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Policlinico

Sleep apnea: rilevanza epidemiologica nel paziente cardiologico

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Scuola di Spec. In Malattie dell'Apparato Cardiovascolare
UNIMORE

Sleep Apnea is:

- Common
- Dangerous
- Easily recognized
- Treatable

Sleep Apnea Risk Factors

- Obesity
- Increasing age
- Male gender
- Anatomic abnormalities of upper airway
- Family history
- Alcohol or sedative use
- Smoking
- Associated conditions

SLEEP APNEA PREVALENCE

- Sleep apnea syndrome of moderate to severe intensity affects
  - 17% of 50-70 year-old men
  - 9% of 50-70 year-old women

Peppard PE et al. Am J Epidemiol 2013

Types of Sleep Disordered Breathing

- Apnea
  - Cessation of airflow $\geq$ 10 seconds
- Hypopnea
  - Decreased airflow $\geq$30% from baseline lasting $\geq$ 10 seconds associated with $\geq$ 4% oxyhemoglobin desaturation

Measures of Sleep Apnea Frequency

- **Apnea Index**
  - # apneas per hour of sleep
- **Apnea / Hypopnea Index (AHI)**
  - # apneas + hypopneas per hour of sleep
- **Respiratory Disturbance Index**
  - # apneas + hypopneas + RERAs per hour of sleep

RERA's =Respiratory Effort Related Arousals

Severity Criteria Based on PSG From the American Academy of Sleep Medicine (Sleep, 1999)

"Mild" sleep apnea is 5-15 events/hr

"Moderate" sleep apnea is 15-30 events/hr

"Severe" sleep apnea is over 30 events/hr

("Events" includes apneas, hypopneas, and RERA's [Respiratory Effort Related Arousals])

SDB with Aging

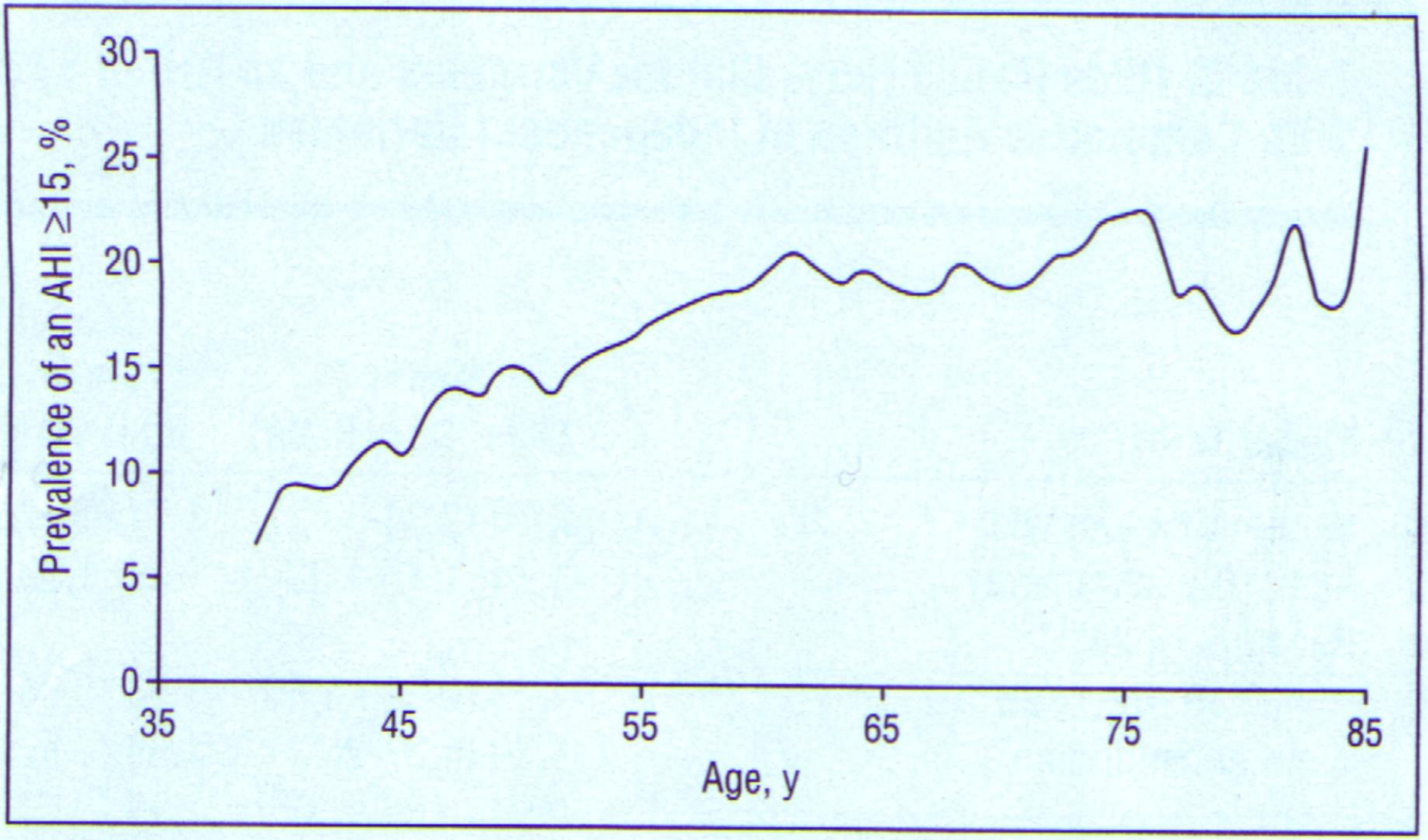
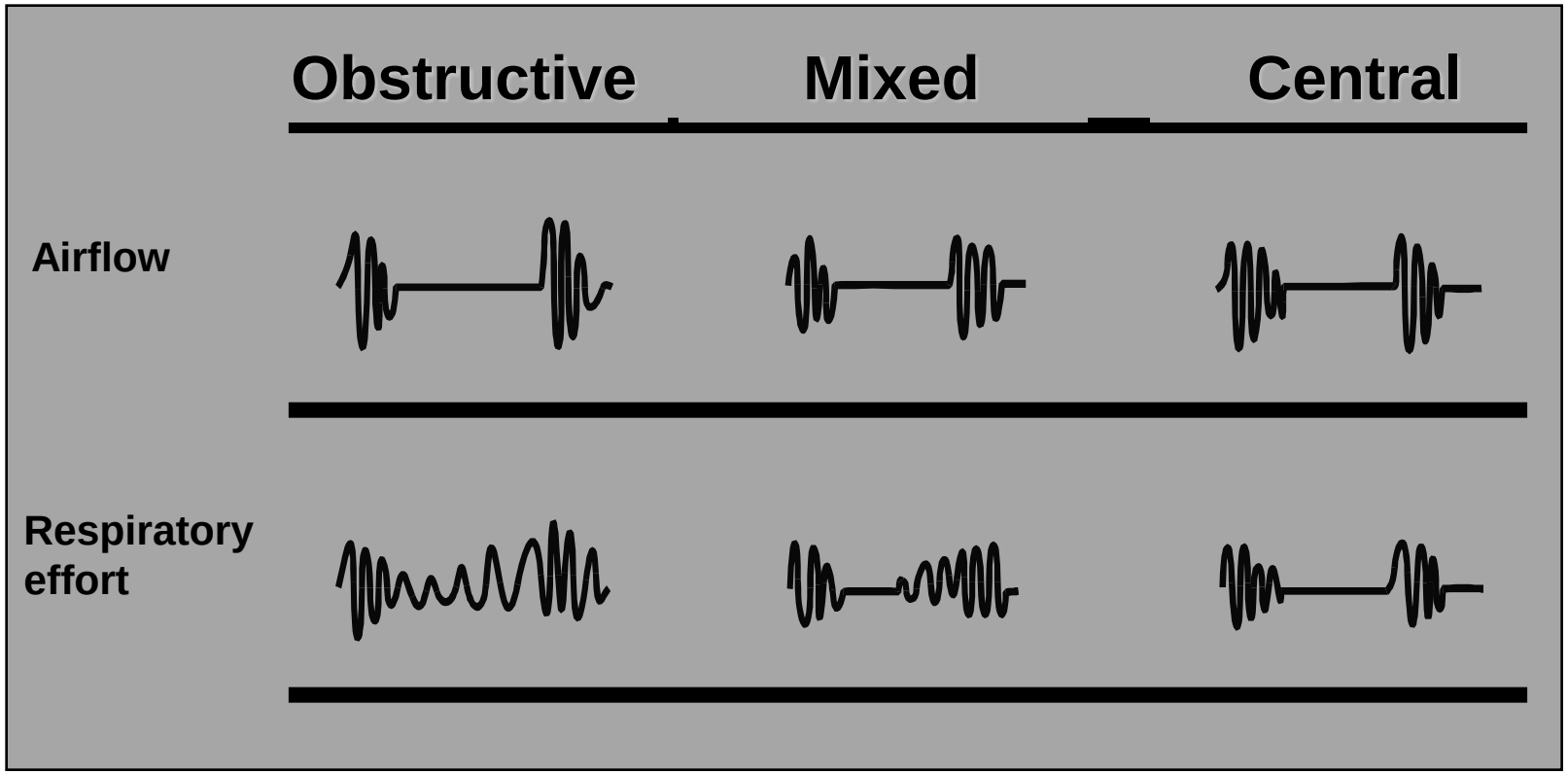


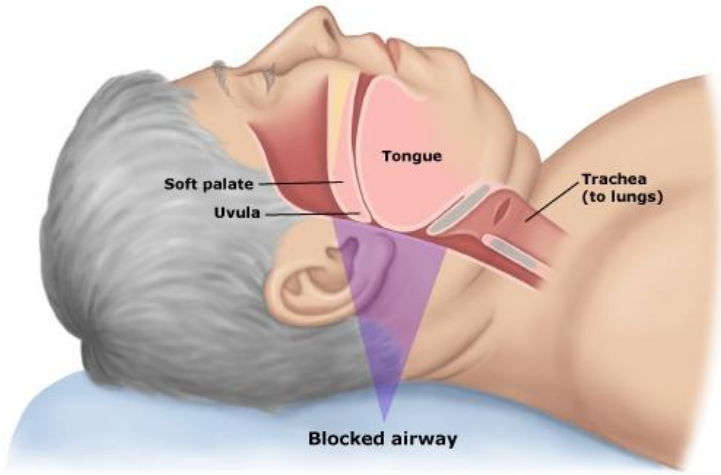
Figure 1. Smoothed plot (5-year moving average) of the prevalence of an apnea-hypopnea index (AHI) of 15 or greater by age.

