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Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery

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IMPORTANCE Unrecognized obstructive sleep apnea increases cardiovascular risks in the general population, but whether obstructive sleep apnea poses a similar risk in the perioperative period remains uncertain.

OBJECTIVES To determine the association between obstructive sleep apnea and 30-day risk of cardiovascular complications after major noncardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS Prospective cohort study involving adult at-risk patients without prior diagnosis of sleep apnea and undergoing major noncardiac surgery from 8 hospitals in 5 countries between January 2012 and July 2017, with follow-up until August 2017. Postoperative monitoring included nocturnal pulse oximetry and measurement of cardiac troponin concentrations.

EXPOSURES Obstructive sleep apnea was classified as mild (respiratory event index [REI] 5-14.9 events/h), moderate (REI 15-30), and severe (REI >30), based on preoperative portable sleep monitoring.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of myocardial injury, cardiac death, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of surgery. Proportional-hazards analysis was used to determine the association between obstructive sleep apnea and postoperative cardiovascular complications.

RESULTS Among a total of 1364 patients recruited for the study, 1218 patients (mean age, 67 [SD, 9] years; 40.2% women) were included in the analyses. At 30 days after surgery, rates of the primary outcome were 30.1% (41/136) for patients with severe OSA, 22.1% (52/235) for patients with moderate OSA, 19.0% (86/452) for patients with mild OSA, and 14.2% (56/395) for patients with no OSA. OSA was associated with higher risk for the primary outcome (adjusted hazard ratio [HR], 1.49 [95% CI, 1.19-2.01]; $P = .01$); however, the association was significant only among patients with severe OSA (adjusted HR, 2.23 [95% CI, 1.49-3.34]; $P = .001$) and not among those with moderate OSA (adjusted HR, 1.47 [95% CI, 0.98-2.09]; $P = .07$) or mild OSA (adjusted HR, 1.36 [95% CI, 0.97-1.91]; $P = .08$) ($P = .01$ for interaction). The mean cumulative duration of oxyhemoglobin desaturation less than 80% during the first 3 postoperative nights in patients with cardiovascular complications (23.1 [95% CI, 15.5-27.7] minutes) was longer than in those without (10.2 [95% CI, 7.8-10.9] minutes) ($P < .001$). No significant interaction effects on perioperative outcomes were observed with type of anesthesia, use of postoperative opioids, and supplemental oxygen therapy.

CONCLUSIONS AND RELEVANCE Among at-risk adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative cardiovascular complications. Further research would be needed to assess whether interventions can modify this risk.

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Obstructive sleep apnea (OSA) is the most common type of sleep-disordered breathing and is characterized by cyclical alterations between pharyngeal collapse and arousals during sleep.[1] Consequently, there are recurrent episodes of nocturnal hypoxemia, hypercapnia, endothelial dysfunction, hypercoagulability, and sympathetic overactivity.[2] In the general population, OSA is associated with higher risk of cardiovascular complications[3] such as hypertension,[4] myocardial ischemia, heart failure,[5] arrhythmias, stroke,[6] and sudden cardiac death.[7]

General anesthetics, sedatives, and postoperative analgesics are potent respiratory depressants that relax the upper airway dilator muscles and impair ventilatory response to hypoxemia and hypercapnia.[1] Each of these events exacerbates OSA and may predispose patients to postoperative cardiovascular complications. In this respect, perioperative mismanagement of OSA has led to serious medicolegal consequences.[8] However, recent analyses of large database repositories showed conflicting results. Depending on the selected end points, OSA was associated with worse,[9-14] equivocal,[10,12,15] or better outcome[10,11] after surgery. Uncertainty remains whether unrecognized OSA adversely affects postoperative outcomes.

Based on preoperative overnight sleep studies, the Postoperative Vascular Complications in Unrecognized OSA (POSA) study was designed to determine the association between OSA and a composite of cardiac death, myocardial injury, heart failure, thromboembolism, atrial fibrillation, and stroke within 30 days of noncardiac surgery.

Key Points

Question What is the relationship between unrecognized obstructive sleep apnea (OSA) and 30-day cardiovascular complications after major noncardiac surgery?

Findings In this prospective cohort study that included 1218 at-risk patients undergoing major noncardiac surgery, the rate of a composite outcome of postoperative cardiovascular events (myocardial injury, cardiac death, congestive heart failure, thromboembolism, atrial fibrillation, and stroke) among those with OSA vs no OSA was 21.7% vs 14.2%, a difference that was statistically significant. However, the difference was significant only for the subgroup with severe OSA.

Meaning Among patients undergoing major noncardiac surgery, severe OSA was significantly associated with 30-day cardiovascular complications.

Methods

Study Design and Participants

This was a multicenter, prospective cohort study of patients undergoing major noncardiac surgery. Ethics approval was obtained for all participating centers, and all patients provided written informed consent. We reported the trial objectives, design, and methods previously.[16]

We recruited patients who were 45 years or older and undergoing major noncardiac surgery (intraperitoneal, major orthopedic, or vascular). Patients were eligible for the study if they had 1 or more risk factors for postoperative cardiovascular events (ie, history of coronary artery disease, heart failure, stroke or transient ischemic attack, diabetes requiring treatment, and renal impairment with preoperative plasma creatinine concentration >1.98 mg/dL [175 µmol/L]). We excluded patients with prior diagnosis of obstructive sleep apnea or undergoing corrective surgery for OSA (eg, tonsillectomy, uvulopalatopharyngoplasty, tracheostomy), or anticipated to require prolonged (>2 days) mechanical lung ventilation after surgery.

Procedures

Patients underwent a preoperative overnight sleep study using a type 3 portable sleep monitoring device (ApneaLink Plus; ResMed).[17] Sleep studies were performed either at home within the preceding month (34.1%) or in the surgical ward on the night before surgery (65.9%). In addition, we used a high-resolution pulse oximeter wristwatch (PULSOX-300i; Konica Minolta Sensing Inc) to monitor oxyhemoglobin saturation. Monitors were applied to the patients by experienced research staff at bedtime and were collected the following morning. Recordings were transferred to the coordinating center for subsequent analysis. We scored the sleep-associated apnea and hypopnea events according to American Academy of Sleep Medicine criteria (eAppendix 1 in the Supplement).[18] Respiratory event index (REI) was calculated as the number of these events per hour of recording. Mild OSA was diagnosed when REI was 5 to 14.9, moderate OSA when REI was 15 to 30, and severe OSA when REI was greater than 30.[18,19] Based on the pulse oximetry signals obtained from the wristwatch, we also calculated the oxygen desaturation index (ODI) as the number of events (duration >10 seconds) per hour when there was a decrease in oxyhemoglobin saturation of 4% or more from baseline.[20]

Before surgery, research staff interviewed all patients to record their baseline characteristics and risk factors for postoperative cardiovascular complications. Patients also indicated their race and ethnicity from a list of fixed categories, so that differences in OSA by race or ethnicity could be determined. In addition, we assessed patients' risk for OSA using the STOP-Bang (Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Circumference, and Gender) screening tool (scores range from 0-8, with a score of 0-2 indicating low risk; 3-4, moderate risk; and 5-8, high risk).[21]

Patients, the attending surgical team, and research staff who collected the outcome data were blinded to the results of the sleep study, STOP-Bang questionnaire scores, and oximetry recordings until 30 days after surgery. After this time, we referred patients with abnormal sleep study findings to their local sleep clinic for further management of care.

Follow-up

All types of anesthetic techniques were permitted, and surgery was performed according to routine standard of care at each site. After surgery, electrocardiograms and venous blood samples (for measuring plasma cardiac troponin concentrations) were collected at 6 to 12 hours and then daily during the

first 3 days after surgery. Additional echocardiograms and lung scans were performed, if clinically indicated, to ascertain the diagnosis of cardiac complications. During the first 3 postoperative nights, we recorded oxyhemoglobin saturation using the PULSOX-300i device. All patients were followed up regularly up to 30 days after surgery. Patients discharged home were contacted by telephone. The interview was conducted in a structured fashion. If patients or their relatives indicated that an event had occurred, we contacted the attending physicians or hospitals to obtain documentation.

Outcomes

The primary outcome was a composite of myocardial injury, cardiac death, congestive heart failure, thromboembolism, new atrial fibrillation, and stroke within 30 days of surgery. The prespecified secondary outcomes were unplanned tracheal intubation or postoperative lung ventilation, readmission to the intensive care unit (ICU), and infections. Details regarding the outcome definitions are listed in eAppendix 2 in the Supplement. All outcome events were evaluated by adjudicators blinded to the results of the sleep study.

Statistical Analysis

We estimated that a sample size of 1200 patients was required to ensure a stable regression model with an anticipated primary event rate of 4%.[16] Crude comparisons among patients with varying severity of OSA was performed using analysis of variance, Kruskal-Wallis test, or χ^2 test, as appropriate. We used Cox proportional-hazards models to determine the association between outcome events and OSA, except for unplanned tracheal intubation or postoperative lung ventilation and readmission to the ICU, for which we used logistic-regression analysis. The independent variables consisted of severity of OSA (severe, moderate, mild, or no disease) and factors previously shown to adversely affect outcomes.[22,23] These included age, history of coronary artery disease, congestive heart failure, stroke or transient ischemic attack, diabetes mellitus, chronic renal impairment, peripheral vascular disease, chronic obstructive pulmonary disease, abdominal or vascular surgery, and surgery for cancer. In addition, we included baseline variables that were unbalanced in patients with different severity of OSA—ethnicity, history of hypertension, and preoperative use of β-blockers. The proportionality assumption was evaluated by Schoenfeld residuals test. Collinearity was assessed by variance inflation factor, with a cutoff threshold of 10.[24] We also undertook a random-effects (frailty) Cox model to account for possible site-clustering effect.[25] The adjusted hazard ratios (HRs) for different severity of OSA were compared among groups using χ^2 test.

We used a general linear model to determine the association between nocturnal hypoxia and the primary outcome. In this model, severity of postoperative hypoxia was expressed as ODI. Other covariates included in the model were risk factors for the primary outcome as described above. We repeated the analysis to determine the association between the primary outcome and other measures of nocturnal hypoxia, including the lowest oxyhemoglobin saturation and the duration of oxyhemoglobin desaturation less than 80% and less than 90% recorded.

We also analyzed the primary outcome in prespecified subgroups of patients with the following characteristics: general or regional anesthesia, volatile-based anesthesia or propofol infusion, the number of postoperative nights with supplemental oxygen therapy, receiving (or not receiving) opioids after surgery, using (or not using) patient-controlled analgesia, and whether the surgery was considered minimally invasive. Subgroup analyses were performed using Cox models with the addition of corresponding interaction terms.

To better understand the basis of adverse outcomes, we performed post hoc analyses by repeating the Cox models using individual components of the primary outcome as the dependent variable. In addition, we conducted a sensitivity analysis to determine the validity of myocardial injury as an outcome measure. In this analysis, myocardial injury in the composite primary outcome was replaced by myocardial infarction according to the universal definition.[26] A post hoc comparison of the length of hospital stay in patients with different severity of OSA was also performed using log-rank test. In-hospital deaths were assigned with the longest length of stay.

For the association between outcomes and preoperative risk assessment for OSA based on the STOP-Bang screening tool, we repeated the primary analysis by stratifying patients as low-, intermediate-, and high-risk. We planned to conduct multiple imputations if there were more than 5% missing data on the outcomes or baseline variables included in the regression models. There was no adjustment for multiple comparisons; therefore, the results of the secondary analyses, subgroup analyses, and other analyses should be interpreted as exploratory.

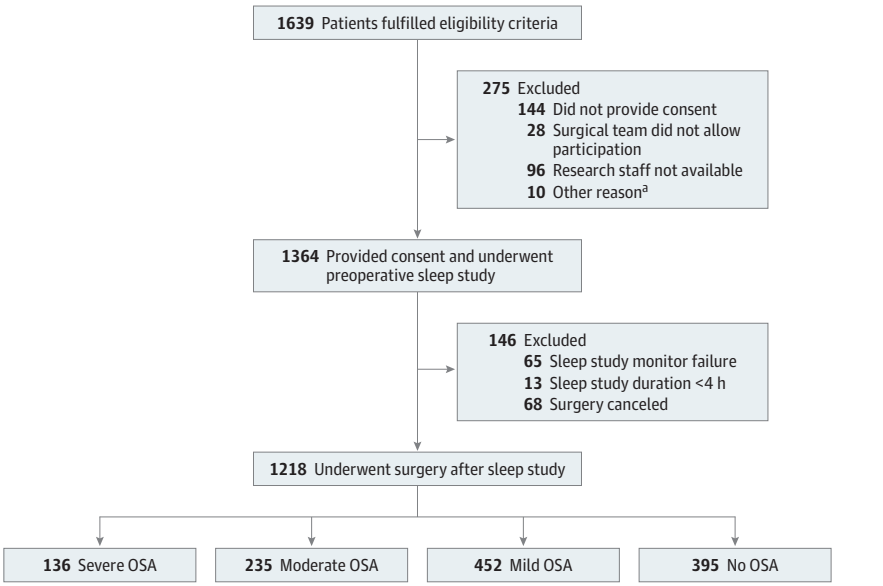
All tests were 2-sided, and $P<.05$ was designated as statistically significant. Analyses were performed using Stata Release 13 (StataCorp) and R version 3.5.2 (R Project for Statistical Computing).

Results

A total of 1364 patients were recruited from 8 hospitals in 5 countries between January 2012 and July 2017. We excluded 78 patients because sleep recordings (<4 hours) were unsatisfactory for analysis. Another 68 patients were excluded because surgery was canceled and could not be rescheduled within the subsequent month. Overall, 1218 patients who completed a preoperative sleep study and had undergone major noncardiac surgery were included in the current analyses (**Figure 1**). Among these patients, 67.6% had unrecognized OSA (REI ≥5), 30.5% had at least moderate OSA (REI ≥15), and 11.2% had severe OSA (REI >30). Details of preoperative sleep studies are reported in eTable 1 in the Supplement. All patients completed 30 days follow-up; no imputation of data was performed.

Table 1 summarizes patient characteristics, type of surgery, preoperative medications, and results of preoperative sleep studies. A total of 59.8% patients had at least 2 risk factors for cardiac disease. The most commonly performed surgical

Figure 1. Screening, Enrollment, and Assessment of Study Participants



OSA indicates obstructive sleep apnea.

[a] Include family refusal (n = 4) and enrollment in another study (n = 6).

procedures were intraperitoneal (35.0%) or major orthopedic (29.9%), 42.1% of procedures were performed for cancer, and 28.3% were performed using a minimally invasive approach. Patients with OSA had a higher mean age and higher mean body mass index, and 63.7% were men. These patients had a higher rate of hypertension (85.9%), and 37.3% were taking β-blockers before surgery. The details of anesthetic administration and use of postoperative analgesia are presented in eTable 2 and eTable 3, respectively, in the Supplement. Perioperative anesthetic management was not different between groups. At least 1 postoperative measurement of cardiac troponin concentration was obtained for 95.8% of patients (eTable 4 in the Supplement).

Outcomes

The primary outcome occurred in 235 patients (19.3%) within 30 days of surgery. Among these patients, 17 (1.4%) died of cardiac cause; 205 (16.8%) had myocardial injury; 21 (1.7%) had congestive heart failure; 30 (2.5%) had atrial fibrillation; 10 (0.8%) had thromboembolism; and 5 (0.4%) had stroke. In patients with myocardial injury, 67 (5.5%) had ischemic symptoms, changes in electrocardiogram or cardiac imaging, and fulfilled the diagnosis of myocardial infarction.[26] Age, renal impairment, peripheral vascular disease, and OSA were independent risk factors for postoperative cardiovascular events (eTable 5 in the Supplement). There was no collinearity between variables. The Cox models showed no interaction between severity of OSA and age (P = .06 for interaction), preexisting renal impairment (P = .07 for interaction), and history of peripheral vascular disease (P = .56 for interaction).

