Journal of Cardiovascular Disease Research

ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 06, 2023

Assessment of cardiac functions using two-dimensional transthoracic and speckle tracking echocardiography after treatment with SGLT2 inhibitors in Patients with HFrEF

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Abstract:

Background and Objective: Recently, the antidiabetic drug sodium-glucose cotransporter type 2 inhibitor (SGLT2i) has been approved among the drugs that reduce mortality in patients with Heart failure with reduced ejection fraction (HFrEF). The impact of SGLT2i inhibitors on the left ventricle longitudinal myocardial function in heart failure (HF) patients remained vague. The effect of SGLT2i on left ventricular remodeling and function in patients with HFrEF was studied using speckle tracking (STE) and traditional echocardiography.

Objectives: Studying the effects of SGLT2i on left ventricular remodeling and function in HFrEF patients using STE and traditional echocardiography.

Methods:

- 300 patients with HFrEF were included.
- Study design: This prospective observational study involves 300 patients with HFrEF-administered SGLT2i (Empagliflozin and Dapagliflozin) and the classical treatment of heart failure. Then the patients were examined 2, 4, and 6 months after treatment with laboratory investigations of baseline glycosylated hemoglobin (HbA1C), glomerular filtration rate (eGFR), 2D echo, and STE studies.

Results:

The mean age was 50±9.2 for males and females. The mean weight, height, and body mass index (BMI) were 85.6±8.8 kg, 178.6±7.2 cm, and 26.6±2.9, respectively. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 115.3±5.1 and 75.4±4.5, respectively. The mean heart rate was 79.9±10.2. The mean respiratory rate was15±2.2. Regarding functional NYHA class, 0.2 %, 12%, 87.1%, and 0.7% of the patients were in class I, II, III, and IV, respectively. The lab investigations before the treatment: mean HbA1C was 4.2±0.6, and eGFR was 66.4±9.3. Using Empagliflozin, left ventricular ejection fraction (LVEF) showed a significant improvement from 34.73±2.9 at baseline to 34.91±1.2, 35.42±3.5, and 36.54±3.6 at 2, 4, and 6 months (p=0.001), respectively. In addition, Global longitudinal strain GLS showed a remarkable enhancement from -15.67±2.74 to -16.5±3.19, -

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17.32±3.21, -18.03±3.05 at 2, 4, and 6 months (p=0.001), respectively as indicated by GLS A2. While GLS A4 indicated that GLS was changed from -15.66±2.65 to -16.50±3.31, -17.41±3.23, and -17.93±3.32 (p=0.001). By Employing Dapagliflozin, LVEF showed significant improvement from 34.87±2.86 at baseline to 34.87±2.86, 35.05±3.01, and 37.53±4.1 at 2, 4, and 6 months (p=0.001), respectively. GLS showed a remarkable improvement similar to the improvement observed with Empagliflozin. E/e′ significantly reduced from 11.2±2.7 to 9.1±2.3 cm/s after administration of Empagliflozin and Dapagliflozin within 6 months (p=0.01). Left atrial volume index (LAVI) improved from 45.6 ± 15.3 to 37.5 ±6.5 (ml/m^2) (p=0.001) after 6 months. The results revealed a significant increase of ejection fraction at 4 and 6 months of follow-up and a significant improvement of global longitudinal strain at 2, 4, and 6 months with patients given SGLT2i.

Conclusion: SGLT2i was associated with improving left ventricular (LV) longitudinal myocardial function, further enhancing LV diastolic function. SGLT2i is associated with increased ejection fraction (EF) and LV longitudinal myocardial function improvement, subsequently ameliorating LV diastolic function. The Dapa group had a more significant improvement in LVEF at four months and six months compared to the Empa group. The Empa group showed a significant improvement in HbA1C at six months compared to the Dapa group.

Keywords: Sodium-glucose cotransporter type 2 inhibitors, left atrial volume index, left ventricular diastolic function, Heart failure reduced ejection fraction failure, Global longitudinal strain

1. Introduction:

Heart failure (HF) is commonly diagnosed in patients over 65, with high morbidity and mortality. It is a compound clinical syndrome associated with constitutional and functional impairment of ventricular filling or blood ejection [1]. There are two categories of HF based on the systolic and diastolic dysfunction. With decreased ejection fraction (HFrEF), HF occurs when the left ventricular ejection fraction (LVEF) is under 40%. The second category is heart failure with preserved ejection fraction (HFpEF) when the LVEF equals or exceeds 50% [2].

