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Clinical Investigation

Cardioprotective Effects of Sodium-Glucose Cotransporter 2 Inhibitors and Their Possible Association With Normalization of the Circadian Index of Heart Rhythm

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Abstract

Background: Updated recommendations for the treatment of heart failure with reduced ejection fraction (HFrEF) include sodium-glucose cotransporter 2 (SGLT2) inhibitors and other long-established HFrEF therapies. These drugs' mechanisms of action have yet to be fully clarified.

Objective: This study evaluated the effects of SGLT2 inhibitors on the modulation of autonomic function at 1 month beyond conventional HF therapy.

Methods: This single-center, observational, prospective study was conducted from January 2020 to December 2022. Patients with type 2 diabetes who had ischemic HFrEF and met the study criteria were considered for SGLT2 inhibitor treatment with empagliflozin or dapagliflozin. Changes in the circadian index were used as the primary outcome to assess the early effects of SGLT2 inhibitors on autonomic function. Changes in functional effort capacity and laboratory findings were also evaluated. Participants' circadian index was measured by a 24-hour rhythm Holter monitoring recorder (BTL-08 Holter H100). A symptom-limited treadmill test assessed patients' effort capacities. Tests were repeated after 1 month of therapy.

Results: The mean (SD) age of the 151 participants was 56.95 (7.29) years; their mean (SD) left ventricular EF was 35.69% (7.10%), and 95 participants were men (62.9%). From baseline to 1 month, mean (SD) daytime heart rate (80.63 [9.17] vs 77.67 [8.04] beats per minute; $P = .004$) and nighttime heart rate (76.83 [11.34] vs 73.81 [10.25] beats per minute; $P = .03$) decreased significantly. Variation in the circadian indexes (mean [SD], 1.04 [0.02] vs 1.10 [0.04]; $P < .001$) was statistically significant, favoring increased modulation of autonomic function. The increases in exercise duration (mean [SD], 8.88 [3.69] minutes and median [IQR], 8.81 [5.76-12.13] minutes vs 9.72 [3.14] and 9.59 [7.24-12.22] minutes; $P = .04$) and exercise capacity (mean [SD], 203.38 [65.18] m and median [IQR], 119.22 [149.43-259.15] m vs 335.61 [51.39] and 325.79 [293.59-376.91] m; $P < .001$] were also significant.

Conclusion: The use of SGLT2 inhibitors during early treatment can favorably affect both autonomic dysfunction and functional effort capacity of patients with type 2 diabetes with ischemic HFrEF.

Keywords: Heart failure, reduced ejection fraction; sodium-glucose transporter 2 inhibitors; heart rate; physical exertion

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Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of glucose-lowering drugs currently indicated as first- or second-line treatments of type 2 diabetes in patients with established cardiovascular disease, high or very high cardiovascular risk, kidney disease, or heart failure (HF). An update in 2019 to the management protocols of hyperglycemia in type 2 diabetes established that for patients with or without atherosclerotic cardiovascular disease but with HF with reduced ejection fraction (HFrEF; EF <45%), SGLT2 inhibitor treatment should be considered to reduce hospitalization for HF, major adverse cardiovascular events, and cardiovascular death independent of the baseline glycated hemoglobin (HbA_{1c}) target.[1] The consistent effect of these agents has led to a reduction in hospitalization rates for HF in these patients; additionally, several major cardiovascular outcome trials with SGLT2 inhibitors have shown a significant reduction in major adverse cardiovascular events and cardiovascular death.[2-5] These drugs are complex agents and have multiple effects on the body; thus, their mechanisms of action are a promising research field. In addition to the diuretic and anti-inflammatory effects of SGLT2 inhibitors, their myocardial energetic mechanism of action requires further research. This study primarily aimed to resolve the relationship between the emerging data regarding the treatment of HFrEF with SGLT2 inhibitors in patients with type 2 diabetes and the effects on autonomic function modulation during the early stage of treatment.

Key Points

- The mechanism of action of SGLT2 inhibitors is a promising research field.
- According to the results of this study, a significant decrease in daytime and nighttime heart rates—specifically, a circadian index value closer to normal levels—suggests that the mechanism of action of the current drug group has effects on sympathetic and neurologic dysfunction of patients with HF.
- This study's findings may provide insight into the positive effects of the current medicine group.

Abbreviations and Acronyms

BRS	baroreflex sensitivity
HbA_{1c}	glycated hemoglobin
HDL	high-density lipoprotein
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
LDL	low-density lipoprotein
LVEF	left ventricular ejection fraction
SGLT2	sodium-glucose cotransporter 2

Patients and Methods

Study Objectives

The objective of the present single-center, observational, prospective study was to evaluate the effects of SGLT2 inhibitors beyond conventional HF therapy after the first month of treatment. Patients were screened for eligibility from January 2020 to December 2022. Eligibility criteria included (1) age older than 18 years; (2) having HFrEF with left ventricular EF (LVEF) below 40%, with New York Heart Association class I to III symptoms; and (3) having type 2 diabetes.

