Association Between Treated and Untreated Obstructive Sleep Apnea and Risk of Hypertension

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Context Systemic hypertension is prevalent among patients with obstructive sleep apnea (OSA). Short-term studies indicate that continuous positive airway pressure (CPAP) therapy reduces blood pressure in patients with hypertension and OSA.

Objective To determine whether CPAP therapy is associated with a lower risk of incident hypertension.

Design, Setting, and Participants A prospective cohort study of 1889 participants without hypertension who were referred to a sleep center in Zaragoza, Spain, for nocturnal polysomnography between January 1, 1994, and December 31, 2000. Incident hypertension was documented at annual follow-up visits up to January 1, 2011. Multivariable models adjusted for confounding factors, including change in body mass index from baseline to censored time, were used to calculate hazard ratios (HRs) of incident hypertension in participants without OSA (controls), with untreated OSA, and in those treated with CPAP therapy according to national guidelines.

Main Outcome Measure Incidence of new-onset hypertension.

Results During 21 003 person-years of follow-up (median, 12.2 years), 705 cases (37.3%) of incident hypertension were observed. The crude incidence of hypertension per 100 person-years was 2.19 (95% CI, 1.71-2.67) in controls, 3.34 (95% CI, 2.85-3.82) in patients with OSA ineligible for CPAP therapy, 5.84 (95% CI, 4.82-6.86) in patients with OSA who declined CPAP therapy, 5.12 (95% CI, 3.76-6.47) in patients with OSA nonadherent to CPAP therapy, and 3.06 (95% CI, 2.70-3.41) in patients with OSA and treated with CPAP therapy. Compared with controls, the adjusted HRs for incident hypertension were greater among patients with OSA ineligible for CPAP therapy (1.33; 95% CI, 1.01-1.75), among those who declined CPAP therapy (1.96; 95% CI, 1.44-2.66), and among those nonadherent to CPAP therapy (1.78; 95% CI, 1.23-2.58), whereas the HR was lower in patients with OSA who were treated with CPAP therapy (0.71; 95% CI, 0.53-0.94).

Conclusion Compared with participants without OSA, the presence of OSA was associated with increased adjusted risk of incident hypertension; however, treatment with CPAP therapy was associated with a lower risk of hypertension.

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Obstructive sleep apnea (OSA), a prevalent condition that is estimated to affect 17% of US adults, is associated with an increased risk for cardiovascular diseases and overall mortality.[1-5] Although treatment of OSA with continuous positive airway pressure (CPAP) therapy is associated with decreased overall cardiovascular risk, its efficacy in preventing new-onset hypertension is unknown.[2]

Several cross-sectional studies link OSA to arterial hypertension, a major risk factor for fatal and nonfatal cardiovascular events.[6-10] However, the association between OSA and increased rate of incident hypertension has not been observed consistently in prospective studies.[11,12] A relatively short follow-up period (<5 years) and a limited inclusion of patients with severe OSA hinder conclusions regarding the association of OSA with incident hypertension.[11,12] Furthermore, the contribution of change in body weight over time, a well-established risk factor for both hypertension and OSA, to the development of new-onset hypertension has not been investigated in patients with OSA.[13]

Treatment of OSA eliminates repetitive episodes of hypoxia associated with transient cessation of breathing and stabilizes cardiovascular function.[14] Short-term studies indicate that CPAP use is associated with a reduction in blood pressure in patients with hypertension and OSA.[15] Whether long-term

See also pp 2161 and 2197.

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CPAP therapy prevents or reduces the rate of new-onset hypertension in patients with OSA has not been investigated. We hypothesized that OSA is an independent risk factor for the development of new-onset hypertension and that long-term CPAP therapy reduces this risk regardless of change in body weight over time.

METHODS

Study Population

We used data from the Zaragoza Sleep Cohort Study, a prospective clinical-based observational study of patients referred for evaluation of sleep-disordered breathing.[2] All participants were referred to the sleep center by their primary care physicians for evaluation of suspected sleep-disordered breathing based on complaints such as snoring, daytime fatigue, and daytime sleepiness. Participants who fulfilled all inclusion criteria (no self-reported history of hypertension, no current or former treatment for hypertension, a systolic blood pressure [SBP] level <140 mm Hg, and a diastolic blood pressure [DBP] level <90 mm Hg) and none of the exclusion criteria (history of cardiopulmonary disease, neurological, kidney, or liver diseases, diabetes, or malignancy; previous upper airway or pulmonary surgery; or previous treatment for snoring or OSA) were enrolled. All participants underwent nocturnal polysomnography. Those patients with apnea-hypopnea index (AHI) of less than 5 events per hour of sleep served as controls (patients without OSA), whereas those patients with an AHI of 5 or more were diagnosed with OSA. The study was approved by the ethics committee of the Instituto Aragonés de Investigacion, Zaragoza, Spain, and all participants gave written informed consent.

