

The Current State of Sleep Apnea Prevalence and Outcomes

Vahid Mohsenin, M.D., FCCP, FAASM
Professor of Medicine
Section of Pulmonary, Critical Care and & Sleep Medicine
Yale University School of Medicine
New Haven, Connecticut, USA



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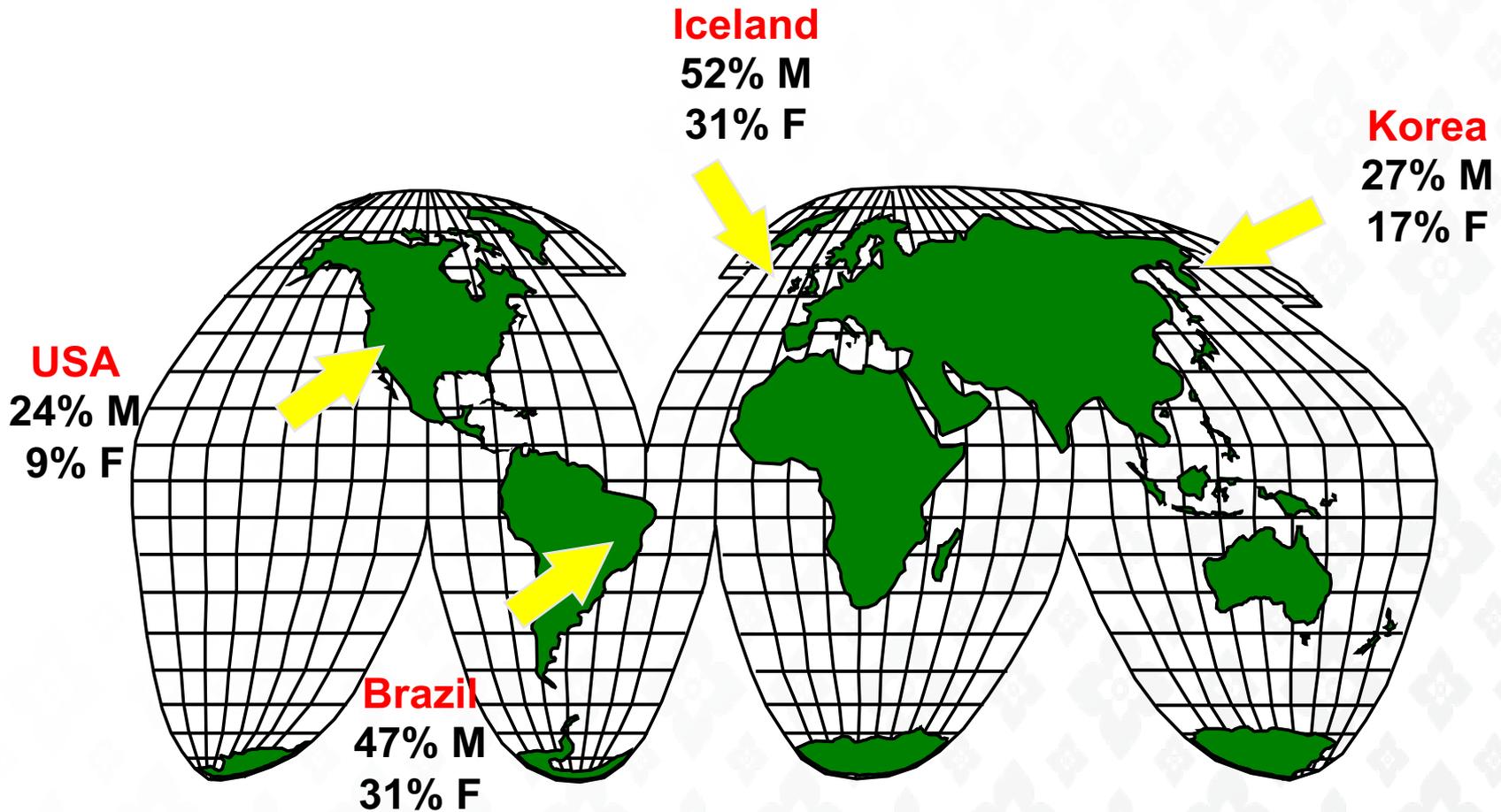
Disclosures
None to declare

Outline

- Prevalence of sleep-breathing disorders across the globe
- Established complications of obstructive sleep apnea
- Treatment outcomes and risk reduction

Sleep-disordered Breathing

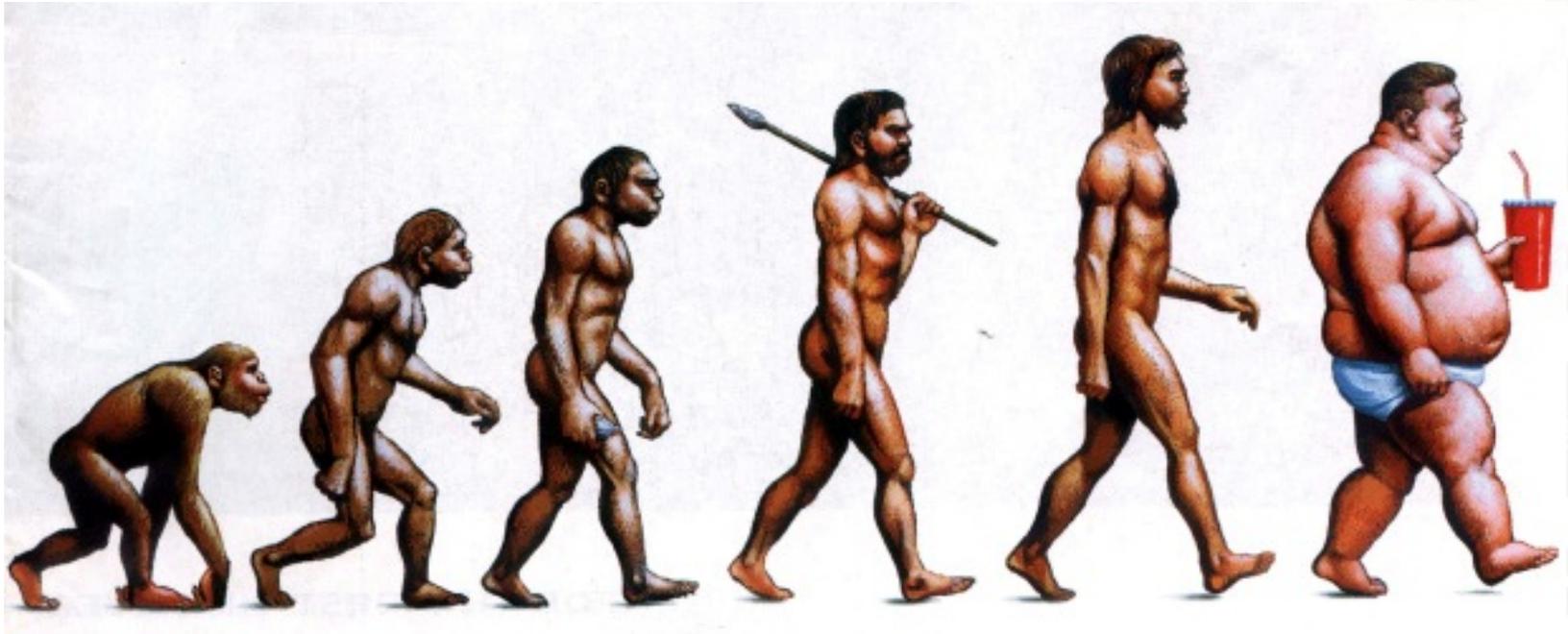
Magnitude of the problem
(AHI ≥ 5 /hr)



Prevalence of Sleep-disordered Breathing

Study	Type of Study	Country	Number	Age	Sex	AHI \geq 5/h	AHI \geq 15/h
Wisconsin Cohort, 1988	Population-based	USA	602	30-60	M F	24% 9%	9% 4%
Olson et al., 1995	Population-based	Australia	441	35-69	M F	78% 57%	26% 8%
Duran et al., 2001	Population-based	Spain	555	30-70	M F	26% 28%	14% 7%
Sleep Heart Health, 1999	Population-based	USA	1824	\geq 40	All	51%	22%
Monica II Cohort, 2008	Population-based	Poland	676	\geq 30	M F	37% 19%	n.a. n.a.
Kim et al., 2004	Population-based	Korea	457	40-69	M F	27% 17%	10% 7%
Tufik et al., 2010	Population-based	Brazil	1042	20-80	M F	47% 31%	25% 10%
Sforza et al., 2011	Population-based	France	641	>65	M F	n.a. n.a.	67% 51%
Heinzer et al., 2015	Population-based	Swiss	2121	40-85	M F	84% 61%	50% 23%
Arnardottir et al., 2016	Population-based	Iceland	400	42-66	M F	52% 31%	23% 10%
Tan et al., 2016	Population-based	Singapore	242	21-79	M F	n.a. n.a.	39% 19%

Obesity is by far the number one risk factor for metabolic syndrome and sleep apnea



Millions of years

< 200 years

OSA is more prevalent in men than women, except for postmenopausal women and massively obese females



Obesity is by far the number one risk factor for sleep apnea but there are others.



Macroglossia



Large tonsils



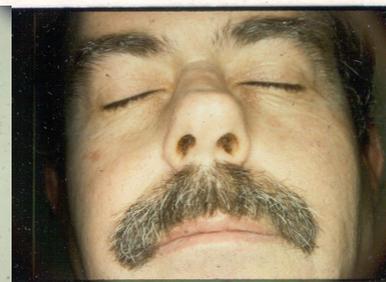
Racial differences in risk



Redundant Soft palate



Retrognathia

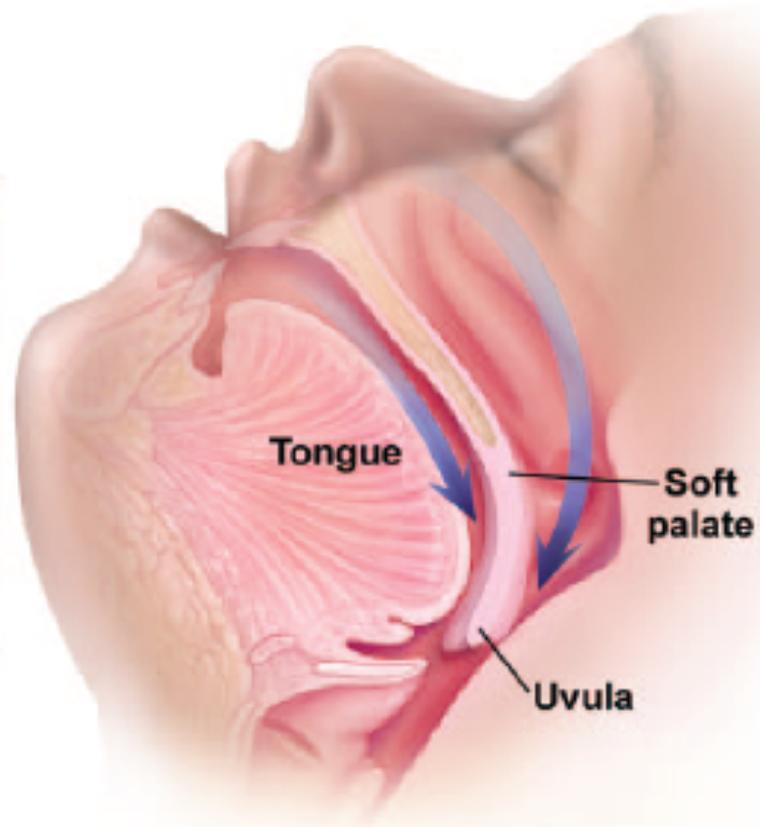
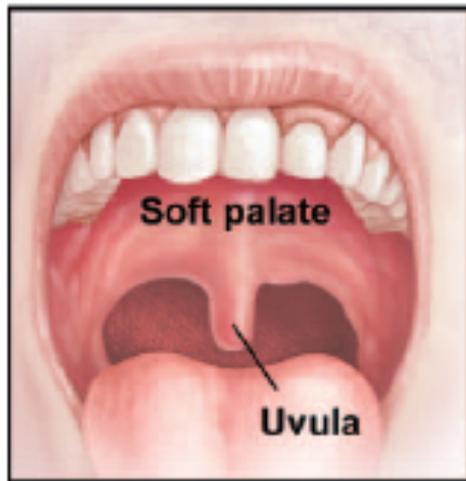


