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Effect of Dapagliflozin on Left Atrial Strain Parameters in Diabetic Patients with Paroxysmal Atrial Fibrillation

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Abstract

Background: **Atrial fibrillation (AF) is a common arrythmia in diabetes mellitus (DM). Left atrial strain (LAS) and electromechanical delay (EMD) are important AF predictors.** ***Aim:*** **To investigate the effect of dapagliflozin added to the standard antidiabetic treatment on LAS and EMD in type 2 DM (T2DM) patients with paroxysmal AF.** ***Subjects and Methods*****: Diabetic patients in sinus rhythm with history of paroxysmal AF diagnosed by Holter electrocardiogram (ECG) or hospitalization were assigned into 2 groups. Dapagliflozin group: dapagliflozin 10 mg added to the standard antidiabetic treatment. Control group: standard antidiabetic treatment without added Sodium-Glucose-Cotransporter inhibitors (SGLT2i). Both groups were on beta blockers to prevent AF recurrence. We assessed baseline characteristics, echocardiography, LAS, EMD, and paroxysmal AF prevalence in both groups.** ***Results:*** **Dapagliflozin group (113 patients) has a postive improvement in diastolic function (E/e' reduced from 9.9±2.4 to 7.8±1.8, P< 0.01), LA reservoir strain (26.5±7.9% to 28.9±3.8%, P< 0.015), LA contraction strain (10.8±4.9% to 12.2±5.9%, P< 0.021), and interatrial EMD (29.75±7.53 to 21.72±4.51 milliseconds, P< 0.029) at 12-months follow-up. Likewise, paroxysmal AF has occurred in 7.1% of dapagliflozin group vs 13.8% in control group at 12-months follow-up, P value <0.01. Control group (109 patients) hasn't significant change of echocardiographic parameters at 12-months follow-up.** ***Conclusion*****: Dapagliflozin addition to the standard antidiabetic treatment was associated with reduction of LA strain and interatrial electromechanical delay in type 2 DM patients who have paroxysmal AF. Moreover, this was associated with reduction of paroxysmal AF recurrence as documented by Holter ECG or hospitalization.**

Keywords: Dapagliflozin, Diabetes Mellitus, LA Strain, Paroxysmal AF, Interatrial EMD

Introduction

Atrial fibrillation (AF) is a particularly common kind of cardiac arrhythmia in adults, with an estimated lifetime probability of occurring 23%[(1)]. The shift from paroxysmal to chronic atrial fibrillation involves harmful atrial changes that worsen the condition and drive-up healthcare costs and hospitalizations. Addressing this is vital for better patient outcomes[(2)]. Diabetes mellitus (DM), which raises the risk of arrhythmogenesis and contributes to the structural and electrical remodeling of the atria, is a major factor in the development and progression of AF. The complex interplay between oxidative stress, glycemic variability and chronic inflammation, plays a critical role in promoting structural and electromechanical changes in the atrial tissue[(3)] . The progression of

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AF is influenced by multiple underlying mechanisms, including microvascular dysfunction, cardiac myocyte hypertrophy, and elevated proinflammatory cytokines. These factors lead to increased fibrosis and stiffness within the left ventricle and atrium, contributing to significant myocardial remodeling. In the context of T2DM, this remodeling process disrupts electrical activity and induces diastolic dysfunction, resulted in higher left ventricular end-diastolic pressure (LVEDP) [4]. With major prognostic implications, the function of LA has drawn a lot of attention as a crucial factor in determining clinical outcomes[5]. Although the Left Atrial Volume Index (LAVI) is widely used as a marker of left atrial function, it lacks sufficient sensitivity in identifying improvements related to diastolic dysfunction. This limitation underscores the need for more precise diagnostic tools to evaluate changes in left atrial performance[6]. Two-dimensional speckle-tracking echocardiography (2D-STE) is now a dependable and accurate method for measuring cardiac deformation quantitatively. Left atrial strain (LAS) parameters are recognized as dependable predictors of AF[7]. In addition to their predictive capability, LAS parameters play a crucial diagnostic role in identifying elevated filling pressures. These include pulmonary artery wedge pressure, LA filling pressure, and left ventricular end-diastolic pressure (LVEDP), making LAS a valuable tool for assessing cardiac function and hemodynamic status[8]. Intra-andinter-atrial electromechanical delay (EMD) are well-established indicators of atrial morphology and electrophysiological integrity. Research has demonstrated that disruptions in the uniform propagation of electrical impulses, combined with prolonged P wave indices and extended electromechanical coupling intervals, play a significant role in increasing the susceptibility to AF. These indicators offer important information on the anatomical and functional alterations linked to atrial arrhythmogenesis[9]. Non-invasive techniques, such as evaluating atrial electromechanical delay (EMD) using tissue Doppler imaging (TDI) via transthoracic echocardiography, are widely utilized to estimate the risk of AF. EMD time, which reflects the heterogeneity in atrial conduction, is measured as the interval between the initiation of electrical activity and the onset of mechanical contraction in the myocardium. Prolonged EMD times, as detected through TDI, are well-documented markers of an increased likelihood of developing AF[10]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a group of oral medications that primarily function to lower blood glucose levels. They provide substantial therapeutic benefits for individuals with diabetes mellitus (DM) and have shown significant efficacy in managing atherosclerotic cardiovascular disease and heart failure (HF)[11]. The cardiovascular benefits of SGLT2 inhibitors are believed to result from several mechanisms, including volume reduction achieved through the inhibition of glucose reabsorption in the proximal renal tubules[12]. Despite the promising cardiovascular benefits of SGLT2 inhibitors, their specific impact on LAS remains uncertain. Thus, the purpose of this study is to examine how dapagliflozin, at a dosage of 10 mg, affects LAS and electromechanical delay EMD in individuals with paroxysmal atrial fibrillation and type 2 diabetes.