Clinical Data

Demographic, anthropometric, and clinical data were obtained at recruitment using specific questionnaires and standard measurements by investigators (J.M.M., M.F., D.N., S.J.C., and E.V.). Daytime somnolence was assessed using the Epworth Sleepiness Scale.[16] Height and weight were measured and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Investigators reviewed baseline sleep studies and performed CPAP titration studies in all study participants as a part of their clinical duties in the sleep center; therefore, they could not have been blinded to the presence or absence of OSA. Blood pressure was measured by certified nurses blinded to the presence or absence of OSA according to international guidelines.[17] Arterial pressure was measured 3 times with a sphygmomanometer while the patient was in the sitting position after 5 minutes of rest. The mean of the last 2 readings was recorded for study. Hypertension was defined as an SBP at rest of at least 140 mm Hg, a DBP at rest of at least 90 mm Hg, or treatment with antihypertensive medication.[17]

Current smoking was defined as daily smoking of any number of cigarettes, cigars, or pipes. Alcohol use was defined as the consumption of an alcoholic beverage at least 3 times per week. Cardiovascular disease was considered present whenever there was documented hospitalization for myocardial infarction, unstable angina, stroke, coronary bypass graft surgery, or coronary angioplasty. The diagnosis of other prevalent chronic diseases was established according to the clinical history and use of specific medications.

Fasting blood samples were obtained for the measurement of serum lipid and plasma glucose levels. Dyslipidemia was considered present if the participant was taking lipid-lowering medication at recruitment or had serum total cholesterol or triglyceride levels out of the normal range. The presence of diabetes was defined based on history of physician diagnosis of diabetes, use of antidiabetic medication, or an increased plasma glucose level (≥126 mg/dL; to convert to millimoles per liter, multiply by 0.055).

Sleep Study

The details of the overnight sleep study have been described previously.[2] Sleep-stage scoring was performed by trained technicians according to standard criteria.[18] Apnea was defined as the complete cessation of airflow for more than 10 seconds, and hypopnea as a discernible reduction in airflow or thoracoabdominal excursion lasting at least 10 seconds, accompanied by at least 4% decrease in oxygen saturation. The AHI was defined as the total number of apneas and hypopneas per hour of sleep. An AHI of at least 5 events per hour of sleep established the diagnosis of OSA (mild OSA: AHI = 5.0-14.9; moderate OSA: AHI = 15.0-29.9; and severe OSA: AHI ≥ 30.0).[19] Patients with OSA who were eligible to receive CPAP therapy underwent fully attended nocturnal CPAP titration as described in the eMethods (http://www.jama.com).

OSA Treatment

Treatment of OSA followed the Spanish National Guidelines for the management of OSA (eMethods).[20] Nasal CPAP therapy treatment was recommended for all patients with an AHI of at least 30 events per hour and for patients with an AHI of 5.0 to 29.9 events per hour and coexisting daytime sleepiness that interferes with daily activities (eTable 1). Patients treated with CPAP therapy were followed up at the clinic 3 and 6 months after starting treatment. At each clinic visit, adherence with CPAP therapy was assessed using the built-in timer. A mean daily use of more than 4 hours per day is required to maintain CPAP prescription. If after a reinforcement period of 3 additional months the patient still used CPAP less than 4 hours per night, CPAP therapy was removed and an alternative treatment (surgery, oral appliances, or conservative measures) was offered. Among the 922 patients who initiated treatment, 98 (10.6%) withdrew CPAP therapy and were considered nonadherent (FIGURE 1). Baseline characteristics of this subgroup were similar to those of the CPAP adherent group (eTable 1). Surgical procedures that were performed in patients who were nonadherent with CPAP therapy and in those who de-

