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Early Left Ventricular Function Following ACS Events in a Diverse Group of Patients Receiving Dapagliflozin or Empagliflozin for Type 2 Diabetes Mellitus

Akut Koroner Sendrom Sonrası Erken Sol Ventrikül Fonksiyonu: Tip 2 Diyabetes Mellituslu Dapagliflozin veya Empagliflozin Kullanan Çeşitli Hasta Gruplarında Karşılaştırmalı Analiz

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Abstract

Objective: Sodium-glucose co-transporter-2 inhibitors such as dapagliflozin and empagliflozin have demonstrated cardioprotective effects, but their impact on early left ventricular function after acute coronary syndrome (ACS) remains unclear. This study aimed to compare the effects of dapagliflozin and empagliflozin on early post-ACS left ventricular ejection fraction (LVEF) in patients with type 2 diabetes mellitus (T2DM) and to identify predictors of reduced LVEF.

Material and Methods: This retrospective study included 354 patients with T2DM who were hospitalized with an ACS event while on dapagliflozin (n=133) or empagliflozin (n=221) therapy. Demographic, clinical, and echocardiographic data were collected. LVEF was classified as preserved ($\geq 50\%$), mildly reduced (41-49%), or reduced ($\leq 40\%$). Multivariable logistic regression was used to identify independent predictors of reduced LVEF.

Results: Post-ACS LVEF values were similar between the dapagliflozin and empagliflozin groups ($p=0.809$). However, STEMI ($p<0.001$) and immigrant status ($p=0.023$) were independently associated with reduced LVEF ($\leq 40\%$). Among all patients with LVEF $<50\%$, only STEMI remained an independent predictor ($p<0.001$).

Conclusion: Although dapagliflozin and empagliflozin recipients had similar LVEF in the early post-ACS period, it appears that having an immigrant background and suffering from STEMI are risk factors for substantial LVEF decrease in patients with T2DM.

Keywords: Dapagliflozin, empagliflozin, type 2 diabetes mellitus, acute coronary syndrome, left ventricular ejection fraction

Öz

Amaç: Dapagliflozin ve empagliflozin gibi sodyum-glukoz ko-taşıyıcı-2 inhibitörlerinin kardiyoprotektif etkileri bilinmekle birlikte, akut koroner sendrom (AKS) sonrası erken sol ventrikül fonksiyonuna etkileri net değildir. Bu çalışma, tip 2 diyabetes mellituslu (T2DM) hastalarda dapagliflozin ve empagliflozinin AKS sonrası erken dönemde sol ventrikül ejeksiyon fraksiyonu (LVEF) üzerindeki etkilerini karşılaştırmayı ve azalmış LVEF için yordayıcı faktörleri saptamayı amaçlamıştır.

Yöntem ve Gereçler: Bu retrospektif çalışmaya, dapagliflozin (n=133) veya empagliflozin (n=221) tedavisi almakta iken AKS nedeniyle hastaneye yatırılan toplam 354 T2DM hastası dahil edilmiştir. Demografik, klinik ve ekokardiyografik veriler değerlendirildi. LVEF; korunmuş ($\geq 50\%$), hafif azalmış (%41-49) ve azalmış (≤ 40) olarak sınıflandırıldı. Azalmış LVEF ile ilişkili bağımsız faktörleri belirlemek için çok değişkenli lojistik regresyon analizi kullanıldı.



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Bulgular: AKS sonrası LVEF değerleri dapagliflozin ve empagliflozin grupları arasında benzerdi ($p=0,809$). Bununla birlikte STEMI ($p<0,001$) ve göçmen olma durumu ($p=0,023$) azalmış LVEF (≤ 40) ile bağımsız olarak ilişkili bulundu. LVEF <50 olan tüm hastalar arasında ise yalnızca STEMI bağımsız bir yordayıcı olarak kaldı ($p<0,001$).

Sonuç: Dapagliflozin ve empagliflozin kullanan hastaların AKS sonrası erken dönemdeki LVEF değerleri benzer olsa da, T2DM hastalarında göçmen kökenli olmanın ve STEMI geçirmiş olmanın LVEF'de belirgin düşüş için risk faktörleri olduğu görülmektedir.