Apnea Patterns



Definition of OSA

- Obstructive sleep apnea (OSA) is a disorder in which a person frequently stops breathing during his or her sleep.
- It results from an obstruction of the upper airway during sleep that occurs because of inadequate motor tone of the tongue and/or airway dilator muscles.



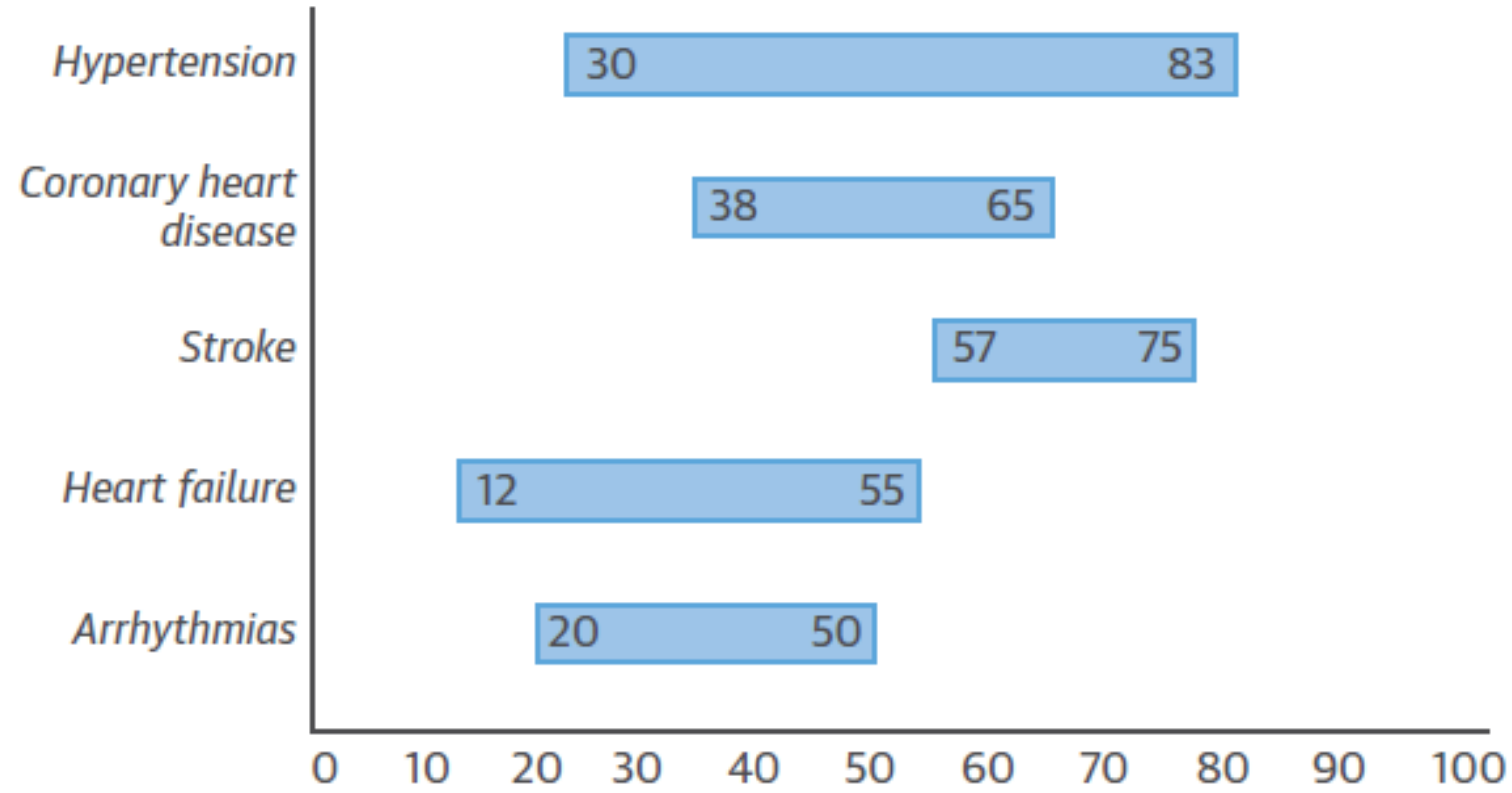
Mayo Clin Proc. 2011 Jun; 86(6): 549–555.

Epidemiology of OSA

- Prevalence of OSA: **3-7% in men** and **2-5% in women** (but some studies found 9% in adult women and 24% in adult men).
- Among patients with a BMI>28 OSA is present in 41%.
- Prevalence of OSA is about 78% in morbidly obese patients who present for bariatric surgery.
- Up to 93% of women and 82% of men may have undiagnosed moderate to severe OSA.

Punjabi NM, *Proc Am Thorac Soc.* 2008;5:136-143
Vgontzas AN et al., *Arch Intern Med.* 1994;154:1705-1711
Lopez PP et al., *Am Surg.* 2008;74:834-838
Young T et al., *Sleep*. 1997;20:705-706

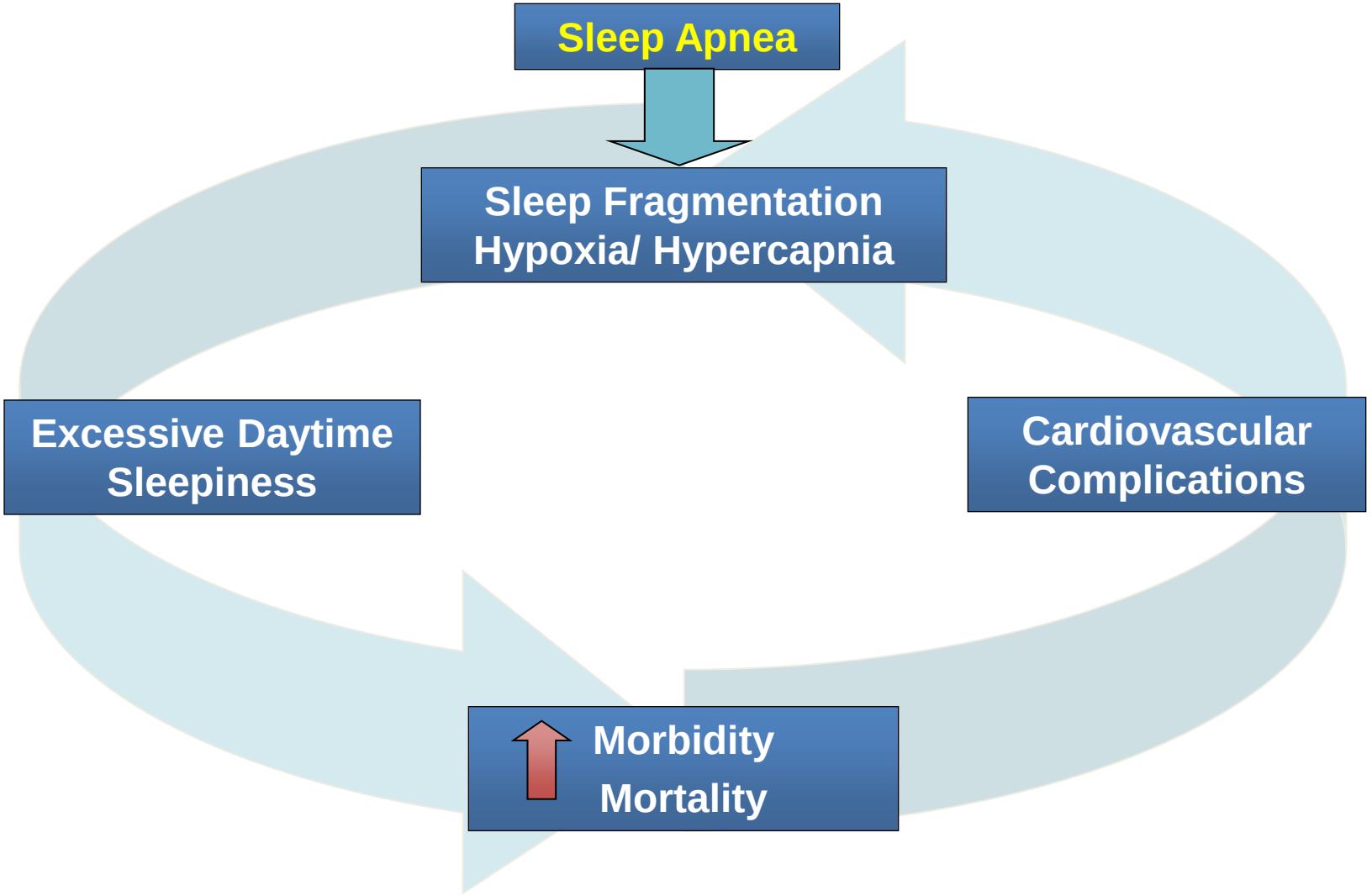
FIGURE 5 Prevalence (%) of OSA in CVD



The lower limit is invariably using an AHI of ≥15/h, indicating presence of moderate-to-severe OSA. The upper part of the range relates to a lower threshold of ≥5/h. CVD = cardiovascular disease; OSA = obstructive sleep apnea.

