

Clinical Research

Win Ratio Analysis for Peak-Flow Adaptive Servoventilation in Treating Sleep Apnoea in Heart Failure With Reduced Ejection Fraction

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See editorial by Turgeon and MacDonald, pages 1422-1424 of this issue.

ABSTRACT

Background: Conventionally, cardiovascular trials evaluate impact on morbid and mortal events. “Win ratio” analyses adding symptom relief and quality of life end points can assess broader intervention effects. Applying win ratio principles, we conducted a *post hoc* analysis of ADVENT-HF trial findings.

Methods: ADVENT-HF examined the impact of treating obstructive (OSA) or central (CSA) sleep apnoea with the use of peak flow-triggered adaptive servoventilation (ASV_{PF}) in patients with heart failure with reduced ejection fraction. After pre-randomisation stratification into OSA (n = 533) and CSA (n = 198) cohorts, participants were randomly allocated to standard care (n = 375) or standard care plus ASV_{PF} (n = 356). The following trial end points were compared over shared follow-up time of pairs of treated and control participants in a descending hierarchic order: 1) all-cause death; 2) cardiovascular hospitalisations; 3) improvement from baseline at 1 year in 2 or more of the Epworth Sleepiness Scale, Minnesota Living With Heart Failure Quality of Life, or New York Heart Association functional class scores; 4) change from baseline in the sum of stage N3 and rapid eye movement (REM) sleep stage duration; and 5) change from baseline in arousals.

Results: The win ratio calculated on sequential addition of outcomes to the hierarchy was 1.18 (95% CI 1.00-1.39). The win difference was 7.6%. The principal contributions to the latter were quality of life

RÉSUMÉ

Contexte : Traditionnellement, les essais cliniques cardiovasculaires évaluent l'impact d'une intervention sur les événements morbides et mortels. Les analyses de « win ratio », qui intègrent des critères d'évaluation tels que le soulagement des symptômes et la qualité de vie, permettent d'évaluer les effets d'une intervention de manière plus globale. En appliquant les principes du « win ratio », nous avons mené une analyse *a posteriori* des résultats de l'essai clinique ADVENT-HF.

Méthodologie : L'essai ADVENT-HF a examiné l'impact du traitement de l'apnée obstructive du sommeil (AOS) ou de l'apnée centrale du sommeil (ACS) à l'aide d'une ventilation auto-asservie déclenchée par le débit de pointe (ASV_{PF}) chez des patients atteints d'insuffisance cardiaque avec fraction d'éjection réduite. Après une stratification pré-randomisation en cohortes AOS (n = 533) ou ACS (n = 198), les participants ont été randomisés entre soins standard (n = 375) ou soins standard associés à l'ASV_{PF} (n = 356). Les critères d'évaluation suivants ont été comparés sur une période de suivi commune entre des paires de participants traités et témoins, par ordre hiérarchique décroissant : 1) mortalité toutes causes confondues; 2) hospitalisations pour cause cardiovasculaire; 3) amélioration par rapport à l'état initial à 1 an, pour au moins deux des scores suivants : échelle de somnolence d'Epworth, qualité de vie selon le « Minnesota Living with Heart Failure Quality of Life » ou selon la classe fonctionnelle de la New York Heart Association; 4) variation par rapport à la valeur

Keywords: adaptive servoventilation; central sleep apnoea; heart failure; obstructive sleep apnoea; mortality; quality of life; win ratio

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See page 1536 for disclosure information.

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The Adaptive Servoventilation on Survival and Hospital Admissions in Heart Failure (ADVENT-HF; NCT01128816) trial was the largest to examine the impact of treating obstructive (OSA) or central (CSA) sleep apnoea in patients with heart failure with reduced ejection fraction (HFrEF) using peak flow-triggered adaptive servoventilation (ASV_{PF}).¹ ASV_{PF} abolished both forms of sleep apnoea and the accompanying hypoxemia effectively and safely. However, unforeseen extrinsic events reduced recruitment and event rates.¹

(4.2%) and time in stage 3 plus REM sleep (2.1%). Ranking quality of life second increased the win ratio to 1.22 (95% CI 1.04-1.43) and the win difference to 9.1%.

Conclusions: A win ratio analysis incorporating ADVENT-HF clinical and patient-relevant end points favours overall ASV_{PF} treatment benefit. ASV_{PF} appeared to be more effective in the CSA cohort in terms of adherence, sleep structure, and quality of life.

Secondary Analysis of ADVENT-HF: NCT01128816.

The ADVENT-HF trial found no statistically significant effect on the primary composite end point, comprising all-cause mortality, cardiovascular hospitalisations, heart transplant, left ventricular device implantation, new-onset atrial fibrillation and appropriate defibrillator discharge. Nevertheless, abolishing these sleep-related breathing disorders improved sleep quality and architecture, symptoms of day-time sleepiness and heart failure, and heart failure-related quality of life indices. Importantly, ADVENT-HF was the first large randomised clinical trial (RCT) of treating sleep-related breathing disorders in HFrEF to demonstrate such impact on sleep quality.

When the trial was designed, the statistical plan of analysis followed contemporary convention, focusing on time to first occurrence of morbid and mortal events. However, since then, heart failure commentators have placed greater weight on patient-focused end points, such as relief of symptoms, and alternate analytic methods have emerged and achieved widespread application. One such method, termed the “win ratio,”² first assigns a hierarchy of importance to clinically meaningful outcomes from the trial. Then, within pairs comprising 1 control and 1 treated participant, the method steps down the hierarchy, making comparisons at each level, stopping when either the intervention or control participant is declared to be the “winner,” or when the comparisons are completed without a winner, such that the pair is tied. The ratio of the number of pairs where the intervention participant wins to the number where the control participant wins is the win ratio, which has been described as a “valuable tool in the analysis of RCTs.”²⁻⁵ Furthermore, it has been noted that adding a quantitative outcome such as a quality of life score has proven to be valuable in assessing the broader effects of an intervention in instances where trials fell short on statistical power for the primary outcome.⁴ The purpose of the present *post hoc* analysis of ADVENT-HF trial events was to apply win ratio principles to examine the impact of abolishing OSA and CSA on a hierarchy of mortality, morbidity, and symptom-related end points.

