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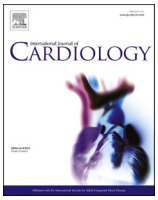

Impact of sacubitril/valsartan and gliflozins on cardiac resynchronization therapy response in ischemic and non-ischemic heart failure patients

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ABSTRACT

Aims: Angiotensin receptor-neprilysin inhibitor (ARNi) and sodium-glucose co-transporter 2 inhibitor (SGLT2i) improve outcomes in heart failure with reduced ejection fraction (HFrEF) patients, however their effects in cardiac resynchronization therapy (CRT) recipients have been scarcely explored. This study investigated whether ARNi and SGLT2i 1) improve the rate of clinical and echocardiographic CRT response and 2) have different impact based on the ischemic or non-ischemic etiology.

Methods: HFrEF patients referred for CRT implant were grouped in no treatment (group 1), only ARNi (group 2) and both ARNi and SGLT2i (group 3). Clinical and echocardiographic response were evaluated at 12 months.

Results: A total of 178 patients were enrolled. At one-year follow-up, 74.4% patients in group 2 ($p = 0.031$) and 88.9% in group 3 ($p = 0.014$) were classified as clinical responders vs 54.5% in the no treatments group. In multivariable analysis, ARNi/SGLT2i use was an independent predictor of CRT response (OR 3.72; CI 95%, 1.40–10.98; $p = 0.011$), confirmed in both groups 2 and 3. At 12 months, the median Δ LVEF increase was 6% and 8.5% in groups 2 and 3 respectively, vs 4.5% in group 1 ($p = 0.042$ and $p = 0.029$) with significantly more echocardiographic responders in groups 2 and 3 (76% and 78% vs 50%, $p = 0.003$ and $p = 0.036$). Significantly more ischemic HFrEF patients than non-ischemic were considered clinical and echocardiographic responders in the treatment groups.

Conclusions: ARNi alone or in combination with SGLT2i in CRT patients improves the clinical and echocardiographic response at 12 months. Ischemic patients seem to benefit more from these treatments.

1. Introduction

Recent studies have demonstrated that angiotensin receptor-neprilysin inhibitor (ARNi or sacubitril/valsartan, S/V) and sodium-glucose co-transporter 2 inhibitors (SGLT2i or gliflozins) reduce the risk of cardiovascular mortality and worsening of heart failure in patients with reduced ejection fraction (HFrEF) (1–3). Current European guidelines recommend in class I as key first-line treatment the angiotensin-converting enzyme inhibitor or ARNi and gliflozins on top of beta-blockers and mineralocorticoid receptor antagonist (4). Furthermore, cardiac resynchronization therapy (CRT) is an established treatment for therapy-refractory mild to severe HFrEF patients with left ventricular conduction delay and is recommended for symptomatic patients despite optimal medical therapy for at least 3 months (5), however, up to 30–50% of CRT recipients do not benefit from this therapy (6), and so far, many efforts have been done to find the determinants of this lack of response to CRT. The clinical benefit of ARNi and SGLT2i initiation is net in non-device-bearing patients (7,8), but in large multicentric trials only a minority of patients already had a cardiac resynchronization therapy with defibrillator (CRTD), and in a real-world setting a significant gap in their prescription exists (9). Moreover, it has been recently demonstrated the efficacy of ARNi in patients who were already recipients but not responding to CRT (10) and that the effectiveness of ARNi was greater in non-CRT-eligible patients based on QRS morphology compared to CRT-eligible patients with a wide QRS (11).

The present study aims to evaluate in a cohort of CRTD patients 1)

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[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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whether ARNi alone or in combination with SGLT2i improves the rate of clinical and echocardiographic CRT response at 12 months 2) whether these drugs have different effects based on the ischemic or non-ischemic etiology of the HFrEF.

2. Methods

This was a single-center observational retrospective study including all HFrEF symptomatic patients consecutively referred for CRTD implantation at the Department of Cardiology of Federico II University of Naples, from January 2015 to August 2022. All patients received CRTD according to the guidelines of the European Society of Cardiology (12) and were included in the local clinical database. Each patient signed the informed consent for data collection and for inclusion in the study.

