- **Official title**: Effect of Empagliflozin 10 vs 25 mg on LV remodeling in diabetic patients with anterior STEMI with reduced LVEF who underwent primary PCI

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Protocol of a thesis for partial fulfillment of MD Degree in Cardiology

Title of the Protocol: Effect of Empagliflozin ten versus twenty five milligrams on left ventricular remodeling in diabetic patients with anterior ST segment elevation myocardial infarction with reduced left ventricular ejection fraction who underwent primary percutaneous coronary angioplasty.

Postgraduate Student: - Hany Nazmy Taalab
Degree: MSc,Cardiology

Director: Prof. Dr. Zainab Abdel Salam Fahmy
Academic Position: Professor
Department: Cardiology, Ain Shams University

Co-DIRECTOR: Asst. Prof Dr. Adel Mohamed Shabana
Academic Position: Assistant professor
Department: Cardiology department, Ain Shams University

Co- DIRECTOR: Asst. Prof Dr. Sameh Attia Amin
Academic Position: Associate Professor
Department: Cardiology, Ain Shams University

Co-DIRECTOR: Dr. Mina Maged Abdullah
Academic Position: Lecturer
Department: Cardiology department, Ain Shams University

Faculty of Medicine
Ain Shams University
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1.INTRODUCTION/ REVIEW :

Anterior STEMI (A-STEMI) has the worst prognosis among all infarct sites mostly due to larger infarct size. Patients with A-STEMI experience a more complicated in-hospital and follow-up course and are at greater risk for acute regional dilatation and thinning of the infarct zone.(1)

Adverse post infarction left ventricular (LV) remodeling is a major cause of heart failure (HF) in the United States today. This is due in part to the welcomed increase in patient survival due to early initiation of reperfusion therapies after acute myocardial infarction (AMI).(2)

While angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta blockers and sacubitril/valsartan are the pillars of pharmacologic therapy for HF with reduced ejection fraction (HFrEF), the benefits are most often seen in patients with large infarcts and individuals who are not candidates for reperfusion therapies. Their use, however, relates to no more than a 20–25% reduction in major adverse cardiac events (MACE). Thus, there is clearly a need to develop additional therapeutic strategies. (2)

One approach that holds considerable promise is the use of a relatively new class of drugs used to treat type 2 diabetes mellitus (T2DM), specifically sodium–glucose co-transporter 2 (SGLT-2) inhibitors (gliflozin class). A major driver for the use of these drugs in the setting of HF is the EMPA-REG OUTCOME trial. This was the first large randomized clinical trial that showed empagliflozin (EMPA), a specific SGLT-2 inhibitor, was not only effective in reducing MACE but that the outcome was driven primarily by a reduction in cardiovascular deaths and hospitalization for heart failure.(2)

Myocardial metabolic remodeling is integral to HF development, with a shift from free fatty acids (FFA) utilization (which produce many ATP (adenosine triphosphate) molecules but also requires many oxygen molecules) in healthy myocardium toward glucose consumption (which produce less ATP but is more oxygen-efficient in failing hearts. Although past research focused exclusively on FFA and glucose, the heart possesses metabolic flexibility and is an omnivore capable of oxidizing other substrates such as ketone bodies (KB), lactate, and branched-chain amino acid (BCAA). Importantly, KB are the most energetically efficient fuel because they produce many ATP molecules while showing the lowest oxygen requirements. Of note, empagliflozin-induced glycosuria reduces both plasma glucose and insulin levels and increases both lipolysis and plasma glucagon concentration (thus resembling fasting state), which causes ketogenesis and hyperketonemia. (3)

Accurate measurements of left ventricular volumes and function are important in the management of patients with various cardiac abnormalities. M mode and cross-sectional echocardiography are the most commonly used methods to measure left ventricular volumes and function.(4)

Recently, improvements in 2D echocardiographic image resolution have enabled detection of tissue pixels and tracking of these acoustic markers from frame to frame. The tissue velocity is estimated from the local frame-to-frame displacement; the automatic evaluation of the velocity at a point is determined by comparison of the displacement of the image data around that point in two consecutive frames. These methods have been used, in several different formulations, in many research fields and fall in the category known as Optical Flow commonly referred as Speckle Tracking in ultrasound imaging. (5)

Speckle tracking echocardiography has shown to be accurate in detecting subclinical myocardial dysfunction when most of the conventional echocardiograph parameters were normal or reported inconsistent results.(6)

2. AIM/ OBJECTIVES

The study aims to compare the doses of 10 versus 25 milligrams of Empagliflozin among diabetic patients with Anterior STEMI with reduced LVEF who underwent PPCI regarding MACE and LV remodeling for 6 months duration.

