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SCIENTIFIC INVESTIGATIONS

Moderate obstructive sleep apnea and cardiovascular outcomes in older adults: a propensity score–matched multicenter study (CPAGE-MODE study)

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Study Objectives: Obstructive sleep apnea (OSA) has been associated with cardiovascular events (CVEs), although recent randomized controlled trials have not demonstrated that long-term continuous positive airway pressure (CPAP) prevents CVEs. Our objective was to determine the effect of CPAP on older adults with moderate OSA regarding CVE reduction.

Methods: An observational and multicenter study of a cohort of older adults (> 70 years of age) diagnosed with moderate OSA (apnea-hypopnea index 15.0–29.9 events/h) was conducted. Two groups were formed: (1) CPAP treatment and (2) standard of care. The primary endpoint was CVE occurrence after OSA diagnosis. Association with CPAP treatment was assessed by propensity score matching and inverse weighting probability. Secondary endpoints were incidence of CVE separately and time to first CVE.

Results: A total of 614 patients were included. After matching, 236 older adults (111 men, mean age 75.9 ± 4.7 years) with a follow-up of 47 months (interquartile range: 29.6–64.0 months) were considered for primary and secondary endpoint evaluations. Forty-one patients presented at least 1 CVE (17.4%): 20 were in the standard-of-care group (16.9%) and 21 were in the CPAP group (17.8%), with a relative risk of 1.05 (95% confidence interval [CI], 0.60–1.83; $P = .43$) for CPAP treatment. Inverse probability weighting of the initial 614 patients determined an adjusted relative risk of 1.24 (95% CI, 0.79–1.96; $P = .35$) for CPAP treatment. No statistical differences were found in secondary endpoint analyses.

Conclusions: CPAP should not be prescribed to reduce CVE probability in older adults with moderate OSA.

Keywords: obstructive sleep apnea, cardiovascular epidemiology, geriatric medicine

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BRIEF SUMMARY

Current Knowledge/Study Rationale: While obstructive sleep apnea is considered a risk factor for cardiovascular events due to its inherent sleep fragmentation and intermittent hypoxia, recent randomized clinical trials have demonstrated marginal or no effects of continuous positive airway pressure treatment as a protective factor for different population groups in which older adults have been underrepresented.

Study Impact: This study provides observational evidence of the effects of continuous positive airway pressure for older adults with moderate obstructive sleep apnea after propensity score matching and inverse weighting probability. No reduction in the occurrence of cardiovascular events (ischemic heart disease, atrial fibrillation, stroke) was found after 4 years of follow-up despite adherence to treatment.

INTRODUCTION

Obstructive sleep apnea (OSA) is a complex and common chronic disease defined by the presence of repetitive episodes of upper airway collapse, affecting 20%–30% of the general population.[1] Given the association of OSA with daytime sleepiness and decreased quality of life, it is an important health problem worldwide.[2] Moreover, it has long been considered a treatable risk factor for cardiovascular events (CVEs) due to its inherent intermittent hypoxia and sleep fragmentation.[3] However, recent randomized clinical trials (RCTs) have not demonstrated a beneficial effect of its treatment with continuous positive airway pressure (CPAP) on CVE morbidity or mortality as a primary outcome.[4–6] Regarding older adults, contradictory data can also be found. Some authors have stated that CPAP reduces the probability of CVE mortality, especially in older adults with severe OSA,[7–9] whereas others have proposed that less intense presentations of OSA might, in fact,

protect this population, offering an ischemic preconditioning scenario of mild to moderate hypoxia, which would then lead to angiogenesis and other compensatory mechanisms.[10–13] Other authors have determined worst cardiovascular and all-mortality outcomes in patients with moderate OSA.[14] Notwithstanding, these considerations have been based on observational data usually assessed by multivariate analysis, such as binary logistic regression or Cox analysis, with a potential selection bias of patients treated with CPAP.[15,16] Propensity score matching (PSM) is a statistical method that was introduced by Rosenbaum and Rubin in 1983 and can be defined as the conditional probability of being treated given the covariates.[17] In observational studies, PSM is used to adjust confounding factors by creating subsets of samples with balanced covariates among the study groups; thus, the results should resemble the expected equal distribution of the baseline characteristics of an RCT.[18] PSM has been recently used in historic cohorts[19,20] and is considered to be superior to multivariate regression analysis in a small-sample-size scenario.[18,21,22] The aim of this study was to determine the effect of long-term CPAP on CVEs in older adults with moderate OSA in a multicenter PSM population.