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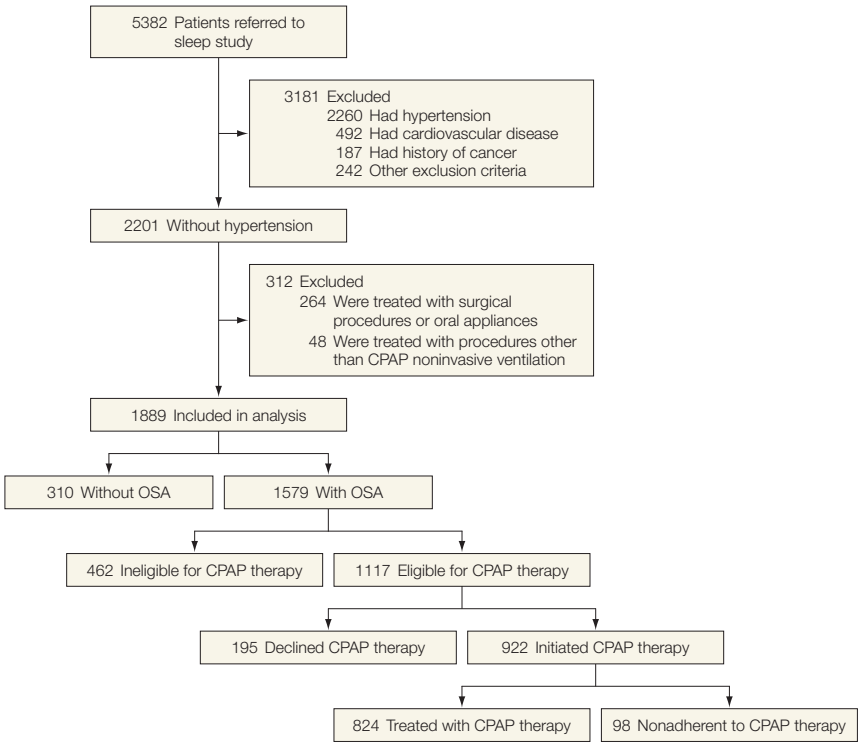
clined CPAP therapy are shown in eTable 2.

Follow-up

Patients were followed up annually in the sleep center. Anthropometric and clinical data were collected at each annual visit. Blood pressure was measured as described above and incident hypertension was diagnosed if (1) a patient reported a new physician diagnosis of hypertension and antihypertensive treatment had been started since last visit, or (2) a mean SBP of at least 140 mm Hg or a mean DBP of at least 90 mm Hg was recorded on 2 or more follow-up visits separated by at least 1 week.[17] A complete medication list was obtained at each annual visit from the information provided by the Department of Pharmacy of Health Services of Aragon and medication adherence with lipid-lowering and antihypertensive medications was evaluated as previously described.[21] There were no missing data for baseline variables or data obtained at each annual visit.

Figure 1. Study Flow Diagram



CPAP indicates continuous positive airway pressure; OSA, obstructive sleep apnea. Nineteen participants were lost to follow-up, of whom 4 were controls, 4 were ineligible for CPAP therapy, 3 declined CPAP therapy, and 8 were treated with CPAP therapy. Seventy-nine participants died (43 from cardiovascular causes and 36 from noncardiovascular causes), of whom 8 were controls, 20 were ineligible for CPAP therapy, 15 declined CPAP therapy, 4 were nonadherent to CPAP therapy, and 32 were treated with CPAP therapy.

Statistical Analysis

Patients with OSA were divided into 4 groups based on their CPAP treatment status: (1) ineligible for CPAP therapy according to the national guidelines, (2) eligible for CPAP therapy but declined, (3) started CPAP therapy but were nonadherent, and (4) treated with CPAP therapy. Irrespective of CPAP therapy, patients who did not develop incident hypertension were censored either at the time of death, time of the last follow-up, or on January 1, 2011, whichever came first. In addition, patients who initially declined CPAP therapy but accepted it later were censored at the time when CPAP therapy was started.

Crude incidence rate of new-onset hypertension was calculated as the number of patients with incident hypertension divided by the total number of patient-years under observation and expressed as the number of events per 100 patient-years. Cumulative incidence of new-onset hypertension for each group was estimated using the Kaplan-Meier method and compared with the log-rank test, with Bonferroni adjustment for multiple comparisons. To test whether the incidence rate of new-onset hypertension increases with OSA severity (measured by AHI), participants without OSA were compared with untreated patients with OSA, including those ineligible for CPAP therapy, those who were eligible for CPAP therapy but declined, and those who started CPAP therapy but were nonadherent. The analysis was performed by using the Kaplan-Meier survival functions of the time to new-onset hypertension in each of the following OSA severity categories: (1) without OSA (AHI, <5.0), (2) mild OSA (AHI, 5.0-14.9), (3) moderate OSA (AHI, 15.0-29.9), and (4) severe OSA (AHI, ≥ 30.0).

