



Left Ventricular Systolic Function After 3 Months of SGLT2 Inhibitor Therapy in Heart Failure Patients with Reduced Ejection Fraction

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Abstract

Not much is known about the effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on echocardiographic parameters of left ventricular (LV) systolic function in patients with heart failure and reduced ejection fraction (HFrEF).

We prospectively included 59 outpatients with HFrEF: 41 patients received SGLT2i with OMT (SGLT2i+ group), whereas eighteen patients received OMT without SGLT2i (SGLT2i– group). Myocardial work index (MWI), 3D ejection fraction (3D LVEF), and global longitudinal strain (GLS) were measured at baseline and after 3 months following treatment. At 3-month follow-up, the SGLT2i+ group showed significantly greater improvement in MWI than the SGLT2i– group. In both groups, there was a significant improvement in 3D LVEF and LV GLS, circulating NT-proBNP levels, and NYHA functional class, with significantly greater improvement in the SGLT2i+ group.

In conclusion, the addition of SGLT2i to fully optimized background medical therapy resulted in a greater improvement of LV systolic function among outpatients with HFrEF.

Keywords Echocardiography · Global longitudinal strain · Myocardial work index · 3D-ejection fraction · Myocardial work efficiency · SGLT2 inhibitors · Heart failure with reduced ejection fraction

Abbreviations

ARNI	Angiotensin receptor-neprilysin inhibitors
BB	Beta blocker
CABG	Coronary artery bypass grafting
CRT	Cardiac resynchronization therapy

eGFR	Estimated glomerular filtration rate
GWI	Global work index
GCW	Global constructive work
GWW	Global wasted work
GWE	Global work efficiency
ICD	Implantable cardioverter device
LVEDV	Left ventricular end-diastolic volume
LV GLS	Left ventricular global longitudinal strain
LVESV	Left ventricular end-systolic volume
LVEF	Left ventricular ejection fraction
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCI	Percutaneous coronary intervention
TAPSE	Tricuspid annular plane systolic excursion

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Ivona Mustapic and Darija Bakovic contributed equally to this work.

Key Message: Patients receiving SGLT2i in addition to fully optimized HFrEF therapy consisting of ARNi, BB, and MRA improved LV systolic function more than non-recipients.

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Key Messages

What Is Already Known on This Topic?

- It is known that SGLT2 inhibition in heart failure with reduced ejection fraction (HFrEF) promotes reverse car-

diac remodeling and is associated with better clinical outcomes.

- SGLT2 inhibition has been associated with reduced left ventricular (LV) and left atrial volumes in HFrEF; however, its relationship with contemporary echocardiographic parameters of global LV systolic function, including global longitudinal strain and myocardial work have not been fully investigated.

What Does This Study Add?

- In outpatients with HFrEF, addition of dapagliflozin or empagliflozin to optimal background medical therapy (OMT) was associated with a significant improvement in global work index and global work efficiency compared to OMT without SGLT2 inhibitor.
- Outpatients with HFrEF receiving SGLT2 inhibitor also had a more meaningful improvement in 3D left ventricular ejection fraction and global longitudinal strain compared to those receiving OMT without SGLT2 inhibitor, after the 3-month follow-up.
- Similarly, addition of SGLT2 inhibitor to sacubitril/valsartan, beta-blocker, and mineralocorticoid receptor antagonist was associated with a greater reduction in circulating natriuretic peptides and NYHA functional class.

How Might This Study Affect Research, Practice, or Policy?

- This study shows that adding vs. omitting SGLT2 inhibitor to OMT in outpatients with HFrEF was associated with a significantly greater improvement in LV systolic function accompanied with a more robust reduction in markers of neurohumoral burden and NYHA class during the 3-month follow-up.

Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have an established place in the therapy of heart failure with reduced ejection fraction (HFrEF), as they have been shown to significantly reduce all-cause mortality, cardiovascular mortality, and hospitalizations in HFrEF patients, regardless of the presence of diabetes mellitus [1, 2]. The growing evidence of the effect of SGLT2i on cardiac remodeling through cellular, molecular, vascular, interstitial, and electrical effects justifies its role as fundamental HFrEF therapy [3–5]. Measurement of the effect of SGLT2i therapy on left ventricular systolic function (LV) has previously been assessed by changes in heart size and volume and changes in ejection fraction [6]. In current clinical practice, the assessment of LV systolic function is still mainly based on the

measurement of LV ejection fraction (LVEF), which remains the gold standard despite some notable limitations [7].

In the last decade, LV global longitudinal strain (GLS) has emerged as a more accurate predictor of poor outcomes, revealing subtle abnormalities and preclinical LV systolic dysfunction [8]. The disadvantage of GLS and LVEF measurements is their dependence on pressure and volume loading [9]. Global myocardial work index (GWI) is a new load-independent echocardiographic parameter derived from pressure-strain loops. The GWI came into the limelight after Russell and colleagues demonstrated a good correlation of the invasively measured pressure-volume loop with the noninvasive pressure-strain loop (PSL) as an equivalent for myocardial performance [10, 11]. Of interest, studies have shown that GWI reflects regional glucose metabolism of LV compared to 18-fluorodeoxyglucose-positron emission tomography (PET) [10]. Taken together, a growing body of data suggests that GWI measurement may have additional value as a predictor of outcomes and response to pharmacological treatment in many cardiovascular diseases such as HF [12].

The present study prospectively investigated the effect of 3-month treatment with SGLT2i added to optimal medical therapy (OMT) on echocardiographic myocardial work indices, compared to the OMT control group. SGLT2i were added to maximally tolerated doses of OMT including sacubitril-valsartan (ARNI), mineralocorticoid antagonist (MRA), and beta-blocker (BB). We also investigated the change in plasma levels of N-terminal-pro-b-type natriuretic peptide (NT-proBNP) and functional status (as assessed by the New York Heart Association (NYHA) scale), after 3 months of addition of SGLT2i vs continuing OMT alone.

