

# Obstructive sleep apnoea and cardiovascular disease



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Obstructive sleep apnoea (OSA) is a common health concern caused by repeated episodes of collapse of the upper airway during sleep. The events associated with OSA lead to brain arousal, intrathoracic pressure changes, and intermittent episodes of hypoxaemia and reoxygenation. These events activate pathways such as oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, and metabolic dysregulation that predispose patients with OSA to hypertension and atherosclerosis. OSA is a common cause of systemic hypertension and should be suspected in hypertensive individuals, especially those with resistant hypertension. In patients with OSA, continuous positive airway pressure (CPAP) treatment reduces blood pressure, and its effects are related to compliance and baseline blood pressure. Evidence suggests that OSA is a risk factor for stroke and heart failure. An association between coronary heart disease and OSA seems to be limited to middle-aged men (30–70 years). Cardiac rhythm disorders occur in about half of patients with OSA, but their clinical relevance is still unknown. The association of OSA with cardiovascular risk is mainly based on studies in men, and an association has yet to be established in women. Data on older patients is similarly scarce. Currently, there is not enough evidence to support treatment with CPAP for primary or secondary prevention of cardiovascular disease.

## Introduction

Obstructive sleep apnoea (OSA) is a common disease that affects 3–7% of the middle-aged population (30–70 years) and becomes more prevalent with age.<sup>1</sup> It is caused by intermittent collapse of the upper airway during sleep, which leads to transient asphyxia. Although OSA can be asymptomatic, clinically it is characterised by intermittent snoring, unrefreshing sleep, and daytime sleepiness. OSA is an important public health issue, because it is associated with development of cardiovascular events, negative effect on quality of life, and has a causative role in traffic accidents. Only around 10% of individuals with OSA are diagnosed and treated. This shortfall has direct consequences on public health because of the high financial costs of untreated OSA. The events associated with collapse of the upper airway lead to brain arousal, changes in intrathoracic pressure, and intermittent episodes of hypoxaemia and reoxygenation. These events take place in repetitive cycles during sleep and induce the activation of various pathways (intermediate mechanisms) that predispose to atherosclerosis. Basic research and epidemiological and clinical data support the notion that OSA has a role in the initiation or progression of several cardiovascular diseases. In this Review, we describe mechanisms by which OSA might contribute to pathogenesis of cardiovascular disease, and assess clinical and epidemiological evidence of such an association.

## Intermediate mechanisms linking OSA with cardiovascular disease

The mechanisms for initiation and aggravation of cardiovascular disease have not been fully elucidated. Several pathogenic factors are proposed as intermediate mechanisms linking OSA with cardiovascular disease, mainly oxidative stress, sympathetic activation, inflammation, hypercoagulability, endothelial dysfunction, and metabolic dysregulation (figure). Although described here separately, these mechanisms are closely interrelated and manifest simultaneously in patients with OSA.

## Oxidative stress

Oxidative stress arises from an imbalance in redox status between the production and removal of reactive oxygen species (ROS). ROS can react with and cause damage to lipids, proteins, and nucleic acids, which is the pathogenic basis of age-related and chronic diseases such as cancer, cardiovascular disease, diabetes, chronic inflammation, and neurodegenerative disorders. The hypothesis that intermittent hypoxia causes oxidative stress stems from observations that hypoxia and reoxygenation injury triggers an increase in ROS production, mainly during restoration of tissue oxygenation.<sup>2,3</sup> Non-randomised controlled trials in patients with OSA have shown increases in ROS production in monocyte and granulocyte subpopulations,<sup>4</sup> isoprostane concentration in exhaled condensate,<sup>5</sup> and serum malondialdehyde<sup>6</sup> and neutrophil superoxide production.<sup>7</sup> A randomised trial showed that patients with OSA had significantly higher isoprostane and lower nitric oxide concentrations than healthy individuals, and that these were normalised by CPAP therapy.<sup>8</sup> In addition to an increase in ROS production, some researchers have suggested that sleep apnoea might enhance oxidative stress by reducing the antioxidant capacity of blood.<sup>9</sup> The degree of oxidative stress in patients with OSA varies and is uncommon in patients with no comorbidities.<sup>4</sup> Also, sex-related differences in susceptibility to oxidative stress have been noted; in oxidative brain injuries experimentally induced in mice, premenopausal females had greater protection than age-matched males or ovariectomised age-matched females.<sup>10</sup> This sex-related susceptibility could be related to differences in cardiovascular morbidity associated with OSA.

## Sympathetic activation

Increased activity of the sympathetic nervous system constricts blood vessels and increases cardiac output. The degree of sympathetic nervous system activation correlates with the severity of the increase in blood pressure, and is

