Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors for the secondary prevention of myocardial infarction

Abstract

Background: Survivors of myocardial infarction (MI) remain at high risk of recurrent events despite standard secondary prevention. Although studies suggest that SGLT2 inhibitors reduce major cardiovascular events, their specific efficacy for secondary MI, timing of benefit, and real-world adherence remain unclear. This study evaluated the clinical impact and adherence behaviours of SGLT2 inhibitors among MI survivors.

Methods: The data was drawn from a randomised controlled trial of 1988 MI survivors assigned to SGLT2 inhibitors plus usual care or usual care alone, with follow-up over five years. The primary endpoints were time to secondary MI and systolic blood pressure at 12 months, with medication adherence also assessed. Multivariable logistic regression, time-dependent Cox proportional hazards models, and multivariable linear regression were used.

Results: Pre-randomisation BMI was the only factor associated with adherence, with higher BMI increasing the odds of adherence (OR 1.06; 95% CI: 1.02-1.10; p=0.004). SGLT2 inhibitor treatment reduced the overall hazard of secondary MI by 22% (HR 0.78; 95% CI: 0.67-0.91; p=0.002). However, this effect was time-dependent: no benefit was observed in the first 1.5 years (HR 1.38; 95% CI: 0.83-2.29; p=0.22), but a 27% hazard reduction emerged between 1.5 and 5 years (HR 0.73; 95% CI: 0.62-0.87; p<0.001). Systolic blood pressure decreased by an average of 1.9 mmHg (95% CI: -2.61 to -1.20; p<0.001).

Conclusion: SGLT2 inhibitors are an effective treatment for secondary prevention of MI, although their benefits are most pronounced after 1.5 years of treatment. Strategies that encourage long-term adherence, particularly in patients with lower BMI, may enhance clinical outcomes.

Background

Myocardial infarction (MI) is one of the leading causes of death in the developed world. It is defined as irreversible necrosis of myocardial tissue, resulting from a decrease or stoppage of blood flow to a portion of the heart [1]. While advancements in managing acute MI have improved survival rates significantly – with an estimated 1.4 million people surviving MI in the UK [2] – this population remains at high risk of a wide range of further health conditions, including recurrent cardiac events.

Given the growing number of MI survivors, effective secondary prevention measures are crucial. Traditional approaches include lifestyle modifications and drug treatments such as statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors [3]. Despite these interventions, cardiovascular risk amongst survivors remains high, emphasising the need for additional therapeutic strategies.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a class of glucose-lowering drugs that have emerged as a promising treatment for secondary MI. Although originally designed for lowering blood sugar in adults with type 2 diabetes, recent literature has found that SGLT2i appear to moderately reduce the risk of major adverse cardiovascular events (MACE) - a composite endpoint of heart failure, MI, and cardiovascular death [4].

Recent studies have delved into this association in greater depth. Large-scale trials and meta-analyses have shown their ability to reduce the risk of both primary and secondary incidence of MACE [5]. However, there remain significant gaps in the literature regarding their specific impact on secondary MI, the temporal onset of treatment effect, and how patient behaviour influences effectiveness in real-world settings - all of which are crucial for clinical decision-making.

Therefore, this research seeks to assess the clinical impact and adherence behaviour associated with SGLT2 inhibitors for MI survivors. Specifically, this research addresses three key aims: (1) identify baseline predictors of treatment adherence; (2) assess the efficacy of SGLT2 inhibitors in reducing the risk of secondary MI; and (3) determine the impact of treatment on systolic blood pressure.

Methods

Study Participants

This study analysed data from a randomised controlled trial (RCT) designed to evaluate the efficacy of SGLT2 inhibitors in mitigating the risk of secondary MI and lowering systolic blood pressure. The study population comprised 1988 patients aged 18-69 who had survived an MI between 1 February 2017 and 31 July 2018. Participants were recruited from four regions across England and were randomly assigned 1:1 to receive either SGLT2i plus usual care (intervention group), or just usual care (control group). Participants were routinely followed up for a maximum of five years after randomisation, with secondary MI events identified through linked hospital records. An interim assessment was conducted approximately 12 months after randomisation to measure weight and systolic blood pressure. This assessment also served to monitor treatment adherence for participants in the intervention group.

