Guideline

Position paper on the management of patients with obstructive sleep apnea and hypertension: Joint recommendations by the European Society of Hypertension, by the European Respiratory Society and by the members of European COST (COoperation in Scientific and Technological research) ACTION B26 on Obstructive Sleep Apnea

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This article is aimed at addressing the current state of the art in epidemiology, pathophysiology, diagnostic procedures and treatment options for appropriate management of obstructive sleep apnea (OSA) in cardiovascular (particularly hypertensive) patients, as well as for the management of cardiovascular diseases (particularly arterial hypertension) in OSA patients. The present document is the result of the work done by a panel of experts participating in the European Union COST (COoperation in Scientific and Technological research) ACTION B26 on OSA, with the endorsement of the European Respiratory Society (ERS) and the European Society of Hypertension (ESH). These recommendations are particularly aimed at reminding cardiovascular experts to consider the occurrence of sleep-related breathing disorders in patients with high blood pressure. They are at the same time aimed at reminding respiration experts to consider the occurrence of hypertension in patients with respiratory problems at night.

Keywords: arterial hypertension, continuous positive airway pressure treatment, guidelines, hypertension treatment, obstructive sleep apnea

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHI, apnea hypopnea index; AV, atrioventricular; BP, blood pressure; CHF, congestive heart failure; CPAP, continuous positive airway pressure; CSA, central sleep apnea; CVD, cardiovascular diseases; DBP, diastolic blood pressure; IL-8, interleukine-8; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OSA, obstructive sleep apnea; OSAS, obstructive sleep apnea syndrome; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure; SRBD, sleep-related breathing disorders; SVES, supraventricular extrasystoles; TNF-α, tumor necrosis factor-α

INTRODUCTION

This article is aimed at addressing the current state of the art in epidemiology, pathophysiology, diagnostic procedures and treatment options for appropriate management of obstructive sleep apnea (OSA) in hypertensive patients, as well as for the management of arterial hypertension in OSA patients. The present document is the result of the work done by a panel of experts from different European countries participating in the European Union COST (COoperation in Scientific and Technological research) ACTION B26 on OSA (see 'Acknowledgements' section), with the endorsement of the

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European Respiratory Society (ERS) and the European Society of Hypertension (ESH). For the readers' convenience, additional material is provided on the *Journal of Hypertension* website.

The present recommendations have been prepared following a careful methodological approach, the details of which are summarized in supplementary digital content S1 on the journal website, http://links.lww.com/HJH/A158.

ASSOCIATION OF OBSTRUCTIVE SLEEP APNEA WITH HYPERTENSION

Sleep-related breathing disorders (SRBDs) include habitual snoring, OSA, central sleep apnea (CSA), OSA syndrome (OSAS), that is, OSA accompanied by daytime symptoms, Cheyne–Stokes breathing and sleep hypoventilation syndrome [1]. Obstructive breathing alterations during sleep are listed in Box 1.

Since the first polysomnographic descriptions, OSA events at night are known to be accompanied by acute changes in cardiovascular parameters. These acute effects mainly include the occurrence of wide swings of blood pressure (BP) and heart rate as a result of alternating obstructive apnea and hyperventilation episodes during sleep [2].

OSA has been linked to long-term consequences, too. Untreated OSA not only increases the risk for car accidents, worsens quality of life, mood and cognitive performance but is also proposed as an additional and independent risk factor for cardiovascular diseases.

Box 1 Definitions of obstructive breathing alterations during sleep

Obstructive Sleep Apnea: obstructive breathing event with complete upper airways obstruction (residual air flow below 20% of the preceding period of stable breathing, i.e. reduction in air flow > 80%). Each events should last at least 10 s

Obstructive Sleep Hypopnea: Obstructive breathing event with a reduction of airflow between 70 and 20% of the preceding period of stable breathing. Each events should last at least 10 s

RERA: respiratory effort-related arousal. Events characterized by increased respiratory effort during sleep caused by flow limitation in the upper airways that is terminated by an arousal from sleep. These events are typically not associated with significant hypoxemia.

AHI: apnea–hypopnea index. Number of apnea and hypopnea per hour of sleep.

OSA: obstructive sleep apnea. Mild = AHI between 5 and below 15, moderate = AHI between 15 and below 30 and severe = AHI above 30 per hour.

RDI: respiratory disturbance index. Summarizes both the AHI and the RERA indices together.

Snoring: a noise induced by vibration of upper airways. It is a symptom reflecting a compromised air flow in the upper airways and is complex to assess in a quantifiable manner.

OSA syndrome (OSAS) (American Academy of Sleep Medicine): combination of at least five obstructive breathing episodes per hour during sleep (apneas, hypopneas and RERA events) and the following diagnostic criteria (A and/or B to be fulfilled).

A. Excessive daytime sleepiness that is not better explained by other factors.
B. Two or more of the following symptoms that are not better explained by other factors:
   a. Choking or gasping during sleep
   b. Recurrent awakenings from sleep
   c. Unrefreshing sleep
   d. Daytime fatigue
   e. Impaired concentration.

(It is important to distinguish between OSA as a laboratory diagnosis and OSAS that represents the combination of OSA and symptoms as a fully established clinical syndrome).

Indeed, OSA has been acknowledged as a novel, frequent and modifiable cause of systemic resistant hypertension in both European and American guidelines for the management of arterial hypertension. Scientific data and clinical awareness about the interaction between OSA and hypertension are continuously increasing. Particularly, there is increasing evidence that diagnosis of an association between OSA and hypertension, as well as the need of their combined treatment, should be considered in patients with refractory hypertension and nondipping profile [3–5].

