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Mary Ann Liebert
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Effect of SGLT2 Inhibitors on Atrial Electromechanical Delay in Patients with Type 2 Diabetes

Muhammed Erzurum, MD[1], Mehmet Ali Felekoğlu, MD[2], Nadire Isık Erol Algül, MD[3], Alperen Taş, MD[4], Nail Burak Özbeyaz, MD[5], Engin Algül, MD[6], Faruk Aydinyilmaz, MD[7], Kamuran Kalkan, MD[8], and Tolga Han Efe, MD[6]

Abstract

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been associated with lower atrial fibrillation (AF) incidence in diabetes mellitus (DM). Atrial electromechanical delay (AEMD) is an electrophysiological marker related to AF development. This study evaluated AEMD changes in type 2 DM patients treated with an SGLT2 inhibitor (dapagliflozin or empagliflozin). Baseline and 4-month follow-up data of 50 patients with type 2 diabetes who initiated SGLT2 inhibitor therapy were retrospectively obtained from medical records and analyzed. AEMD was measured using echocardiography and tissue Doppler. Inter-AEMD and intra-AEMD intervals were calculated. Left atrial volume (LAVOL) significantly decreased (45.23 ± 9.27 vs 42.21 ± 9.16; $P < .001$), while left intra-AEMD (19.58 ± 7.53 vs 16.76 ± 7.53; $P < .001$), right intra-AEMD (14.42 ± 5.81 vs 12.46 ± 8.05; $P = .016$), and inter-AEMD (34 ± 9.41 vs 29.22 ± 9.44; $P < .001$) were significantly reduced. Inter-AEMD change correlated with LAVOL, E/E′ ratio, body mass index, and mean blood pressure changes (all $P < .05$). In diabetic patients treated with SGLT2 inhibitors, AEMD reduction was observed after 4 months, with favorable metabolic and hemodynamic effects. These findings suggest that SGLT2 inhibitors may protect against AF by improving atrial electromechanical function.

Keywords

atrial fibrillation, diabetes mellitus, atrial electromechanical delay, sodium–glucose cotransporter 2 (SGLT2) inhibitors

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, usually lifelong, resulting from impaired insulin secretion and/or ineffective utilization of the insulin produced.[1] It leads to increased morbidity and mortality due to microvascular and macrovascular complications.[1] Chronic hyperglycemia facilitates the development of cardiovascular disease by causing structural and functional impairments in various organ systems, particularly in the vascular endothelium.[2] Through mechanisms such as endothelial dysfunction, oxidative stress, inflammation, electrolyte imbalances, and autonomic nervous system disturbances, DM directly affects the cardiovascular system, thereby predisposing to the development of cardiomyopathy, coronary artery disease (CAD), heart failure (HF), and various arrhythmias.[2] In this context, cardiac rhythm disturbances observed in patients with DM hold particular clinical significance.

Among these complications, atrial fibrillation (AF), a common cardiac arrhythmia, is a supraventricular tachyarrhythmia associated with significant increases in morbidity and mortality.[3] AF is associated with a fivefold increased risk of stroke and a twofold increased risk of mortality.[3] It is also associated with HF, prolonged hospitalization, reduced quality of life, and decreased exercise capacity.[1,3] These findings have increased the importance of elucidating the underlying

[1]Department of Cardiology, Karabük Training and Research Hospital, Turkey
[2]Department of Cardiology, Yunus Emre State Hospital, Eskişehir, Turkey
[3]Department of Cardiology, Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Ankara, Turkey
[4]Department of Cardiology, Ahi Evran University Training and Research Hospital, Kırşehir, Turkey
[5]Department of Cardiology, Ankara University, Faculty of Medicine, Ankara, Turkey
[6]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Turkey
[7]Department of Cardiology, Erzurum City Hospital, Erzurum, Turkey
[8]Department of Cardiology, Ankara Bilkent City Hospital, Ankara, Turkey

Corresponding Author:
Muhammed Erzurum, MD, Department of Cardiology, Faculty of Medicine, Karabük University, Karabük 78000, Turkey.
Email: muhammederzurum42@gmail.com

mechanisms and identifying the risk factors associated with the development of AF in patients with type 2 DM.[3]

It has been demonstrated that type 2 DM is significantly associated with an increased risk of developing AF.[4] The underlying mechanisms are considered multifactorial, with myocardial remodeling due to insulin resistance, cardiac fibrosis resulting from an enhanced inflammatory response associated with increased epicardial adipose tissue, and alterations in atrial electrical properties emerging as the main contributing processes.[5-7] Prolonged interatrial conduction times, extended action potential duration, and increased atrial effective refractory period dispersion are among the proarrhythmic electrophysiological mechanisms observed in diabetic patients.[5]

Several pharmacological options are currently available for the treatment of diabetes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are antidiabetic agents that act by inhibiting SGLT2, a transporter responsible for glucose reabsorption in the proximal renal tubules, thereby inducing glucosuria, osmotic diuresis, and natriuresis.[8] In several recent large-scale placebo-controlled randomized trials, SGLT2 inhibitors have been shown to potentially reduce cardiovascular outcomes, particularly the risk of HF and all-cause mortality.[9-11] Given the beneficial effects of SGLT2 inhibitors on the cardiovascular system, elucidating their impact on AF development and the underlying mechanisms mediating these effects holds significant scientific importance.

