Original Article

Nocturnal supports for patients with central sleep apnea and heart failure: a systemic review and network meta-analysis of randomized controlled trials

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Background: Sleep apnea probably brings poor outcomes of chronic heart failure (CHF), and some methods show benefit to patients with heart failure (HF) and central sleep apnea (CSA). Our study based on the randomized controlled trials (RCTs) to find out the most beneficial therapy of nocturnal support to decrease the apnea hypopnea index (AHI).

Methods: The PubMed, and the Web of Science were used to find out the included studies. RevMan 5.3 and Stata 15.1 were performed to this systemic review and network meta-analysis.

Results: After searching and screening the articles, finally we included 14 articles with total 919 patients, and 4 arms [adaptive servo ventilation (ASV), continuous positive airway pressure (CPAP), oxygen treatment, control]. Compared with the control group, the therapeutic regimens did not show significant difference in AHI. Ranking the different nocturnal supports in the order of estimated probabilities of each treatment by using the network meta-analysis, the result showed that ASV was the best one (87.8%), followed by oxygen (12.2%), CPAP (0%), and control (0%).

Conclusions: Based on our study, the adoptive servo ventilation is probably the best choice to down the AHI in patients with HF and CSA.

Keywords: Heart failure (HF); central sleep apnea (CSA); adoptive servo ventilation (ASV)

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Introduction

Nowadays, heart failure (HF) is increasingly common, resulting in death in elderly patients (1). A large number of novel regimens developed for HF are palliative rather than curative, so the problems of high morbidity and mortality still exist. The sleep disordered breathing (SDB) is increasingly recognized as a crucial comorbidity in patients with HF, the prevalence of SDB is as high as 50–60% in these patients (2-4). Patients with HF and sleep apnea have poor outcomes, and they have quite poor survival quality.

It is proved that obstructive sleep apnea (OSA) and central sleep apnea (CSA) are both closely associated with HF (5-7). There were some studies about that nocturnal supports could help HF people have quality life shown up (8,9). They raised and developed a theory to use the nocturnal supports to down the incidence of sleep apnea and hypopnea. As a kind of nocturnal supports, CPAP is regarded as a quite useful method to treat OSA, but in

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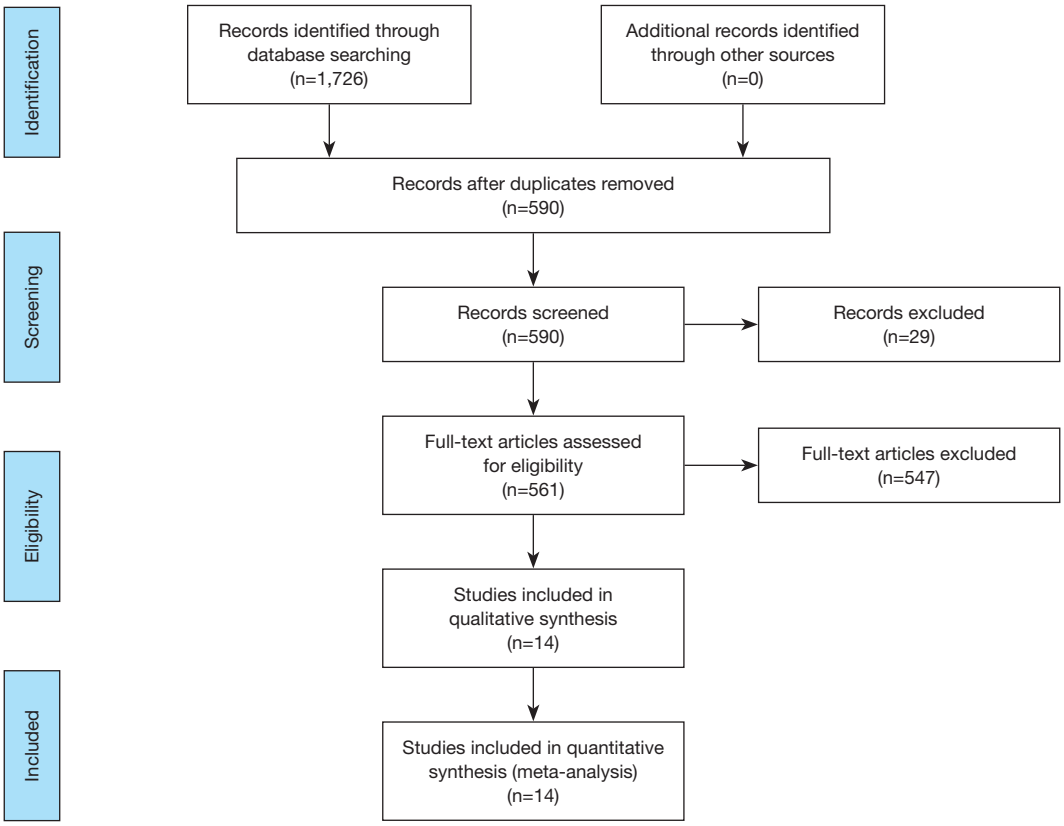

