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FACE study: 2-year follow-up of adaptive servo-ventilation for sleep-disordered breathing in a chronic heart failure cohort

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ABSTRACT

Background: Sleep-disordered breathing (SDB) is a common comorbidity in patients with heart failure (HF) and is associated with worse prognosis.
Objectives: This study evaluated the effects of adaptive servo-ventilation (ASV) on morbidity and mortality in a large heterogeneous population of HF patients with different etiologies/phenotypes.
Methods: Consecutive HF patients with predominant central sleep apnea (± obstructive sleep apnea) indicated for ASV were included; the control group included patients who refused or stopped ASV before three months follow-up. Six homogenous clusters were determined using the latent class analysis (LCA) method. The primary endpoint was time to composite first event (all-cause death, lifesaving cardiovascular intervention, or unplanned hospitalization for worsening of chronic HF).
Results: Of 503 patients at baseline, 324 underwent 2-year follow-up. Compared to control group, 2-year primary endpoint event-free survival was significantly greater in patients in ASV group only in univariable analysis (1.67, 95% [1.12–2.49]; p = 0.01). Secondary endpoints, event-free of cardiovascular death or heart failure-related hospitalization and all-cause death or all-cause hospitalization were positively impacted by ASV (univariate and multivariable analysis). LCA identified two groups, with preserved and mid-range left ventricular ejection fraction (LVEF) and severe hypoxia, in whom ASV increase prognosis benefit.
Conclusions: Patients with HF and SDB are a highly heterogeneous group identified using LCA. Systematic deep phenotyping is essential to ensure that ASV is prescribed to those benefit from therapy, as ASV use in patients with severe hypoxic burden and those with HFpEF was associated with a significant reduction in cardiovascular events and mortality.
Clinical trial registration: https://clinicaltrials.gov/ct2/show/NCT01831128.

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Abbreviations

ASV	adaptive servo-ventilation
Co CSA-OSA	Coexistent central and obstructive sleep apnea (20<central AHI<50%)
CPAP	continuous positive airway pressure
CSA	central sleep apnea
FACE	French Cohort Study of Chronic Heart Failure Patients with Central Sleep Apnea Eligible for Adaptive Servo-Ventilation
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
AHI	Apnea Hypopnea Index
LCA	latent class analysis
OSA	obstructive sleep apnea
SDB	sleep-disordered breathing
TE-CSA	Treatment emergent central sleep apnea (CSA that occurs on CPAP)

1. Introduction

Heart failure (HF) refers to a complex clinical syndrome in which the heart is unable to supply enough blood to the systemic circulation to meet the body's needs [1]. Symptoms including breathlessness, fatigue, weakness and fluid retention are persistent, and are associated with reduced quality of life [2,3]. Despite advances in pharmacological and device therapy, HF remains a significant cause of morbidity and mortality, and is a global public health issue [4].

HF is a heterogeneous disease, with different etiologies, left ventricular function and comorbidities. When divided into categories based on the left ventricular ejection fraction (LVEF), patients with LVEF <40% are classified as having HF with reduced ejection fraction (HFrEF), those with LVEF ≥50% have HF with preserved ejection fraction (HFpEF), and when LVEF is between 40% and 50%, patients have HF with mildly reduced ejection fraction (HFmrEF) [5]. Most current knowledge and therapies relate to HFrEF, despite the fact that HFpEF is at least as common and is associated with similar symptom burden and adverse outcomes to HFrEF [6–8].

For all patients with HF, but especially those with HFpEF, there is increasing focus on managing comorbidities to improve clinical outcomes [9]. One such comorbidity is sleep-disordered breathing (SDB), which is highly prevalent in patients with HF and remains present despite improvement in HF medical and electrophysiologic management [10–14]. There are two main forms of SDB: obstructive sleep apnea (OSA) and central sleep apnea (CSA). Both American Academy of Sleep Medicine and European Respiratory Society guidelines define predominant CSA as ≥50% central events, predominant OSA as <50% central events (including pure OSA as <20% central events and co-existent CSA-OSA with central events between 20 and 50%) [13].

The presence of SDB in patients with HF is associated with worse prognosis [15]. However, randomized controlled trials have failed to find any benefit of treating CSA with either continuous positive airway pressure (CPAP) or adaptive servo-ventilation (ASV) in patients with HFrEF [16,17]. The only randomized trial to include patients with HFpEF was stopped early, but the results of a prespecified subgroup analysis suggested that ASV might improve outcomes in these patients [18].

The French Cohort Study of Chronic Heart Failure Patients with Central Sleep Apnea Eligible for Adaptive Servo-Ventilation (FACE) evaluated the effects of ASV therapy on morbidity and mortality in a large heterogeneous population of patients with HF of different etiologies, LVEF ranges (HFrEF, HFmrEF, HFpEF) and severity, and different SDB phenotypes (CSA, co-existing CSA/OSA or TE-CSA). Latent class analysis (LCA) based on 3-month FACE study data categorized patients into six clusters based on 21 parameters from HF condition to SDB characteristics, resulting in meaningful clinical phenotypes [19]. This categorization effectively differentiated between clusters with respect to prognosis at the 3-month follow-up (see graphical abstract) [19].

The current analysis used 2-year follow-up data from the FACE study to determine whether the effects of ASV differed between patient clusters.