At 30 days after surgery, rates of the primary outcome were 30.1% (41/136) for patients with severe OSA, 22.1% (52/235) for patients with moderate OSA, 19.0% (86/452) for patients with mild OSA, and 14.2% (56/395) for patients with no OSA (**Figure 2**). Compared with the reference group (patients without OSA), OSA was associated with higher risk for the primary outcome (adjusted HR, 1.49 [95% CI, 1.19-2.01]; P = .01). However, the association was only significant among patients with severe OSA (adjusted HR, 2.23 [95% CI, 1.49-3.34]; P = .001) and not among those with moderate OSA (adjusted HR, 1.47 [95% CI, 0.98-2.09]; P = .07) or mild OSA (adjusted HR, 1.36 [95% CI, 0.97-1.91]; P = .08) (P = .01 for interaction). There was no evidence for nonproportionality of hazards (P = .22) or site clustering (eTable 6 in the Supplement).

In the post hoc analyses, severe OSA was also associated with cardiac death (adjusted HR, 13.66 [95% CI, 1.63-114.19]), myocardial injury (adjusted HR, 1.80 [95% CI, 1.17-2.77]), congestive heart failure (adjusted HR, 6.55 [95% CI, 1.71-25.06]), and atrial fibrillation (adjusted HR, 3.96 [95% CI, 1.24-12.60]) (**Table 2**). In a sensitivity analysis that replaced myocardial injury with myocardial infarction in the primary outcome, severe OSA remained independently associated with postoperative cardiovascular complications (eTable 7 and eFigure 1 in the Supplement). OSA was also associated with infective outcomes, unplanned tracheal intubation, or postoperative lung ventilation and readmission to the ICU (Table 2). The association between OSA and postoperative cardiovascular events was similar across all subgroups of patients (P > .14 for interaction) (**Figure 3**). The associations in subgroup analysis were unchanged with varying severity of OSA (eFigures 2-4 in the Supplement). The median length of hospital stay in all patients was 5 days (interquartile range, 4-8) and was similar between different severities of OSA (P = .08 by log-rank test) (eFigure 5 in the Supplement).

STOP-Bang Score and Outcomes

Based on the preoperative STOP-Bang risk score questionnaire, 317 patients (26.3%) were rated as at high risk for OSA,

Table 1. Characteristics: Patients, Surgery, Preoperative Medications, and Preoperative Sleep Study Findings

Characteristic	No. (%)				*P* Value[a]
	Severe OSA	Moderate OSA	Mild OSA	No OSA	
No. of patients	136 (11.2)	235 (19.3)	452 (37.1)	395 (32.4)	
Age, mean (SD), y	68 (9)	68 (9)	68 (9)	66 (9)	
45-64	39 (28.7)	73 (31.1)	159 (35.2)	162 (41.0)	.004
65-74	61 (44.9)	110 (46.8)	181 (40.0)	161 (40.8)	
≥75	36 (26.5)	52 (22.1)	112 (24.8)	72 (18.2)	
Sex					
Men	107 (78.7)	155 (66.0)	262 (58.0)	204 (51.6)	<.001
Women	29 (21.3)	80 (34.0)	190 (42.0)	191 (48.4)	
Race/ethnicity					
Chinese	68 (50.0)	108 (46.0)	254 (56.2)	236 (59.7)	.002
Malay	27 (19.9)	55 (23.4)	51 (11.3)	62 (15.7)	
White	23 (16.9)	40 (17.0)	74 (16.4)	46 (11.6)	
Indian	17 (12.5)	29 (12.3)	70 (15.5)	45 (11.4)	
Other[b]	1 (0.7)	3 (1.3)	3 (0.7)	6 (1.5)	
Risk factors for postoperative cardiovascular event					
Hypertension	128 (94.1)	210 (89.4)	369 (81.6)	330 (83.5)	.001
Coronary artery disease	44 (32.4)	74 (31.5)	124 (27.4)	89 (22.5)	.04
Diabetes receiving insulin treatment	22 (16.2)	36 (15.3)	66 (14.6)	73 (18.5)	.84
Stroke or transient ischemic attack	23 (16.9)	38 (16.2)	62 (13.7)	54 (13.7)	.66
Current smoker	23 (16.9)	23 (9.8)	45 (10.0)	46 (11.6)	.14
Peripheral vascular disease	18 (13.2)	30 (12.8)	44 (9.7)	35 (8.9)	.29
Preoperative creatinine concentration >1.98 mg/dL (175 µmol/L)	11 (8.1)	16 (6.8)	19 (4.2)	25 (6.3)	.26
Congestive heart failure	6 (4.4)	15 (6.4)	15 (3.3)	24 (6.1)	.19
COPD	9 (6.6)	15 (6.4)	17 (3.8)	19 (4.8)	.36
Anthropometric measures, mean (SD)					
Body mass index[e]	31.0 (20.1)	27.5 (5.8)	26.5 (4.8)	25.2 (4.9)	<.001
Neck circumference, cm	41 (3)	39 (4)	39 (3)	37 (3)	<.001
Waist circumference, cm	99 (12)	93 (15	92 (11)	90 (12)	<.001
Surgery					
Major noncardiac					
Intraperitoneal	34 (25.0)	70 (29.8)	157 (34.7)	166 (42.0)	.41
Orthopedic	45 (33.1)	70 (29.8)	148 (32.7)	101 (25.6)	
Vascular	25 (18.4)	49 (20.9)	51 (11.3)	42 (10.6)	
Other[c]	32 (23.5)	46 (19.6)	96 (21.2)	86 (21.8)	
Cancer	52 (38.2)	81 (34.6)	187 (41.4)	192 (48.6)	.004
Minimally invasive[d]	37 (27.2)	47 (20.0)	140 (31.0)	121 (30.6)	.01
Preoperative Medications					
Statin	106 (77.9)	164 (69.8)	320 (452)	264 (66.8)	.11
ACE inhibitor or ARB	74 (54.4)	132 (56.2)	237 (52.4)	202 (51.1)	.65
β-Blocker	57 (41.9)	101 (43.0)	149 (33.0)	108 (27.3)	<.001
Aspirin	31 (22.8)	69 (29.4)	110 (24.3)	99 (25.1)	.46
Clopidogrel	7 (5.1)	6 (2.6)	28 (6.2)	14 (3.5)	.11
Preoperative Sleep Studies					
Site of measurement					
Home	47 (34.6)	82 (34.9)	167 (36.9)	119 (30.1)	.21
Hospital	89 (65.4)	153 (65.1)	285 (63.1)	276 (69.9)	
Results, median (IQR)					
Respiratory event index, events/h[f]	40 (35-52)	20 (17-24)	8 (6-10)	2 (1-3)	<.001
Oxygen desaturation index, events/h[g]	37 (30-44)	20 (16-25)	9 (7-12)	3 (2-5)	<.001
STOP-Bang score[h]	5 (4-6)	4 (3-5)	3 (3-4)	3 (2-4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; OSA, obstructive sleep apnea; STOP-Bang, Snoring, Tiredness, Observed Apnea, High Blood Pressure, Body Mass Index, Age, Neck Circumference, Gender.

[a] For tests to determine imbalance among groups; continuous variables were compared using analysis of variance, and categorical variables were compared using Pearson χ^2 test.

[b] Included black and Arab.

[c] Included major urologic surgery, major hernia repair, and spine surgery.

[d] Determined by attending surgeon.

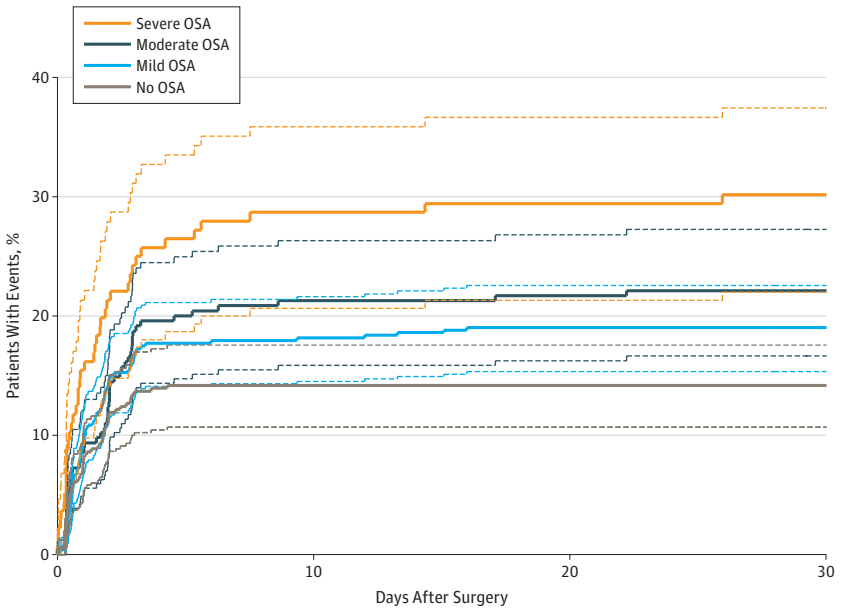
[e] Calculated as weight in kilograms divided by height in meters squared.

[f] Number of apnea and hypopnea events per hour of recording.

[g] Number of events per hour of oximetry recording in which oxyhemoglobin saturation decreased by 4% or more from baseline for 10 or more seconds.

[h] A risk score for OSA (range, 0 [low risk] to 8 [high risk]).

Figure 2. Kaplan-Meier Estimates of the Primary Composite Outcome (Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery)



No. at risk				
Severe OSA	136	98	97	95
Moderate OSA	235	186	185	183
Mild OSA	452	371	367	366
No OSA	395	340	340	340

Dashed lines indicate 95% confidence intervals. Median follow-up time was 30 days (interquartile range [IQR], 30-32) for patients with severe obstructive sleep apnea (OSA), 30 days (IQR, 30-32) for those with moderate OSA; 30 days (IQR, 30-31) for those with mild OSA, and 30 days (IQR, 30-33) for those with no OSA.

648 (53.2%) at intermediate risk, and 253 (20.8%) at low risk (eTable 8 and eTable 9 in the Supplement). Being a high-risk patient was significantly associated with increased rate of primary outcome (adjusted HR, 1.68 [95% CI, 1.11-2.54]), myocardial injury, and ICU readmission (eTable 10 and eFigure 6 in the Supplement). Being an intermediate-risk patient was significantly associated with ICU readmission and wound infection.

Postoperative Nocturnal Oximetry Monitoring

A total of 1131 patients (92.9%) received nocturnal oximetry monitoring during the first night after surgery, 1076 (88.3%) during the second night, and 983 (80.7%) during the third night (eFigures 7-9 in the Supplement). In patients without OSA, there was a significant increase in ODI after surgery ($P < .001$ for general linear model). In contrast, ODI in patients with OSA was reduced during the first 2 nights and returned to baseline on the third night after surgery. These changes were associated with supplemental oxygen administration ($P = .009$ for general linear model) (eFigure 7 in the Supplement). There was no difference in ODI, lowest oxyhemoglobin saturation, and maximum heart rate in patients with and without postoperative cardiovascular events (eTable 12 in the Supplement). However, the mean cumulative duration of oxyhemoglobin desaturation less than 80% during the first 3 postoperative nights for patients with cardiovascular complications (23.1 [95% CI, 15.5-27.7] minutes) was longer than for patients with no cardiovascular complications (10.2 [95% CI, 7.8-10.9] minutes) ($P < .001$ for general linear model) (eTable 12 and eFigure 10 in the Supplement).

Discussion

In this study of adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative vascular complications.

Kaw et al[27] conducted a meta-analysis of 9 cohort and case-control studies (n = 2615 patients) that evaluated the association between OSA and postoperative cardiovascular complications. They reported an increased risk with OSA (odds ratio, 2.07 [95% CI, 1.23-3.50]), but there were few events (event rate, 2.6%), and the studies used less stringent criteria to diagnose OSA and postoperative cardiovascular complications. More recently, the Society of Anesthesia and Sleep Medicine reported a systematic review of 61 studies, including analyses of large-scale national databases,[9-15] to examine the association of OSA with perioperative outcomes.[28] Although a large number of patients were included (N = 8 969 583), there were substantial variations in outcome definitions and duration of follow-up, and the studies reported inconsistent results. In particular, it is unclear whether patients in the control groups of the 61 studies had unrecognized OSA, and those who had a preoperative diagnosis of OSA may have received extra treatment to modify perioperative outcomes. This heterogeneity precluded quantitative analysis of data.

In this study, a representative sample of patients undergoing major noncardiac surgery was included. Standardized preoperative sleep monitoring was performed to diagnose OSA, and patients were stratified according to disease severity. All patients

Table 2. Association Between Severity of Obstructive Sleep Apnea and Postoperative Cardiovascular Events

	Events/Total, No. (%)	Unadjusted HR (95%CI)	*P* Value	Adjusted HR (95%CI)	*P* Value
Primary Outcome (Cardiac Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke)					
Severe OSA	41/136 (30.1)	2.33 (1.55-3.48)	<.001	2.23 (1.49-3.34)	.001
Moderate OSA	52/235 (22.1)	1.59 (1.09-2.32)	.02	1.47 (0.98-2.09)	.07
Mild OSA	86/452 (19.0)	1.37 (0.98-1.91)	.07	1.36 (0.97-1.91)	.08
No OSA	56/395 (14.2)	1 [Reference]		1 [Reference]	
Post Hoc Analysis of Components of Primary Outcome					
Cardiac death[a]					
Severe OSA	6/136 (4.4)	17.90 (2.16-148.69)	.008	13.56 (1.60-114.19)	.02
Moderate OSA	8/235 (3.4)	13.57 (1.70-108.53)	.01	10.56 (1.31-84.89)	.03
Mild OSA	2/452 (0.4)	1.75 (0.16-19.31)	.65	1.43 (0.93-15.93)	.77
No OSA	1/395 (0.3)	1 [Reference]		1 [Reference]	
Myocardial injury[b]					
Severe OSA	35/124 (28.2)	2.11 (1.37-3.24)	.001	1.80 (1.17-2.77)	.008
Moderate OSA	41/220 (18.6)	1.34 (0.89-2.02)	.16	1.20 (0.80-1.81)	.39
Mild OSA	77/416 (18.5)	1.32 (0.93-1.88)	.12	1.37 (0.93-1.89)	.12
No OSA	52/364 (14.3)	1 [Reference]		1 [Reference]	
Congestive heart failure[c]					
Severe OSA	8/136 (5.9)	7.86 (2.09-29.62)	.002	7.04 (1.86-26.66)	.004
Moderate OSA	6/235 (2.6)	3.39 (0.85-13.57)	.08	3.12 (0.78-12.50)	.10
Mild OSA	4/452 (0.9)	1.17 (0.26-5.20)	.84	1.10 (0.25-4.97)	.89
No OSA	3/395 (0.8)	1 [Reference]		1 [Reference]	
Thromboembolism[d]					
Severe OSA	1/136 (0.7)	2.91 (0.18-46.57)	.45	2.66 (0.17-42.86)	.49
Moderate OSA	4/235 (1.7)	6.78 (0.76-60.70)	.09	6.38 (0.71-57.34)	.10
Mild OSA	4/452 (0.9)	3.51 (0.39-31.41)	.26	3.42 (0.38-30.70)	.27
No OSA	1/395 (0.3)	1 [Reference]		1 [Reference]	
New-onset atrial fibrillation[e]					
Severe OSA	7/136 (5.1)	4.13 (1.31-13.02)	.02	3.75 (1.19-11.87)	.03
Moderate OSA	7/235 (3.0)	2.37 (0.75-7.45)	.14	2.18 (0.69-6.89)	.82
Mild OSA	11/452 (2.4)	1.75 (0.60-5.11)	.31	1.89 (0.66-5.46)	.24
No OSA	5/395 (1.3)	1 [Reference]		1 [Reference]	
Stroke[f]					
Severe OSA	1/136 (0.7)	1.45 (0.13-15.99)	.76	1.14 (0.10-12.67)	.92
Moderate OSA	1/235 (0.4)	0.84 (0.08-9.26)	.89	0.76 (0.07-8.33)	.82
Mild OSA	1/452 (0.2)	0.44 (0.04-4.80)	.50	0.38 (0.03-4.15)	.42
No OSA	2/395 (0.5)	1 [Reference]		1 [Reference]	
Secondary Outcomes					
Unplanned admission or readmission to ICU[g]					
Severe OSA	15/136 (11.0)	OR, 6.87 (2.74-17.24)	<.001	OR, 6.60 (2.61-16.70)	<.001
Moderate OSA	20/235 (8.5)	OR, 5.16 (2.15-12.39)	<.001	OR, 4.99 (2.06-12.06)	<.001
Mild OSA	26/452 (5.8)	OR, 3.38 (1.45-7.88)	.005	OR, 3.55 (1.52-8.31)	.005
No OSA	7/395 (1.8)	1 [Reference]		1 [Reference]	
Unplanned tracheal intubation or postoperative lung ventilation[h]					
Severe OSA	18/136 (13.2)	OR, 6.54 (2.86-14.95)	<.001	OR, 6.16 (2.51-15.16)	<.001
Moderate OSA	31/235 (13.2)	OR, 6.52 (3.04-13.95)	<.001	OR, 6.26 (2.85-13.75)	<.001
Mild OSA	23/452 (5.1)	OR, 2.29 (1.05-5.03)	.04	OR, 2.28 (1.04-5.03)	.04
No OSA	9/395 (2.3)	1 [Reference]		1 [Reference]	

