Cardiovascular manifestations in obstructive sleep apnea: current evidence and potential mechanisms

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- cardiovascular disease
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ABSTRACT
Obstructive sleep apnea (OSA) is an increasingly prevalent health concern characterized by repeated episodes of pharyngeal collapse during sleep. It is frequently associated with daytime sleepiness and impaired functional capacity, but it is also linked to cardiovascular disease by a growing body of epidemiological, clinical, and translational research. The severity of OSA is traditionally evaluated by the apnea-hypopnea index (AHI), but the value of this marker as a predictor of cardiovascular outcomes is limited. Thus, there is an increasing focus on alternative classification methods such as the hypoxic burden, other polysomnographic traits, and phenotypic subgroups based on clinical symptoms. There is a need to identify subgroups of patients with OSA who will benefit most from treatment, as recent large randomized controlled trials in selected populations have failed to show benefit in reducing overall cardiovascular mortality. Obstructive sleep apnea adversely affects cardiovascular structure and function by several distinct mechanisms such as intermittent hypoxia, sleep fragmentation, and intrathoracic pressure swings. These mechanisms lead to sympathetic activation, inflammation, and oxidative stress, which may result in the clinical consequences of OSA such as hypertension, coronary artery disease, heart failure, and cerebrovascular disease. This review focuses on the epidemiology and potential mechanisms of cardiovascular diseases in OSA. Furthermore, we will briefly discuss the role of personalized medicine, alternative treatment options, and precise phenotyping to optimize treatment of this complex condition and its associated cardiovascular risk.

Introduction
Obstructive sleep apnea (OSA) is a growing public health problem.\(^1\) The prevalence of the disorder has been increasing rapidly over the last 2 decades in line with the obesity epidemic in the developed world.\(^2\)\(^-\)\(^4\) It is estimated that OSA affects nearly 1 billion people worldwide.\(^5\) However, a significant proportion of patients remain undiagnosed,\(^6\) with one estimate suggesting that more than 30 million people are undiagnosed in Europe alone.\(^1\) There is a male to female predominance of 2 to 1, and OSA is more common in the middle-aged and elderly population.\(^6\)

Obstructive sleep apnea is characterized by recurrent partial or complete upper airway collapse during sleep leading to intermittent hypoxia (IH) and recurrent arousals culminating in disrupted sleep quality that typically manifests as nonrestorative sleep and excessive daytime sleepiness (EDS).\(^7\)\(^-\)\(^8\)

In addition to EDS, OSA is associated with reduced quality of life, poor cognitive function, and road traffic accidents, independent of age or sex.\(^9\)\(^-\)\(^11\) The principal morbidity and mortality of the condition, however, are due to the increased risk of the development and progression of numerous CVDs.\(^5\)

A large body of evidence has accumulated to date strengthening the association between OSA and CVD, with increased risk persisting after correction for common cardiovascular risk factors.\(^12\) Obstructive sleep apnea is associated with increased incidence of systemic arterial hypertension, coronary artery disease, congestive cardiac failure, and stroke,\(^4\)\(^,\)\(^13\)\(^,\)\(^14\) and although
the evidence for these associations is not fully conclusive, it points towards a significant burden of disease caused by OSA.

The gold standard treatment for OSA is continuous positive airway pressure (CPAP), which acts to splint the upper airway open during sleep and very effectively treats excessive daytime sleepiness and improves quality of life. However, its effect on long-term cardiovascular outcomes has been called into question by a number of recent studies (TABLE 1) which we will discuss below. One potential reason for this lack of benefit is poor adherence to CPAP in both research and general populations.

This review aims to summarize the epidemiology of CVD in patients with OSA, the current evidence on pathogenic mechanisms linking OSA and cardiovascular disease (CVD), and briefly discusses the clinical implications and effects of CPAP and other treatment modalities, in order to identify priorities for future research and promote a move towards personalized therapies.

### Epidemiology of Cardiovascular Diseases in Obstructive Sleep Apnea

#### Systemic arterial hypertension

Hypertension is a well-recognized and well-studied complication of OSA with epidemiological data suggesting that there is a strong relationship between OSA and systemic arterial hypertension. Cross-sectional population-based studies consistently find an increased prevalence of hypertension in patients with OSA compared with controls. This finding persists even after controlling for potential confounders such as age and obesity, with approximately 50% of patients with OSA having coexisting hypertension.