Methods

This study was designed as a single-center, prospective, single-blinded study in which the echocardiographic expert (sonographer) was blinded regarding treatment assignment (SGLT2i administered vs. not administered as an adjunct to optimized background medical therapy). The study was conducted at the Cardiovascular Diseases Department, University Hospital of Split, Croatia, from March 2021 to April 2022. The study was conducted in full compliance with the principles of the Declaration of Helsinki from 2013 and with the approval of the Ethics Committee of the University Hospital of Split, filed under number 2181-147/01/06/M.S.-20-02. All participants read and signed the informed consent.

We consecutively enrolled outpatients with HFrEF on optimized medical therapy defined by the guidelines of the European Society of Cardiology (ESC) that were in use at the time when the study was initiated (2016 edition) [13]. The study included patients with a diagnosis

Table 1 Baseline characteristics of HF_rEF patients randomized to two groups with respect to treatment (SGLT2+ group and SGLT2– group)

Variable	SGLT2i+ group (N = 41)	SGLT2i– group (N = 18)	p-value*
Age, years	64.8 ± 13.2	67.8 ± 12.7	0.730
Male gender, N (%)	30 (73.2)	16 (88.9)	0.307
Dilatative cardiomyopathy, N (%)	25 (61)	9 (50)	0.569
Ischemic cardiomyopathy, N (%)	16 (39)	9 (50)	0.569
Systolic blood pressure, mm Hg	127 ± 22	123 ± 18	0.544
Diastolic blood pressure, mm Hg	76 ± 14	73 ± 10	0.219
Heart rate, bpm	82 ± 22	81 ± 21	0.488
NYHA class II (%)	15 (83.3)	29 (70.7)	0.156
NYHA class III (%)	3 (16.7)	12 (29.3)	
Arterial hypertension, N (%)	26 (63.4)	13 (72.2)	0.565
Diabetes mellitus, N (%)	16 (39)	2 (11.1)	0.037**
Dyslipidemia, N (%)	19 (46.3)	11 (61.1)	0.399
Atrial fibrillation, N (%)	11 (26.8)	8 (44.4)	0.231
Coronary revascularization (PCI or CABG), N (%)	15 (36.6)	10 (55.6)	0.253
Smoking, N (%)	6 (33.3)	15 (36.6)	0.810
Sacubitril/valsartan use, N (%)	41 (100)	18 (100)	1
Sacubitril/valsartan total daily dose, mg	236.6 ± 99.4	250 ± 115	0.206
BB use, N (%)	41 (100)	18 (100)	1
BB mean daily dose, mg	3.9 ± 1.4	3.8 ± 1.9	0.271
BB median daily dose, mg	5 (2.5–7.5)	5 (2.5–7.5)	0.446
MRA use, N (%)	41 (100)	18 (100)	1
MRA total daily dose, mg	32.3 ± 11.5	34.7 ± 12.5	0.211
Furosemide use, N (%)	21 (51.2)	10 (55.6)	0.785
Furosemide total daily dose, mg	37.1 ± 79.1	61.4 ± 78.8	0.236
Statin use, N (%)	19 (46.3)	10 (55.6)	0.580
Acetylsalicylic acid use, N (%)	18 (43.9)	11 (61.1)	0.267
Oral anticoagulant use, N (%)	16 (39)	9 (50)	0.569
CRT/ICD implanted, N (%)	5 (12.2)	5 (27.8)	0.256
3D LVEF, %	29.8 ± 8.9	28.5 ± 8.5	0.827
LVEDV, mL	210 ± 78	223 ± 71	0.740
LVESV, mL	126 ± 62	139 ± 67	0.576
LV GLS, %	-7.9 ± 3.4	-7.8 ± 3.8	0.087
GWI, mm Hg%	724 ± 461	634 ± 429	0.839
GCW, mm Hg%	996 ± 455	924 ± 445	0.952
GWW, mm Hg%	253 ± 166	271 ± 153	0.982
GWE, %	75.2 ± 10.5	73.1 ± 11.5	0.321
E/A ratio	1.2 ± 0.7	1.2 ± 0.7	0.907
E/E' ratio	14.7 ± 6.0	13.6 ± 5.2	0.297
TAPSE, mm	11.0 ± 4.7	10.4 ± 3.7	0.165
Hematocrit, L/L	0.42 ± 0.05	0.45 ± 0.05	0.608
Glucose, mmol/L	6.9 ± 1.8	6.2 ± 2.1	0.858
Creatinine, μmol/L	101 ± 26	109 ± 35	0.626
eGFR, mL/min/1.73m ²	68 ± 20	64 ± 19	0.601
Potassium, mmol/L	4.3 ± 0.7	4.4 ± 0.4	0.207
NT-proBNP, pg/mL	5407 ± 5829	4237 ± 5207	0.499
C-reactive protein, mg/L	9.5 ± 16.9	8.6 ± 19.5	0.812

Data are presented as mean ± standard deviation or N (%) or median (interquartile range) within the category of interest

*p-value is derived from t-test for independent samples or Chi-square test, as appropriate

**Two-tailed p-value with $p < 0.05$ considered statistically significant

Abbreviations: BB, beta blocker; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GWI, global work index; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; ICD, implantable cardioverter device; LVEDV, left ventricular end-diastolic volume; LVGLS, left ventricular global longitudinal strain; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion

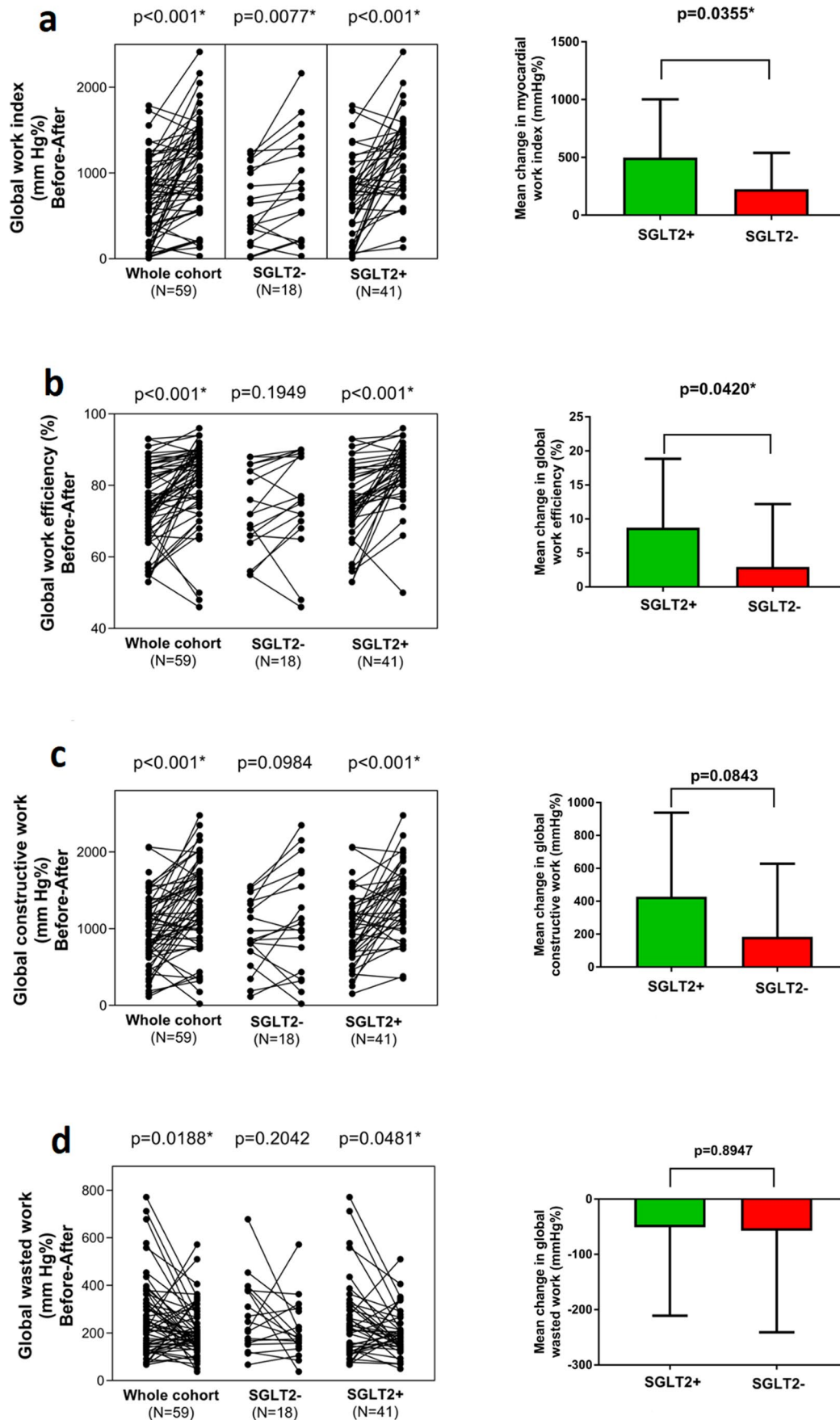


Fig. 1 Left images: changes from baseline to follow-up in the whole cohort, group without SGLT2 inhibitors, and group with SGLT2 inhibitor. Right images: comparison of mean changes between group with and without SGLT2 inhibitor. **a** differences in global myocardial work index (GWI); **b** differences in global work efficiency (GWE); **c** differences in global constructive work (GCW); **d** differences in global wasted work (GWW); **t*-test of independent samples; all results were significant at two-tailed *p*-value < 0.05

of HFrEF according to ESC guidelines for diagnosis and management of acute and chronic heart failure [13] aged 18 or older with LVEF <40%. At the time of inclusion, patients already had to be on guideline-recommended OMT including sacubitril-valsartan (ARNI), beta-blocker (BB), and mineralocorticoid receptor antagonists (MRA) on the highest tolerable daily doses, in addition to other symptomatic therapy such as loop diuretics. Furthermore, only patients with functional symptom severity class II and III on the NYHA scale with concomitant NT-proBNP value >125 pg/mL were included in the study. We excluded patients that had symptomatic hypotension (systolic blood pressure < 95 mmHg), impaired renal function (eGFR < 30 ml/min/1.73 m² calculated by the CKD-EPI formula), and potassium serum levels > 5.2 mmol/L, liver dysfunction (defined as hepatic parameters such as ALT, AST, and/or ALP elevated ≥3 times above the upper 99th reference percentile), biliary cirrhosis and cholestasis, active malignant disease (irrelevant of the stage and type of malignancy), current use of hormonal therapy, chemotherapy or immunotherapy, presence of the artificial (mechanical or biological) heart valve, severe aortic stenosis, acute coronary syndrome within the last 3 months, percutaneous coronary intervention or acute cerebrovascular incident within 3 months prior to the date of enrollment, pregnancy, or breastfeeding. Furthermore, due to potential interaction with left ventricular structure and function, patients with diabetes mellitus treated with DPP4 inhibitors and GLP receptor agonists were excluded from the study. Finally, patients that were not able to provide written informed consent or declined to participate in the study were not enrolled. Similarly, from the primary analysis, we excluded all patients that withdrew from the study due to any reason or that suffered any major medical condition not related to primary disease but with the potential to affect cardiovascular outcomes or lead to death before the study completion.

From March 2021 until September 2021, 47 patients were randomized into two groups using a random number generator: (a) SGLT2i+ group (either empagliflozin or dapagliflozin 10 mg once daily added to the current OMT, *N* = 26); and (b) SGLT2i− group (a group of patients treated with the continuation of identical OMT but without the addition of SGLT2 inhibitor, *N* = 21).

