Rev Esp Cardiol. 2025;xx(x):xxx–xxx

Original article

Impact of dapagliflozin on key pathophysiological pathways underlying chronic heart failure progression: the DAPA-MODA biomarker study

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Article history:
Received 12 August 2025
Accepted 13 November 2025

Keywords:
Heart failure
Biomarkers
Dapagliflozin

ABSTRACT

Introduction and objectives: Dapagliflozin improves clinical outcomes in patients with chronic heart failure (HF), irrespective of left ventricular ejection fraction. However, its effects on circulating biomarkers that reflect distinct pathophysiological pathways remain incompletely understood.
Methods: DAPA-MODA is a prospective, multicenter, single-arm study that enrolled patients with stable chronic HF receiving optimized guideline-directed medical therapy, excluding sodium-glucose cotransporter-2 inhibitors. In a predefined biomarker substudy (n = 156; 63.5% men; age 70.5 ± 10.6 years; 67.9% with left ventricular ejection fraction > 40%), 11 biomarkers representing 5 key biological pathways (cardiac stress, inflammation, neurohormonal activation, congestion, and fibrosis) were measured at baseline, 1 month, and 6 months.
Results: At baseline, markers of myocardial stress were frequently elevated (NT-proBNP [95.5%] and MR-proANP [34.8%]), as was troponin for myocardial injury (73.5%). Inflammatory (IL-6 [40%], CRP [35%], GDF-15 [56%]) and neuro-endocrine stress (copeptin [43%]) markers were also commonly raised. In contrast, elevations in congestion (MR-proADM, CA-125) and fibrosis markers (ST2, PINP) were less frequent, reflecting diverse pathophysiological involvement. Dapagliflozin led to significant reductions in NT-proBNP and MR-proADM levels by 6 months. Reductions in MR-proANP, CRP, IL-6, copeptin, and PINP were confined to patients with elevated baseline levels. ST2 and CA-125 remained unchanged, while GDF-15 levels increased modestly.
Conclusions: Dapagliflozin favorably modulates several key pathophysiological pathways involved in chronic HF progression, with differential effects among biomarkers by acting particularly on those that are elevated at baseline.

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https://doi.org/10.1016/j.rec.2025.11.014

Please cite this article in press as: Martínez-Pina V, et al. Impact of dapagliflozin on key pathophysiological pathways underlying chronic heart failure progression: the DAPA-MODA biomarker study. *Rev Esp Cardiol.* 2026. https://doi.org/10.1016/j.rec.2025.11.014

Impacto de la dapagliflozina en vías fisiopatológicas clave en la progresión de la insuficiencia cardiaca crónica: estudio DAPA-MODA de biomarcadores

Palabras clave:
Insuficiencia cardiaca
Biomarcadores
Dapagliflozina

RESUMEN

Introducción y objetivos: La dapagliflozina reduce complicaciones en pacientes con insuficiencia cardiaca (IC) crónica, independientemente de la fracción de eyección del ventrículo izquierdo. Sin embargo, aún no se comprenden completamente sus efectos sobre los biomarcadores circulantes que reflejan diferentes vías fisiopatológicas.
Métodos: DAPA-MODA fue un estudio prospectivo, multicéntrico y de un solo grupo que incluyó a pacientes con IC crónica estable que recibían tratamiento optimizado, excluyendo inhibidores del cotransportador de sodio y glucosa tipo 2. En un subestudio preestablecido (n = 156, 63,5% varones; 70,5 ± 10,6 años; 67,9% fracción de eyección del ventrículo izquierdo > 40%), se midieron 11 biomarcadores que representan 5 vías fisiopatológicas clave (estrés cardiaco, inflamación, activación neurohormonal, congestión y fibrosis) al inicio, al mes y a los 6 meses.
Resultados: Los marcadores de estrés miocárdico (NT-proBNP [95,5%], MR-proANP [34,8%]) y de lesión miocárdica (troponina T [73,5%]) estaban frecuentemente elevados, al igual que aquellos de activación inflamatoria (IL-6 [40%], PCR [35%], GDF-15 [56%]) y neuroendocrina (copeptina [43%]). Por el contrario, las elevaciones en marcadores de congestión (MR-proADM, CA-125) y fibrosis (ST2, PINP) fueron poco frecuentes. La dapagliflozina produjo reducciones significativas en los niveles de NT-proBNP y MR-proADM a los 6 meses. Las reducciones en MR-proANP, PCR, IL-6, copeptina y PINP se limitaron a pacientes con niveles basales elevados. Por el contrario, ST2 y CA-125 se mantuvieron sin cambios, y el GDF-15 aumentó ligeramente.
Conclusiones: La dapagliflozina modula favorablemente los diferentes mecanismos fisiopatológicos clave en la progresión de la IC crónica, actuando de forma preferente sobre biomarcadores con valores elevados que reflejan ejes biológicos alterados.

Abbreviations

HF: heart failure
LVEF: left ventricular ejection fraction
SGLT2i: sodium-glucose cotransporter 2 inhibitors
NT-proBNP: N-terminal pro-B-type natriuretic peptide
hsTNT: high-sensitivity troponin T
MR-proANP: mid-regional pro-atrial natriuretic peptide

INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are currently recommended in clinical guidelines for the treatment of heart failure (HF) over the full spectrum of left ventricular ejection fraction (LVEF).[1] Robust evidence supports their clinical benefits, including a consistent reduction in the risk of HF decompensation, hospitalizations, and cardiovascular mortality.[2] The beneficial effects of SGLT2i are thought to arise from multiple cardiovascular mechanisms, encompassing both cardiac and renal protective pathways.[3]

Circulating biomarkers play a pivotal role in elucidating the pathophysiological effects of cardiovascular therapies. Among these, B-type natriuretic peptides are the most extensively validated biomarkers in HF, supporting diagnosis, monitoring, and risk stratification by reflecting myocardial stretch.[4] HF pathophysiology involves complex interactions among several maladaptive processes, including inflammation, fibrosis, congestion, and systemic neurohormonal dysregulation. However, the pathophysiology of HF involves a complex interplay of maladaptive biological processes, including inflammation, fibrosis, congestion, and systemic neurohormonal dysregulation. Although SGLT2i have demonstrated broad clinical benefits, their effect on cardiac biomarkers remains incompletely defined. Existing studies often evaluate a limited subset of biomarkers, focus on specific LVEF phenotypes, or report inconsistent findings, particularly with respect to B-type natriuretic peptides and inflammatory markers.[5–8] Moreover, there is a notable lack of data addressing the effects of SGLT2i on atrial natriuretic peptides, neurohormonal stress markers, and biomarkers of congestion and fibrosis.

