Electrophysiology

Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation—Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

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Background Obstructive sleep apnea (OSA) is common in patients with atrial fibrillation (AF). Little is known about the impact of OSA on AF treatment and long-term outcomes. We studied whether patients with OSA have a greater likelihood of progressing to more persistent forms of AF or require more hospitalizations and/or worse outcomes compared with patients without OSA.

Methods A total of 10,132 patients were enrolled between June 2010 and August 2011 in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) and followed for up to 2 years. The prevalence of OSA and continuous positive airway pressure (CPAP) treatment was captured at baseline. The association between OSA and major cardiovascular outcomes was analyzed using multivariable hierarchical logistic regression modeling and Cox frailty regression model.

Results Of the 10,132 patients with AF, 1,841 had OSA. Patients with OSA were more symptomatic (22% vs 16% severe/disabling symptoms; $P < .0001$) and more often on rhythm control therapy (35% vs 31%; $P = .0037$). In adjusted analyses, patients with OSA had higher risk of hospitalization (hazard ratio [HR], 1.12; 95% CI, 1.03-1.22; $P = .0078$), but no difference in the risks of death (HR, 0.94; 95% CI, 0.77-1.15; $P = .54$); the composite of CV death, myocardial infarction, and stroke/transient ischemic attack (HR, 1.07; 95% CI, 0.85-1.34; $P = .57$); major bleeding (HR, 1.18; 95% CI, 0.96-1.46; $P = .11$); or AF progression (HR, 1.06; 95% CI, 0.89-1.28; $P = .51$). Patients with OSA on CPAP treatment were less likely to progress to more permanent forms of AF compared with patients without CPAP (HR, 0.66; 95% CI, 0.46-0.94; $P = .021$).

Conclusion Compared with those without, AF patients with OSA have worse symptoms and higher risks of hospitalization, but similar mortality, major adverse cardiovascular outcome, and AF progression rates.

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Obstructive sleep apnea (OSA) has been shown to be independently associated with increased cardiovascular morbidity, including hypertension, congestive heart failure, ischemic heart disease, and stroke.[1-3] Patients with OSA have a higher prevalence of atrial fibrillation (AF) than patients without OSA,[4-7] and patients with OSA are more likely to develop new-onset AF, independent of obesity.[7] Obstructive sleep apnea is also associated with an increased risk of AF after coronary bypass surgery, higher recurrence rates of AF after cardioversion, and higher relapse rates of AF after AF catheter ablation.[8-16]

Although patients with OSA have been shown to have higher rates of cardiovascular morbidity than patients without OSA,[1,2] whether ambulatory patients with AF

and OSA experience greater AF progression or worse outcomes than those without OSA remains unknown. Furthermore, although preliminary data indicate that continuous positive airway pressure (CPAP) treatment may be associated with lower recurrence rates of AF after cardioversion,[14] the broader impact of CPAP treatment on outcomes in patients with AF is largely unknown. Therefore, the objectives of this study were (1) to define the frequency of diagnosed OSA among a nationwide AF population; (2) to determine whether OSA is associated with worse outcomes including hospitalizations, AF complications, and survival; (3) to characterize whether OSA is associated with arrhythmic progression of AF; and (4) to determine whether CPAP treatment is associated with outcomes in patients with AF and OSA.

Methods

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) is a contemporary registry of outpatients in the United States with AF. Its design has been described in detail elsewhere.[17] In brief, a nationally representative sample of sites was invited to participate, and an adaptive design was used to ensure provider and geographic heterogeneity. Consecutive patients with AF meeting the inclusion criteria (at least 18 years of age, electrocardiographic evidence of AF, providing informed consent) and none of the exclusion criteria (life expectancy of <6 months or AF secondary to reversible conditions) were enrolled.

Data collection included demographics, past medical history, type of AF and prior interventions, ongoing antithrombotic therapy, vital signs, laboratory studies, and electrocardiographic and echocardiographic findings. The prevalence of clinician-defined OSA (ie, diagnosis or history of OSA) at baseline and CPAP treatment ("currently undergoing CPAP therapy") was captured. In ORBIT-AF, follow-up data collection occurs at 6-month intervals for a minimum of 2 years. Two-year outcomes were analyzed in this cohort study.

