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ORIGINAL ARTICLE
Heart failure/cardiomyopathy

SGLT2 inhibitors and cardiovascular outcomes in patients with acute myocardial infarction: a retrospective cohort analysis

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Aims Sodium-glucose cotransporter 2 inhibitors (SGLT2-Is) improve heart failure (HF) outcomes but their effects on acute myocardial infarction (AMI) remain poorly characterized. This study aimed to evaluate the 1-year cardiovascular outcomes of SGLT2-Is among patients with AMI.

Methods and results We conducted an observational, retrospective cohort study using TriNetX data, including patients aged ≥18 with AMI identified via ICD-10 codes regardless of left ventricular ejection fraction (LVEF), categorized by SGLT2-Is use. Propensity score matching (PSM) was performed to balance baseline demographics, comorbidities, and medication use. Adjusted odds ratios (aORs) were estimated for the primary outcome (recurrent AMI) and the secondary outcomes (acute HF hospitalizations, stroke, all-cause hospitalizations, all-cause mortality, new-onset atrial fibrillation, and cardiac arrest). After PSM, 89 554 patients were analysed (44 777 SGLT2-Is users; 44 777 non-users). The mean age was ∼68 years in both cohorts with a similarly high burden of cardiovascular comorbidities. Mean follow-up duration was 290.854 days for SGLT2-Is users and 284.465 days for non-users. SGLT2-Is use was linked to lower rates of recurrent AMI [aOR: 0.459; 95% confidence interval (CI): 0.367–0.551], all-cause hospitalizations (aOR: 0.782; 95% CI: 0.762–0.803), all-cause mortality (aOR: 0.640; 95% CI: 0.612–0.670), and cardiac arrest (aOR: 0.834; 95% CI: 0.773–0.900). No differences were observed in acute HF hospitalizations, new-onset atrial fibrillation, or stroke.

Conclusion SGLT2-Is are associated with improved cardiovascular outcomes in patients with AMI, including reductions in recurrent AMI, all-cause hospitalizations and mortality, and cardiac arrest. These findings emphasize the need for prospective clinical trials involving patients with AMI and other cardiovascular comorbidities, regardless of LVEF, to confirm these results.

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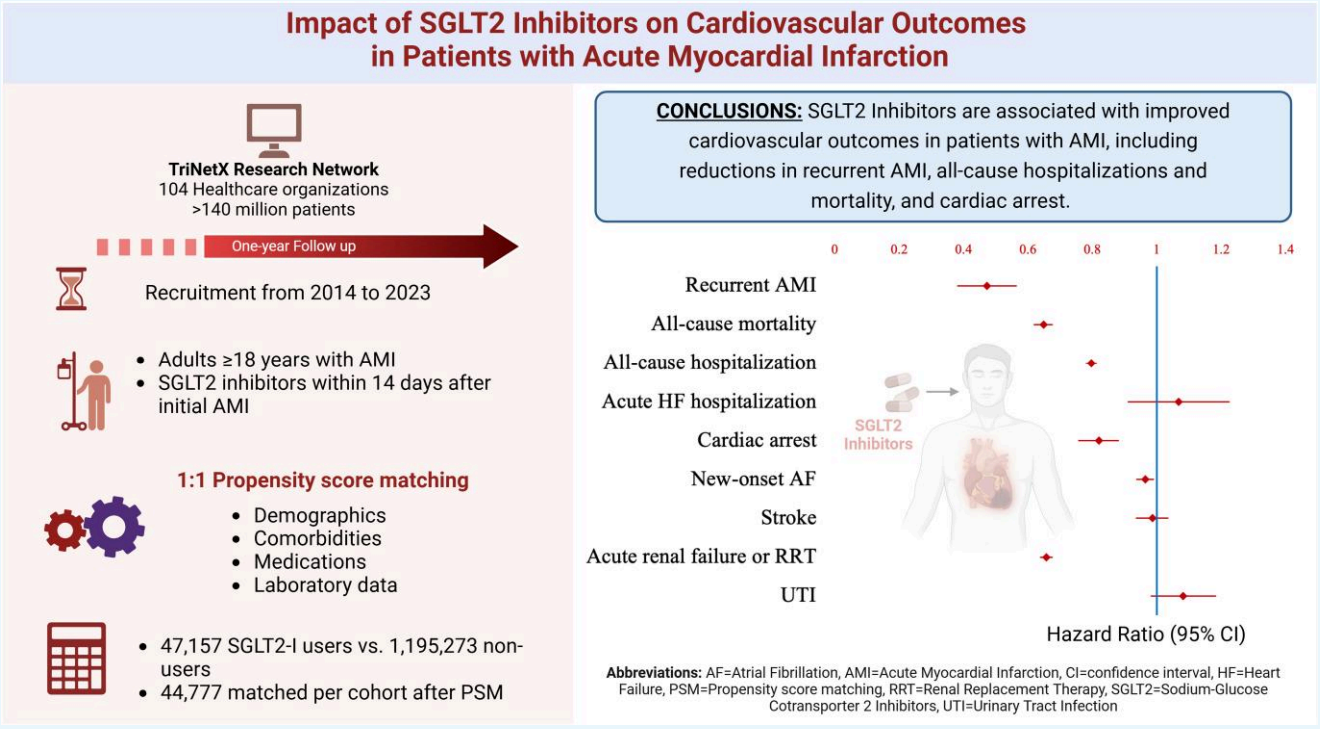
Graphical abstract



