



Beneficial Effects of Continuous Positive Airway Pressure Treatment in Obstructive Sleep Apnoea: The Evidence

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ABSTRACT

Several meta-analyses have been published on the effects of obstructive sleep apnoea treatment with continuous positive airway pressure. However, an updated, evidence-based summary on the effects of continuous positive airway pressure on outcomes should help clinicians and researchers to navigate through the existing literature, since a PubMed search using the keywords continuous positive airway pressure (CPAP), “obstructive sleep apnea” and “meta-analysis” retrieved over 100 papers (July 2016). The aim of this review is to provide updated evidence-based information on the effects of continuous positive airway pressure on mortality, cardio-metabolic outcomes, inflammatory markers, sleepiness, car accidents, cognitive dysfunction, and quality of life in obstructive sleep apnoea. Recent randomised controlled trials and longitudinal studies not yet included in meta-analyses will also be discussed. Overall, evidence exists for positive effects of continuous positive airway pressure treatment on mortality, systemic hypertension, daytime sleepiness and car accidents, and quality of life. Positive effects on cognitive dysfunction, cardiovascular outcomes, and metabolic and inflammatory variables are still uncertain and require further study. (BRN Rev. 2017;3:42-55)

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INTRODUCTION

In 1997, the first systematic review on the health effects of obstructive sleep apnoea (OSA) and the effectiveness of continuous positive airway pressure (CPAP) treatment recognised a positive effect of CPAP on sleepiness, but concluded that, due to lack of adequately performed studies, “the relevance of OSA to public health has been exaggerated” and “the effectiveness of CPAP has been poorly evaluated”¹. The scientific community reacted with deep discomfort, but the paper effectively highlighted the need for evidence-based data on OSA and its treatment. Almost 20 years later, a PubMed search using the keywords “CPAP”, “obstructive sleep apnea” and “meta-analysis” retrieved over 100 papers (July 2016). This review aims at summarising such huge amounts of information by focusing on some relevant outcomes, namely the effects of CPAP on mortality, blood pressure, metabolic outcomes, sleepiness, driving and occupational accidents, cognitive dysfunction, and quality of life in patients with OSA. We excluded meta-analyses not reporting studies on the effects of CPAP (n = 48), those on nasal steroids (n = 2), positional therapy (n = 1), upper airway surgery (n = 4), and mandibular advancement devices (n = 3). In addition, we did not consider meta-analyses on the effects of CPAP on pulmonary hypertension (n = 2), post-operative outcomes (n = 2), sexual dysfunction (n = 1), use of automatic positive airway pressure devices for treatment (n = 5), or pressure titration (n = 1), or nocturia (n = 1). Finally, the results of recent randomised or longitudinal studies on cardiovascular outcomes of major clinical relevance, but not yet included in meta-analyses, will be briefly discussed.

Figure 1 summarises the number of meta-analyses published for each of the items chosen for this review article. Double-digit numbers were found for blood pressure, metabolic variables, and sleepiness/cognitive dysfunction. Three to five meta-analyses analysed data on the effects of CPAP on mortality, driving or occupational accidents, inflammatory markers, and endothelial/vascular function. Fewer meta-analyses were published on the remaining items listed above. Overall, the full spectrum of medical consequences of OSA has been considered. However, the picture is still incomplete and will be further refined when the results of on-going trials on outcomes of treated and untreated OSA in patients with cardiovascular diseases will become fully available.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON MORTALITY

Increased cardiovascular mortality has been reported in meta-analyses on patients with untreated severe OSA^{2,3}. Three meta-analyses have assessed the effects of CPAP treatment by analysis of observational cohorts, and reported either a non-significant protective trend⁴, or decreased cardiovascular mortality in patients on CPAP⁵. The protective effect of CPAP has been recently confirmed by the largest meta-analysis to date, with regard to both all-cause and cardiovascular mortality in patients with severe OSA⁶.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON SYSTEMIC BLOOD PRESSURE

The relationship between OSA and systemic hypertension is complex, and very relevant for