Subjects and Methods

This prospective, single-center cohort study was carried out on a series of consecutive patients with type 2 diabetes mellitus and a confirmed diagnosis of paroxysmal atrial fibrillation, who were admitted to the cardiology department at

Suez Canal University Hospital. The Suez Canal University Faculty of Medicine's (FOMSCU) ethical review board examined and approved the study protocol.

Population and data collection

A total of 291 consecutive patients with diabetes and a recent history of paroxysmal atrial fibrillation within the past six months were screened. An episode of AF that ends within seven days after beginning, either naturally or with medical assistance, is referred to as paroxysmal AF. They were diagnosed by Holter ECG or documented attack of AF that required hospitalization or emergency room (ER) admission. Only 256 patients were eligible to participate in this study and 35 patients were ineligible. Of those 256 patients, 222 patients were enrolled, 25 patients declined participation, and 9 patients had a very poor echocardiographic window. Eligible patients were on antidiabetic treatment not including any SGLT2i and were on betablockers according to their cardiology treating physician. Participants were randomly allocated to receive either dapagliflozin 10 mg or a placebo, alongside their current antidiabetic treatments and beta blockers, as outlined in Figure 1.

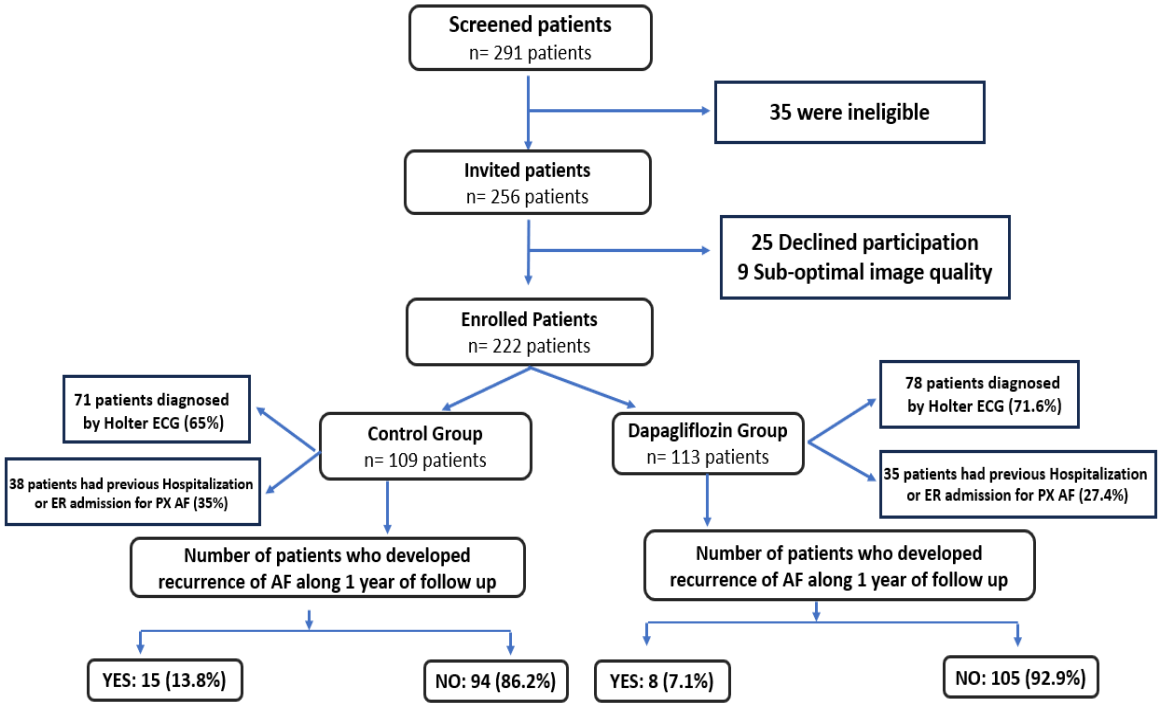

Figure 1. The study flow chart.

Eligible patients were ≥18 years-old, type 2 DM with HbA1c >7 on antidiabetic drugs other than dapagliflozin or any SGLT2i with history of recent (within 6 months) paroxysmal AF (Paroxysmal AF was defined as non-sustained episodes of AF converting to sinus rhythm in < 7 d.) and already on maximally tolerated dose of beta blockers with creatinine clearance of ≥ 60 ml/min. Every patient has completed the informed consent form and read the patient information leaflets.

If a patient's estimated glomerular filtration rate (eGFR) was less than 60 ml/min/1.73 m2, which denotes severe renal damage, they were not allowed to continue in the trial. Participants were also excluded if they had a diagnosis of type 1 diabetes mellitus (DM), systolic blood pressure less than 95 mm Hg, or clinical

hypotension. These criteria were established to ensure patient safety and maintain the integrity of the study outcomes. Patients were also excluded if they have history of diabetic ketoacidosis, recurrent urinary tract infection, thyroid dysfunction, permanent AF/Atrial Flutter, heart block, permanent pacemaker, moderate valvular regurgitation or stenosis, acute coronary syndrome, stroke within 6 months, cancer, liver failure, or unable to provide informed consent. Patients who are already on SGLT2 inhibitors or have contraindication to use it were also excluded.

Study protocol

