

Continuous Positive Airway Pressure Treatment Reduces Mortality in Patients with Ischemic Stroke and Obstructive Sleep Apnea

A 5-Year Follow-up Study

Miguel Ángel Martínez-García¹, Juan José Soler-Cataluña¹, Laura Ejarque-Martínez², Youssef Soriano², Pilar Román-Sánchez², Ferrán Barbé Illa³, Josep María Montserrat Canal⁴, and Joaquín Durán-Cantolla⁵

¹Pneumology Unit and ²Internal Medicine Service, Requena General Hospital, Valencia; ³Pneumology Service, Arnau de Vilanova Hospital and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERes), Lleida; ⁴Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clinic and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERes), Barcelona; and ⁵Sleep Disorders Unit, Txagorritxu Hospital and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERes), Vitoria, Spain

Rationale: Obstructive sleep apnea (OSA) is an independent risk factor for stroke, but little is known about the role of continuous positive airway pressure (CPAP) on mortality in patients with stroke.

Objectives: To analyze the independent impact of long-term CPAP treatment on mortality in patients with ischemic stroke.

Methods: Prospective observational study in 166 patients with ischemic stroke. Sleep study was performed in all of them and CPAP treatment was offered in the case of moderate to severe cases. Patients were followed-up for 5 years to analyze the risk of mortality.

Measurements and Main Results: Of 223 patients consecutively admitted for stroke, a sleep study was performed on 166 of them (2 mo after the acute event). Thirty-one had an apnea-hypopnea index (AHI) of less than 10; 39 had an AHI between 10 and 19, and 96 had an AHI of 20 or greater. CPAP treatment was offered when AHI was 20 or greater. Patients were followed up in our outpatient clinic at 1, 3, and 6 months, and for every 6 months thereafter for 5 years (prospective observational study). Mortality data were recorded from our computer database and official death certificates. The mean age of subjects was 73.3 ± 11 years (59% males), and the mean AHI was 26 (for all patients with a predominance of obstructive events). Patients with an AHI of 20 or greater who did not tolerate CPAP ($n = 68$) showed an increase adjusted risk of mortality (hazard ratio [HR], 2.69; 95% confidence interval [CI], 1.32–5.61) compared with patients with an AHI of less than 20 ($n = 70$), and an increased adjusted risk of mortality (HR, 1.58; 95% CI, 1.01–2.49; $P = 0.04$) compared with patients with moderate to severe OSA who tolerated CPAP ($n = 28$). There were no differences in mortality among patients without OSA, patients with mild disease, and patients who tolerated CPAP.

Conclusions: Our results suggest that long-term CPAP treatment in moderate to severe OSA and ischemic stroke is associated with a reduction in excess risk of mortality.

Keywords: stroke; continuous positive airway pressure; obstructive sleep apnea; mortality; cerebrovascular disease

Stroke ranks second after ischemic heart disease as a cause of death and disability-adjusted life-years lost in high-income countries worldwide. Approximately 80% of strokes are caused by focal cerebral ischemia due to arterial occlusion (1). Nonmodifi-

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Obstructive sleep apnea (OSA) is an independent risk factor for stroke and cardiovascular death, but little is known about the role of continuous positive airway pressure (CPAP) on mortality in stroke patients with OSA.

What This Study Adds to the Field

The results of this study confirm an increase of mortality in patients with ischemic stroke with moderate to severe OSA and suggest that CPAP treatment lowers the risk of mortality in these patients.

able stroke risk factors include age, race, sex, and a family history of cardiovascular disorders, whereas the most important modifiable risk factors include arterial hypertension, diabetes mellitus, obesity, dyslipidemia, carotid stenosis, current smoking, established cardiovascular disease, and atrial fibrillation (2). Survivors of an ischemic stroke have an increased risk of suffering another vascular event, especially another stroke, which is a major source of increased mortality and morbidity (2, 3). The rates of 30-day mortality after a first-ever stroke have been estimated as being between 10 and 17%, and the 5-year survival rate is 40% (4).