Methods

Study summary

The ADVENT-HF trial protocol, institutional ethics approval and informed consent processes, CONSORT flow diagram, and

initiale de la somme de la durée du sommeil de stade N3 et du sommeil paradoxal (REM) ; et 5) variation par rapport à la valeur initiale du nombre de micro-éveils.

Résultats : Le « win ratio » calculé par ajout séquentiel et hiérarchique des critères d'évaluation était de 1,18 (intervalle de confiance [IC] à 95 % : 1,00-1,39). La différence de bénéfice était de 7,6 %. Les principales contributions à cette dernière étaient la qualité de vie (4,2 %) et la durée du sommeil de stade 3 et du sommeil paradoxal (2,1 %). Le fait de classer la qualité de vie en deuxième position a fait passer le « win ratio » à 1,22 (IC à 95 % : 1,04-1,43) et la différence de bénéfice à 9,1 %.

Conclusions : Une analyse de « win ratio » intégrant les critères cliniques et les critères pertinents pour les patients de l'essai ADVENT-HF est en faveur d'un bénéfice global du traitement par ASV_{PF}. L'ASV_{PF} est apparu plus efficace dans la cohorte ACS en termes d'observance, de structure du sommeil et de qualité de vie.

Analyse secondaire des résultats de ADVENT-HF: NCT01128816.

primary and principal secondary end point data have been previously published.¹ Consent forms permitting publication of ADVENT-HF trial data were obtained from all patients.

In brief, ADVENT-HF was a parallel-group, open-label, phase 3 randomised controlled trial of ASV_{PF} with concealed allocation and blinded outcome assessments, conducted at 49 sites in 9 countries, involving adults with stable treated heart failure, left ventricular ejection fraction $\leq 45\%$, and sleep-disordered breathing (apnoea-hypopnoea index [AHI] ≥ 15 events/h of sleep). Before randomisation, potential participants underwent in-laboratory overnight polysomnography. Core Sleep Laboratory scoring of sleep stages, arousals from sleep, and identification and quantitation of obstructive and central apnoeas and hypopnoeas conformed to standard contemporary criteria.¹ Sleep-disordered breathing was stratified *a priori* into either predominantly OSA with an Epworth Sleepiness Scale (ESS) score⁶ of ≤ 10 or predominantly CSA. Individuals with OSA and an ESS score > 10 were excluded. Eligible participants were stratified by study site and sleep apnoea type (OSA or CSA) and then randomly assigned in a 1:1 ratio, with permuted blocks of sizes 4 and 6 in random order, to continue guideline-directed heart failure therapy alone or to add ASV_{PF} to treat OSA and CSA. Clinical status was reviewed and Minnesota Living With Heart Failure Questionnaire (MLFHFQ) score, ESS score, and New York Heart Association (NYHA) functional class were assessed 1, 3, and 6 months after randomisation and every 6 months thereafter to a maximum of 5 years. Polysomnography was repeated 1 month after random assignment. Participants who were randomly allocated ASV_{PF} wore the device during this study. The primary end point was the cumulative incidence of the composite end point of all-cause mortality, first admission to hospital for a cardiovascular indication, new-onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock. All-cause mortality was a secondary end point. Analysis for the primary outcome was according to intention to treat. Mean and maximum follow-ups were 3.7 and 5 years, respectively.

Hierarchic analysis

Win ratio analysis was conducted according to current recommendations.^{2,3,5} The levels in the hierarchy of specific

ADVENT-HF trial end points selected for comparison were, in descending order: 1) all-cause death, including heart transplantation and left ventricular assist device implantation, which were prespecified as such in the ADVENT-HF protocol; 2) number of cardiovascular hospitalisations; 3) a quality of life composite, comprising the ESS score, the MLFHQ scale, and the NYHA dyspnoea class; 4) change from baseline in the sum of stage N3 and rapid eye movement (REM) sleep stage duration; and 5) change from baseline in the frequency of arousals per hour of sleep (Arousal Index). Within each treated and control patient pair, the following rules were used to assign a winner: All-cause death (level 1) and numbers of hospitalisations (level 2) were compared over the shared follow-up time within the pair. A win on the quality of life composite (level 3) was assigned to the patient who had the more favourable score on 2 or more of the 3 indices. Details concerning the custom code generated to perform this analysis, which was not feasible with existing software, are provided in [Supplemental Appendix S1](#). Wins on the 2 polysomnography outcomes (levels 4 and 5) were assigned to the patient with a larger increase from baseline in the sum of REM and stage N3 sleep and to the patient with a larger decrease from baseline in the arousal index. If either member of a pair was missing the outcomes needed to decide a winner at a particular level of the hierarchy, or if the 2 members had the same value of the outcome, the pair were considered to be tied at that level. The win ratio was calculated without stratification (based on all pairs of the ASV_{PF} and control patients) and within strata formed by the predominant apnoea type used by ADVENT-HF in the stratified randomisation. Win ratio estimates were pooled across strata with the use of the Mantel-Haenszel method.⁷ The contribution of each level of the hierarchy to the win ratio was presented as a figure, as suggested by Gregson et al.⁵

In addition, 2 secondary sensitivity analyses were performed. Acknowledging that many patients with heart failure value long-term quality of life considerations over freedom from hospitalisation, in the first analysis, the quality of life composite was evaluated before hospitalisations. In the second analysis, new-onset atrial fibrillation or flutter and appropriate implanted defibrillator discharge (2 trial primary end points with infrequent occurrence) were pooled with cardiovascular hospitalisations; this tier was relabelled as nonfatal cardiovascular events.

