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CARDIOVASCULAR MORTALITY IN OBSTRUCTIVE SLEEP APNEA IN THE ELDERLY. ROLE OF LONG-TERM CPAP TREATMENT

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CLEAN VERSION

CARDIOVASCULAR MORTALITY IN OBSTRUCTIVE SLEEP APNEA IN THE ELDERLY. ROLE OF LONG-TERM CPAP TREATMENT

A PROSPECTIVE OBSERVATIONAL STUDY

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-Dr. M.A. Martínez-García designed the study, contributed to data acquisition and interpretation, supervised the study and wrote the manuscript.

-Dr. F Campos-Rodríguez designed the study, contributed to data acquisition and interpretation and approved the final version to be published.

-Dr. P. Catalán-Serra contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.

-Dr J.J. Soler-Cataluña performed statistical analyses and contributed to data interpretation, critically revised the manuscript and approved the final version to be published.
-Dr. I. De la Cruz contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.
-Dr J. Duran-Cantolla contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.
-Dr JM. Montserrat assisted in data interpretation, critically revised the manuscript and approved the final version to be published.

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AT A GLANCE COMMENTARY

Scientific Knowledge on this subject

In middle-age subjects, obstructive sleep apnea is a risk factor for cardiovascular death and CPAP treatment seems to significantly reduce this risk, but whether it is also a risk factor and the effect of CPAP in the elderly are unknown

What This Study Adds to this 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.

ABSTRACT

Rationale: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular death in middle-age 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 assess whether continuous positive airway pressure (CPAP) treatment is associated with a change in risk in the elderly.

Methods and Measurements: Prospective, observational study of a consecutive cohort of elderly patients (≥65 years) studied for suspicion of OSA between 1998 and 2007.

Patients with an apnea-hypopnea index (AHI)<15 were the control group. OSA was defined as mild to moderate [AHI of 15 to 29] or severe [AHI≥30]. Patients with OSA were classified as CPAP-treated (adherence ≥4 hours per day) or untreated (adherence<4 hours per day or not prescribed). Participants were followed up until December 2009. The endpoint was cardiovascular death. A multivariate Cox survival analysis was used to determine the independent impact of OSA and CPAP treatment on cardiovascular mortality.

Main Results: 939 elderly were studied (median follow-up, 69 months). Compared with the control group, the fully adjusted hazard ratios for cardiovascular mortality were 2.25 (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.

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

Word count (Abstract): 240

Keywords: Elderly; older; obstructive sleep apnea; cardiovascular events; stroke; ischemic heart disease; heart failure; continuous positive airway pressure.

INTRODUCTION

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 [CVE]) (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 non-fatal CVE (4, 8-10).

Although we are aware that the prevalence of OSA increases with age (11,12), very 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 out of four sleep studies is carried out on an individual aged over 65, 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), while 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 a greater cardio- 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 aged ≥65 years, 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 aged ≥65 referred to the sleep units of the Requena Hospital (Valencia, Spain) or Valme Hospital (Seville, Spain) for suspected OSA between December 1998 and December 2007. Exclusion criteria were 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), dichotomic cardiovascular risk factors: smoking (≥30 packs/year), alcohol intake (gr/day), arterial hypertension (systolic or diastolic blood pressure ≥140/90 in two or more outpatient measurements or use of anti-hypertensive medication), fasting glucose levels higher than 7 mmol/L (125 mg/dL) in two or more measurements or use of antihyperglycemic medication or dyslipidemia (fasting levels of total cholesterol or triglycerides higher than 5.17 mmol/L [>200 mg/dL]), respectively, or use of antihyperlipidemic medication. Heart failure was defined via the collection of ecocardiographic 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 presence 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 using 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 & Co. KG, Wurzburg, Germany or Embletta PDS; ResMed, Sydney, Australia) (34,35). PSG included continuous recording of electro-encephalogram, electro-oculogram, electro-myogram, electro-cardiogram, evaluations of the nasal airflow, thoracic and abdominal band movements, and arterial oxygen saturation (SaO2), according to standard criteria (36). RP included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements and Sa02. A full PSG was performed to all the patients undergoing RP who presented recording artifacts, 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 interruption of oronasal airflow >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 >10 seconds associated with a desaturation ≥4% (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≥15, and was classified as mild-moderate (AHI between 15 and 29) or

severe (AHI≥30). CPAP treatment was offered to all the patients with AHI≥30, regardless of symptoms, and to those with 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 auto-titrating CPAP device. The patients were told to follow their usual lifestyle when undertaking the sleep studies, as regards 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 ≥4 hours per 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 non-compliant (average use <4 hours/day).

