Sleep Apnea and Cardiovascular Disease

Lessons From Recent Trials and Need for Team Science

ABSTRACT: Emerging research highlights the complex interrelationships between sleep-disordered breathing and cardiovascular disease, presenting clinical and research opportunities as well as challenges. Patients presenting to cardiology clinics have a high prevalence of obstructive and central sleep apnea associated with Cheyne-Stokes respiration. Multiple mechanisms have been identified by which sleep disturbances adversely affect cardiovascular structure and function. Epidemiological research indicates that obstructive sleep apnea is associated with increases in the incidence and progression of coronary heart disease, heart failure, stroke, and atrial fibrillation. Central sleep apnea associated with Cheyne-Stokes respiration predicts incident heart failure and atrial fibrillation; among patients with heart failure, it strongly predicts mortality. Thus, a strong literature provides the mechanistic and empirical bases for considering obstructive sleep apnea and central sleep apnea associated with Cheyne-Stokes respiration as potentially modifiable risk factors for cardiovascular disease. Data from small trials provide evidence that treatment of obstructive sleep apnea with continuous positive airway pressure improves not only patient-reported outcomes such as sleepiness, quality of life, and mood but also intermediate cardiovascular end points such as blood pressure, cardiac ejection fraction, vascular parameters, and arrhythmias. However, data from large-scale randomized controlled trials do not currently support a role for positive pressure therapies for reducing cardiovascular mortality. The results of 2 recent large randomized controlled trials, published in 2015 and 2016, raise questions about the effectiveness of pressure therapies in reducing clinical end points, although 1 trial supported the beneficial effect of continuous positive airway pressure on quality of life, mood, and work absenteeism. This review provides a contextual framework for interpreting the results of recent studies, key clinical messages, and suggestions for future sleep and cardiovascular research, which include further consideration of individual risk factors, use of existing and new multimodality therapies that also address adherence, and implementation of trials that are sufficiently powered to target end points and to support subgroup analyses. These goals may best be addressed through strengthening collaboration among the cardiology, sleep medicine, and clinical trial communities.

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Human beings spend about one-third of their lives sleeping. Sleep is no longer considered a passive and homogeneous state but is understood to consist of cyclic periods of complex and changing brain activity, behavior, and physiology.[1] Over the last decades, dramatic growth in the sleep medicine field occurred concurrently with marked advances in clinical and basic research. Sleep disturbances, particularly obstructive sleep apnea (OSA), were identified to affect or covary with numerous health outcomes and physiological processes, particularly cardiovascular disease (Figure 1). Blood pressure and heart rate normally change across the sleep period, and evidence from basic, translational, and clinical research identified adverse cardiovascular responses to disturbed sleep, particularly as a result of OSA and its associated intermittent hypoxia and sleep fragmentation.[2,3] Notably, repetitive collapse of the upper airway and impaired gas exchange with intermittent hypoxia was shown to result in sleep disruption. The associated surges in sympathetic activity were shown to result in acute blood pressure elevations, release of inflammatory mediators, lipolysis, and worsened insulin resistance.[3] Cardiac remodeling, common in patients with OSA, was attributed to exposures to hypoxemia, catecholamine excess, blood pressure elevation, and intrathoracic pressure swings affecting preload and afterload and left atrial and ventricular transmural pressures.

The observational evidence showing that OSA occurs commonly in both the general population and patients with cardiovascular disease and associates with both coronary and cerebrovascular morbidity and mortality[4–6] suggested the possibility of targeting OSA as a novel and modifiable cardiovascular risk factor. Recognition of the high frequency of other sleep disorders occurring in patients with cardiovascular disease such as central sleep apnea (CSA)/Cheyne-Stokes respiration (CSR),[7] insomnia,[8] and short sleep duration[9] also suggested the potential benefits of more broadly considering sleep health as fundamental to cardiovascular health,[10] encouraging consideration of including sleep disturbances in the top 10 potentially modifiable cardiovascular risk factors.[11]

Despite the high prevalence of OSA, there is considerable uncertainty about the role for systematic screening. Improvement in major cardiovascular end points has not been shown in clinical trials, and the US Preventive Health Services Task Force[12] has recommended against screening asymptomatic patients in the general population. On the other hand, patients with heart disease may present with less typical symptoms of sleep apnea such as fatigue or insomnia rather than sleepiness, and it can therefore be difficult to differentiate symptoms of OSA from underlying medical conditions. Other areas of concern are limitations of animal models that may not resemble sleep disturbances in humans and the potential for some analyses to be biased by residual confounding, especially in terms of the influences of adiposity. However, the leading criticism is the limited evidence from rigorous and well-powered randomized controlled trials designed to address the impact of treatment on meaningful clinical outcomes, as noted by a recent meta-analysis.[13] Compared with other research areas, the use of randomized trials in sleep is in its infancy, reflecting both the relatively recent emergence of sleep medicine as an academic discipline and the challenges in designing and implementing nonpharmacological intervention studies. The main aims of this perspective are to discuss the implications of several recently published trials, to contextualize the results, and to identify future directions. We highlight studies that address the impact of noninvasive ventilation, namely continuous positive airway pressure (CPAP) and adaptive servo-ventilation (ASV), noting the current paucity of data addressing additional treatments (eg, nocturnal oxygen supplementation, pharmacological treatments) for the treatment of OSA or CSA-CSR on clinical end points.

