ORIGINAL ARTICLE

Effect of Positive Airway Pressure on Cardiovascular Outcomes in Coronary Artery Disease Patients with Nonsleepy Obstructive Sleep Apnea

The RICCADSA Randomized Controlled Trial

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Abstract

Rationale: Obstructive sleep apnea (OSA) is common in patients with coronary artery disease (CAD), many of whom do not report daytime sleepiness. First-line treatment for symptomatic OSA is continuous positive airway pressure (CPAP), but its value in patients without daytime sleepiness is uncertain.

Objectives: To determine the effects of CPAP on long-term adverse cardiovascular outcome risk in patients with CAD with nonsleepy OSA.

Methods: This single-center, prospective, randomized, controlled, open-label, blinded evaluation trial was conducted between December 2005 and November 2010. Consecutive patients with newly revascularized CAD and OSA (apnea–hypopnea index $\geq$15/h) without daytime sleepiness (Epworth Sleepiness Scale score $<$10) were randomized to auto-titrating CPAP (n = 122) or no positive airway pressure (n = 122).

Measurements and Main Results: The primary endpoint was the first event of repeat revascularization, myocardial infarction, stroke, or cardiovascular mortality. Median follow-up was 57 months. The incidence of the primary endpoint did not differ significantly in patients who did versus did not receive CPAP (18.1% vs. 22.1%; hazard ratio, 0.80; 95% confidence interval, 0.46–1.41; $P = 0.449$). Adjusted on-treatment analysis showed a significant cardiovascular risk reduction in those who used CPAP for $\geq$4 versus $<$4 hours per night or did not receive treatment (hazard ratio, 0.29; 95% confidence interval, 0.10–0.86; $P = 0.026$).

Conclusions: Routine prescription of CPAP to patients with CAD with nonsleepy OSA did not significantly reduce long-term adverse cardiovascular outcomes in the intention-to-treat population. There was a significant reduction after adjustment for baseline comorbidities and compliance with the treatment.

Clinical trial registered with www.clinicaltrials.gov (NCT 00519597).

Keywords: obstructive sleep apnea; coronary artery disease; cardiovascular outcomes

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At a Glance Commentary

Scientific Knowledge on the Subject: Obstructive sleep apnea is common in patients with coronary artery disease, many of whom do not report daytime sleepiness. Continuous positive airway pressure is the first-line treatment for symptomatic obstructive sleep apnea, but its value in patients without daytime sleepiness is uncertain.

What This Study Adds to the Field: This is the first randomized controlled study to address impact of continuous positive airway pressure on adverse cardiovascular outcomes in revascularized patients with coronary artery disease with obstructive sleep apnea but no daytime sleepiness. Routine prescription of the device did not reduce the adverse outcomes in this high-risk population in intention-to-treat analysis. There was a significant reduction after adjustment for baseline comorbidities and compliance with treatment.

Coronary artery disease (CAD) is one of the most common health problems in Western countries, having a poor prognosis and a high risk of mortality (1). Moreover, an increasing number of patients with CAD undergo percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) with a considerable risk of relapse of CAD in the years following the intervention, despite advances in medical treatment and revascularization techniques (2, 3).

Many of the traditional risk factors contributing to adverse outcomes in these patients are managed. However, obstructive sleep apnea (OSA), a common condition in patients with CAD (4), has largely been neglected. The paucity of data on the contribution of OSA to adverse outcomes in cardiac patients has been highlighted by the American Heart Association/American College of Cardiology (5), and probably contributes to a lack of recognition of OSA in the CAD setting.

