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Left ventricular reverse remodeling after combined ARNI and SGLT2 therapy in heart failure patients with reduced or mildly reduced ejection fraction

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ABSTRACT

Background: Cardiac remodeling is an adverse phenomenon linked to heart failure (HF) progression. Cardiac remodeling could represent the real therapeutic goal in the treatment of patients with HF and reduced ejection fraction (HFrEF), being potentially reversed through different pharmacotherapies. Currently, there are well-established drugs such as ACEi/ARBs and β-blockers with anti-remodeling effects. More recently, ARNI effects on cardiac remodeling were also demonstrated; additional potential benefits of gliflozins remain non clearly demonstrated.

Aim of study: To evaluate possible changes in cardiac remodeling in patients with HFrEF/HFmrEF in treatment with ARNI or ARNI plus SGLT2i and the potential benefit on cardiac remodeling of adding SGLT2i to ARNI.

Methods: Between June 2021 and August 2023, 100 consecutive patients with HFrEF/HFmrEF underwent conventional and advanced echocardiography (TDI, 2DSTE): patients were therefore divided into three groups according to therapy with neither ARNI nor SGLT2i, just ARNI or both. After 3 months, all patients underwent echocardiographic follow-up.

Results: After a 3 months of therapy, significant improvements were observed for LVEF, LVEDD, LVEDV, LVESV, LV mass, E/e', LV GLS, TAPSE (ANOVA $p< 0.01$ in all cases), RV S' velocity (ANOVA $p< 0.001$).

The trend in favor of additional treatment with SGTL2i over ARNI remained statistically significant even after multivariable analysis ($p< 0.001$ for LVEF, LVEDD; $p< 0.01$ for LV GLS, TAPSE, TRVS; $p< 0.05$ for LV mass).

Conclusions: SGLT2i therapy when added to the standard treatment for HFrEF and HFmrEF is associated with an improved biventricular function and ventricular dimensions at follow-up.

1. Introduction

Heart failure (HF) is a clinical syndrome with a high prevalence in Western countries, often associated with rehospitalizations and increased mortality in the first months after discharge [1]. The progression of HF can be revealed through a dilation of the cardiac

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chambers associated with systolic/diastolic dysfunction, defined as remodeling. Cardiac remodelling is a combination of physiologic and pathophysiologic changes occurring in response to cardiac injury, pressure overload, or volume overload through different types of insults, which share common pathways [2]. Consequently, functional, structural, biochemical, as well as cellular and molecular changes are observed as the heart remodels, in a deleterious process linked with progressive ventricular dysfunction and HF decompensation [3].

Treatments indicated in patients with (NYHA class II–IV) HF with reduced left ventricular ejection fraction (HFrEF. LVEF<40 %) are provided in the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic HF [4], resembling the so called 'four pillars' for the pharmacological management of patients with HFrEF. ACE-i or Sacubitril/Valsartan (ARNI), beta-blockers, mineral-corticoid receptor antagonists (MRA) and Sodium-glucose-co-transporter-2-inhibitors (SGLT2i) are all indicated in HFrEF to improve cardiovascular outcome. A recent update in the 2023 recommended SGLT2i drugs also for the management of patients with HFmrEF and HFpEF [5].

Cardiac remodeling could represent the real therapeutic goal in the treatment of patients with HFrEF, being potentially reversed through different therapies [6]. The remodeling effect of ARNI [7,8] and SGLT2i have been already shown in several clinical studies [9,10]. Less is known however on possible combined effect of both new classes of drugs, ARNI and SGLT2i, in improving LV function. We therefore sought to investigate, in patients with chronic HF and reduced / mildly reduced LVEF, the therapeutic impact of combined ARNI/SGLT2i on cardiac remodelling evaluated by echocardiography.

2. Methods

One hundred consecutive subjects, enrolled in the Daunia Heart Failure registry [11,12,13] were included in this study from June 2021 to August 2023. Inclusion criteria were: CHF with LVEF < 50 %, age $>$ 18 years, glomerular filtration rate (eGFR) $>$ 30 ml/min/1,73 m^2, medical therapy with ACE-i/ARBs, MRI, and beta-blockers for HF. Exclusion criteria were HFpEF (LVEF ≥ 50 %), type-1 diabetes mellitus (DM), recurrent urinary tract infections, poor echo window, eGFR < 30 ml/min/1,73 m^2, cardiac resynchronization therapy (CRT) device, MitraClip, percutaneous coronary intervention (PCI), and coronary artery by-pass graft (CABG) within the previous 3 months.

