SUPPLEMENTAL MATERIALS Treatment of Central Sleep Apnea in Adults

All Literature Search Terms

(("sleep"[MeSH Terms] AND "apnea"[MeSH Terms]) OR "central sleep apnea"[All Fields] OR "central sleep apnoea"[All Fields] OR "CSA"[All Fields] AND ("heart failure"[All Fields] OR "reduced ejection fraction"[All Fields] OR "Cheyne Stokes"[All Fields] OR "Cheyne Stokes Respiration"[All Fields] OR "medication"[All Fields] OR "substance"[All Fields] OR "narcotics"[All Fields] OR "opioids"[All Fields] OR "medical condition"[All Fields] OR "condition"[All Fields] OR "disorder"[All Fields] OR "stroke"[All Fields] OR "end-stage renal disease" [All Fields] OR "spinal cord injury" [All Fields] OR "neurologic disorder" [All Fields] OR "traumatic brain injury" [All Fields] OR "high altitude" [All Fields] OR "high altitude periodic breathing"[All Fields] OR "hypoxia"[All Fields] OR "hypoxemic"[All Fields] OR "treatment emergent"[All Fields] OR "therapy emergent"[All Fields])) AND ("carbonic anhydrase inhibitors"[All Fields] OR "zolpidem"[All Fields] OR "triazolam"[All Fields] OR "temazepam"[All Fields] OR "hypnotics"[All Fields] OR "intervention" [All Fields] OR "treatment" [All Fields] OR "pharmacological" [All Fields] OR "medication"[All Fields] OR "pharmacotherapy"[All Fields] OR "positive airway pressure"[All Fields] OR "PAP"[All Fields] OR "APAP"[All Fields] OR "automatic positive airway pressure"[All Fields] OR "bilevel pressure"[All Fields] OR "BPAP"[All Fields] OR "continuous positive airway pressure"[All Fields] OR "CPAP"[All Fields] OR "Adaptive Servo-Ventilation"[All Fields] OR "oxygen"[All Fields] OR "oxygen therapy"[All Fields] OR "phrenic nerve stimulation"[All Fields] OR "positional therapy"[All Fields])) AND (Adult[MeSH Terms] OR Adult[All Fields]) Filters applied: Clinical Study, Clinical Trial, Controlled Clinical Trial, Multicenter Study, Observational Study, Randomized Controlled Trial, Humans, English

Exclusion Criteria

Exclusion criteria are applied during the abstract review of all retrieved publications. Studies that meet <u>any</u> of the exclusion criteria are rejected from the systematic review.

- A. Publication type
 - a. Book and book chapters
 - b. Conference abstracts
 - c. Dissertations
 - d. Editorials
 - e. Letters to the editor
 - f. Methods papers
 - g. Case reports or case series
 - h. Single case design or pilot
 - i. Review papers (systematic reviews, narrative reviews, and meta-analysis)
- B. Study type
 - a. animal research
- C. Language
 - a. non-English
- D. Patients
 - a. Did not undergo treatment for central sleep apnea
 - b. Not adults (anyone under 18 years of age)

Inclusion Criteria

Inclusion criteria are applied during the full publication review of all publications that were not rejected during the abstract review. Studies that **meet all inclusion criteria will be accepted as evidence to use in the systematic review.**

- A. Outcomes of interest (must meet at least 1)
 - a. Apnea-hypopnea index
 - b. Daytime functioning or work performance
 - c. Disease severity
 - d. Fatigue
 - e. Insomnia
 - f. Vigilance/alertness
 - g. Overall quality of life
 - h. Oxygen desaturation index
 - i. Sleep quality (patient reported)
 - j. Sleepiness during the day
 - k. Cardiovascular disease/stroke
 - I. Cognitive functioning
 - m. Hospitalization
 - n. Mortality
 - o. Sleep quality (psg)
 - p. Cycle length
 - q. Mental quality of life
 - r. Vigilance/alertness, wakefulness
- B. Publication type
 - a. RCTs:
 - i. Intervention vs placebo
 - ii. Intervention vs no treatment
 - iii. Intervention vs standard of care
 - iv. Intervention vs sham
 - b. Observational studies: longitudinally/cross-sectionally examines the effect(s) of the intervention
- C. Patients
 - a. Adults with a diagnosis of central sleep apnea
- D. Interventions (must include at least 1)
 - a. Acetazolamide
 - b. Triazolam
 - c. Hypnotics
 - d. Zolpidem
 - e. PAP therapy
 - f. APAP
 - g. BPAP

- h. CPAP
- i. ASV
- j. Oxygen therapy
- k. Phrenic nerve stimulation
- I. Positional therapy

Abbreviations:

6MWD – 6-minute walk distance AHI – Apnea hypopnea index

ASV – Adaptive servo ventilation

BNP – B-type natriuretic peptide

BPAP – Bilevel positive airway pressure

BPAP-ST – Bilevel positive airway pressure-spontaneous time

CAHI – Central apnea hypopnea index

- CAI Central apnea index
- CSA Central sleep apnea

CST – Clinical significance threshold

CPAP – Continuous positive airway pressure

DBP - Diastolic blood pressure

ESS – Epworth Sleepiness Scale

GRADE – Grading of Recommendations, Assessment, Development and Evaluation

HR - Heart rate

LVEF - Left ventricular ejection fraction

MLHFQ - Minnesota living with heart failure questionnaire

MWT – Maintenance of wakefulness test

NT pro-BNP - N-terminal pro-B-type natriuretic peptide

NYHA - New York Heart Association classification

ODI – Oxygen desaturation index

PAP - Positive airway pressure

PASAT - Paced auditory serial addition task

PICO - Patient, intervention, comparator, outcome

POMS-A – Profile of moods-adolescent

PSG – Polysomnography

PSQI – Pittsburgh sleep quality index

PVT – Psychomotor vigilance test

RCT – Randomized controlled trial

REM – Rapid eye movement

SD – Standard deviation

SF-36 – Short form 36 health questionnaire

SMD – Standardized mean-difference

SBP - Systolic blood pressure

SSS - Stanford Sleepiness Scale

SWS – Slow-wave sleep

TIB – Time in bed

PICO 1: Adults with primary CSA, CSA due to heart failure, CSA due to a medical condition or disorder, CSA due to a medication or substance, treatment- emergent CSA

CPAP

Summary of Findings (GRADE)

Table S1 CPAP in adults with CSA

References: Bradley 2005, Granton 1996, Kasai 2010, Kasai 2013, Köhnlein 2002, Naughton 1994, Naughton 1995, Naughton 1995 (Am J Resp), Philippe 2006, Sin 2000, Teschler 2001

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	CPAP vs. baseline or control	
Excessive sleepiness [ESS]	⊕⊖⊖⊖ VERY LOW ^{a, b}	The mean difference in the CPAP group was 1.86 points fewer (3.71 fewer to 0.0 fewer) compared to baseline	42 (3 RCTS)
Disease severity [AHI]	⊕⊕⊕⊕ нісн	The mean difference in the CPAP group was 17.43 events/ hour fewer (21.01 fewer to 13.86 fewer) compared to control	363 (6 RCTs)
Disease severity [CAI]	⊕⊕⊖⊖ LOW ^{b,c}	The mean difference in the CPAP group was 17.3 events/hour lower (25.76 lower to 8.84 lower) compared to control	28 (1 RCTs)
Cardiovascular disease [6MWD]	⊕⊕⊕⊖ MODERATE ^c	The mean difference in the CPAP group was 20.8 meters more (6.14 more to 35.46 more) compared to control	258 (1 RCT)
Hospitalizations [Hospitalizations per patient per year]	⊕⊕⊕⊖ MODERATE₫	The mean difference in the CPAP group was 0.05 events higher (0.11 lower to 0.21 higher) compared to control	258 (1 RCT)
Mortality [reported deaths]		The risk ratio in the CPAP group was 0.87 (0.58 to 1.28) with an absolute risk of 19 fewer per 1,000 (63 fewer to 42 more) compared to control	324 (2 RCTs)

a. Downgraded quality of evidence due to RCT data analyzed using pre- and posttreatment values

b. Imprecision due to small sample size (<200 participants)

c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

d. Imprecision is present because of a small number of events leading to wide confidence intervals

e. Imprecision due to the 95% CI includes possibility for important benefit and harm

Critical Outcomes

Figure S1. CPAP vs. Baseline (Excessive sleepiness, ESS) [CST= -2 pts], RCTs (single-arm preposttreatment data)

	CPAP Baseline							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.1.1 CSA due to CHF									
Kasai 2010	5.7	3.5	15	8.4	3.9	15	47.7%	-2.70 [-5.35, -0.05]	
Kasai 2013	6.7	4	11	7.2	2.3	11	45.2%	-0.50 [-3.23, 2.23]	
Köhnlein 2002	7.5	9.6	16	12.3	10.4	16	7.1%	-4.80 [-11.74, 2.14]	
Subtotal (95% CI)			42			42	100.0%	-1.86 [-3.71, -0.00]	◆
Heterogeneity: Tau ² =	0.05; C	hi²=	2.03, df	'= 2 (P =	= 0.36)); I ² = 2°	%		
Test for overall effect: .	Z = 1.98	6 (P =	0.05)						
Total (95% CI)			42			42	100.0%	-1.86 [-3.71, -0.00]	•
Heterogeneity: Tau ² =	0.05; C	hi² =	2.03, df	= 2 (P =	= 0.36)				
Test for overall effect: Z = 1.96 (P = 0.05)									-20 -10 0 10 20 Eavours CPAP Eavours Baseline
Test for subgroup diffe	erences	: Not	applica	able					

Figure S2. CPAP vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs

	CPAP		С	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 CSA due to heart failure									
Bradley 2005	-21	16	128	-2	18	130	73.9%	-19.00 [-23.15, -14.85]	
Granton 1996	17	21	9	19	22.6	8	2.9%	-2.00 [-22.82, 18.82]	
Naughton 1994	23.2	20.8	12	36.7	30.9	6	1.7%	-13.50 [-40.88, 13.88]	
Naughton 1995	18.5	18	9	28.6	21.6	9	3.8%	-10.10 [-28.47, 8.27]	
Naughton 1995 (Am J Respir Crit Care Med)	14.7	15.2	12	27	17.3	12	7.5%	-12.30 [-25.33, 0.73]	
Teschler 2001	26.8	17.2	14	44.5	12.7	14	10.2%	-17.70 [-28.90, -6.50]	
Subtotal (95% CI)			184			179	100.0%	-17.43 [-21.01, -13.86]	◆
Heterogeneity: Tau ² = 0.00; Chi ² = 3.95, df = 5	(P = 0.58	5); I ² =	0%						
Test for overall effect: Z = 9.57 (P < 0.00001)									
Total (95% CI)			184			179	100.0%	-17.43 [-21.01, -13.86]	•
Heterogeneity: Tau ² = 0.00; Chi ² = 3.95, df = 5	(P = 0.58	6); ² =	0%						-50 -25 0 25 50
Test for overall effect: Z = 9.57 (P < 0.00001)									Favours CPAP Favours Control
Test for subgroup differences: Not applicable									

Teschler 2001, Naughton 1994, Granton 1996, Naughton 1995, Naughton (Am J Respir Crit Care Med) 1995: SEM converted to SD; Bradley 2005: data reported as change from baseline.

Figure S3. CPAP vs. Control (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCT

		CPAP			Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
17.3.1 IC \$D3								
Teschler 2001	18.5	11.9733	14	35.8	10.8508	14	-17.30 [-25.76, -8.84]	
								-20 -10 0 10 20
								Favours CPAP Favours Control

Teschler 2001: SEM converted to SD

Figure S4. CPAP vs. Control (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT

	С	PAP		Co	ontro	I	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
17.4.1 IC \$D3									
Teschler 2001	22.6	3.8	14	38.2	2.6	14	-15.60 [-18.01, -13.19]	+-	
								Favours CPAP Favours Control	

*Teschler 2001: Change from baseline

Figure S5. CPAP	vs. Control (Cardi	ovascular disease	, 6MWD (chang	ge score)	[CST= +32 meters], RCT
	•					

	CPAP			C	ontrol		Mean Difference		Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	l, 95% Cl			
17.7.1 IC \$D3													
Bradley 2005	20	55	128	-0.8	64.8	130	20.80 [6.14, 35.46]						
								-50	-25				
								-50 Fa	vours Control	Favours CPA	р Э		

Figure S6. CPAP vs. Control (Cardiovascular disease, LVEF (%)) [CST= +5%], RCTs

	C	CPAP Control						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.6.1 IC \$D3									
Granton 1996	32.6	6.6	9	19.5	2.8	8	17.8%	13.10 [8.37, 17.83]	_ _
Naughton 1994	20.3	3.2	12	19	3.8	6	19.8%	1.30 [-2.24, 4.84]	
Naughton 1995	28.9	5.2	12	19.2	2.4	12	20.3%	9.70 [6.46, 12.94]	_ _ _
Naughton 1995 (Am J Respir Crit Care Med)	23.5	5.2	9	18.4	3.4	9	18.9%	5.10 [1.04, 9.16]	
Sin 2000	2.5	0.1	14	0.5	0.7	15	23.2%	2.00 [1.64, 2.36]	•
Subtotal (95% CI)			56			50	100.0%	5.99 [1.85, 10.12]	◆
Heterogeneity: Tau ² = 19.15; Chi ² = 44.37, df =	4 (P ≤ 0.	0000)1); I² =	91%					
Test for overall effect: Z = 2.84 (P = 0.005)									
Total (95% CI)			56			50	100.0%	5.99 [1.85, 10.12]	◆
Heterogeneity: Tau ² = 19.15; Chi ² = 44.37, df =	4 (P ≤ 0.	0000)1); I² =	91%				-	-20 -10 0 10 20
Test for overall effect: Z = 2.84 (P = 0.005)									Eavours Control Eavours CPAP
Test for subgroup differences: Not applicable									

Figure S7. CPAP vs. Control (Cardiovascular disease, Systolic BP (mmHg)) [CST= - 2 mmHg], RCT

	CPAP			C	ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Naughton 1995	119.6	26.1	9	105	18.3	9	14.60 [-6.23, 35.43]	· · · · · · · · · · · ·
								-50 -25 0 25 50
								Favours CPAP Favours Control

Figure S8. CPAP vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT

	CPAP			C	ontrol		Mean Difference	Mean Difference				
Study or Subgroup	Mean SD Total			Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 9	5% CI	
Naughton 1995	72	13.2	9	71.9	13.8	9	0.10 [-12.38, 12.58]					
								-20	-10		10 nunuura Cantral	20
									Favours C	PAP F	avours Control	

Figure S9. CPAP vs. Control (Cardiovascular disease, HR (beats/min)) [No CST], RCT

	CPAP			C	ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Naughton 1995	71.2	13.8	9	77.7	16.8	9	-6.50 [-20.70, 7.70]	
								-20 -10 0 10 20
								Favours CPAP Favours Control

Fi	gure S10.	CPAP vs.	. Control (Hos	pitalizations	, Hos	pitalizations	per	patient	per v	vear)	[No	CST]	, RC	Г

	Expe	rimen	tal	C	ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
17.13.1 IC \$D3								
Bradley 2005	0.61	0.72	128	0.56	0.56	130	0.05 [-0.11, 0.21]	_ +
								Favours CPAP Favours Control

Figure S11. CPAP vs. Control (Mortality, reported deaths) [CST= 0.8], RCTs

	CPA	Р	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.12.1 IC \$D3							
Sin 2000	8	31	14	35	32.1%	0.65 [0.31, 1.33]	
Bradley 2005	27	128	28	130	67.9%	0.98 [0.61, 1.57]	
Subtotal (95% CI)		159		165	100.0%	0.87 [0.59, 1.29]	•
Total events	35		42				
Heterogeneity: Chi ² =	0.90, df=	1 (P=	0.34); l² =	= 0%			
Test for overall effect:	Z = 0.69 ((P = 0.4)	9)				
Total (95% CI)		159		165	100.0%	0.87 [0.59, 1.29]	-
Total events	35		42				
Heterogeneity: Chi ² =	0.90, df=	1 (P =	0.34); l² =	= 0%			
Test for overall effect:	Z = 0.69 ((P = 0.4	9)				Eavours CPAP Eavours Control
Test for subgroup diff	erences:	Not ap	plicable				

· ·		CDAD	-	D	analina			Moon Difforonco	Mean Difference
Study or Subaroup	Moon	CPAP	Total	Moon	aseiiiie	Total	Woight	Weall Difference	Weall Difference
2.2.4 Drimony CSA	Weall	30	Total	Weall	30	Total	weight	IV, Rahuom, 95% Ci	IV, Railuoin, 95% Ci
Z.J.T Phillidly C.SA	6.0			20.4	47.4		740	24 00 / 22 47 47 62	
Verbreesken 2002	5.2	3.7	23	30.1	17.4	23	7.1%	-24.90 [-32.17, -17.03]	
Zhong 2021	8 9	9	9	00	10	9	0.0% 5.0%	-42.00[-03.43,-30.07] 64.00[66.04_44.06]	
Subtotal (95% CI)	0	(.)	9 41	00		9 41	18.9%	-39.80 [-57.55, -22.05]	◆
Heterogeneity: Tau ² :	= 217.98;	Chi ^z =	18.42, (df = 2 (P	< 0.00	01); I ^e =	89%		
Test for overall effect	: Z = 4.39	(P ≤ 0.	0001)						
2.3.2 CSA due to CH	F								
Arzt 2005	12.2	13.5	14	35.9	15	14	6.2%	-23.70 [-34.27, -13.13]	_ -
Arzt 2008	22	4	14	46	4	14	7.9%	-24.00 [-26.96, -21.04]	+
Arzt 2009	22.2	12.6	10	41.8	19.2	10	5.2%	-19.60 [-33.83, -5.37]	<u> </u>
Dohi 2008	17.7	31.9	20	52.3	36.1	20	3.7%	-34.60 [-55.71, -13.49]	
Hu 2006	18.5	5	11	30.9	8.3	11	7.4%	-12.40 [-18.13, -6.67]	
Kasai 2010	15.4	12.8	15	38.6	13.9	15	6.5%	-23.20 [-32.76, -13.64]	_ _
Kasai 2013	23.1	9.1	11	23	7.9	11	7.1%	0.10 [-7.02, 7.22]	-
Köhnlein 2002	7.7	22.4	16	26.7	42.8	16	3.2%	-19.00 [-42.67, 4.67]	
Philippe 2006	14.19	18.29	13	40.89	13.51	13	5.7%	-26.70 [-39.06, -14.34]	
Randerath 2012	17	17.9	25	40.8	17.1	25	6.5%	-23.80 [-33.50, -14.10]	_ —
Terziyski 2016	23.1	18.6	10	57.6	23.3	10	4.2%	-34.50 [-52.98, -16.02]	
Subtotal (95% CI)			159			159	63.8%	-20.55 [-26.77, -14.32]	◆
Heterogeneity: Tau ² :	= 74.34; (Chi² = 5	1.15, df	'= 10 (P	< 0.00	001); I ^z	= 80%		
Test for overall effect	: Z = 6.47	(P ≤ 0.	00001)						
225664									
2.3.5 C SA due to me	dication	or subs	stance		.				
Shapiro 2015	17.4	20.1	31	38.8	31.1	31	5.6%	-21.40 [-34.44, -8.36]	(
Troitino 2014	5.6	2	8	34.2	13.6	8	6.5%	-28.60 [-38.13, -19.07]	
Subtotal (95% CI)				= -			12.1%	-20.09 [-33.78, -18.40]	▼
Heterogeneity: I au*:	= 0.00; CI	hr=0./	16, df =	1 (P = 0	.38); 1*=	= 0%			
l est for overall effect	:Z=6.65	• (P < U.	00001)						
2.3.6 TEC SA									
Morgenthaler 2014	aa	11 1	19	37 9	20.3	19	5 3 %	-28 00 [-42 09 -13 91]	_
Subtotal (95% CI)	0.0	11.1	19	57.5	20.0	19	5.3%	-28.00 [-42.09, -13.91]	◆
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z = 3.90	I (P ≤ 0.	0001)						
Total (95% CI)			259			259	100.0%	25 10 [30 70 10 60]	
Hotorogonoity: Tou2	- 07 02:7	nhi z – O	0023 6 10 44	- 16 /0	~ 0.00	2.30 1043-12	- 020%	-20119 [-30110, -10.09]	
Toot for everall offect	- 37.02,0 • 7 - 0.00	2011°=9 :7D 2 0	0.40, UI 000043	- 10 (P	~ 0.00	001), IF	- 0370		-50 -25 0 25 50
Test for subaroun dit	. 2 – 0.90 Terences	r (r ≥ 0. 1 Chi² =	4 80 4	f= 3 (P	= 0.10\	P = 37	5%		Favours CPAP Favours Baseline

Figure S12. CPAP vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs (singlearm pre- posttreatment data) and observational studies

Kohnlein 2002: SEM converted to SD; Philippe 2006: data extracted from graph; Dohi 2008: data from responders and nonresponders pooled, SEM converted to SD; Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD. Figure S13. CPAP vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCTs (singlearm pre- posttreatment data) and observational studies

	CPAP Baseline							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.4.1 CSA due to CHE	:								
Hu 2006	15.4	4.2	11	26.1	6.5	11	28.0%	-10.70 [-15.27, -6.13]	
Randerath 2012	2.6	5.5	25	7.1	10.5	25	27.9%	-4.50 [-9.15, 0.15]	
Subtotal (95% CI)			36			36	55.9%	-7.61 [-13.69, -1.54]	
Heterogeneity: Tau ² =	: 13.69; C	>hi²=	3.47, di	f=1 (P:	= 0.06)); I ² = 7′	%		
Test for overall effect:	Z= 2.46	(P = (D.01)						
242664 due to me	diantian								
2.4.2 C SA due to me	dication	orsu	ostance	e 					
Shapiro 2015	8.4	12.4	31	16.1	18.8	31	20.3%	-7.70 [-15.63, 0.23]	
Subtotal (95% CI)			21			21	20.5%	-1.10 [-15.05, 0.25]	
Heterogeneity: Not ap	plicable	~ ·							
lest for overall effect:	Z = 1.90	(P = (J.U6)						
2.4.3 TEC \$4									
Morgenthaler 2014	4.8	64	10	22.6	12.6	10	73.8%	-17 80 6-24 15 -11 451	
Subtotal (95% CI)	4.0	0.4	19	22.0	12.0	19	23.8%	-17.80 [-24.15, -11.45]	•
Heterogeneity: Not as	nnlicable								-
Test for overall effect:	7 = 5.49	(P < (1 00001	n					
	2 0.10	· ·		·/					
Total (95% CI)			86			86	100.0%	-10.05 [-15.60, -4.51]	•
Heterogeneity: Tau² =	23.07; C	>hi²=	11.46, (df = 3 (F	? = 0.0I	09); I * =	74%	-	
Test for overall effect:	Z = 3.56	(P = 0	0.0004)						Favours CPAP Favours Baseline
Test for subgroup dif	ferences:	: Chi ²	= 6.22,	df = 2 (F	^o = 0.0	4), ² =	67.9%		

Figure S14. CPAP vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% change from baseline], RCTs (singlearm pre- posttreatment data) and observational studies

	C	PAP		Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
2.5.1 CSA due to CHF									
Randerath 2012	10.7	8.7	25	21.8	11.5	25	92.0%	-11.10 [-16.75, -5.45]	Ⅰ -₩-
Terziyski 2016	21.3	18.7	10	41.6	24.6	10	8.0%	-20.30 [-39.45, -1.15]	
Subtotal (95% CI)			35			35	100.0%	-11.84 [-17.26, -6.42]	▲
Heterogeneity: Chi ² =	0.82, df	= 1 (P	= 0.37)	; I ^z = 09	6				
Test for overall effect:	Z = 4.28) (P < ().0001)						
Total (95% CI)			35			35	100.0%	-11.84 [-17.26, -6.42]	▲
Heterogeneity: Chi ² =	0.82, df	= 1 (P	= 0.37)	; I ² = 09	6				
Test for overall effect:	Z = 4.28) (P < ().0001)						-50 -25 0 25 50 Eavours CPAP Eavours Baseline
Test for subgroup diff	erences	: Not a	pplicat	ole					Tavours of Ar Tavours Dasellife

Figure S15. CPAP vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT (singlearm pre- posttreatment data) and observational studies

	С	PAP		Ba	seline)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.6.1 Primary CSA									
Verbraecken 2002	6	6	9	48	36	9	9.8%	-42.00 [-65.84, -18.16]	
Subtotal (95% CI)			9			9	9.8%	-42.00 [-65.84, -18.16]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z= 3.45	(P = 0).0006)						
2.6.2 CSA due to CHF									
Arzt 2005	6.2	2.3	14	39.7	5.2	14	28.1%	-33.50 [-36.48, -30.52]	•
Arzt 2008	22	6	14	42	4	14	27.6%	-20.00 [-23.78, -16.22]	•
Arzt 2009	4.5	6.4	10	35.3	24.3	10	15.8%	-30.80 [-46.37, -15.23]	
Subtotal (95% CI)			38			38	71.4%	-27.70 [-38.80, -16.60]	◆
Heterogeneity: Tau ² =	79.71; C	≻hi²=	30.35, i	df = 2 (P	< 0.00	0001); I	² = 93%		
Test for overall effect:	Z= 4.89	(P < 0	0.00001)					
2.6.3 CSA due to med	lication	or sub	ostance	•					
Shaniro 2015	15.1	20.2	31	32.8	29.2	31	18.8%	-17 70 [-30 20 -5 20]	
Subtotal (95% CI)	10.1	20.2	31	02.0	20.2	31	18.8%	-17.70 [-30.20, -5.20]	•
Heterogeneity: Not an	nlicable								-
Test for overall effect:	Z = 2.78	(P = 0).006)						
			,						
Total (95% CI)			78			78	100.0%	-27.21 [-36.38, -18.04]	◆
Heterogeneity: Tau ² =	75.68; C	≿hi²=	34.37, (df = 4 (P	< 0.00	0001); I	z = 88%		
Test for overall effect:	Z = 5.82	(P < 0	0.00001)					Favoure CPAP Favoure Baseline
Test for subgroup diff	erences:	Chi ≇∘	= 3.48.	df = 2 (F	^o = 0.1	8), I ^z =	42.6%		

* Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S16. CPAP vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% change from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



Kohnlein: data extracted from the graph; SEM converted to SD

		CPAP		B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.9.1 CSA due to CHF									
Arzt 2005	35.7	9.7283	14	31.7	9.7283	14	6.6%	4.00 [-3.21, 11.21]	
Arzt 2009	36.8	6.2	10	33	10	10	6.5%	3.80 [-3.49, 11.09]	
Dohi 2008	39.2	12.1	9	29.9	8.1	9	4.3%	9.30 [-0.21, 18.81]	
Karavidas 2011	34.7	5.8	11	26	4	7	11.5%	8.70 [4.17, 13.23]	
Kasai 2010	37.9	10.9	15	36	8.1	15	7.0%	1.90 [-4.97, 8.77]	
Kasai 2013	31.9	6.1	11	32.9	5.9	11	10.3%	-1.00 [-6.02, 4.02]	
Philippe 2006	27.4	14	13	30	9	13	4.7%	-2.60 [-11.65, 6.45]	
Randerath 2012	48.1	11.9	34	43.2	16.4	34	7.1%	4.90 [-1.91, 11.71]	
Tkacova 1997	28.2	15.9	9	20.2	12.6	9	2.4%	8.00 [-5.25, 21.25]	
Subtotal (95% CI)			126			122	60.4%	3.91 [1.03, 6.78]	•
Heterogeneity: Tau ² =	: 6.13; C	hi² = 11.9	97, df =	8 (P = 0	.15); I² =	33%			
Test for overall effect:	Z = 2.66	6 (P = 0.0	08)						
2.9.3 CSA due to CHF	: Unsup	pressed							
Arzt 2007	0.3	4.2241	43	0.4	3.6991	55	20.0%	-0.10 [-1.70, 1.50]	+
Subtotal (95% CI)			43			55	20.0%	-0.10 [-1.70, 1.50]	•
Heterogeneity: Not ap	plicable	l.							
Test for overall effect:	Z = 0.12	? (P = 0.9	0)						
2.9.4 CSA due to CHF	: Suppre	essed							
Arzt 2007	3.6	5.6532	57	0.4	3.6991	55	19.6%	3.20 [1.44, 4.96]	
Subtotal (95% CI)			57			55	19.6%	3.20 [1.44, 4.96]	◆
Heterogeneity: Not as	plicable								
Test for overall effect:	Z = 3.58	6 (P = 0.0	004)						
Total (95% CI)			226			232	100.0%	2.97 [0.77, 5.17]	◆
Heterogeneity: Tau ² =	5.62; C	hi ² = 23.4	6, df =	10 (P =	0.009); P	²= 57%		-	
Test for overall effect:	Z = 2.65	6 (P = 0.0	08)						-20 -10 0 10 20 Eavours Baseline Eavours CPAP
Test for subgroup diff	rences	: Chi² = 9).92, df	= 2 (P =	0.007), (² = 79.8	3%		

Figure S17. CPAP vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= 5%], RCTs (single-arm preposttreatment data) and observational studies

Figure S18. CPAP vs. Baseline (Cardiovascular disease, Systolic BP (mmHg)) [CST= - 2 mmHg], RCTs (single-arm pre- posttreatment data) and observational studies



Figure S19. CPAP vs. Baseline (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCTs (single-arm pre- posttreatment data) and observational studies

	C	PAP		Ba	seline)	Mean Difference Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.11.1 Primary CSA											
Gorbachevski 2020	63.8	13.5	20	62.4	12.1	20	9.6%	1.40 [-6.55, 9.35]			
Subtotal (95% CI)			20			20	9.6%	1.40 [-6.55, 9.35]			
Heterogeneity: Not ap	plicable										
Test for overall effect: 2	Z = 0.35	(P = 0	1.73)								
	_										
2.11.2 CSA due to CH	F										
Arzt 2005	70	4	14	72	3	14	60.4%	-2.00 [-4.62, 0.62]			
Kasai 2010	78.2	7.4	15	75.7	8.7	15	17.3%	2.50 [-3.28, 8.28]			
Kasai 2013	82.3	10	11	79.5	5.8	11	12.7%	2.80 [-4.03, 9.63]			
Subtotal (95% CI)			40			40	90.4%	0.02 [-3.37, 3.42]	-		
Heterogeneity: Tau ² =	3.55; Cł	ni ≈ = 3.	13, df=	= 2 (P =	0.21);	l ^z = 369	6				
Test for overall effect: 2	Z = 0.01	(P = 0	1.99)								
T-4-1405W 00							400.00				
Total (95% CI)			60			60	100.0%	-0.29 [-2.82, 2.25]	🛨		
Heterogeneity: Tau ² =	0.98; Cł	ni² = 3.	40, df=	= 3 (P =	0.33);	I ² = 129	6		-20 -10 0 10 20		
Test for overall effect: 3	Z = 0.22	(P = 0	1.82)						Favours CPAP Favours Baseline		
Test for subgroup diffe	erences	: Chi ≇⊧	= 0.10,	df = 1 (F	P = 0.7	5), I ^z = I	0%				

Figure S20. CPAP vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], RCTs (single-arm preposttreatment data) and observational studies

	(CPAP		N	o CPAP	-		Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI		
2.12.1 Primary CSA												
Gorbachevski 2020	56.4	7	20	59.1	9.1	20	73.2%	-2.70 [-7.73, 2.33]				
Subtotal (95% CI)			20			20	73.2%	-2.70 [-7.73, 2.33]				
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z=1.05	(P = 0.2)	9)									
2.12.2 CSA due to CH	F											
Arzt 2005	66	11.225	14	67	11.225	14	26.8%	-1.00 [-9.32, 7.32]				
Subtotal (95% CI)			14			14	26.8%	-1.00 [-9.32, 7.32]				
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.24	(P = 0.8)	1)									
T-4-1/050/ 00							400.00					
Total (95% CI)			34			34	100.0%	-2.24 [-6.55, 2.06]				
Heterogeneity: Chi ² =	0.12, df=	= 1 (P = 0	0.73); Iª	= 0%					-20	-10 0 10	20	
Test for overall effect:	Z=1.02	(P = 0.3)	1)							Favours CPAP Favours No CPAP		
Test for subgroup difference	erences:	<u>Chi² = 0</u>	<u>.12, df</u> :	<u>= 1 (P =</u>	0.73), I ^z :	= 0%						

Figure S21. CPAP vs. Baseline (Cardiovascular disease, NT pro-BNP, ng/mL) [CST=50% reduction], RCTs (single-arm pre- posttreatment data) and observational studies

		CPAP			aseline		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI			
2.13.1 CSA due to CH	IF											
Randerath 2012	847.3	1,848.1	25	686.7	978.7	25	160.60 [-659.16, 980.36]					
								-1000	-500 (1000	
								-1000	Favours CPAP	Favours Ba	seline	

Randerath 2012 NT-pro BNP ng/ml

Figure S22. CPAP vs. Baseline (Cardiovascular disease, BNP pg/mL) [CST=50% reduction], RCTs (singlearm pre- posttreatment data) and observational studies

		CPAP		Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.14.1 CSA due to CH	łF								
Kasai 2010	239.3	277.7	15	235.8	244.1	15	27.8%	3.50 [-183.61, 190.61]	_
Kasai 2013	193.5	78.97	11	22.4	117.6	11	33.0%	171.10 [87.39, 254.81]	-
Subtotal (95% CI)			26			26	60.8%	109.05 [-49.57, 267.66]	-
Heterogeneity: Tau ² =	: 8576.0	5; Chi ⁼ =	= 2.57, c	if = 1 (P =	= 0.11);	 ² = 619	6		
Test for overall effect:	Z=1.36	5 (P = 0.	18)						
2.14.2 CSA due to CH	IF: Resp	onders							
Dohi 2008	219.1	142.5	9	422.7	234	9	28.3%	-203.60 [-382.59, -24.61]	e
Subtotal (95% CI)			9			9	28.3%	-203.60 [-382.59, -24.61]	◆
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z = 2.23	8 (P = 0.	03)						
2.14.3 CSA due to CH	IF: Non-I	respond	lers						
Dohi 2008	898.6	455.6	7	1,218.4	591.5	7	10.9%	-319.80 [-872.89, 233.29]	
Subtotal (95% CI)			7			7	10.9%	-319.80 [-872.89, 233.29]	
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z=1.13	8 (P = 0.	26)						
Total (95% CI)			42			42	100.0%	-35.04 [-256.24, 186.15]	-
Heterogeneity: Tau ² =	: 36740.	66; Chi 	= 16.83	3, df = 3 (l	P = 0.00)08); I ř :	= 82%		
Test for overall effect:	Z = 0.31	(P = 0.	76)						Favours CPAP Favours Baseline
Test for subaroup dif	ferences	: Chi ^z =	7.58, dt	f = 2 (P =	0.02), P	² = 73.6	%		

Kasai 2010 BNP pg/ml; Kasai 2013 reported BNP pg/ml median (IQR); figure 2 in Dohi 2008 BNP pg/ml

Important Outcomes

Figure S23. CPAP vs. Control (Fatigue subscale, Chronic Heart Failure Questionnaire) [CST= + 2 pts for fatigue], RCTs

	C	PAP		С	ontrol	_		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
17.5.1 IC \$D3									
Granton 1996	21.2	4.5	9	15.3	6.5	8	20.4%	5.90 [0.52, 11.28]	_
Naughton 1995 (Am J Respir Crit Care Med) Subtotal (95% CI)	5.6	4.16	12 21	0.8	2.42	12 20	79.6% 100.0%	4.80 [2.08, 7.52] 5.02 [2.59, 7.45]	
Heterogeneity: Chi ^z = 0.13, df = 1 (P = 0.72); i ^z = Test for overall effect: Z = 4.05 (P < 0.0001)	: 0%								
Total (95% CI) Heterogeneity: Chi ² = 0.13, df = 1 (P = 0.72); i ² =	: 0%		21			20	100.0%	5.02 [2.59, 7.45]	-20 -10 0 10 20
Test for overall effect: Z = 4.05 (P < 0.0001) Test for subgroup differences: Not applicable									Favours Control Favours CPAP

Figure S24 CPAP vs. Control (Sleep architecture (PSG), Sleep efficiency) [CST=10%], RCT

	С	PAP		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.16.1 ICSD3									
Naughton 1995	58	21	9	69	15	9	20.7%	-11.00 [-27.86, 5.86]	
Naughton 1995 (Am J Respir Crit Care Med)	63	20.8	12	72	13.9	12	25.7%	-9.00 [-23.15, 5.15]	
Ruttanaumpawan 2009	70.2	15.7	97	67.8	16.6	108	53.7%	2.40 [-2.02, 6.82]	
Subtotal (95% CI)			118			129	100.0%	-3.30 [-12.73, 6.14]	
Heterogeneity: Tau ² = 38.09; Chi ² = 4.22, df = 2	(P = 0.1	2); I² =	53%						
Test for overall effect: Z = 0.68 (P = 0.49)									
Total (95% CI)			118			129	100.0%	-3.30 [-12.73, 6.14]	
Heterogeneity: Tau ² = 38.09; Chi ² = 4.22, df = 2	(P = 0.1	2); l = =	53%						
Test for overall effect: Z = 0.68 (P = 0.49)									Eavours Control Eavours CPAP
Test for subgroup differences: Not applicable									

Figure S25. CPAP vs. Control	(Sleep architecture (P	SG). Total Sleep	Time) [CST=15 min]. RCT

	(PAP		C	ontrol			Mean Difference		Mean Di	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
1.18.1 IC SD3												
Granton 1996	229	19	9	243	22	8	34.1%	-14.00 [-33.66, 5.66]			+	
Naughton 1994	252	83.1	12	240	44.1	6	7.7%	12.00 [-46.79, 70.79]			•	-
Naughton 1995	222	90	9	234	54	9	5.8%	-12.00 [-80.57, 56.57]	-		<u> </u>	
Naughton 1995 (Am J Respir Crit Care Med)	240	83.1	12	258	62.4	12	7.6%	-18.00 [-76.80, 40.80]	-		<u> </u>	
Ruttanaumpawan 2009	318	73.9	97	308.9	77.6	108	32.5%	9.10 [-11.65, 29.85]				
Teschler 2001	256	59.9	14	212	59.9	14	12.3%	44.00 [-0.37, 88.37]			-	
Subtotal (95% CI)			153			157	100.0%	2.42 [-14.98, 19.82]				
Heterogeneity: Tau ² = 130.35; Chi ² = 7.10, df =	5 (P = 0	.21); I ^z	= 30%									
Test for overall effect: Z = 0.27 (P = 0.79)												
Total (95% CI)			153			157	100.0%	2.42 [-14.98, 19.82]				
Heterogeneity: Tau ² = 130.35; Chi ² = 7.10, df =	5 (P = 0	.21); I ²	= 30%						100	1		400
Test for overall effect: Z = 0.27 (P = 0.79)									-100	-50 Eavoure Control	Eavoure CRAP	100
Test for subgroup differences: Not applicable										Favours Control	Favours CEAF	

Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD

Figure S26. CPAP vs. Control (Sleep architecture (PSG), REM%) [CST= +5% of TST], RCT

								-		
		0	PAP		C	ontrol			Std. Mean Difference	Std. Mean Difference
l	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
ſ	1.19.1 IC SD3									
	Granton 1996	38	8	9	46	11	8	5.8%	-0.80 [-1.80, 0.20]	
	Naughton 1994	36	20.8	12	36	29.4	6	6.0%	0.00 [-0.98, 0.98]	
	Naughton 1995	36	18	9	48	18	9	6.3%	-0.63 [-1.59, 0.32]	
	Naughton 1995 (Am J Respir Crit Care Med)	42	41.6	12	54	20.8	12	8.8%	-0.35 [-1.16, 0.46]	
	Ruttanaumpawan 2009	13.3	7	97	12.7	7.9	108	62.9%	0.08 [-0.19, 0.35]	
	Teschler 2001	10.5	1.4	14	12	9	14	10.3%	-0.23 [-0.97, 0.52]	
	Subtotal (95% CI)			153			157	100.0%	-0.09 [-0.33, 0.15]	•
	Heterogeneity: Tau ² = 0.00; Chi ² = 5.19, df = 5 (P = 0.39	3); I 2 = 1	4%						
	Test for overall effect: Z = 0.73 (P = 0.47)									
				452			457	400.0%	0.00 [0.22 0.45]	
	10tal (95% CI)			155			157	100.0%	-0.09 [-0.33, 0.15]	🕶
	Heterogeneity: Tau ² = 0.00; Chi ² = 5.19, df = 5 (P = 0.39	3); 2 =	4%						-2 -1 0 1 2
I	Test for overall effect: Z = 0.73 (P = 0.47)									Favours Control Favours CPAP
I	Test for subgroup differences: Not applicable									

Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD; Granton 1996 REM, minutes; Naughton 1994/1995/1995 (AJRCCM) REM hours -converted to minutes; Ruttanaumpawan 2009 REM%, Teschler 2001 REM%. The weighted average of the post intervention standard deviation of percent REM across Ruttanaumpawan and Teschler is 7.2. Re-expressed as percent REM, there was a mean decrease of -0.65% (95% CI -2.4, 1.08).

