Adaptive servo-ventilation for sleep-disordered breathing in patients with heart failure with reduced ejection fraction (ADVENT-HF): a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial

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Summary

Background In patients with heart failure and reduced ejection fraction, sleep-disordered breathing, comprising obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), is associated with increased morbidity, mortality, and sleep disruption. We hypothesised that treating sleep-disordered breathing with a peak-flow triggered adaptive servo-ventilation (ASV) device would improve cardiovascular outcomes in patients with heart failure and reduced ejection fraction.

Methods We conducted a multicentre, multinational, parallel-group, open-label, phase 3 randomised controlled trial of peak-flow triggered ASV in patients aged 18 years or older with heart failure and reduced ejection fraction (left ventricular ejection fraction ≤45%) who were stabilised on optimal medical therapy with co-existing sleep-disordered breathing (apnoea-hypopnoea index [AHI] ≥15 events/h of sleep), with concealed allocation and blinded outcome assessments. The trial was carried out at 49 hospitals in nine countries. **Sleep-disordered breathing was stratified into predominantly OSA with an Epworth Sleepiness Scale score of 10 or lower or predominantly CSA.** Participants were randomly assigned to standard optimal treatment alone or standard optimal treatment with the addition of ASV (1:1), stratified by study site and sleep apnoea type (ie, CSA or OSA), with permuted blocks of sizes 4 and 6 in random order. Clinical evaluations were performed and Minnesota Living with Heart Failure Questionnaire, Epworth Sleepiness Scale, and New York Heart Association class were assessed at months 1, 3, and 6 following randomisation and every 6 months thereafter to a maximum of 5 years. The primary endpoint was the cumulative incidence of the composite of all-cause mortality, first admission to hospital for a cardiovascular reason, new onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock. All-cause mortality was a secondary endpoint. Analysis for the primary outcome was done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov (NCT01128816) and the International Standard Randomised Controlled Trial Number Register (ISRCTN67500535), and the trial is complete.

Findings The first and last enrolments were Sept 22, 2010, and March 20, 2021. Enrolments terminated prematurely due to COVID-19-related restrictions. 1127 patients were screened, of whom 731 (65%) patients were randomly assigned to receive standard care (n=375; mean AHI 42·8 events per h of sleep [SD 20·9]) or standard care plus ASV (n=356; 43·3 events per h of sleep [20·5]). Follow-up of all patients ended at the latest on June 15, 2021, when the trial was terminated prematurely due to a recall of the ASV device due to potential disintegration of the motor sound-abatement material. Over the course of the trial, 41 (6%) of participants withdrew consent and 34 (5%) were lost to follow-up. **In the ASV group, the mean AHI decreased to 2·8–3·7 events per h over the course of the trial, with associated improvements in sleep quality assessed 1 month following randomisation.** Over a mean follow-up period of 3·6 years (SD 1·6), ASV had no effect on the primary composite outcome (180 events in the control group *vs* 166 in the ASV group; hazard ratio [HR] 0·95, 95% CI 0·77–1·18; p=0·67) or the secondary endpoint of all-cause mortality (88 deaths in the control group *vs.* 76 in the ASV group; 0·89, 0·66–1·21; p=0·47). For patients with OSA, the HR for all-cause mortality was 1·00 (0·68–1·46; p=0·98) and for CSA was 0·74 (0·44–1·23; p=0·25). No safety issue related to ASV use was identified.

Interpretation In patients with heart failure and reduced ejection fraction and sleep-disordered breathing, ASV had no effect on the primary composite outcome or mortality but eliminated sleep-disordered breathing safely.

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Research in context

Evidence before this study

We searched the English literature in PubMed using the search terms "heart failure", "sleep-disordered breathing", "obstructive sleep apnoea", "central sleep apnoea", "clinical trials", and "positive airway pressure" for studies published from Jan 1, 1981, to Apr 30, 2023. Sleep-disordered breathing, comprising obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), is common and associated with increased morbidity, mortality, and poor sleep quality in patients with heart failure with reduced ejection fraction. However, to date, there is no evidence from randomised controlled trials that treating OSA or CSA in patients with heart failure and reduced ejection fraction improves morbidity, mortality, overall sleep quality, or quality of life, and to our knowledge, no large randomised controlled trial involving patients with heart failure and reduced ejection fraction has assessed the effects of treating OSA on these outcomes. A small trial involving patients with heart failure with reduced ejection fraction and OSA reported that continuous positive airway pressure (CPAP) reduced the frequency of arousals from sleep but did not improve sleep quality. Regarding CSA, a multicentre trial showed that CPAP attenuated but did not abolish CSA, and had no effect on morbidity, mortality, or sleep quality. However, among a subset in whom CPAP did abolish CSA, mortality was lower than in the control group whose CSA was not treated. These results led to the hypothesis that, to improve outcomes in people with CSA, abolition of CSA might be a crucial therapeutic target. Adaptive servo-ventilation (ASV) was initially developed specifically to control CSA, but not OSA. Because we planned to treat both OSA and CSA in this trial, we used a newer iteration of ASV designed to control both OSA and CSA. While the present trial was in progress, the results of a randomised controlled trial involving patients with heart failure and reduced ejection fraction and CSA (the SERVE-HF trial) were published, in which the initial iteration of ASV did control CSA but increased mortality. Based on this finding, the European Society of Cardiology Guidelines for the treatment of chronic heart failure concluded that, in patients with heart failure and reduced ejection fraction, ASV is contraindicated for people with CSA. Consequently, its clinical use for this purpose ceased. Taken together, those previous trials leave unanswered the question of whether treating OSA in patients with heart failure and reduced ejection fraction can improve morbidity, mortality, and sleep quality. They also suggest that treatment of CSA using the initial iteration of ASV is harmful.

Added value of this study

This trial aimed to establish whether treating sleep-disordered breathing in patients with heart failure and reduced ejection fraction with an ASV device designed to eliminate both OSA and CSA would reduce the composite primary endpoint of all-cause mortality, first cardiovascular hospitalisation, new onset atrial fibrillation or flutter, and appropriate implanted cardioverter-defibrillator shock. Due to the results of the SERVE-HF trial, COVID-19 related restrictions, and ASV device recall, our study did not reach its prespecified sample size. Over a mean follow-up of 3·6 years (SD 1·6), we identified that ASV had no significant effect on the primary endpoint or mortality in the entire cohort or in those with OSA or CSA. Importantly, ASV did not increase mortality in those with CSA. ASV abolished both OSA and CSA in association with improvements in sleep quality characterised by a reduction in arousal frequency and a shift from the lighter to the deeper more restorative stages of sleep in both the OSA and CSA subgroups. These improvements were accompanied by improvements in quality of life, heart failure and reduced ejection fraction symptoms, and degree of sleepiness.

Implications of all the available evidence

ASV had no significant impact on the primary composite endpoint or mortality overall, but the number of patients with CSA was too small to provide a definitive answer on benefit or harm with respect to these two endpoints in that subgroup. Importantly, it did not increase mortality in those with either OSA or CSA, even though the mean duration was 1 year longer than the SERVE-HF trial, which targeted only patients with CSA. By abolishing OSA and CSA, ASV induced improvements in sleep quality that were accompanied by improvements in quality of life and symptoms. Thus, in patients with heart failure and reduced ejection fraction, the ASV device used herein can control both OSA and CSA safely and can improve sleep quality, health-related quality of life and symptoms, but not cardiovascular morbidity or mortality. These novel findings argue that there might be a role for selective application of the ASV treatment strategy used herein as adjunctive therapy for patients with heart failure and reduced ejection fraction and sleep-disordered breathing, including CSA, to reduce symptom burden.

Introduction

Sleep-disordered breathing, comprising both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), affects approximately 50% of patients with heart failure and reduced ejection fraction[1–3] and is associated with increased morbidity and mortality.[4,5] To our knowledge, no randomised controlled trial has assessed the effect of treating OSA in patients with heart failure and reduced ejection fraction on such outcomes. For CSA, a multicentre randomised controlled trial involving 258 participants with heart failure and reduced ejection fraction showed that treating this condition by continuous positive airway pressure (CPAP) did not affect heart-transplant-free survival or the rate of admissions to hospital for cardiovascular reasons.[6] Of note, in the study, CPAP only attenuated CSA, and the resultant mean residual apnoea-hypopnoea index (AHI) was 19 events per h. In a post-hoc analysis, the subset of participants in whom CPAP reduced the AHI to less than 15 events per h had significantly improved heart-transplant-free survival

compared with the control group whose CSA was untreated (hazard ratio [HR] 0·37, 95% CI 0·14–0·97; p=0·043).[7] This finding stimulated the hypothesis that, morbidity, mortality, and quality of life would improve if CSA in patients with heart failure and reduced ejection fraction could be eliminated by a more effective device.