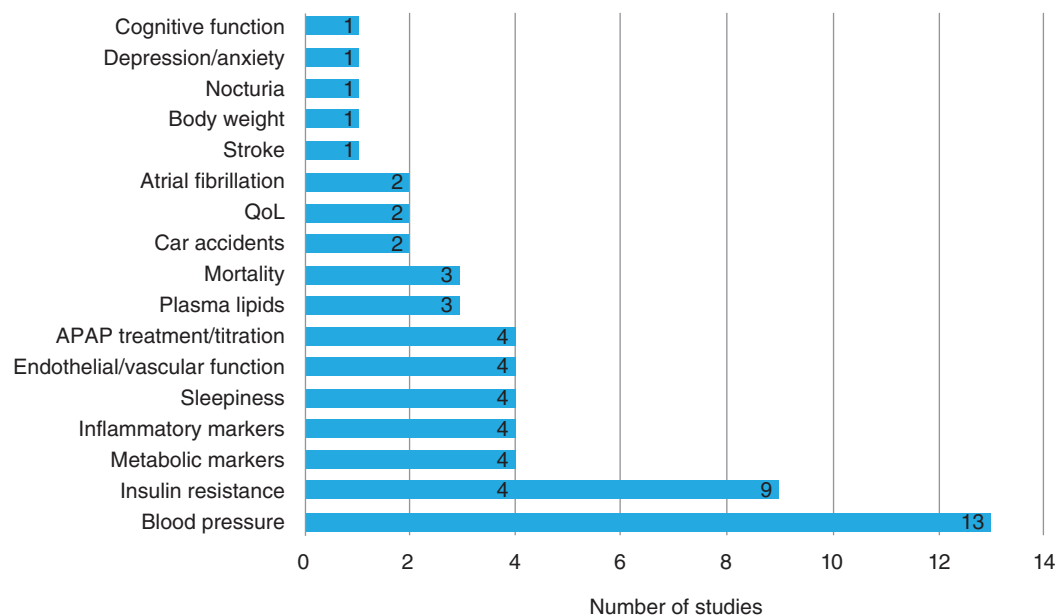


FIGURE 1. Summary of meta-analyses on the effects of continuous positive airway pressure in patients with obstructive sleep apnoea. PubMed search was performed in July 2016. QoL: quality of life; APAP: automatic positive airway pressure.

the assessment of cardiovascular risk⁷. Several meta-analyses were published in the last decade on randomised controlled trials (RCT) assessing the effects of CPAP on blood pressure (BP). There are methodological differences, as some meta-analyses ($n = 7$) analysed studies reporting office BP and/or nocturnal and diurnal values obtained by ambulatory blood pressure monitoring (ABPM)⁸⁻¹⁴, while others ($n = 2$) only considered ABPM studies^{15,16}. Three studies examined the effects of CPAP in OSA patients with resistant hypertension¹⁷⁻¹⁹. More recently, a meta-analysis assessed the effects of CPAP withdrawal on BP²⁰.

There is agreement that CPAP treatment is associated with decreases in BP^{8,11,15}. On CPAP,

BP falls by a few mmHg, and additional drug treatment for hypertension is necessary to reach normal BP values in hypertensive patients^{21,22}. Variability in results can be explained by OSA severity, i.e. larger BP falls were usually seen in patients with high apnoea hypopnea index and compliance to CPAP treatment; i.e. better results were obtained in patients using CPAP for at least four hours per night¹³. In addition, there was a trend for BP to decrease more in patients with higher baseline BP¹³, and the largest falls were observed in patients with poorly controlled hypertension despite pharmacological treatment, i.e. “resistant” hypertension¹⁷⁻¹⁹. Finally, results vary according to the technique used for BP measurement, and larger decreases in nocturnal than diurnal

BP values were found in studies using ABPM compared to studies based on daytime BP measurements^{10,14,16}. In general, the reduction in diastolic BP was more consistent compared to the decrease in systolic BP. In patients with minimally symptomatic OSA, CPAP decreased office diastolic BP only in patients who used CPAP for at least four hours/night¹²; whether such a decrease may be sufficient to recommend CPAP treatment in a population with low adherence to treatment remains a matter of debate. Withdrawal of CPAP for two weeks caused significant rebounds in systolic and diastolic BP, with an average difference between patients continuing and interrupting treatment of 5 mmHg in office and 8-9 mmHg in home systolic and diastolic BP²⁰.