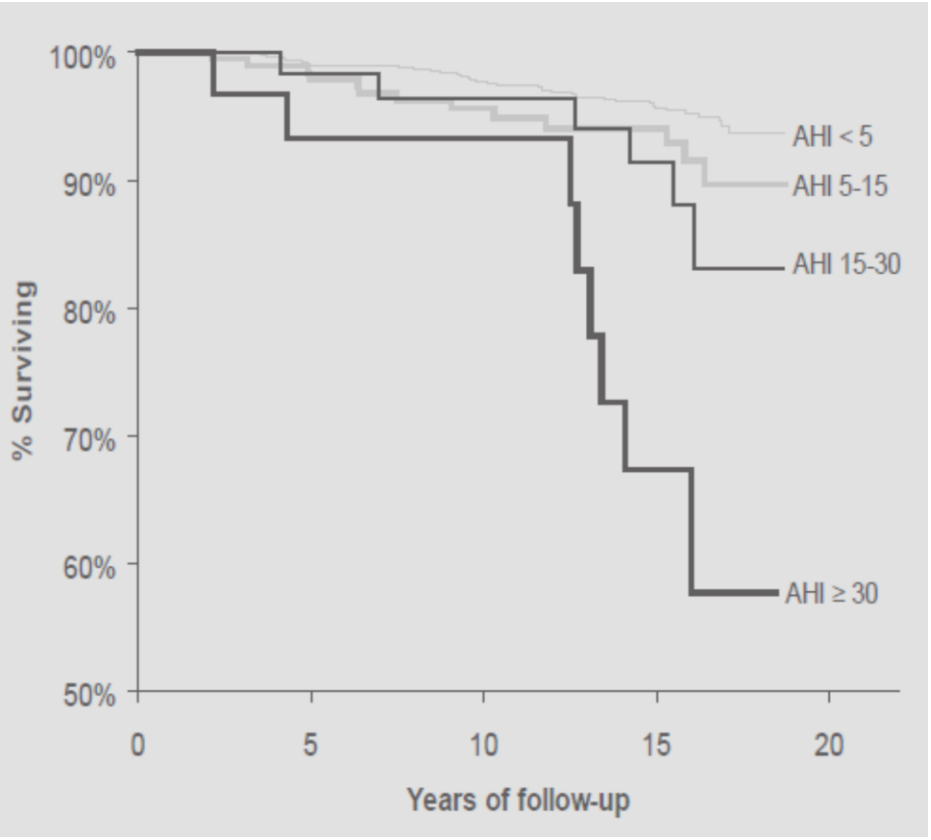
Javaheri, S. et al. J Am Coll Cardiol. 2017;69(7):841-58.

Clinical Consequences



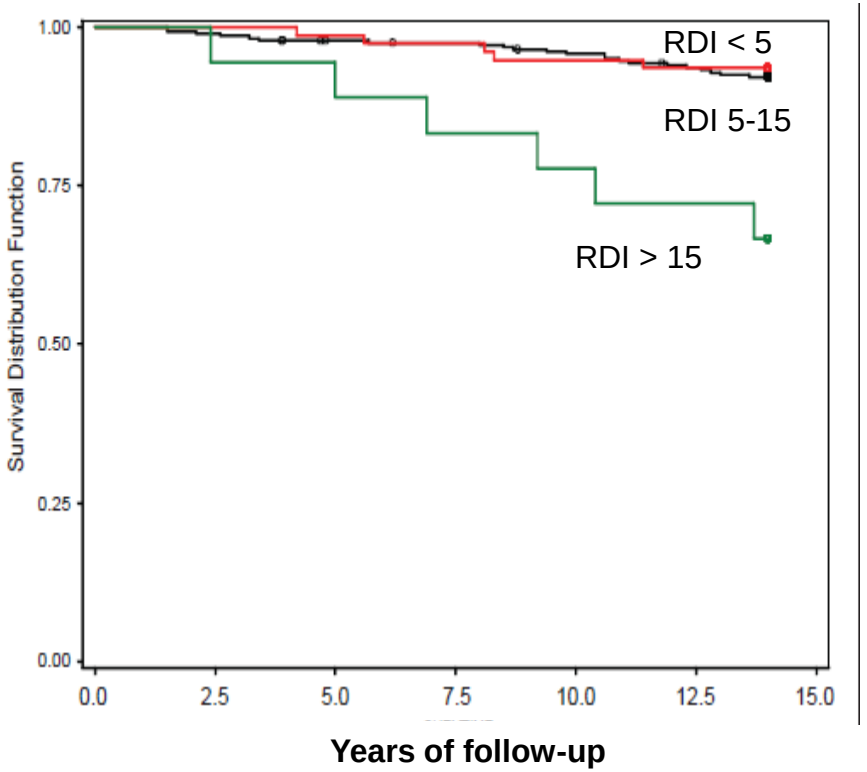
Consequences: Mortality

Wisconsin Cohort



Young et al. Sleep 2008; 31:1071-1078

Busselton, Australia



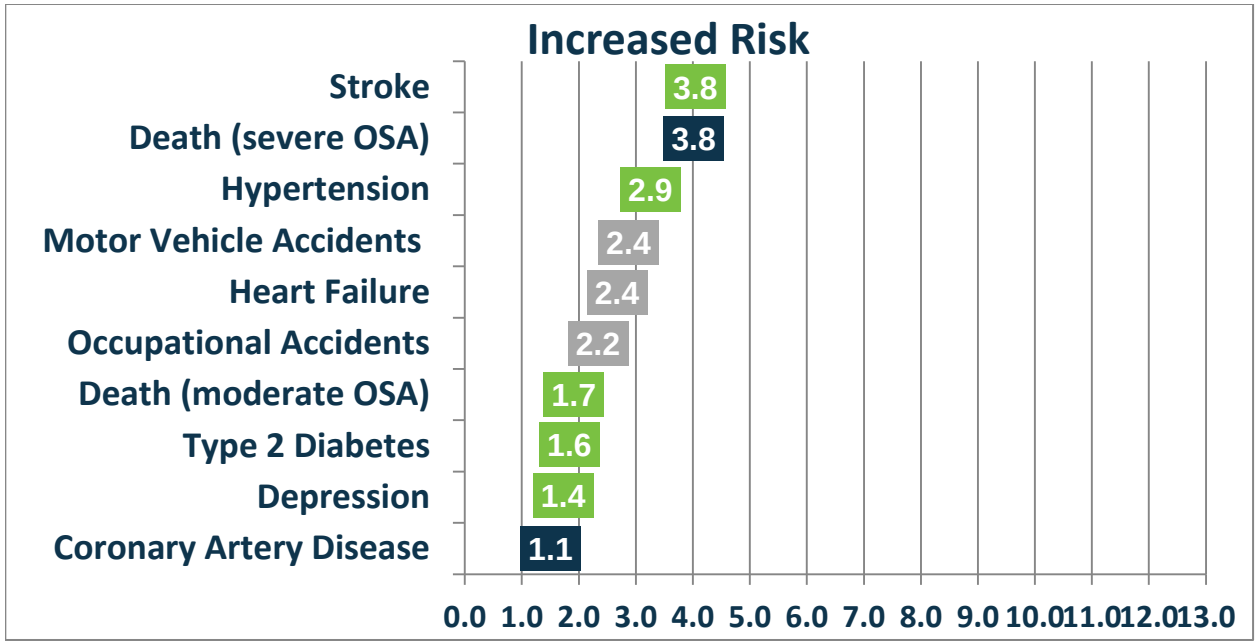
Marshall et al. Sleep 2008; 31:1079-1085

CLINICAL ASPECTS OF OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea is a risk factor for cardiovascular disease and stroke.

Culebras A. Overview of sleep and stroke. In: Culebras A, editor. Sleep, stroke and cardiovascular disease. Cambridge University Press, 2013, p 1.

RISK OF STROKE AND OTHER CONDITIONS IN SLEEP APNEA



OSA and Stroke

- Increasing sleep apnea severity is associated with greater stroke risk.
- Patients with severe sleep apnea have **three- to fourfold increased odds of stroke**.