While the study was ongoing in September 2021, new ESC guidance was published recommending the use of SGLT2 inhibitors as a foundational drug in HFrEF management (class recommendation IA) [5]. Due to this fact, all HFrEF patients enrolled in the study after September 2021 (*N* = 16) were prescribed an SGLT2i resulting in a 2:1 ratio between patients with added SGLT2 vs. no SGLT2 inhibitor, 42 vs. 21 patients, respectively. There was no crossover between the groups, nor were there any changes in the daily dosage of their fundamental therapy (the same starting dose of OMT was given during the 3-month follow-up period). Patients from the group without SGLT2i after follow-up were assigned to SGLT2i according to the newest recommendation but were not followed further.

All patients underwent a comprehensive echocardiographic examination, physical examination, medical interview, and biochemical laboratory testing at baseline and repeated at the 3-month follow-up examination (3mFU). All echocardiographic measurements were performed by the same certified echocardiography consultant, blinded to the participant's treatment allocation, and, at the end of the study, validated by another cardiology consultant to determine the possibility of measurement error. A detailed description of the procedures performed on each participating patient is provided in the Appendix 1.

An echocardiographic examination included measurements of 2D speckle tracking echocardiography with LV global longitudinal strain (GLS, −%) assessment, global myocardial work analysis encompassing global work index (GWI, mmHg%), global work efficiency (GWE, %), global constructive work (GCW, mmHg%) and global wasted work (GWW, mmHg%), and three-dimensional measurements of volumes (mL) and LVEF (%).

The primary outcome was defined as the change in echocardiographic parameters of myocardial work and other parameters of myocardial function at 3-month follow-up compared to baseline in each group and whole cohort. Secondary outcomes included (a) mean changes in echocardiographic parameters of myocardial work and other parameters of myocardial function from baseline to 3-month follow-up compared between two groups; (b) subanalysis of predefined endpoints among patients with added SGLT2i stratified by sex, diabetes mellitus, and etiology of cardiomyopathy (dilated vs. ischemic cardiomyopathy).

Statistical Analysis

All data analyses were performed with SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA) and Prism, version 9.0.1. (GraphPad, La Jolla, CA, USA). Continuous data were presented as mean ± standard deviation (SD) whereas categorical variables were shown as whole

numbers (N) and percentages (%). The normality of data distribution was examined with the Kolmogorov-Smirnov test. The *t*-test for independent samples was utilized to measure potential differences between two groups of interest (SGLT2i users vs. SGLT2i non-users and other subgroups, as appropriate). The echocardiographic variables of interest, NYHA functional class, and circulating NT-proBNP levels were specifically examined in the “before-after” fashion in which initial values (at baseline) were pairwise compared to values obtained at 3-month follow-up by using paired *t*-test for within the group analyses. For the “before-after” comparison analysis between two groups of interest (SGLT2i+ group vs. SGLT2i– group), we used repeated measures ANOVA analysis. The mean change (Δ , delta) represented the average numerical change from baseline to follow-up at all instances. The Chi-square (χ^2) test was used to examine differences between groups of interest with respect to categorical variables. In all cases, two-sided significant (*p*) values were reported, and results that reached *p* < 0.05 were considered statistically significant.

Results

A total of 63 consecutive HF_rEF patients were enrolled in the study with the intention to treat (ITT). During the planned follow-up period of 3 months (3mFU), four patients (6.3% of the total intention-to-treat number) were excluded from the study. The reasons were as follows: (a) one patient from the SGLT2i+ group withdrew consent to participate due to relocation to another state; (b) two patients from the SGLT2i– group suffered from a severe form of COVID-19 infection requiring machine respiratory support and consequently had impaired cardiac function; (c) one patient from the SGLT2i– group died after 5 weeks of follow-up due to sudden cardiac death. A total of 59 patients (41 patients in the SGLT2i+ group and 18 patients in the SGLT2i– group) completed the study per the protocol, and their data were analyzed. Among these patients, none had infections or unplanned hospitalizations during the three months follow-up.

Baseline characteristics of patients in both groups (SGLT2i+ vs. SGLT2i–) did not differ significantly with respect to age, sex, NYHA status, arterial blood pressure, etiology of cardiomyopathy, renal function, and circulating NT-proBNP levels (Table 1). All patients in each group were taking ARNI, BBs, and MRAs at baseline, and these drugs were titrated to the maximum tolerated daily dose. Both groups were similar with respect to the mean

daily dose of these baseline medications. The SGLT2i+ group had a significantly higher prevalence of diabetes mellitus at baseline than the SGLT2i nonusers group (39 vs. 11%, respectively). The burden of other comorbidities (hypertension, hyperlipidemia, atrial fibrillation) was similar between the groups.

Patients took sacubitril/valsartan for 3–11 months and BB and MRA for 12–22 months. All included patients received bisoprolol as BB, and those patients receiving loop diuretics all received furosemide.

Myocardial Work Parameters

Significant improvement in all myocardial work parameters from baseline to follow-up was observed in the entire cohort (Fig. 1), with significantly greater improvement in the group of patients who received SGLT2i. The group that did not receive SGLT2i did not show significant before-after improvement in three of four MW indices (GCW *p* = 0.098, GWW *p* = 0.202, GWE *p* = 0.194), except for GWI (*p* = 0.043), while this was achieved in the group receiving SGLT2i for all indices (GCW *p* < 0.001, GWW *p* = 0.048, GWE *p* < 0.001, GWI *p* < 0.001) (Fig. 1). Notably, in the SGLT2i+ group GWI increased by 499 ± 504 mm Hg%, while in the SGLT2i– group, the increase was 224 ± 315 mm Hg%, *p* = 0.035 (Fig. 1a, Table 2). Similarly, GWE increased by 8.7 ± 10.1 % in the SGLT2i+ group and by 2.9 ± 9.3 % in the SGLT2i– group, *p* = 0.042 (Fig. 1b, Table 2). While the improvement in the indices of GCW and GWW was numerically more in the SGLT2i+ group than in the SGLT2i– group, these results did not reach statistical significance (*p* = 0.084 and *p* = 0.894 respectively) (Fig. 1c, d, respectively; Table 2).

