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META-ANALYSIS

A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea

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Aims To assess whether continuous positive airway pressure (CPAP) therapy reduces major adverse cardiovascular events (MACE) in patients with moderate-to-severe obstructive sleep apnoea (OSA).

Methods and results A total of 235 articles were recovered using MEDLINE, EMBASE and Cochrane library (inception–December 2016) and references contained in the identified articles. Seven randomized controlled trials (RCTs) were selected for final analysis. Analysis of 4268 patients demonstrated non-significant 26% relative risk reduction in MACE with CPAP [risk ratio (RR) 0.74; 95% confidence interval (CI) 0.47–1.17; $P = 0.19$, $I^2 = 48\%$]. A series of sensitivity analyses suggested that increased CPAP usage time yielded significant risk reduction in MACE. and stroke. Subgroup analysis revealed that CPAP adherence time ≥4 hours (h)/night reduced the risk of MACE by 57% (RR 0.43; 95% CI 0.23–0.80; $P = 0.01$, $I^2 = 0\%$). CPAP therapy showed no beneficial effect on myocardial infarction (MI), all-cause mortality, atrial fibrillation/flutter (AF), or heart failure (HF) ($P > 0.05$). CPAP had positive effect on mood and reduced the daytime sleepiness [Epworth Sleepiness Scale (ESS): mean difference (MD) -2.50, 95% CI - 3.62, -1.39; $P < 0.001$, $I^2 = 81\%$].

Conclusion CPAP therapy might reduce MACE and stroke among subjects with CPAP time exceeding 4 h/night. Additional randomized trials mandating adequate CPAP time adherence are required to confirm this impression.

Keywords Continuous airway pressure • Obstructive sleep apnoea • Cardiovascular events • Stroke

Introduction

The European Society of Cardiology (ESC) acknowledges the direct relation of obstructive sleep apnoea (OSA) with cardiovascular (CV) events. Continuous positive airway pressure (CPAP) therapy is the gold standard available to alleviate OSA.[1] However, CPAP effects on CV morbidity and mortality remain unproven. The Sleep Apnea Cardiovascular Endpoints (SAVE) trial has addressed this issue by assessing the effects of CPAP therapy in patients with moderate–to-severe OSA bearing clinically significant CV disease.[2] The SAVE trial suggested that CPAP therapy failed to reduce CV events with a mean CPAP usage time of 3.3 h/night [hazard ratio (HR) 1.10, 95% confidence interval (CI) 0.91–1.32; $P = 0.34$]. However, the same trial observed a non-significant trend in favour of the CPAP arm when data were adjusted for better compliance time (≥4 h/night) (HR 0.80, 95%CI 0.60–1.07; $P = 0.13$). Similar favourable trend with adequate nightly CPAP time (≥4 h/night) was noticed in The Randomized Intervention with CPAP in Coronary Artery Disease (CAD) and Sleep Apnea (RICCADSA) study and by Barbe and colleagues.[3,4]

This led to a hypothesis that increasing CPAP adherence time can have positive impact on CV morbidity and mortality. Previous reports were either limited to assessing change in left ventricular dysfunction, blood pressure, or mortality or were published before the contemporary RICCADSA and SAVE trials.[2,3,5,6] Consequently, we performed a meta-analysis to address these issues.

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Methods

Data sources and searches

Two authors (H.R. and M.L.) carried out the search using MEDLINE, EMBASE, and the Cochrane Library from inception to December 2016. An electronic search was supplemented by review of the references cited within this article. The search strategy is described in detail in supplementary material. Duplicates were removed manually and through EndNote X7 (Thompson ISI ResearchSoft, Philadelphia, PA, USA).

Study selection

The following inclusion criteria were set: (i) Only randomized controlled trials (RCTs) with patients with moderate-to-severe OSA who were randomized to either a CPAP therapy group or a control group (usual care, oxygen therapy, or sham CPAP) were selected and (ii) the included studies had to report outcomes of interest (see below) in an adult population (aged ≥18 years) with follow-up at ≥3 months. Initially 235 articles were retrieved and after diligent screening 7 RCTs were included. Meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[7] The study selection process is illustrated in *Figure 1*.

Quality assessment and data extraction

Two authors (H.R. and M.L.) independently extracted the data using a standardized collection form incorporating baseline characteristics, events, sample size, mean, standard deviations, crude point estimates, or standard error estimates. For continuous outcomes, the authors extracted data on differences between the two interventions at the time of follow-up in addition to any changes from baseline. When possible, estimates adjusted for the baseline measurements were selected. When reported, we acquired outcomes from an intention-to-treat (ITT) analysis. Data were appraised by C.D. and S.U.K., and discrepancies were resolved by discussion and agreement or by third-party review. The risk of bias assessment was done at the study level, and methodological quality assessment was done using the Cochrane bias risk assessment tool[8] (see Supplementary material online, *Table S1*).

