

CARDIOVASCULAR CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA (SLEEPING WITH AN ENEMY)



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- No Financial interests, affiliations, or investments in companies or organizations related to this presentation.
- This lecture is not sponsored by any company or organization.

OBJECTIVES

Discuss prevalence and pathophysiology of OSA.

Acute and Chronic physiological effects of OSA.

Impact of Sleep Apnea on Cardiovascular Disorders.

Newer Treatment modalities for Obstructive sleep apnea – Beyond CPAP.

PREVALENCE OF OSA

- Overall Prevalence: 9% to 36%.
- Males: 13% to 33%.
- Females: 6% to 19%.
- Greater in Obese men and women compared with overweight men and women.
- Prevalence is increase with age (90% in men and 78% in women).
- Overall, Advancing age, male sex, and higher BMI increase OSA prevalence.

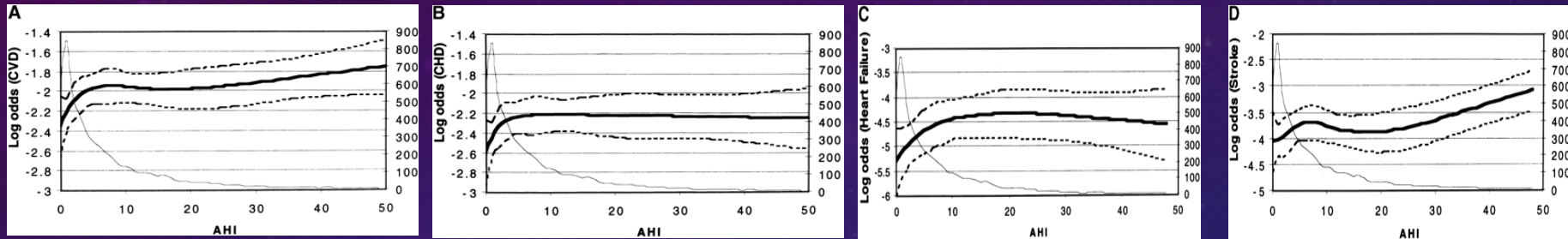
Senaratna CV et al: Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep medicine reviews. Volume 34, August 2017, {Pages 70-81.

SLEEP QUALITY AND QUANTITY AND CARDIOVASCULAR CONSEQUENCES

- Sleep duration and cardiovascular mortality:
 - < 6.5 hours: 15%
 - **> 6.5 to <7.5 hours: 11%**
 - > 7.5 hours: 17%

Kim JH et al: Sleep duration and mortality in patients with coronary artery disease.
AJC. Volume 13, Issue 6, March 2019. p 874-881.

IS SLEEP APNEA A RISK FACTOR FOR CARDIOVASCULAR DISEASE?



Cardiovascular Disease

Coronary artery disease

Heart Failure

Stroke

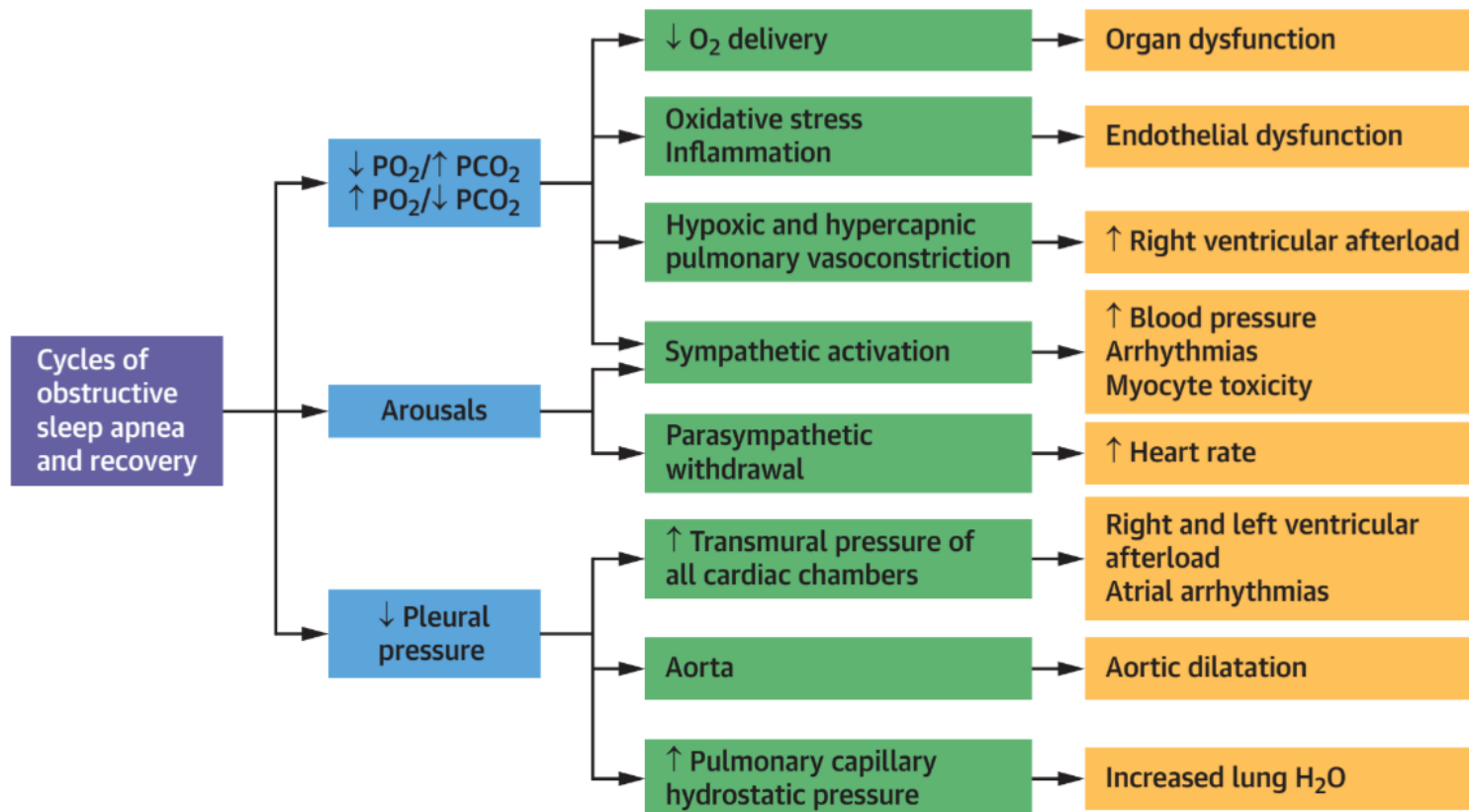
- Population based study in 6,424 patients undergoing sleep study.
- 16% reported at least one manifestation of CVD.
- SDB was associated more strongly with self reported heart failure and stroke rather than self-reported CAD.
- AHI and its correlate “percent of sleep time in hypoxemia” was fairly associated with prevalent CVD with relative odds of 2.1 to 2.5.