3D Left Ventricular Ejection Fraction and LV Global Longitudinal Strain

The entire cohort achieved statistically significant improvement from baseline to follow-up in 3D LVEF and LV GLS parameters (*p* < 0.001 and *p* < 0.001, respectively) (Fig. 2). Both groups achieved statistically significant improvement in 3D LVEF from baseline to follow-up, but a significantly higher magnitude of improvement was observed in the SGLT2i+ group (12.2 ± 8.9 %, *p* < 0.001), compared to the SGLT2i– group (5.1 ± 9.9 %, *p* = 0.043), between groups *p* = 0.009. The same was observed in the results of LVGLS. In the SGLT2i+ group, the improvement of LV GLS was 3.9 ± 3.6 % (*p* < 0.001) compared to 1.6 ± 2.7 % (*p* = 0.018) in the SGLT2i– group, between groups *p* = 0.023 (Fig. 2a, b, Table 2).

Table 2 Mean changes in echocardiographic parameters of myocardial work and other parameters of myocardial function from baseline to follow-up

VARIABLE	SGLT2+ group (N = 41)	SGLT2- group (N = 18)	p-value*
3D LVEF, %	+12.2 ± 8.9	+5.1 ± 9.9	0.009**
LV GLS, %	+3.9 ± 3.6	+1.6 ± 2.7	0.023**
Global work index, mm Hg%	+499 ± 504	+224 ± 315	0.036**
Global constructive work, mm Hg%	+428 ± 511	+183 ± 445	0.084
Global wasted work, mm Hg%	-51 ± 160	-57 ± 184	0.895
Global work efficiency, %	+8.7 ± 10.1	+2.9 ± 9.3	0.042**
NYHA functional class	-0.40 ± 0.58	+0.06 ± 0.54	0.011**
NT-proBNP level, pg/mL	-3790 ± 5665	-701 ± 3438	0.004**

*t-test of independent samples

**Result significant at two-tailed p-value < 0.05

Abbreviations: LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N-terminal-pro-brain natriuretic peptide

NT-proBNP and NYHA Functional Class

Both groups showed a statistically significant decrease in circulating NT-proBNP levels and improvement in NYHA-class ($p < 0.001$ and $p = 0.003$, respectively) (Fig. 2c, d). The decrease in circulating NT-proBNP levels, from baseline to follow-up, was significant in the SGLT2i+ group (-3790 ± 5665 pg/mL, $p < 0.001$), whereas this change was not significant in the SGLT2i- group (-701 ± 3438 pg/mL, $p = 0.061$) (Fig. 2c, Table 2.). When comparing the mean change in NT-proBNP levels between groups, the SGLT2i+ group showed a significantly greater decrease in NT-proBNP levels compared to the SGLT2i- group, $p = 0.003$ (Table 2). Functional syndrome capacity as assessed by the NYHA scale, from baseline to follow-up, improved significantly in the SGLT2i+ group, whereas this was not the case in the SGLT2i- group (Fig. 2d). In the SGLT2+ group, there was a mean decrease in functional burden assessed by the NYHA scale by 0.40 ± 0.58 points ($p < 0.001$), whereas functional burden remained nearly the same in the SGLT2i- group (NYHA function increase by 0.06 ± 0.54 points, $p = 0.668$), as shown in Table 2.

The Proportion of Patients Who Achieved Significant Improvement in NT-proBNP Reduction and GWI Increases at Follow-Up

As shown in Fig. 3, a significantly greater proportion of patients in the SGLT2i+ group achieved NT-proBNP levels <1000 pg/mL at follow-up, compared to the SGLT2i- group (68.3 vs. 39.0%, respectively, $p = 0.034$). Similarly, the GWI greater than 750 mm Hg% at follow-up was achieved more frequently by patients treated with SGLT2i compared to patients not treated with SGLT2i (80.5 vs. 50.0%, respectively $p = 0.017$).

Subanalysis in Relation to Sex, Diabetes Status, and Cardiomyopathy Type in Patients Receiving an SGLT2 Inhibitor

Patients treated with SGLT2i did not differ in predefined endpoints when stratified by sex, diabetes mellitus, and etiology of cardiomyopathy (dilated non-ischemic vs. ischemic cardiomyopathy), as shown in Table 3, except for the greater reduction in GWW values in patients with dilated vs. ischemic cardiomyopathy ($p = 0.023$).

Discussion

In our prospective follow-up study, we observed significant improvement in GWI, GWE, GLS, and 3D-LVEF in HFrEF outpatients receiving SGLT2i (empagliflozin or dapagliflozin) compared with well-matched HFrEF outpatients not receiving SGLT2i, with concomitant reduction in NT-proBNP levels and improvement in functional status.

