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# Sacubitril-valsartan initiation in chronic heart failure patients impacts sleep apnea: the ENTRESTO-SAS study

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## Abstract

**Aims** Optimizing medical cardiac treatment for sleep apnoea (SA) in patients with chronic heart failure and reduced ejection fraction (HFrEF) is an expert Grade C recommendation based on six studies encompassing a total of 67 patients only. Whether sacubitril–valsartan (SV), a cornerstone of HFrEF medical treatment, impacts SA is unknown and requires evaluation.

**Methods and results** The ENTRESTO-SAS trial is a six-centre, prospective, open-label real-life cohort study (NCT02916160). Ambulatory patients eligible for SV (i.e. HFrEF adults who remain symptomatic despite optimal treatment) were evaluated before and after 3 months of SV (including nocturnal ventilatory polygraphy); 118 patients were final analysed [median age was 66 (IQ<sub>25–75</sub>: 56–73) years, 81.4% male, 36.5% New York Heart Association III–IV, N-terminal pro-B-type natriuretic peptide level of 1564 (701–3376) ng/L, left ventricular ejection fraction of 30 (25–34)%, 60.7% ischaemic HFrEF, 97.5% initially treated with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 83.9% with beta-blockers, 64.4% with mineralocorticoid receptor antagonists, and 74.6% with diuretics]. Three groups were defined according to initial central/obstructive apnoea–hypopnoea indices (AHIs): G1 ( $n = 49$ ,  $AHI_{\text{central}} \geq 5/\text{h}$  and  $AHI_{\text{obstructive}} < 15/\text{h}$ ); G2 ( $n = 27$ ,  $AHI_{\text{obstructive}} \geq 15/\text{h}$ ); and G3 ( $n = 42$ ,  $AHI_{\text{central}} < 5/\text{h}$  and  $AHI_{\text{obstructive}} < 15/\text{h}$ ). At 3 months, the AHI (main predefined outcome) decreased significantly by  $-7.10/\text{h}$  (IQ<sub>25–75</sub>:  $-16.10$  to  $0.40$ ;  $P < 0.001$ ) in G1 + G2 without positive airway pressure treatment (45 patients, median initial AHI of 24.20 (IQ<sub>25–75</sub>: 16.40–43.50)/h). Of these, 24.4% presented an AHI decrease  $\geq 50\%$  and 37.78% had a final AHI  $< 15/\text{h}$  (tendency for improvement from an initial value of 20%:  $P = 0.0574$ ). For G1 patients ( $n = 37$ ), AHI significantly decreased from a median of 22.90 (16.00–43.50)/h to 19.20 (12.70–31.10)/h ( $P = 0.002$ ). For G2 patients ( $n = 8$ ), AHI decreased from a median of 30.10 (26.40–47.60)/h to 22.75 (14.60–36.90)/h (statistically non-significant,  $P = 0.059$ ).

**Conclusions** In this real-life population, SV treatment for 3 months in SA patients is associated with a significant decrease in AHI. These results support the current guidelines that recommend first an optimization of the HFrEF treatment in patients with HFrEF and central SA. A potential positive airway pressure sparing effect merits further investigation.

**Keywords** Continuous positive airway pressure; Heart failure; Sacubitril–valsartan; Sleep apnoea; Sleep-disordered breathing

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## Introduction

In developed countries, chronic heart failure (CHF) is a common disease affecting at least 1–2% of the adult population.<sup>1</sup> CHF patients still have a poor prognosis despite significant advances in therapy: more than half of elderly and/or HF hospitalized patients die within 5 years.<sup>2–4</sup>

Sleep apnoea [SA, either predominantly obstructive SA (OSA) or predominantly central SA (CSA)] is a highly prevalent co-morbidity in CHF patients associated with even worse outcomes. At least 50% of CHF patients have moderate to severe SA [i.e. SA with an apnoea–hypopnoea index (AHI) of  $\geq 15/h$ ],<sup>5,6</sup> reaching up to 76% in patients with heart failure and reduced ejection fraction (HFrEF).<sup>7</sup> While OSA is considered an independent risk factor increasing CHF morbidity and mortality,<sup>8,9</sup> CSA appears to be more a CHF severity marker, reflecting left ventricular dysfunction.<sup>10</sup> However, all SA phenotypes are associated with an increase in sympathetic activity leading to harmful conditions in this CHF context. Such may include renin–angiotensin–aldosterone system stimulation with salt and water retention, tachycardia, or peripheral vasoconstriction.<sup>5,6</sup> As a consequence, SA is considered as a potential therapeutic target in CHF as underlined by the 2017 European Respiratory Society Task Force.<sup>11</sup>

Sleep apnoea treatment modalities in CHF are not supported by a high level of evidence, especially as concerns chronic HFrEF. Whereas treating OSA with continuous positive airway pressure (CPAP) is supported by non-randomized/cohort studies reporting a decrease in mortality,<sup>12–14</sup> ventilatory treatment for CSA remains a matter of debate, in particular for patients with HFrEF.<sup>11,15,16</sup> In the context of the SERVE-HF study<sup>17</sup> and pending the ADVENT-HF study results,<sup>18</sup> optimization HFrEF management is first recommended to improve CSA in clinical practice (expert Grade C recommendation,<sup>11</sup> based on six studies encompassing a total of 67 patients only<sup>19</sup>).

The combination therapy sacubitril–valsartan (SV) has known mechanisms of action likely to counteract the pathophysiology of both OSA and CSA in CHF patients (extracellular fluid overload, cardiac injury, and sympathetic nervous system activation).<sup>19</sup> Thereby, SV interferes with neurohumoral systems and improves CHF by decreasing renin–angiotensin–aldosterone and sympathetic activity, both possible actors also involved in the pathophysiology of SA.<sup>20,21</sup> In the current context, it is therefore a good candidate for correcting SA in CHF patients. To date, due to its beneficial effects in terms of mortality, hospitalization, or quality of life, SV is the cornerstone of medical treatment for HFrEF patients who remain symptomatic [i.e. patients defined as New York Heart Association (NYHA) Classes II–IV] despite optimal treatment with an angiotensin-converting enzyme (ACE) inhibitor, a beta-blocker, and a mineralocorticoid receptor antagonist.<sup>1,22–24</sup> Whether SV impacts SA in patients with HFrEF is unknown.

In the multicentre ENTRESTO-SAS trial, we sought to assess whether SV initiation could improve SA outcomes in the HFrEF patients treated under real-life conditions.

## Methods

The ENTRESTO-SAS trial is a 3 month, multicentre, prospective, open-label, real-life cohort study (NCT02916160) conducted from 22 September 2016 to 15 December 2019. The protocol complied with the Declaration of Helsinki and was reviewed and approved by an independent ethics committee (Comité de Protection des Personnes Sud Méditerranée IV; Reference Number 2016-A00331-50).

