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

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Abstract

Background: SGLT2 inhibitors are hypothesised for their potential role in prevention strategies for myocardial infarction survivors. This study explores factors influencing medication adherence and the efficacy of SGLT2 inhibitors on the risk of secondary MI. Its effect on systolic blood pressure reduction is also investigated.
Methods: A longitudinal study was conducted with participants in two treatment groups, receiving usual care and SGLT2 inhibitors. The main aims of this study are investigated through a series of regression analyses and tests, including Logistic regression, Cox regression, Student's t-test and Linear regression.
Results: Baseline BMI was positively correlated with medication adherence. In males, SGLT2 inhibitors significantly reduced the risk of secondary MI, particularly after the first 1.5 years. No significant effect was observed in females. Systolic blood pressure showed a significant decrease in participants allocated to the SGLT2 inhibitors group.
Conclusions: This study confirms the efficacy of SGLT2 inhibitors for male MI survival from secondary cardiac risk. The gender disparity in participant numbers and subsequent event rates suggests a need for further research to ascertain the effects of SGLT2 inhibitors in females.

1. Introduction

Myocardial Infarction (MI), a prominent subtype of Coronary Heart Disease (CHD), significantly impacts public health in the UK. Over a million survivors emphasise the importance of managing post-MI complications and preventing secondary cardiac events (1).

Originally developed to lower blood glucose levels (2), the applications of SGLT2 inhibitors have evolved to include weight management and blood pressure reduction (3; 5). This broadened scope of use suggests their potential in comprehensive cardiac care, particularly for MI survivors at risk of recurrent cardiac events(4). The target population comprises individuals who have survived MI and are at risk of subsequent cardiac events.

Data

Data have been collected from a randomised control trial spanning four distinct UK regions, capturing a cohort of 1,988 MI survivors aged between 18 and 69, followed over five years with an interim checkpoint at 12 months post-randomisation. Trial outcomes, demographic characteristics, blood pressure, and anthropometric measures at baseline and interim assessment are included. This trial's rich dataset includes no missing values, allowing for a more reliable analysis of trial outcomes.

Aims and Hypotheses

The report aims to investigate the efficacy of SGLT2 inhibitors in reducing subsequent MI risks. Specific objectives and corresponding hypotheses include:

Aim 1: Identify factors influencing adherence to SGLT2 inhibitors among MI survivors.
Hypothesis 1: Adherence to SGLT2 inhibitors inversely correlates with age, suggesting older patients may exhibit reduced compliance. Additionally, adherence rates are presumed to be lower in males and in individuals with higher BMI indices.

Aim 2: Assess the impact of SGLT2 inhibitors on the incidence of secondary MI.
Hypothesis 2: SGLT2 inhibitors have a beneficial effect on the incidence of secondary MI, suggesting that post-MI patients on SGLT2 inhibitors are less likely to experience a subsequent MI compared to those receiving usual care.

Aim 3: Evaluate the influence of SGLT2 inhibitors on systolic blood pressure at the interim assessment.
Hypothesis 3: There is a negative association between the use of SGLT2 inhibitors and systolic blood pressure at the interim assessment, implying a more pronounced reduction in blood pressure among those on this medication.

2. Methods

Prior to addressing the specific aims, we present summary statistics to provide an overview of the information included in the dataset. This encompasses demographic characteristics, treatment adherence, and clinical outcomes. Notably, some participants in the SGLT2 group did not adhere to the allocated drug; therefore, an intention-to-treat analysis is conducted for all aims. This analytical approach ensures that all participants initially allocated to the treatment group are included in the analysis, irrespective of their actual ad-

herence to the treatment.

Aim 1: Logistic Regression

To assess the association between participant characteristics and adherence to SGLT2 inhibitors, logistic regression analysis is employed. The outcome for this aim is adherence to medication among the SGLT2 group. The exposures of interest include age, sex, and baseline body mass index (BMI), etc. This method is adapted due to the binary nature of the outcome (adherence).