Follow-up

The follow-up ended on 31 December 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 endpoint data could not be established at the end of the study.

Main endpoint of the study

The study's main endpoint, designed before the study started, was cardiovascular death (defined as death from stroke, heart failure or myocardial infarction). Secondary endpoints 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 out-patient 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, USA) was used for the analysis. On the basis of the results of the sleep study and CPAP treatment, 4 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 hours/day). Normality in the variables distribution was assessed by using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean (SD) or median (IQR) and qualitative variables as absolute values and percentages. The baseline differences between the groups were analyzed using the one-way ANOVA test with Bonferroni correction or the 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 with the 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 due to non-cardiovascular 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´s proportional hazard model analysis to determine the variables independently associated with mortality in the study groups. The following variables were finally selected to entered in the Cox model: age, BMI, gender, ESS, smoking habit, arterial hypertension, diabetes mellitus, dyslipidemia, respiratory failure, previous CVE and OSA groups. The results were expressed as HR and 95% confidence interval, and a p value <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 different 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 different OSA groups. Lastly, a subgroup of patients aged ≥75 were also analyzed and the risks of all-cause mortality and specific cardiovascular and non-cardiovascular mortality were also compared between the studied OSA groups.

RESULTS

Initially, 1,005 elderly patients with suspected OSA were included; 62 were excluded and four 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 CVE, type of sleep study and reference clinic. The median follow-up was 69 months [interquartile range, 49 to 87 months], 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 who used CPAP ≥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% with 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 non-treated OSA group presented a non-significant increase in cumulative cardiovascular mortality compared to the control group (log-rank test, 3.13, p=0.08). Cumulative cardiovascular mortality in the CPAP-treated

OSA group was similar to those of the non-OSA group (log-rank test, 0.09; p=0.77).

Table 3 shows the fully adjusted Cox analysis. In order 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 to the control group. No significant differences in cardiovascular mortality were observed, however, between OSA patients treated with CPAP, mild-moderate OSA patients 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 to 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 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 (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] vs 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, while 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 OSA patients, as reflected by an increase in night-time blood pressure (24), CVE (25,27), arrhythmias (26), and mortality (28,29). Other authors, however, have concluded that OSA does not cause excess of mortality in an elderly person, as opposed to a young one (16,17). In this respect, *Punjabi et al (16)*, analyzing the subgroup of individuals aged over 70 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 the sleep-disordered breathing severity. *Lavie et al* explained 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 neo-vascularization (19). This hypothesis has recently 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 to 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 aged under 70 (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 subgroup of elderly patients with OSA (25) or stroke (median age of stroke patients: 72 years) (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 et al* 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 neo-vascularization (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 et al* (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 with severe OSA, and the results of our study, where 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 et al* (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 clinicallly based and therefore includes a high percentage of patients with severe OSA (IAH≥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 et al* observed that CPAP provided protection against both fatal and non-fatal CVE in middle-aged males (4), and *Campos-Rodriguez et al* has recently reported similar results in women (44), although none of these two studies analyzed elderly people separately (4). Our study shows, for the first time, that CPAP treatment in patients aged ≥65 years of both sexes (as well as in the subgroup ≥75 years) 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.

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 in the literature, 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 very little information would have been lost. We used a cut-off of 15 in the AHI 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<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 and 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. Third, 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 like Spain by using a diagnostic algorithm that would incorporate validated RP

and PSG (32,33). In any case, the error liable to be made with 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 considerated 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 4 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 cut-off point of 4 hours per 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.