Medical history, heart rate, systolic blood pressure, Body Mass Index, NYHA functional class, and medications were recorded and monitored. All patients underwent blood analysis. All patients were subject to evaluation of left and right ventricle function, by echocardiography (conventional, Tissue Doppler Imaging (TDI) and strain echocardiography) in an ambulatory setting, under resting conditions at the beginning and after 3 months of therapy with SGLT2i.

The follow-up time for patients was of three months from the start of the therapy.

2.1. Echocardiography

Conventional echocardiography was used to assess dimensional parameters (LV dimensions, Atrial dimensions, Left atrial area, Atrial and Ventricular Volumes, Left ventricular mass), functional parameters of the left ventricle (LVEF) and of Right ventricle (tricuspid annular plane systolic excursion (TAPSE), tissue Doppler velocity of the lateral tricuspid annulus S′, value of systolic Pulmonary Artery Pressures (sPAP) [14]), Doppler/Color parameters (trans-mitral early E and late diastolic A LV filling peak velocities, E/A ratio LV filling velocity, TDI measurements, included E′ and E/E′ ratio).

LV dimensions and LVEF were calculated according to recommendations from the joint ASE/ESC (American Society of Echocardiography/European Society of Cardiology) guidelines [15].

sPAP were estimated using the approach of calculating the systolic pressure gradient between right ventricle and right atrium by the maximum velocity of the tricuspid regurgitant jet, using the modified Bernoulli equation and then adding to this value the estimated right atrial pressures based on both sizes of the inferior vena cava and the change in caliber of this vessel with respiration, according to international recommendations [14]. The degree of tricuspid regurgitation was evaluated by the color mode. Transthoracic echocardiography was performed using an EPIQ 7C ultrasound system with X5-1 matrix array transducer (Philips Healthcare). All echocardiographic studies were performed and interpreted by experienced physicians, who were blinded of clinical data.

Patients were considered as positively remodeling in case of improved values at follow up examination compared to baseline values: changes in parameters were considered as a continuous variable.

2.2. Speckle-tracking strain analysis for GLS

Speckle-tracking strain analysis was performed for each patient with the aid of a dedicated software (Qlab 10) that evaluates LV longitudinal function, assessed in terms of GLS. Briefly, apical 4-, 2- and long-axis views, with the Digital Imaging and Communications in Medicine (DICOM) formatted file images, were uploaded onto a personal computer for subsequent off-line GLS analysis. Longitudinal speckle-tracking strain was calculated applying an automated contouring detection algorithm and regions of interest manual adjustments were performed where necessary. GLS was then determined as the 16 LV segments averaged longitudinal strain peaks and was expressed as an absolute value in accordance with current recommendations of the EACVI/ASE/Industry Task Force [16].

2.3. Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with Student's *t*-test, for paired and unpaired groups as required, categorical variables as percentages and compared with X^2 test. Differences among groups were assessed with one-way ANOVA. Correlations were assessed with Pearson's test. Differences significant at univariable analysis were used for a multivariable regression analysis model. A $p < 0.05$ was considered as statistically significant.

Sample sizing With differences at echocardiography parameters as previously reported, a 80 % power, and an alpha < 0.05, groups with at least 15 patients were required for significant one-way ANOVA comparisons [9].

3. Results

One hundred consecutive HF outpatients and LVEF < 50 % were enrolled in the study; their characteristics are given in Table I and Supplement Table S1. 84 % were men, most in NYHA class II (60 %, 37 % class III). 79 % had an implantable cardiac device (30 % CRT-D), 76 % were on therapy with ACEi/ARB/ARNI drugs, 94 % with β-blocker, 61 % with MRA, 84 % with loop diuretic.

