

The Impact of Sodium-Glucose Cotransporter-2 Inhibitors on Atrial Electromechanical Conduction Time

Sodyum-Glukoz Kotransporter-2 İnhibitörlerinin Atriyal Elektromekanik İleti Zamanı Üzerine Etkisi

ABSTRACT

Objective: This study aims to explore the impact of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, a newer class of oral antidiabetic drugs, on atrial electromechanical delay (EMD) in patients with type 2 diabetes mellitus (DM). This is particularly relevant given the significantly higher incidence of atrial fibrillation (AF) in diabetic patients compared to the general population. Atrial electromechanical delay is recognized as an important factor influencing the development of atrial fibrillation.

Methods: This study included 30 type 2 DM patients (53.3% female, mean age 60.07 ± 10.03 years), initiating treatment with SGLT-2 inhibitors. The patients were assessed using echocardiography at baseline and again at 6 months, focusing on basic echocardiographic parameters and atrial electromechanical delay times (EMD) measured via tissue Doppler imaging.

Results: No significant changes were observed in intra-atrial EMD times. However, significant reductions were noted in interatrial EMD times, decreasing from 15.13 ± 5.87 ms to 13.20 ± 6.12 ms ($P = 0.029$). Statistically significant shortening occurred in lateral pulmonary acceleration (PA) times (from 58.73 ± 6.41 ms to 54.37 ± 6.97 ms, $P < 0.001$), septal PA times (from 50.90 ± 6.02 ms to 48.23 ± 5), and tricuspid PA times (from 43.60 ± 6.28 ms to 41.30 ± 5.60 ms, $P = 0.003$). Additionally, there was a significant reduction in the E/e' ratio from 8.13 ± 4.0 to 6.50 ± 2.37 ($P = 0.003$).

Conclusion: SGLT-2 inhibitors might positively influence atrial electromechanical conduction, reducing DM-related functional impairments and the risk of arrhythmias, particularly AF.

Keywords: Atrial electromechanical delay, atrial fibrillation, diabetes mellitus, SGLT-2 inhibitors

ÖZET

Amaç: Diyabetik hastalarda atrial fibrilasyon (AF) sıklığının normal popülasyona göre anlamlı derecede arttığı gösterilmiştir. Atriyal elektromekanik gecikme, atrial fibrilasyonun önemli bir belirleyicisi olarak bilinir. Bu çalışmada tip 2 diyabetes mellituslu (DM) hastalarda görece yeni oral antidiyabetik ilaçlar olan sodyum-glukoz kotransporter-2 (SGLT-2) inhibitörlerinin atriyal elektromekanik gecikme (EMG) zamanı üzerine etkilerini araştırılması amaçlanmaktadır.

Yöntem: Çalışmaya SGLT-2 inhibitörü başlanacak olan (%53,3 kadın, yaş ortalaması 60,07 ± 10,03 yıl) 30 tip 2 DM hastası alındı. Hastalar başlangıçta ve 6 ay sonra ekokardiyografi ile değerlendirildi. Temel ekokardiyografik bulguları ve doku Doppler ile atrial elektromekanik gecikme zamanları hesaplandı.

Bulgular: İntra-atriyal EMG zamanlarında anlamlı azalma izlenmezken, inter-atriyal EMG zamanlarında anlamlı kısalma izlendi, 15,13 ± 5,87 ms olan interatriyal EMG sürelerinin kontrolde 13,20 ± 6,12 ms'e gerilediği ($P = 0,029$) bulundu. Lateral PA sürelerinde (58,73 ± 6,41 ms'den 54,37 ± 6,97 ms'e, $P < 0,001$), septal PA sürelerinde (50,90 ± 6,02 ms'den 48,23 ± 5,88 ms'e, $P < 0,001$) ve triküspit PA sürelerinde (43,60 ± 6,28 ms'den 41,30 ± 5,60 ms'ye, $P = 0,003$) istatistiksel olarak anlamlı kısaltmalar gözlemlendi. E/e' değerlerinde 8,13 ± 4,0'den 6,50 ± 2,37'e anlamlı azalma görüldü ($P = 0,003$).

Sonuç: SGLT-2 inhibitörleri atriumun elektromekanik iletimi üzerinde iyileştirici etkilere sahip olabilir ve böylece SGLT-2 inhibitörleri, DM ilişkili atriumlardaki fonksiyonel bozukluk ve başta AF olmak üzere aritmilerden koruyabilir.

Anahtar Kelimeler: Atriyal elektromekanik gecikme, atrial fibrilasyon, diyabetes mellitus, SGLT-2 inhibitörleri

ORIGINAL ARTICLE

KLİNİK ÇALIŞMA

Enes Çelik¹ 

Murat Kerkütlüoğlu¹ 

Murat Şahin² 

Ekrem Aksu¹ 

Akif Serhat Balcıoğlu¹ 

¹Department of Cardiology, Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Kahramanmaraş, Türkiye

²Department of Endocrinology, Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Kahramanmaraş, Türkiye

Corresponding author:

Enes Çelik

✉ enescelikmd@gmail.com

Received: September 11, 2023

Accepted: January 28, 2024

Cite this article as: Çelik E, Kerkütlüoğlu M, Şahin M, Aksu E, Balcıoğlu AS.