Prolongation of HFrEF patients' survival has been only documented with beta-blockers, ACEIs, angiotensin receptor neprilysin inhibitors, hydralazine plus nitrate, and aldosterone antagonists. Therefore, accurate diagnosis and assessment of the heart are necessary. Two-dimensional (2D) echocardiography is applied for HF patients to assess left ventricular (LV) function visually, but its interpretations are distinctive and may lead to semi-quantitative data [3]. Reisner et al. [4] initially introduced the submission of speckle tracking (STE) to echocardiography in 2004 by using global longitudinal strain. Recently, STE has assisted clinicians in getting more certain data related to the strain of both the ventricles and atria [5].

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Speckle tracking provides backscatter images from an ultrasound beam across the frame that matches the best comparable area. A well-trained echocardiogram specialist can obtain significant images to develop prominent of all heart chambers recordings. STE completes the conventional echocardiogram using software that measures rotation, twist, and torsion by degrees [6].

Almost patients with HF have symptoms linked to the defect in left ventricular myocardial function, like dyspnea, intolerance to exercise, and fluid retention, which cause significant physical limitations and affect the patient's quality of life [7]. The scope of management of HFrEF is to improve the symptoms and prolong patient survival which classically involves; diuretics, beta-blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor**,** hydralazine plus nitrate, neprilysin inhibitors, digoxin, and aldosterone antagonists [8].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of drugs used for glucose-lowering and act as antidiabetics. Many randomized studies have concluded the cardioprotective impacts of mainly three SGLT2 inhibitors; empagliflozin, Dapagliflozin, and canagliflozin; within the first months after initiating the treatment irrespective of the existence or absence of diabetes mellitus (DM) and therefore, these drugs have increasingly used not only in the treatment but also in the prevention of HF [9].

The glucose reduction results of these agents are due to the inhibition of renal glucose reuptake in the proximal tubule with a subsequent decrease in blood glucose levels. But the cardioprotective effect of these drugs is due to different origins. Many hypotheses may explain the advantages of these drugs in HF involving volume regulation, cardio-renal mechanisms, metabolic effects, direct impact on cardiac contractility, improved cardiac remodeling, ion-homeostasis, and decreased inflammation and oxidative stress [10].

This study aimed to evaluate the effects of SGLT2i on left ventricular remodeling and function in patients with HFrEF using STE and traditional echocardiography over 300 patients who had HFrEF enrolled in Minia Cardiothoracic University Hospital. The effect of SGLT2i on left ventricle remodeling and function in patients with HFrEF using STE and traditional echocardiography will be studied.

2. Patients and methods:

Patients:

From March 2022 to October 2022, Minia Cardiothoracic University Hospital enrolled 300 patients with HFrEF in this study. The New York Heart Association classes of HF; HF NYHA classes were II-IV and LVEF $\leq$ 40% on echocardiography in the prior six months. The inclusion criteria were ambulatory patients aged 18 years with HF NYHA classes II-IV and LVEF $\leq$ 40% on echocardiography in the prior six months. Patients with stable symptoms and appropriate HF therapy in the past three months were included, as were

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patients without a known history of diabetes or diabetes remission and with a baseline glycosylated hemoglobin (HbA1c) level < 5.7%. Additionally, patients with a glomerular filtration rate estimated at (eGFR) ≥ 45 mL/min/1.73 m² assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation (2009) were eligible for inclusion [11].

Excluded from the study were pregnant or breast-feeding females, those planning to become pregnant during the study period, patients with a history of diabetes mellitus or diabetes in remission, those who had experienced acute coronary syndrome, cardiac surgery, or stroke within the last three months, individuals listed for heart transplantation or implanted with LV assist devices, patients with cardiomyopathy due to any cause or severe valvular heart disease, those experiencing acute decompensated heart failure, individuals who had received implantable cardioverter defibrillators or cardiac resynchronization therapy within the last three months, patients who had continuously used parenteral inotropic agents, those with systolic blood pressure <90 mmHg, patients with eGFR <45 mL/min/1.73 m² using the CKD-EPI creatinine equation, individuals with cancer or any life-threatening condition, and patients with psychiatric diseases.