Patients were therefore classified into 3 groups: patients neither in treatment neither with ARNI nor SGLT2i (Control group, N = 24), patients in treatment with ARNI (N = 28), and patients in treatment with

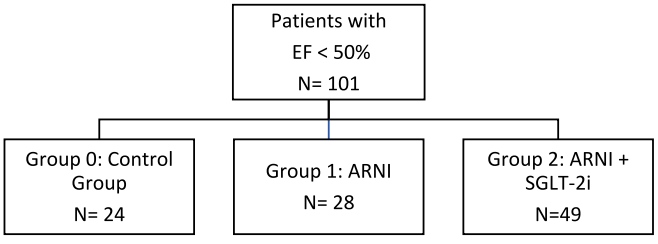

Fig. 1. Graphical representation of the subjects included in the study.

both ARNI and SGLT2i (N = 49). A Graphical representation of the population is reported in the Fig. 1. A comparison between groups at baseline is given in Table 1,Table 2. Baseline significant differences were found for the prevalence of atrial fibrillation/flutter (ANOVA p = 0.034), diabetes (ANOVA p = 0.001), beta-blockers (ANOVA p = 0.033), MRI (ANOVA p = 0.003).

After a 3 months of therapy, significant improvements were observed for LVEF, LVEDD, LVEDV, LVESV, LV mass, E/e', LV GLS, TAPSE (ANOVA p < 0.01 in all cases), RV S' velocity (ANOVA p < 0.001) (Fig. 2).

The trend in favor of additional treatment with SGTL2i over ARNI remained statistically significant even after multivariable analysis in a regression model including most variables statistically significant at univariable analysis (age, gender, diabetes, atrial fibrillation, beta-blockers and MRI therapy, baseline LVEF and LVEDD) (p < 0.001 for LVEF, LVEDD; p < 0.01 for LV GLS, TAPSE, TRVS; p < 0.05 for LV mass).

4. Discussion

In this study we show for the first time an additional reverse remodeling effect of SGLT2i over ARNI in subjects with HF and reduced / mildly reduced LVEF.

Therapy induced reverse remodeling has been understood as responsible for the significant improvement in the prognosis of HF and it is currently acknowledged as a measure of therapy efficacy.

While the effects of ARNI on the remodeling of the ventricular chambers have been reported [17,18,19], there are not many data available on a possible additional effect of SGLT2i [20,21]. The introduction of ARNI represented a significant advancement in the therapy of HFrEF, with a 20 % reduction in cardiovascular death risk and a 21 % decrease in HF hospitalization compared to the Renin-Angiotensin System (RAS) blocker enalapril [22]. Subsequent studies confirmed that ARNI's prognostic benefits correlate with substantial improvements in echocardiographic parameters [23,24,25].

The cardiovascular benefits of SGLT2i have been reported in several randomized controlled trials, especially their role in reducing the risk of composite worsening of HF in HFrEF [26,27] and in Type 2 Diabetes [28,29]. However, an interesting question remains open: which are the potential direct and indirect mechanisms to explain the effects of SGLT2-i on myocardial remodeling? It is likely that SGLT2-i activate several mechanisms intersecting hemodynamic, metabolic, and neurohumoral pathways that go beyond the glucose-lowering effect. At the same time, together with some possible new and unconventional pathways, some "simple" established effects of SGLT2-I as modest weight loss and blood pressure reduction, diuretic and reno-protective effects may be specifically advantageous in patients with obesity, those with hypertension and patients with HF and renal disease [30].

The distinct cardioprotective mechanisms of ARNI and SGLT2i

Table 1
. Population's characteristics and changes at follow up.

	All	neither	ARNI	ARNI+ SGLT2i	
	100	N 23	N 28	N 49	p
Male (%)	85	78	89	86	0.3480
Age (years)	69 ± 10	71 ± 9	67 ± 12	69 ± 9	0.3270
Diabetes (%)	73	96	82	57	**0.0010**
Hypertension (%)	83	91	75	84	0.2810
Ischemic heart disease (%)	52	65	43	51	0.3470
Atrial fibrillation (%)	32	52	29	24	**0.0340**
Implantable device (%)	80	74	100	67	0.1730
Beta-blockers (%)	94	100	100	88	**0.0330**
MRI (%)	62	35	64	73	**0.0030**
NYHA class	2.3 ± 0.5	2.2 ± 0.5	2.4 ± 0.5	2.4 ± 0.5	0.1820
LVEF (%)	34 ± 7	40 ± 7	30 ± 5	34 ± 6	**0.0001**
Changes in					
LVEF (%)		1 ± 8	15 ± 12	18 ± 18	**0.0050**
LVEDD		3 ± 10 %	−1±5 %	−5 ± 7 %	**0.0040**
LVESD		5 ± 13 %	−4±10 %	−2 ± 12 %	0.3040
LVEDV		−1 ± 17 %	−2±10 %	−4 ± 20 %	**0.0080**
LVESV		0 ± 18 %	−9±12 %	−9 ± 24 %	**0.0020**
LV mass		7 ± 26 %	−4 ± 18 %	−7 ± 15 %	**0.0040**
LV indexed mass		8 ± 24 %	−4 ± 19 %	−10 ± 20 %	0.0530
E/e'		2 ± 32 %	−7 ± 32 %	−12 ± 29 %	**0.0060**
LV GLS		2 ± 7 %	25 ± 30 %	30 ± 26 %	**0.0060**
TAPSE		2 ± 14 %	7 ± 15 %	14 ± 14 %	**0.0030**
RV S' velocity		−9 ± 14 %	14 ± 30 %	12 ± 11 %	**0.0001**
sPAP		4 ± 21 %	−5 ± 32 %	−12 ± 23 %	**0.0660**

