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

Randomised Trial of Adaptive Servo-ventilation for Sleep-Disordered Breathing in Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Background: In patients with heart failure and reduced ejection fraction (HFrEF), sleep disordered breathing (SDB), comprising obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), is associated with increased morbidity, mortality and sleep disruption. We hypothesized that treating SDB will improve cardiovascular outcomes.

Methods: We conducted a randomised trial of treating OSA and CSA with peak-flow triggered adaptive servo-ventilation (ASV) in patients with HFrEF. The primary endpoint was the composite of all-cause mortality, first cardiovascular hospitalisation, new onset atrial fibrillation-flutter, and appropriate cardioverter-defibrillator shock. A secondary endpoint was all-cause mortality. Pre-specified separate analyses for those with OSA and CSA were also performed.

Findings: The first and last enrolments were September 22, 2010 and March 20, 2021. Enrollments terminated prematurely due to COVID-19-related restrictions. 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 abating material. Of 731 participants, 375 were randomised to control and 356 to ASV. ASV reduced the apnoea-hypopnoea index from 43.3±20.5 (mean±SD) to under 5 per hr of sleep throughout the trial with associated improvements in sleep quality. Over a mean follow-up of 3.6 yr, ASV had no effect on the primary endpoint (Hazard Ratio [HR], 0.97; 95% Confidence Interval [CI] 0.78-1.20, p=0.77) or all-cause mortality (HR, 0.89; 95% CI, 0.66-1.21; p=0.47). For patients with OSA the HR for all-cause mortality was 1.00 (95% CI, 0.68-1.46; p=0.98) and for CSA, 0.74 (95% CI, 0.44-1.23; p=0.25).

Interpretation: In patients with HFrEF and SDB, ASV had no effect on the primary endpoint or mortality but eliminated SDB safely.

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Research in context

Evidence before this study

Sleep-disordered breathing (SDB), 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 (HFrEF). However, to date, there is no evidence from randomised trials that treating OSA or CSA in patients with HFrEF improves morbidity, mortality, overall sleep quality or quality of life, and no large randomised trial involving patients with HFrEF has assessed the effects of treating OSA on these outcomes. A small trial involving patients with HErEF 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 multi-centre 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. This led to the hypothesis that to improve outcomes in those with CSA, abolition of CSA may be a critical 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 employed a newer iteration of ASV designed to control both OSA and CSA by automatically adjusting expiratory and inspiratory positive airway pressures, respectively. Default pressure settings were also lower than on the initial iteration of ASV. While the present trial was in progress, the results of a randomised trial involving patients with HFrEF and CSA (SERVE-HF) 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 HFrEF, ASV is contraindicated for therapy of CSA. Consequently, its clinical use for this purpose ceased. Taken together, those previous trials leave unanswered the question as to whether treating OSA in patients with HFrEF 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 was designed to determine whether treating SDB in patients with HFrEF with an ASV device designed to eliminate both OSA and CSA, will reduce the composite primary endpoint of all-cause mortality, first cardiovascular hospitalisation, new onset atrial fibrillation/flutter, and appropriate implanted cardioverter-defibrillator shock. Secondary endpoints included all-cause mortality, apnoea-hypopnoea index, sleep quality, quality of life and symptoms. In addition to analyzing the entire cohort, there were pre-specified separate analyses of primary and secondary outcomes for those with OSA and those with CSA. At the time the SERVE-HF trial results were announced, our Data and Safety Monitoring Committee examined outcomes data and found no safety signal related to the use of the newer iteration of ASV in our patients, and recommended continuation of the trial. Later, however, because of COVID-19-related restrictions and Philips recall of positive pressure devices, the trial was terminated prematurely. These external events resulted in marked under-recruitment of patients with CSA. A total of 731 patients were randomized: 533 with OSA and 198 with CSA. Over a mean follow-up of 3.6 yr, we found that ASV had no effect on the primary endpoint or mortality in the either 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 characterized 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 sub-groups. These improvements were accompanied by improvements in quality of life assessed by the Minnesota Living with Heart Failure Questionnaire, HFrEF symptoms assessed by New York Heart Association Class and sleepiness as assessed by the Epworth Sleepiness Scale score.

Implications of all the available evidence

ASV had no significant impact on the primary composite endpoint or mortality overall, but was underpowered to provide a definitive answer for patients with CSA. Importantly, it did not increase mortality in those with either OSA or CSA, even though the mean duration was one-year longer than the original ASV trial, targeting 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 HFrEF, 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.

INTRODUCTION

Sleep-disordered breathing (SDB), comprising both obstructive sleep apnoea (OSA) and central sleep apnoea (CSA), affects approximately 50% of patients with heart failure and reduced ejection fraction (HFrEF) [1-3] and is associated with increased morbidity and mortality[4,5]. To date, no randomised trial has assessed the effect of treating OSA in patients with HFrEF on such outcomes. For CSA, a multi-centre randomised trial involving 258 participants with HFrEF showed that treating this condition by continuous positive airway pressure (CPAP) did not affect heart transplant-free survival or the rate of cardiovascular hospitalisations [6]. However, CPAP only attenuated CSA and the resultant mean residual apnoea-hypopnoea index (AHI) was 19 events per hr. In a post-hoc analysis, the subset of subjects in whom CPAP reduced the AHI <15 events per hr experienced improved heart transplant-free survival compared to the control group [7]. This finding stimulated the hypothesis that, morbidity, mortality and quality of life would improve if CSA in patients with HFrEF could be eliminated by a more effective device.

Adaptive servo-ventilation (ASV) was developed specifically to treat CSA more effectively than CPAP. The initial iteration of ASV was designed to eliminate central events by automatically adjusting inspiratory pressure, but had no algorithm to automatically adjust expiratory pressure to eliminate obstructive events.[8] Since, in this trial, we planned to include patients with either OSA or CSA, and since both types of events can co-exist in the same individual we employed a newer iteration of ASV employing a peak flow algorithm (BiPAP autoSV Advanced, Philips Respironics) that automatically adjusts inspiratory pressure to control CSA and expiratory pressure to control OSA. It has been shown to eliminate both CSA and OSA in patients with HFrEF.[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 HFrEF, treatment of co-existing OSA or CSA by this ASV device would reduce cardiovascular morbidity and mortality, and improve sleep and quality of life [10].

METHODS:

See reference [10] and Appendix for further details.

Trial Design

ADVENT-HF was a multi-centre, multinational, randomised, parallel-group, open-label trial of ASV versus no ASV involving patients with HFrEF and SBD, with concealed allocation and blinded outcome assessments. A detailed protocol has been published [10]. The University Health Network (Toronto, Canada) was the trial sponsor. An Executive Committee (Appendix) at the University Health Network and Sinai Health System in Toronto designed the trial and the detailed protocol was developed by the Global Coordinating Centre who was primarily responsible for its conduct, including initiating all trial sites and monitoring them. The trial was conducted at 49 sites in 9 countries 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 prior to participation. A Data Safety and Monitoring Committee (DSMC) was created to regularly review trial progress and provide recommendations on trial continuance.

Participants

Eligible participants were 18 years of age or older with a history of chronic HFrEF with a left ventricular ejection fraction (LVEF) ≤ 45%, stabilized on optimal medical therapy, as per prevailing country-specific society guidelines, and SDB, defined as an AHI ≥15 events per hr. They were stratified as predominantly OSA (≥50% events obstructive) or CSA (>50% of events central). For those with predominantly OSA, those with complaints of excessive daytime sleepiness or an Epworth Sleepiness Scale (ESS) score of >10 [11] were excluded on ethical grounds, since treating such patients with CPAP improves their alertness and quality of life.[12] For those with predominantly CSA there was no limit on the ESS score. Other exclusion criteria are listed in the Appendix.

