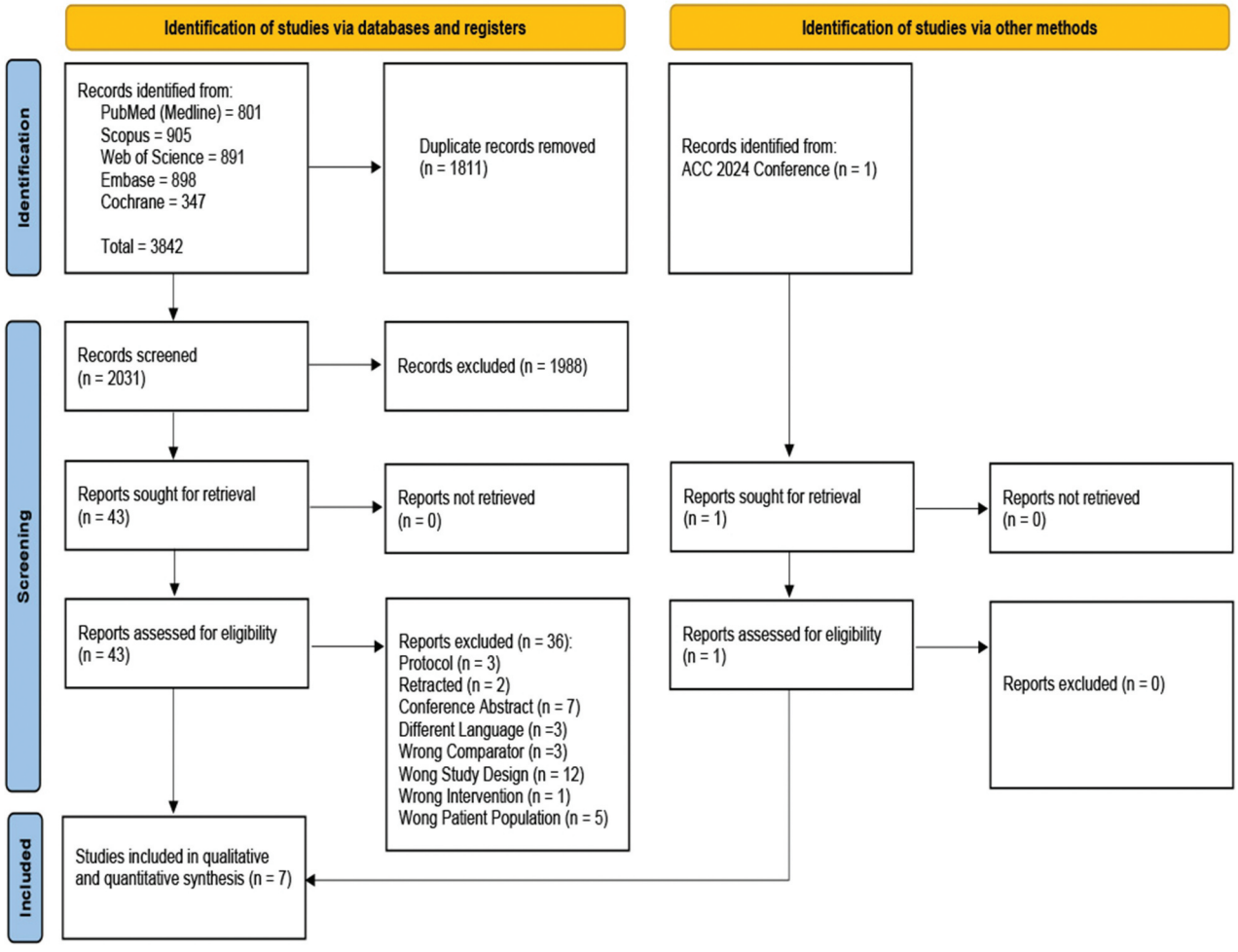


Figure 1. PRISMA flow chart of the screening process.

included studies' summary characteristics and the participants' baseline characteristics are outlined in (Tables 1 and 2).

3.3. Risk of bias and certainty of evidence

After assessing seven RCTs by ROB-2, five RCTs showed a low risk of bias. In contrast, two RCTs had some concerns due to concerns in the randomization process, deviations from the intervention, or selection of the reported results (Figure 2). Certainty of evidence is demonstrated in the GRADE evidence profile (Table 3).

3.4. Primary outcomes

3.4.1. Major adverse cardiac events (MACE)

Three studies evaluated the frequency of MACE between SGLT-2is users and non-SGLT-2is users, suggesting no significant reduction in MACE for SGLT-2is users (RR = 0.94, 95% CI [0.68, 1.29], $p = 0.69$). There was no heterogeneity across the studies ($p = 1.00$, $I^2 = 0\%$) (Figure 3(a)).

3.4.2. Cardiac death

Six studies assessed the risk of cardiac death between individuals using SGLT-2is and those not using them. The pooled analysis did not show a statistically significant difference (RR = 1.02, 95% CI [0.83, 1.27], $p = 0.82$). The heterogeneity was low ($p = 0.99$, $I^2 = 0\%$) (Figure 3(b)).

3.5. Secondary outcomes

3.5.1. Clinical outcomes

The Pooled analysis showed no significant difference in reduction in all-cause mortality between the two groups (RR = 1.01, 95% CI [0.84, 1.21], $p = 0.93$) (Figure 4(a)). However, the SGLT-2is group was associated with a significant reduction in heart failure events compared to the non-SGLT-2is (RR = 0.76, 95% CI [0.63, 0.91], $p < 0.01$) (Figure 4(b)). Also, there was no difference between SGLT-2is and non-SGLT-2is groups in risk for RE-MI (RR = 1.06, 95% CI [0.65, 1.70], $p = 0.82$) (Figure 4(c)) and incidence of stroke (RR = 0.61, 95% CI [0.29, 1.28], $p = 0.19$) (Figure 4(d)).

The pooled studies were homogenous in all-cause mortality ($p = 0.74$, $I^2 = 0\%$), heart Failure ($p = 0.57$, $I^2 = 0\%$), RE-MI ($p = 0.80$, $I^2 = 0\%$), and stroke ($p = 0.93$, $I^2 = 0\%$).

3.5.2. Other parameters

The pooled analysis indicated an improvement in LVEF in those who were taking SGLT2is (MD = 1.86, 95% CI [1.58, 2.14], $p < 0.01$) (Figure 5(a)), demonstrating statistical significance. In contrast, there was no difference between the groups in terms of change in NT-proBNP level (MD = 37.59, 95% CI [−10.59, 85.76], $p = 0.13$) (Figure 5(b)), change in HbA1C level (MD = −0.16, 95% CI [−0.46, 0.14], $p = 0.30$) (Figure 5(c)), body weight change (MD = 0.11, 95% CI [−2.78, 2.99], $p = 0.94$) (Figure 5(d)), and eGFR change (MD = 1.35, 95% CI [−4.01, 6.70] $p = 0.62$) (Figure 5(e)).

