ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 2784–2796
Published online 6 July 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12877

ORIGINAL RESEARCH ARTICLE

Sodium glucose cotransporter-2 inhibitor was associated with an improvement in left ventricular systolic function in patients with type 2 diabetes mellitus with impaired left ventricular systolic function

Yi-Hsin Chan[1,2,3], Tzyy-Jer Hsu[1], Chun-Li Wang[1,2], Yi-Wei Kao[4], Chien-Ying Huang[1] and Pao-Hsien Chu[1,2]*

[1]*The Cardiovascular Department, Chang Gung Memorial Hospital, Linkou, Taoyuan, 33305, Taiwan;* [2]*College of Medicine, Chang Gung University, Taoyuan, 33302, Taiwan;* [3]*Microscopy Core Laboratory, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan;* [4]*Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, Taipei, Taiwan*

Abstract

Aims Recent studies indicated that sodium glucose cotransporter-2 inhibitors (SGLT2i) reduced heart failure hospitalization in patients with type 2 diabetes mellitus (T2DM). However, whether SGTL2i can improve left ventricular (LV) systolic and diastolic function remained unclear. This study aimed to compare the change in echocardiographic parameters in T2DM patients receiving SGLT2i with a different baseline LV ejection fraction (LVEF). The change in echocardiographic parameters was also compared between T2DM patients treated with SGLT2i and those treated with dipeptidyl peptidase-4 inhibitor (DPP4i).

Methods and results This multicentre cohort study consecutively enrolled 665, 119, and 132 T2DM patients treated with SGLT2i with a preserved (≥50%), moderately reduced (40–50%), and reduced baseline LVEF (<40%), respectively, with paired baseline and post-treatment echocardiographic data available between 1 June 2016 and 31 May 2018. There were 212 patients treated with DPP4i with paired baseline and post-treatment echocardiographic data available at the same time. For those patients treated with DPP4i, 45 patients had impaired baseline LVEF of <50%. Echocardiographic parameters, including LVEF, LV end-diastolic volume, LV end-systolic volume (LVESV), and LV diastolic function, were analysed at baseline and after treatment. After a median SGLT2i treatment period of 230 days, patients with reduced LVEF were associated with an improvement in LVEF from 29.4 ± 7.4% to 42.2 ± 15.2% ($P < 0.0001$) and decrease in LVESV from 133.2 ± 49.2 to 117.4 ± 60.1 mL ($P = 0.0002$). Patients with moderately reduced LVEF were associated with an improvement in LVEF from 44.8 ± 2.9% to 49.7 ± 12.4% ($P < 0.0001$) and decrease in LVESV from 90.7 ± 31.1 to 80.0 ± 36.2 mL ($P = 0.0017$). Patients with preserved LVEF did not show an improvement in LVEF and LVESV after SGLT2i treatment. There were no significant changes of LV end-diastolic volume, LV diastolic function, and LV wall thickness in three study groups after SGLT2i treatment. In contrast, patients with impaired baseline LVEF (<50%) did not show any change in LVEF and LVESV after DPP4i treatment.

Conclusions Sodium glucose cotransporter-2 inhibitor was associated with an improvement in LV systolic function in patients with T2DM with reduced and moderately reduced LVEF. In contrast, DPP4i treatment was not associated with any improvement in LVEF among patients with impaired LVEF.

Keywords Type 2 diabetes mellitus; Sodium glucose cotransporter-2 inhibitor; Dipeptidyl peptidase-4 inhibitor; Heart failure; Echocardiography

Received: 11 January 2020; Revised: 25 May 2020; Accepted: 16 June 2020
**Correspondence to: Pao-Hsien Chu, MD, FAHA, FACC, FESC, The Cardiovascular Department, Chang Gung Memorial Hospital, Linkou, Taoyuan 33305, Taiwan; College of Medicine, Chang Gung University, Taoyuan 33302, Taiwan. Email: taipei.chu@gmail.com*
†*These authors contributed equally to the study and manuscript.*

Introduction

Type 2 diabetes mellitus (T2DM) increases the risk of heart failure, including reduced and preserved left ventricular ejection fraction (LVEF), and cardiovascular events and mortality.[1,2] Sodium glucose cotransporter-2 inhibitors (SGLT2i) are a new class of anti-hyperglycaemic agents that inhibit urinary glucose reabsorption.[3] Of note, SGTL2i reduced the blood sugar level and blood pressure, body weight, and albumin level via an insulin-independent mechanism in patients with T2DM. Furthermore, three large randomized controlled trials with EMPA-REG OUTCOME (empagliflozin), CANVAS Program (canagliflozin), and DECLARE–TIMI 58 (dapagliflozin) all demonstrated that three SGLT2i, compared with the current standard-of-care diabetes management, significantly reduced the risk of heart failure hospitalization in patients with T2DM with/without established cardiovascular diseases.[4–6] In contrast, several dipeptidyl peptidase-4 inhibitor (DPP4i) (e.g. saxagliptin, alogliptin, vildagliptin, and linagliptin) increased adverse heart failure events in patients with T2DM with/without a history of heart failure when compared with placebo.[7–10] However, there was no objective evaluation of the change in cardiac function in patients with T2DM treated with SGLT2i or DPP4i in those pivotal trials, and it was unclear whether the reduced risk of hospitalization due to heart failure in patients with T2DM treated with SGLT2i resulted from the reduction in body loading (e.g. reduction in body weight or salt loading by SGLT2i treatment) or improvement in cardiac systolic or diastolic function mediated by SGLT2i treatment objectively. The underlying mechanism associated with a favourable outcome of SGLT2i treatment on cardiac function is not well known. The present study aimed to investigate the effect of SGLT2i on LV systolic and diastolic function and heart chamber size, as measured by two-dimensional (2D) echocardiography, in patients with T2DM with a different baseline LVEF in the real-world practice. The change in echocardiographic parameters was compared between patients with T2DM treated with SGLT2i and those treated with DPP4i.

Methods

Database

In the present study, all patients' data were obtained from the Chang Gung Memorial Hospital (CGMH) Medical System, which comprised four tertiary care medical centres and three major teaching hospitals with a total of 10 050 beds and admits approximately 280 000 patients annually in Taiwan.[11] The advantage of the CGMH medical database is that each patient's detailed chart record, diagnosis, imaging, and laboratory data are all available.[12] The identification number and personal information of each patient are encrypted and de-identified using a consistent encrypting procedure; therefore, informed consent was waived for this study.

Study design

The study is a retrospective, multicentre, and observational study. There were 42 561 patients with T2DM aged ≥18 years newly receiving SGLT2i or DPP4i from 1 June 2016 to 31 May 2018. Among these, a total of 1433 and 236 patients treated with SGLT2i and DPP4i have a paired data of baseline and post-treatment 2D echocardiography available. The date of baseline echocardiography was further restricted within 6 months before the drug index date, and the date of post-treatment echocardiography was limited to 3–18 months after drug index date. Finally, a total of 916 and 212 consecutive patients with T2DM receiving SGLT2i and DPP4i, respectively, were enrolled in the analysis. The study protocol complied with the Declaration of Helsinki and was approved by the Institutional Review Board of the CGMH.

Conventional echocardiography

The patients underwent transthoracic 2D echocardiography using a commercially available system (Vivid 9, General Electric Vingmed Ultrasound, Horten, Norway). Thickness of left ventricular (LV) intraventricular septum and free wall, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were assessed from parasternal or apical views using the standard M-mode or 2D Simpson method. Transmitral E wave, filling velocity during atrial systole (A wave), deceleration time, and e′ velocity were measured using tissue Doppler echocardiography. The e′ velocity was calculated from the average of the lateral and septal values.

Covariates

Baseline covariates referred to any claim record with the abovementioned diagnoses or medication codes prior to the index date. The ischaemic aetiology of patients with T2DM was defined by one of the following criteria: (i) ≥75% luminal diameter stenosis of the main epicardial coronary artery; (ii) history of myocardial infarction or coronary revascularization; and (iii) myocardial ischaemia or infarction documented by myocardial perfusion imaging. A history of any prescription drug was confined to medications used at least once within 3 months preceding the drug index date. Important laboratory data, including body weight, resting heart rate, systolic and diastolic blood pressure, serum haemoglobin A1c level, haemoglobin level, platelet count, estimated glomerular filtration rate, alanine aminotransferase level, lipid profiles, and uric acid level, were based on the measurements performed within 6 months before the drug index date.