During the past few years, efforts have been made to determine new preventable and treatable stroke risk factors. Early recognition of these factors is essential for optimizing therapeutic procedures, especially those with a known effective treatment. In this sense, obstructive sleep apnea (OSA) has also been suggested as a modifiable and independent risk factor for stroke as defined by international guidelines (2, 3), and some studies have demonstrated that patients with stroke and OSA have an increased risk of death or new vascular events (5–8).

OSA affects 2 to 4% of the general middle-aged population and greater than 20% of the elderly population (9, 10). Continuous positive airway pressure (CPAP) is the most recognized and cost-effective treatment for OSA (11). It has been stated that long-term CPAP improves cardiovascular prognosis in patients with OSA (12) via various mechanisms (13–17). However, to our knowledge, there is no study available that analyzes the impact of long-term CPAP treatment on mortality in patients with stroke and for whom OSA is very common. We therefore undertook a 5-year prospective observational follow-up study with the goal of analyzing the impact of long-term CPAP treatment on mortality in patients affected by an ischemic stroke and OSA.

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Correspondence and requests for reprints should be addressed to Miguel Ángel Martínez-García, M.D., Unidad de Neumología, Hospital General de Requena, Paraje Casablanca s/n 46340, Valencia, Spain. E-mail: miangel@comv.es

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METHODS

Patients

All patients consecutively admitted in our center during an 18-month period with the diagnosis of acute ischemic stroke were recruited. Those patients who passed the acute phase of the neurological event (alive at least 2 mo from the onset of the stroke) were included in the study and a sleep study was performed. Patients previously treated with CPAP and those in a terminal stage of the disease at the moment of the evaluation (Glasgow Coma Scale score <8) were excluded. Patients diagnosed with heart or respiratory failure were also excluded. The study protocol was approved by the Requena General Hospital Ethics Committee, and all patients gave informed consent to inclusion in the study.

Assessment of Baseline Stroke and Vascular Risk Factors

The diagnosis and location of acute ischemic stroke were determined following international guidelines (2, 3) and were based on an evaluation of the existing neurological defects and brain-computed tomography scans conducted within hours after patient admission and several days later. Functional disability and neurological impairment were evaluated using validated neurological scales: the Barthel Index (18) (at discharge) and the Glasgow score (at admission) (19). The Barthel Index assesses daily activity on a scale of 0 to 100 (with a score of 100 corresponding to patients with full autonomy). Following a stroke, patients received antiplatelet treatment in all cases and anticoagulant treatment in cases of atrial fibrillation, in the absence of contraindications of anticoagulant treatment.

Data were collected from all patients on demographic, clinical, (age, sex, sleep-history and Epworth Sleepiness Scale self-reports of their status before the acute stroke) (20), anthropometric (body mass [BMI] index in kg/m^2 , measured at the start and end of the study) and other past vascular risk factors, including arterial hypertension (defined according to international guidelines (21) or through the current use of antihypertensive drugs); smoking status (current [>10 cigarettes/d] or past/never smoker); atrial fibrillation; diabetes mellitus; peripheral fibrinogen levels in mg/dl ; hypercholesterolemia (>250 mg/dl in peripheral blood); previous ischemic disease, including stroke, transient ischemic attack, and ischemic heart disease; and carotid stenosis. Significant internal carotid stenosis was considered when greater than 50% of the vascular lumen was affected as assessed by continuous Doppler flowmetry, transcranial Doppler flowmetry, and magnetic resonance angiographic confirmation, where appropriate. In the stable phase of a stroke, an EKG and a blood sample test were performed to reassess current or new vascular risk factors, as well as controlling them and optimizing their treatment.

