Cardiovascular Diabetology

HYPOTHESIS

Open Access

Early hemodynamic impact of SGLT2 inhibitors in overweight cardiometabolic heart failure: beyond fluid offloading to vascular adaptation– a preliminary report

Nadia Salerno[1], Jessica Ielapi[1], Angelica Cersosimo[1], Isabella Leo[1], Assunta Di Costanzo[2], Giuseppe Armentaro[2], Salvatore De Rosa[2], Angela Sciacqua[2], Sabato Sorrentino[2*] and Daniele Torella[1*]

Abstract

Background Heart failure (HF) is increasingly recognized as a heterogeneous cardiometabolic disorder, often in the context of overweight/obesity independently from diabetes. Sodium-glucose cotransporter-2 inhibitors (SGLT2i) reduce HF hospitalizations and cardiovascular mortality across ejection fraction (EF) categories, yet their early hemodynamic effects in cardiometabolic HF, and with preserved ejection fraction (HFpEF) in particular, remain underexplored.

Methods A prospective, single-center study included 20 consecutive HF patients receiving SGLT2i alongside optimized therapy. Transthoracic echocardiography and non-invasive bioimpedance assessments (NICaS system) were performed at baseline and after 4 weeks.

Results The median patient age was 75 years [58–84], with 14 patients (70%) being overweight/obese, and only 4 patients with diabetes. The majority (65%) had HF with preserved EF (HFpEF), 25% with mildly reduced EF (HFmrEF), and 10% with reduced EF (HFrEF). At a median follow-up of 33 days [30–68], significant reductions were observed in body weight (67.65 kg [46-99.20] to 65.50 kg [46.30–97], $p=0.027$) and systolic blood pressure (130 mmHg [100–150] to 116.50 mmHg [100–141], $p=0.015$). Hemodynamic assessments revealed a significant decrease in total peripheral resistance index (TPRi, 3616.50 dynes·sec·cm3 [1600–5024] to 3098.50 dynes·sec·cm3 [1608–4684], $p=0.002$). The left atrial volume index decreased significantly (42.84 ml/m^2 [27-69.40] to 41.15 ml/m^2 [26-62.60], $p<0.001$); a significant decrease in peak tricuspid regurgitation velocity [2.52 m/Sect. (1.30–3.20]), vs. 2.21 m/Sect. (1.44–2.92), $p=0.023$] and in pulmonary artery systolic pressure (PASP) [31.0 mmHg (15.0–40.0) vs. 25.50 mmHg (15.0-38.0-), $p=0.010$] was observed. Patients with HFrEF or HFmrEF showed significant reduction in total body water (66.33 [51.45–74.45] vs. 58.68 [55.13–66.50]), while HFpEF patients (overweight/obese, $n=11$, 79%) had a significant reduction in TPRi (3681 dynes·sec·cm3 [1600–5024] vs. 3085 dynes·sec·cm3 [1608–4684] $p=0.005$).

*Correspondence:
Sabato Sorrentino
sorrentino@unicz.it
Daniele Torella
dtorella@unicz.it

Full list of author information is available at the end of the article

Conclusions Early hemodynamic responses to SGLT2i may differ across HF subtypes. In overweight patients with cardiometabolic HFpEF, our preliminary findings suggest an association with reduced vascular resistance, while in HFrEF/HFmrEF, the primary benefit appears to be volume unloading. However, the vascular effects of SGLT2i remain uncertain, and given the small sample size, these results should be interpreted as hypothesis-generating. Our findings also highlight the potential role of non-invasive hemodynamic monitoring in guiding therapy in HF.

Keywords Heart failure, Sodium-glucose cotransporter 2 inhibitors, Hemodynamics, Non-invasive monitoring

Introduction

Heart failure (HF) remains a significant global health challenge, associated with substantial morbidity and mortality despite advances in prevention, diagnosis, and treatment strategies [1, 2]. Among the various HF subtypes, HF with preserved ejection fraction (HFpEF) now accounts for approximately 50% of all HF cases [3, 4]. Unlike HF with reduced ejection fraction (HFrEF), therapeutic options for HFpEF are limited, as recommended treatments effective for HFrEF have not demonstrated similar efficacy in improving primary outcomes for HFpEF patients [5–7]. This divergence underscores the distinct pathophysiological mechanisms underlying these two conditions. Recently, landmark clinical trials, including DELIVER [8] and EMPEROR-Preserved [9], have demonstrated significant reductions in HF hospitalizations and cardiovascular mortality with sodium-glucose cotransporter-2 inhibitors (SGLT2i) in HFpEF patients, establishing this class of drugs as the only therapy with a Class I recommendation for HFpEF management [7].

The precise mechanisms by which SGLT2i confer these clinical benefits are not yet fully understood and may vary according to the HF phenotype. Notably, a pooled analysis of over 21,000 patients from five randomized controlled trials revealed that SGLT2i significantly reduced cardiovascular death and HF hospitalizations, with benefits emerging within the first month and being sustained from four months onward [10]. These effects may be partly attributed to the short-term blood pressure-lowering properties of SGLT2i, which reduce cardiac afterload and enhance ventricular-arterial coupling [11]. This hemodynamic improvement increases cardiac efficiency and promotes reverse cardiac remodeling, as consistently demonstrated by imaging studies [12–15]. Moreover, emerging evidence suggests that the cardioprotective benefits provided by SGLT2 inhibitors are mediated through mechanisms reminiscent of calorie restriction, including weight loss, ketogenesis, and nutrient-deprivation signaling [16].

The quantification of hemodynamic parameters (i.e. cardiac output, cardiac index, stroke volume, cardiac power, and peripheral resistance), may offer unique insights in this context [17]. Although thermodilution via right heart catheterization remains the gold standard for measuring these parameters [18], techniques based on bioimpedance analysis have proven to be an accurate, non-invasive alternative [19]. For instance, the integration of the total-body impedance cardiography-based Non-Invasive Cardiac System (NICaS) into routine clinical evaluation has already been demonstrated to offer a reliable method for monitoring the hemodynamic status of HF patients and assessing improvements following therapy [20].

Despite the known benefits of SGLT2i, the early hemodynamic effects and cardiac remodeling induced by SGLT2i across different HF phenotypes remain insufficiently characterized. Understanding these short-term impacts could provide deeper insights into the mechanisms of SGLT2i and optimize their therapeutic use in HF management [16]. Accordingly, this study aimed to investigate the early effects of SGLT2i on hemodynamic parameters and cardiac remodeling, stratified by the HF phenotype.

Methods

Study design

This prospective, single-center observational study was conducted at "Renato Dulbecco" University Hospital in Catanzaro, Italy. Patients enrolled in the study underwent clinical examination, six-minute walking test (6MWT), echocardiographic and non-invasive hemodynamic evaluation at baseline and 1 month after starting SGLT2i therapy, on top of optimal medical therapy (OMT). Laboratory data were collected for all patients both at baseline and at 1-month follow-up. All patients provided written informed consent. All study procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the Calabria Region Local Ethics Committee (Protocol Register No. 170, May 30, 2024).

Study population

Consecutive patients diagnosed with HF and naïve to SGLT2i were enrolled in the study between June 2024 and December 2024. A baseline visit and a 1-month follow-up in-person visit were conducted to collect data on clinical status, echocardiographic and non-invasive hemodynamic parameters, which were included in a prespecified dataset. The key exclusion criteria were: [1] patients with severe renal impairment (stage IV or V); [2] patients with congenital heart disease [3], patient with previous acute coronary syndrome in the past three months, and [4] patients aged ≤18 years.

Echocardiographic assessment

At baseline and 4-weeks after initiating SGLT2i therapy, comprehensive transthoracic echocardiography was performed using Philips EPIQ 7 ultrasound system (Philips Healthcare, Amsterdam, Netherlands), equipped with an X5-1 xMatrix array transducer. Data acquisition and interpretation adhered to the 2015 American Society of Echocardiography (ASE) guidelines for chamber quantification [22]. Briefly, left ventricular (LV) structure and function were assessed using LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) via the biplane Simpson method. The LV mass index was calculated by incorporating LV end-diastolic diameter (LVEDD), posterior wall thickness (PWED), and interventricular septal thickness (IVSED). Diastolic function was evaluated through transmitral flow (E/A ratio) and tissue Doppler imaging (TDI) of lateral and septal mitral annulus velocities, with E/e' ratio and left atrial volume index (LAVi) values [23].

Right ventricular (RV) function was assessed via the tricuspid annular plane systolic excursion (TAPSE) and the systolic velocity (S'). Systolic pulmonary artery pressure (PASP) was calculated using the peak tricuspid regurgitant velocity (TRVmax) and the estimated right atrial pressure (RAP), with TAPSE/PASP used to evaluate RV-pulmonary artery coupling [24].

Speckle-tracking echocardiography (STE) was performed per EACVI/ASE recommendations, analyzing LV global longitudinal strain (GLS), left atrial strain (reservoir, conduit, and contraction phases), and RV strain (free wall and global) [25, 26].