(continued)

Table 2. Association Between Severity of Obstructive Sleep Apnea and Postoperative Cardiovascular Events (continued)

	Events/Total, No. (%)	Unadjusted HR (95%CI)	*P* Value	Adjusted HR (95%CI)	*P* Value
Pneumonia[i]					
Severe OSA	5/136 (3.7)	2.92 (0.85-10.09)	.09	3.03 (0.87-10.50)	.08
Moderate OSA	10/235 (4.3)	3.41 (1.17-9.97)	.03	3.47 (1.18-10.20)	.02
Mild OSA	16/452 (3.5)	2.84 (1.04-7.76)	.04	2.83 (1.04-7.78)	.04
No OSA	5/395 (1.3)	1 [Reference]		1 [Reference]	
Wound infection[j]					
Severe OSA	10/136 (7.4)	1.06 (0.51-2.20)	.87	1.07 (0.52-2.23)	.85
Moderate OSA	27/235 (11.5)	1.73 (1.01-2.95)	.04	1.73 (0.99-2.95)	.05
Mild OSA	34/452 (7.5)	1.08 (0.65-1.80)	.77	1.10 (0.67-1.85)	.69
No OSA	27/395 (6.8)	1 [Reference]		1 [Reference]	
Other infections[k]					
Severe OSA	11/136 (8.1)	2.50 (1.12-5.58)	.03	2.31 (1.03-5.18)	.04
Moderate OSA	21/235 (8.9)	2.79 (1.40-5.56)	.004	2.68 (1.34-5.36)	.005
Mild OSA	25/452 (5.5)	1.70 (0.87-3.32)	.12	1.67 (0.85-3.27)	.14
No OSA	13/395 (3.3)	1 [Reference]		1 [Reference]	
Postoperative delirium[l]					
Severe OSA	8/136 (5.9)	2.15 (0.87-5.36)	.10	1.87 (0.75-4.66)	.18
Moderate OSA	15/235 (6.4)	2.32 (1.07-5.05)	.03	2.09 (0.96-4.56)	.06
Mild OSA	20/452 (4.4)	1.60 (0.77-3.35)	.21	1.52 (0.73-3.18)	.27
No OSA	12/395 (3.0)	1 [Reference]		1 [Reference]	

Abbreviations: HR, hazard ratio; ICU, intensive care unit; OR, odds ratio; OSA, obstructive sleep apnea.

[a] Death due to a cardiovascular cause (eg, myocardial infarction, arrhythmias, pulmonary embolism) within 30 days of surgery.

[b] An increase of 65 ng/L or greater in postoperative high-sensitivity troponin T concentration or an absolute change of 5 ng/L or greater when troponin T concentration is in the range between 20 ng/L to less than 65 ng/L, irrespective of ischemic symptoms or electrocardiographic changes.

[c] Elevated jugular venous pressure, respiratory crackles, or presence of third heart sound and at least 1 radiographic feature (vascular redistribution, interstitial edema, or alveolar pulmonary edema).

[d] Included either pulmonary embolism (confirmed by ventilation-perfusion lung scan, helical computed tomography or pulmonary angiography) or deep venous thrombosis (confirmed by compression ultrasonography, computed tomography, or contrast venography).

[e] Electrocardiographic documentation of atrial fibrillation occurred after surgery with or without symptoms or treatment.

[f] New focal neurologic deficit thought to be vascular in origin, with signs or symptoms that last more than 24 hours.

[g] Unplanned ICU admission or readmission from ward because of perioperative events after surgery.

[h] Included unplanned invasive or noninvasive (continuous or bi-level positive airway pressure) lung ventilation within 30 days of surgery.

[i] Infiltrate, cavitation, consolidation, or effusion confirmed by chest radiography or computed tomography, in association with change in sputum production or positive microbial culture of blood or respiratory secretion.

[j] Purulent discharge from surgical wound with or without a positive microbial culture, or pathogenic organisms isolated from aseptically obtained microbial culture.

[k] Included those of the urinary tract, upper respiratory tract, and central nervous system.

[l] Assessed daily in the mornings after surgery using the confusion assessment method.

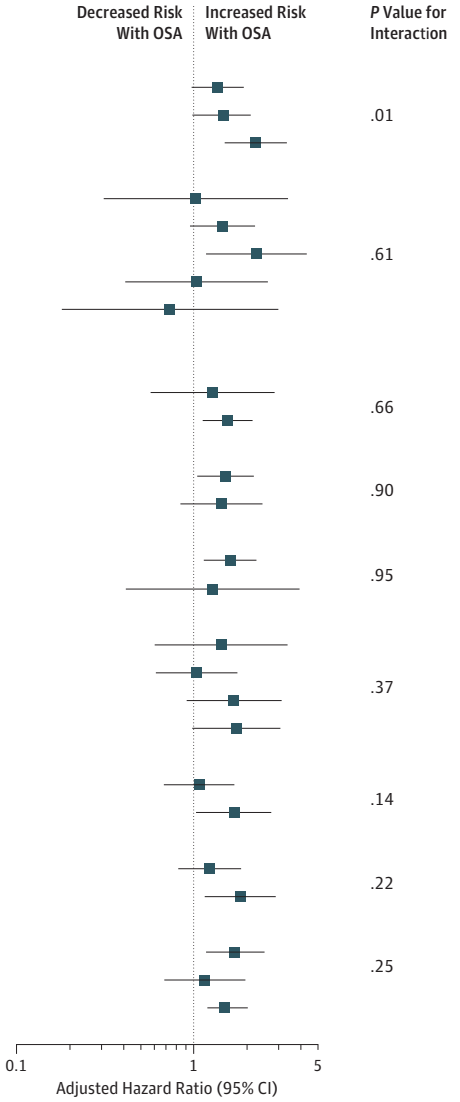
completed follow-up, and postoperative monitoring of troponin concentrations was used to detect myocardial injury.

This study demonstrated that severe OSA was associated with increased risk of postoperative cardiovascular events. Despite a substantial decrease in ODI with oxygen therapy in patients with OSA during the first 3 postoperative nights, supplemental oxygen did not modify the association between OSA and postoperative cardiovascular event. Given that these events were associated with longer duration of severe oxyhemoglobin desaturation (<80%), more aggressive interventions may be required. Currently, positive airway pressure and oral appliances have been shown to overcome the collapsed upper airway and to relieve severe desaturation in nonoperative settings.[29,30] However, high-level evidence demonstrating the effect of these measures on perioperative outcomes is lacking.[31,32] Further clinical trials are now required to test if additional monitoring or alternative interventions would reduce the risk.

In contrast to the current guideline recommendations,[33] regional analgesia or avoidance of postoperative opioids were

Figure 3. Subgroup Analyses of the Primary Composite Outcome (Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery)

	No. of Patients With Event/Total No.of Patients		Adjusted Hazard Ratio (95% CI)	P Value for Interaction
	No OSA	OSA		
Severity of OSA				
Mild	56/395	86/425	1.36 (0.97-1.91)	
Moderate	56/395	52/235	1.47 (0.98-2.09)	.01
Severe	56/395	41/136	2.23 (1.49-3.34)	
Body mass index[a]				
<18.5	5/20	6/21	1.02 (0.31-3.39)	
18.5-24.9	31/194	76/300	1.45 (0.95-2.21)	
25.0-29.9	11/119	62/298	2.25 (1.17-4.32)	.61
30.0-34.9	6/44	26/298	1.04 (0.41-2.61)	
≥35.0	3/18	9/69	0.73 (0.18-2.99)	
Type of anesthesia				
General				
No	8/11	26/186	1.27 (0.57-2.85)	.66
Yes	48/314	153/637	1.55 (1.12-2.14)	
Regional or neuraxial block				
No	38/248	121/502	1.51 (1.04-2.18)	.90
Yes	18/147	58/321	1.43 (0.84-2.43)	
Anesthetic agents				
Volatile-based	44/295	143/595	1.60 (1.14-2.25)	.95
Propofol infusion	4/34	13/84	1.28 (0.41-3.94)	
Oxygen administration after surgery				
None	8/107	17/185	1.42 (0.60-3.37)	
1 Night	19/128	53/279	1.03 (0.61-1.76)	.37
2 Nights	14/89	42/169	1.68 (0.91-3.12)	
3 Nights	15/71	67/190	1.73 (0.98-3.07)	
Postoperative opioid administration				
No	27/172	64/339	1.07 (0.68-1.69)	.14
Yes	29/223	115/484	1.70 (1.03-2.73)	
Postoperative patient-controlled analgesia administration				
No	33/207	85/411	1.23 (0.82-1.84)	.22
Yes	23/188	94/412	1.83 (1.15-2.89)	
Minimally invasive surgery				
No	35/274	133/599	1.70 (1.17-2.50)	.25
Yes	21/121	46/224	1.15 (0.68-1.95)	
Overall	56/395	179/823	1.49 (1.19-2.01)	



OSA indicates obstructive sleep apnea.

[a] Calculated as weight in kilograms divided by height in meters squared.

not associated with better outcome. These data are consistent with a retrospective analysis of an administrative database of 30 294 patients with documented OSA undergoing hip or knee arthroplasties with neuraxial block, general anesthesia, or both.[34] The study showed no change in postoperative cardiac or respiratory complications with neuraxial or general anesthesia. However, blood transfusion, requirement for postoperative mechanical lung ventilation, and ICU admission were decreased with neuraxial block. In the current study, patients undergoing major noncardiac surgery were recruited, few received regional blocks, and the majority required larger doses of systemic opioids for postoperative analgesia. This may have limited the statistical power to detect important interactions between OSA, anesthetic techniques, and postoperative analgesia.

Limitations

This study has several limitations. First, electroencephalograms were not recorded in the preoperative sleep studies. Thus, it was not possible to track whether patients were asleep during measurement, and this may have underestimated the severity of OSA. Second, perioperative management was not controlled, but there was no difference in the administration of anesthesia and analgesics in patients with varying degrees of OSA. Although the surgical team was blinded to the results of the preoperative sleep study, recognition of minor

respiratory events, such as episodes of apnea and higher level of sedation in the postanesthetic care unit and surgical ward, may have influenced perioperative management. This may include reducing doses of opioids or prolonging supplemental oxygen therapy. It is unclear how these interventions may affect perioperative outcomes. Nevertheless, the event rates reported in this study would represent the expected perioperative outcomes associated with untreated OSA in contemporary anesthetic practice for major noncardiac surgery. Third, the results should not be extrapolated to ambulatory procedures or minor surgery, for which anesthetic and analgesic techniques may have a larger effect on perioperative adverse events. Fourth, 54.7% of patients in this study were Chinese. Although Chinese patients with OSA have a lower body mass index and distinct differences in craniofacial anatomy compared with white patients,[35,36] it remains unclear how these differences might influence outcomes.

Conclusions

Among at-risk adults undergoing major noncardiac surgery, unrecognized severe obstructive sleep apnea was significantly associated with increased risk of 30-day postoperative cardiovascular complications. Further research would be needed to assess whether interventions can modify this risk.

ARTICLE INFORMATION

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Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Definitions of Respiratory Events During Sleep

ApneaLink Plus measurements

The following signals were recorded: respiratory flow (nasal pressure), breathing sounds (snore), respiratory effort, heart rate and oximetry.

Successful monitoring required at least 4 hours of recordings.

Parameters measured:

(1) Apnea event is defined as an episode of airflow reduction ≥ 90% from baseline for ≥ 10 seconds.

(2) Apnea index is the number of apnea events per hour of recording.

(3) Hypopnea event is defined as an episode of airflow reduction ≥ 30% from baseline for ≥ 10 seconds and associated with ≥ 3% oxyhemoglobin desaturation.

(4) Hypopnea index is the number of hypopnea events per hour of recording.

(5) Respiratory event index is the number of apnea and hypopnea events per hour of recording.

PULSOX-300i measurement

The following signals were recorded: pulse oximetry and heart rate.

Parameter measured:

Oxygen desaturation index is the number of events per hour of oximetry recording where oxyhemoglobin saturation decreased by ≥ 4% from baseline for ≥ 10 seconds.

