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Impact of OSA on Cardiovascular Events After Coronary Artery Bypass Surgery

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BACKGROUND: The impact of OSA on new cardiovascular events in patients undergoing coronary artery bypass graft (CABG) surgery is poorly explored.

METHODS: Consecutive patients referred for CABG underwent clinical evaluation and standard polysomnography in the preoperative period. CABG surgery data, including percentage of off-pump and on-pump CABG, number of grafts, and intraoperative complications, were collected. The primary end point was major adverse cardiac or cerebrovascular events (MACCEs) (combined events of all-cause death, myocardial infarction, repeated revascularization, and cerebrovascular events). Secondary end points included individual MACCEs, typical angina, and arrhythmias. Patients were evaluated at 30 days (short-term) and up to 6.1 years (long term) after CABG.

RESULTS: We studied 67 patients (50 men; mean age, 58 ± 8 years; mean BMI, 28.5 ± 4.1 kg/m^2). OSA (apnea-hypopnea index ≥ 15 events/h) was present in 56% of the population. The patients were followed for a mean of 4.5 years (range, 3.2-6.1 years). No differences were observed in the short-term follow-up. In contrast, MACCE (35% vs 16%, $P = .02$), new revascularization (19% vs 0%, $P = .01$), episodes of typical angina (30% vs 7%, $P = .02$), and atrial fibrillation (22% vs 0%, $P = .0068$) were more common in patients with than without OSA in the long-term follow-up. OSA was an independent factor associated with the occurrence of MACCE, repeated revascularization, typical angina, and atrial fibrillation in the multivariate analysis.

CONCLUSIONS: OSA is independently associated with a higher rate of long-term cardiovascular events after CABG and may have prognostic and economic significance in CABG surgery.

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ABBREVIATIONS: AHI = apnea-hypopnea index; CABG = coronary artery bypass graft; CAD = coronary artery disease; MACCE = major adverse cardiac or cerebrovascular event

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OSA is characterized by recurrent episodes of upper airway obstruction during sleep promoting sleep fragmentation and intermittent hypoxia.[1] Current prevalence of OSA in the general adult population indicated that one-third of sleep studies showed some degree of OSA.[2] Among adults 30 to 70 years of age, approximately 13% of men and 6% of women have moderate to severe forms of OSA (apnea-hypopnea index [AHI] $\geq$ 15 events/h of sleep).[2] Previous studies suggested that OSA is also common among candidates for surgery.[3,4] Despite the high prevalence of OSA among patients referred to surgery, the impact of untreated OSA in the perioperative events is not well established. Most of the evidence is based on noncardiac surgeries and short-term (in-hospital) follow-up.[4-6] Patients with OSA appear to be at increased risk for pulmonary complications[6] and need for intensive care services, which may increase health-care costs.[7]

Although long-term adverse effects of OSA on health-related outcomes are well documented in nonsurgical populations,[8,9] its effects on perioperative risks have only recently gained increasing interest.[10,11]

In the present study, we aimed to explore the potential impact of OSA on postoperative events at 30 days (short-term) and in the long-term follow-up in patients undergoing coronary artery bypass graft (CABG) surgery. The primary end point was major adverse cardiac or cerebrovascular events (MACCEs) (all-cause death, myocardial infarction, repeated revascularization, and cerebrovascular events). Secondary end points included individual MACCEs, new episodes of typical angina, and arrhythmias. We hypothesized that OSA is independently associated with higher rates of cardiovascular events in both short- and long-term follow-up after CABG.

Materials and Methods

Participants

We studied consecutive patients with severe coronary artery disease (CAD) over 40 years of age referred for CABG at the Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil.[3] This is a follow-up study from a previous investigation devoted to validating the diagnosis of OSA with portable sleep monitors among consecutive patients referred for elective CABG.[3] Details on patient recruitment were previously reported.[3] Patients were excluded if they had a previous diagnosis of OSA, history of stroke with severe disability, decompensated heart failure, or CABG combined with other cardiac surgery. All procedures were performed in accordance with institutional guidelines. The protocol was approved by the System Documentation and Scientific Review Committee of Research, Hospital das Clinicas, University of São Paulo Medical School (number 168/06), and informed consent was obtained from all participants.

Preoperative Clinical Evaluation

All participants underwent a detailed history and physical examination, including anthropometric and BP measurements. All subjects underwent an overnight standard polysomnography performed at the sleep laboratory as previously described.[3] Hypopnea was defined as a 50% airflow lasting $\geq$ 10 s associated with oxygen desaturation of $>$ 3% or with an arousal. Apnea was defined when cessation of airflow lasted $\geq$ 10 s and was further classified based on the presence or absence of respiratory effort as central, obstructive, or mixed.[12] The total recording time was used as the denominator to calculate the AHI.[1] OSA was defined by an AHI $\geq$ 15 events/h of sleep.[3] All sleep studies were scored in a blinded fashion and interpreted by an experienced sleep physician (F. S. N.).