The DAPA-MODA study enrolled stable patients with chronic HF over the entire LVEF spectrum.[9] This investigation assessed the impact of initiating dapagliflozin on cardiac remodeling over a 6-month period in patients receiving optimized guideline-directed medical therapy (GDMT) without prior SGLT2i exposure. In the primary analysis, dapagliflozin produced favorable effects on both atrial and ventricular remodeling. Here, we present findings from a prespecified substudy evaluating the effects of dapagliflozin on circulating biomarkers representing 5 key pathophysiological pathways implicated in HF progression.

METHODS

Study design and population

The DAPA-MODA trial (ClinicalTrials.gov identifier: NCT04707352) is a multicenter, single-arm, open-label, prospective interventional study specifically designed to assess the effect of dapagliflozin on cardiac remodeling parameters over a 6-month period in stable patients with chronic HF, irrespective of LVEF or diabetes status. The study design and inclusion criteria have been previously published.[9] Briefly, the study population consisted of stable outpatients with an established diagnosis of chronic HF, who had experienced no episodes of worsening HF and were receiving stable doses of contemporary guideline-directed medical therapy (GDMT), including oral diuretics, during the 4 weeks prior to enrollment. For the present biomarker substudy, the analysis included patients with available blood samples at baseline (n = 156) and at least one follow-up sample at either 30 days

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(n = 151) and/or 180 days (n = 140). By 180 days, 16 patients (10%) had discontinued participation and therefore did not provide further blood samples. Reasons for discontinuation included withdrawal of consent (n = 4), loss to follow-up (n = 7), and death (n = 5).

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the protocol received approval from the Research Ethics Committee of Hospital Clínico Universitario Virgen de la Arrixaca.

Sampling

All eligible participants received dapagliflozin 10 mg once daily for 180 days. Blood samples were obtained at baseline (within 0-24 hours prior to the first dose of dapagliflozin), and again at 30 days and 180 days. Samples were collected locally during the scheduled study visits. All specimens were subsequently transferred to the central Biobank of the Region of Murcia (BIOBANC-MUR), which is registered in the National Registry of Biobanks (B0000859), following established standard operating procedures and with approval from the corresponding Ethics Committee. Biomarker analyses were performed centrally after completion of the study.

Biomarkers

The biomarkers assessed in this study were: N-terminal pro–B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hsTNT), interleukin-6 (IL-6), growth differentiation factor-15 (GDF-15), procollagen type I N-terminal propeptide (P1NP), carbohydrate antigen-125 (CA-125), C-reactive protein (CRP), soluble suppression of tumorigenicity-2 (ST2), mid-regional proatrial natriuretic peptide (MR-proANP), mid-regional proadrenomedullin (MR-proADM), and copeptin. Biomarkers were categorized according to their predominant biological pathway into 5 predefined groups: cardiac stress (NT-proBNP and MR-proANP) and injury (hsTNT), inflammation (CRP, IL-6, and GDF-15), fibrosis and extracellular matrix remodeling (P1NP and ST2), congestion (MR-proADM and CA-125), and neuroendocrine stress (copeptin).

Cutoff values for each biomarker were predefined based on reference ranges reported in the literature as part of a pre-specified analysis. These thresholds reflect the upper limits observed in healthy populations and were used to classify patients at baseline as either within or above the normal range.[10–20] Values are detailed in table S1.

NT-proBNP, hsTNT, IL-6, GDF-15, P1NP, and CA-125 were measured on the Cobas e801 analyzer (Roche, Switzerland) using the corresponding Elecsys (Roche) fully automated electrochemiluminescence immunoassays (proBNP II, Troponin T hs, IL-6, GDF-15, Total P1NP, and CA 125 II). All of these assays use a sandwich immunoassay format and are based on biotin-streptavidin technology.

CRP was measured using the CRP4 immunoturbidimetric assay (Roche), based on particle-enhanced immunological agglutination, on a Cobas c702 analyzer (Roche). ST2 was quantified using the SEQUENT-IA ST2 assay (Critical Diagnostics, United States), a latex bead-based turbidimetric immunoassay, adapted for use on the Cobas c702 analyzer (Roche).

MR-proANP, MR-proADM, and copeptin were measured using the BRAHMS MR-proANP, MR-proADM, and Copeptin proAVP assays on the BRAHMS Kryptor Compact Plus platform (Thermo Fisher Scientific, United States). These assays use time-resolved amplified cryptate emission (TRACE) technology, which measures the delayed fluorescence emitted by the immune complex.

Statistical analysis

Baseline characteristics are presented as mean ± standard deviation or median [interquartile range] for continuous variables, as appropriate, and as counts (percentages) for categorical variables. Normality was assessed using graphical methods (Q-Q plots, histograms, and boxplots) and the Kolmogorov-Smirnov test. Continuous variables with skewed distributions were log-transformed to approximate normality. All biomarker values were log-transformed due to their nonnormal distribution, and changes over time are expressed as geometric mean ratios.

Longitudinal changes from baseline were evaluated using linear mixed-effects models, with time specified as a within-subject factor and baseline biomarker category (normal vs elevated) as a between-subject factor. Models were adjusted for baseline biomarker concentrations and the following prespecified clinical covariates: age, sex, LVEF, diabetes status, estimated glomerular filtration rate (eGFR), and New York Heart Association (NYHA) functional class. Least-squares means were used to estimate within- and between-group differences, and 95% confidence intervals (95%CI) were derived using the delta method.

Interaction terms between time and 2 clinically relevant variables (diabetes and LVEF) were examined to determine whether biomarker trajectories differed among these subgroups. Between-group comparisons for continuous variables were performed using either the Student t test or the Mann-Whitney U test, depending on data distribution. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate.

For multiple comparisons across the three time points (baseline, day 30, and day 180), the Dunnett correction was applied to control the type I error rate. All statistical tests were 2-sided, with a significance level set at $P < .05$. All analyses were conducted using R version 4.3, with the *emmeans* package used to estimate marginal means.

