RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HYPERTENSION.

Joint Recommendations by The European Society of Hypertension, The European Respiratory Society, and by members of European COST Action B26 on Obstructive Sleep Apnea.

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Short Title: How to manage patients with OSA and Hypertension

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Abstract
This paper 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 (in particular hypertensive) patients, as well as for the management of cardiovascular diseases (in particular 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 in particular 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.

Introduction
This paper 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 appendix), with the endorsement of the European Respiratory Society (ERS) and the European Society of Hypertension (ESH). For the readers’ convenience, additional material is provided on the journal website.
The present recommendations have been prepared following a careful methodological approach, the details of which are summarized in file S.1 on the Journal website.

1. Association of OSA with hypertension, and hypertension with OSA.

Sleep Related Breathing Disorders (SRBD) include habitual snoring, obstructive sleep apnea (OSA), central sleep apnea (CSA), obstructive sleep apnea syndrome (OSAS), i.e. 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. 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.

Indeed, OSA has been acknowledged as a novel, frequent and modifiable cause of systemic arterial 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. In particular, 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 non-dipping 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] studies 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 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 subjects with respiratory disturbance index >30 were found to be hypertensive. Conversely, approximately 40% of hypertensive patients are diagnosed with OSA [26].

Several factors may affect the relationship between BP and OSA, including age and gender [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 role of OSA on BP regulation in children has been also suggested, although the body of evidence is still limited compared to 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 and Epworth scales) is related to hypertension independently of obesity; in this study among non-obese (BMI <30) 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 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 non-pregnant patients, although treating pre-eclampsia with CPAP cannot be recommended as a routine procedure.

2. Mechanisms of increased CV risk in OSA 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, and 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 of 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 time 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 continuous positive airway pressure (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 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]. On the other hand, a recent paper suggests that antagonism of mineralcorticoid receptors by spironolactone reduces 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 that this was only true for patients with resistant hypertension. No relationship between plasma aldosterone and sleep apnea severity was noted in normotensive control subjects [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 relationship between the activity of the renin-angiotensin-aldosterone system 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 importance of these potential 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 reoxygenation in OSA generate reactive oxygen species and oxidative stress, increase circulating levels of adhesion molecules, and also preferentially activates NF-κB and related cytokines such as TNF-α and IL-8, thus promoting inflammation [47]. This may contribute to the increased cardiovascular risk typical of OSA patients, given the suggested 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 subjects. However, the possibility of an independent relationship of leptin and other adipocytokines (such as adiponectin and ghrelin) with OSA requires further investigation [49,51,52].

Genetic aspects of hypertension in OSA

The genetic contribution to differences in BP 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 is available. The presence of gene polymorphisms potentiating hypertension may or may not be shared between patients with OSA and those with essential hypertension. Candidate gene studies only 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].

3. Cardiovascular events and organ damage in OSA patients (OSA 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 subjects 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].

Ischaemic heart disease. Published prospective and cross-sectional reports, suggest an association of OSA and coronary artery disease 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 coronary artery disease 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 to 1.21] per 10-unit increase in apnea-hypopnea index [AHI]) but not in older men or in women of any age [61;62].

_Sleep apnea and Stroke._ Severe OSA in a Swedish cohort (182 middle-aged men) is associated with a very high cardiovascular risk: over 10 years, 14% of this group are predicted to experience a stroke and 23% a myocardial infarction (36% combined risk) [63]. Prospective data in a larger population confirmed that in a community-based sample of middle-aged and older adults (5,422 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 CVD, including stroke, was significantly associated with sleep-disordered breathing in men [64].

A survey on 6424 patients of the Sleep Heart Study [65] showed a relative stroke risk of 1.58 for patients with an AHI >10/h compared to patients without SA. Moreover in another prospective cohort study [60] patients with an AHI >10/h had in a 3 years follow-up an increased relative combined stroke and death risk of 1.97, rising to 3.3 when AHI was >36/h.

Finally a recent evidence-based work has concluded that OSA increases the risk of stroke independently of other cerebrovascular risk factors [66].

_Congestive Heart Failure (CHF)._ According to recent studies show that untreated sleep apnea may promote left ventricular dysfunction, disease progression, and increased mortality in heart failure patients [67].