2. Methods

2.1. Study design

The multicenter, prospective, observational cohort FACE study (NCT01831128) was conducted at 28 centers in Europe between November 2009 and September 2018 [20]. Ethical approval, the study protocol was approved by 'Le Comité consultatif sur le traitement de l'information en matière de recherche en santé' (C.C.T.I.R.S no 09.418). The study was conducted in accordance with local laws/regulations, International Conference on Harmonization-Good Clinical Practice (ICH-GCP), ISO 14155 Standard Operating Procedures, and the Declaration of Helsinki and its current revision. An Executive Steering Committee provided independent oversight of the study.

2.2. Participants

Eligible patients had HFrEF, HFmrEF or HFpEF based on current European Society of Cardiology definitions [5,21], predominant CSA, coexistent CSA-OSA uncontrolled by CPAP, or OSA with treatment emergent CSA (TE-CSA) on continuous positive airway pressure (CPAP) were considered as an indication for ASV therapy, and no contraindication for positive airway pressure therapy. A comprehensive list of inclusion and exclusion criteria is available in the design paper [20]. Full details have been reported previously and in the online supplement [20].

Synopsis (see graphical abstract, online supplement, and previous published paper design [20] and results for details [19]).

All eligible patients were treated using ASV. ASV therapy (PaceWave™, AutosetCS™; ResMed) was initiated in hospital; pressure settings were titrated based on respiratory monitoring and patients were instructed to use the device for ≥5 h every night. Two groups of patients were constituted following the 3-month visit follow-up. The ASV group includes those using ASV more than 3 h of sleep per day and the control group consists of patients who refused ASV, stopped treatment before or were not compliant at 3-month visit follow-up. Follow-up visit were them completed at least every 6 months until 2 years of follow-up. We used latent class analysis to determine 6 clinical phenotypes (i.e. LCA 1 to 6 phenotypes), based on 21 clinical and cardiorespiratory variables [19]. Briefly, these previously reported phenotypes individualized participants that exhibited significant clinical parameters (central versus obstructive sleep apnea, hypoxic burden, preserved versus reduced left ventricular ejection fraction, comorbidities, and age). In fact, at three months' follow-up, these phenotypes already showed a different prognosis of the primary endpoint [19].

2.3. Follow-up

Patients attended clinic follow-up visits at baseline, and after 3 months, 1 year and 2 years of follow-up [20]. At each visit, functional status (based on the New York Heart Association [NYHA] classification) was evaluated, the occurrence of any primary endpoint event since the last visit was recorded, and patients completed the Epworth Sleepiness Scale (ESS) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

2.4. Outcomes

The primary endpoint was the time to first event of the composite of all-cause death, life-saving cardiovascular intervention, or unplanned hospitalization (or unplanned prolongation of a planned hospitalization) for worsening of chronic HF.

Secondary 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 hospitalization rather than unplanned hospitalization for worsening of chronic HF. Additional secondary endpoints are reported in the online supplement.

2.5. Statistical analysis

Statistical analyses were performed using SAS v9.4 (SAS Institute), and a p-value of ≤ 0.05 was defined as statistically significant. Baseline comparisons between groups were performed using the Mann-Whitney test for quantitative variables and the Chi-squared test or Fisher test for qualitative variables.

All available data were included in the analyses unless consent for data usage was revoked [20]. Variables with <20% missing values were imputed using multiple imputations: ten imputed datasets were constituted using a Monte-Carlo Markov Chain for quantitative variables and fully conditional specification for qualitative variables. Imputed datasets were combined using Rubin's rules. Two-year event-free survival (primary and secondary endpoints) was estimated using the Kaplan-Meier method and compared between the ASV and control groups using a two-sided log-rank test. In addition, for each outcome a complementary analysis was performed using a univariable model and a multivariable Cox model adjusted for variables of interest. Change in NYHA class was analyzed using a likelihood Chi-square test, and continuous endpoints were evaluated using analysis of covariance (ANCOVA) with the baseline value as a covariate (if available); variables with right-skewed distributions within each treatment group were log-transformed before analysis. A sensitivity analysis was performed using an extended control group that included not only patients who