Several non-invasive electrocardiographic and combined electro-echocardiographic methods have been defined to predict the development of AF. Prolongation of intra- and interatrial conduction times, referred to as atrial electromechanical delay (AEMD), is a well-established electrophysiological finding that has been shown to be associated with the development and recurrence of AF in patients with or without heart disease.[12] Inter-AEMD refers to the electromechanical coupling time (PA) interval difference between the lateral mitral and tricuspid annuli, whereas intra-AEMD denotes the PA interval difference between annuli within the same atrium. AEMD has been proposed as an early marker of AF in several large-scale studies.[13]

Although several mechanisms have been proposed to explain the reduction in AF incidence with SGLT2 inhibitors, data remain scarce regarding whether this effect is associated with AEMD, a well-known predictor of AF, and whether a decrease in AEMD contributes to reducing AF incidence. The present study aimed to evaluate the difference between AEMD measured prior to the initiation of SGLT2 inhibitor therapy and AEMD measured at the end of the 4th month in patients with type 2 DM on background metformin treatment.

Materials and Methods

This study was designed as a retrospective analysis of patients diagnosed with type 2 DM in routine clinical practice. Patients aged 35 to 75 years with a confirmed diagnosis of type 2 DM who were on metformin therapy and subsequently initiated on an SGLT2 inhibitor were included. The diagnosis and treatment of DM were determined and implemented in accordance with current clinical guidelines.[14,15] The exclusion criteria were: age >75 years, insulin-dependent DM, CAD, HF, moderate-to-severe valvular heart disease, any arrhythmia, obstructive sleep apnea syndrome, chronic lung disease, liver failure, systemic inflammatory disease, renal failure, malignancy, history of cerebrovascular events, history of pulmonary embolism, hypothyroidism, hyperthyroidism, and body mass index (BMI) >35. To eliminate the confounding effect of elevated blood pressure on AEMD measurements, the study included only normotensive patients. Clinical data, medication history, and laboratory findings of the patients were obtained from hospital records.

A total of 50 patients who met the inclusion criteria after applying the exclusion parameters were enrolled in the study (Figure 1). Baseline measurements and those obtained at the end of the 4th month were compared. The study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital with decision number 114/15 dated 28/06/2021. The study was conducted in accordance with the ethical principles and standards of the Declaration of Helsinki and Good Clinical Practice guidelines.

Electrocardiographic Measurements

To increase measurement accuracy, ECGs were digitally magnified and examined. The QT interval was measured in milliseconds (ms) from the beginning of the Q wave (or the R wave if the Q wave was absent) to the point where the descending limb of the T wave intersected the isoelectric line. Among the leads in which the end of the T wave could be clearly identified, the lead with the longest QT interval was considered. Leads with a U wave or an indistinct termination of the T wave were excluded. The corrected QT (QTc) interval was calculated using Bazett's formula ($QT/\sqrt{R\text{-}R}$). All measurements were performed twice. Each ECG was evaluated independently by 2 cardiologists, and interobserver agreement was achieved.

Echocardiographic Measurements

The measurements were performed in accordance with the recommendations of the American Society of Echocardiography (ASE),[16] using a Philips Healthcare iE33 xMATRIX Echocardiography system (Philips Medical System, Andover, MA, USA) with an S5-1 transducer. All images were obtained in a single-lead mode under continuous ECG monitoring. Each measurement represented the average of at least three consecutive cardiac cycles.

Atrial electromechanical properties were assessed using tissue Doppler imaging (TDI). The Nyquist limit (velocity scale) was set at 15 to 20 cm/s, and the monitor sweep speed was adjusted to 50 to 100 mm/s to optimize the spectral display of myocardial velocities. Standard 2-dimensional apical