Endpoint Selection

This study assessed two primary endpoints. The first endpoint was the time from randomisation to the occurrence of secondary MI (measured in days). Participants who did not experience an MI event during the study were censored at the date of loss to follow-up or at the end of the five-year study period (1826 days), whichever occurred first. The second primary endpoint was systolic blood pressure (mmHg) mea-

sured at the 12-month interim assessment.

The secondary endpoint was medication adherence, which was evaluated only for participants in the intervention group at the 12-month interim assessment and recorded as a binary flag (adherent/non-adherent) based on participant self-report.

Statistical Analysis

A multivariable logistic regression model was fitted to investigate whether participant age, sex, or pre-randomisation BMI were associated with adherence to SGLT2 inhibitors. This analysis was restricted to the intervention arm (n = 997), and the model was adjusted for region and baseline systolic blood pressure to control for potential systemic differences in demographics and adherence bias respectively. The model assumptions were verified visually and statistically. Multicollinearity was tested using the Variance Inflation Factor (VIF), and with all values close to 1, this indicated no significant multicollinearity. The nature and size of the trial satisfied the assumptions of independent observations and large sample size.

To assess the effect of SGLT2 inhibitors on secondary MI, the cumulative probability of remaining free from secondary MI was estimated using the Kaplan-Meier method. The curves were stratified by treatment allocation and compared using the log-rank test. All efficacy analyses were performed on the intention-to-treat population. To quantify the treatment effect, a Cox proportional hazards model was fitted to estimate Hazard Ratios (HRs) and 95% Confidence Intervals (CIs). Adjustments were made for age, sex, region, baseline BMI, and baseline SBP; clinical characteristics known to influence cardiovascular outcomes based on previous scientific knowledge and external literature. The proportional hazards assumption was tested using scaled Schoenfeld residuals. Treatment allocation violated the proportional hazards assumption ($p<0.05$), revealing a varying treatment effect over time. Consequently, a time-dependent analysis was conducted by partitioning the follow-up period into two intervals (0-1.5 years and 1.5-5 years), and the final model included an interaction term between treatment allocation and time interval.

A multivariable linear regression model was used to estimate the effect of SGLT2 inhibitors on systolic blood pressure after 12 months. This model was chosen as it allowed for adjustment of systolic blood pressure at baseline, which captured most of the variability in the data, thus making the treatment effect estimate much more sensitive. The model further controlled for baseline BMI, age, sex, and region. Assumptions of the linear model were confirmed through residual checks. Visual inspection of the Residuals vs. Fitted plots confirmed strong linearity and homoscedasticity, while the Q-Q plot confirmed the normality of residuals.

Subgroup analyses were conducted for both primary endpoints to explore sex-specific differences in the efficacy of SGLT2i treatments. This was achieved by introducing an interaction term between allocation and sex into the time-split Cox and multivariable linear regression models.

Results

Descriptive Statistics

A total of 1988 participants were included in the analysis, with 997 patients (50.2%) assigned to the SGLT2i arm. The mean age at recruitment was 60 (SD 8) years, and each region of England was similarly represented. As shown in **Table. 1**, the baseline characteristics were well-matched between the treatment and control arms, suggesting successful randomisation. The cohort was predominantly male (85%), and the mean BMI was 30.3kg/m^2 (SD 4.4), classifying the average participant as obese (BMI $\geq$ 30kg/m^2).