Furthermore, large prospective longitudinal studies, such as the WSCS (Wisconsin Sleep Cohort Study), and a later prospective Spanish study, found moderate-to-severe OSA to be an independent risk factor for incident hypertension in patients who were normotensive at baseline. In the WSCS, participants with moderate-to-severe OSA had a 3.2-fold increase in the odds of developing hypertension compared with those without OSA and similarly, in the Spanish study, there was an increased incidence of hypertension in patients with untreated OSA compared with those not undergoing treatment.

Even mild OSA has been reported as an independent risk factor for incident hypertension in patients younger than 60 years.

### Table 1: Trials assessing the impact of therapy on cardiovascular events in patients with obstructive sleep apnea

| Trial descriptor | Outcomes | Treatment | Design, number of participants, treatment | Median follow-up, y | Primary outcome and results |
|------------------|----------|-----------|------------------------------------------|---------------------|----------------------------|
| Sánchez-de-la-Torre et al, 2020 (ISAACCS) | Prevalence of composite outcome of cardiovascular events (cardiovascular death or nonfatal events) | CPAP + usual care vs usual care alone | 2834 patients admitted with ACS, evaluated for OSA with polysomnography and randomized if AHI >15 events/h of sleep, control group without OSA included for comparison | 3.35 | No difference between groups in the incidence of the primary outcome of repeat cardiovascular events. OSA was not associated with an increased risk of cardiovascular events during follow-up when compared with controls. OSA was associated with an increased risk of recurrent cardiovascular events in patients with no previous heart disease and admission for a first ACS |
| McEvoy et al, 2016 (SAVE) | Composite outcome of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack | CPAP + usual care vs usual care alone | 2717 nonsleepy patients with moderate-severe OSA and established cardiovascular disease | 3.7 | No difference in the incidence of the primary composite outcome measure or any secondary outcome measure. Secondary analysis of patients adherent to CPAP for >4 h/night showed a lower risk of death and of stroke |
| Peker et al, 2016 (RICCADSA) | First event of repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality | CPAP vs no CPAP | 244 patients with moderate or severe OSA who did not have daytime sleepiness underwent coronary revascularization prior to trial randomization | 4.75 | No difference between groups in the incidence of the composite endpoint. In the intention-to-treat analysis adherence >4 h/night had lower cardiovascular risk than untreated patients or those receiving CPAP <4 h/night |
| Barbé et al, 2012 | Incidence of systemic hypertension or cardiovascular event | CPAP vs no CPAP | 725 nonsleepy patients with AHI >20 events/h of sleep with no previous cardiovascular disease | 4 | No difference between groups in the incidence of the composite primary outcome. A post hoc analysis suggested a relative risk reduction of 28% in occurrence of primary outcome in patients who were adherent to CPAP therapy (>4 h/night) |

Abbreviations: ACS, acute coronary syndrome; AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.
Notably, hypertension in OSA has several distinctive characteristics, with an increased prevalence of resistant hypertension, masked hypertension, and nondipping nocturnal blood pressure patterns observed in the OSA population.

Resistant hypertension is defined as failure to achieve blood pressure (BP) control to levels less than 140/90 mm Hg despite pharmacological treatment with 3 antihypertensive drugs (including a diuretic). The association between OSA and hypertension appears to be particularly prominent in this subgroup. In studies, OSA is found in up to 83% of patients with resistant hypertension.24,25 Also, patients with resistant hypertension have a 2.5-fold increased risk of OSA compared with other hypertensive participants.26 Finally, a meta-analysis of randomized controlled trials (RCTs) has shown improved BP in particular nocturnal BP in patients with OSA and resistant hypertension treated with CPAP.31

Often, OSA and nocturnal hypertension are not recognized or are masked. Distinct from white-coat hypertension, where BP is elevated in clinical environments but normal at other times, people with masked hypertension have normal BP on review, but elevated BP at other times.27 Masked hypertension is a common feature in patients with OSA, with an increased prevalence in that population compared with the general population.33,34 and is associated with dyslipidemia, increases in arterial stiffness, increased risk of diabetes, sustained hypertension, and CVD.32

