

# Effects of Obstructive Sleep Apnea Therapy on Cardiovascular Disease

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## KEYWORDS

- Obstructive sleep apnea • Subclinical atherosclerosis • Coronary heart disease
- Cardiac arrhythmias • Stroke

## KEY POINTS

- Sleep apnea occurs when the upper airway collapses during sleep resulting in a cycle of hypoxemia, increased respiratory effort, frequent arousals, and increased sympathetic activity.
- OSA has been associated with numerous cardiovascular conditions.
- The impact of treatment of OSA on cardiovascular outcomes has been investigated.

## OVERVIEW OF OBSTRUCTIVE SLEEP APNEA AND ASSOCIATED CARDIOVASCULAR OUTCOMES

Obstructive sleep apnea (OSA) is exceedingly prevalent in the United States. It occurs when the upper airway collapses during sleep resulting in a cycle of hypoxemia, increased respiratory effort, frequent arousals, and increased sympathetic activity. OSA syndrome (OSAS) is clinically defined as an apnea-hypopnea index (AHI) greater than or equal to five per hour in the presence of daytime sleepiness. However, sleep medicine has not determined precise definitions for this terminology and often OSA and OSAS are used interchangeably. It is estimated that among the western population, 24% of men and 9% of women have OSA (AHI  $\geq 5$ ).<sup>1</sup>

OSA has been associated with numerous cardiovascular conditions including hypertension,<sup>2</sup>

coronary heart disease,<sup>3,4</sup> cardiac arrhythmias,<sup>5</sup> heart failure,<sup>6,7</sup> stroke,<sup>8</sup> and sudden death.<sup>9</sup> Although the specific mechanisms that explain these individual associations have not been fully delineated plausible factors that contribute to an overall increased vascular risk in the setting of underlying OSA have been investigated. They include (but are not limited to) sympathetic activation,<sup>10</sup> metabolic dysregulation,<sup>11–14</sup> endothelial dysfunction,<sup>15,16</sup> oxidative stress,<sup>17</sup> and autonomic dysfunction.<sup>18</sup>

The impact of treatment of OSA on cardiovascular outcomes has also been investigated, albeit not as extensively as the association studies mentioned previously (**Table 1**). Moreover, most OSA treatment investigations are predominantly observational in nature. A limited number of randomized trials exist because of ethical concerns pertaining to withholding treatment of OSA for prolonged periods of time (over 3–6 months).

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**Table 1**  
**Summary of key studies on impact of OSA treatment on CVD**

CVD of Interest	Type of Study	Sample Size	Duration of Treatment	Impact of Treatment of OSA
Subclinical atherosclerosis <sup>22</sup>	Randomized controlled study	N = 24 (males only)	4 mo of CPAP	Significant decrease in carotid intima-media thickness in treatment group
Subclinical atherosclerosis <sup>23</sup>	Randomized, double-blind, placebo-controlled trial	N = 86 (cross-over design with 1 mo wash-out period)	3 mo of CPAP	Significant decrease in carotid intima-media thickness posttreatment
Subclinical atherosclerosis <sup>24</sup>	Nonrandomized study	N = 50	12 mo CPAP	Significant long-term beneficial impact of CPAP therapy on carotid intima-media thickness
Arrhythmias <sup>29</sup>	Nonrandomized study	N = 316	1 night of CPAP	Significant reduction in occurrence of paroxysmal atrial fibrillation, sinus bradycardia, and sinus pause
Arrhythmias <sup>30</sup>	Randomized controlled trial	N = 83 (males only)	1 mo	No significant change in the frequency of any cardiac arrhythmias
Arrhythmias <sup>31</sup>	Nonrandomized study	N = 29 (patients with heart failure with both obstructive and central sleep apnea)	1 night of CPAP	Significant reduction in nocturnal premature ventricular contractions and couplets
Arrhythmias <sup>32</sup>	Nonrandomized study	N = 23	14 mo CPAP	Significant decrease in sinus pauses and bradycardia No significant difference in supraventricular arrhythmias
Coronary artery disease and stroke <sup>35</sup>	Nonrandomized study	N = 1347 (men only)	10 y follow-up	Significantly fewer number of nonfatal and fatal coronary and cerebrovascular events in treated patients with OSA compared with untreated patients with severe OSA

*Abbreviations:* CPAP, continuous positive airway pressure; CVD, cardiovascular disease.

