

Cardiovascular Mortality in Obstructive Sleep Apnea in the Elderly: Role of Long-Term Continuous Positive Airway Pressure Treatment

A Prospective Observational Study

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Rationale: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular death in middle-aged subjects, but it is not known whether it is also a risk factor in the elderly.

Objectives: To investigate whether OSA is a risk factor for cardiovascular death and to assess whether continuous positive airway pressure (CPAP) treatment is associated with a change in risk in the elderly.

Methods: Prospective, observational study of a consecutive cohort of elderly patients (≥ 65 yr) studied for suspicion of OSA between 1998 and 2007. Patients with an apnea-hypopnea index (AHI) less than 15 were the control group. OSA was defined as mild to moderate (AHI, 15–29) or severe (AHI, ≥ 30). Patients with OSA were classified as CPAP-treated (adherence ≥ 4 h/d) or untreated (adherence < 4 h/d or not prescribed). Participants were monitored until December 2009. The end point was cardiovascular death. A multivariate Cox survival analysis was used to determine the independent impact of OSA and CPAP treatment on cardiovascular mortality.

Measurements and Main Results: A total of 939 elderly were studied (median follow-up, 69 mo). Compared with the control group, the fully adjusted hazard ratios for cardiovascular mortality were 2.25 (confidence interval [CI], 1.41 to 3.61) for the untreated severe OSA group, 0.93 (CI, 0.46 to 1.89) for the CPAP-treated group, and 1.38 (CI, 0.73 to 2.64) for the untreated mild to moderate OSA group.

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In middle-aged subjects, obstructive sleep apnea is a risk factor for cardiovascular death and continuous positive airway pressure (CPAP) treatment seems to significantly reduce this risk. However, it is not known whether obstructive sleep apnea is a risk factor for the elderly, or what the effect of CPAP on this population might be.

What This Study Adds to the Field

Severe obstructive sleep apnea not treated with CPAP is associated with cardiovascular death in the elderly, and adequate CPAP treatment may reduce this risk.

Conclusions: Severe OSA not treated with CPAP is associated with cardiovascular death in the elderly, and adequate CPAP treatment may reduce this risk.

Keywords: elderly; older; obstructive sleep apnea; cardiovascular events; continuous positive airway pressure

Nowadays there is little doubt that obstructive sleep apnea (OSA) is a public health problem, on account of both its high prevalence in the general population (1) and its association with increased morbidity and mortality in the short term (traffic and workplace accidents) (2, 3) and the long term (arterial hypertension and cardiovascular events [CVEs]) (4, 5). Continuous positive airway pressure (CPAP) is the most cost-effective treatment for severe or symptomatic forms of OSA (6), and it has demonstrated a positive effect on blood pressure levels (7) and the incidence of fatal and nonfatal CVEs (4, 8–10).

Although we are aware that the prevalence of OSA increases with age (11, 12), few studies have analyzed the impact of OSA or CPAP treatment in a series exclusively comprising elderly people. This is probably because it is difficult to establish a distinction between the physiological and the pathological aspects, and because various comorbidities that act as confounding variables are often present. Despite this lack of scientific evidence, one of four sleep studies is performed on an individual older than 65 years, and CPAP treatment is prescribed in two-thirds of these cases (13).

Some authors have observed an excess of all-cause mortality in patients with severe untreated OSA (14, 15), especially in young people (16–18), whereas elderly individuals could present some compensatory mechanisms that would allow them to resist the

action of intermittent hypoxia (19–21). Other authors, however, have observed that the presence of moderate–severe untreated OSA, even at an advanced age, is associated with greater cardiovascular and cerebrovascular risk (8, 22–27), as well as a higher mortality rate (28, 29), and that CPAP treatment seems to significantly reduce this risk (8, 23). In the light of this controversy, the ageing population and the growing demands of elderly people in our sleep units make it imperative to carry out studies that broaden our scientific evidence on this issue, as their conclusions could be immediately applicable to clinical practice. Therefore, the objective of our study was to analyze the impact of OSA and CPAP treatment on cardiovascular mortality in a large range of individuals of both sexes, all at least 65 years of age, who were referred to sleep units for suspected OSA.

Some of the results of the study have previously been reported in the form of an abstract (30).

METHODS

We performed a prospective observational study of consecutive patients at least 65 years of age and referred between December 1998 and December 2007 to the sleep units of Requena Hospital (Valencia, Spain) or Valme Hospital (Seville, Spain) for suspected OSA. Exclusion criteria included previous treatment with CPAP, unwillingness to undergo a sleep study, and the presence of a central sleep apnea syndrome (more than 50% of apneic events). The ethics committees of both institutions approved the study.

