Obstructive Sleep Apnea and Cardiovascular Disease

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PCCSM

Pulmonary, Critical Care, and Sleep Medicine

Yale CENTERS FOR SLEEP MEDICINE

Incidence of and risk factors for nodding off at scientific sessions

Kenneth Rockwood, David B. Hogan, Christopher J. Patterson; for the Nodding at Presentations (NAP) Investigators

Journal of the Canadian Medical Association, 2006

Table 1: Risk factors for nodding off at lectures

Factor	Odds ratio (and 95% CI)
Environmental	
Dim lighting	1.6 (0.8–2.5)
Warm room temperature	1.4 (0.9–1.6)
Comfortable seating	1.0 (0.7–1.3)
Audiovisual	
Poor slides	1.8 (1.3–2.0)
Failure to speak into microphone	1.7 (1.3–2.1)
Circadian	
Early morning	1.3 (0.9–1.8)
Post prandial	1.7 (0.9–2.3)
Speaker-related	
Monotonous tone	6.8 (5.4–8.0)
Tweed jacket	2.1 (1.7–3.0)
Losing place in lecture	2.0 (1.5–2.6)

Note: CI = confidence interval.

Sleep Apnea and Cardiovascular Disease (CVD)

- Evidence linking sleep apnea to CVD
- Mechanisms of CVD in sleep apnea
- Strategies examining impact treating sleep apnea on CVD

Sleep Apnea and Cardiovascular Disease (CVD)

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Standard Polysomnography

- EEG, EOG, EMG → Presence/stage of sleep
- EKG → Cardiac rate/rhythm
- Airflow → Apnea/hypopnea
- Chest/abd, bands → Respiratory effort
- Pulse oximetry → Arterial oxygen sat
- Left/right leg EMG → Leg movements (PLMs)

The Sleep Cycle

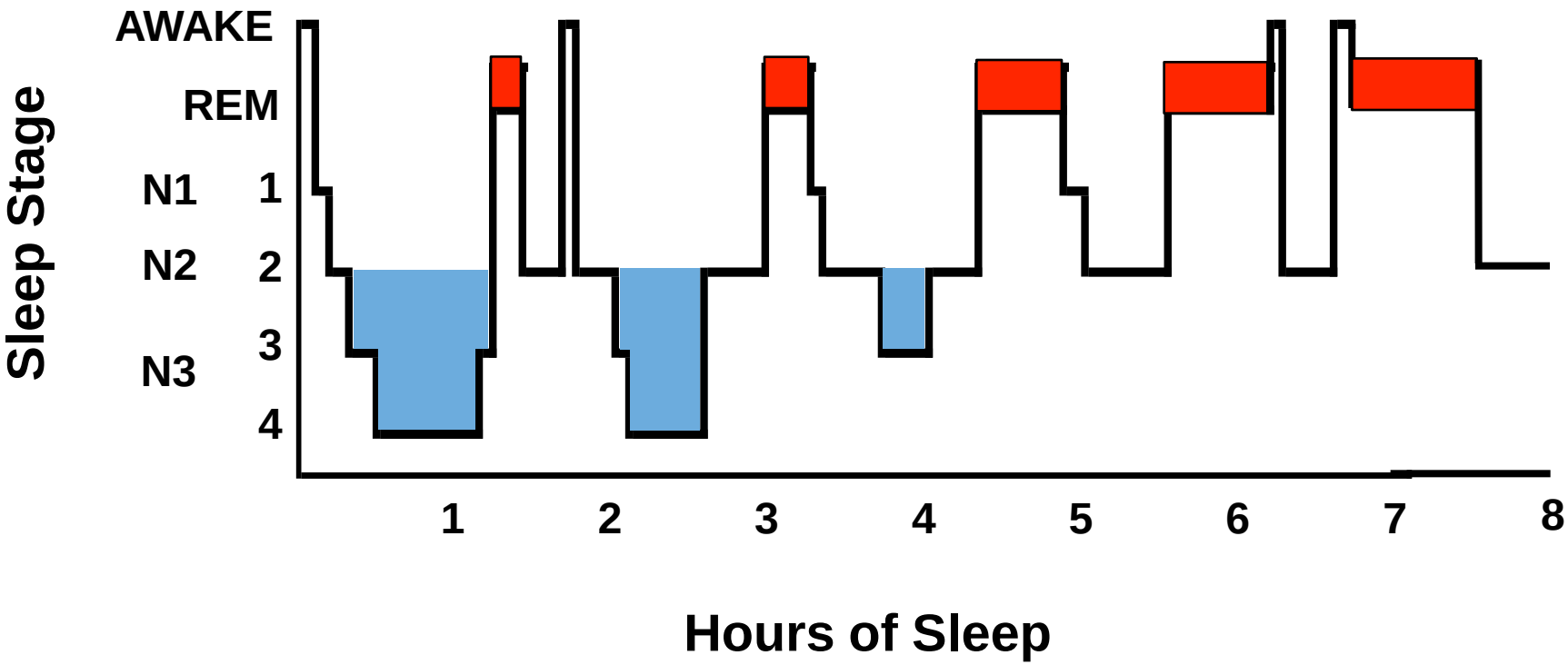
Alternating states of sleep that occur over an ~8-hours

- **NREM:** Non-rapid Eye Movement; Stages N1-N3 or 1-4; ~80% of night

Deep Slow Wave Sleep (N3 or Stages 3&4)

- **REM:** Rapid Eye Movement; Dreams occur; ~20% of night

REM Sleep



Physiology of Normal Sleep

- **NREM Sleep (80%)**
  - ↓ Sympathetic nerve activity, HR, and BP ('nocturnal dipping')
  - ↓ Cerebral blood flow
  - Regular breathing pattern
  - ↓ Minute Ventilation
  - ↓ Muscle tone
- **REM Sleep (20%)**
  - Sympathetic nerve activity, HR, and BP similar to awake
  - ↑ Cerebral blood flow
  - Irregular breathing pattern
  - Breathing dependent on diaphragm
  - Absent muscle tone

Chokroverty; Sleep Disorders Medicine 1999

Definitions and Severity Criteria

- Apnea: Cessation of airflow > 10 sec (valid measure of breathing)
- Hypopnea: Decrease in airflow by 30%, associated with a >4% oxygen desaturation (best inter/intrascorer reliability)
- Severity Criteria:
  - Mild: 5-15 events per hour
  - Moderate: >15-30 events per hour
  - Severe: >30 events per hour

AASM Task Force; Sleep 1999

Prevalence in Middle Aged Adults

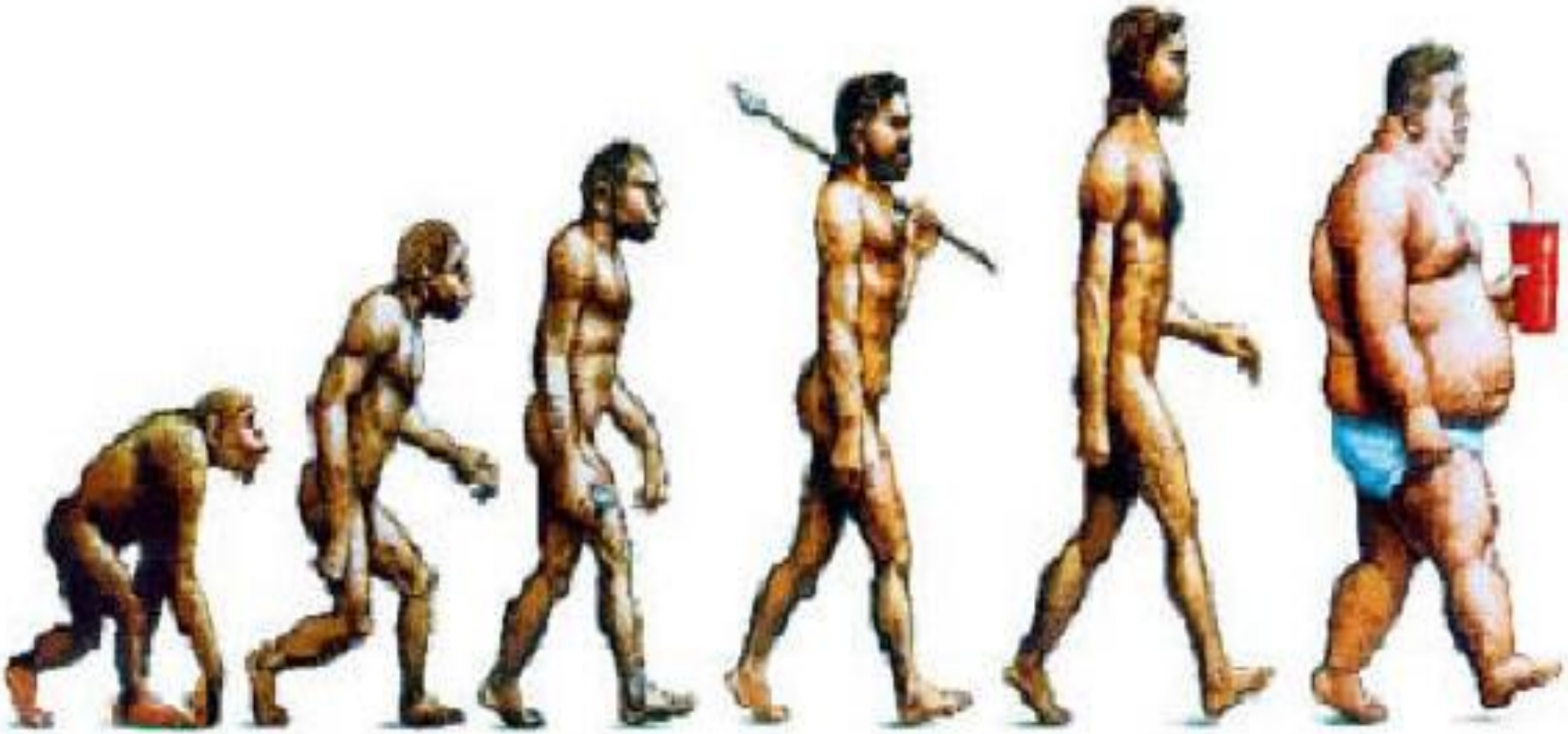
	% Men	% Women
$AHI \geq 5$	24	9
AHI ≥ 5 + daytime somnolence	4	2

AHI = Apnea Hypopnea Index

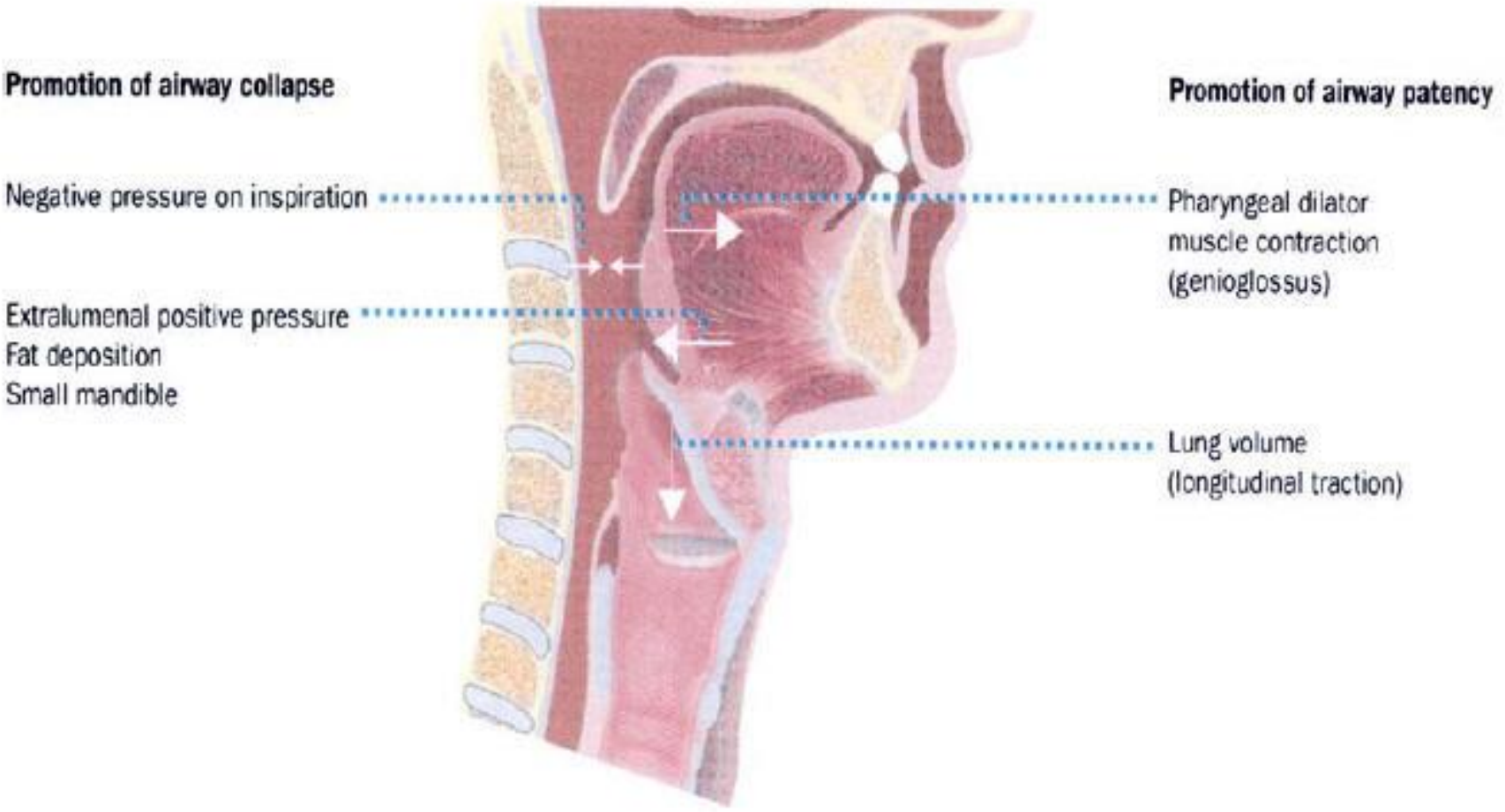
Young; NEJM 1993

Risk Factors for Sleep Apnea

- Male gender
- Increasing age
- Post-menopausal state
- Hypothyroidism
- Alcohol/sedating medications
- Obstructive lesions of the upper airway
- Craniofacial abnormalities (e.g., retrognathia)
- Obesity



Pathogenesis of Obstructive Sleep Apnea

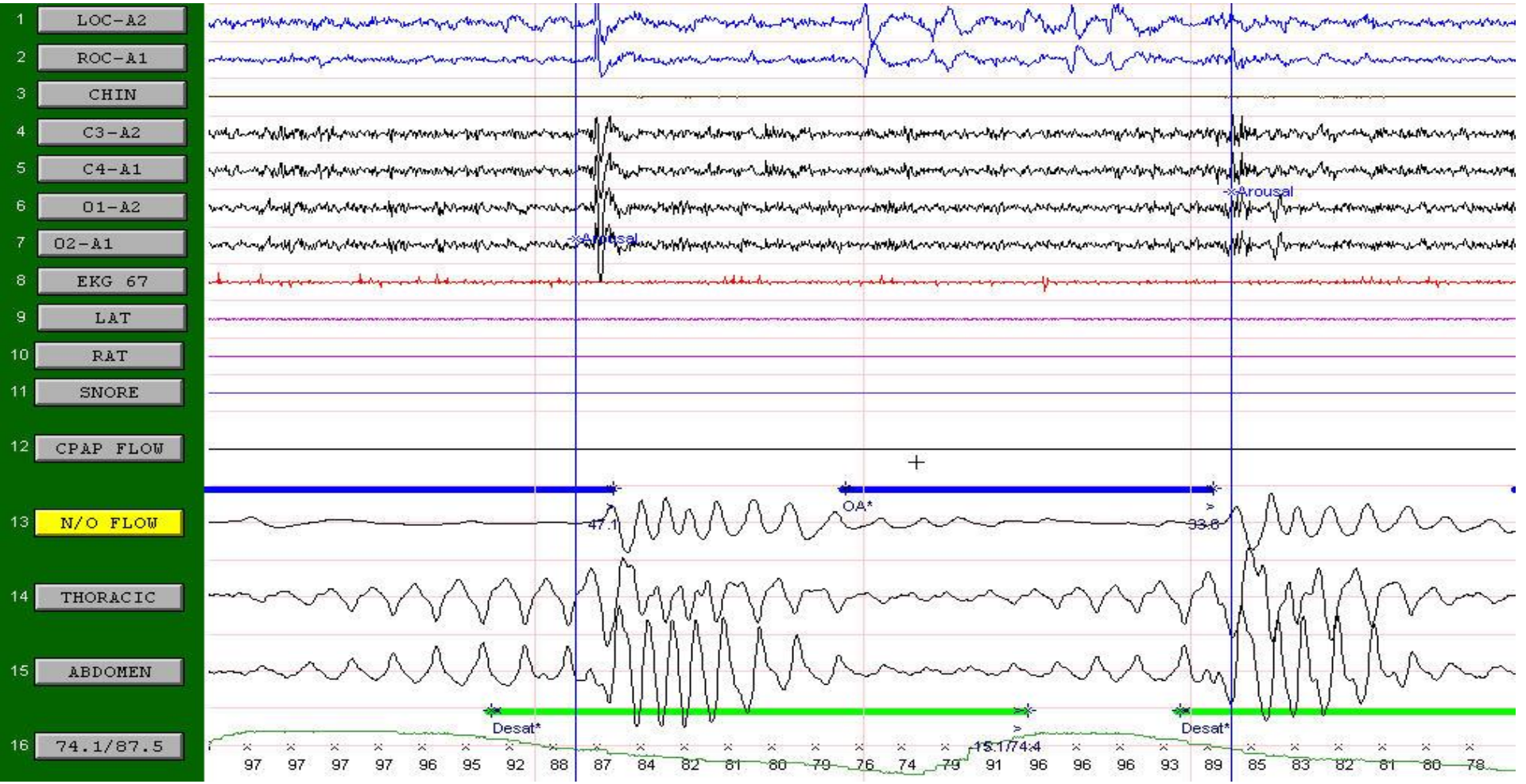


White, AJRCCM, 2005

Common Symptoms

- Loud snoring
- Excessive daytime sleepiness
- Morning headaches (cerebral vasodilation)
- Neuropsychiatric and cognitive symptoms
  - Depression/emotional instability
  - Short-term memory loss
  - Impaired concentration
- Breathing pauses (*bed partner history is key*)