Expiration



Inspiration

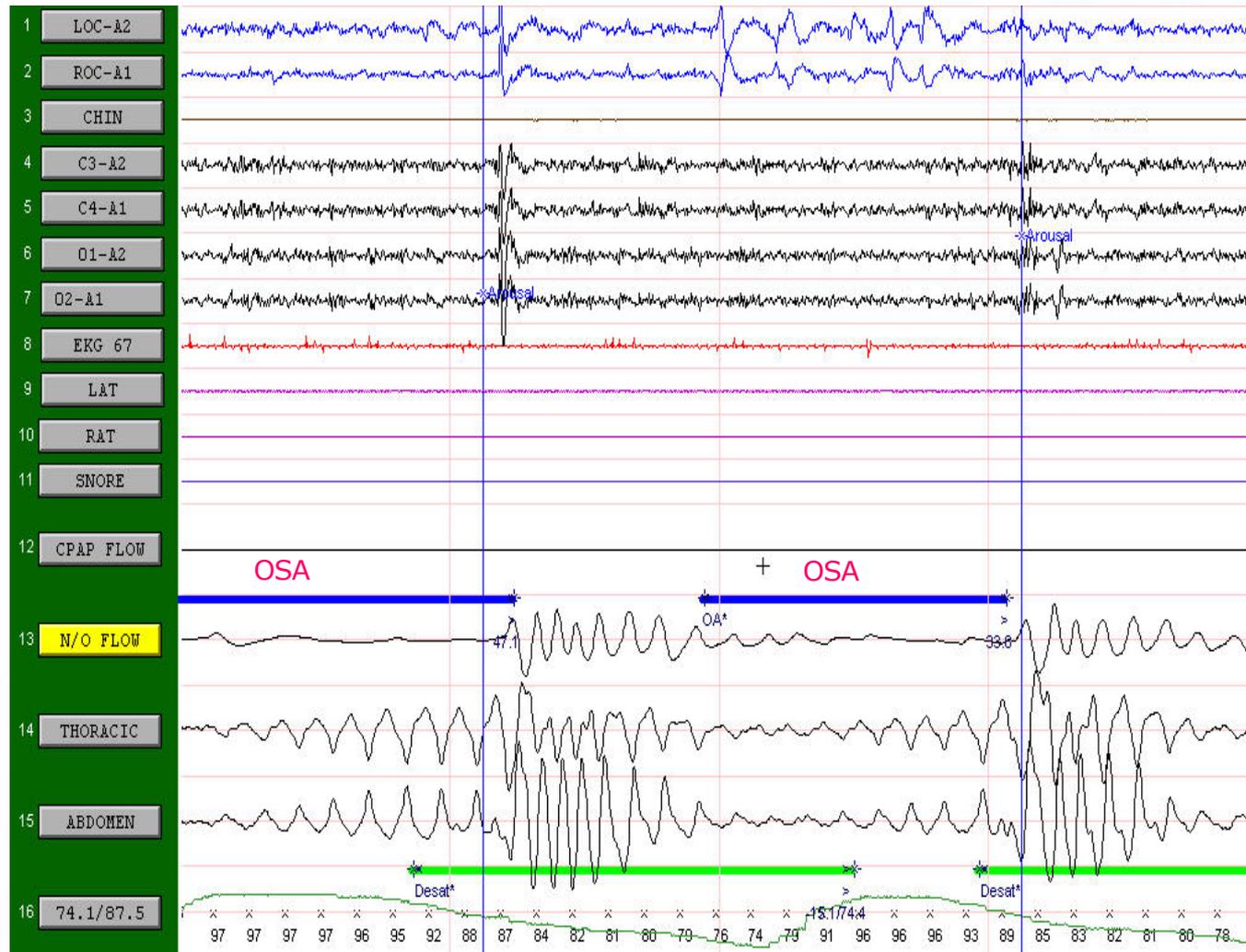
Site of airway obstruction in sleep apnea



What is obstructive sleep apnea?

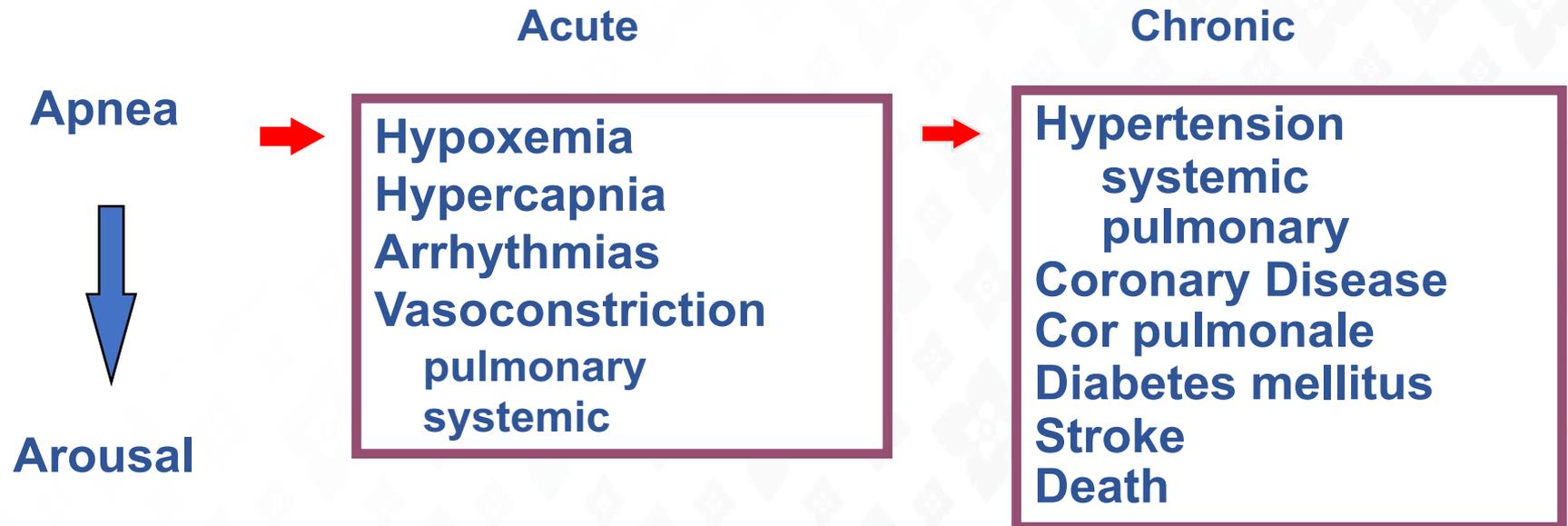


Recurrent upper airway obstruction during sleep



60-second epoch

Acute and Chronic Consequences of Sleep Apnea



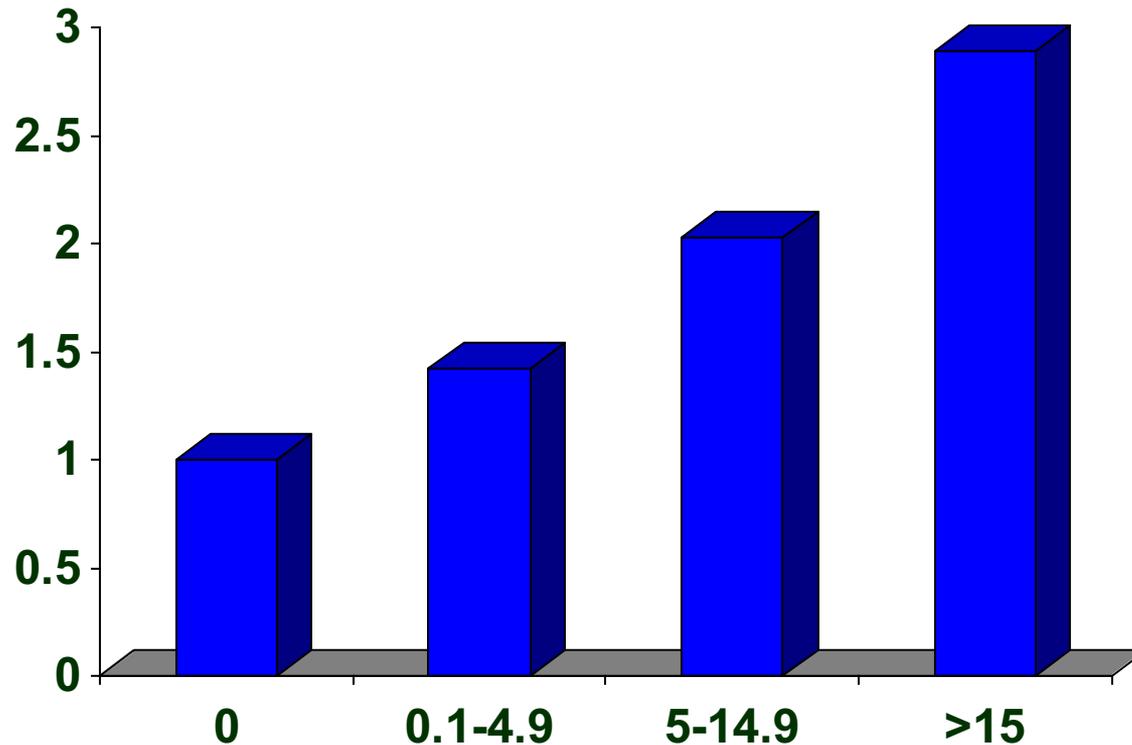
Pathophysiological features of OSA

- Intermittent hypoxia
- Fluctuations in intrathoracic pressure
- Recurring arousals
- Cell and molecular mechanisms that include:
 - Sympathetic excitation
 - Systemic inflammation and oxidative stress
 - Metabolic and endothelial dysfunction



Cardiovascular & Cerebrovascular Complications of OSA

OSA causes systemic hypertension



OSA is very common in patients with drug-resistant hypertension and recent hypertension guidelines indicate OSA as a leading cause of secondary hypertension

Obstructive sleep apnea increases risk of cardiac arrhythmias, particularly atrial fibrillation. Sleep Heart Health Study

TABLE 3.

