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Original Article

Continuous positive airway pressure for adults with obstructive sleep apnea and cardiovascular disease: a meta-analysis of randomized trials

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ABSTRACT

Background: It remains uncertain whether continuous positive airway pressure (CPAP) therapy would significantly impact hard clinical outcomes in patients with obstructive sleep apnea (OSA). This meta-analysis aimed to assess the effects of CPAP in survival and secondary prevention of major cardiovascular events in patients with OSA and cardiovascular disease (CVD).

Methods: PubMed, Cochrane CENTRAL, LILACS, and SciElo databases (up to January 2018) were searched for randomized trials that compared CPAP with no active treatment in adults with OSA and CVD. The primary outcomes were all-cause death, cardiovascular death, acute myocardial infarction, stroke, and any major cardiovascular event. We used risk ratios (RR) and 95% confidence interval (CI) as the effect measures for dichotomous data, and weighted mean difference (WMD) and 95% CI for continuous variables. We used the random-effects method for meta-analysis.

Results: Nine trials involving 3314 patients contributed data for meta-analysis of at least one outcome. The duration (median) of CPAP treatment varied from one month to 56.9 months. The pooled RR (95% CI) was 0.86 (0.60–1.23, $I^2 = 0.0\%$) for all-cause death, 0.58 (0.19–1.74, $I^2 = 47\%$) for cardiovascular death, 1.11 (0.76–1.62, $I^2 = 0.0\%$) for myocardial infarction, 0.77 (0.46–1.28, $I^2 = 16\%$) for stroke, and 0.93 (0.70–1.24, $I^2 = 49\%$) for any major cardiovascular event. The quality of evidence for these outcomes was low.

Conclusions: Low-quality evidence suggests that CPAP therapy does not significantly improve survival or prevent major cardiovascular events in adults with OSA and cardiovascular disease.

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction during sleep that results in hypopnea (reduced airflow) or apnea (complete airflow cessation), and intermittent hypoxia and arousal from sleep [1]. Moderate to severe OSA is associated with increased cardiovascular morbidity and mortality [2–5]. The mechanisms linking OSA to cardiovascular disease (CVD) are incompletely understood, but likely include sympathetic activation, vascular endothelial dysfunction, oxidative stress, systemic inflammation, coagulation, and metabolic dysregulation [6,7].

Current guidelines recommend continuous positive airway pressure (CPAP) therapy for patients with moderate to severe OSA [8–10]. Moderate-quality evidence shows that CPAP therapy improves sleep measures compared with control or sham devices in patients with at least moderate OSA [8]. However, it remains uncertain whether CPAP therapy would significantly impact hard clinical outcomes, such as death and cardiovascular events, in patients with OSA.

Two previous systematic reviews have assessed the effects of positive airway pressure on cardiovascular morbidity and mortality in patients with sleep apnea [11,12]. Both reviews reported no significant effects of positive airway pressure on survival and major

Abbreviations List: CPAP, Continuous positive airway pressure; CVD, Cardiovascular disease; HF, Heart failure; LILACS, Latin American & Caribbean Health Sciences Literature; LVEF, Left ventricular ejection fraction; OSA, Obstructive sleep apnea; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement; RCT, Randomized controlled trial; RR, Risk ratios; SciElo, Scientific electronic library online; WMD, Weighted mean difference.

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cardiovascular outcomes. The first review [11] included 10 highly heterogeneous trials, which varied in patient selection (OSA in eight trials and central sleep apnea in two trials), outcome measures (primary prevention of CVD in five trials and secondary prevention in another five trials) and intervention (CPAP in nine trials and adaptive servo-ventilation in one trial). The second review [12] included four trials that assessed the effects of CPAP in patients with OSA, of which one was a primary prevention trial and three were secondary prevention trials. The safety and tolerance of long-term CPAP therapy in patients with OSA have not been addressed by two previous reviews.

We conducted this meta-analysis of randomized trials to assess the effects of CPAP in survival and secondary prevention of major cardiovascular events in adult patients with OSA and established cardiovascular disease, compared to no active treatment. We also assessed the safety and tolerance of CPAP therapy in these patients.

2. Methods

We followed the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) [13] to conduct and report this systematic review and meta-analysis. The review protocol was registered on PROSPERO, an International Prospective Register of Systematic Reviews (registration number CRD42016050916) [14].