Aim 2: Cox Proportional Hazards Regression

The effect of treatment on the incidence of secondary MI during follow-up is examined using survival analysis with Cox proportional hazards regression. The event of interest is the occurrence of a secondary MI during the follow-up period. The exposure of interest is the intervention received(SGLT2 inhibitors or usual care). This method is chosen due to the time-to-event nature of the data. Participants who do not experience the event by the end of the follow-up period are considered right-censored in the analysis. The analysis is stratified by sex, and an exploration of the time variability of this effect is also conducted.

Aim 3: Linear Regression and T-test

To evaluate the impact of SGLT2 inhibitors on the change in systolic blood pressure, linear regression analysis and the Student's t-test are utilised. The outcome of interest is the reduction in systolic blood pressure between randomisation and the interim assessment. The exposure of interest is the same as aim 2. These methods are appropriate as the outcome variable is continuous.

3. Results

Table 1 revealed congruence in the demographic characteristics of both groups (age/gender/regional representations), thereby establishing a foundational equivalence for further analysis. Moreover, there was a discernibly greater reduction in body weight among participants in the SGLT2 group, corroborating the emerging usage of SGLT2 inhibitors in weight management mentioned in the introduction. The weight reduction observed was more pronounced in males (-11.2kg), as compared to females (-10kg). This differential impact highlights a potential gender-specific response to SGLT2 inhibitor therapy, warranting further investigation. Furthermore, a more substantial decline in systolic blood pressure was recorded in the SGLT2 group. This factor will be investigated more in Aim 3.

Aim 1

The mathematical definition of the logistic regression is presented below:

$$\text{Adherence}(0/1) \sim \text{Binormial}(1, p)$$
$$\text{logit}(p) = \beta_0 + \beta_1 \cdot \text{factor}$$

Each factor is used to fit this logistic regression with $Adherence(0/1)$, and β_1 is the coefficient represents the expected change in the log-odds of adherence for a one-unit change in the factor.

Since only the SGLT2 group exhibits non-adherence to their medication, the subsequent analysis for aim 1 will exclusively concentrate on this group. For anthropometric measures, weight and height are known to have a high correlation with BMI (correlation coefficients of 0.715 and -0.465, respectively). Therefore, only BMI is taken into account in the analysis.

Table 2 presents a high rate of adherence to SGLT2 inhibitors, with 81.5% (813 individuals) consistently taking their medication. This high adherence rate suggests that the majority of participants are following the allocated therapeutic regimen, which can be critical for the effectiveness of the treatment.

A significant positive association is found between baseline BMI and medication adherence. Specifically, each additional unit increase in BMI is associated with increased odds of adherence (Estimate: 0.05; 95% CI: 0.013 to 0.089; p-value: 0.009). Also shown in *Figure 1*, the mean baseline BMI for the adherent subgroup (30.6) is slightly higher than that of the non-adherent subgroup (29.7).

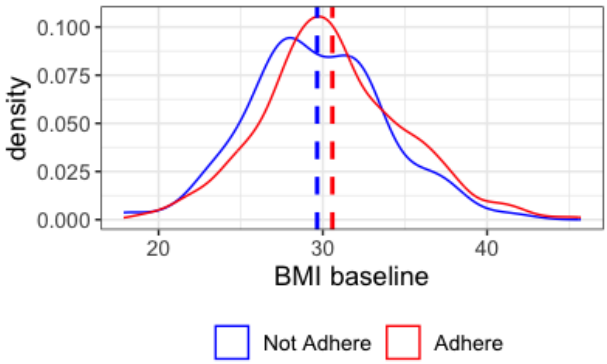

Figure 1. This plot compares BMI baseline distribution between Adhere and Not Adhere groups. The vertical line presents mean value of BMI in each group.

No significant associations were identified for other factors, including age, sex, and systolic blood pressure at both baseline and follow-up. Their respective p-values(>0.05) and confidence intervals(including the zero value) suggest that these variables do not significantly influence adherence to SGLT2 inhibitors.

