



REVIEW ARTICLE

Obstructive sleep apnea and cardiovascular risk

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Abstract Patients with obstructive sleep apnea (OSA) experience repetitive episodes of upper airway obstruction due to recurrent collapse during sleep. This leads to intermittent hypoxia episodes, which, through complex pathophysiological mechanisms, trigger sympathetic overactivation, endothelial dysfunction, hypercoagulation, and metabolic dysregulation. Consequently, other cardiovascular risk factors such as hypertension, metabolic syndrome, and diabetes are induced. Furthermore, this enhances target organ damage, affecting the heart, arteries, and kidneys, leading to an increased risk of cardiovascular morbidity and mortality. Among the various treatments for OSA, Continuous Positive Airway Pressure (CPAP) has been extensively studied. To date, this treatment has shown mild benefits in reducing blood pressure, particularly noticeable in patients with resistant hypertension. Furthermore, CPAP treatment appears to reduce cardiovascular events, both in primary and secondary prevention, though this benefit is limited to individuals with good compliance (CPAP use ≥ 4 h/night). Future research perspectives in OSA seem to focus on identifying patients in whom the condition significantly influences cardiovascular risk, thus determining those who would benefit the most from treatment in the reduction of cardiovascular risk.

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PALABRAS CLAVE

Apnea obstructiva del
sueño;
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Apnea obstructiva del sueño y riesgo cardiovascular

Resumen Los sujetos con apnea obstructiva del sueño (AOS) sufren episodios repetidos de obstrucción de la vía aérea superior durante el sueño, debido a su colapso recurrente, que condicionan fenómenos de hipoxia intermitente. Esta, a través de mecanismos fisiopatológicos complejos, desencadena una hiperactivación simpática, disfunción endotelial, estado de hipercoagulabilidad y desregulación metabólica. Como resultado, se ve facilitada la aparición de otros factores de riesgo cardiovascular, como la hipertensión, síndrome metabólico o diabetes,

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se ve potenciada la lesión de órganos diana en corazón, arterias y riñones, así como un mayor riesgo de eventos y morbilidad cardiovascular. De entre las medidas terapéuticas del AOS, la más estudiada respecto a su potencial en reducción del riesgo cardiovascular, es el tratamiento con presión positiva continua sobre la vía aérea, la CPAP. Hasta la fecha, esta ha demostrado beneficios muy moderados en reducción de presión arterial, más evidentes en sujetos con hipertensión resistente, así como beneficios en reducción de eventos, tanto en prevención primaria como secundaria, aunque restringidos a aquellos sujetos con buena adherencia al tratamiento (uso $\geq$ 4 h/ noche). Las nuevas vías de investigación sobre el AOS parecen centrarse en buscar nuevos medios que permitan identificar a aquellos sujetos, en los que esta patología, es más determinante en el riesgo cardiovascular y que más se podrían beneficiar con su tratamiento, en términos de reducción del mismo.

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Introduction

Obstructive sleep apnoea (OSA) consists of repeated episodes of upper airway obstruction due to its collapse during sleep. Consequently, the subject suffers recurrent episodes of hypoxemia and reoxygenation leading to nocturnal arousals, sleep fragmentation and sympathetic over activity. This all results in non-restorative sleep that is associated with daytime sleepiness, deterioration in quality of life, and metabolic and cardiovascular disease.¹ The syndrome is significantly prevalent, especially in the middle-aged adult population. Here, previous studies have reported that between 34% of men and 17% of women in these age ranges meet the criteria for the diagnosis of OSA.² The fact that the risk of suffering from OSA is closely related to obesity, the prevalence of which continues to rise in developed countries, suggests that increasingly more subjects will begin to suffer from this disease.³