Because of its potential prognostic importance [6], the association between OSA and hypertension has been investigated through several study designs, such as cross-sectional [7–12] and longitudinal [13–15] investigations in the general population, cross-sectional studies in OSA patients [16,17], case–control studies [18] and questionnaire-based surveys in snorers [19–25]. Although part of such association may be mediated by coexisting risk factors, such as obesity, a large body of evidence supports an independent role of OSA in the pathogenesis of daytime hypertension, even if this issue is still a matter of debate [13–15]. Prevalence of hypertension in OSAS patients ranges from 35 to 80% and appears to be influenced by OSA severity. Over 60% of individuals with respiratory disturbance index of more than 30 were found to be hypertensive. Conversely, approximately 40% of hypertensive patients are diagnosed with OSA [26].

Several factors may affect the relationship between high BP and OSA, including age and sex [27,28]. OSA is associated with hypertension more strongly in young to middle-aged adults (<50 years of age) than in older adults [13,29], as confirmed by population-based cross-sectional [7] and longitudinal [13] studies. A significant effect of OSA on BP regulation in children has been also suggested, although the body of evidence is still limited compared with data in adults [30–32].

A specific condition for which an association has been suggested between high BP and sleep disordered breathing is pregnancy-related hypertension, but the studies on this issue suffer from some methodological limitations (small sample size, few polysomnographic studies) [33–35]. Thus, further studies on this issue are needed. In this context, a recent study on 220 pregnant women has shown that OSA (although identified only using Berlin questionnaire and Epworth Sleepiness Scale) is related to hypertension independent of obesity; in this study among nonobese (BMI $<30\,kg/m^2$) pregnant women, frequency of preeclampsia was significantly higher among those with OSA (adjusted odds ratio 6.58, 95% confidence interval 1.04, 38.51; $P = 0.035$) [36].

The pathogenetic link between obstruction of upper airway during sleep and hypertension during pregnancy is also supported by the positive effects of continuous positive airway pressure (CPAP) on BP levels in pregnant hypertensive women [37,38]. Accordingly, treatment of OSA in pregnant women should be undertaken along the same lines as for nonpregnant patients, although treating preeclampsia with CPAP cannot be recommended as a routine procedure.

MECHANISMS OF INCREASED CARDIOVASCULAR RISK IN OBSTRUCTIVE SLEEP APNEA PATIENTS

Given the above described independent link between OSA and hypertension, it is important to define the mechanisms that might be responsible for it, as well as for the relationship between OSA and target organ damage and for the increased cardiovascular risk reported in these patients. Among the possible mechanisms, the following should be considered with particular attention.

Autonomic alterations

OSA patients are characterized by a derangement in autonomic cardiovascular regulation both during the night and during the day. During apneic episodes, an increase in efferent sympathetic neural activity occurs, as shown by microneurographic studies in humans and by experimental studies in animals [39]. This increase in sympathetic activity is largely due to chemoreflex stimulation, triggered by the reduction in arterial oxygen pressure and by hypercapnia occurring during each apneic episode, which represents one of the major factors responsible for the increases in BP and heart rate that accompany resumption of ventilation after each apneic episode.

The hypoxic and hypercapnic reflexes triggered by apneic events, through involvement of central autonomic neural mechanisms, generate an increase in sympathetic nerve activity and cyclical changes in parasympathetic cardiac modulation, as documented by the increases in norepinephrine plasma levels, in muscle sympathetic nervous activity during wakefulness and sleep, as well as by the increase in the spectral components of heart rate variability that reflect sympathetic activations and by the decrease of spontaneous baroreceptor reflex sensitivity in severe OSA patients.

The repeated occurrence of OSA and of the associated intermittent hypoxemia over prolonged periods are known to chronically activate the sympathetic nervous system through the resulting chemoreflex activation and are also associated with a blunting of cardiovascular reflexes with afferent fibers stemming from baroreceptor or pulmonary receptors. In particular, the sensitivity of baroreflex control of the heart has been shown to be depressed in OSAS during different sleep stages [40], an alteration that is secondary to the chemoreflex activation by intermittent hypoxia, and contributes to both the acute and chronic increases in BP and heart rate observed in OSA patients. The reduction of baroreflex sensitivity in OSA has been shown to improve after chronic treatment with CPAP [41]. The degree of autonomic impairment occurring at night in OSA may have an impact also on daytime symptoms and has been proposed as a marker of excessive daytime sleepiness [42].

Altered mechanics of ventilation (acute physiologic effects of negative intrathoracic pressure)

In patients with sleep-disordered breathing, ineffective inspiratory efforts are a hallmark of obstructive events. The interruption of airflow, despite persisting vigorous respiratory efforts against the occluded airway, leads to abrupt progressive decreases in intrathoracic pressure, which may have important effects on ventricular loading conditions as well as on autonomic cardiac modulation (due to stimulation of vagal thoracic afferent).

Renin–angiotensin–aldosterone system and sleep apnea

There are very limited data trying to correlate OSA with various markers of renin–angiotensin–aldosterone system (RAAS) activity, based on studies of insufficient size [43,44]. It has also been claimed that OSA might increase aldosterone secretion, and that this might be one of the mechanisms of the resulting resistant hypertension [26]. In parallel, a recent article suggests that antagonism of mineralocorticoid receptors by spironolactone reduces apnea–hypopnea index (AHI) affecting the number of both central and obstructive events [45]. Whether increased aldosterone levels may help explain the interactions between OSA and resistant hypertension is an important question and one that has been explored by Calhoun and colleagues. In a work utilizing polysomnographic diagnosis of sleep apnea, they reported that there was a positive correlation between plasma aldosterone concentrations and OSA severity, but this was only true for patients with resistant hypertension. No relationship between plasma aldosterone and sleep apnea severity was noted in normotensive control individuals [46]. Thus, whether sleep apnea plays a role in increasing aldosterone levels *per se* remains to be ascertained. In general, more evidence is needed on the complex relationship between the activity of the RAAS and OSA.

