CPAP for secondary cardiovascular prevention in obstructive sleep apnoea patients: not only one moon, but many stars

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Shareable abstract (@ERSpublications)
RCTs failed to demonstrate CPAP therapy efficacy in preventing secondary major adverse cardiovascular events. Exclusion of sleepy patients and a low CPAP adherence limit their external validity. RCTs may not be sufficient to capture the diversity of OSA. https://bit.ly/3qNhUZP

Cite this article as: Baillieul S, Shah NM, Dharmasena R, *et al*. CPAP for secondary cardiovascular prevention in obstructive sleep apnoea patients: not only one moon, but many stars. *Breathe* 2022; 18: 220148 [DOI: 10.1183/20734735.0148-2022].

Received: 26 June 2022
Accepted: 14 Sept 2022

Abstract

While continuous positive airway pressure (CPAP) therapy has a strong evidence base for the treatment of obstructive sleep apnoea (OSA), its impact on cardiovascular comorbidity remains unclear. This journal club reviews three recent randomised controlled trials aimed to evaluate the impact of CPAP therapy in secondary prevention of cerebrovascular and coronary heart disease (SAVE trial), comorbid coronary heart disease (RICCADSA trial) and in patients admitted with acute coronary syndrome (ISAACC trial). All three trials included patients with moderate-to-severe OSA and excluded patients with severe daytime sleepiness. When CPAP was compared with usual care, they all reported no difference in a similar primary composite end-point including death from cardiovascular disease, cardiac events, and strokes. These trials faced the same methodological challenges, including a low primary end-point incidence, the exclusion of sleepy patients, and a low CPAP adherence. Therefore, caution must be taken when broadening their results to the wider OSA population. Although randomised controlled trials provide a high level of evidence, they may not be sufficient to capture the diversity of OSA. Large-scale, real-world data may be able to provide a more rounded and generalisable picture of the effects of routine clinical use of CPAP on cardiovascular morbimortality.

Commentary on:

- McEvoy RD, *et al.* CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med* 2016; 375: 919–931.
- Peker Y, *et al.* Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016; 194: 613–620.
- Peker Y, *et al.* Effect of obstructive sleep apnea and CPAP treatment on cardiovascular outcomes in acute coronary syndrome in the RICCADSA trial. *J Clin Med* 2020; 9: 4051.
- Sanchez-de-la-Torre M, *et al.* Effect of obstructive sleep apnoea and its treatment with continuous positive airway pressure on the prevalence of cardiovascular events in patients with acute coronary syndrome (ISAACC study): a randomised controlled trial. *Lancet Respir Med* 2020; 8: 359–367.

Context

"Shoot for the moon. Even if you miss, you'll land among the stars."

Norman Vincent Peale

Obstructive sleep apnoea (OSA) is one of the most prevalent chronic diseases, affecting approximately one billion people globally [1, 2]. OSA is common in patients with cardiovascular diseases with estimates of prevalence of 40–60% [3]. OSA is considered a major health problem, being associated with detrimental cardiovascular, metabolic, and neurocognitive consequences, as well as bothersome diurnal symptoms that adversely impact daytime function and work productivity [4]. Continuous positive airway pressure (CPAP) is the first-line treatment for severe OSA [4, 5], and is currently used nightly by millions of individuals worldwide. Recent cost-effectiveness investigations support that treating OSA with CPAP may also be beneficial in reducing health costs [6, 7]. CPAP therapy improves excessive daytime sleepiness and quality of life in OSA patients [8]. CPAP therapy has also been demonstrated to improve blood pressure [9] and resistant hypertension [10], as well as left ventricular mechanical overload and the incidence of arrhythmias [10] in randomised controlled studies. While observational data suggests CPAP therapy may lower the prevalence of cardiovascular complications and death from cardiovascular causes [11], its efficacy in preventing secondary cardiovascular risk is still debated as the evidence remains conflicting. In this journal club, we will put into perspective the evidence on the effect of CPAP therapy in preventing cardiovascular morbimortality arising from randomised controlled trials (RCTs) and summarise the perspectives in the field.