Pooled studies were homogenous in LVEF change ($p = 0.32$, $I^2 = 13\%$), Change in NT-proBNP Levels ($p = 0.94$, $I^2 = 0\%$), Change in HBA1C level ($p = 0.87$, $I^2 = 0\%$), and eGFR change ($p = 0.89$, $I^2 = 0\%$).

However, pooled studies were heterogeneous in body weight change ($I^2 = 96\%$, $p < 0.01$). Regarding body weight change, leave-one-out sensitivity analysis resolved the heterogeneity by omitting James et al. 2023 ($I^2 = 0\%$) and omitting Aden et al. 2022 ($I^2 = 0\%$) (Figure S1).

3.5.3. Safety outcomes

The pooled analysis did not show any significant difference between the SGLT2i and placebo groups in terms of the incidence of any adverse events (RR = 1.00, 95% CI [0.93, 1.08], $p = 0.93$) (Figure 6(a)), adverse events leading to discontinuation (RR = 1.10, 95% CI [0.89, 1.36], $p = 0.37$) (Figure 6(b)), and serious adverse events (RR = 1.00, 95% CI [0.93, 1.07], $p = 0.91$) (Figure 6(c)).

The pooled studies were homogenous in any adverse events ($p = 0.27$, $I^2 = 23\%$), adverse events leading to discontinuation ($p = 0.35$, $I^2 = 4\%$), and serious adverse events ($p = 0.22$, $I^2 = 35\%$).

4. Discussion

4.1. Summary of the findings

This systematic review and meta-analysis demonstrated with a moderate level of certainty that SGLT2is are not effective for the secondary prevention of the following AMI-related outcomes: MACE, cardiac death, all-cause mortality, RE-MI, and stroke. However, there was a lower susceptibility to heart failure admissions following AMI in the SGLT2is group as compared to the placebo group. Additionally, AMI survivors who received SGLT2is displayed significantly higher LVEF but comparable NT-proBNP levels and changes in HbA1C, body weight, and eGFR compared to controls. The safety analysis revealed that SGLT2is are well-tolerated drugs in the setting of post-AMI.

4.2. No impact of SGLT2is on mortality and other acute morbidities

Early deaths after AMI occur mainly due to cardiogenic shock, anoxic brain damage, and malignant arrhythmia, whereas late deaths are primarily attributed to reinfarction and congestive heart failure [18]. In the recent DAPA-MI study, there were similar rates of the composite of time to cardiovascular death/hospitalization for HF in dapagliflozin and placebo groups [14].

In the context of AMI, SGLT2is therapy would not prevent acute events such as cardiogenic shock, stroke, malignant arrhythmia, and AMI recurrence. These outcomes depend on critical prognostic factors, notably revascularization quality and earliness, infarct severity, and patient comorbidities. Traditional secondary prevention drugs in AMI survivors, particularly aspirin, were shown to prevent acute cardiovascular events and mortality, clearly due to an anticipated anti-thrombotic action [19,20]. Nevertheless, it remains uncertain if the other post-discharge drugs, such as angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers and

Table 1. Summary characteristics of the included studies.

Study ID	References	Study design	No. of centers	Blinding status	Country	Total participants	Intervention	Control	Database recruitment duration	Follow up duration	Primary outcome
Adel et al. 2022	[11]	Multi-center, double-blinded, randomized controlled trial	Two	Double-blinded	Iran	106	Empagliflozin	Placebo	NA	6 months	Cardiovascular outcomes
Butler et al. 2024 (EMPACT-MI)	[12]	Double-blind, placebo-controlled, randomized controlled trial	480	Double Blinded	22 countries	6522	Empagliflozin	Placebo	21 months	17.9 months	The primary end point was a composite of hospitalization for heart failure or death from any cause as assessed in a time-to-first-event analysis.
Dayem et al. 2023 (DCAMI)	[13]	Single-center, double-blinded, randomized controlled trial	One	Double-blinded	Egypt	100	Dapagliflozin	No SGLT2i	NA	3 months	(1) a change in NT-proBNP levels from baseline to 12 weeks postanterior STEMI AND/OR (2) a change in left ventricular ejection fraction, end-diastolic volume, and/or left ventricular mass index.
James et al. 2023 (DAPA-MI)	[14]	Multi-center, double-blinded, randomized controlled trial.	39	Double-blinded	Sweden and UK	4017	Dapagliflozin	Placebo	NA	12 ± 1 months	Composite of death, hospitalization for heart failure, nonfatal MI, atrial fibrillation/flutter, type 2 diabetes mellitus.
Shimizu et al. 2020 (EMBODY)	[15]	Prospective, multicenter, randomized, double-blind, placebo-controlled trial		Double Blinded	Japan	96	Empagliflozin	Placebo.	12 Months	6 months	the change from baseline to 24 weeks in heart rate variability.
Verma et al.2019 (EMPA-HEART CardioLink-6)	[16]	Double-blind, placebo-controlled, randomized investigator-initiated clinical trial	Single	Double Blinded	Canada	90	Empagliflozin	Placebo	6 months	6 months	the change in LV Mi from baseline to 6 months
Lewinski et al. 2022(EMMY)	[17]	Multi-center, double-blinded, randomized controlled trial.	11	Double-blinded	Austria	476	Empagliflozin	Placebo	11 May 2017 to 3 May 2022	6 months	N-terminal pro-hormone of brain natriuretic peptide (NTproBNP) change over 26 weeks

STEMI: ST-Elevation myocardial infarction, LV Mi: Left ventricular mass index, MI: myocardial infarction.

Table 2. Characteristics of the included studies' participants.

