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ANA MARGARIDA CRAVO BARRADAS

Reducing atrial fibrillation burden in heart failure: the added value of sacubitril/valsartan

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Reducing atrial fibrillation burden in heart failure: the added value of sacubitril/valsartan

Ana Barradas[1], Diogo Fernandes[2], Inês Fonseca[2], Natália António[1,2*]

[1]Faculty of Medicine, University of Coimbra, Portugal

[2]Cardiology Department, Coimbra Hospital and Universitary Centre, Coimbra, Portugal

Institute of Pharmacology and Therapeutics, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

*Corresponding author: natalia.antonio@gmail.com

ABSTRACT

Introduction: Atrial fibrillation (AF) is the most common cardiac arrhythmia among Heart Failure patients (HF). Individuals that suffer from HF and AF have a worse prognosis than individuals that suffer from one condition only. Sacubitril/Valsartan (Sac/Val), indicated for HF patients with reduced ejection fraction (HFrEF), might improve AF condition as well but its added value is still controversial. In this retrospective, self-controlled single-centered study we analyzed the effect of Sac/Val in AF burden.

Materials and Methods: Cardiac Resynchronization Therapy-Implantable Cardioverter Defibrillator (CRT-D) carriers were listed. From those, patients on Sac/Val were selected for the study if CRT-D implantation had been prior to drug initiation. For each patient, equal time length control (before Sac/Val initiation) and exposure (after Sac/Val initiation) periods were defined. We analyzed AF burden by comparing frequency and mean value of paroxysmal events and the overall variation in AF status (without, paroxysmal, persistent or permanent). Non-sustained ventricular tachycardia (NsVT), defibrillator shocks and anti-tachycardia (ATP) events were also analyzed as well as variation of NYHA, echocardiographic parameters, analytical parameters and HF-related hospitalizations and emergency episodes.

Results: A total of 72 patients were included in the study (26.4% women/73.3% men) with a mean left ventricular ejection fraction (LVEF) of 33.6±10.7%. After Sac/Val, there was a reduction in NYHA functional class (2.00±0.748 to 1.85±0.613, p=0.043) concomitant with an increase in LVEF (from 31.67%±9.28 to 37.33±14.49, p=0.027). Total amount of AF episodes and mean paroxysmal episodes (among those with paroxysmal AF or without AF) was numerically reduced after Sac/Val initiation, though variation was not statistically significant. Likewise, amount of defibrillator shocks and that of participants with ≥ 1 ATP events also decreased. NsVT aggravated after drug initiation, though differences were not statistically significant. Creatinine and potassium plasma concentrations increased (p=0.009 and p=0.096, respectively) whereas NT-ProBNP decreased (p=0.691). Hospitalizations and

emergency episodes showed a numerical increase though none of these variations was statistically significant.

Conclusion: Our results suggest that Sac/Val has an additional benefit to prevent AF episodes. Among patients without AF or with known paroxysmal AF, there was a numerical reduction in AF paroxysmal episodes as well as in the mean paroxysmal events per patient after Sac/Val initiation. In addition, our patients showed a marked increase in LVEF after drug initiation concomitantly with a decrease in NYHA category.

KEYWORDS

Sacubitril/Valsartan, Heart Failure, Atrial Fibrillation, Ventricular Tachycardia, Cardiac Resynchronization Therapy, Implantable Cardioverter Defibrillator

INTRODUCTION

Heart failure (HF) is a condition that is estimated to affect 64.3 million people worldwide (1). Its prevalence is estimated as 8.3% among older adults and 3.4% among all adults. Furthermore, the mortality rates attributed to HF increased 3,73% every year, from 2011 to 2015, for both sexes and race-ethnicity groups (2). Up to 50% of patients die suddenly (3).

Around 70% of HF patients suffer from comorbidities (4) and the presence of multiple comorbidities is one of the main determinants of prognosis and life quality. Type 2 diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD) and sleep disordered breathing are some of the most common (4). Atrial fibrillation (AF) is the most prevalent cardiac arrythmia among HF patients and both coexist frequently. On one hand, AF is associated with the development and deterioration of the left ventricle dysfunction. On the other hand, left ventricle dysfunction promotes electrical and structural alterations on the left atria that facilitate the initiation and maintenance of AF (5). It is also known that individuals that suffer from HF and AF have a worse prognosis than individuals that suffer from one condition only (6). Not only AF worsens hemodynamics and exacerbates HF, but it is also a cause of inappropriate shocks when incorrectly identified by implantable cardioverter defibrillators (ICDs) as a ventricular tachyarrhytmia (7). In fact, malignant ventricular arrythmia, including ventricular tachycardia and ventricular fibrillation (VF), are also a common complication of HF and account for 50-60% of HF patients mortality (8).