Paroxysmal AF was defined as recurrent AF episodes that terminate spontaneously within 7 days; persistent AF as recurrent AF that is sustained for more than 7 days; and permanent AF as AF in which the presence of the AF is accepted.[18] Progression in AF type was considered as a binary outcome (either "the same/better" or "worsening"); worsening was defined as (1) paroxysmal AF at baseline (or "first detected/new onset" AF becoming paroxysmal AF at next available follow-up) becoming persistent or permanent at the last follow-up visit or (2) persistent AF at baseline (or "first detected/new onset" AF becoming persistent AF at next available follow-up) becoming permanent at the last follow-up visit.[19]

The baseline ORBIT-AF population included 10,132 patients enrolled between June 2010 and August 2011 from 176 sites. Data on CPAP treatment were lacking in 4 patients, yielding a study population of 1,837 patients with OSA for the analyses regarding CPAP. For the outcomes analysis for patients with OSA vs patients with no OSA, patients without any follow-up data were excluded (n = 490). For the outcomes analysis for CPAP treatment vs no CPAP treatment, patients without any follow-up data (n = 78) and patients from sites with less than 6 patients were excluded (n = 135) from the analysis. Sites with less than 6 patients were excluded because these sites had too little information to make within-site comparisons and therefore caused model convergence problems. The exclusion was necessary for the adjusted analysis and was implemented in the unadjusted analysis as well, for consistency. Data are presented as frequencies and percentages for categorical variables and medians (interquartile range) for continuous variables. Groups are compared using the χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables.

To examine both the unadjusted and adjusted association between OSA and each of the 4 outcomes (all-cause death; first all-cause hospitalization; the composite of first event of cardiovascular death, stroke/non–central nervous system embolism, transient ischemic attack [TIA], or myocardial infarction; first major bleed) within 2 years of baseline enrollment in the registry, a multivariable Cox frailty regression model that accounts for the variability in outcomes between sites was used. For each outcome, backward selection with stay criteria of $P < .05$ for candidate variables, a prespecified candidate variable list was performed on the first imputed dataset to construct the Cox frailty regression model. All continuous variables were evaluated for nonlinearity with the outcome, and those that did not meet the linear relationship criteria ($P < .05$) were accounted for using linear splines. Missing data were multiply imputed, and final estimates and standard errors reflect the combined analysis over 5 imputed datasets. For AF progression, a multivariable hierarchical logistic regression model was fit including site as a random effect. The same model construction method described for the aforementioned outcomes was used to construct the model for AF progression. Hazard ratio/odds ratio (HR/OR) with corresponding 95% CI and P value are presented.

To explore the CPAP treatment effect in OSA on outcomes, the treatment effect was adjusted for treatment selection bias via propensity score stratification. The predicted probability of receiving treatment for individuals, given their patient characteristics and site participation, was obtained. Because site was included as a fixed effect to obtain the propensity scores, we excluded patients from small sites (patients from sites with <6 patients) from the analysis to obtain stable estimates. The propensity scores were then stratified into quintiles. These quintiles formed strata in the final Cox proportional hazard model that accounted for variability in outcomes between sites for all the outcomes except

