Title

Risk of major cardiovascular and neurologic events with obstructive sleep apnea among patients with atrial fibrillation

Authors

Dalgaard, Frederik
North, Rebecca
Pieper, Karen
et al.

Publication Date

2020-05-01

DOI

10.1016/j.ahj.2020.01.001

Peer reviewed

Published in final edited form as:

Am Heart J. 2020 May ; 223: 65–71. doi:10.1016/j.ahj.2020.01.001.

Risk of major cardiovascular and neurologic events with obstructive sleep apnea among patients with atrial fibrillation

Frederik Dalgaard, MD[a,b], **Rebecca North, MR**[c], **Karen Pieper, MS**[b], **Gregg C. Fonarow, MD**[d], **Peter R. Kowey, MD**[e], **Bernard J. Gersh, MB, ChB, D.Phil**[f], **Kenneth W. Mahaffey, MD**[g], **Sean Pokorney, MD**[b], **Benjamin A. Steinberg, MD, MHS**[h], **Gerald Naccarelli, MD**[i], **Larry A. Allen, MD**[j], **James A. Reiffel, MD**[k], **Michael Ezekowitz, MD**[l], **Daniel E. Singer, MD**[m], **Paul S. Chan, MD, MSc**[n], **Eric D. Peterson, MD, MPH**[b], **Jonathan P. Piccini, MD, MHS**[b]

[a]Department of Cardiology, Herlev and Gentofte Hospital, Copenhagen, Denmark,

[b]Duke Clinical Research Institute, Duke University, Durham, NC,

[c]Department of Statistics, North Carolina State University, Raleigh, NC,

[d]Department of Medicine, Division of Cardiology, Ahmanson-UCLA Cardiomyopathy Center, Ronald Reagan-UCLA Medical Center, Los Angeles, CA,

[e]Division of Cardiovascular Disease, Lankenau Heart Institute, Wynnewood, PA,

[f]Mayo Clinic College of Medicine, Rochester, MN,

[g]Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Palo Alto, CA,

[h]Department of Medicine, University of Utah, Salt Lake City, UT,

[i]Penn State Health Milton S. Hershey Medical Center, Penn State College of Medicine, Hershey, PA,

[j]University of Colorado School of Medicine, Aurora, CO,

[k]College of Physicians and Surgeons, Columbia University, New York, NY,

[l]Jefferson Medical College, Philadelphia, PA,

[m]Division of General Internal Medicine, Massachusetts General Hospital, Boston, MA,

[n]University of Missouri-Kansas City School of Medicine, Kansas City, MO. T. Jared Bunch, MD, served as guest editor for this article.

Abstract

Background—Obstructive sleep apnea (OSA) is a known risk factor for atrial fibrillation (AF). However, it remains unclear whether OSA is independently associated with worse cardiovascular and neurological outcomes in patients with AF.

Reprint requests: Jonathan P. Piccini, MD, MHS, Duke Clinical Research Institute, Morris St, Durham 27701, NC. Jonathan.piccini@duke.edu.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2020.01.001.

Methods—We used the ORBIT-AF I and ORBIT-AF II to conduct a retrospective cohort study of 22,760 patients with AF with and without OSA. Adjusted multivariable Cox proportional hazards models was used to determine whether OSA was associated with increased risk for major adverse cardiac and neurologic events (MACNEs) (cardiovascular death, myocardial infarction, stroke/transient ischemic attack/non–central nervous system embolism (stroke/SE), and new-onset heart failure], combined and individually.

Results—A total of 4,045 (17.8%) patients had OSA at baseline. Median follow-up time was 1.5 (interquartile range: 1–2.2) years, and 1,895 patients experienced a MACNE. OSA patients were younger (median [interquartile range] 68 [61–75] years vs 74 [66–81] years), were more likely male (70.7% vs 55.3%), and had increased body mass index (median 34.6 kg/m^2 [29.8–40.2] vs 28.7 kg/m^2 [25.2–33.0]). Those with OSA had a higher prevalence of concomitant comorbidities such as diabetes, chronic obstructive pulmonary disease, and heart failure. OSA patients had higher use of antithrombotic therapy. After adjustment, the presence of OSA was significantly associated with MACNE (hazard ratio: 1.16 [95% CI: 1.03–1.31], $P = .011$). OSA was also an independent risk factor for stroke/SE beyond the CHA_2DS_2-VASc risk factors (HR: 1.38 [95% CI 1.12–1.70], $P = .003$) but not cardiovascular death, myocardial infarction, new-onset heart failure, or major bleeding.

Conclusions—Among patients with AF, OSA is an independent risk factor for MACNE and, more specifically, stroke/SE.