Figure 1 Flow graph.

patients with CSA, the results of some studies showed that some patients with HF and CSA are quite insensitive to CPAP treatment (10,11).

There were some different kinds of nocturnal supports [adaptive servo ventilation (ASV), continuous positive airway pressure (CPAP), oxygen treatment] being studied in previous researches, however, few network meta-analysis integrated these studies to investigate what kind of nocturnal supports could better help people with HF and CSA. The previous meta-analysis only compared the ASV with other treatments (12). So, we try to conduct the study to guide clinical practice.

Methods

Search strategy

Two authors independently reviewed the identified abstracts and selected articles to full review. The third reviewer addressed the discrepancies. The reference lists of eligible studies and relevant papers were also manually searched and reviewed. The search terms were "central sleep apnea", "heart failure". The search date was until 2019/1/22. Finally, we found 1,726 articles, 590 of them existing after excluding duplications, then we excluded 29 articles through reading the title and abstract, and excluded 547 articles through reading the whole articles, finally, 14 RCTs (9,13-25) were included by reading the whole articles (*Figure 1*).

Inclusion and exclusion

Inclusions contain: (I) researched study about using nocturnal supports for treating patients with HF and CSA, (II) outcome: apnea and hypopnea index, (III) randomized controlled trial (RCTs), (IV) only be published by English.

Exclusions contain: (I) review, retrospective research, case report, (II) insufficient data in the articles.

Data elected

For each selected publication, the following baselines and study characteristics were extracted: first author, publication

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year, country, participant characteristics, age inclusion, total number of experiment and control group, follow up, and other baseline characteristics of these studies were concluded below (*Table 1*). Primary outcome measure was the incidence of apnea and hypopnea per hour.

Risk of bias assessment

Risk of bias of trials included in this meta-analysis was assessed according to the recommendations of the Cochrane Handbook of Systematic Reviews of Interventions, in the following domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective outcome reporting) (http://handbook.cochrane.org). Jadad scale was used to calculate the quality of every enrolled study.

Statistic analysis

We pooled data and used odd ratios (OR) for the dichotomy outcome: the incidence of apnea and hypopnea per hour. The Total numbers of patients occurring apnea and hypopnea per hour were multiplied by 2 to produce new total numbers, which were bigger than the apnea hypopnea index (AHI) multiplied by the number of HF patients in each group. All statistical analyses were carried out with Review Manager 5.3 (The Cochrane Collaboration) and Stata 15.1.

Results

The studies included in our meta-analysis were all RCTs, published from 1995 to 2017. The studies were conducted in Canada (13,14,18,19,22), Germany (16,17,23), and Japan (9,15,20,21,24,25). *Table 1* presents the basic characteristics of included trials and demographic data of participants. Seven trials were multicenter studies and the Jadad Scales of all included studies ranged from 2 to 5.

In our study, we totally included 14 RCTs with 919 patients about nocturnal supports in treating patients with HF and CSA to explore which supports can decrease the apnea and hypopnea per hour. The qualities of the article evaluations are as followed (*Figures 2,3*).