Elimination of obstructive apneas and hypopneas with nasal continuous positive airway pressure (CPAP) is first-line treatment for OSA, reducing daytime sleepiness and improving quality of life (6). However, most patients with CAD with OSA do not experience daytime sleepiness (i.e., asymptomatic), and there is currently no clearly established rationale for treatment of such patients, notwithstanding clinical practice guidelines from the American Academy of Sleep Medicine that generally recommend CPAP treatment for OSA (7). Observational studies have demonstrated that CPAP is beneficial in patients with CAD and OSA who are adherent to treatment (8–10). There are many published short-term randomized controlled trials (RCTs) with CPAP, especially in patients with OSA with systemic hypertension, and CPAP has been shown to effectively lower blood pressure (BP) in these patients (11, 12). However, other trials suggest no benefit of CPAP in those without daytime sleepiness (13, 14), except one, suggesting a significant BP reduction in patients with newly diagnosed hypertension (15). Overall, there is good evidence to suggest that symptomatic patients with OSA should be treated with CPAP to reduce daytime sleepiness (6) and the risk of traffic accidents (16), and also perhaps to lower BP in hypertensive patients with OSA (11, 12, 15). Nevertheless, evidence from long-term prospective RCTs to determine whether cardiac patients with nonsleepy OSA should be offered CPAP treatment to reduce cardiovascular morbidity and mortality is lacking.

The RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA) trial investigated the effects of CPAP on the risk of cardiovascular events in patients with CAD and concomitant OSA without daytime sleepiness. Some of the results have been previously reported in the form of an abstract (17).

Methods

Study Design and Patients

Methodologic details have been published previously (18, 19), and are fully detailed in the online supplement. The target population comprised adult patients with angiography-verified CAD who had undergone PCI or CABG in Skaraborg County, West Sweden, in the previous 6 months, and had an apnea–hypopnea index (AHI) of less than 5 or greater than or equal to 15 per hour during a sleep study (*see* online supplement). Patients with existing OSA, an AHI of 5.0–14.9 per hour, and predominantly central apneas with Cheyne-Stokes respiration were excluded (Figure 1). Patients were recruited between December 2005 and November 2010, and follow-up was completed in May 2013. The study was a single-center (two sites), prospective, open, randomized, parallel, interventional, superiority trial of CPAP in patients with CAD with nonsleepy OSA (AHI $\geq$15/h; Epworth Sleepiness Scale [ESS] score $<$10) (Figure 1). Patients with CAD and sleepy OSA phenotype (AHI $\geq$15/h; ESS score $\geq$10) receiving CPAP and patients with CAD without OSA were followed as additional control subjects in observational arm for further *post hoc* comparisons (to be reported separately).

Study Oversight

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Gothenburg (approval No. 207-05; 09.13.2005; amendment T744-10; 11.26.2010; amendment T512-11; 06.16.2011), and all patients provided written informed consent. A blinded interim analysis was conducted in February 2010, and the protocol was amended with a new power calculation for the primary endpoints (*see* later). An independent clinical event committee reviewed all data obtained from hospital records and death certificates by the end of May 2013, unaware of patient identities and group allocation. A data monitoring board reviewed the protocol and monitored a random 10% selection of the database for baseline clinical data and follow-up procedures, including CPAP adherence and primary endpoints. All authors prepared the manuscript for publication, and made the decision to submit the manuscript without input from or review by ResMed Foundation and ResMed Ltd., who partly funded the trial by institutional grants. All authors guarantee the accuracy and completeness of the data. The trial was registered with the national researchweb.org (FoU i Sverige – Research and development in Sweden; No. VGSKAS-4731; 04.29.2005) and with ClinicalTrials.gov (NCT 00519597).

Sleep Studies, Group Assignment, and Randomization

Details of home sleep recordings (cardiorespiratory polygraphy [PG]) and in-hospital polysomnography (PSG) and randomization procedures are provided in