Obstructive sleep apnea (OSA) is characterized by recurrent partial or complete collapse of the upper airway leading to frequent interruption of respiration and sleep. During the last 2 decades, OSA has been recognized as an increasingly common condition occurring in up to 17% of men and 10% of women aged between 50 and 70 years.[1,2] OSA is also a known risk factor for developing and exacerbating multiple cardiovascular diseases including atrial fibrillation (AF).[3–8]

In patients with AF, OSA has been shown to be associated with a higher risk of recurrent AF after catheter ablation and cardioversion,[9,10] an increased risk of AF progression,[11] and reduced effectiveness of antiarrhythmic drug therapy.[12] To date, few observational studies of patients with AF have investigated whether those with OSA are at increased risk of ischemic cardiovascular or neurological events, and results, to date, have been conflicting.[11,13,14]

We sought to determine if OSA is independently associated with an increased risk of cardiovascular and neurologic events. We specifically wished to address (1) the prevalence of OSA in community-treated AF patients, (2) the characteristics and treatment patterns of those with OSA compared to those without OSA, and (3) if the presence of OSA contributed to increased risk of major cardiovascular and neurologic events.

Methods

The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF I) and ORBIT-AF II are 2 prospective multicenter nationwide registries that enrolled patients with incident and prevalent AF across the United States. Recruiting physicians and sites included a heterogeneous group of health care professionals including internal medicine,

primary care physicians, general cardiologists, and electrophysiologists. The design and methods of these registries have been described in-depth elsewhere.[15,16] In brief, patients ≥18 years with an electrocardiogram of AF (≥21 years for ORBIT-AF II) that were able to adhere to follow-up visits and able to provide consent were eligible for inclusion. AF patients were excluded if any of these conditions were met: life expectancy b6 months, solitary atrial flutter without AF, or reversible secondary AF. Patients were followed by 6-month intervals, up to a maximum of 3 years for ORBIT-AF I and maximum of 2 years in ORBIT-AF II.

The ORBIT-AF I registry enrolled 10,137 patients from 176 sites between June 2010 and August 2011. The ORBIT-AF II registry enrolled 13,404 patients from 244 sites between February 2013 and July 2016. The patients' first visit during time of enrollment at a participating clinic was the baseline visit. For both registries, a Web-based case report form was used to obtain patient characteristics such as patient demographics, medical history, current pharmacotherapy, and clinical testing including ECG characteristics. In ORBIT II, QRS duration was also obtained. Follow-up data included cardiovascular events, bleeding events, hospitalizations, and mortality.

Patients enrolled in the ORBIT-AF I and ORBIT-AF II studies gave written informed consent, and sites received regulatory board approval pursuant to local regulations. The study was coordinated by the Duke Clinical Research Institute and approved by the Duke University Institutional Review Board.

Study cohort

This cohort study included 22,760 AF patients from ORBIT-AF I and ORBIT-AF II enrolled at 340 sites. We included all patients with data on baseline OSA status and with available follow-up data.

Definitions and outcomes

Patients were considered to have OSA at the enrolling clinician's personal discretion from the medical history. The prior diagnosis of OSA or the use of continuous positive airway pressure (CPAP), as defined by clinical personnel, was captured at baseline. The primary outcome was major adverse cardiac and neurologic event (MACNE), a composite outcome of cardiovascular death, myocardial infarction, stroke/transient ischemic attack/non–central nervous system embolism (stroke/SE), and new-onset heart failure. Secondary outcomes were the individual components of MACNE, major bleeding, and hospitalization for bleeding. For patients having an event, *time to event* was defined from the baseline enrollment visit date to the event date. Patients without an event were followed until death or last follow-up date.

Statistical analysis

Baseline characteristics, stratified by OSA status, were compared using the Wilcoxon rank-sum test for continuous variables and the approximate χ^2 test for categorical variables. Incidence rates were computed as number of events per 100-person years.

To assess the independent relationship between OSA and outcomes, Cox proportional hazards models were constructed. The proportional hazards assumption for OSA was assessed for each of the outcomes with the cumulative sums of the Martingale residuals,[17] and no major violations were found. Candidate variables for model inclusion and adjustments for each outcome are shown in Appendix 1. Covariates for adjustment were previously identified using a backward selection process with an α for inclusion of .05. A robust covariance estimate was included in each model to account for the correlation within each site. For the outcome of stroke, incidence rates were computed as the number of events per 100-person years stratified by the presence of OSA and oral anticoagulant (OAC) treatment. From the adjusted Cox proportional hazards model, the interaction between OAC treatment and the presence of OSA was tested with the likelihood-ratio test. Additionally, for the outcome of stroke, we compared a model containing the components of the CHA_2DS_2-VASc risk score to a model that included both the CHA_2DS_2-VASc risk covariates and OSA to evaluate the change in the *c*-index. The statistical significance of difference between the 2 predictive models was evaluated with the change in likelihood-ratio χ^2 statistics. All analyses were evaluated with a 2-sided significance level of .05. As a subgroup analysis, we described the event rates by the presence of OSA for stroke/SE and MACNE for those with CHA_2DS_2-VASc score less than 2.

