Cardioprotective Effect of Sodium Glucose Co-transporter Type 2 Inhibitors on The ST Segment Elevation Myocardial Infarction Diabetic Patients undergoing Primary Percutaneous Coronary Intervention

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Abstract:

Background: Myocardial infarction (MI) remains the leading cause of death worldwide, especially when combined with type 2 diabetes mellitus (T2DM). Many trials have established the cardiovascular benefits of Sodium-Glucose cotransporter 2 inhibitors (SGLT-2i) in diabetic patients at high cardiovascular risk. **Aim:** To evaluate the cardioprotective effect of SGLT-2I in STEMI diabetic patients undergoing primary percutaneous coronary intervention. **Patients and methods:** This Comparative cross-sectional study was conducted on 30 diabetic patients with ST segment elevation myocardial infarction (STEMI) undergoing Primary PCI, at Cardiology department, Zagazig University hospital. Based on admission antidiabetic therapy; the patients were equally divided into diabetic patients not on SGLT2I, and second group diabetic patients on SGLT2I (including Empagliflozin and Dapagliflozin). **Results:** The current study showed hs-TnI levels (I hs-TnI, II hs-TnI, III hs-TnI and hs-TnI peak) were significantly higher in non SGLT2I group compared to SGLT2I group ($P<0.05$), with no significant difference between both groups regarding CK-MB**,** also WMSI was significantly higher in non SGLT2I group compared to SGLT2I group ($P=0.007$). Incidence of all cause death was significantly higher in non SGLT2I group compared to SGLT2I group ($P=0.027$). HF hospitalization was significantly higher in non SGLT2I group compared to SGLT2I group ($P=0.010$). MACE was significantly higher in non SGLT2I group compared to SGLT2I group ($P=0.022$). The multivariate regression analysis revealed that hs-TnI peak, serum creatinine after 24 hr., mitral regurgitation on discharge, and complete revascularization were the only significant predictors of cardiovascular death. The multivariate regression analysis revealed that serum creatinine after 24 hr., mitral regurgitation on discharge, complete revascularization and receiving SGLT2-I were the only significant predictors of MACE**.** The multivariate regression analysis revealed that complete revascularization and receiving SGLT2-I was the only significant predictors of HF hospitalization. **Conclusion:** In diabetic patients with AMI, the use of SGLT2 inhibitors was associated with a documented cardioprotecton.

Keywords: Myocardial Infarction; Diabetes ; PPCI; STEMI; Cardioprotective Effect.

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Introduction:

Diabetes mellitus type 2 (T2DM) has been shown to be associated with increased in-hospital mortality in patients undergoing primary percutaneous coronary intervention (PCI), and this association holds true when patients have cardiogenic shock[(1)].

Although PCI limits tissue damage inflicted by myocardial ischemia, this intervention typically does not halt or even reverse the loss of functional myocardium[(2)].

Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have demonstrated their ability to lower blood glucose levels by reducing glucose reabsorption in the proximal convoluted tubules of the kidney. SGLT2 inhibitor treatment preserved left ventricular function, activated cardio-protective signaling pathways, exerted antioxidative and anti-inflammatory effects, and ameliorated mitochondrial dysfunction[(3)].

Dedicated heart failure trials, the efficacy of SGLT2 inhibitors in individuals who had heart failure with reduced ejection fraction, with and without type 2 diabetes, suggesting that the salutary effects of these agents are not confined to diabetic conditions. Ischemic heart disease is the leading cause of death worldwide, and frequently manifests in myocardial infarction. Timely reperfusion is the single most effective intervention to limit ischemic injury. Therefore, this study aimed to assess the cardioprotective effect in STEMI diabetic patients undergoing primary percutaneous coronary intervention at Cardiology Department at Zagazig University Hospital [(4)].

Patients and Methods

This Comparative cross-sectional study was conducted on 30 diabetic patients with ST segment elevation myocardial infarction (STEMI) undergoing Primary PCI, at Cardiology Department, Zagazig University hospital.

Inclusion & Exclusion criteria:

Adult diabetic patients with STEMI undergoing Primary PCI. While, patients with advanced renal and hepatic disorder. Baseline glomerular filtration rate (eGFR) $\leq$ 45 mL/min/1.73 m2. patients with chronic heart failure, valvular heart disease, a significant arrhythmia, and need for emergent coronary artery bypass surgery. Contraindications to Dual Antiplatelets therapy (DAPT) including aspirin, clopidogrel and ticagrelor were excluded.

Clinical Evaluation:

All patients were subjected to Full history taking and complete clinical and laboratory investigations.

- ***Echocardiography:***

Based on the type of echocardiographic image used (M-mode, and two-dimension echo cardiography and the equations used to determine left ventricular (LV) volumes. Using a standard transthoracic echocardiography sequence, each myocardial segment is assigned a score from 1 to 4. The 16-segment model of myocardial segmentation is recommended, as the apical cap of the 17-segment model is a contractile and therefore more appropriate for perfusion imaging.