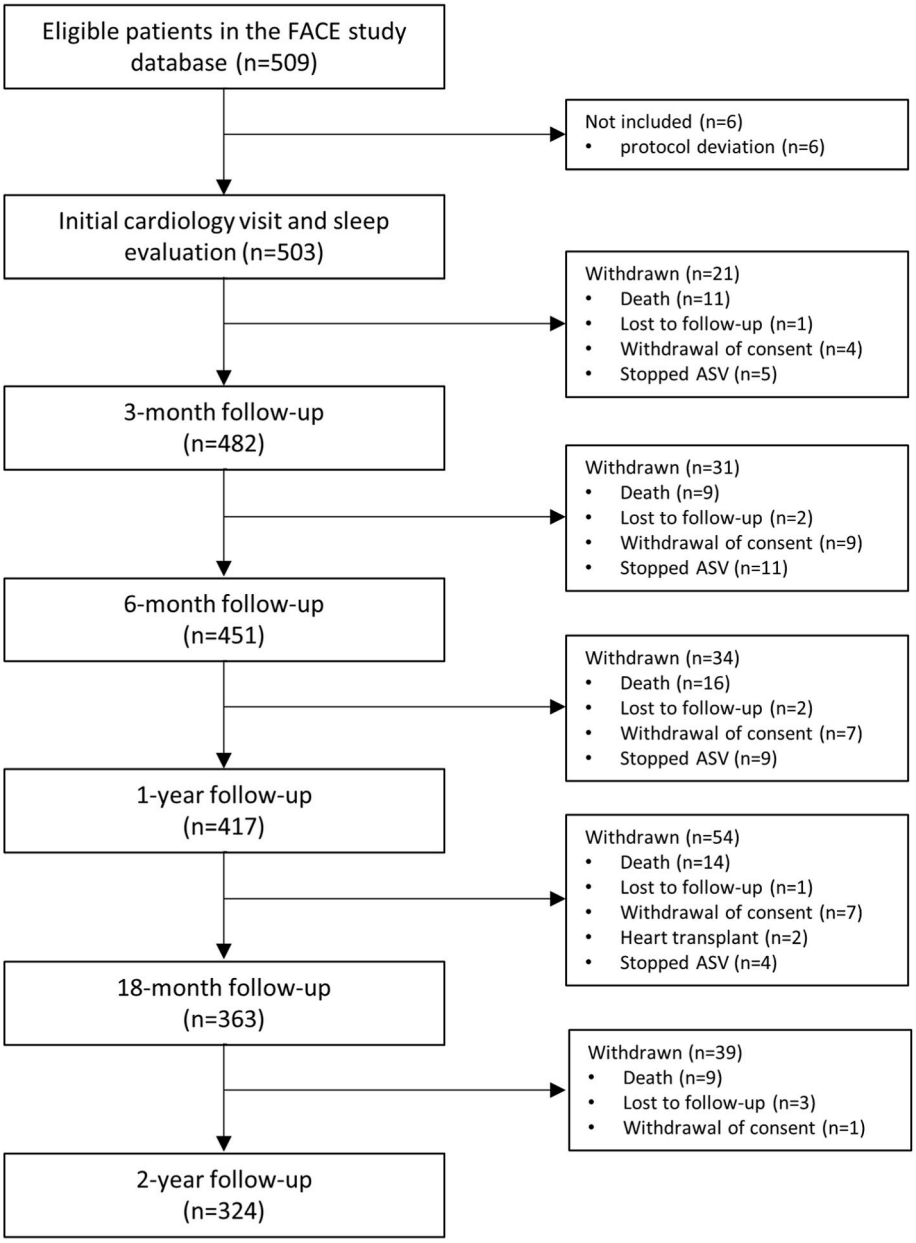

Fig. 1. Patient flow chart. ASV, adaptive servo-ventilation.

refused ASV at 3-month follow-up but also those who stopped ASV after 3-month or decreased ASV usage to <3 h/night at 2 years.

3. Results

3.1. Study population

Assessment of SDB was performed in 509 patients with indication for ASV, of whom six were excluded and 503 underwent baseline assessments; 324 remained in the study at the 2-year follow-up (Fig. 1). The study population was characterized by a high degree of heterogeneity; full details have been published previously [19] and are reported in the online supplement (Table 1).

Baseline characteristics and comorbidities for patients who accepted or declined ASV by patient's cluster are presented in Table 2. For further detail about the population and compliance to ASV see online supplement.

3.2. Impact of ASV on outcomes in the overall population

Two-year primary endpoint event-free survival was significantly greater in patients who accepted ASV compared with the control group (univariable Cox model HR 1.67, 95% CI 1.12–2.49: log-rank test p = 0.01) (Fig. 3, Table 3). On univariable analysis, ASV usage was also associated with significantly lower rates of all-cause hospitalization, HF-related hospitalization, and cardiovascular death (Table 3). Significant reductions in cardiovascular death or HF-related hospitalization and all-cause death or all-cause hospitalization in the ASV group compared with control were statistically significant on both univariable and adjusted multivariable analysis (Table 3).

Table 1
Demographic and clinical characteristics at baseline based on usage of adaptive servo-ventilation.

Variable	Non-ASV (n = 101)	ASV (n = 402)	p-value
Male, n (%)	82 (81.2)	362 (90)	0.01
Age, years	72.9 [62.3–80]	71.9 [64.8–78.4]	0.91
Body mass index, kg/m^2	25.6 [22.7–28.3]	28.7 [25.5–32.3]	<0.01
Current smoker, n (%)	44 (44)	190 (47.3)	0.56
Alcohol use, n (%)	12 (12)	57 (14.2)	0.57
Cardiac stimulator/defibrillator, n (%)	43 (42.6)	93 (23.3)	<0.01
Heart failure etiology, n (%)			<0.01
Ischemic	51 (50.5)	209 (52.5)	
Dilated cardiomyopathy	11 (10.9)	25 (6.3)	
Hypertension	5 (5)	69 (17.3)	
Valvular	8 (7.9)	30 (7.5)	
Alcoholic	3 (3)	2 (0.5)	
Other	23 (22.8)	63 (15.8)	
LVEF, %	40 [30–50]	50 [38–60]	<0.01
NYHA class, n (%)			<0.01
I	8 (8.2)	75 (21.6)	
II	39 (40.2)	154 (44.4)	
III	41 (42.3)	105 (30.3)	
IV	9 (9.3)	13 (3.7)	
Comorbidities, n (%)			
Hypertension	70 (69.3)	291 (72.4)	0.54
Diabetes	35 (34.7)	154 (38.3)	0.50
Dyslipidemia	51 (51)	242 (60.3)	0.09
Stroke/transient ischemic attack	31 (30.7)	82 (20.4)	0.03
Atrial fibrillation	42 (42)	162 (40.4)	0.77
Other arrhythmias	17 (16.8)	79 (19.7)	0.52
COPD	9 (8.9)	49 (12.2)	0.36
Depression	5 (5)	31 (7.7)	0.40