Patients were not eligible to participate if they had LVEF above 40%, left bundle branch block, or atrial fibrillation; had undergone cardiac resynchronization therapy; had a glomerular filtration rate below 60 mL/min/1.73 m^2; had a body mass index above 35; were undergoing chemotherapeutic treatment for active malignancy; had experienced a recent (within 12 weeks) myocardial infarction; worked the evening or night shift; were pregnant or lactating; had been hospitalized with acute decompensated HF; or had New York Heart Association class IV HF symptoms.

The primary end point was assessment of the early effects of SGLT2 inhibitors on autonomic function in patients with HFrEF and type 2 diabetes. The secondary end points were changes in the laboratory tests and functional effort capacity of the patients.

The study was performed according to the Declaration of Helsinki and was approved by the hospital ethics committee (approved on December 13, 2019; No. 3). All participants provided written informed consent.

Clinical Evaluations

Patients with diabetes with ischemic HF who were followed up with medical treatment in the cardiology outpatient clinic and met the study criteria were included in the study. A total of 151 patients, previously determined by power analysis, received consultation with an endocrinologist. The appropriate SGLT2 inhibitor medication, either empagliflozin or dapagliflozin, was initiated for each patient, as determined by the endocrinologist.

The baseline measurements before therapy began included the following:

- A physical examination
- Blood pressure measurements using a 24-hour noninvasive ambulatory blood pressure recorder (PHYSIO-PORT-PAR Medizintechhnik recorder; Medizintechhnik)
- Circadian index evaluation using a 24-hour rhythm Holter monitoring recorder (BTL-08 Holter H100; Holter)
- Laboratory tests (fasting blood glucose level, complete blood count, b-type natriuretic peptide, HbA_{1c} level, kidney function, and lipid profile)
- Assessment of functional effort capacity using a symptom-limited treadmill test at a fixed speed (2.5 km/h; grade 0) restricted to a maximum of 15 minutes (with a preprocedure trial performed for patients who had not previously performed an exercise test)

Follow-up visits by telephone calls took place at 2 weeks, including an evaluation of safety and potential side effects of the drug.

The final follow-up visit was at the end of the first month after beginning SGLT2 inhibitor treatment. Tests performed at the beginning of the study were repeated at the end of the first month.

The effects of therapy on modulation of autonomic function were assessed using rhythm Holter monitoring. Changes in mean daytime heart rate, nighttime heart rate, and the circadian index were used to evaluate the effects of SGLT2 inhibitor use at the first month.

Statistical Analysis

The power analysis was calculated as 1.00, with a type I error level of .05, for 151 participants, with the effect size value calculated over the circadian index values. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as the mean (SD) or as the mean (SD) and median (IQR), depending on their distribution. The Shapiro-Wilk test was used as an analysis of conformity to the normal distribution. Group comparisons were performed using the Student *t* test or paired *t* test for normally distributed data; the Mann-Whitney *U* test or the Wilcoxon matched-pairs test was applied when the data distribution was not normal. The χ^2 test or Fisher exact χ^2 test was used for categorical variables. All statistical analyses were performed using SPSS Statistics, version 21.0, software (2012 release; IBM Corp). $P<.05$ was considered statistically significant.

Results

A total of 151 patients with type 2 diabetes and reduced EF (mean [SD] LVEF, 35.69% [7.10%]) underwent clinical evaluations. There were 95 men (62.9%) and 56 women (37.1%) aged 41 to 76 years (mean [SD], 56.95 [7.29] years). All participants were in sinus rhythm and had stable coronary artery disease, treated with surgery or stenting. Symptoms of congestive HF ranged from New York Heart Association class I (n = 29 [19.2%]) to class III. All participants were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers for HF therapy, and other medications. Table I provides information about the patients' characteristics at the time of enrollment.

Effects of Therapy on Circadian Index

From baseline to 1 month, there was a statistically significant decrease in mean (SD) daytime heart rate (80.63 [9.17] vs 77.67 [8.04] beats per minute; $P=.004$) and nighttime heart rate (76.83 [11.34] vs 73.81 [10.25] beats per minute; $P=.03$). A statistically significant difference in the mean (SD) circadian index (1.04 [0.02] vs 1.10 [0.04]; $P<.001$) was found, favoring an increase in the modulation of autonomic function (Fig. 1). The effects of empagliflozin or dapagliflozin therapy on heart rate or circadian index were sex neutral, and using either empagliflozin or dapagliflozin did not affect the primary end points of the study ($P>.05$ for all).

Effects of Therapy on Ambulatory Blood Pressure Measurements

Ambulatory blood pressure measurements, including systolic, diastolic, and mean arterial blood pressures for the entire day, daytime, and nighttime, showed no statistically significant differences ($P>.05$ for all).