Study ID	References	Number of patients in each group		Age (Years), Mean (SD)		Gender (Male), N. (%)		SBP, Mean (SD)		DBP, Mean (SD)		Hba1c (%)		Heart Rate, mean (SD)		e GFR (mL/min/ 1.73 m2), mean (sd)		Smoking, mean (SD)	
		SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control
Adel et al. 2022	[11]	45	48	55 (4.63)	57 (4.19)	27 (60.0)	29 (60.4)	132.1 (25.85)	128.75 (18.15)	80 (11.5)	77.9 (14.4)	7.8 (0.9)	7.65 (0.72)	NA	NA	72 (16.8)	73 (15.1)	NA	NA
Butler et al. 2024 (EMPACT-MI)	[12]	3260	3262	63.6 (11.0)	63.7 (10.8)	2448 (75.1)	2449 (75.1)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dayem et al. 2023 (DCAMI)	[13]	50	50	55.24 (13.2)	56.70 (11.5)	42 (84.0)	41 (82.0)	NA	NA	NA	NA	NA	NA	NA	NA	82.61 (14.31)	85.49 (13.49)	34 (68.0)	32 (64.0)
James et al. 2023 (DAPA-MI)	[14]	2019	1998	63.0 (11.06)	62.8 (10.64)	1631 (80.8)	1579 (79.0)	119.1 (16.23)	118.7 (16.62)	73.0 (10.83)	72.4 (10.59)	5.7 (0.58)	5.7 (0.51)	NA	NA	83.5 (17.12)	83.4 (16.91)	NA	NA
Shimizu et al. 2020 (EMBODY)	[15]	46	50	63.9 (10.4)	64.6 (11.6)	38 (82.6)	39 (78.0)	129.7 (11.9)	123.1 (15.7)	NA	NA	6.82 (1.00)	6.89 (0.92)	70.3 (11.0)	71.5 (11.4)	64.6 (15.0)	66.1 (15.7)	24 (52.2)	27 (54.0)
Verma et al.2019 (EMPA-HEART CardioLink-6)	[16]	49	48	63.3 (9.16)	64 (12.23)	44 (90)	46 (96)	130.3 (17.57)	135 (16.05)	75 (9.9)	76.33 (7.64)	7.9 (0.8)	8.0 (0.9)	NA	NA	87.67 (15.28)	88 (19.9)	20 (41)	22 (46)
Lewinski et al. 2022(EMMY)	[17]	237	239	57.7 (8.9)	58 (9.7)	195 (82)	197 (82)	124 (11.2)	124.7 (9.7)	79 (8.2)	79.3 (8.5)	5.7 (0.4)	5.7 (0.4)	NA	NA	90.3 (17.2)	90.3 (17.9)	171 (72)	170 (72)

Study ID	Baseline Medication, N. (%)								Comorbidities N. (%)							
	Antiplatelets, n (%)		Lipid-lowering therapy, n (%)		β-Blocker, n (%		ACEi/ARB/ARNi, n (%)		STEMI		NSTEMI		HTN		DM		Previous MI	
	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control	SGLT-2i	Control
Adel et al. 2022	NA	NA	NA	NA	NA	NA	NA	NA	27 (60)	23 (50)	2 (4.4)	4 (8.3)	26 (57.8)	32 (66.7)	NA	NA	NA	NA
Butler et al. 2024 (EMPACT-MI)	NA	NA	NA	NA	NA	NA	NA	NA	2444 (75.0)	2401 (73.6)	814 (25.0)	861 (26.4)	2262 (69.4)	2276 (69.8)	1035 (31.7)	1046 (32.1)	388 (11.9)	459 (14.1)
Dayem et al. 2023 (DCAMI)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	32 (64.0)	29 (58.0)	NA	NA	NA	NA
James et al. 2023 (DAPA-MI)	1970 (97.6)	1938 (97.0)	NA	NA	1805 (89.4)	1797 (89.9)	1868 (92.5)	1835 (91.8)	1465 (72.6)	1428 (71.5)	544 (26.9)	562 (28.1)	766 (37.9)	716 (35.8)	NA	NA	178 (8.8)	189 (9.5)
Shimizu et al. 2020 (EMBODY)	46 (100)	50 (100)	44 (95.7)	48 (96)	41 (89.1)	38 (76.0)	45 (97.8)	47 (94)	NA	NA	NA	NA	38 (82.6)	39 (78.0)	46 (100)	50 (100)	NA	NA
Verma et al.2019 (EMPA-HEART CardioLink-6)	40 (82)	15 (31)	47 (96)	46 (96)	38 (78)	39 (81)	40 (82)	41 (85)	NA	NA	NA	NA	2 (4)	4 (8)	44 (100)	46 (100)	19 (39)	21 (44)
Lewinski et al. 2022(EMMY)	237 (100)	239 (100)	237 (100)	239 (100)	223 (94)	234 (98)	NA	NA	NA	NA	NA	NA	92 (39)	107 (45)	30 (13)	33 (14)	14 (5.9)	9 (3.8)

SBP Systolic Blood Pressure; DBP Diastolic Blood Pressure.
eGFR Estimated glomerular Filtration rate; HTN Hypertension; DM Diabetes Mellitus; MI Myocardial Infarction.
ACEi Angiotensin converting enzyme inhibitor; ARN Aldosterone receptor blocker; ARNI Angiotensin Receptor-Neprilysin Inhibitor.

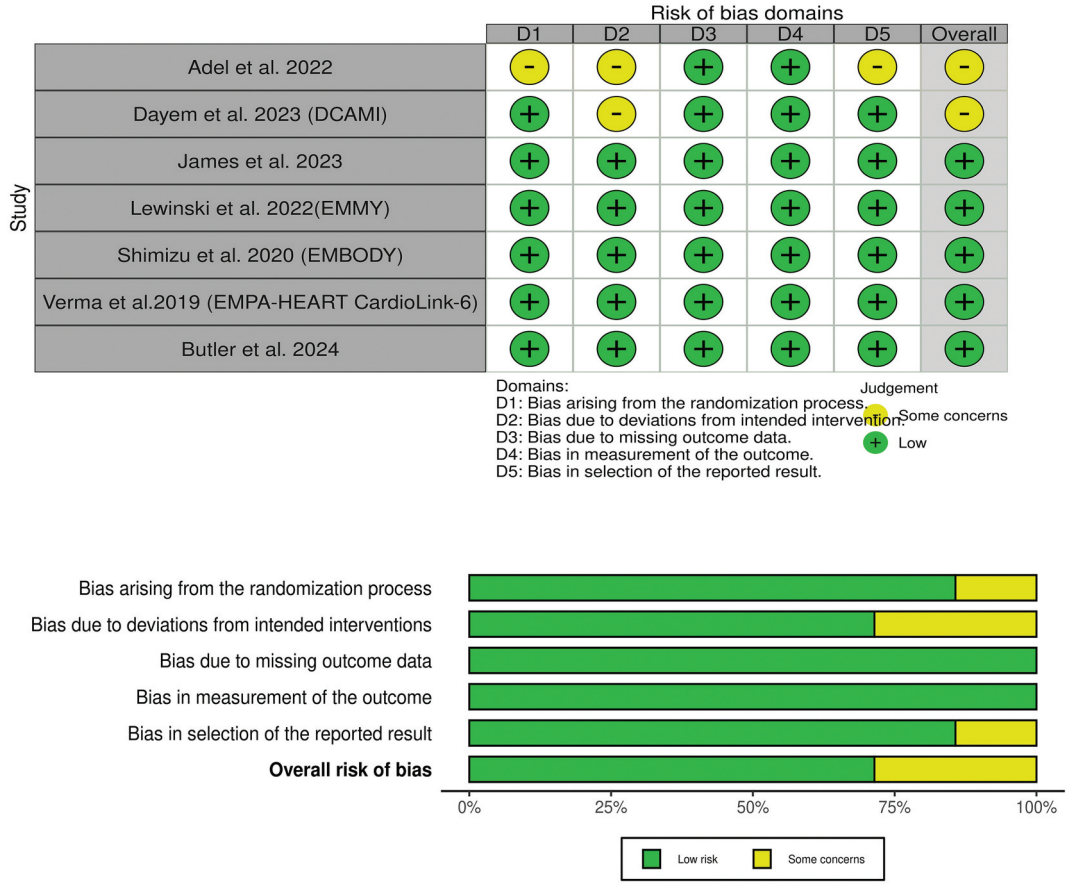


Figure 2. Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = green, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review.

beta-blockers, have beneficial prognostic effects independent of heart failure. Especially, since the emergent recent data show no impact of these drugs in decreasing mortality among post-AMI patients without heart failure [21–23], perhaps this can be explained by the fact that the benefit of these drugs on survival after AMI is highly driven by their anti-remodeling and LV function promoting effects. Likewise, it appears that the cardio-protective role of SGLT2is following AMI manifests essentially by preventing heart failure development and preserving LV function.