### SUBCLINICAL ATHEROSCLEROSIS

Atherosclerosis, a chronic disorder characterized by lipid accumulation and inflammation in the

vascular wall, has been proposed as a mechanistic link between OSA and cardiovascular disease. Atherosclerosis is usually asymptomatic for many years before its manifestation in the form

of a cardiovascular event, such as myocardial infarction. This presence of clinically inapparent atherosclerosis (ie, subclinical atherosclerosis) can be measured using several noninvasive and invasive techniques including B-mode ultrasound, computed tomography, magnetic resonance imaging, and catheter-based angiography. Several noninvasive measures of subclinical atherosclerosis have been identified and include carotid intima-media thickness<sup>19</sup> and arterial stiffness,<sup>20</sup> with the latter determined using pulse wave velocity or other techniques.<sup>21</sup> This section reviews the studies that have examined the influence of continuous positive airway pressure (CPAP) treatment on the previously noted measures of subclinical atherosclerosis.

Drager and colleagues<sup>22</sup> designed a randomized controlled study to test the hypothesis, "treatment of OSA with CPAP therapy significantly improves validated markers of early signs of atherosclerosis, namely carotid intima-media thickness (primary outcome), arterial stiffness, and carotid diameter (secondary outcomes)". In this study they excluded individuals with any comorbidity including hypertension, diabetes, heart failure, coronary artery disease (CAD), stroke, smoking, and chronic use of medications. All patients underwent a routine attended, in-laboratory polysomnogram. They defined apnea as complete cessation of airflow for at least 10 seconds, associated with oxygen desaturation of 3% and hypopnea as a 50% reduction in airflow for at least 10 seconds associated with oxygen desaturation of 3%. The investigators only included those patients with severe OSA (AHI >30 events per hour) who were naive to treatment. A total of 400 patients with severe OSA were screened, of whom 24 males (age,  $46 \pm 6$ ) met the rigorous inclusion criteria. The patients were randomized to receive no treatment (control,  $N = 12$ ) or CPAP ( $N = 12$ ) for 4 months. The CPAP intensity was determined by overnight CPAP titration studies and CPAP compliance was objectively measured throughout the course of the trial. The main outcome variables for the study were measured using a high-resolution echo-tracking system (for carotid intima-media thickness) and a noninvasive automatic device (for carotid-femoral pulse-wave velocity). The baseline characteristics were similar in the two groups with no significant difference in the mean age, body mass index (BMI), waist/hip ratio, day and night systolic and diastolic blood pressure, daytime sleepiness, and baseline levels of carotid intima-media thickness and carotid-femoral pulse-wave velocity. The mean AHI was  $62 \pm 22$  in the control group and  $56 \pm 22$  in the CPAP group ( $P = .52$ ). The results of this study revealed a significant decrease in

carotid intima-media thickness ( $707 \pm 105$  vs  $645 \pm 95$   $\mu\text{m}$ ;  $P = .04$ ) and pulse-wave velocity ( $10.4 \pm 1.0$  vs  $9.3 \pm 0.9$  m/s;  $P < .001$ ) in patients with severe OSA who were treated with CPAP (4 months) versus those with severe OSA who received no CPAP treatment. No significant changes occurred in BMI, glucose, cholesterol, and blood pressure. The authors concluded that treatment of OSA with CPAP improved markers of subclinical atherosclerosis in middle-aged overweight men with severe OSA who were free of underlying risk factors including hypertension and smoking. This study supports the notion that OSA is an independent risk factor for atherosclerosis.

Sharma and colleagues<sup>23</sup> demonstrated similar findings in a randomized, double-blind, placebo-controlled trial to assess the impact of treatment of OSA with CPAP on metabolic syndrome and its constituents. As part of this trial, patients with OSA underwent 3 months of therapeutic CPAP with subsequent 3 months of sham-CPAP (interspersed with a 1-month washout period). They measured various components of metabolic syndrome, as well as carotid intima-media thickness. In this trial, they found that patients with OSA who were adherent with CPAP therapy (average use of 5 hours per night) had significantly reduced carotid intima-media thickness compared with those who were less adherent (carotid intima-media thickness  $0.034$  vs  $0.014$  mm;  $P < .05$ ).