Primary Percutaneous coronary Intervention (PPCI):

All patients underwent selective coronary angiography using the Judkins percutaneous trans-femoral or trans-radial technique. Philips Allura Xper FD20 was the used imaging system. The type of stent used (bare metal or drug eluting) and the

decision to use tirofiban were left to the operator's discretion. Culprit lesions were treated with stent implantation and balloon angioplasty if necessary. Coronary angiograms were recorded in digital media for quantitative analysis (Dicom-viewer; MedCom GmbH, Darmstadt, Germany). Digital angiograms were analyzed by 2 independent and experienced interventional cardiologists who were blinded to all data. In the case of disagreement, the final decision was made by consensus with a third independent cardiologist. The left main coronary artery (LMCA) left anterior descending (LAD), circumflex (Cx), and right coronary artery (RCA) were defined as large coronary vessels.

- ***TIMI Flow Grade,*[(5)]:**

Blood flow was evaluated with the TIMI flow grades as: Grade 0: no antegrade blood flow through the vascular occlusion (no perfusion); Grade 1: a small amount of contrast agent can pass through the stenosis but cannot fill the distal coronary bed (penetration without perfusion); Grade 2: the contrast agent can fill the distal coronary bed, but the filling speed is slow (partial perfusion); Grade 3: the contrast agent fills the distal coronary bed quickly and completely (complete perfusion).

- ***Myocardial Blush Grades,*[(6)]:**

Myocardial Blush Grades as: Grade 0 (MBG-0): Failure of dye to enter the microvasculature. Either minimal or no ground glass appearance or opacification of the myocardium in the distribution of the culprit artery indicating lack of tissue-level perfusion. Grade I (NIBG-1): Dye slowly enters but fails to exit the or opacification of the myocardium in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 seconds between injections). Grade 2 (MEIG-2): Delayed entry and exit of dye from the microvasculature. There is the ground glass appearance or opacification of the myocardium in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase. Grade 3 (MBG-3): Normal entry and exit of dye from the microvasculature. There is the ground glass appearance or pacification of the myocardium in the distribution of the culprit lesion that dears normally and is either gone or only mildly/moderately persistent at the end of the washout phase.

- ***Killip Classification,* [(7)]:**

This system focuses on physical examination and the development of heart failure to predict risk, described as: Class I: No evidence of heart failure (mortality 6%); Class II: Findings of mild to moderate heart failure (S3 gallop, rales < half-way up lung fields or elevated jugular venous pressure (mortality 17%); Class III: Pulmonary edema (mortality 38%); Class IV: Cardiogenic shock defined as systolic blood pressure <90 and signs of hypoperfusion such as oliguria, cyanosis, and sweating (mortality 67%).

- **GRACE Score:**

A clinical risk prediction tool for estimating the cumulative 6-month risk of death and death or myocardial infarction. The components of the GRACE risk score include: age of the patient, heart rate,

systolic blood pressure, serum creatinine level, Killip class, cardiac arrest at admission, ST-segment deviation on the ECG, and elevated cardiac enzymes[8].

- **Endpoints:**

A major adverse cardiovascular event (MACE) refers to a combined or composite clinical endpoint that is used for outcome evaluations in clinical trials for cardiovascular research. A major adverse cardiovascular/clinical event is employed as a surrogate measure of the safety and effectiveness of a particular intervention. In the context of percutaneous coronary interventions (PCI), a major adverse cardiovascular event has been defined as being one of the following: cardiovascular mortality, recurrent AMI, stent thrombosis, and repeat revascularization including bypass graft.

In- hospital clinical outcomes included length of hospital stay, occurrence of acute heart failure (AHF), and mortality risk of after discharge, new-onset cardiac arrhythmias, and hypotensive events.

The cardiac protection was assessed by:

1. Infarct size[9].
2. Clinical heart failure[10].
3. MACE (Hospitalization for heart failure & death)[11].

Statistical analysis:

Using SPSS v28 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant. Kaplan Meier curve was used to show the time to the incidence of all cause death, HF hospitalization and MACE. Multivariate logistic regression was also used to estimate the relationship between a dependent variable and more independent variables.

RESULTS

The current study showed hs-TnI levels (I hs-TnI, II hs-TnI, III hs-TnI and hs-TnI peak) were significantly higher in non SGLT2I group compared to SGLT2I group (P<0.05), with no significant difference between both groups regarding CK-MB **(Table 1).**

All cause death was significantly lower in SGLT2I group compared to non SGLT2I group (P=0.027) with (HR= 0.1757 (95%CI) 0.03886 to 0.7941) **(Figure 1).**

HF hospitalization was significantly lower in SGLT2I group compared to non SGLT2I group (P=0.010) with (HR= 0.1556 (95%CI) 0.03783 to 0.6400) **(Figure 2).**

The incidence of MACE was significantly higher in non SGLT2I group compared to SGLT2I group (P=0.022) with (HR= 0.2230 (95%CI) 0.06201 to 0.8020) **(Figure 3).**

The multivariate regression analysis revealed that hs-TnI peak, serum creatinine after 24 hr., mitral regurgitation on discharge, and complete revascularization were the only significant predictors of cardiovascular death **(Table 2).**

The multivariate regression analysis revealed that serum creatinine after 24 hr., mitral regurgitation on discharge, complete revascularization and receiving SGLT2-I were the only significant predictors of MACE **(Table 3).**

The multivariate regression analysis revealed that complete revascularization and receiving SGLT2-I were the only significant predictors of HF hospitalization **(Table 4).**