In AMI survivors, deaths due to heart failure occur after a median time of 2 years in contrast to the other abovementioned etiologies, which occur before a median time of 6 months [19]. Since the involved studies in our analysis did not reach 2 years of follow-up (except James et al., who achieved 29.0 months of maximum follow-up, whereas the remaining trials did not exceed 6 months), it is most likely that the deaths occurred mainly from other causes than post-AMI heart failure. Thus, the benefit of SGLT2is in decreasing mortality from heart failure – which seems to be the primary potential way SGLT2is can affect survival– could not be evaluated. We hypothesize that SGLT2is may not change short- and medium-term mortality but may reduce long-term mortality (≥2 years post-AMI) through their opposing action to the progressive development of post-ischemic heart failure and myocardial remodeling. Based on this, the prognostic impact of SGLT2is in post-AMI patients could be specifically dependent on heart failure/LV dysfunction outcome. Hence, this is consistent with the accumulated evidence supporting the efficacy of SGLT2is in reducing the risk of cardiovascular mortality in heart failure patients regardless of AMI status [24].

4.3. SGLT2is decrease heart failure events and improve LVEF

SGLT2 is expressed in human cardiomyocytes of diabetic and non-diabetic patients and is likely involved in metabolic pathways such as the regulation of glycolysis and mitochondrial oxidation [25]. Moreover, following AMI, the expression of SGLT2 in infarct tissues increases significantly, thus promoting post-ischemic cardiac fibrogenesis. Remarkably, inhibition of SGLT2 in cardiac fibroblasts led to anti-fibrotic effects via downregulation of collagen I and collagen III, which was associated with improved cardiac function in AMI rat models [26]. In addition, experimental evidence has demonstrated that SGLT2is are linked to lower infarct area expansion [27]; the latter is a key mechanism of myocardium hypertrophy in ischemic heart [28]. Another possible anti-heart failure mechanism of SGLT2is is the inhibition of immune cell infiltration (e.g., NLRP3 inflammasome) in the myocardium [29], which is an important promoter of fibrosis and remodeling

Table 3. GRADE evidence profile.

Certainty assessment						
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence
MACE						
4210 (3 RCTs)	not serious	not serious	not serious	very serious[a,b]	none	⨁⨁◯◯ Low
Cardiac Death						
11301 (6 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate
All-Cause Mortality						
11308 (6 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High
Heart Failure						
7191 (4 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate
Recurrent MI						
4210 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low
Stroke						
4210 (3 RCTs)	not serious	not serious	not serious	very serious[b]	none	⨁⨁◯◯ Low
LVEF						
759 (4 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High
NT-proBNB						
293 (3 RCTs)	serious[c]	not serious	not serious	very serious[d]	none	⨁◯◯◯ Very low
HbA1C						
286 (3 RCTs)	serious[e]	not serious	not serious	very serious[d]	none	⨁◯◯◯ Very low
Body Weight						
4207 (3 RCTs)	very serious[f]	very serious[g]	not serious	very serious[a]	none	⨁◯◯◯ Very low
eGFR						
286 (3 RCTs)	serious[h]	not serious	not serious	very serious[a]	none	⨁◯◯◯ Very low
Any Adverse Event						
6656 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High
Adverse Events Leading to Drug Discontinuation						
10577 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate
Any Serious Adverse Event						
10523 (3 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ High

Explanations.
[a]A wide confidence interval that does not exclude the risk of appreciable harm/benefit.
[b]A wide confidence interval that does not exclude the risk of appreciable harm/benefit, with a low number of events (<300 events).
[c]Dayem et al. showed overall some concerns of bias, with 35% of the pooled analysis weight.
[d]A wide confidence interval that does not exclude the risk of appreciable harm/benefit, with a low number of participants (<400 participants).
[e]Adel et al. showed overall some concerns of bias, with 35% of the pooled analysis weight.
[f]Adel et al. showed overall some concerns of bias, with 45% of the pooled analysis weight.
[g]I2 > 75%.
[h]Adel et al. showed an overall some concerns of bias, with 32% of the pooled analysis weight.

in heart failure pathogenesis [30]. Clinical data further show that SGLT2 reverses cardiac remodeling while improving LV systolic function. These advantages were more pronounced in heart failure with reduced EF (HFrEF) patients than those with preserved EF (HFpEF) [31]. Paradoxically, we found no difference in NT-proBNP levels between SGLT2is and control groups. Given the high sensibility and specificity of NT-proBNP levels as a biomarker for LV dysfunction, the reason for this discordance is ambiguous.

4.4. Implications for future research

The main focus of clinical interventions in AMI survivors is the reduction of disease morbimortality and recurrences, essentially through risk reduction therapy. Hence, any drug that is effective in the secondary prevention of major adverse outcomes after AMI is warranted on condition that its benefits overcome its risks. SGLT2is, although they do not appear to have substantial clinical advantages in preventing post-AMI cardiac and non-cardiac deaths and major acute events (MACE, RE-MI, and stroke), their benefit in decreasing heart failure risk is significant and worthy of more investigation. Notably, heart failure is a critical, common morbidity after AMI as it leads to frequent hospitalizations and is a factor of poor prognosis [32,33]. Therefore, SGLT2is may need further evaluation as an adjuvant or alternative option to the currently recommended post-discharge pharmacological therapies, particularly ACE inhibitors, angiotensin receptor blockers, and beta-blockers [34].