Recent studies have highlighted two important new findings not yet analysed by available meta-analyses. First, systemic hypertension could be linked to respiratory events in REM sleep, possibly related to high sympathetic activity in this sleep stage²³⁻²⁵. Second, fixed CPAP was more effective than automatic CPAP in decreasing diastolic BP²⁶. In summary, the positive effect of CPAP on BP is evidence-based and confirmed by observational long-term longitudinal studies^{27,28}. Figure 2 summarises the most relevant clinical variables reported to modulate the BP response to CPAP treatment.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON METABOLIC VARIABLES

A large group of meta-analyses assessed the effects of CPAP on energy metabolism in OSA

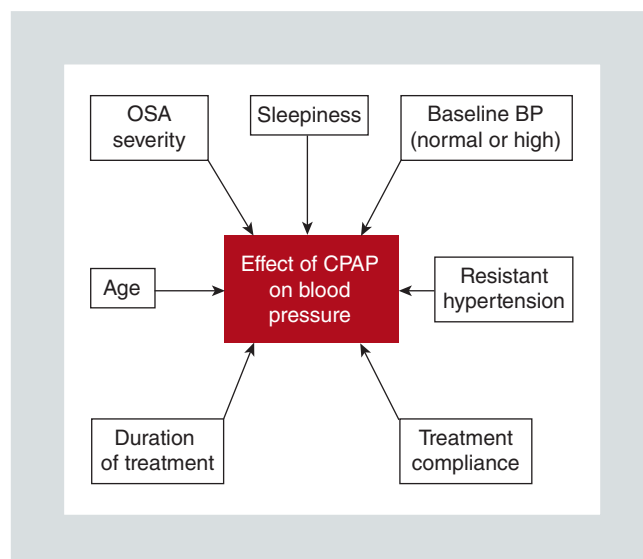


FIGURE 2. Summary of the different factors found to affect blood pressure changes in obstructive sleep apnoea after continuous positive airway pressure treatment.

BP: blood pressure; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea.

patients. Intermittent hypoxia, sleep fragmentation, and obesity concur to cause or worsen insulin resistance, as shown by experimental and clinical studies²⁹. Moreover, a recent meta-analysis showed that CPAP treatment is associated with an increase in body weight³⁰, which may further contribute to insulin resistance in treated OSA patients. Decreased resting energy expenditure, in part explained by decreased sympathetic activation, has been recently demonstrated after CPAP treatment for three months³¹.

Meta-analyses examined the effects of CPAP on insulin resistance and other markers of glycemic control in non-diabetic (n = 5 studies) and diabetic (n = 4 studies) patients with OSA, respectively. CPAP improved insulin resistance assessed by the homeostatic model assessment (HOMA) index in four studies examining non-diabetic subjects³²⁻³⁵, while the

meta-analysis by Hecht et al.³⁶ reported non-significant changes. In diabetic patients, some meta-analyses assessed CPAP-associated changes in glycemic control by measuring glycosylated haemoglobin (HbA1c) levels. No significant effect of CPAP on HbA1c was reported by three studies³⁷⁻³⁹, but a small improvement in the HOMA index was found by two studies^{37,38}. These rather disappointing results could be the consequence of at least two factors. On the one hand, a prolonged duration of CPAP treatment, beyond the four hours considered as good compliance, may be necessary to positively affect glucose metabolism in OSA patients⁴⁰; on the other hand, obesity exerts a powerful effect, and diet, alone or associated with CPAP treatment, but not CPAP treatment alone, positively modified metabolism⁴¹. Furthermore, the effect of CPAP could be more evident in lean as compared to obese patients⁴². Finally, levels of glycemic control at baseline in diabetic patients may affect the post-CPAP results, as suggested by a comparison of two recently published randomised controlled studies^{43,44}.