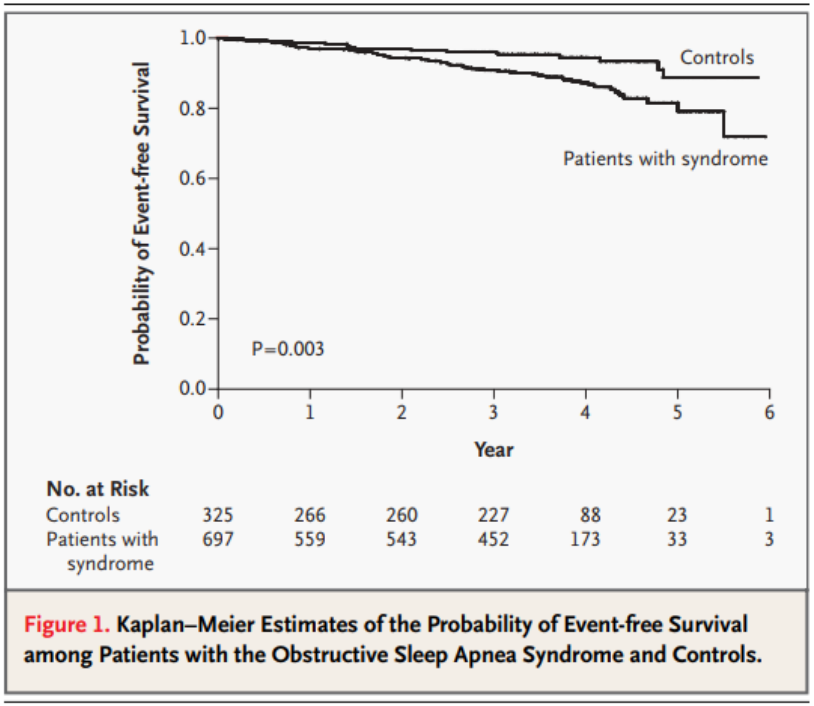


Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

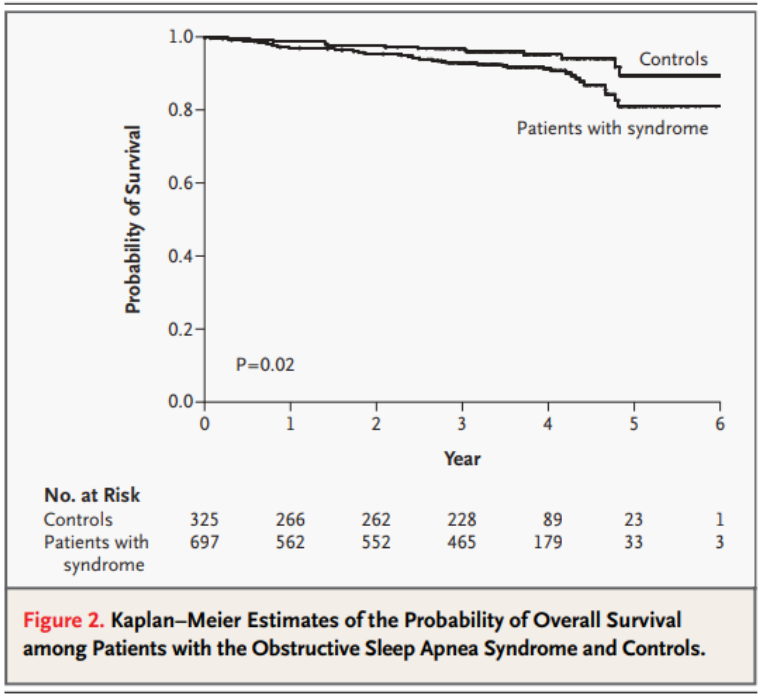
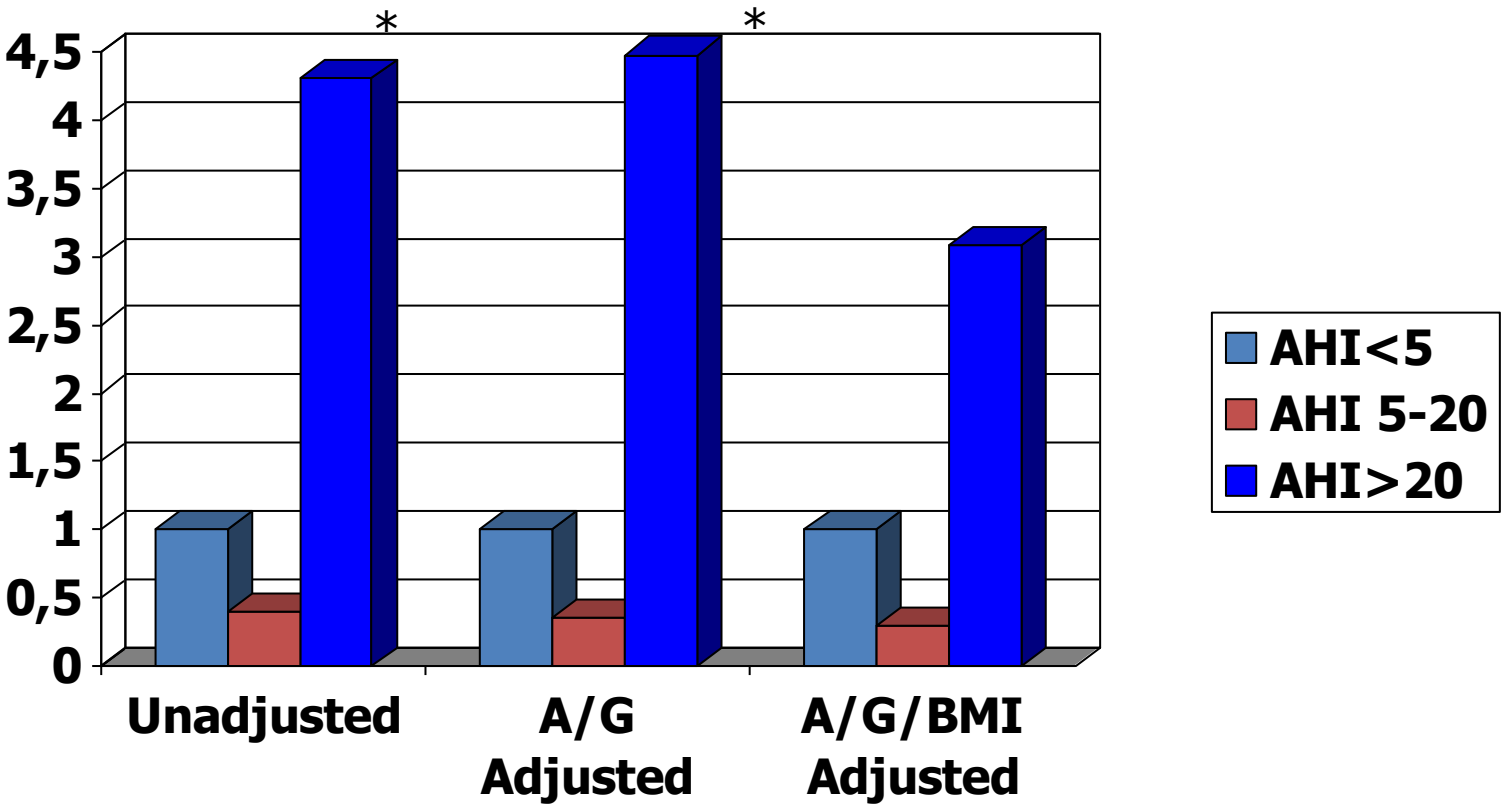


Figure 2. Kaplan–Meier Estimates of the Probability of Overall Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

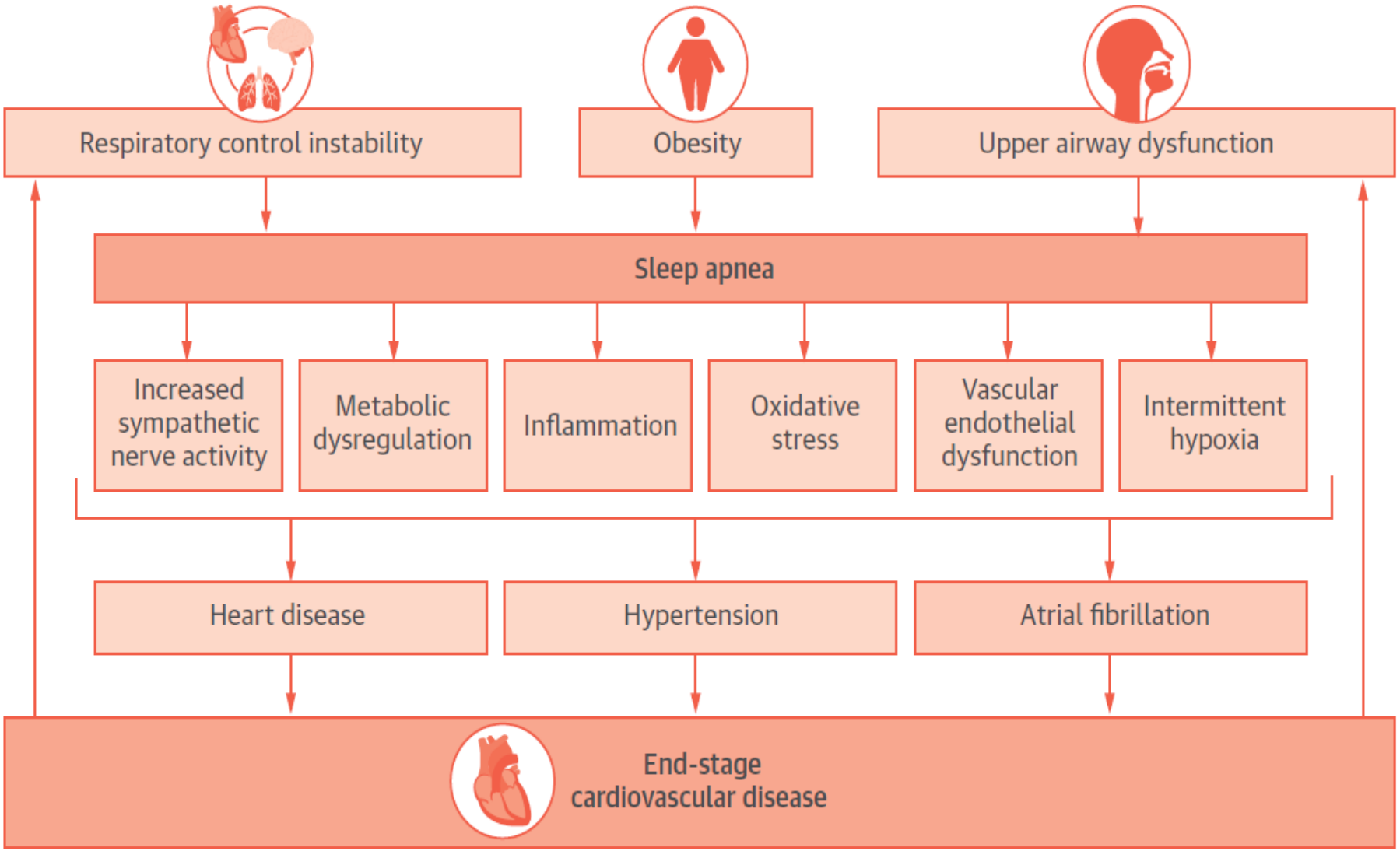
Bassetti CL et al., Stroke 2006; 37: 967–972.
Yaggi HK et al., N Engl J Med 2005;353: 2034–2041.
Redline S et al., Am J Respir Crit Care Med 2010; 182: 269–277.

