ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 1352–1360
doi:10.1002/ejhf.2884

RESEARCH ARTICLE

Impact of dapagliflozin on cardiac remodelling in patients with chronic heart failure: The DAPA-MODA study

Domingo A. Pascual-Figal[1,2,3,4]*, J. Luis Zamorano[4,5], Mar Domingo[6], Herminio Morillas[7], Julio Nuñez[4,8], Marta Cobo Marcos[4,9], Alejandro Riquelme-Pérez[2,4], Albert Teis[6], Enrique Santas[8], Cesar Caro-Martinez[1], Jose Manuel Pinilla[10], Jose F. Rodriguez-Palomares[4,11], David Dobarro[4,12], M. Alejandra Restrepo-Córdoba[13], J. Ramón González-Juanatey[4,14], and Antoni Bayés Genís[4,6], on behalf of DAPA-MODA Study Investigators

[1]Cardiology Department, Hospital Clínico Universitario Virgen de la Arrixaca, Instituto IMIB-Pascual Parrilla, Murcia, Spain; [2]Medicine Department, Universidad de Murcia, Murcia, Spain; [3]Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC), Madrid, Spain; [4]Centro de Investigación Biomédica en Red, CIBERCV, Madrid, Spain; [5]Cardiology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [6]Cardiology Department, Hospital Universitari Germans Trias i Pujol. l'Institut del Cor, Badalona, Spain; [7]Cardiology Department, Hospital de Dénia-MarinaSalud, Denia, Spain; [8]Cardiology Department, Hospital Clínico Universitario de Valencia, Valencia, Spain; [9]Cardiology Department, Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [10]Cardiology Department, Hospital Universitario Virgen de la Victoria, Málaga, Spain; [11]Cardiology Department, Hospital Universitario Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain; [12]Cardiology Department, Hospital Álvaro Cunqueiro, IIS Galicia Sur, Vigo, Spain; [13]Cardiology Department, Hospital Clínico San Carlos, Madrid, Spain; and [14]Cardiology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain

Received 26 April 2023; revised 4 May 2023; accepted 8 May 2023; online publish-ahead-of-print 7 June 2023

Aims

Dapagliflozin improves the prognosis of patients with heart failure (HF), regardless of left ventricular ejection fraction (LVEF). However, its effect on cardiac remodelling parameters, specifically left atrial (LA) remodelling, is not well established.

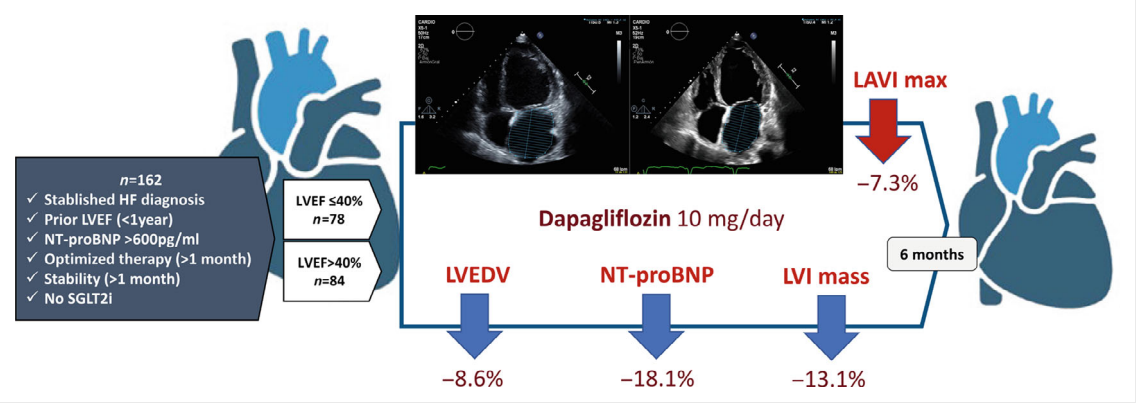
Methods and results

The DAPA-MODA trial (NCT04707352) is a multicentre, single-arm, open-label, prospective and interventional study that aimed to evaluate the effect of dapagliflozin on cardiac remodelling parameters over 6 months. Patients with stable chronic HF receiving optimized guideline-directed therapy, except for any sodium–glucose cotransporter 2 inhibitor, were included. Echocardiography was performed at baseline, 30 and 180 days, and analysed by a central core-lab in a blinded manner to both patient and time. The primary endpoint was the change in maximal LA volume index (LAVI). A total of 162 patients (64.2% men, 70.5 ± 10.6 years, 52% LVEF >40%) were included in the study. At baseline, LA dilatation was observed (LAVI 48.1 ± 22.6 ml/m^2) and LA parameters were similar between LVEF-based phenotypes (≤40% vs. >40%). LAVI showed a significant reduction at 180 days (−6.6% [95% confidence interval −11.1, −1.8], $p = 0.008$), primarily due to a decrease in reservoir volume (−13.8% [95% confidence interval −22.5, −4], $p = 0.007$). Left ventricular geometry improved with significant reductions in left ventricular mass index (−13.9% [95% confidence interval −18.7, −8.7], $p < 0.001$), end-diastolic volume (−8.0% [95% confidence interval −11.6, −4.2], $p < 0.001$) and end-systolic volume (−11.9% [95% confidence interval −16.7, −6.8], $p < 0.001$) at 180 days. N-terminal pro-B-type natriuretic peptide (NT-proBNP) showed a significant reduction at 180 days (−18.2% [95% confidence interval −27.1, −8.2], $p < 0.001$), without changes in filling Doppler measures.

*Corresponding author. Cardiology Department, University of Murcia, LAIB, Room 2.52, Av. Buenavista s/n, 30120 Murcia, Spain. Tel: +34 868 888163, Email: dpascual@um.es
Listed in online supplementary *Appendix S2*.

Conclusion Dapagliflozin administration in stable out-setting patients with chronic HF and optimized therapy results in global reverse remodelling of cardiac structure, including reductions in LA volumes and improvement in left ventricular geometry and NT-proBNP concentrations.