Table (1): Clinical investigations cardiac biomarkers of the studied groups

		Total (n=30)	Non SGLT2I group (n=15)	SGLT2I group (n=15)	P value
Age	Mean± SD Range	67.34±3.65 60-72	66.14±5.25 60-72	68.37±5.25 60-72	0.18
CK-MB (U/L)	Mean± SD Range	169.9±38.8 103 - 223	159.0 ± 42.1 103 - 223	180.7 ± 33.08 107 - 222	0.127
I hs-TnI (ng/L)	Mean± SD Range	651.9±492.5 131 - 1904	960.8 ± 514.76 147 - 1904	343.1 ± 181.91 131 - 649	<0.001*
II hs-TnI (ng/L)	Mean± SD Range	3512.7±2752.2 233 - 8786	5853.8 ± 1912.29 1205 - 8786	1171.5 ± 537.25 233 - 1747	<0.001*
III hs-TnI (ng/L)	Mean± SD Range	2749.2±2837.6 224 - 8893	4762.9 ± 2810.7 580 - 8893	735.4 ± 298.24 224 - 1262	<0.001*
hs-TnI peak (ng/L)	Mean± SD Range	3396.6±2635.8 297 - 9053	5467.4 ± 2210.42 1989 - 9053	1325.7 ± 562.39 297 - 2208	<0.001*

CK-MB: creatine kinase myocardial band, hs-TnI: high-sensitivity cardiac troponin I, *:statistically significant as p value <0.05.

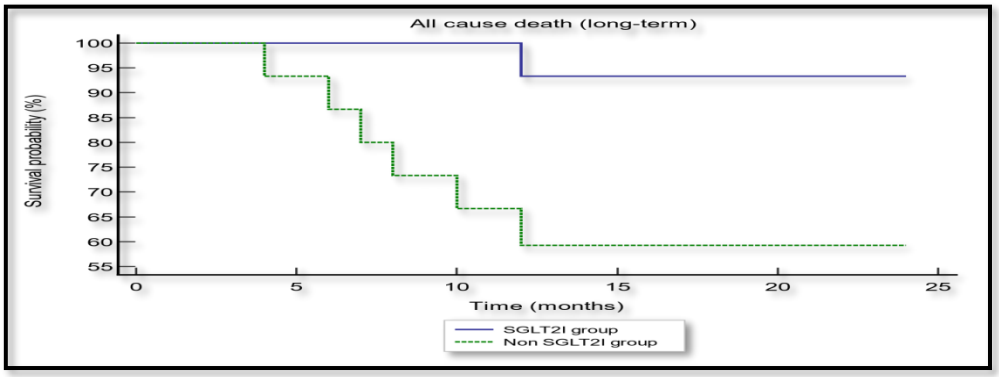

Figure 1: All cause death outcome in the studied groups

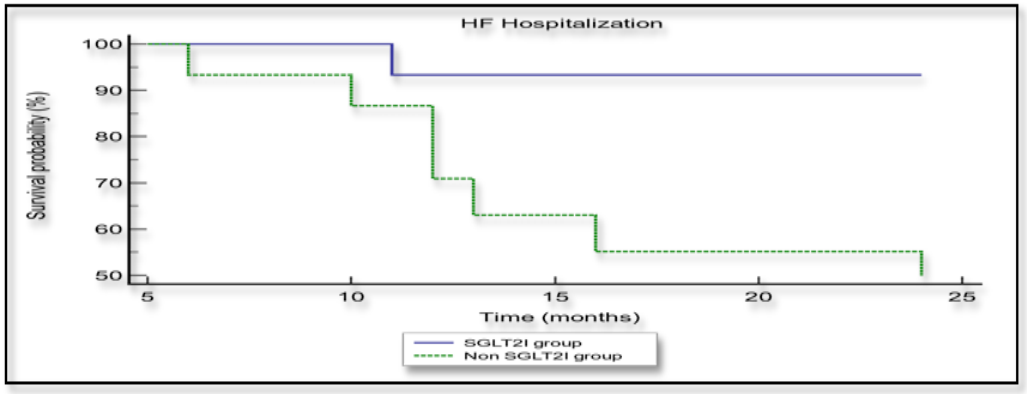

Figure 2: HF hospitalization outcome in the studied groups

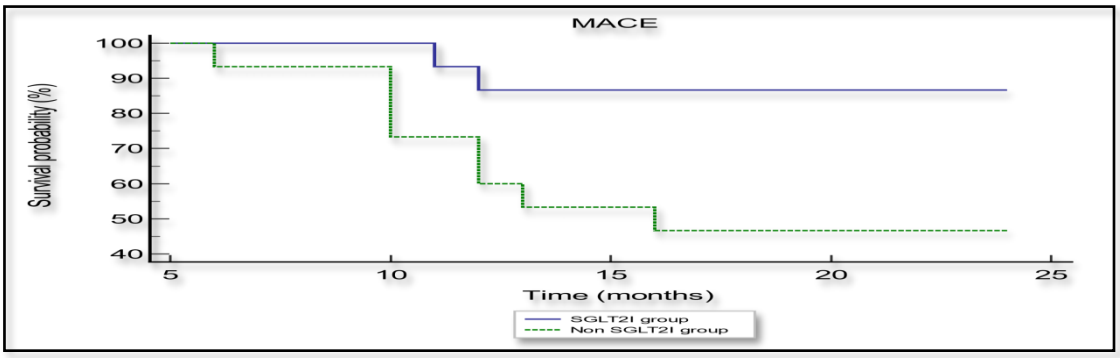

Figure 3: MACE outcome in the studied groups

Table (2): Multivariate regression analysis for prediction of Incidence of cardiovascular death