Table 1. Baseline Characteristics of Study Participants by Treatment Allocation

Characteristic	Usual Care N = 991	SGLT2 N = 997	Total Population
Age (years)			
Mean (SD)	60 (8)	60 (8)	60 (8)
Sex			
Female	149 (15%)	150 (15%)	299 (15%)
Male	842 (85%)	847 (85%)	1,689 (85%)
Region			
North East	215 (22%)	197 (20%)	412 (21%)
North West	277 (28%)	255 (26%)	532 (27%)
South East	272 (27%)	292 (29%)	564 (28%)
West Midlands	227 (23%)	253 (25%)	480 (24%)
Baseline BMI (kg/m^2)			
Mean (SD)	30.1 (4.4)	30.4 (4.3)	30.3 (4.4)
Baseline Systolic BP (mmHg)			
Mean (SD)	142 (12)	142 (12)	142 (12)
Median [Q1, Q3]	142 [134, 150]	142 [133, 150]	142 [134, 150]

Furthermore, the mean systolic blood pressure was 142 mmHg (SD 12), indicating that a large proportion of the cohort had stage 2 hypertension ($\geq$ 140 mmHg). Therefore, the study population represents a clinically high-risk group.

Adherence to SGLT2 inhibitors

Table 2. Predictors of SGLT2 Adherence

Characteristic	Odds Ratio	95% CI	P-value
Age	0.99	0.97, 1.01	0.36
Sex: Female	1.24	0.79, 2.02	0.37
Baseline BMI	1.06	1.02, 1.10	0.004
Abbreviations: CI = Confidence Interval, OR = Odds Ratio			

For patients allocated to the SGLT2i treatment (n = 997), 813 (82%) adhered to the medication, while 184 (18%) did not, as self-reported in the interim assessment. In the multivariable logistic regression model (**Table. 2**), baseline BMI was the only clear predictor of adherence. There was strong evidence of a positive linear association, where every 1kg/m^2 increase in BMI was associated with a 6% increase in the odds of adherence (OR 1.06; 95% CI: 1.02-1.10; p=0.004). Conversely, there was no evidence that

age (OR 0.99; 95% CI: 0.97-1.01; p=0.36) or sex (OR 1.24 for females; 95% CI: 0.79-2.02; p=0.37) were associated with adherence behaviour.

Secondary MI rates for SGLT2 inhibitor treatment vs Usual care

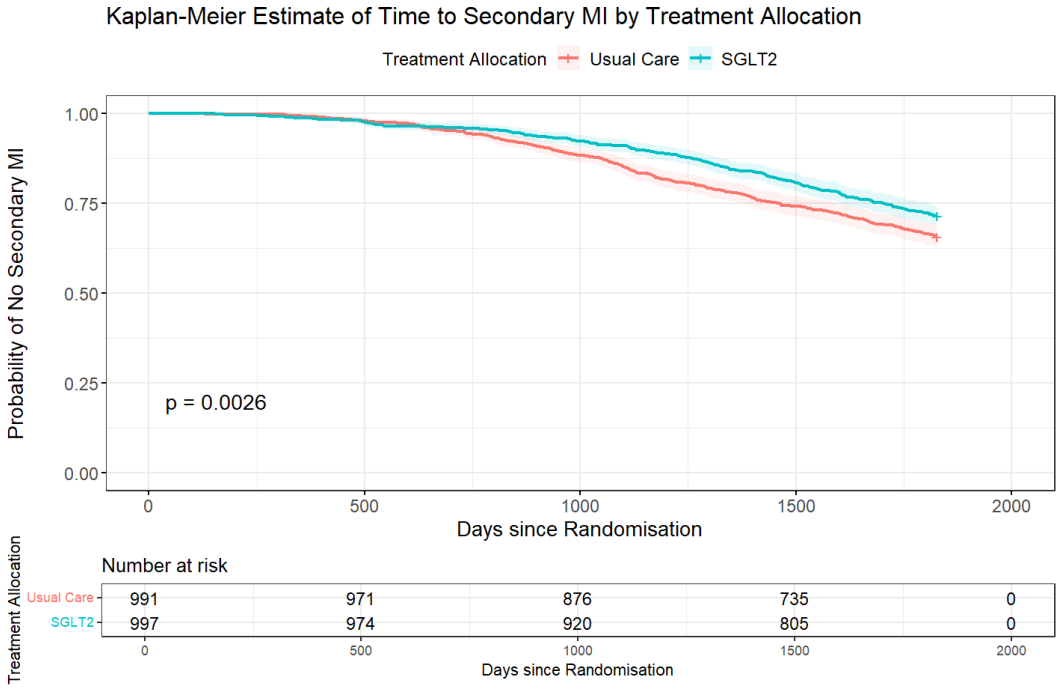

Figure 1: Kaplan-Meier Estimate of Time to Secondary MI by Treatment Allocation. The figure displays the probability of remaining free from secondary MI over the follow-up period (0 - 1826 days). The red line represents the Usual Care group (n=991), and the blue line represents the SGLT2 inhibitor group (n=997). The shaded areas represent 95% confidence intervals.