RESULTS

Baseline concentrations

A total of 156 patients with chronic HF were included (63.5% men; mean age 70.5 ± 10.6 years; 67.9% with LVEF > 40%). Clinical characteristics of the study population are presented in the supplementary material (table S2). Baseline biomarker concentrations, obtained immediately before initiating dapagliflozin, are shown in table 1. Based on established reference values, most patients exhibited elevated cardiac biomarkers, with NT-proBNP elevated in 95.5% and high-sensitivity troponin T in 73.5%, whereas a smaller proportion had elevated MR-proANP (34.8%). Inflammatory markers related to the IL-1 axis were elevated in fewer than half of the patients (IL-6 in 40% and CRP in 35%), while GDF-15 was elevated in 56%. Most patients had normal levels of congestion biomarkers, with MR-proADM elevated in 20% and CA-125 in 8%. Regarding neuroendocrine stress, copeptin was elevated in 43% of patients. Biomarkers of fibrosis and matrix remodeling were elevated least frequently (ST2 in 8% and P1NP in 14%).

Effect of dapagliflozin in cardiac biomarkers

Changes in circulating biomarker concentrations after initiation of dapagliflozin are summarized in table 2, with relative changes from baseline illustrated in figure 1, figure 2, figure 3 and figure 4. A significant reduction in NT-proBNP concentration was observed, driven primarily by decreases among patients with elevated

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Table 1
Baseline biomarker concentrations

Biomarkers	All (n = 156)
Cardiac	
NT-proBNP, pg/mL	1409 [950-1940]
Elevated NT-proBNP *	149 (95.5)
MR-proANP, pmol/L	172 [114-229]
Elevated MR-proANP *	54 (34.8)
hsTNT, pg/mL	19.2 [14.3-31.0]
Elevated hsTNT *	114 (73.5)
Inflammatory	
ST2, ng/mL	24.3 [19.0-33.5]
Elevated ST2 *	13 (8.5)
CRP, mg/dL	0.27 [0.11-0.72]
Elevated CRP *	54 (34.6)
IL-6, pg/mL	5.67 [3.51-11.0]
Elevated IL-6 *	63 (40.4)
GDF15, pg/mL	2028 [1289-3521]
Elevated GDF15 *	87 (56.5)
Fibrosis, matrix remodelling	
P1NP, ng/mL	51.1 [36.9-81.9]
Elevated P1NP *	22 (14.1)
Congestion	
MR-proADM, nmol/L	0.28 [0.19-0.46]
Elevated MR-proADM *	31 (20.1)
CA-125, U/mL	13.3 [9.33-20.0]
Elevated CA-125 *	13 (8.3)
Stress	
Copeptin, pmol/L	11.3 [6.41-19.2]
Elevated copeptin *	66 (42.6)

CA-125, cancer antigen 125; CRP, C-reactive protein; GDF15, growth differentiation factor 15; hsTNT, high-sensitivity troponin T; IL-6, interleukin 6; MR-proADM, mid-regional pro adrenomedullin; MR-proANP, mid-regional proatrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; P1NP, procollagen type 1 N-terminal propeptide; ST2, soluble suppression of tumorigenicity 2.
The data are presented as No. (%), mean ± standard deviation, or median [interquartile range].
* The threshold used to classify the biomarkers as elevated is available in table S1 (Supplementary data).

baseline levels; this effect was already evident at day 30 (figure 1). Although no significant changes were seen in overall MR-proANP concentrations (Table 2), patients with elevated baseline levels exhibited a significant reduction (figure 1). In contrast, high-sensitivity troponin T (hsTnT9 concentrations remained stable with no significant change throughout follow-up.

Effect of dapagliflozin in inflammation

For inflammatory biomarkers (figure 2), CRP and IL-6 demonstrated similar patterns. Although no significant overall changes were detected (table 2), patients with elevated baseline levels experienced significant reductions beginning at day 30, whereas those with baseline values within the normal range showed modest increases that remained within normal limits. GDF-15, in contrast, showed an overall increase (table 2), largely attributable to rises among patients with normal baseline concentrations (figure 2).

Effect of dapagliflozin in neuro-endocrine and congestion biomarkers

Among congestion biomarkers, MR-proADM concentrations declined over the follow-up period (table 2), irrespective of baseline values. By 180 days, most patients (82.4%) had reached concentrations within the normal range (figure 3). CA-125 remained stable throughout follow-up, both in the overall cohort and when stratified by baseline status.

For the neuroendocrine stress biomarker copeptin, an apparent increase at day 30 was explained by a transient rise among patients with normal baseline levels. In contrast, patients with elevated baseline concentrations experienced a significant decline in copeptin levels (figure 3).

Effect of dapagliflozin on fibrosis biomarkers

A slight but significant reduction in P1NP was observed, again restricted to patients with elevated baseline concentrations, while ST2 demonstrated the opposite pattern: an initial increase primarily driven by patients with baseline values within the normal range (figure 4).

Table 2
Changes in biomarker parameters from baseline to 30 days and 180 days

Biomarker, units	Baseline vs 30 days			Baseline vs 180 days		
	LS mean change (95%CI)	% change (95%CI)	*p*	LS mean change (95%CI)	% change (95%CI)	*p*
NT – proBNP, pg/ml	−36.9 (−174 to 100)	−7.90 (−16.2 to 1.10)	.883	−121 (−295 to 53.6)	−17.6 (−26.5 to −7.60)	.001
MR – proANP, pmol/L	12.4 (−3.75 to 28.6)	1.00 (−5.40 to 7.80)	.762	−0.86 (−12.9 to 11.2)	−3.10 (−9.30 to 3.60)	.351
hsTNT, pg/mL	−0.12 (−1.67 to 1.44)	−0.10 (−5.20 to 5.20)	.960	0.75 (−0.91 to 2.41)	1.10 (−4.30 to 6.90)	.687
ST2, ng/mL	1.10 (−2.75 to 4.95)	1.40 (−4.50 to 7.70)	.653	1.74 (−1.49 to 5.00)	8.30 (1.90 to 15.1)	.011
CRP, mg/dL	0.08 (−0.19 to 0.36)	9.00 (−6.90 to 27.6)	.283	0.03 (−0.16 to 0.23)	5.00 (−12.3 to 25.6)	.594
IL – 6, pg/mL	−0.95 (−3.90 to 2.00)	4.40 (−6.60 to 16.8)	.446	5.85 (−3.78 to 15.5)	7.70 (−5.90 to 23.2)	.280
GDF15, pg/mL	313 (113 to 514)	14.2 (7.90 to 20.8)	<.001	534 (110 to 958)	15.8 (8.50 to 23.5)	<.001
P1NP, ng/mL	−1.79 (−5.28 to 1.70)	−3.60 (−7.80 to 0.70)	.102	4.96 (−0.66 to 10.6)	6.70 (−0.10 to 14.0)	.055
MR – proADM, nmol/L	0.03 (−0.01 to 0.07)	8.30 (−3.10 to 21.1)	.159	0.01 (−0.08 to 0.09)	−3.60 (−48.6 to −22.9)	<.001
CA – 125, U/mL	−1.25 (−4.03 to 1.53)	−2.60 (−6.80 to 1.90)	.248	1.83 (−4.12 to 7.78)	4.70 (−3.40 to 13.6)	.262
Copeptin, pmol/L	2.49 (1.30 to 3.69)	20.7 (11.9 to 30.2)	<.001	−0.35 (−1.93 to 1.23)	−5.00 (−14.3 to 5.30)	.325