ADJUSTED AND UNADJUSTED ODDS RATIOS RELATING ARRHYTHMIA OCCURRENCE AND SLEEP-DISORDERED BREATHING

Arrhythmia Type	Unadjusted Odds Ratio	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI	Odds Ratio* (95% CI) Adjusted for Age, Sex, BMI, CHD
Nonsustained ventricular tachycardia	4.64 (1.48–14.57)	3.72 (1.13–12.2)	3.40 (1.03–11.2)
Complex ventricular ectopy	1.96 (1.28–3.00)	1.81 (1.16–2.84)	1.74 (1.11–2.74)
Atrial fibrillation	5.66 (1.56–20.52)	3.85 (1.00–14.93)	4.02 (1.03–15.74)

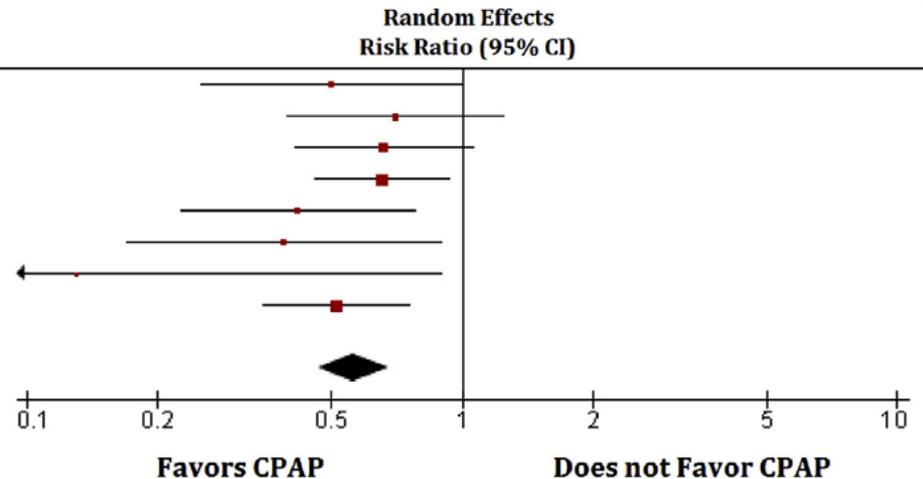
Definition of abbreviations: BMI = body mass index; CHD = coronary heart disease; CI = confidence interval.

*Results of logistic regression analysis with SDB as the exposure, n = 228 with SDB and n = 338 without SDB.

CPAP reduces recurrence risk of atrial fibrillation

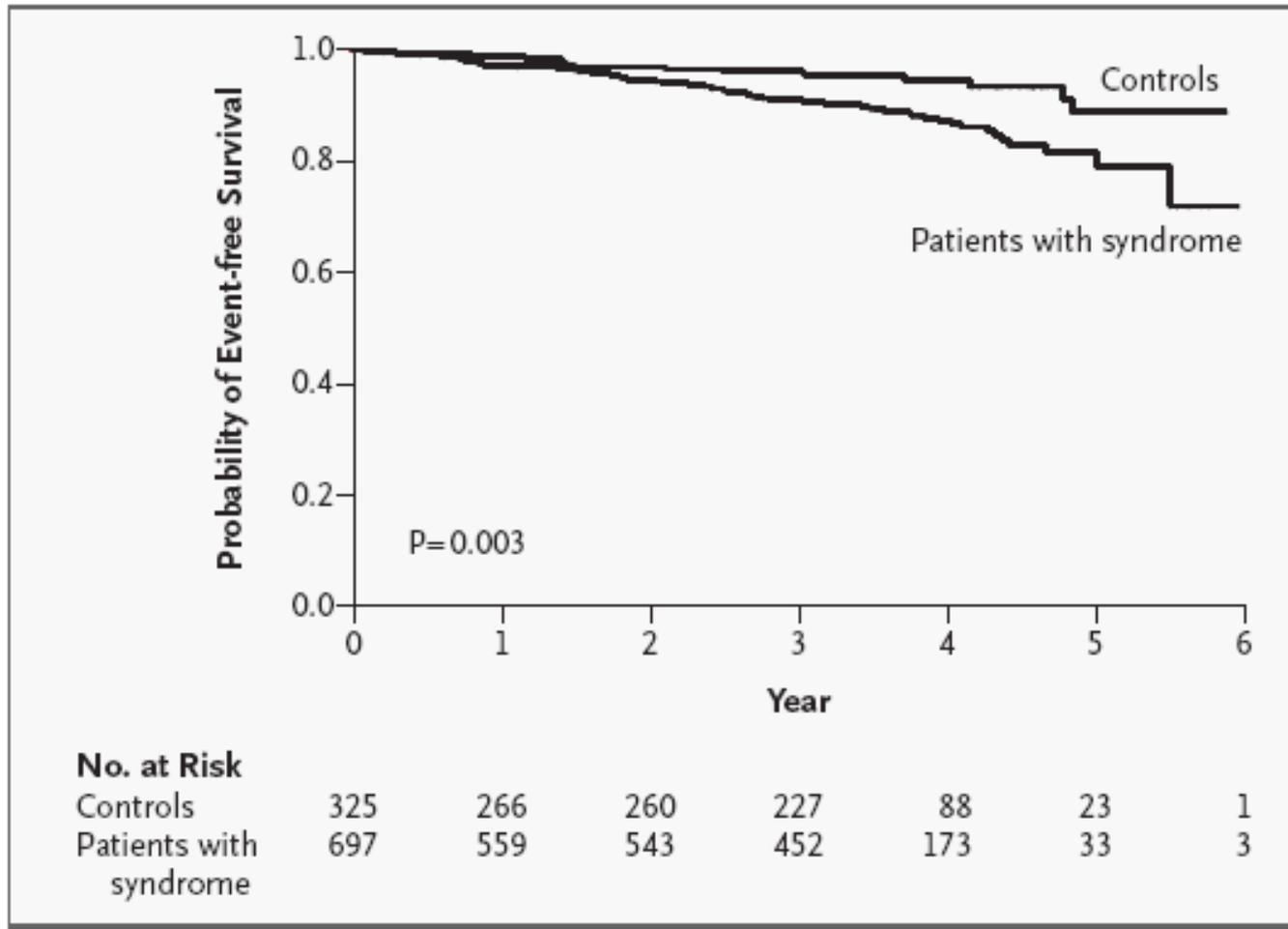
Study	log Risk Ratio	SE	Weight	Risk Ratio (95% CI)
Kanagala 2003	-0.690	0.349	7.5%	0.50 [0.25, 0.99]
Jongnarangsin 2007	-0.351	0.29	10.8%	0.70 [0.40, 1.24]
Craig 2008	-0.416	0.24	15.8%	0.66 [0.41, 1.06]
Patel 2010	-0.421	0.181	27.7%	0.66 [0.46, 0.94]
Naruse 2013	-0.868	0.316	9.1%	0.42 [0.23, 0.78]
Bazan 2013	-0.942	0.422	5.1%	0.39 [0.17, 0.89]
Fein 2013	-2.04	0.982	0.9%	0.13 [0.02, 0.89]
Neilan 2013	-0.664	0.198	23.2%	0.51 [0.35, 0.76]
Total (95% CI)			100%	0.56 [0.47, 0.68]

Heterogeneity Tau = 0.0 Chi² = 5.91, df = 7 (p = 0.55), I² = 0%
 Test for overall effect Z = 6.00 (p < 0.001)



CPAP treated patients had a 42% decreased risk of AF

OSA independently increases risk of stroke and death Yale Prospective Cohort



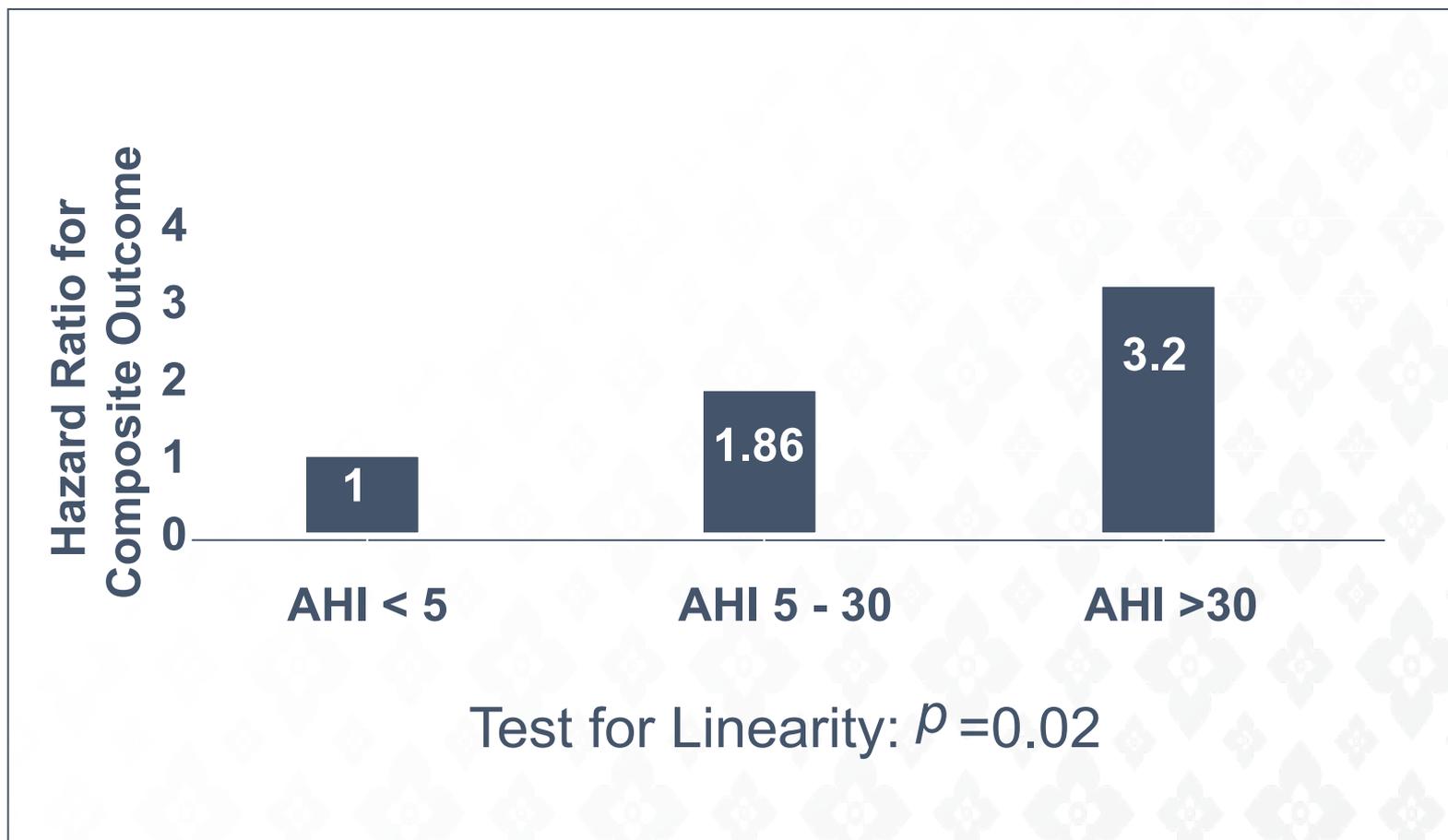
OSA independently increases the risk of stroke and death

Table 2. Unadjusted and Adjusted Hazard Ratios for the Risk of Stroke or Death from Any Cause.

