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Incremental value of mineralocorticoid receptor antagonists in patients with heart failure with reduced ejection fraction treated with sacubitril/valsartan

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ABSTRACT

Aims We investigated the incremental advantage in terms of N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction in patients affected by heart failure with reduced ejection fraction (HFrEF) treated with sacubitril/valsartan (S/V) and mineralocorticoid receptor antagonists (MRA) versus patients treated with S/V only.

Methods Consecutive adult patients with a left ventricular ejection fraction (LVEF) of ≤40% who were followed in our outpatient clinic from January 2016 to December 2019 and treated with S/V were analysed.

Results Out of eligible 147 patients, 99 were treated with S/V+MRA at baseline and 48 patients were treated with S/V. Patients treated with S/V+MRA were significantly younger (61.5 vs 67.8 years, p=0.006), had better basal renal function (serum creatinine 1.2 vs 1.4 mg/dL, p=0.006) and lower LVEF (30.9% vs 33.1%, p=0.039). At follow-up at 8–16 months, 84 out of 99 patients continued to be on S/V+MRA, and 39 out of 48 patients continued to be on S/V. Between these two groups, at follow-up, LVEF did not vary significantly, ΔNT-proBNP was not significantly different (–215.7 vs –165.9 pg/mL, p=0.93) and neither was the rate of hospitalisation for heart failure (9.5% vs 12.8%, p=0.58). Using general linear models, both age and basal NT-proBNP influenced significantly ΔNT-proBNP (respectively, p=0.002; p=0.005), while treatment with S/V+MRA versus S/V only did not significantly influence ΔNT-proBNP (p=0.462).

Conclusion Even with the limitations of a small retrospective study, our results generate the hypothesis that MRA might not provide any additional value in patients with HFrEF treated with S/V. Larger studies are needed to test if MRA should remain a standard treatment in patients with HFrEF treated with S/V.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous trials have shown clinical superiority of mineralocorticoid receptor antagonists (MRA) when they were tested against a placebo control in addition to standard therapy in heart failure with reduced ejection fraction (HFrEF).

WHAT THIS STUDY ADDS

⇒ Our results support the hypothesis that the use of sacubitril/valsartan (S/V) without MRA might not be inferior to a strategy combining S/V and MRA in patients with HFrEF.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Larger, prospective studies are needed to confirm this hypothesis, which would allow for simplifying treatment and follow-up in patients with HFrEF.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a major cause of morbidity and mortality worldwide. However, stepwise improvements have been made in pharmacotherapy in the last three decades, significantly delaying clinical progression and prolonging disease-free survival. Combination therapy with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB), a beta blocker (BB) and a mineralocorticoid receptor antagonist (MRA) has been the corner stone of guideline-recommended therapy for patients with HFrEF for several years.[1–3] Besides adding sodium/glucose cotransporter 2 (SGLT2) inhibitors to the standard regimen,[4] most recent guidelines have introduced sacubitril/valsartan (S/V) as a potential replacement for ACEi and ARB.[1] S/V (formerly known as LCZ 696) is an angiotensin receptor neprilysin inhibitor (ARNI) demonstrated to be superior to enalapril in patients with HFrEF and is therefore recommended as a more effective alternative to ACEi or ARBs in patients with persisting symptoms to be used in conjunction with other evidence-based treatments.[5–10] In clinical practice, many patients with HFrEF do not tolerate the recommended target doses of S/V due to its lowering effects on blood pressure. Since MRA reduce blood pressure as well, the concomitant use of MRA further limits

the dose of S/V to be administered in some patients. Previous trials have shown clinical superiority of MRA when they were tested against a placebo control in addition to standard therapy including renin–angiotensin-system inhibitors and beta blockers.[11 12] MRA carries a significant risk of worsening renal function and leading to hyperkalaemia, which is why in real world practice, the prescription of MRA remains lower than that of other guideline-recommended drugs, in particular in vulnerable groups of patients such as the elderly, patients with chronic kidney disease or patients suffering from hyperkalaemia.[13 14]

Several studies have highlighted the importance of a combined use of disease-modifying drugs in HFrEF,[15–18] but, to our knowledge, there is no study that investigated the incremental value of MRA in patients with HFrEF treated with S/V at less-than-target dose.

