ORIGINAL RESEARCH

Impact of Obstructive Sleep Apnea on Platelet Function Profiles in Patients With Acute Coronary Syndrome Taking Dual Antiplatelet Therapy

Wei Gong, MD, PhD; Xiao Wang, MD, PhD; Jingyao Fan, MD; Shaoping Nie, MD, PhD; Yongxiang Wei, MD, PhD

***Background*—**Obstructive sleep apnea (OSA) is a novel risk factor for acute coronary syndrome (ACS). Several studies have shown OSA to be associated with induced platelet reactivity. However, whether OSA have effects on platelet function profiles in ACS patients taking dual antiplatelet therapy remains unexplored.

***Methods and Results*—**This was a cross-sectional observational study, in which ACS patients taking maintenance aspirin and clopidogrel therapy were included. OSA was defined as an apnea-hypopnea index ≥15 events/hour. The inhibitory rate of arachidonic acid or adenosine diphosphate pathway were assessed with thrombelastography and defined patients with high residual on-treatment platelet reactivity. Platelet indices were obtained from routine analysis of blood samples using an automated blood cell counter. A total of 127 ACS patients taking dual antiplatelet therapy were analyzed. Platelet volume indices, including mean platelet volume and platelet large cell ratio, were significantly increased in patients with OSA. Patients with OSA (n=68) had significantly lower inhibitory rate of adenosine diphosphate receptor pathway (P=0.028) compared with those without (n=59). After adjustment for potential confounders, patients with OSA were more likely to have high residual on-treatment platelet reactivity after clopidogrel therapy (adjusted odds ratio: 3.25, 95% confidence interval: 1.19–8.87, P=0.021).

***Conclusions*—**In ACS patients taking dual antiplatelet therapy, OSA is associated with an increased level of platelet volume indices, reduced clopidogrel-induced antiplatelet effects and a greater prevalence of high residual on-treatment platelet reactivity.
(*J Am Heart Assoc*. 2018;7:e008808. DOI: 10.1161/JAHA.118.008808.)

Key Words: acute coronary syndrome • dual antiplatelet therapy • obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction during sleep, and is usually associated with a wide range of cardiovascular, metabolic, and neurocognitive disorders and may lead to increased morbidity and mortality.[1,2] A prevalence of OSA up to 66% has been reported in the early phase of acute coronary syndrome (ACS).[3] And about 50% of patients with percutaneous coronary intervention (PCI) suffer from OSA.[4,5] Importantly, patients with OSA experience an increased risk of adverse outcomes after PCI.[4,5] Recent findings from meta-analysis suggested that OSA appears to increase the risk of cardiac death, non-fatal myocardial infarction (MI), and coronary revascularization in patients after PCI.[4] Outcomes in ACS patients with moderate/severe OSA have shown to be worse compared with normal or mild OSA patients.[6]

In fact, OSA can impact the platelet function.[7,8] Gunbey et al have found that platelet aggregation was correlated with apnea-hypopnea index (AHI).[9] The platelet distribution width (PDW) and mean platelet volume (MPV) of OSA patients were significantly increased.[9] Rahangdale et al have reported that adenosine 5′-diphosphate (ADP)-induced platelet aggregation was markedly increased in OSA patients.[7] In addition, platelet reactivity and MPV levels decreased significantly after continuous positive airway pressure (CPAP) therapy in

From the Emergency & Critical Care Center, Beijing Anzhen Hospital, Capital Medical University, Beijing, China (W.G., X.W., J.F., S.N.); The Beijing Key Laboratory of Upper Airway Dysfunction Related Cardiovascular Disease, Beijing Anzhen Hospital, Beijing, China (W.G., X.W., J.F., S.N., Y.W.); Beijing Institute of Heart, Lung, and Blood Vessel Diseases, Beijing, China (W.G., X.W., J.F., S.N., Y.W.).

Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/7/15/e008808/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Yongxiang Wei, MD, PhD and Shaoping Nie, MD, PhD, Beijing Anzhen Hospital, Capital Medical University, No. 2 Anzhen Road, Chaoyang District, Beijing 100029, China. E-mails: weiyongxiang@vip.sina.com; spnie@ccmu.edu.cn

Received February 2, 2018; accepted June 14, 2018.

Clinical Perspective

What Is New?

- In acute coronary syndrome (ACS) patients taking maintenance aspirin and clopidogrel therapy, obstructive sleep apnea (OSA) is associated with increased level of platelet volume indices, reduced clopidogrel-induced antiplatelet effects and a greater prevalence of high residual on-treatment platelet reactivity.
- These findings may explain the elevated prevalence of ischemic complications among ACS patients with OSA.

What Are the Clinical Implications?

- This results suggest that OSA affects platelet function and pharmacodynamic profiles of antiplatelet drugs in ACS patients.
- These findings may explain why some ACS patients with OSA have worse clinical prognosis than others and suggest the potential need for further categorizing this already high-risk cohort of patients into those with and without OSA.
- This study enables a better understanding of individual risk profiles of patients with ACS and OSA, and suggests future development of targeted treatment strategies may be beneficial for these patients.

patients with OSA.[10] Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and an oral inhibitor of the platelet $P2Y_{12}$ receptor for ADP, is the cornerstone of drug therapy for post-PCI or ACS patients. However, it remains unclear whether OSA affects platelet function and pharmacodynamic profiles of antiplatelet drugs in patients taking DAPT.

The aim of the present study was to assess the impact of OSA on platelet function profiles in ACS patients taking DAPT.

Methods

The data, analytic 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 Subjects

This cross-sectional observational study is an ancillary study of the OSA-ACS Project (a prospective cohort study of NCT03362385 [Impact of Obstructive Sleep Apnea and Continuous Positive Airway Pressure Therapy on Outcomes in Patients with Acute Coronary Syndrome: The OSA-ACS Project]). The aim of that large-scale, prospective cohort study was to delineate the whole picture of the association of OSA with short- and long-term outcomes of patients with ACS and the effect of CPAP treatment on the incidence of new cardiovascular events. In this study, we evaluated patients consecutively admitted to Beijing Anzhen Hospital (Beijing, China) with a diagnosis of ACS from June 2015 to May 2017. ACS was defined according to ACS related guidelines.[11,12] Patients were eligible for platelet function analyses if they were in their maintenance steady-state phase (at least 7 days) of DAPT with aspirin (100 mg/day) and clopidogrel (75 mg/day). After patients agreed to participate and the consent form was signed, all patients underwent an overnight sleep study to assess the presence of OSA.

