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Relationship Between CPAP Termination and All-Cause Mortality

A French Nationwide Database Analysis

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BACKGROUND: Randomized controlled trials have failed to demonstrate an effect of CPAP therapy on mortality. However, these studies have a number of important limitations, including low CPAP adherence, patient selection, and a small number of mortality events.

RESEARCH QUESTION: What are the effects of CPAP therapy termination in the first year on all-cause mortality in OSA patients from the Nationwide Claims Data Lake for Sleep Apnoea study?

STUDY DESIGN AND METHODS: Data from the Système National des Données de Santé (SNDS) database, the French national health insurance reimbursement system, for all new CPAP users ≥ 18 years of age were analyzed. The SNDS contains comprehensive, individualized, and anonymized data on health spending reimbursements for > 99% of all individuals living in France. OSA diagnosis was based on specific disease codes, whereas CPAP prescription was identified using specific treatment method codes. CPAP therapy termination was defined as the cessation of CPAP reimbursements triggered by the respiratory physician or sleep specialist in charge of follow-up. Patients who terminated therapy in the first year were propensity score matched with those who continued to use CPAP. The primary outcome was all-cause mortality. Three-year survival was visualized using Kaplan-Meier curves. Contributors to mortality also were determined.

RESULTS: Data from two matched groups each including 88,007 patients were included (mean age, 60 years; 64% men). Continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination (hazard ratio [HR], 0.61; 95% CI, 0.57-0.65; $P < .01$, log-rank test). Incident heart failure also was less common in patients who continued vs terminated CPAP therapy (HR, 0.77; 95% CI, 0.71-0.82; $P < .01$).

INTERPRETATION: These real-world data from a comprehensive, unbiased database highlight the potential for ongoing use of CPAP treatment to reduce all-cause mortality in patients with OSA.

CHEST 2022; ■(■):■-■

KEY WORDS: adherence; CPAP; mortality; OSA

ABBREVIATIONS: HR = hazard ratio; SAVE = Sleep Apnea Cardiovascular Endpoints; SNDS = Système National des Données de Santé

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Take-home Points

Study Question: What are the effects of CPAP therapy termination in the first year on all-cause mortality in patients with OSA from the Nationwide Claims Data Lake for Sleep Apnoea study?

Results: In matched patient groups, continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination. In addition, incidence heart failure was significantly less common in patients who continued versus terminated CPAP therapy in the first year.

Interpretation: These data highlight the potential for ongoing use of CPAP to reduce all-cause mortality in patients with OSA.

OSA is characterized by repeated upper airway collapse during sleep. These episodes are associated with several important consequences, including sympathetic activation, marked negative intrathoracic pressure swings, intermittent oxygen desaturation, hypercapnia, and arousal from sleep. In turn, these effects are thought to contribute to common comorbidities in patients with OSA, including hypertension, cardiovascular and cerebrovascular disease, and metabolic abnormalities.[1-4] These comorbidities could be responsible for the increased all-cause mortality risk that has been reported in patients with OSA.[5-10]

Despite the reported association between OSA and mortality, randomized clinical trials evaluating the effects of treating OSA on cardiovascular events and all-cause death have not demonstrated any beneficial effect of CPAP therapy, the gold standard treatment for moderate to severe OSA.[11-13] However, the ability of CPAP to influence hard mortality end points may have been limited by several factors, including low adherence to CPAP and patient selection. In addition, the total number of mortality events was low in all randomized trials, limiting statistical power to detect between-group differences and perhaps not representative of what happens in the real world. Thus, although randomized controlled trials provide a high level of evidence, real-world data may be able to provide a more accurate and generalizable picture of the effects of routine clinical use of CPAP on mortality.

The Nationwide Claims Data Lake for Sleep Apnoea study uses data from the Système National des Données de Santé (SNDS) database, the French national health insurance reimbursement system. This analysis investigated all-cause mortality in new users of CPAP who terminated therapy during the first year or continued with long-term CPAP therapy.

