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ORIGINAL RESEARCH

Dapagliflozin Effects on Cardiac Deformation in Heart Failure and Secondary Clinical Outcome

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ABSTRACT

BACKGROUND Sodium-glucose cotransporter 2 inhibitors were shown to reduce morbidity and mortality in patients with heart failure.

OBJECTIVES This study aims to assess potential effects of dapagliflozin in nondiabetic patients with heart failure with reduced ejection fraction (HFrEF) and heart failure with mildly reduced ejection fraction (HFmrEF) on cardiac function assessed by speckle tracking echocardiography (STE).

METHODS This randomized, prospective, single-center, open-label trial compared consecutive nondiabetic outpatients with HFrEF or HFmrEF receiving dapagliflozin with patients treated with optimal medical therapy (OMT) except sodium-glucose cotransporter type 2 inhibitors. Primary endpoint was the presence of a significant modification of left ventricular global longitudinal strain, diastolic function (as peak atrial longitudinal strain) and right ventricular function by STE from baseline to 6 months. Cardiovascular events and parameters of congestion were assessed as safety-exploratory endpoints.

RESULTS Overall, 88 patients (38% HFmrEF) were enrolled and randomized to start dapagliflozin on top of OMT (n = 44) or to continue with OMT (n = 44). All STE values improved in the dapagliflozin group after 6 months, whereas there was a nonsignificant improvement in OMT group. Moreover, when comparing the modification of STE parameters at follow-up in patients with HFrEF and HFmrEF, only the main treatment effect resulted statistically significant in both groups ($P < 0.0001$), indicating a significant difference between dapagliflozin and OMT.

CONCLUSIONS This study provided randomized data on the beneficial effect of dapagliflozin in nondiabetic patients with HFrEF and HFmrEF in terms of myocardial performance measured by the most sensitive echocardiographic technique, ie, STE. This suggests its usefulness for left ventricular reverse remodeling and better quality of life in patients with HFrEF and HFmrEF. (Effects of Dapagliflozin on cardiac deformation and clinical outcomes in heart failure with reduced and mildly reduced ejection fraction [DAPA ECHO trial]; EudraCT number: 2021-005394-66)
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

FWRVLS = free-wall right ventricular longitudinal strain

GLS = global longitudinal strain

HF = heart failure

HFmrEF = heart failure with mildly reduced ejection fraction

HFrEF = heart failure with reduced ejection fraction

LA = left atrial

LV = left ventricle

OMT = optimal medical therapy

PALS = peak atrial longitudinal strain

SGLT2i = sodium-glucose cotransporter type 2 inhibitor

STE = speckle tracking echocardiography

Sodium-glucose cotransporter 2 inhibitors (SGLT2is), among which dapagliflozin, have demonstrated an important role in the reduction of cardiovascular events in patients with heart failure (HF) with or without type 2 diabetes mellitus. In fact, these have been recommended by international guidelines for the treatment of patients with HF with level IA recommendation.[1-3] Indeed, in the DECLARE-TIMI-58[3] (Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events) and DAPA-HF[4] (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) randomized trials for dapagliflozin, SGLT2i showed improved survival, hospitalizations, and quality of life in both diabetic and nondiabetic patients with heart failure with reduced ejection fraction (HFrEF). Beyond the well-known metabolic effects, SGLT2is also have important natriuretic and osmotic diuretic effects, thus improving cardiac preload and afterload.[4-9] The recent DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) trial demonstrated that dapagliflozin reduced the risk of worsening HF or cardiovascular death also in patients with heart failure with mildly reduced ejection fraction (HFmrEF) or heart failure with preserved ejection fraction (HFpEF).[10]

Importantly, some studies have shown that SGLT2is could provide left ventricular (LV) reverse remodeling[11] and an improvement of systolic and diastolic function.[12-14] Most of these results are limited to HFrEF and mainly use basic echocardiographic parameters to explore cardiac improvement after therapy. Besides, few studies have been conducted to evaluate the positive effects of dapagliflozin using advanced echocardiographic techniques, such as speckle tracking echocardiography (STE), which emerged as a more accurate technique for the evaluation of systolic and diastolic function in different clinical scenarios, especially in HF, regardless of LV ejection fraction.[15-18] STE has already proved useful to assess early LV reverse remodeling after treatment with other drugs, such as sacubitril/valsartan, in patients with HFrEF.[19,20] In patients with diabetes mellitus, a considerable association between treatment with dapagliflozin and LV strain improvement has been proven.[21-23]

The present study aims to provide prospective and randomized data on the effects of dapagliflozin on top of optimal medical therapy (OMT) on myocardial function and geometry, assessed by STE, in nondiabetic patients with HFrEF and HFmrEF, compared with the previous standard of care.[24]