Aim 2

Survival time between entering the trial and the occurrence of secondary MI is computed, in the unit of week. Participants who do not experience the event by the end of the follow-up period is filled with default 260.86 weeks (i.e. five-year follow-up).

By plotting the Kaplan-Meier estimate (*Figure 2*) and

Table 1. Summary Statistics

N = 1988	**SGLT2 Group** mean±SD or number (%)		**Usual Care Group** mean±SD or number (%)	
(A) Demographic characteristics	Total		Total	
Number	997		991	
Age, Year	60.1±7.55		60.1±7.55	
Gender				
Female	150(15%)		149(15%)	
Male	847(85%)		842(85%)	
Region				
North East	197(20%)		215(22%)	
North West	255(26%)		277(28%)	
South East	292(29%)		272(27%)	
West Midlands	253(25%)		227(23%)	
(B) Anthropometric measures & Blood pressure	Female	Male	Female	Male
Weight [b], kg	77.3±8.43	97±10.2	76.6±8.91	96.5±10.7
Weight [f], kg	67.3±9.13	85.8±12	73.4±9	91.5±12.5
Height [b], cm	165±8.22	178±7.78	165±8.71	179±7.93
Body Mass Index/BMI [b], kg/m^2	28.7±4.35	30.7±4.28	28.5±4.48	30.4±4.27
Systolic Blood Pressure [b], mm/Mg	142±12.3	142±12.2	142±12.3	142±11.7
Systolic Blood Pressure [f], mm/Mg	133±14.4	133±14	135±13.9	135±13.7

[b] measures collected at baseline.
[f] measures collected at follow-up interim assessment 12 months after randomisation.

Table 2. Aim 1 results

Factors	**Estimate 95% CI**	**p-value**	**Adhere** (N=813)	**Not Adhere** (N=184)
Age, Year	-0.001 [-0.023, 0.020]	0.92	60.1	60.1
Sex: Male	-0.009 [-0.564, 0.353]	0.701	689 (84.7%)	158 (85%)
BMI [b]	0.05 [0.013, 0.089]	**0.009**	30.6	29.7
Systolic Blood Pressure [b]	0.0000163 [-0.013, 0.013]	0.998	142	142
Systolic Blood Pressure [f]	-0.001 [-0.012, 0.011]	0.888	133	133

[b] measures collected at baseline.
[f] measures collected at follow-up interim assessment 12 months after randomisation.
The results shown in Adhere and Not Adhere columns are the mean value or number(%) of each factor.

Nelson-Aalen estimate (*Figure 3*), we visualise the survival functions and cumulative hazard functions (in logarithmic scale) for participants over time in weeks, stratified by treatment (SGLT2 vs. usual care) and sex (male vs. female).

Graphically, the results suggest that SGLT2 inhibitors may confer a survival advantage over usual care, as evidenced by both higher survival probabilities and lower cumulative hazards for participants in this treatment. Moreover, the separation of the curves in both plots indicates that the differences between the groups may be maintained over time. This speculation is further examined by a log-rank test with a chi-square statistic of 24.4 and a p-value of 2e-05. Thus, there is a statistically significant difference in the survival experiences of the four groups stratified by treatment and sex.

In order to further quantify the effectiveness of SGLT2 inhibitors, we fit the following Cox regression models. Due to the result of aim 1, baseline BMI also should be controlled