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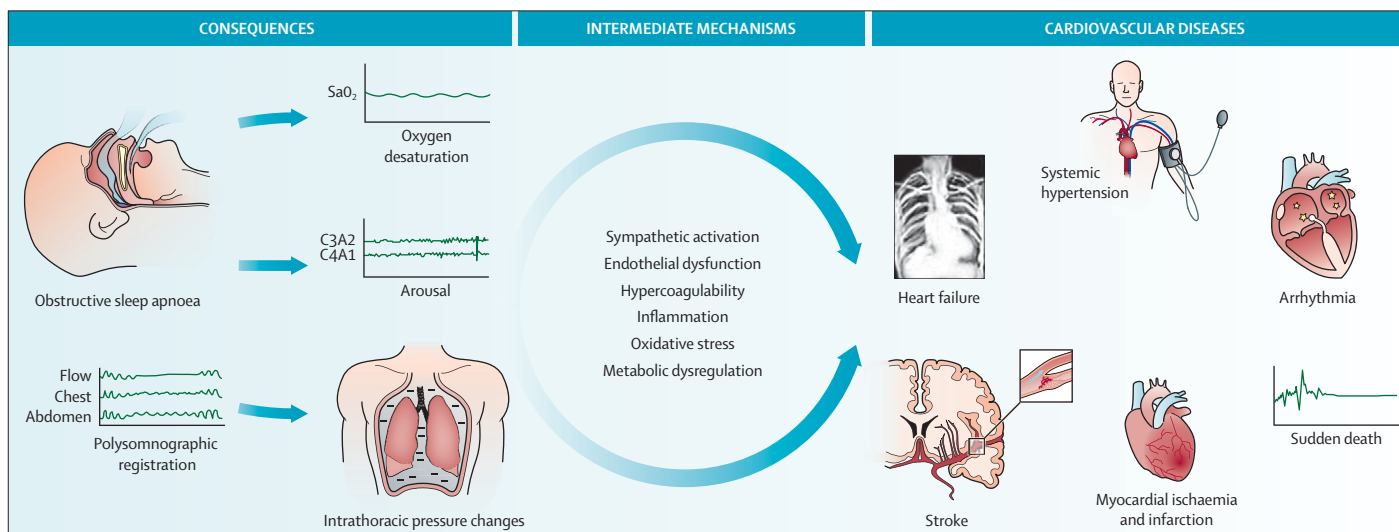
November 6, 2012

[http://dx.doi.org/10.1016/S2213-2600\(12\)70051-6](http://dx.doi.org/10.1016/S2213-2600(12)70051-6)

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**Figure:** Obstructive sleep apnoea consequences and intermediate mechanisms that potentially contribute to risk of cardiovascular disease

The events associated with collapse of the upper airway lead to brain arousal, intrathoracic pressure changes, and hypoxaemia and reoxygenation. Several intermediate mechanisms link obstructive sleep apnoea with the initiation and progression of cardiovascular diseases. SaO<sub>2</sub>=oxygen saturation. C3A2 and C4A1=electroencephalographic channels.

more pronounced in the context of metabolic diseases such as diabetes, obesity, and the metabolic syndrome.<sup>11</sup> Measurement of sympathetic nerve activity in muscle yields accurate and direct information about sympathetic nerve impulses. Moreover, sympathetic tone can be evaluated by measurement of plasma and urinary catecholamines. There is evidence that sleep apnoea might be associated with increased sympathetic activity.<sup>12</sup> Hypoxia and hypercapnia act synergistically to heighten sympathetic activity,<sup>13</sup> and this effect is especially marked during the apnoeic event. Patients with sleep apnoea have a high frequency of arousals from sleep, which induce a sympathetic burst during each apnoeic episode. Patients with OSA have high sympathetic activity when awake, with further increases in blood pressure and sympathetic activity during sleep.<sup>12</sup> Several randomised trials have shown that CPAP treatment reduces sympathetic nervous system activity and attenuates the increased sympathetic tone in patients with OSA.<sup>14–16</sup>

### Inflammation

Obstructive sleep apnoea seems to be associated with local and systemic inflammation. Local inflammatory changes could be partly due to snoring, which triggers vibration frequencies associated with soft-tissue damage. Histological analysis of tissues from patients with OSA undergoing uvulopalatopharyngoplasty shows substantial subepithelial oedema, excessive plasma cell infiltration, and reduction in the surface area of connective tissue papillae, which provide anchorage for the epithelium. Polymorphonuclear leucocytes are also increased in nasal lavage fluid of patients with OSA, compared with people without OSA.<sup>17</sup> In addition to local inflammation, systemic inflammation is seen in patients with OSA. Chronic inflammation has been closely related to the formation

and progression of atherosclerosis. In patients with OSA, activation of redox-sensitive gene expression is suggested by an increase in specific protein products, including inflammatory cytokines; this implies the participation of redox-sensitive transcription factors, such as hypoxia-inducible factor-1, activator protein-1, and nuclear factor  $\kappa$ B (NF- $\kappa$ B). NF- $\kappa$ B is one of the key regulators of inflammation, immune response, and cell survival. A non-randomised study suggested that NF- $\kappa$ B is highly activated in patients with OSA compared with healthy controls, and that CPAP treatment reduces NF- $\kappa$ B activation.<sup>18</sup> Several studies of patients with OSA have reported raised plasma concentrations of other inflammatory markers, such as cytokines (including interleukin-6 and tumour necrosis factor  $\alpha$ ), matrix metalloproteinases, and acute phase proteins, as well as endothelial adhesion molecules, such as intercellular adhesion molecule 1 and vascular cell adhesion molecules.<sup>19</sup> Furthermore, adipokines are involved in a range of processes, including immunity and inflammation,<sup>20</sup> and several studies have shown that patients with OSA have higher concentrations of proinflammatory adipokines than patients without OSA.<sup>21</sup> These proinflammatory adipokines seem to contribute substantially to the inflammatory state of obese patients. Obesity is the most common comorbidity and is present in more than half of patients with OSA. Obesity is considered a chronic inflammatory situation in itself, therefore it might be the most important confounding factor in the association between sleep apnoea and inflammation. In fact, Guilleminault and coworkers<sup>22</sup> reported that obesity had a strong association with C-reactive protein but not with OSA. A randomised trial by Kohler and colleagues<sup>23</sup> reported no improvement in inflammatory markers after CPAP treatment.