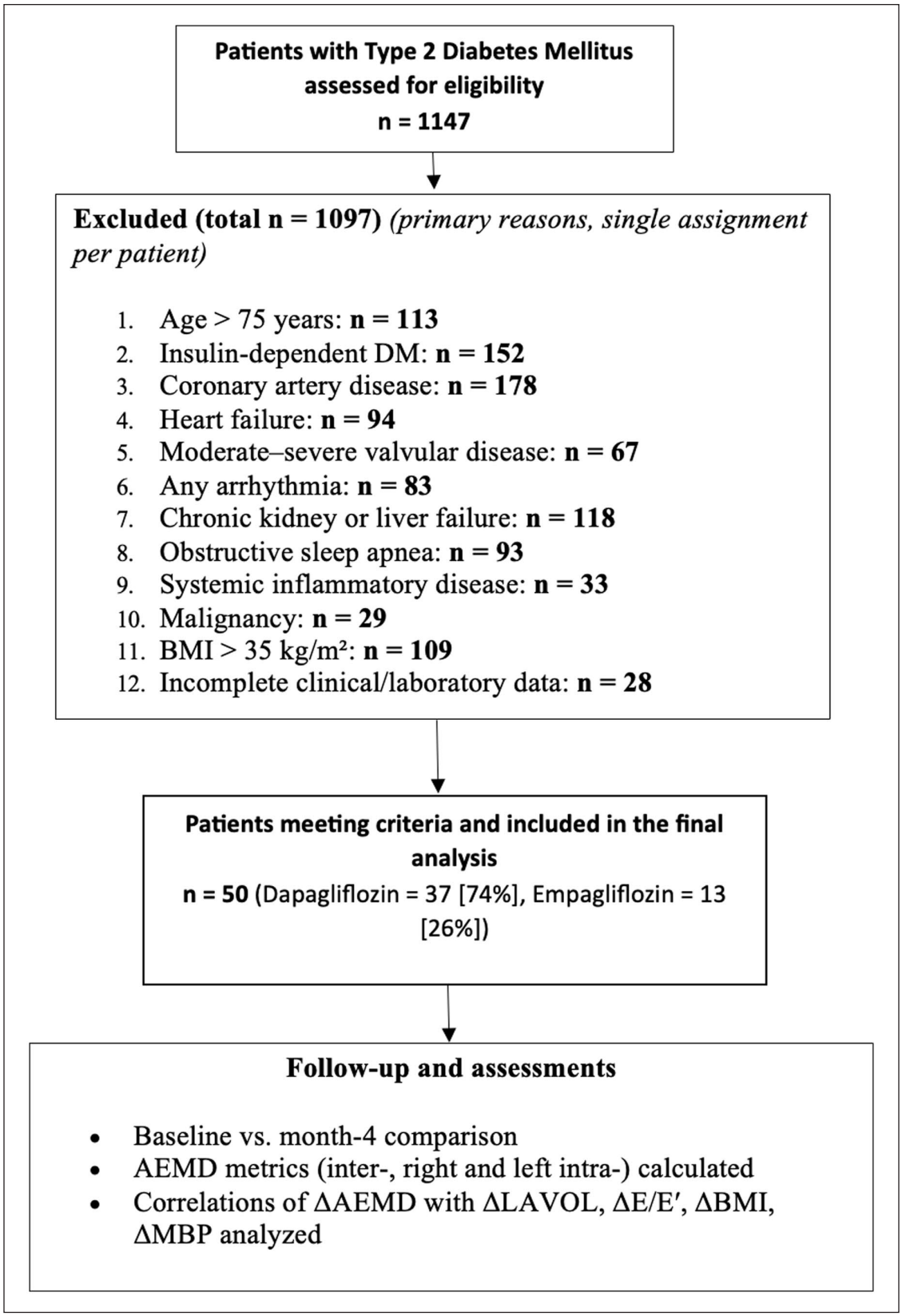

Figure 1. Flowchart showing patient selection and inclusion in the final analysis.
Abbreviations: DM, Diabetes mellitus; BMI, Body mass index; AEMD, Atrial electromechanical delay; ΔAEMD, Change in atrial electromechanical delay; ΔLAVOL, Change in left atrial volume; ΔE/E′, Change in the ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (E′); ΔBMI, Change in body mass index; ΔMBP, Change in mean blood pressure.

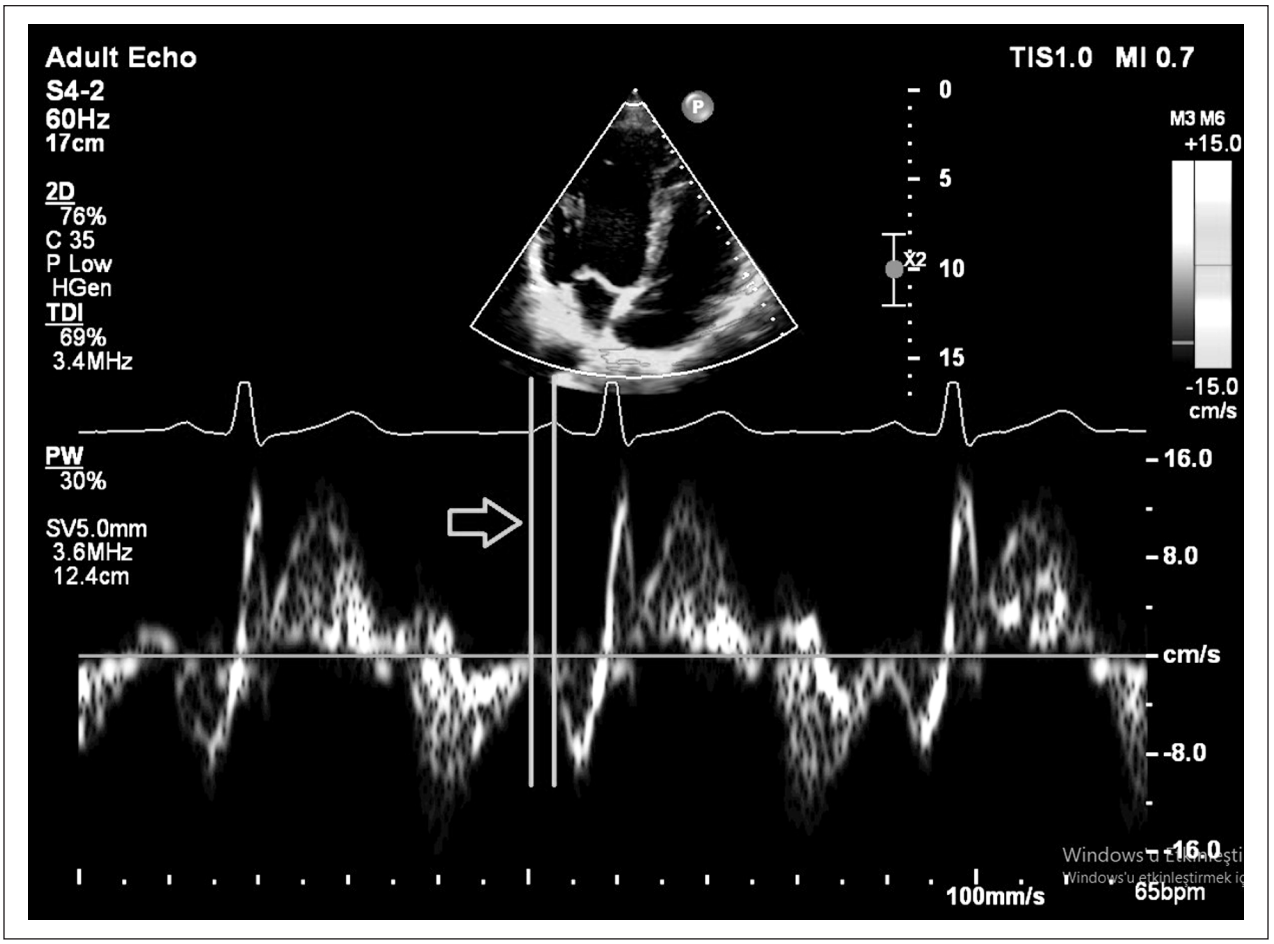

Figure 2. Measurement of the PA interval (atrial electromechanical coupling time) using tissue Doppler imaging.
Abbreviations: PA, Electromechanical coupling time (interval from the onset of the P wave to the onset of atrial contraction [Am wave]); TDI, Tissue Doppler imaging; Am, Atrial contraction wave.

