


BMJ Open Cohort profile: FACE, prospective follow-up of chronic heart failure patients with sleep-disordered breathing indicated for adaptive servo ventilation

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ABSTRACT

Purpose FACE is a prospective cohort study designed to assess the effect of adding adaptive servoventilation (ASV) to standard care on morbidity and mortality in patients with chronic heart failure (HF) with preserved (HFpEF), mid-range (HFmrEF) or reduced ejection fraction (HFrEF) who have sleep-disordered breathing (SDB) with an indication for ASV. We describe the study design, ongoing data collection and baseline participant characteristics.

Participants Consecutive patients with HFpEF, HFmrEF or HFrEF plus SDB with central sleep apnoea (CSA) and indication for ASV were enrolled in the study cohort between November 2009 and December 2018; the ASV group includes those treated with ASV and the control group consists of patients who refused ASV or stopped treatment early. Follow-up is based on standard clinical practice, with visits at inclusion, after 3, 12 and 24 months of follow-up. Primary endpoint is the time to first event: all-cause death or unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening of HF, cardiovascular death or unplanned hospitalisation for worsening of HF, and all-cause death or all-cause unplanned hospitalisation.

Findings to date 503 patients have been enrolled, mean age of 72 years, 88% male, 31% with HFrEF. HF was commonly of ischaemic origin, and the number of comorbidities was high. SDB was severe (median Apnoea–Hypopnoea Index 42/hour), and CSA was the main indication for ASV (69%). HF was highly symptomatic; most patients were in NYHA class II (38%) or III (29%).

Future plans Patient follow-up is ongoing. Given the heterogeneous nature of the enrolled population, a decision was made to use latent class analysis to define homogeneous patient subgroups, and then evaluate outcomes by cluster, and in the ASV and control groups (overall and within patient clusters). First analysis will be performed after 3 months, a second analysis at the 2-year follow-up.

Trial registration number NCT01831128; Pre-results.

Strengths and limitations of this study

- The FACE trial is being conducted in a clinical practice setting across a range of centres (private and academic), covers a range of adaptive servo ventilation (ASV) indications and includes patients with all types of heart failure (HF) (including those with preserved ejection fraction (HFpEF)), which should maximise the clinical relevance of the study findings.
- Although a control group of untreated patients is included in the study, the observational cohort design could introduce bias in favour of the treated group.
- The study population is from a limited geographical area, potentially limiting the generalisability of the results due to the healthcare setting and type of healthcare professionals participating.
- Baseline characteristics showed a heterogeneous population with a variety of different clinical presentations (including type of sleep-disordered breathing, HF and comorbidities), which may be suited for further evaluation using a cluster analysis approach.
- This is the only prospective cohort study including a large number of HFpEF patients with central sleep apnoea treated with ASV, and the results should provide data that will be interesting and relevant to healthcare stakeholders, clinicians and researchers.

INTRODUCTION

Heart failure (HF) is common and is associated with significant mortality, morbidity and healthcare expenditure. As such, it has been identified as an important clinical and public health problem.^{1,2} Despite progress in reducing systolic HF-related mortality, hospitalisations and readmissions for HF remain frequent.¹ Guidelines recommend therapy with β -blockers, ACE inhibitors and other pharmacological agents, as well as device-based management such as cardiac resynchronisation therapy.³ However, many



patients with HF have persistent symptoms and most will eventually die from cardiovascular causes, often from progressive HF. In particular, the proportion of patients with HF with preserved left ventricular ejection fraction (LVEF; HFpEF), for which there is no specific treatment, is growing.⁴ Therefore, new interventions that ameliorate symptoms, improve quality of life and reduce hospital admissions and mortality in patients with chronic HF are needed. It is likely that these new interventions will be targeted to specific subgroups of patients with HF rather than applying to the entire population. One such approach that is the subject of growing awareness and interest is the treatment of sleep-disordered breathing (SDB).

SDB is very common in patients with HF, with a reported prevalence up to 70%.^{5,6} There are two main types of SDB: obstructive sleep apnoea (OSA) and central sleep apnoea (CSA); the latter may manifest as a periodic breathing pattern (also referred to as Cheyne-Stokes respiration (CSR)). OSA results from obstruction of the upper airway, CSA is characterised by an increase in the drive to breathe causing breathing instability during sleep, and periodic breathing consists of periods of hyperventilation in association with waxing and waning tidal volume alternating with periods of CSA.