Obstructive Sleep Apnea (OSA)



Mechanisms:

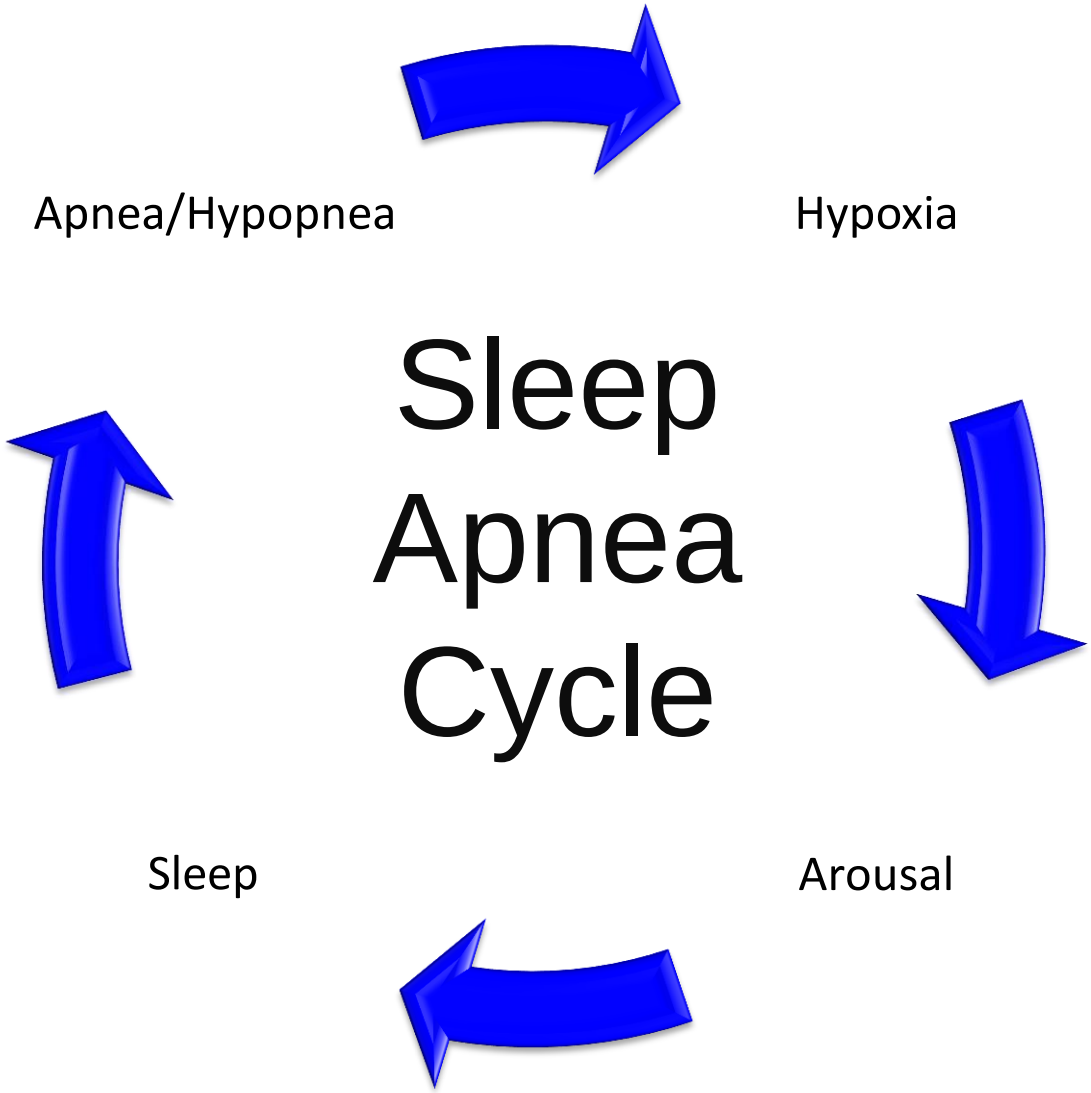
- Upper airway obstruction, decreased muscle tone, fat deposition, small mandible
- Negative inspiratory pressure

Description:

- Respiratory effort present
- Positional component
- Worsen in deeper NREM, REM
- Arousal at termination of apnea

Result:

- Intermittent (cyclical hypoxemia)
- Arousal sympathetic activation
- Impaired Sleep architecture
- Mechanical Load


Apnea/Hypopnea
Hypoxia
Sleep Apnea Cycle
Sleep
Arousal

Sleep Apnea and Diurnal Hypertension

Apnea Hypopnea Index	Adjusted* Odds Ratio
0	[1.00]
1-4	1.42
5-14	2.03
≥15	2.89

*adjusted for age, gender, BMI, waist circumference, alcohol, tobacco use, and baseline hypertension.

P for trend=0.002

Peppard, NEJM, 2000

Sleep Heart Health Study Cross-Sectional Results

- Large community study
- N = 6,424
- Among OSA
  - ↑ Prevalence stroke
  - ↑ Cardiovascular disease

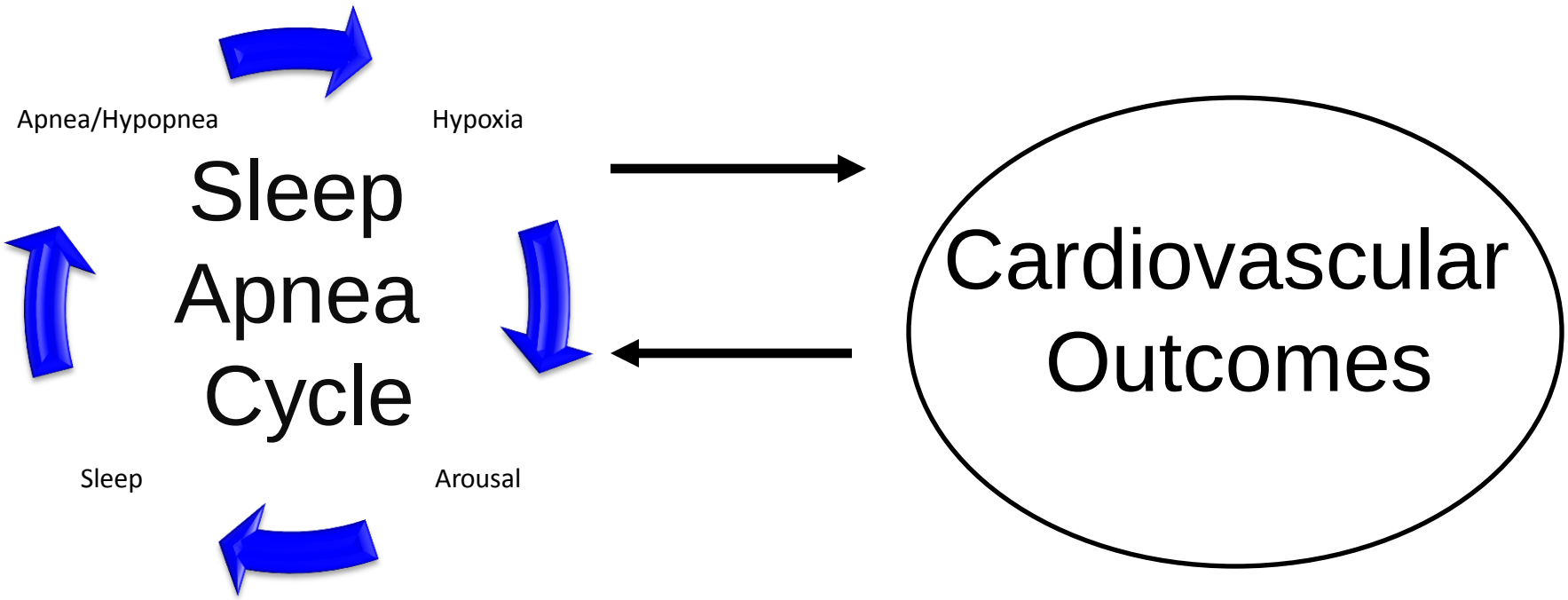
ADJUSTED* RELATIVE ODDS (95% CONFIDENCE INTERVAL) OF PREVALENT CORONARY HEART DISEASE, HEART FAILURE, OR STROKE, ACCORDING TO QUARTILE OF THE APNEA–HYPOPNEA INDEX

	Quartile				
	I	II	III	IV	p Value†
Coronary heart disease					
Full model	1.0	1.01 (0.77–1.32)	1.20 (0.92–1.57)	1.22 (0.93–1.59)	0.08
Parsimonious model	1.0	0.92 (0.71–1.20)	1.20 (0.93–1.54)	1.27 (0.99–1.62)	0.004
Stroke					
Full model	1.0	1.24 (0.76–2.01)	1.38 (0.86–2.83)	1.55 (0.96–2.50)	0.06
Parsimonious model	1.0	1.15 (0.72–1.83)	1.42 (0.91–2.21)	1.58 (1.02–2.46)	0.03

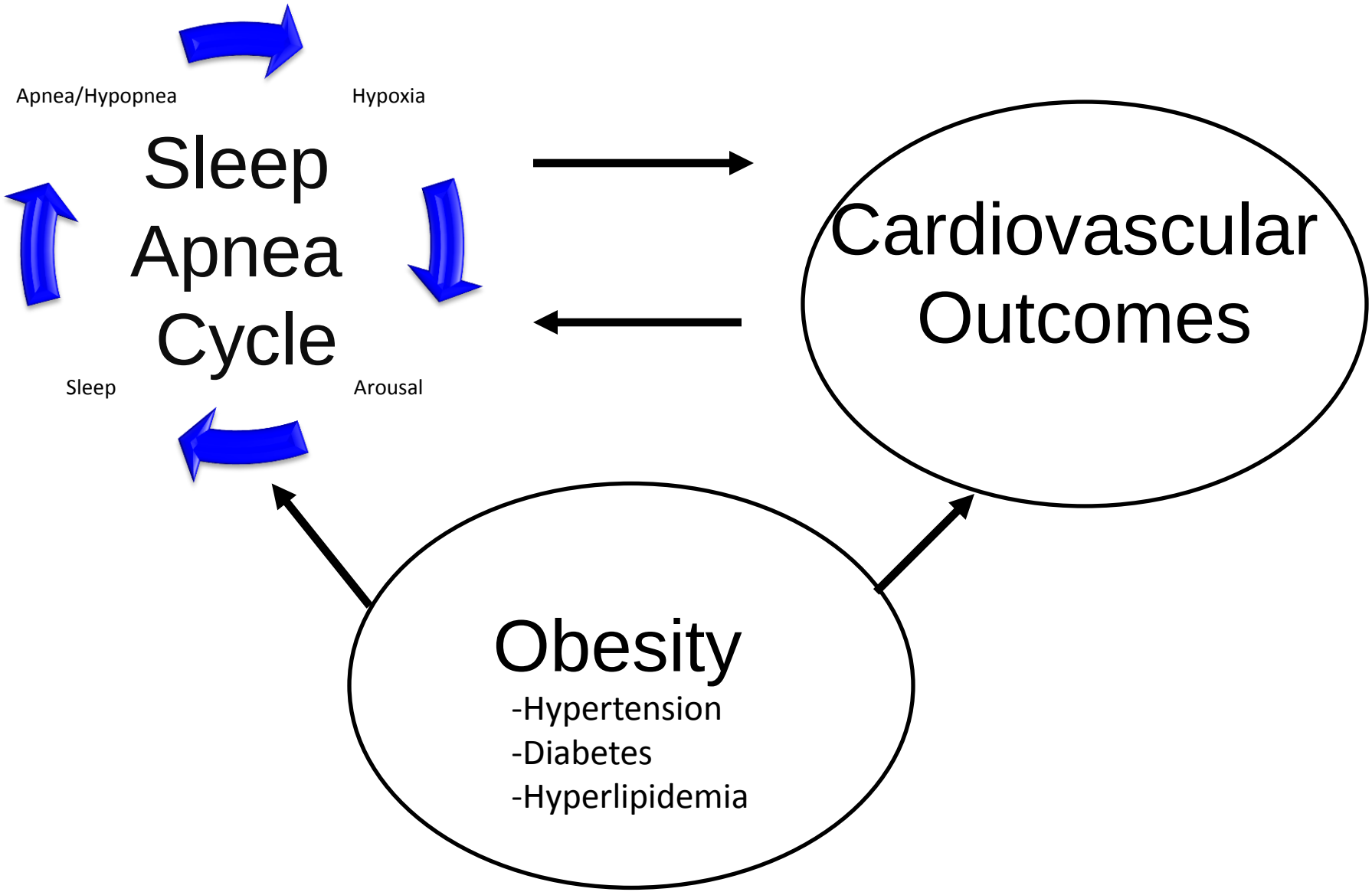
Full model: age, race, sex, smoking, diabetes, HTN, antihypertensive use, SBP, BMI, cholesterol.
Parsimonious model: took out antihypertensive use

Shahar, AJRCCM, 2001

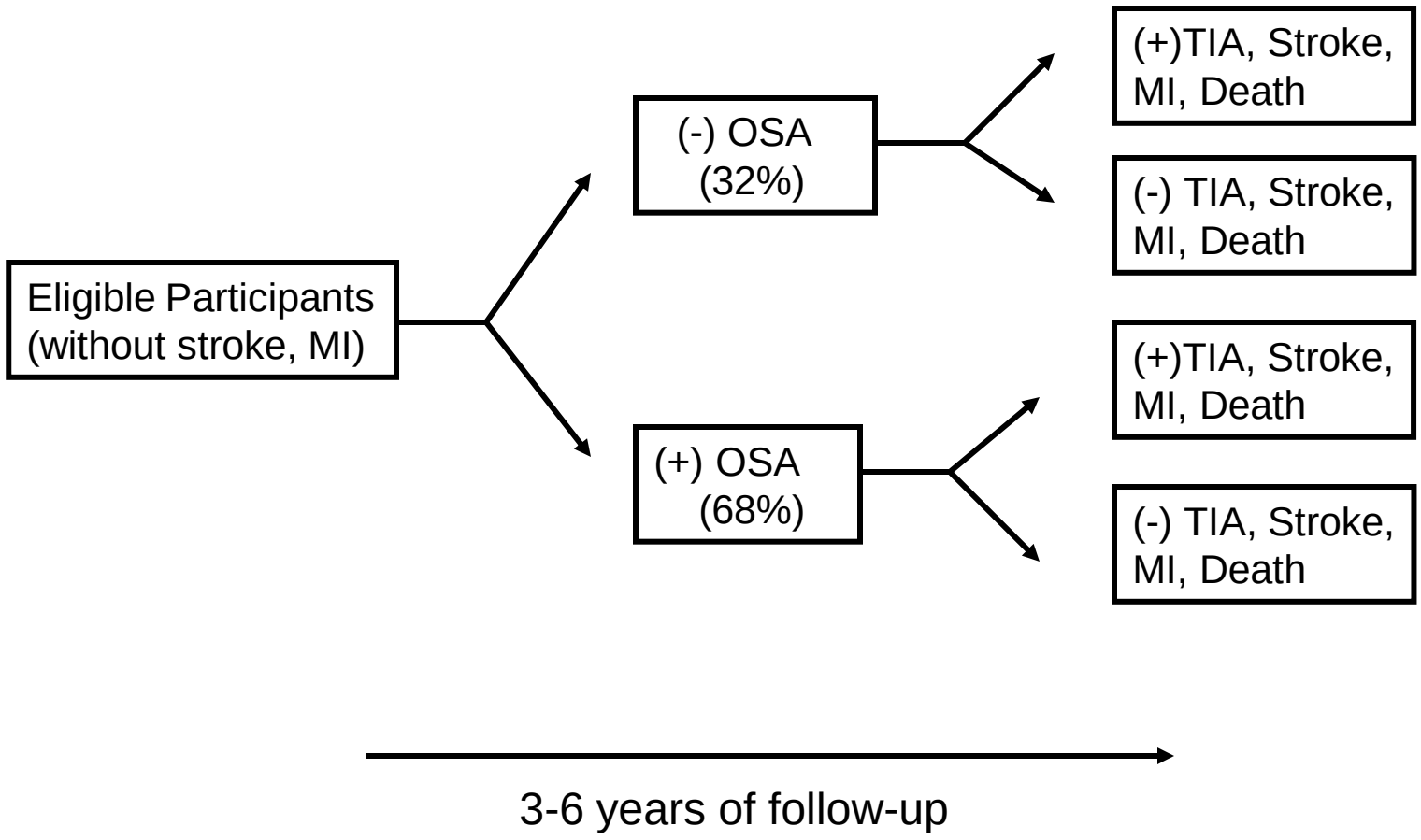
Causal Direction?