Studies involving 24-hour ambulatory BP monitoring have shown that a nondipping nocturnal blood pressure, defined as a drop in blood pressure at night of less than 10%, is particularly prevalent in OSA populations.35,36 Furthermore, a nondipping BP pattern is highly suggestive of OSA, regardless of symptom profile, and the presence of a nondipping nocturnal blood pressure profile is associated with an increased incidence of cardiovascular events regardless of the underlying blood pressure value.37 In one normotensive cohort of patients, the adjusted hazard ratio of cardiovascular events in nondippers was 2.44 compared with dippers.28 Moreover, cardiovascular events are more frequent in patients with OSA and a nondipping BP profile even in the absence of diagnosed hypertension.39

Coronary artery disease/ischemic heart disease

The SHHS (Sleep Heart Health Study) and the WSCS have provided much of the data regarding coronary artery disease (CAD) and OSA. The WSCS participants were younger and had a much stronger association between CAD and OSA, whereby an AHI of more than 30 events/h of sleep resulted in a 2-fold risk of incident coronary artery disease.28 On the other hand, the SHHS reported an equivocal relationship between OSA and incident CAD, finding an increased risk in men younger than 70 years with a hazard ratio of 1.68.41 Meta-analyses support the theory that OSA confers an increased risk of CAD in men, while the relationship between OSA and CAD in women is weaker.42

Imaging studies have also suggested a relationship between CAD and OSA, with a number of studies linking OSA and coronary artery calcification (CAC). Coronary artery calcification is of interest as a possible surrogate marker for primary prevention studies of CAD in patients with OSA, although little is known to date about the influence of CPAP therapy on coronary imaging findings. A report from this department found a significant relationship between OSA severity and the presence and volume of subclinical coronary atherosclerosis, with the relationship remaining when controlled for potentially confounding factors.43 Another German community-based observational study found that OSA was independently related to the amount of CAC found on computed tomography in men under 65 years, and a North American community-based study found a high prevalence of OSA in patients with CAD and an AHI of more than 30 events/h of sleep independently predicted the prevalence of CAC.

Congestive cardiac failure

Sleep-disordered breathing accompanied up to 75% of chronic congestive heart failure cases,44 and the hazard ratio for OSA as a risk factor for incident heart failure with both reduced ejection fraction and heart failure with preserved ejection fraction (HFpEF) was 2.4 in one large study.45 The severity of IH has been shown to be a stronger predictor of outcome than the number of apnea episodes per night. In one study of patients with congestive heart failure, those with minimum oxygen saturation levels in the lowest quartile had a 5-year survival of 50%, while those in the highest quartile had a 5-year survival of 80%.55

The pathophysiology of HFpEF is linked to oxidative stress, sympathetic nervous system activation, and systemic inflammation, all of which are also linked to OSA and to other common comorbidities such as diabetes and obesity.55 Similarly, OSA is strongly linked to the development of atrial fibrillation (AF) and hypertension, which may additionally promote the development of the condition. Data are lacking as to whether treatment with CPAP may ameliorate the progression of HFpEF; however, one small observational study of 36 patients with HFpEF and moderate-severe OSA suggested that treatment with CPAP improved symptoms, cardiac diastolic function, and brain natriuretic peptide (BNP).56

Both OSA and central sleep apnea are prevalent among patients with heart failure. Central sleep apnea in patients with heart failure tends to be associated with Cheyne-Stokes breathing, and is characterized by central apneas that occur during the decrescendo portion of the cyclic respiratory pattern.53 Treatment of central sleep apnea in patients with heart failure in general was called into question by the SERVE-HF study,54 which found a higher incidence of all-cause and
cardiovascular mortality in patients with central sleep apnea treated with adaptive servo-ventilation (servo-controlled inspiratory pressure support on top of expiratory positive airway pressure). Posited reasons for this negative outcome included a reduction in cardiac output with positive airway pressure in some patients, or a possible beneficial aspect to the Cheyne-Stokes respiration seen in central sleep apnea and eliminated by adaptive servo-ventilation. A more recent meta-analysis incorporating this study concluded that periodic short-term adaptive servo-ventilation may be of benefit as an adjunctive therapy for patients with central sleep apnea and heart failure; however, prolonged treatment may have negative effects, possibly due to the accumulating stress on the heart working harder against long-term positive airway pressure.55