Results

A total of 731 eligible patients (mean left ventricular ejection fraction $33.2\% \pm 7.8\%$; mean $\pm$ S.D.) were randomly allocated to receive standard care ($n = 375$; mean AHI 42.8 ± 20.9 events/h of sleep) or standard care plus ASV_{PF} ($n = 356$; 43.3 ± 20.5 events/h of sleep). Of these, 533 patients constituted the OSA cohort and 198 patients the CSA cohort. There was no important difference, at baseline, in medical therapies or clinical characteristics between those allocated to the control group and those allocated to ASV_{PF} ([Table 1](#)). Of those allocated to standard care, 332 participants completed the study; 13 (all with OSA) were initiated on continuous positive airway pressure by their treating physicians. Of those allocated to treatment (ie, ASV_{PF}), 324 participants completed the study, of whom 72 discontinued ASV_{PF}.

Hazard ratios (HRs) for all-cause mortality in those allocated ASV_{PF} were 0.89 overall (95% CI 0.66-1.21; $P = 0.47$), 1.00 in the cohort with OSA (95% CI 0.68-1.46; $P = 0.98$), and, 0.74 in the cohort with CSA (95% CI 0.44-1.23; $P = 0.25$). The numbers first admitted to hospital for a cardiovascular reason were similar between participants

Table 1. Participant characteristics at randomisation

	Control			ASV _{PF}		
	All	OSA	CSA	All	OSA	CSA
n	375	269	106	356	264	92
Age, y	63.6 $\pm$ 10.1	62.1 $\pm$ 10.0	65.2 $\pm$ 10.3	62.7 $\pm$ 11.1	60.5 $\pm$ 10.5	67.1 $\pm$ 11.5
Male sex	327 (87)	228 (85)	99 (93)	318 (89)	228 (86)	90 (98)
Body mass index, kg/m ² *	30.7 $\pm$ 5.6	31.4 $\pm$ 5.9	28.7 $\pm$ 4.8	30.8 $\pm$ 6.1	31.4 $\pm$ 6.2	29.1 $\pm$ 5.3
Left ventricular ejection fraction, % *	33.3 $\pm$ 7.9	33.8 $\pm$ 4.8	32.1 $\pm$ 7.9	33.1 $\pm$ 7.7	33.6 $\pm$ 7.2	31.4 $\pm$ 9.1
Sleep apnoea type, n (%)	375	269 (71.7)	106 (28.3)	356	264 (74.2)	92 (25.8)
Apnoea-hypopnoea index, events/h	42.8 $\pm$ 20.9	39.7 $\pm$ 21.1	50.6 $\pm$ 18.3	43.3 $\pm$ 20.5	40.7 $\pm$ 20.8	50.5 $\pm$ 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
Epworth Sleepiness Scale score	6.4 $\pm$ 3.3	6.0 $\pm$ 2.9	7.4 $\pm$ 4.0	6.0 $\pm$ 3.5	5.6 $\pm$ 3.0	7.2 $\pm$ 4.5
Minnesota Living with Heart Failure Questionnaire score	32.5 $\pm$ 21.9	32.9 $\pm$ 21.8	31.5 $\pm$ 22.4	33.1 $\pm$ 23.0	33.4 $\pm$ 22.6	32.5 $\pm$ 24.1
New York Heart Association functional class						
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)
Total sleep time, h	5.1 $\pm$ 1.3	5.1 $\pm$ 1.3	4.8 $\pm$ 1.2	5.2 $\pm$ 1.3	5.3 $\pm$ 1.3	4.8 $\pm$ 1.4
Sleep efficiency, %	70 $\pm$ 15	71 $\pm$ 16	68 $\pm$ 14	71 $\pm$ 17	73 $\pm$ 16	66 $\pm$ 19
Stage N1, min	42.1 $\pm$ 30.1	38.2 $\pm$ 26.9	52.0 $\pm$ 35.1	43.5 $\pm$ 31.7	42.6 $\pm$ 32.1	46.0 $\pm$ 30.8
Stage N2, min	189.7 $\pm$ 57.3	194.5 $\pm$ 57.0	177.3 $\pm$ 56.4	196.4 $\pm$ 61.5	201.5 $\pm$ 59.9	181.7 $\pm$ 63.7
Stage N3, min	31.4 $\pm$ 27.9	34.1 $\pm$ 29.2	24.7 $\pm$ 22.9	30.1 $\pm$ 27.4	32.2 $\pm$ 27.2	24.28 $\pm$ 27.4
Stage REM, min	40.1 $\pm$ 25.2	41.3 $\pm$ 25.6	36.9 $\pm$ 24.3	40.2 $\pm$ 27.7	42.0 $\pm$ 28.5	34.8 $\pm$ 24.8
Arousal index, no. of events/h*	41.3 $\pm$ 22.9	39.8 $\pm$ 20.8	47.2 $\pm$ 26.7	41.1 $\pm$ 19.9	39.8 $\pm$ 19.2	44.9 $\pm$ 21.3

Values are mean $\pm$ SD or n (%).