95% CI, 95% confidence interval; CA-125, cancer antigen 125; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; hsTnT, high-sensitivity troponin T; IL-6, interleukin 6; LVEF, left ventricular ejection fraction; MR-proADM, mid-regional proadrenomedullin; MR-proANP, mid-regional proatrial natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; P1NP, procollagen type I N-terminal propeptide; ST2, soluble suppression of tumorigenicity 2.

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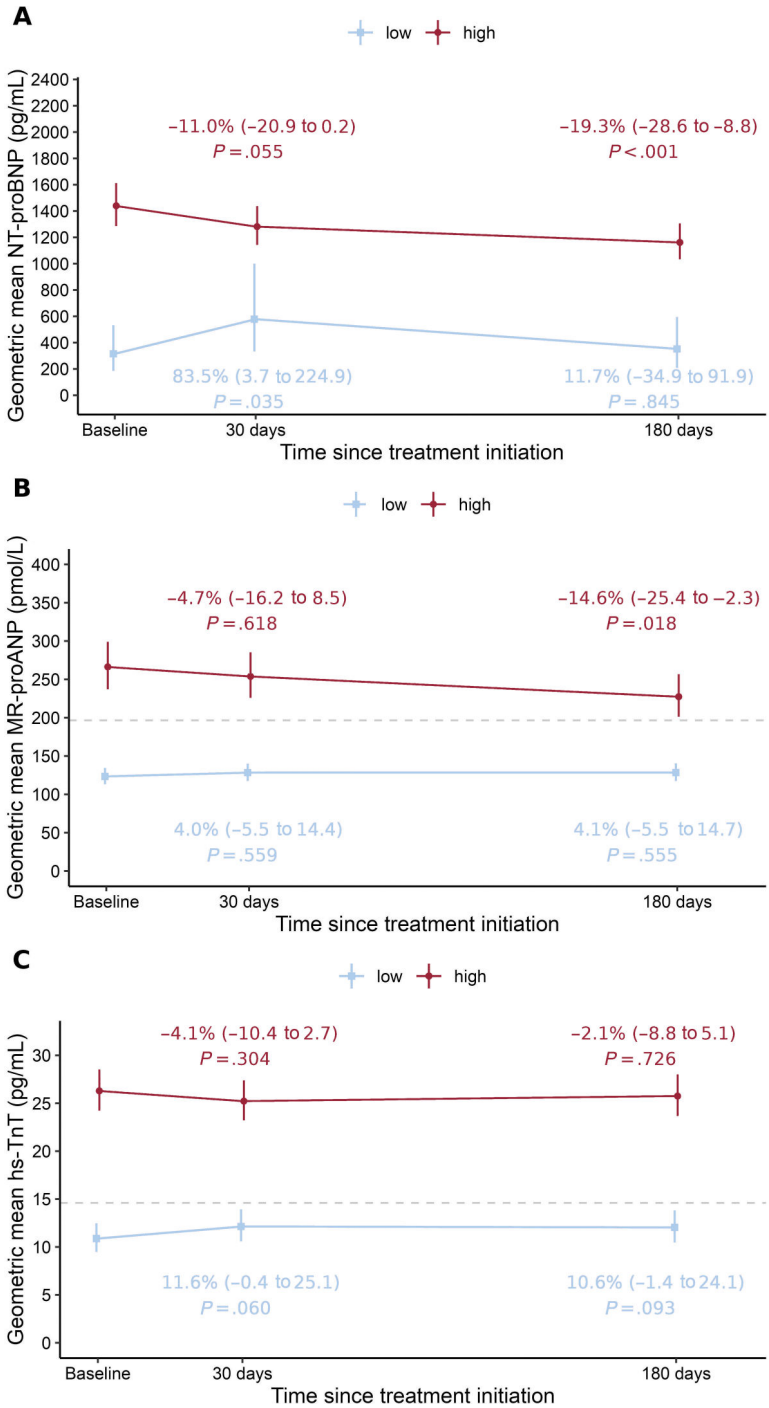

Figure 1. Changes in the cardiac biomarkers NT-proBNP (A), MR-proANP (B), and hsTnT (C) during the follow-up period (baseline, 30 days, and 180 days), differentiating patients as below or above the predefined cut-off points. Data are presented as adjusted marginal means (least-squares means) estimated from linear mixed-effects models, together with 95% confidence intervals. hsTNT, high-sensitivity troponin T; MR-proANP, mid-regional proatrial natriuretic peptide; NT-proBNP, N-terminal probrain natriuretic peptide.

Interaction analyses

Exploratory interaction analyses between time and diabetes status or LVEF revealed no statistically significant effects for any biomarker ($P > .1$ for all analysis), indicating that biomarker trajectories were consistent irrespective of baseline LVEF phenotype or diabetic status.