Figure S27. CPAP vs. Control (Sleep architecture (PSG), SWS%) [CST= +5% of TST], RCT

	(CPAP		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.27.1 IC \$D3									
Granton 1996	30	5	9	3	17	8	10.6%	2.11 [0.86, 3.35]	
Naughton 1994	30	20.8	12	6	14.7	6	12.7%	1.20 [0.12, 2.27]	
Naughton 1995	24	108	9	6	54	9	14.9%	0.20 [-0.73, 1.13]	
Naughton 1995 (Am J Respir Crit Care Med)	24	41.6	12	12	20.8	12	16.9%	0.35 [-0.46, 1.16]	
Ruttanaumpawan 2009	10.8	11.7	97	10.3	10.8	108	27.0%	0.04 [-0.23, 0.32]	
Teschler 2001	16.6	11.2	14	13.9	7.9	14	18.0%	0.27 [-0.47, 1.02]	
Subtotal (95% CI)			153			157	100.0%	0.53 [0.02, 1.03]	-
Heterogeneity: Tau ² = 0.23; Chi ² = 13.63, df = 1	5 (P = 0.0	02); I ² =	63%						
Test for overall effect: Z = 2.02 (P = 0.04)									
Total (95% CI)			153			157	100.0%	0.53 [0.02, 1.03]	
Heterogeneity: Tau ² = 0.23; Chi ² = 13.63, df = :	5 (P = 0.0	02); I 2 =	: 63%						
Test for overall effect: Z = 2.02 (P = 0.04)									Favours Control Eavours CPAP
Test for subgroup differences: Not applicable									

Naughton 1994, 1995, 1995 and Teschler 2001 SEM is converted to SD; Granton 1996 SWS, minutes; Naughton 1994/1995/1995 (AJRCCM) SWS hours -converted to minutes; Ruttanaumpawan 2009 SWS%, Teschler 2001 SWS%. The weighted average of the post intervention standard deviation of percent SWS across Ruttanaumpawan and Teschler is 11.04. Re-expressed as percent SWS, there was a mean increase of 5.9% (95% CI 0.22, 11.74).

|--|

		CPAP		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.28.1 IC \$D3									
Naughton 1994	0.1	0.0001	12	0.3	0.25	6	5.8%	-1.36 [-2.46, -0.26]	
Ruttanaumpawan 2009	16.8	15.3	97	18.9	12.9	108	94.2%	-0.15 [-0.42, 0.13]	
Subtotal (95% CI)			109			114	100.0%	-0.22 [-0.49, 0.05]	◆
Heterogeneity: Chi ² = 4.39	, df = 1 ((P = 0.04)							
Test for overall effect: Z = 1	l.62 (P =	= 0.11)							
Total (95% CI)			109			114	100.0%	-0.22 [-0.49, 0.05]	•
Heterogeneity: Chi ² = 4.39	, df = 1 (
Test for overall effect: Z = 1	l.62 (P =		Eavours CPAP Eavours Control						
Test for subgroup differen	ces: No	t applicat	ole						

Naughton 1994 S1 hours, SEM is converted to SD; Ruttanaumpawan 2009 N1%. The weighted average of the post intervention standard deviation of percent N1 for Ruttanaumpawan is 14.03. Re-expressed as percent N1, there was a mean decrease of - 3.09% (95% CI -6.87, 0.7).

Figure S29. CPAP vs. Control (Sleep architecture (PSG), Sleep stage N2(%)) [CST= -5% of TST], RCTs

	0	PAP		С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.24.1 IC \$D3									
Naughton 1994	2.8	0.7	12	3	0.73	6	7.2%	-0.27 [-1.25, 0.72]	
Ruttanaumpawan 2009 Subtotal (95% CI)	59	15.3	97 109	58	14.4	108 114	92.8% 100.0%	0.07 [-0.21, 0.34] 0.04 [-0.22, 0.31]	
Heterogeneity: Chi ² = 0.41 Test for overall effect: Z = 0	, df = 1 ().32 (P =	P = 0. 0.75)	52); I² =	0%					
Total (95% CI) Heterogeneity: Chi ² = 0.41 Test for overall effect: Z = 0 Test for subgroup differen	, df = 1 ().32 (P = ces: No	P = 0.: : 0.75) t appli	109 52); I² = cable	0%		114	100.0%	0.04 [-0.22, 0.31]	-1 -0.5 0 0.5 1 Favours CPAP Favours Control

Naughton 1994 S2 hours, SEM is converted to SD; Ruttanaumpawan 2009 N2 %. The weighted average of the post intervention standard deviation of percent N2 for Ruttanaumpawan is 14.8. Re-expressed as percent N2, there was a mean increase of 0.6% (95% CI -3.26, 4.59).

Figure S30. CPAP vs. Control (Sleep architecture (PSG), Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs

	0	PAP		C	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
17.16.1 IC SD3										
Granton 1996	19	3	9	26	7	8	20.7%	-7.00 [-12.23, -1.77]		
Naughton 1994	24.2	8	12	42.8	25.5	6	10.7%	-18.60 [-39.50, 2.30]		
Naughton 1995	21.4	8.1	9	33.9	20.4	9	14.7%	-12.50 [-26.84, 1.84]		
Naughton 1995 (Am J Respir Crit Care Med)	23.5	15.2	12	30.6	17.3	12	15.6%	-7.10 [-20.13, 5.93]		
Ruttanaumpawan 2009	24.3	19.5	97	26.3	18.6	108	20.7%	-2.00 [-7.23, 3.23]		
Teschler 2001	32	13.8	14	66.7	14.2	14	17.5%	-34.70 [-45.07, -24.33]		
Subtotal (95% CI)			153			157	100.0%	-12.88 [-22.40, -3.36]	\bullet	
Heterogeneity: Tau ² = 106.68; Chi ² = 31.99, df	= 5 (P <	0.0000	01); I ^z =	84%						
Test for overall effect: Z = 2.65 (P = 0.008)										
Total (05% CI)			452			457	100.0%	40.001.00.40.2.261		
10tal (95% CI)	_		153			157	100.0%	-12.88 [-22.40, -3.30]		
Heterogeneity: Tau ² = 106.68; Chi ² = 31.99, df = 5 (P < 0.00001); l ² = 84%										
Test for overall effect: Z = 2.65 (P = 0.008)										
Test for subgroup differences: Not applicable										

Figure S31. CPAP vs. Baseline (Sleep architecture (PSG), Sleep efficiency) [CST=10%], RCTs (single-arm pre- posttreatment data) and observational studies

		CPAP		I	Baseline			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
2.17.1 Primary CSA												
Verbraecken 2002	65	18	9	50	21	9	5.0%	15.00 [-3.07, 33.07]				
Subtotal (95% CI)			9			9	5.0%	15.00 [-3.07, 33.07]				
Heterogeneity: Not ap	oplicable											
Test for overall effect:	Z=1.63	(P = 0.1	0)									
2.17.2 CSA due to CH	11-											
Arzt 2005	81.3	11.225	14	80.3	16.8375	14	10.4%	1.00 [-9.60, 11.60]				
Arzt 2008	79	2	14	73	3	14	22.9%	6.00 [4.11, 7.89]				
Arzt 2009	84	15	10	85	8	10	10.5%	-1.00 [-11.54, 9.54]				
Hu 2006	84.8	3	11	68.4	11	11	15.7%	16.40 [9.66, 23.14]				
Terziyski 2016	70.7	20.2	10	66	22.6	10	4.7%	4.70 [-14.09, 23.49]				
Subtotal (95% CI)			29	=		29	04.1%	0.44 [0.34, 12.33]				
Heterogeneity: Tauh= 25,26; Chin= 11,56; dt = 4 (P = 0.02); P = 65% Test for overall effect: 7 = 2.14 (P = 0.03)												
l est for overall effect:	: Z = 2.14	(P = 0.0	3)									
2 17 3 C SA due to m	odicatio		tanco									
2.17.5 C3A due to III		0.7	24	07.0	0.0	24	40.00	4 40 1 5 50 0 001				
Subtotal (95% CI)	00.0	9.7	31	07.9	0.3	31	19.3%	-1.10[-5.59, 3.39]	-			
Hotorogeneity: Not ar	onlicoblo		51				10.070	-110 [-5.55, 5.55]	T			
Tect for overall effect:	7 – 0 19	/P - 0.6	2)									
	. 2 - 0.40	(1 - 0.0	3)									
2.17.4 TEC \$A												
Morgenthaler 2014	80.7	13.4	19	72.3	16.7	19	11.5%	8.40 [-1.23, 18.03]				
Subtotal (95% CI)			19			19	11.5%	8.40 [-1.23, 18.03]				
Heterogeneity: Not as	oplicable								_			
Test for overall effect	Z=1.71	(P = 0.0	9)									
Total (95% CI)			118			118	100.0%	5.67 [1.12, 10.22]	◆			
Heterogeneity: Tau ² =	= 22.61; (Chi ² = 22	.18, df:	= 7 (P =	0.002); I ^z =	= 68%						
Test for overall effect:	Z= 2.44	(P = 0.0	1)						-50 -25 0 25 50 Favours Baseline Favours CPAP			
Test for subgroup dif	ferences	: Chi² = 7	'.40, df	= 3 (P =	0.06), I ² =	59.5%						

Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S32. CPAP vs. Baseline (Sleep architecture (PSG), Total Sleep Time) [CST=15 min], RCTs (singlearm pre-posttreatment data) and observational studies

• •									
	(CPAP		B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.16.1 C SA due to C	HF								
Arzt 2008	371	12	14	331	17	14	19.4%	40.00 [29.10, 50.90]	+
Hu 2006	425	23.7	11	282.5	78.1	11	17.1%	142.50 [94.27, 190.73]	_
Kasai 2013	313.8	65	11	342.5	75.4	11	16.1%	-28.70 [-87.53, 30.13]	
Terziyski 2016	298.7	107	10	315.1	115.7	10	12.3%	-16.40 [-114.08, 81.28]	
Subtotal (95% CI)			46			46	64.9%	39.93 [-24.62, 104.47]	-
Heterogeneity: Tau ²	= 3495.8	4; Chi ^z	= 23.7	3, df = 3	(P < 0.0	0001); I	≃ =87%		
Test for overall effec	t: Z = 1.21	I (P = 0).23)						
2.16.2 CSA due med	dication of	or subs	stance						
Shapiro 2015	386.6	60.2	31	409	57.8	31	18.6%	-22.40 [-51.78, 6.98]	
Subtotal (95% CI)			31			31	18.6%	-22.40 [-51.78, 6.98]	-
Heterogeneity: Not a	opplicable	9							
Test for overall effec	t: Z = 1.49	9 (P = 0).14)						
2.16.3 TEC SA									
Morgenthaler 2014	373.1	65.5	19	186	103.7	19	16.5%	187.10 [131.95, 242.25]	
Subtotal (95% CI)			19			19	16.5%	187.10 [131.95, 242.25]	-
Heterogeneity: Not a	opplicable	9							
Test for overall effec	t: Z = 6.65	5 (P < 0).0000°	1)					
Total (05% CI)			0.0			00	400.0%	53 46 F 2 07 400 301	
Total (95% CI)			90			90	100.0%	52.10 [-5.87, 108.20]	
Heterogeneity: lau*	= 4172.2	3; Chi r	= 68.5	2, df = 5	(P < 0.1	JUUU1)	; l*= 93%	-	-200 -100 0 100 200
Test for overall effec	t:∠=1.82	2 (P = l	J.U7)		(D) . 0 . 0	0004			Favours Baseline Favours CPAP
Lestior subdroup di	merences	∵ Chi≝:	= 43 38	£. dī = 2.	(P < 11 11	100115	in = 95.49	λo	

-	(PAP		В	aseline			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl			
2.19.1 Primary CSA												
Troitino 2014	15.5	10.6	23	17.4	13.8	23	9.8%	-1.90 [-9.01, 5.21]				
Verbraecken 2002	12	18	9	6	36	9	1.5%	6.00 [-20.30, 32.30]				
Zhang 2021	23.6	9.76	9	8.4	5.32	9	9.6%	15.20 [7.94, 22.46]				
Subtotal (95% CI)			41			41	20.9%	6.52 [-7.34, 20.38]				
Heterogeneity: Tau ² =	107.69	; Chi z =	= 10.87	, df = 2 ((P = 0.0)	04); I² =	82%					
Test for overall effect:	Z = 0.92	2 (P = 0).36)									
2 10 2 C SA due to CH	IF											
Apt 2009	" 1/1 1	1 /	1.4	0.0	1.2	1.4	17.5%	1 20 12 22 5 171				
Kasai 2000	14.1	5.7	14	3.3 16	1.2	14	13.5%	-5 00 [0.20, 0.17]				
Köhnlein 2002	10.29	18.6	16	815	25.68	16	3.6%	2 14 - 13 40 17 68	.			
Randerath 2002	16.20	8.8	25	15.6	9.2	25	12.7%	1 00 [-3 99 5 99]	_ _			
Terzivski 2016	16.9	9	10	7.7	6.3	10	10.2%	9.20 [2.39, 16.01]				
Subtotal (95% CI)		Ū	76	• • •	0.0	76	57.5%	2.10 [-2.50, 6.70]	◆			
Heterogeneity: Tau ² =	18.42:	Chi ^z =	19.40.	df = 4 (F	, = 0.00	07); I ^z =	79%					
Test for overall effect:	Z = 0.89	9 (P = 0).37)									
2.19.3 C SA due to me	edicatio	n or si	Ibstan	ce								
Shapiro 2015	11.8	9.1	31	11.4	8.3	31	13.7%	0.40 [-3.94, 4.74]				
Froitino 2014	11.7	11.3	20	9.6	11.8	34	7.9%	2.10 [-6.68, 10.88]				
Subtotal (95% CI)	0.00.0	ь: 7 о	10 -16	4.00	0.701.13	CO .	21.0%	0.75 [-3.15, 4.02]	–			
Heterogeneity: Tau-=	- 0.00; C	nr=u 2/00	.12, ar = 1.743	= 1 (P =	0.73); 1-	.= 0%						
restion overall effect.	∠ = 0.37	(⊢=(.71)									
Total (95% CI)			156			182	100.0%	2.79 [-0.53, 6.11]	◆			
Heterogeneity: Tau ² = 16.12; Chi ² = 33.83, df = 9 (P < 0.0001); l ² = 73%												
Test for overall effect:	Z=1.65	5 (P = 0).10)						-20 -10 U 10 20 Eavours Baseline Eavours CPAP			
Test for subgroup diff	erences	: Chi²	= 0.72,	df = 2 (I	P = 0.70), I ^z = 0	%					

Figure S33. CPAP vs. Baseline (Sleep architecture, PSG, REM%) [CST=5% of TST], RCTs (single-arm preposttreatment data) and observational studies

Figure S34. CPAP vs. Baseline (Sleep architecture, PSG Sleep Stage N1%), [CST=5% of TST], RCTs (singlearm pre-posttreatment data) and observational studies

<u> </u>			-						
	0	PAP		B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.20.1 Primary CSA									
Troitino 2014	13.1	21.7	23	26.3	19.7	61	17.5%	-13.20 [-23.35, -3.05]	_
Zhang 2021	7.38	5.56	9	26.66	16.62	9	15.5%	-19.28 [-30.73, -7.83]	
Subtotal (95% CI)			32			70	32.9%	-15.88 [-23.47, -8.28]	\bullet
Heterogeneity: Tau ² =	0.00; C	hi² = 0	.61, df=	= 1 (P =	0.44); l ^a	'= 0%			
Test for overall effect:	Z = 4.10) (P < ().0001)						
2.20.2 CSA due to CH	F								
Terziyski 2016	12.1	15.4	10	15.5	8.3	10	16.4%	-3.40 [-14.24, 7.44]	
Subtotal (95% CI)			10			10	16.4%	-3.40 [-14.24, 7.44]	
Heterogeneity: Not ap	plicable	•							
Test for overall effect:	Z = 0.61	(P = 0).54)						
2 20 2 C C A due te me									
2.20.3 C SA due to me	edicatio	n or st	Ibstan	ce					
Shapiro 2015	9.2	8.5	31	11	10	31	28.1%	-1.80 [-6.42, 2.82]	
Troitino 2014	11.3	9.6	8	13.7	9.3	34	22.6%	-2.40 [-9.75, 4.95]	
Subtotal (95% CI)			39			65	50.7%	-1.97 [-5.88, 1.94]	•
Heterogeneity: Tau² =	0.00; C	hi ² = 0	.02, df=	= 1 (P =	0.89); l ^a	'= 0%			
Test for overall effect:	Z = 0.99	9 (P = 0).32)						
T-4-1 (05% OD							400.00	0.001.40.00.0751	
Total (95% CI)			81			145	100.0%	-6.89 [-13.03, -0.75]	
Heterogeneity: Tau ² =	29.34; (Chi ² =	10.87,	df = 4 (F	' = 0.03)); I* = 63	3%		-20 -10 0 10 20
Test for overall effect:	Z = 2.20) (P = ().03)						Favours CPAP Favours Baseline
Test for subgroup difficult	erences	∷ Chi ≩⊭	= 10.24	. df = 2	(P = 0.0)	06), I ^z :	= 80.5%		

Figure S35. CPAP vs. Baseline (Sleep architecture, PSG Sleep Stage N2%), [CST=5% of TST], RCTs (singlearm pre- posttreatment data) and observational studies

	0	PAP		В	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.21.1 Primary CSA									
Troitino 2014	66.1	20.2	23	65.7	19.1	61	20.6%	0.40 [-9.15, 9.95]	-+
Zhang 2021 Subtotal (95% CI)	49.93	14.4	9 32	55.13	10.42	9 70	15.0% 35.6%	-5.20 [-16.81, 6.41] -1.86 [-9.23, 5.52]	
Heterogeneity: Tau ² = Test for overall effect:	0.00; Cl Z = 0.49	hi² = 0 I (P = (.53, df= 0.62)	= 1 (P =	0.47); I ²	2 = 0%			
2.21.2 CSA due to CH	IF								
Terziyski 2016 Subtotal (95% CI)	49.4	16.7	10 10	63.5	19.5	10 10	8.6% <mark>8.6%</mark>	-14.10 [-30.01, 1.81] - 14.10 [-30.01, 1.81]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=1.74	(P = 0	0.08)						
2.21.3 C SA due to me	edication	n or si	ubstan	ce					
Shapiro 2015	76.2	12.2	31	73.3	13	31	37.5%	2.90 [-3.38, 9.18]	
Troitino 2014 Subtotal (95% CI)	74.4	13.7	8 39	78.3	11.8	34 65	18.3% 55.8%	-3.90 [-14.19, 6.39] 0.77 [-5.41, 6.95]	
Heterogeneity: Tau ² =	4.22; C	hi² = 1	.22, df=	= 1 (P =	0.27); P	'= 18%			T
Test for overall effect:	Z = 0.24	(P = (0.81)						
Total (95% CI)			81			145	100.0%	-1.53 [-6.40, 3.34]	•
Heterogeneity: Tau ² =	6.20; C	hi² = 4	.98, df=	= 4 (P =	0.29); l ^a	'= 20%			-50 -25 0 25 50
Test for overall effect:	Z = 0.61	(P = 0	0.54)						Favours CPAP Favours Baseline
Test for subaroup diff	erences	: Chi²:	= 2.94.	df = 2 (ł	P = 0.23), I ^z = 3	1.9%		

Figure S36. CPAP vs. Baseline (Sleep architecture, PSG, SWS%) [CST=5% of TST], RCTs (single-arm preposttreatment data) and observational studies

		CPAP		B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.22.1 Primary CSA									
Troitino 2014	2.3	4.9	23	1.9	6.3	61	22.5%	0.40 [-2.15, 2.95]	+
Zhang 2021	19.13	15.17	9	9.81	10.62	9	8.8%	9.32 [-2.78, 21.42]	<u> </u>
Subtotal (95% CI)			32			70	31.3%	2.82 [-4.95, 10.59]	-
Heterogeneity: Tau ² =	: 19.89; (Chi² = 2	.00, df=	= 1 (P =	0.16); l ^a	= 50%			
Test for overall effect:	Z = 0.71	(P = 0.	48)						
0.00.0 COA due to CI									
2.22.2 C SA due to CH	11-								
Arzt 2008	24.4	3.6	14	15.9	2.6	14	22.8%	8.50 [6.17, 10.83]	
Kasai 2013	9.8	5.4	11	13.4	9.6	11	16.1%	-3.60 [-10.11, 2.91]	
Köhnlein 2002	33.13	41.56	16	21.27	45.48	16	2.0%	11.86 [-18.33, 42.05]	
Terziyski 2016	21.5	12.3	10	13.3	19.8	10	6.9%	8.20 [-6.25, 22.65]	
Subtotal (95% CI)			51 4 00 14			51	41.8%	4.59 [-3.87, 13.05]	
Heterogeneity: lau*=	: 44.30; (Chi*=1	1.89, di	r= 3 (P =	= 0.008;	; i* = 75	0%		
Test for overall effect:	Z = 1.06	(P = 0.	29)						
2.22.3 C SA due to me	edicatio	n or sub	stance	e					
Troitino 2014	2.7	4.2	8	1.9	6.4	34	21.0%	0.80 [-2.82, 4.42]	
Subtotal (95% CI)			8			34	21.0%	0.80 [-2.82, 4.42]	•
Heterogeneity: Not ap	plicable	1							
Test for overall effect:	Z = 0.43) (P = 0.	66)						
									•
Total (95% CI)			91			155	100.0%	3.24 [-1.24, 7.72]	🕈
Heterogeneity: Tau ² =	: 21.53; (Chi ^z = 3	1.54, di	f= 6 (P ·	< 0.000 ⁻	1); I ² = 8	31%		-50 -25 0 25 50
Test for overall effect:	Z=1.42	? (P = 0.	16)						Favours Baseline Favours CPAP
Test for subaroup diff	ferences	: Chi ^z =	0.76. d	f= 2 (P	= 0.68).	$ ^{2} = 0\%$	5		

	CPAP			Bas	selin	е	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
5.18.1 IC SD3								
Verbraecken 2002	53	12	9	44	15	9	9.00 [-3.55, 21.55]	
								-20 -10 0 10 20
								Favours CPAP Favours Baseline

Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S38. CPAP vs. Baseline (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs (single-arm pre- posttreatment data) and observational studies

	С	PAP		Ba	seline	;		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.24.1 IC \$D3									
Troitino 2014	20.1	7.9	23	38.1	26.5	23	81.3%	-18.00 [-29.30, -6.70]	
Verbraecken 2002	6	3	9	29	36	9	18.7%	-23.00 [-46.60, 0.60]	
Subtotal (95% CI)			32			32	100.0%	-18.93 [-29.13, -8.74]	◆
Heterogeneity: Chi ² =	0.14, df	= 1 ($P = 0.7^{\circ}$	1); I² = 0	%				
Test for overall effect:	Z = 3.64	4 (P =	0.0003	3)					
Total (95% CI)			32			32	100.0%	-18.93 [-29.13, -8.74]	◆
Heterogeneity: Chi ² =	0.14, df	= 1 ($P = 0.7^{\circ}$	1); I ² = 0	%				
Test for overall effect:	Z = 3.64	4 (P =	0.0003	3)					Favours CPAP Favours Baseline
Test for subgroup diff	erences	: Not	applica	able					avours of At Tavours Dasenne

Verbraeken 2002, timepoints analyzed=Night 1 (Diagnostic procedure) vs Night 3 (after one month treatment with CPAP and with application of CPAP at the time of the measurement), SEM converted to SD

Figure S39. CPAP vs. Baseline (Daytime functioning, SF-36) [CST= 3 pts], RCT (single-arm preposttreatment data)

	CPAP			Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
16.25.1 IC SD3								
Köhnlein 2002	45.4	26.2	16	17.9	32.7	16	27.50 [6.97, 48.03]	——+——
								-50 -25 0 25 50
								Favours Baseline Favours CPAP
L								

BPAP with a backup rate

Summary of Findings (GRADE)

Table S2 BPAP with a backup rate in adults with CSA

References: Cao 2014, Dellweg 2013, Dohi 2008, Fietze 2008, Hu 2006, Kasai 2005, Morgenthaler 2007, Teschler 2001, Troitino 2014

Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference BPAP with a backup rate vs. baseline	No of Participants (studies)
Excessive sleepiness	⊕○○○	The mean difference in the BPAP with a backup rate group was 2.1 points lower (4.53 lower to 0.33 higher) compared to baseline	20
[ESS]	VERY LOW ^{a,b,c}		(1 RCT)

Disease severity	⊕○○○	The mean difference in the BPAP with a backup rate group was 33.65 events/hour lower (41.44 lower to 25.86 lower) compared to baseline	128						
[AHI]	VERY LOW ^{a,b}		(9 studies)						
Disease severity	⊕○○○	The mean difference in the BPAP with a backup rate group was 15.66 events/hour lower (25.12 lower to 6.2 lower) compared to baseline	69						
[CAI]	VERY LOW ^{a,b}		(5 studies)						
Disease severity	⊕○○○	The mean difference in the BPAP with a backup rate group was 15.5 events/hour lower (19.95 lower to 11.05 lower) compared to baseline	11						
[CAHI]	VERY LOW ^{a,b}		(1 RCT)						
Cardiovascular disease	⊕○○○	The mean difference in the BPAP with a backup rate group was 7.83% higher (3.12 higher to 12.54 higher) compared to baseline	34						
[LVEF]	VERY LOW ^{a,b}		(3 RCTs)						
a. Downgraded guality of evidence due to data analyzed using pre- and posttreatment values									

b. Imprecision due to small sample size (<200 participants)

c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

Critical Outcomes

Figure S40. BPAP with a backup rate vs. Baseline (Excessive sleepiness, ESS) [CST= - 2 points], RCT (single-arm pre- posttreatment data)

	BPAP-ST Baseline						Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.1.1 CSA due to hea	rt failure	3								
Fietze 2008	8.1	3.5	20	10.2	4.3	20	-2.10 [-4.53, 0.33]			
								10	-5 0 5	
								-10	Favours BPAP-ST Favours Basel	ine

Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

Figure S41. BPAP-with a backup rate vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies

	BP	AP-ST	Г	Ba	seline			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.2.1 Primary CSA										
Troitino 2014	3.2	2.1	13	42.5	24	13	9.0%	-39.30 [-52.40, -26.20]		
Subtotal (95% CI)			13			13	9.0%	-39.30 [-52.40, -26.20]	◆	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 5.88	(P < (0.00001)						
1.2.2 CSA due to hea	rt failure	9								
Dohi 2008	8.4	4.7	9	54.4	7.8	9	11.3%	-46.00 [-51.95, -40.05]	—	
Fietze 2008	16.4	16.1	20	34.9	20.4	20	9.6%	-18.50 [-29.89, -7.11]	_ -	
Hu 2006	14.3	3.9	11	30.9	8.3	11	11.4%	-16.60 [-22.02, -11.18]	+	
Kasai 2005	10.4	9	7	49.4	16.1	7	8.8%	-39.00 [-52.66, -25.34]	_ -	
Morgenthaler 2007	1.5	1.5	6	46	22.7	6	7.3%	-44.50 [-62.70, -26.30]		
Teschler 2001	14.8	8.6	14	44.5	12.7	14	10.7%	-29.70 [-37.73, -21.67]		
Subtotal (95% CI)			67			67	59.1%	-31.86 [-44.11, -19.61]	◆	
Heterogeneity: Tau ² =	203.56;	Chi z =	= 59.29	, df = 5 ((P < 0.0	00001)	; I ² = 92%			
Test for overall effect:	Z = 5.10	I (P < 0	0.00001)						
1.2.3 CSA due to me	dication	or sub	ostance	e						
Cao 2014	16.3	20.9	18	50.3	22.2	18	8.7%	-34.00 [-48.09, -19.91]	_ _	
Troitino 2014	4.4	2.9	6	51.6	36.3	6	4.5%	-47.20 [-76.34, -18.06]		
Subtotal (95% CI)			24			24	13.2%	-36.50 [-49.18, -23.82]	◆	
Heterogeneity: Tau ² =	: 0.00; Cl	hi ² = 0	.64, df=	= 1 (P =	0.42);	l² = 0%				
Test for overall effect:	Z= 5.64	(P < 0	0.00001)						
1 2 4 TEC SA										
Dellweg 2013	16.5	g	15	112	1/1 0	30	11 1 96	-27 70 1-34 39 -21 011	+	
Morgenthaler 2007	6.9	88	, J Q	10 A	25.4	Q	7.6%	-27.70 [-59.33, -21.01]	_	
Subtotal (95% CI)	0.0	0.0	24	43.4	20.4	39	18.7%	-32.96 [-46.92, -19.00]	•	
Heterogeneity: Tau ² =	66.76:0	Chi²=	2.51. di	f=1 (P=	= 0.11)	: I ² = 6(196		-	
Test for overall effect:	Z= 4.63	(P < (0.00001)	,					
Total (95% CI)			129			143	100.0%	-33 65 [.41 44 .25 86]	•	
Hotorogonoity: Tou? -	120.02	⊂hi≩-	- 65 21	df = 10	/D 2 0	00004		-55,05 [-1 1,14, -25,00]	▼	
Teet for overall effect:	7 = 9.49	(P < 0	- 00.21 1.00004	, ur = 10 D	0 - 0	.00001	71 - 005	v	-100 -50 Ó 5Ó 1	00'
Test for subaroun diff	erences	∶Chi " ∍	= 0.80	df = 3 (F	P = 0.8	5), ² =	0%		Favours BPAP-ST Favours Baseline	

Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period ; Dohi 2008: baseline compared to BPAP-ST, 6-month follow-up; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, data reported as RDI; Morgenthaler 2007: diagnostic polysomnograms were done as a split night protocol, baseline compared to BPAP-ST, single night protocol; Dellweg 2013: baseline data included participants in both the ASV and the BPAP-ST groups, 6-week follow-up; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD; Cao 2014: pre-entry baseline PSG compared to BPAP-ST, the second overnight study was conducted within 2 weeks of the first assessment; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention night Figure S42. BPAP-with a backup rate vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies

	BP	AP-S	Г	Ba	seline	;		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.3.1 CSA due to hea	art failure								
Kasai 2005	8.1	4.5	7	39	14.3	7	15.4%	-30.90 [-42.01, -19.79]	(
Morgenthaler 2007	0.5	0.5	6	22.7	14.8	6	14.9%	-22.20 [-34.05, -10.35]	_
Teschler 2001	8.4	7.1	14	35.8	10.9	14	17.7%	-27.40 [-34.21, -20.59]	_ -
Subtotal (95% CI)			27			27	48.0%	-27.16 [-32.38, -21.95]	◆
Heterogeneity: Tau ² =	= 0.00; Cł	ni² = 1	.11, df=	= 2 (P =	0.57);	$ ^{2} = 0\%$			
Test for overall effect:	Z=10.2	1 (P <	0.0000	01)					
1.3.2 CSA due to me	dication	or sul	ostance	е					
Cao 2014	9.4	18.8	18	13	18.7	18	14.7%	-3.60 [-15.85, 8.65]	
Subtotal (95% CI)			18			18	14.7%	-3.60 [-15.85, 8.65]	-
Heterogeneity: Not ap	pplicable								
Test for overall effect:	Z = 0.58	(P = 0	0.56)						
1.3.3 TEC \$A									
Dellweg 2013	10.2	5.1	15	17.7	13.3	30	18.3%	-7.50 [-12.91, -2.09]	
Morgenthaler 2007	1.1	1.3	9	5.6	4.6	9	19.1%	-4.50 [-7.62, -1.38]	
Subtotal (95% CI)			24			39	37.4%	-5.25 [-7.95, -2.54]	◆
Heterogeneity: Tau ² =	= 0.00; Cł	ni z = 0	.89, df=	= 1 (P =	0.35);	$l^{2} = 0\%$			
Test for overall effect:	Z = 3.80	(P = 0)	0.0001)						
Total (95% CI)			69			84	100.0%	-15.66 [-25.12, -6.20]	
Heterogeneity: Tau ² =	= 119.78;	Chi ² =	= 56.43	, df = 5 (P < 0.	00001)	; I ^z = 91%		
Test for overall effect:	Z= 3.24	(P = 0)	0.001)						-50 -25 0 25 50 Eavours BPAP-ST Eavours Baseline
Test for subgroup dif	ferences:	Chi ²	= 54.43	3. df = 2	(P < 0	00001), l² = 96.3	1%	Favouis DEAF-ST Favouis Dasellite

Morgenthaler 2007: diagnostic polysomnograms were done as a split night protocol, baseline compared to BPAP-ST, single night protocol; Dellweg 2013: baseline data included participants in both the ASV and the BPAP-ST groups, 6-week follow-up; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD; Cao 2014: pre-entry baseline PSG compared to BPAP-ST, the second overnight study was conducted within 2 weeks of the first assessment; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Figure S43. BPAP-with a backup rate vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data)

	BP	AP-S	Т	Co	ontro	1	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.4.1 C SA due to hea	rt failure)							
Hu 2006	10.6	3.8	11	26.1	6.5	11	-15.50 [-19.95, -11.05]		
							-	-20 -10 0 10 20	
								Favours BPAP-ST Favours Baseline	

Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights.