Procedures

Screening

Consenting patients participated in a screening visit to document demographic data, medical history, etiology of HFrEF, medications, blood pressure and heart rate, stages of HF [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 from the ESS score [11].

Echocardiography

M-mode and 2-D images were obtained from the standard parasternal and apical windows and submitted to the Core Echocardiography Laboratory at the Toronto General Hospital for analysis. Biplane Simpson's method [16] was used to calculate LVEF.

Polysomnography

Participants underwent attended in-laboratory overnight polysomnograms (PSG) three months or less before randomization. All PSGs were transmitted electronically to the Core Sleep Laboratory at the Toronto Rehabilitation Institute 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 ≥ 3%/hour of sleep.

Randomisation and masking

Eligible subjects were randomised in a 1:1 ratio to either standard optimal treatment for HFrEF alone or with the addition of ASV, using an internet-based randomisation system (Randomize.net, Interrand Inc. Ottawa, ON, Canada) that stratified by study site and sleep apnea type (CSA or OSA) and used permuted blocks of sizes 4 and 6 in random order.[10]

ASV Titration

Participants randomised to peak-flow triggered ASV (BiPAP autoSV Advanced or BiPAP autoSV Advanced System One, Philips Respironics, Murrysville, PA, USA) had this initiated within 72 h of randomisation during a second PSG that was transmitted to the Core Sleep Laboratory where the effective pressures were determined. These were then programmed into subjects' ASV devices at trial sites (Appendix, page 3 and Table A1).

Follow-up

One month after randomisation, subjects underwent a follow-up PSG. For those randomised to ASV, ASV was worn during the study. Clinical evaluations were performed and MLHFQ, ESS and NYHA class were assessed at one, three, and six months and every six months thereafter to a maximum of five years (Appendix, Table A2). After five 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 averaged at study visits. 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.

Endpoints and assessments

The primary study endpoint was the cumulative incidence of the composite of all-cause mortality (including death and death equivalents, i.e., heart transplantation and left ventricular assist device implantation), first CV hospitalisation, new onset atrial fibrillation/flutter requiring anticoagulation but not hospitalisation, and delivery of an appropriate ICD shock. Secondary endpoints included in this paper were: 1) cumulative incidence of all-cause mortality; 2) cumulative incidence of cardiovascular mortality; 3) cumulative incidence of all CV hospitalisations, 4) changes in AHI and sleep structure, 5) change in NYHA class; 6) change in quality of life assessed by the MLHFQ; and, 7) change in ESS score. With respect to CV hospitalisations, ICD shocks and new onset atrial fibrillation/flutter, if one was the first event, it was considered to be a primary endpoint, in which case participants continued to be followed and any subsequent deaths, CV hospitalisations, or appropriate ICD shocks were considered secondary endpoints. Heart transplantation and left ventricular assist device implantation were considered terminal censoring events.

Statistical analysis

We assumed a larger effect size of ASV for OSA than for CSA based on findings from another study involving patients with OSA[20] and the CANPAP study [6]. We calculated that a sample size of 860 patients with SDB (430 OSA and 430 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 to control, a control group rate of 0.35 events per year, and an overall type 1 error rate of 0.05 [10]. Non-proportionality of hazards for the treatment effect was checked using plots of Schoenfeld residuals and a test based on weighted residuals.

The primary intention-to-treat analysis compared the rate of occurrence of the first primary event between the ASV and control groups using a Cox proportional hazards model, with separate pre-specified analyses according to sleep apnoea type (OSA and CSA)[10]. Death from any cause was deemed a primary endpoint if it occurred outside the hospital or during a first hospitalisation. Interim analyses by the Data and Safety Monitoring Committee (DSMC) 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.[21] All p-values reported are nominal, with no correction for multiple testing.

The on-treatment analysis of the primary event included eligible subjects compliant with study treatment (ASV), defined as use of at least 50% of the total sleep time from the baseline PSG per night during the course of the trial.[10] Regarding the control group, those who did not cross-over to treatment were considered compliant by-definition. In the ASV group, we calculated average daily use of ASV over time T from randomization and classified those with values ≥ 50% of the baseline sleep duration as being compliant. Outcomes from time T 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-teat analysis. This analysis was repeated with compliance defined over landmark times of 0.5, 1.0, 2 and 3 years.

Comparisons of changes in sleep variables from baseline to the one-month follow-up were performed by two-way repeated measures ANOVA. 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 subject 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.

Role of the funding source

The trial was funded jointly by the Canadian Institutes of Health Research and, in accordance with its University Industry Partnership Program, by Philips RS North America LLC, who also provided ASV devices. Neither funding source participated in the design or conduct of the trial, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to submit its findings for publication.

RESULTS

The first and last enrolments were September 22, 2010 and March 20, 2021. On 13 May, 2015, while ADVENT-HF was in progress, the sponsor of the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF) trial [22] issued a Field Safety Notice reporting increased mortality in patients with CSA allocated to their ASV device and stating that ASV was contraindicated for therapy of patients with HFrEF and predominantly CSA. Although the ASV device used in ADVENT-HF differed from that used in SERVE-HF, the Executive Committee immediately suspended ADVENT-HF enrollment pending a review by the DSMC of stratified analyses of primary and secondary outcomes by sleep apnoea phenotype. The DSMC 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 DSMC 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 PSGs. Consequently, the Executive Committee suspended recruitment in March 2021. Follow-up continued until June 15, 2021, when Philips' identification of disintegration of motor sound-abatement material triggered a world-wide recall of all their positive airway pressure devices, including that used in ADVENT-HF, which obliged the trial's termination.

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As shown in Figure 1, 1,127 patients were screened for eligibility of whom 386 were screen failures due either to LVEF >45% or an AHI <15. Of the initial 741 eligible patients who were randomized, 10 were wrongfully randomized due to protocol violations (Appendix, page 10). Accordingly, a total of 731 randomized participants were included in intention-to-treat analysis: 375 allocated to control, and 356 to ASV (Figure 1). Of these, 533 participants (72.8%) had predominantly OSA and 198 (27.2%) had predominantly CSA (Table 1). The very high percentage of obstructive events in the OSA sub-group (85.6%) and of central events in the CSA sub-group (73.3%), indicate that both forms of apnoea were present in these participants but that the two sub-groups were widely separated in terms of their predominant type of SDB.

Baseline characteristics of the subjects are provided in Table 1. Participants were predominantly male. Overall, participants had only mild daytime sleepiness (mean ESS score ± SD, 6.2 ± 3.4). In general, those 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 those allocated to control or ASV. Of those included in the intention-to-treat analysis, 656 patients (89.7%) completed the trial.

During the trial, 13 (4.5%) patients in the control group, all with OSA, were initiated on CPAP, while 83 (23.0%) allocated ASV either did not start or discontinued it (22.7% in the OSA and 25.0% in the CSA sub-group). 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 February 28, 2020. Overall, cumulative average daily ASV use for the entire group over the course of the trial ranged between 4.4 h at 1 month to 3.8 h at 5-years. Corresponding hours of use were between 4.4 and 3.3 for the OSA sub-group and between 4.6 and 4.0 for the CSA sub-group (Appendix, Table A5). Applied pressures were recorded (Appendix, Table A6). For the entire ASV cohort, the mean AHI taken from participants' ASV devices ranged between 3.0 and 3.8 events per h over the course of the trial: for the OSA sub-group, between 2.7 and 3.4, and for the CSA sub-group, between 3.8 and 4.9 events per h (Appendix, Table A7).