Sleep Studies and CPAP Treatment

All the patients included in the study underwent a respiratory polygraphic evaluation in the stable phase of stroke (2 mo after the acute episode). CPAP treatment was offered to all patients with an AHI of 20 or greater. Nasal ventilation was measured using a nasal cannula, which was connected to a pressure transducer in the device. Respiratory events were identified by analyzing the nasal flow as well as thoracoabdominal bands and oxygen saturation records. Apnea was considered if there was a decrease in the ventilatory signal by 75% or more when averaged over each 2-second interval for at least 10 seconds. Hypopnea was defined as a decrease in ventilatory signal between 25 and 50% with at least 3% decrease in SaO_2 . AHI was defined as the number of respiratory events (i.e., apneas or hypopneas) documented per hour of recording. Obstructive apnea was considered if there were thoracoabdominal movements. In the case of central apnea, thoracoabdominal movements were absent. All respiratory events were classified by manual analysis. All variables were calculated per hour of total study time, as this system does not record sleep stage. After a period of acclimatization, automatic titration was performed, following the procedure published by our group (22). All tests were performed in our hospital in rooms prepared for this purpose by trained personnel. Tests in which the patient claimed to have slept at least 4 hours were considered valid. Tests involving some technical malfunction or patient-caused disconnection resulting in less than 4 hours of valid recording were considered invalid, and the sleep study was repeated. Throughout the study, contact was maintained with the patient to provide instructions on the treatment and to solve any possible problems, especially with respect to adverse effects or adjustments to the

mask. Both diagnostic and autotitration polygraphic studies were performed, using a validated portable system (AutoSet Portable Plus II; ResMed, Sydney, Australia) as described elsewhere (23, 24).

Follow-up

After the diagnostic sleep study, four groups (Figure 1) were established and subjected to follow-up for 5 years: (1) patients without sleep apnea (AHI <10), (2) patients with mild sleep apnea (AHI 10–19), (3) patients with moderate to severe sleep apnea (AHI ≥ 20) who could tolerate CPAP treatment, and (4) patients with moderate-severe sleep apnea (AHI ≥ 20) who could not tolerate CPAP treatment. All patients included in the study were followed up in our out-patient clinic at 1, 3, and 6 months, and every 6 months after that for 5 years, to monitor adherence to treatment, review their general status and new vascular events, and to maintain a record of protocol. CPAP treatment was considered adequate when the system counter registered more than 4 hours per night (at least 70% of the days). CPAP adherence was checked during all the medical visits undertaken during the study. At the end of follow-up, any mortality, along with the dates and causes, were carefully recorded from our computer database and official death certificates. In the case of doubtful information, we contacted patients' relatives by phone.

Statistical Analysis

All statistical analyses were done using a commercial statistical package (SPSS 14.0; SPSS Inc, Chicago, IL). Baseline data were presented as means \pm SD or proportions. The comparison of baseline variables between groups was assessed using one-way ANOVA analysis with the Bonferroni correction to compare groups in pairs. The primary outcome was all-cause mortality. Cox proportional hazard regressions (stepwise forward) were used to assess the independent impact of several cutoff levels of AHI and the effect of CPAP treatment on mortality from the onset of stroke and after adjustment for the following confounding variables (full adjusted model): age, sex, stroke severity (Barthel Index), previous stroke or transient ischemic attack, previous ischemic heart disease, atrial fibrillation, arterial hypertension, diabetes mellitus, hypercholesterolemia, fibrinogen levels (mg/dl), BMI (kg/m^2), current smoking, and the presence of significant carotid stenosis ($>50\%$). The *P* value for inclusion of a variable in the model had to be lower than 0.1, and the *P* value to remove the variable greater than 0.1. Survival curves for each studied group were constructed using the results obtained from the fully adjusted model of the Cox proportional hazard regression analyses. HR and 95% CI were used to assess the unadjusted and adjusted relationships between the studied variables and mortality. All reported variables are two-sided and *P* was considered significant at the level of 0.05.

RESULTS

As shown in Figure 1, 189 of 223 consecutive patients admitted with a diagnosis of ischemic stroke survived for at least 2 months after the ischemic cerebrovascular episode. None of the patients were diagnosed with heart or respiratory failure. After the inclusion and exclusion criteria were assessed, a sleep study was performed on 166 patients from this group at 58 ± 2 days after the neurological event. Mean age was 73.3 ± 11 years, with a range of 38 to 97 years (59% male). Mean AHI was 26 ± 16.7 with greater than 90% of an obstructive nature (central AHI, 2.1 ± 3.3 ; range 0–18) and mean Epworth Sleepiness Scale was 9.1 ± 3.4 . Thirty-one patients (18.7%) showed an AHI less than 10, 39 patients (23.5%) had an AHI between 10 and 19, and 96 patients (57.8%) had an AHI of 20 or greater. None of the patients presented a predominance of central events.

