POLISH HEART JOURNAL

Kardiologia Polska
The Official Peer-reviewed Journal of the Polish Cardiac Society since 1957

Online first
This is a provisional PDF only. Copyedited and fully formatted version will be made available soon

ISSN 0022–9032 e-ISSN 1897–4279

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

Authors: Halil Ibrahim Biter, Sinem Cakal, Beytullah Cakal, Ziya Aapaydin, Ali Yasar Kilinc, Huseyin Oguz, Sinan Yildiz, Hasan Ogur, Erdal Belen, Emel Simsek

Article type: Original article

Received: February 22, 2024

Accepted: May 7, 2024

Early publication date: May 9, 2024

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

Short title: Changes in strain echocardiography: SGLT-2 inhibitor use in patients with preserved EF

Halil Ibrahim Biter[1], Sinem Cakal[1], Beytullah Cakal[2], Ziya Aapaydin[1], Ali Yasar Kilinc[3], Huseyin Oguz[1], Sinan Yildiz[1], Hasan Ogur[1], Erdal Belen[1], Emel Simsek[4]

[1]Department of Cardiology, Sultangazi Haseki Training and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, Istanbul Medipol University, Istanbul, Turkey
[3]Istanbul Arnavutkoy State Hospital, Istanbul, Turkey
[4]Department of Internal Medicine, Sultangazi Haseki Training and Research Hospital, Istanbul, Turkey

Correspondence to:
Halil Ibrahim Biter
Department of Cardiology,
Sultangazi Haseki Training and Research Hospital,
34260 Istanbul, Turkey,
phone: +90 212 453 20 00,
e-mail: abrahambiter@hotmail.com

WHAT'S NEW?

The positive effects of SGLT2 inhibitors in diabetic patients with preserved EF regardless of coronary artery disease status have been demonstrated for the first time by strain echocardiography.

ABSTRACT

Background: Optimal glycemic control is necessary in order to prevent cardiovascular events to a large extent in patients with type 2 diabetes. The positive effects of sodium-glucose

cotransporter-2 inhibitors (SGLT2i) on cardiovascular events and mortality in these patients have been demonstrated in previous studies, although their mechanisms are not clear.

Aims: We aimed to compare the effect 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 were performed by blinded sonographers, at baseline and 1-month, 6-month of treatment. The initial and sixth month biochemical blood tests and N-terminal pro-B-type natriuretic peptide levels of the patients were drawn.

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 for both groups. Left ventricular ejection fraction, global, 2-chamber and 3-chamber strain values were improved significantly following SGLTi administration for 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 indicating that they might have a positive effect on outcomes of 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 have not yet been fully elucidated, they appear to involve direct hemodynamic effects as well as metabolic effects, as these agents enhance renal glucose excretion thereby increasing diuresis, 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 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 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 case of preserved LVEF [7, 8]. However, clinical studies of the effects of SGLT2i on the parameters of myocardial deformation are scarce. Although LV longitudinal strain has been previously measured by cardiac magnetic resonance, there is important knowledge gap regarding the use of speckle-tracking echocardiography in patients treated with SGLT2i. In current study, we aimed to compare the effects 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 single 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). 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 echo window and presence of atrial fibrillation.

Data collection and follow-up

Clinical and echocardiographic evaluations were performed at baseline, at the end of 1 month, and after 6 months of follow-up. All patients consisted of patients prescribed either empaglifozin or dapaglifozin. Patients were classified into two groups as 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 as the control group. The same sonographers, blinded to clinical data, baseline echocardiographic data, and presence/absence of CAD, performed both echocardiographic studies.

Standard echocardiographic examination

Two-dimensional transthoracic echocardiography was obtained with commercially available systems (iE33 Phillips 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. 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 the 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 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 (4-chamber, 3-chamber, and 2-chamber).

Statistical analysis

Variables were presented as means (standard deviations), numbers (percentage) and medians (interquartile ranges [IQRs]) as appropriate. The χ^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 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 case of significant differences after ANOVA, the Bonferroni *post hoc* test analysis was used to identify to identify inter-phase changes. A *P*-value threshold below 0.05 was considered significant. All statistical analyses were analysed by using the Statistical Package for the Social Sciences version 24.0 software program (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), RAS 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% 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 for both groups.