For the intention to treat analysis, the mean follow-up time to first primary event or censoring was 2.7 years, and mean time in the study ending in death or end of follow-up was 3.6 years during which there were 346 primary events. As displayed in Figure 2, ASV had no significant effect on the primary endpoint for the entire cohort (p=0.67, Figure 2A), the OSA (p=0.82, Figure 2B) or CSA sub-groups (p=0.66, Figure 2C). The majority of the 346 primary events were cardiovascular hospitalisations and deaths (Appendix, Table A8). There was no significant interaction between treatment effect of ASV according to OSA or CSA status (1.06; 95% CI, 0.67-1.66; p=0.82). There were no deaths or other serious adverse events attributed to ASV device use.

With respect to the on-treatment analysis, for the 13 subjects 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 subjects and compliant control subjects (Appendix, Table A9).
All primary endpoints and deaths were captured. There were 164 deaths of which 125 were cardiovascular-related (Appendix, Table A10). 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 (HR, 0.96; 95% CI, 0.68-1.36; p=0.82), nor for the OSA (HR, 1.13; 95% CI, 0.72-1.79; p=0.59) or CSA sub-groups (HR, 0.75; 95% CI, 0.43-1.32; p=0.32). There was no significant interaction between treatment effect of ASV according to OSA or CSA status (1.35; 95% CI, 0.71-2.55; p=0.36).

There were 283 initial cardiovascular hospitalisations. The first-cardiovascular hospitalisation rate was unaffected by ASV for the entire cohort (HR, 1.06; 95% confidence interval [CI], 0.84-1.33; p=0.65), the OSA sub-group (HR, 1.08; 95% CI, 0.82-1.43; p=0.60) and the CSA sub-group (HR, 1.02; 95% CI, 0.67-1.56; p=0.91).

Differences in sleep variables between baseline and one-month are presented in Table 2. Compared to the control group, the ASV group experienced significant decreases in AHI, oxygen desaturation index, and increases in mean SaO_2 and lowest SaO_2 ($p<0.001$ for the entire cohort and $p<0.001$- 0.003 in the OSA and CSA sub-groups), and significant improvement in sleep quality, with fewer total and respiratory-related arousals, less time spent in N1 sleep, more in N3 and REM sleep ($p<0.001$ for the entire cohort and $p<0.001$-0.005 in the OSA and CSA sub-groups). See Appendix, Table A11 for further details.

As displayed in Figure 3, over the entire trial period, compared to the control group, the ASV group experienced significant improvements in MLHFQ score for the entire cohort (-2.8; 95% CI, -4.5 to -1.2; p=0.0009), the OSA sub-group (p=0.0280) and the CSA sub-group (p=0.0036). Compared to the control group, the ASV group experienced significant improvements in ESS scores for the entire cohort (-1.0; 95% CI, 0.6 to 1.3; p<0.0001), the OSA sub-group (p=0.0001) and the CSA sub-group (p<0.0001).

After one and two years, compared to the control group, those randomised to ASV experienced a significant improvement in NYHA class for the entire group (one-year, p=0.049 and two-years, p=0.012) and at two years in the CSA sub-group (p=0.040), but not in either year in the OSA sub-group (Appendix, Table A12). 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 pre-specified secondary outcomes not reported herein due to space limitations, it is our intention to publish these in future manuscripts.[23]

DISCUSSION

ADVENT-HF is the first trial to address the effects of an ASV device designed to treat both forms of SDB, OSA and CSA, in patients with HFrEF on morbidity, mortality, sleep quality and quality of life. It is also the largest randomised trial to test the impact of treating non-sleepy patients with HFrEF and OSA on these endpoints. ADVENT-HF yielded several observations that have important clinical implications. Foremost, although ASV eliminated both OSA and CSA over the full five-years of follow-up, it had no significant impact on the primary endpoint or mortality. This was most apparent in the larger OSA sub-group. 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 46% of the pre-specified sample size of CSA patients were recruited. Importantly, ADVENT-HF found no adverse safety signal overall or in either the OSA or CSA sub-groups. The trial also demonstrated for the first time that treatment of SDB in HFrEF patients with the newer iteration of ASV improves sleep quality, health-related quality of life and symptoms overall and in both sub-groups.

Separate analyses were performed in those with predominantly OSA and those with predominantly CSA, as pre-specified. 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 HFrEF, in which treatment with CPAP had no effect on cardiovascular morbidity and mortality[24,25]. 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 HFrEF and co-existing 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[22] among those allocated to the initial iteration of ASV [22,26]. In ADVENT-HF, no evidence of harm in treating CSA in patients with HFrEF emerged with a newer iteration of ASV, and in particular, no increase in all-cause mortality or sudden death (Appendix, Table A8), even though the mean duration of follow-up (3.6 years) was a year longer than in SERVE-HF. Regrettably, ADVENT-HF cannot answer whether the form of ASV it applied differs significantly in its impact on mortality, since our study was underpowered to address this outcome. However, because the ASV-treated group experienced improvement in sleep quality, quality of life, and symptoms that were not observed in the SERVE-HF trial, differences in the ventilatory properties of the ASV devices used in these two trials merit discussion.

SERVE-HF tested the initial iteration of ASV that was triggered by falls in minute-ventilation during central events and had relatively high expiratory and pressure support default settings of 5 and 3 cmH_2O, respectively, so that the minimum inspiratory pressure applied was 8 cmH_2O.[19] The newer iteration of ASV employed in ADVENT-HF had lower default expiratory and pressure support settings of 4 and 0 cmH_2O, such that the minimum inspiratory pressure applied would be only 4 cmH_2O [10,23]. Comparing applied ASV pressures between the two trials at the same time-points up to 48 months post-randomization[19] reveals that median expiratory pressure in our patients with CSA was similar, but pressure support was approximately 1.6 cmH_2O lower (Appendix, Table A6). Furthermore, the iteration of ASV used in ADVENT-HF has been shown to generate less minute ventilation overnight than the ASV

employed in SERVE-HF.[27] These differences in ventilatory properties could result in a lower tendency to induce hyperventilation and its adverse consequences, such as respiratory alkalosis, hypokalemia and cardiac arrhythmias in patients allocated to ASV in ADVENT-HF.[28-30] Additionally, unlike the ASV used in SERVE-HF, the ASV used in our trial was designed to automatically eliminate obstructive events that frequently co-exist in patients with predominant CSA, possibly contributing to improvements in sleep quality, quality of life and symptoms in ADVENT-HF. Other notable differences that might account for such divergent effects on sleep quality and symptoms between the two trials include initiation of therapy in ADVENT-HF via a nasal mask, centralized prescription of pressure settings, and differences in patient populations with lower age and NYHA class. Also, in SERVE-HF, among those randomized to ASV, mortality was higher in those with an LVEF <30% versus those with an LVEF >30%. However, within the CSA group, we found no difference in mortality in those randomized to ASV between NYHA classes III and IV versus classes I and II (Appendix, Table A11) nor between those with an LVEF <30 compared to ≥30%. (Appendix, Figure A1). Taken together these data favour differences in the type of ASV employed to explain differences in mortality between ADVENT-HF and SERVE-HF among patients with CSA. While our findings suggest a role for this iteration of ASV to treat CSA, in order to determine unambiguously whether newer iterations of ASV have a place in reducing cardiovascular morbidity and mortality in patients with HFrEF, sufficiently-powered future studies will need to take these technical considerations into account.

A recent *Lancet* Editorial emphasized that although poor sleep quality has an adverse impact on quality of life in patients with medical disorders, sleep quality is seldom assessed in clinical trials[31]. In the ADVENT-HF trial, objective measures of sleep quality were acquired through baseline and follow-up PSGs. A unique finding was that alleviation of SDB by ASV enhanced sleep quality, with less fragmentation by arousals and a significant shift from the lighter to the deeper restorative stages of sleep that were similar in both the OSA and CSA sub-groups. These findings contrast with those of prior randomised trials in which SDB in patients with HFrEF was treated, but did not improve overall sleep structure.[6,19,32,33] However, follow-up PSGs were only performed one month after randomization, so that 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 sub-groups, and NYHA class for the entire group and CSA sub-group. Although improvements in MLHFQ and ESS scores were small, they were sustained over the five-year duration of trial participation, and were also associated with improvements in NYHA class and objective improvements 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 trials involving patients with HFrEF, treating SDB did not improve quality of life or symptoms.[22,33,34] . Widespread implementation of effective drug and implanted device therapies has reduced HFrEF 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 SDB by the iteration of ASV employed in ADVENT-HF contributes to this goal.