Statistical analyses

Continuous variables were expressed as mean ± standard deviation or as median (range). Proportions were compared using analysis of variance. The change in all echocardiographic parameters before and after treatment was compared using paired *t*-test. Predictive variables for outcome were estimated using the multivariate Cox proportional hazard regression models. Variables with interest in *Table 1* were selected to include in the multivariate model in *Table 3*. In all tests, a *P* value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of patients treated with SGLT2i with a preserved (≥50%), moderately reduced (40–50%), and reduced (<40%) baseline LVEF

A total of 916 consecutive patients treated with SGLT2i with paired baseline and post-treatment echocardiographic data available between 1 June 2016 and 31 May 2018 were enrolled. Of these patients, 595 and 321 were using empagliflozin and dapagliflozin, respectively. Moreover, 665, 119, and 132 patients treated with SGLT2i have preserved (≥50%), moderately preserved (40–50%), and reduced (<40%) baseline LVEF, respectively. Compared with patients with preserved LVEF of ≥50%, patients with moderately reduced or reduced LVEF were younger, were less likely female, and had a higher prevalence of ischaemic heart disease. Patients with moderately reduced or reduced LVEF had a higher haemoglobin A1c level but a comparable estimated glomerular filtration rate compared with patients with preserved LVEF. For baseline medication, patients with moderately reduced or reduced LVEF had a higher prescription of heart failure medications, such as beta-blocker, renin–angiotensin system blocker, mineralocorticoid receptor antagonist, diuretics, nitrate, and digoxin, than patients with preserved LVEF (*Table 1*).

Change in haemodynamics and echocardiographic parameters in patients with preserved (≥50%), moderately reduced (40–50%), and reduced (<40%) baseline LVEF after SGLT2i treatment

The changes in haemodynamics and echocardiographic parameter in the three study groups before and after treatment are summarized in *Table 2* and *Figure 1*. After a median treatment period of 230 (25th–75th percentile, 161–316) days, the reduced LVEF group was associated with an improvement in LVEF from 29.4 ± 7.4% to 42.2 ± 15.2% ($P < .0001$) and decrease in LVESV from 133.2 ± 49.3 to 117.4 ± 60.1 mL ($P = 0.0002$) after SGLT2i treatment. After a median treatment period of 243 (25th–75th percentile, 173–330) days, the moderately reduced LVEF group was associated with an improvement in LVEF from 44.8 ± 2.9% to 49.7 ± 12.4% ($P < .0001$) and decrease in LVESV from 90.7 ± 31.1 to 80.0 ± 36.2 mL ($P = 0.0017$). In contrast, the preserved LVEF group did not show any change in LVEF and LVESV after SGLT2i treatment. There were no significant changes in other echocardiographic parameters, including LVEDV, LV diastolic function, or LV wall thickness, in the three study groups after SGLT2i treatment (*Table 2*). In the haemodynamic change after SGLT2i treatment, both patients with preserved and reduced baseline LVEF were associated with a decrease in body weight (both $P < 0.01$). Of note, patients with moderately reduced and reduced baseline LVEF were both associated with a decrease in resting heart rate as well as diastolic blood pressure (*Table 2*).

We further analysed our patients according to ischaemic ($n = 390$) or non-ischaemic aetiology ($n = 526$). Generally, the result of subgroup analysis persisted in both subgroups: moderately reduced and reduced LVEF were both associated with an improvement in LVEF and decrease in LVESV after SGLT2i treatment. In contrast, the preserved LVEF group did not show any change in LVEF and LVESV in either the ischaemic or non-ischaemic subgroup after SGLT2i treatment (*Table 2*).

We further compared the change in LVEF and LVESV in patients with impaired LVEF (<50%) according to different time periods after SGLT2i treatment. Of 251 patients with impaired LVEF (<50%), 84, 79, 47, and 41 patients had paired echocardiography data after 3–6, 6–9, 9–12, and ≥12 months of SGLT2i treatment. It is noted that the use of SGLT2i was associated with improved LVEF and LVESV as early as 3–6 months after treatment (*Figure 2*).

Baseline characteristics of patients with an impaired baseline LVEF (<50%) treated with DPP4i vs. SGLT2i

We further compared the change in echocardiographic parameters between patients with impaired LVEF (<50%) treated with SGLT2i and those treated with DPP4i. Among the 212 patients treated with DPP4i, 45 patients had impaired baseline LVEF <50%. *Table 3* summarized the baseline characteristics between the DPP4i and SGLT2i groups. Generally, there was no difference in the baseline co-morbidities, heart failure and anti-diabetic medications, and baseline echocardiographic parameters between the DPP4i and SGLT2i groups.

Table 1 Clinical and echocardiographic characteristics in type 2 diabetes mellitus patients treated with sodium glucose cotransporter-2 inhibitor with different baseline left ventricular ejection function

	All patients (n = 916)	Group 1 Baseline LVEF ≥50% (n = 665)	Group 2 Baseline LVEF 40–50% (n = 119)	Group 3 Baseline LVEF <40% (n = 132)	P value (ANOVA)
Clinical characteristics					
Age (years)	64.0 ± 11.3	64.8 ± 11.0	62.6 ± 11.2	60.9 ± 12.6*	**0.001**
Female	279 (30.5)	235 (35.3)	20 (16.8)*	24 (18.2)*	**<0.001**
Ischaemic heart aetiology	390 (42.6)	249 (37.4)	63 (52.9)*	78 (59.1)*	**<0.001**
Hypertension	663 (72.4)	513 (77.1)	74 (62.2)*	76 (57.6)*	**<0.001**
Dyslipidaemia	615 (67.1)	477 (71.7)	72 (60.5)*	66 (50.0)*	**<0.001**
Cerebral vascular accidents	87 (9.5)	63 (9.5)	9 (7.6)	15 (11.4)	0.591
Chronic lung disease	65 (7.1)	47 (7.1)	9 (7.6)	9 (6.8)	0.973
Chronic liver disease	175 (19.1)	144 (21.7)	15 (12.6)	16 (12.1)*	**0.006**
Chronic kidney disease	297 (34.2)	230 (34.6)	31 (26.1)	36 (27.3)	0.073
Peripheral artery disease	21 (2.3)	15 (2.3)	3 (2.5)	3 (2.3)	0.984
Gout	111 (12.1)	79 (11.9)	13 (10.9)	19 (14.4)	0.659
Malignancy	79 (8.6)	63 (9.5)	11 (9.2)	5 (3.8)	0.101
Baseline laboratory data					
HbA1c (%)	8.6 ± 1.7	8.4 ± 1.7	9.0 ± 1.7*	8.9 ± 2.0*	**<0.001**
Haemoglobin (g/dL)	13.3 ± 2.1	13.3 ± 2.0	13.4 ± 2.3	13.3 ± 2.3	0.891
Platelet count (1000/μL)	224.4 ± 70.4	227.6 ± 71.7	229.1 ± 71.6	208.7 ± 62.7*	**0.038**
Estimated GFR (mL/min/m^2)	80.7 ± 31.0	81.4 ± 31.1	82.5 ± 30.8	75.7 ± 30.8	0.121
ALT (U/L)	36.6 ± 111.1	30.3 ± 21.9	29.9 ± 26.5	74.2 ± 284.9*,†	**<0.001**
Triglycerides (mg/dL)	193.0 ± 248.8	189.0 ± 175.2	245.1 ± 538.3	165.8 ± 108.9	**0.031**
LDL (mg/dL)	89.4 ± 32.4	89.8 ± 29.0	83.5 ± 29.8	93.4 ± 37.4	0.054
HDL (mg/dL)	40.5 ± 11.2	41.2 ± 10.9	39.1 ± 10.7	38.1 ± 12.3*	**0.004**
Uric acid (mg/dL)	6.3 ± 2.0	6.1 ± 1.7	6.3 ± 2.2	7.3 ± 2.5*,†	**<0.001**
Height (cm)	161.7 ± 13.2	160.7 ± 14.6	163.5 ± 8.1	165.3 ± 8.5*	**0.001**
Weight (kg)	73.1 ± 15.1	73.2 ± 14.1	72.7 ± 15.3	73.4 ± 17.3	0.830
Systolic BP (mmHg)	136.2 ± 21.8	137.4 ± 21.1	135.7 ± 22.5	130.5 ± 23.5*	0.051
Diastolic BP (mmHg)	76.1 ± 12.9	75.7 ± 12.6	76.8 ± 12.9	76.9 ± 14.2	0.279
Heart rate (b.p.m.)	81.7 ± 14.2	80.8 ± 13.7	82.8 ± 14.5	84.7 ± 15.9*	**0.004**
Baseline medications					
Anti-platelet agent	674 (73.6)	476 (71.6)	96 (80.7)	102 (77.3)	0.068
Statin	627 (68.5)	452 (78.0)	82 (68.9)	93 (70.5)	0.849
Non-dihydropyridine CCB	103 (11.2)	91 (13.7)	6 (5.0)*	6 (4.6)*	**0.001**
Dihydropyridine CCB	178 (19.4)	142 (21.4)	21 (17.7)	15 (11.4)*	**0.026**
Beta-blocker	681 (74.3)	461 (69.3)	104 (87.4)*	116 (87.9)*	**<0.001**
ACEI or ARB or ARNI	744 (81.2)	519 (78.1)	107 (89.9)*	118 (89.4)*	**<0.001**
MRA	143 (15.6)	45 (6.8)	27 (22.7)*	71 (53.8)*,†	**<0.001**
Loop diuretics	275 (30.0)	124 (18.7)	58 (48.7)*	93 (70.5)*,†	**<0.001**
Nitrate	238 (26.0)	141 (21.2)	40 (33.6)*	57 (32.2)*	**<0.001**
Digoxin	72 (7.9)	34 (5.1)	10 (8.4)*	28 (21.2)*,†	**<0.001**
Anti-diabetic agent					
DPP4i	432 (47.2)	312 (46.9)	58 (48.7)	62 (47.0)	0.934
SU	526 (57.4)	375 (56.4)	69 (58.0)	82 (62.1)	0.474
Metformin	769 (84.0)	568 (85.4)	98 (82.4)	103 (78.0)	0.095
Glinide	34 (3.7)	17 (2.6)	6 (5.0)	11 (8.3)*	**0.004**
Glitazone	203 (22.2)	173 (26.0)	18 (15.1)*	12 (9.1)*	**<0.001**
Acarbose	199 (21.7)	152 (22.9)	25 (21.0)	22 (16.7)	**0**.284