Methods:

Methods Study design: This prospective observational study will be conducted in a single center in Minia cardiothoracic university hospital. Data collection and follow-up will be performed at baseline and after 2,4,6 months of empagliflozin and Dapagliflozin administration (N=300 patients), 2D echo, and Doppler studies. Routine echocardiography data will include dimensions, volumes, and systolic and diastolic functions. Strain analyses Myocardial strain will be measured using STE. All patients were subjected to careful history investigation and complete physical examination. HbA1c and eGFR were assessed, and baseline transthoracic echocardiography and electrocardiogram were done after the approval of the medical ethical committee and written informed consent was gained.

The study randomly assigned 300 patients into two groups: the Empa group (n=149) received Empagliflozin 10 mg/day in addition to standard heart failure treatment. In contrast, the Dapa group (n=151) received Dapagliflozin 10 mg/day in addition to standard heart failure treatment. The groups were assigned based on the day of the week that the patients were admitted to the hospital. Patients admitted on Saturday, Sunday, and Monday were given Empagliflozin, while those admitted on Tuesday, Wednesday, and Thursday were given Dapagliflozin. Follow-up evaluations were conducted every two months for six months, during which blood pressure, eGFR, and HbA1c were measured.

All patients underwent a resting echocardiographic examination using our echocardiography system (Acuson SC2000 PRIME ultrasound system, Siemens, Germany). The standard echocardiographic measurements were acquired according to the existing

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guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging. Then STE analysis was done for each patient with a single software to evaluate LV longitudinal function assessed in terms of GLS visualized as color coded. GLS was then set as the averaged peak longitudinal strain of 16 LV segments and expressed as an absolute value according to the existing guidelines [12].

All patients were exposed to the following measurements; Left Ventricle-end systolic volume (LVESV), Left Ventricle-end diastolic volume (LVESV), and LV Ejection Fraction (EF). The primary study endpoints are the changes in LVESV, LVESV, LV Ejection Fraction (EF), and LV global longitudinal strain (GLS) in the 6th month compared with the baseline value.

Statistical analysis:

The data were coded, tabulated, and analyzed using SPSS 20

3. Results:

Table 1 displays the sociodemographic and clinical data of 300 patients at their first presentation. Demographic data are illustrated in Table 1. The mean age was 51.07±9.1, with 115 (38.3%) males and 185 (61.7%) females. The mean weight, height, body mass index (BMI), and body surface area (BSA) were 85.66 ± 8.67, 178.92 ± 6.68, 26.6±2.9 and 3.19 ± 14.3, respectively. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 115.4 ± 5.3 and 75.32 ± 4.5, respectively. The mean heart rate was 79.16 ± 10.2. The mean respiratory rate was 15.09 ± 2.2. Regarding functional NYHA class, 0 (0 %), 34 (11.3%), 265 (88.3%), and 1(0.3%) patients were class I, II, III, and IV, respectively.

Table (1): Sociodemographic and clinical data of study participants at the first presentation

Sociodemographic and clinical data at the first presentation Total (N=300)	
Age	51.07±9.1
Sex	
Male	115 (38.3%)
Female	185 (61.7%)
Weight	85.66 ± 8.67
Height	178.92 ± 6.68
BMI	26.61 ± 2.96
BSA	3.19 ± 14.3
SBP	115.4 ± 5.3
DBP	75.32 ± 4.5
Heart Rate	79.16 ± 10.2
Respiratory Rate	15.09 ± 2.2
Functional NYHA class	
I	-

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II	34 (11.3%)
III	265 (88.3%)
IV	1 (0.3%)
SGLT2i administration	
On Empagliflozin	149 (49.7%)
On Dapagliflozin	151 (50.3%)

The lab investigations of patients at first presentation were as follows; mean HbA1C was 4.26 ± 0.69, and eGFR was 66.8 ± 9.31, as presented in Table 2.

