Treatment of OSA Reduces the Risk of Repeat Revascularization After Percutaneous Coronary Intervention

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BACKGROUND: The impact of OSA treatment with CPAP on percutaneous coronary intervention (PCI) outcomes remains largely unknown.

METHODS: Between 2002 and 2012, we identified 390 patients with OSA who had undergone PCI. OSA was diagnosed through in-laboratory sleep studies and defined by an apnea-hypopnea index ≥ 5 events/h. The cohort was divided into three groups: (1) moderate-severe OSA successfully treated with CPAP ($n = 128$), (2) untreated moderate-severe OSA ($n = 167$), and (3) untreated mild OSA ($n = 95$). Main outcomes included repeat revascularization, major adverse cardiac events (MACEs) (ie, death, nonfatal myocardial infarction, repeat revascularization), and major adverse cardiac or cerebrovascular events (MACCEs). The median follow-up period was 4.8 years (interquartile range, 3.0-7.1).

RESULTS: The untreated moderate-severe OSA group had a higher incidence of repeat revascularization than the treated moderate-severe OSA group (25.1% vs 14.1%, $P = .019$). There were no differences in mortality ($P = .64$), MACE ($P = .33$), and MACCE ($P = .76$) among the groups. In multivariate analysis adjusted for potential confounders, untreated moderate-severe OSA was associated with increased risk of repeat revascularization (hazard ratio, 2.13; 95% CI, 1.19-3.81; $P = .011$).

CONCLUSIONS: Untreated moderate-severe OSA was independently associated with a significant increased risk of repeat revascularization after PCI. CPAP treatment reduced this risk.

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ABBREVIATIONS: ACE-I = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin receptor blocker; HR = hazard ratio; IQR = interquartile range; MACE = major adverse cardiac event; MACCE = major adverse cardiac or cerebrovascular event; MDCT = multidetector CT; PCI = percutaneous coronary intervention; TLR = target lesion revascularization

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OSA is a highly prevalent chronic condition that has been strongly associated with various forms of cardiovascular disease.¹⁻³ OSA leads to increased sympathetic excitation, oxidative stress, elevation of inflammatory mediators, reduced fibrinolytic activity with increased plasma viscosity, and endothelial dysfunction.⁴⁻⁸ Moreover, untreated OSA reduces endothelial repair capacity.^{9,10} All these pathophysiologic mechanisms can promote atherogenesis,¹¹ hypertension,^{12,13} arrhythmogenesis,^{14,15} and ultimately cardiac death in both clinical cohorts¹⁶⁻¹⁹ and community-based cohorts.^{20,21}

A study found that moderate-severe OSA was present in 422 of 662 patients (63.7%) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft.²² Furthermore, moderate-severe OSA is an independent predictor of worse clinical and angiographic outcomes after PCI²³⁻²⁵ or myocardial infarction.^{26,27}

Materials and Methods

Study Population

Figure 1 illustrates how patients were selected for the final analytic cohort. From 2002 to 2012, we retrospectively identified 2,610 patients with OSA defined by an apnea-hypopnea index (AHI) ≥ 5 events/h based on in-laboratory sleep study. Of these, 390 patients were included in the current analysis. These patients had PCI for coronary artery disease (69.2% for acute coronary syndrome) and had moderate-severe OSA defined by an AHI ≥ 15 events/h ($n = 295$) or mild OSA defined by an AHI of 5 to 14.9 events/h ($n = 95$). The sleep studies were either full-montage in-laboratory polysomnograms or in-laboratory limited-montage cardiorespiratory polygraphy. All sleep studies included at least 7.5 h of recording time in the sleep laboratory. Further details on polysomnography and polygraphy techniques are provided in e-Appendix 1. An AHI ≥ 5 events/h with at least 80% of all events being obstructive in nature was required for the definition of OSA. Moderate-severe OSA was defined as an AHI ≥ 15 events/h, and mild OSA was defined as an AHI of 5 to 14.9 events/h. In keeping with the guidelines of the Chinese Society of Sleep Breathing Disorders,^{31,32} CPAP was recommended to all patients with moderate-severe OSA. Patients with moderate-severe OSA underwent CPAP titration (details provided in e-Appendix 1) and were prescribed auto-CPAP devices.