The presence of SDB is associated with increased mortality in patients with HF.^{7–9} Mechanisms by which SDB may be detrimental to cardiac function include tissue hypoxia and repetitive arousal from sleep, both of which increase sympathetic nervous system activity.^{7,10,11} Treatment of OSA with continuous positive airway pressure (CPAP) rapidly reduces intermittent hypoxia and arousals, and, over time, reduces elevated sympathetic activity.¹² Meta-analysis data showed that CPAP treatment significantly improved cardiac function in patients with OSA and HF.¹³ In addition, the results of a cohort study in patients with HF with OSA indicated improved survival in

patients who were compliant with CPAP therapy.¹⁴ There are a number of strategies that might help alleviate CSA with periodic breathing, including oxygen therapy and CPAP, but the most effective is adaptive servo ventilation (ASV).¹⁵

ASV is a non-invasive ventilatory therapy that provides positive expiratory airway pressure and inspiratory pressure support, which is servo controlled based on monitoring of minute ventilation. It automatically adjusts pressure support to stabilise and reduce ventilation in patients with CSA and period breathing. Treatment with ASV has been shown to reduce respiratory events and normalise the breathing pattern.^{15,16} A number of smaller and/or observational studies, and a meta-analysis, have shown improvements in symptoms and measures of cardiac function, exercise tolerance and quality of life during treatment with ASV therapy.^{17–21} However, more recently, the results of the large, randomised Treatment of SDB with Predominant CSA by Adaptive Servo Ventilation in Patients with HF (SERVE-HF) trial reported a neutral primary endpoint result when ASV was added to optimal medical therapy in patients with HF with reduced LVEF (HFrfEF), and mortality was actually higher in patients randomised to ASV.²² However, the indication for ASV in the SERVE-HF trial only represents about one-third of the potential ASV indications.^{23,24} Other indications include treatment-emergent CSA, idiopathic CSA, opioid-induced CSA and CSA in patients with HFpEF²⁴; the latter population is currently being investigated in the FACIL-VAA study (NCT02835638). Thus, the place of ASV therapy in patients with HF with SDB is the subject of ongoing debate, and additional data are needed.

The FACE trial is a European multicentre prospective observational cohort study designed to assess the effect of ASV therapy on morbidity and mortality in patients with HFpEF, HFrfEF or HF with mid-range LVEF (HFmrEF) and central SDB or coexisting CSA and OSA.

Table 1 Patient inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ Age ≥18 years ▶ Chronic HF according to current European Society of Cardiology guidelines,³ with or without LV systolic dysfunction (LVEF determined using echocardiography (performed within the previous 3 months), radionuclide angiography, left ventriculography or cardiac MRI). ▶ Sleep apnoea requiring ASV treatment, where sleep apnoea (AHI >15/hour) is diagnosed based on PG (total recording time) or PSG (total sleep time), with flow measurement performed using a nasal cannula and respiratory effort measured by plethysmography, and defined as follows²⁶: <ul style="list-style-type: none"> – CSA: >50% central events – Co-existing CSA-OSA: >20% central events – OSA: <20% central events 	<ul style="list-style-type: none"> ▶ PAP therapy contraindicated (symptomatic hypotension or significant intravascular volume depletion, pneumothorax or pneumomediastinum or nasal bleeding). ▶ Significant COPD or known hypercapnia precluding the use of servo-adapted ventilation. ▶ Unable to comply with follow-up protocol. ▶ Life-expectancy <1 year for disease unrelated to chronic HF.

AHI, Apnoea–Hypopnoea Index; ASV, adaptive servo ventilation; COPD, chronic obstructive pulmonary disease; CSA, central sleep apnoea; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnoea; PAP, positive airway therapy; PG, polygraphy; PSG, polysomnography.