Values are median [interquartile range], or number of patients (%).
ASV, adaptive servo-ventilation; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

3.3. Outcomes by patient phenotype

Patient phenotypes based on LCA (six homogeneous patient clusters) have been described previously [19]. On univariable analysis, primary endpoint event-free survival was worst in cluster 1 patients (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.36–1.12), intermediate in those from clusters 2, 3 and 4 (HR [95% CI] values 0.63 [0.36–1.12], 0.63 [0.34–1.15] and 0.71 [0.42–1.21], respectively), and less severe in clusters 5 and 6 (0.44 [0.25–0.77] and 0.34 [0.15–0.79], respectively) (Supplementary Table III). Findings were similar for analysis of the cardiovascular death or HF-related hospitalization endpoint (Supplementary Figure I, Supplementary Table III), and the all-cause death or all-cause hospitalization endpoint (Supplementary Figure II, Supplementary Table III). In the multivariable Cox model adjusted for age, sex, BMI, use of ASV, presence of HFrEF and presence of CSA, patients in Cluster 2 were still at significantly lower risk of all-cause death compared with those in Cluster 1 (Supplementary Table IV).

3.4. Effects of ASV by patient phenotype

In the univariable model, primary endpoint event-free survival did not differ between the ASV-treated and control groups in Clusters 1, 2 and 3 (Fig. 4A–C, Table 4). In contrast, use of ASV by patients in Clusters 4 and 5 was associated with significantly better primary endpoint event-free survival versus the corresponding control group (Fig. 4D & E, Table 4). Further details on secondary outcomes are reported in the online supplement.

On multivariable analysis, the risk of all-cause death or all-cause hospitalization was significantly lower in the ASV versus control group in Cluster 4 (Table 5).

3.5. Sensitivity analysis

The sensitivity analysis based on ASV compliance is reported in the online supplement.

4. Discussion

Two-year follow-up data from the FACE study show that more than half of all patients with chronic HF and SDB benefitted from ASV therapy. When patients were grouped into clusters using LCA, clusters showed markedly different ASV acceptance and prognosis.

The current findings enhance and reinforce the FACE study 3-month follow-up data [19] showing that usage of ASV was associated with significant reductions in morbidity and mortality in patients from Clusters 4 and 5 (i.e. those who are older, male, with more hypoxic burden, obese, hypertensive, and have HFmrEF and both CSA and OSA) and Cluster 6 (i.e. old, mostly male, with more hypoxic burden, and HFpEF and OSA). However, this benefit on prognosis was not present in patients from Clusters 1 and 2 (i.e., those with a higher NYHA class, HFrEF, lower BMI, an implanted cardiac device, and/or current smoking habit, and CSA or OSA) and Cluster 3 (i.e., those with a higher age, both males and females, and with HFmrEF and mild SDB). Interestingly, patients in Clusters 4, 5 and 6 (i.e., those who benefited from therapy) showed the highest rates of ASV acceptance, at 91.9%, 91.6% and 100%, respectively.

The presence of SDB in patients with chronic HF worsens prognosis and increases mortality risk compared to similar patients without SDB [22]. Over three-quarters of chronic HF patients (76%) also have SDB [14]. This implies that health professionals in charge of these conditions need knowledge about the presentation and the consequences of this association [23].

Use of ASV has been shown to solve the challenging issue of abnormal ventilation during sleep in patients with HF [24,25]. However, although several studies have been performed over the last decade, controversies remain regarding the putative benefit of treating SDB with

Table 2
Demographic and comorbidities at baseline by adaptive servo-ventilation usage within each patient cluster.