Table (2): Lab investigations of study participants at the first presentation

	Total (N=300)
HbA1C	4.26 ± 0.69
eGFR	66.8 ± 9.31

Table 3 presents the echocardiography data of the study participants. Table 3 provides information on the left ventricular ejection fraction (LVEF%) and the global longitudinal strain (GLS apical four-chamber and GLS apical two-chamber views). The LVEF% of the study participants is presented as 34.9 ± 2.8, indicating that the average LVEF% is reduced, consistent with the heart failure diagnosis with reduced ejection fraction (HFrEF). The GLS values for A4 and A2 are also presented, a measure of the function of the heart muscle. Concerning echocardiography data of patients at first presentation, the LVEF% mean was 34.8 ± 2.88. the mean of global longitudinal strain apical four-chamber (GLS A4) and GLS A2 were -15.4±2.6 and -15.5±2.8. as shown in Table 3.

Table (3): Echocardiography data of study participants at the first presentation

	Total (N=300)
LVEF%	34.9 ± 2.8
GLS A4	-15.6 ± 2.8
GLS A2	-15.5 ± 2.8

Tables 4 and 5 provide information on the changes in lab investigations and echocardiography data of the two groups (Empa and Dapa) at different time points (baseline, two months, four months, and six months) after treatment. The tables show each group's mean HbA1C, eGFR, LVEF, GLS A4, and GLS A2 at each time point and the p-values for comparing these to the baseline values. Tables 4 and 5 showed the Lab and Echocardiography data changes at baseline, after 2, 4, and 6 months among Empa and Dapa

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groups, which revealed HbA1C was significantly decreased at six months after treatment, eGFR showed a minimal increase but insignificant statistically. LVEF was significantly increased at 4 and 6 months follow-up, as shown in Figure 1. GLS A4 and GLS A2 showed significant improvement at 2, 4, and 6 months after treatment. Figure 1 shows that the variation in the first two months was negligible.

Table (4): Lab investigations and Echocardiography changes at baseline, after two months, four months, and six months among the Empa group (n=149)

	Baseline	Two months	Four months	Six months
HbA1C	4.29±0.70	4.21±0.66	4.21±0.66	3.82±0.51
P value from baseline	-	0.33	0.33	**0.001 ***
eGFR	66.79±9.19	67.05±9.93	67.54±9.75	68.30±9.07
P value from baseline	-	0.81	0.48	0.15
LVEF	34.73±2.9	34.73±2.9	35.42±3.5	36.54±3.6
P value from baseline	-	-	**0.001 ***	**0.001 ***
GLS A4	-15.67±2.74	-16.5±3.19	-17.32±3.21	-18.03±3.05
P value from baseline	-	**0.001 ***	**0.001 ***	**0.001 ***
GLS A2	-15.66±2.65	-16.50±3.31	-17.41±3.23	-17.93±3.32
P value from baseline	-	**0.001 ***	**0.001 ***	**0.001 ***

Table (5): Lab investigations and Echocardiography changes at baseline, after two months, four months, and six months among the Dapa group (n=151)

	Baseline	Two months	Four months	Six months
HbA1C	4.23±0.69	4.23± 0.65	4.23± 0.65	3.72±0.49
P value from baseline	-	0.96	0.96	**0.001 ***
eGFR	66.81±9.46	66.99±10.73	67.27±10.40	67.89±9.85
P value from baseline	-	0.89	0.71	0.38
LVEF	34.87±2.86	34.87±2.86	35.05±3.01	37.53±4.1
P value from baseline	-	-	**0.02***	**0.001 ***
GLS A4	-15.54±2.77	-16.84±3.49	-18.48±2.23	-19.61±2.98
P value from baseline	-	**0.001 ***	**0.001 ***	**0.001 ***
GLS A2	-15.53±2.78	-16.64±3.47	-17.97±3.32	-18.71±3.99
P value from baseline		**0.001 ***	**0.001 ***	**0.001 ***