Adaptive servo-ventilation (ASV) was developed specifically to treat people with CSA more effectively than does CPAP. The initial iteration of ASV was designed to eliminate central events by automatically adjusting inspiratory pressure, but it had no algorithm to automatically adjust expiratory pressure to eliminate obstructive events.[8] Because we planned to include patients with either OSA or CSA in our trial, and given that both types of events can coexist in the same individual, we used a newer iteration of ASV with a peak flow algorithm that automatically adjusts inspiratory pressure to control CSA and expiratory pressure to control OSA. This version has been shown to eliminate both CSA and OSA in patients with heart failure and reduced ejection fraction.[9] The Effect of Adaptive Servo-Ventilation on Survival and Cardiovascular Hospital Admissions in Patients with Heart Failure and Sleep Apnoea (ADVENT-HF) trial was designed to test the hypothesis that, in patients with heart failure and reduced ejection fraction, treatment of coexisting OSA or CSA by this ASV device would reduce cardiovascular morbidity and mortality and improve sleep and quality of life.[10]

Methods

Study design

The ADVENT-HF trial was a multicentre, multinational, randomised controlled, parallel-group, open-label, phase 3 trial of standard optimal treatment versus ASV plus standard optimal treatment in patients with heart failure and reduced ejection fraction and sleep-disordered breathing, with concealed allocation and masked outcome assessments. A detailed protocol has been previously published.[10] The University Health Network (Toronto, ON, Canada) was the trial sponsor. An executive committee (appendix p 3) at the University Health Network and Sinai Health System (Toronto, ON, Canada) designed the trial and the detailed protocol was developed by the Global Coordinating Centre based at the University Health Network Toronto Rehabilitation Institute (KITE), which was primarily responsible for trial conduct, including initiating all trial sites and monitoring them. The trial was conducted at 49 hospitals in nine countries (ie, Canada, Brazil, France, Germany, Italy, Japan, Spain, the UK, and the USA) in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by all appropriate regulatory authorities and ethics committees at each site. All participants provided written informed consent before participation. A data safety and monitoring committee was created to regularly review trial progress and provide recommendations on trial continuance.[11]

Participants

Eligible participants were 18 years or older with at least a 3 month history of heart failure and a left ventricular ejection fraction (LVEF) of 45% or less, who were stabilised on optimal medical therapy, as per prevailing country-specific society guidelines; had no changes in cardiac medication in the 2 weeks before randomisation; had started beta-blocker therapy at least 3 months before randomisation, if on beta-blockers; and had sleep-disordered breathing, defined as an AHI of 15 or more events per h of sleep. Participants were stratified as predominantly OSA (≥50% of events were obstructive) or CSA (>50% of events were central). For participants with predominantly OSA, those with complaints of excessive daytime sleepiness or an Epworth Sleepiness Scale (ESS) score of more than 10 were excluded on ethical grounds,[12] because treating such patients with CPAP improves their alertness and quality of life.[11] For those with predominantly CSA, there was no limit on the ESS score. Other exclusion criteria are listed in the appendix (p 7).[10]

Randomisation and masking

Eligible participants were randomly assigned to either standard optimal treatment for heart failure and reduced ejection fraction alone or with the addition of ASV (1:1), using an automated internet-based randomisation system (Randomize.net, Interrand, Ottawa, ON, Canada) that stratified by study site and sleep apnoea type (ie, CSA or OSA) and used permuted blocks of sizes 4 and 6 in random order.[10] At each site, a research coordinator, from whom this randomisation process was concealed, enrolled subjects, administered questionnaires, and followed participants as per protocol for the duration of the trial. These research coordinators could not be masked subsequently to treatment allocation, but none was involved in the performance of baseline or follow-up polysomnograms, the initiation of ASV, or the outcome of safety events. The evaluation of events was adjudicated by an independent Event Adjudication Committee (appendix p 3). To mask its members as to participant allocation, the trial manager, who did not participate in event adjudication, reviewed all source documents sent to the Global Coordinating Centre and redacted from such all references to sleep apnoea and its treatment before distributing this material to committee members. For each event reviewed, each member of the committee was obliged to certify in writing that this process had not inadvertently led to their unmasking.

See Online for appendix

Procedures

Consenting patients participated in a screening visit to document demographic data, medical history, cause of heart failure and reduced ejection fraction, medications, blood pressure and heart rate, stages of heart failure,[13] and New York Heart Association (NYHA) class. Health-related quality of life was assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a sensitive and

reliable measure of changes in heart failure status,[14,15] and sleepiness was assessed with the ESS score.[12]

Screening echocardiography was carried out by qualified sonographers or cardiologists. M-mode and two-dimensional images were obtained from the standard parasternal and apical windows and submitted to the Core Echocardiography Laboratory at the Toronto General Hospital (Toronto, ON, Canada) for analysis. Biplane Simpson's method[16] was used to calculate LVEF.

Participants underwent in-laboratory overnight polysomnograms, with a technologist in attendance, 3 months or less before randomisation. All polysomnograms were transmitted electronically to the Core Sleep Laboratory at the Toronto Rehabilitation Institute (KITE; Toronto, ON, Canada) for subsequent analysis. Scoring of sleep stages and arousals from sleep conformed to standard criteria.[17,18] Obstructive and central apnoeas and hypopnoeas were defined as previously described.[6,10,19] The oxygen desaturation index was quantified as the number of dips in SaO_2 of more than or equal to 3%/h of sleep.

Participants randomly assigned to peak-flow triggered ASV (BiPAP autoSV Advanced or BiPAP autoSV Advanced System One, Philips Respironics, Murrysville, PA, USA) had this treatment initiated within 72 h of assignment during a second polysomnogram that was transmitted to the Core Sleep Laboratory, where the effective pressures were determined. These pressures were then programmed into the ASV devices at trial sites (appendix pp 8, 13).

1 month after random assignment to a treatment group, participants underwent a follow-up polysomnogram. For participants who were randomly assigned to ASV, the ASV device was worn during the study. Clinical evaluations were performed and MLHFQ, ESS, and NYHA class were assessed at months 1, 3, and 6 following randomisation and every 6 months thereafter to a maximum of 5 years (appendix pp 14–15). After 5 years, participants underwent an end-of-study evaluation, during which the half-yearly assessments were replicated. For calculating ASV compliance, cumulative hours of use were recorded and the mean was calculated at each study visit. A value of 0 was recorded from the time of non-initiation or from the time of discontinuation of ASV. Where data were missing due to missed visits, no data were entered, and we did not impute hours of use.

Additional information on study procedures is included in the appendix (pp 10, 14–15)

Outcomes

This Article focuses on patient-centred endpoints that would be most likely to influence clinicians' or patients' treatment decisions. The primary study endpoint, as assessed over the course of the study, was the cumulative incidence of the earliest death from any cause (including death and death equivalents—ie, heart transplantation and left ventricular assist device implantation), first admission to hospital for a cardiovascular reason, new onset atrial fibrillation or flutter requiring anticoagulation but not admission to hospital, and delivery of an appropriate implantable cardioverter-defibrillator shock not resulting in admission to hospital. The primary endpoint was assessed in all participants who were randomly assigned to a treatment group. Death from any cause was deemed a primary endpoint if it occurred outside the hospital or during a first admission to hospital. Secondary endpoints included in this Article were cumulative incidence of all-cause mortality, cumulative incidence of cardiovascular mortality, cumulative incidence of all admissions to hospital for cardiovascular reasons, new onset atrial fibrillation or flutter requiring anticoagulation but not admission to hospital, and delivery of an appropriate implantable cardioverter-defibrillator shock not resulting in admission to hospital, changes in AHI and sleep structure, change in NYHA class, change in quality of life assessed by the MLHFQ, and change in ESS score. Secondary endpoints were assessed in all participants who were randomly assigned to a treatment group, over the course of the trial. When the primary outcome was not a death or a death equivalent (ie, admission to hospital for cardiovascular reasons, implantable cardioverter defibrillator shock, or new onset atrial fibrillation or flutter), participants continued to be followed for the occurrence of secondary endpoints.

With respect to the remaining prespecified secondary outcomes (ie, echocardiographic assessment of LVEF, left ventricular end-diastolic volume, left ventricular mass, plasma concentrations of N-terminal pro-brain natriuretic peptide, and 6-minute walking test distance, number of days alive and not in hospital, and cardiac resynchronisation or ICD implantations), these endpoints are not reported herein because they are unlikely to influence decisions about treatment of sleep-disordered breathing in patients with heart failure and reduced ejection fraction.[10] We intend to publish these in future manuscripts.[20]

To evaluate safety, all serious adverse events that were adjudicated as neither primary nor secondary endpoints were reviewed by the Data and Safety Monitoring Committee. These data were collected for all randomised participants.