Figure S44. BPAP-with a backup rate vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies

	BP	AP-S	Г	Ba	seline)		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
1.5.1 CSA due to hea	rt failur	е									
Fietze 2008	12.4	15	20	33.3	34	20	21.9%	-20.90 [-37.19, -4.61]		_ _	
Teschler 2001	11.4	6.7	14	38.2	9.7	14	42.8%	-26.80 [-32.98, -20.62]		-	
Subtotal (95% CI)			34			34	64.7%	-26.06 [-31.83, -20.28]		◆	
Heterogeneity: Tau ² =	0.00; C	hi² = I	0.44, di	í = 1 (P =	0.51)	; I2 = 09	ж				
Test for overall effect:	Z = 8.85	5 (P <	0.0000)1)							
1.5.2 TEC \$A											
Dellweg 2013	21.1	9.2	15	33.6	22.9	30	35.3%	-12.50 [-21.92, -3.08]			
Subtotal (95% CI)			15			30	35.3%	-12.50 [-21.92, -3.08]		◆	
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 2.60) (P =	0.009)								
Total (95% CI)			49			64	100.0%	-20.46 [-30.55, -10.38]		◆	
Heterogeneity: Tau ² =	51.92;	Chi ^z =	6.22,	df = 2 (P	= 0.04	4); I≊ = 6	68%		400		
Test for overall effect:	Z = 3.98	3 (P <	0.0001)					-100	-50 U 50 Eavoure PPAP ST Eavoure Pacoline	100
Test for subgroup diff	erences	: Chi	² = 5.78	df=1 (P = 0.	02), i ² =	= 82.7%)

Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Figure S45. BPAP-with a backup rate vs. Baseline (Disease Severity, percentage sleep time with oxygen saturation <90 %) [CST= ≥ 50% reduction from baseline], RCTs (single-arm pre- posttreatment data) and observational studies



Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies -3 months later, data extracted from figure 1, SEM converted to SD; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S46. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, LVEF) [CST= + 5%], RCT (single-arm pre- posttreatment data) and observational studies

	BF	PAP-S	Г	E	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.7.1 CSA due to hea	art failur	е							
Dohi 2008	43	13.8	7	30.3	6.7	7	17.2%	12.70 [1.34, 24.06]	_
Fietze 2008	31.1	10.5	20	25.5	9.2	20	59.2%	5.60 [-0.52, 11.72]	├──■ ───
Kasai 2005	46.2	10.6	7	36.3	7.6727	7	23.6%	9.90 [0.21, 19.59]	
Subtotal (95% CI)			34			34	100.0%	7.83 [3.12, 12.54]	
Heterogeneity: Chi ² =	1.39, df	= 2 (P	= 0.50)); I ^z = 09	6				
Test for overall effect	: Z = 3.26	6 (P = 0	0.001)						
Total (95% CI)			34			34	100.0%	7.83 [3.12, 12.54]	•
Heterogeneity: Chi ² =	: 1.39, df	= 2 (P	= 0.50)); I² = 09	6			_	
Test for overall effect	: Z = 3.26	6 (P = ().001)						-20 -10 0 10 20 Eavours Pacialina, Eavours PPAP ST
Test for subgroup dif	ferences	: Not s	nnlical	hle					Favours baseline Favours DFAF-ST

Dohi 2008: baseline compared to BPAP-ST, 6-month follow-up; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Kasai 2005: participants in control group refused BPAP-ST following diagnosis of CSA-CSR, 3-month follow-up, SEM converted to SD

Figure S47. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, BNP, pg/mL) [CST= - 50% reduction from baseline], Observational Study



Data from figure 2 in Dohi 2008, BNP pg/ml: baseline compared to BPAP-ST, 6-month follow-up

Figure S48. BPAP-with a backup rate vs. Control (Cardiovascular Disease, BNP, pg/mL) [CST= - 50% reduction from baseline], Observational Study

	В	PAP-ST		0	Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.2.1 CSA due to hear	rt failure	e						
Kasai 2005	474.7	257.6	7	725.3	311.1	7	-250.60 [-549.81, 48.61]	
								-1000 -500 0 500 1000
								Favours BPAP-ST Favours Control

Data from figure 5 in Kasai 2005: participants in control group refused BPAP-ST following diagnosis of CSA-CSR, 3-month followup, SEM converted to SD; BNP pg/ml. Baseline BPAP-ST 993.6 +/- 332

Figure S49. BPAP-with a backup rate vs. Baseline (Cardiovascular Disease, HR) [No CST], Observational Study



*Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up Willson 2001: Follow-up duration unclear

Important Outcomes

Figure S50. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=+15 minutes], Observational Studies

	BP	AP-S	Г	Ba	seline)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.20.1 CSA due to he	art failu	re							
Fietze 2008	311.7	80.6	20	325.3	52	20	21.1%	-13.60 [-55.64, 28.44]	
Hu 2006	427	20.9	11	282.5	78.1	11	20.4%	144.50 [96.72, 192.28]	
Teschler 2001	283	52.4	14	212	59.9	14	21.1%	71.00 [29.31, 112.69]	
Willson 2001	283	53	9	271	79	9	18.6%	12.00 [-50.15, 74.15]	
Subtotal (95% CI)			54			54	81.3%	53.93 [-16.04, 123.89]	
Heterogeneity: Tau ² =	4479.2	1; Chi ^a	= 26.1	1, df = 3	(P < 0	1.00001); l ^z = 899	б	
Test for overall effect:	Z = 1.51	(P = ().13)						
4 00 0 75 0 0 4									
1.20.2 TEC SA									
Dellweg 2013	277	82	15	252	90	15	18.7%	25.00 [-36.61, 86.61]	
Subtotal (95% CI)			15			15	18.7%	25.00 [-36.61, 86.61]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.80) (P = (0.43)						
T-4-1 (050) 00							400.00	40 50 50 07 400 001	
Total (95% CI)			69			69	100.0%	48.58 [-9.07, 106.22]	
Heterogeneity: Tau ² =	3638.9	1; Chi	= 26.8	6, df = 4	(P < 0	1.0001)	; I² = 85%		-200 -100 0 100 200
Test for overall effect:	Z=1.65	5 (P = ().10)						Favours Baseline Favours BPAP-ST
Test for subgroup diff	<u>erences</u>	: Chi²	<u>= 0.37,</u>	<u>df = 1 (F</u>	<u>P = 0.5</u>	4), ² =	0%		

Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up; Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up; Willson 2001: Follow-up duration unclear; Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention

Figure S51. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep Efficiency)

[CST=+10%], Observational Studies

	BP	AP-ST	Г	Co	ontro	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.19.1 CSA due to he	art failur	е							
Hu 2006	84.7	3	11	68.4	11	11	40.9%	16.30 [9.56, 23.04]	
Willson 2001	68	8	9	62	16	9	32.6%	6.00 [-5.69, 17.69]	
Subtotal (95% CI)			20			20	73.5%	12.30 [2.46, 22.14]	
Heterogeneity: Tau ² =	: 29.36; C	hi² =	2.24, d	f = 1 (P :	= 0.1	3); I 2 = 9	55%		
Test for overall effect:	Z=2.45	(P = 0	0.01)						
1.19.2 TEC SA									
Dellweg 2013	63.3	22.1	15	68.4	21	15	26.5%	-5.10 [-20.53, 10.33]	
Subtotal (95% CI)			15			15	26.5%	-5.10 [-20.53, 10.33]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.65	(P = 0	0.52)						
Total (95% CI)			35			35	100.0%	7.27 [-4.78, 19.32]	
Heterogeneity: Tau ² =	: 80.49; C	hi²=	7.25, d	f = 2 (P :	= 0.0	3); I 2 = 1	72%		
Test for overall effect:	Z = 1.18	(P = 0	0.24)						Favours Baseline Favours BPAP-ST
Test for subgroup diff	ferences:	Chi ^z :	= 3.47.	df = 1 (8)	[•] = 0	.06), I ^z :	= 71.2%		

Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up

Willson 2001: Follow-up duration unclear

Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention

Figure S52. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], Observational Studies

	BP	AP-ST	[Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.10.1 Primary CSA									
Troitino 2014	12.6	22.3	13	26.3	19.7	61	23.1%	-13.70 [-26.79, -0.61]	
Subtotal (95% CI)			13			61	23.1%	-13.70 [-26.79, -0.61]	
Heterogeneity: Not app	olicable								
Test for overall effect: Z	Z = 2.05	5 (P = 0	0.04)						
1.10.2 CSA due to hea	rt failu	re							
Fietro 2008	3 8 6	1/10	20	347	1/6	20	26.6%	1 90 67 24 11 041	
Subtotal (95% CI)	50.0	14.5	20	J4.r	14.0	20	35.5%	1.90 [-7.24, 11.04]	-
Heterogeneity: Not app	licable	1							
Test for overall effect: Z	Z = 0.41	(P = 0).68)						
1.10.4 CSA due to me	dicatio	n or su	Ibstan	ce					
Troitino 2014	9.9	8.9	6	13.7	9.3	34	41.4%	-3.80 [-11.58, 3.98]	
Subtotal (95% CI)			6			34	41.4%	-3.80 [-11.58, 3.98]	
Heterogeneity: Not app	licable								
Test for overall effect: 2	Z = 0.96	6 (P = 0	0.34)						
T-4-1 (054) 00							400.00		
Total (95% CI)			39			115	100.0%	-4.06 [-11.66, 3.54]	
Heterogeneity: Tau ² = 2	20.59; (Chi²=∶	3.68, di	f=2(P:	= 0.16)); l² = 48	3%		-50 -25 0 25 50
Test for overall effect: Z	1 = 1.05) (P = 0	1.30)			o) 17	15.00		Favours BPAP-ST Favours Baseline

*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N1 %; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, reported as N1%

Figure S53. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], Observational Studies



*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N2 %; Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, N2%

Figure S54. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Sleep stage N3%) [CST=+5% of TST], Observational Studies

	BP	AP-ST	Γ	Ba	selin	e		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.12.1 Primary CSA									
Troitino 2014 Subtotal (95% CI)	2.1	4.4	13 13	1.9	6.3	61 <mark>61</mark>	26.5% 26.5%	0.20 [-2.67, 3.07] 0.20 [-2.67, 3.07]	. ↓
Heterogeneity: Not ap Test for overall effect:	plicable Z = 0.14	(P = 0).89)						
1.12.2 C SA due to he	art failui	re							
Fietze 2008	12.2	8.2	20	11.2	6.2	20	17.1%	1.00 [-3.51, 5.51]	_
Kasai 2005	16.8	14.8	7	4	6.3	7	3.7%	12.80 [0.88, 24.72]	
Teschler 2001	21.1	10.5	14	13.9	7.9	14	9.5%	7.20 [0.32, 14.08]	
Willson 2001	12	9	9	8	6	9	9.1%	4.00 [-3.07, 11.07]	
Subtotal (95% CI)			50			50	39.5%	4.57 [0.29, 8.84]	◆
Heterogeneity: Tau² = Test for overall effect:	6.64; Cl Z = 2.09	ni² = 4 (P = 0	.62, df=).04)	= 3 (P =	0.20)	; I² = 3(5%		
1.12.3 C SA due to me	edicatior	i or si	Ibstand	e					
Troitino 2014 Subtotal (95% CI)	2.4	3.7	6 6	1.9	6.4	34 34	21.4% 21.4%	0.50 [-3.16, 4.16] 0.50 [-3.16, 4.16]	*
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.27	(P = 0).79)						
1.12.4 TEC \$A									
Dellweg 2013	16.9	8.2	15	11.4	7.7	15	12.6%	5.50 [-0.19, 11.19]	_
Subtotal (95% CI)			15			15	12.6%	5.50 [-0.19, 11.19]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.89	(P = 0).06)						
Total (95% CI)			84			160	100.0%	2.55 [0.14, 4.97]	◆
Heterogeneity: Tau ² =	3.59; Cl	ni = 9	.43, df=	= 6 (P =	0.15)	; I2 = 36	6%	-	
Test for overall effect:	Z = 2.07	(P = 0).04)						Favours Baseline Favours BPAP-ST
Test for subaroun diff	erences	. Chi≩:	= 4 90	df = 3/8	P = 0	18) I ^z a	- 38 8%		

*Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period, N3% Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up, N3% Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up, SWS%; Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD, SWS%; Willson 2001: Follow-up duration unclear, SWS%; Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD, SWS%

Figure S55. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, REM %) [CST=+5% of TST], Observational Studies

	BP	AP-ST	Γ	Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.14.1 Primary CSA									
Troitino 2014	16.7	15	13	17.4	13.8	61	4.3%	-0.70 [-9.56, 8.16]	
Subtotal (95% CI)			13			61	4.3%	-0.70 [-9.56, 8.16]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z=0.15	(P = 0).88)						
1.14.2 CSA due to he	art failur	е							
Fietze 2008	13.5		20	11.4	61	20	1/ 9%	2106238658	
Hu 2006	13.5	3.5	11	11.4	2.1	11	37 396	1 80 -0 61 4 21	+ -
Kasai 2005	14.8	4.5	7	57	6.3	7	9.6%	9 10 [3 36 14 84]	
Teschler 2001	16	7.1	14	12	7.1	14	11 2%	4 00 [-1 26 9 26]	
Willson 2001	16	6		13	7		8.8%	3.00 [-3.02, 9.02]	
Subtotal (95% CI)		-	61			61	81.8%	3.31 [0.99, 5.63]	◆
Heterogeneity: Tau ² =	2.01; Ch	i² = 5	.58, df=	= 4 (P =	0.23);	P = 289	%		
Test for overall effect:	Z= 2.79	(P = 0).005)						
1.14.3 TEC SA									
Dellweg 2013	10.8	5.7	15	11.8	9.3	15	10.3%	-1.00 [-6.52, 4.52]	
Subtotal (95% CI)			15			15	10.3%	-1.00 [-6.52, 4.52]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.36	(P = 0).72)						
1 14 4 C SA due to me	dication	01.61	ibetan	-0					
Traiting 2014	111	11.1	in stain	0.0	11.0	24	260	4 50 1 5 33 44 331	
Subtotal (95% CI)	14.1	11.1	6	9.0	11.0	34	3.6%	4.50 [-5.23, 14.23]	
Heterogeneity: Not an	nlicable						0.070		
Test for overall effect:	7 = 0.91	(P = (1 361						
	_ 0.01		,						
Total (95% CI)			95			171	100.0%	2.60 [0.73, 4.48]	◆
Heterogeneity: Tau ² =	0.94; Ch	i² = 7	.99, df=	= 7 (P =	0.33);	P =129	%		
Test for overall effect:	Z= 2.72	(P = 0).007)						-20 -10 0 10 20 Eavours Baseline Eavours BPAP-ST
Test for subaroup diff	erences:	Chi ²	= 2.67.	df = 3 (ł	^o = 0.4	5), l² =	0%		Favous Dasenne Favouis BFAF-ST

Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period

Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up

Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD

Willson 2001: Follow-up duration unclear

Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S56. BPAP-with a backup rate vs. Control (Sleep architecture, PSG, SWS% and REM%) [No CST], RCTs

	BP	AP-S	Т	Co	ontro	I	Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.15.1 CSA due to he	art failu	re								
Teschler 2001	37.1	9.4	14	25.9	8.6	14	11.20 [4.53, 17.87]		+	
								-20	-10 0 10	20
									Favours Control Favours BPAP	-ST

Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

	BP	AP-ST	Г	Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	/lean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.16.1 Primary CSA									
Troitino 2014 Subtotal (95% CI)	17.3	9.3	13 13	38.1	26.5	61 <mark>61</mark>	15.0% 15.0%	-20.80 [-29.15, -12.45] - 20.80 [-29.15, -12.45]	•
Heterogeneity: Not appli	icable								
Test for overall effect: Z	= 4.88	(P < 0	0.00001)					
1.16.2 CSA due to hear	t failur	е							
Hu 2006	13.7	4.9	11	31.3	13.2	11	15.0%	-17.60 [-25.92, -9.28]	_
Kasai 2005	12.5	5	7	45.5	24	7	11.7%	-33.00 [-51.16, -14.84]	
Teschler 2001	18.4	5.2	14	66.7	14.2	14	15.1%	-48.30 [-56.22, -40.38]	- -
Willson 2001	17	- 7	9	42	6	9	15.6%	-25.00 [-31.02, -18.98]	
Subtotal (95% CI)			41			41	57.4%	-30.81 [-45.09, -16.53]	
Heterogeneity: Tau ² = 18	33.65;	Chi²=	= 31.77	, df = 3 (P < 0.	00001)	I² = 91%		
Test for overall effect: Z :	= 4.23	(P < 0).0001)						
1.16.3 CSA due to medi	cation	i or su	ibstan	ce					
Troitino 2014 Subtotal (95% CI)	21.6	9.2	6 6	21.4	20.2	34 34	14.5% 14.5%	0.20 [-9.81, 10.21] 0.20 [-9.81, 10.21]	
Heterogeneity: Not appli	icable								
Test for overall effect: Z	= 0.04	(P = 0).97)						
1.16.4 TEC SA									
Dellweg 2013	25	20.1	15	33.8	20	15	13.1%	-8.80 [-23.15, 5.55]	
Subtotal (95% CI)			15			15	13.1%	-8.80 [-23.15, 5.55]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z =	= 1.20	(P = 0).23)						
Total (95% CI)			75			151	100.0%	-21.94 [-33.59, -10.29]	◆
Heterogeneity: Tau ² = 2 ⁴	17.23;	Chi ^z =	66.77	.df=6(P < 0.1	00001);	I² = 91%		
Test for overall effect: Z:	= 3.69	(P = 0)).0002)						-50 -25 U 25 5U
Test for subaroup differe	ences:	Chi ²∶	= <u>16.08</u>), df = 3	(P = 0.	001), l ^a	= <u>81.3</u> %		

Figure S57. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Arousal Index) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational Studies

Troitino 2014: baseline compared to BPAP-ST, retrospective chart over a 5-year period

Dellweg 2013: diagnostic night compared to BPAP-ST, 6-week follow-up

Kasai 2005: Changes in the polysomnographic findings between the diagnostic and titration sleep studies, data extracted from figure 1, SEM converted to SD

Willson 2001: Follow-up duration unclear

Teschler 2001: prospective randomized crossover design, one night per intervention, untreated night preceded the intervention nights, SEM converted to SD

Hu 2006: randomized crossover design, one night per intervention, untreated night preceded the intervention nights

Figure S58. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Movement arousals) [CST=25% percent reduction from baseline], Observational Studies

	BP	AP-ST	ſ	Ba	selin	е	Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.18.1 CSA due to hea	art failu	re								
Fietze 2008	10.2	12.5	20	4.7	4.7	20	5.50 [-0.35, 11.35]			
								-20	-10 0 10	20
									Favours BPAP-ST Favours Baseline	

Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

Figure 59. BPAP-with a backup rate vs. Baseline (Sleep architecture, PSG, Respiratory-related arousals) [CST=25% percent reduction from baseline], Observational Studies



Fietze 2008: diagnostic night compared to BPAP-ST, 6-week follow-up

BPAP (without a backup rate)

Summary of Findings (GRADE)

Table S3 BPAP in adults with CSA

References: Noda 2007					
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference BPAP vs. baseline or control	No of Participants (studies)		
Disease severity [AHI]	⊕○○○ VERY LOW ^{a,b,c}	The mean difference in the BPAP group was 23.1 events/hour lower (31.08 lower to 15.12 lower) compared to baseline	10 (1 RCT)		
Disease severity [CAI]	⊕○○○ VERY LOW ^{a,b,c}	The mean difference in the BPAP group was 10.6 events/hour lower (11.13 lower to 10.07 lower) compared to baseline	10 (1 RCT)		
Cardiovascular disease [LVEF]	OOO VERY LOW ^{b,c,d}	The mean difference in the BPAP group was 13% higher (3 higher to 23 higher) compared to control	10 (1 RCT)		
Cardiovascular disease [NYHA functional class score]*	⊕⊕⊖⊖ LOW ^{b,c}	The mean difference in the BPAP group was 0.7 lower (1.26 lower to 0.14 lower) compared to control	10 (1 RCT)		

a. Downgraded quality of evidence due to RCT data analyzed using pre- and posttreatment values

b. Imprecision due to small sample size (<200 participants)

c. Indirectness in the intervention

 Imprecision due to the 95% CI includes possibility for important benefit and no effect *CST not established by the task force

Critical Outcomes

Figure S60. BPAP vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline] RCT (singlearm pre- posttreatment data)



Noda 2007: SEM converted to SD, only baseline vs post-treatment data available for BPAP group. BPAP group had an 82% reduction in AHI from baseline.

Figure S61. BPAP vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT (single-arm pre- posttreatment data)

	В	PAP		Control			Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
2.2.1 CSA due to Hea	rt Failur	е									
Noda 2007	0.6	0.6	10	11.2	0.6	10	-10.60 [-11.13, -10.07]		+		
								-20	-10		20
								-20	Eavours BPAP	Favours Control	20
									, areard bring	, arears control	

Noda 2007: SEM converted to SD, only baseline vs post-treatment data available for BPAP group. BPAP group had a 96% reduction in CAI from baseline.

Figure S62. BPAP vs. Control (Cardiovascular Disease, LVEF) [CST= +5%], RCT

	E	BPAP		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.1 CSA due to Hea	rt Failur	e						
Noda 2007	50.8	11.1	10	37.8	11.7	11	13.00 [3.25, 22.75]	— + — –
								-20 -10 0 10 20
								Favours Control Favours BPAP

Noda 2007: SEM converted to SD

Figure S63. BPAP vs. Control (Cardiovascular Disease, BNP, pg/mL) [CST= -50% reduction from baseline], RCT

	E	BPAP		0	Control	Mean Difference			Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
1.3.1 CSA due to Hea	rt Failur	е									
Noda 2007	32.7	55.7	10	139	184.7	11	-106.30 [-220.78, 8.18]				
								-1000	-500 0	50	1 1000
								-1000	Favours BPAP	Favours Cor	trol

Noda 2007: SEM converted to SD; BNP pg/ml. Baseline BPAP BNP 162.8 +/- 44.5(SE)

Figure S64. BPAP vs. Control (Cardiovascular Disease, Systolic BP) [CST= - 2 mmHg], RCT

	В	PAP		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.5.1 CSA due to Hea	rt Failur	е						
Noda 2007	109.6	9.8	10	121	24.9	11	-11.40 [-27.32, 4.52]	-++
							-	
								Favours BPAP Favours Control

Noda 2007: SEM converted to SD

Figure S65. BPAP vs. Control (Cardiovascular Disease, Diastolic BP) [CST= - 1 mmHg], RCT

	BPAP				Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 CSA due to Hea	rt Failur	e						
Noda 2007	65.8	11.068	10	73	12.6491	10	-7.20 [-17.62, 3.22]	
								-20 -10 0 10 20
								Favours BPAP Favours Control

Noda 2007: SEM converted to SD

Figure S66. BPAP vs. Control (Cardiovascular Disease, NYHA functional class score) [No CST], RCT

	В	PAP		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.1.1 CSA due to Hea	rt Failur	е						
Noda 2007	1.3	0.6	10	2	0.7	11	-0.70 [-1.26, -0.14]	-+
								Favours Control Favours BPAP

Noda 2007: SEM converted to SD

Figure S67. BPAP vs. Control (Cardiovascular Disease, HR) [No CST], RCT

	BPAP				Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 CSA due to Hea	rt Failur	e						
Noda 2007	70	8.2219	10	74.5	21.8197	10	-4.50 [-18.95, 9.95]	
								-20 -10 0 10 20
								Favours BPAP Favours Control

Noda 2007: SEM converted to SD

Important Outcomes

None

ASV

Summary of Findings (GRADE)

Table S4 ASV in adults with CSA

References: Arzt 2013, Bradley 2023, Cowie 2015, Daubert 2018, Hetzenecker 2016 (Sl Med), Ilious 2018, Miyata 2012, O'Connor 2017, Szollosi 2006, Tamisier 2022, Toyama 2017, Yoshihisa 2012 (EJHF)

Outcomes [Tool]	Certainty of the evidence	Absolute Difference	No of Participants (studies)
	(GRADE)	ASV vs. control	
Excessive sleepiness [ESS]	⊕⊕⊕⊖ MODERATE [®]	The mean difference in the ASV group was 0.57 points lower (0.96 lower to 0.18 lower) compared to control	1518 (3 RCTs)
Disease severity [AHI]	⊕⊕⊕⊖ MODERATE ^b	The mean difference in the ASV group was 24.07 events/hour lower (30.22 lower to 17.92 lower) compared to control	770 (10 RCTs)
Disease severity [CAI]	⊕⊕⊕⊖ MODERATE ^b	The mean difference in the ASV group was 11.43 events/hour lower (15.42 lower to 7.44 lower) compared to control	315 (4 RCTs)
Disease severity [CAHI]	⊕⊕⊕⊖ MODERATE ^c	The mean difference in the ASV group was 15 events/hour lower (20.56 lower to 9.44 lower) compared to control	63 (1 RCT)
Cardiovascular disease [6MWD]	⊕⊕⊕⊖ MODERATE ^d	The mean difference in the ASV group was 10.68 meters Iower (38.21 lower to 16.85 higher) compared to control	1528 (3 RCTs)
Cardiovascular disease [NYHA classification score]*	⊕⊕⊕⊖ MODERATE ^c	The mean difference in the ASV group was 0.5 lower (0.82 lower to 0.18 lower) compared to control	30 (1 RCT)
Hospitalization [incidence (times/year)]		The risk ratio in the ASV group was 1.11 (0.86 to 1.43) with an absolute risk of 44 more per 1,000 (56 fewer to 173 more) compared to control	1649 (3 RCTs)
Mortality [reported deaths]		The risk ratio in the ASV group was 1.0 (0.71 to 1.41) with an absolute risk of 0 fewer per 1,000 (80 fewer to 114 more) compared to control	1716 (4 RCTs)

a. Risk of bias due to lack of blinding of the investigators and participants

b. Risk of bias due to overall loss to follow-up leading to concerns about generalizability

c. Imprecision due to small sample size (<200 participants)

d. Imprecision due to the 95% CI includes possibility for important harm and no effect

e. Imprecision due to the 95% CI includes possibility for important benefit and harm

Critical Outcomes

Figure S68. ASV vs. Control (Excessive sleepiness, ESS) [CST= -2 pts], RCTs

	ASV Control							Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 CSA due to hea	rt failure	e: HFr	'EF						
Arzt 2013	8.1	4.2	32	8.4	4.6	35	3.5%	-0.30 [-2.41, 1.81]	
Cowie 2015	-1.15	3.7	666	-0.52	3.9	659	92.1%	-0.63 [-1.04, -0.22]	
O'Connor 2017	-1.6	5.6	65	-2.1	5.1	61	4.4%	0.50 [-1.37, 2.37]	
Subtotal (95% CI)			763			755	100.0%	-0.57 [-0.96, -0.18]	•
Heterogeneity: Tau ² =	0.00; CI	hi² = '	1.41, dt	í= 2 (P =	= 0.50	0); I ≃ = 0)%		
Test for overall effect:	Z = 2.84	(P =	0.005)						
Total (95% CI)			763			755	100.0%	-0.57 [-0.96, -0.18]	◆
Heterogeneity: Tau ² =	0.00; CI	hi² = '	1.41, df	r= 2 (P =	= 0.50	0); I ≃ = 0)%		
Test for overall effect:	Z = 2.84	(P =	0.005)						-10 -5 0 5 10 Eavours ASV Eavours Control
Test for subgroup diff	erences	: Not	applica	able					

Cowie 2015: data was extracted from the graph. 12-month data was used, data reported as a change from baseline

O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change from baseline

		ASV		С	ontrol			Mean Difference		Mean Dif	ference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Randor	n, 95% Cl	
1.2.1 CSA due to heart failure: H	FrEF											
Arzt 2013	11	10	32	47	22	35	10.4%	-36.00 [-44.07, -27.93]				
Bradley 2023	-36.1	18.7	84	-0.3	20.9	93	11.4%	-35.80 [-41.63, -29.97]				
Hetzenecker 2016 (Sleep Med)	10	10	32	47	22	31	10.2%	-37.00 [-45.48, -28.52]				
lliou 2018	16.3	30.9	22	29.5	49.5	18	3.8%	-13.20 [-39.46, 13.06]			_	
Miyata 2012	5.9	6.3	11	28.1	14.4	11	9.8%	-22.20 [-31.49, -12.91]				
O'Connor 2017	-28.3	16.9	65	-17.9	22.3	61	10.9%	-10.40 [-17.34, -3.46]				
Szollosi 2006	14	3.8	10	30	6.6	10	11.8%	-16.00 [-20.72, -11.28]		+		
Tamisier 2022	12.1	14.5	92	33.9	19.7	97	11.7%	-21.80 [-26.71, -16.89]		-		
Toyama 2017	-20.8	14.6	15	-0.5	8.1	15	10.2%	-20.30 [-28.75, -11.85]				
Subtotal (95% CI)			363			371	90.3%	-24.28 [-31.00, -17.56]		•		
Heterogeneity: Tau ² = 84.91; Chi	² = 61.07	', df = 1	8 (P < 0	.00001)	; I ² = 8	7%						
Test for overall effect: Z = 7.08 (P	< 0.000	01)										
1.2.2 CSA due to heart failue: HF	pEF											
Yoshihisa 2012 (Euro J HF)	-30.2	12.2	18	-8.2	16.6	18	9.7%	-22.00 [-31.52, -12.48]				
Subtotal (95% CI)			18			18	9.7%	-22.00 [-31.52, -12.48]		•		
Heterogeneity: Not applicable												
Test for overall effect: Z = 4.53 (P	< 0.000	01)										
Total (95% CI)			381			389	100.0%	-24.07 [-30.22, -17.92]		•		
Heterogeneity: Tau ² = 77.68; Chi ² = 61.15, df = 9 (P < 0.00001); I ² = 85%										-50 0		100
Test for overall effect: Z = 7.67 (P		-100	Eavours ASV	Eavours Control	100							
Test for subgroup differences: C			r avoars Aov									

Figure S69. ASV vs. Control (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCTs

Arzt 2013: non-ICSD3, 12-week follow-up; Bradley 2023: 1-month data presented, data reported as a change from baseline; Hetzenecker 2016: optimal medical management or optimal medical management plus ASV therapy, 12-week study; Illiou 2018: nocturnal ventilation on top of exercise training (V + ET group) or to exercise training alone (ET group), median trial duration was 34 [28—48] days, SD calculated from median and IQR; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Szollosi 2006: single night study; Toyama 2017: 6-month study, data reported as a change score; Tamisier 2022: 12-month data reported, SERVE-HF sub-study; Arzt 2013: non-ICSD3, 12-week follow-up; AHI change from baseline was -74% reduction.

Figure S70. ASV vs. Control (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT

	ASV Control							Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
1.3.1 CSA due to heart failure	: HFrEF											
Arzt 2013	5	5	32	20	15	35	25.9%	-15.00 [-20.26, -9.74]	_ -			
Miyata 2012	0.6	1.5	11	14.9	8.4	11	26.9%	-14.30 [-19.34, -9.26]	_			
Tamisier 2022	2.8	7.9	93	11.8	15.8	97	34.4%	-9.00 [-12.53, -5.47]				
Subtotal (95% CI)			136			143	87.2%	-12.38 [-16.45, -8.30]	◆			
Heterogeneity: Tau ² = 7.53; Cł	hi² = 4.78	, df = .	2 (P = 0).09); I ^z :	= 58%							
Test for overall effect: Z = 5.95 (P ≺ 0.00001)												
1.3.2 CSA due to heart failue:	HFpEF											
Yoshihisa 2012 (Euro J HF)	-9	16.5	18	-4.3	12.4	18	12.8%	-4.70 [-14.24, 4.84]				
Subtotal (95% CI)			18			18	12.8%	-4.70 [-14.24, 4.84]				
Heterogeneity: Not applicable												
Test for overall effect: Z = 0.97	(P = 0.3	3)										
Total (95% CI)			154			161	100.0%	-11.43 [-15.42, -7.44]	•			
Heterogeneity: Tau ² = 8.81; Cł	hi² = 6.73											
Test for overall effect: Z = 5.61	(P < 0.0		Eavours ASV Eavours Control									
Test for subgroup differences	· Chiž – D											

Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors. CAI change from baseline was -83% reduction. ; Tamisier 2022: 12-month data reported, SERVE-HF sub-study; Arzt 2013: non-ICSD3, 12-week follow-up

Figure S71. ASV vs. Control (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], RCT

	A		Co	ntro		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 CSA due to heart failure								
Hetzenecker 2016 (Sleep Med)	5	5	32	20	15	31	-15.00 [-20.56, -9.44]	+
								Favours ASV Favours Control

Hetzenecker 2016: optimal medical management or optimal medical management plus ASV therapy, 12-week study.

Figure S72. ASV vs Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT

		ASV		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.5.1 CSA due to hea	rt failur	е							
Bradley 2023	-34.3	18.6	84	-0.3	20.9	93	19.8%	-34.00 [-39.82, -28.18]	
Miyata 2012	3.3	3.7	11	15.2	7.8	11	20.3%	-11.90 [-17.00, -6.80]	
O'Connor 2017	-28.3	17.5	65	-16.3	20.5	61	19.1%	-12.00 [-18.68, -5.32]	_ _
Szollosi 2006	18.6	4.7	10	32.6	7.8	10	19.9%	-14.00 [-19.64, -8.36]	
Tamisier 2022	13.5	13.6	93	29.3	17.7	96	20.8%	-15.80 [-20.29, -11.31]	-
Subtotal (95% CI)			263			271	100.0%	-17.53 [-25.26, -9.79]	◆
Heterogeneity: Tau ² =	69.81;+	Chi²=	40.10,	df = 4 (F	° < 0.0	0001); I	l²=90%		
Test for overall effect:	Z = 4.44	↓ (P < (0.00001	I)					
Total (95% CI)			263			271	100.0%	-17.53 [-25.26, -9.79]	◆
Heterogeneity: Tau ² =	69.81;+	Chi²=	40.10,	df = 4 (F	° < 0.0	0001); I	l² = 90%		-20 -10 0 10 20
Test for overall effect:	Z = 4.44	↓ (P < (0.00001	I)					Eavours ASV Eavours Control
Test for subgroup diff	erences	: Not a	applicat	ble					

Bradley 2023: 1-month data presented, data reported as a change from baseline; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors'; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Szollosi 2006: single night study;; Tamisier 2022: 12-month data reported, SERVE-HF sub-study

Figure S73. ASV vs. Control (Disease Severity, % of TST with oxygen saturation <90%) [CST= ≥ 50% reduction from baseline], RCT

	A	SV		Co	ontrol	I	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.6.1 CSA due to hear	rt failure	÷							
Miyata 2012	1.9	4.1	11	7.2	2.9	11	-5.30 [-8.27, -2.33]		
								-10 -5 0 5	10
								Favours ASV Favours Contro	ol

Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, data received from authors;

Figure S74. ASV vs. Control (Cardiovascular disease, 6MWD (change score)) [CST=+ 32 meters], RCTs

		ASV			Control			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
1.7.1 CSA due to heart	t failure									
Cowie 2015	-13	118.2879	666	-13.7	108.5108	659	69.8%	0.70 [-11.52, 12.92]		
Daubert 2018	262.94	428.7	40	287.2	198.4	37	3.3%	-24.26 [-171.69, 123.17]		
O'Connor 2017	22.6	131.3	65	61.2	117.4	61	26.8%	-38.60 [-82.04, 4.84]		
Subtotal (95% CI)			771			757	100.0%	-10.68 [-38.21, 16.85]		
Heterogeneity: Tau ² = 2	243.74; (Chi² = 3.00,	df = 2 (P = 0.22	2); I² = 33%					
Test for overall effect: Z	Z = 0.76 ((P = 0.45)								
Total (95% CI)			771			757	100.0%	-10.68 [-38.21, 16.85]		
Heterogeneity: Tau ² = 2	243.74; (Chi² = 3.00,	df = 2 (P = 0.22	2); I ^z = 33%					200
Test for overall effect: Z	Z = 0.76 ((P = 0.45)							Eavours Control Eavours ASV	200
Test for subgroup diffe	rences:	Not applica	ble							

*O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Cowie 2015: 95% confidence intervals converted to SD, data is reported as a change from baseline, data extracted from

graph in supplemental document, 12-month study; Daubert 2018: IQR converted to SD, data extracted from graph, optimal medical therapy (OMT) or treatment with ASV and OMT, 6-month trial

•			•				-		-
		ASV			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.8.1 CSA due to hea	art failure	е							
Arzt 2013	33.1	8.6	32	31.7	8.9	35	13.1%	1.40 [-2.79, 5.59]	
Cowie 2018	3.16	7.5383	124	1.83	7.5383	124	25.2%	1.33 [-0.55, 3.21]	+=-
Daubert 2018	4.3	6.6	40	4.6	9.4	37	15.3%	-0.30 [-3.95, 3.35]	
Miyata 2012	36	11.2	11	32.2	8.8	11	4.7%	3.80 [-4.62, 12.22]	
O'Connor 2017	3.712	6.318	65	4.953	9.501	61	19.5%	-1.24 [-4.08, 1.60]	
Toyama 2017	5.3	3.9	15	0.7	2.6	15	22.2%	4.60 [2.23, 6.97]	
Subtotal (95% CI)			287			283	100.0%	1.43 [-0.53, 3.39]	◆
Heterogeneity: Tau ² =	= 3.05; C ⁱ	hi ² = 11.3	39, df=	5 (P = 0	1.04); I ^z =	56%			
Test for overall effect	: Z = 1.43	8 (P = 0.1	5)						
Total (05% CI)			207			202	100.0%	4 42 [0 52 2 20]	
Total (95% CI)			201			200	100.0%	1.45 [-0.55, 5.59]	
Heterogeneity: lau*=	= 3.05; Cl	nr=11.3	39, df =	5 (P = L	1.04); 1* =	56%			-20 -10 0 10 20
l est for overall effect	:∠=1.43 	3 (P = 0.1	5)						Favours Control Favours ASV
1 Toet for euharoun dif	Toroncoc	:: Not ann	hlicahla						

Figure S75. ASV vs. control (Cardiovascular disease, LVE	: (%))) [CST= -	+5%], RCTs
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Cowie 2015: 95% confidence intervals converted to SD, data is reported as a change from baseline, data extracted from graph in supplemental document, 12-month study; Daubert 2018: IQR converted to SD, optimal medical therapy (OMT) or treatment with ASV and OMT, 6-month trial; Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as a change score; Toyama 2017: 6-month study, data reported as a change score

Figure S76. ASV vs. control (Cardiovascular disease, HR (beats/min)) [No CST], RCT

	A	SV		Co	ontrol	l	Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.10.1 CSA due to he	art failui	е								
Szollosi 2006	61.3	3.4	10	63.4	2.8	10	-2.10 [-4.83, 0.63]			
								-10	-5 0 5	10
								-10	Favours ASV Favours Control	.0

Szollosi 2006: single night study

Figure S77 . ASV vs. control (Cardiovascular disease, NYHA Class) [No CST], RCT

	A	SV		Co	ontrol	I	Mean Difference		Mean Dif	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
1.11.1 CSA due to he	art failu	re									
Toyama 2017	2.2	0.4	15	2.7	0.5	15	-0.50 [-0.82, -0.18]		+		
								-10	-5		10
								10	Favours ASV	Favours Control	

Toyama 2017: 6-month study
	ASV	1	Cont	Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
1.13.1 CSA due to he	art failure	: HFrEI	F				
Bradley 2023	41	92	43	106	30.4%	1.10 [0.79, 1.52]] —
Cowie 2015	287	666	272	659	52.1%	1.04 [0.92, 1.18]] 📮
O'Connor 2017	22	52	12	50	14.4%	1.76 [0.98, 3.17]	
Subtotal (95% CI)		810		815	97.0%	1.11 [0.92, 1.36]	」 ●
Total events	350		327				
Heterogeneity: Tau ² =	: 0.01; Chi	² = 2.9I	6, df = 2 ((P = 0.2	3); I² = 32	%	
Test for overall effect:	Z=1.08 ((P = 0.2	:8)				
1.13.2 CSA due to he	art failure	: HFpE					
O'Connor 2017	2	13	5	11	3.0%	0.34 [0.08, 1.41]	ı
Subtotal (95% CI)		13		11	3.0%	0.34 [0.08, 1.41]	
Total events	2		5				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.49 ((P = 0.1	4)				
							_
Total (95% CI)		823		826	100.0%	1.11 [0.86, 1.43]	1 🔶
Total events	352		332				
Heterogeneity: Tau ² =	: 0.03; Chi	²= 5.4	4, df = 3 (P = 0.1	4); l² = 45	%	
Test for overall effect:	Z = 0.77 ((P = 0.4	4)				Eavours ASV Eavours Control
Test for subgroup diff	erences:	Chi ^z = :	2.62, df =	1 (P =	0.11), I ^z =	61.8%	

Figure S78. ASV vs. Control (Hospitalizations) [CST= 0.9], RCT

Bradley 2023: 1-month data presented; Cowie 2015: 12-month study; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S79. ASV vs. Control (Mortality, All-cause mortality) [CST= 0.8], RCTs



Bradley 2023: mean follow-up of 3.6 ± 1.6 years, all-cause mortality for CSA participants only; Cowie 2015: 60-month study, all cause deaths (data listed in Table 3); O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial; Arzt 2013: non-ICSD3 diagnostic criteria, 12-week follow-up

Figure S80. ASV vs. Control (Sleep Quality, PSQI) [CST= -3 points], RCT

	A	SV		Co	ontro		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean SD Total		Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI
1.14.1 CSA due to he	art failu	ге							
O'Connor 2017	-2.7	5	65	-3.3	4.9	61	0.60 [-1.13, 2.33]		
								-10	
								10	Favours ASV Favours Control

O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S81. ASV vs. Control (Cardiovascular disease, NT pro-BNP, ng/mL) [CST= - 50% reduction from baseline], RCT

	ASV		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup Mea	n SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.9.1 CSA due to heart fail	Ire							
Daubert 2018 3.1	6 5.7	40	4.36	4.29	37	41.5%	-1.20 [-3.44, 1.04]	
O'Connor 2017 0.1	7 3.4	65	-1.07	6.77	61	58.5%	1.24 [-0.65, 3.13]	
Subtotal (95% CI)		105			98	100.0%	0.23 [-1.22, 1.67]	
Heterogeneity: Chi ² = 2.66,	df = 1 ((P = 0.1	0); l² = 6	2%				
Test for overall effect: Z = 0	31 (P =	= 0.76)						
Total (95% CI)		105			98	100.0%	0.23 [-1.22, 1.67]	
Heterogeneity: Chi ² = 2.66,	df = 1 ((P = 0.1	0); I ^z = 6	2%				
Test for overall effect: Z = 0	31 (P =	= 0.76)						Eavours ASV Eavours Control
Test for subaroup difference	es: No	t applic:	able					

Daubert 2018: data from figure 2, IQR converted to SD, optimal medical therapy (OMT) or treatment with ASV and OMT, 6month trial, NT-pro BNP pg/ml; O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial, data reported as change from baseline, NT-pro BNP pg/ml

Figure S82. ASV vs. Control (Cardiovascular disease, NT pro-BNP, ng/mL) [CST= - 50% reduction from baseline], RCT



Arzt 2013 NT-pro BNP ng/ml; separated from other NT pro-BNP analysis due to extreme variation in values. ASV baseline = 1039(1034) ng/mL

Figure S83. ASV vs. Control (Cardiovascular disease, BNP, pg/mL) [CST= - 50% reduction from baseline], RCT

	ASV		Control			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
1.10.1 CSA due to he	CSA due to heart failure									
Miyata 2012	221	184	11	388	532	11	-167.00 [-499.66, 165.66]			
								— —		
								-1000	-500 0 500 10 Favours ASV Favours Control	000

Miyata 2012: patients with CHF and CSR-CSA who had implanted CRT with defibrillator (CRTD), 6-month trial, Control data received from author; median (IQR) BNP pg/ml

	1	ASV		Ba	selin	е		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.1.1 CSA due to heart	failure								
Campbell 2012	5.9	5.3	10	7.3	4.4	10	3.6%	-1.40 [-5.67, 2.87]	
Correia 2015	6	5	16	12	- 7	16	3.6%	-6.00 [-10.22, -1.78]	
Fietze 2008	8.7	3.9	17	8.1	3.5	17	6.9%	0.60 [-1.89, 3.09]	
Heider 2018	7	4	54	10	4	54	9.9%	-3.00 [-4.51, -1.49]	
Jaffuel 2019	5.7	4.5	105	9.6	5.3	105	10.5%	-3.90 [-5.23, -2.57]	
Javaheri 2015	7.8	- 4	27	12.8	5	27	7.1%	-5.00 [-7.42, -2.58]	
Kasai 2010	5	3.4	16	8.2	4.8	16	5.9%	-3.20 [-6.08, -0.32]	
Kasai 2013	6.8	- 5	23	6.7	4	23	6.6%	0.10 [-2.52, 2.72]	
Roder 2020	5.8	3.7	30	6.3	3.5	30	8.9%	-0.50 [-2.32, 1.32]	
Subtotal (95% CI)			298			298	62.9%	-2.40 [-3.79, -1.02]	•
Heterogeneity: Tau ² = 2.	.84; Chi ²	= 26.	23, df=	= 8 (P =	0.00	10); I ² =	70%		
Test for overall effect: Z	= 3.40 (F	P = 0.1	0007)						
2.1.2 Non-heart failure	CSA								
Brill 2014	6.1	2.7	15	8.6	6.4	15	4.7%	-2.50 [-6.02, 1.02]	— — ——————————————————————————————————
Correia 2015	6	5	9	12	7	9	2.3%	-6.00 [-11.62, -0.38]	
Heider 2018	7	4	60	10	4	60	10.1%	-3.00 [-4.43, -1.57]	
Jaffuel 2019	6.4	5.4	36	10.6	5.4	36	6.9%	-4.20 [-6.69, -1.71]	
Javaheri 2014 (JCSM)	10.4	4.6	20	12.4	4.6	20	6.0%	-2.00 [-4.85, 0.85]	—• — •
Javaheri 2015	7.8	4	27	12.8	5	27	7.1%	-5.00 [-7.42, -2.58]	_
Morgenthaler 2014	0	0	0	0	0	0		Not estimable	
Subtotal (95% CI)			167			167	37.1%	-3.44 [-4.42, -2.47]	◆
Heterogeneity: Tau ² = 0.	.00; Chi ^z	= 4.3	7, df =	5 (P = 0	50);	l ^z = 0%			
Test for overall effect: Z	= 6.93 (F	o < 0.۱	00001)						
Total (95% CI)			465			465	100.0%	-2.84 [-3.78, -1.89]	•
Heterogeneity: Tau ² = 1	.76: Chi ^z	= 32.	54. df=	= 14 (P =	= 0.01	03); ² =	57%		
Test for overall effect: Z	= 5.88 (F	× ٥.۱	00001)			/1 ·			-10 -5 0 5 10
Test for subaroup differ	ences: C	hi ² =	1.44. d	f=1 (P;	= 0.2	3). I ^z = 1	30.7%		Favours ASV Favours Baseline