Cox proportional hazards regression survival models were used to calculate the hazard ratio (HRs) and 95% CIs for the risk of incident hypertension, using study participants with an AHI of less than 5 events per hour as the reference control group. Potential confounders were included in progressive models. Model 1 (the crude model) included the severity of OSA (AHI) and nonmodifiable risk factors, such as age and sex. Model 2 additionally adjusted for baseline SBP and DBP. Model 3 further adjusted for baseline BMI, and model 4 also adjusted for other modifiable risk factors (alcohol use, smoking status, hyperlipidemia, lipid-lowering drugs, glucose, triglycerides, total and high-density lipoprotein cholesterol) and menopausal status. Model 5 further included change in BMI from baseline to the last follow-up visit as a time-dependent covariate. In all models, multiple imputation was used to include participants who were lost to

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follow-up.[22,23] The Cox proportional hazards regression assumptions were tested using Schoenfeld residuals and resulted in nonsignificant findings in all analyses.[24] We performed tests of interaction between the association of CPAP therapy with hypertension incidence and the severity of OSA as well as the association of CPAP therapy with hypertension incidence and the change in BMI during the study follow-up period.

Based on the incidence rate for new-onset hypertension among participants without OSA, the sample size provided 80% power to detect HRs between 1.41 and 1.84 when comparing 4 OSA patient groups separately with participants without OSA. The power is calculated based on a 2-sided log-rank test with a significance level of .0125 to adjust for multiple comparisons using Bonferroni criterion. All statistical analyses were performed using R version 2.10 (Institute for Statistics and Mathematics).

RESULTS

Baseline Characteristics

Between January 1, 1994, and December 31, 2000, 5382 consecutive participants were referred to the sleep center. Baseline characteristics of patients without hypertension included in and excluded from the analysis are shown in eTable 3. A total of 1889 participants without hypertension were included in the final analysis (Figure 1). Among 1579 patients with OSA, 462 were ineligible for CPAP therapy according to the national treatment guidelines, 195 were eligible but declined CPAP therapy, 98 were eligible and started CPAP therapy but were nonadherent, and 824 adhered to CPAP therapy (Figure 1). The reasons for declining CPAP therapy were discomfort (n=79), psychological or social problems (n=63), and unspecified problems (n=50). A total of 117 patients with OSA underwent surgical procedures during follow-up (eTable 2). The study participants who did not have OSA served as controls (n=310).

TABLE 1 shows baseline characteristics of the study participants. Patients with higher AHI tended to have higher BMI, SBP, DBP, plasma glucose levels, and total cholesterol levels, and more daytime somnolence (all P for trend $<.05$). Among patients who declined CPAP therapy (n=195), 139 had severe OSA, 45 had moderate OSA, and 11 had mild OSA (eTable 1). Alcohol consumption, smoking history, and adherence with pharmacological therapies during the follow-up period were similar in patients with mild to moderate OSA who were ineligible for CPAP therapy and in those who declined CPAP therapy (eTable 4).

Unadjusted Incidence of Hypertension

The mean (SD) follow-up of the study was 11.3 (4.2) years (median, 12.2 years). During 21 003 person-years of follow-up, 705 patients (37.3%) developed incident hyper-

Table 1. Baseline Characteristics of 1791 Participants Stratified by Baseline AHI and Treatment With CPAP Therapy[a]