### Hypercoagulability

There is evidence of a hypercoagulability status in patients with OSA, which might contribute to an increased risk of cardiovascular events. Patients with OSA show a morning increase in plasma fibrinogen concentration and whole blood viscosity, as well as low fibrinolytic activity.<sup>24</sup> Furthermore, studies have reported high levels of coagulation factors XIIa, VIIa, and thrombin-antithrombin complex.<sup>25</sup> Patients with OSA show increased platelet activation and aggregation, although the mechanisms of platelet activation are not completely understood and might be related to increased sympathetic activity.<sup>26</sup> Hypoxaemia and repetitive arousals from sleep combine to produce raised concentrations of epinephrine and norepinephrine, and high numbers of circulating catecholamines cause concentration-dependent platelet activation *in vitro* and *in vivo*.<sup>27</sup> Interventional studies have shown that CPAP treatment reduces coagulability and the risk of thrombosis in patients with OSA, although not all coagulability markers were reduced after CPAP treatment.<sup>28–31</sup>

### Endothelial dysfunction

The vascular endothelium is a confluent, cellular monolayer that lines the entire vascular compartment at the interface between blood and the vessel wall. The vascular endothelium is intimately involved in controlling vasomotor tone and is the main regulator of vascular haemostasis. The endothelium continuously adjusts the balance between vasoconstriction and vasodilatation; if this balance is tilted towards vasoconstriction, endothelial dysfunction occurs, causing damage to the arterial wall. Endothelial dysfunction occurs in response to cardiovascular risk factors and can precede or accelerate the development of atherosclerosis.<sup>32</sup> Assessment of endothelial function in OSA involves functional evaluation of vascular responses—ie, recording changes in blood flow in response to endothelium-dependent vasodilators or hypoxaemia, quantification of levels of circulating apoptotic endothelial cells, and measuring plasma concentrations of various endothelial biomarkers.<sup>33</sup> Several studies show indirect evidence of reduced nitric oxide availability and high plasma concentrations of adhesion molecules, suggesting that inflammation and vascular endothelial dysfunction contribute to the development of vascular diseases in patients with OSA.<sup>4</sup> Moreover, increased sympathetic activation and oxidative stress, common in patients with OSA, might contribute to the development of endothelial dysfunction. Increased oxidative stress reduces nitric oxide availability and increases expression of ROS, which activates inflammatory pathways that facilitate the recruitment and accumulation of blood cells on the vasculature of the endothelial lining.<sup>34</sup> Effective CPAP therapy (>4 h each night) in patients with OSA reverses vascular endothelial dysfunction and inflammation, and enhances endothelial repair capacity.<sup>34</sup>

Nguyen and colleagues<sup>35</sup> showed that CPAP treatment improves microvascular disease and nitroglycerin-induced coronary vasodilation. CPAP withdrawal has also been associated with impaired endothelial function.<sup>36</sup> Cross and coworkers<sup>37</sup> noted that in patients with OSA, endothelial dysfunction is proportional to hypoxaemia and is improved by CPAP therapy. Therefore, evidence shows that OSA directly affects the vascular endothelium by promoting inflammation and oxidative stress, while decreasing nitric oxide availability and repair capacity. Furthermore, CPAP treatment reverses endothelial dysfunction and enhances endothelial repair capacity.

### Metabolic dysregulation

OSA-related factors such as increased sympathetic activity, sleep fragmentation, and intermittent hypoxia contribute to the development of metabolic dysregulation. Metabolic syndrome refers to a group of factors, including insulin resistance, dyslipidaemia, hypertension, and abdominal obesity, that together result in increased cardiovascular risk. Metabolic syndrome is common in patients with OSA, and OSA is frequently found in conditions associated with metabolic abnormalities.<sup>38</sup> Studies show that patients with OSA have higher free fatty acid concentrations than controls, and this could be one of the mechanisms involved in the metabolic complications of OSA.<sup>39</sup> Nevertheless, there is no clear metabolic pattern associated with OSA, and the single components of the metabolic syndrome found in patients with OSA vary. Independent of adiposity, OSA is associated with impairments in insulin sensitivity, glucose effectiveness, pancreatic B-cell function, and dyslipidaemia.<sup>40</sup> There is much debate about whether OSA increases the risk of type 2 diabetes, and whether CPAP treatment could reverse insulin resistance. Phillips and coworkers<sup>16</sup> showed that CPAP reduced post-prandial triglycerides and total cholesterol. Other clinical trials, however, have shown a partial benefit of CPAP treatment for metabolic components. Sharma and colleagues<sup>41</sup> reported that 3 months of CPAP therapy partially reversed metabolic abnormalities. Hoyos and colleagues<sup>42</sup> noted that 12 weeks of CPAP treatment did not improve insulin sensitivity, visceral abdominal fat, or liver fat, and Weinstock and collaborators<sup>43</sup> showed that insulin glucose tolerance was not normalised after CPAP in patients with sleep apnoea and obesity. Since obesity often coexists with OSA, it is not yet clear whether the presence of metabolic disorders is a consequence of OSA or simply reflects the effects of coexisting severe obesity.<sup>44</sup>

### Cardiovascular consequences of sleep apnoea

#### Hypertension

Hypertension is a common feature of patients with OSA. It is estimated that a third of hypertensive patients have OSA, and about half of patients with OSA are hypertensive.<sup>45</sup> OSA is present in about 80% of patients with resistant hypertension, and is the leading recognisable cause of

hypertension in about two-thirds of these patients.<sup>46</sup> The sympathetic activation associated with obstructive events during sleep might blunt nocturnal lowering of blood pressure and result in a higher occurrence of a non-dipping pattern in patients with OSA. In patients with resistant hypertension, other pathogenic pathways might also be involved. Plasma aldosterone concentration is positively associated with the apnoea–hypopnoea index (AHI) in these patients, and OSA severity has been reported as being worse in patients with hyperaldosteronism. One explanation for these findings is that the fluid retention associated with hyperaldosteronism exacerbates OSA by increasing the movement of fluids to the surrounding tissues, particularly in the neck; this might contribute to the increased propensity for airway collapse during sleep. This hypothesis is supported by a study assessing rostral fluid shifts in patients with OSA and resistant hypertension, which showed that the severity of OSA is strongly related to the amount of fluid displaced from the legs overnight.<sup>47,48</sup>