Graphical Abstract



Schematic representation of main findings of DAPA MODA: administration of dapagliflozin over 6 months in stable patients, with chronic heart failure and optimized therapy, was associated with cardiac reverse remodelling, including reductions in left atrial volume, left ventricular mass and dimensions, and NT-proBNP levels. LAVI, left atrial volume index; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVI, left ventricular indexed; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Keywords Heart failure • Left atrium • Remodelling • Biomarkers • Dapagliflozin

Introduction

Dapagliflozin reduces the risk of *de novo* heart failure (HF) in diabetics, and it has shown to improve the prognosis of patients with HF across all ranges of left ventricular ejection fraction (LVEF), by preventing HF decompensations and cardiovascular death.[1] The beneficial effects of dapagliflozin on HF are independent of diabetes status and glycaemic control. This raises the question of what other mechanisms underlie these effects beyond sodium–glucose cotransporter 2 (SGLT2) inhibition. The effect of SGLT2 inhibitors on cardiac remodelling evaluated by imaging and related biomarkers remains uncertain, with scarcity of studies in HF patients and contradictory results mainly focused on patients with diabetes and reduced LVEF.[2–8] Indeed, no data exist supporting a direct effect of dapagliflozin on cardiac geometry, function and biomarkers in presence of HF, irrespective of LVEF.

Adverse myocardial remodelling affecting the left ventricle is a key factor in the progression of HF and current well-established HF phenotypes are based on LVEF. However, other relevant players have received less attention, such as the left atrium. Indeed, the left atrium plays a critical role in cardiac function, particularly in left ventricular (LV) filling during diastole. Additionally, atrial dysfunction can directly lead to pulmonary congestion. Left atrial (LA) remodelling occurs in HF irrespective of the degree of LV systolic dysfunction, and can be observed in the presence of preserved or reduced LVEF.[9–12] The geometry of the left atrium is a predictor for the development of HF in high-risk patients,[9] and has been consistently linked to higher rates of hospitalization and death in patients with HF.[13–19] As a result, atrial disease has become an important concept that has been highlighted in the most recent guidelines for HF from the European Society of Cardiology (ESC).[20] However, there are lacking data about the impact of therapies on reversing LA remodelling and, specifically, no data are available about SGLT2 inhibitors. In addition, improvement in imaging techniques represents an additional opportunity to better understand the role of LA reverse remodelling as a therapeutic target irrespective of LVEF.[10,11,17] The aim of this study was to investigate the impact of dapagliflozin on cardiac remodelling parameters, specifically LA remodelling, in patients with HF regardless of their LVEF.

Methods

The DAPA-MODA trial (NCT04707352) is a multicentre, single-arm, open-label, prospective and interventional study, specifically designed to assess the effect of dapagliflozin on cardiac remodelling parameters over a period of 6 months, in stable patients with chronic HF irrespective of LVEF and diabetes status. The study design is presented in *Figure 1*.

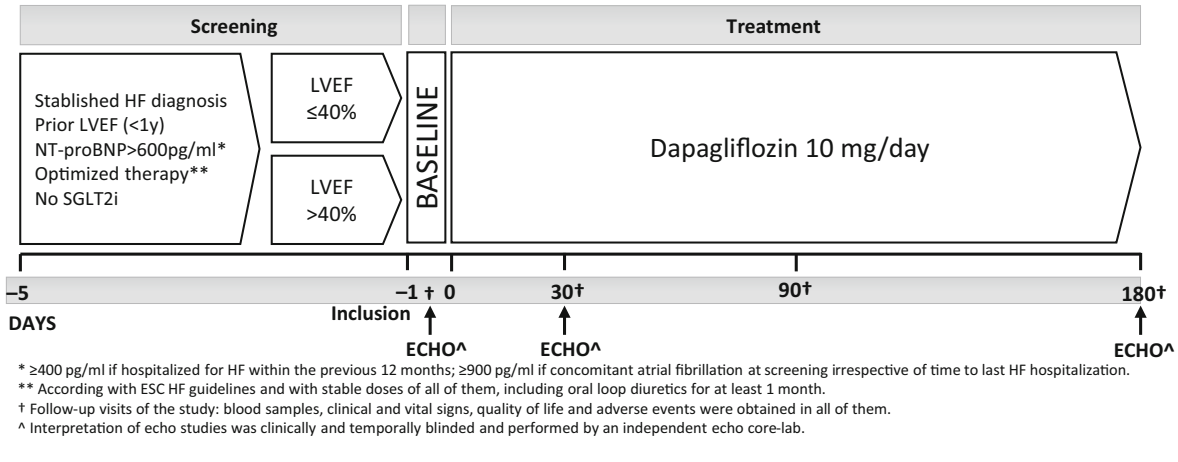


Figure 1 DAPA-MODA study design. ECHO, echocardiography; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Study population

The study population included stable out-setting patients with established diagnosis of chronic HF and receiving an optimized guideline-directed therapy, for at least 1 month, except that they were not on dapagliflozin or any other SGLT2 inhibitor at the time of screening. Subjects eligible for inclusion in this study have to fulfill all of the following criteria: age >18 years; prior diagnosis of HF, with at least one hospitalization for HF at any time; New York Heart Association (NYHA) class I–IV; LVEF available (echocardiogram or cardiac magnetic resonance imaging) within the last 12 months prior to enrolment; treatment according to contemporary guideline recommendations and with stable doses of oral loop diuretics for at least 4 weeks; N-terminal pro-B-type natriuretic peptide (NT-proBNP) >600 pg/ml at screening (≥400 pg/ml if hospitalized for HF within the previous 12 months; ≥900 pg/ml if concomitant atrial fibrillation at screening irrespective of time to last HF hospitalization). Among exclusion criteria, there were: prescription of dapagliflozin or other SGLT2 inhibitor at any time within the previous 6 months; diagnosis of type 1 diabetes mellitus; any worsening HF episode, with or without hospitalization, within 4 weeks prior to enrolment; presence at screening of an estimated glomerular filtration rate <30 ml/min/1.73 m^2 or symptomatic hypotension, or systolic blood pressure <95 mmHg (expanded exclusion criteria are provided in online supplementary *Appendix S1*). The study protocol was approved by the Institutional Ethics Committee (ESR/20/20594), and all participants were required to sign an informed consent prior to enrolment.