METHODS

An observational and multicenter study of a historic cohort of older adults (≥ 70 years of age at OSA diagnosis) was performed. Between June 2008 and December 2018, patients attending 8 sleep units (SUs) located in the Madrid Community Area for suspected OSA were considered for inclusion within the Sleep and Mechanical Ventilation Workgroup of the Respiratory Society of Madrid (NEUMOMADRID). Exclusion criteria included an apnea-hypopnea index (AHI) of < 15 and > 30 events/h, previous treatment with CPAP or bilevel positive airway pressure, and diagnosis of central sleep apnea, obesity hypoventilation syndrome, and/or chronic respiratory failure. This study was conducted in accordance with the amended Declaration of Helsinki and approved by the ethics committees of all participating centers; because of its retrospective nature, no informed consent was obtained from patients. The manuscript was drafted in accordance with the STRengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines.[23]

Data collection

Baseline variables were collected before the sleep study and included age, sex, body mass index (BMI), smoking habits (> 20 pack-years), arterial hypertension (systolic/diastolic > 140/90 mm Hg or use of antihypertensive medication), diabetes (fasting glucose levels > 125 mg/dL in ≥ 2 measures and/or use of antihyperglycemic medication), hyperlipidemia (fasting cholesterol or triglycerides > 200 mg/dL and/or use of antihyperlipidemic medication), and previous CVEs, such as stroke, ischemic heart disease, atrial fibrillation, and/or heart failure. Stroke was defined by the presence of confirmative imaging-based tests and compatible clinical context; heart failure was determined by echocardiographic data and/or other tests indicated for its conclusive diagnosis or by the use of specific medication. Atrial fibrillation was determined by echocardiographic findings and/or the prescription of specific medication. Ischemic heart disease was determined based on conclusive data of coronarography or other myocardial ischemia tests, previous coronary revascularization, and/or prescription of specific antianginal medication. Specialists in the corresponding areas carried out all these tests and treatments. The Spanish version of the Epworth Sleepiness Scale was used to evaluate excessive daytime somnolence.[24]

Sleep study and CPAP treatment

Patients were diagnosed via full standard polysomnography (PSG) or an in-laboratory or in-home respiratory polygraphy (RP) following the American Academy of Sleep Medicine and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) guidelines stated at the time.[25–30] PSG included continuous recordings of an electroencephalogram, electrooculogram, echocardiogram, and electromyogram and evaluations of nasal airflow, thoracic and abdominal band movements, and peripheral oxygen saturation (SpO_2), according to standard criteria. RP included continuous recordings of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and SpO_2. A full PSG was performed in all the patients undergoing RP who had recording-related artifacts or discrepancies between the RP results 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, and/or a self-reported sleep time of < 3 hours. All data were scored manually. Apnea was defined as an interruption of oronasal airflow of > 10 seconds and was classified as obstructive or central depending on whether respiratory effort was present or absent. Hypopnea was defined as a 30%–90% reduction in oronasal airflow of > 10 seconds and was associated with a peripheral oxygen desaturation of ≥ 3%.[29] The AHI was defined as the number of apnea episodes plus hypopnea episodes per hour of sleep (PSG) or recording (RP). Regarding CPAP prescription, the SU physician decided on an individualized prescription in each case and followed the guidelines stated at the time. CPAP settings for all patients were based on automatic positive airway pressure devices, RP, or PSG, if available. Settings were considered adequate when residual AHI was < 5 events/h. Adherence was objectively assessed by reading the time counter of the device. Adequately treated OSA was determined when long-term CPAP adherence was ≥ 4 hours per day and as untreated when CPAP was not prescribed, when the patient declined its use, or when the average cumulative adherence was < 4 hours/day.

Follow-up and primary endpoint

Follow-up ended on March 30, 2020. Visits to the SU outpatient clinic were usually scheduled 3, 6, and 12 months after CPAP prescription and every 12 months after the first year by either the SU personnel or the respiratory therapy provider. All data retrieved from the SU databases were backed up by reviewing the clinical records of hospital, primary care databases, and the information handed out by the provider. A patient was considered lost to follow-up only if the endpoint data could not be established at the

end of the study, although no exclusion from the time-to-event analysis was carried out considering the data from the last clinical observation. The main endpoint was a composite of CVEs, which included stroke, ischemic heart disease, and atrial fibrillation. Secondary endpoints were incidence of the CVEs separately and time to first CVE after OSA diagnosis.

