

## Obstructive Sleep Apnea and Cardiovascular Disease: Where Do We Stand?

A narrative review and position paper from the Turkish Collaboration of Sleep Apnea Cardiovascular Trialists (TURCOSACT), founded by the Turkish Society of Cardiology & Turkish Thoracic Society

### ABSTRACT

Obstructive sleep apnea is common in adults with cardiovascular disease. Accumulating evidence suggests an association between obstructive sleep apnea and cardiovascular disease independent of the traditionally recognized cardiovascular disease risk factors. Observational studies indicate that obstructive sleep apnea is a risk factor for development of cardiovascular disease and that alleviation of obstructive events with positive airway pressure may improve cardiovascular disease outcomes. However, recent randomized controlled trials have not supported the beneficial effect of positive airway pressure in cardiac populations with concomitant obstructive sleep apnea. Some evidence suggests that the relationship between obstructive sleep apnea and traditionally recognized cardiovascular disease risk factors is bidirectional, suggesting that patients with cardiovascular disease may also develop obstructive sleep apnea and that efficient treatment of cardiovascular disease may improve obstructive sleep apnea. Recent data also indicate that the apnea–hypopnea index, which is commonly used as a diagnostic measure of obstructive sleep apnea severity, has limited value as a prognostic measure for cardiovascular disease outcomes. Novel markers of obstructive sleep apnea-associated hypoxic burden and cardiac autonomic response seem to be strong predictors of adverse cardiovascular disease outcomes and response to treatment of obstructive sleep apnea. This narrative review and position paper from the Turkish Collaboration of Sleep Apnea Cardiovascular Trialists aims to update the current evidence about the relationship between obstructive sleep apnea and cardiovascular disease and, consequently, raise awareness for health professionals who deal with cardiovascular and respiratory diseases to improve the ability to direct resources at patients most likely to benefit from treatment of obstructive sleep apnea and optimize treatment of the coexisting cardiovascular diseases. Moreover, the Turkish Collaboration of Sleep Apnea Cardiovascular Trialists aims to contribute to strengthening the efforts of the International Collaboration of Sleep Apnea Cardiovascular Trialists in this context.

**Keywords:** Cardiovascular disease, coronary artery disease, heart failure, hypertension, sleep apnea

### INTRODUCTION

#### Historical Perspective

The relationship between cardiovascular diseases (CVD) and sleep-related breathing disorders has been discussed for many years. "Regular breathing pauses in sleep," which was first described by John Hunter and later by John Cheyne and William Stokes<sup>1</sup> and other respiratory features such as nocturnal dyspnea and orthopnea have been acknowledged by cardiologists as conditions caused by heart diseases in a cause–effect relationship. Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, which has gained interest in the medical community over the last 5 decades. In literature, it was Charles Dickens' description of Joe in *The Posthumous Papers of the Pickwick Club* (first published in 1837),<sup>2</sup> which was the first clear description of the features of OSA:

### REVIEW

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Joe snored heavily, "as if the roaring of cannon were his ordinary lullaby." He was "red-faced" (plethoric), had dropsy (peripheral edema), and "the fat boy's perception was slow" (cognitive dysfunction).

An important knowledge within the sleep research field was introduced by Berger in 1930 with electroencephalography, distinguishing differences between wakefulness and sleep.<sup>3</sup> With the introduction of the electrooculogram in 1953, sleep stages including slow wave sleep and rapid eye movements (REM) were first described.<sup>4</sup> In 1972, Coccagna et al<sup>5</sup> showed that the apneas observed in Pickwickian patients were associated with severe swings in both pulmonary and systemic blood pressure, which further emphasized the importance of treating the condition. Weight reduction was the only treatment option at that time, but tracheostomy was introduced as an effective intervention in a case report in 1969,<sup>6</sup> which was later replicated in case series of patients with life-threatening complications of Pickwickian syndrome.<sup>7</sup> In 1976, Guilleminault et al<sup>8</sup> showed that not only obese but also nonobese individuals could suffer from apneas during sleep caused by obstruction of the upper airway. In the same paper, they used the term obstructive sleep apnea syndrome for the first time and defined the disorder based on sleep recording findings. However, the diagnostic criterion was arbitrary, at least 30 apneas of a minimum duration of 10 seconds each, were detected during sleep, in combination with hypersomnolence.<sup>8</sup> In 1981, Fujita et al<sup>9</sup> introduced uvulopalatopharyngoplasty, which soon became the main surgical approach. The same year, Sullivan et al<sup>10</sup> presented the ground-breaking invention of a noninvasive treatment modality of OSA, continuous positive airway pressure (CPAP), for patients with OSA, which has resulted in many new clinical management protocols and acceleration of research reports within the field.

The first epidemiological definition of OSA as a risk factor for hypertension was reported from the Wisconsin Sleep Cohort in 2000<sup>11</sup> and as a risk factor for the development of CVD in a prospective 7-year observational study of an otherwise healthy sleep clinic cohort in Gothenburg, Sweden, in 2002.<sup>12</sup> These findings were later supported by larger clinical epidemiological studies<sup>13-15</sup> as well as by others suggesting cardioprotective effects of CPAP treatment.<sup>16,17</sup> However, despite the observed benefits of CPAP in prospective clinical cohort studies, intention-to-treat analyses of the randomized controlled trials (RCTs), including the RICCADSA<sup>18</sup> and SAVE<sup>19</sup> studies in 2016, and ISAACC<sup>20</sup> trial in 2020, failed to show beneficial effects of CPAP in patients with an already established CVD and concomitant OSA, which has mainly been attributed to low adherence to CPAP in patients with CVD who do not have symptoms of OSA.<sup>21</sup> Thus, there is still an ongoing debate regarding whether all patients with OSA should be treated, which questions both the causality between OSA and CVD and the effectiveness of CPAP treatment to

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## HIGHLIGHTS

- We recommend screening for obstructive sleep apnea, especially for patients with drug-resistant or poorly controlled or nondipping hypertension and recurrent atrial fibrillation after cardioversion or ablation.
- We also recommend obstructive sleep apnea screening in patients with bradycardia syndrome, those with ventricular tachycardia, and patients with appropriate shocks from implanted cardioverter-defibrillators and adults with coronary artery disease, particularly the ones with nocturnal angina and repeat revascularization.
- Full-night polysomnography is recommended, and when access to polysomnography is limited, portable home sleep apnea tests should be used in cardiac cohorts in collaboration with respiratory and sleep physicians.
- Patients with cardiovascular disease and obstructive sleep apnea should be considered for treatment, including behavioral modifications and weight loss when obesity coexists.
- Positive airway pressure therapy should be offered to patients with cardiovascular disease and moderate to severe obstructive sleep apnea. Oral appliance therapy may be considered for patients with mild to moderate obstructive sleep apnea or for patients not tolerating positive airway pressure.

prevent adverse cardiovascular and cerebrovascular events in those individuals.