Investigational therapy and endpoints

All eligible subjects received dapagliflozin 10 mg daily (*Figure 1*). The study treatment was provided for the duration of the trial from baseline (Day 1) through last visit (Day 180). The scheduled visits were programmed at baseline, 30, 90 and 180 days. The primary endpoint was the change in maximal LA volume indexed to body surface area (LAVI) from baseline to 180 days. The secondary endpoints included the change in other parameters of LA and LV geometry and function, and the change in established related circulating biomarkers (NT-proBNP, and high-sensitivity troponin T [hs-TnT]). As safety endpoints, these included: death (all-cause, HF and cardiovascular related); hospitalization (all-cause, HF and cardiovascular related); worsening HF defined as the need for outpatient intravenous diuretics, due to impairment of HF condition. Change in quality of life was assessed using the EuroQol instrument, where patients rate their overall health on the day of each visit on a 0–100 hash-marked vertical visual analogue scale (EQ-VAS).[21]

Echocardiography and biomarker measurements

The study procedures were performed at baseline (immediately, 0–24 h, before the initiation of dapagliflozin), at 30 days and 180 days. Echocardiographic studies were acquired locally by the same accredited specialists at each centre, and using the same equipment, according to standardized quality criteria per protocol. Echo files (DICOM format) were blinded to patient and time of acquisition and then transmitted in a secure fashion to a study cloud linked to the electronic case report form platform. Only the independent contract research organization had access to the cloud and handled the echo studies in order to confirm that blinding was complete, and metadata and format were correct. Following completion of all study procedures, the studies were transmitted to the accredited central echo core-lab (JLZ), that performed the analysis with no access to data about patient or time, by using a virtual echo station and the Intellispace Platform (Philips, Andover, MA, USA), according to the established protocol and the echocardiographic guidelines of the European Association of Cardiovascular Imaging (EACVI).[22] In the case of lack of enough quality images, or lack of a full cardiac cycle, missing view, non-DICOM images, or significant foreshortening of the cavity, the measurements were considered unreliable, and the patient was excluded from the analysis ($n = 6$). Finally, raw data were automatically downloaded and directly exported for the independent data statistical analysis. Blood samples were obtained locally during the established visits and transferred to the central Biobank of the Region of Murcia, BIOBANC-MUR, registered in the National Registry of Biobanks (B0000859), following standard working procedures and with the approval of the Ethics Committee. NT-proBNP and hs-TnT

were centrally measured (Cobas® 8000 system, Roche Diagnostics) using commercially available electrochemiluminescence immunoassays (Elecsys proBNP II and Troponin T hs, Roche Diagnostics).

Statistical analysis

The sample size was estimated in 162 patients considering a baseline LAVI value of 38 ± 15 ml/m^2 and a reduction of at least 10% in LAVI as a clinically meaningful reverse remodelling response,[11,17,23,24] with a power of 80% and a significance level of 0.05 (2-sided alpha level). The analysis of the primary and secondary endpoints was based on the full analysis set. The safety set consisted of all subjects who received, at least, one dose of the study drug and was used for the analyses of safety variables. For categorical data, frequencies and percentages were presented. For continuous data, the mean (standard deviation) or median (interquartile range [IQR]) was presented according to the type of distribution. Continuous variables with an exponential scale were log-transformed to achieve normality. Changes from baseline were estimated using linear mixed model in logarithmic scale (equivalent to geometric mean ratios), and patients with missing data were excluded. The Dunnett correction was used to correct for multiple comparisons when considering all visits (baseline, 30 days and 180 days). In all analyses, two-sided 95% confidence intervals (CI) and *p*-values were calculated, using a significance level of 0.05. The software used for the analysis was R v4.1, and the emmeans library was used to estimate marginal means from the models.

Results

Study population

A total of 162 patients (64.2% men) were enrolled with a mean age of 70.5 ± 10.6 years (40% >75 years). The study flow chart is presented in online supplementary *Figure S1*. *Table 1* shows clinical characteristics for the entire study population and considering LVEF-based phenotypes at screening: ≤40% ($n = 78$, 48%) or >40% ($n = 84$, 52%). Among clinical characteristics, 43% had permanent atrial fibrillation, 36% had coronary artery disease, 22% were diabetics and most patients were in NYHA class II (80%) at baseline. As a pre-specified inclusion criteria, all patients had a previous HF hospitalization, with a median time from last admission of 1.2 years. The patient characteristics differed between the HF with reduced ejection fraction (HFrEF) and LVEF >40% groups, as expected. Patients in the HFrEF group had higher rates of male sex and ischaemic disease, while patients in the LVEF >40% group were older and had higher rates of hypertension, atrial fibrillation and valvular disease. The patients included in the study were receiving optimized therapy, with a high adherence to guideline-directed treatments for HFrEF. Specifically, 94% of patients were on beta-blockers and renin–angiotensin system inhibitors (or angiotensin receptor–neprilysin inhibitor), and 87% were on mineralocorticoid receptor antagonists. No differences were found in terms of analytical parameters.

Table 2 presents the baseline results of the study procedures. Maximal LAVI was significantly increased, with a mean value of 48.1 ± 22.6 ml/m^2 and a median of 44.8 ml/m^2 (IQR 33.8–56.5), with 42% of patients showing severe LA enlargement (>48 ml/m^2), and all the rest of LA measurements were in pathological ranges. The mean LVEF was 48.5 ± 12.4%. While the LVEF-based groups differed significantly in all parameters related to LV function and remodelling, there were no significant differences in any parameter reflecting LA remodelling or function, suggesting a similar contribution to HF syndrome regardless of LVEF. Median NT-proBNP and hs-TnT was 1411 pg/ml (IQR 950–1955) and 19.40 (IQR 14.30–31.85), respectively, with no significant differences between groups.

Dapagliflozin and changes in left atrial remodelling

Table 3 presents the changes observed in echocardiographic parameters throughout the study. After 30 days, all echo parameters showed a tendency towards improvement, although without statistical significance. The primary endpoint of the study, maximal LAVI, exhibited a slight reduction of −1.7% (95% CI −5.7, 2.5, $p = 0.429$) at 30 days, which became statistically significant at 180 days with a reduction of −6.6% (95% CI −11.1, −1.8, $p = 0.008$). No interaction was observed with relevant subgroups, including LVEF, permanent atrial fibrillation, age and sex (p = NS). At 180 days, 41.2% of patients showed an improvement in LAVI greater than 10% compared to baseline. The reduction in maximal LAVI was attributed to a decrease in LAVI reservoir (−13.8% [95% CI −22.5, −4.0]; $p = 0.007$). However, the minimal LAVI remained unchanged, leading to a reduction in both LA expansion index and LA emptying fraction. Other parameters related to maximal LA dimensions, including diameters, were also improved. In patients with sinus rhythm, a significant reduction in pre-A volume (atrial contraction) was observed (−12.5% [95% CI −18.7, −5.8], $p < 0.001$). There were no significant changes in reservoir, conduction, and contraction components of LA strain parameters. *Figure 2* shows changes in LAVI restricted to patients who fulfilled all programmed visits.