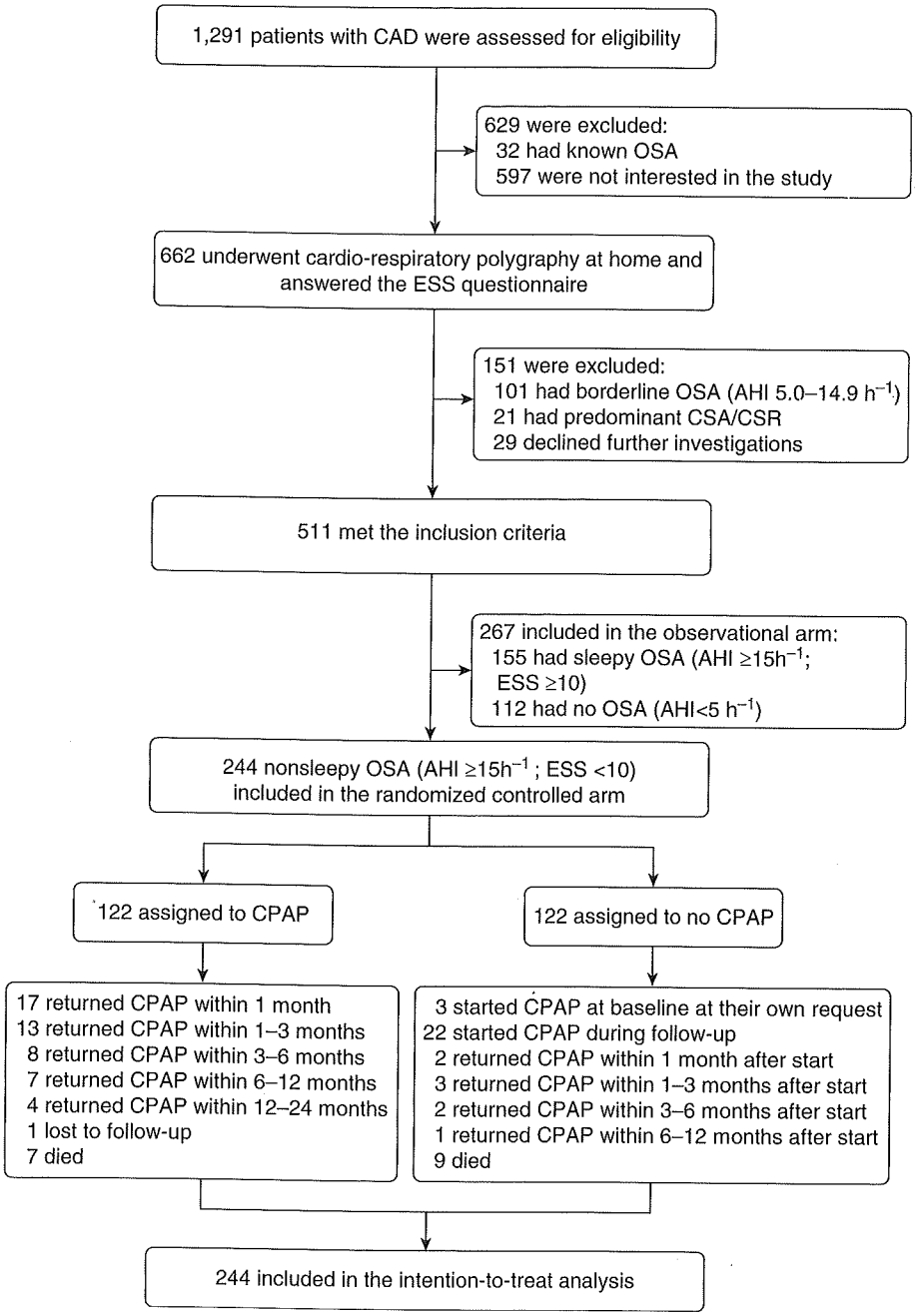

Figure 1. Flow of patients through the study. AHI = apnea–hypopnea index; CAD = coronary artery disease; CPAP = continuous positive airway pressure; CSA-CSR = central sleep apnea–Cheyne-Stokes respiration; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea.

the online supplement. The 1:1 random assignment of patients with CAD and nonsleepy OSA was scheduled with a block size of eight patients (four CPAP, four control subjects) stratified by sex and revascularization type (PCI/CABG).

Interventions and Follow-up

Nonsleepy patients with OSA who were randomized to treatment were fitted with an automatic CPAP device (S8 or S9; ResMed, San Diego, CA) by trained staff. Additional follow-up details, including adherence to CPAP treatment, are provided in the online supplement.

Outcomes

The primary endpoint was a composite of repeat revascularization, myocardial infarction (MI), stroke, and cardiovascular mortality. Information was obtained from patients' medical records and, when necessary, from the Swedish Hospital Discharge Register and the Swedish National Cause of Death Registry. Each event was evaluated separately and as part of the combined endpoint. For patients who experienced more than one event during the follow-up period, only the first event was included in the combined endpoint. All-cause mortality and acute hospital admission for cardiovascular reasons were among the secondary endpoints. Criteria for the cardiovascular diagnosis defined by the independent clinical event committee are available in the online supplement.

