

Sleep Disorders in Stroke (TIA)

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Disclosure

- CO-PI. Sleep for Stroke Management and Recovery Trial (Sleep SMART).
- Sub-PI. A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Suvorexant for the Treatment of Insomnia in Participants with Opioid Use Disorder.
- Member: ABIM, Sleep Medicine Testing Committee
- Artificial intelligence was not used in the creation of this PP

- ▶ Virginia Commonwealth University
- ▶ Richmond, Virginia



Outline

- ▶ Stroke statistics and Mr JP and his wife Mrs JP
- ▶ Post-stroke sleep disorders
- ▶ Pre-stroke sleep disorders
- ▶ Is OSA a risk factor for stroke?
- ▶ Does treating OSA modifies stroke risk?
- ▶ Suggestions



Stroke Statistics

- ▶ Every year, more than **795,000 people** in the United States have a stroke
- ▶ 610,000 of these are **first** or new strokes
- ▶ 185,000 (**quarter**): occur in those who had a prior stroke (**recurrent**)
- ▶ Costs the United States an estimated **\$34 billion** annually
- ▶ Leading cause of long-term **disability**

- ▶ Associated with risk factors
 - ▶ **Modifiable** ******OSA**
 - ▶ Non-modifiable

Reference: CDC



Mr JP

- ▶ 68-year old gentleman who was “stroke alerted” at 7:30 am.
- ▶ He presented with inability to speak and severe weakness of his right arm and right leg and right facial droop.
- ▶ Last known normal (LKN) was the night before. He and his wife had dinner at 6 pm, then watched TV and went to bed around 10 pm.



Arriving at the Emergency Department



- ▶ Head CT showed no bleed. CT angiogram of the brain and neck showed a thrombus/clot in the left middle cerebral artery. The patient was not a candidate for Thrombolytic (> 4.5 hours from LKN).
- ▶ He underwent a successful left MCA Thrombectomy performed by neurosurgery.

Hospital Day Two

- ▶ Mr JP showed improvement. He had mild to moderate language deficit and his right sided weakness showed improvement. He had right visual field cut
- ▶ Our stroke team performed an extensive workup to assess the **cause of the stroke**
- ▶ Hypertension, diabetes mellitus (A1c 8), new onset atrial fibrillation found on EKG, and hyperlipidemia



Secondary Stroke Prevention Measures

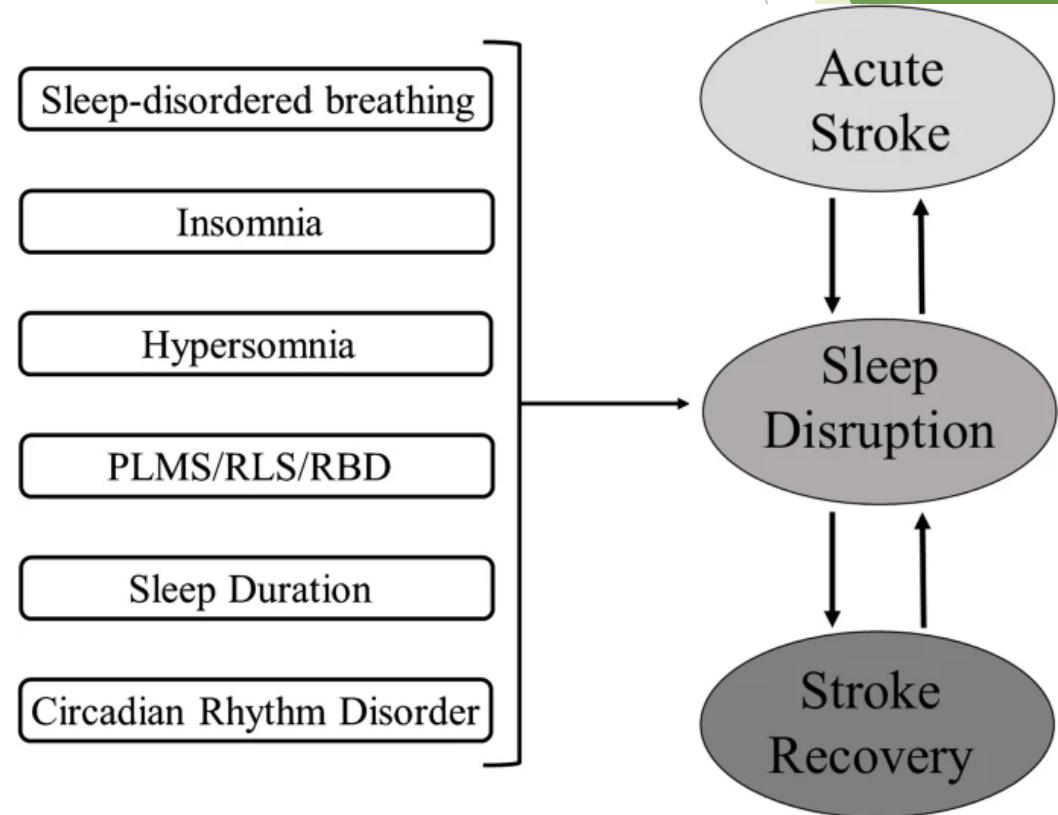
- ▶ Aspirin with a gradual switch to Apixaban for the atrial fibrillation
- ▶ Statin therapy for LDL 126
- ▶ Losartan and amlodipine for hypertension
- ▶ Metformin and insulin for diabetes mellitus
- ▶ Physical therapy, speech therapy
- ▶ Patient is discharged to rehabilitation and then home
- ▶ Stroke clinic and primary care follow up within 2-3 months
 - ▶ Ensure that his vascular risks are addressed, compliant with medications.
 - ▶ Asked about depression. Slight depression.
 - ▶ Re-assess his speech and mobility



A collage of colorful sticky notes (pink, yellow, green, and blue) with black question marks, layered on the left side of the slide. The background features a dark blue-grey area on the right and a green geometric pattern on the far right.

What is Missing?

Screening for Post Stroke Sleep disturbance



Let's check on
Mr JP...
3 months later



Mrs JP is *not* Happy

- ▶ Mrs JP: “He sleeps all day.”
- ▶ PMD referred him to sleep clinic.
- ▶ Bedtime is 10 pm but it takes him 1-2 hours to fall asleep, nightly. Sleeps till 9 am, wakes up, eats breakfast and then wants to sleep for another 2 hours.
- ▶ Sleep quality is poor. Wakes up sometimes and cannot ret sleep.
- ▶ +/- RLS symptoms. Has spastic pain.
- ▶ Snore. Now worse. Has apneic episodes.
- ▶ No dream enactment behavior.
- ▶ Used to own his own business. Now he is unable to run business. He stays home and watches TV and falls asleep off on the couch. No longer engages in social activities. language and speech difficulty. Feels anxious at times