Follow-up

Percentage of off-pump and on-pump CABG, on-pump time (minutes), number of grafts, and intraoperative complications (see standard definitions in e-Appendix 1) were recorded. In the postoperative setting, all patients were initially monitored in the ICU. As previously described,[13] blood samples for serum creatinine kinase MB and troponin determination were collected prior to surgery and every 6 h after surgery, until the peak elevation was determined. We followed up all participants during the hospital stay by performing daily visits. After hospital discharge, we contacted patients (through personal interviews or telephone contact) to determine if postoperative events (see standard definitions in e-Appendix 1) had occurred. All patients had their medical records checked. We performed analyses in the first 30 days after CABG (short-term) and long-term follow-up after CABG. This time frame was previously used by others.[14]

Statistical Analysis

Data were analyzed with SPSS 18.0 (IBM Corporation). After checking normality with the Kolmogorov-Smirnov test, the results were expressed as mean $\pm$ SD, median (interquartile range), or percentage, when appropriate. Wilcoxon signed-rank test and paired Student t or Mann-Whitney U tests were used for independent samples, and the χ^2 test was used to compare the variables of frequency between patients with and without OSA. The time to the first occurrence of any one of the components of the outcomes was described with the use of Kaplan-Meier survival curves, and the comparisons between the two study groups were performed with the use of a log-rank test. For all these procedures, a significance level of 5% was adopted. To check whether OSA is independently associated with the outcomes, we performed a logistic regression analysis. All variables with a P value $<$ 0.1 in the univariate analysis entered in the final model.

Results

We prospectively evaluated 100 patients who underwent elective CABG. None had a previous history of arrhythmias. Sixty-seven patients (50 men) composed the final sample (Fig 1). The baseline characteristics of the entire population are presented in Table 1. The study population was predominantly middle-aged, overweight, and white. The frequency of patients with OSA was 56% (mean AHI, 23.3 $\pm$ 20.3 events/h of sleep).

Compared with patients without OSA, patients with OSA had significantly higher values of waist circumference, lower left ventricular ejection fraction, and greater

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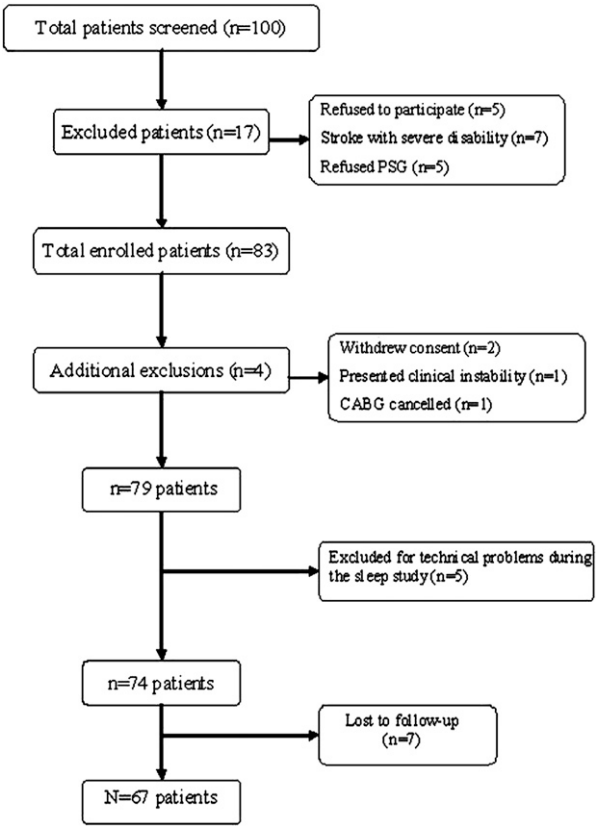

Figure 1 – *Patient recruitment flowchart. CABG = coronary artery bypass graft; PSG = polysomnography.*

use of statins. Patients with OSA were older and had a higher frequency of men than patients without OSA (Table 1), but these differences did not reach statistical significance. No significant differences regarding total and postoperative length of hospital stay (days), percentage of off-pump CABG, on-pump time (minutes), and number of grafts were observed (Table 1). All patients diagnosed with OSA were referred to sleep specialists after hospital discharge. Only one patient used CPAP in the follow-up (our Public Health System did not provide CPAP for treating OSA). However, because the low adherence to CPAP (< 4 h/night), we kept this patient in the final analysis.