Exclusion criteria included: patients aged >75 or <18 years; any previously diagnosed sleep disorder; known OSA on CPAP treatment; known allergies to aspirin or clopidogrel; dialysis; blood dyscrasia; active bleeding or bleeding diathesis; gastrointestinal bleed within last 6 months; hemodynamic instability; acute cerebrovascular event within 3 months; any malignancy; concomitant use of other antithrombotic drugs (oral anticoagulants, dypiridamole, cilostazol) or non-steroid anti-inflammatory drugs; life-limiting chronic disease; serious hepatorenal functional impairment; and hematocrit <25%; platelet count <100 ($1000/mm^3$). The study complied with the Declaration of Helsinki, and was approved by the ethics committee of Beijing Anzhen Hospital. All patients gave their informed written consent.

Overnight Sleep Study

All patients underwent an overnight sleep study after clinically stabilization during hospitalization, using a portable cardiorespiratory monitoring device (The ApneaLink, Resmed, Austrulia). Nasal airflow, arterial oxygen saturation, thoraco-abdominal movements, and snoring episodes were recorded. An obstructive apnea episode was defined by a complete cessation of airflow lasting ≥10 seconds. An episode of hypopnea was defined as a reduction in airflow lasting ≥10 seconds and is associated with oxygen desaturation. Oxygen desaturation is considered as a decrease in SaO_2 >4%. AHI was defined as the number of apneas and hypopneas per hour of sleep. All studies will be manually analyzed by an independent sleep technologist who is not aware of the patients' clinical characteristics. To ensure the accuracy and consistency of analyzing, 50% of all studies will be audited by a masked investigator with expertise in sleep medical. Recruited patients were classified into OSA (AHI ≥15 events/hour) and non-OSA (AHI <15 events/hour) groups.[5,13]

Clinical Data Extraction

The following baseline demographic medical history and a detailed medication history were collected from the medical records of the recruited patients.

The Thrombelastography Platelet Mapping Assay

Thrombelastography Platelet Mapping assay used 4 channels to detect effects of antiplatelet therapy with arachidonic acid and ADP activators. A detailed description of this method is outlined previously.[14] Percentage platelet inhibition is defined by the extent of non-response of the platelet ADP ($P2Y_{12}$) or thromboxane A_2 receptor to the exogenous ADP and arachidonic acid as measured by maximum amplitude (MA). The percentage platelet aggregation to agonist can be calculated by: $[(MA_{ADP/AA}-MA_{Fibrin})/(MA_{Thrombin}-MA_{Fibrin})\times 100]$. Percentage platelet inhibition is thus 100%—the percentage platelet aggregation (%). This calculation is performed by the Thrombelastography Platelet Mapping software. Similarly, the percentage inhibition resulting from the antiplatelets clopidogrel and aspirin can be calculated.[15]

Statistical Analysis

Continuous variables are expressed as the mean±SD or median (interquartile range) for data with a skewed distribution. Patients characteristics were compared using Student *t* test, analysis of variance, or the non-parametric Mann–Whitney test for skewed data. Categorical variables are presented as counts and percentages and were compared by means of the chi-square test or Fisher exact test. Spearman correlation analysis was performed for determination of correlation. A multivariable linear regression model was used to evaluate the independent contribution of the OSA and non-OSA groups to the inhibitory rate of ADP pathway. Control for potential confounders and analysis of independent correlates of high residual on-treatment platelet reactivity (HRPR) were performed with a logistic regression model including age, sex, body mass index, diabetes mellitus, hypertension, prior PCI, and estimated glomerular filtration rate (eGFR) as independent control variables and OSA as the independent study variable of interest. Odds ratio (OR) and 95% confidence interval (CI) were calculated. All tests were 2-sided, and a value of $P<0.05$ was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient Population

A total of 127 ACS patients were studied. Baseline demographic data, clinical characteristics, and laboratory data of patients with (n=68) and without (n=59) OSA were described in Table 1. Of the participants, 88.2% were men; the mean age was 55.23±9.93 years. There were no differences in terms of age, sex, or prevalence of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, prior MI and smoking) among all groups. Patients with OSA have higher body mass index (Table 1). Sleep information was shown in Table 2. AHI, oxygen desaturation index, minimum, and average oxygen saturation, and time of SaO_2 <90% were significantly different between groups ($P<0.001$).

The Impact of OSA on Platelet Volume Indices in ACS Patients Taking DAPT

Platelet volume indices are indicator of platelet activation and play an important role in the pathophysiology of cardiovascular diseases.[16,17] In the study, we found that patients with OSA have higher MPV and platelet large cell ratio values (Figure 1A and 1B). And PDW (%) in OSA group also tended to be higher than that in the non-OSA group (13.1±2.3 versus 12.4±1.9, $P=0.07$), although this was not statistically significant (Figure 1C).

Additionally, correlation of MPV with parameters of sleep was noted. MPV weakly correlated with AHI ($r=0.204$, $P=0.022$), oxygen desaturation index ($r=0.216$, $P=0.023$), and minimum SaO2 (%) ($r=-0.180$, $P=0.044$) (Figure 2). These results suggested that OSA patients have higher MPV and platelet large cell ratio values and tend to have relatively increased platelet activation and atherothrombotic risk.

The Impact of OSA on Pharmacodynamic Profiles of Antiplatelet Drugs

No significant difference in inhibitory rate of arachidonic acid pathway was observed between patients with OSA and those without (Figure 3A). Significant lower inhibitory rate of ADP pathway in patients with OSA compared with those without (Figure 3B). Additionally, correlation of the inhibitory rate of ADP pathway with parameters of sleep was analyzed by Spearman correlation analysis. The inhibitory rate of ADP pathway weakly correlated with mean SaO_2 (%) ($r=0.188$, $P=0.034$) and total percentage of time SaO_2 <90% ($r=-0.198$, $P=0.038$) (Figure 4).

