ORIGINAL ARTICLE

Potential Cardio-protective Role of Dapagliflozin in Post Myocardial Infarction Patients.

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ABSTRACT

Keywords: STEMI, GLS, PCI, Dapagliflozin.

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Background: Type II diabetes mellitus and ischemic heart disease (IHD) commonly coexist and can be dangerous. The sodium glucose cotransporter-II inhibitors (SGLT2i) are a new class of diabetes treatment that reduces IHD hospitalization and cardiovascular (CV) mortality. (SGLT2i) obviously results in a significant decrease in IHD risk; however, the mechanism of these effects is not clear. **Aim of study**: This study aimed to evaluate the possible treatment effect of dapagliflozin on diabetic patients with anterior (STEMI) treated by primary percutaneous coronary intervention (PCI). **Methodology:** A randomized control trial enrolled 60 type II diabetic patients with anterior (STEMI) treated by primary (PCI) from both genders and their ages above 18 years old. The patients were categorized to two groups, Group (A) included 30 patients did not take dapagliflozin but they took the ordinary anti-ischemic & anti heart failure drugs also anti-diabetic medications. Group (B) enrolled 30 patients received dapagliflozin and they treated by ordinary anti-ischemic, anti-heart failure drug therapy and anti-diabetic medications**. Results:** In group (B) treated by dapagliflozin there was statistically highly significant improvement in LV systolic function by GLS, LVEF and LVEDD and LVESD in comparison with group (A) (P value<0.0001). c**onclusion:** Dapagliflozin played a substantial role in cardiac remodeling, including decrease the LVEDD, LVSD as well as improvement in left ventricular systolic function.

INTRODUCTION.

Type II diabetes is associated with a high risk of cardiovascular (CV) disease and cardiovascular (CV) mortality (**Sarwar and his team. (2010)**. The development of heart failure (HF) in patients with diabetes can occur independently of atherosclerotic (CV) disease and the presence of type II diabetes is associated with a poorer prognosis in patients with heart failure (HF) **Khan and his co-workers., (2014)**.

Although improved glycemic control in patients with type II diabetes minimize the risk of microvascular complications, evidence that glucose lowering agents reduce cardiovascular (CV) events or staying in hospital for heart failure (HF) is sparse **Holman and his team., (2014).**

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a new class of antidiabetic agents that have received a lot of attention because of their positive impacts on cardiovascular problems, especially in the context of heart failure (HF).

A study of the dapagliflozin in diseased humans with Heart Failure trial (DAPA-HF), dapagliflozin was compared against standard of care in 4744 patients with established heart failure and found a striking 30% decrease in heart failure hospitalization, 18% reduction in cardiovascular death and significant improvements in heart failure symptom burden **McMurrayand his team., (2019).**

In our study we aimed to evaluate the possible potential cardioprotective role of dapagliflozin on diabetic patients with type II DM, anterior S-T segment elevation myocardial infarction (STEMI) and treated by primary percutaneous coronary intervention (PCI).

PATIENT AND METHODS:

A randomized control study was conducted from the period of January 2021 to January 2022 at cardiology department in Aswan University Hospitals, on 60 patients who were type II diabetes mellitus presented with anterior STEMI and underwent primary PCI to evaluate the effect of dapagliflozin drug(SGLT2 Inhibitor)on 30 cases of all patients (**group A**) before and after 3 months treatment then compare them with the other 30 patients (**group B**) who had the same criteria of diseases but did not receive dapagliflozin ;instead they took other ordinary anti-ischemic drugs and anti-diabetic drugs. Patients not treated by primary percutaneous coronary intervention, not diabetic, or Type I diabetes mellitus and Cirrhotic patients or those who had (eGFR) less than 30mls/min were kept far away from the study.

Then all the patients were collected for our study were subjected to the following: -

I-Proper history taking, include the following:

-General demographic history.

- Onset of ischemic pain at presentation inside the hospital

-Duration of ischemic heart disease.

- Presence of another co morbid disease

II-Clinical Examination:

(A) **Cardiac examination**: including the following:

1-**Electrocardiography (ECG):** Twelve leads resting ECG were done for all patients to detect ischemic changes, rate and rhythm. Indicating all patients had normal sinus rhythm with anterior S-T segment elevation myocardial infarction (STEMI) in all leads and inverted T-wave also.