The impact of sodium-glucose cotransporter-2 inhibitors on atrial electromechanical conduction time. *Türk Kardiyol Dern Ars.* 2024;52(4):237-243.

DOI:10.5543/tkda.2024.27546



Available online at archivestsc.com. Content of this journal is licensed under a Creative Commons Attribution - NonCommercial-NoDerivatives 4.0 International License.

Diabetes mellitus (DM) is a widespread chronic disease closely associated with increased cardiovascular morbidity and mortality.¹ Type 2 diabetes is independently associated with increased risks of both atrial fibrillation (AF) and ischemic stroke.² Extensive evidence from preclinical and clinical studies shows that diabetes is linked to cardiac fibrosis and that these fibrotic alterations play a crucial role in the onset and persistence of AF.³ Individuals with AF and diabetes experience an annual increase in stroke risk by 2% to 3.5%.⁴ In addition to blood sugar management, sodium–glucose cotransporter-2 (SGLT2) inhibitors—newer oral anti-diabetic medications—have demonstrated positive impacts on cardiovascular mortality and hospitalizations rates for heart failure (HF).⁵ Non-invasive methods, such as measuring atrial electromechanical delay (EMD) times through tissue Doppler imaging (TDI) via transthoracic echocardiography, are commonly used to assess the risk of AF. EMD time, indicative of atrial conduction heterogeneity, is measured from the start of electrical activity to the onset of force in the myocardium.⁶ It is established that prolonged atrial EMD times, as observed through TDI, are indicators of AF.^{6,7}

This study involved 30 patients with type 2 diabetes mellitus (DM) who, due to inadequate blood sugar control with existing antidiabetic therapies, were selected to begin treatment with an SGLT-2 inhibitor. The objective was to assess changes in atrial EMD times by analyzing echocardiography and TDI data before and after six months of treatment with an SGLT-2 inhibitor.

Materials and Methods

Study Population

This study was designed as a prospective observational study. It included 30 type 2 DM patients from our clinics who required additional treatment with an SGLT-2 inhibitor because their current antidiabetic medications were insufficient for optimal blood sugar management. No changes were made to their existing treatments except for the introduction of the SGLT-2 inhibitors. Patients with a history of AF or those who experienced an AF episode during the study, had any acute coronary syndrome in the previous year, suffered from heart failure with a reduced ejection fraction (less than 50%), showed signs of heart failure, had moderate to severe heart valve disease, cardiomyopathies, or were undergoing hemodialysis due to renal failure requiring were excluded from the study.

Laboratory and demographic data for the patients were collected. Echocardiographic assessments were performed on all patients

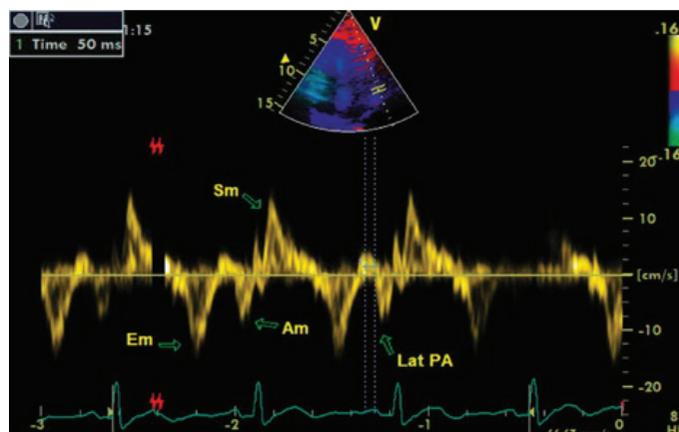


Figure 1. Assessment of atrial conduction time using echocardiography.

before and after the treatment by the same cardiologist, and atrial electromechanical delay times were measured using tissue Doppler.

The study adhered to the ethical guidelines outlined in the Declaration of Helsinki and received approval from the Medical Research Ethics Committee of Kahramanmaraş Sütçü İmam University (Approval Date: June 8, 2021; Approval Number: 2021/20). Each patient provided written informed consent.

Echocardiography

Transthoracic echocardiography was conducted using a GE Vivid E9 device (GE Healthcare, Europe). Routine assessments included measurements of heart chamber dimensions, thickness of the left ventricular (LV) posterior wall and interventricular wall, LV systolic (left ventricular ejection fraction, LVEF) and diastolic functions, and the anatomical and functional characteristics of the heart valves. Continuous single-lead electrocardiographic monitoring was performed throughout the echocardiographic examination. Dimensions and areas of both atria, systolic and diastolic diameters of the right ventricle, end-systolic and end-diastolic areas, tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressures, mitral inflow velocities of E and A waves, and tissue Doppler measurements were recorded in accordance with American Society of Echocardiography standards.⁸ LVEF was calculated using the biplane Simpson's method.