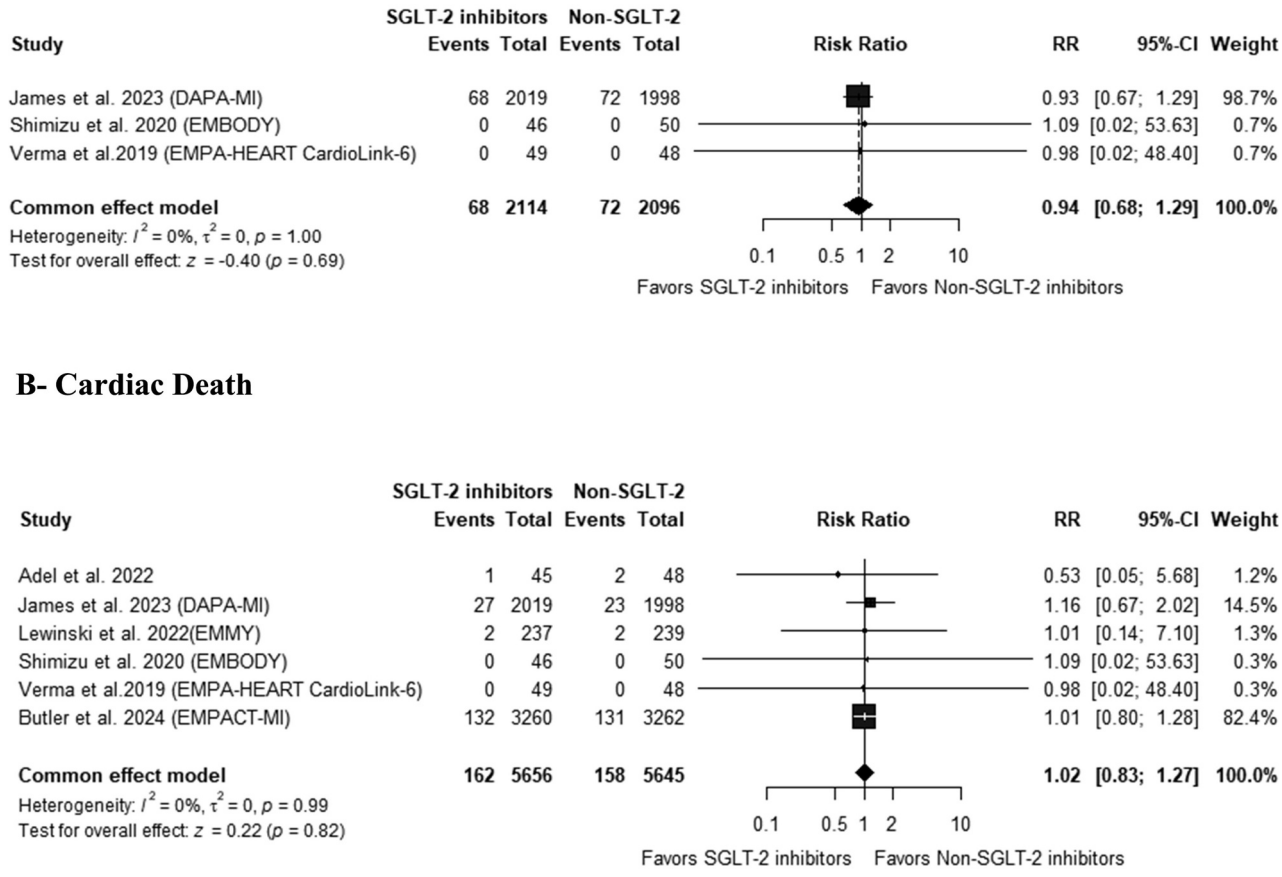


Figure 3. Forest plot of the primary outcomes, RR: risk ratio, CI: confidence interval.

Furthermore, it is still not sure if the beneficial cardioprotective effects of SGLT2is are more pronounced in AMI survivors with T2DM than those without T2DM. This may also be explored by future research. In DAPA-MI (a main study in our analysis), where the use of SGLT2is was found to ameliorate cardiometabolic outcomes [14], it is possible that this effect was driven by the high incidence of AMI-induced LV dysfunction (LV ejection fraction <50% in 73.2% of the participants) at index hospitalization. Therefore, if SGLT2is are considered for routine use after AMI, it is important to note that the benefit of this class may be restricted – or at least more expected – in patients who develop HF or LV dysfunction secondary to the ischemic event. Whereas, the rationale of SGLT2is therapy for secondary prevention after AMI, regardless of HF status, appears less evident.

4.5. Strengths and limitations

This systematic review and meta-analysis included seven studies with a total of 11,407 patients, the largest meta-analysis to our knowledge, and this is the first ever meta-analysis with GRADE-assessed outcomes. This meta-analysis highlights the effectiveness of SGLT2 in post-MI patients, providing robust evidence for their cardioprotective and renal benefits. By synthesizing data, it validates key mechanisms like anti-inflammatory and anti-fibrotic effects and clarifies their efficacy in diabetic and non-diabetic populations. This work addresses critical gaps, strengthening the case for integrating SGLT2 inhibitors into post-MI management protocols. It has the potential to influence clinical guidelines and routine practice while paving the way for further research on therapy timing and long-term outcomes. A similar work was carried out by Idowu et al. who included five RCTs to evaluate the outcomes of combining SGLT2is with conventional guideline-directed post-AMI treatments [35]. The primary outcomes were heart failure hospitalization and all-cause mortality, while secondary outcomes were cardiovascular-related mortality, MACE, and serious adverse effects. Similar to our results, the authors found that patients who received additional treatment with SGLT2is had lesser odds of heart failure hospitalization but comparable odds of all-cause mortality, cardiac-related death, or MACE. However, the study did not test the impact of SGLT2is on LVEF after AMI. Moreover, no metabolic outcome/biomarker was involved in the analysis. More recently, Ahmed et al. [36] reviewed the available evidence on SGLT2is for AMI, showing consistent findings with our meta-analysis and those of Idowu et al. However, their data were also incomplete, containing only records of five RCTs.

On the other hand, in our study we used extensive data from seven RCTs (n = 11,407), some being multicenter, double-blind phase 3 trials. ROB-2 analysis revealed a low risk of bias

