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Jingyao Fan
Capital Medical University

Xiao Wang
Capital Medical University

Xin-Liang Ma
Thomas Jefferson University; Capital Medical University, Xinliang.Ma@jefferson.edu

Virend K. Somers
Mayo Clinic

Shaoping Nie
Capital Medical University

See next page for additional authors

Authors
Jingyao Fan, Xiao Wang, Xin-Liang Ma, Virend K. Somers, Shaoping Nie, and Yongxiang Wei

ORIGINAL RESEARCH

Association of Obstructive Sleep Apnea With Cardiovascular Outcomes in Patients With Acute Coronary Syndrome

Jingyao Fan, MD;* Xiao Wang, MD;* Xinliang Ma, MD, PhD; Virend K. Somers, MD, PhD; Shaoping Nie, MD, PhD; Yongxiang Wei, MD, PhD

***Background*—**The prognostic significance of obstructive sleep apnea (OSA) in patients with acute coronary syndrome (ACS) in the contemporary era is unclear. We performed a large, prospective cohort study and did a landmark analysis to delineate the association of OSA with subsequent cardiovascular events after ACS onset.

***Methods and Results*—**Between June 2015 and May 2017, consecutive eligible patients admitted for ACS underwent cardiorespiratory polygraphy during hospitalization. OSA was defined as an apnea-hypopnea index ≥15 events·h^{-1}. The primary end point was major adverse cardiovascular and cerebrovascular event (MACCE), including cardiovascular death, myocardial infarction, stroke, ischemia-driven revascularization, or hospitalization for unstable angina or heart failure. OSA was present in 403 of 804 (50.1%) patients. During median follow-up of 1 year, cumulative incidence of MACCE was significantly higher in the OSA group than in the non-OSA group (log-rank, *P*=0.041). Multivariate analysis showed that OSA was nominally associated with incidence of MACCE (adjusted hazard ratio, 1.55; 95% CI, 0.94–2.57; *P*=0.085). In the landmark analysis, patients with OSA had 3.9 times the risk of incurring a MACCE after 1 year (adjusted hazard ratio, 3.87; 95% CI, 1.20–12.46; *P*=0.023), but no increased risk was found within 1-year follow-up (adjusted hazard ratio, 1.18; 95% CI, 0.67–2.09; *P*=0.575). No significant differences were found in the incidence of cardiovascular death, myocardial infarction, and ischemia-driven revascularization, except for a higher rate of hospitalization for unstable angina in the OSA group than in the non-OSA group (adjusted hazard ratio, 2.10; 95% CI, 1.09–4.05; *P*=0.027).

***Conclusions*—**There was no independent correlation between OSA and 1-year MACCE after ACS. The increased risk associated with OSA was only observed after 1-year follow-up. Efficacy of OSA treatment as secondary prevention after ACS requires further investigation. **(*J Am Heart Assoc*. 2019;8:e010826. DOI: 10.1161/JAHA.118.010826.)**

Key Words: acute coronary syndrome • obstructive sleep apnea • outcome

Obstructive sleep apnea (OSA) is highly prevalent in patients with cardiovascular diseases.[1,2] Increasing evidence indicates that OSA is associated with incidence and progression of coronary artery disease[3–5] and cerebrovascular disease.[6] Among patients with coronary artery disease, those with acute coronary syndrome (ACS) represent a high-risk subset and generally have higher mortality than patients with stable angina.[7] Compared with the general population, prevalence of OSA is higher in ACS patients and ranges from 36% to 63% across various ethnicities.[8] Previous observational studies have examined whether OSA significantly increased risk of recurrent cardiovascular events in patients with ACS and/or undergoing percutaneous coronary intervention (PCI).[9–12] However, results are inconsistent, and most studies, except the Sleep and Stent study,[12] were not done in the era of new-generation drug-eluting stents and modern antithrombotic therapy, thus precluding definite conclusions in the context of contemporary therapeutic strategies. Given that guideline-based optimal medical therapy was administered after ACS onset, especially within the first year,[13,14] we hypothesized that the prognostic significance of OSA would vary across different time periods after ACS presentation. Therefore, we performed a large-scale, prospective cohort study and did a landmark analysis to delineate the

From the Emergency & Critical Care Center (J.F., X.W., X.M., S.N.) and Department of Otolaryngology Head & Neck Surgery (Y.W.), Beijing Anzhen Hospital, Capital Medical University, Beijing, China; Department of Emergency Medicine, Thomas Jefferson University, Philadelphia, PA (X.M.); Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (V.K.S.).

*Dr Fan and Dr Wang contributed equally to this work.