Table 2 Baseline characteristics of enrolled patients, overall and by usage of ASV

	Overall	Use of ASV		P value
		No*	Yes	
n (%)	503 (100)	101 (20)	402 (80)	
Male, n (%)	442 (88)	82 (81.2)	362 (90)	0.01
Age, years	72 (64–79)	72.9 (62.3–80)	71.9 (64.8–78.4)	0.91
Body mass index, kg/m ²	28 (25–32)	25.6 (22.7–28.3)	28.7 (25.5–32.3)	<0.01
Current smoker, n (%)	232 (46)	44 (44)	190 (47.3)	0.56
Alcohol use, n (%)	66 (14)	12 (12)	57 (14.2)	0.57
Cardiac devices†, n (%)	136 (27)	43 (42.6)	93 (23.3)	<0.01
Heart failure aetiology, n (%)				
Ischaemic	259 (52)	51 (50.5)	209 (52.5)	<0.01
Dilated cardiomyopathy	36 (7)	11 (10.9)	25 (6.3)	
Arterial hypertension	73 (15)	5 (5)	69 (17.3)	
Valvular	31 (8)	8 (7.9)	30 (7.5)	
Alcoholic	5 (1)	3 (3)	2 (0.5)	
Other	85 (17)	23 (22.8)	63 (15.8)	
LVEF, %	49 (34–58)	40 (30–50)	50 (38–60)	<0.01
NYHA class, n (%)*‡				
I	82 (19)	8 (8.2)	75 (21.6)	<0.01
II	190 (43)	39 (40.2)	154 (44.4)	
III	146 (33)	41 (42.3)	105 (30.3)	
IV	20 (5)	9 (9.3)	13 (3.7)	
Comorbidities, n (%)				
Arterial hypertension	360 (72)	70 (69.3)	291 (72.4)	0.54
Diabetes mellitus	188 (38)	35 (34.7)	154 (38.3)	0.50
Dyslipidaemia	292 (58)	51 (51)	242 (60.3)	0.09
Stroke/TIA	113 (23)	31 (30.7)	82 (20.4)	0.03
Atrial fibrillation	202 (40)	42 (42)	162 (40.4)	0.77
Other arrhythmias	96 (19)	17 (16.8)	79 (19.7)	0.52
COPD	58 (12)	9 (8.9)	49 (12.2)	0.36
Depression	36 (7)	5 (5)	31 (7.7)	0.40

Values are median (IQR) or number of patients (%).

*This is the control group, defined as patients who refused or discontinued ASV treatment within the first 3 months or were non-compliant with ASV therapy (device usage <3 hours/night).

†Cardiac device implanted: pacemaker or defibrillator.

‡NYHA class data were available in 438 patients of the 501 patients with polygraphy or polysomnography data; percentages are reported using the whole population as the denominator (the difference from 100% is missing data).

ASV, adaptive servo ventilation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TIA, transient ischaemic attack.

COHORT DESCRIPTION

Study design

Informed consent was obtained from all patients by the local investigator, and the trial is being conducted in accordance with local laws and regulations relevant to the use of medical devices in the country of conduct, International Conference on Harmonisation-Good Clinical Practice, ISO 14155 Standard Operative Procedures, and the Declaration of Helsinki and its current revision.

Participants

Consecutive patients with chronic HFpEF, HFmrEF or HFrfEF (as defined by the European Society of Cardiology HF guidelines²⁵ plus SDB indicated for ASV therapy are eligible for enrolment into the study if they fulfil inclusion and exclusion criteria requirements (table 1). Types of SDB include CSA (>50% central events), coexistent CSA/OSA (>20% central events) and OSA (<20% central events).²⁶ These were treated with first-line ASV therapy

Table 3 Baseline characteristics of enrolled patients, overall and by type of SDB