In contrast to the aforementioned studies, which assessed the short-term impact of CPAP on subclinical atherosclerosis, Hui and colleagues recently reported the long-term impact of CPAP treatment on carotid intima-media thickness.<sup>24</sup> They conducted a cohort study of 50 newly diagnosed patients with OSA (ages 20–80) who received CPAP ( $N = 28$ ) or conservative treatment ( $N = 22$ , at patient's discretion) and were followed prospectively for 12 months. Carotid intima-media thickness was assessed with B-mode ultrasound of the far wall of the distal 10 mm of the common carotid arteries bilaterally at baseline, 6 months, and 12 months. In this study the authors defined OSA using an attended overnight sleep study showing AHI greater than or equal to five per hour of sleep plus excessive daytime sleepiness or the presence of choking or gasping during sleep and recurrent awakenings. At baseline there was no significant difference in the two groups for the following variables: age; BMI; daytime sleepiness; AHI; oxygen saturation (minimum); and existing comorbidities. Additionally, CPAP usage was similar in the two groups at 6 months and 12 months of follow-up. Carotid artery intima-media thicknesses at baseline, 6 months, and 12 months were  $758$  (30),  $721$  (20), and  $705$  (20)  $\mu\text{m}$  for the CPAP group

versus 760 (30), 770 (30), and 778 (30)  $\mu\text{m}$ , respectively, for the group that received conservative treatment ( $P = .002$ ). The authors concluded that CPAP therapy has long-term beneficial impact on the carotid artery intima-media thickness, but as noted, these findings were observational.

A recent study by Buchner and colleagues<sup>25</sup> has also demonstrated a beneficial role of CPAP therapy in patients with OSA on subclinical atherosclerosis. They conducted a nonrandomized 6-month study to determine the impact of CPAP therapy on arterial stiffness as measured by carotid-radial pulse wave velocity. Among patients with OSA who were effectively treated with CPAP, the pulse wave velocity decreased from  $9.6 \pm 1.5$  at baseline to  $8.7 \pm 1.4$  at follow-up ( $P < .05$ ). Patients who were not treated effectively with CPAP had no improvement in arterial wall stiffness measurement. The study does not, however, report on the characteristics of the two groups (effective and noneffective users of CPAP) and it does not provide information on lifestyle and compliance with cardiovascular medications that can confound the relationship between CPAP and the outcome of interest.

In summary, there is accumulating evidence to support a beneficial impact of short- and long-term CPAP therapy on subclinical atherosclerosis in patients with OSA, although caution is warranted because the evidence comes from small studies, and much of it is non-randomized. It is important to acknowledge that most of the studies noted here emphasized the importance of "effective" CPAP therapy (ie, nightly CPAP use of at least 4 hours and up to 6 hours) to significantly improve markers of subclinical atherosclerosis.

## ARRHYTHMIAS

OSA has been shown to be associated with cardiac arrhythmias.<sup>5,26-28</sup> This was documented in a cross-sectional study by Mehra and colleagues<sup>5</sup> using data from the Sleep Heart Health Study. In this study ( $N = 566$ ), OSA was independently associated with atrial fibrillation (odds ratio [OR], 4.02; 95% confidence interval [CI], 1.03–15.74); nonsustained ventricular tachycardia (OR, 3.40; 95% CI, 1.03–11.20); and complex ventricular ectopy (OR, 1.74; 95% CI, 1.11–2.74).

Several studies have examined the effect of CPAP therapy on cardiac arrhythmias. Some of these studies have evaluated short-term impact (diagnostic night vs titration night), whereas others have evaluated a longer-term impact of CPAP therapy on cardiac arrhythmias.

A Japanese study<sup>29</sup> of 1394 participants ( $N = 108$  men; all underwent overnight polysomnography

for the diagnosis of OSA) evaluated the short-term impact of CPAP therapy on various cardiac arrhythmias. The investigators found a significant association between OSA status and the presence of cardiac arrhythmias, such as paroxysmal atrial fibrillation, premature ventricular complexes, sinus bradycardia, and sinus pauses. A total of 1047 of the study participants had an AHI of greater than or equal to 20 per hour. Of these, 316 participants accepted CPAP treatment and underwent a CPAP titration study (roughly 3–4 weeks after the diagnostic test). On the second night of effective CPAP therapy in patients with OSA, a significant reduction in the occurrence of paroxysmal atrial fibrillation ( $P < .001$ ), premature ventricular complexes ( $P = .016$ ), sinus bradycardia ( $P = .001$ ), and sinus pauses ( $P = .004$ ) was found.<sup>29</sup>