The ADVENT-HF trial had several unique strengths. With participants recruited from nine countries on four continents, the present findings likely pertain to the general population with HFrEF and SDB. By including subjects with predominantly OSA or predominantly CSA, we covered the broad spectrum of SDB, and were able to examine, *a priori*, outcomes separately in each distinct sub-group. Core laboratory analysis centralized scoring and interpretation of PSGs ensured high data quality. Our protocol incorporated standard questionnaires enabling evaluation of ASV's impact on both HFrEF and SDB symptoms. Centralized assessments of ASV titrations and prescription of pressure settings likely contributed to excellent control of SDB. Only 4.5% of control participants were initiated on CPAP to treat OSA. It also had some limitations. Adherence to ASV averaged 3.8 h per night over the course of the trial with 23% of participants who either did not initiate or discontinued it at some point. There was a marked predominance of male participants. However, previous randomized trials of therapy for SDB in patients with HFrEF had a similar marked predominance of male participants that reflects the epidemiology of HFrEF and SDB in this age range.[6,22] Because this was an open label study, subjective assessment of quality of life and symptoms may have been open to bias in favour of ASV. However, improvements in these subjective measures among those randomized to ASV were accompanied by objective improvements in sleep structure that likely contributed to improvements in quality of life and symptoms. Also, due to the cumulative impact of factors described above, we recruited only 731 of the predicted 860 participants. Thus, ADVENT-HF did not secure the pre-specified 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 HFrEF being considered for a sleep-disordered breathing treatment with positive pressure airway mask must undergo formal sleep study to document the predominant type of sleep apnoea". 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" [35]. ADVENT-HF treated SDB with a newer iteration of ASV employing a different ventilation algorithm that did not increase morbidity or mortality nor elicit any adverse safety signal in either form of SDB. Nevertheless, it 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 may be a role for selective application of the ASV treatment strategy employed herein as adjunctive therapy for patients with HFrEF and SDB, including CSA, to reduce symptom burden. However, as ADVENT-HF was underpowered, it leaves unanswered the important question whether treating SDB, particularly CSA, with a newer ASV device will reduce morbidity and mortality in patients with HFrEF.

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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, while JSF, AGL and GT helped to edit it. TDB, RJK, JDC, AB, GLF, RP, JMM, and CT made major contributions to trial recruitment. All authors had access to all trial data, reviewed the final manuscript, approved it and had final responsibility for the decision to submit it.

Declaration of interests

Partial funding for this trial, as well as ASV devices, were provided by Philips RS North America LLC. These resources supported the work of all co-authors and trial sites.

Data sharing

Further details on trial data are provided in the Appendix. 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 (UHN) and the custodian of the trial data, the Lunenfeld Tanenbaum Research Institute **(**LTRI), are medical academic institutions. Since the external grants have terminated, neither UHN nor LTRI have the resources required to enter into data sharing agreements with outside parties to allow access to the raw trial data.

Acknowledgments

The trial sponsor was the University Health Network (Toronto, Canada). An Executive Committee (Appendix 1) at the University Health Network and Mount Sinai Hospital in Toronto designed the trial and was primarily responsible for its conduct. Event adjudication of source documents was performed blindly by an adverse events committee. An independent Data and Safety Monitoring Committee monitored un-blinded trial events. The trial was co-funded by the Canadian Institutes of Health Research (operating grant IS2-95225) and, in accordance with its University-Industry Partnership Program, by Philips RS North America LLC, who also provided ASV devices. Neither funding source participated in the design or conduct of the trial, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to submit its findings for publication.

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Figure Legends

Figure 1. Trial profile. ASV=adaptive servo-ventilation. CPAP=continuous positive airway pressure.

Figure 2. Cumulative probability of event curves for the primary endpoint for: A) all patients (180 events in the control group versus 166 in the ASV group), B) patients with obstructive sleep apnoea (122 events in the control group versus 115 in the ASV group) and C) patients with central sleep apnoea (58 events in the control group versus 51 in the ASV group). ASV= adaptive servo-ventilation.

Figure 3. Cumulative probability of event curves for the all-cause mortality for: A) all patients (88 deaths in the control group versus 76 in the ASV group), B) patients with obstructive sleep apnoea (52 deaths in the control group versus 51 in the ASV group) and C) patients with central sleep apnoea (36 deaths in the control group versus 25 in the ASV group). ASV= adaptive servo-ventilation.

Figure 4. Mean differences in Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores between the adaptive servo-ventilation (ASV) and control groups the for: A) all patients, B) patients with central sleep apnoea (CSA) and C) patients with obstructive sleep apnoea (OSA). Over the entire trial period (average), compared to the control group, the ASV group experienced significant improvements in MLHFQ score for the entire cohort (mean decrease, 2.8; 95% CI, 1.2 - 4.5; p=0.0009), the CSA sub-group (mean decrease, 4.6; 95% CI, 1.5 - 7.7; p= 0.0036) and the OSA sub-group (mean decrease, 2.2; 95% CI, 0.2 - 4.2; p=0.028). Mean differences in Epworth Sleepiness (ESS) Scale Scores between the two treatment groups are shown for: D) all patients, E), patients with CSA and F) patients with OSA. The ASV group experienced significant improvements in ESS scores for the entire cohort (mean decrease, 1.0; 95% CI, 0.6 - 1.3; p<0.0001), the CSA sub-group (mean decrease, 1.4; 95% CI, 0.8 - 2.1; p<0.0001), and the OSA sub-group (mean decrease, 0.8; 95% CI, 0.4 - 1.2; p=0.0001).