Changes in Functional Capacity and Quality of Life

There was a statistically significant increase in exercise duration (mean [SD], 8.88 [3.69] minutes and median [IQR], 8.81 [5.76-12.13] minutes vs 9.72 [3.14] minutes and 9.59 [7.24-12.22] minutes; $P=.04$) and exercise capacity (mean [SD], 203.38 [65.18] m and median [IQR], 119.22 [149.43-259.15] m vs 335.61 [51.39] m

TABLE I. Characteristics of Patients at the Time of Enrollment

Variable	Data
SGLT2 inhibitor received, No. (%)	
Empagliflozin	77 (51.0)
Dapagliflozin	74 (49.0)
Age, mean (SD), y	56.95 (7.29)
Sex, No. (%)	
Male	95 (62.9)
Female	56 (37.1)
Blood pressure, mean (SD), mm HG	
Systolic	
Daytime	120.74 (15.24)
Nighttime	114.67 (16.88)
Diastolic	
Daytime	73.91 (6.77)
Nighttime	69.83 (8.12)
Mean	
Daytime	87.84 (10.11)
Nighttime	83.91 (12.63)
Heart rate, mean (SD), beats per minute	
Daytime	81.24 (10.08)
Nighttime	76.92 (10.99)
New York Heart Association class, No. (%)	
I	29 (19.2)
II	78 (51.7)
III	44 (29.1)
Antidiabetic medication, No. (%)	
Insulin	53 (35)
Metformin	103 (68.2)
Dipeptidyl peptidase 4 inhibitor	37 (24.5)
Glucagon-like peptide-1 agonist	3 (1.9)
Medication for heart failure, No. (%)	
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	151 (100)
β-blocker	151 (100)
Mineralocorticoid receptor antagonist	42 (27.8)
Loop diuretic	74 (49.0)
Ivabradine	48 (31.7)
Sacubitril/valsartan	3 (1.9)
Statin	63 (41.7)
Cardiac device (implantable cardioverter-defibrillator)	29 (19.2)
Laboratory counts, mean (SD)	
HbA_{1c}, %	8.19 (1.72)
Creatinine, mg/dL	1.11 (0.225)
Hematocrit, %	37.66 (4.49)
Sodium, mmol/L	138.26 (2.72)
Potassium, mmol/L	4.59 (0.692)
B-type natriuretic peptide, ng/L	372.58 (249.26)

HbA_{1c}, glycated hemoglobin; SGLT2, sodium-glucose cotransporter 2.