Keywords Ischaemic heart disease • SGLT2 • Diabetes • Population-level

Introduction

Acute myocardial infarction (AMI) remains the leading cause of morbidity and mortality worldwide.[1,2] Despite advancements in reperfusion strategies and preventive measures, many still experience adverse cardiovascular events, including recurrent AMI, heart failure (HF), and sudden cardiac death.[1,3] For example, HF following AMI is a strong predictor of death; therefore, it has important prognostic implications in those with coronary artery disease. Sodium-glucose cotransporter 2 inhibitors (SGLT2-Is), initially developed for glycaemic control in type 2 diabetes mellitus (T2DM), have shown substantial cardiovascular benefits, including reductions in major adverse cardiovascular events (MACE), HF hospitalizations, and all-cause mortality in multiple landmark trials in patients with HF with both preserved and reduced ejection fraction and T2DM.[4–8] These benefits are likely attributed to multiple factors including improvements in cardiac metabolism, reduced oxidative stress, attenuation of inflammation, and favourable effects on haemodynamics.[9–11]

While SGLT2-Is have been incorporated into guideline-directed medical therapy for HF in 2022, their impact on outcomes in patients with AMI remains poorly defined.[5] Recent studies have begun to investigate the impact of SGLT2-Is on those with known coronary artery disease. For example, a subgroup analysis of the DECLARE-TIMI 58 trial found that patients with diabetes that had a prior AMI and are on dapagliflozin therapy reduced the risk of MACE, cardiovascular death, and hospitalizations.[12] Moreover, the EMPACT-MI trial, a placebo-controlled trial, investigated the impact of empagliflozin after an initial AMI hospitalization.[13] The cohort on SGLT2-Is, compared with the cohort without SGLT2-I therapy, had a reduced rate of acute HF hospitalizations but no difference in all-cause mortality. However, to date, there remains no large-scale, real-world cohort studies that investigate the impact of SGLT-2 on outcomes following AMI. Therefore, we aimed to investigate the impact of SGLT2-Is on cardiovascular outcomes in patients with AMI.

Methods

Our study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies. Informed consent and ethical board approval were not required, as the analysis relied on de-identified data in an aggregated format from a publicly available federated research database. No interaction or intervention with the human participants was done for this study, which is a secondary analysis of existing data. In accordance with the HIPAA Privacy Rule, all de-identification measures were appropriately implemented.

We queried the TriNetX Analytics Research Network, which is a global federated health research network providing access to electronic medical records, including diagnoses, procedures, medications, laboratory values, and genomic information, for more than 140 000 000 patients at the time of our search, across 104 healthcare organizations (HCOs). This study was completed as a retrospective cohort analysis using data, including patients aged ≥18 years with AMI identified through the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM), diagnosed between 1 January 2014 and 31 December 2023. Patients were stratified into cohorts based on SGLT2-I initiation. All patients that were not on SGLT-Is prior to the initial AMI event and were then started on SGLT2-Is within the first 14 days after initial AMI event were included in the SGLT2-I cohort; whereas all patients that

were not on SGLT2-Is both before or after the initial AMI event were included in the non-SGLT2-I cohort. Both cohorts were followed for up to 1-year post-initial AMI event to evaluate for outcomes. Propensity score matching (PSM) was performed to balance baseline demographics (e.g. sex, age, race, and ethnicity), comorbidities [e.g. hypertension, diabetes, chronic kidney disease, HF, overweight/obesity, stroke, dyslipidaemia, sleep apnoea, nicotine use, alcohol use, social determinants of health (ICD10-Z55-65)], medication use (e.g. HF therapies, dyslipidaemia medications, anti-hypertensive therapies, anticoagulation, diabetic medications, and anti-platelet agents), and other key clinical factors (e.g. left ventricular ejection fraction, body mass index, haemoglobin A1c, creatinine, and NT-proBNP).

Primary outcome of this study was recurrent AMI. Secondary outcomes included acute HF hospitalizations, stroke, all-cause hospitalizations, cardiac arrest, new-onset atrial fibrillation (AF), and all-cause mortality. Safety outcomes included acute renal failure or need for renal replacement therapy and urinary tract infections. Outcome definitions are described in *Supplementary Materials*. All outcomes were analysed starting 2 weeks after the first occurrence of the index AMI and continuing until 1 year.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD) and compared using independent-sample *t*-test, whereas categorical variables were expressed as frequencies (*n*, %) and analysed using χ^2 test. A 1:1 PSM was performed using a built-in algorithm that applies the greedy nearest-neighbour method with a calliper of 0.1 pooled SDs to control for baseline differences between patient cohorts. A standardized mean difference of <0.1 between cohorts for all characteristics was considered well-matched. Adjusted odds ratios (aORs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for primary and secondary outcomes. Survival analysis was performed by plotting Kaplan–Meier curves and conducting log-rank tests to compare the two cohorts, with statistical significance defined as a two-sided *P*-value of <0.05. We used the the TriNetX platform and R for computational analysis.[14]