Data Collection

Baseline variables. All the baseline variables were systematically recorded, using a standardized protocol, before the sleep study, with the participants in a stable condition. The following variables were assessed: age, sex, hospital of reference, body mass index (BMI), type of sleep study (polysomnography vs. respiratory polygraphy), previous CVE (stroke, heart failure, arrhythmias, and ischemic heart disease), alcohol intake (grams per day), and dichotomous cardiovascular risk factors: smoking (≥ 30 pack-years), arterial hypertension (systolic/diastolic blood pressure $\geq 140/90$ in two or more outpatient measurements or use of antihypertensive medication), fasting glucose levels higher than 7 mmol/L (125 mg/dl) in two or more measurements or use of antihyperglycemic medication and dyslipidemia (fasting levels of total cholesterol or triglycerides higher than 5.17 mmol/L [>200 mg/dl]), or use of antihyperlipidemic medication. Heart failure was defined via the collection of echocardiographic data or other tests indicated for its conclusive diagnosis, or via the prescription of specific medication; arrhythmias were defined by their detection by ECG or by the patient's adherence to specific treatment; ischemic heart disease was defined by the results of conclusive tests, myocardial infarction, angina, or previous coronary revascularization, or the prescription of antianginal medication; and, finally, stroke was defined by the presence of confirmative image tests and a compatible clinical picture, as assessed by a neurological specialist. All these tests and treatments were implemented by the corresponding specialists. The OSA-related clinical history and sleep study results were also recorded. Hypersomnia was evaluated on the basis of the validated Spanish version of the Epworth Sleepiness Scale (ESS) (31). Patients with cardiovascular risk factors or previous cardiovascular events received appropriate medical treatment, under the supervision of the corresponding physician.

Sleep Study and CPAP Treatment

We followed the Spanish Society of Pneumology and Thoracic Surgery guidelines for diagnosis and treatment of OSA (32, 33). Every participant was subjected to a sleep study, either full standard polysomnography (PSG) (Compumedics PS, Melbourne, Australia) or respiratory polygraphy (RP) with a device previously validated against PSG (Apnoscreen II plus [Erich Jaeger GmbH and Co. KG, Würzburg, Germany] or Embletta PDS [ResMed, Sydney, Australia]) (34, 35). PSG included continuous recording of electroencephalogram, electro-

oculogram, electromyogram, and electrocardiogram; and evaluations of nasal airflow, thoracic and abdominal band movements, and SaO_2 , according to standard criteria (36). RP included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and SaO_2 . A full PSG was performed on all the patients undergoing RP who presented recording artifacts, a discrepancy between the RP result and the pretest clinical probability/suspicion of OSA (especially in patients with a high pretest probability and RP results with no alterations), predominance of central events, or a subjective sleep time of less than 3 hours. All the data were recorded manually by the investigators. Apnea was defined as an interruption of oronasal airflow exceeding 10 seconds, and it was classified as obstructive or central, depending on whether respiratory effort was present or absent. Hypopnea was defined as a 30–90% reduction in the oronasal airflow exceeding 10 seconds and associated with a desaturation of 4% or more (37). The apnea–hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep (PSG) or recording (RP). OSA was diagnosed if the AHI was equal to or more than 15, and was classified as mild to moderate (AHI between 15 and 29) or severe (AHI ≥ 30). CPAP treatment was offered to all the patients with an AHI of at least 30, regardless of symptoms, and to those with an AHI between 15 and 29 and OSA symptoms, especially daytime hypersomnia (an ESS > 10) not explained by any other cause. CPAP was titrated in the sleep laboratory on a second night by either full standard PSG or an autotitrating CPAP device. The patients were told to follow their usual lifestyle when undertaking the sleep studies, regarding both their habitual medication and other circumstances.

Adherence to CPAP was always objectively assessed by reading the time counter of the device from the start of treatment to the end of follow-up (death or censorship). Patients were classified as being adequately treated with CPAP if treatment had been started and the average cumulative adherence was at least 4 hours/day, and as untreated if CPAP was not prescribed or if the patient declined to use or could not tolerate the device or was persistently noncompliant (average use, < 4 h/d).

Follow-up

The follow-up ended on December 31, 2009. The patients with OSA were reviewed at 3-month intervals during the first year and every 12 months thereafter in the outpatient sleep clinic of one of the two centers, using a standardized protocol. All the data recorded from the outpatient sleep clinic were backed up by reviewing the clinical histories and the hospitals' computer databases, as well as those of primary care. In case of any doubt or lack of information, an additional medical visit was arranged. A patient was considered lost to follow-up only if the end-point data could not be established at the end of the study.

Main End Point of the Study

The study's main end point, designed before the study started, was cardiovascular death (defined as death from stroke, heart failure, or myocardial infarction). Secondary end points included all-cause mortality and mortality from stroke, heart failure, and myocardial infarction. Vital status at the end of follow-up was thoroughly assessed by using multiple concurrent approaches, including review of hospital and outpatient medical records and computerized databases, and when necessary, by contacting the patient, patient's relatives, or primary care physician. When a participant died, information about the cause and date of death was obtained from the hospital medical records if the patient died in the hospital, or from official death certificates.

