Registry on the Treatment of Central and Complex Sleep-Disordered Breathing with Adaptive Servo-Ventilation (READ-ASV): protocol and cohort profile

Michael Arzt[1], Oliver Munt[2], Jean-Louis Pépin[3], Raphael Heinzer[4], Raphaela Kübeck[5], Ulrike von Hehn[6], Daniela Ehrsam-Tosi[7], Adam Benjafield[8] and Holger Woehrle[9] for the READ-ASV investigators[10]

[1]Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany. [2]ResMed Science Centre, Martinsried, Germany. [3]Université Grenoble Alpes, Laboratoire HP2, U1300 Inserm, CHU Grenoble Alpes, Grenoble, France. [4]Centre d'Investigation et de Recherche sur le Sommeil, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. [5]The Clinical Research Institute, Munich, Germany. [6]medistat GmbH, Krummwisch, Germany. [7]ResMed Science Centre, Basil, Switzerland. [8]ResMed Science Center, Sydney, NSW, Australia. [9]Sleep and Ventilation Center Blaubeuren, Ulm, Germany. [10]A full list of investigators and study centres is provided in the supplementary material.

Corresponding author: Michael Arzt (michael.arzt@klinik.uni-regensburg.de)

Shareable abstract (@ERSpublications)
The most common indications for adaptive servo-ventilation in the READ-ASV registry were treatment-emergent CSA and CSA associated with cardiovascular disease; daytime sleepiness and impaired disease-specific quality of life were common https://bit.ly/3iKAkKa

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Abstract

Background Although adaptive servo-ventilation (ASV) effectively supresses central sleep apnoea (CSA), little is known about real-world indications of ASV therapy and its effects on quality of life (QoL).

Methods This report details the design, baseline characteristics, indications for ASV and symptom burden in patients enrolled in the Registry on the Treatment of Central and Complex Sleep-Disordered Breathing with Adaptive Servo-Ventilation (READ-ASV). This multicentre, European, non-interventional trial enrolled participants prescribed ASV in clinical practice between September 2017 and March 2021. An expert review board assigned participants to ASV indications using a guideline-based semi-automated algorithm. The primary end-point was change in disease-specific QoL based on the Functional Outcomes of Sleep Questionnaire (FOSQ) from baseline to 12-month follow-up.

Results The registry population includes 801 participants (age 67±12 years, 14% female). Indications for ASV were treatment-emergent or persistent CSA (56%), CSA in cardiovascular disease (31%), unclassified CSA (2%), coexisting obstructive sleep apnoea and CSA (4%), obstructive sleep apnoea (3%), CSA in stroke (2%) and opioid-induced CSA (1%). Baseline mean apnoea–hypopnoea index was 48±23 events·h^{-1} (⩾30 events·h^{-1} in 78%), FOSQ score was 16.7±3.0 (<17.9 in 54%) and Epworth Sleepiness Scale (ESS) score was 8.8±4.9 (>10 in 34%); 62% of patients were symptomatic (FOSQ score <17.9 or ESS score >10).

Conclusion The most common indications for ASV were treatment-emergent or persistent CSA or CSA in cardiovascular disease (excluding systolic heart failure). Patients using ASV in clinical practice had severe sleep-disordered breathing and were often symptomatic. One-year follow-up will provide data on the effects of ASV on QoL, respiratory parameters and clinical outcomes in these patients.

Introduction

Sleep-disordered breathing (SDB) refers to the limitation or cessation of airflow during sleep due to obstructive apnoeas and hypopneas (obstructive sleep apnoea (OSA)) or a lack of respiratory drive (central sleep apnoea (CSA)). The estimated prevalence of SDB in the general population is 1–31% in women and 3–50% in men, with variations based on age, comorbidities and ethnicity [1–4]. In patients with heart failure, rates of SDB in those with preserved, midrange or reduced ejection fraction have recently been reported to be 36%, 41% and 48%, respectively [5]. SDB has several important clinical consequences, including daytime sleepiness [6], progression or exacerbation of coexisting disease (*e.g.* hypertension, depression, diabetes, heart failure, stroke) [7–13] and impaired quality of life (QoL) [14–16].

CSA is characterised by a diminishing or cessation of respiratory drive and absence of respiratory effort [17]. Cheyne–Stokes respiration (CSR) is a type of CSA that shows a characteristic waxing and waning pattern of ventilation [17]. Continuous positive airway pressure (PAP) that splints open the upper airway is not able to adapt to the shallow breathing patterns and breathing cessation characteristic of CSA/CSR. In contrast, bilevel PAP therapy using adaptive servo-ventilation (ASV) provides a variable level of pressure support according to the needs of the patient [18, 19].

ASV has been shown to effectively ameliorate CSA by reducing the number of apnoea events and the apnoea–hypopnoea index (AHI) [20–22]. Research into the use of ASV in CSA has largely focused on patients with heart failure with reduced ejection fraction (HFrEF) [23]. Randomised clinical trial findings in this patient group resulted in a contraindication for ASV in HFrEF patients with predominant CSA and HFrEF with left ventricular ejection fraction (LVEF) ⩽45% [24, 25]. However, the prevalence of SDB is also high in patients with heart failure and preserved ejection fraction [5], a population that is expected to continue to grow [26, 27]. Although there are some data on the use of ASV in populations representative of clinical practice, studies have largely focused on patients with heart failure [28, 29]. Therefore, there remains a relative lack of data on the real-world indications for ASV, the prevalence of symptomatic CSA in ASV users and the effects of ASV in other patient groups encountered in sleep laboratory settings [30–32]. In addition, little is known about the influence of ASV therapy on health-related QoL in appropriately treated sleep clinic patients with SDB.