Table I. Baseline characteristics by OSA

	Overall	No OSA	OSA	
	(N = 10,132)	(n = 8291)	(n = 1841)	*P*
Age, y	75 (67-82)	76 (68-82)	69 (62-77)	<.0001
Male	58	55	69	<.0001
Race				
White	89	89	88	.0004
Black or African American	5.0	4.6	6.7	
Hispanic	4.2	4.4	3.2	
Other	1.4	1.4	1.5	
Medical history				
Hypertension	83	82	87	<.0001
Hyperlipidemia	72	71	76	<.0001
Diabetes	29	27	42	<.0001
Chronic obstructive pulmonary disease	16	15	25	<.0001
Prior myocardial infarction	16	16	16	.69
Heart failure	33	31	40	<.0001
Valvular disease	25	26	22	.0002
Peripheral vascular disease	13	13	13	.91
Prior cerebrovascular events	16	16	16	.76
Stroke (all-cause)	8.9	9.0	8.3	.36
Nonhemorrhagic	8.0	8.1	7.2	.21
Hemorrhagic	0.8	0.8	0.8	.99
Other intracranial bleeding	0.9	1.0	0.8	.41
Gastrointestinal bleeding	9.0	8.8	10	.0343
Cognitive impairment or dementia	3.1	3.1	2.9	.60
Frailty	5.8	6.1	4.3	.0029
Smoking	48	47	55	<.0001
Alcohol abuse	4.0	3.7	5.5	.0004
BMI, kg/m^2	29 (25-34)	28 (25-32)	34 (29-40)	<.0001
Systolic blood pressure, mm Hg	126 (116-138)	126 (116-138)	125 (116-136)	.85
Diastolic blood pressure, mm Hg	72 (66-80)	72 (66-80)	73 (68-80)	.0033
Left ventricular ejection fraction >50%	70	70	72	.96
Left atrial diameter, cm	4.4 (3.9-5.0)	4.4 (3.9-5.0)	4.6 (4.1-5.1)	<.0001

Continuous variables are presented as median and inter-quartile range.

AF progression. Because AF progression was a binary outcome, the quintiles formed strata in a logistic regression model that was fit by generalized estimating equations with a compound symmetric correlation structure to reflect clustering within sites. Both unadjusted and adjusted HR/OR were obtained using methods to account for clustering within sites. Corresponding 95% CI and *P* value are presented for the association between CPAP and outcomes. The list of candidate variables for all analyzed outcomes is provided in the online Appendix Supplementary material.

All statistical analyses of the aggregate, deidentified data were performed by the Duke Clinical Research Institute using SAS software (version 9.3, SAS Institute, Cary, North Carolina). All *P* values were 2 sided. The Duke Clinical Research Institute was the central coordinating and statistical center for the ORBIT-AF registry, to which deidentified data were sent from the sponsor for statistical analysis. The ORBIT-AF Registry is approved by the Duke Institutional Review Board (approval number Pro00017596), and all participating sites obtained institutional review board approval pursuant to local requirements. All subjects provided written, informed consent.

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The ORBIT-AF registry is sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ.

Results

Of 10,132 patients enrolled in ORBIT-AF, 18% (n = 1,841) had OSA at baseline. Table I shows the baseline characteristics overall and by the presence of OSA. Patients with OSA were younger (69 [62-77] vs 76 [68-82] years; $P < .0001$), more often male (69% vs 55%; $P < .0001$), and had more comorbidities than patients without OSA, including a greater frequency of a history of heart failure, hypertension, diabetes, and hyperlipidemia. Patients with OSA were more likely to have a history of smoking and had a higher prevalence of chronic obstructive pulmonary disease. The body mass

Table II. Atrial fibrillation history by OSA

	Overall	No OSA	OSA	
	(N = 10,132)	(n = 8291)	(n = 1841)	*P*
AF type				
First detected/new onset	4.7	5.0	3.7	.043
Paroxysmal	51	51	50	
Persistent	17	17	18	
Permanent	28	28	28	
Family history of AF	15	14	17	.0091
Duration of AF diagnosis, m	47 (17-93)	47 (17-94)	46 (18-91)	.92
Sinus rhythm on most recent ECG	33	33	34	.93
EHRA symptom level				
No symptoms	38	39	33	<.0001
Mild	45	45	45	
Severe	15	14	19	
Disabling	1.8	1.7	2.7	
$CHADS_2$ risk groups				
0	6.4	6.6	5.3	.73
1	22	22	23	
≥2	72	72	72	
CHA_2DS_2-VASc score (mean ± SD)	3.9 ± 1.8	4.0 ± 1.8	3.7 ± 1.8	<.0001
Prior treatment				
Oral anticoagulation therapy	82	81	85	<.0001
Antiarrhythmic drug	45	44	52	<.0001
Prior cardioversions	30	28	38	<.0001
Prior catheter ablation of AF	5.5	5.0	7.7	<.0001
Current treatment				
Oral anticoagulation therapy	76	75	79	.0020
Antiarrhythmic drug	29	28	33	<.0001
Rhythm strategy	32	31	35	.0037