Baseline demographic information, physical examination, 12-lead ECG, echocardiography, LAS, interatrial EMD delay, and 24-hour Holter ECG at baseline and 12-month subsequent studies were all part of the patients' screening and evaluation. Blood samples were obtained from patients upon admission to assess electrolyte levels, liver and kidney function and complete blood count. Dapagliflozin group: patients have received dapagliflozin 10 mg once daily added to their current antidiabetic medications. Control group: patients have their current antidiabetic treatment plus placebo.

Study endpoints

Patients have been followed-up at the cardiology department- Suez Canal university hospital by clinical evaluation, echocardiography and Holter ECG. The primary endpoint was improvement of LAS detected by 2D echocardiography speckle tracking at 12-months follow-up after the initiation of dapagliflozin 10 mg added to current antidiabetic drugs. The secondary endpoints were reduction of interatrial EMD and paroxysmal AF episodes detected by twenty four-hour Holter ECG or documented hospitalization, at 12-months follow-up.

12-Leads Surface ECG

All subjects were placed in a supine posture and given a twelve-lead surface electrocardiogram (ECG). To guarantee accuracy, the ECG recordings were made using a calibration standard of 1 mV/cm and a paper speed of 25 mm/s. The recorded ECG strips were then processed and analyzed using the automated calculation features of the Schiller MT-101 ECG device, providing precise and reliable measurements for further evaluation.

Ambulatory 24-hour Holter ECG

All patients were subjected to twenty four-hour Holter monitoring at both baseline and the twelve-month follow-up, utilizing a commercially available Schiller device within our facility. It was done for detection and quantification of supraventricular arrhythmias especially AF: episode of >30 seconds of AF is considered as paroxysmal AF[13]. All Holter recordings were electronically transferred to the Holter Laboratory at Suez Canal University Hospital, where segments with excessive noise were eliminated. The recordings were analyzed and evaluated by experienced consultant cardiologists, all of whom were blind from the information provided by patients.

Echocardiography

Echocardiographic examinations were conducted utilizing a commercially available system (General Electric Healthcare Company, Vivid ig) with 2.5-MHz phased array probe. Two cardiologists, blinded to the laboratory and clinical data, have independently analyzed echocardiography and Holter ECG. Continuous single-lead electrocardiographic monitoring was performed throughout the echocardiographic examination. The evaluation included an

evaluation of the left ventricular ejection fraction (LVEF) as well as key parameters of diastolic function to analyze overall cardiac performance. Additionally, LAS was measured using two-dimensional echocardiography. High-quality pictures were captured at a frame rate of 60 to 80 frames per second, specifically focusing on the LA from both apical 2 and 4 chamber views. These images were processed using specialized software to ensure precise and detailed analysis of LA strain[14].

