# The impact of using SGLT-2 inhibitor on left ventricular longitudinal strain and NT-proBNP levels during six-month follow-up in diabetic patients with and without coronary artery disease with preserved ejection fraction

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## ABSTRACT

**Background:** Optimal glycemic control is necessary to prevent cardiovascular events in patients with type 2 diabetes. The positive impact of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on cardiovascular events and mortality in these patients has been demonstrated by previous studies although the mechanism is unclear.

**Aims:** We aimed to compare the influence of SGLT2i on left ventricular remodeling and strain in diabetic patients with coronary artery disease (CAD) and without CAD during 6-month follow-up.

**Methods:** Between October 2021 and June 2022, 100 diabetic patients with preserved ejection fraction (HbA1c levels 6.5–10%) were started on SGLT2i (empagliflozin or dapagliflozin) and were prospectively followed up. Conventional and speckle-tracking echocardiography was performed by blinded sonographers, at baseline and then at 1 month and 6 months of treatment. After 6 months, the initial and biochemical blood tests were administered, and N-terminal pro-B-type natriuretic peptide levels of the patients were measured.

**Results:** Patients with CAD were older ($P = 0.008$), more frequently hypertensive ($P = 0.035$), and had dyslipidemia ($P = 0.021$). N-terminal pro-B-type natriuretic peptide levels did not change significantly after treatment in both groups. Left ventricular ejection fraction, global, 2-chamber, and 3-chamber strain values were improved significantly following SGLTi administration for the overall patient cohort, regardless of CAD status ($P < 0.05$ for all groups).

**Conclusions:** Treatment with SGLT2i resulted in improvement in left ventricular strain parameters, which indicates that they might have a positive impact on outcomes for diabetic patients with preserved EF.

**Key words:** heart failure, preserved ejection fraction, strain echocardiography

## INTRODUCTION

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) have recently been shown to improve cardiovascular outcomes in individuals at high cardiovascular risk with type 2 diabetes mellitus (T2DM) [1]. Although the mechanisms of SGLT2i action have not yet been fully elucidated, they appear to involve direct hemodynamic effects and metabolic effects, as these agents enhance renal glucose excretion thereby increasing diuresis; they reduce blood pressure, preload and afterload, and alleviate cardiac remodeling [2].

Heart failure with preserved ejection fraction (HFpEF) now accounts for approximately half of all heart failure cases, with its prevalence rising among patients with hypertension, atrial fibrillation, and diabetes [3]. Given

WHAT'S NEW?

Using strain echocardiography, we have demonstrated, for the first time, positive effects of sodium-glucose co-transporter 2 inhibitors in diabetic patients with preserved EF, regardless of their coronary artery disease status, which involve improved left ventricular strain parameters, have been demonstrated for the first time by strain echocardiography.

the lack of treatment options indicated for HFpEF, after many years of research in the field of HFpEF, SGLT2i have been recommended recently regardless of the percentage of left ventricular ejection fraction (LVEF) [4–6].

Left ventricular (LV) longitudinal myocardial systolic function and LV diastolic function are thought to be simultaneously impaired in patients with diabetes, even in the case of preserved LVEF [7, 8]. However, clinical studies on the impact of SGLT2i on the parameters of myocardial deformation are scarce. Although LV longitudinal strain has been previously measured by cardiac magnetic resonance, there is an important knowledge gap regarding the use of speckle-tracking echocardiography in patients treated with SGLT2i. In this study, we aimed to compare the influence of SGLT2i on LV remodeling and function in patients with preserved EF with and without coronary artery disease (CAD).

## METHODS

### Study design and participants

This study was a prospective observational study conducted in a center in Istanbul, Turkey. The patients were started on SGLT2i therapy due to T2DM in the internal medicine department. Between October 2021 and June 2022, 100 diabetic patients who were at least 18 years old and had glycated hemoglobin levels between 6.5% and 10.0% were prospectively included in the study (Figure 1). The exclusion criteria were determined as type 1 DM, current use of SGLT2i, renal failure (glomerular filtration rate <45 ml/min/1.73 $m^2$), pregnancy, EF below <50%, moderate to severe valve disease, or inadequate echocardiographic windows and the presence of atrial fibrillation.