Tissue Doppler Echocardiography

Tissue Doppler echocardiography was executed using a 3.5–4.0 MHz transducer. After setting the Nyquist limits to 15–20 cm/s, data were collected from the LV lateral mitral annulus, LV septal mitral annulus, and right ventricular tricuspid annulus using Doppler in the apical four-chamber view. Peak systolic (s/Sm), late diastolic (a'/Am), early diastolic (e'/Em) velocities, isovolumetric contraction time, isovolumetric relaxation time (IVRT), and ejection times were recorded from the mitral and tricuspid annuli. Atrial electromechanical conduction time (PA) was measured from the onset of the concurrent electrocardiographic P wave to the onset of the late diastolic wave on tissue Doppler. Measurements were taken at the septal mitral annulus (septal PA), lateral mitral annulus (lateral PA), and right ventricular tricuspid annulus (tricuspid PA) (Figure 1).

ABBREVIATIONS

AF	Atrial fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
DM	Diabetes mellitus
eGFR	Estimated Glomerular Filtration Rate
EMD	Electromechanical delay times
HF	Heart failure
IVRT	Isovolumetric relaxation time
LDH	Lactate Dehydrogenase
LV	Left ventricular
LVEF	Left ventricular ejection fraction
SGLT-2	Sodium–glucose cotransporter-2
TAPSE	Tricuspid annular plane systolic excursion

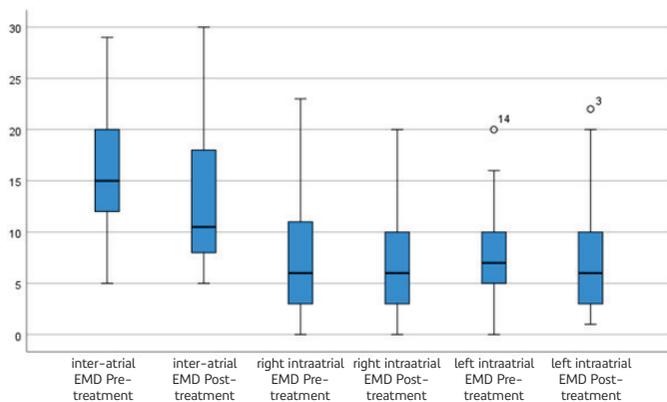


Figure 2. Box plots depicting variations in right intra-atrial EMD, left intra-atrial EMD and interatrial EMD.

The difference between tricuspid PA and lateral PA was noted as interatrial EMD, between septal PA and tricuspid PA as right intra-atrial EMD, and between septal PA and lateral PA as left intra-atrial EMD (Figure 2).^{9,10}

Statistical Analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 20.0 (IBM SPSS Statistics for Windows, Version 22, IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation, and categorical variables were presented as numbers and percentages. The normality of data was assessed using the Shapiro-Wilk test. Baseline data from the period without SGLT-2 inhibitor use were compared to data collected after a minimum of six months on SGLT-2 inhibitors. The dependent samples T-test was used to compare parameters between two related groups, while the Mann-Whitney U test was utilized for parameters that did not adhere to a normal distribution. Differences in categorical variables were evaluated using chi-square analysis. A p-value of less than 0.05 was deemed significant for all statistical analyses.

Sample sizes were determined with a focus on interatrial electromechanical delay (EMD) times, which are commonly used parameters to evaluate atrial electromechanical delay. In a similar study on EMD, the interatrial EMD times were approximately 29.65 and 26.96. Therefore, a sample size of 27 was determined to achieve 80% statistical power. From those who visited our clinic, 30 patients who met the inclusion criteria were enrolled in the study.¹¹

Results

The basic characteristics of the participants are summarized in Table 1. The study included 30 patients with type 2 DM, of whom 14 (46.7%) were male and 16 (53.3%) were female. These patients were initiating treatment with SGLT-2 inhibitors. The mean age of the patients was 60.07 ± 10.03 years. A total of 20 (66.7%) patients had concomitant hypertension, 2 (6.7%) had a history of cerebrovascular accidents, and 10 (33.3%) had coronary artery disease. Of the participants, 25 (83.3%) were prescribed dapagliflozin and 5 (16.6%) empagliflozin. Table 2 details the biochemical profiles of the patients at baseline and after 24 weeks of SGLT-2 inhibitor therapy. The

Table 1. Basic Characteristics of Patients

Basic Characteristics (n=30)	
Age (mean ± SD) years	60.07 ± 10.03
Gender	
Male, number (%)	14 (46.7)
Female, number (%)	16 (53.3)
Hypertension, number (%)	20 (66.7)
Cerebrovascular accident, number (%)	2 (6.7)
Coronary artery disease, number (%)	10 (33.3)
Dapagliflozin users, number (%)	25 (83.3)
Empagliflozin users, number (%)	5 (16.6)
SD, Standard Deviation.	