2-**Echocardiography (ECHO):** ECG trace transthoracic echocardiography examination was performed using **(VIVID 95-TRANS THORACIS**) machine. It was done at left lateral position, while patient holding breath after expiration and m-mode and 2D pictures were acquired to evaluate regional wall motion abnormalities, (LVEF), (LVESD) and (LVEDD). Speckle tracking was done also with the same machine to evaluate GLS.

3- **Coronary angiography and primary percutaneous coronary intervention (PCI)**.

(B) Laboratory investigations: including the following

1- Liver enzyme function test: in the form of two enzymes, Alanine amino transferase (ALT) and Aspartate aminotransferase (AST) enzymes.

2- Evaluation of kidney function test in the form of Serum creatinine level and Blood urea level.
3- Evaluation of glycosylated hemoglobin (HbA1C.

4- Evaluation of blood glucose level test.

5- Evaluation of total lipid profile.

Ethical consideration

The study was approved by the Institutional Ethics Committee Faculty of Medicine, Aswan University. Moreover, a written consent was given by the surrogate decision maker.

Statistical analysis

The data were analyzed by SPSS (statistical package for social science) version 26.0 on IBM compatible computer (SPSS Inc., Chicago, IL, USA). The qualitative data were described as number and percentage "n (%)" and analyzed by using Chi square test and Fisher's exact test. Quantitative data were tested for normality using Shapiro-Wilks test, assuming normality at P-value > 0.05. Quantitative data were described as mean, standard deviation and range, using Student's"t" test, if normally distributed, or Mann-Whitney U-test, and Kruskal-Walli's test, if not normally distributed. The accepted level of significance in this thesis was started at 0.05(p-Value <0.05 was considered significant). P-Value: level of significance: p>0.05: Non-Significant (NS) p<0.05: Significant(S) p<0.01: Highly Significant (HS)

RESULTS:

The study consisted of 60 adult type II diabetic patients presented with anterior STEMI and underwent primary PCI and the patients categorized into two groups, **group A**, had 30 Patients that received dapagliflozin plus anti-ischemic and other anti-diabetic drugs and **group B,** included 30 cases that received anti-diabetic and anti-ischemic without dapagliflozin. There was no significant difference between the two groups as regard age, gender or risk factors, (P value > 0.05). The age of the studied group ranged from 32 to 76 years with mean ±SD of 54.87±10.93. The studied groups included (15) females (25%) and (45) males (75%). **(Table1).** There was no significant difference between both groups as regard onset of pain at time of admission, most of the patients presented within the first 6hs (P-value was < 0.05), (**Figure 1).** There was no significant difference between both groups as regard echocardiographic data at baseline, including LVEF, GLS, LVEDD and LVESD (P value >0.05) but after 3ms of PCI and treatment with dapagliflozin we noticed a significant difference between both groups as regard echocardiographic data, patients in (group A) had a significant improvement in LVEF, GLS, LVEDD and LVESD than patients in (group B) that not receiving dapagliflozin (P value <0.01). (**Table 2)**. As regard laboratory findings, there were no significant differences between both groups of the study as regard liver functions, renal functions and HBAIC but after 3ms of follow up we noticed a significant reduction of the level of ALT and AST in group A than group B (p value <0.01), also there was a significant improvement in the level of HbAIc, LDL-c and TG in group A than group B (p value <0.01). **(Table 3).**

DISCUSSION.

Cardiovascular (CV) benefits of SGLT2 inhibitors in Type II DM have been reported in three large outcome studies investigating the effects of empagliflozin (**Zinman and his co-workers.,2016)**, canagliflozin (**Neal and his co-workers., (2017)** and dapagliflozin (**Wiviottand his co-workers., (2019)**. On a study of the dapagliflozin in Patients with Heart Failure trial (DAPA-HF), dapagliflozin was compared against standard of care in 4744 patients with established heart failure and found a striking 30% reduction in heart failure hospitalization, 18% reduction in cardiovascular death and significant improvements in heart failure symptom burden (**McMurrayand his team., (2019).**