Outcome measures

Primary outcome

Major adverse cardiovascular events (MACE): composite of myocardial infarction (MI), stroke, and CV mortality.

Secondary outcomes

Myocardial infarction, stroke, CV mortality, non-CV mortality, all-cause mortality, atrial fibrillation/flutter (AF), heart failure (HF), change in systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index, Epworth Sleepiness Scale (ESS), and Hospital Anxiety and Depression Scale (HADS). Definitions of the endpoints are reported in the supplementary material.

Statistical analysis

Outcomes from all the studies were combined using the DerSimonian and Laird random-effects model.[9] Dichotomous

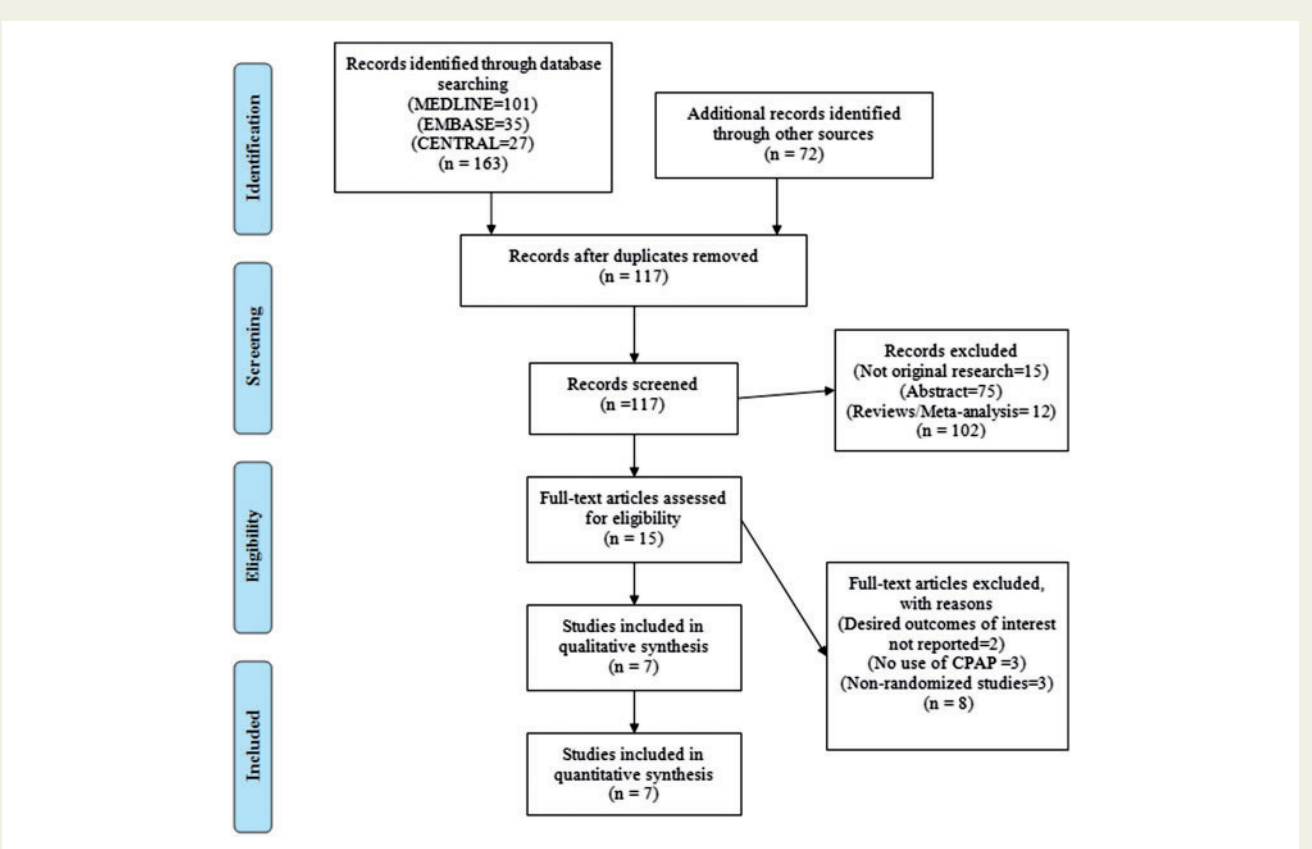

Figure 1 Search strategy: study selection process through preferred reporting items for systematic reviews and meta-analyses.

estimates were reported as risk ratio (RR), and continuous variables were reported as mean difference (MD) with 95% CI. A *P*-value of 0.05 was set as significant. Heterogeneity was assessed using Q statistics with I^2 with values >50% consistent with a high degree of heterogeneity.[10]

A series of sensitivity analyses to assess the impact of CPAP adherence time on the primary endpoint and important CV outcomes were performed. This included serial exclusion of studies with low CPAP adherence time, exclusion of the SAVE trial which carried the highest weight in pooled analysis, and by replacing the SAVE trial's ITT estimates with estimates of a pre-specified analysis (defined by CPAP treatment at an average of ≥4 h/night, using one-to-one matching of CPAP adherers to patients from the usual care arm who never used CPAP).[2] A subgroup analysis based on CPAP adherence time was performed. All analyses were conducted using Comprehensive Meta-analysis software version 2.2 (Biostat, Englewood, NJ, USA).