Statistical analysis

We assumed a larger effect size of ASV for OSA than for CSA on the basis of findings from another study involving patients with OSA[21] and the CANPAP study.[6] We calculated that a sample size of 860 patients with sleep-disordered breathing (ie, 430 with OSA and 430 with CSA) would give rise to 540 primary events and provide 82% power to detect a treatment effect comprising a hazard ratio (HR) of 0·75 for OSA and 0·80 for CSA (combined 0·775) in a Cox proportional hazards analysis, allowing for a dropout rate of 2% per year, a 2% per year crossover rate from treatment group to control

group, a control group rate of 0·35 events per year, and an overall type 1 error rate of 0·05.[10] Interim analyses by the data and safety monitoring committee were planned to occur after 50% (n=270) and 75% (n=405) of primary events were adjudicated with two-sided critical p-value thresholds calculated using the O'Brien-Fleming alpha-spending rule (appendix p 9).[22]

We present within-treatment-group summaries of participant characteristics and study outcomes using means and SDs for continuous variables and counts and percentages for categorical variables. The primary analysis compared the rate of occurrence of the first primary event between the ASV and control groups in all correctly randomised patients (ie, the intention-to-treat sample), using a Cox proportional hazards model, with stratification according to sleep apnoea type (ie, OSA and CSA) and a frailty term for study centre. Follow-up was censored at the earliest of 5 years from randomisation, the study closing date, or patient withdrawal. Non-proportionality of hazards for the treatment effect was checked using plots of Schoenfeld residuals and a test based on weighted residuals.

Separate prespecified analyses were performed according to sleep apnoea type (ie, OSA and CSA) by refitting this model with an interaction term between the stratum and treatment variables and also by separately fitting models to estimate treatment effects in each subgroup.[10]

The per protocol analysis of the primary event included eligible participants who were compliant with study treatment (ASV), defined as use of at least 50% of the total sleep time from the baseline polysomnogram per night during the course of the trial.[10] Regarding the control group, participants who did not cross over to treatment of sleep-disordered breathing were considered compliant by definition. Participants were included in this analysis only up until the time that those assigned to the control group crossed over to CPAP, or those assigned to receive ASV discontinued it. In the ASV group, we calculated mean daily use of ASV over time from the date of random assignment to the group and classified those with values of at least 50% of the baseline sleep duration as being compliant. Outcomes from this time onwards were compared between the control group and compliant patients in the ASV group using the same Cox-model approach as used for the intention-to-treat analysis. This analysis was repeated with compliance defined over landmark times of 0·5 years, 1·0 years, 2·0 years, and 3·0 years.

Each secondary time-to-event outcome was compared between groups in the intention-to-treat sample using the same Cox model approach used for the primary outcome, with appropriate modifications to censoring and subgroup analyses for mortality and admissions to hospital for cardiovascular reasons. Participants were followed from assignment to a treatment group to the earliest of the specific secondary event, with death, heart transplantation, and left ventricular assist device implantation considered as additional censoring events for non-fatal endpoints.

Comparisons of changes in sleep variables from baseline to the 1-month follow-up were performed by ANCOVA using the corresponding baseline value as a covariate. The MLHFQ and ESS were treated as continuous variables and compared between groups using a linear mixed effects model that included categorical variables for time and treatment group, an interaction between time and treatment group, and a constraint that the means were equal at baseline. Models also included a random effect for participant and a first-order autocorrelation structure for residuals. For each outcome, a likelihood ratio test found that a model with a constant post-baseline treatment effect was no worse than a model with different treatment effects at each time, so results from the simpler models are presented. NYHA class was compared between groups at each time point using a proportional odds model, adjusting for sleep apnoea type and baseline NYHA class. Subgroup analyses for the MLHFQ, ESS, and NHYA first fitted models with an interaction of treatment with sleep apnoea type and then estimated treatment effects separately in each subgroup. Further details of the analytical methods used for NYHA class are shown in the appendix (p 28).

Three post-hoc analyses were performed in light of events that occurred subsequent to the trial's conception, on the announcement of the results of the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial.[23] The first was to address potential differences in characteristics of patients with CSA in our trial before and after the ResMed Field Safety Notice was issued on May 13, 2015, which indicated higher mortality in participants who were randomly assigned to receive the earlier form of ASV in SERVE-HF than in participants assigned to the control group, by comparing their characteristics. The second and third were to address the observations that mortality was proportionally higher in patients with CSA in NYHA classes III and IV than in those in NYHA classes I and II and in those with an LVEF of lower than 30% versus those with an LVEF of 30% or higher who were randomly assigned to the ASV group relative to the corresponding control groups by performing similar comparisons among our patients with CSA.

All p values reported are nominal, with no correction for multiple testing. Statistical analyses were done using R (version 4.3.0) and SAS (version 9.4). This trial is registered with ClinicalTrials.gov (NCT01128816) and the International Standard Randomised Controlled Trial Number Register (ISRCTN67500535).

Role of the funding source

Philips RS North America provided the ASV devices. The funders of the study had no role in study design, data

collection, data analysis, data interpretation, or writing of the report.

Results

The first and last participant enrolments were Sept 22, 2010, and March 20, 2021. 1127 patients were screened for eligibility, of whom 386 did not meet the inclusion criteria principally due either to LVEF of more than 45% or an AHI of less than 15. Of the initial 741 eligible patients who were randomly assigned to a treatment group, ten were wrongfully assigned due to protocol violations (appendix p 10). Accordingly, a total of 731 participants were included in intention-to-treat analysis: 375 allocated to control and 356 to ASV (figure 1). Details of enrolment by country are available in the appendix (p 16). At the time of the issuance of the Field Safety Notice regarding results of the SERVE-HF trial stating that ASV was contraindicated for therapy of patients with heart failure and reduced ejection fraction and predominantly CSA,[24] 111 patients with CSA had been enrolled into the trial (appendix p 17). Although the ASV device used in the ADVENT-HF trial differed from that used in the SERVE-HF trial, the executive committee immediately suspended ADVENT-HF trial enrolment pending a review by the Data and Safety Monitoring Committee of stratified analyses of primary and secondary outcomes by sleep apnoea phenotype. The Data and Safety Monitoring Committee identified no safety concerns and recommended continuation of the trial as per protocol. All ethics boards were informed of the review and recommendations and consent forms were revised accordingly. All enrolled patients were then re-consented. However, authorities in Germany and France prohibited further recruitment of patients with CSA, and in other countries referrals of such patients declined. Following completion of the first interim analysis, the Data and Safety Monitoring Committee again recommended continuation of the trial as per protocol. However, the declaration of COVID-19 as a pandemic in March, 2020, forced most study sites to prohibit in-person assessments and polysomnograms. Consequently, the Executive Committee suspended recruitment on March 21, 2021. Follow-up continued until June 15, 2021, when the identification of disintegration of motor sound-abatement material triggered a worldwide recall of all Philips positive airway pressure devices, including those used in the ADVENT-HF trial, which obliged termination of the trial. Over the course of the trial, 41 (6%) participants withdrew consent and 34 (5%) were lost to follow-up (figure 1).

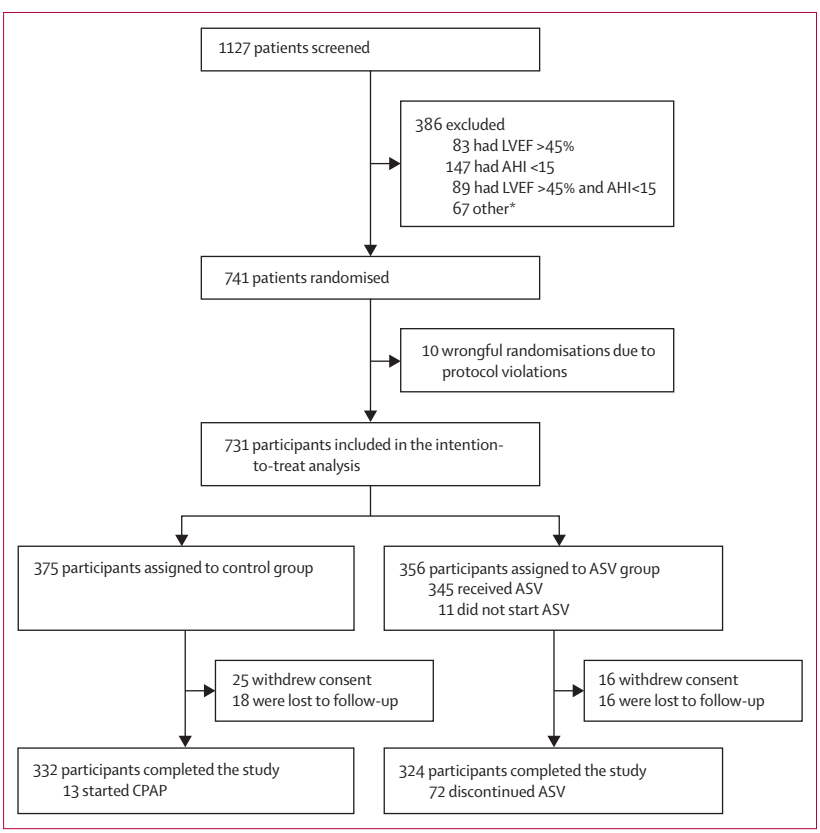


Figure 1: **Trial profile**
AHI=apnoea-hypopnoea index. ASV=adaptive servo-ventilation. CPAP=continuous positive airway pressure. LVEF=left ventricular ejection fraction. *Other refers to exclusions due to American Heart Association class, ongoing medical treatment, inability to give consent, presence of a left ventricular assist device, and other clinical factors.