Our study provides new data on the effects of SGLT2 inhibitors on advanced echocardiographic parameters of left ventricular systolic function in ambulatory patients with chronic HFrEF, which have been understudied in previous studies. To date, several studies have examined the effects of SGLT2i treatment on the LV function [14]. The only quantification of the effect of SGLT2i on echocardiographic myocardial work parameters was shown by Ikonomidis et al. who studied the effect of insulin, GLP-1RA, SGLT2i, and their combination in patients with type 2 diabetes mellitus (T2DM) independent of baseline LVEF values or HFrEF therapy [15]. Their study showed a greater increase in GWI among patients using GLP-1RA or a combination of GLP-1RA and SGLT2i compared with insulin-only users [15]. In addition, myocardial work indices were used to evaluate the therapeutic effect when sacubitril/valsartan was added

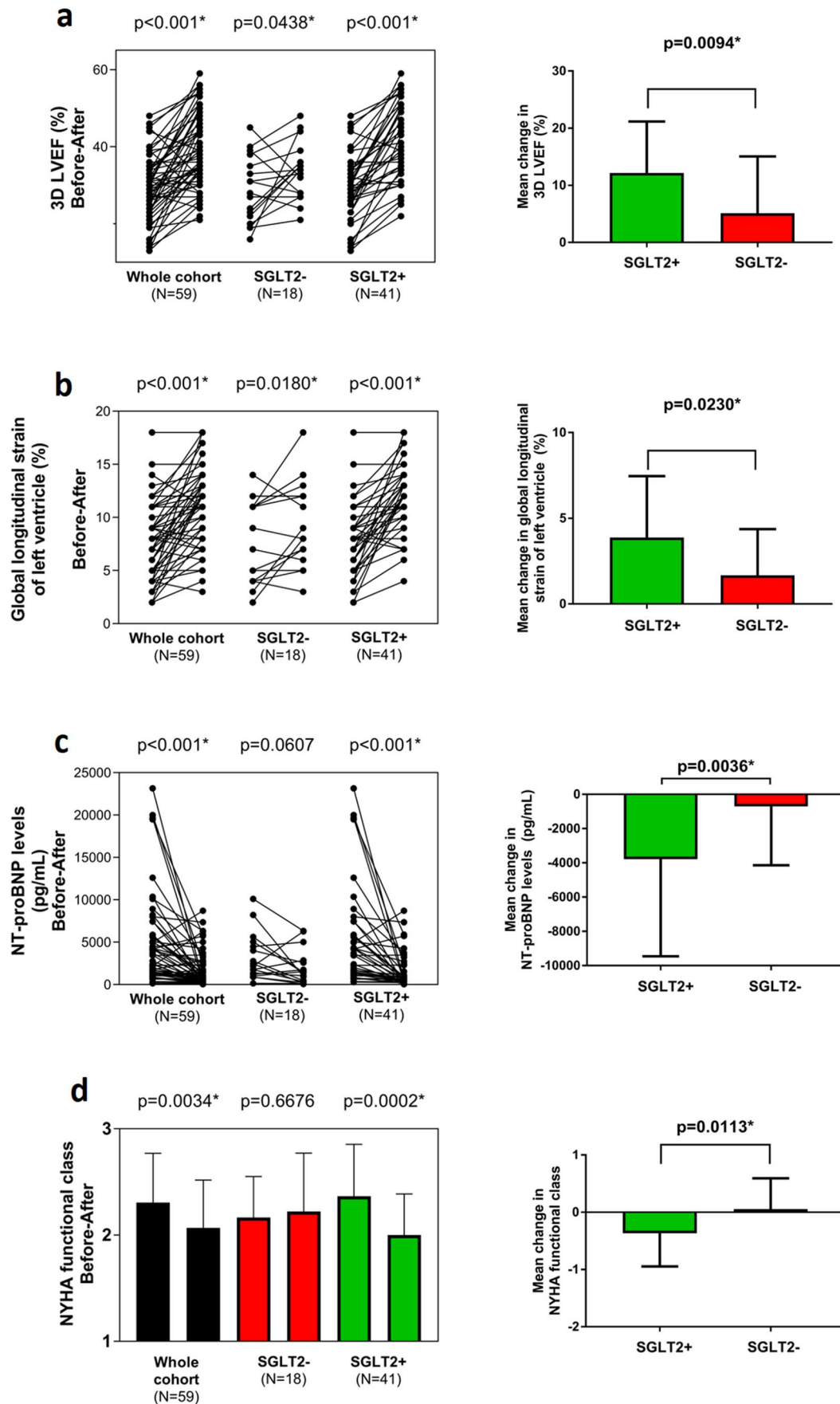


Fig. 2 Left images: changes from baseline to follow-up in the whole cohort, group without SGLT2 inhibitors, and group with SGLT2 inhibitor. Right images: comparison of mean changes between group with and without SGLT2 inhibitor. **a** differences in 3D left ventricular ejection fraction (LVEF); **b** differences in global longitudinal strain (GLS) of left ventricle; **c** differences in circulating N-terminal-pro-brain natriuretic peptide (NT-proBNP) levels; **d** differences in New York Heart Association (NYHA) functional status; **t*-test of independent samples; all results were significant at two-tailed *p*-value < 0.05

to BB and MRA during 6 months of therapy and showed an improvement in GCW and GWE [16, 17]. Therefore, to the best of our knowledge, the present study is the first to investigate and quantify the effects of adding SGLT2i to maximally optimized medical therapy, consisting of sacubitril/valsartan, MRA, and BB, on myocardial work indices in the population of ambulatory HFrEF patients.

An important role of GWI was first demonstrated by Wang et al. in their retrospective analysis, which showed that HFrEF patients with a GWI of <750 mm Hg% had significantly more adverse outcomes such as all-cause death and HF hospitalization, compared to patients with higher values [18]. In our study, a significantly higher proportion of patients in the SGLT2i+ group had recovery of GWI above the cut-off value of 750 mm Hg% compared with the group that did not use SGLT2i. Furthermore, our study showed that both treatment groups had significant improvement from baseline to follow-up in terms of LV GLS, but the recovery in LV GLS was more pronounced in SGLT2 users. Lee et al. failed to demonstrate a difference in GLS with empagliflozin compared with placebo [19], in contrast to the results of Gamaza-Chulian et al. who demonstrated a significant improvement in GLS associated with the use of SGLT2i in patients with T2DM [20].