Results

The patient selection process started with >140 000 000 individuals in the TrinetX Research Network, from which 1 242 430 patients with AMI were identified (*Figure 1*). Prior to PSM, the analysis included 47 157 patients that were initiated on SGLT2-Is within 14 days post-AMI and 1 195 273 patients with AMI and without initiation of SGLT2-Is. Patients on SGLT2-Is had a higher prevalence of cardiovascular comorbidities, including hypertension, dyslipidaemia, overweight/obesity, cerebral infarction, chronic kidney disease, HF, and DM, and were more likely to be on cardiovascular medications at baseline. After PSM, both cohorts included 44 777 patients with minimized baseline differences (standardized differences <0.1) (*Table 1* and *Figure 2*). The mean follow-up duration after matching was 290.854 (SD 127.208) days for SGLT2-I users and 284.465 (SD 133.573) days for non-users. The mean age was ~68 years in both cohorts.

The primary outcome (recurrent AMI) within 1 year of follow-up after the first occurrence of the index AMI was significantly lower in patients on SGLT2-Is (29.1%, *n* = 13 040) compared with those not on

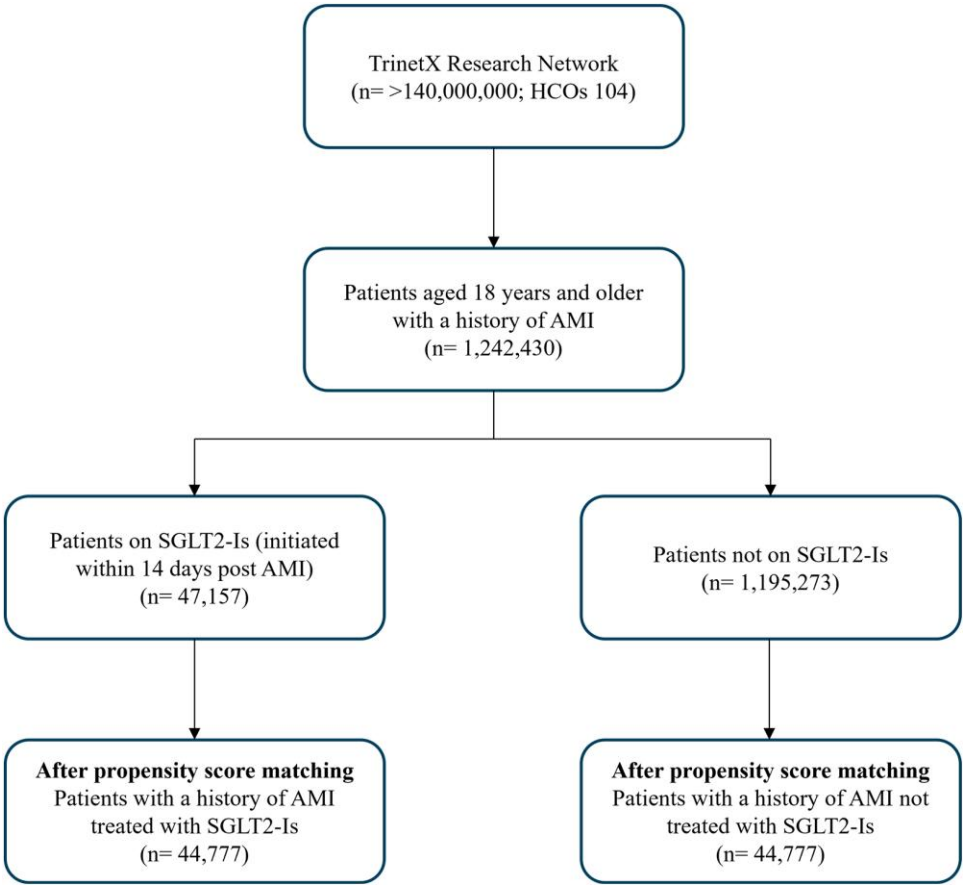


Figure 1 Patient selection process. AMI, acute myocardial infarction; HCOs, health care organizations; SGLT2-I, sodium-glucose cotransporter 2 inhibitor.

Table 1 Baseline characteristics of the patient cohort before and after propensity score matching