‘Confounding’?



Yale Observational Cohort Study



Obstructive Sleep Apnea as a Risk Factor for Stroke and Death

H. Klar Yaggi, M.D., M.P.H., John Concato, M.D., M.P.H., Walter N. Kernan, M.D., Judith H. Lichtman, Ph.D., M.P.H., Lawrence M. Brass, M.D., and Vahid Mohsenin, M.D.

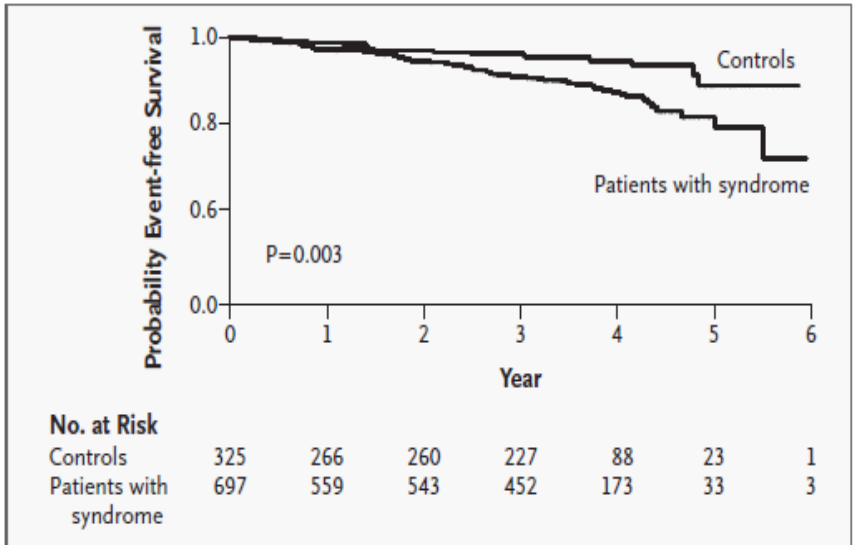


Figure 1. Kaplan–Meier Estimates of the Probability of Event-free Survival among Patients with the Obstructive Sleep Apnea Syndrome and Controls.

Table 3. Trend Analysis for the Relationship between Increased Severity of the Obstructive Sleep Apnea Syndrome and the Composite Outcome of Stroke or Death from Any Cause (N=1022).*

Severity of Syndrome	Stroke or Death		Mean Follow-up Period	Hazard Ratio (95% CI)
	No. of Events	No. of Patients	yr	
AHI ≤3 (reference score)	13	271	3.08	1.00
AHI 4–12	21	258	3.06	1.75 (0.88–3.49)
AHI 13–36	20	243	3.09	1.74 (0.87–3.51)
AHI >36	34	250	2.78	3.30 (1.74–6.26)

Risk of TIA, Stroke, or Death

Covariate	Unadjusted Hazard Ratio (95% C.I.)	Adjusted Hazard Ratio (95% C.I.)
Age (yrs)	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)
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)
Diabetes Mellitus	1.56 (1.02-2.59)	1.31 (0.76-1.26)
Hyperlipidemia	1.04 (0.64-1.68)	1.01 (0.61-1.66)
Hypertension	1.48 (1.01-2.28)	1.20 (0.75-1.90)
Atrial Fibrillation	1.56 (0.79-3.12)	0.91 (0.45-1.86)
Obstructive Sleep Apnea	2.24 (1.30-3.86)	1.97 (1.12-3.28)

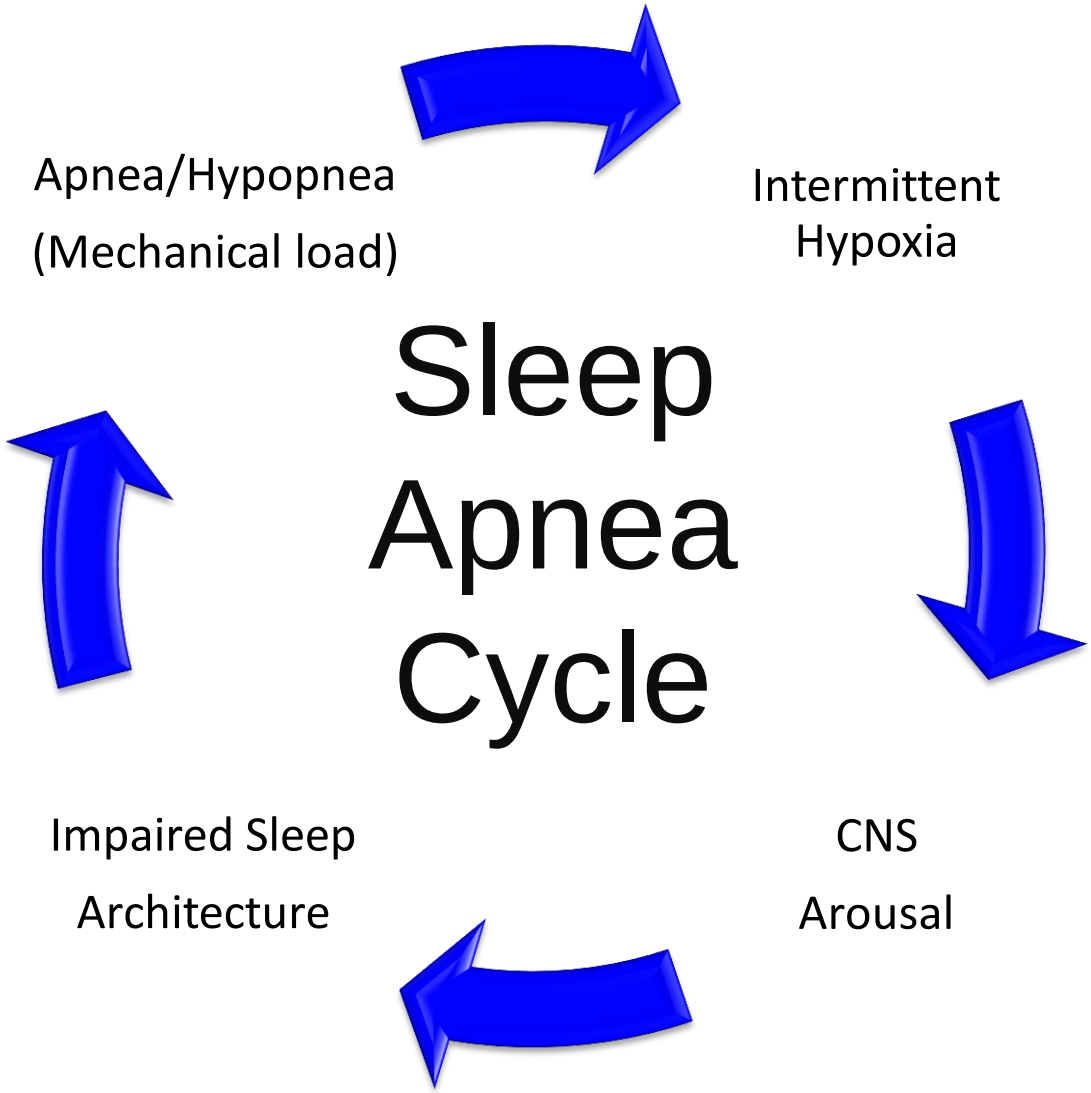
Yaggi, NEJM, 2005

Selected Prospective Observational Studies of OSA and Cardiovascular Outcomes

- Myocardial Infraction: Peker, Eur Respir J, 2006
- Congestive Heart Failure: Gottlieb, Circulation, 2010
- Fatal/Non-fatal cardiovascular events: Marin, Lancet, 2005
- Nocturnal sudden death: Gami, NEJM, 2005
- All cause mortality: Young, Sleep, 2008

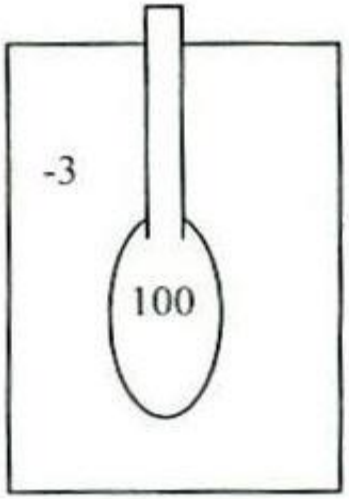
Sleep Apnea and Cardiovascular Disease (CVD)

- Evidence linking sleep apnea to CVD
- Mechanisms of CVD in sleep apnea


Sleep Apnea Cycle
Apnea/Hypopnea (Mechanical load)
Intermittent Hypoxia
CNS Arousal
Impaired Sleep Architecture

Mechanical Load in Sleep Apnea

BASELINE



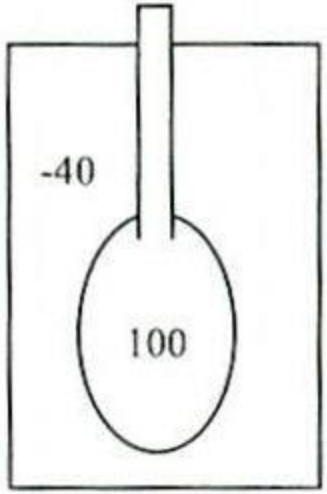
Ptm = 103

(Mueller maneuver)

Obstructive Apnea

- ↑ Transmural pressure (afterload)
- ↓ Cardiac output

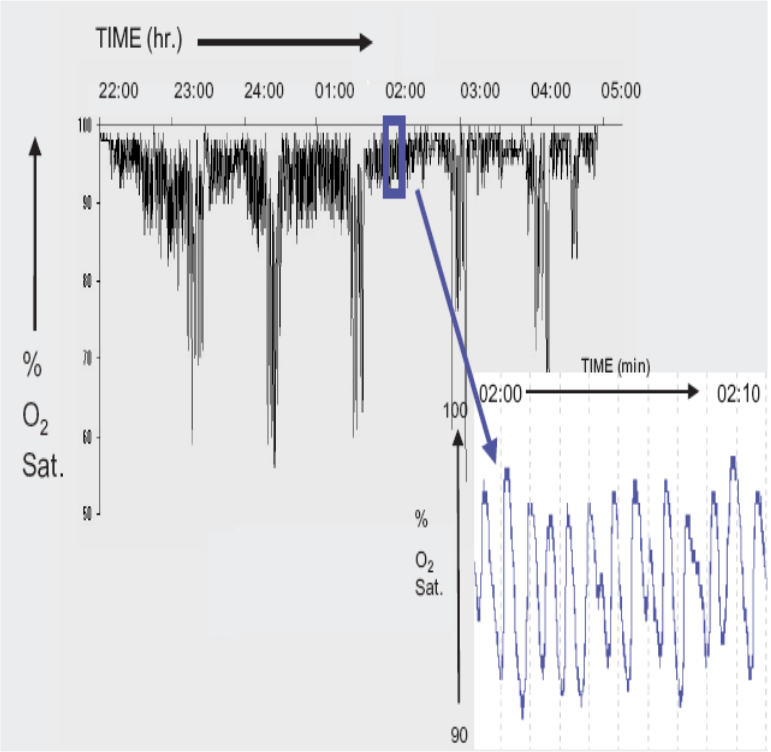
END OF APNEA



Ptm = 140

Bradley, Marcel Decker, 2000

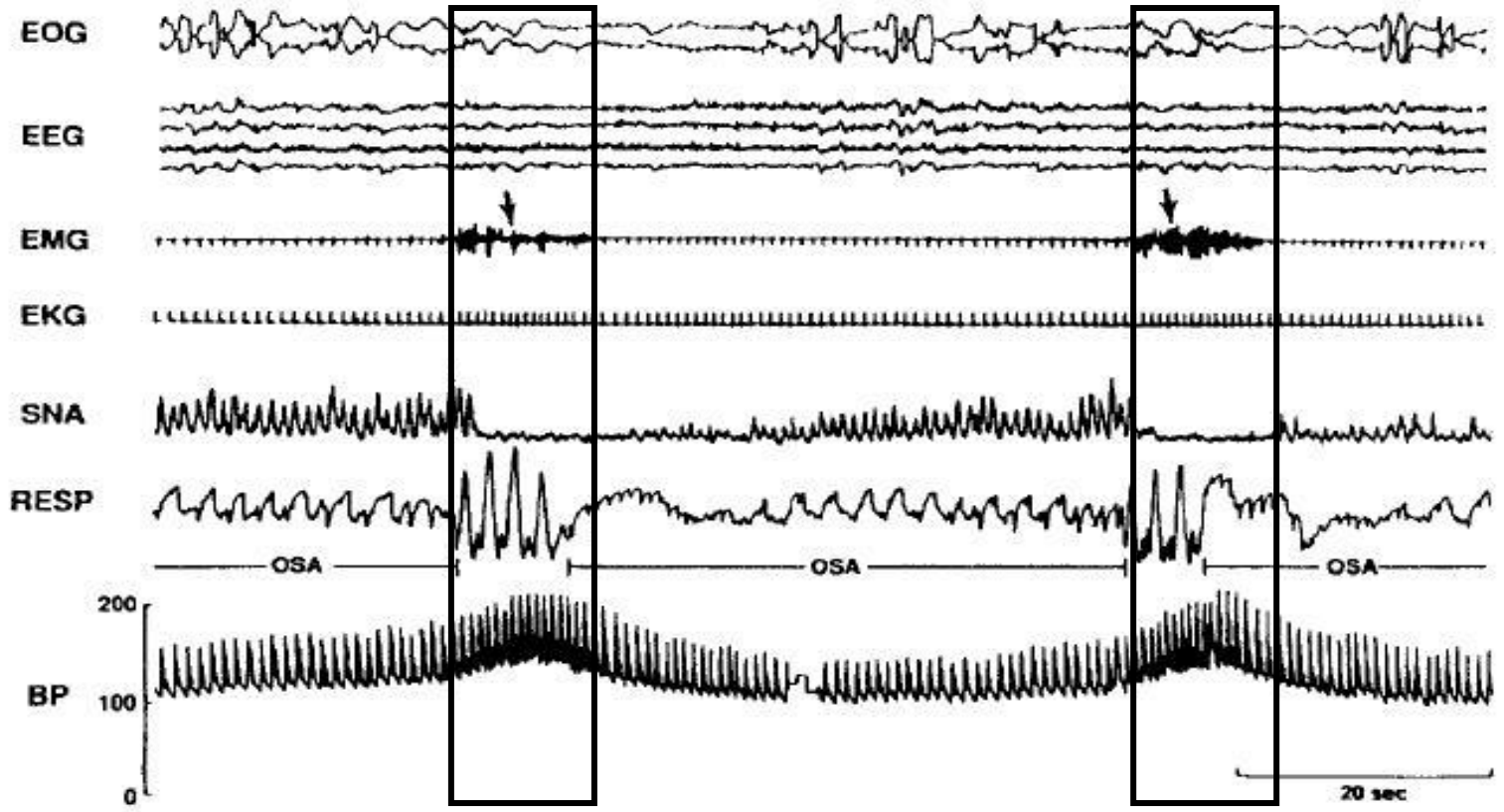
Intermittent Hypoxia



- Repetitive episodes of hypoxia and re-oxygenation throughout the night
- Oxidative Stress
- Activation of vascular inflammatory pathways leading to atherosclerosis