CPAP adherence was confirmed by reviewing the patients' medical records from clinical follow-ups at 1, 3, 6, and 9 months; 1 year; and annually thereafter. To be considered a successful CPAP user, a patient had to report using CPAP at least 70% of the nights per week and at least 4 h of use per night for > 3 months. OSA was successfully treated with CPAP in 128 patients (CPAP+/AHI ≥ 15). Among patients in the OSA treatment group, 80.5% ($n = 103$) initiated CPAP treatment before PCI, whereas 19.5% ($n = 25$) initiated treatment immediately after PCI. In addition, 83.6% ($n = 107$) used CPAP > 6 months after PCI, and 16.4% ($n = 21$) used CPAP for 3 to 6 months after undergoing PCI. Patients who refused CPAP therapy ($n = 79$) or were not adherent to CPAP ($n = 88$) were assigned to the untreated moderate-severe OSA group (CPAP-/AHI ≥ 15 ; $n = 167$). Of the 88 patients who were not adherent to CPAP therapy, 81 (92%) used CPAP for < 1 month.

The Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, approved the use of clinical data for this study (2013030). Given the retrospective nature of the study, the need for informed consent was waived.

Although drug-eluting stents and intensive secondary prevention have led to improved outcomes after PCI, repeat revascularization remains relatively common, raising the possibility that treatment of OSA may be an effective secondary prevention in patients undergoing coronary revascularization procedures. CPAP therapy effectively treats OSA by splinting the upper airway and preventing repetitive episodes of hypoxemia/hypercapnia due to upper airway obstruction and attenuates sympathetic tone.^{28,29} Although effective treatment of moderate-severe OSA with CPAP has been shown to reduce cardiovascular morbidity and mortality,^{16,17,30} its effect on repeat revascularization in patients undergoing PCI remains poorly characterized. To this end, the present study aimed to examine the effect of OSA and CPAP treatment on long-term cardiovascular outcomes in patients undergoing PCI.

Procedure and Pharmacologic Therapy

All PCIs were performed according to current practice guidelines as described in e-Appendix 1. Clinical follow-up after PCI was performed at 1, 3, 6, and 9 months; 1 year; and annually thereafter (see e-Appendix 1 for further details). Adherence with medications was ascertained based on prescription refills and review of medical records.

Outcome Measures

All outcomes of interest were confirmed by source documentation and adjudicated by the local events committee at Beijing Anzhen Hospital, Capital Medical University. The following information was collected: death, nonfatal myocardial infarction, stroke, repeat revascularization (including target lesion revascularization [TLR] and non-TLR), and stent thrombosis. The main outcome measures were freedom from repeat revascularization; major adverse cardiac events (MACEs), including death, nonfatal myocardial infarction, repeat revascularization, and stent thrombosis; and major adverse cardiac or cerebrovascular events (MACCEs) (MACE or stroke). Further details on outcome measures are provided in e-Appendix 1.

Statistical Analysis

Baseline clinical variables were compared between groups using *t* test and analysis of variance or Mann-Whitney nonparametric test when the frequency distribution was skewed (continuous variables). Categorical variables were compared using χ^2 test. Event-free survival was estimated by the Kaplan-Meier survival function. The log-rank test was used to assess differences between groups, and a Cox proportional hazard regression model was used to identify independent predictors of repeat revascularization, MACE, and MACCE. Results are reported as hazard ratios (HRs) together with associated 95% CIs. $P < .05$ was considered statistically significant. In univariate analysis, we considered the following variables as potential prognostic factors: age, sex, BMI, clinical presentation (ie, stable angina, non-ST-segment elevation acute coronary syndromes, ST-segment elevation myocardial infarction), smoking, hypertension, type 2 diabetes, dyslipidemia, history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, renal failure, heart failure (left ventricular ejection fraction $\leq 40\%$), extent of diseased or treated vessel, PCI type (ie, emergency vs elective), adjunctive medical therapy (ie, aspirin, thienopyridine, β -blockers, statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blockers [ACE-I/ARBs]), and OSA group (ie, CPAP+/AHI > 15 , CPAP-/AHI ≥ 15 ,

Figure 1 – Study cohort profiles. AHI = apnea-hypopnea index; CABG = coronary artery bypass graft; DES = drug-eluting stent; PCI = percutaneous coronary intervention.

CPAP+/AHI 5-14.9). Variables with a significant unadjusted association with cardiovascular events were entered into a forward step-wise Cox model after forcing the entry of group as a variable. The

P-to-enter value had to be < .05 and the *P*-to-remove value > .1. Statistical analyses were performed with SPSS version 18.0 software (IBM).