Anahtar Kelimeler: Dapagliflozin, empagliflozin, tip 2 diyabetes mellitus, akut koroner sendrom, sol ventrikül ejeksiyon fraksiyonu

INTRODUCTION

Acute coronary syndrome (ACS) is a broad spectrum of clinical conditions caused by sudden occlusion or severe narrowing of the coronary arteries, leading to myocardial ischemia (1,2). This leading cause of mortality is classified into three: ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina pectoris (USAP) (1,3). Heart failure (HF), which can be described as insufficient cardiac pumping function, is a major clinical concern in patients with ACS that occurs in approximately 10-20% of post-ACS patients (4). Post-ACS HF is closely associated with left ventricular dysfunction following MI, leading not only to a significant decline in quality of life but also to increased mortality (5,6). One of the most frequently used parameters in HF assessment is the left ventricular ejection fraction (LVEF), which is the ratio of blood ejected from the ventricle volume with each systole (5,6). Low LVEF is directly correlated with poor long-term prognosis (6), and therefore, post-ACS LVEF monitoring has become an essential component of clinical management.

Type 2 diabetes mellitus (T2DM) and cardiovascular disease are two conditions that are closely associated with quality of life and have synergetic impacts on prognosis. In recent years, the cardioprotective effects of novel antidiabetic agents have been studied to a great extent, with particularly strong benefits observed in recipients of sodium-glucose co-transporter-2 (SGLT-2) inhibitors (such as dapagliflozin and empagliflozin) (7-9). These medications prevent hyperglycemia by reducing renal glucose reabsorption while also exerting diuresis and improving myocardial energy metabolism (10-12). SGLT-2 inhibitors have been demonstrated to reduce hospitalization rates and cardiovascular events in patients with HF (13-15). However, their effects on LVEF in the acute post-ACS phase remain insufficiently studied.

This study aims to retrospectively evaluate T2DM patients receiving dapagliflozin and empagliflozin in terms of LVEF during the acute post-ACS period, and to also compare these two medications in this respect. This evaluation could provide novel insights into the acute-phase utility of SGLT-2 inhibitors, which may generate new data contributing to the limited body of research in this field.

MATERIAL AND METHODS

Study Design and Participants

This was a retrospective evaluation of a T2DM cohort (≥ 18 years of age), conducted at University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, İstanbul, Türkiye between January 2021 and December 2022. The study was approved by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (decision no: 56-2024, date: 01.08.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant ethical guidelines for medical research involving human subjects. All subjects with T2DM who were receiving dapagliflozin or empagliflozin treatment were reviewed to examine hospitalization due to an ACS event. Eligible patients had to have been using dapagliflozin (10 mg/day) or empagliflozin (10 mg/day) as monotherapy for at least one year. Subjects were excluded if they had a diagnosis of pancreatic disease, liver failure, or acute infection. Exclusion criteria further included patients who could not be followed up or treated due to treatment refusal, those using antidiabetic medications other than dapagliflozin or empagliflozin, those receiving insulin therapy, and those using dapagliflozin or empagliflozin irregularly or at doses other than the standard 10 mg/day.

Data Collection

Patient data, including age, sex, migration status, anthropometric measurements (body mass index), smoking status, previous comorbidities, type of ACS event, post-event LVEF levels, and mortality status, were obtained from the hospital's electronic records.

Smoking status was categorized as follows: non-smokers: individuals who had never smoked or had smoked fewer than 100 cigarettes in their lifetime; ex-smokers: individuals who had smoked more than 100 cigarettes in their lifetime but had quit for at least six months; passive smokers: individuals who did not smoke but were regularly exposed to secondhand smoke; active smokers: individuals who regularly smoked cigarettes or other tobacco products (16). Immigrant status was defined as individuals who were born outside of Türkiye and had relocated

to Türkiye, regardless of legal residency status or duration of residence. This information was obtained from the hospital's demographic registration system.

Pre-event LVEF values were not available for the majority of patients due to the retrospective nature of the study and lack of routine echocardiographic assessments prior to the index ACS event. Therefore, changes in LVEF from baseline could not be evaluated.