Methods

Table 1 provides an overview of the characteristics of participants included in the RCTs assessing the effects of CPAP treatment on cardiovascular morbimortality.

SAVE

The *Sleep Apnea cardioVascular Endpoints* trial (SAVE; ClinicalTrials.gov identifier: NCT00738179) [12] was an international, multicentre (89 clinical centres, seven countries), randomised, parallel-group, open-label trial, with blinded end-point assessment. Moderate-to-severe OSA adults between 45 and 75 years of age with comorbid coronary artery or cerebrovascular disease were recruited.

OSA diagnosis was based on a type III sleep study device (ApneaLink, ResMed) and retained for an oxygen desaturation index (4%) ⩾12 per h of recording and confirmed by review of the data at a central core sleep laboratory. Patients were excluded from the study if they reported severe daytime sleepiness (Epworth Sleepiness Scale (ESS) score >15) or were considered to have a high risk of a road traffic accident due to excessive daytime sleepiness, as well as if they had very severe hypoxaemia (oxygen saturation measured by pulse oximetry <80% for >10% of recording time), or a Cheyne–Stokes respiration pattern on the ApneaLink nasal pressure recording. To ensure a minimal adherence to CPAP therapy (⩾3 h

TABLE 1 General characteristics of the participants included in the randomised controlled trials assessing the effects of continuous positive airway pressure (CPAP) treatment on cardiovascular morbimortality

	SAVE study [12]	RICCADSA study [13]	ISAACC study [15]
Inclusion criteria	Moderate-severe OSA (ODI ⩾12 events·h^{-1})	Moderate-severe OSA (AHI ⩾15 events·h^{-1})	Moderate-severe OSA (AHI ⩾15 events·h^{-1})
	Coronary artery disease or cerebrovascular disease	Coronary artery disease	Acute coronary syndrome
Exclusion criteria	Severe daytime sleepiness (ESS >15/24)	Excessive daytime sleepiness (ESS ⩾10/24)	Excessive daytime sleepiness (ESS >10/24)
Age, years	61	66	60
Men, %	81	85	84
ESS	7.4	5.5	5.2
AHI, events·h^{-1}	31	29	36
Number of events, n (%)	CPAP: 229 (17%)	CPAP: 22 (18%)	CPAP: 98 (16%)
	Usual care: 207 (15%)	Usual care: 27 (22%)	Usual care: 108 (17%)
CPAP use, mean±SD, h per night	3.3±2.3	Not stated	2.8±2.7

Age, ESS, AHI are presented as the mean values for the study cohort. AHI: apnoea–hypopnoea index; ESS: Epworth sleepiness scale; ODI: oxygen desaturation index; OSA: obstructive sleep apnoea.

per night on average), patients were subjected to a 1-week sham CPAP run-in period. Eligible patients were then randomly assigned to receive usual care alone (advice on healthful sleep habits and lifestyle changes to minimise OSA) or CPAP therapy plus usual care. The primary composite end-point was death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for unstable angina, heart failure or transient ischaemic attack, and was assessed at 1, 3, 6, and 12 months and annually thereafter, with a phone call every 6 months between annual clinic visits.

RICCADSA

The *Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnea* trial (RICCADSA; ClinicalTrials.gov identifier: NCT00519597) was a single-centre, open-label, blinded evaluation RCT that assessed the effects of CPAP on long-term adverse cardiovascular outcome risk in patients with angiography-verified coronary artery disease (CAD) [13]. Inclusion criteria were percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for CAD in the 6 months prior to enrolment in the study and the absence (apnoea–hypopnoea index (AHI) <5 events·h^{-1}) or presence of moderate-to-severe OSA (AHI ⩾15 events·h^{-1}) [14]. OSA diagnosis was based on home sleep cardiorespiratory polygraphy and in-hospital polysomnography (PSG). Patients with already treated OSA, presenting Cheyne–Stokes breathing or with mild OSA (AHI ⩾5 events·h^{-1} and <15 events·h^{-1}) were excluded. Patients without OSA and sleepy moderate-to-severe OSA patients (ESS ⩾10) were included in an observational arm. Non-sleepy OSA patients (ESS ⩽10) were randomly assigned in a 1:1 manner, with stratification by sex and revascularisation type, to CPAP therapy or no CPAP therapy. The primary end-point was a composite of cardiovascular mortality, myocardial infarction, stroke and repeated revascularisation assessed over a 3-year follow-up period. In case of multiple events during the follow-up period, only the first event was included in the combined end-point.