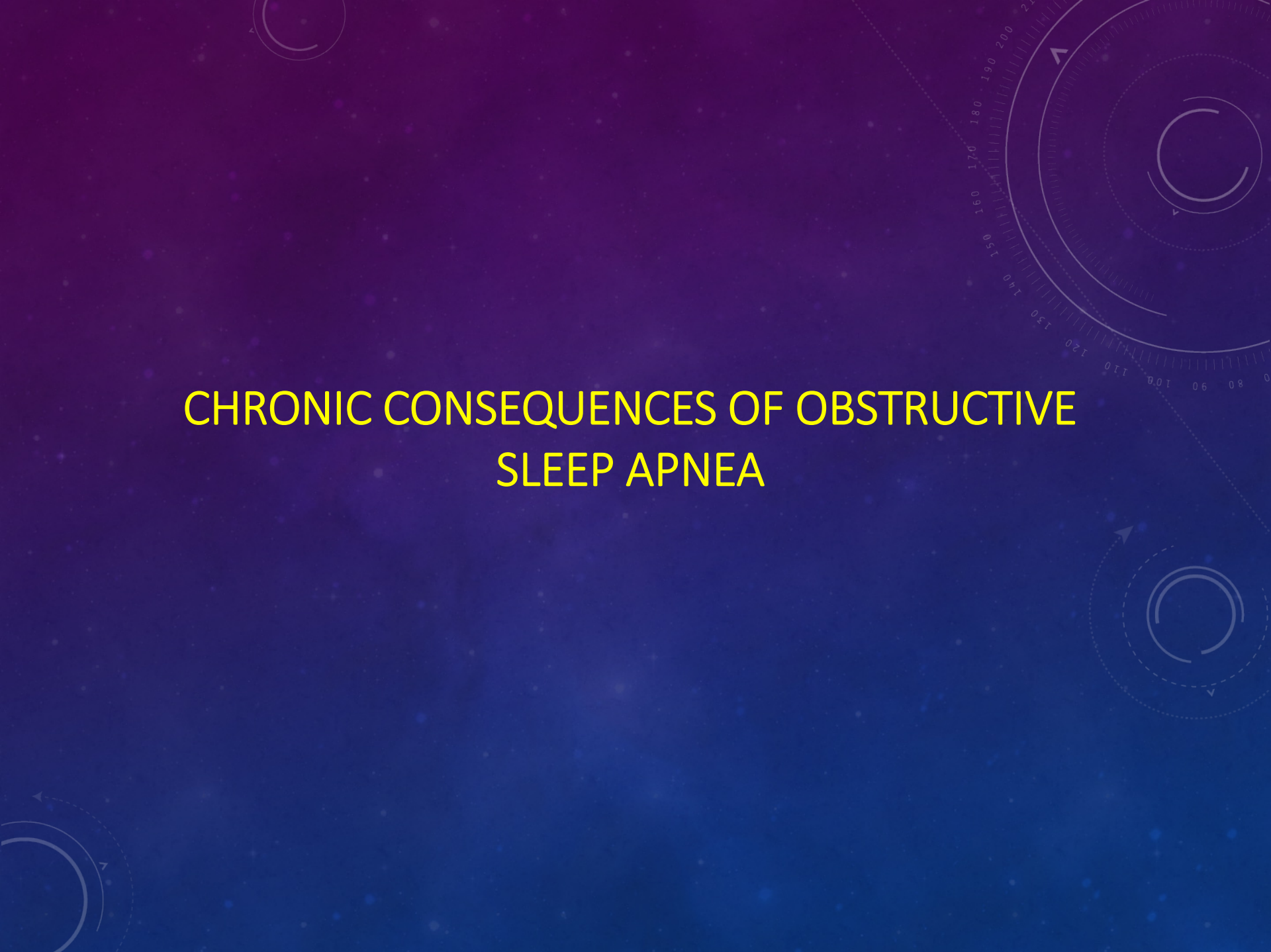
PATHO-PHYSIOLOGIC CHANGES IN OSA CAUSING CARDIOVASCULAR DISORDERS

- **Acute Effects**
 - Intermittent Hypoxia
 - Repeated Arousals
 - Negative intra-thoracic pressure swings
- **Chronic Effects**
 - **Vascular and endothelial effects**
 - Atherosclerosis
 - Platelet Aggregation & Coagulation
 - Elevated C-Reactive Protein
 - **Autonomic Cardiovascular function**
 - Peripheral chemoreceptors and sympathetic nervous system activity
 - Baroreflexes
 - Heart Rate variability (HRV)

PATHOPHYSIOLOGICAL CONSEQUENCES OF SLEEP APNEA SYNDROME

Biological Pathways Mediating Cardiovascular Consequences of Sleep Apnea

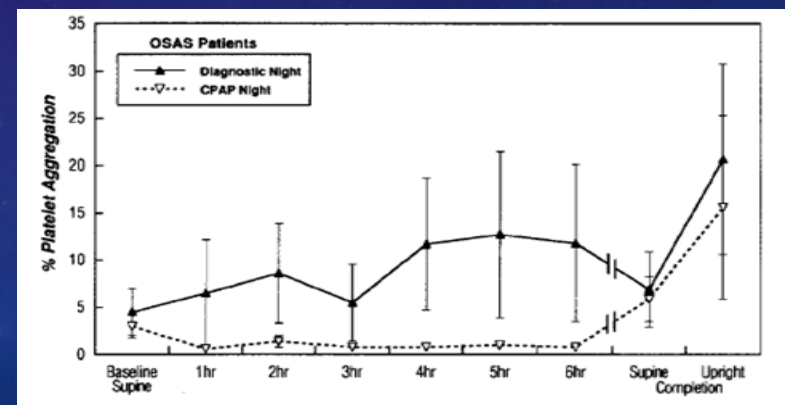
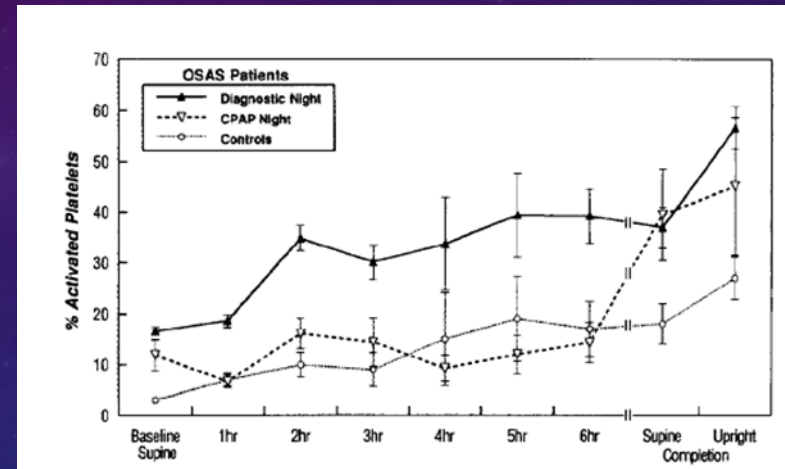




CHRONIC CONSEQUENCES OF OBSTRUCTIVE
SLEEP APNEA

PLATELET ACTIVATION & AGGREGATION IN OSA

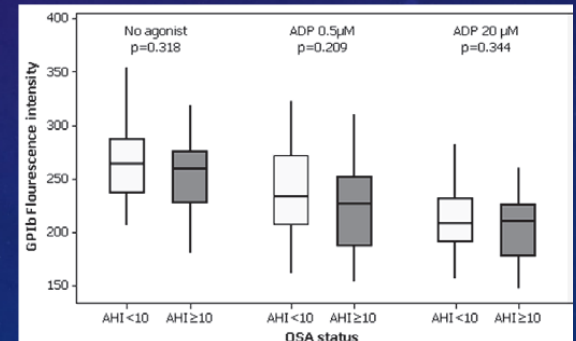
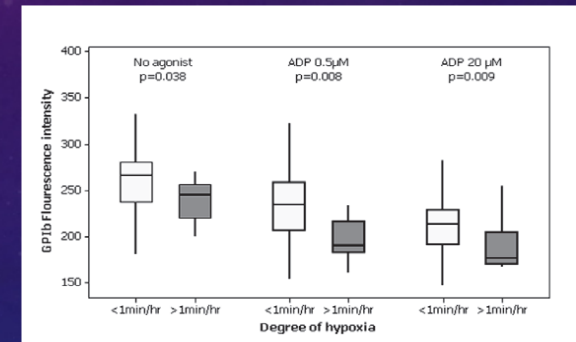
- Small Study group
- Significant increase in sACT (spontaneous platelet activation) and sACG (platelet aggregation) in OSA compared to baseline values.
- No relationship was found between degree of OSA or nadir of O₂ desaturation.
- Marked reduction of sACT and sACG following application of N-CPAP.



Bokinsky et al: Spontaneous platelet activation and aggregation during OSA and its response to therapy with N-CPAP. Chest. Vol 108; No. 3; 625-630, 1995.