Endothelial dysfunction

Endothelial dysfunction has also been shown to occur in OSA patients in studies that assessed forearm vascular flow, intima–media thickness, carotid–femoral pulse-wave velocity, number of circulating endothelial progenitor cells and vascular endothelial growth factor. A role for this dysfunction in the pathogenesis of cardiovascular complications in OSA has been supported by various experimental studies carried out with proper methodology [47]. Several studies have also suggested hypercoagulability in patients with OSA, but these investigations were generally limited by small numbers and/or inadequate control for potential confounding variables such as obesity and smoking [48,49]. The functional potential importance of these changes in OSA patients remains, however, unknown, and it cannot be excluded that the observed cardiovascular changes might be unrelated to endothelial dysfunction.

Inflammation

The current interest in inflammatory components of cardiovascular risk has stimulated studies showing that in OSA patients, there is an activation of reactive oxygen species. Apnea-induced cyclic hypoxia and re-oxygenation in OSA generate reactive oxygen species and oxidative stress, increase circulating levels of adhesion molecules, and also preferentially activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and related cytokines such as tumor necrosis factor-α (TNF-α) and interleukine-8 (IL-8), thus promoting inflammation [47].

This may contribute to the increased cardiovascular risk typical of OSA patients, given the well established role of inflammation in the development of atherosclerosis. However, studies focusing on whether blocking the inflammatory reactions might also reduce the cardiovascular complications of OSA would be required.

Metabolic factors

OSA and metabolic syndrome and/or type 2 diabetes frequently co-exist and potentially interact metabolically and hemodynamically. Solid evidence suggestive of impaired glucose tolerance in OSA is available, dealing mainly with insulin resistance [49,50]. Moreover, it has been suggested in a smaller number of studies that OSA patients also show a higher degree of leptin resistance compared with non-OSA individuals. However, the possibility of an independent relationship of leptin and other adipocytokines (such as adiponectin and ghrelin) with OSA requires further investigation [49–52].

Genetic aspects of hypertension in obstructive sleep apnea

The genetic contribution to differences in BP among individuals in a population is thought to amount up to 30–40%. From family and epidemiological studies, it is clear that a complex interplay between heritable and environmental factors such as dietary sodium intake, alcohol consumption, stress and body weight results in final expression of hypertension [53,54]. Limited data on the genetic contribution to the association between OSA and hypertension are available. The presence of gene polymorphisms potentiating hypertension may or may not be shared between patients with OSA and those with essential hypertension. Only candidate gene studies have been performed to date in the OSA population; they are generally small, the patients have been poorly phenotyped and most results have not been replicated. A summary of these studies has recently been published [55].

CARDIOVASCULAR EVENTS AND ORGAN DAMAGE IN OBSTRUCTIVE SLEEP APNEA PATIENTS (OBSTRUCTIVE SLEEP APNEA AS A CAUSE OF CARDIOVASCULAR COMPLICATIONS)

Severe untreated OSA (AHI > 30) has been linked to fatal and nonfatal cardiovascular events, and all-cause mortality. This association is not convincing in the subgroup of individuals with mild OSA. Moreover visceral fat volume contributes to cardiovascular risk even after controlling for BMI and waist circumference. Thus, despite efforts to control for obesity as a covariate, there is the lingering concern that there could be differences in the degree of visceral obesity between those with OSA who died and those who did not [56–60].

Ischemic heart disease

Published prospective and cross-sectional reports, suggest an association of OSA and coronary artery disease (CAD) and that untreated OSA may adversely influence prognosis in patients with CAD. However, the interpretation of these data is still controversial, because the link between OSA and CAD could be related to age and obesity. In the Sleep Heart Health study, after adjustment for multiple risk factors, OSA was a barely significant predictor of incident coronary heart disease (myocardial infarction, revascularization procedure or coronary heart disease death) only in men up to 70 years of age [adjusted hazard ratio 1.10 (95% confidence interval 1.00–1.21] per 10-unit increase in AHI], but not in older men or in women of any age [59,61].

Sleep apnea and stroke

Severe OSA in a Swedish cohort (182 middle-aged men) was associated with a very high cardiovascular risk: over 10 years, 14% of this group was predicted to experience a stroke and 23% a myocardial infarction (36% combined risk) [62].

Prospective data in a larger population confirmed that in a community-based sample of middle-aged and older adults (5422 participants without a history of stroke at the baseline examination and untreated for sleep apnea, who were followed for a median of 8.7 years), incident cardiovascular diseases, including stroke, was significantly associated with sleep-disordered breathing in men [63].

A survey on 6424 patients of the Sleep Heart Study [64] showed a relative stroke risk of 1.58 for patients with an AHI more than 10 per hour compared with patients without sleep apnea. Moreover in another prospective cohort study [60], patients with an AHI more than 10 per hour had in a 3-year follow-up an increased relative combined stroke and death risk of 1.97, rising to 3.3 when AHI was more than 36 per hour.

Finally, a recent evidence-based work has concluded that OSA increases the risk of stroke independently of other cerebrovascular risk factors [65].

Congestive heart failure

According to recent studies, untreated sleep apnea may promote left ventricular dysfunction, disease progression and increased mortality in heart failure patients [66].

In the Sleep Heart Health Study, the presence of OSA conferred a 2.38 relative risk in the likelihood of having heart failure, independent of other known risk factors [61].

However, as most data were obtained in elderly patients, the role of OSA in increasing the risk for heart failure in relatively young patients is uncertain.

Target organ damage

Strong evidence has been obtained on the crucial role of target organ damage in determining the cardiovascular risk of individuals with high BP. Methods for evaluating organ damage are mentioned in detail in the recent ESH–ESC 2007 Hypertension Guidelines and in their 2009 reappraisal [3,4]. Data are also available that show that OSA may favor appearance of hypertension-related organ damage.

Blood vessels

OSA and hypertension are independently associated with increased stiffness of large arteries that may contribute to left ventricular remodeling. Individuals with OSA were shown to have higher values of aortic stiffness, and lower large arteries distensibility, than that of controls. A blunted

endothelium-dependent dilatation, increased carotid intima–media thickness and increased aortic stiffness, all known early signs of atherosclerosis, have been observed in patients with OSA [67].

