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Laura Sofia Cardelli, Mariarosaria Magaldi, Audrey Agullo, Gaetan Richard, Erika Nogue, et al.. Sacubitril/valsartan has an underestimated impact on the right ventricle in patients with sleep-disordered breathing, especially central sleep apnoea syndrome. Archives of cardiovascular diseases, In press, Online ahead of print. 10.1016/j.acvd.2024.04.003 . hal-04580913

HAL Id: hal-04580913

<https://hal.science/hal-04580913>

Submitted on 29 May 2024

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Sacubitril/valsartan has an underestimated impact on the right ventricle in patients with sleep-disordered breathing, especially central sleep apnoea syndrome

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Keywords :

Heart failure Sacubitril/valsartan Sleep apnoea syndrome Right ventricular function Nocturnal ventilatory polygraphy A

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Abbreviations

AHI apnoea-hypopnoea index CHF chronic heart failure HFrEF heart failure with reduced ejection fraction LV left ventricle/ventricular LVEF left ventricular ejection fraction NVP nocturnal ventilatory polygraphy RV right ventricle/ventricular SDB sleep-disordered breathings PAP pulmonary artery systolic pressure S/V sacubitril/valsartan TAPSE tricuspid annular plane systolic excursion¹

Abstract

Background.

– Sacubitril/valsartan has been demonstrated to significantly improve left ventricular performance and remodelling in patients with heart failure. However, its effects on the right ventricle in patients with chronic heart failure and sleep-disordered breathing (SDB) have not been studied.

Aim.

– To investigate the impact of sacubitril/valsartan treatment on right ventricular function in patients with SDB.

Methods.

– This was a subanalysis of an observational prospective multicentre study involving 101 patients. At inclusion, patients were evaluated by echocardiography and nocturnal ventilatory poly-graphy, which allowed patients to be divided into three groups: “central-SDB”; “obstructive-SDB”; and “no-SDB”.

Results.

– After 3 months of sacubitril/valsartan therapy, a positive impact on right ventricular function was observed. In the general population, tricuspid annular plane systolic excursion increased by $+1.32 \pm 4.74$ mm ($P = 0.024$) and systolic pulmonary artery pressure decreased by -3.1 ± 10.91 mmHg ($P = 0.048$). The central-SDB group experienced the greatest echocardiographic improvement, with a significant increase in tricuspid annular plane systolic excursion of $+2.1 \pm 4.9$ mm ($P = 0.045$) and a significant reduction in systolic pulmonary artery pressure of -8.4 ± 9.7 mmHg ($P = 0.001$).

Conclusions.

– Sacubitril/valsartan improved right ventricular function in patients with heart failure and SDB after only 3 months of treatment. The greatest improvement in right ventricular function was observed in the central-SDB group.

1. Background

In recent decades, sacubitril/valsartan (S/V), an angiotensin receptor/neprilysin inhibitor, has emerged as a pivotal treatment for heart failure with reduced ejection fraction (HFrEF) [1]. Because of various aetiologies and pathophysiological pathways, it is common for patients with HFrEF to have coexisting left ventricular (LV) and right ventricular (RV) dysfunction [2]. The predominant beneficial effect of S/V has been evaluated for the left ventricle (LV) [3], but only a few studies and a meta-analysis have shown a real benefit for the right ventricle (RV) [4–8].

Furthermore, the quest to improve the outcomes of patients with chronic heart failure (CHF) has focused recently not only on the underlying disease, but also on the associated comorbidities. Among the main comorbidities, sleep-disordered breathing (SDB), in the two main forms of central sleep apnoea and obstructive sleep apnoea, is a frequent chronic disorder in patients with CHF, and leads to high morbidity and mortality [9]. Both central and obstructive sleep apnoea are associated with increased sympathetic activity that is known to be deleterious in the context of heart failure, impacting LV and RV function [10, 11].

Recently, Jaffuel et al. showed a reduction in the apnoea-hypopnoea index (AHI) in patients with SDB after 3 months of treatment with S/V [12, 13]. However, there are still no data regarding the impact of S/V on RV function in patients with SDB.

The purpose of the present subanalysis was to investigate the impact of S/V treatment on RV function in patients with SDB. Because of the intricate pathophysiology between SDB and the RV, leading to a vicious circle, and the beneficial impact of S/V on LV remodelling, we hypothesized that S/V might exert a beneficial effect more prominently in patients with both HFrEF and SDB. Furthermore, the hypothesis was that S/V could improve cardiac function, especially in those patients with central sleep apnoea, who, to date, cannot even benefit from specific ventilatory treatment.

2. Methods

This was a subanalysis of the ENTRESTO-SAS trial [12], which has been published previously; it was an observational prospective multicentre open-label real-life cohort study. The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the 2002 Declaration of Helsinki. The study was registered on 9 September 2016 on ClinicalTrials.gov with the identification number NCT02916160.

2.1. Study design; inclusion and exclusion criteria

These aspects of the study have been published elsewhere [12]. Briefly, clinically stable outpatients aged ≥ 18 years, with symptomatic HFrEF (New York Heart Association grade \geq II and left ventricular ejection fraction [LVEF] $\leq 35\%$) and eligible for S/V treatment, were enrolled in the study. Specific requirements included stable condition at the time of clinical evaluation and optimized medical treatment based on current heart failure guidelines available during the study [1]. Exclusion criteria were inability to take S/V (because of known

hypersensitivity to the drug or one of the excipients), pregnancy and/or lactation status, current continuous positive airway pressure treatment or the presence of at least one associated condition (including severe renal failure [glomerular filtration rate < 30 mL/m²], history of angio-oedema, severe hepatopathy, severe ongoing hyperkalaemia and life expectancy < 6months). All participants received and signed a written informed consent form and were free to withdraw at any time during the study.