### Data collection and follow-up

Clinical and echocardiographic evaluations were performed at baseline, at the end of month 1, and after 6 months of follow-up. All patients were on either empagliflozin or dapagliflozin. Patients were allocated into two groups: those with CAD (history of previous percutaneous coronary intervention or coronary bypass operation, or those with 50% or more stenosis in at least one coronary artery on coronary angiography) and those without CAD (the control group). The same sonographers, blinded to clinical data, baseline echocardiographic data, and the presence/absence of CAD, performed both echocardiographic studies.

### Standard echocardiographic examination

Two-dimensional transthoracic echocardiography was obtained with commercially available systems (iE33 Philips Medical Systems, the Best, the Netherlands) equipped with 3.5 MHz or M5S transducers. All tests were performed by two experienced sonographers within the first 2 days after enrollment.

From the parasternal long-axis view, LV end-diastolic and end-systolic diameters were measured using M-mode, and the LV mass was derived from the Devereux formula and indexed to body surface area. LV end-diastolic and end-systolic volumes, LVEF, and left atrial volumes were measured from apical four- and two-chamber views. The left atrial volume index was calculated by dividing LA volume by body surface area of subjects. Peak early diastolic (E) and late diastolic (A) wave velocities were measured by pulsed wave Doppler recordings from an apical 4-chamber view. The peak early diastolic myocardial velocity (E') was measured by Doppler tissue imaging in the apical 4-chamber view. The E/e' ratio was obtained as a measure of LV filling pressures. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography/European Society of Cardiovascular Imaging [9].

### Strain analysis

Myocardial strain was measured using speckle-tracking echocardiography. After the acquisition, the studies were stored for offline analysis with the EchoPAC software (v30 12; GE Vingmad Ultrasound AS). Endo- and epicardial 15-point contours were defined by the software's automated border tracking algorithm in end-diastole to cover the whole cardiac wall if needed, the region of interest was adjusted manually in case of suboptimal tracking. Left ventricular global longitudinal strain (GLS) was averaged at end-systole of the 18 segments derived from the three apical values (4-chamber, 3-chamber, and 2-chamber).

### Statistical analysis

Variables were presented as means (standard deviations), numbers (percentages), and medians (interquartile ranges [IQRs]) as appropriate. The $\chi^2$ test was used to compare categorical variables between the groups, while the Kolmogorov–Smirnov test was employed if the variables were normally distributed. Comparisons between continuous variables were performed using the independent samples t-test or Mann–Whitney U test as appropriate. Changes in LVEF and strain levels were compared using repeated-measures analyses of variance (ANOVA). In the case of significant differences after ANOVA, the Bonferroni *post hoc* test analysis was used to identify inter-phase changes. A *P*-value threshold below 0.05 was considered