	Overall	Type of SDB*		P value
		CSA	eCSA or co-ex CSA/OSA	
n (%)	503 (100)	345 (69)	156 (31)	
Male, n (%)	442 (88)	311 (90.1)	131 (84)	0.05
Age, years	72 (64–79)	72 (65–79)	73 (65–78)	0.93
Body mass index, kg/m ²	28 (25–32)	27 (24–32)	30 (26–32)	0.01
Current smoker, n (%)	232 (46)	166 (48)	66 (43)	0.24
Alcohol use, n (%)	66 (14)	58 (17)	11 (7)	<0.01
Cardiac devices†, n (%)	136 (27)	84 (25)	52 (33)	0.04
Heart failure aetiology, n (%)				
Ischaemic	259 (52)	182 (53)	77 (51)	0.19
Dilated cardiomyopathy	36 (7)	25 (7)	11 (7)	
Arterial hypertension	73 (15)	45 (13)	28 (18)	
Valvular	31 (8)	31 (9)	7 (5)	
Alcoholic	5 (1)	5 (2)	0 (0)	
Other	85 (17)	56 (16)	29 (19)	
LVEF, %	49 (34–58)	48 (35–58)	50 (33–57)	0.87
NYHA class, n (%)‡				
I	82 (19)	62 (20.1)	20 (15.5)	0.30
II	190 (43)	138 (44.7)	52 (40.3)	
III	146 (33)	97 (31.4)	49 (38)	
IV	20 (5)	12 (3.9)	8 (6.2)	
Comorbidities, n (%)				
Arterial hypertension	360 (72)	249 (72)	111 (72)	0.90
Diabetes mellitus	188 (38)	127 (37)	61 (39)	0.59
Dyslipidaemia	292 (58)	202 (59)	90 (58)	0.86
Stroke/TIA	113 (23)	84 (24)	29 (19)	0.16
Atrial fibrillation	202 (40)	140 (41)	62 (40)	0.86
Other arrhythmias	96 (19)	65 (19)	31 (20)	0.77
COPD	58 (12)	38 (11)	20 (13)	0.56
Depression	36 (7)	20 (6)	16 (10)	0.07

Values are median (IQR) or number of patients (%).

*Type of sleep-disordered breathing data were unavailable in two patients.

†Cardiac device implanted: pacemaker or defibrillator.

‡NYHA class data were available in 438 patients of the 501 patients with polygraphy or polysomnography data; percentages are reported using the whole population as the denominator (the difference from 100% is missing data).

Co-ex CSA/OSA, coexisting central sleep apnoea/obstructive sleep apnoea; COPD, chronic obstructive pulmonary disease; eCSA, emergent central sleep apnoea; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SDB, sleep-disordered breathing; TIA, transient ischaemic attack.

for CSA and coexistent CSA/OSA, or second-line ASV therapy after CPAP failure for OSA. Periodic breathing or CSR was defined as at least three episodes of continuous cycles of waxing and waning tidal volumes with periods of hyperventilation separated by central apnoeas or hypopnoeas (the same as in the SERVE-HF study).²² The control group is made up of similar patients who either refuse ASV therapy or discontinue treatment within the first 3 months. The target sample size was at least 400 patients, who will be followed for ≥ 2 years. The first

patient was enrolled in November 2009 and enrolment was completed in September 2018.

Sleep recordings

SDB diagnosis was based on full-night polysomnography (PSG) performed at a sleep centre (n=142) or type 3 polygraphy (PG) performed at home or at health centre (n=261). For both the following parameters were recorded: ventilation using nasal airflow pressure recorded by nasal pressure prongs together with the sum

Table 4 Baseline characteristics of enrolled patients by heart failure classes based on LVEF, as defined by the European Society of cardiology heart failure guidelines

	Heart failure class			P value
	HFrEF	HFmrEF	HFpEF	
n (%), †	143 (31)	91 (19)	233 (50)	
Male, n (%)	130 (91)	82 (90)	203 (87)	0.48
Age, years	68 (59–76)	71 (64–78)‡	74 (66–80)	<0.01
Body mass index, kg/m ²	27 (23–31)	27 (25–31)‡	29 (26–32)	<0.01
LVEF, % (n=468)	30 (25–34)‡	45 (40–45)‡	57 (51–65)‡	<0.01
NYHA class, n (%)*				
I	14 (10.3)	5 (5.5)‡	57 (28.1)‡	<0.01
II	51 (37.5)	38 (45.8)	94 (46.3)	
III	61 (44.9)	36 (43.4)	45 (22.2)	
IV	10 (7.4)	4 (4.8)	7 (3.4)	
Heart rate, beats/min	69 (60–74)	69 (60–79)	69 (60–76)	0.96
Systolic BP, mm Hg	120 (103–130)‡	128 (115–142)‡	130 (120–143)	<0.01
Diastolic BP, mm Hg	70 (61–80)	71 (65–80)‡	74 (68–80)	0.02
MLHFQ score	36 (23–57)	31 (12–42)‡	23 (14–43)	<0.01
Haemoglobin, g/L	140 (120–150)	130 (120–140)	140 (120–150)	0.43
Creatinine, mmol/L	116 (98–140)	108 (87–134)‡	99 (84–125)	<0.01
BNP, pg/mL (n=108)	422 (293–648)	333 (128–134)‡	100 (33–221)‡	<0.01
NT-proBNP, pg/mL (n=221)	2377 (1043–4502)	1665 (756–4550)‡	758 (290–2046)‡	<0.01
eGFR, mL/min/1.73 m ² (CKD-EPI)	56 (42–70)	55 (43–74)	62 (47–80)	0.18