Sacubitril/valsartan (Sac/val) is a sodium salt supramolecular complex of sacubitril pro-drug, a neprilysin inhibitor, and of valsartan, an angiotensin receptor antagonist (ARA) (9). This orally administered ARA-neprilysin inhibitor was approved in 2015 by the European Medical Agency, after publication of PARADIGM-HF clinical trial results (10). PARADIGM-HF showed reduction in sudden cardiac death events and hospitalization in HF patients with reduced ejection fraction (HFrEF) (11), and it is therefore considered one the cornerstones of drug treatment (12). While it also holds a potential anti-arrhythmic

effect, this added value of Sac/Val is still controversial, with some studies suggesting a reduction in ventricular arrhythmias (VA) and in AF leading to a reduction in the amount of ICD interventions (13).
In this retrospective study we aimed to evaluate whether Sac/Val impacts on AF burden in patients with previously known paroxysmal AF. Our study population were HF patients with CRT-D followed at the Cardiology Department of a tertiary hospital, who initiated Sac/Val after CRT-ICD implantation. We also analyzed the incidence of VA, ICD shocks and anti-tachycardia pacing (ATP) events before and after Sac/Val, as well as HF hospitalizations and emergency episodes.

MATERIALS AND METHODS

Study population and inclusion/exclusion criteria

This is a retrospective, self-controlled single-centered study conducted at a tertiary hospital. Criteria to define the study population included: 1) to be a CRT-D carrier; 2) to have initiated Sac/Val at least 3 months after implanting the device; 3) to be on Sac/Val for at least 3 months. To identify our study population, initially we listed all patients enrolled in the CRT-D follow up appointments database between 2nd of January 2019 and 24th of May 2022. Next, we evaluated electronic health records from the Portuguese hospital information management software (SCLINICO) and from the drug electronic prescription system (PEM). Based on the Sac/Val initiation date, we therefore defined, for each patient, two equal time length study intervals: one before Sac/Val exposure and another after Sac/Val exposure. Patients were excluded if their drug compliance was explicitly categorized as bad or doubtful.
The study was approved by the local Ethics Committee of the CHUC/Faculty of Medicine of the University of Coimbra, with approval number PI OBS.SF.174-2022.

Data collection

Data was collected from SCLINICO and CardioBase (Cardiology Information System). For each patient, we retrieved demographic characteristics and CRT-D implantation dates. Baseline variables, such as NYHA class, guideline directed medical therapy (GDMT) and comorbidities were retrieved, if available at the time Sac/Val was initiated. Likewise, laboratory analysis, LVEF, left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) and left atrial end diastolic volume (LAEDV) were retrieved as close as possible to Sac/Val initiation date (but not older than one year) and endpoint (between 3 months and one year after Sac/Val initiation), respectively. LVEF was retrieved either from echocardiographic reports available at CardioBase (preferably), otherwise from clinical registries. In addition, we retrieved the number and date of HF related emergency episodes and hospitalizations.
Time since CRT-D implantation was calculated as the difference between Sal/Val initiation and device implantation dates. NYHA categories were converted into continuous quantitative variables in order to obtain a mean value.
CRT-D episodes were noted by date of occurrence and respective number of events. For each patient time interval, we retrieved information from CRT-D follow up episodes, including non-sustained

ventricular tachycardia (NsVT), paroxysmal AF episodes, defibrillator shocks and anti-tachycardia pacing (ATP).

Statistics

Continuous variables were tested for normality using he Kolmogorov-Smirnov or Shapiro-Wilk test, as appropriate. Continuous variables are expressed as mean ± standard deviation if normally distributed and compared with the paired *t* test. Categorical data were expressed as numbers and percentages and compared with the Wilcoxon signed-ranked test or McNemar as appropriate. Statistical significance was always set as a two-tailored probability level of < 0.05. Statics were performed using SPSS version 28.0.1.1. (IBM, Chicago, IL, USA).