four-chamber views were obtained to visualize the free walls of the right and left ventricles from the apex to the atrioventricular valve annulus. In TDI mode, the PW Doppler cursor was placed at the lateral mitral, septal mitral, and tricuspid annuli, and recordings were obtained. From each annulus, measurements of early diastolic myocardial velocity (E′), late diastolic wave (Am), and atrial systolic wave (A) were performed.

Electromechanical coupling time was defined as the interval from the onset of the P wave to the beginning of the atrial contraction (Am wave) observed on TDI, and this interval was designated as the PA interval (Figure 2). This interval represents the time delay between atrial electrical activation and the onset of atrial mechanical contraction. The PA intervals measured from the lateral mitral, septal mitral, and lateral tricuspid annuli were termed PA lateral, PA septal, and PA tricuspid, respectively. The difference between the lateral and septal PA intervals was defined as left intra-AEMD, the difference between septal and tricuspid PA intervals as right intra-AEMD, and the difference between lateral and tricuspid PA intervals as inter-AEMD.

Statistical Analysis

The normality of variable distributions was assessed using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean ± standard deviation for normally distributed variables, and as median with minimum-maximum values for non-normally distributed variables. Categorical variables were presented as case numbers and percentages (%). For the comparison of parameters at baseline and at the 4th month, the paired samples t-test was applied to continuous variables with normal distribution, whereas the Wilcoxon Signed-Rank Test was used for non-normally distributed variables. Correlation analyses were performed using Pearson correlation for normally distributed variables and Spearman correlation for non-normally distributed variables. A P-value of $<.05$ 2-sided was considered statistically significant in all analyses. Statistical analyses were conducted using the SPSS software, version 24 (IBM Corp., Armonk, NY, USA).

Table 1. Baseline Clinical, Demographic, and Laboratory Characteristics of the Patients.

Age (years)	**55.6 (38-72)**
Sex, n (%)	Male = 23(46) Female = 27(54)
Age at diagnosis (years)	46.5 (31-55)
Disease duration (months)	107.0 (36-240)
Smoking status, n (%)	Yes 23(46) No 27(54)
SGLT2i, n (%)	Dapagliflozin = 37(74) Empagliflozin = 13(26)
Weight (kg)	80.8 (61-109)
BMI (kg/m^2)	29.9 ± 3.1
SBP (mmHg)	122.2 ± 6.3
DBP (mmHg)	71.5 (62-80)
MBP (mmHg)	88.3 ± 4.9
HbA1c (%)	8.8 (6.8-14.2)
Fasting plasma glucose (mg/dL)	188.5 (126-414)
Creatinine (mg/dL)	0.75 (0.49-1.12)
Total cholesterol (mg/dL)	163 ± 42
Triglycerides (mg/dL)	187 ± 69
HDL-C (mg/dL)	39 (20-72)
LDL-C (mg/dL)	105 (43-224)
Hemoglobin (g/dL)	14.1 (11.8-17.6)
NT-proBNP (ng/L)	49.80 (5-122)

Parameters with normal distribution are presented as mean ± standard deviation (SD), non-normally distributed parameters are expressed as median (minimum–maximum), and categorical variables as number (percentage).
Abbreviations: SGLT2i, Sodium-glucose cotransporter-2 inhibitors; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MBP, Mean blood pressure; HbA1c, Glycated hemoglobin; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Results

The mean age of the patients was 55.6 years (range: 38-72), and 27 (54%) were female. Dapagliflozin was initiated in 74% (n = 37) of the patients at a dose of 10 mg once daily, while 26% (n = 13) received empagliflozin at a dose of 10 mg once daily. The baseline clinical, demographic, and laboratory characteristics of all patients are presented in Table 1.

At the 4-month follow-up after initiation of SGLT2 inhibitor therapy, a statistically significant reduction in BMI was observed (29.9 ± 3.1 vs 28.0 ± 2.6 kg/m^2; $P < .001$). Systolic blood pressure decreased from 122.2 ± 6.3 mmHg to 118.7 ± 6.3 mmHg ($P < .001$), diastolic blood pressure from 71.5 mmHg (62-80) to 68.5 mmHg (56-80) ($P < .001$), and mean blood pressure (MBP) from 88.3 ± 4.9 mmHg to 85.2 ± 5.2 mmHg ($P < .001$). The mean HbA1c level decreased significantly from 8.8% (6.8-14.2) to 7.3% (5.8-10.6) ($P < .001$). Regarding lipid parameters, no significant differences were observed in total cholesterol, triglycerides, or high density lipoprotein cholesterol (HDL-C) levels ($P = .651$, $P = .503$, and $P = .422$, respectively), whereas low density lipoprotein cholesterol (LDL-C) decreased significantly from 104.9 mg/dL (43-224) to 100.4 mg/dL (43-224) ($P = .041$). N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels also decreased significantly from 49.8 ng/L (5-122) to 45.3 ng/L (5-146.6) ($P = .003$). No significant difference was observed regarding concomitant statin therapy ($P = .182$) (Table 2).

