Review Article

Cardiovascular outcomes of continuous positive airway pressure therapy for obstructive sleep apnea

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Abstract: Obstructive sleep apnea is a common disorder with increased risk for cardiovascular morbidity and mortality. The first choice of treatment of obstructive sleep apnea is continuous positive airway pressure, which reduces excessive daytime sleepiness and improves quality of life in sleep clinic cohorts. Nevertheless, the majority of patients with cardiovascular disease and concomitant obstructive sleep apnea do not report daytime sleepiness, and adherence to treatment is insufficient particularly in this group. The current article aims to give an updated overview of the impact of continuous positive airway pressure therapy on cardiovascular outcomes mainly based on the observational studies and the recent randomized controlled trials.

Keywords: Obstructive sleep apnea (OSA); cardiovascular outcomes; continuous positive airway pressure (CPAP); randomized controlled trial (RCT)

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Introduction

Obstructive sleep apnea (OSA) is a highly common condition (23.4% of women, 49.7% of men) based on the recent largest population study (HypnoLaus cohort) (1), adapting an apnea-hypopnea-index (AHI) of at least 15/h, according to the American Academy of Sleep Medicine 2012 scoring criteria (2). When excessive daytime sleepiness (EDS), defined as an Epworth sleepiness scale (ESS) score >10 was included, the prevalence of AHI ≥5/h with EDS was 5.9% in women, and 12.5% in men (1). The prevalence is even higher in clinical cohorts with cardiovascular disease (CVD) (3). The first choice of treatment of OSA is continuous positive airway pressure (CPAP), which reduces EDS and improves quality of life (4). However, the majority of patients with CVD and concomitant OSA do not report EDS, and adherence to CPAP is challenging particularly in this group. Other treatment modalities for OSA include active weight loss for individuals with obesity, oral appliance therapy (OAT), surgical approaches (i.e., uvulopalatopharyngoplasty or maxillofacial surgery), nervus hypoglossus stimulation (5). Weight loss in obese OSA patients has shown to result in a reduction of AHI and improved sleep efficiency (6). Moreover, avoidance of the supine sleeping position may reduce AHI in patients with mild, position-dependent OSA (7). To date, there is no efficient pharmacological therapy for OSA. Positive effects of weight reduction on cardiovascular outcomes was recently reviewed by Hudgel (8), a systematic review of effect of surgical treatment on cardiovascular outcomes

was published by Halle *et al.* (9), and an intensive systematic review and meta-analysis of the cardiovascular effects of OAT was recently published by de Vries *et al.* (10). The current review focuses on the literature regarding the observational studies and randomized controlled trials (RCT) addressing the impact of CPAP treatment on cardiovascular outcomes.

The mechanisms involved in the cardiovascular consequences of OSA have been widely reviewed (3). Sleep fragmentation and intermittent hypoxia may trigger sympathetic overstimulation, oxidative stress, vascular inflammation, endothelial dysfunction, arterial stiffness, hypercoagulation, which all may cause atherosclerosis and development of CVD. Thus, efficient treatment of the underlying OSA would eliminate the increased risk burden. Despite the demonstrated beneficial effect of the CPAP treatment of OSA on cardiovascular outcomes in the great majority of the prospective observational studies, the results from the RCTs have been conflicting.

Impact of CPAP therapy on cardiovascular mechanisms

Individual studies cited in this overview addressing the effect of CPAP treatment on cardiovascular mechanisms are summarized in *Table 1*. Other studies not shown in the *Table 1* are included in the meta-analyses referred under the corresponding sections below.

Sympathetic overstimulation and autonomic dysfunction

Observational studies

Early observational studies with CPAP therapy have suggested that efficient treatment may reduce the increased sympathetic activity in OSA patients (11,12), not only during sleep but also during daytime, especially in hypertensive OSA (13). In another observational study, Narkiewicz *et al.* (14) measured blood pressure (BP), heart rate and muscle sympathetic nerve activity (MSNA) in 11 normotensive, otherwise healthy patients with OSA who were treated with CPAP. The measurements were obtained at baseline, and repeated after 1 month, 6 months, and 12 months of CPAP treatment, and the values were compared with those recorded in nine otherwise healthy untreated OSA patients. While BP and heart rate did not change over time in both treated and untreated patients, there was a significant decrease in MSNA in the CPAP group, and this decrease was evident after both 6 and 12 months of CPAP therapy. The authors concluded that CPAP treatment decreased the MSNA in patients with OSA, and this reduction was evident first after an extended duration of therapy (14). In another prospective observational study, Pinto *et al.* (15) addressed the impact of one month of CPAP treatment on plasma nitrate and urinary norepinephrine levels in 36 patients with mild-to-moderate OSA and 31 patients with severe OSA, and found significant improvements in the severe OSA group but not in the individuals with mild-to-moderate OSA. There is also data suggesting that effective CPAP treatment may reverse the impaired autonomic dysfunction in OSA patients. Moreover, CPAP withdrawal even for one week was associated with a marked increase in sympathetic activity (47). More recently, Henderson *et al.* (16) studied the impact of CPAP treatment on MSNA and its relationship with brainstem activity measured by magnetic resonance imaging in 15 control and 15 OSA subjects before and after 6 and 12 months of CPAP treatment in the OSA group (16). The researchers found that MSNA was greatly elevated in patients with OSA, and there was significant reduction after CPAP treatment. Moreover, this MSNA reduction was associated with restoration of MSNA-related brainstem activity and structural changes in the medullary raphe, rostral ventrolateral medulla, dorsolateral pons, and ventral midbrain after 6 and 12 months of CPAP treatment (16).