Figure S84. ASV vs. Baseline (Excessive sleepiness, ESS) [CST= -2 pts], Observational studies

Figure S85. ASV vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], Observational Studies

		ASV		Ba	seline			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	
2.4.2 CSA due to heart f	failure									
Arzt 2008	4	1	14	22	4	14	3.2%	-18.00 [-20.16, -15.84]	+	
Campbell 2012	5	6.3	10	63	30	10	2.0%	-58.00 [-77.00, -39.00]		
Carnevale 2011	6.8	14.4	33	54	24	33	2.8%	-47.20 [-56.75, -37.65]		
Correia 2015	4	3	16	44	18	16	2.8%	-40.00 [-48.94, -31.06]		
D'Elia 2013	2.84	1.1	19	41.37	17.5	19	2.9%	-38.53 [-46.41, -30.65]		
Fietze 2008	11.2	9.4	17	31.7	9.8	17	3.0%	-20.50 [-26.96, -14.04]		
Hastings 2010	8	14.6	11	49	35.1	11	1.7%	-41.00 [-63.47, -18.53]		
Heider 2018	7	7	54	54	23	54	3.0%	-47.00 [-53.41, -40.59]		
Hetland 2017	1.9	2	14	35.6	16.3	14	2.9%	-33.70 [-42.30, -25.10]		
Hetzenecker 2016	9.5	15.2	34	46.3	14.4	34	3.0%	-36.80 [-43.84, -29.76]		
Jaffuel 2019	1.9	1.95	105	52.1	21	105	3.1%	-50.20 [-54.23, -46.17]		
Javaheri 2011	6	6	37	53	23	37	2.9%	-47.00 [-54.66, -39.34]		
Javaneri 2015	12	20	27	55	24	27	2.6%	-43.00 [-54.78, -31.22]		
Kasal 2013 Magazathalay 2007	2	1.4	23	23.1	9.1	23	3.1%	-21.10 [-24.86, -17.34]	~	
Morgenthaler 2007	U 6 0	0.000001	24	51.9	45.0	21	2.8%	-51.90 [-61.65, -42.15]		
Didenburg 2015	5.3	10.9	21	33.1	10.0	21	2.9%	-27.80 [-35.94, -19.00]		
Prinippe 2006 Dondoroth 2000	21	10.7	12	47	10.0	12	2.370	40.00[-00.92,-31.06]		
Ranueratin 2009 Dondorath 2012	2.1	2.4	26	43.0	24	26	2.470	-41.70 [-00.00, -20.00] 25 70 [44 20 27 11]		
Ranueraur 2012 Dodor 2020	211.1	11.0	20	40.0	23.0	20	2.870	-30.70 [-44.29, -27.11]		
Topphar 2020	د د م	24	14	40	10	14	3.0%	-42.00[-47.00,-30.17]		
Voehihies 2001	0.3	12.4	42	44.0	26.6	42	2.0%	-30.20 [-44.00, -31.32]		
Vochibica 2012	0.1	12.1	42 60	272	10.0	42 60	2.070	-20.00 [-30.04, -21.10]		
Subtotal (95% CI)	0.1	10.0	637	57.5	10.2	652	64.1%	-37.86 [-43.58, -32.14]	•	
Heterogeneity: Tau ² – 17	72.61 · CI	ni≅ — 381 27	df = 2	7/P ≤ 0	00001)· I≊ = 0	196		•	
Test for overall effect: 7 :	= 12 97 /	P < 0.0000.21	, ui = 2. 1)	2 (1 - 0	.00001	7.1 - 5				
	12.01 \	. 0.0000	.,							
2.4.6 Non-heart failure (CSA									
Brill 2014	6.7	8.5	15	43.5	39.8	15	1.9%	-36.80 [-57.40, -16.20]		
Cao 2014	2.5	3.5	18	50.3	22.2	18	2.7%	-47.80 [-58.18, -37.42]		
Correia 2015	7	10	16	44	18	16	2.7%	-37.00 [-47.09, -26.91]		
Dellweg 2013	7.4	4.2	15	27.7	9.7	15	3.1%	-20.30 [-25.65, -14.95]		
Heider 2018	7	6	60	50	23	60	3.0%	-43.00 [-49.01, -36.99]		
Jaffuel 2019	2.5	3.3	36	50.6	20.2	36	3.0%	-48.10 [-54.79, -41.41]		
Javaheri 2014 (JCSM)	23	18	20	61	30	20	2.3%	-38.00 [-53.33, -22.67]		
Javaheri 2015	12	20	27	55	24	27	2.6%	-43.00 [-54.78, -31.22]		
Morgenthaler 2007	1.6	3.6	9	49.4	25.4	9	2.2%	-47.80 [-64.56, -31.04]		
Morgenthaler 2014	4.4	9.6	29	35.1	25.3	29	2.8%	-30.70 [-40.55, -20.85]		
Randerath 2009	2.1	2.4	12	43.8	24	12	2.4%	-41.70 [-55.35, -28.05]		
Randerath 2009	2.1	2.4	12	43.8	24	12	2.4%	-41.70 [-55.35, -28.05]		
Shapiro 2015	0.2	0.8	31	38.8	31.1	31	2.7%	-38.60 [-49.55, -27.65]		
Troitino 2014	5.2	2.4	12	39.4	31.9	12	2.1%	-34.20 [-52.30, -16.10]		
Subtotal (95% CI)			312			312	35.9%	-39.00 [-45.00, -33.01]	●	
Heterogeneity: Tau ² = 93	3.51; Chi	т= 61.27, d Б = 0.0000	t = 13 (I	- < 0.00	iUU1); l	r= 799	6			
l est for overall effect: Z =	= 12.75 (P < 0.0000	1)							
Total (95% CI)			949			964	100.0%	-38.27 [-42.66, -33.88]	◆	
Heterogeneity: Tau ² = 15	56.71; Cł	ni² = 463.62	, df = 3	6 (P < 0	.00001); I2 = 9	2%			-
Test for overall effect: Z =	= 17.09 (P < 0.0000	1)						-50 -25 U 25 50 Eavoure ASV Eavoure Paceline	
Test for subaroup differe	ences: C	hi² = 0.07. c	lf = 1 (F	= 0.79). I ² = 0	%				

Figure S86. ASV vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], **Observational Studies**

	Mean Difference												
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
2.4.2 CSA due to heart fa	ilure												
Campbell 2012	2.1	4.9	10	52.8	33.2	10	2.1%	-50.70 [-71.50, -29.90]					
D'Elia 2013	0.06	0.0001	19	16.9	17.5	19	4.7%	-16.84 [-24.71, -8.97]	- -				
Hetzenecker 2016	2.7	13.6	34	25.1	12.5	34	5.0%	-22.40 [-28.61, -16.19]					
Javaheri 2011	3	4	37	16	19	37	5.0%	-13.00 [-19.26, -6.74]					
Javaheri 2015	1	2	27	23	18	27	4.9%	-22.00 [-28.83, -15.17]					
Koyama 2013	0	0	10	0	0	10		Not estimable					
Morgenthaler 2007	0	0.0001	6	22.7	14.8	6	3.7%	-22.70 [-34.54, -10.86]					
Oldenburg 2015	0	0.0001	21	14.6	11.9	21	5.3%	-14.60 [-19.69, -9.51]	-				
Randerath 2009	2.8	2.1	12	37.7	20.4	12	3.8%	-34.90 [-46.50, -23.30]					
Randerath 2012	1.7	4.7	36	6.3	6.4	36	5.7%	-4.60 [-7.19, -2.01]	*				
Teschler 2001	3.3	0.5	14	5.8	2.9	14	5.8%	-2.50 [-4.04, -0.96]	•				
Yoshihisa 2012	1.1	1.6	42	17.6	14.2	42	5.4%	-16.50 [-20.82, -12.18]	+				
Yoshihisa 2013	1.1	1.5	50	16.4	13.7	50	5.5%	-15.30 [-19.12, -11.48]	÷				
Subtotal (95% CI)			318			318	56.9%	-17.40 [-22.74, -12.05]	•				
Heterogeneity: Tau ² = 74.	11; Chi	i ^z = 177.3	9, df = 1	11 (P ≺	0.0000)1); I²=	94%						
Test for overall effect: Z =													
2.4.6 Non-heart failure C	SA												
Cao 2014	0.4	0.8	18	13	18.7	18	4.5%	-12.60 [-21.253.95]	_ —				
Dellweg 2013	1.5	1.7	15	18.2	7.1	15	5.5%	-16.70 [-20.3913.01]	+				
Javaheri 2014 (JCSM)	0	0.001	20	32	31	20	3.3%	-32.00 [-45.59, -18,41]					
Javaheri 2015	1	2	27	23	18	27	4.9%	-22.00 -28.8315.17					
Morgenthaler 2007	0.1	0.3	9	5.6	4.6	9	5.6%	-5.50 [-8.51, -2.49]	+				
Morgenthaler 2014	0.7	3.4	29	2.7	4.6	29	5.7%	-2.00 [-4.08, 0.08]	-				
Randerath 2009	1.7	2	12	31	17.5	12	4.2%	-29.30 [-39.27, -19.33]	<u> </u>				
Randerath 2009	1.7	2	12	31	17.5	12	4.2%	-29.30 [-39.27, -19.33]	<u> </u>				
Shapiro 2015	0.2	0.8	31	9.7	15.2	31	5.2%	-9.50 [-14.86, -4.14]					
Subtotal (95% CI)			173			173	43.1%	-16.43 [-22.77, -10.09]	◆				
Heterogeneity: Tau ² = 79.	88; Chi	i ^z = 120.4	4, df = 3	8 (P < 0	.00001); IZ = 9	93%						
Test for overall effect: Z =	5.08 (F	o < 0.0000	01)										
Total (95% Cl) 491 491 100.0% -16.77 [-20.55, -12.99]													
Heterogeneity: Tau ² = 63.	74; Chi	i² = 297.8	9, df = 3	20 (P ≺	0.0000	01); I² =	93%		-50 -25 0 25 50				
Test for overall effect: Z =	8.69 (F	° < 0.0000	01)						Favours ASV Favours Baseline				
Test for subgroup differe	<u>nces: C</u>	hi² = 0.05	5 <u>. df = 1</u>	(P = 0.)	8 <u>2), I</u> ²:	= 0%			avoire never i avoire baseline				

Figure S87. ASV vs Baseline (Disease Severity, CAHI) [CST= ≥ 50% reduction from baseline], Observational Studies

	1	SV		Ba	Mean Difference	Mean Difference								
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI					
2.5.1 CSA due to hear	rt failur	e												
Randerath 2012	6.9	8.3	36	23.1	13.2	36	33.2%	-16.20 [-21.29, -11.11]						
Roder 2020	2	3	30	35	15	30	33.0%	-33.00 [-38.47, -27.53]						
Subtotal (95% CI)			66			66	66.2%	-24.57 [-41.03, -8.11]						
Heterogeneity: Tau ² =	133.84	Chi⁼	= 19.3	9, df = 1	(P < 0	.0001);	i² = 95%							
Test for overall effect: .	Test for overall effect: Z = 2.92 (P = 0.003)													
2.5.2 Non-heart failur	e C SA													
Randerath 2009	1.3	1	12	5.5	5.8	12	33.8%	-4.20 [-7.53, -0.87]						
Subtotal (95% CI)			12			12	33.8%	-4.20 [-7.53, -0.87]	◆					
Heterogeneity: Not ap	plicable													
Test for overall effect: .	Z = 2.47	' (P =	0.01)											
Total (95% CI)			78			78	100.0%	-17.69 [-34.34, -1.04]						
Heterogeneity: Tau ² =	210.73	Chi ²	= 79.6	2, df = 2	(P < 0	.00001); I² = 9 79	6						
Test for overall effect: .	Z = 2.08) (P =	0.04)						-50 -25 0 25 50 Eavours ASV Eavours Baseline					
Test for subgroup diffe	erences	: Chi	² = 5.65	i, df = 1	(P = 0)	02), I ^z =	= 82.3%		avoirs //ov Tavoirs Dasenne					

Figure S88. ASV vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], Observational study

		ASV		Ba	seline	÷		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.6.1 CSA due to hea	rt failure	;							
Fietze 2008	14.7	11	17	26.5	12.2	17	9.6%	-11.80 [-19.61, -3.99]	_ -
Heider 2018	8	7	54	52	23	54	10.3%	-44.00 [-50.41, -37.59]	- - -
Oldenburg 2015	8.2	11.8	21	31.3	17.9	21	8.9%	-23.10 [-32.27, -13.93]	<u> </u>
Roder 2020	5	4	30	33	16	30	10.5%	-28.00 [-33.90, -22.10]	- - -
Teschler 2001	5.2	0.6	14	38.2	2.6	14	11.9%	-33.00 [-34.40, -31.60]	•
Yoshihisa 2012	6.5	15.2	42	27.5	-21.00 [-27.72, -14.28]				
Yoshihisa 2013	7.3	15.7	50	-21.30 [-27.96, -14.64]					
Subtotal (95% CI)			228	-26.37 [-33.07, -19.67]	◆				
Heterogeneity: Tau ² =	70.59; (Chi²=	66.39,	df = 6 (F	° < 0.0	0001); I	²= 91%		
Test for overall effect:	Z = 7.72	(P < 0	0.00001	I) –					
2.6.2 Non-heart failur	re CSA								
Dellweg 2013	4.8	3.4	15	24.3	11.9	15	10.3%	-19.50 [-25.76, -13.24]	
Heider 2018	10	11	60	48	24	60	10.1%	-38.00 [-44.68, -31.32]	—
Shapiro 2015	5.9	8.6	31	32.8	29.2	31	8.1%	-26.90 [-37.62, -16.18]	
Subtotal (95% CI)			106			106	28.6%	-28.16 [-40.49, -15.82]	\bullet
Heterogeneity: Tau ² =	102.31;	Chi²=	= 15.72	, df = 2 ((P = 0.1)	0004); I	²= 87%		
Test for overall effect:	Z = 4.47	(P < 0	0.00001	I)					
Total (95% CI)			334			334	100.0%	-26.90 [-32.31, -21.50]	◆
Heterogeneity: Tau ² =	63.38; (Chi²=							
Test for overall effect:	Z = 9.76	(P < 0	0.00001	I)					Favours ASV Favours Baseline
Test for subgroup diff	erences	: Chi ² ∍	= 0.06.	df = 1 (F	P = 0.8	0), I ^z =	0%		Tavours //ov Tavours Dasenne

Figure S89. ASV vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational studies

[
		ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.8.1 CSA due to hea	rt failure	9							
Javaheri 2015	7	19	27	12	17	27	9.8%	-5.00 [-14.62, 4.62]	
Oldenburg 2015	3.7	10.9	21	17.5	18.4	21	10.4%	-13.80 [-22.95, -4.65]	-
Randerath 2009	3.2	6.9	12	14.2	16.2	12	9.4%	-11.00 [-20.96, -1.04]	
Roder 2020	7	16	30	28	45	30	4.3%	-21.00 [-38.09, -3.91]	
Yoshihisa 2012	1.1	4	42	9.7	16.7	42	16.8%	-8.60 [-13.79, -3.41]	
Yoshihisa 2013	0.9	2.7	50	10.1	16.5	50	17.9%	-9.20 [-13.83, -4.57]	
Subtotal (95% CI)			182			182	68.5%	-9.58 [-12.47, -6.69]	◆
Subtotal (95% CI) 182 182 Heterogeneity: Tau ² = 0.00; Chi ² = 3.64, df = 5 (P = 0.60); I ² = 0 External content of the con									
Test for overall effect:	Z = 6.50) (P < (0.00001	1)					
2.8.2 Non-heart failur	e CSA								
Javaheri 2015	7	19	27	12	17	27	9.8%	-5.00 [-14.62, 4.62]	
Morgenthaler 2014	6.2	14.9	29	12.7	16.1	29	12.0%	-6.50 [-14.48, 1.48]	
Troitino 2014	15.7	8.2	12	41.8	25.1	34	9.8%	-26.10 [-35.73, -16.47]	
Subtotal (95% CI)			68			90	31.5%	-12.41 [-25.26, 0.44]	
Heterogeneity: Tau ² =	107.47;	Chi⁼⊧	= 12.09	, df = 2 ((P = 0.	002); I ^z	= 83%		
Test for overall effect: $Z = 1.89$ (P = 0.06)									
Total (95% CI)			250			272	100.0%	-10.75 [-14.66, -6.85]	◆
Heterogeneity: Tau ² = 16.59; Chi ² = 16.24, df = 8 (P = 0.04); I ² =						4); I² = €	51%		
Test for overall effect: Z = 5.40 (P < 0.00001)									-50 -25 0 25 50 Favoure ASV Favoure Baseline
Test for subaroup diff	erences	: Chi ₹	= 0.18.	df = 1 (1	P = 0.6	(7), ² =	0%		

Figure S90. ASV vs. Baseline (Disease Severity, oxygen saturation >90% (%)) [CST= ≥ 50% increase from baseline], Observational studies

	4	ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.7.1 CSA due to hear	rt failure	•							
Ramar 2012	92.6	15.4	61	83.9	16.9	61	71.5%	8.70 [2.96, 14.44]	
Subtotal (95% CI)			61			61	11.5%	8.70 [2.96, 14.44]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.97	(P = 0).003)						
2.7.2 Non-heart failur	e CSA								
Ramar 2012	90.5	16.1	47	78.3	27.4	47	28.5%	12.20 [3.11, 21.29]	
Subtotal (95% CI)			47			47	28.5%	12.20 [3.11, 21.29]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 2.63	(P = 0	(800.0						
Total (95% CI)			108			108	100.0%	9.70 [4.85, 14.55]	-
Heterogeneity: Chi ² =	0.41, df:	= 1 (P	= 0.52)); I ^z = 0%	6				
Test for overall effect:	Z = 3.92	(P < 0	0.0001)						Favours Baseline Favours ASV
Test for subgroup diffe	erences:	: Chi ⁼∶	= 0.41,	df = 1 (F	^o = 0.5	2), I ² =	0%		

Figure S91. ASV vs. Control (Disease Severity, Apnea Index) [CST= ≥ 50% reduction from baseline], Observational Study

Γ		A	۱SV		Co	ontro	l	Mean Difference	Mean Difference		
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI	
ſ	2.10.1 CSA due to he	art failu	re: HI	Fref							
	Oldenburg 2018	2.9	0.7	100	9.3	3.3	34	-6.40 [-7.52, -5.28]			
									-10 -5		10
									Favours ASV	Favours Control	10
L											

6-month data extracted from figure 1.

Figure S92. ASV vs. Control (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational studies

		ASV		C	ontrol		Mean Difference	Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
2.13.1 CSA due to he	art failu	re: HFi	EF							
Oldenburg 2018	13.7	11.3	98	47.8	17.9	31	-34.10 [-40.79, -27.41]	+		
								-100 -50 (1 50	100
								Favours ASV	Favours Control	
								Favours ASV	Favours Control	

6-month data extracted from figure 1.

Figure S93. ASV vs. Baseline (Cardiovascular disease, 6MWD) [CST= +32 meters], Observational studi	es
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		ASV		B	aseline			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
2.15.1 CSA due to he	eart failu	ге								
Campbell 2012	370	88.3	7	365	54.8	7	15.9%	5.00 [-71.99, 81.99]		
Hetland 2017	368.8	183.7	9	418	136.5	9	4.2%	-49.20 [-198.72, 100.32]		
Kasai 2010	428.3	64.7	15	393.3	61.5	15	46.1%	35.00 [-10.17, 80.17]	+-∎	
Kasai 2013	383.7	64.9	12	368.2	67	12	33.8%	15.50 [-37.28, 68.28]		
Subtotal (95% CI)			43			43	100.0%	20.10 [-10.58, 50.78]	★	
Heterogeneity: Tau ² =	= 0.00; C	hi² = 1.4	2, df =	3 (P = 0	.70); l² =	= 0%				
Test for overall effect: $Z = 1.28$ (P = 0.20)										
Total (95% CI)			43			43	100.0%	20.10 [-10.58, 50.78]	★	
Heterogeneity: Tau ² = 0.00; Chi ² = 1.42, df = 3 (P = 0.70); i ² = 0%										
Test for overall effect	: Z = 1.28	8 (P = 0.	20)						Favours Baseline Favours ASV	
Test for subaroup dif	ferences	: Not ap	plicabl	е						

Hetland 2017: median, IQR converted to mean and SD

Figure S94. ASV vs. Control (Cardiovascular disease, 6MWD) [CST= +32 meters], Observational studies

	Α	SV		Control			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
2.16.1 CSA due to he	art failui	re: H	Fref									
Oldenburg 2018	372.3	22	80	369	30	39	3.30 [-7.28, 13.88]	+ +				
								-20 -10 0 10 20				
								Favours Control Favours ASV				
				_		_						

6-month data extracted from figure 1.

Figure S95. ASV vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= +5%], Observational studies

		ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.17.1 CSA due to he	art failu	re							
Campbell 2012	34.97	16.33	7	28	10.5	7	2.7%	6.97 [-7.41, 21.35]	
Fietze 2008	28.8	9.8	37	25.1	8.5	37	32.4%	3.70 [-0.48, 7.88]	+=-
Hetland 2017	41.3	21	9	39	22.7	9	1.4%	2.30 [-17.90, 22.50]	
Kasai 2010	44.8	4.7	16	35.7	12.9	16	12.5%	9.10 [2.37, 15.83]	_
Kasai 2013	37.8	9.1	12	32	7.9	12	12.2%	5.80 [-1.02, 12.62]	+
Koyama 2013	47	10.6	26	43.8	10.4	26	17.4%	3.20 [-2.51, 8.91]	+ -
Philippe 2006	35.7	5.2	7	29	9	12	13.9%	6.70 [0.31, 13.09]	
Randerath 2012	45.5	16	26	47.4	15.9	26	7.5%	-1.90 [-10.57, 6.77]	
Subtotal (95% CI)			140			145	100.0%	4.61 [2.23, 6.99]	◆
Heterogeneity: Tau ² =	0.00; Ci	hi² = 4.9	8, df =	7 (P = 0	.66); I ^z	= 0%			
Test for overall effect:	Z = 3.80	(P = 0.	0001)						
Total (95% CI)			140			145	100.0%	4.61 [2.23, 6.99]	◆
Heterogeneity: Tau ² =	0.00; Ci	hi² = 4.9	8, df =	7 (P = 0	.66); I ^z	= 0%			
Test for overall effect:	Z = 3.80	(P = 0.	0001)						-50 -25 0 25 50 Favours Baseline Favours ASV
Test for subgroup diff	erences	: Not ap	plicabl	е					Tavono basenne Tavono Aov

1 Iguie 330, A3V V3, cultului (caluluvasculai ulsease, LVLI 1/01/1C31 – +3/01, Obselvational studi	Figure S96. ASV vs. Control ((Cardiovascular disease.	LVEF (%)) [CST= +5%]	. Observational studio
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		ASV		Co	ontro			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.18.1 CSA due to he	art failu	re: HFi	TEF									
Hastings 2010	36.9	16.4	11	31.2	9.7	8	3.2%	5.70 [-6.09, 17.49]				
Oldenburg 2018 Subtotal (95% CI)	33.4	1.7	89 100	30.7	11	103 111	96.8% 100.0%	2.70 [0.55, 4.85] 2.80 [0.68, 4.92]				
Subtract (95% Ct) 100 111 100.0% 2.80 [0.08, 4.92] Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); l² = 0% Test for overall effect: Z = 2.59 (P = 0.010) Test for overall effect: Z = 2.59 (P = 0.010)												
Total (95% CI)			100			111	100.0%	2.80 [0.68, 4.92]	◆			
Heterogeneity: Chi ² =	0.24, df	= 1 (P	= 0.62)); I ^z = 09	6							
Test for overall effect:	Z = 2.59	9 (P = 0).010)						Favours Control Favours ASV			
Test for subgroup diff	erences	:: Not a	opplical	ole								

Oldenburg 2018: data extracted from graph; 6-month data presented Hastings 2010: 6-month data

Figure S97. ASV vs. Baseline (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], Observational studies

		ASV		Ba	seline)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.23.1 Primary CSA									
Gorbachevski 2020 Subtotal (95% CI)	106.1	12.8	20 20	105.7	16	20 20	12.7% 12.7%	0.40 [-8.58, 9.38] 0.40 [-8.58, 9.38]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.09	(P = 0	1.93)						
2.23.2 CSA due to hea	art failu	re							
Gorbachevski 2020	98.5	21.5	17	100.2	31.2	17	3.2%	-1.70 [-19.71, 16.31]	
Hetland 2017	118	14.8	14	129	16.5	14	7.6%	-11.00 [-22.61, 0.61]	
Kasai 2010	118.2	20.4	15	119.7	17	15	5.7%	-1.50 [-14.94, 11.94]	
Kasai 2013	122	15.9	23	130.7	13.4	23	14.2%	-8.70 [-17.20, -0.20]	
Oldenburg 2015	121.7	20	21	123.2	22.2	21	6.3%	-1.50 [-14.28, 11.28]	
Roder 2020	128	23	30	129	30	30	5.6%	-1.00 [-14.53, 12.53]	
Yoshihisa 2012	103.6	13.9	42	113.3	19.1	42	20.1%	-9.70 [-16.84, -2.56]	
Yoshihisa 2013	109.2	14.4	50	114.1	18.3	50	24.6%	-4.90 [-11.35, 1.55]	
Subtotal (95% CI)			212			212	87.3%	-6.32 [-9.75, -2.89]	•
Heterogeneity: Tau ² =	0.00; CI	hi = 3.	.86, df=	= 7 (P =	0.80);	l² = 0%			
Test for overall effect:	Z = 3.61	(P = 0).0003)						
Total (95% CI)			232			232	100.0%	-5.47 [-8.67, -2.27]	•
Heterogeneity: Tau ² =	0.00; CI	hi² = 5.	74, df=	= 8 (P =	0.68);	l² = 0%			
Test for overall effect:	Z = 3.35	(P = 0	1.0008)						Favours ASV Favours Baseline
Test for subgroup diffe	erences	: Chi ^z -	= 1.88.	df = 1 (F	P = 0.1	7), I ^z =	46.8%		ravours //ov Tavours Dasenne



Observational studies

		ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.24.1 CSA due to he	art failu	re: HFr	ΈF						
Hastings 2010	-5.8	14.6	11	3.4	14.8	8	64.7%	-9.20 [-22.60, 4.20]	
Koyama 2013	112.8	12.4	10	125.8	26.5	10	35.3%	-13.00 [-31.13, 5.13]	
Subtotal (95% CI)			21			18	100.0%	-10.54 [-21.32, 0.24]	\bullet
Heterogeneity: Chi ² =	0.11, df	= 1 (P	= 0.74)); I ^z = 09	6				
Test for overall effect:	Z = 1.92	? (P = 0).06)						
Total (95% CI)			21			18	100.0%	-10.54 [-21.32, 0.24]	\bullet
Heterogeneity: Chi ² =	0.11, df	= 1 (P	= 0.74)); I² = 09	6				
Test for overall effect:	Z = 1.92	? (P = 0).06)						-50 -25 0 25 50 Eavours ASV Eavours Control
Test for subgroup diff	erences	: Not a	pplicat	ole					

Figure S99. ASV vs. Baseline (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], Observational studies



Figure S100. ASV vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], Observational studies

		ASV		Ba	seline	•		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
2.22.1 CSA due to he	2.22.1 C SA due to heart failure: HFrEF												
Hastings 2010	-9.8	11.9	11	-5.8	10.7	8	43.5%	-4.00 [-14.22, 6.22]					
Koyama 2013	69	6.9	10	75.8	12.7	10	56.5%	-6.80 [-15.76, 2.16]					
Subtotal (95% CI)			21			18	100.0%	-5.58 [-12.32, 1.15]	\bullet				
Heterogeneity: Chi ² =	0.16, df	= 1 (P	= 0.69); I= 09	6								
Test for overall effect:	Z = 1.62	: (P = 0).10)										
Total (95% CI)			21			18	100.0%	-5.58 [-12.32, 1.15]					
Heterogeneity: Chi ² =	0.16, df	= 1 (P	= 0.69); I= 09	6								
Test for overall effect:	Z = 1.62	: (P = 0).10)						Eavours ASV Eavours Control				
Test for subaroup diff	erences	: Not a	pplical	ole	_								

		ASV		Ba	seline	;		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.19.1 Non-heart failu	ire CSA								
Gorbachevski 2020 Subtotal (95% CI)	58.4	8.4	20 20	59.1	9.1	20 20	11.4% 11.4%	-0.70 [-6.13, 4.73] - 0.70 [-6.13, 4.73]	-
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.25	(P = 0).80)						
2.19.2 CSA due to he	art failui	re							
D'Elia 2013	62	7	19	68	10	19	11.1%	-6.00 [-11.49, -0.51]	_
Fietze 2008	63.9	9.8	17	62.8	8.6	17	8.7%	1.10 [-5.10, 7.30]	
Gorbachevski 2020	61.9	8.8	17	66.2	10	17	8.3%	-4.30 [-10.63, 2.03]	
Koyama 2013	72.5	4.8	10	79.1	10.3	10	6.7%	-6.60 [-13.64, 0.44]	
Oldenburg 2015	62	12.6	21	66	12.2	21	5.9%	-4.00 [-11.50, 3.50]	
Roder 2020	60	12	30	62	12	30	9.1%	-2.00 [-8.07, 4.07]	
Yoshihisa 2012	67.4	9.8	42	72.1	10.8	42	17.2%	-4.70 [-9.11, -0.29]	
Yoshihisa 2013	67.5	9.6	50	71.9	10.5	50	21.5%	-4.40 [-8.34, -0.46]	
Subtotal (95% CI)			206			206	88.6%	-4.00 [-5.95, -2.06]	◆
Heterogeneity: Tau ² =	0.00; Cł	hi² = 4.	.20, df=	= 7 (P =	0.76);	l² = 0%			
Test for overall effect:	Z = 4.04	(P < 0).0001)						
T-1-1 (05% 01)							400.00		
Total (95% CI)			226			226	100.0%	-3.63 [-5.46, -1.80]	🕶
Heterogeneity: Tau ² =	0.00; Cł	ni² = 5.	.46, df=	= 8 (P =	0.71);	I ² = 0%			-20 -10 0 10 20
Test for overall effect:	Z = 3.89	(P = 0).0001)						Favours ASV Favours Baseline
Test for subgroup diff	erences	: Chi²÷	= 1.26,	df = 1 (F	P = 0.2	6), I ^z = .	20.7%		

Figure S101. ASV vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], Observational studies

Figure S102. ASV vs. Control (Cardiovascular disease, HR (beats/min)) [No CST], Observational studies

	A	۱SV		C	ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.20.2 CSA due to he	art failu	re						
Koyama 2013	72.5	4.8	10	79.1	10.3	10	-6.60 [-13.64, 0.44]	
								Favours ASV Favours Control

Figure S103. ASV vs. Baseline (Cardiovascular disease, NT pro-BNP, pg/mL) [CST= - 50% reduction from baseline], Observational studies

		ASV		B	aseline			Mean Difference		Mean Diff	erence	-
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random	n, 95% CI	
2.25.1 CSA due to he	eart failure	;										
Campbell 2012	1,412.3	2,148	7	2,181	1,395	7	2.0%	-768.70 [-2666.06, 1128.66]	←			
Randerath 2012	230.4	297.4	36	537.3	891.8	36	75.8%	-306.90 [-613.99, 0.19]				
Roder 2020	4,995	15,648	30	5,951	18,250	30	0.1%	-956.00 [-9558.45, 7646.45]	•			
Yoshihisa 2013	824.7	1,203.5	50	1,093.1	1,658.8	50	22.1%	-268.40 [-836.45, 299.65]				
Subtotal (95% CI)			123			123	100.0%	-308.17 [-575.48, -40.85]				
Heterogeneity: Tau ² =	= 0.00; Chi	²=0.27, ¢	if = 3 (F	P = 0.97);	I ² = 0%							
Test for overall effect:	: Z = 2.26 (P = 0.02)										
Total (95% CI)			123			123	100.0%	-308.17 [-575.48, -40.85]				
Heterogeneity: Tau ² =	= 0.00; Chi	²= 0.27, c	lf = 3 (F	P = 0.97);	I²=0%				-1000	-500 0	500	1000
Test for overall effect:	: Z = 2.26 (P = 0.02)							-1000	Eavours ASV	Favours Baselir	ie 1000
Test for subaroup diff	ferences: I	Not applic	able									-

Campbell 2012: NT-BNP pmol/L, median IQR converted to m, SD converted to pg/mL; Randerath 2012: NT-proBNP (ng/L); Roder 2020: NT-proBNP (pg/mL); Yoshihisa 2013: NT-proBNP, pg/mL, median IQR converted to m, SD

Figure S104. ASV vs. Baseline (Cardiovascular disease, BNP pg/mL) [CST= - 50% reduction from baseline], Observational studies

		ASV		В	aseline			Mean Difference	Me	ean Differenc	e:	
Study or Subgroup	Mean	SD.	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, I	Random, 95%	CI	
2.26.1 CSA due to he	art failu	re										
D'Elia 2019	84	26.3	5	298	30	5	31.2%	-214.00 [-248.97, -179.03]		-		
Hetland 2017	150.9	213.3	14	201.5	282.5	14	14.7%	-50.60 [-236.02, 134.82]				
Kasai 2010	245.5	289.8	15	281	303.9	15	12.5%	-35.50 [-248.01, 177.01]				
Kasai 2013	177	201.9	12	241.5	197	12	17.1%	-64.50 [-224.10, 95.10]				
Pepperell 2003	323	250	15	502	524	15	8.0%	-179.00 [-472.81, 114.81]				
Yoshihisa 2012	227.8	377	42	255	397.2	42	16.5%	-27.20 [-192.82, 138.42]				
Subtotal (95% CI)			103			103	100.0%	-108.54 [-204.27, -12.82]		◆		
Heterogeneity: Tau ² =	7319.3	3; Chi ≃ =	= 12.10	, df = 5 ((P = 0.0)	3); I^z = §	59%					
Test for overall effect:	Z = 2.22	(P = 0.)	03)									
Total (95% CI)			103			103	100.0%	-108.54 [-204.27, -12.82]		◆		
Heterogeneity: Tau ² =	: 7319.3	3; Chi ⁼ =	= 12.10	, df = 5 ((P = 0.0)	3); I² = \$	59%		1000 500			1000
Test for overall effect:	Z = 2.22	: (P = 0.)	03)						-1000 -500 Eavours		re Rocolin	0000
Test for subgroup diff	ferences	· Not an	nlicabl	е					1 avours		15 Daseiiii	6

D'Elia 2019: BNP pg/mL; Hetland: median IQR converted to m, SD, BNP ng/L; Kasai 2010: BNP pg/mL; Kasai 2013: BNP pg/mL, median IQR converted to m, SD; Pepperell 2003: median and IQR converted to mean and SD, BNP (pg/ml); Yoshihisa 2012: BNP pg/mL, median IQR converted to m, SD

Figure S105. ASV vs. Control (Cardiovascular disease, NT pro-BNP, pg/mL) [CST=50% reduction from baseline], Observational studies

		ASV		C	ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.27.1 CSA due to he	art failu	re: HFrE	F					
Oldenburg 2018	1,498	336.6	93	1,737.9	621.4	21	-239.90 [-514.34, 34.54]	I
								Favours ASV Favours Control
						_		

Oldenburg 2018: data extracted from graph, 6-month data presented NT pro- BNP (pg/ml)

Figure S106. ASV vs. Control (Cardiovascular disease, BNP, pmol/L) [CST=50% reduction from baseline], Observational studies

60					wean Difference	wean Difference
50	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
re: HFr	EF					
40.2	11	13.5	13.8	8	20.80 [-4.81, 46.41]	
						-50 -25 0 25 50
						Favours ASV Favours Control
	40.2	re: HFrEF 40.2 11	40.2 11 13.5	re: HFrEF 40.2 11 13.5 13.8	rre: HFrEF 40.2 11 13.5 13.8 8	re: HFrEF 40.2 11 13.5 13.8 8 20.80 [-4.81, 46.41]

Hastings 2010: pmol/L

Figure S107. ASV vs. Control (Cardiovascular disease, BNP, In BNP) [CST=50% reduction], Observational studies



Koyama 2013: In BNP

Important Outcomes

Figure S108. ASV vs. Control (Daytime Functioning, Minnesota Living with Heart Failure Questionnaire) [No CST] points], RCTs

		ASV		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.16.1 CSA due to he	art failu	re							
Arzt 2013	-8.2	16.4	32	-1.15	15	31	5.9%	-7.05 [-14.81, 0.71]	-
Cowie 2015	-1.7	18.4	666	-1.94	17.8	659	94.1%	0.24 [-1.71, 2.19]	
Subtotal (95% CI)			698			690	100.0%	-0.19 [-2.08, 1.70]	•
Heterogeneity: Chi ² =	3.19, df	= 1 (P	= 0.07)); I² = 69	%				
Test for overall effect:	Z = 0.20) (P = ().84)						
Total (95% CI)			698			690	100.0%	-0.19 [-2.08, 1.70]	•
Heterogeneity: Chi ² =	3.19, df	= 1 (P	= 0.07)); l ^z = 69	%				
Test for overall effect:	Z = 0.20) (P = ().84)						-10 -5 0 5 10 Eavours ASV Eavours Control
Test for subgroup diff	erences	: Not a	applicat	ble					

Cowie 2015: CI converted to SD, used 12-month timepoint, extracted from the graph, adjusted change score reported

Figure S109. ASV vs. Control (Daytime Functioning, Specific Activity Scale) [No CST], RCTs

	A	SV		Co	ontro		Mean Difference		се			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI				
1.15.1 CSA due to he	art failu	ге										
Toyama 2017	5	1	15	4.2	0.9	15	0.80 [0.12, 1.48]				-	
								-4	-2	<u> </u>		4
								Favo	urs AS\			

Toyama 2017: 6-month study

Figure S110. ASV vs. Control (Daytime Functioning, Duke Activity Status Index) [No CST], RCTs

		ASV		C	ontrol		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IN	/, Fixed, 9	5% CI	
1.17.1 CSA due to hea	art failu	re										
O'Connor 2017	3.73	13.4	65	5.24	14.5	61	-1.51 [-6.39, 3.37]					
								-10		<u> </u>	<u></u>	10
								-10	Favours C	ontrol Fa	avours ASV	10

O'Connor 2017: ASV plus optimized medical therapy (OMT) or OMT alone (control), 6-month trial

Figure S111. ASV vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], RCTs

			ASV		C	ontrol			Mean Difference	Mean Difference
Stu	udy or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1	9.1 CSA due to heart failure									
Bra	adley 2023	24.6	77.4	84	7.6	74.9	93	26.4%	17.00 [-5.49, 39.49]	+ - -
Het	tzenecker 2016 (Sleep Med)	393	67	32	368	60	31	18.1%	25.00 [-6.38, 56.38]	+
Szo	ollosi 2006	282	24	10	294	24	10	28.1%	-12.00 [-33.04, 9.04]	
Tar	misier 2022	299.8	71.7	99	282	84.8	103	27.4%	17.80 [-3.83, 39.43]	
Sul	btotal (95% CI)			225			237	100.0%	10.52 [-6.12, 27.17]	◆
Het	terogeneity: Tau ² = 141.53; C	hi² = 5.94	, df = 3	3 (P = 0	.11); I ^z =	: 50%				
Tes	st for overall effect: Z = 1.24 (F	o = 0.22)								
Tot	tal (95% CI)			225			237	100.0%	10.52 [-6.12, 27.17]	◆
Het	terogeneity: Tau ² = 141.53; C	hi² = 5.94	, df = 3	3 (P = 0	.11); I ² =	: 50%			-	
Tes	st for overall effect: Z = 1.24 (F	° = 0.22)								Eavours Control Eavours ASV
Tes	st for subgroup differences: N	lot applic	able							

Bradley 2023 TST minutes (change score).