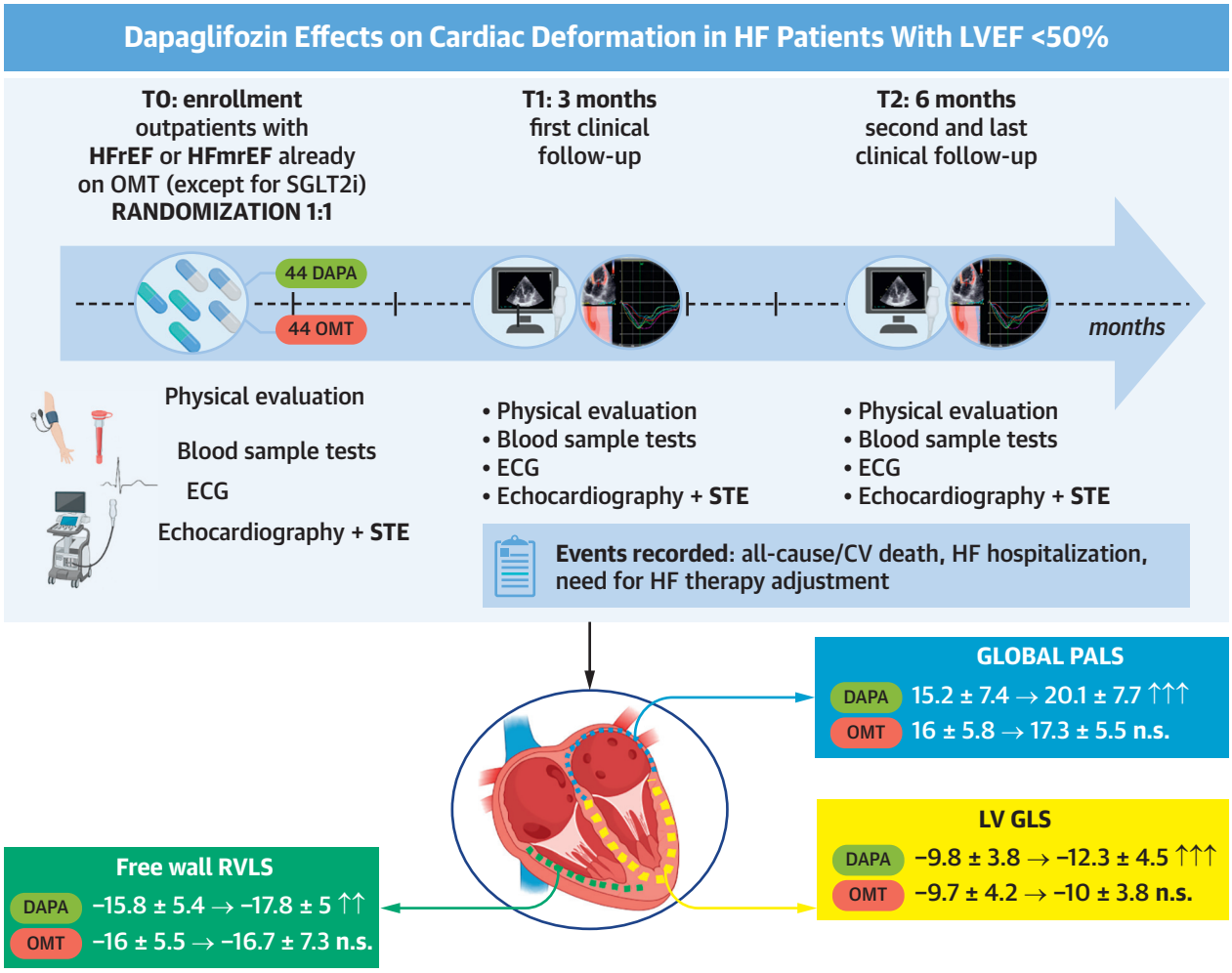
METHODS

STUDY POPULATION. This randomized, prospective, single-center, open-label trial (DAPA ECHO trial; EudraCT number: 2021-005394-66) compared nondiabetic patients with HFrEF or HFmrEF receiving dapagliflozin with patients treated with OMT, except for SGLT2i, according to the previous European Society of Cardiology HF guidelines (the trial was designed in 2020).[24] Thus, in this paper "OMT" will indicate a combination of an angiotensin-converting-enzyme inhibitor or an angiotensin receptor-neprilysin inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist, as tolerated. Patients underwent clinical, biohumoral, and echocardiographic evaluation at baseline, then, were randomized either to receive dapagliflozin 10 mg once daily on top of OMT or to continue OMT. After 3 months and 6 months from randomization, patients underwent a new clinical, biohumoral, and echocardiographic evaluation to assess the changes over time of all deriving data, with particular focus on STE (**Central Illustration**). Patients with stable OMT for at least 6 months before baseline evaluation were enrolled. Patients with missing data, atrial fibrillation at the time of enrollment, history of diabetes mellitus, or creatinine clearance <30 mL/min were excluded. For the complete list of exclusion criteria see Supplemental Methods 1.