Correspondence to: Shaoping Nie, MD, PhD, Emergency & Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, 2 Anzhen Rd, Chaoyang District, Beijing 100029, China. E-mail: spnie@ccmu.edu.cn and Yongxiang Wei, MD, PhD, Department of Otolaryngology Head & Neck Surgery, Beijing Anzhen Hospital, Capital Medical University, 2 Anzhen Rd, Chaoyang District, Beijing 100029, China. E-mail: weiyongxiang@vip.sina.com

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Clinical Perspective

What Is New?

- There was no independent correlation between obstructive sleep apnea (OSA) and 1-year major adverse cardiovascular and cerebrovascular event after acute coronary syndrome.
- Patients with OSA had 3.9 times the risk of incurring a major adverse cardiovascular and cerebrovascular event after 1 year, but no increased risk was evident within 1 year.
- No significant differences were found in the incidence of cardiovascular death, myocardial infarction, and ischemia-driven revascularization, except for a higher rate of hospitalization for unstable angina in the OSA group than in the non-OSA group.

What Are the Clinical Implications?

- The adverse effect of OSA in acute coronary syndrome patients might become more pronounced with an increasing duration of follow-up.
- Treatment effects of continuous positive airway pressure for secondary prevention of acute coronary syndrome still need to be evaluated.
- Appropriate timing and duration of intervention warrants further investigation, given that any randomized trial of continuous positive airway pressure or other therapy for ≤1 year will be unlikely to demonstrate significant benefit of therapy, given the absence of significant risk associated with OSA within the first year of acute coronary syndrome.

association of OSA with subsequent cardiovascular outcomes in patients with ACS.

Methods

Data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Population

The OSA-ACS project (NCT03362385) is a large-scale, single-center, prospective, observational study to assess the association of OSA with cardiovascular outcomes of patients with ACS in the contemporary era. For the current study, we performed a landmark analysis at a median follow-up of 1 year. Consecutive patients aged 18 to 85 years and admitted for ACS to the Emergency & Critical Care Center of Beijing Anzhen Hospital, Capital Medical University between June 2015 and May 2017 were eligible for inclusion. ACS was defined as acute presentation of coronary disease, including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina. Exclusion criteria were as follows: cardiogenic shock, cardiac arrest, previous or current use of continuous positive airway pressure (CPAP), malignancy, and failed sleep study (patients without adequate and satisfactory signal recording). Patients with predominantly central sleep apnea (≥50% central events or central apnea hypopnea index [AHI] ≥10·h^{-1}) and those receiving regular CPAP therapy (>3 months) after hospitalization were excluded from the analysis. This study conformed to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines and was conducted in accord with the Declaration of Helsinki. The Ethics Committee of Beijing Anzhen Hospital, Capital Medical University approved the study (2013025). All patients provided informed consent.

Overnight Sleep Study

All patients underwent an overnight sleep study after clinical stabilization during hospitalization (within 2 weeks after admission) using portable cardiorespiratory polygraphy (ApneaLink, Resmed, Australia), which was validated in the SAVE (Sleep Apnea Cardiovascular Endpoints) study.[15,16] Nasal airflow, thoracoabdominal movements, arterial oxygen saturation, and snoring episodes were recorded. An apnea was defined by an absence of airflow lasting ≥10 seconds (obstructive if thoracoabdominal movement was present and central if thoracoabdominal movement was absent). Hypopnea was defined as a reduction in airflow of >30% for ≥10 seconds and associated with a decrease in arterial oxygen saturation >4%. AHI was defined as the number of apneas and hypopneas per hour of total recording time. Recruited patients were categorized into OSA (AHI ≥15 events·h^{-1}) and non-OSA (AHI <15 events·h^{-1}) groups. A minimum of 3 hours of satisfactory polygraphy signal recording was considered as a valid test. All studies were double scored manually by independent sleep technologists (J.F., X.W.). Further scoring was performed in cases of discrepancy by a senior consultant in sleep medicine (Y.W.).

Procedures and Management

All patients received standard care during index ACS hospitalization according to current guidelines.[13,14] PCI with stenting or coronary artery bypass grafting was performed if clinically indicated. At discharge, all patients were prescribed aspirin (100 mg per day) and clopidogrel (75 mg per day) or ticagrelor (90 mg twice a day) for at least 1 year unless there were contraindications. For patients with moderate-to-severe sleep apnea (AHI ≥15), particularly those with excessive daytime sleepiness, we referred them to a sleep center for further evaluation and consideration of CPAP therapy.

Follow-up and Outcomes

Follow-up started at the time of the sleep study and was performed at 1 month, 3 months, 6 months, 1 year, and then every 6 months thereafter (at least 3 months and up to 2 years). Clinical events were collected by clinic visit, medical chart review, or telephone calls by an investigator who was blinded to patients' sleep results. All clinical events were confirmed by source documentation and were adjudicated by the clinical event committee.