The diagnosis and management of OSA is carried out in sleep units following established guidelines.⁴ In these units, after a clinical assessment that includes evaluation of the degree of sleepiness through validated scales such as the Epworth Sleep Scale (ESS) and comorbidities, especially cardiovascular risk factors, a sleep study, polysomnography or polygraphy is performed. Through this, the apnoea-hypopnoea index (AHI) is obtained, which is the sum of apnoeas and hypopnoeas per hour of sleep, defining apnoea as the absence or reduction of airflow lasting 10 seconds or more and hypopnoea as a reduction in airflow of 30%–90% also lasting 10 or more seconds, associated with arousal or a drop in O₂ saturation $\geq$ 4%. Depending on the AHI value, the severity of the syndrome is established. Thus, it can be mild (AHI: 5–14 events/h), moderate (AHI: 15–29 events/h), or severe (AHI: $\geq$ 30 events/h).⁵

The indication for treatment and its options are essentially conditioned by the severity of the disease and the associated symptoms.⁴

Against this backdrop, our review will focus on those aspects that relate OSA to cardiovascular risk, either from the pathophysiological or clinical point of view, as a precursor to other risk factors, damage to target organs or

cardiovascular morbidity and mortality. Beyond this, we will focus on the existing evidence about whether the treatment of this condition provides benefits in cardiovascular prevention.

Pathophysiological aspects

In patients with OSA, repeated episodes of hypoxia and arousals lead to a whole cascade of pathophysiological phenomena with unfavourable final effects (Fig. 1). On the one hand, via activation of arterial chemo-receptors, sympathetic over activity occurs,^{6,7} which generates peripheral vasoconstriction and vascular remodelling, facilitating the development of hypertension.⁸ Likewise, this increase in sympathetic activity at the adrenal and renal level determines an increase in the activity of the renin-angiotensin-aldosterone system.⁹ The consequences of this are more pressor effect, due to the action of angiotensin II, and hydrosaline retention from aldosterone. Secondly, as a result of intermittent hypoxia, a large amount of free radicals are produced which activate inflammatory phenomena that damage the vascular endothelium, leading to its dysfunction.^{10,11} As a consequence, the production of nitric oxide (NO)¹² decreases, attenuating its vasodilatory effect, and the production of a powerful vasoconstrictor, endothelin-1,¹³ increases. The oxidation of lipoproteins, expression of adhesion molecules, as well as the adhesion of monocytes to endothelial cells and the proliferation of smooth muscle cells of the vessels are simultaneously enhanced. All of this facilitates the development of atherosclerosis. A third significant factor is the state of hypercoagulability,¹⁴ produced by intermittent hypoxia and the increase in circulating catecholamines through greater platelet activity¹⁵ and a state of blood hyperviscosity due to an increase in haematocrit.¹⁶

Finally, also worthy of mention is the metabolic deregulation that is associated with the syndrome. In OSA, increased sympathetic activity lowers insulin secretion, and also induces insulin resistance. The latter seems to be contributed by sleep fragmentation, which causes an increase