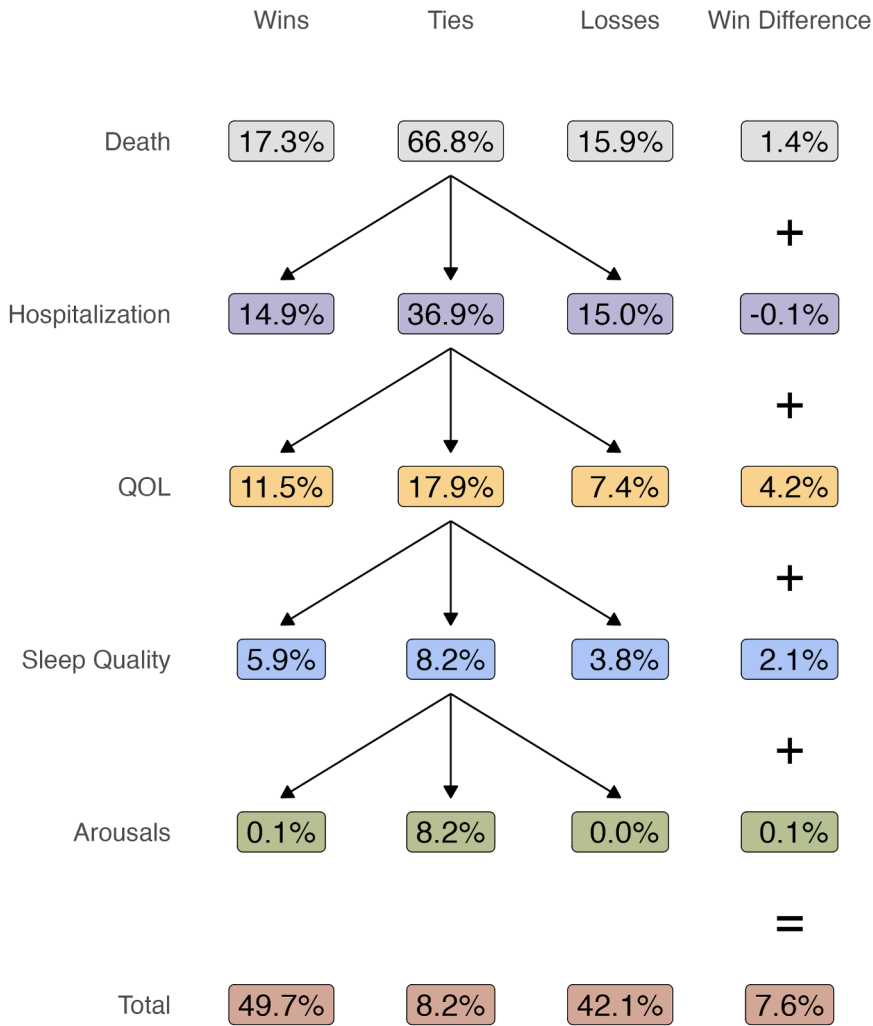
ASV_{PF}, peak flow-triggered adaptive servoventilation; CSA, central sleep apnoea; OSA, obstructive sleep apnoea; REM, rapid eye movement.

randomised to ASV_{PF} and control patients overall (HR 1.06, 95% CI 0.84-1.33; $P = 0.65$), in the OSA cohort (HR 1.08, 95% CI 0.82-1.43; $P = 0.60$) and in the CSA cohort (HR 1.02, 95% CI 0.67-1.56; $P = 0.91$). At 1 year, the MLHFQ score, ESS score, and NYHA functional class improved in those allocated to ASV_{PF}. Data for each component are presented in [Supplemental Table S1](#). The sum of stage N3 sleep and REM stage sleep increased by a mean of 1.1 ± 42 minutes in the control group vs 19.5 ± 49 minutes in those allocated to ASV_{PF} ($P < 0.0001$). For the OSA cohort and the CSA cohort, respectively, these differences were 1.1 ± 41 minutes vs 17.2 ± 49 minutes ($P = 0.0001$) and 1.0 ± 44 minutes vs 25.6 ± 46 minutes ($P = 0.0004$). The mean arousal frequency fell by 1.3 events/h in the control group and 18 events/h in those allocated to ASV_{PF} ($P < 0.0001$), with similar changes noted in these groups within the OSA cohort and the CSA cohort.¹

In a nonstratified analysis of 133,500 pairs, the win ratio was 1.18 (95% CI 1.00-1.39) and the win difference was 7.6%. The principal contributions to this win difference were improvement in quality of life measures at 1 year (4.2%) and improvement in time spent in stage 3 and REM sleep (2.1%) ([Central Illustration](#)).

When stratified according to predominant sleep-disordered breathing phenotype, the win ratio for the OSA cohort (71,016 pairs) was 1.12 (0.93-1.36), the win ratio for the CSA cohort (9,752 pairs) was 1.31 (95% CI 0.94-1.81), and the pooled win ratio, which is a weighted average of the stratum-specific win ratios, was 1.17 (95% CI 0.99-1.38), with a P value for heterogeneity of 0.44.

In the secondary analysis, when the quality of life composite was ranked above cardiovascular hospitalisations or the sum of nonfatal cardiovascular events, the win ratio was 1.22 (95% CI 1.04-1.43) in the nonstratified analysis. The win



Win Ratio = 49.7%/42.1% = 1.18 [95% CI: 1.00, 1.39]

Central Illustration. Sequential win differences for hierarchy of ADVENT-HF outcomes in nonstratified analysis. QOL, quality of life composite, comprising improvement from baseline to 1 year in 2 or more of the Epworth Sleepiness Scale, Minnesota Living with Heart Failure Quality of Life scale, and New York Heart Association dyspnea class. Win ratios = 49.7%/42.1% = 1.18 (95% CI 1.00-1.39).

difference for the quality of life composite increased from 4.2% to 6.6% (Central Illustration; Fig. 1). The overall win difference was 9.1% (Fig. 2). When stratified according to predominant sleep apnoea phenotype, the win ratio for the OSA cohort was 1.14 (95% CI 0.95-1.38), the win ratio for the CSA cohort was 1.39 (95% CI 1.01-1.91), and the pooled win ratio was 1.20 (95% CI 1.02-1.41), with a *P* value for heterogeneity of 0.30.