Of the 731 participants included in the intention-to-treat analysis, 533 (73%) participants had predominantly OSA and 198 (27%) had predominantly CSA (table 1). The high proportion of obstructive events in the OSA subgroup and of central events in the CSA subgroup indicate that both forms of apnoea were present in these participants but that the two subgroups were widely separated in terms of their predominant type of sleep-disordered breathing.

Participants were predominantly male. Overall, participants had only mild daytime sleepiness (mean ESS score 6·2, SD 3·4). Generally, participants with CSA had shorter total sleep time, more frequent arousals, higher ESS scores, and higher AHI and O_2 desaturation indices than those with OSA. Cardiovascular and sleep characteristics were similar in participants who were allocated to control or ASV. Of 731 patients included in the intention to treat analysis, 656 (90%) patients completed the trial.

During the trial, 13 (3%) of 375 patients in the control group, all with OSA (13 [5%] of 269 patients with OSA), were initiated on CPAP, and 83 (23%) of 356 participants who were allocated to ASV either did not start or discontinued it (60 [23%] of 264 in the OSA subgroup and 23 [25%] of 92 in the CSA subgroup). After imposition of COVID-19-related restrictions, few centres were able to acquire compliance data from the ASV secure digital cards. Accordingly, hours of use are reported only until Feb 28, 2020. Overall, cumulative mean daily ASV use for the entire group over the course of the trial was 4·4 h at 1 month and 3·8 h at 5 years. Corresponding hours of use were 4·4 h and 3·3 h for the OSA subgroup and 4·6 h and 4·0 h for the CSA subgroup (appendix p 19). Applied ASV pressures were recorded (appendix p 20). For the entire

	Control group			ASV group		
	All (n=375)	OSA (n=269)	CSA (n=106)	All (n=356)	OSA (n=264)	CSA (n=92)
Age, years	63·6 (10·1)	62·1 (10·0)	65·2 (10·3)	62·7 (11·1)	60·5 (10·5)	67·1 (11·5)
Sex						
Male	327 (87%)	228 (85%)	99 (93%)	318 (89%)	228 (86%)	90 (98%)
Female	48 (13%)	41 (15%)	7 (7%)	38 (11%)	36 (14%)	2 (2%)
BMI, kg/m²	30·7 (5·6)	31·4 (5·9)	28·7 (4·8)	30·8 (6·1)	31·4 (6·2)	29·1 (5·3)
Cause of heart failure						
Ischaemic	201 (54%)	132 (49%)	69 (65%)	190 (53%)	135 (51%)	55 (60%)
Non-ischaemic	172 (46%)	135 (50%)	37 (35%)	164 (46%)	127 (48%)	37 (40%)
New York Heart Association Class						
I	61 (16%)	47 (17%)	14 (13%)	59 (17%)	46 (17%)	13 (14%)
II	236 (63%)	167 (62%)	69 (65%)	216 (61%)	165 (63%)	51 (55%)
III	70 (19%)	52 (19%)	18 (17%)	78 (22%)	50 (19%)	28 (30%)
IV	8 (2%)	3 (1%)	5 (4%)	3 (1%)	3 (1%)	0
Minnesota Living with Heart Failure Questionnaire score	32·5 (21·9)	32·9 (21·8)	31·5 (22·4)	33·1 (23·0)	33·4 (22·6)	32·5 (24·1)
Left ventricular ejection fraction, %	33·3% (7·9)	33·8% (4·8)	32·1% (7·9)	33·1% (7·7)	33·6% (7·2)	31·4% (9·1)
Systolic blood pressure, mm Hg	118·1 (18·4)	121·4 (19·3)	115·9 (20·5)	117·0 (17·4)	120·5 (18·6)	118·3 (19·6)
Diastolic blood pressure, mm Hg	71·2 (11·6)	73·7 (12·1)	70·0 (12·7)	71·7 (11·5)	73·2 (12·7)	71·2 (12·3)
History of hypertension	247 (66%)	179 (67%)	68 (64%)	257 (72%)	187 (71%)	70 (76%)
Atrial fibrillation or flutter	108 (29%)	69 (26%)	39 (37%)	93 (26%)	63 (24%)	30 (33%)
Medications						
ACE inhibitors, angiotensin 2 receptor blockers, angiotensin receptor-neprilysin inhibitor	341 (91%)	248 (92%)	93 (88%)	319 (90%)	243 (92%)	76 (83%)
Beta-blockers	352 (94%)	254 (94%)	98 (92%)	339 (95%)	254 (96%)	85 (92%)
Mineralocorticoid receptor antagonists	212 (57%)	162 (60%)	50 (47%)	194 (54%)	153 (58%)	41 (45%)
SGLT2 inhibitors	44 (12%)	33 (12%)	11 (10%)	36 (10%)	34 (13%)	2 (2%)
Loop diuretics	287 (77%)	207 (77%)	80 (75%)	265 (74%)	195 (74%)	70 (76%)
Cardiac glycosides	57 (15%)	36 (13%)	21 (20%)	54 (15%)	33 (13%)	21 (23%)
Amiodarone	55 (15%)	39 (14%)	16 (15%)	63 (18%)	46 (17%)	17 (18%)
Other antiarrhythmic	7 (2%)	7 (3%)	0	8 (2%)	7 (3%)	1 (1%)
Devices						
Pacemaker	69 (18%)	49 (18%)	20 (19%)	67 (19%)	38 (14%)	29 (32%)
CRT	36 (10%)	24 (9%)	12 (11%)	32 (9%)	22 (8%)	10 (11%)
ICD	139 (37%)	99 (37%)	40 (38%)	138 (39%)	98 (37%)	40 (43%)
Epworth Sleepiness Scale score	6·4 (3·3)	6·0 (2·9)	7·4 (4·0)	6·0 (3·5)	5·6 (3·0)	7·2 (4·5)
Apnoea-hypopnoea index, events per h	42·8 (20·9)	39·7 (21·1)	50·6 (18·3)	43·3 (20·5)	40·7 (20·8)	50·5 (18·1)
Obstructive events, %	68·6% (30·8)	85·6% (13·9)	24·8% (14·8)	70·5% (30·0)	85·8% (15·3)	26·7% (14·8)
Central events, %	31·4% (30·8)	14·4% (13·9)	75·2% (14·8)	29·5% (30·0)	14·2% (15·3)	73·3% (14·8)
3% O_2 desaturation index, events per h	39·1 (22·2)	36·4 (22·5)	45·9 (19·8)	39·7 (21·6)	37·8 (22·4)	45·1 (18·2)
SaO_2, %	93·2% (2·6)	93·1% (21·7)	93·5% (2·4)	93·0% (3·4)	92·8% (3·7)	93·5% (2·5)
Minimum SaO_2, %	79·2% (10·2)	78·9% (10·3)	80·1% (10·0)	78·1% (11·8)	77·8% (12·5)	78·8% (10·2)
Arousal index, events per h	41·3 (22·9)	39·8 (20·8)	47·2 (26·7)	41·1 (19·9)	39·8 (19·2)	44·9 (21·3)
Total sleep time, h	5·1 (1·3)	5·1 (1·3)	4·8 (1·2)	5·2 (1·3)	5·3 (1·3)	4·8 (1·4)
Sleep efficiency, %	70% (15)	71% (16)	68% (14)	71% (17)	73% (16)	66% (19)
Time in stage N1, min	42·1 (30·1)	38·2 (26·9)	52·0 (35·1)	43·5 (31·7)	42·6 (32·1)	46·0 (30·8)
Time in stage N2, min	189·7 (57·3)	194·5 (57·0)	177·3 (56·4)	196·4 (61·5)	201·5 (59·9)	181·7 (63·7)
Time in stage N3, min	31·4 (27·9)	34·1 (29·2)	24·7 (22·9)	30·1 (27·4)	32·2 (27·2)	24·3 (27·4)
Time in stage REM, min	40·1 (25·2)	41·3 (25·6)	36·9 (24·3)	40·2 (27·7)	42·0 (28·5)	34·8 (24·8)

Data are mean (SD) or n (%). ASV=adaptive servo-ventilation. OSA=obstructive sleep apnoea. CSA=central sleep apnoea. CRT=cardiac resynchronisation therapy. ICD=implanted cardioverter defibrillator. REM=rapid eye movement. SaO_2=arterial oxyhaemoglobin.