Characteristic	Before PSM—On SGLT2-Is ($n = 47\,157$)	Before PSM—Not on SGLT2-Is ($n = 1\,195\,273$)	Before PSM—Standardized Difference	After PSM—On SGLT2-Is ($n = 44\,777$)	After PSM—Not on SGLT2-Is ($n = 44\,777$)	After PSM—Standardized Difference
Demographics						
Age, years	67.9 ± 12.2	72.0 ± 13.9	0.312	68.5 ± 11.9	68.8 ± 13.3	0.024
Female	14 521 (30.8%)	478 670 (40.0%)	0.194	14 078 (31.4%)	14 211 (31.7%)	0.006
Hispanic or Latino	2859 (6.1%)	58 236 (4.9%)	0.052	2674 (6.0%)	2659 (5.9%)	0.001
White	27 286 (57.9%)	783 216 (65.5%)	0.158	26 201 (58.5%)	25 878 (57.8%)	0.015
Black or African American	8064 (17.1%)	170 362 (14.3%)	0.078	7600 (17.0%)	7655 (17.1%)	0.003
Comorbidities						
Hypertension	37 887 (80.3%)	609 039 (51.0%)	0.651	35 966 (80.3%)	35 677 (79.7%)	0.016
Dyslipidaemia	34 501 (73.2%)	490 192 (41.0%)	0.687	32 641 (72.9%)	32 212 (71.9%)	0.021
Atrial fibrillation and flutter	13 201 (28.0%)	163 490 (13.7%)	0.358	12 561 (28.1%)	12 673 (28.3%)	0.006
Cerebral infarction	5566 (11.8%)	80 037 (6.7%)	0.177	5311 (11.9%)	5362 (12.0%)	0.004
Chronic kidney disease	14 846 (31.5%)	209 273 (17.5%)	0.329	14 360 (32.1%)	14 743 (32.9%)	0.018
Heart failure	29 433 (62.4%)	209 822 (17.6%)	1.030	27 204 (60.8%)	27 815 (62.1%)	0.028
Diabetes mellitus	30 663 (65.0%)	296 101 (24.8%)	0.885	28 610 (63.9%)	29 407 (65.7%)	0.037
Overweight and obesity	17 855 (37.9%)	188 025 (15.7%)	0.516	16 643 (37.2%)	16 934 (37.8%)	0.013
Disorders of lipoprotein metabolism	34 501 (73.2%)	490 192 (41.0%)	0.687	32 641 (72.9%)	32 212 (71.9%)	0.021
Persons with socioeconomic hazards	3328 (7.1%)	31 892 (2.7%)	0.205	3003 (6.7%)	3008 (6.7%)	0.001
History of nicotine dependence	13 016 (27.6%)	161 964 (13.6%)	0.353	12 269 (27.4%)	12 463 (27.8%)	0.010
Sleep apnoea	11 092 (23.5%)	119 684 (10.0%)	0.368	10 461 (23.4%)	10 699 (23.9%)	0.013
Alcohol related disorders	3419 (7.3%)	49 445 (4.1%)	0.135	3213 (7.2%)	3137 (7.0%)	0.007
Peripheral vascular diseases	6961 (14.8%)	104 147 (8.7%)	0.189	6732 (15.0%)	6782 (15.1%)	0.003
Percutaneous coronary intervention	34 801 (73.8%)	828 324 (69.3%)	0.279	32 731 (73.1%)	32 642 (72.9%)	0.006
Coronary artery bypass grafting	7875 (16.7%)	170 924 (14.3%)	0.238	7343 (16.4%)	7047 (15.8%)	0.009
Medications						
Calcium channel blockers	25 164 (53.4%)	314 028 (26.3%)	0.576	23 662 (52.8%)	23 853 (53.3%)	0.004
Beta blockers	38 076 (80.7%)	490 453 (41.0%)	0.891	35 844 (80.1%)	35 648 (79.6%)	0.011
Anti-lipidaemia agents	39 012 (82.7%)	472 965 (39.6%)	0.988	36 742 (82.1%)	36 433 (81.4%)	0.018
ACE inhibitors	22 366 (47.4%)	298 028 (24.9%)	0.482	21 169 (47.3%)	21 358 (47.7%)	0.008
ARBs	22 689 (48.1%)	184 344 (15.4%)	0.750	20 674 (46.2%)	20 580 (46.0%)	0.004
Loop diuretics	27 660 (58.7%)	269 060 (22.5%)	0.792	25 770 (57.6%)	26 229 (58.6%)	0.021
Spironolactone	12 880 (27.3%)	62 818 (5.3%)	0.626	11 301 (25.2%)	11 441 (25.6%)	0.007
Digoxin	3079 (6.5%)	29 495 (2.5%)	0.197	2899 (6.5%)	2945 (6.6%)	0.004
Metformin	17 668 (37.5%)	115 437 (9.7%)	0.694	16 154 (36.1%)	16 977 (37.9%)	0.038

Continued

Table 1 *Continued*

Characteristic	Before PSM—On SGLT2-Is ($n = 47\,157$)	Before PSM—Not on SGLT2-Is ($n = 1\,195\,273$)	Before PSM—Standardized Difference	After PSM—On SGLT2-Is ($n = 44\,777$)	After PSM—Not on SGLT2-Is ($n = 44\,777$)	After PSM—Standardized Difference
Insulin	27 662 (58.7%)	246 182 (20.6%)	0.845	25 742 (57.5%)	26 489 (59.2%)	0.034
Anticoagulation	37 652 (79.8%)	450 725 (36.5%)	0.947	35 338 (78.9%)	35 113 (78.4%)	0.012
Anti-platelet Agents	38 790 (82.3%)	464 399 (38.9%)	0.991	36 498 (81.5%)	36 101 (80.6%)	0.023
Antiarrhythmics	32 010 (67.9%)	435 725 (36.5%)	0.663	30 099 (67.2%)	29 978 (66.9%)	0.001
Lab values						
BMI, kg/m^2	30.6 ± 7.5	29.0 ± 7.2	0.222	30.5 ± 7.5	30.5 ± 7.9	0.119
Creatinine	1.2 ± 1.9	1.4 ± 2.0	0.126	1.2 ± 2.0	1.7 ± 2.1	0.060
Left ventricular Ejection Fraction	41.9 ± 16.4	56.0 ± 13.9	0.929	43.2 ± 16.4	45.2 ± 17.2	0.080
Natriuretic Peptide	5051.6 ± 8079.7	4438.2 ± 9412.4	0.070	5121.5 ± 8206.0	5693.8 ± 10693.7	0.045
Haemoglobin A1c	7.4 ± 2.1	6.6 ± 1.9	0.445	7.4 ± 2.0	7.2 ± 2.1	0.032

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; BMI, body mass index; SGLT2-I, sodium-glucose cotransporter 2 inhibitor; PSM, propensity score matching.