Dapagliflozin and changes in left ventricular remodelling and biomarkers

An improvement in all parameters related to LV geometry was observed (*Table 3*), with an earlier response seen in terms of volumes at 30 days. At 180 days, a significant reduction in LV mass index was observed (−13.9% [95% CI −18.7, −8.7], $p < 0.001$). The reduction in LV end-diastolic volume (−8.0% [95% CI −11.6, −4.2], $p < 0.001$) and LV end-systolic volume (−11.9% [95% CI −16.7, −6.8], $p < 0.001$) at 180 days was associated with an improvement in LVEF (5.0% [95% CI 0.2–9.9], $p = 0.040$) and global longitudinal strain (8.9% [95% CI 0.6–17.9], $p = 0.036$). Although no change was observed in Doppler filling pressures, NT-proBNP concentrations showed a trend toward early reduction at 30 days (−8.3% [95% CI −16.6, 0.7], $p = 0.070$), which reached significance at 180 days (−18.2% [95% CI −27.1, −8.2], $p < 0.001$). Hs-TnT concentrations were steady across the study visits (baseline vs. 180 days: 1.2% [95% CI −4.2, 6.9], $p = 0.667$). *Figure 3* shows changes in LV mass index and NT-proBNP levels restricted to patients who fulfilled all programmed visits.

Table 1 Baseline clinical characteristics

	Overall	LVEF group		p-value
		≤40%	>40%	
Patients, *n*	162	78	84	
Age, years	70.5 ± 10.6	67.9 ± 11.0	72.9 ± 9.73	0.003
Male sex	104 (64.2)	56 (71.8)	48 (57.1)	0.071
BMI, kg/m^2	28.3 ± 5.30	28.4 ± 4.98	28.2 ± 5.69	0.895
Clinical variables				
SBP, mmHg	124 ± 16.0	122 ± 16.8	126 ± 15.0	0.118
DBP, mmHg	72.3 ± 10.8	73.5 ± 12.2	71.3 ± 9.28	0.196
Heart rate, bpm	71.7 ± 14.9	69.7 ± 12.9	73.5 ± 16.5	0.105
NYHA class I/II/III/IV, %	11/80/10/0	10/81/9/0	11/79/11/0	0.959
Medical history				
Hypertension	91 (56.2)	36 (46.2)	55 (65.5)	0.017
Diabetes	35 (21.6)	17 (21.8)	18 (21.4)	1.000
Dyslipidaemia	87 (53.7)	40 (51.3)	47 (56.0)	0.637
Smoking	21 (13.0)	11 (14.1)	10 (11.9)	0.816
Cancer history	34 (21.0)	9 (11.5)	25 (29.8)	0.006
COPD	27 (16.7)	7 (9.0)	20 (23.8)	0.012
CVD or PVD	31 (19.1)	13 (16.7)	18 (21.4)	0.549
Coronary artery disease	58 (35.8)	30 (38.5)	28 (33.3)	0.516
Prior AMI	36 (22.2)	23 (29.5)	13 (15.5)	0.038
Coronary revascularization	38 (23.5)	21 (26.9)	17 (20.2)	0.356
Permanent AF rhythm	69 (42.6)	24 (30.8)	45 (53.6)	0.004
Pacemaker	18 (11.1)	7 (9.0)	11 (13.1)	0.460
ICD	27 (16.7)	24 (30.8)	3 (3.6)	<0.001
Valvular disease	20 (12.3)	5 (6.4)	15 (17.9)	0.032
Last HF admission, years	1.2 [0.4–3.6]	1.2 [0.4–4.3]	1.0 [0.5–2.7]	0.347
Laboratory				
Creatinine, mg/dl	1.17 ± 0.37	1.22 ± 0.37	1.13 ± 0.35	0.125
eGFR, ml/min/1.73 m^2	64.9 ± 20.1	63.5 ± 18.4	66.2 ± 21.6	0.405
Sodium, mmol/L	140 ± 3.36	140 ± 3.15	140 ± 3.56	0.890
Potassium, mmol/L	4.37 ± 0.50	4.41 ± 0.43	4.33 ± 0.56	0.330
Haemoglobin, g/dl	13.6 ± 2.21	13.7 ± 2.60	13.5 ± 1.77	0.604
Medication				
Beta-blockers	142 (87.7)	73 (93.6)	69 (82.1)	0.032
ACEI/ARB	58 (35.8)	25 (32.1)	33 (39.3)	0.413
Sacubitril/valsartan	65 (40.1)	48 (61.5)	17 (20.2)	<0.001
Aldosterone antagonists	108 (66.7)	68 (87.2)	40 (47.6)	<0.001
Oral furosemide	133 (82.2)	61 (78.2)	72 (85.7)	0.226
Oral furosemide dose, mg/day	40 [40–80]	40 [40–80]	70 [40–120]	0.002
Thiazides	14 (8.6)	2 (2.6)	12 (14.3)	0.010
Digoxin	30 (18.5)	15 (19.2)	15 (17.9)	0.842
Antiplatelets	42 (25.9)	25 (32.1)	17 (20.2)	0.107
Anticoagulant	108 (66.7)	46 (59.0)	62 (73.8)	0.066
Statins	102 (63.0)	54 (69.2)	48 (57.1)	0.143
Metformin	21 (13.0)	11 (14.1)	10 (11.9)	0.816

Values are given as mean ± standard deviation, *n* (%), or median [interquartile range].
ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; PVD, peripheral vascular disease; SBP, systolic blood pressure.

Clinical evolution and adverse events

For the entire population, a reduction in body mass index and systolic blood pressure was observed at 180 days, with no changes in heart rate, and a parallel improvement in self-reported quality of life (EQ-VAS). During the follow-up period, 4 patients died (2.5%), 7 (4.3%) were hospitalized due to HF, 11 (6.8%) required outpatient intravenous diuretics and 18 (11.1%) were hospitalized due to non-HF related reasons. Overall, 22 (13.6%) experienced any

Table 2 Baseline study variables in the entire population and according to left ventricular ejection fraction categorization at screening