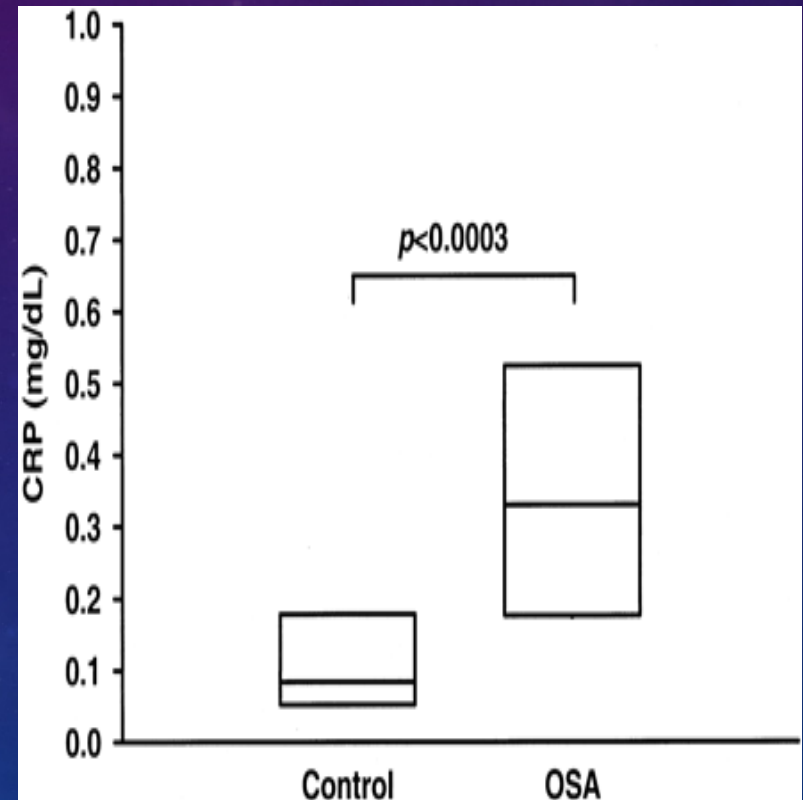
PLATELET ACTIVATION & HYPOXIA

- Platelet surface glycoprotein Ib (GPIb) plays a key role in primary hemostasis and arterial thrombosis and is down regulated upon activation of platelets.
- Subjects who had oxygen desaturation (expressed as minutes of time spent with an SaO₂ < 90% per hour of sleep) had lower GPIb fluorescence in circulating platelets.
- In multivariate analyses, only nocturnal hypoxemia and femal gender predicted agonist response.
- The degree of hypoxemia in OSA may be viewed as a possible marker for adverse atherothrombotic consequences of OSA.



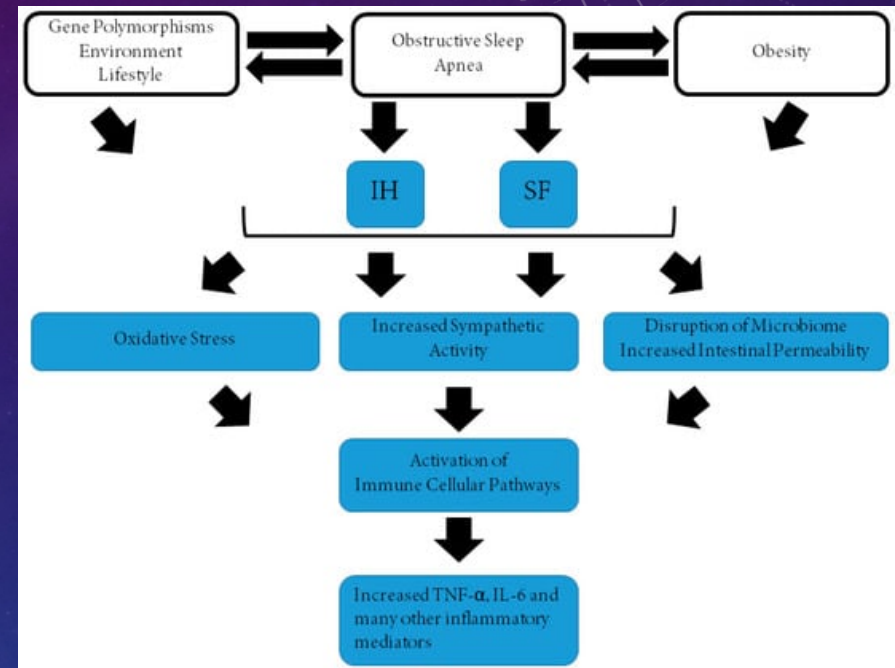
ELEVATED CRP IN OSA

- CRP – important serum maker for cardiovascular risk determination.
- Plasma CRP levels are higher in patients with OSA (0.33) versus (0.09) in controls (P = 0.008).
- Significant positive relationship between CRP and AHI (p=0.008).
- CRP levels are independently associated with OSA severity (p= 0.032).
- Levels of CRP in OSA comparable to the levels in healthy persons without OSA who are at high risk for future cardiovascular event.



SYSTEMIC INFLAMMATION AND OXIDATIVE STRESS

- TNF – alpha and Interleukin -8.
- Lead to leukocyte migration into vascular endothelium.
- Hypoxia - Increased production of reactive oxygen radicals and plasma lipid peroxidation.
- This vascular endothelial injury leads to atherosclerosis.



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PROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN SLEEP-DISORDERED BREATHING AND HYPERTENSION

PAUL E. PEPPARD, PH.D., TERRY YOUNG, PH.D., MARI PALTA, PH.D., AND JAMES SKATRUD, M.D.

- Prospective data from Wisconsin sleep cohort study.
- Odds ratios:

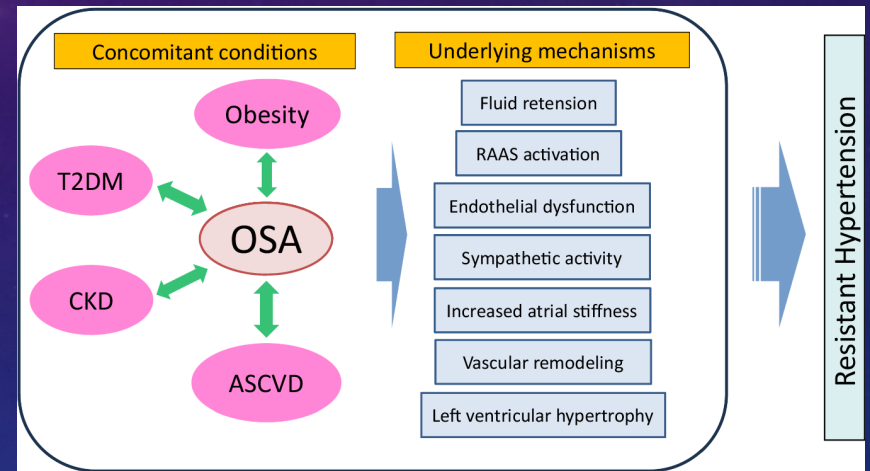
	<u>Baseline</u>	<u>4Yr FU</u>
AHI 0-5 /hr.	1.39	1.40
Mod (AHI) 5-15 /hr.	1.92	1.97
Severe (AHI >15 /hr.	2.66	2.77
- Patients with moderate to severe OSA had two and three times, the odds of having hypertension than those without OSA.
- Even patients with minimal SDB (AHI 0-5/hr) had higher odds of HTN than those with no episodes of SDB (AHI 0/hr).

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

OSA AND HYPERTENSION

- 30-50% of patients with hypertension have OSA
- 50% of the patients with OSA have hypertension.
- 80% of patients with resistant hypertension have OSA.
- Incidence of hypertension increases with the severity of OSA (dose response relationship).

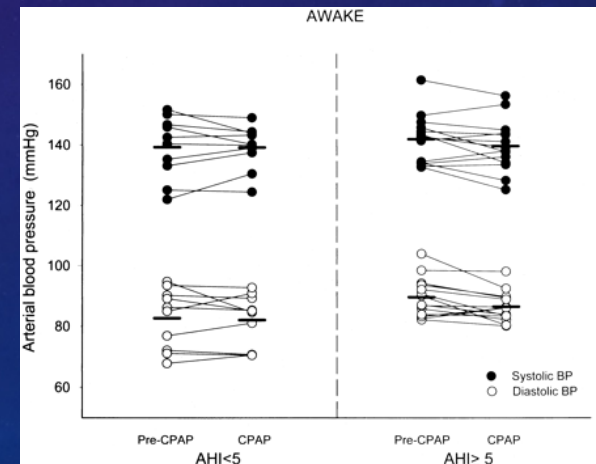
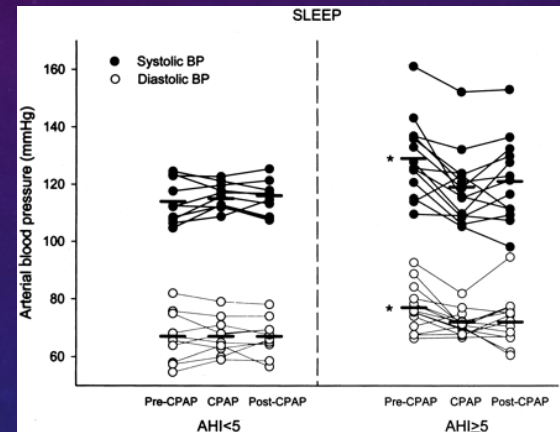


Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. *N. Engl J Med.* 2000;342:1378–84.

