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JACC STATE-OF-THE-ART REVIEW

Treatment of OSA and its Impact on Cardiovascular Disease, Part 2

JACC State-of-the-Art Review

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ABSTRACT

Many studies have shown an association of obstructive sleep apnea (OSA) with incident cardiovascular diseases, particularly when comorbid with insomnia, excessive sleepiness, obesity hypoventilation syndrome, and chronic obstructive pulmonary disease. Randomized controlled trials (RCTs) have demonstrated that treatment of OSA with positive airway pressure devices (CPAP) improves systemic hypertension, particularly in those with resistant hypertension who are adherent to CPAP. However, large RCTs have not shown long-term benefits of CPAP on hard cardiovascular outcomes, but post hoc analyses of these RCTs have demonstrated improved hard outcomes in those who use CPAP adequately. In theory, low CPAP adherence and patient selection may have contributed to neutral results in intention-to-treat analyses. Only by further research into clinical, translational, and basic underlying mechanisms is major progress likely to continue. This review highlights the various treatment approaches for sleep disorders, particularly OSA comorbid with various other disorders, the potential reasons for null results of RCTs treating OSA with CPAP, and suggested approaches for future trials. (JACC. 2024;84:1224–1240) © 2024 by the American College of Cardiology Foundation.

In part 1 of the State-of-the-Art Review, we reviewed various sleep disorders including insomnia and obstructive sleep apnea (OSA) and associated cerebrocardiovascular diseases. In part 2, we focus on current therapeutic options for sleep disorders including insomnia, OSA comorbid with insomnia (COMISA), with morbid obesity (obesity hypoventilation syndrome [OHS]), and OSA with chronic obstructive pulmonary disease (overlap syndrome), and their impact on incident cardiovascular disease (CVD).

TREATMENT OF CHRONIC INSOMNIA AND INCIDENT CVD

Multiple studies have suggested that chronic insomnia is often associated with increased sympathetic activity, up-regulation of the inflammatory

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HIGHLIGHTS

- Chronic insomnia is a common disorder and could lead to CVD and neurocognitive dysfunction.
- Limited number of studies suggest that treatment of insomnia, with or without comorbid OSA, could improve sleep and potential CV outcomes. Large RCTs are needed.
- OSA plays a major role causing or contributing to the progression of CVD.
- Post hoc analyses of RCTs treating OSA with CPAP show that adequate CPAP users benefit from a reduction in incident CVD.
- The field is in need of large RCTs with CPAP and other devices with hard CV endpoints.

cascade, and incident CVD (see part 1). Further, extension of wakefulness is associated with activation of the elevated orexin pathway neurohormones,[1] which are known to also promote sympathetic hyperactivity. It is therefore plausible that treatment of insomnia with short sleep duration by improving sleep quality could lead to improved CV outcomes. It is plausible that treatment of insomnia by improving sleep quantity could lead to improved CV outcomes.

There are limited randomized controlled trials (RCTs) evaluating the impact of insomnia treatment on CVD outcomes. Cognitive behavioral therapy for insomnia (CBTi) is considered first-line therapy. Two pilot studies have been performed. The first study[2] randomized 29 patients with insomnia to CBTi or sleep hygiene and found a clinically, but not statistically, significant reduction in insomnia severity. Additionally, there was a 3 mm Hg reduction in systolic blood pressure (BP) in the treatment arm compared with a 0.5-mm Hg increase in the control arm ($P = 0.5$, Cohen's D = 0.22). There was a small reduction (1.1 mm Hg) in diastolic BP in the treatment arm compared with an increase of 0.8 mm Hg in the control arm ($P = 0.4$, Cohen's D = 025).

Another randomized study[3] enrolling 23 heart failure (HF) patients found clinically significant improvement in insomnia symptoms, quality of life, and mood in the CBTi group compared with the control group. Long-term studies are needed to determine whether treatment of insomnia could improve CV function in HF.

Although CBTi is the recommended first-line treatment of insomnia, pharmacologic agents are often used in clinical practice. Benzodiazepine receptor agonists have been commonly used to treat insomnia. These medications exert their effects on gamma amino butyric acid (GABA), a widely distributed inhibitory neurotransmitter in the brain that promotes sleep. In 1 RCT with a benzodiazepine,[4] 402 patients with insomnia and hypertension were randomized to either estazolam (n = 202) or placebo (n = 200) for 4 weeks. The reductions in systolic and diastolic BP were significantly greater in the active arm compared with the control arm: 10.5 mm Hg vs 2.5 mm Hg and 8.1 mm Hg vs 2.7 mm Hg, respectively ($P < 0.001$).

Although chronic insomnia can occur in isolation, when associated with OSA (COMISA),[5] it conveys a poorer prognosis compared with either condition alone.[6] At least 3 RCTs have used CBTi in patients with COMISA. In 1 of these RCTs, 145 patients with COMISA (untreated moderate-to-severe OSA, Apnea-Hypopnea Index [AHI] ≥15 events/h of sleep) were randomized to CBTi or to a no-treatment control group. Overnight sleep studies were completed pretreatment and posttreatment. With CBTi, there was a 7.5 event/h greater AHI difference (mean decrease 5.5 events/h [95% CI: 1.3-9.7 events/h) compared with the control arm (mean increase 2.0 events/h [95% CI: −2.0 to 6.1 events/h]). The CBTi group also had a greater reduction in total number ($P = 0.029$) and duration ($P = 0.031$) of awakenings. This study suggests that insomnia disorder may exacerbate OSA, providing support for treating insomnia in the presence of OSA. Several other RCTs [6-9] have assessed the combination of CBTi and positive airway pressure (PAP), and found that concurrent CBTi and PAP use is superior to PAP alone on insomnia outcomes, which in the long run may improve CV outcomes, particularly if CBTi improves PAP adherence.

Regarding benzodiazepines used commonly to treat insomnia, there are concerns for the potential to compromise breathing, particularly in those with moderate-to-severe OSA.[10] More recently, dual-orexin receptor antagonists (DORAs) have been

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
AHI = Apnea-Hypopnea Index
ASV = adaptive servoventilation
BMI = body mass index
BP = blood pressure
CAD = coronary artery disease
CBTi = cognitive behavioral therapy for insomnia
CHF = congestive heart failure
COMISA = obstructive sleep apnea comorbid with insomnia
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
CV = cardiovascular
CVD = cardiovascular disease
DORA = dual-orexin receptor antagonist
FDA = U.S. Food and Drug Administration
HF = heart failure
HFrEF = heart failure with reduced ejection fraction
HNS = hypoglossal nerve stimulation
LG = loop gain
MAD = mandibular advancement device
NIV = noninvasive ventilation
OHS = obesity hypoventilation syndrome
OSA = obstructive sleep apnea
PAH = pulmonary arterial hypertension
PAP = positive airway pressure
PH = pulmonary hypertension
RCT = randomized controlled trial
RV = right ventricular
RYGB = Roux-en-Y gastric bypass
UC = usual care