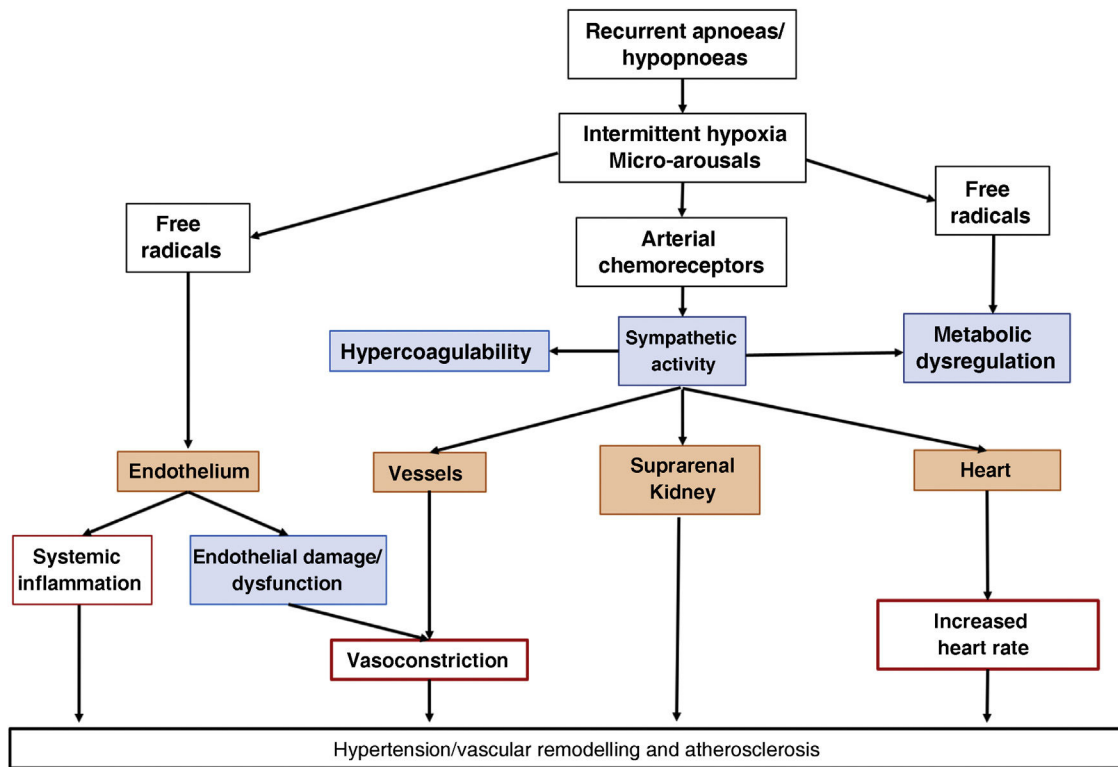


Figure 1 Pathophysiological aspects of obstructive sleep apnoea.

in IL-6 and TNF alpha and a decrease in adiponectin levels, as well as intermittent hypoxia.¹⁷ All of this produces a metabolic state prone to the development of metabolic syndrome and diabetes, which has been demonstrated in clinical studies.^{18,19} In the case of diabetes, the association appears to be even independent of the concurrence of obesity.¹⁹ Metabolic deregulation also seems to imply the tendency to present an unfavourable lipid profile,^{20,21} with increased total cholesterol, low-density lipoproteins and triglycerides, as well as lower levels of high-density lipoproteins.²¹

Alongside all this and in parallel, some unfavourable haemodynamic effects also take place. On the one hand, distention of the rib cage with the upper airway closed generates negative intrathoracic pressure that increases venous return to the right ventricle, increasing filling pressures and stress on the interventricular septum. This fact, added to the increase in afterload due to associated hypertension, facilitates the development of ventricular hypertrophy.²² Furthermore, nocturnal recumbency and negative pressure in the upper body during apnoeas also facilitate the migration of fluid from the extremities. This phenomenon can promote oedema of parapharyngeal tissues and collapse of the upper airway,²³ further facilitating apnoeas.

Obstructive sleep apnoea and hypertension

Available evidence provided by epidemiological studies seems to draw a close relationship between OSA and hyper-

tension. Some 30%–50% of patients with hypertension have OSA,²⁴ with this prevalence rising to 71%–90% in the case of patients with resistant hypertension.²⁵ Conversely, up to 35%–80% of patients with OSA have hypertension²⁶ (Fig. 2).

In a famous prospective study Peppard et al.²⁷ definitively established the causal relationship between OSA and hypertension, in principle independent of the concurrence of other confounding factors such as obesity. Other studies have provided data on how this relationship behaves. On the one hand, the relationship is more evident the more severe the syndrome (higher AHI in the sleep study),²⁸ in patients with associated drowsiness,²⁹ in men³⁰ and in those who concentrate more apnoeic episodes in the REM phase of sleep.³¹ Furthermore, the strength of the association seems to weaken with age, especially after 60 years of age,³² and comes into question based on the results of 2 studies. In the Sleep Heart Health Study (SHH), the 5-year risk of developing hypertension was not related to OSA.³³ Likewise, in the Vitoria cohort, in which 1,180 subjects were monitored for an average period of 7.5 years, after a baseline sleep study, no association was found between OSA and hypertension after adjusting for age, sex and body mass index (BMI).³⁴

Beyond this, there is the potential of OSA to unfavourably alter the circadian pattern of blood pressure, essentially at the expense of inducing an increase in nocturnal pressure,³⁵ that could undoubtedly impact a greater cardiovascular risk in affected subjects.