The International Collaboration of Sleep Apnea Trialists (INCOSACT) is a consortium initiated by sleep medicine physicians, cardiologists, and researchers from 16 countries with a shared interest in producing evidence-based reports for managing OSA treatment in adults in order to improve CVD outcomes.<sup>22</sup> A recent international survey conducted by INCOSACT addressed cardiologists' perspectives on OSA risk and screening in patients with atrial fibrillation (AF).<sup>23</sup> The United States, Japan, Sweden, and Turkey accounted for two-thirds of 863 responses from cardiologists. Despite the fact that a majority expressed firmness that combined OSA and AF treatment was superior to AF treatment alone for improving outcomes of AF, only a minority of the participating cardiologists referred patients with AF for OSA testing. Interestingly, while half of the screened patients with AF had OSA, CPAP was prescribed in less than half of them, highlighting the view that a better evidence degree from RCTs is needed to support this practice.<sup>23</sup>

The Turkish Collaboration of Sleep Apnea Cardiovascular Trialists (TURCOSACT) was founded in April 2022 as a consortium consisting of 7 physicians and researchers from the Turkish Cardiology Society and 7 physicians and researchers from the Sleep-Related Breathing Disorders Working Group of the Turkish Thoracic Society with the inspiration during conduction of the aforementioned INCOSACT survey. Hence, the current narrative review and position paper aimed to be the first product of the TURCOSACT reporting an update of the current evidence about the relationship between OSA and CVD, and consequently raising awareness for health professionals who deal with cardiovascular and respiratory

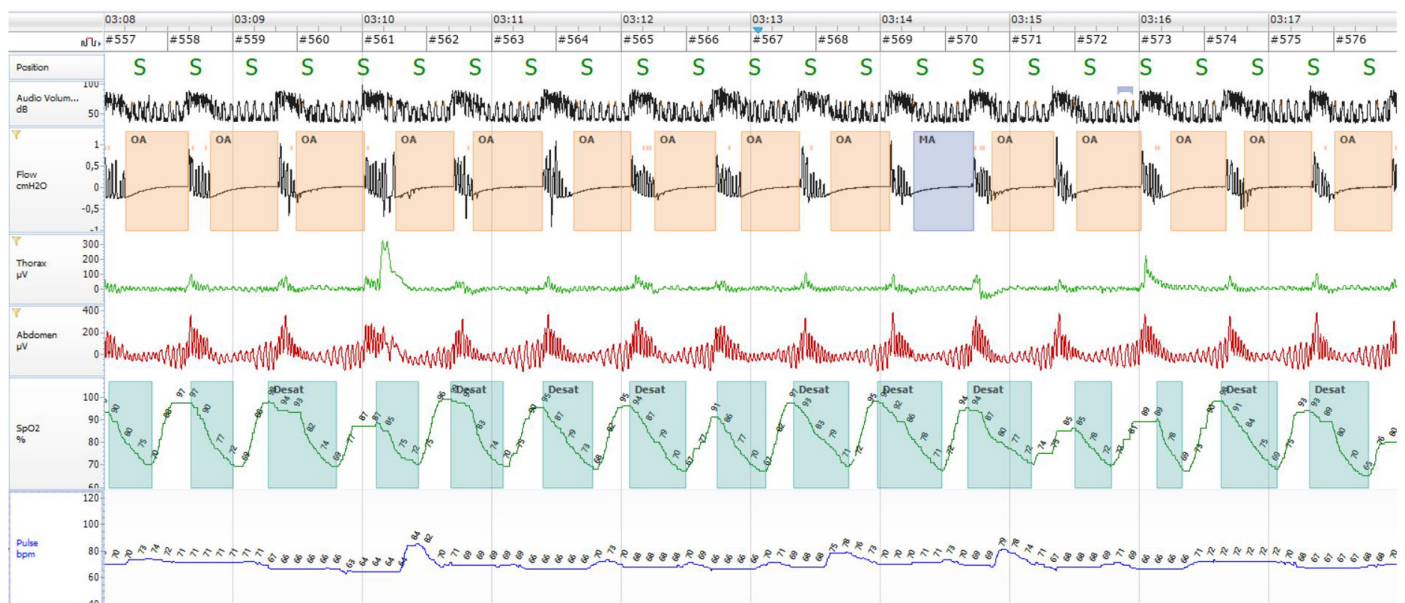
diseases to identify patients who would be most likely to benefit from treatment of OSA and optimizing treatment of the coexisting CVDs. Moreover, the current paper also aims to contribute to the TURCOSACT to strengthen the efforts of INCOSACT for broader national, regional, and global collaborations in this field.

### Sleep-Related Breathing Disorders

According to the recent International Classification of Sleep Disorders (ICSD)-3, sleep-related breathing disorders are categorized as (1) OSA disorders (adult vs. pediatric), (2) central sleep apnea (CSA) syndromes (mainly CSA with Hunter–Cheyne–Stokes breathing), CSA due to medication or substance as well as treatment-emergent CSA due overventilation with CPAP or other positive airway pressure (PAP) devices), (3) sleep-related hypoventilation syndromes (mainly obesity hypoventilation syndrome [OHS]), and (4) sleep-related hypoxemia disorder (as may be seen in patients with chronic thromboembolic pulmonary hypertension).<sup>24</sup> Moreover, OSA and OHS may coexist (overlap syndrome), and CVD patients with OSA may also have concomitant CSA with Hunter–Cheyne–Stokes breathing. Notwithstanding, this position paper solely aims to focus on the association between OSA and CVD, highlighting the current evidence level of the causality issues, gaps in knowledge, challenges, and future perspectives in this context.