Statistical analysis

Baseline characteristics are presented according to the 2 proposed groups for the endpoint analysis—namely, patients with CPAP (despite the hours/night use) or standard of care. Qualitative variables are presented as absolute values and percentages, and quantitative variables as means and standard deviations, median and interquartile range (IQR), or range if needed. Normal distribution was assessed with the Kolmogorov-Smirnov test. Baseline differences of quantitative variables were analyzed using a Student *t* test in case of normal distribution or by the Kruskal-Wallis test when normality was not achieved. Qualitative variables were compared using the χ^2 test with the Fisher exact correction. To assess potential selection bias, the PSM analysis was performed using a logistic regression analysis to create a propensity score for the treatment groups (CPAP despite the hours/night use or standard of care) with a logistic regression model. Several variables were entered into the PSM model: (1) age, (2) male sex, (3) body mass index, (4) Epworth Sleepiness Scale scores, (5) previous CVEs, (6) AHI, and (7) arterial oxygen saturation ($T_{90\%}$). One-to-one matching without replacement was performed with a 0.2 caliper width,[31,32] and the resulting score-matched pairs were used in subsequent analyses. Cumulative time free of CVEs was analyzed with the Kaplan-Meier method. Strengths of associations are expressed as relative risk ratio (RR) for binary outcomes or as hazard ratio for cumulative time results with 95% confidence intervals (CIs). A P value ≤ .05 was considered statistically significant. Diagnostic and residual plots were examined to test the proportional hazard assumptions, for which none of them were statistically significant. Sensitivity analysis was performed for the subgroups of patients showing adherence to CPAP and those without previous CVEs.

Sensitivity analyses involve determining whether different outcomes would be obtained under different scenarios in a "what if" fashion, considering the usual threshold of ≥ 4 hours/night of CPAP of previous studies,[5–8] and more recently, the existence of previous CVEs.[33] The one-at-a-time method, which removes 1 determined variable (such as CPAP adherence or previous CVE) without changes in the rest of items, was used, after which it repeats the process of removing every variable after returning the first variable to its nominal value.[34] To assess the plausibility of the association of respiratory disturbances during the rapid eye movement sleep stage and CVEs,[35] a subgroup analysis of patients with ≥ 6 hours/night of CPAP use ("super adherent" patients) was also performed. For further assessment of selection bias, inverse probability weighting was used to account for baseline differences between the treatment groups in the entire population. Fitted logistic models to predict treatment at baseline using the same variables included in the PSM model were constructed, and weights were calculated following the methodology described elsewhere.[15] A weighted population (adjusted sample) was subsequently constructed. Data management and statistical analyses were performed using STATA (StataCorp 2019, Stata Statistical Software: Release 16; StataCorp LP, College Station, TX).

RESULTS

A total of 614 patients were included in the study, and their baseline variables and sleep study results are presented in **Table 1** before and after PSM. After matching, 236 patients with a mean age of 75.9 ± 4.7 years (range: 70–92 years), 111 of whom were males (47%), and with a mean body mass index of 30.6 ± 5.4 kg/m^2 (range: 17.8–59.0 kg/m^2) were considered for primary and secondary endpoint analyses. Previous CVE before moderate OSA diagnosis was observed in 75 older adults of the matched population (31.8%), and long-term CPAP adherence was observed in 76 older adults (32.2% of the entire group, 64.4% of the CPAP prescription subgroup). Mean CPAP use was 5.2 ± 2.6 hours/night in which 51 patients had at least 6 hours/night of use (21.6% of the entire group, 43.2% of the CPAP prescription group).

In the matched population, during the median follow-up of 46.8 months (IQR: 29.6–64.0 months), 41 patients presented at least 1 CVE (17.4%): 20 in the standard-of-care group (16.9%) and 21 in the CPAP group (17.8%) with an RR of 1.05 (95% CI, 0.60–1.83; P = .43) for CPAP treatment as a nonsignificant protective CVE factor. Thirty-six patients had 1 CVE (15.3%), and 5 of them had 2 events (2.1%). After being combined, 46 CVEs took place: 14 ischemic heart disease episodes (5.9%), 10 strokes (4.2%), and 22 atrial fibrillations (9.3%). Primary and secondary endpoints analyses are presented in **Table 2**. Median time to the first CVE during follow-up was 45.8 months (IQR: 29.5–64.1 months). The CPAP group presented a longer median time to the first CVE (47.8 months; IQR: 7.1–88.6 months) than the standard-of-care group (44.1 months; IQR: 37.6–50.5 months) although no statistical differences were found (log-rank 0.10; P = .75), as shown in **Figure 1**. Time to first event in the unmatched cohort is shown in **Figure 2;** no statistical differences were found (log-rank 0.01; P = .91). Sensitivity analyses of long-term CPAP adherence and the subgroup of patients without previous CVEs are presented in **Table 3** and **Table 4**, respectively, for which no statistical differences were found. Moreover, no statistical differences were found in the "super adherent" CPAP group regarding the primary endpoint (RR = 1.03; 95% CI, 0.45–2.31). Finally, inverse probability weighting of the initial 614 patients was determined, and an adjusted RR of 1.24 (95% CI, 0.79–1.96; P = .35) was used for CPAP prescription as a nonstatistically significant predictive factor for CVE. Time to first CVE according to CPAP adherence is presented in **Figure 3** in both unmatched and matched cohorts, and no statistical differences were found.

