Supplemental Methods

Definition of study endpoints

Cardiovascular death

Death related to proximate cardiovascular causes (eg, myocardial infarction, cardiogenic shock, stroke, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes), procedure-related complications, or any death unless an unequivocal non-cardiovascular cause could be established.

Myocardial infarction

Myocardial infarction is defined as spontaneous ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction according to the third universal definition[1].

Any one of the following criteria meets the diagnosis of myocardial infarction:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL and with at least one of the following:
  - Symptoms of ischemia
  - (Presumed) new significant ST-T wave changes or new LBBB
  - Development of pathological Q waves
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial infarction and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased

Stroke

Stroke is defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following subclassifications:

- Ischemic stroke
- Intracerebral hemorrhage
- Stroke of undetermined etiology

Hospitalization for heart failure

Hospitalization for heart failure (HF) is defined as an event where the patient is admitted to the hospital with a primary diagnosis of HF where the length of stay is at least 24 h, where the patient exhibits new or worsening symptoms of HF (dyspnea, decreased exercise tolerance, fatigue, worsened end-organ perfusion, or volume overload) on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF.

Hospitalization for unstable angina

Hospitalization for unstable angina is defined as unscheduled hospitalization for the management of unstable angina, occurring within 24 h of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-h stay. This classification requires that 4 separate criteria be met: a) worsening ischemic discomfort; b) unscheduled hospitalization; c) objective evidence of myocardial ischemia; d) negative cardiac biomarkers.

Ischemia-driven revascularization

Ischemia-driven revascularization was defined as any repeat PCI or CABG performed for either: myocardial infarction, unstable angina, stable angina, or documented silent ischemia. Repeat revascularization was further classified into target vessel or non-target vessel revascularization as well as PCI or CABG.

Sample size

According to our prior data[2], the prevalence of obstructive sleep apnea (OSA) was 50.1% based on an apnea hypopnea index ≥15. Assuming a 5% absolute increase[2,3] in the event rate for ACS patients with OSA compared with those without OSA, the expected event rate for acute coronary syndrome (ACS) patients with OSA is 20% and that for ACS without OSA is 15% at a median follow-up of 2 years. A sample size of 1,812 patients in OSA (n=906) and non-OSA (n=906) groups would have 80% power at a two-sided α level of 0.05. With a dropout rate of 10% (failed sleep study, regular CPAP therapy, loss to follow-up, etc), a total of 2,014 patients will be required.

Reference:

1. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Circulation. 2012;126(16):2020-35.

2. Fan J, Wang X, Ma X, Somers VK, Nie S, Wei Y. Association of Obstructive Sleep Apnea With Cardiovascular Outcomes in Patients With Acute Coronary Syndrome. J Am Heart Assoc. 2019;8(2):e010826.

3. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. Circulation. 2016;133(21):2008-2017.

Supplemental Table S1. Baseline Demographic, Clinical, and Procedural Characteristics by Sex

Variables	Women (n=298)	Men (n=1,629)	P value
Demographics			
Age, mean±SD, years	64.0±8.2	55.0±10.3	<0.001
BMI, mean±SD, kg/m^2	26.8±3.9	27.1±3.6	0.04
Waist-to-hip ratio, median (IQR)	0.96 (0.92-1.00)	0.98 (0.95-1.02)	<0.001
Neck circumference, median (IQR), cm	37 (35-39)	41 (39-43)	<0.001
Systolic BP, median (IQR), mmHg	130 (120-141)	126 (116-137)	<0.001
Diastolic BP, median (IQR), mmHg	72 (68-80)	77 (70-85)	<0.001
Medical history			
Diabetes	121 (40.6)	488 (30.0)	<0.001
Hypertension	240 (80.5)	1007 (61.8)	<0.001
Hyperlipidemia	122 (40.9)	515 (31.6)	0.002
Family history of premature CAD	17 (5.7)	87 (5.3)	0.80
Prior stroke	42 (14.1)	165 (10.1)	0.04
Prior myocardial infarction	25 (8.4)	291 (17.9)	<0.001
Prior PCI	54 (18.1)	345 (21.2)	0.23
Prior CABG	6 (2.0)	23 (1.4)	0.44
Smoking			<0.001
No	262 (87.9)	392 (24.1)	
Current	28 (9.4)	885 (54.3)	
Previous	8 (2.7)	352 (21.6)	
Drinking			<0.001
No	283 (95.0)	898 (55.1)	

