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# Positive Airway Pressure Adherence, Mortality, and Cardiovascular Events in Patients with Sleep Apnea

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## Keywords:

obstructive sleep apnea; cardiovascular diseases; mortality; positive airway pressure; adherence

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# Abstract

## Rationale:

Randomized controlled trials showed no effect of positive airway pressure (PAP) therapy for obstructive sleep apnea (OSA) on cardiovascular (CV) risk. However, patient selection and low PAP adherence preclude the generalization of their data to clinical samples.

## Objectives:

To evaluate the association between hours of PAP use, mortality, and CV morbidity in real-life conditions.

## Methods:

Data from the Pays de la Loire Cohort were linked to health administrative data to identify incident major adverse cardiovascular events (MACEs; a composite outcome of mortality, stroke, and cardiac diseases) in patients with OSA who were prescribed PAP. Cox proportional hazards analyses were conducted to evaluate the association between MACEs and quartiles of average daily PAP use over the study period.

## Measurements and Main Results:

After a median follow-up of 6.6 years, 961 of 5,138 patients experienced MACEs. Considering nonadherent patients (0–4 h/night) as the reference group, adjusted hazard ratios (95% confidence intervals) for MACEs were 0.87 (0.73–1.04) for the 4–6 h/night group, 0.75 (0.62–0.92) for the 6–7 h/night group, and 0.78 (0.65–0.93) for the >7 h/night group ( $P = 0.0130$ ). Sensitivity analyses using causal inference approaches confirmed the association of PAP use with MACEs. The association was stronger in male patients ( $P$  value for interaction = 0.0004), patients without overt CV disease at diagnosis ( $P, 0.0001$ ), and those belonging to the excessively sleepy symptom subtype ( $P = 0.060$ ).

## Conclusions:

These real-life clinical data demonstrate a dose–response relationship between PAP adherence and incident MACEs in OSA. Patient support programs may help improve PAP adherence and CV outcomes in patients with OSA.

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Obstructive sleep apnea (OSA) is a highly prevalent disease characterized by repetitive episodes of partial (hypopnea) or complete (apnea) obstruction of the upper airways during sleep, resulting in intermittent hypoxia, increased intrathoracic pressure swings, and sleep fragmentation. It is estimated that 425 million adults worldwide aged 30–69 years have moderate-to-severe OSA (1). Untreated OSA is recognized as an independent risk factor for cardiovascular (CV) diseases, including hypertension, atrial fibrillation, coronary heart disease, heart failure, and stroke (see [2–4] for comprehensive reviews and meta-analyses).

Clinical data from prospective cohorts are supported by mechanistic studies showing that OSA-related intermittent hypoxia and sleep fragmentation can activate several pathogenic pathways implicated in the development of CV diseases, including autonomic activation, inflammation, oxidative stress, endothelial dysfunction, and metabolic derangements (2, 3, 5). Positive airway pressure (PAP), the reference therapy for moderate-to-severe OSA, reduces blood pressure (6) and might also improve endothelial function (7) and inflammatory status (8).

Despite the accumulation of clinical and experimental data suggesting that OSA is a modifiable risk factor for CV disease, whether adherent PAP therapy of OSA has a preventive effect on mortality and CV morbidity remains uncertain. Indeed, current evidence from randomized controlled trials (RCTs) suggests a lack of association between PAP therapy and secondary CV disease prevention (9–11). However, RCTs evaluating the impact of PAP therapy on CV outcomes were performed in minimally symptomatic patients with moderate-to-severe OSA, for which strict inclusion criteria were applied, which precludes the generalization of their data to clinical samples. A recent study has estimated that among sleep clinic patients diagnosed with OSA, only 0.8–7.5% met the eligibility criteria to participate in one of these three RCTs (12). Compared with RCT participants, sleep clinic patients with OSA were younger, sleepier, more likely to be female, and less likely to have established CV disease. Furthermore, being minimally symptomatic, RCT participants were poorly adherent, which does not allow any conclusion to be drawn on the effect of PAP therapy adherence on incident CV events (9–11). It is unethical to perform an RCT of PAP versus no treatment in patients with symptomatic OSA over a long period of time. Real-world observational data represent a promising method for overcoming the sample selection biases described recently in RCTs of CV endpoints in the context of OSA (13).

The aim of the present study was to evaluate whether long-term PAP therapy adherence was associated in a dose dependent manner with a reduction of all-cause mortality and CV morbidity in patients with OSA from the multicenter Pays de la Loire Sleep Cohort. Some of the results of these studies have been reported previously in the form of an abstract (14).

## **Methods**

### **Study Design and Population**

The study relied on the data collected by the multicenter Pays de la Loire Sleep Cohort longitudinal study, which was further linked with data from the French administrative health care database (Système National des Données de Santé [SNDS]; see [15–18] for details). All patients with newly diagnosed OSA (apnea–hypopnea index [AHI]>5 events/h of sleep [or recording] on in-laboratory polysomnography [PSG] or type 3 home sleep apnea testing) who had started PAP treatment at home between May 15, 2007, and December 31, 2018, and had available SNDS data were included in the study. All participants had given their written informed consent.

## **Baseline Evaluation**

Each patient completed surveys that included anthropometric data, smoking habits, alcohol consumption, medical history, and medication use (15–18). Patients were evaluated by either home sleep apnea testing or PSG, according to pretest clinical probability of OSA (19). Respiratory events were scored manually using recommended criteria (20). The sleep apnea-specific hypoxic burden (SASHB) was calculated as previously described (18, 21, 22).

## **Adherence to PAP Therapy and CV Active Drugs**

PAP therapy was prescribed in patients with severe OSA and in those with mild-to-moderate OSA and CV comorbidities or those with severe daytime sleepiness.

Objective daily PAP use was monitored at each follow-up (5 mo, 12 mo, and annually) on the basis of digital downloads from PAP devices and documented in the database (23). Patients were divided into four groups according to quartiles of the average daily PAP use observed over the study period.

Adherence to CV active drugs (b-blockers, platelet aggregation inhibitors, antihypertensive drugs, and lipid-modifying agents; see Table E1 in the online supplement for Anatomical Therapeutic Chemical codes) was assessed annually from the SNDS database during the follow-up period using the medication possession ratio (MPR), which corresponds to the number of days of treatment delivered divided by the number of days of follow-up. Patients with an MPR >80% are considered as treatment adherent (24). Patients with an MPR <80% for at least one of the four categories of CV active drugs were considered as nonadherent.

## **Outcome Variables**

Major adverse cardiovascular events (MACEs), the primary composite outcome of the study, was defined using SNDS data as the first hospitalization for myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure or all-cause death (see [18] for details). Participants were followed up from PAP therapy initiation to the end of December 2019 or the occurrence of a primary outcome, whichever occurred first.