Results

In seven RCTs (CPAP = 2122 and control = 2146), mean age of study participants was 62 years (range 52–71 years), 79.5% were male, 59% had hypertension (HTN), 52% had CAD, and 33% had diabetes mellitus. Barbé *et al.*[4] excluded patients with a prior CV history, and all other studies studied CPAP for secondary prevention. The Heart Biomarker Evaluation in Apnea Treatment (HeartBeat) trial reported three arm comparisons [CPAP, healthy lifestyle and sleep education, and nocturnal supplemental oxygen (NSO)].[11] Data were extracted from the CPAP and NSO arms for analysis. Baseline characteristics of the participants are reported in *Table 1*, whereas *Table 2* contains the results for the entire study population. Study characteristics are described in detail in Supplementary material online, *Table S2*.

Primary outcomes

Major adverse cardiovascular events: at mean follow-up duration of 37 months and mean CPAP adherence time 3.5 h/night, CPAP therapy did not significantly decrease the risk of MACE (RR 0.74, 95% CI 0.47–1.17; $P = 0.19$, $I^2 = 48$) (*Figure 2*). Stepwise exclusion of studies with low CPAP usage time [a multicentre RCT and economic evaluation of CPAP for the treatment of OSA syndrome in older people (PREDICT) and RICADDSA] yielded a non-significant 43% risk reduction in MACE with CPAP therapy.[3,12] The additional exclusion of SAVE trial generated a significant 58% risk reduction in MACE.[2] These results remained consistent even when the SAVE trial was removed exclusively or when the SAVE trial's ITT estimates were replaced with estimates of a pre-specified analysis in the sensitivity analysis (*Table 3*). Similarly, in subgroup analysis, patients showed

Table 1 Baseline demographic details of studies

	Barbe F *et al.*[4]	PREDICT.[12,a]	Huang *et al.*[13]	HeartBeat[11,b]	Parra *et al.*[14]	RICCADSA[3]	SAVE[2]
Follow-up duration (months)	48	12	36	3	60	57	43
CPAP adherence time (h/night)	4	2.2	4.5	3.5	4	3	3.3
Groups	CPAP/no active intervention	CPAP/no active intervention	CPAP/no active Intervention	CPAP/NSO	NCPAP/no active intervention	CPAP/no intervention	CPAP/no active intervention
Sample size	357/366	140/138	36/37	97/94	57/69	122/122	1346/1341
Mean age (years)	52/52	71/71	62/63	63/63	64/66	65/66	61/61
Male (%)	88/84	86/79	78/87	76/69	72/70	82/86	81/81
Mean Epworth Sleepiness Scale	6/6	12/12	9/8	8/9	7/5	5/7	7/7
Mean apnoea–hypopnoea index/h	42/35	29/28	28/29	25/24	≥20/20	28/29	29/29
Mean neck circumference (cm)	42/42	42/44	41/41	NR	41.9/42.3	NR	41/41
Mean BMI (kg/m^2)	31/31	34/34	28/28	33/35	30/29	28/28	29/28
Smoker (%)	32/36	84/80	53/62	4/11	46/32	18/14	16/15
Coronary artery disease (%)	0/0	30/36	31/38	51/54	12.7/17.6	100/100	77/81
Diabetes mellitus (%)	NR/NR	29/31	33/38	47/43	38/37	28/20	30/29
Hypertension (%)	53/50	70/75	NR/NR	84/88	60/63	69/59	79/78
Previous stroke (%)	NR/NR	11/14	NR/NR	NR/NR	100/100	NR/NR	53/54

[a]Results are reported for initial randomized population. In all, 17% lost during follow-up, and 83% of the remaining participants were included in final analysis.
[b]Information is reported for only CPAP and NSO groups.
CPAP, continuous positive airway pressure; HeartBeat, The Heart Biomarker Evaluation in Apnea Treatment; NR, not reported; NSO, nocturnal supplemental oxygen; PREDICT, A multicentre randomized controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people; RICCADSA, The Randomized Intervention with CPAP in Coronary artery disease and OSA; SAVE, sleep apnoea cardiovascular endpoints.