### Study design

The ENTRESTO-SAS study design is summarized in *Figure 1* and has been previously reported.<sup>19</sup> Briefly, ambulatory patients eligible for SV treatment were invited to participate in the study [i.e. HFrEF patients who remain symptomatic (NYHA Classes II–IV) despite optimal treatment]. After inclusion and exclusion criteria verification, a pre-therapeutic evaluation [including nocturnal ventilatory polygraphy (P)] was performed. SV was started after the P, and cardiological surveillance deployed to achieve the optimal SV treatment dose. At 3 months, a final evaluation was performed. For patients presenting with SA at baseline (i.e.  $AHI_{\text{central}} \geq 5/h$  and/or  $AHI_{\text{obstructive}} \geq 15/h$ ), the latter included a second diagnostic P (without CPAP if applicable).

### Group definitions

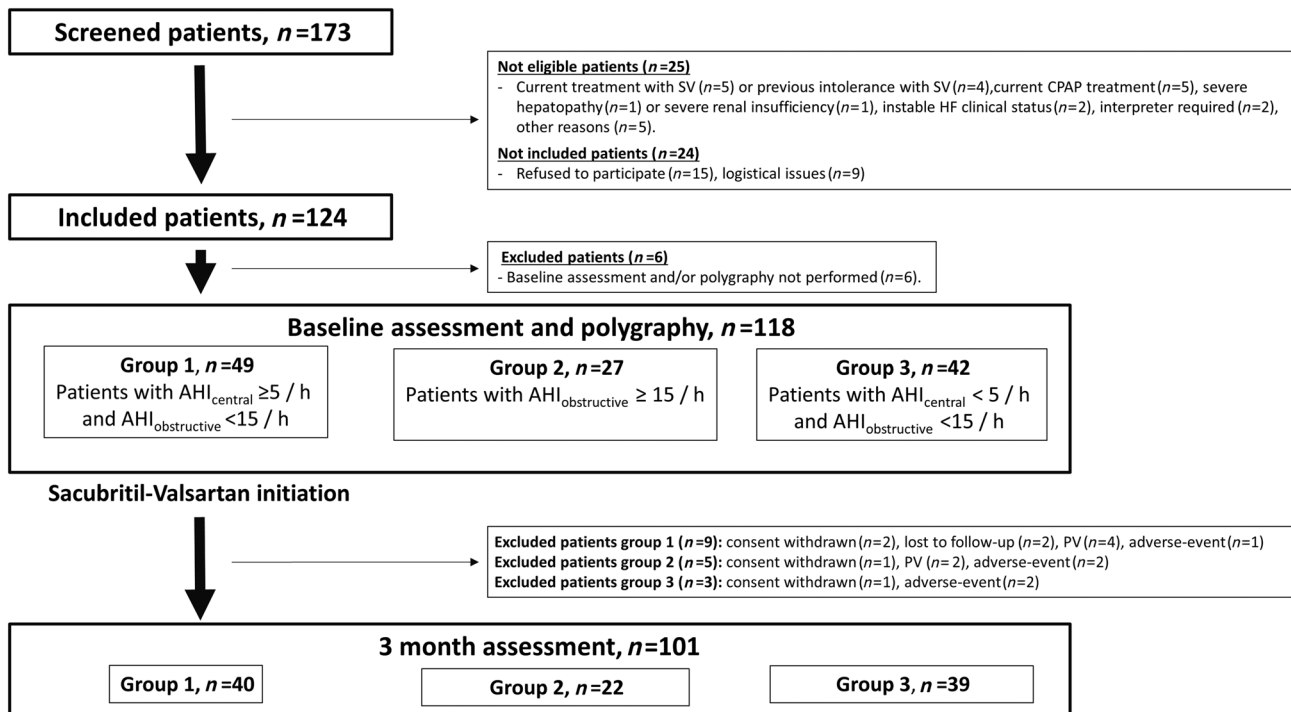
Based on the initial P results, three groups were generated; G1:  $AHI_{\text{central}} \geq 5/h$  and  $AHI_{\text{obstructive}} < 15/h$ ; G2:  $AHI_{\text{obstructive}} \geq 15/h$  regardless of the  $AHI_{\text{central}}$ ; and G3:  $AHI_{\text{central}} < 5/h$  and  $AHI_{\text{obstructive}} < 15/h$  (see Supporting Information, *Appendix S1*).

### Outcomes

The main predefined outcome was the change in AHI before vs. after 3 months of SV in G1 and G2 patients without positive airway pressure (PAP) treatment. The two main secondary outcomes were the proportion of these patients with a  $\geq 50\%$  decrease in their AHI or a final  $AHI < 15/h$ . For these AHI outcomes, the 2012 American Academy of Sleep Medicine recommendations were used to characterize not only apnoea and hypopnoea events but also the event phenotype (central, obstructive, and mixed).<sup>25</sup> The apnoea/hypopnoea criteria used as scoring rules are detailed in Supporting Information, *Appendix S1*. CPAP-treated patients were analysed separately as planned in the design paper.<sup>19</sup>

For quality-of-life outcomes, the following validated scales and questionnaires were used: Minnesota Living with Heart

**Figure 1** Study flow chart. Overview of screened, eligible, included, and excluded patients. Assessments included a physical examination, echocardiography, laboratory testing, the Minnesota Living with Heart Failure Questionnaire, the EQ-5D-3L questionnaire, the Epworth Sleepiness Scale, and the New York Heart Association score. Polygraphy was performed for Groups 1–3 at baseline and at 3 months for Groups 1 and 2. AHI, apnoea–hypopnoea index; CPAP, continuous positive airway pressure; HF, heart failure; PV, protocol violation; SV, sacubritil–valsartan.



Failure Questionnaire,<sup>26</sup> EQ-5D-3L Questionnaire,<sup>27</sup> and Epworth Sleepiness Scale.<sup>28</sup>

## Statistical methods

Continuous data were expressed as medians, inter-quartile ranges (IQ<sub>25–75</sub>), and ranges [min–max]. Qualitative parameters were expressed as numbers and percentages. Three group comparisons were performed using ANOVA or Kruskal–Wallis tests for quantitative data. Qualitative variables were compared using  $\chi^2$  or Fisher’s exact tests. In case of a significant global effect, pairwise comparisons were performed using Holm corrections for multiple comparisons. Evolutions between initial and final evaluations were studied using Student’s paired tests or Wilcoxon paired test for quantitative variables and exact McNemar test for qualitative parameters. A bilateral  $P$  value of  $<0.05$  was considered as indicating statistical significance. Missing data were not replaced. All analyses were conducted by the Clinical Research and Epidemiology Unit at the Montpellier University Hospitals using SAS (Enterprise Guide, Version 7.13; SAS Institute, Cary, NC, USA).