Primary endpoint was the presence of a significant modification of LV global longitudinal strain (GLS), diastolic function (as left atrial [LA] reservoir strain or peak atrial longitudinal strain [PALS]) and right ventricular strain from baseline to 6 months. As safety endpoint, all-cause mortality, cardiovascular mortality, and hospitalizations for HF after 6 months of treatment with dapagliflozin were evaluated. As the exploratory endpoint, NYHA functional class and N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline and after 6 months as markers of HF symptoms and congestion[25] and need for therapeutic adjustment during follow-up were assessed.

All patients provided written informed consent. All study procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the Italian Medicines Agency (injunction number: EudraCT 2021-005394-66_SC 23851 PROT. 12240) and the Tuscany Region Local Ethic Committee for Clinical Trial-section south-west extended area (approval number: 21021, date: February 21, 2022).

CENTRAL ILLUSTRATION **Dapagliflozin Effects on Cardiac Deformation in Heart Failure With Ejection Fraction <50% and Secondary Clinical Outcome (DAPA ECHO trial)**



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Design of the trial and results of the primary outcome. CV = cardiovascular; DAPA = dapagliflozin; ECG = electrocardiogram; GLS = global longitudinal strain; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; PALS = peak atrial longitudinal strain; RVLS = right ventricular longitudinal strain; STE = speckle tracking echocardiography.

BASIC ECHOCARDIOGRAPHIC MEASURES. Echocardiography was performed using a fully equipped machine (Vivid E9, GE) in the left lateral decubitus position with a stable electrocardiographic tracing, by experienced operators. All parameters were measured according to the European Association of Cardiovascular Imaging/American Society of Echocardiography guidelines.[26] LV diameters and thickness were measured in left parasternal long-axis view; LV volumes and ejection fraction (using Simpson method), LA area and LA maximum volume (then indexed for body surface area), and right ventricular diameter in apical 4-chamber view. Maximum early diastolic (E) and late diastolic (A) velocities were assessed by transmitral pulsed-wave Doppler to calculate E/A ratio; then, early diastolic (e′) annular velocities were obtained by tissue Doppler imaging to calculate E/e′ ratio as index of the LV filling pressure. Tricuspid annular plane systolic excursion by M-mode and tricuspid s′ wave by tissue Doppler imaging were assessed as markers of right ventricular function. Systolic pulmonary artery pressure was

estimated as the sum of transtricuspid pressure peak systolic gradient and right atrial pressure derived from the diameter and collapsibility of the inferior vena cava. Valvular heart diseases were quantified by bidimensional (2D) echocardiography according to American Society of Echocardiography recommendations.[26]

SPECKLE TRACKING ECHOCARDIOGRAPHY. Dedicated views for LV, LA, and right ventricular STE, with a good visualization of all chambers and a reliable delineation of the endocardial border were acquired on 2D gray-scale echocardiography during 3 consecutive cardiac cycles with a frame rate of 40 to 80 frames per second and a stable electrocardiographic tracing. Then, off-line analysis was performed using the dedicated 2D strain software (Echopac, GE) by a single experienced and independent echocardiographer blinded to other data. The endocardial border was manually traced in apical views, delineating a region of interest (ROI) of 6 segments for each view. Then, necessary manual adjustments of the ROI were performed and the longitudinal strain curves for each segment were generated by the software. LV GLS was calculated as the average of apical 4, 2, and 3 chambers longitudinal strain curves.

LA reservoir strain ("Global PALS") and LA contraction strain (PACS) were calculated at the end of the reservoir and contraction phase, respectively, as the average of all LA segments in apical 4- and 2-chamber views, using QRS complex as the starting point.[27] Median values for LA reservoir strain in healthy individuals are reported as 47% in people 20-40 years old, 41% in people 40-60 years old, and 36% in people >60 years. Even though the lower limit of normality of LA reservoir strain is vendor and age-dependent, values <19%-23% are considered abnormally low.[28]

Global right ventricular longitudinal strain (RVLS) was calculated as average of all right ventricular segmental strain. Free-wall right ventricular longitudinal strain (FWRVLS) was derived by a ROI of 3 segments (basal, medial, apical) including only right ventricular free-wall. In patients in whom some segments were excluded for the lack of adequate tracking, strain was calculated by averaging values measured in the remaining segments. Intraoperator reproducibility was blindly tested in a random sample of 20 patients using an identical cine-loop for each view calculating intraclass correlation coefficient.

STATISTICAL ANALYSIS. Patients have been randomized to either the dapagliflozin or OMT group on information-technology basis using the method of block randomization with a block size of 4 to ensure a balanced allocation of patients to each treatment group while maintaining the ability to manage potential confounding variables effectively. A random number generator function has been adopted using the statistical software and simple randomization was organized at the level of blocks to obtain balanced treatment groups.

Data are expressed as means ± SD for continuous normal variables, median (IQR) (continuous non-normal variables), or as counts and percentages (binary variables). The Kolmogorov-Smirnov test was used to test parameters for normality.

Analysis per protocol was operated. Changes over time of all data in the overall study population were evaluated using paired-sample Student's *t*-test or Wilcoxon Signed Rank test. Patients were then divided into 2 groups: patients treated with dapagliflozin and with OMT. The differences between the 2 groups in clinical and echocardiographic parameters at baseline and during follow-up were analyzed using 2-way analysis of variance (ANOVA).