DISCUSSION

This study characterizes the pathophysiological profile of a well-defined cohort of patients with established chronic heart failure, using 11 circulating biomarkers that reflect 5 key biological pathways involved in the pathogenesis of HF. It also evaluates their response to the initiation of dapagliflozin. In this population,

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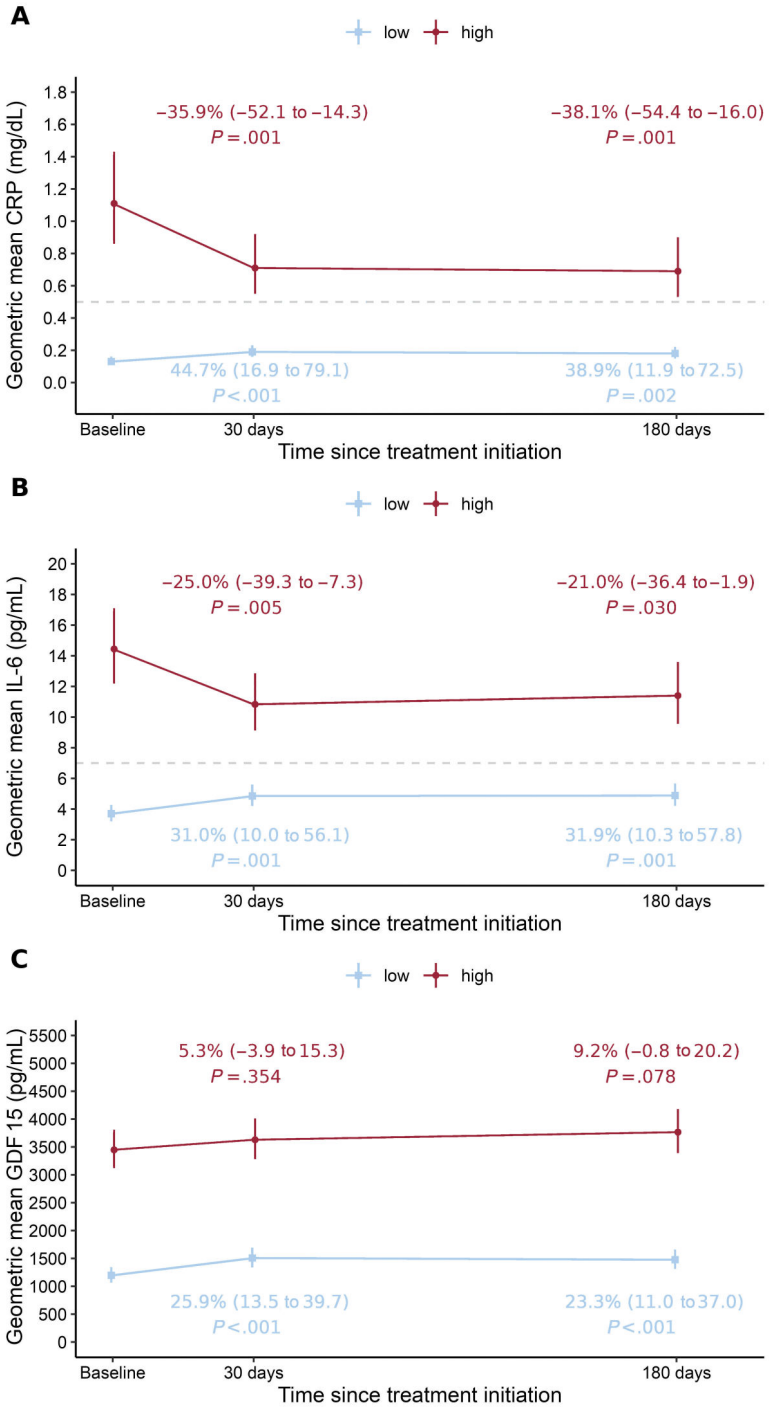

Figure 2. Changes in the inflammation biomarkers CRP (A), IL-6 (B,) and GDF-15 (C) during the follow-up period (baseline, 30 days, and 180 days), differentiating patients as below or above the predefined cut-off points. Data are presented as adjusted marginal means (least-squares means) estimated from linear mixed-effects models, together with 95% confidence intervals. CRP, C-reactive protein; GDF-15, growth differentiation factor 15; IL-6, interleukin 6.

biomarkers of cardiac stress, inflammation, and neuroendocrine activation emerged as the primary indicators of the presence of disease. Furthermore, dapagliflozin initiation was associated with improvements across several pathophysiological pathways, including reductions in cardiac natriuretic peptides (NT-proBNP and MR-proANP), inflammatory markers within the IL-1 axis (CRP and IL-6), MR-proADM, copeptin, and P1NP. Notably, these effects were most pronounced in patients with elevated baseline levels (figure 5).

We assessed NT-proBNP and MR-proANP levels as indicators of ventricular and atrial cardiac stress, respectively, and hsTnT levels as a marker of myocardial injury. Both natriuretic peptides, NT-proBNP and MR-proANP, showed a significant reduction over the 180-day period in patients with elevated baseline levels. This observation agrees with previous evidence demonstrating that treatment with SGLT2i exerts a beneficial effect in lowering NT-proBNP concentrations in patients with heart failure, irrespective of reduced or preserved ejection fraction.[6] Atrial natriuretic