	Baseline AHI, Events/h						
		Patients With OSA Ineligible for CPAP Therapy		Patients With OSA Eligible for CPAP Therapy			
				Declined CPAP Therapy		Treated With CPAP Therapy	
Characteristics	Controls <5.0 (n = 310)	5.0-14.9 (n = 276)	15.0-29.9 (n = 186)	<30.0 (n = 56)	≥30.0 (n = 139)	<30.0 (n = 245)	≥30.0 (n = 579)
Age, mean (SD), y	49.7 (10.5)	49.2 (10.8)	50.1 (10.6)	49.8 (10.4)	49.9 (11.0)	49.6 (10.1)	49.5 (9.7)
			No. (%)				
Male sex	243 (78)	211 (76)	145 (78)	44 (78)	114 (82)	194 (79)	489 (84)
Alcohol use, ≥3 drinks/wk	80 (26)	75 (27)	47 (25)	11 (19)	34 (24)	59 (24)	151 (26)
Current smoker	77 (25)	72 (26)	45 (24)	14 (25)	33 (24)	59 (24)	150 (26)
Hyperlipidemia	28 (9)	30 (11)	26 (14)	8 (14)	21 (15)	31 (13)	94 (16)
Lowering-lipid use	22 (7)	24 (9)	21 (11)	6 (11)	18 (13)	24 (10)	77 (13)
			Mean (SD)				
Plasma glucose, mg/dL	91.7 (12.2)	93.7 (12.4)	94.8 (12.1)	92.3 (12.6)	94.3 (12.5)	96.2 (11.9)	95.8 (12.4)
Triglycerides, mg/dL	112.7 (42.0)	117.5 (48.5)	118.4 (50.1)	113.2 (51.2)	120.8 (46.3)	119.9 (45.1)	118.4 (19.0)
Total cholesterol, mg/dL	205.7 (40.9)	206.3 (40.6)	206.1 (42.6)	205.9 (41.4)	206.0 (45.9)	211.3 (37.0)	211.6 (40.8)
HDL cholesterol, mg/dL	53.1 (12.8)	52.6 (13.1)	51.9 (12.9)	52.1 (13.2)	50.6 (11.1)	50.6 (11.5)	50.4 (12.7)
BMI	28.1 (3.2)	28.8 (4.1)	29.6 (3.8)	28.7 (3.6)	30.8 (3.9)	30.4 (3.8)	31.4 (3.9)
SBP, mm Hg	118.4 (8.1)	119.1 (8.8)	120.1 (8.8)	120 (8.0)	123.1 (8.8)	122.6 (8.8)	123.4 (8.6)
DBP, mm Hg	74.2 (7.6)	74.2 (7.8)	74.9 (7.1)	74.6 (7.5)	76.4 (6.9)	76.7 (8.2)	77.8 (7.7)
Epworth Sleepiness Scale (range, 0-24)	6.9 (3.1)	8.2 (3.7)	9.7 (3.7)	10.5 (4.3)	12.5 (4.3)	13.9 (3.1)	12.8 (4.8)
AHI, events/h	2.6 (1.3)	9.7 (2.8)	20.9 (4.4)	19.1 (5.5)	44.3 (13.3)	19.7 (6.0)	50.3 (16.3)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index, calculated as weight in kilograms divided by square of height in meters; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; OSA, obstructive sleep apnea; SBP, systolic blood pressure.
SI conversions: To convert plasma glucose to mmol/L, multiply by 0.055; triglycerides to mmol/L, multiply by 0.0113; and total and HDL cholesterol to mmol/L, multiply by 0.0259.
[a] Participants without OSA were controls. Data from 98 patients nonadherent to CPAP therapy are shown in eTable 1.

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tension. Of the 705 study participants who developed hypertension, 656 (93%) were diagnosed by their primary care physicians and were receiving antihypertensive medications at the time of their follow-up visit. The remaining 49 participants were diagnosed in the sleep center. Sensitivity analysis separating 2 subgroups (incidence rate of new-onset hypertension based on primary care physician diagnosis vs blood pressure measurement in the sleep center) showed no significant difference in the rate of incident hypertension ($P=.21$). Characteristics of participants who remained normotensive and those who developed hypertension are shown in eTable 5.

Compared with controls (crude incidence rate, 2.19; 95% CI, 1.71-2.67), the unadjusted incidence of new-onset hypertension (per 100 person-years) was greater among patients with OSA who were ineligible for CPAP therapy (3.34; 95% CI, 2.85-3.82; $P<.001$), among those who declined CPAP therapy (5.84; 95% CI, 4.82-6.86; $P<.001$), among those who were nonadherent with CPAP therapy (5.12; 95% CI, 3.76-6.47; $P<.001$), and among patients with OSA who were treated with CPAP therapy (3.06; 95% CI, 2.70-3.41; $P=.003$) (**Table 2**). After stratification based on severity of OSA (measured by AHI), the incidence of hypertension was similar within each OSA severity category among patients who were ineligible for CPAP therapy, among those who declined CPAP therapy, and among those who were nonadherent to CPAP therapy ($P=.67$ for mild OSA, $P=.68$ for moderate OSA, and $P=.43$ for severe OSA) (**Table 3**). The incidence of new-onset hypertension was lower among patients with severe OSA who were treated with CPAP therapy compared with patients with untreated severe OSA, whereas patients with mild OSA who were treated and untreated had similar incidence of hypertension. **Figure 2** shows the Kaplan-Meier survival function for new-onset hypertension in controls and in patients with OSA who were untreated. The incidence of hypertension increased with severity of OSA (log-rank $P<.001$).