The primary end point was major adverse cardiovascular and cerebrovascular event (MACCE), defined as a composite of cardiovascular death, myocardial infarction (MI), stroke, ischemia-driven revascularization, or hospitalization for unstable angina or heart failure. Secondary end points included components of primary end point, all-cause death, all repeat revascularization, and a composite of all events. All end points were defined in accord with the proposed definitions by the Standardized Data Collection for Cardiovascular Trials Initiative.[17] Briefly, cardiovascular death was defined as death related to proximate cardiovascular causes, procedure-related complications, or any death unless an unequivocal noncardiovascular cause could be established. MI was defined as recurrence of spontaneous ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction. Stroke included ischemic stroke and hemorrhagic stroke, which were verified by neurologists. Ischemia-driven revascularization was defined as any repeat PCI or coronary artery bypass grafting performed for either: MI, unstable angina, stable angina, or documented silent ischemia. Repeat revascularization was further classified into target vessel or nontarget-vessel revascularization as well as PCI or coronary artery bypass grafting.

Statistical Analyses

Continuous variables are shown as mean±SD or median (first and third quartiles) and were compared by using the Student *t* test or Mann–Whitney *U* test. Categorical variables are presented as the number (percentage) and were compared using χ^2 statistics or Fisher's exact test, as appropriate.

Time-to-event data were summarized as Kaplan–Meier estimates and were compared by the log-rank test. Multivariable Cox regression analyses were performed to determine independent predictors of MACCE and other cardiovascular events, and the adjusted hazard ratio (HR) with 95% CI were calculated. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into the Cox regression models. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models. If the patient experienced more than 1 event during the follow-up period, only the first event was included in the analysis. Landmark analyses were performed according to a cut-off point of 1 year after sleep study, with HRs calculated separately for events that occurred within 1 year and those that occurred after 1 year.

All statistical analyses were conducted with SPSS (version 22.0[IBM SPSS Inc, Armonk, NY) and Stata software (version 11.2; StataCorp LP, College Station, TX). A 2-sided $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

In total, 899 consecutive eligible patients with ACS were prospectively enrolled, of whom 867 underwent a successful overnight sleep study. After exclusion of patients according to predefined criteria, 804 patients were included in the final analysis (Figure 1). Mean patient age was 57.5±10.2 years, and 82.6% were male. Patients with OSA had higher body mass index ($P<0.001$) and waist-to-hip ratio ($P<0.001$). Medical history was comparable between OSA and non-OSA groups, except previous PCI or coronary artery bypass grafting, which was more frequent in the OSA group (Table 1).

Results of Sleep Study

Median total recording time was 472 (405–536) minutes. AHI ranged from 0.0 to 97.9. Prevalence of OSA was 50.1% based on diagnostic criteria of AHI ≥15. Patients with OSA exhibited lower minimum oxygen saturation and excessive daytime sleepiness than those without OSA. Detailed information is described in Table 2.

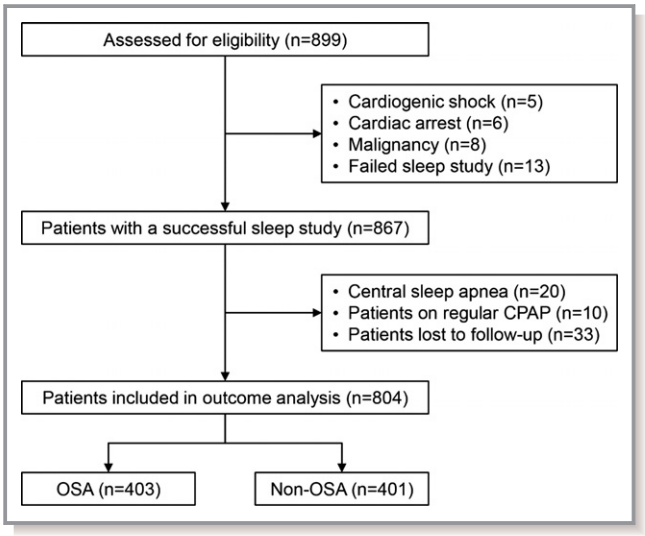

Figure 1. Study flowchart. CPAP indicates continuous positive airway pressure; OSA, obstructive sleep apnea.