Heart

Compared with normotensive individuals without OSA, left atrial diameter, interventricular septal thickness, left ventricular posterior wall thickness, left ventricular mass index and prevalence of left ventricular hypertrophy were increased to a similar extent in normotensive individuals with OSA and in patients with hypertension without OSA, with a significant further increase in individuals affected by both OSA and hypertension [68,69].

Both right ventricular and left ventricular systolic and diastolic functions are impaired in patients having OSA with or without hypertension [70]. Thus, OSA, independent of obesity and of hypertension, may induce cardiac changes that could predispose to atrial fibrillation and heart failure [69].

Cardiovascular diseases leading to pacemaker implantations are suspected of being associated with a high rate of undiagnosed OSA [71]. After treatment with continuous positive air pressure (CPAP), significant improvements were observed in cardiac symptoms and in hemodynamic parameters, as well as in left and right ventricular morphology and function [72–74].

Urinary albumin excretion

The prevalence of OSA in patients with chronic kidney diseases is higher than in the general population, and an association between OSA and proteinuria as well as an improvement of proteinuria after OSA treatment, have been described. However, whether such a link is independent of BMI and BP values is still controversial. Thus, the relationship between proteinuria and OSA warrants further evaluation [75,76].

Retina

Alterations in retinal vascular function resulting from OSA and arterial hypertension can impair optic nerve function, leaving it vulnerable to ischemic events. Some eye disorders may occur in association with OSA including nonarteritic anterior ischemic optic neuropathy, papilledema secondary to raised intracranial pressure and an optic neuropathy with an associated visual field defect that may mimic glaucoma. There is conflicting evidence as to whether an association exists between OSA and glaucoma [77,78].

SLEEP-RELATED BREATHING DISORDERS IN PATIENTS WITH CARDIOVASCULAR AND CEREBROVASCULAR DISEASES (SLEEP-RELATED BREATHING DISORDER AS A CONSEQUENCE OF CARDIOVASCULAR DISEASES)

Chronic heart failure

The SRBD commonly linked to heart failure is CSA [79], but the prevalence of OSA in chronic heart failure (CHF) patients is relatively high (between 10 and 25%) possibly due to upper airway narrowing by fluid accumulation in the neck while supine [80]. Prevalence of OSA in CHF is likely to rise because of the emerging epidemics of obesity [81]. Untreated OSA is associated with an increased risk of death independently of confounding factors in patients with CHF [82].

Stroke

Prevalence of breathing alterations during sleep is higher in patients with acute ischemic stroke or transient ischemic attacks (50–70%) [83,84] than that in the general population, both because stroke may favor occurrence of OSA and because OSA may be a risk factor for stroke. This should be considered when assessing and treating stroke patients.

CSA and central periodic breathing or Cheyne–Stokes breathing may appear in up to 30–40% of acute stroke patients [85–86], reflecting a new-onset stroke-associated condition. In the transition from the acute to the subacute phase of stroke, sleep apnea tends to improve but more than 50% of patients still exhibit an AHI of at least 10 per hour 3 months after the acute event [86–89], because obstructive events improve less than central ones [86].

Little is known about the clinical relevance of OSA in the acute phase (first few days) of ischemic stroke, and the limited information available suggests an association between OSA severity and stroke severity [85,90]. Considering the evolution in the weeks/months following stroke, SRBD was shown to be associated with duration of hospitalization [90,91], increased mortality [92–94] and poor functional outcome [90,95].

DIAGNOSTIC ASPECTS

Diagnosing obstructive sleep apnea in patients with hypertension

The diagnosis of OSA(S) is based on the composite of symptoms, clinical findings and an overnight recording of sleep and breathing parameters. Sleep-disordered breathing events are well defined according to international guidelines [96]. The frequency of event occurrence during sleep is referred to as the AHI, whereas the respiratory disturbance index is the sum of the AHI and the respiratory effort-related arousal indices (see Box 1).

Table 1 [97] provides the definition of OSAS by the American Academy of Sleep Medicine, Table 2 [1] summarizes the diagnostic criteria listed in the International Classification of Sleep Disorders and detailed symptoms and signs are reported in Table 3. A proposed diagnostic algorithm is showed in Fig. 1.

Patient history and questionnaires

A structured interview or specific questionnaires can be helpful in the routine assessment of the clinical features of OSA(S) in patients with arterial hypertension [98,99]. However, it has been clearly demonstrated that their sensitivity and specificity for the daytime assessment of OSA(S) and excessive daytime sleepiness is insufficiently low [100]. Methods for the objective assessment of daytime sleepiness

TABLE 1. Definition of obstructive sleep apnea syndrome (American Academy of Sleep Medicine)

A. Excessive daytime sleepiness that is not better explained by other factors
B. Two or more of the following symptoms that are not better explained by other factors:
a. Choking or gasping during sleep
b. Recurrent awakenings from sleep
c. Unrefreshing sleep
d. Daytime fatigue
e. Impaired concentration

A combination of at least five obstructive breathing episodes per hour during sleep (apneas, hypopneas and respiratory effort-related arousal events) and at least one of the following above criteria [97].

are available on the website (see supplementary digital content S2, http://links.lww.com/HJH/A158).

Technical devices for the classification and quantification of sleep disordered breathing

The methods for diagnosing OSA include polysomnography (level 1 and 2 device), polygraphy (level 3 device) and limited channel (level 4) devices (Table 4).

Diagnosing hypertension in patients with obstructive sleep apnea: assessment of obstructive sleep apnea contribution to resistant hypertension

The 2007 ESH–ESC hypertension management guidelines define resistant or refractory hypertension a condition in which a therapeutic plan that has included attention to lifestyle measures and the prescription of at least three drugs (including a diuretic) in adequate doses has failed to lower SBP and DBP to goal. This definition is in line with that provided by the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High BP (JNC VII), which defined resistant hypertension as 'the failure to attain goal BP in patients who are adhering to full doses of an appropriate three-drug regimen that includes a diuretic. [3–5]. In specialized hypertension clinics, the prevalence of resistant hypertension ranges from 5 to 18% of the hypertensive population. Patients with drug-resistant hypertension are at greater risk for stroke, renal insufficiency and comorbid cardiovascular events than patients whose BP is well controlled by medical therapy.