Conflicts of interest

None of the authors have any financial or other potential conflict of interest.
-Dr. M.A. Martínez-García has no financial or other potential conflict of interest.
-Dr. F Campos-Rodríguez has no financial or other potential conflict of interest.
-Dr. P. Catalán-Serra has no financial or other potential conflict of interest.
-Dr J.J. Soler-Cataluña has no financial or other potential conflict of interest.
-Dr. I. De la Cruz has no financial or other potential conflict of interest.
-Dr J. Duran-Cantolla has no financial or other potential conflict of interest.
-Dr JM. Montserrat has no financial or other potential conflict of interest.

The corresponding author (Dr. Martínez-García) confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. All the authors have approved this final draft.

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Table 1. Baseline characteristics of the sample population according to OSA groups

Variables	**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)
Gender (% 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/hour)	6.6 (3.7)	21.3 (4.5)	58.6 (20.9)	52.2 (23.5)
Smoked ≥ 30 packs/yr	41%	42%	47%	41%
Alcohol intake (gr/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, n (%)*	59%	27%	56%	30%
Type of sleep study**	37%	53%	30%	45%

Data tabulated by mean (standard deviation) for quantitative variables and percentage for qualitative variables.
EES: Epworth Sleepiness Scale; AHT: Arterial hypertension; CVE: Cardiovascular events; AHI: Apnea-Hypopnea Index; BMI: Body Mass Index
*Requena Hospital, Valencia, Spain
** Full standard polysomnography

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

Table 2. Causes of death

	AHI <15 (n=155)	AHI 15-29 without CPAP (n=108)	AHI ≥30 without CPAP (n=173)	OSA with CPAP (n=503)
Causes of death				
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**

Data tabulated as absolute number

Table 3. Variables associated with cardiovascular death. Unadjusted, partially adjusted and fully adjusted Cox multivariate regression analysis

Variables	*Unadjusted*		*Partially Adjusted*		*Fully Adjusted*	
	HR (CI 95%)	***p***	***HR (CI 95%)***	***p***	***HR (CI 95%)***	***p***
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
Gender	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 packs of cigarettes per year)	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

Partially adjusted: adjusted for OSA group, age, gender, type of sleep study, sleep clinic, body mass index (BMI), diabetes mellitus, smoke habit, Epworth Sleepiness Scale (ESS) and dyslipidemia.

Fully adjusted: variables included in the partially adjusted analysis plus previous cardiovascular events (CVE) and arterial hypertension (AHT)

OSA: Obstructive Sleep Apnea; AHI: Apnea-Hypopnea Index; CPAP: Continuous Positive Airway Pressure

Table 4. Variables associated with cardiovascular death in elderly patients who started CPAP treatment (n = 698). Adjusted multivariate Cox regression analysis, including CPAP compliance and AHI as continuous variables.

Variables	***Fully Adjusted model ****	
	HR (95%CI)	***p***
Age	1.07 (1.02-1.13)	0.005
Gender	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 cig/day)	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

Table 5. Variables associated with cardiovascular death in untreated patients (n = 436). Adjusted multivariate Cox regression analysis including AHI as a continuous variable.

Variables	***Fully Adjusted model ****	
	HR (95%CI)	***p***
Age	1.08 (1.03-1.14)	0.003
Gender	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 cig/day)	0.96 (0.50-1.85)	0.91
AHI	1.02 (1.00-1.02)	0.005

Figure legends

Figure 1. Patients' flow chart profile

Figure 2. Kaplan Meier cardiovascular cumulative mortality curves for study Groups

AHI = apnea hypopnea index. CPAP = continuous positive airway pressure.

Log-rank test: 113.8; p=0.001 for the comparison between severe untreated OSA and control group.

Log-rank test: 3.13; p=0.08 for the comparison between untreated mild-to-moderate OSA and control group.

Log-rank test: 0.09; p=0.77 for the comparison between CPAP-treated OSA group and control group.

Figure 3. Hazard ratio (95% CI) of the various analyses of general mortality, cardiovascular mortality, and types of cardiovascular and non-cardiovascular events studied with respect to the control group without OSA

*The risk of death from stroke has been also adjusted by the presence of atrial fibrillation.