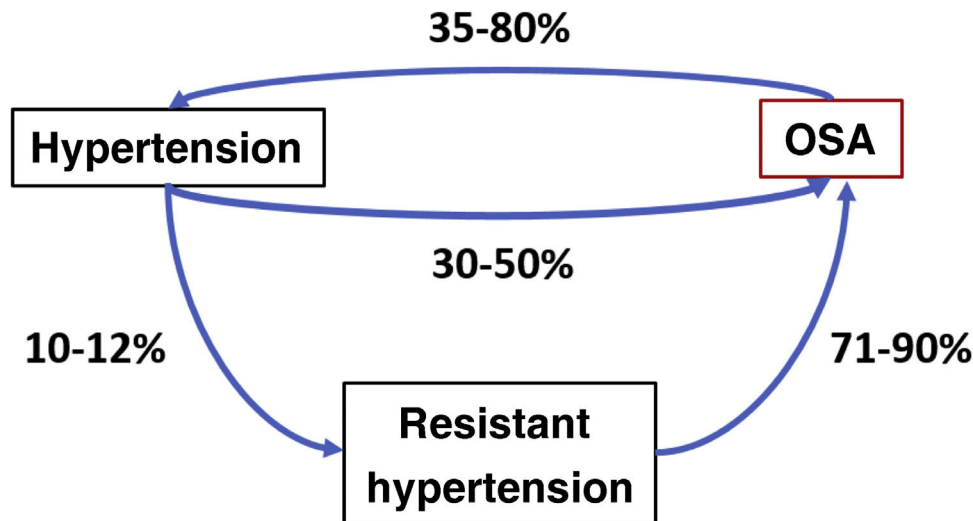


Figure 2 Epidemiological relationship between hypertension and obstructive sleep apnoea.

Obstructive sleep apnoea and subclinical organic injury

The relationship between OSA and cardiovascular risk is not only restricted to facilitating other risk factors but also to directly inducing subclinical organic injury, which could be considered the stage prior to the presentation of events. A SHH sub-study carried out with 2,058 middle-aged subjects found that the ventricular mass index, the main parameter to assess left ventricular hypertrophy (LVH), was significantly related to the AHI and the degree of hypoxemia in the sleep study. This was the result after adjusting for multiple confounding factors such as BMI; toxic habits (smoking and alcohol consumption); systolic blood pressure (SBP); antihypertensive treatment; diabetes, and a history of myocardial infarction.³⁶ A subsequent meta-analysis confirmed the relationship between LVH and disease severity.³⁷

Regarding subclinical atherosclerosis, 2 meta-analyses, one with 16 studies and 1,415 patients³⁸ and another that included 18 studies with a total of 1,896 patients,³⁹ showed a significant relationship between OSA and an increase in the intima-media index, when subjects with the disease were compared with control populations. Beyond this, there also seems to be a dose-response effect³⁹ in addition to the effects of hypertension at the same level.⁴⁰ More recently, this relationship has been confirmed in plaque (focal carotid thickening >1.5 mm) and modulated by age, essentially evident in subjects under 68 years of age.⁴¹

Finally, OSA has also been related to subclinical kidney damage, both with greater urinary albumin excretion⁴² and with a greater annual rate of drop in glomerular filtration rate than in controls.⁴³ However, another long-term longitudinal follow-up study, also of a large cohort of subjects, did not replicate these results in terms of a drop in glomerular filtration rate.⁴⁴ These discrepancies were related to differences in the populations studied, who were much healthier, with less prevalence of OSA and less comorbidity in the study by Canales et al. It is possible, therefore, that for the harmful action of OSA on the kidney to become evident, the

concurrence of other comorbidities or a high prevalence of the disease in the population studied would be necessary.