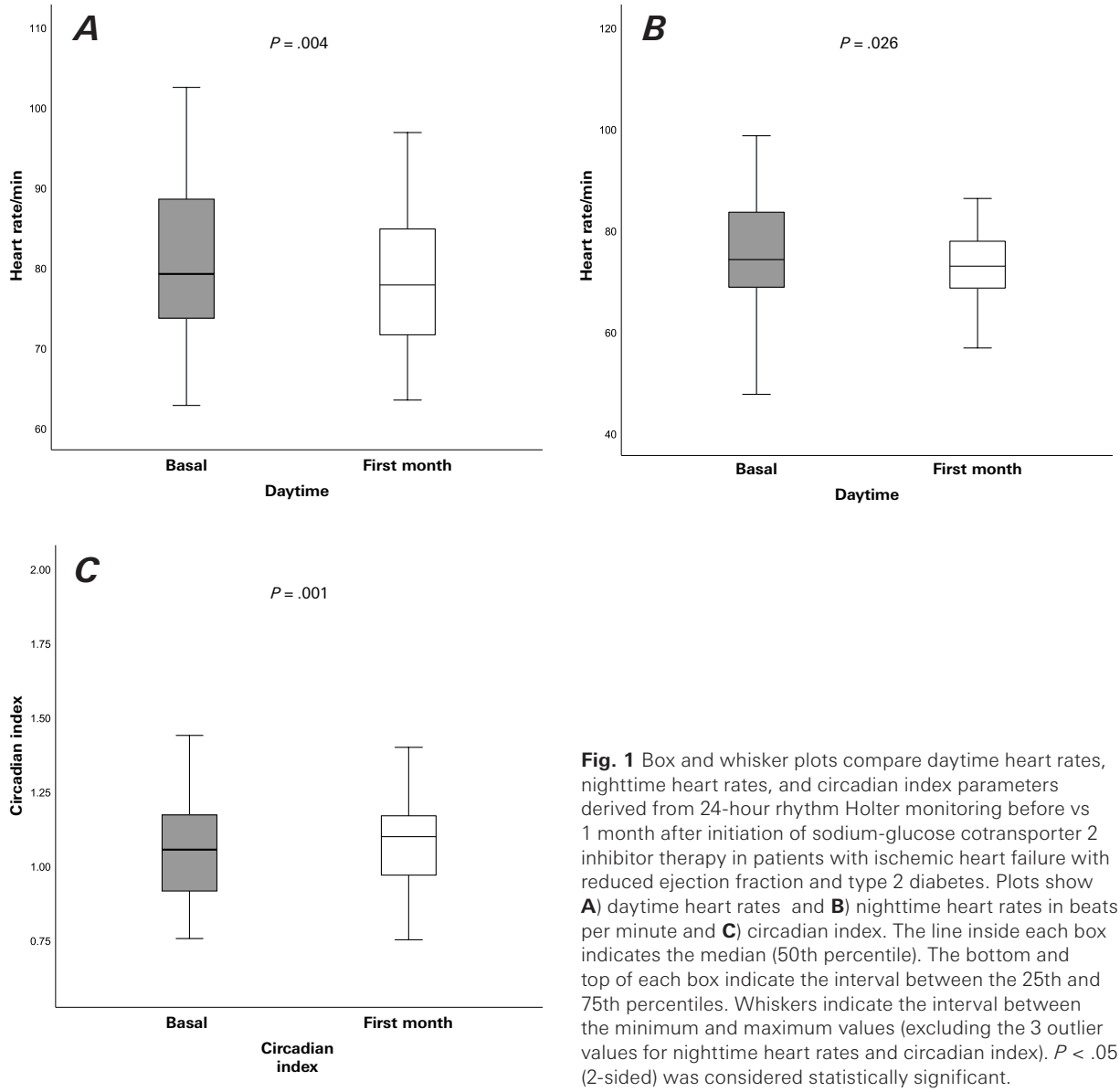

Fig. 1 Box and whisker plots compare daytime heart rates, nighttime heart rates, and circadian index parameters derived from 24-hour rhythm Holter monitoring before vs 1 month after initiation of sodium-glucose cotransporter 2 inhibitor therapy in patients with ischemic heart failure with reduced ejection fraction and type 2 diabetes. Plots show **A**) daytime heart rates and **B**) nighttime heart rates in beats per minute and **C**) circadian index. The line inside each box indicates the median (50th percentile). The bottom and top of each box indicate the interval between the 25th and 75th percentiles. Whiskers indicate the interval between the minimum and maximum values (excluding the 3 outlier values for nighttime heart rates and circadian index). $P < .05$ (2-sided) was considered statistically significant.

and 325.79 [293.59-376.91] m; $P<.001$) from baseline to 1 month after starting therapy (Fig. 2).

Biochemical Changes

There was a statistically significant decrease in fasting glucose levels at the first month (mean [SD], 9.56 [3.32] mmol/L, or 172.23 [59.90] mg/dL, and median [IQR], 9.84 [6.23-15.67] mmol/L, or 177.35 [112.18-282.43] mg/dL vs 8.58 [4.14] mmol/L, or 154.56 [74.66] mg/dL, and 8.34 [5.11-13.81] mmol/L, or 150.31 [92.16-248.74] mg/dL; $P=.02$). Although HbA_{1c} levels were lower after the first month of the therapy, the difference was statistically nonsignificant (mean [SD], 0.08 [0.02], or 8.19% [1.72%], and median [IQR], 0.08 [0.07-0.11], or 8.11% [7.11%-10.88%], vs 0.08 [0.01], or 7.91% [1.18%], and 0.08 [0.07-0.09], or 7.86% [7.11%-9.36%]; $P=.09$). The difference in HbA_{1c} level was statistically nonsignificant for both the dapagliflozin and empagliflozin groups after the first month of therapy ($P>.05$ for both).

The effect of therapy on the lipid profile varied. There was a statistically significant increase in triglyceride levels (mean [SD], 2.02 [0.69] mmol/L, or 177.78 [60.72]