Diagnosis, Classification and Outcomes

ACS diagnosis was established based on clinical symptoms, electrocardiographic findings, and cardiac biomarker levels. Patients were classified into the three ACS subtypes (USAP, NSTEMI, or STEMI) based on the American College of Cardiology (ACC) guidelines (1). Left ventricular function was assessed by LVEF measurements performed with echocardiography within the first week of hospitalization.

The primary outcome of the study was LVEF. According to the 2022 AHA/ACC/HFSA guidelines (4), patients were categorized based on their LVEF values as follows: preserved LVEF ($\geq 50\%$): normal or minimally impaired systolic function; mildly reduced LVEF (41-49%): mild systolic dysfunction with some impairment in cardiac output; reduced LVEF ($\leq 40\%$): moderate to severe systolic dysfunction, often associated with an increased risk of adverse cardiovascular events. Patients were also grouped based on their treatment with either dapagliflozin or empagliflozin.

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). A p-value of <0.05 was considered statistically significant. The normality of data distribution was assessed using histograms and Q-Q plots. Descriptive statistics were presented as mean \pm standard deviation for normally distributed continuous variables,

median (25th-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. Comparisons between groups were performed using the Student's t-test or Mann-Whitney U test for continuous variables, depending on the normality of the distribution. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Logistic regression analysis was performed to assess associations between variables and LVEF. All variables were initially analyzed using univariable logistic regression, and statistically significant variables were subsequently included in a multivariable logistic regression model.

RESULTS

A total of 354 patients were included in the study, with 221 (62.43%) in the empagliflozin group and 133 (37.57%) in the dapagliflozin group. The mean age of all participants was 57.79 ± 9.90 years, and 255 (72.03%) were male. There were no significant differences between the dapagliflozin and empagliflozin groups in terms of age ($p=0.323$) and sex ($p=0.096$). The prevalence of renal disease was significantly higher in the dapagliflozin group ($p=0.018$). Additionally, the percentage of NSTEMI patients was higher in the dapagliflozin group, while the empagliflozin group had a significantly higher percentage of STEMI patients ($p=0.045$). No significant differences were observed between the groups regarding LVEF ($p=0.809$) and mortality ($p=0.095$) (Table 1).

Multivariable logistic regression analysis revealed that being an immigrant [odds ratio (OR): 4.037, 95% confidence interval (CI): 1.211-13.452, $p=0.023$] and having suffered from STEMI (OR: 2.673, 95% CI: 1.580-4.521, $p<0.001$) were independently associated with reduced LVEF ($\leq 40\%$) (Table 2). When analyzed for mildly reduced or reduced LVEF (by pooling all patients with $<50\%$ LVEF), the only independent factor was STEMI (OR: 2.625, 95% CI: 1.694-4.068, $p<0.001$) (Table 3).

Table 1. Summary of patients' characteristics with regard to SGLT-2 inhibitor

	SGLT-2 inhibitor			p
	Total (n=354)	Dapagliflozin (n=133)	Empagliflozin (n=221)	
Age	57.79 ± 9.90	58.46 ± 9.90	57.38 ± 9.89	0.323 [†]
Sex				
Female	99 (27.97%)	44 (33.08%)	55 (24.89%)	0.096 [§]
Male	255 (72.03%)	89 (66.92%)	166 (75.11%)	
Immigrant	12 (3.39%)	5 (3.76%)	7 (3.17%)	0.769 [#]
Body mass index, kg/m ²	29.91 ± 4.43	30.06 ± 4.54	29.82 ± 4.37	0.629 [†]