Discussion

In this *post hoc* analysis of the ADVENT-HF trial data, win ratio principles were applied to examine the impact of abolishing OSA and CSA on a hierarchy of paired mortality, morbidity, and symptom-related end points. The principal

novel findings were a positive win ratio (1.18, 95% CI 1.00-1.39) and a win difference of 7.6%. When stratified first by sleep-disordered breathing cohort, smaller sample sizes led to broader confidence intervals within strata, but ratios still consistent with an overall treatment benefit: 1.12 for OSA and 1.31 for CSA. Considering the adverse effects on mortality in patients with CSA and HFrEF in the SERVE-HF trial, which tested an earlier iteration of ASV (minute ventilation triggered; ASV_{MV}),^{1,8} the latter ratio is particularly reassuring.

The ADVENT-HF trial was the largest randomised controlled trial to evaluate the impact of a positive airway pressure intervention on mortality and cardiovascular outcomes in patients with HFrEF and OSA and the largest to evaluate the impact of ASV_{PF} on these outcomes in patients

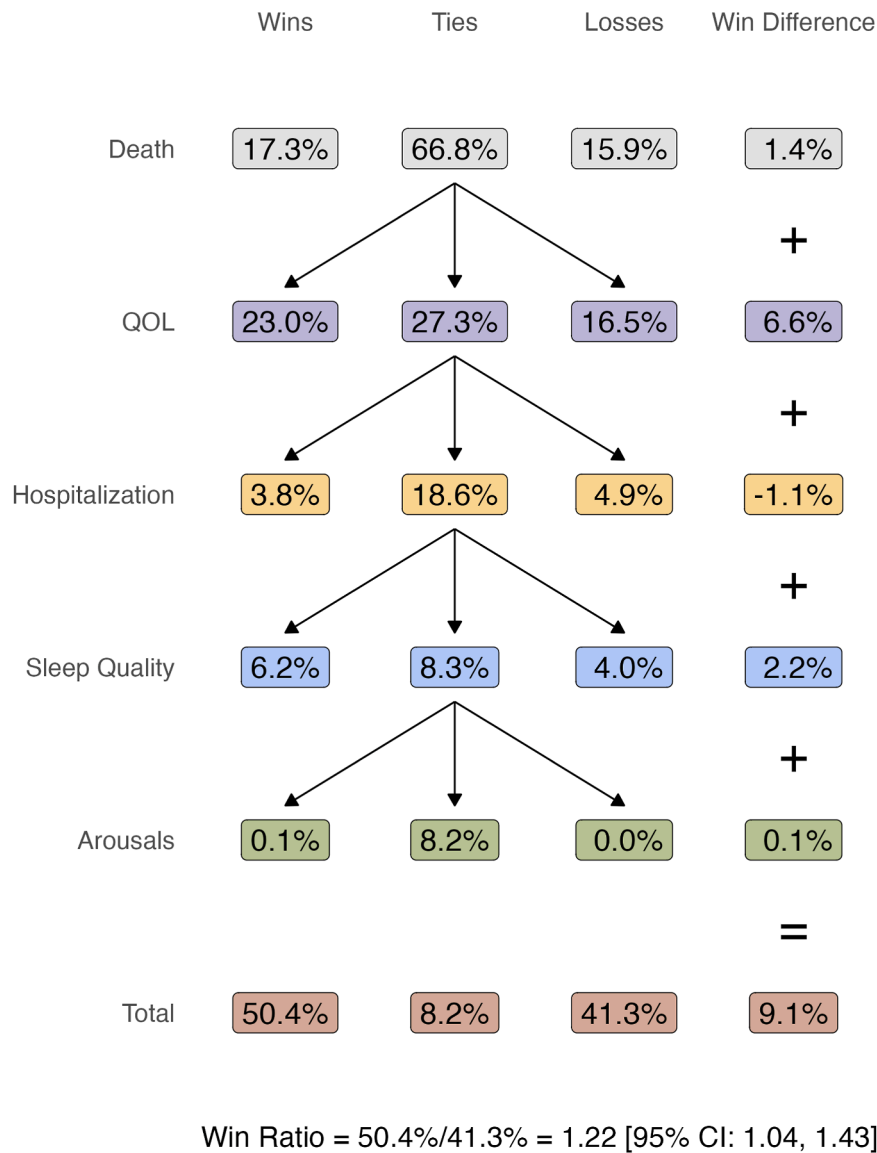


Figure 1. Sequential win differences for hierarchy of ADVENT-HF outcomes in nonstratified sensitivity analysis with QOL and hospitalization rankings reversed. QOL, quality of life composite, comprising improvement from baseline to 1 year in 2 or more of the Epworth Sleepiness Scale, Minnesota Living with Heart Failure Quality of Life scale, and New York Heart Association dyspnea class. Win ratio = 50.5%/41.4% = 1.22 (95% CI 1.04-1.43).

with CSA. At its conception, assuming a control group rate of 0.35 events/y, it was calculated that a sample of 860 patients, equally split between OSA and CSA, would give rise to 540 primary events over 5 years and provide 82% power (at a 5% type 1 error) to detect a treatment effect with HRs of 0.75 for OSA and 0.80 for CSA (combined 0.775) in a Cox proportional hazards analysis.⁹

This objective was thwarted by unanticipated circumstances, resulting in a lower than anticipated number of primary events. In 2015, increased mortality rates detected in the SERVE-HF trial among those randomly allocated to ASV_{MY}, which used a different, CSA-specific, treatment algorithm,⁸ triggered a Field Safety Notice¹⁰ declaring that ASV was contraindicated for therapy of CSA in patients with HFrEF. French and German regulatory authorities then prohibited recruitment of patients with CSA into ADVENT-HF. In other participating countries, the rate of enrollment declined. In March 2021, Covid-19–related closure of in-hospital sleep laboratories caused enrollment to cease. In June 2021, worldwide recall of Philips positive airway devices because of potential disintegration of the motor sound-abatement material obliged premature termination of follow-up.¹