Non-invasive hemodynamic assessment

Non-invasive hemodynamic assessment was conducted using the FDA-approved total-body impedance cardiography-based Non-Invasive Cardiac System (NICaS) (NI Medical Ltd, Ra'anana, Israel). The device detects bioimpedance changes in peripheral tissues by applying a low-intensity electrical current through the body via two pairs of tetrapolar sensors positioned in a wrist-to-ankle configuration. Before initiating the analysis, patient-specific information, including sex, age, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), hematocrit, sodium levels, peripheral oxygen saturation, and electrode positioning, was entered into the system.

Measurements were performed with patients in the supine position after a 5-minute rest period to ensure hemodynamic stability. The NICaS system collects a minimum of five measurements per patient to enhance reliability, providing the average of these readings as the final result. The parameters provided include stroke volume (SV), cardiac output (CO), cardiac index (CI), mean arterial pressure (MAP), cardiac power (CP), total peripheral resistance (TPR) and its indexed value (TPRi), total body water (TBW), and the Granov-Goor Index (GGI) [27–30].

Statistical analysis

Continuous variables are presented as median [min-max], categorical variables are reported as frequencies and percentages. Comparisons were made using either the paired Student's t-test or the appropriate nonparametric tests. All tests were conducted at a two-sided alpha level of 0.05, which was deemed statistically significant. Statistical analysis was performed using GraphPad Prism version 6.00 for Macintosh (GraphPad Software, La Jolla, CA, USA).

Results

Baseline characteristics

A total of 20 patients naïve for treatment with SGLT2i (either empagliflozin, $n = 11$ or dapagliflozin, $n = 9$) were enrolled from June 2024 to December 2024. The median age of the population enrolled was 75 years [58–84], and 12 (60%) of patients were male. Table 1 summarizes baseline clinical characteristics. Briefly, typical cardiovascular risk factors were largely prevalent, including 18 (90%) patients with hypertension, 18 (90%) with dyslipidaemia, 9 (45%) reporting previous smoking habit, and 4 (20%) treated for diabetes mellitus. Furthermore, 8 (40%) patients had history of previous myocardial infarction, 10 (50%) received percutaneous coronary interventions, and 5 (25%) surgical revascularizations. Atrial fibrillation was present in 9 (45%) patients, 4 (20%) in a permanent form. Furthermore, about a quarter of patients presented chronic kidney disease (CKD) and the median value of glomerular filtrate was 62.90 [30-91.50] mL/min/1.73m^2. Importantly, two-thirds of the patients were overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2) (total of $n = 14$, 70%) (Table 1).

Finally, among the enrolled patients 65% presented with HFpEF, 25% with HFmrEF and 10% with HFrEF (baseline clinical characteristics across HF groups are summarized in **Supplementary Table 1**).

Changes in clinical, echocardiographic and non-invasive hemodynamic parameters and fluid indices

Table 2 summarizes the echocardiographic and hemodynamic parameters at baseline and follow-up. The median follow-up was 33 days [30–68]. Significant reductions in both body weight (kg) (67.65 [46-99.20] vs. 65.50 [46.30–97]; $p = 0.027$) and SBP (mmHg) (130 [100–150] vs. 116.50 [100–141]; $p = 0.015$) were observed. No significant differences were found in biochemical parameters, except for a significant increase in haemoglobin level (g/dl) (12.90 [9.60–15.50] vs. 13.20 [9.70–15.40] $p = 0.034$). All patients had elevated NT-proBNP values (pg/mL) at

Table 1 Baseline characteristics

General characteristics	
Age (years)	75 [58–84]
Male sex	12 (60)
Weight (kg)	68 [46-99.20]
BMI (kg/m^2)	26.40 [20.40–37.70]
< 25	6 (30)
≥25 to < 30	9 (45)
≥30	5 (25)
Smoker	9 (45)
Dyslipidemia	18 (90)
Diabetes	4 (20)
Hypertension	18 (90)
Prior Myocardial infarction	8 (40)
Prior PCI	10 (50)
Prior CABG	5 (25)
CIED	3 (15)
CKD	5 (25)
COPD	4 (20)
OSAS	1 (5)
Atrial Fibrillation	9 (45)
paroxysmal	5 (25)
persistent	0 (0)
permanent	4 (20)
HF type	20 (100)
HFpEF	13 (65)
HFmrEF	5 (25)
HFrEF	2 (10)
Drugs therapy	
Beta-blocker	18 (90)
Calcium channel blockers	1 (5)
ACEi	11 (55)
ARB	3 (15)
ARNI	2 (10)
MRA	4 (20)
Loop Diuretic	12 (60)
Thiazide Diuretic	1 (5)
SGLT2i	20 (100)
Empaglifozin	11 (55)
Dapaglifozin	9 (45)

Values are expressed as median [min-max] or n (%)

BMI- Body mass index; HF-Heart failure; HFpEF-Heart failure with preserved ejection fraction; HFmrEF- Heart failure with mildly reduced ejection fraction; HFrEF- Heart failure with reduced ejection fraction; PCI- Percutaneous coronary intervention; CABG- Coronary artery bypass graft surgery; CIED- Cardiac implantable electronic device; CKD– Chronic kidney disease; COPD- Chronic obstructive pulmonary disease; OSAS- Obstructive sleep apnea syndrome; ACEi– ACE inhibitor; ARB– Angiotensin receptor blocker; ARNI– Angiotensin receptor neprilisin inhibitor; MRA– Mineralocorticoids receptor antagonists; SGLT2i- Sodium-glucose co-transporter 2 inhibitors

baseline (906.50 [231–7287]), with no statistically significant trend toward reduction at follow-up (505 [146.60–8927], $p = 0.328$).

At echocardiographic evaluation there was a significant decrease in LAVi (ml/m^2) (42.84 [27-69.40] vs. 41.15 [26-62.60], $p < 0.001$), in peak TR velocity (m/sec) (2.52 [1.30–3.20] vs. 2.21 [1.44–2.92], $p = 0.023$) and in PASP (mmHg) (31 [15–40] vs. 25.50 [15–38], $p = 0.010$). Assessing the hemodynamic effects of SGLT2i initiation, a slight reduced MAP was observed (mmHg) (91.50 [74–109] vs. 83.50 [63–106], $p = 0.015$). Furthermore, SGLT2i also favourably influenced the TPR (dn*s/cm^5), both as absolute values (2048.50 [1082–2767] vs. 1776 [1061–2863] $p = 0.004$) and as indexed values (dn*s/cm^3) (3616.50 [1600–5024] vs. 3098.50 [1608–4684], $p = 0.002$). Finally, no differences were observed in the 6MWT (m) at follow-up (390 [120–480] vs. 390 [120–540], $p = 0.231$).

At follow-up, when considering only the overweight and obese patients ($n = 14$), these patients exhibited a significant reduction in body weight (77.25 kg [57.80–99.20] vs. 74.05 kg [57.60–97], $p = 0.031$) and SBP (132.50 mmHg [110–150] vs. 122 mmHg [104–141], $p = 0.039$). Although NT-proBNP levels were not significantly lower (609.5 pg/mL [231–1759] vs. 381 pg/mL [146.60–1803], $p = 0.322$), significant reductions were observed in EDV (105.05 mL [62.60–240] vs. 93.45 mL [60–236], $p = 0.036$), ESV (45.40 mL [27.60–173] vs. 39.40 mL [26–169], $p = 0.009$), LAVi (44.70 mL/m² [30–69.40] vs. 40.50 mL/m² [29–62.6], $p = 0.008$), and PASP (27 mmHg [15–40] vs. 24.5 mmHg [15–35], $p = 0.036$). Moreover, NICaS measurements revealed a significant decrease in MAP (95.5 mmHg [78–109] vs. 87.5 mmHg [63–106], $p = 0.043$), TPR (2048.5 dns/cm^5 [1577–2767] vs. 1657.5 dns/cm^5 [1259–2863], $p = 0.002$), and TPRi (3616.5 dns/cm^3 [2911–5024] vs. 3098.5 dns/cm^3 [2400–4684], $p = 0.001$) (Table 3). Notably, in patients with a BMI < 25 kg/m²(n = 6), no significant changes were observed in any parameter at follow-up.

Changes in echocardiographic and non-invasive hemodynamic parameters and fluid indices across HF phenotypes

Table 4 summarizes the clinical, echocardiographic, non-invasive hemodynamic parameters and fluid indices of patients with HFrEF and HFmrEF. In these subsets of patients, a significant reduction in weight was observed. NT-proBNP values were not significantly lower at follow-up (1759 pg/mL [296–7287] vs. 1326 [237–8927] $p = 0.594$). Additionally, notable decreases were recorded in LAVi (ml/m^2) (45.50 [38-58.60] vs. 41 [32-44.90], $p < 0.03$), and in PASP (mmHg) (30 [23–38] vs. 25 [15–33], $p = 0.013$) (Fig. 1).

Regarding hemodynamic parameters and fluid indices, no substantial differences were found, except for a reduction in TBW (% weight): 66.33 [51.45–74.45] vs. 58.68 [55.13–66.50], $p = 0.047$) (Fig. 2).