Methods

Data Source

This analysis included data from the French SNDS database, which contains comprehensive, individualized and anonymized data on health spending reimbursements for > 99% of all individuals living in France. The Nationwide Claims Data Lake for Sleep Apnoea project was approved by the Commission Nationale Informatique et Liberté, the French information technology and personal data protection authority. Specific approval was obtained from the Commission Nationale Informatique et Liberté to perform this study (Identifier: DR-2019-78, no. 919194).

Study Population

Eligible patients were adults ≥ 18 years of age who had not previously used CPAP and had initiated CPAP therapy between January 2015 and December 2016. OSA diagnosis was based on specific disease codes, whereas CPAP prescription was identified using specific treatment method codes.[14]

Patients who terminated CPAP during the first year of therapy were matched with those who continued CPAP therapy for 1 year using propensity score matching to eliminate the influence of biases and confounding factors affecting both therapy termination and mortality rates in the therapy termination and therapy continuation groups. Propensity score matching was based on the following factors: patient demographics (age and sex), insurance coverage, socioeconomic status, and comorbidities (stroke, heart failure, peripheral arterial occlusive disease, hypertension, diabetes mellitus, other cardiovascular diseases, COPD, bariatric surgery, neurotic disorders, use of psychotropic medication, and kidney diseases). To account for possible selection bias, a sensitivity analysis was performed in the untruncated cohort with CPAP initiation being the starting date in a survival Cox model with CPAP continuation as a time-dependent covariate. Variables for adjustments were the same variables used for the propensity score analysis.

Study Parameters and Follow-up

One year after CPAP initiation, the propensity score was applied to select a matched population of CPAP users and nonusers; patients then were followed up for an additional 3 years (e-Fig 1). CPAP therapy termination was defined as the cessation of CPAP reimbursements triggered by the respiratory physician or sleep specialist in charge of follow-up. French national recommendations for reimbursement are CPAP device use of > 4 h/night. Reimbursement rates progressively decrease when very low adherence to CPAP occurs, although delivery and reimbursement of therapy can continue when CPAP use is 2 to 4 h/night, with a requirement for additional patient education and coaching. A mandatory follow-up visit occurs at 4 months after CPAP initiation, then every year thereafter to determine treatment reimbursement renewal.

For this analysis, it was assumed that CPAP termination was linked with nonadherence. Individuals with a valid and documented reason for stopping CPAP therapy (ie, sleep apnea cure after bariatric

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surgery, otorhinolaryngology surgery, switch to oral appliances, death) were censored in the Kaplan-Meier analysis. In the SNDS database, mortality is defined by the registered date of death, but the cause of death is not available.

Statistical Analysis

Data are expressed as median (interquartile range) for quantitative data and as number (percentage) for qualitative data. Comparisons between groups (CPAP termination vs CPAP continuation) were performed using the Student *t* test for quantitative data and the χ^2 test for qualitative data. Mortality and the cumulative incidence rate for heart failure were compared using Kaplan-Meier curves, and between-group comparisons were performed by using the log-rank test. These analyses also were performed separately for men and women.

The primary objective was assessed using a propensity score analysis. First, a propensity score model was performed to compute the factors associated significantly with the probability of CPAP termination during the first year. A nonparsimonious multivariate regression model was created including all major factors (list of variables and results in e-Table 1). A 1:1 greedy matching was performed with a caliper of 0.1%. Standardized differences were used to ensure the quality of the propensity score matching. The standardized difference was reduced for all variables after matching (e-Fig 2). Finally, a semiparametric Cox model was used to assess the impact of CPAP termination or continuation on outcomes (mortality, incident heart failure, incident coronary artery disease, new hospitalization for diabetes, incident arrhythmias, and incident hypertension); cancer was not evaluated because of the comparatively short follow-up time for this analysis. To account for mortality as a competing event for all outcomes, sensitivity analyses were performed considering only patients who were alive. Hazard proportionality assumption was not checked, and hazard ratio (HR) values must be interpreted as an average HR, rather than instantaneous HR.[15]

Analyses were performed using Python version 3.6.7 software with the libraries Numpy version 1.18.1 and Pandas version 0.24.2 for data management and analysis, Statsmodel version 0.12.1 for logistic regression, and Lifelines version 0.14.1 for Kaplan-Meier curves and Cox models. A *P* value of .05 was considered statistically significant.