Network evidence of the comparisons between the different nocturnal supports is showed in *Figure 4*. Compared with the control group, all therapeutic regimens (ASV, oxygen therapy, CPAP) did not decrease the apnea hypopnea per hour in all patients with the OR (95% CI) value of 1.67 (95% CI, 0.49–5.74), 0.32 (95% CI, 0.04–2.55), 2.51 (95% CI, 0.36–17.74), respectively. In addition, there was no significant difference between these therapeutic regimens (*Figures 5,6*).

The inconsistency test showed that the comparison could be performed by consistency (P>0.05) (*Table 2*). In the rank of network meta-analysis, we found that ASV (87.8%) was the most effective nocturnal support to decrease the apnea and hypopnea index, followed by oxygen treatment (12.2%), control (0.0%), CPAP (0.0%) (*Table 3*).

Potential publication bias of nocturnal supports used for treating patients with HF and CSA was performed and showed as funnel plot (*Figure 7*). Netweight of analysis was showed in *Figure 8*.

Discussion

In our study, ASV was the best choice treatment used in decreasing AHI in patients with HF and CSA. ASV could also improve cardiac function and quality of life (QOL). What's more, the mode of ASV could be divided into flow-triggered ASV and volume-triggered ASV. Volume-triggered ASV was probably better in treating patients with central sleep apnea, because the volume-triggered ASV device applied a minimal difference of 3 cmH_2O between minimal IPAP and EPAP, and could be better used in patients with coexisting OSA and CSR-CSA (20). The result of the SERVE-HF randomized trial was not included in our study, because it only contained the post-treatment AHI data in patients treated with ASV (26), for generating meta-analysis, we need the post-treatment AHI in both ASV and control group.

According to the previous researches about traditional CPAP mode used for treating patients with HF and central sleep apnea, there were some people un-responsive to CPAP treatment in these articles, which called them complex CPAP and insensitive CPAP (10,11). The results of our study demonstrated that the CPAP was less useful in treating these patients. However, some studies indicated that CPAP could increase transplant-free survival in patients whom CPAP sufficiently suppressed sleep-disordered breathing (SDB) than the control group, showing that CPAP were beneficial to long-term outcomes in the suppressing group (13). On the one hand, CPAP could alter intra-thoracic pressure, cardiac filling pressures, diastolic volumes, and afterload (27). On the other hand, CPAP induced significant reductions of apnea

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Table 1 Characteristics of studies included in the network meta-analysis