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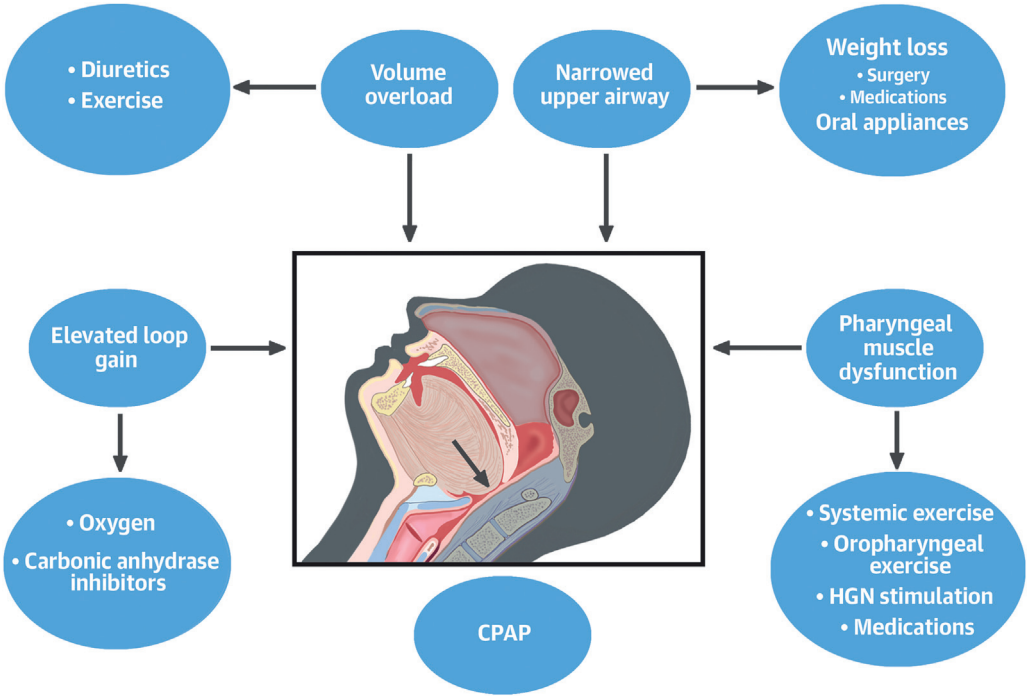
CENTRAL ILLUSTRATION **Phenotypic Therapeutic Options in Obstructive Sleep Apnea**



Javaheri S, et al. JACC. 2024;84(13):1224–1240.

The figure depicts various mechanisms which could be target of therapy in obstructive sleep apnea. Although continuous positive airway pressure (CPAP) device is the most effective therapeutic option, other variables could also be targeted as depicted. HGN = hypoglossal nerve.

approved for treatment of chronic insomnia. These medications exert sleep promotion by antagonizing wake-promoting endogenous orexin neuropeptides at orexin receptors and should not cause respiratory depression.[11-14] The impact of DORAs on CV outcomes in people with insomnia or with COMISA is unclear but worthy of future investigation.

TREATMENT OF OSA AND INCIDENT CVD

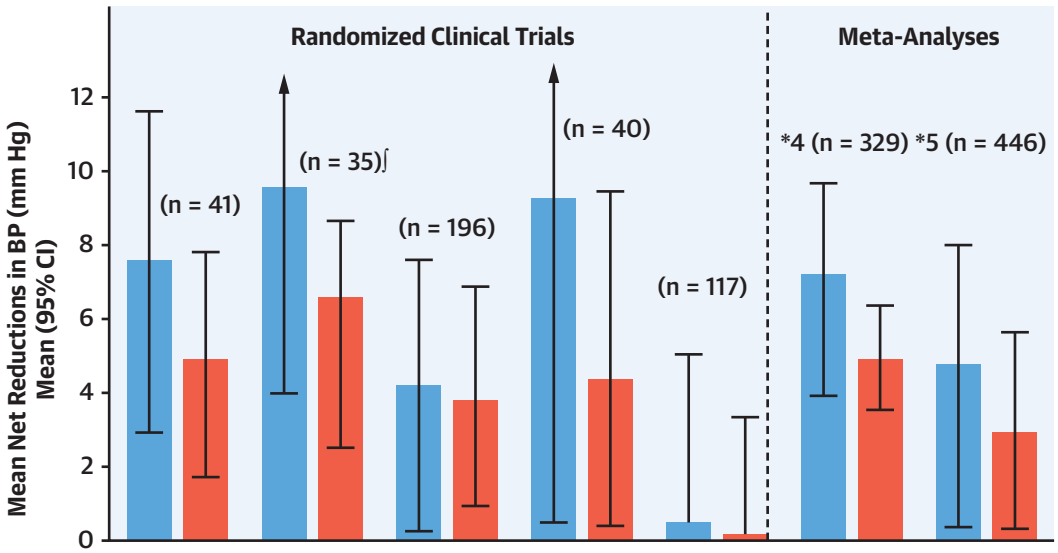
While asleep, the final common pathway causing an obstructive apnea or hypopnea is relaxation of the genioglossus muscle, with the tongue falling backward and closing (apnea) or narrowing (hypopnea) the pharyngeal airway. Nonetheless, multiple other factors can cause or contribute to OSA pathogenesis, and these phenotypes/endotypes are depicted in the **Central Illustration** and discussed in the following text.

POSITIVE AIRWAY PRESSURE. PAP devices are the mainstay of therapy for OSA. These devices increase intrapharyngeal pressure, widening the pharyngeal airway in a dose-dependent manner, thereby preventing upper airway occlusion. In the following text, we discuss RCTs for treatment of OSA with a continuous positive airway pressure (CPAP) device on 5 OSA-specific CV consequences: 1) systemic hypertension; 2) pulmonary hypertension; 3) HF; 4) OHS; and 5) overlap syndrome.

Impact of treatment of OSA with CPAP on systemic hypertension. Hypertension is highly prevalent and is the leading risk factor causing incident CVD such as stroke, HF, and premature death.[15] Many studies, reviewed in part 1, have shown OSA contributing to hypertension and resistant hypertension.

Multiple RCTs with 24-hour ambulatory BP monitoring have shown a modest effect of use of CPAP on reducing BP, equivalent to 2.5 mm Hg in 24-hour systolic and diastolic BP.[16] By contrast, the effect of CPAP in reducing BP is more pronounced in resistant hypertension (**Figure 1**). In these patients, RCTs show significant reduction in systolic BP ranging between 4.7 to 7.2 mm Hg and diastolic BP ranging from 2.9 to

FIGURE 1 Effect of CPAP Therapy on BP in Patients With Resistant Hypertension



	Lozano (2010)	Pedrosa (2013)	Martinez-Garcia (2014)	De Oliveira (2014)	Muxfeldt (2015)	Iftikhar (2014)	Liu (2015)
24 h-SBP	7.6	9.6	4.2	9.3	0.5	7.21	4.78
24 h-DBP	4.9	6.6	3.8	4.4	0.2	4.99	2.95

The figure includes the results of the randomized controlled trials published to date. Positive figures mean improvement in blood pressure (BP) level with continuous positive airway pressure (CPAP) treatment (net changes). From Javaheri et al.[17] DBP = diastolic blood pressure; SBP = systolic blood pressure.