DISCUSSION

The main finding of our study was the lack of any observed beneficial effects of CPAP prescription in older adults diagnosed

Table 1—Patient characteristics of older adults with moderate obstructive sleep apnea by treatment group.

Characteristics	Unmatched Cohort				Matched Cohort			
	All Patients (n = 614)	CPAP Group (n = 388)	Standard of Care (n = 226)	*P* Value	All Patients (n = 236)	CPAP Group (n = 118)	Standard of Care (n = 118)	*P* Value
Age, y	76.0 (4.7)	75.9 (4.6)	76.3 (4.9)	.39	75.9 (4.7)	75.9 (4.9)	76.0 (4.5)	.67
Sex, male	318 (51.8)	205 (52.8)	113 (50.0)	.50	115 (48.7)	56 (47.4)	59 (50.0)	.43
Body mass index, kg/m^2	30.6 (5.4)	30.8 (5.1)	30.3 (5.8)	.36	30.4 (5.4)	30.3 (4.9)	30.5 (5.9)	.97
Obesity	269 (43.8)	178 (45.9)	91 (40.3)	.05	113 (47.9)	58 (49.2)	55 (46.6)	.79
Tobacco	219 (35.7)	143 (36.8)	76 (33.6)	.04	66 (28.0)	32 (27.1)	36 (30.5)	.88
High blood pressure	441 (71.8)	296 (76.3)	145 (64.2)	<.01	167 (70.8)	84 (71.2)	83 (70.3)	.75
Diabetes	167 (27.2)	115 (29.6)	52 (23.0)	.11	63 (26.7)	33 (28.0)	30 (25.4)	.77
Dyslipidemia	304 (49.5)	209 (53.9)	95 (42.0)	<.01	116 (49.2)	61 (51.7)	55 (46.6)	.47
Previous ischemic heart disease	106 (17.3)	83 (21.4)	23 (10.2)	<.01	23 (9.7)	11 (9.3)	12 (10.2)	1.00
Previous stroke	67 (10.9)	49 (12.6)	18 (8.0)	.11	24 (10.2)	12 (10.2)	12 (10.2)	1.00
Previous atrial fibrillation	108 (17.6)	74 (19.1)	34 (15.0)	.27	33 (14.0)	19 (16.1))	14 (11.9)	.45
Previous congestive heart failure	78 (12.7)	49 (12.6)	29 (12.8)	.90	26 (11.0)	11 (9.3)	15 (12.7)	.53
Without previous CVE	362 (59.0)	213 (54.9)	149 (65.9)	<.01	161 (68.2)	80 (67.8)	81 (68.6)	1.00
ESS, points	8.7 (4.7)	9.4 (4.9)	7.5 (4.3)	<.01	8.2 (4.4)	8.2 (4.4)	8.3 (4.4)	.89
Polysomnography	126 (20.5)	68 (17.5)	58 (25.7)	.06	61 (25.8)	29 (24.5)	32 (27.1)	.87
AHI, events/h	21.5 (4.5)	22.6 (4.3)	19.6 (4.3)	<.01	20.2 (4.2)	20.3 (4.1)	20.1 (4.3)	.78
ODI, desaturations/h	23.4 (12.1)	24.5 (11.6)	21.8 (12.8)	<.01	23.3 (12.4)	23.5 (12.7)	23.1 (12.2)	.92
Minimum SpO_2, %	77.7 (10.1)	76.9 (10.0)	79.0 (10.1)	<.01	77.7 (10.0)	77.6 (10.3)	77.8 (9.8)	.71
Mean SpO_2, %	90.9 (4.6)	90.5 (5.5)	91.5 (2.7)	<.01	91.0 (6.0)	90.4 (8.1)	91.6 (2.5)	.22
$T_{90\%}$, %	13.0 (4.0–42.5)	17.2 (4.6–49.8)	9.0 (2.6–28.0)	<.01	10.0 (3.0–29.8)	9.65 (2.9–33.0)	10.0 (3.0–25.3)	.90