Table 1. Baseline Patient Characteristics

Variables	All (n=804)	OSA (n=403)	Non-OSA (n=401)	*P* Value
Demographics				
Age, y	57.5±10.2	57.7±10.2	57.2±10.2	0.501
Male	664 (82.6)	342 (84.9)	322 (80.3)	0.088
Height, cm	168.5±7.4	168.7±7.4	168.3±7.5	0.477
Weight, kg	76.0±12.2	78.8±12.4	73.0±11.3	<0.001
BMI, $kg \cdot m^{-2}$	26.7±3.6	27.7±3.5	25.8±3.4	<0.001
Waist-to-hip ratio	0.98 (0.95–1.02)	0.99 (0.96–1.02)	0.98 (0.94–1.01)	<0.001
Neck circumference, cm	40 (38–42)	41 (39–43)	40 (37–41)	<0.001
Systolic BP, mm Hg	125 (115–138)	126 (115–140)	125 (116–137)	0.563
Diastolic BP, mm Hg	74 (70–84)	75 (70–85)	73 (68–82)	0.012
Medical history				
Diabetes mellitus	248 (30.8)	121 (30.0)	127 (31.7)	0.613
Hypertension	530 (65.9)	275 (68.2)	255 (63.6)	0.165
Hyperlipidemia	210 (26.1)	107 (26.6)	103 (25.7)	0.780
Family history of premature CAD	59 (7.3)	28 (7.0)	31 (7.1)	0.700
Previous stroke	76 (9.5)	41 (10.2)	35 (8.7)	0.484
Previous myocardial infarction	118 (14.7)	61 (15.1)	57 (14.2)	0.712
Previous PCI	141 (17.5)	83 (20.6)	58 (14.5)	0.022
Previous CABG	11 (1.4)	9 (2.2)	2 (0.5)	0.034
Smoking				0.973
No	288 (35.8)	145 (36.0)	143 (35.7)	
Current	406 (50.5)	202 (50.1)	204 (50.9)	
Previous	110 (13.7)	56 (13.9)	54 (13.5)	

Data are presented as mean±SD, median (first quartile, third quartile), or n (%). BMI indicates body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention; OSA, obstructive sleep apnea.

Procedures and Medications

Procedure and medication information is shown in Table 3. Most patients received invasive procedures, with coronary angiography in 97.8%. There were more PCIs (*P*=0.018) and stenting (*P*=0.029) procedures in patients with OSA than in those without OSA. Prescribed medications on discharge did not differ between the OSA and non-OSA groups.

Primary End Point

During a median follow-up of 1 year (0.7–1.7), 81 (10.1%) patients had MACCE—51 (12.7%) in the OSA group and 30 (7.5%) in the non-OSA group (Table 4). Kaplan–Meier analysis showed that cumulative incidence of MACCE was significantly higher in the OSA group than in the non-OSA group (log-rank, *P*=0.041; Figure 2A). OSA predicted incidence of MACCE in unadjusted analysis (HR, 1.59; 95% CI, 1.01–2.50; *P*=0.043; Table 5). After adjustment for age, sex, body mass index, hypertension, diabetes mellitus, clinical presentation, PCI procedure, and minimum arterial oxygen saturation, presence of OSA was nominally associated with incidence of MACCE, but this fell short of statistical significance (HR, 1.55; 95% CI, 0.94–2.57; *P*=0.085; Table 5).

In the landmark analysis (Figure 2B and Table 5), there was no significant difference in the incidence of MACCE between the OSA and non-OSA groups within 1-year follow-up (adjusted HR, 1.18; 95% CI, 0.67–2.09; *P*=0.575). In contrast, during the period after 1 year, patients with OSA had a 3.9-fold higher risk of MACCE (adjusted HR, 3.87; 95% CI, 1.20–12.46; *P*=0.023).

Secondary and Other End Points

Crude numbers of events are listed in Table 4. In general, most events came from hospitalization for unstable angina or ischemia-driven revascularization. In Kaplan–Meier analyses,

Table 2. Results of Sleep Study

Variables	All (n=804)	OSA (n=403)	Non-OSA (n=401)	*P* Value
AHI, events·h^{-1}	15.0 (7.4–31.2)	31.2 (21.8–43.8)	7.4 (3.8–10.6)	<0.001
ODI, events·h^{-1}	14.4 (7.4–29.5)	29.5 (21.2–43.3)	7.8 (4.2–11.2)	<0.001
Minimum SaO_2, %	85 (79–88)	82 (75–86)	87 (84–90)	<0.001
Mean SaO_2, %	94 (93–95)	93 (92–94)	95 (94–96)	<0.001
Time with SaO_2 <90%, %	1.2 (0.1–7.2)	5.2 (1.2–13.4)	0.2 (0.0–1.4)	<0.001
Epworth sleepiness scale	8.3±5.0	8.9±4.9	7.7±5.1	0.029

