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Effect of Continuous Positive Airway Pressure on the Incidence of Hypertension and Cardiovascular Events in Nonsleepy Patients With Obstructive Sleep Apnea

A Randomized Controlled Trial

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Context Continuous positive airway pressure (CPAP) is the first-line treatment for patients with symptomatic obstructive sleep apnea (OSA). However, its indication for all patients with sleep-disordered breathing, regardless of daytime symptoms, is unclear.

Objective To evaluate the effect of CPAP treatment on the incidence of hypertension or cardiovascular events in a cohort of nonsleepy patients with OSA.

Design, Setting, and Patients Multicenter, parallel-group, randomized controlled trial in 14 teaching hospitals in Spain. Between May 2004 and May 2006, 725 consecutive patients were enrolled who had an apnea-hypopnea index of 20 h^{-1} or greater and an Epworth Sleepiness Scale score of 10 or less (scores range from 0-24, with values <10 suggesting no daytime sleepiness). Exclusion criteria were previous cardiovascular event, physical or psychological incapacity, chronic disease, or drug or alcohol addiction. Follow-up ended in May 2009.

Intervention Patients were allocated to receive CPAP treatment or no active intervention. All participants received dietary counseling and sleep hygiene advice.

Main Outcome Measures Incidence of either systemic hypertension (taking antihypertensive medication or blood pressure greater than 140/90 mm Hg) or cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, or cardiovascular death).

Results Seven hundred twenty-three patients underwent follow-up for a median of 4 (interquartile range, 2.7-4.4) years (1 patient from each group did not receive allocated treatment); 357 in the CPAP group and 366 in the control group were included in the analysis. In the CPAP group there were 68 patients with new hypertension and 28 cardiovascular events (17 unstable angina or arrhythmia, 3 nonfatal stroke, 3 heart failure, 2 nonfatal myocardial infarction, 2 transient ischemic attack, 1 cardiovascular death). In the control group there were 79 patients with new hypertension and 31 cardiovascular events (11 unstable angina or arrhythmia, 8 nonfatal myocardial infarction, 5 transient ischemic attack, 5 heart failure, 2 nonfatal stroke). The hypertension or cardiovascular event incidence density rate was 9.20 per 100 person-years (95% CI, 7.36-11.04) in the CPAP group and 11.02 per 100 person-years (95% CI, 8.96-13.08) in the control group. The incidence density ratio was 0.83 (95% CI, 0.63-1.1; $P=.20$).

Conclusions In patients with OSA without daytime sleepiness, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events. However, the study may have had limited power to detect a significant difference.

Trial Registration clinicaltrials.gov Identifier: NCT00127348

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OBSTRUCTIVE SLEEP APNEA (OSA) is a common disease that affects 3% to 7% of the general population.[1,2] Sleep apnea is caused by the collapse of the upper airway during sleep, which leads to transient asphyxia. These events lead to brain arousal, intermittent hypoxemia (which induces hypersomnolence), poor quality of life, and metabolic disturbances. Cross-sectional and longitudinal studies have shown an association between OSA and hyperten-

See also pp 2169 and 2197.

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sion,[3,4] and OSA has been associated with cardiovascular diseases,[5-7] although this association is attenuated in some studies when adjusted for age and obesity.[8]

Continuous positive airway pressure (CPAP) acts as a pneumatic splint to the upper airway during sleep and corrects the obstruction, improving daytime sleepiness and quality of life in patients with OSA.[9] Also, CPAP treatment can reduce blood pressure in these patients.[10] Observational studies suggest that CPAP treatment reduces the incidence of fatal and nonfatal cardiovascular events in patients with severe[11] and moderate[12] OSA. However, none of these studies were randomized. To perform such studies in symptomatic patients would be unethical because available evidence of the effectiveness of CPAP on symptom control and accident risk precludes the possibility of withholding treatment in a long-term study. The indication for CPAP treatment in nonsleepy patients is under debate. Two short-term randomized controlled trials have shown no effect of CPAP on blood pressure and clinical variables in nonsleepy patients with OSA.[13,14] Nonetheless, because of the high incidence of cardiovascular complications in patients with OSA, some authors advocate the long-term use of CPAP treatment for all patients with sleep-disordered breathing, regardless of daytime symptoms.[15]

The primary objective of this study was to evaluate the effect of CPAP treatment on the incidence of hypertension or cardiovascular events in a cohort of nonsleepy patients with OSA. We studied this composite outcome because hypertension and cardiovascular events have been associated with OSA, they share related pathological pathways, and their clinical relevance has been established.[16] The secondary objective was to evaluate the relationship between OSA severity and the incidence of hypertension or cardiovascular events.