LAS is evaluated by measuring the extent of longitudinal deformation that occurs in every part of the left atrial during a single cardiac cycle. This process provides a detailed analysis of the atrium's mechanical function by assessing its ability to stretch and contract, reflecting both its reservoir and contractile roles in cardiac performance. The A and E Doppler waveforms of apical inflow in the 4-chamber view are utilized to determine the transition points, such as the termination of early left ventricular expansion and the beginning of the contraction of the atrium. The precise phases of atrial function throughout the cardiac cycle are identified using the LA strain curve, providing detailed insights into atrial dynamics. This method ensures accurate evaluation of functional parameters, which are critical for understanding atrial behavior and identifying potential disruptions in its performance. Left atrial (LA) deformation progresses through three separate phases, with strain levels classified as negative or positive depending on whether the atrium is extending or contracting during each phase:

1. **Reservoir Phase**: This phase begins around the end of ventricular diastole, signified by the closure of the mitral valve, and continues until the valve reopens. It includes important cardiac cycle functions such as isovolumic contraction, ejection, and relaxation of the left ventricle. During this phase, the left atrium serves as a reservoir, accommodating pulmonary venous return while the ventricle contracts.
2. **Conduit Phase**: In individuals with sinus rhythm, this phase, which is started by the mitral valve's opening, lasts during diastasis till the start of LA contraction. It lasts until ventricular diastole is finished, which is indicated by mitral valve closure, in people with atrial fibrillation (AF). Throughout this phase, the left atrium functions passively, facilitating the movement of blood from the pulmonary veins into the left ventricle.
3. **Contraction Phase**: When the mitral valve closes at the conclusion of ventricular diastole, this phase comes to an end. It starts when the left atrium contracts vigorously. It emphasizes the function of the atrium in improving ventricular filling and is mostly seen in individuals having sinus rhythm.

For the purpose of strain measurements, the left ventricular end-diastole is established as the reference (zero) point, ensuring a standardized baseline for assessing atrial deformation throughout the cardiac cycle. This methodological approach provides a precise evaluation of LA function and its role in overall cardiac performance[15]. Tissue Doppler echocardiography was performed with the Nyquist velocity limits set between 15 and 20 cm/s to optimize the accuracy of data collection. Using Doppler imaging from the apical four-chamber view, the assessment concentrated on three important areas: the right ventricle tricuspid annulus, the left ventricle septal mitral annulus, and the left ventricular lateral mitral annulus. Various cardiac parameters were recorded, including peak systolic velocity (s/Sm), early diastolic velocity (e'/Em), and late diastolic velocity (a'/Am). In order to as-

sess heart function thoroughly, isovolumetric contracting time, isovolumetric time for relaxation (IVRT), and eject time were also recorded at the atrial and tricuspid annuli. The atrial electromechanical conduction time (PA) was evaluated by measuring the interval between the start of the P wave on the electrocardiogram (ECG) and the beginning of the late diastolic wave identified using tissue Doppler imaging. The measurements were taken from three specific anatomical locations: the septal mitral annulus (septal PA), the lateral mitral annulus (lateral PA), and the tricuspid annulus (tricuspid PA), providing a comprehensive assessment of atrial conduction dynamics. These measurements provide valuable insights into atrial conduction dynamics, helping to assess electromechanical coupling and identify potential conduction delays within the atria.

The differences between these conduction times were used to calculate various electromechanical delays (EMDs):

- The difference between tricuspid PA and lateral PA reflected interatrial EMD.
- The difference between septal PA and tricuspid PA represented right intra-atrial EMD.
- The difference between septal PA and lateral PA corresponded to left intra-atrial EMD.

This method provides a detailed assessment of conduction delays and mechanical asynchrony in the atria, offering valuable insights into atrial electrophysiology and potential arrhythmic risks [16,17].