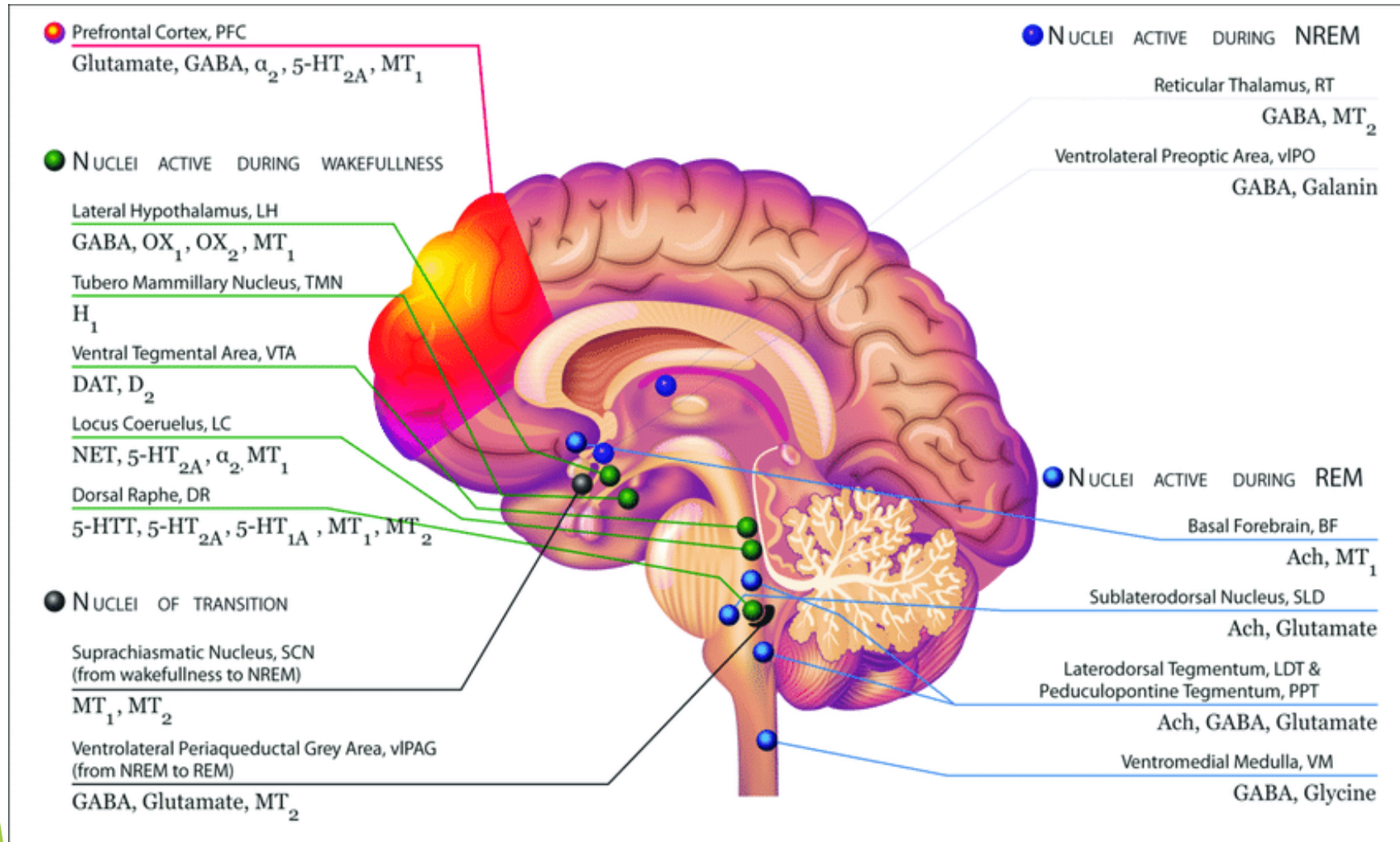
► Post-stroke sleep disorder

vs

Pre-stroke sleep disorders



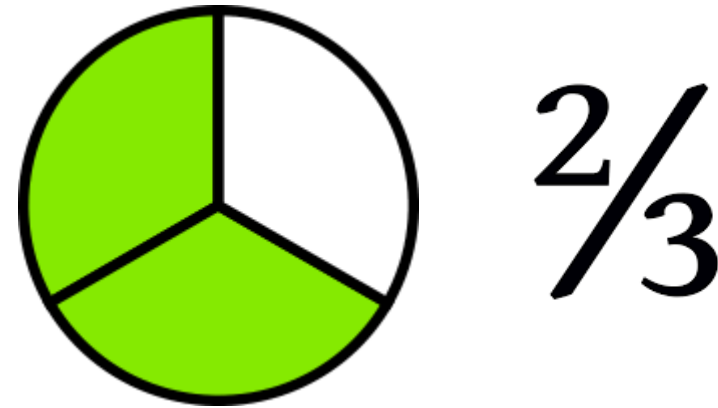
What Could Go Wrong After the Stroke ?



- Differential Function of Melatonin MT1 and MT2 Receptors in REM and NREM Sleep. *Frontiers in endocrinology*. 2019

Post Stroke Sleep Disordered Breathing

- ▶ About Two third of stroke patients have sleep apnea
- ▶ Obstructive sleep apnea (OSA)
- ▶ Rare central sleep apnea
- ▶ Seldom screened or treated for OSA



Johnson KG, Johnson DC. J ClinSleep Med 2010; 6:131-137

Skolarus LE, et al. Stroke 2012; 43:1143-1145



Post-Stroke Insomnia

- ▶ 30%
- ▶ Female, depression and anxiety, poor functional outcome
- ▶ Mechanism: disruption of the sleep mechanism, hypersomnia during the day, new onset RLS or PLMS, sleep apnea, psychotropic medications, and disruption of the circadian rhythm
- ▶ Actigraphy and sleep diary (if able, family) helpful
- ▶ Treatment: Improve daytime environment (light, family engagement, mobility as tolerated) and nighttime environment (decrease noise and light, soothing sounds). Can consider sedative hypnotic (avoid benzodiazepines). Caution with delirium
- ▶ Natural light has been shown to improve sleep quality and fatigue



Post-Stroke Hypersomnia



- ▶ 10-20%
- ▶ Improves but... in cases with bilateral paramedian thalamic strokes and upper brainstem, it persists and disabling
- ▶ Wake mechanisms are disrupted due to stroke. OSA.
- ▶ Sedentary lifestyle, heart failure, medication effect, and depression
- ▶ Diagnosis: clinically, ESS, actigraphy. Sleep study to rule out OSA
- ▶ Treatment: Challenging
 - ▶ Treat depression
 - ▶ Wake promoting agents such as modafinil
 - ▶ Careful with stimulant due to sympathetic effect
 - ▶ Improve sleep hygiene, family engagement, light and activity during the day



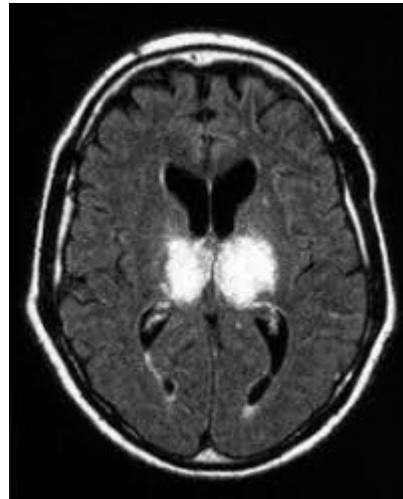


ARTICLE

0977 Bilateral thalamic strokes presenting as acute hypersomnia

Alattar, Maha ; Nguyen, Tri

Sleep (New York, N.Y.), 2023-05, Vol.46 (Supplement_1), p.A431-A431



Post-Stroke RLS and PLMS

- ▶ 8%
- ▶ PLMS is more frequent in patient with RLS than without RLS
- ▶ Post stroke RLS predicts worse stroke outcomes and lower quality of life
- ▶ Female, low serum Ferritin and depression
- ▶ Subcortical stroke (caudate, pontine, thalamic)
- ▶ Diagnosis: Similar
- ▶ Treatment: No data specific to stroke. Avoid opioids

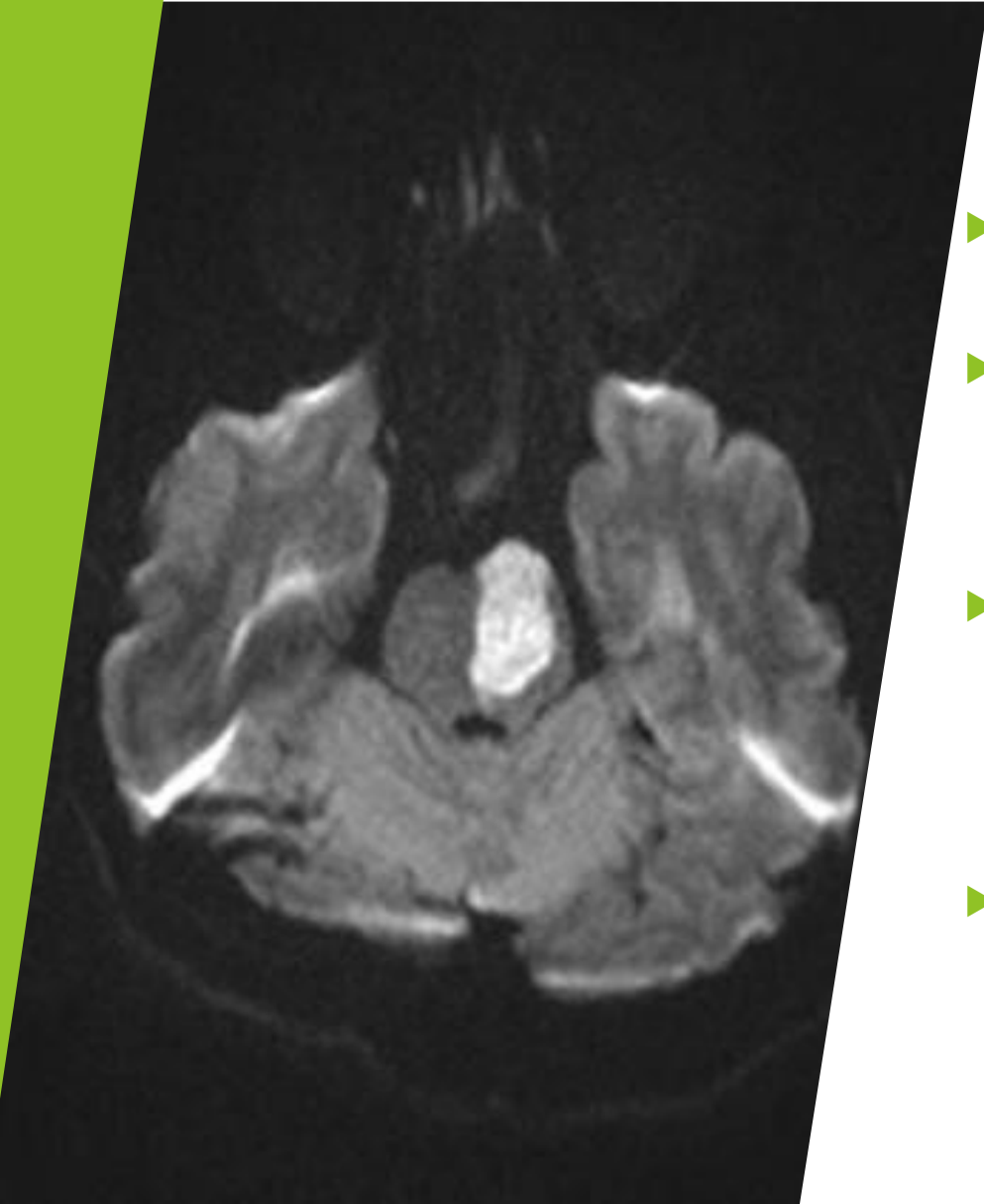
Shiina T, Suzuki K, Okamura M, Matsubara T, Hirata K. Restless legs syndrome and its variants in acute ischemic stroke. *Acta Neurol Scand*. 2019