## **Statistical Analysis**

Comparisons between groups were performed using the chi-square test for qualitative variables and a nonparametric Mann-Whitney test for quantitative variables. Because a low rate of missing values was observed (the worst case being observed for the Epworth Sleepiness Scale, 2.3% of missing values), a simple imputation was performed by considering the median value for quantitative variables and most observed frequency for qualitative variables. MACE incidence density rate values were computed in person-years, and a Poisson estimation of the confidence interval was calculated.

Cox proportional hazards models were used to evaluate the associations between quartiles of the average daily PAP use and incident MACEs. Further analyses were performed to consider all-cause mortality and nonfatal CV events individually. Fine and Gray competing risk regressions were used to account for the competing risk of death for non-fatal CV events risk assessment.

Sensitivity analyses were performed by introducing PAP adherence in the model as a continuous variable, then as a time-dependent binary variable according to the median value. Further sensitivity analyses were conducted by using the inverse probability of treatment weight (IPTW) estimator to account for causal inference (17, 25). The E-value was used to assess the minimum strength of association that an unmeasured confounder would need to have with both PAP adherence and MACEs to negate the observed association, independent of all included covariates (26). See the online supplement data for details.

Subgroup analyses were performed by considering age, sex, history of CV disease and CV active drugs (nontreated, nonadherent, or adherent), baseline indices of sleepiness, OSA and nocturnal hypoxia severity, and symptom subtypes identified by latent class analyses (see [18]). All statistical analyses were performed with SAS 9.4 software (SAS Institute). Associations were considered statistically significant with a P value  $\leq 0.05$  (see the online supplement data for details).

## Results

### Patient Characteristics

Of 6,956 eligible patients, 1,774 were not linked to the SNDS dataset, and 44 had missing PAP adherence data (Figure 1). Thus, the final study sample comprised 5,138 patients with a median (interquartile range) age of 64 (55–73) years. As shown in Table 1, the study population consisted of typical patients with OSA (median AHI, 37 [28–52] events/h) who were predominantly male (69.6%) and obese or overweight (median body mass index, 31 [27–35] kg/m<sup>2</sup>) and had frequent CV, metabolic, and mental comorbidities. The prevalence of each variable according to symptom subtypes identified by latent class analysis is presented in Figure E1. Of 3,065 patients treated with CV active drugs, 1,239 (40.4%) were nonadherent to at least one drug category.

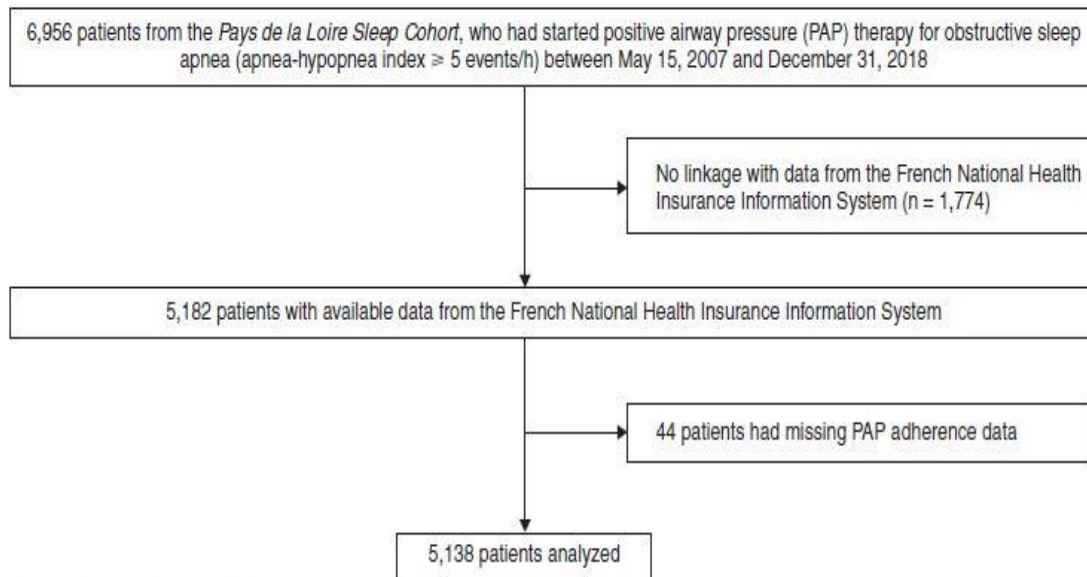
### Adherence to PAP and CV

#### Active Drugs

During follow-up, the median PAP adherence was 5.9 (4.1–7.2) h/night. On the basis of quartiles of average daily PAP use, 1,311 patients (25.5%) were considered as PAP nonadherent (mean daily PAP use, 0–4 h), and 3,827 (74.5%) were PAP adherent with a mean PAP daily PAP use of 4–6 hours ( $n = 1,364$ ; 26.5%), 6–7 hours ( $n = 991$ ; 19.4%), or >7 hours ( $n = 1,472$ ; 28.6%). As shown in Figure 2 and Table E2, patients with lower PAP adherence were also slightly but significantly less adherent to CV active drugs, particularly for lipid-lowering and antihypertensive drugs.

### Primary Objective

After a median follow-up of 6.6 years (4.2–9.1) since PAP initiation, 961 (19%) patients experienced MACEs, including 316 deaths and 645 nonfatal CV events (incidence density rates, 20.2 [95% confidence interval, 18.6–21.8] and 30.1 [28.2–32.0] per 1,000 person-years, respectively). As shown in Table 1, significant differences were observed in terms of baseline characteristics, medical history, CV active drug prescription, and PAP adherence between patients who did and those who did not experience MACEs.