Previous studies have demonstrated that suboptimal response to antiplatelet agents was affected by many factors.[18,19] Simple linear regression analysis showed that the inhibitory rate of ADP pathway may be associated with age, sex, OSA, hypertension, eGFR, platelet counts and β-blockers ($P<0.1$) (Table S1). To further examine the relationship OSA and the inhibitory rate of ADP pathway, we used a multivariable linear regression model to evaluate the independent contribution of the OSA and non-OSA groups to the inhibitory rate of ADP pathway after adjusting for age, sex, hypertension, eGFR,

Table 1. Patients Characteristics

Variables	All (n=127)	OSA Group (n=68)	Non-OSA Group (n=59)	*P* Value
Age, y	55.2±9.9	55.9±10.5	54.5±9.2	0.42
Male	112 (88.2)	62 (91.2)	50 (84.7)	0.29
Diabetes mellitus	37 (29.1)	19 (27.9)	18 (30.5)	0.85
BMI, kg/m^2	26.6 [24.6, 28.7]	27.7 [25.3, 29.3]	25.9 [24.2, 27.7]	0.02
Smoking	76 (59.8)	36 (52.9)	40 (67.8)	0.10
Alcohol	53 (41.7)	33 (48.5)	20 (33.9)	0.10
Medical history				
Hypertension	76 (59.8)	44 (64.7)	32 (54.2)	0.28
Dyslipidemia	30 (23.6)	17 (25.0)	13 (22.0)	0.83
Prior MI	16 (12.6)	6 (8.5)	10 (16.2)	0.28
Prior PCI	20 (15.7)	14 (20.6)	6 (10.2)	0.14
Prior CABG	2 (1.6)	1 (1.5)	1 (1.7)	1.00
Prior stroke	11 (8.7)	8 (11.8)	3 (5.1)	0.22
ACS category				
UA	45 (35.4)	26 (38.3)	19 (32.2)	0.60
NSTEMI	33 (26.0)	13 (19.1)	20 (33.9)	0.09
STEMI	49 (38.6)	29 (42.6)	20 (33.9)	0.41
PCI	100 (78.7)	55 (80.9)	45 (76.3)	0.66
Medication				
PPIs	107 (84.3)	56 (82.4)	51 (86.4)	0.63
ACEI	78 (61.4)	43 (63.2)	35 (59.3)	0.72
ARB	21 (16.5)	12 (17.6)	9 (15.3)	0.81
Diuretics	5 (3.9)	3 (4.4)	2 (3.4)	1.00
Statin	127 (100.0)	68 (100.0)	59 (100)	-
β-blockers	111 (87.4)	58 (85.3)	53 (89.8)	0.59
Calcium antagonists	17 (13.4)	11 (16.2)	6 (10.2)	0.44
Laboratory data				
Platelet count, 1000/mm^3	211.5 [179.8, 248.3]	207.0 [172.0, 249.0]	213.0 [185.0, 248.0]	0.42
Plateletcrit (%)	0.20 [0.18, 0.24]	0.20 [0.18, 0.25]	0.21 [0.18, 0.24]	0.88
Hematocrit, %	41.94±3.63	41.82±3.43	42.08±3.88	0.68
WBC, 1000/mm^3	8.56±2.77	8.87±2.76	8.20±2.76	0.17
HbA1c, %	6.58±1.37	6.55±1.29	6.60±1.46	0.85
Creatinine, μmol/L	75.0 [68.0, 85.0]	76.5 [71.0, 86.5]	74.0 [66.0 83.0]	0.08
eGFR, mL/min per 1.73 m^2	97.7 [83.8, 109.0]	94.5 [83.0, 106.5]	102.0 [85.4, 114.3]	0.14

Data given as n (%), mean±SD or median [IQR]. *P* value is moderate/severe OSA vs without or with mild OSA. ACEI indicates angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; HbA1c, hemoglobin A1c; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; WBC, white blood cell counts.

platelet counts and β-blockers. These results showed that the presence or not of OSA significantly contributed to the inhibitory rate of ADP pathway (β: −10.57, 95% CI: −19.68 to −1.45, *P*=0.023) (Table 3), suggesting that OSA is associated with reduced clopidogrel-induced antiplatelet effects.

OSA and HRPR

In the overall study population, inhibitory rates of ADP pathway quartile cut points for the 25th, 50th, and 75th percentiles of the study population were 26.8%, 47.8%, and 66.9%, respectively. The lower quartile identified patients with

Table 2. Sleep Information

Variables	All (n=127)	OSA Group (n=68)	Non-OSA Group (n=59)	*P* Value
AHI, events/h	16.0 [8.0, 34.0]	32.8 [24.0, 52.0]	8.0 [4.0, 10.9]	<0.001
ODI, events/h	16.0 [7.0, 36.0]	36.0 [22.5, 51.0]	7.0 [4.0, 11.0]	<0.001
Minimum SaO_2 (%)	85.0 [80.0, 88.0]	83.0 [76.0, 86.0]	88.0 [85.0, 89.0]	<0.001
Mean SaO_2 (%)	94.0 [93.0, 95.0]	93.0 [92.0, 94.0]	95.0 [94.0, 96.0]	<0.001
Total percentage of time of SaO_2 <90%	1.0 [0.0, 8.0]	6.0 [1.0, 17.5]	0.0 [0.0, 1.0]	<0.001

Data given as median [IQR]. AHI indicates apnea-hypopnea index; IQR, Interquartile range; ODI, oxygen desaturation index; OSA, obstructive sleep apnea.

HRPR.[20] As Figure 5 showed, patients with OSA were more likely to have HRPR than those non-OSA (33.8% versus 13.6%, *P*=0.012).

To further investigate the impact of OSA on HRPR, we classified the included patients into 2 groups (non-HRPR and HRPR) according to the inhibitory rates of ADP pathway. The characteristics and demographic variables of the patient groups are shown in Table S2. AHI, OSA, Prior MI, and eGFR were significantly different between groups (Table S2). Logistic regression analysis showed that OSA significantly associated with HRPR (OR: 3.26, 95% CI: 1.33–8.01, *P*=0.010). After adjustment for potential confounders (age, sex, body mass index, diabetes mellitus, hypertension, prior PCI, and eGFR), OSA remained markedly associated with HRPR (adjusted OR: 3.25, 95% CI: 1.19–8.87, *P*=0.021).

Discussion

The present study showed that in ACS receiving maintenance aspirin and clopidogrel therapy, the presence of OSA is associated with higher levels of MPV and L-PCR compared with patients with non-OSA. In particular, these patients with OSA also have higher degrees of platelet reactivity after clopidogrel therapy. Additionally, after adjustment for potential confounders, patients with OSA had a 3.25-fold increase in the likelihood of showing HRPR after clopidogrel therapy. Overall, these findings are indicative not only of the presence of a hyper-reactive platelet phenotype but also of dysfunctional ADP signaling mediated $P2Y_{12}$ receptor. Therefore, these observations might explain the elevated prevalence of ischemic complications, including stent thrombosis, among CAD patients with OSA.

