



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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**The Impact of Dapagliflozin on Cardiac LV
Systolic function in patients with ST
Elevation Myocardial Infarction undergoing
Primary Percutaneous Coronary
Intervention who developed Post MI LV
Dysfunction**

Thesis

*Submitted for Partial Fulfillment of Master's Degree in
Cardiology*

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List of Contents

Title	Page No.
List of Abbreviations.....	i
List of Tables	iii
List of Figures	iv
Introduction	1
Aim of the Work.....	4
Review of Literature	
ST-Elevation Myocardial Infarction (STEMI)	5
Dapagliflozin.....	15
Patients and Methods.....	21
Results	27
Discussion	37
Limitations.....	40
Summary	41
Conclusion.....	43
Recommendations	44
References	45
Arabic Summary	—

List of Abbreviations

Abb.	Full term
ACE-I.....	Angiotensin-converting enzyme inhibitors
ACS.....	Acute Coronary Syndrome
AHAs	Antihyperglycemic agents
ARNI.....	Angiotensin Receptor-Nepilysin Inhibitor
BP	Blood pressure
CAD	Coronary artery disease
CBC	Complete blood picture
CCU	Coronary care unit
CV	Cardiovascular
DM	Diabetes Mellitus
ECG	Electrocardiogram
eGFR.....	Estimated Glomerular Filtration Rate
ESRD	End stage renal disease
FH.....	Family history
FMF	Familial Mediterranean fever
FPG.....	Fasting plasma glucose
GFR	Glomerular filtration rate
GLS.....	Global Longitudinal Strain
HbA1c	Hemoglobin A1c
HF.....	Heart failure
HFrEF	HF with reduced ejection fraction
HTN.....	Hypertension
INR	International normalized ratio
LV	Left ventricular
LVEDV	Left ventricular end- diastolic volume
LVEF	Left ventricular ejection fraction

List of Abbreviations Cont...

Abb.	Full term
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MRA.....	Mineralocorticoid receptor antagonists
MVD	Multi-vessel disease
NYHA	New York Heart Association
OMT.....	Optimal medical therapy
PCI.....	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
PTD.....	Pain to door
QoL	Quality of life
RV	Right ventricular
SD	Standard deviation
SGLT2	Sodium-glucose cotransporter 2
SPSS	Statistical Package for the Social Science
STEMI	ST-Elevation Myocardial Infarction
T2D	Type 2 diabetes
TAPSE.....	Tricuspid annular plane systolic excursion
TCFA	Thin cap fibroatheroma
TIMI	Thrombolysis in myocardial infarction risk score
WHO.....	World Health Organization
WMSI.....	Wall motion score index

List of Tables

Table No.	Title	Page No.
Table (1):	ECG criteria for ST-elevation myocardial infarction	7
Table (2):	Descriptive table for demographic data, CAD risk factors and co-morbidities of all the studied patients.	27
Table (3):	Descriptive table for clinical presentation of all the studied patients.	29
Table (4):	Comparison between group A and group B among demographic data.....	30
Table (5):	Comparison between group A and group B among CAD risk factors and co-morbidities of the studied patients.	31
Table (6):	Comparison between group A and group B among PTD, ECG, TIMI flow, post-MI F of the studied patients.	33
Table (7):	Comparison between group A and group B among follow-up EF of the studied patients.....	34
Table (8):	Comparison between post-Mi EF and follow-up EF regarding diabetic patients in group A and group B.....	35
Table (9):	Comparison between post-Mi EF and follow-up EF regarding non diabetic patients in group A and group B.....	36

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Apical 4C View showing EF by Modified Simpson's method	25
Figure (2):	Descriptive for gender of the studied patients.....	28
Figure (3):	Descriptive for co-morbidities of the studied patients.....	28
Figure (4):	Descriptive for ECG of the studied patients.....	29
Figure (5):	Comparison between group A and group B among ECG results of the studied patients.	33
Figure (6):	Comparison between group A and group B among Follow-up EF results of the studied patients.....	34
Figure (7):	Comparison between follow-up EF regarding diabetic patients in group A and group B.	35

INTRODUCTION

Acute myocardial infarction is the most severe manifestation of coronary artery disease, which causes more than 2.4 million deaths in the USA, more than 4 million deaths in Europe and northern Asia, and more than a third of deaths in developed nations annually ^[1-2]. Primary PCI is the treatment of choice for acute coronary syndrome with STEMI ^[3].

Primary percutaneous coronary intervention (PPCI) has revolutionized the management and outcome of acute myocardial infarction (MI) ^[4,5]. It is the reperfusion strategy of choice throughout the developed world, with 90,000 procedures performed annually in the United States alone ^[6,7]. Contemporary PPCI in the United Kingdom is characterized by door-to-balloon times of < 60 min, radial access, second generation drug-eluting stents and tailored use of antiplatelet and antithrombotic agents ^[8,9]. The introduction of PPCI and adjunctive therapies have driven a reduction in inpatient mortality following acute MI from 20% in the late 1980s to approximately 5-7% in contemporary series ^[10,11].

Despite this success, coronary artery disease remains the commonest cause of heart failure (HF) ^[12]. HF after MI is the major driver of late morbidity, mortality and healthcare cost. Several factors, such as recurrent myocardial ischemia, infarct size, ventricular remodeling, stunned myocardium, mechanical complications, and hibernating myocardium influence the

appearance of left ventricular systolic dysfunction with or without clinical HF after MI ^[13–15].