RESULTS

Population demographics

A total of 72 patients fulfilled the eligibility criteria. Mean age of participants was 68.3 ± 12 years (table 1). Patients initiated Sac/Val between October 2017 and June 2022. Around 26% of participants were women. Follow up times ranged from 2.8 to 57.1 months, with a mean of 20.8 months/participant. The mean duration of time from CRT-D implantation to Sac/Val initiation was 61.33 months (approximately 5 years and 1 month).

At baseline, mean LVEF was 33.6%. Regarding NYHA categories, 50% of the patients were in NYHA II, while 21.9 and 28.1 were in NYHA I and III, respectively. There were no patients in NYHA IV. Mean serum levels of creatinine, potassium and AST were within normality range (0.6-1.2 mg/dL, 3.5-5 mmol/L and 15-40 U/L respectively), NT-ProBNP were elevated above chronic heart failure diagnostic threshold (around 125 ng/L).

More than half of the patients were, at the time of Sac/Val initiation, diagnosed with hypertension, dyslipidemia and type 2 diabetes mellitus, 17% suffered from CKD and 4% from COPD. Before Sac/Val initiation, most patients were under beta-blocker (92.6%) and loop diuretic therapy (83.3%), 77.8% were taking either ACE-I or ARB and only 22.2% were under SGLT2 inhibitor. Around 33% of patients were under amiodarone, 24.1% under digoxin and 11.1% under ivabradine. Regarding other drugs, 37.2% of the patients were taking more than 5 other drugs and 42.6% were taking between 3 and 5.

Table 1. Characteristics of overall study population at baseline.

Demographics	
Age (years)	68.3 ± 12.2
Female/Male (%)	26.4 / 73.3
Mean time since CRT-D Implantation (months)	61.33 ± 37.2
Echocardiographic features	
LVEF (%)	33.6 ± 10.7
LVEDV (ml)	143.2 ± 62.6
LVESV (ml)	91 ± 46.19
LAEDV/BSA (ml/m2)	43.5 ml/m^2
NYHA class (%)	
I	21.9
II	50
III	28.1
IV	0
Laboratory analysis	
Serum creatinine (mg/dL)	1.1 ± 0.4
Potassium (mmol/L)	4.6 ± 0.5
ProBNP (pg/ml)	177.5 ± 214.4
NT-ProBNP (pg/ml)	1898.7 ± 3073
AST (U/L)	25.8 ± 10.0
Comorbidities (%)	
Hypertension	66.7
Dyslipidemia	57.7
Diabetes	50.9
CKD	17
COPD	4
Guideline directed heart failure therapy (%)	
ACE-I or ARB	77.8
Beta-blocker	92.6
Aldosterone antagonist	68.5
Loop diuretic	83.3
Ivabradine	11.1
Digoxin	24.1
Amiodarone	33.3
SGLT2 inhibitor	22.2
Number of drugs (%)	
[0-2]	20.4
[3-5]	42.6
> 5	37.2

Data is represented as mean ± standard deviation. CRT-D: cardiac resynchronization therapy-defibrillator; LVEF: left ventricular ejection fraction; LVEDV: left ventricular end diastolic volume; LVESV; left ventricular end systolic volume; LAEDV/BSA: left atrial end diastolic volume/body surface area; NYHA: New York Heart Association; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ACE-I: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; iSGLT2: sodium-glucose transporter type 2 inhibitor

Evolution of patient characteristics following Sac/Val

Median NYHA category was reduced from 2.00±0.748 to 1.85±0.613 (*p*=0.043) after Sac/Val initiation. There was an overall reduction (-5) in the number of NYHA III patients with a concomitant increase in NYHA II patients (+5) (figure 1) and it was statistically significant.