In order to avoid possible confounding factors and make our population homogeneous, we included only ischemic (ICM) and non-ischemic (NICM) patients excluding other reversible causes of HF (such as acute viral myocarditis, alcohol-induced heart disease and tachycardia-related cardiomyopathy), valvular diseases, chemotherapy-induced and dilated-phase hypertrophic cardiomyopathy. Additional exclusion criteria were age below 18, lack of complete echocardiography or medical therapy data at 12-months follow-up and patients in ARNi or SGLT2i treatment > three months before CRTD implant.

Patients were divided into the following categories based on the pharmacological therapy at implantation time: group 1, not on ARNi and SGLT2i; group 2, on ARNi only; and group 3, on both ARNi and SGLT2i treatments. We excluded from the analysis the five patients in only SGLT2i therapy due to the small sample size.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Ethics Committee.

2.1. Baseline characteristics, follow-up data and Heart Failure etiology

Data were retrieved from our local database. A standard clinical and echocardiographic examination conforming to current recommendations was performed in all patients prior to CRT implantation and at least twice during the first year of follow-up. Device interrogation was performed within two months from the implant, with evaluation of biventricular pacing and optimization protocol. Any adjustment in therapy, particularly for ARNi and gliflozins use, was recorded.

Before CRTD implantation, all patients without a known coronary artery assessment underwent to coronarography at our center. Following the categorization from previous studies (13), patients were classified as ICM if they had a documented history of myocardial infarction or of a coronary revascularization procedure or a significant coronary artery disease at coronarography with angina pectoris or other coronary-related symptoms. NICM was defined in the absence of each of the aforementioned criteria for ICM, implying a systolic dysfunction leading to HF not due to coronary disease or any other recognized cause.

2.2. Definition of clinical and echocardiographic response to CRT

Clinical response was evaluated at 12 months after CRT implant using the Clinical Response (CR) definition (14): a positive response was assigned to patients who remained alive without any HF hospitalization during the first year and experienced an improvement of at least one NYHA class or remained in NYHA class I or II.

Furthermore, patients were classified as echocardiographic CRT responders if they had LV reverse remodeling at 12 months, evaluated as a LVEF improvement $\geq$5% or a LVESV reduction $\geq$15%, as previously published (15–18).

2.3. Statistical analysis

Data distribution was assessed through visual analysis of the boxplot for each variable. Continuous variables were expressed as mean $\pm$ Standard Deviation (SE) if normally distributed or as median [interquartile range (IQR)] in the case of skewed distribution and compared between groups by means of a *t*-test for unpaired samples or Wilcoxon-Mann-Whitney non-parametric test, respectively; categorical variables were reported as absolute and relative frequencies and comparisons between groups were performed with $\chi 2$ test. Pairwise testing with the Holm correction was applied to account for multiple comparisons. Analysis of variance test and one-way ANOVA were used to test all factorial covariates with more than two levels.

To evaluate the clinical and echocardiographic CRT response, we used a stepwise logistic regression: characteristics significantly ($p < 0.05$) or nearly significantly ($p < 0.10$) in the univariable analysis were first entered as candidate variables in a multivariable logistic regression analysis. The final multivariable model was selected using a backward-elimination algorithm after testing residual deviance with ANOVA. In a similar way, we ran a multivariable linear regression model to evaluate the correlation between the covariates and the change in LVEF. Results of these models were expressed as odds ratios (ORs) and mean differences with the corresponding 95% confidence intervals (CIs).

Clinically relevant interactions with the main covariate were tested in all models.

All tests were two tailed, and values of $p < 0.05$ were considered significant. Statistical analysis was performed using R version 4.2.1 (R foundation, Vienna, Austria). Graphics were performed using GraphPad Prism software version 9.0.

3. Results

3.1. Study population

Overall, 252 patients underwent CRTD implant, of these 178 were included in our study population (Fig. 1S in the Supplement). During the first-year, 39 (21.9%) patients were assuming only ARNi (group 2), 18 (10.1%) both SGLT2i and ARNi (group 3) and 121 (68%) weren't (group 1). In the two treatment groups, timing and doses of these drugs varied among patients as evidenced in supplemental Fig. 2S. Baseline characteristics are shown in Table 1.