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

LVEF, global, 2-chamber and 3-chamber strain values were improved significantly after SGLTi administration for overall patient cohort. LVEF increased significantly during six month follow-up (*P* <0.001) Compared to baseline (56.33%), 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 comparison of LVEF (*P* = 0.32) was 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 three time points for all patient cohort (*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 both 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 increased values at 6-month follow-up compared to basal strain values however comparison 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 months 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 these values were better in patients without CAD (P <0.001). *Post hoc* analysis showed this difference occurred at first month (17.8 [3.5] vs. 18.6 [3.1]; P = 0.02) and sixth month 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 sixth month follow-up for CAD+ group (P = 0.04) but no improvement occurred at CAD– patients. For CAD+ group, improvement was only relevant at sixth month compared to baseline (P = 0.03) whereas comparison between first month and sixth (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 at first month and sixth month apical 4-chamber measures compared to strain values before SLT2i prescription (P = 0.02 and P <0.001 for CAD– group; P = 0.03 and P = 0.003 for CAD+ group, respectively) however first and sixth month apical 4-chamber strain rate comparison 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 effects of treatment with SGLT2i on health status in HFpEF patients are limited [10–13]. The presence of T2DM is a major contributor to the development of HFpEF as well as related to worse outcomes for patients with HFrEF and HFpEF [13]. To reduce the significant burden of heart failure, adding SGLT2i in patients with T2DM achieved significant improvement in LV diastolic dysfunction based on diastolic stress echocardiography [14]. Diastolic dysfunction is thought to be first marker of preclinical impairment during the course of diabetic cardiomyopathy detected by GLS [15]. Ernande et al. demonstrated that T2DM patients with normal LV function have impaired LV longitudinal myocardial dysfunction [GLS < 18%] even in case of normal diastolic function (baseline GLS 17.9 [2.2] in the current study). This finding

supports that preceding HFpEF diagnosis, LV GLS analysis might play a new role for assessing subtle LV diastolic dysfunction which will lead to diastolic heart failure.

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 of which 69% consist of HFpEF subjects [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 canaglifozin on LV diastolic function in diabetic patients with preserved LVEF concluded that among LV diastolic function parameters, E/e' and left ventricular mass index had significantly improved 3 months after canagliflozin treatment [17]. In current study, only 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 support that early administration of SGLT2i in T2DM patients might delay HFpEF diagnosis.

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

Study limitations

This study comprised a small number of patients and did not use a placebo-controlled group, so that 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 follow-up precludes assessment regarding the durability of the observed benefit of SGLT2i over left ventricular strain parameters.

CONCLUSIONS

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

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: A review on recent drug based therapeutics. Biomed Pharmacother. 2020; 131: 110708, doi: 10.1016/j.biopha.2020.110708, indexed in Pubmed: 32927252.
2. Chin KL, Ofori-Asenso R, Hopper I, et al. Potential mechanisms underlying the cardiovascular benefits of sodium glucose cotransporter 2 inhibitors: a systematic review of data from preclinical studies. Cardiovasc Res. 2019; 115(2): 266–276, doi: 10.1093/cvr/cvy295, indexed in Pubmed: 30475996.
3. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med. 2015; 175(6): 996–1004, doi: 10.1001/jamainternmed.2015.0924, indexed in Pubmed: 25895156.
4. Kasprzak JD, Gorczyca-Głowacka I, Sobczak-Kaleta M, et al. Pharmacotherapy of heart failure A.D. 2023. Expert opinion of Working Group on Cardiovascular Pharmacotherapy, Polish Cardiac Society. Kardiol Pol. 2023; 81(5): 537–556, doi: 10.33963/KP.a2023.0110, indexed in Pubmed: 37179465.
5. Pabel S, Wagner S, Bollenberg H, et al. Empagliflozin directly improves diastolic function in human heart failure. Eur J Heart Fail. 2018; 20(12): 1690–1700, doi: 10.1002/ejhf.1328, indexed in Pubmed: 30328645.
6. Kapłon-Cieślicka A, Vardas P, Grabowski M, et al. Tailoring guideline-directed medical therapy in heart failure with reduced ejection fraction: A practical guide. Kardiol Pol. 2023 [Epub ahead of print]; 81(9): 850–858, doi: 10.33963/v.kp.97062, indexed in Pubmed: 37660390.

7. Ernande L, Bergerot C, Rietzschel E, et al. Diastolic dysfunction in patients with type 2 diabetes mellitus: Is it really the first marker of diabetic cardiomyopathy? J Am Soc Echocardiography. 2011; 24(11): 1268–1275.e1, doi: 10.1016/j.echo.2011.07.017, indexed in Pubmed: 21907542.
8. Ernande L, Rietzschel ER, Bergerot C, et al. Impaired myocardial radial function in asymptomatic patients with type 2 diabetes mellitus: A speckle-tracking imaging study. J Am Soc Echocardiogr. 2010; 23(12): 1266–1272, doi: 10.1016/j.echo.2010.09.007, indexed in Pubmed: 20932716.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
10. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385(16): 1451–1461, doi: 10.1056/nejmoa2107038, indexed in Pubmed: 34449189.
11. Chandra A, Vaduganathan M, Lewis EF, et al. Health-related quality of life in heart failure with preserved ejection fraction: The PARAGON-HF trial. JACC Heart Fail. 2019; 7(10): 862–874, doi: 10.1016/j.jchf.2019.05.015, indexed in Pubmed: 31302043.
12. Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021; 23(7): 1217–1225, doi: 10.1002/ejhf.2249, indexed in Pubmed: 34051124.
13. Vazquez-Benitez G, Desai JR, Xu S, et al. Preventable major cardiovascular events associated with uncontrolled glucose, blood pressure, and lipids and active smoking in adults with diabetes with and without cardiovascular disease: a contemporary analysis. Diabetes Care. 2015; 38(5): 905–912, doi: 10.2337/dc14-1877, indexed in Pubmed: 25710922.
14. Shim CY, Seo J, Cho I, et al. Randomized, controlled trial to evaluate the effect of dapagliflozin on left ventricular diastolic function in patients with type 2 diabetes mellitus: The IDDIA trial. Circulation. 2021; 143(5): 510–512, doi: 10.1161/CIRCULATIONAHA.120.051992, indexed in Pubmed: 33186508.