	OR	95% CI	P value
Age (years)	0.775	0.5529 to 1.0876	0.140
Sex	1.4000	0.1191 to 16.4594	0.789
BMI (Kg/m^2)	1.3594	0.7906 to 2.3373	0.266
Smoking	1.1872	0.0773 to 18.2344	0.902
Hypertension	0.8025	0.5635 to 1.1430	0.222
Dyslipidemia	0.6034	0.3469 to 1.0497	0.073
Angina	0.7031	0.4747 to 1.0412	0.078
CKD	0.6510	0.0446 to 9.4971	0.753
PAD	0.7411	0.5306 to 1.0351	0.079
COPD	0.2709	0.0039 to 18.6217	0.545
Family history of CAD	0.2095	0.0046 to 9.5101	0.422
Previous PCI	0.5694	0.3084 to 1.0515	0.072
Prior CABG	0.0949	0.0012 to 7.3174	0.288
Prior MI	0.7889	0.5833 to 1.0669	0.123
AF	0.7830	0.5722 to 1.0713	0.126
HR (beats/min)	1.1221	0.9090 to 1.3850	0.284
SBP (mmHg)	1.0261	0.9390 to 1.1212	0.570
DBP (mmHg)	1.036	0.9016 to 1.1904	0.618
INR	0.7673	0.2336 to 2.5204	0.662
PT (sec)	0.823	0.2628 to 2.5774	0.738
PTT (sec)	0.9953	0.6597 to 1.5017	0.982
Total cholesterol (mg/dL)	0.9649	0.9147 to 1.0179	0.191
Triglycerides (mg/dL)	0.9541	0.8631 to 1.0547	0.358
HDL (mg/dL)	0.8602	0.6359 to 1.1635	0.329

LDL (mg/dL)	0.9016	0.7237 to 1.1231	0.355
CK-MB (U/L)	0.9677	0.9205 to 1.0173	0.198
hs-TnI peak (ng/L)	1.0006	1.0000 to 1.0011	0.039*
Hb after 24 hr (g/dL)	0.0437	0.0018 to 1.0565	0.054
PLT after 24 hr (*10^9/L)	0.9790	0.9442 to 1.0150	0.249
WBCs after 24 hr (*10^9/L)	0.4649	0.1146 to 1.8865	0.283
Lymphocytes after 24 hr (*10^9/L)	0.0384	0.0010 to 1.5039	0.081
Neutrophil after 24 hr (*10^9/L)	3.1623	0.4997 to 20.0102	0.221
NLR after 24 hr	0.0006	0.0000 to 29.6087	0.158
HbA1c after 24 hr (%)	0.7279	0.1774 to 2.9873	0.659
CRP after 24 hr (mg/dL)	1.3561	0.7522 to 2.4449	0.311
S. creatinine after 24 hr (mg/dL)	3.3116	1.1687 to 9.3841	0.024*
TIMI flow after PCI	0.0974	0.0073 to 1.2926	0.078
Affected vessel	0.2641	0.0234 to 2.9805	0.282
Killip Class	4.5345	0.2796 to 73.5340	0.288
GRACE Score	1.017	0.9378 to 1.1028	0.684
Myocardial blush grades	4.209	0.5347 to 33.1342	0.172
EF on discharge (%)	0.4429	0.1594 to 1.2312	0.118
ST resolution on discharge	0.5958	0.3089 to 1.1490	0.122
RWMA on discharge	0.1913	0.0066 to 5.5691	0.336
Mitral regurgitation on discharge	12.6000	1.0717 to 148.134	0.027*
Hospital stay (days)	1.6144	0.5940 to 4.3879	0.347
Complete revascularization	0.0794	0.0068 to 0.9331	0.043*
SGLT2-I	0.0952	0.0061 to 1.4977	0.094

*OR: odds ratio, CI: confidence interval, BMI: body mass index, CKD: chronic kidney disease, PAD: peripheral artery disease, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, MI: myocardial infarction, AF: atrial fibrillation, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, INR: international normalized ratio, PT: prothrombin time, PTT: partial thromboplastin time, HDL: high density lipoprotein, LDL: low density lipoprotein, CK-MB: creatine kinase myocardial band, hs-TnI: high-sensitivity cardiac troponin I, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, NLR: neutrophil lymphocyte ratio, CPR: C-reactive protein, TIMI: thrombolysis in myocardial infarction, EF: ejection fraction, RWMA: regional wall motion abnormalities, *: statistically significant as p value <0.05.*