Shiina K: Obstructive sleep apnea-related hypertension: a review. *Hypertension research* 47, 3085-3098; 2024.

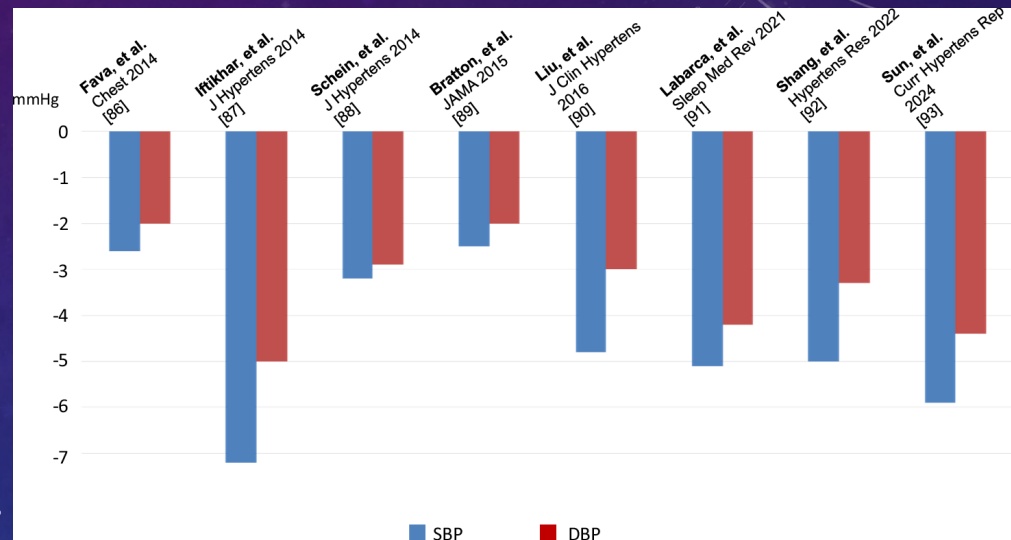
CPAP TREATMENT ON HYPERTENSION

- Patients with SDB had significant decrease in SBP & DBP both during sleep and awake after 3 weeks of CPAP.
- Mean nighttime BP
 - SBP decreased by 10.4 mm Hg ($p=0.0003$).
 - DBP decreased by 5.2 mm Hg ($p=0.024$).
- Mean Day time BP
 - Systolic BP decreased by 2.7 mm Hg ($p=0.07$).
 - DBP decreased by 2.3 mm Hg ($p=0.08$).



EFFECT OF CPAP ON HYPERTENSION

- Effect of CPAP on BP variables:
 - Higher BMI.
 - Severe OSA (AHI > 30).
 - Hypersomnolence.
 - Higher BP values.
 - Untreated Hypertension.
 - Nocturnal Hypertension.
 - Treatment- resistant hypertension.
 - Adherence to CPAP.



CPAP has modest but significant BP-lowering effects of 2–7 mmHg in SBP and of 2–5 mmHg in DBP in OSA-related hypertension

ISCHEMIA AND OSA

- Nocturnal ST-segment changes are common in patients with OSA – 30%.¹
- ST segment depression episodes are related to sleep fragmentation and sympathetic tone.²
- ST-segment depressions are more frequent in those with severe sleep apnea or prior complaints of nocturnal angina.³
- CPAP treatment significantly reduces the total number of events.⁴

1. Hanly et al: ST-segment depression during sleep in obstructive sleep apnea. [*The American Journal of Cardiology* Volume 71, Issue 15](#), 1 June 1993, Pages 1341-1345.

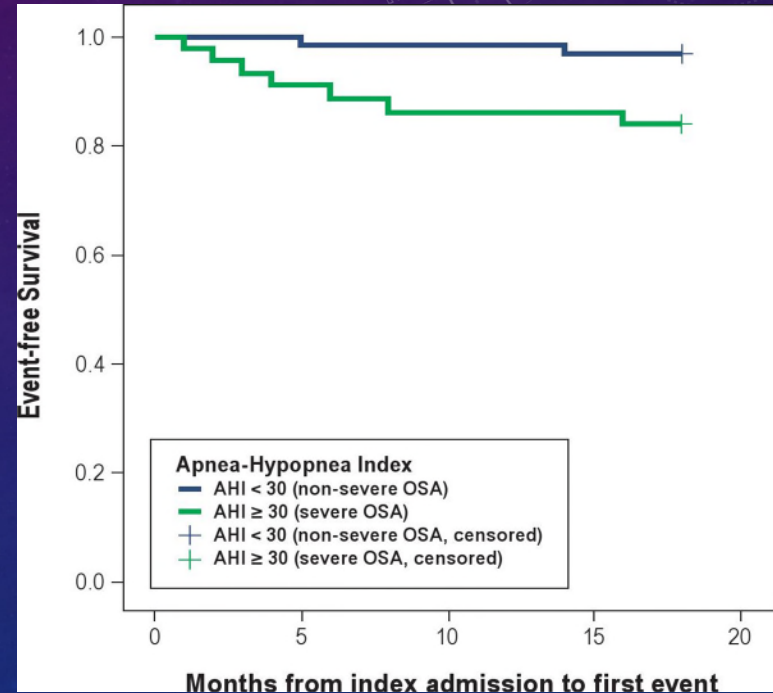
2. Fernandez et al: Cardiac rhythm disturbances and ST-segment depression episodes in OSA and its mechanisms. *Chest*, Vol 127; 15-22; 2005.

3. Philip et al: ST segment abnormality, angina during sleep and OSA. *Sleep* 1993; 16; 558-559.

4. Harbison et al: Cardiac rhythm disturbances in OSA :effects of CPAP therapy. *Chest* 118; 591-595; 2000.

OBSTRUCTIVE SLEEP APNEA & MYOCARDIAL INFARCTION

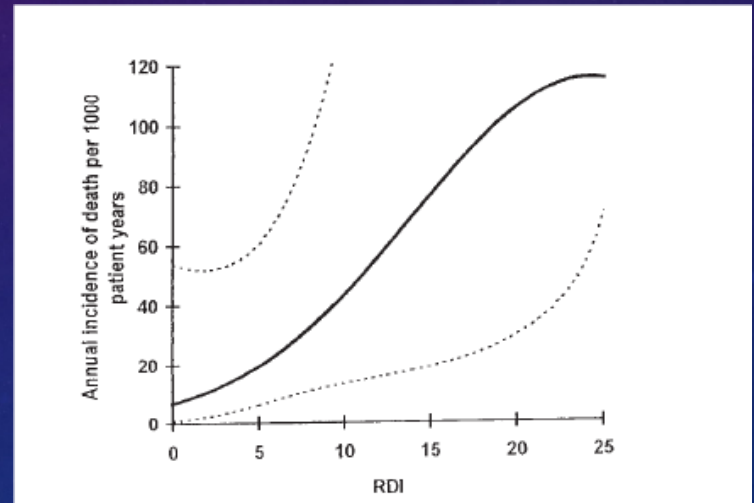
- Prospective longitudinal cohort study
- 105 PATIENTS:
 - 44 (42%) had severe OSA and 61 (58%) non-severe OSA.
 - Between 1- and 18-month follow-up without OSA treatment.
 - The incidence of major adverse events was significantly higher in the severe OSA group (15.9% versus 3.3%, adjusted HR: 5.36, 95% CI: 1.01 to 28.53, $p = 0.049$).
 - Kaplan-Meier event-free survival curves showed the event-free survival rates in the severe OSA group was significantly worse than that in the non-severe OSA group ($p = 0.021$).
- 42% of the patients admitted with STEMI have undiagnosed severe OSA



Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation* 2010;122:352-60

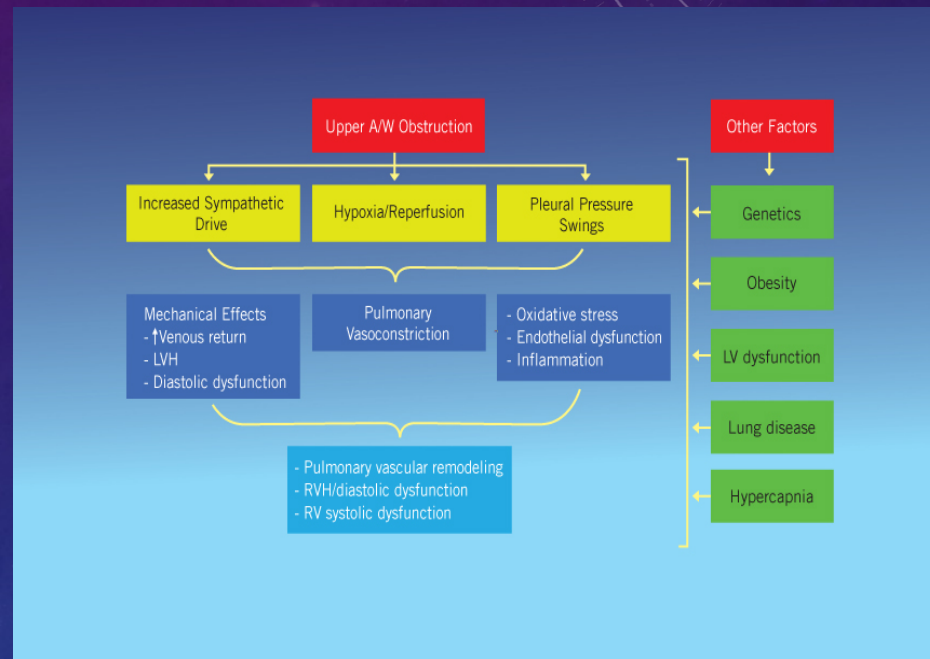
CAD, OSA AND MORTALITY

- Myocardial ischemia during sleep in patients with OSA may be silent but no reports on the prevalence of OSA among patients with CAD with silent nocturnal ischemia.
- In patients with CAD, OSA is a poor prognostic indicator. Significant high mortality (38%) than those without OSA (9%, $p=0.018$).
- Respiratory disturbance Index (RDI) is the independent predictor of cardiovascular mortality ($p=0.007$).



OSA & PULMONARY HYPERTENSION

- In the largest series published to date, 17% patients with OSA appear to have pulmonary hypertension.
- Animal experiments have shown that intermittent hypoxia (4-8 hours per day) is sufficient to induce a sustained rise in PAP and RV hypertrophy.
- OSA patients with PH often have concomitant cardiac or pulmonary disease, leading to the speculation that such comorbidities are a prerequisite for the development of significant PH and RV failure in OSA.
- PH in association with OSA is mainly precapillary in nature.
- However, given the prevalence of morbid obesity, hypertension, and left ventricular systolic and diastolic dysfunction in this population, it is likely that postcapillary factors play an important role.
- Diastolic dysfunction and left ventricular hypertrophy with elevated PCWP have been demonstrated in OSA patients without any other evidence of underlying cardiac disease and may contribute to pulmonary hypertension.

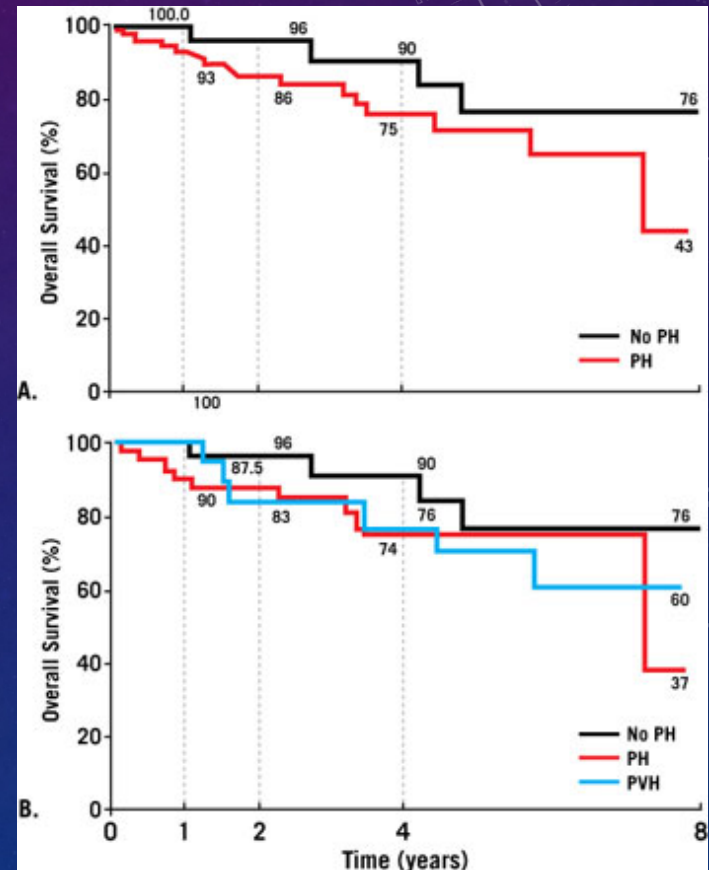


1. McGoon M, Gutterman D, Steen V, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126(1 Suppl):14S-34S.

2. Chaouat A, Weitzenblum E, Krieger J, Oswald M, Kessler R. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients. *Chest*. 1996;109(2):380-386

SIGNIFICANCE OF PULMONARY HYPERTENSION IN OSA

- OSA patients with PH have lower functional capacity (as measured by 6-minute walk distance) and more dyspnea compared to OSA patients without PH.
- Mortality may be increased in patients with PH and that in addition to factors such as age, FEV1, DLCO, and AHI, pulmonary hemodynamics are important correlates of increased mortality in patients with OSA.
- CPAP therapy has a modest role in improving pulmonary hemodynamics in OSA and is less likely to normalize the more severe elevations in PAP.

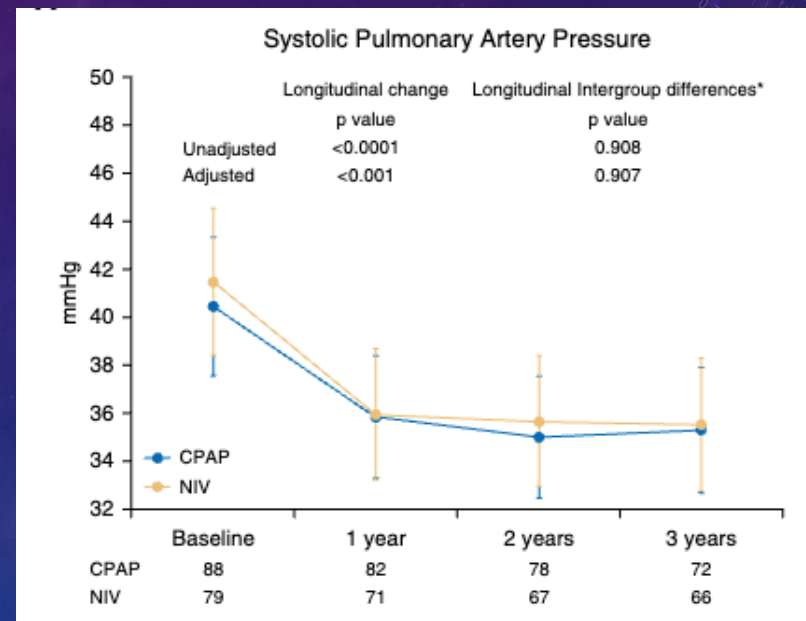


Minai OA, Ricaurte B, Kaw R, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am J Cardiol.* 2009;104(9):1300-1306

Atwood CW Jr, McCrory D, Garcia JG, Abman SH, Ahearn GS; American College of Chest Physicians. Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl):72S-77S.

IMPACT OF CPAP ON PULMONARY HYPERTENSION

- 196 patients with OSA and OHS with Pulmonary hypertension.
- Results:
 - Improved RVSP
 - Improved left ventricle diastolic function.
 - No difference in LVEF.
 - Improvement in chronic dyspnea.



Masa JF: Echocardiographic changes with positive airway pressure therapy in obesity hypoventilation syndrome. American Journal of Respiratory and Critical Care Medicine Volume 201 Number 5 | March 1 2020. The Pickwick study.