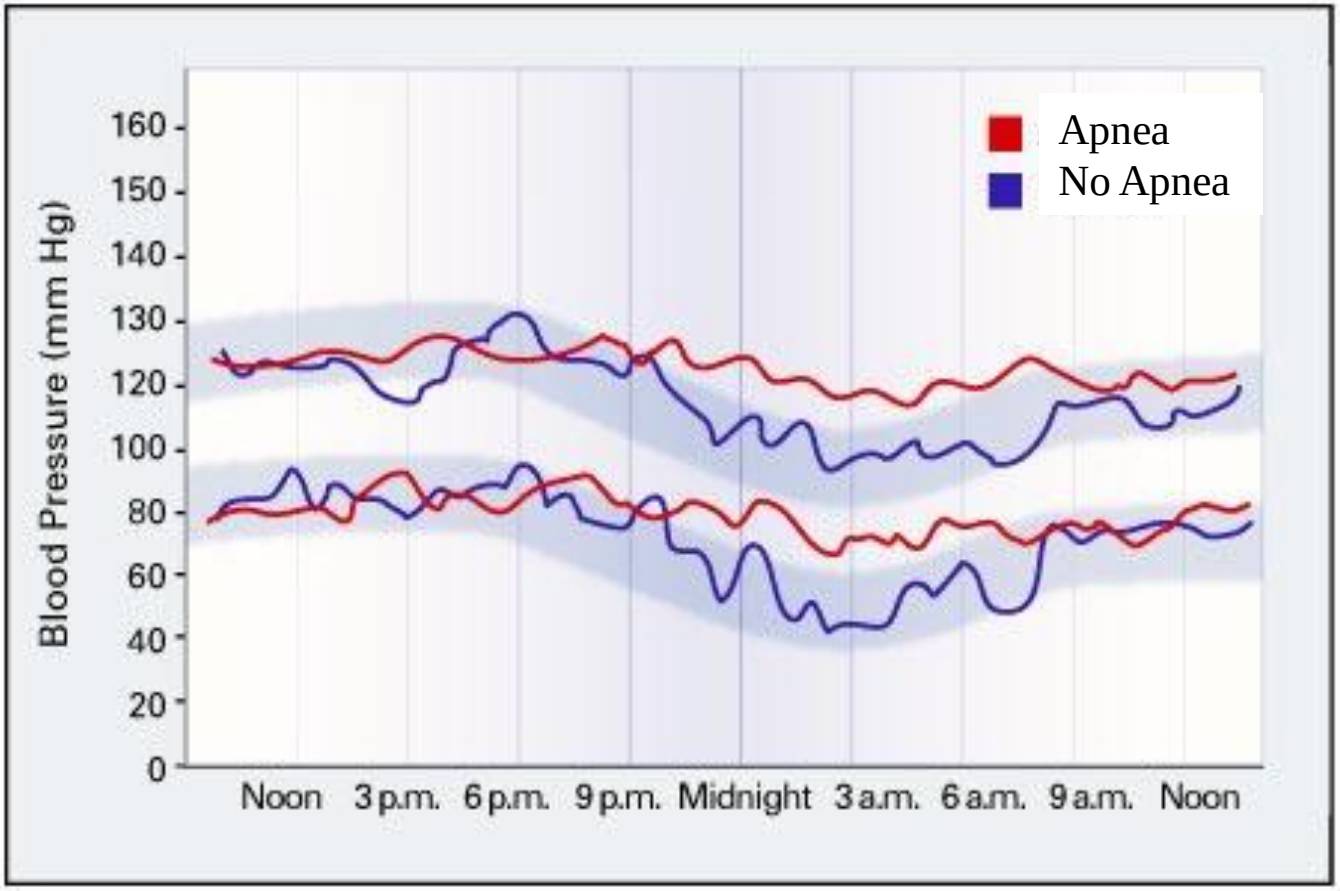
Hayashi, Chest, 2003
Lavie, Sleep Med Review, 2004
Ryan, Circulation, 2005
Savransky, AJRCCM, 2007

Sympathetic Nervous System Activation



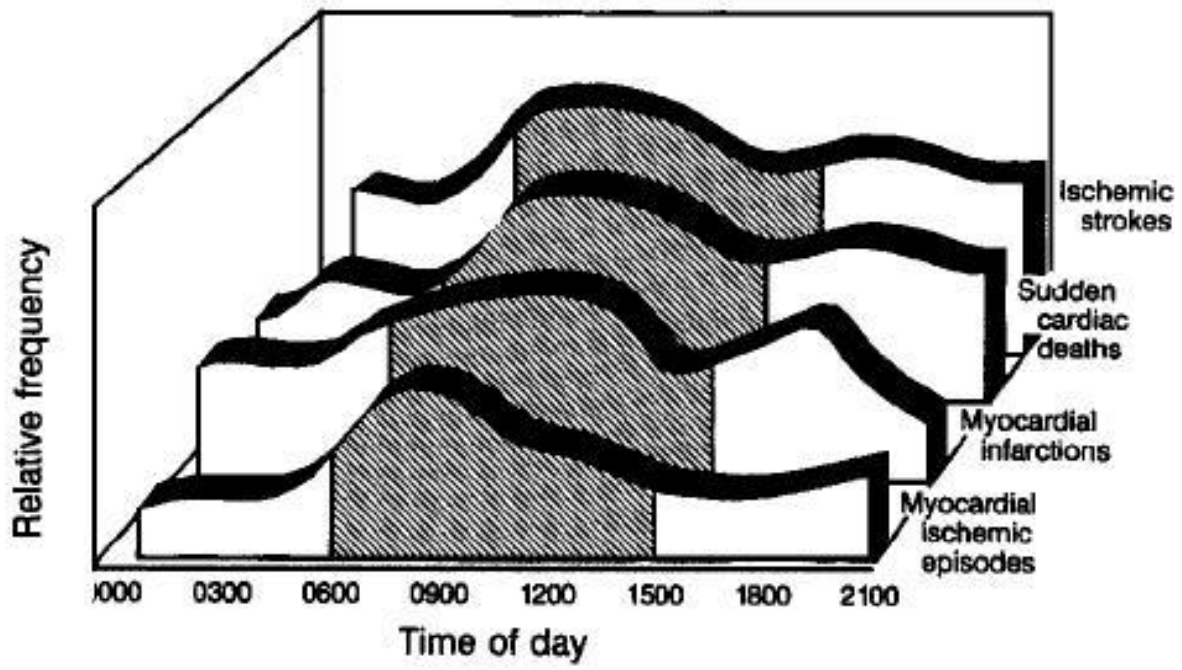
Wolk, Circulation, 2003

Circadian Blood Pressure and “Non-dipping”



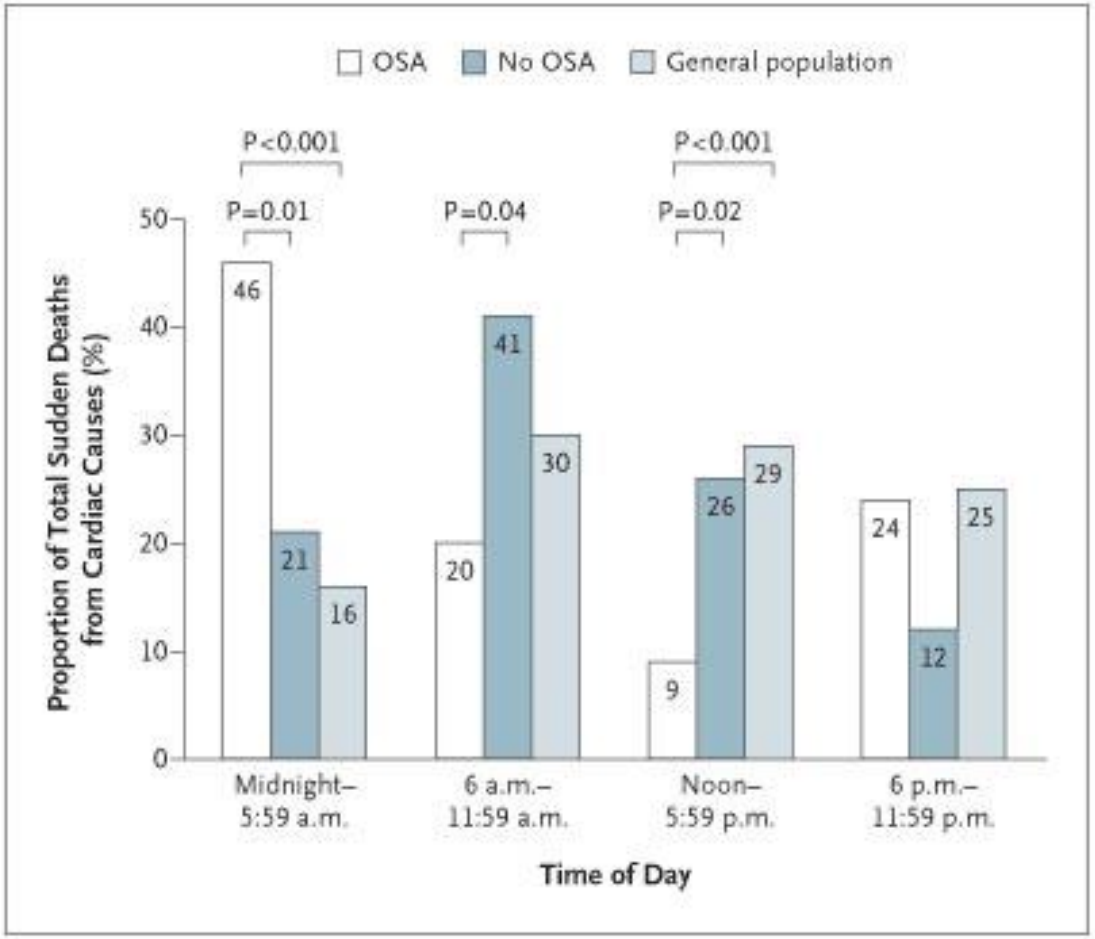
Somers, J Clin Invest, 1995
Ancoli-Israel, Chest, 2002
Hla, Sleep, 2008

Normal Circadian Variation in Vascular Events



Marler; Stroke 1989

Day-night Pattern of Sudden Death in Obstructive Sleep Apnea



Gami; NEJM 2005

Impaired Sleep Architecture and Metabolic Dysregulation

- Short sleep duration:
  - ↓ Glucose tolerance, ↓ insulin release[1]
  - ↑ Hunger/appetite, Δ in leptin and ghrelin[2]
  - ↑ Risk type 2 diabetes[3]
- Sleep apnea:
  - ↓ Glucose tolerance, ↓ insulin release[4]
  - ↑ Risk type 2 diabetes[5]

1. Spiegel, Lancet, 1999
2. Spiegel, Ann Intern, Med 2004
3. Yaggi, Diabetes Care, 2006
4. IP, AJRCCM, 2001
5. Botros, Am J Med, 2009

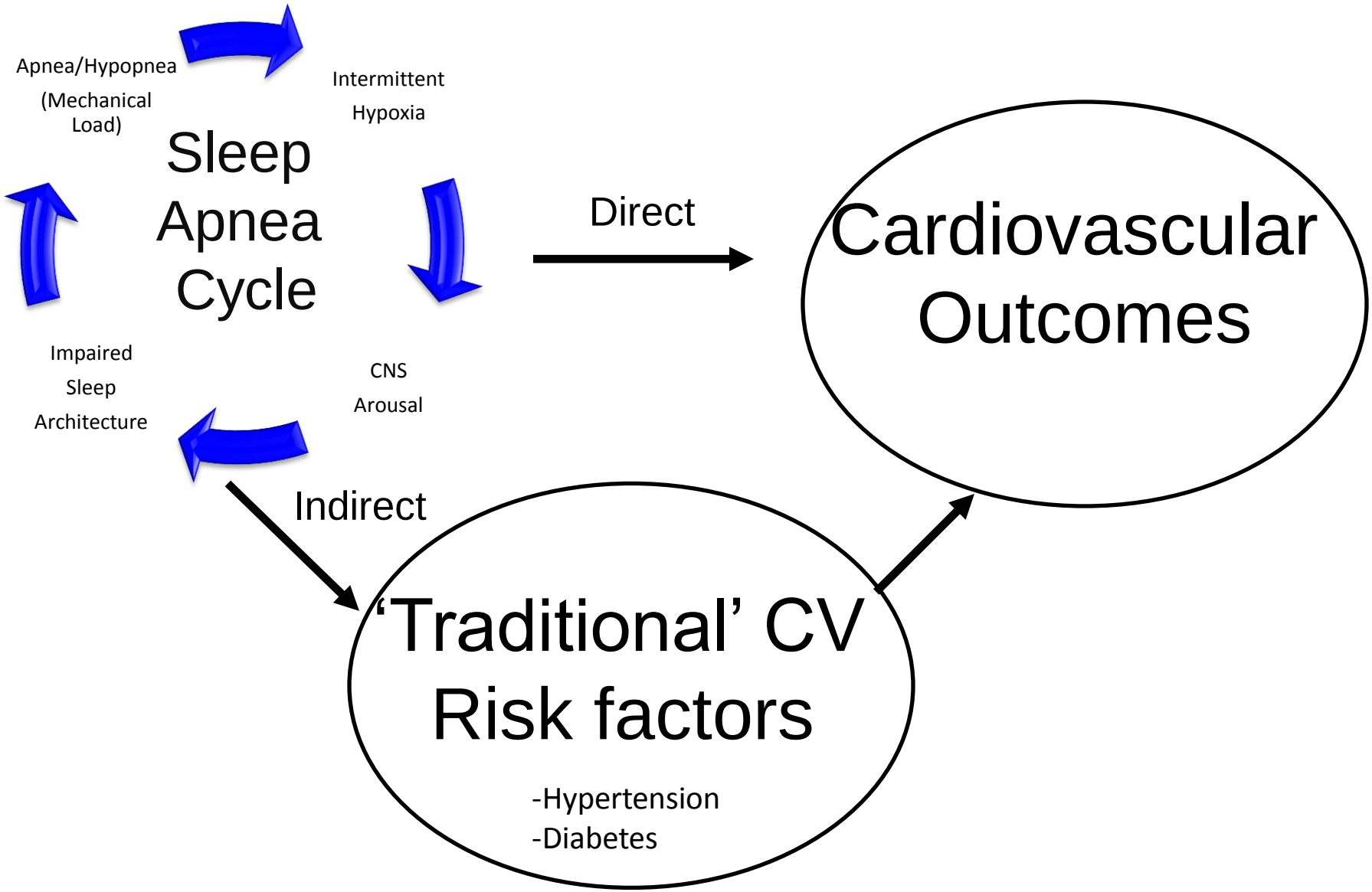
Obstructive Sleep Apnea as a Risk Factor for Type 2 Diabetes Mellitus

Covariate	**Unadjusted HR (95%CI)**	**Adjusted HR (95% CI)**
Age	0.99 (0.98-1.02)	1.00 (0.98-1.02)
Gender	1.41 (0.44-4.51)	1.09 (0.34-3.57)
Race (non-caucasian)	1.35 (0.64-2.85)	1.13 (0.56-2.30)
Fasting Glucose	1.04 (1.04-1.05)	1.05 (1.03-1.06)
BMI	1.06 (1.03-1.09)	1.04 (1.01-1.07)
Change in BMI	0.73 (0.69-0.78)	0.76 (0.70-0.83)
Sleep Apnea*	1.53 (1.21-94)	1.43 (1.10-1.86)

* Per Quartile of AHI

Botros, Am J Med, 2009

Conceptual Model



Risk is Greater for Stroke than for Coronary Heart Disease

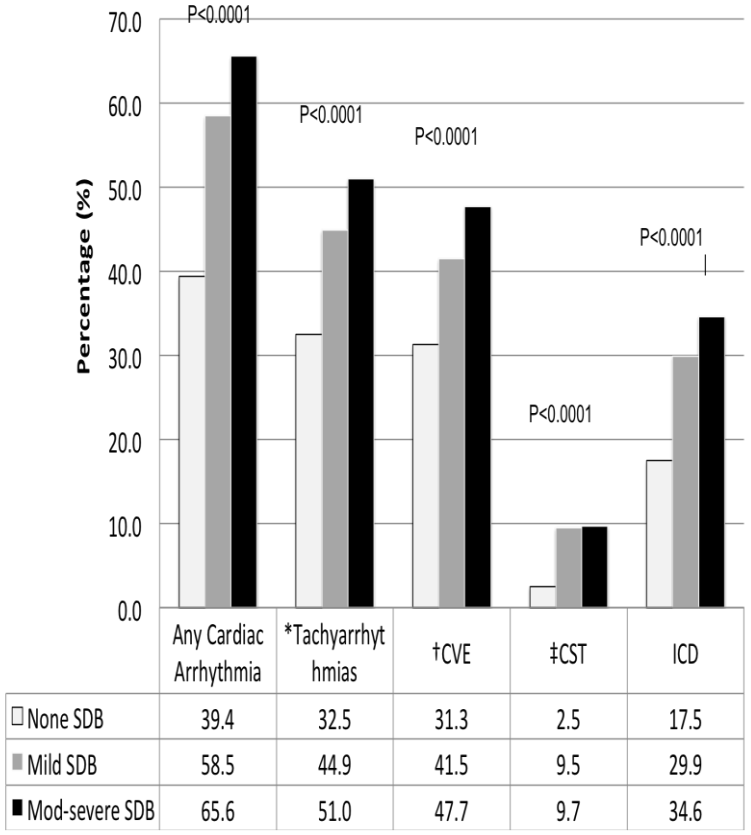
		Adjusted HR Stroke	Adjusted HR CHD
Gottlieb 2010	Sleep Heart Health Study (men)	2.9	1.5
Redline 2010			
Arzt 2005	Wisconsin Sleep Cohort Study	3.8	2.4
Hla 2015			
Mooe 2001		3.4	1.0
Yaggi 2005	Yale Centers for Sleep Medicine	3.0	2.1
Shah 2010			
Campos-Rodriguez 2014		6.4	1.8