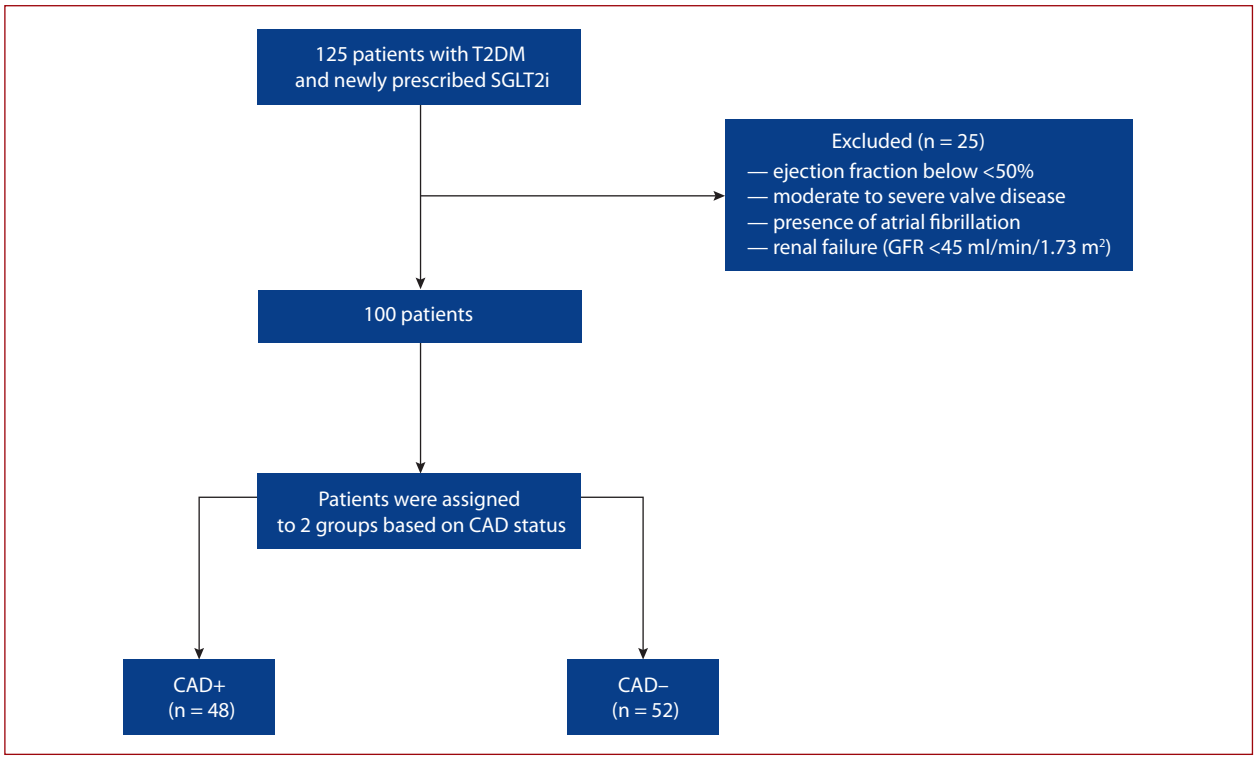


**Figure 1.** Flow diagram for inclusion in the study

Abbreviations: CAD, coronary artery disease; GFR, glomerular filtration rate; SGLT2i, sodium-glucose cotransporter 2 inhibitors; T2DM, type 2 diabetes mellitus

significant. All statistical analyses were performed using Statistical Package for the Social Sciences version 24.0 software (IBM Corp., Armonk, NY, US).

## RESULTS

### Baseline characteristics

Patients with CAD were older ($P$ = 0.008), more frequently hypertensive ($P$ = 0.035), and had dyslipidemia ($P$ = 0.02). As expected, the rate of beta-blockers (29 [60.4%] vs. 10 [10.2%]; $P$ <0.001), renin-angiotensin system blockers (39 [81.3%] vs. 27 [51.9%]; $P$ <0.01), and statins (26 [54.2%], vs. 12 [23.1%]; $P$ <0.01) was higher in the CAD group (Table 1). About two-thirds of both groups were prescribed empagliflozin (66% of the overall cohort, 31/48, 64.6% vs. 33/52, 63.5% in patients with CAD+ and CAD–, respectively). There was no difference in terms of other demographic, clinical, and laboratory parameters in both groups.

### Change in GLS at baseline and 1 month and 6 months after SGLT2i treatment

LVEF, global, 2-chamber, and 3-chamber strain values were improved significantly after SGLTi administration for the overall patient cohort. LVEF increased significantly during the six-month follow-up ($P$ <0.001). Compared to baseline (56.33%), the one-month (58.1%) and 6-month (59.3%) LVEF values increased ($P$ = 0.011 vs. $P$ <0.001), whereas first-month and sixth-month comparisons of LVEF ($P$ = 0.32) were similar after SGLT2i initiation (Table 2).