Three patients died from sudden death.

MARKED VERSION

CARDIOVASCULAR MORTALITY IN OBSTRUCTIVE SLEEP APNEA IN THE ELDERLY. ROLE OF LONG-TERM CPAP TREATMENT

A PROSPECTIVE OBSERVATIONAL STUDY

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-Dr. P. Catalán-Serra contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.

-Dr J.J. Soler-Cataluña performed statistical analyses and contributed to data interpretation, critically revised the manuscript and approved the final version to be published.
-Dr. I. De la Cruz contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.
-Dr J. Duran-Cantolla contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version to be published.
-Dr JM. Montserrat assisted in data interpretation, critically revised the manuscript and approved the final version to be published.

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AT A GLANCE COMMENTARY

Scientific Knowledge on this subject

In middle-age subjects, obstructive sleep apnea is a risk factor for cardiovascular death and CPAP treatment seems to significantly reduce this risk, but whether it is also a risk factor and the effect of CPAP in the elderly are unknown

What This Study Adds to this 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.

ABSTRACT

Rationale: Obstructive sleep apnea (OSA) is a risk factor for cardiovascular death in middle-age 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 assess whether continuous positive airway pressure (CPAP) treatment is associated with a change in risk in the elderly.

Methods and Measurements: Prospective, observational study of a consecutive cohort of elderly patients (≥65 years) studied for suspicion of OSA between 1998 and 2007.

Patients with an apnea-hypopnea index (AHI)<15 were the control group. OSA was defined as mild to moderate [AHI of 15 to 29] or severe [AHI≥30]. Patients with OSA were classified as CPAP-treated (adherence ≥4 hours per day) or untreated (adherence<4 hours per day or not prescribed). Participants were followed up until December 2009. The endpoint was cardiovascular death. A multivariate Cox survival analysis was used to determine the independent impact of OSA and CPAP treatment on cardiovascular mortality.

Main Results: 939 elderly were studied (median follow-up, 69 months). Compared with the control group, the fully adjusted hazard ratios for cardiovascular mortality were 2.25 (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.

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

Word count (Abstract): 240

Keywords: Elderly; older; obstructive sleep apnea; cardiovascular events; stroke; ischemic heart disease; heart failure; continuous positive airway pressure.

INTRODUCTION

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 [CVE]) (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 non-fatal CVE (4, 8-10).

Although we are aware that the prevalence of OSA increases with age (11,12), very 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 out of four sleep studies is carried out on an individual aged over 65, 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), while 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 a greater cardio- 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 aged ≥65 years, 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 aged ≥65 referred to the sleep units of the Requena Hospital (Valencia, Spain) or Valme Hospital (Seville, Spain) for suspected OSA between December 1998 and December 2007. Exclusion criteria were 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), dichotomic cardiovascular risk factors: smoking (≥30 packs/year), alcohol intake (gr/day), arterial hypertension (systolic or diastolic blood pressure ≥140/90 in two or more outpatient measurements or use of anti-hypertensive medication), fasting glucose levels higher than 7 mmol/L (125 mg/dL) in two or more measurements or use of antihyperglycemic medication or dyslipidemia (fasting levels of total cholesterol or triglycerides higher than 5.17 mmol/L [>200 mg/dL]), respectively, or use of antihyperlipidemic medication. Heart failure was defined via the collection of ecocardiographic 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 presence 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 using 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 & Co. KG, Wurzburg, Germany or Embletta PDS; ResMed, Sydney, Australia) (34,35). PSG included continuous recording of electro-encephalogram, electro-oculogram, electro-myogram, electro-cardiogram, evaluations of the nasal airflow, thoracic and abdominal band movements, and arterial oxygen saturation (SaO2), according to standard criteria (36). RP included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements and Sa02. A full PSG was performed to all the patients undergoing RP who presented recording artifacts, 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 interruption of oronasal airflow >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 >10 seconds associated with a desaturation ≥4% (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≥15, and was classified as mild-moderate (AHI between 15 and 29) or

severe (AHI≥30). CPAP treatment was offered to all the patients with AHI≥30, regardless of symptoms, and to those with 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 auto-titrating CPAP device. The patients were told to follow their usual lifestyle when undertaking the sleep studies, as regards 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 ≥4 hours per 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 non-compliant (average use <4 hours/day).