Adjusted Hypertension Risk

Using Cox proportional hazards regression survival models, adjustments for potential confounders were performed in a stepwise manner in 5 dif-

Table 2. Crude Rates of Incident Hypertension in Controls and Patients With Treated and Untreated OSA

		Patients With OSA			
	Controls[a] (n = 310)	Ineligible for CPAP Therapy (n = 462)	Declined CPAP Therapy (n = 195)	Nonadherent to CPAP Therapy (n = 98)	Treated With CPAP Therapy (n = 824)
AHI at baseline, mean (SD)	2.6 (1.3)	14.2 (6.6)	37.1 (16.3)	31.3 (13.4)	41.2 (19.9)
Incident hypertension, No. (%)	78 (25)	175 (38)	119 (61)	53 (53)	280 (34)
Total No. observed, person-years	3563	5239	2037	1015	9149
Crude incidence rate, No. per 100 person-years (95% CI)	2.19 (1.71-2.67)	3.34 (2.85-3.82)	5.84 (4.82-6.86)	5.12 (3.76-6.47)	3.06 (2.70-3.41)
P value		<.001	<.001	<.001	.003

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.
[a] Participants without OSA were controls. *P* values were calculated from 2-sided log-rank test comparing each of the patients with OSA groups with the control group.

Table 3. Crude Rates of Incident Hypertension in Patients With Treated and Untreated OSA Stratified by Severity[a]

	Patients With OSA				
	Ineligible for CPAP Therapy	Declined CPAP Therapy	Nonadherent to CPAP Therapy	Treated With CPAP Therapy	*P* Value[b]
		Mild OSA			
No. at risk	276	11	11	57	
Incident hypertension, No. (%)	96 (34.8)	4 (3.6)	5 (4.5)	14 (24.6)	
Crude incidence rate, No. per 100 person-years (95% CI)	3.02 (2.43-3.61)	2.88 (0.10-5.66)	4.05 (0.57-7.53)	2.12 (1.02-3.22)	.15
		Moderate OSA			
No. at risk	186	45	27	190	
Incident hypertension, No. (%)	79 (42.5)	18 (40.0)	12 (44.4)	62 (32.6)	
Crude incidence rate, No. per 100 person-years (95% CI)	3.84 (3.01-4.67)	3.77 (2.06-5.48)	4.36 (1.95-6.77)	2.91 (2.20-3.62)	.07
		Severe OSA			
No. at risk	NA	139	60	577	
Incident hypertension, No. (%)	NA	97 (69.8)	35 (58.3)	204 (35.3)	
Crude incidence rate, No. per 100 person-years (95% CI)	NA	6.83 (5.52-8.14)	5.68 (3.58-7.51)	3.21 (2.78-3.64)	<.001

Abbreviations: CPAP, continuous positive airway pressure; NA, not applicable; OSA, obstructive sleep apnea.
[a] Severity of OSA was defined by the apnea-hypopnea index (AHI) as mild OSA (AHI, 5.0-14.9), moderate OSA (AHI, 15.0-29.9), and severe OSA (AHI, ≥30.0).
[b] Obtained by comparing the rate of incident hypertension in CPAP therapy group with the remaining groups within each severity category using log-rank test.

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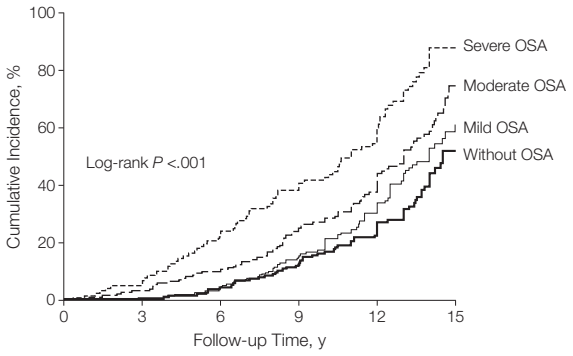
ferent predictive models (TABLE 4). Nineteen participants who were lost to follow-up were handled by multiple imputation; sensitivity analysis excluding these participants yielded similar results (eTable 6). Compared with controls, the risk for new-onset hypertension was greater among all groups of patients with OSA who were untreated (ineligible for CPAP therapy, those who declined CPAP therapy, and those who were nonadherent to CPAP therapy) in model 1 (adjusted for AHI, age, and sex), model 2 (further adjusted for baseline SBP and DBP), and model 3 (additionally adjusted for baseline BMI) (Table 4). In contrast, patients with OSA who were treated with CPAP therapy had a risk for new-onset hypertension similar to controls after adjustment for AHI, age, sex, baseline SBP and DBP, and BMI (models 1-3). Further adjustment for the remaining baseline covariates (model 4) did not significantly alter the results.