In the present study, 3D-estimated LVEF improved significantly in both treatment groups, but in agreement with previous results, a significantly greater improvement was achieved in SGLT2 inhibitor users compared with nonusers. A post hoc analysis of the EMPIRE-HF study, which focused on left ventricular remodeling in HFrEF patients treated with empagliflozin versus placebo after 12 weeks of therapy, showed a significant reduction in LV and left atrial volume without a relevant change in LVEF. It should be noted, however, that only 33% of patients in this study were taking ARNI, whereas approximately 60% were taking MRA, which contrasts with our study in which all patients were taking maximum tolerated daily doses of background therapy of ARNI, MRA, and BB [21]. The estimation of LVEF by TTE showed no significant improvement associated with the addition of SGLT2i so far [14]. Estimation of LVEF using the Simpson biplane method is dependent on the image plane and other geometric assumptions [22], whereas 3D measurement of LVEF offers better reproducibility and

less inter- and intra-observer variability. In addition, 3D LVEF appears to be a better predictor of adverse events than 2D LVEF and has a strong correlation with LVEF measured by CMR [22, 23].

From the biochemical point of view of neurohumoral stress on LV, our study showed that the addition of SGLT2i to HFrEF background therapy was associated with a significantly greater reduction in circulating levels of NT-proBNP at 3 months compared with no addition. Previous studies have shown that NT-proBNP levels < 1000 pg/mL achieved at follow-up may serve as a robust predictor of lower mortality and future hospitalization rates in HFrEF patients [24]. Consistent with these observations, in our study, a greater proportion of patients in the SGLT2i+ group had their NT-proBNP levels reduced to less than 1000 pg/mL compared with the SGLT2i- group. The study EMPIRE-HF, which enrolled low-risk HFrEF patients with mild symptoms treated with empagliflozin for 12 weeks, showed neither a significant reduction in serum levels of NT-proBNP nor an improvement in daily activity [25], whereas the study SUGAR-DM-HF, which investigated the use of empagliflozin in patients with T2DM and HFrEF, showed a 28% reduction in NT-proBNP levels [19]. In addition, our study showed a significant decrease in symptomatic burden in patients receiving SGLT2i compared with patients not receiving SGLT2i, as measured by NYHA functional classification thus showing a strong concordance with observed echocardiographic and biochemical improvements.

A subanalysis of changes in parameters of interest from baseline to follow-up in HFrEF patients receiving an SGLT2 inhibitor showed that there were no significant differences in these parameters with respect to sex and DM status, whereas patients with nonischemic idiopathic cardiomyopathy appeared to have a greater numerical improvement in all parameters compared with patients with ischemic cardiomyopathy but without reaching statistical significance. Interestingly, a subanalysis of the study PARADIGM-HF, which focused on HFrEF etiology, showed a similar benefit of sacubitril/valsartan in both etiologic groups, although the risk reduction of adverse events was numerically greater in patients with nonischemic idiopathic cardiomyopathy than in patients with ischemic cardiomyopathy [26]. A benefit signal along the same lines was observed in the subanalysis of the DAPA-HF trial, which showed that dapagliflozin had a similar effect on cardiovascular death regardless of the type of heart failure, although the risk reduction was numerically greater in patients with nonischemic idiopathic cardiomyopathy than in patients with ischemic cardiomyopathy [27]. These findings are complementary to our observations noted in our HFrEF population treated with SGLT2i.

The demonstrated results of positive LV remodeling as measured by echocardiographic parameters, NT-proBNP levels, and improvement in functional status can be

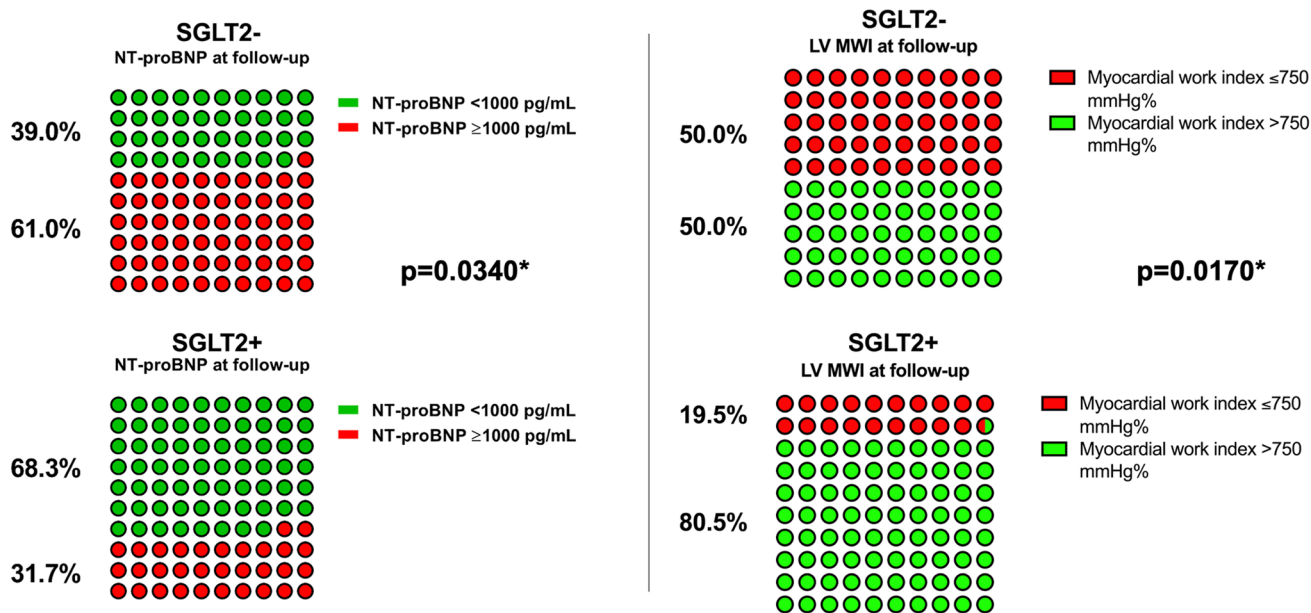


Fig. 3 The left side of the image shows the proportion of the patients from the group without SGLT2i (top image) and the group with addition of SGLT2i (bottom image) in terms of reaching the cut-off value of NT-proBNP levels below 1000 pg/mL; the right side of the image

shows the proportion of patients from the group without SGLT2i (top image) and the group with addition of SGLT2i (bottom image) in terms of reaching the cut-off value of GWI greater than 750 mm Hg%