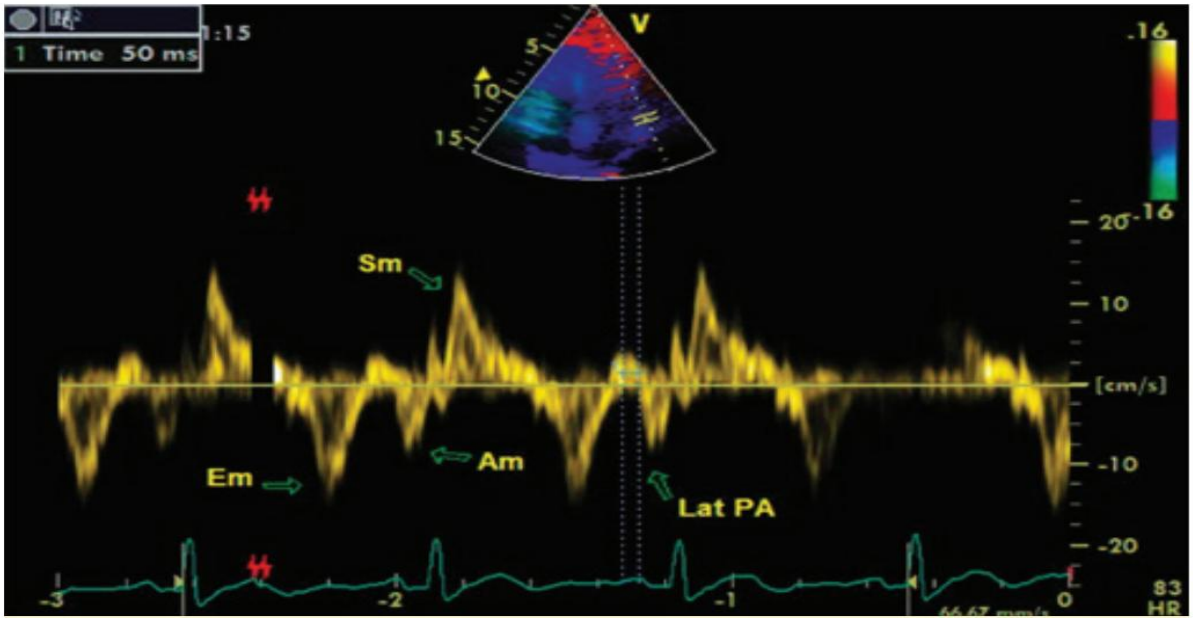

Figure 2. Assessment of atrial conduction time using echocardiography

Statistical Analysis

Data was collected in predesigned questionnaire papers and were coded and entered in Microsoft Excel Worksheet. The Statistical Program for Social Science (SPSS V-27) for Windows was used to organise and analyse the data. While categorical data were shown as percentages with their corresponding frequencies, continuous variables were provided as mean values with their standard deviation (SD). The χ^2 test was employed to assess associations between categorical variables. An independent sample t-test was

used to evaluate group differences for normally distributed data. Additionally, linear regression analysis was performed to further compare variations between the groups. Cumulative incidence trends over time were visualized using Kaplan–Meier curves, with the log-rank test applied to determine the statistical significance of observed differences. To adjust for potential discrepancies in baseline characteristics, multivariable Cox regression analysis was utilized. This approach facilitated the estimation of odds ratios (ORs) along with 95% confidence intervals (CIs), ensuring a comprehensive evaluation of the associations. A significance threshold of $P < 0.05$ was established for all statistical analyses.

Results

We have recruited 222 T2DM patients from June 2023 to December 2024 on the standard of care antidiabetic treatment, they all had recent paroxysmal AF (within 6 months) on maximally tolerated dose of beta blockers and were in sinus rhythm at the time of examination. Dapagliflozin group (113 patients): standard of care treatment of T2DM and maximally tolerated dose of beta blockers plus Dapagliflozin 10 mg. Control group (109 patients): standard of care treatment of T2DM (not including any SGLT2i) and maximally tolerated dose of beta blockers. Baseline characteristics are presented in Table 1; it was comparable in both groups. In dapagliflozin vs control group, respectively: the mean age was (61.3±3.6 years vs 60.2±4.7 years), the mean body mass index (BMI) was (31.5±4.2 kg/m2 vs 31.3±3.9 kg/m2), male gender was predominant (73.5% vs 72.5%), mean glycated hemoglobin was (7.4±0.9% vs 7.6±1.1) and diabetes duration was (8 vs 7 years).