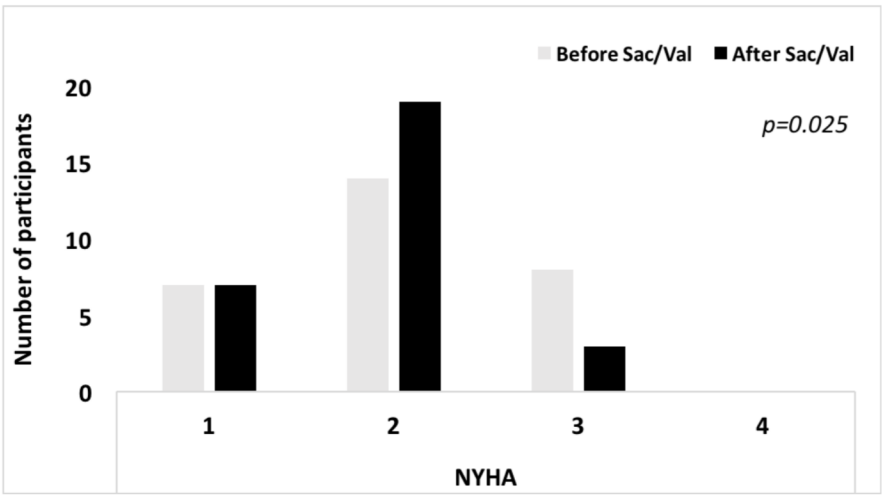

Figure 1. Number of patients per NYHA category is represented below. Statistical significance was obtained with Wilcoxon signed ranked test.

Variation of analytical values (table 4) shows increased creatinine plasma concentration (*p*=0.009), as well as potassium (p=0.096). NT-proBNP and AST follow a decreasing trend. Variation of echocardiographic parameters suggests a beneficial effect from Sac/Val with LVEF increase (p=0.027) and LAEDV decrease (p=0.464). LVESV and LVEDV variation was not calculated due to missing data.

Table 4. Variation of analytical values and echocardiographic features before and after Sac/Val initiation.

	Before Sac/Val	After Sac/Val	*p*-value
Analytical values			
Creatinine (mg/dL)	1.08 ± 0.37	1.18 ± 0.41	0.009*
Potassium (mmol/L)	4.59 ± 0.44	4.7 ± 0.50	0.096
NT-ProBNP (pg/mL)	1630.8 ± 2852.7	1436.47 ± 1743.04	0.691
AST (U/L)	25.06 ± 10.59	22.42 ±11.12	0.260
Echocardiographic fatures			
LVEF (%)	31.67 ± 9.28	37.33 ± 14.49	0.027*
LAEDV (ml/m^2)	44.44 ± 12.813	37.32 ± 15.240	0.464

*Data is represented as mean ± standard deviation. Statistical significance was calculated with paired t-test (*p < 0.05).*

HF-related hospitalizations and ER episodes show an increasing trend, although statistical significance was not obtained in any of the analyzed items (table 5).

From our study population, six patients died up to the last follow up. Death causes were cancer complications (1), respiratory tract infection (3), septic shock (1) and decompensated heart failure (1). There were no sudden cardiac deaths.

Table 5. HF-related hospitalization and emergency episodes before and after Sac/Val initiation.

	Before Sac/Val	After Sac/Val	*p*-value
HF-related hospitalization			
Participants with ≥ 1	5	8	0.581
Total number of hospitalizations	5	10	0.317
Mean (participants with ≥1)	0.38	0.69	0.337
Mean (all participants)	0.07	0.13	0.437
HF-related emergency episode			
Participants with ≥ 1	6	8	0.774
Total number of ER episodes	7	11	0.484
Mean (participants with ≥ 1)	0.54	0.85	0.455
Mean (all participants)	0.10	0.15	0.321

*Data is represented as either frequency or mean. Significance was obtained with paired student t-test or McNemar (*p<0.05).*

CRT-D registered events following Sac/Val

The amount of NsVT, as well as defibrillator shocks and ATP events, was analyzed before and after Sac/Val initiation (table 6). One patient had an arrhythmic storm during the follow up period after Sac/Val initiation (472 NsVT and 35 defibrillator shocks) and was therefore considered an outlier and excluded from this analysis. While the total amount of NsVT increases after Sac/Val initiation, the total number of participants with at least one registered defibrillator shock or ATP events decreases, as well as the total amount of defibrillator shocks. Furthermore, the mean number of defibrillator shocks decreases after Sac/Val initiation. However, none of these variations is statistically significant.

Table 6. Frequency and mean NsVT, ATP and defibrillator shock events before and after Sac/Val initiation.