Figure S112. ASV vs. Co	ontrol (Sleep architecture.	PSG. Slee	p efficiency)	[CST=+10%]. RCT
		,		

		ASV		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.18.1 CSA due to heart failure									
Bradley 2023	5.4	16.2	84	0.8	15.8	93	21.8%	4.60 [-0.12, 9.32]	
Hetzenecker 2016 (Sleep Med)	77	9	32	69	11	31	20.0%	8.00 [3.03, 12.97]	
Miyata 2012	75	11.5	11	76.6	4.8	11	10.1%	-1.60 [-8.96, 5.76]	
Szollosi 2006	76.9	4	10	72.4	5.9	10	24.2%	4.50 [0.08, 8.92]	
Tamisier 2022	68.8	14.9	99	62.6	17.3	103	24.0%	6.20 [1.75, 10.65]	
Subtotal (95% CI)			236			248	100.0%	5.02 [2.57, 7.46]	●
Heterogeneity: Tau ² = 1.35; Chi ² =	= 4.84, d	f = 4 (F	P = 0.30	0); I² = 1	7%				
Test for overall effect: Z = 4.02 (P	< 0.000	1)							
Total (95% CI)			236			248	100.0%	5.02 [2.57, 7.46]	•
Heterogeneity: Tau ² = 1.35; Chi ² =	= 4.84, d	f = 4 (F	P = 0.30	0); I ^z = 1	7%				-20 -10 0 10 20
Test for overall effect: Z = 4.02 (P	1)							Favours Control Favours ASV	
Test for subgroup differences: No	ot applic	able							

Bradley 2023 change score data at 1 month.

Figure S113. ASV vs. Control (Sleep architecture, PSG, REM%) [CST=+5% of TST], RCTs

		ASV		С	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.22.1 CSA due to heart failure									
Bradley 2023	13.5	25.5	84	1	30.1	93	36.4%	0.44 [0.15, 0.74]	
Hetzenecker 2016 (Sleep Med)	16	8	32	11	8	31	12.7%	0.62 [0.11, 1.12]	· · · · · · · · · · · · · · · · · · ·
Miyata 2012	16.9	4.9	11	16.9	5.6	11	4.6%	0.00 [-0.84, 0.84]	
Szollosi 2006	14.8	1.8	10	13.9	2.4	10	4.1%	0.41 [-0.48, 1.29]	
Tamisier 2022	60.6	30	99	51.3	29.9	103	42.2%	0.31 [0.03, 0.59]	
Subtotal (95% CI)			236			248	100.0%	0.39 [0.21, 0.57]	
Heterogeneity: Tau ² = 0.00; Chi ² =	= 2.06, d	f = 4 (F	P = 0.72	2); I ² = 0	%				
Test for overall effect: Z = 4.21 (P	< 0.000	1)							
Total (95% CI)			236			248	100.0%	0.39 [0.21, 0.57]	•
Heterogeneity: Tau ² = 0.00; Chi ² =	= 2.06. d	f = 4 (F	P = 0.72	2): P = 0	%				
Test for overall effect: Z = 4.21 (P	< 0.000	1)							-1 -0.5 0 0.5 1
Test for subgroup differences: No	ot applic	able							Favours Control Favours ASV

Bradley 2023 REM sleep, minutes (change score); Hetzenecker 2016 (SM) REM %; Miyata 2012 REM %* (control data received from authors); Szollosi 2006 REM %; Tamisier 2022 REM minutes. The weighted average of the post intervention standard deviation of percent REM across Hetzenecker, Miyata, and Szollosi is 6.3. Re-expressed as percent REM, there was a mean increase of 2.5% (95% CI 1.3, 3.6)

Figure S114. ASV vs. Control (Sleep architecture, PSG, Arousals) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCTs

		ASV		С	ontrol			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	I	
1.24.1 CSA due to heart failure												
Bradley 2023	-19.3	21.2	84	0.2	18.3	93	30.9%	-19.50 [-25.36, -13.64]		-		
Hetzenecker 2016 (Sleep Med)	29	18	32	41	20	31	12.0%	-12.00 [-21.41, -2.59]				
Miyata 2012	-16.4	20.6	11	-0.6	13.2	11	5.1%	-15.80 [-30.26, -1.34]				
Szollosi 2006	23.7	2.5	10	39.6	7.3	10	46.4%	-15.90 [-20.68, -11.12]				
Tamisier 2022	63.7	48.2	99	83.6	51.1	103	5.7%	-19.90 [-33.59, -6.21]				
Subtotal (95% CI)			236			248	100.0%	-16.76 [-20.02, -13.51]		◆		
Heterogeneity: Tau ² = 0.00; Chi ²	= 2.17, d	lf = 4 (l	P = 0.71	1); I ^z = 0	%							
Test for overall effect: Z = 10.09 (P < 0.00	001)										
										•		
Total (95% CI)			236			248	100.0%	-16.76 [-20.02, -13.51]		•		
Heterogeneity: Tau ² = 0.00; Chi ²	= 2.17, d	lf = 4 (I	P = 0.71	1); I² = 0	%				-50	-25 0	25	
Test for overall effect: Z = 10.09 (P < 0.00	001)							-30	Eavours ASV Eavours (Control	50
Test for subaroup differences: N	ot applic	able								- area of the ravea of	0.0111.01	

Miyata: control data received from authors; Hetzenecker 2016 (Sleep Med): change from baseline data; Tamisier 2022: data points reported at 3 and 12 months, 12-month data included in analysis

|--|

		ASV		Co	ontro			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.23.1 CSA due to heart failure									
Bradley 2023	12.2	32.6	84	0	24	93	37.5%	0.43 [0.13, 0.73]	
Hetzenecker 2016 (Sleep Med)	0.9	3.3	32	2	6	31	29.4%	-0.23 [-0.72, 0.27]	
Miyata 2012	8.9	13.7	11	2.3	2.2	11	17.5%	0.65 [-0.21, 1.51]	
Szollosi 2006	9.8	1.9	10	7.9	1.8	10	15.7%	0.98 [0.04, 1.92]	
Subtotal (95% CI)			137			145	100.0%	0.36 [-0.10, 0.82]	◆
Heterogeneity: Tau ² = 0.13; Chi ² :	= 7.61, d	f= 3 (F	P = 0.05	5); I² = 61	1%				
Test for overall effect: Z = 1.53 (P	= 0.13)								
Total (95% CI)			137			145	100.0%	0.36 [-0.10, 0.82]	-
Heterogeneity: Tau ² = 0.13; Chi ² :	= 7.61, d	f = 3 (F	P = 0.05	5); I = 61	1%				
Test for overall effect: Z = 1.53 (P	= 0.13)								Eavours Control Eavours ASV
Test for subaroun differences: N	nt annlic	ahle							

Bradely 2023 – SWS, minutes (change score); Hetzenecker 2016 (SM) SWS %; Miyata 2012 SWS % (control data received from authors); Szollosi 2006 SWS %. The weighted average of the post intervention standard deviation of percent SWS across Hetzenecker, Miyata, and Szollosi is 4.8. Re-expressed as percent REM, there was a mean increase of 1.6% (95% CI -0.48, 3.9)

Figure S116. ASV vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], RCTs

		ASV		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.24.1 CSA due to heart failure									
Bradley 2023	-18.5	33	84	-0.8	29.9	93	32.2%	-0.56 [-0.86, -0.26]	-
Hetzenecker 2016 (Sleep Med)	14	8	32	23	20	31	26.1%	-0.59 [-1.09, -0.08]	
Szollosi 2006	12.6	1.8	10	22.8	4	10	8.9%	-3.15 [-4.55, -1.75]	
Tamisier 2022	52.2	37.2	99	70.3	44.6	103	32.8%	-0.44 [-0.72, -0.16]	-
Subtotal (95% CI)			225			237	100.0%	-0.76 [-1.24, -0.28]	◆
Heterogeneity: Tau ² = 0.16; Chi ² =	= 13.92,	df = 3	(P = 0.0)	003); i² =	: 78%				
Test for overall effect: Z = 3.11 (P	= 0.002))							
Total (95% CI)			225			237	100.0%	-0.76 [-1.24, -0.28]	◆
Heterogeneity: Tau ² = 0.16; Chi ² =	= 13.92,	df = 3	(P = 0.0	003); I ² =	: 78%				
Test for overall effect: Z = 3.11 (P	= 0.002))							Eavours ASV Eavours Control
Test for subgroup differences: No	ot applic	able							

Bradley 2023 N1 minutes; Hetzenecker 2016 (SM) N1%; Szollosi 2006 N1%; Tamisier 2022 N1 minutes. The weighted average of the post intervention standard deviation of percent N1 across Hetzenecker and Szollosi is 11.4. Re-expressed as percent N1, there was a mean decrease of -8.7% (95% CI -14.1, -3.2).

Figure S117. ASV vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], RCTs

		ASV		C	ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.25.1 CSA due to heart failure									
Bradley 2023	13.2	71.1	84	3.7	61.7	93	31.9%	0.14 [-0.15, 0.44]	
Hetzenecker 2016 (Sleep Med)	69	9	32	63	17	31	25.4%	0.44 [-0.06, 0.94]	⊢ ∎
Szollosi 2006	62.4	3.1	10	55.3	2.6	10	10.2%	2.38 [1.18, 3.58]	
Tamisier 2022	158.2	64.5	99	143.4	63.1	103	32.5%	0.23 [-0.05, 0.51]	
Subtotal (95% CI)			225			237	100.0%	0.47 [0.02, 0.92]	◆
Heterogeneity: Tau ² = 0.14; Chi ² :	= 13.03,	df = 3	(P = 0.0)	005); I^z =	: 77%				
Test for overall effect: Z = 2.06 (P	= 0.04)								
Total (95% CI)			225			237	100.0%	0.47 [0.02, 0.92]	◆
Heterogeneity: Tau ² = 0.14; Chi ² :	= 13.03,	df = 3	(P = 0.0)	005); I^z =	: 77%				
Test for overall effect: Z = 2.06 (P	= 0.04)								Favours ASV Favours Control
Test for subgroup differences: N	ot applic	able							ravours //ov Travours Control

Bradley 2023 N2 minutes; Hetzenecker 2016 (SM) N2%; Szollosi 2006 N2%; Tamisier 2022 N2 minutes. The weighted average of the post intervention standard deviation of percent N2 across Hetzenecker and Szollosi is 10.6. Re-expressed as percent N2, there was a mean increase of 4.98% (95% CI 0.21, 9.75).

Figure S118. ASV vs. Control (Sleep architecture, PSG, Respiratory arousals) [CST=25% reduction from baseline], RCTs

		ASV		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.25.1 CSA due to heart failure									
Bradley 2023	-24.4	18.5	84	0	19.7	93	25.1%	-24.40 [-30.03, -18.77]	_
Hetzenecker 2016 (Sleep Med)	6	7	32	27	23	31	22.1%	-21.00 [-29.45, -12.55]	_
Szollosi 2006	11.4	2.7	10	27.3	8	10	25.4%	-15.90 [-21.13, -10.67]	_ _
Tamisier 2022	5.4	7.1	99	13.1	10.7	103	27.4%	-7.70 [-10.20, -5.20]	+
Subtotal (95% CI)			225			237	100.0%	-16.91 [-25.55, -8.27]	
Heterogeneity: Tau ² = 69.27; Chi ²	²= 36.53	, df = 3	3 (P < 0	.00001)	; I² = 9	2%			
Test for overall effect: Z = 3.84 (P	= 0.000	1)							
Total (95% CI)			225			237	100.0%	-16.91 [-25.55, -8.27]	
Heterogeneity: Tau ² = 69.27; Chi ²									
Test for overall effect: Z = 3.84 (P	Favours ASV Favours Control								
Test for subgroup differences: No	ot applic	able							

Change from baseline: ASV=-49.92% (Note: baseline data for Szollosi was not available)



	ASV Control							Mean Difference	Mean Diff	erence		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed,	95% CI	
2.27.1 CSA due to he	art failu	re										
Campbell 2012	37.1	28.9	7	46.7	28.7	7	22.7%	-9.60 [-39.77, 20.57]				
Hastings 2010	24	18	11	30	21	11	77.3%	-6.00 [-22.34, 10.34]			_	
Subtotal (95% CI)			18			18	100.0%	-6.82 [-21.19, 7.55]		-		
Heterogeneity: Chi ² =	0.04, df	= 1 (P	= 0.84)); I ^z = 09	6							
Test for overall effect:	Z = 0.93	(P = 0).35)									
Total (95% CI)			18			18	100.0%	-6.82 [-21.19, 7.55]		-		
Heterogeneity: Chi ² =	0.04, df	= 1 (P	= 0.84)); I ž = 09	6				-100	-50 0		100
Test for overall effect:	Z = 0.93	(P = 0).35)						-100	Eavours ASV	Favours Baseline	100
Test for subgroup diff	erences	: Not a	pplical	ole						1 4104/07/07	areare basenne	

Figure S120. ASV vs. Control (Daytime functioning, SF-36) [No CST], Observational Study

		ASV		Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.28.1 CSA due to he	art failu	re						
Hastings 2010	75	42.4	11	36.6	67	8	38.40 [-14.36, 91.16]	
								Favours Baseline Favours ASV

		ASV		В	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.36.1 Non-heart failur	e C SA								
Dellweg 2013	277	103	15	235	84	15	3.9%	42.00 [-25.26, 109.26]	
Heider 2018	324	57	60	279	73	60	7.2%	45.00 [21.56, 68.44]	
Javaheri 2014 (JCSM)	324	60	20	324	60	20	6.1%	0.00 [-37.19, 37.19]	
Morgenthaler 2014	363.5	55.9	29	213.9	120.8	29	5.2%	149.60 [101.15, 198.05]	
Randerath 2009	326.7	70.3	12	329.6	78.2	12	4.4%	-2.90 [-62.40, 56.60]	
Randerath 2009	326.7	70.3	12	329.6	78.2	12	4.4%	-2.90 [-62.40, 56.60]	
Shapiro 2015	377.6	85	31	409	57.8	31	6.2%	-31.40 [-67.58, 4.78]	
Subtotal (95% CI)			179			179	37.2%	28.26 [-13.89, 70.41]	-
Heterogeneity: Tau ² = 2	635.83; (Chi ^z = -	40.99, i	df = 6 (P	< 0.000	001); P	= 85%		
Test for overall effect: Z	= 1.31 (F	P = 0.19	9)						
2.36.2 CSA due to hear	t failure								
Arzt 2008	371	12	14	331	17	14	7.9%	40.00 [29.10, 50.90]	-
Campbell 2012	312.7	52.6	10	264.9	61.6	10	5.0%	47.80 [-2.40, 98.00]	
Fietze 2008	343.5	65.7	17	354.7	82.6	17	5.1%	-11.20 [-61.37, 38.97]	
Heider 2018	329	64	54	279	73	54	7.0%	50.00 [24.11, 75.89]	
Hetzenecker 2016	374	- 77	34	376	59	34	6.5%	-2.00 [-34.61, 30.61]	_
Kasai 2013	387.1	65.2	23	367.9	68.9	23	6.0%	19.20 [-19.57, 57.97]	
Oldenburg 2015	432	59	36	436	48	36	7.1%	-4.00 [-28.85, 20.85]	
Randerath 2012	280.9	63.6	36	312.9	69.6	36	6.6%	-32.00 [-62.80, -1.20]	
Roder 2020	313	54	30	316	66	30	6.6%	-3.00 [-33.52, 27.52]	
Teschler 2001	307	71.1	14	212	59.9	14	5.2%	95.00 [46.30, 143.70]	
Subtotal (95% CI)			268			268	62.8%	18.64 [-2.21, 39.49]	•
Heterogeneity: Tau ² = 8	23.79; C	hi² = 4	5.82, di	f= 9 (P ·	< 0.000I	01); I² =	80%		
Test for overall effect: Z	= 1.75 (F	P = 0.0	8)						
Total (95% CI)			447			447	100.0%	22.22 [3.84, 40.61]	◆
Heterogeneity: Tau ² = 1	087.39; (Chi² = I	86.88,	df=16 (P < 0.01	0001); I	≈ =82%		
Test for overall effect: Z	= 2.37 (F	P = 0.0	2)						Favours Baseline Favours ASV
Test for subgroup differ	ences: C	≿hi² = 0	1.16, df	= 1 (P =	0.69), (²=0%			

Figure S121. ASV vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], Observational studies

Figure S122. ASV vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST=+15 min], Observational study

ASV.		Co	ntrol	l i	Mean Difference	Mean Di	ference		
SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
ге									
60	21	330	36	21	1.80 [-28.13, 31.73]			<u> </u>	
						-100 -1	 50 0	51	1 100
						F	avours ASV	Favours Col	ntrol
	SD re 60	SD Total re 60 21	SD Total Mean re 60 21 330	SD Total Mean SD re 60 21 330 36	SD Total Mean SD Total re 60 21 330 36 21	SD Total Mean SD Total IV, Fixed, 95% CI re 60 21 330 36 21 1.80 [-28.13, 31.73]	SD Total Mean SD Total IV, Fixed, 95% Cl re 60 21 330 36 21 1.80 [-28.13, 31.73] 60 21 330 36 21 1.80 [-28.13, 31.73]	SD Total Mean SD Total IV, Fixed, 95% Cl IV, Fixed 60 21 330 36 21 1.80 [-28.13, 31.73]	SD Total Mean SD Total IV, Fixed, 95% Cl IV, Fixed, 95% Cl re 60 21 330 36 21 1.80 [-28.13, 31.73] -100 -50 0 50 -100 -50 0 50 <t< td=""></t<>

		ASV		Ba	seline			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.29.1 Non-heart failure	CSA										
Dellweg 2013	64.4	20.4	15	61	22.1	15	2.8%	3.40 [-11.82, 18.62]			
Heider 2018	81	12	60	71	16	60	9.3%	10.00 [4.94, 15.06]			
Javaheri 2014 (JCSM)	80	16	20	78	11	20	6.1%	2.00 [-6.51, 10.51]			
Javaheri 2015	83	12	27	84	10	27	8.4%	-1.00 [-6.89, 4.89]			
Morgenthaler 2014	80.5	10.1	29	75.1	15.2	29	7.7%	5.40 [-1.24, 12.04]	+		
Shapiro 2015	83.3	13.9	31	87.9	8.3	31	8.6%	-4.60 [-10.30, 1.10]			
Subtotal (95% CI)			182			182	42.8%	2.50 [-2.65, 7.65]	*		
Heterogeneity: Tau ² = 27	'.02; Chi	* =16.	48, df=	= 5 (P =	0.006)	; I ² = 70	1%				
Test for overall effect: Z =	= 0.95 (F	² = 0.3	4)								
2.29.2 CSA due to heart	failure										
Arzt 2008	89	11	14	79	2	14	8.5%	10.00 [4.14, 15.86]			
Hastings 2010	78	8.5	11	61	12.4	11	5.8%	17.00 [8.12, 25.88]			
Heider 2018	77	15	54	76	15	54	8.7%	1.00 [-4.66, 6.66]			
Hetzenecker 2016	81.9	12.7	34	78.7	12.5	34	8.3%	3.20 [-2.79, 9.19]			
Javaheri 2011	76	12	37	73	12	37	8.9%	3.00 [-2.47, 8.47]			
Yoshihisa 2012	71.4	12.4	42	67.2	14.1	42	8.6%	4.20 [-1.48, 9.88]	+		
Yoshihisa 2013	73.8	14.8	50	69.1	15	50	8.5%	4.70 [-1.14, 10.54]			
Subtotal (95% CI)			242			242	57.2%	5.50 [2.17, 8.83]	•		
Heterogeneity: Tau ² = 10).49; Chi	² =12.	.67, df=	= 6 (P =	0.05);	I ^z = 539	6				
Test for overall effect: Z =	= 3.24 (F	? = 0.0I	01)								
Total (95% CI)			424			424	100.0%	4.28 [1.43, 7.14]	•		
Heterogeneity: Tau ² = 16	6.11; Chi	* = 30.	.87, df=	= 12 (P =	= 0.002	2); I 2 = 6	i1%	-			
Test for overall effect: Z = 2.95 (P = 0.003) -20 -20 -20 -20 -20 -20 -20 -20 -20 -20											
Test for subgroup differe	ences: C	hi² = 0	1.92, df:	= 1 (P =	0.34).	$ ^{2} = 0\%$					

Figure S123. ASV vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=+10%], Observational studies

		ASV		Ba	seline			Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
2.30.1 Non-heart failure	CSA											
Dellweg 2013	12.6	9	15	9.3	8	15	3.8%	3.30 [-2.79, 9.39]				
Heider 2018	18	8	60	11	8	60	6.1%	7.00 [4.14, 9.86]				
Javaheri 2014 (JCSM)	8	8	20	10	7	20	4.7%	-2.00 [-6.66, 2.66]				
Javaheri 2015	14	9	27	11	9	27	4.6%	3.00 [-1.80, 7.80]				
Randerath 2009	19.6	10	12	13.7	8.5	12	3.1%	5.90 [-1.53, 13.33]				
Shapiro 2015	12.3	9.4	31	11.4	8.3	31	4.9%	0.90 [-3.51, 5.31]				
Troitino 2014	7.9	12.3	12	9.6	11.8	12	2.2%	-1.70 [-11.34, 7.94]				
Subtotal (95% CI)			177			177	29.4%	2.70 [-0.26, 5.66]	-			
Heterogeneity: Tau ² = 8.41; Chi ² = 13.99, df = 6 (P = 0.03); l ² = 57%												
Test for overall effect: Z =	: 1.79 (P	= 0.07	7)									
2 30 2 C SA due to heart	failuro											
2.50.2 CSA due to near	10.4	1.0	14	111	1.4	1.4	7.104	0 70 1 4 0 4 0 5 41	_			
Arzi 2006 Comphell 2012	10.4	1.8	14	14.1	1.4	14	1.170	4 00 [0 24 0 04]				
Campbell 2012	10.4	0.0	17	11.0	0.1	10	4.070	4.00 [-0.21, 9.01]				
Fielze 2000	13.4	0.4 6.2	11	13.0	0.2	11	4.070	12 00 [7 56 10 44]				
Hasings 2010 Hoidor 2010	20	0.2	54	10	7.0	54	4.2.70 6.0%	2 00 10 02 6 02				
Heldel 2010	17.1	0 6	24	10	12	24	4.5%	5.00 [-0.02, 0.02]				
lovohori 2011	17.1	0.5	27	12	12	27	4.570	178 0 12 10 10 10 10 10 10 10 10 10 10 10 10 10				
Vacai 2012	101	, 88	22	11	67	22	5.6%	9 AO M 9A 11 061				
Aldenhurg 2015	11.9	0.0 8.1	20	100	9.7 6 Q	23	1,8%	0.40[4.04, 11.30]				
Randerath 2012	147	60.1	26	13.4	7.4	26	5.9%	1 30 [-2.03, 3.43]				
Roder 2020	24	6.0	30	18		30	5.5%	6 00 [2.01, 4.01]				
Yoshihisa 2012	18.2	61	42	18.3	65	42	6.2%	-0.10[-2.80_2.60]				
Yoshihisa 2013	17.3	6	50	18	6.5	50	64%	-0.70[-3.15, 1.75]				
Subtotal (95% CI)	11.0		379		0.0	379	70.6%	3.29 [1.22, 5.37]	◆			
Heterogeneity: Tau ² = 10	.91; Chi	² = 65.	13, df=	: 12 (P <	< 0.000)01); P	= 82%					
Test for overall effect: Z =	: 3.11 (P	= 0.00	02)	`								
Total (95% Cl) 556 556 100.0% 3.10 [1.39, 4.80]												
Heterogeneity: Tau ² = 10	Heterogeneity: Tau ² = 10.30; Chi ² = 83.41, df = 19 (P < 0.00001); I ² = 77%											
Test for overall effect: Z =	Test for overall effect: Z = 3.56 (P = 0.0004) -20 -10 0 10 20 Favours Baseline Favours BSV											
Test for subaroup differe	nces: C	hi ² = 0	.10, df:	= 1 (P =	0.75).	$ ^{2} = 0\%$						

Figure S124. ASV vs. Baseline (Sleep architecture, PSG, REM (%)) [CST=+5% of TST], Observational studies

		ASV		Ba	seline	•	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
2.35.4 Non-heart failure CSA									
Dellweg 2013	14.6	7.1	15	16.9	8.2	15	4.7%	-2.30 [-7.79, 3.19]	
Heider 2018	21	12	60	13	11	60	5.6%	8.00 [3.88, 12.12]	
Javaheri 2014 (JCSM)	0	0.01	20	1	2	20	7.4%	-1.00 [-1.88, -0.12]	-
Javaheri 2015	1	5	27	2	7	27	6.2%	-1.00 [-4.24, 2.24]	
Randerath 2009	9.7	11	12	16.1	11.8	12	2.8%	-6.40 [-15.53, 2.73]	
Troitino 2014	1.9	6.7	12	1.9	6.3	34	5.4%	0.00 [-4.34, 4.34]	<u> </u>
Subtotal (95% CI)			146			168	32.0%	0.14 [-2.76, 3.05]	•
Heterogeneity: Tau ² = 8.36; Chi ²	= 19.54,	df = 5	(P = 0.0)	002); I2 =	:74%				
Test for overall effect: Z = 0.10 (P	= 0.92)								
2.35.5 CSA due to heart failure									
Arzt 2008	25.3	2.4	14	15.9	2.6	14	7.0%	9.40 [7.55, 11.25]	
Fietze 2008	16.5	9.2	10	11.4	8	10	3.5%	5.10 [-2.46, 12.66]	
Heider 2018	16	8	54	13	8	54	6.3%	3.00 [-0.02, 6.02]	— •—
Hetzenecker 2016 (Sleep Med)	0.9	3.3	32	0.3	0.8	32	7.3%	0.60 [-0.58, 1.78]	Ť
Javaheri 2011	16	6	37	13	11	37	5.6%	3.00 [-1.04, 7.04]	
Kasai 2013	10.8	8.7	12	7	6.7	12	4.2%	3.80 [-2.41, 10.01]	
Oldenburg 2015	26.6	10.6	36	21.1	9.4	36	5.2%	5.50 [0.87, 10.13]	
Randerath 2012	19.6	11.1	36	14.7	10.3	36	5.0%	4.90 [-0.05, 9.85]	
Roder 2020	1	4	30	4	6	30	6.6%	-3.00 [-5.58, -0.42]	
Teschler 2001	24.9	9.7	14	13.9	7.9	14	4.0%	11.00 [4.45, 17.55]	
Yoshihisa 2012	4.4	8.1	42	2.1	3.5	42	6.5%	2.30 [-0.37, 4.97]	
Yoshinisa 2013 Subtotol (05% CI)	5.2	8.9	267	2.2	3.5	267	60.0%	3.00 [0.35, 5.65]	
Subiolai (95% CI)		، مار د	307		0.17	307	08.0%	3.14[1.21, 0.22]	\bullet
Teet for every liefest 7 = 2.00 (D	-= 90.19	ν' αι = .	II (P <	0.0000	0;15=	88%			
rest for overall effect: Z = 2.96 (P	= 0.003)							
Total (95% CI)			513			535	100.0%	2.55 [0.61, 4.49]	◆
Heterogeneity: Tau ² = 13.06; Chi	² = 147.5	59, df=	17 (P	< 0.0000	01); I ^z :	= 88%		-	
Test for overall effect: Z = 2.58 (P	= 0.010)							-20 -10 0 10 20 Favours Baseline Favours ASV
Test for subaroup differences: C	hi ² = 3.4	2. df =	1 (P = (0.06), ²÷	= 70.8	%			Tavouis Dasellite Favouis Aov

Figure S125. ASV vs. Baseline (Sleep architecture, PSG, SWS (%)) [CST=+5% of TST], Observational studies

Figure S126. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage N1%) [CST=-5% of TST],

Observational studies

		ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.33.1 Non-heart failure CSA									
Heider 2018	7	8	60	14	11	60	9.9%	-7.00 [-10.44, -3.56]	
Javaheri 2014 (JCSM)	12	11	20	37	21	20	6.5%	-25.00 [-35.39, -14.61]	
Javaheri 2015	11	7	27	18	12	27	9.1%	-7.00 [-12.24, -1.76]	
Shapiro 2015	9.2	8.5	31	11	10.2	31	9.4%	-1.80 [-6.47, 2.87]	
Troitino 2014	11.7	11.8	12	13.7	9.3	34	8.1%	-2.00 [-9.37, 5.37]	
Subtotal (95% CI)			150			172	42.9%	-7.30 [-12.52, -2.09]	•
Heterogeneity: Tau ² = 25.55; Chi ²	= 17.53	l, df = 4	4 (P = 0	.002); I ^z	= 77%	b b			
Test for overall effect: Z = 2.75 (P	= 0.006))							
2 22 2 CCA due to be added									
2.33.2 CSA due to heart failure									
Campbell 2012	15.3	7.3	10	30.3	19.1	10	5.5%	-15.00 [-27.67, -2.33]	
Fietze 2008	31.8	14.5	17	40.1	14.1	17	6.9%	-8.30 [-17.91, 1.31]	
Heider 2018	11	15	54	12	16	54	8.8%	-1.00 [-6.85, 4.85]	
Hetzenecker 2016 (Sleep Med)	14	8	32	23	13	32	9.1%	-9.00 [-14.29, -3.71]	_
Javaheri 2011	17	12	37	19	14	37	8.8%	-2.00 [-7.94, 3.94]	
Oldenburg 2015	15.7	7.9	36	11.3	6.1	36	9.9%	4.40 [1.14, 7.66]	
Roder 2020	13	5	30	34	20	30	8.0%	-21.00 [-28.38, -13.62]	
Subtotal (95% CI)			216			216	57.1%	-6.80 [-13.68, 0.08]	
Heterogeneity: Tau ² = 72.31; Chi ²	= 52.58	l, df = 6	6 (P < 0	.00001)	; ² = 8	9%			
lest for overall effect: Z = 1.94 (P	= 0.05)								
Total (95% CI)			366			399	100.0%	7 03 [11 36 2 70]	
Listere geneity Tev2 - 40.07; Obi2	- 75 07	- de - 4	300 M /D -	0 0000/		050	100.0%	-1.00 [-11.00, -2.70]	
Teet for everall effect: 7 = 2.10 /D	·= 75.37 - 0.004)	,ur=1	II (P <	0.0000	0, 11=	82%			-20 -10 0 10 20
Test for overall effect: Z = 3.18 (P	Favours ASV Favours Baseline								
<u>estior suparoup differences: Cr</u>	117 = 0.01	i, uī =	1 (P = 1)	1.91), I*:	= U%o				

Figure S127. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage N2%) [CST=-5% of TST], Non-randomized studies

		ASV		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
2.34.1 Non heart failure CSA									
Heider 2018	54	13	60	62	13	60	9.5%	-8.00 [-12.65, -3.35]	_ -
Javaheri 2014 (JCSM)	77	12	20	55	20	20	8.1%	22.00 [11.78, 32.22]	
Javaheri 2015	74	11	27	68	13	27	9.1%	6.00 [-0.42, 12.42]	
Morgenthaler 2007	59.2	11.8	0	0	0	0		Not estimable	
Shapiro 2015	76.2	12.2	31	73.3	13	31	9.2%	2.90 [-3.38, 9.18]	
Troitino 2014	75.7	13.1	12	78.3	11.8	34	8.6%	-2.60 [-11.01, 5.81]	
Subtotal (95% CI)			150			172	44.5%	3.49 [-5.31, 12.28]	
Heterogeneity: Tau ² = 86.85; Chi	²= 33.68), df = 4	4 (P ≺ 0	.00001)	; l² = 8	8%			
Test for overall effect: Z = 0.78 (P	= 0.44)								
2.34.2 CSA due to heart failure									
Fietze 2008	38.1	12	17	35.1	10.7	17	8.8%	3.00 [-4.64, 10.64]	
Heider 2018	49	14	54	60	17	54	9.3%	-11.00 [-16.87, -5.13]	
Hetzenecker 2016 (Sleep Med)	69	9	32	62	12	32	9.4%	7.00 [1.80, 12.20]	
Javaheri 2011	55	12	37	67	15	37	9.2%	-12.00 [-18.19, -5.81]	_
Oldenburg 2015	45.9	11.9	36	56.6	7.8	36	9.5%	-10.70 [-15.35, -6.05]	_ _
Roder 2020	62	- 7	30	44	14	30	9.3%	18.00 [12.40, 23.60]	
Subtotal (95% CI)			206			206	55.5%	-0.97 [-11.10, 9.17]	
Heterogeneity: Tau ² = 151.39; Ch	ni² = 94.2	9, df =	5 (P <	0.00001	l); ²=	95%			
Test for overall effect: Z = 0.19 (P	= 0.85)								
Total (95% CI)			356			378	100.0%	1.06 [-5.51, 7.64]	-
Heterogeneity: Tau ² = 112.52; Ch	ni = 128	.59, df	= 10 (F	< 0.000	001); P	'= 92%		-	-20 -10 0 10 20
Test for overall effect: Z = 0.32 (P	= 0.75)								Eavours ASV Eavours Baseline
Test for subgroup differences: C	$hi^2 = 0.41$	2. df =	1 (P = 0)	1.52). P ∶	= 0%				

Figure S128. ASV vs. Baseline (Sleep architecture, PSG, Sleep Stage 1/2%) [No CST], Observational study

	A	۱SV		Ba	selin	е	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.38.1 Non heart fail	ure CSA							
Randerath 2009	73.6	25	12	70.5	11	12	3.10 [-12.35, 18.55]	
								Favours ASV Favours Baseline

		ASV		Ba	seline	•		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl				
2.31.1 Non-heart failure	CSA												
Dellweg 2013	25.6	15.7	15	27.6	15.5	15	4.0%	-2.00 [-13.16, 9.16]	- _				
Heider 2018	13	10	60	24	16	60	6.3%	-11.00 [-15.77, -6.23]	-				
Javaheri 2014 (JCSM)	20	25	20	29	16	20	3.5%	-9.00 [-22.01, 4.01]					
Javaheri 2015	24	14	27	44	21	27	4.6%	-20.00 [-29.52, -10.48]	_ —				
Morgenthaler 2007	2.4	4.5	9	53.1	23.4	9	2.8%	-50.70 [-66.27, -35.13]					
Morgenthaler 2014	25.9	13.5	29	46.3	29.1	29	3.8%	-20.40 [-32.08, -8.72]					
Randerath 2009	12	9.7	12	33.1	17.3	12	4.0%	-21.10 [-32.32, -9.88]	_				
Troitino 2014	15.7	8.2	12	21.4	20.2	12	3.6%	-5.70 [-18.03, 6.63]					
Subtotal (95% CI)			184			184	32.6%	-16.67 [-24.64, -8.71]	•				
Heterogeneity: Tau² = 99	.31; Chi	i ² = 33.	.82, df=	=7(P≺	0.0001	1); I² = 7	79%						
Test for overall effect: Z =	: 4.10 (F	° < 0.0	001)										
2.31.2 CSA due to heart	failure	_											
Arzt 2008	18	3	14	25	4	14	6.9%	-7.00 [-9.62, -4.38]	+				
Campbell 2012	27.1	9.1	10	44.3	13.4	10	4.4%	-17.20 [-27.24, -7.16]	_ _				
Fietze 2008	8.4	11.9	17	18.4	11.6	17	5.1%	-10.00 [-17.90, -2.10]					
Hastings 2010	17	14	11	64	41	11	1.4%	-47.00 [-72.60, -21.40]					
Heider 2018	15	11	54	26	19	54	5.9%	-11.00 [-16.86, -5.14]					
Hetzenecker 2016	22.4	13.6	34	35.1	14.1	34	5.6%	-12.70 [-19.28, -6.12]					
Javaheri 2011	24	11	37	36	23	0		Not estimable					
Kasai 2013	19.9	10.2	23	19.9	10.2	23	5.9%	0.00 [-5.90, 5.90]					
Oldenburg 2015	15.1	9.5	21	10.9	5.2	21	6.3%	4.20 [-0.43, 8.83]	—				
Randerath 2012	20.7	3.2	36	32	17.8	36	5.9%	-11.30 [-17.21, -5.39]					
Roder 2020	1	1	30	16	9	30	6.7%	-15.00 [-18.24, -11.76]					
Yoshihisa 2012	18.6	7.5	42	25.9	9	42	6.7%	-7.30 [-10.84, -3.76]	-				
Yoshihisa 2013	15.7	7.4	50	25.8	10.6	50	6.6%	-10.10 [-13.68, -6.52]					
Subiotal (95% CI)			219			J4Z	07.4%	-9.21[-12.84, -3.37]	•				
Heterogeneity: Tau* = 30	1.56; Chi	r = 69.	.62, dt=	= 11 (P <	< U.UUl	JU1); I*	= 84%						
lest for overall effect: Z =	: 4.97 (H	' < U.U	0001)										
Total (95% CI)			563			526	100.0%	-11.58 [-14.93, -8.23]	•				
Heterogeneity: Tau ² = 40	Heterogeneity: Tau ² = 40.70; Chi ² = 113.18, df = 19 (P < 0.00001); l ² = 83%												
Test for overall effect: Z =	Test for overall effect: Z = 6.77 (P < 0.00001)												
Test for subgroup differe	nces: C	:hi² = 2	.80, df	= 1 (P =	0.09),	I ² = 64	.2%						

Figure S129. ASV vs. Baseline (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational studies

Roder 2020: respiratory arousals, percent change from baseline for the non-heart failure group=-44.94% and heart failure group=-33.29, total change from baseline from all CSA sub-groups=-40.86%

Figure S130. ASV vs. Control (Sleep architecture, PSG, Arousal Index (#/hr)) [CST=25% percent reduction from baseline or reduction to ≤12 events/hr], Observational studies

	A	۱SV		С	ontrol		Mean Difference		Mean D	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI	
2.32.1 CSA due to he	art failu	ге									
Koyama 2013	16.9	9.9	10	35.3	15.2	9	-18.40 [-30.07, -6.73]				
								-100	-50	1 I 0 50	100
									Favours ASV	Favours Cont	rol

Low-flow Oxygen

Summary of Findings (GRADE)

Table S5 Low-flow oxygen in adults with CSA

References: Andreas 1996, Brostrom 2005, Campbell 2012, Hanly 1989, Nakao 2014, Sasayama 2006, Sasayama 2009, Seino 2007, Staniforth 1998, Toyama 2009

Outcomes	Certainty of the	Absolute Difference	No of Participants
[Tool]	evidence		(studies)
	(GRADE)	Low-flow oxygen vs. baseline or control	

Excessive sleepiness [ESS]	⊕⊕⊖⊖ LOW ^{a, b}	The mean difference in the low-flow oxygen group was 0.6 points lower (6.17 lower to 4.97 higher) compared to control	22 (1 RCT)
Disease severity [AHI]	⊕⊕⊕⊕ нісн	The mean difference in the low-flow oxygen group was 11.07 events/hour lower (13.71 lower to 8.43 lower) compared to control	308 (7 RCTs)
Disease severity [CAI]	⊕⊕⊕⊕ нісн	The mean difference in the low-flow oxygen group was 5.91 events/hour lower (8.87 lower to 2.95 lower) compared to control	246 (5 RCTs)
Cardiovascular disease [LVEF]	⊕⊕⊕⊖ MODERATE ^c	The mean difference in the low-flow oxygen group was 5.23 percent higher (2.02 lower to 8.44 higher) compared to control	224 (4 RCTs)
Cardiovascular disease [6MWD]	⊕○○○ VERY LOW ^{a, c, d}	The mean difference in the low-flow oxygen group was 13.73 m higher (29.73 lower to 57.2 higher) compared to baseline	29 (2 non-RCTs)
Hospitalization [incidence (times/year)]	⊕○○○ VERY LOW ^{a,d}	The mean difference in the low-flow oxygen group was 1.6 times/year lower (2.09 lower to 1.11 lower) compared to baseline	53 (1 non-RCT)
Hospitalization [incidence of outpatient visits]	⊕○○○ VERY LOW ^{a,d}	The mean difference in the low-flow oxygen group was 5.2 visits/year lower (8.35 lower to 2.05 lower) compared to baseline	53 (1 non-RCT)
Hospitalization [emergency visits (time/year)]	⊕○○○ VERY LOW ^{a,d}	The mean difference in the low-flow oxygen group was 1.7 times/year lower (2.58 lower to 0.82 lower) compared to baseline	53 (1 non-RCT)
Hospitalization [Length of stay (days)]	⊕○○○ VERY LOW ^{a,d}	The mean difference in the low-flow oxygen group was 4.1 days fewer (22.59 fewer to 14.39 more) compared to baseline	53 (1 non-RCT)
Adverse events	LOM _a	Campbell 2012: 1 out 10 participants died ("heart attack") and 1 out of 10 participants required a hospital admission to CCU Sasayama 2009: 1 out of 51 patients died suddenly from arrhythmia and 7 out of 51 patients were hospitalized for worsening, HF in both groups. Andreas 1996: Three patients (out of 27) in the room air group and two patients (out of 27) in the oxygen group withdrew from the study because of the inconvenience of the nasal prongs, data from these patients not included in final analysis	116 (3 RCTs)

a. Imprecision due to small sample size (<200 participants)

b. Imprecision due to the 95% CI includes possibility for important benefit and harm

c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

d. Downgraded quality of evidence due to data analyzed using pre- and posttreatment values

Critical Outcomes

Figure S131. Oxygen vs. Control (Excessive sleepiness, ESS) [CST= -2 pts], RCT

ſ		Oxygen		Co	ontrol		Mean Difference	ean Differen	се				
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV	, Fixed, 95%	CI	
	Staniforth 1998	9.4	6.3	11	10	7	11	-0.60 [-6.17, 4.97]					
									-10	-5	Ó	5	10
										Favours O	xygen Favoi	urs Control	

Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air delivered at a rate of 2 L/min via nasal cannula.