For the intention-to-treat analysis, only 198 of the anticipated 430 patients with CSA were enrolled. The mean follow-up time to the first primary event or censoring was 2.8 years, and 346 of the anticipated 540 primary events occurred. ASV_{PF}, used on average 4 hours nightly, abolished both OSA and CSA effectively and safely over the course of the trial and improved quality of life indices significantly. For the 198 participants with HFrEF and predominantly CSA, an HR for all-cause mortality of 0.74 (95% CI 0.44–1.23; $P = 0.25$) suggested potential ASV_{PF} treatment benefit. ADVENT-HF was a landmark trial in other respects. Importantly, it was the first large randomised clinical trial of any form of positive airway pressure involving patients with HFrEF to document a significant and substantial improvement in sleep structure and quality with treatment.^{1,11} Considering these findings and the range of patient symptom evaluations integrated into the ADVENT-HF protocol, the question then arises as to whether patients allocated ASV_{PF} derived a net health benefit.

Three developments, pertinent to this question, prompted the present *post hoc* analysis: 1) increasing emphasis and recognition on the value to the patient with heart failure of symptom relief^{12–16}; 2) inclusion of validated patient questionnaires for risk prediction^{12–17}; and 3) the application of novel analytical methods that factor outcomes concordant with patient goals.^{2–5} With equal priority given to each component of a conventional primary composite time-to-event analysis, a constituent less meaningful to the patient may have undue influence on the overall calculation. The win ratio, which prioritises hierarchically the composite's components by patient benefit, addresses this limitation.⁴ In general, the highest priority is ascribed to death, followed by hospitalisations, then changes in self-reported health status, quality of life, and physical function.⁴ Of note, whereas the conventional time-to-first event analysis for a composite outcome would not include a death—the most critical end point—occurring after a hospitalisation, in the win ratio analysis that death would be the first point of comparison within a pair.

Importantly, the principal contributors to the positive ratio in the present primary analysis were wins in patient-focused quotidian values: quality of life and quality of sleep. In the secondary analysis, in which quality of life ranked above cardiovascular hospitalisations, the win difference was augmented, resulting in a win ratio of 1.22 (95% CI 1.04–1.43). Because left ventricular structure and ejection fraction did not change in those allocated to ASV_{PF},¹⁸ improvement within these domains cannot be attributed to greater cardiac output.

The adverse impact of apnoea-induced sleep disruption on mood, fatigue, and other facets of quality of life can be severe, yet sleep quality is rarely evaluated as a clinical trial end point.¹⁹ Individuals with heart failure sleep significantly less than those without heart failure.²⁰ In those with breathing disorders, frequent superimposition of apnoeas and arousals disrupt sleep further. By improving sleep quality, in addition to abolishing apnoea, ASV_{PF} has the potential to lessen the symptomatic consequences of disrupted sleep. In the ASV_{PF}-treated cohort with CSA, there was a remarkable 23.5-minute improvement in the time spent in stage N3 and REM sleep, and a 5-point improvement (considered to be clinically significant²¹) in the MLHFQ score, which includes physical (including difficulty sleeping, resting during the day, and fatigue) as well as emotional and social dimensions. In the ASV_{PF}-treated cohort with OSA, the sum of stage N3 and REM sleep increased, on average, by 17.1 minutes.

Only a minority of patients with HFrEF and sleep-related breathing disorders reports high ESS scores, likely because OSA, CSA, and recurring arousals stimulate the reticular activating and sympathetic nervous systems. These effects carry over into wakefulness and diminish once apnoea is treated.^{22–29} In the ADVENT-HF trial, among those with OSA, an ESS score > 10 , signifying daytime sleepiness, was a key exclusion criterion. Despite relatively low ESS scores at enrollment (5.9 ± 3.0 in the OSA stratum; 7.3 ± 4.2 in the CSA stratum), there was a > 2 point reduction 1 year after enrollment in the ASV_{PF}-treated CSA, indicating alleviation of these sleepiness symptoms.¹ In a “sleepy” population, a change of this magnitude is considered to be clinically important.⁶ In all participants allocated to ASV_{PF}, there was a significant 1-point reduction over the entire follow-up period.¹

Gregson et al.⁵ recently identified 36 randomised clinical trials published from January 2022 to July 2024 involving, in total, 95,722 participants with a cardiovascular disorder allocated to a pharmaceutical intervention (27), a procedure (7), or a treatment strategy (3) with a calculated win ratio. Of these, 3 also calculated a win difference. Win ratios among these 36 trials ranged from 0.81 to 1.95, with the median being 1.275. The 4 win differences ranged from 1.0% to 4.9%. Of the 4 trials that allocated drug or device interventions to participants with chronic stable HFrEF, win ratios ranged from 1.10 (ferric carboxymaltose) to 1.53 (patiromir).⁵

In retrospective analyses, tests of devices, such as percutaneous aortic valve replacement or mitral valve clipping have yielded, in general, higher win differences in terms of death and hospitalisation (26.8% and 17.0%, respectively), relative to tests of drug therapy, such as empagliflozin in patients with heart failure and preserved ejection fraction (2.7%); higher win differences were reported when the hierarchy added

Table 2. Secondary sensitivity analyses with the quality of life (QOL) composite situated third or second in the analytic hierarchy and new-onset atrial fibrillation and appropriate defibrillator discharge excluded or included as nonfatal cardiovascular events