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

Characteristic	Control			ASV		
	All	OSA	CSA	All	OSA	CSA
n	375	269	106	356	264	92
Age, yr.*	63.6±10.1	62.1±10.0	65.2±10.3	62.7±11.1	60.5±10.5	67.1±11.5
Male sex, no. (%)	327 (87.2)	228 (85.4.8)	99 (93.4)	318 (89.3)	228 (86.4)	90 (987.8)
Body mass index, kg/m^2 *	30.7±5.6	31.4±5.9	28.7±4.8	30.8±6.1	31.4±6.2	29.1±5.3
HF etiology, no. (%) - Ischemic	201 (543.9)	132 (49.1)	69 (65.1)	190 (53.4)	135 (51.1)	55 (6059.8)
- Non-ischemic	172 (465.9)	135 (50.2)	37 (354.9)	164 (46.1)	127 (48.1)	37 (40.2)
New York Heart Association Class, no. I	61 (16.3)	47 (17.5)	14 (13.2)	59 (16.6)	46 (17.4)	13 (14.1)
II	236 (62.9)	167 (62.1)	69 (65.1)	216 (60.7)	165 (62.5)	51 (55.4)
III	70 (18.7)	52 (19.3)	18 (17.0)	78 (21.9)	50 (18.9)	28 (30.4)
IV	8 (2.1)	3 (1.1)	5 (4.7)	3 (0.8)	3 (1.1)	0 (0)
Minnesota Living with Heart Failure	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, mmHg *	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, mmHg *	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, no. (%)	247 (665.9)	179 (676.5)	68 (64.2)	257 (72.2)	187 (710.8)	70 (76.1)
Atrial fibrillation or flutter, no. (%)	108 (298.8)	69 (265.7)	39 (376.8)	93 (26.1)	63 (243.9)	30 (332.6)
Medications, n (%)						
ACE/ARB/ARNi	341 (910.9)	248 (92.1)	93 (887.7)	319 (9089.6)	243 (92.0)	76 (832.6)
Beta-blockers	352 (943.9)	254 (94.4)	98 (932.5)	339 (95.2)	254 (96.2)	85 (92.4)
MRAs	212 (576.5)	162 (60.2)	50 (47.2)	194 (554.5)	153 (58.0)	41 (454.6)
SGLT2i	44 (121.7)	33 (12.2)	11 (10.3)	36 (10.1)	34 (132.8)	2 (2.1)
Loop diuretics	287 (776.5)	207 (77.0)	80 (765.5)	265 (74.4)	195 (743.9)	70 (76.1)
Cardiac glycosides	57 (15.2)	36 (13.4)	21 (2019.8)	54 (15.2)	33 (132.5)	21 (232.8)
Amiodarone	55 (154.7)	39 (154.5)	16 (15.1)	63 (187.7)	46 (17.4)	17 (198.5)
Other antiarrhythmic	7 (21.9)	7 (32.6)	0 (0)	8 (2.2)	7 (32.7)	1 (1.1)
Devices, n (%)						
Pacemaker	69 (18.4)	49 (18.2)	20 (198.9)	67 (198.8)	38 (14.4)	29 (321.5)
CRT	36 (109.6)	24 (8.9)	12 (11.3)	32 (9.0)	22 (8.3)	10 (110.9)
ICD	139 (37.1)	99 (376.8)	40 (387.7)	138 (398.8)	98 (37.1)	40 (443.5)
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
Sleep apnoea type, n (%)	375	269 (71.7)	106 (28.3)	356	264 (74.2)	92 (25.8)
Apnoea-hypopnoea index, events/hr*	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	85.6	24.8	70.5	85.8	26.7
Central events, %	31.4	14.4	75.2	29.5	14.2	73.3
3% O_2 desaturation index, events/hr*	39.1±22.2	36.4±22.5	45.9±19.8	39.7±21.6	37.8±22.4	45.1±18.2
Mean 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, no. of events/hr*	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, hr*	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, %	70.1±15.1	71.2±165.5	687.5±143.9	71.2±176.8	732.9±165.9	66.3±198.5
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
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
Stage N3, min	31.4±27.9	34.1±29.2	24.7±22.9	30.1±27.4	32.2±27.2	24.28±27.4
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

* Mean ± standard deviation. ASV=adaptive servo-ventilation. OSA=obstructive sleep apnoea. CSA=central sleep apnoea. ACE=angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARNi, angiotensin receptor/neprilysin inhibitor; MRAs, mineralocorticoid receptor antagonists; SGLT2i, sodium-glucose transport protein 2 inhibitors; CRT, cardiac resynchronization therapy; ICD, implanted cardioverter defibrillator; SaO_2, arterial oxyhemoglobin

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Table 2. Polysomnographic variables: changes from baseline at one-month

	All			OSA			CSA		
Variable	Control n=335	ASV n=318	p	Control n=242	ASV n=234	p	Control n=93	ASV N=84	P
AHI, events/hr sleep	-1.3±17.1	-34.2±20.3	<0.001	-1.6±15.5	-33.5±20.9	<0.001	-0.3±20.9	-36.1±18.7	<0.001
O_2 desaturation index, events/hr sleep	-0.8±17.3	-32.0±21.3	<0.001	-0.6±16.2	-31.2±22.2	<0.001	-1.5±19.9	-34.3±18.6	<0.001
Mean SaO_2, %	-0.01±1.6	1.5±2.9	<0.001	-0.1±1.7	1.6±3.1	<0.001	0.1±1.6	1.0±2.2	0.003
Min SaO_2, %	-0.04±7.2	9.8±11.6	<0.001	-0.1±7.1	10.5±12.0	<0.001	0.2±7.5	7.8±10.1	<0.001
TST, min	2.4±71.6	2.3±76.1	0.988	0.4±70.4	-5.7±74.1	0.359	7.6±74.9	24.6±77.4	0.139
Sleep efficiency, %	-0.7±15.4	1.9±15.5	0.338	0.7±15.3	0.6±15.1	0.945	0.8±15.8	5.4±16.2	0.054
N1 sleep, min	0.3±28.9	-17.5±32.8	<0.001	0.8±28.5	-17.1±32.8	<0.001	-0.8±29.9	-18.5±33.0	<0.001
N2 sleep, min	-0.8±57.8	0.3±64.8	0.820	-2.5±56.2	-4.3±61.9	0.739	3.7±61.7	13.2±71.1	0.343
N3 sleep, min	0.8±27.4	10.5±30.4	<0.001	1.1±28.6	10.0±29.6	0.001	0.01±24.0	12.2±32.6	0.005
REM sleep, min	0.3±26.7	8.9±29.6	<0.001	0.1±25.3	7.3±31.0	0.005	0.9±30.1	13.5±25.2	0.003
Total Arousal Index, events/h sleep	-1.3±17.7	-18.0±22.2	<0.001	-1.8±17.5	-17.6±22.6	<0.001	0.2±18.3	-19.3±21.2	<0.001
Respiratory Arousal Index, events/h sleep	-1.4±16.2	-23.9±19.0	<0.001	-2.0±14.7	-23.7±19.1	<0.001	0.03±19.7	-24.4±18.5	<0.001

Values are mean±standard deviation. OSA=obstructive sleep apnoea. CSA=central sleep apnoea. ASV=adaptive servo-ventilation. AHI=apnoea-hypopnoea index. SaO_2=arterial oxyhemoglobin saturation. TST=total sleep time. REM=rapid eye movement.

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Table 3. On-treatment analysis of the primary event comparing hazard ratios (HR) of adaptive servo-ventilation (ASV)-compliant subjects to compliant control subjects at four landmark times.

Landmark time (years)	Number in control group	Number in ASV group	HR (95% CI)	P-value
0.5	317	186	0.91 (0.69, 1.19)	0.48
1.0	284	165	0.81 (0.59, 1.11)	0.19
2.0	224	134	0.70 (.45, 1.08)	0.11
3.0	171	114	0.64 (0.46, 1.16)	0.14

Figure 1.