Statistical Analysis

The SPSS 17.0 package (SPSS Inc., Chicago, IL) was used for the analysis. On the basis of the results of the sleep study and CPAP treatment, four groups were defined: control group without OSA (AHI < 15), untreated mild–moderate OSA (AHI 15–29), untreated severe OSA (AHI ≥ 30), and OSA with effective CPAP treatment (at least 4 h/d). Normality in the variable distributions was assessed by Kolmogorov–Smirnov test. Continuous variables are expressed as means (SD) or medians (IQR) and qualitative variables as absolute values and percentages. The baseline differences between the groups were analyzed by

one-way analysis of variance with Bonferroni correction or by chi-square test and Fisher exact tests, as appropriate for qualitative variables.

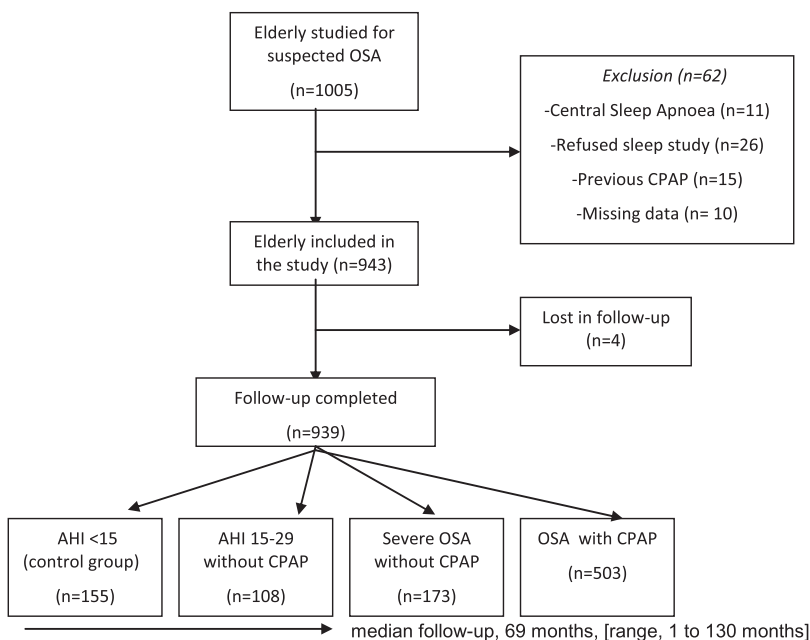
Cumulative cardiovascular mortality for each OSA group was calculated according to the Kaplan-Meier method, and mortality curves were compared by log-rank test. Censoring occurred if CPAP treatment was started (in a subject initially untreated) or if CPAP was withdrawn because of OSA resolution, before the termination of the study. Patients who died of noncardiovascular causes were censored at the time of death. Patients lost to follow-up were excluded from the analysis.

Clinically relevant variables, in the opinion of the researchers, were entered into a Cox proportional hazard model analysis to determine the variables independently associated with mortality in the study groups. The following variables were finally selected to enter in the Cox model: age, BMI, sex, ESS, smoking habit, arterial hypertension, diabetes mellitus, dyslipidemia, respiratory failure, previous CVE, and OSA groups. The results were expressed as hazard ratio (HR) and 95% confidence interval (CI), and a *P* value less than 0.05 was considered statistically significant. Diagnostic and residual plots were examined for all variables to test the proportional hazards assumptions, and none of them were statistically significant.

Sensitivity analyses were performed to clarify the separate contribution of OSA severity and treatment adherence to cardiovascular death. First, to assess the contribution of CPAP adherence, an additional multivariate Cox regression analysis was performed, including only those patients who began CPAP treatment. In this analysis, CPAP adherence and AHI were assessed as continuous variables instead of the various OSA groups. Second, to analyze the contribution of OSA severity, a new multivariate analysis was performed, including only untreated patients. In this analysis, AHI was assessed as a continuous variable instead of the various OSA groups. Last, a subgroup of patients greater than 75 years of age was also analyzed and the risks of all-cause mortality and specific cardiovascular and noncardiovascular mortality were also compared between the studied OSA groups.

RESULTS

Initially, 1005 elderly patients with suspected OSA were included; 62 were excluded and 4 were lost during the follow-up, leaving 939 individuals. Four groups were established: control group (*n* = 155), mild-moderate OSA without CPAP (*n* = 108), severe OSA without CPAP (*n* = 173), and OSA with CPAP (*n* = 503) (Figure 1). The baseline characteristics of the study groups are shown in Table 1. Significant differences were observed between the OSA groups in BMI, ESS, percentage of previous CVEs, type of sleep study, and reference clinic. The



median follow-up was 69 months (interquartile range, 49 to 87 mo), during which 190 deaths occurred (20.2%); 100 of these (52.6%) were of cardiovascular origin (Table 2). Patients had a mean (SD) CPAP compliance of 6.4 (1.4) hours for the OSA group that used CPAP for at least 4 hours/day and 0.9 (0.9) hours for the intolerant OSA group. Fifty-seven percent of the elderly were studied by means of RP and the remaining 43% by PSG.