Variable	Cluster 1		Cluster 2			Cluster 3				Cluster 4	Cluster 5			
	Non-ASV (n = 37)	ASV (n = 42)	p-value	Non-ASV (n = 21)	ASV (n = 68)	p-value	Non-ASV (n = 25)	ASV (n = 42)	p-value	Non-ASV (n = 8)	ASV (n = 91)	p-value	Non-ASV (n = 10)	ASV (n = 109)	p-value
Male, n (%)	35 (94.6)	41 (97.6)	0.48	18 (85.7)	64 (94.1)	0.21	18 (72)	33 (78.6)	0.54	6 (75)	83 (91.2)	0.19	5 (50)	98 (89.9)	<0.01
Age, years	65.7 [53.3–73.4]	66 [59.6–73.6]	0.61	68.3 [60.8–77.2]	68.2 [61.6–76.4]	0.88	76.1 [72.2–83.8]	73.8 [66–79]	0.13	**82.3 [78.8–85.8]**	**74.4 [65.3–79.2]**	**0.01**	76.6 [67.7–85.4]	73.5 [66.2–79.2]	0.31
BMI, kg/m^2	26.7 [23.4–28.3]	26.5 [23.1–29.9]	0.72	25.7 [22.9–28.5]	26.7 [24.5–30.9]	0.19	**23.9 [22.3–26]**	**30.1 [27.3–32.5]**	**<0.01**	**24.3 [22.5–25.4]**	**29 [26.7–32.5]**	**<0.01**	30.5 [22.6–37.5]	29.2 [25.3–32.3]	0.89
ESS	6 [3–8]	6 [4–11]	0.51	6 [5–9]	7.5 [4–12]	0.49	6 [4–11]	5.5 [3–9.5]	0.75	8 [5–11]	6.5 [4–11]	0.54	10 [10-10]	7.5 [4–12]	ESS
MLHFQ score	32.5 [25–53]	25 [14–55]	0.58	26 [9–41]	35 [23.5–51.5]	0.26	29 [20–53]	41 [30–58]	0.11	23 [0–26]	23 [15–45]	0.44	6.5 [1.5–34.5]	23.5 [12.5–44.5]	0.17
Current smoker, n (%)	18 (48.6)	28 (66.7)	0.11	14 (66.7)	37 (54.4)	0.32	6 (25)	17 (40.5)	0.20	4 (50)	33 (36.3)	0.47	2 (20)	52 (47.7)	0.11
Alcohol use, n (%)	8 (21.6)	10 (23.8)	0.82	2 (9.5)	5 (7.4)	0.67	1 (4.2)	4 (9.5)	0.65	0 (0)	14 (15.4)	0.60	1 (10)	16 (14.7)	1.00
Comorbidities, n (%)															
Hypertension	25 (67.6)	25 (59.5)	0.46	12 (57.1)	40 (58.8)	0.89	19 (76)	29 (69)	0.54	8 (100)	72 (79.1)	0.35	6 (60)	86 (78.9)	0.23
Depression	2 (5.4)	2 (4.8)	1.00	1 (4.8)	7 (10.3)	0.67	1 (4)	3 (7.1)	1.00	1 (12.5)	7 (7.7)	0.50	0 (0)	6 (5.5)	1.00
Dyslipidemia	20 (54.1)	29 (70.7)	0.13	13 (61.9)	42 (61.8)	0.99	9 (37.5)	21 (50)	0.33	5 (62.5)	61 (67)	1.00	4 (40)	62 (56.9)	0.34
Stroke/TIA	17 (45.9)	13 (31)	0.17	2 (9.5)	13 (19.1)	0.51	5 (20)	9 (21.4)	1.00	**5 (62.5)**	**14 (15.4)**	**<0.01**	2 (20)	19 (17.4)	1.00
Diabetes	12 (32.4)	17 (40.5)	0.46	12 (57.1)	19 (27.9)	0.01	7 (28)	19 (45.2)	0.16	1 (12.5)	43 (47.3)	0.07	3 (30)	37 (33.9)	1.00
COPD	2 (5.4)	5 (11.9)	0.44	2 (9.5)	8 (11.8)	1.00	2 (8)	7 (16.7)	0.47	2 (25)	8 (8.8)	0.19	1 (10)	13 (11.9)	1.00

Values are median [interquartile range], or number of patients (%). ESS for Epworth Sleep Scale, MLHFQ, Minnesota Living with Heart Failure Questionnaire.
ASV, adaptive servo-ventilation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.
Data ASV/non-ASV are not reported for cluster 6 as all patients accepted ASV at 3-month. Demographic and comorbidities at baseline for each cluster are reported in our previous manuscript [19].

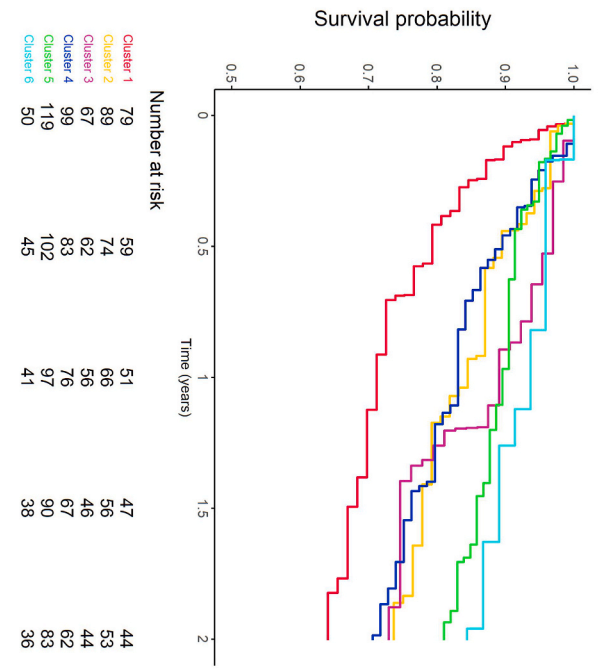

Fig. 2. Kaplan-Meier curves for primary endpoint event-free survival by patient cluster ($p = 0.04$ for difference between clusters; log-rank test).

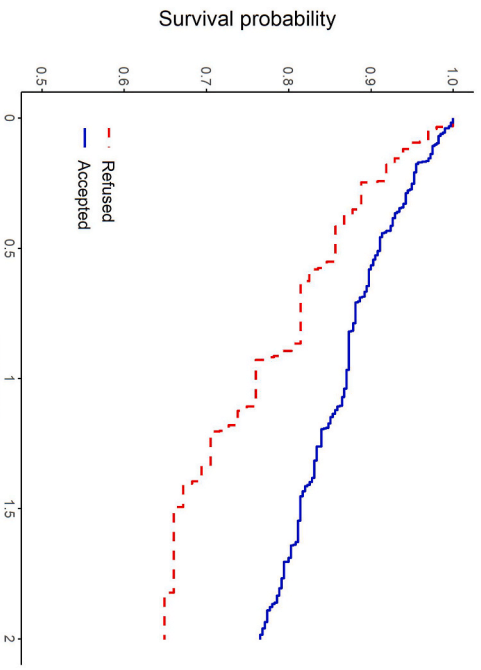

Fig. 3. Kaplan-Meier curves for primary endpoint event-free survival in the adaptive servo-ventilation (ASV)-treated group (patients who accepted or were compliant with ASV at 3-month follow-up) versus the control group (patients who refused or stopped treatment before 3-month visit follow-up.).