Data are presented as mean±SD or median (first quartile, third quartile). AHI indicates apnea-hypopnea index; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; SaO_2, arterial oxygen saturation.

no significant differences were found in the incidence of cardiovascular death, MI, and ischemia-driven revascularization, except for a higher rate of hospitalization for unstable angina in the OSA group than in the non-OSA group (log-rank, *P*=0.033; Figure 3). Similarly, multivariate analysis showed higher risk of unstable angina in patients with OSA compared with those without OSA (HR, 2.10; 95% CI, 1.09–4.05; *P*=0.027; Table 5). Moreover, incidence of all events was significantly higher in the OSA group than in the non-OSA group in the landmark analysis after 1 year (adjusted HR, 3.67; 95% CI, 1.13–11.95; *P*=0.031; Table 5).

Discussion

The prospective cohort study showed that OSA was nominally associated with increased incidence of MACCE in patients with ACS. However, multivariable analysis showed that there was no independent correlation between

Table 3. Clinical Presentations and Management

Variables	All (n=804)	OSA (n=403)	Non-OSA (n=401)	*P* Value
ACS category				0.214
Unstable angina	347 (43.2)	179 (44.4)	168 (41.9)	
NSTEMI	203 (25.2)	91 (22.6)	112 (27.9)	
STEMI	254 (31.6)	133 (33.0)	121 (30.2)	
LVEF, %	60 (55–65)	60 (55–65)	60 (55–65)	0.277
Coronary angiography	786 (97.8)	397 (98.5)	389 (97.0)	0.150
PCI	490 (60.9)	262 (65.0)	228 (56.9)	0.018
Stenting	432 (53.7)	232 (57.6)	200 (49.9)	0.029
Stents implanted, n	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.497
CABG	80 (10.0)	37 (9.2)	43 (10.7)	0.465
Medications on discharge				
Aspirin	754 (93.8)	381 (94.5)	373 (93.0)	0.371
Thienopyridine	720 (89.6)	369 (91.6)	351 (87.5)	0.062
β-blockers	611 (76.0)	313 (77.7)	298 (74.3)	0.266
ACEIs/ARBs	564 (70.1)	291 (72.2)	273 (68.1)	0.201
Statins	762 (94.8)	385 (95.5)	377 (94.0)	0.333
Aldosterone receptor antagonist	47 (5.8)	28 (6.9)	19 (4.7)	0.182
Diuretics	56 (7.0)	34 (8.4)	22 (5.5)	0.100
Calcium antagonists	124 (15.4)	65 (16.1)	59 (14.7)	0.578

Data are presented as median (first quartile, third quartile) or n (%). ACEIs indicates angiotensin-converting enzymes inhibitors; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; STEMI, ST-segment-elevation myocardial infarction.

Table 4. Crude Number of Events During Follow-up

Variables	All (n=804)	OSA (n=403)	Non-OSA (n=401)
MACCE	81 (10.1)	51 (12.7)	30 (7.5)
Cardiovascular death	11 (1.4)	5 (1.2)	6 (1.5)
Myocardial infarction	11 (1.4)	4 (1.0)	7 (1.7)
Stroke	9 (1.1)	6 (1.5)	3 (0.7)
Ischemic	6 (1.0)	4 (1.0)	2 (0.5)
Hemorrhagic	3 (0.4)	2 (0.5)	1 (0.2)
Hospitalization for unstable angina	49 (6.1)	33 (8.2)	16 (4.0)
Hospitalization for heart failure	6 (0.7)	3 (0.7)	3 (0.7)
Ischemia-driven revascularization	27 (3.4)	17 (4.2)	10 (2.5)
All-cause mortality	11 (1.4)	5 (1.2)	6 (1.5)
All repeat revascularization	48 (6.0)	28 (6.9)	20 (5.0)
Target vessel revascularization	14 (1.7)	9 (2.2)	5 (1.2)
Non-target-vessel revascularization	40 (5.0)	23 (5.7)	17 (4.2)
PCI	42 (5.2)	26 (6.5)	16 (4.0)
CABG	6 (0.7)	2 (0.5)	4 (1.0)
Composite of all events	100 (12.4)	61 (15.1)	39 (9.7)

Data are presented as n (%). CABG indicates coronary artery bypass grafting; MACCE major adverse cardiovascular and cerebrovascular event; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention.

OSA and 1-year MACCE after ACS. The difference between the 2 groups was driven by an increase of hospitalizations for unstable angina in the OSA group. In the landmark analysis, patients with OSA had 3.9 times the risk of incurring a MACCE after 1 year, but no increased risk was evident within 1 year, suggesting that the adverse effect of OSA might become more pronounced with an increasing duration of follow-up.