4.9 mm Hg, with large SDs (**Figure 1**).[16] This large scatter implies that some patients may benefit with a large drop in BP, whereas others may have more modest reduction. The reasons for the differing responses have been discussed previously.[16] In general, those who respond the most to CPAP experience more severe OSA, have higher baseline BP, and have higher adherence to CPAP.[16,17] The drop in BP is dose-dependent, that is, there is a greater BP drop with increasing CPAP usage.

Impact of treatment of OSA with CPAP on pulmonary hypertension. OSA and PH could coexist together. OSA could be a cause of pulmonary hypertension (PH), and pulmonary arterial hypertension (PAH) could be comorbid with OSA. As discussed in part 1, OSA can be a cause of mild PH, though PH can be severe if OSA is comorbid with other disorders such as OHS. In 1 small (n = 23) crossover RCT[18] comparing CPAP to sham CPAP, 12 weeks of CPAP therapy led to a 5 mm Hg mean pulmonary arterial pressure decrease ($P < 0.0001$). A second RCT[19] enrolled subjects with OHS, the Pickwick trial discussed in part 1. The results of this study, discussed in the following text under "OHS," also showed significant improvement in PH with PAP therapy.

In regard to PAH, it has been shown to be associated with nocturnal hypoxemia and sleep apnea. In a prospective study, Lowery et al[19] examined the relationships between sleep-related hypoxemia and AHI with cardiac function and survival. Time below saturation of 90% was associated with right ventricular (RV) systolic pressure, RV ejection fraction, mean PAP, RV hypertrophy on electrocardiography, and transplant-free survival. It remains to be determined whether nocturnal supplemental oxygen therapy could improve survival of patients with PAH.

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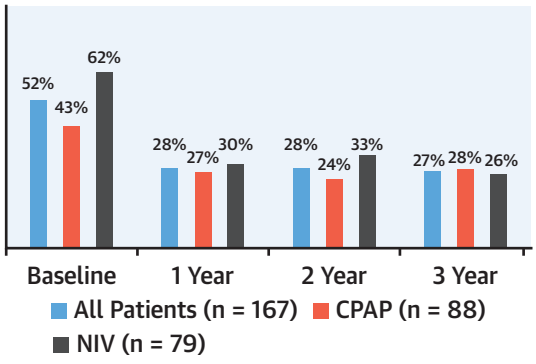
FIGURE 2 Prevalence and Evolution of PH in the Pickwick Trial



This figure shows a significant drop in the prevalence of pulmonary hypertension (PH), which was sustained through the 3-year follow-up. Adapted from Masa et al[19] and Mokhlesi et al.[31] CPAP = continuous positive airway pressure; NIV = noninvasive ventilation.

Impact of treatment of OSA with PAP devices on HF. Studies have used CPAP and adaptive servo-ventilation (ASV) to treat OSA in patients with HF. An early large observational study of Medicare beneficiaries showed that treatment of OSA with CPAP was independently associated with decreased hospital readmission, health care cost, and mortality.[20] Small RCTs in patients with heart failure with reduced ejection fraction (HFrEF) have shown that CPAP treatment has beneficial cardiac effects, decreasing awake sympathetic activity,[21] myocardial sympathetic nerve function and energetics in the case of severe OSA, and increases in left ventricular ejection fraction by about 5% after 1 month of treatment.[22] This latter finding has not been confirmed by another study.[23]

The results of the ADVENT-HF (Effect of Adaptive Servo Ventilation [ASV] on Survival and Hospital Admissions in Heart Failure) trial, an open RCT using ASV vs usual care (UC), has been published recently.[24] Overall, 731 patients with HFrEF comorbid with severe OSA or CSA were randomly assigned to ASV or UC (n = 375). Patients enrolled were primarily nonsleepy, and more had OSA than CSA. Compared with UC, the use of ASV did not lead to a significant benefit in primary (the cumulative incidence of the composite of all-cause mortality, first admission to hospital for a CV reason, new-onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock) or secondary (all-cause mortality) endpoints.

Notably, however, both the quality of sleep and the quality of life improved significantly with ASV, findings that will require corroboration in subsequent controlled studies. We should note that design of the ADVENT-HF trial was different from the SERVE-HF (Treatment of Predominant Central Sleep Apnoea by Adaptive Servo Ventilation in Patients With Heart Failure) trial[25] in which patients with predominantly OSA were excluded.

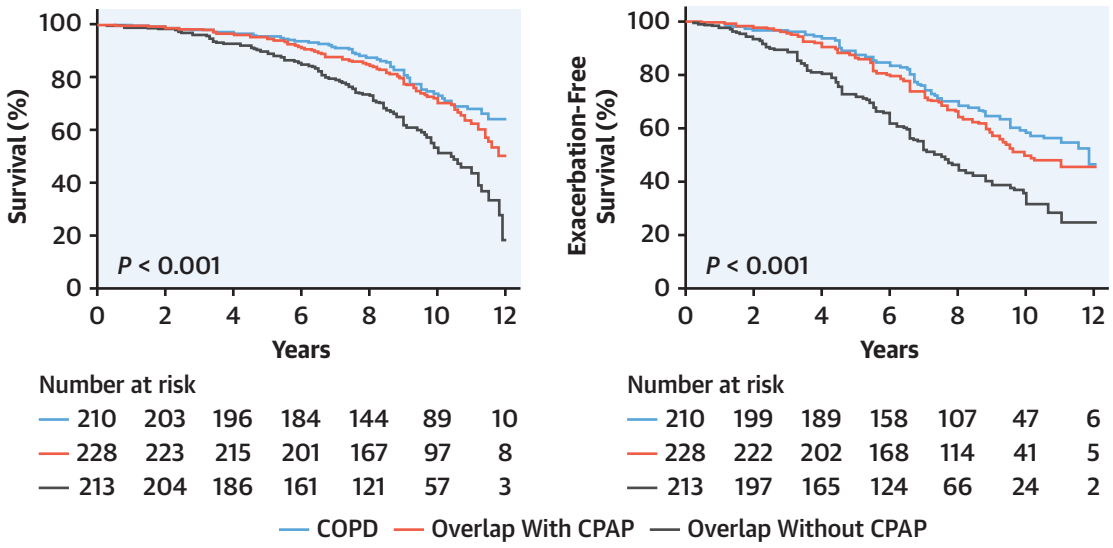
Both CPAP and ASV have been used in patients with heart failure with preserved ejection fraction (HFpEF) comorbid with OSA. One study was performed with CPAP in stable ambulatory patients discussed in the preceding text, showing significant improvement in pulmonary artery pressure.[18] Additionally, compared with sham CPAP, treatment with CPAP resulted in significant increases in the E/A ratio ($P < 0.01$) and reductions in mitral deceleration ($P < 0.01$) and isovolumic relaxation ($P < 0.05$) times.[26]

The study with ASV[27] was executed in hospitalized patients with moderate-to-severe sleep apnea, comorbid with predominantly OSA or CSA. It showed potential beneficial effects of ASV in acute congestive heart failure (CHF) patients, particularly those with HFpEF. This study was terminated prematurely due to safety concerns from a chronic CHF study; thus, additional studies are required regarding ASV in acute CHF.