**Cardiac rhythm disorders: atrial fibrillation** Obstructive sleep apnea is highly prevalent in patients with newly diagnosed AF. One recent study found that 82.4% of patients had a positive home sleep apnea test result.56 Of those, 31.6% had moderate sleep apnea and 23.3% had severe sleep apnea. Screening for sleep apnea in this study resulted in initiation and long-term adherence to CPAP therapy in 45% of these patients. Obstructive sleep apnea is established both as an independent predictor of stroke in patients with AF57 and as a significant risk factor for the development and recurrence of AF.14 Several international guidelines for the management of AF recommend diagnostic workup and treatment of obstructive sleep apnea,59,60 as untreated disease has been shown to reduce the efficacy of both pharmacological and catheter-based antiarrhythmic therapy. The presence of OSA increases the risk of developing AF with a relative risk of 1.7, as found by a recent meta-analysis.61 Multiple observational studies have suggested that CPAP treatment may lower the rate of AF recurrence following electrical cardioversion,62 though data from RCTs are lacking.

Interestingly, symptomatology characteristic of OSA is less predictive in this population than in the general OSA population. Neither the STOP-BANG questionnaire nor the Epworth Sleepiness Scale were predictive of OSA in a large cohort of paroxysmal AF patients.63 Another study found no correlation between self-reported daytime sleepiness and AH1 in 442 consecutive patients with paroxysmal or persistent AF, and the Epworth Sleepiness Scale had no correlation with OSA severity in this population.64

Data tend to support the possibility that intervention reduces paroxysmal AF. In a meta-analysis of 7 prospective cohort studies involving 1087 patients, the use of CPAP was associated with a reduction in AF recurrence, irrespective of whether they underwent pulmonary vein isolation.65 This beneficial effect appears to be stronger for younger, male patients and those with obesity.66

**Cerebrovascular disease and stroke** Obstructive sleep apnea is an independent risk factor for stroke,14 it often progresses following stroke, and it is associated with poorer functional outcomes,66,67 cognitive impairment, higher mortality,14,68,69 and stroke recurrence, thereby impacting on both primary and secondary prevention. Overall, after adjusting for potential confounders (age, sex, body mass index, smoking, hypertension, and diabetes), untreated OSA conveys a 2-fold increased risk of stroke.70

Several prospective studies have shown an independent association of moderate-severe OSA and stroke. In the WSCS, an AH1 of more than 20 events/h of sleep was associated with an increased risk of stroke over the subsequent 4 years.71 A prospective community-based study found men with an AH1 of more than 15 events/h of sleep conferred a 3-fold increased risk of stroke,72 while another study showed a 2-fold increased risk, independent of vascular confounders.14 The risk of stroke is higher in men and increases with increasing AH1,73,74 with a meta-analysis confirming that moderate to severe OSA increases the risk of non-fatal or fatal stroke (pooled relative risk [95% CI], 2.02 [1.4–2.9])75 in this population. In addition, observational studies suggest that OSA negatively influences stroke outcome by predisposing to stroke recurrence, increasing the risk of mortality post stroke and worse functional recovery with increased disability. There is a high prevalence (50%) of sleep disorders after stroke, although only a small proportion of patients are referred for sleep testing in the 3-month post-stroke period.76 A 10-year study showed that patients with moderate to severe OSA, independent of disability, had a 75% increase in risk of early death compared with those without OSA.77 Obstructive sleep apnea predicts worse functional outcomes in stroke, being independently associated with worse functional impairment,57 worse modified Rankin scale scores at discharge,78 and a longer rehabilitation stay79 as compared with those without OSA. Hypertension, and specifically a nondipping BP pattern, is implicated in these adverse outcomes.77

Currently there is insufficient evidence as to whether CPAP provides benefit to patients post stroke with regards to functional and neurological recovery. Observational studies suggest that CPAP is associated with reduced stroke risk,76 improved cognitive and function outcomes17 and mortality,80 but these trials were limited by poor CPAP tolerance and adherence.78 Furthermore, a meta-analysis of available RCTs failed to demonstrate benefit of CPAP treatment on stroke risk reduction, although patients who are adherent (>4 hours per day) may still benefit and thus, a trial of treatment may still be justified.81 The ongoing Sleep SMART (Sleep for Stroke Management and Recovery Trial) is a multisite prospective RCT whose primary outcome is to determine the effect of CPAP on reducing stroke recurrence, incidence of ACS and all-cause mortality,
and impact on stroke outcome at 3 months, which may provide a more conclusive answer on the role of CPAP in stroke.