Table 2 Estimates in entire population

Outcomes	Number of studies (*n*)	Risk ratio (95% CI)	*P*-value (I^2)
MACE	7 (4268)	0.74 (0.47–1.17)	0.19 (48)
MI	7 (4268)	0.99 (0.57–1.72)	0.98 (19)
Stroke	7 (4268)	0.95 (0.72–1.24)	0.69 (0)
CV mortality	5 (3853)	0.70 (0.27–1.80)	0.46 (35)
Non-CV mortality	5 (3853)	1.53 (0.61–3.82)	0.37 (54)
All-cause mortality	5 (3853)	0.95 (0.67–1.34)	0.76 (0)
Atrial fibrillation/flutter	3 (3102)	0.87 (0.38–1.97)	0.73 (47)
Heart failure	3 (3483)	0.95 (0.53–1.73)	0.87 (0)
		Mean difference (95% CI)	***P*-value (I^2)**
Systolic blood pressure (mmHg)	4 (2810)	-1.44 (-3.96, 1.08)	0.26 (73)
Diastolic blood pressure (mmHg)	4 (2810)	-0.36 (-1.28, 0.56)	0.44 (0)
Epworth Sleepiness Scale	4 (3354)	-2.50 (-3.62, -1.39)	<0.001 (81)
BMI (kg/m^2)	3 (1020)	0.45 (-014, 1.03)	0.14 (0)
Hospital Anxiety Depression Scale (anxiety)	2 (2640)	-0.40 (-0.67, -0.13)	<0.001 (0)
Hospital Anxiety Depression Scale (depression)	2 (2640)	-0.70 (-1.09, -0.31)	<0.001 (0)

CV, cardiovascular; CI, confidence interval; MACE, major adverse cardiovascular events; MI, myocardial infarction; *n*, sample size.