In patients with HFpEF, the majority of which were overweight ($n = 8$) or obese ($n = 3$) (total 85%) (Supplementary Table 1), no significant changes in morphometric variables were observed (Table 5). NT-proBNP values were not significantly lower (870 pg/mL [231–6631], vs. 384 [146.60–1803], $p = 0.219$). However, a significant

Table 2 Difference between baseline and after 1 mo of treatment with SGLT2i

	Baseline characteristics	30-days post SGLT2i therapy	*p*-value
General characteristics			
Weight (kg)	67.65 [46-99.20]	65.50 [46.30–97]	**0.027**
SBP (mmHg)	130 [100–150]	116.50 [100–141]	**0.015**
DBP (mmHg)	69.50 [55–90]	70 [45–90]	0.097
HR (bpm)	62.50 [54–90]	65 [47–99]	0.567
6MWT (m)	390 [120–480]	390 [120–540]	0.231
Sat% O_2 at basal time	97 [94–100]	97 [94–100]	0.878
Sat% O_2 at 6 min	97 [88–99]	97 [94–99]	0.335
Biochemical parameters			
Hb (g/dL)	12.90 [9.60–15.50]	13.20 [9.70–15.40]	**0.034**
HCT (%)	39.90 [30.30–44.50]	40.40 [29.80–47.90]	0.293
Creatinine (mg/dL)	0.95 [0.68–2.04]	1.05 [0.77–1.68]	0.484
eGFR (mL/min/1.73m^2)	62.90 [30-91.50]	58.50 [37.30–88.30]	0.589
NT-proBNP (pg/mL)	906.50 [231–7287]	505 [146.60–8927]	0.328
Fasting blood glucose (mg/dL)	89 [76–133]	88 [65–143]	0.889
Glycated hemoglobin (%)	5.95 [5.12–6.40]	5.73 [4.90–6.70]	0.742
Echocardiography parameters			
EDV (mL)	97.10 [62.60–155]	94.05 [60–150]	0.102
ESV (mL)	45.40 [26.60–71.30]	41.50 [26-77.90]	**0.042**
LVMi (g/m^2)	98.44 [49–137]	99.60 [48–128]	0.139
EF (%)	53.80 [19.60–65.20]	54.30 [22-62.80]	**0.045**
LVGLS (%)	16.75 [4.80–22.90]	17.10 [4.70–23.20]	0.835
E wave (cm/sec)	77.55 [37.20–130]	80.40 [33–121]	0.760
A wave (cm/sec)	82.40 [34.60–135]	75.50 [35.60–135]	0.955
E/A	0.80 [0.40–2.30]	0.80 [0.40–1.90]	0.095
Sept E'(cm/sec)	7.14 [3.10–17.70]	6.85 [3.26–12.60]	0.361
Lat E'(cm/sec)	8.71 [3.92–13.10]	7.73 [4.13–14.50]	0.938
E/E'	9.42 [4.50–18.80]	9.03 [5.30–21.50]	0.866
LAVi (ml/m^2)	42.84 [27-69.40]	41.15 [26-62.60]	**< 0.001**
PALS (%)	19.75 [4.60–46.50]	20.20 [4.30–60.50]	0.171
LACD(%)	9.60 [1.90–25.10]	9.35 [2.40–41.60]	0.821
LACT(%)	8.80 [2.10–21.40]	10.25 [1.60–21.60]	0.597
RAVi (ml/m^2)	22.50 [13-44.30]	21 [15–45]	0.867
RVLS free wall (%)	21.6 [7.20–27.7]	21.90 [9.70–27.70]	0.250
RVLS Global (%)	17.90 [5.80–22.90]	18.20 [7.50–27.70]	0.072
TAPSE (mm)	22.20 [18–29]	22 [11–28]	0.739
RV S' (cm/s)	12.80 [9.20–25]	12.35 [6.70–24.50]	0.822
peak TR vel (m/sec)	2.52 [1.30–3.20]	2.21 [1.44–2.92]	**0.023**
PASP (mmHg)	31 [15–40]	25.50 [15–38]	**0.010**
TAPSE/PASP (mm/mmHg)	0.73 [0.53–1.49]	0.85 [0.33–1.73]	0.059
NICaS parameters			
MAP (mmHg)	91.50 [74–109]	83.50 [63–106]	**0.015**
CI (l/min/m^2)	2.07 [1.46–3.70]	2.09 [1.32–3.68]	0.089
CO (l/min)	3.77 [2.54–5.47]	3.72 [2.14–5.58]	0.108
Stroke volume (ml)	55.59 [32.94–76.08]	56.52 [36.88–93.13]	0.303
Stroke volume index (ml/m^2)	31.75 [18.95–48.69]	31.82 [23.24–49.34]	0.359
CPi (w/m^2)	0.41 [0.25–0.61]	0.40 [0.20–0.62]	0.902
TPR (dn*s/cm^5)	2048.50 [1082–2767]	1776 [1061–2863]	**0.004**
TPRi (dn*s/cm^3)	3616.50 [1600–5024]	3098.50 [1608–4684]	**0.002**
GGI	9.25 [5.83–17.70]	10.02 [7.70–18.90]	0.162
RR (l/min)	17 [11–21]	16 [11–24]	0.934
TBW (kg)	44.17 [31.80–65]	42 [30.60–55.70]	0.081

Table 2 (continued)

	Baseline characteristics	30-days post SGLT2i therapy	*p*-value
General characteristics			
TBW (% weight),	63.44 [49.40–77.50]	59.55 [49.80–73.40]	0.268
Basal impedence (ohm)	311.50 [226–391]	317 [244–410]	0.074

Values are expressed as median [min-max] or n (%)

SPB– Systolic blood pressure; DPB– Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV– End-diastolic volume; ESV– End-systolic volume; EF– Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi- Left Ventricular Mass Index; LAVi– Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi– Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP–Pulmonary artery systolic pressure; TAPSE– Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

reduction in LAVi (ml/m^2) (41.37 [26.15-63] vs. 40.32 [23.29–62.25], $p = 0.005$), and a reduction, even if not statistically significant, in right ventricular parameters, including peak TR velocity (m/sec) (2.61 [1.30–3.20] vs. 2.21 [1.67–2.92], $p = 0.108$), PASP (mmHg) (32 [15–40] vs. 26 [16–38], $p = 0.134$), and TAPSE/PASP ratio (0.73 [0.53–1.49] vs. 0.87 [0.60–1.25], $p = 0.154$) were detected (Fig. 3). Interestingly, NICaS measurements revealed a significant reduction in TPR (dn*s/cm^5) (2073 [1082–2767] vs. 1676 [1061–2863], $p = 0.009$) and indexed TPR (dn*s/cm^3) (TPRI: 3681 [1600–5024] vs. 3085 [1608–4684], $p = 0.005$) (Fig. 4). The above data were practically undistinguishable when considering only the overweight/obese HFpEF patients.

Discussion

SGLT2i significantly reduce the risk of cardiovascular death and hospitalization for HF, regardless of EF or glycemic status [6, 7]. These benefits often manifest within the first month of therapy initiation [31]. Several mechanisms have been proposed for the early effects of SGLT2i. The weight loss observed with these drugs is primarily due to reduced extracellular water levels, driven by glycosuric and natriuretic effects during the first days of treatment [32, 33]. Furthermore, SGLT2i modulate the renin-angiotensin-aldosterone system, yielding modest but clinically significant reductions in SBP and DBP of approximately 2.46 mmHg and 1.46 mmHg, respectively [29]. Notably, findings from the DAPASALT study demonstrated a reduction in blood pressure within 24 h of initiating dapagliflozin, without concurrent increases in sodium or fluid excretion, suggesting alternative non-diuretic mechanisms [35]. In our population, we observed a significant decline in blood pressure, demonstrated by a reduction in SBP, and a slight increase in hemoglobin levels and a modest haematocrit elevation. This elevation may be related to the SGLT2i diuresis-driven plasma concentration of red blood cells and to the direct erythropoiesis stimulation via early increases in erythropoietin levels [36–38].

Furthermore, echocardiographic changes underscore the early decongestive effects of SGLT2i, evidenced by a reduction in cardiac preload markers, such as LAVi, and PASP values.

Interestingly, we also observed a reduction in systemic resistance by the NICaS non-invasive hemodynamic assessment in our study population, suggesting that SGLT2 inhibition exerts its protective effects on renal and cardiac properties by negatively regulating the sympathetic nervous system [39–41].

Interestingly, subgroup analyses further revealed phenotype-specific responses. In patients with HFrEF and HFmrEF, significant reductions in preload markers (e.g., LAVi and PASP) and TBW suggest a pronounced natriuretic effect. Conversely, in patients with HFpEF, reduction in SBP was accompanied by significant decreases in TPR. These findings highlight SGLT2i's role in reducing vascular stiffness, enhancing ventricular-arterial coupling, and improving cardiac efficiency—key therapeutic targets in HFpEF. This analysis reinforces previous evidence showing reductions in blood pressure and systemic vascular resistance with dapagliflozin and canagliflozin, likely mediated by improved endothelial function, increased nitric oxide bioavailability, and reduced inflammation and oxidative stress [42–44].