In the Sleep Heart Health Study the presence of OSA conferred a 2.38 relative risk in the likelihood of having HF, independent of other known risk factors [61].
However, since 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 blood pressure. 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 showing 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 (LV) remodeling. Subjects with OSA were shown to have higher values of aortic stiffness, and lower large arteries distensibility than controls. However, given the cross sectional nature of most available observations, it is still to be clarified whether an increased arterial rigidity in OSA is the result of OSA-related hypertension, or, on the contrary, an increased arterial stiffness contributes to BP elevation in this condition. 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 [68].

**Heart.** Compared with normotensive subjects without OSA, left atrial diameter, interventricular septal thickness, LV posterior wall thickness, LV mass index, and prevalence of LV hypertrophy were increased to a similar extent in normotensive with OSA and in patients with hypertension without OSA, with a significant further increase in subjects affected by both OSA and hypertension [69;70]. Both right ventricular and left ventricular systolic and diastolic functions are impaired in patients having OSA with or without hypertension [71]. Thus, OSA, independently of obesity and of hypertension, may induce cardiac changes that could predispose to atrial fibrillation and heart failure [70].

Cardiovascular diseases leading to pacemaker implantations are suspected of being associated with a high rate of undiagnosed OSA [72]. 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 [73-75].

*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 [76;77].

*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: non-arteritic 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 [78;79].

4. **Sleep related breathing disorders in patients with cardio and cerebrovascular diseases**

**CHF (SRBD as a consequence of cardiovascular diseases).** The sleep-related breathing disorder commonly linked to heart failure is central sleep apnea (CSA) [80] but the prevalence of OSA in CHF patients is relatively high (between 10 and 25%) possible due to upper airway narrowing by fluid accumulation in the neck while supine [81]. Prevalence of OSA in CHF is likely to rise because of the emerging epidemics of obesity [82]. Untreated OSA is associated with an increased risk of death independently of confounding factors, in patients with CHF [83].

**Stroke.** Prevalence of breathing alterations during sleep is higher in patients with acute ischemic stroke or transient ischemic attacks (50-70%) [84;85] than 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.

Central SA and central periodic breathing (CPB) or Cheyne-Stokes breathing may appear in up to 30 to 40% of acute stroke patients [84-87], reflecting a new-onset stroke-associated condition. In
the transition from the acute to the subacute phase of stroke SA tends to improve, but more than 50% of patients still exhibit an AHI ≥10/h 3 months after the acute event [87-90], because obstructive events improve less than central ones [87].

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 [86;91]. Considering the evolution in the weeks/months following stroke, SRBD were shown to be associated with duration of hospitalization [91;92], increased mortality [93-95] and poor functional outcome [91;96].

5. Diagnostic aspects

**Diagnosing OSA 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 [97]. The frequency of event occurrence during sleep is referred to as the Apnea Hypopnea Index (AHI), while the Respiratory Disturbance Index (RDI) is the sum of the AHI and the Respiratory Effort Related Arousal (RERA) indices (see BOX 1).

Table 1 provides the definition of Obstructive Sleep Apnea Syndrome by the American Academy of Sleep Medicine [98], Table 2 the diagnostic criteria listed in the International Classification of Sleep Disorders [1] and detailed symptoms and signs are summarized 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 [99;100]. 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 [101].
Methods for the objective assessment of daytime sleepiness are available on the website (see supplemental file on the journal website S.2).

**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 OSA: Assessment of OSA contribution to resistant hypertension** The 2007 European Society of Hypertension- European Society of Cardiology hypertension management guidelines define resistant or refractory hypertension a condition where 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 systolic and diastolic BP 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 specialised 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 [102-104]. Since the night-time systolic BP predicts cardiovascular morbidity and mortality even more accurately than daytime systolic BP, nocturnal increases in systolic BP 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, ABPM monitoring, which improves prediction of cardiovascular risk in hypertensive patients, should be considered in every OSA patient, in particular when resistance to drug treatment is suspected. When using ABPM the impact of sampling interval in reliably assessing night-time BP has been studied by Marrone et al [105], 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 subjects. 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 [106], because BP could be normal in the office but frequently elevated outside the doctor’s office, in particular 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 24h ABPM, and, in some cases, home BP monitoring [107]. The role of home BP monitoring in quantifying BP elevation in OSA patients is still under evaluation, however [107-109]. 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 nighttime 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 OSA 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 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[110]. This occurs both in normotensive and hypertensive OSA subjects. BP may thus be increased during the night, resulting in different ratios between evening and morning values, when ambulatory or only clinic/home BP measurements are reported. This difference has been found related to the severity of sleep apnea although limited to men [111]. SBP values, but not PP, have been found to correlate with AHI, when BP elevation is quantified in terms of mean BP, but not in terms of pulse pressure [112].