**Figure 1.** Flow diagram of the study subjects.

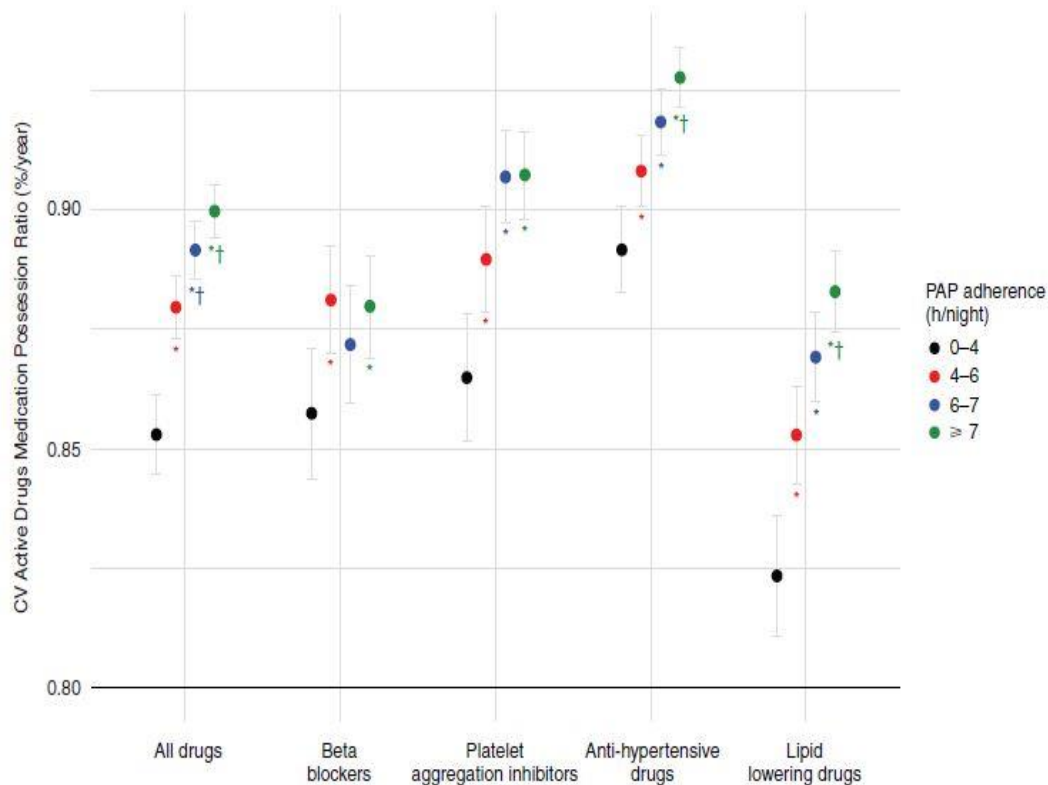
**Table 1.** Description of the Population According to Primary Event (Major Adverse Cardiovascular Events)

Variables	All	No MACEs	MACEs	P Value
No. (%)	5,138	4,177 (81%)	961 (19%)	—
Age, yr	64 [55–73]	63 [53–71]	73 [65–81]	<0.0001
Male sex	3,578 (69.6)	2,802 (67.1)	776 (80.7)	<0.0001
BMI, kg/m <sup>2</sup>	31.1 [27.3–35.5]	30.9 [27.2–35.5]	31.6 [28.35.5]	0.0047
Epworth Sleepiness Scale score	10 [7–14]	10 [7–14]	9 [6–13]	<0.0001
OSA symptom subtypes*				<0.0001
Minimally symptomatic	929 (18.1)	737 (17.7)	192 (20)	
Disturbed sleep	767 (15)	613 (14.7)	154 (16.1)	
Excessively sleepy	2,743 (53.5)	2,288 (54.9)	455 (47.4)	
Moderately sleepy	687 (13.4)	529 (12.7)	158 (16.5)	
Alcohol intake	2,341 (47.1)	1,808 (44.7)	533 (57.3)	<0.0001
Smoking status				<0.0001
Current	1,039 (20.2)	860 (20.6)	179 (18.6)	
Former	1,999 (38.9)	1,533 (36.7)	466 (48.5)	
Never	2,031 (39.5)	1,726 (41.3)	305 (31.7)	
Medical history				
Diabetes	1,026 (20)	714 (17.1)	312 (32.5)	<0.0001
Depression	788 (15.3)	601 (14.4)	187 (19.5)	<0.0001
Hypertension	2,614 (50.9)	1,951 (46.7)	663 (69)	<0.0001
Heart failure	235 (4.6)	95 (2.3)	140 (14.6)	<0.0001
CAD	279 (5.4)	159 (3.8)	120 (12.5)	<0.0001
AF	416 (8.1)	239 (5.7)	177 (18.4)	<0.0001
Stroke	262 (5.1)	209 (5)	53 (5.5)	0.5158
CV active drugs	3,065 (59.6)	2,313 (55.4)	752 (78.3)	<0.0001
β-Blockers	1,418 (46.3)	915 (39.6)	503 (66.9)	<0.0001
Antihypertensives	2,591 (84.5)	1,914 (82.7)	677 (90)	<0.0001
Antiplatelet agents	1,489 (48.6)	958 (41.4)	531 (70.6)	<0.0001
Lipid-lowering drugs	2,129 (69.5)	1,521 (65.8)	608 (80.9)	<0.0001
Polysomnography	1,973 (38.4)	1,710 (40.9)	263 (27.4)	<0.0001
OSA severity				
AHI, events/h	37 [28–52]	36 [27–51]	41 [31–57]	<0.0001
ODI, events/h	30 [17–48]	29 [16–46]	36 [22–54]	<0.0001
T90%, %	7 [1–22]	5 [1–19]	13 [4–37]	<0.0001
SASHB, % min/h <sup>†</sup>	54 [28–107]	51 [27–97]	79 [41–147]	<0.0001
PAP use, h/night	5.9 [3.9–7.2]	5.9 [4.0–7.2]	5.8 [3.8–7.3]	0.6586
PAP use, h/night				0.0384
0–4	1,311 (25.5)	1,053 (25.2)	258 (26.8)	
4–6	1,364 (26.5)	1,117 (26.7)	247 (25.7)	
6–7	991 (19.3)	833 (19.9)	158 (16.4)	
≥7	1,472 (28.6)	1,174 (28.1)	298 (31.0)	
Follow-up, yr	6.6 [4.2–9.1]	6.6 [4.4–9.2]	6.3 [3.4–8.9]	<0.0001

*Definition of abbreviations:* AF = atrial fibrillation; AHI = apnea-hypopnea index; BMI = body mass index; CAD = coronary artery disease; CV = cardiovascular; MACE = major adverse cardiovascular event (a composite outcome of myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure; or all-cause death); ODI = 3% oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; SASHB = sleep apnea-specific hypoxic burden; T90% = percentage of sleep (or recording) time with oxygen saturation <90%.

Values are expressed as median [interquartile range] or count (percent). Missing values, BMI,  $n = 20$  (0.3%); Epworth Sleepiness Scale score,  $n = 117$  (2.2%); alcohol intake,  $n = 147$  (2.8%); smoking status,  $n = 60$  (1.1%).

\*Data for OSA symptom subtypes were available for 5,126 patients.



**Figure 2.** Adherence to CV active drugs according to categories of daily PAP use. CV = cardiovascular; PAP = positive airway pressure. \*Significant difference with 0-4 h/night adherence group and †Significant difference with 4-6 h/night adherence group after Bonferroni correction (significance threshold, 0.008).