Our data do not challenge the role of SGLT2i in modulating intravascular volume in HF but rather propose that their primary acute mechanism extends beyond fluid modulation. The impact of SGLT2i on fluid volume regulation in patients with type 2 diabetes and cardiovascular disease remains significant. Indeed, Tanaka et al. demonstrated that empagliflozin reduced estimated plasma volume (ePV) and extracellular volume (eEV) over 24 weeks, suggesting a mechanistic link between volume reduction and cardiac stress relief [45]. Similarly, luseogliflozin led to a sustained reduction in ePV over 24 weeks in HFpEF patients, with significant associations between ePV changes and lLAVi, reinforcing its potential hemodynamic benefits [46]. In a longer-term analysis, tofogliflozin reduced body weight, ePV, and BNP levels over 52 weeks, but after withdrawal, these parameters rebounded above baseline, highlighting the transient nature of its volume-modulating effects [47]. Finally, in HFrEF patients, empagliflozin reduced stressed blood volume

Table 3 Difference between baseline and after 1 mo of treatment in patients with BMI ≥ 25 kg/m^2

	Baseline	Follow-up	*p*-value
General characteristics			
Weight (kg)	77.25 [57.80–99.20;]	74.05 [57.60–97]	**0.031**
SBP (mmHg)	132.50 [110–150]	122 [104–141]	**0.039**
DBP (mmHg)	77.50 [55–90]	72 [45–90]	0.088
HR (bpm)	62.50 [55–90]	66 [47–99]	0.371
6MWT (m)	375 [120–480]	405 [120–540]	0.132
Sat% O_2 at basal time	97 [95–100]	97 [94–100]	0.836
Sat% O_2 at 6 min	97 [96–98]	97 [94–99]	0.532
Biochemical parameters			
Hb (g/dL)	13 [9.60–15.50]	13.60 [9.70–15.40]	**0.006**
HCT (%)	40.75 [30.30–44.50]	41.50 [29.80–47.90]	0.039
Creatinine (mg/dL)	0.92 [0.75–2.04]	1 [0.77–1.68]	0.924
eGFR (mL/min/1.73m2)	65 [30–90]	65.70 [37.30–88.30]	0.391
NT-proBNP (pg/mL)	609.50 [231–1759]	381 [146.60–1803]	0.322
Fasting blood glucose (mg/dL)	90.50 [81–108]	94.50 [65–110]	0.894
Glycated hemoglobin (%)	5.85 [5.12–6.40]	5.60 [4.90–6.70]	0.751
Echocardiography parameters			
EDV (mL)	105.05 [62.60–240]	93.45 [60–236]	**0.036**
ESV (mL)	45.40 [27.60–173]	39.40 [26–169]	**0.009**
LVMi (g/m^2)	99.52 [52.52-142.24]	97.34 [53.43-129.07]	0.125
EF (%)	54.80 [27.90–60]	56 [28.40–62.80]	0.069
LVGLS (%)	17.10 [9.50–22.90]	17.55 [9.30–21]	0.487
E wave (cm/sec)	84.95 [37.20–130]	83.35 [33–121]	0.437
A wave (cm/sec)	87 [44.50–135]	75.50 [58.20–135]	0.611
E/A	0.70 [0.40–1.30]	0.70 [0.40–1.10]	0.148
Sept E'(cm/sec)	7.91 [5.33–17.70]	7.64 [5.55–12.60]	0.573
Lat E'(cm/sec)	8.03 [3.92–11.70]	7.63 [5.44–14.50]	0.726
E/E'	9.43 [4.50–17.60]	7.98 [5.30–17.90]	0.487
LAVi (ml/m^2)	44.70 [30-69.40]	40.50 [29-62.60]	**0.008**
PALS (%)	18.45 [8.10–28.30]	19.25 [4.30–39.20]	0.351
LACD(%)	9.15 [1.90–21.10]	9.35 [2.90–23.10]	0.573
LACT(%)	8.45 [2.10–19.20]	10.25 [1.60–21.60]	0.618
RAVi (ml/m^2)	21.15 [13-26.10]	20.10 [15–23]	0.744
RVLS free wall (%)	21.65 [7.20–27.70]	21.90 [13.90–29.80]	0.271
RVLS Global (%)	18.15 [5.80–22.90]	19.20 [11.30–27.70]	0.072
TAPSE (mm)	21.60 [18–28]	22 [17–26]	0.904
RV S' (cm/s)	12.60 [11.20–25]	12.45 [10-24.50]	0.959
peak TR vel (m/sec)	2.36 [1.30–3.20]	2.15 [1.44–2.90]	0.056
PASP (mmHg)	27 [15–40]	24.50 [15–35]	**0.036**
TAPSE/PASP (mm/mmHg)	0.73 [0.53–1.49]	0.88 [0.60–1.73]	0.096
NICaS parameters			
MAP (mmHg)	95.50 [78–109]	87.50 [63–106]	**0.043**
CI (l/min/m^2)	2.07 [1.53–2.25]	2.20 [1.42–2.77]	0.082
CO (l/min)	3.77 [2.59–4.48]	3.91 [2.68–5.37]	0.120
Stroke volume (ml)	55.58 [41.05–76.08]	55.02 [36.88–93.13]	0.276
Stroke volume index (ml/m^2)	31.75 [23.06–40.97]	31.43 [23.24–49.34]	0.240
CPi (w/m^2)	0.43 [0.29–0.49]	0.42 [0.24–0.62]	0.937
TPR (dn*s/cm^5)	2048.50 [1577–2767]	1657.50 [1259–2863]	**0.002**
TPRi (dn*s/cm^3)	3616.50 [2911–5024]	3098.50 [2400–4684]	**0.001**
GGI	9.08 [5.83–13.84]	9.72 [7.66–13.98]	0.115
RR (l/min)	16.50 [11–21]	16 [12–24]	0.828
TBW (kg)	44.62 [34.95-65]	45.09 [35.30-55.68]	0.230

Table 3 (continued)

	Baseline	Follow-up	*p*-value
General characteristics			
TBW (% weight)	59.75 [49.40-77.46]	58.83 [49.80–72.50]	0.601
Basal impedence (ohm)	296.50 [226–384]	308 [244–373]	0.297

Values are expressed as median [min-max] or n (%)

SPB– Systolic blood pressure; DPB– Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV– End-diastolic volume; ESV– End-systolic volume; EF– Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi- Left Ventricular Mass Index; LAVi– Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi– Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP–Pulmonary artery systolic pressure; TAPSE– Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

over 12 weeks, with reductions significantly correlated with pulmonary capillary wedge pressure (PCWP), suggesting a direct effect on cardiac preload [48]. Collectively, our and these findings therefore highlight the complex interplay between SGLT2i, volume modulation, and cardiac function.

HFpEF is not a single disease but rather a heterogeneous syndrome encompassing multiple clinical phenotypes. Among these, cardiometabolic HFpEF is the most prevalent, driven by metabolic disorders such as obesity and hypertension. These conditions contribute to lipid accumulation and the activation of maladaptive inflammatory pathways, ultimately leading to progressive fibrosis and organ dysfunction [49]. In our study, 70% of patients were overweight or obese. Our findings indicate that in overweight or obese HF patients (independent from EF subtypes), SGLT2 inhibitors provided benefits comparable to those seen in HFpEF, further supporting the notion that obesity shares key pathophysiological features with HFpEF—commonly referred to as cardiometabolic HFpEF [50]. Accordingly, our findings preliminary indicate that SGLT2i may exert early vascular effects in overweight HFpEF patients, potentially contributing beyond fluid offloading. However, given the ongoing uncertainty regarding the vascular impact of SGLT2i, our findings should be interpreted as hypothesis-generating and require confirmation in larger, well-powered clinical trials to establish their clinical significance.

Limitations

In interpreting the results of the current study, it is important to acknowledge its inherent. limitations. Our study was designed as an exploratory, hypothesis-generating investigation to assess the early hemodynamic effects of SGLT2i in overweight HF (and HFpEF in particular) patients, using non-invasive bioimpedance assessments (NICaS system). We fully acknowledge that the small sample size of our study limits the statistical power and generalizability of our findings. However, it is important to emphasize that preliminary studies of this nature play a crucial role in shaping future research directions by identifying potential mechanistic trends that warrant further investigation. Similar small-scale hemodynamic studies have provided valuable insights into HF pathophysiology and treatment responses, serving as a foundation for subsequent larger trials. Notably, the recently published subanalysis of the EMPAG-HF trial underscores the relevance of early hemodynamic assessments in understanding the acute effects of SGLT2i, despite sample size constraints [51]. While our results should be interpreted with caution, they contribute to the growing body of evidence supporting the hemodynamic benefits of SGLT2i in HF. Future multicenter trials with larger cohorts will be essential to validate our findings and establish their clinical implications more definitively.