## Results

The flow chart of the study is depicted in *Figure 1*. A total of 118 patients were included in the analyses. *Table 1* summarizes patient characteristics at baseline. Among these patients, 41.5% belonged to G1, 22.9% to G2, and 35.6% to G3. G2 patients presented a significant higher body mass index with a median of 28.96 (25.47–32.83) kg/m<sup>2</sup> vs. G3 patients [median 24.69 (21.15–29.39) kg/m<sup>2</sup>,  $P = 0.048$ ]. G1 patients presented not only a significant higher prevalence of atrial fibrillation (35.42%) than G3 patients (7.14%;  $P = 0.004$ ) but also significantly higher serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration levels [median 1816 (1004–3958) vs. 920.5 (248–2200) pg/mL,  $P = 0.037$ ].

### Primary outcome: apnoea–hypopnoea index change after 3 months of sacubritil–valsartan treatment

The main predefined outcome was the change in the AHI after 3 months of SV in G1 and G2 patients without PAP treatment ( $n = 37/40$  patients for G1 and  $n = 8/22$  patients for G2).

**Table 1** Patient characteristics at baseline

	N	Total n = 118	Group 1 n = 49	Group 2 n = 27	Group 3 n = 42	P value
Age (years)	118	66.00 [56.00–73.00]	64.00 [55.00–75.00]	69.00 [57.00–74.00]	66.00 [55.00–72.00]	0.628 <sup>c</sup>
Gender, n (%)	118					0.318 <sup>d</sup>
Male		96 (81.36)	43 (87.76)	21 (77.78)	32 (76.19)	
Female		22 (18.64)	6 (12.24)	6 (22.22)	10 (23.81)	
BMI (kg/m <sup>2</sup> )	118	26.81 [23.18–30.76]	27.38 [23.77–30.25]	28.96 <sup>a</sup> [25.47–32.83]	24.69 <sup>a</sup> [21.15–29.39]	0.039 <sup>f</sup>
Systolic BP (mmHg)	101	120 [110–130]	120 [110–130]	120 [109–125]	120 [110–130]	0.862 <sup>c</sup>
Diastolic BP (mmHg)	101	70 [65–80]	71 [65–80]	70 [65–79]	70 [64–80]	0.932 <sup>f</sup>
Heart rate (b.p.m.)	118	70 [63–80]	69 [63–87]	70 [64–78]	71 [63–76]	0.948 <sup>f</sup>
Co-morbidities						
Active smoking (or stop <1 year), n (%)	118	25 (21.19)	11 (22.45)	6 (22.22)	8 (19.05)	0.914 <sup>d</sup>
Hypertension, n (%)	118	45 (38.14)	19 (38.78)	13 (48.15)	13 (30.95)	0.354 <sup>d</sup>
Diabetes, n (%)	118	25 (21.19)	11 (22.45)	9 (33.33)	5 (11.90)	0.100 <sup>d</sup>
Dyslipidaemia, n (%)	118	42 (35.59)	18 (36.73)	11 (40.74)	13 (30.95)	0.692 <sup>d</sup>
ORD, n (%)	118	10 (8.55)	3 (6.12)	2 (7.41)	5 (12.20)	0.641 <sup>d</sup>
PAD, n (%)	118	16 (13.56)	5 (10.20)	7 (25.93)	4 (9.52)	0.142 <sup>e</sup>
eGFR Cockcroft class, n (%)	117					0.705 <sup>e</sup>
<30		4 (3.42)	1 (2.04)	2 (7.41)	1 (2.44)	
[30–45]		17 (14.53)	8 (16.33)	2 (7.41)	7 (17.07)	
[45–60]		19 (16.24)	8 (16.33)	3 (11.11)	8 (19.51)	
≥60		77 (65.81)	32 (65.31)	20 (74.07)	25 (60.98)	
eGFR Cockcroft (mL/min/1.73 m <sup>2</sup> )	117	74.64 [50.77–94.91]	71.11 [54.68–99.80]	80.25 [50.77–105.68]	70.60 [48.98–90.41]	0.268 <sup>c</sup>
Clinical features of HF						
Ischaemic, n (%)	117	71 (60.68)	31 (63.27)	18 (66.67)	22 (53.66)	0.499 <sup>d</sup>
Hypertensive, n (%)	117	3 (2.56)	2 (4.08)	1 (3.70)	0 (0.00)	0.451 <sup>e</sup>
Valvulopathy, n (%)	117	8 (6.84)	4 (8.16)	2 (7.41)	2 (4.88)	0.899 <sup>e</sup>
Primitive, n (%)	117	30 (25.64)	9 (18.37)	7 (25.93)	14 (34.15)	0.232 <sup>d</sup>
Rhythmic, n (%)	117	23 (19.66)	13 (26.53)	6 (22.22)	4 (9.76)	0.127 <sup>d</sup>
Atrial fibrillation, n (%)	117	24 (20.51)	17 (35.42) <sup>b</sup>	4 (14.81)	3 (7.14) <sup>b</sup>	0.003 <sup>d</sup>
LVEF (%)	118	30.00 [25.00–34.00]	30.00 [25.00–33.00]	30.00 [25.00–30.00]	30.00 [25.00–35.00]	0.853 <sup>f</sup>
NT-proBNP (pg/mL)	110	1564.5 [701–3376]	1816 <sup>b</sup> [1004–3958]	1721 [845–3333]	920.5 <sup>b</sup> [248–2200]	0.029 <sup>f</sup>
NYHA functional class, n (%)	115					
I/II		9/64 [7.83/55.65]	5/30 [10.42/62.50]	2/14 [7.69/53.85]	2/20 [4.88/48.78]	0.141 <sup>d</sup>
III/IV		37/5 [32.17/4.35]	9/4 [18.75/8.33]	10/0 [38.46/0]	18/1 [43.90/2.44]	
Treatment						
Loop diuretics	118	88 (74.58)	39 (79.59)	21 (77.78)	28 (66.67)	0.335 <sup>d</sup>
Spironolactone	118	76 (64.41)	29 (59.18)	21 (77.78)	26 (61.90)	0.246 <sup>d</sup>
ACE inhibitor or ARB	118	115 (97.46)	48 (97.96)	27 (100.00)	40 (95.24)	0.608 <sup>e</sup>
Beta-blocker	118	99 (83.90)	38 (77.55)	26 (96.30)	35 (83.33)	0.083 <sup>e</sup>
Cardiac resynchronization therapy	117	12 (10.26)	6 (12.24)	3 (11.54)	3 (7.14)	0.731 <sup>e</sup>
Pacemaker	117	12 (10.26)	4 (8.16)	5 (18.52)	3 (7.32)	0.283 <sup>e</sup>
ICD	118	55 (46.61)	18 (36.73) <sup>b</sup>	11 (40.74)	26 (61.90) <sup>b</sup>	0.044 <sup>d</sup>

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implanted cardiac defibrillator; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ORD, obstructive respiratory disease; PAD, peripheral arterial disease.

Quantitative variables were described by medians and [IQR<sub>25–75</sub>].