### Definition of Obstructive Sleep Apnea

Obstructive sleep apnea is characterized by intermittent occurrences of complete or partial upper airway obstruction during sleep that results in arousal from sleep and/or a decrease in oxyhemoglobin saturation ( $SpO_2$ )<sup>25</sup> (Figure 1). Obstructive apnea is defined as an at least 90% reduction in airflow for at least 10 seconds in the presence of inspiratory



**Figure 1.** A 10-minute long home sleep apnea test recording illustrating intermittent pauses in airflow (OA) in S position with concomitant drops in oxyhemoglobin saturation ( $SpO_2$  levels (Desat) and fluctuations in the pulse rate. Of note, the snoring intensity (audio volume) reaches 100 dB, and breathing efforts during apneas are registered by the thoracic and abdominal belts indicating that the apneic events are obstructive. OA, obstructive apneas; S, supine.

**Box 1. Diagnostic Evaluation of Obstructive Sleep Apnea****Questionnaires**

STOP-BANG	Mostly for preoperative screening for the high probability of OSA
Berlin Questionnaire	Mostly primary care setting for the high probability of OSA
Modified Berlin Questionnaire	Prognostic evaluation of the high probability of OSA in certain clinical cohorts
Epworth Sleepiness Scale	Sleep clinic cohorts for evaluation of excessive daytime sleepiness

Many individuals in cardiac cohorts do not report OSA-related symptoms.

**HSAT**

For adults with high pretest probability OSA.

Not recommended for general screening of asymptomatic clinical populations.

Risk for underestimation of AHI due to lack of total sleep time if the patient has concomitant insomnia.

**Polysomnography (PSG)**

Underlying conditions that warrant polysomnography include:

Patients with a high pretest probability of OSA and a negative HSAT.

Significant cardiopulmonary disease.

Significant neurological disease (neurodegenerative disease and stroke).

Significant cardiac failure.

Uncontrolled arrhythmia.

Chronic opioid use.

Severe insomnia.

Symptoms of other significant sleep disorders such as narcolepsy, periodic limb movements, and sleep behavior disorder.

**OSA**

Either

(1) AHI  $\geq$  5 events/h HSAT or PSG when typical symptoms of OSA, such as snoring, fatigue, and excessive daytime sleepiness or comorbid conditions are present,

Or

(1) AHI  $\geq$  15 events/h in the absence of symptoms.

AHI, apnea–hypopnea index; HSAT, home sleep apnea test; OSA, obstructive sleep apnea; PSG, polysomnography.

efforts of the upper airway muscles against the occluded airway, and hypopnea is defined as a reduction of at least 30% in airflow for at least 10 seconds associated with 3% or more drops in SpO<sub>2</sub> levels and/or arousal.<sup>26</sup> Obstructive sleep apnea diagnosis is based on the number of apneas and hypopneas per hour of sleep, defined as an apnea–hypopnea index (AHI). According to the ICSD-3, OSA is defined as: either (1) having an AHI of 5 events/h or more on polysomnography (PSG) or home sleep apnea test (HSAT) when typical symptoms of OSA, such as snoring, fatigue, and excessive daytime sleepiness (EDS), or comorbid conditions such as hypertension, coronary artery disease [CAD], or stroke are present; or (2) having an AHI of at least 15 events/h in the absence of symptoms<sup>24</sup> (Box 1).

**Global Prevalence of Obstructive Sleep Apnea**

Estimation of the OSA prevalence in the general population varies depending on the methodology of the study design and the diagnostic threshold to define the presence and severity of OSA. In the early 1990s, population studies in the USA suggested that the occurrence of OSA, using AHI cutoff 5 events/h, was reported to be 9% in women and 24% in men, respectively.<sup>27</sup> A later study showed an increased prevalence, corresponding to 17% in middle-aged (30-70 years) women and 34% in middle-aged men, which was mainly attributed to increasing body mass index (BMI) in adult populations over the last 20 years.<sup>28</sup> The latest population-based study in Europe, the HypnoLaus Study, adapting the

hypopnea definitions of the American Academy of Sleep Medicine (AASM) from 2012, revealed that 61% of women and 84% of men had OSA in an unselected general cohort of 1525 adults.<sup>29</sup> The authors concluded that the prevalence of OSA was highly dependent on technical procedures such as using nasal cannulas which record more subtle breathing variations as hypopneas (instead of thermistors which were used earlier and which are known to have less sensitivity) as well as applying the latest hypopnea definitions, which are more liberal compared to the earlier ones (3% desaturations instead of 4% desaturations, and/or arousals). Globally, OSA has been estimated to affect 936 million individuals aged 30-69 years, based on the AHI threshold of 5 events/h.<sup>30</sup> When the AHI threshold 15 events/h is applied, 425 million individuals in this age group are categorized as having OSA worldwide. The highest prevalence rate in the world was reported in China, followed by USA and Brazil.<sup>30</sup> To date, there is yet no data regarding the OSA prevalence in Turkey based on objective sleep studies. According to a questionnaire-based study, Turkish Adult Population Epidemiology of Sleep, including a nationwide representative sample of 5021 participants, the estimated OSA prevalence has been reported as 14%.<sup>31</sup>

**Pathophysiology of Obstructive Sleep Apnea**

The collapse of the pharyngeal airway is the principal event in OSA and is considered to be a result of several abnormalities in the upper airway anatomy (for instance, retrognathia,

enlarged tonsils, and increased soft tissue in the neck) and its functions.<sup>32</sup> The airway may collapse when the pharyngeal intraluminal pressure exceeds the forces that dilate the pharynx.<sup>33</sup> Consequently, the activity of the upper airway muscles during inspiration, as well as the upper airway size and the physical properties of the pharyngeal wall, determine the state of the upper airway during sleep.<sup>25</sup> Reduced muscle tone and inadequate responsiveness may also increase susceptibility to OSA.<sup>34</sup> An oversensitive ventilatory control system (elevated loop gain) may lead to increased oscillations from the brainstem that lowers the partial pressure of CO<sub>2</sub> in arterial blood below the apnea threshold,<sup>35</sup> and a low respiratory arousal threshold may also lead to obstructive events.<sup>36</sup> Other mechanisms likely contributing to OSA include falling lung volume during sleep, fluid shifts from peripheral tissues (lower extremities) to the neck, and airway edema.<sup>36,37</sup> Likewise, a neuromuscular dysfunction in the muscles controlling the tonus in the upper airways can also induce apneas. The most important muscle for this is the genioglossus, and adequate contraction in this muscle seems to be crucial to avoid apneas during sleep.<sup>38</sup>