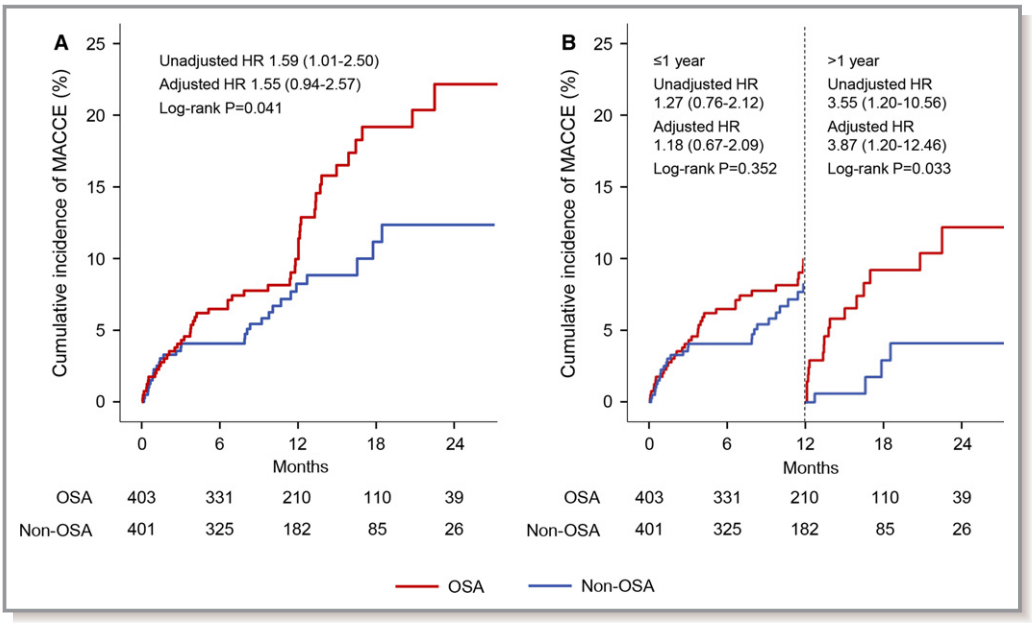

Figure 2. Kaplan–Meier curves for the overall and landmark analysis of MACCE. Cumulative incidences of MACCE are shown in the overall (**A**) and landmark (**B**) analysis, stratified on the basis of a cut-off point at 1 year after sleep study (vertical dashed line). HRs for OSA vs non-OSA groups were calculated separately for events that occurred within 1 year and those that occurred between 1 year and the end of follow-up. HR indicates hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; OSA, obstructive sleep apnea.

Table 5. Overall and Landmark Analysis for the Adverse Events in Patients With OSA Versus Those Without OSA

Variables	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
Overall analysis				
MACCE	1.59 (1.01–2.50)	0.043	1.55 (0.94–2.57)	0.085
Cardiovascular death†	0.80 (0.25–2.63)	0.716	…	…
Myocardial infarction†	0.54 (0.16–1.85)	0.327	…	…
Stroke†	1.93 (0.48–7.71)	0.353	…	…
Ischemia-driven revascularization	1.57 (0.72–3.42)	0.261	1.52 (0.65–3.56)	0.334
Hospitalization for unstable angina	1.89 (1.04–3.44)	0.036	2.10 (1.09–4.05)	0.027
Hospitalization for heart failure†	0.97 (0.20–4.81)	0.972	…	…
All repeat revascularization	1.32 (0.75–2.35)	0.340	1.51 (0.81–2.83)	0.195
Composite of all events	1.48 (0.99–2.21)	0.057	1.54 (0.98–2.40)	0.059
Landmark analysis (≤1 y)				
MACCE	1.27 (0.76–2.12)	0.353	1.18 (0.67–2.09)	0.575
Hospitalization for unstable angina	1.62 (0.79–3.31)	0.187	1.84 (0.84–4.03)	0.130
Ischemic-driven revascularization	1.21 (0.48–3.07)	0.688	1.27 (0.46–3.50)	0.646
All repeat revascularization	1.14 (0.61–2.14)	0.682	1.41 (0.71–2.82)	0.328
Composite of all events	1.26 (0.81–1.96)	0.310	1.28 (0.78–2.09)	0.322
Landmark analysis (>1 y)				
MACCE	3.55 (1.20–10.56)	0.023	3.87 (1.20–12.46)	0.023
Hospitalization for unstable angina	2.68 (0.87–8.21)	0.085	2.82 (0.84–9.51)	0.095
Ischemic-driven revascularization	2.92 (0.61–14.04)	0.182	2.46 (0.46–13.26)	0.295
All repeat revascularization	2.85 (0.59–13.71)	0.192	2.54 (0.47–13.73)	0.278
Composite of all events	3.30 (1.10–9.86)	0.033	3.67 (1.13–11.95)	0.031

HR indicates hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention.
*Model adjusted for age, sex, body mass index, hypertension, and diabetes mellitus, clinical presentation (acute myocardial infarction vs unstable angina), PCI procedure, and minimum SaO_2.
†Multivariate Cox regression and landmark analysis was not done because of too few events.