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), 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 [113], but this technique still needs proper validation according to international protocols [4;107].

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 S3 file on the website. A possible flow chart indicating when to perform ABPM in OSA patients with a suspect of hypertension is reported in Figure 2.
6. Management of OSA 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, since 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, while the link of excess weight and obesity with OSA has long been accepted, it is conversely still debated how much a weight reduction programme can improve OSA and reduce BP [114]. Surprisingly, there are no large scale controlled trials on the effects of weight loss in OSA. Only smaller scale studies of dietary [115], surgical [116] or pharmacological [117] 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% CI, 18%-34%) decrease in AHI [114]. 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 modest and sometimes non-significant reductions of BP[117;118] .

It remains unclear why hypertension in obese subjects 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 and ambulatory BP monitoring. 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 non pharmacological 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 subjects. It has been suggested that a reduction in alcohol intake might help reducing both OSA severity and its BP effects [3-5].

*Exercise* While there are strong theoretical reasons to believe that a formal exercise programme 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 [119]. Giebelhaus et al. 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 to pre-therapy [120].

The possibility of specific exercise programmes 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 OSA*

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 [121]. 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 which 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 (CPAP) Treatment in OSA 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 website 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 ambulatory BP monitoring and in patients with severe OSA that regularly use CPAP every night for at least 5 h/night, and who have pre-existing hypertension. The benefit affects both systolic and diastolic BP, 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;122]. While it has been debated whether CPAP therapy improves BP control in non-sleepy patients, a recent report by Barbè et al. indicates a significant benefit of long term CPAP therapy in OSA patients on BP levels, even among non-sleepy patients [123;124].

Four meta-analyses of studies of CPAP therapy in OSA, have been published in recent years. Bazzano et al. [125] 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 $\sim 2.46 \text{ mm Hg;
mean net change in DBP was −1.83 mm Hg; and mean net change in mean arterial pressure was −2.22 mm Hg. Alajmi et al. [126] 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 subjects. CPAP compared with control reduced SBP by 1.38 mm Hg and diastolic BP by 1.53 mm Hg. Mo and He [127] included randomized, controlled trials published between 2000 to 2006 in both English and Chinese. Study inclusion criteria included treatment duration of at least 4 weeks and measurement of 24-hour ABP before and after CPAP or control (non-CPAP) periods. Seven studies with 471 participants were included. Overall, CPAP reduced 24-hour SBP by 0.95 mm Hg, 24-hour DBP by 1.78 mm Hg, and 24-hour mean BP by 1.25 mm Hg. In the analysis by Haentjens et al. [128] only studies that had used 24-hour ABP assessments were included with 572 patients from 12 randomized, placebo-controlled trials. CPAP treatment compared with placebo reduced 24-hour SBP by 1.64 mm Hg and 24-hour DBP by 1.48 mm Hg. In a prespecified meta-regression analysis, greater CPAP treatment-related reduction in 24-hour mean BP was observed in subjects with more severe OSA and in those most adherent to the use of CPAP.

**Effects of other specific OSA treatments besides CPAP (surgical procedures and oral devices) on BP reduction**

Limited evidence is available on the effects on BP of OSA treatment through surgical procedures or through use of oral appliances, an issue which deserves to be addressed in future studies [129-131]. Very preliminary data are available on the effects of renal sympathetic denervation, through catheter ablation technique in OSA patients, suggesting a reduction of elevated BP of OSA severity and on glycemic control in patients with resistant hypertension [75].

**Treatment of OSA in patients with CV disease**

CHF. Only limited evidence is available on whether treatment of OSA improves mortality in CHF patients but has been reported increased mortality 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 rare [132]

There is no consensus regarding treatment for central sleep apnea. Outcome studies focusing on
cardiovascular endpoints are still necessary to define management strategies for patients with CHF
and either obstructive or central sleep apnea [133-136]

Stroke. Several publications suggest that CPAP treatment could have favorable effects in stroke
patients with OSA [137-141]. 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 CPAP treatment after stroke, and that only 15% remain under treatment during a
6-year follow-up [88].