Contrary to the previously mentioned study, Craig and colleagues<sup>30</sup> found no beneficial role of CPAP therapy on cardiac arrhythmias in patients with OSA. They conducted a randomized controlled trial ( $N = 83$  males; moderate to severe OSA) to investigate the impact of therapeutic CPAP therapy versus subtherapeutic CPAP ( $< 1$  cm H<sub>2</sub>O) on the presence of pauses, bradycardias, and supraventricular and ventricular arrhythmias. Before initiation of the trial and 1 month post effective use of CPAP therapy, all participants underwent three-channel 24-hour electrocardiograms. The two groups were well matched for age, BMI, OSA severity, and cardiovascular history. The trial revealed that there was no significant change in the frequencies of any of the cardiac arrhythmias noted previously (day or night time) after 1 month of CPAP therapy.

Javaheri<sup>31</sup> has also investigated the role of CPAP therapy on cardiac arrhythmias, specifically studying patients with congestive heart failure with a mixture of obstructive and central sleep apnea. A total of 29 patients with heart failure with consecutive polysomnogram studies were recruited and patients with an AHI of 15 or more per hour of sleep ( $N = 21$  central sleep apnea;  $N = 8$  OSA) were identified. These patients were subjected to a second night of CPAP titration study. In patients whose sleep apnea was effectively treated by CPAP, there was a significant reduction in hourly episodes of nocturnal premature ventricular contractions ( $66 \pm 117$  vs  $18 \pm 20$ ;  $P = .055$ ) and couplets ( $3.2 \pm 6$  vs  $0.2 \pm 0.21$ ;  $P = .031$ ).

Another study<sup>32</sup> evaluated the long-term impact of CPAP therapy on arrhythmias in 23 patients ( $N = 16$  men; mean age,  $50 \pm 11$  years) with moderate to severe OSA. Using an insertable loop recorder capable of 16-month cardiac arrhythmia monitoring, this group of investigators assessed the presence of cardiac pauses ( $> 3$  seconds) and

bradycardic episodes (<40 bpm) during a 2-month period before and for 14 months after CPAP therapy. Holter recording (48 hours) was also done in this study before and after CPAP treatment. The investigators found the diagnostic capability of the Holter recording to be insufficient compared with the insertable loop recorder. After 8 weeks of CPAP therapy, the median number of bradycardia events dropped significantly (5.5 to 0.5;  $P = .028$ ). Similarly, the number of pauses decreased 8 weeks post-CPAP treatment. The authors also commented, "Supra-ventricular arrhythmias were present to a lesser extent and did not seem to be affected significantly by CPAP treatment."

The previously cited studies and others<sup>33,34</sup> suggest a beneficial role of CPAP therapy on cardiac arrhythmias. The randomized controlled trial findings from Craig and colleagues<sup>30</sup> did not show any significant difference in the prevalence of cardiac arrhythmias before and after CPAP therapy among patients with OSA. Although this study<sup>30</sup> had numerous strengths, some of the limitations that could account for lack of benefit from CPAP therapy on cardiac arrhythmias included one-time 24-hour cardiac monitoring versus continuous monitoring, which seems to have better capability to detect arrhythmias as demonstrated by Simantirakis and colleagues;<sup>32</sup> and that the study was limited to a short-term follow-up (1 month), such that longer follow-up might have demonstrated benefit, as suggested by others.<sup>32</sup> Further investigations are needed to assess the impact of CPAP on cardiac arrhythmias among patients with OSA. These investigations should include women, use continuous cardiac monitoring, and have follow-up over an extended time period.

## CORONARY HEART DISEASE

OSA has been shown to be an independent risk factor for coronary heart disease events.<sup>3,4,7</sup> The impact of treatment of OSA with CPAP on long-

term cardiovascular outcomes has been investigated in numerous studies. These studies have been largely observational in nature.