SGLT2-Is (43.6%, $n = 19\,506$) [aOR: 0.459 (95% CI: 0.367–0.551), $P < 0.001$] (*Table 2*). Kaplan–Meier analysis demonstrated a significant improvement in recurrent AMI-free survival probability in SGLT2-Is users at the end of the study window [HR: 0.473 (95% CI: 0.382–0.564)] (*Figure 3*).

All-cause mortality was significantly lower in SGLT2-I users [7.6% vs. 11.4%; aOR: 0.640 (95% CI: 0.612–0.670), $P < 0.001$], with significantly improved event-free survival [HR: 0.648 (95% CI: 0.621–0.677)]. Similarly, all-cause hospitalizations were lower in SGLT2-I users [42.3% vs. 48.4%; aOR: 0.782 (95% CI: 0.762–0.803), $P < 0.001$], with improved hospitalization-free survival probability [HR: 0.797 (95% CI: 0.782–0.813)] (*Figure 4*). Acute HF events were similar between SGLT2-I users (26.8%) compared with non-users (25.1%) [aOR: 1.096 (95% CI: 0.945–1.247), $P = 0.156$], with no significant difference in acute HF hospitalization-free survival [HR: 1.068 (95% CI: 0.911–1.225)] (*Figure 5*).

Cardiac arrest occurred less frequently in SGLT2-I users compared with non-SGLT2-I users [2.8% vs. 3.4%, respectively; aOR: 0.834 (95% CI: 0.773–0.900), $P < 0.001$]. Incidence rates among the SGLT2-I cohort compared with the non-SGLT2-I cohort for both strokes [7.1% vs. 7.0%, respectively; aOR: 1.008 (95% CI: 0.958–1.061), $P = 0.764$] and AF [24.0% vs. 24.3%, respectively; aOR: 0.982 (95% CI: 0.952–1.012), $P = 0.239$] were similar.

Safety outcomes

Incidence of acute renal failure or need for renal replacement therapy was less frequent in SGLT2-I users [19.4% vs. 27.0%; aOR: 0.652 (95% CI: 0.632–0.673), $P < 0.001$]. However, urinary tract infections were similar among SGLT2-I users compared with non-SGLT2-I users [9.8% vs. 9.3%, respectively; aOR: 1.063 (95% CI: 0.965–1.161), $P = 0.653$].

Discussion

In this retrospective cohort study, we investigated the impact of SGLT2-Is on cardiovascular outcomes in patients following an AMI. Although the impact of SGLT2-Is has been previously explored in a few studies,[15] our results highlight the impact of SGLT2-Is in a real-world cohort in regard to post-AMI cardiovascular outcomes. To the best of our knowledge, this analysis is the largest retrospective cohort study to date. These results are hypothesis generating and emphasize the importance of future clinical trials to focus on cardiovascular outcomes in those presenting with AMI.

Based on the 2022 HF guidelines, SGLT2-Is have shown a significant impact on cardiovascular outcomes, particularly through a reduction in acute HF hospitalizations and cardiovascular mortality, regardless of the presence of T2DM.[5] The DAPA-HF and EMPEROR-Reduced trials specifically demonstrated a significant reduction in HF hospitalizations.[7,16] Our findings suggest that these benefits may be extrapolated to other cardiovascular conditions, such as reducing recurrent AMI and other cardiovascular outcomes in those with known coronary artery disease. One subgroup analysis of the DECLARE-TIMI 58 trial showed that patients with diabetes and recent AMI who were treated with dapagliflozin had improved outcomes in relation to MACE, emphasizing that SGLT2-Is have a benefit beyond HF.[12] This study found that the relative risk reduction in those treated with dapagliflozin was comparable to the relative risk reduction seen in other secondary preventive measures such as anti-platelet agents or lipid-lowering therapies.[17–19] Similarly, a pooled analysis of multiple cardiovascular outcome trials that included SGLT2-I users showed a reduction in MACE in those with known coronary artery disease.[4] Conversely, a trial-level meta-analysis in 2024 showed that SGLT2-Is in diabetic patients may lead to reductions in MACE but not AMI rates or strokes.[20]