RCTs

Among the eight RCTs included in a well-summarized review by Jullian-Desayes *et al.* (48), CPAP treatment had a beneficial effect of CPAP on sympathetic activity in five studies. In a parallel-designed RCT among 38 patients with OSA, Ziegler *et al.* demonstrated that 10 days of CPAP treatment was associated with a significant decrease in daytime catecholamine levels while no significant change was observed in the sham-CPAP group (17). The researchers noted that daytime sympathetic nervous activation was greater in patients with more severe OSA, and that CPAP treatment diminished the daytime sympathetic activity while the potential nighttime effect of CPAP treatment was masked by a small placebo effect (17). In another parallel-designed RCT among 50 patients with OSA, Mills *et al.* (18) randomized 17 patients to CPAP, 16 to sham-CPAP, and 17 to nocturnal oxygen therapy for 2 weeks, respectively. CPAP treatment resulted in significant reductions in plasma norepinephrine levels both by increases in norepinephrine clearance and decreases in diurnal and nocturnal excretion compared with the changes in the other groups (18). In a larger cohort of 102 men with

Table 1 Summary of the articles addressing the impact of CPAP treatment on cardiovascular mechanisms in patients with obstructive sleep apnea

Outcome	First author	Year	OSA (criteria/severity)	Sample size	Main findings	Study design
Sympathetic activity and autonomic dysfunction	Hedner *et al.* (11)	1995	AHI ≥30	14	CPAP reduced sympathetic activity	Observational
	Somers *et al.* (12)	1995	AHI >10	10/10	CPAP reduced sympathetic activity	Observational
	Heitmann *et al.* (13)	2004	AHI >20	8/10	CPAP reduced sympathetic activity in HT patients	Observational
	Narkiewicz *et al.* (14)	1999	Mean AHI =27±6	15/10	CPAP reduced MSNA	Observational
	Pinto *et al.* (15)	2013	AHI >5	31/36	CPAP increased NO, decreased urine-NE in severe OSA	Observational
	Henderson *et al.* (16)	2016	AHI >5	15/15	CPAP reduced MSNA	Observational
	Ziegler *et al.* (17)	2001	AHI >15	20/18	CPAP reduced sympathetic activity	RCT
	Mills *et al.* (18)	2006	AHI >15	17/17/16*	CPAP reduced sympathetic activity	RCT
	Kohler *et al.* (19)	2008	ODI >10	51/51	CPAP reduced 24 h urine catecholamine level	RCT
	Phillips *et al.* (20)	2011	AHI >25	18/19	CPAP reduced 24 h urine NE level	RCT
	Arias *et al.* (21)	2008	AHI >10	13/12	CPAP did not reduce urine NE/E level	RCT
	Alonso-Fernández *et al.* (22)	2009	AHI >10	13/12	CPAP did not reduce urine NE/E level	RCT
	Arias *et al.* (23)	2006	AHI >10	10/11	CPAP did not reduce urine NE/E level	RCT
	Noda *et al.* (24)	2007	AHI >20	14/19	CPAP reduced urine NE level	RCT
	Thunström *et al.* (25)	2016	AHI >15	24/23	CPAP as add-on treatment to losartan reduced sympathetic activity	RCT
Oxidative distress	Carpagnano *et al.* (26)	2003	AHI >20	18/12	CPAP reduced oxidative stress	Observational
	Barceló *et al.* (27)	2006	Mean AHI =49±16	47/37	CPAP increased anti-oxidant capacity	Observational
	Christou *et al.* (28)	2009	AHI ≥30	46/46	CPAP reduced oxidative stress	Observational
	Takahashi *et al.* (29)	2008	AHI >20	41/12	CPAP reduced thioredoxin	Observational
	Alonso-Fernández *et al.* (22)	2009	AHI >10	13/12	CPAP reduced 8-isoprostane	RCT
Vascular inflammation	Ohga *et al.* (30)	2003	Mean AHI =38.3 ±3.1	20/10	CPAP reduced ICAM-1 and IL-8	Observational
	West *et al.* (31)	2007	ODI >10	20/22	CPAP did not reduce CRP, TNF-α, IL-6 ant LTB4	RCT
	Arias *et al.* (21)	2008	AHI >10	13/12	CPAP reduced TNFR-1, did not reduce TNF-α, IL-6 and LTB4	RCT
	Kritikou *et al.* (32)	2014	Mean AHI =33.9±18.8	38/39	CPAP did not improve inflammation	RCT
	Kohler *et al.* (33)	2009	ODI >10	51/49	CPAP did not reduce inflammatory markers	RCT
	Hoyos *et al.* (34)	2012	AHI ≥20	34/31	CPAP did not reduce inflammatory markers	RCT
	Thunström *et al.* (35)	2017	AHI >15	105/115	CPAP did not reduce hs-CRP, TNF-α, IL-8 in patients with CAD and concomitant OSA	RCT

Table 1 (*continued*)

Table 1 (*continued*)

Outcome	First author	Year	OSA (criteria/severity)	Sample size	Main findings	Study design
Endothelial function and arterial stiffness	Bayram *et al.* (36)	2009	AHI >5	29/17	CPAP improved endothelial dysfunction	Observational
	Phillips *et al.* (37)	1999	Mean AHI =74±22	22/12	CPAP reduced endothelin-1	Observational
	Cross *et al.* (38)	2008	AHI >15	27/17	CPAP improved endothelial dysfunction	RCT
	Simpson *et al.* (39)	2013	AHI >20	25/21	CPAP did not improve endothelial dysfunction	RCT
	Ayers *et al.* (40)	2013	ODI >10	20/21	CPAP increased endothelium-derived microparticles	RCT
Coagulation factors	Hui *et al.* (41)	2004	AHI >10	42/23	CPAP reduced platelet activation	Observational
	Chin *et al.* (42)	1996	AHI >20	11	CPAP reduced fibrinogen and blood viscosity	Observational
	von Känel *et al.* (43)	2006	AHI >15	18/16/10*	CPAP reduced plasminogen activator inhibitor-1	RCT
	von Känel *et al.* (44)	2013	AHI >10	25/26	CPAP did not reduce prothrombotic markers	RCT
	Phillips *et al.* (45)	2012	AHI ≥25	29	CPAP reduced coagulability	RCT
	McEwen *et al.* (46)	2012	AHI ≥25	28	CPAP did not reduce fibrinogen	RCT

*, for details of the groups, see references 18 and 43, respectively. AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; E, epinephrine; hs-CRP, high-sensitivity C-reactive protein; HT, hypertension; ICAM, intercellular adhesion molecule; IL, interleukin; LTB, leukotriene B; MSNA, muscle sympathetic nerve activity; NO, nitric oxide; NE, norepinephrine; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RCT, randomized controlled trial; TNF, tumor necrosis factor; TNFR, TNF receptor.