Table 3 Subanalysis of predefined endpoints related to SGLT2 inhibitor treatment stratified by sex, diabetes mellitus, and etiology of cardiomyopathy (CMP)

VARIABLE	Male N = 30	Female N = 11	p-value*	T2DM N = 16	No T2DM N = 25	p-value*	Dilated CMP N = 25	Ischemic CMP N = 16	p-value*
GW diff., mm Hg%	+479 ± 545	+471 ± 493	0.964	+424 ± 461	+511 ± 569	0.612	+530 ± 567	+394 ± 435	0.425
GCW diff., mm Hg%	+439 ± 530	+400 ± 479	0.833	+342 ± 436	+483 ± 556	0.397	+466 ± 560	+370 ± 435	0.565
GWW diff., mm Hg%	-52 ± 167	-49 ± 146	0.954	-55 ± 159	-49 ± 164	0.909	-96 ± 166	-19 ± 124	0.023**
GWE diff., mm Hg%	+9.2 ± 10.6	+7.6 ± 9.0	0.655	+7.1 ± 6.9	+9.7 ± 11.7	0.423	+11.0 ± 10.4	+5.1 ± 8.7	0.067
LV-GLS diff., %	+3.6 ± 3.9	+4.6 ± 2.8	0.478	+3.3 ± 2.2	+4.2 ± 4.2	0.426	+4.0 ± 3.8	+3.6 ± 3.3	0.723
3D LVEF diff., %	+10.7 ± 8.1	+16.3 ± 10.5	0.076	+11.9 ± 8.4	+12.3 ± 9.5	0.896	+4.0 ± 3.8	+12.9 ± 9.5	0.693
NT-proBNP diff., pg/mL	-3227 ± 5084	-5324 ± 7059	0.299	-2408 ± 4255	-4674 ± 6330	0.216	-4147 ± 6232	-3231 ± 4782	0.619
NYHA class diff.	-0.47 ± 0.63	-0.09 ± 0.30=	0.066	-0.31 ± 0.48	-0.40 ± 0.65	0.644	-0.40 ± 0.65	-0.31 ± 0.48	0.644

Data are presented as mean ± standard deviation; + (plus) values denote an increase in the value; - (minus) values denote a decrease in the value from the baseline to follow-up measurement

*t-test for independent samples

**Two-tailed significant result, p < 0.05

Abbreviations: 3D LVEF, 3D left ventricular ejection fraction; CMP, cardiomyopathy; diff, difference; GCW, global constructive work; GWW, global wasted work; GWE, global work efficiency; LV GLS, left ventricular global longitudinal strain; GWI, global work index; NYHA, New York Heart Association; NT-proBNP, N-terminal-pro-brain natriuretic peptide; T2DM, type 2 diabetes mellitus;

explained to some extent by complementary and synergic mechanisms of combined neurohumoral therapy with SGLT2i and ARNI with the rest of foundational therapies in HFrEF. It is an accepted concept that initiation and up-dosing of all four foundational therapies in HFrEF significantly reduce mortality and morbidity through additive effects [28]. Solomon et al performed a subanalysis of DAPA-HF patients taking ARNI with dapagliflozin and showed similar efficacy and safety regardless of using sacubitril/valsartan. They emphasized a possible complementary and additive effect of concomitant use of ARNI and SGLT2i use to reduce morbidity and mortality in patients with HFrEF [29]. A meta-analysis of 6 randomized controlled trials on the reduction of CV-mortality, all-cause mortality, and hospitalization for heart failure with SGLT2is in combination with ARNI compared with ARNI-monotherapy showed a similar effect on the primary endpoint, whereas the combination of SGLT2i and ARNI resulted in a better cardiovascular protective effect [30].

Several limitations should be noted in this study. First, this was a single-center study that involved the patient population at our institution. Although this may be a limitation, it is important to emphasize that all echocardiographic measurements were performed by the same echocardiographic specialist who was blinded to treatment assignment, thus reducing interobserver variability. Second, only a limited number of patients were included in each group, limiting the possibility that some of the results would have reached statistical significance if a larger number of patients had been included. Third, differences were found between the two groups in the presence of T2DM at baseline, but subanalysis for this characteristic did not show an interaction of diabetes mellitus with reported measures of interest, and diabetes mellitus was also not found as a significant independent predictor of the change in these outcomes as per linear regression analysis.

In conclusion, the addition of an SGLT2 inhibitor to sacubitril/valsartan and other maximally tolerated baseline therapies in HFrEF resulted in greater improvement of LV systolic function compared with a treatment regimen without SGLT2i at a 3-month follow-up. Outpatients with HFrEF who received SGLT2i showed significantly greater improvement in myocardial work index and global work efficiency at follow-up along with improvements in GLS, 3D LVEF, and NYHA status and achieved greater reductions in circulating NT-proBNP levels

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Data Availability Data sets generated and/or analyzed during the current study are available on reasonable request from the corresponding author.

Declarations

Ethical Approval The study was conducted from March 2021 to April 2022 at the Clinic for Heart and Vascular Diseases, University Hospital of Split, Croatia. All procedures performed in studies with human participants were in accordance with the principles of the 2013 Declaration of Helsinki and were approved by the Ethics Committee of the University Hospital of Split filed under the number 2181-147/01/06/M.S.-20-02.

Consent to Participate Each potential participant was informed about the design and objectives of the study, and all included patients read and signed the informed consent form for participation.

Consent for Publication Patients signed an informed consent regarding the publication of their data.

Conflict of Interest The authors declare no competing interests.

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