Obstructive Sleep Apnea and Diabetes Independently Add to Cardiovascular Risk After Coronary Revascularization

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Obstructive sleep apnea (OSA) has been shown to be associated with accelerated coronary atherosclerosis (1–3). In the multicenter Sleep and Stent Study, we found that OSA was an independent predictor of major adverse cardiac and cerebrovascular events (MACCE) and cardiovascular mortality post percutaneous coronary intervention (PCI), with adjusted hazard ratios (HR) of 1.57 (95% CI 1.10–2.24) and 2.11 (95% CI 0.91–4.91), respectively (4).

Diabetes mellitus (DM) is an established risk factor of MACCE after PCI and was present in 42% of the patients in the Sleep and Stent Study (4). In this post hoc analysis, we hypothesized that patients with combined OSA and DM were at a particularly high risk of developing MACCE after PCI.

The Sleep and Stent Study was an observational study evaluating the effects of OSA on cardiovascular outcomes in patients undergoing PCI. The detailed methodology and inclusion and exclusion criteria have been published before (5). After an overnight sleep study, the recruited patients were classified as OSA(+) (apnea-hypopnea index ≥15 events per hour) or OSA(−) (<15 events per hour). Studies have suggested the possible interaction between DM and OSA in glycemic control and the progression of chronic diabetic complications (6–8). As such, the primary aim of this post hoc analysis was to determine whether the effects of OSA in the occurrence of cardiovascular outcomes, defined as MACCE composed of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, may be modified by DM status.

The 1,311 patients recruited were reclassified into four groups based on their OSA and DM status (Table 1). There were 271 patients (20.7%) in the OSA(+) DM(+) group, 323 patients (24.6%) in the OSA(+) DM(−) group, 284 patients (21.7%) in the OSA(−) DM(+) group, and 433 patients (33.0%) in the OSA(−) DM(−) group. The distribution of OSA/DM phenotypes varied significantly by sex, ethnicity, and BMI. The mean HbA_{1c} level and the percentage of patients requiring insulin did not differ significantly between the OSA(−) DM(+) and the OSA(+) DM(+) groups. There were no significant differences among the four groups with regard to the indications for angiography, lesion location, or the types of coronary devices used. The diameter of the stents implanted was smaller in the two DM(+) than the two DM(−) groups, regardless of OSA status. The patients were followed up for a median period of 1.9 years.

Fig. 1 demonstrates that the crude cumulative incidence of MACCE was highest in the OSA(+) DM(+) group (3-year estimate 15.1%), but similar in the OSA(+) DM(−) (9.2%), OSA(−) DM(+) (6.4%), and OSA(−) DM(−) (9.8%) groups ($P < 0.001$). Likewise, the crude cumulative incidence of cardiovascular mortality was highest in the OSA(+) DM(+) group (3-year estimate 7.4%), but similar in the OSA(+) DM(−) (2.7%), OSA(−) DM(+) (1.4%), and OSA(−) DM(−) (1.1%) groups ($P = 0.002$).

A priori accounting for DM as an effect modifier by including the interaction between DM and OSA, our analysis showed that OSA was associated with twofold risk in MACCE in patients with DM (adjusted HR 2.03, 95% CI 1.10–3.74, $P = 0.023$) but not in those with no DM (adjusted HR 1.12, 95% CI 0.57–2.17, $P = 0.748$). This was adjusted for potential confounders such as age, sex, ethnicity, BMI, and hypertension.

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Table 1—Baseline demographic and clinical characteristics of study patients

Characteristics	OSA(+) DM(+) (n = 271)	OSA(+) DM(−) (n = 323)	OSA(−) DM(+) (n = 284)	OSA(−) DM(−) (n = 433)	P value
Age (years)	58.8 ± 10.0	59.2 ± 10.5	58.0 ± 9.6	57.2 ± 10.7	0.035
Male sex	234 (86.4)	289 (89.5)	222 (78.2)	372 (85.9)	0.001
Ethnicity					<0.001
Chinese	151 (55.7)	225 (69.7)	156 (54.9)	265 (61.2)	
Malay	54 (19.9)	29 (9.0)	44 (15.5)	32 (7.4)	
Indian	42 (15.5)	51 (15.8)	69 (24.3)	102 (23.6)	
Others	24 (8.9)	18 (5.6)	15 (5.3)	34 (7.9)	
BMI (kg/m^2)	27.2 ± 4.2	26.0 ± 3.5	25.5 ± 3.5	24.7 ± 3.3	<0.001
Waist circumference (cm)	98.0 ± 14.4	93.8 ± 11.8	92.8 ± 12.5	91.1 ± 11.6	<0.001
Cardiovascular risk factors					
Smoking	95 (35.1)	115 (35.6)	88 (31.0)	167 (38.5)	0.228
Hyperlipidemia	191 (70.5)	166 (51.4)	198 (69.7)	223 (51.5)	<0.001
Hypertension	213 (78.6)	191 (59.1)	182 (64.1)	205 (47.3)	<0.001
Diabetes mellitus	271 (100.0)	0 (0.0)	284 (100.0)	0 (0.0)	<0.001
HbA_{1c} (%)	7.96 ± 1.80	—	7.69 ± 1.89	—	0.091
Insulin dependent	41 (15.1)	—	32 (11.3)	—	0.178
Family history of premature CAD	24 (8.9)	15 (4.6)	34 (12.0)	34 (7.9)	0.011
Concomitant conditions					
Previous myocardial infarction	50 (18.5)	61 (18.9)	63 (22.2)	80 (18.5)	0.603
Previous PCI	56 (20.7)	62 (19.2)	64 (22.5)	81 (18.7)	0.617
Previous CABG	16 (5.9)	12 (3.7)	12 (4.2)	12 (2.8)	0.222
Previous stroke/TIA	18 (6.6)	15 (4.6)	24 (8.4)	20 (4.6)	0.121
Chronic kidney disease	24 (8.9)	8 (2.5)	19 (6.7)	9 (2.1)	<0.001
LVEF (%)	52.4 ± 11.4	54.1 ± 10.0	53.2 ± 11.1	54.4 ± 9.9	0.226