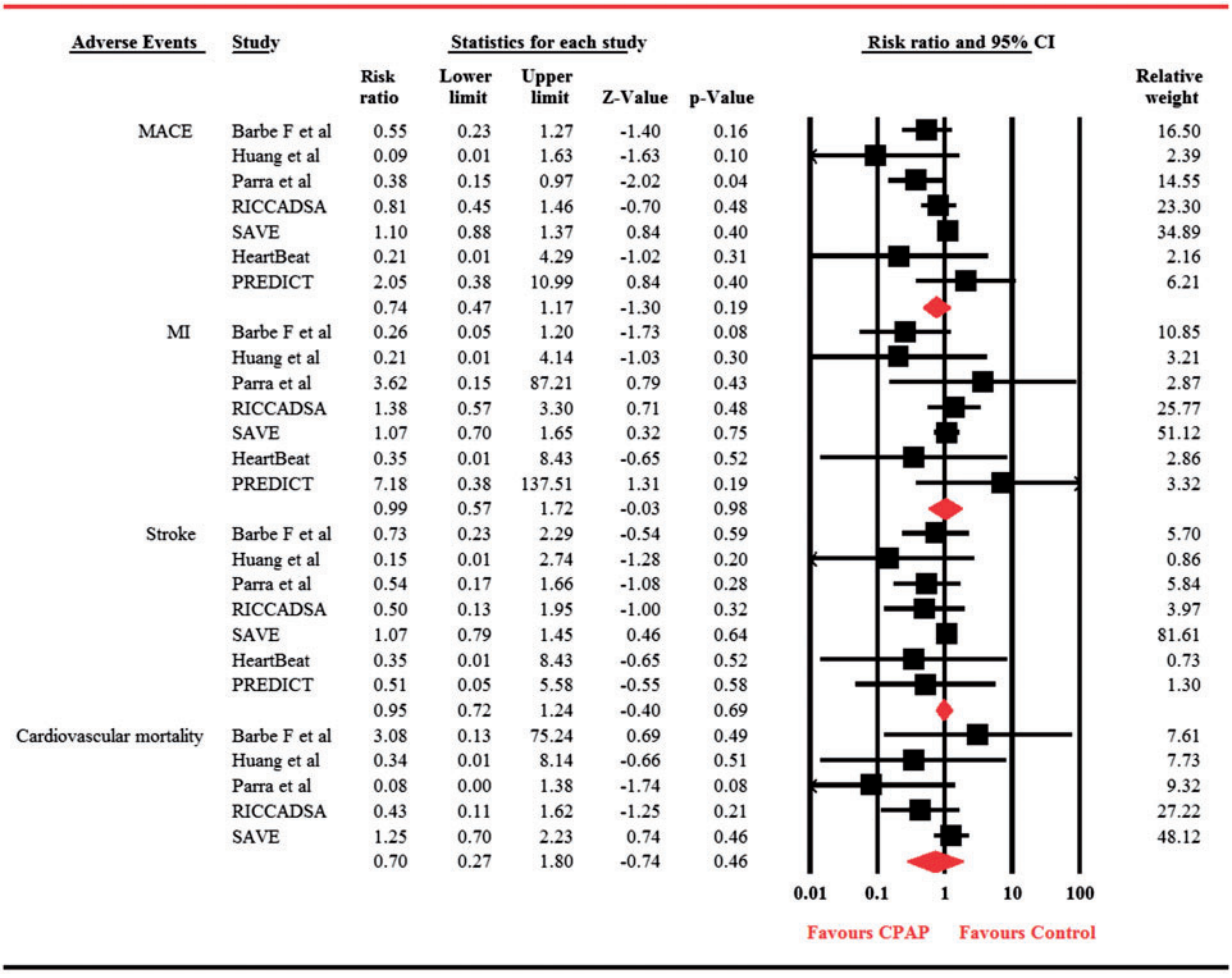

Figure 2 Forest plot showing effect of continuous positive airway pressure (CPAP) vs. control on major adverse cardiovascular endpoints (MACE), myocardial infarction (MI), stroke, and cardiovascular mortality.

Table 3 Sensitivity analyses

Outcomes	Estimates after excluding PREDICT and RICCADSA		Estimates after excluding PREDICT, RICCADSA, and SAVE		Estimates after excluding SAVE only		Estimates after using SAVE's [a]pre-specified estimates	
	RR (95% CI)	*P*-value (I^2)	RR (95% CI)	*P*-value (I^2)	RR (95% CI)	*P*-value (I^2)	RR (95% CI)	*P*-value (I^2)
MACE	0.57 (0.28–1.17)	0.13 (61)	0.42 (0.23–0.76)	<0.001 (0)	0.61 (0.37–1.00)	0.05 (53)	0.70 (0.50–0.98)	0.04 (13)
MI	0.73 (0.32–1.63)	0.44 (22)	0.37 (0.11–1.19)	0.10 (0)	0.87 (0.31–2.39)	0.78 (38)	1.03 (0.54–1.97)	0.92 (21)
Stroke	0.98 (0.74–1.29)	0.88 (0)	0.55 (0.26–1.17)	0.12 (0)	0.54 (0.29–1.01)	0.05 (0)	0.56 (0.37–0.84)	0.01 (0)
CV mortality	0.76 (0.20–2.83)	0.68 (0)	0.40 (0.05–3.33)	0.40 (28)	0.41 (0.14–1.19)	0.10 (68)	0.66 (0.30–1.46)	0.31 (11)
Non-CV mortality	1.51 (0.48–4.79)	0.48 (66)	2.86 (1.03–7.92)	0.04 (0)	2.60 (1.09–6.20)	0.03 (0)	1.43 (0.44–4.63)	0.55 (65)
All-cause mortality	0.98 (0.67–1.41)	0.90 (0)	1.18 (0.44–3.14)	0.74 (26)	0.99 (0.54–1.84)	0.98 (0)	0.81 (0.53–1.24)	0.33 (1)

[a]Pre-specified estimates are reported at CPAP duration >4 h/night.
CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; PREDICT, A multicentre randomized controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people; RICCADSA, The Randomized Intervention with CPAP in Coronary artery disease and OSA; SAVE, sleep apnoea cardiovascular endpoints.

consistent reduction in MACE when CPAP was used ≥4 h/night (RR 0.43, 95% CI 0.23–0.80; $P = 0.01$, $I^2 = 0\%$; *Figure 3*).

Secondary outcomes

Continuous positive airway pressure therapy failed to reduce the risk of MI, CV mortality, non-CV mortality, all-cause mortality, AF, or HF. However, in the sensitivity analyses, the removal of SAVE trial and using the trial's pre-specified estimates showed a significant risk reduction in stroke.[2] The CPAP therapy was associated with non-significant improvement in both SBP (MD -1.44, 95%CI -3.96, -1.08; $P = 0.26$, $I^2 = 70$) and DBP (MD -0.36, 95% CI -1.28, 0.56; $P = 0.44$, $I^2 = 0$). The CPAP therapy significantly reduced the events of daytime sleepiness and had a positive impact on mood by reducing HADS.

Discussion

Treatment with CPAP has been widely implemented in both the inpatient and the outpatient settings. Although CPAP greatly enhances the quality of life and functionality of OSA subjects, the effects of CPAP on CV events remained undefined.[15,16] In this review, we report a non-significant 26% risk reduction in MACE with a mean CPAP usage time of 3.5 h/night. Continuous positive airway pressure also failed to significantly reduce MI, CV mortality, total mortality, AF, and HF (*Table 2*). However, a series of sensitivity analyses confirmed that increased nightly CPAP duration resulted in a favourable effect on MACE, predominantly driven by a significant reduction in stroke (*Table 3*). These results are new and contradictive to previous reports.[5]