During the first visit, baseline data were recorded, including a complete echocardiographic examination (LV systolic size and function, RV function via the tricuspid annular plane systolic excursion [TAPSE] index [in mm] and pulmonary artery systolic pressure[sPAP] value [in mmHg]), according to the international guideline recommendations [14].

Pre-therapeutic nocturnal ventilatory polygraphy (NVP) was performed. NVP analysis allowed collection of data regarding the global AHI, the hypopnea index, the percentage of recording time spent at < 90% saturation, the time spent at < 90% saturation, the desaturation index and the mean saturation index.

Based on the initial NVP results and according to the AHI, patients were divided into three groups in accordance with the 2012 American Academy of Sleep Medicine recommendations [15]: group 1 (central-SDB), central AHI \geq 5/h and obstructive AHI < 15/h; group 2 (obstructive-SDB), obstructive AHI \geq 15/h with or without central sleep apnoea syndrome; group 3 (no-SDB), obstructive AHI < 15/h and central AHI < 5/h.

S/V was started the day after NVP. Patients received S/V orally twice daily with adapted titration during the first 3 months.

In the obstructive-SDB group, treatment with positive airway pressure (i.e. continuous positive airway pressure or bi-level pressure or autoservoventilation) was then discussed, and was started at the investigator's discretion. In the case of predominantly central events and reduced LVEF, the use of autoservoventilation treatment was not allowed.

Re-evaluation by NVP was performed in the central-SDB and obstructive-SDB groups, with monitoring of device data only for the obstructive-SDB group.

The main purpose of the study was to evaluate in patients with SDB the effect of S/V on RV function, then its evolution at **3 months**.

2.2. Statistical analysis

Continuous data were tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean \pm standard deviation. Continuous variables with skewed distribution are reported as median (inter-quartile range). Categorical variables are summarized in terms of counts and percentages. Three group comparisons were performed using analysis of variance (ANOVA) or Kruskal-Wallis tests for quantitative data. Qualitative variables were compared using the χ^2 test or Fisher's exact test in case of a significant global effect. Evolutions between initial and final evaluations were studied using Student's paired test or the Wilcoxon paired test for quantitative variables and

McNemar's exact test for qualitative variables. A bilateral P-value of < 0.05 was considered to indicate statistical significance. Missing data were not imputed. All analyses were conducted by the Clinical Research and Epidemiology Unit at the Montpellier University Hospitals using SAS, version 9.04 (SAS Institute, Cary, NC, USA).

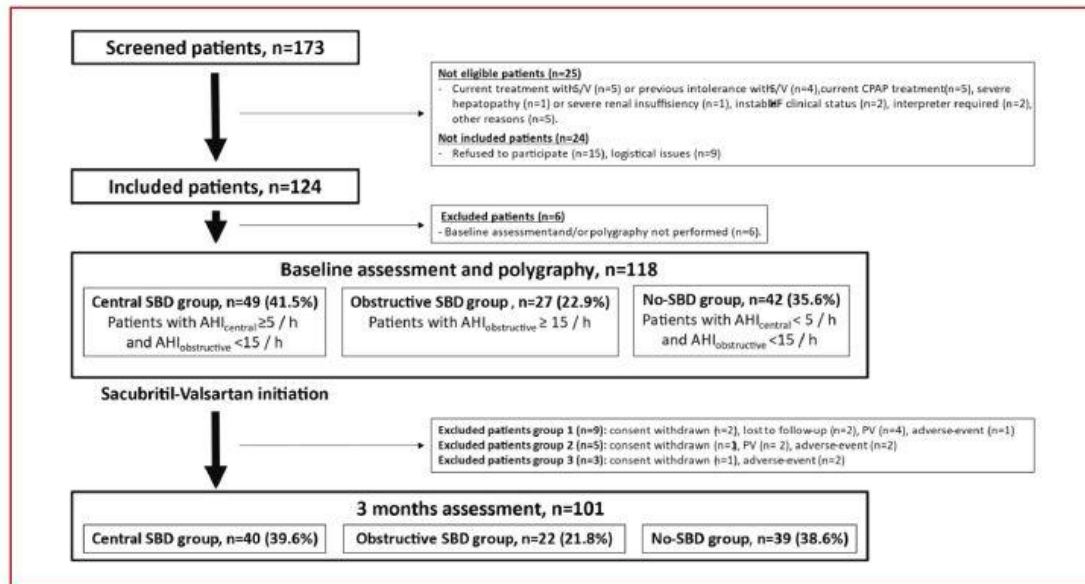


Fig. 1. Study flowchart. AHI: apnoea-hypopnoea index; CPAP: continuous positive airway pressure; HF: heart failure; PV: protocol violation; SDB: sleep disordered breathing; SV: sacubitril/valsartan.

3. Results

The study flowchart is depicted in Fig. 1. One hundred and seventy-three patients were recruited with symptomatic HFrEF between September 2016 and September 2019. Twenty-five patients were excluded because they did not meet the inclusion criteria, and 24 patients were excluded because of consent withdrawal. A total of 118 patients underwent NVP: 41.5% were in the central-SDB group; 22.9% in the obstructive-SDB group; and 35.6% in the no-SDB group. At 3 months, 17 patients were excluded from the analysis (Fig. 1). Four patients (3.4%) did not attend the second visit because of consent withdrawal or loss to follow-up ($n = 2$, 1.7%) or because treatment was interrupted as a result of suspected adverse events ($n = 5$, 4.2%). Therefore, the overall data analysis involved 101 patients for whom the 3-month evaluation was possible.