Table (3): Multivariate regression analysis for prediction of Incidence of MACE

	OR	95% CI	P value
Age (years)	0.944	0.7911 to 1.1265	0.523
Sex	0.4496	0.0433 to 4.6707	0.503
BMI (Kg/m^2)	0.9686	0.7017 to 1.3369	0.846
Smoking	0.9793	0.1819 to 5.2713	0.981
Hypertension	0.8285	0.1138 to 6.0335	0.853
Dyslipidemia	1.3264	0.2217 to 7.9340	0.757
Angina	0.9166	0.7314 to 1.1486	0.449
CKD	0.8978	0.7458 to 1.0808	0.254
PAD	0.7500	0.0386 to 14.5766	0.849
COPD	2.5542	0.2220 to 29.3921	0.452
Family history of CAD	2.5542	0.2220 to 29.3921	0.452
Previous PCI	0.7396	0.0770 to 7.1069	0.794
Prior CABG	0.2333	0.0180 to 3.0264	0.265
Prior MI	0.9312	0.7847 to 1.1052	0.419
AF	0.9383	0.7898 to 1.1148	0.469
HR (beats/min)	1.2016	0.9860 to 1.4644	0.069
SBP (mmHg)	1.0465	0.9719 to 1.1269	0.229
DBP (mmHg)	1.1206	0.9952 to 1.2618	0.060
INR	0.0052	0.0000 to 33.7723	0.240
PT (sec)	1.3825	0.5146 to 3.7144	0.521
PTT (sec)	1.0287	0.7424 to 1.4254	0.865
Total cholesterol (mg/dL)	1.0123	0.9713 to 1.0551	0.561

Triglycerides (mg/dL)	0.9646	0.8847 to 1.0516	0.413
HDL (mg/dL)	1.1629	0.9269 to 1.4591	0.192
LDL (mg/dL)	1.1381	0.9331 to 1.3881	0.202
CK-MB (U/L)	0.9751	0.9493 to 1.0017	0.066
hs-TnI peak (ng/L)	1.0003	0.9999 to 1.0006	0.102
Hb after 24 hr (g/dL)	1.2715	0.3390 to 4.7683	0.722
PLT after 24 hr (*10^9/L)	0.9851	0.9539 to 1.0173	0.359
WBCs after 24 hr (*10^9/L)	0.6303	0.2622 to 1.5152	0.302
Lymphocytes after 24 hr (*10^9/L)	0.1155	0.0074 to 1.8073	0.124
Neutrophil after 24 hr (*10^9/L)	1.9089	0.5435 to 6.7042	0.313
NLR after 24 hr	1.0002	0.9998 to 1.0007	0.313
HbA1c after 24 hr (%)	0.3383	0.0621 to 1.8442	0.210
CRP after 24 hr (mg/dL)	1.3776	0.6836 to 2.7760	0.370
S. creatinine after 24 hr (mg/dL)	2.1556	1.0310 to 4.5069	0.014*
TIMI flow after PCI	0.3545	0.0914 to 1.3759	0.210
Affected vessel	1.5404	0.2295 to 10.3388	0.370
Killip Class	0.3658	0.0556 to 2.4059	0.134
GRACE Score	1.0286	0.9796 to 1.0799	0.657
Myocardial blush grades	1.8309	0.5048 to 6.6412	0.295
EF on discharge (%)	0.8513	0.6064 to 1.1950	0.352
ST resolution on discharge	2.159	0.2325 to 20.0479	0.498
RWMA on discharge	0.9923	0.1239 to 7.9465	0.994
Mitral regurgitation on discharge	12.0000	1.8908 to 76.1582	0.008*
Hospital stay (days)	2.1796	0.9084 to 5.2295	0.081
Complete revascularization	0.0672	0.0099 to 0.4549	0.006*
SGLT2-I	0.0769	0.0080 to 0.7355	0.026*

*OR: odds ratio, CI: confidence interval, BMI: body mass index, CKD: chronic kidney disease, PAD: peripheral artery disease, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, MI: myocardial infarction, AF: atrial fibrillation, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, INR: international normalized ratio, PT: prothrombin time, PTT: partial thromboplastin time, HDL: high density lipoprotein, LDL: low density lipoprotein, CK-MB: creatine kinase myocardial band, hs-TnI: high-sensitivity cardiac troponin I, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, NLR: neutrophil lymphocyte ratio, CPR: C-reactive protein, TIMI: thrombolysis in myocardial infarction, EF: ejection fraction, RWMA: regional wall motion abnormalities, *: statistically significant as p value <0.05.*

Table (4): Multivariate regression analysis for prediction of Incidence of HF hospitalization

	OR	95% CI	P value
Age (years)	0.9030	0.7446 to 1.0951	0.300
Sex	0.5865	0.0545 to 6.3146	0.659
BMI (Kg/m^2)	1.0485	0.7462 to 1.4733	0.784
Smoking	0.6026	0.0922 to 3.9376	0.5969
Hypertension	0.3012	0.0260 to 3.4886	0.599
Dyslipidemia	2.3529	0.3616 to 15.3082	0.596
Angina	0.2050	0.0212 to 1.9775	0.170
CKD	0.7435	0.0480 to 11.5126	0.832
PAD	0.6693	0.0856 to 5.2354	0.702
COPD	0.8837	0.7039 to 1.1096	0.287
Family history of CAD	0.5426	0.0492 to 5.9858	0.617
Previous PCI	2.0792	0.1278 to 33.8271	0.607
Prior CABG	0.5811	0.0350 to 9.6377	0.704
Prior MI	0.8926	0.7392 to 1.0779	0.237
AF	0.3754	0.0152 to 9.2609	0.549
HR (beats/min)	1.1808	0.9976 to 1.3975	0.053
SBP (mmHg)	0.9709	0.9016 to 1.0455	0.435
DBP (mmHg)	1.0651	0.9403 to 1.2065	0.321
INR	0.7504	0.3181 to 1.7699	0.866
PT (sec)	0.8075	0.3091 to 2.1093	0.663