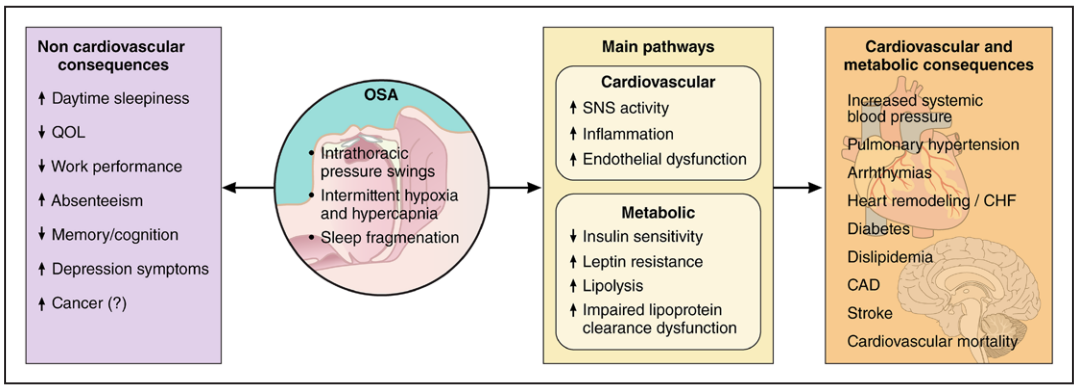

Figure 1. Proposed consequences of obstructive sleep apnea (OSA).
CAD indicates coronary artery disease; CHF, congestive heart failure; QOL, quality of life; and SNS, sympathetic nervous system.

THE IMPACT OF OSA TREATMENT ON CARDIOVASCULAR OUTCOMES

Because of the differences in characteristics of patients and prognosis, we have divided this section into primary and secondary cardiovascular prevention through OSA treatment.

Primary Cardiovascular Prevention

Although clinicians hypothesized that treatment of OSA with CPAP would facilitate weight loss, a recent meta-analysis suggests that the converse is true. Specifically, a meta-analysis reporting on data from >3000 patients showed that abolishing OSA events per se is associated with slight weight gain rather than weight loss, regardless of baseline symptoms and treatment adherence.[14] These new findings underscore the need for patients prescribed CPAP to also receive counseling or support to address long-term weight management needs. Combining weight loss and CPAP may have additive cardiovascular benefits, as suggested by the results of a randomized trial evaluating the impact of CPAP, weight loss, or both.[15]

As described later, a major recent research focus is the evaluation of the influence of CPAP on blood pressure, a key risk factor for cardiovascular disease. More than 30 randomized controlled trials examined blood pressure responses to CPAP. These studies demonstrated a modest but significant blood pressure reduction,[16] especially in those with resistant hypertension.[17,18] Improvements were identified in both daytime and nighttime blood pressure, as well as in nondipping blood pressure profiles. Randomized controlled trials have also evaluated the impact of OSA treatment on surrogate markers of cardiovascular risk such as endothelial dysfunction, arterial stiffness, intima-media thickness, inflammatory markers, insulin sensitivity, cardiac ejection fraction, and cardiac ectopy.[19–23] The evidence is generally consistent with a positive effect of CPAP on vascular and metabolic functions and components of the atherosclerotic process.

The treatment of OSA may reduce the incidence of hypertension, as initially suggested by a small trial that showed normalization of blood pressure among patients with prehypertension or masked hypertension.[24] This important concept was further tested in a large multicenter trial in 14 teaching hospitals in Spain.[25] In this trial, 723 patients with an apnea-hypopnea index >20 events per hour (consistent with moderate to severe OSA) and without excessive daytime sleepiness (Epworth Sleepiness Scale score of ≤10; score range, 0–24, with >10 indicating sleepiness) were randomized to CPAP (n=357) or to a control group (n=366) and followed up for a median duration of 4 years (interquartile range, 2.7–4.4 years). Compared with usual care, CPAP was not associated with a statistically significant reduction in the incidence of hypertension or cardiovascular events in the intention-to-treat analysis. Analyses stratified by CPAP adherence showed that adherent users (defined by CPAP ≥4 hours a night) had a significant reduction in the combined end points (incidence density ratio, 0.69; 95% confidence interval [CI], 0.50–0.94). This finding, however, may be biased by differences in the health characteristics of patients who are adherent compared with those who are nonadherent.

In summary, our current knowledge of primary prevention of cardiovascular disease with CPAP is limited to surrogate end points, combined end points, and observational data.