Continuous variables are presented as median and inter-quartile range. Abbreviation: EHRA, European Heart Rhythm Association

index (BMI) of patients with OSA was higher than in patients without OSA (34 [29-40] vs 28 [25-32] kg/m^2; $P <$ .0001), their left atria larger (left atrial diameter, 4.6 [4.1-5.1] vs 4.4 [3.9-5.0] cm; $P <$ .0001), and the diastolic blood pressure higher.

Table II summarizes the baseline AF characteristics. Patients with OSA were more symptomatic than patients without OSA (22% vs 16% with severe or disabling symptoms; $P <$ .0001). Patients with OSA were more frequently managed with a rhythm-control strategy (35% vs 31%; $P =$ .0037) and consequently were more frequently taking an antiarrhythmic drug (33% vs 28%; $P <$ .0001). They were also more likely to have a history of prior cardioversion (38% vs 28%; $P <$ .0001). There was no difference in the percentage of patients with or without OSA in sinus rhythm on baseline ECG (34% vs 33%; $P =$ .93). Despite similar $CHADS_2$ score, patients with OSA were more often receiving anticoagulation prophylaxis at baseline (79% vs 75%; $P =$ .0020).

Table III summarizes the associations between the outcome variables and OSA. Patients with OSA had higher risk of hospitalization during 2-year follow-up (43 vs 35 events/100 patient-years during follow-up among patients without OSA; adjusted HR, 1.12; 95% CI, 1.03-1.22; $P =$ .0078). In contrast, the risk of death and the composite of cardiovascular death, myocardial infarction, and stroke/TIA as well as major bleeding were similar in both groups. During follow-up, AF progression occurred in 221 (18% of patients with nonpermanent AF at baseline) of the patients with OSA and 984 (18%) of the patients without OSA (adjusted HR, 1.06; 95% CI, 0.89-1.28; $P =$ .51).

Table IV and Figure summarizes the associations between the outcome variables and CPAP treatment in patients with OSA. Of the patients with OSA, 1,067 (58%) were treated with CPAP. Patients with CPAP treatment were younger (68 [62-76] vs 71 [64-78] years; $P <$ .0001), more often male (72% vs 64%; $P =$ .0004), and had a higher BMI (36 [31-41] vs 32 [28-38] kg/m^2; $P <$ .0001) than patients without CPAP treatment. Furthermore, they more often had diabetes mellitus (44% vs 39%; $P =$ .043), but the prevalence of valvular disease was lower (20% vs 24%; $P =$ .042).

In unadjusted and adjusted analyses of patients with OSA, no significant difference in risk was observed between patients on CPAP treatment compared with those not on CPAP for most of the outcomes. The one exception was that a smaller proportion of the patients on CPAP treatment progressed in their AF (16% of patients

Table III. Association of OSA and 2-year outcomes

Outcome	OSA (n = 1763) No. of events (events/100 patient-years)	No OSA (n = 7879) No. of events (events/100 patient-years)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
All-cause death	127 (4.45)	672 (5.35)	0.83 (0.68-1.01)	.057	0.94 (0.77-1.15)	.54
First hospitalization (all-cause)	866 (43.3)	3,324 (35.0)	1.17 (1.09-1.27)	<.0001	1.12 (1.03-1.22)	.0078
CV death, MI, stroke/TIA	106 (3.77)	494 (3.99)	0.96 (0.75-1.15)	.51	1.07 (0.85-1.34)	.57
Major bleeding	123 (4.47)	463 (3.79)	1.18 (0.96-1.44)	.12	1.18 (0.96-1.46)	.11
	OSA (n = 1223)	No OSA (n = 5349)				
Outcome	No. of events (percent)	No. of events (percent)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Progression of AF type	221 (18)	984 (18)	1.05 (0.88-1.24)	.60	1.06 (0.89-1.28)	.51