### Risk Factors for Obstructive Sleep Apnea

#### Gender

Obstructive sleep apnea is more prevalent in men than women (ranging from 13% to 33% in men and 6% to 19% in women in the general adult population).<sup>30</sup> The gender difference decreases following menopause.<sup>39</sup> It has been suggested that men have more collapsible upper airways,<sup>40</sup> elevated chemoreceptor responsiveness,<sup>41</sup> and reduced carbon dioxide sensitivity.<sup>42</sup> Apnea episodes are found to be shorter, and hypopneas are more frequent than apneas, the proportion of supine predominant OSA is lower, and REM-predominant OSA is more prevalent in women than those in men.<sup>43</sup>

#### Age

The association between age and OSA prevalence is in a quadratic fashion; it linearly increases and appears to plateau around the age of 65 years, and then it starts to decline in both men and women,<sup>44-46</sup> which might be explained by decreases in weight or survival bias.<sup>47</sup> An increased mortality rate in the middle-aged population with OSA has also been argued to be a possible explanation for this decline; thus, fewer patients with OSA compared to the middle-aged population without OSA survive.<sup>44</sup>

#### Obesity

Cross-sectional studies have demonstrated a strong relationship between increased BMI and risk of OSA.<sup>48</sup> Studies have reported that 40% of adults with obesity have severe OSA, and more than 70% of patients with OSA in sleep clinic cohorts are obese.<sup>49</sup> A population-based prospective study showed that a 10% weight gain was related to a 6-fold increased risk of OSA progression, and similarly, a 10% weight loss was related to a 26% improvement in the severity of OSA.<sup>11</sup> The underlying mechanisms for the relationship between obesity and OSA are not unclear. It may be related to the effects of fat deposition on airway anatomy and/or changes in upper airway function, alteration in the balance

between ventilatory drive and load as well as reduction in lung volumes.<sup>50</sup> Furthermore, leptin, which is significantly high in obesity, has important effects on regulating chemoreflex function and hence, controlling breathing.<sup>11,50</sup>

#### Smoking

Epidemiological studies suggest that cigarette smoking is a predisposing factor for OSA.<sup>51,52</sup> Possible underlying mechanisms include upper airway inflammation and increased risk for collapsibility of the upper airway muscles in smokers.<sup>52</sup>

#### Alcohol

Alcohol impairs pharyngeal dilator muscle function and the arousal response to apneas. A dose-dependent association between alcohol-intake in the evening and the frequency and duration of obstructive events have been demonstrated.<sup>53</sup>

#### Genetics

Existing studies have shown that OSA occurs more frequently in relatives of individuals with OSA than in the general population, suggesting the role of genetics in the development of this disorder.<sup>54,55</sup> Studies addressing the heritability of OSA severity in terms of AHI have suggested that one-third of the variability in this metric is explained by shared familial factors.<sup>56-58</sup> In this context, obesity explains approximately 40% of the genetic variance in the AHI,<sup>59</sup> which means that the major genetic basis for OSA is due to obesity-independent factors such as craniofacial morphology, the shape of both bony and soft tissue structures and genetic polymorphism, that is, the epsilon-4 allele of the APOE gene.<sup>58,60</sup>

#### Clinical Symptoms of Obstructive Sleep Apnea

Loud snoring, unrefreshing sleep, EDS, fatigue, and witnessed apneas are the most common symptoms reported in patients with OSA.<sup>61</sup> Gastroesophageal reflux, nocturia, and chronic headache in the morning are also more frequently observed in patients with OSA compared to the general population.<sup>61</sup> Nonetheless, these symptoms may be overlooked by physicians in daily practice as most OSA patients already have a substantial number of symptoms related to their comorbid diseases. On the other hand, many individuals with CVD do not report OSA-related symptoms though they may have severe OSA in terms of increased AHI levels.<sup>62</sup>

#### Diagnostic Evaluation of Obstructive Sleep Apnea

As summarized in Box 1, several questionnaires assessing the risk factors for OSA have been developed for different settings. The Berlin Questionnaire (BQ) is widely used mainly in primary care settings<sup>63</sup> and the STOP-BANG (Snoring, Tiredness, Observed Apnea, Blood Pressure, Body Mass Index, Age, Neck Circumference, and Gender) questionnaire is developed mainly for preoperative screening.<sup>64</sup> A modified version of the BQ has recently been used for prognostic evaluation of patients during the COVID-19 pandemic,<sup>65</sup> demonstrating a better sensitivity and specificity than the BQ in adults with a history of COVID-19 infection.<sup>66</sup> The Epworth Sleepiness Scale is a frequently used questionnaire for the assessment of EDS in sleep clinic cohorts.<sup>67</sup> However, an overnight sleep study is required for OSA diagnosis; HSATs are commonly used worldwide due to their lower cost for evaluation of individuals with a high pretest probability of OSA,<sup>68-70</sup>

and is a reasonable alternative to PSG for appropriately selected patients,<sup>71,72</sup> especially in countries with long wait times and high costs for in-hospital PSG, which is otherwise the gold standard method in the diagnosis of OSA.<sup>73</sup> Indeed, a randomized validation study has suggested that PSG confers no advantage over the ambulatory HSAT approach in the initial management of individuals with a high-probability of OSA in terms of diagnosis and CPAP titration and that the ambulator approach may improve adherence to CPAP treatment.<sup>71</sup> Notwithstanding, HSATs are not recommended for general screening of asymptomatic clinical populations. The raw data from the HSAT devices must be reviewed and interpreted by a physician who is either board-certified in sleep medicine or overseen by a board-certified sleep medicine physician.<sup>68,70,72</sup> Patients with a high pretest probability of OSA and a negative HSAT should be further evaluated with PSG<sup>71,73</sup> (Box 1). The severity of OSA is assessed on the severity of the AHI; an AHI 5.0-14.9 events/h is classified as mild OSA, AHI 15.0-29.9 events/h as moderate OSA, and at least 30.0 events/h is classified as severe OSA.<sup>24</sup> In the evaluation of the OSA diagnosis, symptom severity, especially the presence and extent of EDS, which has potentially dangerous effects on traffic safety as well as the severity of oxygen desaturation and sleep fragmentation, are also considered. As recently reviewed, new novel techniques for quantifying overnight hypoxemia (hypoxic burden), cardiac autonomic response to obstructive events, and sleep fragmentation seem to have better prognostic value than the standard OSA metrics.<sup>74,75</sup>