Results of unadjusted and adjusted Cox proportional hazards models are summarized Table 2. All factors associated with the composite outcome with a P value  $\leq 0.15$  were considered in the final model, which included age, sex, Epworth score, alcohol and smoking, medical history of CV disease, hypertension, diabetes, depression, CV active drugs (three modalities: nontreated [n = 2,073; 40.4%], nonadherent [n = 1,239; 24.1%], and adherent [n = 1,826; 35.5%]), type of sleep recording, AHI, and PAP adherence. The fully adjusted model showed a significant association between PAP adherence and MACEs. Figure 3 presents adjusted Kaplan-Meier MACE free survival curves according to PAP adherence group. Considering nonadherent patients (PAP use 0–4 h/night) as the reference group, we found hazard ratios (HRs) (95% confidence intervals) for MACEs of 0.87 (0.73–1.04) for the 4–6 h/night group, 0.75 (0.62–0.92) for the 6–7 h/night group, and 0.78 (0.65–0.93) for patients with an average PAP use  $>7$  h/night (P = 0.0130). By introducing PAP adherence as a continuous variable in the model, we confirmed a significant association with MACEs (HR, 0.964 [0.938–0.991]; P = 0.0093). The association was also confirmed (HR, 0.86 [0.75–0.99]; P = 0.0266) when PAP use was introduced as a time-dependent binary variable ( $>6$  h/night vs.  $\leq 6$  h/night). As shown in Table E3, sensitivity analyses using the IPTW estimator to account for causal inference confirmed the association of PAP use with MACEs. A directed acyclic graph is presented in Figure E2. The E-value showed that with an observed HR of 0.73 (0.67–0.8) in patients using PAP 6–7 h/night, an unmeasured confounder associated with both the MACEs and PAP adherence by a relative risk of approximately twofold each, above and beyond the measured confounders, could explain away the estimate, but weaker confounding could not (Table E4).



**Table 2.** Cox Proportional Hazards Models Assessing the Association of Daily Positive Airway Pressure Use and Other Relevant Factors and Their Association with Incident Major Adverse Cardiovascular Events

	Unadjusted HR [95% CI]	Unadjusted P Value	Adjusted HR [95% CI]	Adjusted P Value
Age	1.06 [1.05–1.07]	<0.0001	1.05 [1.04–1.06]	<0.0001
Male sex	1.88 [1.60–2.22]	<0.0001	1.66 [1.38–1.99]	<0.0001
BMI, kg/m <sup>2</sup>	1.00 [0.99–1.01]	0.4104	—	
Epworth Sleepiness Scale score	0.97 [0.95–0.98]	<0.0001	0.99 [0.98–1.01]	0.2304
Alcohol intake	1.48 [1.30–1.68]	<0.0001	1.01 [0.87–1.16]	0.9375
Smoking status		<0.0001		<0.0001
Current smoker	1.14 [0.94–1.37]		1.61 [1.32–1.97]	
Former smoker	1.63 [1.41–1.89]		1.31 [1.12–1.53]	
Never smoker	Ref.		Ref.	
History of CV disease	4.40 [3.87–5.00]	<0.0001	2.58 [2.24–2.96]	<0.0001
Hypertension	2.39 [2.09–2.74]	<0.0001	1.34 [1.14–1.57]	0.0004
Diabetes	1.89 [1.66–2.15]	<0.0001	1.36 [1.18–1.56]	<0.0001
Depression	1.36 [1.16–1.60]	0.0002	1.59 [1.35–1.88]	<0.0001
Polysomnography	0.58 [0.50–0.67]	<0.0001	1.15 [1.00–1.35]	0.0487
AHI, per 10 units	1.07 [1.04–1.10]	<0.0001	1.03 [0.99–1.07]	0.0702
ODI,* per 10 units	<i>1.08 [1.05–1.11]</i>	<0.0001	<i>1.03 [0.99–1.06]</i>	0.0641
T90%,* per 10 units	<i>1.15 [1.12–1.18]</i>	<0.0001	<i>1.07 [1.03–1.10]</i>	<0.001
SASHB,*† per 10 units	<i>1.01 [1.00–1.01]</i>	<0.0001	<i>1.00 [0.99–1.01]</i>	0.1051
CV active drugs		<0.0001		0.1002
Nontreated	Ref.		Ref.	
Nonadherent	2.65 [2.23–3.15]		0.95 [0.77–1.16]	
Adherent	2.30 [1.95–2.72]		0.83 [0.68–1.02]	
PAP use, h/night		0.0803		0.0130
0–4	Ref.		Ref.	
4–6	0.92 [0.78–1.10]		0.87 [0.73–1.04]	
6–7	0.82 [0.67–1.00]		0.75 [0.62–0.92]	
≥7	1.04 [0.88–1.23]		0.78 [0.65–0.93]	

*Definition of abbreviations:* AHI = apnea-hypopnea index; BMI = body mass index; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MACE = major adverse cardiovascular event; ODI = 3% oxygen desaturation index; PAP = positive airway pressure; Ref. = reference; SASHB = sleep apnea specific hypoxic burden; T90% = percentage of sleep (or recording) time with oxygen saturation <90%.

\*Adjusted HR for ODI, T90%, and SASHB are presented in italics because they were introduced separately in multivariable models to avoid collinearity between these variables and AHI.

†Data for SASHB were available for 3,699 patients.

## Secondary Objectives: All-Cause Mortality and CV Morbidity

When all-cause-mortality and CV morbidity were considered separately, PAP adherence was significantly associated with all-cause mortality ( $P = 0.0006$ ), but the association did not reach statistical significance for all nonfatal CV events ( $P = 0.1510$ ) (Figure 4), stroke ( $n = 149$ ;  $P = 0.3643$ ), coronary heart disease ( $n = 280$ ;  $P = 0.8208$ ), and heart failure ( $n = 348$ ;  $P = 0.4080$ ) (Table E5).