(*Continues*)

Table 1 (continued)

	All patients (n = 916)	Group 1 Baseline LVEF ≥50% (n = 665)	Group 2 Baseline LVEF 40–50% (n = 119)	Group 3 Baseline LVEF <40% (n = 132)	P value (ANOVA)
Insulin	193 (21.1)	127 (19.1)	29 (24.4)	37 (28.0)	**0.045**
Baseline echocardiographic data					
LVEF (%)	59.1 ± 16.4	67.5 ± 8.6	44.8 ± 2.9*	29.4 ± 7.4*,†	**<0.001**
LVEDV (mL)	130.9 ± 49.8	113.9 ± 34.4	162.1 ± 49.4*	189.1 ± 59.2*,†	**<0.001**
LVESV (mL)	58.2 ± 44.2	37.2 ± 17.7	90.7 ± 31.1*	133.2 ± 49.3*,†	**<0.001**
Mitral E/A ratio	0.96 ± 0.68	0.90 ± 0.65	0.97 ± 0.47	1.19 ± 0.91*	**0.011**
Mitral DecT (ms)	201.2 ± 70.7	216.5 ± 71.2	182.7 ± 62.6*	164.7 ± 58.0*	**<0.001**
E/e′ ratio	13.0 ± 6.1	12.1 ± 5.1	13.1 ± 6.9	16.5 ± 7.5*,†	**0.001**
LV IVS (mm)	12.0 ± 2.9	12.3 ± 2.8	11.9 ± 3.0	10.8 ± 3.0*,†	**<0.001**
LV FW (mm)	10.1 ± 2.1	10.8 ± 3.8	10.6 ± 2.3	10.1 ± 2.1	0.092

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; CCB, calcium channel blocker; DecT, deceleration time; DPP4i, dipeptidyl peptidase-4 inhibitor; E/A, ratio of peak early to late diastolic filling velocity; E/e′, mitral early diastolic to early diastolic tissue velocity; FW, free wall; GFR, glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; IVS, intraventricular septum; LDL, low density lipoprotein; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MRA, mineralocorticoid receptor antagonist; SU, sulfonylurea.
Data are expressed as mean ± standard deviation or as numbers (percentage).
$^{*}P < 0.05$ vs. baseline LVEF ≥50% group.
$^{\dagger}P < 0.05$ vs. baseline LVEF 40–50% group.

Change in haemodynamics and echocardiographic parameters in patients with an impaired baseline LVEF (<50%) treated with DPP4i vs. SGLT2i

In the haemodynamic change after treatment, both DPP4i and SGLT2i groups were associated with a decrease in body weight (both $P < 0.05$). Of note, only the SGLT2i group had a decrease in resting heart rate ($P < 0.0001$) as well as diastolic blood pressure ($P = 0.0001$) (*Table 4*). Regarding the change in echocardiographic parameters after treatment, patients with impaired baseline LVEF had an improvement in LVEF from 36.7 ± 9.6% to 45.8 ± 14.4% ($P < 0.0001$) and decrease in LVESV from 113.3 ± 46.8 to 99.9 ± 53.6 mL ($P < 0.0001$) after SGLT2i treatment. In contrast, patients with impaired baseline LVEF did not show any change in LVEF and LVESV after DPP4i treatment (*Table 4* and *Figure 3*). There were no significant changes in other echocardiographic parameters including LVEDV, LV diastolic function, or LV wall thickness in both DPP4i and SGLT2i groups.

Sensitivity analyses were performed using a 1:3 matching of DPP4i (n = 39) to SGLT2i (n = 117) by baseline characteristics presented in *Table 3* to test if the results were still consistent with the main analysis as shown in *Table 4* and *Figure 3*. Supporting Information, *Table S1* shows the baseline characteristics between the paired DPP4i and SGLT2i groups. There was no difference in the baseline characteristics, laboratory data, medications, and echocardiographic parameters between the paired DPP4i and SGLT2i groups after propensity score matching. Consistent with the main analysis, use of SGLT2i, rather than DPP4i, was associated with a decrease in body weight, resting heart rate, and diastolic blood pressure (Supporting Information, *Table S2*). In contrast to DPP4i treatment, SGLT2i treatment was associated with improvement in LVEF and reverse remodelling of LVESV (Supporting Information, *Table S2* and *Figure S1*).