Three meta-analyses have examined the effect of CPAP treatment on plasma lipids⁴⁵⁻⁴⁷. All of them found that total cholesterol decreased after CPAP treatment, while disagreement exists with regard to changes in low-density (LDL) or high-density lipoprotein (HDL) cholesterol and triglycerides levels. The decrease in total cholesterol was associated with good adherence to CPAP treatment, especially in young obese OSA patients⁴⁶. In children, lipid disturbances appeared to be associated with obesity rather than with OSA⁴⁸. Unfortunately, little information is available from the studies on dietary interventions or pharmacological treatment that could have been

started when the patients were first seen by the physicians suspecting or diagnosing OSA. Moreover, the mean changes in plasma lipids were small.

CPAP may also affect non-alcoholic fatty liver disease (NAFLD). Observational studies in children with NAFLD reported an association of OSA and severity of nocturnal hypoxemia with liver fibrosis and inflammatory hepatic markers, independent of obesity⁴⁹. Moreover, nocturnal hypoxemia was associated with altered gut permeability⁵⁰, suggesting an additional mechanism for worsening of liver function in OSA. No such studies are available in adults yet. Two meta-analyses^{51,52} showed a significant association of adult moderate-severe OSA with liver enzymes and biopsy-proved NAFLD, but did not include data on CPAP treatment. The only meta-analysis available showed decreased liver enzymes after CPAP treatment for at least three months⁵³.

Plasma leptin, a pleiotropic adipokine with multiple effects on metabolism, immunity, and ventilation, is increased in OSA, and appears to be strongly modulated by obesity and gender⁵⁴. Several studies assessed the effects of CPAP treatment, and the results of two recent meta-analyses agree on decreased leptin levels after CPAP^{55,56}. Overall, the studies analysed were small (< 500 patients included in meta-analyses), the change in leptin was small, and its clinical significance is still uncertain.

Negative results have also been reported by a meta-analysis on changes in adiponectin after CPAP⁵⁷, whereas insulin-like growth factor-1 (IGF-1) significantly increased after

treatment⁵⁸. Overall, the evidence available on leptin, adiponectin, and IGF-1 does not allow a definitive conclusion on the effects of CPAP treatment.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON INFLAMMATORY MARKERS

Inflammation is a hallmark of OSA, obesity, and atherosclerosis and inflammatory markers are increased in patients with OSA^{59,60}. The effects of CPAP treatment have been explored by many studies. Two meta-analyses summarised the results of the effects of CPAP on tumour necrosis factor-alpha (TNF- α), interleukin-6, and C-reactive protein. Although there was borderline significance for a positive effect of CPAP, the authors underlined the low number of randomised controlled studies and the high heterogeneity of the available studies^{61,62}. A positive effect of CPAP treatment on C-reactive protein was also reported by two additional meta-analyses that remarked that available studies were not of high quality^{63,64}. The systematic review by Jullian-Desayes et al.⁶⁵ reported negative findings for inflammatory markers when only sham-CPAP controlled studies were examined. Therefore, there is some evidence that CPAP may decrease C-reactive protein levels, while further studies are clearly needed for other inflammatory markers.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON SLEEPINESS

Continuous positive airway pressure decreases subjective and objective sleepiness, measured

by the Epworth Sleepiness Scale (ESS) and the multiple sleep latency test (MSLT), respectively. The largest effects were observed in patients with severe OSA and high degree of sleepiness⁶⁶. Other studies (one meta-analysis and one systematic review) confirmed the positive effects of CPAP on subjective daytime sleepiness assessed by ESS (Fig. 3), but found improvement only in the maintenance of wakefulness test (MWT), without significant changes in MSLT after CPAP^{67,68}. The effect of real CPAP treatment on subjective sleepiness was larger than that of placebo, with this explaining 29% of the benefit referred by patients with good compliance to treatment⁶⁹. Therefore, although patient expectations may play some role, there is evidence that CPAP does reduce sleepiness.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON DEPRESSION AND ANXIETY

There are two meta-analyses on the effects of CPAP treatment on depression. Positive effects were reported in the two studies on patients with both OSA and depression, while a high heterogeneity was found for other studies⁷⁰. Patient expectation may in part explain the positive effects of CPAP on depression and anxiety⁷¹.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON CAR AND OCCUPATIONAL ACCIDENTS

Two meta-analyses reported a highly protective effect of CPAP treatment on car accidents,