Abbreviations: BNP, brain natriuretic peptide; NYHA, New York Heart Association; MRI, mineralcorticoid receptor inhibitors. LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; TAPSE, tricuspid annular plane systolic excursion; RV S' velocity, right ventricle S' velocity; E/e', early ventricular filling velocity (**E**) to early diastolic tissue velocity mitral annulus; LV GLS, left ventricle global longitudinal strain; sPAP, systolic pulmonary arterial pressure.

Table 2
Statistically significant multivariable regression analysis for number of drugs used (number of drugs 0 neither, 1 ARNI, 2 ARNI+SGLT2i) and changes in echocardiographic parameters indicative of positive remodeling.

Changes in LVEF	b	Std.Err.	p-value
Number of drugs	0.07658	0.01997	0.0002
Age (years)	0.00139	0.00149	0.3538
Male	−0.03504	0.04074	0.3920
Diabetes	0.00608	003501	0.8626
Baseline LVEF	−0.00268	0.00202	0.1866
changes in sPAP			
number of drugs	−0.07453	003393	0.0308
age (years)	0.00118	0.00259	0.6505
Male	−0.09583	0.06979	0.1734
Diabetes	−0.04610	0.06054	0.4485
baseline sPAP	−0.00811	0.00253	0.0019
changes in TAPSE			
number of drugs	0.06690	001818	0.0004
age (years)	−0.00051	0.00139	0.7126
Male	−0.08299	0.03762	0.0301
Diabetes	0.00748	0.03255	0.8188
baseline TAPSE	−0.01803	0.00437	0.0001
changes in LVEDD			
number of drugs	−0.03240	0.00951	0.0010
age (years)	−0.00029	0.00073	0.6946
Male	0.00602	0.01981	0.7618
Diabetes	0.01193	0.01719	0.4894
baseline LVEF	−0.00217	0.00099	0.0315
changes in NT-proBNP			
number of drugs	−0.32324	0.08410	0.0004
age (years)	0.00185	0.00639	0.7730
Male	0.14661	0.17435	0.4050
Diabetes	−0.11994	0.15289	0.4370
baseline NT-proBNP	−0.00003	0.00003	0.3090
number of drugs: 0 neither, 1 ARNI, 2 ARNI+SGLT2i			

LVEF left ventricular ejection fraction; sPAP systolic pulmonary arterial pressure; TAPSE Tricuspid Annular Plane Systolic Excursion; LVEDD left ventricular end diastolic diameter, NT-proBNP N-terminal pro b-type natriuretic peptide.