Adjusted HRs are calculated using Cox frailty models for all outcomes except the association between OSA and progression of AF, where logistic regression was used to calculate the associated OR. Abbreviation: CV, Cardiovascular; MI, myocardial infarction.

with nonpermanent AF at baseline) compared with the patients not on CPAP treatment (18%; adjusted HR, 0.66; 95% CI, 0.46-0.94; $P = .021$).

Discussion

Nearly 1 in 5 patients with AF in ORBIT-AF carries a diagnosis of OSA. Patients with OSA have worse functional status and slightly higher risks of hospitalization, but similar rates of mortality, AF progression, and major adverse cardiovascular events as patients without OSA. No major differences in hospitalization or cardiovascular outcomes were observed between patients with OSA with or without CPAP treatment; however, AF progression was less common in patients treated with CPAP.

Although a large proportion of patients in ORBIT-AF had diagnosed OSA, the observed 18% is substantially lower than reported in some of the previously published literature on both AF and non-AF populations.[6] This may reflect the fact that ORBIT-AF relies entirely on a history of previously diagnosed OSA; the true prevalence may well have been higher if all patients had been screened with standardized criteria or routine polysomnography. However, it is also possible that the observed prevalence in the ORBIT-AF population more accurately reflects a community-based unselected AF patient population. Not surprisingly, patients with OSA in this study were more frequently male and had a substantially higher BMI than patients without OSA, consistent with the known major risk factors for OSA.[5,20] In addition, a higher prevalence of several diseases (eg, hypertension, congestive heart failure, diabetes) was seen in patients with OSA, compatible with the previously described increased prevalence of cardiovascular diseases in patients with OSA.[1,2,21]

Patients with AF have an increased risk of OSA and vice versa.[4–7] Although OSA and AF have many common risk factors, OSA is an important predictor of new-onset AF, independent of comorbid conditions including obesity.[7,22] Similarly, obesity alone is associated with a higher risk of AF progression (paroxysmal to permanent).[22] Moreover, OSA has also been shown to be associated with more recurrent and symptomatic AF.[13–16] Indicative of a more "aggressive" form of AF, patients with OSA in this study were more symptomatic, had a history of more previous cardioversions and catheter ablations, and more often had been or were currently receiving antiarrhythmic drugs and rhythm control strategy. Despite more frequent use of ablation, antiarrhythmic medications, and the rhythm control strategy, there were no differences in the rates of sinus rhythm at baseline or AF progression during follow-up between patients with and without OSA.

Although patients with OSA have been shown to have higher rates of cardiovascular morbidity than patients without OSA,[1,2] longitudinal outcomes in patients with AF and OSA are lacking. In this study, patients with OSA did have a higher risk of hospitalization compared with AF patients without OSA. The overall hospitalization rate in ORBIT-AF patients was high (about 48% at 2 years) and was even higher (almost 54%) in patients with OSA. However, mortality rates and major adverse cardiovascular events and major bleeding were similar to the risk in patients without OSA. Hence, no difference in major adverse cardiovascular events was seen in patients with or without OSA in this study, and a direct causal effect of OSA in cardiovascular disease remains questionable.[21,23] Similarly, AF did not appear to progress to more persistent/sustained forms more frequently in patients with OSA compared to patients without OSA.