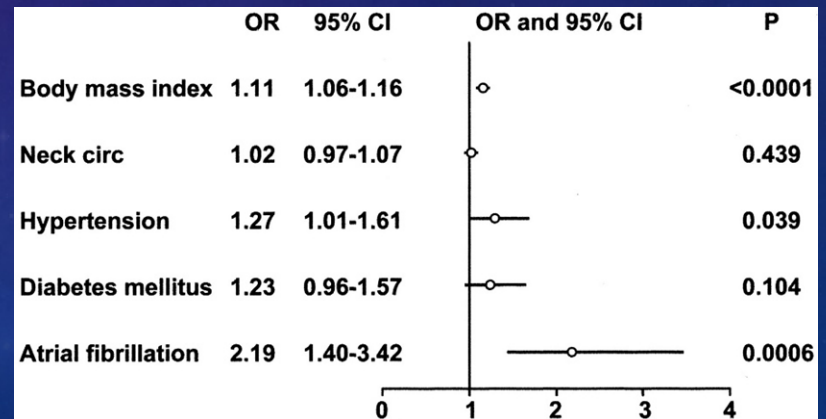
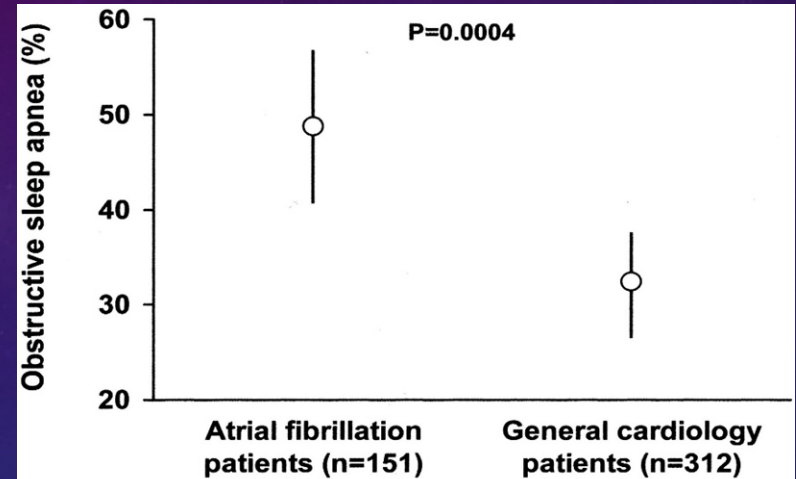
ATRIAL FIBRILLATION AND OSA

OSA is more prevalent in patients with Atrial fibrillation (49% Vs 32%)

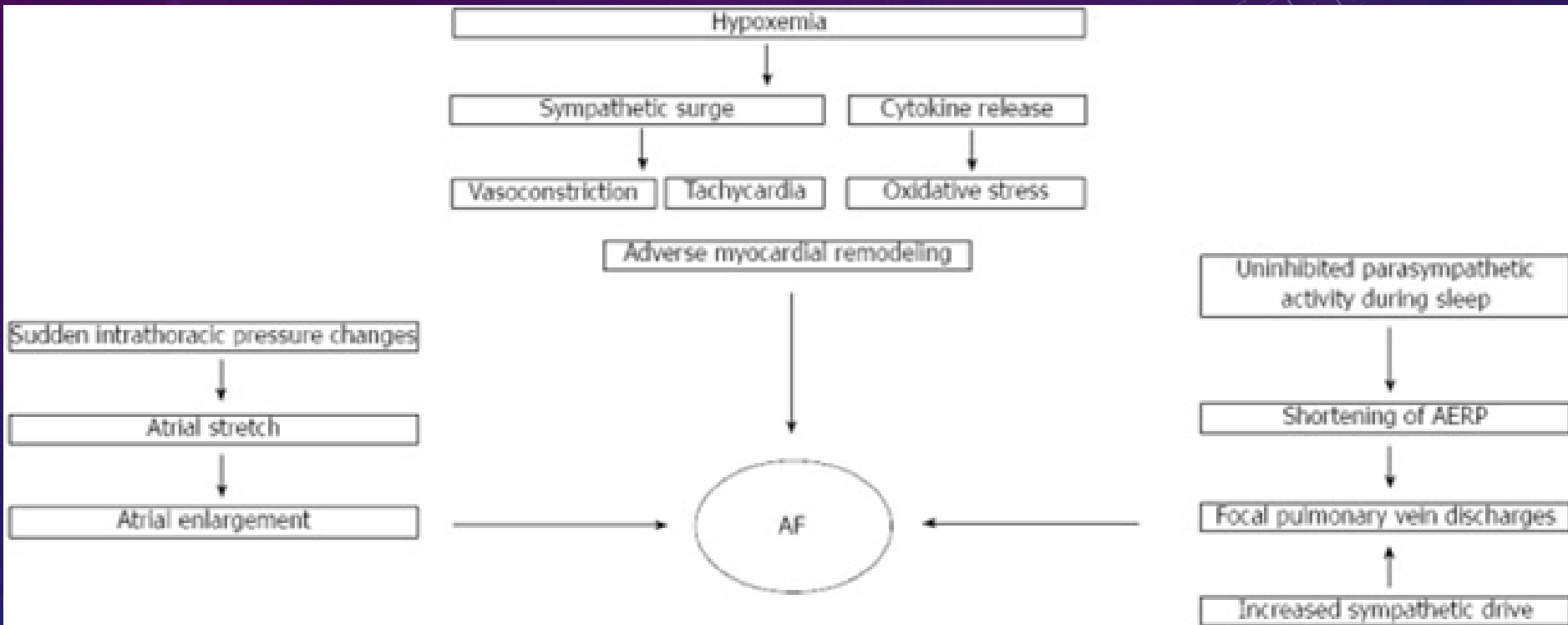
Gami AS, Pressman G, Caples SM, Kanagala R, Gard JJ, Davison DE, Malouf JF, Ammash NM, Friedman PA, Somers VK. Association of atrial fibrillation and obstructive sleep apnea. Circulation. 2004;110:364–367.

ATRIAL FIBRILLATION AND OSA

- Prospective study – 524 patients
- 49% of patients with AF had OSA compared to general cardiology group (32%, $p=0.0004$).
- In patients with OSA, hypoxia, hypercapnia, chemoreceptor excitation, increased sympathetic drive over a period if untreated may initiate or predispose AF.
- Reverse may be true!



PATHOPHYSIOLOGY OF A-FIB IN OSA



IMPACT OF CPAP ON ATRIAL FIBRILLATION IN PATIENTS WITH OSA

- Meta analysis:
 - Patients treated with CPAP had a 42% decreased risk of atrial fibrillation ($p = <0.001$)¹
 - Benefits of CPAP were Stroger for younger, obese and male patients.
 - Use of CPAP lead to significant positive reduction in A-fib complications ($p=0.04$)²

1. Qureshi WT et al: *Meta-Analysis of Continuous Positive Airway Pressure as a Therapy of Atrial Fibrillation in Obstructive Sleep Apnea. Volume 116, Issue 11*1767-1773December 01, 2015.
2. Affas Z et al: *Continuous positive airway pressure reduces the incidence of atrial fibrillation in patients with obstructive sleep apnea: A Meta-Analysis and Systematic Review.*tiSystematic Review. Vol 7. issue 2, 2022 . <https://doi.org/10.51894/001c.34521>