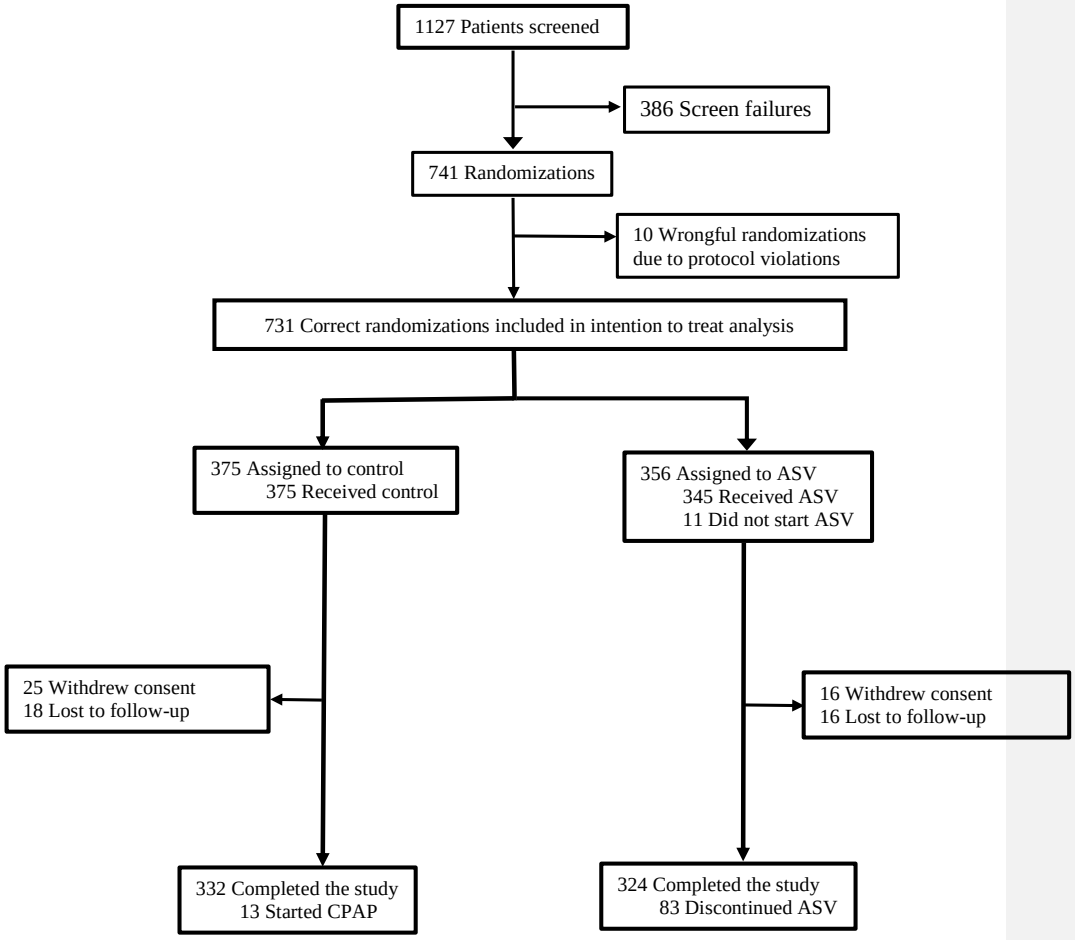
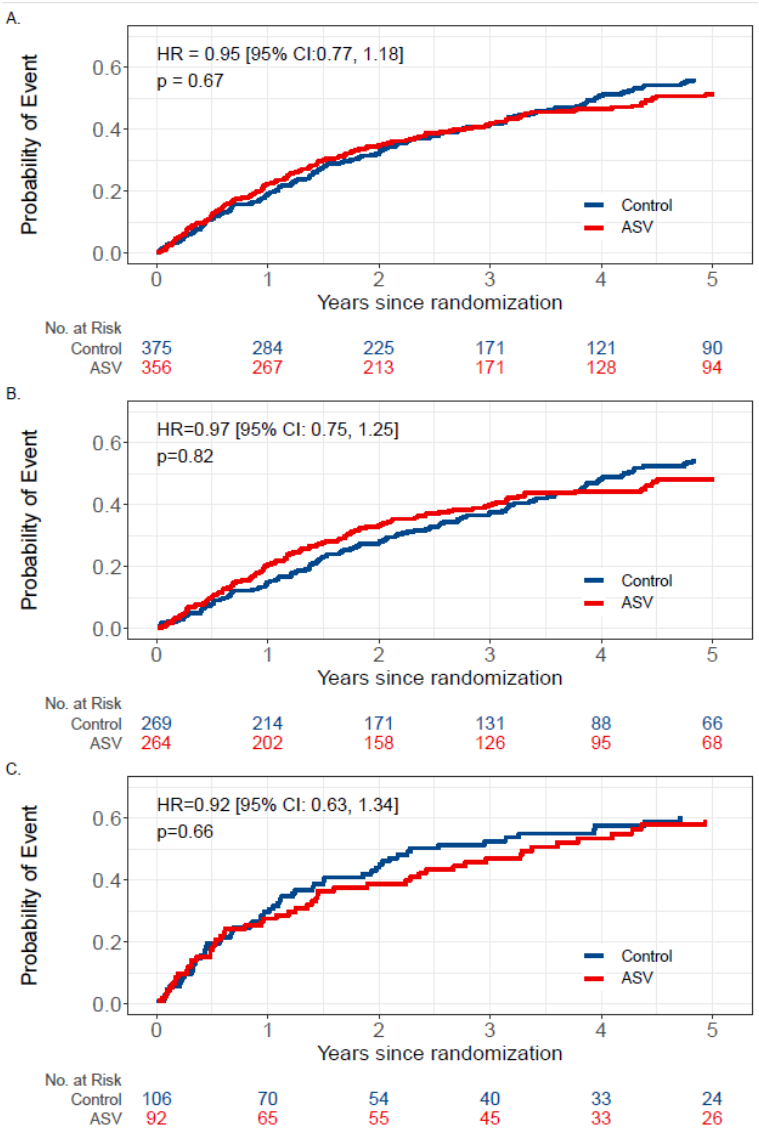

1127 Patients screened
386 Screen failures
741 Randomizations
10 Wrongful randomizations due to protocol violations
731 Correct randomizations included in intention to treat analysis
375 Assigned to control
375 Received control
356 Assigned to ASV
345 Received ASV
11 Did not start ASV
25 Withdrew consent
18 Lost to follow-up
16 Withdrew consent
16 Lost to follow-up
332 Completed the study
13 Started CPAP
324 Completed the study
83 Discontinued ASV

Figure 2.


A.
HR = 0.95 [95% CI:0.77, 1.18]
p = 0.67
Probability of Event
Years since randomization
Control
ASV
No. at Risk
Control 375 284 225 171 121 90
ASV 356 267 213 171 128 94
B.
HR=0.97 [95% CI: 0.75, 1.25]
p=0.82
Probability of Event
Years since randomization
Control
ASV
No. at Risk
Control 269 214 171 131 88 66
ASV 264 202 158 126 95 68
C.
HR=0.92 [95% CI: 0.63, 1.34]
p=0.66
Probability of Event
Years since randomization
Control
ASV
No. at Risk
Control 106 70 54 40 33 24
ASV 92 65 55 45 33 26