Discussion

Main findings

To our best knowledge, this is the largest study to evaluate the change in cardiac function using 2D echocardiography in patients with T2DM after SGLT2i treatment in the real-world daily practice. The main findings of this study are as follows: (i) in a total of 665, 119, and 132 patients with T2DM treated with SGLT2i with a baseline preserved (≥50%), moderately reduced (40–50%), and reduced (<40%) LVEF, a patient with a reduced or moderately reduced LVEF was associated with a significant improvement in LVEF and reverse remodelling of LVESV after SGLT2i treatment. In contrast, there were no significant changes in LVEF or reverse

Table 2 The changes of haemodynamics and echocardiographic parameter for type 2 diabetes mellitus patients taking sodium glucose cotransporter-2 inhibitor groups with different baseline left ventricular ejection fraction at baseline and after treatment

	Baseline LVEF ≥50% (n = 665)			Baseline LVEF 40–50% (n = 119)			Baseline LVEF <40% (n = 132)		
	Baseline	Post-treatment	P value	Baseline	Post-treatment	P value	Baseline	Post-treatment	P value
All patients (n = 916)									
Body weight (kg)	**73.2 ± 14.1**	**72.3 ± 14.5**	**<0.0001**	72.7 ± 15.3	71.6 ± 16.6	0.1179	**73.4 ± 17.3**	**72.0 ± 17.0**	**0.0013**
Heart rate (b.p.m.)	80.8 ± 13.7	80.2 ± 14.9	0.3165	**82.8 ± 14.5**	**77.4 ± 13.7**	**<0.0001**	**84.7 ± 15.9**	**79.3 ± 13.8**	**0.0006**
SBP (mmHg)	137.4 ± 21.1	135.5 ± 19.9	0.0766	135.7 ± 22.5	133.4 ± 22.6	0.3283	130.5 ± 23.5	127.3 ± 21.1	0.0994
DBP (mmHg)	75.7 ± 12.6	75.5 ± 12.0	0.7061	**76.8 ± 12.9**	**74.1 ± 12.6**	**0.0375**	**76.9 ± 14.2**	**73.2 ± 11.9**	**0.0015**
LVEF (%)	67.9 ± 8.3	67.1 ± 10.1	0.0762	**44.8 ± 2.9**	**49.7 ± 12.4**	**<0.0001**	**29.4 ± 7.4**	**42.2 ± 15.2**	**<0.0001**
LVEDV (mL)	113.9 ± 34.4	112.4 ± 34.6	0.2883	162.1 ± 49.4	156.4 ± 44.4	0.1904	189.1 ± 59.2	185.6 ± 64.0	0.5088
LVESV (mL)	37.2 ± 17.6	37.9 ± 20.5	0.3820	**90.7 ± 31.1**	**80.0 ± 36.2**	**0.0017**	**133.2 ± 49.2**	**117.4 ± 60.1**	**0.0002**
E/A ratio	0.89 ± 0.63	0.87 ± 0.32	0.5960	0.97 ± 0.47	0.93 ± 0.61	0.6769	1.19 ± 0.91	1.12 ± 0.97	0.6582
DecT (ms)	217.9 ± 71.6	225.5 ± 76.5	0.2605	182.7 ± 62.6	206.5 ± 79.4	0.1345	164.7 ± 58.0	189.3 ± 87.3	0.0969
E/e′ ratio	12.1 ± 5.1	11.4 ± 3.8	0.0906	13.1 ± 6.9	11.4 ± 4.6	0.1979	16.5 ± 7.5	15.5 ± 10.5	0.6040
LV IVS (mm)	12.3 ± 2.8	12.1 ± 3.1	0.1538	11.9 ± 3.0	11.6 ± 2.9	0.3745	10.8 ± 3.0	10.8 ± 2.6	0.9043
LV FW (mm)	10.8 ± 3.8	10.6 ± 3.2	0.3111	10.6 ± 2.3	11.0 ± 4.7	0.3784	10.1 ± 2.1	10.3 ± 2.2	0.3513
Patients with ischaemic aetiology (n = 390)									
Body weight (kg)	75.0 ± 14.1	74.5 ± 14.2	0.1046	70.8 ± 13.6	68.2 ± 16.5	0.0515	**71.9 ± 17.0**	**70.5 ± 16.6**	**0.0178**
Heart rate (b.p.m.)	**80.8 ± 12.7**	**78.8 ± 12.5**	**0.0287**	**83.5 ± 14.9**	**78.1 ± 12.8**	**0.0037**	**84.7 ± 15.1**	**78.8 ± 14.3**	**0.0032**
SBP (mmHg)	135.9 ± 20.8	134.2 ± 19.7	0.2918	134.1 ± 22.8	129.4 ± 20.4	0.1154	127.8 ± 24.3	125.5 ± 21.9	0.3688
DBP (mmHg)	75.8 ± 12.1	75.2 ± 10.4	0.4634	**75.6 ± 13.5**	**72.9 ± 12.2**	**0.0490**	**75.7 ± 14.7**	**72.3 ± 12.0**	**0.0262**
LVEF (%)	66.6 ± 8.3	65.8 ± 10.3	0.2661	**44.9 ± 2.9**	**49.8 ± 11.7**	**0.0015**	**29.4 ± 7.6**	**42.9 ± 14.9**	**<0.0001**
LVEDV (mL)	119.7 ± 39.1	115.1 ± 36.6	0.0631	155.9 ± 48.3	155.5 ± 48.0	0.9551	181.8 ± 62.8	180.2 ± 61.4	0.8389
LVESV (mL)	41.4 ± 20.5	40.3 ± 21.7	0.4461	87.8 ± 31.5	79.5 ± 36.2	0.0808	**128.0 ± 52.3**	**113.9 ± 57.4**	**0.0102**
E/A ratio	0.95 ± 0.90	0.88 ± 0.32	0.3950	0.96 ± 0.45	1.06 ± 0.75	0.4962	1.19 ± 0.92	1.08 ± 0.82	0.5243
DecT (ms)	**216.8 ± 67.7**	**238.4 ± 74.0**	**0.0275**	168.8 ± 70.8	197.2 ± 62.4	0.1684	160.4 ± 50.2	181.0 ± 77.9	0.1913
E/e′ ratio	11.7 ± 5.5	10.8 ± 3.2	0.1803	11.9 ± 4.0	12.0 ± 4.1	0.9250	17.2 ± 7.6	14.8 ± 7.1	0.1685
LV IVS (mm)	12.3 ± 2.9	11.9 ± 3.1	0.0758	11.3 ± 3.0	11.0 ± 2.8	0.4780	10.5 ± 2.9	10.5 ± 2.6	0.9861
LV FW (mm)	11.0 ± 5.4	10.7 ± 3.1	0.3815	10.6 ± 2.5	11.0 ± 6.2	0.6257	9.9 ± 2.2	10.1 ± 2.2	0.4504
Patients with non-ischaemic aetiology (n = 526)									
Body weight (kg)	**72.2 ± 14.0**	**71.1 ± 14.5**	**0.0001**	74.9 ± 16.9	75.2 ± 16.0	0.8054	**75.4 ± 17.7**	**74.2 ± 17.6**	**0.0203**
Heart rate (b.p.m.)	80.8 ± 14.3	81.0 ± 16.1	0.8652	**82.0 ± 14.5**	**67.7 ± 14.8**	**0.0083**	**84.7 ± 17.2**	**80.1 ± 13.0**	**0.0666**
SBP (mmHg)	138.3 ± 21.3	136.7 ± 19.9	0.1554	137.4 ± 22.2	137.9 ± 24.2	0.8801	134.4 ± 22.0	130.0 ± 19.8	0.1303
DBP (mmHg)	75.6 ± 12.8	75.7 ± 12.8	0.9633	78.1 ± 12.2	76.4 ± 12.9	0.3707	**78.6 ± 13.4**	**74.4 ± 11.7**	**0.0246**
LVEF (%)	68.7 ± 8.3	67.9 ± 10.0	0.1672	**44.7 ± 2.9**	**49.7 ± 13.1**	**0.0052**	**29.5 ± 7.1**	**41.2 ± 15.7**	**<0.0001**
LVEDV (mL)	110.5 ± 30.9	110.8 ± 33.2	0.8375	**169.1 ± 50.1**	**157.4 ± 40.5**	**0.0493**	199.8 ± 52.5	193.3 ± 67.5	0.3962
LVESV (mL)	34.8 ± 15.3	36.4 ± 19.6	0.0907	**94.0 ± 30.6**	**80.5 ± 36.5**	**0.0074**	**140.7 ± 43.9**	**122.4 ± 64.0**	**0.0078**
E/A ratio	0.84 ± 0.30	0.86 ± 0.32	0.5333	0.98 ± 0.49	0.83 ± 0.43	0.0705	1.19 ± 0.91	1.20 ± 1.17	0.9569
DecT (ms)	218.8 ± 74.7	215.7 ± 77.3	0.7306	194.0 ± 54.2	214.1 ± 91.7	0.3758	169.2 ± 66.1	198.0 ± 97.1	0.2689
E/e′ ratio	12.5 ± 4.9	11.8 ± 4.2	0.2877	14.1 ± 8.5	10.9 ± 5.0	0.1560	15.6 ± 7.4	16.6 ± 14.2	0.7945
LV IVS (mm)	12.3 ± 2.8	12.2 ± 3.1	0.6617	12.5 ± 3.0	12.3 ± 2.8	0.5956	11.1 ± 3.0	11.2 ± 2.5	0.8602
LV FW (mm)	10.7 ± 2.4	10.6 ± 3.2	0.5999	10.6 ± 2.2	11.0 ± 2.4	0.2028	10.4 ± 2.0	10.6 ± 2.2	0.5902

DBP, diastolic blood pressure; DecT, deceleration time; E/A, ratio of peak early to late diastolic filling velocity; E/e′, mitral early diastolic to early diastolic tissue velocity; FW, free wall; IVS, intraventricular septum; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; SBP, systolic blood pressure.