Subsequently, a linear mixed-effects model was used to analyze the changes over time of the echocardiographic and clinical parameters for the study endpoints as well as differences between patients treated with dapagliflozin vs OMT with a within-between subjects design (Supplemental Methods 2, Supplemental Table 2). The fixed effects in the linear mixed-effects model included treatment, time, age, gender, and their interactions. Treatment was a categorical variable with 2 levels: dapagliflozin and OMT. Time was a continuous variable measured at baseline (Y0), 3 months, and 6 months. Age and gender were used as stratification factors in the randomization process and included in the model to adjust for any potential confounding. The interactions of age and gender with time were also considered to investigate potential influence on the change in myocardial performance over time. The model also encompassed random effects to account for variability between subjects not explained by the fixed effects. Each subject was treated as a random effect, nested within their treatment groups. This approach captures within-subject correlation and myocardial performance variability over time, yielding a more precise estimate of treatment effects. Random effects were assumed to follow a normal distribution with a mean of zero and variance components to be estimated from the data.

Bonferroni correction was applied for post hoc analysis. A factorial 2-way ANOVA, considering "Treatment" and "Heart Failure (HF)" as factors, was used to study the effects of these 2 factors comparing variable changes over time in HFrEF and HFmrEF groups.

TABLE 1 General and Clinical Characteristics at Baseline of the Whole Study Population and of Patients in the Dapagliflozin Treatment Group and the OMT Treatment Group

	Overall (N = 88)	Dapagliflozin Treatment (n = 44)	OMT Treatment (n = 44)	*P* Value
Age, y	68 ± 13	68 ± 15	68 ± 12	0.99
Male	83 (73)	82 (36)	84 (37)	0.78
BMI	28 ± 5	26.5 ± 3	28 ± 6	0.60
BSA	1.95 ± 0.20	1.93 ± 0.20	1.97 ± 0,24	0.37
sBP, mm Hg	120 ± 15	119 ± 16	122 ± 15	0.32
dBP, mm Hg	72 ± 10	72 ± 11	72 ± 9	0.87
HR, beats/min	68 ± 12	68 ± 13	69 ± 11	0.83
NYHA functional class >II	47 (41)	48 (21)	45 (20)	0.07
Hypertension	71 (61)	72 (31)	70 (30)	0.52
Dyslipidemia	77 (68)	83 (35)	75 (33)	0.34
Current smoker	11 (10)	14 (6)	10 (4)	0.52
Paroxysmal AF	17 (15)	18 (8)	16 (7)	0.78
Coronary artery disease	35 (30)	30 (13)	41 (18)	0.27
Frailty index	0.231 ± 0.085	0.232 ± 0.079	0.230 ± 0.09	0.97
Intracardiac cardioverter defibrillator	31 (27)	30 (13)	32 (14)	0.69
Cardiac resynchronization therapy	15 (13)	14 (6)	16 (7)	0.82
Loop diuretic agents	73 (64)	79 (34)	68 (30)	0.25
Beta-blockers	77 (68)	72 (31)	84 (37)	0.18
ACEIs	28 (25)	36 (16)	21 (9)	0.10
ARNI	66 (58)	61 (26)	73 (32)	0.26
MRA	61 (54)	70 (30)	55 (24)	0.14
NT-proBNP, pg/L	845 (400-1,850)	858 (393-2,207)	822 (398-1,507)	0.72
Hemoglobin, g/dL	13.5 ± 1.6	13.7 ± 1.8	13.3 ± 1.5	0.27
eGFR, mL/min	68 (49-87)	67 (47-88)	68 (53-85)	0.70

Values are expressed as % (n), mean ± SD, or median (IQR).

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BSA = body surface area; dBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HR = heart rate; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-b-type natriuretic peptide; OMT = optimal medical therapy; sBP = systolic blood pressure.

Analyses were performed using the Statistical Package for Social Sciences software, release 20.0 (SPSS). Values of $P < 0.05$ were considered statistically significant.

RESULTS

BASELINE. The overall study population included 88 patients, of whom 44 (50%) were treated with dapagliflozin on top of OMT and 44 (50%) were treated with OMT. Clinical characteristics of the 2 study groups were homogeneous at baseline (Table 1).

Mean age was 68 ± 13 years, 83% were men (73 patients), 62% had HFrEF (55 patients, 28 in the dapagliflozin group and 27 in the OMT group), and 38% had HFmrEF (33 patients, 16 in the dapagliflozin group and 17 in the OMT group). There was no patient with previous atrioventricular node ablation. All patients with cardiac resynchronization therapy had biventricular pacing >95%.

As for echocardiographic parameters at baseline (Table 2), the study population showed LA enlargement (left atrial volume index [LAVI] = 51 ± 19 mL/m^2) and moderate LV dysfunction as evidenced by a mean LV ejection fraction = 37% ± 10% and diastolic dysfunction (average E /e′ = 12 ± 5). Right ventricular dimensions and longitudinal function were nearly normal (right ventricular end-diastolic mean diameter = 31 ± 5 mm, tricuspid annular plane systolic excursion = 19 ± 4 mm).