2.1. Data sources and search strategy

We searched PubMed, Cochrane CENTRAL, LILACS (Latin American & Caribbean Health Sciences Literature), and SciElo (Scientific electronic library online) databases. All databases were searched from inception until January 3, 2018, using the following search strategy: (“obstructive sleep apnoea” OR OSA) AND (“ continuous positive airway pressure” OR CPAP). We used the following filters for the search on PubMed: Clinical Trial, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial, Randomized controlled trial, and Humans. There were no language restrictions. We also searched ClinicalTrials.gov to identify potentially relevant unpublished studies. Reference lists of primary studies were screened for additional relevant trials.

2.2. Study selection

To be included in this meta-analysis, studies had to meet all of following criteria: (1) study design: randomized controlled trial (RCT); (2) participants: adults (>18 years of age) with OSA diagnosed by polysomnography, and any cardiovascular disease; (3) intervention and comparisons: the intervention was CPAP delivered by an interface for at least two weeks, and the comparators were sham-CPAP or Usual care alone; and (4) outcome measures: primary outcomes were all-cause death, cardiovascular death, acute myocardial infarction, stroke and any major cardiovascular event (cardiovascular death, stroke, acute myocardial infarction, angina, transient ischemic attack, revascularization and hospitalization for cardiovascular causes). Secondary outcomes were cardiac systolic or diastolic function, blood pressure, cardiac chamber's size, symptoms of OSA, quality of life, mood, and adverse events. When the trial had repeated outcome measurements, we used the measurement obtained at the longest time-point.

Two review authors independently assessed the titles and abstracts of all citations identified by the searches. We obtained the full articles when they appeared to meet the inclusion criteria, or there were insufficient data in the title and abstract to make a clear decision for their inclusion. The definitive inclusion of trials was made after reviewing the full-text articles. We resolved any disagreements between the two review authors about study inclusion by discussion.

2.3. Data extraction and management

Two review authors independently extracted data from the included studies and cross-checked the extracted data. A standardized form was used to extract the following data: (1) Study characteristics: year of publication, country, and setting of study; (2) Methods: study design, methods of random sequence generation, allocation concealment and blinding, description of withdrawal, and adherence to treatment; (3) Participants: sample size, age, sex, and inclusion and exclusion criteria; (4) Interventions and comparison: CPAP equipment, type of interface, type of control, duration of treatment, and co-interventions; and (5) Outcomes: for continuous outcomes, we extracted sample size, mean (median) and precision of measurements (standard deviation-SD, standard error-SE, 95% CI or interquartile range) of each treatment arm. For dichotomous outcomes, we extracted the number of events and the total number of participants of each treatment arm. Intention-to-treat datasets were used whenever available.

2.4. Assessment of risk of bias

Two authors independently assessed the risk of bias in included trials by examining the six key domains according to the Cochrane guidelines [15]: (1) allocation sequence generation, (2) concealment of allocation, (3) blinding, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other sources of bias. We graded each potential source of bias as yes, no or unclear, relating to whether the potential for bias was low, high or unknown. The two authors independently assessed the quality of evidence of this review using the GRADE approach recommended by the Cochrane Handbook [15].

2.5. Data synthesis and statistical analysis

We performed a meta-analysis for quantitative data synthesis whenever there were available data from the primary studies. For continuous outcomes, the weighted mean difference (WMD) between treatment groups and 95% CI were used as the metrics of effect size. Dichotomous data were synthesized using risk ratios (RR) and 95% CI as the effect measures. We used the random-effects method for meta-analysis which incorporates an estimate of between-study variation (heterogeneity) into the calculation of the common effect. The random-effects method and the fixed-effect method will yield identical results when there is no significant heterogeneity across studies. Otherwise, the random-effects method is more conservative than the fixed-effects method and provides estimates with wider CI [15].

We assessed heterogeneity in results between studies using the Cochrane Q test ($P < 0.1$ considered significant) and the I^2 statistic. The I^2 statistic ranges from 0% to 100% and measures the degree of inconsistency across studies. An I^2 value greater than 50% was considered to indicate substantial heterogeneity [16].