OSA is now considered a novel cardiovascular risk factor, according to the "European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)".[21] Up to 66% of ACS patients have OSA and about 50% of patients with PCI suffer from OSA.[3–5] Meta-analysis demonstrated that cardiac death is 2-fold higher in patients with OSA after successful PCI.[4] The OSA patients also have more aggressive atherosclerotic disease and a greater risk of thrombotic complications, including stent thrombosis.[22] The Sleep and Stent Study enrolled 1311 patients successfully treated with PCI, and >98% of these patients were treated with DAPT. The result of the study showed that OSA is independently associated with subsequent major adverse cardiac and cerebrovascular events, claiming the need for additional studies to evaluate of therapeutic approaches to mitigate OSA-associated risk.[5] Interestingly, some clinical studies showed that severe OSA significantly increases the level of MPV and platelet reactivity, and CPAP therapy significantly reversed this effect.[7,9] Rahangdale et al have previously reported in a small cohort ADP-induced platelet aggregation was markedly increased in OSA patients.[7] However, it remains unclear whether OSA affects the clinical outcomes of CAD patients taking DAPT by influencing platelet function and antiplatelet agent efficacy.

Platelet volume indices are known as indicators of platelet activation and play an important role in the pathophysiology of cardiovascular diseases.[16,17] Recently, Wasilewski et al have reported that all-cause mortality is 1.5-fold higher in non-ST-segment elevation myocardial infarction patients with high MPV values.[17] In earlier studies, MPV and PDW were found to be significantly higher in patients with severe OSA when compared with control subjects.[23,24] In this study, we firstly found that MPV and platelet large cell ratio values of ACS patients taking DAPT with moderate/severe OSA were significantly higher than those without, and that MPV correlated with AHI, oxygen desaturation index, and minimum SaO_2 (%) (Figures 1 and 2). Our results suggested that ACS patients taking DAPT with OSA tend to have an increased platelet activation. Increased platelet activity could contribute to an increased atherothrombotic risk in patients with OSA. CPAP reported to cause a significant decrease in the MPV and PDW values in patients with OSA,[9,10] and this suggested that early diagnosis and CPAP therapy may confer some cardioprotective effects through the reduction of platelet activation.

Suboptimal response to antiplatelet agents or HRPR, in fact, has been associated with an enhanced risk of major cardiovascular events and acute ischemic complications, especially with clopidogrel, where a high HRPR has been described in almost 30% of patients.[18,25,26] In patients with

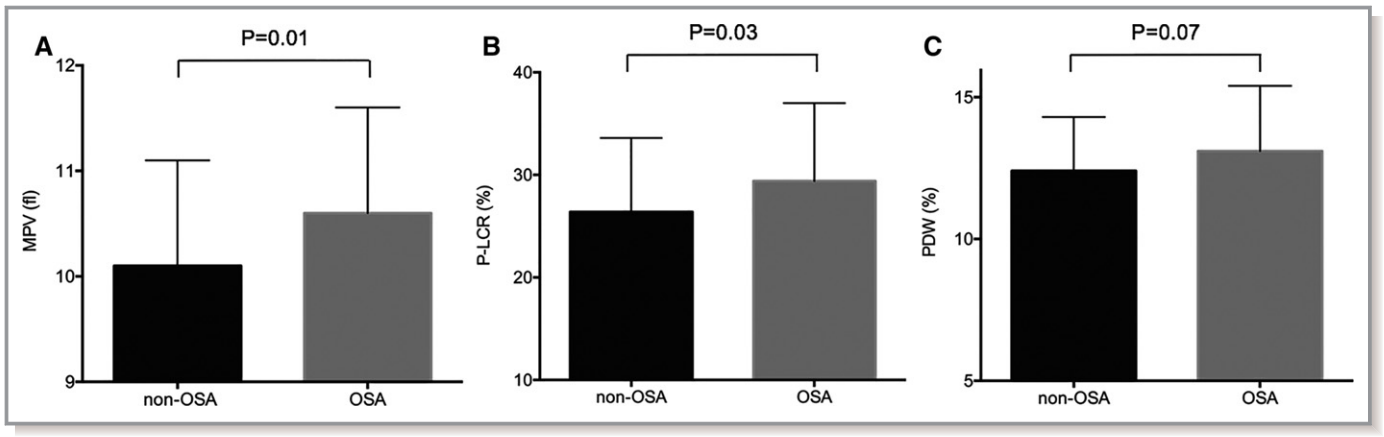

Figure 1. The impact of OSA on platelet volume indices in ACS patients taking DAPT. The level of MPV (A), P-LCR (B) and PDW (C) in patients with and without OSA. ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; MPV, mean platelet volume; OSA, obstructive sleep apnea; PDW, platelet distribution width; P-LCR, platelet large cell ratio.

ACS or undergoing PCI, HRPR is associated with ≈2- to 3-fold greater risk of recurrent ischemic events and about 1.5-fold greater risk of all-cause mortality.[27–29] In particular, this study shows a broad variability platelet function profiles in patients receiving clopidogrel, and OSA is associated with reduced clopidogrel-induced antiplatelet effects and a greater likelihood of having HRPR. Our study findings might contribute to explain why some OSA patients have worse clinical prognosis than others and suggest the potential need for further categorizing this already high-risk cohort of patients into those with and without OSA. This might enable a better understanding of their individual risk profile and allow the future development of targeted treatment strategies for these patients.

The persistence of high-platelet reactivity despite adjunctive clopidogrel therapy underscores the need for more potent platelet inhibition strategies to reduce the risk of recurrence of ischemic events, including high dose of clopidogrel and