Accumulating evidence has shown a clear association between OSA and the incidence of ischaemic stroke.[17–19] The Sleep Heart Health Study reported a higher incidence of stroke in male patients whose obstructive apnoea–hypopnoea index (AHI) was in the highest quartile (AHI > 19) compared to patients whose AHI was in the lowest quartile (AHI < 4) (adjusted HR 2.86, 95% CI 1.10–7.39).[20] However, sleep-disordered breathing has been a frequent observation (40–75% of patients have an AHI ≥ 10) in patients presenting with an acute ischaemic stroke.[19,21–23] The notion that OSA is a potential risk factor for ischaemic stroke is mostly derived from evidence in heart disease and HTN.[24] The proposed mechanisms include a multitude of factors: intrathoracic pressure swings, blood pressure (BP) variations, changes in cerebral autoregulation and blood flow, endothelial dysfunction, metabolic dysregulation, progression of atherosclerosis, and pro-inflammatory states.[16,24] By controlling OSA, CPAP therapy can potentially attenuate this pathological cascade and its deleterious effects[16] (*Figure 4*). For instance, Foster *et al.*[25] demonstrated that a diminished cerebrovascular response to hypoxia among OSA patients was normalized after 4–6 weeks of CPAP therapy. The clinical implications of these effects are further reflected in RCTs.[2,14] Parra *et al.*[14] reported that early CPAP treatment improved long-term CV survival in ischaemic stroke patients with moderate-to-severe OSA (CPAP vs. control: 100% vs. 89.9%, log-rank test 5.887, $P = 0.015$).

The dose–response relationship between CPAP duration and its treatment effect has been supported by former studies, wherein reduction of CV events was only demonstrated at improved CPAP usage time (average nightly duration ≥4 h/night).[2–4] Investigators of SAVE recommended cautious interpretation of their adjusted results, given the involvement of potential confounders.[2] However, a specific and consistent pattern of improved outcomes at better CPAP adherence time highlights the need for clinical trials designed to assess and validate the effects of CPAP quality and nightly usage time on CV outcomes. Investigators of the CPAP in patients with acute coronary syndrome (ACS) and OSA (ISAACC) trial are actively recruiting OSA patients with an AHI ≥ 15/h with ACS and ESS ≤10 to monitor the effects of prolonged CPAP therapy ≥4 h/day on CV events.[26] The results from this study may direct further investigations.

The favourable effects of CPAP on systemic HTN have been well established in the literature. Studies using 24 h of BP monitoring showed improvement in both SBP (up to 2.5 mmHg) and DBP (up to 2 mmHg) with CPAP and even better response for resistant HTN (SBP up to 7.2 mmHg and DBP up to 4.9 mmHg) when compared with suboptimal or conservative management.[27–34] Although our results did not demonstrate a statistically significant reduction in BP