		Oxygen			Control			Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI				
13.2.1 IC \$D3													
Nakao 2014	8.6	10.5	45	18.7	12.2	52	34.1%	-10.10 [-14.62, -5.58]					
Sasayama 2009	8.98	8.43	26	20.75	13.51	25	18.1%	-11.77 [-17.98, -5.56]					
Toyama 2009	5.1	3.4	10	21	12	10	11.6%	-15.90 [-23.63, -8.17]					
Subtotal (95% CI)			81			87	63.8%	-11.63 [-14.93, -8.33]	◆				
Heterogeneity: Tau ² =	: 0.00; Cl	hi²=1.61,	df = 2 (P = 0.45	5); I² = 0%								
Test for overall effect:	Z = 6.90	(P < 0.00)	001)										
13.2.2 non-IC SD3													
Andreas 1996	10	9	22	26	24	22	6.1%	-16.00 [-26.71, -5.29]					
Hanly 1989	18.9	7.2	9	30	14.1	9	6.5%	-11.10 [-21.44, -0.76]					
Sasayama 2006	10	11.6	25	17.1	11.4	31	18.9%	-7.10 [-13.16, -1.04]	_ _				
Staniforth 1998	24.9	12.2715	11	38	16.5831	11	4.7%	-13.10 [-25.29, -0.91]					
Subtotal (95% CI)			67			73	36.2%	-10.09 [-14.47, -5.70]	◆				
Heterogeneity: Tau ² =	= 0.00; Cl	hi² = 2.37,	df = 3 (P = 0.50	0); I² = 0%								
Test for overall effect:	Z = 4.51	(P ≤ 0.00	001)										
Total (95% CI)			148			160	100.0%	-11.07 [-13.71, -8.43]	◆				
Heterogeneity: Tau ² =	: 0.00; Cl	hi² = 4.29,	df = 6 (P = 0.64	4); I² = 0%								
Test for overall effect:	Test for overall effect: Z = 8.23 (P < 0.00001) -20 -10 0 20												
Test for subgroup dif	ferences	: Chi² = 0.0	<u> 30. df =</u>	1 (P = 0)).58), I ² = 0)%			ravours oxygen Tavours control				

Figure S132. Oxygen vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCTs

Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Hanly 1989: SEM converted to SD, AHI during total sleep time used, single night study, compressed air and oxygen were administered through nasal cannula at a rate of 2 to 3 L/min; Sasayama 2006: 12-week study, O₂ was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula; Disease severity (AHI): reduction from baseline O2=-55.3%.

Figure S133. Oxygen vs. Control (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCTs

		-								
Γ		0)	cygen	1	0	Control			Mean Difference	Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
	13.3.1 IC \$D3									
	Nakao 2014	3.6	6.6	45	7.9	9.2	52	27.9%	-4.30 [-7.46, -1.14]	
	Sasayama 2009	3.54	5.4	26	11.27	11.15	25	19.5%	-7.73 [-12.57, -2.89]	_
	Toyama 2009	1.5	1.8	10	9	9.4	10	15.5%	-7.50 [-13.43, -1.57]	
	Subtotal (95% CI)			81			87	62.9%	-5.69 [-8.10, -3.27]	◆
	Heterogeneity: Tau ² =	: 0.00; C	hi² = 1	1.78, di	f= 2 (P :	= 0.41);	I ^z = 0%	I.		
	Test for overall effect:	Z = 4.61	(P <	0.0000	01)					
	13.3.2 non-IC SD3									
	Sasayama 2006	2.8	4.6	25	5.6	6.9	31	28.6%	-2.80 [-5.83, 0.23]	
	Staniforth 1998	3.8	7	11	18.4	13.6	11	8.5%	-14.60 [-23.64, -5.56]	
	Subtotal (95% CI)			36			42	37.1%	-7.90 [-19.36, 3.56]	
	Heterogeneity: Tau ² =	: 57.79; (Chi ^z =	5.89,	df = 1 (F	P = 0.02)); I² = 80	3%		
	Test for overall effect:	Z=1.35	5 (P =	0.18)						
	Total (95% CI)			117			129	100.0%	-5.91 [-8.87, -2.95]	◆
	Heterogeneity: Tau ² =	: 5.57; C	hi = {							
	Test for overall effect:	Z = 3.92	? (P <	Favours Oxygen Favours Control						
1	To add an and a supervise of the		- O L 33	2 0 4 4	-16 - 4	(D - 0.7)	4.1 17	0.07		

Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), l² = 0%

Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Sasayama 2006: 12-week study, O_2 was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula; Disease severity (CAI): reduction from baseline O2=-67.1%

									-	_	
	Oxygei	1	0	Control			Mean Difference		Mean Di	fference	
Study or Subgroup Me	an SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rando	m, 95% Cl	
13.4.1 IC \$D3											
Nakao 2014 5	5.4 7.3	45	18	11.5	52	34.1%	-12.60 [-16.38, -8.82]				
Sasayama 2009 5.1	16 4.5	26	21.93	13.01	25	25.0%	-16.77 [-22.16, -11.38]				
Subtotal (95% CI)						59.1%	-14.23 [-18.21, -10.24]		-		
Heterogeneity: Tau ² = 3.06	; Chi " =	1.54, di	f=1(P:	= 0.21);	$ ^2 = 359$	%					
Test for overall effect: Z = 6	i.99 (P <	0.0000	01)								
13.4.2 non-IC SD3											
Sasayama 2006 5	5.9 8.7	25	16.5	10.7	31	26.5%	-10.60 [-15.68, -5.52]				
Staniforth 1998 2	2.9 3.6	11	23.7	13.6	11	14.4%	-20.80 [-29.11, -12.49]				
Subtotal (95% CI)		36			42	40.9%	-15.15 [-25.08, -5.21]				
Heterogeneity: Tau ² = 39.6	6; Chi <mark></mark> ⁼∘	4.21,	df = 1 (F	P = 0.04)	; I² = 76	6%					
Test for overall effect: Z = 2	.99 (P =	0.003)									
Total (95% CI)		107			119	100.0%	-14.29 [-18.00, -10.59]		•		
Heterogeneity: Tau ² = 6.74	; Chi² =	5.80, di	f = 3 (P :	= 0.12);	l ² = 489	%			15 0		
Test for overall effect: Z = 7	.57 (P <	0.0000	01)					-00	-20 L	Eavoure Pacolino	00
Test for subgroup differen	ces: Chi	² = 0.03	l, df = 1	(P = 0.8	7), l² =	0%			Favours Oxygen	Favouis Dasellite	

Figure S134. Oxygen vs. Control (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCTs

Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2006: 12-week study, O₂ was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula; Staniforth 1998: SEM converted to SD, 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula

Figure S135. Oxygen vs. Control (Disease Severity, oxygen saturation <90%) [CST= ≥ 50% change from baseline], RCT

	Oxygen Control						Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
Andreas 1996	5.3	5.25	22	23.2	16	22	13.7%	-17.90 [-24.94, -10.86]			
Toyama 2009	0.3	0.5	10	4.1	4.5	10	86.3%	-3.80 [-6.61, -0.99]			
Total (95% CI)			32			32	100.0%	-5.73 [-8.34, -3.13]	•		
Heterogeneity: Chi ² = Test for overall effect	13.31, d Z = 4.31	lf=1((P≺(P = 0.0 0.0001)	003); I² :	= 929	6		-	-20 -10 0 10 20 Favours Oxygen Favours Baseline		

Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Andreas 1996: median and range converted to mean and SD, Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights

Figure S136. Oxygen vs. Baseline (Cardiovascular disease, 6MWD) [CST= + 32 meters], observational

	Oxygen Baseline						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Brostrom 2005	390.5	94.3	22	345.4	103.4	22	55.3%	45.10 [-13.38, 103.58]	
Campbell 2012	340	68.5	7	365	54.8	7	44.7%	-25.00 [-89.98, 39.98]	
Total (95% CI)			29			29	100.0%	13.73 [-29.73, 57.20]	-
Heterogeneity: Chi ² = Test for overall effect:	2.47, df Z = 0.62	= 1 (P ? (P = 0	= 0.12)).54)); I² = 60	%				-200 -100 0 100 200 Favours Baseline Favours Oxygen

Brostrom 2005: mean and SD calculated from median and range

	0	xvaen	Mean Difference	Mean Difference							
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
13.5.1 IC \$D3											
Nakao 2014	38.3	13.8	45	34	10.4	52	42.4%	4.30 [-0.62, 9.22]	⊢ ∎−−		
Toyama 2009	37	10	10	27	9	10	14.8%	10.00 [1.66, 18.34]			
Subtotal (95% CI)			55			62	57.2%	6.12 [0.91, 11.32]	-		
Heterogeneity: Tau ² =	4.04; Ch	i r = 1.3	3, df =	1 (P = 0	.25); I ř =	= 25%					
Test for overall effect:	Z = 2.30	(P = 0.1)	D2)								
13.5.2 non IC \$D3											
Pacavama 2006	20.2	106	25	24.4	10.0	24	22.004	2 00 [2 77 40 27]			
Subtotal (95% CI)	30.2	13.0	25	34.4	10.9	31	23.9%	3.80 [-2.77, 10.37]			
Heterogeneity: Not an	nlicable										
Test for overall effect:	Z=1.13	(P = 0.)	26)								
13.5.3 ungrouped											
Sasayama 2009	38.42	15.46	26	33.02	11.16	25	18.9%	5.40 [-1.98, 12.78]			
Subtotal (95% CI)			26			25	18.9%	5.40 [-1.98, 12.78]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z=1.43	(P = 0.1)	15)								
Total (95% CI)			106			118	100.0%	5 23 [2.02, 8.44]	•		
Heterogeneity: Tau ² =	.0.00°.05	i² = 1.5	8 df=	3 (P = 0	66): 17=	:0%		the friend of the	— · · · · · · · · · · · · · ·		
Test for overall effect 7 = 3 20 (P = 0 001) - 20											
Test for subgroup diff	erences:	Chi ² =	0.30. d	f=2(P	= 0.86).	I ² = 0%	5		Favours Control Favours Oxygen		

Figure S137. Oxygen vs. Control (Cardiovascular disease, LVEF (%)) [CST= 5%], RCTs

Nakao 2014: 12-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Sasayama 2009: 52-week study, oxygen delivered at a rate of 3 L/min through a nasal cannula; Toyama 2009: 3-month study, participants in HOT group received nasal 3 L/min oxygen; Sasayama 2006: 12-week study, O₂ was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Figure S138. Oxygen vs. Control (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], RCTs

	Oxygen Control						Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Andreas 1996	136	17	22	135	18	22	47.3%	1.00 [-9.35, 11.35]	
Sasayama 2006	118.8	18.9	25	116.5	18.2	31	52.7%	2.30 [-7.49, 12.09]	
Total (95% CI)			47			53	100.0%	1.69 [-5.43, 8.80]	-
Heterogeneity: Chi ^z = Test for overall effect:	0.03, df Z = 0.46	= 1 (P i (P = (= 0.86)).64)		-20 -10 0 10 20 Favours Oxygen Favours Control				

Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Sasayama 2006: 12-week study, O₂ was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Figure S139. Oxygen vs. Control (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT

	Oxygen Control							Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV,	Fixed, 95	5% CI	
Andreas 1996	79	8	22	82	7	22	61.7%	-3.00 [-7.44, 1.44]					
Sasayama 2006	67.98	10.7	25	69.4	10.7	31	38.3%	-1.42 [-7.06, 4.22]				_	
Total (95% CI)			47			53	100.0%	-2.39 [-5.88, 1.09]		-			
Heterogeneity: Chi ² = Test for overall effect:	0.19, df Z = 1.35	= 1 (P (P = 0	= 0.67)).18)); I ^z = 0%	6				-20	-10 Favours Ox	0 ygen Fa	10 vours Control	20

Andreas 1996: Nasal nocturnal oxygen and room air were administered via nasal prongs with a flow rate of 4 liters/min for seven nights; Sasayama 2006: 12-week study, O₂ was delivered via 92% oxygen concentrator at a rate of 3 L/min through nasal cannula

Fig	gure S140.	Oxygen vs.	. Baseline (Hospit	talizations,	Incidence	(times/	vear))	[No C	CST],	, Observational
C								1 11			,

	0)	cyger	1	Baseline			Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	l, 95% CI		
Seino 2007	0.5	0.7	53	2.1	1.7	53	-1.60 [-2.09, -1.11]		+			
								-4	-2 () 2	2 .	4
									Favours Oxygen	Favours	Baseline	

Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula.

Figure S141. Oxygen vs. Baseline (Hospitalizations, Length of stay (days)) [No CST], Observational

	Oxygen			Ba	seline	<u>;</u>	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Seino 2007	34.6	32.1	53	38.7	60.7	53	-4.10 [-22.59, 14.39]	-50 -25 0 25 50 Favours Oxygen Favours Baseline

Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S142. Oxygen vs. Baseline (Hospitalizations, Outpatient visits (times/year)) [No CST], Observational

	Ox	cyger	I	Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Seino 2007	12.7	4	53	17.9	11	53	-5.20 [-8.35, -2.05]	-10 -5 0 5 10 Favours Oxygen Favours Baseline

Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S143. Oxygen vs. Baseline (Hospitalizations, Emergency visits (times/year)) [No CST], Observational

	Ox	yger	1	Ba	selin	е	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Seino 2007	0.8	2.1	53	2.5	2.5	53	-1.70 [-2.58, -0.82]	
								-4 -2 0 2 4
								Favours Oxygen Favours Baseline

Low-flow oxygen was administered at a rate of 2 L/min via nasal cannula

Figure S144. Oxygen vs. Baseline (Sleep quality (Patient reported), sleep sufficiency index) [No CST], Observational

	0)	cyger	1	Ba	selin	е		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
13.16.1 AHI <20											
Brostrom 2005	99	22	13	89	25	13	70.2%	10.00 [-8.10, 28.10]		-+	
Subtotal (95% CI)			13			13	70.2%	10.00 [-8.10, 28.10]			
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 1.08	8 (P =	0.28)								
13.16.2 AHI >20											
Brostrom 2005	94	28	9	83	32	9	29.8%	11.00 [-16.78, 38.78]			
Subtotal (95% CI)			9			9	29.8%	11.00 [-16.78, 38.78]			
Heterogeneity: Not ap	plicable	!									
Test for overall effect:	Z = 0.78	3 (P =	0.44)								
Total (95% CI)			22			22	100.0%	10.30 [-4.87, 25.46]		-	
Heterogeneity: Chi ² =	0.00, df	= 1 (P = 0.9	5); I² = 0)%				-100		1
Test for overall effect:	Z = 1.33	3 (P =	0.18)						-100	Favours Baseline Favours Oxygen	5
Test for subgroup diff	erences	: Chi	² = 0.00), df = 1	(P =	0.95), F	²=0%			. arears arears arears oxygen	

	Oxygen			Baseline Mean Difference					Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	, Fixed, 95%	CI		
Campbell 2012	6.6	6.6	7	7.3	4.4	7	-0.70 [-6.58, 5.18]		. –				
								-20	-10	Ó	10	20	
									Favours O	kygen Favou	irs Baseline		

Figure S145. Oxygen vs. Control (Excessive sleepiness, ESS) [CST= 2 pts], Observational

Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator

Figure S146. Oxygen vs. Baseline (Disease Severity	r, AHI) [CST= ≥ 50% change from baseline],
Observational	

	0	xygen		Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
14.2.1 IC \$D3									
Arzt 2005	8.7	4.1	10	28.8	3.2	10	10.7%	-20.10 [-23.32, -16.88]	+
Brostrom 2005	27.4	19.8	22	34.7	17.4	22	8.0%	-7.30 [-18.31, 3.71]	
Campbell 2012	5	6.3	10	19.4	15.7	10	8.2%	-14.40 [-24.88, -3.92]	
Javaheri 1999	6	4	36	36	11	36	10.5%	-30.00 [-33.82, -26.18]	+
Shigemitsu 2007	6.23	3.16	18	33.7	11.1	18	10.1%	-27.47 [-32.80, -22.14]	-
Sugimura 2016	12	10	12	32.4	12.6	12	8.8%	-20.40 [-29.50, -11.30]	
Teschler 2001	28.2	13.6	16	44.5	13.6	16	8.6%	-16.30 [-25.72, -6.88]	
Yoshihisa 2012	22.4	20.3	42	39	26.6	42	8.4%	-16.60 [-26.72, -6.48]	
Subtotal (95% CI)			166			166	73.3%	-20.27 [-25.25, -15.29]	•
Heterogeneity: Tau ² =	= 35.90; C	>hi ² = 3	2.86, df	=7(P ≺	0.0001); I ² = 79	9%		
Test for overall effect:	Z = 7.98	(P < 0.	00001)						
14.2.2 non-IC \$D3									
Sakakibara 2005	62.35	10.95	51	101.43	15.67	51	10.2%	-39.08 [-44.33, -33.83]	T
Subtotal (95% CI)			51			51	10.2%	-39.08 [-44.33, -33.83]	•
Heterogeneity: Not ap	oplicable								
Test for overall effect:	Z=14.6	0 (P < (0.00001)					
14.2.3 ungrouned									
Hu 2006	23.6	6.6	11	30.0	83	11	9 8 %	-7 30 613 57 -1 031	-
Krachman 1999	20.0	15	ä	44	27	'a	4 9%	-76.00 [-46.18 -5.82]	(
Krachman 2005	12	17	10	57	61	10	1 9%	-45 00 [-84 25 -5 75]	
Subtotal (95% CI)	12		30		01	30	16.6%	-19.96 [-39.59, -0.32]	
Heterogeneity: Tau ² =	: 192.56	Chi ^z =	618 df	= 2 (P =	0.05) 8	² = 68%			-
Test for overall effect:	7 = 1.99	(P = 0	0.10, 05)		0.00/, 1				
		ų o.	,						
Total (95% CI)			247			247	100.0%	-21.23 [-27.17, -15.29]	◆
Heterogeneity: Tau ² =	= 83.33; 0	⊳hi ² = 9	3.93, df	= 11 (P ·	< 0.000	01); I 2 =	88%		
Test for overall effect:	Z = 7.01	(P < 0.	00001)						-100 -50 0 50 100
Test for subaroup diff	ferences	Chi ² =	26.79	df = 2 (P	< 0.000		= 92.5%		Favours Oxygen Favours Baseline

Arzt 2005: 12-week study, 2 L/min nasal oxygen; Brostrom 2005: 3-month study, oxygen administered at a fixed rate of 2 L/min by nasal cannula; Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator; Javaheri 1999: Single night study, the final amount of O₂ were 2 to 2 ½ l/min in 14, 3 l/min in 10 and 4 l/min in 12 in subjects. ; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Sugimura 2016: two night study, Flow rate of O₂ therapy was 3 L/min via nasal cannula; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Yoshihisa 2012: single night study, administered oxygen at a rate of 3 L/min through a nasal cannula Sakakibara 2005: 2 nights, O₂ 2 l/min; Hu 2006: single night study, nasal oxygen (4 L/min); Krachman 2005: night 2 (1 month of treatment) data used; Krachman 1999: SEM converted to SD, single night study, oxygen administered at 2 L/min by nasal cannula

Figure S147. Oxygen vs. Baseline (Disease Severity,	CAI) [CST= ≥ 50% (change from baseline],
Observational		

	0	xygen		B	aseline			Mean Difference		Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Random, 95% CI		IV, Random, 95%	CI	
14.3.1 IC \$D3												
Campbell 2012	10.8	12.7	10	19.4	15.7	10	23.4%	-8.60 [-21.12, 3.92]				
Javaheri 1999	12.93	18.24	36	28.18	23.09	36	24.7%	-15.25 [-24.86, -5.64]				
Teschler 2001	19.7	10.8	16	35.8	11.6	16	25.4%	-16.10 [-23.87, -8.33]				
Subtotal (95% CI)			62			62	73.5%	-14.41 [-19.85, -8.97]		•		
Heterogeneity: Tau ² =	: 0.00; CI	hi² = 1.0	4, df =	2 (P = 0	.59); l²÷	= 0%						
Test for overall effect:	Z= 5.19	(P ≤ 0.	00001)									
14.3.2 non-IC \$D3												
Sakakibara 2005	16.81	5.76	51	57.16	12.16	51	26.5%	-40.35 [-44.04, -36.66]		• •		
Subtotal (95% CI)			51			51	26.5%	-40.35 [-44.04, -36.66]		•		
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z=21.4	2 (P ≤ 0).00001)								
										-		
Total (95% CI)			113			113	100.0%	-20.55 [-37.67, -3.43]				
Heterogeneity: Tau ² =	: 284.67;	Chi² = I	60.82, (df = 3 (F	o.00 × (001); I ^z	= 95%		-100	-50 0	50	100
Test for overall effect:	Z = 2.35	(P = 0.	02)						-100	Eavours Oxygen Eavou	rs Baseline	100
Test for subgroup diff	ferences	: Chi ² =	59.79,	df = 1 (F	P < 0.00	001), l ^a	= 98.3%				io Dasenne	

Campbell 2012: 8-week study, analysis included pre-post analysis of oxygen arm, Oxygen was delivered through nasal prongs at 2 L/min through an oxygen concentrator; Javaheri 1999: Single night study, the final amount of O_2 were 2 to 2 ½ l/min in 14, 3 l/min in 10 and 4 l/min in 12 in subjects. ; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Sakakibara 2005: 2 nights, O_2 2 l/min

Figure S148. Oxygen vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% change from baseline], Observational

	0	xvaen		Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
14.5.1 IC \$D3									
Arzt 2005	2.5	7.3	10	28	16.4	10	14.9%	-25.50 [-36.63, -14.37]	_
Shigemitsu 2007	1.19	1.12	18	11.89	9.71	18	21.5%	-10.70 [-15.22, -6.18]	
Teschler 2001	4.4	1.6	16	38.2	10.4	16	20.9%	-33.80 [-38.96, -28.64]	
Yoshihisa 2012 Subtotal (95% CI)	6.8	15.6	42 86	27.5	16.2	42 86	19.4% 76.7%	-20.70 [-27.50, -13.90] - 22.55 [-34.53, -10.56]	
Heterogeneity: Tau ² = Test for overall effect:	136.18; Z = 3.69	;Chiᢪ= }(P=(= 44.30 0.0002)	, df = 3	(P < 0.1	00001)	; I² = 93%		
14.5.2 non-ICSD3									
Sakakibara 2005 Subtotal (95% CI)	6.02	1.17	51 51	29.78	5.46	51 51	23.3% 23.3%	-23.76 [-25.29, -22.23] -23.76 [-25.29, -22.23]	•
Heterogeneity: Not ap	plicable	9							
Test for overall effect:	Z = 30.3	39 (P <	0.0000	01)					
Total (95% CI)			137			137	100.0%	-22.72 [-29.83, -15.62]	◆
Heterogeneity: Tau ² =	55.88; (Chi²=	46.87,	df=4(F	° < 0.00	0001); I	²=91%		-50 -25 0 25 50
Test for overall effect:	Z = 6.27	?(P<(0.00001	1)					Eavours Oxygen Eavours Baseline
Test for subaroup diff	erences	: Chi ≃ ∶	= 0.04.	df = 1 (P = 0.8	4), $ ^2 = 1$	0%		r areare exigen i areare basenne

Arzt 2005: 12-week study, 2 L/min nasal oxygen; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Teschler 2001: SEM converted to SD, single night study, nasal oxygen (2 L/min); Yoshihisa 2012: single night study, administered oxygen at a rate of 3 L/min through a nasal cannula; Sakakibara 2005: 2 nights, O₂ 2 l/min

Figure S149. Oxygen vs. Baseline (Disease Severity, CAHI) [CST= ≥ 50% change from baseline], Observational

	Ox	yger	1	Baseline			Mean Difference	Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	
14.4.1 IC \$D3										
Sugimura 2016	11	10	12	31	12.3	12	-20.00 [-28.97, -11.03]	—+ —		
								-50 -25		50
								Favours Oxygen	Favours Baseline	50

Sugimura 2016: two night study, Flow rate of O₂ therapy was 3 L/min via nasal cannula

Figure S150. Oxygen vs. Baseline (Disease Severity, oxygen saturation <90% (%)) [CST= ≥ 50% reduction from baseline], Observational

	Oxygen Baseline							Mean Difference Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Hu 2006	10.6	3.2	11	23	6.9	11	76.4%	-12.40 [-16.89, -7.91]		
Javaheri 1999	0.3	0.3	14	17.2	21.9	14	11.7%	-16.90 [-28.37, -5.43]		
Krachman 1999	6	9	9	17	15	9	11.8%	-11.00 [-22.43, 0.43]		
Total (95% CI)			34			34	100.0%	-12.76 [-16.69, -8.83]	•	
Heterogeneity: Tau ² = Test for overall effect:	0.00; C Z = 6.37	hi ² = '(P <	0.62, d1 0.0000	-20 -10 0 10 20 Favours Oxygen Favours Baseline						

Javaheri 1999: data extracted from figure 3, fully responsive patients, Single night study, the final amount of O₂ were 2 to 2 ½ I/min in 14, 3 I/min in 10 and 4 I/min in 12 in subjects; Hu 2006: single night study, nasal oxygen (4 L/min); Krachman 1999: SEM converted to SD, single night study, oxygen administered at 2 L/min by nasal cannula

Figure S151. Oxygen vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= 5%], Observational

	C	xygen		B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Arzt 2005	32.5	7.3	10	30.9	7.6	10	47.6%	1.60 [-4.93, 8.13]	
Krachman 2005	19	9	10	22	11	10	26.2%	-3.00 [-11.81, 5.81]	
Shigemitsu 2007	46.35	14.85	18	44.73	11.92	18	26.2%	1.62 [-7.18, 10.42]	
Total (95% CI)			38			38	100.0%	0.40 [-4.10, 4.91]	+
Heterogeneity: Tau ² = Test for overall effect:	= 0.00; Cl : Z = 0.17	hi² = 0.7 ' (P = 0.9	-20 -10 0 10 20 Favours Baseline Favours Oxygen						

Arzt 2005: 12-week study, 2 L/min nasal oxygen; Shigemitsu 2007: Single night study, nasal oxygen was administered at 2 l/min and was raised progressively to 3 l/min if disordered breathing resulted in ODI4% >4/h.; Sakakibara 2005: 2 nights, O₂ 2 l/min

Figure S152. Oxygen vs. Control (Cardiovascular disease, BNP (pg/mL)) [CST= 50% change from baseline], RCT

	C	Oxygen		0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Sasayama 2009	62.9	335.3	26	-23.6	165.8	25	13.3%	86.50 [-57.84, 230.84]	
Staniforth 1998	178.4	67.7	11	207.2	67.7	11	86.7%	-28.80 [-85.38, 27.78]	
Total (95% CI)			37			36	100.0%	-13.44 [-66.12, 39.23]	-
Heterogeneity: Chi ² =	: 2.12, df	= 1 (P =							
Test for overall effect	Z = 0.50) (P = 0.	Favours Oxygen Favours Control						

Sasayama 2009: 52-week study, change score reported in (pg/ml), oxygen delivered at a rate of 3 L/min through a nasal cannula; Staniforth 1998: 4-week study, both overnight oxygen and air at a rate of 2 L / min via nasal cannula, serum BNP for oxygen group = 21.1 ± 8 (pmol.L⁻¹) and air group = 24.5 ± 8 (pmol.L⁻¹) converted to pg/ml

Figure S153.	Oxygen vs. Con	rol (Cardiovascula	r disease, HR	(beats/min)) [CST], R	СТ
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	0)	cyger	1	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Andreas 1996	112	15	22	110	13	22	13.5%	2.00 [-6.29, 10.29]	•
Nakao 2014	66	8.4	45	64.3	10.4	52	47.0%	1.70 [-2.04, 5.44]	- +-
Sasayama 2009	-3.1	9.7	26	-0.3	5.3	25	39.5%	-2.80 [-7.07, 1.47]	
Total (95% CI)			93			99	100.0%	-0.04 [-3.27, 3.19]	+
Heterogeneity: Tau ² = Test for overall effect:	2.13; C Z = 0.02	hi² = : ? (P =	2.67, di 0.98)	-20 -10 0 10 20 Favours Oxygen Favours Control					

Figure S154. Oxygen vs. Baseline (Cardiovascular disease, HR (beats/min)) [CST], Observational

				-							
	0	Oxygen Baseline						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI		
Arzt 2005	66	9.5	10	67	9.5	10	1.9%	-1.00 [-9.33, 7.33]]		
Krachman 1999	79	12	9	82	18	9	0.6%	-3.00 [-17.13, 11.13]]		
Sakakibara 2005	67.16	3.09	51	67.11	2.84	51	97.5%	0.05 [-1.10, 1.20]]		
Total (95% CI)			70			70	100.0%	0.01 [-1.13, 1.15]	」		
Heterogeneity: Tau ² =	= 0.00; C	hi² = 0	.24, df :	= 2 (P =	0.89);	$ ^{2} = 0\%$					
Test for overall effect	: Z = 0.02	? (P = 0).99)						Favours Oxygen Favours Baseline		

Krachman 1999: SEM converted to SD

Important Outcomes

Figure S155. Oxygen vs. Control (Daytime functioning, Specific Activity Scale (Mets)) [No CST], RCT

	0	xygen		C	ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
13.11.1 IC SD3											
Sasayama 2009	4.75	1.59	26	3.87	1.24	25	36.4%	0.88 [0.10, 1.66]			
Toyama 2009	5.8	1.2	10	4.3	1	10	23.7%	1.50 [0.53, 2.47]			
Subtotal (95% CI)			36			35	60.0%	1.12 [0.52, 1.73]	•		
Heterogeneity: Tau ² =	0.00; C	hi²= O	.95, df=	= 1 (P =	0.33);	I ² = 0%					
Test for overall effect:	Z = 3.63	(P=0).0003)								
13.11.2 non-IC \$D3											
Sasayama 2006	5	1.5	25	4	1.3	31	40.0%	1.00 [0.25, 1.75]			
Subtotal (95% CI)			25			31	40.0%	1.00 [0.25, 1.75]	•		
Heterogeneity: Not ap	plicable										
Test for overall effect:	Z = 2.63	(P=0).009)								
Total (95% CI)			61			66	100.0%	1.07 [0.60, 1.55]	•		
Heterogeneity: Tau ² =	0.00; C	hi² = 1	.02, df=	= 2 (P =	0.60);	I ^z = 0%					
Test for overall effect: Z = 4.47 (P < 0.00001)											
Test for subgroup diff	erences	: Chi ^z :	<u>= 0.06.</u>	df = 1 (F	<u> </u>	0), I ^z =	0%		raveas control raveas oxygen		

Figure S156. Oxygen vs. Control (Daytime functioning, Anaerobic threshold (AT VO2)) [No CST], RCT

	Oxygen			Co	ontro		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
Toyama 2009	11.9	3.1	10	11.3	2.5	10	0.60 [-1.87, 3.07]				
								-10 -5 0 5 10			
								Favours Control Favours Oxygen			

Figure S157. Oxygen vs.	Control (Daytime	functioning, Peak	VO2) [No CST], RCT
0 /0	```	0,	/ 5 //

	Oxygen Control				ontro	l	Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Toyama 2009	18.3	4.7	10	15.8	3.8	10	2.50 [-1.25, 6.25]		
								-10 -5 0 5 1	10
								Favours Control Favours Oxygen	

Figure S158. Oxygen vs. Control (Daytime functioning, Reitan trail making B (s)) [No CST], RCT

0 /0				• •			0.	
	0	xygen	1	0	Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Staniforth 1998	196	146	11	197	142.6	11	-1.00 [-121.60, 119.60]	-100 -50 0 50 100 Favours Oxygen Favours Control

Figure S159. Oxygen vs. Control (Daytime functioning, Four choice reaction time (s)) [No CST], RCT

	(Oxygen		(Control		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Staniforth 1998	0.86	0.3317	11	0.82	0.3317	11	0.04 [-0.24, 0.32]	-1 -0.5 0 0.5 1 Favours Oxygen Favours Control

Figure S160. Oxygen vs. Control (Daytime functioning, PASAT 2 (s)) [No CST], RCT

	0	Oxygen			ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Staniforth 1998	28	19.9	11	26	19.9	11	2.00 [-14.63, 18.63]	-20 -10 0 10 20 Favours Oxygen Favours Control

Figure S161. Oxygen vs. Control (Daytime functioning, PASAT 4 (s)) [No CST], RCT

	0	Oxygen			ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Staniforth 1998	48	19.9	11	43	23.2	11	5.00 [-13.06, 23.06]	-20 -10 0 10 20 Favours Oxygen Favours Control

Figure S162. Oxygen vs. Control (Quality of Life, Quality of life score (max 240)) [No CST], RCT

	0	Oxygen			ontrol		Mean Difference	Mean Diffe			ence	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fi	xed, 95	% CI	
Staniforth 1998	115	29.8	11	113	33.2	11	2.00 [-24.36, 28.36]			-		
								-50	-25	Ó	25	50
									Favours Cont	rol Fav	vours Oxygen	

	0)	cygen		Control				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andreas 1996	343	56	22	346	86	22	68.2%	-3.00 [-45.88, 39.88]	
Hanly 1989	324.58	69.9	9	275.29	109.8	9	17.4%	49.29 [-35.75, 134.33]	
Staniforth 1998	302	99.5	11	275	122.7	11	14.4%	27.00 [-66.35, 120.35]	
Total (95% CI)			42			42	100.0%	10.40 [-25.03, 45.82]	-
Heterogeneity: Tau ² = Test for overall effect:	= 0.00; Ch : Z = 0.58 (i ^z = 1.3 (P = 0.							