<sup>a</sup>Significant pairwise comparisons after Holm corrections were presented for Group 2 vs. Group 3.

<sup>b</sup>Significant pairwise comparisons after Holm corrections were presented for Group 1 vs. Group 3.

<sup>c</sup>Statistical tests used were presented, on *P* values, for ANOVA.

<sup>d</sup>Statistical tests used were presented, on *P* values, for  $\chi^2$  test.

<sup>e</sup>Statistical tests used were presented, on *P* values, for Fisher's exact test.

<sup>f</sup>Statistical tests used were presented, on *P* values, for Kruskal–Wallis test.

Table 2 summarizes the *P* results for G1 + G2 patients. Individual data for the AHI are depicted in Figure 2 (for G1 and G2, see panels A and B, respectively). Specific *P* data for G1 and G2 are summarized in Tables 3 and 4, respectively. At 3 months, the AHI primary outcome decreased significantly by a median  $-7.10/h$  ( $-16.10$  to  $0.40$ ),  $P < 0.001$ , in G1 + G2 patients. G1 patients had mainly a central IAH pattern, whereas G2 patients have mainly an obstructive

one. For G1 patients, AHI significantly decreased from a median of  $22.90$  ( $16.00$ – $43.50$ )/h to  $19.20$  ( $12.70$ – $31.10$ )/h ( $P = 0.002$ ). The median AHI difference was  $-6.60$  ( $-11.70$  to  $0.40$ )/h (see Table 3). For G2 patients, AHI decreased from a median of  $30.10$  ( $26.40$ – $47.60$ )/h to  $22.75$  ( $14.60$ – $36.90$ )/h (statistically non-significant,  $P = 0.059$ ). The median AHI difference was  $-12.40$  ( $-23.60$  to  $0.35$ )/h (see Table 4).

**Table 2** Initial (baseline) and final (3 months) polygraphy data in G1 and G2 patients (restricted to patients without positive airway pressure treatment)

	n	G1 + G2 (n = 45)		P value
		Initial	Final	
AHI (events/h)	45	24.20 (16.40–43.50) [8.10–67.00]	20.40 (12.70–31.10) [1.00–55.00]	<0.001 <sup>a</sup>
AHI < 15, n (%)	45	9 (20.00)	17 (37.78)	0.057 <sup>b</sup>
dAHI (events/h)	41	29.40 (17.20–48.60) [0.00–66.00]	27.30 (15.90–40.40) [0.00–58.30]	0.095 <sup>a</sup>
AHI <sub>obstructive</sub> (events/h)	45	4.20 (1.30–10.00) [0.00–27.00]	5.60 (3.60–10.00) [0.00–49.20]	0.611 <sup>a</sup>
AHI <sub>central</sub> (events/h)	45	13.60 (8.20–31.80) [0.00–51.40]	7.00 (3.10–16.60) [0.00–45.00]	<0.001 <sup>c</sup>
OAI (events/h)	45	1.30 (0.10–4.00) [0.00–16.20]	1.40 (0.60–4.00) [0.00–49.10]	0.378 <sup>a</sup>
CAI (events/h)	45	4.00 (1.50–20.50) [0.00–46.10]	2.10 (0.50–5.50) [0.00–45.00]	<0.001 <sup>a</sup>
MAI (events/h)	45	0.10 (0.00–1.40) [0.00–31.00]	0.40 (0.00–1.50) [0.00–39.00]	0.724 <sup>a</sup>
HI (events/h)	44	13.45 (7.90–17.75) [2.50–38.70]	8.45 (4.90–15.40) [0.40–42.80]	0.014 <sup>a</sup>
HI <sub>obstructive</sub> (events/h)	45	1.70 (0.50–6.70) [0.00–20.00]	2.20 (0.70–6.20) [0.00–21.90]	0.811 <sup>a</sup>
HI <sub>central</sub> (events/h)	45	7.20 (2.10–11.30) [0.00–29.80]	3.10 (0.50–7.40) [0.00–29.60]	0.024 <sup>a</sup>
ODI (events/h)	42	–6.32 (±15.79)	–6.20 (–12.70 to 0.90)	0.013 <sup>c</sup>
Mean SpO <sub>2</sub> (%)	44	92.30 (91.35–94.55) [87.90–96.80]	93.05 (91.60–94.70) [88.90–99.60]	0.247 <sup>a</sup>
Minimum SpO <sub>2</sub> (%)	43	83.00 (78.00–86.00) [0.00–91.00]	84.00 (81.00–87.00) [60.00–93.00]	0.036 <sup>a</sup>
Time SpO <sub>2</sub> < 90% (min)	44	23.00 (5.00–96.50) [0.00–311.00]	13.50 (2.50–67.50) [0.00–344.00]	0.129 <sup>a</sup>
Time SpO <sub>2</sub> < 90% (%)	44	8.10 (1.00–22.95) [0.00–81.00]	2.85 (0.40–12.75) [0.00–60.90]	0.020 <sup>a</sup>

AHI, apnoea–hypopnoea index; CAI, central apnoea index; dAHI, dorsal apnoea–hypopnoea index; HI, hypopnoea index; MAI, mixed apnoea index; OAI, obstructive apnoea index; ODI, oxygen desaturation index; SpO<sub>2</sub>, oxygen saturation on pulse oximetry.

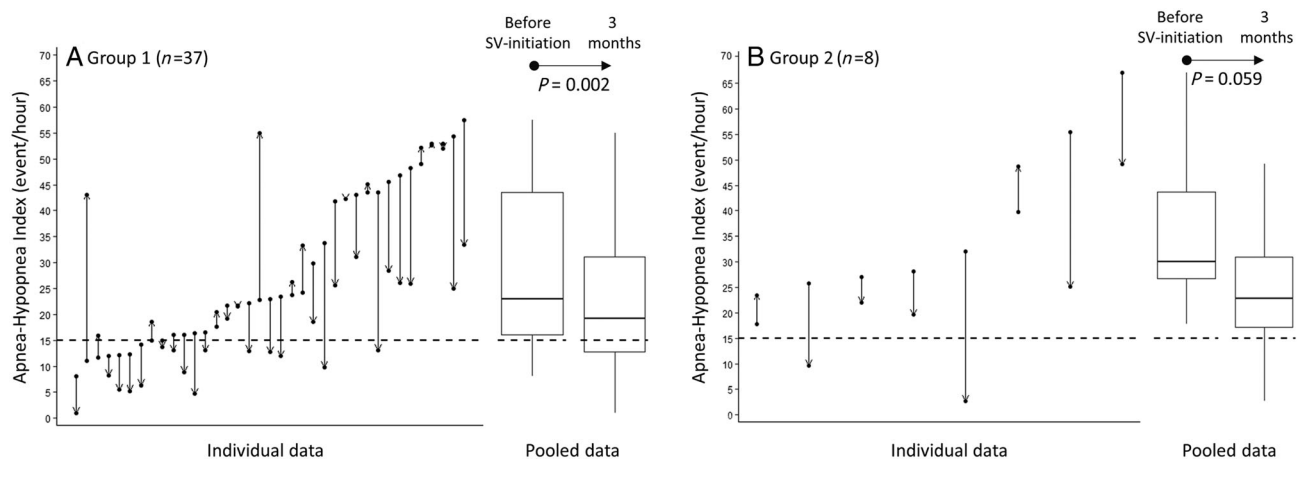
Quantitative variables were described by medians and (I<sub>Q</sub><sub>25–75</sub>) and [I<sub>min–max</sub>].