3. Methodology:

- **Type of Study:** a prospective clinical trial.
- **Study Setting:** Patients presenting to Ain shams university hospitals
- **Study Population**: anterior STEMI patients
- **Study Period**: 6 months
- **Sample Size:** Patients diagnosed with anterior STEMI in the ER fulfilling the inclusion criteria**.** (200 patients) divided into two groups the first will receive 10 mg of Empagliflozin and the other will receive 25 mg.
- **Ethical considerations:** ,

The clinical research study will be conducted in accordance with the current policies, requirements, and regulations of Ain Shams University. Information will be recorded in an appropriate manner to ensure that potential subjects or their authorized representatives are fully aware of the nature and objectives of the clinical study, and the potential risks and benefits of participating in the study. Written informed consent will be obtained from each patient or their authorized representative, prior to any study procedures being carried out.

- ***Inclusion Criteria:***

1- Diabetic patients with anterior STEMI with reduced LVEF who underwent PPCI with successful revascularization and resulting into TIMI III flow and who are receiving SGLTi for the first time.

Exclusion Criteria:

1- patients who did not undergo primary PCI, those treated medically or had thrombolysis
2- Non diabetic patient.
3- Diabetic patient already on SGLTi
4- STEMIs other than anterior.
5- NSTEMI patients.
6- Patients having valvular heart diseases.
7- Patients having renal impairment.
8- Patients with LV myopathies of non-ischemic origin.

4. Study Tools:

A- history taking: including

a- personal history" name, age, marital status and special habits of medical importance e.g smoking and alcohol consumption "
b- past history with special comment on diabetes and other comorbidities e.g hypertension, CKD and dyslipidemia

c- History of present illness with special comment on pain to door interval.
d- Positive family history.
e- Drug history: and to make sure whether patients are receiving SGLTi or not.

B- Examination:

1- General examination: including vital signs and complexion.
2- Local examination including heart and chest auscultation.

C- ECG: all patients will have 12 lead surface ECG at start of the study and during follow up.

D- Echocardiographic Assessment:

1- Standard transthoracic 2D echocardiographic examination:

Standard 2D echocardiography will be performed using GE vivid E70 echocardiography machine; the whole study will be ECG gated in supine or left lateral position. Standard images will be obtained in the parasternal (long- and short-axis views) and apical (2, 3, 4, and 5-chamber images) views. Standard 2D and color Doppler data, triggered to the QRS complex, will be saved in cine-loop format.

M-mode, 2D, TDI as well as pulsed and continuous Doppler flow across the different heart valves in all the standard views will be done according to the recommendations of the American Society of Echocardiography (7).

Heart failure with reduced ejection fraction (HFrEF) was defined as EF less than 40% , Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date.(8)

The definition of left ventricular remodeling using cardiac magnetic resonance following ST-elevation myocardial infarction is highly variable, among studies including highly selected patients. The most frequent left ventricular remodeling criterion were a 20% increase in end-diastolic volumes or a 15% increase in end-systolic volumes.(9)

A composite cut-off value of a 12% to 15% increase in end-systolic volume and a 12% to 20% increase in end-diastolic volume using a follow-up cardiac magnetic resonance imaging 1 to 3 months after myocardial infarction might be proposed as a consensual cut-off for defining adverse left ventricular remodeling.(9)

The following measurements will be focused on and recorded:

1- **Assessment of LV systolic function :**

By applying M-Mode modality to LV in parasternal long axis view, we will measure LV end-diastolic diameter (EDD), LV end-systolic diameter (ESD), IVS and PWT in both systole and diastole LVEF and FS. Also estimation of EF by Simpson biplane method and 2D will be done.