Obstructive sleep apnoea and cardiovascular event risk

Obstructive sleep apnoea and cardiovascular disease (coronary heart disease, heart failure and arrhythmias)

Several studies have suggested that OSA is a risk factor for ischaemic heart disease. In the SHH, 1,927 men and 2,495 women aged 40 years or older were followed up after baseline polysomnography for an average period of 8.7 years. After adjusting for multiple confounders, OSA was a significant predictor of coronary heart disease in men aged <70 years (adjusted hazard ratio: 1.10, 95% CI: 1.00–1.21) for each increase of 10 units in the apnea-hypopnea index (AHI).⁴⁵ Similarly, in a sub-study of the Wisconsin Sleep Cohort Study, follow-up for a median of 24 years of patients with severe OSA (AHI > 30 events/h) revealed that these subjects had a 2.6 times greater risk of developing coronary heart disease or heart failure.⁴⁶ Not only is OSA a risk factor for coronary heart disease, but it is also a risk factor for recurrence of coronary events in patients who already had this diagnosis.⁴⁷ Likewise, it also seems to determine the time at which patients suffer the infarction, being more common at night in patients with OSA,⁴⁸ even when the presentation is sudden death.⁴⁹ For the latter, OSA also seems to have a predictive value, independent of the concurrence of other well-established risk factors.⁵⁰

Although data from the SHH study seem to demonstrate that OSA would be an independent risk factor for atrial fibrillation in patients without known underlying heart disease,⁵¹ and that it appears to increase the risk of recurrence after treatment,⁵² it is still not considered definitively proven that the disease causes atrial fibrillation.⁵³ Finally, OSA could be a risk factor for the development of heart failure at all ages,⁵⁴

in combination with the assumption of poor prognosis for the evolution of this disease when they coexists.

Obstructive sleep apnoea and stroke

OSA has been identified as a potential risk factor for stroke. In a meta-analysis of 5 studies that included 8,435 patients, Loke et al. showed that the syndrome was an independent risk factor for the incidence of stroke (OR: 2.24; 95% CI: 1.57–3.19; $p < .001$), especially in men.⁵⁵ Furthermore, it was observed that the risk increases with the severity of the syndrome.⁵⁶

Apart from being a risk factor, it is also common in patients with established ischaemic, haemorrhagic or transient stroke, where sleep apnoea seems to reach a prevalence of between 71%–72%,^{57,58} and is predominantly obstructive apnoea, since only 7% of patients had central apnoeas.⁵⁸ To complete this relationship, the syndrome as a comorbidity appears to worsen the prognosis of stroke.⁵⁹

Meta-analysis of prospective observational studies

Over the years, different meta-analyses,^{55,60,61} with a growing number of studies and patients, have made it possible to relate both moderate and severe OSA with a higher risk of total cardiovascular disease; major cardiovascular events (MACE)⁶¹; coronary heart disease^{60,61} and stroke,^{55,60,61} with an association comparable to that of other risk factors, and with only severe OSA having been related to cardiovascular death (RR: 2.96; 95% CI: 1.45–6.01; $p = .003$) and death from any cause (RR: 1.54; 95% CI: 1.21–1.97; $p < .001$).⁶¹

Treatment of obstructive sleep apnoea and its effects on blood pressure and cardiovascular risk

The treatment of OSA consists of general guidelines that involve hygienic/dietary measures (cessation of alcohol consumption, avoiding the use of sedatives, physical exercise and sleeping a regular and sufficient number of hours) and also losing weight. The gold standard treatment of OSA which is continuous positive airway pressure (CPAP) or, alternatively, mandibular advancement devices (MAD) or surgery⁴ may be used in addition. Of all these therapeutic options, the most studied, in terms of reducing blood pressure and risk of events, is treatment with CPAP.