Table 1 summarizes patients' characteristics at baseline. In the overall study population, the majority of patients were male (81.2%), with a mean age of 64.6 ± 12.8 years. The three groups of patients had similar clinical features and risk factors. In the general population, the most frequent cause of heart failure was ischaemic heart disease (61.0%). Patients had an implantable cardioverter-defibrillator more frequently in the no-SDB group ($n = 26$, 66.7%) than in the central-SDB group ($n = 15$, 37.5%; $P = 0.0285$) or the obstructive-SDB group ($n = 8$, 36.4%; $P = 0.0443$). The presenting rhythm was less frequently sinus rhythm in the central-SDB group ($n = 23$, 59.0%) compared with in the no-SDB group ($n = 36$, 92.3%; $P = 0.0018$) or the obstructive-SDB group ($n = 20$, 90.9%; $P = 0.0173$).

Table 1
Patients' baseline clinical characteristics.

	Total (n = 101)	Central-SDB (n = 40)	Obstructive-SDB (n = 22)	No-SDB (n = 39)	P
Age (years)	64.56 ± 12.84	64.50 ± 14.29	65.50 ± 12.48	64.10 ± 11.73	0.92
Male sex	82 (81.19)	35 (87.50)	16 (72.73)	31 (79.49)	0.31
BMI (kg/m ²)	26.78 (23.18; 30.85)	26.81 (23.99; 30.39)	29.02 (25.47; 32.66)	24.84 (21.37; 29.76)	0.10
Co-morbidities					
Hypertension	37 (36.63)	15 (37.50)	9 (40.91)	13 (33.33)	0.83
Diabetes	20 (19.80)	9 (22.50)	6 (27.27)	5 (12.82)	0.37
Dyslipidaemia	34 (33.66)	12 (30.00)	9 (40.91)	13 (33.33)	0.68
Active smoking	20 (19.80)	7 (17.50)	6 (27.27)	7 (17.95)	0.62
Chronic inflammatory disease	3 (2.97)	0 (0.00)	2 (9.09)	1 (2.56)	0.06
COPD	9 (9.00)	3 (7.50)	1 (4.55)	5 (13.16)	0.61
Peripheral vascular disease	14 (13.86)	4 (10.00)	6 (27.27)	4 (10.26)	0.16
Pacemaker	10 (10.00)	4 (10.00)	4 (18.18)	2 (5.26)	0.27
CRT	10 (10.00)	5 (12.50)	3 (14.29)	2 (5.13)	0.43
ICD	49 (48.51)	15 (37.50)	8 (36.36)	26 (66.67)	0.0151
Cause of heart failure					
Ischaemic	61 (61.00)	25 (62.50)	14 (63.64)	22 (57.89)	0.88
Hypertensive	3 (3.00)	2 (5.00)	1 (4.55)	0 (0.00)	0.44
Valvular	7 (7.00)	4 (10.00)	1 (4.55)	2 (5.26)	0.69
Dilated cardiomyopathy	25 (25.00)	7 (17.50)	6 (27.27)	12 (31.58)	0.34
Tachycardia-induced cardiomyopathy	20 (20.00)	13 (32.50)	4 (18.18)	3 (7.89)	0.0241
Polygraphic variables at inclusion					
Obstructive AHI (events/h)	6.15 (2.45; 13.10)	2.90 (1.15; 6.90)	24.75 (18.90; 31.30)	5.35 (2.70; 9.00)	< 0.0001
Central AHI (events/h)	5.85 (0.90; 14.20)	16.10 (9.20; 31.35)	6.10 (1.30; 13.20)	0.50 (0.00; 1.60)	< 0.0001
Clinical/biological characteristics at inclusion					
NYHA functional class					0.08
Class I-II	64 (65.31)	30 (76.92)	14 (66.67)	20 (52.63)	
Class III-IV	34 (34.69)	9 (23.08)	7 (33.33)	18 (47.37)	
Systolic blood pressure	119.52 ± 13.63	119.00 ± 13.67	118.94 ± 13.15	120.32 ± 14.19	0.91
Heart rate (beats/min)	69.00 (63.00; 79.00)	69.00 (61.50; 84.00)	69.00 (64.00; 77.00)	71.00 (63.00; 76.00)	0.99
Sinus rhythm	79 (79.00)	23 (58.97)	20 (90.91)	36 (92.31)	0.0006
Left bundle branch block	33 (33.00)	13 (33.33)	11 (50.00)	9 (23.08)	0.10
QRS width (ms)	120.00 (100.00; 138.00)	120.00 (100.00; 142.00)	132.00 (114.00; 150.00)	117.00 (98.00; 130.00)	0.09
NT-proBNP (pg/mL)	1306.00 (636.00; 3105.00)	1811.00 (987.00; 3958.00)	1306.00 (845.00; 3333.00)	820.00 (236.00; 2004.00)	0.0133
Calculated Cockcroft GFR (mL/min/1.73 m ²)	74.31 (51.98; 94.79)	70.66 (54.95; 92.02)	82.22 (50.77; 105.68)	70.71 (48.98; 90.64)	0.45
Haemoglobin (g/dL)	14.05 ± 1.51	14.14 ± 1.60	13.72 ± 1.52	14.13 ± 1.41	0.55
Pharmacological treatment of heart failure					
ACE inhibitor or ARB	98 (97.03)	39 (97.50)	22 (100.00)	37 (94.87)	0.61
Beta-blockers	89 (88.12)	34 (85.00)	22 (100.00)	33 (84.62)	0.12
MRA	65 (64.36)	23 (57.50)	19 (86.36)	23 (58.97)	0.05
Loop diuretics	77 (76.24)	31 (77.50)	18 (81.82)	28 (71.79)	0.66

ACE: angiotensin-converting enzyme; AHI: apnoea-hypopnoea index; ARB: angiotensin receptor blocker; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CRT: cardiac resynchronization therapy; GFR: glomerular filtration rate; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; SDB: sleep disordered breathing. Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). The total number of participants may vary for certain variables because of missing data.