Recent real-world evidence studies suggest that adherence to PAP therapy is associated with a reduction in health care resource utilization, emergency room visits, and hospitalizations in patients with OSA and HFpEF, as well as HFrEF.[28,29]

Impact of treatment of OSA with CPAP on OHS. In the Pickwick trial discussed in part 1, patients with OHS and severe OSA who had echocardiographic evidence of PH at baseline (defined as pulmonary artery systolic pressure ≥40 mm Hg) were randomized to CPAP or noninvasive ventilation (NIV) for 3 years.[30] The NIV device provides ventilation in an attempt to lower $PaCO_2$, this in contrast to CPAP. In 52% of participants who had echocardiographic evidence of PH at baseline, both CPAP and NIV were equally effective in decreasing pulmonary artery systolic pressure (by approximately 8 to 10 mm Hg) and improving left ventricular diastolic dysfunction. The prevalence of PH also decreased (Figure 2). During the follow-up, both CPAP and NIV led to significant improvements in daytime PaO_2 and $PaCO_2$, forced expiratory volume over 1 second (FEV_1), forced vital capacity (FVC), daytime sleepiness, dyspnea, quality of life, and BP. Based on these data, the

FIGURE 3 CPAP Treatment of OSA in the Overlap Syndrome Improves Survival



Long-term outcome study showing that patients with overlap syndrome and moderate or severe obstructive sleep apnea (OSA) treated with continuous positive airway pressure (CPAP) have similar survival rates to those with chronic obstructive pulmonary disease (COPD) alone, whereas those patients with overlap syndrome (COPD with OSA) not treated with CPAP had higher mortality, especially from cardiovascular disease. Adapted with permission of the American Thoracic Society.[34]

American Thoracic Society guidelines recommend CPAP as the initial treatment of stable ambulatory adult patients with OHS and concurrent severe OSA (AHI ≥30 events/h) presenting with chronic stable respiratory failure.[31] Because more than 70% of patients with OHS have severe OSA, this recommendation is applicable to most OHS patients.[30] The impact of weight loss on OHS[32] will be discussed later.

Impact of treatment of OSA with CPAP on overlap syndrome. Effect of CPAP and NIV have been reviewed elsewhere.[33-36] A retrospective observational study found a clinically significant reduction in health care utilization and costs in patients with chronic obstructive pulmonary disease (COPD)-OSA overlap syndrome who were adherent vs nonadherent with CPAP therapy.[33,34] Long-term outcome studies have reported that patients with moderate or severe OSA treated with CPAP had similar survival rates to those with COPD alone, whereas those patients with overlap syndrome not treated with CPAP had higher mortality, especially from CVD (**Figure 3**), and were more likely to experience a severe COPD exacerbation leading to hospitalization.[33]

Interim summary: CPAP is the most efficacious treatment of OSA when tolerated, but when long-term adherence is low, other therapeutic options depicted in the **Central Illustration** should be considered.

THERAPEUTIC OPTIONS ADDRESSING NARROWED UPPER AIRWAY. As depicted in the **Central Illustration**, weight loss and mandibular devices could expand the pharyngeal space and prevent upper airway closure. In the following text, we discuss these options and their impact on OSA and CVD.

Mandibular advancement devices. These devices protrude the mandible thereby opening the pharyngeal airway and reducing airway collapsibility. A mandibular advancement device (MAD) is best used in individuals in whom OSA is due primarily to anatomically narrowed upper airway (**Central Illustration**).[36,37]

Currently, MADs are the main alternative to CPAP, particularly for patients who are intolerant of or refuse CPAP. The most recent American Academy of Sleep Medicine update suggests the role of MAD across the range of OSA severity.[38] A recent meta-analysis of subjects with severe OSA consisting of 3 crossover RCTs and 1 parallel-group RCT pooling data from 151 patients (125 in the CPAP treatment arm and 124 in the MAD treatment arm) concluded that titratable MAD had a similar impact to CPAP on major patient-centered outcomes (sleepiness and quality of life). The treatment adherence and preference were largely in favor of MAD, though CPAP was more efficacious in reducing AHI and oxygen desaturation index.[39] Another meta-analysis including 51 studies and

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4,888 patients reported that both CPAP and MADs were associated with reductions in BP, without any differences between these 2 therapies in terms of BP outcomes.[40] In terms of CV effects, a systematic review of MAD consisting of 16 studies, including 11 RCTs, reported significant reductions in daytime systolic and diastolic BP compared with baseline.[41]

From a phenotypic approach, MAD should be most effective in those in whom the underlying mechanism of upper airway collapse is due to altered anatomical structure with a narrow upper airway.[36] In the aforementioned studies, there was no phenotypic preselection. Hence, there is a need for studies exploring the impact of MAD treatment on CV outcomes in this subgroup.[42]

Weight loss. Obesity affects approximately 42% of U.S. adults and is associated with increased rates of OSA and other comorbidities including hypertension, CVD, type 2 diabetes, and premature death.[43] Obesity is associated with fat deposition in the tongue[44] and within the throat, narrowing the pharyngeal space and facilitating upper airway closure during sleep when the genioglossus muscle relaxes and the togue falls backward (**Central Illustration**). With weight loss, one loses upper body fat, including tongue, throat, and visceral fat, collectively improving OSA. In addition, weight loss provides an incremental reduction in insulin resistance, serum triglyceride levels, and BP (particularly when combined with CPAP).[45]

Both bariatric surgery and antiobesity medications are commonly recommended for weight loss. Among the various bariatric interventions, Roux-en-Y gastric bypass (RYGB) is among the most effective.[46] One long-term RCT[47] comparing UC with RYGB showed that 3 years later, body mass index (BMI) increased with UC (1.7 kg/m^2), whereas it decreased significantly (11 kg/m^2) in the RYGB group. Consistent with changes in BMI, AHI increased by 5 events/h in the UC group who gained weight, whereas AHI decreased by 13 events/h with weight loss.

In a prospective study[48] that included 150 patients undergoing laparoscopic RYGB, 111 patients (73%) had OSA diagnosed by home sleep apnea test with respiratory polygraphy. After 5 years, weight decreased from 130 kg to 101 kg and AHI from 29 to 9 events/h of recording. There was a significant correlation between weight loss and reduction in AHI. Similarly, oxygen desaturation and heart rate decreased, and quality of life improved significantly. Of note, moderate or severe OSA persisted in 14 patients (20%).

A recent study[49] using registry-based nationwide data in Sweden followed patients with sleeve gastrectomy or RYGB with OSA (n = 5,892) and 11,552 matched patients without OSA for a median of 6.8 years. Remission of OSA (defined as discontinuation of CPAP) was seen for 4,334 patients (74%). Patients in remission had a lower risk for overall mortality (cumulative incidence 6.0% vs 9.1%; $P < 0.001$) and major adverse cardiac events (cumulative incidence 3.4% vs 5.8%; $P < 0.001$) at 10 years after operation compared with those who did not reach remission. The risk was similar to that of the control group without OSA at baseline.