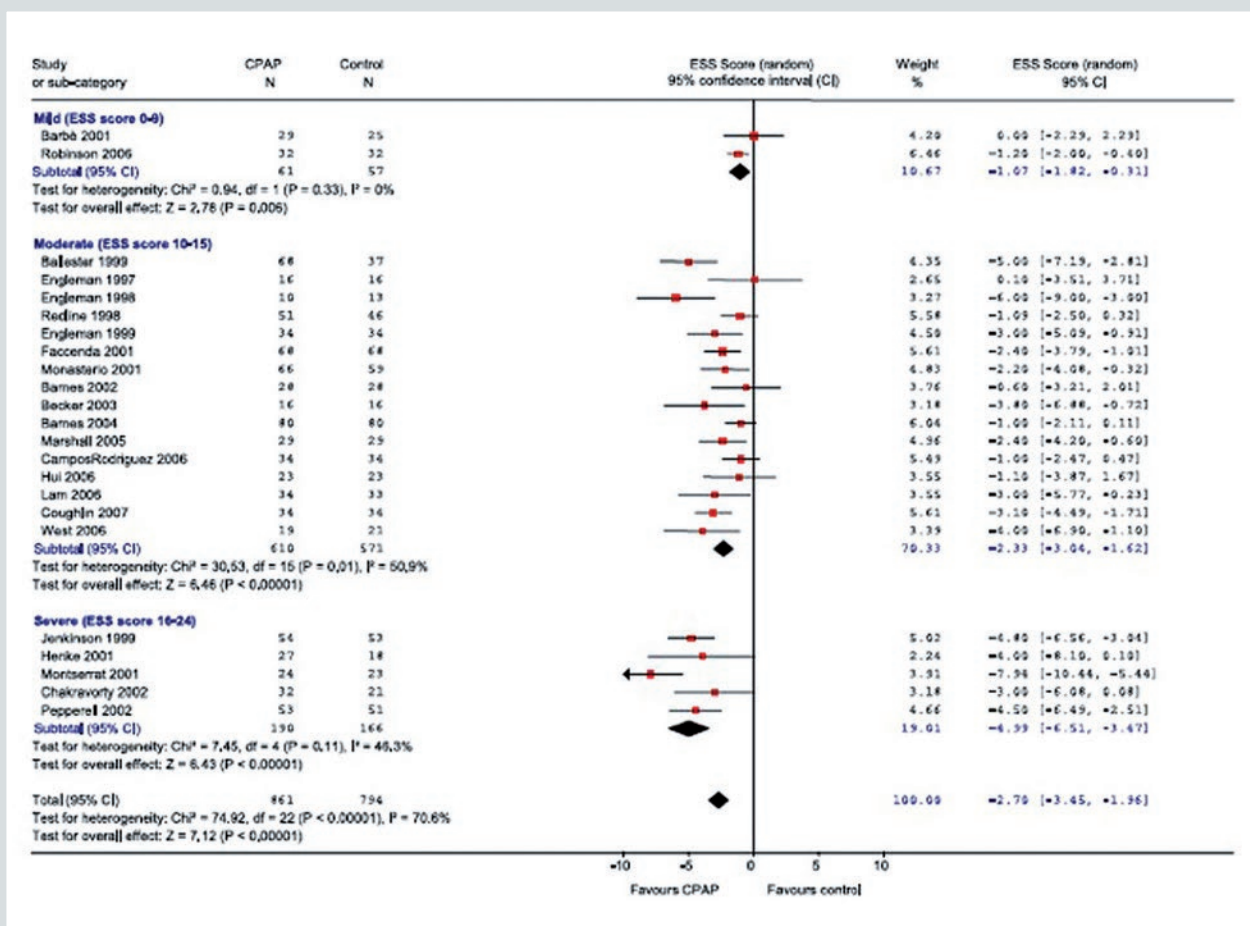


FIGURE 3. Efficacy of continuous positive airway pressure on excessive daytime sleepiness assessed with the Epworth Sleepiness Scale in obstructive sleep apnoea patients. The effect was largest in patients with severe excessive daytime sleepiness (*reproduced with permission from McDaid et al.⁶⁰*).

CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale.

near-miss accidents, and performance at driving simulators in OSA patients^{72,73}. The positive effects of treatment on simulated driving were evident already in the first week of CPAP treatment⁷².

More recently, Garbarino et al.⁷⁴ have reported a high risk of occupational accidents in patients with untreated OSA, not only in commercial vehicle or bus drivers, but also in white and blue collar workers. Unfortunately,

no data are available yet on the effects of CPAP treatment on occupational accidents.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON COGNITIVE DYSFUNCTION

In recent years the effects of CPAP on cognitive function have been analysed. A detailed analysis of the effects of OSA on the different

domains of cognitive function is beyond the scope of this article, and the reader is referred to excellent recent reviews on this topic^{75,76}. The only meta-analysis on the effects of CPAP concluded that only vigilance showed significant improvement after treatment⁷⁷. Interestingly, a recent systematic review reported positive effects of CPAP only in subjects with excessive daytime sleepiness⁷⁸, but more systematic and controlled studies are needed to draw conclusions on this important topic since the studies examined relatively small samples and follow-up was up to six months.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON QUALITY OF LIFE

There are only two meta-analyses on quality of life in CPAP-treated OSA patients. One concluded that there was improved quality of life, sleepiness, and cognitive function after CPAP treatment⁷⁹, the other one underlined that general quality of life scores were not significantly changed after CPAP, but physical function, body pain, energy vitality, and physical component summary of the SF-36 tool increased after CPAP treatment⁸⁰.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON ENDOTHELIAL CELL FUNCTION AND VASCULAR STIFFNESS

Obstructive sleep apnoea is associated with reduced endothelial cell function, decreased

flow-mediated dilation, and increased arterial stiffness, as measured by carotid-femoral pulse wave velocity, or Augmentation Index (AI)⁸¹. Two recent meta-analyses reported evidence for a positive effect of CPAP treatment in restoring endothelial function^{82,83}. However only flow-mediated dilation improved, while nitroglycerin-induced dilation was unchanged after CPAP treatment⁸².

The results of studies on vascular stiffness were discordant. The meta-analysis by Xu et al.⁸² reported no change in arterial stiffness after CPAP, while that by Lin et al.⁸⁴ found evidence for improved arterial stiffness only in hypertensive patients. Whether such positive changes are associated with decreased cardiovascular risk is still unknown.

EFFECTS OF CONTINUOUS POSITIVE AIRWAY PRESSURE ON VENTRICULAR ARRHYTHMIAS AND ATRIAL FIBRILLATION

The only systematic review on the effects of CPAP treatment on occurrence of ventricular arrhythmias concluded that the available studies were too few and heterogeneous so that meta-analysis could not be performed⁸⁵.

More knowledge has been gathered on atrial fibrillation in OSA patients. OSA is a major predictor of relapse of atrial fibrillation after catheter ablation⁸⁶ or coronary artery bypass grafting⁸⁷. The available meta-analyses indicate a clear protective effect of CPAP treatment, since the rate of relapse in patients on CPAP treatment was similar to that of patients without OSA^{88,89} (Fig. 4).