	Before Sac/Val	After Sac/Val	*p*-value
NsVT			
Participants ≥ 1 NsVT	21	25	0.424
Total amount of NsVT	137	176	0.631
Mean NsVT	1.96 ± 4.965	2.63 ± 6.01	0.480
Defibrillator shocks			
Participants ≥ 1 defibrilator shock	10	5	0.581
Total amount of defibrillator shocks	19	12	0.565
Mean defibrillator shocks	0.28 ± 0.820	0.18 ± 0.796	0.748
ATP events			
Participants ≥ 1 ATP	15	13	1.00
Number of ATP events	65	68	0.902
Mean ATP events	0.93 ± 2.804	1 ± 4.39	0.886

One patient had an arrhytmic storm during PostExp period and therefore excluded from this analysis (N=71). Data is represented as either frequency or mean ± standard deviation*. Significance was calculated with paired student t-test, Wilcoxon or McNemar tests, when appropriate. NsVT: non-sustained ventricular tachycardia; ATP: anti-tachycardia pacing*

Before Sac/Val initiation, 33 patients did not have AF, 19 had paroxysmal AF, 15 had permanent AF and 2 had persistent AF. After Sac/Val initiation, the AF status changed for some patients resulting in a positive variation with an overall aggravated AF status, though not statistically significant (p=0.059).

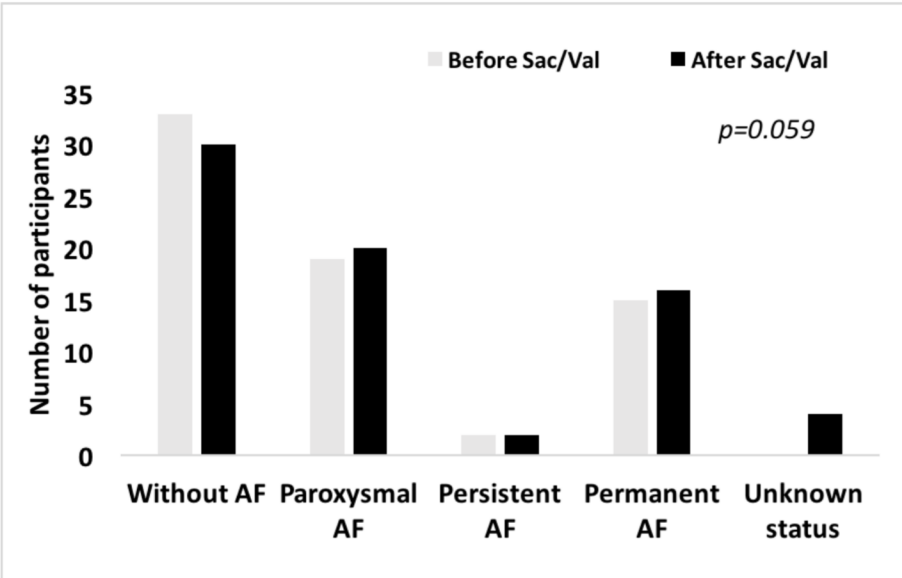

Figure 2. AF status frequency and variation before and after Sac/Val initiation. Statistical significance was obtained with Wilcoxon signed ranked test.

Analysis of AF events among patients with paroxysmal AF or without known AF (table 7) after Sac/Val initiation showed a numerical reduction in the total amount of AF episodes, mean number of episodes per patient (with at least 1 episode) and mean number of episodes within among all patients (N=44), although statistical significance was not achieved.

Table 7. Frequency and mean paroxysmal events (± standard deviation) among patients without AF or with known paroxysmal AF.

	Before Sac/Val	After Sac/Val	*p*-value
Total amount of AF episodes	91	44	0.808
Number of patients ≥ 1 AF paroxysmal episode	9	10	1.00
Mean paroxysmal events per patient (≥ 1 episode)	6.07 ± 14.12	2.65 ± 3.19	0.351
Mean paroxysmal events per patient (all patients)	1.86 ± 8.13	0.9 ± 2.201	0.338

Patients with known persistent or permanent fibrillation at any of the timepoints analyzed were excluded from this analysis (N=44). Statistical significance was calculated with paired student t-test ($p < 0.05$).