We planned to conduct subgroup analyses according to CPAP equipment, type of interface, duration of treatment, the severity of OSA, and type of cardiovascular disease. We also planned to assess publication bias using a funnel plot and Egger's test. However, the small number of included trials precluded such additional analyses. We conducted a post hoc sensitivity analysis excluding trials with a mean duration of CPAP use of fewer than four hours per night or no data available for adherence.

All meta-analyses were performed using Stata version 11.0 (Stata-Corp, College Station, TX, USA).

3. Results

3.1. Literature search and study selection

From 1658 titles identified by the searches, 38 potentially relevant full-text articles were retrieved for further evaluation. Twenty nine articles were excluded for reasons shown in Fig. 1. Thus, a total of nine RCTs [17–25] involving 3314 patients were included in the review.

3.2. Study characteristics and risk of bias

Table 1 shows the characteristics of the nine included trials. Four trials [17,21,24,25] included patients with heart failure (HF), two trials [18,22] included patients with stroke, two trials [18,22] included patients with coronary artery disease (CAD), and one trial [20] included CAD or cerebrovascular disease. OSA was diagnosed by polysomnography in five trials [17,20–22,24], and by a validated portable recording device in three trials [18,19,23].

The duration of CPAP treatment varied from one month to 56.9 months (median). All trials used usual care as the comparator, with the exception of one trial [24] in which sham-CPAP was used. Four trials used appropriate methods for randomization [18–20,22], and two trials [18,22] used sealed envelopes for allocation concealment. The remaining trials did not describe the methods for random sequence generation and allocation concealment (e-Table 1). One trial [24] used sham-CPAP for blinding, and seven trials [17,18,20–23,25] had blinded end-point assessment. Seven trials [17–23] reported the duration of adherence to CPAP, which ranged from 1.4 h/night to 6.9 ± 0.5 h/night (mean ± SD).

3.3. Efficacy of CPAP therapy

3.3.1. Mortality and cardiovascular morbidity

Six trials [18–20,22–24] involving 3233 patients (CPAP group: 1611; Control group: 1622) provided data for the meta-analyses of mortality and major cardiovascular outcomes. The mean (median) follow-up duration varied from three to six years. The e-Table 2 shows the raw data and effect size estimate of each trial. Fig. 2 summarizes the overall results of meta-analyses of five outcomes of mortality and cardiovascular morbidity. The all-cause mortality was 3.4% (54/1611) in the CPAP group, compared to 3.9% (64/1622) in the control group. There was no significant difference between the two groups in terms of all-cause mortality (pooled RR 0.86, 95% CI: 0.60 to 1.23, p = 0.43, I^2 = 0%). The cardiovascular mortality was 1.8% (28/1561) in the CPAP group and 2.2% (35/1569) in the control group. CPAP treatment did not significantly reduce the cardiovascular mortality, compared to the control group (pooled RR 0.58, 95% CI: 0.19 to 1.74, p = 0.32, I^2 = 47.7%). The incidence of myocardial infarction and stroke was 3.5% (54/1561) and 4.7% (73/1561) in the CPAP group, while these incidences were 3.1% (49/1569) and 5.4% (85/1569) in the control group. CPAP treatment did not significantly reduce the risk of myocardial infarction and stroke, with pooled RR (95% CI) of 1.11 (0.76–1.62, p = 0.57, I^2 = 0%) and 0.77 (95% CI: 0.46 to 1.28, p = 0.31, I^2 = 16%), respectively. There was also no significant difference between the CPAP and control groups in terms of the incidence of any major cardiovascular event (CPAP group: 27.1% [437/1611] vs. Control group: 25.2% [409/1622], pooled RR 0.93, 95% CI: 0.70 to 1.24, p = 0.62, I^2 = 49%).

The post hoc sensitivity analyses, excluding three trials with a mean duration of CPAP use less than four hours per night [20,23] or no data available for adherence [24], yielded the pooled RR (95% CI) of 0.76 (0.39–1.48, p = 0.42, I^2 = 0.0%) for all-cause death, 0.32 (0.10–0.98, p = 0.04, I^2 = 47%) for cardiovascular death, 1.27 (0.56–2.87, p = 0.56, I^2 = 0.0%) for myocardial infarction, 0.42 (0.17–1.03, p = 0.06 I^2 = 0.0%) for stroke, and 0.60 (0.26–1.36, p = 0.22, I^2 = 63%) for any major cardiovascular event.