Table 2
Ultrasound characteristics at inclusion.

	Total (n = 101)	Central-SDB (n = 40)	Obstructive-SDB (n = 22)	No-SDB (n = 39)	P
TAPSE (mm)	18.00 (15.00; 21.00)	16.00 (12.00; 19.00)	18.00 (17.00; 21.00)	19.00 (17.00; 21.00)	0.0314
sPAP (mmHg)	38.25 ± 12.36	40.95 ± 11.33	38.00 ± 13.82	35.55 ± 12.66	0.38
LVEF (%)	30.00 (25.00; 35.00)	30.00 (25.00; 34.00)	30.00 (25.00; 35.00)	29.50 (25.00; 37.00)	0.93
LVEDD (mm)	63.15 ± 8.37	61.76 ± 9.18	65.45 ± 6.72	62.97 ± 8.48	0.32
LVESD (mm)	51.53 ± 9.63	51.39 ± 9.56	52.09 ± 6.43	51.33 ± 11.61	0.98
LVEDV (mL)	192.00 (152.50; 228.50)	198.00 (127.50; 255.50)	180.00 (156.00; 268.00)	167.00 (158.00; 221.00)	0.68
LVESV (mL)	128.00 (102.50; 166.50)	140.00 (83.00; 170.00)	112.50 (103.50; 152.00)	115.00 (104.00; 165.00)	0.89
Cardiac output (L/min)	4.20 (3.60; 5.90)	4.10 (3.80; 4.80)	5.30 (4.00; 6.50)	3.95 (3.40; 5.30)	0.24
Mitral E-wave velocity (cm/s)	68.71 ± 30.78	71.19 ± 32.41	70.56 ± 33.78	64.80 ± 27.94	0.78
E/A ratio	1.00 (0.63; 1.86)	1.05 (0.70; 1.50)	1.22 (0.61; 2.13)	0.71 (0.56; 2.33)	0.87
Left atrial volume (mL)	91.45 ± 37.54	96.88 ± 40.96	98.20 ± 36.09	80.43 ± 34.45	0.40

LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESV: left ventricular end-systolic volume; SDB: sleep disordered breathing; sPAP: pulmonary artery pressure; TAPSE: tricuspid annular plane excursion. Data are expressed as median (interquartile range) or mean ± standard deviation. The total number of participants may vary for certain variables because of missing data.

Higher N-terminal prohormone of brain natriuretic peptide values were recorded in the central-SDB group (3156.05 ± 3624.99 pg/mL) than in the no-SDB group (1839.51 ± 2833.65 pg/mL; P = 0.0167). The groups also received similar heart failure therapy.

At inclusion, the median obstructive AHI in the obstructive-SDB group was 24.75 (18.90; 31.30) events/h, whereas the central index in the central-SDB group was 16.10 (9.20–31.35) events/h.

Echocardiographic data at the time of inclusion are shown in Table 2. The mean LVEF was $30.21 \pm 7.71\%$ and the median cardiac output was 4.20 (3.60; 5.90) L/min. Left chamber diameter and volume values all showed ventricular dilatation (mean LV end-diastolic volume was 201.45 ± 82.05 mL). In the whole population, the median TAPSE was 18.00 (15.00; 21.00) mm and the mean sPAP was 38.25 ± 12.36 mmHg. There were no differences in echocardiographic values at inclusion between groups, except for the TAPSE value, which was significantly lower in the central-SDB group than in the no-SDB group: 16.00 (12.00; 19.00) vs. 19.00(17.00; 21.00) ($P = 0.0314$).

3.1. Three-month follow-up

At 3 months, 35 patients (34.65%) completed follow-up with a dose of 97/103 mg twice daily, 29 patients (28.71%) were on an S/V dose of 49/51 mg twice daily and 30 (29.7%) were on an S/V dose of 24/26 mg twice daily.

During the 3-month follow-up period, 19 patients (18.8%) were readmitted (seven for heart failure). No death occurred in the study, and no angio-oedema was observed during follow-up.

After 3 months of S/V therapy, there was a positive impact on RV function. When considering the total population, there was an improvement in RV systolic function assessed by an increase in TAPSE of $+1.32 \pm 4.74$ mm ($P = 0.024$). This improvement remained constant in all three groups ($P = 0.58$) (Online supplement Table A.1 and Fig. 2A). In addition, there was a significant impact on sPAP, which decreased by 3.1 ± 10.91 mmHg ($P = 0.048$). This variation was significantly different between the three groups ($P = 0.022$) (Online supplement Table A.1 and Fig. 2B).

Regarding the evolution of LV function in the whole population, there was a positive impact on LV remodelling assessed by a decrease in LV end-diastolic diameter of -2.55 ± 6.56 mm ($P = 0.001$) and improved cardiac output, which increased by $+0.10(-0.50; 1.70)$ L/min ($P = 0.118$). LVEF had a moderate, but significant, increase of +1% (0%; 7%) ($P < 0.001$).