Data management and statistical analyses were conducted by the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (TS1M5) (SAS Institute, Inc, Cary, NC).

Dr Dalgaard is funded by The Danish Heart Foundation grant 17-R115-A7443–22062 and Gangstedfonden grant A35136. Rebecca North is funded by T32 National Institutes of Health grant HL079896. Dr Steinberg is supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number K23HL143156. Dr Chan is supported by grant 1R01HL123980 from the National Heart, Lung, and Blood Institute. The ORBIT-AF registry was sponsored by Janssen Scientific Affairs, LLC, Raritan, NJ.

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.

Results

Baseline characteristics

Overall, the analysis included 22,760 AF patients among whom the median age (interquartile range [IQR]) was 73 (65–80), years and 13,208 (58.0%) were male. The full baseline characteristics are shown in Table I. The median [IQR] follow-up time was 1.5 [1.0–2.2] years. At baseline, 4,045 (17.8%) AF patients had OSA. Compared with AF patients without OSA, AF patients with OSA were younger (median [IQR] age: 68 [61–75] vs 74 [66–81]) ($P < .0001$) and more often male (70.7% vs 55.3%) ($P < .0001$). Body mass index (BMI) was significantly higher in patients with OSA (median [IQR] BMI: 34.6 kg/m^2 [29.8–40.2] vs 28.7 kg/m^2 [25.2–33.0]) ($P < .0001$). Although younger, AF patients with OSA also had more comorbidities, including diabetes (39.2% vs 25.2%) ($P < .0001$), chronic obstructive pulmonary disease (20.1% vs 12.0%) ($P < .0001$), heart failure (32.2% vs 25.1%) ($P < .0001$), hypertension (86.6% vs 80.0%), and hyperlipidemia (73.2% vs 66.7%)

($P < .0001$). There was little or no difference between the 2 groups in prior cerebrovascular events, prior myocardial infarction, and systolic blood pressure. Median [IQR] CHA_2DS_2-VASc was lower in OSA patients (3.0 [2.0–5.0] vs 4.0 [2.0–5.0]) ($P < 0.001$). This difference was primarily due to the younger age distribution and fewer women. Of ECG characteristics, there was a higher prevalence of left bundle-branch block in OSA patients (10.2% vs 7.8%), and in those with available QRS ECG measurement, median and mean QRS duration were also increased in OSA patients (mean [±SD]: 103.4 [25.4] vs 100.2 [24.1], $P < .0001$) (Supplemental Table S2).

Treatment patterns of patients with and without OSA

Despite lower CHA_2DS_2-VASc scores, patients with OSA were more likely to be treated with OACs (86% vs 83%, $P < 0.0001$) (Table II). OSA patients also had higher frequencies of prescription of single and dual antiplatelet therapy. Aspirin was more frequently used in patients with OSA than in those without OSA (39.4% vs 36.5%, $P = .0005$).

Outcomes in OSA patients

The incidence rate per 100-person years of MACNE was higher in those with OSA than without (3.78 vs 3.71). Similarly, patients with OSA had higher incidence rates of myocardial infarction (0.84 vs 0.78), stroke/SE (1.56 vs 1.45), and new-onset heart failure (1.75 vs 1.66) but not CV death (1.75 vs 1.95). For bleeding outcomes, the incidence rate was higher in those with OSA than without for major bleeding (3.71 vs 3.54) and for bleeding hospitalization (3.33 vs 3.06). For those with CHA_2DS_2-VASc scores of less than 2 (n = 2,811), the incidence rate for stroke was higher for those with OSA compared to those without (0.68 vs 0.44) (Table III). The incidence rate per 100-person years stroke on those treated with OAC was numerically higher in patients with OSA (1.59) than those without OSA (1.42). In the Cox proportional hazard model, we did not find any evidence of effect modification of OAC treatment and the presence of OSA ($P = .2966$) (Supplemental Table S1).