Most recently, weight loss medications have become of major interest,[50-63] receiving considerable media coverage and widespread use. Given their success in promoting weight loss, they are also effective at treating OSA.[50,51]

Glucagon-like peptide-1 (GLP-1) (such as liraglutide and semaglutide), and glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 receptor agonist (tirzepatide) have been approved by the U.S. Food and Drug Administration (FDA) and have been used for treatment of obesity with or without diabetes mellitus type 2. GIP and GLP-1 are incretin hormones that are released in the intestine in response to nutrient intake and stimulate pancreatic beta cell activity, secreting insulin while delaying gastric emptying to reduce food intake.[50,51] They have been approved by the FDA for long-term use in conjunction with lifestyle changes.

Multiple RCTs have shown that incretin-based therapy can promote weight loss and lower hemoglobin A_{1c}.[52-54]

In an RCT enrolling 1,961 adults, the mean change in body weight from baseline to week 68 was −15% (equivalent to 15 kg) with semaglutide once weekly at a dose of 2.4 mg, compared with −2.4% with placebo ($P < 0.001$).[53]

Two incretin-based therapy studies have been reported in patients with OSA. The SCALE Sleep Apnea (Effect of Liraglutide in Obese Subjects With Moderate or Severe Obstructive Sleep Apnoea) trial evaluated liraglutide intervention vs placebo over 32 weeks in moderate-to-severe OSA subjects and reported a small, but statistically significant, improvement in AHI, systolic BP, and HbA_{1c}.[55] The largest and most systematic study has been reported with tirzepatide. Tirzepatide was first approved for type 2 diabetes treatment under the name Mounjaro (Eli Lilly). According to the results of the 72-week SURMOUNT-1 (A Study of Tirzepatide [LY3298176] in Participants With Obesity or Overweight) phase 3 randomized clinical trial, tirzepatide 15 mg weekly led to a 22-kg weight loss after 72 weeks.[54] Most recently, tirzepatide has been approved by the FDA under the trade name of Zepbound[56] (Eli Lilly), and the results for

SURMOUNT-OSA (Obstructive Sleep Apnea Master Protocol GPIF: A Study of Tirzepatide [LY3298176] in Participants With Obstructive Sleep Apnea)[57] were recently published. The investigators conducted 2 randomized trials for OSA patients with obesity: study 1 included patients not using CPAP and study 2 included patients using CPAP. In both study arms, tirzepatide vs placebo led to improvement in the AHI. Investigators observed improvement in secondary outcomes that were prespecified and controlled for multiple comparisons, including: improved systolic BP, improved C-reactive protein levels, improved hypoxic burden, and improved patient-reported outcomes.

The findings of incretin trials have important implications for CVD and OHS.[58-62] In an RCT enrolling 17,604 patients, 8,803 received semaglutide, and 8,801 placebo.[58] The mean duration of exposure to semaglutide or placebo was 34 months. The primary CV endpoint event (a composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke in a time-to-first-event analysis) occurred in 6.5% of the patients on semaglutide compared with 8.0% in the placebo group, a 20% reduction (HR: 0.80; 95% CI: 0.72-0.90; $P < 0.001$). On average, semaglutide treatment resulted in a 9.4% reduction in body weight. In this trial, polysomnography was not performed; thus, it remains unclear to what degree the trial findings were dependent on weight loss, perhaps improving concomitant OSA. Notably, adverse events leading to discontinuation of the trial product occurred in 17% in patents on semaglutide group and 8% with placebo ($P < 0.001$), mostly gastrointestinal side effects.

The most advantageous consequences of therapeutic weight loss occur in the most obese individuals such as those with OHS. In such individuals, weight loss can potentially lead to reversal of hypoventilation and improvement in oxygenation. It has been shown that excess weight is associated with excessive CO_2[61] production contributing to hypercapnia. This has an important clinical implication, suggesting that weight loss by itself could potentially eliminate hypercapnia in OHS.[60]

Last, but not least, weight loss also improves the burden of atrial fibrillation (AF), which may be in part related to improvement in OSA severity.[61,62] In a trial designed to examine the effect of weight reduction vs general lifestyle advice on AF outcomes (n = 150), both arms also received intensive management of CV risk factors, which included OSA diagnosis and management. A reduction in AF burden (defined by cumulative duration and number of episodes) and improvement in AF symptom severity scores concordant with weight reduction was observed. Moreover, weight loss was experienced in both intervention and control groups, and both groups also had improvement in cardiac structure, that is, reduction in interventricular septal thickness and left atrial area.

THERAPEUTIC OPTIONS ADDRESSING VOLUME OVERLOAD. Upper airway edema might contribute to pharyngeal collapsibility, further facilitating upper airway closure. Multiple studies from the Toronto group have shown that in the supine position, there is rostral translocation of fluid from lower extremities resulting in vascular congestion and narrowing of the pharyngeal space, promoting upper airway narrowing.[64-68] Individuals with OSA and obesity frequently have lower extremity edema, particularly if comorbid with HF. Diuretic therapy has been shown to increase the pharyngeal space and improve OSA.[67] In a 2-arm (17 patients in each arm) RCT[68] in patients with coronary artery disease (CAD), after 4 weeks of aerobic exercise, compared with the control group, measurement of leg, neck, and thoracic fluid volumes and upper-airway cross-sectional area improved significantly with exercise. In conjunction with these changes, polysomnography revealed reduction in AHI from 31 to 21 events/h in the exercise group ($P = 0.04$); AHI did not change in the control group. Exercise may also improve OSA by strengthening the tongue muscle and ventilatory control as discussed in related sections.

THERAPEUTIC OPTIONS TO IMPROVE PHARYNGEAL MUSCLE DYSFUNCTION. With removal of the wakefulness drive to breathe, sleep onset reduces dilatory muscle activity, promoting upper airway collapse. This compromise during sleep may account for development of OSA in about 30% of patients.[69] Therefore, targeting stimulation of the genioglossus muscle should be effective in this subgroup of patients; to this end, hypoglossal nerve stimulation (HNS), exercise, and medications have been studied and have shown efficacy (**Central Illustration**).

HNS to improve muscle dysfunction. The FDA has approved HNS for treatment of OSA for CPAP-intolerant individuals with at least moderate OSA (AHI ≥15 events/h). HNS relies on electrical stimulation of the hypoglossal nerve, which innervates the upper airway dilator muscles including the genioglossus muscle.[70,71] However, there are responders and nonresponders, presumably, the former group with predominantly muscle dysfunction causing OSA. So far, no systematic studies have been performed to determine the impact of HNS intervention on CVD outcomes, and a large RCT is needed. Physiologically,

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individuals with impaired genioglossus muscle function determined at baseline may be most amenable to HNS intervention.