Figure 2 shows Kaplan-Meier curves; it can be seen that cumulative cardiovascular mortality was significantly higher in untreated severe OSA compared with the control group (log-rank test, 11.39; *P* = 0.001). The mild-to-moderate nontreated OSA group presented a nonsignificant increase in cumulative cardiovascular mortality compared with the control group (log-rank test, 3.13; *P* = 0.08). Cumulative cardiovascular mortality in the CPAP-treated OSA group was similar to that of the non-OSA group (log-rank test, 0.09; *P* = 0.77).

Table 3 shows the fully adjusted Cox analysis results. To analyze the impact of the type of sleep study and sleep clinic as potential confounders in the final association between OSA and cardiovascular mortality, these two variables were forced into the multivariate adjusted Cox analysis. The final model did not change with the inclusion of both variables. It can be seen that those patients with severe untreated OSA or poor CPAP adherence presented a greater risk of cardiovascular death (HR, 2.25; 95% CI, 1.41 to 3.61; *P* = 0.001) compared with the control group. No significant differences in cardiovascular mortality were observed, however, between patients with OSA treated by CPAP, patients with mild-moderate OSA without treatment, and those without OSA.

Figure 3 shows that untreated severe OSA is associated with an increase in the risk of all-cause mortality (HR, 1.99; 95% CI, 1.42 to 2.81; *P* = 0.001), from stroke (HR, 4.63; 95% CI, 1.03 to 20.8; *P* = 0.046) and from heart failure (HR, 3.93; 95% CI, 1.13 to 13.65; *P* = 0.031), but there was no association with an increased risk of death from ischemic heart disease (HR, 1.09; 95% CI, 0.37 to 3.36; *P* = 0.23) compared with the control group.

CPAP treatment was associated with a reduced risk of all-cause and cardiovascular mortality, as well as death from stroke and heart failure, to levels similar to those of patients without OSA or with untreated, mild-moderate OSA (Figure 2 and Table 3). There were no changes, however, in the risk of death

Figure 1. Patients' flow chart profile. AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea.

TABLE 1. BASELINE CHARACTERISTICS OF SAMPLE POPULATION ACCORDING TO OBSTRUCTIVE SLEEP APNEA GROUPS

Variable	AHI < 15 Control Group (n = 155)	AHI 15–29 without CPAP (n = 108)	AHI ≥ 30 without CPAP (n = 173)	OSA with CPAP (n = 503)
Age, yr	70.9 (4.4)	71.7 (5.2)	71.9 (4.5)	70.1 (4.2)
Sex, % males	60%	65.7%	71.7%	62.2%
BMI, kg/m ²	32.4 (5.1)	33.6 (4.4)	34.8 (6)	35.1 (5.9)
ESS	8.4 (4.5)	7.8 (4.2)	11.4 (4.7)	11.6 (4.9)
AHI, events/h	6.6 (3.7)	21.3 (4.5)	58.6 (20.9)	52.2 (23.5)
Smoked ≥30 pack-years	41%	42%	47%	41%
Alcohol intake, g/d	8.3 (14.4)	8.9 (19.2)	7.8 (19.9)	9.4 (22.4)
AHT	67%	71%	74%	73%
Diabetes	31%	37%	36%	37%
Hyperlipidemia	44%	50%	49%	51%
Previous CVE	31%	46%	44%	33%
Sleep clinic*	59%	27%	56%	30%
Type of sleep study†	37%	53%	30%	45%

Definition of abbreviations: AHI = apnea-hypopnea index; AHT = arterial hypertension; BMI = body mass index; CPAP = continuous positive airway pressure; CVE = cardiovascular events; ESS = Epworth Sleepiness Scale.

Data tabulated as means (standard deviation) for quantitative variables and as percentages for qualitative variables.

$P < 0.001$ for comparisons of age, BMI, ESS, AHI, sleep clinic, type of sleep study, and previous CVE. $P > 0.1$ for comparison of sex, smoking habit, alcohol intake, AHT, diabetes, and hyperlipidemia.

* Requena Hospital (Valencia, Spain).

† Full standard polysomnography.

from ischemic heart disease (Figure 3). This association between untreated severe OSA and an increased risk of cardiovascular mortality (HR, 3.87; 95% CI, 1.12 to 13.3; $P = 0.032$) and the reduction of the risk with CPAP treatment (HR, 1.01; 95% CI, 0.27 to 3.36; $P = 0.98$) was also observed when we analyzed the subgroups of patients 75 years of age or older ($n = 193$; 37 deaths).

In those patients who started CPAP treatment ($n = 698$), compliance as a continuous variable was independently associated with a lower risk of cardiovascular mortality (HR, 0.48; 95% CI, 0.30 to 0.78; $P = 0.003$) (Table 4), whereas in untreated participants ($n = 698$), AHI as a continuous variable was independently associated with increased cardiovascular mortality (HR, 1.01; 95% CI, 1.00 to 1.02; $P = 0.005$) (Table 5).