Statistical Analysis

Descriptive statistics are given as mean ± SD and as numbers (percentages). For baseline differences between the groups, the chi-square test and Fisher exact test were applied. Total sleep time, time spent on supine position and AHI values on the repeated sleep recordings (PG vs. PSG) at the individual level were compared with paired Student *t* test. Pearson correlation analysis was performed to test the linear relationship between the AHI values on PG versus PSG. All statistical tests were two-sided, and a *P* value less than 0.05 was considered significant. Statistical analysis was performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL) and Stata version 14 (StataCorp LP, College Station, TX).

Kaplan-Meier analyses and Cox proportional hazards models were performed in the intention-to-treat (ITT) population to estimate the impact of CPAP on the primary endpoint. For the on-treatment (OT) analysis, a time-dependent Cox model (20, 21) was used to estimate the impact of CPAP usage on the primary endpoint. This approach accounts for the time-varying character of the intervention because subject follow-up is split into multiple intervals according to the visit dates of the CPAP usage evaluation. Originally, visits were planned after 1, 3, 6, and 12 months and then annually until the end of the study. Incomplete usage data caused by missed visits were replaced as follows. One missing episode was replaced by the last observation, if the missing episode was followed by a visit. Two or more subsequent missing visits were replaced by 0. If the data from the first visit after 1 month were missing, they were

replaced by the usage data of the 3-month visit. Multivariate adjustment was made for CPAP nights per period and baseline left ventricular ejection fraction, age, sex, AHI, body mass index, current smoking, revascularization type, former revascularization, acute MI, hypertension, diabetes mellitus, and lung disease.

Sample Size Estimation

At the time of the study start in 2005, available literature suggested that the incidence rate for a combination of cardiovascular mortality, acute MI, and the need for a new revascularization within a year of PCI was 27% (22). Moreover, in a systemic review of the comparative effectiveness of PCI and CABG, the 5-year repeat revascularization rate was reported to be 40.1% in PCI with stents and 9.8% in patients with CABG (23). There were no studies in revascularized patients with CAD and concomitant OSA before 2005 to accurately inform estimates of study power for the primary outcome assessments; therefore, a composite endpoint rate of 25% in nonsleepy patients with untreated OSA over a 3-year follow-up period was hypothesized. The RCT arm was designed to initially comprise a consecutive sample of 200 patients with (100 nonsleepy OSA randomized to CPAP; 100 to no CPAP). It was assumed that approximately 25% of the OSA subjects would be noncompliant with CPAP during the follow-up period. The trial was expected to have an 80% power to detect a risk reduction in the rate of the composite endpoint from 25% to 10% on an ITT basis ($P < 0.05$ level, two-sided test). An interim analysis blinded to randomization group performed in February 2010 revealed an incident rate of 21%, and a CPAP adherence rate of 60% at 1 year, resulting in a protocol amendment. As a result, using an enlarged sample size of 242 patients (121 in each of the randomization arm) and an extended follow-up period of 2 or more years and 7 or fewer years, a significant risk reduction for the primary endpoint from 25% to 12% was hypothesized.

Results

Study Participants

A total of 1,259 patients met the inclusion criteria for screening, of whom 662 (52.7%) agreed to participate in the sleep study (Figure 1). Diagnostic PG was performed at home after an average of 63 days following mechanical revascularization (median, 59 d; interquartile range, 42–78), and patients fulfilling the inclusion criteria for the RCT or the observational arm underwent baseline investigations on average 35 days (median, 30; interquartile range, 20–45) after home sleep recordings.

Baseline Characteristics

A total of 244 patients with CAD and OSA fulfilled the inclusion criteria for the RCT arm. Nonsleepy patients with OSA allocated to CPAP did not differ significantly from nonsleepy patients with OSA allocated to no CPAP with regard to demographic and clinical characteristics (Table 1).