PREVALENCE OF OSA IN STROKE

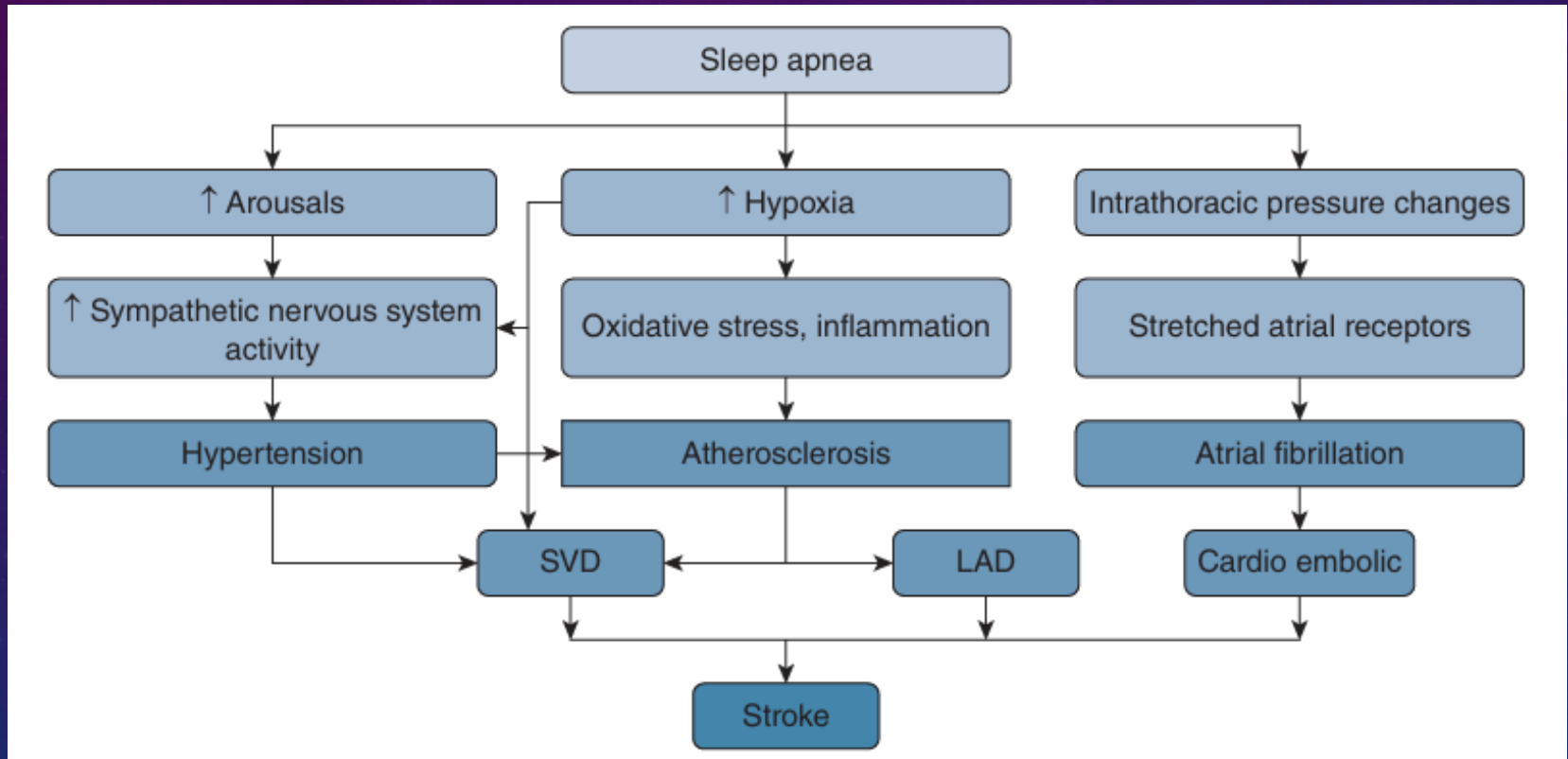
- OSA is an independent risk factor for the increased risk of stroke ¹.
- In a meta-analysis ² that assessed the prevalence of poststroke OSA, it was found:
 - 72% had an AHI > 5
 - 63% had an AHI > 10
 - 38% had an AHI > 20
 - 29% had an AHI > 30
 - Males had a higher percentage than females (65% compared to 48% (p = 0.001).
 - Patients with recurrent strokes had a higher percentage of SDB (than initial strokes (74% compared to 57% p = 0.013).
- OSA was found to be highly prevalent even 6 months following stroke ³.

1. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med.* 2005;353:2034-2041.

2. Johnson KG, Johnson DC. Frequency of sleep apnea in stroke and TIA patients: a meta-analysis. *J Clin Sleep Med.* 2010;6:131-137.

3. Huhtakangas JK, Saaresranta T, Bloigu R, Huhtakangas J. The evolution of sleep apnea six months after acute ischemic stroke and thrombolysis. *J Clin Sleep Med.* 2018;14:2005-2011.1.

PATHOPHYSIOLOGY OF OSA AD STROKE



STROKE AND OSA AND TREATMENT WITH CPAP

- Improve Cognitive function
- Improve sleep quality
- Improve daytime excessive sleepiness
- Improved attention and calculation span.
- No improvement in Neurological status
- No improvements in ADL

	β	Adjusted R ²	p-Value
Δ AHI			
Δ MMSE	0.071	0.114	0.033 *
Δ ESS	0.109	0.220	0.002 *

Δ , difference score between pre-intervention and post-intervention. AHI, apnea-hypopnea index; MMSE, Korean version of the Mini-Mental State Examination; ESS, Epworth Sleepiness Scale. * p-value < 0.05.

Kim H et al: **Improvement of Cognitive Function after Continuous Positive Airway Pressure Treatment for Subacute Stroke Patients with Obstructive Sleep Apnea: A Randomized Controlled Trial.**

Brain Sci. 2019, 9(10), 252

SLEEP & DEATH

Nyx is the goddess of Night

and she had Two sons:

Hypnos: (god of sleep)

Thanatos: (god of death)

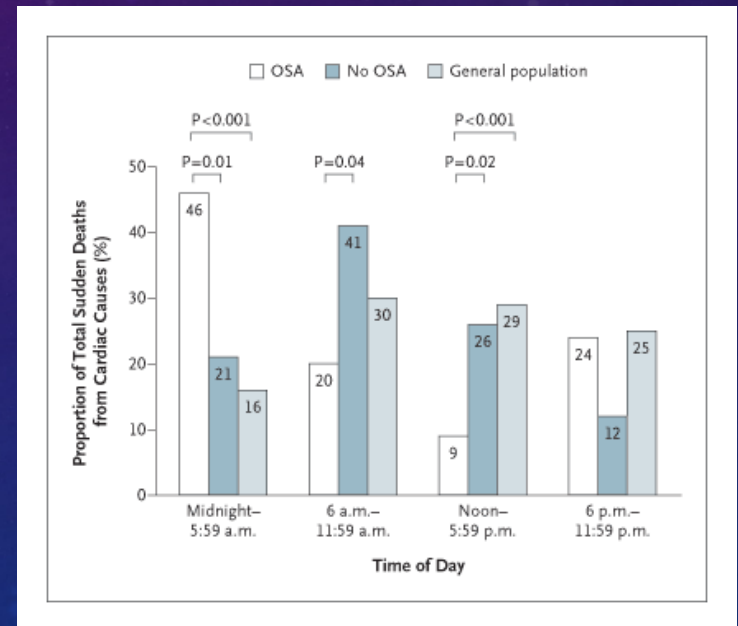
Both Hypnos and Thanatos are brothers.



Hypnos (left) and Thanatos (right) carrying dead Sarpedon, while Hermes watches.

RISK OF SUDDEN DEATH

- Increased mortality if the Apnea index >20/ hr. (37% Vs 4%).¹
- A cardiovascular cause of death is more common among those who snore habitually or often.
- Snoring is a risk factor for sudden death between 4 A.M. and noon among those dying of cardiovascular causes.
- Patients with underlying cardiovascular disease and OSA have 46% more chance of dying between 12 AM to 6 Am than patients without OSA (21%, p=0.01).²



1. He et al: Mortality and apnea index in OSA. Chest; Vol 74; 9-14; 1994.

2. Gami et al: Day-Night Pattern of Sudden Death in Obstructive Sleep Apnea. Vol 352:1206-1214, No.12; Mar 2005.

The background is a dark blue gradient with a subtle pattern of white and light blue circular elements. These include solid and dashed concentric circles, some with arrows indicating direction. A prominent feature is a large, semi-circular scale or gauge on the left side, with numerical markings ranging from 150 to 260. The overall aesthetic is technical and futuristic.

NEWER TREATMENT OPTIONS FOR OBSTRUCTIVE SLEEP APNEA

PHARMACOLOGICAL THERAPY

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for Obstructive Sleep Apnea and Obesity

A PLAIN LANGUAGE SUMMARY

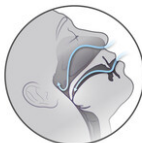
Based on the NEJM publication: Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity by A. Malhotra et al. (published June 21, 2024)

In two trials, researchers assessed the efficacy and safety of tirzepatide for the treatment of adults with obstructive sleep apnea and obesity.

Obstructive sleep apnea is characterized by repetitive pharyngeal collapse during sleep, resulting in apneas and hypopneas. It is also an independent risk factor for cardiovascular disease.

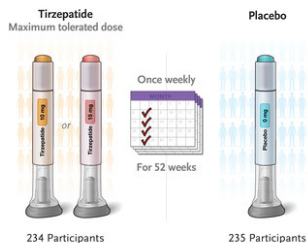
WHY WERE THE TRIALS DONE?

Excess adiposity is a major reversible risk factor for obstructive sleep apnea and its complications. Tirzepatide—a long-acting agonist of the glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor—has been shown to reduce body weight. Whether tirzepatide can treat obstructive sleep apnea is unknown.



HOW WERE THE TRIALS CONDUCTED?

In two trials, 469 adults with moderate-to-severe obstructive sleep apnea and obesity were assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo subcutaneously once weekly for 52 weeks. Trial 1 enrolled participants who were not receiving positive airway pressure (PAP) therapy. Trial 2 enrolled those who were receiving PAP therapy. The primary end point was the change from baseline in the apnea-hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep).