Values are median (IQR) or number of patients (%).

*NYHA class was reported only in 422 of the 468 patients with known LVEF.

†Type of heart failure could not be determined in 36 patients who had missing LVEF data.

‡For significant post hoc test ($p < 0.0167$); note that between group differences in LVEF were expected based on how the groups of heart failure patients were defined.

BNP, B-type natriuretic peptide; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-pro-BNP, amino terminal-pro B-type natriuretic peptide; NYHA, New York Heart Association.

of oronasal thermistor signals, respiratory effort using abdominal and thoracic bands, oxygen saturation (SpO₂) using a finger pulse oximeter, a modified V2 three-lead ECG and body position. For PSG, continuous recordings were taken with electrode positions C3/A2–C4/A1–Cz/01 of the international 10–20 Electrode Placement System, eye movements and chin electromyogram. Sleep stages were scored manually according to the American Academy of Sleep Medicine (AASM) criteria.²⁷ Scoring of respiratory events was performed according to the rules described by the AASM.²⁸ Briefly, an apnoea was defined as the complete cessation of airflow for at least 10s and hypopnea as a reduction of at least 50% in the nasal pressure signal or a decrease of between 30% and 50% associated with either oxygen desaturation of $\geq 3\%$ or an electroencephalogram arousal, both lasting for at least 10s. Apnoeas were classified as obstructive, central or mixed according to the presence or absence of respiratory effort. The classification of hypopnoeas as obstructive or central was based on the thoraco-abdominal band

signal and the shape of the respiratory nasal pressure curve (presence or absence of flow limitation).²⁸ The Apnoea-Hypopnoea Index (AHI) was defined as the number of apnoeas and hypopnoeas per hour of sleep (full-night PSG) or per hour of recording (PG). The ratio between central and obstructive events was expressed as the percentage of central events. Nocturnal oxygen status during sleep was derived from PG/PSG (3% Oxygen Desaturation Index (ODI), time spent with SpO₂ below 90% (TC90), minimum (min SpO₂) and mean SpO₂).

Treatments and follow-up

Patients are being followed up based on current standard clinical practice, with a clinic visit at inclusion, at 3, 12 and 24 months of follow-up, and a final assessment at the end of the study. Each of these visits includes collection of primary endpoint data (occurrence of events since the last visit), assessment of disease-specific quality of life using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and evaluation of sleepiness using the

Table 5 Baseline sleep study data for enrolled patients, overall and by type of SDB

	Overall	Type of SDB*		P value
		CSA	eCSA or co-exCSA/OSA	
Respiratory sleep study data				
n (%)	503 (100)	345 (69)	156 (31)	
AHI/hour	42 (30–55)	43 (32–56)	40 (28–53)	0.04
Central AHI/hour	21 (12–32)	29 (19–41)	12 (5–12)	<0.01
Obstructive AHI/hour	26 (5–24)	6 (1–17)	20 (9–30)	<0.01
Hypopnoea index/hour	16 (12–26)	17 (10–28)	15 (7–23)	0.06
Periodic breathing pattern, n (%)	246 (49)	180 (55)	66 (44)	0.04
Time spent with SpO ₂ <90%, min	33 (5–101)	30 (5–96)	44 (8–109)	0.31
Oxygen desaturation index (≥3%)/hour	36 (23–51)	36 (23–51)	36 (23–51)	0.99
Epworth Sleepiness Scale score	7 (4–11)	7 (4–11)	7 (4–10)	–

Values are median (IQR) or number of patients (%).