Study	Type	Time	Country	Jadad scale	Participant	Age	Groups	Total number	All AHI per hour (baseline to change)	Follow up
Arzt *et al.*	RCT	2007 (published)	Canada	2+1+1+1=5	11 centers	18–79 years	Control *vs.* CPAP	110 *vs.* 100	4,180 to 3,960 *vs.* 3,443 to 1,847	3 months
Hetzenecker *et al.*	RCT	2015 (published)	Germany	2+1+1+1=5	Multi-centers	18–80 years	Control *vs.* ASV	31 *vs.* 32	1,426 to 1,457 *vs.* 1,600 to 320	12 weeks
Granton *et al.*	RCT	1996 (published)	Canada	1+1+0+0=2	1 center	<75 years	Control *vs.* CPAP	8 *vs.* 9	280 to 152 *vs.* 441 to 153	1 months
Randerath *et al.*	RCT	2012 (published)	Germany	1+1+1+1=4	1 center	>18 years	ASV *vs.* CPAP	26 *vs.* 25	1,216.8 to 288.6 *vs.* 1,020 to 425	12 months
Sasayama *et al.*	RCT	2009 (published)	Japan	1+1+0+1=3	19 centers	>20 years	Control *vs.* Oxygen	21 *vs.* 21	420 to 435.75 *vs.* 400.05 to 188.58	12 weeks
Sasayama *et al.*	RCT	2006 (published)	Japan	1+1+0+1=3	20 centers	>20 years	Control *vs.* oxygen	29 *vs.* 25	522 to 495.9 *vs.* 504 to 250	12 weeks
Ruttanaumpawan *et al.*	RCT	2008 (published)	Canada	2+1+0+1=4	19 centers	18–79 years	Control *vs.* CPAP	108 *vs.* 97	4,082.4 to 4,060.8 *vs.* 3,773.3 to 1,707.2	3 months
Toyama *et al.*	RCT	2009 (published)	Japan	1+1+0+0=2	1 center	>20 years	Oxygen *vs.* control	10 *vs.* 10	522 to 102 *vs.* 398 to 420	3 months
Toyama *et al.*	RCT	2016 (published)	Japan	1+1+0+0=2	1 center	42–82 years	ASV *vs.* control	15 *vs.* 15	382.5 to 70.5 *vs.* 375 to 367.5	6 months
O'Connor *et al.*	RCT	2017 (published)	Germany	2+1+0+0=3	Multi-centers	≥21 years	ASV *vs.* control	65 *vs.* 61	2,320.5 to 136.5 *vs.* 2,141.1 to 1,216	6 months
Naughton *et al.*	RCT	1995 (published)	Canada	1+1+0+0=2	1 center	18–75 years	CPAP *vs.* control	9 *vs.* 9	432.9 to 166.5 *vs.* 335.7 to 257.4	1 month
Kasai *et al.*	RCT	2009 (published)	Japan	1+1+0+0=2	Multi-centers	20–80 years	ASV *vs.* CPAP	16 *vs.* 15	580.8 to 14.4 *vs.* 579 to 231	3 months
Kasai *et al.*	RCT	2012 (published)	Japan	1+1+1+1=4	1 center	20–80 years	ASV *vs.* CPAP	12 *vs.* 11	300 to 22 *vs.* 253 to 254.1	3 months
Naughton *et al.*	RCT	1995 (published)	Canada	1+1+0+1=3	1 center	<75 years	CPAP *vs.* control	14 *vs.* 15	604.8 to 205.8 *vs.* 496.5 to 405	1 month

RCT, randomized controlled trial; AHI, apnea and hypopnea index; CPAP, continuous positive airway pressure; ASV, adaptive servo ventilation.

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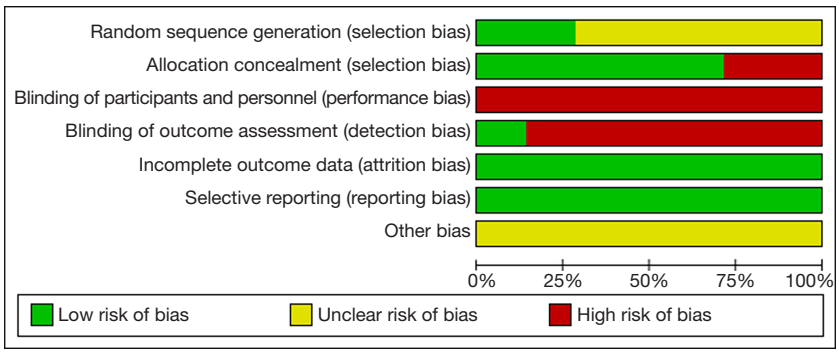

Figure 2 Risk of bias graph.