OSA, Kohler *et al.* (19) randomized 51 patients to CPAP and 51 to sham-CPAP for 4 weeks, and demonstrated significant reductions in 24-h urinary catecholamine excretion as well as improvements in baroreflex sensitivity. In a later study by Phillips *et al.* (20), 28 patients with OSA completed an RCT in a cross-over design, treated by CPAP and sham-CPAP for 2 months, respectively, with a 1 month of wash-out period between the treatment arms. The primary outcome was post-prandial lipidemia, and among secondary outcome studied, 24-h and awake urinary norepinephrine levels were decreased significantly while no changes were observed regarding urinary epinephrine and asleep norepinephrine levels (20). In contrary, Arias *et al.* (21) showed no significant difference regarding the urinary epinephrine and norepinephrine levels in 25 OSA patients randomized to CPAP *vs.* sham-CPAP in a crossover designed study for 12 weeks, respectively. Likewise, in an exactly similar designed crossover RCT, no significant changes in urinary catecholamine levels were observed in 25 OSA patients randomized to CPAP *vs.* sham-CPAP for 12 weeks, respectively (22). Moreover, in another cross-over designed RCT by Arias *et al.* (23), addressing the impact of CPAP primarily on pulmonary hypertension, no significant changes were observed regarding the urinary catecholamine levels in 21 OSA patients randomized to CPAP *vs.* sham-CPAP for 12 weeks, respectively. These neutral trials (21-23) were criticized for the cross-over design for not including a wash-out period, and thus for a potential carry-over effect as a major limitation (48). Among other RCTs not included in that review (48), the study by Noda *et al.* (24) addressing the impact of CPAP on daytime baroreflex sensitivity and nitric oxide production in patients with moderate to severe OSA is also noteworthy. The researchers randomized 14 patients to CPAP for 12 weeks, and 19 patients to no-CPAP showing a significant reduction in the 24-h urinary excretion of norepinephrine as well as significant increase in the daytime baroreflex sensitivity in the CPAP group while there were no significant changes in the control group. More recently, Thunström *et al.* (25) addressed the cardiovascular mechanisms involved in response to an angiotensin II receptor antagonist, losartan, and CPAP as add-on treatment for hypertension and OSA. Newly diagnosed hypertensive patients with or without OSA were treated with losartan 50 mg daily during a 6-week, parallel-design study, and in the second 6-week, the OSA patients continued to receive losartan and were randomly assigned to either CPAP or to no-CPAP. Losartan significantly increased renin levels and reduced

aldosterone levels in the group without OSA while there was no significant decrease in aldosterone levels among OSA patients. Add-on CPAP treatment tended to lower aldosterone levels, but reductions were more pronounced and significant in measures of sympathetic activity (25).

Evidence level

As summarized above and in *Table 1*, the majority of the studies in literature supports that CPAP treatment reduces the sympathetic over-activity in adults with OSA.

Oxidative stress

Observational studies

Carpagnano *et al.* (26) demonstrated higher concentrations of 8-isoprostane in the morning exhaled condensate and plasma of OSA patients compared to concentrations in the healthy obese subjects, and these elevations were observed in the morning but not in the evening, suggesting an association with the nocturnal apneic events. The researchers reported a significant reduction after CPAP therapy (26). An increase in antioxidant capacity has also been suggested in OSA patients after 12 months of CPAP treatment among the ones who were adherent to CPAP (27). In another observational study, Christou *et al.* (28) evaluated oxidative stress markers in blood samples with a commercially available assay in 46 patients with severe OSA, showing increased levels compared with those in 46 controls with no-OSA or mild-to-moderate OSA. The levels of the oxidative stress markers were decreased in the morning following the CPAP titration night, and this reduction was further preserved after 2 months of CPAP treatment (28). Thioredoxin, which is a novel oxidative stress marker, was reduced after 1 month of CPAP treatment in 27 patients with severe OSA (29).

RCTs

Alonso-Fernández *et al.* (22) included 31 patients with OSA in a cross-over design and showed a significant reduction in 8-isoprostane levels and increase in nitrates after 12 weeks of CPAP treatment compared to sham CPAP. However, major concerns with this study were exclusion of the patients with CPAP use <3.5 h/night, and lack of a wash-out period between the treatment arms.

Evidence level

There is yet not sufficient number of RCTs to suggest a beneficial effect of CPAP treatment regarding oxidative stress in adults with OSA.

Vascular inflammation

Observational studies

Many studies have assessed a wide group of circulating inflammatory mediators, but mainly C-reactive protein (CRP) and interleukin (IL)-6. Guo *et al.* (49) performed a meta-analysis focused on the effect of CPAP treatment on CRP involving 1,199 OSA patients from 14 observational studies. The meta-analysis indicated that the overall standardized mean difference (SMD) for the CRP levels was 0.64 units [95% confidence interval (CI), 0.40–0.88] before and after CPAP therapy. Subgroup analysis showed that the decrease in CRP levels was significant first after 3 months of CPAP treatment with a further decline after 6 months (49). Another meta-analysis by Baessler *et al.* (50) included a total of 14 studies with 771 patients pooled for CRP; nine studies with 209 patients pooled for tumor necrosis factor (TNF)-α, and eight studies with 165 patients pooled for IL-6, and demonstrated significant improvement in the levels of CRP and TNF-α, and a trend towards improvement in the levels of IL-6 after CPAP treatment (50). Likewise, the meta-analysis performed by Xie *et al.* (51) included 35 studies involving 1,985 OSA patients; 24 studies on CRP, 16 studies on IL-6, three studies on IL-8, and 12 studies on TNF-α. The results showed significant improvements in all studied inflammatory biomarkers, and the subgroup analyses demonstrated better benefits with therapy duration of at least 3 months, and for patients using CPAP at least 4 h/night (51). Among other inflammatory biomarkers, levels of circulating intercellular adhesion molecule (ICAM)-1, which mediates adhesion of leucocytes to the vascular endothelium, was also reduced in OSA patients after CPAP treatment (30).