Gottlieb, Circulation 2010;122:352
Redline, AJRCCM 2010; 182:269
Arzt, AJRCCM 2005; 172:1447
Hla, Sleep 2015;38:677
Mooe, AJRCCM 2001; 164:1910
Yaggi, N Engl J Med 2005; 353:2034
Shah, Sleep Breath 2010;14:131
Campos-Rodriguez, AJRCCM 2014;189:1544

Association of Nocturnal Arrhythmias with Sleep-disordered Breathing

Arrhythmia Type	Odds ratio	(95% CI)
Nonsustained ventricular tachycardia	3.40	(1.03-11.2)
Complex ventricular ectopy	1.74	(1.11-2.74)
Atrial fibrillation	4.02	(1.03-15.74)

Mehra, AJRCCM, 2006

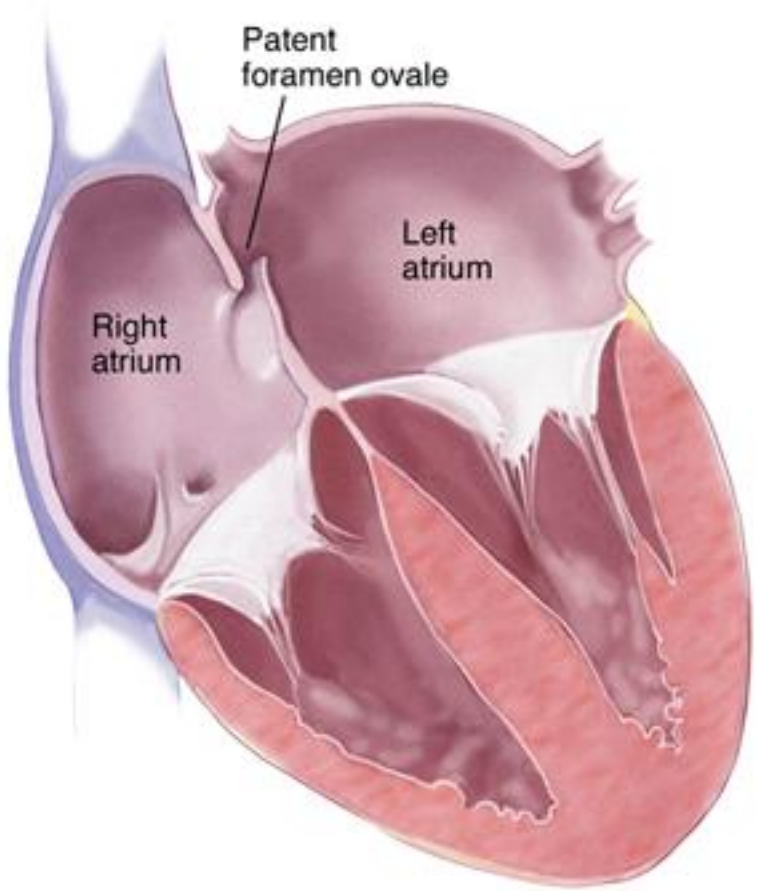


	Any Cardiac Arrhythmia	*Tachyarrhythmias	†CVE	‡CST	ICD
None SDB	39.4	32.5	31.3	2.5	17.5
Mild SDB	58.5	44.9	41.5	9.5	29.9
Mod-severe SDB	65.6	51.0	47.7	9.7	34.6

Selim, J Clin Sleep Med, 2016

Right to Left Shunt through Patent Foramen Ovale (PFO)

- PFO may give rise to ischemic stroke by means of paradoxical embolism
- Increased prevalence of PFO among patients with sleep apnea
- Transient right sided pressure increases during obstructive apneas permit R→L shunting through PFO



Lechat, NEJM, 1988
Beelke, Sleep, 2002
Shanoudy, Chest, 1998

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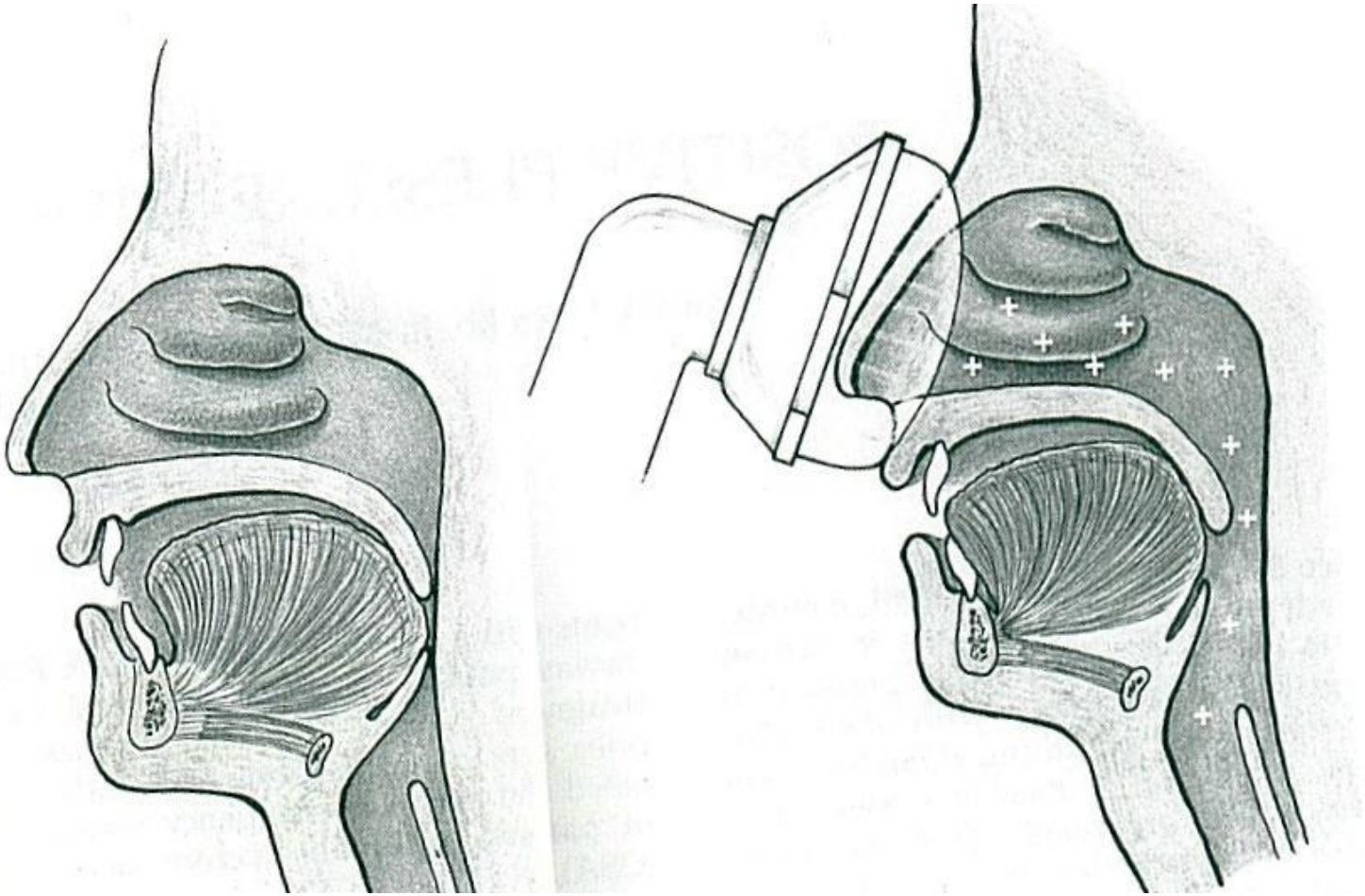
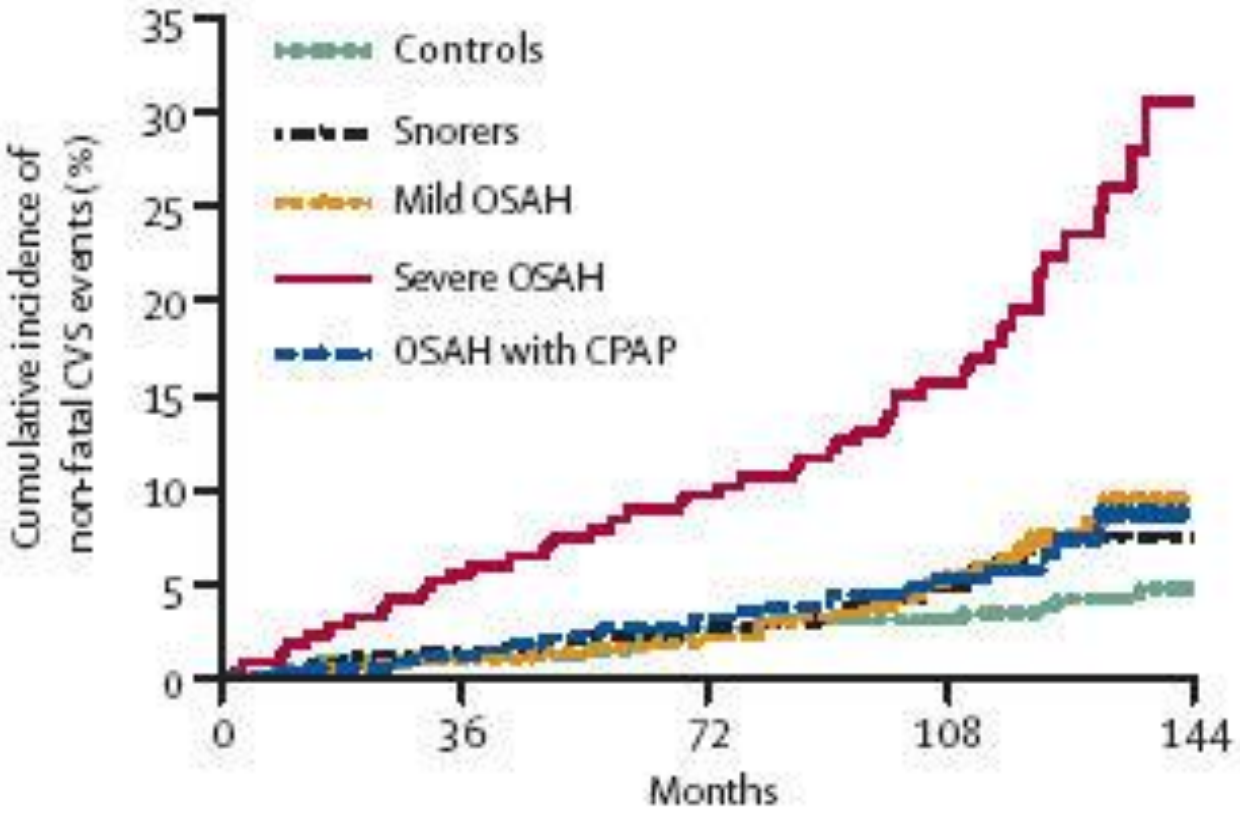
- Strategies examining impact treating sleep apnea on CVD

Continuous Positive Airway Pressure (CPAP)

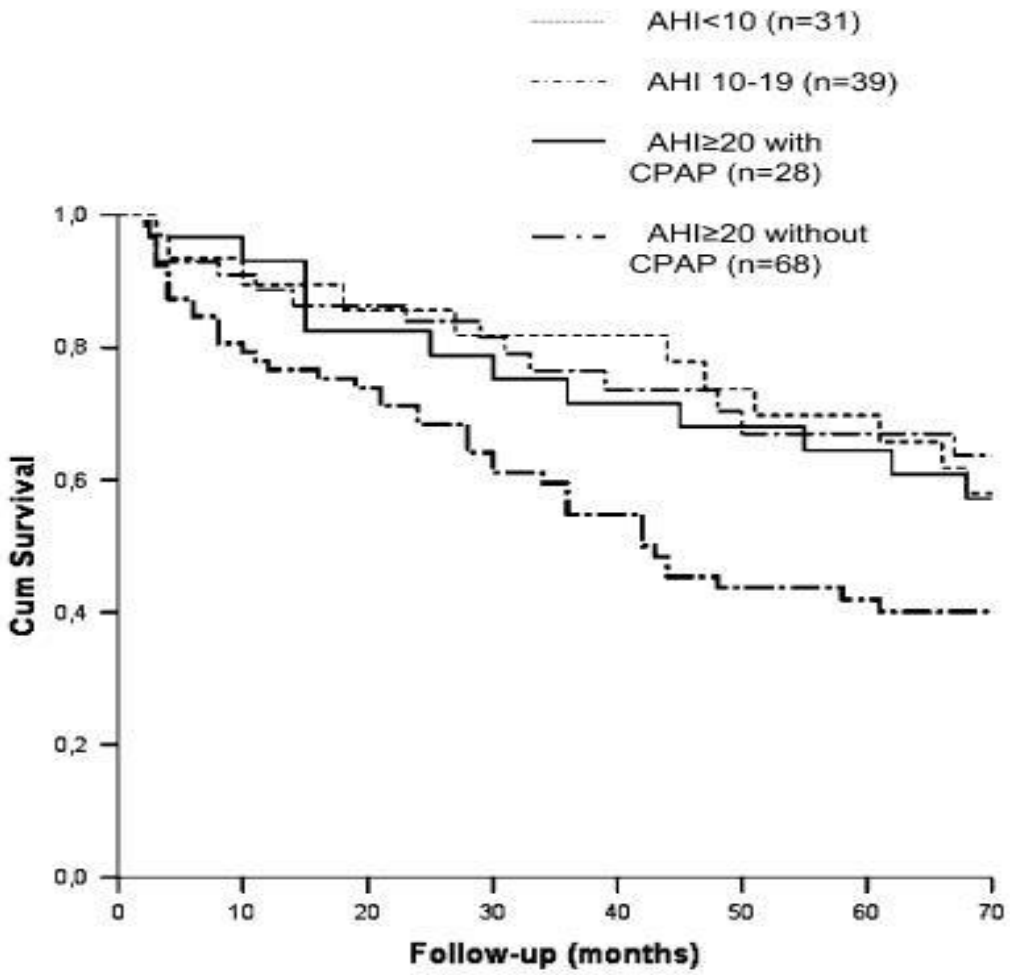


Cardiovascular outcomes in Obstructive Sleep Apnea With and Without Treatment



Marin, Lancet, 2005

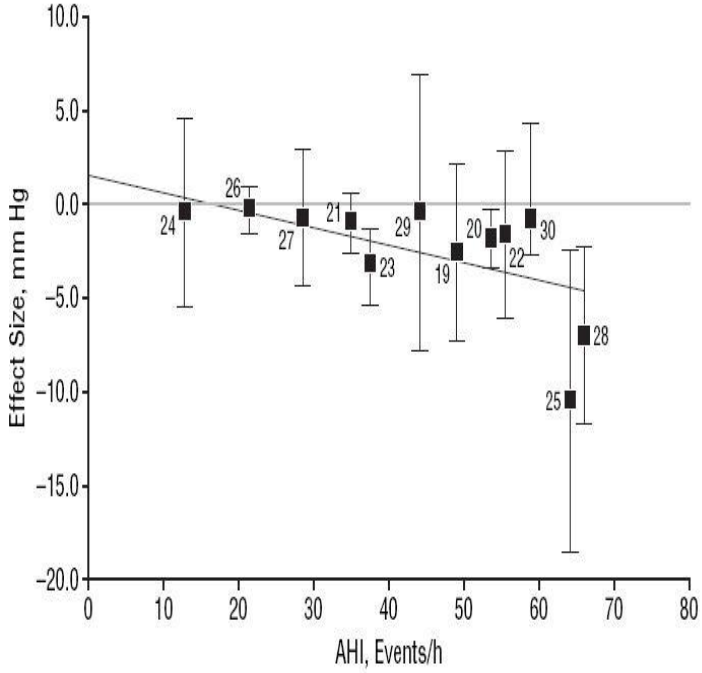
Stroke Mortality in Sleep Apnea With and Without Treatment