Compared with the no treatments group, patients in group 2 were less likely to have COPD (15.3% vs 33.9%, $p = 0.046$) and loop diuretic medications (71.8% vs 88.4%, $p = 0.038$).

3.2. Twelve-months clinical response to CRT

During the first 12-month follow-up, 10 patients (5.8%) died, all due to acute heart failure decompensation and were considered non-clinical responder. Of these, only one patient was in low dose of ARNi therapy (male, suffering from ICM in NYHA class IV).

Based on the CR definition, 74.4% of patients in the ARNi group and 88.9% in the ARNi and SGLT2i group vs 54.5% in the no treatment group were classified as responders ($p = 0.003$ and $p = 0.014$ respectively; Fig. 1A). Univariable and multivariable logistic regression tests disclosed a significant relationship between SLGT2i and/or ARNi treatments and clinical response [$p = 0.011$, OR 3.72 (CI 1.4–10.98)] (Table 2, Model 1). Even when considering groups 2 and 3 separately, the relationship remained significant. A history of atrial fibrillation, low biventricular pacing, and right bundle branch block (RBBB) were negatively associated with the outcome.

Importantly, the only significant interaction in the multivariable analysis was between SGLT2i and/or ARNi treatments and heart failure etiology (p of interaction = 0.043). In the subsequent analysis of subgroups, only in ICM patients SGLT2i and/or ARNi use was a strong predictor of clinical response [$p < 0.001$, OR 11.04 (CI 2.84–55.73)] (Table 2, model 2 and 3). Indeed, considering ICM patients, 76.2% in group 2 and 87.5% in group 3 vs 47.2% in group 1 were considered clinical responder ($p = 0.027$ and $p = 0.010$, respectively), whereas

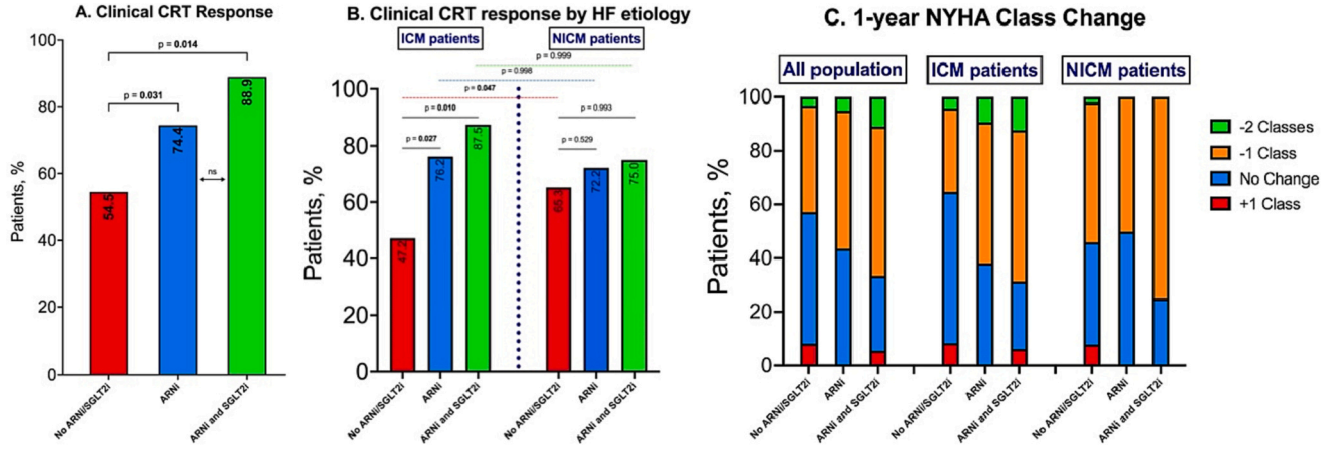

Fig. 1. One-year clinical CRT response rate and NYHA functional class change according to ARNi/SGLT2i treatment and dividing by HF etiology. 1-year clinical response to CRT in no ARNi/SGLT2i, only ARNi and both ARNi and SGLT2i groups in overall population **(A)** and based on HF etiology **(B).** Effectiveness of ARNi and SGLT2i in addition to ARNi treatment in NYHA functional class change compared to baseline at 1-year follow-up in overall population and stratified by HF etiology **(C)**. NICM refers to Non-Ischemic Cardiomyopathy, ICM to Ischemic Cardiomyopathy patients. Statistics: $\chi 2$ tests; analysis of variance test (ANOVA).