Treatment of obstructive sleep apnoea and hypertension

The effect of OSA treatment with CPAP on blood pressure assessed with the most reliable method, which is 24 h ambulatory blood pressure monitoring (ABPM), can be considered moderate. At a general level, a decrease of between 2 to 2.5 mmHg for systolic blood pressure (SBP) and between 1.5 and 2 mmHg for diastolic blood pressure (DBP) occurs.^{62,63} However, this effect is more evident in subjects with resistant hypertension, reaching 4.7 to 7.2 mmHg for SBP and 2.95 to 4.99 mmHg for DBP.^{64–66} Furthermore, these benefits in reducing blood pressure when treating OSA with CPAP

seem to be more significant in relation to nocturnal blood pressure. Attributing the potential reduction in the risk of cardiovascular events with CPAP treatment only to its effects on blood pressure could be a mistake, taking into account everything previously explained regarding the pathophysiology of the disease. As a result, organ protection with CPAP treatment, which goes beyond the mere reduction in blood pressure, cannot be ruled out.

Treatment of obstructive sleep apnoea with CRAP and the reduction in cardiovascular events

In general terms, the reduction of cardiovascular events in patients with OSA with CPAP treatment is conditioned by therapeutic compliance, both in primary and secondary prevention. It has been estimated that compliance with CPAP treatment ≥ 4 h/night is necessary to obtain benefits at this level.

Primary prevention

The most significant study is that of Barbé et al.⁶⁷ who randomised 723 patients, without a history of previous cardiovascular disease, with moderate and severe OSA (AHI > 20), without excessive daytime sleepiness (ESS < 10) to treatment with CPAP (366) or to no intervention (357). At a median follow-up of 4 years (IQR: 2.7–4.4), CPAP treatment did not reduce the incidence of hypertension or cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attack, hospitalisation for unstable angina, arrhythmia, heart failure or cardiovascular death). However, a post hoc analysis suggested that adherence to treatment with CPAP ≥ 4 h/night could reduce the incidence of hypertension or development of cardiovascular events (Table 1).

Secondary prevention

The number of studies at this level is greater, their common denominator being the low average therapeutic compliance with treatment with the device, which was always below 4 h/night, a fact attributed to having been carried out with non-drowsy individuals. In the SAVE⁶⁸ study, 2,717 subjects with previous coronary or cerebrovascular disease, with OSA (IAH > 12) and (ESS < 15), who were randomised to treatment with general measures alone or general measures and CPAP, were followed for 3.7 years. The results did not show benefits, in terms of prevention of cardiovascular events, with CPAP treatment. Despite this, a propensity score-matched analysis between good CPAP treatment adherents (CPAP use ≥ 4 h/night) compared to the standard treatment group seems to suggest that the former had a lower risk of stroke and cerebrovascular events in general.

In the RICCADSA study, 244 subjects with re-vascularised coronary artery disease with OSA (AHI > 15 h and ESS < 10) were randomised to treatment with CPAP or no treatment and followed for a median time of 57 months. Once again, no benefits were observed in reducing events (repeat revascularisation, myocardial infarction, stroke, and cardiovascular mortality). However, again the good, compliant subjects, using CPAP ≥ 4 h/night, obtained a significant reduction in cardiovascular risk when compared to non-compliant sub-

Table 1 Effect of CPAP treatment of OSA on cardiovascular risk. Prospective randomised clinical studies and meta-analysis.

Primary prevention	Number of patients studied	Patient profile	Mean follow-up	OSA and clinical data	Result
Barbe F et al. (2012)	Total: 723 [-]CPAP (366) - No intervention (357)	No history Cardiovascular disease	4 years (IQR: 2,7–4,4)	AHI > 20 ESS < 10	[-]General: No benefit - CPAP ≥ 4 h: Reduction in AH or events
Secondary prevention	Number of patients included	Type of patient	Mean follow-up	AOS	Result
McEvoy RD et al. (2016). SAVE study	Total: 2.687 [-]CPAP (1.346) - Standard treatment (1.341)	Prior coronary or cerebrovascular diseases	3.7 years	AHI > 12 ESS < 15	[-]General: No benefit - CPAP ≥ 4 h: Reduction in cerebrovascular events
Peker Y et al. (2016). RICCADSA study	Total: 244 [-]CPAP (122) - No intervention (122)	Coronary revascularised diseases	57 months (Range: 6.5–90.2)	AHI ≥ 15 ESS < 10	[-]General: No benefit - CPAP ≥ 4 h: Reduction in events
Sánchez de la Torre et al. (2020). ISAACC study	Total: 2.834 [-]OSA: CPAP (633)/no CPAP (631) - No OSA: (603)	ACS	3.35 years (IQR: 1.5–5.31)	AHI ≥ 15 ESS < 10	No benefit
Sánchez-de-la-Torre et al. (2023). Meta-analysis	Total: 4.186 [-]CPAP (2.097) - No CPAP (2.089)	Coronary or cerebrovascular diseases Coronary re-vascularised diseases ACS	3.25 (1.8) years	Mean AHI: 31.2 (17)	General: No benefit CPAP ≥ 4 h: Reduction in events (MACCE)