<sup>a</sup>The statistical tests used are presented on P values for Wilcoxon paired test.

<sup>b</sup>The statistical tests used are presented on P values for McNemar's test with Yates' corrections.

<sup>c</sup>The statistical tests used are presented on P values for Student's paired test.

**Figure 2** Apnoea–hypopnoea index before vs. after 3 months of sacubitril–valsartan (SV). Change in apnoea–hypopnoea index before vs. after 3 months of SV in (A) Group 1 and (B) Group 2 patients without positive airway pressure treatment.



As opposite to these AHI differences, weight differences before and after SV do not reached a statistical significant difference in any of the studied groups. The median weight difference was 1.00 (–2.30 to 3.00) kg,  $P = 0.667$ , for G1 patients; the median weight difference was 1.50 (–1.00 to 6.00) kg,  $P = 0.088$ , for G2 patients; and the median weight difference was 0.00 (–3.00 to 1.00) kg,  $P = 0.075$ , for G3 patients.

Univariate linear regressions with the AHI relative difference as the variable of interest in G1 and G2 patients are depicted in Supporting Information, *Table S1*. Only initial left ventricular ejection fraction (LVEF) is significantly associated with (standardized  $\beta$  coefficient of 0.33,  $P = 0.038$ ).

### Main secondary outcomes: apnoea–hypopnoea index $\geq 50\%$ decrease and final apnoea–hypopnoea index $< 15/h$

The main secondary outcomes were the proportion of G1 and G2 patients with a  $\geq 50\%$  decrease in their AHI or a final AHI  $< 15/h$  (restricted to patients without PAP treatment); 24.4% of the patients presented a  $\geq 50\%$  decrease in their AHI (21.6% for G1 and 37.5% for G2), and 20% presented an initial AHI  $< 15/h$  vs. 37.78% at 3 months,  $P = 0.0574$  (24.3% vs. 40.5% for G1 patients,  $P = 0.146$ ; 0% vs. 25% for G2 patients,  $P = 0.5$ , respectively).

### Secondary outcome: polygraphy and positive airway pressure data for the G1 + G2 populations regardless of positive airway pressure treatment status or sacubitril–valsartan adherence

Initial and final P data for G1 and G2 patients (without restrictions on PAP usage or SV adherence) are depicted in Supporting Information, *Tables S2* and *S3*, respectively. At

the baseline assessment, 57.63% of the 118 patients presented with an initial AHI  $\geq 15/h$  (41/49 in G1 patients, 27/27 G2 patients, and 0/42 G3 patients). PAP data are summarized in Supporting Information, *Table S4*, and exclusively involved CPAP ( $n = 1/40$  for G1 and  $n = 13/22$  for G2). Two G1 patients and one G2 patient were not SV adherent at the P evaluation.

For these G1 patients, AHI significantly decreased from a median of 23.20 (16.00–43.55)/h to 20.95 (12.80–32.20)/h ( $P = 0.003$ ). The median AHI difference was  $-4.10$  (–11.65 to 1.0)/h (see Supporting Information, *Table S2*). For G2 patients, AHI significantly decreased from a median of 37.65 (28.40–45.30)/h to 23.95 (9.60–40.30)/h ( $P = 0.002$ ). The median AHI difference was  $-16.15$  (–27.70 to  $-1.60$ )/h (see Supporting Information, *Table S3*).

### Secondary outcomes: cardiac assessment data

Supporting Information, *Table S5* summarizes the changes in cardiac assessment between baseline and the 3 month evaluation. For the latter, the SV dosage was 24/26 mg for 33.7% of the patients, 49/51 mg for 31.7%, and 97/103 mg for 34.6%. After SV initiation, there was a trend towards a reduction in blood pressure in the three groups that did not reach statistical significance. NYHA class (I and II vs. III and IV) was down-staged in the three groups ( $P = 0.070$  for G1,  $P = 0.453$  for G2, and  $P < 0.001$  for G3). NT-proBNP significantly decreased in the three groups [median change of  $-301.00$  (–887.0 to  $-34.0$ ) pg/mL for G1 ( $P = 0.001$ ),  $-309.00$  (–1281 to 164.0) pg/mL for OSA-G2 ( $P = 0.043$ ), and  $-299.50$  (–802.50 to  $-44.00$ ) pg/mL for G3 ( $P < 0.001$ )]; 51.72% of the whole population presented a change over 30% in NT-proBNP values after SV initiation (without significant differences between groups). The LVEF significantly increased for G1 and G3 [median change of

**Table 3** Change in polygraphy data before (initial) vs. after (final) 3 months of sacubritil–valsartan in G1 patients without positive airway pressure treatment