Results from prospective longitudinal studies suggest that moderate to severe OSA is an independent risk factor for hypertension<sup>49</sup> and for development of a non-dipping blood pressure pattern.<sup>50</sup> Two population-based studies have reported conflicting data. The Sleep Heart Health Study (SHHS)<sup>51</sup> analysed 2470 individuals who were not hypertensive and who were followed up for 5 years. Although a dose–response relationship between AHI and risk of incident hypertension was identified, this association was not found after adjustment for body-mass index (BMI).<sup>51</sup> The Vitoria Sleep Cohort,<sup>52</sup> which included 1180 participants who were followed up for 7.5 years, showed that after adjustment for age, sex, and BMI, there was no association between OSA and hypertension.<sup>52</sup> These studies suggest that the association between OSA and hypertension might not be as strong as was once thought.

#### *Effects of OSA treatment on hypertension*

Several meta-analyses<sup>53–55</sup> have reported that CPAP treatment significantly decreases blood pressure by about 2 mm Hg, and that CPAP compliance and higher baseline blood pressure are predictors of successful blood pressure reduction (table 1). The main concerns with these early studies were the small number of patients enrolled, the presence of non-hypertensive patients, and the short follow-up period. Durán-Cantolla and coworkers<sup>56</sup> did a study of 340 patients with recently diagnosed, untreated hypertension and moderate to severe OSA, who were randomly assigned to CPAP or sham CPAP and followed up for 3 months. Blood pressure was measured by 24-h ambulatory blood pressure monitoring (ABPM). The CPAP group showed a significant decrease in mean ABPM of 1.5 mm Hg. Marin and coworkers<sup>69</sup> did an observational, clinical cohort study in 1889 participants who were not hypertensive and were followed up for 12.2 years. Compared with participants without OSA,

those with untreated OSA had a higher adjusted risk of incident hypertension; patients with OSA adequately treated with CPAP (at least 4 h per day) had a risk of hypertension similar to that of non-OSA participants. In a multicentre, randomised trial involving 359 hypertensive patients with OSA who were randomly assigned to CPAP or conservative treatment for 1 year, Barbé and coworkers<sup>57</sup> showed that CPAP compliance of greater than 5.6 h per night was associated with a reduction in blood pressure of about 3.5 mm Hg.

Theoretically, the effect of CPAP on blood pressure should be greater in patients with resistant hypertension; unfortunately, few studies have investigated this issue. In a randomised trial with 41 patients with ABPM-confirmed resistant hypertension, Lozano and coworkers<sup>58</sup> showed a significant decrease in ABPM in patients who used CPAP more than 5.8 h per day. Martínez-García and coworkers<sup>59</sup> randomly assigned 210 patients with resistant hypertension and an AHI higher than 15 to CPAP or usual treatment for 3 months. In the intention-to-treat analysis, CPAP treatment did not improve ABPM measurements. In a post-hoc analysis, patients with CPAP adherence above the average (>4 h per day) showed a significant reduction in 24-h mean systolic and diastolic blood pressure (5.5 and 4.2 mm Hg, respectively).

Available evidence has led OSA to be considered an identifiable cause of hypertension.<sup>70</sup> Overall, studies examining the effect of CPAP on blood pressure show a slight decrease of about 2 mm Hg. The magnitude of this decrease might be greater in patients with higher baseline blood pressure and higher compliance with CPAP treatment. However, in patients with OSA, the drop in blood pressure associated with CPAP treatment is much lower than the results obtained with antihypertensive drugs.<sup>71</sup>

#### **OSA and non-fatal cardiovascular outcomes**

In a cross-sectional analysis from the SHHS (more than 6000 participants from the general population), participants in the upper AHI quartile were 42% more likely to report at least one cardiovascular disease, compared with those in the lower quartile.<sup>72</sup> In a further longitudinal analysis of more than 4000 participants who were initially free of coronary heart disease and heart failure and were followed up for a median of 8.7 years, the incidence of both conditions increased substantially with increasing OSA severity in men, although the increased incidence of coronary heart disease was only significant in men younger than 70 years.<sup>73</sup>

In an observational study, Marin and colleagues<sup>74</sup> followed 1651 men for 10 years and showed that untreated, severe OSA significantly increased the risk of non-fatal cardiovascular outcomes, compared with healthy participants (odds ratio [OR] 3.17, 95% CI 1.12–7.51;  $p=0.001$ ). Patients with higher CPAP compliance (at least 4 h per day) reduced this risk to the level of non-OSA participants. So far, only one randomised trial has assessed

the long-term effects of CPAP on cardiovascular outcomes. Barbé and coworkers<sup>68</sup> randomly assigned 725 consecutive non-sleepy (Epworth Sleepiness Scale score  $\leq 10$ ) patients with OSA to CPAP or no active intervention, and followed up participants for a mean of 4 years. No difference was found between CPAP-treated and untreated patients with regard to incidence of a composite endpoint of hypertension or cardiovascular events (9.20 vs 11.02 per 100 person-years, respectively; table 1). However, the study had limited power to detect differences between groups. When the results were analysed on the basis of CPAP adherence, patients who