Secondary Cardiovascular Prevention

There is consistent evidence from observational studies indicating that untreated moderate to severe OSA in patients with established coronary disease[26–28] or heart failure[29] associates with increased cardiovascular morbidity and mortality. Given the high prevalence of OSA in patients with cardiovascular disease,[30] the obvious next question is whether OSA treatment prevents new cardiovascular events or decreases mortality in these high-risk patients. Similar to studies of primary prevention, several trials have identified improvement in blood pressure, including 24-hour blood pressure profiles, in patients with existing cardiovascular disease and OSA. In the HeartBEAT study (Heart Biomarker Evaluation in Apnea Treatment), CPAP was compared with supplemental oxygen therapy and usual care in patients with cardiovascular disease or multiple cardiovascular risk factors, most of whom were under the care of cardiologists.[31] Compared with patients in the usual care group, the CPAP group experienced a significant 2.4–mm Hg reduction of 24-hour mean arterial blood pressure, with larger improvements for mean nocturnal blood pressure (by 3.5 mm Hg). This level of blood pressure improvement is consistent with a significant population-based reduction in stroke.

Fewer studies, however, have directly addressed clinical end points. In one of these studies (RICCADSA [Randomized Intervention With Continuous Positive Airway Pressure in Coronary Artery Disease and OSA]),[32] nonsleepy patients with established coronary artery disease and moderate or more severe OSA defined by an apnea-hypopnea index ≥15 events per hour were randomized to CPAP (n=122) or usual care (n=122) in a single center. The primary end point was the first event of repeat coronary revascularization, myocardial infarction, stroke, or cardiovascular mortality. Over a median follow-up of 57 months, the incidence of the primary end point was 18.1% in the CPAP group compared with 22.1% in the control group; this difference was not statistically significant (hazard ratio [HR], 0.80; 95% CI, 0.46–1.41). In the per-protocol analysis, a large, significant cardiovascular risk reduction

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was reported in those who used CPAP for ≥4 hours a night (HR, 0.29; 95% CI, 0.10–0.86). Although this finding is consistent with a positive effect of CPAP among those who use the therapy regularly, the per-protocol analysis also is likely biased by generally more positive health behaviors in adherent compared with nonadherent patients. It is important to note that the sample size of the primary intention-to-treat study was an order of magnitude lower than most major cardiovascular trials, reducing power to detect effects that are generally considered sufficient to change clinical practice.

In the much-awaited SAVE trial (Sleep Apnea Cardiovascular Endpoints),[33] a multicenter, parallel-group, open-label trial with blinded end-point assessment, 2717 patients (≈1700 patients from China) with a history of coronary artery disease or cerebrovascular disease and untreated moderate to severe OSA were randomly assigned to receive CPAP plus usual care (n=1346) or usual care alone (n=1341). Of note, very sleepy patients (Epworth Sleepiness Scale score >15) and patients with severe hypoxemia (oxyhemoglobin saturation <80% for >10% of sleep study time) were excluded, thus limiting the sample to a potentially lower-risk group. The primary outcome was a composite of death resulting from cardiovascular causes, myocardial infarction, stroke, or hospitalization for unstable angina, heart failure, or transient ischemic attack. In a mean follow-up of 3.7 years, CPAP use did not reduce the primary end point (HR with CPAP, 1.10; 95% CI, 0.91–1.32). The lack of an effect on clinical outcomes was observed in multiple prespecified subgroup analyses. As observed in previous studies, CPAP use resulted in significant beneficial effects on quality of life, mood, daytime sleepiness, and work productivity. To estimate the effect in patients who were adherent to CPAP therapy (defined as an average of ≥4 hours a night) over the first 2 years, a prespecified propensity score–matching strategy was used to compare 561 adherent patients with a comparable group of 561 participants from the usual care group. A total of 86 primary end points (15.3%) were observed in the CPAP group versus 98 (17.5%) in the usual care group (HR, 0.80; 95% CI, 0.60–1.07; *P*=0.13). Individuals who were adherent to CPAP therapy had a lower risk of stroke than those in the usual care group (HR, 0.56; 95% CI, 0.32–1.00; *P*=0.05), as well as a lower risk of a composite (not prespecified) end point of cerebral events (HR, 0.52; 95% CI, 0.30–0.90; *P*=0.02). Although these findings were from secondary analyses and not adjusted for multiple testing, the larger effect size seen for cerebrovascular disease is consistent with observational data showing that OSA appears to be more strongly linked to cerebrovascular than to coronary artery disease.[34]