RCTs

West *et al.* (31) randomized 42 men with diabetes mellitus and newly diagnosed OSA to either CPAP or sham-CPAP for 3 months in parallel design in order to primarily address the impact of CPAP treatment on glycaemic control and insulin resistance and found no significant effect. CRP and adiponectin values did not either change significantly. However, the overall compliance was relatively low in both arms (31). In the study of Arias *et al.* (21), 25 male OSA patients were randomized to CPAP *vs.* sham-CPAP in a cross-over design for 12 weeks, respectively, TNF receptor (TNFR)-1 levels significantly decreased in compliant CPAP patients. CPAP treatment had no significant effect

on TNF-α, IL-6 and leukotriene B4 levels (21). However, Kritikou *et al.* (32) did not confirm the changes in TNFR-1 in a cohort of 25 middle-aged men and women randomized to CPAP *vs.* sham-CPAP in a cross-over design for 2 months, respectively. CPAP failed to have significant impact on the other inflammatory biomarkers, CRP, IL-6, leptin and adiponectin despite a good CPAP adherence level in the whole group (32). Another RCT by Kohler *et al.* (33) also failed to show any significant effect of 4 weeks of CPAP treatment in 49 men with moderate to severe OSA compared with subtherapeutic CPAP for 4 weeks in 51 men with the same degree of OSA. The measured inflammatory markers were CRP, IL-6, adiponectin and interferon gamma (33). Hoyos *et al.* (34) randomized 65 non-diabetic men with moderate to severe OSA to CPAP or sham-CPAP for 12 weeks, and studied cardiometabolic variables including blood leptin and adiponectin concentrations. The researchers found no between-group differences at 12 weeks compared to the baseline values (34). Moreover, Kohler *et al.* (52) did not show an increase in inflammatory biomarkers (CRP, IL-6, IL-8, TNF-a) after CPAP withdrawal for 2 weeks. More recently, Thunström *et al.* (35) demonstrated no significant beneficial effect of CPAP over 12 months on the inflammatory biomarkers in the RICCADSA (Randomized Intervention with CPAP in Coronary Artery Disease and Obstructive Sleep Apnea) cohort, except for IL-6 levels, which reduced to the same extent in both CPAP and no-CPAP groups. No between-group differences were observed regarding the CRP, IL-8 and TNF-a values, and there was no significant association between CPAP adherence and changes in the inflammatory biomarker levels in this CAD population with nonsleepy OSA (35).

Evidence level

The results of several meta-analyses of the observational studies suggest significant improvements in the majority of the studied inflammatory biomarkers, and the subgroup analyses demonstrate better benefits with therapy duration of at least 3 months, and for patients using CPAP at least 4 h/night, in sleep clinic cohorts. However, results of the RCTs are not supportive for these conclusions, probably due to relatively small sample sizes, and inclusion of individuals from different clinical cohorts with already established CVDs.

Endothelial function and arterial stiffness

Observational studies

Bayram *et al.* (36) reported that 6 months of CPAP treatment resulted in improvement in endothelial function in normotensive men compared to untreated OSA patients with similar endothelial dysfunction findings at baseline without changes at follow-up. It was also shown that endothelial function was worsened after CPAP withdrawal to the baseline values, supporting the fact that reversal of this dysfunction is dependent on ongoing CPAP use. Increased level of nitric oxide NO and reduced level of endothelin-1 were also documented in OSA patients following CPAP treatment (37).

RCTs

Cross *et al.* (38) measured endothelial function and impact of 6 weeks of CPAP treatment in a randomized, double blind, placebo controlled, cross-over trial among OSA patients with frequent versus less desaturations, and showed a beneficial effect especially in the desaturating OSA patients. In a later study, Simpson *et al.* (39) randomized 50 men with OSA and without diabetes to either CPAP (n=25) or sham-CPAP (n=25) in a parallel-designed, 12-week double-blind study and addressed the effect of treatment on circulating progenitor cells (CPCs) isolated from blood, measured by flow cytometry, and endothelial function, assessed by peripheral arterial tonometry. Neither CPCs nor endothelial function improved significantly after CPAP treatment despite the efficient elimination of the obstructive events by CPAP (39). On the other hand, in another RCT, Ayers *et al.* (40) demonstrated that a 2-week withdrawal of CPAP treatment increased the endothelium-derived microparticles, suggesting that microparticle formation may be causally linked to OSA and may promote endothelial activation (40).

Evidence level

Despite positive findings shown in the observational studies, the results from the few RCTs conducted within this area are not sufficient to support a beneficial effect of CPAP on endothelial function in adults with OSA.

Coagulation factors

Observational studies

Early observational reports were conflicting regarding the effect of CPAP therapy on coagulation factors. CPAP decreased platelet activation (41), and fibrinogen levels (42).

RCTs

OSA has been associated with an increased risk of

atherothrombotic events, and a few studies investigated OSA patients' day/night rhythm of several prothrombotic markers in OSA patients and potential changes with CPAP. von Känel *et al.* (43) showed that CPAP reduced plasminogen activator inhibitor-1 but had no significant impact on hematocrit, whole blood viscosity and other coagulation factors in OSA patients. In another RCT, the same research group showed no significant differences in changes of periodic pattern and in day/night rhythm parameters of prothrombotic markers pre- to post-treatment between the 3 weeks of CPAP and sham-CPAP (44). In the randomized cross-over trial by Phillips *et al.* (45), 28 patients received CPAP or sham CPAP, each for 2 months with a 1-month washout between treatments. After each treatment period, CPAP reduced the early morning level of von Willebrand factor, and nocturnal levels of factor VIII and factor V. On the other hand, there was no difference in fibrin generation between CPAP and sham-CPAP groups in the RCT by McEwen *et al.* (46).

Evidence level

Results from the existing reports are inconclusive and not sufficient to support a beneficial effect of CPAP on coagulation factors patients with OSA.

Impact of CPAP therapy on CVDs and mortality

Individual studies cited in this overview addressing the effect of CPAP treatment on CVDs and mortality are summarized in *Table 2*. Other studies not shown in the *Table 2* are included in the meta-analyses referred under the corresponding sections below.