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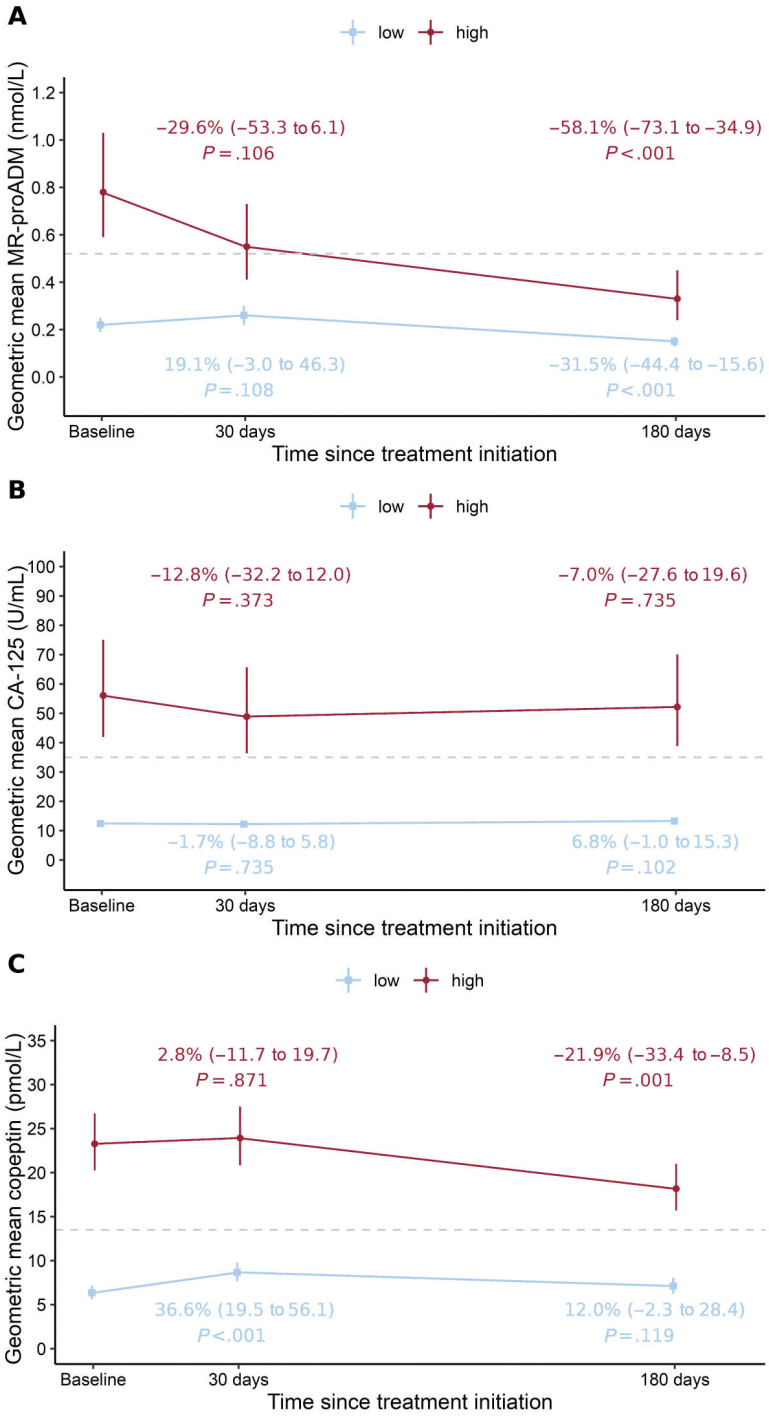

Figure 3. Changes in the congestion biomarkers MR-proADM (A) and CA-125 (B), and neurohormonal stress biomarker copeptine (C) during the follow-up period (baseline, 30 days, and 180 days), differentiating patients as below or above the predefined cut-off points. Data are presented as adjusted marginal means (least-squares means) estimated from linear mixed-effects models, together with 95% confidence intervals. CA-125, cancer antigen 125; MR-proADM, mid-regional proadrenomedullin.

peptides have been less extensively studied; however, some small-scale studies have reported a significant reduction following treatment with SGLT2i.[5] However, hsTnT levels remained stable throughout the study period, consistent with findings from the DAPA-HF trial, which reported a nonsignificant trend toward attenuation of the increase in hsTnT from baseline to 12 months in patients treated with dapagliflozin compared with placebo.[21] It is plausible that SGLT2i may blunt the progressive rise in hsTnT levels in patients with HF, potentially reflecting a deceleration in disease progression.

We also analyzed 3 inflammatory biomarkers: IL-6, CRP, and GDF-15. Among the IL-1 axis-related markers, both IL-6 and CRP levels decreased over the 30-day and 180-day periods. Interestingly, patients with elevated baseline levels experienced a

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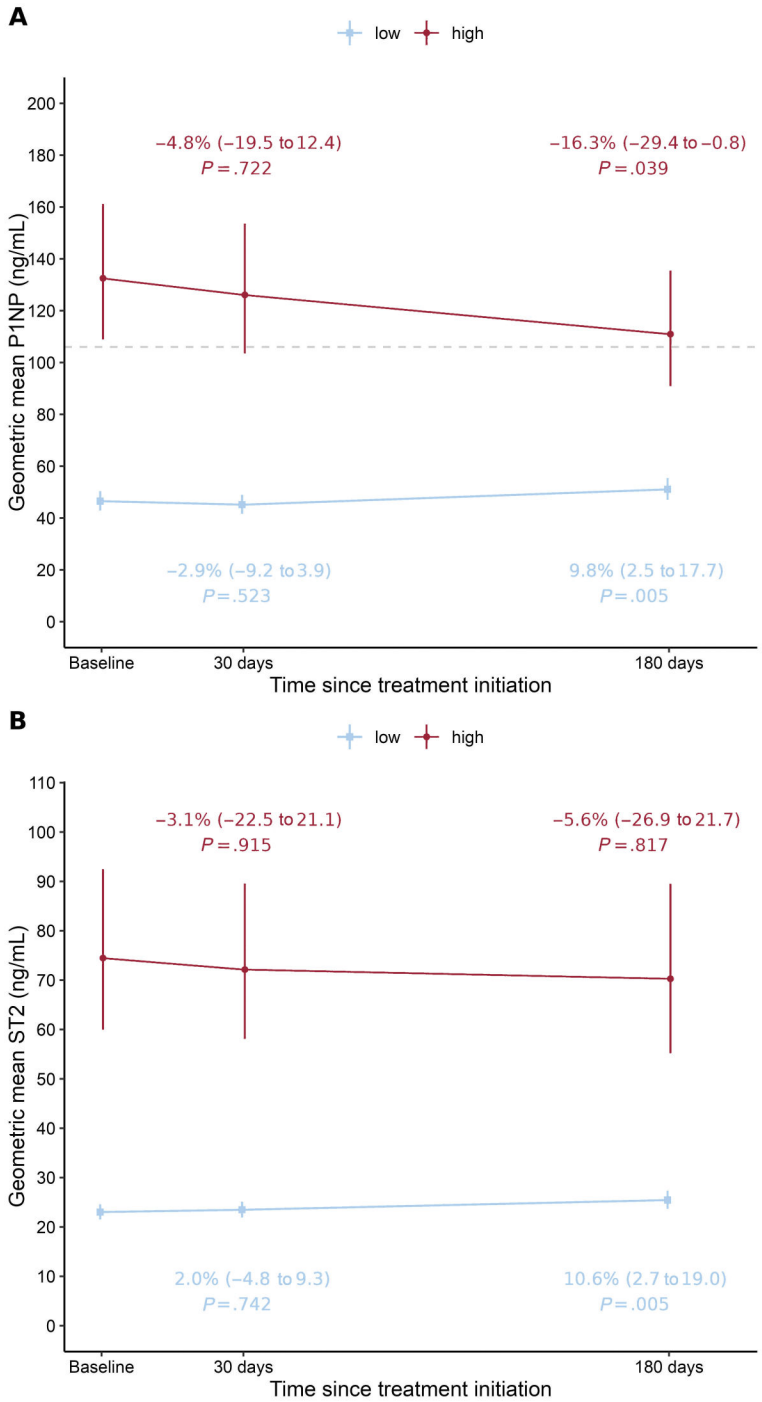