Table 1. Continued

	SGLT-2 inhibitor			p
	Total (n=354)	Dapagliflozin (n=133)	Empagliflozin (n=221)	
Smoking				
Non-smoker	87 (24.65%)	42 (31.82%)	45 (20.36%)	0.083 [§]
Ex-smoker	72 (20.40%)	22 (16.67%)	50 (22.62%)	
Passive smoker	30 (8.50%)	9 (6.82%)	21 (9.50%)	
Active smoker	164 (46.46%)	59 (44.70%)	105 (47.51%)	
Previous comorbidities				
Hypertension	220 (62.15%)	90 (67.67%)	130 (58.82%)	0.097 [§]
Hyperlipidemia	291 (82.20%)	112 (84.21%)	179 (81.00%)	0.534 [§]
COPD	25 (7.06%)	8 (6.02%)	17 (7.69%)	0.702 [§]
Coronary artery disease	112 (31.64%)	43 (32.33%)	69 (31.22%)	0.828 [§]
CABG	20 (5.65%)	10 (7.52%)	10 (4.52%)	0.345 [§]
Peripheral artery disease	24 (6.78%)	10 (7.52%)	14 (6.33%)	0.833 [§]
Cerebrovascular disease	13 (3.67%)	4 (3.01%)	9 (4.07%)	0.773 [#]
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	N/A
Deep vein thrombosis	1 (0.28%)	1 (0.75%)	0 (0.00%)	0.376 [#]
Renal diseases	16 (4.52%)	11 (8.27%)	5 (2.26%)	0.018[§]
Tyroid diseases	30 (8.47%)	10 (7.52%)	20 (9.05%)	0.761 [§]
Malignancy	7 (1.98%)	3 (2.26%)	4 (1.81%)	1.000 [#]
Type of event				
USAP	29 (8.19%)	11 (8.27%)	18 (8.14%)	0.045[§]
NSTEMI	147 (41.53%)	66 (49.62%)	81 (36.65%)*	
STEMI	178 (50.28%)	56 (42.11%)	122 (55.20%)*	
LVEF	50 (43-60)	50 (40-60)	50 (45-60)	0.426 [‡]
Reduced ($\leq 40\%$)	84 (23.73%)	34 (25.56%)	50 (22.62%)	0.809 [§]
Mildly reduced (41-49%)	67 (18.93%)	24 (18.05%)	43 (19.46%)	
Preserved ($\geq 50\%$)	203 (57.34%)	75 (56.39%)	128 (57.92%)	
Mortality	25 (7.06%)	5 (3.76%)	20 (9.05%)	0.095 [§]

Descriptive statistics are presented using mean \pm standard deviation for normally distributed continuous variables, median (25th-75th percentile) for non-normally distributed continuous variables and frequency (percentage) for categorical variables
Statistically significant p-values are shown in bold, †: Student's t-test, ‡: Mann Whitney U test, §: Chi-square test, #: Fisher's exact test, *: Statistically significant category for the variables with three or more categories. N/A: Non-applicable, CABG: Coronary artery bypass grafting, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, NSTEMI: Non-ST-elevation myocardial infarction, SGLT-2: Sodium-glucose co-transporter-2, STEMI: ST-elevation myocardial infarction, USAP: Unstable angina pectoris

Table 2. Associations between variables and reduced LVEF ($\leq 40\%$), logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.994 (0.970-1.019)	0.629	4.037 (1.211-13.452)	0.023
Sex, male	1.571 (0.878- 2.814)	0.128		
Immigrant	4.818 (1.487-15.607)	0.009		

Table 2. Continued

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Body mass index, kg/m ²	1.001 (0.947-1.059)	0.964		
Smoking, active smoker	1.063 (0.651-1.736)	0.807		
Previous comorbidities				
Hypertension	0.924 (0.559-1.527)	0.757		
Hyperlipidemia	0.995 (0.525-1.885)	0.987		
COPD	0.593 (0.198-1.778)	0.351		
Coronary artery disease	1.365 (0.816-2.282)	0.236		
CABG	0.794 (0.258-2.443)	0.687		
Peripheral artery disease	1.671 (0.689-4.055)	0.256		
Cerebrovascular disease	1.450 (0.435-4.834)	0.545		
Deep vein thrombosis	0.000 (0.000-N/A)	1.000		
Renal diseases	2.636 (0.951-7.310)	0.062		
Tyroid diseases	1.187 (0.508-2.774)	0.693		
Malignancy	1.293 (0.246-6.788)	0.762		
Type of event, STEMI	2.788 (1.656-4.696)	<0.001	2.673 (1.580-4.521)	<0.001
SGLT-2 inhibitor, empagliflozin	0.851 (0.516-1.405)	0.529		
Nagelkerke R ²	-		0.087	

CABG: Coronary artery bypass grafting, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, N/A: Non-applicable, OR: Odds ratio, SGLT-2: Sodium-glucose co-transporter-2, STEMI: ST-elevation myocardial infarction

Table 3. Associations between variables and reduced or mildly reduced LVEF (<50%), logistic regression analysis results