## Subgroup Analyses According to Patient Characteristics and OSA Severity

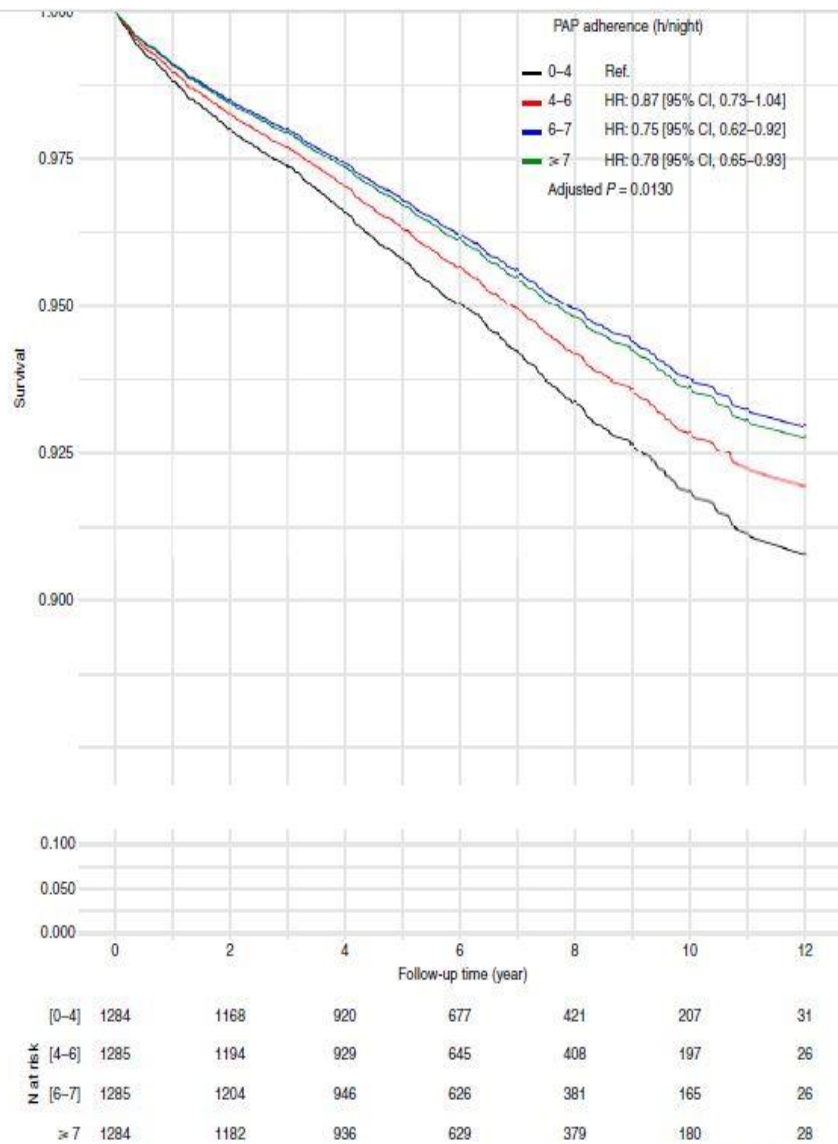
Cox proportional hazards models assessing the association of daily PAP use with MACEs stratified by baseline patient characteristics are presented in Figure 5 and Tables E6 and E7. In subgroup analyses, the association between PAP adherence and incident MACEs was stronger in male patients ( $P$  value for interaction = 0.0004), patients without overt CV disease at diagnosis ( $P, 0.0001$ ), and those belonging to the excessively sleepy symptom subtype ( $P = 0.060$ ). There was also a trend for a stronger association in sleepy patients (Epworth score,  $>11$ ;  $P$  value for interaction = 0.1940) and never or former smokers ( $P$  value for interaction = 0.3858).

When we considered categories of OSA and nocturnal hypoxia severity (Table 3), the association of PAP adherence with incident MACEs reached statistical significance only in patients with the most severe SASHB ( $>83.75\%$  min/h) at diagnosis ( $P = 0.0138$ ), although the result of a formal test for interaction was not significant ( $P = 0.5014$ ). In the subgroup of patients diagnosed by PSG ( $n = 1,683$ ), we found no association of CV response to PAP with baseline slow-wave sleep, sleep fragmentation, and REM-related obstructive events (Table E8).

## Discussion

Within a large, multicenter, clinic-based cohort of patients with OSA, we demonstrated a negative dose–response relationship between PAP adherence and the incidence of MACEs, a composite outcome of major CV events and all-cause-mortality. After a median follow-up of 6.6 years, patients using PAP at least 6 h/night had an ~ 25% reduction of incident MACEs when compared with nonadherent subjects. The association between PAP adherence and MACEs was stronger in male patients, patients without overt CV disease at diagnosis, and those belonging to the excessively sleepy symptom subtype. The association also appeared to be stronger in patients with the most severe SASHB, although the result of a formal test for interaction was not significant.

Whether PAP therapy of OSA has a beneficial impact on CV risk remains unclear. Multiple observational studies have demonstrated that untreated OSA is associated with CV morbidity and mortality, and they have suggested that PAP treatment might improve CV outcomes (27–29). Conversely, we now have four concordant RCTs showing no effect of PAP therapy for OSA on the composite outcome of different fatal and nonfatal CV events (9–11, 30). However, the findings of these RCTs might not be generalizable to the entire OSA population and do not allow one to conclude formally that OSA and its first-line therapy have no effect on CV diseases (31). Three of these four RCTs included patients with overt CV diseases recruited from cardiology or neurology clinics, whereas only 15% of our sleep clinic patients had preexisting CV disease, including stroke (5.1%), coronary heart disease (5.4%), and heart failure (4.6%). A recent post hoc analysis of the ISAACC (Impact of Sleep Apnea syndrome in the evolution of Acute Coronary syndrome. Effect of intervention with CPAP) study showed that among patients with nontreated OSA and acute coronary syndrome, only those with no previous heart disease upon admission had an increased risk of a recurrent CV event compared with the non-OSA group (32). Our study showed no association of PAP adherence with MACEs in the subgroup of patients with preexisting CV disease, although this finding should be interpreted with caution because of an unbalanced sample size. Altogether, these findings suggest that PAP might be more effective for the primary prevention of CV disease than in reversing an altered vascular structure as a secondary prevention strategy.



**Figure 3.** Adjusted Kaplan-Meier survival curves indicating MACE-free survival according to categories of PAP adherence. Adjusted for age, sex, Epworth Sleepiness Scale score, alcohol and smoking habits, medical history of CV disease, hypertension, diabetes, depression, use of cardiovascular active drugs (nontreated, nonadherent, or adherent), type of sleep recording (in-laboratory polysomnography or type 3 home sleep apnea testing), and apnea-hypopnea index. CI = confidence interval; HR = adjusted hazard ratio; MACE = major adverse cardiovascular event, a composite outcome of myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure or all-cause death; PAP = positive airway pressure.