Table 1
Clinical characteristics of the overall population and dividing by ARNi and SGLT2i treatments.

Variable	Overall population	No ARNi/SGLT2i	ARNi	ARNi and SGLT2i	*p* value
No. of patients (%)	**178**	**121 (67.9)**	**39 (21.9)**	**18 (10.1)**	
		Group 1	**Group 2**	**Group 3**	
Age – years	67.5 [60.2; 75.8]	67.2 [59.7; 75]	65.8 [60.9; 75.3]	74.4 [64.6; 74.4]	0.255
Male sex - no. (%)	143 (80.3)	93 (76.9)	34 (87.2)	16 (88.9)	0.232
CRT-D upgrade - no. (%)	40 (22.5)	28 (22.6)	8 (20.5)	4 (22.2)	0.827
Etiology - no. (%)					0.076
NICM	70 (39.3)	49 (40.5)	17 (43.5)	4 (22.2)	
ICM	108 (60.7)	72 (59.5)	21 (53.8)	15 (83.3)	
NYHA Class - no. (%)					0.583
II	55 (30.9)	33 (26.6)	15 (38.5)	6 (33.3)	
III	108 (60.7)	77 (63.6)	21 (53.8)	11 (61.1)	
IV	15 (8.4)	11 (9.1)	3 (7.7)	1 (5.6)	
Cardiac risk factors - no. (%)					
Treatment for Hypertension	152 (85.4)	100 (82.6)	36 (92.3)	16 (88.9)	0.301
Atrial Fibrillation	56 (31.5)	40 (33.1)	9 (23.1)	7 (38.9)	0.244
Dyslipidemia	120 (67.4)	78 (64.5)	27 (69.2)	16 (88.9)	0.102
Diabetes Mellitus	76 (22.5)	54 (44.6)	9 (23.1)	13 (72.2)	0.002
Other Comorbidities					
COPD - no. (%)	52 (29.2)	41 (33.9)	6 (15.3)	5 (27.8)	0.046*, 0.2†
Glomerular filtration rate	61.5 (± 24.0)	59.6 (± 25.5)	67.2 (± 19.7)	62.8 (± 18.7)	0.24*,1†
Previous stroke or TIA - no. (%)	15 (8.4)	8 (6.6)	6 (15.3)	1 (5.6)	0.363
Echocardiographic findings					
LVESV - ml	187 (± 44)	188 (±69)	182 (± 77)	180 (±75)	0.11*,0.13†
LVEF - %	27.8 (± 5.0)	27.4 (± 5.1)	28.6 (± 4.9)	29.2 (± 4.7)	0.48*†
Electrocardiographic findings					
Left bundle-branch block - no. (%)	124 (69.7)	82 (67.7)	27 (69.2)	15 (83.3)	0.532
Baseline QRS duration	156.4 (± 9.9)	157.5 (± 8.9)	159.0 (± 12.6)	160.0 (± 7.6)	0.07*,0.13†
Sinus rhythm at implantation - no. (%)	148 (83.1)	96 (79.3)	34 (87.2)	15 (83.3)	0.134
Biventricular pacing, %	98 [96; 99]	97 [96; 99]	98 [95.5; 99]	98 [97.2; 99]	0.6*,0.8†
Medications - no. (%)					
Beta-blocker	163 (91.6)	113 (93.4)	34 (87.2)	16 (88.9)	0.436
ACEi/ARB (excluding ARNI)	112 (62.9)	112 (92.5)	–	–	–
Amiodarone	27 (15.2)	13 (10.7)	11 (28.2)	3 (16.7)	0.03*, 0.13†
Loop Diuretic	151 (84.8)	107 (88.4)	28 (71.8)	16 (88.8)	0.038*, 0.60†
MRA	95 (53.4)	65 (53.7)	21 (53.8)	9 (50)	0.956
Ivabradine	6 (3.3)	5 (4.1)	1 (2.6)	0 (0)	0.878
Digitalis	5 ()	3 (2.4)	1 (2.6)	1 (5.6)	0.789
Lipid-lowering treatment	147 (82.6)	97 (80.2)	32 (82.1)	17 (94.4)	0.456
Anticoagulants	56 (31.5)	39 (32.2)	10 (25.6)	7 (38.9)	0.554