Table 1: **Characteristics of the patients and heart failure therapy at baseline**

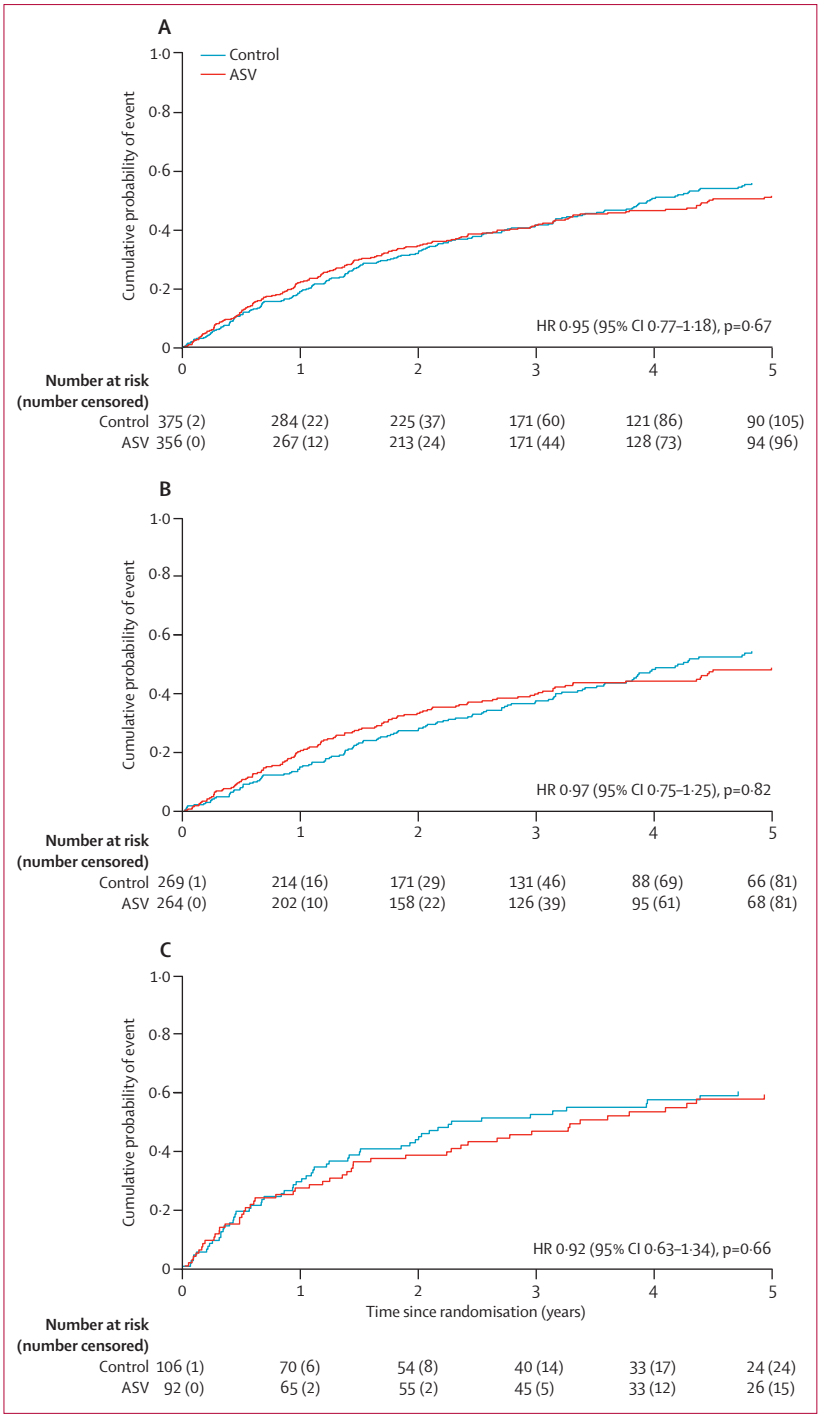


Figure 2: **Cumulative probability of event curves for the primary endpoint**
(A) Probability of event in all patients (180 events in 375 participants in the control group *vs* 166 in 356 participants in the ASV group). (B) Probability of event in patients with obstructive sleep apnoea (122 events in 269 participants in the control group *vs* 115 in 264 participants in the ASV group). (C) Probability of event in patients with central sleep apnoea (58 events in 106 participants in the control group *vs* 51 in 92 participants in the ASV group). ASV=adaptive servo-ventilation. HR=hazard ratio.

ASV cohort, the mean AHI taken from participants' ASV devices ranged between 2·8 events per h and 3·7 events per h over the course of the trial: 2·7–3·3 events per h for the OSA subgroup and 3·6–4·9 events per h for the CSA subgroup (appendix p 20).

For the intention to treat analysis, the mean follow-up time to first primary event or censoring was 2·8 years (SD 1·8), and mean time in the study ending in death or end of follow-up was 3·6 years (SD 1·6), during which there were 346 primary events. ASV had no significant effect on the cumulative incidence of the composite of all-cause mortality, first admission to hospital for cardiovascular reasons, new onset atrial fibrillation or flutter requiring anticoagulation but not admission to hospital, or delivery of an appropriate implantable cardioverter-defibrillator shock for the entire cohort (p=0·67; figure 2A), the OSA subgroup (p=0·82; figure 2B), or the CSA subgroup (p=0·66; figure 2C). The majority of the 346 primary events were admissions to hospital for cardiovascular reasons and deaths (appendix p 21). There was no significant difference in treatment effect of ASV according to OSA or CSA status (interaction HR 1·06, 95% CI 0·67–1·66; p=0·82).

With respect to the per-protocol analysis, for the 13 participants with OSA who crossed over to non-trial CPAP devices, there were no records of dates or hours of use, so anyone in the control group on CPAP was excluded from the per-protocol analysis. There were no significant differences in the HR of the primary event at any of the four landmark times between the ASV-compliant participants and compliant control participants (appendix p 22).

All primary endpoints and deaths were captured. There were 164 deaths, of which 124 were cardiovascular-related (appendix p 23). ASV had no significant effect on all-cause mortality for the entire cohort (p=0·47; figure 3A), nor for those with OSA (p=0·98; figure 3B) or CSA (p=0·25; figure 3C). Similarly, there were no significant effects of ASV on cardiovascular mortality for the entire group (65 deaths in 375 participants in the control group *vs* 59 deaths in 356 participants in the ASV group; HR 0·96, 95% CI 0·68–1·36; p=0·82), nor for the OSA (35 deaths in 269 participants in the control group *vs* 39 deaths in 264 participants in the ASV group; 1·13, 0·72–1·79; p=0·59) or CSA subgroups (30 deaths in 106 participants in the control group *vs* 20 deaths in 92 participants in the ASV group; 0·75, 0·43–1·32; p=0·32). There was no significant difference in treatment effect of ASV according to OSA or CSA status (interaction HR 1·35, 0·71–2·55; p=0·36).

There were 280 initial admissions to hospital for cardiovascular reasons. The first-cardiovascular hospitalisation rate (the number of people first admitted to hospital for a cardiovascular reason) was unaffected by ASV for the entire cohort (138 of 375 participants in the control group *vs* 142 of 356 participants in the ASV group; HR 1·06, 95% CI 0·84–1·33; p=0·65), the OSA subgroup (95 of 269 participants in the control group *vs* 101 of 264 participants in the ASV group; HR 1·08, 0·82–1·43; p=0·60) and the CSA subgroup (43 of 106 participants in

the control group *vs* 41 of 92 participants in the ASV group; HR 1·02, 0·67–1·56; p=0·91).

Differences in sleep structure and other sleep variables between baseline and 1 month are presented in table 2. Compared with the control group, the ASV cohort had significant decreases in AHI and oxygen desaturation index, significant increases in mean SaO_2 and lowest SaO_2, and improvement in sleep quality, as indicated by significantly fewer total and respiratory-related arousals, less time spent in N1 sleep, and more time spent in N3 and rapid-eye movement (REM) sleep; these differences were also apparent in the OSA and CSA subgroups (appendix p 25–27).