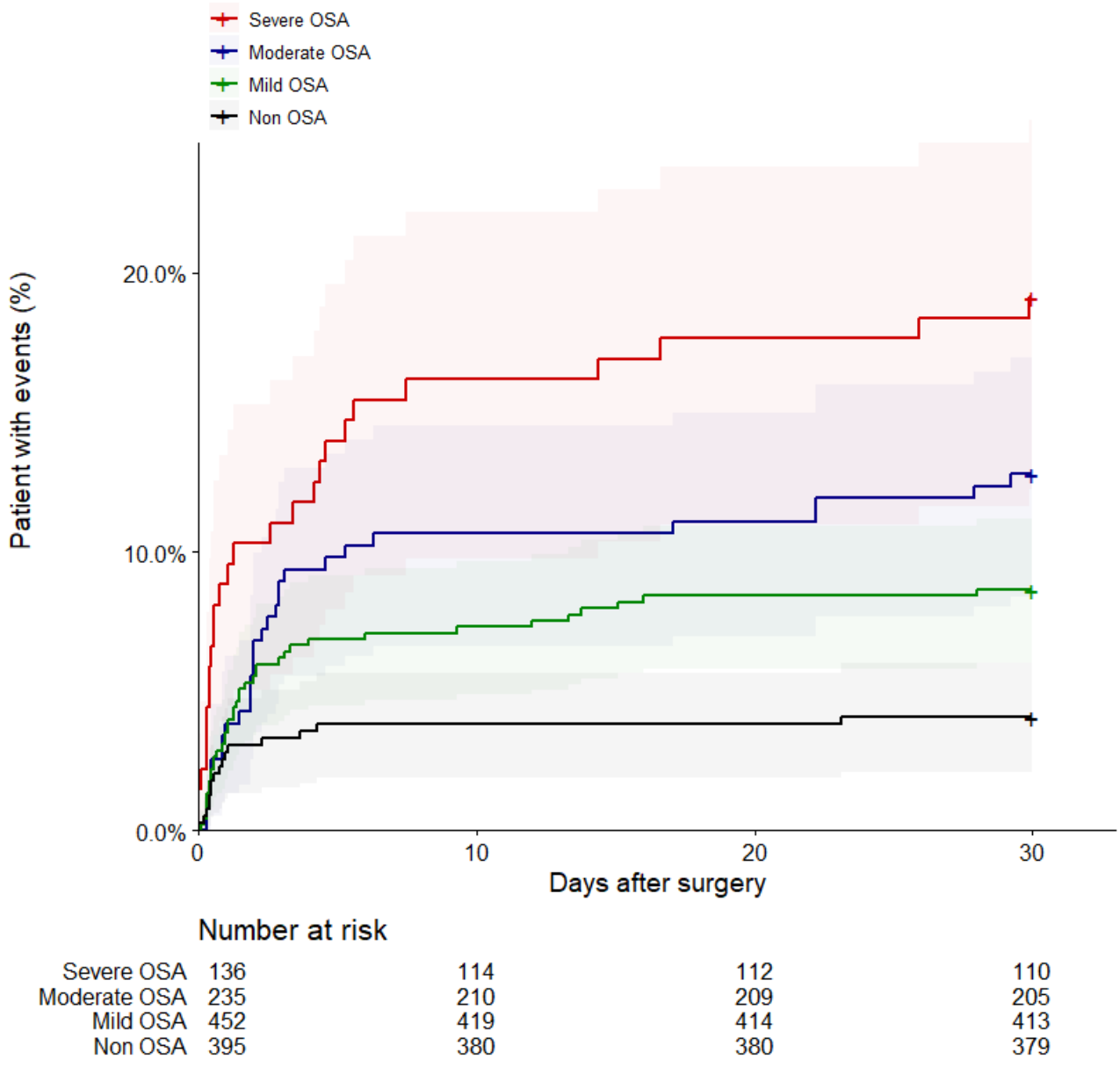
eAppendix 2. Outcome Definitions

Outcome	Definition
Cardiac death	Death attributable to a cardiovascular cause including deaths following myocardial infarction, cardiac arrest, revascularization procedure, pulmonary embolism, deep venous or arterial thrombosis, arrhythmias, stroke and congestive heart failure, or deaths due to an unknown cause.
Myocardial injury after noncardiac surgery	This is an elevated cardiac troponin value[a] within 30 days after surgery without evidence of a non-ischemic etiology, such as pulmonary embolism, sepsis, cardioversion, or known persistent elevated cardiac troponin values.
Myocardial infarction	The diagnosis of myocardial infarction requires any one of the following criterion: (1) Detection of a rise and/or fall of cardiac troponin values with at least one value above the 99th percentile upper reference limit and with at least one of the following: a. Symptoms of ischemia. b. New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block. c. Development of pathological Q waves in the electrocardiogram. d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. e. Identification of an intracoronary thrombus by angiography or autopsy. (2) Pathological Q waves with or without symptoms in the absence of non-ischemic causes. (3) Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause. (4) Pathological findings of a prior myocardial infarction.
Non-fatal cardiac arrest	Nonfatal cardiac arrest is defined as successful resuscitation from ventricular fibrillation, ventricular tachycardia, asystole, or pulseless electrical activity.
Revascularization procedure	This is defined as percutaneous coronary intervention or coronary artery bypass graft surgery.
Pulmonary embolus	Any one of the following: (1) A high probability ventilation/perfusion lung scan; (2) An intraluminal filling defect of segmental or larger artery on a helical CT scan; (3) An intraluminal filling defect on pulmonary angiography; or (4) A positive diagnostic test for deep venous thrombosis (e.g., positive compression ultrasound) with either one of the following: a. low or intermediate probability ventilation/perfusion lung scan;

	b. subsegmental defects or technically inadequate study helical CT scan
Deep venous thrombosis	Any one of the following: (1) Non-compressibility of one or more venous segments on B mode compression ultrasonography; (2) Intraluminal filling defect on contrast enhanced computed tomography; (3) Persistent intraluminal filling defect on contrast venography.
New atrial fibrillation	Atrial fibrillation occurred after surgery with or without angina, heart failure, hypotension, requiring rate controlled drugs or cardioversion.
Stroke	Stroke is defined as a new focal neurological deficit thought to be vascular in origin with signs or symptoms that last > 24 hours or is leading to death.
Congestive heart failure	Any one of the clinical signs: elevated jugular venous pressure, respiratory crackles, or presence of S3 and At least one of radiographic features: vascular redistribution, interstitial edema, or alveolar pulmonary edema.
Pneumonia	Either crackles on physical examinations of chest with one of the followings: (1) purulent sputum or change in sputum characteristics, (2) positive blood culture or isolation of pathogen from transtracheal aspirate, bronchial brushing, or biopsy or chest radiography showing new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: (1) purulent sputum or change in sputum characteristics, (2) positive blood culture or isolation of pathogen from transtracheal aspirate, bronchial brushing, or biopsy (3) isolation of virus or detection of viral antigen from respiratory secretions, (4) diagnostic single antibody titer or fourfold increase in paired serum samples for pathogen, or (5) histopathologic evidence of pneumonia.
Infection/sepsis	Invasion of pathogenic organisms isolated from normally sterile tissue (including wound) or fluid or body cavity. Sepsis is defined by the presence of both infection and a systemic inflammatory response.

[a] Peak high-sensitivity cardiac troponin T concentration ≥65 ng/L or an absolute change of ≥5 ng/L when troponin T between 20 and 64 ng/L within 30 days after surgery

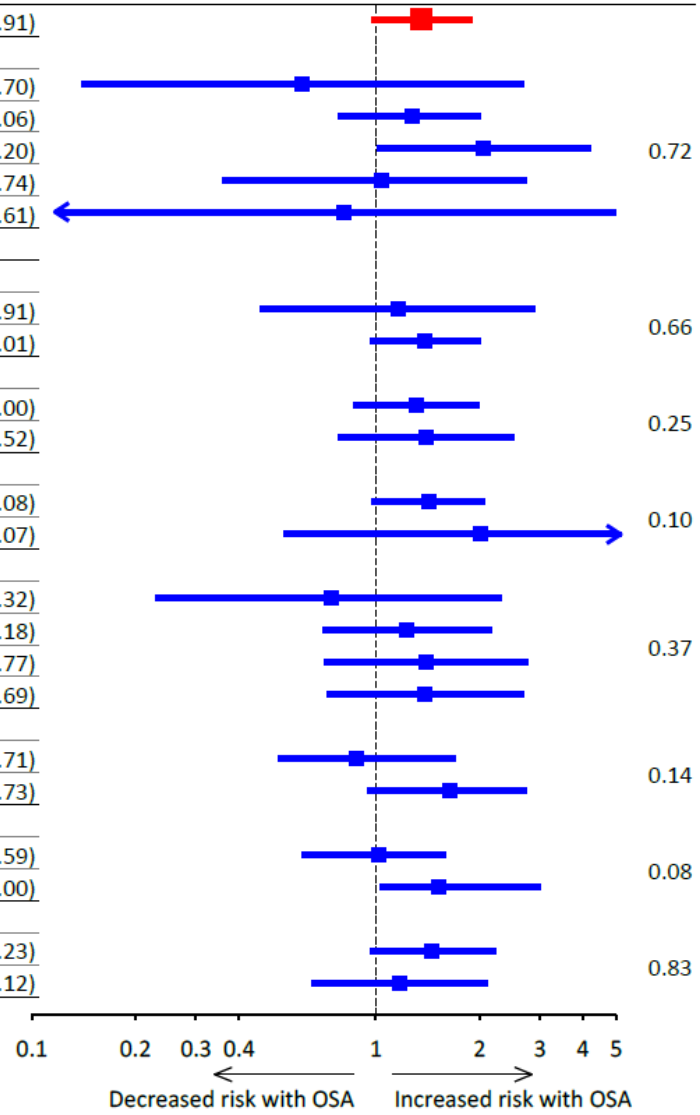
eFigure 1. Kaplan-Meier Estimates of Modified Primary Composite Outcome of Death, Myocardial Infarction, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery



Shaded areas represent 95% confidence intervals
OSA indicates obstructive sleep apnea

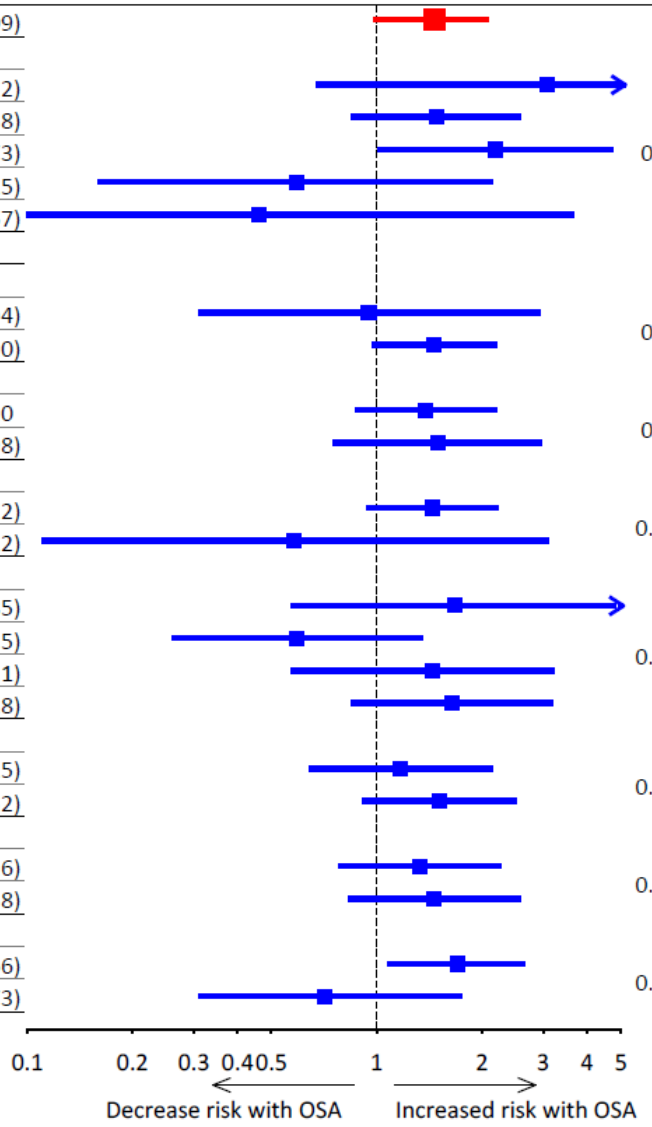
eFigure 2. Subgroup Analyses of Primary Outcome in Patients With Mild vs No Obstructive Sleep Apnea

	No OSA	Mild OSA	Adjusted hazard ratio (95% confidence intervals)	P value for interaction
	No. of patients with event/total no. of patients			
Overall	56/395	86/452	1.36 (0.97-1.91)	
Body mass index – kg/m^2				
< 18.5	5/20	3/16	0.61 (0.14-2.70)	
18.5 – 24.9	31/194	37/177	1.27 (0.78-2.06)	
25.0 – 29.9	11/119	32/169	2.06 (1.01-4.20)	0.72
30.0 – 34.9	6/44	12/69	1.04 (0.36-2.74)	
≥ 35.0	3/18	2/21	0.81 (0.12-5.61)	
Type of anesthesia				
General anesthesia				
No	8/81	13/101	1.16 (0.46-2.91)	0.66
Yes	48/314	73/351	1.39 (0.96-2.01)	
Regional or neuraxial block				
No	38/248	54/273	1.31 (0.86-2.00)	0.25
Yes	18/147	32/179	1.40 (0.78-2.52)	
Anesthetic agents				
Volatile-based	44/295	69/328	1.42 (0.97-2.08)	0.10
Propofol infusion	4/34	7/44	2.01 (0.54-8.07)	
Oxygen administration after surgery				
None	8/107	5/108	0.74 (0.23-2.32)	
One night	19/128	34/162	1.23 (0.70-2.18)	0.37
Two nights	14/89	22/100	1.40 (0.71-2.77)	
Three nights	15/71	25/82	1.39 (0.72-2.69)	
Postoperative opioid administration				
No	27/172	28/193	0.88 (0.52-1.71)	0.14
Yes	29/223	58/259	1.64 (0.95-2.73)	
Postoperative patient-controlled analgesia administration				
No	33/207	37/230	1.02 (0.61-1.59)	0.08
Yes	23/188	49/222	1.52 (1.03-3.00)	
Minimally invasive surgery				
No	35/274	58/312	1.46 (0.96-2.23)	0.83
Yes	21/121	28/140	1.17 (0.65-2.12)	



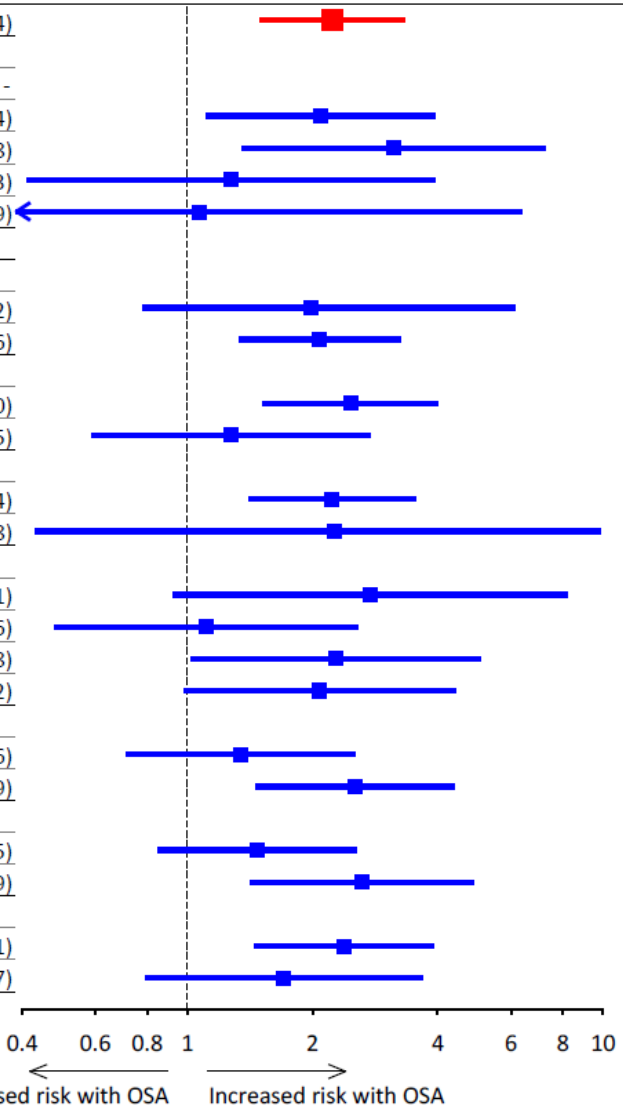
eFigure 3. Subgroup Analyses of Primary Outcome in Patients With Moderate vs No Obstructive Sleep Apnea