Wang XX, Feng Y, Tan EK, Ondo WG, Wu YC. Stroke-related restless legs syndrome: epidemiology, clinical characteristics, and pathophysiology. *Sleep Med*. 2022



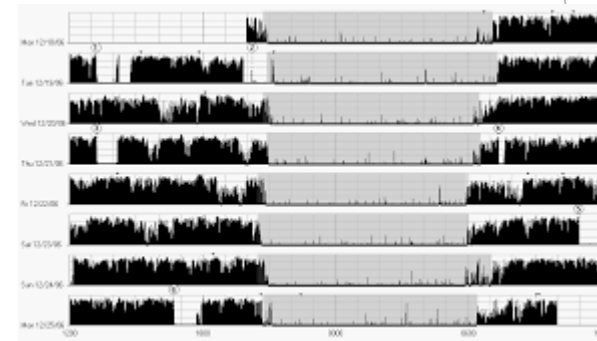
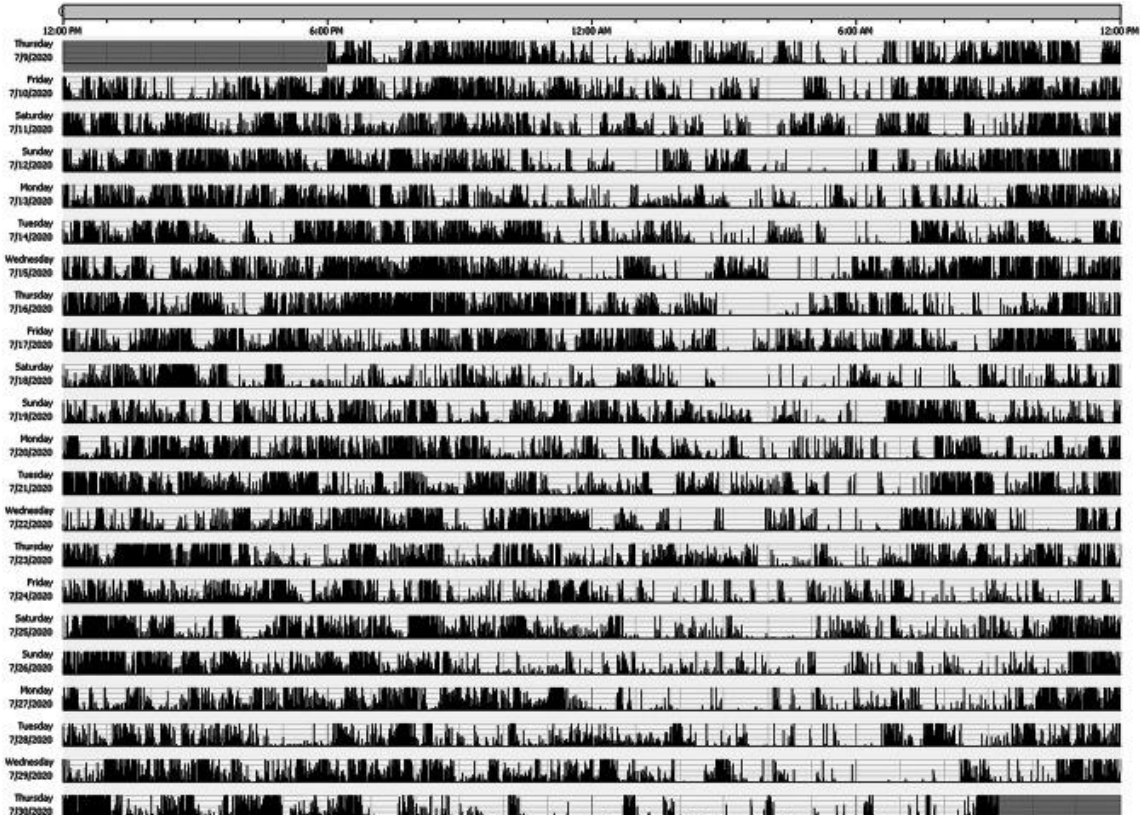
Post-Stroke Disturbance of Dreaming

- ▶ *REM Sleep Behavioral Disorder (RBD)*: Absence of the normal REM atonicity. Dream enactment behavior. 11%. Tegmentum of pons
- ▶ *Peduncular hallucinosis*: occurs during day
 - ▶ Complex, dreamlike visual hallucinations, evening
 - ▶ Pons, midbrain, thalamic
- ▶ *Charcot-Wilbrand Syndrome (CWS)*: altered visual component of dreams. Parieto-occipital, frontal strokes
 - ▶ Decreased re-visualization
 - ▶ REM sleep may be preserved
- ▶ *Incorporation of motor deficit*
 - ▶ Severe motor deficit report persistence of normal motor function within their dreams for years after the stroke
 - ▶ Wake up in the morning is distressing-realization
 - ▶ Others: Handicap is incorporated early in dreams

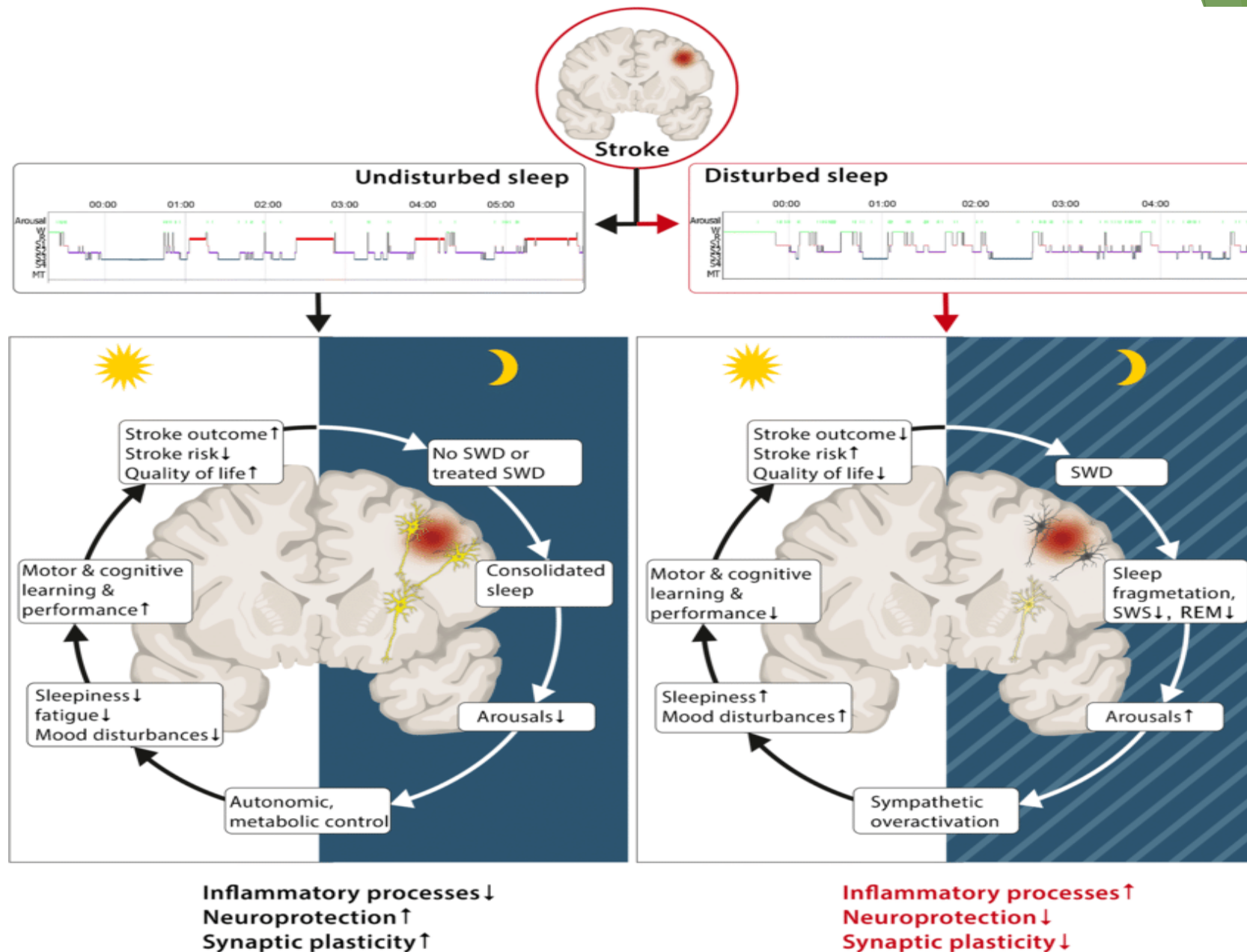


Post-Stroke Sleep Wake Dysregulation

- Altered based on actigraphy and serum melatonin



Steele TA, St Louis EK, Videnovic A, Auger RR. Circadian Rhythm Sleep-Wake Disorders: a Contemporary Review of Neurobiology, Treatment, and Dysregulation in Neurodegenerative Disease. Neurotherapeutics. 2021





Pre-Stroke Sleep Disorders



- ▶ Does insomnia increase the risk for stroke?
- ▶ Hypersomnia?
- ▶ OSA?