	All ($n = 156$)	LVEF ≤40% ($n = 74$)	LVEF >40% ($n = 82$)	*p*-value
Left atrium				
LAVI maximal, ml/m^2	48.10 ± 22.64	47.31 ± 22.27	48.81 ± 23.08	0.685
LAVI reservoir, ml/m^2	13.45 ± 7.25	13.69 ± 6.02	13.23 ± 8.24	0.697
LAVI minimal, ml/m^2	34.65 ± 19.16	33.61 ± 19.88	35.57 ± 18.57	0.531
LA expansion index, %	47.25 ± 33.70	50.55 ± 34.30	44.28 ± 33.09	0.254
LA emptying fraction, %	29.33 ± 12.57	30.87 ± 12.37	27.93 ± 12.66	0.151
LA strain reservoir, %	13.96 ± 8.00	14.48 ± 7.76	13.47 ± 8.23	0.450
LA strain conduct, %	−8.70 ± 5.07	−8.28 ± 5.01	−9.10 ± 5.12	0.328
LA strain contraction[a], %	−8.38 ± 6.32	−7.90 ± 6.67	−9.10 ± 5.80	0.417
Left ventricle				
LVEDVI, ml/m^2	59.96 ± 26.52	74.21 ± 29.15	47.18 ± 15.19	<0.001
LVESVI, ml/m^2	33.13 ± 22.01	45.55 ± 24.64	21.97 ± 10.67	<0.001
LVI mass, g/m^2	119.16 ± 46.28	134.66 ± 49.41	105.35 ± 38.64	<0.001
LVEF, %	48.54 ± 12.41	41.67 ± 12.01	54.71 ± 9.13	<0.001
GLS, %	−11.59 ± 4.15	−10.27 ± 3.67	−13.00 ± 4.19	<0.001
E/e′ ratio	15.57 ± 7.87	16.82 ± 9.76	14.49 ± 5.63	0.074
NT-proBNP, pg/ml	1411 [950–1955]	1269 [897–1778]	1462 [950–2108]	0.480
EQ-VAS, %	70 [60–80]	70 [60–80]	70 [60–80]	0.775

Values are given as mean ± standard deviation or median [interquartile range].
EQ-VAS, EuroQoL visual analogue scale; GLS, global longitudinal strain; LA, left atrial; LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVI, left ventricular end-systolic volume index; LVI, left ventricular indexed; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]Patients with evaluable 'p' at electrocardiogram ($n = 75$).

Table 3 Changes in echocardiographic parameters and clinical endpoints from baseline to 30 days and 180 days

	Baseline vs. 30 days			Baseline vs. 180 days		
	LS mean change (95% CI)	% change (95% CI)	*p*-value	LS mean change (95% CI)	% change (95% CI)	*p*-value
Left atrium						
LAVI maximal	−0.71 (−2.95, 1.52)	−1.7 (−5.7, 2.5)	0.429	−1.96 (−4.39, 0.47)	−6.6 (−11.1, −1.8)	0.008
LAVI reservoir	−0.77 (−2.06, 0.52)	−5.2 (−14.1, 4.5)	0.279	−1.91 (−3.15, −0.66)	−13.8 (−22.5, −4)	0.007
LAVI minimal	0.07 (−1.75, 1.89)	0.4 (−4.2, 5.2)	0.868	−0.48 (−2.2, 1.24)	−2.2 (−7.1, 2.9)	0.393
LA expansion index	−3.66 (−9.05, 1.73)	−5.4 (−15.4, 5.7)	0.324	−8.81 (−14.24, −3.38)	−11.8 (−21.2, −1.4)	0.028
LA emptying fraction	−1.14 (−3.2, 0.93)	−3.6 (−11.3, 4.7)	0.384	−2.79 (−4.79, −0.79)	−7.4 (−14.9, 0.8)	0.076
LA strain reservoir	−0.82 (−1.96, 0.32)	−6.6 (−16.8, 4.8)	0.245	−0.6 (−2.01, 0.8)	−7.4 (−19.9, 7)	0.293
LA strain conduct	−0.38 (−1.29, 0.54)	−9.3 (−23.7, 7.9)	0.419	0.12 (−0.81, 1.06)	−1.6 (−15.2, 14)	0.825
LA strain contraction[a]	0.06 (−1.13, 1.24)	3.2 (−21.6, 36)	0.573	−0.73 (−2.22, 0.75)	−17.3 (−39.6, 13.4)	0.235
Left ventricle						
LVEDV	−2.12 (−4.49, 0.24)	−4.7 (−8.5, −0.8)	0.019	−4.92 (−7.34, −2.51)	−8 (−11.6, −4.2)	<0.001
LVESV	−1.75 (−3.58, 0.08)	−5.6 (−10.1, −0.9)	0.021	−4.4 (−6.27, −2.54)	−11.9 (−16.7, −6.8)	<0.001
LVI mass	−2.17 (−8.21, 3.87)	−2.2 (−7.2, 3)	0.398	−16.46 (−22.82, −10.11)	−13.9 (−18.7, −8.7)	<0.001
LVEF	0.84 (−0.68, 2.36)	2 (−1.6, 5.7)	0.285	2.29 (0.44, 4.15)	4.9 (0.2, 9.9)	0.040
GLS	0.42 (−0.39, 1.23)	1.8 (−6.1, 10.3)	0.664	1.13 (0.25, 2.01)	8.9 (0.6, 17.9)	0.036
E/e′	−0.51 (−1.71, 0.69)	−2.7 (−8.6, 3.6)	0.392	−0.01 (−1.15, 1.17)	−1.5 (−7.5, 4.9)	0.644
Biomarkers						
NT-proBNP	−51.42 (−191.41, 88.57)	−8.3 (−16.6, 0.7)	0.070	−123 (−299, 54.1)	−18.2 (−27.1, −8.2)	<0.001
Clinical variables						
Weight	−0.36 (−1.02, 0.29)	−0.5 (−1.3, 0.3)	0.230	−0.68 (−1.34, −0.01)	−0.9 (−1.7, −0.1)	0.033
SBP	−2.1 (−5.13, 0.93)	−1.7 (−4.1, 0.7)	0.202	−3.9 (−6.97, −0.82)	−3.2 (−5.6, −0.8)	0.007
Heart rate	−0.86 (−3.58, 1.86)	−0.6 (−4.2, 3.1)	0.891	−0.95 (−3.71, 1.81)	−0.9 (−4.5, 2.9)	0.810
EQ-VAS	1.97 (−0.99, 4.92)	4.1 (−1.6, 10.2)	0.203	4.87 (1.86, 7.88)	6.8 (0.8, 13.2)	0.023

CI, confidence interval; EQ-VAS, EuroQoL visual analogue scale; GLS, global longitudinal strain; LA, left atrial; LAVI, left atrial volume index; LS, least squares; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVI, left ventricular indexed; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
[a]Patients with evaluable 'p' at electrocardiogram ($n = 75$).