Table 1 Baseline characteristics of the study groups

	Dapagliflozin group (N=113)	Control group (N=109)	P Value
Age-Years	61.3 ± 3.6	60.2 ± 4.7	0.538
Male-no. (%)	83 (73.5%)	79 (72.5%)	0.124
BMI- KG/m²	31.5 ± 4.2	31.3 ± 3.9	0.841
Systolic Blood Pressure- mmHg	135 ± 18	134 ± 17	0.912
Diastolic Blood Pressure- mmHg	83 ± 15	82 ± 16	0.981
Baseline Heart Rate- bpm	71 ± 13	68 ± 15	0.498
Type 2 DM			
Glycated hemoglobin -%	7.4 ± 0.9	7.6 ± 1.1	0.471
Diabetes Duration-years	8 (4-13)	7 (4-12)	0.521
Insulin treated-no%	29 (25.7%)	25 (22.9%)	0.681
Metformin -no%	77 (68.1%)	72 (66.1%)	0.582
DPPI -no%	36 (31.9%)	31 (28.4%)	0.641
Others -no%	3 (2.7%)	2 (1.8%)	0.558
eGFR-mL/min1.73m²	81 ± 16	84 ± 15	0.712
CHADVASc Score	2 ± 1.4	1.8 ± 1.2	0.08

Data are shown as mean ± SD at baseline and after 12 months. *P* value as calculated by *t*-test for continuous and χ^2 for categorical variables. SD: Standard. BMI indicates body mass index; DPP-4, dipeptidylpeptidase-4; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide.

At baseline and one year later, the data are displayed as mean ± SD. t-test for continuous variables and χ2 for categorical variables to get the P value. SD stands for Standard.

As shown in table 2, dapagliflozin group has shown significant improvement in E/e', the main indicator of diastolic filling pressure (reduced from 9.9±2.4 to 7.8±1.8, P< 0.011), and significant increase in the E/A ratio (0.86±0.22 to 0.95±0.23, P< 0.035), at 12-months follow-up, indicating improvement in LV diastolic function. Additionally, dapagliflozin markedly enhanced LA function over 12 months, as evidenced by a significant increase in LAS reservoir phase values (26.5±7.9% to 28.9±3.8%, P< 0.015) and LAS contraction (10.8±4.9% to 12.2±5.9%, P< 0.021).

Table 2. Echocardiographic data at baseline and one-year follow-up in the study population.

	Dapagliflozin group			Control group		
	Baseline	**12 months**	***P* Value**	**Baseline**	**12 months**	***P* Value**
Basic Echocardiographic Parameters						
LVEF %	59 ± 4	59 ± 5	0.589	58 ± 3	58 ± 4	0.437
LA area- cm²	21 ± 3.5	19 ±3.9	0.531	20 ± 3.7	20 ±4.1	0.232
LAVI-mL/m²	30 ±9	26 ± 7	0.235	31 ± 10	31 ±12	0.387
E - m/sec	0.78 ±0.15	0.76±0.12	0.121	0.76 ± b0.12	0.78±0.15	0.543
A – m/sec	0.81 ± 0.14	0.82 ±0.16	0.538	0.70 ± 0.13	0.71± 0.14	0.421
E/A	0.95 ±0.23	0.86 ± 0.22	**0.035**	1.11 ±0.48	1.23±0.23	0.328
e' septal – m/sec	7.4 ±1.9	7.8 ±1.8	0.561	7.3 ±1.7	6.7 ±1.8	0.178
e' lateral – m/sec	10.3 ±1.7	103 ±1.6	0.662	9.7 ± 1.9	9.5 ± 2.1	0.248
e' mean	8.9 ±1.8	8.8 ±1.9	0.482	8.5 ±1.6	8.7 ±1.9	0.451
E/e'	9.9 ±2.4	7.8 ±1.8	**0.011**	9.4 ± 2.1	9.8 ±1.5	0.533
DT – msec	205 ±46	217±42	0.262	197 ±53	196±48	0.362
Strain parameters (strain%)						
LA- Reservoir	26.5 ±7.9	28.9±3.8	**0.015**	24.6 ± 7.1	24.1±6.1	0.235
LA- Conduit	15.4 ± 4.9	16.7±4.2	0.612	11.6 ± 5.2	11.9±4.8	0.451
LA- Contraction	10.8 ±4.9	12.2±5.9	**0.021**	12.5 ± 4.7	12.6±5.1	0.323
Atrial Electromechanical Conduction Times						
Lateral PA	76.73± 8.38	62.92 ± 8.37	**0.031**	77.64 ± 7.98	78.31± 7.38	0.582
Septal PA	43.40 ± 5.91	39.67 ± 5.23	**0.037**	43.51±5.74	44.13±4.95	0.567
Tricuspid PA	69.15±10.81	57.92 ± 4.79	**0.038**	69.08±10.72	69.19±10.63	0.443
REMD (ms)	31.72 ± 4.82	27.73 ± 7.62	0.329	31.21 ± 5.37	31.89±5.49	0.532
LEMD (ms)	32.19 ± 9.37	28.82 ± 5.73	0.138	32.91 ±4.25	33.34±4.71	0.438
IEMD (ms)	29.75 ± 7.53	21.72 ± 4.51	**0.029**	29.28 ± 7.73	31.12±7.58	0.541

Abbreviations: LA, left atrium; LAVI, left atrial volume index; EMD, Electromechanical Delay; IEMD, interatrial electromechanical delay; LEMD, left-sided intra-atrial electromechanical delay; LVEF, left ventricular ejection fraction; PA, P to A' interval; REMD, right-sided intra-atrial electromechanical delay.