Aims

Aim of the study was to retrospectively analyse differences between patients with HFrEF treated with S/V and MRA and patients treated with S/V only, on top of other guideline-recommended drugs. We chose as primary endpoint the reduction of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration between baseline, namely the first visit at our outpatient clinic, and follow-up at 8–16 months (ΔNT-proBNP). Moreover, we analysed differences in biochemical and clinical features between patients affected by HFrEF treated with S/V and MRA and patients treated only with S/V.

METHODS

Eligibility criteria

For this retrospective study, patients treated with S/V who attended our outpatient clinic for advanced heart failure from January 2016 to December 2019 were identified from a clinical database. Inclusion criteria included therapy with S/V, age ≥18 years and left ventricular ejection fraction (LVEF) of ≤40%. Exclusion criteria included a diagnosis of hypertrophic cardiomyopathy, restrictive cardiomyopathy or arrhythmogenic cardiomyopathy and prior heart transplant or left ventricular assist device.

Patients were grouped by MRA treatment into patients with S/V and MRA (S/V+MRA group) or with S/V only (S/V group), on top of the remaining medical therapy for HFrEF. In patients not receiving MRA, the reason for withholding MRA was assessed from clinical records.

Data from follow-up visits included results of history, physical examination, echocardiography and blood sampling. Plasma NT-proBNP was measured using a commercially available electrochemiluminescence immunoassay (proBNP II, Roche Diagnostic).

For analyses, all data were anonymised. The study conformed to the Declaration of Helsinki and to local regulations for retrospective studies and data handling.

Statistical analysis

Continuous variables are presented as mean and SD if normally distributed, categorical data are reported as number and percentage.

Comparisons of group means of continuous variables were performed using the *t*-test for independent samples or general linear models. Categorical variables were evaluated using Fisher's exact test or Pearson's χ^2 test, where appropriate.

We compared the reduction of NT-proBNP concentration between baseline and follow-up (ΔNT-proBNP) using general linear models (univariate analysis of variance, ANOVA) with ΔNT-proBNP as the outcome (dependent variable) and age, basal serum creatinine and basal NT-proBNP as independent variables. In order to obtain a normal distribution, NT-proBNP was log-transformed before analysis.

P≤0.05 was considered statistically significant.

All statistical analyses were performed using SPSS V.23.0 (IBM, New York, USA).

RESULTS

Overall population

Eligible patients were 147, among which 74 patients (50.3%) had dilated cardiomyopathy, 64 patients (43.6%) had ischaemic heart disease, 5 patients (3.4%) had inflammatory cardiomyopathy and 4 patients (2.7%) had valvular heart disease. Overall, 62 patients (42.2%) began therapy with S/V at baseline, 50 patients (34.0%) were already treated with S/V and its dose remained unchanged, 34 patients (23.1%) were already treated with S/V and increased its dose and 1 patient (0.7%) reduced S/V dose. Among patients who began therapy with S/V at baseline, 41 (66.1%) were in S/V+MRA group and 21 (33.9%) were in S/V group.

At baseline, 99 patients out of 147 were treated with S/V+MRA and 48 patients were treated only with S/V, on top of other guideline-recommended medication. Patients treated with S/V+MRA were significantly younger (61.5±12.7 vs 67.8±13.6 years, p=0.006), had lower LVEF at baseline (30.9±5.7 vs 33.1±6.5%, p=0.039), and had lower burden of atrial fibrillation (20.2% vs 35.4%, p=0.046). In the S/V+MRA group, men were slightly more predominant than in the S/V group, even if not significantly different (82.8% vs 68.8%, p=0.052). Systolic blood pressure did not differ significantly in the two groups at baseline, even if diastolic blood pressure was slightly higher in the S/V+MRA group (75.6±9.8 vs 71.8±9.3 mm Hg, p=0.03). The percentage of patients with implantable cardiac defibrillator and cardiac resynchronisation therapy (CRT) (including CRT-D and CRT-P) was not statistically different in the two groups. Baseline NYHA functional class was similar, as was the dose of S/V at the first visit in our centre. There was no considerable difference in concomitant therapies for heart failure at baseline, with most of the patients taking beta-blockers (96% in S/V+MRA group and 95.8% in S/V group).