Table 3 Clinical and echocardiographic characteristics in type 2 diabetes mellitus patients treated with dipeptidyl peptidase-4 inhibitor vs. sodium glucose cotransporter-2 inhibitor with a reduced left ventricular ejection fraction of <50%

	DPP4i Baseline LVEF <50% (n = 45)	SGLT2i Baseline LVEF <50% (n = 251)	P value
Age (years)	59.3 ± 10.7	61.7 ± 11.9	0.173
Female	9 (20.0)	44 (17.5)	0.705
Ischaemic heart aetiology	23 (51.1)	141 (56.2)	0.537
Hypertension	32 (71.1)	150 (59.7)	0.135
Dyslipidaemia	29 (64.4)	138 (55.0)	0.234
Cerebral vascular accidents	4 (8.9)	23 (9.6)	0.886
Chronic lung disease	8 (17.8)	18 (7.2)	0.083
Chronic liver disease	13 (28.9)	31 (12.4)	0.025
Chronic kidney disease	14 (31.1)	67 (26.7)	0.588
Peripheral artery disease	4 (8.9)	6 (2.4)	**<0.001**
Gout	6 (13.3)	32 (12.8)	0.831
Malignancy	4 (8.9)	16 (6.4)	0.226
HbA1c (%)	8.8 ± 2.2	8.9 ± 1.9	0.722
Haemoglobin (g/dL)	13.3 ± 2.2	13.4 ± 2.3	0.898
Platelet count (1000/μL)	201.3 ± 60.9	217.9 ± 67.4	0.131
Estimated GFR (mL/min/m^2)	75.6 ± 28.3	78.9 ± 30.9	0.483
ALT (U/L)	46.3 ± 89.8	53.1 ± 208.0	0.723
Triglycerides (mg/dL)	173.8 ± 107.7	203.4 ± 380.1	0.308
LDL (mg/dL)	90.8 ± 36.8	88.8 ± 34.3	0.731
HDL (mg/dL)	37.2 ± 9.4	38.6 ± 11.5	0.392
Uric acid (mg/dL)	7.3 ± 2.3	6.8 ± 2.4	0.262
Height (cm)	165.1 ± 7.0	164.5 ± 8.4	0.797
Weight (kg)	75.5 ± 22.3	73.1 ± 16.4	0.646
Systolic BP (mmHg)	126.7 ± 26.3	132.9 ± 23.1	0.144
Diastolic BP (mmHg)	74.4 ± 15.3	76.8 ± 13.6	0.316
Heart rate (b.p.m.)	81.4 ± 15.8	83.8 ± 15.3	0.352
Anti-platelet agent	40 (88.9)	198 (78.9)	0.120
Statin	33 (73.3)	175 (69.7)	0.627
Non-dihydropyridine CCB	3 (6.7)	12 (4.8)	0.597
Dihydropyridine CCB	7 (15.6)	36 (14.3)	0.832
Beta-blocker	42 (93.3)	220 (87.7)	0.272
ACEI or ARB or ARNI	40 (88.9)	225 (89.6)	0.880
MRA	20 (44.4)	98 (39.0)	0.497
Loop diuretics	32 (71.1)	151 (60.2)	0.165
Nitrate	21 (46.7)	97 (38.7)	0.313
Digoxin	10 (22.2)	38 (15.1)	0.237
Anti-diabetic agent			
SU	36 (80.0)	151 (60.2)	**0.011**
Metformin	39 (86.7)	201 (80.1)	0.300
Glinide	3 (6.7)	17 (6.8)	0.979
Glitazone	12 (26.7)	30 (12.0)	**<0.009**
Acarbose	15 (33.3)	47 (18.7)	**0.027**
Insulin	15 (33.3)	66 (26.3)	0.331
LVEF (%)	39.6 ± 7.5	36.7 ± 9.6	0.058
LVEDV (mL)	182.7 ± 60.1	176.4 ± 56.4	0.494
LVESV (mL)	109.6 ± 44.2	113.3 ± 46.8	0.623
Mitral E/A ratio	0.76 ± 0.27	1.08 ± 0.73	0.099
Mitral DecT (ms)	207.2 ± 73.7	173.0 ± 60.5	0.067
E/e′ ratio	11.4 ± 3.5	14.8 ± 7.3	0.271
LV IVS (mm)	11.1 ± 3.3	11.3 ± 3.1	0.739
LV FW (mm)	10.6 ± 2.5	10.3 ± 2.2	0.515

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BP, blood pressure; CCB, calcium channel blocker; DecT, deceleration time; DPP4i, dipeptidyl peptidase-4 inhibitor; E/A, ratio of peak early to late diastolic filling velocity; E/e′, mitral early diastolic to early diastolic tissue velocity; FW, free wall; GFR, glomerular filtration rate; HbA1c, haemoglobin A1c; HDL, high density lipoprotein; IVS, intraventricular septum; LDL, low density lipoprotein; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea.

FIGURE 1 Change in echocardiographic parameters in patients with type 2 diabetes mellitus treated with SGLT2i with preserved (≥50%), moderately reduced (40–50%), and reduced (<40%) baseline LVEF. Both the moderately reduced and reduced LVEF groups had improvement in LVEF and decrease in LVESV after SGLT2i treatment. In contrast, the preserved LVEF group did not show any change in LVEF and LVESV after SGLT2i treatment. There were no significant changes in LVEDV for three study groups after SGLT2i treatment. LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; SGLT2i, sodium glucose cotransporter-2 inhibitor.