Numbers Analyzed

Median follow-up time until mortality, loss to follow-up, or the end of the study was 56.9 months (range, 6.5–90.2). All patients were included in the ITT analysis for primary outcomes; 16 patients died, and one was lost to follow-up (Figure 1). Of 244 patients with AHI greater than or equal to 15 per hour on PG, four had AHI less than 5 per hour on in-hospital PSG the day before the RCT started, 19–54 days after initial at-home PG. Follow-up data for these four patients are provided in Table E1 in the online supplement, and correlations between AHI values on PG versus PSG for the OSA group are shown in Figure E1. Of patients with OSA allocated to CPAP at baseline, 49 returned the device within 2 years. Of the nonsleepy patients with OSA randomized to no CPAP, three wanted to start CPAP at baseline, and 22 during the amended follow-up period because of reaching the nonfatal endpoints and/or completing the initial 3-year follow-up, or developing daytime sleepiness. CPAP compliance data from CPAP devices are shown in Table E2.

Outcomes

Intention-to-treat. Overall, 49 patients reached the combined endpoint during follow-up, 22 (18.1%) in the CPAP group and 27 (22.1%) in the no-CPAP group (not

Table 1. Demographic and Clinical Characteristics of Study Patients at Baseline

	CPAP ($n = 122$)	No CPAP ($n = 122$)	*P* Value
Age, yr	65.5 (8.5)	66.5 (8.2)	0.382
AHI, events/h	28.3 (12.7)	29.3 (14.0)	0.545
ODI, events/h	16.7 (11.4)	16.3 (11.8)	0.804
ESS score	5.5 (2.4)	5.5 (2.2)	0.991
BMI, kg/m^2	28.4 (3.8)	28.5 (3.5)	0.840
LVEF, %	56.9 (9.0)	56.1 (9.9)	0.479
Obesity, %	27.9	27.9	1
Female, %	18.0	13.9	0.382
Current smoker, %	18.0	13.9	0.382
Pulmonary disease, %	3.3	9.8	0.067
Hypertension, %	68.9	59.0	0.110
Acute MI at baseline, %	53.3	45.9	0.249
CABG at baseline, %	27.0	27.0	1
Previous PCI or CABG, %	22.1	18.9	0.526
Diabetes mellitus, %	27.9	20.5	0.178
β-Blocker use, %	91.5	86.7	0.230
Diuretic use, %	20.3	22.7	0.660
CCB use, %	22.9	16.7	0.229
ACE inhibitor use, %	47.5	47.5	0.995
ARB use, %	12.7	16.7	0.389
Anticoagulant use, %*	100	97.5	0.083
Lipid-lowering agent use, %	96.6	93.3	0.248

Definition of abbreviations: ACE = angiotensin-converting enzyme; AHI = apnea–hypopnea index; ARB = angiotensin II receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CCB = calcium channel blocker; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; LVEF = left ventricular ejection fraction; MI = myocardial infarction; ODI = oxygen desaturation index; PCI = percutaneous coronary intervention.
Values are mean (SD) or percentage of patients.
*Anticoagulant use refers to aspirin and/or clopidogrel and/or warfarin use.

significant). The incidence of the composite endpoint was 4.65 (95% confidence interval [CI], 4.56–4.73) per 100 person-years; 4.18 (95% CI, 2.75–6.35) per 100 person-years in the CPAP group versus 5.21 (95% CI, 3.57–7.60) per 100 person-years in the no-CPAP group, respectively ($P = 0.449$). Cumulative incidences of the primary endpoint are illustrated in Figure 2. There were no significant differences in the individual incidences of the endpoints in the PCI and CABG subgroups (*see* Table E3). Univariate predictors of adverse outcomes were diabetes mellitus and former revascularization, whereas CABG at baseline was protective (Table 2). On multivariate analysis, diabetes mellitus (hazard ratio [HR], 2.05; 95% CI, 1.06–3.98; $P = 0.034$) and former revascularization (HR, 3.29; 95% CI, 1.77–6.10; $P < 0.001$) were significantly associated with increased risk for the composite endpoint, whereas CABG at baseline (HR, 0.30; 95% CI, 0.12–0.75; $P < 0.001$) was associated with reduced risk (Table 2).