A landmark study pertinent to this area was from Marin and colleagues.<sup>35</sup> In their study, the investigators recruited 1387 men from a sleep clinic-based sample and an additional 264 healthy men (age- and BMI- matched with an untreated severe OSA subgroup) from a population-based sample. All patients underwent in-laboratory attended polysomnogram. Patients with an AHI greater than 30 per hour and those with an AHI between 5 and 30 plus daytime sleepiness or cardiac failure were offered CPAP therapy. The rest of the patients were offered conservative advice including weight loss, avoidance of alcohol, smoking, and sedatives, and appropriate sleep hygiene. All patients were followed forward in time (10 years) with yearly clinic appointments for the major end point of fatal or nonfatal cardiovascular events (including acute coronary syndromes, myocardial infarction, and stroke).

Objective CPAP compliance was ascertained at each visit. Of the 1347 patients, 377 had simple snoring; 403 had mild-moderate OSA (untreated); 235 had severe OSA (untreated); and 372 had treated OSA with CPAP. The results from this study are detailed in **Table 2**. Patients with untreated severe OSA were found to have an increased risk of fatal and nonfatal cardiovascular events (after adjusting for confounding variables listed in **Table 2**). Patients with no sleep apnea (snorers), untreated mild-moderate OSA, and treated OSA with CPAP had no significant increase in the risk of either fatal or nonfatal cardiac events. The authors of this study did not provide specific ORs for component outcomes (ie, coronary or cerebrovascular event specific). Therefore, it is not possible to determine the impact of CPAP therapy on coronary heart disease-specific events (fatal or nonfatal).<sup>35</sup> Furthermore, the observational nature of this study leaves it open to unmeasured

**Table 2**  
Adjusted OR for nonfatal and fatal cardiovascular events

Diagnostic Group	Adjusted OR <sup>a</sup> (CI, P Value)	
	Nonfatal Cardiovascular Events	Fatal Cardiovascular Events
Snoring	1.32 (0.64–3.01, 0.38)	1.03 (0.31–1.84, 0.88)
Mild-moderate OSA	1.57 (0.62–3.16, 0.22)	1.15 (0.34–2.69, 0.71)
Severe OSA	3.17 (1.12–7.52, 0.001)	2.87 (1.17–7.51, 0.025)
CPAP	1.42 (0.52–3.40, 0.29)	1.05 (0.39–2.21, 0.74)

<sup>a</sup> Variable in the fully adjusted mode includes age; diagnostic group; presence of cardiovascular disease; hypertension; diabetes; lipid disorders; smoking status; alcohol use; systolic and diastolic blood pressure; blood glucose; total cholesterol; triglycerides; and current use of antihypertensive, lipid-lowering, and antidiabetic drugs.

or residual confounding. Despite these limitations, this study was the first of its kind to demonstrate a significant impact of CPAP therapy on cardiovascular outcomes over a long-term period.

Another study by Milleron and colleagues<sup>36</sup> investigated the long-term effect of treating OSA on cardiovascular events in patients with underlying CAD. They found that OSA treatment significantly reduced the number of cardiovascular events (acute coronary syndrome, need for coronary revascularization, hospitalization for heart failure, or cardiovascular death), which occurred in 24% in the treated group versus 58% in the untreated group ( $P < .01$ ) over a period of  $86.5 \pm 39$  months. At baseline, the two groups were similar in risk factors for cardiovascular disease and in corresponding, non-OSA specific therapies. Most patients in the intervention group ( $N = 25$ ) were treated with CPAP ( $N = 21$ ), with a small fraction treated with upper airway surgery ( $N = 4$ ). Similarly, others have shown that treatment of OSA is associated with improved cardiovascular outcomes in the setting of acute or chronic CAD. A recent cohort study<sup>37</sup> of 192 patients with acute myocardial infarction and 96 matched control subjects without CAD (ratio 2:1) revealed that treated patients with OSA ( $AHI \geq 5$  per hour) had a lower risk of recurrent myocardial infarction (adjusted hazard ratio, 0.16; 0.03–0.76, 0.021) and revascularization (adjusted hazard ratio, 0.15; 0.03–0.79, 0.025) compared with untreated patients with OSA.