Because of ethical considerations, previous RCTs with CV endpoints excluded patients with marked excessive daytime sleepiness (mean Epworth score between 5.4 and 7.3 vs. 10.4 in the present sleep clinic population) (9–11, 30). In a recent, large, population-based cohort study, only the “excessively sleepy” subtype was associated with an increased risk of incident CV events compared with subjects without OSA (33). Our group did not replicate the increased CV risk in the excessively sleepy subtype within the clinic-based Pays de la Loire Sleep Cohort, in which subjects undergoing a sleep study with minimal symptoms had more severe comorbidities that increased baseline CV risk (18). Previous studies have demonstrated that the effect of PAP on blood pressure is greater in sleepy than in non-sleepy patients with OSA (34, 35). In line with these previous reports, our study supports the hypothesis that PAP therapy might be more effective for reducing CV risk in patients with the excessively sleepy symptom subtype than in other clinical phenotypes of OSA. Altogether, these findings support the hypothesis that excessive daytime sleepiness may be a surrogate marker of underlying CV risk pathways influenced by OSA and its adequate treatment (33). However, it

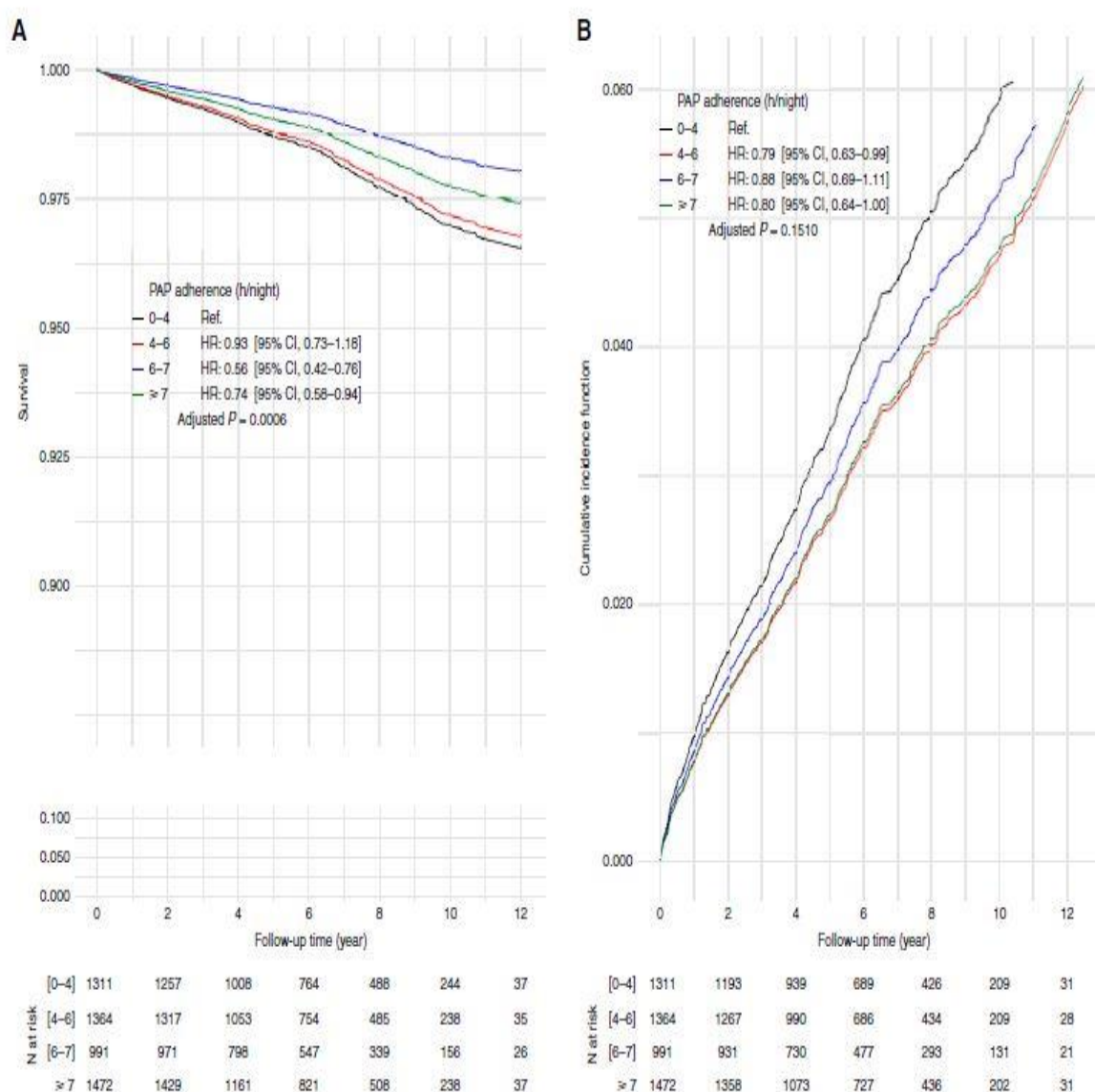
is difficult to foresee how this hypothesis could be tested in a clinical trial, because PAP treatment is indicated for most sleepy patients with OSA, and randomization to a control group would not be ethically feasible. Long-term observational studies among clinical cohorts with appropriate adjustment for confounders are an effective alternative approach to examining the role of PAP in preventing CV events (36).

Most RCTs addressing the impact of PAP therapy on CV risk selected patients on the basis of their AHI (>15 or 20 events/h) (10, 11, 30), and the largest study excluded patients with severe nocturnal hypoxemia (9). There is increasing evidence that common metrics of OSA severity, such as AHI and oxygen desaturation index, do not adequately capture the key aspects of OSA that have a deleterious impact on the CV system. The heterogeneity of CV risk across different subgroups of people with OSA might have contributed to the negative results of RCTs. The SASHB is a novel measure of OSA severity that encapsulates the frequency, duration, and depth of respiratory event-related desaturations (21, 22). The value of SASHB in the prediction of CV events and mortality has been demonstrated in both general population (22) and clinical health settings (18, 37). We have recently shown in the Pays de la Loire Sleep Cohort that patients with OSA who demonstrate elevated SASHB at diagnosis are at higher risk of MACEs at follow-up (18). Within the same cohort, the present study shows that the greatest reduction in the incidence of MACEs among PAP-adherent patients (0.63 [0.44–0.9]) is observed in those with the highest SASHB value at baseline. Although the results of formal tests for interaction were not significant, these findings suggest that SASHB, better than AHI, could help clinicians identify patients with OSA in whom the CV risk is the highest and is most likely to be reduced by sustained and adherent PAP therapy.