Results

Baseline Patient Characteristics

We enrolled 390 patients who underwent PCI (primary coronary stenting) (Fig 1). The cohort included 128 patients with treated moderate-severe OSA (CPAP+/AHI ≥ 15), 167 patients with untreated moderate-severe OSA (CPAP−/AHI ≥ 15), and 95 patients with untreated mild OSA (CPAP−/AHI 5-14.9). Mean age was 56.3 ± 10.1 years, and 84.1% of the patients were men, 34.1% had type 2 diabetes, and 69.2% presented with acute coronary syndromes. The CPAP+/AHI ≥ 15 group had slightly more-severe OSA than the CPAP−/AHI ≥ 15 group, as indicated by a higher AHI (*P* = .002). BMI was higher in the CPAP+/AHI ≥ 15 group than in the CPAP−/AHI 5-14.9 group (*P* < .001). All groups had similar age and associated clinical conditions. Importantly, effective medical therapy, such as aspirin,

antiplatelet agents, β-blockers, statins, and ACE-I/ARBs were prescribed at a high rate in all three groups. Table 1 shows similar rates of adherence to these medications, which were verified through review of medical records and number of prescription refills.

Angiographic and Procedural Characteristics

Among the three groups, 44.6% of patients had single-vessel disease, 60.8% had single-vessel treated disease, and 46.7% were treated with one drug-eluting stent. Additional data regarding angiographic procedural characteristics among the three groups are provided in e-Appendix 1.

Long-term Outcomes

MACCEs during follow-up are listed in Table 2. Over a median of 4.8 years (interquartile range [IQR], 3.0-7.1) of follow-up, 23 (5.9%) patients died; among them, 15 (65.2% or 3.8% of the overall cohort) died of

TABLE 1 Baseline Characteristics

Variable	CPAP+/AHI ≥ 15 (n = 128)	CPAP−/AHI ≥ 15 (n = 167)	CPAP−/AHI 5-14.9 (n = 95)
Age, y	54 (48-62)	56 (49-63)	55 (50-65)
Male sex	106 (82.8)	143 (85.6)	79 (83.2)
BMI, kg/m ²	29.9 (27.5-33.3)	29.5 (27.4-32.1)	27.7 (25.7-29.3) ^a
AHI, events/h	46.3 (35.2-61.0)	40.1 (24.7-55.3) ^b	10.2 (7.7-12.6) ^a
Lowest oxygen saturation, %	78 (70-83)	78 (70-83)	86 (83-88) ^a
Clinical presentation			
Stable angina	40 (31.3)	50 (29.9)	30 (31.6)
NSTACS	65 (50.8)	89 (53.3)	48 (50.5)
STEMI	23 (18.0)	28 (16.8)	17 (17.9)
Current smoker	30 (23.4)	43 (25.7)	22 (23.2)
Type 2 diabetes	41 (32.0)	59 (35.3)	33 (34.7)
Hypertension	96 (75.0)	121 (72.5)	67 (70.5)
Dyslipidemia	55 (43.0)	77 (46.1)	38 (40.0)
Previous myocardial infarction	20 (15.6)	21 (12.6)	12 (12.6)
Previous stroke	14 (10.9)	16 (9.6)	10 (10.5)
Peripheral vascular disease	3 (2.3)	3 (1.8)	1 (1.1)
Renal failure	6 (4.7)	7 (4.2)	2 (2.1)
LVEF, %	60 (53-65)	60 (53-67)	62 (57-68)
LVEF $\leq 40\%$	8 (6.3)	11 (6.7)	7 (7.4)
Medical therapy ^c			
Aspirin	121 (94.5)	160 (95.8)	90 (94.7)
Thienopyridine	120 (93.8)	157 (94.0)	88 (92.6)
β -Blocker	102 (79.7)	132 (79.0)	72 (75.8)
Statin	109 (85.2)	142 (85.0)	80 (84.2)
ACE-I/ARB	86 (67.2)	110 (65.9)	62 (65.3)

Data are presented as median (interquartile range) or No. (%). ACE-I = angiotension-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin receptor blocker; LVEF = left ventricular ejection fraction; NSTACS = non-ST-segment elevation acute coronary syndrome; STEMI = ST-segment elevation myocardial infarction.

^a $P < .001$ vs CPAP+/AHI ≥ 15 group.

^b $P < .01$ vs CPAP+/AHI ≥ 15 group.