RESEARCH ARTICLE

Association Between Insomnia Symptoms and Trajectory With the Risk of Stroke in the Health and Retirement Study

Wendemi Sawadogo, MD, MPH, PhD, Tilahun Adera, PhD, MPH, Maha Alattar, MD, Robert Perera, PhD, and James B. Burch, MS, PhD

Neurology® 2023;101:e475-e488. doi:10.1212/WNL.0000000000207449

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- Health and Retirement Study survey 2002 -2020 data source. Americans older than 50 years and their spouses, from 2002 to 2020 was used as the data source. Only those who were stroke-free at baseline were included in this study. Self-reported Insomnia: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and nonrestorative sleep. Identified insomnia trajectories over time. To investigate the relationship between insomnia symptoms and stroke events reported during the follow-up period. A total of 31,126 participants were included with a mean follow-up of 9 years. The mean age was 61 years. 57% were females.
- Results: Compared with those with no insomnia symptoms, **an increased risk of stroke was observed for those with insomnia symptom** with a dose-response relationship. The association was stronger in participants younger than 50 years than in those aged 50 years and older. The association was stronger for difficulty initiating sleep, followed by difficulty maintaining sleep, waking up too early, and nonrestorative sleep. This association was mediated by diabetes, hypertension, heart disease, and depression.



> J Stroke Cerebrovasc Dis. 2024 Apr;33(4):107615. doi: 10.1016/j.jstrokecerebrovasdis.2024.107615.
Epub 2024 Feb 1.

Sleep duration and all-cause mortality among stroke survivors

Wendemi Sawadogo¹, Tilahun Adera², James B Burch², Maha Alattar³, Robert Perera⁴,
Virginia J Howard⁵

Affiliations + expand

PMID: 38307468 DOI: 10.1016/j.jstrokecerebrovasdis.2024.107615



- ▶ **Methods and Results:** The REasons for Geographic And Racial Differences in Stroke (REGARDS), a national population-based longitudinal study, was the data source. Sleep duration was ascertained between 2013 and 2016 among stroke survivors who were subsequently followed up until death or censored on December 31, 2022. 468 non-Hispanic Black and White stroke survivors were included in this analysis. The mean age was 76.3 years, 52.6% were females
- ▶ **Conclusion:** In this study of stroke survivors, 9 hours or more of sleep per day was associated with an increased risk of all-cause mortality. **This finding suggests that excessive sleep duration may be a warning sign of poor life expectancy in stroke survivors.** However, short sleep (≤ 6 h) was not significantly associated with an increased risk of all-cause mortality.



Obstructive Sleep Apnea and Future Stroke Risk





OSA-Stroke Risk

- ▶ **OSA is an independent risk factor for all strokes and TIA**
 - ▶ Even when controlling for HTN, DM, hyperlipidemia and A fib
- ▶ Moderate to severe OSA and the elderly- have worst stroke risk
- ▶ Silent cerebral infarction (CSI)- Severe OSA
- ▶ OSA+ A fib= higher risk for cardioembolic strokes (than A fib with no OSA)
- ▶ Stroke patients + OSA: Worse prognosis (hospitalization, rehab, cognitive)



Stroke

- ▶ *"This study shows that severe obstructive sleep apnea hypopnea (defined as apnea-hypopnea index ≥ 30) increases the risk of ischemic stroke in the **elderly** population, independent of known confounding factors."*
- ▶ Reference: Munoz R, Duran-Cantolla J, Martinex-Vila E, Gallego J, Rubio R, Aizpuru F, De La Torre G. Severe sleep apnea and risk of ischemic stroke in the elderly. Stroke. 2006 Sep;37(9):2317-21. Epub 2006 Aug 3.

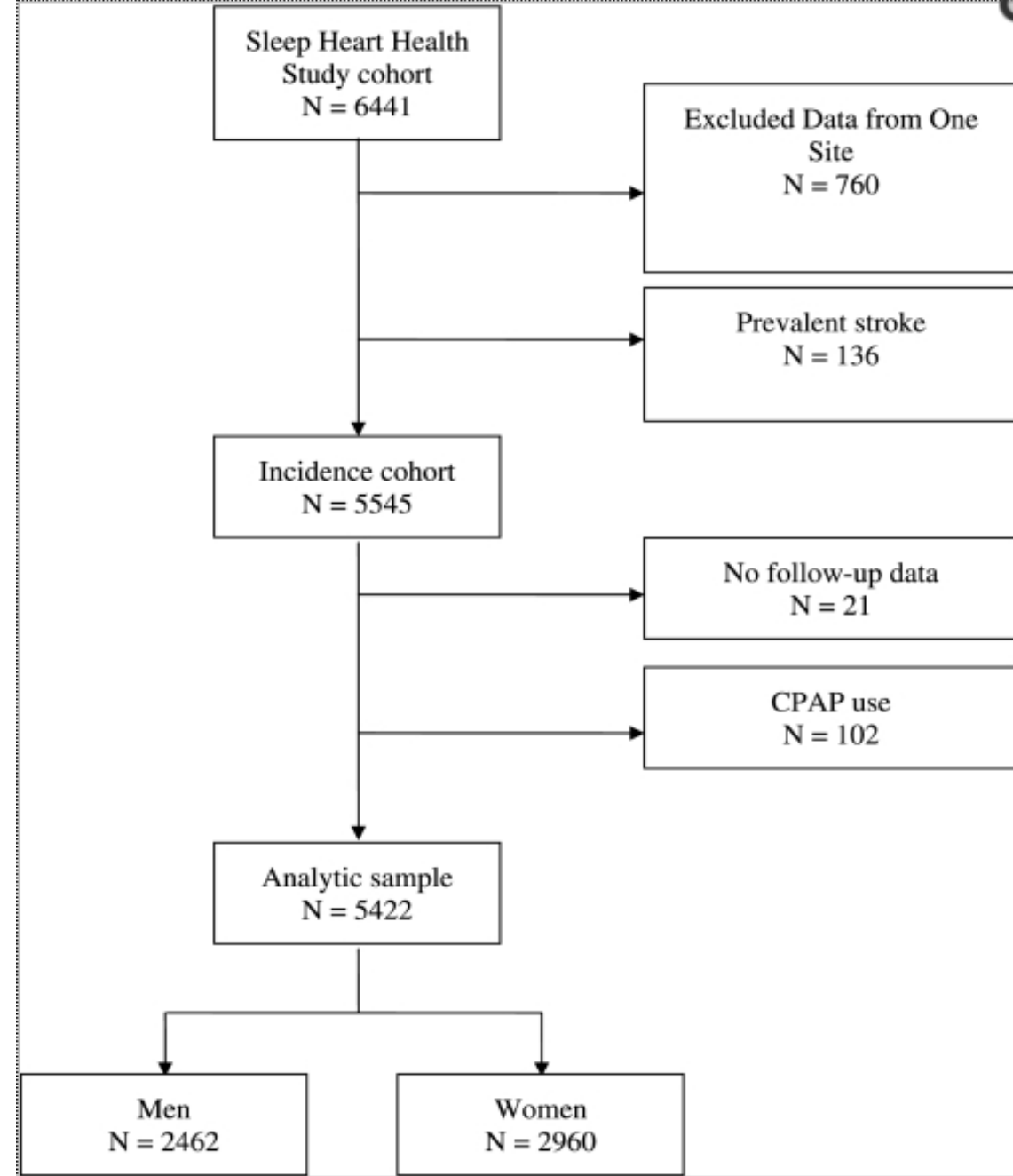


The New England Journal of Medicine

- ▶ *"The obstructive sleep apnea syndrome significantly increases the risk of **stroke** or **death** from any cause, and the increase is independent of other risk factors, including hypertension."*
- ▶ 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 Nov 10;353 (19):2034-41.