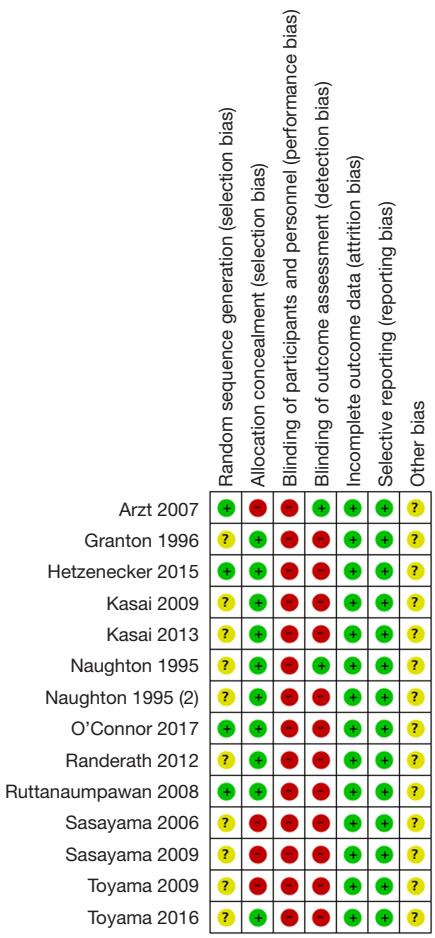

Figure 3 Risk of bias summary.

and arousal from sleep, associated with significant reductions of heart rate (28). In addition, from the results of previous study (29), CPAP was the preferred first-line therapy for symptomatic patients with hyperventilation-related CSA.

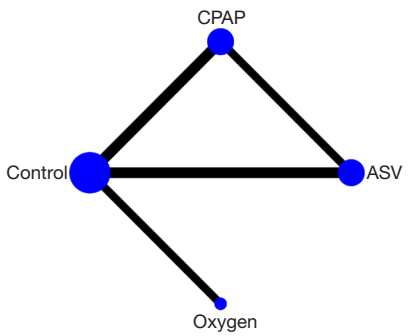

Figure 4 Network evidence of the comparisons for the nocturnal supports. ASV, adaptive survo ventilation; CPAP, continuous positive airway pressure.

Nocturnal oxygen treatment also showed superiority in decreasing AHI. The reasons why oxygen could reduce the CSA are multifactorial. Firstly, a rise of $PaCO_2$ leads to a widening difference between the prevailing $PaCO_2$ and the $PaCO_2$ at the apneic threshold. When the difference between these 2 set points is wide, the occurrence of CSA will be suppressed because a large ventilator overshoot is necessary to reduce $PaCO_2$ below the apneic threshold. Moreover, the suppression of the ventilator responses to hypercapnia. Last but not least, increasing the body stores of oxygen probably buffers oscillations in blood gases with each apnea (24).

Our study included all high quality RCTs, excluding studies designed by randomized cross-over trial and retrospective research, so our study is much more reliable to conduct clinical practice. In our study, the best treatment to down AHI could be ASV. AHI decreasing in chronic heart failure (CHF) patients is associated with significant improvements in left ventricular and right ventricular systolic function and reversing left ventricular

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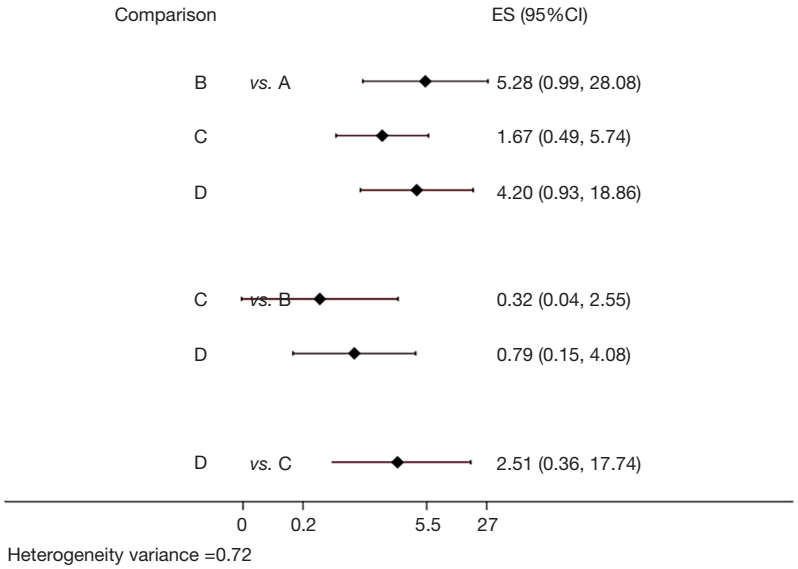

Figure 5 Odd ratios of the comparisons for the nocturnal supports. (A) Adaptive survo ventilation; (B) continuous positive airway pressure; (C) control; (D) oxygen treatment.