Additionally, the decision to conduct follow-up assessments at 30 days may not have captured effects that necessitate longer observation periods. The observational nature of this study further limits the generalizability of its findings.

Conclusions

Our findings suggest that early hemodynamic responses to SGLT2i may differ across HF subtypes, with overweight/obese HFpEF patients showing a reduction in vascular resistance, while HFrEF/HFmrEF patients appear to primarily benefit from volume unloading. These preliminary observations align with the concept of HFpEF as a cardiometabolic disorder driven by vascular dysfunction and metabolic dysregulation, with overweight/obesity as a key contributing factor.

While our data indicate that SGLT2i therapy may be associated with improved vascular compliance and ventricular-arterial coupling, as reflected by reductions in TPR, the overall vascular impact of SGLT2i remains incompletely understood. Given the complex interplay between arterial stiffness, endothelial function, and disease progression in HFpEF, further investigation is warranted to confirm whether these hemodynamic benefits translate into sustained clinical improvements.

Additionally, the observed improvements in echocardiographic parameters—including reductions in LAVi and PASP—suggest a potential role for SGLT2i in favorable cardiac remodeling and enhanced right

Table 4 Difference between baseline and after 1 mo of treatment in HFrEF/HFmrEF patients

	Baseline	Follow-up	*p*-value
General characteristics			
Weight (kg)	68 [46-99.20]	66 [46.30–97]	**0.019**
SBP (mmHg)	125 [100–140]	110 [100–140]	0.318
DBP (mmHg)	69 [63–80]	68 [45–89]	0.498
HR (bpm)	67 [54–83]	61 [53–93]	0.777
6MWT (m)	420 [120–480]	435 [120–510]	0.193
Sat% O_2 at basal time	96 [94–100]	98 [95–100]	0.334
Sat% O_2 at 6 min	97 [88–99]	97.50 [94–99]	0.439
Biochemical parameters			
Hb (g/dL)	13.30 [9.90–15.50]	14.40 [10.40–15.40]	**0.040**
HCT (%)	40.80 [32.60–44.50]	40.80 [33.60–45.10]	0.424
Creatinine (mg/dL)	1.05 [1.00-1.46]	1.06 [0.97–1.53]	0.699
Azotemia (mg/dL)	49 [35–52]	44 [39–46]	0.945
eGFR (mL/min/1.73m^2),	59.30 [36–90]	67.50 [47-82.20]	0.361
NT-proBNP (pg/mL),	1759 [296–7287]	1326 [237–8927]	0.594
Fasting blood glucose (mg/dL)	94 [76–133]	92.50 [72–143]	0.895
Echocardiography parameters			
EDV (mL)	130 [86–240]	143 [85–236]	0.744
ESV (mL)	65.50 [44–193]	71.60 [44–169]	0.352
LVMi (g/m^2)	111 [76–158]	104 [56–202]	0.726
EF (%)	43.40 [19.60–49.60]	41 [22-53.40]	0.296
LVGLS (%)	10.20 [4.80–15.40]	10.20 [4.70–16.70]	0.570
E wave (cm/sec)	76.50 [37.20–111]	79 [33–109]	0.628
A wave (cm/sec)	79.10 [34.60–91.70]	74.40 [35.60–97.50]	0.502
E/A	0.80 [0.40–2.30]	0.80 [0.40–1.90]	0.740
Sept E'(cm/sec)	6.10 [3.10–10.60]	6.10 [3.26–8.10]	0.046
Lat E'(cm/sec)	7.14 [4.80–13.10]	7.20 [4.13–12.40]	0.428
E/E'	12.80 [4.50–18.80]	11.10 [5.30–21.50]	0.881
LAVi (ml/m^2)	45.50 [38-58.60]	41 [32-44.90]	**0.021**
PALS (%)	11.40 [4.60–22.80]	14.70 [5.50–22.30]	0.568
LACD(%)	6.40 [10.50–1.90]	7 [5.40–10.90]	0.739
LACT(%)	8.20 [1.40–19.20]	6.80 [0.80–16.80]	0.281
RAVi (ml/m^2)	23.20 [16.20–44.30]	20.20 [18–45]	0.431
RVLS free wall (%)	14.10 [7.2–23.50]	17.45 [9.70–29.80]	0.356
RVLS Global (%)	11.40 [5.80–18.10]	15.50 [7.50–22.80]	0.268
TAPSE (mm)	23 [21.30–24]	22.10 [11–26]	0.983
RV S' (cm/s)	13.10 [9.20–15.90]	11.20 [6.70–14]	0.157
peak TR vel (m/sec)	2.52 [1.76–2.76]	2.20 [1.44–2.53]	0.139
PASP (mmHg)	30 [23–38]	25 [15–33]	**0.013**
TAPSE/PASP (mm/mmHg)	0.85 [0.69–0.96]	0.76 [0.33–1.73]	0.255
NICaS parameters			
MAP (mmHg)	91 [76–96]	76 [63–104]	0.200
CI (l/min/m^2)	1.85 [1.46–2.85]	2.04 [1.42–2.75]	0.453
CO (l/min)	3.83 [2.54–4.48]	3.56 [2.87–5.37]	0.503
Stroke volume (ml)	57.17 [32.94–70.45]	61.21 [40.42–93.13]	0.539
Stroke volume index (ml/m^2)	28.21 [18.95–44.55]	31.09 [26.36–44.06]	0.695
CPi (w/m^2)	0.39 [0.23–0.58]	0.38 [0.24–0.62]	0.834
TPR (dn*s/cm^5)	1867 [1577–2475]	1893 [1259–2123]	0.191
TPRi (dn*s/cm^3)	3545 [2582–4611]	3112 [2660–4271]	0.147
GGI	8.80 [6.85–15.35]	10.60 [7.66–12.79]	0.507
RR (l/min)	18 [14–20]	17 [12–20]	0.396
TBW (kg)	50.63 [31.83-65]	42.13 [30.60-55.68]	**0.050**

Table 4 (continued)

	Baseline	Follow-up	*p*-value
General characteristics			
TBW (% weight)	66.33 [51.45–74.45]	58.68 [55.13–66.50]	**0.047**
Basal impedence (ohm)	321 [226–391]	386 [244–407]	**0.028**

Values are expressed as median [min-max] or n (%)

SPB– Systolic blood pressure; DPB– Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV– End-diastolic volume; ESV– End-systolic volume; EF– Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi- Left Ventricular Mass Index; LAVi– Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi– Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP–Pulmonary artery systolic pressure; TAPSE– Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

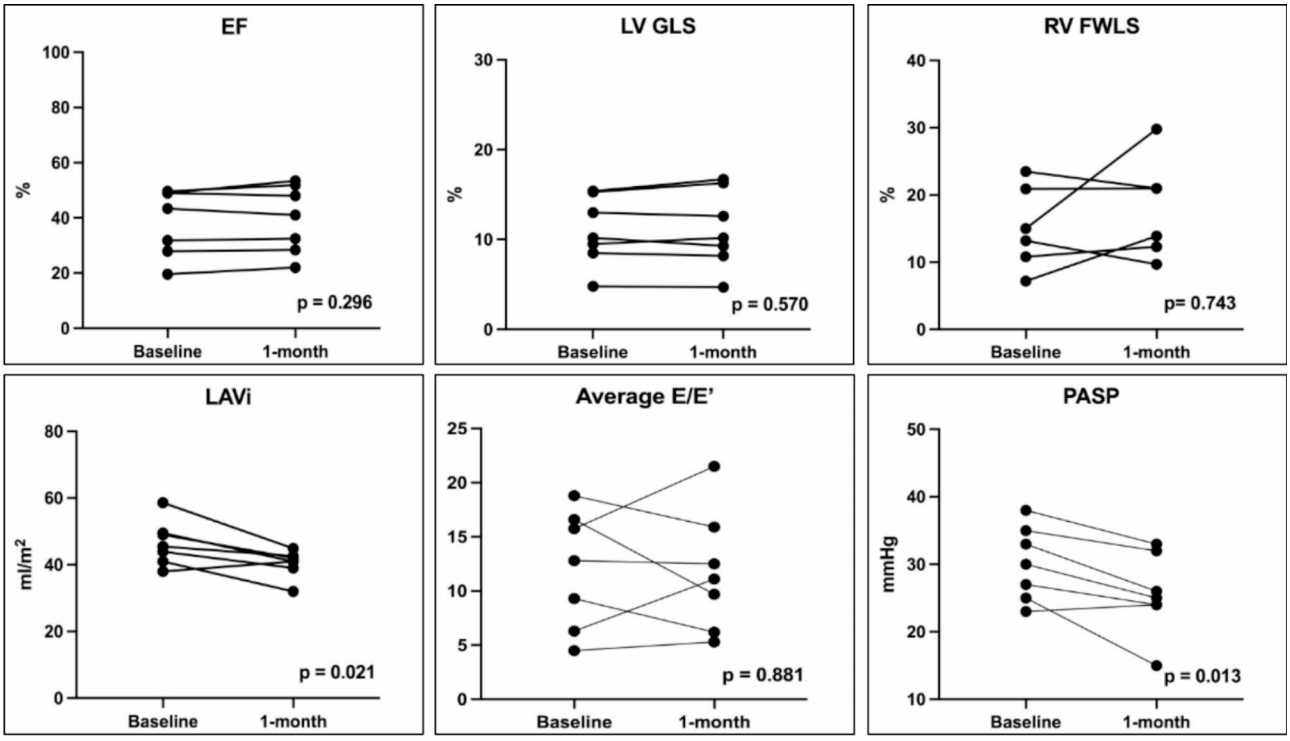

Fig. 1 Early echocardiographic effects of SGLT2i in HFrEF/HFmrEF patients

ventricular-pulmonary artery coupling. However, while these findings may indicate effects beyond simple fluid offloading, their mechanistic basis remains speculative and requires validation in larger, well-powered studies.