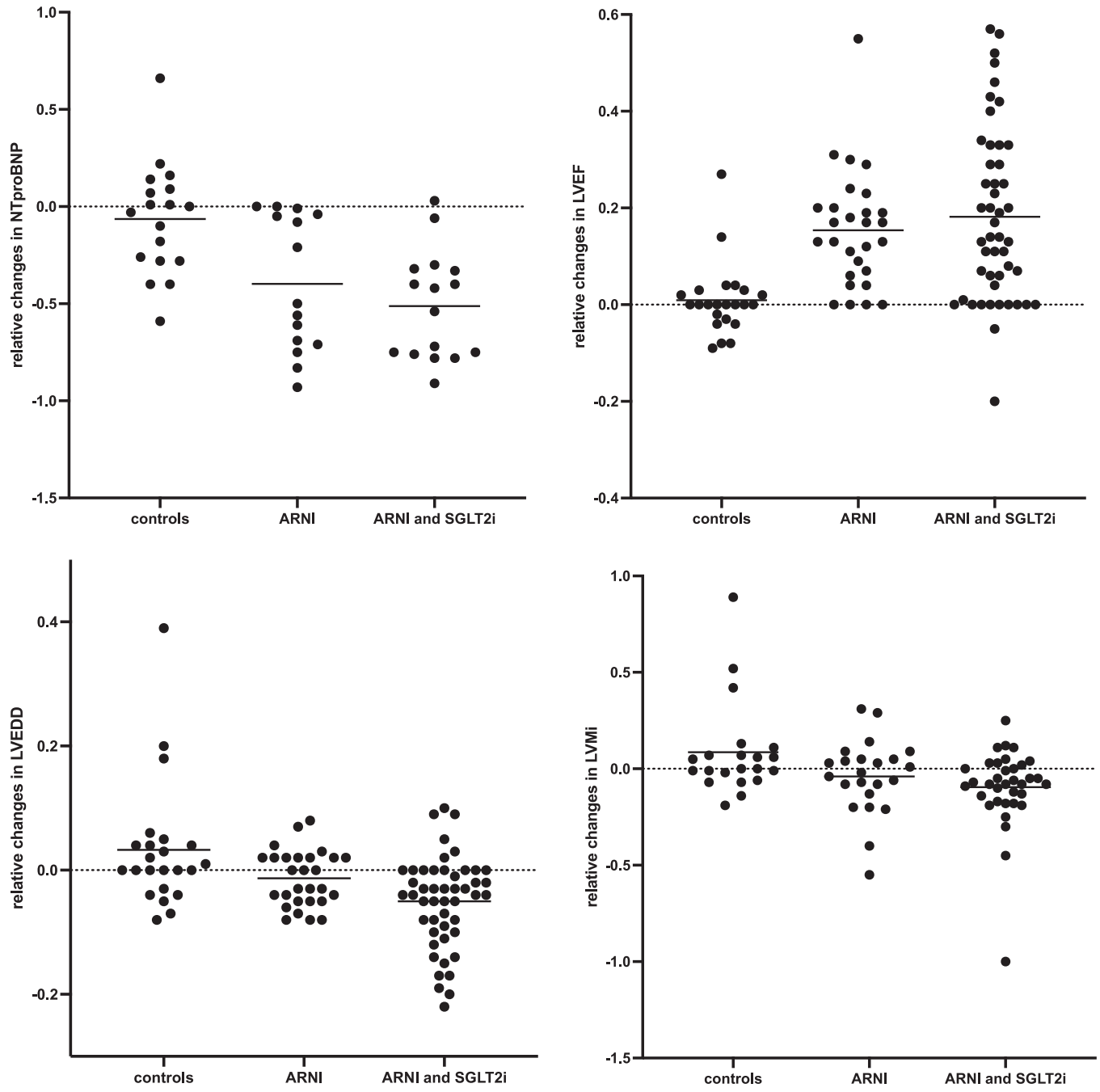

Fig. 2. Changes of echocardiographic parameters and NT-proBNP at 3-month follow up.

suggest potential synergies when used together. Trials like DAPA-HF and EMPEROR-Reduced demonstrated consistent benefits in HFrEF treatment, irrespective of ARNI use [31,32]. While evidence of synergy is often inferred from subgroup analysis, our study, dividing patients into groups based on ARNI and ARNI+SGLT2i use, showed HFrEF patients on combination therapy had more reverse remodeling compared to those on individual or no drug treatment. This aligns with previous research, reinforcing the idea that ARNI and SGLT2i, acting independently, provide additional advantages in HF treatment.

Kim et al. [33], in a retrospective study, found that combining ARNI and SGLT2i resulted in a more significant enhancement of cardiac function and a reduced risk of cardiovascular death and hospitalization for HF in diabetic patients with HFrEF. The combination therapy showed greater improvements in LVEF and a decrease in mitral E/e′ ratio compared to using ARNI or SGLT2i alone or neither. Notably, initiating ARNI therapy first, regardless of baseline SGLT2i use, led to more pronounced cardiac function improvement than vice versa. These findings align with our own results, indicating that the ARNI-SGLT2i combination could enhance clinical outcomes in HFrEF patients, with potential additional advantages associated with early initiation of the combined therapy. Furthermore, our study extends its scope to include non-diabetic individuals, proving a broader perspective for comparative analysis with the referenced study.