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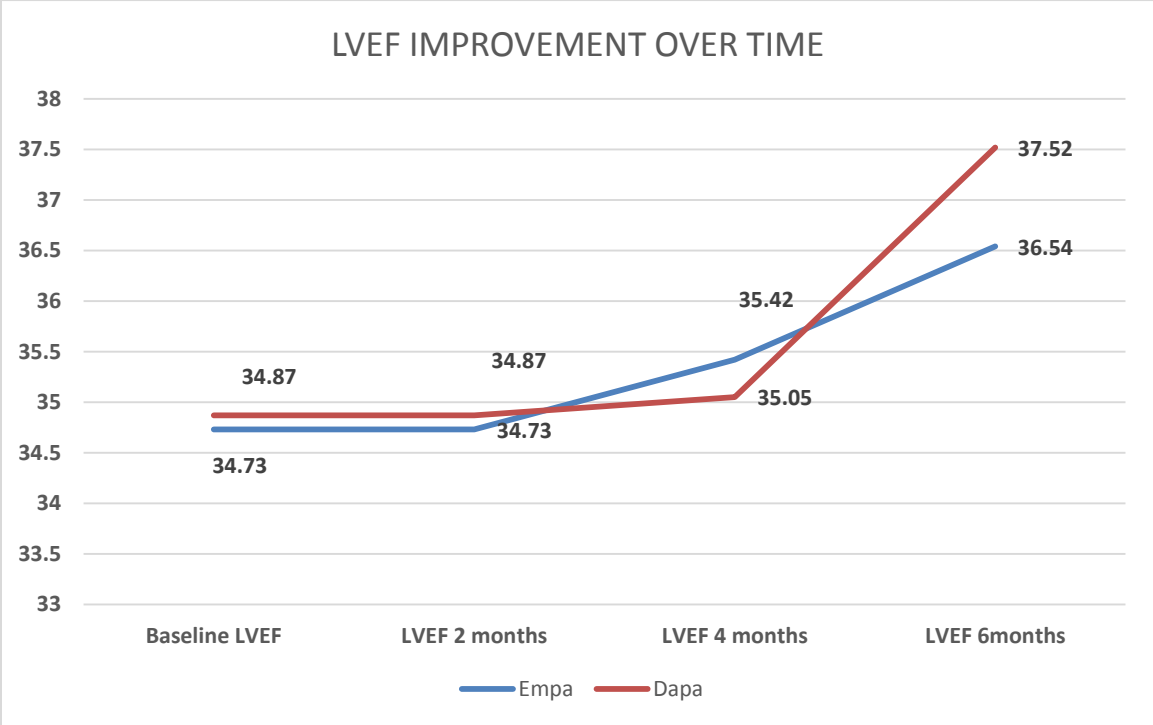

Figure 1: Showing LVEF improvement over time among Empa and Dapa groups

The Empa group's lab investigations and echocardiography changes revealed significant parameter improvements over six months. The lab investigations and echocardiography changes within the Empa group demonstrated positive effects on glycemic control, cardiac function, and myocardial deformation over the six months, as shown in Table 4. The Dapa group's lab investigations and echocardiography showed notable effects throughout the study. The Dapa group's lab investigations and echocardiography changes demonstrated significant improvements in glycemic control, cardiac function, and myocardial deformation throughout the study, as shown in Table 5.

Table 6 shows the functional class of the studied sample at the beginning of the study and after six months of follow-up. The results indicate a significant improvement in functional class, with a decrease in the percentage of patients in Class III and an increase in the percentage of patients in Classes I and II. No patient was in Classes III and V after six months of follow-up, indicating a good response to treatment.

Table 7 shows the 2D parameters of the studied sample at the beginning of the study and after six months of follow-up. The results indicate a significant improvement in LV function, with an increase in LVEF and a decrease in E/e. The reduction in LVESV also suggests an improvement in LV function. However, there was no significant change in LVEDV, indicating that the treatment may have stabilized the disease rather than reversed it. These results suggest that the treatment positively affected LV function and can be considered effective in managing the disease.

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Table (6): Functional class of studied sample, at the beginning versus after six months follow up

Class	At the beginning	After six months	p-value
I	-	132 (41%)	<0.001*
II	34 (11.3%)	168 (59%)	0.032*
III	265 (88.3%)	0 (0%)	<0.001*
IV	1 (0.3%)	0 (0%)	0.022*

Data displayed as numbers and percent%, comparison by Z- test

Table (7): 2D parameters of the studied sample (300 patients)at the beginning versus after six months of treatment with empagliflozin and Dapagliflozin).