Therefore, to address these issues, the Registry on the Treatment of Central and Complex Sleep-Disordered Breathing with Adaptive Servo-Ventilation (READ-ASV) was designed to prospectively evaluate the effects of ASV on health-related QoL, respiratory parameters and clinical outcomes in patients with an indication for ASV therapy in routine clinical practice. This report describes the READ-ASV design and details the baseline characteristics, real-world indications for ASV, symptom burden and health-related QoL for patients who have been enrolled in the registry.

Material and methods

Registry design

READ-ASV is an observational, prospective, multicentre registry that enrolled patients from sleep facilities in countries throughout Europe between September 2017 and March 2021. Prescription of ASV was done in routine clinical care based on the decision of the treating physician according to currently applicable guidelines [30]; no additional treatments or procedures were given. The registry received ethical approval from the relevant committee at each centre. Patients gave written informed consent for the use of their medical data for scientific and educational purposes. This registry is being conducted in agreement with current guidelines and legislations as stated in the Declaration of Helsinki and Good Clinical Practice standards. Guidelines and standards for conducting clinical trials apply: European Directive 93/42/EWG, with 2007/47/EG, national applicable laws and the international standard ISO14155 for clinical trials.

Participants

Eligible patients were those aged ⩾18 years with an indication for treatment with ASV according to applicable medical guidelines who had not previously been treated with ASV (maximum time between ASV initiation and registry enrolment was 7 days) and using an eligible ASV device (ResMed) (usually after a trial of continuous PAP (CPAP) or automatically titrating PAP). In addition, patients had to be able to fully understand information on data protection and provide written informed consent for use of their medical data. Patients with contraindications for ASV therapy based on current guidelines [30, 33] were excluded (including those with chronic, symptomatic heart failure (New York Association class II–IV) with reduced LVEF (⩽45%) and moderate to severe predominant CSA).

Diagnostic procedures

Diagnosis of SDB was performed in accordance with the relevant clinical standards using overnight polysomnography (PSG) or polygraphy (PG). The choice of test was based on current national guidelines [34] and routine clinical practice at each study centre. All PSG and PG recordings were scored according to contemporary guidelines [35, 36]. Based on the number of scored events, the AHI, obstructive apnoea index, central apnoea index and mixed apnoea index were calculated per hour of sleep (PSG) or per hour of recording time (PG). Invalid recordings were excluded and the mean values of the documented recordings were calculated with the number of recordings indicated. Data obtained from PSG also included the average and lowest oxygen saturation during sleep. PG recordings provided data on the number of oxygen desaturations (by 3% from baseline) per hour of recording time.

Classification of ASV indications

Patients were classified based on their underlying SDB (AHI ⩾5 events$\cdot$h^{-1}) and the indication for ASV therapy using data from PSG or PG. The first step in categorising the indication for ASV therapy followed a hierarchical order and was modified from the classification by Randerath *et al.* (table 1) [30]. Thus, when category 1 criteria were not met, eligibility based on category 2 was determined, then category 3 and so on. When cases could not be categorised unequivocally, they were evaluated by an expert review board on a case-by-case basis (figure 1), *e.g.* cases with coexisting OSA–CSA were all a result of the expert review board evaluation. Patients with treatment-emergent CSA (TE-CSA) had an initial diagnosis of OSA or coexisting OSA–CSA and developed new or predominant CSA events during PAP therapy. Data on comorbidities were used to help further refine the indication for ASV.

Baseline assessment of QoL and symptom burden

The following data were collected at baseline: demographic/clinical data, previous ventilation therapy and diagnostic PSG or PG findings. Patients completed the Functional Outcomes of Sleep Questionnaire (FOSQ), Epworth Sleepiness Scale (ESS) and EuroQol-5-Dimension Scale (EQ-5D) at baseline and follow-up; the Pittsburgh Sleep Quality Index (PSQI) was also completed by the first group of enrolled patients, but use of this measure was discontinued based on a protocol amendment dated 16 April 2019 after data from a pilot phase showed that a high proportion of these questionnaires were either not returned or filled out incorrectly.

The FOSQ consists of 30 questions (items) divided into five sub-sections: activity level, vigilance, intimate relationship, general productivity and social outcome. Each question is scored from 1 to 4. The total score ranges from 5 to 20, indicating poor to excellent sleep-related QoL, respectively [37]. The minimal clinically important difference (MCID) in FOSQ score is 1 point [38]. A normal FOSQ score was defined as ⩾17.9 [39].

The ESS is a self-reported measure to assess whether a person would be prone to fall asleep in typical daily situations. It consists of eight questions that can be answered on a scale from 0 (never fall asleep) to 3 (high probability of falling asleep). The total score ranges from 0 to 24, with a score of 6–10 indicating higher normal daytime sleepiness, and scores of 11–12, 13–15 and 16–24 indicating mild, moderate and severe excessive daytime sleepiness (EDS), respectively. A 2-point change in total score has been proposed as the MCID for this measure in patients with OSA [40].

The PSQI contains ten questions divided into seven components, which are rated from 0 (better) to 3 (worse). The seven component scores are added together to get a global score, ranging from 0 to 21 [41]. A threshold score of ⩽5 indicates "good sleep quality" while a global score of >5 indicates "poor sleep quality". The MCID for the PSQI is defined as 3 points [42].