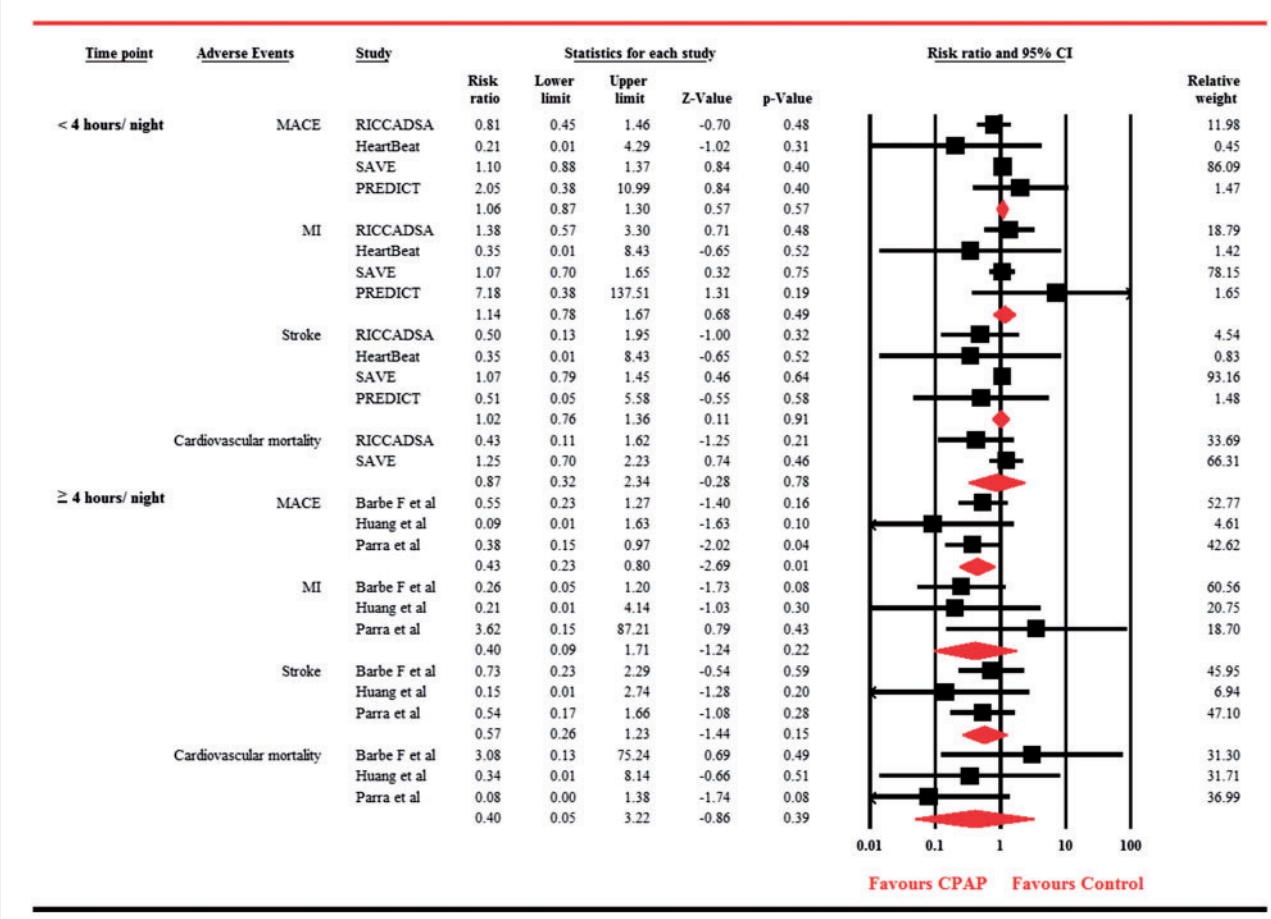

Figure 3 Forest plot showing subgroup analyses with regard to continuous positive airway pressure (CPAP) adherence time on major adverse cardiovascular endpoints (MACE), myocardial infarction (MI), stroke, and cardiovascular mortality.

with CPAP, a favourable trend was apparent. The BP response can be extremely variable depending on the severity of OSA, baseline HTN, and CPAP usage time. The impact of CPAP adherence time on HTN was demonstrated in the Effect of CPAP on BP in Patients With OSA and Resistant HTN (HIPARCO) trial where a linear correlation (decrease of 1.9 mmHg SBP and 1 mmHg DBP for each additional hour of CPAP therapy) was observed.[3] Given the strong association of HTN with CV events, these significant reductions in SBP can also result in better CV outcomes over a period of time.

Current review includes patient with a mean age of 62 years, 79.5% were men, ESS was 7.7, and AHI was 28/h. Although none of these factors have shown strong association with CPAP adherence, the literature is also inconsistent regarding the influence of these factors on CV outcomes.[35] For instance, it is under debate whether AHI or nocturnal hypoxaemia is a better predictor of mortality in cardiac patients. In a systematic review, 18 of 26 studies were shown to have a direct and statistically significant association of AHI with CV events.[35] Conversely, there are data relating nocturnal hypoxaemic burden (time with oxyhaemoglobin saturation <90%) as an independent predictor of mortality.[36,37] With regard to age, OSA patients around 30–75 years are found to carry higher CV risk than the elderly population.[35,38,39] Furthermore, females are in general much less represented in the literature. This may have occurred as the estimated prevalence of OSA is greater in adult males (24%) compared to females (9%) or due to referral or survivor bias by which only healthier older men were referred for a sleep study.[40] There are also some observational data indicating an association of daytime sleepiness with mortality and CV disease.[41,42] Epworth Sleepiness Scale remained the most widely used screening tool for the assessment of daytime sleepiness in clinical and research settings.[1,43] We confirm numerous former reports that CPAP therapy has a remarkable impact on quality of life by reducing daytime sleepiness and improving the mood of patients.

Adequate CPAP adherence remains a challenging issue.[44] One potential concern is that different CPAP modalities [i.e. auto-CPAP (APAP) or fixed CPAP], as shown in the studies contained in current review, can affect adherence.[44] However, this is not supported by a meta-analysis showing comparable outcomes between APAP and standard CPAP with regard to improvement in CPAP adherence (estimate of improvement 0.20 h/night, 95% CI -0.16, 0.57; $P = 0.28$), AHI, and ESS.[45] To improve the overall quality of CPAP, it is essential that ever critical elements that can affect compliance be addressed. Continual CPAP education, adequate monitoring, feedback, and close follow-up can make a tremendous difference on the quality of CPAP therapy. Other common barriers to compliance include claustrophobia; physical limitations related to nasal resistance and improperly fitted masks, airway humidification, and bed partner perception of the