Parameters	At the beginning	After six months	p-value
LVEDV (ml)	139.3±7.3	139.1±10.5	0.830
LVESV(ml)	89.7±4.7	89.0±4.4	<0.001*
E/e	11.2±2.7	9.1±2.3	<0.001*

Quantitative data are displayed mean and standard deviation, comparison by independent sample t-test.

4. Discussion

The obstacles of heart failure management and its financial burden because of hospitalization in decompensated HF cases have significant clinical challenges for cardiovascular medicine [13]. Recently, SGLT2i has demonstrated an additional reduction in HF hospitalization, cardiovascular events, and mortality, particularly for HFrEF patients [14]. So, this article aims to study the effect of SGLT2i on left ventricle remodeling and function in patients with HFrEF using STE and traditional echocardiography.

Tables 4 and 5 suggest that after treatment, the Empa and Dapa groups significantly improved HbA1C, LVEF, GLS A4, and GLS A2 values. However, there were no significant changes in eGFR values in both groups. In addition, Tables 4 and 5 show that the Dapa group had a significantly greater improvement in LVEF at four months and six months compared to the Empa group. While the Empa group showed a significant improvement in HbA1C at six months compared to the Dapa group, as shown in Figure 2.

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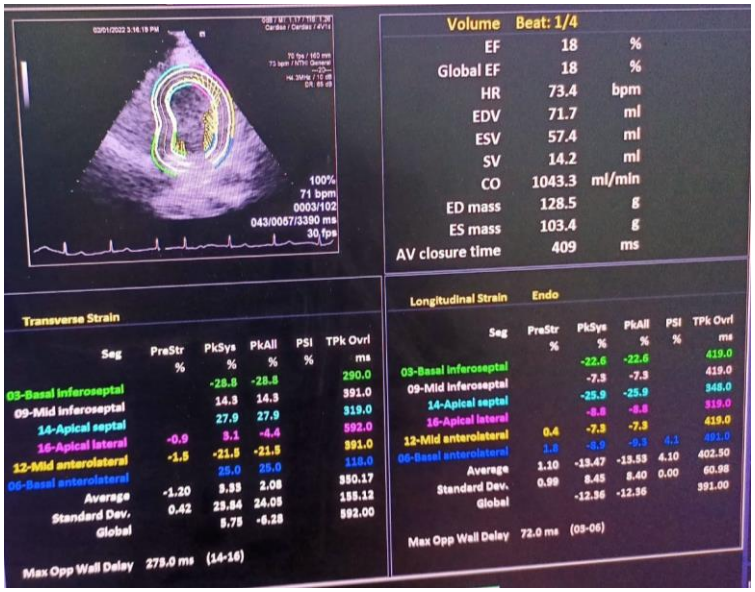
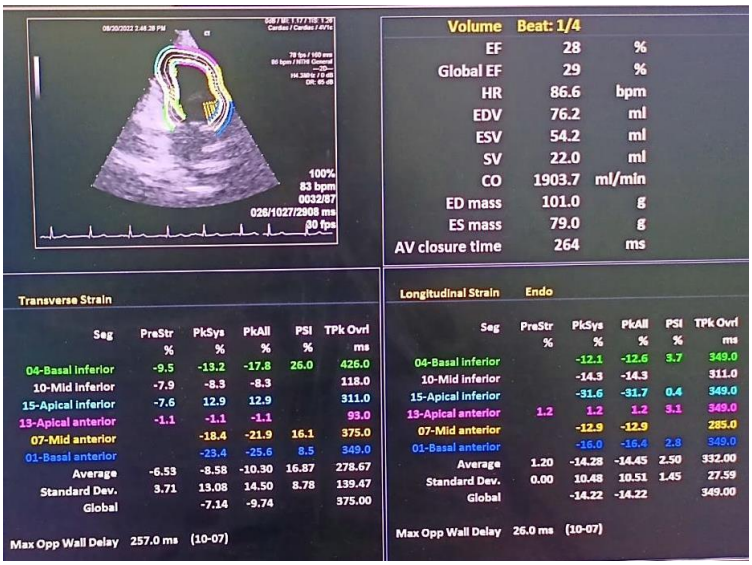


a



b

Figure 2: LVEF at different treatment stages: a) At baseline, b) After 6 months of administration of Empagliflozin