A repeated-measures ANOVA determined that mean GLS, 2-chamber, 3-chamber, and 4-chamber strain values increased substantially across the three time points for all patient cohorts ($P$ <0.001 for GLS; $P$ <0.001 for 2-chamber strain; $P$ <0.003 for 3-chamber strain and $P$ <0.001 for 4-chamber strain). A *post hoc* pairwise comparison using the Bonferroni correction showed an increased GLS score between the initial assessment and 1-month (17.9 vs. 18.6; $P$ <0.001); 6-month (17.9 vs. 18.9; $P$ <0.001) as well as 1-month and 6-month follow-ups (18.6 and 18.9; $P$ = 0.029). Two-chamber (17.8 vs. 18.6; $P$ = 0.048 vs. $P$ <0.001), 3-chamber (18.02 vs. 18.8; $P$ = 0.03 vs. $P$ = 0.004) and 4-chamber strain values (17.8 vs. 19.3; $P$ <0.001 for all) showed an increase at 6-month follow-up compared to basal strain values; however, the comparisons of 1-month and 6-month strain values were similar for 2-chamber (18.24 vs. 18.6, respectively; $P$ = 0.07), 3-chamber (18.54 vs. 18.8, respectively; $P$ = 0.89), and 4-chamber (19 vs. 19.3, respectively; $P$ = 0.66) strain measurements.

Both LV GLS parameters of patients with and without CAD at first and sixth-month follow-up improved compared to basal measurements ($P$ <0.001 for all) (Table 3). *Post hoc* analysis revealed that GLS parameters were similar for both groups at 1-month and 6-month follow-up ($P$ = 0.33 vs. $P$ = 0.13 for CAD– and CAD+ groups, respectively), but once compared to baseline, there was a significant improvement in GLS values for both groups at 1 month and 6-month follow-up ($P$ <0.05 for all).

Two-chamber strain rates did not change in patients with CAD during 6-month follow-up ($P$ = 0.23), whereas

**Table 1.** Demographic, clinical and laboratory parameters of the study cohort grouped according to the presence of coronary artery disease

| Variables | All population (n = 100) | CAD+ (n = 48) | CAD– (n = 52) | *P*-value |
|---|---|---|---|---|
| Female gender, n (%) | 71 (71) | 37 (77.1) | 34 (65.4) | 0.2 |
| Age, years | 58.7 (9.9) | 61.4 (8.6) | 56.2 (10.4) | 0.01 |
| BMI, kg/m$^2$ | 32.0 (4.5) | 31.2 (3.1) | 32.7 (5.4) | 0.11 |
| HT, n (%) | 69 (69) | 38 (79.2) | 31 (59.1) | 0.04 |
| Dyslipidemia, n (%) | 59 (59) | 34 (70.8) | 25 (48.1) | 0.02 |
| Smoking, n (%) | 27 (27) | 16 (33.3) | 11 (21.2) | 0.17 |
| Family history, n (%) | 26 (26) | 14 (29.2) | 12 (23.1) | 0.49 |
| CRF, n (%) | 7 (7) | 3 (6.3) | 4 (7.7) | 0.78 |
| Stroke history, n (%) | 1 (1) | 0 (0) | 1 (1.9) | 0.33 |
| COPD, n (%) | 4 (4) | 0 (0) | 4 (7.7) | 0.05 |
| **Medications** | | | | |
| β-blockers, n (%) | 39 (39) | 29 (60.4) | 10 (19.2) | <0.001 |
| CCBs, n (%) | 41 (41) | 24 (50) | 17 (32.7) | 0.08 |
| RAS-blockers, n (%) | 66 (66) | 39 (81.3) | 27 (51.9) | 0.002 |
| MRAs, n (%) | 5 (5) | 3 (6.3) | 2 (3.8) | 0.58 |
| Statins, n (%) | 38 (38) | 26 (54.2) | 12 (23.1) | 0.001 |
| Empagliflozin, n (%) | 66 (66) | 31 (64.6) | 33 (63.5) | 0.91 |
| Metformin, n (%) | 82(82) | 40 (83.3) | 42 (80.8) | 0.74 |
| **Laboratory tests** | | | | |
| Creatinine, mg/dl | 0.85 (0.28) | 0.89 (0.31) | 0.82 (0.27) | 0.41 |
| TC, mg/dl | 209 (42) | 212 (47) | 207 (47) | 0.61 |
| LDL-C, mg/dl | 133 (33) | 134 (27) | 132 (38) | 0.75 |
| HDL-C, mg/dl | 41.8 (8.6) | 41.1 (8.6) | 42.4 (8.7) | 0.46 |
| Triglyceride, mg/dl | 163 (121–252) | 189 (124–288) | 153 (116–229) | 0.94 |
| NT-proBNP baseline, pg/ml | 100 (55.3–160) | 125 (77–163.8) | 78 (45.6–158.3) | 0.76 |
| NT-proBNP sixth month, pg/ml | 83 (57.3–130) | 92.5 (58.5–127.5) | 80.5 (51.3–146) | 0.43 |
| Hemoglobin, g/dl | 13.3 (1.7) | 13.1 (1.4) | 13.5 (1.8) | 0.44 |
| CRP, mg/dl | 3.30 (1.40–5.70) | 3.40 (1.10–6.30) | 3.10 (1.90–5.10) | 0.94 |