2- **LA dimension measurement:**

Left Atrial dimensions and aorta: The anteroposterior diameter of the left atrium will be measured in the parasternal long-axis view using M mode perpendicular to the aortic root long axis at the level of the aortic sinuses by using the leading-edge to leading-edge convention.

3- **Wall motion abnormalities:**

Using 2D echocardiography in apical and para- sternal windows to assess RSWMA.

4- **Assessment of LV diastolic function:**

Pulsed-wave (PW) Doppler will be applied in the apical 4-chamber view to obtain mitral inflow velocities and assess LV filling. The following measurements of mitral inflow will be recorded: the peak early filling (E-wave) and late diastolic filling (A-wave) velocities, the E/A ratio.

Tissue Doppler imaging (TDI): in apical 4- chamber view, TDI will be applied in the pulse-Doppler mode to allow for a spectral display and recording of mitral annulus velocities at the lateral mitral annulus, medial mitral annulus, and the mean value will be recorded. The measurements obtained are Systolic velocity of the mitral annulus (S), early diastolic annular velocity (E`), and late diastolic annular velocity (A`). The average of 3 readings of lateral E` will be recorded. E/E' ratio (mitral peak early filling velocity/peak mitral lateral annular velocity in early diastole) will be automatically calculated.

5- **Assessment of RV systolic function:**

The TAPSE method is a relatively simple technique used to assess RV longitudinal performance. To perform this measurement, an M-mode cursor will be aligned through the lateral tricuspid annulus in the apical four-chamber view and measurement of the amount of longitudinal motion of the annular plane in systole. TAPSE < 17 mm suggests RV dysfunction.

Also, TDI will be applied in the pulse-Doppler mode to allow for a spectral display and recording of tricuspid annulus velocities at the lateral tricuspid annulus in apical 4 chamber view to assess S of RV with value less than 9.5 suggestive of RV dysfunction.

E- <u>Speckle tracking echocardiography of the left ventricle:</u>

speckle tracking could be used as a predictor for LV remodeling post myocardial infarction with best cut-off value was >-12.5 (Sensitivity 87%, Specificity 85%).(10)

Loops of multiple ECG- gated entire cardiac cycles of the LV from apical 4, 3 and 2 chamber, parasternal long and short axis views will be obtained. The recorded data will be stored and later analyzed with the offline-workstation software EchoPAC Dimension [12.0, General Electrics (GE) Medical Systems GmbH, Germany].

In the end-systolic frame, the endocardial border is traced beginning at one end of the mitral annulus and ending at the other end in each of the apical views.

The software then generates a region-of-interest (ROI) to include the entire myocardial thickness. The width of the ROI can be manually adjusted as required. Care should be taken to avoid including bright, echogenic pericardium in the ROI.

The software then divides the LV myocardium into six segments and generates segmental and global longitudinal strain. As the myocardium usually shortens in the longitudinal direction during systole, the longitudinal strain is displayed below the baseline.

From these curves, peak systolic longitudinal strain is recorded for each of the myocardial segments. The strain values for all the segments are recorded and averaged to obtain the global longitudinal strain (GLS). A topographic representation of the regional and global longitudinal strain of all 17 analyzed segments (Bull's eye configuration) is then automatically generated.

F- 2D Speckle Tracking Echocardiography of the left Atrial Phasic functions (apical four chamber view and apical two chamber view) Parameters:

- Left Atrial Strain during Reservoir phase (LASr): Reflects the left atrium's ability to store blood during ventricular systole.
- Left Atrial Strain during Conduit phase (LAScd): Assesses the passive filling of the left ventricle during early diastole.
- Left Atrial Strain during Contraction phase (LASct): Evaluates the active contraction of the left atrium during late diastole.
- Left atrial maximum volume (LAVmax): It is measured just before the mitral valve opens, at the end of left ventricular systole.

G- Major adverse cardiac events (MACE): composite point of death, repeated hospitalization, re-infarction and new onset heart failure will be observed for six months post catheterization and initiation of SGLTi.

H- Follow up: patients will be followed up for 6 months regarding symptoms and MACE. All echocardiographic study parameters will be repeated at the end of the study period.

5-Statistical Analysis:
All data will be statistically analyzed to compare results in different time (day one then 6 months later)

6. References:

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