Figure 4. Changes in the fibrosis biomarkers P1NP (A) and ST2 (B) during the follow-up period (baseline, 30 days, and 180 days), differentiating patients as below or above the predefined cut-off points. Data are presented as adjusted marginal means (least-squares means) estimated from linear mixed-effects models, together with 95% confidence intervals. P1NP, procollagen type 1 N-terminal propeptide; ST2, soluble suppression of tumorigenicity 2.

significant reduction in both biomarkers, whereas those with low baseline levels exhibited a statistically significant increase, although it was not sufficient to exceed the established threshold. The decrease in IL-6 and CRP levels has been previously described in HF patients receiving dapagliflozin,[8] and it reveals a significant reduction in the inflammatory state. Regarding GDF-15 levels, we observed a significant increase in patients both below and above the normal reference range. Similarly, data from the EMPEROR program and the EMPIRE-HF Biomarker substudy showed that treatment with empagliflozin was associated with a significant elevation in GDF-15 levels.[7,22] Given the concurrent improvements observed in other biomarkers, it seems unlikely that the increase in GDF-15 levels induced by SGLT2i reflects a deterioration in cardiac function. Rather, it has been suggested that GDF-15 may act as a beneficial metabolic regulator, with associations reported between elevated levels and weight loss, improved glucose tolerance, and

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Figure 5. Central illustration. Frequency of elevated biomarkers belonging to the 5 different pathobiological pathways studied in a population of 156 stable ambulatory chronic heart failure patients from the DAPA-MODA trial. The initiation of dapagliflozin was associated with improvements in several pathophysiological systems, predominantly in patients with elevated baseline levels, including both natriuretic peptides (NT-proBNP and MR-proANP), the IL-1 related inflammatory axis (CRP and IL-6), congestion (MR-proADM), neuroendocrine stress (copeptin), and fibrosis (P1NP).
CA-125, cancer antigen 125; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; HF, heart failure; hsTNT, high-sensitivity troponin T; IL-6, interleukin 6; MR-proADM: mid-regional pro adrenomedullin; MR-proANP, mid-regional proatrial natriuretic peptide; NT-proBNP, N-terminal probrain natriuretic peptide; P1NP, procollagen type 1 N-terminal propeptide; ST2, soluble suppression of tumorigenicity 2.

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reduced food intake and appetite.[23] Further research is needed to confirm this apparently contradictory elevation of GDF-15, and the underlying mechanisms and clinical implications in the context of SGLT2 inhibition.

CA-125 and MR-proADM were assessed as biomarkers of congestion. While no significant change was observed in CA-125 levels, MR-proADM showed a significant reduction in patients with elevated baseline values, with the majority reaching normal levels by day 180. Unlike in acute HF, where SGLT2i have been associated with a significant reduction in CA125 levels during the early postdischarge period,[24] the absence of an effect on CA125 in the present study may reflect the clinical stability of the cohort, characterized by low baseline levels. Similar findings have previously been reported in stable HF populations.[25] Interpretation of CA125 may be influenced by the fact that 21% of participants had a history of cancer, although none had an active malignancy in the previous year or a condition affecting life expectancy.

In contrast, the reduction in MR-proADM suggests that this biomarker may reflect changes in vascular permeability rather than a decrease in residual congestion. This biomarker has not been extensively studied in HF patients treated with SGLT2i, but previous studies, such as the EMPIRE-HF trial, reported no significant variation in MR-proADM concentrations.[26]

We also measured copeptin levels as a biomarker of neurohormonal stress. Although levels appeared to increase at 30 days in the overall population, a significant reduction was observed at 180 days among patients with elevated baseline values. This initial rise is consistent with findings from the EMPIRE-HF trial and the DAPA-SHUTTLE trial at 12 and 4 weeks, respectively, and may reflect enhanced vasopressin release in response to early SGLT2i therapy.[26,27] Such a response likely promotes renal water conservation and stabilizes urine volume, thereby counterbalancing the osmotic diuretic effect of glucosuria during the initial phase of treatment.[27] However, this effect does not appear to persist over the longer term, and our findings at 180 days suggest a progressive decline in vasopressin demand, indicative of improved neurohormonal status over time.

Lastly, we examined P1NP and ST2 as biomarkers of extracellular matrix remodeling and fibrosis. P1NP levels showed a significant reduction among patients with elevated baseline values. Although this biomarker has not been extensively studied in patients with chronic heart failure (CHF), the EMPEROR trial reported no significant effect of SGLT2i therapy on P1NP levels.[28] P1NP is known to reflect collagen synthesis and extracellular matrix remodeling. This is central processes in cardiac fibrosis and myocardial stiffening following injury, which contribute to the pathogenesis and progression of CHF. Our findings may indicate a meaningful improvement in this regard. In contrast, no significant changes in ST2 levels were observed, apart from a slight increase among patients with baseline values within the normal reference range. This may reflect sustained fibrotic activation mediated by the IL-33/ST2 signaling pathway,[29,30] which appears unresponsive to SGLT2 inhibition. This finding contrasts with results from a previous small study in which dapagliflozin significantly reduced ST2 levels in HF patients with type 2 diabetes.[8]

Several previous studies have evaluated these pathophysiological pathways in both acute decompensated HF and chronic HF. The EMPIRE-HF trial investigated the effect of empagliflozin over a 12-week period on a selection of similar biomarkers in patients with stable HF with reduced ejection fraction receiving optimal medical therapy, including NT-proBNP, MR-proANP, MR-proADM, and copeptin, among others.[26] In contrast, our study included patients with HF irrespective of LVEF, reflecting the established clinical benefit of SGLT2i throughout the spectrum of LVEF phenotypes. In this population of clinically stable patients receiving optimal HF therapy, dapagliflozin exerted effects on multiple pathophysiological pathways, though its impact was concentrated in a subset of specific biomarkers. These findings provide mechanistic support for the clinical benefits observed with SGLT2 inhibition and suggest which biomarkers may be most useful for monitoring treatment response to this evidence-based therapy.