Compared to patients without OSA, the presence of OSA was associated with an increased risk of MACNE (adjusted hazard ratio [aHR]: 1.16 [95% CI: 1.03–1.31], $P = .0112$) and of stroke/SE (aHR: 1.38 [95% CI: 1.12–1.70], $P = .0025$), but no association was found between OSA and cardiovascular mortality (aHR: 0.95 [95% CI: 0.79–1.14], $P = .5780$), myocardial infarction (aHR: 1.01 [0.76–1.34], $P = .9721$), or new-onset heart failure (aHR: 1.14 [0.89–1.45], $P = .3006$) (Figure 1). There was no association with major bleeding (aHR: 1.04 [95% CI: 0.89–1.20], $P = .6441$), but an increase in hospitalization for bleeding was identified (aHR: 1.18 [95% CI: 1.00–1.40], $P = .0466$).

Prediction of stroke events

To investigate whether OSA provides improved discrimination for the prediction of stroke/SE, we evaluated the addition of OSA to a stroke prediction model that included the components of the CHA_2DS_2-VASc score. A model containing the CHA_2DS_2-VASc factors alone yielded a *C*-index (standard error [SE]) of 0.6867 (0.0125). Addition of OSA to the model containing the CHA_2DS_2-VASc risk factors slightly improved discrimination for

stroke/SE: CHA_2DS_2-VASc risk factors plus OSA yielded 0.6876 (0.0124). The addition of OSA was statistically significant ($\chi^2 = 5.03$, $P = .025$).

Discussion

In this study of 22,760 patients with AF, we investigated the characteristics of patients with OSA and the association between OSA and major adverse cardiovascular and neurologic outcomes. Although OSA presence has been investigated before in ORBIT I with no findings of increased risk of cardiovascular events,[11] the present analysis includes an AF population that is more than twice as large and, thus, has greater power to detect an association between OSA and infrequent cardiovascular events like stroke/SE.

There are 3 main findings in this analysis. First, approximately 1 in 5 patients with AF treated in community practice had a clinical diagnosis of OSA. Second, patients with concomitant OSA were younger but had higher burdens of comorbid disease and higher use of antithrombotic therapy. Finally, OSA was independently associated with an increased risk of MACNE and specifically stroke/SE events, but not CV mortality, myocardial infarction, or new-onset heart failure during follow-up.

These data from the ORBIT cohort confirm that OSA is a common comorbidity in the patients with AF. Our study also agrees with prior work that has found OSA is associated with other cardiovascular risk factors including obesity, type 2 diabetes, hyperlipidemia, hypertension, ischemic heart disease, and heart failure[18] and agrees with studies suggesting that OSA patients have increased QRS duration,[19] maybe due to higher prevalence of left bundle-branch block. As a result, those with OSA have multiple high-risk cardiovascular disease features. However, our results suggest that OSA confers incremental and independent residual risk for adverse cardiovascular and neurologic outcomes.

The increased risk of stroke in the general population with OSA is well known.[20,21] Studies have found that an incremental increase in apnea-hypopnea index increased the risk of stroke by 6% in men.[22] In 2 observational studies of AF patients, there have been conflicting results between the presence of OSA and the risk of stroke, but both studies had severe limitations: 1 study had a small sample size (n = 332), and another study had a very limited OSA prevalence (0.8%).[13,14] The association between OSA and an increased risk of MACNE and specifically stroke/SE events was particularly notable because those patients with OSA had a lower median CHA_2DS_2-VASc score, primarily due to fewer older patients. This raises the hypothesis that OSA may be a useful marker of stroke risk in patients who might not qualify based on the CHA_2DS_2-VASc score alone. We confirmed that patients with CHA_2DS_2-VASc <2 had a low risk of stroke (less than 1%), but there was a higher incidence of stroke in OSA patients compared to those without. Thus, in evaluating borderline cases in patients with stroke risk, OSA might be valuable in the treatment decision. Unfortunately, our event rates for stroke in these patients were too low to statistically quantify the discriminative abilities or to determine the statistical significance of such cases.

Despite a higher use of antithrombotic therapy, OSA was associated with higher rates of stroke/SE, suggesting that OSA may carry a residual risk of stroke. This could also be a sign of confounding by indication, as those at highest risk of stroke are more likely to be treated. This increased use of antithrombotic therapy can potentially explain the higher risk of hospitalizations for bleeding.