results showed no significant changes in estimated Glomerular Filtration Rate (eGFR), creatinine, Blood Urea Nitrogen (BUN), sodium, potassium, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), or gamma-glutamyl transferase (GGT) levels. However, there was a significant reduction in HbA1c, decreasing from 9.33 ± 1.41% to 8.14 ± 1.39% (*P* < 0.001). Similarly, basal fasting plasma glucose (FPG) levels decreased from 207.8 ± 77.7 mg/dL to 180.0 ± 62.1 mg/dL after 24 weeks of SGLT-2 inhibitor treatment (*P* = 0.035). Baseline alanine aminotransferase (ALT) levels also decreased from 24.1 ± 14.9 U/L to 20.4 ± 10.3 U/L over six months (*P* = 0.027). When comparing the baseline echocardiographic data to that at six months post-treatment, no significant changes were observed in the aortic root diameter, LV end-diastolic diameter, interventricular septum thickness, posterior wall thickness, mitral inflow E wave, TAPSE, LVEF, mitral inflow A wave, or pulmonary artery pressure. However, there was a significant increase in the E/A ratio, from 0.72 ± 0.14 to 0.80 ± 0.23 (*P* = 0.02). The LA area, measured in the apical four chambers (A4C), changed from 15.00 ± 4.04 cm² before treatment to 14.72 ± 3.68 cm² post-treatment, with no significant difference detected.

Heart rate measurements were taken with a simultaneous surface electrocardiogram (ECG) during echocardiographic evaluations. Heart rate decreased significantly from a baseline of 83.93 ± 13.25 beats per minute to 76.50 ± 11.44 beats per minute at the 6-month evaluation (*P* < 0.001). A significant reduction was also noted in the E/E' ratio, from 8.13 ± 4.0 to 6.50 ± 2.37 (*P* = 0.003) (Table 3). Tissue Doppler data, compared at baseline and six months, is presented in Table 4. Statistically significant reductions were observed in lateral pulmonary acceleration (PA) times (58.73 ± 6.41 ms to 54.37 ± 6.97 ms, *P* < 0.001), septal PA times (from 50.90 ± 6.02 ms to 48.23 ± 5.88 ms, *P* < 0.001), and tricuspid PA times (from 43.60 ± 6.28 ms to 41.30 ± 5.60 ms, *P* = 0.003).

When comparing interatrial and intra-atrial EMD times, a reduction was observed in interatrial EMD times, which decreased from 15.13 ± 5.87 ms initially to 13.20 ± 6.12 ms at the 6-month follow-up (*P* = 0.029). No significant changes were noted in intra-atrial or left interatrial EMD times.

Table 2. Laboratory Findings

Biochemical Parameters	n	Pre-Treatment	Post-Treatment	P
eGFR (mL/min/1.73 m ²)	30	87.4 ± 15.6	86.8 ± 17.1	0.757
Creatinine (mg/dL)	30	0.83 ± 0.15	0.83 ± 0.20	0.821
BUN (mg/dL)	29	13.57 ± 2.59	14.06 ± 3.69	0.296
HbA1c (%)	27	9.33 ± 1.41	8.14 ± 1.39	<0.001
Fasting Plasma Glucose (mg/dL)	30	207.8 ± 77.7	180.0 ± 62.1	0.035
Total Cholesterol (mg/dL)	21	175.0 ± 60.1	158.1 ± 40.2	0.159
LDL (mg/dL)	28	109.8 ± 44.6	95.0 ± 29.4	0.062
HDL (mg/dL)	23	41.0 ± 8.1	42.2 ± 9.3	0.445
Sodium (mmol/L)	30	138.5 ± 3.1	138.8 ± 3.3	0.556
Potassium (mmol/L)	30	4.60 ± 0.34	4.57 ± 0.36	0.423
LDH (mg/dL)	27	206.8 ± 32.3	206.0 ± 26.7	0.887
AST (U/L)	30	20.1 ± 7.9	18.8 ± 5.6	0.206
ALT (U/L)	30	24.1 ± 14.9	20.4 ± 10.3	0.027
GGT (U/L)	26	34.8 ± 24.8	34.3 ± 25.8	0.672

ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BUN, Blood Urea Nitrogen; eGFR, Estimated Glomerular Filtration Rate; GGT, Gamma Glutamyl Transferase; HbA1c, Glycosylated Hemoglobin; HDL, High-Density Lipoprotein; LDH, Lactate Dehydrogenase; LDL, Low-Density Lipoprotein. Data are presented as mean ± standard deviation.