Overall, our results should be interpreted as hypothesis-generating, as they are derived from a relatively small cohort with limited generalizability. Future multicenter trials with larger sample sizes are essential to establish the robustness of these findings and determine their long-term clinical significance. Finally, non-invasive hemodynamic monitoring may offer valuable insights for precision-guided HF therapy, particularly in overweight/obese HFpEF patients, but further research is needed to refine its clinical utility.

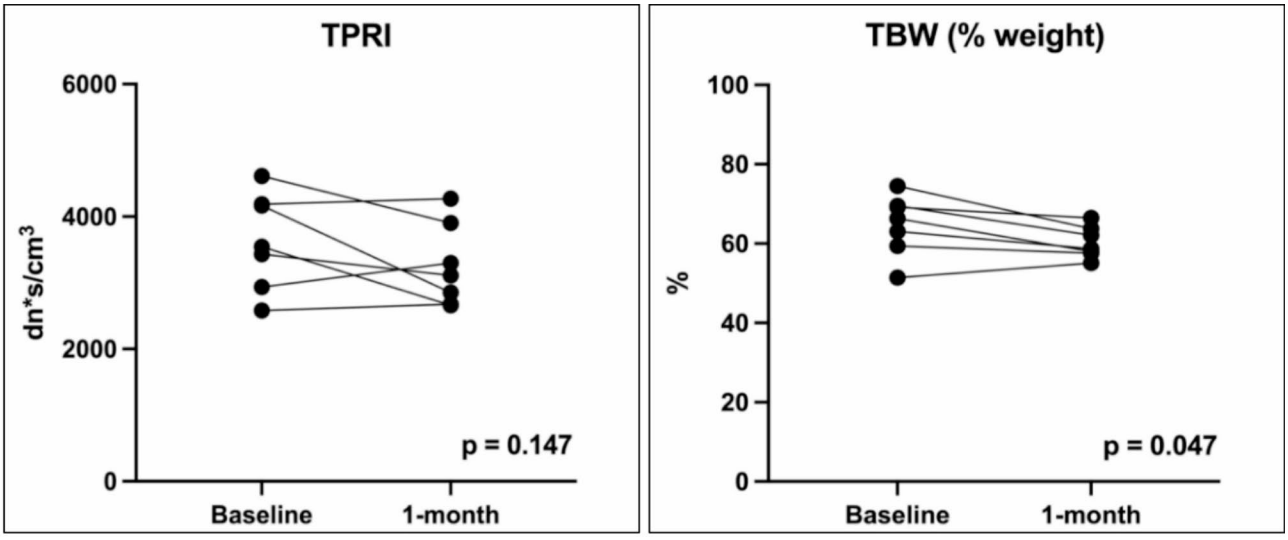

Fig. 2 Early hemodynamic effects of SGLT2i in HFrEF/HFmrEF patients

Table 5 Difference between baseline and after 1 mo of treatment in HFpEF patients

	Baseline	Follow-up	*p*-value
General characteristics			
Weight (kg)	67.30 [51-84.10]	65.50 [54–87]	0.122
SBP (mmHg)	135 [103–150]	120 [104–141]	**0.030**
DBP (mmHg)	70 [55–90]	72 [47–90]	0.101
HR (bpm)	61 [55–90]	66 [47–99]	0.170
6MWT (m)	390 [120–480]	335 [120–540]	0.438
Sat% O_2 at basal time	97 [95–100]	97 [94–100]	0.337
Sat% O_2 at 6 min	97 [95–98]	97 [94–99]	0.613
Biochemical parameters			
Hb (g/dL)	12.80 [9.60–14.60]	12.95 [9.70–15.40]	0.342
HCT (%)	39.80 [30.30–44.40]	40 [29.80–47.90]	0.517
Creatinine (mg/dL)	0.91 [0.75–2.04]	1.05 [0.77–1.68]	0.539
eGFR (mL/min/1.73m2)	64 [30-89.10]	55.40 [37.30–88.30]	0.125
NT-proBNP (pg/mL)	870 [231–6631]	384 [146.60–1803]	0.219
Fasting blood glucose (mg/dL)	88 [81–108]	88 [65–110]	0.837
Glycated hemoglobin (%)	6 [5.12–6.40]	5.80 [5.10–6.70]	0.742
Echocardiography parameters			
EDV (mL)	94.60 [62.60–155]	89.50 [60–150]	0.077
ESV (mL)	40.60 [26.60–71.30]	38.20 [26-77.90]	0.056
LVMi (g/m^2)	90.45 [52.50-121.50]	94.68 [53.43-123.39]	0.246
EF (%)	55.90 [51–60]	58 [51.90–62.80]	0.085
LVGLS (%)	18.70 [15.80–22.90]	18.25 [15-23.20]	0.946
E wave (cm/sec)	78.60 [47.20–130]	81.80 [43.50–121]	0.935
A wave (cm/sec)	87 [44.50–135]	78.90 [58.20–135]	0.811
E/A	0.80 [0.60–1.30]	0.75 [0.70–1.10]	0.090
Sept E'(cm/sec)	7.62 [5.33–17.70]	7.65 [12.60;5.55]	0.764
Lat E'(cm/sec)	8.95 [3.92–12.40]	9.14 [5.44–14.50]	0.758
E/E'	9.20 [6.30–17.60]	8.30 [5.40–17.90]	0.935
LAVi (ml/m^2)	41.37 [26.15-63]	40.32 [23.29–62.25]	**0.005**
PALS (%)	21.70 [8.10–46.50]	24 [4.30–60.50]	0.216
LACD(%)	10.50 [5-25.10]	11.70 [2.90–41.60]	0.535
LACT(%)	9.50 [0.60–21.40]	11.20 [1.60–21.60]	0.464
RAVi (ml/m^2)	20 [13–31]	21 [15–30]	0.758
RVLS free wall (%)	22.60 [11.60-27.74]	22.70 [15.9–30.60]	0.452
RVLS Global (%)	19.30 [10.30–22.90]	19.70 [11.30–27.70]	0.268
TAPSE (mm)	22 [18–28]	22 [20–28]	0.720
RV S' (cm/s)	12.60 [11.20–25]	12.60 [10-24.50]	0.518
peak TR vel (m/sec)	2.61 [1.30–3.20]	2.21 [1.67–2.92]	0.108
PASP (mmHg)	32 [15–40]	26 [16–38]	0.134
TAPSE/PASP (mm/mmHg)	0.73 [0.53–1.49]	0.87 [0.60–1.25]	0.154
NICaS parameters			
MAP (mmHg)	94 [74–109]	85 [68–106]	**0.046**
CI (l/min/m^2)	2.10 [1.53–3.70]	2.25 [1.32–3.68]	0.130
CO (l/min)	3.77 [2.59–5.47]	3.81 [2.14–5.58]	0.136
Stroke volume (ml)	54.96 [41.05–76.08]	56.20 [36.88–84.41]	0.424
Stroke volume index (ml/m^2)	32.82 [23.06–48.69]	31.86 [23.24–49.34]	0.359
CPi (w/m^2)	0.44 [0.29–0.61]	0.44 [0.20–0.60]	0.974
TPR (dn*s/cm^5)	2073 [1082–2767]	1676 [1061–2863]	**0.009**
TPRi (dn*s/cm^3)	3681 [1600–5024]	3085 [1608–4684]	**0.005**
GGI	9.30 [5.83–17.70]	9.65 [8-18.90]	0.164
RR (l/min)	16 [11–21]	16 [11–24]	0.628
TBW (kg)	40.80 [33.20–58.10]	41.86 [31.60–48.30]	0.524

Table 5 (continued)

	Baseline	Follow-up	*p*-value
General characteristics			
TBW (% weight)	62 [49.40–77.50]	60.10 [49.80-73.45]	0.957
Basal impedence (ohm)	311 [226–385;]	317 [283–410]	0.610

Values are expressed as median [min-max] or n (%)