ISAACC

The *Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP* trial (ISAACC study; ClinicalTrials.gov identifier: NCT01335087) was a multicentre (15 hospitals in Spain), open-label, parallel-group RCT that sought to determine whether treating patients diagnosed with OSA with CPAP after suffering from acute coronary syndrome (ACS) resulted in improved cardiovascular morbidity and mortality [15].

Eligibility criteria were an age ⩾18 years, a hospital admission with documented symptoms of ACS and an ESS ⩽10. Exclusion criteria included previous treatment with CPAP, a previously diagnosed sleep disorder, ESS >10, presence of >50% central apnoeas or Cheyne–Stokes breathing and cardiogenic shock. Eligible patients were screened for OSA using respiratory polygraphy 24–72 h after admission for an ACS. Patients with an AHI ⩾15 events·h^{-1} were included in this study. Included participants were randomised (1:1) to receive either CPAP in addition to usual care or usual care alone. The primary outcome was a composite of the first cardiovascular event occurring during the follow-up period, and included death from cardiovascular causes, acute myocardial infarction, stroke, admission with heart failure, unstable angina, or a transient ischaemic attack. Patients were followed-up for a minimum of a year (median (interquartile range (IQR)) follow-up of 3.4 (1.5–5.3) years).

Results

SAVE

In the SAVE RCT, among the 15 325 patients assessed for eligibility, 5844 met the initial eligibility criteria and underwent ApneaLink testing, and 3246 entered the 1-week run-in phase. 2687 patients were randomly assigned to receive CPAP plus usual care (1346 patients) or usual care alone (1341 patients). Overall, the included patients were mostly male (80.9%), with a mean age of 61 years and an ESS score of 7.4. The mean follow-up duration was 3.7 years, and 147 patients discontinued their participation in the study before the final visit.

No significant difference was observed between the two groups in the use of medications for cardiovascular and metabolic conditions, in lifestyle factors (*i.e.* diet and smoking), and in body mass index from inclusion to the end of the study. In the CPAP group, the mean±SD duration of adherence to CPAP therapy was 3.3±2.3 h per night, with 42% of patients presenting good adherence to treatment (⩾4 h per night) during overall follow-up. OSA was well controlled during the follow-up period, as indicated by the mean residual AHI under CPAP of 3.7 events·h^{-1}.

No significant effect of CPAP therapy on the prevention of major cardiovascular events was shown, even in the adjusted analysis. A primary end-point event occurred in 436 participants: 229 (17.0%) in the CPAP group and 207 (15.4%) in the usual-care group (hazard ratio (HR) (95% CI) with CPAP 1.10 (0.91–1.32);

p=0.34). In the pre-planned *post hoc* sensitivity analysis with propensity score matching according to CPAP adherence, patients who were adherent to CPAP therapy had a lower risk of stroke than those in the usual-care group (HR (95% CI) 0.56 (0.32–1.00); p=0.05), as well as a lower risk of the non-prespecified composite end-point of cerebral events (HR (95% CI) 0.52 (0.30–0.90); p=0.02), but these results were not adjusted for multiple testing.

In summary, in the SAVE trial, CPAP therapy had no significant effect on the reduction of incidence of secondary cardio- and cerebrovascular events in non-sleepy OSA patients. However, and even though the cardiovascular effects were not so evident, there was a significant improvement of excessive daytime sleepiness in the CPAP group (p<0.001), a reduction of anxiety and depression, less days of absence from work because of poor health and a greater improvement in quality of life.