In the short-term period, we did not observe any significant differences in patients with and without OSA (Fig 2). At a mean of 4.5 years after CABG (range, 3.2-6.1 years), a primary outcome event (MACCE) was more common in patients with than without OSA (Fig 2, Table 2). Table 2 also shows the secondary outcomes. According to Table 2, the higher rate of MACCEs in patients with OSA is mainly explained by a higher rate of new revascularization in this group (no OSA, 3%; OSA, 22%; $P = .035$). Specifically, most of the repeated procedures in patients with OSA were percutaneous coronary interventions (no OSA, 0%; OSA, 13%; $P = .059$). In patients who required new revascularization, the new cardiac catheterization showed graft failure in 30% (no OSA, no patients; OSA, three patients; $P = .24$) and progression of a previous nonobstructive lesion or de novo coronary lesions in 70% (no OSA, one patient; OSA, six patients; $P = .12$). One patient with OSA presented both graft failure and progression or de novo coronary lesions. Other cardiovascular events were higher in patients with OSA, including new episodes of typical angina and atrial fibrillation. Of note, we did not find significant differences on BMI ($P = .56$) and pharmacologic treatment (acetylsalicylic acid, $P = 1.0$; β-blockers, $P = .48$; calcium channel blockers, $P = .85$; angiotensin-converting enzyme inhibitor/angiotensin receptor blockers, $P = .35$; statins, $P = .72$; and nitrates, $P = .85$) during the follow-up. In the Kaplan-Meier survival curves, the event-free survival rates were lower in patients with OSA for MACCE (Fig 3), new revascularization (Fig 4), typical angina (Fig 5), and atrial fibrillation (Fig 6). In the multivariate analysis (Table 3), the presence of OSA was independently associated with MACCE, repeated revascularization, typical angina, and atrial fibrillation.

Discussion

To our knowledge, this is the first study to evaluate the impact of OSA on short- and long-term cardiovascular events after CABG. We extend our previous findings that OSA is extremely common in patient candidates for CABG.[3] Contrary to our initial hypothesis, we found no short-term differences in cardiovascular events in patients with and without OSA. However, in the long-term follow-up, the rate of MACCE (primary outcome) was higher in patients with than without OSA. This combined end point is mainly explained by the higher need of revascularization procedures in patients with OSA. Moreover, patients with OSA had higher rates of other secondary outcomes (new episodes of typical angina and atrial fibrillation) than patients without OSA. In the multivariate analysis, the presence of OSA was an independent factor associated with the occurrence of MACCE, repeated revascularization, typical angina, and atrial fibrillation. Taken together, the present results clearly highlight that OSA is not an innocent bystander in patients with advanced CAD but may have prognostic and economic significance in the long-term follow-up of patients who undergo CABG.

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TABLE 1] Baseline Characteristics of the Study Population

Characteristics	Total (N = 67)	No OSA (n = 30)	OSA (n = 37)	*P* Value
Age, y	57.4 ± 7.5	55.5 ± 6.7	59.0 ± 7.9	.057
Male sex	50 (75)	19 (63)	31 (84)	.08
White	49 (73)	19 (63)	30 (81)	.16
BMI, kg/m^2	28.5 ± 4.1	27.6 ± 3.3	29.1 ± 4.4	.12
Waist circumference, cm	100.7 ± 4.1	97.1 ± 12.6	103.6 ± 11.2	.008[a]
Neck circumference, cm	39.6 ± 4.1	38.5 ± 3.1	40.4 ± 2.9	.22
Hypertension	55 (82)	24 (80)	31 (84)	.75
Diabetes mellitus	27 (40)	11 (37)	16 (43)	.62
Heart failure	21 (31)	9 (30)	12 (32)	.62
LV ejection fraction, %	53.9 ± 13.7	55.1 ± 13.5	49.2 ± 14.2	<.0001[a]
Medications				
ASA	61 (91)	27 (90)	34 (91)	1.00
β-Blockers	62 (92)	28 (93)	34 (91)	1.00
CCB	4 (6)	2 (6)	2 (5)	1.00
Statins	60 (89)	24 (80)	36 (97)	.04[a]
ACEI/ARB	36 (53)	10 (33)	26 (70)	.003[a]
Nitrate	35 (52)	15 (50)	20 (54)	.80
Follow-up, y	4.5 ± 1.4	4.6 ± 1.3	4.3 ± 1.5	.46
Total length of hospital stay, d	18.4 ± 6.9	18.4 ± 7.5	18.5 ± 6.4	.96
Postoperative length of hospital stay, d	13.9 ± 4.9	13.5 ± 5.2	14.2 ± 4.7	.55
Off-pump CABG	44 (65)	21 (60)	23 (62)	.60
On-pump time, min	70 ± 54.7	75.8 ± 53.5	67.1 ± 55.7	.59
No. of performed grafts				
1 graft	2 (3)	1 (3)	1 (4)	1.00
2 grafts	16 (23)	9 (30)	7 (19)	.38
3 grafts	45 (67)	18 (60)	27 (72)	.30
≥4 grafts	4 (6)	2 (6)	2 (5)	1.00
Sleep data				
AHI	23.3 ± 20.3	7.2 ± 3.4	36.4 ± 18.8	< .0001[a]
Lowest Spo_2	81.7 ± 8.5	84.2 ± 4.7	79.7 ± 10.3	.03[a]
Spo_2, baseline	94.1 ± 2.2	94.8 ± 1.3	93.5 ± 2.5	.01[a]
Total sleep time < 90% Spo_2, %	0.3 (0.0-2.5)	0.0 (0.0-0.45)	1.9 (0.1-5.1)	<.01[a]