Table 1 shows the main baseline characteristics between the four follow-up groups: modifiable and nonmodifiable cardiovascular risk factors and principal OSA and stroke characteristics. Overall, except for age, there were no statistically significant differences between the parameters in the four groups.

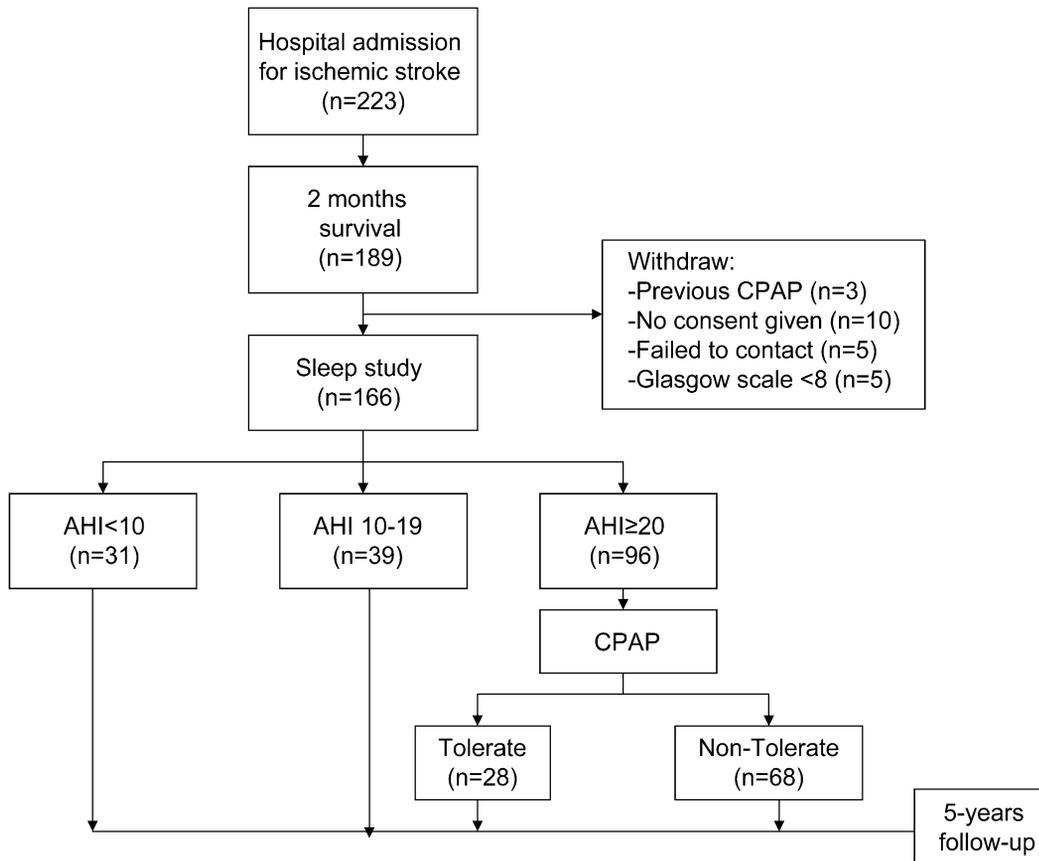


Figure 1. Flowchart of the patients in the study. AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure.