Diuretic therapy consisted predominantly of torasemide (111 patients), and to lesser extent of xipamide (24 patients), furosemide (9 patients) and hydrochlorothiazide (3 patients). Regarding MRA dosage at baseline, most patients assumed Spironolacton 25 mg/day (46.5%) and Eplerenon 25 mg/day (43.4%), with a lower number of patients assuming the highest MRA dosage (respectively 8.1% with Spironolacton 50 mg/day and 2.0% with Eplerenon 50 mg/day). Furthermore, patients treated with S/V+MRA had better basal renal function (serum creatinine 1.2±0.3 vs 1.4±0.6 mg/dL, p=0.006), slightly lower basal NT-proBNP even if not significantly different (1833.0±2376.8 vs 2312.8±2586.2 pg/mL, p=0.267) and lower basal index NT-proBNP/estimated glomerular filtration rate (eGFR) (29.2±46.3 vs 53.1±67.1, p=0.013). More baseline characteristics can be found in table 1.

At follow-up at 8–16 months (mean 13.9 months), 84 out of 99 patients continued to be on S/V+MRA (15 patients discontinued MRA), and 39 out of 48 patients continued to be on S/V only (9 patients began therapy with MRA). Among patients who discontinued MRA, seven patients suspended MRA for arterial hypotension, four patients for deteriorated kidney function, three patients for hyperkalaemia and one patient for gynecomastia. In the S/V+MRA group, at follow-up the S/V dose remained unchanged in 53 patients (63.0%), increased in 26 patients (31.0%) and decreased in 5 patients (6.0%). In the S/V group, at follow-up the S/V dose remained unchanged in 26 patients (66.7%%), increased in 11 patients (28.2%) and decreased in 2 patients (5.1%). Regarding MRA dosage at follow-up, most patients assumed Eplerenon 25 mg/day (54.8%) and Spironolacton 25 mg/day (41.6%), with a lower number of patients assuming the highest MRA dosage (respectively 1.2% with Eplerenon 50 mg/day and 2.4% with Spironolacton 50 mg/day).

At follow-up NYHA functional class was similar, as was the dose of S/V between S/V+MRA group and S/V group. As well systolic and diastolic blood pressure were similar in the two groups at follow-up. Moreover, LVEF did not vary significantly (36.3±9.4 vs 39.8±10.6%, p=0.072), neither did the improvement of LVEF between baseline and follow-up (+5.3±9.0 vs +7.1±10.2%, p=0.309). Patients treated with S/V+MRA had better follow-up renal function (serum creatinine 1.2±0.5 vs 1.5±0.9, p=0.038). The rate of hospitalisation for heart failure did not vary significantly between the two groups (9.5% vs 12.8%, p=0.58). More follow-up characteristics can be found in table 2.

NT-proBNP reduction

At follow-up, NT-proBNP was slightly lower, even if not significantly different, in S/V+MRA group in comparison to S/V group (1281.0±3239.2 vs 2154.8±3245.9 pg/mL, p=0.163). Of note, the reduction in NT-proBNP concentration (ΔNT-proBNP) was not significantly different between the two groups (−215.7±3040.9 vs −165.9±2578.9 pg/mL, p=0.93).

We compared ΔNT-proBNP using general linear models (ANOVA) with ΔNT-proBNP as the outcome (dependent variable) and age, basal NT-proBNP and treatment group (S/V+MRA vs S/V) as independent variables. In order to obtain a normal distribution, NT-proBNP was log-transformed before analysis. Both age and basal NT-proBNP influenced significantly ΔNT-proBNP (respectively 95% CI −0.016 to −0.004, p=0.002; 95% CI 0.078 to 0.418, p=0.005), while treatment with S/V+MRA vs treatment only with S/V did not influence significantly ΔNT-proBNP (95% CI −0.109 to 0.239, p=0.462) (table 3, figure 1).

Analysing the group of patients who discontinued MRA, NT-proBNP mean changed from 3716±4167.8 pg/mL at baseline to 1521.6±1447.5 at follow-up with a ΔNT-proBNP of −2194.4±3592.3 pg/mL. Among patients who began MRA, NT-proBNP mean changed from 2278.9±2194.2 pg/mL at baseline to 1538.8±1986.6 pg/mL at follow-up with a ΔNT-proBNP of −740.1±1122.6 pg/mL. There was no statistically significant difference between ΔNT-proBNP of these two groups (p=0.254).

DISCUSSION

To our knowledge, this is the first study that investigates the incremental value of MRA in patients with HFrEF treated with S/V. Our results generate the hypothesis that MRA might not provide any additional value in patients with HFrEF treated with S/V, as reflected by a lack of additional reduction of NT-proBNP when compared with patients with S/V treatment only. In other words, the results or our study support non-inferiority of a S/V without MRA strategy as compared with standard S/V with MRA strategy.