ACS: acute coronary syndrome; AH: arterial hypertension; AHI: apnoea-hypopnoea index; CPAP: Continuous positive airway pressure; ESS: Epworth Sleep Scale; IQR: interquartile range; MACce: Major adverse cardiac and cerebrovascular events; OSA: obstructive sleep apnoea.

jects <4 h/night or subjects without treatment (HR: .29; 95% CI: .10–.86; $p = .026$).⁶⁹

Again, negative results were present in the ISAACC⁷⁰ study, conducted with 2,834 patients with acute coronary syndrome without drowsiness (ESS < 10). Of these, of the 1,264 who presented OSA on polygraphy (AHI ≥ 15), 633 were randomised to receive CPAP and 631 to receive standard treatment. Of the 1,287 who did not have OSA (AHI < 15), 603 were selected as a control group. After a mean follow-up time of 3.35 years, neither the presence of OSA was associated with an increase in the prevalence of cardiovascular events, nor did CPAP treatment reduce this prevalence in subjects with OSA. This time, no significant benefits were found associated with good adherence to the device (≥4 h/night).

Finally, a recent meta-analysis of these 3 studies⁷¹ with data from 4,186 subjects, definitively established that despite there being no significant differences regarding the risk of major cardiac and cerebrovascular events, between being treated and not treated with CPAP, good adherence to

CPAP was associated with a 31% risk reduction of this type of events, confirming that this was a critical factor (Table 1).

Conclusions and future overview

OSA is a prevalent disease in the population, especially in middle-aged adults. To date, different mechanisms have been described by which the syndrome could induce a higher state of cardiovascular risk, such as sympathetic over activity, endothelial dysfunction, and systemic inflammation, in addition to the induction of hypercoagulability and metabolic deregulation. All of these mechanisms would appear to explain its independent relationship with other risk factors, such as hypertension, risk of diabetes or metabolic syndrome, as well as a higher risk of both cardiometabolic and cerebrovascular events. Despite all this, the most implemented treatment for this pathology, CPAP, only seems to have a moderate effect in terms of reducing blood pressure, which is of considerable magnitude in patients

with resistant hypertension. Along with this, its effectiveness in terms of reducing the risk of events, seems to be restricted to patients with good therapeutic adherence, use of ≥ 4 h/night, both in primary and secondary prevention.

The knowledge acquired to date has encouraged the development of 2 strategies that are already underway. One is to identify subjects with OSA, in whom the entity plays a determining role, either in inducing nocturnal hypertension of decisive prognostic value or, generally increasing cardiovascular risk. In this sense, the fact that a large number of studies have reported that the variables related to hypoxia, its intensity and duration, correlate better with this risk than the AHI, has provided the motivation to search for new variables derived from sleep studies that better estimate the risk. This is the case of the so-called hypoxic burden, which is defined as the area under the desaturation curve associated with respiratory events. Patients with a high hypoxic burden appear to have a higher risk of cardiovascular events and all-cause mortality.⁷² Furthermore, subjects in this situation could be the best responders to CPAP treatment.⁷³ This strategy is complemented with the search for new metabolic, genetic or epigenetic biomarkers, and information on new technological instruments that provide long-term sleep monitoring. With this in place, beyond identifying subjects in whom OSA implies more risk, phenotypes of the disease that could benefit the most from their treatment in terms of a reduction in cardiovascular risk, could be identified.

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Conflict of interests

The authors have no conflict of interest to declare.

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