This study involved 300 patients with HFrEF, their NHYA class from II to IV, newly admitted cases with or without diabetes or having CKD were given empagliflozin (149 patients) and Dapagliflozin (151 patients) besides appropriate HF medications. The results regarding HbA1C and eGFR concluded that HbA1C significantly decreased six months after treatment, while the increase in eGFR was statistically insignificant, as shown in Tables 6

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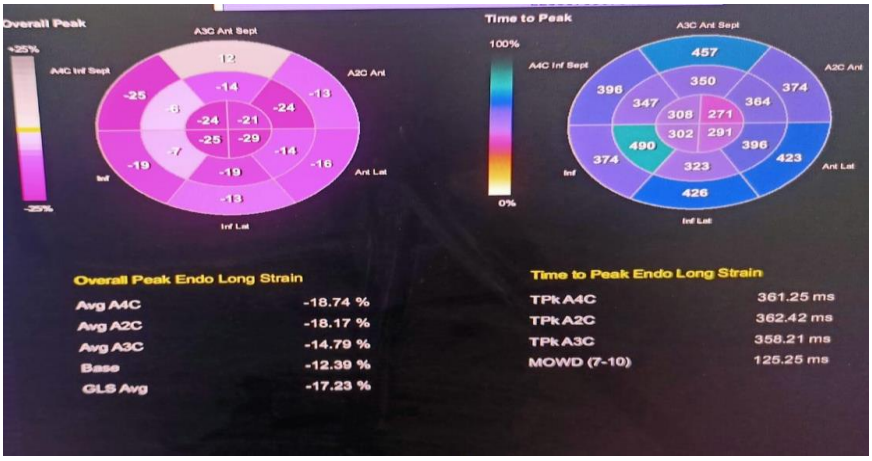
and 7. These results contradict those reported by **Tanaka et al.** [15]. **Tanaka et al.** [15] revealed a decrease in HbA1C but an insignificant and significant reduction in eGFR after six months of dapagliflozin administration in diabetic patients.



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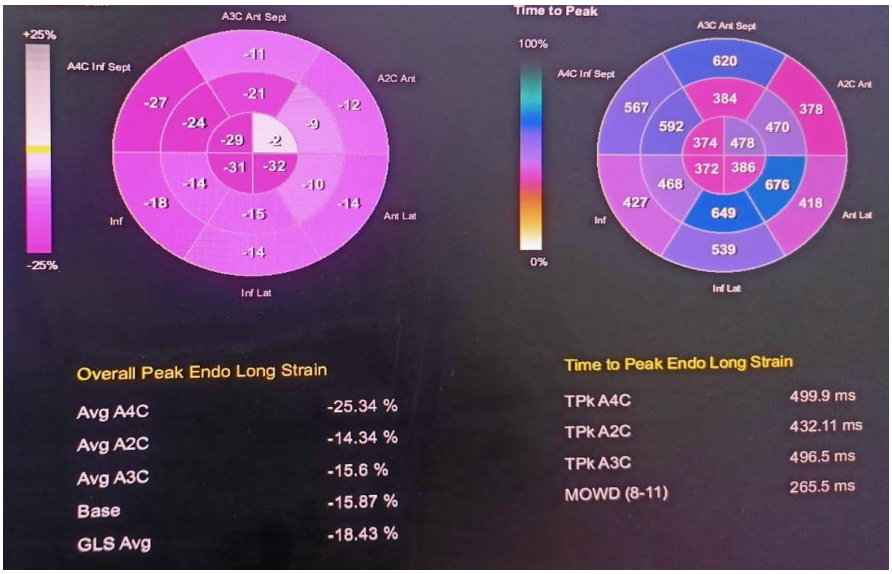

b

Figure 3: Longitudinal strain a) At baseline, b) After 6 months of administration of Dapagliflozin

Regarding LVEF, the results of this study revealed that LVEF has significantly increased after 4 and 6 months of treatment, either with empagliflozin or Dapagliflozin, as shown in Figure 3. These results coincide with **Soga et al.** [16], who assessed the use of Dapagliflozin in 53 diabetic patients (type 2) and stable HFrEF or HFpEF and revealed improved LVEF. In the same perspective, **Kotinas et al.** [17] reported an increase in EF from

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48.40 ± 10.89% to 50.62 ± 10.04% in 312 diabetic patients. Also, the study of **Tanaka et al.** reported a significant increase in EF six months after treatment with Dapagliflozin.