Finally, when the subgroups of patients were analyzed separately according to the type of diagnostic study used (RP [57% of patients] versus full PSG [43% of patients]), the results were similar to those obtained from the overall analysis of the entire group of patients. Thus, in the RP group the risk of cardiovascular death in those patients with severe untreated OSA was significantly higher than that of the control group (HR, 2.49; 95% CI, 1.15 to 5.39; $P = 0.021$), and this risk was normalized in those patients treated with CPAP (HR, 1.14; 95% CI, 0.66 to 1.98; $P = 0.64$). Similarly, a significantly greater risk of cardiovascular death was also observed in those patients with severe untreated OSA in the full PSG, compared with the control group (HR, 2.62; 95% CI, 1.12 to 9.67; $P = 0.034$), and this risk was normalized in those patients treated with CPAP (HR, 0.88; 95% CI, 0.18

to 4.3; $P = 0.88$). In the group with untreated mild-moderate OSA the risk was not significantly greater than that of the control group in either of the two subgroups of patients.

DISCUSSION

The main findings of this study were that, in elderly patients, severe OSA not treated with CPAP was associated with an increase in cardiovascular mortality due to stroke and heart failure, whereas treatment with CPAP was associated with a decrease in this excess of cardiovascular mortality to levels similar to those of patients without OSA.

Although there is little doubt that OSA is a risk factor for cardiovascular mortality, most studies to date have been performed on middle-aged men (4, 10, 17, 18), and there remains some controversy about its effect on the elderly population. Some studies have found a greater adjusted risk of cardiovascular morbidity and mortality in elderly patients with OSA, as reflected by an increase in night-time blood pressure (24), CVEs (25, 27), arrhythmias (26), and mortality (28, 29). Other authors, however, have concluded that OSA does not cause excess mortality in an elderly person, as opposed to a young one (16, 17). In this respect, Punjabi and colleagues (16), analyzing the subgroup of individuals aged over 70 years of both sexes in the population-based cohort of the Sleep Heart Health Study, did not observe any excess of all-cause mortality in relation to sleep-disordered breathing severity. Lavie and Lavie explained

TABLE 2. CAUSES OF DEATH

Cause of Death	AHI < 15 (n = 155)	AHI 15–29 without CPAP (n = 108)	AHI ≥ 30 without CPAP (n = 173)	OSA with CPAP (n = 503)
All causes	26	24	59	81
Cardiovascular	10	15	35	40
Myocardial infarction	5	4	9	13
Stroke	2	7	12	7
Heart failure	3	3	15	17
Sudden death	0	1	0	2
Neoplasia	3	5	12	18
Other causes	13	4	12	23

Definition of abbreviations: AHI = apnea-hypopnea index; CPAP = continuous positive air pressure; OSA = obstructive sleep apnea.

Data tabulated as absolute numbers.

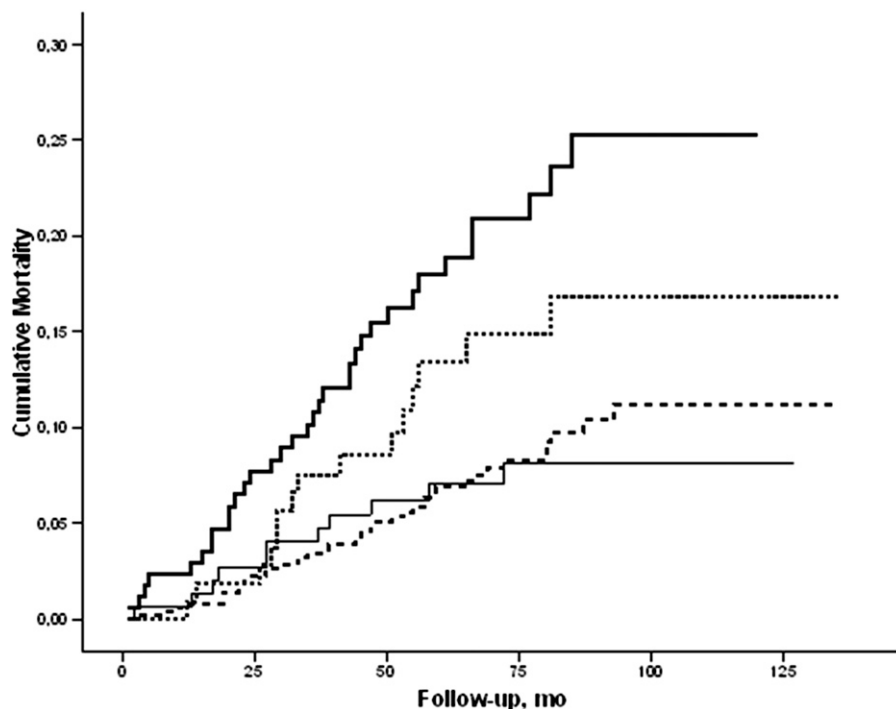


Figure 2. Kaplan-Meier cardiovascular cumulative mortality curves for study. Groups: *thick solid line*, severe OSA untreated with CPAP; *dotted line*, mild to moderate OSA untreated with CPAP; *dashed line*, OSA treated with CPAP; *thin solid line*, control group (AHI < 15). Log-rank test: 11.38; $P = 0.001$ for the comparison between severe untreated OSA group and control group. Log-rank test: 3.13; $P = 0.08$ for the comparison between untreated mild to moderate OSA group and control group. Log-rank test: 0.09; $P = 0.77$ for the comparison between CPAP-treated OSA group and control group. AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; OSA = obstructive sleep apnea.