Recent metanalyses showed that among different drug combinations, ACEi+BB+MRA+Ivabradin and ARNI+BB+MRA+SGLT2i tended to be the combinations associated with lowest mortality endpoints and hospitalisation in patients with HFrEF.[15 16 19 20]

However, in clinical reality, the majority of patients do not receive such combinations at full dosage due to their lowering effects on blood pressure and heart rate. The addition of a MRA frequently means that the effective dose of S/V cannot be raised as much as if no MRA was given. Given the proven positive effects of S/V and the lack of evidence for positive effects of MRA in the presence of ARNI, giving MRA up for a higher dose of S/V seems an appealing strategy, especially in patients with low blood pressure and/or impaired renal function.

When the RALES study showed in 1999 that spironolactone (still the most-prescribed MRA), in addition to standard therapy, reduced the risk of morbidity and mortality in patients with HFrEF,[11] beta blockers had not yet been shown effective or safe in patients with severe HFrEF[21–25] and S/V was not yet introduced. Indeed, in the RALES cohort treated with spironolactone, background therapy included ACEi in 95% of the patients, loop diuretics in

Table 1 Baseline characteristics of S/V+MRA and S/V groups

	Overall population	Group S/V+MRA	Group S/V	P value
n	147	99	48	
Age, years	63.6±13.3	61.5±12.7	67.8±13.6	**0.006**
Males, n (%)	115 (78.2%)	82 (82.8%)	33 (68.8%)	0.052
BMI, kg/m^2	29.4±5.6	30.4±5.8	27.5±4.6	**0.004**
Baseline systolic blood pressure	124.1±18.8	123.5±17.9	125.1±20.5	0.62
Baseline diastolic blood pressure	74.4±9.9	75.6±9.8	71.8±9.3	**0.03**
Cause of heart failure				
Ischaemic heart disease	64 (43.5%)	41 (41.4%)	23 (47.9%)	0.556
Non-ischaemic heart disease	83 (56.5%)	58 (58.6%)	25 (52.1%)	0.966
Baseline NYHA functional class				0.732
II, n (%)	55 (37.4%)	39 (39.4%)	16 (33.3%)	
III, n (%)	82 (55.8%)	53 (53.5%)	29 (60.4%)	
IV, n (%)	10 (6.8%)	7 (7.1%)	3 (6.3%)	
Baseline EF, %	31.6±6.9	30.9±5.7	33.1±6.5	**0.039**
ICD, n (%)	45 (30.6%)	34 (34.3%)	11 (22.9%)	0.159
CRT, n (%)	62 (42.2%)	39 (39.4%)	23 (47.9%)	0.326
Atrial fibrillation, n (%)	37 (25.2%)	20 (20.2%)	17 (35.4%)	**0.046**
Diabetes mellitus, n (%)	45 (30.6%)	29 (29.3%)	16 (33.3%)	0.618
Baseline sacubitril/valsartan				0.568
100 mg/day	77 (52.4%)	51 (51.5%)	26 (54.2%)	
200 mg/day	59 (40.1%)	39 (39.4%)	20 (41.7%)	
400 mg/day	11 (7.5%)	9 (9.1%)	2 (4.1%)	
Baseline mineralocorticoid receptor antagonist				
Spironolacton 25 mg/day		46 (46.5%)		
Spironolacton 50 mg/day		8 (8.1%)		
Eplerenon 25 mg/day		43 (43.4%)		
Eplerenon 25 mg/day		2 (2.0%)		
Concomitant therapies				
Beta-blockers	141 (9.6%)	95 (96.0%)	46 (95.8%)	0.971
Ivabradin	19 (12.9%)	16 (16.2%)	3 (6.3%)	0.093
Amiodaron	12 (8.2%)	7 (7.1%)	5 (10.6%)	0.487
Digitoxin	13 (88.4%)	6 (6.1%)	7 (14.6%)	0.088
Diuretics	123 (83.7%)	86 (86.9%)	37 (77.1%)	0.132
Baseline blood test				
Haemoglobin, g/L	1390±160	1400±160	1370±170	0.225
Creatinine, mg/dL	1.3±0.5	1.2±0.3	1.4±0.6	**0.006**
eGFR, mL/min/1,73m^2	83.6±40.3	92.5±40.9	65.3±32.7	**0.000**
Potassium, mmol/L	4.3±0.4	4.2±0.4	4.3±0.5	0.083
NT-proBNP, pg/mL	1989.6±2448.7	1833.0±2376.8	2312.8±2586.2	0.267
NT-proBNP/eGFR	37.0±54.9	29.2±46.3	53.1±67.1	**0.013**

Bold values are considered statistically significant (p≤0.05).
BMI, body mass index; CRT, cardiac resynchronisation therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ICD, implantable cardiac defibrillator; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; S/V, sacubitril/valsartan.