Over the entire trial period, compared with the control group, the ASV group had significant improvements in mean MLHFQ score for the entire cohort (–2·8, 95% CI –1·2 to –4·5; p=0·0009; figure 4 [excluding 5-year timepoint]; appendix pp 11, 33 [including 5-year timepoint]), the OSA subgroup (–2·2, –0·2 to –4·2; p=0·028), and the CSA subgroup (–4·6, –1·5 to –7·7; p=0·0036). Compared with the control group, the ASV group had significant improvements in mean ESS scores for the entire cohort (–1·0, 95% CI –0·6 to –1·3; p<0·0001; figure 4), the OSA subgroup (–0·8, –0·4 to –1·2; p=0·0001), and the CSA subgroup (–1·4, –0·8 to –2·1; p<0·0001).

Compared with the control group, participants who were assigned to ASV had a significant improvement in NYHA class for the entire group at 1 year and at 2 years (p=0·049 at 1 year and p=0·012 at 2 years) and in the CSA subgroup at 2 years (p=0·040), but not in either year in the OSA subgroup (appendix p 28).

Missing values for MLHFQ, ESS scores, and NYHA class were due to either deaths, missed follow-up clinic appointments, or withdrawal from the trial.

With respect to safety, a complete list of serious adverse events, adjudicated to be non-primary or non-secondary, is presented in the appendix (pp 29–30). No serious adverse events were attributed to ASV device use. The most common non-primary or non-secondary serious adverse events were orthopaedic problems (n=42), gastrointestinal problems (n=39), pneumonia (n=36) and malignancy (n=31).

Regarding post-hoc analyses, we identified no difference in characteristics of the 87 patients with CSA enrolled following the issuance of ReSMed Field Safety Notice compared to 111 enrolled before this notice (appendix p 17), no differences in mortality in participants with CSA who were assigned to ASV between NYHA classes III and IV versus classes I and II (appendix p 24), nor between those with an LVEF of less than 30% compared with an LVEF of at least 30% (p=0·93, appendix p 31).

Discussion

To our knowledge, the ADVENT-HF trial is the first to address the effects of an ASV device designed to treat

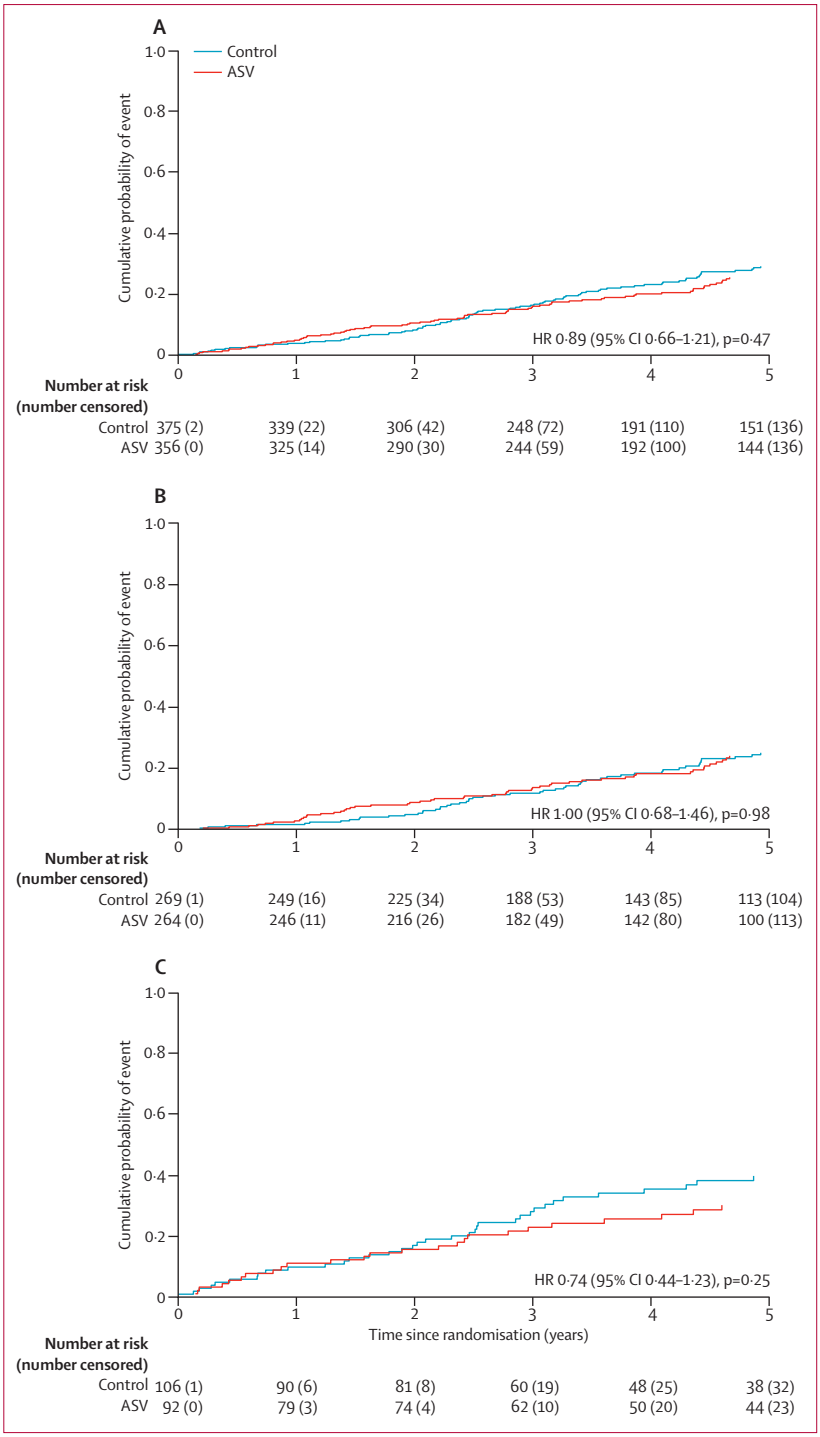


Figure 3: **Cumulative probability of event curves for all-cause mortality**
(A) Probability of event in all patients (88 deaths in 375 participants in the control group *vs* 76 in 356 participants in the ASV group). (B) Probability of event in patients with obstructive sleep apnoea (52 deaths in 269 participants in the control group *vs* 51 in 264 participants in the ASV group). (C) Probability of event in patients with central sleep apnoea (36 deaths in 106 participants in the control group *vs* 25 in 92 participants in the ASV group). ASV=adaptive servo-ventilation.

	All participants			OSA subgroup			CSA subgroup		
	Control group (n=335)	ASV group (n=318)	p value	Control group (n=242)	ASV group (n=234)	p value	Control group (n=93)	ASV group (n=84)	p value
AHI, events per h of sleep	−1·3 (17·1)	−34·2 (20·3)	<0·0001	−1·6 (15·5)	−33·5 (20·9)	<0·0001	−0·3 (20·9)	−36·1 (18·7)	<0·0001
O_2 desaturation index, events per h of sleep	−0·8 (17·3)	−32·0 (21·3)	<0·0001	−0·6 (16·2)	−31·2 (22·2)	<0·0001	−1·5 (19·9)	−34·3 (18·6)	<0·0001
Mean SaO_2, %	0·0 (1·6)	1·5 (2·9)	<0·0001	−0·1 (1·7)	1·6 (3·1)	<0·0001	0·1 (1·6)	1·0 (2·2)	0·0012
Minimum SaO_2, %	0·0 (7·2)	9·8 (11·6)	<0·0001	−0·1 (7·1)	10·5 (12·0)	<0·0001	0·2 (7·5)	7·8 (10·1)	<0·0001
Total sleep time, min	2·4 (71·6)	2·3 (76·1)	0·36	0·4 (70·4)	−5·7 (74·1)	0·87	7·6 (74·9)	24·6 (77·4)	0·13
Sleep efficiency, %	−0·7 (15·4)	1·9 (15·5)	0·074	0·7 (15·3)	0·6 (15·1)	0·42	0·8 (15·8)	5·4 (16·2)	0·046
N1 sleep, min	0·3 (28·9)	−17·5 (32·8)	<0·0001	0·8 (28·5)	−17·1 (32·8)	<0·0001	−0·8 (29·9)	−18·5 (33·0)	<0·0001
N2 sleep, min	−0·8 (57·8)	0·3 (64·8)	0·23	−2·5 (56·2)	−4·3 (61·9)	0·70	3·7 (61·7)	13·2 (71·1)	0·12
N3 sleep, min	0·8 (27·4)	10·5 (30·4)	<0·0001	1·1 (28·6)	9·9 (29·6)	0·0013	0·0 (24·0)	12·2 (32·6)	0·0011
REM sleep, min	0·3 (26·7)	8·9 (29·6)	<0·0001	0·1 (25·3)	7·2 (31·0)	0·0005	1·0 (30·1)	13·5 (25·2)	0·0035
Total arousal index, events per h of sleep	−1·3 (17·7)	−18·0 (22·2)	<0·0001	−1·8 (17·5)	−17·6 (22·6)	<0·0001	0·2 (18·3)	−19·3 (21·2)	<0·0001
Respiratory arousal index, events per h of sleep	−1·4 (16·2)	−23·9 (19·0)	<0·0001	−2·0 (14·7)	−23·7 (19·1)	<0·0001	0·0 (19·7)	−24·4 (18·5)	<0·0001

Data are mean (SD). AHI=apnoea-hypopnoea index. ASV=adaptive servo-ventilation. CSA=central sleep apnoea. OSA=obstructive sleep apnoea. REM=rapid eye movement. SaO_2=arterial oxyhaemoglobin saturation.