Continuous variables are given as means and standard deviations or medians and first and third quartiles (IQR). Categorical variables are presented as numbers and percentages

Abbreviations: BMI, body mass index; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HT, hypertension; LDL-C, low-density lipoprotein cholesterol; MRAs, mineralocorticoid receptor antagonists; RAS, renin–angiotensin system; TC, total cholesterol

these values were better in patients without CAD ($P$ <0.001). *Post hoc* analysis showed this difference occurred in the first month (17.8 [3.5] vs. 18.6 [3.1]; $P$ = 0.02) and the sixth month of follow-up (17.8 [3.5] vs. 19.0 [3.3]; $P$ <0.001), but first month and sixth-month comparison of 2-chamber strain rates did not differ ($P$ = 0.19) for CAD– patients.

Apical 3-chamber strain values improved at the sixth-month follow-up for the CAD+ group ($P$ = 0.04) but no improvement occurred in CAD– patients. For the CAD+ group, improvement was only relevant at the sixth month compared to baseline ($P$ = 0.03), whereas the comparisons between first and sixth-month follow-up ($P$ = 1) as well as baseline and first month ($P$ = 0.09) did not differ significantly.

Apical 4-chamber strain values improved for both groups after SGLT2i initiation ($P$ = 0.001 vs. $P$ <0.001 for CAD + and CAD– groups, respectively). We found a significant increase in the first month and sixth month apical 4-chamber measures compared to strain values before SGLT2i prescription ($P$ = 0.02 and $P$ <0.001 for CAD– group; $P$ = 0.03 and $P$ = 0.003 for CAD+ group, respectively); however, a comparison of the first and sixth-month apical 4-chamber strain rates did not exhibit statistically significant difference ($P$ = 1 for CAD–, $P$ = 0.41 for CAD+ group).

## DISCUSSION

The findings of our study indicate that LV longitudinal myocardial function assessed in terms of GLS for T2DM patients with preserved EF significantly improved after administration of SGLT2i irrespective of CAD status. There was no significant change from baseline to month 6 in NT-proBNP levels after SGLT2i treatment.