Values are mean (± SD), median (interquartile range), or No. (%). ACEI = angiotensin-converting enzyme inhibitor; AHI = apnea-hypopnea index; ARB = angiotensin receptor blocker; ASA = acetylsalicylic acid; CABG = coronary artery bypass graft surgery; CCB = calcium channel blocker; LV = left ventricular; Spo_2 = saturation of peripheral oxygen.
[a]Statistically significant.

The potential impact of OSA after cardiac surgery has been poorly explored in the literature and showed conflicting results. Most studies focused on arrhythmia recurrence within 30 days. For instance, Mooe and colleagues[15] found that nocturnal hypoxemia was an independent predictor of short-term postoperative atrial fibrillation. More recently, Unosawa and colleagues[16] found no significant difference in atrial fibrillation (based on 24-h Holter monitoring) in patients with and without sleep-disordered breathing in patients undergoing cardiac surgery. In our study, we did not find a significant increase in cardiovascular events (including atrial fibrillation) in patients with OSA in the first 30 days. It is possible that the standard care in the postoperative period may mitigate the impact of OSA and the related hypoxemia during sleep. Supporting this hypothesis, we noted that virtually all patients used noninvasive ventilation or oxygen while in the ICU.

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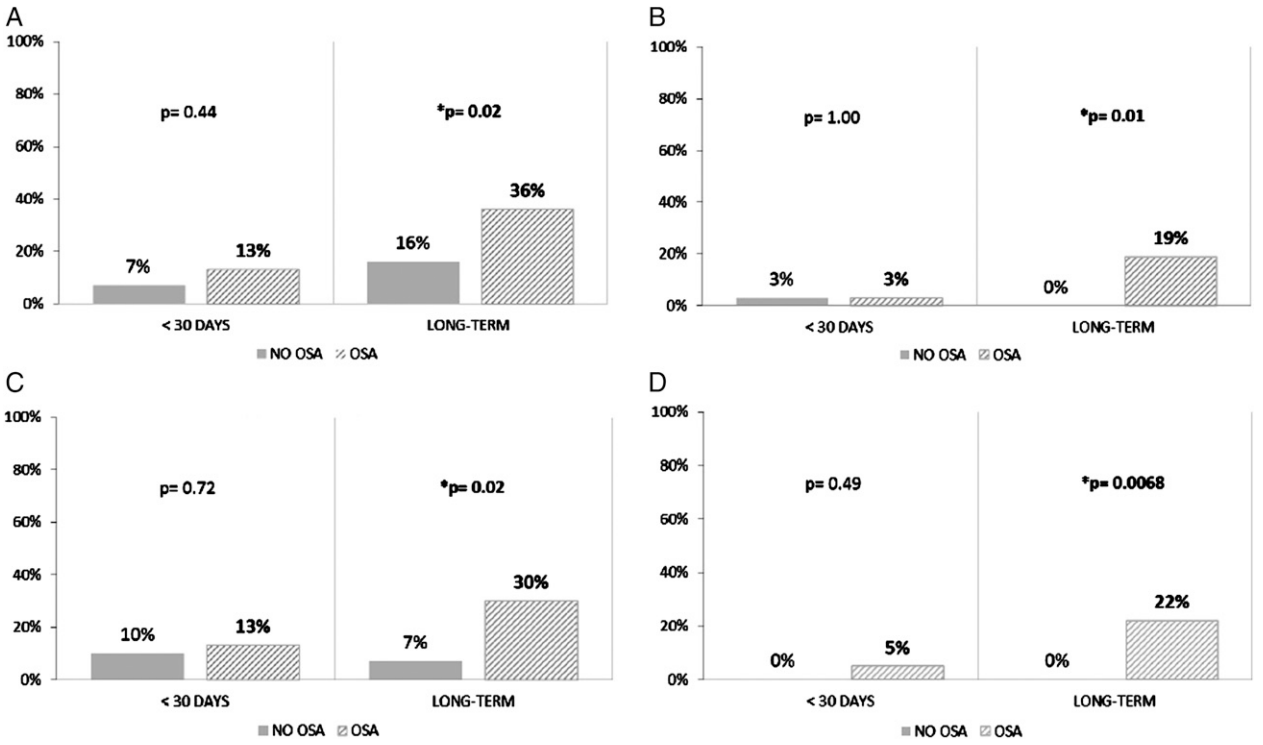