Mortality Analysis in Patients with Sleep Apnea

Eighty-one patients died (48.8%) during follow-up (Table 2). The risk of death in patients with an AHI of 20 or greater who did not tolerate CPAP treatment ($n = 68$; 43 deaths) was higher than in patients with an AHI less than 20 ($n = 70$; 26 deaths) (unadjusted HR, 2.91; 95% CI, 1.46–5.81; $P = 0.001$). After adjustment for 13 confounding variables (see STATISTICAL ANALYSIS; fully adjusted model), the risk did not significantly change (adjusted HR, 2.69; 95% CI, 1.32–5.61; $P = 0.009$). When patients with an AHI less than 20 were further subdivided into those without OSA (AHI <10; $n = 31$) and those with mild disease (AHI 10–19; $n = 39$), the differences between their adjusted mortality risks did not change significantly (11 vs. 15 deaths; Figure 2 and Table 3).

CPAP Tolerance and Impact on Mortality

CPAP treatment was offered to 96 patients (IAH ≥ 20). Forty-three patients (44.8%) did not adhere to treatment and left within the first 6 months. During the follow-up, 25 more patients left treatment or used CPAP for less than 4 hours per night or on less than 70% of nights. In the latter group, the mean duration of treatment was 1.4 ± 1.2 years. At the end of the follow-up, only 28 patients (29.2%) were considered as having had good long-term adherence to CPAP treatment in terms of study design. In this group of patients, the average number of hours of CPAP use was 5.9 ± 2.2 , and the AHI decreased on the night of titration from 26 to 4.1. No patients were lost to follow-up during the study.

Figure 2 shows the survival curve based on the full adjusted model of each of the four studied groups. The mortality risk in patients with moderate to severe OSA who tolerated CPAP treatment ($n = 28$; 12 deaths [42.9%]) was similar to that recorded in patients without OSA or with mild disease. In contrast, patients with moderate to severe OSA who did not tolerate CPAP treatment ($n = 68$; 43 deaths) had a significantly greater fully

adjusted risk of death during the follow-up than those who tolerated CPAP (HR, 1.58; 95% CI, 1.01–2.49; $P = 0.04$) (Table 3). The group of patients with partial tolerance of CPAP ($n = 25$ patients with good tolerance of CPAP for more than 6 mo but less than 5 yr; the mean duration of treatment was 1.4 ± 1.2 yr) did not show significant differences in mortality than the group without tolerance to CPAP (data not shown). In the group of patients who tolerated CPAP, there was no significant correlation between the number of hours of CPAP use and the risk of mortality. There were no significant changes in BMI during the study (28.2 ± 4.2 vs. 28.5 ± 4.3).

The percentage of deaths of cardiovascular origin (stroke, transient ischemic attack, or ischemic heart disease) was significantly higher in the group of moderate to severe OSA who did not tolerate CPAP treatment than in the other studied groups ($P = 0.03$), especially when caused by other ischemic or hemorrhagic stroke events ($P = 0.02$) (Table 2).

DISCUSSION

Our results suggest that patients with ischemic stroke and moderate to severe OSA showed an increased mortality risk, especially in the cardiovascular sphere, independent of the initial severity of the neurological event, cardiovascular risk factors, age, and sex. CPAP treatment, although tolerated only by a small percentage of patients, is associated with a reduction in this excess risk and achieves a mortality risk similar to patients without OSA or mild disease.

International guidelines, based on the results of some well-designed studies (3, 12), state that OSA is an independent risk factor for stroke and cardiovascular death, and that it increases mortality (25–27). Our results concur with the published data, as we found that patients who were stable after stroke and had an AHI of 20 or greater showed an increase in 5-year mortality,

TABLE 1. BASELINE CHARACTERISTICS OF THE FOUR FOLLOW-UP GROUPS: MODIFIABLE AND NONMODIFIABLE CARDIOVASCULAR RISK FACTORS AND PRINCIPAL OSA AND STROKE CHARACTERISTICS