METHODS

Setting and Participants

Recruitment took place in 14 Spanish teaching hospitals between May 2004 and May 2006. Follow-up ended in May 2009. Patients were referred to sleep units for evaluation of observed apneas or snoring. The study was approved by the ethics committee of each participating center, and patients provided written informed consent.

Patients were eligible if they were between 18 and 70 years old, showed 20 or more apneas plus hypopneas per hour (apnea-hypopnea index [AHI]) in an overnight sleep study, and had no daytime hypersomnolence, defined as an Epworth Sleepiness Scale (ESS) score of 10 or lower (ESS scores have a range of 0-24). The exclusion criteria were physical or psychological incapacity, any previous cardiovascular event, chronic disease, drug or alcohol addiction, chronic intake of hypnotics, or refusal to participate in the study. Patients with a history of hypertension were not excluded.

The OSA diagnosis was made using a conventional polysomnographic or cardiorespiratory sleep study. The cardiorespiratory study included, at minimum, continuous recording from nasal cannulae, thoracic-abdominal motion, oxygen saturation, and body position. Results from all sleep studies were analyzed by trained personnel at each participating center, using standard criteria. An apnea was defined as an absence of airflow of 10 seconds or longer and a hypopnea as an airflow reduction (>50%) lasting 10 seconds or longer with a greater than 4% decrease in oxygen saturation. Obstructive apneas were defined as the absence of airflow in the presence of chest or abdominal wall motion. The AHI was calculated based on the average number of apnea plus hypopnea episodes per hour of sleep or recording time.

Randomization, Blinding, and Intervention

Eligible patients were randomly assigned in a 1:1 ratio to receive CPAP treatment or no active intervention. Randomization was performed using a computer-generated list of random numbers in the coordinating center and was stratified by center. The results were mailed in numbered opaque envelopes. The coordinating center saved a sealed copy of the randomization list sent to each center. Blood pressures and all cardiovascular events were assessed objectively by personnel not involved in the study and blinded to patient allocation. Patients, researchers, and the statistician were not blinded to patient allocation.

CPAP titration was performed using conventional polysomnography or an autoCPAP device following a validated protocol.[17] CPAP adherence was measured using the machines' internal clocks. All participants received sleep hygiene advice and dietary counseling for weight loss from the staff of the sleep units. There was no specific weight loss program, and patients were referred to their general practitioner to monitor weight loss.

Outcomes and Follow-up

The primary outcome was the incidence of either systemic hypertension (among participants who were normotensive at baseline) or cardiovascular events (among all participants). The secondary outcome was the association between the incidence of hypertension or cardiovascular events and the severity of OSA assessed by the AHI and oxygen saturation.

Information regarding medication use, OSA severity, sleepiness (ESS score), blood pressure, a basic biochemical assessment, and results of electrocardiography were recorded for each patient at inclusion. Cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, transient ischemic attack, hospitalization for unstable angina or arrhythmia, heart failure, and cardiovascular death. All cardiovascular events were identified by a cardiologist or neurologist not involved in the study and blinded to the patients' randomization status. Hypertension was defined as taking antihypertensive medication or blood pressure greater than 140/90 mm Hg. Blood pressure measurements were taken by experienced nurses, following international guidelines.[18]

Patients were evaluated at 3, 6, and 12 months and annually thereafter. The

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study was designed to follow up patients for at least 3 years. However, follow-up for the main outcome was stopped when the patients developed new-onset hypertension or experienced a cardiovascular event, withdrew informed consent, were unable to complete follow-up, or when there was a change from control group to CPAP treatment. Exposure time was defined as the time between randomization and first cardiovascular event or new-onset hypertension, date of death, date of the last study visit, date of withdrawal, or loss to follow-up.

At each visit a physician recorded cardiovascular events, blood pressure, ESS score, weight, CPAP adherence, medications, alcohol and tobacco consumption, and other clinically relevant events.