Results

Study Population

The Nationwide Claims Data Lake for Sleep Apnoea cohort includes 480,000 patients, of whom 365,301 had undergone at least 1 year of follow-up and did not have a valid reason for CPAP therapy termination (4,882 patients had a valid reason for CPAP termination during the first year) (e-Table 2). Of these 365,301 patients, 76% (n = 277,242) continued CPAP therapy and 24% (n = 88,059) terminated CPAP therapy. After propensity score matching, the study population for this analysis included 88,007 patients in each group (total of 176,014 patients) (Fig 1). As expected, propensity score matching generated two patient groups that were well matched for baseline characteristics (Table 1).

All-Cause Mortality

Over a 3-year observation period, death occurred in 3,204 of 88,007 patients (3.6%) in the CPAP therapy termination group compared with 2,053 of 88,007 patients (2.3%) in the therapy continuation group (e-Table 3). Continuation of CPAP therapy was associated with a significantly lower risk of all-cause death compared with CPAP therapy termination (HR, 0.61; 95% CI, 0.57-0.65; $P < .01$, log-rank test) (Fig 2). The results were similar in men and women (HR, 0.63 [95% CI, 0.57-0.68] and 0.54 [95% CI, 0.47-0.62]; $P <$ .01 for both) (e-Fig 3). The sensitivity analysis also

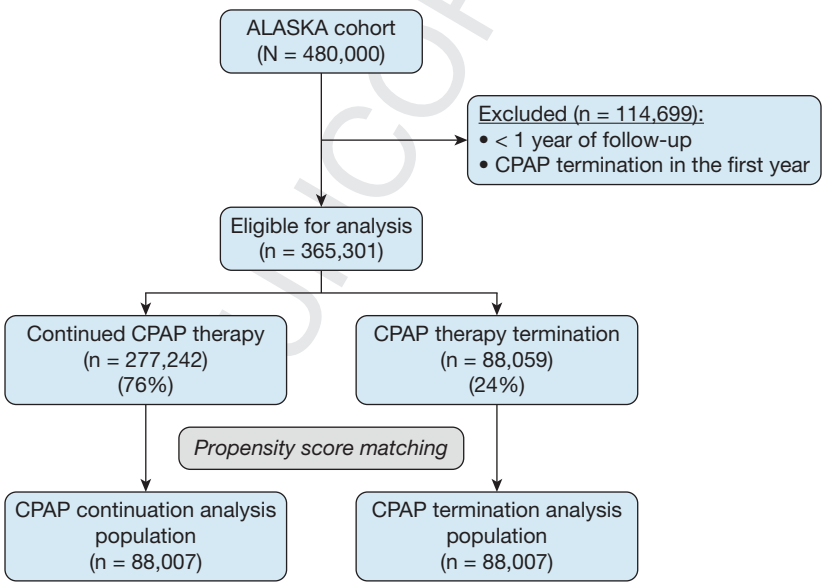

Figure 1 – *Flow chart showing patient inclusion. ALASKA = Nationwide Claims Data Lake for Sleep Apnoea.*

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TABLE 1] Baseline Characteristics of the Matched Study Population

Variable	CPAP Continuation (n = 88,007)	CPAP Termination (n = 88,007)
Age, y	60.0 (70.0-50.0)	59.0 (69.0-49.0)
Female sex	32,227 (36.6)	31,666 (36.0)
Comorbidity		
Chronic psychiatric disorders	4,621 (5.2)	4,606 (5.2)
Stroke	2,735 (3.1)	2,684 (3.1)
Heart failure	2,306 (2.6)	2,046 (2.3)
Coronary heart disease	8,023 (9.1)	8,037 (9.1)
Hypertension	42,568 (48.4)	43,231 (49.1)
Diabetes mellitus	18,610 (21.1)	18,304 (20.8)
COPD	7,156 (8.1)	7,387 (8.4)

Data are presented as No. (%) or median (interquartile range).

showed a significant reduction in all-cause mortality associated with CPAP continuation, with an HR of 0.73 (95% CI, 0.70-0.76; $P < .01$ [10,795 events in 336,415 patients, or an event rate of 3.2%]).