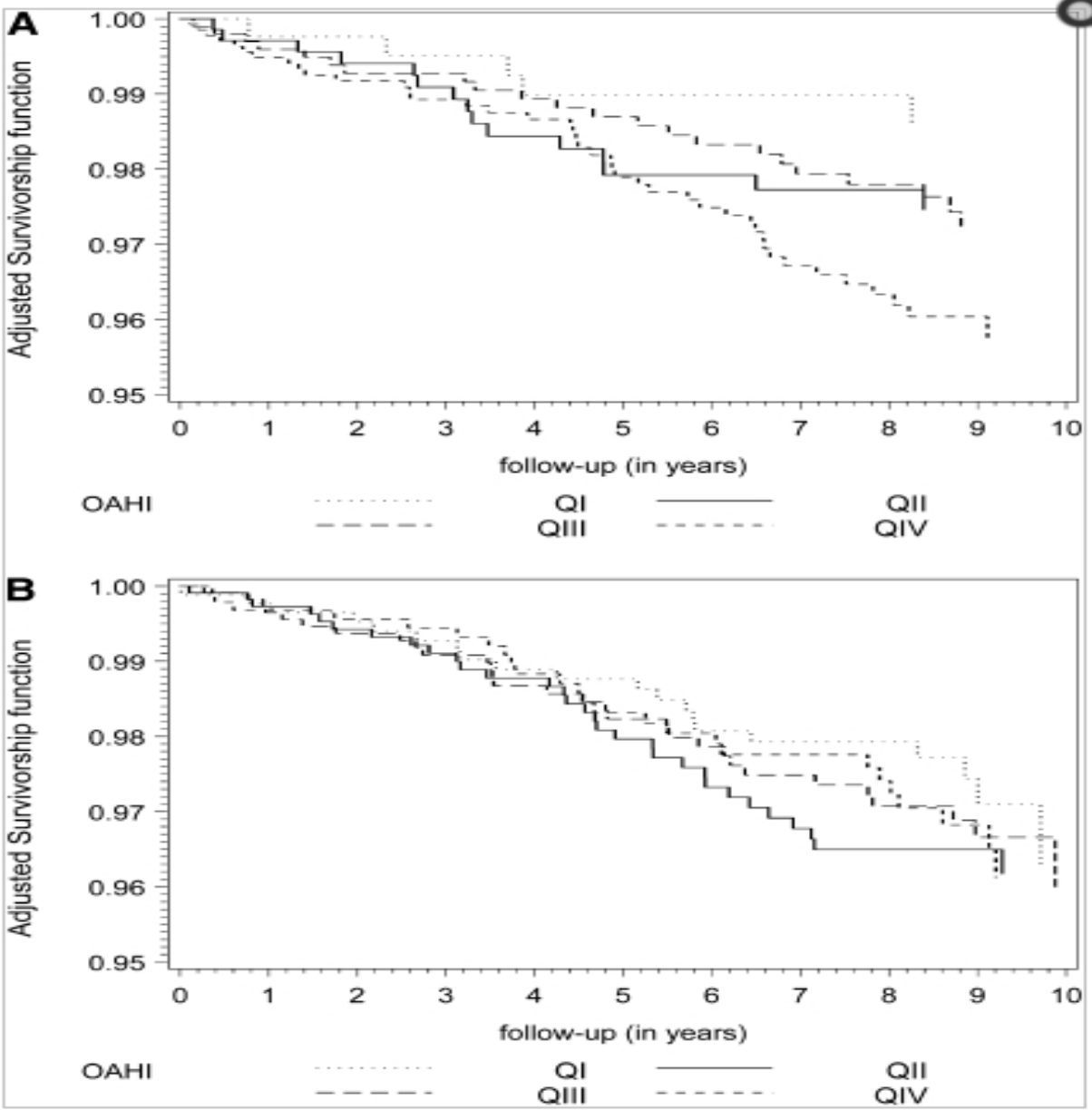
Strong Evidence

The Sleep Heart Health Study (2010)



Obstructive Sleep Apnea-Hypopnea and Incident Stroke The Sleep Heart Health Study
American J of Resp n Critical Care Med 2010

Study schema showing derivation of the analytical sample. CPAP = continuous positive airway pressure.