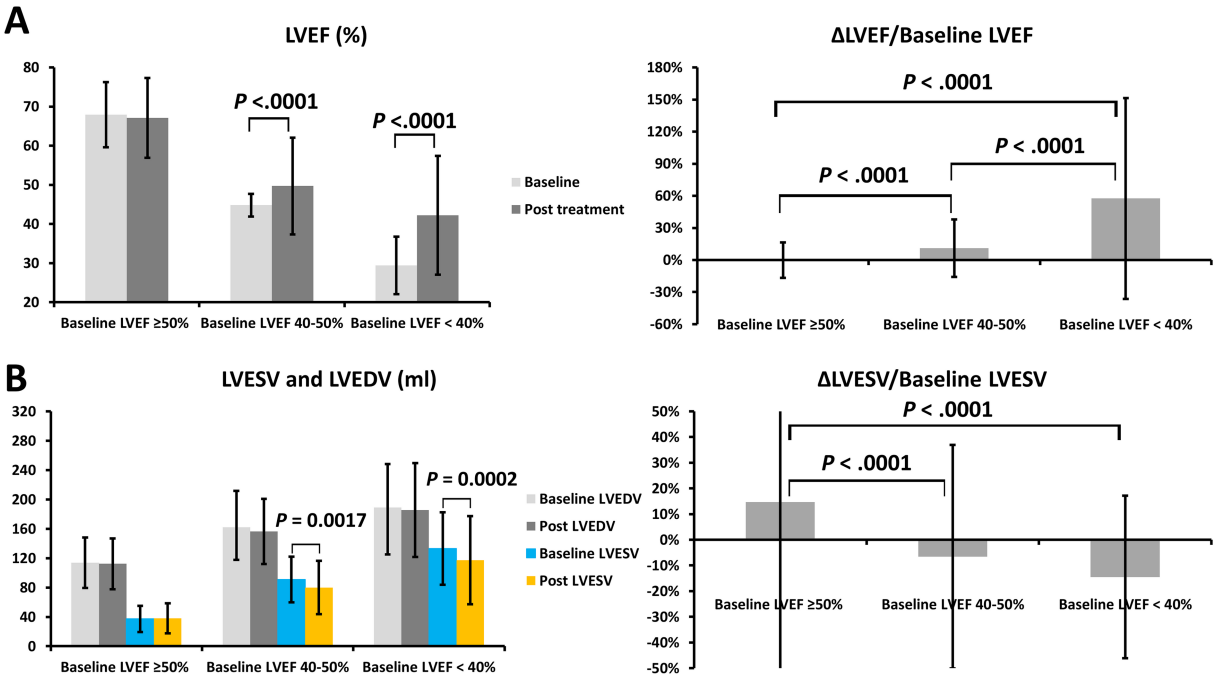
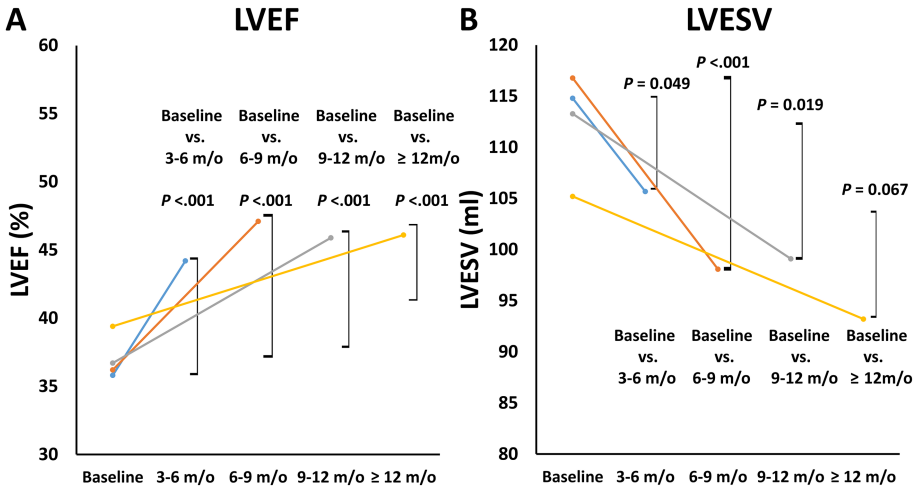


FIGURE 2 Change in LVEF and LVESV in patients with type 2 diabetes mellitus with impaired LVEF (<50%) treated with SGLT2i according to different time periods after SGLT2i treatment. Of 251 patients with impaired LVEF <50%, 84, 79, 47, and 41 patients had paired echocardiography data after 3–6, 6–9, 9–12, and ≥12 months of SGLT2i treatment. It is noted that SGLT2i treatment was associated with a significant improvement in LVEF and LVESV as early as 3–6 months after treatment. LVEF, left ventricular (LV) ejection fraction; LVESV, LV end-systolic volume; m/o, month; SGLT2i, sodium glucose cotransporter-2 inhibitor.



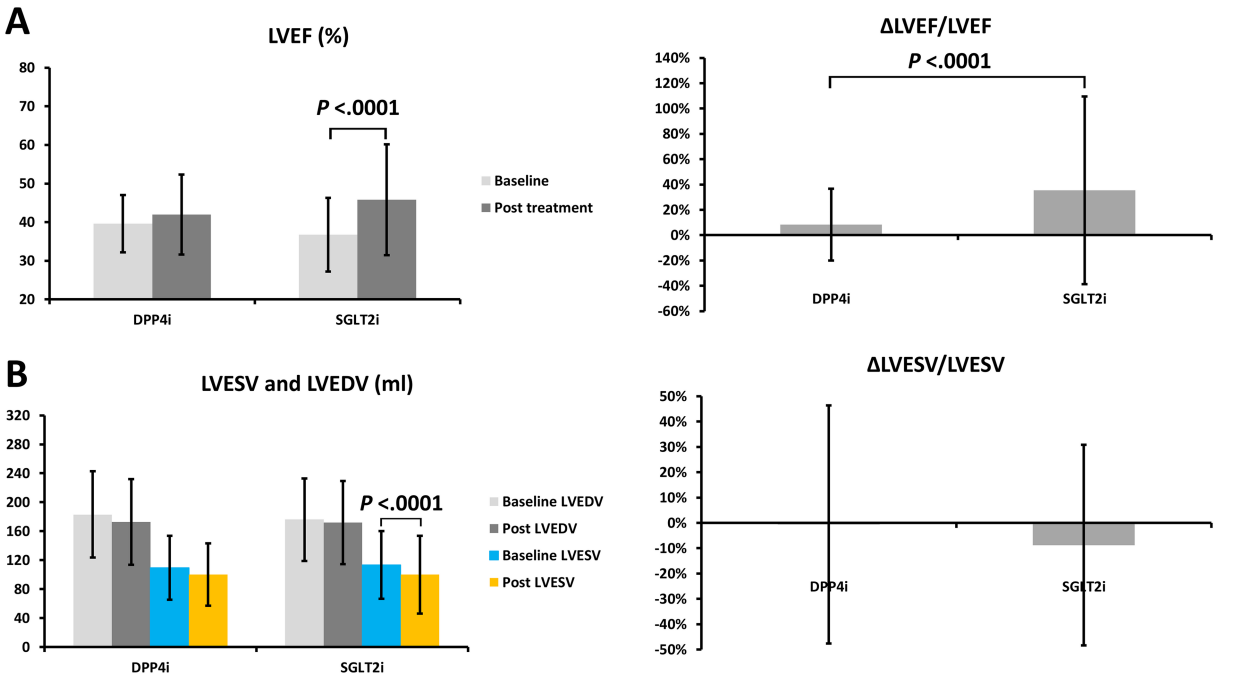
LVESV remodelling for the preserved LVEF group after SGLT2i treatment. (ii) There were no significant changes in other echocardiographic parameters, including LVEDV, LV diastolic function, or LV wall thickness, in the three study groups after SGLT2i treatment. (iii) Compared with patients with impaired baseline LVEF <50% treated with SGLT2i, those with impaired baseline LVEF treated with DPP4i did not show any improvement in LVEF or reverse remodelling in LVESV.

Table 4 The changes of haemodynamics and echocardiographic parameter for type 2 diabetes mellitus patients treated with dipeptidyl peptidase-4 inhibitor and sodium glucose cotransporter-2 inhibitor with a reduced baseline left ventricular ejection fraction of <50% at baseline and after treatment

	DPP4i Baseline LVEF <50% (n = 45)			SGLT2i Baseline LVEF <50% (n = 251)		
	Baseline	Post-treatment	*P* value	Baseline	Post-treatment	*P* value
Body weight (kg)	**75.5 ± 22.2**	**74.5 ± 20.3**	**0.0324**	**73.1 ± 16.4**	**71.8 ± 16.8**	**0.0024**
Heart rate (b.p.m.)	81.4 ± 15.8	81.8 ± 14.6	0.9801	**83.8 ± 15.3**	**78.4 ± 13.7**	**<0.0001**
SBP (mmHg)	126.7 ± 26.2	127.8 ± 20.5	0.6458	132.9 ± 23.1	130.2 ± 22.0	0.0651
DBP (mmHg)	75.7 ± 12.6	75.5 ± 12.0	0.7061	**76.8 ± 13.6**	**73.6 ± 12.2**	**0.0001**
LVEF (%)	39.6 ± 7.5	42.0 ± 10.4	0.1210	**36.7 ± 9.6**	**45.8 ± 14.4**	**<0.0001**
LVEDV (mL)	182.7 ± 60.1	182.7 ± 60.1	0.2892	176.4 ± 56.4	171.8 ± 57.4	0.1932
LVESV (mL)	109.6 ± 44.2	109.6 ± 44.2	0.1198	**113.3 ± 46.8**	**99.9 ± 53.6**	**<0.0001**
E/A ratio	0.76 ± 0.27	0.76 ± 0.31	0.9970	1.08 ± 0.73	1.03 ± 0.81	0.5545
DecT (ms)	207.2 ± 73.7	174.7 ± 93.9	0.3481	173.0 ± 60.5	197.2 ± 83.7	0.0241
E/e' ratio	11.4 ± 3.5	10.6 ± 3.9	0.7656	14.8 ± 7.3	13.4 ± 8.3	0.2411
LV IVS (mm)	11.1 ± 3.3	10.8 ± 3.1	0.4322	11.3 ± 3.1	11.2 ± 2.8	0.5982
LV FW (mm)	10.6 ± 2.5	10.3 ± 3.1	0.6710	10.3 ± 2.2	10.6 ± 3.7	0.2176

DBP, diastolic blood pressure; DecT, deceleration time; DPP4i, dipeptidyl peptidase-4 inhibitor; E/A, ratio of peak early to late diastolic filling velocity; E/e', mitral early diastolic to early diastolic tissue velocity; FW, free wall; IVS, intraventricular septum; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter-2 inhibitor.