*Type of SDB data were unavailable in two patients.

AHI, Apnoea–Hypopnoea Index; Co-ex CSA/OSA, coexisting central sleep apnoea/obstructive sleep apnoea; eCSA, emergent central sleep apnoea; SDB, sleep-disordered breathing; SpO₂, oxygen saturation.

Epworth Sleepiness Scale (ESS). Additional assessments include general medical history, a physical examination and determination of New York Heart Association (NYHA) functional classification. For patients receiving ASV, data from the device (including leaks, residual AHI and compliance) are downloaded at home by a Home Care Provider or at hospital at least every 6 months.

ASV therapy (PaceWave, AutosetCS; ResMed) was initiated in the hospital using standard settings. Pressure levels were adjusted based on the results of respiratory monitoring. First generation devices had a minimum expiratory positive airway pressure (EPAP) of 5 cmH₂O, while PaceWave with auto EPAP had a minimum EPAP of

4 cmH₂O and minimum pressure support of 3 cmH₂O. The PaceWave ASV algorithm sets the mean minute ventilation target to 90% of the patient's own ventilation. Patients were instructed to use the ASV device for at least 5 hours each night, 7 days a week. It was recommended that major mask leaks should be avoided if possible. The target was to reduce the AHI to <10/hour within 1 week (assessed on a home visit by a Home Care Provider and thereafter during clinic visits). If target AHI was not achieved, then mask fitting was reviewed, and device settings are individually adjusted for each patient.

Table 6 Baseline sleep study data for enrolled patients by heart failure classes based on left ventricular ejection fraction, as defined by the European Society of cardiology heart failure guidelines

	Heart failure class*			P value
	HFrEF	HFmrEF	HFpEF	
Respiratory sleep study data				
n (%)	143 (31)	91 (19)	233 (50)	
AHI/hour	35 (27–49)	40 (30–53)†	47 (33–58)	<0.01
Central AHI/hour	22 (13–32)	21 (8–35)†	29 (15–41)†	<0.01
Obstructive AHI/hour	7 (2–20)	10 (2–24)	9 (3–22)	0.61
Hypopnoea Index/hour	15 (8–23)	16 (11–24.5)	18 (9–29)	0.19
Periodic breathing pattern, n (%)	76 (56)	49 (56)	109 (49)	0.34
Time spent with SpO ₂ <90%, min	29 (6–100)	49 (7–120)	32 (4–95)	0.28
Oxygen Desaturation Index (≥3%), /h	32 (21–45)	36 (19–52)†	39 (27–53)	0.02
Epworth Sleepiness Scale score	7 (4–11)	6 (4–11)	7 (4–10)	0.95

Values are median (IQR) or number of patients (%).

*Type of heart failure could not be determined in 36 patients who had missing left ventricular ejection fraction data.

†For significant post hoc test (p<0.0167).

AHI, Apnoea–Hypopnoea Index; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SpO₂, oxygen saturation.

Outcomes

The primary endpoint is the time to first event of the composite of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalisation (or unplanned prolongation of a planned hospitalisation) for worsening of chronic HF. This is the same primary endpoint as the randomised SERVE-HF trial.²² Additional hierarchical endpoints were the same as the primary endpoint but with cardiovascular death rather than all-cause death, and the same as the primary endpoint but with all-cause unplanned hospitalisation rather than unplanned hospitalisation for worsening of chronic HF, both of which were also consistent with SERVE-HF.

Other secondary endpoints included the following: time to death (cardiovascular or all-cause); time to unplanned hospitalisation; proportion of follow-up days (%) during which patients are alive and not hospitalised; number of hospitalisations; and changes in disease-specific quality of life, HF symptoms and medical treatment.

Protocol Amendment

A field safety notice released on 13 May 2015 based on early data from the SERVE-HF study²² necessitated a modification to the study protocol so that patients with HFrEF were no longer eligible to be treated with ASV; enrolment of all other patients meeting the inclusion criteria was continued. Patients with HFrEF who have already been enrolled in the study are continuing to be followed up for as long as possible.