PTT (sec)	1.1526	0.8057 to 1.6490	0.437
Total cholesterol (mg/dL)	1.1814	0.9564 to 1.4594	0.122
Triglycerides (mg/dL)	0.7066	0.4503 to 1.1088	0.131
HDL (mg/dL)	5.63	0.8067 to 39.2943	0.081
LDL (mg/dL)	1.4594	0.9259 to 2.3002	0.103
CK-MB (U/L)	0.9006	0.7963 to 1.0184	0.095
hs-TnI peak (ng/L)	1.0047	0.9995 to 1.0099	0.079
Hb after 24 hr (g/dL)	1.212	0.1507 to 9.7491	0.857
PLT after 24 hr ($*10^9$/L)	1.020	0.9621 to 1.0818	0.504
WBCs after 24 hr ($*10^9$/L)	0.279	0.0537 to 1.4538	0.130
Lymphocytes after 24 hr ($*10^9$/L)	0.5177	0.1001 to 2.6763	0.283
Neutrophil after 24 hr ($*10^9$/L)	6.441	0.0581 to 713.957	0.438
NLR after 24 hr	0.008	0.0000 to 20.1730	0.225
HbA1c after 24 hr (%)	0.0073	0.0000 to 1.0813	0.054
CRP after 24 hr (mg/dL)	2.5606	0.7401 to 8.8590	0.138
S. creatinine after 24 hr (mg/dL)	6.441	0.0581 to 713.957	0.296
TIMI flow after PCI	0.4947	0.1719 to 1.4235	0.192
Affected vessel	0.5203	0.1477 to 1.8325	0.309
Killip Class	0.6771	0.1974 to 2.3223	0.535
GRACE Score	0.9909	0.9552 to 1.0280	0.626
Myocardial blush grades	0.715	0.5061 to 1.0101	0.057
EF on discharge (%)	1.4966	0.1868 to 11.9900	0.704
ST resolution on discharge	2.822	0.2637 to 30.2020	0.391
RWMA on discharge	0.7134	0.3311 to 1.5371	0.389
Mitral regurgitation on discharge	1.0056	0.9691 to 1.0436	0.766
Hospital stay (days)	0.5499	0.1629 to 1.8559	0.335
Complete revascularization	0.0420	0.0041 to 0.4278	0.007*
SGLT2-I	0.2654	0.0204 to 3.4575	0.029*

*OR: odds ratio, CI: confidence interval, BMI: body mass index, CKD: chronic kidney disease, PAD: peripheral artery disease, COPD: chronic obstructive pulmonary disease, CAD: coronary artery disease, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, MI: myocardial infarction, AF: atrial fibrillation, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, INR: international normalized ratio, PT: prothrombin time, PTT: partial thromboplastin time, HDL: high density lipoprotein, LDL: low density lipoprotein, CK-MB: creatine kinase myocardial band, hs-TnI: high-sensitivity cardiac troponin I, Hb: hemoglobin, PLT: platelets, WBCs: white blood cells, NLR: neutrophil lymphocyte ratio, CPR: C-reactive protein, TIMI: thrombolysis in myocardial infarction, EF: ejection fraction, RWMA: regional wall motion abnormalities, *: statistically significant as p value <0.05.*

DISCUSSION:

Previous studies have highlighted the role of SGLT2I in cardioprotection, and these studies need further assessment**.** Therefore, our study provides that the long-term treatment with SGLT2I has cardioprotective effect in STEMI diabetic patients undergoing PPCI.

Results of our study showed that SGLT2 inhibitor therapy started at least 6 months prior to the acute coronary event, gives adequate time for metabolic and hemodynamic benefits that could underlie the observed cardioprotective effects.

The cardioprotective effect of SGLT-2I is likely associated with its ability to improve myocardial energy metabolism. SGLT-2I can increase the utilization of glucose and fatty acids by myocardial cells, shifting the myocardial fuel from glucose to ketone bodies. This transformation increases the (adenosine triphosphate) ATP content in myocardial cells and improves cardiac remodeling. Also, SGLT-2I can prevent early myocardial injury in diabetes and mitigate the progression to HF by modulating the JunD/PPAR-γ pathway.

Regarding cardiac biomarkers, hs-TnI levels (I hs-TnI, II hs-TnI, III hs-TnI and hs-TnI peak) were significantly higher in non SGLT2I group compared to SGLT2I group (P<0.05), with no significant difference between both groups regarding CK-MB.

This can be attributed to the effect of SGLT 2I on infarct size and limitation of progression of ischemia. Previous studies have demonstrated that in the early stage of AMI, SGLT2 inhibitor use reduces the myocardial infarct size through activation of signal transducer and activator of transcription 3 and downregulation of inflammatory responses in the infarcted myocardium[(12)]. In addition, in diabetic mice, SGLT2 inhibitors reduce oxidative stress by decreasing the production of reactive oxygen species and the activity of nicotinamide- adenine dinucleotide phosphate[(13)]. Furthermore, SGLT2 inhibitors also have been shown to reduce oxidative stress through increasing endothelial nitric oxide synthase and nitric oxide formation in porcine endothelial cells [(14)].