**Mechanisms of cardiovascular disease in obstructive sleep apnea**

Intermittent hypoxia is the term given to the repetitive fluctuations in oxygen tension. Obstructive sleep apnea causes a typical pattern of IH with repetitive short cycles of desaturation followed by rapid full reoxygenation. It has been shown that IH has different pathophysiological sequelae to chronic sustained hypoxia. Mild IH seen typically in patients with mild OSA may be cardioprotective via mechanisms similar to ischemic preconditioning. However, severe IH as commonly seen in moderate-severe OSA has been shown in animal studies to cause a sustained rise in blood pressure, to accelerate the course of atherosclerosis, and to increase susceptibility to myocardial infarction. These findings have been corroborated by a human model of IH using healthy volunteers sleeping in hypoxic tents with oscillations in oxygen saturation, which found a sustained rise in BP after 1-4 nights of exposure. In vitro studies have provided further insight into IH-induced cellular responses and signaling mechanisms, such as the state-of-the-art model developed by our laboratory. These mechanistic data tie in with findings from clinical studies demonstrating that markers characterizing the degree of IH are better predictors of hypertension and other CVD than the AHI.

**Sleep fragmentation/recurrent arousals**

Recurrent arousals occur in response to interrupted ventilation with subsequent hypoxia, hypercapnia, and increased respiratory effort in order to restore ventilation and lead to sleep fragmentation and subsequently to EDS, the primary symptom of OSA. Epidemiological data suggest that daytime sleepiness is predictive of elevated cardiovascular risk and sleep fragmentation has been suggested as an underlying mechanism. Ren et al reported that EDS objectively demonstrated by multiple sleep latency testing was an independent predictor of prevalent hypertension in patients with OSA. Mechanistic data are inconclusive in this area; one study found that 12 weeks of sleep fragmentation in mice caused development of endothelial dysfunction and early structural vascular changes, but a recent shorter study (30 days) in mice found no impact on left ventricular (LV) function in healthy or heart failure mice. Thus, the detailed contribution of sleep fragmentation to CVD requires further translational studies.

**Intrathoracic pressure swings**

Increased left ventricular transmural pressures. Repeated pressure changes during apneic events have an adverse effect on the cardiovascular system. During an obstructive event, forced inspiration against an occluded airway generates a large negative intrathoracic pressure. This generates increased LV transmural pressures and contributes to increased afterload. Venous return is also increased which augments right ventricular preload, with consequential right ventricular distension and leftward septal displacement during diastole impairing LV filling. The combined effects of increased LV afterload and reduced preload leads to a reduction in stroke volume and cardiac output. This effect is more pronounced in heart failure patients.

Also, increased LV transmural pressure increased myocardial oxygen demand, while apnea-induced hypoxia leads to coronary vasoconstriction and reduced oxygen delivery. Overall, both in animal and human studies, these changes lead to myocardial ischemia, impaired contractility, and impaired diastolic relaxation, which over time likely contribute to cardiac remodeling and disease.

**Proarrhythmogenesis**

Increased LV afterload due to intrathoracic pressure swings causes acute diastolic dysfunction of thin-walled atria, leading to vagal activation and shortening of the atrial effective refractory period, promoting arrhythmogenesis. Moreover, simulating obstructive apnea using the Mueller maneuver in healthy subjects is proarrhythmogenic resulting in generation of atrial premature beats (shown to be a triggering event in paroxysmal atrial fibrillation) and prolongs ventricular repolarization. Furthermore, as previously mentioned, ventricular remodeling over time as a consequence of repetitive effects of negative intrathoracic pressure alterations is associated with an increased risk of arrhythmogenesis.