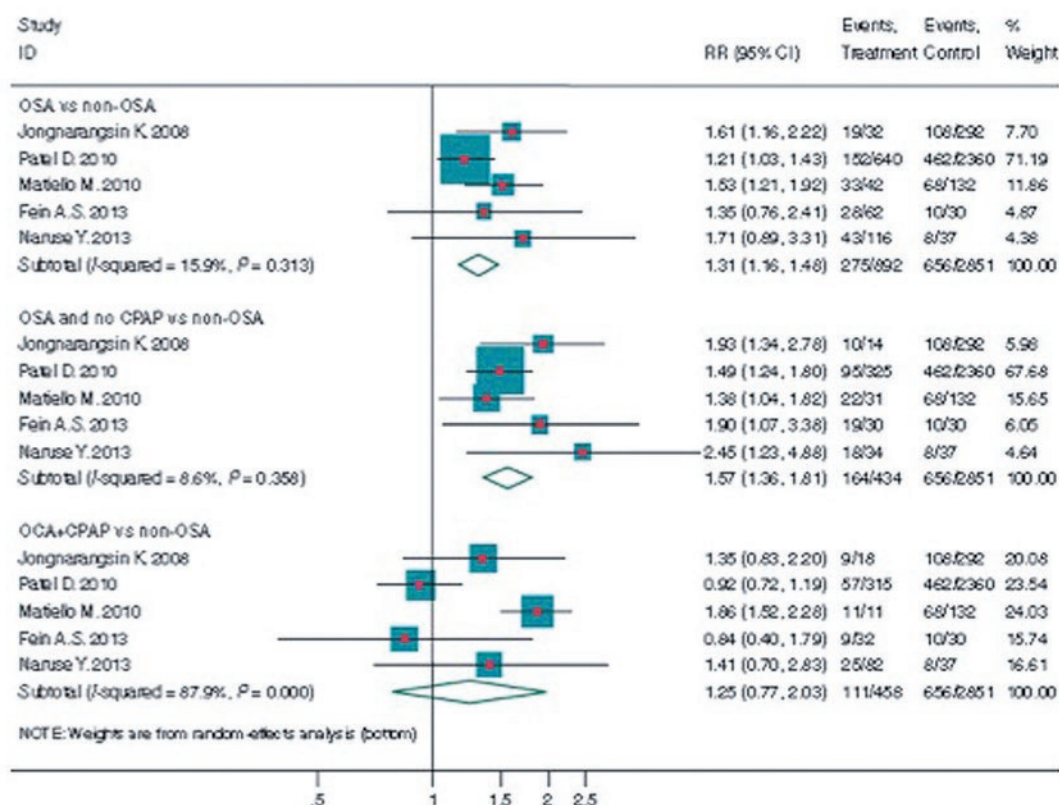


FIGURE 4. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment. Recurrence of atrial fibrillation was more frequent in obstructive sleep apnoea than in non-obstructive sleep apnoea patients (upper panel), and in untreated obstructive sleep apnoea compared to non-obstructive sleep apnoea patients (middle panel). Continuous positive airway pressure normalized the risk of recurrence in obstructive sleep apnoea patients (lower panel) (reproduced with permission from Li et al.⁸⁸).

CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea.

CONTINUOUS POSITIVE AIRWAY PRESSURE AND CARDIOVASCULAR OUTCOMES

Stable coronary artery disease

Observational studies suggest that untreated OSA may worsen prognosis in patients with coronary artery disease^{90,91}, and CPAP treatment may prevent recurrent infarction or need for revascularisation in patients with myocardial infarction and OSA⁹². A recent study

from the Sleep and Stent Study, a prospective multicenter registry, reported that patients with OSA and coronary artery disease showed an increased risk for major adverse cardiac and cerebrovascular disease after percutaneous coronary intervention⁹³. Randomised controlled studies have been designed to address the important clinical question of the impact of CPAP treatment on cardiovascular outcomes. Two of them, the Treatment in Coronary Artery Disease and Sleep Apnea (RICCADSA)⁹⁴ and the Continuous Positive Airway Pressure

Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease (SAVE)⁹⁵ studies, reported that CPAP did not protect against cardiovascular events. Both the RICCADSA and SAVE studies examined long-term cardiovascular outcomes in patients with coronary artery disease and OSA without sleepiness, by randomising patients to receive usual care or usual care and CPAP. The negative results raised some questions. For example, adherence to CPAP treatment was only 3.3 hours in the SAVE study⁹⁵, while use of CPAP for at least four hours per night was associated with significant risk reduction in secondary data analysis in the RICCADSA study⁹⁴. Therefore, it is possible that a higher adherence to treatment would be necessary to show positive effects of CPAP on cardiovascular risk.

Acute coronary syndromes

After acute myocardial infarction, occurrence of sleep disordered breathing was associated with a high myocardial workload, estimated as the product of systolic blood pressure and heart rate⁹⁶. An observational study on short-term prognosis after an acute coronary syndrome event found that OSA patients showed higher troponin levels and a longer stay in the coronary care unit compared to patients without OSA⁹⁷. In addition, OSA severity assessed by the apnoea hypopnea index was associated with increased number of diseased vessels⁹⁷. The on-going Impact of continuous positive airway pressure on patients with Acute Coronary Syndrome and nonsleepy OSA (ISAACC, NCT01335087) study has enrolled patients with acute coronary syndrome and OSA without excessive daytime sleepiness, but results are not available yet⁹⁸.