Sample Size

The sample size was calculated assuming that the incidence of hypertension or new cardiovascular event in this population over a period of 3 years would be 10% annually. This estimation was based on published studies[19] and data provided by the Spanish National Epidemiology Center. We estimated that CPAP would reduce the incidence of new hypertension or cardiovascular events by 60% based on a cohort study by Marin et al[11] that showed a cardiovascular event rate of 2.13 per 100 person-years in an untreated group vs 0.64 per 100 person-years in a group of patients treated with CPAP, a 70% relative rate reduction. We assumed $\alpha = .05$, $\beta = .10$, 2-sided significance testing, and 10% study dropout. Under these assumptions, the study would need to enroll a total of 345 patients per group.

Statistical Analysis

Data were stored in a web-based application. R version 2.10.1 was used for all analyses. Estimated means for treatment adherence, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), and ESS scores during the follow-up period were computed individually for each patient as the area under the curve obtained from the values reported in follow-up visits, taking into account the time between visits and the last available information.

Mann-Whitney tests (or *t* tests if data were normally distributed) and Pearson χ^2 tests with a Yates continuity correction (or Fisher exact tests if expected frequencies were less than 5) were used for continuous and categorical variables, respectively, when comparing the CPAP and control groups. The effect of the CPAP intervention was assessed as an incidence density ratio (IDR) of hypertension or cardiovascular events, and significance was assessed using the Wald test. A modified intention-to-treat approach was used, in which all patients receiving the allocated intervention were included in the analysis of the primary outcome.

For modeling incidence, a Poisson regression model was used and adjusted for intervention group. An additional analysis including random hospital (site) effect was performed because of the hospital imbalances in baseline variables. A goodness-of-fit test for the assumption of a Poisson distribution was performed in every adjusted model to determine if a negative binomial model should be used instead. The use of a Cox proportional hazards regression model was not possible because the data did not satisfy the proportional hazards assumption.[20] Available information was used with no need for imputation.

The cumulative incidence, CI(t), of events at time t was estimated using the incidence density at that time, ID(t), in the equation $CI(t) = 1 - \exp\{-ID(t)*t\}$. Therefore, each point of the graph shows the cumulative incidence after t years of follow-up in the study, expressed as a percentage. A post hoc analysis was performed to assess a possible dose-response relationship. For this analysis, the CPAP group was partitioned based on whether the mean CPAP adherence during follow-up was less than 4 hours.[11] The outcomes in each of these CPAP subgroups were compared with those in the control group. The Kruskal-Wallis rank-sum test was used to analyze the dose-response relationship as well as differences between hospitals in quantitative baseline variables.

The secondary outcome of the study was to assess the association between the incidence of cardiovascular events or hypertension and disease severity. To assess this association, we tested the interaction of severity variables (AHI and time with arterial oxygen saturation [Sa_{O_2}] <90%, dichotomized into 2 groups based on their median values) with the intervention in a Poisson regression model, with the outcome variable being the incidence of hypertension or cardiovascular events.

Differences between baseline values and the mean area under the curve for BMI and ESS score in follow-up visits were calculated for each patient. These differences were compared between intervention groups using the Mann-Whitney nonparametric test.

RESULTS

A total of 725 patients were randomized, with 357 in the CPAP group and 366 in the control group analyzed (FIGURE 1). Baseline variables were comparable between the CPAP and control groups, with the exception of AHI and time with Sa_{O_2} less than 90%. Fifty percent of the sample was hypertensive at inclusion (TABLE 1). Many of the baseline variables had site-specific differences (eTable 1, available at http://www.jama.com).

Follow-up time until a cardiovascular event, loss to follow-up, or the end of the study ranged from 0 to 5.38 years, with a median of 4.0 years (interquartile range [IQR], 2.7-4.4 years). There were no significant differences in median follow-up between groups using the Mann-Whitney test (4.01 years [IQR, 3.01-4.37] for the CPAP group vs 3.96 years [IQR, 2.19-4.38] for the control group; $P = .13$).

Primary Outcome: Effects of CPAP on the Incidence of Hypertension or Cardiovascular Events

A total of 147 patients with new hypertension and 59 cardiovascular events were identified. In the CPAP group, there were 68 patients with new hyperten-