The addition of OSA to a risk model containing the CHA_2DS_2-VASc risk factors resulted in improved discrimination that was statistically significant, but the improvement in discrimination was very modest and clinically insignificant. This leads us to speculate that it might not be OSA itself that drives the increased risk of MACNE as much as the cardiovascular disease and risk factors that accompany OSA.[23] Some evidence seems to support this notion. In patients with cardiovascular disease or cardiovascular disease risk factors, multiple trials have assessed the treatment of OSA by CPAP for secondary prevention. The 2 trials (SAVE and RICCADSA) that investigated cardiovascular adverse events in OSA patients did not find a reduction in cardiovascular events or mortality by CPAP treatment.[24,25] However, a subgroup analysis in the RICCADSA study did indicate that those who were more compliant with CPAP had lower risk of cardiovascular adverse events.

A recent study in 1,218 patients without known OSA undergoing major noncardiac surgery showed that 67.6% of patients had unrecognized OSA and about 10% had severe OSA. The study showed that patients with severe OSA were at 2-fold higher risk of postoperative cardiac complications.[26] This could indicate that our results may have been attenuated by unrecognized OSA, which may lead to this study underestimating its importance.

Overall, this analysis adds to the evidence that the presence of OSA in patients with AF is associated with higher rates of adverse events, notably stroke/SE, but not CV death, myocardial infarction, or new-onset heart failure. Studies are needed to evaluate potential unrecognized OSA in patients with AF, if the severity of OSA in patients with AF affects the risk of MACNE, and to further evaluate the significance of OSA in stroke/SE risk management in AF patients with low risk of stroke.

Limitations

There are several limitations that should be considered when evaluating the results from these analyses. Because of the observational and retrospective nature of our study, we cannot infer causality. Our definition of OSA was limited to a medical history and prior diagnosis. We did not have data from polysomnograms to detect unrecognized OSA or grade the severity of OSA (eg, apnea-hypopnea index). Because of confounding by indication and because, in recent clinical trials, CPAP has been shown not to impact stroke risk, we did not include CPAP. It is also important to consider that some patients may have had undiagnosed OSA and that others may have developed OSA in follow-up. Therefore, any misclassification is expected to be nondifferential and to bias our findings toward the null.

Conclusions

Approximately 1 in 5 patients with AF in community-based US practices has OSA. Patients with OSA were younger, were more likely to be male, had more prevalent cardiovascular diseases and cardiovascular risk factors, and were using more antithrombotic therapy. The presence of OSA was independently associated with higher risk of MACNE, and specifically stroke/SE, but not cardiovascular mortality, myocardial infarction, or new-onset heart failure. Stroke risk in AF patients with OSA needs further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

J. P. P. receives grants for clinical research from Abbott, American Heart Association, Boston Scientific, Gilead, and NHLBI and serves as a consultant to Abbott, Allergan, ARCA Biopharma, Biotronik, Johnson & Johnson, Liva-Nova, Medtronic, Sanofi, Phillips, and Up-to-Date.

F. D.: none.

K. W. M.: Financial disclosures for Dr Mahaffey can be viewed at http://med.stanford.edu/profiles/kenneth_mahaffey.

B. A. S.: research support from Boston Scientific and Janssen; consulting to Janssen and Merit Medical; speaking for NACCME (funded by Sanofi).

G. C. F.: reports consulting for Abbott, Bayer, Janssen, and Medtronic.

D. E. S.: research support from Boehringer Ingelheim and Bristol-Myers Squibb; consulting/advisory board: Boehringer Ingelheim, Bristol-Myers Squibb, Johnson and Johnson, Merck, Pfizer.

References

1. Shamsuzzaman ASM, Gersh BJ, Somers VK. Obstructive sleep apnea. JAMA 2003;290(14):1906. [PubMed: 14532320]
2. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013;177(9):1006–14. [PubMed: 23589584]
3. Todd K, McIntyre WF, Baranchuk A. Obstructive sleep apnea and atrial fibrillation. Nat Sci Sleep 2010;2:39–45. [PubMed: 23616697]
4. Gami AS, Pressman G, Caples SM, et al. Association of atrial fibrillation and obstructive sleep apnea. Circulation 2004;110(4): 364–7. [PubMed: 15249509]
5. Selim B, Won C, Yaggi HK. Cardiovascular consequences of sleep apnea. Clin Chest Med 2010;31(2):203–20. [PubMed: 20488282]
6. Tung P, Anter E. Atrial fibrillation and sleep apnea: considerations for a dual epidemic. J Atr Fibrillation 2016;8(6):1283. [PubMed: 27909488]
7. Sharma S, Culebras A. Sleep apnoea and stroke. Stroke Vasc Neurol 2016;1(4):185–91. [PubMed: 28959482]
8. McDermott M, Brown DL, Chervin RD. Sleep disorders and the risk of stroke. Expert Rev Neurother 2018;18(7):523–31. [PubMed: 29902391]
9. Ng CY, Liu T, Shehata M, et al. Meta-analysis of obstructive sleep apnea as predictor of atrial fibrillation recurrence after catheter ablation. Am J Cardiol 2011;108(1):47–51. [PubMed: 21529734]
10. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 2003;107(20):2589–94. [PubMed: 12743002]