DISCUSSION

This self-controlled study suggests that Sac/Val may prevent AF occurrence in patients without AF or with known paroxysmal AF. Additionally, it confirms the beneficial effect of this HF-modifier drug regarding HF functional status and systolic function.

In theory, Sac/Val holds the potential for attenuating atrial arrhythmias (14) but its benefit is still controversial. The PARAGON-HF trial showed that Sac/Val did not significantly influence the incidence of AF and atrial flutter after randomization in an intention to treat (15). Furthermore, the OUTSTEP trial showed that patients who took Sac/Val for 12 weeks, presented even more AF events than those who took enalapril (16). Recent metadata on randomized clinical trials (RCT) still does not clarify whether Sac/Val attenuates AF but it suggests that Sac/Val benefit is at least comparable to those of ACEi and ARB (17) (18). This analysis is, however limited by the fact that cited RCT were not designed to show an impact on AF occurrence. In some of these trials, it is actually reported as an adverse event instead of a main outcome (17). Therefore, further trials are required in which the primary endpoint is AF occurrence, like that of Pimpini and coworkers, whose preliminary data showed that treatment with Sac/Val decreased the number of patients with at least one episode of atrial tachycardia (AT)/AF per month as well as the number of AT/AF episodes per year (19). Our results showed a numerical reduction in the total amount of AF episodes and mean paroxysmal events per patient, thus suggesting an added value for Sac/Val in HF patients. This reduction may be partially explained by Sac/Val attenuation of atrial remodeling. Previous data indicate that Sac/Val is superior to valsartan alone in attenuating left atrial remodeling after AF ablation (20) and that left atrial volume predicts AF recurrence after

radiofrequency ablation (21). In our cohort, LAEDV was indeed numerically reduced after Sac/Val initiation and though not statistically significant, it indicates a possible atrial reverse remodeling induced by Sac/Val which consequently contributes to AF attenuation.

Analysis of AF status showed that it aggravated after Sac/Val initiation time, what may be explained by the normal progression of HF. In line with our findings, Cikes et al (15) showed that within the group of patients who received Sac/Val, new atrial flutter occurred in 12% of the patients without known previous flutter, although the drug did not influence development of new arrhythmia. Predictors for these included, instead, older age, lower heart rate, higher body mass index and higher NT-proBNP per doubling of NT-proBNP. Similarly, TOP-CAT study showed that within the group that took spironolactone treatment for HF with preserved EF, new patients developed AF but spironolactone did not influence the development of AF during treatment nor did history of AF or AF at enrollment modified the beneficial treatment effect of spironolactone (22). In light of these data, it seems plausible to assume that in our study, AF status aggravation is not a direct effect of Sac/Val but more likely due to other variables including the natural history of HF.

Since Sac/Val acts on the RAAS system, directly through valsartan and indirectly through neprilysin inhibition, it has the potential to promote ventricular reverse remodeling, and ultimately reduce ventricular arrhythmias. Although some authors have reported a beneficial effect of Sac/Val in reducing ventricular arrhythmias (13), recent metadata analysis did not find differences between Sac/Val and the control group (18). Our data shows a numerical reduction in the number of participants with at least ≥ 1 ATP event and defibrillator shocks, as well as mean number of shocks per patient (though not statistically significant).

In our study, functional status and systolic function were notoriously improved after Sac/Val, corroborating previous results (10). NYHA evaluation before and after Sac/Val initiation also showed a significant improvement mainly due to an increase in NYHA II patients with a concomitant decrease from NYHA III. This was also shown in the PARADIGM-HF clinical trial (10), with a positive interaction between Sac/Val and NYHA functional class, superior to that of enalapril, although there was no correlation between NYHA and the effect on death from cardiovascular causes. However, whether this does reflect an improvement in patient functionality should be assessed with more objective scales. In fact, Piepoli and coworkers showed no beneficial effect of Sac/val on either six-minute walk test or daytime physical activity compared to enalapril (16) but pinpointed possible explanations for those findings, such as participant motivation and perpetuated sedentary lifestyle.

Sac/Val benefited systolic function as well, with an increase in LVEF around 6%. Due to LVEDV and LVESV missing data, echocardiographic analysis was limited to LVEF but it was expected that treatment with Sac/Val could reduce both (23). Moreover NT-ProBNP was numerically reduced after Sac/Val initiation. This tendency is reported in several studies and may occur as early as 4 weeks (10) but it is still observed after 12 (24). Although not statistically significant, our data follows that reported in other studies, including metadata analysis (25), reflecting a reduction in cardiac wall stress and ultimately in left ventricular reverse remodeling, which is by itself a therapeutic target in HF.