In summary, IH, sleep fragmentation and intrathoracic pressure swings are the principal contributors to the pathogenesis of CVD in OSA. As a net consequence, they trigger intermediate pathogenic pathways, as detailed in Figure 1, culminating in adverse cardiovascular outcomes. Briefly, some of these intermediate mechanisms are discussed below, but as these mechanisms are complex, a full discussion is outside the scope of this review and have been comprehensively explored elsewhere.

**Intermediate mechanisms**

Sympathetic activation. Sympathetic activation has been shown to be implicated in OSA-associated AF, heart failure, and hypertension. Several studies have provided evidence of sympathetic excitation in patients with OSA. Early clinical studies observed increased urinary catecholamines in patients with OSA when compared with controls, which fell post tracheostomy. Later studies have confirmed elevated urinary and circulating (plasma) catecholamines in patients with OSA, while CPAP has been shown to lead to a significant fall.

Evidence from animal and experimental studies imply that IH and recurrent arousals are likely the principal initiators. In rats, an increase in catecholamine levels accompanies a rise in BP in
response to IH. Moreover, carotid body denervation, adrenal medulla removal, and administration of adrenergic receptor antagonists have been shown to abolish the rise in BP associated with IH. Healthy participants exposed to IH show signs of sympathetic activation characterized by an increase in the activity of the sympathetic peroneal muscle nerve.

Sleep fragmentation also plays a role. Taylor et al found that the arousal index was the strongest index of daytime muscle sympathetic activity in otherwise healthy participants.

Inflammation Inflammation is involved in the pathogenesis of atherosclerosis and related CVD. Obstructive sleep apnea is associated with low-grade systemic inflammation, characterized by circulating markers of inflammation, that is, C-reactive protein, cytokines (eg, interleukin 6, tumor necrosis factor α), and adhesion molecules (vascular cell adhesion molecule 1). Animal and cell culture studies have supported the critical role of IH as a potent inflammatory stimulus which is central to the pathogenesis of vascular disease in OSA. Murine studies, using apolipoprotein E-knockout mice (ApoE−/− mice) showed that atherosclerotic lesions in response to IH are associated with systemic and vascular inflammation. Furthermore, in mice fed a high-cholesterol diet, IH led to atherosclerotic lesions which did not occur in control animals not exposed to IH. Also, cardiovascular remodeling has been shown in mice exposed to IH. Additionally, several experimental studies have shown that IH activates the transcription factor nuclear factor kappa B (NF-κB), a key mediator of proinflammatory responses. A mouse model of IH showed increased activation of NF-κB in cardiovascular tissues, while increased activation of NF-κB was found in cultured monocytes of patients with OSAS. Furthermore, circulating downstream products of NF-κB activation such as tumor necrosis factor α are increased in OSA patients as compared with controls and fall with CPAP therapy supporting the key role of this transcription factor in OSA-associated inflammation. Visceral adipose tissue has emerged as a key source organ of proinflammatory mediators in OSA corroborated by several preclinical studies demonstrating that IH induces a proinflammatory phenotype of adipose tissue. However, while the impact of IH-induced adipose tissue inflammation on metabolic diseases is well-explored, further studies are required to delineate the role of adipose tissue on vascular inflammation and subsequent CVD in OSA.

However, despite numerous studies showing inflammation as an important mediator in IH-induced CVD, the role of anti-inflammatory treatment on the impact of cardiovascular outcomes is poorly investigated.

Oxidative stress Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and antioxidant mechanisms to eliminate them. While ROS play a key role in regulating cell function, at high concentrations, ROS may lead to oxidative stress and subsequent cell damage. Oxidative stress is thought to be a central mechanism in CVD with evidence from cell culture and animal studies linking oxidative stress to the pathogenesis of endothelial dysfunction, vascular inflammation, and atherosclerosis. This process is mostly mediated through disruption of the vasoprotective nitric oxide axis.