	Univariable		Multivariable	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.996 (0.975-1.018)	0.744		
Sex, male	1.526 (0.944-2.466)	0.084		
Immigrant	4.225 (1.124-15.884)	0.033	3.509 (0.908-13.563)	0.069
Body mass index, kg/m ²	1.033 (0.984-1.084)	0.188		
Smoking, active smoker	0.948 (0.621-1.447)	0.804		
Previous comorbidities				
Hypertension	1.008 (0.653-1.556)	0.972		
Hyperlipidemia	0.915 (0.529-1.584)	0.752		
COPD	1.061 (0.467-2.407)	0.888		
Coronary artery disease	1.068 (0.679-1.678)	0.777		
CABG	0.890 (0.355-2.235)	0.805		
Peripheral artery disease	1.148 (0.500-2.639)	0.745		
Cerebrovascular disease	1.159 (0.381-3.520)	0.795		
Deep vein thrombosis	0.000 (0.000-N/A)	1.000		
Renal diseases	1.775 (0.646-4.878)	0.266		
Tyroid diseases	0.887 (0.414-1.903)	0.759		
Malignancy	1.814 (0.400-8.228)	0.440		
Type of event, STEMI	2.706 (1.750-4.182)	<0.001	2.625 (1.694-4.068)	<0.001
SGLT-2 inhibitor, empagliflozin	0.940 (0.608-1.451)	0.778		
Nagelkerke R ²	-		0.090	

CABG: Coronary artery bypass grafting, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, LVEF: Left ventricular ejection fraction, N/A: Non-applicable, OR: Odds ratio, SGLT-2: Sodium-glucose co-transporter-2, STEMI: ST-elevation myocardial infarction

DISCUSSION

This study primarily aimed to compare the early post-event effects of empagliflozin and dapagliflozin on LVEF in patients diagnosed with ACS who had underlying T2DM. As a secondary objective, other factors influencing early post-event LVEF were investigated. The results indicated no significant difference between dapagliflozin and empagliflozin regarding their effects on early post-event LVEF. However, it should be noted that there was a statistically significant imbalance in STEMI prevalence between the two groups ($p=0.045$), with more STEMI cases in the empagliflozin group. Given that STEMI is an independent predictor of reduced LVEF in our regression analysis, this imbalance may have influenced the comparison between the two drugs, although the overall LVEF values remained similar between groups. Independent risk factors affecting early post-event LVEF were identified as being an immigrant and experiencing STEMI. Although STEMI is a foreseeable risk factor, it appears that being an immigrant could cause adverse outcomes regarding cardiac function. This impact might be associated with various patient-, healthcare- and policy-related factors in this subgroup of patients, including problems faced in accessing healthcare and language-related difficulties.

Post-ACS left ventricular remodeling and neurohormonal activation can lead to impaired ventricular function (17). The restrictive mitral filling pattern, detected in approximately 20% of ACS patients, is an indicator of severe diastolic dysfunction and serves as an independent risk factor for both HF and mortality (18). It has been established that T2DM patients have a higher risk of developing HF and left ventricular diastolic dysfunction post-ACS compared to non-diabetic individuals (5). The early-onset and frequently observed left ventricular hypertrophy and diastolic dysfunction in T2DM patients increase the risk of both reduced and preserved LVEF HF (19). Therefore, therapeutic approaches that can prevent adverse ventricular remodeling are of great importance in improving clinical outcomes (17). Echocardiographic studies conducted in stable T2DM patients have shown that SGLT-2 inhibitors may reduce left ventricular mass and improve diastolic function (20,21). However, to the best of our knowledge, no studies have yet been published examining the early post-ACS effects of SGLT-2 inhibitors on left ventricular function. Additionally, studies comparing the cardiac effects of empagliflozin and dapagliflozin remain limited. In the present study, a comparison between these two SGLT-2 inhibitors revealed no significant difference in their effects on early post-ACS LVEF.