On-treatment. There was no significant difference in incidence rates between the groups when applying a cut-off level of 3 hours of CPAP usage per night, but there was a significant between-group difference based on CPAP usage for 4 or more hours per night (six events) versus less than 4 hours per night or no CPAP (43 events) with an HR 0.29 and 95% CI of 0.10–0.86 with covariable adjustments (Table 3). The incidence of the composite endpoint was 2.31 (95% CI, 0.96–5.54) per 100 person-years for CPAP usage for 4 or more hours per night, and 5.32 (95% CI, 3.96–7.15) per 100 person-years for CPAP usage less than 4 hours per night or no CPAP.

Adverse Events

One patient (age 81 yr) with CAD and mechanical aortic valve prosthesis, who was on combination therapy with warfarin and clopidogrel after PCI, could not use the CPAP device because of frequent nasal bleeding on treatment. This patient restarted CPAP therapy without any nasal bleeding when clopidogrel was discontinued 3 years after PCI. Other patient-reported side effects during CPAP fitted with the known tolerability profile of CPAP, and included dry mouth, nasal symptoms, claustrophobia, insomnia, noise problems, and mask fit.

Discussion

This study showed that routine prescription of CPAP to patients with CAD and nonsleepy OSA did not significantly reduce the long-term cardiovascular event rate. A significant beneficial effect of CPAP was seen first after adjusting for baseline comorbidities and CPAP adherence.

To our knowledge, this is the first RCT investigating the effect of CPAP on long-term cardiovascular outcomes in patients with CAD and concomitant OSA without daytime sleepiness. Two RCTs are currently underway investigating the impact of CPAP on long-term outcomes in larger cohorts with established cardiovascular disease (24, 25). Many previous studies that showed beneficial effects of CPAP in patients with CAD and OSA had an observational design. A review of 371 patients with OSA and CAD who underwent PCI reported a significantly lower 5-year cardiac death rate (3%) among 175 patients treated with CPAP compared with 196 untreated patients (10%) (10). Data from a sleep clinic cohort demonstrated that CPAP treatment significantly reduced cardiovascular risk in men with severe OSA (26). Similarly, adequate CPAP treatment has been shown to reduce the risk of a composite endpoint of incident CAD or stroke in women with OSA (27). Moreover, after adjustment for confounding factors, post-MI patients with OSA who were compliant with CPAP had a lower risk of recurrent MI and repeat revascularization than untreated patients, and similar to patients without OSA (28).

In this RCT, CPAP treatment of CAD and nonsleepy patients with OSA did not significantly reduce the rate of adverse cardiovascular outcomes. These results may reflect the fact that getting nonsleepy patients to comply with CPAP is challenging. Between-group differences at baseline may also have influenced the findings. Randomization was not stratified by comorbidities, and there was a higher proportion of patients with acute MI, diabetes mellitus, and hypertension in the CPAP arm. OT analysis showed that CPAP was effective in nonsleepy patients who used the device for 4 or more hours per night, with an adjusted HR that was of similar magnitude to that reported in a previous observational study (27).

Many patients with CAD with OSA do not experience daytime sleepiness, and it has been suggested that nonsleepy patients with OSA might have poor CPAP adherence because they do not experience subjective benefits from therapy (29). This may be the case, although overall adherence in the