Table 2 Follow-up characteristics of S/V+MRA group and S/V group

	Overall population	Group S/V+MRA	Group S/V	P value
n	123	84	39	
Follow-up systolic blood pressure	123.2±18.2	121.6±16.4	126.8±21.4	0.141
Follow-up diastolic blood pressure	73.6±9.5	72.7±8.2	75.4±11.6	0.151
Follow-up NYHA functional class				0.182
I, n (%)	2 (1.6%)	2 (2.4%)	0	
II, n (%)	71 (57.7%)	52 (61.9%)	19 (48.7%)	
III, n (%)	48 (39.1%)	28 (33.3%)	20 (51.3%)	
IV, n (%)	2 (1.6%)	2 (2.4%)	0	
Follow-up EF, %	37.4±9.9	36.3±9.4	39.8±10.6	0.072
Follow-up Δ EF, %	5.8±9.4	5.3±9.0	7.1±10.2	0.309
Follow-up sacubitril/valsartan				0.482
100 mg/day	38 (30.9%)	24 (28.6%)	14 (35.9%)	
200 mg/day	66 (53.7%)	45 (53.5%)	21 (53.8%)	
400 mg/day	19 (15.4%)	15 (17.9%)	4 (10.3%)	
Follow-up mineralocorticoid receptor antagonist				
Spironolacton 25 mg/day		35 (41.6%)		
Spironolacton 50 mg/day		2 (2.4%)		
Eplerenon 25 mg/day		46 (54.8%)		
Eplerenon 50 mg/day		1 (1.2%)		
Follow-up blood test				
Haemoglobin, g/L	1380±60	1410±160	1330±190	**0.03**
Creatinine, mg/dL	1.3±0.6	1.2±0.5	1.5±0.9	**0.038**
eGFR, mL/min/1,73m^2	84.1±44.8	93.2±46.2	64.4±34.5	**0.001**
Potassium, mmol/L	4.3±0.4	4.3±0.4	4.4±0.5	0.051
NT-proBNP, pg/mL	1558.1±3222.9	1281.0±3239.2	2154.8±3245.9	0.163
NT-proBNP/eGFR	33.9±99.3	27.0±110.0	48.7±70.0	0.261
ΔNT-proBNP, pg/mL	−199.9±2891.9	−215.7±3040.9	−165.9±2578.9	0.93
Hospitalisation for heart failure	13 (10.6%)	8 (9.5%)	5 (12.8%)	0.58

Bold values are considered statistically significant (p≤0.05)
EF, ejection fraction; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; S/V, sacubitril/valsartan.

100%, digitoxin in 75% and beta blockers only in 11% of the patients.

Subsequent subanalysis of the PARADIGM-HF trial showed that the benefit of S/V over an ACEi was consistent independently of background therapy.[18] This finding is not in conflict but slightly different from what we demonstrated, namely that the benefit of S/V in terms of NT-proBNP reduction was consistent independently of MRA background therapy. We tested our hypothesis not over an ACEi population, but over a similar S/V population who did not take MRA.

Table 3 ANOVA considering ΔNT-proBNP as the outcome (dependent variable)

	P value	95% CI
Age	0.002	−0.016 to −0.004
Basal NT-ProBNP	0.005	0.078 to 0.418
S/V+MRA group vs S/V group	0.462	−0.109 to 0.239

ANOVA, analysis of variance; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; S/V, sacubitril/valsartan.

In comparison to the PARADIGM-HF population, in our study patients had lower levels of NT-proBNP (median 1631 pg/mL vs 1135 pg/mL) and the cause of heart failure was less predominantly ischaemic (59.9% vs 43.5%). Age, serum creatinine levels and baseline EF were similar between the two study populations.