Regarding STE parameters, patients showed a reduction both of LV and LA strain: mean LV GLS was −9.7% ± 4%, mean global PALS was 15.6% ± 6.6% and mean global PACS was 10.4% ± 7.4%. Right ventricular strain was reduced: FWRVLS = −15.9% ± 5.4% and global right ventricular strain = −13.5% ± 4.7%. Differences between the 2 groups for echocardiographic parameters at baseline are shown in Supplemental Table 1. Intraoperator reproducibility was excellent for all STE variables: intraclass correlation coefficient = 0.99 (IQR: 0.99-0.99) for LV GLS, 0.98 (IQR: 0.97-0.99) for global PALS, 0.96 (IQR: 0.94-0.98) for FWRVLS, 0.95 (IQR: 0.93-0.96) for global right ventricular strain.

TABLE 2 Echocardiographic Characteristics of the Study Population Divided Into Dapagliflozin Group and OMT Group After 6 Months of Treatment and Mean Difference Between Parameters at Baseline and After 6 Months of Treatment (N = 88)

	Overall Baseline		Overall 6 Mo		Difference Between Baseline and After 6 Mo of Treatment			
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	Dapagliflozin Treatment	*P* Value	OMT Treatment	*P* Value
LVEDVi, mL/m^2	85 ± 37	75 (55-106)	84 ± 28	79 (60.5-102.1)	−0.8 (−8.5 to 6.8)	0.83	−0.02 (−7.4 to 7.4)	1.00
LVESVi, mL/m^2	55 ± 31	45 (31-76)	55 ± 34	46 (32.8-77.2)	− 0.8 (−6 to 6.1)	0.79	−0.05 (−6.0 to 6.1)	0.99
LVEF, %	37 ± 10	45 (31-76)	38 ± 12	40 (31.5-45.1)	1.2 (−1.6 to 4.0)	0.38	0.4 (−1.9 to 2.8)	0.71
LAVi, mL/m^2	51 ± 19	49 (39-61)	49 ± 19	47 (34.6-58.3)	−1 (−4.0 to 1.9)	0.49	−2.0 (−5.0 to 2.6)	0.7
E, m/s	0.7 ± 0.3	0.6 (0.5-0.9)	0.69 ± 0.26	0.62 (0.49-0.88)	−0.05 (−0.11 to 0.001)	**0.045**	0.03 (−0.03 to 0.09)	0.28
E′ avg, m/s	0.06 ± 0.02	0.06 (0.05-0.08)	0.08 ± 0.01	0.07 (0.06-0.09)	0.008 (−0.004 to 0.001)	**0.039**	−0.001 (−0.007 to 0.004)	0.68
E/e′ mean	12 ±5	10 (8 ± 15)	11 ± 5	9 (7.6-13)	− 1.7 (−3.2 to 0.25)	**0.022**	0.6 (−0.91 to 2.09)	0.43
TAPSE, mm	19 ± 4	19 (17-22)	19 ± 4	19 (17-22)	−1 (−2.0 to 0)	0.055	0.2 (−1.1 to 0.8)	0.7
sPAP, mm Hg	33 ± 11	30 (25-37)	30 ± 9	30 (25-35)	− 2.9 (−7.3 to 1.5)	0.18	−0.6 (−2.5 to 0.3)	0.27
Global PALS, %	16 ± 7	17 (10-21)	18.8 ± 7.0	20.5 (14-25)	5.12 (3.5 to 6.7)	**<0.001**	1.1 (−0.4 to 2.6)	0.14
Global PACS, %	10 ± 7	9 (5-15)	10.8 ± 5.7	11 (7-17)	1.6 (0.5 to 2.6)	**0.002**	1.0 (−2.7 to 1.9)	0.75
LV GLS, %	−10 ± 4	−10 (−12 to −7)	−11.1 ± 4.1	−11 (−14.3 to −7.8)	−2.5 (−1.8 to −0.4)	**<0.001**	−0.3 (−1.2 to 0.7)	0.53
FWRVLS, %	−16 ± 5	−16 (−20 to −11)	−17.6 ± 6.1	−17.9 (−22 to −12.5)	−2.3 (−4 to −0.8)	**0.005**	−0.7 (−2.7 to 1.3)	0.46
GRVLS, %	−13.4 ± 5	−13.8 (−16.7 to −10)	−14.0 ± 4.8	−13 (−16.4 to −9.8)	−1 (−2.6 to −0.7)	**0.023**	−0.07 (−1.5 to 1.4)	0.92

Values are expressed as mean ± SD or median (IQR). **Bold** indicates statistically significant *P* values.