Exercise to improve muscle dysfunction. Exercise has beneficial effects on OSA.[72,73] Aside from reducing lower extremity edema, both systemic and oropharyngeal exercises have been shown to improve snoring and severity of OSA, presumably by strengthening the tongue.[74] In an observational study, playing the didgeridoo, an Australian Aboriginal wind instrument in the form of a long wooden tube, improved OSA.[75] This result was followed by RCTs in the general population, in those with HF or CAD. There are 3 RCTs, 1 in patients with CAD discussed in the preceding text[68] and 2 in patients with HF.[75,76] In a 4-arm, parallel design RCT[75] compared with the control and CPAP arms, only aerobic exercise was associated with significant collective improvement in subjective daytime sleepiness, quality of life (Minnesota Living with Heart Failure Questionnaire and Short Form [36] Health Survey), and NYHA functional class ($P < 0.05$), even though CPAP was most effective in reducing in AHI.

There are also 2 meta-analyses, 1 with oropharyngeal and 1 with systemic exercise, confirming the results of the aforementioned RCTs. In the first meta-analysis[77] involving 120 adults, selective oropharyngeal exercises reduced snoring and AHI by 50% (25 to 12 events/h of sleep). Similar results were observed with systemic exercise.[78]

Based on the aforementioned studies, in the management of patients with OSA, exercise should routinely be recommended, when applicable. Further, exercise could be a therapeutic option for OSA patients with CVD who refuse CPAP or are intolerant to it. The beneficial effects of exercise are multifactorial and could also be related to decreased rostral fluid redistribution increasing pharyngeal air space discussed earlier in the text, weight loss (if it occurs), and improvement in ventilatory control if up-regulated.[78]

Medications to improve muscle dysfunction. Multiple medications[79-83] have been studied in search of discovering a pharmacological therapy that would be appealing from the patient's point of view. To date, a noradrenergic agent, atomoxetine, combined with an antimuscarinic agent (oxybutynin), has been the most extensively studied. This combination is based on the premise that noradrenergic activity is reduced with sleep onset leading to reduced pharyngeal muscle firing and withdrawal of excitatory amines, an inhibitory muscarinic pathway occurring during REM sleep. In OSA patients, the combination increases genioglossus muscle by 3-fold while asleep.[80] In a recent RCT incorporating 209 patients with OSA, the combination of atomoxetine with oxybutynin[81] was quite effective in improving OSA (AHI improvement of 6 events/h in the intention-to-treat analyses). However, there was a small rise in diastolic BP. Two phase III, multisite, RCTs (Parallel Arm Trial of AD109 and Placebo With Patients With OSA [LunAIRo], NCT05811247; Parallel-Arm Study to Compare AD109 to Placebo With Patients With OSA [SynAIRgy Study], NCT05813275) in which patients are randomized to the combination therapy or placebo over 6 to 12 months are ongoing. In a subset, 24-hour ambulatory blood pressure will be monitored to determine any potential beneficial effect.

THERAPEUTIC OPTIONS ADDRESSING ELEVATED LOOP GAIN. Loop gain (LG) is an engineering term that defines the gain of the negative feedback loop and regulates ventilation in response to a ventilatory disturbance (**Central Illustration**).[84,85] In the context of OSA, and consequent on a reduction in ventilation, if the magnitude of the compensatory increase in ventilation is greater than the magnitude of the preceding apnea or hypopnea, then the system is highly unstable and will fluctuate between under- and overventilation, promoting both OSA[85] and central sleep apnea.[86] This situation of overshoots and undershoots is characteristic of a high LG, and down-regulating these oscillations (ie, lowering gain) should improve OSA. Pharmacologically, carbonic anhydrase inhibitors[79,87-92] and nocturnal supplemental oxygen[93] have been used in OSA trials to lower LG.

Breathing supplemental oxygen decreases the hypoxic and hypercapnic ventilatory response, down-regulating an elevated chemical LG mediated by the chemoreceptors. Given that OSA-related hypoxemic burden is a main determinant of incident CVD, it is expected that treatment of OSA with oxygen could down-regulate a high LG and improve OSA-related CV outcomes. However, in 1 RCT of 3 months' duration, Gottlieb et al[93] randomized patients with OSA to either nocturnal supplemental oxygen or CPAP. At 3 months, compared with CPAP, oxygen was ineffective in lowering the BP, but these patients had mild nocturnal desaturation, and only severe OSA is associated with excess CV mortality. Of note, the patients with high LG had the greatest reduction in BP in a recent post hoc analysis.[92]

Both short- and long-acting acetazolamide improve LG and have been shown to improve OSA.[79,87-92] In a cross-over RCT comparing CPAP, acetazolamide, and CPAP plus acetazolamide, contrary to CPAP, acetazolamide induced a significant reduction of systolic

BP and vascular stiffness. Notably, in contrast to 1 meta-analysis,[89] a second one[91] did not show an improvement in OSA treated with acetazolamide.

IMPACT OF TREATMENT OF OSA WITH CPAP IN WOMEN

The sex-specific differences and considerations in the treatment of OSA in relation to CVD remain understudied. That said, a retrospective cohort study of over 1,000 women over a 5-year follow-up period showed that severe OSA was associated with a 3-fold increased likelihood of CV death, whereas effective CPAP therapy reduced CV-specific mortality.[94] Notably, women with moderate OSA have greater benefit in profiles of circulating biomarkers of inflammation and oxidative stress in post hoc clinical trial data with PAP intervention,[95] findings not observed in men, thereby providing unique biological insights.

IMPACT OF TREATMENT OF OSA WITH CPAP AND OTHER OPTIONS IN CHILDREN

In children, both enlarged tonsils and obesity are intimately associated with OSA. Several studies over the last 2 decades have indicated that OSA in children is associated with increased risk of systemic hypertension, dyslipidemia, and endothelial dysfunction.[96] The increased risk for these morbid consequences may not only impose an immediate adverse effect on CV health during childhood but may also promote the accelerated development of adverse CV outcomes in adulthood.

Adenotonsillectomy, CPAP, and gastric bypass surgery (when concurrent morbid obesity is present) have been used to treat OSA in children. Adenotonsillectomy and weight loss improve OSA by increasing pharyngeal volume (**Central Illustration**). Adenotonsillectomy is the first-line intervention in the management of children diagnosed with OSA. Improvements in cardiac function and structure, BP, some biomarkers of CV risk, and endothelial dysfunction have all been reported, albeit not consistently, requiring further RCTs.[97]

Prevalence of obesity, a major risk factor for OSA, is on the rise in children. A systematic review[98] incorporating 29 cohort studies with a total population of 4,970 obese children who underwent sleeve gastrectomy or RYGB surgery, along with a follow-up study at least 5 years or beyond, showed improvement in BMI, OSA severity, as well as significant remission of type 2 diabetes mellitus, dyslipidemia, and hypertension.

CPAP is recommended for children with OSA if adenotonsillectomy is not performed or if OSA remains unresolved after this surgery. A prospective study[99] in children with OSA reported that CPAP improved OSA over a 1-year period. Epworth Sleepiness Scale scores improved significantly at 1 year from baseline (14 to 8; $P = 0.001$). However, CPAP is also more effective than adenotonsillectomy in lowering BP in hypertensive children.