In the present study we aimed to evaluate the possible potential cardioprotective role of dapagliflozin on diabetic patients with type II DM, anterior (STEMI) and treated by primary (PCI). For that the current study enrolled (60) Patients in number. The patients were divided into two groups; group A included 30 patients received dapagliflozin beside they took ordinary anti-ischemic, anti-heart-failure drug therapy and antidiabetic medications and group B enrolled 30 patients not treated with dapagliflozin, instead they took other traditional anti-ischemic, anti-heart failure drugs and anti-diabetic medications and. The mean age of the studied group ranged between 54.87±10.93 years and there was no significant difference between both groups as regard demographic data. (**P value >0.05**). Table 1

We assessed many laboratory parameters and found that in the group treated by dapagliflozin there was statistically highly significant improvement regarding liver function tests, glucose related tests and lipid profile in compare to baseline and group(B), but we did not report significant difference between both groups (group A and B) regarding renal function tests. Table 3. In harmony with **(Tobita and the team., (2017**) study aimed to assess the efficacy and safety profile of dapagliflozin for the treatment of non-alcoholic steatohepatitis (NASH)-associated with Type II DM, as they found that administration of dapagliflozin for 24 weeks was associated with significant improvement in liver tests (serum concentrations of aspartate aminotransferase (AST), alanine amino transferase(ALT), ferritin, and type IV collagen 7S) as they significantly improved during the study. Insulin concentrations decreased (P-value < 0.01 by Week 24) in combination with significant reductions in fasting plasma glucose (P-value < 0.01) and glycated hemoglobin (HBA1C) (P-value < 0.01) levels. In the same line **(Hu and his Co-workers., (2020) study** found that the alanine aminotransferase (ALT) in patients with hyperglycemia and non-alcoholic fatty liver disease after 12 weeks of treatment with dapagliflozin were significantly better than before treatment with statistically significant differences. They also found in the group treated with dapagliflozin, that triglyceride levels after treatment were significantly lower than before treatment, while other blood lipid profile as total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) did not change before and after treatment.

Dapagliflozin can increase insulin sensitivity and improve insulin resistance by reducing blood sugar, improving lipid metabolism, reducing weight and inflammation. There are also studies as Nakano and the co-workers., (2015) emphasizing that SGLT2 inhibitors have anti-oxidative stress effects and aid to improve insulin resistance.

In our study we assessed the potential role of dapagliflozin on the heart after follow up three months of receiving that medication and we evaluated many diameters related to ventricular structure and function as (LVEDD), (LVESD), (LVGLS) and (LVEF) then we found that; In group A2 (treated by dapagliflozin after 3 months treatment), there was highly statistically significant improvement in all parameters including in (LVEF) and improvement in (GLS) that was higher post treatment and for (LVEDD) and (LVESD) that was lower in post treatment group (P-value<0.0001).

In differ with the current study findings, Eickhoff **and his team. (2020)** aimed to examine the effect of the dapagliflozin on cardiac function in people with Type II diabetes mellitus and albuminuria by double-blind study. They randomized study of 12 weeks treatment with dapagliflozin 10 mg against placebo. They reported that the mean left ventricular ejection fraction (LVEF) was 55.4% after placebo and 54.3% after dapagliflozin (p-value = 0.15), global longitudinal strain (GLS) (−16.1) vs. (−15.9) (p-value = 0.64) and tissue doppler velocity was 10.0 vs. 10.6 (p-value = 0.05). The composite score showed diastolic function improvement of 19.8% (pvalue = 0.021). They concluded that dapagliflozin may have minor effects on diastolic function in people with Type II diabetes mellitus, albuminuria and preserved left ventricular function (LVEF).

In harmony with our findings **a recent meta-analysis (Zhang et al, 2021a)** enrolled a number of 13 randomized-clinical trials containing 1251 patients were analyzed. They illustrated that

(SGLT2I) significantly improved (LV) ejection fraction (P-value = 0.03), left ventricular mass (P-value = 0.002), left ventricular mass index (P-value = 0.02), left ventricular end-systolic volume (P-value = 0.03), left ventricular end-systolic volume index (P-value = 0.02), and E-wave deceleration time (P-value = 0.02) in all population. Subgroup analyses indicated that the favorable effects of SGLT2i on left ventricular remodeling were only significant in heart failure patients, especially heart failure with reduced ejection fraction (HFrEF), regardless of glycemic state.