Table 3. Echocardiographic Parameters

	Pre-Treatment	Post-Treatment	P
Aortic Root (mm)	21.30 ± 2.38	21.37 ± 2.41	0.677
LVDD (mm)	46.03 ± 5.54	45.80 ± 5.70	0.379
IVS (mm)	11.23 ± 1.61	11.07 ± 1.38	0.096
PW (mm)	10.07 ± 1.23	9.73 ± 1.08	0.023
E (m/s)	0.62 ± 0.13	0.64 ± 0.14	0.238
A (m/s)	0.87 ± 0.17	0.83 ± 0.18	0.065
E/A	0.72 ± 0.14	0.80 ± 0.23	0.021
E/e'	8.13 ± 4.0	6.50 ± 2.37	0.003
TAPSE (mm)	26.53 ± 3.04	26.70 ± 3.03	0.556
Ejection Fraction (%)	59.00 ± 5.68	59.10 ± 5.16	0.756
LA Area in A4C (cm ²)	15.00 ± 4.04	14.72 ± 3.68	0.230
Heart Rate (beats/min)	83.93 ± 13.25	76.50 ± 11.44	<0.001
PAP (mmHg)	6.50 ± 9.66	6.33 ± 10.08	0.899

A, Late Transmitral Flow Velocity; A4C, Apical 4 Spaces; E, Early Transmitral Flow Velocity; e', Early Diastolic Mitral Annular Velocity; IVS, Interventricular Septum; LVDD, Left Ventricular End-Diastolic Diameter; LVSD, Left Ventricular End-Systolic Diameter; PAP, Pulmonary Artery Pressure; PW, Posterior Wall; TAPSE, Tricuspid Annular Plane Systolic Excursion. Data are presented as mean ± standard deviation.

Table 4. Atrial Electromechanical Conduction Times

	Pre-Treatment	Post-Treatment	P
Lateral PA (ms)	58.73 ± 6.40	54.37 ± 6.97	<0.001
Septal PA (ms)	50.90 ± 6.02	48.23 ± 5.87	<0.001
Tricuspid PA (ms)	43.60 ± 6.28	41.30 ± 5.59	0.003
Right Intra-Atrial EMD (ms)	7.13 ± 5.48	6.67 ± 5.27	0.527
Left Intra-Atrial EMD (ms)	7.83 ± 4.48	7.30 ± 6.43	0.642
Interatrial EMD (ms)	15.13 ± 5.87	13.20 ± 6.12	0.029

EMD, Electromechanical Delay; PA, Atrial Electromechanical Conduction Time; SGLT-2, Sodium-Glucose Cotransporter-2. Data are presented as mean ± standard deviation.

Discussion

In this study, we investigated the effects of SGLT-2 inhibitors on atrial EMD time, which is a predictor of AF development in patients with type 2 DM. SGLT-2 inhibitors were added to the regimen of patients who could not achieve adequate glycemic control with existing oral antidiabetic medications. After comparing tissue Doppler data before and 6 months post-treatment, our study demonstrated a significant reduction in interatrial EMD times from baseline.

AF is more common in patients with DM, due to a variety of complex mechanisms including structural and autonomic remodeling, electrical remodeling, and chronic atrial inflammation.^{12,13} Stroke, a major complication of AF,⁴ poses a higher risk in patients with both AF and DM than in non-diabetic AF patients.^{4,14} With the rising incidence of DM in recent years, the prevalence and complications of AF are also expected to increase, making early detection and prevention of these conditions critical. Parameters linked to the development and recurrence of AF can be non-invasively assessed using transthoracic echocardiography. The E/e' ratio correlates with LA pressure; an E/e' greater than 15 usually indicates an LA pressure exceeding 15 mmHg. Additionally, an E/e' ratio over 15 in patients with a history of acute myocardial infarction is associated with increased mortality.¹⁵ Increased E/e' ratios, atrial EMD times, and LA enlargement are known to be linked to the recurrence of AF.¹⁶ In the study by Maragkoudakis et al.,¹⁷ echocardiographic evaluations of 30 type 2 DM patients with symptomatic heart failure were conducted 30 days after dapagliflozin was added to their treatment. Following dapagliflozin treatment, the post-treatment E/e' ratio was reduced compared to baseline values, decreasing from 12.4 ± 1.6 to 10.4 ± 1.3 , ($P < 0.001$). In another study, a 24-week course of dapagliflozin treatment was shown to enhance diastolic reserve, although it did not significantly affect the E/e' ratio compared to baseline.¹⁸ In our study, examinations performed six months after starting SGLT-2 inhibitor therapy showed a reduction in the E/e' ratio, which decreased from 8.1 ± 4.0 prior to treatment to 6.5 ± 2.3 after six months of therapy ($P = 0.003$).