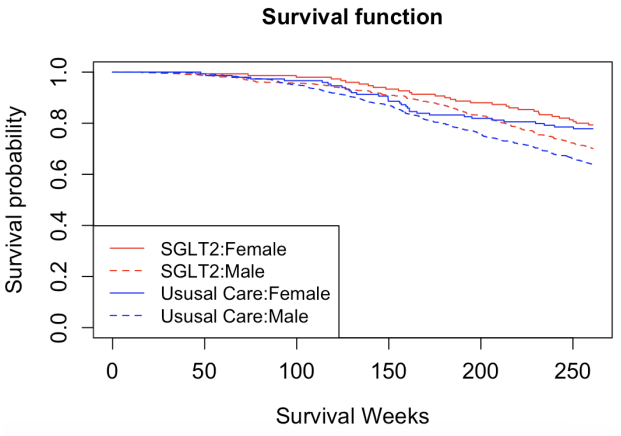

Figure 2. Kaplan-Meier estimate for the survival function

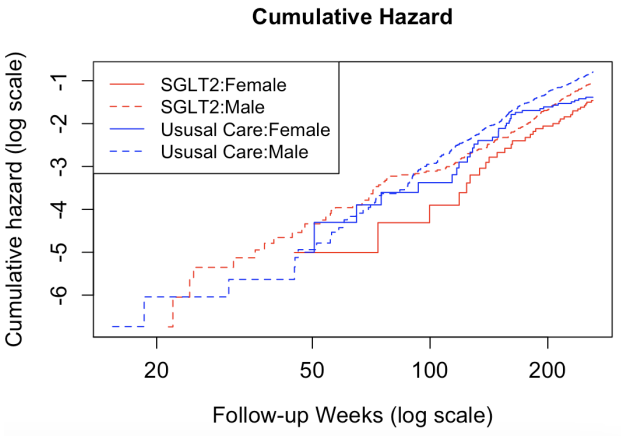

Figure 3. Nelson-Aalen estimate for the cumulative hazard function in log-scale

Table 3. Log-rank test result

Groups	N	Observed	Expected
Usual Care:Male	842	306	253.5
Usual Care:Female	149	33	48
SGLT2:Male	847	253	270.8
SGLT2:Female	150	31	50.7

in our models. Model 1 includes an interaction term to fit the differences in groups.

Model 1 - Treatment:Sex

$$h(t) = h_0(t) \times \exp(\beta_1 \cdot \text{Usual Care:Male} + \beta_2 \cdot \text{Usual Care:Female} + \beta_3 \cdot \text{SGLT2:Male} + \beta_4 \cdot \text{SGLT2:Female} + \beta_5 \cdot \text{BMI baseline})$$

Results from *Table 4* show that for females receiving usual care, the hazard is 0.582 times the hazard for males receiving usual care, with a 95% confidence interval (CI) ranging from 0.406 to 0.834 and a statistically significant p-value of 0.003. This suggests that females have a lower risk compared to males when both receive usual care. For males receiving SGLT2 inhibitors, the hazard is 0.770 times the hazard for males receiving usual care, with a 95% CI from 0.651 to 0.909, which is statistically significant (p=0.002). This indicates that SGLT2 treatment is associated with a lower risk compared to usual care in males. For females receiving SGLT2 inhibitors, the hazard ratio (HR) is 1.155 with a 95% CI from 0.688 to 1.938, but this result is not statistically significant (p=0.586), indicating no clear evidence that the treatment affects risk differently for females compared to males receiving usual care.

Nonetheless, the p-value of the global Schoenfeld test for Model 1 is 0.03551, which indicates that there is evidence to suggest that the proportional hazards assumption is violated in the model. Therefore, a stratified Cox regression, Model 2, is also fitted on each stratum (male/female) data only to further confirm our results.

Model 2 - One stratum (male/female) data only

$$h(t) = h_0(t) \times \exp(\beta_1 \cdot \text{Usual Care+} \beta_2 \cdot \text{SGLT2+} \beta_3 \cdot \text{BMI baseline})$$

For the male stratum, there is statistically significant (p=0.002) evidence that the HR for those receiving SGLT2 inhibitors is 0.769 compared to those receiving usual care, with a 95% CI from 0.651 to 0.909. The proportional hazards assumption is not violated for the male stratum, so we obtain this reliable conclusion that SGLT2 inhibitor is beneficial for males. However, since the assumption is violated for the female stratum, the result for the female stratum is not significant.