ASV on prognosis in chronic HF [16–18,26]. This emphasizes the need to differentiate between subgroups of HF patients who may or may not benefit from ASV treatment [27].

In that context, the current data fulfil a research gap and are highly relevant to clinical practice. First, in the complex heterogeneity of overlapping SDB and HF clinical presentation, LCA showed a continuum of SDB types in patients with HF, rather than strictly CSA or OSA. For example, even those with OSA can develop treatment-emergent CSA during CPAP therapy and these patients can benefit from switching to ASV [28]. Thus, a "one size fits all" approach to treatment will not

Table 3
Univariate and multivariate Cox model showing risk of endpoint events in the non-adaptive servo-ventilation (ASV) versus ASV group. Significant hazard ratio value above 1 illustrates a protective effect of ASV in the overall population.

Outcomes	Hazard ratio (95% confidence interval)			
	Univariate	p-value	Multivariate[a]	p-value
Death or hospitalization for worsening heart failure or heart transplant	1.67 (1.12–2.49)	0.01	1.33 (0.87–2.03)	0.18
Cardiovascular death or heart failure-related hospitalization	**2.30 (1.5–3.53)**	**<0.01**	**1.81 (1.15–2.85)**	**0.01**
All-cause death or all-cause hospitalization	**1.67 (1.21–2.31)**	**<0.01**	**1.50 (1.06–2.11)**	**0.02**
All-cause hospitalization	**1.63 (1.14–2.32)**	**0.01**	1.47 (1.01–2.14)	0.05
Heart failure-related hospitalization	**1.80 (1.11–2.93)**	**0.02**	1.41 (0.84–2.35)	0.19
All-cause death	1.14 (0.61–2.11)	0.68	0.87 (0.46–1.66)	0.67
Cardiovascular death	**2.76 (1.28–5.95)**	**<0.01**	2.03 (0.9–4.59)	0.07

[a] Adjusted for age, sex, body mass index, presence of heart failure with reduced ejection fraction, and presence of central sleep apnea.

optimize individual patient outcomes, as highlighted by our finding of very different outcomes in the ASV and no ASV groups by patient cluster. This highlights the recommendation to perform systematic deep phenotyping in these patients [29,30], including documentation of comorbidities, clinical variables, and precise characterization of SDB subtypes. Consequently, accurate scoring of obstructive and central events, and an adequate measure of hypoxic burden are particularly important because these parameters are key factors in determining prognosis and outcomes during ASV therapy.

The classification of patients with both chronic HF and SDB into clusters (or phenotypes) may help healthcare professionals in clinical decision making. The characteristics of patients in Cluster 1 [19] are most similar to the inclusion criteria of both the SERVE-HF [17] and ADVENT-HF [31] randomized clinical trials, and the cluster 2 for the ADVENT-HF trial. These two clusters were those with the less proportion of patient in NYHA class I or II, and therefore the more severe heart failure status. This may help understanding why these clusters exhibited the worst prognosis [32]. Several hypotheses for explaining cardiovascular adverse effects of ASV in SERVE-HF have been speculated. Among them the ASV device, which had a minimum pressure support above the end expiratory pressure of 3 cmH2O, and thus may not suitably control the hyperventilation state. This may particularly affect the most fragile patients enrolled in SERVE-HF (NYHA class 3 and 4, or NYHA class 2 with recent hospitalizations). Further research is required to explore whether changes in minimum pressure support settings may explain the adverse effects seen in SERVE-HF. In addition, although not reaching statistical significance (with wide confidence intervals), there was some indication that the risk of all-cause death was increased in patients from Cluster 1 who did versus did not use ASV (Table 5). Patients in Cluster 2 have characteristics similar to some patients enrolled in the ADVENT-HF study and were found not to derive any prognostic benefit with ASV therapy. It is interesting to note that all patients in Cluster 6 (older, with better preserved ejection fraction, high BMI, hypoxia, hypertension, and a high incidence of stroke/transient ischemic attack) chose to use ASV. This group mostly included those with OSA, for whom CPAP treatment does not control central events [28,33]. In our practice, this clinical situation represents nearly 3% of all patients using CPAP. It is interesting to note that patients in this cluster showed the best prognosis, and all patients accepted ASV (Fig. 2). Furthermore, in this cluster, the sensitivity analysis showed that those who used ASV for >3 h/night throughout the 2-year follow-up had a better prognosis with respect to all-cause death or hospitalization than those who were not ASV compliant (Supplementary Figs. 5 and 6). The sensitivity analysis was performed using a different definition of the untreated group (n = 171) that included all patients who dropped therapy or were using ASV less than 3 h per night compared to compliant one. Using this cutoff, we found similarly as the principal analysis an overall protective effect of ASV for the primary outcomes compared to non-compliant patient.