The Kaplan-Meier survival curves (**Figure. 1**) highlighted a distinct separation between treatment groups, with the SGLT2i arm showing a higher cumulative probability of no secondary MI beyond the early phase of the study. The log-rank test complemented these findings, showing strong evidence of a difference in survival distributions (p = 0.003).

In the adjusted Cox proportional hazards model, the initial analysis revealed that the SGLT2i group had an overall 22% lower hazard of secondary MI compared to the usual care group (HR 0.78; 95% CI: 0.67-0.91; p=0.002). Independent of treatment allocation, baseline systolic blood pressure was a dominant risk factor; for every 1 mmHg increase, the hazard of secondary MI increased by 5% (HR 1.05; 95% CI: 1.04-1.06; p<0.001). Increasing age was also associated with higher risk (HR 1.03; 95% CI: 1.01-1.04; p<0.001), while female participants had a much lower hazard of secondary MI compared to males (HR 0.59; 95% CI: 0.46-0.77; p<0.001).

The time-split Cox model (**Figure. 2**) confirmed that the treatment effect varied over time (p = 0.02 for interaction). In the first phase (0-1.5 years), there was no clear evidence that SGLT2 inhibitors affected secondary MI compared to usual care (HR 1.38; 95% CI: 0.83-2.29; p=0.22). However, in the following phase (1.5-5 years), the treatment was associated with a sizeable 27% reduction in the hazard of secondary MI (HR 0.73; 95% CI: 0.62-0.87; p<0.001). The effect of other prognostic covariates remained constant across the follow-up period.