	No OSA	Moderate OSA	Adjusted hazard ratio (95% confidence intervals)	P value for interaction
	No. of patients with event/total no. of patients			
Overall	56/395	52/235	1.47 (0.98-2.09)	
Body mass index – kg/m				
< 18.5	5/20	3/5	3.07 (0.67-14.2)	
18.5 – 24.9	31/194	23/81	1.48 (0.85-2.58)	
25.0 – 29.9	11/119	18/87	2.18 (1.01-4.73)	0.25
30.0 – 34.9	6/44	5/35	0.59 (0.16-2.15)	
≥ 35.0	3/18	3/27	0.46 (0.10-3.67)	
Type of anesthesia				
General anesthesia				
No	8/81	5/52	0.95 (0.31-2.94)	0.46
Yes	48/314	47/183	1.46 (0.97-2.20)	
Regional or neuraxial block				
No	38/248	37/148	1.38 (0.87-2.20	0.90
Yes	18/147	15/87	1.50 (0.75-2.98)	
Anesthetic agents				
Volatile-based	44/295	42/171	1.45 (0.94-2.22)	0.63
Propofol infusion	4/34	3/26	0.58 (0.11-3.12)	
Oxygen administration after surgery				
None	8/107	6/47	1.67 (0.57-4.85)	
One night	19/128	10/73	0.59 (0.26-1.35)	0.64
Two nights	14/89	9/40	1.45 (0.57-3.21)	
Three nights	15/71	27/75	1.64 (0.85-3.18)	
Postoperative opioid administration				
No	27/172	19/84	1.17 (0.64-2.15)	0.77
Yes	29/223	33/151	1.51 (0.91-2.52)	
Postoperative patient-controlled analgesia administration				
No	33/207	25/104	1.33 (0.78-2.26)	0.92
Yes	23/188	27/131	1.46 (0.83-2.58)	
Minimally invasive surgery				
No	35/274	44/188	1.70 (1.08-2.66)	0.13
Yes	21/121	8/47	0.71 (0.31-1.73)	

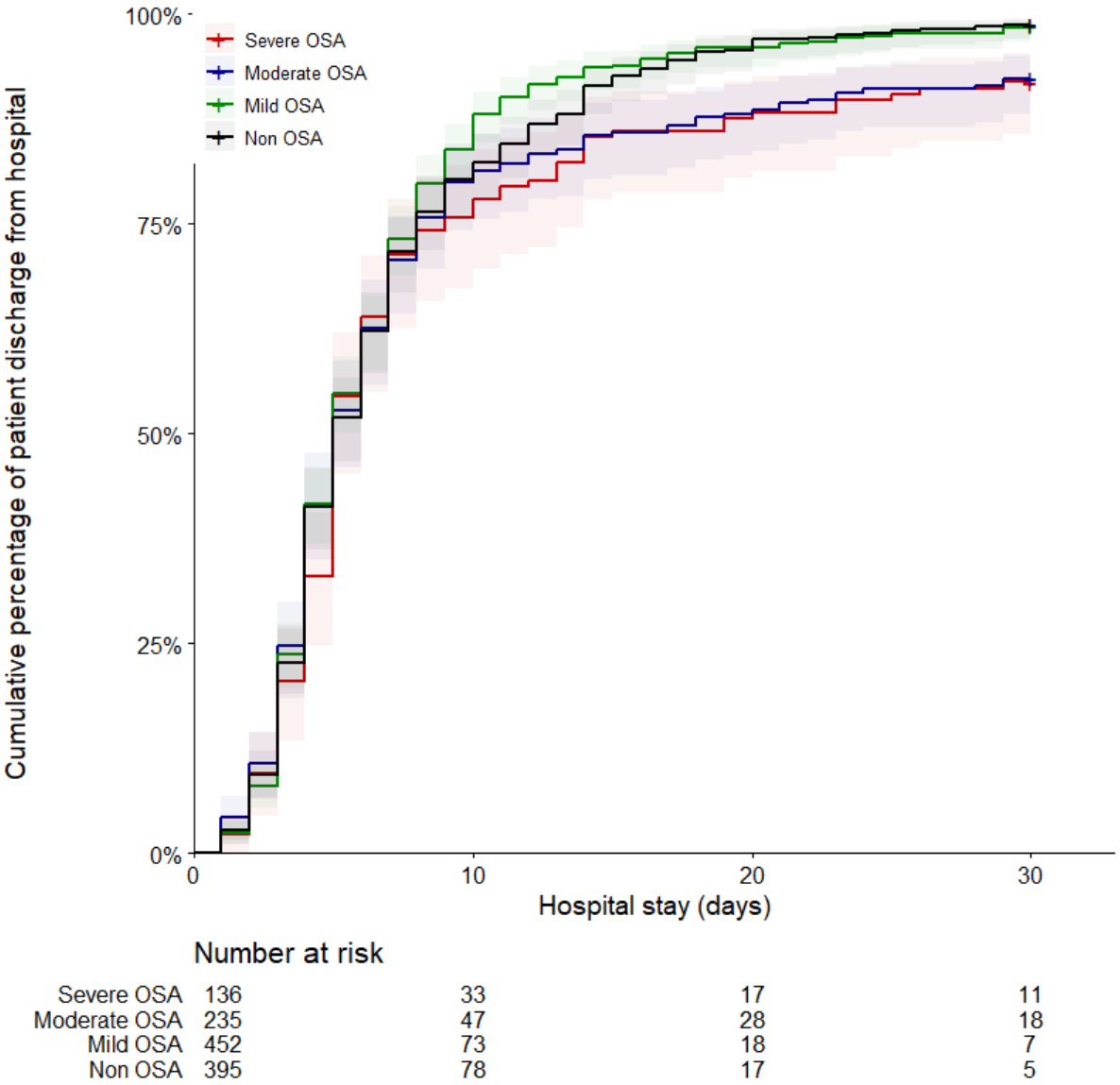


eFigure 4. Subgroup Analyses of Primary Outcome in Patients With Severe vs No Obstructive Sleep Apnea

	No OSA	Severe OSA	Adjusted hazard ratio (95% confidence intervals)	P value for interaction
	No. of patients with event/total no. of patients			
Overall	56/395	41/136	2.23 (1.49-3.34)	
Body mass index – kg/m				
< 18.5	5/20	-	-	
18.5 – 24.9	31/194	16/42	2.09 (1.11-3.94)	
25.0 – 29.9	11/119	12/42	3.13 (1.35-7.28)	0.80
30.0 – 34.9	6/44	9/31	1.27 (0.41-3.93)	
≥ 35.0	3/18	4/21	1.07 (0.18-6.39)	
Type of anesthesia				
General anesthesia				
No	8/81	8/33	1.98 (0.78-6.12)	0.66
Yes	48/314	33/103	2.08 (1.33-3.26)	
Regional or neuraxial block				
No	38/248	30/81	2.47 (1.52-4.00)	0.09
Yes	18/147	11/55	1.27 (0.59-2.75)	
Anesthetic agents				
Volatile-based	44/295	32/96	2.23 (1.41-3.54)	0.95
Propofol infusion	4/34	3/14	2.25 (0.43-9.88)	
Oxygen administration after surgery				
None	8/107	6/30	2.75 (0.92-8.21)	
One night	19/128	9/44	1.11 (0.48-2.56)	0.60
Two nights	14/89	11/29	2.27 (1.02-5.08)	
Three nights	15/71	15/33	2.08 (0.98-4.42)	
Postoperative opioid administration				
No	27/172	15/62	1.34 (0.71-2.56)	0.25
Yes	29/223	24/74	2.53 (1.46-4.39)	
Postoperative patient-controlled analgesia administration				
No	33/207	23/77	1.47 (0.85-2.55)	0.32
Yes	23/188	18/59	2.63 (1.42-4.89)	
Minimally invasive surgery				
No	35/274	31/99	2.38 (1.45-3.91)	0.87
Yes	21/121	10/37	1.70 (0.79-3.67)	



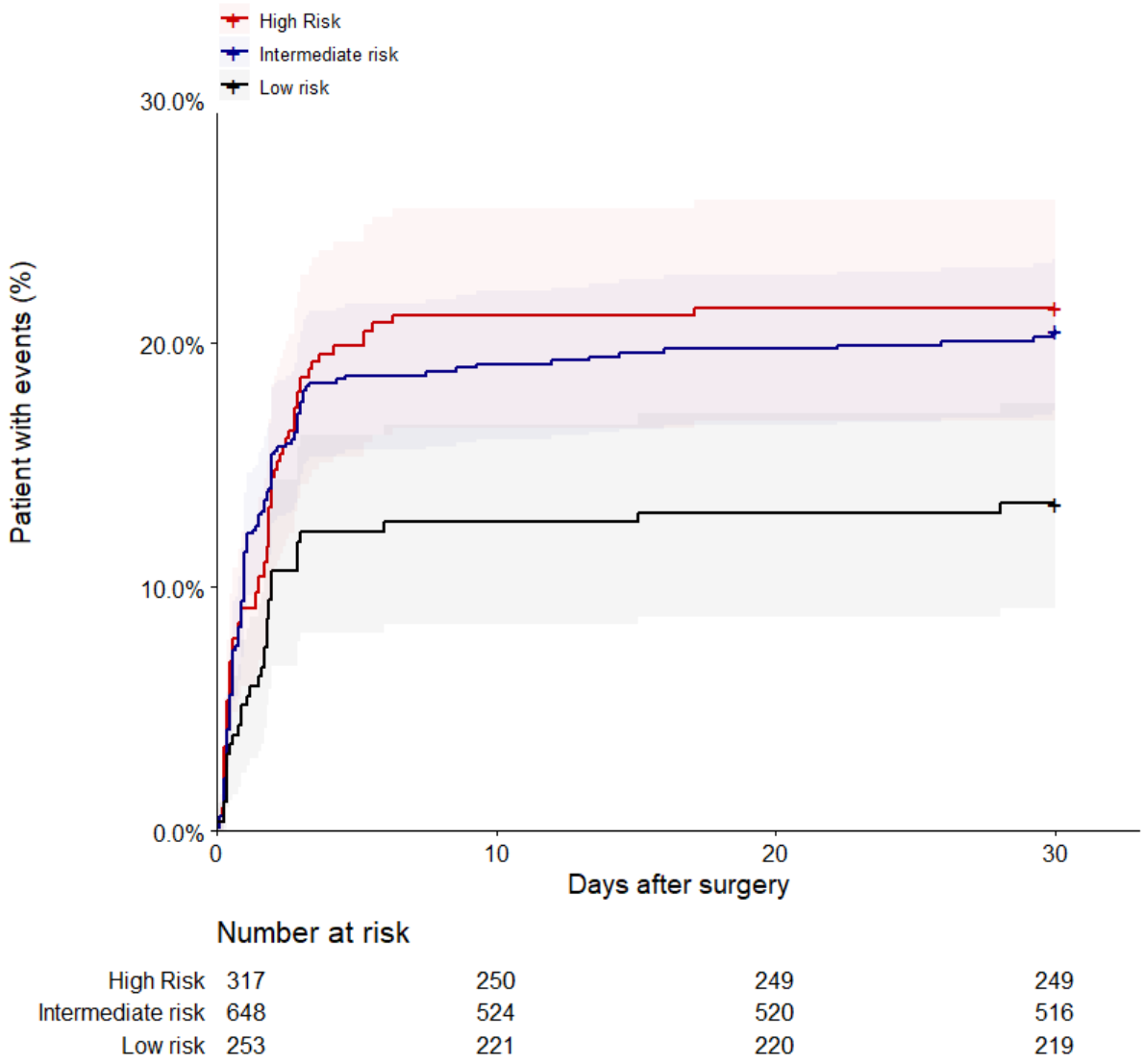
eFigure 5. Kaplan-Meier Estimates of Hospital Discharge



	Median (interquartile range) length of stay
Severe OSA	5.0 (4.0-8.0)
Moderate OSA	5.0 (4.0-8.0)
Mild OSA	5.0 (4.0-8.0)
Non OSA	5.0 (4.0-9.0)

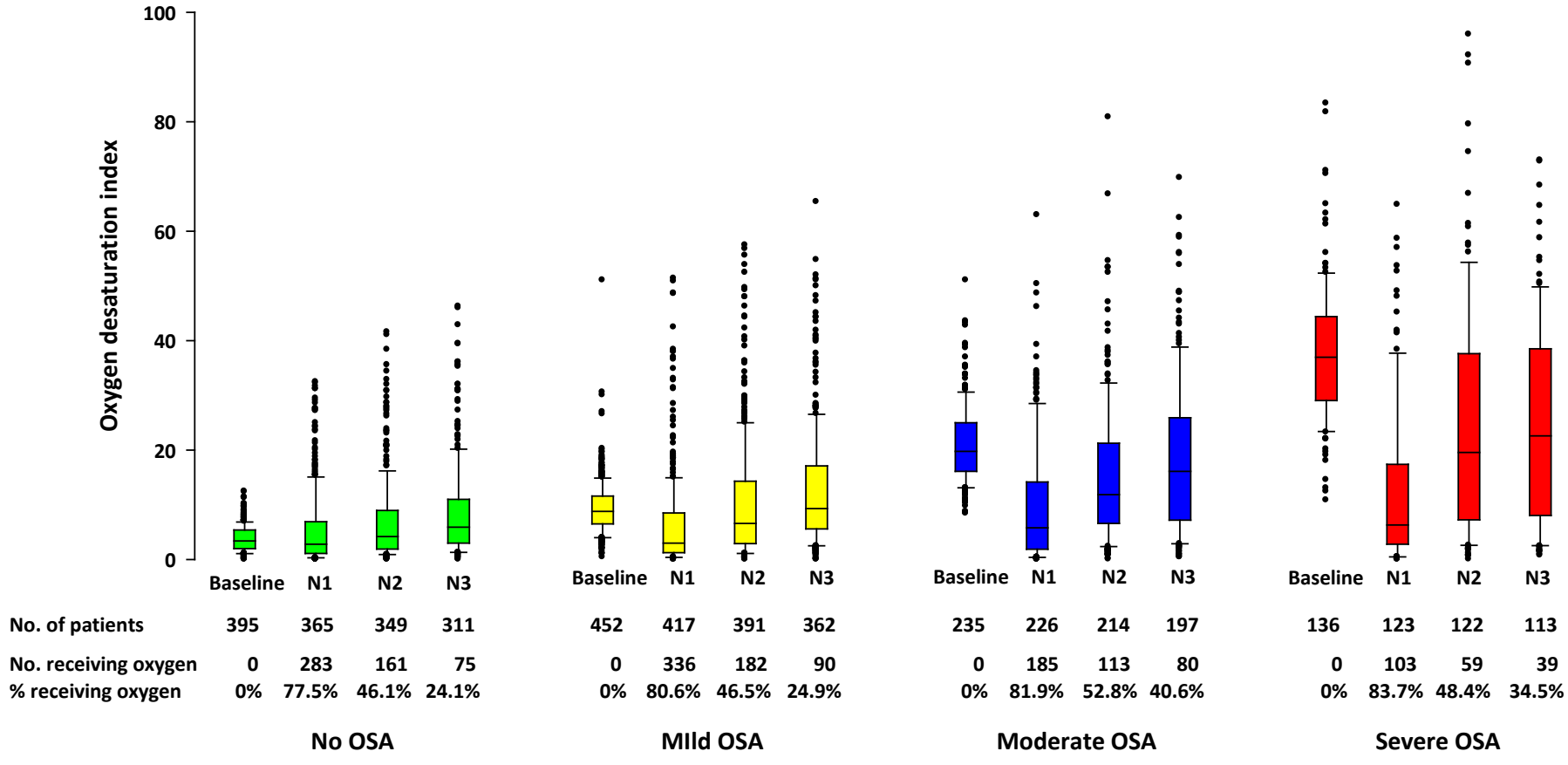
Shaded areas represent 95% confidence intervals

eFigure 6. Kaplan-Meier Estimates of 30-Day Postoperative Cardiovascular Events Based on the STOP-Bang Risk Score