Echocardiographic evaluation of atrial EMD time indicates atrial conduction heterogeneity, defined as the interval between the onset of electrical activity and the generation of force in the myocardium. EMD duration is a measure of both the electrical and functional continuity of atrial myocytes, assessing atrial conduction properties directly associated with AF. It can be determined using TDI and serves as a valuable parameter.¹⁹ It has been demonstrated that paroxysmal AF is linked to increased latency in both interatrial and intraatrial conduction.^{20,21} Moreover, prolonged PA periods have been shown to predict the development of new AF.⁷ For instance, Akyel et al.²² reported that diabetic patients exhibited longer mitral PA durations compared to a control group, with measures of 76.4 ± 15.0 ms for controls versus 86.3 ± 11.7 ms for diabetics ($P < 0.001$). Additionally, Demir et al.²³ found that patients with type 2 DM had longer mitral annulus lateral PA times and greater intra-atrial and interatrial EMD compared to healthy controls. In our study, we found that after treatment with an SGLT-2 inhibitor, the basal values of mitral annulus lateral PA times significantly decreased from 58.73 ± 6.40 ms to 54.37 ± 6.97 ms ($P < 0.001$). While

diastolic functions were normal in the patient groups in these studies, our research detected a minor left ventricular diastolic dysfunction, a crucial indicator of subclinical cardiac involvement in diabetes patients.²⁴

SGLT-2 inhibitors, oral diabetes medications that prevent glucose reabsorption in renal proximal tubules and enhance urine sodium and fluid excretion, thereby reducing intravascular volume,²⁵ have been initially developed as glucose-lowering agents. These inhibitors reduce hospitalizations and cardiovascular deaths from HF in various populations, including those with type 2 diabetes, renal failure, HF, and cardiovascular disease.²⁶ The EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients – Removing Excess Glucose) study, a randomized, double-blind, placebo-controlled trial involving 7,020 individuals with type 2 diabetes, was the first to investigate the cardiovascular effects of SGLT-2 inhibitors.⁵ After a median follow-up of 3.1 years, the primary endpoint of this study—a composite of myocardial infarction, stroke, and cardiovascular death—was significantly lower. The study also noted a 35% reduction in hospitalizations and a 38% decrease in cardiovascular mortality.⁵ Additionally, a meta-analysis of 31 randomized controlled trials indicated a 25% relative risk reduction in AF occurrences, with a similar decrease in the total number of AF episodes.²⁷ Furthermore, another meta-analysis of 16 studies involving 38,335 patients demonstrated that the use of SGLT-2 inhibitors reduced the incidence of AF.²⁸ In subgroup analyses of the DECLARE TIMI 58 (Dapagliflozin Effect on Cardiovascular Events – Thrombolysis In Myocardial Infarction 58) trial, which evaluated the cardiovascular safety of dapagliflozin, it was found that dapagliflozin reduced the risk of initial atrial fibrillation and atrial flutter (AFL) events by 19% and the total number of AF/AFL events by 23% during the follow-up period.²⁹

Various potential direct and indirect cardioprotective effects of SGLT2 inhibitors have been reported.³⁰ Empagliflozin, in particular, has been shown to significantly reduce the volume of epicardial adipose tissue (EAT).³¹ This reduction is critical as EAT can induce fibrosis of the atrial myocardium by secreting adipokines, thereby increasing susceptibility to atrial fibrillation (AF).³² Takano et al.³³ provided evidence that SGLT2 inhibitors enhance cardioprotective effects on heart failure and atrial fibrillation specifically by reducing EAT in humans.

Mechanisms including decreased body weight, enhanced osmotic diuresis and glucose excretion, reduced arterial blood pressure, myocardial remodeling, and delayed fibrosis formation are believed to play crucial roles in the pathophysiology that slows the development of AF in patients treated with SGLT-2 inhibitors.³⁴

Empagliflozin significantly lowered systolic blood pressure compared to placebo in the EMBODY (Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus) study, which examined its impact on cardiac sympathetic activity in type 2 DM patients with acute myocardial infarction. However, the reduction in heart rate did not reach statistical significance.³⁵ Conversely, another study found that tofogliflozin significantly lowered resting heart rate compared to placebo, independent of reductions in HbA1c, body weight, and blood pressure.³⁶ In our study, we observed a decrease in the heart rate from an initial

83.9 ± 13.2 beats per minute to 76.5 ± 11.4 beats per minute after the use of SGLT-2 inhibitor ($P < 0.001$). The inconsistency between studies may be due to differences in the stability of coronary artery disease.

In a study by Aslan et al.,³⁷ a significant decrease in right interatrial EMD times was noted with empagliflozin. They demonstrated that this change was correlated with a reduction in left atrial volume. In our study, we found that the initial left atrial volume measurements were smaller than those reported in the study by Aslan et al.,³⁷ and there was no significant reduction in these values following treatment.

While SGLT-2 inhibitors positively influence the onset of new AF cases and recurrence, our review of the literature did not uncover any studies exploring the impact of this drug class on atrial EMD times associated with AF.

Our study noted a marked decrease in atrial electromyography (EMG) times when patients were treated with SGLT-2 inhibitors compared to baseline measurements. We believe that the reduced AF incidence in type 2 DM patients who use SGLT-2 inhibitors may be linked to this observation, suggesting it as a potential mechanism.