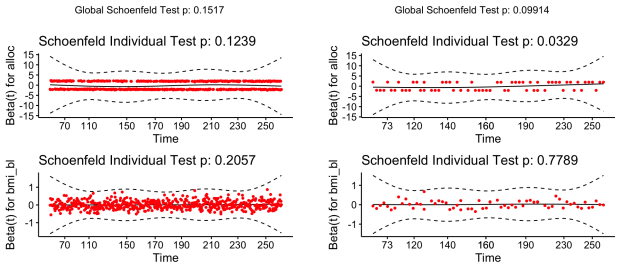

Figure 4. These plots show the Schoenfeld test results for Model 2 for only male data (left plot) and only female data (right plot)

Model 3 - Time-split

$$h(t) = h_0(t) \times \exp(\beta_1 \cdot \text{Usual Care:First1.5yr+} \beta_2 \cdot \text{Usual Care:After1.5yr+} \beta_3 \cdot \text{SGLT2:First1.5yr+} \beta_4 \cdot \text{SGLT2:After1.5yr+} \beta_5 \cdot \text{BMI baseline})$$

Following the important findings from the male subgroup, we conducted a time-split Cox regression analysis to assess the impact of SGLT2 inhibitors over different time periods

Table 4. Aim 2 results.

Model	Variable	HR Estimate	95% CI	p-value
Treatment:Sex	Usual Care:Male	reference		
	Usual Care:Female	0.582	[0.406, 0.834]	**0.003**
	SGLT2:Male	0.770	[0.651, 0.909]	**0.002**
	SGLT2:Female	1.155	[0.688, 1.938]	0.586
Male Stratum	Usual Care	reference		
	SGLT2	0.769	[0.651, 0.909]	**0.002**
Female Stratum	Usual Care	reference		
	SGLT2	0.890	[0.545, 1.453]	0.640
Treatment:Time-split (Male Stratum)	Usual Care:First1.5yr	reference		
	Usual Care:After1.5yr	4.628e-08	[0, Inf]	0.982
	SGLT2:First1.5yr	1.499	[0.874, 2.572]	0.141
	SGLT2:After1.5yr	0.480	[0.272, 0.846]	**0.011**

For simplicity, results for the baseline BMI variable are not shown.

using exclusively male data. The analysis was stratified into two time periods: the initial 1.5 years and the period after 1.5 years up to 5 years after randomization.

An HR of 0.48 demonstrates a 52% reduction in the risk of secondary MI for individuals using SGLT2 inhibitors after 1.5 years compared to the reference period of the initial 1.5 years. This result is statistically significant with a p-value of 0.0112, and the 95% CI:[0.2721, 0.8464] being entirely less than 1, indicating that the risk reduction is statistically significant.

The p-value of 0.9823 indicates that there is no statistically significant difference in the risk of secondary MI after 1.5 years compared to the first 1.5 years in the usual care group.

The results suggest that, for the male stratum, SGLT2 inhibitors do not significantly affect the risk of secondary MI in the initial 1.5 years post-randomisation but are associated with a significantly reduced risk in the period from 1.5 to 5 years.

Aim 3

Before further analysis, we define the difference in systolic blood pressure(SBP) as follows:

$$\text{SBP}_{diff} = \text{SBP}_{follow-up} - \text{SBP}_{baseline}$$

negative value represents a drop in systolic blood pressure between randomisation and the follow-up interim assessment.

As shown in *Figure 5*, the distribution of differences in systolic blood pressure in the usual care group is slightly left shifted than the SGLT2 group, but the mean value of the SGLT2 group (-9.15) is more negative than the mean value of the usual care group (-7.26).