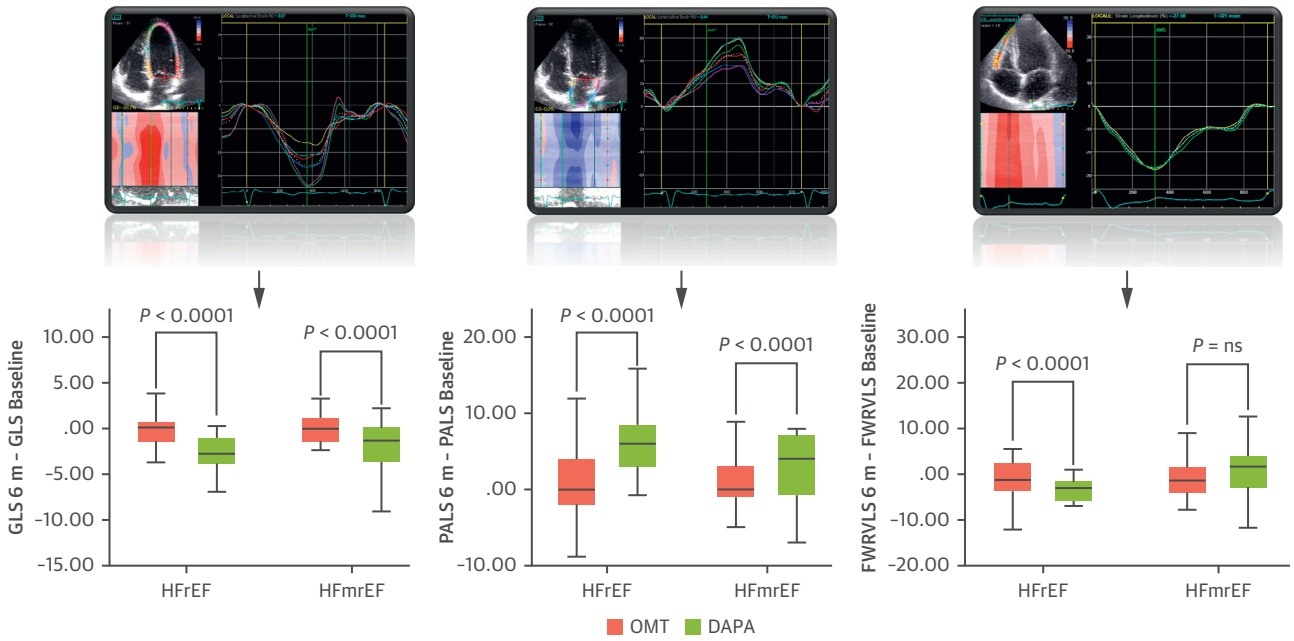
E/e′ mean = early diastolic wave by pulsed-wave Doppler/average early diastolic wave by tissue Doppler imaging in the 3 points of mitral annulus descent; GLS = global longitudinal strain; LA = left atrial; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; PACS = peak atrial contraction strain; PALS = peak atrial longitudinal strain; sPAP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

FOLLOW-UP. Clinical variables did not show significant variation at follow-up in the 2 groups (systolic and diastolic blood pressure at follow-up were 115 ± 14 vs 119 ± 16 mm Hg at baseline; P = 0.14 and 72 ± 9 vs 72 ± 11 mm Hg; P = 0.71 in the dapagliflozin group; 121 ± 16 mm Hg vs 122 ± 15 mm Hg; P = 0.6 and 70 ± 9 mm Hg vs 72 ± 9 mm Hg; P = 0.38 in the OMT group), although a slight improvement of NYHA functional class and N-terminal pro-b-type natriuretic peptide was registered in both groups (−7% NYHA functional class >II in the dapagliflozin group and −2% in the OMT group; NT-proBNP mean difference: −560 [IQR: −1,923 to 801] in the dapagliflozin group vs −90 pg/L [IQR: −399 to 580 pg/L] in the OMT group). Echocardiographic parameters of the 2 study groups at follow-up and their mean changes after 6 months of dapagliflozin or OMT are reported in Table 2. All variables showed an improvement in both study groups; however, the changes were higher in the dapagliflozin group than in the OMT group, in which did not reach statistical significance. There was a significant improvement of LV diastolic function in both groups, whereas both LV and LA volumes showed a trend toward reduction without reaching statistical significance.

As for the primary endpoint, all STE values significantly improved in the dapagliflozin group at the 6-month follow-up (and the improvement was already appreciable at the 3-months follow-up), whereas there was only a slight and nonsignificant improvement in the OMT group (Figure 1, Table 2).