The discrepancy between studies may contribute to the differ in inclusion criteria, sample size and study design included assessment tools and follow up period. The underlying mechanisms of cardiac remodeling are complicated that included molecular series inside cells and the interstitium that act in concert to change the shape, size and mass of the heart following cardiac injury. When some cardiac injuries occur, such as pressure and volume overload, ischemia/reperfusion, myocardial infarction, neuroendocrine activation, complex remodeling cascades such as inflammation, oxidative stress, metabolic abnormalities, mitochondrial dysfunction, autophagy, as well as programmed cell death are triggered resulting in myocyte loss, cardiac hypertrophy and interstitial fibrosis (**Schirone and his co-workers., (2017); Gronda and his co-workers., (2019).** Furthermore, epigenetic changes such as DNA methylation, ATP-dependent chromatin remodeling, histone modifications and non-coding RNA-related mechanisms are thought to be important contributors to antagonize cardiac remodeling (**Hamdani and his team., (2021)**. Remodeling is associated with worse prognosis whereas its reversal is typically accompanied by improved symptoms, better quality of life and lower risk of hospitalization or death (Aimo **and his team., (2019).** Several potential mechanisms have been proposed in previous experimental and clinical studies. To begin, SGLT2 inhibitors have been shown to decrease cardiac preload due to the diuretic and natriuretic effect which could mitigate left ventricular (LV) stretch and wall stress leading to a decrease in left ventricular (LV) "volume" as observed in the current study. **Second,** SGLT2 inhibitors have been linked to a decrease in cardiac afterload by lowering arterial rigidity and blood pressure (**Lee and his co-workers., (2021**). **Third**, SGLT2 inhibitors may minimize cardiac inflammation by inhibiting the activation of the inflammatory of some nucleotide binding domain-like receptor protein 3 (NLRP3). **Fourth**, new research suggests that SGLT2 inhibitors have a cardioprotective effect against ischemia/reperfusion injury possibly by reducing calmodulin kinase II activity (**Lopaschuk G.D and Verma S., 2020). Fifth**, SGLT2 inhibitors may have downstream epigenetic effects in myocardial cells to improve cardiac remodeling (**Napoli and his co-workers.**, ***(2021).*** Furthermore, lots of additional mechanistic benefits of SGLT2 inhibitors on the heart have been proposed which may also reveal the reversed cardiac remodeling such as decreased cardiac oxidative stress, improved myocardial energetics and prevention of the mammalian target of rapamycin pathway **(Lopaschuk G.D and Verma S., 2020)**.

CONCLUSION:

Dapagliflozin (Sodium-glucose cotransporter-2 inhibitors) played an essential role in cardiac remodeling, including decrease the ventricular mass including (LVEDD), (LVSD) as well as improvement in ventricular function by increasing (LVEF) function and GLS by speckle tracking.

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Table 1. Comparison of the personal data of the two studied groups (N =60)

N =60	**Group A (N =30)**	**Group B (N=30)**
(Age years) Mean ±SD	54.8±10.5	54.93±11.4
(Gender)		
Male	24 (80%)	21 (70%)
Female	6 (20%)	9 (30%)
(**Risk factors)**		
Smoking	20 (66.7%)	18 (60%)
Hypertension	12 (40%)	11 (36.7%)
Family history of IHD	8 (26.7%)	2 (6.7%)