The low adherence to PAP therapy observed in most RCTs (2.862.7 and 3.362.3 h/night, respectively, in the SAVE [Sleep Apnea Cardiovascular Endpoints study] and ISAACC studies) might also explain, at least in part, its lack of effect on CV outcomes (9, 11). Three or four hours of PAP use from the beginning of the sleep period would leave 75% of untreated REM obstructive events that were found to be strongly associated with adverse CV outcomes (38). Our finding that PAP therapy is associated with a reduced incidence of MACEs in adherent patients is consistent with previous post hoc analyses and meta-analyses showing that adequate use of PAP (usually defined as at least 4 h/night) might improve CV and cerebrovascular outcomes (9, 10, 39, 40). The large sample size of our study allowed us to evaluate the dose–response relationship between PAP adherence and MACEs. Our findings are consistent with a previous RCT of PAP in hypertensive patients with OSA showing that the effect of PAP on blood pressure was evident only in patients who used the device more than 5.6 h/night (41). Adequate PAP adherence remains a challenging issue. A multidisciplinary approach is required to achieve the desired results, addressing all key factors that can affect treatment adherence and including novel technologies such as telemonitoring and patient support software applications (40).

When the two outcomes were considered separately, PAP adherence remained significantly associated with all cause mortality but not with nonfatal CV events. This result is in agreement with our recent study demonstrating a significant association of OSA severity assessed by SASHB with all-cause mortality but not with nonfatal CV events (18). Altogether, these findings suggest that OSA and its adequate treatment would have a greater impact on the fatal outcome of CV events than on the development of CV diseases. This hypothesis is supported by a French nationwide database study showing that continuation of

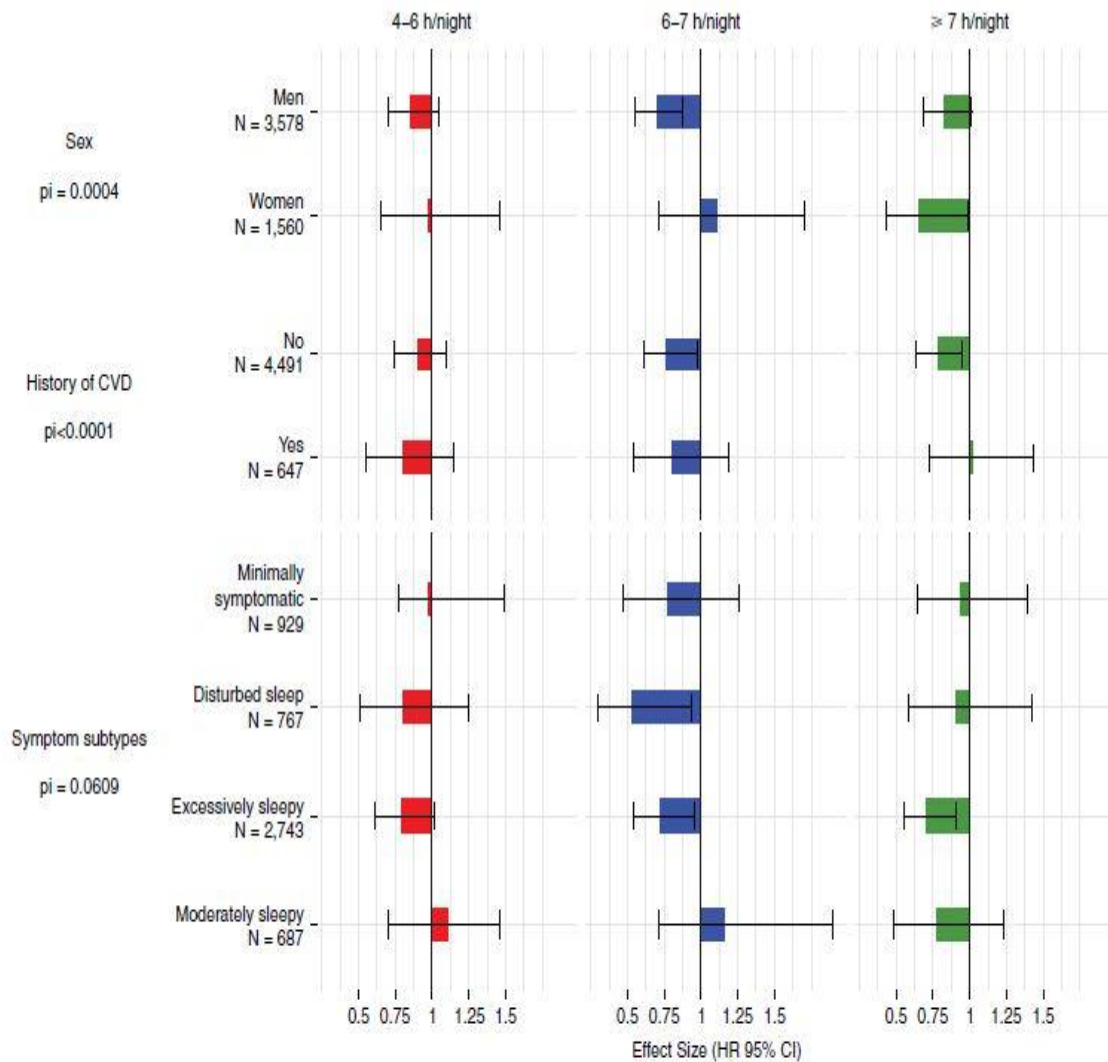
PAP therapy is associated with a significantly lower risk of all-cause death than PAP therapy termination (42).



**Figure 4.** Adjusted Kaplan-Meier survival curves indicating the time to onset of (A) all-cause mortality and (B) nonfatal cardiovascular events, according to categories of PAP adherence. Nonfatal cardiovascular events included myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure. Adjusted for age, sex, Epworth Sleepiness Scale score, alcohol and smoking habits, medical history of CV disease, hypertension, diabetes, depression, use of cardiovascular active drugs (nontreated, nonadherent, or adherent), type of sleep recording (in-laboratory polysomnography or type 3 home sleep apnea testing), and apnea-hypopnea index. CI = confidence interval; HR = adjusted hazard ratio; PAP = continuous positive airway pressure.

Few studies have evaluated whether PAP adherence is associated with CV active drug adherence, and they provided discrepant results (43, 44). Using the administrative database of the Spanish Health Service, Villar and colleagues (43) compared adherence and persistence with three medication categories (antihypertensives, statins, and antiplatelets) between patients with adequate PAP adherence (.4 h/night) and nonadherent patients. The authors concluded that medication adherence and persistence were not different in patients with severe OSA, regardless of whether they were PAP adherent (43). Conversely, a retrospective cohort study in veterans with OSA newly started on PAP therapy showed an association of

adherence to lipid-lowering medications and initial daily PAP adherence (13). In the present study, we demonstrated a slight but statistically significant association between PAP and CV active drug adherence, particularly for lipid-lowering and antihypertensive drugs. However, a healthy user effect is unlikely because the association between PAP adherence and MACEs was significant after adjusting for CV active drug adherence.