FIGURE 3 Change in echocardiographic parameter in patients with type 2 diabetes mellitus with impaired baseline LVEF (<50%) treated with DPP4i vs. SGLT2i. Patients with impaired baseline LVEF had improvement in LVEF and decrease in LVESV after SGLT2i treatment. In contrast, patients with impaired baseline LVEF did not show any change in LVEF and LVESV after DPP4i treatment. There were no significant changes in LVEDV in both DPP4i and SGLT2i groups. DPP4i, dipeptidyl peptidase-4 inhibitor; LVEDV, left ventricular (LV) end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; SGLT2i, sodium glucose cotransporter-2 inhibitor.



Clinical research investigating the effect of SGLT2i on cardiac function

There are relatively few clinical studies evaluating the effect of SGLT2i on LV function and structure. Verma *et al.* investigated the change in cardiac function using cardiac magnetic resonance imaging in 48 patients with T2DM using empagliflozin of 10 mg/day. Compared with placebo treatment, empagliflozin was associated with significant reduction in LV mass index after 6 months. There was no

difference in LVEF and LVESV after empagliflozin treatment.[13] Soga *et al*. also evaluated 53 patients with T2DM with stable heart failure receiving dapagliflozin of 5 mg/day using echocardiography. There were significantly improved LVEF, LV mass, left atrial volume, and E/e′ ratio after the 6 months of treatment.[14] Matsutani *et al*. evaluated the effects of additional treatment with canagliflozin on LV function using echocardiography in 37 patients with T2DM. There was an improvement in E/e′ ratio and reduced LV mass index but without change in cardiac chamber size and LVEF after the 3 months of treatment.[15] Otagaki *et al*. studied 26 consecutive patients with T2DM receiving tofogliflozin and performed echocardiography before and ≥6 months after tofogliflozin administration. Compared with the placebo group, tofogliflozin was associated with an improvement in systolic (LVEF) and diastolic (E/e′ ratio) function after treatment.[16] Generally, the abovementioned studies had an extremely limited patient population, but all of them showed an improvement in LV diastolic function after different SGLT2i treatments. However, the outcomes regarding the improvement in LV systolic function and reverse remodelling of cardiac chamber after SGLT2i treatment showed conflicting results.

In contrast, our study was the largest real-world study enrolling 916 patients treated with SGLT2i, showing that SGLT2i treatment was indeed associated with a significant improvement in LVEF and reverse remodelling of LVESV in T2DM patients with moderately reduced or reduced baseline LVEF specifically. The discrepancy between our findings and those of previous studies might be attributed to the different study populations and increased severity of baseline heart function impairment in our study (27% of patients with an impaired baseline LVEF <50%). Nevertheless, our results are in accordance with the recent study showing that patients with T2DM with worse baseline characteristics benefit more from the SGLT2i treatment.[17] Recently, the subgroup analysis of the DECLARE–TIMI 58 indicated that SGLT2i with dapagliflozin reduced the risk of cardiovascular death or heart failure hospitalization to a greater extent in 671 patients with reduced baseline LVEF (LVEF <45%) than in those without reduced LVEF. This difference was driven by large reductions in cardiovascular death and all-cause mortality in patients with reduced LVEF.[18] However, the major limitation is that the post hoc analysis did not report the following change in echocardiographic parameters in patients with reduced LVEF after SGLT2i treatment. Nevertheless, the improvement in LV systolic function and reverse in LVESV specifically in patients with impaired baseline LVEF in our present study may echo the greater benefit in patients with reduced LVEF as demonstrated in the pivotal trial. Further prospective and randomized controlled studies investigating the cardiovascular outcome and change in cardiac function in SGLT2i treatment are warranted.

Underlying mechanism of SGLT2i in the improvement in cardiac function

In patients with T2DM, LV hypertrophy and impaired diastolic function are more prevalent compared with those in individuals without T2DM.[19] 'Diabetic cardiomyopathy' is thought to be multifactorial, which is initially characterized by myocardial fibrosis and dysfunctional remodelling and associated with LV diastolic dysfunction, followed by progressive LV systolic dysfunction in the late stage.[20] Because only SGLT1 but not SGLT2 receptors were identified in the cardiac tissue,[21] the potential effect of SGLT2i on LV function and structure is hypothesized to be multifactorial and mediated predominantly by metabolic effects and systemic haemodynamics.[19] A number of other biological effects have also been demonstrated with SGLT2i, including improvement in arterial stiffness, vascular resistance, vascular endothelial function, and myocardial fibrosis.[22,23] SGLT2i can also shift myocardial fuel metabolism away from fat/glucose oxidation to a more energy-efficient fuel like ketone bodies, thereby improving myocardial work efficiency and function.[24] Although many hypotheses currently exist, the biological effects of SGLT2i on cardiac function and structure remain uncertain and need further investigation through detailed mechanistic studies.

Effect of DPP4i on cardiac function in T2DM

In contrast to the SGLT2i treatment, DPP4i treatment did not show significant improvement in LVEF or diastolic function in patients with T2DM. The relative effect of DPP4i on the risk of heart failure in patients with T2DM is uncertain, given the relatively short follow-up and low quality of evidence. However, both randomized controlled trials and observational studies suggest that DPP4i may increase risk of heart failure hospitalization in patients with T2DM with existing cardiovascular diseases or multiple cardiovascular risk factors.[25] Nevertheless, our data were compatible with those of recent studies showing that SGLT2i use was associated with a reduced risk of heart failure among patients with T2DM when compared with DPP4i use.[26,27] Further prospective and randomized controlled studies investigating the cardiovascular outcome and change in LV function in patients with T2DM treated with SGLT2i vs. DPP4i are warranted.

Study limitations

The present study had several limitations. First, this is a retrospective and multicentre study. The follow-up echocardiography was performed 6 months before and 3–18 months after the initiation of treatment. We categorized our patients into different time periods after SGLT2i treatment and found that SGLT2i treatment was associated with

improved LVEF and LVESV as early as 3–6 months after treatment. The long range in post-treatment echocardiography is a major limitation in the present study. Although our study is the largest study investigating the change in echocardiographic parameters at baseline and after treatment in patients with T2DM treated with SGLT2i, further well-designed, prospective, and randomized controlled studies with enrolment of more patient populations are still necessary to validate our findings. Second, SGLT2i treatment was associated with a decrease in body weight, resting heart rate, and diastolic blood pressure in our present study, and it is unclear whether the improvement in cardiac systolic function and reverse remodelling of LVESV in patients with T2DM using SGLT2i partially resulted from the weight loss caused by SGLT2i itself or adequate control of hypertension. However, the SGLT2i group with a preserved baseline LVEF and the DPP4i group with an impaired baseline LVEF showed a decrease in body weight but did not show any improvement in cardiac systolic function or reverse LV remodelling in the present study. Third, we also did not report the B-type natriuretic peptide (BNP) data due to limited BNP data available in our database. In the present study, the data of baseline and post-treatment echocardiography were obtained in the outpatient service for each patient with T2DM; therefore, the serum BNP level was not routinely checked in stable patients with T2DM in our daily practice. Fourth, the baseline and post-treatment echocardiography in each patient with T2DM may be performed by different cardiologists. Although all our cardiologists were qualified to perform echocardiography based on a standardized protocol in the CGMH medical system, echocardiography remains largely an operator-dependent technique; therefore, the intra-observer and inter-observer variability of echocardiography cannot be ruled out. Finally, our present study only enrolled Asian patients; therefore, whether the results can be extrapolated to other non-Asian ethnicities remains unclear.