OSA and Stroke



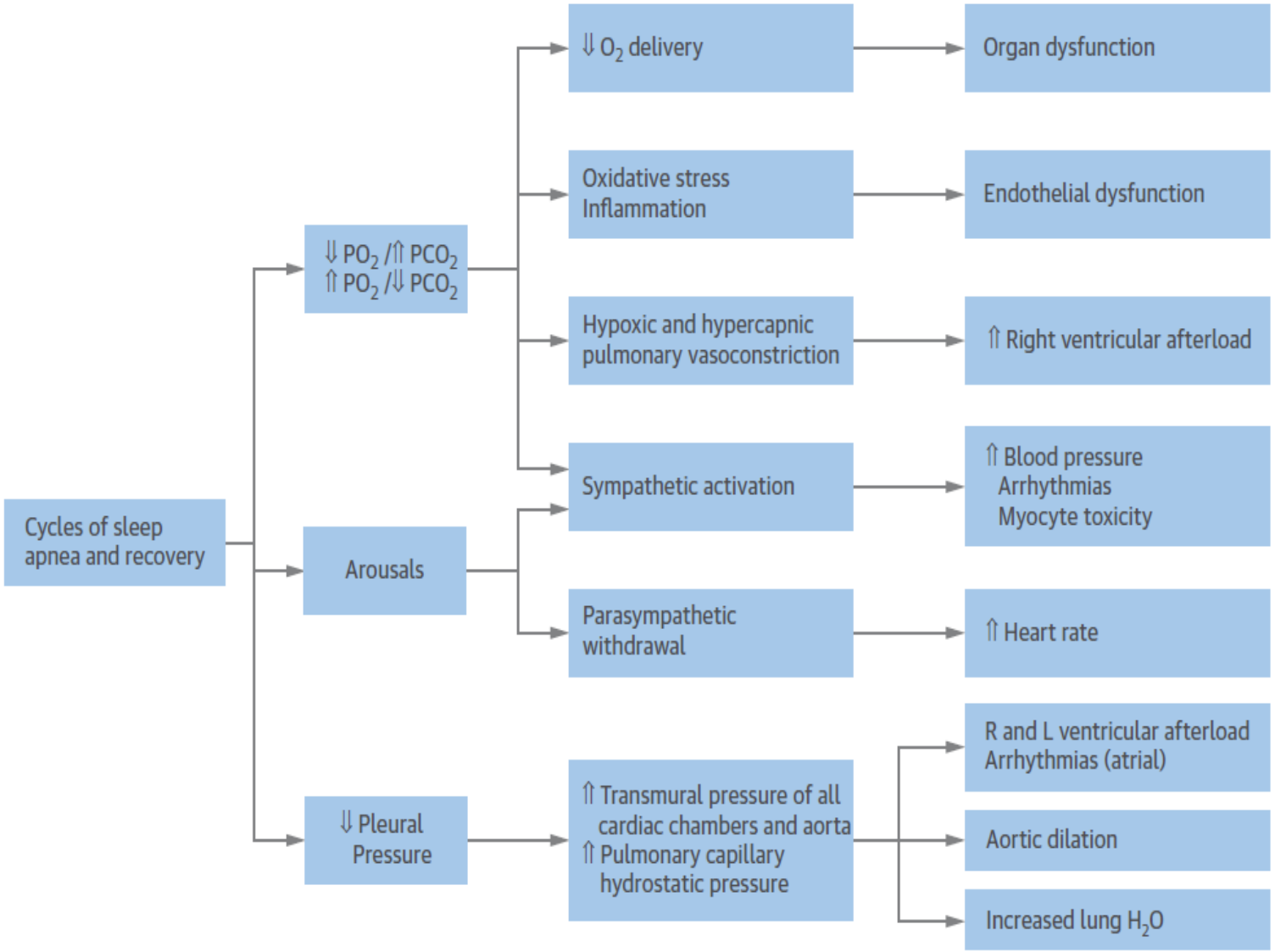
Arzt, et al., AJRCCM 2005; 172:1447.

CENTRAL ILLUSTRATION **Potential Etiological Risk Factors for Sleep Apnea and the Downstream Consequences**



Javaheri, S. et al. J Am Coll Cardiol. 2017;69(7):841-58.

FIGURE 4 Pathophysiological Consequences of Sleep Apnea and Hypopnea



Javaheri, S. et al. J Am Coll Cardiol. 2017;69(7):841-58.

Consequences: Cardiovascular

- Cerebrovascular disease
- Systemic hypertension
- Cardiac arrhythmias
- Cardiovascular disease
  - Myocardial ischemia
  - Congestive heart failure

SLEEP APNEA AND ATRIAL FIBRILLATION

- SA is more prevalent in patients with AF than in high-risk patients with multiple other cardiovascular diseases (49% versus 32%, P=0.0004).
  - **Gami AS et al. Circulation. 2004;110:364**

- SA is more frequent in patients with permanent atrial fibrillation than in age-matched community dwelling subjects (81.6% SA versus 60% control, p=0.03)
  - **Braga B et al. Sleep Med. 2009;10:212**

SLEEP APNEA AND ATRIAL FIBRILLATION

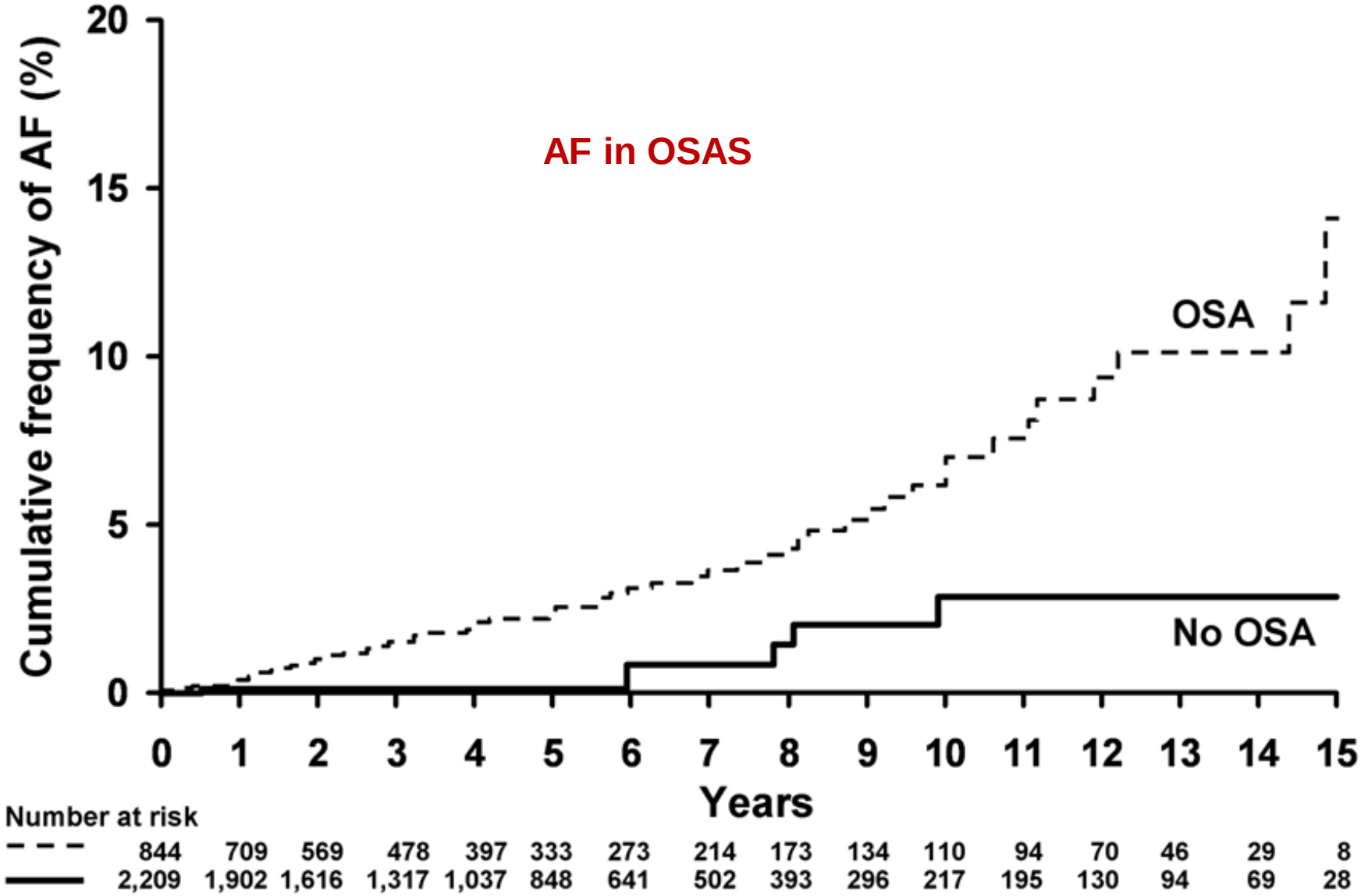
- Obesity and the magnitude of nocturnal oxygen desaturation are independent risk factors for AF in individuals <65 years of age.

  Gami AS. Sleep apnea and atrial fibrillation. In: Culebras A, editor. Sleep, stroke and cardiovascular disease. Cambridge University Press, 2013, p 81.