Baseline E′ was measured as 6.71 ± 1.20 cm/s and increased to 8.37 ± 1.7 cm/s at follow-up ($P < .001$). The E/E′ ratio decreased from 10.75 ± 2.31 to 8.22 ± 2.14 ($P < .001$). Tricuspid annular plane systolic excursion (TAPSE) increased from 26.2 to 27.0 mm ($P = .026$). Baseline lateral, septal, and tricuspid PA intervals were 69.40, 49.82, and 35.40 ms, respectively, and decreased to 58.04, 41.28, and 28.82 ms at follow-up ($P < .001$, respectively). Inter-AEMD decreased from 34 ± 9.41 to 29.22 ± 9.44 ms, left intra-AEMD from 19.58 ± 7.53 to 16.76 ± 7.53 ms, and right intra-AEMD from 14.42 ± 5.81 to 12.46 ± 8.05 ms ($P < .001$, $P < .001$, $P = .016$, respectively). Left atrial volume (LAVOL) decreased by approximately 3 ml ($P < .001$). The corrected QT (QTc) interval decreased significantly from 404.40 ms (368-470) at baseline to 398.60 ms (374-420) at follow-up ($P = .019$) (Table 3).

A positive correlation was found between the change in inter-AEMD and the decrease in LAVOL (r = 0.30; $P < .001$), the decrease in E/E' (r = 0.49; $P < .001$), the decrease in BMI (r = 0.36; $P = .011$), and the decrease in MBP (r = 0.45; $P = .001$) (Figure 3 and Table 4).

Discussion

In the present study, SGLT2 inhibitor therapy led to a significant improvement in AEMD after 4 months of treatment in diabetic patients. While the literature has reported favorable effects of empagliflozin on AEMD, our study differs by evaluating patients treated with dapagliflozin or empagliflozin.[17] Moreover, the higher proportion of patients receiving dapagliflozin in our study population may have contributed to a stronger demonstration of the class effect of SGLT2 inhibitors on AEMD.

The 4-month follow-up interval was selected because previous clinical and electrophysiological studies have demonstrated that atrial reverse remodeling, improvement in diastolic function, and shortening of AEMD can be detected within a relatively short period.[18-22] Moreover, a 4-month timeframe provides sufficient duration to reliably capture meaningful improvements in atrial electromechanical function.[18-22]

Table 2. Baseline and Fourth-Month Clinical and Laboratory Characteristics of Patients Treated with SGLT2 Inhibitors.

Variable	Baseline (Month 0)	Fourth Month	*P* value
Weight (kg)	80.8 (61-109)	75.7 (56-102)	**<.001***
BMI (kg/m^2)	29.9 ± 3.1	28.0 ± 2.6	**<.001***
SBP (mmHg)	122.2 ± 6.3	118.7 ± 6.3	**<.001***
DBP (mmHg)	71.5 (62-80)	68.5 (56-80)	**<.001***
MBP (mmHg)	88.3 ± 4.9	85.2 ± 5.2	**<.001***
HbA1c (%)	8.8 (6.8-14.2)	7.3 (5.8-10.6)	**<.001***
Fasting plasma glucose (mg/dL)	188 (126-414)	142 (95-265)	**<.001***
Creatinine (mg/dL)	0.75 (0.49-1.12)	0.78 (0.52-1.12)	**.008***
Total cholesterol (mg/dL)	163 ± 42	161 ± 33	.651
Triglycerides (mg/dL)	187 ± 69	192 ± 71	.503
HDL-C (mg/dL)	39 (20-72)	40 (27-72)	.422
LDL-C (mg/dL)	105 (43-224)	100 (43-224)	**.041***
Hemoglobin (g/dL)	14.1 (11.8-17.6)	14.2 (11.5-17.6)	.833
NT-proBNP (ng/L)	49.80 (5-122)	45.34 (5-146.6)	**.003***
Statin use, n (%)	45 (90)	48 (96)	.182

Parameters with normal distribution are presented as mean ± standard deviation (SD), non-normally distributed parameters are expressed as median (minimum-maximum), and categorical variables as number (percentage).
Abbreviations: SGLT2, Sodium-glucose cotransporter-2; BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; MBP, Mean blood pressure; HbA1c, Glycated hemoglobin; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
*$P < .05$ was considered statistically significant.
Gray shading is used for visual readability only.

DM is an independent risk factor for the development of AF.[5] The underlying complex pathophysiology involves electrical, structural, electromechanical, and autonomic remodeling.[5] Glucose-lowering therapies may influence the development of AF in either a beneficial or detrimental way. While metformin and thiazolidinediones reduce the risk of AF, insulin increases this risk.[5,23] Sulfonylureas, dipeptidyl peptidase-4 inhibitors, and glucagon-like peptide-1 receptor agonists do not significantly alter the incidence of AF.[5]