	n	Initial		Final		Difference	P value	
		n	Mean (SD)	n	Mean (SD)			
AHI (events/h)	37	22.90	(16.00–43.50) [8.10–57.50]	19.20	(12.70–31.10) [1.00–55.00]	–6.60	(–11.70 to 0.40) [–30.50 to 32.20]	0.002 <sup>a</sup>
AHI < 15, n (%)	37	9	(24.3)	15	(40.5)	—	—	0.146 <sup>b</sup>
dAHI (events/h)	34	29.65	(16.00–48.60) [0.00–63.40]	27.45	(15.90–40.40) [0.00–56.00]	–3.10	(–13.30 to 3.80) [–40.80 to 54.70]	0.266 <sup>c</sup>
AHI <sub>obstructive</sub> (events/h)	37	2.60	(1.20–6.60) [0.00–14.40]	5.40	(2.20–8.50) [0.00–49.20]	0.80	(–0.80 to 5.80) [–10.40 to 44.80]	0.028 <sup>a</sup>
AHI <sub>central</sub> (events/h)	37	13.60	(9.00–31.80) [5.10–51.40]	7.00	(4.00–16.60) [0.10–45.00]	–9.00	(–15.00 to –3.40) [–44.40 to 20.20]	<0.001 <sup>c</sup>
OAI (events/h)	37	0.60	(0.00–1.90) [0.00–8.50]	1.40	(0.30–3.70) [0.00–49.10]	0.60	(–0.40 to 2.60) [–4.60 to 45.70]	0.030 <sup>a</sup>
CAI (events/h)	37	4.90	(1.60–25.00) [0.00–46.10]	2.30	(0.80–5.50) [0.00–45.00]	–1.50	(–11.40 to 0.20) [–45.00 to 6.70]	<0.001 <sup>a</sup>
MAI (events/h)	37	0.10	(0.00–1.20) [0.00–31.00]	0.50	(0.00–1.50) [0.00–39.00]	0.00	(–0.40 to 0.70) [–28.50 to 15.00]	0.651 <sup>a</sup>
HI (events/h)	36	11.90	(7.10–14.65) [2.50–27.50]	7.65	(4.90–13.65) [0.40–42.80]	–3.40	(–7.25 to –0.40) [–13.30 to 33.20]	0.030 <sup>a</sup>
HI <sub>obstructive</sub> (events/h)	37	1.20	(0.20–4.20) [0.00–12.50]	1.90	(0.50–5.40) [0.00–18.70]	0.00	(–0.70 to 1.90) [–9.10 to 17.40]	0.234 <sup>a</sup>
HI <sub>central</sub> (events/h)	37	7.20	(5.10–11.30) [0.00–29.80]	3.10	(0.50–7.30) [0.00–29.60]	–4.70	(–7.50 to 0.60) [–15.80 to 28.20]	0.018 <sup>a</sup>
ODI (events/h)	36	11.90	(7.10–14.65) [2.50–27.50]	7.65	(4.90–13.65) [0.40–42.80]	–3.40	(–7.25 to –0.40) [–13.30 to 33.20]	0.030 <sup>a</sup>
Mean SpO <sub>2</sub> (%)	37	93.00	(91.80–94.60) [87.90–96.80]	93.40	(92.20–94.90) [88.90–99.60]	0.60	(–1.10 to 1.50) [–4.00 to 8.10]	0.313 <sup>a</sup>
Minimum SpO <sub>2</sub> (%)	36	83.50	(78.00–86.00) [0.00–91.00]	84.00	(80.50–86.50) [60.00–93.00]	1.00	(–1.00 to 4.00) [–11.00 to 60.00]	0.0621 <sup>a</sup>
Time SpO <sub>2</sub> < 90% (min)	37	17.00	(3.00–79.00) [0.00–274.00]	7.00	(2.00–42.00) [0.00–344.00]	–3.00	(–20.00 to 4.00) [–203.0 to 231.0]	0.220 <sup>a</sup>
Per cent time SpO <sub>2</sub> < 90% (%)	37	7.70	(0.60–19.00) [0.00–81.00]	1.80	(0.30–8.60) [0.00–60.90]	–0.60	(–10.60 to 0.80) [–79.8 to 37.2]	0.060 <sup>a</sup>

AHI, apnoea–hypopnoea index; CAI, central apnoea index; dAHI, dorsal apnoea–hypopnoea index; HI, hypopnoea index; MAI, mixed apnoea index; OAI, obstructive apnoea index; ODI, oxygen desaturation index; SpO<sub>2</sub>, oxygen saturation on pulse oximetry.

Quantitative variables were described by medians and (I<sub>Q</sub><sub>25–75</sub>) and [I<sub>min–max</sub>].

<sup>a</sup>The statistical tests used are presented on P values for Wilcoxon paired test.

<sup>b</sup>The statistical tests used are presented on P values for McNemar's test with Yates' corrections.

<sup>c</sup>The statistical tests used are presented on P values for Student's paired test.



**Table 4** Change in polygraphy data before (initial) vs. after (final) 3 months of sacubitril–valsartan in G2 patients without positive airway pressure treatment

	n	G2 (n = 8)		P value
		Initial	Final	
AHI (events/h)	8	30.10 (26.40–47.60) [17.80–67.00]	22.75 (14.60–36.90) [2.70–49.10]	0.059 <sup>a</sup>
AHI < 15/h	7	0 (0)	2 (25.0)	0.500 <sup>b</sup>
dAHI (events/h)	8	28.00 (25.50–49.10) [16.70–66.00]	26.00 (10.00–40.50) [0.00–58.30]	0.375 <sup>c</sup>
AHI <sub>obstructive</sub> (events/h)	8	22.85 (18.75–24.75) [17.30–27.00]	11.45 (4.25–19.50) [0.90–23.00]	0.010 <sup>a</sup>
AHI <sub>central</sub> (events/h)	8	6.50 (0.90–25.60) [0.00–33.70]	3.90 (1.10–25.10) [0.00–36.40]	0.919 <sup>a</sup>
OAI (events/h)	8	7.15 (5.60–12.60) [0.00–16.20]	1.50 (1.05–4.10) [0.00–14.80]	0.107 <sup>a</sup>
CAI (events/h)	8	2.60 (0.75–5.65) [0.00–22.30]	1.90 (0.00–7.60) [0.00–22.40]	0.469 <sup>b</sup>
MAI (events/h)	8	0.45 (0.00–3.25) [0.00–8.40]	0.05 (0.00–0.95) [0.00–7.40]	1.000 <sup>c</sup>
HI (events/h)	8	19.85 (17.75–22.90) [9.80–38.70]	17.25 (4.55–21.70) [2.20–32.20]	0.170 <sup>a</sup>
HI <sub>obstructive</sub> (events/h)	8	14.35 (9.30–19.05) [4.70–20.00]	4.35 (1.55–15.90) [0.70–21.90]	0.102 <sup>a</sup>
HI <sub>central</sub> (events/h)	8	2.65 (0.00–13.40) [0.00–27.30]	2.85 (0.25–13.80) [0.00–21.40]	0.831 <sup>a</sup>
ODI (events/h)	7	31.00 (15.30–55.90) [7.00–60.00]	24.00 (11.00–45.90) [4.90–47.30]	0.255 <sup>a</sup>
Mean SpO <sub>2</sub> (%)	7	91.30 (90.00–93.00) [89.10–93.00]	91.80 (91.00–92.10) [89.50–94.40]	0.439 <sup>a</sup>
Minimum SpO <sub>2</sub> (%)	7	83.00 (75.00–87.00) [71.00–89.00]	83.00 (81.00–88.00) [79.00–91.00]	0.291 <sup>a</sup>
Time SpO <sub>2</sub> < 90% (min)	7	182.00 (35.00–279.00) [12.00–311.00]	54.00 (15.00–244.00) [0.00–310.00]	0.403 <sup>a</sup>
Per cent time SpO <sub>2</sub> < 90% (%)	7	19.00 (2.00–48.50) [1.00–55.40]	10.00 (4.00–27.70) [0.00–45.80]	0.177 <sup>a</sup>

AHI, apnoea–hypopnoea index; CAI, central apnoea index; dAHI, dorsal apnoea–hypopnoea index; HI, hypopnoea index; MAI, mixed apnoea index; OAI, obstructive apnoea index; ODI, oxygen desaturation index; SpO<sub>2</sub>, oxygen saturation on pulse oximetry.