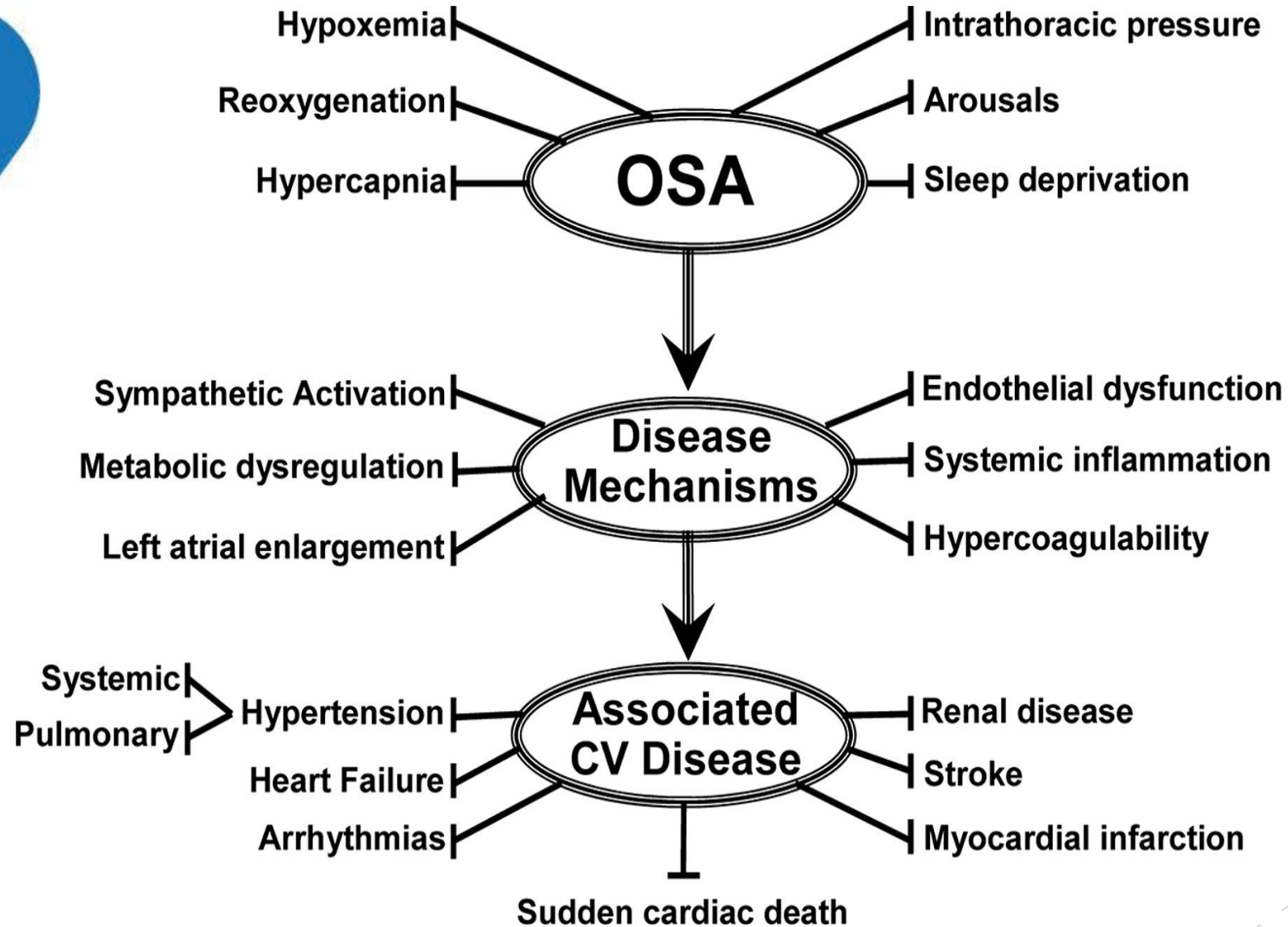


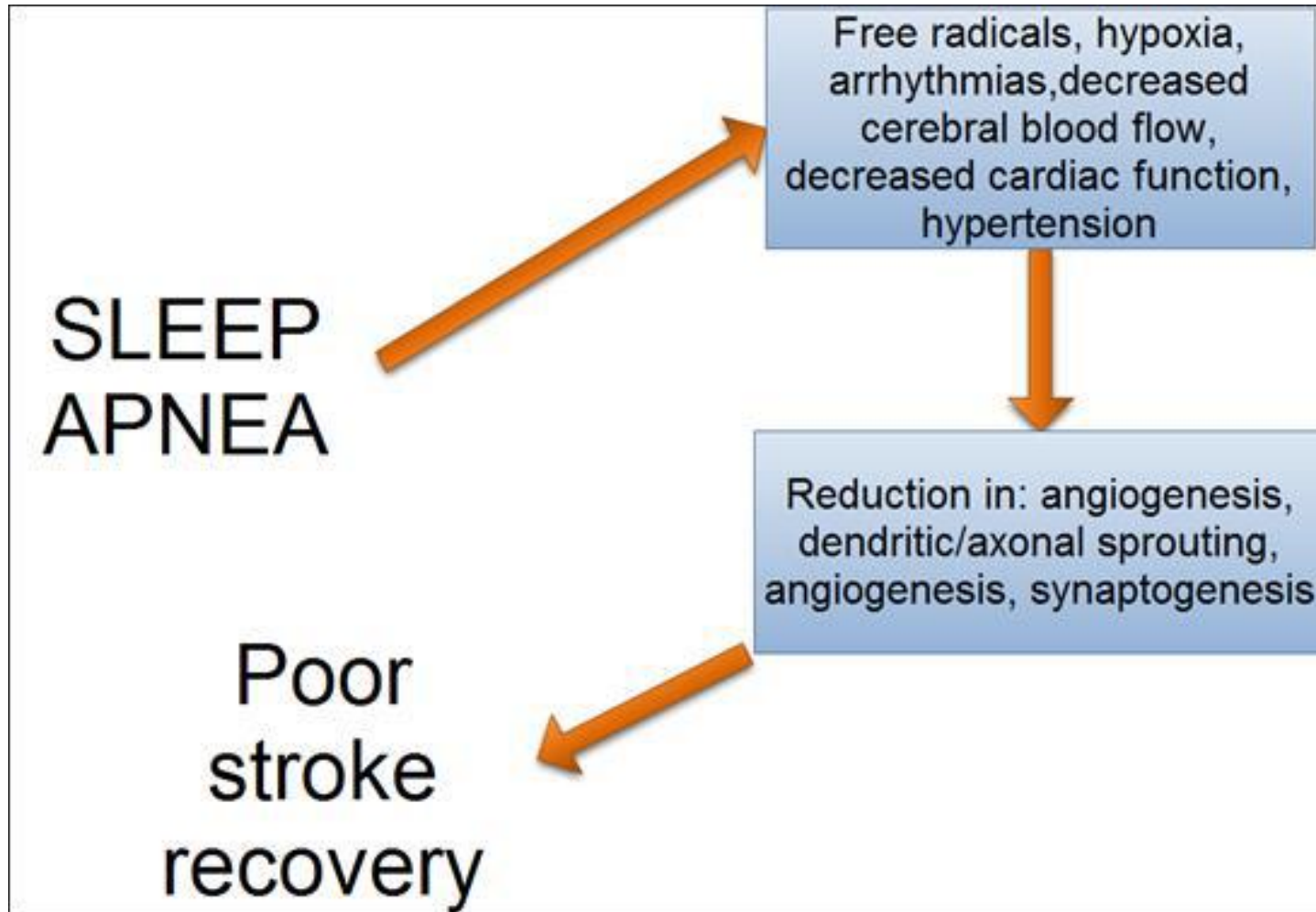
Men

Women

Obstructive Sleep Apnea-Hypopnea and Incident Stroke The Sleep Heart Health Study
American J of Resp n Critical Care Med 2010

Adjusted Kaplan-Meier stroke-free survival estimates as a function of obstructive apnea-hypopnea index (OAHI) quartile. Values are modeled in this graph for white current smoker (A) men and (B) women with no use of antihypertensive medications with mean values of other covariates. The first (OAHI <4.5), second (4.05–9.5), third (9.5–19.1), and fourth quartiles (>19.1) of the OAHI are shown by the various solid and dashed lines indicating the quartiles (see key at bottom of figure).





Hypertension and OSA

- ▶ Blood pressure increases linearly with RDI (AHI)
- ▶ Each 10% decrease in O₂ saturation increases odds of HTN by 13%
- ▶ "SDB, including **snoring**, is an independent risk factor for hypertension (HTN)"
- ▶ A physician should consider the possibility of HTN When any type of sleep disordered breathing is present;
 - ▶ Conversely should consider the possibility of SDB whenever HTN is present



Carotid stenosis

- ▶ Severe OSA is independently associated with carotid artery disease



Schulz R. Eur RespirJ 2005

Diabetes Mellitus, Metabolic Syndrome and OSA

- ▶ OSA worsens DM: Increases risk of diabetes by 1.9 fold independent of other factors
 - ▶ CPAP helpful in some studies; not in others
- ▶ Metabolic syndrome was 9.1 times more likely to be present in patients with OSA

Coughlin et al Eur Heart J. 2004

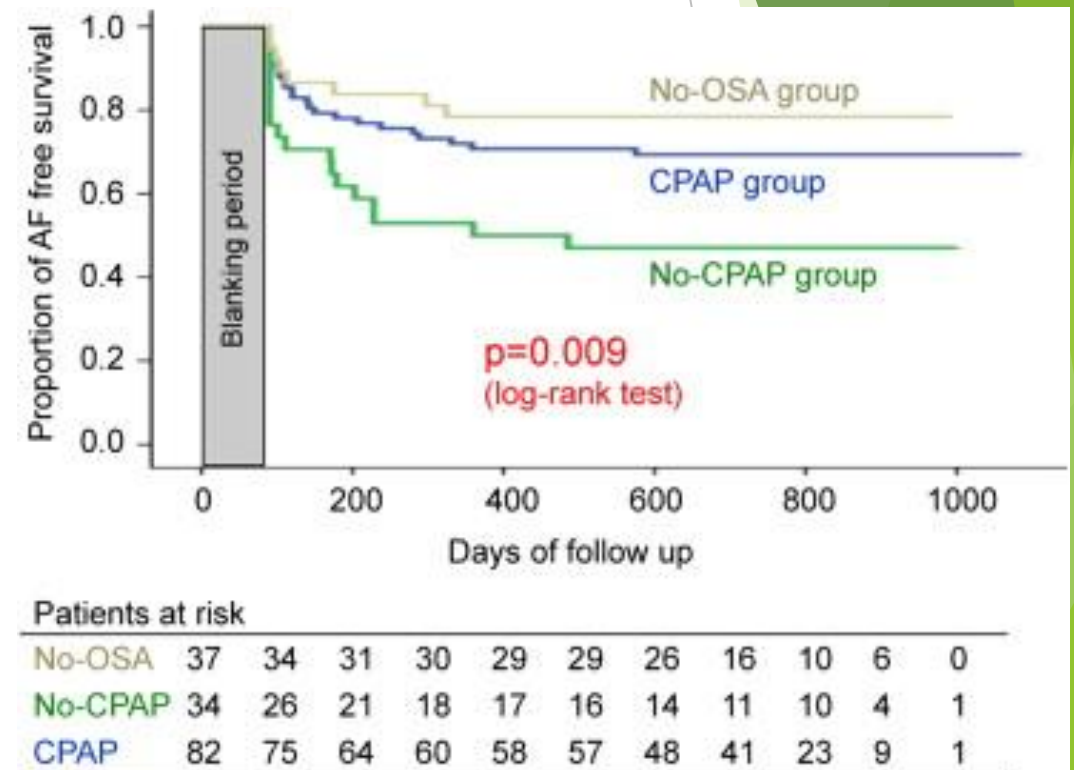
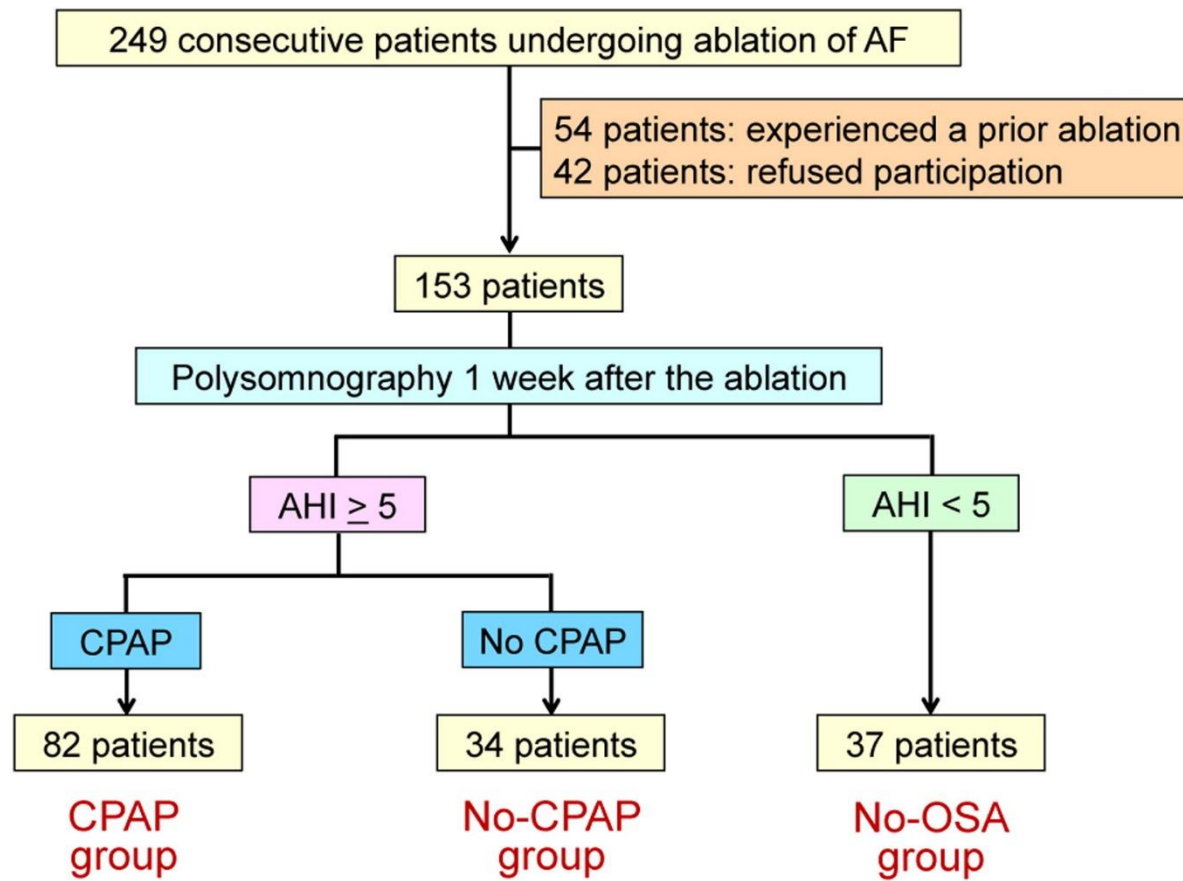


Atrial fibrillation & OSA

- ▶ Patients with OSA have increased risk of atrial fib (OR 4.02). Even after adjustment for age, sex, BMI, and prevalent coronary artery disease
- ▶ Atrial fibrillation is a significant risk for stroke.