Although SGLT2i have been shown to improve symptoms in patients with HFrEF, data on the impact of SGLT2i treatment on health status in HFpEF patients are limited [10–13]. The presence of T2DM is a major contributor to the development of HFpEF and is related to worse outcomes for patients with HFrEF and HFpEF [13]. Adding SGLT2i in T2DM patients to reduce the significant burden of heart failure achieved significant improvement in LV diastolic dysfunction based on diastolic stress echocardiography [14]. Diastolic dysfunction is thought to be the first marker of preclinical impairment during the course of diabetic cardiomyopathy detected by GLS [15]. Ernande

**Table 2.** Echocardiographic parameters of the all study cohort

| Variables | Findings | *P*-value | ANOVA |
|---|---|---|---|
| **Echocardiographic parameters** | | | |
| LV end-diastolic volume$_0$, ml | 51 (49–53) | <0.001 | |
| LV end-diastolic volume$_6$, ml | 50 (48.25–52) | | |
| LV end-systolic volume$_0$, ml | 30 (29–32) | <0.001 | |
| LV end-systolic volume$_6$, ml | 29 (27–31) | | |
| E/E′$_0$ | 11.8 (2.25) | 0.28 | |
| E/E′$_6$ | 11.7 (2.33) | | |
| LAVI$_0$, ml/m$^2$ | 34.74 (2.33) | 0.04 | |
| LAVI$_6$, ml/m$^2$ | 33.41 (2.8) | | |
| LVEF$_0$, % | 56.3 (4.7) | 0.004 | <0.001 |
| LVEF$_1$, % | 58.1 (7.6) | | |
| LVEF$_6$, % | 59.3 (5.8) | | |
| Global longitudinal strain$_0$ | 17.9 (2.2) | | <0.001 |
| Global longitudinal strain$_1$ | 18.6 (2.6) | | |
| Global longitudinal strain$_6$ | 18.9 (2.6) | | |
| Two-chamber strain$_0$ | 17.9 (2.2) | | <0.001 |
| Two-chamber strain$_1$ | 18.2 (2.7) | | |
| Two-chamber strain$_6$ | 18.6 (3.0) | | |
| Three-chamber strain$_0$ | 18.0 (2.7) | | 0.003 |
| Three-chamber strain$_1$ | 18.5 (2.8) | | |
| Three-chamber strain$_6$ | 18.8 (2.9) | | |
| Four-chamber strain$_0$ | 17.8 (2.5) | | <0.001 |
| Four-chamber strain$_1$ | 19.0 (3.5) | | |
| Four-chamber strain$_6$ | 19.3 (3.1) | | |

$_0$Baseline; $_1$ First month follow-up; $_6$ Sixth month follow-up; *P* = Comparison between baseline and sixth month follow-up, *P* = Global strain$_0$ vs. Global strain$_1$; *P* = Global strain$_0$ vs. Global strain$_6$. Data are mean (standard deviation for normally distributed data and median and interquartile range for non-normally distributed data). Repeated-measures of ANOVA assessing for differences in change — in LVEF and strain values when all time points are considered

Abbreviations: LAVI, left atrial volume index; LV, left ventricle; LVEF, left ventricular ejection fraction