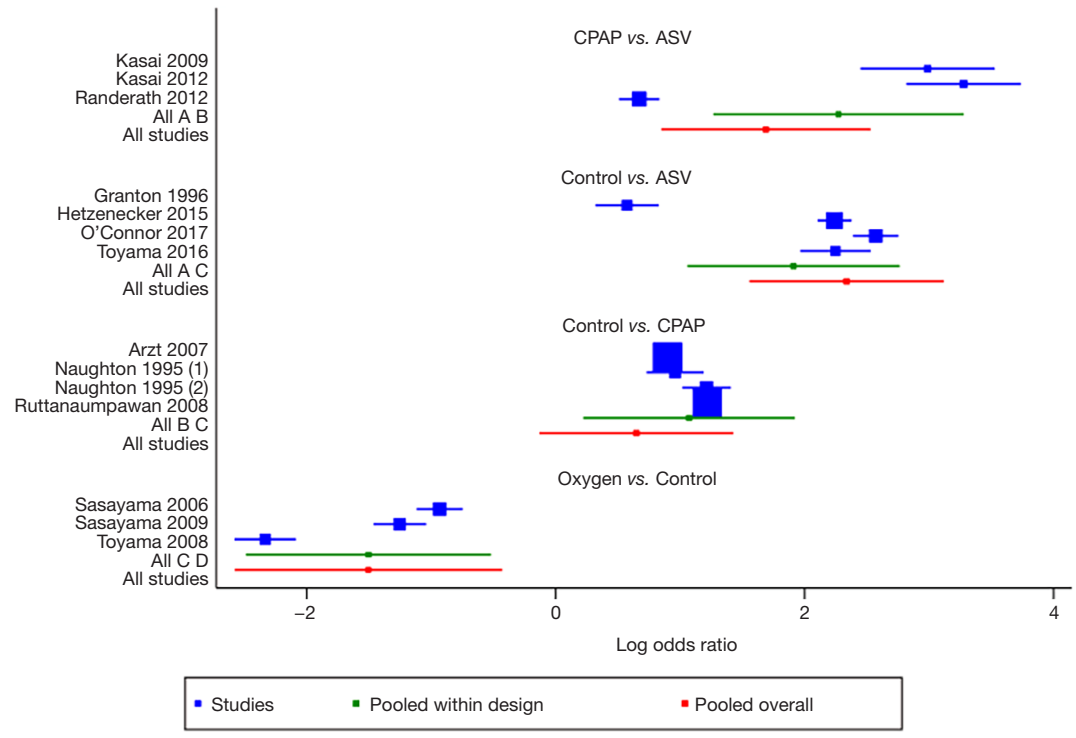

Figure 6 Forest plots of the comparisons for the nocturnal support. ASV, adaptive survo ventilation; CPAP, continuous positive airway pressure. A, adaptive survo ventilation; B, continuous positive airway pressure; C, control; D, oxygen treatment.

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Table 2 Inconsistency test

Comparison	Direct		Indirect		Differ		P
	Coef	Std. Err	Coef	Std. Err	Coef	Std. Err	
A *vs.* B	2.272	0.514	0.839	0.615	1.433	0.801	0.074
A *vs.* C	1.911	0.435	3.344	0.672	−1.433	0.801	0.074
B *vs.* C	1.072	0.434	−0.361	0.673	1.433	0.800	0.074
C *vs.* D	−1.504	0.548	−4.832	768.584	3.328	768.585	0.997

A, adaptive survo ventilation; B, continuous positive airway pressure; C, control; D, oxygen treatment.

Table 3 Estimated probabilities of each treatment being the best

Treatment	Probabilities (%)
ASV	87.8
CPAP	0.0
Control	0.0
Oxygen	12.2

ASV, adaptive survo ventilation; CPAP, continuous positive airway pressure.