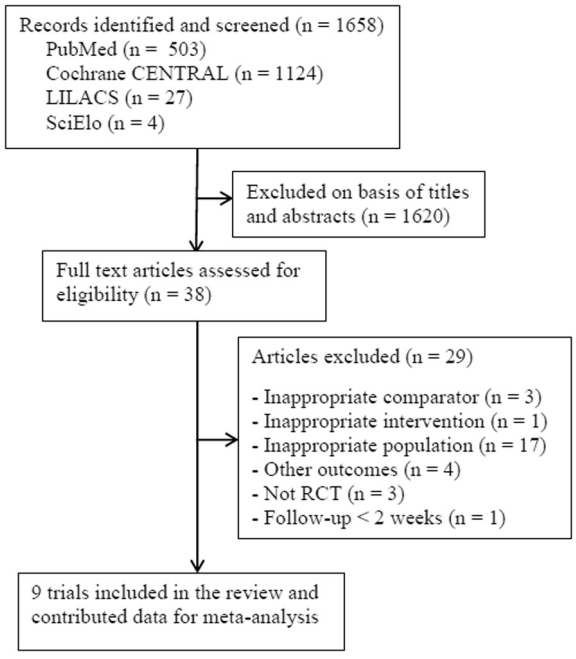

Fig. 1. PRISMA flow diagram of study selection. A flow diagram describes the process of identification, screening, assessment for eligibility, and the inclusion of studies.

3.4. Secondary efficacy outcomes

Table 2 summarizes the overall results of meta-analyses of secondary efficacy outcomes. Four trials [17,21,24,25] involving 141 patients with OSA and heart failure reported the left ventricular ejection fraction (LVEF, %). The meta-analysis showed a significantly higher mean of LVEF in the CPAP group, compared to the control group (pooled WMD 4.10%, 95% CI: 1.39%–6.80%, p = 0.003, I^2 = 0%). CPAP therapy was associated with a significant improvement in the Epworth Sleepiness Scale (ESS) score (four trials [20–22,24] involving 2582 patients, pooled WMD −2.44, 95% CI: −3.39 to −1.50, p = 0.0001, I^2 = 53%), in apnea/hypopnea index (two trials [16,20] involving 64 patients, pooled WMD −23.2 (−40.00 to −6.42), p = 0.01, I^2 = 86%) and in mental-component quality of life score (SF-36) (four trials [19,20,23,24] involving 2619 patients, pooled WMD 1.15, 95% CI: 0.49 to 1.81, p = 0.001, I^2 = 0%). There were no significant differences between the CPAP and control groups in terms of SBP, DBP and physical-component quality of life score.

The e-Table 3 shows the raw data and effect size estimate of secondary efficacy outcomes in each trial.

3.5. Adverse effects of CPAP therapy

Six trials [18,20–24] reported safety and tolerance data of CPAP therapy. One trial [18] described patient-reported side effects that were related to CPAP tolerability, including dry mouth, nasal symptoms, claustrophobia, insomnia, noise problems, and mask fit. However, the incidence of adverse events was not reported among 122 patients treated with CPAP. One large trial [20] reported that the number of serious adverse events, the rate of road-traffic accidents and accidents causing injury did not differ significantly between the CPAP group (n = 1346) and the usual-care group (n = 1341). Another trial [23] reported a high rate of problems with

Table 1
Characteristics of included trials.