Similarly, the LA area decreased (21±3.5 cm2 to 19±3.9 cm2 at 12-monts follow-up, P< 0.531) and the LA volume indexed decreased (30 ±9 mL/m2 to 19±3.9 mL/m2 at 12-monts follow-up, P< 0.235), but these results weren't statistically significant. TDI has shown that lateral pulmonary acceleration (PA) time significantly decreased (76.73±8.38 ms vs 62.92±8.37 ms, P< 0.031), septal PA time has significantly de-

creased (43.40±5.91 ms vs 39.67±5.23ms, P< 0.037), and Tricuspid PA time has significantly decreased (69.15±10.81ms vs 57.92±4.79ms, P< 0.038), in dapagliflozin group at baseline vs 12-months follow-up, respectively. This was aligned with the statistically significant reduction observed in interatrial EMD times, which has fallen from 29.75±7.53 ms at baseline to 21.72±4.51 ms at 12-month follow-up in dapagliflozin group, P< 0.029). But there were no significant alterations in right or left interatrial EMD times. Expectedly, control group showed no statistically significant difference of all echocardiographic parameters at 12-month follow-up.

Of note, LVEF hasn't statistically changed from baseline to 12-months follow-up in either group.

Clinically, paroxysmal AF (documented by 24-hours Holter ECG or hospitalization) was documented in 8 (7.1%) individuals in dapagliflozin group, whereas it was documented in 15 (13.8%) individuals in the control group at 12-months follow-up (P value< 0.01).

Discussion

The primary finding of this study demonstrates that the addition of dapagliflozin to standard antidiabetic therapy and beta-blockers significantly improves left atrial (LA) strain over a 12-month follow-up period in patients with type 2 diabetes mellitus (T2DM) and documented paroxysmal atrial fibrillation (AF). This improvement in LA strain represents the study's primary endpoint, highlighting the potential role of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in enhancing atrial function and reducing AF burden. Beyond the primary outcome, the study also achieved notable secondary endpoints. There was a significant reduction in inter-atrial electromechanical delay (EMD), indicating enhanced atrial conduction and improved synchronization between the atria. Additionally, a marked improvement in left ventricular (LV) diastolic function was observed, reflecting the potential of dapagliflozin to mitigate diastolic dysfunction, a common feature in diabetic cardiomyopathy. These echocardiographic improvements translated into meaningful clinical benefits. Patients in the dapagliflozin group experienced a significant reduction in paroxysmal AF episodes, as documented by 12-month Holter ECG recordings and hospitalization records. This suggests that dapagliflozin may play a role in modifying AF progression by improving atrial mechanics, reducing myocardial fibrosis, and alleviating the electromechanical disturbances that contribute to AF recurrence. These findings reinforce the emerging evidence supporting the cardioprotective and antiarrhythmic properties of SGLT2 inhibitors, particularly in patients with T2DM and AF. Future studies with larger cohorts and longer follow-up durations are warranted to further validate these results and explore the underlying mechanisms responsible for these observed benefits.

As previously discussed, patients with type 2 diabetes mellitus (T2DM) face a heightened risk of developing atrial fibrillation (AF), largely driven by the combined effects of increased left ventricular stiffness and atrial fibrosis. These pathological changes are key contributors to cardiac remodeling, a process that disrupts the structural and functional integrity of the heart. The myocardial remodeling associated with T2DM not only alters the heart's electrical properties but also precipitates diastolic dysfunction, leading to elevated left ventricular end-diastolic pressure (LVEDP)[4].

Our study revealed a significant enhancement in LAS among patients in the

dapagliflozin group compared to the control group, underscoring its potential benefits in improving atrial function. LAS parameters have been widely acknowledged as crucial predictors of AF in various patient populations[7]. As proposed by Thiele et al., LAS can serve as a reliable diagnostic marker for assessing and grading the severity of diastolic dysfunction, offering a distinct advantage over conventional diagnostic criteria[18]. Thiele's findings further support the hypothesis that SGLT2 inhibitors may mitigate myocardial remodeling by reducing left atrial (LA) filling pressure and left ventricular end-diastolic pressure (LVEDP), ultimately decreasing the risk of AF. Sehly et al. demonstrated the beneficial impact of early empagliflozin therapy on left atrial strain (LAS) parameters in patients recovering from acute coronary syndrome. Their findings showed significant improvements in LA reservoir strain, LA conduit function, and LA contraction, highlighting the therapeutic potential of SGLT2 inhibitors in improving atrial mechanics[19].