Quantitative variables were described by medians and (I<sub>Q</sub><sub>25–75</sub>) and [min–max].

<sup>a</sup>The statistical tests used are presented on P values for Student's paired test.

<sup>b</sup>The statistical tests used are presented on P values for McNemar's test with Yates' corrections.

<sup>c</sup>The statistical tests used are presented on P values for Wilcoxon paired test.

2.00 (0.00–10.00)%,  $P = 0.001$ , and median change of 2.00 (0.00–7.00)%,  $P = 0.016$ , respectively]. The tricuspid annular plane systolic excursion significantly increased only in G1 [median change of 1.00 (–1.00 to 5.00) mm,  $P = 0.045$ ] associated with a significant decrease in the pulmonary artery systolic pressure [median change of –7.00 (–16.00 to 0.00) mmHg,  $P = 0.001$ ].

Supporting Information, *Table S6* summarizes the changes in cardiological concomitant treatment between the initial and final P. No significant treatment changes occurred except for switching between SV and ACE inhibitors.

Supporting Information, *Figure S1* depicts the correlations between the AHI relative difference and the relative differences for echocardiographic parameters. These correlations are weak ( $r = -0.15$  to  $0.13$ ) and not statistically significant.

### Secondary outcomes: quality-of-life data

No significant differences between initial and final Epworth Sleepiness Scale scores were observed (see Supporting Information, *Table S7*), regardless of group. On the contrary, the Minnesota Living with Heart Failure Questionnaire total score significantly and favourably decreased for G1 [from 24 (11–51) to 17 (6–33),  $P = 0.003$ ] and G3 [from 31 (10–50) to 18 (6–31),  $P = 0.004$ ]. Finally, the EQ-5D-3L Health Visual Analogue Scale score also favourably increased for G1 [from 60 (50–70) to 75 (60–80),  $P = 0.001$ ] and G3 [from 52.5 (40–70) to 70 (60–80),  $P = 0.016$ ].

### Secondary outcomes: safety data

During the 3 months of the trial, one patient withdrew because of a side effect associated with the SV treatment (angioedema). At 3 months, 38.1% of the patients presented at least one adverse event, as summarized in *Table 5*. The latter included unscheduled hospitalizations for cardiac failure for 17.72% of patients. Symptomatic hypotension was reported in 7.59%, a decrease in estimated glomerular filtration rate  $>30\%$  in 3.80% and hyperkalaemia in 2.53% of patients.

## Discussion

To the best of our knowledge, we report the largest prospective, multicentre, real-life study investigating the effects of an HFrEF-targeting drug on AHI. Three months after starting SV treatment, we observed a significant decrease in AHI [median –7.10/h (IQR<sub>25–75</sub>: –16.10 to 0.40)] in SA HFrEF patients with SV adherence but who were not receiving PAP therapy. Of the latter, 24.4% had an AHI decrease  $\geq 50\%$ , and 17.78% more patients (for a total of 37.78%) had a final AHI  $< 15/h$  (suggesting a potential PAP sparing benefit).

### Similarity with previously reported populations

Among HFrEF patients, the prevalence of SA varies in the literature. Research reports are heterogeneous not only in terms of design and population (HFrEF aetiology and HFrEF

**Table 5** Adverse effects at 3 months

Patients, $n$ (%)	Total $n = 118$	G1 $n = 49$	G2 $n = 27$	G3 $n = 42$	$P$ value
Number of patients with at least 1 AE	45 (38.1)	13 (26.5)	13 (48.2)	19 (45.2)	0.089 <sup>a</sup>
Number of patients with					
1 AE	24 (20.34)	6 (12.24)	6 (22.22)	12 (28.57)	0.126 <sup>b</sup>
2 AE	12 (10.17)	2 (4.08)	4 (14.81)	6 (14.29)	
3 AE	7 (5.93)	4 (8.16)	2 (7.41)	1 (2.38)	
$\geq 4$ AE	2 (1.69)	1 (2.04)	1 (3.70)	0 (0.00)	
AE, $n$ (%)	Total $n = 79$	G1 $n = 26$	G2 $n = 26$	G3 $n = 27$	$P$ value
Unscheduled hospitalization for HF	9 (11.39)	3 (11.54)	2 (7.69)	4 (14.81)	0.904 <sup>b</sup>
Scheduled hospitalization for HF	3 (3.80)	0 (0.00)	3 (11.54)	0 (0.00)	0.066 <sup>b</sup>
Unscheduled hospitalization for cardiological causes other than HF	5 (6.33)	0 (0.00)	1 (3.85)	4 (14.81)	0.120 <sup>b</sup>
Scheduled hospitalization for cardiological causes other than HF	6 (7.59)	4 (15.38)	1 (3.85)	1 (3.70)	0.311 <sup>b</sup>
AE associated with SV intake					
Symptomatic hypotension	6 (7.59)	2 (7.69)	2 (7.69)	2 (7.41)	1.000 <sup>b</sup>
Non-symptomatic hypotension	4 (5.06)	3 (11.54)	0 (0.00)	1 (3.70)	0.215 <sup>b</sup>
Decrease in renal function ( $>30\%$ eGFR) (mL/min/1.73 m <sup>2</sup> )	3 (3.80)	1 (3.85)	0 (0.00)	2 (7.41)	0.769 <sup>b</sup>
Hyperkalaemia ( $>5.5$ mmol/L)	2 (2.53)	2 (7.69)	0 (0.00)	0 (0.00)	0.211 <sup>b</sup>
Angioedema	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Others	41 (51.90)	11 (42.31)	17 (65.38)	13 (48.15)	0.223 <sup>a</sup>

AE, adverse event; eGFR, estimated glomerular filtration rate; HF, heart failure; SV, sacubitril–valsartan.

Qualitative variables were described by numbers and percentages.

<sup>a</sup>Statistical tests used were presented, on  $P$  values, for  $\chi^2$  test.