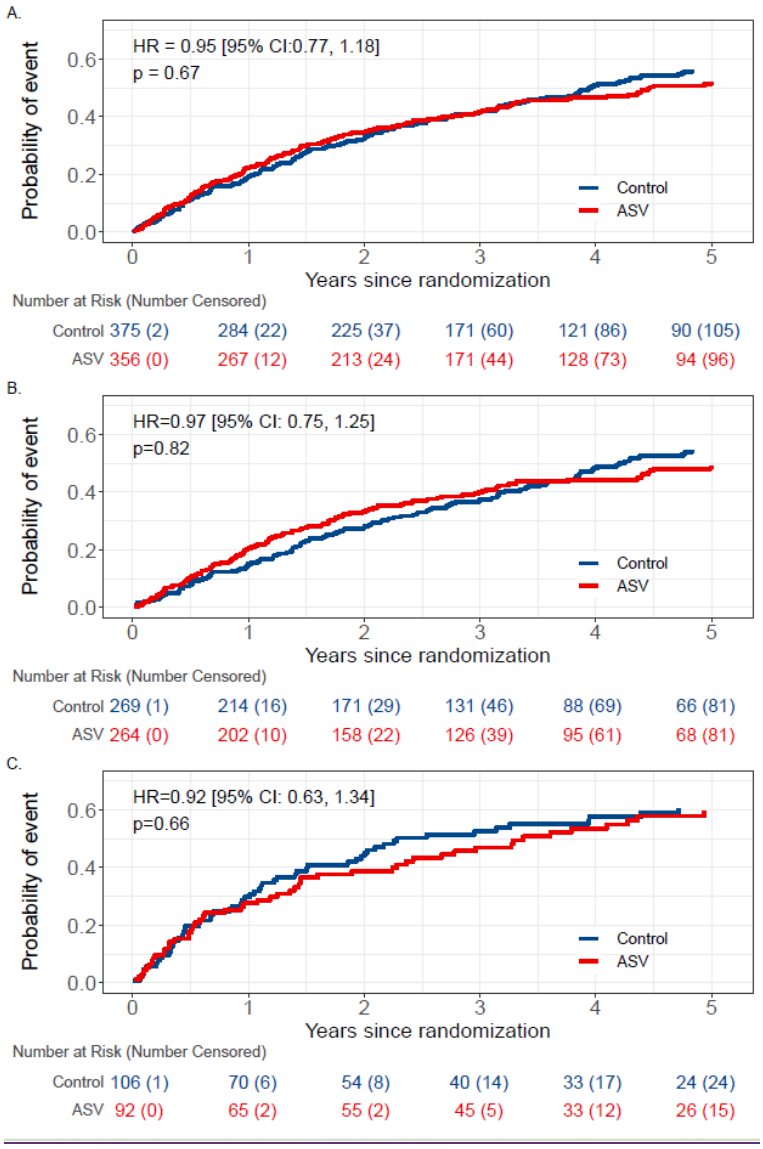
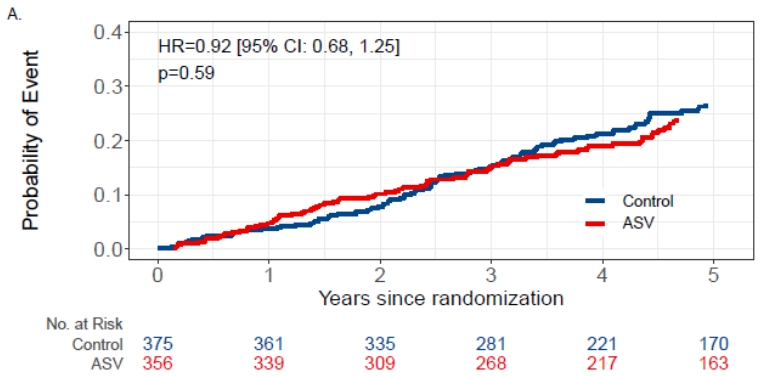
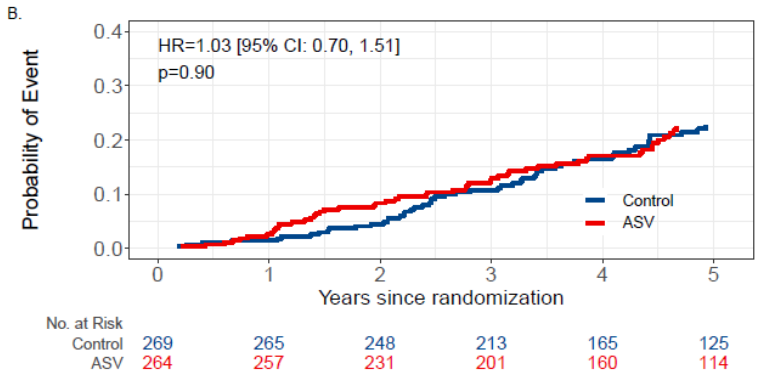
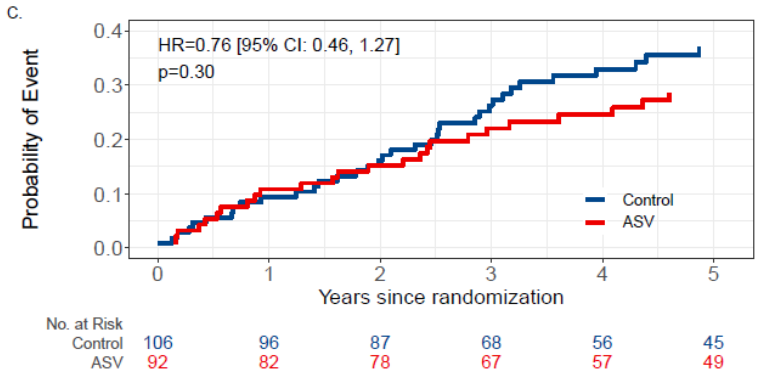

A.
HR = 0.95 [95% CI:0.77, 1.18]
p = 0.67
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 375 (2) 284 (22) 225 (37) 171 (60) 121 (86) 90 (105)
ASV 356 (0) 267 (12) 213 (24) 171 (44) 128 (73) 94 (96)
B.
HR=0.97 [95% CI: 0.75, 1.25]
p=0.82
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 269 (1) 214 (16) 171 (29) 131 (46) 88 (69) 66 (81)
ASV 264 (0) 202 (10) 158 (22) 126 (39) 95 (61) 68 (81)
C.
HR=0.92 [95% CI: 0.63, 1.34]
p=0.66
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 106 (1) 70 (6) 54 (8) 40 (14) 33 (17) 24 (24)
ASV 92 (0) 65 (2) 55 (2) 45 (5) 33 (12) 26 (15)

Figure 3.


A.
HR=0.92 [95% CI: 0.68, 1.25]
p=0.59
Probability of Event
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
5
Years since randomization
Control
ASV
No. at Risk
Control 375 361 335 281 221 170
ASV 356 339 309 268 217 163


B.
HR=1.03 [95% CI: 0.70, 1.51]
p=0.90
Probability of Event
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
5
Years since randomization
Control
ASV
No. at Risk
Control 269 265 248 213 165 125
ASV 264 257 231 201 160 114


C.
HR=0.76 [95% CI: 0.46, 1.27]
p=0.30
Probability of Event
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
5
Years since randomization
Control
ASV
No. at Risk
Control 106 96 87 68 56 45
ASV 92 82 78 67 57 49