The long-term outcomes, including all-cause death, MACE and HF hospitalization were significantly higher in non SGLT2I group compared to SGLT2I group (P<0.05), with no significant difference between both groups regarding other outcome (Re-AMI, Re-PCI, ICD and complete revascularization).

Interestingly, **Chen et al.[(15)]** performed a study on 232 hospitalized patients with acute coronary syndrome and type 2 diabetes mellitus to study the cardio vascular protective effect of SGLT2I on patients with ACS and T2DM. This study showed that early initiation of SGLT-2i can reduce rehospitalization for HF and improve angina symptom in patients with ACS and T2DM. These findings of study suggest that the cardiovascular protective effects of SGLT-2i may extend to patients with ACS and T2DM.[(15)].

In our study, the demonstrated cardioprotective benefits of SGLT2 inhibitors in diabetic patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention came in contrast with findings from another study by **Chen et al. [(15)]** where early initiation of SGLT2 inhibitors (1-5 days before acute coronary syndrome) did not significantly impact the duration of hospital stays or reduce the incidence of acute heart failure during hospitalization[(15)]. This discrepancy can be attributed to the timing of SGLT2 inhibitor initiation.

The Late initiation, as in the referenced study, may not provide sufficient time for these protective mechanisms to take effect, underscoring the importance of longer-term SGLT2 inhibitor therapy in patients with type 2 diabetes mellitus to potentially enhance cardiovascular outcomes. This highlights the need for further research into the optimal timing and duration of SGLT2 inhibitor therapy in this high-risk patient population.

Our findings suggest a robust cardioprotective effect of SGLT2Is in diabetic patients undergoing primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI). This finding aligns with the growing body of evidence suggesting that SGLT2Is extend beyond glucose lowering to confer substantial cardiovascular benefits. Mechanistically, SGLT2Is are thought to improve cardiac

energetics by shifting myocardial metabolism from glucose utilization to ketone bodies and free fatty acids, thereby increasing myocardial efficiency and reducing oxidative stress. Additionally, the reduction in arterial stiffness, improvement in endothelial function, and decrease in ventricular loading due to diuresis and natriuresis may further contribute to the observed outcomes. The significant delay in all-cause mortality emphasizes the potential of SGLT2Is as a pivotal therapeutic option not only for glycemic control but also for the improvement of long-term cardiovascular outcomes in diabetic patients with acute coronary syndromes[(15)].

This can be attributed to the fact that patients with diabetes exhibit a significant upregulation of SGLT-2 in the endothelial cells of carotid artery plaques. This was associated with concomitantly higher levels of inflammatory reactions and thinning of the fibrous caps. Drugs that work on the SGLT-2 system, such as SGLT-2i, can exert anti-inflammatory effects, increase the minimum fibrous cap thickness, and reduce lipid deposits, thereby contributing to a more stable atherosclerotic coronary plaque[**(15)**].

In line with our findings, **Chang et al.,[(16)]** conducted a study to evaluate the association of sodium-glucose cotransporter 2 (SGLT2) inhibitor use with cardiovascular and renal outcomes in type 2 diabetes mellitus patients with stabilized acute myocardial infarction. A total of 1,268 patients admitted to the Coronary Care Unit due to AMI were retrospectively screened. Patients taking SGLT2 inhibitors before or during the AMI hospitalization were assigned as group 1while Patients who never received SGLT2 inhibitors were assigned as group 2 **[(16)]**.. They reported that during a follow-up period that averaged 23.5 ± 15.7 months, it was observed that 3 (4.5%) patients from SGLT2I group and 22 (16.7%) patients from non SGLT2I group were hospitalized due to acute coronary syndrome (ACS). Furthermore, sudden cardiac death occurred in 1 (1.5%) patient in SGLT2I group and 7 (5.3%) patients in non SGLT2I group. This indicates that non SGLT2I group experienced a higher rate of adverse cardiovascular events. Kaplan–Meier survival curves were used to analyze the survival outcomes further, showing that patients in SGLT2I group had a longer survival outcomes more than to those in non SGLT2I group. This evidence suggests that patients treated with SGLT2 inhibitors after an acute myocardial infarction (AMI) have a reduced risk of adverse cardiovascular outcomes compared to those not receiving this medication class[**(16)**].

The multivariate regression analysis revealed that hs-TnI peak, serum creatinine after 24 hr., mitral regurgitation on discharge, and complete revascularization were the only significant predictors of cardiovascular death.

The analysis quantitatively underscores the impact of each factor, with the peak high-sensitivity troponin I (hs-TnI) presenting a modest increase in the risk of cardiovascular death (OR: 1.0006, p=0.039), suggesting that even slight elevations in hs-TnI peak levels are associated with a higher risk. Conversely, complete revascularization emerges as a strong protective factor, reducing the odds of cardiovascular death significantly (OR: 0.0794, p=0.043), indicating a nearly 92% reduction in risk when complete revascularization is achieved.