TABLE 1 Hierarchical categorisation of patient subgroups based on indication for adaptive servo-ventilation therapy

Category	Indication for ASV	Definition
1	Treatment-emergent or persistent CSA	Initial diagnosis of OSA, developed central events or central events persisted during a trial of PAP therapy; or the investigator indicated treatment-emergent or persistent CSA
2	CSA in cardiovascular disease	Initial diagnosis of CSA with coexisting heart failure, atrial fibrillation, coronary artery disease or hypertension (if history of stroke does not prevail)
3	CSA in stroke	Initial diagnosis of CSA with a history of stroke
4	Opioid-induced CSA	Initial diagnosis of CSA and use of opioids
5	Unclassified (idiopathic) CSA	CSA in the absence of other comorbidities
7a	OSA	Initial diagnosis of OSA, and OSA persisted during PAP therapy
7b	Coexisting OSA and CSA	Initial diagnosis of coexisting OSA–CSA or mixed apnoeas that persisted during a trial of PAP therapy, or a diagnosis of OSA where obstructive/central events or mixed apnoeas still occurred during PAP therapy Due to the complexity of this diagnosis, cases in this category were all a result of the expert review board evaluation

ASV: adaptive servo-ventilation; CSA: central sleep apnoea; OSA: obstructive sleep apnoea; PAP: positive airway pressure. Reproduced and modified from [30] with permission.

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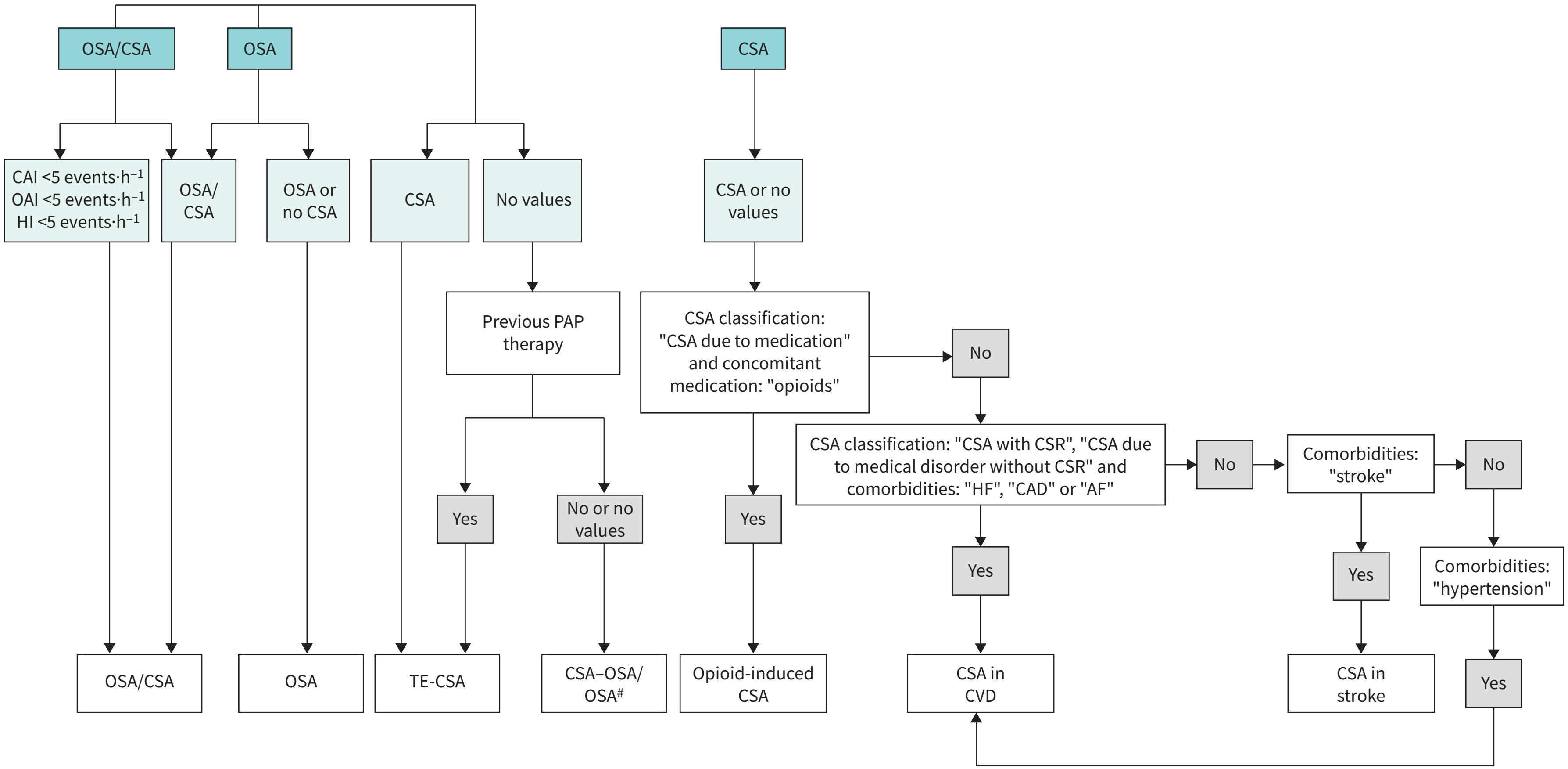

FIGURE 1 Schematic classification of indications for adaptive servo-ventilation (ASV) therapy as defined during expert review board classification. Teal boxes represent diagnostic findings (*e.g.* diagnostic polysomnography or polygraphy or, if these were not available, based on the aetiology provided by the investigator) and blue boxes represent findings during standard positive airway pressure (PAP) therapy but also take into account the reason for a switch to ASV therapy provided by the investigator. OSA: obstructive sleep apnoea; CSA: central sleep apnoea; CAI: central apnoea index; OAI: obstructive apnoea index; HI: hypopnoea index; CSR: Cheyne–Stokes respiration; HF: heart failure; CAD: coronary artery disease; AF: atrial fibrillation; TE-CSA: treatment-emergent or persistent central sleep apnoea; CVD: cardiovascular disease. #: depending on diagnostic information.