Systemic hypertension

Earlier meta-analyses suggested that CPAP is effective in reducing BP both in normotensive and hypertensive OSA subjects although the significance of reduction has been higher in the hypertensive patients (97). Moreover, the studies demonstrated significant reductions in nocturnal and daytime BP especially in OSA patients with therapy-resistant hypertension (97). It has also been suggested that "non-dipping" hypertensive OSA patients may convert to "dippers" after CPAP treatment, thereby, restoring the physiological nocturnal dipping BP pattern (53). Indeed, a 24-month follow-up study demonstrated a dose dependent BP response to CPAP treatment supporting that beneficial effect can be achieved in long-term even in the initially incompletely treated hypertensive OSA subjects (54). On the other hand, neutral findings have been reported in an RCT addressing the effect of 8-week of CPAP treatment on BP in mild OSA (55). In another RCT, conducted in hypertensive OSA patients with no sleepiness, CPAP did not reduce BP (56). These earlier studies have also raised the question whether or not the duration of CPAP treatment plays a major role in this context. In general, greater BP response to CPAP treatment has been associated with CPAP compliance, severity of OSA, daytime sleepiness, and the co-existence of initial hypertension (97).

The results from the more recent RCTs and meta-analyses suggest that CPAP significantly reduces BP in OSA patients. Studies using 24-h BP monitoring (97-102) have shown a decline of 2 to 2.5 mmHg in systolic BP, and 1.5 to 2 mmHg in diastolic BP, respectively, compared with controls, as illustrated in a recent review by Javaheri *et al.* (3). Greater reductions were shown in patients with therapy-resistant hypertension (between 4.7 to 7.2 mmHg for systolic BP, and 2.9 to 4.9 mmHg for diastolic BP, respectively) (3,57-61,103,104).

In one RCT, conducted in a primary care cohort with new-onset hypertension, Durán-Cantolla *et al.* (62) chose CPAP treatment as a single therapy compared with sham-CPAP, showing a small reduction in 24-h BP (2.1 mmHg for systolic BP, and 1.3 mmHg for diastolic BP). In another RCT, Pépin *et al.* (63) compared CPAP with an angiotensin II receptor antagonist, valsartan, in a crossover design. Valsartan was superior to CPAP in lowering BP, and a small but significant reduction was also observed in the CPAP group. After the first part of the study, valsartan and CPAP were combined in a subgroup of patients with uncontrolled BP in the observational, open-label arm of the study, and demonstrated an additional reduction in 24-h BP (63). More recently, Thunström *et al.* (64) addressed the impact of another angiotensin II receptor antagonist, losartan, among patients with newly diagnosed hypertension with and without OSA. The BP drop was significantly less in those with OSA than without. CPAP treatment in addition to losartan resulted in a significant decrease in BP, especially among those who used the device at least 4 h/night (64).

Evidence level

Existing literature, overwhelmed by observational studies, and several well-done RCTs addressing the impact CPAP suggest a beneficial BP lowering effect, especially in nocturnal BP, and especially among OSA patients with

Table 2 Summary of the articles addressing the impact of CPAP treatment on cardiovascular diseases and mortality in patients with obstructive sleep apnea

Outcome	First author	Year	OSA (criteria/ severity)	Sample size	Main findings	Study design
Systemic hypertension	Akashiba *et al.* (53)	1999	AHI >30	38	CPAP changed status from non-dipper to dipper HT	Observational
	Campos-Rodriguez *et al.* (54)	2007	AHI ≥10	55	CPAP improved dipper pattern & reduced diastolic BP	Observational
	Barnes *et al.* (55)	2002	AHI >5	28	CPAP did not reduce 24-BP compared to placebo	RCT
	Robinson *et al.* (56)	2006	ODI >10	35	CPAP reduced blood pressure	RCT
	Muxfeldt *et al.* (57)	2015	AHI ≥15	57/60	CPAP did not improve resistant BP	RCT
	de Oliviera *et al.* (58)	2014	AHI ≥15	24/23	CPAP reduced resistant BP	RCT
	Martínez-García *et al.* (59)	2013	AHI ≥15	98/96	CPAP reduced resistant BP	RCT
	Pedrosa *et al.* (60)	2013	AHI ≥15	20/20	CPAP reduced resistant BP	RCT
	Lozano *et al.* (61)	2010	AHI ≥15	38/37	CPAP reduced resistant BP	RCT
	Durán-Cantolla *et al.* (62)	2010	AHI >15	169/171	CPAP reduced BP	RCT
	Pépin *et al.* (63)	2010	AHI ≥15	14/14	Valsartan was superior to CPAP in lowering BP	RCT
	Thunström *et al.* (64)	2016	AHI ≥15	13/23	CPAP combination with losartan reduced BP	RCT
Pulmonary hypertension	Alchanatis *et al.* (65)	2001	AHI >15	29/12	CPAP reversed mild pulmonary hypertension	Observational
	Sajkov *et al.* (66)	2002	Mean AHI =48.6±5.2	22	CPAP reduced mean pulmonary artery pressure	Observational
	Arias (21)	2006	AHI ≥5	10/11	CPAP reduced pulmonary hypertension	RCT
Cardiac arrhythmias	Kanagala *et al.* (67)	2003	Mean AHI =45±38	12/27	CPAP reduced recurrence of AF	Observational
	Fein *et al.* (68)	2013	AHI >15	32/30/30/22*	CPAP improved AF-free survival	Observational
	Neilan *et al.* (69)	2013	AHI >5	56/57	CPAP reduced risk of AF recurrence	Observational
	Naruse *et al.* (70)	2013	AHI ≥5	82/34	CPAP reduced risk of AF recurrence	Observational
	Holmqvist *et al.* (71)	2015	clinician-defined OSA	937/687	CPAP may reduce AF progression	Observational
	Harbison *et al.* (72)	2000	Mean AHI =23	45	CPAP controlled cardiac rhythm disturbances	Observational
	Roche *et al.* (73)	2005	AHI ≥15	38/38	CPAP reversed ventricular repolarization changes	Observational
	Ryan *et al.* (74)	2005	AHI >20	19/17	CPAP reduced ventricular ectopic beats	RCT

Table 2 (*continued*)

Table 2 (*continued*)