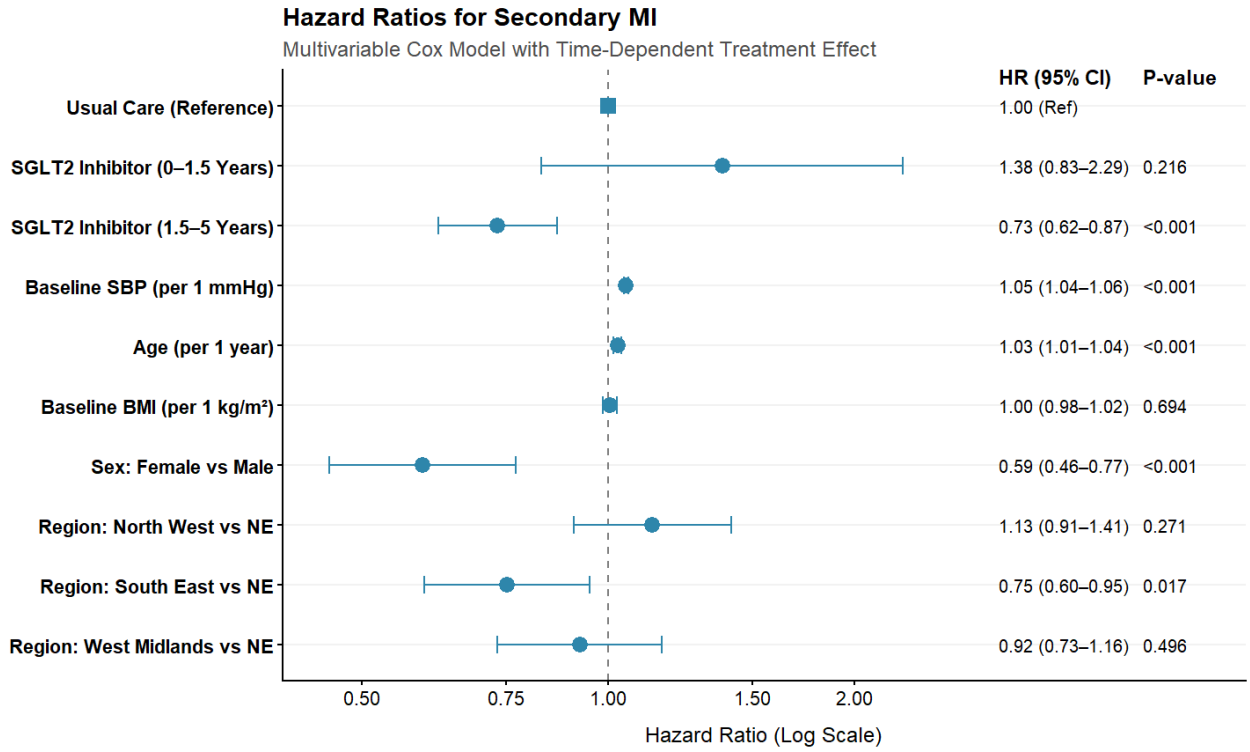

Figure 2: Forest Plot of Hazard Ratios for Secondary Myocardial Infarction. Results from a multivariable Cox proportional hazards model incorporating a time-dependent treatment effect, adjusted for baseline systolic blood pressure (SBP), age, baseline body mass index (BMI), sex, and region. The treatment effect is split into an early phase (0–1.5 years) and a late phase (1.5–5 years). Whiskers indicate 95% confidence intervals.

The subgroup analysis revealed no evidence of effect modification by sex ($p = 0.68$), indicating that the treatment effects found were consistent across both male and female participants.

Systolic Blood Pressure for SLGT2 inhibitor treatment vs usual care

Table 3. Effect of SGLT2 Inhibitors on Systolic Blood Pressure

Characteristic	Coefficient (β)	SE	95% CI	P-value
Treatment Allocation: SGLT2	-1.9	0.360	-2.6, -1.2	<0.001
Baseline SBP	0.94	0.015	0.91, 0.97	<0.001
Age	-0.02	0.024	-0.06, 0.03	0.51
Sex: Female	0.40	0.511	-0.61, 1.4	0.44
Baseline BMI	-0.05	0.043	-0.14, 0.03	0.21

Abbreviations: CI = Confidence Interval, SE = Standard Error

In the multivariable linear regression model (**Table. 3**), there was strong evidence that SGLT2i reduced systolic blood pressure over the 12-month period, with a mean reduction of 1.9 mmHg for participants in the intervention group compared to the control group (95% CI: -2.61 to -1.20; $p<0.001$). The inclusion of baseline blood pressure in the model was necessary and substantially improved the precision

of the estimates, capturing most of the variability in the data (Adjusted R^2 increased from 0.004 to 0.67). There was no evidence that the SGLT2i treatment effect on blood pressure varied by sex ($p = 0.58$).

Discussion

Summary of Main Findings

This study aimed to investigate the clinical efficacy and adherence behaviour of SGLT2 inhibitor therapy for survivors of MI. The results demonstrate three key findings. First, SGLT2i were effective in reducing the hazard of secondary MI, with an overall reduction of 22%. However, this benefit was time-dependent, with no clear effect observed in the first 1.5 years, but a large 27% reduction in risk occurring between 1.5 and 5 years. Second, SGLT2i treatment led to a reduction in systolic blood pressure of 1.9 mmHg over the 12-month period. The third key finding was that baseline BMI was the only clear predictor of medication adherence, whereas no association was observed with age and sex.

Interpretation and Comparison with Literature

The observed 22% reduction in secondary MI (HR 0.78) aligns closely to findings from previous large-scale studies and meta-analyses. For instance, one meta-analysis reported an overall hazard ratio of 0.83 for MACE in patients with prior MI [5], while another reported a hazard ratio of 0.89 for MI in patients with atherosclerotic cardiovascular disease [4].