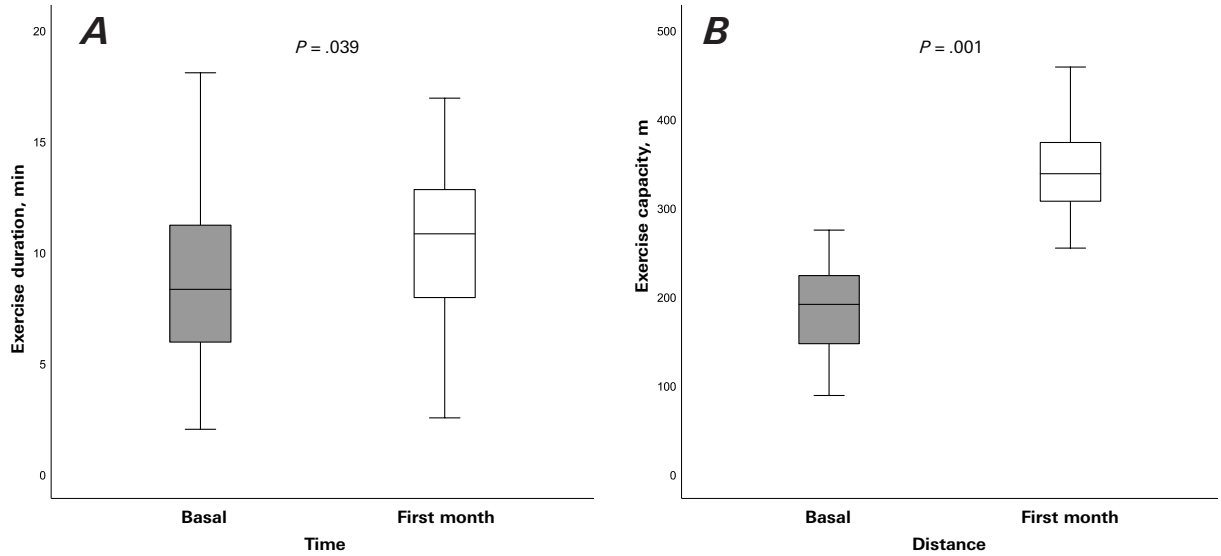

Fig. 2 Box and whisker plots compare **A**) exercise duration and **B**) exercise capacity parameters derived from symptom-limited treadmill tests in patients with ischemic heart failure with reduced ejection fraction and type 2 diabetes before vs 1 month after the initiation of sodium-glucose cotransporter 2 inhibitor therapy. The line inside each box indicates the median (50th percentile). The bottom and top of each box indicate the interval between the 25th and 75th percentiles. Whiskers indicate the interval between the minimum and maximum values. $P < .05$ (2-sided) was considered statistically significant.

mg/dL, and median [IQR], 1.94 [1.48-2.54] mmol/L, or 171.48 [131.36-225.20] mg/dL, vs 2.30 [0.70] mmol/L, or 203.93 [61.74] mg/dL, and 2.41 [1.74-2.55] mmol/L, or 212.98 [154.20-225.66] mg/dL; $P < .001$) and non–high-density lipoprotein (HDL) levels (mean [SD], 3.40 [0.84] mmol/L, or 131.27 [32.43] mg/dL, and median [IQR], 3.41 [2.81-4.06] mmol/L, or 131.69 [108.59-156.62] mg/dL, vs 4.02 [0.80] mmol/L, or 155.21 [30.88] mg/dL, and 4.20 [3.37-4.66] mmol/L, or 162.32 [130.16-180.06] mg/dL; $P < .001$), whereas HDL levels increased significantly (mean [SD], 0.99 [0.12] mmol/L, or 38.37 [4.72] mg/dL, and median [IQR], 1.0 [0.90-1.07] mmol/L, or 38.44 [34.90-41.42] mg/dL, vs 1.03 [0.12] mmol/L, or 39.66 [4.55] mg/dL, and 1.0 [0.91-1.08] mmol/L, or 38.63 [35.22-41.72] mg/dL; $P = .57$). Low-density lipoprotein (LDL) levels were not affected (mean [SD], 2.53 [0.55] mmol/L, or 97.76 [21.34] mg/dL, and median [IQR], 2.49 [2.06-2.99] mmol/L, or 96.25 [79.44-115.56] mg/dL, vs 2.62 [0.56] mmol/L, or 101.24 [21.75], and 2.60 [2.15-3.12] mmol/L, or 100.57 [82.86-120.60] mg/dL; $P = .166$) with 1 month of therapy. The net effect of therapy on the lipid profile was a statistically significant increase in the total cholesterol level (mean [SD], 4.65 [0.87] mmol/L, or 179.58 [33.63] mg/dL, and median [IQR], 4.59 [3.92-5.32] mmol/L, or 177.03 [151.20-205.51] mg/dL, vs 5.05 [0.91] mmol/L, or 194.98 [35.14] mg/dL, and 5.03 [4.33-5.72] mmol/L, or 194.03 [167.26-220.80] mg/dL; $P < .001$).

The effects of treatment on creatinine (mean [SD], 98.12 [19.89] μmol/L, or 1.11 [0.225] mg/dL, vs 99.01 [24.84] μmol/L, or 1.12 [0.281] mg/dL; $P = .73$), sodium (mean [SD], 138.26 [2.72] mmol/L vs 138.56 [3.48] mmol/L; $P = .39$), and potassium (mean [SD], 4.59 [0.691] mmol/L vs 4.45 [0.601] mmol/L; $P = .08$) levels were not statistically significant.

The differences in b-type natriuretic peptide level (mean [SD], 372.59 [249.26] ng/L and median [IQR], 320.30 [159.18-785.33] ng/L vs 365.26 [24.32] and 332.95 [123.34-669.21] ng/L; $P = .49$) and hematocrit level (mean [SD], 37.66% [4.49%] and median [IQR], 37.77% (34.67%-40.23%] vs 38.39% [5.78%] and

38.86% [34.81%-43.02%]; *P*=.20] after the first month of therapy were not statistically significant.

Discussion

On the basis of updated HF guidelines, empagliflozin and dapagliflozin are recommended for all patients with HFrEF independent of etiology. These treatments decrease the hospitalization and mortality rates, thus assuming a class 1A level in the HF therapy pool.[6] Discussions among cardiologists on the main mechanisms of action of these treatments and the role they play in the treatment of HF are ongoing. This study's findings suggest that the proven positive effects of these molecules appear with reference to cardiac autonomic function reaching near-normal levels in the early phases of treatment. The mechanism defined in this study may provide insight into the clinical improvements observed in the early phase of treatment in patients with ischemic HFrEF with the current drug group.