Several studies have addressed the potential contribution of OSA to the development and/or persistence of resistant hypertension. Refractory hypertension in patients with OSA is primarily systolic and relatively more pronounced at night [101–103]. As the night-time SBP predicts cardiovascular morbidity and mortality even more accurately than daytime SBP, nocturnal increases in SBP due to OSA may have particular adverse effects in patients with refractory hypertension.

The evaluation of OSA patients with resistant hypertension should focus on identification of contributing factors and exclusion of other causes of secondary (resistant) hypertension. A diagnosis of OSA should be considered in patients with clinical and biochemical evidence of catecholamine excess in whom a catecholamine-producing tumor cannot be identified. Diagnostic evaluation for other identifiable causes should be tailored for each patient and guided by signs and symptoms.

True resistant hypertension must be distinguished from apparently resistant hypertension, commonly due to a 'white-coat hypertension' or 'isolated office hypertension' condition (BP elevated in the office environment, but normal out of the office). Failure to use appropriate cuffs on large arms of OSA patients might also lead to a serious overestimation of BP values and to a false diagnosis of resistant hypertension. To identify a 'white-coat hypertension' phenomenon as well as to investigate the day and night BP profile, ambulatory blood pressure monitoring (ABPM), which improves prediction of cardiovascular risk in hypertensive patients, should be considered in every OSA patient, particularly when resistance to drug treatment is suspected. When using 24h ABPM, the impact of sampling interval in reliably assessing nighttime BP has been studied by Marrone *et al.* [104], with BP measurements set at intervals of 5, 10, 15, 20 and 30 min. A larger number of inaccurate nocturnal mean BP estimates were obtained in OSAS patients than in control individuals. The authors concluded that OSA patients require more frequent BP measurements to obtain a similar accuracy in nocturnal BP evaluation.

In OSA patients, severity of hypertension might not only be overestimated in case of 'white-coat hypertension', but it might also be underestimated if BP is assessed by office readings only [105], because BP could be normal in the office but frequently elevated outside the doctor's office, particularly during night sleep (a form of the so-called 'masked hypertension').

The occurrence of both white-coat and masked hypertension requires out-of-office BP monitoring to be regularly implemented in OSA patients. This could be obtained through the use of 24 h ABPM and, in some cases, of home

TABLE 2. Diagnostic criteria for obstructive sleep apnea according to the International Classification of Sleep Disorders

A. At least one of the following applies:
i. The patient complains of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue or insomnia
ii. The patient wakes up with breath holding, gasping or choking
iii. Or, the bed partner reports loud snoring, breathing interruptions or both during the patient's sleep
B. Polysomnographic recording shows the following:
i. Five or more scoreable respiratory events (i.e. apneas, hypopneas or respiratory effort-related arousals) per hour of sleep
ii. Evidence of respiratory effort during all or a portion of each sleep event
C. Polysomnographic recording shows the following:
i. Fifteen or more scoreable respiratory events (i.e. apneas, hypopneas or respiratory effort-related arousals) per hour of sleep
ii. Evidence of respiratory effort during all or a portion of each sleep event
D. The disorder is not explained by another current sleep disorder, medical or neurological disorder, medication use or a substance abuse disorder

For obstructive sleep apnea diagnosis A, B and D or C and D must be fulfilled. Data from [1].

TABLE 3. Clinical symptoms, characteristics and objective findings suggesting a high probability for obstructive sleep apnea syndrome

I. OSA-related symptoms and clinical signs
Nighttime: witnessed apneas; loud, frequent and intermittent snoring; dry mouth, thirsty during the night; nocturnal diuresis; choking, dyspnea; disturbed sleep; sweating; nasal congestion, preferably nighttime; family history of snoring and sleep apnea
Daytime: increased daytime sleepiness; daytime fatigue; concentration difficulties, monotony intolerance; morning pain in the throat; headache, preferably in the morning hours
II. Frequent clinical characteristics
Male sex, postmenopausal females; overweight, preferably central obesity (e.g. BMI $>30\,kg/m^2$ indicate 50% probability of OSA, neck circumference above 17 inch in males and 16 inches in females), linkage between history of obesity and snoring/witnessed apneas/sleepiness; history of cardiovascular disease (ischemic heart disease, stroke or heart failure, probability of OSA 30 to >50%); upper airway anatomic abnormalities (enlarged tonsils and uvula, adenoids, macroglossia, according to Friedman classification stage III); retrognathia
III. Objective findings in the cardiovascular/metabolic risk assessment of hypertensive patients
Refractory hypertension (likelihood of OSA 50 to >80%); nocturnal nondipping of 24-h blood pressure; left ventricular hypertrophy; generalized atherosclerotic disease; Holter ECG: nocturnal brady/tachycardia, SA and AV blocks during the sleep period, increased occurrence of SVES/VES during sleep period, atrial fibrillation, paroxysmal nocturnal atrial fibrillation; metabolic disease such as diabetes mellitus

AV, atrioventricular; OSA, obstructive sleep apnea; SVES, supraventricular extrasystoles.

BP monitoring [106]. The role of home BP monitoring in quantifying BP elevation in OSA patients is still under evaluation, however [106–108]. In general, ABPM should be preferred to home BP monitoring due its ability to provide detailed information on BP during night-time, when OSA episodes occur. Although night-time BP can now be obtained also with few recent devices for home BP monitoring, this information is limited by a very low sampling frequency.

Different types of blood pressure measurements in obstructive sleep apnea patients

BP changes can be monitored both in a clinical setting and in daily life, using various techniques aiming at measuring BP in a more continuous way and, thus, at exploring different BP variability components, including not only fast BP changes between minutes or hours in response to physical activity and/or behavioral challenges, but also the circadian changes in BP, whose alteration is known to occur frequently in OSA patients.