Table IV. Association of CPAP treatment and 2-year outcomes

Outcome	CPAP (n = 937) No. of events (events/100 patient-years)	No CPAP (n = 687) No. of events (events/100 patient-years)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
All-cause death	68 (4.44)	54 (4.86)	0.92 (0.67-1.25)	.58	1.10 (0.78-1.54)	.60
First hospitalization (all-cause)	471 (43.9)	329 (41.9)	1.05 (0.93-1.18)	.42	1.10 (0.97-1.24)	.14
CV death, MI, stroke/TIA	57 (3.78)	41 (3.73)	1.02 (0.68-1.52)	.94	1.15 (0.73-1.82)	.55
Major bleeding	71 (4.81)	43 (3.99)	1.20 (0.85-1.71)	.29	1.45 (0.99-2.11)	.06
Outcome	CPAP (n = 602) No. of events (percent)	No CPAP (n = 411) No. of events (percent)	Unadjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Progression of AF type	94 (16)	75 (18)	0.74 (0.55-0.99)	.04	0.66 (0.46-0.94)	.02

Abbreviation: CV, Cardiovascular; MI, myocardial infarction.

Patients with OSA were more often receiving anticoagulation prophylaxis at baseline in ORBIT AF. This is most likely due to the fact that patients with OSA had more cardiovascular comorbidity (eg, hypertension and diabetes) and therefore perceived to be at higher risk of stroke, although their lower age and male predominance actually led to similar $CHADS_2$- and lower CHA_2DS_2-VASc scores.

Apart from behavioral treatment (eg, weight loss, increased physical activity), CPAP treatment is the most common treatment for moderate-to-severe OSA.[24] The rate of CPAP usage in ORBIT-AF was 58% with only minor differences in patient characteristics between patients with and without CPAP treatment. Data on CPAP usage in similar registries are, to the best of our knowledge, lacking. However, given that CPAP treatment is primarily indicated for treatment of moderate to severe OSA and that the adherence to CPAP treatment is known to be low, we believe that 58% of the patients with OSA stating that they are "currently undergoing CPAP therapy" seems reasonable. Although several observational studies have indicated that CPAP treatment may be effective in reducing the cardiovascular event rate in patients with OSA, the observed effect in prospective/randomized studies has at best been modest.[6,21,25–27] Nonrandomized data regarding CPAP treatment of OSA and the likelihood of AF relapse after cardioversion indicate that CPAP is likely beneficial.[14] More recently, specific data regarding CPAP treatment in relation to AF relapse after catheter ablation of AF indicate that CPAP treatment may lower the relapse rate, but randomized comparisons are lacking.[10–12] In keeping with these data, a slightly smaller proportion of patients with OSA on CPAP treatment progressed to more sustained forms of AF in this study. However, there were no statistically significant differences in mortality rates and major adverse cardiovascular events between patients with OSA treated with CPAP and those without CPAP treatment.

Limitations

These data are from a voluntary, observational study and thus are susceptible to the limitations inherent in such methods. These include both selection and reporting biases. Residual measures and unmeasured confounding may influence these findings. Given that the number of test of primary interest was relatively limited, adjustment for multiple comparisons was not made to control type I error because this would have increased the risk of type II error. The diagnosis of OSA in these patients was made on the basis of physician report and medical records. We did not have access to sleep study data, including apnea-hypopnea indices. Likewise, we do not have data on average duration of CPAP use per night in patients on CPAP treatment. This study used 2-year follow-up. It is possible that the differences between OSA and non-OSA as well as between CPAP treated and nontreated patients with OSA would have become more evident over time. On the other hand, our study has several strengths, including a large nationwide cohort with regular follow-up and detailed information on comorbid illness.