11. Holmqvist F, Guan N, Zhu Z, et al. 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). Am Heart J 2015;169(5):647–654.e2. [PubMed: 25965712]
12. Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. Am J Cardiol 2012;110 (3):369–72. [PubMed: 22516529]
13. Yaranov DM, Smyrlis A, Usatii N, et al. Effect of obstructive sleep apnea on frequency of stroke in patients with atrial fibrillation. Am J Cardiol 2015;115(4):461–5. [PubMed: 25529543]
14. Chang C-C, Chiu C-C, Chiang C-H, et al. Obstructive sleep apnea and the risk of ischemic stroke in patients with atrial fibrillation. Int J Cardiol 2015;181:144–6. [PubMed: 25497540]
15. Piccini JP, Fraulo ES, Ansell JE, et al. Outcomes registry for better informed treatment of atrial fibrillation: rationale and design of ORBIT-AF. Am Heart J 2011;162(4):606–612.e1. [PubMed: 21982650]
16. Steinberg BA, Blanco RG, Ollis D, et al. Outcomes registry for better informed treatment of atrial fibrillation II: rationale and design of the ORBIT-AF II registry. Am Heart J 2014;168(2):160–7. [PubMed: 25066554]
17. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of Martingale-based residuals. Biometrika 1993;80(3):557.
18. Gilat H, Vinker S, Buda I, et al. Obstructive sleep apnea and cardiovascular comorbidities: a large epidemiologic study. Medicine (Baltimore) 2014;93(9):e45. [PubMed: 25144324]
19. Gupta S, Cepeda-Valery B, Romero-Corral A, Shamsuzzaman A, Somers VK, Pressman GS. Association between QRS duration and obstructive sleep apnea. J Clin Sleep Med. 8(6):649. [PubMed: 23243398]
20. Yaggi HK, Concato J, Kernan WN, et al. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 2005;353(19): 2034–41. [PubMed: 16282178]
21. Munoz R, Duran-Cantolla J, Martínez-Vila E, et al. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke 2006;37(9): 2317–21. [PubMed: 16888274]
22. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182(2):269–77. [PubMed: 20339144]
23. Khayat R, Patt B, Hayes D Jr. Obstructive sleep apnea: the new cardiovascular disease. Part I: obstructive sleep apnea and the pathogenesis of vascular disease. Heart Fail Rev 2009;14(3):143–53. [PubMed: 18807180]
24. Bradley TD, Logan AG, Kimoff RJ, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 2005;353(19):2025–33. [PubMed: 16282177]
25. Peker Y, Glantz H, Eulenburg C, et al. Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. Am J Respir Crit Care Med 2016;194(5):613–20. [PubMed: 26914592]
26. Chan MTV, Wang CY, Seet E, et al. Association of unrecognized obstructive sleep apnea with postoperative cardiovascular events in patients undergoing major noncardiac surgery. JAMA 2019;321 (18):1788. [PubMed: 31087023]