these paradoxical differences in the results between younger and elderly individuals via the “ischemic preconditioning” hypothesis, according to which long-term intermittent hypoxia in the elderly could trigger the formation of collateral neovascularization (19). This hypothesis has been confirmed by observing that patients with coronary occlusion and OSA presented a greater number of newly formed collaterals, which would theoretically protect them from death after a coronary event (20). According to this hypothesis, we found that severe untreated OSA was not associated with an increase in mortality from ischemic heart disease in elderly patients, compared with those who did not suffer from OSA. Our results are similar to those found in the analysis of the elderly cohort in the Sleep Heart

Health Study, which also found that the incidence of coronary events did not increase in the subgroup of elderly people with OSA, in contrast with men less than 70 years of age (25). In any case, the number of deaths from ischemic heart disease observed in our study is low and so these results should be interpreted with caution.

In contrast, our study found an association between non-treated severe OSA and an increase in overall cardiovascular mortality in elderly people, as a consequence of an increase in deaths from stroke and heart failure. This concurs once again with the findings of two studies that analyzed the Sleep Heart Health Study cohort, which showed an increase in the incidence of new cardiovascular events caused by heart failure in the

TABLE 3. VARIABLES ASSOCIATED WITH CARDIOVASCULAR DEATH: UNADJUSTED, PARTIALLY ADJUSTED, AND FULLY ADJUSTED COX MULTIVARIATE REGRESSION ANALYSIS

Variable	Unadjusted		Partially Adjusted*		Fully Adjusted†	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.09 (1.05–1.14)	0.0001	1.09 (1.04–1.13)	0.0001	1.06 (1.03–1.11)	0.002
Sex	1.19 (0.78–1.80)	0.43	1.45 (0.76–2.77)	0.26	1.64 (0.86–3.13)	0.13
Type of sleep study (PSG)	0.92 (0.61–1.36)	0.67	0.75 (0.36–1.54)	0.43	1.25 (0.61–2.59)	0.55
Sleep clinic	1.25 (0.85–1.87)	0.26	1.54 (0.83–2.86)	0.17	1.64 (0.87–3.01)	0.13
BMI	1.03 (0.99–1.07)	0.06	1.03 (0.99–1.07)	0.06	1.04 (0.99–1.07)	0.06
Smoked (≥ 30 pack-years)	1.37 (0.92–2.02)	0.12	1.67 (0.99–2.81)	0.05	1.53 (0.92–2.56)	0.11
ESS	1.02 (0.98–1.06)	0.29	1.04 (0.99–1.09)	0.10	1.03 (0.99–1.08)	0.13
Dyslipidemia	1.29 (0.86–1.90)	0.22	1.22 (0.81–1.83)	0.34	0.83 (0.55–1.25)	0.37
Diabetes mellitus	2.55 (1.71–3.79)	0.0001	2.54 (1.68–3.84)	0.0001	2.25 (1.47–3.43)	0.0001
Previous CVE	3.05 (2.04–4.55)	0.0001	—	—	2.22 (1.44–3.42)	0.0001
AHT	1.53 (0.94–2.48)	0.07	—	—	1.12 (0.68–1.85)	0.66
OSA group						
AHI < 15	1		1		1	
AHI 15–29 without CPAP	1.98 (0.91–4.32)	0.09	1.62 (0.74–3.54)	0.23	1.38 (0.73–2.64)	0.32
OSA with CPAP	1.11 (0.57–2.16)	0.76	1.07 (0.53–2.17)	0.86	0.93 (0.46–1.89)	0.84
AHI ≥ 30 without CPAP	3.09 (1.57–6.10)	0.001	2.56 (1.24–5.29)	0.011	2.25 (1.41–3.61)	0.001

Definition of abbreviations: AHI = apnea-hypopnea index; AHT = arterial hypertension; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CVE = cardiovascular event; ESS = Epworth Sleepiness Scale; HR = hazard ratio; OSA = obstructive sleep apnea; PSG = polysomnography.

*Partially adjusted: Adjusted for OSA group, age, sex, type of sleep study, sleep clinic, BMI, diabetes mellitus, smoking habit, ESS, and dyslipidemia.

† Fully adjusted: Variables included in the partially adjusted analysis plus previous CVEs and AHT.