In the entire cohort, mean BMI increased significantly during follow-up in patients who developed incident hypertension (from 30.5 [95% CI, 30.1-30.9] to 31.6 [95% CI, 31.2-32.0]; $P<.001$) but not among patients who remained normotensive (eTable 5). The rate of incident hypertension was greater among subgroups that experienced weight gain (eTable 7 and eFigure). After including change in BMI as a covariate in the fully adjusted model (model 5), the HRs for incident hypertension remained greater among patients with OSA who were ineligible for CPAP therapy (1.33; 95% CI, 1.01-1.75), among patients with OSA who declined CPAP therapy (1.96; 95% CI, 1.44-2.66), and among patients with OSA who were nonadherent to CPAP therapy (1.78; 95% CI, 1.23-2.58) compared with controls without OSA (Table 4). In patients with OSA who were treated with CPAP therapy, the risk of new-onset hypertension was lower than in controls in the fully adjusted model (HR, 0.71; 95% CI, 0.53-0.94) (Table 4).

Tests of interaction were performed to assess whether the association of CPAP therapy with lower risk of incident hypertension was affected by the severity of OSA. No significant interaction was observed in any of the 5 Cox proportional hazards regression survival models ($P=.26$, .21, .13, .11, and .07 for models 1 to 5, respectively). The test of interaction between the association of CPAP therapy with lower risk of incident hypertension and change in BMI during the study follow-up period yielded no significant interaction

Figure 2. Cumulative Incidence of Hypertension in Participants Without OSA and Untreated Patients With OSA



No. at risk						
Severe OSA	199	184	141	119	62	37
Moderate OSA	258	222	202	162	114	67
Mild OSA	298	289	260	194	127	59
Without OSA	310	306	269	211	152	72

OSA indicates obstructive sleep apnea. Severity of OSA was defined by the apnea-hypopnea index (AHI) as mild OSA (AHI, 5.0-14.9), moderate OSA (AHI, 15.0-29.9), and severe OSA (AHI, ≥30.0). *P* value reflects an overall log-rank χ^2_3 test, providing an overall survival difference among the 4 study groups.

Table 4. Cox Proportional Hazards Regression Models of Incident Hypertension in Patients With OSA With Multiple Imputations[a]

		Patients With OSA			
	Controls (n = 310)	Ineligible for CPAP Therapy (n = 462)	Declined CPAP Therapy (n = 195)	Nonadherent to CPAP Therapy (n = 98)	Treated With CPAP Therapy (n = 824)
Baseline AHI, mean (SD)	2.6 (1.3)	14.2 (6.6)	37.1 (16.3)	31.3 (13.4)	41.2 (19.9)
	Hazard Ratio (95% CI)				
Model 1, adjusted for AHI, age, and sex	1 [Reference]	1.63 (1.25-2.12)	2.89 (2.18-3.84)	2.70 (1.90-3.83)	1.47 (1.24-1.88)
Model 2, adjusted for model 1 + SBP and DBP	1 [Reference]	1.57 (1.20-2.05)	2.78 (2.08-3.70)	2.50 (1.75-3.56)	1.17 (0.90-1.51)
Model 3, adjusted for model 2 + BMI	1 [Reference]	1.46 (1.12-1.91)	2.54 (1.90-3.39)	2.20 (1.90-3.39)	1.01 (0.78-1.31)
Model 4, adjusted for model 3 + baseline covariates[b]	1 [Reference]	1.39 (1.06-1.82)	2.23 (1.36-3.01)	1.96 (1.36-2.83)	0.83 (0.63-1.11)
Model 5, adjusted for model 4 + change in BMI	1 [Reference]	1.33 (1.01-1.75)	1.96 (1.44-2.66)	1.78 (1.23-2.58)	0.71 (0.53-0.94)

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; DBP, diastolic blood pressure; OSA, obstructive sleep apnea; SBP, systolic blood pressure.
[a] Participants without OSA were controls.
[b] Baseline covariates include alcohol use, smoking status, presence of hyperlipidemia, lipid-lowering medications, glucose, triglycerides, total and high-density lipoprotein cholesterol, and menopausal status.