Figure 2 – *A-D, Frequency of new events at 30 d and in the long-term follow-up of CABG surgery, according to the presence of OSA. A, Major adverse cardiac or cerebrovascular events (MACCE); B, new revascularization (percutaneous coronary intervention [PCI] or CABG); C, typical angina; D, atrial fibrillation. See Figure 1 legend for expansion of other abbreviation.*

In the long-term follow-up, the higher rate of new episodes of MACCE, repeated revascularization, typical angina, and atrial fibrillation in patients with untreated OSA may occur for several reasons. OSA is

TABLE 2] Total Primary and Secondary Outcomes in Patients With and Without OSA

Outcomes	Total (N = 67)	No OSA (n = 30)	OSA (n = 37)	*P* Value
Primary outcome				
MACCE	25 (37)	7 (23)	18 (49)	.043[a]
Secondary outcomes				
Total deaths	4 (6)	1 (3)	3 (8)	.25
Myocardial infarction	2 (3)	1 (3)	1 (3)	1.00
Myocardial infarction, perioperative	9 (13)	4 (13)	5 (13)	1.00
New revascularization, PCI or CABG	9 (13)	1 (3)	8 (22)	.035[a]
Stroke[b]	3 (4)	0 (0)	3 (8)	.25
Typical angina	21 (31)	5 (17)	16 (43)	.03[a]
Pacemaker	2 (3)	0 (0)	2 (5)	.49
Acute pulmonary edema	2 (3)	0 (0)	2 (5)	.49
Arrhythmias[c]	13 (19)	0 (0)	13 (35)	.0003[a]
Atrial fibrillation	10 (15)	0 (0)	10 (27)	.0015[a]
Other arrhythmias	3 (4)	0 (0)	3 (8)	.24
Cardiovascular deaths	3 (4)	1 (3)	2 (5)	1.00

Data are presented as No. (%). MACCE = major adverse cardiac or cerebrovascular event; PCI = percutaneous coronary intervention. See Table 1 legend for expansion of other abbreviations.

[a]Statistically significant.

[b]Two ischemic and one hemorrhagic stroke (all in the OSA group).

[c]This term comprised all kinds of significant arrhythmias, including atrial fibrillation, atrial flutter, supraventricular tachycardia, atrioventricular blocks, ventricular tachycardia, and ventricular fibrillation.

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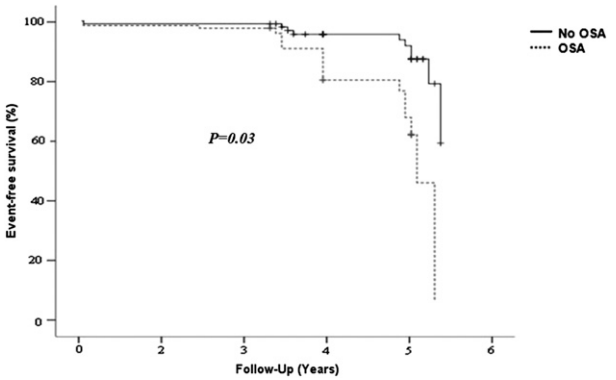

Figure 3 – *Survival rates for total MACCEs according to the presence of OSA. See Figure 2 legend for expansion of abbreviation.*

associated with endothelial dysfunction, low-grade inflammation, oxidative stress, and BP surges[17] that may contribute to atherosclerosis progression and plaque instability in these patients. Heart remodeling, including atrial remodeling,[18] and abnormal atrial substrate[19] observed in patients with OSA may contribute to trigger episodes of atrial fibrillation. This may be particularly true for patients who undergo CABG; a significant proportion of them have systolic and/or diastolic heart failure at baseline. In addition, low-grade inflammation is frequently reported in patients with OSA.[20] Although inflammation was not previously associated with atrial fibrillation in patients with OSA, this important factor may have a role in the atrial fibrillation occurrence.[21] Finally, although no differences in the myocardial infarction occurrence in patients with and without OSA were observed (only repeated revascularization and recurrent episodes of typical angina), it is reasonable to speculate the potential role of myocardial ischemia in triggering atrial fibrillation.[22] Further studies should evaluate the precise mechanisms of cardiovascular events in patients with OSA and advanced CAD.