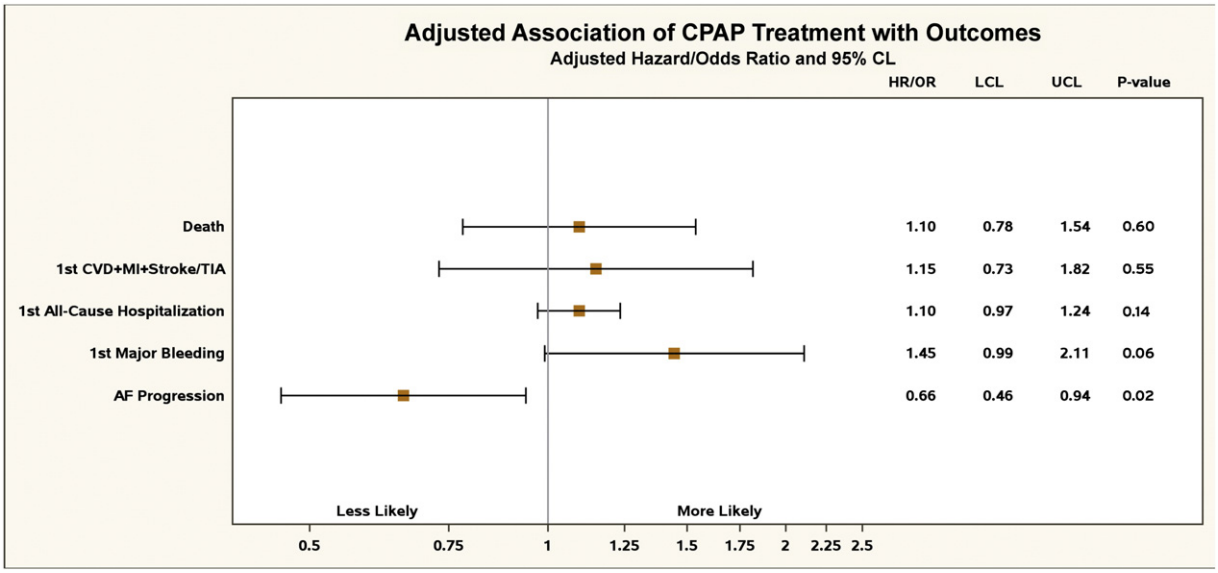
Clinical implications

The frequency of OSA in this nationwide cohort emphasizes the importance of screening for OSA in patients diagnosed with AF. Furthermore, once AF is identified, these data highlight the potential role of CPAP as a means to prevent AF progression and decrease AF burden. The role of CPAP in reducing AF burden is currently being evaluated in clinical trials.

Conclusion

Nearly 1 in 5 patients with AF in our nationally representative cohort study had OSA. Patients with OSA have worse functional status and a higher risk of hospitalization than patients without OSA. However, major adverse

Figure



The figure summarizes the adjusted associations between the outcome variables and CPAP treatment in patients with OSA. Abbreviations: CL, Confidence limit; CVD, cardiovascular death; LCL, lower confidence limit; MI, myocardial infarction; UCL, upper confidence limit.

cardiovascular events and all-cause mortality did not differ between patients with and without OSA. Similarly, AF in patients with OSA did not appear to progress more frequently to more persistent/sustained forms of AF. In patients with OSA, CPAP treatment may attenuate the rate of AF progression.

Author contributions

FH, JPP, and BJG contributed to the conception and design of the study and to the data analyses and interpretation. NG, ZZ, and DNH contributed to the acquisition of data and to data analyses and interpretation. PRK, LAA, GCF, EMH, KWM, JVF, PC, and EDP contributed to the conception and design of the study. All authors contributed to preparation of the manuscript and approved the final version. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Supplementary Appendix. Candidate Variable List for Outcome Models

Demographics

1. Age, years
2. Race—African American/Hispanic/White/others
3. Gender—male/female
4. Level of education—some school/high school graduate/college graduate/post graduate
5. Payor/insurance—Medicare or Medicaid/private/others

Medical history

1. Smoking—current/recent or former/nonsmoker
2. Cancer—yes/no
3. Hypertension—yes/no
4. Osteoporosis—yes/no
5. Diabetes—yes/no
6. Hip fracture—yes/no
7. Hyperthyroidism—yes/no
8. Hypothyroidism—yes/no
9. GI bleed—yes/no
10. OSA—yes/no
11. Dialysis—yes/no
12. Hyperlipidemia—yes/no
13. Anemia—yes/no
14. Cognitive impairment/dementia—yes/no
15. Frailty—yes/no
16. Liver disease—yes/no
17. COPD—yes/no
18. Alcohol abuse—yes/no
19. Drug abuse—yes/no