^cThienopyridine administered at 1-y follow-up and other medical therapy administrated at last follow-up.

cardiovascular causes. Twenty patients (5.1%) had nonfatal myocardial infarction, 33 (8.5%) had strokes, 75 (19.2%) underwent repeat revascularization, and six (1.5%) had definite stent thrombosis confirmed by angiography. In unadjusted comparisons, there were no differences in mortality (4.7% vs 7.2% vs 5.3%, $P = .64$), MACE ($P = .33$), and MACCE ($P = .76$) among the CPAP+/AHI ≥ 15 , CPAP−/AHI ≥ 15 , and CPAP−/AHI 5-14.9 groups, respectively. There was no difference in the follow-up duration among the three groups (5.0 [IQR, 3.1-7.8] years vs 4.7 [IQR, 2.9-7.2] years vs 4.5 [IQR, 3.1- 6.3] years, respectively; $P = .387$).

Repeat Revascularization

Overall, 334 patients (85.6%) had a follow-up angiogram or multidetector CT (MDCT) scan; 129 patients

underwent MDCT scan, and of these, 50 had follow-up angiography because the MDCT scan revealed evidence of restenosis. In contrast, 205 patients underwent angiography directly without undergoing prior MDCT scanning. There were no differences among the CPAP+/AHI ≥ 15 , CPAP−/AHI ≥ 15 , and CPAP−/AHI 5-14.9 groups in the angiographic follow-up (69.5% vs 62.9% vs 64.2%, respectively; $P = .47$) and angiographic or MDCT scan follow-up (86.7% vs 85.0% vs 85.3%, respectively; $P = .91$).

Over a median follow-up of 4.8 years, the incidence of repeat revascularization in the CPAP−/AHI ≥ 15 group was significantly higher than in the CPAP+/AHI ≥ 15 group ($P = .019$). Analysis using non-TLR showed similar results as repeat revascularization (Table 2). Among

TABLE 2] Unadjusted MACCE During 4.8 Y of Follow-up

Variable	CPAP+/AHI ≥ 15 (n = 128)	CPAP−/AHI ≥ 15 (n = 167)	CPAP−/AHI 5-14.9 (n = 95)
Repeat revascularization			
1 y	7 (5.5)	19 (11.4)	7 (7.4)
5 y	15 (11.7)	35 (21.0) ^a	14 (14.7)
Overall	18 (14.1)	42 (25.1) ^a	15 (15.8)
TLR			
1 y	5 (3.9)	10 (6.0)	5 (5.3)
5 y	12 (9.4)	21 (12.6)	12 (12.6)
Overall	15 (11.7)	28 (16.8)	13 (13.7)
Non-TLR			
1 y	4 (3.1)	13 (7.8)	5 (5.3)
5 y	8 (6.3)	22 (13.2)	8 (8.4)
Overall	9 (7.0)	28 (16.8) ^a	8 (8.4)
Nonfatal myocardial infarction	8 (6.3)	6 (3.6)	6 (6.3)
Stroke	11 (8.6)	14 (8.4)	8 (8.4)
Death	6 (4.7)	12 (7.2)	5 (5.3)
MACE			
1 y	12 (9.4)	20 (12.0)	9 (9.5)
5 y	25 (19.5)	48 (28.7)	21 (22.1)
Overall	30 (23.4)	52 (31.1)	25 (26.3)
MACCE			
1 y	13 (10.2)	20 (12.0)	10 (10.5)
5 y	32 (25.0)	52 (31.1)	28 (29.5)
Overall	40 (31.3)	59 (35.3)	32 (33.7)

Data are presented as No. (%). MACE = major adverse cardiac event (death, nonfatal myocardial infarction, repeat revascularization, stent thrombosis); MACCE = major adverse cardiac or cerebrovascular event (major adverse cardiac event or stroke); TLR = target lesion revascularization. See Table 1 legend for expansion of other abbreviation.

^a $P < .05$ vs CPAP+/AHI ≥ 15 group.

the unplanned repeat revascularizations, 26 (34.7% or 6.7% of the overall cohort) were performed for both TLR and non-TLR, 30 (40.0% or 7.7% of the overall cohort) were for only TLR, and 19 (25.3% or 4.9% of the overall cohort) were for only non-TLR; 64 (85.3%) received another stent, eight (10.7%) underwent only balloon inflation, and three (4.0%) underwent coronary artery bypass graft. There were no differences in the repeat revascularization method ($P = .47$) among the three groups. Additional unadjusted subgroup analysis revealed no differences in mortality (6.8% vs 7.6%, $P = .846$), repeat revascularization (27.3% vs 22.8%, $P = .505$), MACE (33.0% vs 29.1%, $P = .593$), and MACCE (36.4% vs 34.2%, $P = .768$) between patients who refused CPAP therapy (n = 79) and patients who were not adherent to CPAP therapy (n = 88).