PARTICIPANTS



WHO
Trial 1 (no PAP therapy):
 234 adults
 Mean age, 48 years
 Men: 67%; Women: 33%

Trial 2 (PAP therapy):
 235 adults
 Mean age, 52 years
 Men: 72%; Women: 28%

CLINICAL STATUS
 Apnea-hypopnea index, at least 15 events per hour (mean, approximately 50)
 Body-mass index, at least 30 (mean, 39)
 No type 1 or type 2 diabetes

TRIAL DESIGN

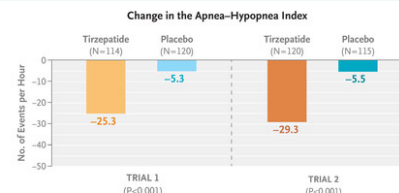
- PHASE 3
- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- DURATION: 52 WEEKS
- LOCATION: 60 SITES ACROSS 9 COUNTRIES

The NEW ENGLAND JOURNAL of MEDICINE

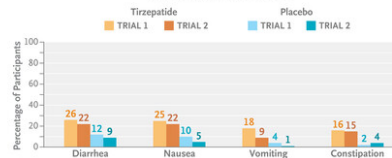
RESULTS

In both trial 1 and trial 2, tirzepatide led to a significantly greater reduction in the AHI at week 52 than placebo.

All key secondary end points also favored tirzepatide over placebo, including the percent change in body weight and changes in systolic blood pressure and high-sensitivity C-reactive protein concentration.



Most Common Adverse Events



The most common adverse events with tirzepatide were gastrointestinal; most were mild to moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

- Long-term cardiovascular outcomes could not be assessed, given the design and relatively short duration of the trials.
- The trials excluded participants who did not have obesity and therefore did not analyze the effect of tirzepatide in people with overweight or normal body-mass index.
- The trials were not designed to assess whether the results differed according to participants' symptoms at baseline.

CONCLUSIONS

In adults with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide given once weekly led to a significantly greater reduction in the apnea-hypopnea index at 52 weeks than placebo.

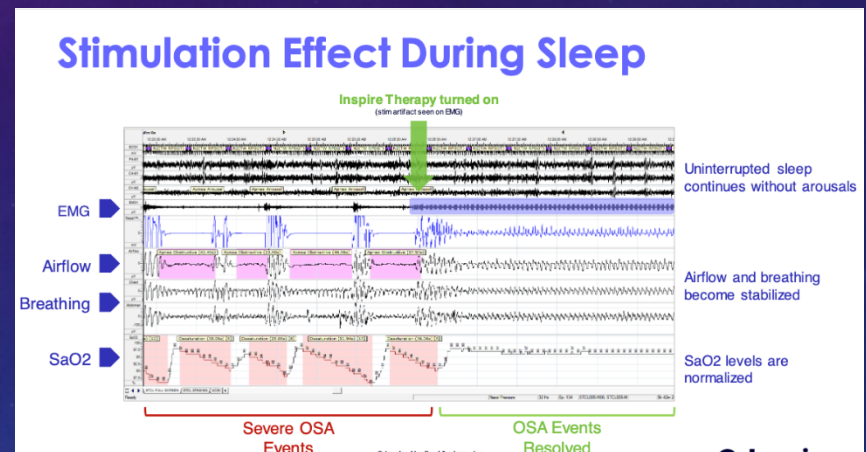
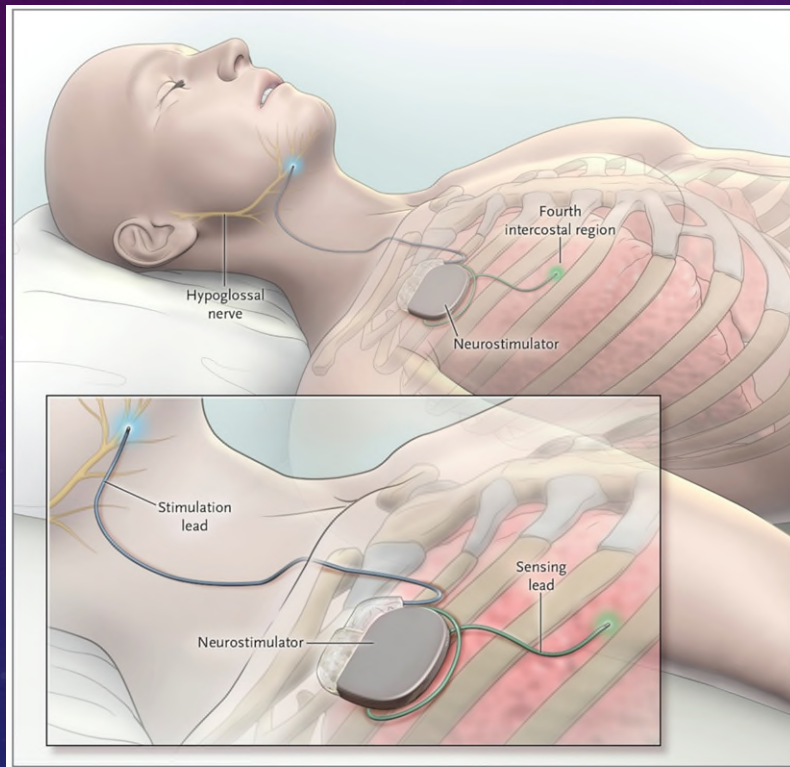
LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT05412004
 Trial funding: Eli Lilly
 Full citation: Malhotra A, Grunstein RR, Fietze L, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med 2024;391:1193-205. DOI: 10.1056/NEJMo2404881
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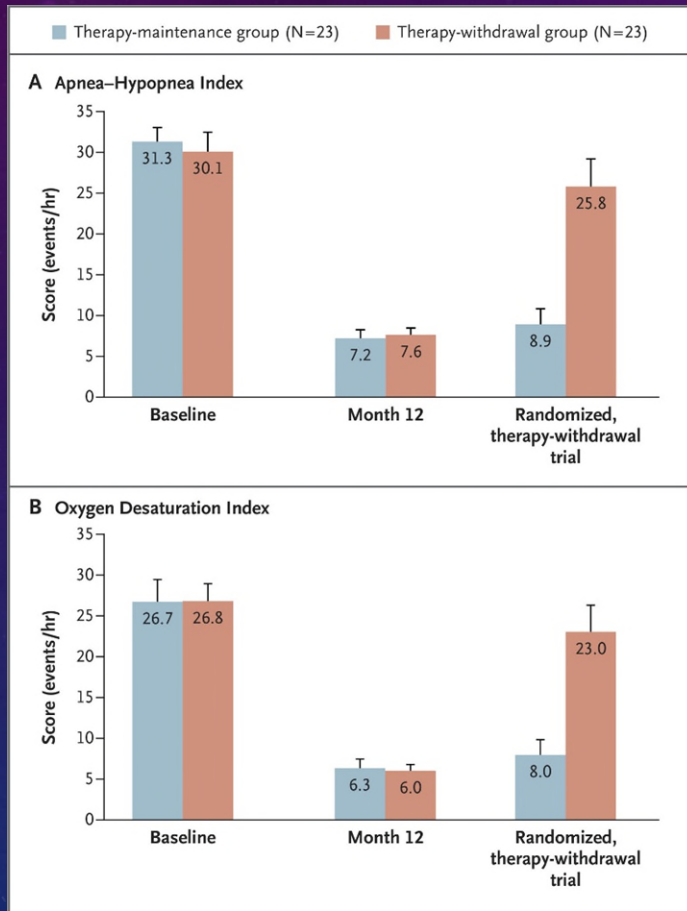
Among persons with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes.

HYPOGLOSSAL NERVE STIMULATION



Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, et al. Upper-airway stimulation for obstructive sleep apnea. *N. Engl J Med.* 2014;370:139–49.

PRIMARY OUTCOME & SIDE EFFECTS



- Expected post surgical events including sore throat from intubation, pain at incision site, and muscle soreness- 88%
- Temporary tongue weakness – 18% (resolved over days to weeks).
- Discomfort associated with stimulation -40%.
- Tongue soreness: 21%
- Overall risk of serious adverse side effects: <2%.

Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, et al. Upper-airway stimulation for obstructive sleep apnea. *N. Engl J Med.* 2014;370:139–49.

SLEEP APNEA
IS LIKE
DREAMING WITH THE ENEMY