Like adults, CPAP adherence rate in children with OSA is variable.[100] Young age, lower BMI, and high AHI are associated with acceptable CPAP adherence. Nevertheless, implementation of behavioral modifications of both child and caretakers as part of the initiation of CPAP is usually associated with improved short-term and long-term adherence. In certain cases where CPAP is poorly tolerated, use of high-flow air via a nasal cannula[101] has been highly effective. There are several mechanisms by which high-flow air via a nasal cannula could improve clinical outcomes in children[101]: 1) reduced anatomical dead space and consequently improved gas mixing in large airways; 2) heating and humidification of inhaled gas; 3) decreased nasal resistance and high nasal inspiratory flow; 4) generation of positive airway pressure (2 to 4 cm H_2O) that results in increased end-expiratory lung volume; and 5) increased alveolar PO_2.

FUTURE DIRECTIONS BASED ON THE LESSONS LEARNED FROM THE RCTs USING CPAP FOR PREVENTION OF INCIDENT CVD

Although large observational studies have reported that CPAP treatment has a beneficial effect on both primary and secondary prevention of major CVD,[17] recent RCTs treating OSA with CPAP have been neutral. In 3 RCTs,[102-104] with the primary outcome being the composite of all-cause mortality, CV mortality, stroke, unstable angina, new-onset AF, myocardial infarction, and HF, the combined, fully adjusted HRs were 0.81 (95% CI: 0.45-1.46), 1.05 (95% CI: 0.84-1.33), and 0.90 (95% CI: 0.70-1.16), respectively.

A similar conclusion was reached in another RCT in participants with acute coronary syndrome.[105]

In 2024, a critical question facing the field of cardiology and sleep is whether treatment of OSA with CPAP is effective in preventing incident primary or secondary CVD, or whether OSA is simply a bystander. It has been proposed that it has been the design/implementation of the studies, and particularly the low CPAP adherence, that led to neutral results.[106]

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We[106] and others[107] have proposed that several factors may have contributed to the null results. First, for ethical reasons, many subjects with severe OSA and hypoxemia were excluded even though only the severity of OSA (AHI ≥30 events/h of sleep)[108,109] and the severity of hypoxemia are associated with CV mortality. Another ethical exclusion criterion was presence of excessive sleepiness. Notably, it has been shown that sleepy OSA patients are at increased risk for CV mortality as compared with nonsleepy patients (for details, see references[106,107]). Perhaps, the most important reason for the null result has been poor adherence with PAP devices. In these trials, the average nightly use of the device was <4 hours, less than the minimal accepted criterion. Because intention-to-treat analysis has been used to determine outcomes, lack of adherence by some participants could have contributed to the null results; a post hoc analysis of RCTs comparing PAP users with nonadherent participants could shed light on this supposition. Indeed, the critical role of adequate adherence has been highlighted in 2 meta-analyses: In the first meta-analysis[110] of 3 RCTs including 4,186 patients with individual participant data showed that on intention-to-treat analysis, comparing the CPAP group with the UC group had no effect on the first major adverse cardiocerebrovascular event (HR: 1.01 [95% CI: 0.87-1.17]). This finding is consistent with the intention-to-treat analysis of individual RCTs. However, an on-treatment analysis revealed a reduced risk of major adverse cardiocerebrovascular events associated with good adherence to CPAP (HR: 0.69 [95% CI: 0.52-0.92]).

In the second meta-analysis[111] of 5 RCTs using per protocol use of CPAP (ie, use of CPAP (≥4 h/d, good CPAP adherence), we compared 943 OSA patients who were CPAP adherent to 1,114 patients with UC alone, the control group. At least 4 h/night, compared with no CPAP therapy, improved the primary composite outcome (HR: 0.68 [95% CI: 0.50-0.92]; $P = 0.01$), with no significant heterogeneity between the included studies. In this meta-analysis, the effect was primarily on cerebrovascular composite outcome (**Figure 4**). One difference between the 2 meta-analyses is that we included 2 RCTs that addressed patients with cerebrovascular disease. In the other meta-analysis, the investigators did not stratify between CV and cerebrovascular events. Here, we must emphasize, in sensitivity analyses of the aforementioned RCTs, healthy user bias could have influenced the beneficial outcome, as people that were adherent might have had other differences from those that are nonadherent.

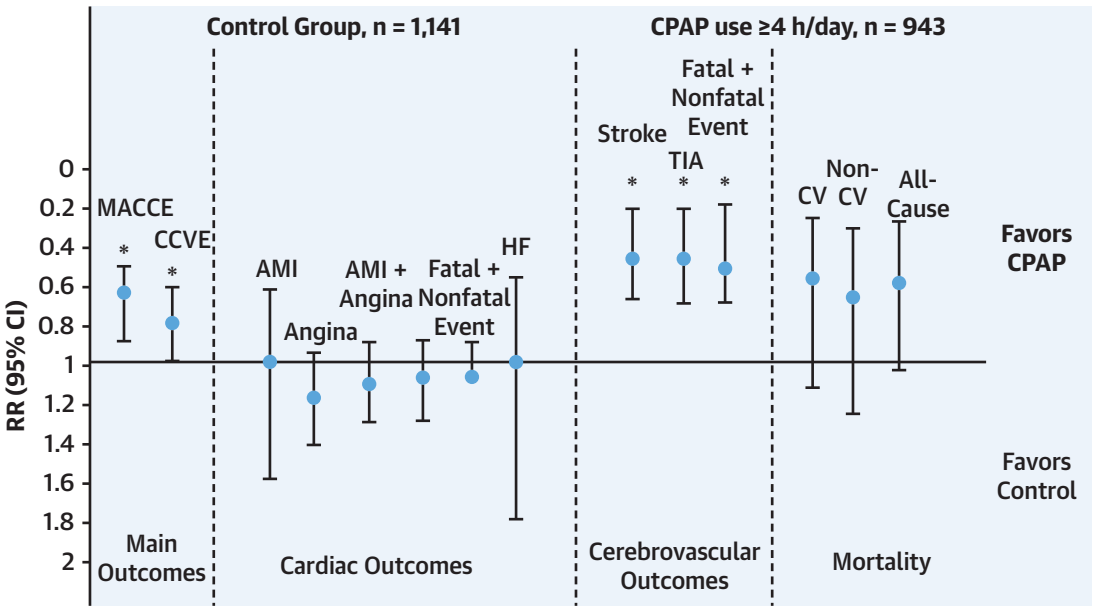
To go forward, several possibilities have been suggested. One alternative is to enroll sleepy patients with OSA and treat them with approved wake-promoting medications.[106] This is done routinely in the management of sleepy OSA patients, given that close to 15% of patients with OSA who are very adherent to CPAP remain sleepy.[112] Another alternative approach is propensity matching.[107] Comparative effectiveness approaches and adaptive trial designs may be used to overcome some ethical concerns of long-term trials of patients not receiving active treatment.