	Outcomes	Treatment	Patient population	Duration of follow-up	Key findings
<b>Hypertension*</b>					
Durán-Cantolla et al (2010) <sup>66</sup>	Blood pressure	Therapeutic CPAP vs sham CPAP	340 patients with untreated hypertension and AHI at least 15/h	3 months	1.5 mm Hg decrease in mean ABPM, 2.1 mm Hg decrease in systolic ABPM, and 1.3 mm Hg decrease in diastolic ABPM
Barbé et al (2010) <sup>57</sup>	Blood pressure	Therapeutic CPAP vs conservative treatment	359 hypertensive patients with AHI at least 20/h, without daytime sleepiness (Epworth Sleepiness Scale score <11)	1 year	Significant decrease in clinic diastolic blood pressure of 2.19 mm Hg. A decrease of 3.5 mm Hg was observed in patients who used CPAP more than 5.6 h per night
Lozano et al (2010) <sup>68</sup>	Blood pressure	Therapeutic CPAP vs conservative treatment	75 patients with resistant hypertension and AHI at least 15/h	3 months	4.9 mm Hg decrease in diastolic ABPM in the CPAP group. Decrease of 6.9 mm Hg in diastolic ABPM and 9.7 mm Hg in systolic ABPM noted in patients adherent to CPAP longer than 5.8 h per night
Martínez-García et al (2012) <sup>59</sup>	Blood pressure	Therapeutic CPAP vs conservative treatment	210 patients with resistant hypertension and AHI at least 15/h	3 months	No changes in ABPM. More patients with CPAP recovered a dipper pattern. Patients with adherence longer than 4 h showed a significant decrease of 5.5 mm Hg in systolic ABPM and 4.2 mm Hg in diastolic ABPM
<b>Stroke</b>					
Hsu et al (2006) <sup>60</sup>	Neurological function	Therapeutic CPAP vs conservative treatment	30 patients with AHI at least 15/h and acute stroke	6 months	No change in neurological function, sleepiness, or health status in the CPAP group. Patients allocated to CPAP had very low adherence (average 1.4 h per night)
Ryan et al (2011) <sup>61</sup>	Neurological function	Therapeutic CPAP vs rehabilitation	48 patients with AHI at least 15/h admitted for rehabilitation within 3 weeks of stroke onset	1 month	CPAP treatment improved functional and motor, but not neurocognitive outcomes
Parra et al (2011) <sup>62</sup>	Neurological function	Therapeutic CPAP vs conservative treatment	140 patients with AHI at least 20/h and acute, first-ever ischaemic stroke	2 years	Cardiovascular event-free survival and neurological recovery was similar in both groups
<b>Heart failure</b>					
Kaneko et al (2003) <sup>63</sup>	LVEF	Therapeutic CPAP vs conservative treatment	24 patients with AHI at least 20/h and LVEF less than 45%	1 month	LVEF increased from 25.0% to 33.8% with CPAP
Egea et al (2008) <sup>64</sup>	LVEF	Therapeutic CPAP vs sham CPAP	60 patients with AHI higher than 10/h and chronic heart failure with LVEF less than 45%	3 months	LVEF increased from 28.8% to 31.0% with CPAP
Arias et al (2005) <sup>65</sup>	Cardiac function	Therapeutic CPAP vs sham CPAP	27 patients with AHI at least 10/h and LVEF less than 50%, and 15 healthy controls	Crossover design, 12 weeks on CPAP and 12 weeks on sham CPAP	At baseline, an abnormal left ventricular filling pattern was present in 15 of 27 patients with OSA and only 3 of 15 in the control group. CPAP significantly improved several diastolic abnormalities
Smith et al (2007) <sup>66</sup>	LVEF and exercise capacity	Auto-titrating CPAP vs sham CPAP	26 patients with AHI at least 15/h and LVEF less than 45%	Crossover design, 6 weeks on autotitrating CPAP and 6 weeks on sham CPAP	Autotitrating CPAP did not improve cardiac function, exercise capacity, or neurohormonal activation. CPAP compliance was low (3.5 h per night)
Mansfield et al (2004) <sup>57</sup>	LVEF, overnight UNE excretion, and quality of life	Therapeutic CPAP vs conservative treatment	55 patients with AHI greater than 5/h and LVEF less than 55%	3 months	CPAP treatment was associated with significant improvements in LVEF (1.5 [SD 1.4%] vs 5.0 [1.0%], $p=0.04$ ), and with reductions in overnight UNE excretion and improvements in quality of life
<b>Composite</b>					
Barbé et al (2012) <sup>68</sup>	Incidence at a composite endpoint (hypertension or cardiovascular events)	Therapeutic CPAP vs conservative treatment	725 patients with AHI at least 20/h, without daytime sleepiness (Epworth score <11)	4 years	Incidence of the composite endpoint was similar in both groups (9.20 vs 11.02 per 100 person-years). In a post-hoc analysis, patients who used CPAP longer than 4 h per night showed a significant decrease in the incidence of the composite endpoint

CPAP=continuous positive airway pressure. OSA=obstructive sleep apnoea. AHI=apnoea-hypopnoea index. LVEF=left ventricular ejection fraction. ABPM=ambulatory blood pressure monitoring. CHF=chronic heart failure. BP=blood pressure. UNE=urinary norepinephrine. \*Only studies done after the 2007 meta-analyses<sup>53,54</sup> have been included.

Table 1: Summary of randomised controlled trials of the effect of CPAP treatment on cardiovascular outcomes in patients with OSA

used CPAP for at least 4 h per day showed a significant decrease in the incidence of the composite endpoint.