## Treatment Options for Obstructive Sleep Apnea

### Positive Airway Pressure

Continuous PAP (CPAP) is the gold standard treatment for patients with moderate to severe OSA (AHI  $\geq$  15 events/h) in the absence of symptoms, but it is also recommended for the treatment of mild OSA patients (AHI 5-15 events/h) in the presence of EDS or other comorbidities such as obesity, hypertension, and cardiac diseases.<sup>76,77</sup> Titration of the pressure which should be applied is usually conducted in sleep laboratories under attended PSG monitoring. Auto-titrating PAP (APAP) is another commercially available treatment option in which the delivered pressure varies depending upon a device-specific algorithm. In general, the device defines normal airflow for the patient and automatically delivers additional pressure when the flow curve is restricted.<sup>78</sup> Auto-titrating PAP devices may be useful for OSA patients, who have obstructive events mainly in the supine position (positional OSA), and those with OSA mainly during REM sleep.<sup>79</sup> According to an official workshop report from the American Thoracic Society/American Academy of Sleep Medicine/American College of Chest Physicians/European Respiratory Society workshop report, home APAP titration has also been shown to be effective as in-lab CPAP titration in considering the home CPAP set-up for management of the patients with OSA.<sup>69</sup>

### Oral Appliance Therapy

Oral appliances include tongue-retaining devices and mandibular advancement devices (MADs). The MADs are more commonly used, especially in patients with mild OSA and in

those who do not tolerate CPAP treatment.<sup>79</sup> The MADs are not as efficient as the PAP devices but may be beneficial in holding the mandible in a forward position, thus, preventing the upper airway muscles from collapsing.<sup>80</sup>

### Upper Airway Surgery

Adenotonsillar hypertrophy is the most common cause of pediatric OSA, and adenotonsillectomy is the first choice of treatment in children and young adults with OSA.<sup>81</sup> Nasal obstruction due to septal deviation may lead to snoring and OSA; intranasal pathology increases upper airway resistance with subsequent collapse, leading to hypopneas.<sup>82</sup> Septoplasty or conchotomi can be considered in certain cases, and these interventions may also be beneficial for patients who have difficulties in tolerating CPAP treatment due to nasal problems.<sup>79</sup> Uvulopalatopharyngoplasty was frequently used in the early 1980s and 1990s with successful results in the beginning regarding the effect on snoring, but later studies showed that those individuals might develop OSA again silent apneas.<sup>79</sup>

### Neurostimulation

Hypoglossal nerve stimulation is a recently developed treatment option for patients who do not tolerate CPAP treatment.<sup>83</sup> It is a pacemaker-like device, which is connected to a wire that attaches a small cuff to the hypoglossal nerve. The device stimulates the hypoglossal nerve and protrudes the tongue, opens the pharyngeal airway, and thus, maintains the upper airway patency. Hypoglossal nerve stimulation has been shown to reduce AHI by almost 70%, from 30 events/h to 9 events/h, with sustained benefit after 3 years.<sup>84</sup>

### Lifestyle Interventions and Medical/Surgical Weight Loss

The most crucial intervention for an efficient treatment in OSA patients with comorbid obesity is long-term weight management. A goal BMI, 25 kg/m<sup>2</sup>, through dietary or bariatric surgical weight loss, has been shown to improve AHI in obese OSA patients.<sup>84</sup> Weight loss may reduce the required pressure levels of PAP treatment in patients with sustained OSA, which is also important for patient comfort. It has been suggested that tongue fat is also increased in obese OSA patients and may explain one mechanism by which weight loss improves OSA severity.<sup>85</sup> In a recent study, Wang et al<sup>85</sup> conducted PSG and upper airway magnetic resonance imaging before and after weight loss interventions (intensive lifestyle modification or bariatric surgery) in adults with obesity and OSA and showed that weight loss was significantly associated with reductions in tongue fat and airway soft tissue, which strongly correlated with reductions in AHI, even after controlling for overall weight loss.

### Positional Therapy

Positional therapy has been developed to prevent patients from lying in the supine position, when OSA is position dependent. Given that the supine position decreases the area of the upper airway and worsens the severity of OSA, avoidance of a supine position has been proposed.<sup>86</sup>

### Drug Treatment

There is yet no established medication for OSA, and a combination of noradrenergic and antimuscarinic drugs has been

suggested as potential pharmacological treatment.<sup>87</sup> In a recent RCT, it has been demonstrated that the combination of atomoxetine plus oxybutynin over one night improved the upper airway collapsibility, increased breathing stability, and reduced the arousal threshold.<sup>88</sup>

### Cardiovascular Mechanisms Linking Obstructive Sleep Apnea to Cardiovascular Diseases

The pathophysiological mechanisms linking OSA to CVD are complex and multifactorial. Frequent arousals from sleep, sleep fragmentation, and intermittent hypoxia lead to increase sympathetic activity (sympathetic overstimulation), increased platelet aggregability (hypercoagulation), endothelial dysfunction with reduced endogenous nitric oxide production, oxidative stress, vascular inflammation, and arterial stiffness, which all may cause atherosclerosis and development of CVD.<sup>25,89</sup> As illustrated in Figure 2, sympathetic overstimulation leads to tachycardia, an increase of afterload via peripheral vasoconstriction, elevations in blood pressure, oscillations in blood pressure (BP) and heart rate, systemic inflammation, and metabolic changes such as insulin resistance and atherogenic dyslipidemia. During obstructive apnea, large negative intrathoracic pressures are generated during inspiratory efforts, which increase transmural pressures across the myocardium,<sup>90</sup> and lead to an increase of left ventricular (LV) afterload. These changes increase the myocardial oxygen demand, leading to myocardial ischemia and hypertrophy. As illustrated in Figure 3, negative intrathoracic pressures, up to -60 mmHg, which are generated during obstructed inspiratory efforts produce transient decreases in left ventricular stroke volume.<sup>91,92</sup> However, a deviation of interventricular septum toward LV from the right ventricle (RV) may occur due to increased venous return to RV, which leads to a restriction in filling of LV. Increased preload and pulmonary congestion may also occur due to increased venous return.<sup>92</sup> The occurrence of intermittent hypoxemia in patients with OSA decreases oxygen delivery to the myocardium, which may promote angina and

arrhythmias. Chronic sympathetic activation may contribute to vascular remodeling via inflammation and/or release of catecholamines that induce vascular wall growth.<sup>93</sup> Systemic inflammation is a well-established feature of OSA, and the primary proatherogenic feature of OSA appears to be intermittent hypoxia.<sup>25,74,89</sup> In a large group of OSA patients without known CVD, nocturnal oxygen saturation levels were predictive of carotid artery thickening and plaque occurrence, independently of hypertension.<sup>94</sup> Several studies suggest that OSA promotes thrombosis due to enhanced platelet activation and aggregation, enhanced erythrocyte adhesiveness and aggregation, increased fibrinogen levels, and diminished fibrinolytic activity.<sup>95,96</sup> Inflammation triggers the secretion of enzymes that disrupt the balance between matrix metalloproteinases and their inhibitors,<sup>97</sup> and OSA-induced inflammatory chemokines and cytokines may lead to plaque rupture.