It is well known that HR fluctuates over time; this variability is closely related to changes in the neural activity to the heart.[7,8] Heart rate variability represents a noninvasive parameter for the autonomic control of the heart. It has been shown as a powerful independent prognostic factor in patients with coronary artery disease;[9] a low heart rate variability count has been related to sudden death.[10] The circadian index is a specific parameter for Holter monitoring that indicates the stability of the circadian heart rate. It is calculated as the ratio of mean daytime heart rate to mean nighttime heart rate in beats per minute. The normal value of the circadian index ranges from 1.24 to 1.44 (mean [SD], 1.32 [0.06]).[11] A reduction of the circadian index to less than 1.2 is found in diseases connected with a decrease in autonomic control of the heart rate.[11]

Diabetes is a typical model of cardiac autonomic abnormality, as patients with congestive HF are typically characterized by autonomic imbalance, with increased sympathetic activity and withdrawal of parasympathetic activity. Autonomic dysfunction, under the effects of vagal depression and sympathetic predominance, presents itself as diabetic cardiovascular autonomic neuropathy and can be diagnosed as tachycardia, reverse dipping, and impaired heart rate variability in clinical practice. Empagliflozin and other SGLT2 inhibitors have a direct cardioprotective role in abating the vagal atrophy seen in type 2 diabetes by decreasing the glycemic load in patients through glucosuria.[12] Moreover, type 2 diabetes is independently associated with decreased baroreflex sensitivity (BRS),[13] and BRS is depressed in the case of HF. Depressed BRS implies persistent tachycardia with a lack of the associated neural reflexes. A study by Hamaoka et al[14] showed that dapagliflozin resulted in a significant decrease in muscle sympathetic nerve activity and heart rate relative to baseline in 11 patients with type 2 diabetes, which indicates the effects of SGLT2 inhibitors on BRS. The present study is also compatible with the current limited literature, which shows that the use of SGLT2 inhibitors in patients with diabetes and HF has a positive effect on autonomic dysfunction. In the present study, the significant decrease in daytime and nighttime heart rates compared with basal measurements and the finding that the circadian index was closer to normal levels indicates that the current positive effects of SGLT2 inhibitors are independent of blood glucose regulation. Probably for this reason, treatment with SGLT2 inhibitors has been recently extended beyond patients with type 2 diabetes and HF, which themselves have roots in sympathetic and neurologic dysfunction, to patients with HF without type 2 diabetes, as emerging data show benefits in this population.[15]

Women adequately treated with current evidence-based medications for acute myocardial infarction and conventional cardiovascular risk factors, such as hypertension, diabetes, smoking, and dyslipidemia, still have an increased risk of death compared with men. The Framingham Study, the Chicago Heart Study, and the Minnesota Heart Study all obtained evidence that patients with diabetes are at a greater risk for development of HF after myocardial infarction and confirmed the higher relative increase in early and late mortality when diabetes appeared in women compared with men.[16] Healthy young women typically have an increased heart rate and reduced heart rate variability compared with men; however, these sex differentials dissipate after 50 years of age.[17,18] Although heart rate variability was not a parameter of this study, heart rates during the daytime and nighttime were the major indicators of circadian index and the primary end point of the study. Although the number of women was lower than expected owing to the incidence of ischemic heart disease in the general population, the positive effects of SGLT2 inhibitors on the circadian index did not depend on sex in this study. Because of the small sample size of women in the study design, women's heart rates and circadian indices could not be compared with those of age-matched men, which limited interpretation of the findings. Therefore,

the current study is not sufficient to investigate whether sex-specific differences exist among the end points of the study.

Previous studies have suggested the beneficial effects of SGLT2 inhibitors with respect to reducing lipid levels; however, the lipid profile results are controversial. Although some have suggested that treatment with SGLT2 inhibitors significantly decreases total cholesterol, LDL cholesterol, and triglyceride levels,[19] others have found no significant change in the serum lipid profile.[20] A meta-analysis of 48 randomized controlled trials revealed that SGLT2 inhibitor therapy led to a significant increase in total cholesterol, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol levels as well as a significant decrease in triglyceride levels and no significant alteration of the LDL/HDL ratio.[21] Although the results of the current study were mostly compatible with the current literature, there were some differences regarding the effects on triglyceride and LDL levels. In the meta-analysis by Sánchez-García,[21] canagliflozin, dapagliflozin, and ipragliflozin provided a significant reduction in triglyceride levels. This finding may explain the differences in the present study's results for participants taking empagliflozin or dapagliflozin. As the mechanism of action in this treatment group becomes clear, the mechanism that causes the lipid spike will also be clarified.