<sup>b</sup>Statistical tests used were presented, on  $P$  values, for Fisher's exact test.

treatment) but also in the diagnostic criteria used for SA detection [i.e. polysomnography (PSG) vs. polygraphy], apnoea/hypopnoea coding rules, and AHI definitions (central/obstructive thresholds).<sup>5–7</sup> In our study, using P and the recommended 2012 American Academy of Sleep Medicine coding rules, 57.63% of the total population had an AHI > 15/h, 20.34% with >50% obstructive events, and 23.73% with >50% central events. These figures are consistent with previous reports as summarized in the 2017 European Respiratory Society Task Force report (CSA at a threshold of AHI  $\geq$  15/h occurs in 21–37% of stable HFrEF patients).<sup>11</sup>

This real-life study in patients with HFrEF and SV initiation is consistent with previous reports not only for baseline characteristics but also regarding impacts on cardiac function and related quality-of-life changes. At baseline, 97.46% were treated with ACE inhibitors or sartans, 83.9% with beta-blockers (median heart rate of 70 b.p.m.), and 64.41% with mineralocorticoid receptor antagonist, as in previous reports.<sup>29–33</sup> After SV initiation, NT-proBNP values decreased by 30% or more in 51.72% of the whole population (a threshold considered as clinically significant<sup>22,34</sup>), which is near the 46.3% reported by Pharithi *et al.*<sup>35</sup> In G1 patients, SV initiation was associated with an improvement in right ventricular function as previously reported.<sup>29,33</sup> SV also improved the NYHA class, the Minnesota Living with Heart Failure Questionnaire scores, and the EQ-5D VAS scores, as previously reported.<sup>30,31</sup>

### Central sleep apnoea treatment modalities in patients with heart failure and reduced ejection fraction

CSA treatment modalities in HFrEF patients are not supported by a high level of evidence, and importantly, poorly efficient CPAP has been demonstrated as harmful in CSA patients.<sup>36</sup> In the context of SERVE-HF study<sup>17</sup> and pending the ADVENT-HF study results,<sup>18</sup> optimizing HFrEF management is recommended to improve CSA in clinical practice (expert Grade C recommendation,<sup>11</sup> based on six studies encompassing a total of just 67 patients<sup>19</sup>). For the 37/40 G1 patients with a mainly CSA pattern and an SV intake but without PAP treatment, we report a significant median AHI difference of  $-6.60$  ( $-11.70$  to  $0.40$ )/h. If we consider that the AHI  $\geq$  15/h threshold is used to initiate a PAP treatment, our data suggest that SV is associated with a PAP sparing effect requiring further investigation (16.2% more G1 patients with a final AHI < 15/h in our study). Interestingly, 25% of our population presented an LVEF  $\geq$  35%, while 32% of the SERVE-HF population presented an LVEF > 36%.<sup>37</sup> During the study, only one G1 patient has a CPAP trial as recommended by the 2017 European Respiratory Society statement (HFrEF patients with CSA can be

treated with CPAP, if CPAP suppresses CSA and improves symptoms, Grade C recommendation).<sup>11</sup>

### Obstructive sleep apnoea treatment modalities in patients with heart failure and reduced ejection fraction

OSA treatment with CPAP is supported by non-randomized/cohort studies reporting a decrease in mortality.<sup>12–14</sup> Pending the ADVENT-HF study results,<sup>18</sup> symptomatic patients are eligible for CPAP treatment.<sup>38</sup> As a consequence, only 9/22 G2 patients were not ‘CPAP treated’, and for the eight patients with SV intake at the 3 month P evaluation, the median AHI difference between initial and final assessment was  $-12.40$  ( $-23.60$  to  $0.35$ )/h,  $P = 0.059$ . Because this difference was mainly the consequence of the change in the obstructive component of the AHI ( $-11.20$  ( $-16.15$  to  $-6.40$ )), we can hypothesized that SV may act via its properties (both diuretic effect and improvement in the global cardiovascular status, hence a decrease in volaemia) and a decrease in upper airway oedema/rostral fluid shift.<sup>39,40</sup> As a matter of fact, HFrEF patients have an increased risk for OSA due to extracellular fluid overload. Achieving fluid homeostasis is a potential point of care because pharyngeal oedema and narrowing may develop during supine sleep with redistribution of fluid from the legs and subsequent pharyngeal collapsibility and airway obstruction in HFrEF patients with OSA. This paves the way for similar approaches regarding all the interventions able to improve globally the fluid homeostasis. These data support the hypothesis of a potential PAP sparing effect of the SV treatment in these patients requiring further research. Unfortunately, our study was not designed to collect the number of G2 patients accepting secondarily the CPAP treatment because of a final AHI  $\geq$  15/h despite the SV treatment.

### Safety

The safety profile of SV in this real-life population was in line with previous reports even though the short-term design of our study (3 months) limited dose escalation. The short titration period may partly explain why high doses were obtained for only 34.6% of the whole population. This appears similar to the 35.7% of patients reported at 7 months in a non-selected cohort,<sup>32</sup> but low compared with a further report mentioning >60% of the patients with a 97/103 mg SV dosage at 6 months.<sup>31</sup> We also report that 12.65% of our patients presented an SV-associated hypotension, which is similar to the fraction (10.3%) reported in the PARASAIL study.<sup>31</sup> Only 3.80% of our whole population presented a 30% decrease in eGFR in comparison, which is quite comparable with the 3.03% reported by Pharithi *et al.*<sup>35</sup>

## Limits and strengths of the study

A limit, but also a strength, of our study is the real-life design. Although randomized controlled trials are the gold standard for evaluating treatment effects, they may not always fully represent what happens in real life because of inherent selection bias.<sup>41–43</sup> A real-life design can also become the only possible design for ethical reasons, as in our case for a treatment that had previously demonstrated a beneficial effect on mortality (SV improves cardiovascular mortality in HFrEF patients) but nevertheless requires investigation.

A 3 month rather than 4 month study was recommended by our ethics committee. As a consequence, only 36.36% of G1 + G2 patients reached the SV high dose. Nevertheless, we observed an SV effect on AHI, reinforcing the potential strength of our approach. At 3 months, a second P was not performed for G3 patients based on our ethics committee's recommendations.

Apnoea–hypopnoea index was determined by a P and not a PSG, which evidently underestimates AHI in comparison. In addition to real-life study design constraints and ethics requirements, we further chose to perform a P rather than a PSG because (i) this reflects current practice around the world when PSG access is limited (the average waiting time for PSG is >2 months in industrialized countries)<sup>44–46</sup> and (ii) delaying SV initiation can worsen outcomes due to the SV effect on mortality.

The sample size of group G1 and G2 should be taken into account to explain some of the non-significant statistical differences for patient characteristics/co-morbidities or cardiological features at baseline.

Our study was not designed to specifically evaluate the effect of SV on PAPS. The observed PAPS decrease with SV in G1 is a matter of debate. These results are only preliminary as the impact on right cavities is an unexpected result deserving to be more deeply investigated.

The concomitant CPAP treatment for 13/22 G2 patients with an OSA pattern limits our conclusions in this group, and the interest of our study mainly concerns the 37/40 G1 patients with CSA patterns. Importantly, we report no significant changes in cardiological medical treatments in G1, which could also explain the benefit on AHI (inducing a bias in our analyses). Considering the AHI  $\geq$  15/h threshold used to initiate a PAP treatment, our data suggest that SV may be associated with a PAP sparing effect. But these data need to be confirmed by specifically designed studies.

## Conclusions

In this real-life population of HFrEF patients with an initial SA diagnostic but no PAP treatment, SV is associated with a significant decrease in AHI at 3 months. Our results support the

current guidelines that recommend first an optimization of the HFrEF treatment in patients with HFrEF and CSA.<sup>11</sup> A potential PAP sparing benefit merits further research.

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## Conflict of interest

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## Data availability statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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