The present study has some strengths and limitations. The strengths include the long-term follow-up, the use of standard polysomnography to the diagnosis of OSA, and the prespecified outcome definitions (e-Appendix 1). The following limitations should be acknowledged: first, this is a single-center study comprising a small sample of patients. The lack of difference in short-term and hard outcomes, such as new episodes of myocardial infarction and deaths, may be due to the lack of power in detecting differences in patients with and without OSA. Second, we did not perform Holter monitoring in the postoperative period. It is possible that some brief episodes of arrhythmias (like paroxysmal atrial fibrillation) were not diagnosed. However, all patients had

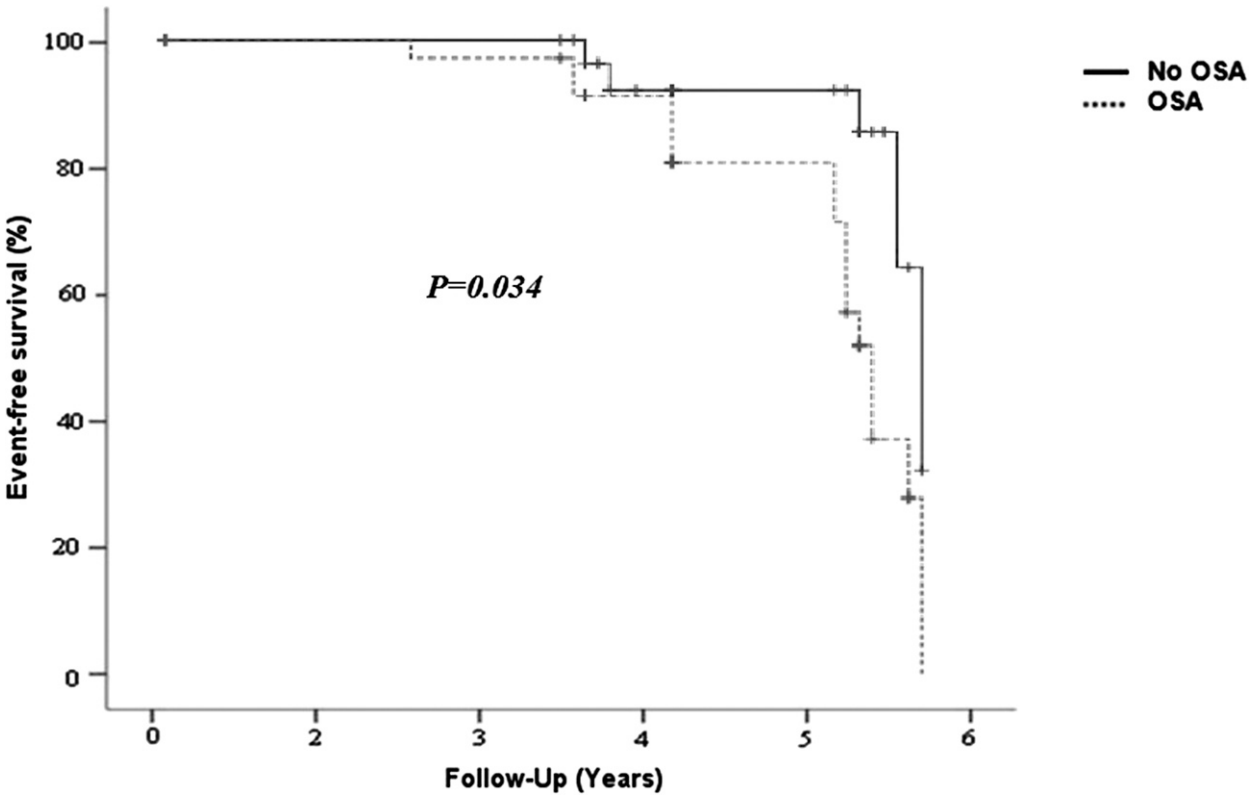

Figure 4 – *Survival rates for new revascularization (PCI or CABG), according to the presence of OSA. See Figure 1 and 2 legends for expansion of abbreviations.*