Factors Contributing to Death

The cumulative incidence of heart failure (based on disease codes entered in the SNDS database) was significantly lower in patients who continued vs terminated CPAP therapy (HR, 0.77; 95% CI, 0.71-0.82; $P < .01$, log-rank test) (e-Table 3, Fig 3). During follow-up, incident hypertension and heart failure occurred significantly less frequently in patients with OSA who continued vs terminated CPAP therapy (e-Table 3, Fig 4). In addition, a trend toward a lower risk of new hospitalizations for diabetes in the therapy continuation vs therapy termination group was found ($P = .06$) (e-Table 3, Fig 4). Sensitivity analysis that excluded patients censored for death during the analysis period yielded similar results to the primary analysis (e-Fig 4).

Discussion

The results of this analysis of a comprehensive, unbiased national dataset showed a significant association between continuation of CPAP during the first year of therapy and lower all-cause mortality. One potential mechanism underlying this association may be the lower rate of incident heart failure seen in the group who continued CPAP compared with those who terminated CPAP therapy. In our main analysis, only patients who survived long-enough to discontinue the use of CPAP were included. As such, patients who either had died, had < 1 year of follow-up, or who discontinued CPAP during the first year were used for propensity score matching, but were not included in the main all-cause mortality analysis. To avoid potential selection bias resulting from arbitrarily splitting the dataset into two groups that were not created at baseline, we performed a sensitivity analysis using CPAP termination as a time-dependent covariate and evaluated its association with overall survival. The results of this sensitivity analysis confirmed and strengthened the study findings by showing that there was a 27% reduction in all-cause mortality in patients who continued CPAP.

Our findings contrast with those of randomized controlled trials evaluating the effects of CPAP on mortality. The Sleep Apnea Cardiovascular Endpoints (SAVE) study, the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome—Effect of Intervention With CPAP study, and the Randomized Intervention with Continuous Positive Airway Pressure in CAD [coronary artery disease] and OSA study investigated the effects of CPAP on a composite end point that included cardiovascular death and nonfatal cardiovascular events.[11-13] All found no significant difference between the CPAP and usual care groups with respect to the primary end point or for cardiovascular death alone as a secondary end point.[11-13] However, several factors may have limited the ability of these studies to detect any statistically significant effect of CPAP on mortality.

First, adherence to treatment was low (3.3 ± 2.3 h/night in SAVE and 2.78 ± 2.73 h/night in the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome—Effect of Intervention With CPAP study),[11,13] and these levels of adherence do not seem to reflect what is seen with CPAP use in broader clinical settings.[16,17] Device use of ≥ 4 h/night may be needed

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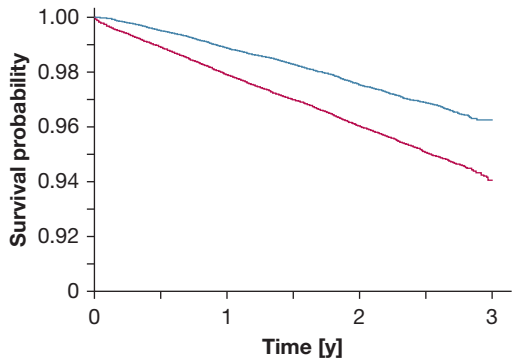

No. at risk				
CPAP therapy termination	88,007	78,025	38,844	0
CPAP therapy continuation	88,007	83,514	41,232	0
All patients	176,014	161,539	80,076	0