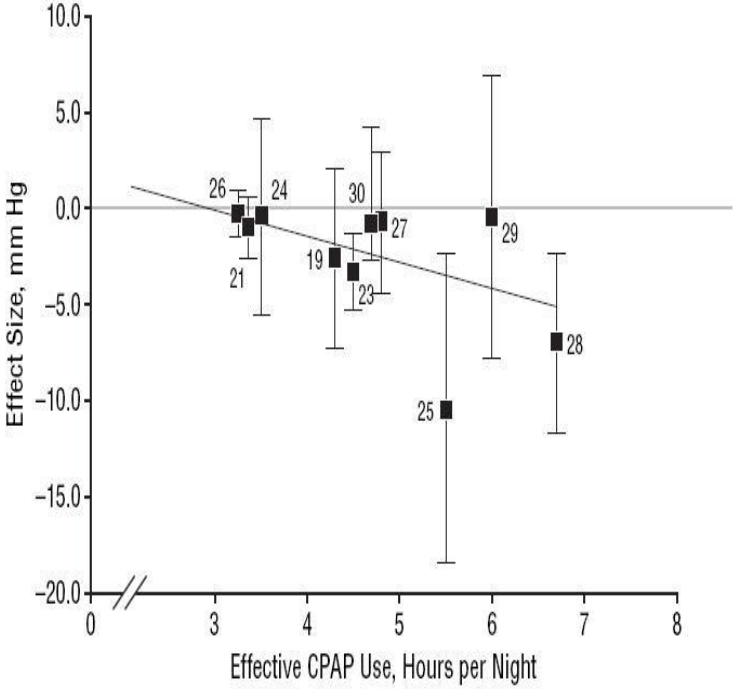
Martinez-Garcia; AJRCCM 2009

Short-term Impact of CPAP on Blood Pressure

Severity of Sleep Apnea



Effective CPAP Use



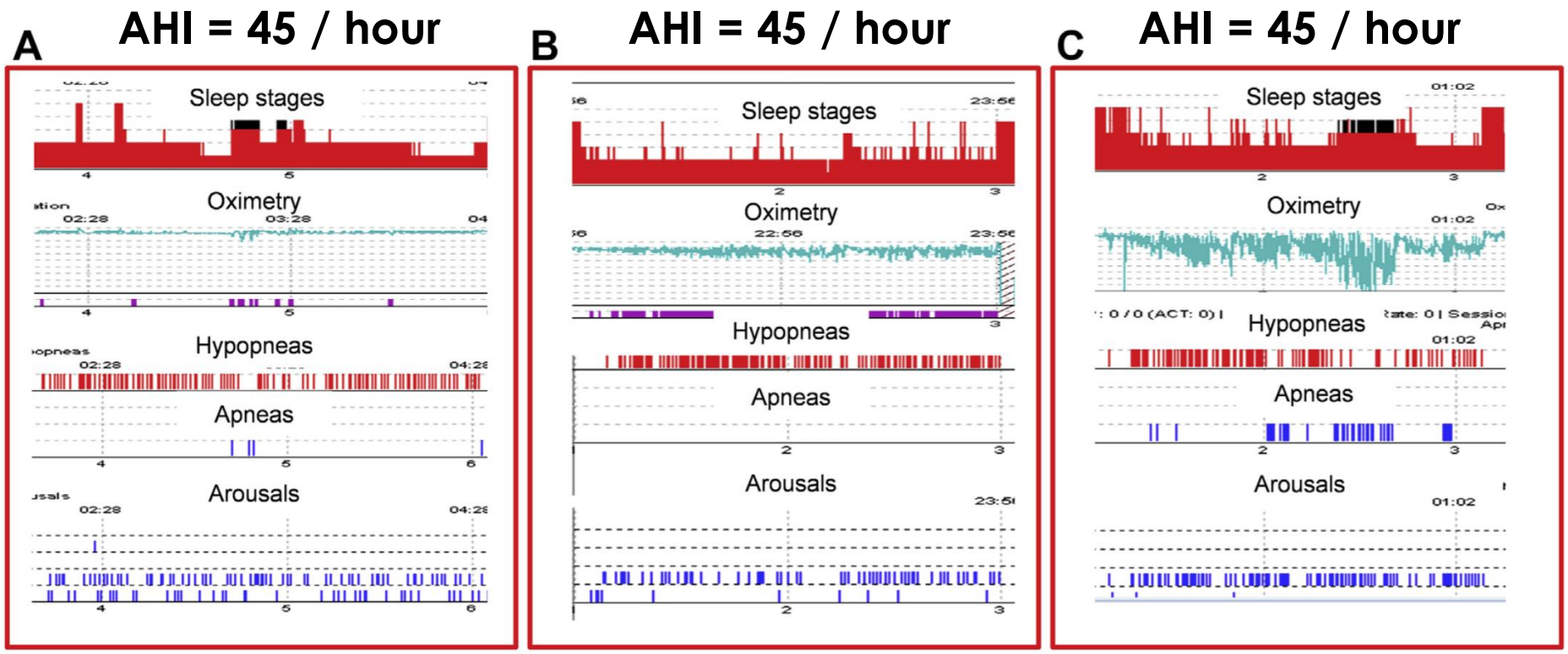
Haentjens, Arch Int Med, 2007

Challenges in Designing Long-Term RCTs Examining Cardiovascular Endpoints Using PAP

- Pharmacological therapies exist for the many of the causal biologic pathways between OSA and CVD
  - Cardiovascular event rates are decreasing
- Treatment adherence with PAP
  - Consistent dose-response relationships observed
  - Treatment during REM sleep may be particularly important
- Conceptual issues regarding equipoise
  - Safety considerations re: control patients over longer term (e.g., drowsiness-related accidents)
- Heterogeneity of sleep apnea

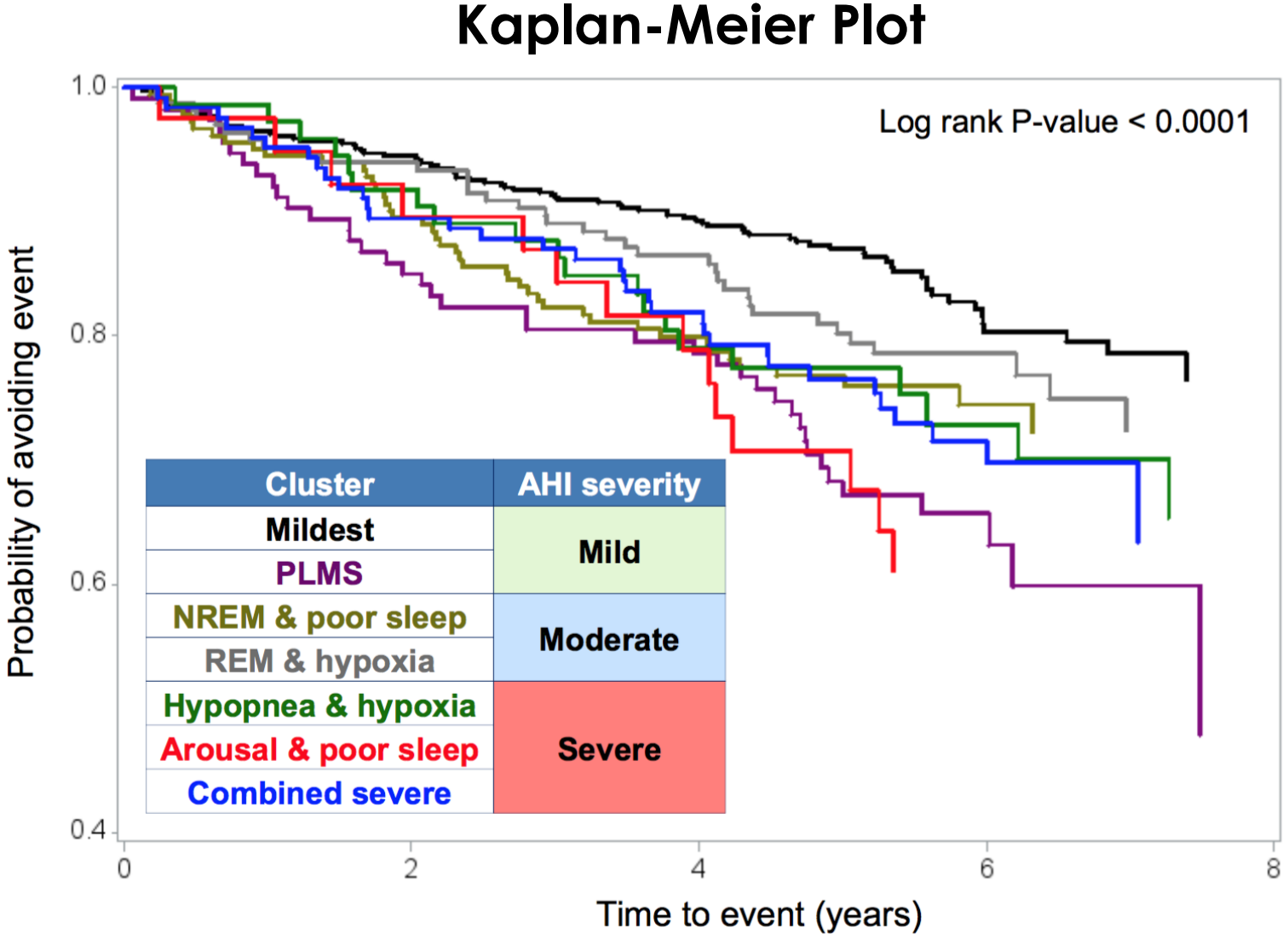
OSA's Heterogeneity

AHI (events/hr)	5 to < 15	15 to < 30	≥ 30
OSA Severity	Mild	Moderate	Severe



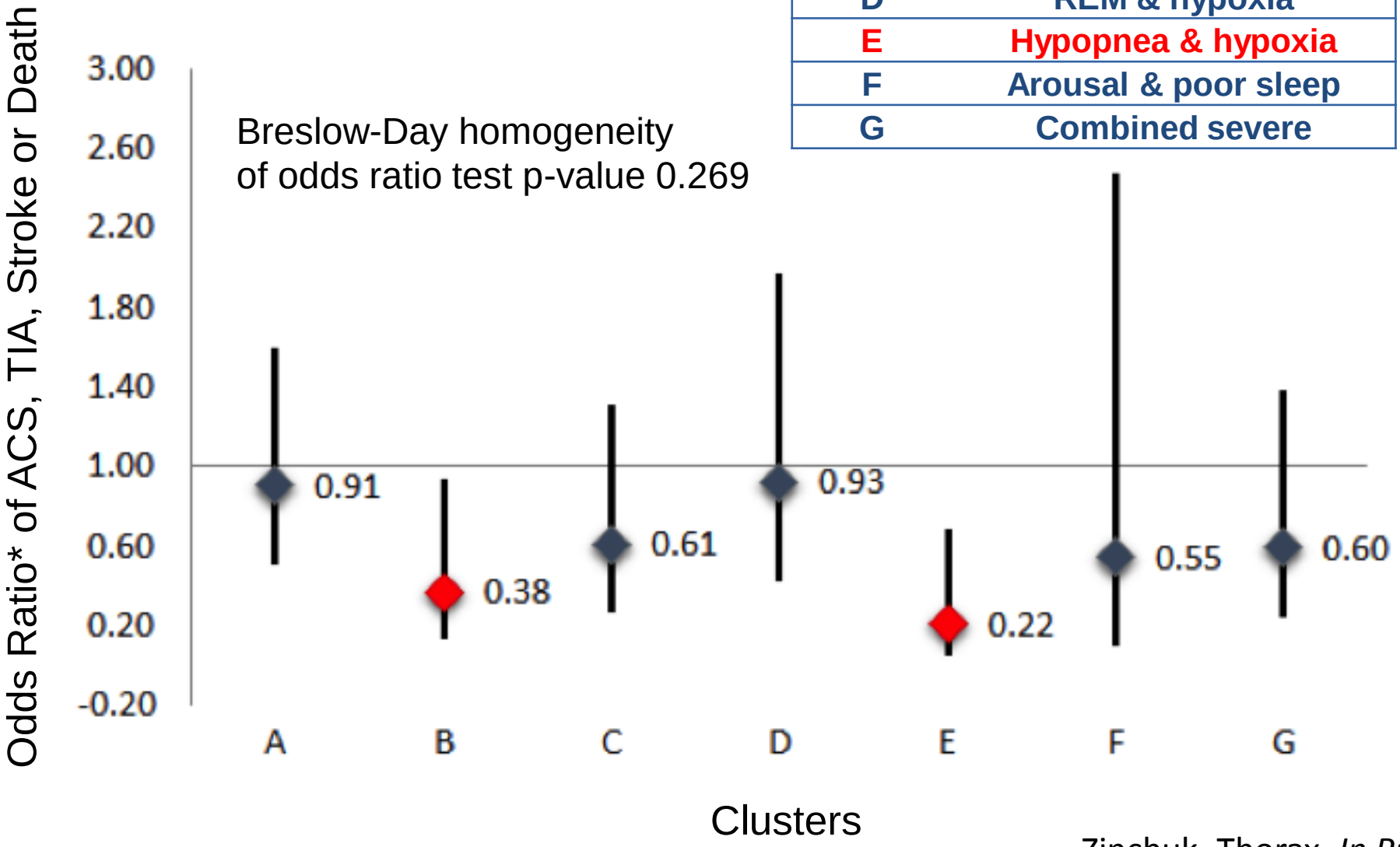
Chest. 2016;149(1):11-13

Results: outcomes & clusters



Zinchuk, Thorax, *In Press*

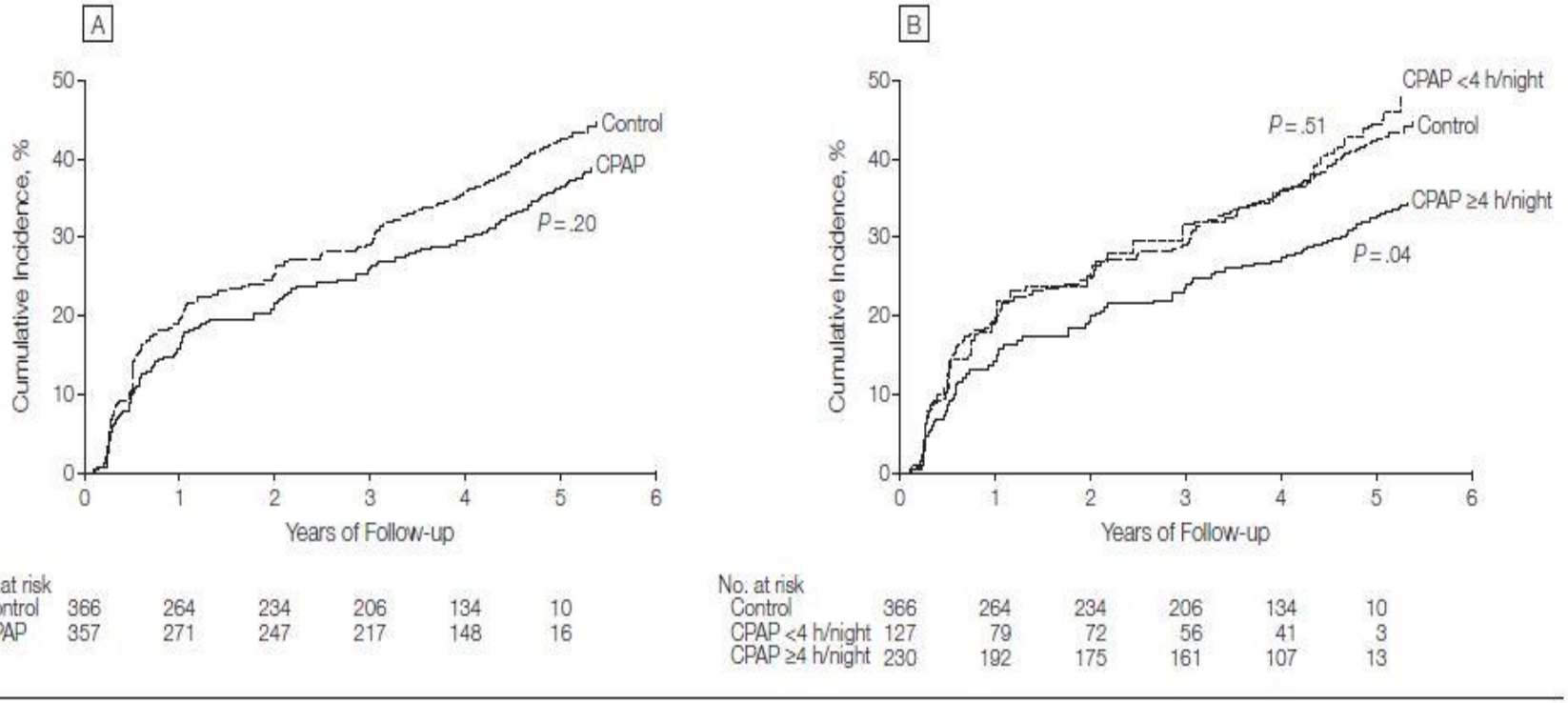
Cluster	Label
A	Mild
B	PLM
C	NREM & poor sleep
D	REM & hypoxia
E	Hypopnea & hypoxia
F	Arousal & poor sleep
G	Combined severe