After 3 months of treatment, patients in the central-SDB group experienced a significant improvement in clinical and echo cardio-graphic variables (Online supplement Table A.1). In particular in this group, LVEF increased by +2.00% (0.0%; 10.0%) ($P = 0.001$) and LV end-diastolic diameter reduced by -2.7 ± 6.9 mm ($P = 0.043$). There was also a significant increase in TAPSE of $+2.1 \pm 4.9$ mm ($P = 0.045$; Fig. 2A) and a reduction in sPAP of -8.4 ± 9.7 mmHg ($P = 0.001$; Fig. 2B).

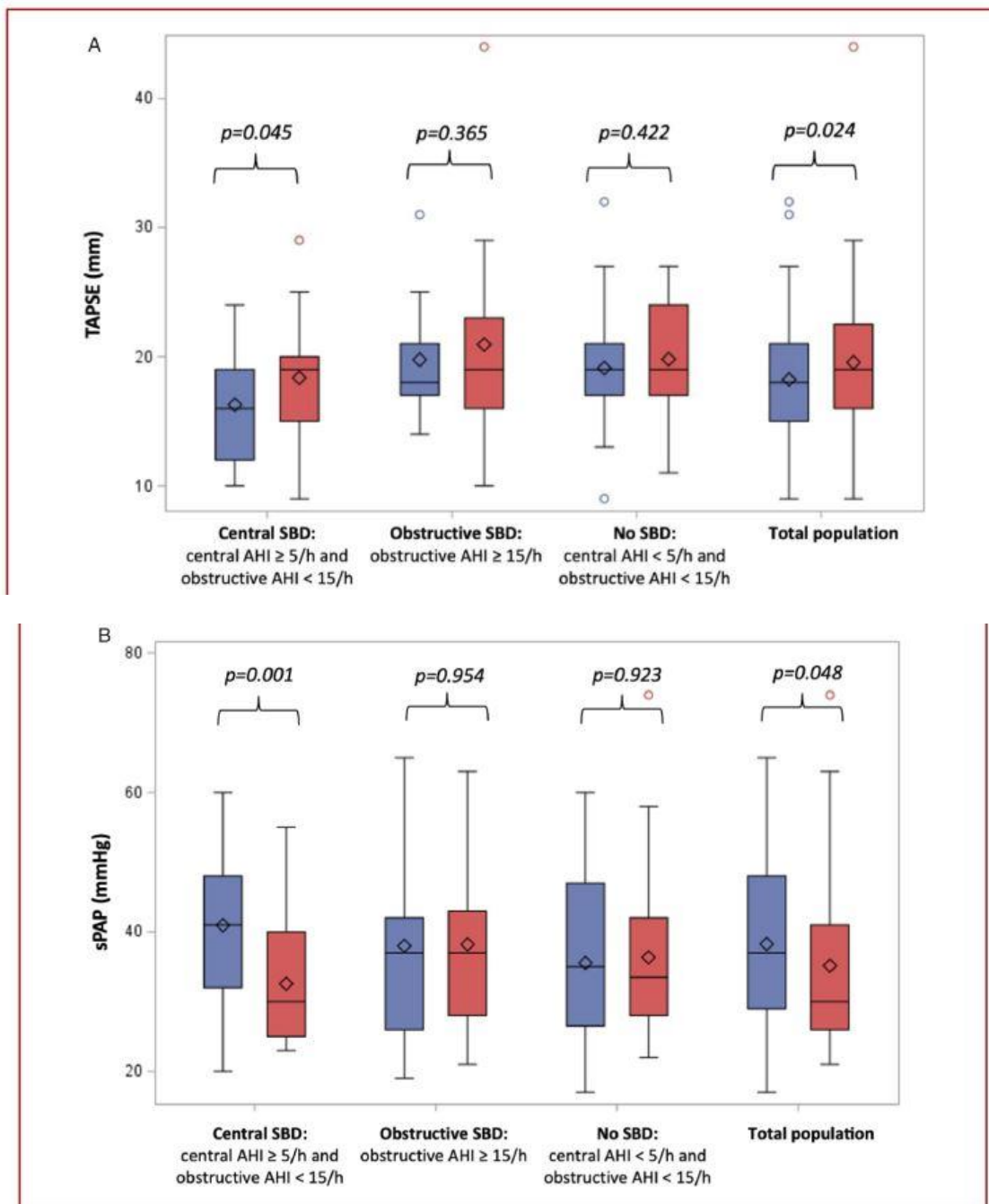


Fig. 2. Change from initial visit to final visit (after 3 months) in echocardiographic variables of right ventricular function for nocturnal ventilatory polygraphy groups. A. Tricuspid annular plane systolic excursion (TAPSE) in mm. B. Systolic pulmonary artery pressure (sPAP) in mmHg. The box represents the Q25–Q75 interquartile range, the line drawn inside is the median value and the diamond is the mean value. Dots represent the outliers. Paired comparison P-values are above the box. AHI: apnoea-hypopnoea index; SDB: sleep disordered breathing; sPAP: pulmonary artery pressure; TAPSE: tricuspid annular plane excursion.

LVEF also increased significantly in the no-SDB group, by +2.0% (0.0%; +7.0) (P = 0.016). In contrast, patients in the obstructive-SDB group showed a trend towards improvement, but without statistical significance.

The 3-month reduction in N-terminal prohormone of brain natriuretic peptide values was significant in all three groups (with the absolute value of difference being higher in the obstructive-SDB group: -309.00 (-1281; +164.0) pg/mL (P = 0.043) (Online supplement Table A.1).

The impact on respiratory indices in patients with SDB has been published elsewhere [13].