Covariate	Unadjusted Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95%)
Age (yr)	1.09 (1.06–1.11)	1.08 (1.06–1.11)
Male sex	0.99 (0.62–1.60)	0.78 (0.48–1.28)
Race		
White (reference group)	1.00	1.00
Black	0.96 (0.39–2.38)	0.98 (0.39–2.46)
Other	0.91 (0.42–1.98)	0.94 (0.43–2.05)
Body-mass index	0.99 (0.97–1.02)	0.99 (0.96–1.02)
Current smoker	1.21 (0.90–1.64)	1.46 (0.78–2.98)
Current consumption of alcohol	1.03 (0.86–1.22)	0.94 (0.75–1.18)
Diabetes mellitus	1.56 (1.02–2.59)	1.31 (0.76–2.26)
Atrial fibrillation	1.56 (0.79–3.12)	0.91 (0.45–1.86)
Hyperlipidemia	1.04 (0.64–1.68)	1.01 (0.61–1.66)
Hypertension	1.48 (0.95–2.28)	1.19 (0.75–1.90)
Obstructive sleep apnea syndrome	2.24 (1.30–3.86)	1.97 (1.12–3.48)

* Hazard ratios were adjusted for all other covariates in the model. CI denotes confidence interval.

A linear trend between the severity of OSA and the risk of stroke and death



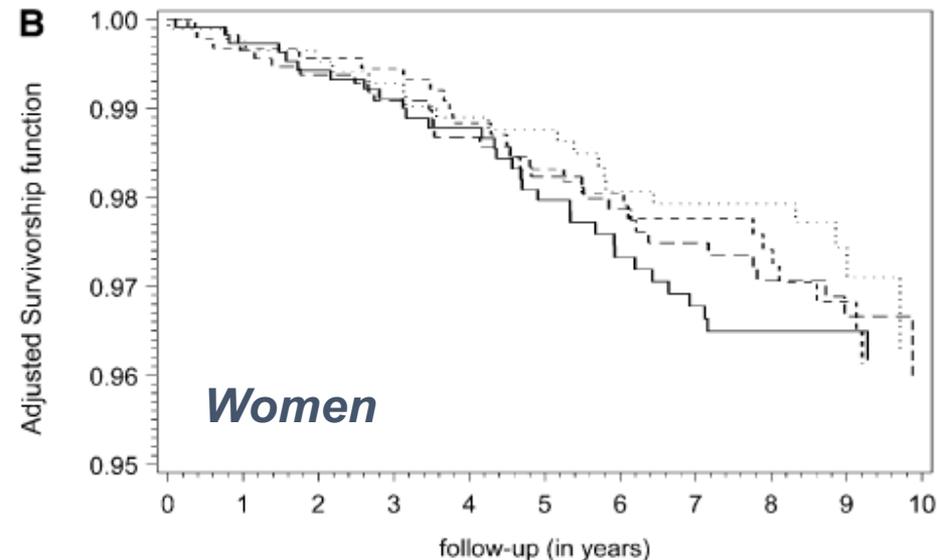
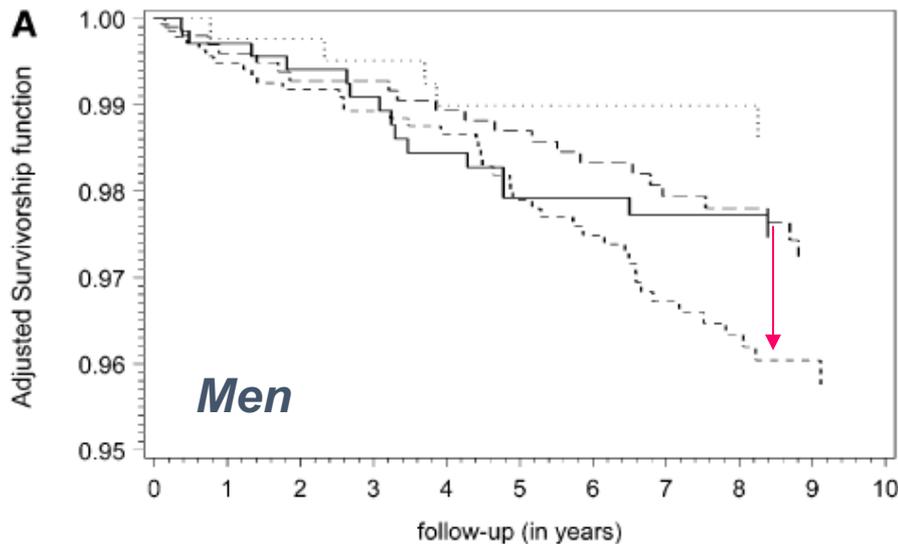
OSA increases risk of stroke in both men and women

(Sleep Heart Health Study- A US Prospective Cohort)

Stroke rate (per 1,000 person-years)–AHI>19

6.6

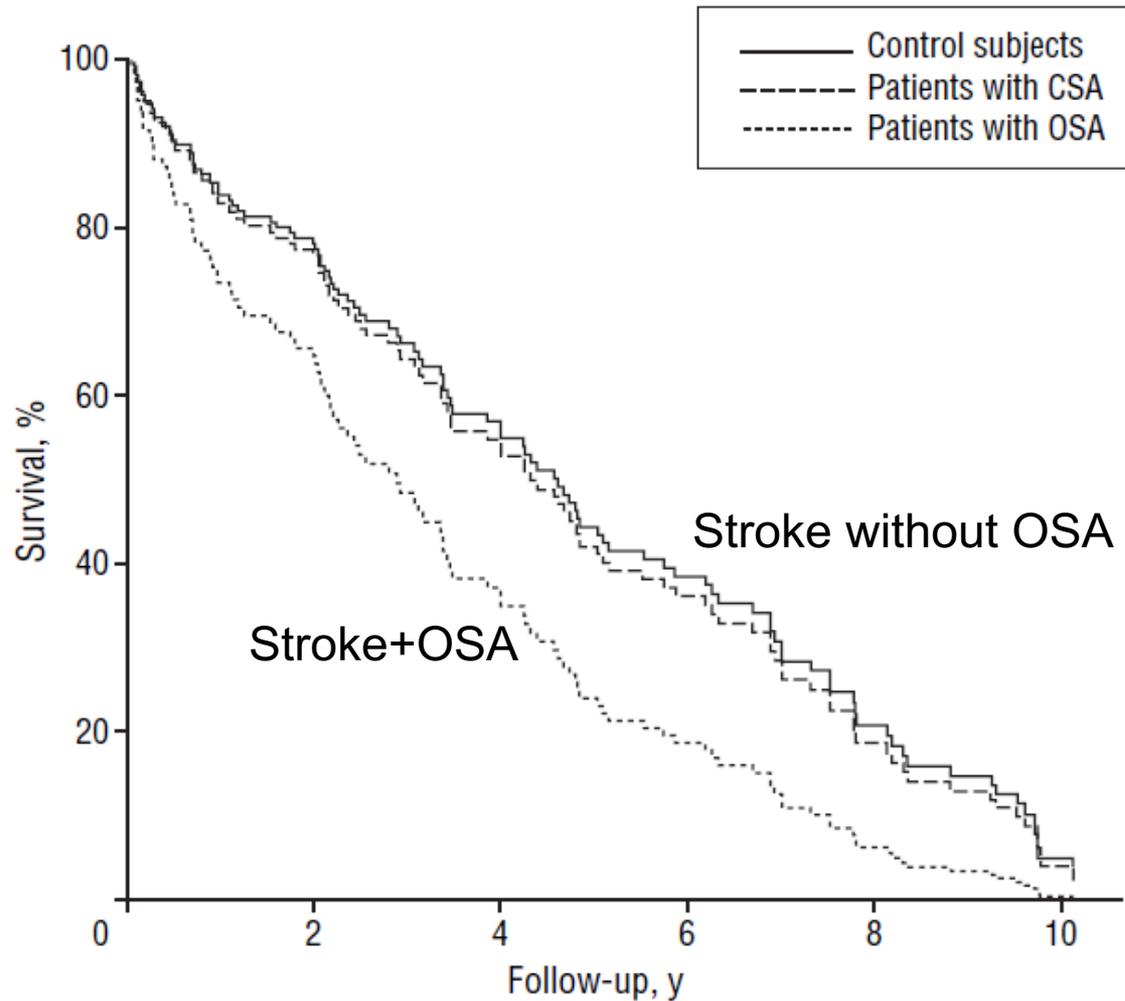
6.1



<u>AHI Quartiles</u>	<u>Odds Ratio</u>	<u>Odds Ratio</u>
<4	1	1
4 - <10	1.86	1.34
10 - <19	1.86	1.20
>19	2.86	1.21

Increased risk of stroke with AHI>25 in women

Obstructive sleep apnea increases risk of death in patients with stroke (Fully-adjusted model)



Cardiovascular outcomes for propensity score-matched CPAP adherent versus usual care patients. SAVE trial (McEvoy...Anderson et al. *N Engl J Med*, 2016)

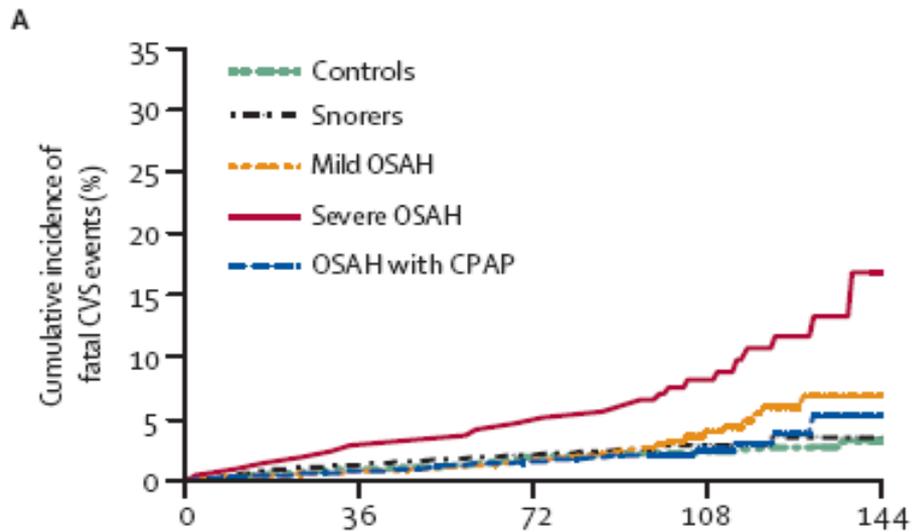
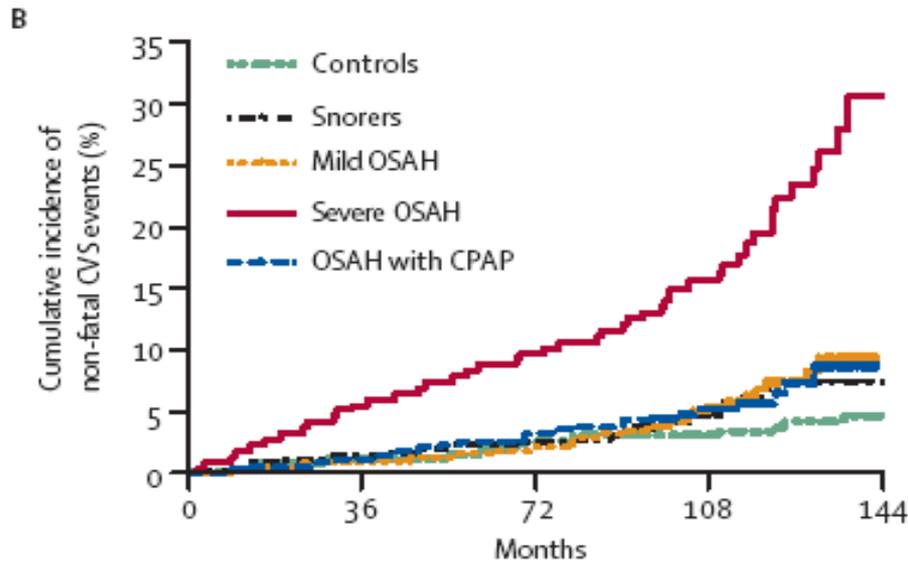
Outcome	CPAP + Usual care (n=561)	Usual care (n=561)	Hazard Ratio (95% CI)	P value
Primary efficacy				
Composite primary outcome, no. (%)	86 (15.3)	98 (17.5)	0.80 (0.60 to 1.07)	0.13
Secondary outcomes				
Components of primary endpoint				
CV Death	12 (2.1)	12 (2.1)	0.90 (0.41 to 2.01)	0.81
Myocardial infarction	18 (3.2)	14 (2.5)	1.19 (0.59 to 2.39)	0.63
Stroke	19 (3.4)	31 (5.5)	0.56 (0.32 to 1.00)	0.05
Hospitalization for heart failure	9 (1.6)	10 (1.8)	0.82 (0.34 to 2.03)	0.67
Hospitalization for unstable angina	44 (7.8)	41 (7.3)	0.99 (0.64 to 1.51)	0.95
Hospitalization for TIA	1 (0.2)	4 (0.7)	0.22 (0.03 to 2.01)	0.18
Other vascular endpoints				
Composite of ischaemic CV events	77 (13.7)	87 (15.5)	0.81 (0.59 to 1.10)	0.17
Composite of major CV events	41 (7.3)	54 (9.6)	0.69 (0.46 to 1.04)	0.08
Composite for cerebral events	20 (3.6)	35 (6.2)	0.52 (0.30 to 0.90)	0.02
Composite for cardiac events	79 (14.1)	73 (13.0)	1.01 (0.74 to 1.39)	0.93
Revascularisation procedures	44 (7.8)	33 (5.9)	1.25 (0.79 to 1.96)	0.34
All-cause death	17 (3.0)	26 (4.6)	0.60 (0.32 to 1.10)	0.10
New onset AF (ECG confirmed)	14 (2.5)	7 (1.2)	1.84 (0.74 to 4.55)	0.19
Newly diagnosed diabetes mellitus	33 (5.9)	40 (7.1)	0.77 (0.48 to 1.27)	0.26