A number of explanations have been proposed to help interpret the SAVE findings, including the relatively low treatment adherence levels. The nature of the "dose-response" association between CPAP adherence and change in cardiovascular disease risk is not well established, and it is plausible that low adherence to CPAP may have contributed to the null result, particularly if accompanied by nonuse during the early morning when rapid eye movement sleep predominates. Rapid eye movement–related apneas are typically long and are associated with deep oxyhemoglobin desaturations and high sympathetic tone; OSA occurring in rapid eye movement sleep is specifically associated with incident or recent-onset hypertension.[35,36] Alternatively, it is possible that cohort studies overestimated the direct effects of OSA on cardiovascular risk as a result of residual confounding by unadjusted risks such as from visceral or ectopic fat. Visceral obesity is strongly associated with increased cardiovascular risk,[37] decreased upper airway size caused by increased tongue volume,[38] and an increase in the severity of OSA.[38,39] Finally, OSA treatment may not confer significant cardiovascular benefit among patients who have existing cardiovascular disease and are under guideline-based cardiovascular disease treatment regimens (that include therapies aimed at managing several of the intermediate mechanisms implicated in OSA: control of blood pressure, glucose, and dyslipidemia).

The finding for a potential benefit in patients who are strongly adherent to CPAP therapy, however, underscores the need for future trials that incorporate strategies to improve CPAP use or incorporate new or additive alternative treatments to OSA. Emerging data also suggest that oral appliances (mandibular advancement devices) lead to blood pressure improvements comparable to those observed with CPAP, suggesting a potential role for this therapy in cardiovascular end point studies.[40]

TREATMENT OF CSA IN PATIENTS WITH HEART FAILURE WITH CSA-CSR

CSA-CSR is a distinct disorder characterized by an oscillatory pattern of ventilation in which central apneas and hypopneas alternate with periods of hyperventilation, typically recognized as a waxing and waning pattern of breathing.[41] CSA occurs in the absence of significant upper airway obstruction, commonly reflecting exaggerated respiratory chemosensitivity associated with cardiac dysfunction and pulmonary congestion.[42] CSA-CSR is associated with sleep fragmentation and sympathetic nervous system activation that could be deleterious to the failing heart over the long term. Indeed, previous investigations suggest that CSA-CSR is a strong independent marker of mortality in patients with heart failure.[7] Thus, suppression of CSA is suggested as a physiologically appropriate target for the treatment of patients with heart failure. This treatment can be considered at 2 levels.[42] The first approach is to aggressively treat the heart failure, a major contributor to, if not the cause of,

CSA-CSR. Optimizing heart failure with guideline-based medications, as well as coronary revascularization and cardiac resynchronization therapy in selected patients, may improve CSA-CSR. However, these approaches result in variable and frequently incomplete improvement in CSA-CSR. The second approach is directed at improving ventilation. Several strategies have been considered. Pharmacological respiratory stimulants (such as theophylline and acetazolamide) were tested in small trials.[43–45] Although significant reductions in respiratory event frequency and improved oxygenation were observed, concern about adverse effects, including cardiac arrhythmias, has limited enthusiasm for these interventions. Nocturnal supplemental oxygen therapy has been proposed as a physiologically sound intervention for decreasing the severity of CSA-CSR by effects on peripheral chemoreceptors (dampening "overshoot" ventilation) and countering acute adverse effects of hypoxia on myocardial function.[46] However, high levels of oxygen can increase systemic vascular resistance, and trials are needed to evaluate the role of this treatment in heart failure and CSA-CSR. Recent research identified the phenomenon of rostral redistribution of peripheral fluid to the lungs and upper airway during sleep.[47] These observations led to recommendations to consider the use of elastic stockings and exercise for reducing peripheral edema, thus reducing both obstructive and central apneas. This idea is supported by a population study reporting that increased walking and living in "walkable" neighborhoods associate with lower levels of sleep apnea,[48] although the impact of interventions needs to be rigorously evaluated.

Positive airway pressure therapy for CSA-CSR gained interest over the last 2 decades. The seminal study, the CANPAP trial (Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure),[49] randomized 258 stable patients with heart failure (mean ejection fraction, 24.5%) and CSA to receive CPAP (128 patients) or no CPAP (130 patients). The mean follow-up was 2 years. As early as 3 months after randomization, CPAP compared with usual care reduced norepinephrine levels and improved cardiac ejection fraction and the distance walked in 6 minutes, with effects occurring in parallel with the attenuation of the CSA events. However, CPAP did not affect survival. Post hoc analysis[50] identified that CPAP did not fully suppress central events in a significant proportion of patients. Analyses stratified by degree of central event suppression identified that the subgroup who experienced improvement in central events had both a greater increase in left ventricular ejection fraction at 3 months and a significantly better transplantation-free survival than control subjects. Although the bases for differential responses to CPAP among patients with CSA-CSR are not well understood, the CANPAP findings reinforced the concept that new therapies are necessary for fully suppressing CSA-CSR.