Table 2: **Changes in polysomnographic variables from baseline at 1 month**

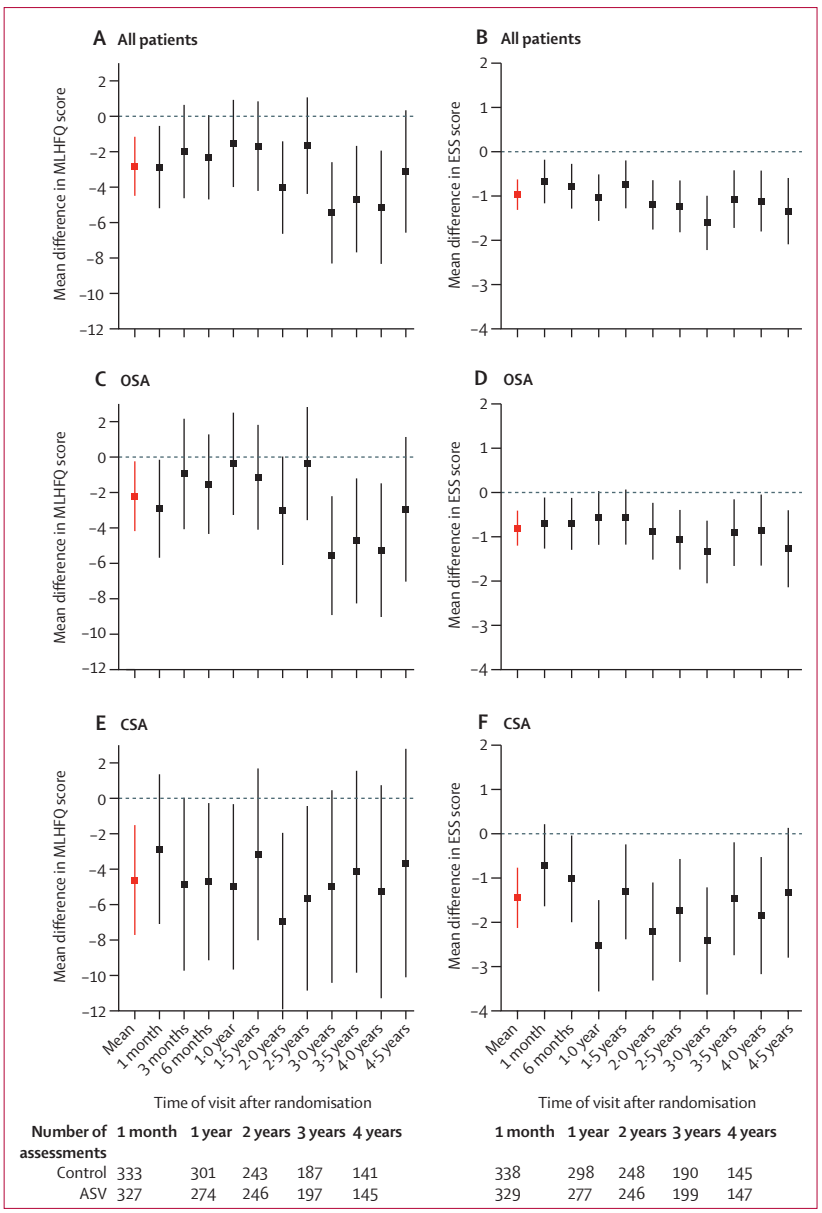
both forms of sleep-disordered breathing (ie, OSA and CSA) in patients with heart failure and reduced ejection fraction, on morbidity, mortality, sleep quality, and quality of life. It is also the largest randomised trial to test the effects of treating non-sleepy patients with heart failure and reduced ejection fraction and OSA on these endpoints. The ADVENT-HF trial yielded several observations that have important clinical implications. Foremost, although ASV eliminated both OSA and CSA over the full 5 years of follow-up, it had no significant effect on the primary composite endpoint or the secondary outcome of mortality. This neutral effect on these two outcomes was most apparent in the larger OSA subgroup. However, the effect of treating patients with CSA on the primary outcome and mortality is less certain because of low recruitment following the publication of the SERVE-HF trial; only 198 (46%) of the 430 prespecified number of patients with CSA were recruited. Importantly, the ADVENT-HF trial identified no adverse safety signal related to ASV use overall or in either of the OSA or CSA subgroups. With respect to the other secondary outcomes included in this article, the trial also showed for the first time that treatment of sleep-disordered breathing in patients with heart failure and reduced ejection fraction with the newer iteration of ASV improves sleep quality, health-related quality of life, and symptoms of sleep-disordered breathing and heart failure overall and in both subgroups.

Separate analyses were performed in people with predominantly OSA and those with predominantly CSA, as prespecified.[10] With respect to OSA, our finding that ASV did not affect the primary endpoint or all-cause mortality is concordant with results of previous trials involving non-sleepy patients with OSA, but without heart failure and reduced ejection fraction, in which treatment with CPAP had no effect on cardiovascular morbidity and mortality.[25,26] Accordingly, there is no evidence to date that abolition of OSA in non-sleepy individuals with OSA by either CPAP or ASV reduces cardiovascular morbidity or mortality. Whether such findings also pertain to treatment of patients with heart failure and reduced ejection fraction and coexisting OSA with excessive daytime sleepiness remains an open question.

In the SERVE-HF trial, involving patients with CSA, there was a significant increase in mortality, principally from sudden death, among those allocated to the initial iteration of ASV.[23,27] In the ADVENT-HF trial, no evidence of harm in treating CSA in patients with heart failure and reduced ejection fraction emerged with a newer iteration of ASV, and in particular, no increase in all-cause mortality or sudden death (appendix p 23), even though the mean duration of follow-up (3·6 years, SD 1·6) was a year longer than in the SERVE-HF trial. Our study was not designed to compare the relative effects of these two types of ASV and thus cannot answer whether the form of ASV it applied differs significantly in its effect on mortality from the earlier mode used in SERVE-HF. However, because the ASV-treated group in ADVENT-HF reported improved sleep quality, quality of life, and symptoms, findings that were not observed in the SERVE-HF trial, and because ASV devices with different sound abatement material that use the same algorithms that controlled OSA and CSA in the

ADVENT-HF trial are now manufactured and sold, differences in the ventilatory properties of the ASV devices used in these two trials merit discussion.

The SERVE-HF trial tested the initial iteration of ASV that was triggered by falls in minute ventilation during central events and had relatively high expiratory default settings of 5 cmH_2O and pressure support default settings of 3 cmH_2O, so that the minimum inspiratory pressure applied was 8 cmH_2O.[8,23] The newer iteration of ASV used in the ADVENT-HF trial had lower default expiratory settings of 4 cmH_2O and pressure support settings of 0 cmH_2O, such that the minimum inspiratory pressure applied would be only 4 cmH_2O.[9] Comparing applied ASV pressures between the two trials at the same timepoints up to 48 months after randomisation[23] shows that median expiratory pressure in our patients with CSA was similar, but pressure support was approximately 1·6 cmH_2O lower (appendix p 19). Furthermore, the iteration of ASV used in the ADVENT-HF trial has been shown to generate less minute ventilation overnight than the ASV used in the SERVE-HF trial.[28] These differences in ventilatory properties could result in a lower tendency to induce hyperventilation and its adverse consequences, such as respiratory alkalosis, hypokalaemia, and cardiac arrhythmias in patients allocated to ASV in the ADVENT-HF trial.[29–31] Additionally, unlike the ASV used in the SERVE-HF trial, the ASV used in our trial was designed to automatically eliminate obstructive events that frequently coexist in patients with predominant CSA, possibly contributing to improvements in sleep quality, quality of life, and symptoms in the ADVENT-HF trial. Other notable differences that might account for such divergent effects on sleep quality and symptoms between the two trials include initiation of therapy in the ADVENT-HF trial via a nasal mask, centralised prescription of pressure settings, and differences in patient populations, with lower age and NYHA class in the ADVENT-HF trial. Also, in the SERVE-HF trial, among participants who were randomly assigned to ASV, mortality was higher in those with an LVEF of less than 30% versus those with an LVEF of at least 30%. However, within the CSA group, we identified no difference in mortality in participants who were assigned to ASV between NYHA classes III and IV versus classes I and II (appendix p 24) nor between those with an LVEF of less than 30% compared with an LVEF of at least 30% (appendix p 31). Taken together these data favour differences in the type of ASV used as an explanation for differences in mortality between the ADVENT-HF trial and the SERVE-HF trial among patients with CSA. Although our findings suggest a role for this iteration of ASV to treat CSA, to establish unambiguously whether newer iterations of ASV have a place in reducing cardiovascular morbidity and mortality in patients with heart failure and reduced ejection fraction, sufficiently powered future studies will need to take these technical considerations into account.