TLR was performed in 56 patients, with 51.8%, 30.4%, and 17.9% due to focal, diffuse, and total occlusion in

stent restenosis, respectively. A trend toward lower focal stent restenosis was seen in the CPAP−/AHI ≥ 15 group compared with the other groups (Fig 2A). Non-TLR was performed in 45 patients, with 66.7% from a baseline stenosis < 50% and 33.3% from a baseline stenosis of 50% to 70%. No difference was seen in baseline lesion stenosis among the three groups (Fig 2B).

Time-to-event analyses for each type of unplanned repeat revascularization are illustrated in Figure 3. The CPAP−/AHI ≥ 15 group had the worst outcome, whereas the best outcome was observed in the CPAP+/AHI ≥ 15 group.

Table 3 summarizes the results of the Cox regression analysis used to obtain the unadjusted and adjusted HRs for the repeat revascularization. In the fully adjusted model, only two predictors of repeat revascularization were found: CPAP−/AHI ≥ 15 (ie, untreated moderate-severe OSA) and age. Further adjustment for medical

Figure 2 – Lesion characteristics for repeat revascularization. A, Target lesion revascularization was performed in 56 patients due to focal, diffuse, or total occlusion in stent restenosis. Focal stent restenosis rate was lower in the untreated moderate-severe OSA group (CPAP–/AHI ≥ 15) compared with other groups ($P = .023$). B, Nontarget lesion revascularization was performed in 45 patients, with 66.7% from a baseline stenosis < 50% and 33.3% from a baseline stenosis of 50% to 70%. There was no difference in the baseline lesion stenosis among the three groups ($P = .961$). See Figure 1 legend for expansion of abbreviation.

therapy during the follow-up, including aspirin, thienopyridine, β -blockers, statins, and ACE-I/ARBs, did not change the results significantly. In the fully adjusted model, untreated moderate-severe OSA was associated with an increased HR of 2.13 (95% CI, 1.19-3.81) for repeat revascularization ($P = .011$). Tables 4 and 5 summarize the results of the Cox regression analyses to estimate the unadjusted and adjusted HR for MACE and MACCE. In the fully adjusted models, untreated moderate-severe OSA was not associated with an increased HR for MACE (HR, 1.19; 95% CI, 0.67-2.12; $P = .55$) and MACCE (HR, 1.16; 95% CI, 0.70-1.92; $P = .57$).

Discussion

This study shows, for the first time to the best of our knowledge, that in patients undergoing PCI, the incidence of repeat revascularization is significantly higher in those with untreated moderate-severe OSA than in those with OSA treated with CPAP. Interestingly, the data show that untreated mild OSA was not associated with an increased risk of repeat revascularization, suggesting a dose-effect relationship between OSA severity and risk of complications after PCI.

Prior studies have reported a significant association between untreated OSA and increased risk of cardiovascular events.^{16-21,30,33-35} Two large observational studies from Spain found that untreated severe OSA was significantly associated with increased risk of fatal and nonfatal cardiovascular events in men and women.^{16,17} Moreover, CPAP treatment reduced this risk in both sexes. However, patients in these studies were not selected on the basis of known coronary artery disease,

and it remains unclear whether the findings apply to patients undergoing PCI. A few studies in patients with coronary artery disease and in patients undergoing PCI showed an increased incidence of the composite outcome of death, nonfatal myocardial infarction, repeat revascularization, and heart failure hospitalization in those with severe OSA compared with no OSA, and CPAP treatment was associated with a decrease in cardiovascular events.^{30,34} However, the outcomes were composite cardiovascular events; therefore, the impact of OSA on repeat revascularization was unclear. Cassar et al³⁰ performed a retrospective analysis of the Mayo Clinic sleep laboratory and PCI databases to identify patients who had undergone PCI and had an AHI ≥ 15 events/h. They found that treatment of moderate-severe OSA with CPAP (based on patients' subjective CPAP adherence reports) was associated with reduced cardiac death after PCI. They found, however, no difference in MACE or MACCE between treated and untreated moderate-severe OSA groups during up to 5 years of follow-up. This study was limited by not having a group of patients with mild OSA. Moreover, Cassar et al³⁰ did not perform multivariate regression analysis to adjust for important confounders. More recently, Fernandes et al²⁵ reported that symptoms of sleep disturbances were independently associated with a higher rate of MACE (primarily due to repeat revascularization) in patients undergoing PCI. By design, this study was limited by sleep disturbances not being objectively measured by sleep studies. Garcia-Rio et al³³ reported that OSA was an independent risk factor for repeat revascularization in patients with acute myocardial