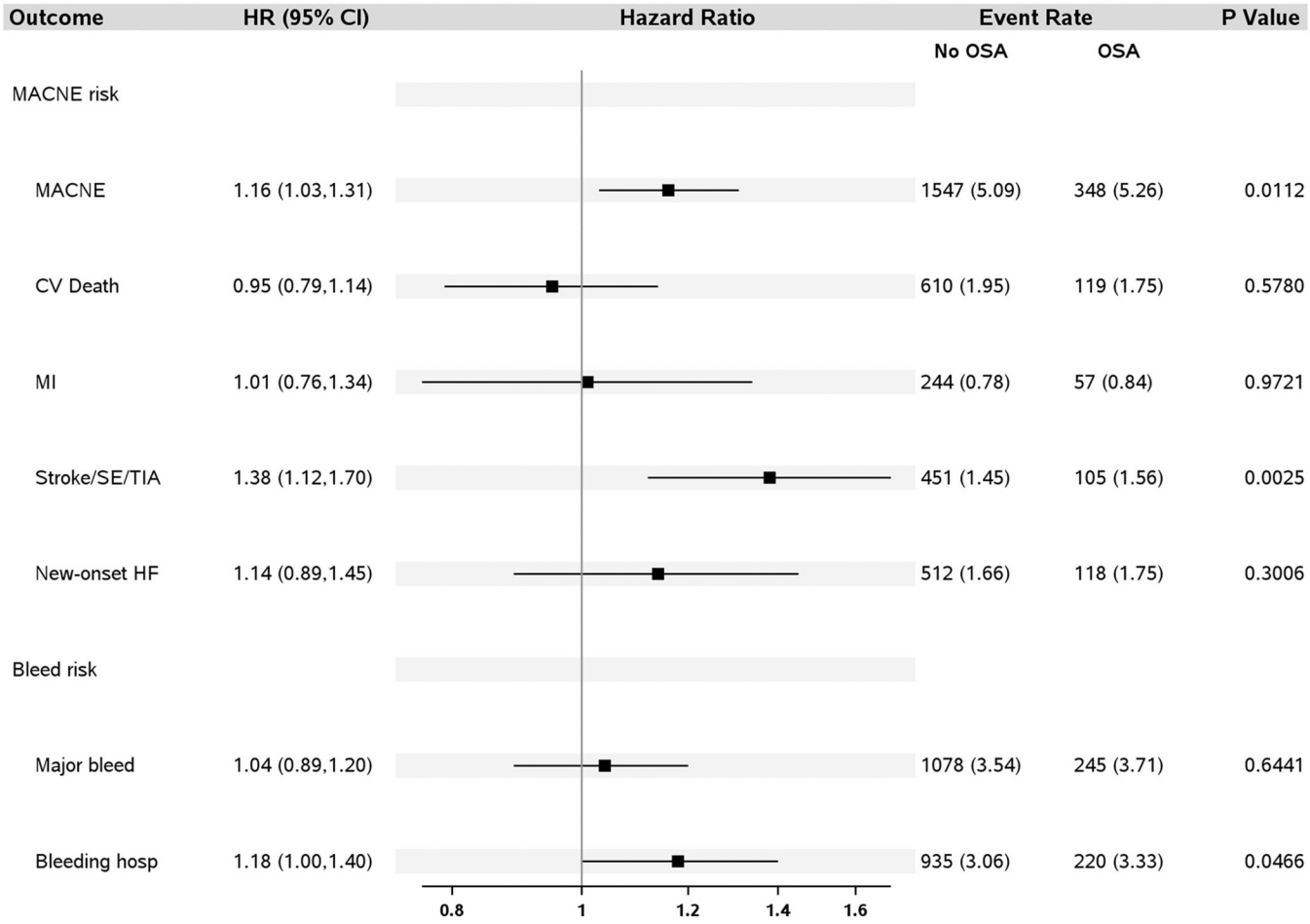

Figure 1.

Hazard ratios with 95% CIs for the association between OSA and MACNEs and bleeding events. *TIA*, transient ischemic attack; *bleed hosp*, hospitalization for bleeding.

Table I.

Baseline characteristics by OSA

Characteristic	Overall N = 22,760	OSA n = 4045	No OSA n = 18,715	*P*
Age (y)	73.0 (65.0–80.0)	68.0 (61.0–75.0)	74.0 (66.0–81.0)	<.0001
Male	13,208 (58.0)	2860 (70.7)	10,348 (55.3)	<.0001
Race				<.0001
White	19,903 (87.5)	3565 (88.2)	16,338 (87.4)	
Black/African American	1127 (5.0)	251 (6.2)	876 (4.7)	
Hispanic	1073 (4.7)	141 (3.5)	932 (5.0)	
Other/not reported	641 (2.8)	83 (2.1)	558 (3.0)	
Medical history				
Hypertension	18,474 (81.2)	3501 (86.6)	14,973 (80.0)	<.0001
Hyperlipidemia	15,451 (67.9)	2960 (73.2)	12,491 (66.7)	<.0001
Diabetes	6294 (27.7)	1584 (39.2)	4710 (25.2)	<.0001
Chronic obstructive pulmonary disease	3065 (13.5)	814 (20.1)	2251 (12.0)	<.0001
Prior MI	2903 (12.8)	538 (13.3)	2365 (12.6)	0.2524
Congestive heart failure	6001 (26.4)	1304 (32.2)	4697 (25.1)	<.0001
Valvular disease	4140 (18.2)	639 (15.8)	3501 (18.7)	<.0001
Peripheral vascular disease	2358 (10.4)	450 (11.1)	1908 (10.2)	0.0785
Prior cerebrovascular events	3000 (13.2)	529 (13.1)	2471 (13.2)	0.8307
Stroke (all-cause)	1678 (7.4)	282 (7.0)	1396 (7.5)	0.2807
Nonhemorrhagic	1479 (6.5)	244 (6.0)	1235 (6.6)	0.1870
Hemorrhagic	160 (0.7)	29 (0.7)	131 (0.7)	0.9050
Other intracranial bleeding	154 (0.7)	34 (0.8)	120 (0.6)	0.1610
Gastrointestinal bleeding	1463 (6.4)	312 (7.7)	1151 (6.2)	0.0002
Cognitive impairment or dementia	489 (2.1)	84 (2.1)	405 (2.2)	0.7281
Frailty	993 (4.4)	129 (3.2)	864 (4.6)	<.0001
Smoking	10,919 (48.0)	2162 (53.4)	8757 (46.8)	<.0001
Alcohol abuse	861 (3.8)	202 (5.0)	659 (3.5)	<.0001
BMI, kg/m^2	29.5 (25.7–34.5)	34.6 (29.8–40.2)	28.7 (25.2–33.0)	<.0001
Heart rate, beat/min	72.0 (63.0–81.0)	72.0 (64.0–82.0)	71.0 (63.0–81.0)	0.0033