15. Mochizuki Y, Tanaka H, Matsumoto K, et al. Clinical features of subclinical left ventricular systolic dysfunction in patients with diabetes mellitus. Cardiovasc Diabetol. 2015; 14: 37, doi: 10.1186/s12933-015-0201-8, indexed in Pubmed: 25889250.
16. Tanaka H, Soga F, Tatsumi K, et al. Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. Cardiovasc Diabetol. 2020; 19(1): 6, doi: 10.1186/s12933-019-0985-z, indexed in Pubmed: 31910853.
17. Matsutani D, Sakamoto M, Kayama Y, et al. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. Cardiovasc Diabetol. 2018; 17(1): 73, doi: 10.1186/s12933-018-0717-9, indexed in Pubmed: 29788955.
18. van Veldhuisen DJ, Linssen GCM, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol. 2013; 61(14): 1498–1506, doi: 10.1016/j.jacc.2012.12.044, indexed in Pubmed: 23500300.
19. Nassif ME, Windsor SL, Tang F, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: The DEFINE-HF trial. Circulation. 2019; 140(18): 1463–1476, doi: 10.1161/CIRCULATIONAHA.119.042929, indexed in Pubmed: 31524498.

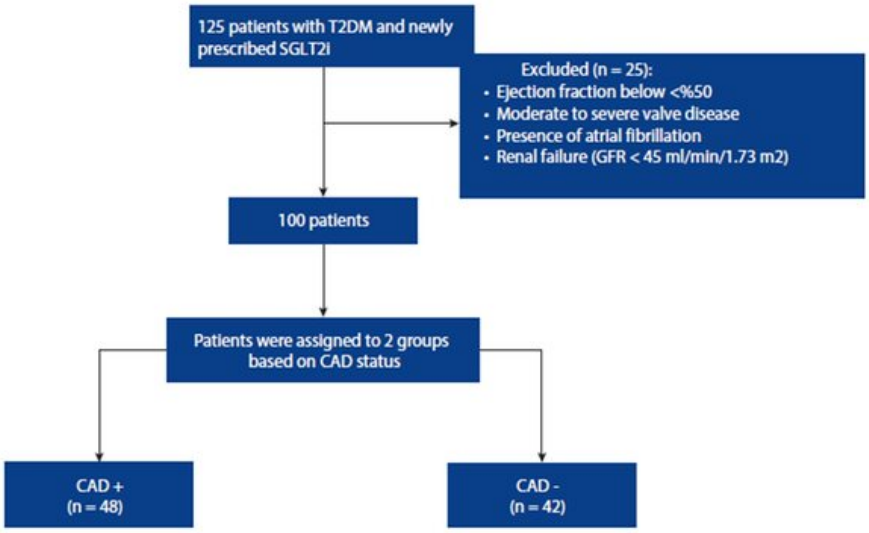

Figure 1. Flow diagram for inclusion in the study

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

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				
Betablockers, 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	100 (55.3-160)	125 (77-163.8)	78 (45.6-158.3)	0.76
NT-proBNP sixth month	83 (57.3-130)	92.5 (58.5-127.5)	80.5 (51.3-146)	0.43
Hemoglobin, gr/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

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)

	CAD+ (n = 48)		**CAD– (n = 52)**		***P*$_0$**
Variables	**Findings**	***P*-value**	**Findings**	***P*-value**	
LV end-diastolic volume$_0$, ml	98.3 (13.5)		93.83 (20.7)		0.21
LV end-diastolic volume$_6$, ml	97.3 (14.0)	0.53	95.623 (17.2)	0.53	0.59
LV end-systolic volume$_0$, ml	44.4 (8.4)		41.50 (9.3)		0.11
LV end-systolic volume$_6$, ml	42 (9.4)	0.013	38.35 (9.1)	0.011	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