Baseline characteristics and treatments in overall population ($n = 178$) and dividing by no ARNi/SGLT2i ($n = 121$), only ARNi ($n = 39$) and both ARNi and SGLT2i ($n = 18$) groups. Data are expressed as number (%), mean ± standard deviation or median (25th; 75th percentile). Biventricular pacing refers to the 1-year finding. Glomerular filtration rate was calculated in ml/min/1.73m^2, baseline QRS duration in milliseconds. NICM = Non-Ischemic Cardiomyopathy; ICM = Ischemic Cardiomyopathy; COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack; LVESV = Left Ventricular End-Systolic volume; LVEF = Left Ventricular Ejection Fraction; ACE-I/ARB = Angiotensin Converting Enzyme Inhibitors/Angiotensin II Receptor Blockers; MRA = Mineralocorticoid Receptor Antagonist. Statistics: $\chi 2$ tests; analysis of variance test and one-way ANOVA; pairwise testing with Holm correction. * refers to the p value between group 2 vs group 1; † between group 3 vs group 1. All p values between group 2 and 3 were not significant.

Table 2
Predictors of clinical CRT response in overall population and divided by HF etiology.

Variables	Odds Ratios (95% CIs) - Univariable Analysis	p value	Odds Ratios (95% CIs) - Multivariable Analysis	p value
	A. Overall population (178 patients)		**Model 1**	
No ARNI/ SGLT2i	Reference	na	Reference	na
ARNi	2.42 (1.11–5.62)	0.031	3.34 (1.21–11.53)	0.040
ARNi and SGLT2i	6.67 (1.79–43.33)	0.014	7.59 (1.45–27.52)	0.031
SGLT2i and/or ARNi*	3.13 (1.54–6.71)	0.002	3.72 (1.40–10.98)	0.011
Age (Years)	1 (0.97–1.03)	0.864	–	–
Gender – Male	1.13 (0.52–2.40)	0.748	–	–
Upgrade Procedure	1.80 (0.85–4.03)	0.136	–	–
Etiology, NICM	Reference	na	Reference	na
ICM	0.64 (0.43–1.11)	0.097	0.49 (0.20–1.13)	0.101
Baseline NYHA Class – II/III	Reference	na	–	–
IV	0.37 (0.11–1.07)	0.070	0.79 (0.17–3.56)	0.765
Treatment for Hypertension	1.26 (0.53–2.91)	0.596	–	–
Atrial Fibrillation	0.30 (0.15–0.58)	<0.001	0.37 (0.13–0.75)	0.012
Dyslipidemia	1.79 (0.86–3.11)	0.119	–	–
Diabetes mellitus	0.96 (0.52–1.78)	0.902	–	–
COPD	0.45 (0.23–0.86)	0.016	0.83 (0.35–1.98)	0.667
Glomerular filtration rate	1.01 (0.99–1.02)	0.119	–	–
Previous Stroke or TIA	1.73 (0.57–6.47)	0.364	–	–
Baseline LVESV, ml	0.87 (0.79–0.91)	<0.001	–	–
Baseline LVEF, %	1.12 (1.05–1.19)	<0.001	1.14 (1.041.25)	0.005
ECG - LBBB	Reference	na	Reference	na
RBBB	0.37 (0.18–0.73)	<0.001	0.42 (0.17–0.99)	0.049
Baseline QRS Duration	1.03 (1.01–1.07)	0.029	1.02 (0.98–1.07)	0.209
Rhythm at implant (AF)	0.33 (0.14- 0.73)	0.007	–	–
Biventricular pacing, %	1.45 (1.26–1.71)	<0.001	1.44 (1.21–1.74)	<0.001
Beta-Blocker	1.50 (0.50–4.38)	0.453	–	–
Amiodarone	0.45 (0.24–1.11)	0.079	0.25 (1.01–1.13)	0.082
Loop Diuretic	0.53 (0.20–1.28)	0.178	–	–
MRA	0.60 (0.32–1.11)	0.110	–	–
Lipid-Lowering Treatment	1.63 (0.77–3.51)	0.201	–	–
	B. Sub-group analysis ICM (108 patients)		**Model 2**	
No ARNi/ SGLT2i	Reference	na	Reference	na
SGLT2i and/or ARNi*	4.66 (1.89–12.82)	0.001	11.04 (2.84–55.73)	0.001
	NICM (70 patients)		**Model 3**	
No ARNi/ SGLT2i	Reference	na	Reference	na
SGLT2i and/or ARNi*	1.69 (0.55–5.88)	0.379	1.39 (0.19–10.87)	0.740