Conclusions

The largest real-world study indicated that SGLT2i treatment was associated with an improvement in LV systolic function in T2DM patients with reduced or moderately reduced rather than preserved baseline LVEF. The advantage of SGLT2i treatment in improving cardiac function persisted in the patient subgroup with an ischaemic or non-ischaemic aetiology. In contrast, patients with impaired baseline LVEF did not show any improvement in LVEF or reverse remodelling of LVESV after DPP4i treatment.

Acknowledgements

This study is based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital.

Conflict of interest

None declared.

Funding

This study was supported by grants 106-2314-B-182A-115-MY3 and 105-2628-B-182A-003-MY3 from the Ministry of Science and Technology and grants CMRPG3F1633, CMRPG3E1681, CMRPG3E1682, CMRPG3E1683, and CORPG3G0351 from Chang Gung Memorial Hospital, Linkou, Taiwan.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The change of echocardiographic parameter for paired T2DM patients with an impaired baseline LVEF ($<$ 50%) treated with DPP4i versus SGLT2i after 1:3 propensity score matching. Those patients with an impaired baseline LVEF were associated with an improvement of LVEF and decrease of LVESV after SGLT2i treatment (n = 117). In the contrast, the patients with an impaired baseline LVEF did not showed any change of LVEF and LVESV after DPP4i treatment (n = 39). There were no significant change of LVEDV for both DPP4i and SGLT2i groups. DPP4i = dipeptidyl peptidase-4 inhibitor; LVEF = left ventricular (LV) ejection fraction; LVEDV = LV end diastolic volume; LVESV = LV end systolic volume; SGLT2i = sodium glucose cotransporter-2 inhibitor; T2DM = type 2 diabetes mellitus

Table S1. *Clinical and echocardiographic characteristics in paired type 2 diabetes mellitus (T2DM) patients treated with dipeptidyl peptidase-4 inhibitor (DPP4i) vs. sodium glucose co-transporter-2 inhibitor (SGLT2i) with a reduced LVEF of $<$ 50% after 1:3 propensity score matching*

Table S2. *The changes of hemodynamics and echocardiographic parameter for paired T2DM patients treated with DPP4i and SGLT2i after 1:3 propensity score matching with a reduced baseline LVEF of $<$50% at baseline and after treatment*

References

1. Vazquez-Benitez G, Desai JR, Xu S, Goodrich GK, Schroeder EB, Nichols GA, Segal J, Butler MG, Karter AJ, Steiner JF, Newton KM, Morales LS, Pathak RD, Thomas A, Reynolds K, Kirchner HL, Waitzfelder B, Elston Lafata J, Adibhatla R, Xu Z, O'Connor PJ. 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**: 905–912.
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. *JAMA* 1979; **241**: 2035–2038.
3. Gallo LA, Wright EM, Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. *Diab Vasc Dis Res* 2015; **12**: 78–89.
4. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, Investigators E-RO. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373**: 2117–2128.
5. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR, Group CPC. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; **377**: 644–657.
6. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS, Investigators D-T. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; **380**: 347–357.
7. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL, Committee S-TS, Investigators*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014; **130**: 1579–1588.
8. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB, Investigators E. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015; **385**: 2067–2076.
9. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, Lewsey JD, Krum H, Committees VT, Investigators. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail* 2018; **6**: 8–17.
10. Rosenstock J, Marx N, Neubacher D, Seck T, Patel S, Woerle HJ, Johansen OE. Cardiovascular safety of linagliptin in type 2 diabetes: a comprehensive patient-level pooled analysis of prospectively adjudicated cardiovascular events. *Cardiovasc Diabetol* 2015; **14**: 57.
11. Wang CL, Wu VC, Kuo CF, Chu PH, Tseng HJ, Wen MS, Chang SH. Efficacy and safety of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with impaired liver function: a retrospective cohort study. *J Am Heart Assoc* 2018; **7**: e009263.
12. Wang CL, Wu VC, Lee CH, Kuo CF, Chen YL, Chu PH, Chen SW, Wen MS, See LC, Chang SH. Effectiveness and safety of non-vitamin-K antagonist oral anticoagulants versus warfarin in atrial fibrillation patients with thrombocytopenia. *J Thromb Thrombolysis* 2019; **47**: 512–519.
13. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, Zuo F, Quan A, Farkouh ME, Fitchett DH, Goodman SG, Goldenberg RM, Al-Omran M, Gilbert RE, Bhatt DL, Leiter LA, Juni P, Zinman B, Connelly KA, Investigators E-HC. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. *Circulation* 2019; **140**: 1693–1702.
14. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, Hirata KI. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol* 2018; **17**: 132.
15. Matsutani D, Sakamoto M, Kayama Y, Takeda N, Horiuchi R, Utsunomiya K. Effect of canagliflozin on left ventricular diastolic function in patients with type 2 diabetes. *Cardiovasc Diabetol* 2018; **17**: 73.
16. Otagaki M, Matsumura K, Kin H, Fujii K, Shibutani H, Matsumoto H, Takahashi H, Park H, Yamamoto Y, Sugiura T, Shiojima I. Effect of tofogliflozin on systolic and diastolic cardiac function in type 2 diabetic patients. *Cardiovasc Drugs Ther* 2019; **33**: 435–442.
17. Hsu JC, Wang CY, Su MM, Lin LY, Yang WS. Effect of empagliflozin on cardiac function, adiposity, and diffuse fibrosis in patients with type 2 diabetes mellitus. *Sci Rep* 2019; **9**: 15348.
18. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Bonaca MP, Ruff CT, Desai AS, Goto S, Johansson PA, Gause-Nilsson I, Johanson P, Langkilde AM, Raz I, Sabatine MS, Wiviott SD. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation* 2019; **139**: 2528–2536.
19. Lan NSR, Fegan PG, Yeap BB, Dwivedi G. The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: current evidence and future directions. *ESC Heart Fail* 2019; **6**: 927–935.
20. McMurray JJ, Gerstein HC, Holman RR, Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. *Lancet Diabetes Endocrinol* 2014; **2**: 843–851.
21. Di Franco A, Cantini G, Tani A, Coppini R, Zecchi-Orlandini S, Raimondi L, Luconi M, Mannucci E. Sodium-dependent glucose transporters (SGLT) in human ischemic heart: a new potential pharmacological target. *Int J Cardiol* 2017; **243**: 86–90.
22. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC, Johansen OE. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. *Diabetes Obes Metab* 2015; **17**: 1180–1193.
23. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* 2017; **104**: 298–310.
24. Mudaliar S, Alloju S, Henry RR. Can a shift in fuel energetics explain the beneficial cardiorenal outcomes in the EMPA-REG OUTCOME study? A unifying hypothesis. *Diabetes Care* 2016; **39**: 1115–1122.
25. Li L, Li S, Deng K, Liu J, Vandvik PO, Zhao P, Zhang L, Shen J, Bala MM, Sohani ZN, Wong E, Busse JW, Ebrahim S, Malaga G, Rios LP, Wang Y, Chen Q, Guyatt GH, Sun X. Dipeptidyl peptidase-4 inhibitors and risk of heart failure in type 2 diabetes: systematic review and meta-analysis of randomised and observational studies. *BMJ* 2016; **352**: i610.
26. Pasternak B, Ueda P, Eliasson B, Svensson AM, Franzen S, Gudbjornsdottir S, Hveem K, Jonasson C, Wintzell V, Melbye M, Svanstrom H. Use of sodium glucose cotransporter 2 inhibitors and risk of major

cardiovascular events and heart failure: Scandinavian register based cohort study. *BMJ* 2019; **366**: l4772.

27. Patorno E, Pawar A, Franklin JM, Najafzadeh M, Deruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, Schneeweiss S. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. *Circulation* 2019; **139**: 2822–2830.