Figure S163. Oxygen vs. Control (Sleep architecture, PSG, Total Sleep Time) [CST= 15 min], RCT

Hanly 1989: SEM converted to SD

Figure S164. Oxygen vs. Control (Sleep architecture, PSG, REM (%)) [CST= 5% of TST], RCT

	0	xygen		C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Andreas 1996	18	9	22	17	8	22	55.4%	1.00 [-4.03, 6.03]	
Hanly 1989	20.97	6.45	9	16.59	9.63	9	24.5%	4.38 [-3.19, 11.95]	
Staniforth 1998	16	10	11	13	10	11	20.1%	3.00 [-5.36, 11.36]	
Total (95% CI)			42			42	100.0%	2.23 [-1.52, 5.98]	-
Heterogeneity: Tau ² Test for overall effec	= 0.00; C t: Z = 1.17	hi² = 0 ' (P = (.57, df=).24)	= 2 (P =	0.75);	I² = 0%			-20 -10 0 10 20 Favours Control Favours Oxygen

Figure S165. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST=5% of TST], RCT

	Oxygen Control							Mean Difference Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
Andreas 1996	21	13	22	35	24	22	54.4%	-14.00 [-25.41, -2.59]		
Hanly 1989	15.18	7.65	9	27.64	17.46	9	45.6%	-12.46 [-24.91, -0.01]		
Total (95% CI)			31			31	100.0%	-13.30 [-21.71, -4.89]		
Heterogeneity: Chi ² =	0.03, df	= 1 (P	= 0.86)); IZ = 09	6					
Test for overall effect	Z = 3.10) (P = (0.002)						Favours Oxygen Favours Control	

Hanly 1989: SEM converted to SD

Figure S166. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST=5% of TST], RCT

	0	xygen		0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Andreas 1996	56	12	22	46	21	22	55.1%	10.00 [-0.11, 20.11]	
Hanly 1989	55.31	9.45	9	48.84	14.31	9	44.9%	6.47 [-4.73, 17.67]	
Total (95% CI)			31			31	100.0%	8.42 [0.91, 15.92]	-
Heterogeneity: Chi ² =	0.21, df	= 1 (P	= 0.65)); I ² = 09	6				
Test for overall effect:	Z = 2.20	I (P = (0.03)		Favours Oxygen Favours Control				

Figure S167. Oxygen vs. Control (Sleep architecture, PSG, SWS%) [CST=5% of TST], RCT

	Oxygen (ontro	I		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Andreas 1996	6.55	5.5	22	3.9	3.6	22	86.7%	2.65 [-0.10, 5.40]	
Hanly 1989	8.24	8.25	9	5.12	6.9	9	13.3%	3.12 [-3.91, 10.15]	
Total (95% CI)			31			31	100.0%	2.71 [0.15, 5.27]	◆
Heterogeneity: Chi ² = Test for overall effect:	0.01, df Z = 2.08	= 1 (P } (P = 0	= 0.90)).04)		-20 -10 0 10 20 Favours Control Favours Oxygen				

Andreas 1996: median and range converted to mean and SD

Figure S168. Oxygen vs. Control (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCTs

	Oxygen			(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Andreas 1996	15	9	22	20	13	22	34.4%	-5.00 [-11.61, 1.61]	
Hanly 1989	13.8	5.64	9	30.37	25.23	9	8.1%	-16.57 [-33.46, 0.32]	
Staniforth 1998	5.8	4.6	11	7.6	4.3	11	57.5%	-1.80 [-5.52, 1.92]	
Total (95% CI)			42			42	100.0%	-4.09 [-9.14, 0.96]	•
Heterogeneity: Tau ^z = Test for overall effect:	: 7.94; C Z = 1.59	hi² = 3) (P = (-50 -25 0 25 50 Favours Oxygen Favours Control						

Figure S169. Oxygen vs. Control (Daytime functioning, Minnesota Living with Heart Failure) [CST], Observational

	Oxygen Baseline							Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
14.17.1										
Campbell 2012 Subtotal (95% CI)	40.6	25.8	7 7	46.7	28.7	7 7	19.7% 19.7%	-6.10 [-34.69, 22.49] -6.10 [-34.69, 22.49]	-	
Heterogeneity: Not ap	plicable	9								
Test for overall effect:	Z = 0.42	2 (P = 0).68)							
14.17.2 AHI <20										
Brostrom 2005	35	22.1	13	38.7	22.7	13	54.2%	-3.70 [-20.92, 13.52]		
Subtotal (95% CI)			13			13	54.2%	-3.70 [-20.92, 13.52]	-	
Heterogeneity: Not ap	plicable	9								
Test for overall effect:	Z = 0.42	2 (P = 0).67)							
14.17.3 AHI >20										
Brostrom 2005	32.7	23.1	9	40.5	30.1	9	26.2%	-7.80 [-32.59, 16.99]		
Subtotal (95% CI)			9			9	26.2%	-7.80 [-32.59, 16.99]		
Heterogeneity: Not ap	plicable	9								
Test for overall effect:	Z = 0.62	2 (P = 0).54)							
Total (95% CI)			29			29	100.0%	-5.24 [-17.92, 7.43]		
Heterogeneity: Tau² =	0.00; C	hi² = 0	.08, df=	= 2 (P =	0.96);	I ² = 0%			-100 -50 0 50	100
Test for overall effect:	Z = 0.81	I (P = 0).42)						Favours Oxygen Favours Baseline	
Test for subaroup diff	erences	s: Chi ž a	= 0.08.	df = 2 (l)	<u>P = 0.9</u>	6), I ^z =	0%	_		

	0	xygen		Ba	seline	;		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
14.18.1 IC SD3										
Arzt 2005	85.3	10.8	10	85.6	7.6	10	9.5%	-0.30 [-8.49, 7.89]		
Franklin 1997	71.6	13.7	20	78.3	12.9	20	9.5%	-6.70 [-14.95, 1.55]		
Hu 2006	79.7	6.2	11	68.4	11	11	10.0%	11.30 [3.84, 18.76]		
Javaheri 1999	82.2	15.9	36	72.1	14.1	36	10.4%	10.10 [3.16, 17.04]		
Krachman 1999	81	3	9	82	9	9	10.9%	-1.00 [-7.20, 5.20]		
Krachman 2005	70	9	10	64	18	10	6.9%	6.00 [-6.47, 18.47]		
Teschler 2001	92	5.6	16	77	6.4	16	12.2%	15.00 [10.83, 19.17]		
Yoshihisa 2012	71.4	12.4	42	67.2	14.1	42	11.2%	4.20 [-1.48, 9.88]		
Subtotal (95% CI)			154			154	80.5%	5.07 [-0.50, 10.64]	◆	
Heterogeneity: Tau ² =	50.19; 0	Chi ≃ =∶	37.21,	df = 7 (P	< 0.0	0001); I	≈ = 81%			
Test for overall effect:	Z=1.78) (P = 0).07)							
14.18.2 AHI <20										
Brostrom 2005	73.9	10	13	71.9	9.1	13	10.1%	2.00 [-5.35, 9.35]		
Subtotal (95% CI)			13			13	10.1%	2.00 [-5.35, 9.35]	-	
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.53) (P = 0	0.59)							
14.18.3 AHI >20										
Brostrom 2005	75.1	10.9	9	73.5	6.4	9	9.5%	1.60 [-6.66, 9.86]		
Subtotal (95% CI)			9			9	9.5%	1.60 [-6.66, 9.86]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.38) (P = 0).70)							
Total (95% CI)			176			176	100.0%	4.46 [-0.20, 9.13]	◆	
Heterogeneity: Tau ² =	42.07; 0	Chi²=∘	40.07,	df = 9 (P	< 0.0	0001);1	² =78%			
Test for overall effect:	Z = 1.88) (P = 0	0.06)						Favours Baseline Favours Oxygen	
Test for subgroup differences: Chi ² = 0.67, df = 2 (P = 0.72), l ² = 0%										

Figure S170. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=10%], Observational

Arzt 2005: SEM converted to SD; Franklin 1997: median and range converted to mean and SD; Brostrom 2005: median and range converted to mean and SD; Javaheri 1999: data extracted from figure 3; Krachman 1999: SEM converted to SD; Teschler 2001: SEM converted to SD

Figure S171. Oxygen vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST= 15 min], Observational

	Oxygen Baseline					•		Mean Difference Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
14.19.1										
Campbell 2012	312.7	52.6	10	312	58.3	10	10.5%	0.70 [-47.97, 49.37]	ŧ	
Franklin 1997	405.3	69.9	20	393.5	78.1	20	11.3%	11.80 [-34.14, 57.74]		
Javaheri 1999	268	82	36	266	50	36	17.3%	2.00 [-29.37, 33.37]	_	
Krachman 1999	297	39	9	324	60	9	11.0%	-27.00 [-73.75, 19.75]		
Krachman 2005	274	57	10	273	90	10	6.7%	1.00 [-65.03, 67.03]		
Teschler 2001	279	44	16	212	64	16	14.2%	67.00 [28.94, 105.06]		
Subtotal (95% CI)			101			101	71.0%	11.09 [-16.20, 38.39]		
Heterogeneity: Tau ² =	633.13;	Chi ^z =	: 11.39	, df = 5 ((P = 0.)	04); I ^z =	56%			
Test for overall effect:	Z = 0.80) (P = 0	1.43)							
14.19.2 AHI <20										
Brostrom 2005	355.1	47.8	13	344.9	43.9	13	15.4%	10.20 [-25.08, 45.48]	_	
Subtotal (95% CI)			13			13	15.4%	10.20 [-25.08, 45.48]		
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.57	' (P = 0	1.57)							
44.40.2 410.520										
14.19.3 AHI >20		50 F					40.000			
Brostrom 2005 Subtotal (95% CI)	355.2	52.5	9	352.8	30.1	9	13.6%	2.40 [-37.14, 41.94]		
Hotorogonoity Not on	nliaahla		9			5	13.070	2.40 [-37.14, 41.34]		
Test for everall effect:	7 – 0.13		041							
restion overall ellect.	2 - 0.12	. (r – t	.51)							
Total (95% CI)			123			123	100.0%	10.25 [-8.92, 29.41]		
Heterogeneity: Tau ² =	296.74;	Chi ^z =	11.62	, df = 7 ((P = 0.1	11); I ^z =	40%			
Test for overall effect:	Z = 1.05	5 (P = 0	.29)						-100 -50 0 50 100 Eavours Baseline Eavours Ovvigen	
Test for subgroup diff	erences	: Chi²∍	= 0.13,	df = 2 (F	P = 0.9	4), ² =	0%		Favours Dasenne Favours Oxygen	

Teschler 2001: SEM converted to SD; Krachman 1999: SEM converted to SD; Campbell 2012: median and range converted to mean and SD Franklin 1997: median and range converted to mean and SD

Figure S172. Oxygen vs.	Baseline (S	leep architectu	re, PSG	, REM%)	[CST=5% of TST], Observational

	Oxygen Baseline							Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI			
14.20.1												
Campbell 2012	18.2	2.5	10	11.6	6.1	10	10.1%	6.60 [2.51, 10.69]	——————————————————————————————————————			
Franklin 1997	12.6	5	20	11.6	6.1	20	13.3%	1.00 [-2.46, 4.46]	_			
Hu 2006	13.7	3.2	11	11.3	2.1	11	24.1%	2.40 [0.14, 4.66]				
Javaheri 1999	13	10	36	15	12	36	6.9%	-2.00 [-7.10, 3.10]				
Krachman 1999	17	9	9	17	12	9	2.0%	0.00 [-9.80, 9.80]				
Krachman 2005	23	8	10	19	9	10	3.4%	4.00 [-3.46, 11.46]				
Teschler 2001	12.7	7.6	16	12	7.6	16	6.5%	0.70 [-4.57, 5.97]				
Yoshihisa 2012	18.2	6.1	42	18.3	6.5	42	19.2%	-0.10 [-2.80, 2.60]	-			
Subtotal (95% CI)			154			154	85.6%	1.64 [-0.11, 3.40]	◆			
Heterogeneity: Tau ² =	1.93; C	hi²=	10.40, i	df = 7 (P	= 0.1	17); I² =	33%					
Test for overall effect:	Z = 1.83	(P =	0.07)									
14.20.2 AHI <20												
Brostrom 2005	20.5	6.3	13	19.8	5.4	13	8.6%	0.70 [-3.81, 5.21]				
Subtotal (95% CI)			13			13	8.6%	0.70 [-3.81, 5.21]				
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.30) (P =	0.76)									
14.20.3 AHI >20												
Brostrom 2005	17.7	6.3	9	17.6	5.8	9	5.9%	0.10 [-5.49, 5.69]				
Subtotal (95% CI)			9			9	5.9%	0.10 [-5.49, 5.69]				
Heterogeneity: Not ap	plicable											
Test for overall effect:	Z = 0.04	(P =	0.97)									
Total (05% CI)			470			470	400.0%	4 47 10 05 2 001				
Total (95% CI)		=	1/6			1/6	100.0%	1.47 [0.05, 2.89]				
Heterogeneity: fau ² =	0.86; C	nı=	10.80,1	ат=9 (P	= 0.1	29); 1*=	17%		-20 -10 0 10 20			
lest for overall effect:	Z = 2.03	F (P =	U.U4)						Favours Baseline Favours Oxygen			
Lest for subgroup diff	Test for subgroup differences: Chi ² = 0.37, df = 2 (P = 0.83), l ² = 0%											
Krachman 1999: SEM converted to SD; Krachman 2005 oxygen data from night 2; Teschler 2001: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Figure S173. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=5% of TST], Observational

	0	xygen		Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
14.21.1									
Campbell 2012	13.7	6.1	10	30.3	19.1	10	3.9%	-16.60 [-29.03, -4.17]	
Franklin 1997	31.3	15.6	20	37.1	18.6	20	5.2%	-5.80 [-16.44, 4.84]	
Javaheri 1999	45	30	36	43	25	36	3.7%	2.00 [-10.76, 14.76]	
Krachman 1999	13	6	9	11	6	9	14.9%	2.00 [-3.54, 7.54]	
Krachman 2005	12	11	10	16	14	10	4.9%	-4.00 [-15.04, 7.04]	
Subtotal (95% CI)			85			85	32.6%	-3.58 [-10.01, 2.85]	
Heterogeneity: Tau ² =	26.87; 0	Chi²=	8.29, dt	f=4(P:	= 0.08)	; I ² = 52	2%		
Test for overall effect:	Z = 1.09	(P = 0).28)						
14.21.2 AHI < 20									
Brostrom 2005	7.1	2.4	13	6.8	2.5	13	38.5%	0.30 [-1.58, 2.18]	+
Subtotal (95% CI)			13			13	38.5%	0.30 [-1.58, 2.18]	◆
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.31	(P = 0).75)						
14.21.3 AHI > 20									
Brostrom 2005	9.9	3.9	9	9.2	2.5	9	29.0%	0.70 [-2.33, 3.73]	
Subtotal (95% CI)			9			9	29.0%	0.70 [-2.33, 3.73]	—
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.45	(P = 0).65)						
T-1-LIOFN OD			407			407	400.00		
Total (95% CI)			107			107	100.0%	-0.46 [-3.02, 2.11]	🕇
Heterogeneity: Tau ² =	3.54; CI	hi ^z = 9	.38, df=	= 6 (P =	0.15);	I ^z = 369	%	-	-20 -10 0 10 20
Test for overall effect:	Z = 0.35	(P = 0).73)						Favours Oxygen Favours Baseline
Test for subaroup diff	erences	∶Chi ² ⊹	= 1.44.	df = 2 (f)	P = 0.4	 9), ² = 1 	0%		

Krachman 1999: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Figure S174. Oxygen vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=5% of TST], Observational

	0	xygen		Ba	seline	÷		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
14.22.1									
Franklin 1997	54.6	12.4	20	47.5	12.4	20	12.6%	7.10 [-0.59, 14.79]	
Javaheri 1999	41	27	36	42	24	36	5.3%	-1.00 [-12.80, 10.80]	
Krachman 1999	65	9	9	67	12	9	7.8%	-2.00 [-11.80, 7.80]	
Krachman 2005	62	9	10	64	10	10	10.7%	-2.00 [-10.34, 6.34]	
Subtotal (95% CI)			75			75	36.4%	1.20 [-3.62, 6.03]	
Heterogeneity: Tau ² =	2.72; C	hi = 3	.37, df=	= 3 (P =	0.34);	$ ^{2} = 119$	%		
Test for overall effect:	Z = 0.49) (P = 0).63)						
14.22.2 AHI >20									
Brostrom 2005	39.55	5.4	13	39	5.64	13	41.3%	0.55 [-3.69, 4.79]	_ _
Subtotal (95% CI)			13			13	41.3%	0.55 [-3.69, 4.79]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.25	5 (P = 0).80)						
14.22.3 AHI <20									
Brostrom 2005	37.5	6.7	9	37	5.8	9	22.2%	0.50 [-5.29, 6.29]	
Subtotal (95% CI)			9			9	22.2%	0.50 [-5.29, 6.29]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.17	' (P = ().87)						
Total (05% CI)			07			07	400.08	0.04 [4.02 2 54]	
Total (95% CI)	0.00.01	L 2 0	97	6 (D)	0.000	9/ 17 0~	100.0%	0.81 [-1.92, 3.54]	
Heterogeneity: lau* =	0.00; Cl	nr=3	.44, df :	= 5 (P =	0.63);	17 = 0%			-20 -10 0 10 20
Test for overall effect:	∠ = 0.58	3 (P = l 、 ついさ	J.56) - 0.05	46-0.0		0) 17	oor		Favours Oxygen Favours Baseline
	erences	: Chifi	= 0.05,	ar = Z(1)	-= 0.9	<u>(8), I* =</u>	0%		
Franklin 1997: media	an and	range	conve	erted to	o mea	an and	SD		

Figure S175. Oxygen vs. Baseline (Sleep architecture, PSG, SWS%) [CST=5% of TST], Observational

	Ox	cyger	1	Ba	selin	е		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
14.23.1 IC \$D3									
Teschler 2001	18.4	9.6	16	13.9	8.4	16	4.4%	4.50 [-1.75, 10.75]	
Yoshihisa 2012	3	4.3	42	2.1	3.5	42	61.7%	0.90 [-0.78, 2.58]	-
Subtotal (95% CI)			58			58	66.2%	1.39 [-1.03, 3.81]	-
Heterogeneity: Tau ² =	1.03; CI	hi² =	1.19, di	f=1 (P=	= 0.2	3); I ² = 1	16%		
Test for overall effect:	Z = 1.13) (P =	0.26)						
14.23.2 AHI <20									
Brostrom 2005	11.6	5.5	13	10.6	5.9	13	9.0%	1.00 [-3.38, 5.38]	
Subtotal (95% CI)			13			13	9.0%	1.00 [-3.38, 5.38]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 0.45	i (P =	0.65)						
14.23.3 AHI >20									
Brostrom 2005	10.7	3.4	9	9.1	2.2	9	24.8%	1.60 [-1.05, 4.25]	
Subtotal (95% CI)			9			9	24.8%	1.60 [-1.05, 4.25]	
Heterogeneity: Not ap	plicable								
Test for overall effect:	Z = 1.19	(P =	0.24)						
Total (95% CI)			80			80	100.0%	1.24 [-0.07, 2.56]	◆
Heterogeneity: Tau ² =	0.00; Cl	hi²=	1.29, dt	f= 3 (P =	= 0.73	3); I = = ()%	_	
Test for overall effect:	Z = 1.85	i (P =	0.06)						Favours Baseline Favours Oxygen
Test for subgroup diff	erences	: Chi	² = 0.05	i, df = 2	(P = I	0.97), l ^a	'= 0%		- arearo Edecanico - arouro oxygen

Mean Difference Baseline Mean Difference Oxygen IV, Random, 95% CI IV, Random, 95% CI Study or Subgroup Mean SD Total Mean SD Total Weight 14.24.1 Arzt 2005 29.5 23.4 22.9 20.9 10 10 4.2% -6.60 [-26.05, 12.85] Campbell 2012 28.1 8.8 10 44.3 13.4 10 8.2% -16.20 [-26.14, -6.26] Franklin 1997 10.5% -3.50 [-9.35, 2.35] 16.1 8.5 20 19.6 10.3 20 Hu 2006 15 7.1 11 31.3 13.2 11 8.8% -16.30 [-25.16, -7.44] Javaheri 1999 28.5 24.8 9.0% -15.20 [-23.72, -6.68] 13.3 8.1 36 36 Krachman 1999 9 9 9 14 15 -9 7.4% -5.00 [-16.43, 6.43] Krachman 2005 10 3 10 11 9 10 10.4% -1.00 [-6.88, 4.88] 8.7% -35.00 [-43.92, -26.08] Teschler 2001 31.7 10 16 66.7 15.2 16 Yoshihisa 2012 11.5% 18.6 7.5 42 25.9 9 42 -7.30 [-10.84, -3.76] Subtotal (95% CI) 164 164 78.7% -11.71 [-18.09, -5.34] Heterogeneity: Tau² = 73.51; Chi² = 51.25, df = 8 (P < 0.00001); l² = 84% Test for overall effect: Z = 3.60 (P = 0.0003) 14.24.2 AHI <20 Brostrom 2005 15.7 2.9 13 18.2 3 13 12.0% -2.50 [-4.77, -0.23] Subtotal (95% CI) 13 12.0% -2.50 [-4.77, -0.23] 13 Heterogeneity: Not applicable Test for overall effect: Z = 2.16 (P = 0.03) 14.24.3 AHI >20 Brostrom 2005 -5.20 [-13.06, 2.66] 21.3 6.7 q 26.5 10 9 9.3% Subtotal (95% CI) 9 9 9.3% -5.20 [-13.06, 2.66] Heterogeneity: Not applicable Test for overall effect: Z = 1.30 (P = 0.19) Total (95% CI) 186 186 100.0% -9.92 [-14.83, -5.01] Heterogeneity: Tau² = 51.06; Chi² = 67.51, df = 10 (P < 0.00001); l² = 85% ⊢ -50 -25 'n 25 50 Test for overall effect: Z = 3.96 (P < 0.0001) Favours Oxygen Favours Baseline Test for subgroup differences: Chi² = 7.28, df = 2 (P = 0.03), l² = 72.5%

Figure S176. Oxygen vs. Baseline (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], Observational

Teschler 2001: SEM converted to SD; Franklin 1997: median and range converted to mean and SD

Acetazolamide

Summary of Findings (GRADE)

Table S6 Acetazolamide in adults with CSA

References: Ginter 2020, Java	heri 2006, Naghan 2	020		
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Acetazolamide vs. placebo	No of Participants (studies)	
Excessive sleepiness [ESS]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the acetazolamide group was 2.7 points lower (5.42 lower to 0.02 higher) compared to placebo	20 (1 RCT)	
Disease severity [AHI]		The mean difference in the acetazolamide group was 16.57 events/hour lower (28.43 lower to 4.71 lower) compared to placebo	76 (3 RCTs)	
Disease severity [CAI]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the acetazolamide group was 7.65 events/hour lower (13.8 lower to 1.51 lower) compared to placebo	56 (2 RCTs)	
Cardiovascular disease [LVEF]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the acetazolamide group was 1 percent higher (-5.81 lower to 7.81 higher) compared to placebo	24 (1 RCTs)	
a. Imprecision due to the b. Imprecision due to si	ne 95% Cl includes p mall sample size (<2	ossibility for important benefit and no effect 00 participants)		

Critical Outcomes

Figure S177. Acetazolamide vs. Placebo (Excessive sleepiness, ESS) [CST= - 2 points], RCT

	Aceta	Pla	cebo	D	Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.1.1 CSA due to med	lication o	r sub	stance						
Naghan 2020	14	3.2	10	16.7	3	10	-2.70 [-5.42, 0.02]		
									10
								Favours Acetazolamide Favours Placebo	10

Naghan 2020: Acetazolamide 250 mg 1 h before sleep for 6 nights, the Epworth sleepiness scale results range from 0 to 24

Figure S178. Acetazolamide vs. Placebo (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCT



Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period Baseline AHI: Able-bodied= 21 ± 13.8, SCI=27.2 ± 32; Naghan 2020: Acetazolamide was prescribed one dose 250 mg and just 1 h before sleep for 6 nights; Javaheri 2006: Patients received three identical capsules of either placebo or one acetazolamide and two potassium chloride capsules. Potassium chloride (total, 30 mEq) was given to compensate for acetazolamide-induced urinary potassium loss. Acetazolamide was administered at 3.5 mg/kg and increased to 4 mg/kg AHI change from baseline was -56% reduction.

Figure S179. Acetazolamide vs. Placebo (Disease Severity, CAI) [CST= ≥ 50% change from baseline], RCT

-									
	Aceta	zolam	ide	PI	acebo)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.3.1 Primary CSA a	nd CSA du	ue to r	nedica	l condit	ion				
Ginter 2020 Subtotal (95% CI)	0.6	1.5	16 16	6.3	13.1	16 16	90.4% 90.4%	-5.70 [-12.16, 0.76] - 5.70 [-12.16, 0.76]	-
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z=1.73	(P = 0	.08)						
1.3.2 CSA due to hea	art failure								
Javaheri 2006 Subtotal (95% CI)	23	21	12 12	49	28	12 12	9.6% <mark>9.6%</mark>	-26.00 [-45.80, -6.20] - 26.00 [-45.80, -6.20]	
Heterogeneity: Not a	pplicable								
Test for overall effect	: Z = 2.57	(P = 0	.01)						
Total (95% CI)			28			28	100.0%	-7.65 [-13.80, -1.51]	•
Heterogeneity: Chi ² =	= 3.65, df =	: 1 (P :	= 0.06)	; I² = 739	%				
Test for overall effect	: Z = 2.44	(P = 0	.01)						Favours Acetazolamide Favours Placebo
Toet for subgroup dit	fforoncoc:	Chiž-	2.86	df = 1 /P	-0.0	8) 12 - 1	20 8 05		r avours neotacolamilae i r avours i racebo

Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period, Baseline CAI: Able-bodied= 2.8 ± 4.5 , SCI= 7.3 ± 14.6 ; Javaheri 2006: Patients received three identical capsules of either placebo or one acetazolamide and two potassium chloride capsules. Potassium chloride (total, 30 mEq) was given to compensate for acetazolamide-induced urinary potassium loss. Acetazolamide was administered at 3.5 mg/kg and increased to 4 mg/kg; CAI change from baseline was -49% reduction.

Figure S180. Acetazolamide vs. Placebo (Cardiovascular disease, LVEF (%)) [CST= +5%], RCT

-					•			
	Acetaz	olam	ide	Pla	icebo)	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.6.1 CSA due to hea	rt failure							
Javaheri 2006	21	8	12	20	9	12	1.00 [-5.81, 7.81]	
								Favours Placebo Favours Acetazolamide

Figure S181. Acetazolamide vs. Placebo (Sleep Quality, Subjective Questionnaire) [No CST], RCT

	Acetazola	mide	Place	bo	Risk Ratio		Risk	Ratio	
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% CI	
1.11.1 CSA due to he	art failure								
Javaheri 2006	7	12	1	12	7.00 [1.01, 48.54]				
									100
						0.01	Favours Placebo	Favours Aceta	zolamide

Javaheri 2006: improvement of sleep quality on placebo vs acetazolamide, higher number represents an improvement, patients were asked specifically if they felt improved in comparing the first arm versus the second arm of the study

Figure S182. Acetazolamide vs. Placebo (Disease Severity, ODI) [CST= ≥ 50% change from baseline], RCT

	Aceta	zolam	ide	C	ontrol		Mean Difference	Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV	, Fixed, 9	5% CI	
1.4.1 Primary CSA a	nd CSA du	ie to r	nedica	l condit	ion							
Ginter 2020	7.5	8.3	8	19.2	15.2	8	-11.70 [-23.70, 0.30]					
								-50	-25	Ó	25	50
								Favor	urs Acetazola	imide Fa	avours Control	

Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period, Baseline ODI: Able-bodied= 8.9 ± 13 , SCI= 19.9 ± 34.1

Figure S183. Acetazolamide vs. Placebo (Disease Severity, oxygen saturation < 90%) [CST= ≥ 50% change from baseline], RCT

	-									
ſ		Aceta	azolam	ide	Pl	acebo			Mean Difference	Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
ſ	1.5.1 CSA due to me	dication	or sub	stance						
	Naghan 2020	94.9	29.7	10	150.1	68.7	10	15.1%	-55.20 [-101.59, -8.81]	
	Subtotal (95% CI)			10			10	15.1%	-55.20 [-101.59, -8.81]	
	Heterogeneity: Not ap	plicable								
	Test for overall effect:	Z = 2.33	(P = 0	.02)						
	1.5.2 CSA due to hea	rt failure	9							
	Javaheri 2006	6	13	12	19	32	12	84.9%	-13.00 [-32.54, 6.54]	
	Subtotal (95% CI)			12			12	84.9%	-13.00 [-32.54, 6.54]	-
	Heterogeneity: Not ap	oplicable								
	Test for overall effect:	Z=1.30	(P = 0	.19)						
	Total (95% CI)			22			22	100.0%	-19.36 [-37.37, -1.35]	\bullet
	Heterogeneity: Chi ² =	2.70, df	= 1 (P :	= 0.10);	l² = 639	%				
	Test for overall effect:	Z= 2.11	(P = 0	.04)						Eavours Placebo Eavours Acetazolamide
	Test for subgroup diff	ferences	: Chi ² =	: 2.70, 0	;f=1 (P	= 0.11)), I ² = €	33.0%		

Figure S184. Acetazolamide vs. Placebo (Cardiovascular disease, Systolic BP (mmHg)) [CST= -2 mmHg], RCT

	Acetaz	olam	ide	Pla	cebo)	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.7.1 CSA due to hea	rt failure							
Javaheri 2006	108	13	12	113	15	12	-5.00 [-16.23, 6.23]	
								-20 -10 0 10 20
								Favours Acetazolamide Favours Placebo

Figure S185. Acetazolamide vs. Placebo (Cardiovascular disease, Diastolic BP (mmHg)) [CST= -1 mmHg], RCT

Acetaz	olam	ide	Pla	cebo	0	Mean Difference	Mean Difference	
Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
rt failure								
69	10	12	69	9	12	0.00 [-7.61, 7.61]		_
							-10 -5 0 5	10
							Favours Acetazolamide Favours Placebo	
	Acetaz <u>Mean</u> rt failure 69	Acetazolami Mean SD rt failure 69 10	Acetazolamide Mean SD Total rt failure 69 10 12	Acetazolamide Pla Mean SD Total Mean rt failure 69 10 12 69	Acetazolamide Placebo Mean SD Total Mean SD rt failure 69 10 12 69 9	Acetazolamide Placebo Mean SD Total Mean SD Total rt failure 69 10 12 69 9 12	Acetazolamide Placebo Mean Difference Mean SD Total Mean SD Total IV, Fixed, 95% CI rt failure 69 10 12 69 9 12 0.00 [-7.61, 7.61]	Acetazolamide Placebo Mean Difference Mean Difference Mean SD Total IV, Fixed, 95% Cl IV, Fixed, 95% Cl It failure 0 12 69 9 12 0.00 [-7.61, 7.61] -10 -5 0 5 Favours Acetazolamide Favours Placebo

Figure S186. Acetazolamide vs. Placebo (Cardiovascular disease, HR (beats/min)) [No CST], RCT

	Acetazolamide			Pla	ceb)	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.9.1 CSA due to hea	rt failure							
Javaheri 2006	74	17	12	74	17	12	0.00 [-13.60, 13.60]	
								Favours Acetazolamide Favours Placebo
		_						

Figure S187. Acetazolamide vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% change from baseline], Observational

	Acetazolamide				Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.1.1 Primary CSA									
DeBacker 1995	12.8	10.85	14	37.2	23.1983	14	69.9%	-24.40 [-37.82, -10.98]	
Verbraecken 1998	11	8.49	8	39	28.2843	8	30.1%	-28.00 [-48.46, -7.54]	
Subtotal (95% CI)			22			22	100.0%	-25.48 [-36.70, -14.26]	\bullet
Heterogeneity: Chi ² =	0.08, df	= 1 (P =	0.77);	I ² = 0%					
Test for overall effect:	Z = 4.45	5 (P < 0.)	00001)						
Total (95% CI)			22			22	100.0%	-25.48 [-36.70, -14.26]	\bullet
Heterogeneity: Chi ² =	0.08, df	= 1 (P =	: 0.77);	I ² = 0%				-50 -25 0 25 50	
Test for overall effect:	Z=4.46	5 (P ≤ 0.0	00001)				Favours Acetazolamide Eavours Placebo		
Test for subaroup diff	erences	: Not ap	plicabl	е					

DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=65.6%; Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=71.8%

Figure S188. Acetazolamide vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% change from baseline],

	Ace	tazolamid	e		Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.2.1 Primary CSA									
DeBacker 1995	5.6	10.8508	14	25.5	25.4433	14	65.6%	-19.90 [-34.39, -5.41]	
Verbraecken 1998	4	5.6569	8	26	28.2843	8	34.4%	-22.00 [-41.99, -2.01]	
Subtotal (95% CI)			22			22	100.0%	-20.62 [-32.35, -8.89]	
Heterogeneity: Chi ² =	0.03, df	= 1 (P = 0.	87); I ² =	= 0%					
Test for overall effect:	Z = 3.45	i (P = 0.00	06)						
Total (05% CI)			22			22	100.0%	20 62 [22 25 0 00]	
Total (95% CI)			22			22	100.0%	-20.02 [-32.35, -8.89]	
Heterogeneity: Chi ² =	0.03, df	= 1 (P = 0.	87); l² =	= 0%					-50 -25 0 25 50
Test for overall effect:	Z = 3.45	i (P = 0.00	06)						Eavours Acetazolamide Eavours Baseline
Test for subgroup diffe	erences	: Not appli	cable						Tavouro Acetazolarina en avouro Dasenne

DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=78%; Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD, reduction from baseline=84.6%

Important Outcomes

Figure S189. Acetazolamide vs. Placebo (Fatigue, Subjective Questionnaire) [No CST], RCT

	Acetazolamide		Place	bo	Risk Ratio				
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% Cl		M-H, Fixe	d, 95% Cl	
1.10.1 CSA due to he	art failure								
Javaheri 2006	7	12	2	12	3.50 [0.91, 13.53]				_
						0.01	0.1) 100
							Favours Placebo	Favours Aceta	zolamide
L									

Javaheri 2006: improvement of daytime fatigue on placebo vs acetazolamide, higher number represents an improvement, patients were asked specifically if they felt improved in comparing the first arm versus the second arm of the study

Figure S190. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep efficiency) [CST=10%], RCT

-				10. C						
ſ		Aceta	zolam	ide	C	ontrol			Mean Difference	Mean Difference
L	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	1.12.1 Primary CSA an	id CSA d	lue to r	medica	al condit	tion				
	Ginter 2020	79.1	12.2	16	83.5	10.6	16	82.2%	-4.40 [-12.32, 3.52]	
	Subtotal (95% CI)			16			16	82.2%	-4.40 [-12.32, 3.52]	
	Heterogeneity: Not app	licable								
	Test for overall effect: Z	(= 1.09 ((P = 0.2)	28)						
	1.12.3 CSA due to hea	rt failure	3							
	Javaheri 2014 (ATS)	73	16	6	62	14	6	17.8%	11.00 [-6.01, 28.01]	
	Subtotal (95% CI)			6			6	17.8%	11.00 [-6.01, 28.01]	
	Heterogeneity: Not app	licable								
	Test for overall effect: Z	:= 1.27 ((P = 0.2)	21)						
	Total (95% CI)			22			22	100.0%	-1.66 [-8.84, 5.52]	-
	Heterogeneity: Chi ² = 2	.59, df =	1 (P =	0.11);	l² = 61%	6				
	Test for overall effect: Z	(= 0.45 ((P = 0.6	<u>35)</u>						Favours Placebo Favours Acetazolamide
L	Test for subaroun diffe	rences.	Chi ² = 1	2.59 d	f = 1 (P)	$= 0.11^{\circ}$	$1^{2} = 6^{1}$	1 4 %		

Ginter 2020: patients received oral acetazolamide (ACZ) 500 mg twice a day or placebo twice a day. Crossover RCT with 1 week washout period; Javaheri 2014: patients received three identical capsules that were received orally 1 hour before bedtime for six nights; the three capsules consisted of three placebos or one acetazolamide (3.5 mg/kg) and two potassium chloride capsules (total 30 mEq) to compensate for acetazolamide-induced urinary potassium loss. Crossover studies were performed after a 2-week washout period.

•					-	•	-	•	• •	-		
	Acetaz	olam	ide	Pla	cebo	D	Mean Difference		Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% Cl		
1.13.1 CSA due to hea	art failure											
Javaheri 2014 (ATS)	293	66	6	251	59	6	42.00 [-28.83, 112.83]					
								-200	-100	<u> </u>	100	200
								200	Favours Placebo	Favours Ad	etazolan	nide

Figure S191. Acetazolamide vs. Placebo (Sleep architecture, PSG, Total sleep time) [CST=15 min], RCT

Javaheri 2014: patients received three identical capsules that were received orally 1 hour before bedtime for six nights; the three capsules consisted of three placebos or one acetazolamide (3.5 mg/kg) and two potassium chloride capsules (total 30 mEq) to compensate for acetazolamide-induced urinary potassium loss. Crossover studies were performed after a 2-week washout period.

Figure S192. Acetazolamide vs. Placebo (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], RCT

	Acetazolamide Placebo				icebo)	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.14.1 CSA due to he	art failure	•						
Javaheri 2006	17	6	12	22	18	12	-5.00 [-15.74, 5.74]	
							-	
								Favours Acetazolamide Favours Placebo

Baseline arousal index for acetazolamide group was 30(25).

Figure S193. Acetazolamide vs. Baseline (Sleep architecture, PSG, Sleep efficiency) [CST=10%], Pre- vs post-treatment non-randomized studies

	Acetazolamide			1	Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD.	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.4.1 Primary CSA									
DeBacker 1995	72	14.97	14	69	26.19	14	59.9%	3.00 [-12.80, 18.80]	
Verbraecken 1998	74	11.3137	8	68	25.4558	8	40.1%	6.00 [-13.30, 25.30]	_
Subtotal (95% CI)			22			22	100.0%	4.20 [-8.02, 16.43]	
Heterogeneity: Chi ² =	0.06, df	= 1 (P = 0.	81); P =	= 0%					
Test for overall effect	Z = 0.67	7 (P = 0.50))						
Total (95% CI)			22			22	100.0%	4.20 [-8.02, 16.43]	
Heterogeneity: Chi ² =	0.06, df	= 1 (P = 0.	81); i ř =	= 0%					
Test for overall effect:	Z = 0.67	r (P = 0.50))						-20 -10 U 10 20 Equatra Basalina Equatra Acatazalamida
Test for subgroup dif	ferences	: Not appli	cable						Favours dasenne Favours Acetazolamide

DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S194. Acetazolamide vs. Baseline (Sleep architecture, PSG, Total Sleep Time) [CST=15 min], Prevs post-treatment non-randomized studies

	Ace	etazolamio	le		Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.3.1 Primary CSA									
DeBacker 1995	324	78.5748	14	308	108.5081	14	57.5%	16.00 [-54.18, 86.18]	
Verbraecken 1998	343	67.8823	8	296	96.1665	8	42.5%	47.00 [-34.57, 128.57]	
Subtotal (95% CI)			22			22	100.0%	29.19 [-24.01, 82.38]	
Heterogeneity: Chi ² =	0.32, df	= 1 (P = 0	.57); l² =	= 0%					
Test for overall effect	Z=1.08	8 (P = 0.28)						
Total (95% CI)			22			22	100.0%	29.19 [-24.01, 82.38]	
Heterogeneity: Chi ² =	0.32, df	= 1 (P = 0	.57); l² =	= 0%					
Test for overall effect:	Z=1.08	3 (P = 0.28)						-100 -50 0 50 100
Test for subgroup dif	ferences	: Not anni	, icable						Favours Baseline Favours Acetazoramide

* DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S195. Acetazolamide vs. Baseline (Sleep architecture, PSG, REM (%)) [CST=5% of TST], Pre- vs post-treatment non-randomized studies

	Acetazolamide				Baseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.5.1 Primary CSA									
DeBacker 1995	13	7.4833	14	9	7.4833	14	61.9%	4.00 [-1.54, 9.54]	-
Verbraecken 1998	15	8.4853	8	8	5.6569	8	38.1%	7.00 [-0.07, 14.07]	
Subtotal (95% CI)			22			22	100.0%	5.14 [0.78, 9.50]	
Heterogeneity: Chi ² =	: 0.43, df	'= 1 (P =	0.51); P	²= 0%					
Test for overall effect	: Z = 2.31	1 (P = 0.0	2)						
T () (050) 00								5 4 4 FO 70 0 COL	
Total (95% CI)			22			22	100.0%	5.14 [0.78, 9.50]	
Heterogeneity: Chi ² =	: 0.43, df	'= 1 (P =	0.51); P	²=0%					
Test for overall effect:	: Z = 2.31	1 (P = 0.0	2)						-20 -10 0 10 20 Favours Baseline Favours Acetazolamide
Test for subaroup dif	ferences	s: Not app	olicable						Favours Dasenne Favours Acetazorannue

DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD

Figure S196. Acetazolamide vs. Baseline (Sleep architecture, PSG, Arousals) [CST=25% change from baseline or reduction to ≤12 events/hr], Pre- vs. post-treatment non-randomized studies

	Acetazolamide							Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI			
2.6.1 Primary CSA												
DeBacker 1995	40	18.7083	14	62	41.1582	14	63.1%	-22.00 [-45.68, 1.68]	B			
Verbraecken 1998	41	25.4558	8	54	36.7696	8	36.9%	-13.00 [-43.99, 17.99]				
Subtotal (95% CI)			22			22	100.0%	-18.68 [-37.50, 0.14]				
Heterogeneity: Chi ² =	Heterogeneity: Chi ² = 0.20, df = 1 (P = 0.65); l ² = 0%											
Test for overall effect:	Z = 1.95	5 (P = 0.05)									
Total (95% CI)			22			22	100.0%	-18.68 [-37.50, 0.14]				
Heterogeneity: Chi ² = 0.20, df = 1 (P = 0.65); l ² = 0%												
Test for overall effect:	Z = 1.95	5 (P = 0.05)						Favours Acetazolamide Favours Baseline			
Test for subgroup diff	ferences	: Not appl	icable						avours Acctazorannos - Lavours Daseinte			

DeBacker 1995: Baseline (Night 1) vs 1 month on Acetazolamide (Night 3), 250 mg Acetazolamide, SEM converted to SD Verbraecken 1998: Baseline (Night 1) vs 1 month on Acetazolamide (Night 2), 250 mg Acetazolamide, SEM converted to SD Approximately a 43% reduction from baseline

TPNS

Summary of findings (GRADE)

Table S7 TPNS for adults with CSA

References: Costanzo 2016, Potratz 2021											
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference TPNS vs. baseline or control	No of Participants (studies)								
Excessive sleepiness [ESS]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the TPNS group was 3.7 points lower (5.47 lower to 1.93 lower) compared to control	131 (1 RCT)								
Disease severity [AHI]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the TPNS group was 25 events/hour lower (31.26 lower to 18.74 lower) compared to control	131 (1 RCT)								
Disease severity [CAI]	⊕⊕⊕⊖ MODERATE ^b	The mean difference in the TPNS group was 17.3 events/hour lower (21.94 lower to 12.66 lower) compared to control	131 (1 RCT)								
Disease severity [ODI]	⊕⊕⊖⊖ LOW ^{a,b}	The mean difference in the TPNS group was 16.2 events/hour lower (23.49 lower to 8.91 lower) compared to control	131 (1 RCT)								
Cardiovascular disease [6MWD]	⊕⊖⊖⊖ VERY LOW ^{b,c, d}	The mean difference in the TPNS group was 40.5 meters higher (53.79 lower to 134.78 higher) compared to baseline	24 (1 non-RCT)								