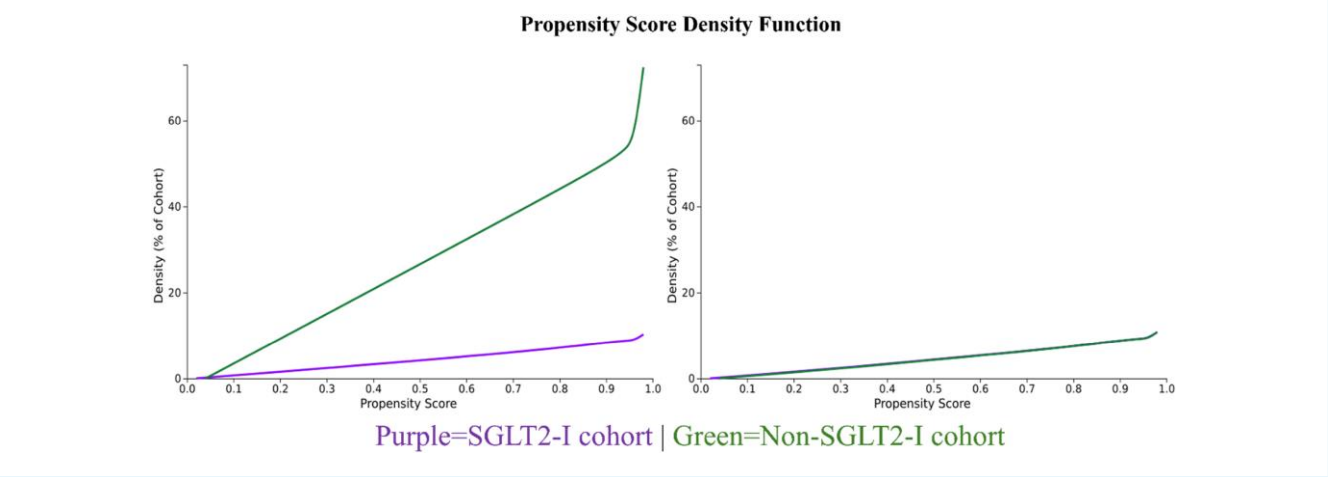


Figure 2 Propensity score density function. Pre- and post-propensity score matching. SGLT2-I, sodium-glucose cotransporter 2 inhibitor.

Table 2 Outcomes between cohorts

Outcome	AMI with SGLT2-Is (*N* = 44 777) Events	AMI with SGLT2-Is (%)	AMI without SGLT2-Is (*N* = 44 777) Events	AMI without SGLT2-Is (%)	Adjusted Odds ratio (95% CI)	*P*-value	Hazard ratio (95% CI)
Recurrent AMI	13 040	29.1	19 506	43.6	0.459 (0.367–0.551)	<0.001	0.473 (0.382–0.564)
All-cause mortality	3422	7.6	5124	11.4	0.640 (0.612–0.670)	<0.001	0.648 (0.621–0.677)
All-cause hospitalizations	18 963	42.3	21 683	48.4	0.782 (0.762–0.803)	<0.001	0.797 (0.782–0.813)
Acute HF hospitalizations	12 008	26.8	11 223	25.1	1.096 (0.945–1.247)	0.156	1.068 (0.911–1.225)
Cardiac arrest	1263	2.8	1506	3.4	0.834 (0.773–0.900)	<0.001	0.821 (0.762–0.885)
New-onset AF	10 745	24	10 896	24.3	0.982 (0.952–1.012)	0.239	0.964 (0.938–0.990)
Stroke	3164	7.1	3141	7.0	1.008 (0.958–1.061)	0.764	0.987 (0.939–1.037)
Acute renal failure or RRT	8695	19.4	12 085	27.0	0.652 (0.632–0.673)	<0.001	0.657 (0.639–0.675)
Urinary tract infection	4374	9.8	4153	9.3	1.063 (0.965–1.161)	0.653	1.082 (0.982–1.182)

Comparison between the two cohorts (acute myocardial infarction with and without sodium-glucose cotransporter 2 inhibitors) in cardiovascular and non-cardiovascular outcomes.
Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; CI, confidence interval; HF, heart failure; SGLT2-I, sodium-glucose cotransporter 2 inhibitor; RRT, renal replacement therapy.

Our study indicates that SGLT2-Is are associated with a reduction in recurrent AMI events, all-cause hospitalizations and mortality, and cardiac arrest in patients with AMI. Our findings are in contrary to those seen in the EMPACT-MI trial, which revealed that the addition of empagliflozin within 14 days of an initial AMI episode led to a reduction in HF hospitalizations but not all-cause mortality.[13] This may be secondary to the differences in baseline demographics, clinical comorbidity burden, and medication use in our cohorts. For example, as compared with the EMPACT-MI study, our cohorts after PSM included older patients (mean age = 68 years), greater female representation but reduced presence of White patients, higher rates of cardiovascular comorbidities (i.e. AF, T2DM, and hypertension), and the higher use of cardiovascular-related medications (i.e. HF-related medications). Similarly, the DAPA-MI trial investigated the impact of dapagliflozin on outcomes post-AMI in patients with impaired left ventricular systolic function, finding no impact on cardiovascular death or HF hospitalizations.[21] Our cohorts differed from the cohorts in the DAPA-MI trial as we included all patients that met our inclusion criteria, regardless of baseline left ventricular systolic function.

However, our results are consistent with prior studies done in populations with known diabetes,[15,22] which have been shown to improve all-cause mortality. This suggests a potential role of SGLT2-Is to improve overall haemodynamic function in those with high-risk or known coronary artery disease, improving survival probabilities and mitigating adverse outcomes.[22,23] The benefits to longer-term cardiovascular outcomes may also be attributed to improvements in metabolic stability, similarly to studies investigating the impact of SGLT2-Is in HF and chronic kidney disease.[24,25] Comparable benefits have been noted with another class of diabetes medications, glucagon-like peptide-1 receptor agonists (GLP-1 RAs). For instance, the LEADER trial demonstrated that liraglutide reduced MACE in patients with type 2 diabetes and atherosclerotic cardiovascular disease.[26] However, specific outcomes in patients with prior AMI were not reported in this trial.