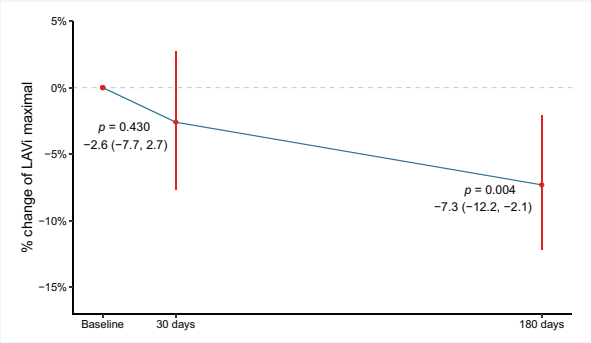


Figure 2 Changes in maximal left atrial volume index (LAVi) in the population with all programmed visits completed ($n = 138$).

serious adverse event, and five patients (3.1%) had to discontinue dapagliflozin permanently (online supplementary *Table S1*). The rates of the rest of medications were steady across visits except for furosemide (online supplementary *Table S2*), with a significant lower rate at 180 days versus baseline (82% vs. 66%, $p = 0.005$).

Discussion

The DAPA-MODA study revealed that dapagliflozin treatment in chronic HF patients with stable clinical condition led to both atrial and ventricular reverse remodelling, as well as improvements in associated biomarkers (*Graphical Abstract*). These findings provide important insights into the mechanisms underlying the benefits of SGLT2 inhibitors across all stages of HF. Prior to this study, there were limited data available on the ability of SGLT2 inhibitors to reverse remodelling of both the atrial and ventricular regions, and the data on the left ventricle were sparse and inconsistent.

The study's key finding was that dapagliflozin had similar positive effects on LA geometry and function in patients with chronic HF, regardless of LVEF-based phenotypes. Even after accounting for higher rates of permanent atrial fibrillation in patients with LVEF >40%, this finding remained consistent. However, it is worth noting that the studied population had long-standing chronic HF and well-optimized treatment, yet a significant proportion of patients (42%) had severely dilated left atria and all evaluated LA parameters were affected, indicating an established LA disease. The relationship between left atrium and HF progression is unclear. LA disease could contribute to HF irrespective of LVEF, or it may simply reflect a passive role in HF, representing the chronicity of elevated LV pressures across the LVEF spectrum.

In addition, this study supports an association between treatment with dapagliflozin and reduction in LAVI, which is the most reliable and established marker of LA remodelling and dysfunction. This change in LA geometry lays in the concept of LA reverse remodelling, which refers to the temporal process leading to a reduction in LA volume and/or a restoration of specific functional parameters.[11,25] While the link between elevated LAVI and unfavourable clinical outcomes is well established,[10–15] there is a scarcity of data regarding the effectiveness of therapies in reversing LA disease and their correlation with clinical outcomes. In patients with HFrEF, resynchronization therapy has a favourable impact on LAVI and the degree of improvement correlates with the risk of adverse events.[26,27] The PROVE-HF trial, similar in design to the DAPA-MODA study, evaluated the effect of sacubitril/valsartan on LAVI in HFrEF patients and found a significant reduction (-4.4 ml/m^2, $p < 0.001$) after 6 months.[23] The EVALUATE-HF trial also reported similar findings compared to enalapril. In HFpEF patients,[28] sacubitril/valsartan has shown a positive effect on LAVI, with a reduction observed in the PARAMOUNT study (-2.6 ± 7.3 ml/m^2, $p = 0.007$)[24] and in the TOPCAT echocardiographic sub-study, each 1 ml reduction in LAVI at 18 months was associated with a 3% lower risk of the primary endpoint after adjusting for baseline LAVI.[29]

There is a limited amount of data available on the effects of SGLT2 inhibitors on LA remodelling, and the majority of these studies have focused on patients with diabetes and HFrEF.[23,24,28,29] In a small randomized study ($n = 56$), dapagliflozin had no effect in either LAVI or LV remodelling at 12 months.[7] In other small randomized trial with empagliflozin ($n = 105$), while LAVI did not change, a reduction in LV volumes was observed by using cardiac magnetic resonance at 36 weeks.[2] In another small observational

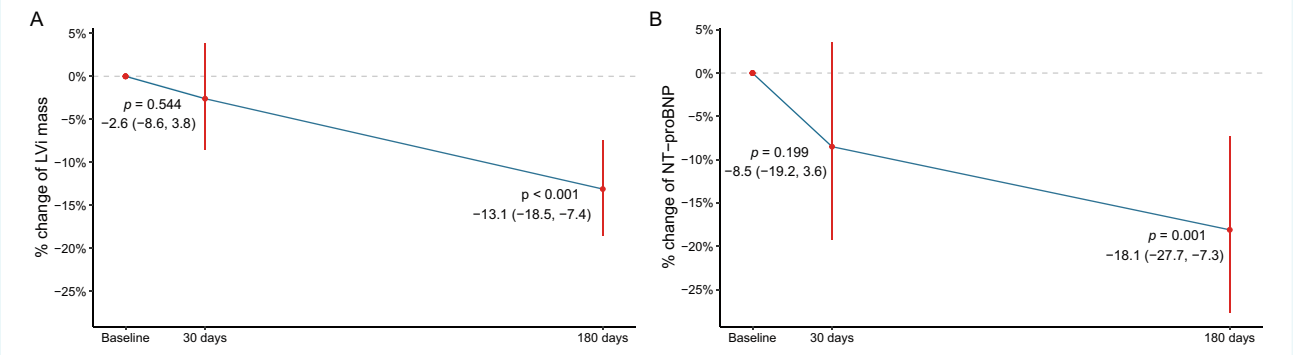


Figure 3 Changes in left ventricular indexed (LVi) mass (*A*) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations (*B*) in the population with all programmed visits completed ($n = 138$).

study with 58 patients (69% HFpEF), dapagliflozin administration was associated with a reduction of LAVI, as well as Doppler filling measures and LV mass index.[3] The DAPA-MODA study showed that treatment with dapagliflozin was associated with a reduction in maximal LAVI, which was attributed to a reduction in the reservoir volume during ventricular systole (LA diastole), which mainly correlates with LA diastolic filling and preload. It should be explained by decongestion and haemodynamic effects; indeed, need for diuretics also decreased during the follow-up. In terms of LA emptying, no effect was observed in emptying volumes and, given that minimal LA did not change, LA global emptying fraction was slightly lower. LA strain parameters have received special attention in the last years in an attempt to improve the ability to understand atrial disease, although they are not yet clinically validated and reproducibility is variable.[30] In the studied population, strain measures did not change. This neutral effect might be explained by the high rate of atrial fibrillation in this population and/or the presence of a more advanced LA disease. The DAPA-MODA study participants had a significantly larger LAVI (mean of 48 ml/m^2) than other studies,[26,28] indicating advanced LA disease reflecting chronicity and stability in the inclusion criteria. This could limit dapagliflozin's impact on strain and function parameters, reinforcing the role of a hemodynamic effect. However, despite no effect on emptying and strain parameters, improvement in LAVI and LA expansion index suggests a meaningful enhancement in LA remodelling and reduction of LA filling stress. LAVI reduction was greater than 10% in 41.2% of patients, representing a clinically meaningful reverse LA remodelling response.[11,17,23,24]