Data are n (%) or mean ± SD. CABG, coronary artery bypass grafting; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

To the best of our knowledge, there have been no published reports comparing the relative impact of OSA versus DM and the combined impact of OSA and DM on clinical outcomes after PCI. Our most striking finding is that the presence of OSA in DM patients markedly increases MACCE in patients after PCI. After adjustment for age, sex, ethnicity, BMI, and hypertension, OSA was associated with twofold risk of both MACCE and cardiovascular mortality among those with DM and no difference in risk among non-DM patients. These findings suggest that patients with combined DM and OSA were prevalent and at the highest risk for developing MACCE after successful PCI. While only hypothesis generating, these observations raise the possibility that identification of high-risk phenotype is necessary to demonstrate the benefits of OSA treatment on cardiovascular outcomes. In this regard, the pivotal Sleep Apnea cardioVascular Endpoints (SAVE) trial, with one-third of patients having DM, failed to demonstrate the benefit of continuous positive airway pressure therapy (9). In light of our findings, future studies to evaluate the effects of OSA treatment on patients with coronary artery disease and DM are warranted.

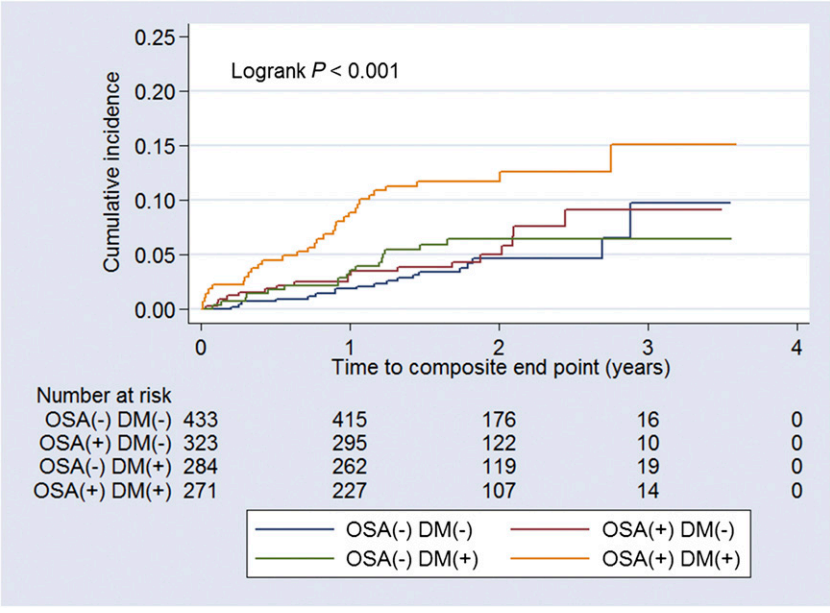

Figure 1—Kaplan-Meier cumulative incidence curves for primary end point. Primary end point comprises cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke.

There are several limitations of this study that should be considered when evaluating our findings. This was a post hoc analysis of a completed observational study without a proper sample size calculation. Data on diabetes status were based on physician diagnosis supported by details of treatment rather than fasting glucose measurements or glucose tolerance testing. This may have resulted in misclassification. We did not collect

detailed information on DM such as disease duration or presence of microvascular complications and could not accurately account for the effect of glycemic control on the development of MACCE in this study. The Sleep and Stent Study did not include systematic repeat coronary angiography, and therefore the effects of OSA and the possible effect modification of DM on in-stent restenosis could be a target of future research. The effects of gender on this observed combined prognostic impact remains unknown as only a small number of female patients were recruited, making meaningful gender-based analysis impossible. Finally, our study population was largely Asian; it is uncertain whether our findings can be generalized to other ethnic groups.

In summary, we found that the combination of OSA and DM is a strong risk marker for the occurrence of MACCE after PCI. With increasing awareness of OSA as a cardiovascular risk marker, our findings suggest that future clinical trials to examine the role of OSA intervention as a secondary cardiovascular prevention strategy in patients with DM are highly warranted.

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