Characteristic	Overall N = 22,760	OSA n = 4045	No OSA n = 18,715	*P*
Systolic blood pressure, mm Hg	126.0 (116.0–138.0)	126.0 (117.0–138.0)	126.0 (116.0–138.0)	0.9452
Diastolic blood pressure, mm Hg	74.0 (67.0–80.0)	74.0 (68.0–82.0)	73.0 (67.0–80.0)	<.0001
AF in baseline ECG	11887 (52.3)	2088 (51.6)	9799 (52.4)	0.3705
Intraventricular conduction				<.0001
RBBB	819 (3.6)	126 (3.1)	693 (3.7)	
LBBB	1855 (8.2)	409 (10.2)	1446 (7.8)	
Nonspecific IVCD	1558 (6.9)	323 (8.0)	1235 (6.7)	
None	1097 (4.9)	194 (4.8)	903 (4.9)	
Unknown, ventricularly paced	17228 (76.4)	2970 (73.8)	14258 (76.9)	
Left ventricular ejection fraction >50%	16241 (79.7)	2948 (79.2)	13293 (79.8)	0.1945

Continuous variables are presented as median (IQR). Categorical variables are presented as frequencies (percentages).

MI, Myocardial infarction; *RBBB*, right bundle-branch block; *LBBB*, left bundle-branch block; *IVCD*, intraventricular conduction disorder.

Table II.

Antithrombotic treatment patterns among patients with and without OSA

Treatment	Overall N = 22,760	OSA n = 4045	No OSA n = 18,715	*P*
OAC	18,959 (83.3%)	3477 (86.0%)	15,482 (82.7%)	<.0001
Warfarin vs NOAC				.5352
NOAC	10,210 (44.9%)	1856 (45.9%)	8354 (44.6%)	
Warfarin	8749 (38.4%)	1621 (40.1%)	7128 (38.1%)	.0185
Dabigatran	1116 (4.9%)	225 (5.6%)	891 (4.8%)	.0323
Rivaroxaban	4703 (20.7%)	861 (21.3%)	3842 (20.5%)	.0368
Apixaban	4288 (18.8%)	751 (18.6%)	3537 (18.9%)	.7859
Edoxaban	107 (0.5%)	21 (0.5%)	86 (0.5%)	.5391
Antiplatelet therapy				<.0001
None	13,754 (60.4%)	2332 (57.7%)	11,422 (61.0%)	
SAPT	8268 (36.3%)	1549 (38.3%)	6719 (35.9%)	
DAPT	721 (3.2%)	162 (4.0%)	559 (3.0%)	
Aspirin	8426 (37.0%)	1594 (39.4%)	6832 (36.5%)	.0005
Clopidogrel	1213 (5.3%)	263 (6.5%)	950 (5.1%)	.0003
Prasugrel	33 (0.1%)	10 (0.2%)	23 (0.1%)	.0595
Ticagrelor	33 (0.1%)	5 (0.1%)	28 (0.1%)	.6935
Aggrenox	23 (0.1%)	3 (0.1%)	20 (0.1%)	.5528

Continuous variables are presented as median (IQR). Categorical variables are presented as frequencies (percentages). *NOAC*, Nonoral anticoagulant; *SAPT*, single antiplatelet therapy; DAPT, dual antiplatelet therapy.

Table III.

Event rates among patients with CHA_2DS_2-VASc score less than 2 (n = 2811)

		OSA	
Outcome	**Overall**	**No**	**Yes**
MACNE	38 (0.89)	30 (0.88)	8 (0.92)
Stroke, non-CNS embolism, or TIA	21 (0.49)	15 (0.44)	6 (0.68)

CNS, central nervous system.