As previously mentioned in this document, the physiologic reduction in BP during sleep is frequently blunted in OSA [109]. This occurs both in normotensive and hypertensive OSA individuals. BP may, thus, be increased during the night, resulting in different ratios between evening and morning values, when either ambulatory, home or clinic BP measurements are reported. This difference has been found related to the severity of sleep apnea, although limited to men [110]. SBP values have been found to correlate with AHI, when BP elevation is quantified in terms of mean BP, but not in terms of pulse pressure [111].

In addition to ABPM and home BP monitoring, other methods for BP assessment have been used in OSA. Continuous BP measurements can be obtained using beat-to-beat BP recording with photoplethysmographic finger cuff devices (such as Finapres, Finometer or Portapres, Finapres Medical Systems, Amsterdam, the Netherlands; Task force Monitor, CNSystems, Graz, Austria;

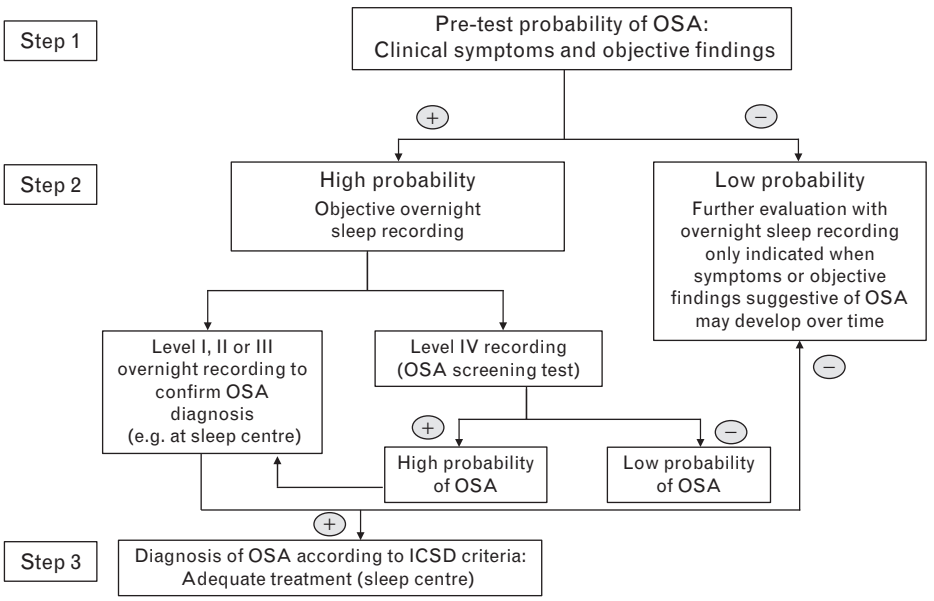

FIGURE 1 Proposed diagnostic algorithm for obstructive sleep apnea.

TABLE 4. Diagnostic tools for the evaluation of obstructive sleep apnea syndrome

	Parameters measured
Level 1 Attended, in-laboratory polysomnography	Polysomnography including electroencephalogram, electromyogram, ECG or heart rate, airflow, respiratory effort and oxygen saturation; additional externally assessed parameters can be included (e.g. blood pressure, esophageal pressure, transcutaneous CO_2), video surveillance; investigation performed in the sleep laboratory under continuous supervision
Level 2 Unattended polysomnography in the hospital/sleep unit or at home	Polysomnography including electroencephalogram, electromyogram, ECG or heart rate, airflow, respiratory effort and oxygen saturation; investigation performed without any supervision
Level 3 Polygraphic limited channel recording, mainly modified portable sleep apnea monitoring	Minimum of four channels including ventilation or airflow (at least two channels to detect respiratory movements or respiratory effort and airflow), heart rate or ECG and oxygen saturation
Level 4 Single-channel or two-channel device	One or two channels, typically including oxygen saturation or airflow

Levels of sleep monitoring and type of monitoring device and setting are mentioned in the firs column.

Nexfin, BMEYE, Amsterdam, the Netehrlands), which allow a more detailed quantification of possible changes in BP variability in patients affected by OSA. Lastly, another indirect technique, based on assessment of pulse transit time, has been suggested to reflect BP changes [112], but this technique still needs proper validation according to international protocols [4,106].

The features of the most common BP measurement techniques to be used in diagnosing hypertension in OSA are summarized in Box 2, and supplemental information can be consulted in the supplementary digital content S3 (http://links.lww.com/HJH/A158).

MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA AND ASSOCIATED HYPERTENSION

Lifestyle changes

Lifestyle changes should be considered as an integral part in the management of all patients with OSAS, including hypertensive OSAS, as obesity and a sedentary lifestyle are very common in such patients. Patients with mild OSAS may be adequately managed by this intervention alone. Patients with mild OSA should be instructed to avoid sleeping in the supine position, when polysomnographic recordings demonstrate OSA events to occur in such a posture.

Obesity: weight loss

The association between obesity and OSA has been acknowledged since a long time and weight loss could be very beneficial in the management of OSA and OSA-related complications. However, although the link of excess body weight and obesity with OSA has long been accepted, it is conversely still debated how much a weight reduction program can improve OSA and reduce BP [113]. Surprisingly, there are no large-scale controlled trials on the effects of weight loss in OSA. Only smaller scale studies of dietary [114], surgical [115] or pharmacological [116] weight loss have consistently shown that considerable reduction of various indices of OSA severity is obtained by weight loss. In an observational study, a weight loss of 10% predicted a 26% (95% confidence interval 18–34%) decrease in AHI [113]. However, in only a few of these small-scale observational studies, information on BP changes was provided, and even massive weight loss and the related reduction of OSA, was found to result in proportionally

Box 2 Diagnosing hypertension in patients with obstructive sleep apnea; different types of blood pressure measurement

Office blood pressure (BP) measurement
Advantages: cornerstone in the approach to hypertension diagnosis and management over more than a century; easily available; and related to outcome in large epidemiological and intervention studies.
Limitations: intrinsic inaccuracy of the auscultatory technique (mainly for DBP and in specific populations); observer's bias and digit preference; only isolated measurement allowed; interference by white-coat effect; inability to account for physiologic BP variability; and no information on nocturnal BP.