Stroke

Only recently, a meta-analysis was published focussing on the effects of CPAP on the risk for stroke⁹⁹. The results analysed were discordant, since a protective effect of CPAP treatment was found in cohort studies, but not in RCTs or studies using administrative data. The protective effect of CPAP against stroke was larger than for cardiac events.

Chronic heart failure

A recent meta-analysis exploring the effects of CPAP on all-cause and cardiovascular mortality in patients with chronic heart failure (CHF) did not show any significant change¹⁰⁰. The topic of sleep-disordered breathing in CHF patients is complicated by the frequent occurrence of both central and obstructive events, and is currently being re-examined after the negative results of the Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE_HF) trial showing that adaptive servo-ventilation in CHF patients is associated with increased mortality in patients with low ejection fraction¹⁰¹. The results of the on-going randomised multicenter trial ADVENT-HF, (Effect of ASV on Survival and Hospital Admissions in HF, NCT01128816), will help define the therapeutic strategy to be used in CHF patients with sleep apnoea^{102,103}.

CONCLUSIONS

Compared to the state of the art in 1997, evidence-based effects of CPAP treatment have been demonstrated in the last two decades by

TABLE 1. Summary of the evidence on the effects of CPAP treatment

Outcomes	Evidence
All-cause and cardiovascular mortality	Moderate
Blood pressure	Strong
Insulin resistance	Weak-moderate
Plasma lipids	No evidence, except for total cholesterol (weak)
Liver damage	Weak/no evidence
Leptin, adiponectin, IGF-1	Weak/no evidence
TNF-alpha, IL-6	Weak
C-reactive protein	Moderate
Sleepiness	Strong
Car/occupational accidents	Strong
Cognitive dysfunction	Weak/no evidence
Quality of life	Weak/no evidence
Endothelial function	Strong
Arterial stiffness	Weak/no evidence
Recurrence of atrial fibrillation	Strong
Cardiovascular outcomes in CAD	No evidence

CAD: coronary artery disease; IGF: insulin like growth factor; IL: interleukin; TNF: tumour necrosis factor.

randomised controlled studies and meta-analyses. Table 1 summarises the current level of evidence regarding CPAP treatment, which appears strong for the effects on blood pressure, sleepiness, car accidents, and prevention of recurrent atrial fibrillation. All the other items examined show lower levels of evidence. On-going studies will help clarify the long-term effects of CPAP treatment, especially on cardiovascular outcomes, and ascertain whether CPAP treatment is beneficial in subpopulations of patients at high risk.

There is an apparent discrepancy between the results of meta-analyses on general and

cardiovascular mortality on the one hand, and the recent data from RCTs on cardiovascular outcomes after CPAP treatment. Both cohort studies and RCTs have limitations, the former because of low level of evidence due to lack of randomisation, the latter because of the poor level of compliance to CPAP treatment.

Adherence to CPAP is known to be unsatisfactory in asymptomatic patients, who account for about half of the patients with OSA according to current estimates¹⁰⁴. CPAP is one of the few medical treatments with effective measurement of the “dose” actually taken by the patient. Currently, a minimum of four hours per night for at least 70% of the nights is used as a threshold of compliance¹⁰⁵. In future studies, the effects of CPAP should be assessed by using hours of compliance as a dose treatment variable to quantitatively weigh the magnitude of therapeutic effect.

Identification of subgroups of patients likely to benefit most from CPAP treatment is important in order to optimise the therapeutic strategy in the long term. More data are needed in elderly patients and women, as most studies to date have examined male middle-aged patients, and the features of OSA appear age- and gender-dependent. Overall, the data show that CPAP is an effective treatment, although to date there is no evidence that it positively affects cardiovascular risk.

CONFLICT OF INTEREST

Dr. Bonsignore has nothing to disclose, Dr. Marrone has nothing to disclose, Dr. McNicholas has nothing to disclose.

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