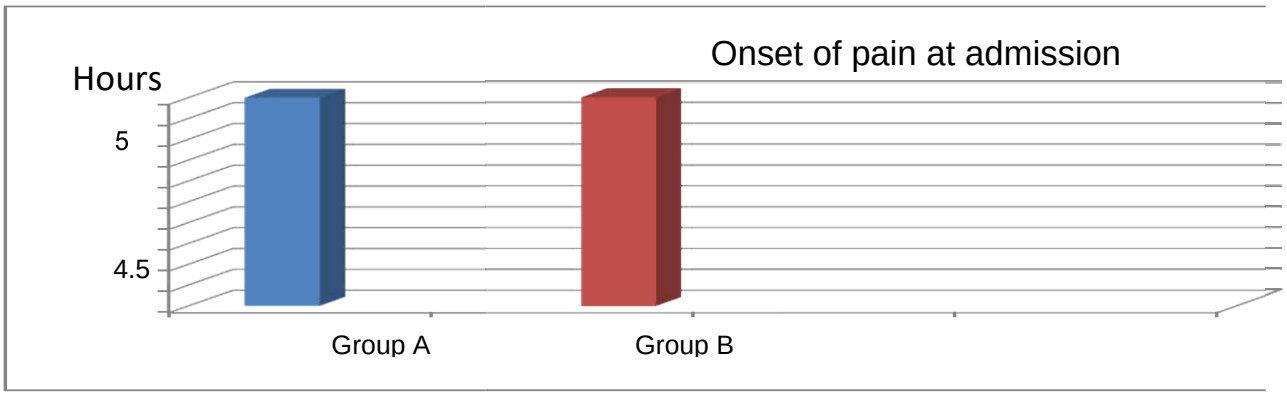

Figure (1): represents the Comparison between the two groups (Group A and Group B) as regarding the onset of pain at admission.

Table 2. Comparison between the studied groups (A and B) as regard echocardiographic parameters

Estimated parameters	Group A (n =30)		Group B (n =30)	
	GroupA1 Dapa-treated patients first seen	**GroupA2** Dapa -treated patients after 3 months follow up	**GroupB1** Non-Dapa treated patients, first seen	**GroupB2** Non-Dapa treated patients seen after 3 months follow up
LVEF (%)	42.57±3.93	50.03±4.71**	44.9±5.37	47.31±3.32*
LVEDD (cm)	6.26±0.63	5.12±0.77**	4.97±3.80	4.90±0.31*
LVESD (cm)	5±0.71	4.01±0.89**	4.59±0.97	3.87±0.61*
(GLS)	-8.83±0.62	-12.25±0.93**	-9.11±0.68	-11.12±0.61*

P-value* (<0.05): comparison between group A1 and B1 (non-significant),
P-value** (<0.01) :(highly significant): comparison between group A2 and B2. **GLS**: global longitudinal strain, **LVEF**: left ventricular ejection fraction. **LVEDD**: left ventricular end diastolic diameter. **LVESD**: left ventricular end systolic diameter.

Table 3). Comparison of the two studied groups (A and B) as regard laboratory findings before and after treatment (n =60)

Groups of the patients	Group A		Group B	
Biochemical analysis of groups (n=60)	**Group A1 (n =30)**	**Group A2 (n =30)**	**Group B1 (n =30)**	**Group B2 (n =30)**
Liver function tests ALT(IU/L)	**62.85**±5.51	26.27±7.74**	65.41±7.22	60.21±6.40*
AST(IU/L)	**36.78**±8.41	25.57±8.98**	34.33±3.19	30.12±2.26*
Renal function tests Urea(mg/dl)	29.39±9.1	27.39±10.32	26.53±4.51	25.61±3.79
Creatinine (mg/dl)	0.94±0.28	0.97±0.15	0.89±0.23	0.90±0.28
Glucose related tests HbA1c (%)	8.48±2.63	6.17±0.82**	**7.22**±2.50	6.25±1.41*
RBS (mg/dl)	213.53±39.61	170.9±52.58**	218.6±32.11	199.13±44.12*
Lipid profile				

LDL-c (mg/dl)	123.63±33.51	78.06±24.45**	120.13±38.51	95.15±30.21*
Triglyceride(mg/dl)	158.27±36.73	118.23±29.32**	149.95±46.8	140.5±19.7*
HDL-c (mg/dl)	36.36±10.89	35.23±8.71	42.27±13.72	40.41±11.64
VLDL-c (mg/dl)	28.34±17.29	26.99±15.15	30.43±19.51	29.32±17.22
Total cholesterol(mg/dl)	178.44±34.22	83.23±21.41**	193.57±48.79	120.32±33.23*

P-value* (<0.05): comparison between group A1 and B1 (non-significant), **P-value**** (<0.01) :(highly significant): comparison between group A2 and B2

ALT: alanine transaminase AST; aspartate transaminase RBS: random blood sugar LDL-c: low density lipid cholesterol HDL-C: high density lipid cholesterol VLDL-c: very low-density lipid cholesterol