#### OSA and cardiovascular mortality

Evidence from population-based and clinical cohorts suggests that severe OSA might be associated with increased death—particularly cardiovascular death. Two population-based cohorts, the Wisconsin Sleep Cohort<sup>75</sup> and the SHHS,<sup>76</sup> prospectively followed up 1522 participants for 18 years and 6441 individuals for 8.2 years, respectively. In both cohorts, and compared with non-OSA participants, severe OSA was independently associated with increased all-cause and cardiovascular mortality, although this association was stronger in Wisconsin Sleep Cohort (hazard ratio [HR] 5.2, 95% CI 1.4–19.2; *p* value not reported) than in the SHHS (HR 1.46, 1.14–1.86; *p* value not reported). Mild to moderate OSA was not associated with increased mortality.<sup>76–78</sup>

Yaggi and coworkers<sup>79</sup> showed that patients with an AHI greater than 5 had a two-times increase in the adjusted risk of stroke or death compared with non-OSA participants, and the risk of development of the composite endpoint increased in a dose-response manner with increasing severity of OSA. Even in patients without previous cardiovascular disease, the presence of OSA was an independent predictor of cardiovascular mortality.<sup>80</sup> Gami and coworkers<sup>81</sup> showed that AHI was correlated with the risk of sudden death from cardiac causes from midnight to 6 am. CPAP treatment has been associated with reduced mortality in observational studies. Marin and coworkers<sup>74</sup> reported that men with untreated, severe OSA had a nearly three-times increase in cardiovascular mortality, whereas those with similar OSA severity who received CPAP treatment showed a risk of fatal events similar to that of non-OSA participants. In this study, mild to moderate OSA was not linked with mortality. Other observational studies have found a similar protective effect of CPAP on cardiovascular mortality.<sup>82</sup>

Available evidence suggests that severe OSA is linked with greater cardiovascular risk, including death.<sup>83</sup> Whether milder forms of the disorder also predict cardiovascular outcomes, as some researchers have suggested,<sup>84</sup> remains unclear. In observational studies CPAP treatment reduces cardiovascular risks. Ongoing large, multicentre, randomised trials will hopefully shed some light on these issues (table 2).

#### Specific cardiovascular consequences of OSA

##### Stroke

Obstructive sleep apnoea can precede or be a consequence of stroke. Vascular injury to the respiratory and upper-airway muscles brain centres can precipitate central or obstructive events. Parra and coworkers<sup>85</sup> noted that 3 months after a stroke, the number of central events significantly decreased, whereas the number of obstructive events remained unchanged,

suggesting that obstructive events might be present before neurological vascular damage. In accordance with this hypothesis, the prevalence of OSA is higher in stroke patients than in the general population, ranging from 50–70%.<sup>86</sup> Similarly, patients with recurrent strokes had a higher prevalence of OSA than those with first-time strokes (74% vs 57%).<sup>86</sup>

Longitudinal, population-based studies suggest that OSA can be a risk factor for stroke. Data from the SHHS<sup>87</sup> showed that OSA significantly increased (three times) the incidence of ischaemic stroke in men, and this association was confirmed in elderly patients.<sup>88</sup> Arzt and coworkers<sup>89</sup> reported a similar increase in incident stroke in patients with OSA, albeit without significance when adjusted for confounders (OR 3.08, 95% CI 0.74–12.81; *p*=0.12). In clinical cohorts, Valham and coworkers<sup>90</sup> found that OSA was independently associated with an increased risk of stroke in 392 patients with coronary heart disease who were followed up for 10 years. Sahlin and coworkers<sup>91</sup> prospectively followed up 132 patients with stroke and showed that the risk of death was higher among patients with moderate to severe OSA. A recent meta-analysis<sup>83</sup> shows that each 10-unit increase in the AHI is associated with a relative increase of 36% in the odds of having a cerebrovascular event.

CPAP therapy normalises the blunted cerebral blood flow response to hypoxia observed in patients with OSA, and reduces carotid intima-media thickness.<sup>92</sup> Although early treatment of OSA in stroke patients should, in principle, protect them from further brain damage and improve functional recovery, available data are conflicting (table 1).<sup>60,61</sup> Observational studies have found a beneficial effect of CPAP on cardiovascular outcomes. Martinez-Garcia and coworkers<sup>93,94</sup> prospectively followed up 166 patients with ischaemic stroke and AHI at least 20; those who used CPAP for at least 4 h per day had a risk of mortality and incidence of non-fatal cardiovascular events similar to that of the control group, whereas patients with OSA who did not tolerate CPAP had an increased adjusted risk of mortality (HR 1.58, 95% CI 1.01–2.49; *p*=0.04) and incident cardiovascular events (HR 2.87, 1.11–7.71; *p*=0.03). However, these positive findings have not been replicated in a randomised trial. Parra and coworkers<sup>62</sup> followed up 140 patients with acute first-time stroke and AHI of at least 20 who were randomised to CPAP or habitual treatment for 2 years. CPAP treatment did not improve survival or functional outcomes, despite an average compliance of 5.3 h per day. A key point in investigating the role of CPAP in stroke is the timing of treatment, which, in most studies, did not begin during the acute phase (first 24 h) of stroke onset, but several days later.

In summary, available data suggest that OSA might be a predisposing risk factor for stroke.<sup>83</sup> The role of CPAP therapy is much less clear; acceptance of the device and early treatment after the onset of a stroke might be key points for achieving better outcomes.