RICCADSA

In the RICCADSA trial 244 patients were randomly assigned to auto-titrating CPAP (n=122) or no CPAP therapy (n=122) within 6 months after PCI or CABG for CAD. There was no difference between the two groups at inclusion. All patients were included in the intention-to-treat analysis, and median follow-up time until mortality, loss to follow-up, or the end of the study was 56.9 months (range: 6.5–90.2).

Regarding the primary outcome, no benefit of CPAP therapy was found. 49 patients reached the combined end-point during follow-up, 22 (18.1%) in the CPAP group and 27 (22.1%) in the no CPAP group (HR (95% CI) 0.80 (0.46–1.41); p=0.45). Adjusted on-treatment analysis with an adherence cut-off of ⩾4 h per night of CPAP usage showed a significant between-group difference (⩾4 h per night: six events *versus* <4 h per night or no CPAP: 43 events; HR (95% CI) 0.29 (0.10–0.86)) even after adjustments for covariables such as age, sex, body mass index, AHI, current smoking, and cardiovascular risk factors.

The authors recently published the results of the extended analysis of the RICCADSA study [16]. In this analysis, participants with non-sleepy OSA (AHI ⩾15 events·h^{-1}, ESS score <10; n=171) were randomised to CPAP (n=86) or no-CPAP (n=85) therapy. The sleepy OSA patients (AHI ⩾15 events·h^{-1} and ESS ⩾10) who were offered CPAP, and the ones with no-OSA (AHI <5 events·h^{-1}) were included in the observational arm. Over a median 4.7-year follow-up, CPAP-usage of at least 4 h·day^{-1} was associated with a significant risk reduction (adjusted HR (95% CI) 0.17 (0.03–0.81); p=0.03) compared with CPAP usage <4 h·day^{-1} or no-CPAP.

The RICCADSA study conducted on a representative sample of moderate-to-severe, non-sleepy OSA patients with a history of CAD demonstrated no effect of CPAP therapy on average. However, adherence seemed to play a key role in the effect of CPAP in secondary prevention, with a significant reduction of incidence of secondary cardiovascular events and mortality in patients using their therapy for at least 4 h per night.

ISAACC

In the ISAACC study, over the 7-year period of inclusion, 2834 patients with ACS underwent respiratory polygraphy. 2551 were recruited, of whom 1287 patients did not have OSA, and 603 patients (46.85%) were randomly assigned to the reference group. 1264 (49.55%) patients had OSA (AHI of more than 15 events·h^{-1}) and were randomly assigned to the CPAP (n=633) or the usual care group (n=631). In OSA groups, mean ESS was 5.2 and mean AHI was 36 events·h^{-1}. The number of patients who completed 1 year of follow-up in each group was 552 (88%) in the CPAP group, 549 (88%) in the usual care group, and 511 (86%) in the reference group, for a median follow-up duration of 3.35 years (IQR 1.50–5.31).

In intention-to-treat analysis, the prevalence of the primary outcome was similar between CPAP and usual care groups during follow-up: 98 (16%) and 108 (17%) cardiovascular events occurred in the CPAP and usual care groups, respectively (HR (95% CI) 0.89 (0.68–1.17); p=0.40). Surprisingly, the prevalence of cardiovascular events was similar between patients in the reference group (90 (15%) events) and those in the usual care group (102 (17%) events) during follow-up (HR 1.01 (0.76–1.35); p=0.93). Regarding secondary outcomes, CPAP therapy was associated with a marginal improvement in ESS and blood pressure and had no effect on self-reported quality of life. These results should be interpreted in light of the low mean time of CPAP usage (2.78±2.73 h per night), well below the recommended 4 h per night. The authors further divided the CPAP group into a good adherence group (mean CPAP usage ⩾4 h per night) and a poor adherence group (mean CPAP usage <4 h per night) and compared these subgroups with the usual care group for incidence of cardiovascular events. In the good adherence group, 18% (41 out of 227) of the patients presented a cardiovascular event, compared with 15% (56 out of 377) in the poor adherence group, and 17% (102 out of 607) in the usual care group (nonsignificant).