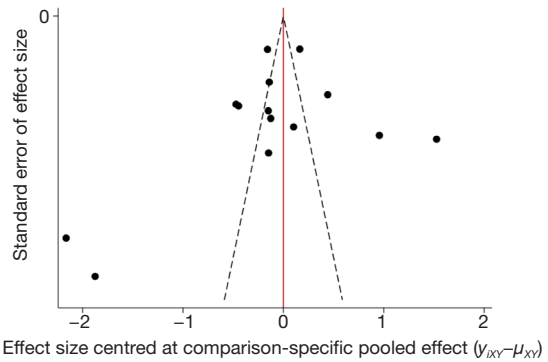

Figure 7 Funnel plot.

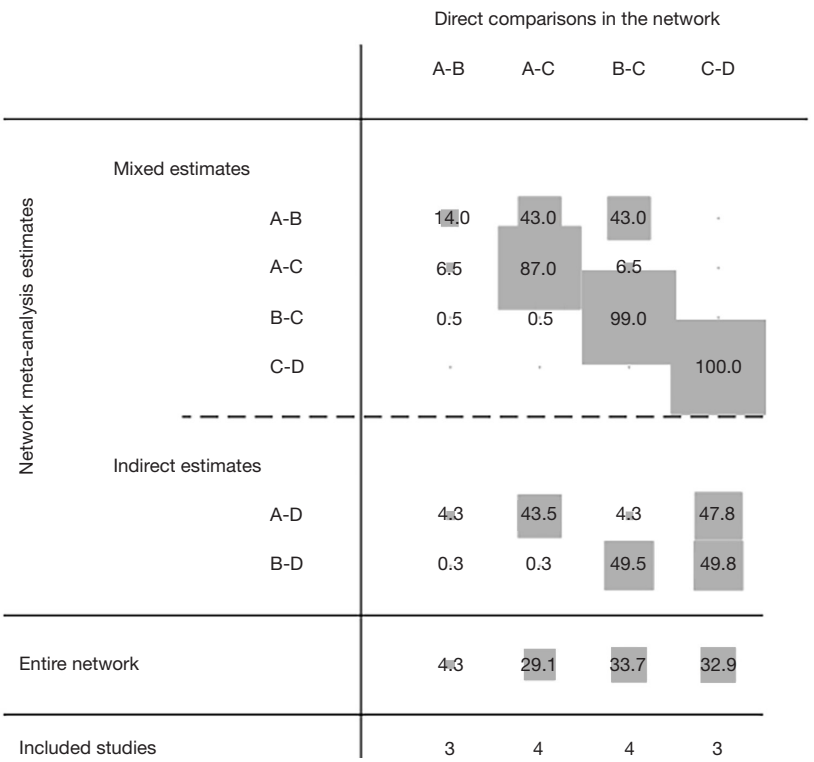

Figure 8 Netweight of analysis. A, adaptive survo ventilation; B, continuous positive airway pressure; C, control; D, oxygen treatment.

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reconstruction (r-LVR) (30), but the further mortality and morbidity should be discussed.

The American Academy Sleep Medicine (AASM) recommended against using of ASV to treat heart failure-associated CSA in patients with an ejection fraction ≤45% and moderate or severe CSA based on available data (12). In our network meta-analysis, most inclusion criteria of included studies matched to ejection fraction ≤45% however, four of them were different (17,20,21,23).

However, our study also exposes the disadvantages. Firstly, our study excluded the studies comparing with Bi-level ventilation mode because there were no RCTs about this mode of ventilation. Furthermore, the control and CPAP group showed the similar probability of the best choice of treatments, although some patients were insensitive to CPAP, many patients could get benefit from this treatment. Lastly, only 3 of the included studies compared ASV *vs.* CPAP, whereas all other included studies compared a specific support mode (ASV, CPAP or oxygen) with control.

Conclusions

All in all, we suggest that patients with HF and CSA use nocturnal support treatments to decrease the incidence of apnea and hypopnea, and ASV is probably the best choice of nocturnal support to decrease AHI in these patients, but the specific appropriate patients in ASV treating should be carefully identified according to previous guidelines and studies.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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