	Acronym	Country	Patient condition	Intervention	Primary outcome	Number enrolled
<b>Cardiovascular outcomes</b>						
NCT00738179	SAVE	Multinational	Stable (>3 months) cardiovascular or cerebrovascular disease	CPAP vs conservative treatment	Serious cardiovascular endpoints or cardiovascular mortality	5000
NCT01335087	ISAACC	Spain	Acute coronary artery disease	CPAP vs conservative treatment	Serious cardiovascular endpoints or cardiovascular mortality	1864
NCT00733343	SERVE-HF	Multinational	OSA and congestive heart failure	Adaptive servoventilation vs conservative treatment	Mortality or hospitalisation	1116
NCT01128816	ADVENT-HF	Multinational	OSA and heart failure	Adaptive servoventilation vs conservative treatment	Death or hospitalisation for a cardiovascular cause	860
NCT00519597	RICCADSA	Sweden	Coronary artery disease (with recent percutaneous coronary intervention or coronary artery bypass graft)	CPAP vs conservative treatment	Serious cardiovascular endpoints or cardiovascular mortality	510
NCT01461473	COMET	USA	OSA and arterial hypertension	CPAP vs oral appliance	24 h ambulatory blood pressure monitoring	238
<b>Intermediate mechanisms</b>						
NCT01086800	HeartBEAT	USA	OSA and risk factors for coronary artery disease and cardiovascular disease	CPAP vs other interventions*	Cardiovascular biomarkers	325
NCT00607893	SASS	USA	OSA	CPAP vs sham CPAP	Oxidative stress	250
CPAP=continuous positive airway pressure. *Included healthy lifestyle, sleep education, and supplemental oxygen.						

**Table 2: Ongoing randomised controlled trials assessing the effect of treatment for OSA on cardiovascular outcomes or intermediate mechanisms**

### Coronary heart disease

The prevalence of OSA in patients with coronary heart disease is about two times higher than in the general population, and up to 70% of patients admitted for acute coronary heart disease have undiagnosed OSA. Coronary artery calcifications, a marker of subclinical coronary disease, were present in 67% of patients with OSA versus 31% of those without OSA.<sup>95</sup> OSA has also been implicated as a risk factor for nocturnal ischaemic events. Kuniyoshi and coworkers<sup>96</sup> reported that myocardial infarction occurred between 12 am and 6 am in 32% of patients with OSA, versus 7% of patients without OSA.

In men, OSA might be an independent risk factor for developing coronary heart disease,<sup>73</sup> or for having a poorer outcome, in patients with previous coronary heart disease. Peker and coworkers<sup>97</sup> prospectively followed up 308 snorers with no previous heart disease; over 7 years, the presence of OSA versus no OSA was associated with an increased adjusted relative risk for development of coronary heart disease of 4.6 (95% CI 1.8–11.6;  $p=0.001$ ). Yumino and coworkers<sup>98</sup> reported that OSA is an independent predictor of a worse outcome after percutaneous coronary intervention in patients with acute coronary heart disease. However, epidemiological studies did not find a clear association between OSA and coronary heart disease after adjustment for confounders.<sup>73</sup>

Overall, although increasing evidence suggests that OSA is an independent risk factor for coronary heart disease, this association is not yet as clear-cut as it is for hypertension and OSA, and more research is needed.<sup>83</sup>

### Arrhythmias

Cardiac rhythm disorders have been described in patients with OSA, the most common types being unsustained ventricular tachycardia, sinus arrest, and second-degree

atrioventricular conduction block.<sup>99</sup> Bradyarrhythmias can be provoked by cardiac vagal activation caused by apnoea-related hypoxaemia in otherwise structurally normal hearts. Although one study showed that arrhythmias were 18 times more likely to occur after an apnoeic event than after normal breathing,<sup>100</sup> the prevalence and clinical relevance of cardiac arrhythmias in patients with OSA are still unknown.

Mehra and coworkers<sup>101</sup> reported that individuals with severe OSA were four times more likely than those without OSA (AHI <5) to have atrial fibrillation. A decrease in nocturnal oxygen saturation has been identified as a predictor of incident atrial fibrillation, independent of obesity.<sup>102</sup> Untreated OSA versus treated OSA has also been associated with a higher recurrence of atrial fibrillation after cardioversion and a higher risk of ablation failure.<sup>103</sup> By contrast with these findings, several studies have reported an increased prevalence of atrial fibrillation in patients with central, but not obstructive, sleep apnoea,<sup>104</sup> suggesting that heart failure, rather than OSA, might be a key point in this association.

### Heart failure

OSA might induce or worsen heart failure via several mechanisms, independent of hypertension. Hypoxaemia, a hallmark of OSA, is an independent predictor of impaired ventricular relaxation and myocardial contractility. Repetitive and acute reductions in intrathoracic pressure cause an increase in left ventricular afterload and a decrease in left ventricular preload, accompanied by reductions in stroke volume. Studies in both children and adults have found an association between OSA and asymptomatic, early cardiac remodelling, which suggests that OSA is associated with altered cardiac structure and function.<sup>105</sup> Whether these effects of OSA can cause heart

failure has yet to be established, but they might worsen a pre-existing heart failure.

Patients with OSA have been reported to have lower left ventricular ejection fraction (LVEF) and other measurements of systolic and diastolic dysfunction, compared with controls. The prevalence of OSA in patients with systolic and diastolic heart failure ranges from 11–55%,<sup>65,98</sup> and the degree of impairment might be linked to OSA severity.<sup>105</sup> Results from cross-sectional and longitudinal analyses from the SHHS show an independent association between OSA and the risk of reporting or developing heart failure.<sup>72,73</sup>

There is some controversy as to whether sleep apnoea increases mortality in patients with heart failure. Roebuck and coworkers<sup>106</sup> followed up 78 patients with heart failure and very reduced LVEF for 52 months, and found a similar prevalence of sleep apnoea in survivors and non-survivors. However, in two observational studies, OSA was independently associated with mortality in ischaemic<sup>107</sup> or non-ischaemic heart failure.<sup>108</sup> Several randomised trials have shown a beneficial effect of CPAP on cardiac function, with improvements in left ventricular systolic and diastolic function, but with small sample sizes and short follow-up periods (table 1).<sup>63,64,67</sup> In a randomised trial with a crossover design, 6 weeks of autotitrating CPAP did not lead to improvement in subjective or objective measures of heart failure severity.<sup>66</sup> The effect of OSA treatment on clinical outcomes, beyond physiological improvements, remains to be established.