Adherence to CPAP tends to reduce the risk of cerebral events in OSA.

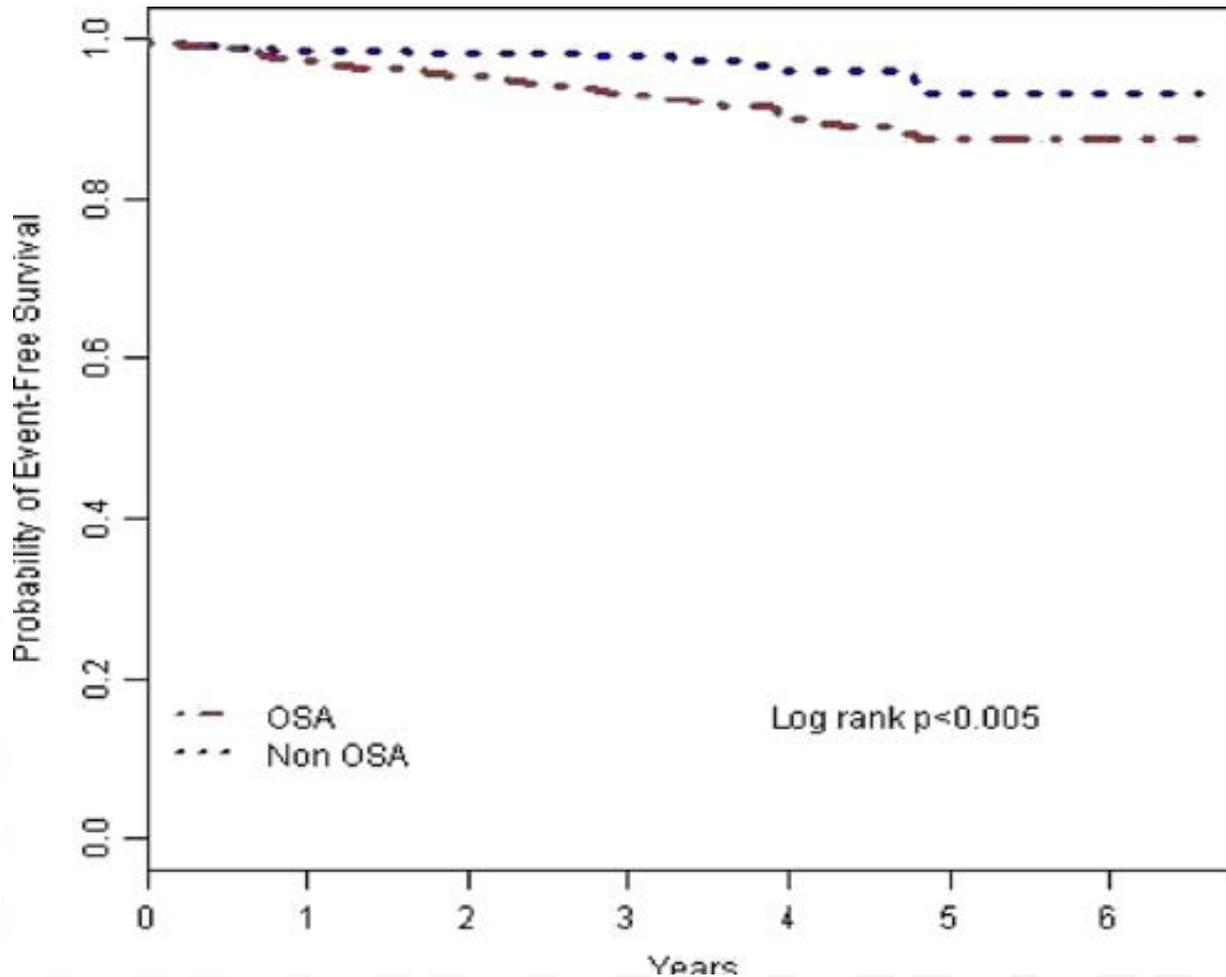
Martinez showed that patients with moderate-to-severe OSA who were admitted for stroke and used CPAP had a lower risk of subsequent strokes than those who did not (1). Another study also showed that those with stroke and OSA had greater improvement in function after 30 days if they used CPAP for at least 6.5 hours per night compared to those that did not (2).

Increased risks of fatal and non-fatal cardiovascular events in OSA

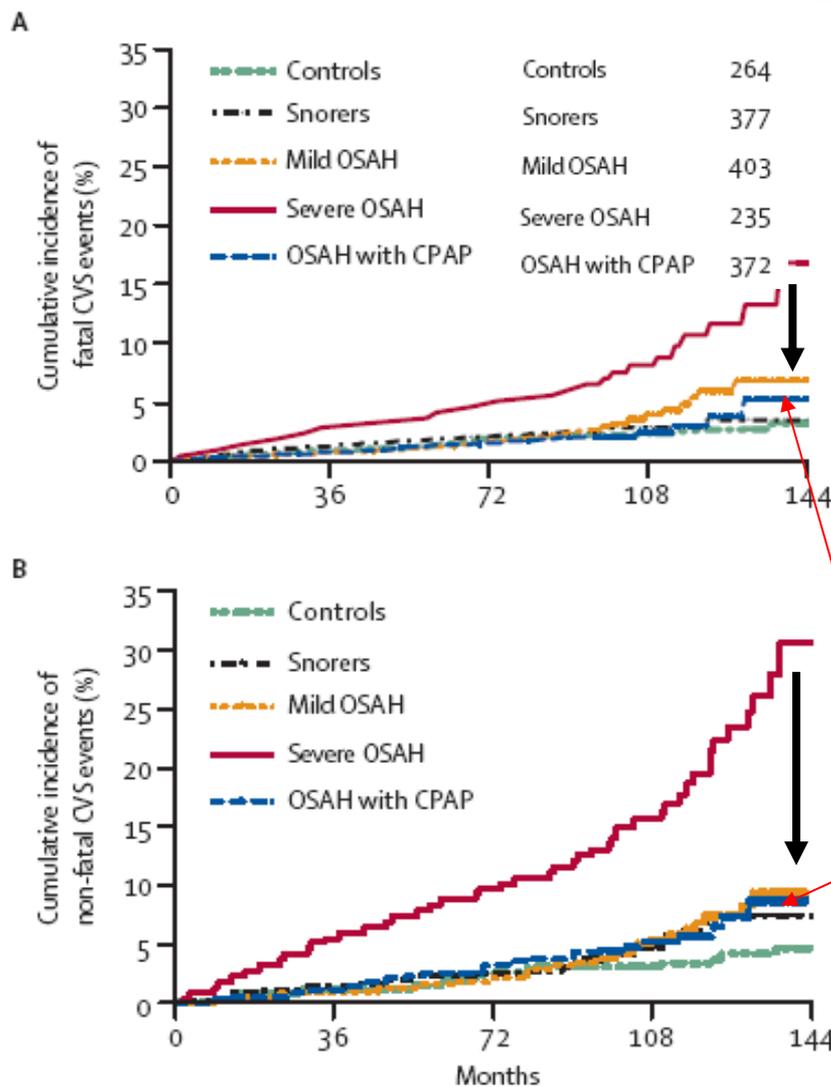
A 10-year Spanish prospective observational study



Obstructive sleep apnea increases risk of new coronary events or cardiovascular death- Yale Prospective Cohort



CPAP significantly reduces the risk of fatal and non-fatal cardiovascular events including stroke in patients with OSA. An observation study



CPAP significantly reduces the risk

Untreated, severe OSA was independently associated with cardiovascular death and adequate CPAP treatment was independently associated with decreased mortality risk in this Spanish Women Cohort Observational study.