Despite improvements in NYHA category and systolic function, we did not see a reduction in HF-related hospitalizations and emergency episodes, after Sac/Val initiation. In fact, these numbers increased, which may reflect one of our study limitations, since there could be missing data on hospitalizations and ER episodes occurring outside our center. On the other hand, follow up times are extensive which severely ages the study population from beginning till end of the study, increasing the chances of complications. In fact, 32% of our patients were followed for at least 4 years and a considerable 14% for at least 6 years. Thus, these results may reflect a bias of our ageing study population and despite these results, there were no reported sudden cardiac death among our patients.

Noteworthy creatinine was statistically significantly increased after Sac/Val initiation. Compared to valsartan, creatinine levels above 2.5 mg/dL were reported less frequently in the Sac/Val group among HFrEF patients (10) and compared to irbesartan, another ARB, Sac/Val has similar effects in kidney function within CKD patients (26). Sac/Val in fact slows down the natural deterioration of the estimated glomerular filtration rate (27). Thus, although in our study creatinine levels after Sac/Val initiation are increased, they are within the upper limit of normality range (1,2 mg/dL) and may reflect a deterioration in renal function accompanying HF natural history that would be otherwise faster.

CONCLUSION

Our results suggest that Sac/Val has an additional benefit in patients with AF. Among patients without AF or with known paroxysmal AF, there was a numerical reduction in AF paroxysmal episodes as well as in the mean paroxysmal events per patient after Sac/Val initiation. Additionally, our data confirms the beneficial effect of this HF-modifier drug regarding HF systolic function and functional status, as our patients showed a marked increase in LVEF after drug initiation concomitantly with a decrease in NYHA category.

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REFERENCES

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov;392(10159):1789–858.
2. Sidney S, Quesenberry CP, Jaffe MG, Sorel M, Go AS, Rana JS. Heterogeneity in national U.S. mortality trends within heart disease subgroups, 2000-2015. BMC Cardiovasc Disord. 2017 Jul 18;17(1).

3. Fang JC, Ewald GA, Allen LA, Butler J, Westlake Canary CA, Colvin-Adams M, et al. Advanced (stage D) heart failure: A statement from the heart failure society of america guidelines committee. J Card Fail. 2015 Jun 1;21(6):519–34.
4. Tomasoni D, Adamo M, Anker MS, von Haehling S, Coats AJS, Metra M. Heart failure in the last year: progress and perspective. Vol. 7, ESC Heart Failure. Wiley-Blackwell; 2020. p. 3505–30.
5. Richter S, di Biase L, Hindricks G. Atrial fibrillation ablation in heart failure. Vol. 40, European Heart Journal. Oxford University Press; 2019. p. 663–72.
6. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, et al. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: The Framingham heart study. Circulation. 2003 Jun 17;107(23):2920–5.
7. Peterson PN, Greenlee RT, Go AS, Magid DJ, Cassidy-Bushrow A, Garcia-Montilla R, et al. Comparison of inappropriate shocks and other health outcomes between single- and dual-chamber implantable cardioverter-defibrillators for primary prevention of sudden cardiac death: Results from the cardiovascular research network longitudinal study of implantable cardioverter-defibrillators. J Am Heart Assoc. 2017 Nov 1;6(11).
8. Thompson BS. Sudden cardiac death and heart failure. AACN Adv Crit Care. 2009;20(4):356–65.
9. Marques da Silva P, Aguiar C. Sacubitril/valsartan: An important piece in the therapeutic puzzle of heart failure. Vol. 36, Revista Portuguesa de Cardiologia. Sociedade Portuguesa de Cardiologia; 2017. p. 655–68.
10. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. New England Journal of Medicine. 2014 Sep 11;371(11):993–1004.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug 1;18(8):891–975.
12. McDonagh TA, Metra M, Adamo M, Baumbach A, Böhm M, Burri H, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Vol. 42, European Heart Journal. Oxford University Press; 2021. p. 3599–726.
13. Martens P, Nuyens D, Rivero-Ayerza M, van Herendael H, Vercammen J, Ceyssens W, et al. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. Clinical Research in Cardiology. 2019 Oct 1;108(10):1074–82.
14. Li L yi fei, Lou Q, Liu G zhong, Lv J chen, Yun F xiang, Li T kai, et al. Sacubitril/valsartan attenuates atrial electrical and structural remodelling in a rabbit model of atrial fibrillation. Eur J Pharmacol. 2020 Aug 15;881.