	AHI (0–9)	AHI (10–19)	AHI ≥20 Without CPAP	AHI ≥20 With CPAP
n	31	39	68	28
Age, yr	69.5 ± 11.8*	73.5 ± 11.4	75.8 ± 9.4*	71.3 ± 11.9
Gender, % males	19 (61.3)	19 (48.7)	46 (67.6)	14 (50)
BMI, kg/m ²	29.3 ± 4.4	28.9 ± 4.3	27.8 ± 4.5	26.6 ± 3.8
Hypertension, %	20 (64.5)	24 (61.6)	48 (70.6)	17 (60.7)
Previous stroke or TIA, %	10 (32.3)	10 (25.7)	23 (33.8)	7 (25)
Previous IHD, %	7 (22.6)	6 (15.4)	17 (25)	4 (14.3)
Atrial fibrillation, %	7 (22.6)	6 (15.4)	20 (29.4)	5 (17.9)
Fibrinogen levels, mg/dl	335 ± 105	337 ± 88	328 ± 90.6	335 ± 84
Hypercholesterolemia, %	14 (45.2)	19 (48.7)	36 (52.9)	15 (53.6)
Current smoking, %	18.5 (8.1)	13 (33.3)	38 (55.9)	13 (46.4)
Carotid stenosis, %	5 (16.1)	4 (10.3)	12 (17.6)	8 (28.6)
Diabetes mellitus, %	9 (29)	18 (46.2)	28 (41.1)	8 (28.6)
AHI, n (events/h)	5.4 ± 2.1	15 ± 4.2	35.4 ± 11.9	41.2 ± 13.9
CT90%, %	6.1 (11)	7.2 (15.9)	10.6 (13.2)	10.8 (11.7)
Epworth Sleepiness Scale	7.6 ± 4.7	7.8 ± 4.1	8 ± 4.9	9.7 ± 4.5
Barthel Index	69.7 ± 35.6	70.6 ± 39	57.7 ± 8.7	78.2 ± 30
Glasgow Scale	14.5 ± 1.6	14.3 ± 1.7	14.1 ± 1.8	14.6 ± 1.2
LACI/POCI/TACI/PACI, %	36/19/23/22	33/13/26/28	32/16/22/30	36/18/25/21

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CT90% = nocturnal time spent with arterial oxygen saturation <90%; IHD = ischemic heart disease; LACI = lacunar syndromes; OSA = obstructive sleep apnea; PACI = partial anterior circulation syndromes; POCI = partial posterior circulation syndromes; TACI = total anterior circulation syndromes; TIA = transient ischemic attack.

Data are presented as mean ± SD or n (%) unless otherwise indicated.

* $P = 0.038$.

especially mortality caused by cardiovascular events, compared with patients with stroke and an AHI of less than 20. We did not observe excessive mortality in patients with stroke and mild OSA (i.e., AHI 10–19), although some authors state that even patients with mild disease have an excessive cardiovascular risk (28). It is possible that the explanation for this phenomenon lies in the fact that the patients in our study were older (greater than 70 yr of age), an expected situation in stroke patients, and it is known that the number of respiratory events during sleep increase with age on a physiological level and could not be responsible for an excess of mortality by itself in many cases (29). It is possible that this elevated mean age in our patients also explains the elevated prevalence of OSA seen in our study (81% with an AHI >10). In this respect, Ancoli-Israel and colleagues showed excess mortality in elderly people with an

AHI greater than 20 (30). In accordance with these results, we chose this AHI cutoff point to analyze the risk of death in our patients with stroke and to prescribe CPAP treatment.

Little is known about the impact of CPAP treatment on patients with stroke and OSA. Wessendorf and colleagues (31) observed that CPAP was associated with improved well being and decreased nocturnal blood pressure in the stable phase of the neurological event, and Sandberg and colleagues (32) concluded that CPAP treatment reduced post-stroke depressive symptoms, a major problem in patients with stroke. Our group recently published findings showing that patients with OSA who have suffered from stroke had a higher risk of new vascular events (especially another stroke) than patients without OSA, and that CPAP treatment was effective in decreasing this excess of new vascular events after 18 months of follow-up (5). However, this short follow-up period (only 18 mo) and the small number of patients who tolerated CPAP (a constant in almost all the studies on this topic) did not allow us to analyze the impact of CPAP on mortality. We increased the number of patients in our study and the length of follow-up to analyze the effect of CPAP on long-term mortality in patients with stroke.