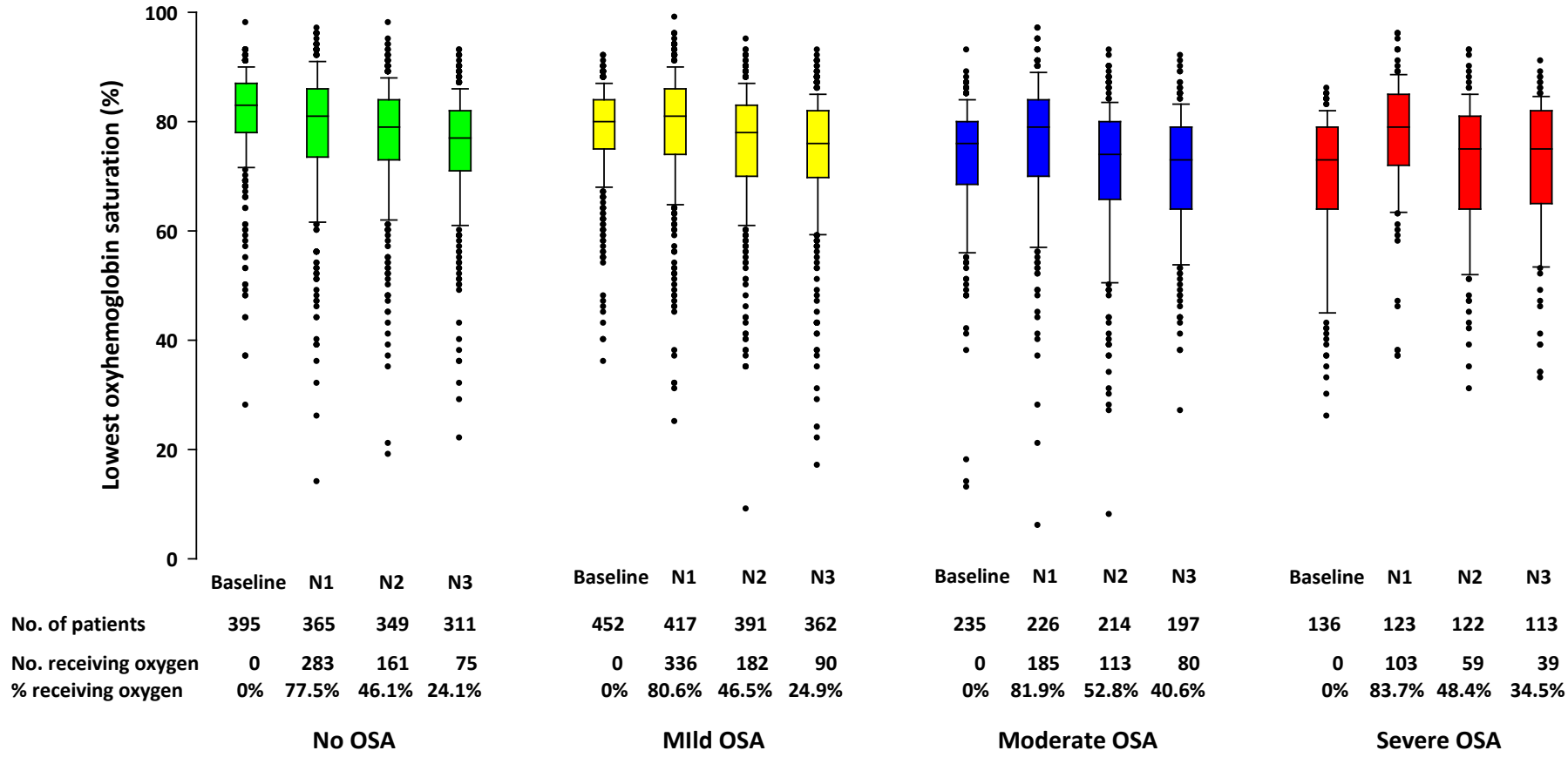
Shaded areas represent 95% confidence intervals

eFigure 7. Changes of Oxygen Desaturation Index Before and After Surgery in Patients With and Without Obstructive Sleep Apnea



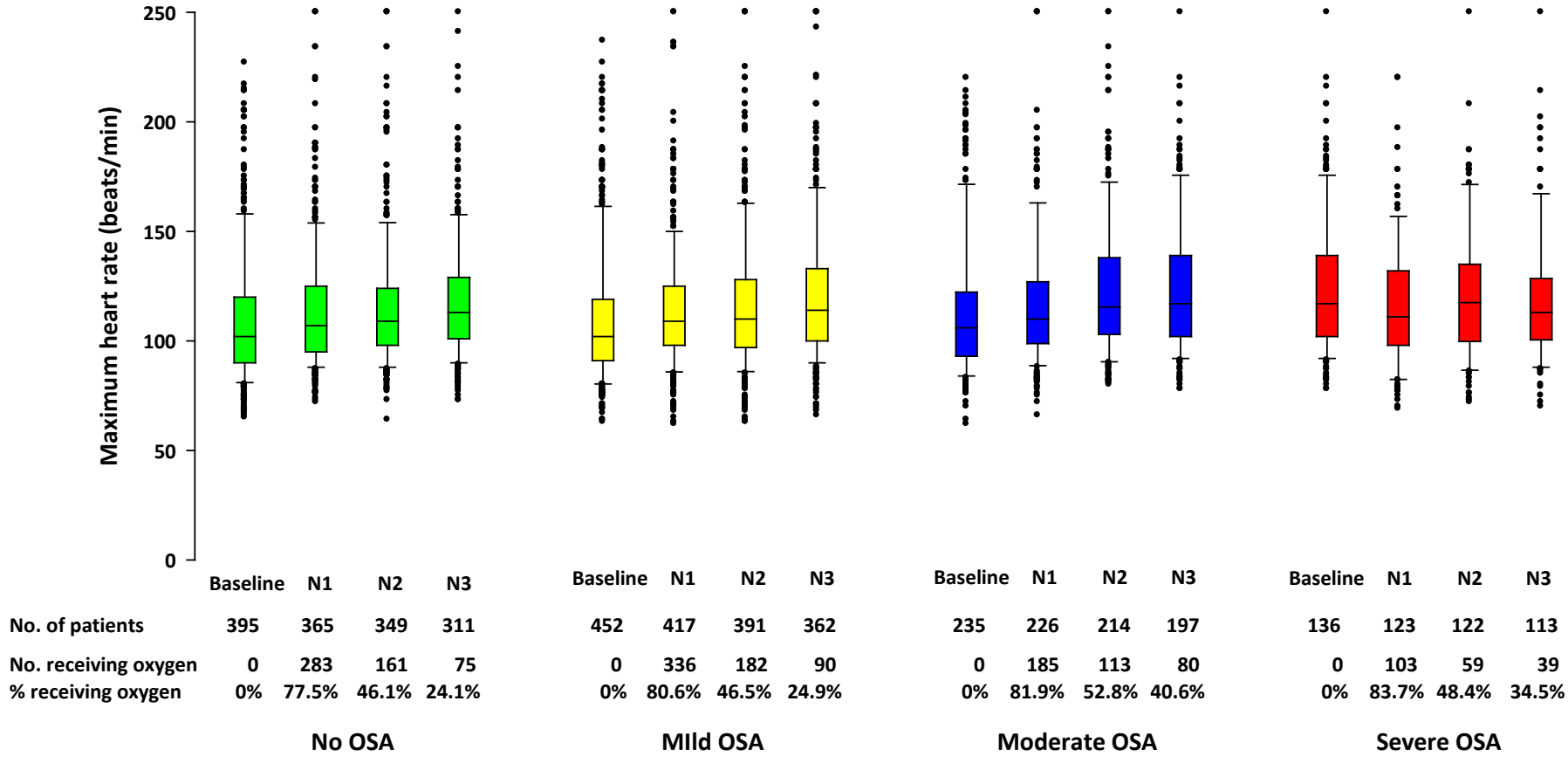
N1, N2 and N3 indicates the first, second and third night, respectively.
The horizontal line in each box represents the median value, and the top and bottom of the boxes are the interquartile range. The error bars indicate 95% confidence intervals, and the dots are outliers

eFigure 8. Lowest Oxyhemoglobin Saturation Before and After Surgery in Patients With and Without Obstructive Sleep Apnea



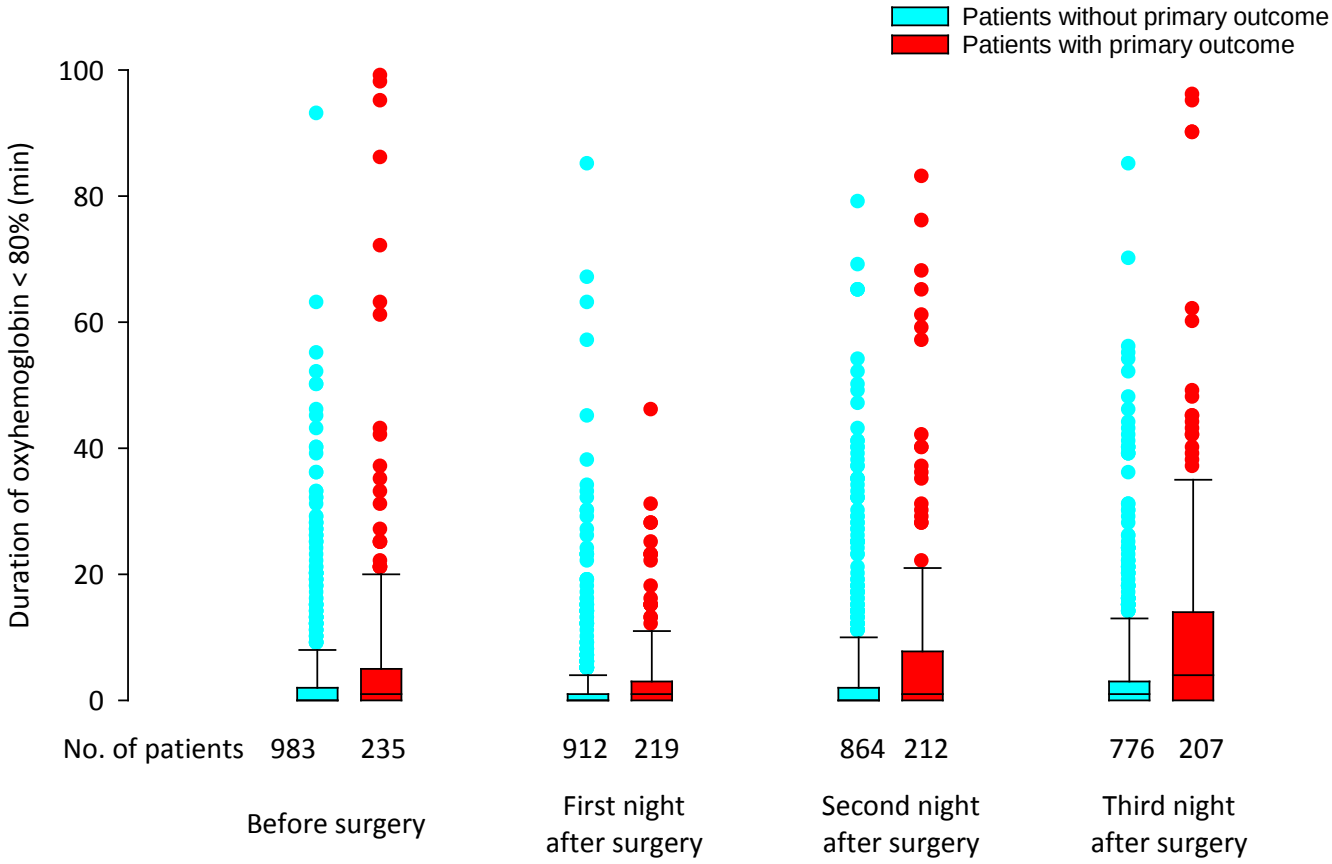
N1, N2 and N3 indicates the first, second and third night, respectively.
The horizontal line in each box represents the median value, and the top and bottom of the boxes are the interquartile range. The error bars indicate 95% confidence intervals, and the dots are outliers

eFigure 9. Highest Heart Rate Before and After Surgery in Patients With and Without Obstructive Sleep Apnea



N1, N2 and N3 indicates the first, second and third night, respectively.
The horizontal line in each box represents the median value, and the top and bottom of the boxes are the interquartile range. The error bars indicate 95% confidence intervals, and the dots are outliers

eFigure 10. Duration of Oxyhemoglobin Saturation <80% in Patients Who Did and Did Not Have the Primary Outcome



N1, N2 and N3 indicates the first, second and third night, respectively.
The horizontal line in each box represents the median value, and the top and bottom of the boxes are the interquartile range. The error bars indicate 95% confidence intervals, and the dots are outliers

eTable 1. Preoperative Sleep Study Results

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA
No. of patients	1,218	395	452	235	136
	Means (SD)				
Sleep study before surgery, hours	79 (114)	69 (109)	88 (122)	79 (108)	82 (113)
Evaluation period, hours	9.4 (2.3)	9.5 (2.3)	9.4 (2.4)	9.1 (2.2)	9.4 (2.3)
Respiratory event index, events/h[a]	12.7 (13.8)	1.9 (1.4)	8.6 (2.7)	20.8 (4.5)	44.2 (12.0)
Apnea index, events/h[b]	6.6 (10.5)	0.7 (1.0)	3.5 (3.1)	9.8 (6.0)	28.4 (16.0)
Unclassified apnea	0.9 (4.1)	0.1 (0.4)	0.4 (1.1)	1.2 (2.4)	4.9 (10.9)
Obstructive apnea	4.7 (8.3)	0.5 (1.0)	2.6 (2.9)	7.0 (5.6)	19.9 (15.1)
Central apnea	0.8 (2.4)	0.1 (0.4)	0.4 (0.9)	1.4 (2.5)	3.2 (5.4)
Mixed apnea	0.1 (0.3)	0.0 (0.1)	0.0 (0.3)	0.1 (0.3)	0.3 (0.6
Hypopnea index, events/h[c]	6.2 (6.9)	1.2 (1.3)	5.2 (3.2)	10.7 (6.1)	15.9 (11.3)
Percent flow limited breaths without snoring	29.8 (15.7)	33.0 (17.6)	30.3 (14.8)	27.1 (13.7)	23.8 (13.6)
Percent flow limited breaths with snoring	2.2 (4.7)	1.1 (3.0)	1.9 (4.2)	3.7 (6.3)	4.0 (5.6)
Oxygen desaturation index, events/h[d]	12.9 (12.1)	3.8 (2.4)	9.2 (3.9)	20.9 (6.7)	37.7 (12.5)
Lowest SpO_2, %	77 (11)	81 (9)	78 (9)	73 (12)	69 (14)
Average SpO_2, %	95 (3)	95 (2)	94 (2)	93 (3)	95 (3)
Duration SpO_2 < 90%, min	28.4 (53.3)	10.7 (29.8)	20.1 (34.0)	42.6 (57.0)	83.1 (94.8)
Duration SpO_2 < 80%, min	4.0 (14.4)	0.9 (2.7)	2.2 (5.7)	6.1 (13.6)	12.2 (18.0)
Lowest pulse rate, beats/min	48 (12)	49 (12)	49 (11)	44 (13)	45 (12)
Average pulse rate, beats/min	69 (11)	69 (12)	68 (11)	68 (10)	70 (11)
Highest pulse rate, beats/min	112 (33)	110 (31)	111 (32)	116 (34)	118 (37)

Abbreviations: OSA, obstructive sleep apnea; SD, standard deviations; SpO_2, oxyhemoglobin saturation

[a] Respiratory event index is the number of apnea and hypopnea events per hour of recording.