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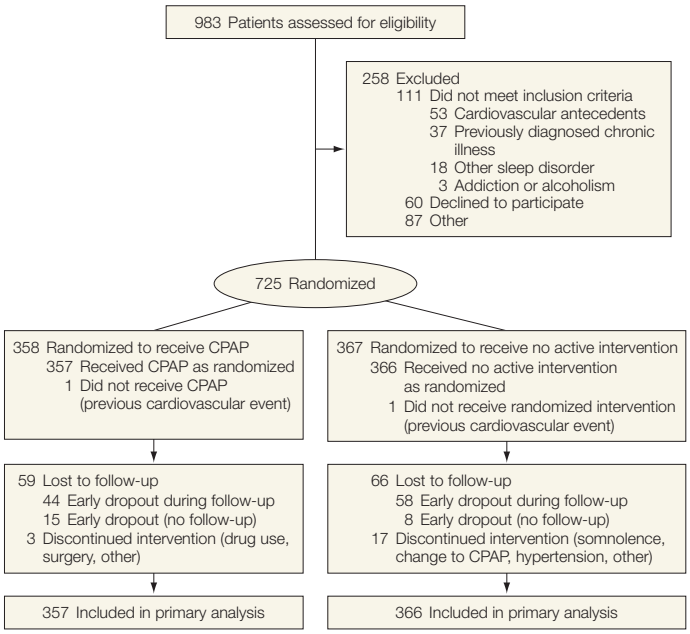
Figure 1. Participant Flow



Only those patients excluded in the allocation process were excluded from the analysis. Discontinuation of intervention was more frequent in the control group, in which patients were excluded because of somnolence (n=7), change to continuous positive airway pressure (CPAP) (n=5), hypertension (n=2), drug abuse (n=1), pregnancy (n=1), or other cause (n=1).

sion and 28 cardiovascular events (17 hospitalizations for unstable angina or arrhythmia, 3 nonfatal stroke, 3 heart failure, 2 nonfatal myocardial infarction, 2 transient ischemic attack, 1 cardiovascular death). In the control group, there were 79 patients with new hypertension and 31 cardiovascular events (11 hospitalizations for unstable angina or arrhythmia, 8 nonfatal myocardial infarction, 5 transient ischemic attack, 5 heart failure, 2 nonfatal stroke). The incidence density rate for hypertension or cardiovascular events in the CPAP group was 11.02 per 100 person-years and in the control group was 9.20 per 100 person-years. The IDR was 0.83 (95% CI, 0.63-1.1; $P=.20$) (TABLE 2 and FIGURE 2A). Adjustment for random hospital (site) effect did not substantially modify these results (TABLE 3)

Secondary Outcomes: Relationship Between Incidence of Events and OSA Severity

Disease severity was assessed using AHI and time with SaO_2 less than 90%. The effect of CPAP on the incidence of hypertension or cardiovascular events with reference to the control group showed no significant differences across subgroups of AHI ($P=.48$) or the percentage of time with SaO_2 less than 90% ($P=.23$). No significant interaction was found between treatment group and each of the disease severity variables.

Subgroup Analyses

The mean CPAP adherence ranged from 0 to 8.76 h/night, with a median of 5.00 h/night (IQR, 2.18-6.25). In a post hoc analysis, we partitioned the patients in the CPAP group based on a mean adherence of 4 h/night.[11] There were 127 patients (36%) with a mean adherence less than 4 h/night (median, 1.00 [IQR, 0.00-2.75]) and 230 with adherence of 4h/night or longer (median, 5.96 [IQR, 5.05-6.70]). There were significant differences between these subgroups in AHI, time with SaO_2 less than 90%, neck circumference, BMI, and hypertension when compared at baseline (TABLE 4).

Primary Outcome by Adherence Subgroups

Patients who used CPAP for less than 4 h/night had an IDR of 1.13 (95% CI, 0.78-1.64; $P=.51$), compared with the control group. In contrast, patients who used CPAP for 4 h/night or longer had an IDR of 0.72 (95% CI. 0.52-0.98; $P=.04$) (Table 2 and Figure 2B). Adjustment for random hospital (site) effect did not substantially modify these results (Table 3).

Secondary Outcome by Adherence Subgroups

In post hoc analyses the effect of CPAP on the incidence of hypertension or cardiovascular events with reference to the control group showed a significant interaction with time with SaO_2 less than 90% when CPAP was partitioned based on a threshold of 4 hours of adherence ($P=.03$), while interaction with AHI remained nonsignificant ($P=.57$). Thus, the effect of CPAP was significantly different when taking into account adherence, depending on whether the value of the percentage of time with SaO_2 less than 90% was greater than the overall median of 6.8%.