Study ID and country	Participants (Inclusion Criteria)	Intervention and control	Duration of treatment	Outcomes and time-points of assessment
Kaneko 2003 [17], two centers, Canada	Patients (mean age: 55.5 yr; male: 87%) with HF, LVEF $\leq$ 45% by gated radionuclide angiography, AHI $\geq$ 20/h of which > 50% were obstructive.	- A metered CPAP, with pressure adjusted to abolish apneas/hypopnoeas, or highest level tolerated (n = 12) - Usual care (n = 12) Duration of adherence to CPAP (mean ± SD): 6.2 ± 0.5 h/night	One month	LVEF, LVEDV, LVESV, HR, SBP, DBP, AHI, arousals, S_aO_2, total sleep time Time-points of assessment: 1 month.
Peker 2016 [18], single center, Sweden	Patients (mean age: 66 yr; male: 84%) with angiography-verified CAD and nonsleepy OSA (AHI $\geq$ 15/h, ESS score < 10).	- An auto-titrating nasal CPAP (n = 122) - Usual care (n = 122) Duration of adherence to CPAP: from 4.4 ± 2.3 h/night at 1 month (n = 105) to 6.9 ± 1.2 h/night at 5 yr (n = 21).	A median (range) of 56.9 months (6.5–90.2)	Repeat revascularization, MI, stroke, cardiovascular mortality, all-cause mortality, hospital admission Time-points of assessment: 1, 3, 6, 12 months, and annually after that.
Parra 2015 [19], single center, Spain	Patients aged < 75 yr (mean age: 64.7 yr; male: 71%) with first-ever ischemic stroke, AHI $\geq$ 20/h predominantly obstructive (>80%), and at least one of the following conditions: habitual snoring, observed apneas or history of hypertension or heart disease.	- An auto-titrating nasal CPAP started during hospital admission between three and six days after stroke onset (n = 57) - Usual care (n = 69) Duration of adherence to CPAP: 5.3 ± 1.9 h/night	24 months	Quality of life, cardiac ischemic events, stroke recurrence, cardiovascular mortality Time-points of assessment: 1, 3, 12, 24 months, and telephone contact at 68 months.
McEvoy 2016 [20], 89 centers in Australia, Brazil, China, India, Spain, and the USA	Patients aged 45–75 yr (mean age: 61.2 yr; male: 80.9%) with CAD or cerebrovascular disease, moderate to severe obstructive apnea (oxygen desaturation index defined as the number per hour that S_aO_2 drops by $\geq$ 4% from baseline: $\geq$ 12), ESS score $\leq$ 15.	- An automated mask-delivered CPAP at 90th percentile of pressure calculated by the device (n = 1346) - Usual care (n = 1341) Duration of adherence to CPAP: 3.3 ± 2.3 h/night during follow-up (from 4.4 ± 2.2 h/night at one month to 3.5 ± 2.4 h/night at 12 months)	A mean of 3,7 yr	A composite of cardiovascular deaths, myocardial infarction, stroke, hospitalization for heart failure, transient ischemic attack, individual components of the composite endpoint, revascularization, new-onset atrial fibrillation, new-onset diabetes, all-cause deaths, SBP, DBP, symptoms of OSA, quality of life, mood Time-points of assessment: 1, 3, 6, 12 months, and annually after that.