Our study demonstrated that the use of dapagliflozin 10 mg in patients with type 2 diabetes mellitus (T2DM), previously diagnosed with paroxysmal atrial fibrillation (AF) and receiving beta-blockers, significantly reduced the recurrence of paroxysmal AF. This was confirmed through Holter ECG monitoring and hospital admission records, highlighting the efficacy of dapagliflozin in reducing AF burden. SGLT2 inhibitors have demonstrated the ability to reverse both electrical and structural remodeling of the atria. They improve mitochondrial function and enhance biogenesis, which may contribute to their protective effects in T2DM patients. Such mechanisms are particularly relevant in preventing AF associated with diabetes[20]. In addition, SGLT2 inhibitors may inhibit sodium-hydrogen exchange in myocardial cells, decrease sympathetic nervous system activity, and reduce the accumulation and inflammation of perivisceral adipose tissue. These mechanisms contribute to the antiarrhythmic properties of SGLT2 inhibitors. Supporting this, Li et al. reported an 18% reduction in the risk of atrial fibrillation (AF) and related composite events, including atrial flutter (AFL), in patients receiving SGLT2 inhibitor therapy[21].

Regarding echocardiographic, tissue Doppler parameters and interatrial EMD time, our study demonstrated a significant reduction in the E/e' ratio and interatrial EMD times in the dapagliflozin group at the 12-month follow-up. The E/e' ratio, an echocardiographic marker of left ventricular filling pressure and diastolic dysfunction, is a key predictor of atrial arrhythmia. In a study conducted by Maragkoudakis et al., echocardiographic evaluations of 30 T2DM patients with symptomatic heart failure were performed 30 days after dapagliflozin was added to their treatment regimen. Results showed a significant improvement in the E/e' ratio following dapagliflozin therapy[22]. Similarly, Enes et al. reported a notable decrease in E/e' ratio after six months of SGLT2 inhibitor therapy, with values dropping from 8.1 ± 4.0 to 6.5 ± 2.3 ($P < 0.003$), further supporting the beneficial impact of SGLT2 inhibitors on diastolic function[23].

Interatrial EMD, assessed through tissue Doppler imaging (TDI), is a measure of atrial conduction heterogeneity, defined as the time interval between the onset of atrial electrical activity and the mechanical contraction of the atrium. Prolonged EMD times are directly linked to atrial arrhythmogenesis and increased susceptibility to AF[24]. Patients with paroxysmal AF often exhibit greater delays in both interatrial and intra-atrial conduction. In a study by Demir et al., T2DM patients were found to have significantly longer mitral annulus lateral PA times and higher intra-atrial and

interatrial EMD compared to healthy controls[25]. Our findings align with these studies, emphasizing the role of dapagliflozin in improving atrial conduction properties and reducing AF risk. By lowering the E/e' ratio and shortening atrial EMD times, dapagliflozin may reduce left atrial strain and mitigate arrhythmogenic triggers. Our study demonstrated that the addition of dapagliflozin to standard antidiabetic medications and beta-blockers in T2DM patients with paroxysmal atrial fibrillation (AF) significantly reduced the recurrence of paroxysmal AF at the 12-month follow-up. This clinical outcome is strongly linked to the improvements we observed in diastolic function, left atrial (LA) strain, and LA electromechanical delay (EMD). The enhanced cardiac function achieved in the dapagliflozin group directly contributed to the reduced incidence of paroxysmal AF over the follow-up period.

The improvements in atrial function and conduction properties observed in our study provide strong evidence that dapagliflozin, when added to standard therapy, can reduce paroxysmal AF recurrence in T2DM patients. These findings, corroborated by Holter ECG recordings, highlight the potential of SGLT2 inhibitors in addressing the structural and electrophysiological mechanisms underlying AF, further solidifying their role in cardiovascular risk management.

Conclusion

Dapagliflozin addition to the standard antidiabetic treatment was associated with reduction of LA strain and interatrial electro-mechanical delay in type 2 DM patients who have paroxysmal AF. Moreover, this was associated with reduction of paroxysmal AF recurrence as documented by Holter ECG or hospitalization. These findings support the theory of the anti-arrhythmic effect of SGLT2 inhibitors.

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