Another stratified analysis was conducted, adjusting for AHI. The sample was first divided into subgroups based on the percentage of time with SaO_2 less than 90% (with a cutpoint of 6.8% of the time). These subgroups were then divided again based on CPAP adherence (with a cutpoint of 4 h/night). For 6.8% of time or less with SaO_2 less than 90%, the IDR was 0.71 (95% CI, 0.40-1.27; $P=.25$) for CPAP adherence less than 4 h/night and 0.72 (95% CI, 0.45-1.15; $P=.17$) for CPAP adherence of 4 h/night or longer. For greater than 6.8% of time with SaO_2 less than 90%, the IDR was 1.89 (95% CI, 1.14-3.13; $P=.01$) for CPAP adherence less than 4 h/night and 0.71 (95% CI, 0.45-1.13; $P=.15$) for CPAP adherence of 4 h/night or longer. Thus, IDR differed significantly from the control group only in the subgroup with greater than 6.8% of time with SaO_2 less than 90% and CPAP adherence less than 4 h/night.

Additional Results

The separate incidence of cardiovascular events or new-onset hypertension

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is reported in the supplementary online content. When assessed separately, CPAP did not show any statistically significant effect on the incidence of new cardiovascular events (eTable 2, eTable 3, and eFigure 1) or on new-onset hypertension (eTable 4, eTable 5, and eFigure 2).

There were 8 deaths in the CPAP group and 3 in the control group. The IDR for death was 2.6 (95% CI, 0.70-11.8; $P=.16$). Of the patients assigned to CPAP, 5 died of cancer, 1 of cardiovascular causes, 1 of trauma, and another of unknown causes. Among controls, the causes of death were cancer for 2 and unknown for 1.

Decreases in BMI were significantly greater in the control group than in the CPAP group, with a significant difference of 0.25 (95% CI, 0.04-0.46; $P=.02$) (eTable 6). Both groups had changes in ESS scores, but these changes were significantly less in the control group than in the CPAP group (0.2 vs 1.3; $P<.001$), with a significant difference of –1.1 (95% CI, –1.4 to –0.7; $P<.001$) (eTable 7).

COMMENT

This study suggests that in patients with OSA and without daytime sleepiness, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events. However, a larger study or longer follow-up might have been able to identify a significant association between treatment and outcome. A post hoc analysis suggested that CPAP treatment may reduce the incidence of hypertension or cardiovascular events in patients with CPAP adherence of 4 h/night or longer. The disease severity assessed by the AHI and time with Sa_{O_2} less than 90% was not related to the incidence of hypertension or cardiovascular events. However, patients with worse oxygen saturation at night and with CPAP adherence of less than 4 h/night showed a higher rate of hypertension or cardiovascular events than the control group.

Compelling evidence indicates that severe OSA is associated with an increased incidence of hypertension, cardiovascular events, or sudden death during sleep.[4,6,7,21] Three systematic reviews,[22-24] 4 meta-analyses including 21 randomized controlled trials,[10,25-27] and 3 recent studies[28-30] have evaluated the effect of CPAP therapy on blood pressure in patients with OSA. Results showed significant blood pressure reductions, especially in patients with more severe OSA.[25,26] However, evidence for an effect of CPAP treatment

Table 1. Patient Characteristics at Baseline

Characteristic	Control (n = 366)	CPAP (n = 357)	*P* Value[a]
Age, mean (SD), y	51.8 (11.01)	52.0 (10.90)	.75[b]
Men, No. (%)	306 (83.6)	313 (87.7)	.12
Body mass index, mean (SD)[c]	31.1 (4.98)	31.3 (4.86)	.45[b]
Neck circumference, mean (SD), cm	42.0 (3.70)	42.4 (3.64)	.19
Current smoking, No. (%)	94 (25.7)	113 (31.7)	.09
Any alcohol use, No. (%)	129 (46.7)	131 (48.3)	.77
Blood pressure, mean (SD), mm Hg			
Systolic	130.9 (16.89)	131.6 (16.56)	.58[b]
Diastolic	79.9 (11.46)	80.0 (11.41)	.99[b]
Hypertension, No. (%)	183 (50.0)	190 (53.2)	.43
Any antihypertensive drugs, No. (%)	82 (22.4)	95 (26.6)	.22
ACE inhibitors, No. (%)	48 (13.1)	48 (13.4)	.98
Angiotensin II receptor blockers, No. (%)	8 (2.2)	11 (3.1)	.60
Calcium channel blockers, No. (%)	11 (3.0)	19 (5.3)	.17
β-Blockers, No. (%)	17 (4.6)	21 (5.9)	.56
Diuretics, No. (%)	29 (7.9)	30 (8.4)	.92
≥1 Antihypertensive drug treatment, No. (%)	26 (7.1)	30 (8.4)	.61
Epworth Sleepiness Scale score	6.5 (2.24)	6.5 (2.27)	.95[b]
Apnea-hypopnea index, median (IQR), h^{-1}	35 (26-49)	42 (29-59)	<.001[d]
Time with Sa_{O_2} <90%, median (IQR), %	6 (1.6-15.0)	8 (2.0-22.8)	.04[d]
Diagnosis by polysomnography, No. (%)	186 (50.8)	198 (55.5)	.24
Glucose, median (IQR), mg/dL	97 (90-109)	98 (90-108)	.80[d]
Lipids, mg/dL			
Total cholesterol, mean (SD)	213.0 (41.78)	212.6 (43.28)	.89[b]
Triglycerides, median (IQR)	116.5 (84.3-169.0)	122.5 (86.3-175.0)	.26[d]
Altered electrocardiogram, No. (%)	20 (5.5)	20 (5.6%)	.93