Outcome	First author	Year	OSA (criteria/ severity)	Sample size	Main findings	Study design
Heart failure	Javaheri *et al.* (75)	2000	AHI ≥15	29	CPAP reduced ventricular irritability	Observational
	Shivalkar (76)	2006	Mean AHI =42±24	43/40	CPAP reversed e structural and functional heart abnormalities	Observational
	Kasai *et al.* (77)	2008	AHI ≥15	65/23	CPAP reduced risk of death among patients with HF and OSA	Observational
	Akar Bayram *et al.* (78)	2009	AHI >15	28/18	CPAP improved LV systolic and diastolic function	Observational
	Kaneko *et al.* (79)	2003	AHI ??	12/12	CPAP improved LV systolic function	RCT
	Usui *et al.* (80)	2005	AHI ≥20	8/9	CPAP reduced daytime MSNA, systolic BP and heart rate	RCT
	Hall *et al.* (81)	2014	AHI >10	22/23	CPAP improved myocardial energetics in severe OSA	RCT
	Arias *et al.* (82)	2005	AHI ≥10	14/13	CPAP improved diastolic function	RCT
	Glantz *et al.* (83)	2017	AHI ≥15	87/84	CPAP did not improve diastolic function in CAD with OSA in the ITT population; diastolic relaxation velocity was improved among CPAP users	RCT
Coronary artery disease, cardiovascular mortality, composite cardiovascular outcomes	Peker *et al.* (84)	2006	AHI ≥30	105/203	CPAP treatment reduced incident CAD in OSA	Observational
	Marin *et al.* (85)	2005	AHI >30	372/235/403/377/264*	CPAP reduced risk for mortality	Observational
	Dohorty *et al.* (86)	2005	AHI >15	107/61	CPAP reduced risk for cardiovascular mortality	Observational
	Buchner *et al.* (87)	2007	AHI ≥5	364/85	CPAP reduced cardiovascular event risk	Observational
	Cassar *et al.* (88)	2007	AHI ≥15	175/196	CPAP reduced risk for cardiovascular mortality	Observational
	Milleron *et al.* (89)	2004	AHI ≥15	25/29	CPAP reduced risk for cardiovascular events	Observational
	Martínez-García *et al.* (90)	2012	AHI ≥15	503/436	CPAP reduced risk for cardiovascular mortality	Observational
	Campos-Rodrigez *et al.* (91)	2012	AHI ≥10	576/540	CPAP reduced risk for cardiovascular mortality	Observational
	Peker *et al.* (92)	2017	AHI ≥15	155/112	Cardiovascular events showed no increase in sleepy OSA treated with CPAP	Observational
	Barbé *et al.* (93)	2012	AHI ≥20	357/366	CPAP did not reduce cardiovascular events in ITT population Beneficial effects were observed among CPAP users	RCT
	Huang *et al.* (94)	2015	AHI ≥15	42/41	CPAP did not reduce cardiovascular events in ITT population	RCT
	Peker *et al.* (95)	2016	AHI ≥15	122/122	CPAP did not reduce cardiovascular events in ITT population Beneficial effects were observed among CPAP users	RCT
	McEvoy *et al.* (96)	2016	AHI ≥15	1,359/1,358	CPAP did not reduce cardiovascular events in ITT population	RCT

*, for details of the groups, see references 68 and 85, respectively. AF, atrial fibrillation; AHI, apnea hypopnea index; BP, blood pressure; CAD, coronary artery disease; CPAP, continuous positive airway pressure; HT, hypertension; ITT, intention-to-treat; MSNA, muscle sympathetic nerve activity; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; RCT, randomized controlled trial.

therapy-resistant hypertension. Moreover, CPAP as "add-on" treatment to antihypertensive medication seems to be an effective therapy option.

Pulmonary arterial hypertension

Observational studies

In an early observational study, Alchanatis *et al.* (65) demonstrated that 6 months of CPAP treatment improves pulmonary hypertension in patients with OSA. Other observational studies have also shown that treating OSA with CPAP improves pulmonary hypertension (105). Moreover, increased pulmonary vascular reactivity to hypoxia was also reversed by CPAP treatment in pulmonary hypertension patients with concomitant OSA (66).

RCTs

In a smaller RCT with CPAP *vs.* sham-CPAP in 23 patients with OSA and concomitant pulmonary hypertension, effective CPAP treatment for a 12-week period was associated with significant improvements in echocardiographic measurements of pulmonary arterial pressure (from a mean of 30 to 24 mmHg) (23).

Evidence level

Existing literature is not sufficient to draw proper conclusions regarding the impact of CPAP on pulmonary hypertension among patients with OSA.

Cardiac arrhythmias

Observational studies

Among patients with atrial fibrillation (AF) converted to sinus rhythm with electrical cardioversion, the rate of recurrence of the AF within 1 year was significantly higher in inadequately treated OSA patients compared to the efficiently treated subjects (67). Similarly, Fein *et al.* (68) showed that CPAP therapy resulted in higher AF-free survival rate (71.9% *vs.* 36.7%; P=0.01) and AF-free survival off antiarrhythmic drugs or repeat ablation following pulmonary vein isolation (PVI) (65.6% *vs.* 33.3%; P=0.02). AF recurrence rate of CPAP-treated patients was similar to a group of patients without OSA [hazard ratio (HR) 0.7, P=0.46] (68). Neilan *et al.* (69) investigated a consecutive group of 720 patients undergoing a cardiac magnetic resonance study before PVI, and demonstrated that OSA patients had an increased BP, pulmonary artery pressure, right ventricular volume, left atrial size, and left ventricular mass, and that CPAP therapy was associated with a better cardiac structure in these parameters as well as with a lower risk of AF recurrence after PVI (69). Likewise, Naruse *et al.* (70) showed that OSA patients treated with CPAP had a lower recurrence of AF after ablation compared with that in untreated OSA. In a registry-based study, including 10,132 patients in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) and followed for up to 2 years, Holmqvist *et al.* (71) showed that patients with OSA on CPAP treatment were less likely to progress to more permanent forms of AF compared with patients without CPAP (HR 0.66; 95% CI, 0.46–0.94). A meta-analysis, including eight studies with OSA patients (698 CPAP users and 549 non-CPAP users), demonstrated in a random effects model that patients treated with CPAP had a 42% decreased risk of AF (pooled risk ratio, 0.58; 95% CI, 0.47–0.70) (106). A recent expert consensus document on AF identified OSA as a risk factor for AF recurrence after surgical and catheter ablation, and recommended treatment of the OSA (107). The incidence and the severity of ventricular arrhythmias were also reduced by CPAP treatment (72). Furthermore, ventricular repolarization changes, which may contribute to higher ventricular irritability, were reversed by CPAP treatment (73).