4. Discussion

After 3 months of treatment, S/V improved RV function in patients with both heart failure and SDB. More specifically, patients with central sleep apnoea syndrome seemed to derive greater benefit in terms of RV function. Although some studies and meta-analyses have shown a positive effect of S/V on RV function [4–8], to the best of our knowledge, the effect has not been evaluated prospectively in patients with heart failure and SDB. SDB is a highly prevalent co-morbidity in patients with CHF, and potentially impacts prognosis. The prevalence of SDB, pre-dominantly either central or obstructive sleep apnoea, has been reported in up to 76% of patients with CHF with HFrEF [16]. Whereas obstructive sleep apnoea has been shown to be an independent risk factor for the development of CHF [17], and to increase the morbidity and mortality of CHF [18], central sleep apnoea also appears to be a marker of CHF severity, and is thought to mirror cardiac dysfunction [19,20]. However, both central and obstructive sleep apnoea interfere with neurohumoral systems, and thus may worsen CHF, for example, by increasing sympathetic and renin-angiotensin-aldosterone activity, salt and water retention, tachycardia or peripheral vasoconstriction [10, 11]. S/V has a dual effect: neprilysin inhibition and inactivation of the renin-angiotensin-aldosterone system. Through inactivation of many neuro hormones (such as angiotensin II, aldosterone and endothelin-1), modulation of gene expression (such as trans-forming growth factor- β_1) and promotion of re-endothelization, S/V leads to natriuresis, vasodilation and anti-apoptotic, anti-fibro-tic, anti-inflammatory and antithrombotic reactions, as well as decreased cardiac hypertrophy, and ultimately decreases cardiac decompensations [21–23]. More precisely, regarding right cavities, S/V might improve function by inducing RV function recovery and decreasing its afterload by multiple mechanisms, which has been demonstrated in some studies [24,25]. Regarding SDB, the combination therapy of S/V has mechanisms of action known to counteract the pathophysiology of both obstructive and central sleep apnoea in patients with CHF (e.g. extracellular fluid overload, cardiac injury and sympathetic nervous system activation) [12]. Jaffuel et al. [13] demonstrated how S/V improves respiratory indices (e.g. AHI) in patients with SDB, and particularly in those with central sleep apnoea, who received drug treatment alone without ventilatory treatment. Consistent with the literature [26–28], symptomatic patients with HFrEF in our study experienced a substantial improvement in cardiac function variables (both right and left) after S/V treatment. Importantly, our study provides data supporting a positive impact of S/V on RV function in patients with HFrEF and SDB, especially in the subgroup of patients with central sleep apnoea syndrome. Our data agree with those of the Daunia 2020 registry, although this was a smaller cohort of 60 patients, demonstrating an increase in TAPSE of +1.3 mm and a reduction in sPAP of –3.7 mmHg, with an independent improvement in LV variables [5, 24]. This also encourages the widespread use of TAPSE, which remains the cornerstone of RV evaluation in patients with both heart failure and SDB, and is very easy to obtain by all cardiologists as well as non-

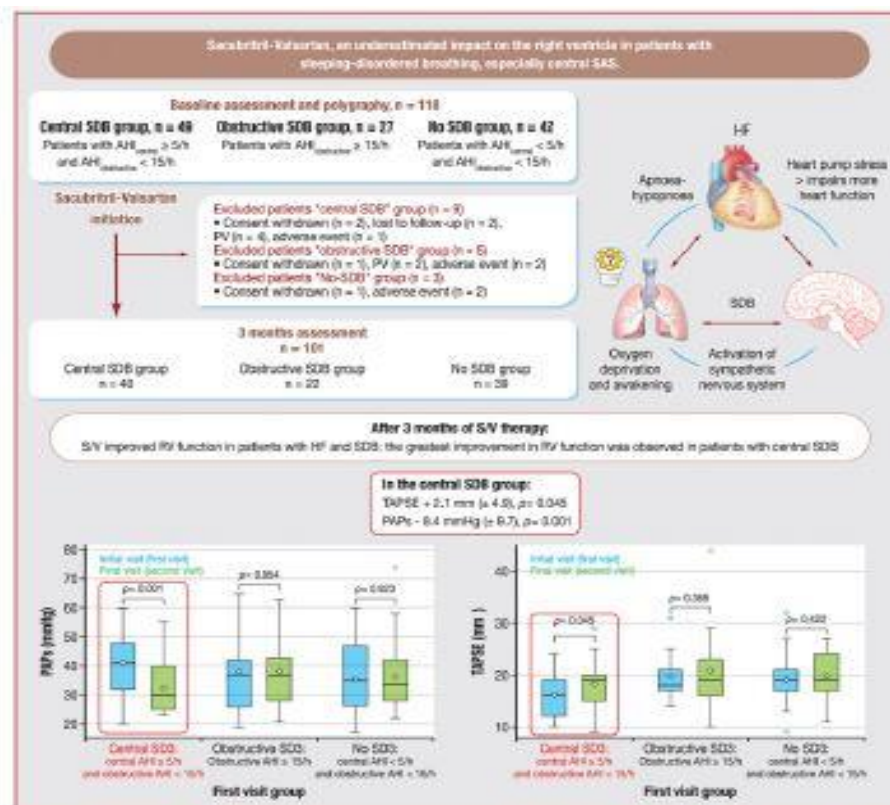
expert sonographers. Importantly, the greatest improvements after 3 months of S/V treatment occurred in the central-SDB group. In these patients there was a significant increase in TAPSE of $+2.1 \pm 4.9$ mm ($P = 0.045$) and a reduction in sPAP of -8.4 ± 9.7 mmHg ($P = 0.001$). These results can be explained in several ways. Firstly, the central sleep apnoea subpopulation could be considered the most severe, and therefore could benefit most from this drug. Secondly, as the pathophysiological pathways are intricate, S/V could more effectively target common pathways, particularly the neurohormonal and sympathetic, activated by heart failure itself, but also in central sleep apnoea. Thirdly, a specific beneficial impact on sympathetic stimulation could help to reduce alveolar hyperventilation and avoid hypocapnia/hypercapnia cycles that favour central sleep apnoea [29]. Additionally, S/V could directly reduce preload by a diuretic effect, and be responsible for improving LVEF and LV remodelling (the so-called interrelationship between LV and RV), as noted above [3]. Finally, central sleep apnoea in heart failure is probably caused by instability of ventilatory control systems, and patients with central sleep apnoea exhibit increased chemo-responsiveness that promotes hyperventilation and hypocapnia [20, 30, 31]. A contributing factor to hyperventilation is the stimulation of pulmonary vagal irritant receptors by pulmonary venous congestion. Induced hyperventilation often pushes arterial carbon dioxide pressure below the apnoeic threshold, leading to a reduction in central respiratory drive [20, 30, 31]. From the patho-physiological point of view, S/V could then have pleiotropic effects that are promising in the complex interrelationship between heart failure and central sleep apnoea syndrome. All of these considerations are interesting, but are probably also intricate in various ways, depending on the clinical profile (such as improvement in central events and/or improvement in global cardiac remodelling). Furthermore, dynamic effects may occur with various pathophysiological pathways, as a result of increased treatment, rehabilitation, etc. However, one strength of our work was to show such effects in a very short-time frame: in less than 3 months, we were able to show prominent changes in clinically reliable data. The other two groups of patients also experienced improvements in RV function variables, although these were not significant. We cannot exclude a lack of power. Therefore, our data suggest that the initial management of patients with SDB and CHF should be optimization of heart failure treatment [1, 30–32]. In favour of this, some recent publications support a similar impact of dapagliflozin in terms of improving SDB [33]. Our results are even more promising, because the greatest effect was observed in patients with central sleep apnoea syndrome; these patients lack effective ventilatory treatment [11, 34, 35] because of the possible negative impact on the RV by auto-served ventilation in this setting [34, 35]. Therefore, S/V is of paramount importance in the recovery of cardiac function; the beneficial impact is not only on the LV, which is well established, but also on the right cavities. S/V is beneficial in patients with SDB, particularly in those with greater comorbidities and the most severe form (central SDB).