SPB– Systolic blood pressure; DPB– Diastolic blood pressure; HR-Heart rate; 6MWT- 6-min walk test; Hb- Hemoglobin; HCT- hematocrit; eGFR- Estimated glomerular filtration rate; NT-pro-BNP- N-terminal pro b-type natriuretic peptide; EDV– End-diastolic volume; ESV– End-systolic volume; EF– Ejection fraction; LVGLS- left ventricular global longitudinal strain; LVMi- Left Ventricular Mass Index; LAVi– Left atrial volume index; PALS- Peak atrial longitudinal strain; LACD - Left atrial conduit strain; LACT - Left atrial contraction strain; RAVi– Right atrial volume index; RV- Right ventricle; RVLS- Right ventricle longitudinal strain; PASP–Pulmonary artery systolic pressure; TAPSE– Tricuspid annular plane systolic excursion; TR-Tricuspid regurgitation; MAP- Mean arterial pressure; CI- Cardiac index; CO- Cardiac output; CPi- Cardiac power index; TPR- Total peripheral resistance; TPRi- Total peripheral resistance index; GGI-Granov-Goor index; RR-Respiratory rate; TBW-Total body water

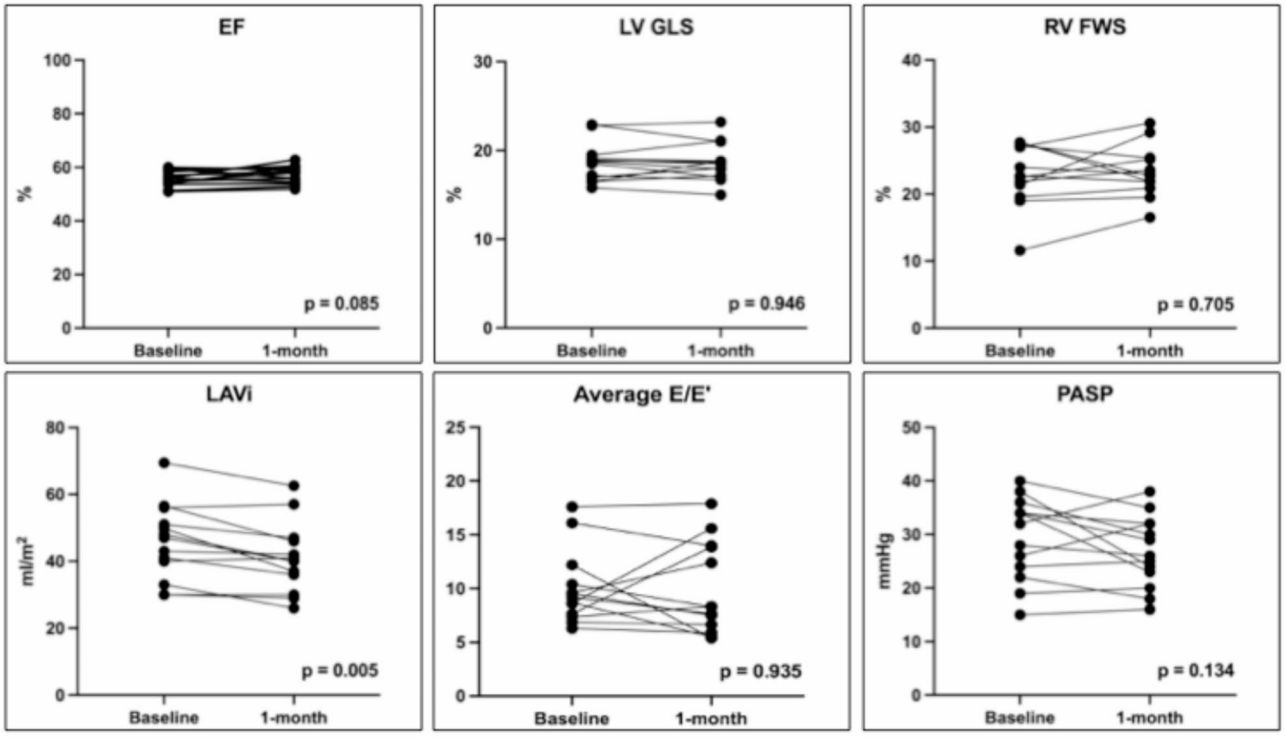

Fig. 3 Early echocardiographic effects of SGLT2i in HFpEF patients

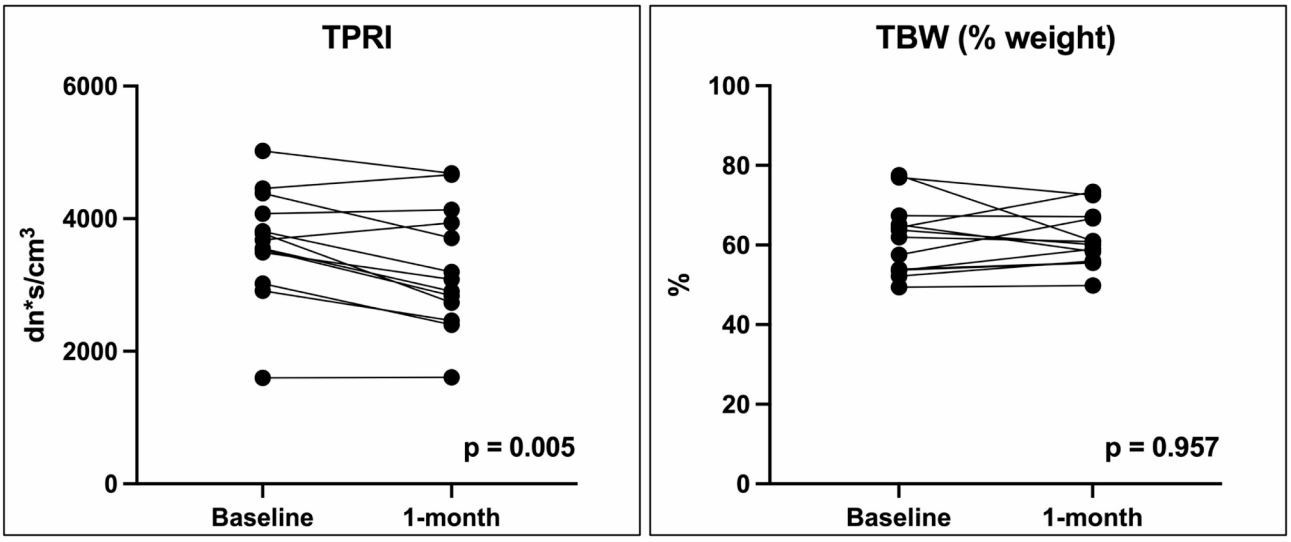

Fig. 4 Early hemodynamic effects of SGLT2i in HFpEF patients

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02699-4.

Supplementary Material 1

Author contributions

Nadia Salerno: Writing– review & editing, Writing– original draft, Funding acquisition, Data curation. Angela Sciacqua and Salvatore De Rosa: Supervision. Jessica Jelapi, Angelica Cersosismo, Isabella Leo, Assunta Di Costanzo, Giuseppe Armentaro: Formal analysis, Data curation. Daniele Torella,: Writing– review & editing, Writing– original draft, Funding acquisition, Conceptualization. Sabato Sorrentino: Writing– review & editing, Writing– original draft, Formal analysis, Data curation.

Funding

This work was supported by grants from the Italian Ministry of University and Research (PNRR—National Center for Gene Therapy and Drugs based on RNA Technology No. CN00000041) and from the Italian Ministry of Health (POS4 "Cal-Hub-Ria" No. T4-AN-09; PNRRMAD-2022-12376814). All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Availability of data and materials

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethics Committee (Protocol Register No. 170, May 30, 2024). All patients provided written informed consent before participating in the study.

Consent for publication

All authors listed above approved the manuscript for publication.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Experimental and Clinical Medicine, Magna Graecia University, 88100 Catanzaro, Italy
[2]Department of Medical and Surgical Sciences, Magna Graecia University, 88100 Catanzaro, Italy

Received: 18 February 2025 / Accepted: 20 March 2025
Published online: 26 March 2025

References

1. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovascular Res. 2023;118(17):3272–87.
2. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global public health burden of heart failure: an updated review. Card Fail Rev. 2023;9:e11.
3. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function. J Am Coll Cardiol. 2004;43(3):317–27.
4. Kapelios CJ, Shahim B, Lund LH, Savarese G, Epidemiology. Clinical characteristics and Cause-specific outcomes in heart failure with preserved ejection fraction. Card Fail Rev. 2023;9:e14.
5. Harper AR, Patel HC, Lyon AR. Heart failure with preserved ejection fraction. Clin Med (Lond). 2018;18(Suppl 2):s24–9.
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599–726.
7. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023;44(37):3627–39.
8. Mc Causland FR, Claggett BL, Vaduganathan M, Desai AS, Jhund P, De Boer RA, et al. Dapagliflozin and kidney outcomes in patients with heart failure with mildly reduced or preserved ejection fraction: A prespecified analysis of the DELIVER randomized clinical trial. JAMA Cardiol. 2023;8(1):56.
9. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–61.
10. Chen K, Nie Z, Shi R, Yu D, Wang Q, Shao F, et al. Time to benefit of Sodium-Glucose Cotransporter-2 inhibitors among patients with heart failure. JAMA Netw Open. 2023;6(8):e2330754.
11. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose Co-Transporter 2 (SGLT2) inhibitors: A State-of-the-Art review. JACC Basic Transl Sci. 2020;5(6):632–44.
12. Pastore MC, Stefanini A, Mandoli GE, Piu P, Diviggiano EE, Iuliano MA, et al. Dapagliflozin effects on cardiac deformation in heart failure and secondary clinical outcome. JACC: Cardiovasc Imaging. 2024;17(12):1399–408.
13. Cersosimo A, Salerno N, Sabatino J, Scatteia A, Bisaccia G, De Rosa S, et al. Underlying mechanisms and cardioprotective effects of SGLT2i and GLP-1Ra: insights from cardiovascular magnetic resonance. Cardiovasc Diabetol. 2024;23(1):94.
14. Wee CF, Teo YH, Teo YN, Syn NL, See RM, Leong S, et al. Effects of sodium/glucose cotransporter 2 (SGLT2) inhibitors on cardiac imaging parameters:

A systematic review and Meta-analysis of randomized controlled trials. J Cardiovasc Imaging. 2022;30(3):153.
15. Carluccio E, Biagioli P, Reboldi G, Mengoni A, Lauciello R, Zuchi C, et al. Left ventricular remodeling response to SGLT2 inhibitors in heart failure: an updated meta-analysis of randomized controlled studies. Cardiovasc Diabetol. 2023;22(1):235.
16. Fuerlinger A, Stockner A, Sedej S, Abdellatif M. Caloric restriction and its mimetics in heart failure with preserved ejection fraction: mechanisms and therapeutic potential. Cardiovasc Diabetol. 2025;24(1):21.
17. Hsu S, Fang JC, Borlaug BA. Hemodynamics for the heart failure clinician: A State-of-the-Art review. J Card Fail. 2022;28(1):133–48.
18. Manzi L, Sperandeo L, Forzano I, Castiello DS, Florimonte D, Paolillo R, et al. Contemporary evidence and practice on right heart catheterization in patients with acute or chronic heart failure. Diagnostics. 2024;14(2):136.
19. Al Younis SM, Hadjileontiadis LJ, Stefanini C, Khandoker AH. Non-invasive technologies for heart failure, systolic and diastolic dysfunction modeling: a scoping review. Front Bioeng Biotechnol. 2023;11:1261022.
20. Anshory M, Kuan WS, Rohman MS, Waranugraha Y, Kamila PA, Iskandar A, et al. Can non-invasive cardiac hemodynamics and fluid content system (NICaS) parameters predict acute heart failure outcomes in Caucasian and Asian patients in the emergency department? Adv Med Sci. 2024;69(1):81–9.
21. Voorrips SN, Saucedo-Orozco H, Sánchez-Aguilera PI, De Boer RA, Van der Meer P, Westenbrink BD. Could SGLT2 inhibitors improve exercise intolerance in chronic heart failure?? Int J Mol Sci. 2022;23(15):8631.
22. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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–e3914.
23. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr. 2016;29(4):277–314.
24. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American society of echocardiography. J Am Soc Echocardiogr. 2010;23(7):685–713.
25. Badano LP, Kolias TJ, Muraru D, Abraham TP, Aurigemma G, Edvardsen T, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry task force to standardize deformation imaging. Eur Heart J - Cardiovasc Imaging. 2018;19(6):591–600.
26. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry task force to standardize deformation imaging. Eur Heart J - Cardiovasc Imaging. 2015;16(1):1–11.
27. Cotter G, Moshkovitz Y, Kaluski E, Cohen AJ, Miller H, Goor D, et al. Accurate, noninvasive continuous monitoring of cardiac output by Whole-Body electrical bioimpedance. Chest. 2004;125(4):1431–40.
28. Cotter G, Schachner A, Sasson L, Dekel H, Moshkovitz Y. Impedance cardiography revisited. Physiol Meas. 2006;27(9):817–27.
29. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition. 1989;5(5):303–11. discussion 312–313.
30. Cohen AJ, Arnaudov D, Zabeeda D, Schultheis L, Lashinger J, Schachner A. Non-invasive measurement of cardiac output during coronary artery bypass grafting. Eur J Cardiothorac Surg. 1998;14(1):64–9.
31. Dixit NM, Ziaeian B, Fonarow GC. SGLT2 inhibitors in heart failure. Heart Fail Clin. 2022;18(4):587–96.
32. Thomas MC, Cherney DZI. The actions of SGLT2 inhibitors on metabolism, renal function and blood pressure. Diabetologia. 2018;61(10):2098–107.
33. Griffin M, Rao VS, Ivey-Miranda J, Fleming J, Mahoney D, Maulion C, et al. Empagliflozin Heart Failure: Diuret Cardiorenal Eff Circulation. 2020;142(11):1028–39.
34. Palmiero G, Cesaro A, Vetrano E, Pafundi PC, Galiero R, Caturano A, et al. Impact of SGLT2 inhibitors on heart failure: from pathophysiology to clinical effects. Int J Mol Sci. 2021;22(11):5863.
35. Scholtes RA, Muskiet MHA, Van Baar MJB, Hesp AC, Greasley PJ, Karlsson C, et al. Natriuretic effect of two weeks of Dapagliflozin treatment in patients with type 2 diabetes and preserved kidney function during standardized sodium intake: results of the DAPASALT trial. Diabetes Care. 2021;44(2):440–7.
36. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. Circulation. 2019;139(17):1985–7.
37. Lambers Heerspink HJ, De Zeeuw D, Wie L, Leslie B, List J. Dapagliflozin a glucose-regulating drug with diuretic properties in subjects with type 2 diabetes. Diabetes Obes Metabolism. 2013;15(9):853–62.
38. Nomoto H, Miyoshi H, Sugawara H, Ono K, Yanagiya S, Oita M, et al. A randomized controlled trial comparing the effects of Dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin. Diabetol Metab Syndr. 2017;9(1):54.
39. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.
40. Tang J, Ye L, Yan Q, Zhang X, Wang L. Effects of sodium-Glucose cotransporter 2 inhibitors on water and sodium metabolism. Front Pharmacol. 2022;13:800490.
41. Sano M. A new class of drugs for heart failure: SGLT2 inhibitors reduce sympathetic overactivity. J Cardiol. 2018;71(5):471–6.
42. Solini A, Giannini L, Seghieri M, Vitolo E, Taddei S, Ghiadoni L, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. Cardiovasc Diabetol. 2017;16(1):138.
43. Sezai A, Sekino H, Unosawa S, Taoka M, Osaka S, Tanaka M. Canagliflozin for Japanese patients with chronic heart failure and type II diabetes. Cardiovasc Diabetol. 2019;18(1):76.
44. Shigiyama F, Kumashiro N, Miyagi M, Ikehara K, Kanda E, Uchino H, et al. Effectiveness of Dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. Cardiovasc Diabetol. 2017;16(1):84.
45. Tanaka A, Shimabukuro M, Teragawa H, Okada Y, Takamura T, Taguchi I, Toyoda S, Tomiyama H, Ueda S, Higashi Y, Node K. EMBLEM investigators. Reduction of estimated fluid volumes following initiation of empagliflozin in patients with type 2 diabetes and cardiovascular disease: a secondary analysis of the placebo-controlled, randomized EMBLEM trial. Cardiovasc Diabetol. 2021;20(1):105.
46. Nakashima M, Miyoshi T, Ejiri K, Kihara H, Hata Y, Nagano T, et al. Effects of Luseogliflozin on estimated plasma volume in patients with heart failure with preserved ejection fraction. ESC Heart Fail. 2022;9(1):712–20.
47. Matsubayashi Y, Yoshida A, Suganami H, Oe M, Sato T, Yaguchi Y, et al. Association of estimated plasma volume and weight loss after long-term administration and subsequent discontinuation of the sodium-glucose cotransporter-2 inhibitor Tofogliflozin. Diabetes Obes Metab. 2021;23(7):1660–5.
48. Omar M, Jensen J, Burkhoff D, Frederiksen PH, Kistorp C, Videbæk L, et al. Effect of empagliflozin on blood volume redistribution in patients with chronic heart failure and reduced ejection fraction: an analysis from the empire HF randomized clinical trial. Circ Heart Fail. 2022;15(3):e009156.
49. Capone F, Vettor R, Schiattarella GG. Cardiometabolic HFpEF: NASH of the heart. Circulation. 2023;147(6):451–3.
50. Borlaug BA, Jensen MD, Kitzman DW, Lam CSP, Obokata M, Rider OJ. Obesity and heart failure with preserved ejection fraction: new insights and pathophysiological targets. Cardiovascular Res. 2023;118(18):3434–50.
51. Bogoviku J, Nguyen TD, Westphal JG, Aftanski P, Moebius-Winkler S, Haertel F, et al. Acute effects of empagliflozin on left atrial and ventricular filling parameters using echocardiography-a subanalysis of the EMPAG-HF trial. Eur Heart J Cardiovasc Pharmacother. 2025;11(2):190–7.

Publisher's note