#### OSA and cardiovascular consequences in specific populations: women and the elderly

About 2–3% of middle-aged women have OSA. Women and men differ with regard to prevalence, clinical presentation, pathogenesis, and severity of this sleep disorder.<sup>109</sup> Despite these differences, the role of OSA as a cardiovascular risk factor in women has not been established and most studies have only included men.<sup>74,79,110</sup> It has been reported that women might be more susceptible to the cardiovascular consequences of OSA,<sup>111</sup> but the few

studies addressing this topic have yielded conflicting results. Research from the SHHS cohort<sup>73,76,87</sup> did not find any association between OSA and mortality or other incident cardiovascular outcomes, including stroke and coronary heart disease, in 3000 women followed up for more than 8 years. However, severe OSA accounted for only 3% of all the women sampled in the SHHS, which might have biased the results. Campos-Rodriguez and coworkers<sup>112</sup> did an observational study with 1116 consecutive women referred for suspected OSA. After 6 years of follow-up, the group with untreated, severe OSA had an increased adjusted risk of cardiovascular death (HR 3.50, 95% CI 1.23–9.98;  $p=0.019$ ), whereas women with severe OSA who used CPAP for 4 h or more had a mortality risk similar to that of the control group. The results suggest that, as in men, severe OSA might be an independent risk factor for cardiovascular death in women, and that adequate CPAP therapy might protect against it.

The question of whether OSA increases adverse cardiovascular outcomes in elderly patients is controversial. Lavie and coworkers<sup>113</sup> followed up 14589 men for a median of 4.6 years, and noted that mortality declined with age in patients with OSA, and that only patients younger than 50 years showed an excess mortality rate compared with the general population. Analysis of the SHHS cohort also showed an association between mortality and other incident cardiovascular outcomes and severe OSA, but only in individuals younger than 70 years.<sup>73,76</sup>

By contrast, several studies have reported increased mortality and incidence of stroke in elderly patients with moderate to severe OSA, as well as a protective effect from CPAP treatment.<sup>88,93,94</sup> A recent study by Martinez-Garcia and coworkers,<sup>114</sup> who followed up 939 elderly patients with suspected OSA, showed that untreated, severe OSA was associated with increased cardiovascular mortality risk, independent of confounders (HR 2.25, 95% CI 1.41–3.61;  $p=0.001$ ), and that CPAP treatment might reduce this risk. When specific causes of death were separately analysed, untreated severe OSA was associated with death from stroke and heart failure, but not with death from coronary heart disease.

#### Search strategy and selection criteria

We searched PubMed for articles published through July, 2012, with the terms “sleep apnoea”, “sleep apnea”, “OSA”, “hypertension”, “myocardial ischaemia”, “myocardial infarction”, “arrhythmias”, “heart failure”, “stroke”, “sudden death”, “oxidative stress”, “sympathetic activation”, “inflammation”, “hypercoagulability”, “diabetes”, “dyslipidemia”, “metabolic dysregulation”, “metabolic syndrome”, and “endothelial dysfunction”. We mainly selected publications from the past 5 years, but did not exclude widely referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we considered relevant. Only articles published in English were selected.

#### Conclusions: clinical practice and research agenda

Obstructive sleep apnoea should be suspected in hypertensive individuals, particularly in patients with resistant hypertension. CPAP treatment reduces blood pressure, with effectiveness related to initial blood pressure and treatment compliance. OSA is probably a risk factor for cardiovascular disease or cardiovascular death. Available data suggest that stroke and heart failure are the most relevant events related to OSA. Risk of coronary heart disease might be limited to middle-aged men with OSA. There is limited evidence that OSA is related to an increase in clinically relevant arrhythmias. There is no clear evidence so far to support treatment with CPAP for primary or secondary cardiovascular



disease prevention. There are no relevant data on the effect of other OSA treatment options on the incidence or development of cardiovascular events. Our knowledge of the role of OSA as a cardiovascular risk factor is mainly supported by studies in men, and this association still needs to be established in women and in elderly patients.

Several important issues should be addressed in future research. We need to clearly identify the effect of OSA as a risk factor for serious cardiovascular outcomes, and the role of CPAP as a treatment strategy for primary or secondary prevention. The results of ongoing trials will help to shed light on these issues (table 2). Ongoing trials will also help clarify the relevance of intermediate mechanisms linking OSA with pathogenesis of cardiovascular disease, since current evidence is contradictory (table 2). Moreover, it will be clinically useful to identify specific phenotypes associated with increased susceptibility to cardiovascular risk, and to explore the protective mechanism that prevents cardiovascular damage in some patients with OSA. Furthermore, it is necessary to evaluate the clinical effects of other treatments, such as drugs, lifestyle changes, and mandibular advancement devices, on prevention of cardiovascular events. Finally, studies focused on women and elderly patients are needed, to assess cardiovascular risk and the effects of intervention.

#### Contributors

All authors reviewed the literature, wrote and revised the paper, and had final responsibility for the decision to submit for publication.

#### Conflicts of interest

FB has received a research grant from ResMed Inc, Australia, a company that develops products related to sleep apnoea, and support from the Health Research Fund, Spanish Ministry of Health, to develop clinical trials. All other authors declare that they have no conflicts of interest.

#### Acknowledgments

We thank Ferran B Miró for his inspired artwork for the figure.

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