Abbreviations: ACE, angiotensin-converting enzyme; CPAP, continuous positive airway pressure; IQR, interquartile range; Sa_{O_2}, arterial oxygen saturation.
SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; total cholesterol values to mmol/L, multiply by 0.0259; triglycerides values to mmol/L, multiply by 0.0113.
[a] Pearson χ^2 test *P* value except as noted.
[b] From *t* test.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] From Mann-Whitney test.

Table 2. Risk for New Hypertension or Cardiovascular Event

	Intention-to-Treat Analysis		Analysis by Adherence to CPAP Use	
	Control (n = 366)	CPAP (n = 357)	CPAP <4 h/Night (n = 127)	CPAP ≥4 h/Night (n = 230)
Events	110	96	37	59
Person-years	997.837	1043.436	296.4271	747.0089
Events per 100 person-years (95% CI)	11.02 (8.96-13.08)	9.20 (7.36-11.04)	12.48 (8.46-16.50)	7.90 (5.88-9.91)
IDR (95% CI)	1 [Reference]	0.83 (0.63-1.10)	1.13 (0.78-1.64)	0.72 (0.52-0.98)
P value[a]		.20	.51	.04

Abbreviations: CPAP, continuous positive airway pressure; IDR, incidence density ratio.
[a] From Wald test.

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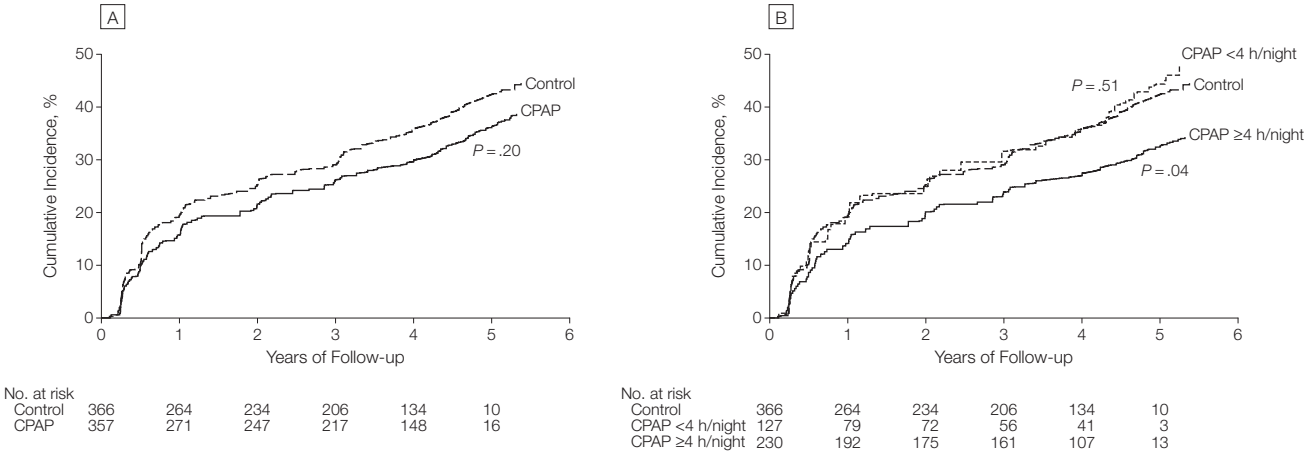
Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up



A, Cumulative incidence of hypertension or cardiovascular events for the intervention groups during follow-up and the *P* value for the incidence density ratio of continuous positive airway pressure (CPAP) vs control (Wald test). B, Panel A with CPAP group stratified according to adherence (<4 vs ≥4 h/night) and the *P* values for their incidence density ratios in reference to the control group.