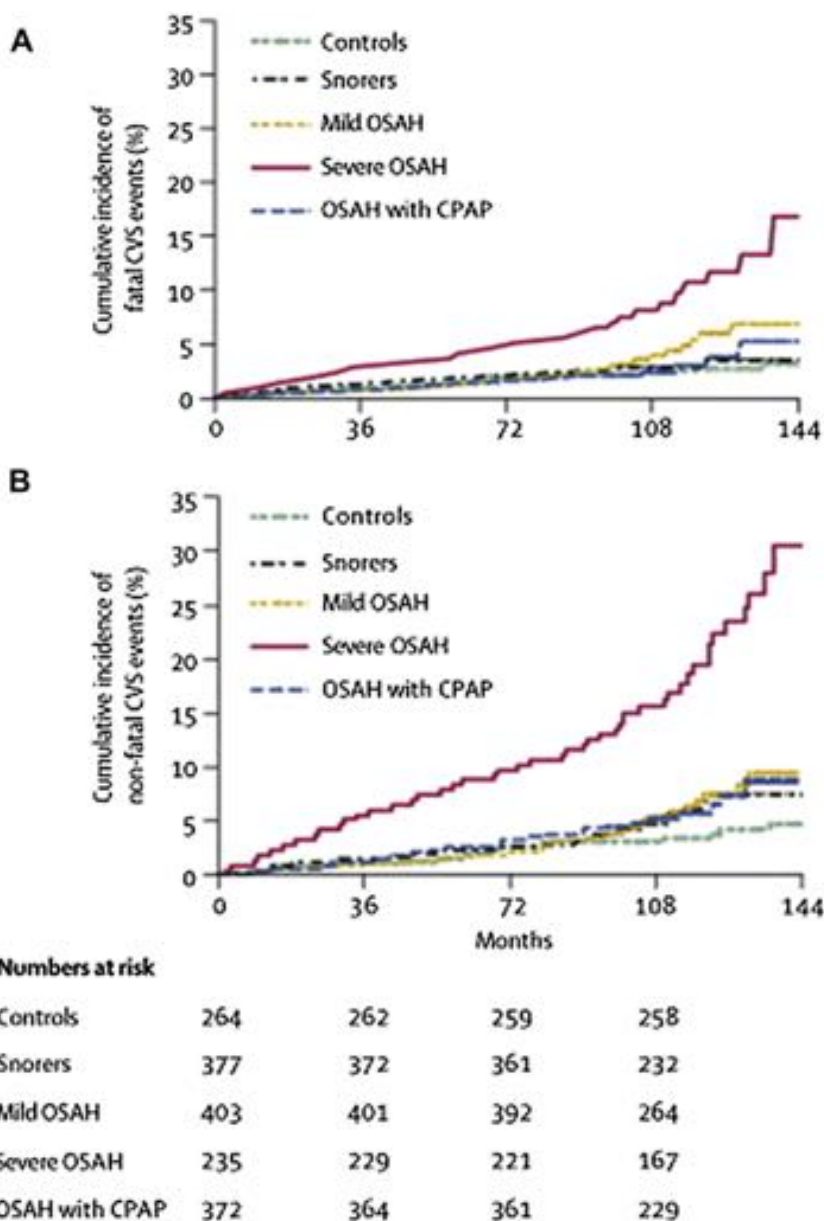
Despite such data suggesting a beneficial role of treatment of OSA on cardiovascular outcomes (either in the setting of CAD<sup>36</sup> or outside of the setting of acute coronary syndromes<sup>35</sup>), there is as yet no evidence from large-scale randomized studies regarding this question. In the last few years, however, several randomized clinical trials have been launched to assess the impact of OSA treatment on the risk of cardiovascular disease. One such trial, currently underway in Europe, is the Randomized Intervention with CPAP in CAD and OSA (RICCADSA) Study<sup>38</sup> ( $N = 400$  patients). It will assess the impact of CPAP on a composite end point of new coronary revascularization, myocardial infarction, stroke, and cardiovascular mortality among those with both CAD and OSA. Similarly, in the United States, a multi-center study called the Heart Biomarker Evaluation in Apnea Treatment was recently completed (August 2012). This study randomized patients with OSA and CAD or CAD risk factors to CPAP, nocturnal oxygen, and healthy lifestyle instruction. The major goal of this trial is to determine whether CPAP or oxygen alter cardiac biomarkers including (but not limited to) measures of systemic

inflammation and oxidative stress, cardiac rhythm, impulse generation, and myocardial ischemia or stress. Finally, another clinical trial, Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease<sup>39</sup> (SAVE), is underway and will be the largest clinical trial to date in the sleep apnea field (anticipated completion September 2015). "The overall aim of SAVE is to determine if CPAP can reduce the risk of heart attack, stroke or heart failure for people with OSA." This trial plans to recruit 5000 participants and will be multi-center, involving various countries including China, India, Australia, and New Zealand. Similar to the RICCADSA trial, it will evaluate the impact of OSA treatment with CPAP on incidence of serious cardiovascular events among those with established cardiovascular disease.