QOL 3rd in hierarchy	Stratified analysis			Unstratified analysis		
	Win ratio			Wins/ties/losses	Win difference	Win ratio
	CSA	OSA	Pooled estimate			
AF and ICD as CV events						
Excluded	1.29 (0.93-1.79)	1.13 (0.93-1.36)	1.17 (0.99-1.38)	49.7%/8.2%/42.1%	7.6%	1.18 (1.00-1.39)
Included	1.25 (0.90-1.73)	1.13 (0.93-1.37)	1.16 (0.99-1.37)	49.6%/8.2%/42.3%	7.3%	1.17 (0.99-1.38)
QOL 2nd in hierarchy	Stratified analysis			Unstratified analysis		
	Win ratio			Wins/ties/losses	Win difference	Win ratio
	CSA	OSA	Pooled estimate			
AF and ICD as CV events						
Excluded	1.39 (1.01-1.91)	1.14 (0.95-1.38)	1.20 (1.02-1.41)	50.4%/8.2%/41.3%	9.1%	1.22 (1.04-1.43)
Included	1.38 (1.00-1.89)	1.15 (0.95-1.38)	1.20 (1.02- 1.41)	50.5%/8.2%/41.4%	9.1%	1.22 (1.04-1.43)

Ranges in parentheses are 95% confidence intervals. Pooled estimates were calculated with the use of the Mantel-Haenszel approach. *P* values for heterogeneity between the OSA and CSA strata were, with QOL 3rd, 0.48 and 0.60 and, with QOL 2nd, 0.30 and 0.33, by exclusion and inclusion of AF and ICD as CV events, respectively.

AF, atrial fibrillation or flutter; CV, cardiovascular; ICD, implanted cardioverter-defibrillator; QOL, quality of life composite.

quality of life indices, a measure of functional status, or a surrogate biomarker (14.9% for empagliflozin for acute heart failure; 27.8% for acoramidis for amyloid cardiomyopathy).⁴ In contrast, in a heart failure trial that randomised 43 participants to active phrenic nerve stimulation to treat CSA and 48 to a control group whose implanted device was not activated for 6 months, a 3-tier hierarchic analysis which incorporated longest survival, lowest heart failure hospitalisation rate, and ≥ 2 -category difference in a Patient Global Assessment at 6 months reported a win ratio of 4.92 (95% CI 2.27-10.63) and a win difference of 42%.³⁰ However, rather than abolishing CSA, phrenic nerve stimulation reduced the AHI by $\sim 50\%$, and, because that trial was not designed to evaluate mortality, deaths were very infrequent and therefore played little role in the hierarchic win assessment. The predominant contributor (33.5%) to this win difference was the change in Patient Global Assessment.

Several limitations merit acknowledgement. The present analysis was *post hoc* and exploratory, not an analysis that was prespecified in the ADVENT-HF protocol. A win ratio analysis was not envisaged when the trial was designed in 2008. The lower confidence interval of the win ratio was 1.00 in the nonstratified analysis, which conforms to the primary trial presentation, and 0.99 in the stratified analysis, but because we did not find statistical heterogeneity between the win ratios in the 2 strata, such pooling may have needlessly reduced precision. The principal contributions to the positive win difference were the improved quality of life indices. Although intrinsically subjective, these case report data, which record participants' narrative responses to identical standardised questions posed at each visit, provide the closest reflection of their perceived limitations. Concurrent objective improvement in sleep structure likely contributed to symptom improvement.

The hierarchic progression was conventional, starting with the trial's principal cardiovascular (all-cause death and cardiovascular hospitalisation), before proceeding to symptom, quality of life, and sleep-related end points. Some with heart failure express preference for a life of abbreviated duration but higher quality. Because this *post hoc* analysis was conceived after the trial's termination, there was no opportunity for this hierarchic sequence to be informed by the experience of its

participants. Hypothesising that many with heart failure might have valued long-term symptom improvement over freedom from hospitalisation, we performed a sensitivity analysis in which their hierarchic order was transposed. The result was a greater win difference (9.1% vs 7.6%); the lower 95% confidence limit of the win ratio was 1.04 in the non-stratified analysis and 1.02 in the stratified analysis.

Conclusion

In terms of its primary composite end point, ADVENT-HF was a neutral trial, but as recently argued, to interpret such as evidence of treatment ineffectiveness is a potentially inaccurate oversimplification.³¹ From a holistic perspective, the present win ratio analysis incorporating ADVENT-HF clinical and patient-relevant end points argues in favour of overall treatment benefit. This benefit was amplified in the secondary analysis, which ranked the quality of life composite above hospitalisation. This is an observation of particular importance for patients with HFrEF and CSA, in whom ASV_{PF} treatment safely and effectively abolished CSA, with very good adherence, and improved sleep structure and heart failure-related quality of life indices. Overall, ASV_{PF} tended to be more effective in these respects in those with CSA than with OSA (Table 2). The ASV_{PF} device applied in the ADVENT-HF trial had different effects on mortality, sleep quality, and quality of life indices than the ASV_{MV} algorithm used in the SERVE-HF trial.³²

The present finding that ASV_{PF} has an overall net benefit on clinical outcomes should stimulate future exploration of ASV_{PF} efficacy on cardiovascular end points in adequately powered randomised clinical trials. It also provides stronger evidence in support of the American Academy of Sleep Medicine's conclusions that a systematic review does not support a class effect of ASV on mortality in patients with HFrEF and that ASV can be used to treat CSA in heart failure based on evidence of improved sleep quality.³³

Acknowledgements

The ADVENT-HF Investigators are listed in Supplemental Appendix S2.

Ethics Statement

The ADVENT-HF trial was conducted 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 of the 49 participating hospital sites, in 9 countries.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This is a secondary analysis of a previously published randomised clinical trial. Patient consent forms were obtained from all participants before their enrollment into that trial.

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Disclosures

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Editorial Disclaimer

Given his role as Associate Editor, Dr Floras had no involvement in the peer review of this article and had no access to information regarding its peer review.