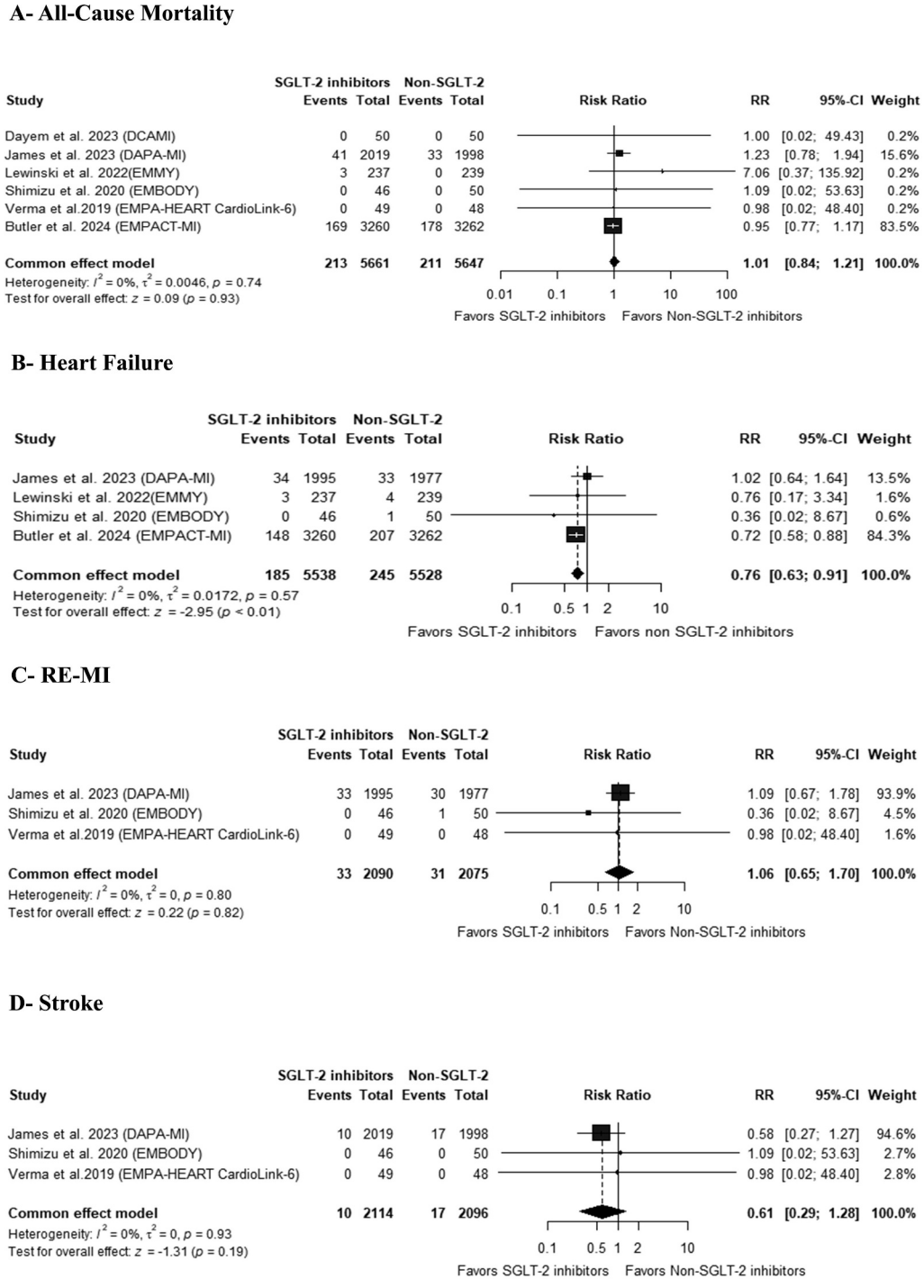


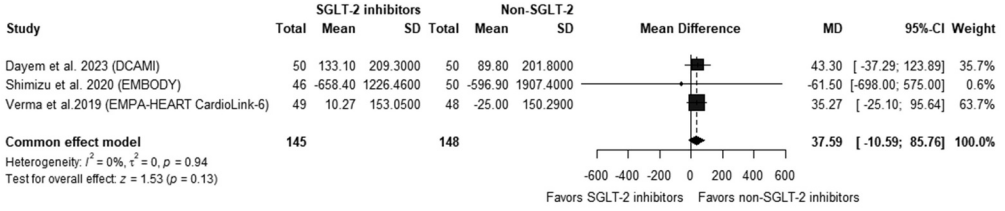
Figure 4. Forest plot of the clinical outcomes, RR: risk ratio, CI: confidence interval.

in the majority of studies. After assessing multiple key morbi-mortality outcomes, including LVEF, we found clinically relevant findings that could lead to important therapeutic implications for secondary prevention of heart failure following AMI. Heterogeneity was overall low across the study outcomes, except for body weight change.

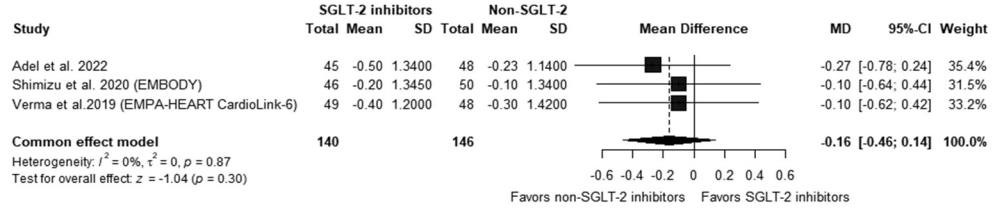
Nevertheless, we acknowledge a few limitations that should be considered when interpreting our results. First, there are a relatively small number of included studies. Second, including RCTs with a small sample size substantially reduces the quality of the extracted data. Third, there are some concerns about the randomization process, deviations from the intervention outcomes (such as in the DAPA-MI trial), or the selection of the reported results. Fourth, the short follow-up period does not exceed 6 months except for the DAPA-MI and EMPACT-MI. As explained in the discussion, this may have impeded full assessment of the SGLT2is benefit, which appears to be tightly dependent on heart failure outcome, a complication with long-term consequences, requiring prolonged investigation. Another limitation of our meta-

A- LVEF

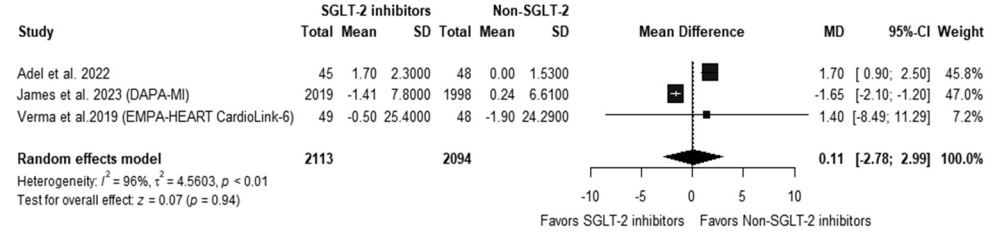
B- NT-proBNP level



C- HBA1C level



D- Body Weight



E- eGFR

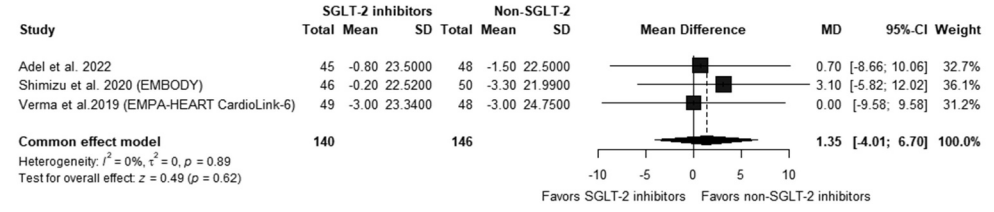


Figure 5. Forest plot of the other parameters, MD: mean difference, RR: risk ratio, CI: confidence interval.

analysis is that larger studies, like EMPACT-MI and DAPA-MI, may have a stronger impact on the results due to their much larger patient populations compared to the smaller studies included.