- ▶ Tung, P et al. J Atr Fibrillation 2016



Naruse Y et al. Concomitant obstructive sleep apnea increases the recurrence of atrial fibrillation following radiofrequency catheter ablation of atrial fibrillation: clinical impact of continuous positive airway pressure therapy. Heart Rhythm. 2013 Mar;10(3):331-7.

OSA and Heart Disease

- ▶ OSA is risk for congestive heart failure
- ▶ OSA is risk for myocardial infarction

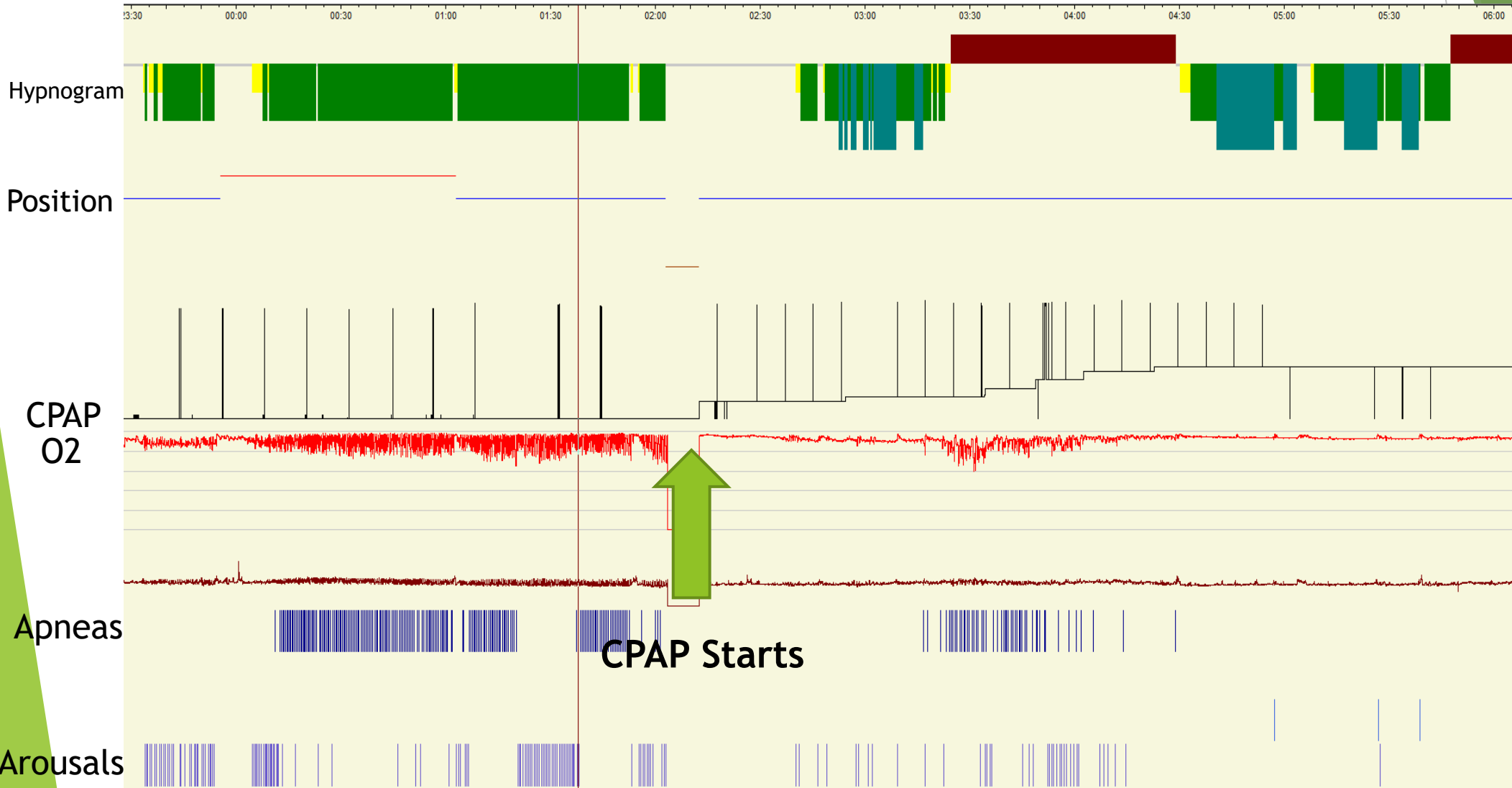
Nieto et al. (*Sleep Heart Health Study*) JAMA 2000;283:1829-36

Garpestad et al. J Appl Phys. 1992;73:1743-48.



MR JP underwent a split-Polysomnogram

Can CPAP prevent a second stroke?





SCIENTIFIC INVESTIGATIONS

CPAP adherence is associated with reduced risk for stroke among older adult Medicare beneficiaries with obstructive sleep apnea

Emerson M. Wickwire, PhD^{1,2}; M. Doyinsola Bailey, MPH³; Virend K. Somers, MD, PhD⁴; Mukta C. Srivastava, MD⁵; Steven M. Scharf, MD, PhD²; Abree M. Johnson, MS⁶; Jennifer S. Albrecht, PhD³

¹Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland; ²Sleep Disorders Center, Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; ³Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland; ⁴Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; ⁵Division of Cardiovascular Medicine, Department of Medicine, University of Maryland School of Medicine, Baltimore, Maryland; ⁶Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, Maryland

Study Objectives: To examine the impact of adherence to continuous positive airway pressure (CPAP) therapy on risk of stroke among a nationally representative sample of older adults with obstructive sleep apnea.

Methods: We performed a retrospective cohort study among Medicare beneficiaries aged ≥ 65 years who were newly diagnosed with obstructive sleep apnea and had initiated CPAP (2009–2013). Monthly indicators of CPAP adherence included charges for machines, masks, or supplies and were summed over a 25-month follow-up to create a CPAP adherence variable. Stroke was modeled as a function of CPAP adherence using generalized estimating equations.

Results: We found that 5,757 beneficiaries met the inclusion criteria and were included in the final sample. Of these, 407 (7%) experienced stroke. After adjusting for demographic and clinical characteristics, CPAP adherence was associated with a reduced risk of stroke (hazard ratio, 0.98; 95% confidence interval, 0.96–0.99) over 25 months, indicating a 2% reduction in risk of stroke for each month of CPAP adherence. When sensitivity analyses were performed to stratify results by time since the first CPAP charge, the protective effect remained significant for the 12- and 6-month but not the 3-month outcome models.

Conclusions: In this national analysis of older adult Medicare beneficiaries with obstructive sleep apnea, CPAP adherence was associated with significantly reduced risk of stroke.

Keywords: obstructive sleep apnea, stroke, cardiovascular, continuous positive airway pressure, CPAP, treatment, adherence, Medicare, older adults

Citation: Wickwire EM, Bailey MD, Somers VK, et al. CPAP adherence is associated with reduced risk for stroke among older adult Medicare beneficiaries with obstructive sleep apnea. *J Clin Sleep Med*. 2021;17(6):1249–1255.