Number of assessments	1 month	1 year	2 years	3 years	4 years
Control	333	301	243	187	141
ASV	327	274	246	197	145

1 month	1 year	2 years	3 years	4 years
338	298	248	190	145
329	277	246	199	147

Figure 4: **Mean differences in MLHFQ and ESS scores between the control and ASV groups over the study period**

Difference in MLHFQ score (A) and difference in ESS score (B) between the ASV and control groups for all patients. Difference in MLHFQ score (C) and difference in ESS score (D) between the ASV and control groups for patients with OSA. Difference in MLHFQ score (E) and difference in ESS score (F) between the ASV and control groups for patients with CSA. Because of few responses to questionnaires and wide CIs, the figure does not include the 5-year follow-up timepoint (appendix p 11 ,32). ASV=adaptive servo-ventilation. CSA=central sleep apnoea. ESS=Epworth Sleepiness Scale. MLHFQ=Minnesota Living with Heart Failure Questionnaire. OSA=obstructive sleep apnoea.

A recent *Lancet* Editorial emphasised that although poor sleep quality has an adverse effect on quality of life in patients with medical disorders, sleep quality is seldom assessed in clinical trials.[32] In the ADVENT-HF trial, objective measures of sleep quality were acquired through baseline and follow-up polysomnograms. A unique finding was that alleviation of sleep-disordered breathing by ASV enhanced sleep quality, with less

fragmentation by arousals and a shift from the lighter stages of sleep, namely N1 to the deeper restorative stages of sleep, namely N3 and REM that were similar in both the OSA and CSA subgroups. These findings contrast with those of previous randomised controlled trials, in which sleep-disordered breathing in patients with heart failure and reduced ejection fraction was treated with CPAP or ASV but neither improved overall sleep structure.[6,19,23,33,34] However, follow-up polysomnograms were only performed 1 month after random assignment to a treatment group in ADVENT-HF, so long-term data on sleep structure could not be assessed.

Such improvement in sleep structure could alter daytime perceptions of quality of life and alertness. Concordant with this concept, ASV improved MLHFQ and ESS scores in the overall cohort, and in the OSA and CSA subgroups, and NYHA class for the entire group and CSA subgroup. Although improvements in MLHFQ and ESS scores were small, they were sustained over the 5-year duration of trial participation and were also associated with improvements in NYHA class and objective improvements in sleep structure. Taken together, improvements in all four of these variables suggest that they were of clinical significance, albeit, modest in degree. Conversely, in other randomised controlled trials involving patients with heart failure and reduced ejection fraction, treating sleep-disordered breathing did not improve quality of life or symptoms.[23,34,35] Widespread implementation of effective drug and implanted device therapies has reduced heart failure and reduced ejection fraction mortality rates but increased its prevalence,[13] obliging greater focus on these patients' quality of life. By consolidating sleep and improving quality of life and symptoms, treatment of sleep-disordered breathing by the iteration of ASV used in the ADVENT-HF trial contributes to this goal.

The ADVENT-HF trial had several unique strengths. With participants recruited from nine countries on four continents, the present findings most likely pertain to the general population with heart failure and reduced ejection fraction and sleep-disordered breathing. By including participants with predominantly OSA or predominantly CSA, we covered the broad spectrum of sleep-disordered breathing, and were able to examine, a priori, outcomes separately in each distinct subgroup. Core laboratory analysis, centralised scoring and interpretation of polysomnograms ensured high data quality. Our protocol incorporated standard questionnaires enabling evaluation of the effect of ASV on both heart failure and reduced ejection fraction and sleep-disordered breathing symptoms. Centralised assessments of ASV titrations and prescription of pressure settings most likely contributed to excellent control of sleep-disordered breathing. Only 13 (5%) of 269 control participants with OSA crossed over to CPAP to treat OSA. The study also had some limitations. Adherence to ASV averaged 3·8 h per day at 5 years (appendix p 20), with 83 (23%) of 356 participants who either did not initiate (n=11) or discontinued it (n=72) at some point. Consistent with the epidemiology of heart failure and reduced ejection fraction and sleep-disordered breathing in this age range, and as with all previous randomised trials of treating sleep-disordered breathing in a similar population, there was a marked predominance of male participants.[6,23] Because this was an open-label study, subjective assessment of quality of life and symptoms might have been open to bias in favour of ASV. However, improvements in these subjective measures among participants who were randomly assigned to ASV were accompanied by objective improvements in sleep structure that most likely contributed to improvements in quality of life and symptoms. Also, due to the cumulative effect of factors described earlier, namely the SERVE-HF field safety notice, COVID-19, and early termination of the trial due to the device recall, we recruited only 731 of the predicted 860 participants. Thus, the ADVENT-HF trial did not secure the prespecified power to detect significant differences in the primary endpoint and all-cause mortality.

As a consequence of the adverse effects of the initial iteration of ASV on mortality used in the SERVE-HF trial, current European Society of Cardiology Guidelines for the treatment of chronic heart failure state that patients "with [heart failure and reduced ejection fraction] being considered for a sleep-disordered breathing treatment with positive pressure airway mask must undergo [a] formal sleep study to document the predominant type of sleep apnoea".[36] Treatment of OSA can be considered to treat nocturnal hypoxaemia, but when "sleep-disordered breathing is caused by CSA, positive airway pressure masks are contraindicated".[36] The ADVENT-HF trial treated sleep-disordered breathing with a newer iteration of ASV, which used a different ventilation algorithm that did not increase morbidity or mortality nor elicit any adverse safety signal in either form of sleep-disordered breathing. Nevertheless, ASV did not reduce morbidity or mortality but did improve objective measures of sleep quality, as well as health-related quality of life and symptoms. These novel findings argue that there might be a role for selective application of the ASV treatment strategy used herein as adjunctive therapy for patients with heart failure and reduced ejection fraction and sleep-disordered breathing, including CSA, to reduce symptom burden. However, as the ADVENT-HF trial was underpowered, it leaves unanswered the important question of whether treating sleep-disordered breathing, particularly CSA, with a newer ASV device will reduce morbidity and mortality in patients with heart failure and reduced ejection fraction.

Contributors

TDB, JSF, AGL and GT designed the trial. TDB, JSF, AGL, GT, RJK, JDC, GLF, MA, SR, GP, TK, MED, and DD served on the steering committee who approved the trial protocol and monitored trial progress. GT is the trial statistician. SY engaged in trial data analysis. TDB wrote the initial draft of the manuscript. JSF, AGL, and GT helped to edit the initial draft. TDB, RJK, JDC, AB, GLF, RP, JMMT, and CT made major contributions

to trial recruitment. TDB, JSF, AGL, and GT accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

Partial funding for this trial, as well as ASV devices, were provided by Philips RS North America. These resources supported the work of all co-authors and trial sites. TDB reports receiving a speaking honorarium from Philips. JSF reports receiving a speaking honorarium and travel expenses from Philips. MA reports receiving speaking honoraria and research grant support from Philips and ResMed. RJK reports receiving speaking honoraria from Eisa and Powell-Mansfield. JMMT reports receiving speaking honoraria from Gebro, Menarini, and Chiesa and research grant support from GSK and AstraZeneca. All other authors declare no competing interests aside from grant support from Philips RS North America to conduct the clinical trial described herein.

Data sharing

Further details on trial data are provided in the appendix (pp 10–31). This was an investigator-initiated trial that was funded by external grants, and at its inception made no provisions for data sharing with outside parties. The trial sponsor, the University Health Network and the custodian of the trial data, the Lunenfeld Tanenbaum Research Institute, are medical academic institutions. Since the external grants have terminated, neither the University Health Network nor the Lunenfeld Tanenbaum Research Institute have the resources required to enter into data sharing agreements with outside parties to allow access to the raw trial data.

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