Table 4. Variables Associated With Cardiovascular Death in Adjusted Multivariate Cox Regression Analysis*

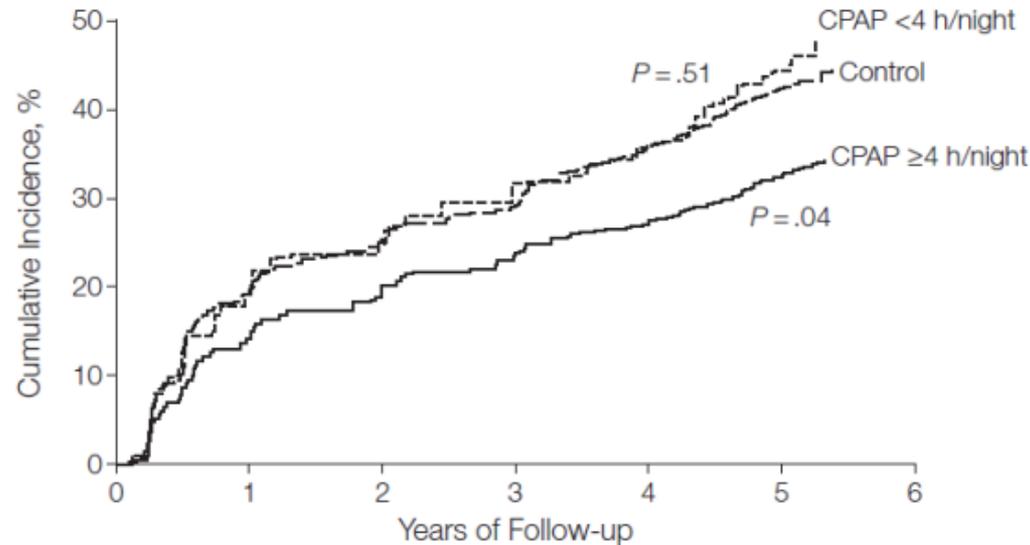
Variable	Hazard Ratio (95% CI)	P Value
Age	1.05 (1.01–1.09)	0.004
Body mass index	1.03 (0.98–1.08)	0.182
Previous cardiovascular events	4.31 (1.97–9.43)	<0.001
Hypertension	2.42 (0.82–7.08)	0.106
Diabetes mellitus	1.41 (0.71–2.80)	0.32
Study group		
AHI <10	1.00 (reference)	
AHI of 10–29 and treated with CPAP	0.19 (0.02–1.67)	0.135
AHI ≥30 and treated with CPAP	0.55 (0.17–1.74)	0.31
AHI of 10–29 and untreated	1.60 (0.52–4.90)	0.40
AHI ≥30 and untreated	<u>3.50 (1.23–9.98)</u>	<u>0.019</u>

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CPAP reduces incident cardiovascular events in patient with better adherence to CPAP. An observational study



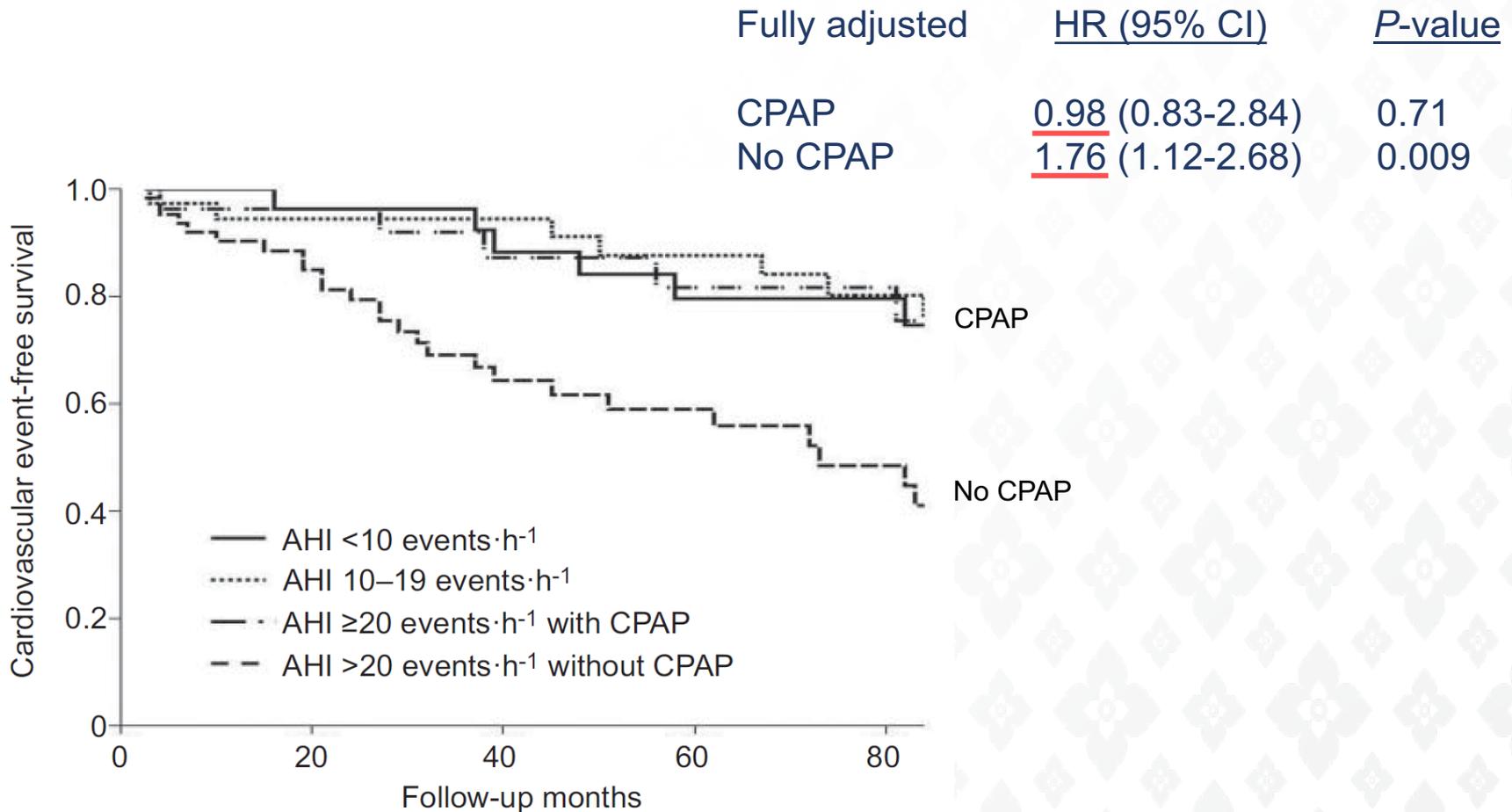
No. at risk						
Control	366	264	234	206	134	10
CPAP <4 h/night	127	79	72	56	41	3
CPAP ≥4 h/night	230	192	175	161	107	13

Incident Hypertension & Cardiovascular Events

	<u>Control (AHI=35)</u>	<u>CPAP (AHI=42)</u>
Hypertension	79	68
Cardiovascular	31	28

CPAP reduces incident cardiovascular events

A 7-year Spanish prospective observational study



Observational clinical studies have shown that OSA increases risk of cardiovascular complications and of death and the use of CPAP is associated with lower rates of cardiovascular complications and of death from cardiovascular causes, especially among patients who are adherent to treatment.

Marin...Agusti. *Lancet*, 2005

Barbe... Montserrat. *JAMA*, 2012

Martínez-García...Montserrat. *Eur Respir J*, 2012

Compos-Rodriguez...Montserrat, *Ann Intern Med*, 2012

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

SAVE study.
A prospective
randomized parallel
study

End Point	CPAP Group (N=1346)	Usual-Care Group (N=1341)	Hazard Ratio (95% CI)	P Value
	<i>no. (%)</i>			
Primary composite end point*	229 (17.0)	207 (15.4)	1.10 (0.91–1.32)	0.34
Secondary end points				
Components of primary end point				
Death from cardiovascular causes	25 (1.9)	20 (1.5)	1.22 (0.68–2.20)	0.50
Myocardial infarction	42 (3.1)	39 (2.9)	1.06 (0.68–1.64)	0.80
Stroke	67 (5.0)	68 (5.1)	0.97 (0.69–1.35)	0.84
Hospitalization for heart failure	17 (1.3)	17 (1.3)	0.98 (0.50–1.92)	0.96
Hospitalization for unstable angina	99 (7.4)	90 (6.7)	1.09 (0.82–1.45)	0.56
Hospitalization for transient ischemic attack	16 (1.2)	9 (0.7)	1.75 (0.77–3.95)	0.18
Other vascular end points				
Composite of ischemic cardiovascular events†	207 (15.4)	191 (14.2)	1.07 (0.88–1.31)	0.49
Composite of major cardiovascular events‡	117 (8.7)	120 (8.9)	0.96 (0.74–1.23)	0.72
Composite of cerebral events§	80 (5.9)	74 (5.5)	1.06 (0.77–1.45)	0.72
Composite of cardiac events¶	167 (12.4)	157 (11.7)	1.06 (0.85–1.31)	0.62
Revascularization procedures	99 (7.4)	74 (5.5)	1.33 (0.98–1.79)	0.07
Death from any cause	40 (3.0)	43 (3.2)	0.91 (0.59–1.40)	0.67
New-onset atrial fibrillation	22 (1.6)	15 (1.1)	1.46 (0.76–2.81)	0.26
Newly diagnosed diabetes	66 (4.9)	76 (5.7)	0.85 (0.61–1.19)	0.35

CPAP as compared with usual care alone, **did not** prevent cardiovascular events in **non-sleepy patients** with moderate-to-severe obstructive sleep apnea and established cardiovascular disease.

CPAP doesn't prevent cardiovascular events in OSA in a prospective randomized trial.

But Can That Be True?

- The study had approximately 2500 participants aged 45-75 (81% men) across 89 clinical centers and 7 countries. (McEvoy et al. *N Engl J Med*, 2016)

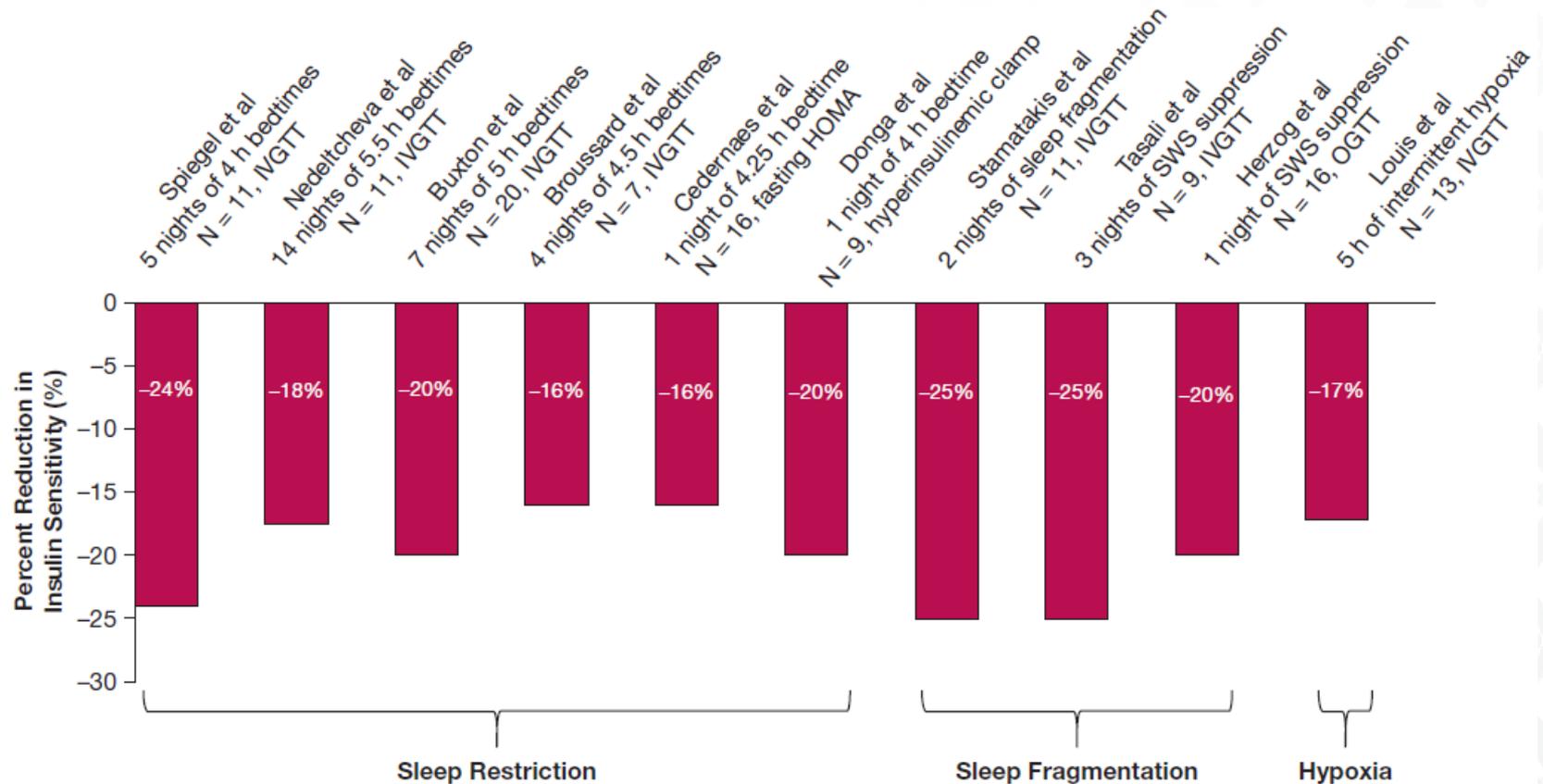
Potential reasons for not showing preventive effect of CPAP on cardiovascular events in OSA

- All of the participants had pre-existing cardiovascular disease
- **Excluded:** people reporting excessive daytime sleepiness, significant oxygen desaturation and people with significant congestive heart failure.
- The mean usage time of CPAP for all participants was 3.3 hours. Only 42 percent of study subjects had “good adherence” to CPAP (as defined as averaging 4 hours of CPAP use per night, but the results were analyzed as if they had all used it. This raises the question of adherence vs lack of therapeutic effect.