Table 3. Poisson Regression Predicting Hypertension or Cardiovascular Events, With Hospital as a Random Effect, Intention-to-Treat Analysis

	Adjusted IDR (95% CI)	*P* Value	Variance, Random Hospital Effect
CPAP vs control group	0.81 (0.61-1.06)	.13	0.1141
CPAP adherence subgroup analysis			
CPAP <4 h/night group vs control group	1.12 (0.77-1.64)	.55	0.1183
CPAP ≥4 h/night group vs control group	0.69 (0.50-0.94)	.02	

Abbreviations: CPAP, continuous positive airway pressure; IDR, incidence density ratio.

on cardiovascular events is less definitive. Peker et al[31] reported a significant increase in the incidence of cardiovascular disease among incompletely treated patients with OSA compared to those who were efficiently treated. Several authors[11,12,32,33] have reported an improvement in long-term survival associated with treatment in different cohorts of patients with OSA. Marin et al[11] followed up a male cohort of treated and untreated patients with OSA, snorers, and the general population for 10 years in an observational study. They showed that CPAP treatment was associated with a lower risk of fatal and nonfatal cardiovascular events in patients with severe OSA when compared with patients who refused CPAP treatment. The incidence of cardiovascular events in patients receiving CPAP treatment was not different from that in the general population or in nonapneic snorers. Overall, observational studies suggest a protective effect of CPAP treatment on cardiovascular events in patients with OSA.

In a post hoc analysis in our study, CPAP was effective in patients who used the treatment for more than 4 h/night. Even in these patients, the magnitude of the effect was less than in previous observational studies.[11] In the study by Marin et al,[11] the group treated with CPAP had an event rate of 0.64 per 100 person-years, whereas the event rate in our treatment group was 2.08 per 100 person-years (eTable 2). These results are not unexpected, because randomized trials often show smaller positive effects than observational studies.

Another possible explanation is that CPAP is less effective in nonsleepy patients. Short-term studies focusing on nonsleepy patients have shown no effect of CPAP on clinical symptoms or blood pressure,[13,14] and a long-term study showed a mild beneficial effect of CPAP on blood pressure only in patients who used CPAP for 5.6 h/night or longer.[28] In our study, the protective association of CPAP use with the incidence of hypertension or cardiovascular events in the subgroup of patients with adherence of 4 h/night or longer was seen despite that subgroup being more obese and having a higher prevalence of hypertension. However, the results of post hoc analyses should be interpreted with caution and considered hypothesis generating. In these analyses, patients were not randomized to the subgroups, and findings may have resulted from a confounding bias, such as the healthy-user effect (eg, adherent CPAP users may be more likely to be adherent with other medications, treatments, exercise, nutrition, or other health maintenance).

It has been postulated that nonsleepy patients treated with CPAP will probably have poor adherence. Our results do not support this statement and show that CPAP treatment is feasible in this population, even in the absence of any specific reinforcement. An unexpected finding was the relatively high number of deaths during follow-

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up. The study sample size was not large enough to reach a conclusion about any relationship to treatment, but this issue deserves further research.

The strengths of our study include its multicentric design and the generalizability of the trial findings. Baseline cardiovascular risk factors were not different between groups, and median follow-up time was similar. Nevertheless, this study has several potential limitations.

First, the lack of effect of CPAP on hypertension or cardiovascular events could be related to an inadequately powered estimation of the sample size. The lack of previous studies suitable for sample size calculation contributed to the difficulty of sample size estimation. The potential protective effect of CPAP was probably overestimated, and a larger study or longer follow-up might have been able to identify a significant association between treatment and outcome. Including patients with hypertension also might have contributed to a lack of study power, because these patients could not develop 1 component of the combined primary end point, incident hypertension. Incident hypertension accounted for more than two-thirds of the primary end point events. Second, medical research personnel were not blinded to patient allocation. However, cardiovascular events and blood pressure were assessed objectively, by personnel not involved in the study and blinded to patient allocation.