Mansfield 2000 [21], single center, Australia	Patients aged 18–80 yr (mean age: 57.3 yr; male: 94%) with CHF, LVEF < 55%, NYHA class $\geq$ II, AHI > 5/h (obstructive).	- Fixed pressure nasal CPAP, titrated manually during overnight polysomnography and continued at the optimally determined fixed pressure (n = 19) - Usual care (n = 21) Duration of adherence to CPAP: 5.6 ± 0.4 h/night	Three months	LVEF, creatinine, SBP, NYHA, ESS score, S_aO_2, BMI, AHI Time-points of assessment: 3 months
Huang 2014 [22], single center, China	Patients aged 45–75 yr (mean age: 62.4 yr; male: 82%) with CAD confirmed by coronary angiography, hypertension (BP > 140/90 mmHg), moderate to severe OSA (AHI $\geq$ 15/h).	-Fixed pressure CPAP set to abolish snoring, obstructive respiratory events, and airflow limitation for 95% of the night (n = 36) - Usual care (n = 37) Duration of adherence to CPAP: 4.5 ± 1.1 h/night	A median (IQR) of 36 months (24–54)	SBP, DBP, acute myocardial infarction, hospitalization for heart failure, need for repeated coronary revascularization, stroke, cardiovascular and cerebrovascular deaths Time-points of assessment: 1, 3 months, and every 6 months after that
Hsu 2006 [23], single center, UK	Patients aged 21–90 yr (mean age: 73.5 yr; male: 66%), 14–19 days after ischemic stroke confirmed by computed tomography scans or magnetic resonance, AHI $\geq$ 30/h predominantly obstructive (<30% events due to central apneas).	- An auto-titrating nasal CPAP (n = 15) - Usual care (n = 15) Mean duration of adherence to CPAP: 1.4 h/night	Eight weeks	Nottingham Extended Activities of Daily Living Index, National Institutes of Health Stroke Score, Barthel Index, Stanford Sleepiness Scale, Addenbrooke's Cognitive Examination and Mini-Mental State Examination, Hospital Anxiety and Depression Subscales, Medical Outcomes Study Short Form 36 Health Survey and subscales, SBP, DBP Time-points of assessment: 8 weeks, 3 months and 6 months.
Egea 2008 [24], eight centers, Spain	Patients (mean age: 63.5 yr; male: 93%) with at least 1 episode of cardiac failure, LVEF < 45% using radionuclide ventriculography, AHI > 10/h	- CPAP with pressure set to abolish snoring, apneas, hypopneas, and episodes of flow limitation (n = 28) - Sham CPAP (n = 32)	Three months	LVEF, hypertension, ESS score, Medical Outcomes Study Short Form 36, Borg scale, NYHA, 6-min walking test, SBP, DBP Time-points of assessment: 3 months
Usui 2005 [25], single center, Canada	Patients (mean age: 53.3 yr; male: 88%) with heart failure > 6 months, LVEF < 46% radionucleotide angiography, > 3 months of stable optimal drug therapy, OSA > 20 AIH with >50% obstructive, and sinus rhythm.	- CPAP with pressure adjusted to abolish apnea and hypopnea or to highest tolerated level (n = 8) - Usual care (n = 9)	1 month	HR, SBP, DBP, and muscle sympathetic nerve activity Time-point of assessment: 1 month