- OSA is a univariate predictor of AF [hazard ratio 2.18, (95% CI, 1.34 to 3.54)]

  Gami AS. J Am Coll Cardiol. 2007;49:565

AF in OSAS



Gami AS et al. J Am Coll Cardiol. 2007;49:565-71.

OSA and Atrial Fibrillation

- Atrial fibrillation is more common in subjects with sleep-disordered breathing : **4.8 versus 0.9%** (p = 0.003).
- Compared with those without sleep-disordered breathing and adjusting for age, sex, body mass index, and prevalent coronary heart disease, individuals with **sleep-disordered breathing had four times the odds of atrial fibrillation**

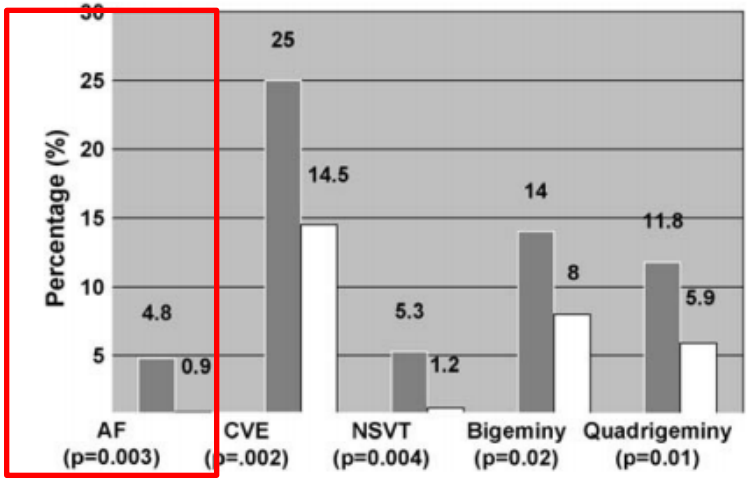


Figure 1. Arrhythmia prevalence (%) according to sleep-disordered breathing (SDB) status. *Shaded bars,* SDB; *open bars,* non-SDB. AF, atrial fibrillation; CVE, complex ventricular ectopy; NSVT, nonsustained ventricular tachycardia. n = 228 with SDB and n = 338 without SDB.

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.

Mehra R et al., Am J Respir Crit Care Med 2006;173:910–916

Prevalence OSAS

Table 1. Prevalence of obstructive sleep apnea in cardiovascular conditions[5,6]

Condition	*Prevalence (%)*
Stroke	43–91
Hypertension	30–83
End-stage kidney disease	40–60
Ischemic heart disease	30–58
Heart failure	12–53
Atrial fibrillation	49
Hypertrophic cardiomyopathy	40

Gonzaga C et al., J Hum Hypertens 2015;29:705–712.

TABLE 1. **History and Physical Examination Findings That Should Raise Suspicion for Obstructive Sleep Apnea**

History	Disruptive snoring
	Witnessed apnea or snorts
	Gasping/choking while sleeping
	Excessive daytime sleepiness
	Difficulty with concentration or short-term memory loss
	Excessive nocturia
	Difficulty with sleep maintenance
	Restless/unrefreshing sleep
	Decreased libido
	Morning headaches
	Irritability
Physical examination	Obese
	Large neck (>42 cm in men, >37 cm in women)[5]
	Retrognathia or micrognathia
	Crowded airway
	Enlarged tonsils
	High-arched hard palate
	Nasal deformities/septal deviation
Comorbid conditions	Resistant hypertension
	Recurrent atrial fibrillation
	Stroke
	Myocardial infarction
	Pulmonary hypertension
	Chronic heart failure

Adapted from *J Clin Sleep Med*,[6] with permission.

OSA and arterial hypertension

- OSA is well established as a risk factor for hypertension, especially in the elderly population.
- Wisconsin Sleep Cohort Study : the risk of developing hypertension was strongly related to the underlying severity of OSA

TABLE 3. ADJUSTED ODDS RATIOS FOR HYPERTENSION AT A FOLLOW-UP SLEEP STUDY, ACCORDING TO THE APNEA–HYPOPNEA INDEX AT BASE LINE.*

BASE-LINE APNEA–HYPOPNEA INDEX	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE
	odds ratio (95% confidence interval)			
0 events/hr†	1.0	1.0	1.0	1.0
0.1–4.9 events/hr	1.66 (1.35–2.03)	1.65 (1.33–2.04)	1.42 (1.14–1.78)	1.42 (1.13–1.78)
5.0–14.9 events/hr	2.74 (1.82–4.12)	2.71 (1.78–4.14)	2.03 (1.29–3.19)	2.03 (1.29–3.17)
≥15.0 events/hr	4.54 (2.46–8.36)	4.47 (2.37–8.43)	2.89 (1.47–5.69)	2.89 (1.46–5.64)
P for trend‡	<0.001	<0.001	0.002	0.002

Peppard PE et al., N Engl J Med 2000; 342: 1378–1384.

OSA and metabolic disorders

- **OSA and obesity commonly coexist** and share multiple patho-physiological mechanisms and **complications** including **glucose metabolism disturbance, dyslipidemia and systemic inflammation**.
- The relationship between OSA and dyslipidemia remains controversial.
- It is not yet definitely concluded whether the reduced sleep time could be considered a risk factor for death, although **the relationship between the reduced sleep time and metabolic and/or inflammatory disorders is increasingly well established.**

Togeiro SM et al., Obesity (Silver Spring) 2013; 21: 847–851.
Ip MS et al., Am J Respir Crit Care Med 2002;165: 670–676.

OSA and metabolic disorders

- The Sleep AHEAD study revealed a high prevalence of OSA in obese diabetic patients, that is, 86,6% of analyzed subjects.

CONCLUSIONS — The most remarkable finding of this study is the exceedingly high prevalence of undiagnosed OSA (86.6%) among obese patients with type 2 diabetes.

CONCLUSIONS — Physicians treating obese patients with type 2 diabetes should consider the possibility of OSA, even in the absence of symptoms, especially in individuals with higher waist circumference and BMI.

Foster GD et al., Diabetes Care 2009; 32: 1017–1019.

- The Sleep Heart Health Study showed that hypoxemia-related sleep disorder was an independent factor for development of insulin resistance and glucose intolerance in the studied population.

DISCUSSION

The results of this cross-sectional study in a large sample of community-dwelling subjects demonstrate that sleep-disordered breathing is independently associated with glucose intolerance and insulin resistance.

Punjabi NM et al., Am J Epidemiol 2004; 160: 521–530.

OSA and coronary atherosclerosis

- OSA patients exhibit metabolic, endothelial and neurohumoral disturbances triggered primarily by intermittent hypoxia, resulting in sympathetic overstimulation.

Association between chronic CAD and OSA

Multivariate analysis for the association between OSA severity measured by AHI quartile and CAC.

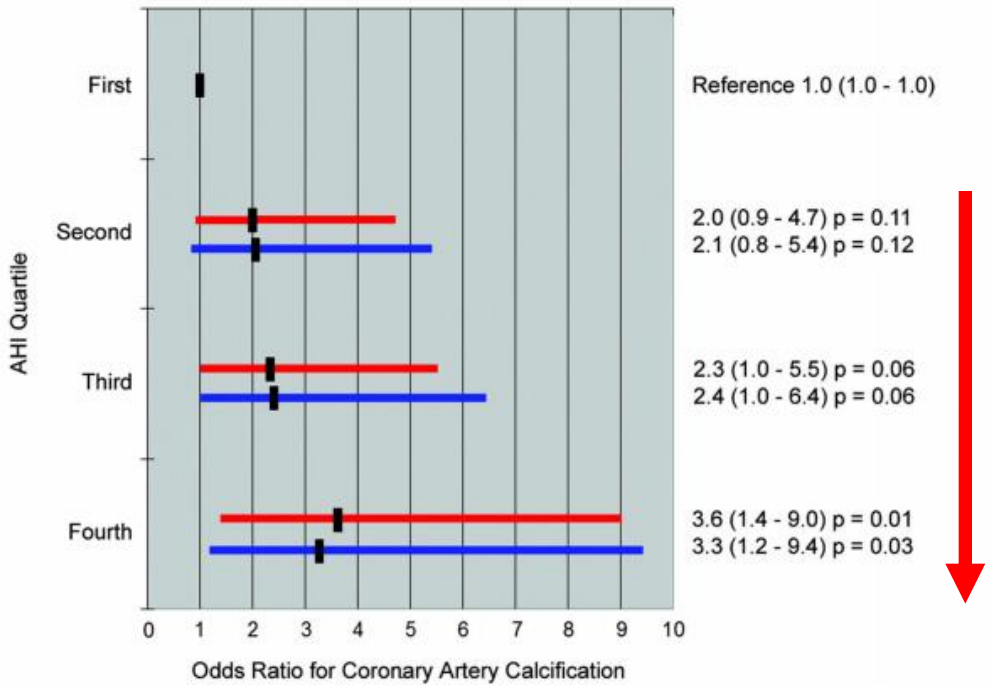


Figure 1.
Multivariate Analysis for the Association Between Obstructive Sleep Apnea Severity Measured by AHI Quartile and Coronary Artery Calcification
■ Adjusted for age and gender
■ Adjusted for age, gender and traditional risk factors
Traditional risk factors = diabetes mellitus, hypercholesterolemia, active smoking, hypertension, and body mass index

Sorajja D et al., Chest 2008; 133: 927–933.

OSA and Heart Failure

- OSA is present in 10–35% (probably underestimated) of patients with heart failure leading to increased nocturnal sympathetic activation with consequent elevation of blood pressure, which contributes to left ventricular dysfunction and especially left ventricular hypertrophy.