### Association between Obstructive Sleep Apnea and Cardiovascular Diseases

Cardiovascular diseases as well as the traditionally recognized risk factors for CVD are common in adults with OSA. Obesity, insulin resistance, diabetes mellitus (DM), and hyperlipidemia aggregate with OSA, which all, may have synergistic and/or additive effects on the development of CVD (hypertension, CAD, heart failure, AF, and stroke). Given the higher prevalence of OSA in CVD cohorts compared to that in the general population, CVD per se may also contribute to the development or worsening of OSA. Thus, the relationship between OSA and CVD may be bidirectional.

### Hypertension

Several cross-sectional and longitudinal studies in the general population have demonstrated an independent association between OSA and hypertension. It has been shown that untreated OSA is associated with an increased risk of prevalent hypertension up to 70% and incident hypertension in sleep clinic cohorts.<sup>98</sup> Similarly, more than 30% of

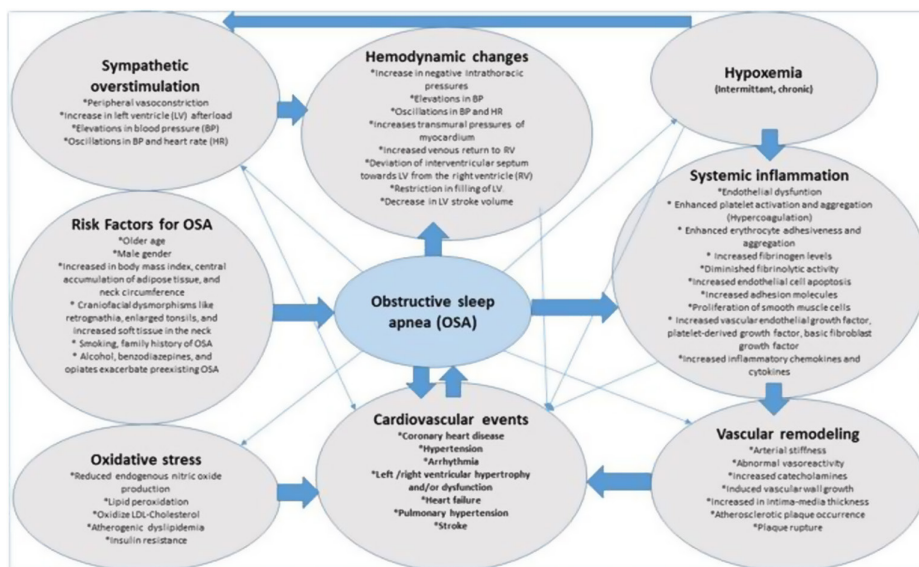
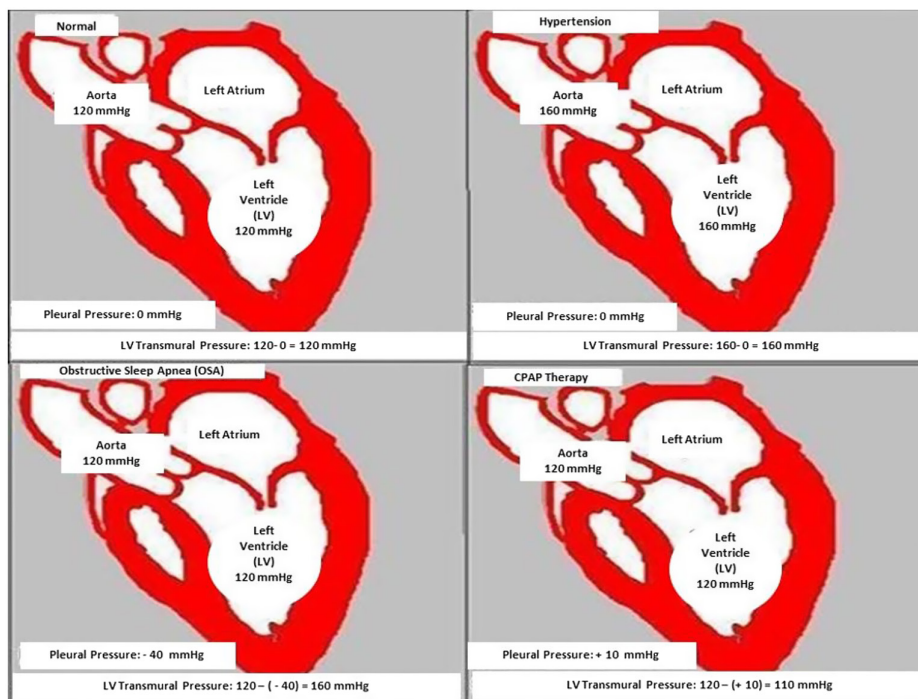


Figure 2. Relationships between obstructive sleep apnea and cardiovascular events.