AHI: apnea/hypopnea index; BMI: body mass index; CAD: coronary artery disease; DBP: diastolic blood pressure; ESS: Epworth Sleepiness Scale; HR: heart rate; IQR: interquartile range; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end systolic volume; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association heart failure class; OSA: obstructive sleep apnoea; S_aO_2: oxygen saturation; SBP: systolic blood pressure; SD: standard deviation; VPB: ventricular premature beats.

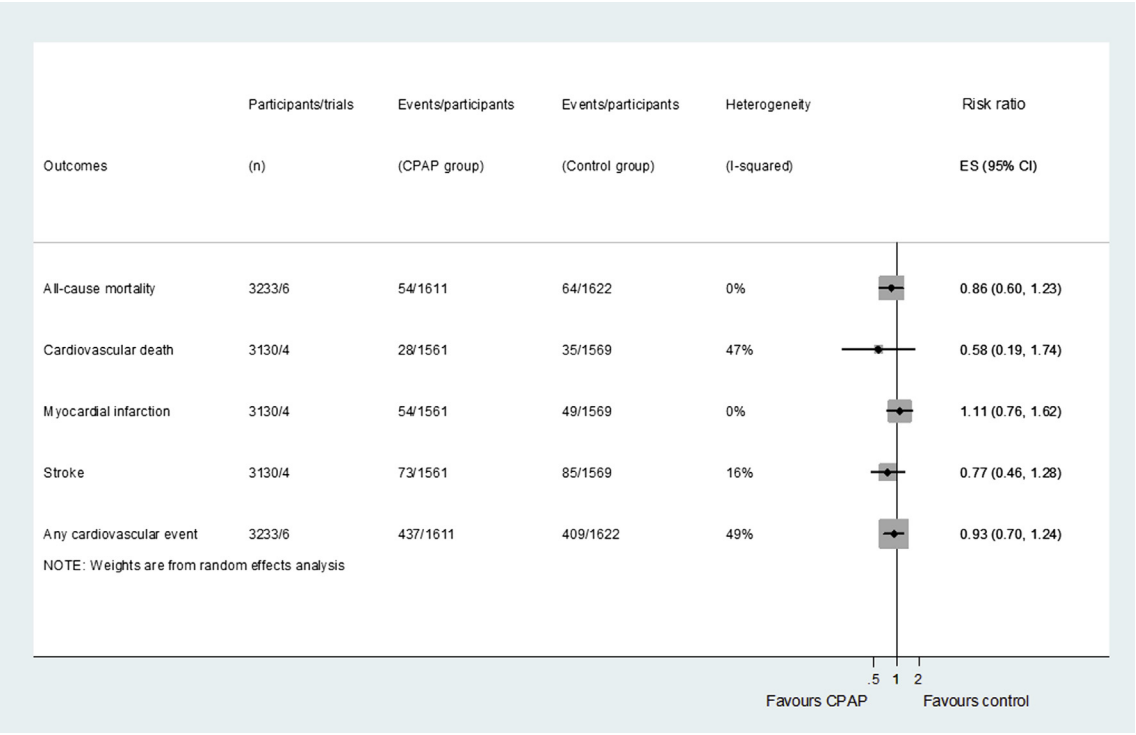

Fig. 2. Effects of CPAP therapy on mortality and major cardiovascular outcomes. Black dots represent overall point estimates of risk ratio, and horizontal lines represent 95% CIs.

Table 2
Meta-analyses of secondary efficacy outcomes.

Outcomes	Participants/Number of trials	Effect size (Pooled WMD, 95% CI, p valor)	Heterogeneity (I^2 statistic)
Apnea/hypopnea index (number/hour)	64/2 [17,21]	−23.2 (−40.00 to −6.42), p = 0.01	86.4%
Epworth Sleepiness Scale score	2582/4 trials [20–22,24]	−2.44 (−3.39 to −1.50), p = 0.0001	53.0%
Systolic blood pressure (mmHg)	2560/7 [17,22–24]	−2.48 (−6.28 to 1.32), p = 0.20	61.4%
Diastolic blood pressure (mmHg)	2520/6 [17,20,22–25]	−0.19 (−1.20 to 0.83), p = 0.72	0%
Left ventricular ejection fraction (%)	141/4 [17,21,24,25]	4.10 (1.39–6.80), p = 0.003	0%
SF-36	2619/4 [19,20,23,24]	0.97 (−0.15 to 2.08), p = 0.08	8.7%
Physical-component score		1.15 (0.49–1.81), p = 0.001	0%
Mental-component score			

SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey range from 0 to 100, with higher scores indicating better quality of life concerning either the physical or mental component.

CPAP use among 15 patients, including problems with either mask or machine (n = eight), upper airway symptoms due to CPAP use (n = eight) and stroke-related symptoms which caused non-compliance (n = nine).

A total of 17 patients were withdrawn due to side effects or intolerance among 1480 patients allocated to CPAP treatment in five trials [20–24].

4. Discussion

This meta-analysis of randomized trials showed no statistically significant effects of CPAP therapy, neither all-cause mortality, cardiovascular mortality, stroke, myocardial infarction nor any major cardiovascular event in adult patients with OSA and cardiovascular disease. The meta-analysis also failed to demonstrate significant effects of CPAP on either systolic or diastolic blood pressure in these patients. On the other hand, the meta-analysis showed that CPAP therapy was associated with an average increase of 4% in left ventricular ejection fraction in patients with OSA and heart failure. CPAP therapy also significantly improved sleep metrics (AHI and ESS score) and mental-component quality of life scores in patients with OSA and CVD.

The main difference between the current and two previous meta-analyses [11,12] is that the current one focused on the effects of CPAP on survival and secondary prevention of major cardiovascular events in patients with OSA and established cardiovascular disease. Despite the difference in study selection and outcome measures, all three meta-analyses presented disappointing null results regarding the effects of positive airway pressure on cardiovascular mortality and morbidity in patients with sleep apnea. One [11] of the two previous meta-analyses included two trials that assessed the effects of CPAP in patients with OSA and no CVD. We pooled the data from these two trials [26,27] showing no significant effects of CPAP on primary prevention of major cardiovascular events (cardiovascular death, nonfatal acute coronary syndrome, nonfatal stroke and hospitalization for unstable angina) (24/552 in the CPAP group vs. 24/562 in the usual care group, pooled RR 1.02, 95% CI 0.54 to 1.94, p = 0.95).