The EQ-5D [43] was used to measure changes in general QoL. Each of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) has three response levels: no problems (score=1), some problems (score=2) and extreme problems (score=3) [44]. In addition, the EQ visual analogue scale (VAS) records the respondent's self-related health on a vertical VAS, with one end of the scale labelled "The worse health you can imagine" (VAS score=0) and the other labelled "The best health you can imagine" (VAS score=100) [44]. An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health [44].

Primary analysis outcomes

The primary outcome for the follow-up analysis is the change in FOSQ score from baseline to follow-up. Secondary outcomes are changes in ESS and EQ-5D scores, change in PSQI score (for patients who completed this questionnaire), device usage patterns, changes in nocturnal respiratory parameters during ASV, the number of hospitalisations for cardiovascular or respiratory causes, and the all-cause mortality rate per year of follow-up. ASV adherence was defined as "good" if device usage was $\geqslant$4 h·day^{-1} on >70% of days. These data will be reported separately when data collection and analysis are complete.

Assessments and follow-up

For the main analysis, follow-up will also include data on device usage and residual respiratory events (downloaded from the ASV device) and adverse events. Data on deaths (any cause) and hospitalisations (due to cardiovascular or respiratory causes) are being collected throughout the study. Patients are being followed up according to local standard practice. This recommends that clinical visits take place one to two times per year, meaning that all participants in the registry should have at least one follow-up visit during the 12-month follow-up period. When an in-person follow-up visit is not possible, follow-up data are collected over the phone or by mail (including severity of SDB and changes in QoL and daytime sleepiness), and device data are downloaded remotely. Reasons for permanent discontinuation of ASV therapy are documented, and characteristics of patients who discontinue therapy are analysed.

Protocol amendments

The first part of the registry comprised a feasibility phase (July 2017 to December 2018), then participating centres were directly transitioned into the main phase in July 2019 (after protocol amendment). Datasets from the two phases will be combined for all analyses. Key protocol amendments included 1) updating the exclusion criteria (chronic, symptomatic heart failure (New York Heart Association class II–VI) with LVEF $\leqslant$45% and moderate to severe predominant CSA), 2) specifying that "naïve to ASV treatment" was defined as a maximum of 7 days between start of ASV therapy and enrolment into the registry and 3) discontinuing use of the PSQI for newly enrolled study patients. Study patients enrolled during the feasibility phase were followed up according to the previous protocol version valid for the feasibility phase.

Sample size

A formal sample size calculation was not performed for this registry. However, a large number of participants is needed to reflect subpopulations such as patients with CSA and stroke or opioid-induced CSA. Therefore, the goal was to enrol up to 1000 patients.

Data analysis plan

Continuous variables are summarised using the number of observations, mean values with standard deviation and/or median values with range. Categorical variables are summarised using the number of observations and percentages.

Linear, logistic or Cox regression models were used to examine the influence of clinical parameters, comorbidities, sleep apnoea characteristics, ASV interface and respiratory events on changes in QoL, sleep quality and compliance during ASV therapy. Linear regression analyses were used to evaluate relationships between hours of ASV usage and QoL outcomes.

Statistical tests were two-sided with a significance level of 5%. Owing to the descriptive nature of the present analysis, no alpha adjustment for multiple testing was applied and the results were interpreted accordingly. Statistical analyses were performed using IBM SPSS Statistics 28 (SPSS Inc., Chicago, IL, USA).

Dissemination

The follow-up results of the READ-ASV registry will be presented at regional, national and international conferences and scientific meetings, with publication in a peer-reviewed journal.

Results

Population

A total of 847 patients were enrolled in the registry. Of these, 22 were not naïve to ASV therapy, 12 did not start ASV therapy (no device, use of other therapy or refusal of ASV) and one patient was found not to meet the inclusion criteria. A further 11 patients were excluded from analyses because it was not possible to classify them by indication for ASV. Therefore, the analysis population included 801 patients (14% female, mean age 67 years, mean body mass index 30.9 $kg \cdot m^{-2}$) (table 2). All 25 patients who had heart failure with LVEF <50% were receiving medical therapy, including an aldosterone antagonist (n=7), angiotensin-converting enzyme inhibitor or angiotensin receptor blocker (n=17), diuretic (n=19), β-blocker (n=19) or antiarrhythmic (n=1); 19 patients were taking a combination of two or more medications.

Indication for ASV

Baseline SDB diagnostic testing was performed using PSG in 509 patients (64%) and PG in 188 patients (23%); full PSG and PG datasets were not available for 104 patients (13%) who had undergone diagnostic testing at another institution prior to transfer to the registry centre (local routine did not call for another diagnostic study).

Based on PSG/PG findings, the indication for ASV therapy was TE-CSA (n=452, 56%), CSA in cardiovascular disease (n=249, 31%), CSA in stroke (n=18, 2%), opioid-induced CSA (n=10, 1%), unclassified CSA (n=14, 2%), coexisting OSA–CSA (n=33, 4%) or OSA (n=25, 3%) (figure 2, table 2). By definition, rates of cardiovascular disease and cardiovascular disease risk factors were lowest in the opioid-induced CSA and unclassified CSA subgroups; the latter two groups also had the lowest mean age compared with the other groups (table 2). The rate of opioid usage was low in all groups apart from the opioid-induced CSA group, which also had a high rate of depression (table 2). Use of other medications reflected the comorbidity profile in each group (table 2). Of the 180 patients who had heart failure (22%), nearly all had preserved or midrange ejection fraction (table 2).