A. Univariable and multivariable (Model 1) logistic regression analysis in overall population. After multiple logistic regression model testing residual deviance with ANOVA, we excluded from the multivariable analysis the covariate Rhythm at implant due to correlation with Atrial Fibrillation. Only one subgroup interaction was identified, between the main covariate ARNi/SGLT2i treatment and heart failure etiology ($p = 0.043$). All other interactions exceeded 0.10. **B.** Univariable and multivariable logistic regression analysis dividing by heart failure etiology. Model 2 and Model 3 were adjusted for the same covariates of Model 1, except for Heart failure Etiology. Biventricular pacing rate refers to the 1-year finding. Glomerular filtration rate was calculated in ml/min/1.73 m^2, baseline QRS duration in milliseconds. NICM = Non-Ischemic Cardiomyopathy; ICM = Ischemic Cardiomyopathy; COPD = Chronic Obstructive Pulmonary Disease; TIA = Transient Ischemic Attack; LVESV = Left Ventricular End-Systolic volume, in milliliters; LVEF = Left Ventricular Ejection Fraction; LBBB = Left Bundle-Branch Block; RBBB = Right Bundle-Branch Block; AF = Atrial fibrillation; MRA = Mineralocorticoid Receptor Antagonist. *"SGLT2i and/or ARNi" refers to the entire population of patients on ARNi and both ARNi and SGLT2i therapy vs no treatment group.

there were no differences between groups in NICM patients (Fig. 1B). Importantly, as shown in Fig. 1B, when considering untreated patients, CRT alone was significantly more effective in NICM compared to ICM patients ($p = 0.047$); however, this difference diminished when ARNi or both ARNi and SGLT2i were added to CRT.

As for the NYHA functional class, it improved by at least 1 class in 56.4% and 66.7% in group 2 and 3, respectively vs 42.8% in the no treatment patients (p = 0.047 and $p = 0.038$, Fig. 1C). Once again, a greater benefit of the ARNi or ARNi and SGLT2i therapy was significantly confirmed only in the ICM group.

3.3. Twelve-months echocardiographic CRT response

According to the echocardiographic definition, there were more CRT responders in groups 2 and 3 than in the no treatment group (76.3% and 77.7% vs 50%, respectively, $p = 0.006$ and $p = 0.036$; Fig. 2A). Table 1S in the supplementary materials details the predictors of echocardiographic CRT response based on univariate and multivariate logistic regression analyses. The interaction between HF etiology and SGLT2i and/or ARNi treatments was not significant.

The Δ LVEF increased of 6% [IQR 5; 9.75%] in the ARNi group and of 8.5% [IQR 5%; 11.8%] in both ARNi and SGLT2i group vs 4.5% [IQR 0%; 8%] in no treatment patients ($p = 0.0112$) (Fig. 2B).

Based on the multivariable linear regression analysis (Supplemental Table S2), SGLT2i and/or ARNi treatments was significantly associated with a Δ LVEF 2.46% average increase higher than no treatments group [$p = 0.007$, Estimate Coefficient = 2.46 (0.74–4.08)]. Indeed, COPD, RBBB and Atrial Fibrillation remained significant negatively and biventricular pacing positively associated with Δ LVEF improvement; instead, ICM was not a negative predictor of Δ LVEF increase.