4.1. Study limitations

The FACE study provides important insights into the relative benefits of ASV usage in HF patients with different clinical phenotypes. However, several limitations need to be considered. One is the non-randomized design that means sources of bias may not be adequately controlled for. Nevertheless, the study population and patient clusters are representative of real-world practice and the study data may therefore offer clinically meaningful insights. However, the total number of patients in some clusters was small, limiting statistical power. Another limitation is that ASV usage (or not) was based on patient decision, and this may be associated with other factors that could influence the disease trajectory and patient outcomes, such as healthy behaviors and adherence to other treatment modalities [34]. On the other hand, ASV (like other pressure support devices) may be difficult to wear in patients with the most severe conditions. Furthermore, this study, like all cohort and observational studies, may not have accounted for some confounding factors, especially time-dependent confounders. Nevertheless, it is increasingly being acknowledged that observational studies produce data with higher levels of generalizability/external validity with regard to research participants and practice settings [35,36].

5. Conclusions

The FACE study highlights the many possible combinations of disease and patient characteristics that create a highly heterogeneous population of patients with HF and SDB. Therefore, it is essential to undertake careful patient selection and phenotyping to ensure that ASV is prescribed to patients most likely to benefit from therapy. This study confirms that patients with HFrEF, or aged patients with mild SDB do not obtain any mortality benefit from treatment with ASV. Conversely, use of ASV in patients with severe hypoxic burden (CSA or uncontrolled OSA) and those with HFpEF and SDB was associated with a significant reduction in cardiovascular events and mortality.

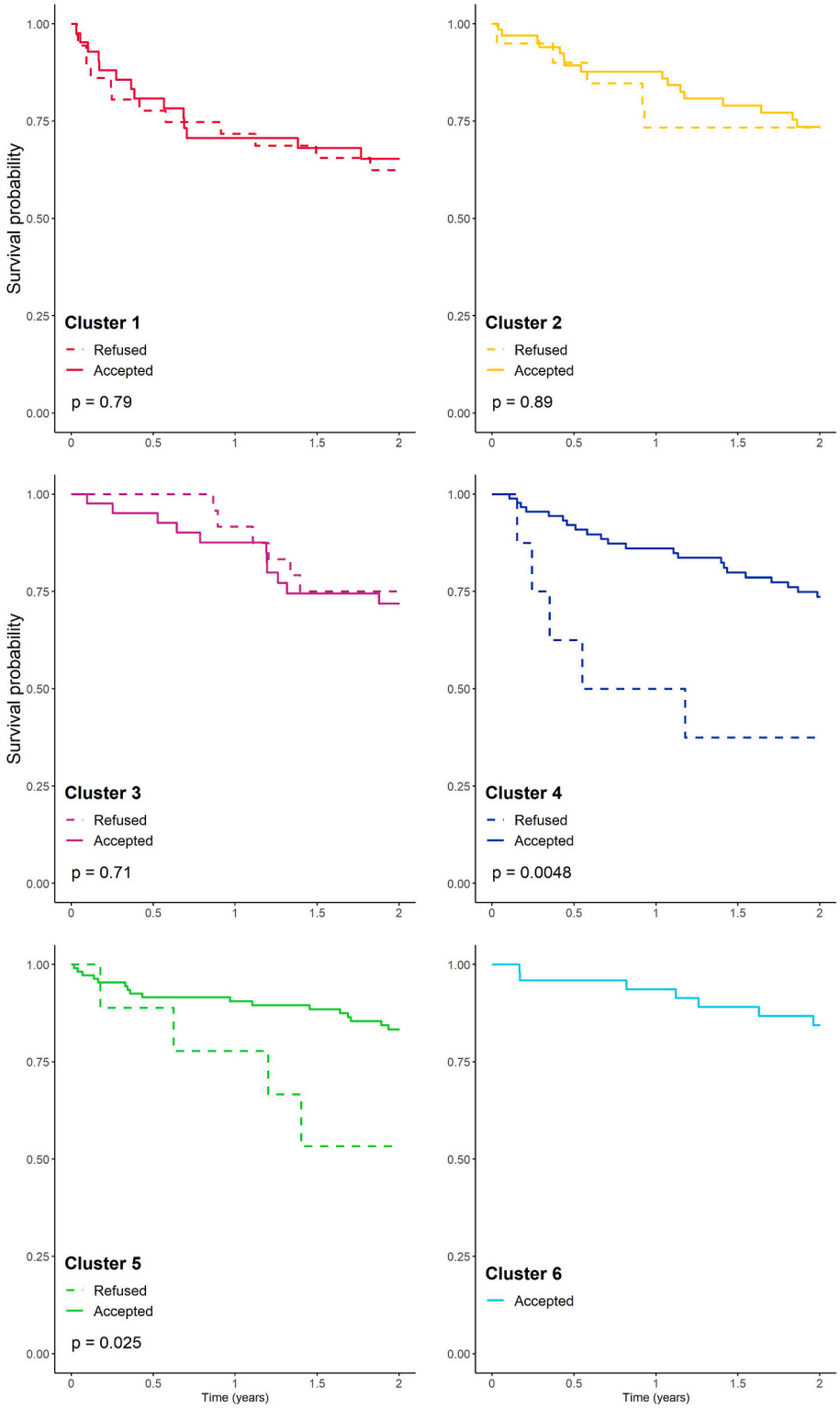

Fig. 4. Kaplan-Meier curves for primary endpoint event-free survival for patients who accepted versus refused adaptive servo-ventilation (ASV) by patient cluster (all patients in Cluster 6 accepted ASV).

Table 4
Univariate Cox model showing risk of endpoint events in the non-adaptive servo-ventilation (ASV) versus ASV group by patient cluster. Significant hazard ratio value above 1 illustrates a protective effect of ASV.