Current	15 (5.0)	622 (38.2)	
Previous	0 (0.0)	109 (6.7)	
Baseline tests			
eGFR	106.6 (85.9-122.8)	104.7 (89.8-120.9)	0.74
Hs-CRP, median (IQR), mg/L	2.1 (0.8-5.7)	2.0 (0.8-6.2)	0.85
LVEF, median (IQR), %	63 (60-67)	61 (55-65)	<0.001
Diagnosis			<0.001
STEMI	40 (13.4)	390 (23.9)	
NSTEMI	51 (17.1)	314 (19.3)	
Unstable angina	207 (69.5)	925 (56.8)	
Procedures			
Coronary angiography	288 (96.6)	1589 (97.5)	0.37
Revascularization	176 (59.1)	1159 (71.1)	<0.001
PCI	157 (52.7)	1052 (64.6)	<0.001
DES use	138/157 (87.9)	913/1052 (86.8)	0.70
Baseline TIMI 0 or 1	40/157 (25.5)	382/1052 (36.3)	0.008
Final TIMI 3	153/157 (97.5)	1036/1052 (98.5)	0.32
CABG	19 (6.4)	111 (6.8)	0.78
Sleep study			
OSA (AHI≥15)	128 (43.0)	886 (54.4)	<0.001
AHI, median (IQR), events·h^{-1}	12.5 (6.2-25.8)	16.9 (8.3-31.4)	<0.001
ODI, median (IQR), events·h^{-1}	14.2 (7.2-25.5)	16.5 (8.9-29.0)	0.015
Sadir SaO$_2$, median (IQR), %	85 (81-88)	85 (81-88)	0.94
Mean SaO$_2$, median (IQR), %	94 (92-95)	94 (93-95)	0.15

Time with SaO$_2$<90%, median (IQR), %	3.0 (0.4-11.0)	2.0 (0.3-9.8)	0.20
Epworth Sleepiness Scale, mean±SD	6.0 (3.0-10.0)	7.0 (4.0-11.5)	0.002
Medications on discharge			
Aspirin	287 (96.3)	1590 (97.6)	0.20
P2Y$_{12}$ inhibitors	269 (90.3)	1499 (92.0)	0.31
β-Blockers	226 (75.8)	1262 (77.5)	0.54
ACEIs/ARBs	192 (64.4)	1003 (61.6)	0.35
Statins	291 (97.7)	1606 (98.6)	0.21

Data are presented as mean±SD, median (IQR), n (%), or n/N (%). ACEI, angiotensin-converting enzymes inhibitor; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DES, drug eluting stent; Hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; PCI, percutaneous coronary intervention; SaO2, arterial oxygen saturation; SD, standard deviation; STEMI, ST-segment-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

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Supplemental Table S2. Association Between Hypoxemia Indicators and Sleepiness with MACCE by Sex

Indicators	Women		Men	
	HR (95% CI)	P value	HR (95% CI)	P value
Nadir SaO$_2$ <median vs. >median	1.20 (0.74-1.94)	0.46	0.89 (0.71-1.10)	0.28
Mean SaO$_2$ <median vs. >median	0.78 (0.48-1.27)	0.31	0.95 (0.75-1.19)	0.62
Time with SaO$_2$<90% >median vs. <median	0.93 (0.56-1.93)	0.77	1.19 (0.95-1.49)	0.13
Epworth Sleepiness Scale >10 vs. ≤10	1.59 (0.71-3.58)	0.26	1.13 (0.84-1.53)	0.42

CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; OSA, obstructive sleep apnea.