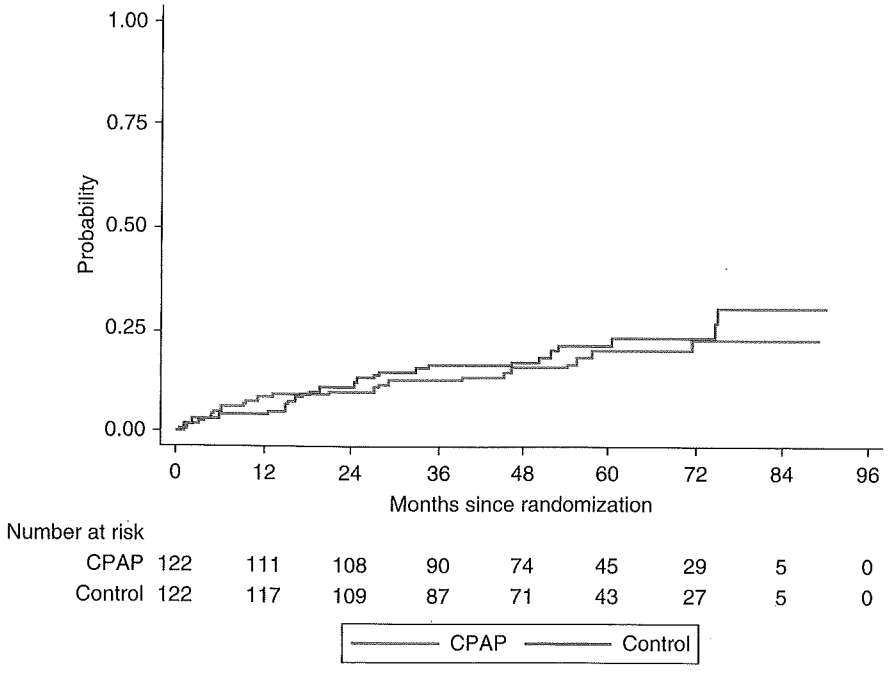

Figure 2. Cumulative incidences of the composite endpoint in the intention-to-treat population. CPAP = continuous positive airway pressure.

Table 2. Cox Regression Analysis of Baseline Covariables Associated with Risk for Adverse Cardiovascular Outcomes in Revascularized Patients with Coronary Artery Disease and Obstructive Sleep Apnea without Daytime Sleepiness in the Intention-to-Treat Analysis (n = 244; 49 Patients Reached the Composite Endpoint)

	Univariate			Multivariate		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
CPAP assignment vs. no CPAP	0.80	0.46–1.41	0.449	0.62	0.34–1.13	0.120
Age	1.02	0.98–1.05	0.372	1.01	0.98–1.05	0.474
Females vs. males	0.48	0.17–1.33	0.155	0.43	0.15–1.23	0.114
Apnea–hypopnea index	1.00	0.98–1.02	0.783	0.99	0.97–1.01	0.363
Body mass index	1.01	0.94–1.09	0.753	0.99	0.91–1.08	0.802
CABG vs. PCI	0.38	0.17–0.84	0.017	0.30	0.12–0.75	0.010
Current smoking	1.29	0.63–2.67	0.485	1.78	0.80–3.96	0.156
Hypertension	1.09	0.60–1.96	0.776	1.59	0.81–3.12	0.176
Diabetes mellitus	1.92	1.06–3.47	0.030	2.05	1.06–3.98	0.034
Acute myocardial infarction	1.02	0.58–1.79	0.947	1.03	0.54–1.94	0.937
Previous PCI or CABG	3.36	1.91–5.93	<0.001	3.29	1.77–6.10	<0.001
Pulmonary disease	1.39	0.50–3.85	0.532	0.95	0.33–2.74	0.925
Left ventricular ejection fraction	0.99	0.96–1.02	0.594	0.99	0.96–1.02	0.513

Definition of abbreviations: CABG = coronary artery bypass grafting; CI = confidence interval; CPAP = continuous positive airway pressure; PCI = percutaneous coronary intervention.

current CAD population did not differ markedly from long-term adherence rates in sleep clinic cohorts (30). Indeed, an observational study of a sleep clinic cohort with CAD suggested comparable adherence to CPAP in sleepy and nonsleepy patients (31), and a larger RCT addressing the impact of CPAP treatment on incident hypertension or cardiovascular events in nonsleepy patients with OSA from sleep clinics reported that 64% of patients were using CPAP for 4 or more hours per night after a median 4-year follow-up (32).

The results of the current study suggest that CPAP treatment is feasible in CAD populations with nonsleepy OSA, given the additional assumption that such high-risk patients might expect greater cardiovascular benefits, and may be more motivated to comply with treatment despite the lack of daytime sleepiness. However, initial data from the SAVE trial suggest a lower CPAP compliance rate than in this study, despite an initial 1-week run-in phase with sham-CPAP to exclude noncompliant patients before randomization (15% of all eligible patients were excluded) (33). Thus, adherence remains a challenging issue when evaluating the cardiovascular benefits of CPAP treatment in patients with CAD and concomitant OSA without daytime sleepiness. Also, the finding that CPAP use for 4 or more hours per night is required to achieve cardiovascular benefits in nonsleepy patients with OSA is similar to the results of a previous *post hoc* analysis (32).