In our cohort, the interaction Treatment by Time was able to explain the variability in the change from baseline. The dapagliflozin group had a LV GLS significant and independent change from baseline and a mean value at follow-up significantly better compared with the OMT group (−2.54 [95% CI: −1.8 to −0.4] vs −0.3 [95% CI: −1.2 to −0.7]), regardless of age, weight, or baseline values. Of interest, with a factorial 2-way ANOVA test conducted to compare the main effects of treatment and HF and their interaction effect on the change from baseline, when comparing the modification of GLS at follow-up in HFrEF and HFmrEF patients (Figure 1), only the main effect treatment was statistically significant in both groups (P < 0.0001), indicating a significant difference between dapagliflozin and OMT (mean difference = −2.8 ± 1.9 vs −0.4 ± 3.7 in HFrEF and −2 ± 3.3 vs −0.2 ± 2.2 in HFmrEF). The same effect was even more evident for global PALS (mean difference = 5.9 ± 4.4 vs mean = −0.8, SD = 5.1 in HFrEF and 3.2 ± 6.6 vs 1.5 ± 4.9 in HFmrEF), while in FWRVLS no significant differences between dapagliflozin and OMT were detected in patients with HFmrEF (mean difference = −3.8 ± 2.4 vs 0.6 ± 7.2 in HFrEF and −0.8 ± 7.7 vs 0.8 ± 5.7 in HFmrEF) (Figure 1). No significant difference was found between the mean differences of LV GLS and global PALS in HFrEF and HFmrEF either in the dapagliflozin or in the OMT group.

FIGURE 1 Myocardial Deformation After Treatment With Dapagliflozin in Patients With HFrEF and HFmrEF



Boxplot of the change-from-baseline response (left: left ventricular global longitudinal strain [GLS]; center: global peak atrial longitudinal strain [PALS]; right: free-wall right ventricular longitudinal strain [FWRVLS]) measured across classes of heart failure and treatment. HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure with reduced ejection fraction.

SAFETY AND EXPLORATORY ENDPOINTS. Overall, after 3 and 6 months of follow-up, cardiovascular deaths were not reported, whereas at 6 months, 1% of patients died of noncardiovascular causes; moreover, only 1 hospitalization for HF (1% of patients) and no episodes of ventricular arrhythmias were reported.

Regarding exploratory outcome, NYHA functional class improved after treatment in both groups; however, the change was 3 times higher for patients treated with dapagliflozin than OMT (7% vs 2%). Finally, 15% (n = 13) of patients needed therapeutic adjustment for worsening HF symptoms during follow-up (4 patients in the dapagliflozin group, 9 in the OMT group). No patients needed adjustment of pacing parameters.

DISCUSSION

To date, this is the first study to assess the effects of dapagliflozin on myocardial deformation assessed by STE in nondiabetic patients with LV ejection fraction <50%. The present trial provides randomized data suggesting 2 main findings: 1) the use of dapagliflozin on top of OMT provides early improvement in cardiac functional remodeling on the LV, LA, and right ventricle leading to amelioration of cardiac systolic and diastolic function compared with OMT alone in nondiabetic patients with both HFrEF and HFmrEF; and 2) STE variables showed significant improvement after therapy in patients with HFrEF and HFmrEF, compared with baseline echocardiographic parameters, allowing an early recognition of response to therapy. In fact, STE provides a noninvasive, quick, highly available and low-cost evaluation of myocardial structure and performance, with comparable accuracy to that of second-level imaging techniques such as cardiac magnetic resonance.[29]

Importantly, our results confirm the role attributed to this drug for remodeling and suggest a similar role in patients with HFmrEF. The reason why, unlike STE values, the echocardiographic measures of LV and LA volumes and LV ejection fraction showed a slight improvement without reaching statistical significance, may be explained by the fact that the modification of strain values precedes that of basic echocardiographic parameters as it is able to detect ultrastructural changes of the myocardium. This is in accordance with previous studies[19,20] and strengthens the importance of STE not only for diagnosis, but also to monitor response to therapy.

In diabetic patients, a considerable correlation between treatment with dapagliflozin and LV strain improvement has already been proven: Tanaka et al[22] showed the association between dapagliflozin and the improvement of GLS, leading to further improvement of LV diastolic function of diabetic patients with stable HF. Brown et al[23] also demonstrated in a randomized controlled trial that dapagliflozin treatment significantly improved GLS in 29 patients with diabetes mellitus and LV hypertrophy. However, they did not analyze nondiabetic patients with HFrEF or HFmrEF.

Also, some studies have suggested some positive effects of SGLT2i on LV reverse remodeling: the DAPA MODA (Impact of Atrial Remodeling of Dapagliflozin in Patients With Heart Failure) study demonstrated in patients with chronic HF and optimized therapy that dapagliflozin administration results in global reverse remodeling (including reductions in LA volumes and improvement in LV geometry).[14] Moreover, in the DACAMI (Impact of Dapagliflozin on Cardiac Function following in Non-Diabetic Patients) trial, nondiabetic patients who presented with myocardial infarction and LVEF <50% were treated with dapagliflozin and showed a significant reduction in NT-proBNP level and in LV mass index compared with placebo, adding further data on the capability of this drug to improve cardiac function.[29] However, this study was focused on a selected cohort of patients with acute coronary syndromes and advanced echocardiographic parameters were not used to investigate LV remodeling. In previous studies, LV GLS has emerged as a good predictor of early LV reverse remodeling, probably caused by its correlation with the extent of myocardial fibrosis.[30] In our study, GLS improvement was significantly higher in patients treated with dapagliflozin in addition to OMT for 6 months, both in patients with HFrEF and HFmrEF. This suggests the potential role of this drug to achieve LV reverse remodeling in HF beyond ejection fraction, with possible improvement of LV function leading to better clinical outcome and lower risk of future events.