The EMPA-REG OUTCOME, Canagliflozin Cardiovascular Assessment Study Program, and DECLARE-TIMI 58 trials have demonstrated that SGLT-2 inhibitors significantly reduce hospitalizations due to HF in T2DM patients with high

cardiovascular risk (13-15). The dapagliflozin and prevention of adverse-outcomes in HF trial further reported that dapagliflozin reduces HF progression and cardiovascular mortality in patients with reduced LVEF HF, regardless of diabetes status (22). A study investigating mortality and hospitalization rates in preserved LVEF HF patients treated with empagliflozin or dapagliflozin found that empagliflozin yielded significantly better composite outcomes in patients who had not been hospitalized for HF in the preceding 12 months (23). Lan et al. (19) examined the early effects of empagliflozin on left ventricular function in T2DM patients with ACS, reporting reductions in left ventricular mass index, improvements in mitral valve E-wave velocity and E/e' ratio, and a decrease in left atrial volume index. These findings suggest some superiority for empagliflozin in terms of left ventricular remodeling and diastolic function post-ACS (19). Similarly, Verma et al. (20) and Matsutani et al. (21) demonstrated that empagliflozin and canagliflozin reduced left ventricular mass index and improved diastolic function in T2DM patients with cardiovascular risk factors. Studies by Soga et al. (24) and Tanaka et al. (25) showed that dapagliflozin improved left ventricular global longitudinal strain, reduced left ventricular mass index, and positively affected diastolic function. However, Tochiya et al. (26) found no significant improvement in left ventricular function with tofogliflozin. The SUGAR-DM-HF trial examined the cardiac effects of empagliflozin in patients with HF with LVEF $\leq 40\%$, showing significant reductions in left ventricular volume indices and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, although no significant changes were observed in left ventricular global longitudinal strain or cardiac magnetic resonance imaging parameters (27). The empagliflozin in acute myocardial infarction (EMPACT-MI) trial investigated the effect of empagliflozin on HF risk in patients with newly developed LVEF $< 45\%$ and/or congestion following acute MI. Findings indicated that empagliflozin reduced HF hospitalizations independent of LVEF levels and congestion status (6). A recent study evaluated dapagliflozin in early post-MI HF, showing significant improvements in NT-proBNP, heart rate variability parameters, and echocardiographic indices (28). A meta-analysis of randomized controlled trials (RCT) including 11,253 patients found that early initiation of SGLT-2 inhibitors significantly reduced HF hospitalizations, but the effect shown in this meta-analysis appeared to be primarily driven by the results of the EMPACT-MI study (29). Additionally, an RCT in non-diabetic patients with anterior STEMI and LVEF $< 50\%$ reported a greater reduction in NT-proBNP and left ventricular mass index in the dapagliflozin group (2).

SGLT-2 inhibitors are strongly recommended in international guidelines for patients with HF, chronic kidney disease, or cardiovascular disease, and subjects with T2DM who are deemed to have high cardiovascular risk (30,31). Although the exact

mechanism of their beneficial effects on HF remains unclear due to the absence of SGLT-2 receptors in human myocardium, these drugs are thought to improve left ventricular structure and function through hemodynamic and metabolic effects (19). All kinds of ischemia-reperfusion (I/R) injury are associated with inflammatory response and oxidative stress (13,32). A meta-analysis of 224 animals across 16 independent studies found that SGLT-2 inhibitors reduced cardiac infarct size by 33%, independent of diabetes status (33). Chronic administration of canagliflozin for four weeks in both diabetic and non-diabetic Zucker rats significantly reduced myocardial infarct size (8). Notably, *ex vivo* application did not have this effect, whereas *in vivo* administration prior to ischemia or during ischemic injury significantly mitigated myocardial damage (34), indicating an underlying mechanism that is indirectly associated with ischemia injury. Potential mechanisms include sodium/hydrogen exchanger (NHE) inhibition and regulation of kinase signaling pathways, with canagliflozin shown to increase AMPK Thr172 phosphorylation in the myocardium (35). Dapagliflozin has demonstrated cardioprotective effects by inhibiting NHE-1, reducing intracellular Na⁺ levels, and suppressing tumor necrosis factor alpha-induced reactive oxygen species (ROS) (10,11). Additionally, reduction of myofibroblast infiltration and collagen deposition have been shown, suggesting antifibrotic properties (11). Similarly, empagliflozin has shown benefits in pre-diabetic and diabetic animal models with myocardial microvascular damage, reducing intracellular Na⁺ and Ca²⁺ levels while inhibiting NHE-1 (12). It also enhances mitochondrial Ca²⁺ levels, signal transducer and activator of transcription 3 phosphorylation, and glucose uptake in cardiomyocytes, while also regulating inflammatory responses and redox signaling (decreased interleukin-6 and inducible nitric oxide synthase expression), which might contribute to cardioprotection (36). Evidence from experimental studies on diabetic rats also appear to suggest mitochondrial protection, overall ROS suppression, and modulation of autophagy (32). Recent studies indicate that empagliflozin normalizes the transcriptomic profile of endothelial cells post-I/R injury, regulating extracellular matrix organization and immune responses (37,38). These findings support the hypothesis that SGLT-2 inhibitors exert direct cardioprotective effects by modulating inflammation and oxidative stress. However, further studies are required to determine the comparative efficacy of different SGLT-2 inhibitors in this context.