RCTs

In patients with OSA and systolic dysfunction, an RCT suggested a 58% reduction in the frequency of ventricular premature complexes during sleep after 1 month of CPAP therapy (74).

Evidence level

Existing literature is mainly based on observational studies suggesting that CPAP may help maintaining sinus rhythm after electrical cardioversion and ablation in patients with AF. Nevertheless, there is a lack of RCTs to draw proper conclusions in this context.

Heart failure

Observational studies

Javaheri (75) showed that the first-night CPAP treatment was effective in eliminating sleep apnea in 55% of 29 male cardiac failure patients with sleep apnea. Long-term effects of CPAP have also been studied. Altered cardiac functions and structural changes in heart failure patients with concomitant OSA were improved after 6 months of

CPAP treatment (76). Kasai *et al.* (77) showed that the risk for death and hospitalization was significantly higher among untreated and less CPAP-complaint OSA patients compared to that among efficiently treated OSA subjects. Akar Bayram *et al.* (78) indicated a significant improvement in left ventricular systolic and diastolic dysfunction after 6 months of CPAP treatment in 28 newly diagnosed moderate to severe OSA patients who were free of structural heart disease, pulmonary disease, diabetes mellitus, dyslipidemia, alcoholism, neuromuscular disease, renal failure or malignancy at baseline.

RCTs

Kaneko *et al.* (79) studied 24 heart failure patients [left ventricular ejection fraction (LVEF) <45%] and concomitant OSA who were receiving optimal medical treatment. Echocardiographic measurements were assessed on the following morning after polysomnography and after 1 month of CPAP treatment (n=12) or no-CPAP (n=12), and average LVEF was increased from 25.0%±2.8% to 33.8%±2.4% (P<0.001) in the CPAP group (79). In a smaller RCT, Usui *et al.* (80) studied MSNA, BP and heart rate of medically treated heart failure patients (ejection fraction <45%) and concomitant OSA (AHI ≥20) in the morning after overnight polysomnography, and repeated the studies 1 month later in patients who were randomized to CPAP (n=8) or no-CPAP (n=9). Significant benefits were shown in the CPAP group regarding the reductions in daytime MSNA, systolic BP and heart rate. Hall *et al.* (81) evaluated 45 cardiac failure patients with OSA using 11C-acetate and 11C-hydroxyephedrine positron emission tomography before and 6 to 8 weeks of CPAP (n=22) or no CPAP (n=23), and CPAP improved myocardial energetics in the severe OSA cases (81). Regarding heart failure with preserved ejection fraction and concomitant OSA, Arias *et al.* (82) randomized 27 consecutive OSA patients to CPAP or sham-CPAP in a double-blind, crossover design for 12 weeks, and demonstrated significant improvement in diastolic function in the CPAP group. A more recent RCT by Glantz *et al.* (83) showed no significant changes after 1 year in diastolic function parameters in the RICCADSA cohort randomized to CPAP compared with the no-CPAP group in the intention-to-treat (ITT) analysis. However, post-hoc on-treatment analysis revealed a significant association between CPAP usage for ≥4 h/night and an increase in diastolic relaxation velocity (odds ratio 2.3, 95% CI, 1.0–4.9; P=0.039) after adjustment for age, sex, BMI, and left atrium diameter at baseline (83).

Evidence level

Some beneficial effects of CPAP have been shown in patients with heart failure and co-existing OSA but more RCTs with larger samples are needed, especially among patients with preserved ejection fraction and OSA.

Coronary artery disease, cardiovascular mortality, composite cardiovascular outcomes

Observational studies

In a prospective observational study of the incident CAD in a sleep-clinic cohort, efficient treatment of OSA had a protective effect (84). In an observational 10-year follow-up study of males from a sleep clinic cohort, Marin *et al.* (85) suggested untreated severe OSA (AHI >30/h) as an independent predictor for cardiovascular mortality while the patients treated with CPAP showed a significantly lower non-fatal and fatal cardiovascular event incidence rates similar to those in the general population. In another observational study, Doherty *et al.* (86) demonstrated a protective effect of the treatment in a cohort of 168 OSA patients over 7.5 years. In a larger OSA population, Buchner *et al.* (87) suggested that efficient CPAP treatment was associated with a 64% reduction in cardiovascular events independent of age, gender, cardiovascular risk factors and baseline comorbidities at 6-year follow-up. In another observational cohort study, Cassar *et al.* (88) found significantly lower incidence of cardiovascular death in OSA patients treated with CPAP following percutaneous coronary intervention (PCI) compared with the untreated OSA patients. In another observational study, Milleron *et al.* (89) demonstrated a significant reduction in the composite cardiovascular end-point (incidence of new coronary events, acute coronary syndrome, hospitalization for cardiac failure and coronary revascularization requirement as well as cardiovascular mortality) in CAD patients with treated OSA compared to OSA patients who refused CPAP. In a prospective, observational study of a consecutive cohort of 939 elderly patients (≥65 years), the fully adjusted HR for cardiovascular mortality were 2.25 (95% CI, 1.41–3.61) for the untreated severe OSA group compared with the control group whereas the risk was not increased (HR 0.93; 95% CI, 0.46–1.89) for the CPAP-treated group (90). A similar study was performed among 1116 women in a sleep-clinic cohort, demonstrating HR of 3.50 (95% CI, 1.23–9.98) for untreated severe OSA compared with the control group while the risk was not increased for the CPAP-treated group (HR 0.55; 95% CI, 0.17–1.74) (91). More recently,

the study of the observational arm of the RICCADSA cohort showed no significant increase in major adverse cardiovascular and cerebrovascular events in CAD patients with sleepy OSA phenotype treated with CPAP compared with the CAD patients without OSA at baseline (adjusted HR 0.96; 95% CI, 0.40–2.31) (92).