Conclusion

Our study demonstrated that 6-month treatment with SGLT-2 inhibitors led to improved interatrial conduction times and significantly reduced atrial EMD times in patients with type 2 DM. These reductions in atrial EMD times may serve as predictive markers for the onset of AF in this patient population. Our findings may help elucidate how SGLT-2 inhibitors benefit patients with type 2 DM by reducing the frequency and recurrence of AF. However, larger patient populations and extended follow-up periods are needed to support our study's findings.

Ethics Committee Approval: This study received approval from the Medical Research Ethics Committee of Kahramanmaraş Sütçü İmam University (Approval Date: June 8, 2021; Approval Number: 2021/20).

Informed consent: Each patient provided written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.Ç., A.S.B.; Design – E.Ç., A.S.B.; Supervision – A.S.B.; Resource – M.K., M.Ş., E.A.; Materials – M.Ş., E.A.; Data Collection and/or Processing – E.Ç., M.K.; Analysis and/or Interpretation – E.Ç., A.S.B.; Literature Review – E.Ç., E.A., A.S.B.; Writing – E.Ç.; Critical Review – A.S.B.

Use of AI for Writing Assistance: The authors declare that AI-assisted technologies were not used in this study.

Conflict of Interest: No conflicts of interest have been received from the authors.

Funding: The authors declared that this study received no financial support.

References

- World Health Organization. (2004). Diabetes Action Now: an initiative of the World Health Organization and the International Diabetes Federation. Accessed April 24, 2024. <https://iris.who.int/handle/10665/42934>
- Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271(11):840-844. [CrossRef]
- Tiwari S, Schirmer H, Jacobsen BK, et al. Association between diastolic dysfunction and future atrial fibrillation in the Tromsø Study from 1994 to 2010. *Heart*. 2015;101(16):1302-1308. [CrossRef]
- Mozaffarian D, Benjamin EJ, Go AS, et al.; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015;131(4):e29-322. Erratum in: *Circulation*. 2015;131(24):e535. Erratum in: *Circulation*. 2016;133(8):e417.
- Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128. [CrossRef]
- Omi W, Nagai H, Takamura M, et al. Doppler tissue analysis of atrial electromechanical coupling in paroxysmal atrial fibrillation. *J Am Soc Echocardiogr*. 2005;18(1):39-44. [CrossRef]
- De Vos CB, Weijs B, Crijns HJ, et al. Atrial tissue Doppler imaging for prediction of new-onset atrial fibrillation. *Heart*. 2009;95(10):835-840. [CrossRef]
- Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.e14. [CrossRef]
- Müller P, Ivanov V, Kara K, et al. Total atrial conduction time to predict occult atrial fibrillation after cryptogenic stroke. *Clin Res Cardiol*. 2017;106(2):113-119. [CrossRef]
- Karantoumanis I, Doundoulakis I, Zafeiropoulos S, et al. Atrial conduction time associated predictors of recurrent atrial fibrillation. *Int J Cardiovasc Imaging*. 2021;37(4):1267-1277. [CrossRef]
- Ziyrek M, Dönmez E, Özcan S, et al. Effect of SGLT-2 inhibitors as an add-on therapy to metformin on P wave indices and atrial electromechanics in type 2 diabetes mellitus patients. *Pacing Clin Electrophysiol*. 2023;46(7):803-810. [CrossRef]
- Bell DSH, Goncalves E. Atrial fibrillation and type 2 diabetes: Prevalence, etiology, pathophysiology and effect of anti-diabetic therapies. *Diabetes Obes Metab*. 2019;21(2):210-217. [CrossRef]
- Wang A, Green JB, Halperin JL, Piccini JP Sr. Atrial Fibrillation and Diabetes Mellitus: JACC Review Topic of the Week. *J Am Coll Cardiol*. 2019;74(8):1107-1115. [CrossRef]
- Gumprecht J, Lip GYH, Sokal A, et al. Relationship between diabetes mellitus and atrial fibrillation prevalence in the Polish population: a report from the Non-invasive Monitoring for Early Detection of Atrial Fibrillation (NOMED-AF) prospective cross-sectional observational study. *Cardiovasc Diabetol*. 2021;20(1):128. [CrossRef]
- Iwahashi N, Kimura K, Kosuge M, et al. E/e' two weeks after onset is a powerful predictor of cardiac death and heart failure in patients with a first-time ST elevation acute myocardial infarction. *J Am Soc Echocardiogr*. 2012;25(12):1290-1298. [CrossRef]
- Maenosono R, Mizukami N, Ichiki H, et al. Total atrial conduction time as a possible predictor of atrial fibrillation recurrence after catheter ablation for paroxysmal atrial fibrillation: relationship between electrical atrial remodeling and structural atrial remodeling time courses. *J Med Ultrason* (2007). 2021;48(3):295-306. [CrossRef]
- Maragkoudakis S, Marketou M, Katsi V, et al. The early effect of dapagliflozin on strain and tissue Doppler parameters of diastolic function in diabetic patients with heart failure with reduced ejection fraction. *Arch Med Sci Atheroscler Dis*. 2021;6:e176-e181. [CrossRef]
- Shim CY, Seo J, Cho I, et al. Randomized, Controlled Trial to Evaluate the Effect of Dapagliflozin on Left Ventricular Diastolic Function in Patients With Type 2 Diabetes Mellitus: The IDIA Trial. *Circulation*. 2021;143(5):510-512. [CrossRef]
- Müller P, Weijs B, Bemelmans NMAA, et al. Echocardiography-derived total atrial conduction time (PA-TDI duration): risk stratification and guidance in atrial fibrillation management. *Clin Res Cardiol*. 2021;110(11):1734-1742. [CrossRef]