In several meta-analyses of clinical trials, SGLT2 inhibitors were not associated with new-onset AF when compared with placebo.[24] Moreover, in cardiovascular outcome trials, no significant difference in new-onset AF was reported in patients treated with SGLT2 inhibitors.[25-27] However, in a meta-analysis including large studies with SGLT2 inhibitors, a lower incidence of AF was demonstrated in DM patients treated with SGLT2 inhibitors.[28] Although large cardiovascular outcome trials did not demonstrate a significant reduction in AF incidence, these trials were not designed or powered to evaluate AF as a primary endpoint.[25-27] When AF data from these large studies were subsequently pooled in meta-analyses, a modest but statistically significant class effect of SGLT2 inhibitors in reducing AF incidence emerged, suggesting that earlier neutral findings likely reflected endpoint limitations rather than a true absence of benefit.[28] It has been suggested that the beneficial effects of SGLT2 inhibitors, such as reductions in HbA1c, blood pressure, and body weight, may play a role in decreasing the incidence of AF.[28] Some of the structural changes observed following SGLT2 inhibitor therapy that are associated with a reduced incidence of AF are: increased urinary glucose excretion leads to osmotic diuresis, which results in a reduction in arterial blood pressure, thereby delaying myocardial structural remodeling and attenuating atrial fibrosis.[29] Glucose loss through diuresis contributes to weight reduction, and weight loss has been shown to decrease atrial enlargement and the occurrence of AF.[30] Studies in diabetic animal models have demonstrated that SGLT2 inhibitors directly promote the improvement of cardiac fibrosis.[28] Shao et al[31] demonstrated that SGLT2 inhibitors improve mitochondrial function, thereby markedly reducing atrial remodeling and cardiac fibrosis.[31] Habibi et al[22] suggested that empagliflozin may improve pro-fibrotic signaling and the associated interstitial fibrosis.[22]

One of the beneficial effects of SGLT2 inhibitors is the reduction of epicardial adipose tissue (EAT).[32] It has been reported that EAT is associated with the initiation, maintenance, and recurrence of AF.[33] Epicardial fat thickness has been shown to be increased in diabetic individuals and to be greater in those with ischemic stroke.[34,35] In animal models, dapagliflozin has been shown to reduce plasma glucose, adipokine

Table 3. Comparison of Electrocardiographic and Echocardiographic Parameters at Baseline and at the Fourth Month in Patients Treated with SGLT2 Inhibitors.

Variable	Baseline (Month 0)	Fourth Month	*P* value
LVEF (%)	62.9 (60-68)	62.6 (60-68)	.083
LVEDD (cm)	4.60 ± 0.31	4.58 ± 0.25	.392
LVESD (cm)	2.54 (1.8-3.2)	2.48 (1.8-2.9)	.325
Septal wall (cm)	1.00 (0.8-1.1)	1.01 (0.7-1.3)	.907
Posterior wall (cm)	0.97 (0.8-1.2)	0.98 (0.7-1.3)	.369
Left atrium (cm)	3.68 (3.1-4.4)	3.68 (3.1-4.5)	.645
E (cm/s)	70.32 ± 12.17	66.18 ± 12.12	**.006***
A (cm/s)	83.83 ± 16.70	84.92 ± 19.08	.704
E/A	0.75 ± 0.10	0.76 ± 0.17	.552
Septal E' (cm/s)	6.71 ± 1.20	8.37 ± 1.7	**<.001***
E/E'	10.75 ± 2.31	8.22 ± 2.14	**<.001***
TAPSE (mm)	26.2 (18-37)	27.0 (23-37)	**.026***
PA lateral (ms)	69.40 (39-93)	58.04 (35-82)	**<.001***
PA septal (ms)	49.82 (28-68)	41.28 (28-61)	**<.001***
PA tricuspid (ms)	35.40 ± 5.59	28.82 ± 5.45	**<.001***
Inter-AEMD (ms)	34 ± 9.41	29.22 ± 9.44	**<.001***
Right intra-AEMD (ms)	14.42 ± 5.81	12.46 ± 8.05	**.016***
Left intra-AEMD (ms)	19.58 ± 7.53	16.76 ± 7.53	**<.001***
LAVOL (ml)	45.23 ± 9.27	42.21 ± 9.16	**<.001***
Heart rate (beats/min)	86.1 ± 16.1	86.1 ± 13.2	.983
QTc (ms)	404.40 (368-470)	398.60 (374-420)	**.019***

Parameters with normal distribution are presented as mean ± standard deviation (SD), non-normally distributed parameters are expressed as median (minimum-maximum), and categorical variables as number (percentage).
Abbreviations: SGLT2, Sodium-glucose cotransporter-2; LVEF, Left ventricular ejection fraction; LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; E, Early transmitral flow velocity; A, Late transmitral flow velocity; E′, Early diastolic mitral annular velocity; TAPSE, Tricuspid annular plane systolic excursion; AEMD, Atrial electromechanical delay; PA, Electromechanical coupling time; LAVOL, Left atrial volume; QTc, Corrected QT interval.
*$P < .05$ was considered statistically significant. Bold values indicate statistically significant results.
Gray shading is used for visual readability only.

levels, and adipocyte size.[36] In human studies, dapagliflozin has been shown to positively affect epicardial adipocyte differentiation and reduce the secretion of pro-inflammatory chemokines.[37] These findings suggest that the reduction in EAT may represent one of the potential mechanisms by which SGLT2 inhibitors decrease the incidence of AF.

LA enlargement, increased LV wall thickness, alterations in reduced LV fractional shortening, elevation of E/E′ as an indicator of diastolic dysfunction, and prolongation of AEMD have been shown to be associated with the development and recurrence of AF.[12,13,38-40] An increase of 5 mm in LA size, a 5% reduction in LV fractional shortening, and a 4 mm increase in septal and posterior LV wall thickness have been identified as being associated with an increased incidence of AF.[38] In the study conducted by Atas et al[41], no significant differences were observed in LV diameters or ejection fraction, which reflect LV systolic function, between non-hypertensive diabetic patients and the non-diabetic control group.[41] However, diabetic patients had significantly higher E/E' ratios and LAVOL values.[41] In the study conducted by Demir et al[42], inter-AEMD as well as right and left intra-AEMD were found to be significantly higher in patients with type 2 DM compared with the control group.[42] A positive correlation was identified between inter-AEMD and LAVOL.[42] In addition, AEMD was observed to be higher in patients with type 2 DM than in the normal population.[42]