In a retrospective, open-label study, specifically the ADD DAPA trial [34], the impact of adding dapagliflozin to ARNI revealed a noteworthy enhancement in mean LVEF, a reduction in NYHA functional class, and diminished levels of NT-pro BNP. More recently, Jiang et al. [35], analyzing data from real-world, reported the combined use of sacubitril/

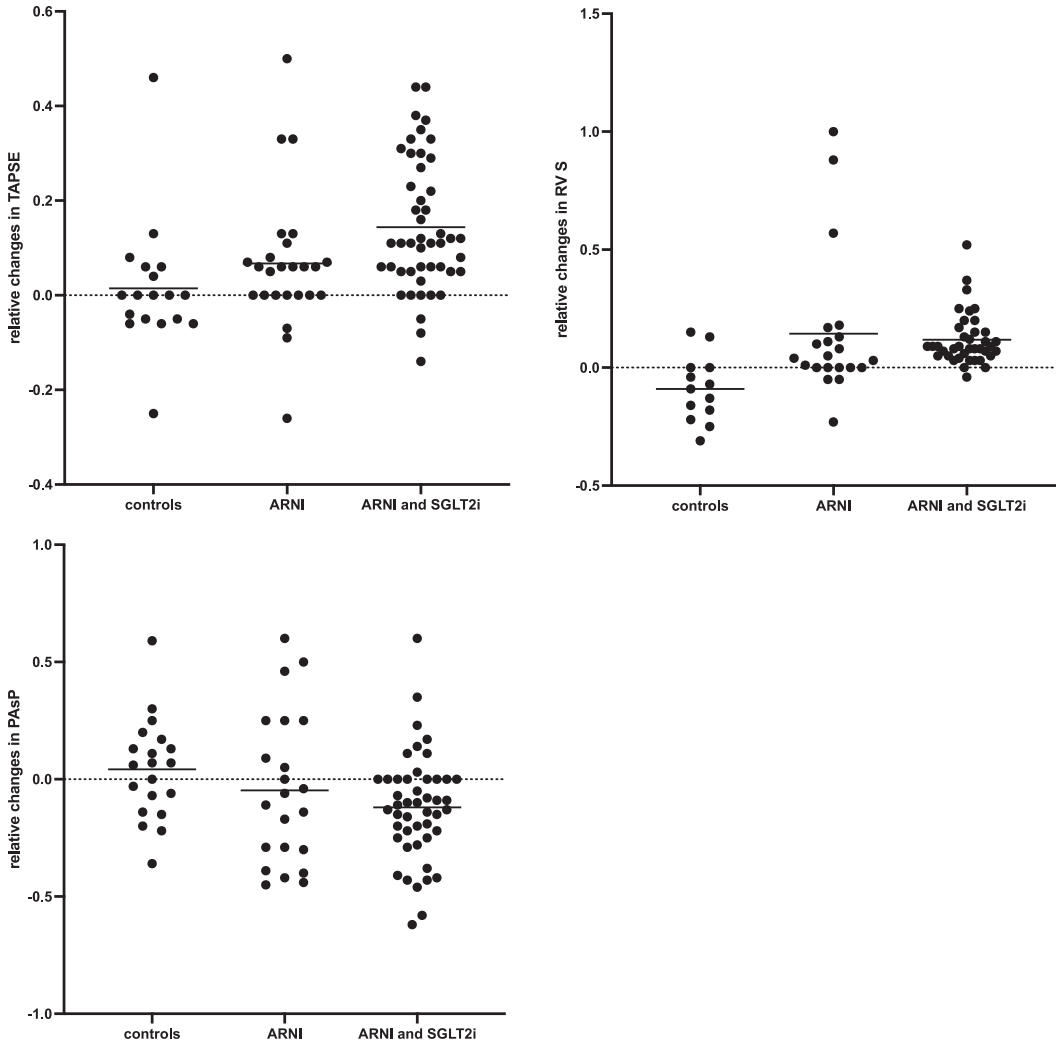

Fig. 2. (*continued*).

valsartan and dapagliflozin was associated with improved cardiac function in patents with HFrEF, and led to greater reductions in LAD and NT-proBNP levels compared to sacubitril/valsartan monotherapy.