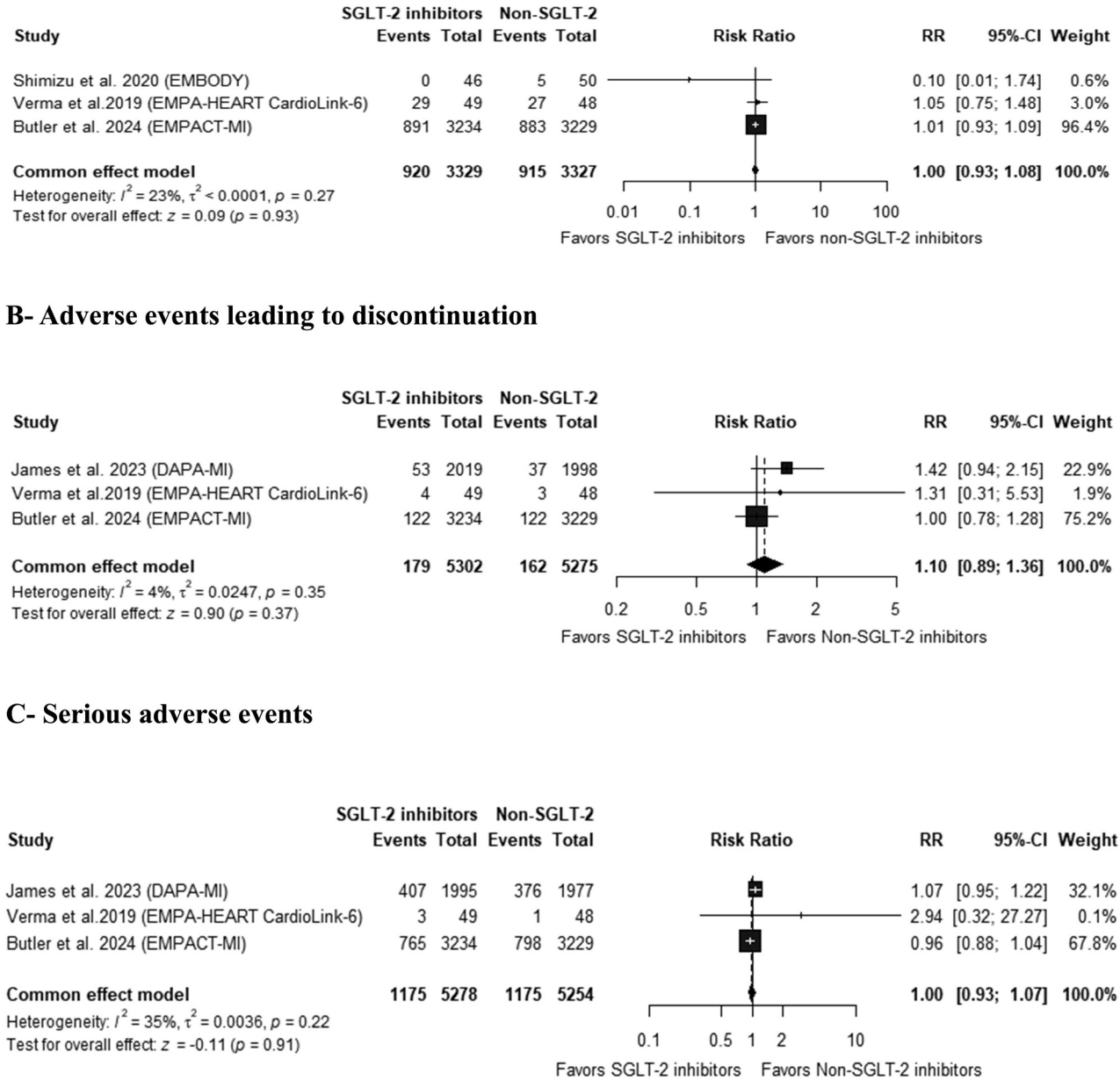


Figure 6. Forest plot of the safety outcomes, RR: risk ratio, CI: confidence interval.

5. Conclusion

Available evidence from clinical trials indicates that the use of SGLT2is in post-AMI patients does not affect the incidence of mortality and major acute outcomes. In contrast, SGLT2is are superior to placebo in reducing heart failure and LV dysfunction, which is consistent with the findings of previous studies on patients without AMI. This suggests that the central benefit of SGLT2i as post-AMI adjuvant treatment is to preserve LV function and prevent heart failure admissions, which may have positive repercussions on long-term cardiovascular morbid mortality. Nevertheless, because the RCTs conducted so far have been limited by a short follow-up period, it is unclear if SGLT2is can prolong survival after AMI. Therefore, there is a need for more RCTs to assess the impact of SGLT2is on AMI survivors in the short and long term.

Acknowledgments

The abstract was presented at the European Society of Cardiology (ESC Congress) 2024 London.

Author contributions

UK conceived the idea. UK designed the research workflow. UK searched the databases. AMA, MMA, and ME screened the retrieved records, extracted relevant data, assessed the quality of evidence, and BA resolved the conflicts. AMA performed the analysis. UK, YK, and AMT wrote the final

manuscript. MT and BA supervised the project. All authors have read and agreed to the final version of the manuscript.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Funding

This paper was not funded.

ORCID

Mustafa Turkmani http://orcid.org/0009-0001-4261-0638

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Thygesen K, Alpert J, Jaffe A, et al. Correction: fourth universal definition of myocardial infarction. Circulation. 2018;138(20):e652–e652. doi: 10.1161/CIR.0000000000000617
2. Mahmoud AN, Taduru SS, Mentias A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: a population-based analysis. JACC: Cardiovasc Interventions. 2018;11(1):80–90. doi: 10.1016/j.jcin.2017.08.016
3. Solini A, Giannini L, Seghieri M, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol. 2017;16(1):1–9. doi: 10.1186/s12933-017-0621-8
4. He Z, Lam K, Zhao W, et al. SGLT-2 inhibitors and euglycemic diabetic ketoacidosis/diabetic ketoacidosis in FAERS: a pharmacovigilance assessment. Acta Diabetol. 2023;60(3):401–411. doi: 10.1007/s00592-022-02015-6
5. Furtado RH, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction: subanalysis from the DECLARE-TIMI 58 trial. Circulation. 2019;139(22):2516–2527. doi: 10.1161/CIRCULATIONAHA.119.039996
6. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi: 10.1136/bmj.n71
7. Higgins JPT, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. Version 6. Cochrane; 2019. doi: 10.1002/9781119536604
8. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898
9. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008;336(7651):995–998. doi: 10.1136/bmj.39490.551019.BE
10. Guyatt G-B. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2009;9:8. doi: 10.1136/bmj.39489.470347.AD
11. Adel SMH, Jorfi F, Mombeini H, et al. Effect of a low dose of empagliflozin on short-term outcomes in type 2 diabetics with acute coronary syndrome after percutaneous coronary intervention. Saudi Med J. 2022;43(5):458. doi: 10.15537/smj.2022.43.5.20220018