Poor treatment adherence is a major concern and has been proposed as the main reason for the lack of effectiveness of CPAP on survival and cardiovascular outcomes in patients with OSA. The

propensity-score matched analysis of the SAVE trial showed that, compared to usual care, CPAP use ≥4 hours per night was associated with a significantly lower risk of stroke and non-prespecified composite endpoint of cerebral events, but not primary composite cardiovascular events [10]. The secondary on-treatment analysis of another trial showed a significant effect of CPAP use ≥4 hours per night in reducing the risk of cardiovascular events in patients with non-sleep OSA and CVD, compared to CPAP use <4 hours per night or no-CPAP [18]. However, residual self-selection bias and multiple comparisons may have contributed to such "positive" results. The sensitivity analyses in the current meta-analysis and the subgroup analyses in the previous meta-analysis [11] failed to show consistent results regarding the effects of longer CPAP use (≥4 hours per night) on cardiovascular outcomes in patients with sleep apnea. The impact of increased adherence to CPAP therapy and the threshold level of nightly PAP use required to reduce cardiovascular risk remains to be better defined.

The pooled analysis of data from four small trials involving 141 patients with OSA and heart failure showed an average increase of 4% in left ventricular ejection fraction among those treated with CPAP. The magnitude of such increase in LVEF is similar to that related to one-year treatment with hydralazine plus isosorbide dinitrate which significantly impacted the mortality, as shown by a pharmacologic intervention trial in 642 patients with chronic heart failure [28]. Given that the patients in the four trials were already on optimal drug therapy, such additional improvement in LVEF associated with CPAP therapy should be considered clinically relevant.

The current meta-analysis showed that CPAP therapy was effective in improving sleep outcomes and mental-component quality of life scores, but not in reducing blood pressure or improving physical-component quality of life scores in patients with OSA and CVD, The data from six trials included in this meta-analysis showed an overall good safety profile of long-term CPAP therapy in patients with OSA and CVD. Of 1480 patients allocated to CPAP, only 17 (1.1%) were withdrawn due to side effects or intolerance. The patient-reported side effects included dry mouth, nasal or eye symptoms, noise problem and mask fit or leak problems. Overall, approximately 5%–15% of patients treated with CPAP reported adverse effects that they considered to be substantial [8]. They are potentially transient and not serious enough to cause withdrawal from the study but increasing side effect score at one month was found to be independently associated with reduced CPAP adherence at 12 months of treatment [29]. However, an association between CPAP side effects and treatment adherence has not been consistently reported by other studies [30–32].

Caution must be taken when interpreting and extrapolating the results of this meta-analysis. First, the majority of included patients were non-sleepy OSA subjects who may have less severe disease and lower adherence and response to CPAP therapy. They may not represent patients who are routinely seen in real-world clinical practice. Second, there was considerable clinical heterogeneity between the included trials regarding the type of CVD, diagnostic criteria for OSA and duration of CPAP therapy. Third, the number of included trials is relatively small, and one study (SAVE trial) [20] has contributed more than 50% of the weight in the meta-analyses of all outcomes. Fourth, based on the GRADE approach [15], the overall quality of evidence from this meta-analysis was graded as low, due to above-mentioned clinical heterogeneity and imprecision of the effect estimate (the 95% CIs include appreciable benefit and harm). This means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate [33].

Despite that the current and previous meta-analyses of randomized trials yielded statistically null results, the point estimates of effects suggest the possibility of potential benefits of CPAP therapy on survival and some cardiovascular outcomes in patients with OSA at risk or with an established cardiovascular disease, which should be confirmed by further studies. Thus, current evidence is insufficient to recommend for or against the use of CPAP for the purpose of improving survival or preventing major cardiovascular events in patients with OSA. Until further robust evidence is available, it seems more prudent to follow current guidelines recommending the use of CPAP in patients with moderate to severe OSA, especially those with excessive daytime sleepiness, given the well-established effects on sleep outcomes, potential cardiovascular benefits and lack of serious side effects of such a therapy. As a general rule, the optimal individualized treatment strategy should be established for each patient with OSA, based on disease severity, comorbidities, and patient response.

Author contributions

Dr. Felipe da Silva Paulitsch conceptualized and designed the study, participated in the literature search, trial selection, quality assessment, data collection, and data interpretation, and drafted the protocol and the review article.

Dr. Linjie Zhang contributed to the study's conception and design, literature search, trial selection, quality assessment, and data collection. He conducted all data analyses, critically reviewed and approved the manuscript. Dr. Zhang is the guarantor of this research and takes responsibility for the integrity of this work as a whole.

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Conflict of interest

The authors have no conflicts of interest to disclose.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.09.030.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.09.030.

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