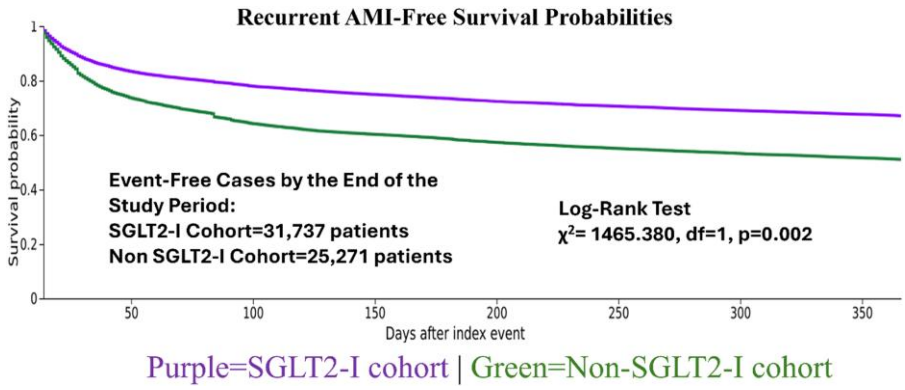


Figure 3 Kaplan–Meier survival probabilities. Recurrent acute myocardial infarction-free survival probabilities among the two cohorts (acute myocardial infarction with and without sodium-glucose cotransporter 2 inhibitors). AMI, acute myocardial infarction; SGLT2-I, sodium-glucose cotransporter 2 inhibitor.

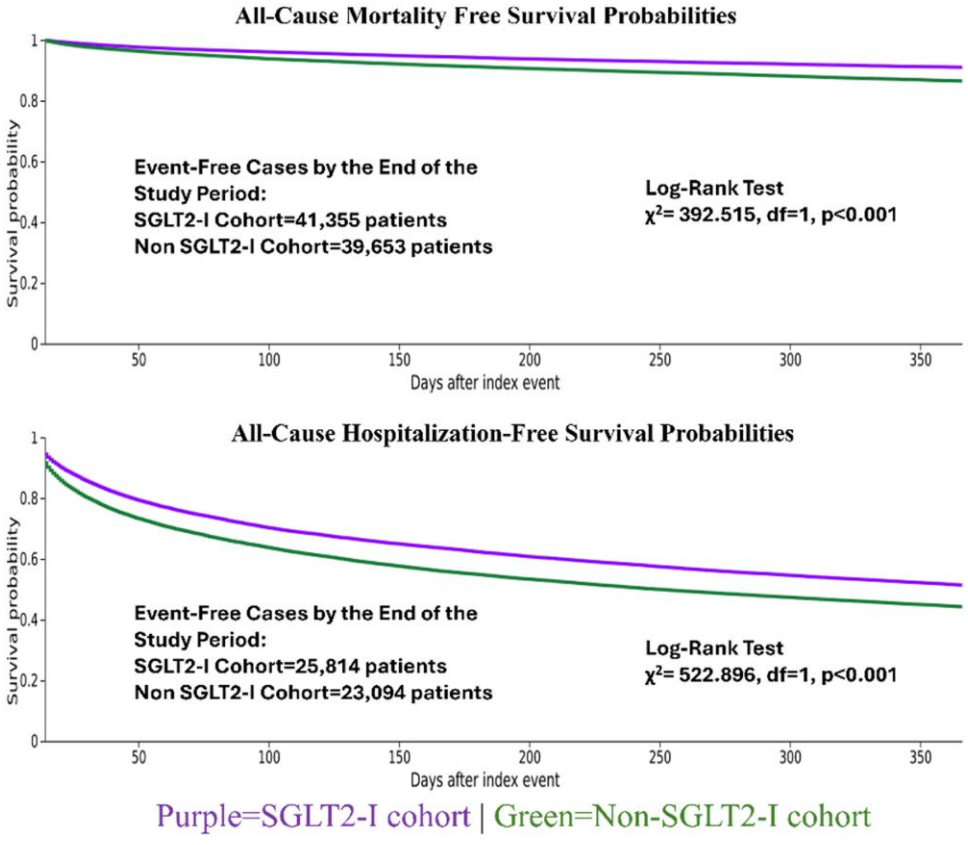


Figure 4 Kaplan–Meier survival probabilities. All-cause mortality and hospitalization-free survival probabilities among the two cohorts (acute myocardial infarction with and without sodium-glucose cotransporter 2 inhibitors). AMI, acute myocardial infarction; SGLT2-I, sodium-glucose cotransporter 2 inhibitor.

While the mechanisms of GLP-1 RAs differ from those of SGLT2-Is, these findings suggest that improved metabolic health likely contributes to enhanced cardiovascular stability through complex interrelated pathways.