It can be concluded then: Suboptimal use of CPAP is no better than sham CPAP in prevention of future cardiovascular events in non-sleepy OSA patients.

Metabolic Complications of OSA

Changes in insulin sensitivity following sleep manipulations in healthy human subjects



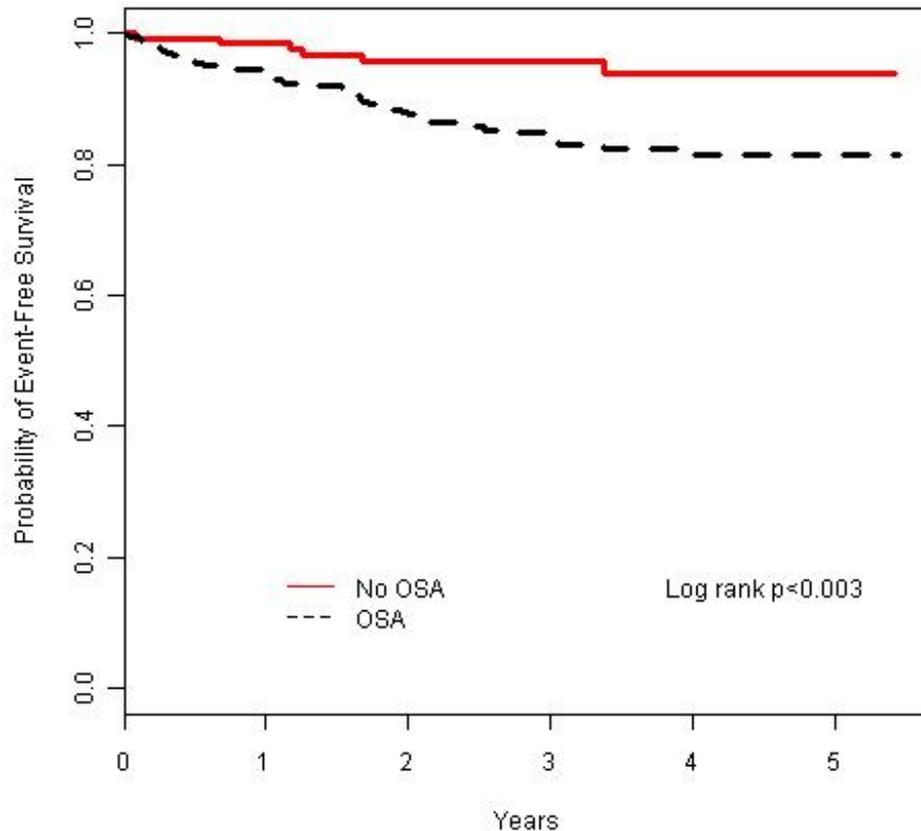
Increased insulin resistance due to sleep disturbances and hypoxia

Prospective cohort studies on the relationship between OSA and incident Diabetes

Study/Year	No.	Setting	Mean Age (y)	Mean BMI (kg/m ²)	Male Sex (%)	Sleep Assessment	Follow-up (y)	Results
Reichmuth et al ⁶⁷ /2005	1,387	USA	49.0	28.9	56.0	AHI ≥ 5 by polysomnography	4	No association between OSA and incident diabetes
Botros et al ⁶³ /2009	544	USA	61.5	33.2	93.4	AHI ≥ 8 by polysomnography	2.7	OSA was associated with diabetes; HR, 1.43 (95% CI, 1.10-1.86)
Marshall et al ⁶⁰ /2009	295	Australia	53.1	26.6	41.3	RDI ≥ 5 from a 4-channel home monitoring device (heart rate, oxygen saturation, snoring, and body position)	4	Moderate to severe OSA (RDI ≥ 15) was associated with diabetes, OR, 13.45 (95% CI, 1.59-114.11)
Celen et al ⁶⁵ /2010	168	Sweden	48.2	26.6	81.6	4% ODI ≥ 30 events/night using nocturnal oximetry, nasal and oral airflow, respiratory motion, and body movement	16	OSA was associated with diabetes in women—OR, 11.78 (95% CI, 1.14-121.7)—but not in men
Muraki et al ⁶¹ /2010	4,606	Japan	57.6	23.5	34.7	3% ODI ≥ 5 events/h using pulse oximetry	3	Moderate OSA (ODI ≥ 15) was associated with diabetes; HR, 1.69 (95% CI, 1.04-2.76)
Lindberg et al ⁶⁶ /2012	141	Sweden	57.5	26.9	100.0	ODI > 5 by polysomnography	11.3	ODI > 5 was associated with diabetes; OR, 4.4 (95% CI, 1.1-18.1)
Boyko et al ⁶⁴ /2013	47,093	USA	36.7	26.3	25.3	Report of a physician diagnosis of OSA	6	OSA was associated with diabetes; OR, 1.78 (95% CI, 1.39-2.28)
Kendzerska et al ⁵⁹ /2014	8,678	Canada	48.0	28.4	62.0	AHI ≥ 5 by polysomnography	5.6	AHI > 30 was associated with diabetes; HR, 1.31 (95% CI, 1.07-1.61)
Appleton et al ⁵⁸ /2015	736	Australia	59.7	28.4	100	8-channel in-home unattended polysomnography, measured at the last follow-up	4.7	Severe OSA (AHI ≥ 30) was associated with diabetes; OR, 2.6 (95% CI, 1.1-6.1) ODI ≥ 16 was associated with diabetes; OR, 1.85 (95% CI, 1.06-3.21)
Nagayoshi et al ⁶² /2016	1,453	USA	62.5	28.3	46.3	AHI ≥ 5 by unattended in-home polysomnography	12.8	Severe OSA (AHI ≥ 30) was associated with diabetes; HR 1.71 (95% CI, 1.08-2.71), whereas mild and moderate OSA were not associated with diabetes Results were similar for those with BMI ≥ 30 kg/m ²