Home BP monitoring
Advantages: a number of measurements during the day and also over several days, weeks or months are possible. Assessment of treatment effects at different times of the day and over extended periods; no alarm reaction to BP measurement; good reproducibility; good prognostic value; relatively low cost; patient friendliness (in semiautomatic devices); involvement of patient in hypertension management; possibility of digital storage, printout, personal computer download or teletransmission of BP values (in some devices/systems); and improvement of patients' compliance to treatment improvement of hypertension control rates.
Limitations: need of patient training (short for automated devices); possible use of inaccurate devices; measurement errors; limited reliability of BP values reported by patients; induction of anxiety, resulting in excessive monitoring; treatment changes made by patients on the basis of casual home measurements without doctor's guidance; normality thresholds and therapeutic targets still debated; and lack of night recordings.

Twenty-four hour ambulatory BP monitoring
Advantages: no observer bias and digit preference; large number of BP values available over 24 h in daily life, particularly in true ambulatory conditions; no alerting reaction to BP automated measurements (no white-coat effect); higher reproducibility of 24 h average BP; no placebo effect; allows assessment of 24 h, daytime, nighttime and hourly BP values; allows assessment of BP variability (although limited with discontinuous BP monitoring); allows assessment of day–night BP changes ('dippers', 'nondippers', 'extreme dippers'), better if performed over repeated recordings; 24 h average BP more closely related to target organ damage of hypertension; superior prognostic value of 24 h, daytime or night-time average BP; and allows assessment of effectiveness and time distribution of BP control by treatment over 24 h, also through mathematical indices (trough/peak ratio and smoothness index).
Limitations: possible inaccuracy of automated BP readings; interference with patient's daily activities; quality of sleep affected to a greater or lesser degree; limited reproducibility of hourly BP values; reference 'normal' ambulatory BP values still under debate; and need for more evidence on prognostic value of different ambulatory BP monitoring parameters; and high costs.

Beat-by-beat BP monitoring
Advantages: possibility to accurately assess beat-by-beat BP variability.
Limitations: invasive methods –poorly suited to a clinical setting; noninvasive methods: possible inaccuracies due to pulse wave distortion in peripheral arteries, limited availability because of relatively high cost and need of expert operators.

modest and sometimes nonsignificant reductions in BP [116,117].

It remains unclear why hypertension in obese individuals with OSA appears to be proportionally resistant to weight loss in spite of the sometimes pronounced effects on OSA severity. One possibility is that obesity, hypertension and OSA share a common trait that characterizes at least a subgroup of patients with sleep-disordered breathing. An additional factor to be considered is the type of BP measurement used. Only in a minority of cases, objective and reproducible BP measurements were employed, such as home BP monitoring and ABPM. Other factors potentially interfering with the BP effects of weight loss and reduction in OSA severity include duration of hypertension and occurrence of target organ damage, because the occurrence of structural cardiovascular changes in patients with long-lasting hypertension might make the BP elevation less sensitive to a nonpharmacological treatment.

Ethanol

Ethanol ingestion increases the frequency and duration of apneas because of the combined effects of reducing upper airways muscle tone and depressing the arousal response. It is also known that moderate-to-heavy alcohol consumption may lead to a BP increase, both in normotensive and in hypertensive individuals. It has been suggested that a reduction in alcohol intake might help reducing both OSA severity and its BP effects [3–5].

Exercise

Although there are strong theoretical reasons to believe that a formal exercise program may benefit OSA, there are remarkably few objective data on this subject. Indirect evidence on the relationship between exercise and OSA comes from the Wisconsin sleep cohort study, which showed that lack of exercise was associated with increased severity of sleep-disordered breathing even after adjustment for BMI [118]. Giebelhaus *et al.* [119] evaluated the impact of a 6-month structured exercise program on OSA severity in a small group of OSA patients, who were being treated concurrently with CPAP and demonstrated a reduction in AHI off CPAP compared with pretherapy.

The possibility of specific exercise programs targeting the upper airways dilating muscles has been considered, but there are no objective data to support the efficacy of such an approach. Nonetheless, regular aerobic exercise training has been reported to be associated with a BP reduction in hypertension [3–5].

Choice of antihypertensive drugs in hypertensive patients with obstructive sleep apnea

The choice of antihypertensive medications in hypertensive patients with concomitant OSA may have specific implications for their optimal clinical management. The effects of antihypertensive agents on OSA activity are not uniform. Only few studies compared different agents through parallel group or cross-over designs. Unfortunately, statistical power was usually poor due to low patient numbers. Although a decline in OSA severity may be associated with BP reduction, such reduction may also be possibly related to a direct effect of the drug itself [120]. Finally, effects of long-term treatment with certain antihypertensive agents on OSA severity have never been systematically addressed during clinical trials. In general, there is no obvious antihypertensive drug class that has repetitively demonstrated superior antihypertensive efficacy in OSA patients [43]. In summary, additional clinical research is needed in order to identify preferred compounds for an adequate BP control in this group of high-risk patients.

Continuous positive airway pressure treatment in obstructive sleep apnea patients with hypertension

Many studies have assessed the impact of active therapy of OSA on BP levels both in normotensive and hypertensive patients with variable results (see Table S1).

The various reports have employed widely different methodologies, ranging from short-term placebo-controlled protocols to long-term observational studies. Despite the widely differing methodologies, the overall findings of these reports is that CPAP therapy in OSAS results in a lowering of BP levels, which is most pronounced when assessed by ABPM and in patients with severe OSA that regularly use CPAP every night for at least 5 h per night, and who have preexisting hypertension. The benefit affects both SBP and DBP and is evident both during wakefulness and sleep.