Although the precise mechanisms underlying the cardiovascular benefits of SGLT2-Is remain unclear, several plausible hypotheses have been proposed. These include the restoration of tubule-glomerular feedback, attenuation of sympathetic nervous system activity, and

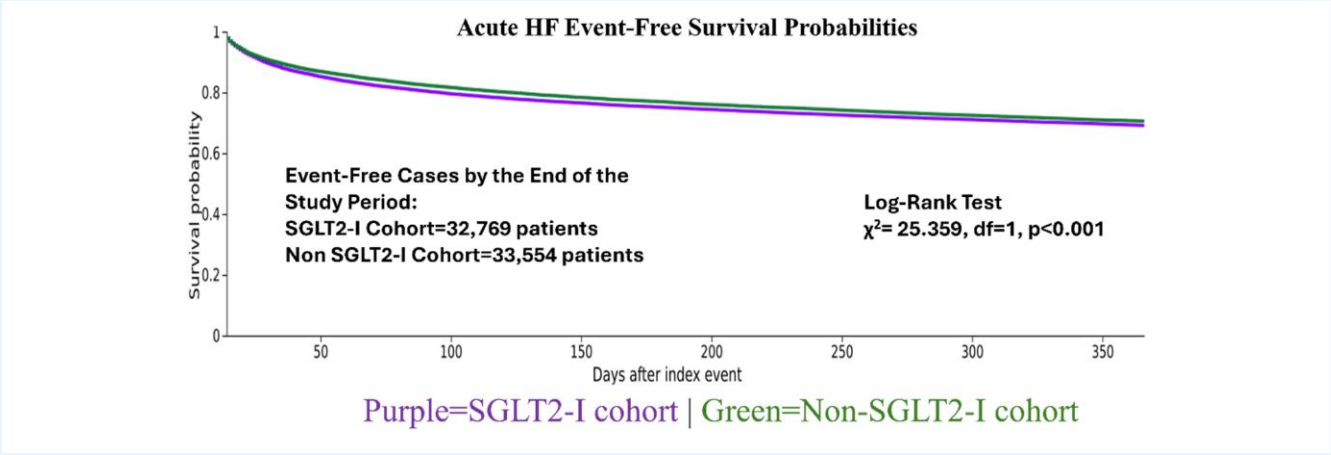


Figure 5 Kaplan–Meier survival probabilities. Acute heart failure event-free survival probabilities among the two cohorts (acute myocardial infarction with and without sodium-glucose cotransporter 2 inhibitors). AMI, acute myocardial infarction; HF, heart failure; SGLT2-I, sodium-glucose cotransporter 2 inhibitor.

modulation of the renin–angiotensin–aldosterone system.[10] Additional mechanisms such as improved heart fuel energetics, diuresis with subsequent reduction in ventricular overload, and inhibition of the sodium-hydrogen exchanger pump have also been suggested.[27–29] Furthermore, SGLT2-Is may enhance haemodynamics, particularly by reducing cardiac preload, and potentially contribute to coronary plaque stability, thereby lowering the incidence of MACE.[30–32] Collectively, these mechanisms may provide overall myocardial protection, explaining the benefits of SGLT2-Is in both atherosclerotic cardiovascular disease and HF.

Acute myocardial infarction remains a leading cause of hospital admission in the USA, with a national average of one AMI every 42 s, according to the Heart Disease and Stroke Statistics-2016 Update.[33] Survivors of AMI represent a growing population at increased risk of developing HF or mortality.[34] Consequently, there is an ongoing need for effective therapeutic strategies to improve cardiovascular outcomes in these patients. This high-risk group has been the focus of numerous clinical trials and large-scale observational studies evaluating early interventions.[35] Many of these therapies, now standard treatments for HF, have proved effective in reducing cardiovascular mortality and the incidence of HF post-AMI. Addressing the ongoing challenges of preventing AMI-related mortality and hospitalizations in this patient population remains an urgent clinical need that is rapidly advancing. This makes our findings particularly novel and highlights the potential of SGLT2-Is as a promising therapeutic approach in this broader patient population. To our knowledge, this study is the first large-scale real-world investigation assessing the effectiveness of SGLT2-Is in improving cardiovascular outcomes in the post-AMI period.

Limitations

Our retrospective cohort study has several limitations that warrant consideration. First, like many large healthcare databases, the TriNetX platform is prone to miscoding and under-reporting of diagnoses, procedures, and medications. Second, the reliance on electronic health records means that certain clinical nuances, such as physician assessments, patient-reported outcomes, and non-hospital treatments, may not be captured. Third, because the TriNetX database primarily includes patients from large HCOs, our findings may not fully generalize to more diverse or underrepresented populations. Additionally, despite using PSM to balance covariates, residual confounding due to unmeasured clinical factors may persist. Nevertheless, the strengths of our study lie in its large cohort sizes and its distinction as the largest real-world, retrospective cohort studies to evaluate cardiovascular outcomes in patients with known AMI treated with SGLT2-Is.

Conclusions

Our study concludes that the use of SGLT2-Is in patients with AMI is associated with lower rates of recurrent AMI, acute HF hospitalizations, stroke, all-cause hospitalizations, cardiac arrest, and all-cause mortality. This suggests that SGLT2-Is may confer protective cardiovascular outcomes in patients with AMI. Although these findings are hypothesis generating, they highlight the need for prospective clinical trials to validate these results.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

All data were provided by the TriNetX in aggregate format, as provided in this manuscript. Individual level data are not available. Data will be made available through the TriNetX platform if the researcher's affiliated institution is associated with the TriNetX repository.

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