Of note, the relevance of each factor responsible for HF after MI depends on the time to the establishment of cardiac dysfunction following coronary occlusion. Myocyte loss, hibernating myocardium, and ventricular remodeling are the principal causes of heart failure. Among these factors, ventricular remodeling is the most important ^[13].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a unique class of oral glucose-lowering agents that reduce glucose reabsorption in the renal proximal tubes, thereby enhancing urinary glucose excretion via an insulin-independent mechanism. Trials on empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program) and dapagliflozin (DECLARE-TIMI 58), have demonstrated that these agents can significantly reduce heart failure (HF) hospitalizations within months in patients with type 2 diabetes (T2D) at high cardiovascular (CV) risk ^[16–18]. In the DAPA-HF trial, dapagliflozin significantly reduced the incidence of worsening HF and CV mortality in patients with HF with reduced ejection fraction (HFrEF), with or without diabetes ^[19].

Therapies that prevent adverse LV remodeling are crucial to improve outcomes ^[20]. To date, no published studies have investigated the effect of SGLT2 inhibitors on LV systolic function in the early post-ACS period. Accordingly, the present

study aimed to investigate whether dapagliflozin, initiated at discharge, is associated with improvements in LV systolic function in patients with HF following an admission with STEMI compared to placebo, or not.

AIM OF THE WORK

The aim of this work is to study the impact of dapagliflozin on LV systolic function in patients with ST Elevation Myocardial Infarction undergoing primary percutaneous Coronary Intervention who developed post MI LV dysfunction regardless their diabetic status versus placebo.

Chapter 1

ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)

Myocardial infarction (MI) is a clinical entity involving myocardial ischemia that manifests with ECG changes and chest pain ^[21]. The current 2018 clinical definition of MI is based on the confirmation of the myocardial ischemic injury with abnormal cardiac biomarkers ^[22]. An acute ST-elevation myocardial infarction (STEMI) entails transmural myocardial ischemia that results in myocardial injury or necrosis ^[23].

Etiology

An ST-elevation myocardial infarction occurs from occlusion of one or more of the coronary arteries that supply the heart with blood. This abrupt disruption of blood flow is a result of an obstructing thrombus on top of plaque rupture, erosion, fissuring, or dissection of coronary arteries.

Dyslipidaemia, diabetes mellitus, hypertension, smoking, and a family history of coronary artery disease are the major risk factors for STEMI ^[24-25].

Epidemiology

In the United States, the estimated annual incidence of MI is 550,000 new and 200,000 recurrent patients. In 2013, a

fatal MI was diagnosed in 116,793 persons in the United States with 57% occurring in men and 43% in women. The average age of incidence of a first MI is 65.1 years for men and 72 years for women. The ST-elevation myocardial infarction represents 38% of acute coronary syndrome ^[26].

According to the latest WHO data published in 2018 Coronary Heart Disease Deaths in Egypt reached 163,171 or 29.38% of total deaths ^[27].

Pathophysiology

For an acute thrombotic coronary event to cause ST-segment elevation on a surface ECG, there should be a complete and persistent occlusion of blood flow in the culprit coronary vessel.

Sudden onset plaque rupture can occur on top of coronary atherosclerosis in the presence of high-risk thin cap fibroatheroma (TCFA) ^[28]. This results in changes in vascular endothelium resulting in a cascade of platelet stimulation including adhesion, activation, and aggregation resulting in thrombus formation ^[29].

Evaluation

Evaluation of patients with acute chest pain should begin with an electrocardiogram (ECG) and troponin level. The American College of Cardiology, American Heart Association,

European Society of Cardiology, and the World Heart Federation committee established the ECG criteria for ST-elevation myocardial infarction (STEMI) (Table 1) ^[22].

Table (1): ECG criteria for ST-elevation myocardial infarction ^[22].

▪ New ST-segment elevation at the J point in 2 contiguous leads with the cut-off point as greater than 0.1 mV in all leads other than V2 or V3
▪ In leads V2-V3 the cut-off point is greater than 0.2 mV in men older than 40 years old and greater than 0.25 in men younger than 40 years old, or greater than 0.15 mV in women
○ Patients with a pre-existing left bundle branch block can be further evaluated using Sugarbush's criteria ○ ST-segment elevation of 1 mm or more that is concordant with (in the same direction as) the QRS complex ○ ST-segment depression of 1 mm or more in lead V1, V2, or V3 ○ ST-segment elevation of 5 mm or more that is discordant with (in the opposite direction) the QRS complex

Treatment / Management

After making the diagnosis of acute ST-elevation myocardial infarction, intravenous access should be obtained, and cardiac monitoring started immediately. In presence of hypoxemia ($\text{Sao}_2 < 90\%$ or $\text{Pao}_2 < 60$ mm Hg) or at risk for hypoxemia oxygen therapy can help ^[30-31]. Patients should undergo percutaneous coronary intervention (PCI) within 60 minutes of presentation at a PCI-capable hospital or within 120 minutes if transfer to a PCI-capable hospital is required ^[32]. Fibrinolytic therapy should be initiated within 10 minutes of