4.1. Strengths and limitations

This was an observational multicentre study with its associated well-known bias, but it reflects real-life practice. Hence, the results from our analysis should be considered only as hypothesis-generating. Other limitations must be considered. Firstly, a restricted number of patients were included. In addition, a significant amount of echocardiographic data were

missing from both the initial and final evaluations, and this was definitely a limitation of our subanalysis. Despite this, we were able to show a significant difference in the primary outcome. Secondly, the ultrasound data were not analysed blindly by a core laboratory, but were collected from the ultrasound reports. This certainly inserted biases (such as the experience of the operators, the different ultrasound machines used in the various centres and inter- and intra-observer variability) that are difficult to detect and undo. Thirdly, AHI was determined by NVP and not polysomnography, which obviously underestimates AHI in comparison. Fourthly, it might have been interesting to extend the ultrasound analysis by including two-dimensional strain measurements, but this analysis was performed too infrequently. On the other hand, this could appear as a strength too, as the variables studied are easy to obtain in real-life practice and could then be easily integrated into daily practice.

Fifthly, the study was performed before the availability in France of sodium-glucose co-transporter-2 inhibitors, so no patients received them, even for extracardiac indications. Finally, the 3-month follow-up allowed us to show early results of the treatment, but longer-term evaluation could have allowed us to confirm these initial data.



Central illustration. Sacubitril/valsartan (S/V) has an underestimated impact on the right ventricle in patients with sleep-disordered breathing (SDB), especially central sleep apnoea syndrome. AHI: apnoea-hypopnoea index; HF: heart failure; PV: protocol violation; RV: right ventricular; sPAP: pulmonary artery pressure; TAPSE: tricuspid annular plane excursion.

5. Conclusion

Treatment with S/V results in short-term improvement of RV function in patients with both heart failure and SDB, especially in patients with central SDB. S/V results in a significant improvement in RV function assessed by TAPSE and sPAP, which are easy variables to obtain. This study opens important perspectives for the treatment of SDB in patients with heart failure, which should be evaluated on a larger scale and confirmed with prospective randomized clinical trials (Central illustration).

Funding

This work is a subanalysis from the initial work supported by an unrestricted grant from Novartis. Novartis had no role in the design and conduct of the study; the collection, management, analysis and interpretation of the data; the preparation, review or approval of the manuscript; or the decision **to submit the manuscript for publication. Online supplement.**

.Disclosure of interest

The authors declare that they have no competing interest.

Références

[1] Mc Donagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42: 3599–726.

[2] Iglesias-Garriz I, Olalla-Gomez C, Garrote C, Lopez-Benito M, Martin J, Alonso D, et al. Contribution of right ventricular dysfunction to heart failure mortality: a meta-analysis. *Rev Cardiovasc Med* 2012;13: e62–9.

[3] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371: 993–1004.

[4] Bayard G, Da Costa A, Pierrard R, Romeyer-Bouchard C, Guichard JB, Isaaq K. Impact of sacubitril/valsartan on echo parameters in heart failure patients with reduced ejection fraction a prospective evaluation. *Int J Cardiol Heart Vasc* 2019;25: 100418.