**Figure 3.** During systole, LV transmural pressure rises to 160 mmHg from 120 mmHg due to an increase of intrapleural negative pressure like  $-40$  mmHg in OSA. This condition is equal to a high (e.g., 160 mmHg) blood pressure, aortic, and LV pressure such as in hypertension. The CPAP therapy decreases LV transmural pressure by increasing intrapleural pressure, like  $+10$  mmHg, in patients with OSA. CPAP, continuous positive airway pressure; LV, left ventricle; OSA, obstructive sleep apnea.

adults in hypertensive cohorts were reported to have mild to severe OSA,<sup>25,99</sup> and the prevalence is even higher among drug-resistant hypertensive patients.<sup>100</sup> A dose-response relationship has also been demonstrated between the severity of OSA and BP levels, especially at night-time and early in the morning.<sup>101</sup> A meta-analysis confirmed an independent association between OSA and incident hypertension,<sup>102</sup> and nondipping nocturnal BP has shown to be predictive of OSA, independent of OSA-related symptoms.<sup>103</sup> Moreover, REM-predominant OSA has been associated with incident nondipping BP.<sup>104</sup> Increased sympathetic system activity due to obstructive events has been suggested to be the principal pathogenic mechanism.<sup>105</sup> Several meta-analyses have demonstrated a positive effect of CPAP on systemic hypertension.<sup>107,108</sup> While the overall BP-lowering effect of CPAP is small at 2 mm Hg in 24 h average BP,<sup>109</sup> the effect is greater in younger individuals and those with severe oxygen desaturation or uncontrolled hypertension,<sup>110</sup> and in CPAP-adherent patients.<sup>111,112</sup> CPAP as an add-on treatment to antihypertensive medication has shown to be beneficial in newly diagnosed hypertensive patients with concomitant OSA.<sup>113</sup> Non-CPAP therapies of OSA have also been evaluated in patients with hypertension. In a meta-analysis of oral appliance therapies, BP reduction was 2-3 mm Hg, quite comparable to that reported in the meta-analysis of CPAP studies.<sup>114</sup> On the other hand, some evidence from animal and small human studies suggests that fluctuations in BP can influence upper airway tone, and the reduction in BP may reduce OSA severity.<sup>115</sup> Moreover, a meta-analysis of 11 studies suggests

that antihypertensive medications, especially diuretics, may reduce AHI.<sup>116</sup> In a randomized proof-of-concept study of 60 patients with drug-resistant hypertension, renal denervation significantly decreased BP at 3 and 6 months after the intervention with concomitant modest reductions in OSA severity.<sup>117</sup> Thus, the relationship between OSA and hypertension might be bidirectional.

### Coronary Artery Disease

Obstructive sleep apnea is highly prevalent (38%-65%) in patients with CAD,<sup>118</sup> particularly among those with nocturnal angina,<sup>119</sup> and efficient treatment of OSA has shown to be protective against the development of CAD in an early observational study of a sleep clinic cohort.<sup>120</sup> In another longitudinal study of males from a larger sleep clinic cohort, Marin et al<sup>13</sup> suggested that untreated severe OSA (AHI > 30/h) was an independent predictor of cardiovascular mortality, whereas OSA patients treated with CPAP showed a significantly lower nonfatal and fatal cardiovascular event incidence rates similar to those in the general population.<sup>13</sup> Other observational studies have also found beneficial effects of CPAP treatment in CAD patients with OSA.<sup>121,122</sup> However, the aforementioned RCTs RICCADSA, SAVE, and ISAACC trials failed to show the cardiovascular benefits of CPAP in intention-to-treat populations.<sup>18-20</sup> Several reasons have been proposed for the neutral results, including poor adherence to CPAP therapy in those trials and that they largely excluded individuals with excessive sleepiness.<sup>21</sup> Since excessively sleepy patients cannot be randomized to



no therapy due to ethical concerns, the need for alternative study designs has emerged.<sup>21,123,124</sup> A recent meta-analysis of the RCTs addressing adverse CV outcomes concluded that CPAP utilization to OSA patients was not associated with cardiovascular benefits except in the subgroup that used the device at least 4 h/night.<sup>125</sup> These results were supported by another post hoc meta-analysis of the cardiovascular RCTs.<sup>126</sup> In the literature, there is also some evidence demonstrating a high prevalence of OSA among patients with the acute coronary syndrome, which did not persist 6 months later,<sup>127</sup> indicating that the association between OSA and CAD might be bidirectional. More recently, Azarbarzin et al<sup>128</sup> have shown that the protective effect of CPAP in patients with CAD and OSA was modified by the delta heart rate response; particularly adults with higher delta heart rate response exhibit greater cardiovascular benefit from CPAP therapy. It has also been demonstrated that CVD benefits of efficient treatment of OSA with CPAP in patients with CAD are stronger among the patients with nonsleepy OSA phenotype.<sup>129</sup>

### Heart Failure

Epidemiological studies have suggested that OSA is associated with an increased risk of incident heart failure (HF),<sup>130</sup> and the risk increase was proportional to the severity of OSA. Concomitant OSA is associated with increased hospital readmissions and an increased rate of postdischarge mortality in patients with HF.<sup>131</sup> On the other hand, many individuals with HF and concomitant OSA do not report excessive sleepiness, and they may also have lower BMI, supporting the notion that HF may predispose to OSA.<sup>132</sup> Patients with HF have a lower stroke volume, promoting fluid retention, and nocturnal redistribution of fluid in the recumbent position to the parapharyngeal area has been suggested to increase upper airway resistance and collapsibility.<sup>133</sup> Thus, the relationship between OSA and HF seems to be bidirectional.<sup>134</sup> Given that HF can aggravate OSA by affecting the upper airways due to due to increased central venous pressure in a supine position, it should be ensured to reduce the preload and interstitial pressure in the lungs by optimally regulating the treatment of HF.<sup>135</sup> Medications including beta-blockers, renin-angiotensin-aldosterone system inhibitors, mineralocorticoid receptor antagonists, and sodium-glucose transport protein 2 inhibitors should be considered in patients with HF with reduced ejection fraction. In addition, diuretics that we use to relieve congestion can also reduce the severity of OSA by reducing fluid shifts and reducing congestion in the lungs and cervical region.<sup>136</sup> PAP therapy, which is the most important step in the treatment of OSA has been shown to improve LVEF with a decrease in systolic BP, heart rate, and LV-diastolic diameter in HF patients with LVEF <45%.<sup>137</sup> On the other hand, there are also studies showing that PAP treatment has no effect on LVEF and the need for hospitalization.<sup>77</sup> According to the 2017 American Heart Association/American College of Cardiology HF guideline, PAP therapy was recommended as a possibly reasonable treatment strategy (Class IIb) to improve sleep quality and daytime sleepiness in patients with CVD and OSA.<sup>138</sup>

## Arrhythmias

### Atrial fibrillation

Atrial fibrillation is the most common arrhythmia associated with OSA in population studies.<sup>139,140</sup> It has been suggested that OSA may trigger the onset of AF and may contribute to its persistence. Postoperative AF has also been reported among patients with OSA undergoing coronary artery bypass grafting surgery.<sup>141,142</sup> Meta-analyses have shown that OSA is associated with an increased risk of recurrent AF after successful catheter ablation, and CPAP treatment for AF patients with OSA might decrease the recurrent risks.<sup>143,144</sup> However, a recent RCT failed to show a protective effect.<sup>145</sup>