In theory, it is unknown which body compartments and tissues change after the initiation of treatment with SGLT2 inhibitors. The reported outcomes could be related to the loss of fat mass by a negative effect on energy balance, the loss of sodium and extracellular volume by a diuretic effect, or a combination of both. This study reported clinically meaningful improvements in HF-related health status besides nonsignificant improvement in natriuretic peptides. It is possible that SGLT2 inhibitors may selectively reduce interstitial fluid and that this, in turn, may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics.[22] Compared with a loop diuretic (bumetanide), dapagliflozin was associated with a greater reduction in interstitial vs intravascular volume.[23] Therefore, the present study suggests that, unlike classical diuretics, the SGLT2 inhibitors had a positive effect in patients with HFrEF by removing the water from the extravascular adipose tissue rather than the intravascular volume, which resulted in a significant increase in functional effort capacity without a significant decrease in blood pressure, b-type natriuretic peptide, or hematocrit levels. The positive effects of SGLT2 inhibitors on the autonomic function of the heart in this study was in accordance with the limited reflex neurohumoral stimulation.

These SGLT2 inhibitors are relatively weak glucose-lowering agents,[24] and the benefits of this new class of drugs extend beyond glycemic control. Definitive proof of this concept emerged from a trial that examined the effect of dapagliflozin in patients with HF, wherein the efficacy of dapagliflozin was entirely consistent in those with and without diabetes.[25] In meta-analyses of clinical trials comparing SGLT2 inhibitors with placebo or active comparators (eg, metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, and insulin), SGLT2 inhibitors reduced HbA_{1c} by approximately 0.5 to 0.7 percentage points (mean difference vs active comparators, –0.06% to –0.1%) compared with placebo.[26-29] Two meta-analyses reported that canagliflozin was more efficacious than its 2 counterparts, dapagliflozin and empagliflozin, in reducing HbA_{1c} levels,[30,31] but there have been no head-to-head trials of the different -flozins. In the present study, when the effects of empagliflozin or dapagliflozin molecules on HbA_{1c} levels were compared, it was found that the effect of a specific -flozin molecule on HbA_{1c} level was not significant, but this study included a small sample size with a short follow-up. Head-to-head comparative trials are needed to assess the potential differences in this regard, with longer follow-up periods and larger populations.

Limitations

Although the enrollment of the study participants started before the COVID-19 pandemic was declared in Turkey, it continued under the influence of the pandemic, similar to the process implemented in other studies worldwide during this time. Hospital admissions of patients with type 2 diabetes and HF who were at high risk for COVID-19 decreased during this period because of government-imposed restrictions and fear of being infected. Therefore, the number of participants in the study remained below the planned number under pandemic conditions. Although all the participants had LVEF below 40%, only 3 participants had undergone sacubitril/valsartan therapy, which is currently thought to be a significant regimen for optimal medical treatment in patients with HFrEF. Unfortunately, it is not possible to say that the patients were under optimal medical treatment in this study. Despite growing awareness of the role of sex in the management of cardiovascular disease, female patients are not sufficiently represented in clinical trials, including in the present study.

Conclusions

The results of this study showed that the SGLT2 drug group in the new generation of type 2 diabetes treatment had positive effects on both autonomic dysfunction and functional effort capacity in patients with HFrEF after 1 month of the therapy. Different SGLT2 inhibitors were used in the study. No difference was found in the primary end points at the molecular level, which indicates that these results may reflect the group effects of SGLT2 inhibitors.

Article Information

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References

1. Buse JB, Wexler DJ, Tsapas A, et al. 2019 Update to: management of hyperglycemia in type 2 diabetes, 2018. a consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2020;43(2):487-493. doi:10.2337/dci19-0066
2. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373(22):2117-2128. doi:10.1056/NEJMoa1504720
3. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377(7):644-657. doi:10.1056/NEJMoa1611925
4. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357. doi:10.1056/NEJMoa1812389
5. Cherney D. Cardiovascular outcomes following ertugliflozin treatment in patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. In: *Evaluation of Ertugliflozin Efficacy and Safety—VERTIS CV.* Presented at: ADA 2020; June 12-16, 2020; virtual.
6. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines update: defining a new pharmacologic standard of care for heart failure with reduced ejection fraction. *Can J Cardiol.* 2021;37(4):531-546. doi:10.1016/j.cjca.2021.01.017
7. Levy MN, Martin PJ, Stuesse SL. Neural regulation of the heart beat. *Annu Rev Physiol.* 1981;43:443-453. doi:10.1146/annurev.ph.43.030181.002303
8. Koizumi K, Terui N, Kollai M. Effect of cardiac vagal and sympathetic nerve activity on heart rate in rhythmic fluctuations. *J Auton Nerv Syst.* 1985;12(2-3):251-259. doi:10.1016/0165-1838(85)90065-7
9. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol.* 1987;59(4):256-262. doi:10.1016/0002-9149(87)90795-8
10. Martin GJ, Magid NM, Myers G, et al. Heart rate variability and sudden death secondary to coronary artery disease during ambulatory electrocardiographic monitoring. *Am J Cardiol.* 1987;60(1):86-89. doi:10.1016/0002-9149(87)90990-8
11. Makarov L. Circadian index, as a additional parameter for assessment of the heart rhythm in patients with heart failure. Presented at: ISHNE Heart Failure World-Wide Web Symposium. International Society for Holter and Noninvasive Electrocardiology; January 2006. doi:10.13140/RG.2.1.3204.6246
12. Nashawi M, Sheikh O, Battisha A, Ghali A, Chilton R. Neural tone and cardio-renal outcomes in patients with type 2 diabetes mellitus: a review of the literature with a focus on SGLT2 inhibitors. *Heart Fail Rev.* 2021;26(3):643-652. doi:10.1007/s10741-020-10046-w
13. Cseh D, Climie RE, Offredo L, et al. Type 2 diabetes mellitus is independently associated with decreased neural baroreflex sensitivity: the Paris Prospective Study III. *Arterioscler Thromb Vasc Biol.* 2020;40(5):1420-1428. doi:10.1161/ATVBAHA.120.314102
14. Hamaoka T, Murai H, Sugimoto H, et al. Effect of sodium glucose cotransporter 2 inhibitor on sympathetic nerve activity in type 2 diabetes mellitus patients. *Eur Heart J.* 2019;40(suppl 1):ehz748.0064. doi:10.1093/eurheartj/ehz748.0064
15. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303
16. Pan WH, Cedres LB, Liu K, et al. Relationship of clinical diabetes and asymptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. *Am J Epidemiol.* 123(3):504-516. doi:10.1093/oxfordjournals.aje.a114266
17. Voss A, Schroeder R, Heitmann A, Peters A, Perz S. Short-term heart rate variability–influence of gender and age in healthy subjects. *PLoS One.* 2015;10(3):e0118308. doi:10.1371/journal.pone.0118308
18. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol.* 1998;31(3):593-601. doi:10.1016/s0735-1097(97)00554-8