15. Cikes M, Planinc I, Claggett B, Cunningham J, Milicic D, Sweitzer N, et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: The PARAGON-HF Trial. JACC Heart Fail. 2022 May 1;10(5):336–46.
16. Piepoli MF, Hussain RI, Comin-Colet J, Dosantos R, Ferber P, Jaarsma T, et al. OUTSTEP-HF: randomised controlled trial comparing short-term effects of sacubitril/valsartan versus enalapril on daily physical activity in patients with chronic heart failure with reduced ejection fraction. Eur J Heart Fail. 2021 Jan 1;23(1):127–35.
17. Liu X, Liu H, Wang L, Zhang L, Xu Q. Role of sacubitril-valsartan in the prevention of atrial fibrillation occurrence in patients with heart failure: A systematic review and metaanalysis of randomized controlled trials. PLoS One. 2022 Jan 1;17(1 January).
18. Liu XH, Wang GL, Xu Q, Zhang L, Liu HJ. Effect of sacubitril/valsartan on the occurrence of cardiac arrhythmias and the risk of sudden cardiac death in heart failure: A meta-analysis of randomized controlled trials. Vol. 9, Frontiers in Cardiovascular Medicine. Frontiers Media S.A.; 2022.
19. Guerra F, Pimpini L, Flori M, Contadini D, Stronati G, Gioacchini F, et al. Sacubitril/valsartan reduces atrial fibrillation and supraventricular arrhythmias in patients with HFrEF and remote monitoring: preliminary data from the SAVE THE RHYTHM. Eur Heart J [Internet]. 2020 Nov 1;41(Supplement_2):ehaa946.0926. Available from: https://doi.org/10.1093/ehjci/ehaa946.0926
20. Yang L, Zhang M, Hao Z, Wang N, Zhang M. Sacubitril/valsartan attenuates atrial structural remodelling in atrial fibrillation patients. ESC Heart Fail. 2022 Aug 1;9(4):2428–34.
21. Njoku A, Kannabhiran M, Arora R, Reddy P, Gopinathannair R, Lakkireddy D, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: A meta-analysis. Europace. 2018 Jan 1;20(1):33–42.
22. Cikes M, Claggett B, Shah AM, Desai AS, Lewis EF, Shah SJ, et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: The TOPCAT Trial. JACC Heart Fail. 2018 Aug 1;6(8):689–97.
23. Zhou X, Zhu H, Zheng Y, Tan X, Tong X. A systematic review and meta-analysis of sacubitril-valsartan in the treatment of ventricular remodeling in patients with heart failure after acute myocardial infarction. Vol. 9, Frontiers in Cardiovascular Medicine. Frontiers Media S.A.; 2022.
24. Pieske B, Wachter R, Shah SJ, Baldridge A, Szeczoedy P, Ibram G, et al. Effect of Sacubitril/Valsartan vs Standard Medical Therapies on Plasma NT-proBNP Concentration and Submaximal Exercise Capacity in Patients With Heart Failure and Preserved Ejection Fraction. JAMA. 2021 Nov 16;326(19):1919.
25. Chen Y, He Q, Mo DC, Chen L, Lu JL, Li RX, et al. The angiotensin receptor and neprilysin inhibitor, LCZ696, in heart failure: A meta-analysis of randomized controlled trials. Vol. 101, Medicine (United States). Lippincott Williams and Wilkins; 2022. p. E30904.
26. Haynes R, Judge PK, Staplin N, Herrington WG, Storey BC, Bethel A, et al. Effects of sacubitril/valsartan versus irbesartan in patients with chronic kidney disease: A randomized double-blind trial. Circulation. 2018;138(15):1505–14.

27. Damman K, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, et al. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. JACC Heart Fail. 2018 Jun 1;6(6):489–98.