Very few data exist about CPAP treatment during acute stroke [142], but CPAP treatment can be
taken into account individually, mainly in patients with mild-moderate neurological deficits,
moderate-severe obstructive SA (AHI >30/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 [143].

7. 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 a formal grading
of the strength of the evidence provided. This is partly because the link between OSA and
hypertension and OSA and cardiovascular risk represents an issue still under evaluation. In
particular, 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 of BP level and, in general, on the reduction of 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 and ambulatory BP monitoring. 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 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 investigate the really important issue as to whether OSA treatment has any beneficial effects on cardiovascular outcomes.

Nonetheless, while 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 sleep related breathing disorders in patients with a diagnosis of hypertension. Failure to do so is likely to limit the effectiveness of interventions aimed at reducing the risk of cardiovascular events in patients followed-up either in sleep or in hypertension centers.
FIGURE 1 Proposed diagnostic algorithm for obstructive sleep apnea.
BOX 1 – DEFINITIONS of breathing alterations during 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 event should last at least 10 seconds

**Hypopnea:** Obstructive breathing event with a reduction of airflow between 70 and 20% of the preceding period of stable breathing. Each event should last at least 10 seconds
RERA: Respiratory Effort Related Arousal. events characterized by increased respiratory effort during sleep caused by flow limitation in the upper airways which 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 mild = AHI between 5 and below 15,
- OSA moderate = AHI between 15 and below 30
- OSA severe = AHI above 30 per hour.

RDI: The 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.

Obstructive Sleep Apnea Syndrome (OSAS) (American Academy of Sleep Medicine): combination of at least 5 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 which represents the combination of OSA and symptoms as a fully established clinical syndrome).

BOX 2 Diagnosing Hypertension in patients with OSA; different type of BP measurement

1. OFFICE BP MEASUREMENT
   ADVANTAGES: 1. Cornerstone in the approach to hypertension diagnosis and management over more than a century; 2. Easily available; 3. Related to outcome in large epidemiological and intervention studies

   LIMITATIONS: 1. Intrinsic inaccuracy of the auscultatory technique (mainly for diastolic BP and in specific populations); 2. Observer’s bias and digit preference; 3. Only isolated
measurement allowed; 4. Interference by white coat effect; 5. Inability to account for physiologic BP variability; 6. No information on nocturnal BP

2. HOME BPMONITORING
ADVANTAGES: 1. 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; 2. No alarm reaction to BP measurement; 3. Good reproducibility; 4. Good prognostic value; 5. Relatively low cost; 6. Patient-friendliness (in semiautomatic devices); 7. Involvement of patient in hypertension management; 8. Possibility of digital storage, printout, PC download or teletransmission of BP values (in some devices/systems); 9. Improvement of patients’ compliance to treatment Improvement of hypertension control rates
LIMITATIONS: 1. Need of patient training (short for automated devices); 2. Possible use of inaccurate devices; 3. Measurement errors; 4. Limited reliability of BP values reported by patients; 5. Induction of anxiety, resulting in excessive monitoring; 6. Treatment changes made by patients on the basis of casual home measurements without doctor’s guidance; 7. Normality thresholds and therapeutic targets still debated; 8. Lack of night recordings

3. 24h AMBULATORY BP MONITORING
ADVANTAGES: 1. No observer bias and digit preference; 2. Large number of BP values available over 24 h in daily life particularly in true ambulatory conditions; 3. No alerting reaction to BP automated measurements (no WCE); 3. Higher reproducibility of 24 h average BP; 4. No placebo effect; 5. Allows assessment of 24 h, daytime, night-time and hourly BP values; 6. Allows assessment of BP variability (although limited with discontinuous BP monitoring); 7. Allows assessment of day–night BP changes (‘dippers’, ‘non-dippers’, ‘extreme dippers’); better if performed over repeated recordings; 8. 24 h Average BP more closely related to target-organ damage of hypertension; 9. Superior prognostic value of 24 h, daytime or night-time average BP; 10. 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: 1. Possible inaccuracy of automated BP readings; 2. Interference with patient’s daily activities; 3. Quality of sleep affected to a greater or lesser degree; 4. Limited reproducibility of hourly BP values; 5. Reference ‘normal’ ambulatory BP values still under debate; 6. Need for more evidence on prognostic value of different ABPM parameters; 6. High costs