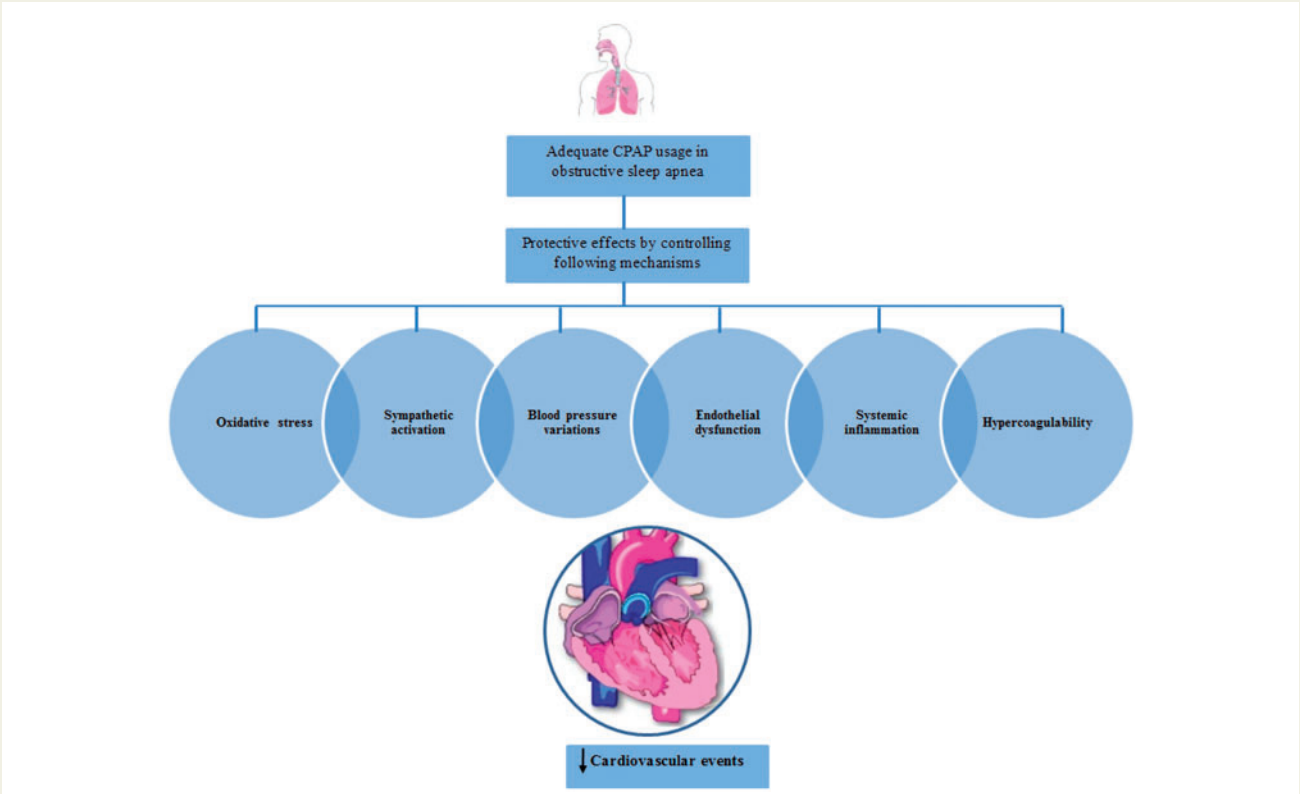

Figure 4 Central illustration showing effect of continuous positive airway pressure (CPAP) therapy in reducing cardiovascular events.

treatment.[44] Therefore, a multidisciplinary approach is required to address these issues and achieve the desired results. Moreover, given the emerging role of technological advancements such as tele monitoring and Web applications, future studies should include these technologies to explore their impact on CPAP compliance.[46]

Limitations

This meta-analysis is hampered by several limitations. First, there is a considerable degree of heterogeneity with regard to the different study designs, burden of co-morbidities, methods of CPAP application, and sleep evaluation. Second, as highly symptomatic patients had been excluded from the majority of RCTs as it would have been considered unethical to withhold treatment in this population, this review predominantly generates evidence in patients with mild-to-moderate symptoms. Third, adjustments were not made for the subset of patients with severe nocturnal hypoxaemia and not reporting timing of CPAP (i.e. early vs. late at night). This is an important factor to consider, because duration of apnaeic or hypopnaeic events and severity of oxygen desaturation tends to worsen during rapid eye movement (REM) sleep compared with non-REM sleep. REM sleep has been associated with HTN, which can then impact CV outcome. Fourth, since most of the evidence is derived from patients with clinically active CV disease, the favourable CV effects of CPAP may be limited for secondary prevention. Fifth, since the publication bias was not assessed due to smaller number of studies, it is a potential limitation. Finally, it is also possible that the study population and duration of follow-up along with the inherent event rates of the populations studied were not adequately powered to generate statistically significant effects on CV endpoints.

Conclusions

This meta-analysis suggests that in subjects with moderate–to-severe OSA, CPAP compliance for the duration of ≥4 h/night may reduce the risk of MACE driven mostly by reducing the risk of stroke. Additional RCTs with improved CPAP quality and duration are required to confirm these observations. CPAP therapy results in a favourable effect on mood and daytime sleepiness.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: none declared.

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