In the present study, fasting glucose, HbA1c, blood pressure, and BMI were found to be reduced at follow-up, consistent with previous studies on SGLT2 inhibitors.[26,28,43] Although the increase in creatinine levels reached statistical significance, its magnitude was small and is consistent with the well-described early and typically transient hemodynamic effect of SGLT2 inhibitors mediated by tubuloglomerular feedback, reinforcing the pharmacological mechanism of these agents rather than indicating renal injury.[26,28,43] Taken together, these findings are consistent

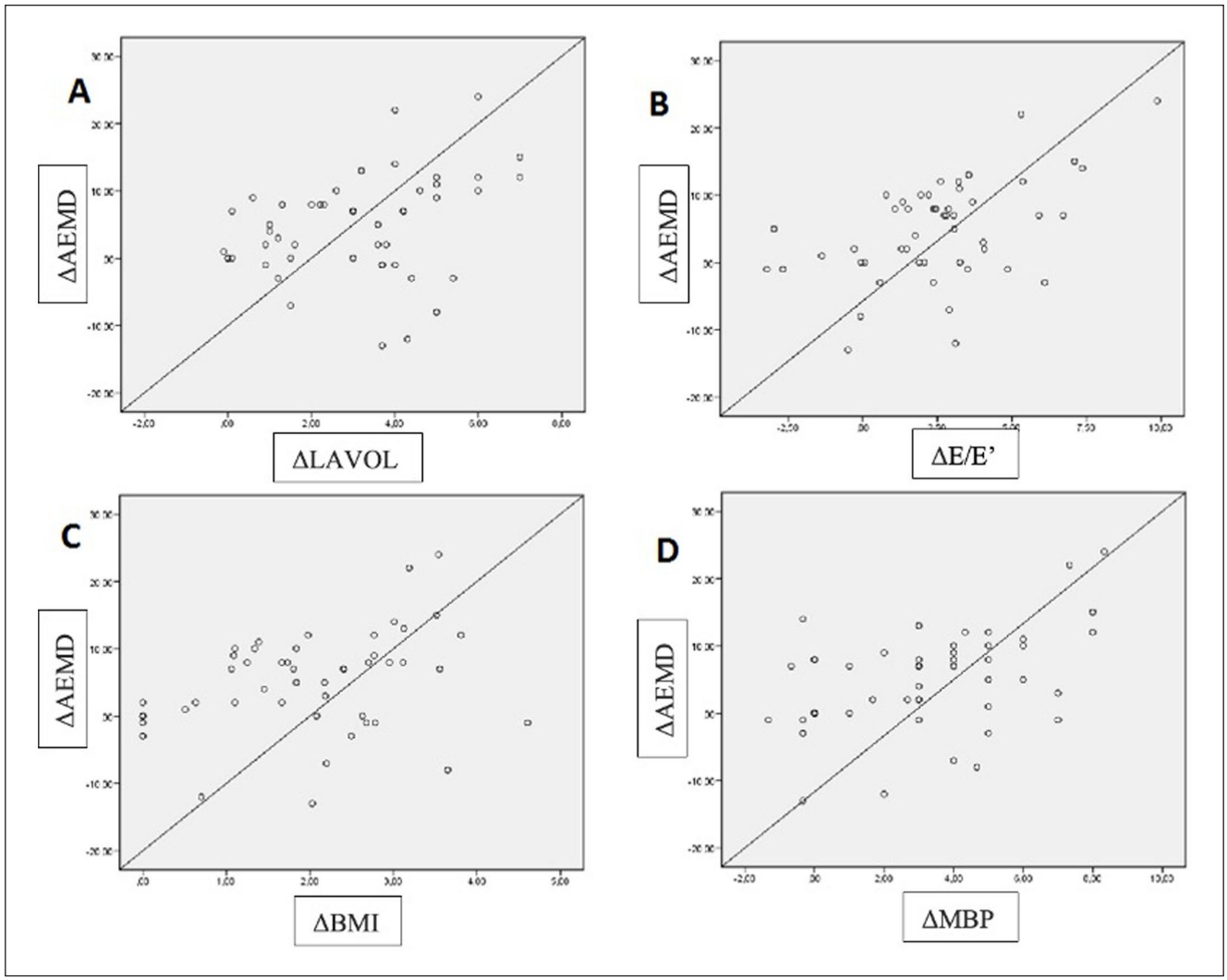

Figure 3. Correlation analysis between ΔAEMD and changes in LAVOL, E/E′, BMI, and MBP.
Abbreviations: ΔAEMD, Change in atrial electromechanical delay; LAVOL, Left atrial volume; E/E′, Ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (E′); BMI, Body mass index; MBP, Mean blood pressure.

Table 4. Correlations Between Changes in Inter-AEMD and Clinical Parameters.

	Change amount	r	*P* value
Δ*LAVOL	3.02 ± 1.9	0.30	**<.001**
ΔE/E′	2.53 ± 2.6	0.49	**<.001**
ΔBMI	1.93 ± 1.18	0.36	**.011**
ΔMBP	3.07 ± 2.68	0.45	**.001**
ΔHbA1c	1.47 ± 1.43	0.16	.266

Abbreviations: AEMD, Atrial electromechanical delay; LAVOL, Left atrial volume; E, Early transmitral flow velocity; E′, Early diastolic mitral annular velocity; BMI, Body mass index; MBP, Mean blood pressure; HbA1c, Glycated hemoglobin.
*Δ indicates change.
$P < .05$ was considered statistically significant. Bold values indicate statistically significant results.
Gray shading is used for visual readability only.

with the well-known general characteristics of SGLT2 inhibitors.[26,28,43] In a study including stable heart failure patients with normal BNP levels treated with dapagliflozin, no significant changes in BNP levels were observed following therapy; however, a significant reduction was detected in patients with BNP levels ≥100 pg/mL.[44] In a study involving patients with NT-proBNP levels within the normal range, empagliflozin treatment was associated with a reduction in NT-proBNP levels during the first four weeks; however, this effect was no longer evident by the end of the third month.[45] In our study, NT-proBNP levels were found to decrease even when within the normal range. Indeed, reductions in natriuretic peptides within the normal range have been suggested to exert beneficial effects on cardiovascular risk and mortality.[46] The reductions in LAVOL and blood pressure observed in our study may represent mechanisms that explain the decrease in NT-proBNP levels.