**Figure 5.** Subgroup analysis of adjusted hazard ratio (95% confidence interval) for MACEs according to daily PAP use, considering 0-4 h/night as the reference group. Adjusted for age, sex, Epworth Sleepiness Scale score, alcohol and smoking habits, medical history of CV disease, hypertension, diabetes, depression, use of cardiovascular active drugs (nontreated, nonadherent, or adherent), type of sleep recording (in-laboratory polysomnography or type 3 home sleep apnea testing), and apnea-hypopnea index. Hazard ratio was adjusted for sex, history of CV disease and active drug prescription, and the corresponding variable was removed from the model. CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; HR = adjusted hazard ratio; MACE = major adverse cardiovascular event, a composite outcome of myocardial infarction, stroke, exacerbation of congestive heart failure, or a revascularization procedure or all-cause death; PAP = positive airway pressure; pi = P value for interaction.

The strengths of the present study include a multicenter design and a large sample of unselected patients, suggesting that our findings are generalizable to the majority of patients with PAP-treated OSA. The ability to study clinical outcomes in large population or clinic-based samples is a potential strength of health administrative data. The SNDS database now covers 98.8% of the French population, more than 66million persons, from birth (or immigration) to death (or emigration) (45). Unlike clinical trials, the linkage between clinical

cohort data and SNDS data allows long-term follow-up with limited attrition bias. Some limitations should also be considered when interpreting the findings of our study. The main limitation of the present study is its observational design, which does not allow us to draw a formal conclusion regarding the causal link between PAP adherence and MACEs. Potential unmeasured confounding factors, such as nutrition, physical activity, and sleep duration, may have contributed to the incidence of MACEs. However, sensitivity analyses using a causal inference approach (25) provided evidence of the robustness of the observed association, and the E-value showed that there was a low risk that an unmeasured confounder biased the result (26).

**Table 3.** Cox Proportional Hazards Models Assessing the Association of Daily Positive Airway Pressure Use with Major Adverse Cardiovascular Events, Stratified by Indices of Obstructive Sleep Apnea Severity

	No.	Adjusted* Hazard Ratio [95% Confidence Interval]				P Value
		0–4 h	4–6 h	6–7 h	≥7 h	
OSA severity <sup>†</sup>						
Mild	264	Ref.	1.9 [0.71–5.08]	0.86 [0.17–4.46]	1.3 [0.44–3.86]	0.5514
Moderate	1,124	Ref.	0.63 [0.41–0.95]	0.62 [0.39–1]	0.75 [0.48–1.17]	0.0950
Severe	3,750	Ref.	0.91 [0.74–1.11]	0.78 [0.62–0.97]	0.8 [0.66–0.97]	0.0629
ODI, events/h <sup>‡</sup>						
5–17	959	Ref.	0.99 [0.61–1.61]	0.95 [0.53–1.68]	0.68 [0.4–1.17]	0.4978
17–36	1,796	Ref.	0.8 [0.59–1.1]	0.62 [0.43–0.89]	0.91 [0.68–1.24]	0.0605
≥36	1,989	Ref.	0.83 [0.64–1.08]	0.72 [0.54–0.97]	0.72 [0.56–0.93]	0.0540
T90%, % <sup>§</sup>						
0–2.1	1,737	Ref.	0.95 [0.66–1.36]	0.65 [0.41–1.03]	0.67 [0.45–1]	0.1003
2.1–15	1,647	Ref.	0.87 [0.64–1.19]	0.88 [0.62–1.24]	0.82 [0.6–1.12]	0.6473
≥15	1,717	Ref.	0.83 [0.63–1.09]	0.68 [0.50–0.92]	0.77 [0.6–0.99]	0.0649
SASHB, % min/h <sup>  </sup>						
0–35.89	1,232	Ref.	1.34 [0.87–2.09]	0.75 [0.42–1.34]	1.1 [0.7–1.75]	0.2149
35.94–83.75	1,234	Ref.	1.08 [0.75–1.57]	0.9 [0.58–1.39]	0.88 [0.58–1.33]	0.7158
≥83.75	1,233	Ref.	0.72 [0.53–1]	0.63 [0.44–0.90]	0.64 [0.48–0.86]	0.0138

*Definition of abbreviations:* ODI = 3% oxygen desaturation index; OSA = obstructive sleep apnea; Ref. = reference; SASHB = sleep apnea specific hypoxic burden; T90% = percentage of sleep (or recording) time with oxygen saturation <90%.

The following commonly used cutoffs for apnea–hypopnea index were used to define categories of OSA severity: 5–15, mild OSA; 15–30, moderate OSA; ≥30, severe OSA.

\*Adjusted for age, sex, Epworth Sleepiness Scale score, alcohol and smoking habits, medical history of cardiovascular disease, hypertension, diabetes, depression, use of cardiovascular active drugs (nontreated, nonadherent, or adherent), type of sleep recording (in-laboratory polysomnography or type 3 home sleep apnea testing), and apnea–hypopnea index.

<sup>†</sup>P for interaction = 0.6329.

<sup>‡</sup>P for interaction = 0.4298.

<sup>§</sup>P for interaction = 0.7344.

<sup>||</sup>P for interaction = 0.5014.

Whether adherent PAP therapy is associated with a reduced mortality in OSA has great clinical and public health significance. We acknowledge that we did not have precise data on the specific causes of death in our study, as was the case in several cohort studies evaluating CV outcomes in OSA (18, 42, 46). However, several arguments allow us to consider that the reduction in mortality observed in PAP adherent patients was mainly related to CV diseases in our study. Cancer and CV diseases are by far the two leading causes of death, both in the general French population (47) and in OSA population- or clinic-based cohorts (48–50). A reduction in cancer mortality with PAP therapy seems very unlikely, given the results recently reported by our group in the Pays de le Loire Sleep Cohort. Using a propensity score IPTW analysis, we demonstrated that adherent 5-year PAP therapy had no effect on cancer risk (17). In the present study, the most important reduction in MACE incidence was observed in PAP-adherent patients who displayed high SASHB in a diagnostic sleep study. In population-based cohorts, SASHB was more strongly associated with CV mortality than with all-cause-mortality (22).

Although it did not reach statistical significance, our study showed a trend toward a reduction in the incidence of nonfatal CV events in PAP-adherent patients (P = 0.15).

## Conclusions

These real-life clinical data demonstrate a dose–response relationship between PAP adherence and incident MACEs in OSA. Patient support programs may help improve PAP adherence and CV outcomes in patients with OSA. Clinical phenotyping might be useful for early identification of patients with OSA in whom adherent PAP therapy is most likely to improve CV outcomes. \_

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