The secondary aim of our study was to identify other factors associated with low LVEF following ACS. Our findings show that being an immigrant and STEMI are significantly associated with low LVEF in the early post-ACS period, indicating that these groups are at high risk for cardiac dysfunction after ACS. STEMI, can cause severe myocardial damage, leading to a

significant decrease in LVEF, and is a widely recognized factor of poor outcome (3). Previous studies have also shown that the development of HF is strongly associated with factors such as high pulmonary artery pressure, elevated cardiac enzyme levels, advanced age, female sex, diabetes, hypertension, angina, and a history of coronary artery disease with low LVEF (39,40). However, our study suggests that being an immigrant may also be an independent risk factor, which is a unique result that warrants population-wide studies to examine the factors involved in this negative outcome. Our study emphasizes the need for close monitoring of these patients. It is crucial to re-iterate that immigrants may be more vulnerable to cardiovascular diseases due to limited access to healthcare, lower socioeconomic status, and different dietary or lifestyle habits. Based on our data, it would be feasible to suggest closer monitoring of immigrant patients and perhaps more aggressive treatment, particularly in the early period after ACS.

Study Limitations

To the best of our knowledge, this study makes several unique contributions to the existing literature. First, it provides the first direct head-to-head comparison of dapagliflozin and empagliflozin effects on early post-ACS LVEF in patients with T2DM. Second, and perhaps most notably, it identifies immigrant status as an independent predictor of reduced LVEF following ACS, a finding not previously reported in the literature. This observation highlights the importance of considering social determinants of health and healthcare access disparities when assessing cardiovascular outcomes in diverse patient populations. However, there are some limitations. The retrospective design of the study makes it difficult to establish a cause-and-effect relationship, while the single-center nature limits its generalizability. It is also possible that immigrants were less-likely to attend follow-up studies unless they were experiencing poor outcomes. Furthermore, the lack of a control group not using SGLT-2 inhibitors may present a limitation in assessing the positive impact of these drugs, but there are multiple clinical trials on this topic, and therefore, we aimed to perform a comparative analysis between these two SGLT-2 inhibitors. The absence of a non-diabetic patient group means that the results are only applicable to the diabetic population, and the lack of diabetes duration data could have biased results. Pre-event LVEF values were unknown in the great majority of patients: thus, the possible differences in LVEF change from baseline could not be examined.

CONCLUSION

Our study reports that T2DM patients receiving dapagliflozin and empagliflozin had similar LVEF values in the early post-ACS event period, suggesting similar cardioprotective effects in this

population. Being an immigrant and STEMI were identified as independent risk factors for reduced post-event LVEF ($\leq 40\%$). This draws attention to the unique aspect of immigrant status on cardiac outcome among T2DM patients receiving similar treatments, which must be explored in future studies. While SGLT-2 inhibitors are known to have positive effects on ventricular functions post-ACS in both diabetic and non-diabetic patients, more studies are needed to establish their superiority over one another.

*Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital (decision no: 56-2024, date: 01.08.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki and relevant ethical guidelines for medical research involving human subjects.

Informed Consent: Due to retrospective design of study, it is not necessary and not possible to take informed consent from recruited patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., Concept: Ö.Ö., E.B., Design: Ö.Ö., E.B., Data Collection or Processing: Ö.Ö., Analysis or Interpretation: Ö.Ö., E.B., Literature Search: Ö.Ö., E.B., Writing: Ö.Ö., E.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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