[b] Apnea index is the number of apnea events (airflow reduction ≥ 90% from baseline for ≥ 10 seconds) per hour of recording.

[c] Hypopnea index is the number of hypopnea events (airflow reduction ≥ 30% from baseline for ≥ 10 seconds and associated with ≥ 3% oxyhemoglobin desaturation) per hour of recording.

[d] Oxygen desaturation index is the number of events per hour of oximetry recording (derived from the wristwatch) where oxyhemoglobin saturation decreased by ≥ 4% from baseline for ≥ 10 seconds.

eTable 2. Details of Anesthetic Administration

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA	*P* values
No. of patients	1,218	395	452	235	136	
Regional block, no. (%)						0.82
Spinal anesthesia	286 (23.5)	83 (21.0)	108 (23.9)	59 (25.1)	36 (26.5)	
Epidural anesthesia	115 (9.4)	32(8.1)	48 (10.6)	24 (10.2)	11 (8.1)	
Nerve block	190 (15.6)	63 (15.9)	76 (16.8)	29 (12.3)	22 (16.2)	
General anesthesia, no. (%)	951 (78.1)	314 (79.5)	351 (77.7)	183 (77.9)	103 (75.7)	0.81
Anesthetic drug used						
Fentanyl, no. (%)	986 (81.0)	329 (83.3)	358 (79.2)	188 (80.0)	111 (81.6)	0.48
Dosage, μg/kg, mean (SD)	2.2 (2.3)	2.3 (2.6)	2.2 (2.3)	2.2 (2.2)	1.9 (1.9)	0.82
Morphine, no. (%)	711 (58.4)	248 (62.8)	251 (55.5)	132 (56.2)	80 (58.8)	0.16
Dosage, mg/kg, mean (SD)	0.11 (0.08)	0.11 (0.06)	0.10 (0.05)	0.12 (0.14)	0.09 (0.06)	0.27
Remifentanil, no. (%)	169 (13.9)	58 (14.7)	62 (13.7)	30 (12.8)	19 (14.0)	0.93
Propofol infusion, no. (%)	118 (9.7)	34 (8.6)	44 (9.7)	26 (11.1)	14 (10.3)	0.78
Targeted plasma concentration, μg/ml, mean (SD)	3.5 (0.7)	3.6 (0.8)	3.5 (0.6)	3.3 (0.6)	3.5 (0.7)	0.50
Inhalational anesthesia						0.80
Isoflurane, no. (%)	62 (7.0)	29 (9.8)	19 (5.8)	9 (5.3)	5 (5.2)	
Sevoflurane, no. (%)	608 (68.3)	201 (68.1)	226 (68.9)	109 (63.7)	72 (75.0)	
Desflurane, no. (%)	220 (24.7)	65 (22.0)	83 (25.3)	53 (31.0)	19 (19.8)	
End-tidal concentration, MAC-equivalents[a]), mean (SD)	0.94 (0.22)	0.95 (0.21)	0.94 (0.23)	0.93 (0.21)	0.93 (0.22)	0.27
Inspired oxygen concentration, %, mean (SD)	40.1 (7.5)	40.2 (7.3)	40.0 (7.6)	40.2 (7.2)	40.2 (8.1)	0.98
Core temperature at wound closure, °C, mean (SD)	36.1 (0.8)	36.1 (0.8)	36.2 (0.8)	36.0 (0.8)	36.1 (0.9)	0.06
Duration of anesthesia, hour, mean (SD)	3.8 (2.3)	3.9 (2.3)	3.7 (2.1)	3.7 (2.3)	3.9 (2.7)	0.55

Abbreviations: OSA, obstructive sleep apnea; SD, standard deviations

[a] MAC denotes minimum alveolar concentration and indicates the potency of volatile anesthetics.

eTable 3. Postoperative Analgesic Techniques

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA	*P* values
No. of patients	1,218	395	452	235	136	
Postoperative use of opioid, no. (%)	707 (58)	223 (56.5)	259 (57.3)	151 (64.3)	74 (54.4)	0.17
Patient controlled analgesia of opioid, no. (%)	600 (49.3)	188 (47.6)	222 (49.1)	131 (55.7)	59 (43.4)	0.10
Non-steroidal anti-inflammatory drugs, no. (%)	675 (55.4)	206 (52.2)	267 (59.1)	131 (55.7)	71 (52.2)	0.19
Tramadol, no. (%)	681 (55.9)	231 (58.5)	252 (55.8)	125 (53.2)	73 (53.7)	0.56
Neuraxial block, no. (%)	130 (10.7)	33 (8.4)	50 (11.1)	29 (12.3)	18 (13.2)	0.27
Nerve block, no. (%)	77 (6.3)	23 (5.8)	32 (7.1)	12 (5.1)	10 (7.4)	0.70

Abbreviations: OSA, obstructive sleep apnea

eTable 4. Postoperative Troponin Measurements

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA	*P* values
No. of patients	1,218	395	452	235	136	
No. of troponin measurements performed, No. (%)						0.75
4	963 (79.1)	306 (77.5)	363 (80.3)	183 (77.9)	111 (81.6)	
3	134 (11.0)	48 (12.2)	42 (9.3)	29 (12.3)	15 (11.0)	
2	62 (5.1)	17 (4.3)	24 (5.3)	16 (6.8)	5 (3.7)	
1	8 (0.7)	3 (0.8)	3 (0.7)	1 (0.4)	1 (0.7)	
0	51 (4.2)	21 (5.3)	20 (4.4)	6 (2.9)	4 (2.9)	

Abbreviation: OSA, obstructive sleep apnea

eTable 5. Preoperative Predictors for Postoperative Cardiovascular Events

Risk factors	No. event/Total no. (%)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Population attributable risk (95% CI)
Age group						
45-64 y	56/433 (12.9)	Reference		Reference		15.6 (8.4-22.3)
65-74 y	98/513 (19.1)	1.52 (1.09-2.11)	0.01	1.45 (1.04-2.03)	0.03	
≥75 y	81/272 (29.8)	2.49 (1.77-3.51)	<0.001	2.30 (1.60-3.32)	<0.001	
Sex						
Female	69/490 (14.1)	Reference	<0.001	Reference	0.08	–
Male	166/728 (22.8)	1.70 (1.28-2.25)		1.30 (0.97-1.76)		
Ethnicity						
Malay	30/195 (15.4)	Reference		Reference		–
Caucasian	31/183 (16.9)	1.09 (0.66-1.80)	0.74	0.96 (0.56-1.66)	0.89	
Chinese	141/666 (21.2)	1.45 (0.98-2.15)	0.07	1.19 (0.78-1.84)	0.42	
Indian	32/161 (19.9)	1.31 (0.79-2.15)	0.29	1.61 (0.96-2.70)	0.07	
Hypertension						
No	23/181 (12.7)	Reference		Reference		–
Yes	212/1037 (20.4)	1.70 (1.10-2.61)	0.02	1.45 (0.93-2.26)	0.10	
Coronary artery disease						
No	150/887 (16.9)	Reference		Reference		–
Yes	85/331 (25.7)	1.58 (1.21-2.07)	0.001	1.11 (0.82-1.52)	0.50	
Congestive heart failure						
No	214/1158 (18.5)	Reference		Reference		–
Yes	21/60 (35.0)	2.22 (1.42-3.48)	<0.001	1.57 (0.96-2.57)	0.07	
Peripheral vascular disease						
No	193/1091 (17.7)	Reference		Reference		8.3 (3.5-12.9)
Yes	42/127 (33.1)	2.07 (1.48-2.89)	<0.001	1.59 (1.09-2.31)	0.02	
Stroke or transient ischemic attack						
No	184/1041 (17.7)	Reference		Reference		–
Yes	51/177 (28.8)	1.73 (1.27-2.36)	0.001	1.27 (0.91-1.76)	0.16	
Diabetes mellitus						
No	67/280 (23.9)	Reference		Reference		–
Yes	168/938 (17.9)	0.72 (0.54-0.96)	0.02	0.81 (0.60-1.11)	0.19	

Risk factors	No. event/Total no. (%)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Population attributable risk (95% CI)
Chronic obstructive pulmonary disease						
No	218/1158 (18.8)	Reference		Reference		–
Yes	17/60 (28.3)	1.53 (0.94-2.51)	0.09	1.05 (0.62-1.77)	0.86	
Risk factors	No. event/Total no. (%)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Population attributable risk (95% CI)
Renal impairment						
No	202/1147 (17.6)	Reference		Reference		8.7 (4.6-12.6)
Yes	33/71 (46.5)	3.54 (2.45-5.12)	<0.001	3.57 (2.40-5.30)	<0.001	
Current smokers						
No	210/1081 (19.4)	Reference		Reference		–
Yes	25/137 (18.2)	0.92 (0.61-1.39)	0.69	0.88 (0.57-1.35)	0.55	
Surgery for malignancy						
No	123/705 (17.4)	Reference		Reference		–
Yes	112/512 (21.9)	1.30 (1.00-1.67)	0.05	1.11 (0.74-1.66)	0.62	
Intraperitoneal surgery						
No	107/642 (16.7)	Reference		Reference		–
Yes	128/576 (22.2)	1.38 (1.07-1.79)	0.01	1.45 (0.99-2.13)	0.06	
Preoperative use of β blockers						
No	137/803 (17.1)	Reference		Reference		–
Yes	98/415 (23.6)	1.43 (1.11-1.86)	0.006	1.09 (0.82-1.44)	0.57	
Obstructive sleep apnea (OSA)						
No OSA	56/395 (14.2)	Reference		Reference		22.4 (14.9-29.9)
Mild OSA	86/452 (19.0)	1.37 (0.98-1.91)	0.07	1.36 (0.97-1.90)	0.08	
Moderate OSA	52/235 (22.1)	1.59 (1.09-2.32)	0.02	1.43 (0.98-2.09)	0.07	
Severe OSA	41/136 (30.1)	2.33 (1.55-3.48)	<0.001	2.04 (1.33-2.99)	0.001	

Abbreviations: HR, hazard ratios; CI, confidence intervals

eTable 6. Association Between Severity of Obstructive Sleep Apnea and Primary Outcome Stratified by Sites

Outcome	No. events/Total (%)	Unadjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Site 1					
No OSA	11/67 (16.4)	Reference		Reference	
Mild OSA	25/113 (22.1)	1.39 (0.69-2.83)	0.36	1.30 (0.64-2.66)	0.47
Moderate OSA	7/65 (10.8)	0.63 (0.24-1.61)	0.33	0.64 (0.25-1.65)	0.35
Severe OSA	8/34 (23.5)	1.49 (0.60-3.70)	0.39	1.31 (0.52-3.29)	0.57
Site 2					
No OSA	4/35 (11.4)	Reference		Reference	
Mild OSA	5/50 (10.0)	0.88 (0.24-3.26)	0.84	0.69 (0.18-2.67)	0.59
Moderate OSA	3/17 (17.6)	1.56 (0.35-6.98)	0.56	1.33 (0.26-6.85)	0.73
Severe OSA	1/16 (6.3)	0.55 (0.06-4.91)	0.59	0.62 (0.07-5.62)	0.67
Site 3					
No OSA	4/70 (5.7)	Reference		Reference	
Mild OSA	14/80 (17.5)	3.22 (1.06-9.79)	0.04	3.27 (1.07-10.04)	0.38
Moderate OSA	10/42 (23.8)	4.42 (1.39-14.11)	0.01	4.27 (1.33-13.68)	0.15
Severe OSA	8/26 (30.8)	6.11 (1.84-20.29)	0.003	5.72 (1.72-19.09)	0.005
Site 4					
No OSA	5/43 (11.6)	Reference		Reference	
Mild OSA	5/37 (13.5)	1.24 (0.36-4.28)	0.74	1.31 (0.37-4.64)	0.67
Moderate OSA	7/45 (15.6)	1.39 (0.44-4.39)	0.57	1.36 (0.41-4.53)	0.61
Severe OSA	5/16 (31.3)	3.03 (0.88-10.47)	0.08	3.39 (0.90-12.74)	0.07
Site 5					
No OSA	0/1 (0.0)	Reference		Reference	
Mild OSA	1/3 (33.3)	–	–	–	–
Moderate OSA	0/2 (0.0)	–	–	–	–
Severe OSA	1/6 (16.7)	–	–	–	–
Site 6					
No OSA	0/2 (0.0)	Reference		Reference	
Mild OSA	0/1 (0.0)	–	–	–	–
Moderate OSA	0/1 (0.0)	–	–	–	–
Severe OSA	0/0	–	–	–	–
Site 7					
No OSA	32/166 (19.3)	Reference		Reference	
Mild OSA	33/145 (22.8)	1.17 (0.72-1.91)	0.52	1.15 (0.71-1.88)	0.57
Moderate OSA	22/53 (41.5)	2.34 (1.36-4.02)	0.002	1.68 (0.96-2.94)	0.07
Severe OSA	15/39 (38.5)	2.30 (1.25-4.25)	0.008	1.96 (1.05-3.64)	0.03
Site 8					
No OSA	0/11 (0.0)	Reference		Reference	
Mild OSA	3/23 (13.0)	–	–	–	–
Moderate OSA	3/10 (30.0)	–	–	–	–
Severe OSA	4/5 (80.0)	–	–	–	–

eTable 7. Post hoc Analysis on the Association Between Severity of Obstructive Sleep Apnea and Modified Primary Outcome

	No. events/Total (%)	Unadjusted HR (95%CI)	*P* value	Adjusted HR (95%CI)	*P* value
Modified primary outcome[a]: cardiac death, myocardial infarction, congestive heart failure, thromboembolism, new atrial fibrillation and stroke					
No OSA	16/395 (4.1)	Reference		Reference	
Mild OSA	39/452 (8.6)	2.96 (0.95-8.07)	0.05	1.36 (0.97-1.90)	0.08
Moderate OSA	30/235 (12.8)	3.41 (1.20-9.71)	0.02	1.43 (0.98-2.09)	0.07
Severe OSA	26/136 (19.1)	3.82 (1.30-11.20)	0.003	2.04 (1.33-2.99)	0.001
Myocardial infarction					
No OSA	11/395 (2.8)	Reference		Reference	
Mild OSA	26/452 (5.8)	2.10 (1.04-4.25)	0.04	2.03 (1.00-4.12)	0.05
Moderate OSA	16/235 (6.8)	2.48 (1.15-5.33)	0.02	2.12 (0.98-4.57)	0.06
Severe OSA	14/136 (10.3)	3.85 (1.75-8.49)	0.001	3.20 (1.45-7.08)	0.004

Abbreviations: OSA, obstructive sleep apnea; CI, confidence intervals
[a]Myocardial injury replaced by myocardial infarction

eTable 8. STOP-Bang Risk Score in Patients With Different Severity of Obstructive Sleep Apnea

STOP-Bang Risk[a]	Severity of OSA based on apnea-hypopnea index			
	No OSA	Mild OSA	Moderate OSA	Severe OSA
Low risk, no. (%)	121 (30.6)	94 (20.8)	33 (14.0)	5 (3.7)
Moderate risk, no. (%)	217 (54.9)	260 57.5)	119 (50.6)	52 (38.2)
High risk, no. (%)[b]	57 (14.4)	98 (21.7)	83 (35.3)	79 (58.1)

[a] STOP-Bang denotes Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, age, neck circumference, and gender. Scores range from 0 to 8; with a score of 0-2 indicating low risk; 3-4 moderate risk and 5-8 high risk.