In OSA, repetitive episodes of hypoxia, followed by reoxygenation, likely illicit cell damage through ROS production. Several animal studies have demonstrated that IH leads to excesses of ROS and lipid peroxidation. In rodent models, IH-induced oxidative stress is characterized by superoxide anion production, increase in lipid peroxidation in vessels, heart, and brain, and an increase in nicotinamide adenine dinucleotide phosphate oxidase expression. Also, in rodents, the beneficial effects of antioxidant treatment during IH has been shown, with abolishment of endothelial dysfunction, vascular remodeling, and hypertension. However, the role of oxidative stress in CVD in humans remains controversial. Studies evaluating oxidative stress...
(by measuring oxidative stress markers such as F2-isoprostanes, oxidized low-density lipoprotein) in OSA have yielded equivocal results. This may be due in part to differences in the number of participants, selection criteria, and study design.\textsuperscript{123} Moreover, CPAP has failed to show benefit in several RCTs\textsuperscript{106} and so far, antioxidant treatment has failed to improve the cardiometabolic consequences of OSA, albeit this subject needs exploration in larger RCTs.\textsuperscript{124} Further, more detailed accounts of the pathophysiological processes that lead to adverse cardiovascular and metabolic outcomes in OSA are reviewed and detailed elsewhere.\textsuperscript{13,79,88,125}

Effect of continuous positive airway pressure treatment on cardiovascular events The gold standard treatment for OSA is CPAP, which acts to splint open the upper airways during sleep, as mentioned earlier. It has positive effects on daytime sleepiness and quality of life, but the long-term treatment effect of adequate CPAP therapy on cardiovascular health remains controversial. There is consistent evidence in epidemiological studies that there are higher cardiovascular-related morbidity and mortality rates in patients with severe untreated OSA than in patients on CPAP or patients who do not have severe OSA.\textsuperscript{126} However, one major limitation of nonrandomized studies of CPAP treatment is that patients who are nonadherent to CPAP therapy may also be noncompliant with other aspects of chronic disease management.\textsuperscript{127,128} Recent large-scale randomized CPAP studies have attempted to define the benefits of CPAP, but adherence has been a universal stumbling block.

One Spanish study looked at primary prevention of CVD by randomizing patients with moderate or severe OSA without daytime sleepiness to CPAP or conservative treatment.\textsuperscript{129} Their endpoints included the need for antihypertensive drugs (AHT) or the development of a number of cardiovascular endpoints. No difference was found after 4 years of follow-up between patients randomized to CPAP and those to conservative treatment. However, a post hoc subanalysis suggested that if adherence was more than 4 h/night, the incidence of AHT and cardiac events was reduced.

Studies evaluating the effect of CPAP on hypertension suggest a benefit of OSA treatment. Randomized controlled trials and meta-analyses have found that CPAP significantly reduces systolic and diastolic BP, albeit the effect size is small (mean, 2.6 mm Hg).\textsuperscript{130} However, this level of reduction is clinically relevant as evidence suggests that a reduction in BP of 1 to 2 mm Hg is associated with a reduction in major cardiovascular events, stroke, and heart failure.\textsuperscript{131} Moreover, the benefit of CPAP might be more marked in those with resistant hypertension\textsuperscript{132} and when used in combination with drug therapy.\textsuperscript{133} However, some studies failed to show a consistent benefit with CPAP on blood pressure.\textsuperscript{129,134,135} The conflicting results may represent different study populations, CPAP adherence rates, sample size, and duration of follow-up. For example, most studies comprised patient with EDS. In those in which this cohort of patient was excluded, no reduction in BP was shown following CPAP initiation,\textsuperscript{133} highlighting the importance of personalized treatment approaches.

The role of CPAP therapy on cardiovascular outcomes in general remains a topic of substantial debate. In the RICCADSA trial, 244 patients with moderate or severe OSA who did not have daytime sleepiness underwent coronary revascularization and were randomized to CPAP or conservative treatment for 57 months.\textsuperscript{136} There was no difference in the composite endpoint of repeat revascularization, myocardial infarction, stroke and cardiovascular mortality in the intention-to-treat analysis, but again, adherence of more than 4 h/night had lower cardiovascular risk than untreated patients or those receiving CPAP less than 4 h/night. In the SAVE (Sleep Apnea Cardiovascular Endpoints) study, patients with established cardiovascular or cerebrovascular disease along with moderate-severe OSA were randomized to CPAP plus usual care or usual care alone.\textsuperscript{137} The oxygen desaturation index was used to define moderate-severe OSA, and the primary outcome was a composite of death from cardiovascular causes, myocardial infarction, stroke, hospitalization for heart failure, acute coronary symptoms, or TIA. CPAP use did not significantly reduce occurrence of the primary endpoint in the intention-to-treat analysis. However, again propensity score-matched analyses showed that patients with good CPAP adherence had a lower risk of stroke and a lower risk of the composite endpoint of cerebrovascular events.