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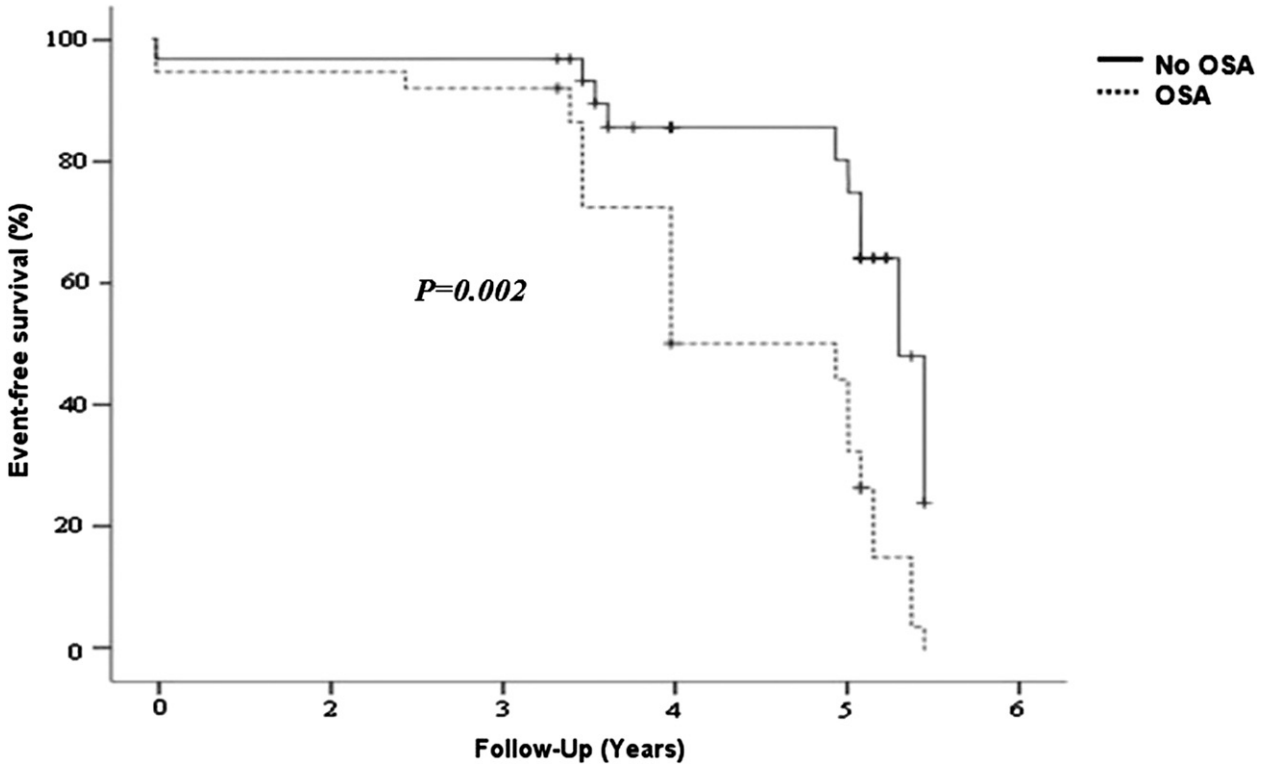