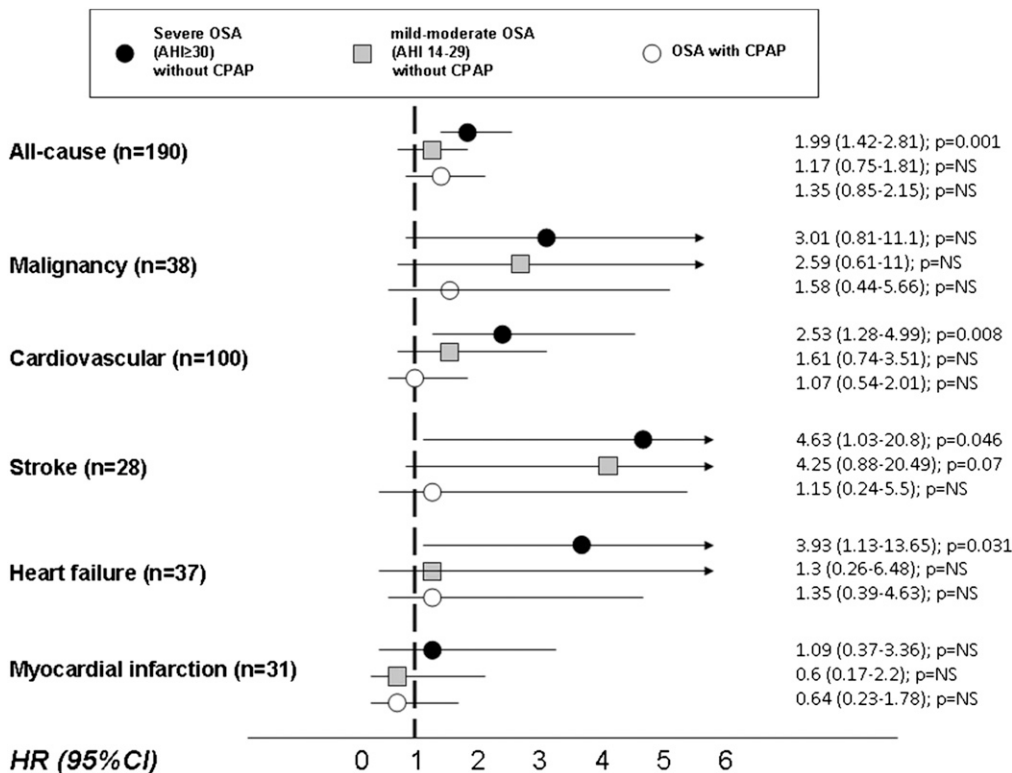


Figure 3. Hazard ratio (95% confidence interval) of the various analyses of general mortality, cardiovascular mortality, and types of cardiovascular and noncardiovascular events studied with respect to the control group without OSA. Note: The risk of death from stroke has also been adjusted for the presence of atrial fibrillation. Three patients experienced sudden death. AHI = apnea-hypopnea index; CI = confidence interval; CPAP = continuous positive airway pressure; HR = hazard ratio; NS = not significant; OSA = obstructive sleep apnea.

subgroup of elderly patients with OSA (25) or stroke (median age of patients with stroke, 72 yr) (27), although cardiovascular mortality was not analyzed in these studies. Although it could be supposed that the “ischemic preconditioning” hypothesis would endorse protection against intermittent hypoxia in any type of cardiovascular event, most of the data available on this compensatory mechanism derive from studies investigating its effect on coronary circulation (38–40), and the effect on cerebral circulation is much more open to debate, particularly in the case of elderly people (41–43). Thus, Wegener and colleagues reported that the protection provided against stroke development by an earlier period of cerebral ischemia (e.g., transient ischemic attack) does not depend on new vascular formation but rather on triggering intrinsic neuroprotective mechanisms unrelated to neovascularization (42).

Although an analysis of all-cause mortality was not our main objective, it is important to comment on the discrepancies observed between the results found by Punjabi and colleagues (16) in their analysis of the cohort from the Sleep Heart Health Study, where no excess of all-cause mortality was observed in individuals over 70 years of age with severe OSA, and the results of our study, in which an excess of mortality was found in elderly patients with untreated severe OSA. We believe that the explanation for this discrepancy lies in the different origins and characteristics of the series analyzed in the two studies. Whereas the study by Punjabi and colleagues (16) was population-based and therefore probably comprised a group of individuals with a low-risk cardiovascular risk profile and included a lower percentage of individuals with severe OSA, our study is clinically based and therefore includes a high percentage of patients with severe OSA (AHI ≥ 30; 62.6%) and a higher cardiovascular risk profile (38.5% of our patients had a previous history of cardiovascular events and 52.6% of the deaths were of cardiovascular origin).

To our knowledge, there is no study in the literature to date that analyzes the long-term impact of CPAP treatment on cardiovascular mortality in a large series consisting exclusively of elderly

people. Marin and colleagues observed that CPAP provided protection against both fatal and nonfatal CVEs in middle-aged males (4), and Campos-Rodríguez and colleagues have reported similar results in women (44), although neither of these two studies analyzed elderly people separately (4). Our study shows, for the first time, that CPAP treatment in patients 65 years of age or older of both sexes (as well as in the subgroup ≥ 75 yr) normalizes the adjusted excess of general mortality (particularly of cardiovascular origin). This finding echoes the case of middle-aged men and could be explained by a reduction in deaths caused by cerebrovascular events and heart failure, without any changes in the mortality from coronary events.