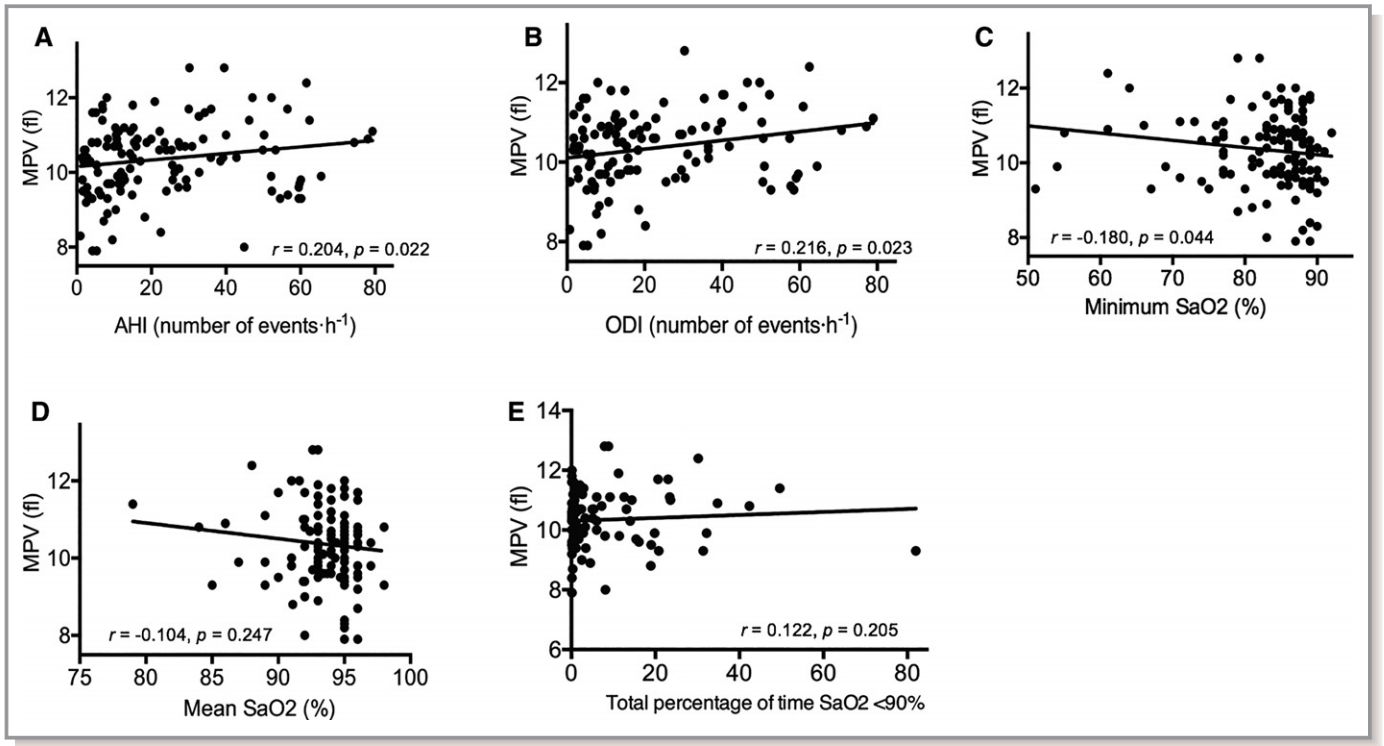

Figure 2. Correlation between MPV and parameters of sleep. Correlation between MPV and AHI (A), ODI (B), and minimum SaO_2 (%) (C), mean SaO_2 (%) (D), and total percentage of time of SaO_2<90% (E). AHI indicates apnea-hypopnea index; MPV, mean platelet volume; ODI, oxygen desaturation index.

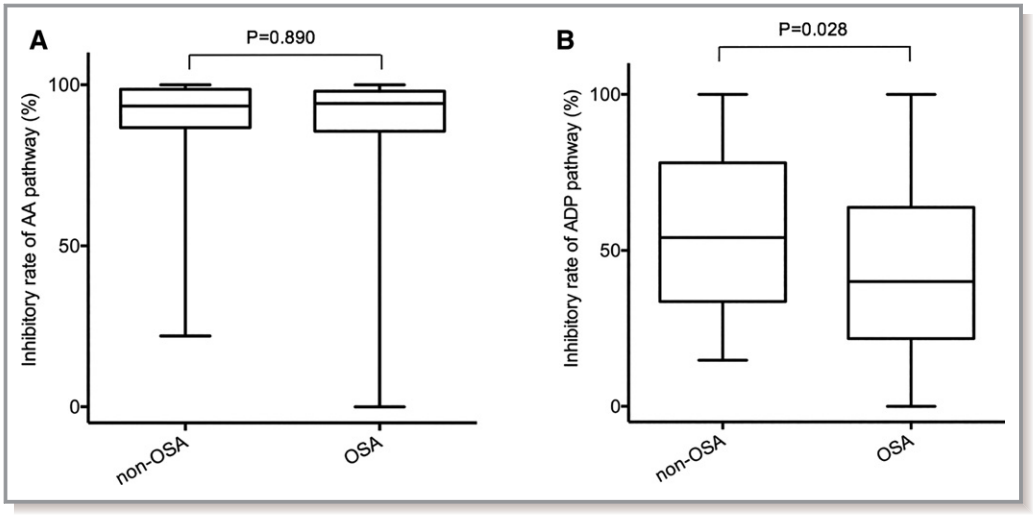

Figure 3. The impact of OSA on the inhibitory rate of arachidonic acid or ADP pathway. (A) No significant differences in inhibitory rate of arachidonic acid pathway was observed between patients with OSA and those without; (B) Patients with OSA had significantly lower inhibitory rate of ADP pathway compared with those without. The central box represents the values between the lower and upper quartiles, and the middle line is the median. AA indicates arachidonic acid; ADP, adenosine diphosphate; OSA, obstructive sleep apnea.

new antiplatelet agents. The new $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) have a more predictable response, greater potency and faster onset of characteristics, thus making them the treatment of choice in patients receiving clopidogrel therapy with HRPR. Nowadays, new oral $P2Y_{12}$ inhibitors have evidentially been recommended for the treatment of ACS, as