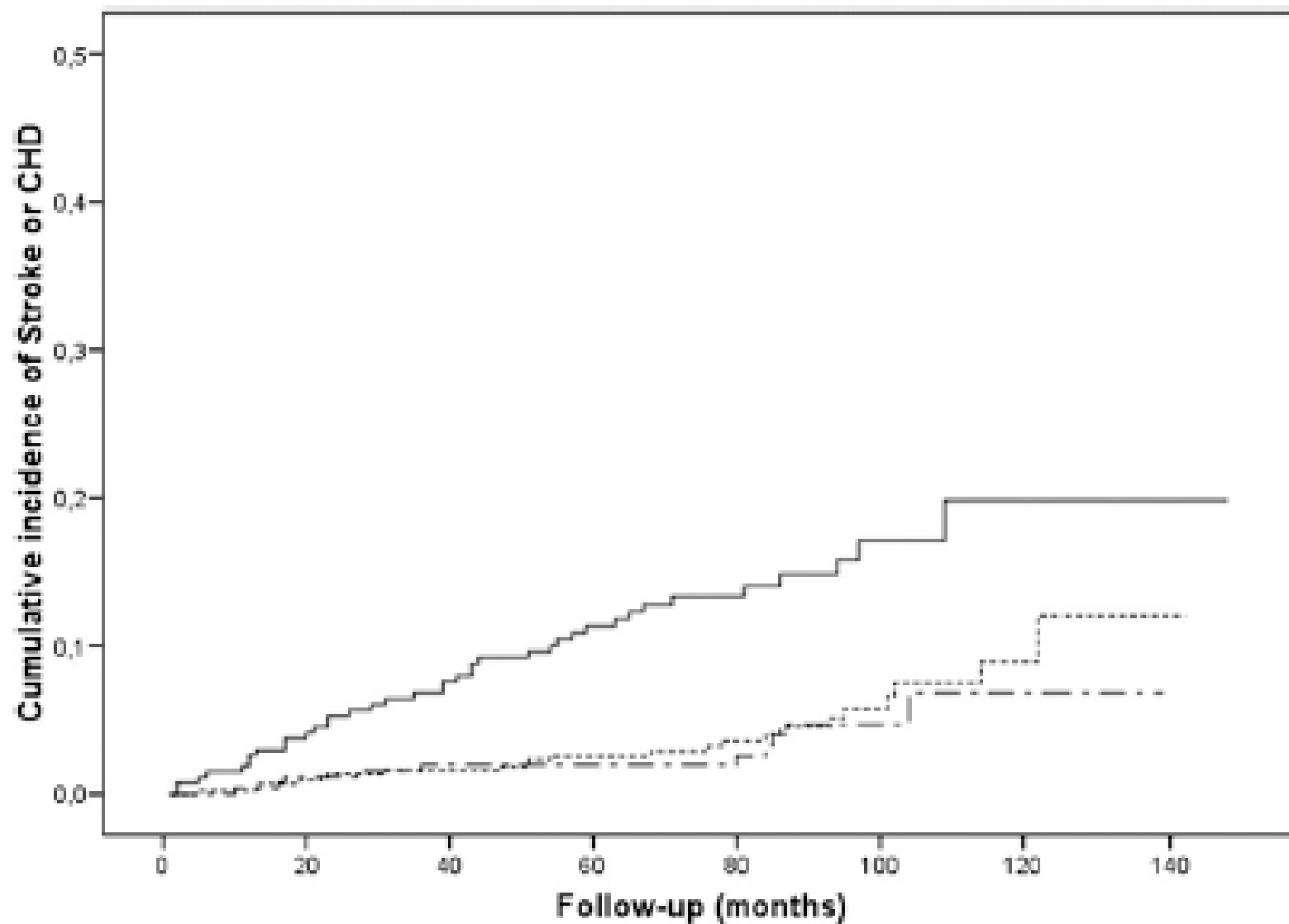
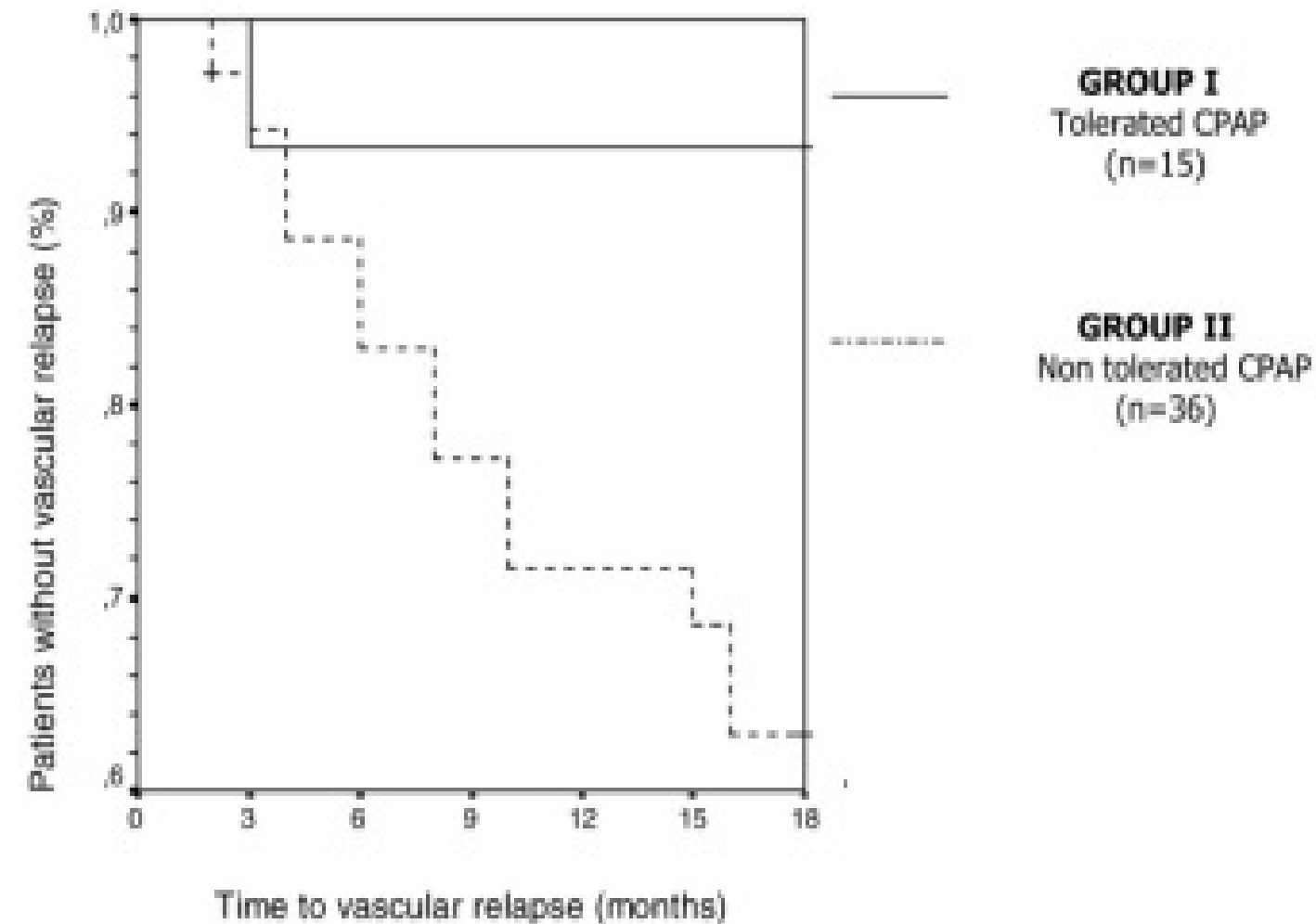


Figure 2. Kaplan-Meier cardiovascular cumulative incidence curves for study groups. AHI = apnea-hypopnea index; CHD = coronary heart disease. *Dashed line*, AHI less than 10 (control group). *Dotted line*, AHI greater than or equal to 10 treated with continuous positive airway pressure. *Solid line*, AHI greater than or equal to 10 untreated. The cumulative incidence of stroke or CHD was significantly higher in the group of women with AHI greater than or equal to 10 and untreated compared with the control group (AHI < 10): $P < 0.0005$.

“In **women**, untreated OSA is associated with increased incidence of serious cardiovascular outcomes, particularly incident stroke. Adequate **CPAP** treatment seems to **reduce** this risk.”

Ref: Role of Sleep Apnea and Continuous Positive Airway Pressure Therapy in the Incidence of Stroke or Coronary Heart Disease in Women

Am J Respir Crit Care Med 2014 June



“We concluded that **CPAP treatment** during 18 months in patients with an AHI $\geq$ 20 afforded **significant protection against new vascular events** after ischemic stroke.”

Ref: Chest October 2005

Figure 1. Kaplan-Meier survival curves for assessing the recurrence of VEs in the patient groups conformed according to CPAP tolerance. Log-rank test ($p = 0.03$) between groups 1 and 2 adjusted for the presence of AF.



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Sleep SMART Summary

The primary goals of this study are to determine whether treatment of obstructive sleep apnea (OSA) with positive airway pressure starting shortly after acute ischemic stroke or high risk TIA (1) reduces recurrent stroke, acute coronary syndrome, and all-cause mortality during 6 months after the event, and (2) improves stroke outcomes at 3 months in patients who experienced an ischemic stroke.

Prior studies have shown a clear independent association between OSA, which has a prevalence similar to hypertension among stroke patients, and development of stroke and poor outcomes after ischemic stroke. If the Sleep SMART hypotheses are confirmed, a new strategy to prevent stroke recurrence and improve stroke recovery will be available.

- ▶ Decreased **mortality**
- ▶ Decreases incidence of **new** strokes (2 prevention)
- ▶ Reduces **risks**: Hypertension, DM, heart disease, Atrial Fibrillation
- ▶ Improved cognitive/alertness and depressive symptoms
- ▶ Improved recovery/physical disability in post-stroke **rehabilitation**
- ▶ **Better sleep**

Why treat
OSA in stroke
patients?

Challenges of CPAP in Stroke

- ▶ Poor adherence (25%)
- ▶ Aphasia, dysarthria, facial weakness, arm weakness, cognitive limitation
- ▶ Depression, lack of motivation
- ▶ Suggestions:
 - ▶ Need a buddy/helper
 - ▶ Encouragement, feedback
 - ▶ Realistic- not all night but few hours better than none.
 - ▶ Give time. Some deficits will improve. Patient might be able to tolerate later

Suggestions

- ▶ Screen your patients with stroke/TIA for sleep disturbance
 - ▶ Inpatient or outpatient settings
- ▶ OSA, insomnia, hypersomnia, RLS, abnormal dreams
- ▶ Educate healthcare providers including APP, primary care physicians, neurologists, cardiologist etc.
- ▶ Questionnaires, Pulse oximetry
- ▶ Sleep studies: HSAT versus in-lab PSG

Thank you

Questions?