In our study, we found that patients treated with S/V without MRA were significantly older with slightly higher predominance of female gender and had higher burden of atrial fibrillation, despite a better LVEF. Moreover,

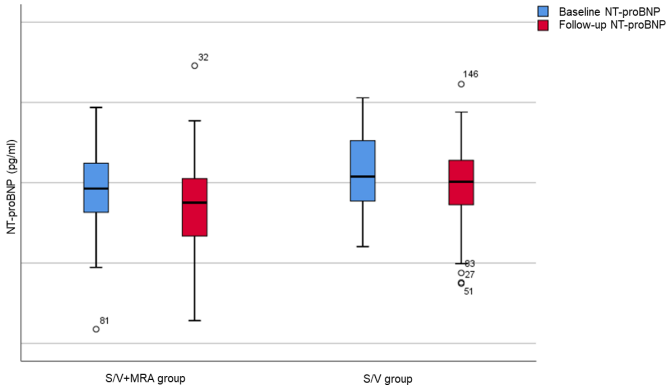

Figure 1 ΔNT-proBNP between baseline and follow-up in S/V+MRA group and S/V group. NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist; S/V, sacubitril/valsartan.

they had worse renal function, slightly higher potassium levels, slightly higher basal NT-proBNP and significantly higher index NT-proBNP/eGFR. We analysed NT-proBNP indexed to eGFR since it is known that there is an important interrelationship between cardiac and renal dysfunction.[26 27] These differences in patient characteristics are best explained by a lower tendency towards prescribing a MRA among treating physicians in patients with advanced heart failure and chronic kidney disease due to the increased risk for renal failure and hyperkalaemia with MRA.[13 28 29] Among our patients who discontinued MRA during follow-up, seven patients suspended MRA for arterial hypotension, four patients for worsening renal function, three patients for hyperkalaemia and one patient for gynecomastia.

At follow-up, NYHA functional class was similar, and neither LVEF nor the improvement of LVEF between baseline and follow-up differed significantly. There was no significant difference in the dose of S/V between the two groups, which was less than the recommended target dose in>90% of patients at baseline and still >80% at follow-up in both groups. The rate of hospitalisation for heart failure was similar between S/V+MRA group and S/V group and in line with those reported in the literature,[5] further supporting non-inferiority of the S/V without MRA strategy and demonstrating the representative burden of disease of the patients enrolled in this study.

Regarding the primary endpoint of our study, namely the reduction in NT-proBNP concentration, results did not vary significantly between S/V+MRA and S/V groups (-216 vs −166 pg/mL, p=0.93). Moreover, using general linear models (ANOVA), treatment with S/V+MRA vs treatment with S/V only did not influence significantly ΔNT-proBNP (95% CI −0.109 to 0.239, p=0.462).

The findings of our study seem to be in conflict with a metanalysis by Komajda *et al*.[16] However, the authors of another recently published metanalysis[20] of 69 randomised controlled trials, which found that the combination of neurohormonal inhibitors and more recent compounds such as SGLT2i was superior to neurohormonal inhibition alone, concluded that it was not possible to discriminate between the effects of different patterns of background neurohormonal inhibition, and that patient-level data would be necessary to achieve this scope.

Indeed, we think that these results bring new insights into finding the best combination of disease-modifying drugs for HFrEF, raising the hypothesis that mineralocorticoid receptor antagonists might not bring any additional benefit in patients treated with sacubitril/valsartan.

Given the design of our study, all limitations of a retrospective study apply to this work. The number of patients included in the analysis of this mono-centre study is limited, and thus our findings might not be representative for the entire population of patients with HFrEF. Moreover, baseline characteristics differ between the two groups in several aspects, potentially confounding the incremental change in NT-proBNP level. Other limitations are the unknown time of MRA initiation and the uptitration of S/V during the follow-up period, making NT-proBNP variation more difficult to judge. Finally, we have chosen a biochemical endpoint, which does not provide the same prognostic strength as hard endpoints such as cardiovascular death or hospitalisation for heart failure.

However, given the standardised and comprehensive assessment of patients treated in our advanced heart failure clinic and the statistical analyses performed, we are confident that the results deserve validation in prospective trials.

In conclusion, the results of this study support the hypothesis that the use of S/V without MRA might not be inferior to a strategy combining S/V and MRA as currently recommended in patients with HFrEF. Larger, prospective studies are needed to confirm this hypothesis, which if corroborated would allow for simplifying treatment and follow-up and for preventing side effects caused by MRA in patients with HFrEF.

Contributors DM conceived, designed the study and guarantees for the work. ABe, ABi and KN did the analysis. ABe and DM drafted the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval For analyses, all data were anonymised. The study conformed to the Declaration of Helsinki and to local regulations for retrospective studies and data handling. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

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