An attractive alternative to CPAP is ASV, described for the first time in 2001.[51] ASV is a noninvasive ventilator therapy that alleviates CSA by delivering servo-controlled inspiratory pressure support on top of expiratory positive airway pressure, thus adjusting pressure support in response to breath-by-breath changes in ventilation.[52] Figure 2 summarizes the principle of ASV. Preliminary evidence suggested that ASV is more effective than oxygen, CPAP,[46] and bilevel positive airway pressure in treating CSA-CSR.[54] Moreover, ASV was able to improve surrogate markers of cardiovascular risk such as sympathetic activation,[55] NT-proBNP (N-terminal pro–brain natriuretic peptide),[56] and left ventricular ejection fraction.[56,57] These promising results stimulated interest in testing the ability of ASV to prevent fatal and nonfatal events in patients with heart failure and CSA-CSR. The first major multinational trial to test this hypothesis, the SERVE-HF trial (Adaptive Servo Ventilation in Patients With Heart Failure),[58] enrolled 1325 patients with a left ventricular ejection fraction of ≤45%, New York Heart Association class III or IV heart failure, or New York Heart Association class II heart failure with at least 1 heart failure–related hospitalization within the 24 months before randomization and stable, guideline-based medical treatment. Patients were randomized to usual care plus ASV or usual care

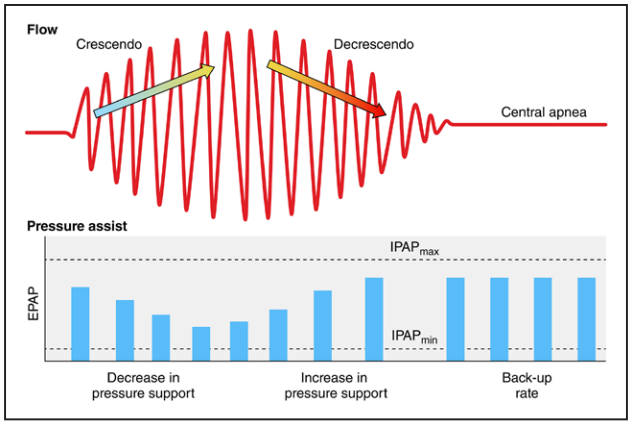

Figure 2. Adaptive servo-ventilation.
The air flow tracing depicts a classic crescendo and decrescendo pattern of Cheyne-Stokes respiration, followed by an ensuing central apnea. The servo-controlled automatic adjustment of the inspiratory positive airway pressure (IPAP) level is inversely related to the changes in peak flow over a moving time window. Specifically, during the crescendo pattern of peak flow rates, the IPAP level decreases in order to dampen the rise in inspiratory peak flow rate. Conversely, during the decrescendo pattern of peak flow rates, the IPAP level increases in order to dampen the fall in inspiratory peak flow rate. Therefore, the servo system dampens the inherent oscillatory behavior of the patient's breathing pattern and smooths respiration. During a central apnea, however, the device backup rate kicks in and ventilates the patient. EPAP indicates expiratory positive airway pressure. Modified from Antonescu-Turcu and Parthasarathy[53] with permission. Copyright © 2010, Daedalus Enterprises.

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alone. The primary end point in the time-to-event analysis was the first event of death resulting from any cause, lifesaving cardiovascular intervention (cardiac transplantation, implantation of a ventricular assist device, resuscitation after sudden cardiac arrest, or appropriate lifesaving shock), or unplanned hospitalization for worsening heart failure. At a mean follow-up of 31 months, no differences in the composite end point were observed in the 2 groups. However, an unexpected 34% increase in all-cause and cardiovascular death occurred in the ASV group. The bases for the early and sustained increase in cardiovascular mortality seen in the ASV group remain to be elucidated. Several commentaries have been published.[59,60] Suggested explanations include inadequate average treatment adherence; negative effects of the specific pressure therapy used, particularly in a setting of markedly impaired left ventricular function; adverse effects associated with potential induction of alkalosis; and loss of a postulated beneficial effect of CSR.

Figure 3 summarizes the key points discussed so far, highlighting potential scenarios for the role of OSA and CSA-CSR in cardiovascular disease.

NONCARDIOVASCULAR OUTCOMES

Patient-reported outcomes and health-related quality of life are important components of disease management to improve patient well-being and important end points in clinical trials. Cardiovascular disease is associated with reduced quality of life,[61] as is even a mild degree of OSA.[62] There is growing interest in OSA treatment as a means for improving quality of life and well-being in patients with heart disease. Several randomized clinical trials evaluated the impact of CPAP treatment on symptoms, health-related quality of life, and mood as secondary outcomes.[63–65] Despite low to modest levels of CPAP adherence, these trials showed that, compared with control conditions, CPAP resulted in improved physical functioning, vitality, and mood, as well as less sleepiness and pain and fewer missed workdays.[34,66,67] The results of these trials, which ranged in duration from 3 months to >3 years,[34,67] support the beneficial effects of CPAP on outcomes of importance to patients, providers, and healthcare systems.