Figure 5 – *Survival rates for typical angina according to the presence of OSA.*

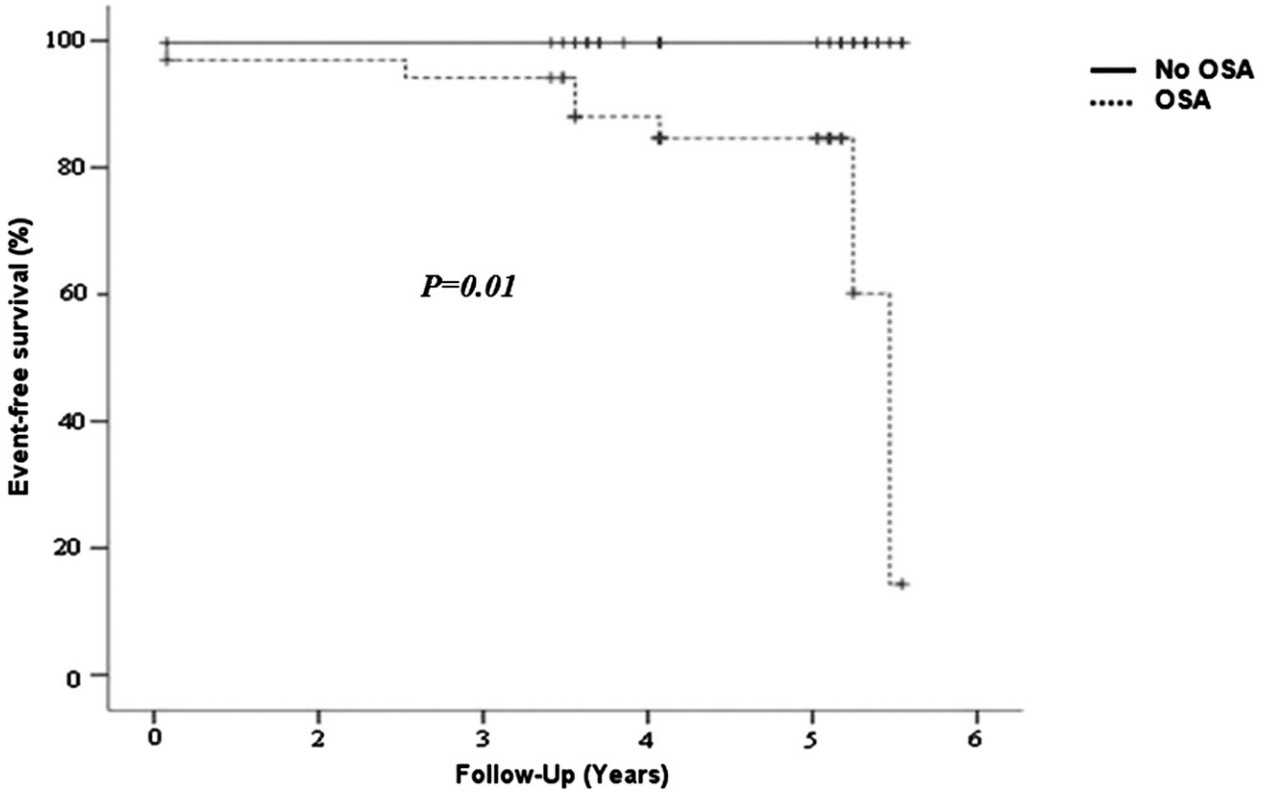

Figure 6 – *Survival rates for atrial fibrillation according to the presence of OSA.*

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TABLE 3] Multivariate Analysis Addressing the Independent Variables Associated With Long-term Events

Variables	MACCE			New Revascularization (PCI or CABG)			Typical Angina			Atrial Fibrillation		
	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value	OR	(95% CI)	*P* Value
Age, y	3.24[a]	(1.00-30.22)[a]	.02[a]	1.06	(1.01-1.76)	.30	13.35[a]	(1.36-176.34)[a]	.01[a]	4.18	(0.44-44.2)	.28
Male sex	0.90	(0.35-1.89)	.23	0.20	(0.00-0.33)	1.00	0.78	(0.45-1.14)	.30	0.92	(0.80-1.59)	.86
Waist circumference, cm	1.28	(0.94-1.92)	.09	0.61	(0.31-1.24)	.30	1.18	(0.91-1.59)	.15	1.56	(0.98-1.95)	.10
Statins	0.44	(0.02-5.89)	.59	0.32	(0.00-1.02)	.13	1.00	(0.09-21.05)	.98	0.22	(0.00-3.21)	.40
ACEI/ARB	1.01	(0.13-3.54)	.87	1.56	(0.65-49.21)	.12	4.01	(0.76-39.60)	.10	0.33	(0.11-6.20)	.30
LV ejection fraction	1.12	(0.99-1.34)	.30	1.68	(1.02-1.89)	.28	1.15	(1.00-1.59)	.46	1.00	(0.98-1.08)	.38
OSA	4.10[a]	(1.94-385.24)[a]	.004[a]	2.02[a]	(1.21-64.22)[a]	.01[a]	10.05[a]	(1.12-62.25)[a]	.02[a]	12.56[a]	(1.44-159.21)[a]	.006[a]

See Table 1 and 2 legends for expansion of abbreviations.
[a]Statistically significant.

continuous ECG monitoring in the ICU. We may argue that it is not feasible to perform continuous monitoring for such a long-term follow-up. Therefore, our study design is in agreement with "real life" clinical practice.

In conclusion, we are not able to find significant impact of OSA in the short-term follow-up. In contrast, OSA is independently associated with a higher rate of new cardiovascular events (MACCE, repeated revascularization, recurrent angina, and atrial fibrillation) in the long-term follow-up of patients who undergo CABG. These results are consistent with previous evidence showing that OSA is an independent predictor for clinical and angiographic outcomes after percutaneous coronary intervention.[23] Because OSA is very frequent and underdiagnosed in this population,[3] future investigations should address the impact of treatment of patients with OSA clinically indicated for the CABG procedure.

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

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