A reduction in inter-AEMD is known to be associated with a lower incidence of AF.[12,13] In our study, baseline inter-AEMD and intra-AEMD measurements were found to be longer compared with the data of diabetic patients reported in other studies.[47-49] In particular, lateral AEMD was found to be longer compared with previous studies in the literature. This finding supports that the study was conducted in a population at high risk for AF development. Previous studies have shown that lateral AEMD increases with advancing age and larger LA size.[47,48] The longer duration of lateral AEMD observed in our study may be explained by the higher mean age and larger LA size of our patients compared with those reported in previous studies. It is likely that other pathophysiological and electrophysiological mechanisms, such as atrial fibrosis induced by DM, may also have contributed to this prolongation. Indeed, a study conducted in patients with DM also found lateral AEMD to be higher than that reported in other studies.[50] Furthermore, while no statistically significant difference was detected in LA diameter at follow-up, LAVOL was significantly reduced. In a study conducted by Ermiş et al,[51] no change in LA diameter was observed in prehypertensive patients compared with the control group.[51] This suggests that mild changes in blood pressure are not expected to immediately alter LA diameter in the early period, and our study results support this notion. In a study conducted by Soga et al[44] with dapagliflozin, a significant reduction in LA volume index was observed at the 6-month follow-up. This reduction was attributed to decreased preload and increased diuresis.[44] The reduction in LAVOL observed in our study may be explained by a similar mechanism.

It has been demonstrated in the literature that AEMD increases with larger LA size.[47,48] This is because the timing of mechanical activation at each reference point—namely the lateral mitral, septal mitral, and RV tricuspid annuli—depends on their distance from the sinus node. SGLT2 inhibitors have been shown to improve diastolic function and significantly reduce E/E' ratios.[52] In our study, the significant reduction in E/E' may be attributed to the improvement in diastolic function. One of the mechanisms underlying the reduction in AEMD observed in our study may be the improvement in diastolic dysfunction, as AEMD has been reported to be longer in patients with left ventricular diastolic dysfunction.[53] The correlation we observed further supports this effect.

Importantly, the correlation coefficients observed in our study help clarify the mechanisms underlying AEMD reduction. The strongest correlation was found between ΔAEMD and ΔE/E′ ($r=0.49$), indicating that improvement in diastolic function plays a major role in the shortening of AEMD. Moderate correlations with ΔMBP ($r=0.45$) and ΔBMI ($r=0.36$) suggest that blood pressure reduction and metabolic improvement also contribute meaningfully, although to a lesser extent. Finally, the weak-to-moderate correlation with ΔLAVOL ($r=0.30$) supports a complementary role of atrial structural remodeling. Taken together, these findings demonstrate that the reduction in inter-AEMD during SGLT2 inhibitor therapy is multifactorial rather than driven by a single dominant pathway.

No association was found between changes in AEMD and HbA1c. Similarly, studies conducted in diabetic patients have also reported no relationship between AEMD and HbA1c or fasting plasma glucose levels.[50] This suggests that the reduction in AEMD in patients receiving SGLT2 inhibitors may result not so much from glucose levels or their control, but rather from the clinical and hemodynamic improvements provided by SGLT2 inhibitors.

Limitations

The main limitations of this study are its retrospective design and the relatively small sample size. Given its retrospective nature, the present study is susceptible to selection bias because SGLT2 inhibitors were prescribed only to a subgroup of eligible patients based on the treating physicians' clinical judgement rather than through random allocation. Moreover, unmeasured confounders such as diet, physical activity, medication adherence, and other lifestyle factors may have influenced the results. Therefore, the causal inference should be interpreted with caution. Long-term monitoring of the study population for the development of overt or subclinical AF would have provided stronger evidence for establishing causality. In this context, future studies with larger cohorts and longer follow-up, incorporating atrial electrophysiological assessments and imaging modalities such as MRI to evaluate atrial remodeling processes, will broaden our understanding of the mechanisms by which SGLT2 inhibitors may reduce the incidence of AF.

Conclusion

In the present study, diabetic patients receiving SGLT2 inhibitor therapy demonstrated not only favorable metabolic effects but also a significant reduction in AEMD after 4 months of follow-up. This finding suggests that SGLT2 inhibitors may contribute to a lower incidence of AF in diabetic populations by positively influencing atrial electrical remodeling.

Authors' Note

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ORCID iDs

Muhammed Erzurum https://orcid.org/0000-0002-0911-1271
Mehmet Ali Felekoğlu https://orcid.org/0000-0001-7991-5139
Nadire Isık Erol Algül https://orcid.org/0009-0002-8160-0499
Alperen Taş https://orcid.org/0000-0002-1696-7449
Nail Burak Özbeyaz https://orcid.org/0000-0002-7132-4286
Engin Algül https://orcid.org/0000-0003-1539-4738
Faruk Aydinyilmaz https://orcid.org/0000-0003-1088-3559
Kamuran Kalkan https://orcid.org/0000-0001-6204-316X
Tolga Han Efe https://orcid.org/0000-0001-6015-9679

Author Contributions

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

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