In a post hoc analysis of the Empire HF trial [36], compared to with placebo, empagliflozin reduced the left ventricular end-systolic volume index (LVESVI), left ventricular end-diastolic volume index (LVEDVI) and left atrial volume index (LAVI), in patients treated with and without ARNI at baseline. Furthermore, no treatment-by-ARNI subgroup interaction were found. Unlike the results of our study, unaffected by baseline ARNI treatment, empagliflozin did not improve LVEF.

Unlike previous studies, after a 3 months of therapy, our data show the improvement on left and right ventricular remodeling through the significant improvement of several echocardiographic parameters (LVEF, LVEDD, LVEDV, LVESV, LV mass, E/e', LV GLS, TAPSE and RV S' velocity). The trend in favor of additional treatment with SGTL2i over ARNI remained statistically significant for LVEF, LVEDD, LV GLS, TAPSE and TRVS even after multivariable analysis. Our results are in line with a recent meta-analysis [37] derived by six studies that demonstrated significantly improvement of LVEDV, LVEDV index, LVESV; LVEF in patients with HFrEF in patients treated with SGLT2i, comparing with control.

Our research expands upon these results by demonstrating an amelioration also in the function of the right ventricle. This improvement is evidenced by enhancements in TAPSE, RV S' velocity, and a simultaneous reduction in sPAP. To the best of our knowledge, in this study we show for the first time an additional reverse remodeling effect of SGLT2i over ARNI by enhancements in TAPSE, RV S' velocity, and a simultaneous reduction ins sPAP in subjects with HF and reduced / mildly reduced LVEF. These findings are in line with another study [38], where patients with HFrEF receiving optimal medical therapy plus SGLT2i showed a significant improvement from the baseline to 3-month follow-up in all the measured RV echocardiographic parameters.

We have already demonstrated in a smaller size study [39] that the addition of SGLT2i to the optimal therapy for HFrEF was associated with a significant improvement in both LV (LVEF and LV global longitudinal strain) and RV function (RV global and free wall longitudinal strain). These findings are confirmed by the results from a recent study by Ge et al. [40], which demonstrated that in patients with pulmonary hypertension due to left heart diseases, both the mPAP and sPAP decrease, and mPAP and sPAP levels in the study group treated with dapagliflozin plus ARNI were lower than those in the control group (addiction of only ARNI to the baseline therapy).

These preliminary data should be confirmed in larger randomized studies enrolling larger populations with more homogeneous patients.

5. Conclusions

SGLT2i therapy when added to the standard treatment for HFrEF and HFmrEF is associated with an improved biventricular function and ventricular dimensions at follow-up.

6. Limitations

Several limitations must be acknowledged for the present study. Firstly, the inclusion of a relatively small number of patients and events requires cautious interpretation of the study results. Secondly, the observational nature of the study introduces inherent limitations. Moreover, the study exclusively focused on patients with HF and LVEF < 50 %, thereby restricting the generalizability of the findings to those with HFpEF. Baseline differences between 3 groups are too large to derive definitive conclusions. The remarkable difference between genders during the enrollment may be considered as a further limitation. Not all patients included in the study take the four pillars of therapy because they were enrolled in the study at the time of the debut of the new drugs for clinical practice.

Further investigations are warranted to assess the applicability of our findings to these specific populations.

CRediT authorship contribution statement

Michele Correale: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Damiano D'Alessandro:** Data curation, Investigation. **Lucia Tricarico:** Data curation, Investigation. **Vincenzo Ceci:** Data curation, Investigation. **Pietro Mazzeo:** Data curation, Investigation. **Raffaele Capasso:** Data curation, Investigation. **Salvatore Ferrara:** Data curation, Investigation. **Massimo Barile:** Data curation, Investigation. **Nicola Di Nunno:** Data curation, Investigation. **Luciano Rossi:** Data curation, Investigation. **Antonio Vitullo:** Data curation, Investigation. **Michele Granatiero:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft. **Mattia Granato:** Data curation, Investigation. **Massimo Iacoviello:** Data curation, Investigation. **Natale Daniele Brunetti:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101492.

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