The authors of the ISAACC study concluded that in newly diagnosed, non-sleepy OSA patients with ACS, CPAP therapy had no beneficial effect on preventing secondary cardiovascular events. Moreover, the incidence of cardiovascular events seems not to be related to CPAP compliance or OSA severity. Although the results of this large trial are consistent with previous RCTs investigating the impact of CPAP therapy on secondary cardiovascular outcome in OSA patients, the inclusion of non-sleepy patients may, as in the SAVE trial, have negatively affected the outcome of this study, as this group may be at lower cardiovascular risk when compared with excessively sleepy patients [17]. This limits the external validity of the study, rendering a conclusion on the benefits of CPAP as secondary prevention on cardiovascular mortality and morbidity in patients with OSA who have suffered from ACS hard to draw.

Commentary

This journal club is focused on three recent major RCTs (SAVE, RICCADSA and ISAACC studies) [12, 13, 15, 16] assessing the effects of CPAP therapy in lowering cardiovascular morbimortality in secondary prevention in patients diagnosed with moderate-to-severe OSA. The three RCTs failed to demonstrate a clear benefit of CPAP therapy acutely (ISAACC study) [15] or more chronically (SAVE, RICCADSA studies) [12, 13, 16] after the initial cardiovascular event.

If CPAP remains indubitably the first-line treatment for symptomatic OSA [18], poor CPAP adherence (defined as a cut-off of <4 h per night and/or less than 70% of nights) in minimally symptomatic patients remains a challenge for clinicians. Specifically, this combination of factors (poor CPAP adherence and minimally symptomatic OSA) is the unifying characteristic of the populations included in the RCTs discussed in the present article. Although RCTs are methodologically the most robust and relevant, they may also be subject to several limitations, that should be discussed in the context of the evaluation of CPAP therapy.

First, the total number of secondary cardiovascular events in the different RCTs was low, limiting the ability to detect between-group differences, with sufficient statistical power. A recent study by Pépin *et al.* [19], based on large-scale, real-world data (88 007 patients included), showed that continuation of CPAP therapy when compared with CPAP therapy termination was associated with a significantly lower risk of all-cause death (HR (95% CI) 0.61 (0.57–0.65); p<0.01). Thus, large population-based cohort studies may be able to provide a more rounded picture of the effects of routine clinical use of CPAP on multiple outcomes, including cardiovascular morbimortality, and could represent a complement to RCTs in the future.

Second, the representativity of the highly selected study populations compared with the OSA population in general is arguable [20]. It is now acknowledged that OSA is a highly heterogeneous condition, covering distinct endophenotypes, defined as the association of clinical manifestations of OSA (phenotypes) and their underlying pathophysiological traits (endotypes) [21]. One of the major limitations of the RCTs is the inclusion of non-sleepy OSA patients or the exclusion of extremely sleepy patients. In the RICCADSA study [13] and in the ISAACC study [15], exclusion of sleepy patients (ESS ⩾10) may have potentially led to exclusion of patients who might benefit the most from CPAP therapy. However, for ethical reasons, OSA patients with excessive daytime sleepiness should be offered treatment. Excessive daytime sleepiness thus represents both a methodological challenge faced by many OSA trials as well as a clinical facet of OSA syndrome that physicians must consider in their treatment choice and evaluation of treatment efficacy. In that respect, symptom clusters are being increasingly recognised and have been reported as being associated with different cardiovascular morbidity risk profiles [17], with excessively sleepy patients being at higher risk of cardiovascular morbimortality compared with patients presenting with less excessive daytime sleepiness [17]. Symptom clusters of OSA, once further validated in large prospective cohorts against outcomes, may help to further tailor treatment guidelines in OSA [18].