Figure 3 – Time-to-event analyses. A, Cumulative incidence of unplanned repeat revascularization. The untreated moderate-severe OSA group (CPAP–/AHI ≥ 15) had a higher incidence of repeat revascularization than the treated moderate-severe OSA group (CPAP+/AHI ≥ 15) (P = .023). B, Cumulative incidence of target lesion revascularization. There was no significant difference in target lesion revascularization among the three groups. C, Cumulative incidence of nontarget lesion revascularization. The untreated moderate-severe OSA group (CPAP–/AHI ≥ 15) had a higher incidence of repeat revascularization than the treated moderate-severe OSA group (CPAP+/AHI ≥ 15) (P = .016). See Figure 1 legend for expansion of abbreviation.

infarction admitted to the coronary care unit, and CPAP treatment reduced this risk over time.

The present findings extend those of previous studies. We focused on repeat revascularization after PCI. Specifically, we compared the incidence of both TLR and non-TLR in untreated patients and patients treated with CPAP with moderate-severe OSA as well as those with mild OSA. The relatively large sample size allowed us to perform multivariate regression analysis to adjust for important confounders. The novel finding of the present study is that the incidence of repeat revascularization in patients with untreated moderate-severe OSA (CPAP–/AHI ≥ 15) undergoing PCI is significantly higher than in patients with moderate-severe OSA treated with CPAP. Untreated OSA was mostly associated with non-TLR. Although the number of the diseased vessels

has been reported as a predictor of non-TLR,^{36,37} in the present study, there was no significant difference in the number of the diseased vessels among the groups. However, two-thirds of non-TLR in the CPAP–/AHI ≥ 15 group was a result of a baseline stenosis < 50% by angiography. Previous studies^{38–40} have showed that although lesions responsible for MACEs appear to be angiographically mild in nature, intravascular ultrasonography reveals either a small luminal area, a large plaque burden, or the presence of a thin-cap fibroatheroma, findings consistent with the results of pathologic studies. Future studies should examine the role of more-aggressive surveillance for atherosclerotic progression and even more intensive or novel antiatherosclerotic therapies to help to reduce the incidence of disease progression in patients undergoing coronary revascularization.

TABLE 3] Unadjusted, Partially Adjusted, and Fully Adjusted HRs for Repeat Revascularization

Variable	Unadjusted HR (95% CI)	P Value	Partially Adjusted HR (95% CI)	P Value	Fully Adjusted HR (95% CI)	P Value
Age (by 1 y)	1.04 (1.02-1.07)	<.001	1.04 (1.02-1.07)	.002	1.04 (1.01-1.07)	.005
Group ^a						
Untreated moderate-severe OSA (CPAP-/AHI ≥ 15)	2.05 (1.18-3.57)	.011	2.06 (1.16-3.66)	.014	2.13 (1.19-3.81)	.011
Untreated mild OSA (CPAP-/AHI 5-14.9)	1.35 (0.64-2.52)	.504	1.12 (0.53-2.35)	.768	1.15 (0.55-2.43)	.707

In the partially adjusted model, the covariates included age, sex, BMI, clinical presentation (ie, stable angina, NSTACS, STEMI), smoking, hypertension, type 2 diabetes, dyslipidemia, history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, renal failure, heart failure (LVEF ≤ 40%), extent of diseased or treated vessel, PCI type (ie, emergency vs elective), and OSA group (ie CPAP+/AHI ≥ 15, CPAP-/AHI ≥ 15, and CPAP-/AHI 5-14.9). In the fully adjusted model, the covariates included all those in the partially adjusted model plus adjunctive medical therapy (ie, aspirin, thienopyridine, β-blockers, statins, ACE-I/ARBs). HR = hazard ratio; PCI = percutaneous coronary intervention. See Table 1 legend for expansion of other abbreviations.