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in model 5 (P=.06). There was no association between Epworth Sleepiness Scale score and incident hypertension both for those patients who were not eligible for CPAP therapy and for those who declined CPAP therapy (eTable 8). Sensitivity analysis excluding the first 2 years of follow-up yielded similar results as those presented above.

COMMENT

Our study findings suggest that untreated OSA is associated with an increased risk for developing new-onset hypertension and that long-term CPAP therapy is associated with a reduction in such risk. After accounting for body weight changes that occurred in both participants without OSA and with OSA who were treated and untreated, weight gain over a decade does not appear to diminish a protective association of CPAP therapy against development of new-onset hypertension in OSA. Our observational findings suggest that OSA appears to be a modifiable risk factor for new-onset hypertension. Such findings are clinically relevant considering that OSA, despite a high prevalence in Western populations, remains overwhelmingly unrecognized and untreated.[25,26]

Two previous studies that evaluated the association between OSA and the risk for incident hypertension reported conflicting results.[11,12] The Wisconsin Sleep Cohort Study[11] showed that the risk of incident hypertension correlated with severity of OSA in middle-age patients. In contrast, the Sleep Heart Health Study[12] failed to show an association between OSA and the risk of incident hypertension among community-based older individuals, including those with severe OSA. However, the majority of participants in both studies had mild OSA, with less than 13% of patients having moderate to severe OSA. Relatively healthy individuals with mild OSA might be at low risk for developing cardiovascular complications over 10 years.[2-4] A relatively short follow-up period of OSA cohorts predominantly comprising patients with mild OSA may explain discrepant findings. In addition, change in body weight over time, an important confounder for incident hypertension, was not taken into account in these prospective studies.[11,12] Our study addressed these limitations by following up a large cohort of patients with moderate to severe OSA for more than a decade, and by considering the effects of cumulative weight gain and other potential confounding factors on incident hypertension.

Our findings support previous reports that showed an independent association between OSA and increased cardiovascular morbidity.[2-5] The association between untreated OSA and increased risk for developing new-onset hypertension persisted even after adjustment for potential confounding variables, including baseline BMI and change in BMI over time. These findings are concordant with reports that support OSA as a predominant contributor to vascular dysfunction in obesity.[27-29] Considering the high prevalence of unsuspected OSA among obese patients, the vascular risk that is commonly attributed to obesity may in part be related to OSA. The lower risk for new-onset hypertension associated with effective therapy for OSA strengthens the rationale for screening and prompt treatment of OSA in patients who are overweight and obese.

An important potential limitation of our study stems from its observational nature. Patients with OSA who are willing to adhere to CPAP therapy may be more health conscious and thus more adherent to other treatment modalities and more likely to do well. Although robust literature suggests that good adherence with pharmacological therapies, including placebo, beneficially affects survival, low adherence to prescribed medications does not explain the excess mortality in patients with hypertension.[30,31] Furthermore, adherence with pharmacological therapies does not consistently correlate with adherence with medical devices such as CPAP.[21,32] In our study, the adherence to antihypertensive and lipid-lowering medications was similar among patients who adhered to CPAP therapy and those who did not. In addition, health-related behavior such as alcohol consumption and smoking were similar among patients with OSA who were not treated with CPAP therapy because of ineligibility and among those who declined treatment. The findings of our observational study suggest that the severity of OSA may be an important determinant of incident hypertension in untreated OSA regardless of the rationale underlying the absence of CPAP therapy. However, the potential bias related to group assignment based on adherence to therapy, which is inherent in observational study design, precludes definitive causal conclusions regarding the affect of CPAP therapy on the risk for hypertension in OSA.

Treatment with CPAP has become the standard of care for moderate to severe OSA, and thus long-term randomization of patients with OSA to CPAP therapy vs no CPAP therapy may no longer be feasible.[19] Although CPAP therapy was not allocated randomly to our patients, the associated lower excess risk of hypertension strongly suggests that OSA may be an independent modifiable risk factor for development of new-onset hypertension. The observed correlation between severity of OSA and the magnitude of risk for hypertension further supports OSA as a major contributor to cardiovascular risk. In conclusion, compared with participants without OSA, untreated OSA was associated with an increased risk of new-onset hypertension, whereas treatment with CPAP therapy was associated with a lower risk of new-onset hypertension.

Author Contribution: Dr Marin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Analysis and interpretation: Marin, Agusti, Villar, Forner, Barbé, Wei, F.J. Nieto, Jelic.
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