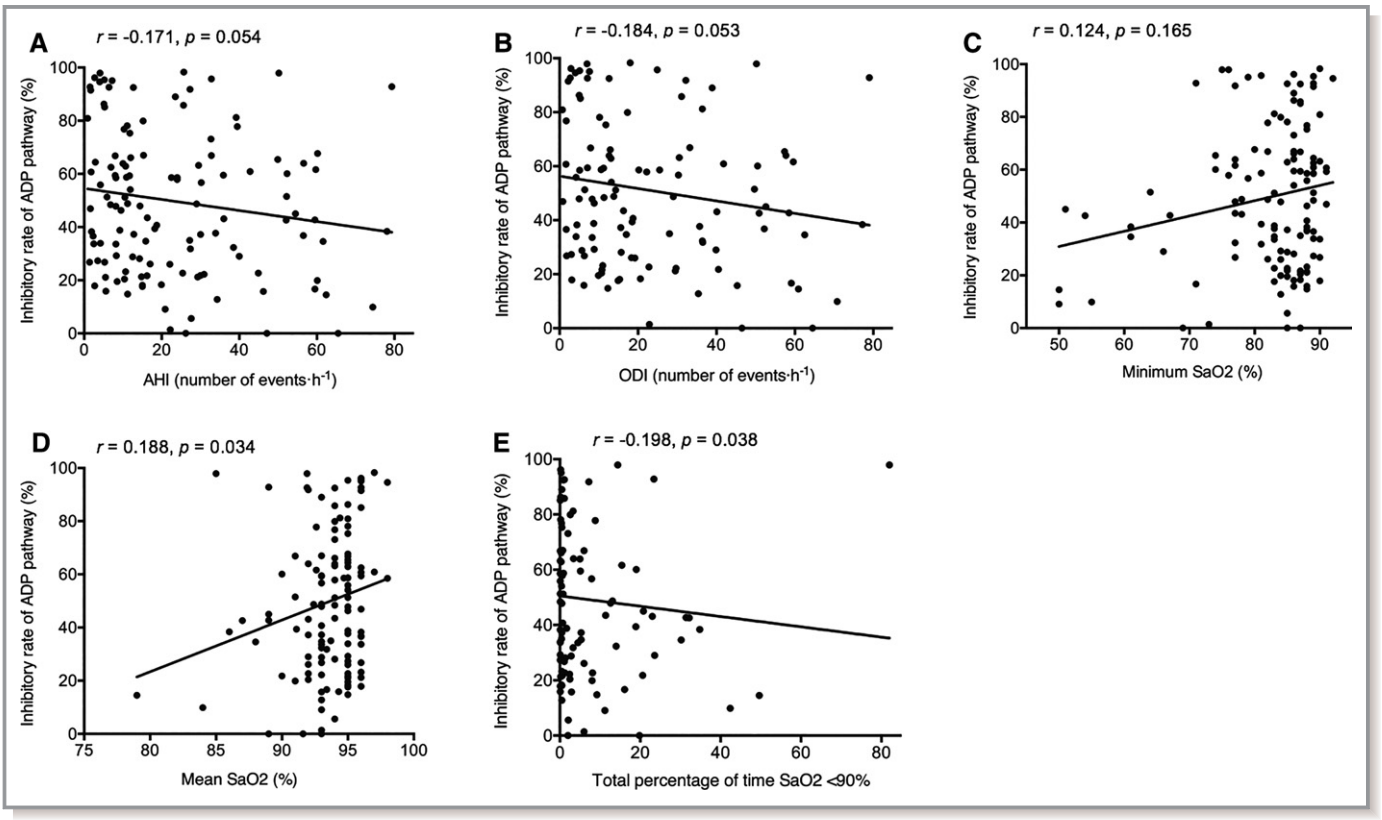

Figure 4. Correlation between inhibitory rate of ADP pathway and parameters of sleep. Correlation between inhibitory rate of ADP pathway and AHI (A), ODI (B), and minimum SaO_2 (%) (C), mean SaO_2 (%) (D), and total percentage of time of SaO_2<90% (E). ADP indicates adenosine diphosphate; AHI, apnea-hypopnea index; ODI, oxygen desaturation index.

Table 3. Multivariable Linear Regression Analysis of the Inhibitory Rate of ADP Receptor Pathway (Presence or Not of OSA)

Variables	β (95% CI)	*P* Value
Age, y	−0.03 (−0.58, 0.53)	0.930
Male	9.56 (−5.36, 24.48)	0.207
Group		
Non-OSA	Reference	
OSA	−10.57 (−19.68, −1.45)	0.023
Hypertension	5.09 (−4.02, 14.20)	0.271
eGFR, mL/min per 1.73 m^2	0.24 (0.02, 0.47)	0.035
Platelet counts, 1000/mm^3	0.08 (0.00, 0.16)	0.043
β-blockers	−13.918 (−27.72, −0.12)	0.048

ADP indicates adenosine diphosphate; CI, Confidence interval; eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnea.

they show a reduction in cardiovascular events compared with clopidogrel.[11,12] However, it may be argued that high-platelet reactivity alone cannot be used as a good indicator for using more potent platelet inhibition, because if OSA also exists, then reducing the potential benefits of ischemic events may be offset by the bleeding rate. In fact, OSA is well-established to be associated with increased bleeding risk.[30–32] Indeed, evaluating outcome data in OSA patients will provide more insights on the risk-benefit ratio of antithrombotic strategies, particularly with the introduction of novel and more potent agents.

Several limitations of this study should be noted. First, this is a cross-sectional observational study of independent groups and suffers from the apparent limitations of a non-randomized trial. In an attempt to account for these limitations, we also made comparisons that were adjusted for several clinical variables. Because of the large number of variables introduced, we cannot rule out a potential of overfitting models. Second, in the present study, we assessed the impact of OSA on pharmacodynamic profiles of antiplatelet drugs according to thrombelastography. No data (eg, glycoprotein IIb/IIIa activation and P-selectin expression) were available to evaluate platelet activation. Third, this study excluded elderly patients (aged >75 years), which could have included patients who exhibited the most severe OSA.

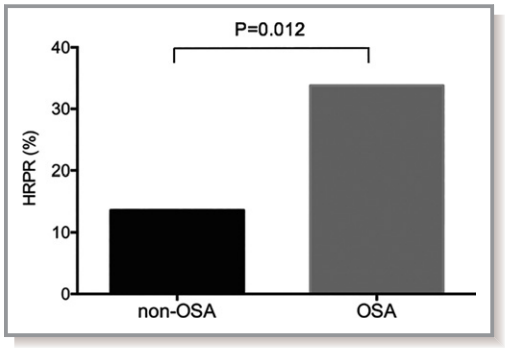

Figure 5. Prevalence of HRPR in patients with OSA and non-OSA. HRPR indicates high residual on-treatment platelet reactivity; OSA, obstructive sleep apnea.

Conclusion

To the best of our knowledge, this is the first study providing a potential underlying mechanism to explain why OSA patients with CAD have worse outcomes. In ACS patients taking maintenance aspirin and clopidogrel therapy, OSA is associated with an increased level of platelet-volume indices, reduced clopidogrel-induced antiplatelet effects, and a greater prevalence of HRPR.

Sources of Funding

This study was supported by grants from the National Natural Science Foundation of China (81600213, 81600209, and 81670222), Capital Medical University Foundation-Clinical Research Cooperation Fund (16JL17), International Science & Technology Cooperation Program of China (2015DFA30160), Beijing Municipal Science & Technology Commission (Z141100006014057), Beijing Municipal Administration of Hospitals' Youth Program (QML20160605).