The substantial increase in risk with serum creatinine levels after 24 hours (OR: 3.3116, p=0.024) points to the critical role of renal function post-PCI in patient outcomes, with higher creatinine levels signaling a more than threefold increase in the risk of cardiovascular death. Mitral regurgitation on discharge dramatically elevates the risk (OR: 12.6000, p=0.027), suggesting that patients with persistent mitral regurgitation post-PCI are at a markedly higher risk of cardiovascular mortality, possibly due to ongoing hemodynamic stress and left ventricular dysfunction.

Regarding the in hospital outcome, cardiovascular death was significantly higher in non SGLT2I group compared to SGLT2I group (P= 0.031), with no significant difference between both groups regarding other Inhospital outcome (Arrhythmia, Re-AMI, Re-PCI, LABP, CI-AKI and hospital stay).

This finding suggests that beyond the individual predictors of peak high-sensitivity troponin I (hs-TnI), post-24-hour serum creatinine levels, mitral regurgitation on discharge, and complete revascularization, the use of SGLT2 inhibitors itself plays a protective role against cardiovascular death in this patient population.

This specificity indicates that SGLT2 inhibitors have a role in reducing cardiovascular death is both clinically significant and potentially mediated through mechanisms that warrant further investigation.

The multivariate regression analysis revealed that serum creatinine after 24 hr., mitral regurgitation on discharge, complete revascularization and receiving SGLT2-I were the only significant predictors of MACE.

Firstly, an increase in serum creatinine levels 24 hours post-procedure significantly predicts MACE, with an odds ratio (OR) of 2.1556 (p=0.014). This implies that patients experiencing a rise in creatinine levels are over twice as likely to encounter MACE, suggesting that acute kidney injury or worsening renal function post-percutaneous coronary intervention (PCI) is a critical marker of adverse outcomes, likely reflecting the broader impact of renal impairment on cardiovascular health.

Mitral regurgitation on discharge stands out with an OR of 12.0000 (p=0.008), indicating that patients with this condition are twelve times more likely to experience MACE. This finding underscores the severe prognostic implications of valvular dysfunction post-PCI, potentially due to its association with left ventricular dysfunction, increased cardiac workload, and adverse remodeling.

Conversely, complete revascularization emerges as a robust protective factor against MACE, with an OR of 0.0672 (p=0.006). This translates to a striking 93% reduction in the risk of MACE, emphasizing the paramount importance of achieving full revascularization to ensure optimal blood flow and myocardial perfusion, thereby minimizing the risk of recurrent ischemic events.

Furthermore, receiving SGLT2 inhibitors is associated with a substantial reduction in the risk of MACE, evidenced by an OR of 0.0769 (p=0.026). This indicates that patients on SGLT2 inhibitors are approximately 92% less likely to suffer from MACE, highlighting the potent

cardioprotective effects of these medications.

The underlying mechanisms could include improved glycemic control, diuretic effects leading to reduced preload and afterload, and direct beneficial effects on cardiac cells and vascular function.

Confirming our results, **Chang et al.**[16] found that among diabetic patients with stabilized AMI, SGLT2 inhibitor use, and a lower baseline renal function were both independent predictors of adverse cardiovascular outcomes[16].

Similarly, **Chen et al.** [15] in their study found that rehospitalization for ACS or HF was lower in the SGLT-2I group than in the non-SGLT-2I group.

The multivariate regression analysis revealed that complete revascularization and receiving SGLT2-I were the only significant predictors for protection from HF hospitalization.

Complete revascularization is highlighted as a paramount protective factor, with an odds ratio (OR) of 0.0420 (p=0.007). This translates to a dramatic 95.8% reduction in the risk of HF hospitalization, emphasizing the critical importance of restoring optimal blood flow to the entire myocardium. Complete revascularization ensures that all significant blockages are addressed, thereby potentially preventing areas of the heart muscle from suffering ischemia that could lead to heart failure.

Receiving SGLT2 inhibitors also significantly reduces the risk of HF hospitalization, with an OR of 0.2654 (p=0.029). This indicates that patients on SGLT2 inhibitors have a 73.5% lower risk of being hospitalized for heart failure compared to those not receiving these medications. The cardioprotective effects of SGLT2 inhibitors could be attributed to several mechanisms, including improved glycemic control, reduction of blood pressure, weight loss, diuretic effects that alleviate cardiac preload and afterload, and direct beneficial effects on cardiac and vascular tissues[16].

Conclusion:

Our findings are hypothesis generating and provide new insights into the cardioprotective role of SGLT2-I in the setting of CAD pointing out the potential clinical impact of these drugs in improving cardiovascular outcomes after AMI.

Recommendations

We recommended the use of SGLT2-I for T2DM patients especially those at high risk of AMI and its complications.

Longer follow-up periods are essential to assess the long-term efficacy and safety of SGLT2 inhibitors, including their impact on mortality, recurrent myocardial infarction, and heart failure hospitalizations.

Further studies should investigate the underlying mechanisms through which SGLT2 inhibitors exert their cardioprotective effects, especially in the context of ischemia-reperfusion injury and myocardial recovery post-PCI.

Well-designed randomized controlled trials (RCTs) are needed to establish a causal relationship between SGLT2 inhibitor use and improved cardiovascular outcomes in diabetic STEMI patients. Randomization would help minimize selection bias and confounding variables.

Ethical Consideration:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee (IRB#10447-15-2-2023). Written informed consent of all the

participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Conflict of interest:

The authors declare no conflict of interest.

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