Our study shows that 5 years of follow-up with CPAP treatment provides protection from the excessive mortality, especially cardiovascular mortality, in patients with OSA who have suffered from a stroke when compared with patients with OSA who have no tolerance for this treatment. The mortality in the OSA group that tolerated CPAP was similar to that of the group without OSA or with mild disease. It is possible that other mechanisms are involved in this positive impact of CPAP on mortality over and above the positive impact on blood pressure levels. Studies have shown that CPAP treatment decreases other known cardiovascular risk factors in patients with stroke, including carotid stenosis (33), fibrinogen levels (34), and some atheromatosis or inflammatory markers (35), but we did not directly analyze the impact of CPAP on these cardiovascular factors in the present study.

The most important limitations of our study can be summarized as follows: first, the low percentage of adherence to CPAP treatment among our patients (nearly 30%). This limitation is

TABLE 2. COMPARISON OF THE CAUSES OF CARDIOVASCULAR AND NON-CARDIOVASCULAR DEATHS BETWEEN THE STUDIED GROUPS

	AHI (0–9)	AHI (10–19)	AHI ≥20 Without CPAP	AHI ≥20 With CPAP
n	31	39	68	28
Deaths, n (%)	11 (35.5)	15 (38.5)	43 (68.3)*	12 (49.6)
Cardiovascular deaths, n (%)	6 (54.5)	8 (53.3)	29 (67.4)*	6 (50)
Stroke deaths, n	5	5	21†	5
Ischemic stroke	4	4	17†	3
Hemorrhagic stroke	1	1	4	2
Cardiac deaths, n	1	2	8	1
Noncardiovascular deaths, n (%)	5 (45.5)	7 (46.7)	14 (32.6)*	6 (50)
Tumors, n	1	1	2	0
Infections, n	0	2	4	2
Lung disease, n	2	2	5	1
Other, n	2	2	3	3

Definition of abbreviations: AHI = apnea–hypopnea index; CPAP = continuous positive airway pressure.

* $P = 0.02$ between nontolerant CPAP and other groups.

† $P = 0.03$ between nontolerant CPAP and other groups.

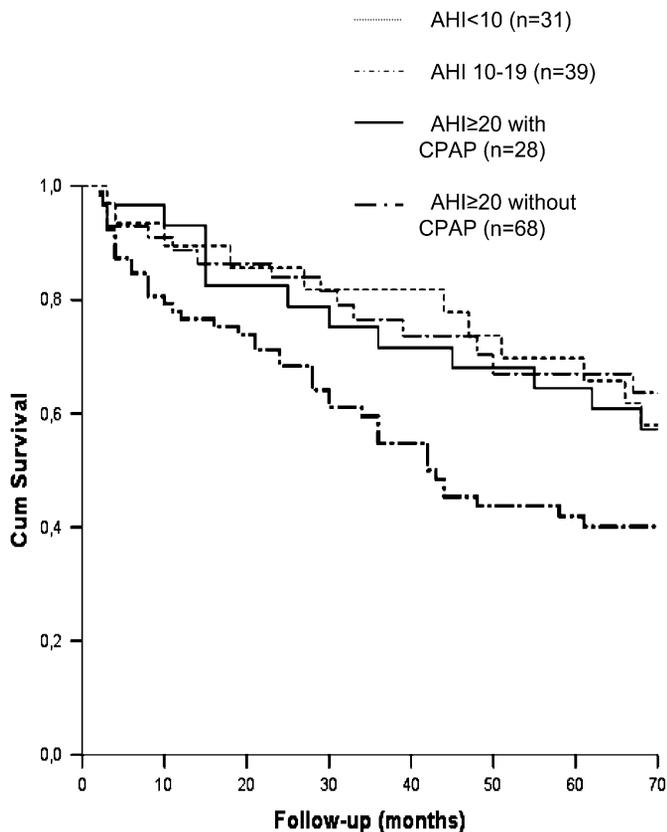


Figure 2. Accumulated survival curve for study groups of patients with stroke, by apnea-hypopnea index (AHI) cutoff point and continuous airway pressure (CPAP) tolerance. The group of patients with stroke with an AHI of 20 or greater and poor tolerance of CPAP showed more mortality than the rest of the patients after 5 years of follow-up. Cum = cumulative.