A one-side two-sample Student's t-test is used to examine this difference in mean values. Our null hypothesis is H_0: the mean value of SBP_{diff} of the SGLT2 group is not less

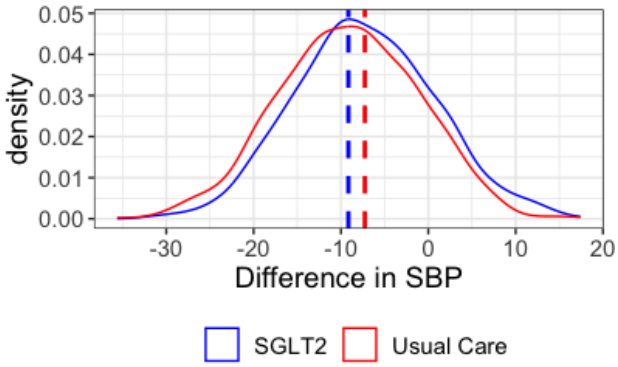

Figure 5. This plot compares the distribution of differences in systolic blood pressure between treatment groups. The vertical line presents the mean value of the difference in each group.

than the mean value of SBP_{diff} of the usual care group.

In addition, linear regression, defined below, is also used to double-confirm the effect of SGLT2 inhibitors on systolic blood pressure.

$$\text{SBP}_{diff} = \beta_0 + \beta_1 \cdot \text{Treatment}$$

Table 5. Aim 3 results

Model	p-value	Estimate 95% CI
Student's t-test	<0.001	
Linear Regression	<0.001	β_1 =-1.881 [-2.589, -1.175]

The t-test result shows there is statistically significant (p<0.001) evidence to reject H_0 and the estimate of β_1 (-1.881). From the result of linear regression, the estimated value of β_0 is -1.8819, indicating that, on average,

the systolic blood pressure difference for the SGLT2 group is 1.8819 units lower than that for the usual care group. This result is also statistically significant ($p<0.001$).

Both results support the hypothesis that participants receiving SGLT2 inhibitors have a statistically significant lower systolic blood pressure at the interim assessment compared to those receiving usual care.

4. Discussion

The present investigation meticulously explored the influence of baseline characteristics on medication adherence, the efficacy of SGLT2 inhibitors on secondary myocardial infarction incidence, and their effect on systolic blood pressure control.

Conclusions

Aim 1 underscored baseline body mass index (BMI) as a determinant of medication adherence, with higher baseline BMI being associated with increased likelihood of adherence. This finding introduces the notion that individuals with a higher BMI may perceive a greater necessity or derive more immediate benefit from pharmacotherapy, thereby enhancing their adherence patterns.

Aim 2 illuminated the efficacy of SGLT2 inhibitors in male participants, signifying an overall reduction in the risk of secondary MI. The time-split analysis revealed that the impact of SGLT2 inhibitors varies over time; no significant effect was noted in the initial 1.5 years post-randomisation, yet a substantial reduction in risk was evident between 1.5 to 5 years. This time efficacy change suggests a delayed yet persistent protective mechanism of SGLT2 inhibitors against secondary MI in males. Conversely, the effect in female participants did not reach statistical significance, which may be indicative of intrinsic sex-based therapeutic disparities.

Aim 3's outcomes affirm that SGLT2 inhibitor treatment confers a significant reduction in systolic blood pressure, aligning with emerging evidence that positions these agents as multifaceted in their therapeutic benefits beyond glycaemic control.

Limitations

A notable limitation of this study is the gender disparity among the participants, where females comprised merely 15% of the dataset. The consequent paucity of events within female subgroups—approximately only 30 events per treatment arm—poses a methodological constraint that likely attenuated the statistical power necessary to discern the impact of SGLT2 inhibitors in females.

Further Research

Firstly, the relationship between weight loss and the reduction in systolic blood pressure observed warrants a focused investigation to unravel potential causal interdependencies. Secondly, the reduction in systolic blood pressure merits examination as a potential prognostic indicator for subsequent MI events. Thirdly, comparative analyses to determine the relative predictive value of weight loss versus systolic blood pressure reduction on cardiovascular outcomes would significantly enhance our understanding of optimal indicators for therapeutic monitoring. Such inquiries could elucidate mechanistic insights and inform patient-tailored therapeutic strategies.

References

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