Despite therapeutic advances, including greater use of reperfusion therapy and modern antithrombotic therapy, mortality following ACS remains substantial. In the national registries of the European Society of Cardiology countries, in-hospital mortality of ST-segment elevation myocardial infarction patients varies between 4% and 12%,[18] and reported 1-year mortality among ST-segment elevation myocardial infarction patients in angiography registries is ≈10%.[19,20] Consequently, it is important to identify potential factors that might contribute to worsening of clinical outcomes in patients with ACS.

OSA-mediated intermittent hypoxia, triggered by repetitive bursts of apneas and hypopneas, is a major contributing factor to cardiovascular impairment.[21] Recurrent cycles of hypoxemia with reoxygenation promote oxidative stress, sympathetic activation, and inflammatory responses, resulting in endothelial dysfunction[21] and reduction of repair capacity,[22] which exacerbate progression of atherosclerosis and plaque instability. Based on intravascular ultrasound, patients with OSA had a larger total atheroma volume than those without OSA.[4] In a large ACS cohort study, OSA was associated with an increased number of diseased vessels.[23] In our study, there were more PCI procedures in OSA patients. In addition, patients with OSA showed increased platelet activation and aggregation[24] and reduced fibrinolytic capacity,[25] all of which predispose to thrombotic events. Several observational studies and meta-analysis have shown a higher risk of long-term cardiovascular events in patients with OSA,[9–12,26] but most studies were done in the era before new-generation drug-eluting stents and potent antiplatelet therapy. To the best of our knowledge, the present study is 1 of the largest cohorts to examine impact of OSA on cardiovascular outcomes of ACS patients in the contemporary era. Our results demonstrate that patients with OSA might have a greater risk of MACCE after ACS onset, even if most patients have received revascularization and optimal medical therapy.

Specifically, our results indicate that increased risk in OSA patients was obvious only after 1 year. This may be explained by the fact that patients are under guideline-based therapy