CPAP therapy termination
CPAP therapy continuation

Figure 2 – *Kaplan-Meier curves showing all-cause mortality.*

for the benefits of therapy to be realized.[12,18] For example, in the Randomized Intervention with Continuous Positive Airway Pressure in CAD [coronary artery disease] and OSA study, a preplanned analysis in patient subgroups using CPAP for ≥ 4 h/night vs < 4 h/night showed that those using CPAP for ≥ 4 h/night had a significantly lower rate of composite end point events, including mortality (adjusted HR, 0.29; 95% CI, 0.10-0.86; $P = .026$).[12] Furthermore, in the SAVE study, patients with OSA who were adherent to CPAP therapy showed a lower risk of stroke and the composite end point of cerebral events than those in the usual care group.[11] Second, the trials included highly selected patient populations, namely nonsleepy patients with OSA with existing cardiovascular disease. In particular, the noninclusion of patients with excessive daytime sleepiness from randomized controlled trials for ethical reasons might exclude a group likely to adhere and respond well to CPAP therapy.[19] Recently, a comparison was made between consecutive sleep clinic patients (n = 3,965) and participants in the prominent recent randomized controlled trials examining the effect of CPAP on adverse cardiovascular outcomes in OSA.[20] Less than 20% of real-world patients with OSA assembled the eligibility criteria of randomized controlled trials, and routine clinic patients with OSA were younger, sleepier, and more likely to be women.[20] Finally, the total number of mortality events in each study was very small (25 in the CPAP group and 20 in the usual care group in the SAVE study, and 12 in the CPAP group and 14 in the usual care group in the Impact of Sleep Apnea Syndrome in the Evolution of Acute Coronary Syndrome—Effect of Intervention With CPAP study), limiting statistical power for this end point.

In contrast, the current analysis included all patients with OSA in France with an indication for CPAP therapy, making it applicable to general populations, and the large number of deaths provides adequate power for mortality analyses. Furthermore, differentiating between patients who continued using CPAP and those who did not provides a clearer picture of the benefits of CPAP use. Thus, although randomized controlled trials provide the highest level of evidence, real-world data may provide a better indication of overall effectiveness in patient populations likely to be encountered in routine clinical practice. Others also recently suggested that design features and enrolled populations in randomized controlled trials of CPAP therapy in patients with OSA limit the ability of these trials to identify the benefits of treatment.[21] Contrary to classical observational studies with exposed and unexposed patients, the discontinuation design provides a more homogeneous initial study population on which the applied propensity score matching further limits unmeasured bias. Specifically, it recently was suggested that observational studies using propensity scores can overcome the ethical limitations around inclusion of patients with sleep apnea who experience excessive daytime sleepiness into randomized controlled trials.[22] The US Food and Drug Administration also has indicated that studies using propensity score methods are appropriate to support approval of medical devices such as CPAP.[23]

Two other recent real-world studies also reported a significant association between CPAP use and lower all-cause mortality.[24,25] Similar to our approach, a retrospective analysis of patients from a sleep clinic in Japan used propensity score matching to create two study populations of patients with OSA, in this case, those who used CPAP and those who did not. After a median follow-up of 6 to 7 years, the all-cause mortality rate was significantly lower in those who did vs did not use CPAP (4.2% vs 7.4%; HR, 0.56; 95% CI, 0.41-0.78).[25] This approximate doubling of all-cause mortality risk in patients with OSA not using CPAP was similar to that in

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our study for patients who stopped vs continued CPAP therapy.

The comparison group in a population-based longitudinal study from Spain was patients without OSA, who were found to be at significantly higher risk of all-cause death than patients with OSA prescribed CPAP after adjustment for comorbidities and previous health-care resource use (HR, 0.44 [95% CI, 0.36-0.54] in men and 0.44 [95% CI, 0.28-0.68] in women).[24]

In an earlier study, Woehrle et al[26] analyzed a large German health-care database and found that patients who received a diagnosis of sleep apnea and were treated with CPAP showed a significantly lower all-cause mortality rate after 3 and 4 years of follow-up compared with control participants who had a diagnosis of sleep apnea, but were not treated with CPAP. Our findings are consistent with those of the German study, which also used propensity score matching to generate the two study groups. However, our sample size is substantially larger and the source of participants more comprehensive than previous similar studies.