4. BEAT-BY-BEAT BPMONITORING
ADVANTAGES: Possibility to accurately assess beat by beat BP variability
LIMITATIONS: 1. Invasive methods: poorly suited to a clinical setting; 2. Noninvasive methods: possible inaccuracies due to pulse wave distortion in peripheral arteries; limited availability because of relatively high cost; need of expert operators.

TABLE 1
Definition of Obstructive Sleep Apnea Syndrome (OSAS) (American Academy of Sleep Medicine): a combination of at least 5 obstructive breathing episodes per hour during sleep (apneas, hypopneas and RERA events) and at least one of the following criteria [98]:

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.

TABLE 2: Diagnostic criteria for Obstructive Sleep Apnea (OSA) according to the International Classification of Sleep Disorders, 2nd edition: Obstructive Sleep Apnea in adults [1].
A. At least one of the following applies:
   - The patient complies of unintentional sleep episodes during wakefulness, daytime sleepiness, unrefreshing sleep, fatigue, or insomnia;
   - ii. The patient wakes up with breathholding, gasping, or choking; or
   - iii. The bed partner reports loud snoring, breathing interruptions, or both during the patient’s sleep
B. Polysomnographic recording shows the following:
   - Five or more scoreable respiratory events (ie, apneas, hypopneas, or respiratory effort related arousals (RERA)) per hour of sleep:
   - ii. Evidence of respiratory effort during all or a portion of each sleep event
OR
C. Polysomnographic recording shows the following:
   - Fifteen or more scoreable respiratory events (ie, apneas, hypopneas, or respiratory effort related arousals (RERA)) 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 OSA diagnosis A, B and D or C and D must be fulfilled

TABLE 3: Clinical symptoms, characteristics and objective findings suggesting a high probability for obstructive sleep apnea syndrome (OSAS)
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 Gender,* postmenopausal females; *Overweight,* preferably central obesity (e.g. BMI > 30 kg/m² 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->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-> 80%); Nocturnal Non Dipping of 24 hour 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 like diabetes mellitus

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**TABLE 4: Diagnostic tools for the evaluation of Obstructive Sleep Apnea Syndrome**

<table>
<thead>
<tr>
<th>Levels of sleep monitoring</th>
<th>Type of Monitoring device and setting</th>
<th>Parameters measured</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td>Attended, in lab polysomnography</td>
<td>Polysomnography including electroencephalogram, electromyogram, electrocardiogram or heart rate, airflow, respiratory effort, and oxygen saturation; additional externally assessed parameters can be</td>
</tr>
<tr>
<td>Level 2</td>
<td>Unattended polysomnography in the hospital/sleep unit or at home</td>
<td>Polysomnography including electroencephalogram, electromyogram, electrocardiogram or heart rate, airflow, respiratory effort, and oxygen saturation; investigation performed without any supervision</td>
</tr>
<tr>
<td>Level 3</td>
<td>Polygraphic limited channel recording, mainly modified portable sleep apnea monitoring</td>
<td>Minimum of 4 channels including ventilation or airflow (at least 2 channels to detect respiratory movements or respiratory effort and airflow), heart rate or electrocardiography, and oxygen saturation</td>
</tr>
<tr>
<td>Level 4</td>
<td>Single or two channel device</td>
<td>One or 2 channels, typically including oxygen saturation or airflow</td>
</tr>
</tbody>
</table>

SUPPLEMENTAL MATERIAL PROVIDED ON THE JOURNAL WEBSITE:

A] SUPPLEMENTAL FILES:

S1 - Methodology of Position paper: Search strategy for identification of studies

S2 – Patient history and questionnaires

S3 - Specific Blood Pressure Monitoring data in the general population and in OSA patients

S4 - EPWORTH SLEEPINESS SCALE

TABLE S1 Summary data on randomized controlled trials on the effects of CPAP treatment on BPin OSA patients ordered by duration of CPAP treatment

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APPENDIX
COST Action B26 - Management Committee Members

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