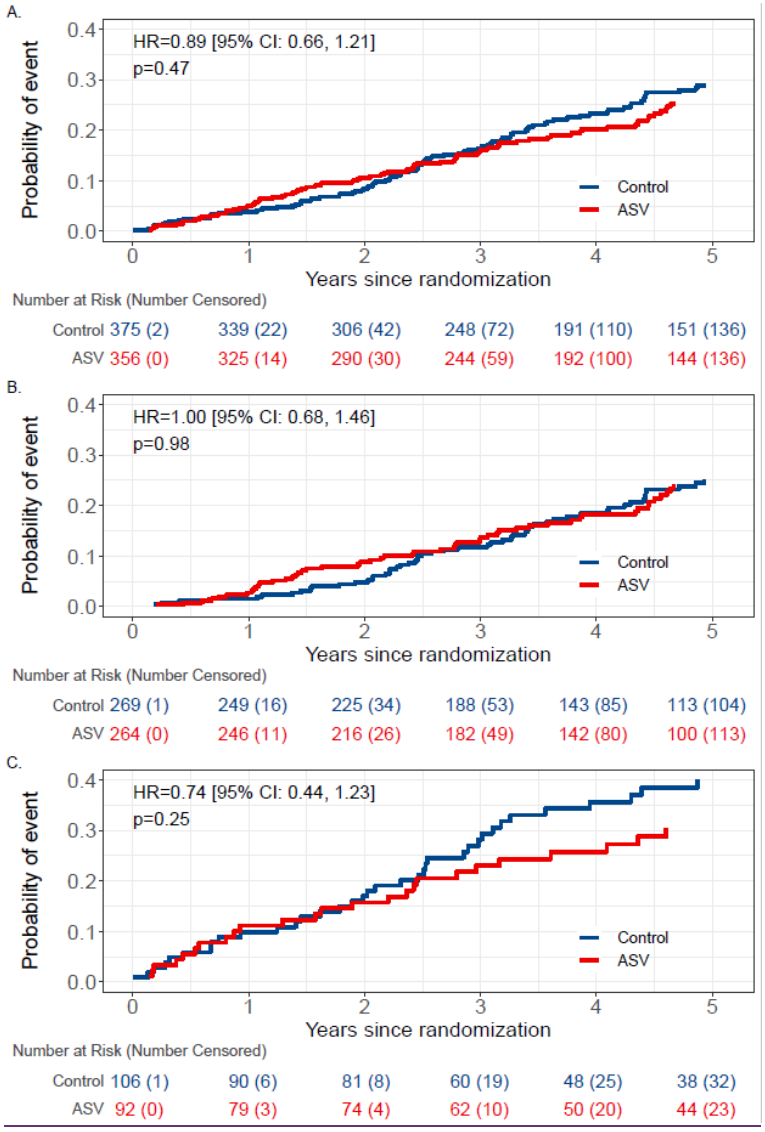
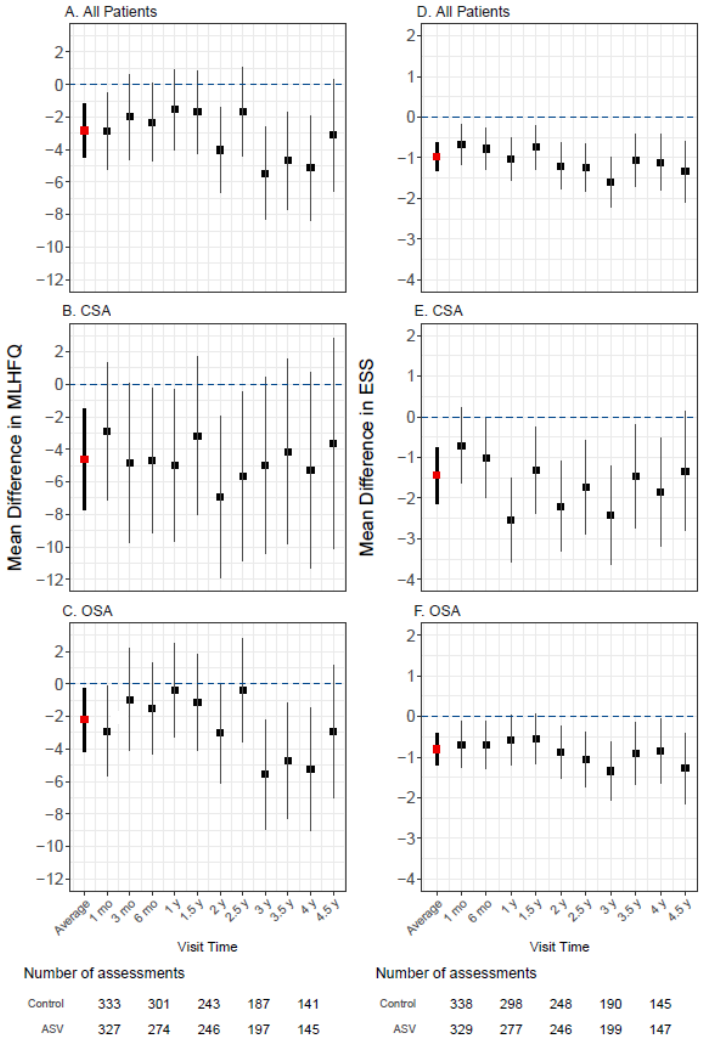
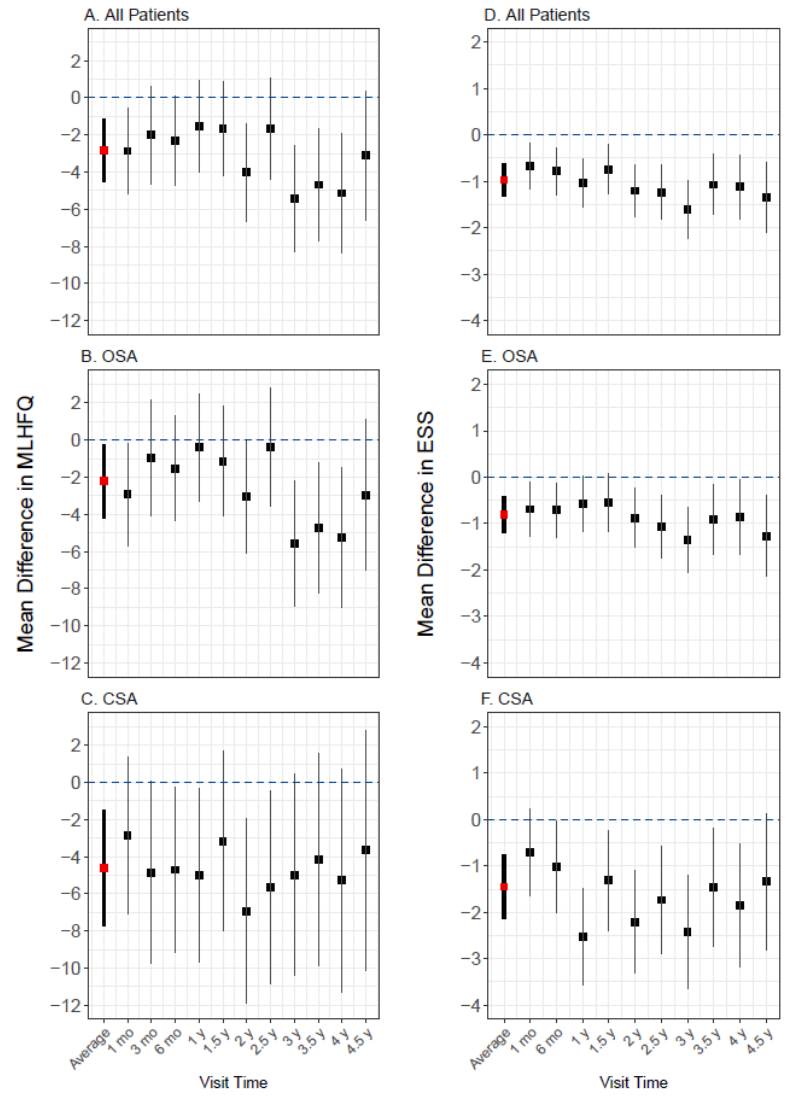

A.
HR=0.89 [95% CI: 0.66, 1.21]
p=0.47
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 375 (2) 339 (22) 306 (42) 248 (72) 191 (110) 151 (136)
ASV 356 (0) 325 (14) 290 (30) 244 (59) 192 (100) 144 (136)
B.
HR=1.00 [95% CI: 0.68, 1.46]
p=0.98
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 269 (1) 249 (16) 225 (34) 188 (53) 143 (85) 113 (104)
ASV 264 (0) 246 (11) 216 (26) 182 (49) 142 (80) 100 (113)
C.
HR=0.74 [95% CI: 0.44, 1.23]
p=0.25
Probability of event
Years since randomization
Control
ASV
Number at Risk (Number Censored)
Control 106 (1) 90 (6) 81 (8) 60 (19) 48 (25) 38 (32)
ASV 92 (0) 79 (3) 74 (4) 62 (10) 50 (20) 44 (23)

Figure 4.


A. All Patients
B. CSA
C. OSA
D. All Patients
E. CSA
F. OSA
Mean Difference in MLHFQ
Mean Difference in ESS
Average
1 mo
3 mo
6 mo
1 y
1.5 y
2 y
2.5 y
3 y
3.5 y
4 y
4.5 y
Visit Time
Number of assessments
Control 333 301 243 187 141
ASV 327 274 246 197 145
Number of assessments
Control 338 298 248 190 145
ASV 329 277 246 199 147


A. All Patients
B. OSA
C. CSA
D. All Patients
E. OSA
F. CSA
Mean Difference in MLHFQ
Mean Difference in ESS
Average
1 mo
3 mo
6 mo
1 y
1.5 y
2 y
2.5 y
3 y
3.5 y
4 y
4.5 y
Visit Time
Visit Time
Number of assessments
Control 333 301 243 187 141
ASV 327 274 246 197 145
Number of assessments
Control 338 298 248 190 145
ASV 329 277 246 199 147