A large retrospective cohort study of Medicare beneficiaries with newly diagnosed heart failure found that those who were screened for and had a diagnosis of sleep-disordered breathing (SDB) and were treated with CPAP were significantly less likely to die over 2 years of follow-up than those screened for and with a diagnosis of sleep-disordered breathing who were not treated with CPAP (HR, 0.49; 95% CI, 0.29-0.84).[27] These data highlight an important link between sleep-disordered breathing and heart failure that is reflected in our study finding that patients who continued CPAP therapy during the first year were significantly less likely to demonstrate incident heart failure than those who terminated therapy. This result is consistent with a recent study showing a significant association between hypoxic burden and the rate of incident heart failure in patients with OSA.[28]

A link between CPAP use and lower mortality also was identified in a prospective cohort study from the United Kingdom.[29] Patients with OSA syndrome who were treated with CPAP for > 5 years were significantly more likely to be alive at the end of the study (mean follow-up, 14.8 ± 3.7 years), with a relative risk for survival of 5.63 (95% CI, 4.83-6.58; $P < .001$). Similarly, patients who did not adhere to CPAP therapy in the first year of therapy were at higher risk of death over the subsequent median 2.4-year follow-up period (adjusted HR, 1.74; 95% CI, 1.32-2.28) in a Swedish national registry-based cohort

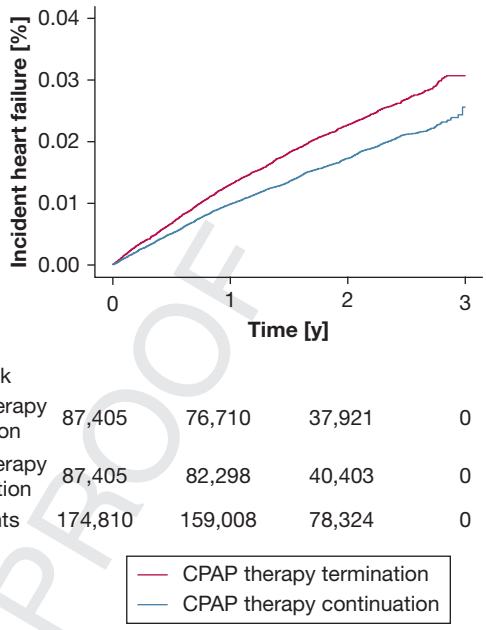

Figure 3 – *Line graph showing cumulative incidence of heart failure.*

study.[30] Health system data from Catalan, Spain, also showed a reduction in population-level mortality with CPAP treatment, but this effect was seen only in men.[31] This contrasts with our study, where reductions in mortality were seen consistently in both men and women.

Although we do not currently have precise data on the specific causes of death in our study (the database includes date of death, but not the cause), based on the information available, it seemed that incident hypertension and heart failure potentially were important contributors to death in the group of patients who terminated CPAP therapy. In two other recent real-world studies, the association between CPAP nonuse and mortality seemed to be driven largely by malignancy-related deaths.[24,25] However, these studies had a longer duration of follow-up (median, 5.5-6.5 years)[24,25] compared with only 3 years for our analysis. Longer follow-up durations also have been used in studies evaluating the link between OSA and cancer.[32-34]

The significant negative impact of terminating CPAP therapy in the first year highlights the importance of strategies to improve adherence to, and continuation with, CPAP. A personalized medicine approach using telemedicine-based support programs already has been shown to improve positive airway pressure use and to reduce the number of patients terminating therapy in real-world settings.[35,36] Therefore, implementation of these strategies and the associated improvement in