PERSPECTIVES AND NEEDS

The Table summarizes the key messages to our patients, challenges, and a proposed research agenda. There is a need for continuing high-quality basic and translational research to understand the mechanisms by which OSA and CSA-CSR contribute to cardiovascular diseases, further strengthening collaborations among cardiologists, sleep medicine clinicians, and clinical trialists. Improvements in experimental designs using animal models may help better inform translational approaches to human sleep apnea. There is also a need to better understand the variability in responses to treatment, which is likely manifold, including differences in baseline characteristics of patients in regard to severity and duration of sleep apnea, age, types of cardiovascular diseases, and other risk factors, as well as differences in residual apneic activity and sleep with treatment.

Data from 2 ongoing randomized clinical trials may clarify some unanswered questions. For instance, the ISAACC trial[68] (Continuous Positive Airway Pressure [CPAP] in Patients With Acute Coronary Syndrome and Obstructive Sleep Apnea [OSA]; NCT01335087) is a multicenter study from Spain developed to evaluate the impact of OSA and its treatment on outcomes in 1864 patients with acute coronary syndrome. The primary aim is to determine whether CPAP treatment will reduce the rate of composite cardiovascular events in patients with acute coronary syndrome and co-occurring OSA. The ADVENT trial (Effect of Adapto-Servo-Ventilation on Survival and Hospitalizations; NCT01128816)[69] is a multicenter study designed to assess the effects of ASV on survival and frequency of hospital admissions in patients with heart failure and OSA or CSA-CSR. The estimated enrollment is 860 patients. The primary composite outcome will be death, first cardiovascular hospital admission, or new-onset atrial fibrillation/flutter requiring anticoagulation, but not hospitalization or delivery of an appropriate shock from an implanted cardiac defibrillation not resulting in hospitalization.

Priority Areas for Future Trials

There is a critical need for well-powered and rigorous trials that address the impact of OSA treatment on the secondary prevention of atrial fibrillation and the prevention and treatment of preserved ejection fraction heart failure and stroke. Lessons from earlier trials can inform these studies. In particular, new studies may benefit from careful identification of subgroups most likely to respond to the intervention, larger sample size (allowing detection of clinically relevant effects across stratum), and incorporation of methods for improving treatment adherence over long periods of observation such as addition of motivational education to CPAP interventions, a strategy that recently was shown to significantly improve CPAP adherence in patients with OSA and cardiovascular disease.[70] It should be emphasized that the largest trial of sleep apnea and cardiovascular disease (SAVE) is one-tenth the size of many primary and secondary multinational cardiovascular disease trials. The cardiology community has long recognized that the relatively modest rates of clinical events, even in high-risk patients, require very large samples to detect clinically relevant reductions of event rates by 15% to 25%; this scale of investigation has not yet been attempted in sleep medicine but clearly is needed.