Data are presented as n (%), mean (SD), or median (interquartile range), unless otherwise indicated. AHI = apnea-hypopnea index, CPAP = continuous positive airway pressure, CVE = cardiovascular event, ESS = Epworth Sleepiness Scale, ODI = oxyhemoglobin desaturation index, SpO_2 = peripheral oxygen saturation by pulse oximetry, $T_{90\%}$ = time under 90% of oxygen saturation measured by pulse oximetry.

with moderate OSA with respect to CVEs after assessing selection bias based on PSM and inverse probability weighting. Additionally, no positive effect of CPAP as a primary intervention was observed in patients with no CVE prior to OSA diagnosis or in those who showed long-term adherence to CPAP of at least 4 hours/night.

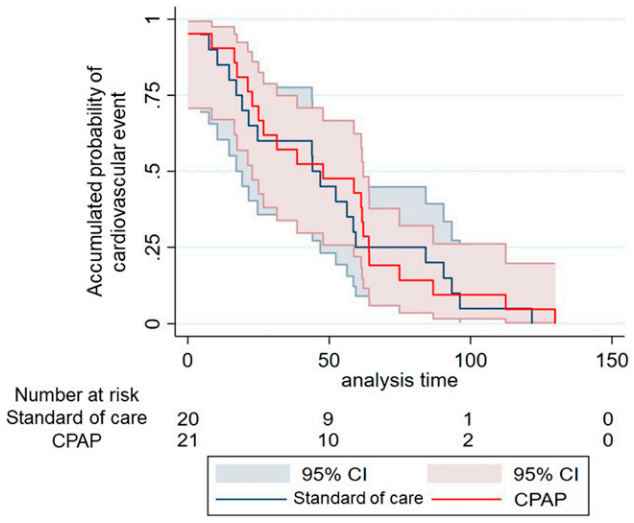
These findings are consistent with those of RCTs such as the Sleep Apnea Cardiovascular Endpoints (SAVE) or the Randomized Intervention With CPAP in Coronary Artery Disease and Sleep Apnea (RICCADSA) studies[4,6] and more recently the Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome: effect of intervention with CPAP

Table 2—Primary and secondary endpoints analyses of the matched cohort of older adults with moderate obstructive sleep apnea according to treatment group.

	CPAP (n = 118)	Standard of Care (n = 118)	Strength of Association	*P* Value
Primary endpoint				
Cardiovascular event composite	21 (17.8)	20 (16.9)	RR 1.05 (0.60–1.83)	.43
Secondary endpoints				
Incident ischemic heart disease	7 (5.9)	7 (5.9)	RR 1.00 (0.36–2.76)	.50
Incident stroke	7 (5.9)	3 (2.5)	RR 2.33 (0.62–8.81)	.10
Incident atrial fibrillation	10 (8.5)	12 (10.2)	RR 0.82 (0.38–1.85)	.32
Time to first cardiovascular event in months, median (IQR)	47.8 (7.1–88.6)	44.1 (37.6–50.5)	HR 0.90 (0.48–1.69)	.75

Data are presented as n (%) or median (IQR), unless otherwise indicated. CPAP = continuous positive airway pressure, HR = hazard ratio, IQR = interquartile range, RR = risk ratio.

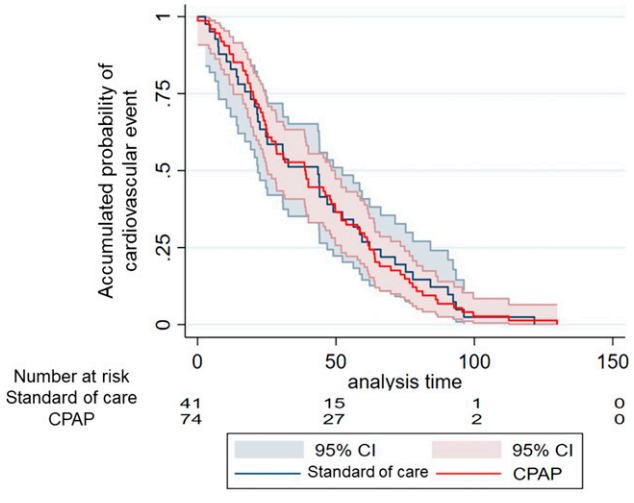
Figure 1—Time to first CVE, matched cohort.



CI = confidence interval, CPAP = continuous positive airway pressure, CVE = cardiovascular event.