Cardiovascular history

1. Family history of AF—yes/no
2. Peripheral vascular disease—yes/no
3. Sinus node dysfunction/sick sinus syndrome—yes/no
4. Stroke or TIA—yes/no
5. Congestive heart failure (CHF)—no CHF/NYHA Class I/NYHA Class II/NYHA Class III or NYHA Class IV
6. Significant valvular disease—yes/no
7. Prior valve replacement/repair—yes/no

Coronary artery disease history

1. History of coronary artery disease—yes/no
2. Prior MI—yes/no
3. Prior CABG—yes/no
4. Any PCI—yes/no

Vital signs and AF status

1. Height, cm
2. Weight, kg
3. Heart rate, beat/min
4. Diastolic blood pressure, mm Hg
5. Systolic blood pressure, mm Hg
6. Body mass index, kg/m^2 (For imputation purpose, we will impute individual components which are weight, height)
7. Intraventricular conduction—RBBB/LBBB/nonspecific IVCD or unknown-ventricularly paced/none

Echocardiographic assessment (TTE or TEE)

1. LVEF—normal (>50%)/mild dysfunction (>40%, <50%)/moderate dysfunction (>30%, <40%)/severe dysfunction (<30%)
2. LAD type—normal/mild enlargement/moderate enlargement/severe enlargement

Laboratory data

1. eGFR (MDRD), mg/dL (For imputation purpose, we will impute individual components which are age, gender, race, and serum creatinine)
2. Hemotocrit, % (fill in from hemoglobin by hemoglobin*3 if missing)

Atrial fibrillation diagnosis

1. Type of AF—first detected or new onset/paroxysmal AF/persistent AF/permanent AF
2. EHRA score—no symptoms/mild/severe/disabling
3. Management strategy—rate control/rhythm control
4. Prior cardioversions—yes/no
5. Prior antiarrhythmic drug—yes/no
6. Catheter ablation of AF—yes/no
7. AV Node or HIS bundle ablation—yes/no

Functional status

1. Functional status—living independently/living with assistance or resides in assisted living facility or resides in skilled nursing home or bedbound

Provider or site

1. PI/site specialty—cardiology/electrophysiology/family practice or internal medicine

Covariates included in regression model for each outcome

All-cause death

- Level of education, rhythm control, cognitive impairment/dementia, hyperlipidemia, linear spline for eGFR ≤80 mg/dL, linear spline eGFR >80 mg/dL, LAD type, cancer, diastolic blood pressure truncated at 70, intraventricular conduction, frailty, height heart rate, hematocrit, diabetes, smoking, linear spline for systolic blood

pressure ≤120 mm Hg, COPD, BMI truncated at 30 kg/m², sex, CHF, age, and functional status

First all-cause hospitalization

- Linear spline forage ≤70 years, linear spline forage >70, years BMI, weight, osteoporosis, height, PCI, cancer, OSA, anemia, frailty, insurance status, history of CAD, PI/Site specialty, prior antiarrhythmic drug use, peripheral vascular disease, functional status, linear spline for heart rate >68 beat/min, diabetes, hematocrit, linear spline for eGFR ≤ 80 mg/dL, COPD, diastolic blood pressure truncated at 70 beat/min, EHRA score, and CHF

Composite of CVD death, stroke or non–central nervous system embolism, TIA or MI

- AF type, diabetes, history of CAD, BMI, LAD type, sex, height, diastolic blood pressure, AV node/HIS bundle ablation, LVEF type, COPD, stroke/TIA, CHF, functional status, eGFR and age

Major bleeding

- COPD, OSA, LAD type, cancer, functional status, level of education, intraventricular conduction, rhythm control, smoking status, significant valvular disease, eGFR, insurance status, history of GI bleed, anemia, and hematocrit

AF progression

- Catheter ablation, hypertension, congestive heart failure, cognitive impairment/dementia, history of drug abuse, systolic blood pressure, EHRA score, AV node/HIS bundle ablation, LAD type, age prior cardioversions rhythm control, and linear spline for heart rate between 66 and 88 beat/min