The delayed onset of treatment efficacy was the most notable finding from this research. Although few studies have conducted a direct time-split, a group of researchers performed a time-stratified analysis on the DECLARE-TIMI 28 trial, discovering that dapagliflozin was associated with risk reduction only during the 12–24-month period [6]. Although timing of prior MI events was not available in the dataset, it is reasonable to assume that participants were recruited relatively soon after their first MI event, which closely matches these findings.

The observed reduction in systolic blood pressure (1.9 mmHg) is modest in comparison with the average reductions reported in the literature (2–4 mmHg) [7]. However, several studies within the same meta-analysis reported reductions of less than 2 mmHg, indicating that the results are not outliers and are still consistent with the known effects of SGLT2 inhibitors.

Regarding medication adherence, the finding that higher BMI is associated with better adherence is an interesting discovery. One possible explanation is that patients with obesity may view the drug's weight-loss side effect as an added benefit and are consequently more diligent in adhering. In contrast, leaner patients may be less motivated by this effect, while those with very low BMI may have concerns about further weight-loss.

Study Limitations

First, the analysis could not control for unmeasured confounders, such as smoking status, physical activity, and comorbidities, which are known drivers of MI risk [8]. Another limitation was that adherence was self-reported at a single time point, which may have led to an overestimation of the true adherence rates due to participants overstating their adherence to avoid disappointing clinicians. Moreover, the term "usual care" in the control group is ambiguous and may refer to different levels of therapy across the four recruitment regions, potentially skewing results. Lastly, the study cohort represents a high-risk demographic (older age, obesity, stage 2 hypertension) and therefore caution should be taken when generalising these estimates to lower-risk groups.

Conclusion

Survivors of MI remain at a high risk of subsequent MI. SGLT2 inhibitors represent a valuable therapeutic option for secondary prevention, offering a sizeable reduction in recurrent events, with the greatest benefit observed beyond 1.5 years of treatment. This can partially be attributed to the lowering of systolic blood pressure due to treatment, and other long-term mechanisms of the drug. As a result of this research, clinical strategies should focus on encouraging long-term persistence with treatment - particularly for patients with lower BMI, who appear less likely to adhere over time.

References

[1] Lung National Heart, Blood Institute, et al. What are the signs and symptoms of coronary heart disease. *Bethesda: National Heart, Lung, and Blood Institute*, 2016.

[2] Marlous Hall, Lesley Smith, Jianhua Wu, Chris Hayward, Jonathan A Batty, Paul C Lambert, Harry Hemingway, and Chris P Gale. Health outcomes after myocardial infarction: a population study of 56 million people in england. *Plos Medicine*, 21(2):e1004343, 2024.

[3] JS Skinner, A Cooper, and GS Feder. Secondary prevention for patients following a myocardial infarction: summary of nice guidance. *Heart*, 93(7):862–864, 2007.

[4] Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo HM Furtado, et al. Sglt2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*, 393(10166):31–39, 2019.

[5] Guijun He, Guosu Yang, Xiaoyu Huang, Duan Luo, Chao Tang, and Zhen Zhang. Sglt2 inhibitors for prevention of primary and secondary cardiovascular outcomes: a meta-analysis of randomized controlled trials. *Heart & Lung*, 59:109–116, 2023.

[6] Remo HM Furtado, Marc P Bonaca, Itamar Raz, Thomas A Zelniker, Ofri Mosenzon, Avivit Cahn, Julia Kuder, Sabina A Murphy, Deepak L Bhatt, Lawrence A Leiter, 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*, 139(22):2516–2527, 2019.

[7] Jamie L Benham, Jane E Booth, Ronald J Sigal, Stella S Daskalopoulou, Alexander A Leung, and Doreen M Rabi. Systematic review and meta-analysis: Sglt2 inhibitors, blood pressure and cardiovascular outcomes. *IJC Heart & Vasculature*, 33:100725, 2021.

[8] Salim Yusuf, Steven Hawken, Stephanie Ôunpuu, Tony Dans, Alvaro Avezum, Fernando Lanas, Matthew McQueen, Andrzej Budaj, Prem Pais, John Varigos, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the interheart study): case-control study. *The lancet*, 364(9438):937–952, 2004.