OSA increases risk of incident type 2 diabetes by a Hazard Ratio of 1.35

OSA increases risk of type 2 diabetes mellitus in adults

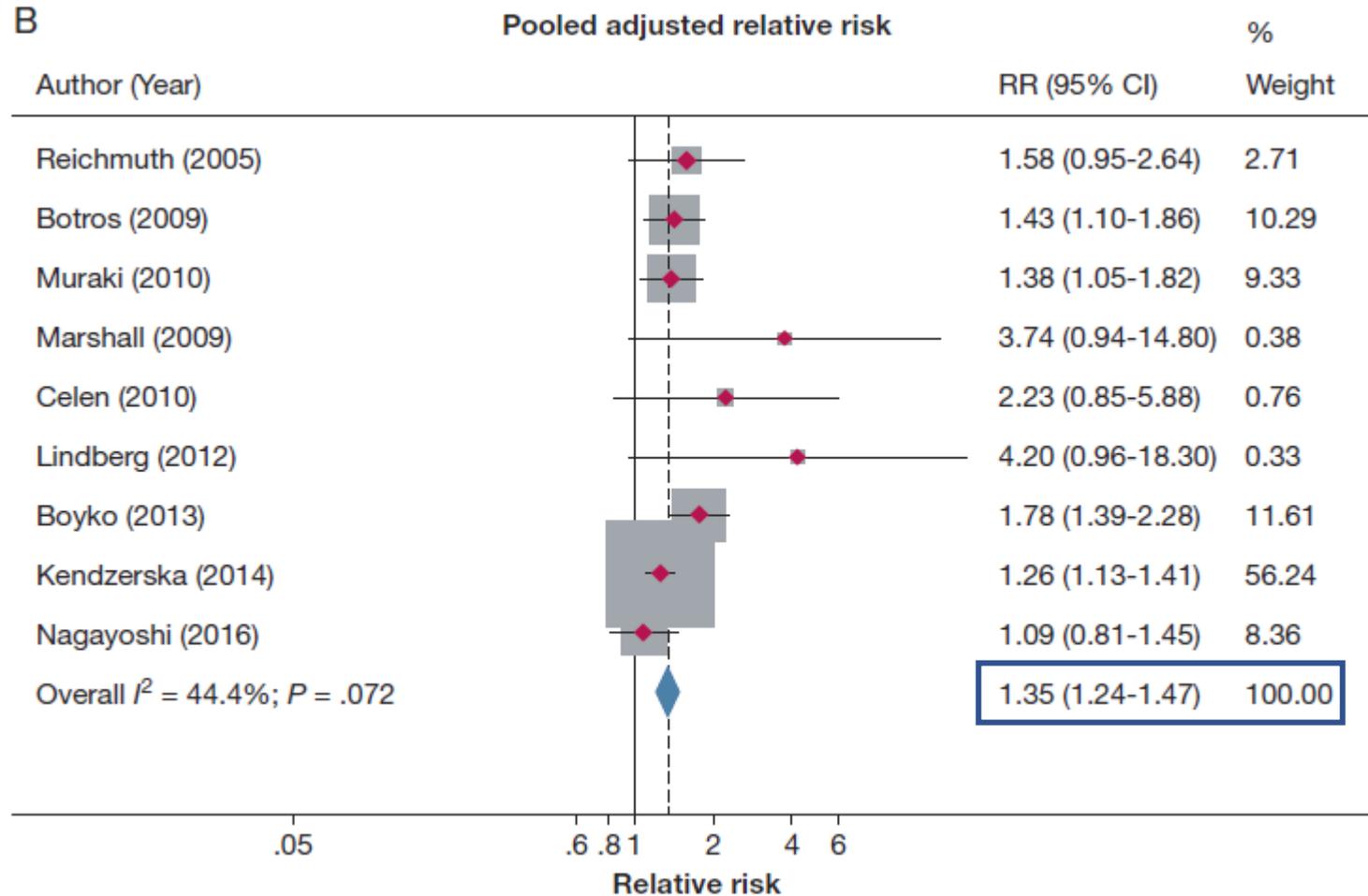


Adjusted **HR 1.43** (CI 1.10-1.86)
 $P=0.008$
 $n=544$

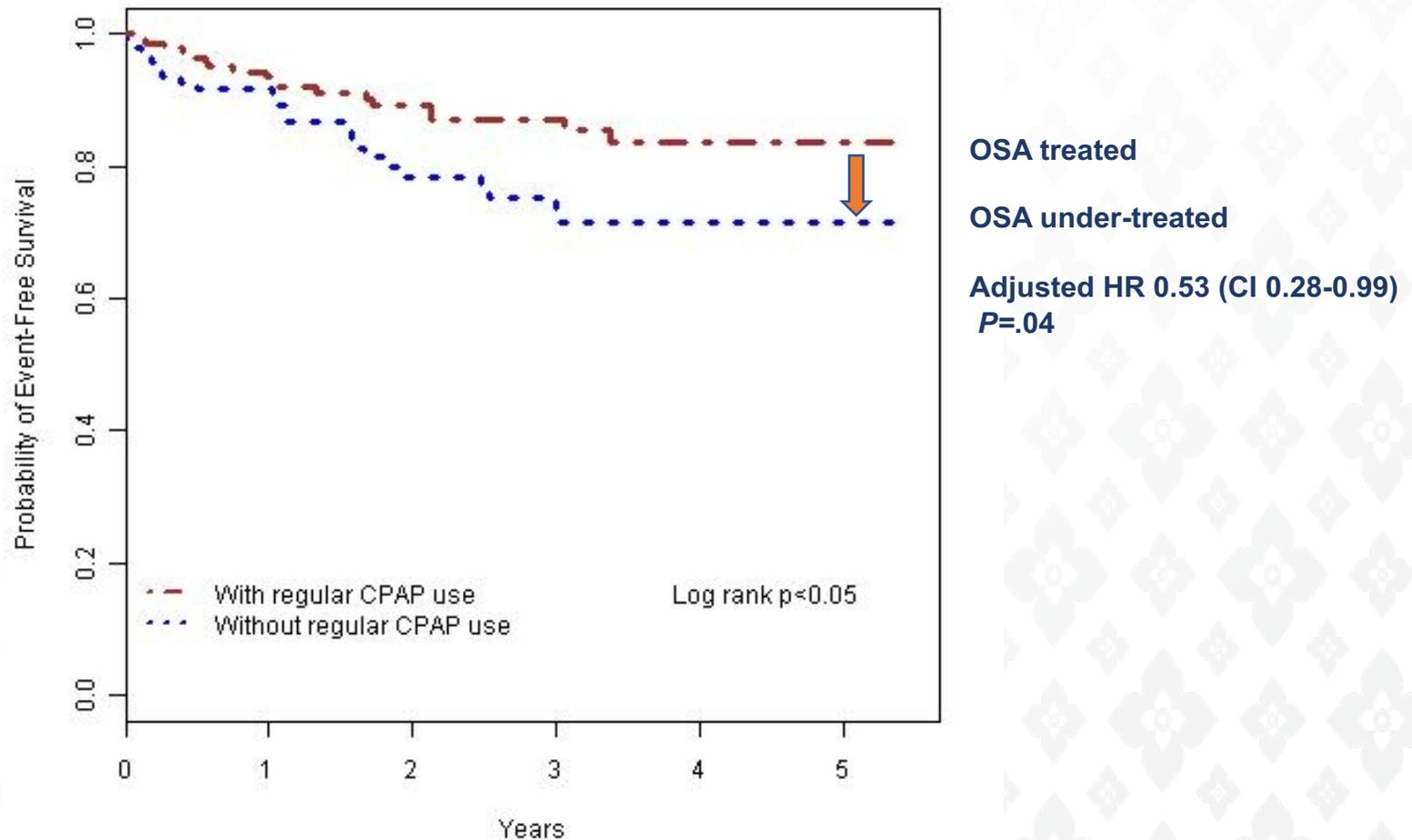
Prospective study of incident diabetes mellitus in OSA
The West Haven VA Cohort-Yale

Botros...Mohsenin. *Am J Med*, 2009

OSA is associated with greater risk of incident diabetes



Effective treatment of OSA with CPAP decreases incident diabetes



Conclusions

RCT studies have shown that treatment with CPAP

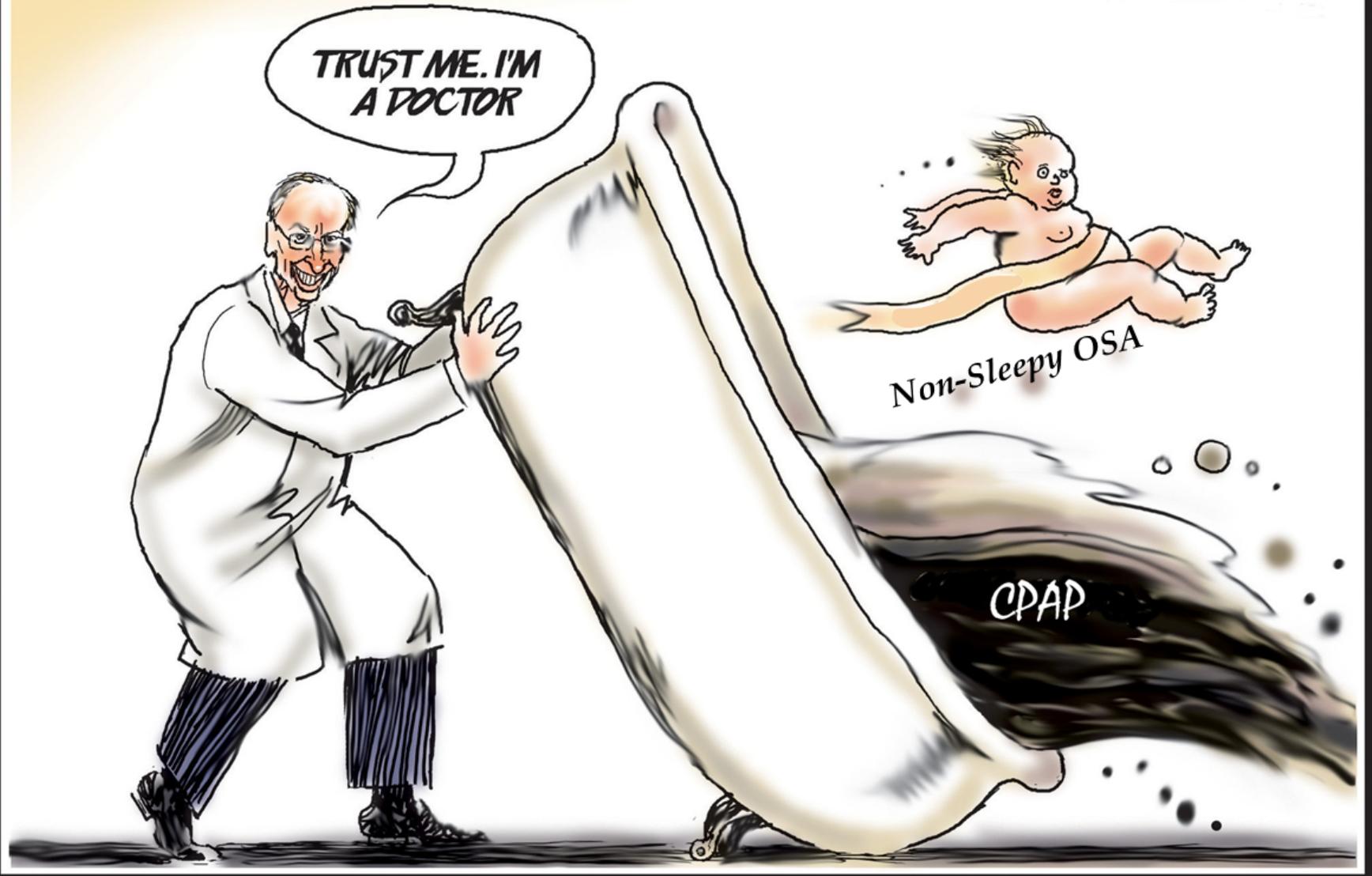
- Lowers systolic blood pressure
- Improves endothelial function
- Increases insulin sensitivity
- Reduces risk of stroke

But not secondary prevention of cardiac events. However, as before CPAP compliant patients had fewer cardiac events.

So, for the time being, it is premature to consider withholding CPAP therapy in non-sleepy patients with OSA

THROWING THE BABY OUT WITH THE BATHWATER...

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Risk of obstructive sleep apnea is increased by?

- A. Obesity
- B. Male sex
- C. Racial background
- D. Post-menopausal state
- E. All of the above

Risk of obstructive sleep apnea is increased by?

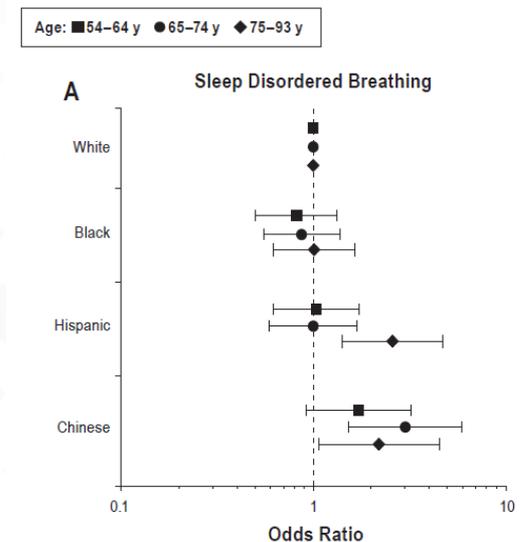
- A. Obesity
- B. Male sex
- C. Racial background
- D. Post-menopausal state
- E. All of the above

Answer: E

All of the above factors can increase risk of OSA.

Chinese, Hispanics and African blacks are at higher risk of OSA, independent of obesity and other known risk factors.

Chen et al. MESA Cohort. *Sleep* 2015



Obstructive sleep apnea, assessed in mid-life, is independently associated with higher levels of cardiac injury marker, higher incident heart failure or death among women compared to men.

- A. False
- B. True

Obstructive sleep apnea, assessed in mid-life, is independently associated with higher levels of cardiac injury marker, higher incident heart failure or death among women compared to men.

A. False

B. True

Answer: B

Sex specific differences exist in the relationship between OSA and cardiovascular disease. In a large community-based study, more than 1500 middle-aged men and women were followed for 13.6 ± 3.2 years for incident coronary disease, heart failure, and CV and all-cause mortality. Women had higher incident heart failure or death compared to men.

Roca et al. *Circulation*, 2015

Recent long-term randomized controlled trials have cast doubt on benefits to cardiovascular co-morbidities from active treatment of OSA, especially where cardiovascular disease is already established. However, benefits are more likely in patients who are compliant with therapy.

- A. True
- B. False

Recent long-term randomized controlled trials have cast doubt on benefits to cardiovascular co-morbidities from active treatment of OSA, especially where cardiovascular disease is already established. However, benefits are more likely in patients who are compliant with therapy.

- A. True
- B. False

Answer: A

Observational clinical studies have shown that OSA increases risk of cardiovascular (CV) complications and of death and the use of CPAP is associated with lower rates of CV complications or CV death. More recent long-term randomized controlled studies such as the SAVE and RICCADSA trials have failed to show benefits from CPAP therapy in the secondary prevention of cardiovascular morbidity or mortality in patient cohorts with moderate to severe OSA and pre-existing cardiovascular disease. However, CPAP compliance was poor in both studies, and the RICCADSA trial demonstrated a significant benefit in cardiovascular outcomes among patients using CPAP >4 hours per night.