Supplemental Table S3. Crude Number of Events by Sex and OSA Categories.

| Variables	Women (n=298)		Men (n=1,629)	
	OSA (n=128)	Non-OSA (n=170)	OSA (n=886)	Non-OSA (n=743)
MACCE	36 (28.1)	32 (18.8)	191 (21.6)	130 (17.5)
Cardiovascular death	2 (1.6)	1 (0.6)	17 (1.9)	13 (1.7)
Myocardial infarction	5 (3.9)	3 (1.8)	28 (3.2)	15 (2.0)
Stroke	3 (2.3)	7 (4.1)	22 (2.5)	11 (1.5)
Ischemic	3 (2.3)	4 (2.4)	18 (2.0)	10 (1.3)
Hemorrhagic	0 (0.0)	3 (1.8)	4 (0.5)	1 (0.1)
Hospitalization for unstable angina	30 (23.4)	22 (12.9)	125 (14.1)	95 (12.8)
Hospitalization for heart failure	0 (0.0)	2 (1.2)	11 (1.2)	8 (1.1)
Ischemia-driven revascularization	17 (13.3)	10 (5.9)	77 (8.7)	55 (7.4)
Composite for cardiovascular death, myocardial infarction, or ischemic stroke	10 (7.8)	8 (4.7)	62 (7.0)	34 (4.7)
Composite for cardiac events	33 (25.8)	27 (15.9)	172 (19.4)	121 (16.3)
All-cause death	4 (3.1)	5 (2.9)	19 (2.1)	18 (2.4)
All repeat revascularization	21 (16.4)	11 (6.5)	108 (12.2)	87 (11.7)
Target vessel revascularization	11 (8.6)	9 (5.3)	53 (6.0)	40 (5.4)
Non-target vessel revascularization	13 (10.2)	4 (2.4)	73 (8.2)	52 (7.0)
PCI	21 (16.4)	10 (5.9)	100 (11.3)	82 (11.0)
CABG	0 (0.0)	1 (0.6)	8 (0.9)	7 (0.9)

Data are presented as n (%). CABG, coronary artery bypass grafting; MACCE, major adverse cardiovascular and cerebrovascular event; PCI, percutaneous coronary intervention; OSA, obstructive sleep apnea.

Supplemental Table S4. Association of OSA with Risk of MACCE According to Subgroups.

Subgroups	OSA (n=1,014)	Non-OSA (n=913)	Adjusted HR (95% CI)*	P value	P for interaction
Age					
<65	159/769 (20.7)	118/714 (16.5)	1.31 (1.02, 1.68)	0.037	0.73
≥65	68/245 (27.8)	44/199 (22.1)	1.30 (0.88, 1.93)	0.19	
Hypertension					
Yes	167/691 (24.2)	105/556 (18.9)	1.35 (1.05, 1.74)	0.022	0.30
No	60/323 (18.6)	57/357 (16.0)	1.17 (0.81, 1.71)	0.41	
Diabetes mellitus					
Yes	89/319 (27.9)	54/290 (18.6)	1.58 (1.11, 2.24)	0.011	0.12
No	138/695 (19.9)	108/623 (17.3)	1.15 (0.88, 1.50)	0.30	
Hyperlipidemia					
Yes	68/343 (19.8)	43/294 (14.6)	1.40 (0.93, 2.10)	0.11	0.84
No	159/671 (23.7)	119/619 (19.2)	1.25 (0.98, 1.61)	0.77	
Prior CAD					
Yes	100/445 (22.5)	67/372 (18.0)	1.37 (0.99, 1.89)	0.06	0.91
No	127/569 (22.3)	95/541 (17.6)	1.21 (0.91, 1.60)	0.18	
Clinical presentation					
UAP	118/572 (20.6)	90/560 (16.1)	1.30 (0.98, 1.73)	0.07	0.98
AMI	109/442 (24.7)	72/353 (20.4)	1.27 (0.92, 1.73)	0.14	

Data are presented as n/N (%). AMI, acute myocardial infarction; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; OSA, obstructive sleep apnea; UAP, unstable angina pectoris. *Adjusted for age, body mass index, smoking (no [referent], past, current), hypertension, diabetes mellitus, hyperlipidemia, prior myocardial infarction, prior stroke, and clinical presentation (unstable angina [referent], acute myocardial infarction).