References

- Bradley TD, Logan AG, Lorenzi Filho G, et al. 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. *Lancet Respir Med* 2024;12:153-66.
- Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite end points in clinical trials based on clinical priorities. *Eur Heart J* 2012;33:176-82.
- Finkelstein DM, Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Stat Med* 1999;18:1341-54.
- Pocock SJ, Gregson J, Collier TJ, Ferreira JP, Stone GW. The win ratio in cardiology trials: lessons learnt, new developments, and wise future use. *Eur Heart J* 2024;45:4684-99.
- Gregson J, Taylor D, Owen R, et al. Hierarchical composite outcomes and win ratio methods in cardiovascular trials: a review and consequent guidance. *Circulation* 2025;151:1606-19.
- Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: minimum clinically important difference in obstructive sleep apnea. *Am J Respir Crit Care Med* 2018;197:961-3.
- Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. *J Biopharm Stat* 2018;28:778-96.
- Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. *N Engl J Med* 2015;373:1095-105.
- Lyons OD, Floras JS, Logan AG, et al. Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: The ADVENT-HF trial. *Eur J Heart Fail* 2017;19:579-87.
- ResMed: Urgent field safety notice. Preprint posted online. www.resmed.com/magnetupdate.
- Ruttanaumpawan P, Logan AG, Floras JS, Bradley TD; CANPAP Investigators. Effect of continuous positive airway pressure on sleep structure in heart failure patients with central sleep apnea. *Sleep* 2009;32:91-8.
- Zannad F, Stein K, Garcia AA, et al. Clinical outcome end points in heart failure trials: a European Society of Cardiology Heart Failure Association consensus document. *Eur J Heart Fail* 2013;15:1082-94.
- Potoka MA, Abraham WT, Fiuzat M, et al. Functional and symptomatic clinical trial end points: the HFC-ARC Scientific Expert Panel. *JACC Heart Fail* 2022;10:889-901.
- Cannata A, Bromage DI, Piper SE, McDonagh TA. Heart failure with preserved ejection fraction: prioritizing patients' symptoms. *J Am Coll Cardiol* 2024;84:258-9.
- Sideris K, Zhang M, Wohlfahrt P, et al. Integration of patient reported quality-of-life data into risk assessment in heart failure. *J Card Fail* 2025;31:761-70.
- Volterrani M, Halasz G, Adamopoulos S, et al. Quality of life in heart failure. The heart of the matter. A scientific statement of the Heart Failure Association and the European Association of Preventive Cardiology of the European Society of Cardiology. *Eur J Heart Fail* 2025;27:1159-73.
- Burns DJP, Arora J, Okunade O, et al. International Consortium for Health Outcomes Measurement (ICHOM): standardized patient-centered outcomes measurement set for heart failure patients. *JACC Heart Fail* 2020;8:212-22.
- Yatsu S, Woo A, Horvath CM, et al. LV structure and function in HFrEF with and without peak-flow-triggered adaptive servo-ventilation-treated sleep-disordered breathing. *JACC Heart Fail* 2026;14:102434.
- Waking up to the importance of sleep. *Lancet* 2022;400(10357):973.
- Arzt M, Young T, Finn L, et al. Sleepiness and sleep in patients with both systolic heart failure and obstructive sleep apnea. *Arch Intern Med* 2006;166:1716-22.
- Rector TS, Tschumperlin LK, Kubo SH, et al. Use of the Living with Heart Failure questionnaire to ascertain patients' perspectives on improvement in quality of life versus risk of drug-induced death. *J Card Fail* 1995;1:201-6.
- Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. *J Clin Invest* 1995;96:1897-904.
- Spaak J, Egri ZJ, Kubo T, et al. Muscle sympathetic nerve activity during wakefulness in heart failure patients with and without sleep apnea. *Hypertension* 2005;46:1327-32.
- Usui K, Bradley TD, Spaak J, et al. Inhibition of awake sympathetic nerve activity of heart failure patients with obstructive sleep apnea by nocturnal continuous positive airway pressure. *J Am Coll Cardiol* 2005;45:2008-11.

25. Taylor KS, Murai H, Millar PJ, et al. Arousal from sleep and sympathetic excitation during wakefulness. *Hypertension* 2016;68:1467-74.
26. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. *N Engl J Med* 2005;353:2025-33.
27. Naughton MT, Benard DC, Liu PP, et al. Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. *Am J Respir Crit Care Med* 1995;152:473-9.
28. Taranto Montemurro L, Floras JS, Picton P, et al. Relationship of heart rate variability to sleepiness in patients with obstructive sleep apnea with and without heart failure. *J Clin Sleep Med* 2014;10:271-6.
29. Taranto Montemurro L, Floras JS, Millar PJ, et al. Inverse relationship of subjective daytime sleepiness to sympathetic activity in patients with heart failure and obstructive sleep apnea. *Chest* 2012;142:1222-8.
30. Abraham WT, Oldenburg O, Lainscak M, et al. Win ratio analysis of transvenous phrenic nerve stimulation to treat central sleep apnoea in heart failure. *ESC Heart Fail* 2025;12:80-6.
31. Khan MS, Jamil A, Januzzi JL, et al. POINT: statistical nonsignificance, likelihood ratio, and the interpretation of clinical trial evidence: insights from heart failure randomized trials. *J Card Fail* 2024;30:1629-32.
32. Bradley TD, Logan AG, Floras JS. Treating sleep disordered breathing for cardiovascular outcomes: observational and randomised trial evidence. *Eur Respir J* 2024;64:2401033.
33. Badr MS, Khayat RN, Allam JS, et al. Treatment of central sleep apnea in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2025;21:2181-91.

Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at <https://doi.org/10.1016/j.cjca.2026.03.019>.