SDB was classified as severe (AHI ⩾30 $events \cdot h^{-1}$) in 78% of patients, moderate (AHI ⩾15 and <30 $events \cdot h^{-1}$) in 18% and mild (AHI ⩾5 and <15 $events \cdot h^{-1}$) in 4%. Mean AHI for the total population was 48.5±22.2 $events \cdot h^{-1}$; mean AHI was highest in the subgroups with opioid-induced CSA (62.8±37.3 $events \cdot h^{-1}$) and coexisting OSA–CSA (49.3±22.2 $events \cdot h^{-1}$) and lowest in those with unclassified CSA (31.6±12.1 $events \cdot h^{-1}$) (table 3). The data presented in table 3 were the latest available diagnostic PG/PSG measurements without PAP therapy (median number of days between diagnostic PG/PSG and enrolment was 42 days). In the TE-CSA group the mean central apnoea index was 6±7 $events \cdot h^{-1}$ (table 3) without therapy and 14±13 $events \cdot h^{-1}$ on CPAP or bilevel PAP therapy without back-up frequency (before the prescription of ASV/inclusion in the registry).

Overall, the severity of sleep apnoea was similar between men and women, with a higher proportion of obstructive apnoeas compared with central apnoeas in women *versus* men (supplementary table S1).

Baseline symptom burden and health-related QoL

The average FOSQ score at baseline (16.7±3.0; n=756) indicated that the patient population had impaired health-related QoL. Mean FOSQ scores were generally similar between the different patient subgroups, except for the opioid-induced CSA group, which had greater health-related QoL impairment than the other groups (mean baseline FOSQ score 12.6±3.5). The proportion of patients with a FOSQ score <17.9 was highest in the opioid-induced CSA and unclassified CSA groups but was above 50% in all groups except for those with coexisting OSA–CSA (figure 3a).

The mean ESS score at baseline (8.8±5; n=720) was not indicative of EDS overall. However, the mean ESS score in individuals with opioid-induced CSA or unclassified CSA (11.9±4.1 and 11.6±6.3, respectively) indicated mild EDS in these subgroups. Again, it was the opioid-induced and unclassified CSA groups that had the highest proportion of patients with an ESS score >10, but at least a third of patients in the other indication groups had an ESS score indicative of EDS (figure 3b).

The proportion of symptomatic patients (FOSQ score <17.9 or ESS score >10) was 62% overall, ranging from 54% in the coexisting OSA–CSA group to 80% and 90% in the CSA in stroke and opioid-induced CSA groups, respectively (figure 3c). More than two-thirds of patients in all indication groups, apart from OSA, had a PSQI score >5 at baseline, indicating poor sleep quality (supplementary figure S1).

Overall, 414 of 756 patients with evaluation of the FOSQ score and 397 of 720 with evaluation of the ESS score had received another form of PAP therapy previously. A group-wise comparison of mean FOSQ and

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TABLE 2 Demographic data, comorbidities and medication for the total study population, and in patient subgroups based on indication for adaptive servo-ventilation therapy

	Total	TE-CSA	CSA in CVD	CSA in stroke	Opioid-induced CSA	Unclassified CSA	OSA–CSA	OSA
Patients, n	801	452	249	18	10	14	33	25
Age, years	67.0±11.8	67.3±11.8	67.9±10.2	66.2±11.8	49.6±8.4	48.2±15.6	67.2±13.3	68.2±12.6
Female	112 (14.0)	66 (14.6)	26 (10.4)	1 (5.6)	3 (30.0)	2 (14.3)	6 (18.2)	8 (32.0)
Body mass index, kg·m^{-2}	30.9±5.4	31.6±5.6	30.2±4.8	28.2±3.6	29.2±6.2	27.9±4.0	31.4±5.6	31.5±6.1
Cardiovascular risk factors and comorbidities								
Hypertension	629 (78.5)	342 (75.7)	228 (91.6)	11 (61.1)	1 (10.0)	0 (0.0)	26 (78.8)	21 (84.0)
Diabetes	203 (25.3)	115 (25.4)	65 (26.1)	5 (27.8)	0 (0.0)	0 (0.0)	12 (36.4)	6 (24.0)
Atrial fibrillation	257 (32.1)	122 (27.0)	112 (45.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (48.5)	7 (28.0)
Coronary artery disease	233 (29.1)	116 (25.7)	102 (41.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (27.3)	6 (24.0)
Heart failure	185 (23.1)	105 (23.2)	66 (26.9)	0 (0.0)	0 (0.0)	0 (0.0)	10 (30.3)	4 (16.0)
HFpEF	160	95	51	0	0	0	10	4
HFmrEF	24	10	14	0	0	0	0	0
HFrEF	1	0	1	0	0	0	0	0
Stroke	92 (11.5)	47 (10.4)	22 (8.8)	18 (100.0)	0 (0.0)	0 (0.0)	1 (3.0)	4 (16.0)
Depression	92 (11.5)	53 (11.7)	22 (8.8)	3 (16.7)	3 (30.0)	2 (14.3)	5 (15.2)	4 (16.0)
Medication								
Opioids	86 (10.7)	38 (8.4)	26 (10.4)	3 (16.7)	10 (100.0)	0 (0.0)	3 (9.1)	6 (24.0)
Aldosterone antagonists	67 (8.4)	41 (9.1)	19 (7.6)	2 (11.1)	0 (0.0)	0 (0.0)	3 (9.1)	2 (8.0)
ACE inhibitors	391 (48.8)	214 (47.3)	146 (58.6)	7 (38.9)	1 (10.0)	0 (0.0)	14 (42.4)	9 (36.0)
Diuretics	333 (41.6)	175 (38.7)	120 (48.2)	7 (38.9)	3 (30.0)	0 (0.0)	14 (42.4)	14 (56.0)
β-blocker	422 (52.7)	226 (50.0)	154 (61.8)	5 (27.8)	3 (30.0)	0 (0.0)	19 (57.6)	15 (60.0)