RCTs

The first RCT for the effect of CPAP on long-term cardiovascular outcomes was conducted in sleep clinic cohorts in Spain. Barbé *et al.* (93) investigated nonsleepy patients (ESS score <11) with OSA (AHI ≥20/h), and free of a CVD at baseline, who were randomized to CPAP (n=357) or no-CPAP (n=366), and were followed for a median of 4 years. CPAP did not result in a significant reduction in the incidence of the primary composite outcome (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, or cardiovascular death) in ITT analysis. However, in post-hoc adherence analysis, patients using the device for at least 4 h/night did achieve a benefit (incidence density ratio 0.72; 95% CI, 0.52–0.98) (93).

The second RCT in a sleep clinic cohort was performed by Huang *et al.* (94), who investigated nonsleepy or mildly sleepy patients (ESS <15) with OSA (AHI ≥15/h), and concomitant hypertension and CAD at baseline, who were randomized to CPAP (n=42), or no-CPAP (n=41), and were followed for a median of 36 months. CPAP did not result in a significant reduction in the incidence of the primary composite outcome (new-onset acute myocardial infarction, hospitalization for heart failure, coronary revascularization, stroke, and death associated with cardiovascular and cerebrovascular disease) with 1 event in CPAP group, and 5 events in the no-CPAP group, respectively (94). Despite a relatively high adherence to CPAP treatment, the small sample size for the composite outcomes was a major limitation.

The first RCT in a CAD cohort for long-term outcomes was the RICCADSA study (95), which was a single-center trial performed in Sweden between 2005 to 2013. Newly revascularized CAD patients with nonsleepy (ESS <10) OSA (AHI ≥15/h) were randomized to auto-titrating CPAP (n=122) or no-CPAP (n=122), and were followed for a median of 57 months. The incidence of the primary composite cardiovascular endpoint (new revascularization, myocardial infarction, stroke or cardiovascular mortality) did not differ between the two groups. However, adjusted on-treatment analysis demonstrated a significant risk reduction in those who used CPAP for at least 4 h/night (adjusted HR 0.29; 95% CI, 0.10–0.86) (95).

To date, the largest RCT in CAD and/or cerebrovascular cohorts was the SAVE (Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Disease) trial (96). McEvoy *et al.* enrolled 2,717 nonsleepy or mildly sleepy (ESS <15) with a history of CAD or cerebrovascular disease and concomitant OSA (oxygen desaturation index ≥12/h on a two-channel home sleep recording device), who were randomized to CPAP or no-CPAP. The primary composite endpoint was cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. After an average follow-up of 3.7 years, a primary end-point event occurred in 17.0% of the patients in the CPAP group, and in 15.4% of the patients in no-CPAP (HR for CPAP 1.10; 95% CI, 0.91–1.32) in the ITT analysis, and there was no significant effect of CPAP on any of the individual cardiovascular endpoints. In the CPAP group, the mean duration of adherence to CPAP therapy was 3.3 h per night, and 42% had adequate adherence, defined as CPAP usage ≥4 h/night at 2-year follow-up. One-to-one propensity-score matching was performed to compare 561 patients who were adherent to CPAP therapy with 561 patients in the no-CPAP group. In this secondary analysis, a lower risk of a composite endpoint of cerebral events was found in the CPAP-adherent group (HR 0.52; 95% CI, 0.30–0.90) (96). The relatively low level of CPAP adherence, especially in patients with established CVD, was suggested to be one of the major limitations in that study (108). Moreover, the use of a two-channel equipment for the OSA diagnosis at baseline was criticized as this device has limitations in differentiating central and obstructive events (3). It was possible that patients with Cheyne-Stokes respiration were included, particularly considering that this kind of breathing disorder is common in patients with stroke and HF associated with CAD (3).

A recent meta-analysis by Abuzaid *et al.* (109) including the above mentioned RCTs (93-96) concluded that CPAP utilization to OSA patients was not associated with improved cardiovascular outcomes except in the subgroup that used the device at least 4 h/night. Another meta-analysis by Yu *et al.* (110) including 10 trials [9 CPAP and 1 adaptive servo-ventilator (ASV)] reported no evidence of different associations for CPAP *vs.* ASV, and meta-regressions identified no associations of treatment with outcomes for different levels of apnea severity, follow-

up duration, or adherence to treatment. However, the combination of heterogeneous group of studies including sleep clinic and cardiac and cerebrovascular cohorts, as well as inclusion of adults with OSA and central sleep apnea was pointed out as one of the major methodological concerns that were criticized in another commentary (111).

Evidence level

The evidence level is scarce to suggest CPAP treatment to nonsleepy or mildly sleepy OSA patients in order to solely reduce risk for long-term cardiovascular outcomes and mortality.

Conclusions

OSA is a common disorder with increased cardiovascular morbidity and mortality. Despite an accumulating research evidence regarding the beneficial effect of CPAP treatment on cardiovascular outcomes in observational studies, the majority of the recent RCTs have failed to demonstrate convincing evidence for benefits, except in patients with hypertension. It seems that the required level of CPAP adherence is too high to achieve in patients with more advanced CVD such as CAD and stroke, especially when these individuals are nonsleepy. As recently suggested by Drager *et al.* (112) on behalf of the INCOSACT Initiative (International Collaboration of Sleep Apnea Cardiovascular Trialists), there is a need for further consideration of individual risk factors, and use of new multimodality therapies that also address improvements in adherence. Moreover, a randomization of sleepy OSA patients to no treatment is not ethically feasible since excluding significant sleepiness in CPAP RCTs would mean excluding populations that would benefit from treatment. As previously pointed out, further carefully designed RCTs are needed to overcome the limitations of the recent trials before one may abandon CPAP treatment in OSA patients at risk or with established CVD (111). These goals urge strengthening collaboration among cardiology, sleep medicine, and clinical trial researchers (112). Moreover, as clearly stated in a recent report from an *ad hoc* working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society (113), future perspectives should consider individual risk factors, and implementation of trials that are appropriately powered to target end-points and to support subgroup analyses. These perspectives also confirm the concept of P4 medicine as a roadmap for improving care in OSA that is personalised, predictive, preventive and participatory in nature (114).

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Footnote

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