Patient and public involvement

Patients and/or public were not involved in the study design and study enrolment.

Sample size

Based on data from observational studies,^{29,30} it was assumed that treatment of SDB with positive airway pressure therapies would halve the morbidity and mortality rate. Therefore, a sample size of 300 patients would be sufficient to detect a similar decrease in risk with a type 1 error (α) of 5% and a power of 90%. The target sample size was set at 400 to allow for drop-outs. After enrolment of patients with HFrEF was suspended, the sample size was revised to a target of at least 300 patients with HFmrEF and HFpEF.

Statistical analyses

All primary and secondary endpoints are being assessed in the modified intention-to-treat population, which includes all enrolled patients meeting the eligibility criteria. Event-free survival will be estimated using the Kaplan-Meier method and compared between the ASV and control groups using a two-sided log-rank test (significance $p < 0.05$). Secondary endpoints will be analysed according to the type of scale: time-to-event endpoints will be analysed in the same ways as the primary endpoint; dichotomous variables (improvement in NYHA class) will be analysed using a likelihood X^2 test; continuous endpoints will be analysed by analysis of covariance including the baseline value as a covariate

if available; variables with right-skewed distributions within random groups will be log-transformed prior to analysis.

Extended analyses will be conducted using linear, logistic or Cox proportional hazards regression models (to explore further the influence of patient characteristics and clinical conditions on outcome). The list of covariates includes age, gender, body mass index, study site, comorbidities, severity of SDB (AHI 15–30/hour, AHI ≥ 30 /hour, ODI/hour), NYHA functional classification, reduced/preserved LVEF, ESS score and proportion of periodic breathing 20%/20%–50%/50% of recording time, all determined at baseline.

Finally, a latent class analysis (LCA) method will be used to identify homogeneous patient subgroups. LCA is based on a probabilistic method that classifies every patient into a dedicated cluster. Each patient has the highest probability of belonging to their own cluster. Local independence assumption will be checked, which means that all variables used in the LCA model will be tested for pair independence. Identified clusters will be described and compared using the non-parametric Kruskal-Wallis test for qualitative variables and the X^2 test for qualitative variables.

Baseline characteristics

A total of 509 patients underwent baseline sleep assessment (screening). Of these, 6 were not included, leaving 503 patients who had baseline sleep and cardiovascular assessment (table 2). Patients had a median age of 72 years (IQR 64–79), tended to be overweight (based on body mass index), and the majority were male (88%). Indications for ASV were CSA (69% of patients), and uncontrolled OSA (emergent CSA) or coexistent CSA/OSA not controlled by CPAP therapy (31% of patients). Overall, HF was most commonly ischaemic in origin, and type of SDB did not vary by HF aetiology (table 2). However, body mass index was higher in patients with OSA or coexisting CSA than in those with CSA, while alcohol consumption and the rate of direct cardioverter implantation were higher in the subgroup of patients with CSA (table 3). The majority of patients were in NYHA class II (38%) or III (29%), especially those with HFrEF (tables 1 and 4). About half of the patient population had HFpEF, about one-third had HFrEF, and the remainder had HFmrEF (table 4). Comorbidities were common (table 2), especially arterial hypertension, dyslipidaemia, atrial fibrillation and diabetes mellitus, although these did not differ based on the type of SDB (table 3) or HF (data not shown).

HF was highly symptomatic, as demonstrated by the median MLHFQ score (29; IQR 16–48), and patients with HFrEF had the worst quality of life (table 4).

Baseline sleep study data showed severe SDB, with a median baseline AHI of 42/hour in the overall population (table 5). Nearly half of all patients showed a periodic breathing pattern, and the central AHI was 21/hour. By definition, patients with CSA were more likely to show a periodic breathing pattern. They also had a higher AHI (table 5). Interestingly, patients with HFpEF showed more severe SDB in terms of the AHI and ODI (table 6). The ESS

score did not indicate the presence of daytime sleepiness. In the subset of patients who underwent PSG, this showed a higher wake time to sleep onset and less slow wave sleep in patients with CSA (online supplementary table S1) and in those with HFrEF (online supplementary table S2).