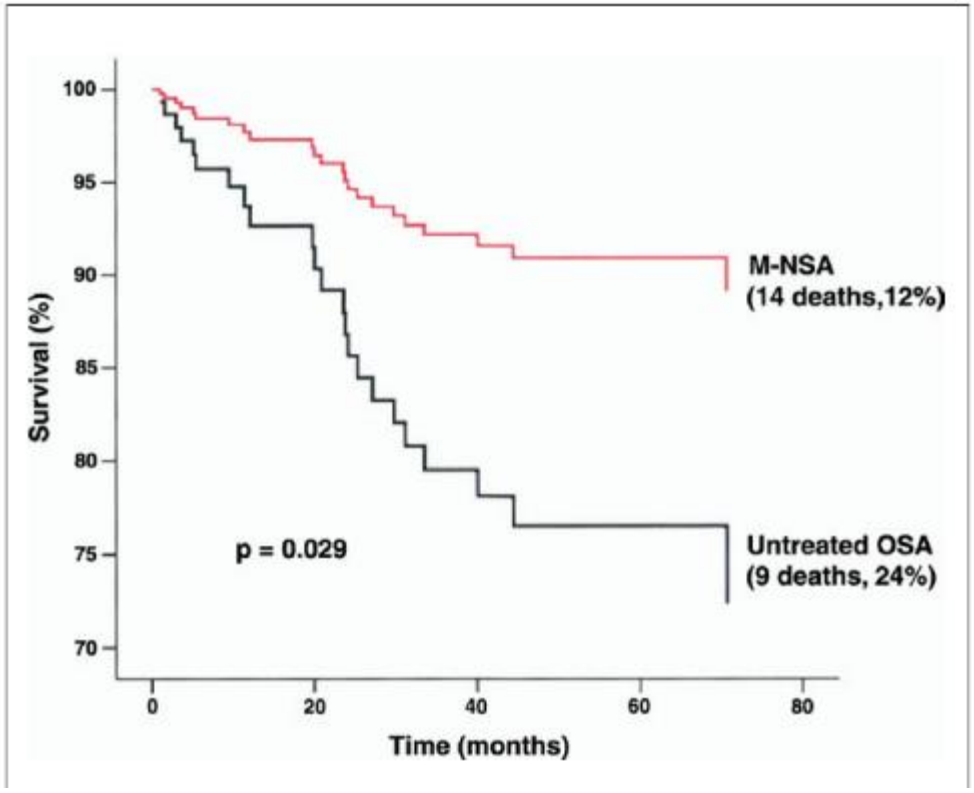


Figure 2 **Multivariable Cox Proportional Hazards Survival Plots for Patients With M-NSA Versus Untreated OSA**

Multivariable Cox proportional hazards plots showing worse survival of heart failure patients with untreated obstructive sleep apnea (OSA) than in those with mild to no sleep apnea (M-NSA) (hazard ratio = 2.81, p = 0.029) after adjusting for significant confounders (left ventricular ejection fraction, New York Heart Association functional class, and age per Table 3). The adjusted survival curves are shown at the average values of these confounders.

Wang H et al., J Am Coll Cardiol 2007; 49: 1625–1631.

OSA and bradycardias

Studies	Subjects	Outcomes/Prevalence
Tilkian *et al.*[45]	15	Marked sinus arrhythmia in14 patients
		Extreme sinus bradycardia in 6
		Asystole in 5
		Second-degree atrioventricular block in 2
		Ventricular arrhythmias--complex premature ventricular beats in 10
		Ventricular tachycardia in 2 patients
Guilleminault *et al.*[22]	400	Bradyarrhythmias in 18% of patients
		Sustained ventricular tachycardia in 2%
		Sinus arrest in 11%
		Second-degree atrioventricular block in 8%
		Frequent premature ventricular contractions in 19%
Flemons *et al.*[39]	263	Complex ventricular ectopy (including ventricular tachycardia) in 1.3% of patients
		Frequent ventricular premature beats (>30/h) in 2.6%
		Second-degree atrioventricular block in 1.3%
		Sinus arrest in 5.2% patients
Becker *et al.*[46]	239	Sinus arrest and atrioventricular (AV) block in 30% of patients
Mooe *et al.*[47]	121	Atrial fibrillation (AF) in 32% of patient with apnea–hypopnea index (AHI) >5 or =5 and in 18% patients with AHI <5
		Atrial fibrillation in 39% of patients with oxygen desaturation index (ODI) >5 or =5 and in 18% of patients with ODI <5
Javaheri *et al.*[48]	81	Atrial fibrillation in 32% of patients
Simantirakis *et al.*[50]	23	Rhythm disturbances in 48% of patients
Gami *et al.*[51]	524	OSA more prevalent in patients with AF (n = 151) than in high-risk patients with multiple other cardiovascular diseases
Porthan *et al.*[52]	115	Sleep apnea syndrome common in lone AF
Mehra *et al.*[18]	566	Atrial fibrillation in 4.8% of patients
		Nonsustained ventricular tachycardia in 5.3%
		Complex ventricular ectopy in 25.0% of patients

Ann Thorac Med. 2010 Jan-Mar; 5(1): 10–17

Can CPAP reverse bradyarrhythmias in patients with OSA?

J Clin Sleep Med. 2006 Oct 15;2(4):454-7.

Night-time bradyarrhythmia in a patient with mild obstructive sleep apnea syndrome is reversed with CPAP treatment.

Dziewas R[1], Imai T, Dittrich R, Humpert M, Hopmann B, Böntert M, Lüdemann P, Young P.

CONCLUSION: The data indicate that OSA syndrome predisposes to clinically significant cardiac rhythm disturbances that can be successfully controlled by nCPAP therapy.

Harbison J et al., Chest. 2000 Sep;118(3):591-5

Hence, CPAP treatment may not reverse long-term structural remodeling which triggers arrhythmia; however, it may decrease further progression of such events. Therefore, treatment of OSA with CPAP therapy should be considered as an adjunct to the medical therapy for arrhythmia and/or other related conditions and not as a sole treatment. Finally, it remains to be determined whether early screening of OSA in patients with arrhythmia and subsequent treatment administration is protective in terms of long-term cardiovascular morbidity and mortality.

Clinical Medicine Insights: Therapeutics, 2017 Vol9: 1–10

Further studies are needed!

Treatment of OSAS

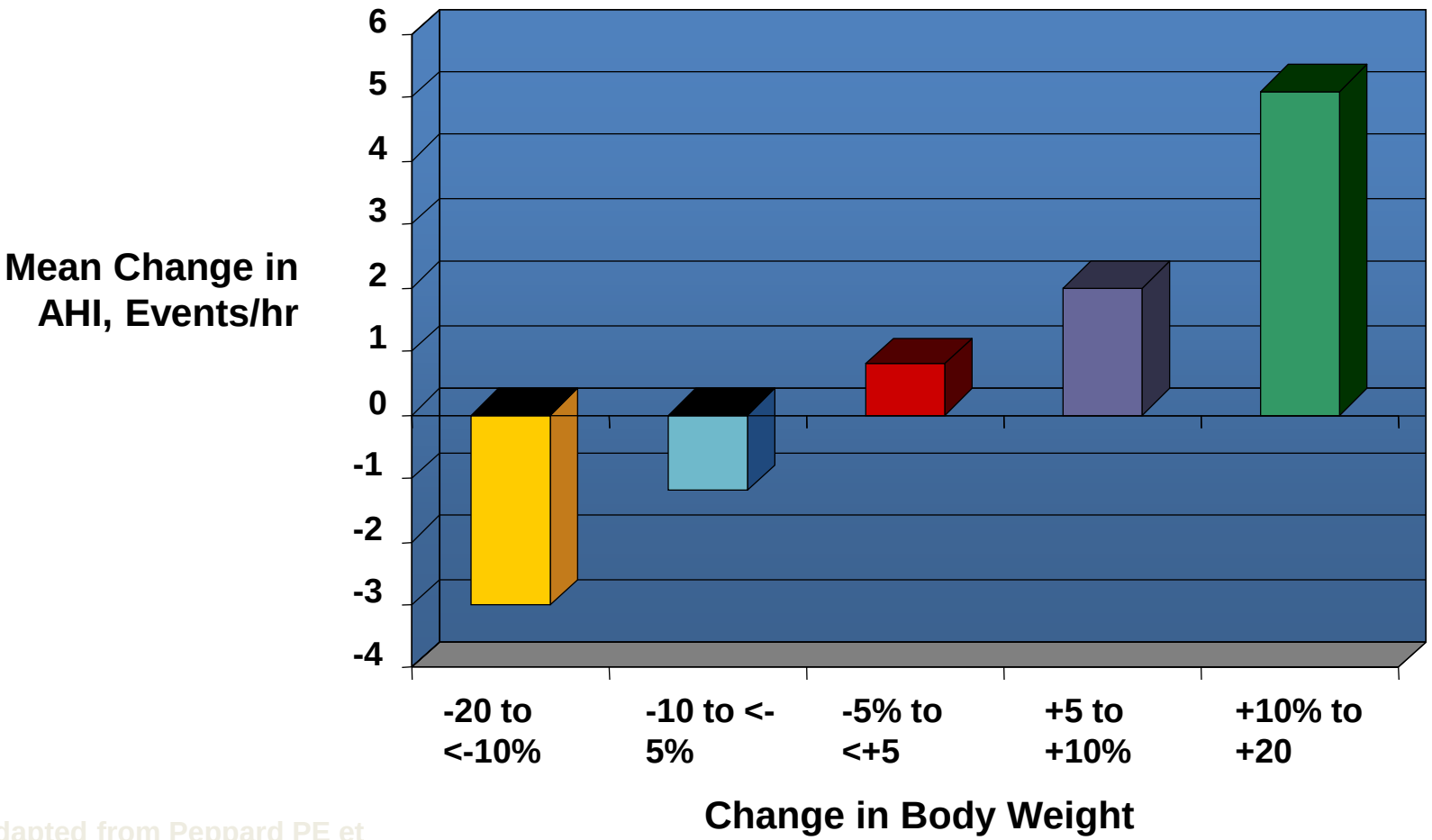
- Behavioral changes:
  - avoiding alcohol, caffeine before sleep
  - increased physical activity
  - Avoiding naps at unusual hours
  - discontinuation of sedating drugs
  - obesity control
  - postural changes

The gold-standard treatment of OSA is continuous positive airway pressure (CPAP)

Behavioral Interventions

- Encourage patients to:
  - Lose weight
  - Avoid alcohol and sedatives
  - Avoid sleep deprivation
  - Avoid supine sleep position
  - Stop smoking

Weight Loss and Sleep Apnea



Adapted from Peppard PE et al. JAMA 2000;284.