Similarly, different clusters of polysomnographic features of OSA have been described as being associated with different risk profiles of cardiovascular events [22]. More targeted randomised studies are needed with consideration of OSA clusters to identify which groups may benefit from CPAP therapy. Moreover, at a time when the ability of the AHI to precisely capture the multi-pathophysiological facets of OSA is debated [23, 24] evaluation of other PSG-derived metrics may be highly helpful to improve risk stratification, as well as to improve the identification of the pathophysiological mechanisms at stake in upper airway collapsibility at a patient level. Advances in knowledge regarding OSA pathophysiology have shown that pharyngeal collapse, the hallmark of OSA, results not only from anatomical narrowing of the upper airways which is the main target of CPAP therapy [25]. Impairment of muscle responsiveness, arousal threshold and respiratory drive also contributes to the pathophysiology of OSA [25]. This may partly explain the high CPAP therapy termination rates in unselected OSA populations [26]. In the era of precision medicine in OSA [27], the identification of these specific endophenotypes of OSA is a

prerequisite for risk stratification [28] and the development of tailored alternatives to the current "one size fits all" CPAP therapy approach [25].

CPAP remains the primary treatment option in severe OSA, with proven benefits on OSA-related daytime symptoms and quality of life [8]. In the RCTs discussed above, CPAP adherence was a determining factor, as CPAP therapy usage for at least 4 h per night was associated with a significant risk reduction in the occurrence of secondary major cardiovascular events. Recent meta-analyses provide a reappraisal of the results of these RCTs and help to identify the key determinants of CPAP effect on cardiovascular risk reduction, including CPAP adherence. In a meta-analysis [29] of ten RCTs (n=7266 patients), no significant association of CPAP therapy compared with no treatment (or sham CPAP) on a composite outcome of cardiovascular events was found. Meta-regressions did not identify any association of CPAP therapy with cardiovascular events for different rates of adherence to CPAP therapy [29]. More recently, a meta-analysis of five large trials conducted in OSA patients (including the SAVE and RICCADSA trials) reported that CPAP therapy for at least 4 h per night compared to usual care alone was associated with a risk reduction for the occurrence of major adverse cardio- and cerebrovascular events [30]. In a larger meta-analysis including moderate-to-severe OSA patients (nine RCTs and four cohort studies, with a total of 7379 participants) [31], CPAP therapy was shown as being effective in reducing the risk of stroke in patients with good treatment adherence. Overall, CPAP efficacy is contingent on patient usage and adherence to treatment, and this parameter may have negatively impacted the results of the discussed RCTs.

Implications for practice

OSA is an acknowledged cardiovascular risk factor, as well as a modulator of the occurrence, severity, and progression of chronic diseases/comorbidities. We do not have yet strong, prospective data on the role of CPAP in primary cardiovascular risk prevention. Controversies about the cardiovascular impact of CPAP in secondary prevention must not dampen the positive effects of CPAP on the quality of life of millions of patients. These controversies arise from methodological aspects (lack of well-designed, long-term prospective studies), the high heterogeneity of OSA clinical phenotypes, and the parameters used for disease severity categorisation, as well as adherence levels to CPAP therapy.

Adherence is one of the major determinants of CPAP efficacy, as well as a true challenge in clinical practice. The integration of strategies to improve and maintain adherence over time should be implemented in every OSA care pathway. These strategies should go beyond the traditional mask adjustment, residual AHI, and leaks assessment, to also take into consideration bed partners [32, 33], the involvement of multidisciplinary teams, including home care providers and nurses [34], as well as the use of telemedicine [35].

Although RCTs provide a high level of evidence, they may not be sufficient to capture the diversity of OSA, both in terms of clinical presentation and underlying pathophysiological mechanisms. Large-scale, real-world data may be able to provide a more rounded picture of the effects of routine clinical use of CPAP on multiple outcomes, including cardiovascular morbimortality [19]. Moreover, considering that the best treatment is the one that fulfils the needs of individual patients, precision medicine in OSA [27] may require the validation of adjuvant or alternative therapies to CPAP targeting specific endophenotypic traits [25]. Thus, the future of OSA care looks promising, patient-centred, and physiologically based, and physicians should not only aim for the moon, but also take into consideration many rising stars.

Conflicts of interest: The authors have no conflict of interest to declare.

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