(ISAACC) study,[5] for which no positive effects of CPAP were observed for secondary prevention of CVEs. Contradictory results are found within the existing evidence. To explain this phenomenon, some authors consider that once a CVE has occurred, the damage is already done and the deleterious OSA effect would be diluted and go unnoticed,[33] and others concluded that, in a morbid population with metabolic syndrome, OSA did not lead to any differences in mediators of cardiometabolic disease for which obesity could cause downgrading of the expected negative effect of OSA.[36] Following this line of thinking, the most recent meta-analysis that includes 9 RCTs concluded that low-quality evidence suggests that CPAP therapy does not significantly improve survival or prevent major CVEs in adults with OSA and cardiovascular disease.[37] Some of the highlights of this low-quality evidence involve the variability in sample sizes, follow-up, run-in periods, and adherence assessment, along with blinding difficulties and the unethical approach of not treating patients experiencing excessive daytime somnolence, which is usually excluded from randomized studies. One may argue that patients under a higher burden of OSA and, hypothetically, under the most cardiovascular risk are not adequately represented in RCTs due to this last consideration. On the contrary, other authors have stated that moderate to severe OSA without CPAP treatment is associated with subsequent CVEs,[38] especially in patients with long-term adherence of at least 4 hours,[39] and others have found a beneficial effect of OSA treatment on the incidence of stroke.[40,41] Less than one-third of our matched cohort presented major CVEs before receiving a moderate OSA diagnosis, a process that may have influenced our results since the SU personnel were probably more prone to prescribe CPAP. That bias was the case for the unmatched cohort, although no differences were found in the matched one since that was the purpose of running a propensity score. Nonetheless, one could expect that CVE-naïve patients would benefit from a CPAP device; yet no differences were found when compared with standard of care. Evidence is lacking on this matter, and future studies should address primary cardiovascular prevention as an endpoint to elucidate the true role of positive airway pressure in the natural history of the disease.

Figure 2—Time to first CVE, unmatched cohort.



CI = confidence interval, CPAP = continuous positive airway pressure, CVE = cardiovascular event.

With regard to older adults as a specific population, the evidence for OSA treatment in RCTs is rather scarce. In fact, to the best of our knowledge, only 1 published study exists so far. Ponce et al[42] found that CPAP treatment resulted in a significant improvement in diurnal hypersomnia, some sleep-related symptoms, and quality of life domains in 145 patients > 70 years old who had moderate OSA, although no effects on either neurocognitive tests or blood pressure levels were observed after 3 months. Observational studies have reported beneficial effects of CPAP adherence on major CVEs only in older adults with severe OSA, and no statistical differences were found in patients with mild to moderate presentations of the disease.[8,9,43,44] However, these studies did not address older adult patients with moderate OSA as the main population, and the only study specifically addressing them is the one by Ponce et al. Furthermore, the usual statistical approach of the aforementioned observational studies was based on multivariate analyses with a potential selection bias, regardless of adjustment for several confounders.[15,16,31,32] Hence, it is possible that even severe OSA is not associated with CVE mortality or morbidity in older adults, a finding that would not be different from the RCT results, which included patients aged at least 40 years old.

Previous work has hypothesized about ischemic preconditioning through the activation of adaptive mechanisms involving coronary artery occlusion and reperfusion to overcome nocturnal intermittent hypoxia secondary to OSA,[45] which might explain why moderate OSA could prevent subsequent major CVEs instead of producing them. Thus, the potential

Table 3—Sensitivity analysis of older adults with treated moderate OSA according to long-term adherence to continuous positive airway pressure.

	Treated OSA (n = 76)	Nontreated OSA (n = 160)	Strength of Association	*P* Value
Primary endpoint				
Cardiovascular event composite	11 (14.5)	30 (18.6)	RR 0.77 (0.41–1.46)	.21
Secondary endpoints				
Incident ischemic heart disease	5 (6.6)	9 (5.6)	RR 1.17 (0.41–3.37)	.38
Incident stroke	3 (3.9)	7 (4.4)	RR 0.90 (0.24–3.39)	.44
Incident atrial fibrillation	3 (3.9)	19 (11.9)	RR 0.33 (0.10–1.09)	.07
Time to first cardiovascular event in months, median (IQR)	61.3 (46.4–76.2)	38.6 (13.0–64.2)	HR 0.60 (0.29–1.24)	.17

Data are presented as n (%) or median (IQR), unless otherwise indicated. HR = hazard ratio, IQR = interquartile range, OSA = obstructive sleep apnea, RR = risk ratio.

effects of OSA in promoting cardioprotective mechanisms would be noticed in patients with previous heart disease who are in need of greater collateral blood-flow supply than in those patients without previous heart disease.[33] However, this hypothesis has not been confirmed in patients with OSA, and conclusive evidence is not available. Given the numerous interacting mechanisms, we consider it likely that OSA is associated with an increase in CVEs in patients with specific underlying characteristics, which may be grouped as a phenotype, and further research should address this consideration.