On the contrary, many studies reported no change or difference in LVEF, as reported by **Verma et al.** [18] and **Cohen et al.** [19]. This difference may be attributed to the fact that both studies were conducted over cases with diabetes, which is a co-morbidity on the heart, and also, small sample sizes were investigated; 10 and 25 patients, respectively.

GLS A4 and GLS A2 significantly improved at 2, 4, and 6 months follow-up after treatment. These results agreed with **Tanaka et al.** [15], who evaluated the effect of Dapagliflozin on LV diastolic functional indices, E/e′ ratio and GLS; in people with diabetes and showed significant improvement in GLS at six months follow-up.

Similarly, **Verma et al.** [18] evaluated the Empagliflozin effect on left ventricle mass and diastolic function in people with diabetes. The results showed that LV diastolic function had improved according to the early lateral e′ change. Also, **Sakai and Miura** [20] evaluated SGLT2 inhibitors (Empagliflozin, Luseogliflozin, and Tofogliflozin) use in 184 patients with HFpEF and diabetic type 2**.** They revealed improved diastolic function parameters using the E/A and E/e′ ratios.

To our knowledge, few studies reported data concerning STE echocardiography to demonstrate changes in strain parameters, LV structure, and function, as most studies evaluated the effect of these agents on HF hospitalization as concluded by the clinical trials using Dapagliflozin (DECLARE-TIMI) [21] and empagliflozin (EMPA-REG OUTCOME trial) [22]. It was reported that the usage of these agents led to a significant decrease in the major adverse cardiovascular events than placebo, more over a reduction of the selected primary outcomes like cardiovascular death and hospitalization. In the same direction, **McMurray et al.** [23] investigated 4744 cases with HFrEF. The findings revealed a significant decrease in the risk of worsening heart failure (HF) or death from cardiovascular events in the dapagliflozin group compared to the placebo group, regardless of the absence or presence of type 2 diabetes mellitus (T2DM).

Based on these results, it is concluded that using SGLT2i as empagliflozin and Dapagliflozin as an add-on therapy for patients with HFrEF is beneficial. We suggest that SGLT2 inhibitors may have a potential role in managing LV dysfunction, which may theoretically lead to a decrease in HF hospitalization with such agents.

Evaluating the efficacy of these drug figures in patients with heart failure associated with CKD is recommended. More research is needed to assess these drugs' benefits in acute decompensated HF cases. The clinical treatment improved the patients' function class and quality of life,

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5. Conclusions:

SGLT2i is associated with increased EF and LV longitudinal myocardial function improvement, with subsequent amelioration of LV diastolic function. SGLT2i is associated with increased EF and LV longitudinal myocardial function improvement, with subsequent amelioration of LV diastolic function. The clinical treatment improved the patients' function class and quality of life. However, Further study with a more significant number is recommended to evaluate the efficacy of these drug figures in heart failure patients associated with CKD.

The Dapa group had a significantly greater improvement in LVEF at four months and six months compared to the Empa group. In contrast, the Empa group showed a significant improvement in HbA1C at six months compared to the Dapa group. Throughout the study, both groups showed positive effects in glycemic control, cardiac function, and myocardial deformation.

Ethical considerations: The study protocol and all procedures were approved by the ethical committee of the Faculty of Medicine, Minia University. All participants provided written informed consent before getting involved in the study. The steps, the aims, the potential benefits, and the hazards were all discussed with the patients or their relatives.

Author Contributions: *All authors contributed to the study's concept and design. All authors participated in the clinical study. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by Amr Setouhi and Hazem Farrag, and all authors commented on previous versions. All authors read and approved the final manuscript.*

Source of funding: None.

Conflict of interest: None.

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