Thus, it is clear that poor adherence to CPAP affects therapeutic response in patients with OSA, and that improved patient selection and phenotyping is required for optimal treatment benefit. Furthermore, most studies excluded the most-sleepy patients, which represent a specific phenotype that may not be representative of the general OSA population in terms of comorbidity risk.\textsuperscript{138} The recent report of Mazzotti et al,\textsuperscript{139} who evaluated the relationship of different symptom subtypes, indicated that the sleepiness subtype is associated with a significantly higher incidence of adverse cardiovascular outcomes compared with other subtypes.

Future directions A number of important questions remain open regarding the diagnosis, risk stratification, and treatment of OSA. It is increasingly clear that conventional measures of OSA severity such as the AHI, do not correlate well with the severity of clinical symptoms.\textsuperscript{140-143} nor do they correlate optimally with associated cardiovascular morbidity and mortality.\textsuperscript{142} Markers such as the hypoxic burden, which characterize the severity of IH as a key pathophysiological trigger of CVD, appear to be better correlated with end-organ consequences of OSA. Data
from the ESADA (European Sleep Apnoea Database) cohort study showed that the AHI was not an independent predictor of prevalent hypertension after adjustment for the oxygen desaturation index (ODI), whereas the ODI was a significant independent predictor (OR, 2.01; 95% CI, 1.61–2.51) for the fourth quartile as compared with the first quartile of the 4% ODI. Another recent cohort study in 2872 men found that patients with severe nocturnal hypoxemia had a 1.8-fold increased risk of stroke compared with those without nocturnal hypoxia, and nocturnal hypoxemia was an independent risk factor for major adverse cardiac events.

Ongoing research into management of CVD in OSA is complicated by the early adoption of CPAP and its confirmed effect on quality of life, sleepiness, and road traffic accidents, leading to difficulty carrying out RCTs especially in patients who report EDS. This has led to the exclusion of very sleepy patients from large randomized trials of CPAP therapy and this may have contributed in part to their equivocal results. Furthermore, most trials of CPAP have been in the context of secondary prevention of CVD. However, CPAP may be most beneficial for early CVD but primary prevention trials are particularly difficult to design in OSA, given the large cohort and prolonged follow-up required, along with the difficulties in withholding CPAP.

Phenotyping of OSA will be crucial for future clinical disease classification and therapeutic modality selection, especially as therapeutic options expand. Cluster analyses have shown promise but need to be validated using prospective studies, and several phenotypic subgroups are now recognized that vary in polysomnography findings, clinical features, and risk of complications. Traits such as a high burden of periodic leg movements of sleep, frequent arousals and more severe hypoxia despite a low AHI (<15 events/h of sleep) are predictive of adverse CVD outcome, and symptom subtypes such as excessive sleepiness or comorbid insomnia may predict an increased risk of congestive cardiac failure or comorbid CVD.

Efforts have also been made more recently to subclassify patients with OSA by their underlying pathophysiological mechanisms, such as impaired anatomy, a low arousal threshold, ventilatory control instability, and ineffective upper airway muscles during sleep. A number of overlapping phenotypes have been recognized. This improved phenotyping reveals potential targets for pharmacologic therapy of OSA, although this area remains in its infancy. Of these, the weight-loss promoting agent, liraglutide, is a promising pharmaceutical compound to establish an indication for OSA but requires further evaluation. A number of antidepressant medications have been used to target a low arousal threshold. Finally, there are studies ongoing into using transcutaneous electrical stimulation to increase neuromuscular tone of the upper airway dilator muscles of patients with OSA during sleep.

In summary, a personalized medicine approach that encompasses a range of patient factors has an increasingly important role in this complex and multifactorial disease process. Some OSA phenotypes may drive CVD or metabolic dysfunction to a greater degree than others, and thus accurate phenotyping may be a better approach in the prediction of adverse outcomes or death than the AHI. Appropriate patient selection will allow targeted use of CPAP and other therapeutic options, with the aim of improving long-term cardiovascular health in this patient cohort.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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