Sleep-Position Training

Cardiovascular effects of CPAP in patients with OSAS

- ↓systemic hypertension
- ↑LV systolic and diastolic function
- ↓LV end-diastolic diameter
- ↓pulmonary hypertension

Full face mask, side straps

Nasal pillow mask, ballcap-style straps

Nasal pillow mask, side straps

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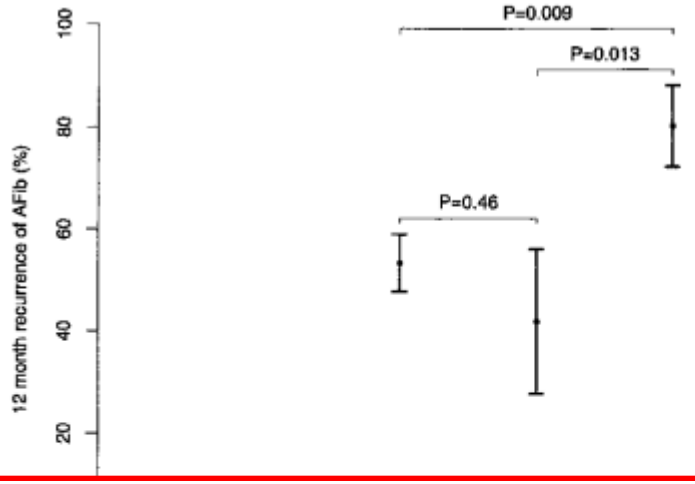
Kaneko Y et al., NEJM 2003;348:1233-41
Arias MA et al., Eur Heart J 2006;27:110613
Parra O et al., J Sleep Res 2015;24:47-53

Beneficial of treatment with CPAP

Obstructive Sleep Apnea and the Recurrence of Atrial Fibrillation

Kanagala, MD; Narayana S. Murali, MD; Paul A. Friedman, MD; Naser M. Ammash, M
Bernard J. Gersh, MB ChB, DPhil; Karla V. Ballman, PhD;
Abu S.M. Shamsuzzaman, MD, PhD; Virend K. Somers, MD, PhD



Conclusions—Patients with untreated OSA have a higher recurrence of AF after cardioversion than patients without a polysomnographic diagnosis of sleep apnea. Appropriate treatment with CPAP in OSA patients is associated with lower recurrence of AF. **(*Circulation*. 2003;107:2589-2594.)**

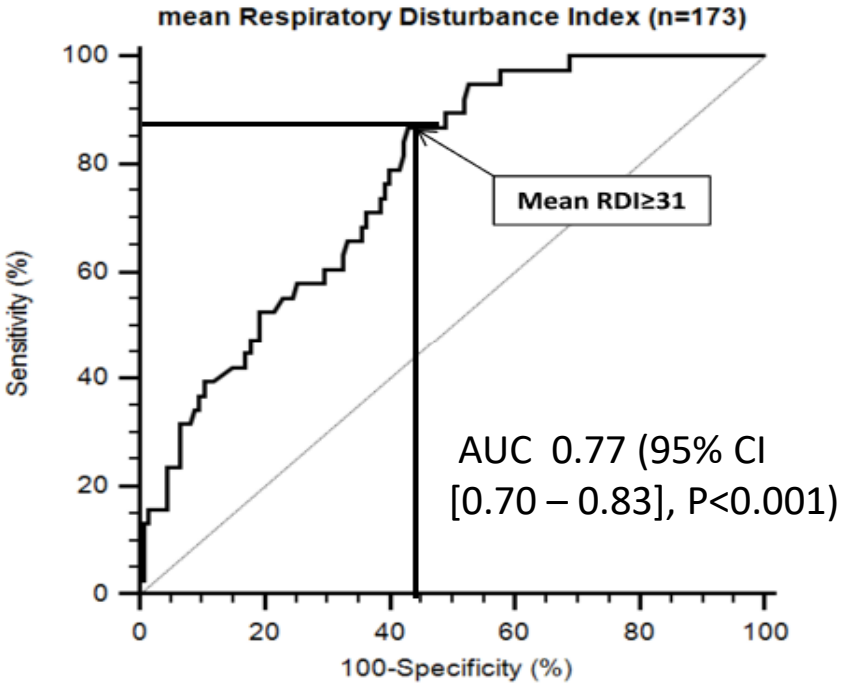
Figure 1. Recurrence of AF at 12 months comparing patients who did not have sleep studies (controls) with treated OSA patients and with untreated (including noncompliant) OSA patients (mean±SD).

Kanagala R et al., Circulation. 2003;107:2589-2594

OSAS E DIAGNOSTICA DEVICES IMPIANTABILI

The Implantable Cardioverter Defibrillator-computed Respiratory Disturbance Index accurately identifies severe sleep apnea: the DASAP-HF study.

Pts 265



Optimal cutoff of the "RDI value" to identify severe Sleep Apnea:

31 events/h

Sensitivity: 87% (95% CI 72%-96%)

Specificity: 56% (95% CI 48%-66%)

CONCLUSION: The RDI accurately identified severe SA and demonstrated good agreement with AHI. Therefore, it may serve as an efficient tool for screening patients at risk of SA.

D'Onofrio A et al., Heart Rhythm. 2018 Feb;15(2):211-217

Pacemaker-detected severe sleep apnea predicts new-onset atrial fibrillation

Pts 160

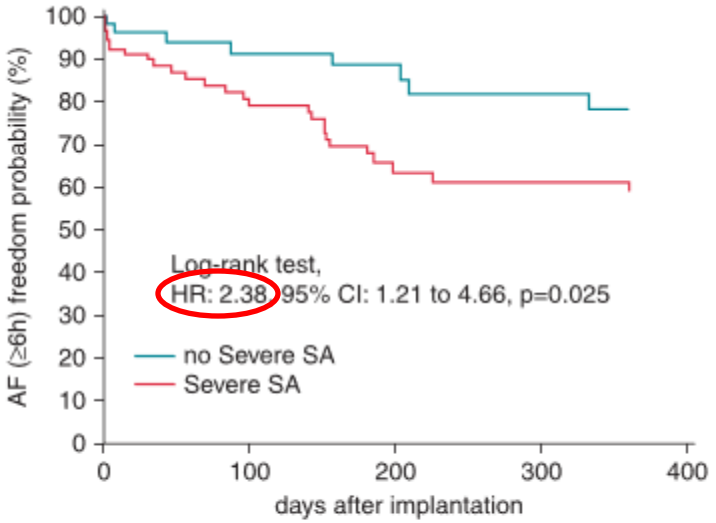


Figure 4 Kaplan–Meier estimates of time to AF (≥6 h in a day) over the entire follow-up period, stratified by presence or absence of severe SA at baseline.

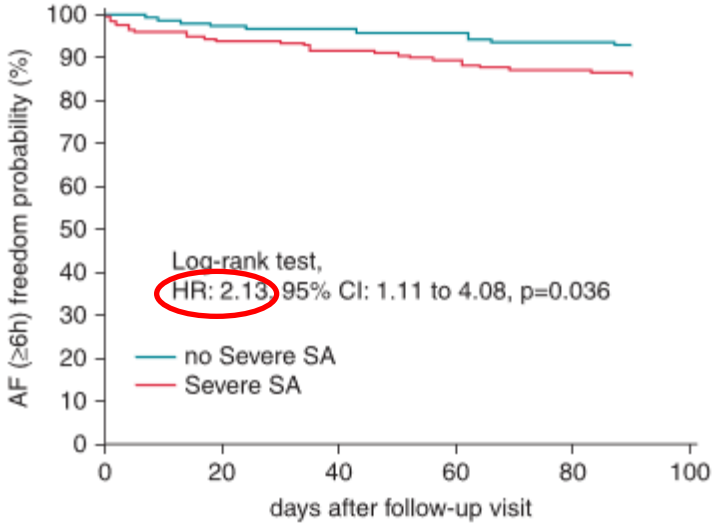


Figure 5 Kaplan–Meier estimates of time to AF (≥6 h in a day) over the 3-month period after routine follow-up visit, stratified by presence or absence of severe SA diagnosed during the week before follow-up visit.

Conclusions In pacemaker patients, device-diagnosed severe SA was independently associated with a higher risk of AF (≥6 h/day) and new-onset AF. In particular, severe SA on follow-up data review identified patients who were ~2-fold more likely to experience an AF episode in the next 3 months.

Mazza A et al., Europace 2017 Dec 1;19(12):1937-1943

GREAT INTEREST !!

- OSA is a very common disease and it's often underdiagnosed
- There is evidence of a positive relationship between OSAS and hypertension, CAD, AF, stroke and HF
- Definitive diagnosis of OSA requires a polysomnography
- The gold-standard treatment is continuous positive airway pressure (CPAP)
- CPAP therapy might reduce MACE and stroke among subjects with CPAP time exceeding 4 h/night
- Advanced PM algorithms are a promising tools to identify OSA outside the clinic or at home