TABLE 4. VARIABLES ASSOCIATED WITH CARDIOVASCULAR DEATH IN ELDERLY PATIENTS WHO STARTED CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP) TREATMENT*: ADJUSTED MULTIVARIATE COX REGRESSION ANALYSIS, INCLUDING CPAP COMPLIANCE AND APNEA-HYPOPNEA INDEX AS CONTINUOUS VARIABLES

Variable	Fully Adjusted Model	
	HR (95% CI)	P Value
Age	1.07 (1.02–1.13)	0.005
Sex	1.66 (0.70–3.98)	0.25
Body mass index	1.03 (0.99–1.08)	0.14
ESS	1.03 (0.98–1.08)	0.30
Previous CV events	2.08 (1.26–3.43)	0.004
Hypertension	1.20 (0.66–2.19)	0.54
Diabetes mellitus	2.66 (1.63–4.34)	<0.001
Hyperlipidemia	1.59 (0.98–2.58)	0.06
Smoked (≥30 pack-years)	1.90 (1.02–3.55)	0.04
AHI	1.01 (0.99–1.02)	0.36
CPAP adherence	0.48 (0.30–0.78)	0.003

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; CPAP = continuous positive airway pressure; CV = cardiovascular; ESS = Epworth Sleepiness Scale; HR = hazard ratio.

* n = 698.

TABLE 5. VARIABLES ASSOCIATED WITH CARDIOVASCULAR DEATH IN UNTREATED PATIENTS*: ADJUSTED MULTIVARIATE COX REGRESSION ANALYSIS INCLUDING APNEA-HYPOPNEA INDEX AS A CONTINUOUS VARIABLE

Variable	Fully Adjusted Model	
	HR (95% CI)	P Value
Age	1.08 (1.03–1.14)	0.003
Sex	1.02 (0.52–1.99)	0.96
Body mass index	1.02 (0.98–1.07)	0.34
ESS	1.02 (0.96–1.08)	0.47
Previous CV events	1.92 (1.08–3.4)	0.026
Hypertension	1.32 (0.65–2.66)	0.45
Diabetes mellitus	1.41 (0.80–2.46)	0.24
Hyperlipidemia	1.08 (0.64–1.82)	0.79
Smoked (≥ 30 pack-years)	0.96 (0.50–1.85)	0.91
AHI	1.02 (1.00–1.02)	0.005

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; CV = cardiovascular; ESS = Epworth Sleepiness Scale; HR = hazard ratio.

*n = 436.

The outstanding strengths of our study are the significant number of participants and the prolonged follow-up, making it possible to evaluate, for the first time, the impact of CPAP treatment in a wide-ranging series consisting exclusively of elderly people, with only a limited amount of missing data. Both participating hospitals were ideally situated, geographically, for this type of long-term study as their catchment areas are characterized by scarce movement of population and a single hospital for referrals. This meant that little information would have been lost. We used an AHI cutoff of 15 for the diagnosis of OSA (control group) in the elderly with clinical suspicion of OSA, as older individuals present an increase in the number of age-related respiratory events during sleep (12, 28, 29). In fact, less than 5% of our patients presented an AHI less than 5. The principal limitations of our study are as follows: first, the main limitation is that it does not feature any randomized intervention, but this would raise ethical issues in a prolonged study of this kind. Second, the statistical power is reduced in the analysis of the subgroups of patients 75 years of age or older and in the separate analysis of the different causes of cardiovascular death, so any change in this classification would provoke proportionally large changes in the event rates, meaning that these results must be interpreted with caution. The third limitation concerns the use of RP as a diagnostic method in a high percentage of patients. We wanted to carry out a real-life study that followed the practice of many countries, such as Spain, by using a diagnostic algorithm that would incorporate validated RP and PSG (32, 33). In any case, the error liable to be made by the use of RP is an underestimation of AHI through the use of the recording time (longer than the sleep time), which could lead to the classification of patients with severe OSA as mild-moderate. This means that if a full PSG had been used as a diagnostic method for all the patients the differences in cardiovascular mortality found between the groups not treated with CPAP and the other groups would probably have been greater; therefore, the use of RP does not undermine the conclusions of our study but, rather, reinforces them. Furthermore, all the RP devices used in the present study were correctly validated. Fourth, we have considered good compliance with CPAP to be a nightly use of at least 4 hours, measured by the device's internal counter. The commonly accepted definition of good compliance includes not only this number of hours but also the use of the device for at least four nights per week (or 70% of nights) (45), but this information was not available for our study. In any case, we undertook a parallel

analysis using compliance with CPAP, in number of hours of use per day, as a continuous variable, and the results were similar to those obtained by using the cutoff point of 4 hours/day to define good compliance. Finally, the causes of death were not verified by an autopsy, although every effort was made to check the veracity of the cause of death in all cases.

In conclusion, we have provided the first evidence that severe untreated OSA is associated with cardiovascular mortality in elderly people of both sexes. This excess of mortality seems to be the result of an increase in mortality from cerebrovascular and heart failure and CPAP treatment is associated with a decrease in the risk of mortality to levels similar to those found in patients without OSA. Although additional research is required, we believe this study is an important step in developing evidence for this common but relatively understudied disorder in the elderly.

Author disclosures are available with the text of this article at www.atsjournals.org.

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