Identification of daytime sleepiness as a factor associated with OSA and hypertension is not a new finding [42,121]. Although it has been debated whether CPAP therapy improves BP control in nonsleepy patients, a recent report by Barbé *et al.* [122] indicates a significant benefit of long-term CPAP therapy in OSA patients on BP levels, even among nonsleepy patients, provided that a sufficiently long follow-up is allowed [123].

Four meta-analyses of studies of CPAP therapy in OSA have been published in recent years. Bazzano *et al.* [124] included in their meta-analysis 16 randomized clinical trials published between 1980 and 2006, with a total of 818 participants, that compared CPAP to control, had a minimum treatment duration of 2 weeks and reported BP changes during the intervention or control period. Mean net change in SBP for those treated with CPAP compared with control was −2.46 mmHg; mean net change in DBP was −1.83 mmHg; and mean net change in mean arterial pressure was −2.22 mmHg. Alajmi *et al.* [125] performed a comprehensive literature search up to July 2006 to identify 10 randomized, controlled trials that included an appropriate control group and reported SBP and DBP before and after CPAP or control. The analysis included data from 587 individuals. CPAP compared with control reduced SBP by 1.38 mmHg and DBP by 1.53 mmHg. Mo and He [126] included randomized, controlled trials published between 2000 and 2006 in both English and Chinese languages. Study inclusion criteria included treatment duration of at least 4 weeks and measurement of 24-h ABP before and after CPAP or control (non-CPAP) periods. Seven studies with 471 participants were included. Overall, CPAP reduced 24-h SBP by 0.95 mmHg, 24-h DBP by 1.78 mmHg and 24-h mean BP by 1.25 mmHg. In the analysis by Haentjens *et al.* [127], only studies that had

used 24-h ABP assessments were included with 572 patients from 12 randomized, placebo-controlled trials. CPAP treatment compared with placebo reduced 24-h SBP by 1.64 mmHg and 24-h DBP by 1.48 mmHg. In a prespecified meta-regression analysis, greater CPAP treatment-related reduction in 24-h mean BP was observed in individuals with more severe OSA and in those most adherent to the use of CPAP.

Effects of other specific obstructive sleep apnea treatments besides continuous positive airway pressure (surgical procedures and oral devices) on blood pressure reduction

Limited evidence is available on the effects on BP of OSA treatment through surgical procedures or through use of oral appliances, an issue that deserves to be addressed in future studies [128–130]. Very preliminary data are available on the effects of renal sympathetic denervation, through catheter ablation technique in OSA patients, suggesting a reduction in elevated BP, in OSA severity and an improvement in glycemic control in patients with resistant hypertension [74].

Treatment of obstructive sleep apnea in patients with CV disease

Chronic heart failure

Only limited evidence is available on whether treatment of OSA improves mortality in CHF patients. However, an increased mortality has been reported in patients with untreated OSA and CHF, and all agree that OSA treatment decreases mortality, albeit suspicion of OSA in CHF patents and its treatment are rarely considered [131].

There is no consensus regarding treatment for CSA in CHF patients. Outcome studies focusing on cardiovascular endpoints are still necessary to define management strategies for patients with CHF and either OSA or CSA [132–135].

Stroke

Several publications suggest that CPAP treatment could have favorable effects in stroke patients with OSA [136–140]. Despite this, CPAP acceptance represents a major problem in treating this type of patients. Previous studies have documented that only about 50% (45–70%) of patients can be put under regular CPAP treatment after stroke, and that only 15% remain under treatment during a 6-year follow-up [87].

Very few data exist about CPAP treatment during acute stroke [141], but CPAP treatment can be taken into account individually, mainly in patients with mild-to-moderate neurological deficits, moderate-to-severe OSA (AHI $>$ 30 per h) and high cardiovascular risk profile.

In patients presenting predominantly with central apneas or central periodic breathing oxygen may be beneficial. The benefit of a CPAP treatment in stroke patients with central apneas or central periodic breathing has not been proven yet. A novel method of ventilator support called 'adaptive servoventilation' was shown to prevent central apneas in stroke patients with heart failure more efficiently than CPAP or oxygen [142].

PROBLEMS AND PERSPECTIVES

This document intends to provide a guide to the management of patients with both OSA and arterial hypertension, by gathering the information provided by available studies, without however a formal grading of the strength of the evidence provided. This is partly because the link between OSA and hypertension and that between OSA and cardiovascular risk represent issues still under evaluation. Particularly, more evidence from longitudinal trials is needed on the impact of OSA on cardiovascular risk in women, on the causal link between OSAS and arterial hypertension or diabetes mellitus and on the effects of OSA treatment with CPAP or other interventions on the reduction in BP level and, in general, on the reduction in patients' cardiovascular risk.

Additional issues to be investigated include patients' compliance with CPAP treatment, and the relation between OSA and hypertension explored by the use of home BP monitoring and ABPM. Probably because of the scanty use of these more correct BP measuring methodologies, the existence of a causal link between OSA and hypertension is still matter of debate. Finally, as far as treatment of OSA is concerned, the number of randomized controlled trials so far has been too small, and we need more and larger prospective randomized trials to test the efficacy of CPAP and other therapeutic interventions in lowering BP. No trial has been of a sufficiently large size yet to satisfactorily investigate the really important issue as to whether OSA treatment has any beneficial effects on cardiovascular outcomes.

Nonetheless, although there are no doubts that the complex link between OSA, hypertension and cardiovascular risk deserves further studies, the available evidence is certainly sufficient to recommend greater attention both to the identification and to treatment of the BP increase associated with OSA as well as to the detection of SRBDs in patients with a diagnosis of hypertension. Failure to do so is likely to limit the effectiveness of interventions aimed at lowering BP and at reducing the risk of cardiovascular events in patients followed up either in sleep or in hypertension centers.

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Conflicts of interest

There are no conflicts of interest.

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