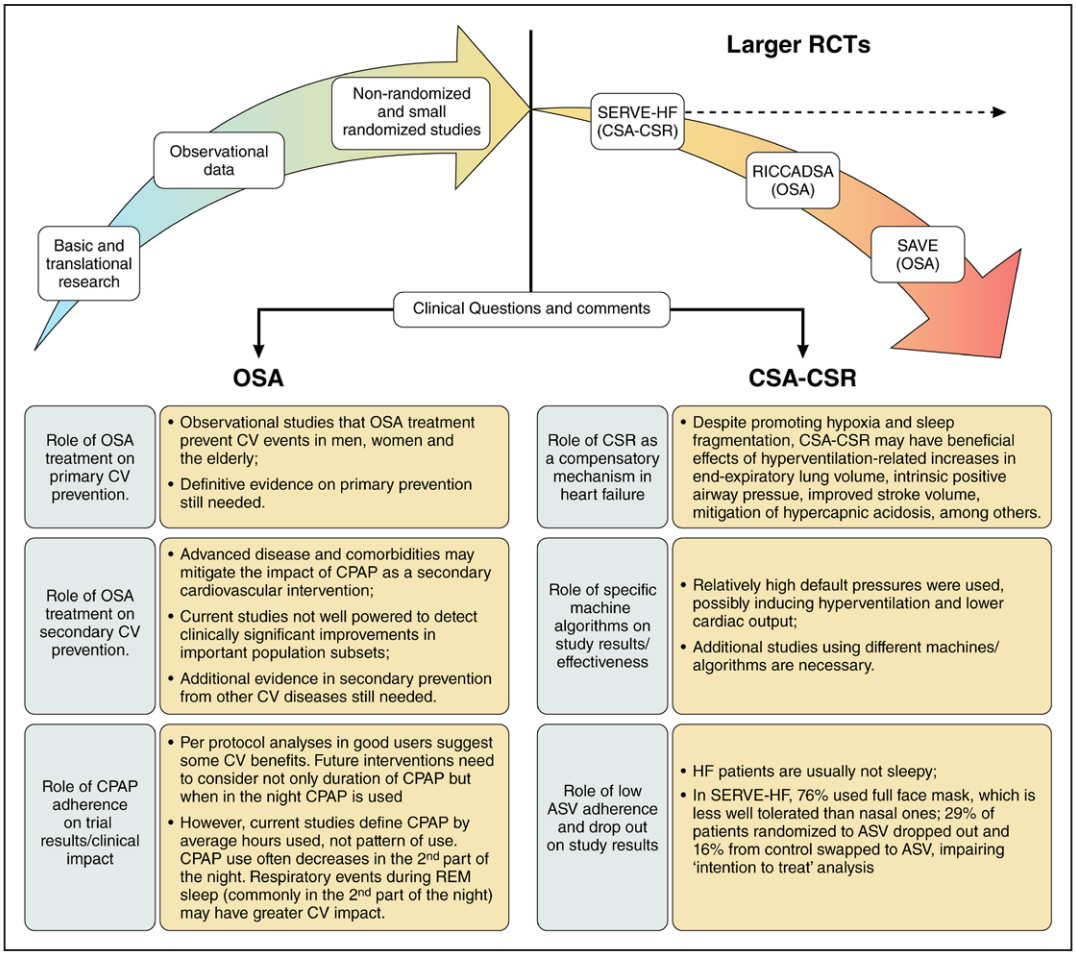

Figure 3. The crossroads of obstructive sleep apnea (OSA) and central sleep apnea associated with Cheyne-Stokes respiration (CSA-CSR) on cardiovascular (CV) diseases.
Consistent evidence provides biological plausibility for supporting OSA as a potential cardiovascular risk factor and the detrimental effects of CSA-CSR in patients with heart failure (HF), but recent larger randomized controlled trial (RCT) results have not matched expectations (dotted line). All quoted studies (SERVE-HF [Adaptive Servo Ventilation in Patients With Heart Failure], RICCADSA [Randomized Intervention With Continuous Positive Airway Pressure in Coronary Artery Disease and OSA], and SAVE [Sleep Apnea Cardiovascular Endpoints]) had neutral results on the primary end point. However, in the SERVE-HF trial, all-cause mortality and cardiovascular mortality (secondary end points) were significantly higher in the adaptive servo-ventilation (ASV) group than in the control group. The potential reasons for these results are discussed at the **bottom**. CPAP indicates continuous positive airway pressure; and REM, rapid eye movement.

Whether composite outcomes are most appropriate should be weighed against data suggesting heterogeneity in the strength of associations between sleep apnea and different cardiovascular disease outcomes.

Development of Better Diagnostic/ Prognostic Tools, New Treatments, and Personalized Medicine for OSA and CSA

The most common diagnostic metric used for characterizing sleep apnea severity, the apnea-hypopnea index, does not strongly predict adverse health outcomes or response to treatment. The apparent variation in susceptibility to sleepiness, cognitive deficits, and cardiovascular disease for any given apnea-hypopnea index level suggests a need to develop improved measurements of disease and to identify important disease-modifying factors. In the beginning of the era of precision medicine, biomarkers of cardiovascular risk may help to select individuals at greatest risk for sleep apnea–related physiological stress and those most likely to respond to specific, and possibly alternative, treatments. New measures of sleep apnea pathophysiology such as quantitative measures of ventilatory drive or airway collapsibility may help to better define patient subgroups.

There is a strong need for developing new and effective treatments for OSA and CSA-CSR, with deliberate tailoring of such treatments to the diverse needs and pathophysiology of specific subgroups of patients such