Zinchuk, Thorax, *In Pres*

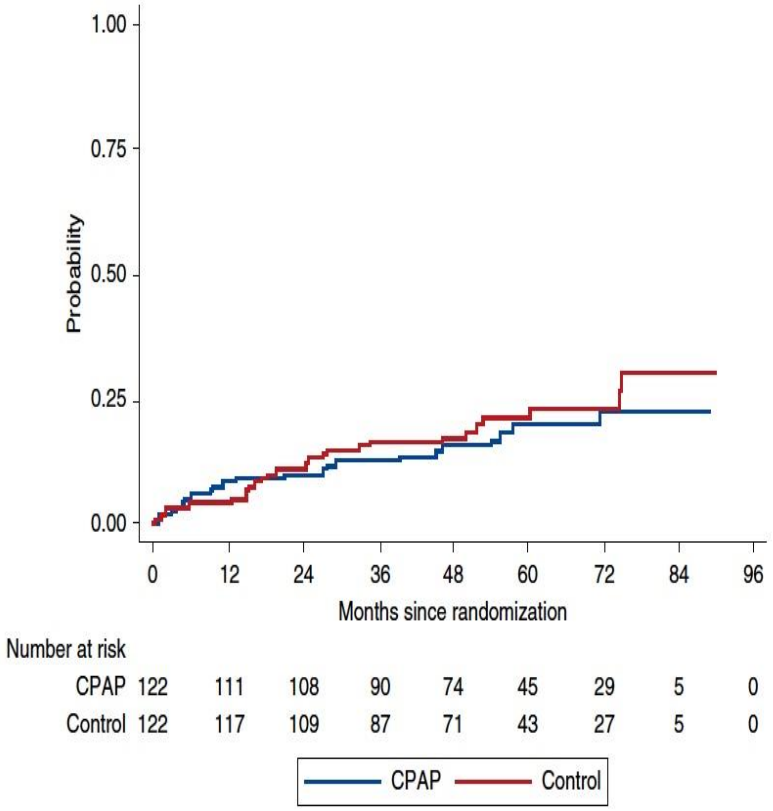
CPAP on Incidence of Hypertension and Cardiovascular Events among Non-sleepy Patients

Figure 2. Cumulative Incidence of Hypertension or Cardiovascular Events During Follow-up



Barbe, JAMA, 2012

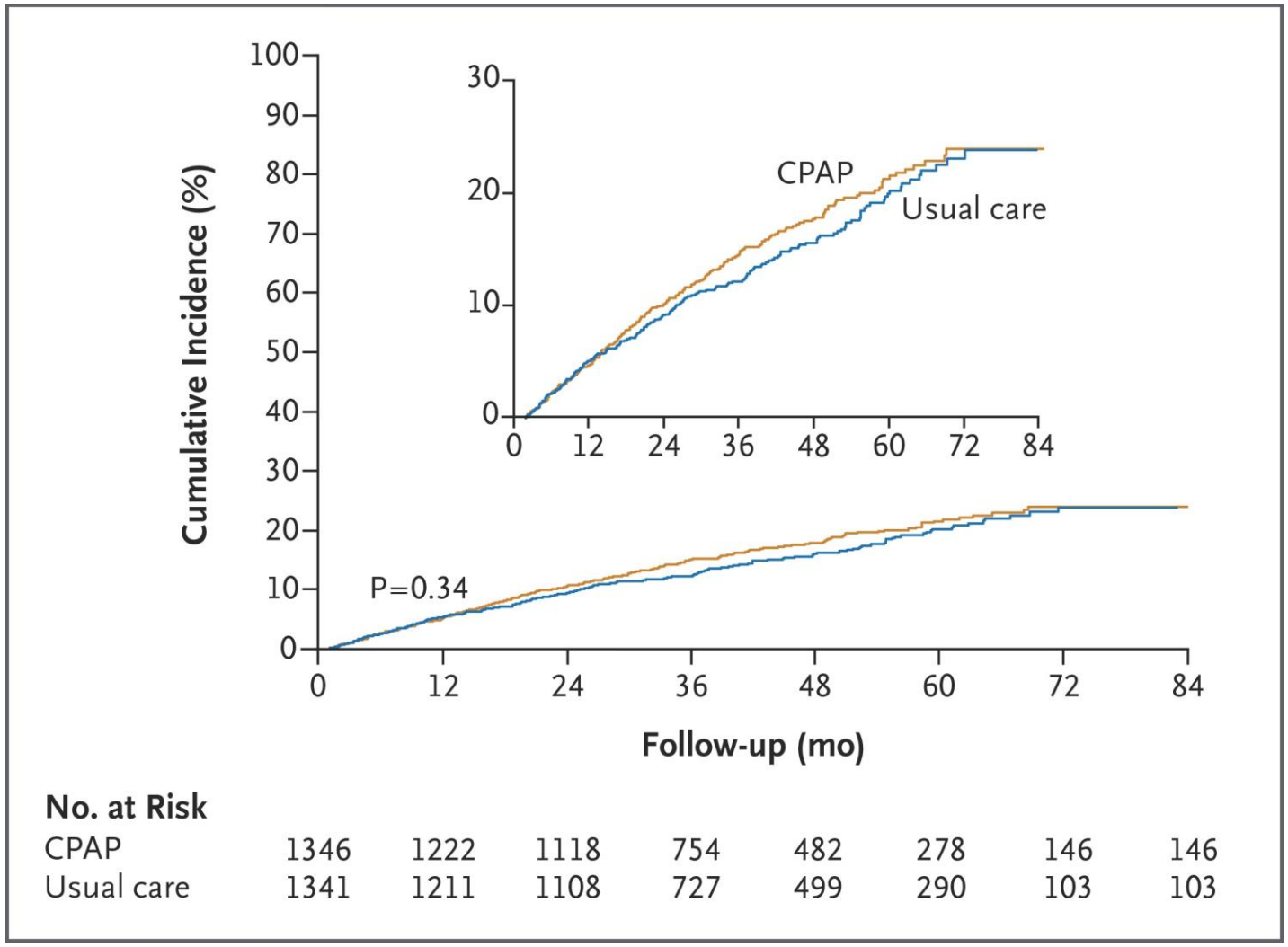
CPAP on Cardiovascular Outcomes in Patients with CAD and Non-sleepy OSA



	Univariate			Multivariate*		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
CPAP usage ≥3 h/night	0.64	0.31–1.33	0.234	0.91	0.16–5.13	0.911
CPAP usage ≥4 h/night	0.43	0.18–1.02	0.057	0.29	0.10–0.86	0.026
CPAP usage ≥5 h/night	0.43	0.17–1.09	0.075	0.34	0.10–1.12	0.075

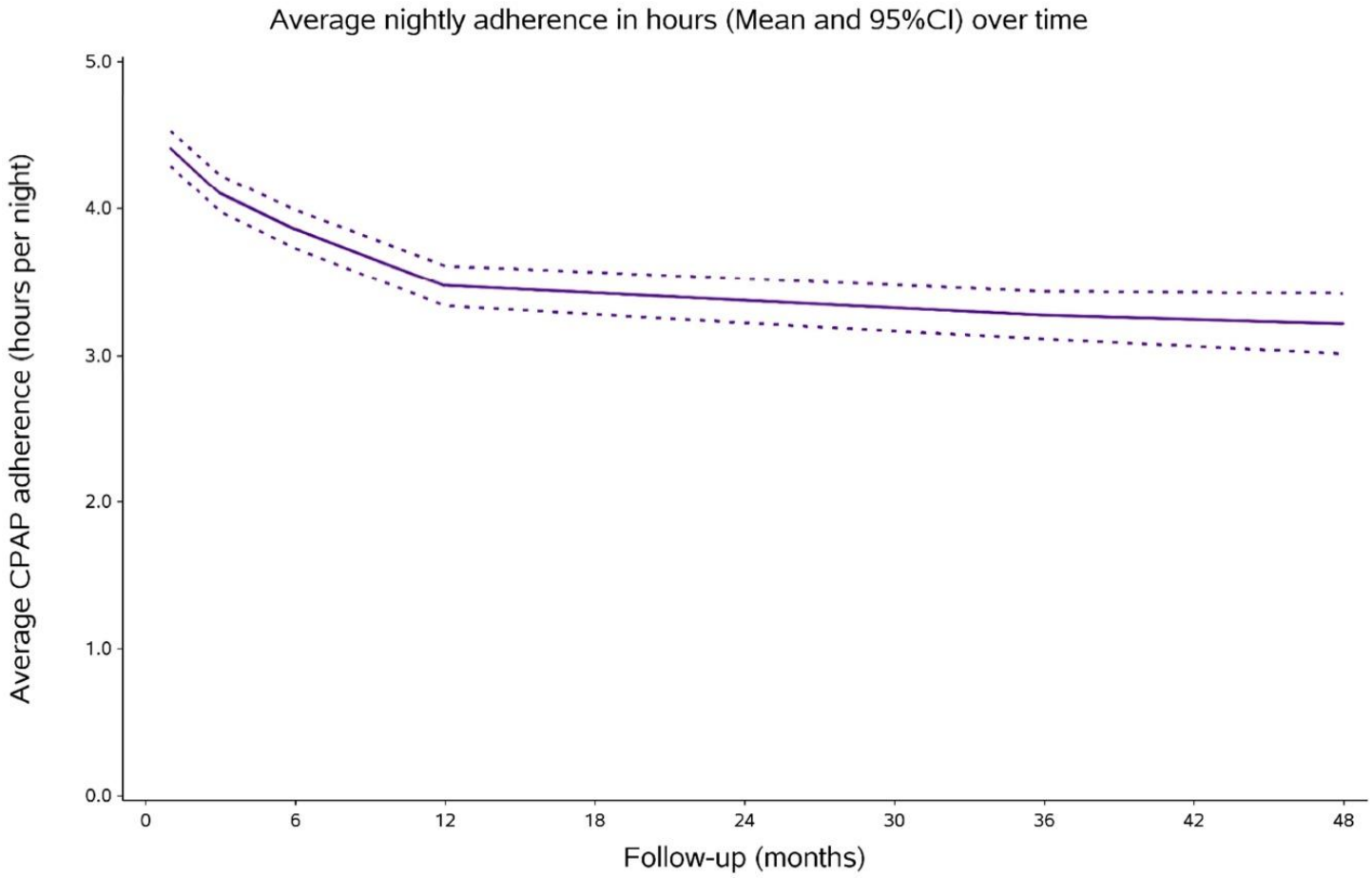
Peker, AJRCCM, 2016

SAVE Trial



McEvoy, NEJM, 2016

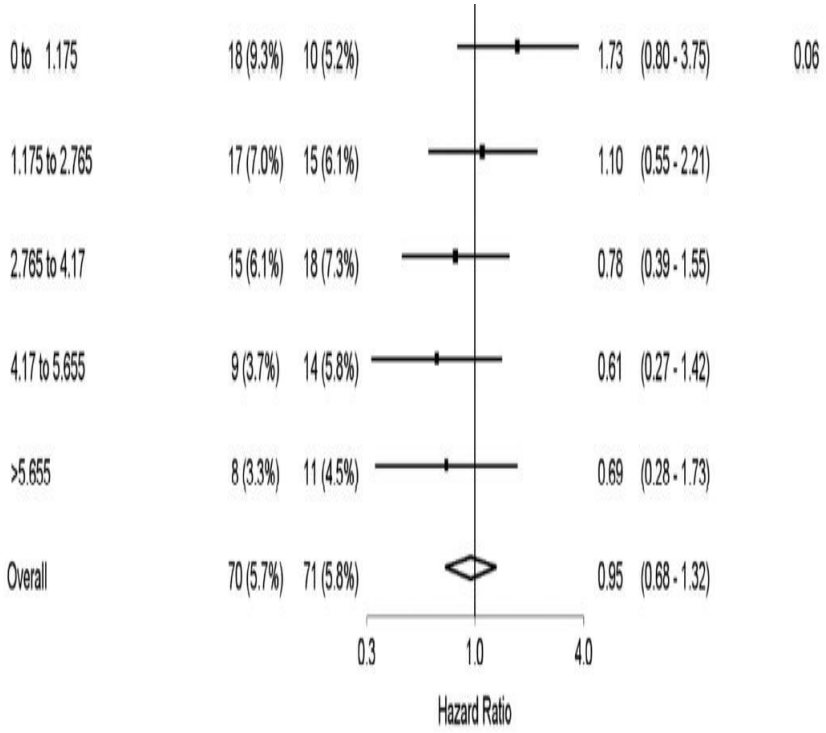
SAVE TRIAL: CPAP Adherence Over Time



McEvoy, NEJM, 2016

SAVE Trial and Stroke Outcomes

Dose-Response



Propensity-Score Matched

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

McEvoy, NEJM, 2016

Acute Stroke Epidemiology

- Patients with acute TIA/minor stroke ideal candidates for prevention of recurrent vascular events
  - ↑ recurrent vascular events despite current prevention strategies.
  - 25% of patients with TIA have completed stroke, MI, death in with 90 days of initial event (half of these events occur in the first 72 hours)
- New approach to reduce recurrent vascular event rate is needed (particularly in acute post-TIA period)
- The treatment of sleep apnea may represent a novel therapeutic target

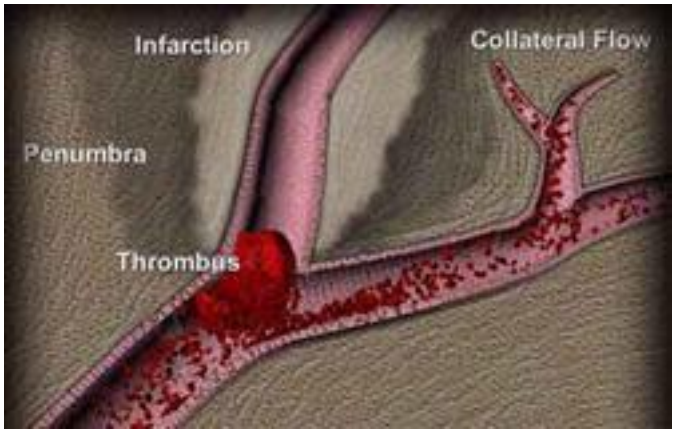
AHA Statistical Update, 2015
Johnston, NEJM, 2002
Johnston, JAMA, 2000
Yaggi, Lancet Neurology, 2002

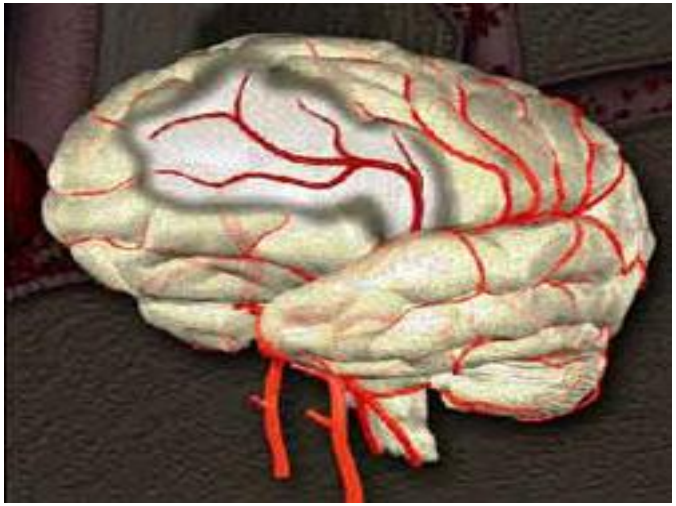
Unique Challenges in Treating Sleep Apnea Among Patients with Stroke

- Screening
  - Less excessive daytime sleepiness
  - Lower BMI
  - AHA stroke Guidelines recommend objective testing
- Logistical
  - Impaired mobility
  - Competing demands
- Adherence
  - Cognitive dysfunction
  - Weakness in extremities
  - Facial droop
  - Less excessive daytime sleepiness

Bassetti, Neurology, 2009
Arzt, Stroke, 2011

Early Treatment of Sleep Apnea in Acute Stroke: The Concept of the Ischemic Penumbra





- Within the ischemic cerebrovascular bed, there are two major zones of injury: the core ischemic zone and the “ischemic penumbra” (ischemic but still viable tissue)

Feasibility Study Methods: Overview

Design: Randomized controlled trial (90 days)

Sample: TIA patients (focal neurologic deficit < 24 hours confirmed by study neurologist)

Setting: Emergency departments/inpatients at 3 CT hospitals

Intervention (N=45):

- Early/immediate Auto-CPAP (ideally within 1st or 2nd night of TIA) for 90 days (stopped if no evidence of sleep apnea/responding to flow limitation)
- Sleep study at 90 days.

Control (N=25): Usual care.

Time to CPAP

Time	Intervention: (n=45)
From TIA symptom onset, Hours: mean (+/-SD)	39 (23)
<24 hours: n (%)	8 (18)
≥ 24 < 48 hours: n (%)	27 (60)
≥ 48 hours	10 (22)

Yaggi, Stroke, 2010

Auto-Titrating CPAP Use

CPAP Use Category	Intervention Patients on CPAP
Number hrs/night used: mean (+/-SD)	5.6 (1.9)
Range	1.5-8.5
CPAP Use: N (%)	-
None: 0 hrs/night or 0 nights	0 (0)
Some: <4 hrs/night or <70% nights	14 (48)
Good: ≥4 hrs/night and ≥ 70% nights	15 (52)

Yaggi, Stroke, 2010

Recurrent Vascular Events: (Intention-To-Treat)

	(+) Outcome	(-) Outcome	
Intervention	1 (2%)	44 (98%)	45
Control	3 (12%)	22 (88%)	25

Yaggi, Stroke, 2010

Recurrent Vascular Events: (CPAP Use Category)

	(+) Outcome	(-) Outcome	
Good	0 (0%)	15 (100%)	15
Some	1 (7%)	12 (93%)	14
None	3 (18%)	14 (82%)	17

Yaggi, Stroke, 2010

CPAP Results in Improvement in Stroke Severity at 30-days in Patients with Sleep apnea and Acute Stroke

Outcome:	**Overall ITT**			**Sleep Apnea by CPAP Use†**		
	Intervention (N=31)	Control (N=24)	P-value	None (N=13)	Some (N=6)	Excellent (N=10)
Stroke severity (NIHSS) median change from baseline to 30-days	-3.0	-1.0	0.03	-1.0	-2.5	-3.0

Bravata, Sleep, 2012

Early Treatment of Sleep Apnea in Acute Stroke: Recovery

Recovery of original circuity

- Recovery of surviving intra-lesional neurons
- Inflammatory pathways

Adaptation of remaining circuity

- Neuroplasticity
- Role of glymphatic system?