Life expectancy has improved substantially due to medical advances, and a thorough knowledge of disease in older adults is therefore needed. An increasing incidence of OSA with age has been described,[46] although current guidelines do not address special considerations in relation to its diagnosis or treatment in older adults.[47] Consequently, whether a CPAP device should or should not be prescribed to older adult patients often raises a reasonable doubt as its role has not been adequately determined, and as lack of symptoms or an already impaired quality of life due to other comorbidities may bias the decision of a physician treating these patients.[48] For instance, the mean ESS of our cohort despite matching was not high, which supports the idea that many of these devices were prescribed based on the CVE protection factor, and this surely is a potential bias with respect to our results. Nonetheless, this study presents potentially useful information for SU personnel in charge of CPAP prescriptions and follow-ups for which CVE prevention does not seem to be obtained in this scenario, highlighting that aiming at other objectives, such as quality of sleep and consequently of life, is possibly more relevant for these patients.

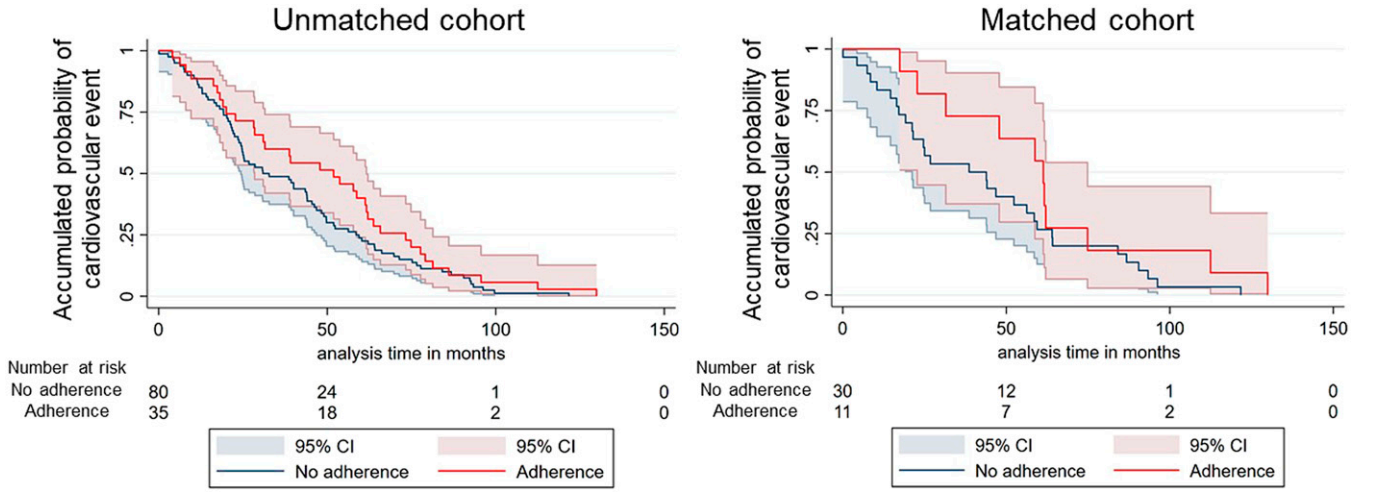
Before the acknowledgment of the study limitations and strengths, we should take into account that the definition of hypopnea using the 3% desaturation criteria is not widely used in the United States, and thus a moderate OSA group based on this percentage might be a mild to moderate group using the 4% criteria, a difference that may have affected our results.[49,50] Notwithstanding this consideration, a recent International Consensus Document on OSA led by SEPAR, which included representatives from Spain, Argentina, Brazil, Colombia, France, Mexico, and Portugal, stated that hypopnea is a discernible reduction (approximately ≥ 30% and < 90%) of the respiratory signal amplitude for at least 10 seconds, accompanied by a desaturation

Table 4—Sensitivity analysis of patients diagnosed with moderate obstructive sleep apnea and without previous cardiovascular events according to CPAP or usual care treatment.