Table. Take-Home Messages and Proposed Research Agenda

Scenario	What Can We Tell Our Patients?	Challenges and Future Research Agenda
OSA:		
Primary prevention	CPAP lowers blood pressure and may improve insulin sensitivity. Good adherence to CPAP likely prevents incident hypertension and may reduce the occurrence of adverse cardiovascular events in patients with moderate to severe OSA. Patients should not expect weight loss with OSA treatment.	While sleep apnea is highly prevalent among patients seen in cardiology practices, only a small portion of patients are diagnosed, and symptomatic patients may present with atypical symptoms. Tools are needed to improve screening. Hard end points such as mortality require large sample sizes and long periods of follow-up. Large pragmatic trials evaluating the end points of hypertension, stroke, myocardial infarction, arrhythmias (eg, atrial fibrillation), and preserved and reduced ejection fraction heart failure are needed. This will require international collaboration.
Secondary prevention	CPAP treatment improves blood pressure, including measurements made in the office and overnight blood pressure. In patients with previous coronary or cerebrovascular disease, CPAP treatment does not improve survival, but adherent patients may have a lower risk of stroke. Overall quality of life, mood, and work productivity are improved with CPAP therapy. In heart failure, CPAP therapy does not lead to longer survival. Small nonrandomized studies suggest that OSA treatment can prevent atrial fibrillation recurrence.	Improved strategies to improve CPAP adherence are needed, and existing strategies should be incorporated into studies. Development of biomarkers to identify individuals likely to respond to treatment or to be at increased risk for cardiovascular disease may improve trial power. It is difficult to estimate the duration of sleep apnea before the initiation of therapy. Duration of untreated disease may modify response to treatment. Tools for estimating duration of sleep apnea are needed. For ethical reasons, some trials excluded sleepy patients, limiting our ability to assess the impact of OSA treatment on cardiovascular events in these patients. Women are underrepresented in clinical trials of sleep apnea despite an increase in prevalence of sleep apnea after menopause and high rates of heart failure and stroke in older women. Patients with severe hypoxemia are excluded from many trials, limiting inferences for patients who may be at the highest risk for cardiovascular complications. Mild OSA is frequently excluded in randomized trials of cardiovascular end points. Most observational data suggest stronger associations between cardiovascular end points and moderate to severe OSA compared with mild OSA. However, OSA severity can be underappreciated in some patients using routine sleep studies, especially home-based sleep apnea testing.
CSA-CSR:		
Secondary prevention	Among patients with heart failure and CSA-CSR, CPAP therapy does not improve survival. Those using CPAP should be closely monitored by their doctors, who should determine the effectiveness and appropriateness of continued use of CPAP. In the SERVE-HF trial, all-cause mortality and cardiovascular mortality were increased in the group who received adaptive servo-ventilation (ASV) group. ASV should not be initiated in patients with ejection fraction <45% and predominant central sleep apnea until other studies clarify whether these results are a consequence of the specific device that was used.	Many patients with CSA have a variable proportion of events that are obstructive and it can be hard to accurately distinguish between obstructive and central event subtypes. Prognosis and variations in treatment response may reflect differences in the pathophysiology of these events, which are not well characterized. Large clinical trials of new (neurostimulator) and old (oxygen) treatments are needed. Further elucidation of bidirectional and interacting pathways between heart failure and sleep apnea is needed. There is a need to understand whether CSA-CSR itself is an adaptive or harmful condition in heart failure and whether long-term use of pressure-based devices (CPAP or ASV) adversely affects cardiac function in patients with heart failure. Future studies are needed that include stringent safety features and test low or physiological optimized pressure levels. Future enhancements in therapies such as customized nasal masks, behavioral support to optimize ASV adherence, and strategies for optimizing retention and minimizing crossover rates are needed.

ASV indicates adaptive servo-ventilation; CPAP, continuous positive airway pressure; CSA, central sleep apnea; CSR, Cheyne-Stokes respiration; OSA, obstructive sleep apnea; and SERVE-HF, Adaptive Servo Ventilation in Patients With Heart Failure.

as those with underlying cardiovascular disease or heart failure or those identified through use of biomarkers of susceptibility. Patients with sleep apnea are heterogeneous with respect to disease pathogenesis. Physiological studies show that patients with sleep apnea have variable combinations of abnormalities in airway anatomy, neuromuscular responsiveness, respiratory chemosensitivity, and loop gain,[71] with each of these components potentially responsive to different single or combinations of therapeutic interventions. Although poor adherence to CPAP is often considered a "failure" of the patient to comply with therapy, it is likely that a proportion of the poor adherence observed clinically reflects the use patterns in patients who experience suboptimal responses to a fixed (CPAP) or variable (auto positive airway pressure, ASV) pressure treatment and require alternative treatments. For example, a small proportion of patients may develop central apneas when exposed to positive pressure therapy, a disorder called complex sleep apnea. New therapies such as hypoglossal nerve stimulation for the treatment of OSA[72] and an implantable device that transvenously stimulates the phrenic nerve, causing diaphragmatic contraction for CSA,[73] hold promise as physiologically grounded treatments for selected patients. Older treatments such as nocturnal oxygen supplementation also may have a role

in treating selected patients such as those with augmented loop gain and CSA, although they need to be rigorously evaluated with randomized controlled trials. Finally, a "stepped" approach to treatment that considers the many comorbidities of patients with heart disease and integrates behavioral, pharmacological, and device-based treatments provides a future paradigm for providing the patient with both sleep apnea and cardiovascular disease an individually optimized treatment.

Creating Partnerships and Cross-Fertilization

There is increasing interest in developing integrated models of care among specialists and between specialists and primary care practitioners. There are fertile opportunities for sleep medicine and cardiology to develop comanagement practices given the high coaggregation of sleep-disordered breathing and cardiovascular disease and the potential for bidirectional associations. Similar synergies are possible in advancing a research agenda to generate better evidence to guide treatment of sleep-disordered breathing. The practice of cardiovascular medicine has benefited from large, rigorous, multinational randomized controlled trials that evaluated a wide range of behavioral, pharmacological, and device-based interventions. With a growing set of available interventions for treating sleep apnea, the sleep medicine field is poised to partner with the cardiology community.

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FOOTNOTES

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Sleep Apnea and Cardiovascular Disease: Lessons From Recent Trials and Need for Team Science

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