20. Cui QQ, Zhang W, Wang H, et al. Assessment of atrial electromechanical coupling and influential factors in nonrheumatic paroxysmal atrial fibrillation. *Clin Cardiol.* 2008;31(2):74-78. [\[CrossRef\]](#)
21. Ozer N, Yavuz B, Can I, et al. Doppler tissue evaluation of intra-atrial and interatrial electromechanical delay and comparison with P-wave dispersion in patients with mitral stenosis. *J Am Soc Echocardiogr.* 2005;18(9):945-948. [\[CrossRef\]](#)
22. Akyel A, Oksüz F, Karadeniz M, Yarlıoğlu M, Ergün G, Cankurt T, Yozgat A, Keskin Ariel M, Aral Y, Murat SN. Atrial electromechanical delay in type 2 diabetes mellitus. *Wien Klin Wochenschr.* 2014;126(3-4):101-105. [\[CrossRef\]](#)
23. Demir K, Avci A, Kaya Z, et al. Assessment of atrial electromechanical delay and P-wave dispersion in patients with type 2 diabetes mellitus. *J Cardiol.* 2016;67(4):378-383. [\[CrossRef\]](#)
24. Grigorescu ED, Lacatusu CM, Floria M, Mihai BM, Cretu I, Sorodoc L. Left Ventricular Diastolic Dysfunction in Type 2 Diabetes-Progress and Perspectives. *Diagnostics (Basel).* 2019;9(3):121. [\[CrossRef\]](#)
25. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res.* 2015;12(2):78-89. [\[CrossRef\]](#)
26. Singh AK, Singh R. Heart failure hospitalization with SGLT-2 inhibitors: a systematic review and meta-analysis of randomized controlled and observational studies. *Expert Rev Clin Pharmacol.* 2019;12(4):299-308. [\[CrossRef\]](#)
27. Pandey AK, Okaj I, Kaur H, et al. Sodium-Glucose Co-Transporter Inhibitors and Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc.* 2021;10(17):e022222. [\[CrossRef\]](#)
28. Usman MS, Siddiqi TJ, Memon MM, et al. Sodium-glucose co-transporter2 inhibitors and cardiovascular outcomes: A systematic review and meta-analysis. *Eur J Prev Cardiol.* 2018;25(5):495-502. [\[CrossRef\]](#)
29. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. *Circulation.* 2020;141(15):1227-1234. [\[CrossRef\]](#)
30. Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci.* 2020;5(6):632-644. [\[CrossRef\]](#)
31. Requena-Ibáñez JA, Santos-Gallego CG, Rodríguez-Cordero A, et al. Mechanistic Insights of Empagliflozin in Nondiabetic Patients With HFrEF: From the EMPA-TROPISM Study. *JACC Heart Fail.* 2021;9(8):578-589. [\[CrossRef\]](#)
32. Nakanishi K, Fukuda S, Tanaka A, et al. Peri-atrial epicardial adipose tissue is associated with new-onset nonvalvular atrial fibrillation. *Circ J.* 2012;76(12):2748-2754. [\[CrossRef\]](#)
33. Takano M, Kondo H, Harada T, et al. Empagliflozin Suppresses the Differentiation/Maturation of Human Epicardial Preadipocytes and Improves Paracrine Secretome Profile. *JACC Basic Transl Sci.* 2023;8(9):1081-1097. [\[CrossRef\]](#)
34. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. *Diabetologia.* 2018;61(10):2108-2117. [\[CrossRef\]](#)
35. Shimizu W, Kubota Y, Hoshika Y, et.; EMBODY trial investigators. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. *Cardiovasc Diabetol.* 2020;19(1):148. [\[CrossRef\]](#)
36. Nojima T, Matsubayashi Y, Yoshida A, et al. Influence of an SGLT2 inhibitor, tofogliflozin, on the resting heart rate in relation to adipose tissue insulin resistance. *Diabet Med.* 2020;37(8):1316-1325. [\[CrossRef\]](#)
37. Aslan M, Oksen D, Kaynak C, Ozudogru O. Impact of empagliflozin on left atrial mechanical and conduction functions in patients with type 2 diabetes mellitus. *J Clin Ultrasound.* 2023;51(3):398-404. [\[CrossRef\]](#)