### Other Arrhythmias

Bradycardia is common in patients with OSA. It has been demonstrated that 58% of patients with implanted pacemakers for sick sinus syndrome had previously undiagnosed OSA.<sup>146</sup> Literature regarding the association of OSA with ventricular arrhythmias is relatively scarce and inconclusive.<sup>147</sup> However, an increased risk of sudden cardiac death has been reported in patients with severe OSA.<sup>148</sup>

### Pulmonary Hypertension

Pulmonary hypertension is uncommon and generally mild in OSA unless other conditions, such as COPD or daytime hypoventilation, coexist.<sup>149</sup> Obstructive sleep apnea alone is responsible for a small increase in pulmonary arterial pressure, whose clinical impact has yet not been demonstrated.<sup>150</sup> On the other hand, patients with pulmonary hypertension are at risk of developing both OSA and central apneas as well as a worsening of ventilation-perfusion mismatch and nocturnal hypoxemia, and OSA in patients with pulmonary hypertension should indicate the start of PAP treatment to avoid worsening of pulmonary hypertension.<sup>150</sup>

### Hyperlipidemia, Metabolic Syndrome, and Diabetes

Obstructive sleep apnea is associated with hyperlipidemia, but a recent meta-analysis has shown that CPAP treatment decreases total cholesterol at a small magnitude but has no effect on other markers of hyperlipidemia, suggesting that future CPAP studies in patients with OSA should target combined treatment strategies with lifestyle modifications and/or anti-hyperlipidemic medications in the primary as well as secondary cardiovascular prevention models.<sup>151</sup> Metabolic syndrome, which is a prediabetic state related to central obesity and increased cardiovascular risk, is also highly prevalent in adults with OSA.<sup>152</sup> The main feature of the metabolic syndrome is insulin resistance, and OSA has been shown to play an important role in the development of insulin resistance, mainly through intermittent hypoxia<sup>153</sup> and sleep fragmentation.<sup>154</sup> An observational study has demonstrated associations between OSA and insulin resistance that are independent of obesity.<sup>155</sup> However, CPAP treatment does not modify visceral fat or metabolic variables unless concurrent weight loss is achieved.<sup>156</sup>

Several cross-sectional cohort studies have demonstrated an independent association between OSA and type 2 DM<sup>157</sup> and a pooled estimate of relative risk for DM from 9 studies was 1.7 (95% CI 1.5-1.8).<sup>158</sup> Less is known regarding the

prospective studies of incident DM. One community-based 10-year follow-up study showed an adjusted OR of 4.4 (95% CI 1.1-18.0) for incident DM in middle-aged men with OSA compared to those without OSA, and there was an inverse relationship between AHI and insulin sensitivity index at follow-up.<sup>159</sup> Continuous positive airway pressure RCTs in diabetic patients with OSA have been inconclusive, some showing no benefit regarding diabetic control or insulin sensitivity, whereas some others reported benefit.<sup>158</sup> It has also been shown that untreated OSA in diabetic patients is related to increased risk of neuropathy,<sup>160</sup> diabetic retinopathy,<sup>161</sup> and diabetic nephropathy.<sup>162</sup> A meta-analysis has demonstrated that efficient treatment of OSA with CPAP may prevent severe consequences of diabetes.<sup>163</sup> On the other hand, there is also data suggesting that individuals with DM are at high-risk of developing OSA, mainly due to neuropathy affecting the upper airway muscles and disturbances in ventilatory control.<sup>134</sup> A retrospective primary care cohort study including over 1 million subjects demonstrated an adjusted incidence rate ratio of 1.48 (95% CI 1.42-1.55;  $P < .001$ ) for incident OSA in patients with DM compared with those without DM.<sup>164</sup> In another large longitudinal study of almost 300 000 healthcare professionals, OSA was an independent risk factor for incident DM, and conversely, insulin-dependent DM was an independent risk factor for OSA in women.<sup>165</sup> Taken together, there is evidence for a bidirectional association between OSA and DM, but evidence of benefit from CPAP is dependent on adherence to the CPAP treatment.<sup>144</sup>

## FUTURE PERSPECTIVES AND SUMMARY RECOMMENDATIONS

- Despite its high occurrence in patients with CVD and worse prognosis of cardiac patients with concomitant OSA, this condition is often underrecognized and undertreated in cardiovascular practice.
- Recent data indicates that AHI, which is commonly used as a diagnostic measure of OSA severity, is not the best prognostic measure for CVD outcomes.
- Novel markers of OSA-associated hypoxic burden and cardiac autonomic response seem to be strong predictors of adverse CV outcomes and response to treatment of OSA.
- Based on the current evidence about the association between OSA and CVD, we recommend screening for OSA, especially for patients with drug-resistant or poorly controlled or nondipping hypertension as well as recurrent AF after cardioversion or ablation.
- We also recommend OSA screening in patients with brady-tachy syndrome, those with ventricular tachycardia, and patients with appropriate shocks from implanted cardioverter-defibrillators as well as adults with CAD, particularly the ones with nocturnal angina and repeat revascularization.
- A full-night PSG is recommended, and when access to PSG is limited, HSATs should be used in CVD cohorts under the guidance and in collaboration with the respiratory and sleep physicians.
- Though the evidence level from the recent CPAP RCTs is weak mainly due to challenges in CPAP adherence,

all patients with CVD and OSA should be considered for treatment, including behavioral modifications and weight loss when obesity coexists.

- Continuous positive airway pressure should be offered to patients with CVD and moderate to severe OSA, and oral appliance therapy may be considered for patients with mild-to-moderate OSA or for patients not tolerating CPAP.
- As recently highlighted in a comprehensive review<sup>74</sup> as well as in a statement report from the American Heart Association,<sup>166</sup> the development of wearable devices and possibilities for remote monitoring technology is promising new opportunities for screening for OSA in high-risk individuals with CVD.
- National registries, such as the Turkish Sleep Apnea Database (TURKAPNE), a national, multicenter, observational, prospective cohort study (ClinicalTrials.gov: NCT02784977)<sup>167</sup> may provide collaborative research protocols in combination with similar registries including cardiac and metabolic disorders.
- Patients with OSA in sleep clinic cohorts may get benefit from early consultation with cardiologists to evaluate the CVD risk and possibly mitigate the severity of OSA.

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