Follow-up

The follow-up ended on 31 December 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 endpoint data could not be established at the end of the study.

Main endpoint of the study

The study's main endpoint, designed before the study started, was cardiovascular death (defined as death from stroke, heart failure or myocardial infarction). Secondary endpoints 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 out-patient 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, USA) was used for the analysis. On the basis of the results of the sleep study and CPAP treatment, 4 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 hours/day). Normality in the variables distribution was assessed by using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean (SD) or median (IQR) and qualitative variables as absolute values and percentages. The baseline differences between the groups were analyzed using the one-way ANOVA test with Bonferroni correction or the 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 with the 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 due to non-cardiovascular 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´s proportional hazard model analysis to determine the variables independently associated with mortality in the study groups. The following variables were finally selected to entered in the Cox model: age, BMI, gender, ESS, smoking habit, arterial hypertension, diabetes mellitus, dyslipidemia, respiratory failure, previous CVE and OSA groups. The results were expressed as HR and 95% confidence interval, and a p value <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 different 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 different OSA groups. Lastly, a subgroup of patients aged ≥75 were also analyzed and the risks of all-cause mortality and specific cardiovascular and non-cardiovascular mortality were also compared between the studied OSA groups.

RESULTS

Initially, 1,005 elderly patients with suspected OSA were included; 62 were excluded and four 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 CVE, type of sleep study and reference clinic. The median follow-up was 69 months [interquartile range, 49 to 87 months], 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 who used CPAP ≥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% with 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 non-treated OSA group presented a non-significant increase in cumulative cardiovascular mortality compared to the control group (log-rank test, 3.13, p=0.08). Cumulative cardiovascular mortality in the CPAP-treated

OSA group was similar to those of the non-OSA group (log-rank test, 0.09; p=0.77).

Table 3 shows the fully adjusted Cox analysis. In order 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 to the control group. No significant differences in cardiovascular mortality were observed, however, between OSA patients treated with CPAP, mild-moderate OSA patients 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 to 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 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 (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] vs 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 ~~but not in mortality from ischemic heart disease myocardial infarction~~, while 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 OSA patients, as reflected by an increase in night-time blood pressure (24), CVE (25,27), arrhythmias (26), and mortality (28,29). Other authors, however, have concluded that OSA does not cause excess of mortality in an elderly person, as opposed to a young one (16,17). In this respect, *Punjabi et al (16)*, analyzing the subgroup of individuals aged over 70 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 the sleep-disordered breathing severity. *Lavie et al* explained 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 neo-vascularization (19). This hypothesis has recently 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 to 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 aged under 70 (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 subgroup of elderly patients with OSA (25) or stroke (median age of stroke patients: 72 years) (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 et al* 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 neo-vascularization (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 et al* (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 with severe OSA, and the results of our study, where 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 et al* (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 clinicallly based and therefore includes a high percentage of patients with severe OSA (IAH≥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 et al* observed that CPAP provided protection against both fatal and non-fatal CVE in middle-aged males (4), and *Campos-Rodriguez et al* has recently reported similar results in women (44), although none of these two studies analyzed elderly people separately (4). Our study shows, for the first time, that CPAP treatment in patients aged ≥65 years of both sexes (as well as in the subgroup ≥75 years) 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.

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 in the literature, 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 very little information would have been lost. We used a cut-off of 15 in the AHI 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<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 and 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. Third, 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 like Spain by using a diagnostic algorithm that would incorporate validated RP

and PSG (32,33). In any case, the error liable to be made with 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 considerated 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 4 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 cut-off point of 4 hours per 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 ~~(but not from ischemic heart disease),~~ 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.