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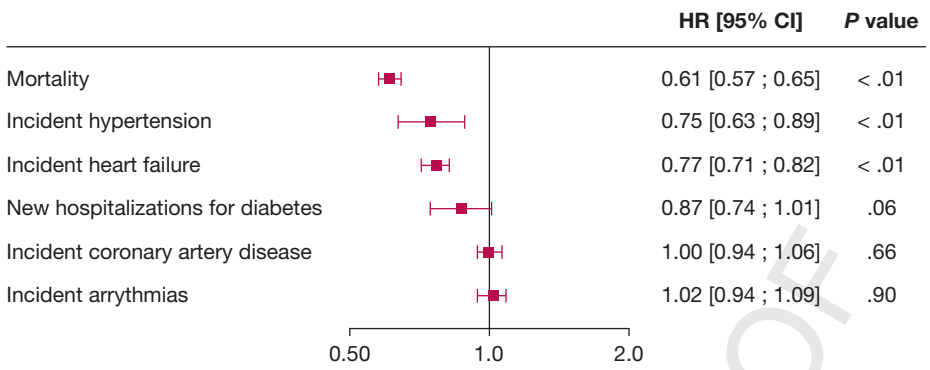

Figure 4 – *Forest plot showing risk of all-cause mortality and factors potentially contributing to death. HR of < 1 indicates a lower risk with CPAP continuation. HR = hazard ratio.*

CPAP continuation rates have the potential to impact positively on death rates. However, additional prospective studies are needed to determine the effects of different telemonitoring programs and patient engagement tools on hard clinical end points, including mortality.

The database used is an important strength of this study. The French SNDS is currently one of the best anonymized claims databases in the world because of its size (600 TB) and its unbiased recruitment (including > 99% of the total French population). It is not specific to any insurer, health-care provider, or CPAP device brand. In addition, we performed careful and extended propensity score matching to ensure comparability between the CPAP termination and CPAP continuation groups, and a large number of mortality events were available for analysis (n = 5,257).

Several limitations also need to be considered when interpreting the study findings. As has been highlighted previously,[14,36,37] several weaknesses exist in databases that are designed for administrative purposes, rather than clinical research, including a lack of data for some potentially important parameters. In the context of this study, that means that no apnea-hypopnea index data are available, so OSA severity is unknown. However, the fact that all patients fulfilled the criteria for initiation of CPAP provides some indication that OSA was at least moderate in severity. Also some limitations of propensity score matching in this context exist because it was a post hoc process based on available information only, meaning that we do not have data to allow propensity matching on important covariates that might modify the relationship between OSA exposure and outcomes, such as OSA severity, sleepiness, health behaviors, adherence data, and BMI. Several studies have addressed the link between sleepiness phenotypes, OSA severity (ie, hypoxic burden), and incident cardiovascular events.[19,38] Contrary to general population cohorts, in routine real-world practice, symptom subtypes were not associated with major adverse cardiovascular events after adjustment for confounders.[38] Because our data did not include measurements of sleepiness and hypoxic burden, we did not account for these confounders in our propensity matching. Therefore, potentially relevant covariates such as nutrition, physical activity, and sleep duration (all of which potentially are linked with mortality) were not included. In addition, because of French privacy requirements, the SNDS does not contain data on smoking habits, alcohol intake, or BMI. Furthermore, we do not have any data about the actual hours of CPAP use because the database defines CPAP use as a binary parameter (yes or no). In the future, it may be possible to link SNDS records with CPAP telemonitoring data and to link individual anthropometric and lifestyle profiles, which would allow investigation of the dose-response relationship between CPAP adherence and mortality.

Interpretation

This study showed that continued use of CPAP during the first year after therapy initiation is associated with a significant reduction in mortality in a large national cohort of patients with OSA compared with CPAP therapy termination. This finding adds to a growing body of evidence for the beneficial effects of CPAP use on survival. Additional research is needed to clarify the impact of CPAP on specific causes of death and to determine the relationship between hours of CPAP use and mortality benefit.

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