This improvement may be a result not only of SGTL2i favorable effects on left heart functional remodeling, but also of their natriuretic and osmotic diuretic effect, which reflects on the reduction of cardiac preload and afterload and consequently on an improvement of myocardial deformation parameters, which are load sensitive.

Global PALS has affirmed its role as an index of LV filling pressures and diastolic function; in fact, it was integrated in the diagnostic algorithm for HFpEF by the European Association of Cardiovascular Imaging.[31,32] In addition, it has shown a strong negative correlation with NYHA functional class[33] and NT-proBNP in acute and chronic HF.[34]

In patients with HF and loop diuretic resistance, dapagliflozin showed effects at relieving congestion comparable to metolazone, with analogous changes in pulmonary congestion and volume assessment score.[35] Thiele et al[36] highlighted that SGLT2i significantly improved LA reservoir and contraction strain after 3 months of treatment, compared with placebo, in patients with type 2 diabetes mellitus.

In our study, treatment with dapagliflozin resulted in an improvement of global PALS significantly higher than with OMT at 6 months' treatment follow-up. This finding, associated with a significant reduction in E/e′ mean, systolic pulmonary artery pressure and NT-proBNP (even if not statistically significant) highlights an improvement in congestive state in the dapagliflozin group without any significant effect on reduction in systolic and diastolic blood pressure, both in HFrEF and HFmrEF patients. In fact, SGLT2i has been shown to modulate several inflammatory pathways by reducing the level of circulating cytokines, oxidative stress, and fibrosis, which are a known pathological element in diastolic dysfunction and HFpEF.[8]

Compared with LV GLS, the higher beneficial effect shown for global PALS in patients treated with dapagliflozin in HFrEF than in HFmrEF confirms the hypothesis that this may be the most accurate STE parameter to evaluate the effect of treatment as improvement of congestive state, regardless of LV ejection fraction. In fact, the LA may be primarily affected by tissue alterations with myocyte apoptosis and fibrosis, also called "intrinsic atrial myopathy," independently of the degree of LV dysfunction. Moreover, the reduction of LA function is influenced by LV compliance, which mainly expresses LV diastolic function rather than systolic function.[37] In fact, many authors have shown that LA strain is a predictor of LV filling pressures, prognosis, and functional capacity in HF independent from ejection fraction.[38-41]

All this given, this study confirmed the importance of the use of dapagliflozin for the treatment of nondiabetic patients with HFrEF and strengthens its role for the treatment of nondiabetic patients with HFmrEF, because an early improvement of myocardial structure and function is evident also with more sensitive and advanced echocardiographic parameters compared with OMT without SGLT2i, which reflects also on better clinical outcome. Moreover, it suggests the use of STE as an additional method in routine clinical practice for the optimization of treatment of these patients.

STUDY LIMITATIONS. This study has some limitations: first, the small number of patients considered, which implies that bigger prospective studies are needed to confirm our analysis. Moreover, this is a single-center study characterized by an open-label design; however, the patients underwent randomization before starting treatment and the primary endpoint consisted of changes of echocardiographic measures over time, which could not be influenced by this design. Then, although we included patients with stable therapy for 6 months before enrollment and we registered therapeutic adjustments as an exploratory endpoint, a small percentage of bias could have been generated by a concomitant titration of angiotensin receptor-neprilysin inhibitor therapy in those patients who required therapeutic adjustment (only 4 in the dapagliflozin group). Last, the dependence of STE on image quality and correct acquisition should be considered, although a high feasibility has been demonstrated in many studies.[27,42]

CONCLUSIONS

This single-center, prospective study provided randomized data on the early beneficial effect of dapagliflozin on myocardial deformation assessed by STE in nondiabetic patients with HFrEF and HFmrEF, suggesting its value to enhance left heart functional remodeling and diastolic function in these patients, leading to an improvement of congestive state and symptoms. These data provide further evidence about the utility of dapagliflozin in nondiabetic patients with HF (importantly, HFmrEF as well), to ameliorate their outcome and quality of life, and suggest the increasing use of STE not only for diagnosis, but also for assessing the response to treatment in HF patients.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: The results of this trial offer information to enhance clinical and medical competencies for ambulatory care and lifelong treatment of HF and also diagnostic competencies, particularly echocardiography, suggesting the additional use of advanced echocardiography to guide HF therapy.

TRANSLATIONAL OUTLOOK: The DAPA ECHO trial provides further evidence suggesting the use of dapagliflozin in nondiabetic patients with HFrEF and HFmrEF, due to its proven benefits on myocardial systolic and diastolic function detected by high-sensitive indices. Moreover, it provides randomized data about the important role of STE not only for diagnosis, but also for monitoring the response to treatment in patients with HF. Bigger studies are warranted to confirm our analysis.

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APPENDIX For an expanded Methods section as well as supplemental figures, please see the online version of this paper.