•• **Adding low-dose empagliflozin to standard care post-PCI in diabetic ACS patients showed no significant reduction in adverse cardiovascular outcomes over 6 months.**

12. Butler J, Filippatos G, Jamal Siddiqi T, et al. Empagliflozin, health status, and quality of life in patients with heart failure and preserved ejection fraction: the EMPEROR-Preserved trial. Circulation. 2022;145(3):184–193. doi: 10.1161/CIRCULATIONAHA.121.057812

•• **In heart failure patients with preserved ejection fraction, empagliflozin reduced major heart failure risks across baseline KCCQ scores and improved health-related quality of life, with benefits evident early and sustained for at least one year.**

13. Dayem KA, Younis O, Zarif B, et al. Impact of dapagliflozin on cardiac function following anterior myocardial infarction in non-diabetic patients–dacami (a randomized controlled clinical trial). Int J Cardiol. 2023;379:9–14. doi: 10.1016/j.ijcard.2023.03.002

•• **Dapagliflozin may help prevent left ventricular dysfunction and preserve cardiac function following AMI.**

14. James S, Erlinge D, Storey RF, et al. Dapagliflozin in myocardial infarction without diabetes or heart failure. Eur Heart J - Cardiovasc Pharmacother. 2024;3(2):91–92. doi: 10.1093/ehjcvp/pvad096

•• **In patients with acute MI, one year of dapagliflozin treatment significantly improved cardiometabolic outcomes but had no effect on cardiovascular death or heart failure hospitalization.**

15. Shimizu W, Kubota Y, Hoshika Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. Cardiovasc Diabetol. 2020;19(1):1–12. doi: 10.1186/s12933-020-01127-z

•• **This is the first RCT to examine the effects of empagliflozin on cardiac sympathetic and parasympathetic activity in patients with T2DM and AMI.**

16. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. Circulation. 2019;140(21):1693–1702. doi: 10.1161/CIRCULATIONAHA.119.042375

•• **In patients with type 2 diabetes and coronary artery disease, 6 months of empagliflozin treatment significantly reduced LV mass indexed to body surface area but had no effect on cardiovascular death or heart failure hospitalization.**

17. von Lewinski D, Kolesnik E, Tripolt NJ, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J. 2022;43(41):4421–4432. doi: 10.1093/eurheartj/ehac494

•• **In patients with a recent myocardial infarction, empagliflozin was associated with a significantly greater reduction in NT-proBNP over 4 months, along with notable improvements in echocardiographic functional and structural parameters.**

18. Pedersen F, Butrymovich V, Kelbæk H, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. J Am Coll Cardiol. 2014;64(20):2101–2108. doi: 10.1016/j.jacc.2014.08.037
19. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849–1860. doi: 10.1016/S0140-6736(09)60503-1
20. Russo RG, Wikler D, Rahimi K, et al. Self-administration of aspirin after chest pain for the prevention of premature cardiovascular mortality in the United States: a population-based analysis. J Am Heart Assoc. 2024;13(11):e032778. doi: 10.1161/JAHA.123.032778
21. Chen R, Liu C, Zhou P, et al. Prognostic impacts of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in acute coronary syndrome patients without heart failure. Front Pharmacol. 2022;13:663811. doi: 10.3389/fphar.2022.663811
22. Dondo TB, Hall M, West RM, et al. β-blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol. 2017;69(22):2710–2720. doi: 10.1016/j.jacc.2017.03.578
23. Yndigegn T, Lindahl B, Mars K, et al. Beta-blockers after myocardial infarction and preserved ejection fraction. N Engl J Med. 2024;390(15):1372–1381. doi: 10.1056/NEJMoa2401479
24. Cardoso R, Graffunder FP, Ternes CM, et al. SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients

with heart failure: a systematic review and meta-analysis. EClinicalMedicine. 2021;36:100933. doi: 10.1016/j.eclinm.2021.100933
25. Marfella R, Scisciola L, D'Onofrio N, et al. Sodium-glucose cotransporter-2 (SGLT2) expression in diabetic and non-diabetic failing human cardiomyocytes. Pharmacol Res. 2022;184:106448. doi: 10.1016/j.phrs.2022.106448
26. Li G, Zhao C, Fang SJE, et al. SGLT2 promotes cardiac fibrosis following myocardial infarction and is regulated by miR-141. Exp Ther Med. 2021;22(1):1–9. doi: 10.3892/etm.2021.10147
27. Andreadou I, Bell RM, Bøtker HE, et al. SGLT2 inhibitors reduce infarct size in reperfused ischemic heart and improve cardiac function during ischemic episodes in preclinical models. Biochim Et Biophys Acta (BBA) - Mol Basis Disease. 2020;1866(7):165770. doi: 10.1016/j.bbadis.2020.165770
28. French BA, Kramer CMJDDTDM. Mechanisms of postinfarct left ventricular remodeling. Drug Discov Today: Disease Mechanisms. 2007;4(3):185–196. doi: 10.1016/j.ddmec.2007.12.006
29. Lopaschuk GD, Verma SJBt TS. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. JACC: Basic Transl Sci. 2020;5(6):632–644. doi: 10.1016/j.jacbts.2020.02.004
30. Zheng Y, Xu L, Dong N, et al. NLRP3 inflammasome: the rising star in cardiovascular diseases. Front Cardiovasc Med. 2022;9:927061. doi: 10.3389/fcvm.2022.927061
31. Carluccio E, Biagioli P, Reboldi G, et al. Left ventricular remodeling response to SGLT2 inhibitors in heart failure: an updated meta-analysis of randomized controlled studies. Cardiovasc Diabetol. 2023;22(1):235. doi: 10.1186/s12933-023-01970-w
32. Jenča D, Melenovský V, Stehlik J, et al. Heart failure after myocardial infarction: incidence and predictors. ESC Heart Fail. 2021;8(1):222–237. doi: 10.1002/ehf2.13144
33. Sulo G, Igland J, Vollset SE, et al. Heart failure complicating acute myocardial infarction; burden and timing of occurrence: a nation-wide analysis including 86 771 patients from the cardiovascular disease in Norway (CVDNOR) Project. Project. 2016;5(1):e002667. doi: 10.1161/JAHA.115.002667
34. Bahit MC, Kochar A, Granger C. Post-myocardial infarction heart failure. JACC: Heart Fail. 2018;6(3):179–186. doi: 10.1016/j.jchf.2017.09.015
35. Idowu A, Adebolu O, Wattanachayakul P, et al. Cardiovascular outcomes of sodium-glucose co-transporter 2 inhibitors use after myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Curr Probl Cardiol. 2024;49(8):102648. doi: 10.1016/j.cpcardiol.2024.102648
36. Ahmed M, Jain H, Javaid H, et al. Efficacy of sodium-glucose cotransporter-2 inhibitors in patients with acute myocardial infarction: a meta-analysis of randomised controlled trials. Endocrinol, Diabetes Metab. 2024;7(5):e514. doi: 10.1002/edm2.514