Conflicts of interest

None of the authors have any financial or other potential conflict of interest.
-Dr. M.A. Martínez-García has no financial or other potential conflict of interest.
-Dr. F Campos-Rodríguez has no financial or other potential conflict of interest.
-Dr. P. Catalán-Serra has no financial or other potential conflict of interest.
-Dr J.J. Soler-Cataluña has no financial or other potential conflict of interest.
-Dr. I. De la Cruz has no financial or other potential conflict of interest.
-Dr J. Duran-Cantolla has no financial or other potential conflict of interest.
-Dr JM. Montserrat has no financial or other potential conflict of interest.

The corresponding author (Dr. Martínez-García) confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication. All the authors have approved this final draft.

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Table 1. Baseline characteristics of the sample population according to OSA groups

Variables	**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)
Gender (% 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/hour)	6.6 (3.7)	21.3 (4.5)	58.6 (20.9)	52.2 (23.5)
Smoked ≥ 30 packs/yr	41%	42%	47%	41%
Alcohol intake (gr/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, n (%)*	59%	27%	56%	30%
Type of sleep study**	37%	53%	30%	45%

Data tabulated by mean (standard deviation) for quantitative variables and percentage for qualitative variables.
EES: Epworth Sleepiness Scale; AHT: Arterial hypertension; CVE: Cardiovascular events; AHI: Apnea-Hypopnea Index; BMI: Body Mass Index
*Requena Hospital, Valencia, Spain
** Full standard polysomnography

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 gender, smoking habit, AHT, diabetes and hyperlipidemia

Table 2. Causes of death

	AHI <15 (n=155)	AHI 15-29 without CPAP (n=108)	AHI ≥30 without CPAP (n=173)	OSA with CPAP (n=503)
Causes of death				
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**

Data tabulated as absolute number

Table 3. Variables associated with cardiovascular death. Unadjusted, partially adjusted and fully adjusted Cox multivariate regression analysis

Variables	*Unadjusted*		*Partially Adjusted*		*Fully Adjusted*	
	HR (CI 95%)	*p*	*HR (CI 95%)*	*p*	*HR (CI 95%)*	*p*
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
Gender	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 packs of cigarettes per year)	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

Partially adjusted: adjusted for OSA group, age, gender, type of sleep study, sleep clinic, body mass index (BMI), diabetes mellitus, smoke habit, Epworth Sleepiness Scale (ESS) and dyslipidemia.

Fully adjusted: variables included in the partially adjusted analysis plus previous cardiovascular events (CVE) and arterial hypertension (AHT)

OSA: Obstructive Sleep Apnea; AHI: Apnea-Hypopnea Index; CPAP: Continuous Positive Airway Pressure

Table 4. Variables associated with cardiovascular death in elderly patients who started CPAP treatment (n = 698). Adjusted multivariate Cox regression analysis, including CPAP compliance and AHI as continuous variables.

Variables	*Fully Adjusted model **	
	HR (95%CI)	*p*
Age	1.07 (1.02-1.13)	0.005
Gender	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 cig/day)	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

Table 5. Variables associated with cardiovascular death in untreated patients (n = 436). Adjusted multivariate Cox regression analysis including AHI as a continuous variable.

Variables	*Fully Adjusted model **	
	HR (95%CI)	*p*
Age	1.08 (1.03-1.14)	0.003
Gender	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 cig/day)	0.96 (0.50-1.85)	0.91
AHI	1.02 (1.00-1.02)	0.005

Figure legends

Figure 1. Patients' flow chart profile

Figure 2. Kaplan Meier cardiovascular cumulative mortality curves for study Groups

AHI = apnea hypopnea index. CPAP = continuous positive airway pressure.

Log-rank test: 113.8; p=0.001 for the comparison between severe untreated OSA and control group.

Log-rank test: 3.13; p=0.08 for the comparison between untreated mild-to-moderate OSA and control group.

Log-rank test: 0.09; p=0.77 for the comparison between CPAP-treated OSA group and control group.

Figure 3. Hazard ratio (95% CI) of the various analyses of general mortality, cardiovascular mortality, and types of cardiovascular and non-cardiovascular events studied with respect to the control group without OSA

*The risk of death from stroke has been also adjusted by the presence of atrial fibrillation.

Three patients died from sudden death.