19. Calapkulu M, Cander S, Gul OO, Ersoy C. Lipid profile in type 2 diabetic patients with new dapagliflozin treatment; actual clinical experience data of six months retrospective lipid profile from single center. *Diabetes Metab Syndr.* 2019;13(2):1031-1034. doi:10.1016/j.dsx.2019.01.016
20. Katsuyama H, Hamasaki H, Adachi H, et al. Effects of sodium-glucose cotransporter 2 inhibitors on metabolic parameters in patients with type 2 diabetes: a chart-based analysis. *J Clin Med Res.* 2016;8(3):237-243. doi:10.14740/jocmr2467w
21. Sánchez-García A, Simental-Mendía M, Millán-Alanís JM, Simental-Mendía LE. Effect of sodium-glucose co-transporter 2 inhibitors on lipid profile: a systematic review and meta-analysis of 48 randomized controlled trials. *Pharmacol Res.* 2020;160:105068. doi:10.1016/j.phrs.2020.105068
22. 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. doi:10.1016/j.jacbts.2020.02.004
23. Hallow KM, Helmlinger G, Greasley PJ, McMurray JJV, Boulton DW. Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis. *Diabetes Obes Metab.* 2018;20(3):479-487. doi:10.1111/dom.13126
24. DeSantis A. Sodium-glucose cotransporter 2 inhibitors for the treatment of hyperglycemia in type 2 diabetes mellitus. UpToDate. Updated August 2, 2023. Accessed November 6, 2023. https://www.uptodate.com/contents/sodium-glucose-cotransporter-2-inhibitors-for-the-treatment-of-hyperglycemia-in-type-2-diabetes-mellitus
25. McMurray JJV, DeMets DL, Inzucchi SE, et al. A trial to evaluate the effect of the sodium-glucose co-transporter 2 inhibitor dapagliflozin on morbidity and mortality in patients with heart failure and reduced left ventricular ejection fraction (DAPA-HF). *Eur J Heart Fail.* 2019;21(5):665-675. doi:10.1002/ejhf.1432
26. Musso G, Gambino R, Cassader M, Pagano G. A novel approach to control hyperglycemia in type 2 diabetes: sodium glucose co-transport (SGLT) inhibitors: systematic review and meta-analysis of randomized trials. *Ann Med.* 2012; 44(4):375-393. doi:10.3109/07853890.2011.560181
27. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. *Ann Intern Med.* 2013;159(4):262-272. doi:10.7326/0003-4819-159-4-201308200-00007
28. Sun YN, Zhou Y, Chen X, Che WS, Leung SW. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. *BMJ Open.* 2014; 4(4):e004619. doi:10.1136/bmjopen-2013-004619
29. Liu XY, Zhang N, Chen R, et al. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2 years. *J Diabetes Complications.* 2015;29(8):1295-1303. doi:10.1016/j.jdiacomp.2015.07.011
30. Johnston R, Uthman O, Cummins E, et al. Canagliflozin, dapagliflozin and empagliflozin monotherapy for treating type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess.* 2017;21(2):1-218. doi:10.3310/hta21020
31. Zaccardi F, Webb DR, Htike ZZ, Youssef D, Khunti K, Davies MJ. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab.* 2016;18(8):783-794. doi:10.1111/dom.12670