Third, at baseline the CPAP group had higher AHI scores and slightly greater time with Sa_{O_2} less than 90%. These differences, although statistically significant, were likely to be of little clinical relevance, because both groups had severe OSA, and all other characteristics and cardiovascular risk factors were similar between the groups at baseline. Fourth, blood pressure values were measured at clinic visits, an approach that can be affected by the white coat effect, observer bias, limited reproducibility, and the intrinsic inaccuracy of the examiner's auscultation technique. However, measurements were taken by experienced nurses following international guidelines. Fifth, one possible explanation for the smaller effect size of CPAP in this trial compared with prior studies is that the titration protocols may have been less effective, resulting in an elevated residual AHI on CPAP treatment. Although we do not know if this occurred, our CPAP titration protocol has been validated in previous studies performed by our research group.[17]

In conclusion, in this study of patients with OSA without daytime sleepiness, the prescription of CPAP compared with usual care did not result in a statistically significant reduction in the incidence of hypertension or cardiovascular events. However, the study may have had limited power to detect a significant difference. A post hoc analysis suggested that CPAP treatment may reduce the incidence of hypertension or cardiovascular events in patients with CPAP adherence of 4 h/night or longer.

Table 4. Comparison of Subgroups of CPAP Adherence at Baseline

	CPAP <4h/Night (n = 127)	CPAP ≥4h/Night (n = 230)	*P* Value[a]
Age, mean (SD), y	51.9 (10.16)	52.1 (11.31)	.85
Men, No. (%)	112 (88.2)	201 (87.4)	.96
Body mass index, mean (SD)[b]	30.4 (4.85)	31.8 (4.81)	.009
Neck circumference, mean (SD), cm	41.7 (3.59)	42.8 (3.62)	.01
Current smoking, No. (%)	42 (33.1)	71 (30.9)	.76
Any alcohol use, No. (%)	43 (47.3)	88 (48.9)	.90
Blood pressure, mean (SD), mm Hg			
Systolic	129.3 (16.84)	132.9 (16.30)	.053
Diastolic	78.6 (11.86)	80.7 (11.11)	.11
Hypertension, No. (%)	58 (45.7)	132 (57.4)	.04
Any antihypertensive drugs, No. (%)	28 (22.0)	67 (29.1)	.19
ACE inhibitors, mean (SD)	17 (13.4)	31 (13.5)	.89
Angiotensin II receptor blockers, No. (%)	6 (4.7)	5 (2.2)	.31
Calcium channel blockers, No. (%)	4 (3.1)	15 (6.5)	.27
β-Blockers, No. (%)	4 (3.1)	17 (7.4)	.16
Diuretics, No. (%)	8 (6.3)	22 (9.6)	.39
≥1 Antihypertensive drug treatment, No. (%)	9 (7.1)	21 (9.1)	.64
Epworth Sleepiness Scale score	6.6 (2.18)	6.5 (2.33)	.74
Apnea-hypopnea index, median (IQR), h^{-1}	33 (27-53)	47 (33-63)	<.001[c]
Time with Sa_{O_2} <90%, median (IQR)	5 (1.1-15.0)	10 (2.2-27.0)	.005[c]
Diagnosis by polysomnography, No. (%)	74 (58.3)	124 (53.9)	.50
Glucose, median (IQR), mg/dL	99 (91-105)	98 (90-110)	.97[c]
Lipids, mg/dL			
Total cholesterol, mean (SD)	216.2 (46.63)	210.6 (41.38)	.28
Triglycerides, median (IQR)	117 (84.0-177.3)	125 (87.0-171.3)	.40[c]
Altered electrocardiogram, No. (%)	4 (3.1)	16 (7.0)	.21
Automatic CPAP titration, No. (%)	101 (79.5)	178 (77.4)	.74
CPAP pressure, median (IQR), cm H_2O	8 (7-9)	9 (7-10)	.07[c]

Abbreviations: ACE, angiotensin-converting enzyme; CPAP, continuous positive airway pressure; IQR, interquartile range; Sa_{O_2}, arterial oxygen saturation.
SI conversion factors: To convert glucose values to mmol/L, multiply by 0.0555; total cholesterol values to mmol/L, multiply by 0.0259; triglycerides values to mmol/L, multiply by 0.0113.
[a] From *t* test except as noted.
[b] Calculated as weight in kilograms divided by height in meters squared.
[c] From Mann-Whitney test

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Online-Only Material: The eAppendix, eFigures 1 and 2, eTables 1-7, and the Author Video Interview are available at http://www.jama.com.

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