Regarding the changes in LV remodelling, a favourable effect of SGLT2 inhibitors on LV remodelling has been found in patients with type 2 diabetes and/or HFrEF,[2,3,6] with a more pronounced effect on LV mass than LV volumes.[4] Indeed, in type 2 diabetic patients and LV hypertrophy, but not HF, dapagliflozin was associated with a reduction in LV mass.[31] However, in a recent randomized controlled trial that involved patients at risk of HF, without diabetes or HF, empagliflozin did not demonstrate any significant impact on LV remodelling.[32] It has been suggested that cardiac anti-remodelling effects of SGLT2 inhibitors are particularly significant in patients with HF.[5] The DAPA-MODA study showed that dapagliflozin improved cardiac geometry by reducing LV dimensions and mass (−14%), leading to mild improvements in systolic function. These results provide further evidence of the positive effects of dapagliflozin on cardiac health, especially in patients with chronic HF, regardless of diabetes status or LVEF phenotype. NT-proBNP concentrations showed early improvement at 30 days and reached significance with a mean drop of −18% at 6 months in the DAPA-MODA study. In comparison, the EMPEROR-Reduced trial showed that empagliflozin reduced NT-proBNP by 5−13% compared to placebo across multiple timepoints, which correlated with clinical endpoints.[33] However, in the DEFINE-HF trial with HFrEF patients, dapagliflozin did not show an apparent reduction of NT-proBNP levels at 3 months, but a higher proportion of patients had a reduction >20% with dapagliflozin than placebo.[8] DAPA-MODA's broader population, including HFpEF patients, provides further evidence of SGLT2 inhibitor's effect on natriuretic peptides, albeit the magnitude of the reduction was relatively small compared to other therapies. Notably, natriuretic peptides play a beneficial role in cardiovascular pathophysiology, and the observed disconnection between reduction in cardiac stress and lower production of natriuretic peptides could potentially explain the results.

This study has several limitations inherent to the open-label observational design. The lack of a control group precludes to establish definitive conclusions about causality and the effect of dapagliflozin in studied parameters. However, this limitation is partially overcome by the inclusion criteria that ensured clinical stability of patients, which supports that the observed effects were due to the introduction of dapagliflozin and not to the natural evolution of patients. Furthermore, the interpretation of the echo parameters was conducted in a blinded manner for both patient and time, which strengthens the reliability of the findings. Finally, the observed changes in clinical parameters are in agreement with the known effects of SGLT2 inhibitors, apart from the fact that there is no room for a placebo-controlled design with current evidence.

In conclusion, the DAPA-MODA study demonstrated that initiation of dapagliflozin in patients with stable chronic HF is associated with a reduction of LAVI, LV mass and concentration of natriuretic peptides after 6 months. These findings support the concept of left atrium as part of global adverse remodelling in HF, regardless of LVEF, and suggest that dapagliflozin may have the ability to reverse cardiac remodelling as part of its benefit in HF patients.

Supplementary Information

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

Acknowledgements

We are grateful for the generous contribution of the patients and the collaboration of the Biobank Network of the Region of Murcia, BIOBANC-MUR, registration number B.0000859.

Funding

This study has been sponsored by Sociedad Española de Cardiología and has received funding by a non-conditional investigational grant from AstraZeneca Farmacéutica Spain.

Conflict of interest: D.A.P.F. has received consultancy and speaker fees and lectures from AstraZeneca, Novartis, Roche Diagnostics, Pfizer, Vifor, Rovi, Bayer. J.L.Z. has received speaker fees from Pfizer, Bayer, Daichii and Novartis. H.M. has received speaker fees from AstraZeneca. J.N. has received consultancy and speaker fees and lectures from AstraZeneca, Alleviant, Amgen, Bayer, Boehringer Ingelheim, CSL VIFOR, Daiichi Sankyo, GSK, Lilly, Pfizer, Novartis, NovoNordisk, and Rovi. A.B.G. has participated in advisory boards and/or lectured for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche Diagnostics, Vifor. All other authors have nothing to disclose.

References

1. Jhund PS, Kondo T, Butt JH, Docherty KF, Claggett BL, Desai AS, *et al.* Dapagliflozin across the range of ejection fraction in patients with heart failure: A patient-level, pooled meta-analysis of DAPA-HF and DELIVER. *Nat Med.* 2022;**28**:1956−1964. https://doi.org/10.1038/s41591-022-01971-4
2. Lee MMY, Brooksbank KJM, Wetherall K, Mangion K, Roditi G, Campbell RT, *et al.* Effect of empagliflozin on left ventricular volumes in patients with