STRENGTHS AND LIMITATIONS

Strengths

FACE is a prospective, observational multicentre cohort study conducted in a real-world setting. The population being studied is unselected patients with HF and SDB, either central or not controlled by CPAP. SDB is common in patients with chronic HF regardless of their LVEF and is associated with worse prognosis.^{5–9} The FACE study will provide data on patients with chronic HF with CSA/CSR that is complementary to that generated by randomised controlled trials. Other key features of the FACE study are the inclusion of patients with HFrEF, HFmrEF or HFpEF, and those with or without coexisting obstructive apnoea that is not controlled by CPAP, allowing the effects of ASV therapy in these different patient subgroups to be compared. This will help to further define the effectiveness of ASV for controlling SDB in patients with CSA/CSR who also have obstructive apnoea events, about which there is currently only limited data.^{31–32} In addition, HFpEF is not well studied compared with HFrEF, but is increasing in prevalence as the population ages (accounting for approximately half of all HF cases in the community). ASV has been shown to correct SDB, improve diastolic and right ventricular function and reduce natriuretic peptide levels in patients with HFpEF,^{33–34} and the FACE results will expand this knowledge.

The FACE study will also provide important insights into compliance with nocturnal positive pressure ventilation therapy, and the FACE cohort will be the first group of HF patients for whom ASV data are evaluated using device remote monitoring. There are currently no trial data specifically addressing compliance with nocturnal ventilation, and determinants of compliance, in patients with HF.

FACE is being conducted in a clinical practice setting across a range of centres (both private and academic), covers a range of ASV indications, and includes patients with all forms of HF (ie, HFrEF, HFmrEF and HFpEF), which should maximise the clinical relevance of the study findings. Furthermore, this is the only prospective cohort study including a large number of HFpEF patients with CSA treated with ASV, and the results should provide data that will be interesting and relevant to healthcare stakeholders, clinicians and researchers. Overall, the FACE study findings have the potential to provide important information to help individualise therapeutic strategies targeted at reducing morbidity and mortality in patients with HF and SDB.

Limitations

One of the main limitations of this study is the observational cohort design, which could introduce bias in favour of the ASV-treated group. In addition, although an untreated

control group is included, these patients are those who either refuse ASV therapy or discontinue treatment within the first 3 months. Therefore, the characteristics of these patients might include variables that could influence patient outcome other than use versus non-use of ASV. It is also important to note that the sample size of HFrEF patients is smaller than originally planned because enrolment of patients matching the SERVE-HF inclusion criteria had to be stopped after the results of the study showed an higher rate of cardiovascular mortality in patients allocated to ASV versus control.²² However, the fact that HFrEF patients enrolled prior to that time continue to be followed up provides the opportunity to gather additional data on the use of ASV in this important patient population, particularly over a longer follow-up period. Finally, although the real-world nature of the data obtained in the FACE study is one of its strengths, the fact that the study population is from a limited geographical area potentially limits the external validity of study results to different healthcare settings.

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Collaborators The FACE prospective cohort will continue to collect data up to 2 years of follow-up. The findings should allow analysis and generation of clinically relevant data on the use of ASV in a broad range of patients with HF. Access to the FACE study data must be granted by the Steering committee of the study and is therefore not open access. The research team welcomes all potential collaborations with other researchers. For further information, please email the corresponding author at rtamisier@chu-grenoble.fr.

Contributors RT, J-LP, TD, J-MD, SB, FL and M-PD defined the study concept and designed the study. RT, J-LP, TD, J-MD, JAV, AP, FG and M-PD participated to data acquisition. Analysis and interpretation of data were performed by RT, J-LP, TD, J-MD, JAV, SB, AP, FG and M-PD. Drafting of the manuscript was done by RT, J-LP, SB and FL. Critical revision of the manuscript for important intellectual content was performed by RT, J-LP, TD, J-MD, JAV, SB, FL, AP, FG and M-PD. Statistical analysis were performed by SB, J-LP and RT. The Study was supervised by RT, J-LP, TD, J-MD, JAV, SB, FL and M-PD.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Data availability statement Data may be obtained from a third party and are not publicly available. The data are not freely available and access must be granted by the steering committee but we welcome any potential collaboration with other researchers. For further information, please email RT (RTamisier@chu-grenoble.fr).

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