Data are presented as n (%) or mean±SD, unless otherwise indicated. TE-CSA: treatment-emergent or persistent central sleep apnoea; CSA: central sleep apnoea; CVD: cardiovascular disease; OSA: obstructive sleep apnoea; HFpEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with midrange ejection fraction; HFrEF: heart failure with reduced ejection fraction; ACE: angiotensin-converting enzyme.

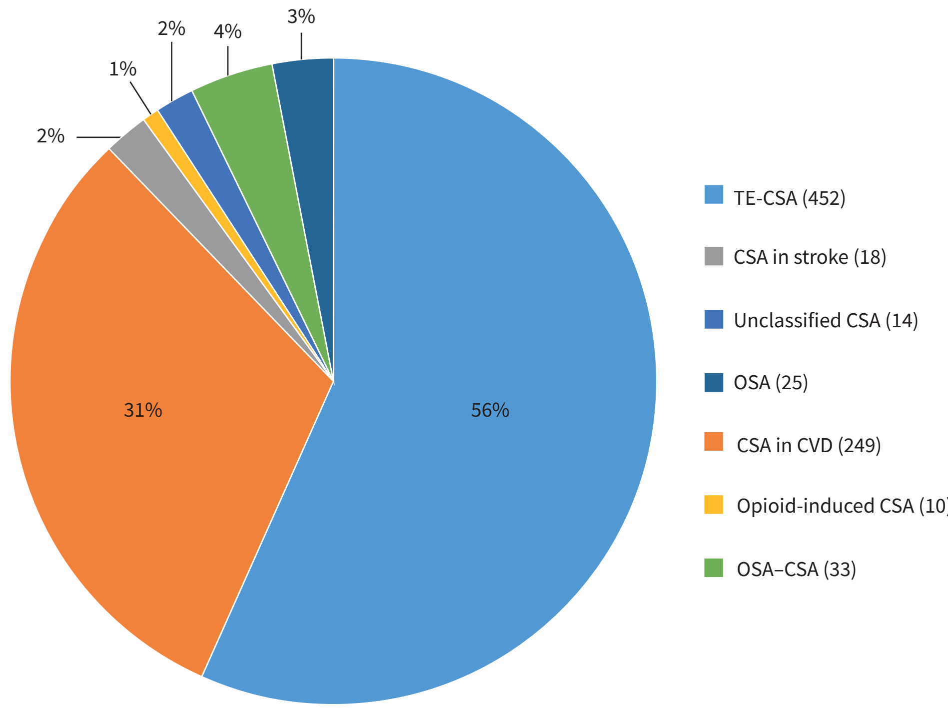

FIGURE 2 Indication for adaptive servo-ventilation therapy. TE-CSA: treatment-emergent or persistent central sleep apnoea; CSA: central sleep apnoea; CVD: cardiovascular disease; OSA: obstructive sleep apnoea.

ESS scores did not find any significant differences between those with *versus* without previous usage of CPAP or bilevel PAP therapy (FOSQ 16.6±3.1 *versus* 16.7±3.0, respectively, p=0.875; ESS score 8.9±5.2 *versus* 8.7±4.8, respectively, p=0.628).

Baseline findings for general QoL were consistent with data on sleepiness and disease-specific QoL, with opioid users having severely impaired QoL and patients with all other ASV indications also have impaired general QoL (supplementary figure S2).

Despite having similar sleep apnoea severity, women reported a higher symptom burden, longer sleep onset latency and more impaired health-related QoL than men and were more likely to be symptomatic (FOSQ score <17.9 or ESS score >10) (supplementary table S2).

TABLE 3 PG/PSG findings (last available diagnostic PG/PSG without any PAP therapy) for the total study population, and in patient subgroups based on indication for adaptive servo-ventilation therapy

	Total	TE-CSA[#]	CSA in CVD	CSA in stroke	Opioid-induced CSA	Unclassified CSA	OSA–CSA	OSA
Patients, n	801	452	249	18	10	14	33	25
AHI	48±22 (694)	49±23 (354)	48±20 (246)	48±27 (18)	70±35 (9)	32±12 (14)	49±22 (32)	45±21 (21)
CAI	13±14 (576)	6±7 (264)	20±14 (240)	25±26 (17)	33±25 (9)	11±8 (14)	7±7 (25)	3±3 (7)
OAI	15±16 (591)	20±17 (337)	5±4 (180)	7±6 (10)	8±9 (7)	3±3 (7)	18±15 (29)	32±19 (21)
MAI	9±10 (434)	8±10 (229)	9±12 (155)	7±5 (7)	10±17 (7)	5±2 (3)	11±9 (24)	2±1 (9)
HI	19±14 (663)	20±14 (339)	19±15 (234)	19±13 (17)	24±21 (9)	18±11 (14)	20±16 (29)	11±10 (21)

Data are presented as the mean±SD number of events per hour (number of patients with data), unless otherwise stated. PG: polygraphy; PSG: polysomnography; PAP: positive airway pressure; TE-CSA: treatment-emergent or persistent central sleep apnoea; CSA: central sleep apnoea; CVD: cardiovascular disease; OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; CAI: central apnoea index; OAI: obstructive apnoea index; MAI: mixed apnoea index; HI: hypopnoea index. [#]: in the TE-CSA group on continuous or PAP therapy without back-up frequency (before the prescription of adaptive servo-ventilation/inclusion in the registry), the mean CAI was per definition numerically higher compared to the diagnostic PG/PSG (14±13 events·h^{-1} *versus* 6±7 events·h^{-1}).