Cardiovascular disease	⊕⊖⊖⊖	The mean difference in the TPNS group was 0.5% lower	24
[LVEF]	VERY LOW ^{b,c,d}	(8.46 lower to 7.46 higher) compared to baseline	(1 non-RCT)
Mortality [reported deaths]	⊕⊕⊖⊖ LOW ^{b,d}	The risk ratio in the TPNS group was 1.07 (0.15 to 7.39) with an absolute risk of 2 more per 1,000 (22 fewer to 164 more) compared to control	151 (1 RCT)

a. Imprecision due to the 95% CI includes possibility for important benefit and no effect

b. Imprecision due to small sample size (<200 participants)

c. Downgraded quality of evidence due to data analyzed using pre- and posttreatment values

d. Imprecision due to the 95% CI includes possibility for important benefit and harm

Critical Outcomes

Figure S197. TPNS vs. Control (Sleepiness during the day, ESS) [CST= -2 points], RCT

	Phrenic Ner	enic Nerve Stimulation			ontro		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	ed, 95% Cl	
Costanzo 2016	-3.6	5.6	58	0.1	4.5	73	-3.70 [-5.47, -1.93]	⊢ -10	-5 Favours PNS	0 5 3 Favours Control	10

Costanzo 2016: change scores

Figure S198. TPNS vs. Control (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], RCT

-		-							
	Phrenic Ne	erve Stimu	lation	Control Mean Difference				Mean E)ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixe	d, 95% Cl
Costanzo 2016	-23.9	18.6	58	1.1	17.6	73	-25.00 [-31.26, -18.74]		0 10 20 Favours Control

Costanzo 2016: change scores

Figure S199. TPNS vs. Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT

	Phrenic Ner	Phrenic Nerve Stimulation			ontrol		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Costanzo 2016	24.7	21	58	40.9	21.3	73	-16.20 [-23.49, -8.91]	

* Costanzo 2016: change from baseline

Figure S200. TPNS vs. Control (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], RCT

	Phrenic Ner	ve Stimu	lation	C	ontrol		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI		
Costanzo 2016	6	9.2	58	23.3	17.4	73	-17.30 [-21.94, -12.66]	-20 -10 Favours PNS	0 10 20 Favours Control		

* Costanzo 2016: change from baseline

Figure S201. TPNS vs. Baseline (Cardiovascular disease, LVEF (%)) [CST= +5%], single-arm pre- and post-treatment

	Phrenic Ne	Phrenic Nerve Stimulation			seline)	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Potratz 2021	41.9	14.7	24	42.4	13.4	24	-0.50 [-8.46, 7.46]	
								-20 -10 0 10 20
								Favours Baseline Favours PNS

Figure S202. TPNS vs. Baseline (Cardiovascular disease, 6MWD) [CST=+ 32 meters], single-arm pre- and post-treatment

	Phrenic Ne	B	aseline		Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Potratz 2021	410	169.7	24	369.5	163.5	24	40.50 [-53.78, 134.78]	

Figure S203. TPNS vs. Control (Mortality, Number of deaths) [CST= risk ratio of 0.8], RCT

	Phrenic Nerve Stimul	Cont	rol	Risk Ratio		Risk	Ratio		
Study or Subgroup	Events	Events	Total	M-H, Fixed, 95% Cl		M-H, Fixe	ed, 95% CI		
Costanzo 2016	2	73	2	78	1.07 [0.15, 7.39]	L 0.01	0.1 Favours PNS	10 Favours Control	100

Figure S204. TPNS vs. Baseline (Disease Severity, AHI) [CST= ≥ 50% reduction from baseline], singlearm pre- and post-treatment, observational studies



Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S205. TPNS vs. Baseline (Disease Severity, CAI) [CST= ≥ 50% reduction from baseline], singlearm pre- and post-treatment, observational studies

	Phrenic Ner	Phrenic Nerve Stimulation						Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Abraham 2015	4.5	7.2	44	28.1	14.7	44	40.2%	-23.60 [-28.44, -18.76]	
Ponikowski 2011	2.1	4.1	16	25.2	22	16	26.4%	-23.10 [-34.07, -12.13]	
Potratz 2021	7.2	10	24	18	16.8	24	33.4%	-10.80 [-18.62, -2.98]	
Total (95% CI)			84			84	100.0%	-19.19 [-27.82, -10.57]	◆
Heterogeneity: Tau ² = Test for overall effect:	42.03; Chi² = 7 Z = 4.36 (P ≤ 0	7.70, df = 2 (.0001)	(P = 0.0	12); I² = 1	74%				-20 -10 0 10 20 Favours PNS Favours Baseline

Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S206. TPNS vs. Baseline (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], singlearm pre- and post-treatment, observational studies

	Phrenic Ne	erve Stimul	ation	Ba	seline			Mean Difference		Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
Abraham 2015	22.9	13.3	44	46	18.8	44	55.7%	-23.10 [-29.90, -16.30]				
Ponikowski 2011	13.6	10.6	16	29.6	11.4	16	44.3%	-16.00 [-23.63, -8.37]				
Total (95% CI)			60			60	100.0%	-19.95 [-25.03, -14.88]		•		
Heterogeneity: Chi ² = Test for overall effect:	1.85, df = 1 (F Z = 7.70 (P ≺	e = 0.17); l² 0.00001)	= 46%						-50	-25 Favours PNS) 25 Favours Baseline	50 9

Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S207. TPNS vs. Baseline (Disease Severity, Percentage of sleep with oxygen saturation <90%) [CST= ≥ 50% reduction from baseline], single-arm pre- and post-treatment, observational studies

	Phrenic Ne	Phrenic Nerve Stimulation			seline)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Costanzo 2018 (Am J Cardiol)	11.5	16.1	58	16.5	17.9	58	51.5%	-5.00 [-11.20, 1.20]	
Potratz 2021	8.1	9.8	24	19.5	12.6	24	48.5%	-11.40 [-17.79, -5.01]	
Total (95% CI)			82			82	100.0%	-8.10 [-12.55, -3.66]	◆
Heterogeneity: Chi ² = 1.99, df = 1	$(P = 0.16); I^2$	= 50%							-20 -10 0 10 20
Test for overall effect: Z = 3.57 (P	= 0.0004)								Favours PNS Favours Baseline

Figure S208. TPNS vs. Baseline (Cardiovascular disease, HR (beats/min)) [No CST], single-arm pre- and post-treatment

	Phrenic Nerve Stimulation			Bas	selin	е	Mean Difference		Mean Di	ifference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI	
Ponikowski 2011	69.6	20.3	16	72.1	22	16	-2.50 [-17.17, 12.17]	⊢ -100	-50 Favours PNS	0 50 Favours Baseline	100 e

*Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S209. TPNS vs. Baseline (Cardiovascular disease, BNP, pg/mL) [CST= 50% reduction], single-arm pre- and post-treatment

	Phrenic Nerve Stimulation Baseline				Baseline		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% Cl	
Potratz 2021	835.4	2,045.3	24	630.4	1,682.8	24	205.00 [-854.64, 1264.64]	-1000	-500 Favours PNS	0 500 Favours Baseli	1000 ne

BNP pg/ml

Figure S210. TPNS vs. Baseline (Fatigue, FSS) [CST= - 0.5 point], observational studies

	Phrenic Nerv	ve Stimula	ation	Ba	selin	е	Mean Difference		Mean Dif	ference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	, 95% CI	
11.5.1 IC \$D3											
Javaheri 2020	3.1	1.7	12	4.1	1.2	14	-1.00 [-2.15, 0.15]			-	
								-4	-2	1 2	4
								·	Favours PNS	Favours B	aseline

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Important Outcomes

Figure S211. TPNS vs. Control (Quality of Life, Patient Global Assessment) [No CST], RCT

	Phrenic Nerve Stimu	lation	Contr	ol	Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Costanzo 2018 (Am J Cardiol)	46	58	10	73	5.79 [3.21, 10.45]	0.01 0.1 1 10 100 Favours Control Favours PNS

6-month data for percentage of patient showing mild or marked/moderate improvement, data from figure 6

Figure S212. TPNS vs. Control (Sleep architecture, PSG, REM%) [CST=+5% of TST], RCT

	Phrenic Ner	ve Stimula	tion	Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Costanzo 2016	12.6	8.7	58	11.2	7.4	73	1.40 [-1.41, 4.21]	· · · · · · · · · · · · · · · · · · ·
								-10 -5 0 5 10
								Favours Control Favours PNS

Figure S213. TPNS vs. Control (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCT

	Phrenic Ne	Phrenic Nerve Stimulation			ontrol		Mean Difference		fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	I, 95% CI	
Costanzo 2016	25.4	14.3	58	38.9	19.5	73	-13.50 [-19.29, -7.71]		_ +		
								-50	-25 () 25	50
									Favours PNS	Favours Control	

Baseline arousal index for TPNS was 45.6 (18.9)

Figure S214. TPNS vs. Baseline (Quality of Life, SF-12) [CST= + 4 points], Observational study

	Phrenic Ne	rve Stimul	ation	Ba	seline	•	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
11.8.1 IC \$D3								
Javaheri 2020	46.5	19.8	14	46.5	19.8	14	0.00 [-14.67, 14.67]	
								-20 -10 Ó 10 20
								Favours Baseline Favours PNS
lavahari 2020 6 may	ath data m	adian and	lintor		. rong		warted to CD	

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Figure S215. TPNS vs. Baseline (Quality of Life, EQ-5D) [No CST], Observational study

	Phrenic Ne	ve Stimula	ation	Ba	selin	е	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
11.9.1 IC \$D3								
Javaheri 2020	78.2	20.6	14	84.3	8.2	14	-6.10 [-17.71, 5.51]	
								· · · · · · · · · · · · · · · · · · ·
								-20 -10 0 10 20
								Favours Baseline Favours PNS

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD

Figure S216. TPNS vs. Baseline (Total Sleep Time, PSG) [CST=+15 min], single-arm pre- and post-treatment, observational studies

	Phrenic Ne	Phrenic Nerve Stimulation			seline	ŧ	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Ponikowski 2011	254.4	63.4	16	241.1	58.5	16	13.30 [-28.97, 55.57]	-100 -50 0 50 100 Favours Baseline Favours PNS

Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S217. TPNS vs. Baseline (Sleep architecture, PSG, Sleep Efficiency) [CST=+15 min], single-arm pre- and post-treatment, observational studies

	Phrenic Ne	Phrenic Nerve Stimulation			seline	•	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Abraham 2015	81.4	12.5	44	69.3	16.8	44	12.10 [5.91, 18.29]	-20 -10 0 10 20 Favours Baseline Favours PNS

Figure S218. TPNS vs. Baseline (Sleep architecture, PSG, REM%) [CST=+5% of TST], single-arm pre- and post-treatment, observational studies

	Phrenic Ner	ve Stimula	tion	B	aseline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Abraham 2015	17.4	6.9	44	11.2	6.3	44	62.0%	6.20 [3.44, 8.96]	
Javaheri 2020	16.7	6.6	14	14.6	7.4	14	17.5%	2.10 [-3.09, 7.29]	-
Ponikowski 2011	16.6	9.8	16	17	0.0001	16	20.5%	-0.40 [-5.20, 4.40]	
Total (95% CI)			74			74	100.0%	4.13 [1.96, 6.30]	◆
Heterogeneity: Chi ² =	6.17, df = 2 (P =	= 0.05); l ² =	= 68%					-	
Test for overall effect:	Z = 3.72 (P = 0	.0002)							Favours Baseline Favours PNS

Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S219. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N1%) [CST=-5% of TST], single-arm pre- and post-treatment, observational studies

	Phrenic Ne	rve Stimula	tion	Ba	seline	•		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Javaheri 2020	20.3	13.2	14	27.2	18.9	14	54.8%	-6.90 [-18.98, 5.18]	
Ponikowski 2011	18.8	17.1	16	22.3	21.1	16	45.2%	-3.50 [-16.81, 9.81]	
Total (95% CI)			30			30	100.0%	-5.36 [-14.31, 3.58]	
Heterogeneity: Chi ² =	0.14, df = 1 (P	= 0.71); l ² =	= 0%						
Test for overall effect:	Z = 1.18 (P = 1	0.24)							Favours PNS Favours Baseline

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S220. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N2%) [CST=-5% of TST], single-arm pre- and post-treatment, observational studies

	Phrenic Ne	rve Stimul	ation	Ba	seline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Javaheri 2020	56.9	14.8	14	50.5	4.9	14	79.7%	6.40 [-1.77, 14.57]	
Ponikowski 2011	55.2	26	16	51.4	20.3	16	20.3%	3.80 [-12.36, 19.96]	
Total (95% CI)			30			30	100.0%	5.87 [-1.42, 13.16]	
Heterogeneity: Chi ² = Test for overall effect:	0.08, df = 1 (P Z = 1.58 (P = 1	= 0.78); I² 0.11)	= 0%						-20 -10 0 10 20 Favours PNS Favours Baseline

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S221. TPNS vs. Baseline (Sleep architecture, PSG, Sleep stage N3%) [CST=+5% of TST], singlearm pre- and post-treatment, observational studies

	Phrenic Ne	rve Stimula	ation	Ba	selin	е		Mean Difference	Mean Difference
Study or Subgroup	Study or Subgroup Mean SD Tota				SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Javaheri 2020	7.9	9.1	14	5	6.6	14	59.1%	2.90 [-2.99, 8.79]	
Ponikowski 2011	4.7	10.6	16	5.2	9.8	16	40.9%	-0.50 [-7.57, 6.57]	
Total (95% CI)			30			30	100.0%	1.51 [-3.02, 6.03]	-
Heterogeneity: Chi ² = 0 Test for overall effect: 2	D.52, df = 1 (P Z = 0.65 (P = 1	2 = 0.47); I 2 : 0.51)	= 0%						-20 -10 0 10 20 Favours Baseline Favours PNS

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD; Ponikowski 2011: median and inter-quartile range converted to mean and SD

Figure S222. TPNS vs. Baseline (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], single-arm pre- and post-treatment, observational studies

Phrenic Ne	rve Stimul	ation	Ba	seline	•		Mean Difference	Mean Difference		
Study or Subgroup Mean SD Tota						Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI		
24.7	12.3	44	35.5	18.4	44	75.0%	-10.80 [-17.34, -4.26]			
16.3	14.6	16	31.3	17.9	16	25.0%	-15.00 [-26.32, -3.68]			
		60			60	100.0%	-11.85 [-17.51, -6.19]	◆		
0.40, df = 1 (P	= 0.53); l²	= 0%								
Test for overall effect: Z = 4.10 (P < 0.0001) -20 -10 0 10 20 Favours PNS Favours Baseline										
	Phrenic Ne Mean 24.7 16.3 0.40, df = 1 (P Z = 4.10 (P < 1	Phrenic Nerve Stimul Mean SD 24.7 12.3 16.3 14.6 0.40, df = 1 (P = 0.53); I ² 24.10 (P < 0.0001)	Phrenic Nerve Stimulation Mean SD Total 24.7 12.3 44 16.3 14.6 16 60 0.40, df=1 (P=0.53); IP=0% 24.10 (P < 0.0001)	Phrenic Nerve Stimulation Ba Mean SD Total Mean 24.7 12.3 44 35.5 16.3 14.6 16 31.3 60 0.40, df = 1 (P = 0.53); I ² = 0% Z = 4.10 (P < 0.0001)	Phrenic Nerve Stimulation Baseline Mean SD Total Mean SD 24.7 12.3 44 35.5 18.4 16.3 14.6 16 31.3 17.9 60 0.40, df = 1 (P = 0.53); IP = 0% 24.10 (P < 0.0001)	Phrenic Nerve Stimulation Baseline Mean SD Total Mean SD Total 24.7 12.3 44 35.5 18.4 44 16.3 14.6 16 31.3 17.9 16 60 60 60 60 24.0 24.10 (P = 0.53); IP = 0% 24.10 (P < 0.0001)	Phrenic Nerve Stimulation Baseline Mean SD Total Mean SD Total Weight 24.7 12.3 44 35.5 18.4 44 75.0% 16.3 14.6 16 31.3 17.9 16 25.0% 60 60 60 100.0% 24.10 (P < 0.53); I ² = 0% 24.10 (P < 0.0001) 24.10 (P < 0.0001)	Phrenic Nerve Stimulation Baseline Mean Difference Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI 24.7 12.3 44 35.5 18.4 44 75.0% -10.80 [-17.34, -4.26] 16.3 14.6 16 31.3 17.9 16 25.0% -15.00 [-26.32, -3.68] 60 60 100.0% -11.85 [-17.51, -6.19] -1.40, df = 1 (P = 0.53); I ² = 0% -24.10 (P < 0.0001)		

Javaheri 2020, 6-month data, median and inter-quartile range converted to SD, reduction from baseline=50.8%; Ponikowski 2011: median and inter-quartile range converted to mean and SD

PICO 2: Adults with CSA due to high altitude

Low-flow oxygen

Summary of findings table (GRADE)

Table S8. Low-flow oxygen for adults with CSA due to high altitude

References: Heinrich 2019, Or	r 2018			
Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Low-flow oxygen vs. control	No of Participants (studies)	
Excessive sleepiness [SSS]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the low-flow oxygen group was 0.6 points lower (0.94 lower to 0.26 lower) compared to control	14 (1 RCT)	
Disease severity [ODI]	€⊕⊖⊖ LOM₽	The mean difference in the low-flow oxygen group was 14.7 events/hour lower (23.72 lower to 5.68 lower) compared to control	14 (1 RCT)	
Daytime functioning* [AMS]	⊕⊕⊖⊖ Low⁵	The mean difference in the low-flow oxygen group was 1 point lower (2.27 lower to 0.27 higher) compared to control	14 (1 RCT)	
Quality of life* [POMS-A confusion]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the low-flow oxygen group was 1.1 points lower (1.91 lower to 0.29 lower) compared to control	17 (1 RCT)	
Quality of life* [POMS-A fatigue]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the low-flow oxygen group was 3.2 Iower (6.28 lower to 0.12 lower) compared to control	17 (1 RCT)	

a. Risk of bias due to lack of blinding of patients

b. Imprecision due to small sample size (<200 participants)

* No CST

Critical Outcomes

Figure S223. Oxygen vs. Control (Excessive sleepiness, SSS) [CST=-1 points], RCT



Orr 2018: SEM converted to SD, single night per arm

Figure S2	24. Oxygen vs	. Control (Diseas	e Severity, OD	I) [CST= ≥ 50%	6 reduction from	baseline], RCT

	0)	cyger	1	С	ontrol		Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
1.2.1 IC \$D3									
Orr 2018	0.5	0.7	14	15.2	17.2	14	-14.70 [-23.72, -5.68]	i	
								-20 -10 0 10 20 Favours Oxygen Favours Control	

Orr 2018: SEM converted to SD, single night per arm

Figure S225. Oxygen vs. Control (Daytime Functioning, AMS) [No CST], RCT

	0)	cyger	I	Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Orr 2018	1.4	1.5	14	2.4	1.9	14	-1.00 [-2.27, 0.27]	-4 -2 0 2 4 Favours Oxygen Favours Control

Orr 2018: SEM converted to SD, single night per arm

Figure S226. Oxygen vs. Control (Quality of Life, POMS-A (Confusion Score) [No CST], RCT

	0	xygen		Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Heinrich 2019	1	0.03	17	2.1	1.7	17	-1.10 [-1.91, -0.29]	
								-4 -2 0 2 4 Favours Oxygen Favours Control

Heinrich 2019: data extracted from graph; CI interval converted to SD

Figure S227. Oxygen vs. Control (Quality of Life, POMS-A (Fatigue Score) [No CST], RCT

	Ox	yger	I	Co	ontro		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
Heinrich 2019	2.6	2.9	17	5.8	5.8	17	-3.20 [-6.28, -0.12]			
								-10	-5 0 5	10
									Favours Oxygen Favours Control	

Heinrich 2019: data extracted from graph; CI interval converted to SD

Important Outcomes

Figure S228. Oxygen vs. Control (Sleep architecture, PSG, Arousal Index) [CST=25% reduction from baseline or reduction to ≤12 events/hr], RCT



Orr 2018: SEM converted to SD, single night per arm

Figure S229. Oxygen vs. Control (Sleep architecture, PSG, Sleep stage N1%,) [CST= +5% of TST], RCT

	C)xygen		(Control		Mean Difference	Mean Difference			
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	i, 95% Cl	
Orr 2018	6.2	2.245	14	9.8	4.1158	14	-3.60 [-6.06, -1.14]	H			
								-10	Favours Oxygen	Favours Control	10

Orr 2018: SEM converted to SD, single night per arm

Acetazolamide

Summary of Findings (GRADE)

Table S9 Acetazolamide in adults with CSA due to high altitude

Outcomes [Tool] Certainty of the evidence (GRADE) Absolute Difference No of Participan (studies) Disease severity [AHI] $\bigoplus \bigoplus \bigcirc \bigcirc$ Low ^a The mean difference in the acetazolamide group was Low ^a 20 21 events/hour lower (34.68 lower to 7.32 lower) compared to control 20 (1 RCT) Disease severity [Desaturation index] $\bigoplus \bigoplus \bigcirc \bigcirc$ Low ^a The mean difference in the acetazolamide group was 20 21 events/hour lower (45.19 lower to 15.41 lower) compared to control 20 (1 RCT) Disease severity [Desaturation index] $\bigoplus \bigoplus \bigcirc \bigcirc$ Low ^a The mean difference in the acetazolamide group was 20 30.3 events/hour lower (45.19 lower to 15.41 lower) compared to control 20 (1 RCT) Disease severity [% time with periodic $\bigoplus \bigcirc \bigcirc \bigcirc$ VERY LOW ^{a,b,c} The mean difference in the acetazolamide group was 23.7 percent lower (49.55 lower to 2.15 higher) compared to control 4	References: Hackett 1987, Fis	her 2004			
Disease severity Image: Disease severity	Outcomes [Tool]	Certainty of the evidence (GRADE)	Absolute Difference Acetazolamide vs. control	No of Participants (studies)	
Disease severity (Desaturation index] (Desaturation index] The mean difference in the acetazolamide group was 30.3 events/hour lower (45.19 lower to 15.41 lower) (1 RCT) 20 (1 RCT) Disease severity (D) (D)	Disease severity [AHI]	rom _a	The mean difference in the acetazolamide group was 21 events/hour lower (34.68 lower to 7.32 lower) compared to control	20 (1 RCT)	
Disease severity OO The mean difference in the acetazolamide group was 23.7 4 [% time with periodic VERY LOW ^{3,b,c} Percent lower (49.55 lower to 2.15 higher) compared to 4 [seathing] (1 RCT)	Disease severity [Desaturation index]	LOM ₃ ⊕⊕⊖⊖	The mean difference in the acetazolamide group was 30.3 events/hour lower (45.19 lower to 15.41 lower) compared to control	20 (1 RCT)	
0.00000	Disease severity [% time with periodic breathing]	⊕○○○ VERY LOW ^{a,b,c}	The mean difference in the acetazolamide group was 23.7 percent lower (49.55 lower to 2.15 higher) compared to control	4 (1 RCT)	
Disease severity [oxygen saturation <70%] VERY LOW ^{3,b} The mean difference in the acetazolamide group was 11.82 percent lower (17.73 lower to 5.91 lower) compared to control 4 (1 RCT)	Disease severity [oxygen saturation <70%]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the acetazolamide group was 11.82 percent lower (17.73 lower to 5.91 lower) compared to control	4 (1 RCT)	

a. Imprecision due to small sample size (<200 participants)

b. Indirectness in the measurement of the outcome

c. Imprecision due to the 95% CI includes possibility for important benefit and no effect

Critical Outcomes

Figure S230. Acetazolamide vs. Control (Disease Severity, AHI) [CST= ≥ 50% change from baseline], RCT

				-					-				
Aceta	zolam	ide	Co	ontro	I	Mean Difference	Mean Difference						
Mean	SD	Total	Mean	SD	Total	I IV, Fixed, 95% CI IV, Fixed, 95% CI							
2	1.8	10	23	22	10	-21.00 [-34.68, -7.32]	—— — —						
-50 -25 U 25 50													
						Favours Acetazolamide Favours Control							
	Aceta: Mean 2	Acetazolam Mean SD 2 1.8	Acetazolamide Mean SD Total 2 1.8 10	Acetazolamide Co Mean SD Total Mean 2 1.8 10 23	Acetazolamide Contro Mean SD Total Mean SD 2 1.8 10 23 22	AcetazolamideControlMeanSDTotalMeanSDTotal21.810232210	AcetazolamideControlMean DifferenceMeanSDTotalMeanSDTotal21.810232210-21.00 [-34.68, -7.32]	Acetazolamide Control Mean Difference Mean Difference Mean SD Total NV, Fixed, 95% CI IV, Fixed 2 1.8 10 23 22 10 -21.00 [-34.68, -7.32]	Acetazolamide Control Mean Difference Mean Difference Mean SD Total Moan SD Total IV, Fixed, 95% CI 2 1.8 10 23 22 10 -21.00 [-34.68, -7.32] -50 -25 0 25 Favours Acetazolamide Favours Control				

Fischer 2004: median and range converted to mean and SD, Night 2 data used.

Figure S231. Acetazolamide vs. Control (Disease Severity, Desaturation Index) [CST= ≥ 50% change from baseline], RCT

	Acetaz	zolam	ide	Co	ntro	I	Mean Difference	Mean Di	fference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI		
Fischer 2004	5.5	1.2	10	35.8	24	10	-30.30 [-45.19, -15.41]	· · · ·			
								-50 -25 0 25 50 Favours Acetazolamide Favours Control			

Fischer 2004: median and range converted to mean and SD, Night 2 data used.

Figure S232. Acetazolamide vs. Control (Disease Severity, % time with periodic breathing) [CST= ≥ 50% change from baseline], RCT

	Aceta	zolam	ide	C	ontrol		Mean Difference		м	ean Differenc	е	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV	, Fixed, 95% C	1	
Hackett 1987	17.2	8.7	4	40.9	24.9	4	-23.70 [-49.55, 2.15]					
								-100	-50	0	50	100
								Favo	urs Acetazola	amide Favou	s Control	

Hackett 1987: data extracted from graph

Figure S233. Acetazolamide vs. Control (Disease Severity, oxygen saturation < 70%) [CST= ≥ 50% change from baseline], RCT

	Aceta	zolam	ide	Co	ontro	1	Mean Difference	Mean Difference	e
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% C	1
Hackett 1987	1.08	0.65	4	12.9	6	4	-11.82 [-17.73, -5.91] -	-20 -10 0 Favours Acetazolamide Favou	10 20 rs Control

Hackett 1987: data extracted from graph

Important Outcomes

Figure S234. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep efficiency) [CST= + 10%], RCT

	Aceta	zolam	ide	Co	ontro		Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Fischer 2004	81	4.1	10	92.7	2.1	10	-11.70 [-14.56, -8.84]					
								-20	-10	0	10	20
									Favours Control	Favours A	cetazola	mide

Fischer 2004: Night 1 data

Figure S235. Acetazolamide vs. Control (Sleep architecture, PSG, Arousal Index) [CST= - 25% change from baseline or reduction to ≤12 events/hr], RCT

	Acetaz	zolam	ide	Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fischer 2004	10.3	4	10	20.3	15	10	-10.00 [-19.62, -0.38]	-20 -10 0 10 20 Favours Acetazolamide Favours Control

Fischer 2004: Night 2 data

Figure S236. Acetazolamide vs. Control (Sleep architecture, PSG, REM %,) [CST= + 5% of TST], RCT

0					•			•		••
	Aceta	zolam	ide	Co	ntrol		Mean Difference		Mean Di	ifference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed	d, 95% CI
Fischer 2004	14.8	5.4	10	11.1	5	10	3.70 [-0.86, 8.26]			
								-10	-5	
									Favours Control	Favours Acetazolamide

Fischer 2004: Night 1 data

Figure S237. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N1%) [CST= - 5% of TST], RCT

	Aceta	zolam	ide	Co	ontro	I	Mean Difference	Mean Di	fference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed	l, 95% Cl	
Fischer 2004	5.6	2.6	10	13.8	7.3	10	-8.20 [-13.00, -3.40]			20
								Favours Acetazolamide	Favours Control	20

Fischer 2004: Night 1 data

Figure S238. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N2%) [CST= - 5% of TST], RCT

	Aceta	zolam	ide	Co	ontrol	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Fischer 2004	54.3	5.5	10	54.1	7.7	10	0.20 [-5.66, 6.06]	· · · · · · · · · · · · · · · · · · ·
								-10 -5 0 5 10
								Favours Acetazolamide Favours Control

Fischer 2004: Night 1 data

Figure S239. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N3%) [CST= + 5%], RCT

	Aceta	zolam	ide	Co	ontro	l i	Mean Difference		Mean D	ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% CI		
Fischer 2004	6.8	3.5	10	6.3	2.4	10	0.50 [-2.13, 3.13]			+		
								-10	-5	0	5	10
									Favours Control	Favours Ac	etazolamid	е

Fischer 2004: Night 1 data

Figure S240. Acetazolamide vs. Control (Sleep architecture, PSG, Sleep stage N4%) [No CST], RCT

	Aceta	zolam	ide	Co	ontro		Mean Difference		N	lean Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		P	V, Fixed, 95% C	1	
Fischer 2004	16.6	5.1	10	12.7	8.5	10	3.90 [-2.24, 10.04]					
								-20	-10	Ó	10	20
									Favours C	Control Favou	rs Acetazolan	nide

Fischer 2004: Night 1 data

ASV

Summary of Findings (GRADE)

Table S10 ASV for adults with CSA due to high altitude

References: Heinrich 2019, Or	r 2018		
Outcomes	Certainty of the	Absolute Difference	No of Participants
[Tool]	evidence		(studies)
	(GRADE)	ASV vs. control	
Excessive sleepiness [SSS]	⊕○○○ VERY LOW ^{a,b,c}	The mean difference in the ASV group was 0.2 points lower (1.01 lower to 0.61 higher) compared to control	14 (1 RCT)
Disease severity [ODI]	⊕○○○ VERY LOW ^{a,b}	The mean difference in the ASV group was 6.9 events/hour lower (16.73 lower to 2.93 higher) compared to control	14 (1 RCT)
Daytime functioning*	⊕⊕⊖⊖	The mean difference in the ASV group was 0.3 points lower (1.45 lower to 0.85 higher) compared to control	14
[AMS]	LOWª		(1 RCT)
Quality of life*	OOO	The mean difference in the ASV group was 0.6 points lower (1.47 lower to 0.27 higher) compared to control	17
[POMS-A confusion]	VERY LOW ^{a,c}		(1 RCT)
Quality of life*	⊕○○○	The mean difference in the ASV group was 1 point lower	17
[POMS-A fatigue]	VERY LOW ^{a,c}	(4.73 lower to 2.73 higher) compared to control	(1 RCT)

a. Imprecision due to small sample size (<200 participants)

b. Imprecision due to the 95% CI includes possibility for important benefit and no effect

c. Risk of bias due to lack of blinding of the participants

* No CST

Critical Outcomes

Figure S241. ASV vs. Control (Excessive sleepiness, SSS) [CST= -1 points], RCT

	4	\SV		Co	ontro	I	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Orr 2018	3.2	1.5	14	3.4	0.4	14	-0.20 [-1.01, 0.61]	· · · · · ·
								-2 -1 0 1 2
								Favours ASV Favours Control

Orr 2018: SEM converted to SD, single night per arm

Figure S242. ASV vs. Control (Disease Severity, ODI) [CST= ≥ 50% reduction from baseline], RCT

A	SV		C	ontrol		Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
8.3	7.5	14	15.2	17.2	14	-6.90 [-16.73, 2.93]	
						-	
							Favours ASV Favours Control
	A Mean 8.3	ASV Mean SD 8.3 7.5	ASV Mean SD Total 8.3 7.5 14	ASV Co Mean <u>SD Total Mean</u> 8.3 7.5 14 15.2	ASV Control Mean SD Total Mean SD 8.3 7.5 14 15.2 17.2	ASV Control Mean SD Total Mean SD Total 8.3 7.5 14 15.2 17.2 14	ASV Control Mean Difference Mean SD Total IV, Fixed, 95% Cl 8.3 7.5 14 15.2 17.2 14 -6.90 [-16.73, 2.93]

Orr 2018: SEM converted to SD, single night per arm

Figure S243. ASV vs. Control (Daytime Functioning, AMS) [No CST], RCT

	1	ASV		Co	ontro		Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Orr 2018	2.1	1.1	14	2.4	1.9	14	-0.30 [-1.45, 0.85]	-4	-2 0 2 4 Favours ASV Favours Control

Orr 2018: SEM converted to SD, single night per arm

Figure S244. ASV vs. Control (Quality of Life, POMS-A (Confusion Score)) [No CST], RCT

	1	۱SV		Co	ontro		Mean Difference		Mean D)ifference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV, Fixe	d, 95% Cl		
Heinrich 2019	1.5	0.7	17	2.1	1.7	17	-0.60 [-1.47, 0.27]	-4	-2 Favours ASV	0 / Favours	l 2 Control	4

Heinrich 2019: data extracted from graph; Cl interval converted to SD

Figure S245. ASV vs. Control (Quality of Life, POMS-A (Fatigue Score)) [No CST], RCT

	4	sv		Co	ontro		Mean Difference		Me	an Differenc	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI		IV,	Fixed, 95% 0		
Heinrich 2019	4.8	5.3	17	5.8	5.8	17	-1.00 [-4.73, 2.73]					
								-10	-5	Ó	5	10
									Favours	ASV Favou	rs Control	

Heinrich 2019: data extracted from graph; CI interval converted to SD

Important Outcomes

Figure S246. ASV vs. Control (Sleep architecture, PSG, Arousal Index, PSG) [CST= ≥25% reduction from baseline or reduction to ≤12 events/hr], RCT

	A	SV		Co	ontro	l	Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
2.6.1 IC \$D3								
Orr 2018	12.3	6.4	14	11.6	3.7	14	0.70 [-3.17, 4.57]	· · · · · · · · · · · · · · · · · · ·
								Favours ASV Favours Control

Orr 2018: SEM converted to SD, single night per arm

Figure S247. ASV vs. Control (Sleep architecture, PSG, Sleep stage N1%,) [CST = +5 TST], RCT

	A	SV		Co	ontro		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	I IV, Fixed, 95% CI
Orr 2018	10.2	6	14	9.8	4.1	14	0.40 [-3.41, 4.21]	
								Favours ASV Favours Control

Orr 2018: SEM converted to SD, single night per arm

Short Citation	Intervention(s)	Diagnostic Criteria
Abraham 2015	TPNS	ICSD
Andreas 1996	Oxygen	non-ICSD
Arzt 2005	CPAP, Oxygen	ICSD
Arzt 2007	СРАР	non-ICSD
Arzt 2008	ASV, BPAP with backup rate, CPAP	ICSD
Arzt 2009	СРАР	non-ICSD
Arzt 2013	ASV	non-ICSD
Bradley 2005	СРАР	ICSD
Bradley 2023	ASV	ICSD
Brill 2014	ASV	non-ICSD
Broström 2005	Oxygen	ICSD
Campbell 2012	ASV, Oxygen	ICSD
Cao 2014	ASV, BPAP with backup rate	non- ICSD
Carnevale 2011	ASV	ICSD
Correia 2015	ASV	non-ICSD
Costanzo 2016	TPNS	ICSD
Cowie 2015	ASV	ICSD
Daubert 2018	ASV	non-ICSD
DeBacker 1995	Acetazolamide	ICSD
D'Elia 2013	ASV	ICSD
Dellweg 2013	ASV, BPAP with backup rate	ICSD
Dohi 2008	BPAP with backup rate, CPAP	non-ICSD
Fietze 2008	ASV, BPAP with backup rate	ICSD
Fischer 2004	High altitude Acetazolamide	ICSD
Franklin 1997	Oxygen	ICSD
Ginter 2020	Acetazolamide	non-ICSD
Gorbachevski 2020	ASV, CPAP	ICSD
Granton 1996	СРАР	ICSD
Hackett 1987	High altitude Acetazolamide	ICSD
Hanly 1989	Oxygen	non-ICSD

Table S11. List of studies using ICSD* vs. non-ICSD** diagnostic criteria

Hastings 2010	ASV	non-ICSD
Heider 2018	ASV	ICSD
Heinrich 2019	High altitude ASV, High altitude Oxygen	ICSD
Hetland 2017	ASV	ICSD
Hetzenecker 2016	ASV. CPAP	ICSD
Hetzenecker 2016 (Sleep Med)	ASV	ICSD
Hu 2006	BPAP with backup rate, CPAP, Oxygen	non-ICSD
Iliou 2018	ASV	ICSD
Jaffuel 2019	ASV	ICSD
Javaheri 1999	Oxygen	ICSD
Javaheri 2006	Acetazolamide	ICSD
Javaheri 2011	ASV	non-ICSD
Javaheri 2014 (JCSM)	ASV	ICSD
Javaheri 2014	Acetazolamide	ICSD
Javaheri 2015	ASV	
Javaheri 2020	TPNS	
Karavidas 2011		
Karavidas 2011	RPAR with backup rate	
Kasal 2003		
Kasai 2010		
Kasal 2013	ASV, CPAP	ICSD
Konnielin 2002		ICSD
Koyama 2013	ASV	ICSD
Krachman 1999	Uxygen	ICSD
Krachman 2005	Oxygen	ICSD
Miyata 2012	ASV	ICSD
Morgenthaler 2007	ASV, BPAP with backup rate	ICSD
Morgenthaler 2014	ASV, CPAP	ICSD
Naghan 2020	Acetazolamide	non-ICSD
Nakao 2014	Oxygen	ICSD
Naughton 1994	СРАР	ICSD
Naughton 1995	СРАР	ICSD
Naughton 1995 (Am J Respir Crit Care Med)	СРАР	ICSD
Noda 2007	ВРАР	ICSD
O'Connor 2017	ASV	non-ICSD
Oldenburg 2015	ASV	ICSD
Oldenburg 2018	ASV	ICSD
Orr 2018	High altitude ASV, High altitude Oxygen	ICSD
Pepperell 2003	ASV	ICSD
Philippe 2006	ASV, CPAP	non-ICSD
Ponikowski 2012	TPNS	ICSD
Potratz 2021	TPNS	ICSD
Ramar 2012	ASV	ICSD
Randerath 2012	ASV, CPAP	ICSD
Randerath 2009	ASV	non-ICSD
Roder 2020	ASV	ICSD
Ruttanaumpawan 2009	СРАР	ICSD
Sakakibara 2005	Oxygen	non-ICSD
Sasayama 2006	Oxygen	non-ICSD
Sasayama 2009	Oxygen	ICSD
Seino 2007	Oxygen	ICSD
Shapiro 2015	ASV. CPAP	ICSD
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Shigemitsu 2007	Oxygen	non-ICSD	
Sin 2000	СРАР	ICSD	
Staniforth 1998	Oxygen	ICSD	
Sugimura 2016	Oxygen	ICSD	
Szollosi 2006	ASV	ICSD	
Tamisier 2022	ASV	non-ICSD	
Terziyski 2016	СРАР	ICSD	
Toschlor 2001	ASV, BPAP with backup rate, CPAP,		
Teschief 2001	Oxygen		
Tkacova 1997	СРАР	ICSD	
Toyama 2009	Oxygen	ICSD	
Toyama 2017	ASV	non-ICSD	
Troitino 2014	ASV, BPAP with backup rate, CPAP	non-ICSD	
Verbraecken 1998	Acetazolamide	ICSD	
Verbraecken 2002	СРАР	ICSD	
Willson 2001	BPAP with backup rate	ICSD	
Yoshihisa 2012	ASV, Oxygen	ICSD	
Yoshihisa 2013	ASV	non-ICSD	
Yoshihisa 2013 (Eur J Heart Fail)	ASV	non-ICSD	
Zhang 2021	СРАР	non-ICSD	

ICSD - International Classification of Sleep Disorders

*Five or more central respiratory events (central apneas or central hypopneas) per hour of sleep. The total number of central apneas plus central hypopneas is > 50% of the total number of apneas and hypopneas. ** The total number of central apneas plus central hypopneas is 20-50% of the total number of apneas and

hypopheas.

TPNS – transvenous phrenic nerve stimulation; CPAP – continuous positive airway pressure; ASV – adaptive servo-ventilation; BPAP – bilevel positive airway pressure

CPAP = 76% of studies met ICSD criteria; BPAP without a backup rate = 45%; BPAP = 100%; ASV = 69%; Oxygen = 71%; Acetazolamide = 67%; TPNS = 100%; high altitude = 100%