Disclosures

None.

References

1. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. *Circulation*. 2017;136:1840–1850.
2. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehra R, Pack AI, Polotsky VY, Redline S, Somers VK. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. *J Am Coll Cardiol*. 2017;69:841–858.
3. Lee CH, Khoo SM, Tai BC, Chong EY, Lau C, Than Y, Shi DX, Lee LC, Kailasam A, Low AF, Teo SG, Tan HC. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. *Chest*. 2009;135:1488–1495.
4. Qu H, Guo M, Zhang Y, Shi DZ. Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies. *Sleep Breath*. 2018;22:33–40.
5. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, Loo G, Koo CY, Gao XF, Chandra S, Yang XX, Furlan SF, Ge Z, Mundhekar A, Zhang WW, Uchôa CH, Kharwar RB, Chan PF, Chen SL, Chan MY, Richards AM, Tan HC, Ong TH, Roldan G, Tai BC, Drager LF, Zhang JJ. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. *Circulation*. 2016;133:2008–2017.
6. Wu H, Yuan X, Wang L, Sun J, Liu J, Wei Y. The relationship between obstructive sleep apnea hypopnea syndrome and inflammatory markers and quality of life in subjects with acute coronary syndrome. *Respir Care*. 2016;61:1207–1216.

7. Rahangdale S, Yeh SY, Novack V, Stevenson K, Barnard MR, Furman MI, Frelinger AL, Michelson AD, Malhotra A. The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. *J Clin Sleep Med*. 2011;7:172–178.
8. Toraldo DM, De Benedetto M, Scoditti E, De Nuccio F. Obstructive sleep apnea syndrome: coagulation anomalies and treatment with continuous positive airway pressure. *Sleep Breath*. 2016;20:457–465.
9. Gunbey E, Karabulut I, Karabulut H, Zaim M. Impact of multilevel surgical treatment on mean platelet volume in patients with obstructive sleep apnea syndrome. *J Craniofac Surg*. 2015;26:1287–1289.
10. Varol E, Ozturk O, Yucel H, Gonca T, Has M, Dogan A, Akkaya A. The effects of continuous positive airway pressure therapy on mean platelet volume in patients with obstructive sleep apnea. *Platelets*. 2011;22:552–556.
11. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:267–315.
12. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177.
13. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc*. 2008;5:136–143.
14. Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thrombelastography Platelet Mapping. *Br J Anaesth*. 2009;102:492–498.
15. Hobson AR, Agarwala RA, Swallow RA, Dawkins KD, Curzen NP. Thrombelastography: current clinical applications and its potential role in interventional cardiology. *Platelets*. 2006;17:509–518.
16. Öztürk ZA, Dag MS, Kuyumcu ME, Cam H, Yesil Y, Yilmaz N, Aydinli M, Kadayifci A, Kepekci Y. Could platelet indices be new biomarkers for inflammatory bowel diseases? *Eur Rev Med Pharmacol Sci*. 2013;17:334–341.
17. Wasilewski J, Desperak P, Hawranek M, Ciślak A, Osadnik T, Pyka Ł, Gawlita M, Bujak K, Niedziela J, Krawczyk M, Gąsior M. Prognostic implications of mean platelet volume on short- and long-term outcomes among patients with non-ST-segment elevation myocardial infarction treated with percutaneous coronary intervention: a single-center large observational study. *Platelets*. 2016;27:452–458.
18. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation*. 2003;107:2908–2913.
19. Zhang YJ, Li MP, Tang J, Chen XP. Pharmacokinetic and pharmacodynamic responses to clopidogrel: evidences and perspectives. *Int J Environ Res Public Health*. 2017;14:E301.
20. Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabaté M, Ferreiro JL, Ueno M, Jimenez-Quevedo P, Alfonso F, Bass TA, Macaya C, Fernandez-Ortiz A. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. *J Am Coll Cardiol*. 2010;55:1139–1146.
21. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–1701.
22. Li Y, Yang S, Chen S, Guo X, Chen Y. Patients with symptoms and characteristics consistent with obstructive sleep apnea are at a higher risk for acute and subacute stent thrombosis after percutaneous coronary stent implantation: a single-center case-control study. *BMC Cardiovasc Disord*. 2017;17:226.
23. Nena E, Papanas N, Steiropoulos P, Zikidou P, Zarogoulidis P, Pita E, Constantinidis TC, Maltezos E, Mikhailidis DP, Bouros D. Mean platelet volume and platelet distribution width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? *Platelets*. 2012;23:447–454.
24. Pyo JS, Cho WJ. Mean platelet volume, platelet distribution width, and platelet count in varicocele: a systematic review and meta-analysis. *Cell Physiol Biochem*. 2016;38:2239–2246.
25. Valenti R, Marcucci R, Capodanno D, De Luca G, Migliorini A, Gori AM, Parodi G, Giusti B, Carrabba N, Paniccia R, Cantini G, Marrani M, Gensini GF, Abbate R, Antoniucci D. Residual platelet reactivity to predict long-term clinical outcomes after clopidogrel loading in patients with acute coronary syndromes: comparison of different cutoff values by light transmission aggregometry from the responsiveness to clopidogrel and stent thrombosis 2-acute coronary syndrome study. *J Thromb Thrombolysis*. 2015;40:76–82.
26. Nguyen TA, Diodati JG, Pharand C. Resistance to clopidogrel: a review of the evidence. *J Am Coll Cardiol*. 2005;45:1157–1164.
27. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, Deneer VH, Harmsze AM, van der Heyden JA, Rensing BJ, Suttorp MJ, Hackeng CM, ten Berg JM. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA*. 2010;303:754–762.
28. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. *JAMA*. 2011;306:1215–1223.
29. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freynhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. *Eur Heart J*. 2015;36:1762–1771.
30. Pontes-Neto OM, Fernandes RM, Sander HH, da Silva LA, Mariano DC, Nobre F, Simão G, de Araujo DB, dos Santos AC, Leite JP. Obstructive sleep apnea is frequent in patients with hypertensive intracerebral hemorrhage and is related to perihematoma edema. *Cerebrovasc Dis*. 2010;29:36–42.
31. Hwang D, Shakir N, Limann B, Sison C, Kalra S, Shulman L, Souza Ade C, Greenberg H. Association of sleep-disordered breathing with postoperative complications. *Chest*. 2008;133:1128–1134.
32. Song TJ, Park JH, Choi KH, Chang Y, Moon J, Kim JH, Choi Y, Kim YJ, Lee HW. Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease. *Sleep Med*. 2017;30:36–42.