Specifically, in groups 2 and 3 compared to no treatments group, the Δ LVEF improved in ICM patients [5% (IQR 3.5; 7%) and 8.5% (IQR 4.5; 12%) vs 2% (IQR -1; 7%), $p = 0.096$ and $p = 0.019$, Fig. 2C]. Also in the NICM group there was an improvement in groups 2 and 3 compared to group 1 [6% (IQR 5; 12.2%) and [8% (IQR 6.5; 9.5%)] vs 6% (IQR 0.5; 9.5%); p = ns] although without reaching statistical significance (Fig. 2C). Among non-responders, less patients in groups 2 and 3 than in the no treatments group had no increase or a reduction of LVEF (Δ LVEF<0%) (5.3 and 5.6% vs 24.1%, $p = 0.012$). There were no significant differences among groups in the rate of super-responders (LVEF improvement ≥10%) (Fig. 3S in supplementary material).

4. Discussion

The main findings of our study are the following: 1) ARNi alone or in combination with SGLT2i increases clinical and echocardiographic response rate to CRT and improve the cardiac function at 12-month follow-up; 2) their combined benefits along with CRT are especially tangible in ICM patients.

The CRT non-responsiveness constitutes a burning challenge, with around 30–50% of patients not experiencing significant benefits (6); many efforts have been made for optimizing response, including the introduction of novel therapies. Among these, ARNi and SGLT2i have proven an overwhelming benefit in HF patients (19). However, in our

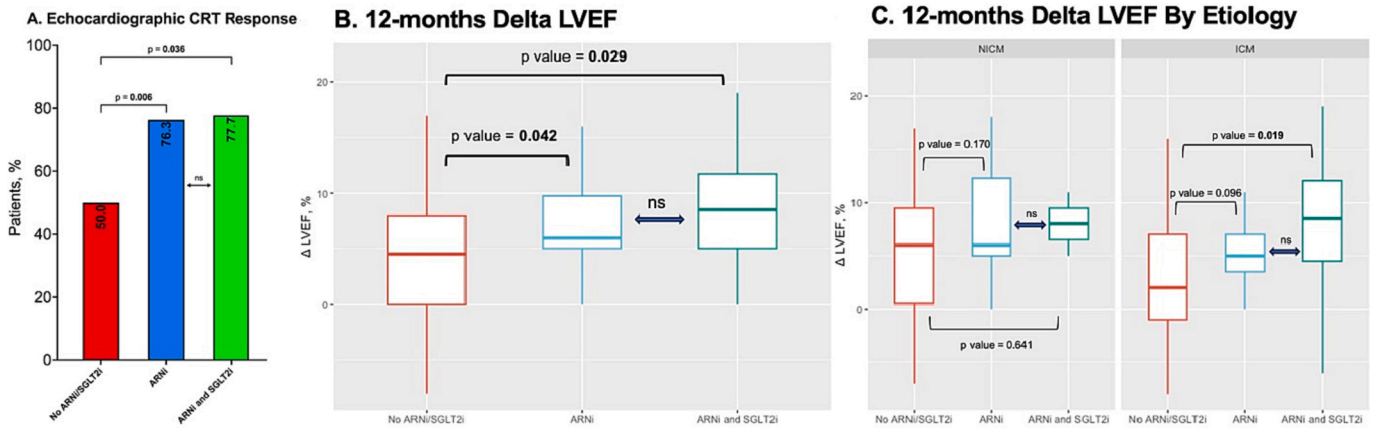

Fig. 2. Echocardiographic CRT response and Delta LVEF at 1-year follow-up according to ARNi/SGLT2i treatment and dividing by HF etiology. (A) 1-year echocardiographic CRT response rate (evaluated as an improvement of 5% of LVEF or a reduction of 15% of LVESV) in 168 alive patients according to ARNi and SGLT2i treatment. (B) Impact of ARNi and SGLT2i in addition to ARNi on Delta LVEF change at 12-months echocardiographic evaluation in overall 168 patients and (C) dividing by HF etiology. Boxplots show the median (central mark) with the 25th and 75th percentiles (box edges), and minimum and maximum values (whiskers). Statistics: $\chi 2$ tests; analysis of variance test and one-way ANOVA; pairwise testing with Holm correction. NICM refers to Non-Ischemic Cardiomyopathy, ICM to Ischemic Cardiomyopathy patients.