Outcomes	Hazard ratio (95% confidence interval)				
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Death or hospitalization for worsening heart failure or heart transplant	1.11 (0.52–2.36)	1.08 (0.39–2.94)	0.83 (0.31–2.25)	3.69 (1.39–9.79)**	3.26 (1.09–9.74)*
Cardiovascular death or heart failure-related hospitalization	1.92 (0.8–4.64)	1.32 (0.47–3.72)	0.91 (0.33–2.51)	**4.54 (1.49–13.85)****	**3.85 (1.26–11.75)***
All-cause death or all-cause hospitalization	1.21 (0.64–2.29)	1.36 (0.66–2.80)	0.99 (0.45–2.17)	**5.60 (2.42–13.0)****	1.62 (0.57–4.60)
All-cause hospitalization	1.61 (0.76–3.41)	1.27 (0.6–2.69)	0.91 (0.38–2.16)	**3.89 (1.32–11.45)****	1.7 (0.6–4.84)
Heart failure-related hospitalization	1.52 (0.57–4.09)	1.05 (0.34–3.23)	0.88 (0.26–3.00)	2.44 (0.55–10.86)	**3.85 (1.26–11.75)***
All-cause death	0.43 (0.14–1.38)	1.08 (0.22–5.35)	1.07 (0.3–3.81)	**3.79 (1.06–13.61)***	0
Cardiovascular death	1.06 (0.26–4.23)	1.59 (0.14–17.5)	1.59 (0.4–6.35)	**13.84 (1.95–98.45)****	0

*p < 0.05; **p < 0.01.

Table 5
Multivariate Cox model showing risk of endpoint events in the non-adaptive servo-ventilation (ASV) versus ASV group by patient cluster. Significant hazard ratio value above 1 illustrates the protective effect of ASV. Multivariate cox model was adjusted for age, sex, body mass index, presence of heart failure with reduced ejection fraction, and presence of central sleep apnea.

Outcomes	Hazard ratio (95% confidence interval)				
	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Death or hospitalization for worsening heart failure or heart transplant	1.14 (0.53–2.43)	1.21 (0.42–3.45)	0.76 (0.26–2.28)	2.26 (0.64–8.02)	2.48 (0.55–11.1)
Cardiovascular death or heart failure-related hospitalization	1.85 (0.76–4.49)	1.73 (0.58–5.16)	0.86 (0.28–2.62)	4.12 (0.85–20.04)	2.65 (0.57–12.34)
All-cause death or all-cause hospitalization	1.31 (0.69–2.50)	1.53 (0.72–3.28)	0.93 (0.37–2.33)	**4.57 (1.46–14.3)***	1.43 (0.46–4.43)
All-cause hospitalization	1.70 (0.79–3.63)	1.46 (0.66–3.23)	0.96 (0.35–2.61)	3.54 (0.88–14.27)	1.45 (0.46–4.57)
Heart failure-related hospitalization	1.51 (0.56–4.10)	1.36 (0.41–4.45)	1.05 (0.27–4.08)	2.00 (0.30–13.2)	2.65 (0.57–12.34)
All-cause death	0.47 (0.15–1.52)	0.68 (0.11–4.04)	0.76 (0.18–3.26)	1.50 (0.32–6.96)	0
Cardiovascular death	1.17 (0.29–4.75)	2.38 (0.2–27.91)	1.04 (0.22–4.96)	7.06 (0.38–130.95)	0

*p < 0.01.

Clinical perspectives

COMPETENCY IN MEDICAL KNOWLEDGE: Management strategies to improve outcomes for patients with heart failure (HF), especially those with mid-range or preserved ejection (HFmrEF or HFpEF) is increasingly focusing on comorbidities. Sleep-disordered breathing (SDB) is a common comorbidity in patients with HF and is associated with worse prognosis. This study showed that patients with HF can be categorized into six distinct clusters and that the impact of treating SDB with adaptive servo-ventilation (ASV) on clinical outcomes varies by patient phenotype. ASV had a beneficial impact on prognosis in patients with either HFmrEF and both central and obstructive sleep apnea, or HFpEF and OSA. These groups are characterized by a high proportion of male patients with obesity and high hypoxic burden.

TRANSLATIONAL OUTLOOK 1: Treatment of SDB with ASV has value in carefully selected groups of patients with HF.

TRANSLATIONAL OUTLOOK 2: Clinical management of patients with HF should include thorough evaluation and characterization of SDB, and careful phenotyping to ensure the use of ASV in patients who will achieve prognostic benefit from this therapy.

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Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request (rtamisier@chu-grenoble.fr).

CRediT authorship contribution statement

Renaud Tamisier: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Thibaud Damy:** Formal analysis, Writing – review & editing. **Sébastien Bailly:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Frédéric Goutorbe:** Writing – review & editing. **Jean-Marc Davy:** Formal analysis, Writing – review & editing. **Florent Lavergne:** Writting – review & editing. **Alain Palot:** Writing – review & editing. **Johan A. Verbraecken:** Writing – review & editing. **Marie-Pia d'Ortho:** Conceptualization, Formal analysis, Writing – review & editing. **Jean-Louis Pépin:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of competing interest

J-L.P., T.D., J-M.D., R.T. and M-P.d'O. are FACE study investigators and steering committee members for ResMed.

A.P. and F.G. are FACE study investigators for ResMed.

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Appendix A. Supplementary data

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