^aTreatment group (CPAP+/AHI ≥ 15) served as the reference group.

OSA is believed to be mechanistically linked to atherosclerosis through the initiation of endothelial injury by repetitive bursts of sympathetic activity that occur with apneas and hypopneas, leading to surges in BP and oxidative stress brought on by intermittent hypoxemia.

Moreover, untreated OSA reduces endothelial repair capacity.⁶⁻¹⁰ Treatment of OSA has been associated with reductions in circulating inflammatory and thrombotic factors and improvement of endothelial dysfunction,⁵ suggesting that treatment may delay progression of atherosclerosis.¹¹ Reducing repeat revascularization or secondary prevention is an important goal in the management of patients undergoing PCI. The observed strong association between untreated OSA and a higher incidence of repeat revascularization raises the question

of whether OSA should be diagnosed and treated early after successful PCI. Ultimately, additional studies are needed to provide better insights into the mechanisms by which OSA therapy may improve atherosclerosis.

This study has several limitations. First and foremost, the retrospective observational nature of the study does not address the direction of causality. Nonetheless, there are ample pathophysiologic mechanisms that support biologic plausibility to explain the increased risk of repeat revascularization after PCI in untreated moderate-severe OSA. Although a randomized controlled trial would offer superior evidence, we believe that the present study provides substantial clinically relevant evidence that untreated moderate-severe OSA is associated

TABLE 4] Unadjusted, Partially Adjusted, and Fully Adjusted HRs for MACE

Variable	Unadjusted HR (95% CI)	P Value	Partially Adjusted HR (95% CI)	P Value	Fully Adjusted HR (95% CI)	P Value
Age (by 1 y)	1.05 (1.03-1.06)	<.001	1.04 (1.01-1.06)	.001	1.03 (1.01-1.06)	.005
Male sex	0.47 (0.31-0.73)	.001	0.57 (0.34-0.97)	.038	0.51 (0.30-0.86)	.012
Hypertension	1.05 (0.69-1.61)	.807	1.21 (0.76-1.93)	.428	2.01 (1.06-3.82)	.033
Previous myocardial infarction	1.54 (0.93-2.53)	.091	1.95 (1.11-3.45)	.021	1.77 (0.99-3.13)	.051
ACE-I/ARB	...	...	Not included in model	...	0.51 (0.29-0.90)	.020
Untreated moderate-severe OSA ^a (CPAP-/AHI ≥ 15)	1.52 (0.97-2.38)	.070	1.51 (0.94-2.43)	.087	1.52 (0.94-2.56)	.088
Untreated mild OSA ^a (CPAP-/AHI 5-14.9)	1.27 (0.75-2.17)	.375	1.17 (0.66-2.09)	.583	1.19 (0.67-2.12)	.554

In the partially adjusted model, the covariates included age, sex, BMI, clinical presentation (ie, stable angina, NSTACS, STEMI), smoking, hypertension, type 2 diabetes, dyslipidemia, history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, renal failure, heart failure (LVEF ≤ 40%), extent of diseased or treated vessel, PCI type (ie, emergency vs elective), and OSA group (ie CPAP+/AHI ≥ 15, CPAP-/AHI ≥ 15, and CPAP-/AHI 5-14.9). In the fully adjusted model, the covariates included all those in the partially adjusted model plus adjunctive medical therapy (ie, aspirin, thienopyridine, β-blockers, statins, ACE-I/ARBs). See Tables 1-3 legends for expansion of abbreviations.

^aTreatment group (CPAP+/AHI ≥ 15) served as the reference group.

TABLE 5] Unadjusted, Partially Adjusted, and Fully Adjusted HRs for MACCE

Variable	Unadjusted HR (95% CI)	P Value	Partially Adjusted HR (95% CI)	P Value	Fully Adjusted HR (95% CI)	P Value
Age (by 1 y)	1.04 (1.02-1.06)	<.001	1.03 (1.01-1.05)	.001	1.03 (1.01-1.05)	.005
Thienopyridine	0.48 (0.26-0.87)	.015	Not included in model	...	0.44 (0.22-0.87)	.019
ACE-I/ARB	0.79 (0.56-1.13)	.192	Not included in model	...	0.47 (0.28-0.78)	.004
Untreated moderate-severe OSA ^a (CPAP−/AHI ≥ 15)	1.27 (0.85-1.90)	.242	1.22 (0.79-1.85)	.365	1.22 (0.79-1.87)	.360
Untreated mild OSA ^a (CPAP−/AHI 5-14.9)	1.24 (0.78-1.98)	.363	1.14 (0.69-1.89)	.609	1.16 (0.69-1.92)	.571