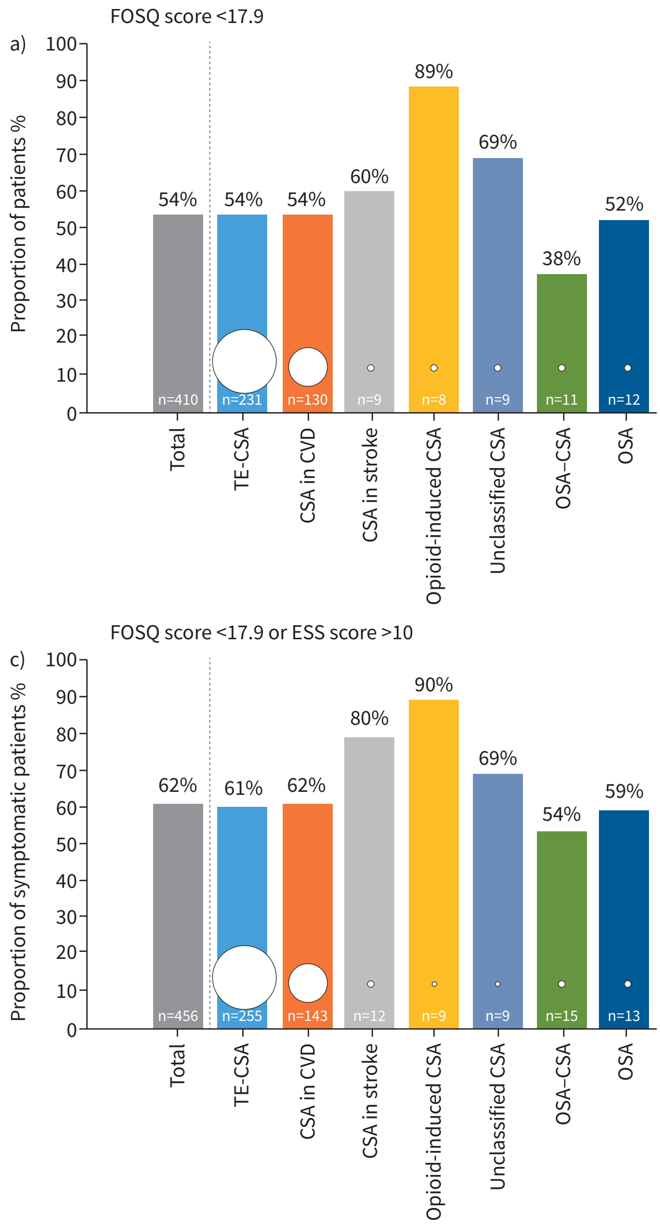

FIGURE 3 Proportion of patients in the total population and by indication subgroup that was symptomatic based on a) a Functional Outcomes of Sleep Questionnaire (FOSQ) score <17.9 (n=410 of 756), b) an Epworth Sleepiness Scale (ESS) score >10 (n=246 of 720) and c) an FOSQ score <17.9 or an ESS score >10 (n=456 of 736). The numbers and circles at the bottom of the columns indicate the size of the respective subgroup. TE-CSA: treatment-emergent or persistent central sleep apnoea; CSA: central sleep apnoea; CVD: cardiovascular disease; OSA: obstructive sleep apnoea.

Discussion

Key findings from the baseline data of READ-ASV include the identification of TE-CSA and CSA in cardiovascular disease as the most common indications for ASV therapy in clinical practice, the presence of severe sleep apnoea in most participants, a high symptom burden and moderately impaired health-related QoL.

Although the findings of the SERVE-HF study [25] resulted in a clear contraindication for ASV in patients with heart failure and LVEF ⩽45%, this group only comprises a small subset of the total group that could be treated with ASV [45, 46], and there are also non-heart failure patients with a variety of forms of SDB who could benefit from ASV therapy [47]. READ-ASV is the largest prospective registry or study to date investigating the usage and effects of ASV in a real-world cohort with SDB. One real-world registry with

214 enrolled patients has reported data on the clinical characteristics of patients receiving ASV in clinical practice [48]. There is only one other registry (FACE) that has recruited patients receiving ASV therapy in the post-SERVE-HF era, but the focus was still largely on use of ASV in patients with heart failure [29]. The FACE study was initiated prior to 2015, but inclusion/exclusion criteria were modified to exclude patients with predominant CSA and a LVEF of ⩽45% after publication of the SERVE-HF study findings [29]. Three-month follow-up data from that study, which included 503 patients, were used to define six clinically relevant subgroups (phenotypes) for patients with heart failure and SDB [28]. Acceptance of ASV therapy was highest in the subgroups characterised by a high proportion of older, male patients with higher body mass index, hypoxia and comorbidities such as hypertension and stroke [28]. These patients also comprised some of the READ-ASV registry population who were prescribed ASV. However, indications for ASV were broader than just those relating to cardiovascular disease.