Our study builds upon insights from previous multibiomarker investigations, such as the EMPIRE-HF trial, and contributes to the growing body of evidence regarding the effects of SGLT2i therapy on distinct pathophysiological pathways in HF. Importantly, it should be emphasized that a simple analysis based solely on absolute biomarker concentrations may lead to misleading or invalid conclusions. Categorization into high and low biomarker levels was prespecified and defined before conducting statistical analyses, based on established reference normal values for each biomarker, and the therapeutic effect of dapagliflozin became evident only when considering baseline overactivation of the relevant pathways. The most pronounced effect was observed in cardiac natriuretic peptides, but meaningful changes were also detected in biomarkers related to inflammation, congestion, neurohormonal stress, and extracellular matrix remodeling.

Overall, all our findings highlight a key observation: the effect of treatment on circulating biomarkers appears to depend on their baseline levels. Patients with elevated baseline values experienced a more pronounced response in biomarkers, whereas those with values within the normal range showed minimal or no changes. This pattern suggests a differential biological response, potentially reflecting a normalization process rather than a uniform pharmacological effect. These results support the relevance of baseline biomarker profiling to better understand individual treatment responses.

Limitations

The main limitation of this study is its open-label design without a control group, which restricts the ability to establish definitive causal links between dapagliflozin and biomarker changes. At the time of the study, implementing an internal control group was not feasible. We recognize that, under such circumstances, adjusted analyses incorporating external cohorts should be included in future research. To mitigate this limitation, all participants were clinically stable, allowing a more confident attribution of effects to the treatment. Biomarker analyses were performed with investigators blinded to patient identity and sampling time, enhancing reliability. Findings are limited to stable ambulatory chronic HF patients and may not apply to acute settings. Additionally, the low event rate prevents prognostic interpretation. These limitations highlight the need for cautious interpretation of the results.

CONCLUSIONS

In a population of stable chronic HF patients from the DAPA-MODA trial, dapagliflozin initiation was associated with improvements in several pathophysiological systems, including both natriuretic peptides (NT-proBNP and MR-proANP), IL-1 related inflammatory axis (CRP and IL-6), congestion (MR-proADM), neuroendocrine stress (copeptin) and fibrosis (P1NP). These effects were predominantly observed in patients with elevated baseline levels.

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FUNDING

This study was sponsored by the Spanish Society of Cardiology and has received funding by an unconditional investigational grant from Astra Zeneca.

ETHICAL CONSIDERATIONS

The study protocol was approved by the Institutional Ethics Committees (ESR/20/20594), and all participants were required to sign an informed consent prior to enrolment. The investigation was conducted in accordance with the principles outlined in the Declaration of Helsinki, and SAGER guidelines regarding potential sex/gender bias have been followed.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this article.

AUTHORS' CONTRIBUTIONS

Each author contributed significantly to the submitted work as follows: V. Martínez-Pina contributed to data collection and interpretation, as well as drafting and revising the final manuscript. A. Riquelme-Pérez contributed to the statistical analysis and interpretation of the data, and to drafting and revising the final manuscript. A. Bayés Genís, J. Nuñez, I. Cebreiros, H. Morillas, M. Cobo-Marcos, J. M. García-Pinilla, J. F. Rodríguez-Palomares, D. Dobarro, M. A. Restrepo-Córdoba, J. R. González-Juanatey, and J. L. Zamorano critically revised the manuscript for important intellectual content. J. A. Noguera-Velasco and D. A. Pascual-Figal contributed to the conception and design of the work, the analysis and interpretation of data, and critically revised the manuscript for important intellectual content. All authors approved the final version of this manuscript.

CONFLICTS OF INTEREST

D. A. Pascual-Figal has received consultancy and speaker fees from AstraZeneca, Novartis, Roche Diagnostics, Pfizer, Vifor, Rovi, and Bayer. A. Bayés-Genís has participated in advisory boards and/or delivered lectures for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor. H. Morillas has received speaker fees from AstraZeneca. J. Nuñez has received consultancy and speaker fees from AstraZeneca, Alleviant, Amgen, Bayer, Boehringer Ingelheim, CSL Vifor, Daiichi Sankyo, GSK, Lilly, Pfizer, Novartis, Novo Nordisk, and Rovi. M. Cobo reports consultancy and lecture fees from AstraZeneca, Vifor Pharma, Novartis, Rovi, Boehringer Ingelheim, Novo Nordisk, and Bayer. The remaining authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

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

APPENDIX A. DAPA-MODA STUDY INVESTIGATORS

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APPENDIX B. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rec.2025.11.014

WHAT IS KNOWN ABOUT THE TOPIC?

- SGLT2i are currently recommended in clinical guidelines for the treatment of HF, regardless of LVEF.
- The beneficial effects of SGLT2i are mediated through multiple cardiovascular mechanisms, including both cardiac and renal protection.
- However, data on the impact of SGLT2i on biomarkers remain incomplete, with some studies assessing only some of them and others with inconsistent findings, particularly concerning B-type natriuretic peptides and inflammatory markers.

WHAT DOES THIS STUDY ADD?

- In a well-defined population with stable chronic HF, including both reduced and preserved LVEF, there was a predominance of alterations in cardiac biomarkers of both stress and damage, as well as neuroendocrine stress and inflammatory markers, with minimal involvement of markers of congestion and fibrosis.
- Dapagliflozin initiation was associated with improvements in elevated biomarkers reflecting disrupted pathways, which included both natriuretic peptides (NT-proBNP and MR-proANP), IL-1 inflammatory axis (CRP and IL-6), congestion (MR-proADM), neuro-endocrine stress (copeptin) and fibrosis (P1NP).
- This study highlights the broad biological effects of dapagliflozin in reversing and slowing the progression of chronic HF, showing its influence on multiple pathophysiological systems, but with a differential effect on altered biomarkers.

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