**Table 3.** Comparison of the echocardiographic parameters of patients with and without coronary artery disease (CAD)

| Variables | CAD+ (n = 48) | | CAD– (n = 52) | | $P_0$ |
|---|---|---|---|---|---|
| | Findings | *P*-value | Findings | *P*-value | |
| LV end-diastolic volume$_0$, ml | 98.3 (13.5) | 0.53 | 93.83 (20.7) | 0.53 | 0.21 |
| LV end-diastolic volume$_6$, ml | 97.3 (14.0) | | 95.623 (17.2) | | 0.59 |
| LV end-systolic volume$_0$, ml | 44.4 (8.4) | 0.013 | 41.50 (9.3) | 0.011 | 0.11 |
| LV end-systolic volume$_6$, ml | 42 (9.4) | | 38.35 (9.1) | | 0.06 |
| LVEF$_0$, % | 55.3 (3.7) | 0.08 | 57.2 (5.3) | <0.001 | 0.042 |
| LVEF$_1$, % | 56.2 (8.5) | | 59.8 (6.2) | | 0.016 |
| LVEF$_6$, % | 57.8 (5.1) | | 60.6 (6.2) | | 0.016 |
| Global strain$_0$ | 17.7 (1.8) | <0.001 | 18.0 (2.6) | <0.001 | 0.516 |
| Global strain$_1$ | 18.2 (2.1) | | 18.9 (2.9) | | 0.138 |
| Global strain$_6$ | 18.6 (2.4) | | 19.2 (2.8) | | 0.264 |
| Two-chamber strain$_0$ | 17.8 (2.4) | 0.23 | 17.8 (3.5) | <0.001 | 0.974 |
| Two-chamber strain$_1$ | 17.9 (2.2) | | 18.6 (3.1) | | 0.181 |
| Two-chamber strain$_6$ | 18.2 (2.6) | | 19.0 (3.3) | | 0.148 |
| Three-chamber strain$_0$ | 17.8 (2.7) | 0.04 | 18.2 (2.6) | 0.10 | 0.523 |
| Three-chamber strain$_1$ | 18.4 (3.0) | | 18.7 (2.69) | | 0.548 |
| Three-chamber strain$_6$ | 18.7 (2.9) | | 18.9 (3.0) | | 0.791 |
| Four-chamber strain$_0$ | 17.6 (2.1) | 0.001 | 18.0 (2.8) | <0.001 | 0.356 |
| Four-chamber strain$_1$ | 18.4 (2.3) | | 19.6 (4.3) | | 0.082 |
| Four-chamber strain$_6$ | 18.9 (2.9) | | 19.7 (3.3) | | 0.253 |

P$^0$ = Comparison of values in patients with CAD vs. patients without CAD; *P*-value, independent samples T test or repeated-measures ANOVA assessing for differences in change-in LVEF and strain values within the groups when all time points are considered

Abbreviations: see Table 2

et al. demonstrated that T2DM patients with normal LV function have impaired LV longitudinal myocardial dysfunction (GLS < 18%) even in the case of normal diastolic function (baseline GLS 17.9 [2.2] in our study). This finding supports the hypothesis LV GLS analysis might play a new role in assessing subtle LV diastolic dysfunction which will lead to diastolic heart failure before HFpEF diagnosis.

Tanaka et al. examined the association of LV longitudinal myocardial function with LV diastolic function after administration of SGLT2i in T2DM patients with stable heart failure with 69% of subjects with HFpEF [16]. They found that SGLT2i showed superior cardiovascular effects in terms of GLS improvement for HFpEF patients compared to non-HFpEF patients.

Recently, a prospective single-center study assessing the impact of canagliflozin on LV diastolic function in diabetic patients with preserved LVEF concluded that among LV diastolic function parameters, E/e' and the left ventricular mass index had significantly improved 3 months after canagliflozin treatment [17]. In our study, only the left atrial volume index was decreased after SGLT2i treatment (baseline 34.74 [2.33], 33.41 [2.8] at 6 months; $P = 0.04$). Our results confirm that early administration of SGLT2i in T2DM patients might delay HFpEF diagnosis.

Even though natriuretic peptide levels are excellent prognostic markers for chronic heart failure, their clinical power for HFpEF patients is less clear [18]. Nevertheless, a significant decline in NT-proBNP levels was not observed during 6 months of treatment in this study. Comparing our results with previous data from comparably sized trials, dapagliflozin treatment had been also shown to have no significant effect on natriuretic peptides [19]. The possible reasons could be the small sample size and the fact that the patients in this study were in the early stage of HFpEF (Stage A), thus exhibiting less severe symptoms, and also having no long-term data.

### *Study limitations*

This study involved a small number of patients and did not use a placebo-controlled group, so future prospective studies with larger patient populations including placebo-controlled groups will be needed to confirm the results of our study. The relatively short duration of the follow-up precludes assessment of the durability of the observed benefit of SGLT2i for improving left ventricular strain parameters.

## CONCLUSIONS

SGLT2i therapy improved LV longitudinal myocardial function, thus it could enhance further improvement of LV diastolic function for T2DM patients with preserved EF regardless of CAD status.

### *Article information*

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