Supplemental Figure S1. Cumulative Incidence of CV Death, MI, Ischemic Stroke, and Composite of These Outcomes by Sex and OSA Categories.
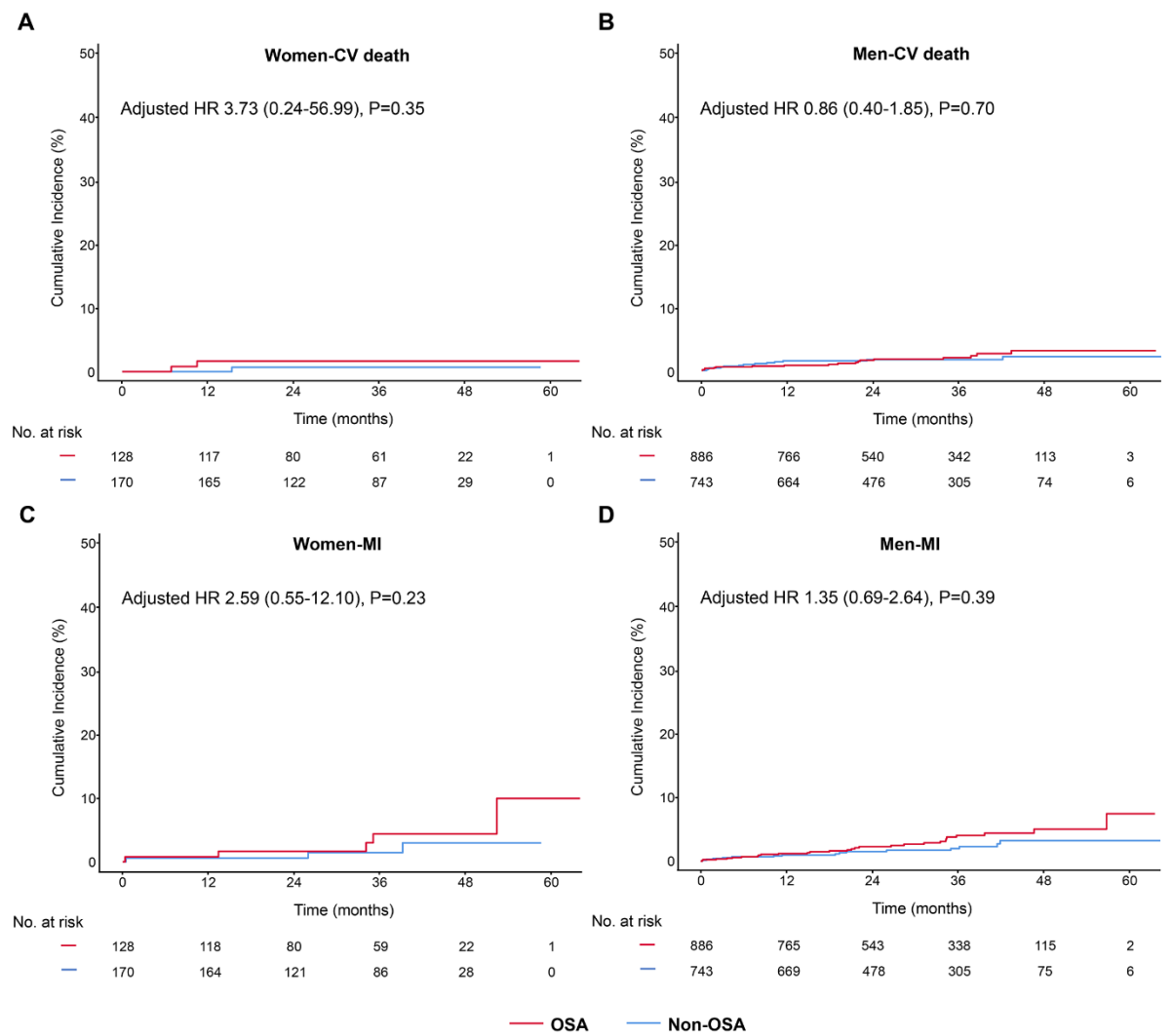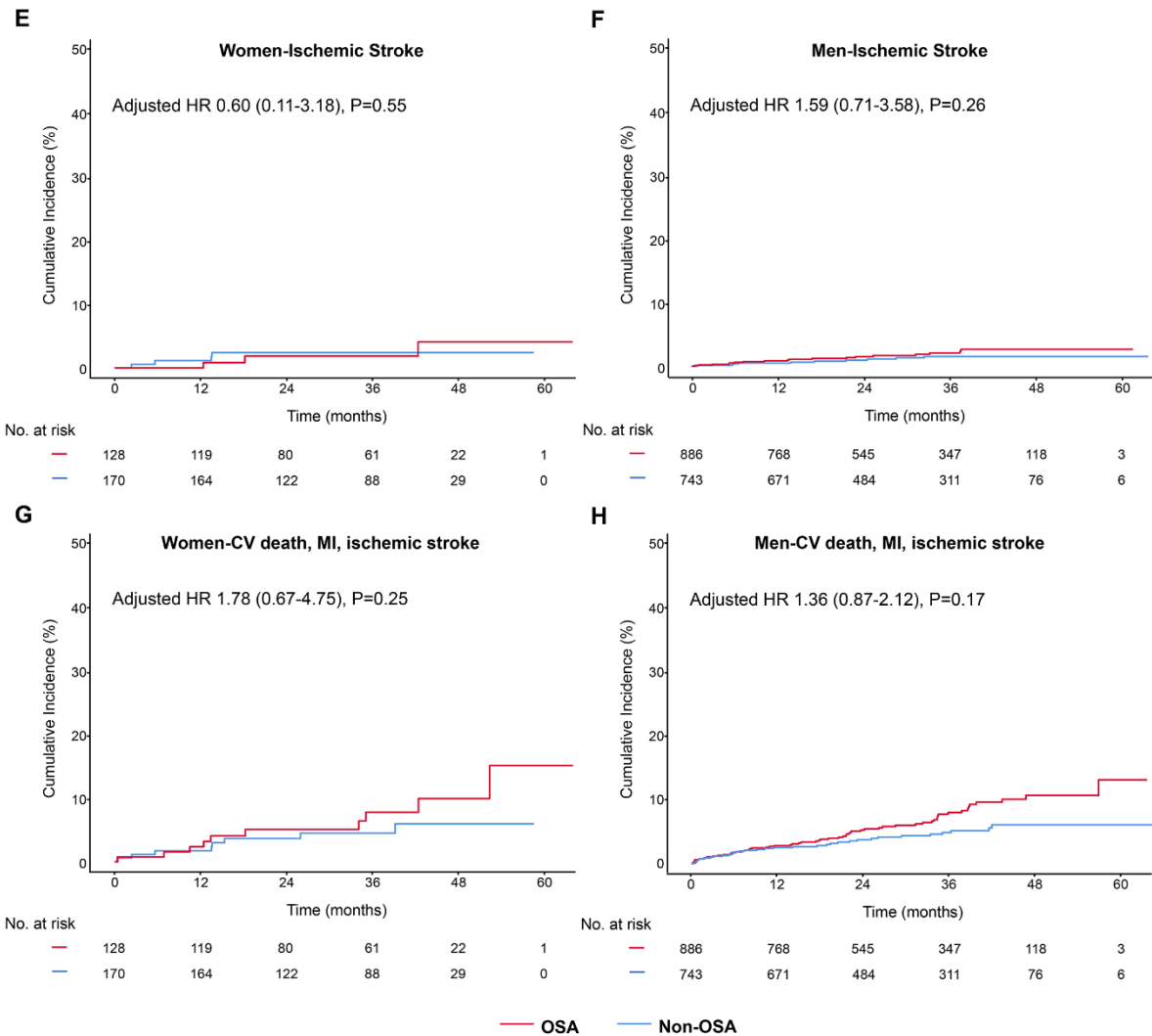
Kaplan-Meier estimates and fully-adjusted HR for CV death, MI, ischemic stroke, and composite of these outcomes between OSA and non-OSA groups in women (A, C, E, G) and men (B, D, F, H). CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; OSA, obstructive sleep apnea.