Clinical trials such as these are essential to assessing the impact of CPAP therapy on important clinical outcomes, specifically those pertaining to the cardiovascular system. However, ethical and regulatory topics continue to be a major focus of concern for investigators in the field of sleep medicine. A recent article by Brown and colleagues<sup>40</sup> reviews important information (including follow-up duration) on ethical issues pertaining to the design and conduct of clinical trials in OSA.

## STROKE

The incidence of stroke approaches 800,000 cases per year, and this disorder ranks as the fourth leading cause of death, in the United States.<sup>41</sup> Established risk factors for cerebrovascular disease include atrial fibrillation, age older than 65 years, arterial hypertension, heart disease, asymptomatic carotid stenosis, history of transient ischemic attack (TIA), alcohol abuse, smoking, diabetes mellitus, and hypercholesterolemia.<sup>41</sup> These factors account only partially for the variability in stroke incidence, however, so far efforts aimed at stroke prevention require identification of additional modifiable risk factors. One such factor that has emerged in recent years is the presence of sleep-related breathing disorders (SRBDs), which comprise OSA, snoring, upper airway resistance syndrome, and central sleep apnea (including Cheyne-Stokes breathing).<sup>42,43</sup> SRBDs are highly prevalent in the general population, affecting 2% to 4% of adults.<sup>1</sup> Much higher rates are consistently observed in the population of patients who have suffered a stroke or TIA, however, with estimates ranging from 44% to 72% across series.<sup>42–45</sup> Data accumulated from prospective observational studies implicate SRBDs in the



**Fig. 1.** Data from a large observational cohort study that compared rates of fatal and nonfatal cardiovascular events (including percutaneous or surgical coronary revascularization, myocardial infarction, stroke) in patients with OSA versus simple snorers or healthy participants. The presence of severe OSA (AHI >30) was associated with a significantly increased risk of fatal (A) and nonfatal (B) cardiovascular events. cardiovascular system; OSA. (From Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnea-hypopnea with or without treatment with continuous positive airway pressure: an observational study. *Lancet* 2005;365:1046–53; with permission.)

pathogenesis of ischemic stroke.<sup>42,43,45,46</sup> Therefore, SRBDs offer an important target for future studies aimed at improving stroke outcomes.

The mainstay for treatment of SRBDs is positive airway pressure, with the particular type of therapy determined by the specific SRBD. Existing data have been mixed regarding whether CPAP

use can improve outcomes in patients with stroke. Most studies to date have been limited by small sample sizes, methodologic flaws, and non-randomized design. There are not yet data from randomized controlled trials supporting a benefit of CPAP for either primary or secondary stroke prevention.

One large observational study<sup>35</sup> followed more than 1000 individuals who were either diagnosed with OSA; simple snorers (AHI <5); or healthy adults. CPAP therapy was recommended to all patients with OSA and either AHI greater than 30 or AHI 5 to 30 with symptoms of excessive daytime sleepiness or coexistent heart failure. Over the course of 10 years, patients with untreated severe OSA (AHI >30) had a significantly higher incidence of fatal and nonfatal cardiovascular events than did healthy subjects (**Fig. 1**). By contrast, similar outcomes were seen in patients with OSA treated with CPAP and healthy participants. These data support a possible benefit of CPAP for improving cardiovascular and cerebrovascular outcomes in patients with severe OSA. Because this was not a randomized trial, however, it is possible that the poorer outcomes seen in the patients with severe OSA who refused CPAP may reflect confounding risk factors, such as poor adherence to other medical therapies and the presence of unaccounted comorbidities.

In summary, current knowledge remains limited regarding whether CPAP therapy can modify the natural history of stroke. At present there are no established guidelines recommending screening for SRBDs in patients with stroke or TIA. Because approximately 15% of strokes are preceded by a TIA, patients with TIA or minor stroke may represent particularly important candidates for CPAP as a means of prevention of subsequent cerebrovascular events. We await the results of several ongoing trials<sup>47–49</sup> examining the impact of CPAP therapy on clinical outcomes in patients with underlying cerebrovascular disease and SRBDs.

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