	CPAP (n = 80)	Standard of Care (n = 81)	Strength of Association	*P* Value
Primary endpoint				
Cardiovascular event composite	13 (16.2)	14 (17.3)	RR 0.94 (0.47–1.87)	.86
Secondary endpoints				
Incident ischemic heart disease	5 (6.2)	4 (4.9)	RR 1.26 (0.35–4.54)	.36
Incident stroke	2 (2.5)	3 (3.7)	RR 0.67 (0.12–3.93)	.66
Incident atrial fibrillation	7 (8.8)	9 (11.1)	RR 0.78 (0.31–2.01)	.62
Time to first cardiovascular event in months, median (IQR)	61.2 (53.4–64.0)	56.3 (34.8–77.7)	HR 0.87 (0.40–1.91)	.87

Data are presented as n (%) or median (IQR), unless otherwise indicated. CPAP = continuous positive airway pressure, HR = hazard ratio, IQR = interquartile range, RR = risk ratio.

Figure 3—Time to first CVE according to CPAP adherence in both unmatched and matched cohorts.



CI = confidence interval, CPAP = continuous positive airway pressure, CVE = cardiovascular event.

of at least 3% and/or a electroencephalography-detected microarousal.[51] More consensus is clearly needed on this matter.

Limitations

Our study has several limitations. Due to its retrospective observational nature and despite the use of PSM, the possibility of unmeasured confounding factors cannot be ruled out. As Sackett,[52] one of the fathers of evidence-based medicine, stated in 1973, dozens of forms of bias can undermine a clinical study, and multivariable methods cannot take all of them into account as they can only adjust for what is accurately measured and explicitly added to the multivariable model. Given the enrollment period of 10 years, we also acknowledge the possibility of timing bias for which RCT evidence in the last 5 years might have led the SU personnel to not prescribe CPAP devices, at least not for CVE reduction purposes. Moreover, the same physician was not in charge of CPAP prescription and follow-up over the entire study period, and this difference could have induced a possibility of bias since self-reported means and methods to evaluate clinical scenarios and social factors may have differed over time. A relevant limitation is that quality of life related to CPAP treatment or OSA symptoms was not assessed, which seems to be a more relevant factor than CVE prevention based on our results and those observed in others. Recent investigations have also emphasized the importance of hypoxic burden toward CVEs and mortality, which considers the severity and length of desaturations.[53] Unfortunately, we do not have further information on the subject besides features such as $T_{90\%}$ or the fact that every sleep study included at least 4 hours of sleep. Hypoxic burden studies are somewhat recent, and our cohort goes back to 2008, when we did not take this aspect into consideration. Another limitation is that we did not specifically assess rapid eye movement sleep–related OSA, which seems to be related to worst health outcomes in general.[35,54] We analyzed this aspect indirectly and found that "super adherent" patients did not present better CVE results. However, this difference is not enough to assess rapid eye movement sleep properly and may have biased our findings. Finally, the study was based on SU populations, so its findings cannot be extrapolated to the general population, and all interpretations should be carried out with caution.

Strengths

Our study also has strengths. To our knowledge, this is the first study to specifically assess older adult patients with moderate OSA and the effect of long-term CPAP regarding CVE prevention after applying what we consider a more suitable statistical approach than the usual multivariate logistic regression analysis. In our study, the rate of adherence in the subgroup of CPAP prescription was nearly 65%, which is not much different from similar studies conducted in younger groups. Despite the complexity of following a population with a lack of evidence with respect to the best diagnosis or treatment approach, reaching CPAP adherence figures comparable to those in previous studies in older adults should suggest proper selection criteria. Furthermore, we performed sensitivity analysis in pursuit of phenotyping this population, such as patients without previous CVEs or those with long-term adherence to CPAP, which adds value to the design of future randomized studies.

CONCLUSIONS

Older adult patients are more likely to increase in our SU, and despite this study's observational design, we believe it provides evidence of no effect of long-term CPAP for CVE prevention and that every patient should be evaluated individually by experienced physicians, who may thoroughly address other aspects in this scenario, such as quality of sleep and life.

ABBREVIATIONS

CI, confidence interval
CPAP, continuous positive airway pressure
CVE, cardiovascular event
IQR, interquartile range
OSA, obstructive sleep apnea
PSG, polysomnography
PSM, propensity score matching
RCT, randomized clinical trial
RP, respiratory polygraphy
RR, risk ratio
SU, sleep unit

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at Hospital General Universitario Gregorio Marañón, Madrid, Spain; Hospital Universitario 12 de Octubre, Madrid, Spain; Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; Hospital Universitario Ramón y Cajal, Madrid, Spain; Hospital Universitario Infanta Leonor, Madrid, Spain; Hospital Universitario Infanta Sofía, Madrid, Spain; Hospital Universitario La Princesa, Madrid, Spain; and Hospital Universitario de Getafe, Madrid, Spain. The authors report no conflicts of interest.