Finally, as discussed in the preceding text, 2 meta-analyses have concluded that the key reason explaining the lack of protective effect of CPAP in RCTs has been the low adherence. One way to overcome this is to conduct a trial with a design similar to cardiology RCTs that have used a running-in period and only enrolled those who were adherent or showed no side effects of a particular medication used in the trial.[113] Therefore, a long run-in period with sham CPAP and exclusion of nonadherent subjects would allow enrollment of patients with adequate CPAP adherence. CPAP adherence could be further enhanced taking advantage of educational, supportive, and behavioral interventions.

Multiple recent studies have suggested that OSA is a heterogeneous disorder (**Central Illustration**) such that OSA heterogeneity may have contributed to the null effect of CPAP, diluting its effect. Aside from AHI that has been used as the main criterion for participation in previous RCTs, new polysomnographic biomarkers have evolved heralding poor prognosis and predictors of OSA-reflated CV mortality.[114]

We already have alluded to hypoxic burden, which has been associated with hard CV outcomes,[108] and notably such individuals were excluded in previous RCTs. But in 1 study,[92] administration of nocturnal supplemental oxygen failed to decrease 24-hour BP, this in contrast to CPAP. However, these individuals had very mild oxygen desaturation, and the results are not surprising. Any future study should not exclude patients who experience severe hypoxemia during sleep due to OSA, and the appropriate dose of oxygen needs to be determined during sleep studies. Another polysomnographic biomarker of OSA is the autonomic response to obstructive events. Although during apnea, heart rate decreases (similar to the diving reflex), post-event, there is an abrupt rise in heart rate, which is further augmented if the respiratory event is also associated with electroencephalographic cortical arousal.[115] This rise in the heart rate has been associated with CV mortality.[116]

FIGURE 4 Effective Use of CPAP Improves Cerebrocardiovascular Outcomes and All-Cause Mortality



The y-axis shows the risk ratio (RR) with 95% CI; the x-axis shows the different types of individual and composite cardiovascular (CV) events. *$P < 0.05$. Reprinted with permission of the American Thoracic Society.[111] AMI = acute myocardial infarction; CCVE = cardiocerebrovascular event; CPAP = continuous positive airway pressure; HF = heart failure; MACCE = major adverse cardiocerebrovascular events; TIA = transient ischemic attack.

Another biomarker, which has been shown to predict BP response to CPAP treatment in patients with resistant hypertension and OSA, is a singular cluster of 3 plasma microRNAs.[117] An RCT using this biomarker in a placebo design could determine the critical role (or absence thereof) of this biomarker in resistant hypertension.

FUTURE DIRECTIONS FOR NON-PAP THERAPY OF INSOMNIA AND OSA

Given the high prevalence of insomnia and its adverse CV consequences, either insomnia alone or with OSA (COMISA [Comorbid Insomnia and Sleep Apnea]), the field needs large systematic placebo-controlled RCTs to treat insomnia with approved DORAS to determine potential improvement in hard CV outcomes and neurocognitive dysfunction.

Exercise has been shown to strengthen the tongue and, based on the current literature, could be potentially curative for treatment of mild-to-moderate OSA. This needs to be determined in a long-term trial that should include measures of CV biomarkers and 24-hour BP monitoring as the first approach.

There is also a need for more robust studies for comparative effectiveness of treatment of OSA relative to CPAP for CV outcomes. Examples include MAD devices and HNS. Although CPAP is more effective than MADs in reducing the AHI, there is a growing body of evidence demonstrating comparable benefits between MADs and CPAP in ameliorating OSA associated CV risk. The repeated failure to demonstrate the CV benefits of CPAP due to poor adherence, and the emergence of MADs as a viable alternative, suggest it is time to reconsider the relative merits of CPAP and MADs. So far, most of the studies on the effects of MADs on CV risk have been small-scale and have focused on BP reduction. Further evaluation of the potential of MADs in improving CV outcomes are urgently needed.

Similarly, HNS has been used for treatment of OSA in the CPAP intolerant or those who refuse CPAP, but there are no systematic studies to demonstrate its effectiveness on any hard outcomes of CVD, biomarkers of CVD or hypertension. Therefore, a large-scale RCT is needed with hard outcomes as the primary endpoint.

As mentioned throughout this review, different pathophysiological mechanisms in addition to the classical anatomical burden have been shown to contribute to the obstruction of the upper airway. In fact, up to two-thirds of OSA patients may have 1 or

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more nonanatomic pathophysiologic mechanisms involved in upper airway collapse.[69] If the mechanisms involved in upper airway obstruction (**Central Illustration**) were easy to identify in clinical practice using data obtained from routine sleep studies without specialized equipment or interventions, a tailored, personalized OSA therapy could be provided, including some non-CPAP therapies, discussed earlier, as first-line treatments. However, further research is needed to define phenotypic subgroups of patients who are most amenable to the different available OSA therapies.

Last, manipulation of gut microbiota could have a therapeutic role.[118-125] OSA has been implicated in inducing adverse changes in the gut microbiome in both animal models and epidemiologic studies. Considering the relatively modest or even disappointing results reported by RCTs with CPAP treatment of OSA and prevention of CV adverse outcomes, interventions aimed at reversing the gut dysbiosis have been advanced as viable adjuvant therapy to PAP[118] At this time, no prospective RCT has been conducted to examine this issue. However, some preliminary findings from murine models are encouraging. Indeed, *Lactobacillus rhamnosus* GG administration in a rodent model of high-fat diet and OSA resulted in increased expression of nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant pathways along with reduced myocardial remodeling as well as mitigation of systemic hypertension.[119] Similarly, exogenous acetate administration in a rodent model of OSA ameliorated the systemic hypertension attributable to gut dysbiosis.[120] Probiotic treatment consisting of a mixture of 8 different probiotic microorganisms markedly attenuated or even abolished the adverse effects of fecal microbiota transfer from intermittent hypoxia exposed mice to naive mice on systemic BP and coronary artery vascular function. Thus, expanded exploration of the putative microorganisms underlying protective CV functions in the context of sleep-disordered breathing, and randomized trials incorporating individualized pre- and probiotic strategies as adjuvant management strategies of PAP-treated OSA patients seem warranted.[117,118]

WOMEN AND OSA

Future investigations should focus on sex-specific endophenotypes indicative of PAP responsivity; the effect of different types of OSA treatment including HNS and oral appliances on CV outcomes in women vs men; and the benefit of treatment of REM-related OSA given its predilection to women and sex-specific differences in CV outcome type.

CONCLUSIONS

Considerable progress has been made regarding our understanding of sleep health and its impact on the CV system. Although the mechanisms linking sleep apnea to cardiometabolic risk are well established, definitive randomized trials showing improvements in hard outcomes with interventions such as CPAP are still lacking. Such studies are needed in children and adults including women, as well as those with OHS, overlap syndrome and OSA comorbid with diabetes mellitus type 2, and with HFpEF. Studies in women, particularly during pregnancy, are also lacking. This review has discussed the pathophysiologic mechanisms underlying the relationship between OSA and cardiocerebrovascular disease, potential reasons for null results of RCTs treating OSA with CPAP, and suggested approaches for future trials.

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