CPAP is not the only treatment option for OSA. In a recent RCT, adherence to a weight loss regimen and CPAP resulted in incremental BP reductions compared with either intervention alone (34). There is also accumulating evidence for a beneficial impact of mandibular advancement devices on BP in patients with OSA (35, 36). Moreover, given the emergence of new mechanical and pharmacologic interventions in sleep medicine (37), improved "personalization" of OSA therapy may be possible through better characterization of individual patient pathophysiology.

Despite the lack of conclusive evidence for a beneficial effect of CPAP in the current trial, the high prevalence of OSA in the entire study population (19) indicates that OSA should be considered when assessing the impact of different treatments (e.g., lipid-lowering agents, bare-metal vs. drug-eluting stents) in revascularized CAD cohorts. Effective treatment of OSA with CPAP, or other approaches, is challenging in patients

Table 3. Cox Regression Analysis of the Association between Time-Dependent CPAP Usage and Adverse Cardiovascular Outcomes in 244 Revascularized Patients with Coronary Artery Disease and Obstructive Sleep Apnea without Daytime Sleepiness (49 Patients Reached the Composite Endpoint)

	Univariate			Multivariate*		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
CPAP usage ⩾3 h/night	0.64	0.31–1.33	0.234	0.91	0.16–5.13	0.911
CPAP usage ⩾4 h/night	0.43	0.18–1.02	0.057	0.29	0.10–0.86	0.026
CPAP usage ⩾5 h/night	0.43	0.17–1.09	0.075	0.34	0.10–1.12	0.075

Definition of abbreviations: CI = confidence interval; CPAP = continuous positive airway pressure.
*Adjusted for CPAP nights per period, age, sex, body mass index, apnea–hypopnea index, current smoking, pulmonary disease, hypertension, diabetes mellitus, acute myocardial infarction, revascularization type at baseline, former revascularization, and left ventricular ejection fraction at baseline.

with CAD with nonsleepy OSA, but needs to be evaluated in secondary prevention models.

The strengths of this study include its randomized controlled design for patients with CAD and nonsleepy OSA with only one lost to follow-up. Although the inclusion rate for eligible patients for sleep screening was only 53%, the inclusion design was consecutive, and there were no significant differences in baseline characteristics of patients undergoing versus not undergoing sleep study (19).

This study also had a number of limitations. First, it was a single-center trial with two sites, which limits generalizability of results across geographic regions. Second, "nonsleepy" OSA relied on an ESS threshold, which may not reflect an objective sleepiness. However, this is a generally accepted tool for subjective daytime sleepiness, and other methods, such as Multiple Sleep Latency Test (38), which is used as an objective tool, is time consuming and not feasible to run for the large-scale cardiac populations. Third, the study was underpowered for the ITT arm for several reasons. CPAP adherence in patients with CAD and nonsleepy OSA was lower than initially expected, which possibly resulted in an inadequately powered sample size estimation. Although CPAP adherence rates were slightly higher than those reported in the SAVE trial (33), those data had not been published when the current study started or when the interim analysis was performed. Furthermore, revascularized patients with CAD were a heterogeneous group, including both PCI and CABG, and both acute/subacute and elective PCI, and the apparent treatment effect was far smaller than anticipated because of an optimistic first assumption.

Fourth, the trial was open-label, and had no placebo control arm. As previously discussed (39), there is no true sham CPAP or other appropriate placebo for CPAP in a long-term trial in patients with cardiovascular disease. It is also possible that sham CPAP consisting of a mask attached to tubing, but without pressure application, would worsen sleep disturbance and act as a "negative placebo" (40). Finally, results of the OT analysis must be interpreted with care because device usage is patient-driven and self-selection bias cannot be excluded.

In conclusion, routine CPAP prescription of CPAP to patients with CAD with nonsleepy OSA did not significantly reduce long-term adverse outcomes. However, the study may have had limited power to detect a significant difference in the ITT population. The risk reduction was observed first after adjustment for baseline comorbidities and CPAP adherence. These findings need to be further explored in larger clinical cohorts with more homogenous CAD populations. ■

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