- [5] Correale M, Mallardi A, Mazzeo P, Tricarico L, Diella C, Romano V, et al. Sacubitril/valsartan improves right ventricular function in a real-life population of patients with chronic heart failure: the Daunia Heart Failure Registry. *Int J Cardiol Heart Vasc* 2020;27:100486.
- [6] Polito MV, Silverio A, Rispoli A, Vitulano G, Auria F, De Angelis E, et al. Clinical and echocardiographic benefit of Sacubitril/Valsartan in a real-world population with HF with reduced ejection fraction. *Sci Rep* 2020;10:6665.
- [7] Romano G, Vitale G, Ajello L, Agnese V, Bellavia D, Caccamo G, et al. The effects of Sacubitril/Valsartan on clinical, biochemical and echocardiographic parameters in patients with heart failure with reduced ejection fraction: the “ Hemodynamic Recovery”. *J Clin Med* 2019;8: 2165.
- [8] Zhang J, Du L, Qin X, Guo X. Effect of Sacubitril/Valsartan on the right ventricular function and pulmonary hypertension in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of observational studies. *J Am Heart Assoc* 2022;11:e024449.
- [9] Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. *Eur Respir J* 2017;49.
- [10] Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol* 2017;69:841–58.
- [11] Pearse SG, Cowie MR. Sleep-disordered breathing in heart failure. *Eur J Heart Fail* 2016;18:353–61. [12] Jaffuel D, Molinari N, Berdague P, Pathak A, Galinier M, Dupuis M, et al. Impact of sacubitril-valsartan combination in patients with chronic heart failure and sleep apnoea syndrome: the ENTRESTO-SAS study design. *ESC Heart Fail* 2018;5:222–30.
- [13] Jaffuel D, Nogue E, Berdague P, Galinier M, Fournier P, Dupuis M, et al. Sacubitril-valsartan initiation in chronic heart failure patients impacts sleep apnea: the ENTRESTO-SAS study. *ESC Heart Fail* 2021;8:2513–26.
- [14] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults :an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16: 233–70.
- [15] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012;8: 597–619.

- [16] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. *Eur J Heart Fail* 2007;9: 251–7.
- [17] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;122: 352–60.
- [18] Khayat R, Jarjoura D, Porter K, Sow A, Wannemacher J, Dohar R, et al. Sleep disordered breathing and post-discharge mortality in patients with acute heart failure. *Eur Heart J* 2015;36: 1463–9.[
- [19] Grimm W, Sosnovskaya A, Timmesfeld N, Hildebrandt O, Koehler U. Prognostic impact of central sleep apnea in patients with heart failure. *J Card Fail* 2015;21: 126–33.
- [20] Naughton MT. Heart failure and sleep-disordered breathing. The chicken or the egg? *Am J Respir Crit Care Med* 2016;193: 482–3.
- [21] D'Elia E, Iacovoni A, Vaduganathan M, Lorini FL, Perlini S, Senni M. Neprilysin inhibition in heart failure: mechanisms and substrates beyond modulating natriuretic peptides. *Eur J Heart Fail* 2017;19:710–7.
- [22] Salazar J, Rojas-Quintero J, Cano C, Perez JL, Ramirez P, Carrasquero R, et al. Neprilysin: a potential therapeutic target of arterial hypertension? *Curr Cardiol Rev* 2020;16:25–35.
- [23] Wong P C, Guo J, Zhang A. The renal and cardiovascular effects of natriuretic peptides. *Adv Physiol Educ* 2017;41:179–85.7
- [24] Correale M, Mazzeo P, Magnesa M, Fortunato M, Tricarico L, Leopizzi A, et al. Predictors of right ventricular function improvement with sacubitril/valsartan in a real-life population of patients with chronic heart failure. *Clin Physiol Funct Imaging* 2021;41: 505–13.
- [25] Sharifi Kia D, Benza E, Bachman TN, Tushak C, Kim K, Simon MA. Angiotensin receptor-neprilysin inhibition attenuates right ventricular remodeling in pulmonary hypertension. *J Am Heart Assoc* 2020;9: e015708.
- [26] Januzzi Jr JL, Prescott MF, Butler J, Felker GM, Maisel AS, Mc Cague K, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. *JAMA* 2019; 322: 1085–95.
- [27] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure :rationale for and design of

the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial(PARADIGM-HF). *Eur J Heart Fail* 2013;15: 1062–73.

[28] Wang Y, Zhou R, Lu C, Chen Q, Xu T, Li D. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. *J Am Heart Assoc* 2019;8:e012272.

[29] Mansukhani MP, Kara T, Caples SM, Somers VK. Chemo reflexes, sleep apnea, and sympathetic dysregulation. *Curr Hypertens Rep* 2014;16:476.

[30] Costanzo MR, Khayat R, Ponikowski P, Augostini R, Stellbrink C, Mianulli M, et al. Mechanisms and clinical consequences of untreated central sleep apnea in heart failure. *J Am Coll Cardiol* 2015;65:72–84

[31] Khayat R, Small R, Rathman L, Krueger S, Gocke B, Clark L, et al. Sleep-disordered breathing in heart failure: identifying and treating an important but often unrecognized comorbidity in heart failure patients. *J Card Fail* 2013;19: 431–44.

[32] Aurora RN, Chowdhuri S, Ramar K, Bista SR, Casey KR, Lamm CI, et al. The treatment of central sleep apnea syndromes in adults: practice parameters with an evidence-based literature review and meta-analyses. *Sleep* 2012;35:17–40.

[33] Jaffuel D, Bouchaut Y, Mallet JP, Vidal C, Molinari N, Bourdin A, et al. Dapagliflozin initiation in chronic heart failure patients improves central sleep apnoea. *ERJ Open Res* 2023;9.

[34] Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373: 1095–105

[35] Lyons OD, Floras JS, Logan AG, Beanlands R, Cantolla JD, Fitzpatrick M, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J Heart Fail* 2017;19: 579–87.8