[b] High STOP-Bang risk score predicted severe OSA with sensitivity and specificity of 58.1% and 78.0%, respectively, C-index 0.714 (95%CI: 0.670-0.758), $P < 0.001$.

eTable 9. Characteristics of Patients With STOP-Bang Risk Score

	Low risk	Intermediate risk	High risk	*P* value[a]
STOP-Bang score	0 – 2	3 – 4	5 – 8	
No. of patients	253	648	317	
(95%CI)	20.8 (18.6-23.1)	53.2 (50.4-56.0)	26.3 (23.6-28.6)	
Age group, no. (%)				0.93
45-64 y	94 (37.2)	226 (34.9)	113 (35.6)	
65-74 y	102 (40.3)	274 (42.3)	137 (43.2)	
≥75 y	57 (22.5)	148 (22.8)	67 (21.1)	
Male sex, no. (%)	49 (19.4)	413 (63.7)	266 (83.9)	<0.001
Race/ethnicity, no. (%)				<0.001
Chinese	121 (47.8)	380 (58.6)	165 (52.1)	
Malay	49 (19.4)	111 (17.1)	35 (11.0)	
White	33 (13.0)	76 (11.7)	74 (23.3)	
Indian	44 (17.4)	78 (12.0)	39 (12.3)	
Others[b]	6 (2.4)	3 (0.5)	4 (1.3)	
Patient fulfilling the entry criteria, no. (%)				
Hypertension	147 (58.1)	587 (90.6)	303 (95.6)	<0.001
Coronary artery disease	44 (17.4)	179 (27.6)	108 (34.1)	<0.001
Diabetes receiving insulin treatment	196 (77.5)	487 (75.2)	255 (80.4)	0.18
Stroke or transient ischemic attack	34 (13.4)	95 (14.7)	48 (15.1)	0.84
Current smoker	20 (7.9)	74 (11.4)	43 (13.6)	<0.001
Peripheral vascular disease	17 (6.7)	69 (10.6)	41 (12.9)	0.05
Preoperative creatinine concentration > 175 μmol/L	15 (5.9)	41 (6.3)	15 (4.7)	0.61
Congestive heart failure	15 (5.9)	31 (4.8)	14 (4.4)	0.69
Chronic pulmonary obstructive disease	8 (3.2)	26 (4.0)	26 (8.2)	0.006
Type of surgery, no. (%)				0.16
Intraperitoneal surgery	117 (46.2)	317 (48.9)	142 (44.8)	
Vascular surgery	26 (10.3)	98 (15.1)	45 (14.2)	
Major orthopedic surgery	83 (32.9)	172 (26.6)	109 (34.4)	
Others	26 (10.3)	160 (24.7)	23 (34.4)	
Cancer surgery, no. (%)	99 (39.1)	288 (44.4)	125 (39.6)	0.20
Minimally invasive surgery, no. (%)	46 (18.2)	204 (31.5)	95 (30.0)	<0.001
Preoperative medication, no. (%)				
Statin	153 (60.5)	464 (71.6)	237 (74.8)	0.001
ACE inhibitor or ARB	107 (42.3)	345 (53.2)	193 (60.9)	<0.001
β blocker	70 (27.7)	219 (33.8)	126 (39.7)	0.01
Aspirin	53 (20.9)	171 (26.4)	85 (26.8)	0.19
Clopidogrel	9 (3.6)	31 (4.8)	15 (4.7)	0.71
Anthropometric measurements, mean (SD)				
Body mass index, kg/m^2	24.7 (4.1)	26.2 (6)	29.5 (12.7)	<0.001
Neck circumference, cm	36.0 (2.8)	38.3 (3.0)	41.0 (3.4)	<0.001
Waist, cm	88.4 (11.9)	91.8 (11.8)	96.6 (13.4)	<0.001
Preoperative sleep study characteristics, median (IQR)				
Respiratory event index, events/h	5 (2-9)	8 (3-15)	15 (7-30.3)	
Oxygen desaturation index, events/h	6.5 (3.3-11.0)	8.2 (4.1-15.8)	14.7 (7-26.9)	
Epworth Sleepiness Scale score	4 (2-6)	4 (2-7)	5 (3-9)	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; OSA, obstructive sleep apnea; CI, confidence intervals; SD, standard deviations; IQR, interquartile range

[a] *P* value for tests to determine imbalance among groups, continuous variables were compared using analysis of variance and categorical variables were compared using Pearson's χ^2 test.

[b] Other races/ethnicities included black and Arab.

[c] Other surgery included major urological, major hernia repair and spine surgery.

eTable 10. STOP-Bang Risk Score and Outcome

	No. events/Total (%)	Unadjusted HR or OR (95%CI)	*P* value	Adjusted HR or OR (95%CI)	*P* value
Primary outcome: cardiac death, myocardial injury, congestive heart failure, thromboembolism, new atrial fibrillation and stroke					
Low risk	34/253 (13.4)	Reference		Reference	
Intermediate risk	133/648 (20.5)	1.60 (1.10-2.33)	0.02	1.50 (1.00-2.18)	0.05
High risk	68/317 (21.5)	1.67 (1.11-2.52)	0.01	1.68 (1.11-2.54)	0.01
Post hoc analysis on the components of primary outcome					
Cardiac death					
Low risk	1/253 (0.4)	Reference		Reference	
Intermediate risk	12/648 (1.9)	4.71 (0.61-36.22)	0.14	3.57 (0.46-27.86)	0.22
High risk	4/317 (1.3)	3.21 (0.36-28.72)	0.30	2.54 (0.28-23.10)	0.41
Myocardial injury					
Low risk	30/240 (12.5)	Reference		Reference	
Intermediate risk	117/621 (18.8)	1.39 (0.91-2.11)	0.12	1.48 (0.99-2.21)	0.06
High risk	58/306 (19.0)	1.45 (0.92-2.31)	0.11	1.63 (1.06-2.54)	0.03
Congestive heart failure					
Low risk	2/253 (0.8)	Reference		Reference	
Intermediate risk	12/648 (1.9)	2.35 (0.53-10.49)	0.26	2.31 (0.48-9.83)	0.32
High risk	7/317 (2.2)	2.80 (0.58-13.47)	0.20	2.51 (0.51-12.38)	0.26
Thromboembolism					
Low risk	0/253 (0.0)	Reference		Reference	
Intermediate risk	6/648 (0.9)	-		-	
High risk	4/317 (1.3)	-		-	
New onset atrial fibrillation					
Low risk	5/253 (2.0)	Reference		Reference	
Intermediate risk	15/648 (2.3)	1.47 (0.49-4.43)	0.49	1.16 (0.46-3.18)	0.55
High risk	10/317 (3.2)	2.01 (0.63-6.41)	0.24	1.65 (0.56-4.83)	0.22
Stroke					
Low risk	0/253 (0.0)	Reference		Reference	
Intermediate risk	3/648 (0.5)	-		-	
High risk	2/317 (0.6)	-		-	
Secondary Outcomes					
Unplanned or readmission to ICU[a]					
Low risk	6/253 (2.4)	Reference		Reference	
Intermediate risk	41/648 (6.3)	2.78 (1.17-6.63)	0.02	2.69 (1.12-6.44)	0.03
High risk	21/317 (6.6)	2.92 (1.16-7.35)	0.02	2.86 (1.13-7.23)	0.03
Unplanned tracheal intubation or postoperative lung ventilation[a]					
Low risk	10/253 (4.0)	Reference		Reference	
Intermediate risk	52/648 (8.0)	2.12 (1.06-4.24)	0.03	2.06 (0.95-3.91)	0.07
High risk	19/317 (6.0)	1.55 (0.71-3.39)	0.27	1.50 (0.70-3.54)	0.28
Pneumonia					
Low risk	6/253 (2.4)	Reference		Reference	
Intermediate risk	21/648 (3.2)	1.37 (0.55-3.40)	0.50	1.28 (0.51-319)	0.60
High risk	9/317 (2.8)	1.20 (0.43-3.37)	0.73	1.06 (0.36-3.09)	0.92
Wound infection					
Low risk	12/253 (4.7)	Reference		Reference	
Intermediate risk	60/648 (9.3)	1.98 (1.07-3.69)	0.03	1.95 (1.05-3.64)	0.03
High risk	26/317 (8.2)	1.78 (0.90-3.52)	0.10	1.70 (0.86-3.37)	0.12

	No. events/Total (%)	Unadjusted HR or OR (95%CI)	*P* value	Adjusted HR or OR (95%CI)	*P* value
Other infections[b]					
Low risk	9/253 (3.6)	Reference		Reference	
Intermediate risk	44/648 (6.8)	1.93 (0.94-3.96)	0.07	1.84 (0.89-3.79)	0.10
High risk	17/317 (5.4)	1.52 (0.68-3.40)	0.31	1.35 (0.59-3.08)	0.48
	No. events/Total (%)	Unadjusted HR or OR (95%CI)	*P* value	Adjusted HR or OR (95%CI)	*P* value
Postoperative delirium					
Low risk	9 (3.6)	Reference		Reference	
Intermediate risk	30 (4.6)	1.27 (0.60-2.68)	0.53	1.23 (0.58-2.61)	0.59
High risk	16 (5.0)	1.43 (0.63-3.24)	0.39	1.46 (0.64-3.30)	0.37

Abbreviations: HR, hazard ratio; OR, odds ratio; OSA, obstructive sleep apnea; CI, confidence intervals; ICU, intensive care unit.

[a] Outcomes are expressed as odds ratios.

[b] Other infections included urinary tract, upper respiratory tract and central nervous system infection.

eTable 11. Postoperative Oxygen Administration

	All patients	No OSA	Mild OSA	Moderate OSA	Severe OSA	*P* value
No. of patients	1,218	395	452	235	136	
No. of nights with oxygen supplement, median (IQR)[a]	1 (1-2)	1 (0-2)	1 (1-2)	1 (1-3)	1 (1-2)	0.004
First night						
Patients receiving supplemental oxygen, No. (%)	907 (74.5)	283 (71.6)	336 (74.3)	185 (78.7)	103 (75.7)	0.26
Types of devices, No. (%)						0.15
Nasal cannula	600 (49.3)	189 (47.8)	229 (50.7)	119 (50.6)	63 (46.3)	
Simple facemask	220 (18.1)	73 (18.5)	82 (18.1)	41 (17.4)	24(17.6)	
Non-rebreathing mask	7 (0.6)	2 (0.5)	2 (0.4)	3 (1.3)	0 (0)	
Non-invasive ventilation devices[b]	63 (5.2)	9 (2.3)	21 (4.6)	20 (8.5)	13 (9.6)	
Duration of oxygen administration, hours, mean (SD)	12.4 (5.7)	12.4 (5.6)	11.9 (5.2)	13.0 (6.4)	12.8 (6.2)	0.12
Second night						
Patients receiving supplemental oxygen, No. (%)	515 (42.3)	161 (40.8)	182 (40.3)	113 (48.1)	59 (43.4)	0.22
Types of devices, No. (%)						0.004
Nasal cannula	407 (33.4)	131 (33.2)	157 (34.7)	80 (34.0)	39 (28.7)	
Simple facemask	59 (4.8)	15 (3.8)	13 (2.9)	22 (9.4)	9 (6.6)	
Non-rebreathing mask	13 (1.1)	6 (1.5)	2 (0.4)	3 (1.3)	2 (1.5)	
Non-invasive ventilation devices[b]	25 (2.1)	3 (0.8)	9 (2.0)	7 (3.0)	6 (4.4)	
Duration of oxygen administration, hours, mean (SD)	11.7 (5.8)	10.8 (5.0)	11.5 (5.4)	13.5 (7.0)	11.8 (5.8)	0.001
Third night						
Patients receiving supplemental oxygen,No. (%)	284 (23.3)	75 (19.0)	90 (19.9)	80 (34.0)	39 (28.7)	<0.001
Types of devices, No. (%)						<0.001
Nasal cannula	220 (18.1)	65 (16.5)	73 (16.2)	56 (23.8)	26 (19.1)	
Simple facemask	15 (1.2)	1 (0.3)	4 (0.9)	6 (2.6)	4 (2.9)	
Non-rebreathing mask	5 (0.4)	0 (0)	2 (0.4)	3 (1.3)	0 (0)	
Non-invasive ventilation devices[b]	15 (1.2)	1 (0.3)	4 (0.9)	6 (2.6)	4 (2.9)	
Duration of oxygen administration, hours, mean (SD)	11.4 (6.2)	10.8 (6.0)	11.4 (5.8)	12.0 (6.9)	11.1 (6.2)	0.65

Abbreviation: OSA, obstructive sleep apnea; IQR, interquartile range; SD, standard deviations

[a] Individual patient may use more than one oxygen delivering devices,

[b] Non-invasive ventilation devices include continuous positive airway pressure (CPAP), bilevel positive airway pressure (biPAP) ventilation

eTable 12. Changes of Oximetry and Heart Rate in Patients Who Did and Did Not Have the Primary Outcome

		Patients without primary outcome	Patients with primary outcome	*P* values
Oxygen administration, No. (%)				
Before surgery		—	—	
After surgery	Night 1	706 (71.8)	201 (85.5)	<0.001[a]
	Night 2	377 (38.4)	138 (58.7)	<0.001[a]
	Night 3	193 (19.6)	91 (38.7)	<0.001[a]
Duration of oxygen administered, hours, mean (95%CI)				0.37[b]
Before surgery				
After surgery	Night 1	13.4 (12.5-14.3)	12.1 (10.7-13.4)	
	Night 2	13.3 (12.3-14.3)	12.9 (11.3-14.2)	
	Night 3	11.6 (10.7-12.6)	11.5 (10.1-12.8)	
Oxygen desaturation index, events/h, mean (95%CI)				0.20[b]
Before surgery		12.6 (11.7-13.5)	15.6 (13.9-17.4)	
After surgery	Night 1	7.1 (6.4-7.8)	7.3 (6.0-8.7)	
	Night 2	12.2 (11.1-13.2)	12.2 (10.2-14.2)	
	Night 3	13.6 (12.6-14.6)	14.1 (12.3-16.0)	
Lowest oxyhemoglobin saturation, mean (95%CI)				0.15[b]
Before surgery		77.2 (76.4-78.0)	75.9 (74.4-77.5)	
After surgery	Night 1	78.4 (77.5-79.3)	76.7 (75.0-78.5)	
	Night 2	74.6 (73.7-75.5)	73.7 (71.9-75.4)	
	Night 3	73.3 (72.4-74.2)	73.4 (71.2-75.1)	
Highest heart rate* – beats/min, mean (95%CI)				0.78[b]
Before surgery		113 (110-115)	107 (102-112)	
After surgery	Night 1	114 (112-117)	116 (112-121)	
	Night 2	118 (115-120)	122 (117-126)	
	Night 3	121 (119-124)	123 (118-127)	
Duration of oxyhemoglobin saturation <90%, min, mean (95%CI)				0.88[b]
Before surgery		24.4 (20.6-28.1)	37.1 (29.9-44.3)	
After surgery	Night 1	20.4 (16.5-24.2)	19.5 (12.1-27.0)	
	Night 2	51.7 (44.4-59.0)	43.0 (28.9-57.2)	
	Night 3	51.7 (44.7-58.7)	51.0 (37.4-64.6)	
Duration of oxyhemoglobin saturation <80%, min, mean (95%CI)				<0.001[b]
Before surgery		2.9 (2.2-3.6)	6.9 (5.4-8.3)	
After surgery	Night 1	1.9 (1.3-2.4)	4.2 (3.1-5.4)	
	Night 2	4.0 (3.1-4.9)	8.0 (6.2-9.8)	
	Night 3	4.3 (3.4-5.1)	10.9 (9.3-12.5)	

Abbreviation: CI, confidence intervals
[a] Chi-square test
[b] General linear model