best knowledge, no studies have evaluated the effectiveness of these drugs when administered concurrently withCRT. Indeed, in the 2021 ESC guidelines for HF, ARNi and SGLT2i are a class I indication in patients NYHA class II-IV heart failure with LVEF ≤40% to reduce the risk of HF hospitalization and death (4), but precise indications on a combination with CRT are currently lacking, as the main clinical trials that contributed to study the impact of ARNi and SGLT2i on outcomes in patients with HFrEF had only a little proportion of patients with CRT and did not assess the impact of these drugs when given concurrently with CRT (1,20–22). In a recent study, Russo et al. (10) analyzed the impact of ARNi in 190 CRTD non-responder patients, with a median follow-up of 20 months: about 20% of their population improved cardiac function and were classified as additional responders. Moreover, an elegant work of Huang et al. (11) demonstrated that the effectiveness of ARNi was greater regarding the improvement of LVEF and LVESV in non-CRT-eligible group compared to LBBB and a QRS > 130 msec or RBBB and a QRS > 150 msec; nevertheless, echocardiographic improvement occurs in both groups, albeit to varying degrees. Based on these premises, it appears that CRT, ARNi and SGLT2i may exert a distinct yet equally significant pathophysiological impact on the progression of HFrEF; indeed, in our study, ARNi and gliflozins had a notable efficacy particularly in those patients where CRT alone is less effective, thus supporting this hypothesis.

4.1. Impact of ARNi and SGLT2i in clinical and echocardiographic CRT response

In our cohort of 178 patients, approximately 75% of ARNi and SGLT2i recipients experienced clinical and echocardiographic benefits 12-months after CRT implant and were classified as CRT responders. This rate was higher than in the no ARNi/SGLT2i group, however it reached statistical significance only in ICM patients. Previous studies reported that CRT reduced all-cause mortality similarly in both ICM and NICM patients (23), however sub-analysis of randomized studies demonstrated the occurrence of more favorable reverse remodeling in NICM compared to ICM (13,24–26). In the REVERSE study, 50–59% in ICM vs 74–83% in NICM patients (based on different response criteria) were considered CRT responders after 1-year follow-up (25), percentages similar to those of our no ARNi/SGLT2i group. By contrast, in our study the effectiveness of CRT in ARNi and SGLT2i groups was consistent regardless HF etiology, but especially in ICM patients that least responded to the CRT.

Considering only echocardiographic parameters, our data proved that the effect of ARNi alone or in combination with SGLT2i was consistent especially in ICM patients, with a greater Δ LVEF increase compared to only CRT group, particularly in both ARNi and SGLT2i recipients. In a meta-analysis of over 10.000 patients, ARNi was associated with a mean LVEF increase of +5,11% compared to patients treated with ACEI/ARB therapy and a similar effect was confirmed in the prospective PROVE-HF study (21,27). Regarding SGLT2i, likewise the two recent SUGAR-DM-HF and EMPA-TROPISM trials suggested favorable reverse remodeling in term of LVESV reduction and both LVESV reduction and LVEF improvement, respectively (28,29). Our data are concordant with these literature findings and assume a potential additional role of ARNi alone or in combination with gliflozins in CRT patients.

4.2. Limitations

This study has several limitations that require to be addressed. Firstly, the retrospective nature of our study posed challenges in data collection and retrieving complete information.

Second, we don't have data regarding 6-min walk test, B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide, and all of these may be a surrogate of reverse remodeling as shown in previous studies.

Thirdly, in our population patients on SGLT2i treatment were only 5, thus we decided to exclude them from the analysis. On the other hand, in clinical practice, ARNi was introduced first, so patients taking only SGLT2i are most probably only those with contraindications to the Sacubitril/Valsartan use.

Finally, although our study had a relatively small sample size, to our knowledge this is the first study analyzing clinical and echocardiographic CRT response in patients with ARNi and SGLT2i. Therefore, our study fills a gap in current knowledge and may, despite its limitations, encourage future prospective well sampled studies to assess the synergistic impact of ARNi and in particular SGLT2i (also considered individually).

5. Conclusion

ARNi alone or in combination with SGLT2i in CRT patients improves clinical and echocardiographic response at 12-months follow-up. Further studies with larger sample size are needed to confirm that this translates in improved outcome and survival at long term follow-up.

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Declaration of Competing Interest

None.

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Appendix A. Supplementary data

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