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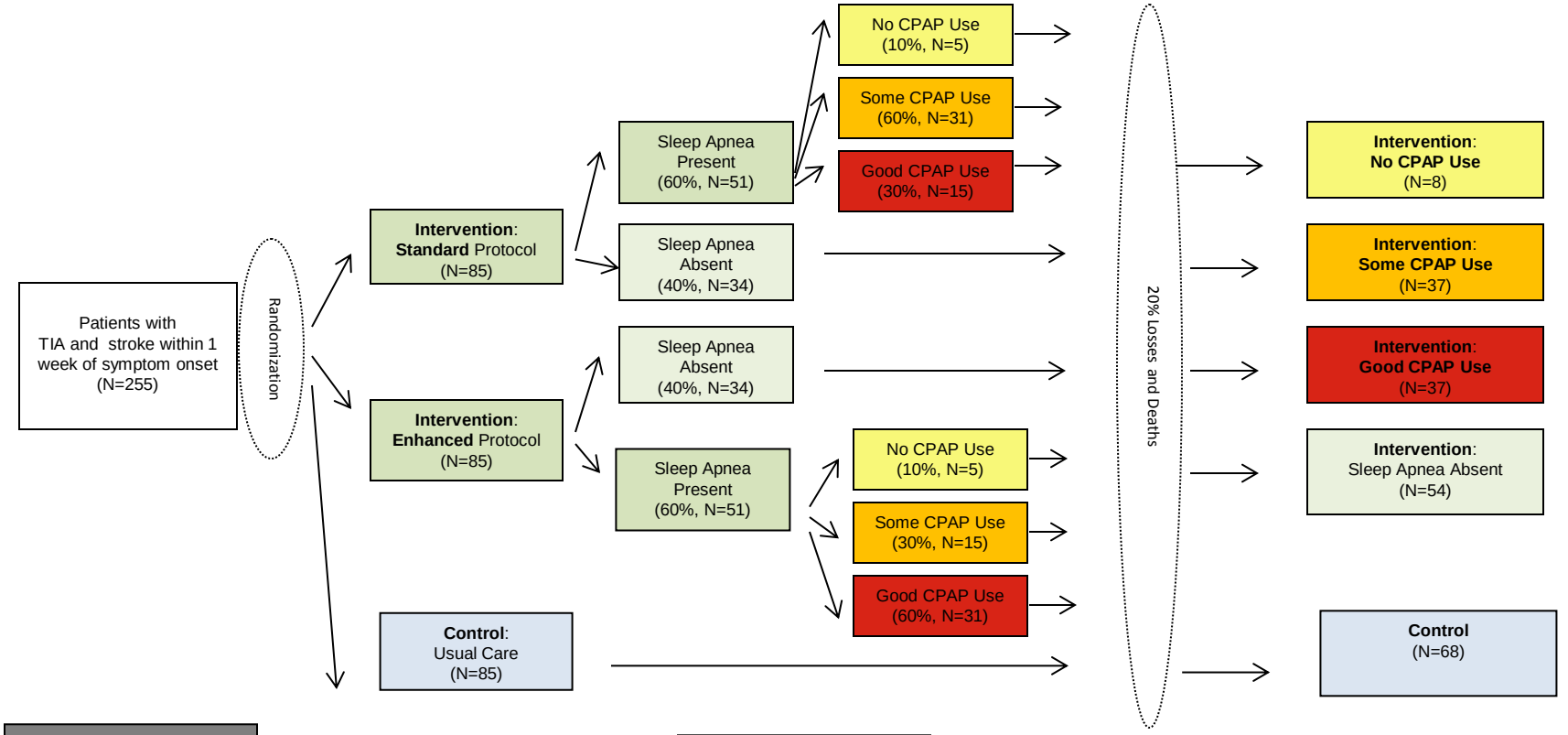
Sleep Tight Study Design:
A Diagnosis and Treatment Intervention Strategy Effectiveness Trial



Baseline Assessments

- Serum physiologic measures
- 24 hour blood pressure
- Holter monitor
- Flow-mediated vasodilation
- Carotid intima-media thickness
- Patient reported measures
- Polysomnography (intervention)

Process Measures

- Recruitment
- Retention
- CPAP Adherence
- Safety

Outcome Assessments (6M-1Y Post Enrollment)

- Serum physiologic measures
- 24 hour blood pressure
- Holter monitor
- Flow-mediated vasodilation
- Carotid intima-media thickness
- Patient reported measures
- Cardiovascular outcomes
- Polysomnography

Sleep Data

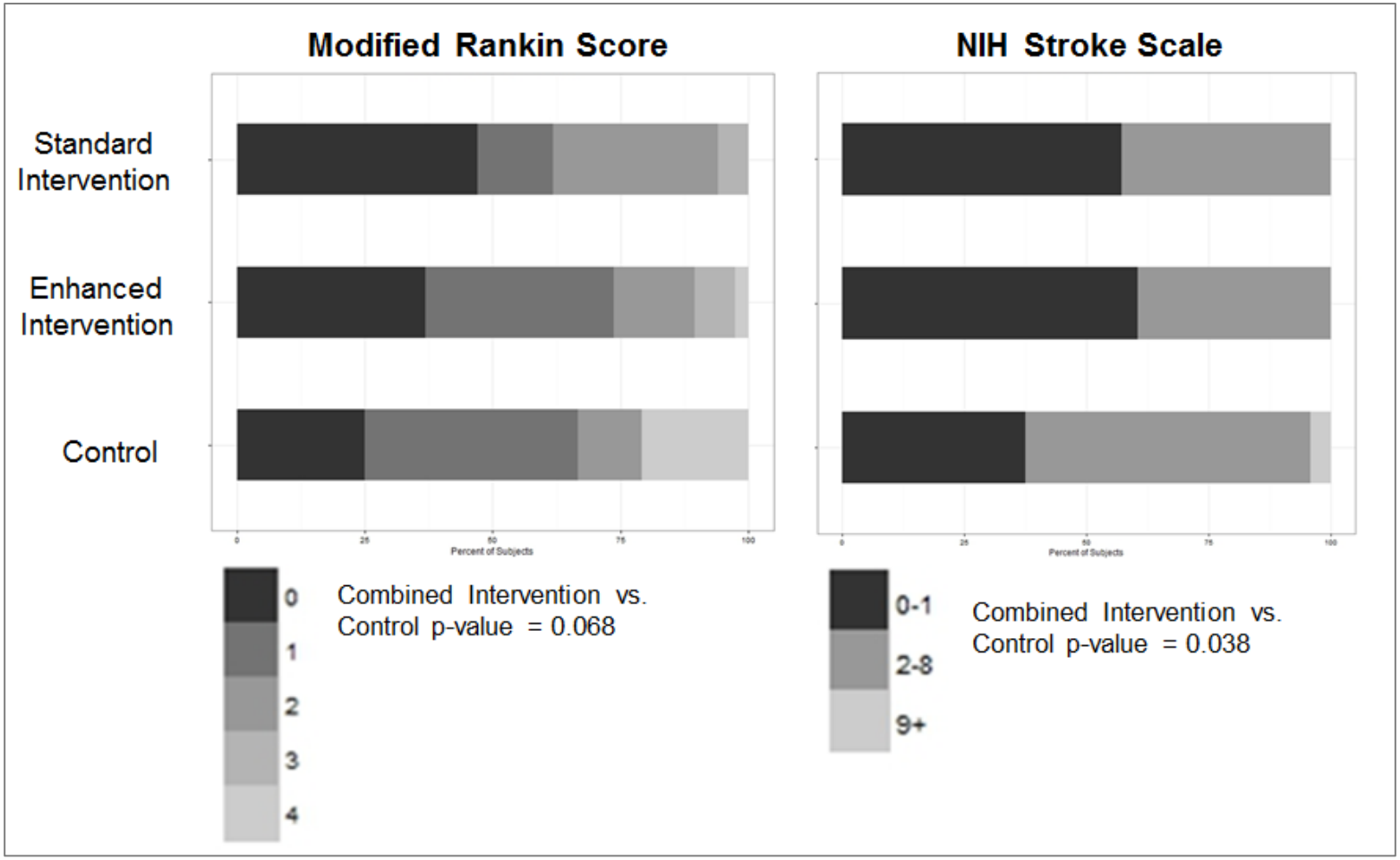
Polysomnographic Feature	Control* (n=84)	Intervention*		P-Value
		Standard (n=86)	Enhanced (n=82)	
Obstructive sleep apnea: (%)	69.0	73.6	80.4	0.35
Central sleep apnea: (%)	3.4	0	0	0.30
AHI, events/hr (Mean ± SD)*	28.5 ± 21.1	23.7 ± 19.6	21.6± 17.8	0.39
Oxygen Desat Index (4%) ,(Mean ± SD)*	20.6 ± 25.8	17.4 ± 17.7	21.0 ± 32.1	0.26
T90, (Mean ± SD)*	6.2 ± 5.7	4.8 ± 10.1	7.0 ± 11.2	0.78
Arousal Index (Mean ± SD)*	25.8 ± 14.9	21.7 ± 10.9	24.4 ± 13.0	0.54
Epworth Sleepiness Scale	8.4 ± 5.4	6.9 ± 5.0	7.0 ± 3.9	0.64

* Among patients with Sleep Apnea

CPAP Adherence

Outcome		Intervention Patients with Sleep Apnea		Unadjusted† P-Value	Adjusted† P-Value
		Standard	Enhanced		
CPAP Adherence Categories:* n (%)				0.81	0.95
Good		14 (38.9)	18 (40.0)		
Some		11 (30.6)	16 (35.6)		
None/Poor		11 (30.6)	11 (24.4)		
Number of hours of CPAP use per CPAP-use night	n	35	45	0.46	0.65
	Mean ± SD	3.9 ± 2.1	4.3 ± 2.4		
	Median (range)	4.5 (0.2-7.5)	4.5 (0.1-9.4)		
Number of hours of CPAP use per night	n	35	45	0.30	0.51
	Mean ± SD	3.3 ± 2.3	3.4 ± 2.8		
	Median (range)	3.4 (0.0-7.6)	3.7 (0.0-8.8)		

Sleep Tight Final Clinical Outcomes Among Patients with Sleep Apnea



Recurrent Vascular Event Rate

Endpoint		Control			Intervention Arms		
		N	% of those randomized	Rate per 100 person-years of follow-up	N	% of those randomized	Rate per 100 person-years of follow-up
WHOLE COHORT		84	100	68.7	168	100	127.3
All-cause Mortality	People	2	2.4	2.9	4	2.4	3.1
Cardiovascular Death	People	0	0.0	0.0	3	1.8	2.4
Non-Cardiovascular Death	People	2	2.4	2.9	1	0.6	0.8
Stroke	People	6	7.1		6	3.6	
	Events	6		8.7	7		5.5
Acute Myocardial Infarction (AMI)	People	1	1.2		0	0.0	
	Events	1		1.5	0		0.0
Unstable Angina Hospitalization	People	0	0.0		0	0.0	
	Events	0		0.0	0		0.0
Coronary Revascularization Urgent	People	0	0.0		3	1.8	
	Events	0		0.0	3		2.4
Any Above Events	**People**	**9**	**10.7**		**10**	**6.0**	
	Events	**9**		**13.1**	**14**		**11.0**

Summary: Evidence/Mechanisms

- Sleep apnea is independently associated with TIA, Stroke, M.I., cardiovascular mortality, all-cause mortality.
- Association between sleep apnea and diabetes/HTN suggests that these factors may be on the causal pathway between sleep apnea and cardiovascular disease.
- Mechanisms for the cardiovascular risk conferred by sleep apnea include intermittent hypoxia, sympathetic nervous system activation, mechanical load, and impaired sleep architecture

Summary: OSA's Heterogeneity

- AHI may not be the best predictor of OSA-related morbidity
- There is significant physiologic heterogeneity in sleep apnea with implications for risk of cardiovascular outcomes and responsiveness to treatment
- Multiple sleep-associated stressors that reflect distinct pathophysiologic pathways can be measured using sleep monitoring and may serve to better predict outcomes and benefits of treatment

Summary: Treatment Strategies

- Prospective observational studies suggests treatment with CPAP attenuates risk of cardiovascular/cerebrovascular outcomes
- Short-term randomized trial looking at intermediate measures of cardiovascular
- Long-term randomized controlled trials have not confirmed this benefit.
- Challenges exist in conducting long-term randomized controlled trials with CPAP: (i.e.,CPAP adherence, equipoise, and physiologic heterogeneity of sleep apnea)
- Treatment of sleep apnea may represent a novel therapeutic target for acute TIA/stroke that could lead to improved patient outcomes

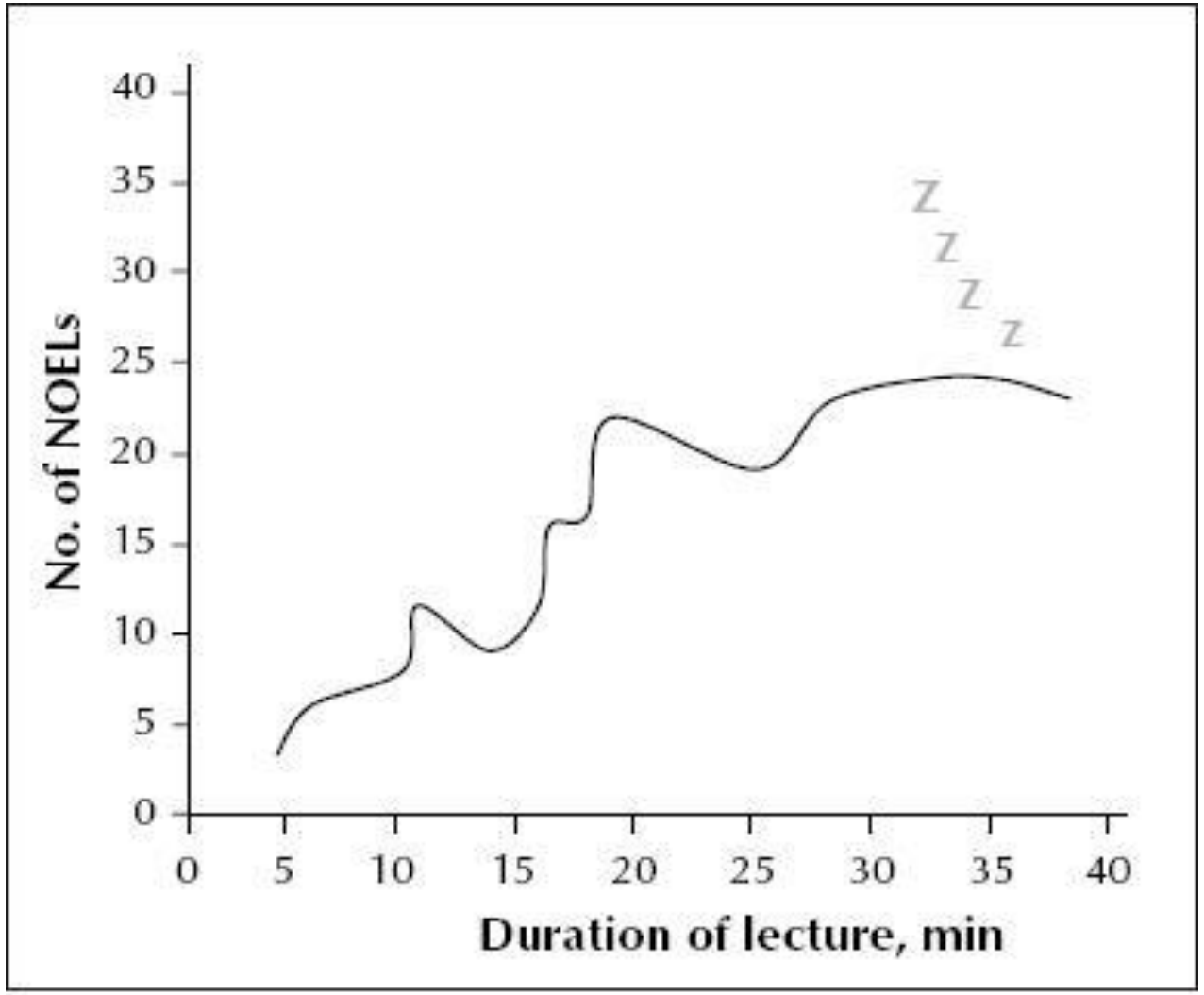


Fig. 1: Special incidence density curve, showing number of nodding-off events per lecture (NOELs) per 100 attendees over length of time of presentation.

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