SUPPLEMENTAL MATERIAL

Table S1. Simple linear regression analysis of the inhibitory rate of ADP receptor pathway.

Variables	**β (95% CI)**	***P* value**
Age	-0.46 (-0.94, 0.25)	0.063
Male	13.71 (-1.15, 28.57)	0.070
BMI (kg/m^2)	-0.20 (-1.52, 1.13)	0.770
Smoking	7.94 (-1.87, 17.75)	0.112
Alcohol	2.57 (-7.28, 12.41)	0.607
Medical history		
Diabetes	-4.10 (-14.77, 6.58)	0.449
Hypertension	8.92 (-0.86，18.71)	0.074
Dyslipidemia	1.97 (-9.46, 13.41)	0.733
Prior MI	-7.80 (-22.38, 6.78)	0.292
Prior stroke	6.81 (-10.43, 24.04)	0.436
Diagnosis		
STEMI	-0.56 (-10.55, 9.42)	0.911
Sleep information		
AHI (events/h)	-0.21 (-0.45, 0.04)	0.099
ODI (events/h)	-0.23 (-0.49, 0.03)	0.086
Minimum SaO_2 (%)	0.58 (0.03, 1.12)	0.039
Mean SaO_2 (%)	1.97 (0.20, 3.74)	0.029
Time of SaO_2<90%	-0.16 (-0.59, 0.26)	0.445
Moderate/severe OSA	-11.18 (-20.72, -1.64)	0.022
Medication		
PPIs	4.15 (-9.18, 17.47)	0.539
ACEI	-1.36 (-11.34, 8.62)	0.787
ARB	-3.40 (-16.46, 9.67)	0.608
Diuretics	-3.43 (-28.41, 22.55)	0.786
β-blockers	-13.87 (-28.30, 0.57)	0.060

Calcium antagonists	0.49 (-13.78, 14.76)	0.946
Laboratory data		
Platelet count (1,000/mm^3)	0.99 (0.02, 0.18)	0.015
Platelet crit (%)	87.59 (3.11, 172.07)	0.042
MPV (fl)	-1.40 (-6.39, 3.60)	0.580
PDW (%)	0.99 (-1.30, 3.27)	0.394
P-LCR (%)	0.05 (-0.61, 0.70)	0.889
HbA1C (%)	0.79 (-3.01, 4.61)	0.678
Creatinine (μmol/l)	-0.02 (-0.29, 0.24)	0.858
eGFR (ml/min/1.73m^2)	0.35 (0.14, 0.56)	0.001

ACS indicates acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitors; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HRPR, high residual on-treatment platelet reactivity; MI, myocardial infarction; MPV, mean platelet volume; ODI, oxygen desaturation index; IQR, interquartile range; PCI, percutaneous coronary intervention; PDW, platelet distribution width; P-LCR, platelet large cell ratio; PPIs, proton pump inhibitors; SD, standard deviation; and STEMI, ST-segment elevation myocardial infarction.

Table S2. Characteristics of patients with non-HRPR and HRPR.

Variables	Non-HRPR (n=96)	HRPR (n=31)	*P* value
Age, years	54.96±10.15	55.97±9.43	0.63
Male	86 (89.58)	26 (83.87)	0.52
BMI (kg/m^2)	26.6 [24.5, 28.7]	27.0 [24.8, 29.4]	0.65
Smoking	60 (62.50)	16 (51.61)	0.30
Alcohol	41 (42.71)	12 (38.71)	0.84
Medical history			
Diabetes	29 (30.21)	8 (225.81)	0.82
Hypertension	61 (63.54)	15 (48.39)	0.15
Dyslipidemia	24 (25.00)	6 (19.35)	0.63
Prior MI	12 (12.50)	4 (12.90)	1.00
Prior PCI	11 (11.56)	9 (29.03)	0.04
Prior CABG	2 (1.50)	0 (0.00)	1.00
Prior Stroke	8 (8.33)	3 (9.68)	0.73
Sleep information			
AHI (events/h)	13.50 [6.83, 32.95]	22.20 [15.00, 45.00]	0.03
ODI (events/h)	14.00 [6.00, 36.00]	22.00 [11.25, 43.75]	0.05
Minimum SaO_2 (%)	86.00 [79.25, 88.00]	85.00 [83.00, 87.00]	0.45
Mean SaO_2 (%)	94.00 [93.00, 95.00]	93.00 [92.00, 95.00]	0.22
Time of SaO_2<90%	1.00 [0.00, 5.75]	2.00 [0.00, 9.00]	0.19
OSA	45 (46.88)	23 (74.19)	0.01
Diagnosis			
Type of ACS (STEMI)	35 (36.46)	14 (45.16)	0.40
Medication			
PPIs	82 (85.42)	25 (80.65)	0.57
ACEI	61 (63.54)	17 (54.84)	0.40
ARB	13 (13.54)	8 (25.81)	0.16
Diuretics	3 (3.13)	2 (6.45)	0.60
Satin	96 (100)	31 (100)	—
β-blockers	81 (84.38)	30 (96.77)	0.12
Calcium antagonists	13 (13.54)	4 (12.90)	1.00
Laboratory data			
Platelet count (1,000/mm^3)	212.00 [181.00, 249.00]	201.00 [171.00, 246.00]	0.49
Platelet crit (%)	0.20 [0.17, 0.24]	0.20 [0.18, 0.25]	0.66
MPV (fl)	10.30±1.00	10.55±0.90	0.21
PDW (%)	12.82±2.23	12.62±1.88	0.65
P-LCR (%)	27.70±7.63	28.85±7.28	0.46
HbA1C (%)	6.67±1.50	6.27±1.20	0.25

Creatinine (μmol/l)	74.00 [67.00, 83.00]	79.00 [74.00, 87.00]	0.06
eGFR (ml/min/1.73m^2)	101.87 [85.83, 113.37]	90.83 [79.05, 101.87]	0.02

Data given as No. (%), mean ± SD or median [IQR]. *P* value is non-HRPR vs. HRPR. ACS indicates acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitors; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HRPR, high residual on-treatment platelet reactivity; MI, myocardial infarction; MPV, mean platelet volume; ODI, oxygen desaturation index; IQR, interquartile range; PCI, percutaneous coronary intervention; PDW, platelet distribution width; P-LCR, platelet large cell ratio; PPIs, proton pump inhibitors; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.