In the partially adjusted models, the covariates included age, sex, BMI, clinical presentation (ie, stable angina, NSTACS, STEMI), smoking, hypertension, type 2 diabetes, dyslipidemia, history of myocardial infarction, cerebrovascular disease, peripheral arterial disease, renal failure, heart failure (LVEF ≤ 40%), extent of diseased or treated vessel, PCI type (ie, emergency vs elective), and OSA group (ie CPAP+/AHI ≥ 15, CPAP−/AHI ≥ 15, and CPAP−/AHI 5-14.9). In the fully adjusted model, the covariates included all those in the partially adjusted model plus adjunctive medical therapy (ie, aspirin, thienopyridine, β-blockers, statins, ACE-I/ARBs). See Tables 1-3 legends for expansion of abbreviations.

^aTreatment group (CPAP+/AHI ≥ 15) served as the reference group.

with an increased risk of repeat revascularization after PCI and that this risk can be mitigated with CPAP therapy. Another important limitation is the risk of selection bias inherent to observational studies. However, patients with treated and untreated moderate-severe OSA were fairly similar in their demographic characteristics, comorbidities, PCI interventions, and pharmacotherapies. Although the single-center design of the study provides some degree of uniformity in the overall management of patients with coronary artery disease after PCI, it limits the generalizability of the findings. Therefore, additional studies are needed to corroborate the findings in more diverse patient populations. Despite the relatively large sample size, the number of deaths, acute myocardial infarctions, and strokes were low. It is certainly possible that with a larger sample size we would have been able to demonstrate significant difference in these relatively rare outcomes among the groups. The AHI was slightly higher in the CPAP+/AHI ≥ 15 group than in the CPAP−/AHI ≥ 15 group (46.3 vs 40.1, $P < .01$). It remains unknown whether this statistically significant difference in baseline AHI is clinically relevant. It is plausible that patients with slightly worse OSA benefited more from CPAP therapy. Another potential limitation is that patients in the untreated moderate-severe OSA group may have also been at risk for increased nonadherence to other medical treatments. We tried to minimize this risk by carefully reviewing medical records and prescription refills to demonstrate that medication adherence to important cardiovascular medications was not different between the treated and untreated moderate-severe OSA groups up to at least 1 year of follow-up after the index PCI. The strategy of reviewing pharmacy

records for prescription refills as a marker of medication adherence has been well described in the cardiovascular literature.⁴¹ Villar et al⁴² examined adherence to cardiovascular medications (ie, antihypertensive, lipid-lowering, and antiplatelet drugs) in two groups of patients with severe OSA and cardiovascular disease: those who were adherent to CPAP treatment and those who refused treatment or were nonadherent to CPAP. They found no difference in the rates of medication adherence between the two groups, suggesting that nonadherence to CPAP does not necessarily imply nonadherence to pharmacotherapy. The present findings are in line with Villar et al⁴² and reinforce the notion that untreated moderate-severe OSA may be an independent risk factor for repeat revascularization after PCI. Another limitation was that CPAP adherence was based on subjective patient report rather than on objective adherence data obtained from the CPAP devices. However, to minimize this limitation, we extracted subjective CPAP adherence data from every clinic visit. From these data, it remains unclear whether CPAP treatment of 3 to 6 months can effectively reduce cardiovascular events during a follow-up period of 4.8 years. In the present cohort, 83.6% ($n = 107$) used CPAP for > 6 months and 16.4% ($n = 21$) used CPAP for 3 to 6 months. We cannot perform a meaningful subgroup analysis given that the subset using CPAP for only 3 to 6 months was small. We believe that larger prospective studies are necessary to address the duration of CPAP therapy necessary to reduce cardiovascular events after PCI.

In summary, this study provides new evidence that untreated moderate-severe OSA is an independent risk factor for repeat revascularization after PCI and that CPAP

therapy can reduce this risk. Moreover, mild untreated OSA does not appear to be associated with an increased risk of repeat revascularization. Although untreated moderate-severe OSA was not associated with an increased

risk of death in this cohort, we believe that timely diagnosis and treatment in patients undergoing PCI can serve as a clinically relevant method of secondary prevention to decrease the risk of repeat revascularization.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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