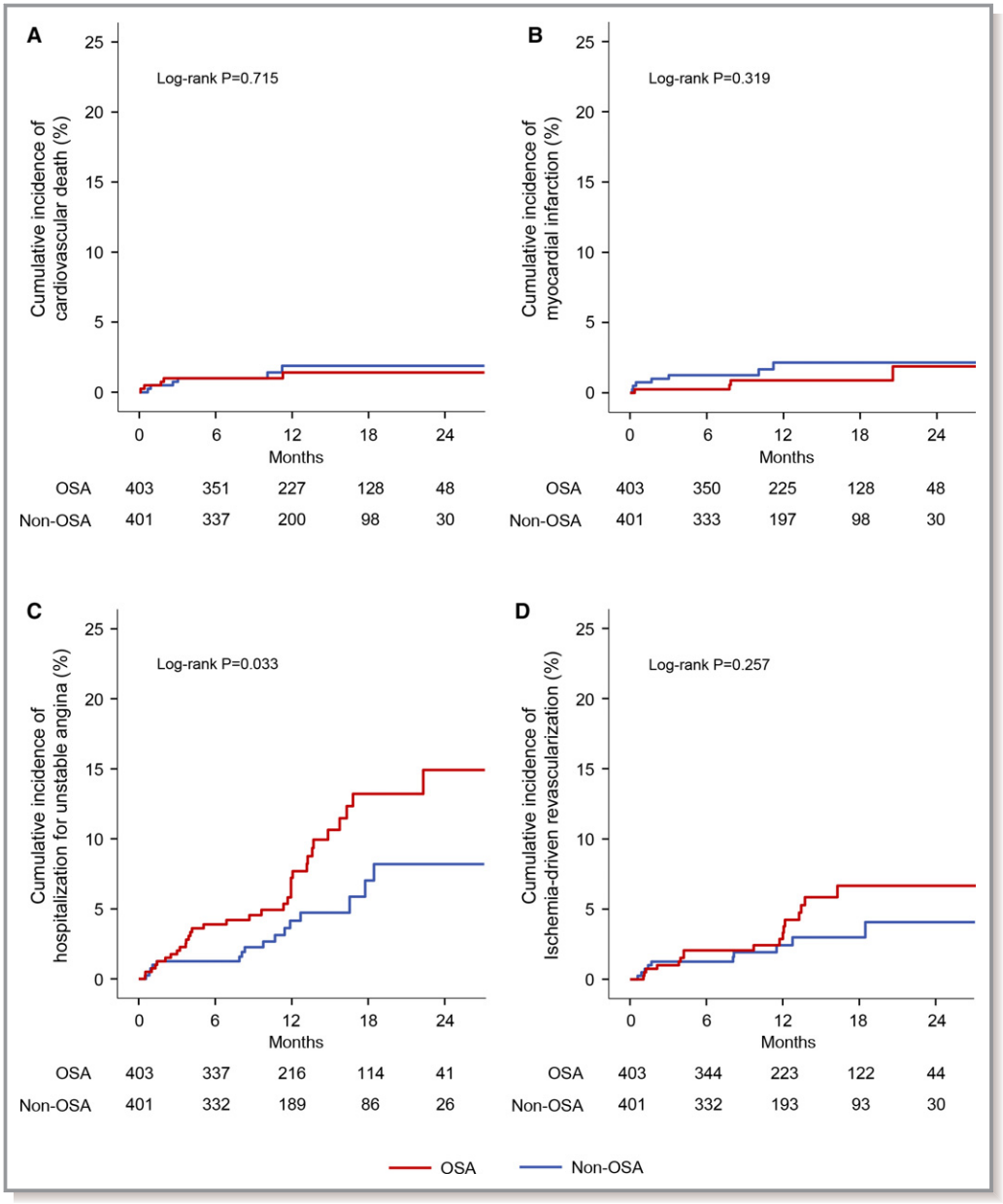

Figure 3. Kaplan–Meier curves for the individual cardiovascular events. Shown are the cumulative incidences of cardiovascular death (**A**), myocardial infarction (**B**), hospitalization for unstable angina (**C**), and ischemia-driven revascularization (**D**). OSA indicates obstructive sleep apnea.

after ACS presentation (especially within 1 year), including intensive antiplatelet therapy and control of blood pressure, dyslipidemia, and glucose, which are also the intermediate mechanisms implicated in OSA.[2] Furthermore, some reports suggested that OSA may play a cardioprotective role in the acute phase of MI.[27] In contrast, OSA may have a chronic deleterious effect in the long run, which was verified in our study showing increased events after 1 year, consistent with previous studies with long-term follow-up.[9,28]

According to recent randomized trials and meta-analysis, treatment of OSA with CPAP may not confer significant cardiovascular benefit among patients with established cardiovascular disease.[29–31] In a trial that enrolled 224 patients with OSA and coronary artery disease who had undergone revascularization, no difference was found in a composite end point of repeat revascularization, MI, stroke, or cardiovascular death in patients with CPAP versus those without CPAP therapy. The Kaplan–Meier curve suggests that CPAP may be harmful in the first 12 months following randomization, and modest benefits may emerge in the long-term follow-up.[29] Specifically, despite recommendations for treatment, the vast majority of patients in our study did not proceed to consideration for CPAP therapy

because of unawareness of significance of OSA, a finding also observed in another study of OSA patients after MI.[32] In this case, treatment effects of CPAP for secondary prevention of coronary artery disease still need to be evaluated, especially in a high-risk group (ACS, MI, etc). Also, the appropriate duration of intervention warrants further investigation, given that any randomized trial of CPAP or other therapy for 1 year or less will be unlikely to demonstrate significant benefit of therapy, given the absence of significant risk associated with OSA within the first year of ACS.

Study Limitations

First, OSA was detected by cardiorespiratory monitoring rather than complete polysomnography. Although the portable devices may underestimate AHI as a consequence of overestimating actual sleeping time, it is a simple and safe way to identify OSA in this high-risk patient population. Second, whereas it is possible that severity of OSA may change in the weeks after ACS,[33] this is true for OSA evaluation in the setting of any acute disease, including heart failure. Also, patients in our study received a sleep study after clinical stabilization, thus minimizing the potential bias. Third, follow-up duration was relatively shorter. Also, a previous study indicated that nocturnal hypoxemia in OSA is a predictor of poor outcome after MI in the long run.[32] Therefore, longer follow-up of this cohort is needed. Finally, this study is a single-center study that recruited primarily East-Asian patients. Studies pertaining to other ethnicities are needed.

Conclusions

In this prospective cohort study, OSA was not independently associated with a higher incidence of MACCE in patients with ACS. However, an increased risk associated with OSA was observed during the period after 1 year. Efficacy of CPAP therapy for secondary prevention and timing of intervention after ACS need further evaluation.

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Disclosures

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