a constant in all studies on this topic because of the great difficulty of treating patients who have had a stroke with CPAP, especially those with chronic sequelae, and because the lack of somnolence in most cases. Nevertheless, our study attained the highest percentage of patients tolerating long-term CPAP therapy among the published studies on the stable phase of neurological events. We think that we achieved this percentage because of our efforts

TABLE 3. UNADJUSTED AND FULLY ADJUSTED HAZARD RATIO VALUES FOR DEATH IN PATIENTS WITH ISCHEMIC STROKE USING COX ADJUSTED PROPORTIONAL REGRESSION

Variables	Unadjusted Model		Fully Adjusted Model*	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.06 (1.03–1.09)	0.0001	1.04 (1.01–1.07)	0.005
Barthel Index	0.98 (0.97–0.99)	0.0001	0.98 (0.98–0.99)	0.0001
Previous stroke or TIA	1.79 (1.14–2.8)	0.011	1.59 (1.01–2.5)	0.04
AHI <10	0.57 (0.30–1.08)	0.86	0.79 (0.33–1.85)	0.58
AHI 10–19	0.68 (0.39–1.2)	0.17	0.88 (0.4–1.97)	0.76
AHI ≥20 without CPAP	2.12 (1.37–3.3)	0.001	1.58 (1.01–2.49)	0.04
AHI ≥20 with CPAP	0.76 (0.41–1.41)	0.37	1.3 (0.64–2.65)	0.47

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; CPAP = continuous positive airway pressure; HR = hazard ratio; TIA = transient ischemic attack.

* Adjusted by age, sex, Barthel index, AHI, and CPAP treatment groups, previous stroke or transient ischemic attack (TIA), diabetes, hypercholesterolemia, body mass index, current smoking, arterial hypertension, atrial fibrillation, significant carotid stenosis, and fibrinogen levels.

to resolve all problems in follow-up and to educate our patients, families, and general practitioners in CPAP therapy. Second, the present study could introduce a selection bias when comparing patients who tolerate CPAP therapy with those who do not, insofar as intolerant patients could have a distinct profile for adherence to other treatments that result in an increase in cardiovascular risk, which could explain their excessive mortality rates. Although this could be the case, we used a multivariate statistical analysis to take into account all the confounding parameters (full model) that we considered important for explaining the differences in mortality. Furthermore, we think that the performance of a 5-year follow-up study using a randomized placebo design could have ethical implications because of the long follow-up period. Third, possible changes that could have taken place during the study period in modifiable cardiovascular risk factors were not analyzed, so we cannot rule out the possibility that they may exist and have an influence on the mortality of study subjects. Only BMI was measured before and after the study, and no significant changes were observed. We also cannot rule out the existence of variables in this study that were not analyzed and may have influenced mortality, especially variables related to physical or mental sequelae of the acute stroke that were not included in the neurological scales used. Nevertheless, we have included a multivariate analysis of those variables that we believe are the most important for adjusting the results, including the Barthel Index, a widely known and validated measure for quantifying the impact of stroke on patients (18). Finally, although the ResMed AutoSet system has been well-validated for obstructive events in populations with a high probability of having OSA, as in our series (23), it is not validated for central respiratory events, which are relatively frequent in patients experiencing acute stroke. In any case, we do not believe that this has an important impact in our conclusions, because central events are frequent in the acute phase of stroke and dramatically decrease (as obstructive events do) over time to the stable phase (24, 36), the phase in which we performed the diagnostic sleep study. Moreover, a recent study demonstrated that after 10 years of follow-up, central events do not have an impact on the mortality of patients with stroke (7).

In conclusion, our results suggest that moderate to severe OSA in patients with stroke has an unfavorable effect on long-term mortality. CPAP treatment is associated with a reduction in this excess risk. However, due to the less-than-optimal compliance with this treatment, there is a need for more studies that focus on improving the adherence to and tolerance of CPAP treatment in these patients.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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