type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). *Circulation*. 2021;**143**:516–525. https://doi.org/10.1161/CIRCULATIONAHA.120.052186
3. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, *et al.* Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018;**17**:132. https://doi.org/10.1186/s12933-018-0775-z
4. Dhingra NK, Mistry N, Puar P, Verma R, Anker S, Mazer CD, *et al.* SGLT2 inhibitors and cardiac remodelling: A systematic review and meta-analysis of randomized cardiac magnetic resonance imaging trials. *ESC Heart Fail*. 2021;**8**:4693–4700. https://doi.org/10.1002/ehf2.13645
5. Fan G, Guo DL. The effect of sodium-glucose cotransporter-2 inhibitors on cardiac structure remodeling and function: A meta-analysis of randomized controlled trials. *Eur J Intern Med*. 2023;**114**:49–57. https://doi.org/10.1016/j.ejim.2023.04.002
6. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, Garcia-Ropero A, Mancini D, Pinney S, *et al.*, EMPA-TROPISM (ATRU-4) Investigators. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol*. 2021;**77**:243–255. https://doi.org/10.1016/j.jacc.2020.11.008
7. Singh JSS, Mordi IR, Vickneson K, Fathi A, Donnan PT, Mohan M, *et al.* Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: The REFORM trial. *Diabetes Care*. 2020;**43**:1356–1359. https://doi.org/10.2337/dc19-2187
8. Nassif ME, Windsor S, Tang F, Khariton Y, Husain M, Inzucchi S, *et al.* Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction. *Circulation*. 2019;**140**:1463–1476. https://doi.org/10.1161/CIRCULATIONAHA.119.042929
9. Fang F, Lee APW, Yu CM. Left atrial function in heart failure with impaired and preserved ejection fraction. *Curr Opin Cardiol*. 2014;**29**:430–436. https://doi.org/10.1097/HCO.0000000000000091
10. Triposkiadis F, Pieske B, Butler J, Parissis J, Giamouzis G, Skoularigis J, *et al.* Global left atrial failure in heart failure. *Eur J Heart Fail*. 2016;**18**:1307–1320. https://doi.org/10.1002/ejhf.645
11. Thomas L, Abhayaratna WP. Left atrial reverse remodeling: Mechanisms, evaluation, and clinical significance. *JACC Cardiovasc Imaging*. 2017;**10**:65–77. https://doi.org/10.1016/j.jcmg.2016.11.003
12. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail*. 2015;**8**:295–303. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001667
13. Bisbal F, Baranchuk A, Braunwald E, Bayés de Luna A, Bayés-Genís A. Atrial failure as a clinical entity: JACC review topic of the week. *J Am Coll Cardiol*. 2020;**75**:222–232. https://doi.org/10.1016/j.jacc.2019.11.013
14. Vazquez R, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, *et al.*, MUSIC Investigators. The MUSIC risk score: A simple method for predicting mortality in ambulatory patients with chronic heart failure. *Eur Heart J*. 2009;**30**:1088–1096. https://doi.org/10.1093/eurheartj/ehp032
15. Patel DA, Lavie CJ, Gilliland YE, Shah SB, Dinshaw HK, Milani RV. Prediction of all-cause mortality by the left atrial volume index in patients with normal left ventricular filling pressure and preserved ejection fraction. *Mayo Clin Proc*. 2015;**90**:1499–1505. https://doi.org/10.1016/j.mayocp.2015.07.021
16. Khan MS, Memon MM, Murad MH, Vaduganathan M, Greene SJ, Hall M, *et al.* Left atrial function in heart failure with preserved ejection fraction: A systematic review and meta-analysis. *Eur J Heart Fail*. 2020;**22**:472–485. https://doi.org/10.1002/ejhf.1643
17. Hoit BD. Left atrial size and function: Role in prognosis. *J Am Coll Cardiol*. 2014;**63**:493–505. https://doi.org/10.1016/j.jacc.2013.10.055
18. Carpenito M, Fanti D, Mega S, Benfari G, Bono MC, Rossi A, *et al.* The central role of left atrium in heart failure. *Front Cardiovasc Med*. 2021;**8**:704762. https://doi.org/10.3389/fcvm.2021.704762
19. Bayes-Genis A, Vazquez R, Puig T, Fernandez-Palomeque C, Fabregat J, Bardají A, *et al.*, MUSIC Study Group. Left atrial enlargement and NT-proBNP as predictors of sudden cardiac death in patients with heart failure. *Eur J Heart Fail*. 2007;**9**:802–807. https://doi.org/10.1016/j.ejheart.2007.05.001
20. 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: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
21. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;**20**:1727–1736. https://doi.org/10.1007/s11136-011-9903-x
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. *Eur Heart J Cardiovasc Imaging*. 2015;**16**:233–271. https://doi.org/10.1093/ehjci/jev014
23. Januzzi JL, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, *et al.*, PROVE-HF Investigators. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA*. 2019;**322**:1085–1095. https://doi.org/10.1001/jama.2019.12821
24. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, *et al.*, Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: A phase 2 double-blind randomised controlled trial. *Lancet*. 2012;**380**:1387–1395. https://doi.org/10.1016/S0140-6736(12)61227-6
25. Inciardi RM, Bonelli A, Biering-Sorensen T, Cameli M, Pagnesi M, Lombardi CM, *et al.* Left atrial disease and left atrial reverse remodelling across different stages of heart failure development and progression: A new target for prevention and treatment. *Eur J Heart Fail*. 2022;**24**:959–975. https://doi.org/10.1002/ejhf.2562
26. Kloosterman M, Rienstra M, Mulder BA, Van Gelder IC, Maass AH. Atrial reverse remodelling is associated with outcome of cardiac resynchronization therapy. *Europace*. 2016;**18**:1211–1219. https://doi.org/10.1093/europace/euv382
27. Mathias A, Moss AJ, McNitt S, Zareba W, Goldenberg I, Solomon SD, *et al.* Clinical implications of complete left-sided reverse remodeling with cardiac resynchronization therapy: A MADIT-CRT substudy. *J Am Coll Cardiol*. 2016;**68**:1268–1276. https://doi.org/10.1016/j.jacc.2016.06.051
28. Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, *et al.*, EVALUATE-HF Investigators. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: A randomized clinical trial. *JAMA*. 2019;**322**:1077–1084. https://doi.org/10.1001/jama.2019.12843
29. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Deswal A, Anand IS, *et al.* Prognostic importance of changes in cardiac structure and function in heart failure with preserved ejection fraction and the impact of spironolactone. *Circ Heart Fail*. 2015;**8**:1052–1058. https://doi.org/10.1161/CIRCHEARTFAILURE.115.002249
30. Cho GY, Hwang IC. Left atrial strain measurement: A new normal for diastolic assessment? *JACC Cardiovasc Imaging*. 2020;**13**:2327–2329. https://doi.org/10.1016/j.jcmg.2020.05.014
31. Brown AJM, Gandy S, McCrimmon R, Houston JG, Struthers AD, Lang CC. A randomized controlled trial of dapagliflozin on left ventricular hypertrophy in people with type two diabetes: The DAPA-LVH trial. *Eur Heart J*. 2020;**41**:3421–3432. https://doi.org/10.1093/eurheartj/ehaa419
32. Connelly KA, Mazer CD, Puar P, Teoh H, Wang CH, Mason T, *et al.* Empagliflozin and left ventricular remodeling in people without diabetes: Primary results of the EMPA-HEART 2 CardioLink-7 randomized clinical trial. *Circulation*. 2023;**147**:284–295. https://doi.org/10.1161/CIRCULATIONAHA.122.062769
33. Januzzi JL, Zannad F, Anker SD, Butler J, Filippatos G, Pocock SJ, *et al.*, EMPEROR-Reduced Trial Committees and Investigators. Prognostic importance of NT-proBNP and effect of empagliflozin in the EMPEROR-Reduced trial. *J Am Coll Cardiol*. 2021;**78**:1321–1332. https://doi.org/10.1016/j.jacc.2021.07.046