TE-CSA was the most common indication for ASV in the READ-ASV registry, documented in approximately half of all patients. This is consistent with data from a German study, which reported that TE-CSA was the indication for ASV therapy in 67% of the 264 patients studied [49]. In contrast, 20% of patients enrolled in a prospective study of ASV in clinical practice had TE-CSA, whereas most ASV users (60%) had pre-existing CSA [48]. The official definition of TE-CSA states that cardiovascular disease should be ruled out as a cause for TE-CSA [30]. However, the definition used in this registry simply required patients to have an initial diagnosis of OSA and then to have persistent or newly developed CSA during a trial of CPAP, irrespective of the presence of comorbidities (including cardiovascular disease). This difference compared with current guidelines is a limitation of the registry. However, most patients with TE-CSA also have cardiovascular comorbidities, as also documented in other registries [48–50]. Furthermore, the prevalence of TE-CSA or persistent CSA in patients with normal levels of B-type natriuretic peptide has been shown to be low [51], while TE-CSA is common in patients with OSA and heart failure initially treated with CPAP [50]. Another limitation is the lack of systematic detailed information regarding the time between the initiation of CPAP and a subsequent prescription for ASV as well as details of the CPAP titration procedure such as pressure overshooting or leakage. Taken together, these data highlight the close association between TE-CSA and cardiovascular disease, and suggest that the definition used in our registry is applicable to real-world practice.

Findings have to be interpreted in the light of the following limitations. Although PSG is considered to be the gold standard to diagnose the severity and type of SDB, some patients in the European READ-ASV registry were diagnosed using PG according to national guidelines and routine clinical practice. This may have led to an underestimation of the AHI in those patients diagnosed using PG. Because specific criteria to classify central and obstructive hypopneas, such as arousal timing and classification of rapid eye movement (REM) and non-REM sleep from PSG [52], were not available in all patients, discrimination between OSA and CSA was based on discrimination between central and obstructive apnoeas as described and validated previously [53]. It cannot be ruled out that some patients with a small proportion of apnoeas may have been misclassified to CSA rather than OSA in clinical routine.

A strength of READ-ASV is the recruitment of 112 women with an indication for ASV, who, compared to men, have fewer cardiovascular comorbidities and are less often diagnosed with CSA [5]. Women reported a higher symptom burden and more impaired health-related QoL than men, despite having similar sleep apnoea severity (supplementary tables S1 and S2).

Although our data and others [49] indicate that ASV is often used for the management of TE-CSA in clinical practice, there has not yet been a single randomised controlled trial of ASV in this patient population. This is an important area for future research, but a consistent definition of TE-CSA needs to be determined to allow robust studies designed to facilitate better understanding of the effects of ASV in TE-CSA.

In addition to showing that TE-CSA is predominantly a "cardiovascular cohort", CSA in cardiovascular disease was the second-most common indication for ASV therapy in the real-world READ-ASV registry, in line with previous findings [49]. This highlights the close association between the presence of CSA and cardiovascular disease, and is the area where most previous research on ASV has been focused, including both clinical trials and registry data [23, 28, 29, 54]. Some patients with cardiovascular disease (specifically those with systolic heart failure and LVEF ⩽45%) should not be treated with ASV, but this is a small subset of the total number of patients who might benefit from therapy.

One point to note when interpreting data from READ-ASV is that hypertension was included in the hierarchical definition of cardiovascular disease in this study. While not strictly a cardiovascular disease itself, hypertension is one of the most important cardiovascular disease risk factors [55, 56]. Furthermore, hypertension was a common comorbidity in patients who accepted ASV therapy in the FACE study, highlighting the relevance of coexisting hypertension in patients with SDB.

In this sleep clinic population with indications for ASV therapy, the proportion of symptomatic patients was relatively high, at 62%. Looking at an ESS score >10 only, the proportion of patients in the current registry meeting the criteria for EDS was 34%, much higher than in the SchlaHF-XT registry where 14% of patients had an ESS score of ⩾11 [5]. In contrast to our sleepy and symptomatic patient group, the FACE registry included a non-sleepy population with a median ESS score of 7 [29], while the mean ESS score at baseline in the SERVE-HF and CAT-HF trials was also indicative of a lack of daytime sleepiness [25, 57]. This is not unexpected because patient selection criteria for the READ-ASV registry differ from those in clinical trials where it is not ethical to randomise symptomatic patients to a control/untreated group. In addition, the majority of ASV studies to date have been conducted in patients with CSA and HFrEF. However, this patient group is characterised by a lack of sleepiness [58, 59], meaning they are less likely to have impaired health-related QoL and making it very difficult to determine the effects of ASV on important patient-reported outcomes such as symptoms and QoL. Some indication for an improvement in QoL has been reported for patients with heart failure and CSA based on a meta-analysis of available clinical trial data, but evidence quality is low and study heterogeneity is high [23].

The high proportion of patients categorised as symptomatic at baseline means that the READ-ASV registry is well placed to determine the effects of ASV on the primary analysis end-point of health-related QoL. This is a clinically relevant end-point for symptomatic patients and allows holistic evaluation of the therapeutic effects of ASV.

Thus, although randomised clinical trials theoretically provide the highest levels of clinical evidence, the external generalisability of data from randomised controlled trials of ASV is limited by the necessity for strict patient inclusion and exclusion criteria, and the enrolment of patients without relevant daytime sleepiness or impaired QoL. Therefore, the goal of the READ-ASV registry is to fill these knowledge gaps based on real-world data from patients treated with ASV therapy. Data from this and other registries in the field, such as FACIL-VAA (NCT02835638) and FACE [28, 29], will provide important data to help inform healthcare decision-making [60]. Baseline data show that this clinically relevant population includes mostly patients with TE-CSA or CSA in cardiovascular disease, who have severe sleep apnoea and moderate functional impairment.

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